

Copper Phosphoramidite-Catalyzed Enantioselective Desymmetrization of *meso*-Cyclic Allylic Bisdiethyl Phosphates

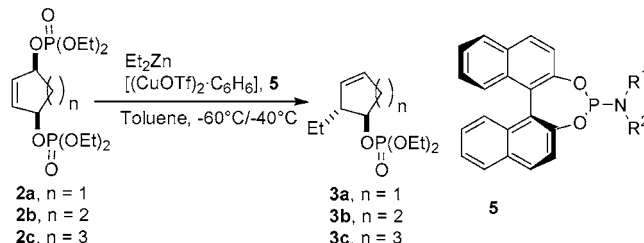
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ABSTRACT



A highly regio-, diastereo-, and enantioselective desymmetrization of five-, six-, and seven-membered *meso*-cyclic allylic bis-diethyl phosphates (2a, 2b, and 2c, respectively) was obtained with diethylzinc, using catalytic amounts of $[\text{Cu}(\text{OTf})_2]_2 \cdot \text{C}_6\text{H}_6$ and phosphoramidite ligands 5. Enantiomeric excesses of up to 87, 94, and >98% were obtained for the addition of diethylzinc to cyclopentene, cyclohexene, and cycloheptene bis-diethyl phosphates, respectively.

meso-Cyclic allylic diols are powerful substrates for the construction of enantiomerically enriched functionalized products. Their desymmetrization has been realized by acylation or by allylic substitution, which can occur via $\text{S}_{\text{N}}2$ or $\text{S}_{\text{N}}2'$ (allylic displacement) mechanisms, with either retention or inversion.¹ The palladium-catalyzed desymmetrization, pioneered by Trost, is usually performed with soft nucleophiles and takes place via the $\text{S}_{\text{N}}2$ mechanism.² A somewhat related enantioselective ring opening of *meso*-

oxabicyclic alkenes with organometallic reagents was reported by Lautens and co-workers (palladium-catalyzed addition of alkylzinc reagents and Rh^{I} -catalyzed addition of arylboronic acids)³ and by Pineschi, Feringa, and co-workers (Cu^{I} -catalyzed addition of alkylzinc reagents).⁴ Whereas in

(2) For recent accounts, see: (a) Graening, T.; Schmalz, H.-G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2580–2584. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2944.

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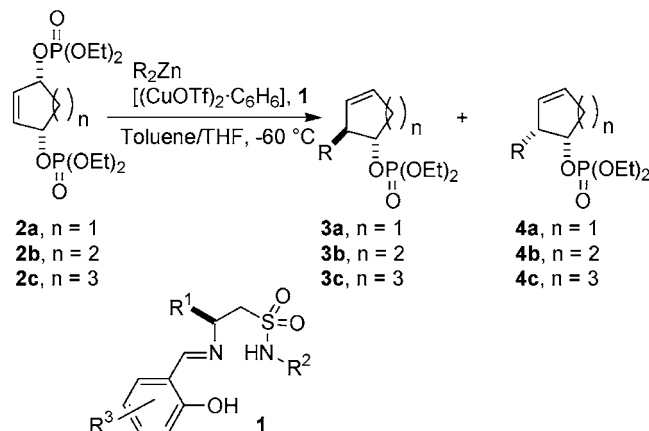
[‡] University of Milano.

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(1) For a recent review, see: Willis, M. C. *J. Chem. Soc., Perkin Trans. I* **1999**, 1765–1784.

the first case the reaction occurs via the S_N2' mechanism with retention (the nucleophile attacks from the same side of the allylic leaving group),³ in the second case the allylic displacement reaction takes place with inversion.⁴ Piarulli, Gennari, and co-workers have recently disclosed a new highly regio-, diastereo-, and enantioselective desymmetrization of *meso*-cyclic allylic bisdiethyl phosphates with organozinc reagents⁵ catalyzed by copper(I) complexes of chiral Schiff base ligands **1** (Scheme 1).⁶ In the case of *meso*-

