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Enantioselective opening of cyclic vinyl epoxides with organoaluminium reagents catalysed by copper salts

Olivier Equey and Alexandre Alexakis*

Département de Chimie Organique, Université de Genève, 30 quai Ernest-Ansermet, 1211 Geneva 4, Switzerland

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Abstract—Herein we report conditions for the enantioselective conjugate addition of trialkylaluminium reagents to cyclic vinyl epoxides catalysed by copper salts and chiral phosphorus-based ligands. The reaction must be carried out in THF, otherwise we observed only oligomeric products. The best ees have been obtained with CuTC as the copper salt and a 2,2′-binaphthyl-based phosphorus ligand. Both opening products (S_N2 and $S_N2′$ pathways) were obtained with good enantioselectivity and moderate to good regioselectivity.
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1. Introduction

The reaction of organometallic reagents under copper catalysis conditions belong to the most important methods for the asymmetric construction of carbon–carbon bonds.[1] Among these, enantioselective substitution reactions on a wide variety of allylic substrates by the use of Grignard and organozinc reagents have received particular attention.[2] Vinyl epoxides can be regarded as a subclass of allylic substrates.[3] Nucleophilic attack can in principle take place on three of the four consecutive functionalised carbon atoms (pathways A, B or C, Scheme 1). Nucleophilic addition to the least hindered epoxide carbon affords the 1,2-addition product (path A), however this pathway is not commonly observed. Nucleophilic attack to the carbon adjacent to the double bond (allylic position) affords the regioisomeric S_N2 addition product, usually obtained in ring-opening reactions (path B). Finally, the conjugate addition of the nucleophile to the vinyl carbon gives the $S_N2′$ addition product (path C). The ratio of $S_N2′:S_N2$ products is very sensitive to the type of organometallic reagent or catalyst used.

Pineschi et al.[4] have successfully applied the conditions developed by Feringa et al.[5] for the enantioselective 1,4-addition of organozinc reagents to enones mediated with a chiral copper complex based on BINOL-phosphoramidite (*S,R,R*)-**L1** to the $S_N2′$ displacement of cyclic allylic epoxides (Table 1). The reaction was performed under kinetic resolution conditions (0.5 equiv R_2Zn). This clearly demonstrated that one enantiomer of the racemic epoxide reacted preferentially (Scheme 2).[4a]

The highest enantioselectivity was observed for the addition of Me_2Zn to 1,3-cycloheptadiene monoepoxide **7** (96%) (entry 5).
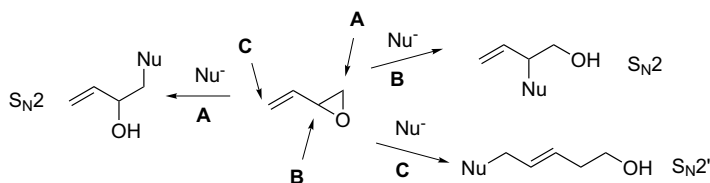
Scheme 1. Potential reaction products arising from nucleophilic addition with organometallic reagents.

* Corresponding author. Tel.: +41-022-3796522; fax: +41-022-3793215; e-mail: alexandre.alexakis@chiorg.unige.ch

Table 1. Enantioselective conjugate addition of dialkylzinc reagents to vinyl epoxides **1**, **4** and **7** catalysed by Cu(OTf)$_2$ and **L1**
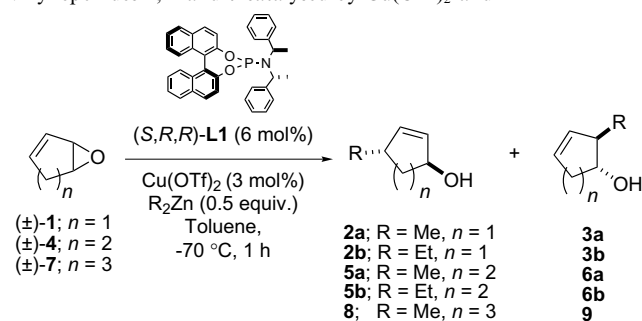
Entry	Substrate	R$_2$Zn	Yield (%)	Ee S$_N$2′ (%)	S$_N$2′:S$_N$2
1	1	Me$_2$Zn	12[a]	50	75:25
2	1	Et$_2$Zn	8[a]	54	92:8
3	4	Me$_2$Zn	33[b]	92 (−)	93:7
4	4	Et$_2$Zn	32[b]	91 (−)	98:2
5	7	Me$_2$Zn	38[b]	96 (−)	94:6

