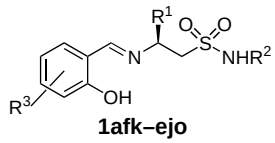
Desymmetrization of meso Compounds

A Catalytic and Enantioselective Desymmetrization of *meso* Cyclic Allylic Bisdiethylphosphates with Organozinc Reagents**

Umberto Piarulli, Philippe Daubos, Christelle Claverie, Maryline Roux, and Cesare Gennari**



1afk–ejo

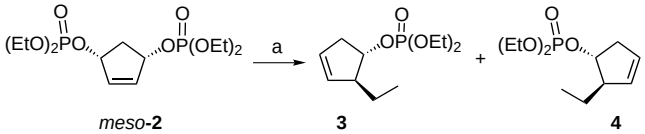
a: R^1 = Me
b: R^1 = *i*Pr
c: R^1 = *i*Bu
d: R^1 = CH_2Ph
e: R^1 = *t*Bu
f: R^2 = CH_2Ph
g: R^2 = (*R*)-CH(Me)Cy
h: R^2 = (*S*)-CH(Me)Cy
i: R^2 = *i*Pr
j: R^2 = $CHPh_2$
k: R^3 = H
l: R^3 = 3,5-*t*Bu_2
m: R^3 = 3,5-Cl_2
n: R^3 = 5,6-$(CH)_4$-
o: R^3 = 3-Ph

Catalytic enantioselective desymmetrization of *meso* compounds is a powerful tool for the construction of enantiomerically enriched functionalized products.[1] *meso* Cyclic allylic diol derivatives are challenging substrates for the asymmetric allylic substitution reaction,[2] owing to the potential competition of several reaction pathways. In particular, S_N2' and S_N2 substitutions can occur, and both with either retention or inversion of stereochemistry. In the case of S_N2 substitution, in which an allylic alcohol derivative is obtained, a second allylic substitution might occur through the S_N2' or S_N2 mechanism, with either retention or inversion of stereochemistry. Based on this complex scenario, up to 15 isomers (seven pairs of enantiomers and one *meso* compound) could, in principle, be obtained.

Herein we present a new highly regio-, diastereo-, and enantioselective desymmetrization of *meso,* cyclic allylic bisdiethylphosphates with organozinc reagents[3] catalyzed by copper(I) complexes of chiral Schiff base ligands **1**.[4] *cis*-4-Cyclopentene-1,3-diol was transformed into the corresponding bisdiethylphosphate **2** by deprotonation with *n*BuLi and reaction with diethylchlorophosphate in THF/TMEDA (4:1).[5] Reaction of *meso*-4-cyclopentene-1,3-bisdiethylphosphate (**2**) with diethylzinc in the presence of $(CuOTf)_2{\cdot}C_6H_6$ ($Tf = CF_3SO_2$) (10 mol%) and chiral ligand **1cjl** in toluene/THF (95:5 v/v) at −78°C afforded only the product arising from the S_N2' mechanism with inversion of stereochemistry, with an enantiomeric ratio **3**/**4** of 87:13 in favor of the *S,S* enantiomer (Scheme 1).[6–8] Other copper sources (CuCN, $Cu(OTf)_2$) and other solvents (pure toluene, pure THF, CH_2Cl_2, *n*-hexane) gave lower yields and poorer selectivities.