Scheme 1. Desymmetrization of *meso*-Cyclic Allylic Bisdiethyl Phosphates with Organozinc Reagents Catalyzed by Copper(I) Complexes of Chiral Schiff Base Ligands **1**



4-cyclopentene-1,3-bisdiethyl phosphate (**2a**), only the product arising from the allylic displacement (S_N2') mechanism with inversion (**3a**) was obtained with excellent yield and enantiomeric excess (ee) up to 88% after screening a library of 125 Schiff-base ligands **1**. Reaction of diethylzinc with *meso*-2-cyclohexene-1,4-bisdiethyl phosphate (**2b**), on the contrary, gave the allylic displacement products originating from either inversion (**3b**) or retention (**4b**) with good diastereoselectivity (81:19–4:96), depending on the solvent and the ligand used. However, very low ees were obtained. The reaction of *meso*-2-cycloheptene-1,4-bisdiethyl phosphate (**2c**) afforded only the product arising from the allylic displacement with inversion (**3c**), albeit with modest ee (up to 56%).

The Groningen group has demonstrated that phosphoramidites of general structure **5** serve as very effective ligands in a number of catalytic asymmetric carbon–carbon bond-forming reactions.⁷ These include the already mentioned copper-catalyzed ring opening of oxabicyclic alkenes,⁴ the conjugate addition of dialkylzincs to enones⁸ and nitro alkenes,⁹ the ring opening of vinyl epoxides,¹⁰ the desym-

metrization of methylenecycloalkene oxides,¹¹ the allylic alkylation of cinnamyl derivatives,¹² and the rhodium-catalyzed addition of arylboronic acids.¹³

In this paper we report a highly enantioselective desymmetrization of *meso*-4-cyclopentene-1,3-bisdiethyl phosphate (**2a**), *meso*-2-cyclohexene-1,4-bisdiethyl phosphate (**2b**), and *meso*-2-cycloheptene-1,4-bisdiethyl phosphate (**2c**) with diethylzinc catalyzed by copper(I) complexes of phosphoramidite ligands **5** (Figure 1).

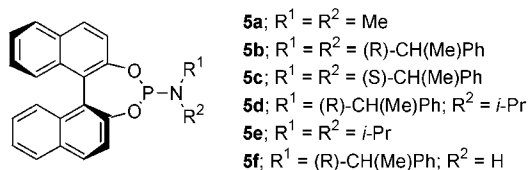


Figure 1. Structure of the phosphoramidite ligands **5**.

Copper complexes of ligands **5a–f** were obtained in situ by stirring Cu^+OTf with 2 equiv of the appropriate ligand in toluene (45 min, rt). Reaction of *meso*-4-cyclopentene-1,3-bisdiethyl phosphate (**2a**), readily obtained from commercially available *meso*-4-cyclopentene-1,3-diol,¹⁴ with 2.0 equiv of Et_2Zn in the presence of 10 mol % of the copper-phosphoramidite complexes afforded the product arising from allylic displacement with inversion (**3a**, $\text{R} = \text{Et}$) in variable yields and enantiomeric excesses (Table 1). In particular, the screening of the ligands revealed that good yields and enantiomeric excesses were obtained when phosphoramidite ligands with bulkier secondary amine substituents were used (entries 2–4). Varying the temperature with the best ligand (**5b**) increased the enantiomeric excess to 87% at -40°C (entry 7). Dimethylzinc was considerably less reactive than diethylzinc; the reaction had to be run at 0°C to obtain **3a** ($\text{R} = \text{Me}$) with a fair conversion (54%), still associated with a good ee (87%, Table 1, entry 10).¹⁵

meso-2-Cyclohexene-1,4-bisdiethyl phosphate (**2b**) was obtained starting from cyclohexadiene via a palladium-

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(13) Boiteau, J. G.; Imbos, R.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 682–685 and 1385.

(14) *cis*-4-Cyclopentene-1,3-diol was transformed into the corresponding bisdiethyl phosphate (**2**) by deprotonation with *n*-BuLi and reaction with diethylchlorophosphate in THF/TMEDA (4/1); see: Yu, K. L.; Ko, K. Y.; Fraser-Reid, B. *Synth. Commun.* **1988**, 465–468.