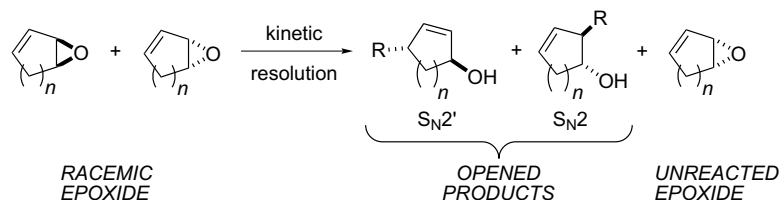[a] GC yield determined using 2-cyclohexen-1-ol as internal standard.
[b] Isolated yield. Maximum yield = 50%, based on reacted epoxide.

In the search for a catalytic system to open enantioselectively saturated epoxides with organoaluminium, we found conditions for the copper-catalysed enantioselective opening of vinyl epoxides with trialkylaluminium. Herein we focus mainly on the transfer of a methyl group because it is more interesting from a synthetic point of view.

2. Results and discussion

First, the reaction was carried out under the conditions developed by Pineschi et al., described above for the kinetic resolution of racemic vinyl epoxides. We used **L1** (either 5 mol% or 2.5 mol%), Cu(OTf)$_2$ (2.5 mol%) and 0.5 equiv of Et$_3$Al in toluene (−70 to −30 °C) for the resolution of racemic 1,3-cyclohexadiene monoepoxide **4** (Table 2). In both cases, we observed a complex mixture of oligomeric products and of S$_N$2 and S$_N$2′ products *anti*-**5b** and *anti*-**6b** in favour of the product arising from a S$_N$2 substitution.

We next turned our attention to the work of Fraser and Woodward,[6] who have developed conditions for the enantioselective 1,4-addition of organoaluminium reagents to simple enones. We reasoned that by using their conditions we could resolve our problems and avoid the formation of oligomers during the reaction.

Table 2. Enantioselective conjugate addition of triethylaluminium reagents to vinyl epoxide **4** following Pineschi's conditions

Entry	**L1** (mol%)	Cu(OTf)$_2$ (mol%)	L1/[Cu]	Yield	S$_N$2′:S$_N$2[a]
1	5	2.5	2/1	ND[b]	1:1.3
2	2.5	2.5	1/1	ND[b]	1:3
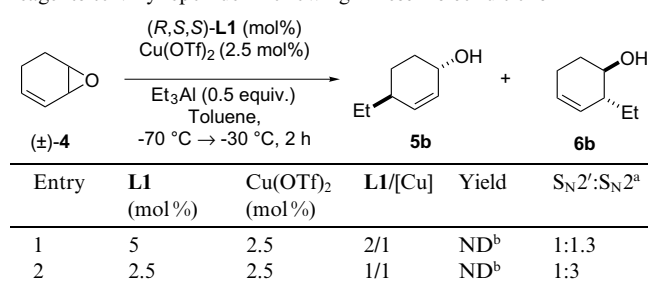
[a] Ratio determined by ^{1}H NMR of the crude product.
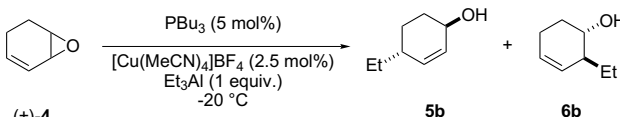[b] ND = not determined because of the presence of oligomers.

