Chemical Science

EDGE ARTICLE

Cite this: *Chem. Sci.*, 2020, **11**, 5328

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

Juri Skotnitzki, Alexander Kremsmair, Daniel Keefer, ‡ Franziska Schüppel, Brieuc Le Cacher de Bonneville, Regina de Vivie-Riedle and Paul Knochel *

Received 26th November 2019
Accepted 7th April 2020

DOI: 10.1039/c9sc05982b

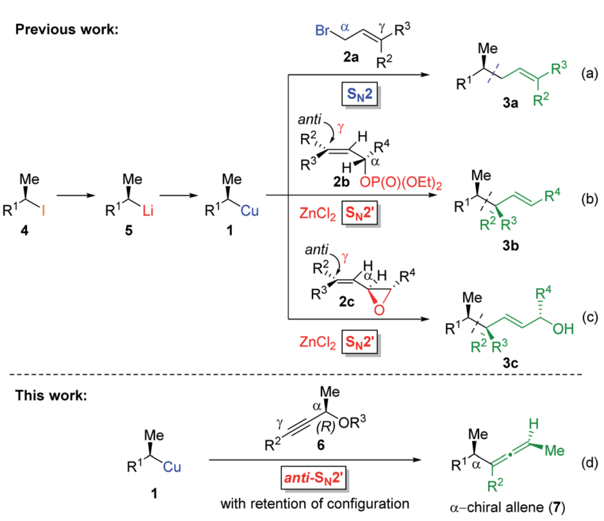
rsc.li/chemical-science

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 performend 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.[2–4] Axially chiral allenes are generally prepared from enantioenriched propargylic substrates[3] 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.[1e] 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.[5] Thereby, the stereochemistry of the α-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)).[6,7] These organocopper reagents were prepared from the corresponding alkyl iodide **4** *via* I/Li-exchange reaction leading to alkyllithium reagent **5**. Subsequent transmetalation with CuBr·P(OEt)$_3$ afforded alkylcopper reagent **1**.[8] 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** (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 S_N2'-products **3b** (γ : α > 99 : 1; (b)).[6] Furthermore, we reported *anti*-S_N2'-substitutions of secondary alkylcopper-zinc reagents with allylic epoxides **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 (3*S*,6*R*,7*S*)-zingiberenol.[7]



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.

Department of Chemistry, Ludwig-Maximilians-Universitaet, Butenandtstrasse 5-13, 81377 München, Germany. E-mail: paul.knochel@cup.uni-muenchen.de

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c9sc05982b

‡ Present address: Department of Chemistry, University of California Irvine, California 92697, United States.

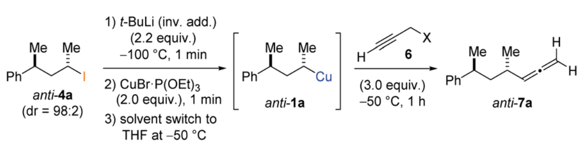
Herein, we wish to report the *anti*-S_N2'-substitution of secondary alkylcopper reagents **1** with chiral propargylic phosphates **6** leading to α-chiral allenes of type **7** with retention of the configuration (see Scheme 1(d)). Remarkably, this overall *anti*-S_N2'-substitution reaction proceeded 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 S_N2'-reaction. Thus, we prepared the secondary alkyllithium reagent *anti*-**5a** *via* I/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 $CuBr\cdot P(OEt)_3$ (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.[6] Subsequent addition of the propargylic bromide[9a] (**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 °C. The use of propargylic acetate (**6b**)[9b] showed a similar result (entry 2). Switching to pentafluorobenzoate (**6c**)[9c] or diphenylphosphate (**6d**)[9d] 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**[9e] 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).[10,11] 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.