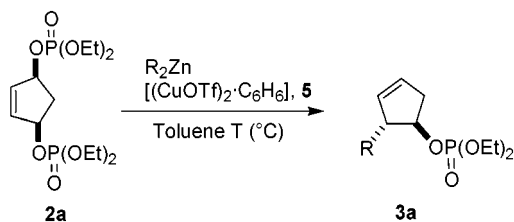
(15) Reactions at -40 or -20°C showed poor conversions (15–20%) associated with slightly better ees (90–93%).

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Table 1. Allylic Alkylation of **2a** with R_2Zn in the Presence of Copper Complexes of Phosphoramidites **5a–f**^a



entry	ligand	R	T (°C)	product	
				yield (%) ^b	ee % ^c (configuration) ^d
1	5a	Et	-60	10	24 (<i>R,R</i>)
2	5b	Et	-60	>98	74 (<i>R,R</i>)
3	5c	Et	-60	20	60 (<i>R,R</i>)
4	5d	Et	-60	30	58 (<i>R,R</i>)
5	5e	Et	-60	65	10 (<i>R,R</i>)
6	5f	Et	-60	13	0
7	5b	Et	-40	>98	87 (<i>R,R</i>)
8	5b	Et	-20	>98	84 (<i>R,R</i>)
9	5b	Et	0	>98	81 (<i>R,R</i>)
10	5b	Me	0	54	87 (<i>R,R</i>)

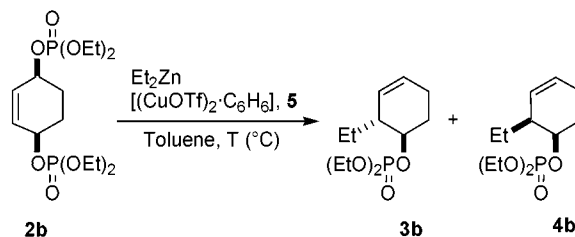
^a Reaction conditions: $[CuOTf]_2 \cdot C_6H_6$ (0.05 equiv), ligand **5** (0.2 equiv), R_2Zn (2.0 equiv), **2a** (1.0 equiv), toluene, 15 h. ^b GC yield. ^c Determined by GC: MEGADEX DMEPE β , OV 1701, 25 m, film 0.25 μ m, carrier H_2 (70 kPa). ^d Absolute configuration was determined as previously described.⁵

catalyzed 1,4-diacetoxylation,¹⁶ followed by hydrolysis and phosphorylation using the same procedure as for the five-membered substrate **2a**.¹⁴ Reaction with Et_2Zn afforded variable proportions of two products, namely, those arising from the allylic displacement (S_N2') with either inversion (**3b**) or retention (**4b**) (Table 2). In particular, small ligands (e.g., **5a**, entry 1) and higher reaction temperatures (cf. entries 7–9, 10–11) afforded larger proportions of product **4b**, whereas ligands bearing bulkier amine substituents and lower temperatures favored the formation of product **3b**. An enantiomeric excess of up to 82% was obtained for the product arising from allylic displacement (S_N2') with inversion, using ligand **5b** at $-60^\circ C$, albeit in rather low yield (entry 2). Increasing the reaction temperature to $-40^\circ C$ improved both the yield (77%) and the enantiomeric excess (90%, entry 7). Interestingly, ligand **5c** comprising *S,S*-BINOL and the *S,S*-diamine moiety afforded a very promising 76% ee at $-60^\circ C$ (entry 3), which could be improved to 94%, with 69% yield, by increasing the temperature to $-40^\circ C$ (entry 10). It should be noted that this is one of the few cases where the matched combination arises in **5** from *S,S*-BINOL and the *S,S*-diamine.^{10,11} Product **4b**, on the other hand, was always isolated as a racemic mixture.