They used a chiral ligand derived from monothiobinaphthol **L2**, [Cu(MeCN)$_4$]BF$_4$ as copper salt and the reaction was carried out in THF at −20 °C (Table 3). When we used their conditions with racemic monoepoxide **4** and 0.5 equiv of Et$_3$Al, the reaction afforded a 2:1 mixture of S$_N$2′ products *anti*- and *syn*-**5b**, with 20% overall yield (entry 1). The ee was zero for both products, but interestingly, we did not observe any oligomers, as previously seen with the conditions of Pineschi et al. The reaction was also carried out with Me$_3$Al. We obtained again a 2:1 mixture of S$_N$2′ products *anti*- and *syn*-**5a**, but in favour of the *anti*-isomer (entry 2). The ee was again zero for both products.

In order to understand better why we did not observe any oligomers under Woodward's conditions, we carried out the reaction with an achiral phosphine instead of

Table 3. Enantioselective conjugate addition of trialkyl aluminium reagents to vinyl epoxide **4** following Woodward's conditions

Entry	R$_3$Al	Yield[a] (%)	Ee (*anti*) (%)	Ee (*syn*) (%)	*anti:syn*[b]
1	Et$_3$Al	20	0	0	1:2
2	Me$_3$Al	18	0	0	2:1
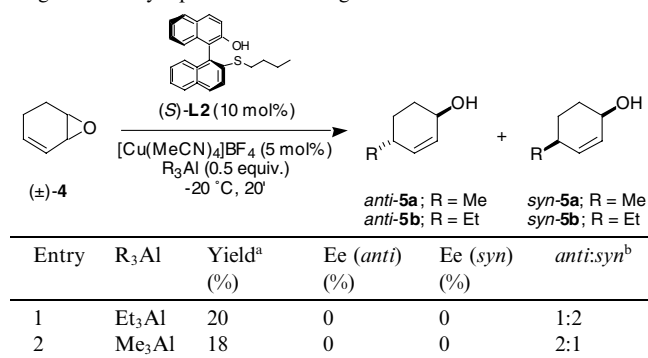
[a] Isolated yield. Maximum yield = 50%, based on reacted epoxide.
[b] Ratio determined by ^{1}H NMR of the crude product. We did not observe any S$_N$2 opening products.

Scheme 2. Kinetic resolution of racemic vinyl epoxides (max. yield = 50%).

Table 4. Influence of the solvent on the conjugate addition of Et_3Al to vinyl epoxide **4** catalysed by $[Cu(CH_3CN)_4]BF_4$ and PBu_3
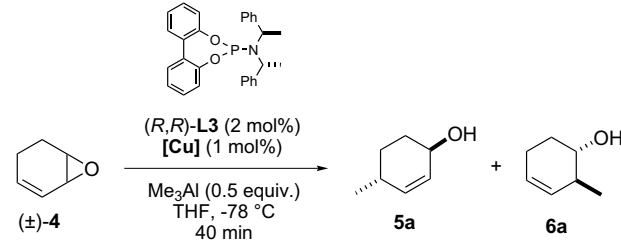

Entry	Solvent	Time	Yield (%)	$S_N2':S_N2^a$
1	THF	20 min	54	7.3:1
2	CH_2Cl_2	40 min	0^b	—
3	Toluene	40 min	0^b	—
4	Et_2O	40 min	0^b	—
5	THF	40 min	18^c	9:1
6	THF	4 h	0^d	—

[a] Ratio determined by ^1H NMR of the crude product.
[b] Degradation products mainly.
[c] The reaction was carried out with 5 mol% of copper salt without any phosphine.
[d] The reaction was carried out with 5 mol% of phosphine without any copper salt.[7] The epoxide was not recovered.