A library of 125 ligands **1**[4c] was screened: Cu^I complexes were preformed in situ by stirring a solution of ligand **1** (10 mol%) with $(CuOTf)_2{\cdot}C_6H_6$ (10 mol%) in toluene/THF (95:5) at room temperature. Diethylzinc (solution in toluene) and 4-cyclopentene-1,3-bisdiethylphosphate (**2**) were then added to the mixture at −78°C, and the reaction mixture was stirred for 15 h before quenching. The most interesting results are shown in Table 1: The best enantiomeric ratio (94:6) in favor of the *S,S* enantiomer **3** was observed in the presence of ligands **1cjo** and **1cjm**.[7,8] We found that an increase in the temperature to −60°C did not have a detrimental effect on the enantioselectivity. Instead, complete conversion and almost quantitative yield were observed (for example, ligand **1cjo**: >98% yield, 88% *ee*; ligand **1cjm**: >98% yield, 88% *ee*; ligand **1cjl**: 80% yield, 74% *ee*). Interestingly, ligands with different steric hindrance but with the same absolute configuration at the stereogenic center bearing R^1 may lead to opposite enantiomeric ratios (!) (Table 1, entries 7–9). An enantiomeric ratio of up to 76:24 in favor of (*R,R*)-**4** was obtained in the presence of ligand **1egk**. As a rule of thumb, substituted salicylaldehydes (R^3 = 3,5-Cl_2; 3-Ph; 3,5-*t*Bu; 5,6-$(CH)_4$-), bulky amines ($R^2 = CHPh_2$), and relatively small substituents at the stereogenic center (R^1 = *i*Bu, Me) favor the formation of enantiomer (*S,S*)-**3**, whereas unsubstituted salicylaldehydes (R^3 = H) and relatively small amines (e.g. $R^2 = CH_2Ph$) tend to favor the formation of enantiomer (*R,R*)-**4**.

To investigate the scope of this new reaction, different organozinc reagents were tested with bisdiethylphosphate **2** in the presence of the ligands that gave the best results in the previous screening (**1cjo, 1cjm**) (Scheme 2). In the case of dimethylzinc, the reaction gave exclusively the product



Scheme 1. Enantioselective allylic alkylation of **2** with Et_2Zn, catalyzed by $(CuOTf)_2{\cdot}C_6H_6$/**1**. Screening of the library of ligands **1**. a) 1) $(CuOTf)_2{\cdot}C_6H_6$ (10 mol%), **1** (10 mol%), toluene/THF (95:5), room temperature, 45 min; 2) Et_2Zn (1.1 M in toluene), −78°C, 15 h.

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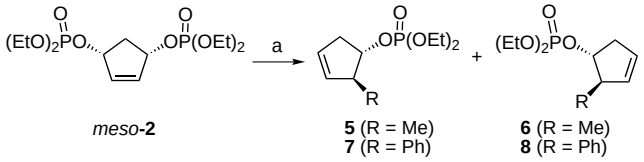
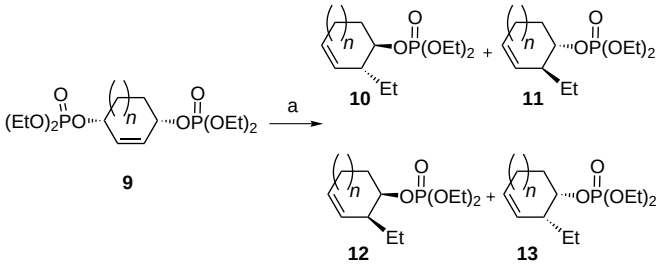
Table 1: Selected results from the high-throughput screening of the library of ligands **1**.[a]

Entry	**1**	R^1	R^2	R^3	**3**/**4**	Yield [%]
1	**cjo**	*i*Bu	$CHPh_2$	3-Ph	94:6	54
2	**cjm**	*i*Bu	$CHPh_2$	3,5-Cl_2	94:6	47
3	**cjl**	*i*Bu	$CHPh_2$	3,5-*t*Bu_2	87:13	42
4	**ajm**	Me	$CHPh_2$	3,5-Cl_2	86:14	62
5	**cjk**	*i*Bu	$CHPh_2$	H	84:16	54
6	**cjn**	*i*Bu	$CHPh_2$	5,6-$(CH)_4$-	83:17	49
7	**afk**	Me	CH_2Ph	H	31:69	13
8	**bfk**	*i*Pr	CH_2Ph	H	30:70	12
9	**egk**	*t*Bu	(*R*)-CH(Me)Cy	H	24:76	26

[a] $[CuOTf]_2{\cdot}C_6H_6$ (0.1 equiv), **1** (0.1 equiv), Et_2Zn (2.0 equiv), **2** (1.0 equiv), toluene/THF (95:5), −78 °C, 15 h.