Reaction of the seven-membered-ring substrate **2c** (Table 3), obtained following the same route as for **2b**, afforded only the product arising from allylic displacement (S_N2') with inversion (**3c**) with excellent enantiomeric excess (>98%)

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Table 2. Allylic Alkylation of **2b** with Et_2Zn in the Presence of Copper Complexes of Phosphoramidites **5a–f**^a



entry	ligand	T (°C)	product		ee % of 3b ^c (configuration) ^d
			yield (%) ^b	3b/4b	
1	5a	-60	13	31/69	35 (<i>R,R</i>)
2	5b	-60	35	76/24	82 (<i>R,R</i>)
3	5c	-60	16	87/13	76 (<i>R,R</i>)
4	5d	-60	3	79/21	68 (<i>R,R</i>)
5	5e	-60	10	69/31	48 (<i>R,R</i>)
6	5f	-60	0		
7	5b	-40	77	87/13	90 (<i>R,R</i>)
8	5b	-20	89	67/33	84 (<i>R,R</i>)
9	5b	0	85	44/56	52 (<i>R,R</i>)
10	5c	-40	69	85/15	94 (<i>R,R</i>)
11	5c	-20	88	68/32	93 (<i>R,R</i>)

^a Reaction conditions: $[CuOTf]_2 \cdot C_6H_6$ (0.05 equiv), ligand **5** (0.2 equiv), Et_2Zn (2.0 equiv), **2b** (1.0 equiv), toluene, 15 h. ^b Isolated yield. ^c Determined by GC: MEGADEX DMEPE β , OV 1701, 25 m, film 0.25 μ m, carrier H_2 (70 kPa), after reduction of the phosphate ester to alcohol with $LiAlH_4$ in diethyl ether (quantitative yield). ^d Absolute configuration was determined by reduction of **3b** to the corresponding alcohol ($LiAlH_4$, Et_2O) and comparison of the optical rotation ($[\alpha]_D$) with the literature value.¹⁰

and isolated yield (85–86%) using ligands **5b** and **5c** (entries 4, 5). This is a case of very remarkable chemo-, regio-, stereo-, and enantiocontrol, where the potential competition of several reaction pathways might in principle lead to up to 15 different reaction products and only one is obtained.¹⁷

Product **3c** was reduced to the corresponding alcohol with $LiAlH_4$ in diethyl ether (quantitative yield). The enantiomeric excess was measured by 1H NMR spectroscopy, after derivatization of the resulting alcohol with (*R*)-(+)- α -methoxy- α -(trifluoromethyl) phenylacetic acid, DCC, and 4-DMAP in dichloromethane (quantitative yield).¹⁸ The absolute configuration of product **3c** was also assigned from the NMR data of its Mosher ester derivatives.^{19,20} The esters were assumed to adopt a conformation with the H–C–O–

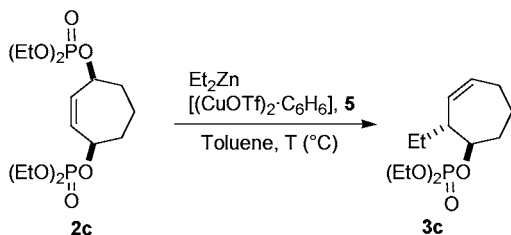
(17) In particular, S_N2' and S_N2 substitutions could occur, and both with either retention or inversion of configuration. In the case of the S_N2 , where an allylic alcohol derivative is obtained, a second allylic substitution could occur, via the S_N2' or S_N2 mechanism, with either retention or inversion. On the basis of this complex scenario, up to 15 different reaction products (7 pairs of enantiomers and 1 *meso*-compound) could in principle be obtained.

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(19) Diastereomeric esters were prepared using (*R*)-(+)- α -methoxy- α -(trifluoromethyl) phenylacetic acid with an unbalanced mixture of enantiomeric alcohols **3c**.

(20) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.