Table 5. Copper salt optimisation for the enantioselective conjugate addition of Me_3Al reagent to vinyl epoxide **4** catalysed by **L3**

Entry	[Cu]	Conversion[a] (%)	Ee **5a** (%)	$S_N2':S_N2^b$
1	$[Cu(CH_3CN)_4]BF_4$	50	13	92:8
2	$Cu(OAc)_2 \cdot H_2O$	47	14	93:7
3	$Cu(F_3acac)_2$	42	21	93:7
4	$Cu(F_3OAc)_2 \cdot xH_2O$	38	20	91:9
5	CuTC	39	29	93:7
6	$Cu(OTf)_2$	10	17	92:8
7	$Cu(acac)_2$	44	10	94:6
8	CuSCN	6	23	92:8

[a] GC yield. The products have not been purified. Conversion based on reacted epoxide.
[b] Ratio determined by ^1H NMR of the crude product.

chiral ligand **L2**. We obtained a 7.3:1 mixture of S_N2' and S_N2 products (Table 4, entry 1). We did not observe any more *syn*-**5b** isomer. The ligand clearly has an influence on the course of the reaction. The same reaction was then carried out in solvents other than THF in order to see the influence of the solvent (entries 2–4). Surprisingly, the use of other solvents was detrimental for the reaction as we just observed oligomers. When the reaction was carried out in THF without any phosphine (just with 5 mol% of copper salt), we observed background reaction (entry 5). We obtained a 9:1 mixture of S_N2' and S_N2 products *anti*-**5b** and **6b** but the yield was lower compared to the reaction done with a catalytic amount of phosphine and copper salt, thus indicating that the reaction was slower (entry 5 vs entry 1). However the presence of copper salt was necessary, otherwise the products did not form (entry 6).

We then replaced the achiral phosphine with the inexpensive chiral ligand **L3**, derived from biphenol and bis-(*R*)-1-phenylethylamine.[8] This chiral ligand has been developed in our group for the asymmetric 1,4-addition of organozinc reagents on enones.[8,9] The reaction was carried out with Me_3Al at −78 °C in order to avoid background reaction, as observed with PBu_3 at −20 °C (see Table 4, entry 5). We obtained the S_N2' product *anti*-**5a** with 13% ee and a good $S_N2':S_N2$ ratio (Table 5, entry 1). We screened many other copper salts. The best ee (29%) was obtained with CuTC (entry 5). We decided to carry out all reactions with CuTC as the copper salt for the rest of our study. With copper triflate, the copper salt typically used by Pineschi et al.[4] with organozinc reagents, the conversion was low (only 10%) (entry 6).

Both enantiomers of ligand **L1** have been tested at this temperature (Table 6, entries 1 and 2). We obtained 61% ee for the S_N2' product *anti*-**5a** with (*S,S,S*)-**L1** and 45% with (*R,S,S*)-**L1**. Not only the ee, but also the yield and the $S_N2':S_N2$ ratio were better with (*S,S,S*)-**L1** over (*R,S,S*)-**L1**. Other ligands were tested (Table 6, entries 3–8). The presence of the methoxy groups on the phenyl

groups of the amine moiety had a very detrimental effect on the enantioselectivity of the reaction (entries 3 and 4). Noteworthy are the ligands having a biphenol moiety instead of a binaphthol unit show a lower ee (entry 5 vs entries 3 and 4 and entry 8 vs entries 6 and 7) and the ligands with an (*S*)-configuration for the binaphthol moiety gave better results than those with an (*R*)-configuration (entry 1 vs entry 2, entry 3 vs entry 4 and entry 6 vs entry 7). Thus the best ee was obtained with ligand (*S,S,S*)-**L1**.
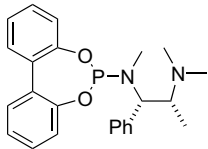
We then explored the influence of the temperature on the ee (Table 7), which led to further improvement. The ee value of *anti*-**5a** rose at higher temperatures. The best ee was measured at −40 °C (82%) (entry 4). Although the $S_N2':S_N2$ ratio was slightly lower than at −78 °C, the difference was not huge. Moreover, at this temperature, changing the Cu/**L1** ratio had no effect on the ee (entry 5 vs entry 4). At a higher temperature though, the ee began to drop.

