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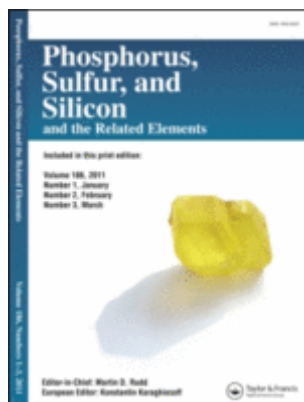
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Keywords:	calixarenes, phosphonates, phosphines, chirality, stereoselective synthesis, catalysis

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Chiral phosphorus-containing calixarenes

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GRAPHICAL ABSTRACT

Abstract Phosphorus-containing inherently chiral calix[4]arenes as well as calix[4]arenes substituted with phosphinoferrrocene chiral groups at the lower rim are described. Stereoselective synthesis, structure, and catalytic properties of the chiral calixarenes are discussed.

Keywords calixarenes, phosphonates, phosphines, chirality, stereoselective synthesis, catalysis.

INTRODUCTION

Calixarenes^{1,2} are cup-shaped macrocyclic compounds easily synthesized by one pot cyclocondensation of *para*-substituted phenols with formaldehyde. Calixarenes are easily **amenable** to chemical modification at the upper wide rim or at the lower narrow rim of the macrocycle. Due to their cup-shaped architecture calixarenes can recognize and separate similar in properties guests such as anions, cations and neutral organic molecules or **biomolecules**. Calixarenes modified with chiral moieties or asymmetrically substituted (inherently chiral) calixarenes discriminate of enantiomers of optically active molecules. The ability of the calixarenes to the enantiodiscrimination opens wide perspectives for their application in chiral technologies such as enantioselective sensors, shift reagents for NMR, catalysts of asymmetrical synthesis, sorbents for chromatography, nonlinear optic materials, one enantiomere drug design, etc³⁻⁶.

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This paper is devoted to the phosphorus-contained chiral calixarenes. There are several reasons of interest to the chiral calixarenes bearing phosphorus. First of all phosphorus has rich chemistry and opens wide perspectives in design of the chiral receptors. Phosphorus is biologically friendly element and chiral organophosphorus compounds play important role in biochemistry and medicine. Chiral phosphines and phosphites are very popular ligands in metallocomplexing catalysis⁷.

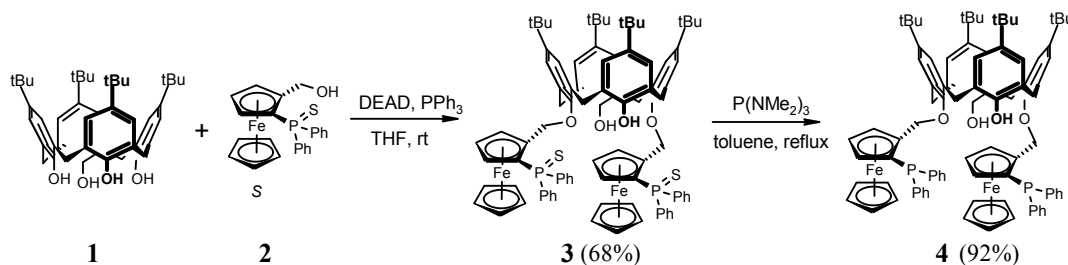
RESULTS AND DISCUSSION

There are two families of the chiral phosphorus-contained calixarenes. The first one consists of the calixarenes functionalized with chiral substituents. The second family is so-called inherently chiral calixarenes.

It is well documented that calixarenes modified with phosphine or phosphite moieties are widely used as ligands of metallocomplexing catalysts for organic synthesis⁸. It is also known that metallocomplexes of chiral phosphino ferrocenes catalyze of the asymmetrical reactions⁹. So, it was idea to decorate the calixarene platform with a chiral phosphino ferrocene group and investigate catalytical properties of this conjugate.

