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TETRAHEDRON: *ASYMMETRY*

Enantioselective desymmetrization of a phospholene *meso*-epoxide

K. Michał Pietrusiewicz,[a,b,*] Marek Koprowski[c] and Zbigniew Pakulski[b]

[a]*Department of Organic Chemistry, Maria Curie-Skłodowska University, Gliniana 33, 20-614 Lublin, Poland*
[b]*Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warszawa, Poland*
[c]*Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Sienkiewicza 112, 90-363 Łódz, Poland*

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Abstract—*Cinchona* alkaloids serve as effective chiral bases in the enantioselective rearrangement of 3-phospholene epoxide. The reaction results in the formation of a *P*,*C*-chirogenic 3-hydroxy-2-phospholene derivative with up to 52% e.e. A stereochemical course for the epoxide rearrangement involving *anti*-β-proton abstraction is implied.

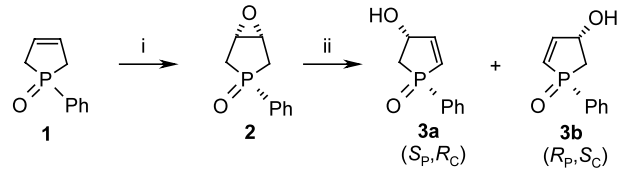
Asymmetric rearrangements of achiral epoxides to enantiomerically enriched allylic alcohols by the action of chiral organolithium bases has recently emerged as one of the most useful methodologies in the field of asymmetric synthesis.[1] It is accepted that these rearrangements proceed via initial lithium coordination to the epoxy oxygen followed by abstraction of a *syn*-β-proton.[2] In the last two decades a number of successful strategies based on this transformation have been developed for targeted syntheses of enantiomerically enriched cyclic and acyclic compounds containing carbon stereogenic centers.[1,3]

In the course of our research program directed towards the synthesis of *P*-chirogenic monophosphines[4] we wanted to utilize this methodology to create a phosphorus stereogenic center embedded within a five-membered ring. We chose 3-phospholene epoxide **2** as a suitable substrate as it is readily available in diastereomerically pure form by a literature procedure involving oxidation of 1-phenyl-3-phospholene oxide **1** with *m*-chloroperbenzoic acid.[5,6] It is also already known that epoxide **2** rearranges efficiently to 3-hydroxy-2-phospholene **3** in the presence of triethylamine in refluxing ethanol.[5] We anticipated that the use of a chiral base in lieu of triethylamine would result in an efficient asymmetric synthesis of **3** (Scheme 1).

Treatment of epoxide **2** in Et_2O or THF solutions at −78°C with chiral base systems known to be very effective catalysts for enantioselective epoxide rearrangement reactions,[7–10] such as LDA/(*S*)-(+)-1-(2-pyrrolidinylmethyl)pyrrolidine, *sec*-BuLi/sparteine, *n*-BuLi/sparteine or *n*-BuLi/bis[(*S*)-1-phenylethyl]-amine, afforded the desired hydroxyphospholene **3** in good chemical yields (53–79%) but with very poor or no asymmetric induction (0–8% e.e.).

More promising results were obtained when *Cinchona* alkaloids were used as free amine catalysts for the rearrangement:test reactions with these bases were carried out at 20°C or 55–60°C using 0.5 or 1.0 equiv. of base in ethanol or dichloromethane and were typically completed over prolonged reaction times in order to achieve higher conversions. The results of the screening in dichloromethane, which proved to be the better solvent are presented in Table 1.

As shown in Table 1, the highest enantiomeric purities of alcohol **3** were obtained in the reactions performed in the presence of quinidine (52% e.e., entry 8) and cinchonine (47% e.e., entry 6) which both favored the



1 **2** **3a** (S_P,R_C) **3b** (R_P,S_C)

Scheme 1. *Reagents and conditions*: (i) 1.5 equiv. *m*-CPBA, $CHCl_3$, reflux, 10 h, 84%; (ii) base, see Table 1.