Scheme 2. Enantioselective allylic alkylation of **2** with R_2Zn, catalyzed by $(CuOTf)_2{\cdot}C_6H_6$/**1cjo** or $(CuOTf)_2{\cdot}C_6H_6$/**1cjm**. a) 1) $(CuOTf)_2{\cdot}C_6H_6$ (10 mol%), **1cjo** or **1cjm** (10 mol%), toluene/THF (95:5), room temperature, 45 min; 2) R_2Zn, −60 °C, 15 h.



Scheme 3. Allylic alkylation of **9** with Et_2Zn, catalyzed by $(CuOTf)_2{\cdot}C_6H_6$/**1**. a) 1) $(CuOTf)_2{\cdot}C_6H_6$ (10 mol%), **1** (10 mol%), room temperature, 45 min; 2) Et_2Zn, −78 or −60 °C, 15 h.

arising from the S_N2' substitution with inversion of stereochemistry (ligand **1cjm**, −60 °C), in moderate yield (40%) and excellent enantiomeric ratio (**5**/**6** 97:3) in favor of the *S,S* enantiomer (**5**, R = Me).[7,8] Allylic phenylation was possible in the reaction of bisdiethylphosphate **2** with a mixture of diphenylzinc and dimethylzinc (2:1).[9] The phenyl group was preferably transferred (Ph transfer vs. Me transfer = 48:1), giving the product of S_N2' substitution with inversion of stereochemistry in moderate yield (60%) and fair enantiomeric ratio (**7**/**8** 84:16 with ligand **1cjo**, −60 °C) in favor of the *S,R* enantiomer (**7**, R = Ph).[7,10]

Reaction of diethylzinc with *cis*-2-cyclohexene-1,4-bisdiethylphosphate[11] (**9**, $n = 1$) (Scheme 3) gave the S_N2' products originating from either inversion (**10** and **11**) or retention of stereochemistry (**12** and **13**) with good diastereoselectivity (81:19–4:96), depending on the solvent and the ligand used. However, racemic mixtures were invariably produced.[12] Preliminary studies with *cis*-2-cycloheptene-1,4-bisdiethylphosphate[11] (**9**, $n = 2$) indicate that only the products arising from the S_N2' substitution with inversion of stereochemistry (**10** + **11**) are formed, with moderate enantiomeric excess (e.g. 56% *ee* with ligand **1cjk**, −60 °C).[10]

In conclusion, we have disclosed a new highly regio-, diastereo-, and enantioselective desymmetrization of *meso* cyclic allylic bisdiethylphosphates with organozinc reagents catalyzed by copper(I) complexes of chiral Schiff base ligands **1**. Further investigations into the scope and limitations of this reaction are currently underway.

Experimental Section

General Procedure: Ligand **1** (0.017 mmol) was dissolved in dry toluene/THF (95:5 v/v; 1.5 mL) in a flame-dried flask under argon. $(CuOTf)_2{\cdot}C_6H_6$ (4.7 mg, 0.017 mmol) was subsequently added, and the resulting greenish solution was stirred at room temperature for 45 min. The reaction mixture was cooled to −78 °C and treated with Et_2Zn (1.1 M solution in toluene; 0.310 mL, 0.340 mmol). After 10 min, *meso*-**2** (60 mg, 0.170 mmol) was added. The reaction mixture was stirred at −78 °C for 15 h, then quenched with a saturated aqueous solution of NH_4Cl (1 mL), and diluted with ethyl acetate (1 mL). The organic phase was separated and filtered through celite. *n*-Decane (0.033 mL, 0.170 mmol) was added, and a sample of the crude reaction mixture (1 μL) was then injected into a GC instrument equipped with a chiral capillary column for determination of yields and enantiomeric ratios (**3**/**4**). Column: MEGADEX DMEPEβ, OV 1701, 25 m, film 0.25 μm; carrier: H_2 (70 kPa); injector 250 °C; detector 250 °C; oven temperature 110 °C, 0.8 °C min^{-1} to 140 °C; t_R: 0.91 min (*n*-decane), 17.7 min ((1*R*,2*R*)-**4**), 18.0 min ((1*S*,2*S*)-**3**), and 39.8 min (*meso*-**2**).

