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Turning Renewable Feedstocks into a Valuable and Efficient Chiral Phosphate Salt Catalyst

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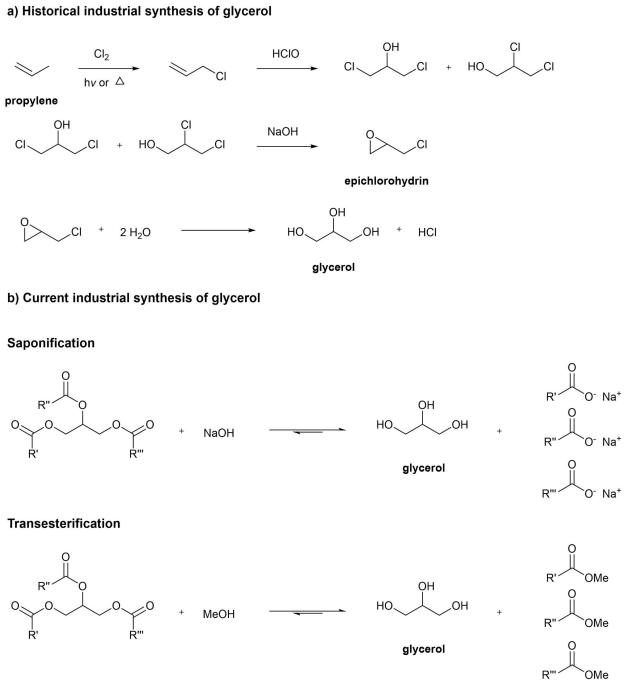
This work is dedicated in loving memory of Achille Antenucci Sr.

Abstract: Solketal, the chiral acetonide of glycerol, has been employed as the starting material in the design of a novel punctually chiral phosphate sodium salt for catalytic applications in organic and asymmetric synthesis. The racemate and the two enantiomers of the substrate are economic and commercially available, straightforwardly prepared in high yields from naturally occurring feedstocks. Therefore, remarkably, both enantiomers of the final catalyst can be synthesized by simple procedures in high yield and in compliance with several principles of green chemistry. To further demonstrate the usefulness of the novel catalyst, its application in a solventless protocol for cyanohydrin synthesis from a series of aldehydes has been presented.

1. Introduction

Glycerol (IUPAC name 1,2,3-propanetriol) is one of the first organic compounds isolated, through saponification of fats in the presence of alkaline ashes; the earliest evidences of this reaction date back to ancient Mesopotamia.[1] While around the middle 20th century its industrial scale production was mainly carried out from fossil fuel sources (propylene derivative epichlorohydrin, Scheme 1a), the growing demand for saving non renewable resources has driven to a reassessment of triglyceride alkaline hydrolysis. Nowadays, then, saponification of fats and oils with sodium hydroxide is the preferred strategy for large scale supply of this compound, together with trans-esterification with methanol that occurs during biodiesel production process, for which glycerol is a waste byproduct (Scheme 1b). In light of these well-established processes, glycerol is an abundant renewable resource, whose easy



Scheme 1. Historical and current methods for industrial scale synthesis of glycerol.

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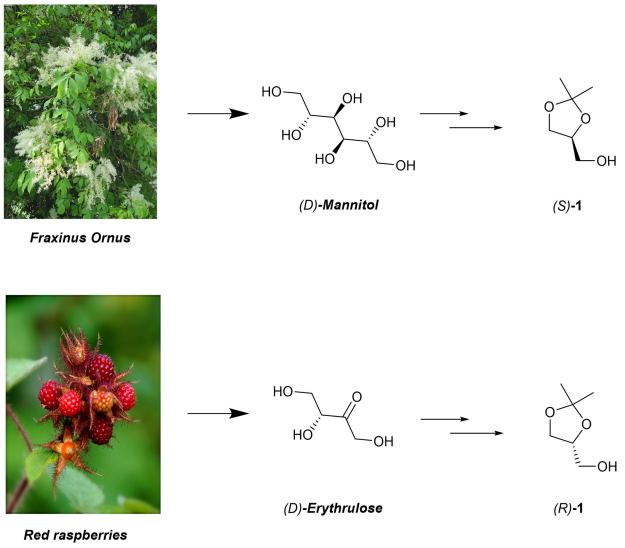
accessibility and low price make it perfectly suitable as a starting material for the synthesis of several valuable chemical compounds: amino acids,[2] carboxylic acids,[3] acetins,[4] among others.[5] Indeed, during the first decade of the 21st century, glycerol chemistry has received considerable attention, partially due to a growing inspiration to the green chemistry perspective, whose 7th principle states that renewable feedstocks and raw materials, most of which are naturally occurring, should be preferred whenever possible within the framework of chemical transformations.[6]