* Corresponding author. E-mail: kmp@icho.edu.pl

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Table 1. Rearrangement of **2** in the presence of alkaloid bases in dichloromethane solution

Entry	Base (equiv.)	Temp. (°C)	Time (days)	Isolated yield (%)	Major enantiomer	$[\alpha]_D^{20}$ ($CHCl_3$)	Enantiomeric excess (%)[a]
1	Quinine (0.5)	55	5	25	**3a**	+36 (*c* 1.0)	19
2	Quinine (1.0)	20	90	60	**3a**	+34 (*c* 1.1)	18
3	Cinchonidine (0.5)	60	2	19	**3a**	+11 (*c* 1.0)	6
4	Cinchonidine (1.0)	20	90	62	**3a**	+39 (*c* 0.8)	21
5	Cinchonine (0.5)	60	2	13	**3b**	−39 (*c* 1.0)	21
6	Cinchonine (1.0)	20	90	77	**3b**	−87 (*c* 0.9)	47
7	Quinidine (0.5)	60	2	22	**3b**	−50 (*c* 1.0)	27
8	Quinidine (0.5)	20	90	41	**3b**	−96 (*c* 0.3)	52
9	Quinidine (1.0)	20	90	72	**3b**	−72 (*c* 1.5)	39
10	Sparteine (1.0)	20	90	78	–	–	0
11	Brucine (1.0)	20	90	40	–	–	0
12	*O*-Acetyl quinidine (1.0)	20	90	0	–	–	–

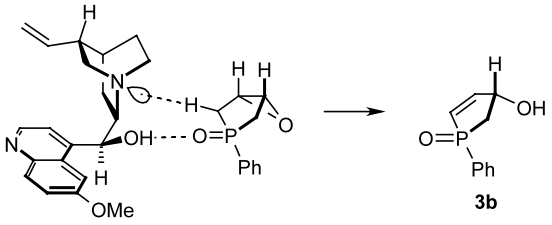
[a] Enantiomeric excesses were determined by comparison of specific rotation values with the known value for diastereomerically pure (S_P,R_C)-(+)-**3a** ($[\alpha]_D^{20}$ +184.8 (*c* 1.98, $CHCl_3$)).[5]

formation of (−)-**3b**. The two quasi-enantiomeric bases, quinine and cinchonidine, afforded predominantly (+)-**3a** (entries 1–4). Interestingly, chiral bases which lacked a free hydroxyl functionality were non-selective. Sparteine and brucine produced racemic **3** (entries 10 and 11) and *O*-protected quinidine was completely ineffective in the reaction (entry 12).

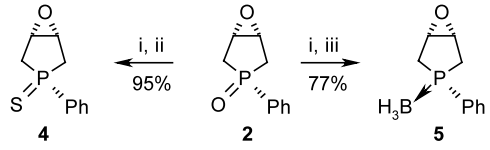
The above stereochemical results, and the failure of chiral lithium amide bases to induce asymmetry in the studied rearrangement, most likely result from the effect of the Ph-P=O functionality present in the substrate structure. It has already been demonstrated that the Ph-P=O group in five-membered rings facilitates abstraction of adjacent protons which are *syn* to the phosphoryl oxygen.[11] It is also well known that the basic phosphoryl oxygen is an efficient donor site for binding to protons and metal ions.[12] It is thus reasonable to tentatively assume that in the present case the rearrangement process is initiated by coordination of the alkaloid to epoxide **2** through hydrogen bonding between the alkaloid hydroxyl and epoxide phosphoryl functionalities, as shown in Scheme 2.

Following pre-association of the base and substrate, the base abstracts the more easily accessible of the two enantiotopic β-protons (in this case the proton *anti* to the epoxide oxygen) depending on the stereochemistry of the alkaloid molecule. The absolute configurations of **3b**, prevailing in the reactions catalyzed by quinidine and cinchonine, and of **3a**,[5] formed predominantly in the reactions with quinine and cinchonidine, agree with the proposed mechanistic picture.

An additional observation that the corresponding epoxy phospholene sulfide **4** and borane **5** (Scheme 3), both unable to participate in similar hydrogen bonding, fail to undergo the rearrangement under the same conditions as those used for the successful reactions of **2** with quinidine and chinchonidine is also in line with the above proposal.



Scheme 2. Preferred quinidine approach to epoxide **2**.



Scheme 3. *Reagents and conditions*: (i) $PhSiH_3$; (ii) S_8; (iii) BH_3·THF.

In summary, we have demonstrated that the asymmetric rearrangement of a phospholene *meso*-epoxide can be used to generate a stereogenic phosphorus center in a cyclic five-membered ring system. The rearrangement is best effected with *Cinchona* alkaloids which, unlike lithium amide bases, are most likely to operate in the studied system via the mechanism involving *anti*-β-proton abstraction. Quasi-enantiomeric alkaloid bases give products of opposite configuration.

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