As a reagent for the calixarene modification we used *S*-enantiomer of thiophosphino(methylol)ferrocene **2** possessing a planar chirality¹⁰. By the Mitsunobu reaction the chiral thiophosphinoferrocene moieties were connected to distal oxygen atoms at the lower rim of tetrahydroxycalixarene **1** and chiral bis-(thiophosphinoferrocenyl)calixarene **3** was formed. After that sulfur atoms were removed from **3** by the reaction with triamidophosphite and desirable calixarene **4** with two chiral phosphinoferrocenyl groups at the lower rim was obtained with high total yield (Scheme 1, Figure 1).

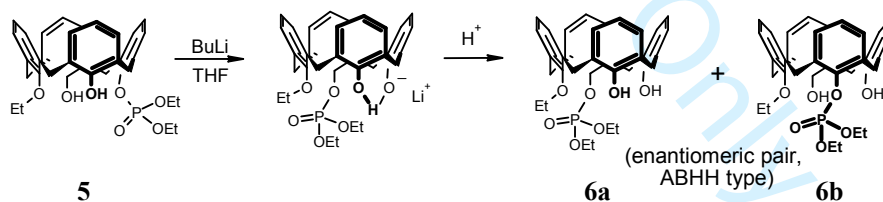
The bis-(phosphinoferrocenyl)calixarene ligand **4** displayed good catalytic activity and enantioselectivity in the asymmetric Tsuji-Trost reaction. In the presence of the ligand the alkylation of 1,3-diphenylpropenyl acetate by dimethylmalonate occurs with good chemical yield and high enantiomeric excess 86%¹⁰.



Scheme 1 Synthesis and of bis(diphenylphosphino)ferrocenylcalixarene **4**

Figure 1 X-ray structure of calixarene **4**

Another topic of the research is the inherently chiral calixarenes. Chirality of the compounds is induced by asymmetric disposition of any achiral substituents at the macrocyclic scaffold. The main method for synthesis of the phosphorus-containing inherently chiral calixarenes is phosphorotropic isomerisation of the symmetrical distally phosphorylated alkoxyalixarenes **5** into chiral 1,2-regioisomers **6a,b** (Scheme 2)¹¹.

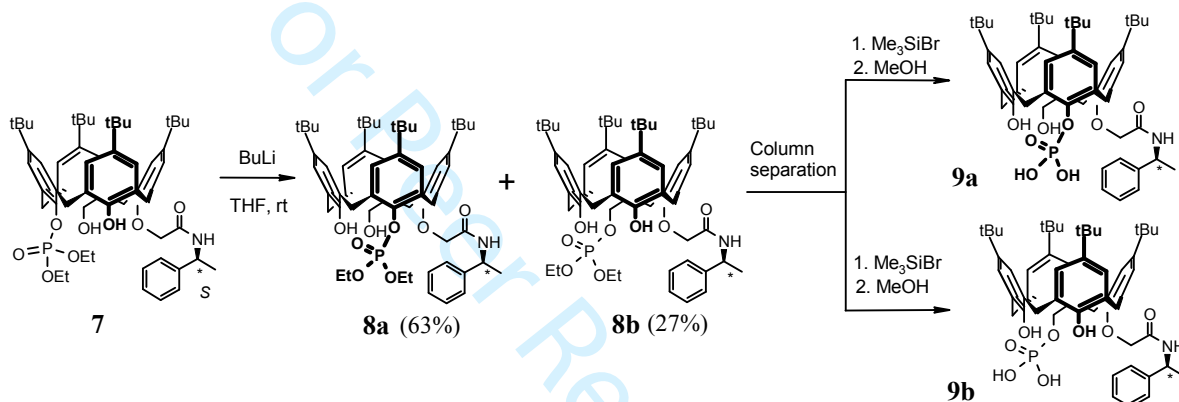


Scheme 2 Phosphorotropic isomerization of the symmetrical calixarenes **5** into chiral 1,2-regioisomers **6a,b**

It should be noted that the isomerisation is not stereoselective. Phosphorus with the same probability migrates to the both oxygen atoms and racemic mixture of two enantiomers **6a** and **6b** is formed. The calixarenphosphates **6** have been converted into free acids and their diastereomeric salts with chiral L-phenylethylamine were separated by the achiral HPLC method¹¹.