The final optimised conditions[10] were applied to other substrates. For cyclopentadiene monoepoxide **1** (Table 8), with a 1:1 Cu/**L1** ratio, after 15 min at −40 °C, we did not observe the formation of substitution products. The starting material remained unchanged (entry 1). However with a 3:3 Cu/**L1** ratio after 2 h at −40 °C, we obtained a 61:39 mixture of S_N2' and S_N2 substitution products (entry 2). The S_N2' product *anti*-**2a** was obtained with 87% ee while product *anti*-**3a** arising from a S_N2 substitution had an ee of 99%. Although the overall yield was low (10%), the results obtained with Me_3Al are better than those obtained by Pineschi et al.[4a] Organoaluminium allowed in this case improvement of the results obtained with dimethylzinc.

Table 6. Chiral ligand optimisation for the enantioselective conjugate addition of Me_3Al to vinyl epoxide **4** catalysed by CuTC and a phosphorus-based chiral ligand
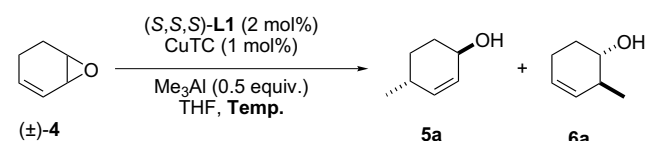
Entry	L*	Yield[a] (%)	Ee 5a (%)	$S_N2':S_N2$[b]
1	(S,S,S)-**L1**	50	61 (−)	98:2
2	(R,S,S)-**L1**	23	45 (+)	92:8
3	(S,S,S)-**L4**	21	10 (−)	98:2
4	(R,S,S)-**L4**	31	8 (+)	98:2
5	(S,S)-**L5**	29	0	98:2
6	(S,S,R)-**L6**	43	41 (−)	97:3
7	(R,S,R)-**L6**	9	17 (+)	98:2

Table 6 (*continued*)

Entry	L*	Yield[a] (%)	Ee **5a** (%)	$S_N2':S_N2$[b]
8	(*S*,*R*)-**L7**	15	10 (−)	98:2

[a] GC yield determined using tetradecane as the internal standard. Maximum yield = 50%, based on reacted epoxide.
[b] Ratio determined by chiral GC.

Table 7. Temperature optimisation for the enantioselective conjugate addition of Me$_3$Al to vinyl epoxide **4** catalysed by CuTC and **L1**
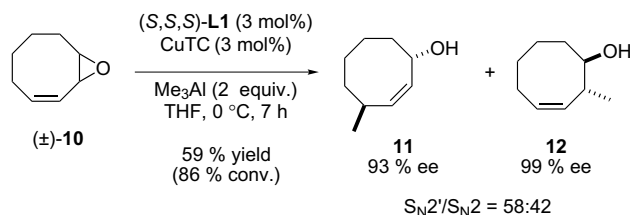
Entry	Temperature (°C)	Time (min)	Yield[a] (%)	Ee **5a** (%)	$S_N2':S_N2$[b]
1	−70	10	20	58 (−)	99:1
2	−60	10	32	71 (−)	98:2
3	−50	12	38	76 (−)	97:3
4	−40	14	45	82 (−)	94:6
5	−40	13	44	82 (−)[c]	94:6
6	−30	12	47	78 (−)	93:7
7	−20	14	47	63 (−)	89:11

[a] GC yield determined using tetradecane as internal standard. Maximum yield = 50%, based on reacted epoxide.
[b] Ratio determined by chiral GC.
[c] The reaction was carried out with 1 mol % of CuTC and 1 mol % of **L1**.