More recently, in compliance to the 5th principle of green chemistry, glycerol has been used as a solvent itself or in the preparation of deep eutectic solvents (DESs),[7] a new generation of green media for chemical synthesis.[8] However, to the best of our knowledge, no application of glycerol has instead been disclosed as the starting material for the design of catalysts. Indeed, naturally occurring chiral backbones (e.g. Cinchona alkaloids,[9] amino acids,[10]) are fundamental starting materials to synthesize various chiral organocatalysts and ligands of organometallic catalysts for asymmetric synthesis. Glycerol is, however, prochiral, but its desymmetrization has been performed either by biocatalysis[11] or organocatalysis,[12] including peptide catalysis,[13] in order to provide low cost chiral building blocks. Alternative synthetic approaches,[12] including the use of chiral auxiliaries,[14] are also available, while direct asymmetric acetalyzation/ketalization of glycerol still remains a major challenge. Nevertheless solketal, the acetonide of glycerol, is a non expensive and easily accessible chiral derivative, and both of its enantiomers derive from chiral pool compounds, namely *D*-mannitol (extracted from the cortex of *Fraxinus Ornus*[15]) and *D*-erythrulose (extracted from red raspberries[16]) (Scheme 2).

Currently, common phosphoric acid chiral organocatalysts are 7 terms cyclic diesters of H_3PO_4 derived from biaryl (BINOL, VANOL, VAPOL), spirocyclic (SPINOL) and tartaric acid derived (TADDOL, diethyl tartrate) diols.[17] Known chiral 6 member cyclic PAs (chlocyphos, anycyphos, phencyphos, etc.) have only been employed as resolution agents for chiral amines.[18] No example of catalysis from 5 member cyclic PAs or their derivatives has been described in the literature yet. Herein, we present the synthesis, for catalytic purposes, of the first member of the family of phosphatidic acids or cycloglycerophosphates (cGPAs), a novel class of punctually chiral phosphates. The main features of this route are: easiness of preparation in high overall yield and in compliance to several principles of green chemistry, the accessibility of both enantiomers and the low cost of their precursors. Furthermore, we demonstrate its practical usefulness in the solventless addition of TMSCN to aldehydes to afford geminal cyanohydrins.



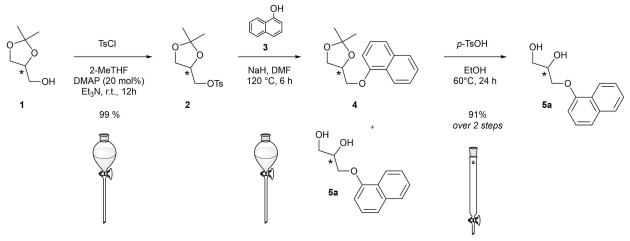
Scheme 2. Chiral pool sources for both enantiomers of solketal **1**.

2. Results and discussion

We began our synthesis (Scheme 3) from solketal **1**, whose quantitative derivatization into the corresponding tosylate **2** was carried out in DCM in the presence of triethylamine and a catalytic amount of DMAP. Chloroform and pyridine are known suitable alternative solvents for the same reaction;[19] however, in the perspective of designing a fully sustainable route we decided to employ 2-methyltetrahydrofuran (2-MeTHF), a biomass-derived green solvent,[20] which allowed to afford the crude product in quantitative yield as well as in DCM, while avoiding class 2 solvents. Nucleophilic displacement on the crude tosylate **2** with 1-naphthol **3** in DMF in the presence of sodium hydride afforded quantitatively a mixture of 1-naphthoyl derivative **4** and the corresponding diol **5a**, which is the product of the following reaction. The same reaction gave no conversion to **4** in greener organic solvents, such as 2-MeTHF or CPME, under reflux. The hydrolysis of the subsequent ketal, run on the reaction crude following a known literature procedure (10% aq. HCl),[21] was however disappointingly low (68% over 2 steps).

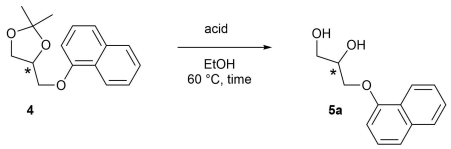
For this reason, a quick screening was performed in order to replace HCl with an organic acid. *p*-Toluenesulphonic acid (PTSA), (+)-camphorsulphonic acid ((+)-CSA) and *o*-benzenedisulfonimide (OBS), which was first introduced by our group as a Brønsted acid organocatalyst,[22] were the subject of our screening (Table 1).