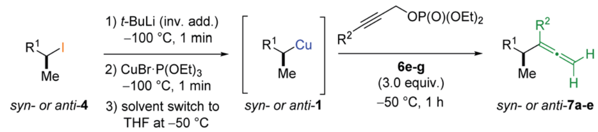
Table 1 Stereoretentive preparation of secondary alkylcopper reagent *anti*-**1a** and subsequent reaction with various propargylic substrates **6** leading to the allene *anti*-**7a**

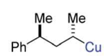
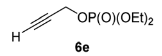
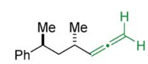
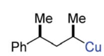
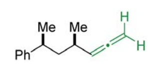
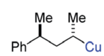
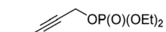
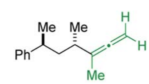
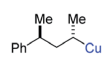
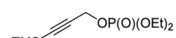
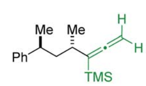
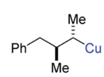
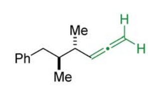
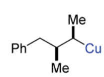
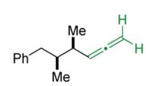
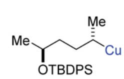
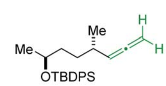
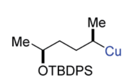
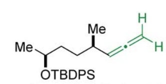


Entry	Electrophile	Yield of *anti*-**7a**[a] (%)	dr of *anti*-**7a**[a]
1	**6a**: X = Br	Traces	—
2	**6b**: X = OAc	5	90 : 10
3	**6c**: X = $OCOC_6F_5$	48	91 : 9
4	**6d**: X = $OP(O)(OPh)_2$	50	93 : 7
5	**6e**: X = $OP(O)(OEt)_2$	59	98 : 2

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

Table 2 Stereoselective preparation of diastereomerically pure allenes **7a–e** starting from alkyl iodides **4a–c**

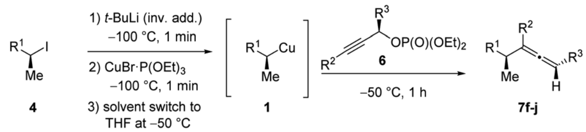


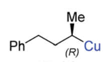
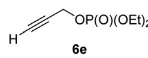
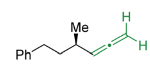
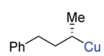
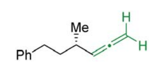
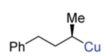
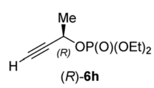
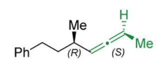
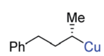
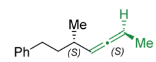
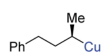
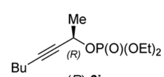
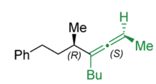
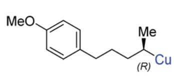
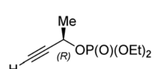
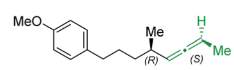
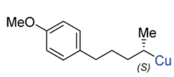
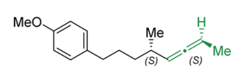
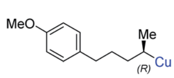
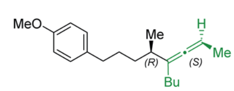
Entry	Alkylcopper	Electrophile **6**	Product of type **7**[a,b]
1	 *anti*-**1a**	 **6e**	 *anti*-**7a**, 55% yield, dr = 98:2
2	 *syn*-**1a**	**6e**	 *syn*-**7a**, 46% yield, dr = 6:94
3	 *anti*-**1a**	 **6f**	 *anti*-**7b**, 65% yield, dr = 97:3
4	 *anti*-**1a**	 **6g**	 *anti*-**7c**, 61% yield,[c]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

[a] The diastereoselectivity (dr; *anti* : *syn* ratio) was determined by ^1H- or ^{13}C-NMR analysis. [b] The S_N2' to S_N2 ratio was higher than 99 : 1. [c] 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 α-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,[12] led to the α-chiral disubstituted allene (*R*,*S*)-**7g**[13] in 43% yield with high *anti*-S_N2'-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;[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_N2'-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**^{a,b,c}
1	 (*R*)-**1d**	 **6e**	 (*R*)-**7f**, 41% yield, er = 93:7
2	 (*S*)-**1d**	**6e**	 (*S*)-**7f**, 48% yield, er = 10:90
3	 (*R*)-**1d**	 (*R*)-**6h** (er = 99:1)	 (*R*,*S*)-**7g**, 43% yield (dr = 92:8; er = 99:1)
4	 (*S*)-**1d**	(*R*)-**6h** (er = 99 : 1)	 (*S*,*S*)-**7g**, 49% yield, (dr = 12:88; er = 99:1)
5	 (*R*)-**1d**	 (*R*)-**6i** (er = 99:1)	 (*R*,*S*)-**7h**, 59% yield, (dr = 91:9; er = 99:1)
6	 (*R*)-**1e**	 (*R*)-**6h** (er = 99:1)	 (*R*,*S*)-**7i**, 52% yield, (dr = 93:7; er = 99:1)
7	 (*S*)-**1e**	(*R*)-**6h** (er = 99 : 1)	 (*S*,*S*)-**7i**, 54% yield, (dr = 12:88; er = 99:1)
8	 (*R*)-**1e**	(*R*)-**6i** (er = 99 : 1)	 (*R*,*S*)-**7j**, 51% yield, (dr = 92:8; er = 99:1)