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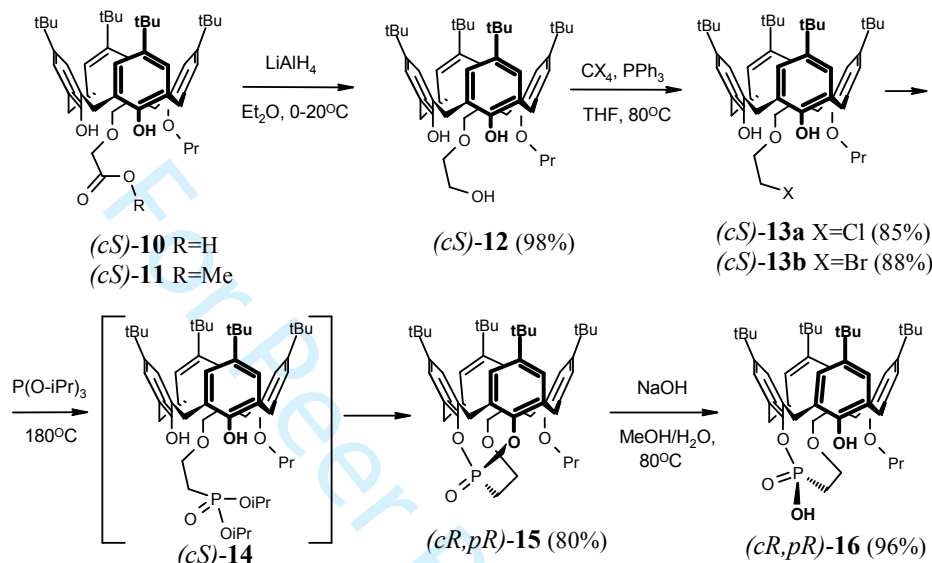
The phosphorotropic isomerisation of the calixarene phosphate **7** bearing a chiral phenylethylamide auxiliary group in distal position is stereoselective. Phosphorus preferably migrates to one oxygen atom. Two diastereomers of the inherently chiral calixarene **8a,b** were formed in this condition with diastereomeric excess of 36% (Scheme 3)¹². The diastereomers were separated by the column chromatography on silica-gel. Each isomer was transformed into inherently chiral calixarene phosphorus acids **9** and structure of the acids was examined by NMR and X-Ray methods.



Scheme 3 Stereoselective phosphorotropic isomerization of calixarenes **7** into diastereomers **8a,b**

Optically pure calixarene phosphonous acid **16** was synthesized in accordance with Scheme 4¹³. As the building blocks we used optically pure chiral calixarene acetic acid **10** or its methyl ester **11**¹⁴. The acid **10** and ester **11** have been reduced to calixarene ethanol **12** by the reaction with lithium aluminum hydride. Following the Appel reaction, alcohol **12** was transformed into calixarene ethylchloride **13a** or bromine **13b**. Chloride **13a** was converted to calixarene ethylphosphonate **14** by the Arbuzov reaction with triisopropyl phosphite. However, under rigid conditions of the phosphorylation (180 °C) the phosphonate **14** due to intermolecular *trans*-esterification in accordance with the Gloede's scheme¹⁵ was transformed into spiroposphonate **15** with high yield. The spiroposphonate **15** was hydrolyzed to cyclic phosphonous acid **16** by the reaction with sodium hydroxide. The reaction is highly stereospecific. Exclusively one P-O bond was hydrolyzed and phosphonous acid **16** was formed in optically pure form with practically quantitative yield.

The optically pure calixarene phosphonous acid **16** catalyses the asymmetrical **Diels-Alder** cyclisation of imines with Danishefsky diene¹³. Unfortunately enantiomeric excess of the reaction is low.



Scheme 4 Synthesis of inherently chiral calixarene phosphonous acid **16**

The enantiomerically pure propoxydibromocalixarene **17**¹⁶ possessing reactive OH groups at the lower rim and hydrogen or bromine atoms in *para*-position can be used as versatile synthon for design of phosphorylated chiral catalysts (Scheme 5)¹⁷. An attempt to exchange the proximal bromine atoms at the upper rim on phosphine oxide groups by the Nickel catalyzed Arbuzov reaction was failed, perhaps due to a sterical reason. To activate the bromine atoms the *cone* conformation was transformed into *partial cone* one by introduction two benzoyl groups into the molecule. The benzoyl derivative **18** bearing two bromine atoms at the opposite sides of the macrocycle was phosphorylated by the Nickel catalyzed Arbuzov reaction with formation of diphosphine dioxide **19** in the *partial cone* conformation with a high yield. Hydrolytical debenzoylation of the diphosphine dioxide **19** returned the calixarene skeleton into the initial *cone* conformation. Reduction of the diphosphine dioxide **20** by phenylsilane leads to enantiomerically pure inherently chiral calixarene diphosphine **21**.