Table 3. Allylic Alkylation of **2a** with Et₂Zn in the Presence of Copper Complexes of Phosphoramidites **5a–c**^a



entry	ligand	T (°C)	product	
			yield (%) ^b	ee % ^c (configuration) ^d
1	5a	−60	5	nd
2	5b	−60	81	98 (<i>R,R</i>)
3	5c	−60	75	>98 (<i>R,R</i>)
4	5b	−40	85	>98 (<i>R,R</i>)
5	5c	−40	86	>98 (<i>R,R</i>)

^a Reaction conditions: [CuOTf]₂·C₆H₆ (0.05 equiv), ligand **5** (0.2 equiv), Et₂Zn (2.0 equiv), **2c** (1.0 equiv), toluene, 15 h. ^b Isolated yield. ^c Determined by ¹H NMR analysis of the Mosher esters, after reduction of the phosphate ester to alcohol with LiAlH₄ in diethyl ether (quantitative yield). ^d Absolute configuration was determined by analysis of the Mosher ester (see text).

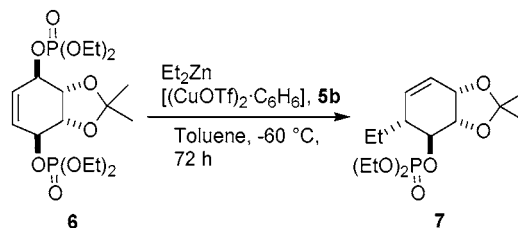
(C=O)–C–CF₃ fragment in one plane. The signals assigned to the methyl group of the ethyl substituent in the 2-position and to the vinylic proton in the 3-position of the seven-membered ring appeared at a higher field in the more abundant diastereomeric ester than the signals of the corresponding protons in the minor diastereomer; therefore, the absolute configuration of the major ester was assigned as (*R,R*).²⁰

To test the applicability of this synthetic methodology to more functionalized substrates, we performed the reaction on compound **6**,²¹ a derivative of conduritol A, using **5b** as the ligand (Scheme 2).

Much to our delight, compound **7**, derived from allylic displacement (S_N2') with inversion, was obtained in 52% yield (74% based on recovered **6**) as a single diastereomer, in 86% enantiomeric excess.^{22,23} It is worth noting that a fully functionalized cyclohexane derivative, containing four

(21) Johnson, C. R.; Plé, P. A.; Adams, J. P. *J. Chem. Soc., Chem. Commun.* **1991**, 1006–1007.

Scheme 2. Desymmetrization of Functionalized Substrate **6**^a



^a Reaction conditions: [CuOTf]₂·C₆H₆ (0.05 equiv), ligand **5b** (0.2 equiv), Et₂Zn (2.0 equiv), **6** (1.0 equiv).

contiguous stereocenters and a double bond, was obtained as a single diastereomer and in high enantiomeric excess from an achiral starting material.

In summary, we have developed a highly regio-, diastereo-, and enantioselective desymmetrization of five-, six-, and seven-membered *meso*-cyclic allylic bis-diethyl phosphates (**2a**, **2b**, and **2c**, respectively) with diethylzinc using catalytic amounts of [Cu(OTf)₂·C₆H₆] and phosphoramidite ligands **5**. Studies toward the extension of the scope of this reaction, using different organozinc reagents and other functionalized substrates, are currently underway in our laboratories.

Acknowledgment. We thank the European Commission (IHP Network Grant “CombiCat” HPRN-CT-2000-00014) for financial support and for postdoctoral fellowships to C. Claverie (HPRN-CT-2000-00014) and P. Daubos (“Marie Curie” HPMF-CT-2001-01318). We also thank “Merck Research Laboratories” (Merck’s Academic Development Program Award to C. Gennari, 2002) and MIUR COFIN 2002 (2002031849) for financial support. U. Piarulli thanks the Dipartimento di Chimica Organica e Industriale (University of Milano) for the hospitality.

Supporting Information Available: Experimental details and characterization data, including ¹H, ³¹P, and ¹³C NMR, IR, MS, and HRMS spectra and GC conditions. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(22) Absolute configuration of compound **7** has not yet been assigned.
(23) Reaction performed at −40 °C gave compound **7** in higher isolated yield (78%) but with lower ee (65%).