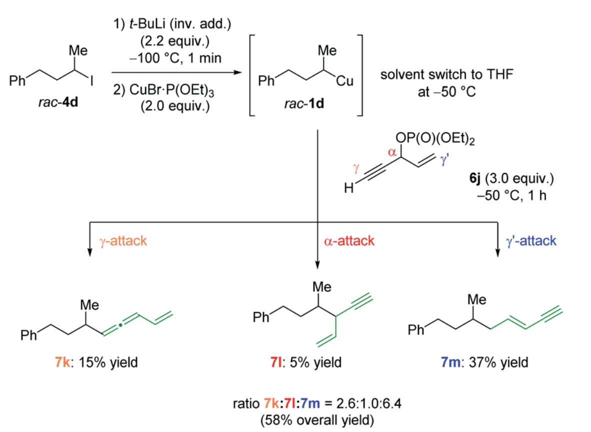
[a] The diastereoselectivity (dr; *anti* : *syn* ratio) was determined by ^{1}H- or ^{13}C-NMR analysis. [b] The S_N2' to S_N2 ratio was higher than 99 : 1. [c] The enantiomeric ratio (er) was determined by chiral GC-analysis.

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 tetrasubstituted allenes would be of high interest for organic synthesis.

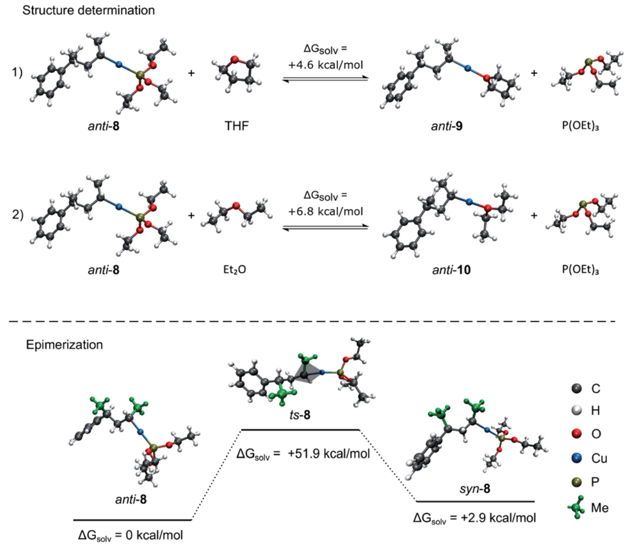
To get a better understanding of the regioselectivity, we have prepared the racemic phosphate **6j**, which contains a propargylic moiety (see Scheme 2).[15] The nucleophilic organocopper reagent *rac*-**1d** can undergo a substitution either in the α-position (S_N2-substitution of the phosphate), the γ-position (S_N2'-attack on the propargylic site) or γ′-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[16] 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 S_N2'-substitution of the allylic phosphate (γ′-position) compared to the propargylic moiety (γ-position).

Computational calculations

Furthermore, DFT-calculations[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).[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 phosphite ($P(OEt)_3$; *anti*-**8**), tetrahydrofuran (THF; *anti*-**9**) and diethyl ether (Et_2O; *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 ($\Delta G = +4.6$ kcal mol^{-1}; see Scheme 3, (**1**)). Similar results were obtained for the substitution of $P(OEt)_3$ with Et_2O ($\Delta G = +6.8$ 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 Et_2O 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 ($\Delta G = +2.9$ kcal mol^{-1}; see Scheme 3). This result is in agreement with previous reported findings.[20]



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



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

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 polymolecular 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*-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.

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.

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10 The use of a phenyl group in α-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 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 $ZnCl_2$ 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).

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 ESI.†

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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 ESI.†

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