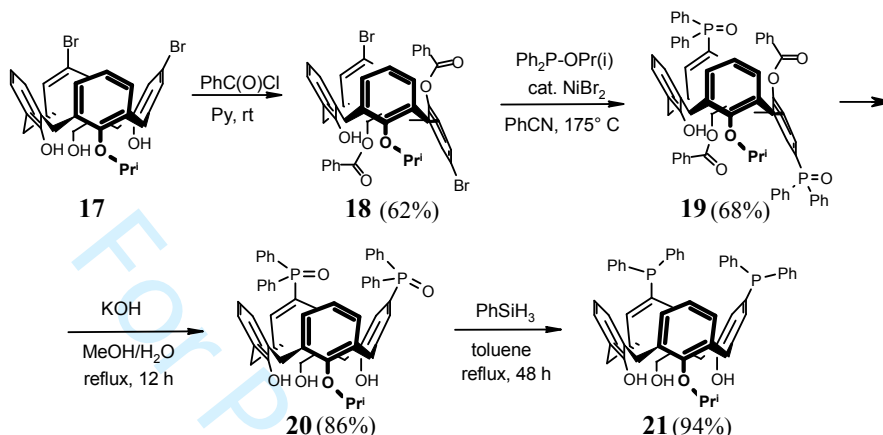
In order to obtain new calixarenes phosphorylated in the upper rim, the inherently chiral dibenzoylpropoxycalixarene **22** in the *partial cone* conformation was synthesized. Regioselective bromination, nitration and formylation of **22** at the *para*-position of unsubstituted

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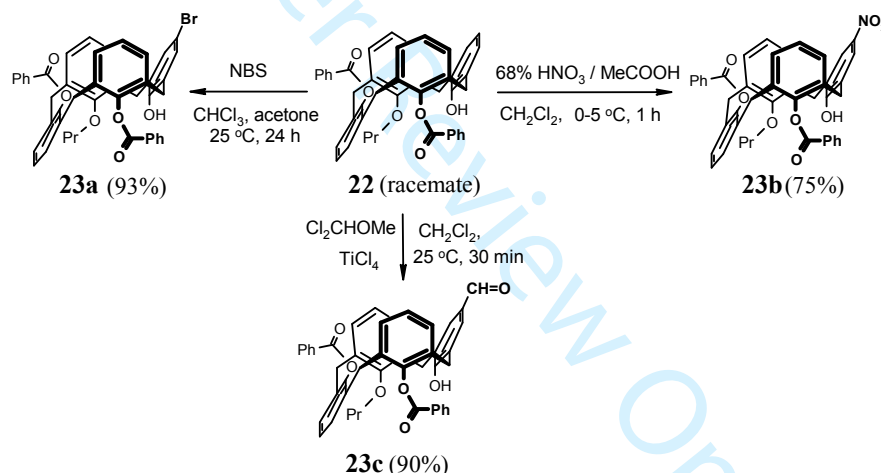
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phenol ring lead to corresponding bromo **23a**, nitro **23b** and formyl **23c** derivatives suitable for further phosphorylation (Scheme 6)¹⁸.

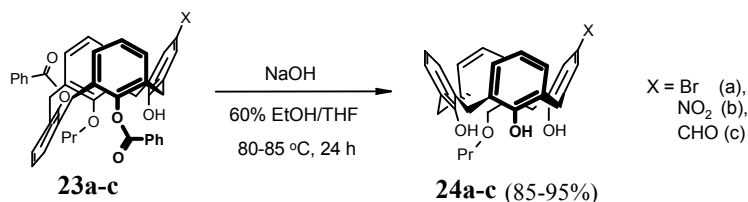


Scheme 5 Synthesis of enantiomerically pure inherently chiral calix[4]arene diphosphine **21**



Scheme 6 Synthesis of chiral building blocks **23a-c** in the *partial cone* conformation

The benzoyl groups of calixarenes **23** were removed by hydrolysis with sodium hydroxide to form the upper rim functionalized ethoxycalixarenes **24** in the *cone* conformation.