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[6] The chiral copper complex appears to be essential to obtain the reaction product. In fact, the addition of Et_2Zn in the presence of $(CuOTf)_2{\cdot}C_6H_6$ and in the absence of the chiral ligand gave only starting material and minute amounts of **3**/**4** (8 %).

[7] CuCN (3.5 equiv) mediated allylic alkylation of (1*R*,3*S*)-(+)-*cis*-4-cyclopentene-1,3-diol 1-acetate with EtMgCl (3.0 equiv) in THF at −18→0 °C gave (1*S*,2*S*)-*trans*-2-ethyl-3-cyclopenten-1-ol selectively, through S_N2' substitution of the acetate with inversion. This compound was then reacted with $(EtO)_2POCl$ (pyridine, DMAP, CH_2Cl_2) to give enantiomerically pure **3** $[\alpha]_D = +84.0°$ ($CHCl_3$, $c = 1.2$). The above synthetic sequence was also performed with MeMgCl and PhMgCl instead of EtMgCl, yielding enantiomerically pure (1*S*,2*S*)-**5** (R = Me) and (1*S*,2*R*)-**7** (R = Ph). See: a) M. Ito, M. G. Murugesh, Y. Kobayashi, *Tetrahedron Lett.* **2001**, *42*, 423 – 427; b) M. Ito, M. Matsuumi, M. G. Murugesh, Y. Kobayashi, *J. Org. Chem.* **2001**, *66*, 5881 – 5889; c) Y. Kobayashi, M. Ito, J. Igarashi, *Tetrahedron Lett.* **2002**, *43*, 4829 – 4832.

[8] The crude reaction mixture was injected into a GC instrument equipped with a chiral capillary column for the determination of *ee* values (column: MEGADEX DMEPEβ, OV 1701, 25 m, film 0.25 μm, carrier: H_2 (70 kPa)). For the determination of **3**/**4** ratio, see Experimental Section. Determination of **5**/**6** (R = Me) ratio: injector 250 °C, detector 250 °C, oven temperature 90 °C, 0.8 °C min^{-1} to 130 °C, t_R: 26.2 min ((1*R*,2*R*)-**6**) and 26.7 min ((1*S*,2*S*)-**5**).

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[10] The enantiomeric ratios (**7**/**8** (R = Ph), **10**:**11**, $n = 2$) was determined after reduction of the phosphate ester with $LiAlH_4$ in diethyl ether (quant. yield), and derivatization of the resulting alcohol with (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, dicyclohexyl carbodiimide, 4-dimethylaminopyridine in dichloromethane (quant. yield). The ratio of the two diastereomeric Mosher esters was assessed by ^1H NMR spectroscopy; see: a) J. A. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512 – 519; b) G. R. Sullivan, J. A. Dale, H. S. Mosher, *J. Org. Chem.* **1973**, *38*, 2143 – 2147.

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[12] At present we do not have a convincing rationale for this unexpected result. However, a possible reason for the different behavior of the cycloalkene derivatives **2** and **9** ($n = 1$, $n = 2$) might be related to their symmetry. Indeed, whereas the cyclopentene derivative **2** and the cycloheptene derivative **9** ($n = 2$) can exist and react in a C_S conformation (plane symmetric), the cyclohexene derivative **9** ($n = 1$) is better described as a mixture of readily interconverting enantiomers.

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