Scheme 3. Enantioselective conjugate addition of Me$_3$Al reagent to vinyl epoxide **10** catalysed by CuTC and **L1**.

was much more better than that obtained by Pineschi et al.[4f] with dimethylzinc (lit. = 64%). The $S_N2':S_N2$ ratio was similar than to that obtained by Pineschi et al., but the reaction was much quicker and needed only 2 equiv of oragnometallic reagent.
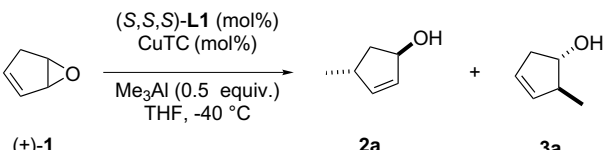
The reaction was also carried out with cyclooctadiene monoepoxide **10**. The reaction was performed with 2 equiv of Me$_3$Al at 0 °C, because vinyl epoxide **10** is much less reactive than the vinyl epoxides derived from the five- and six-membered ring (Scheme 3). After 7 h, we obtained a 58:42 mixture of S_N2' and S_N2 substitution products with a 59% overall yield (conv. = 86%) (entry 1). S_N2' product *anti*-**11** was obtained with 93% ee while product *anti*-**12** arising from a S_N2 substitution had an ee of 99%. The ee measured for product *anti*-**11**

3. Conclusion

Optimisation of the reaction conditions has led to an alternative system for the enantioselective formation of carbon–carbon bonds with cyclic vinyl epoxides. We found that the solvent played a central role in the conjugate addition of organoaluminium reagents to vinyl epoxides. Best results were obtained with CuTC as copper salt and phosphoramidite ligand **L1**. A 1:1 Cu/ **L1** ratio allowed the efficient opening of cyclohexadiene monoepoxide **1**. We have also shown that the ee was temperature dependent, with the best ee being obtained at −40 °C with our conditions. The reaction has also been carried out with other cyclic substrates. Further

Table 8. Enantioselective conjugate addition of Me$_3$Al to vinyl epoxide **1** catalysed by CuTC and **L1**

Entry	L* (mol %)	[Cu] (mol%)	Time	Yield (%)	Ee **2a** (%)	Ee **3a** (%)	$S_N2':S_N2$[a]
1	1	1	15 min	0[b]	—	—	—
2	3	3	2 h	10[c]	87	99	61:39

[a] Ratio determined by chiral GC.
[b] All the starting material has been recovered.
[c] Isolated yield. Maximum yield = 50%, based on reacted epoxide.

work is currently in progress in order to extend the reaction to acyclic substrates and to test other ligands.

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10. Typical procedure: In a Schlenk tube under a nitrogen atmosphere were placed 1.9 mg (0.01 mmol) of CuTC and 5.4 mg (0.01 mmol) of (S,S,S)-**L1** in THF (3 mL). The solution was stirred 30–40 min at rt. The solution was then cooled to $-40\,°C$ (external temperature) and we added dropwise 250 µL (0.5 mmol) of a 2 M solution of Me_3Al in heptane. The reaction mixture was stirred for 5 min at $-40\,°C$ before we added a solution of cyclohexadiene monoepoxide **4** (96 mg, 1 mmol) in THF (2 mL). The reaction mixture was then stirred at $-40\,°C$. After 15 min, the reaction was quenched with MeOH (2 mL) and a 30% solution of potassium tartrate (4 mL). The reaction mixture was stirred for 1 h at rt. The aqueous phase was extracted with Et_2O (3x). The organic phases were washed with brine (1x), dried over $MgSO_4$, filtered and the solvents removed under reduced pressure. The crude product was purified by FC (cyclohexane/AcOEt 9:1). We obtained 43 mg (38%) of pure products as a 94:6 mixture of S_N2' and S_N2 products. Enantiomer separation by chiral GC on CHIRALDEX B-TA (30 m, He, 50 cm/s), T: 55 °C isotherm, t_R (epoxide) = 6.15 min, t_R (epoxide) = 6.51 min; t_R (S_N2 product) = 16.50 min (no enantiomer separation); t_R (S_N2' product) = 22.92 min, t_R (S_N2' product) = 24.53 min.