Scheme 7 Synthesis of chiral building blocks **24a-c** in the *cone* conformation

RUNNING TITLE 50 CHARACTERS OR LESS**CONCLUSIONS**

Calix[4]arene modified with two chiral phosphinoferrocenyl moieties at the lower rim was synthesized by the Mitsunobu reaction of *tert*-butyltetrahydroxycalixarene with *S*-enantiomer of thiophosphino(methylol)ferrocene with a high yield. Convenient methods of synthesis of the inherently chiral calix[4]arenes asymmetrically substituted with achiral diphenylphosphino moieties at the upper rim as well as with phosphorus acid moieties at the lower rim were developed. The chiral phosphorus-contained calix[4]arenes are promising molecular platform for design of catalysts of asymmetrical reactions or stereochemically pure bio-active compounds as well.

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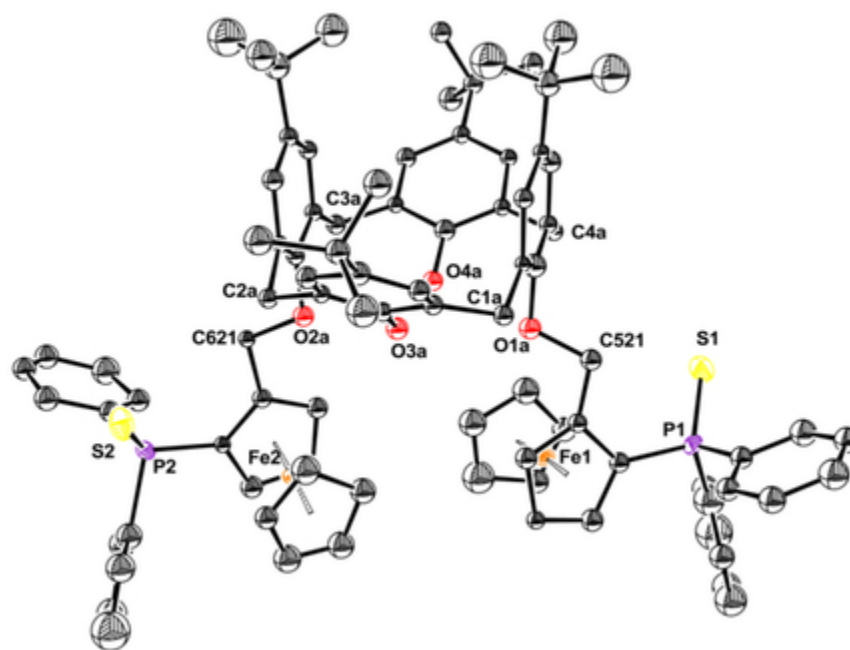
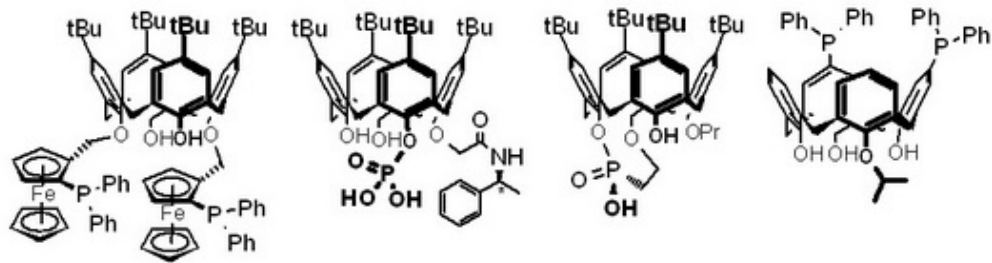


Figure 1 X-ray structure of calixarene 4

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Stereoselective synthesis, structure, and catalytic properties of the chiral calixarenes are discussed

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