While the employment of a large excess of HCl allows to afford the product in satisfactory yield after 24 h (Table 1,



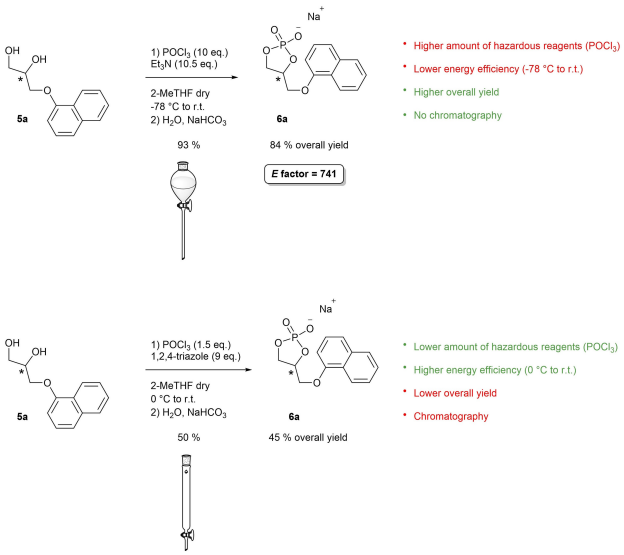
Scheme 3. Optimised synthetic route towards chiral O-1-naphthoyl glycerol derivative **5**.

Table 1. Optimisation of the acidic hydrolysis of ketal **4** in ethanol at 60 °C.



Entry	Acid[a]	Loading	Time [h]	Yield [%]
1[b]	HCl 37%	11.5 eq.	24 h	75
2	PTSA	20 mol%	24 h	65
3	PTSA	40 mol%	24 h	84
4	PTSA	40 mol%	48 h	91
5	(+)-CSA	40 mol%	48 h	87
6	OBS	40 mol%	48 h	75

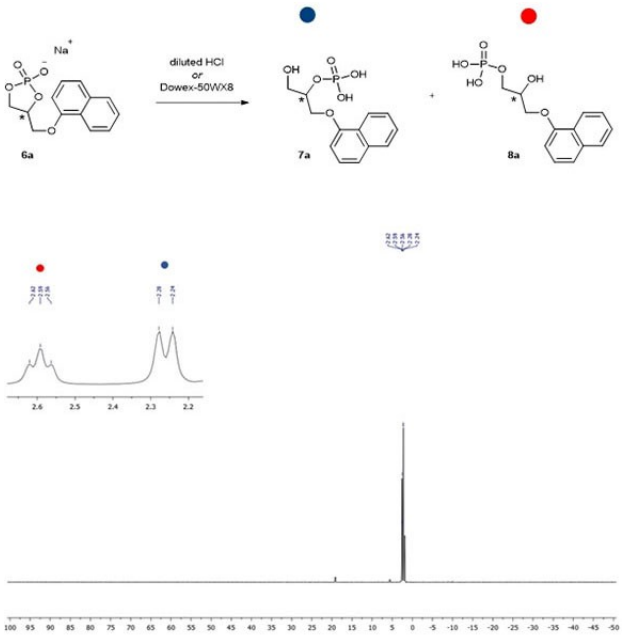
[a] All the reactions were performed in absolute ethanol and with a 1.5 M concentration with respect to compound **4**, if not differently stated. [b] Reaction performed at room temperature in a 1:1 solution of EtOH/HCl 37% with a 1.0 M concentration with respect to compound **4**.



Scheme 4. Comparison between the two phosphorylation approaches to the final catalyst **6a**.

entry 1), better results could be obtainment by adding sub stoichiometric PTSA (entries 3–4), as long as the catalyst loading and the reaction time are sufficient; indeed, 20 mol% PTSA yields only 65% of diol **5a** after 24 h (entry 2). (+)-CSA and OBS gave inferior results in the same conditions (entries 5–6). The best conditions found showed that the reaction can be directly performed on crude **4**, thus avoiding a chromatographic purification. However, complete evaporation of DMF and selective crystallization in methanol of bis(naphthalen-1-yloxy)methane **13**, that was formed in the reaction environment as a byproduct, are crucial steps in order to ensure reproducibility, also on a larger scale. The ketal hydrolysis was consequently performed with 40 mol% PTSA at 60 °C in ethanol, affording pure 3-(naphthalen-1-yloxy)glycerol **5a** in 91% yield over 2 steps after chromatographic purification (Scheme 3). The final phosphorylation step was then performed with an excess of $POCl_3$ and triethylamine in anhydrous 2-MeTHF at −78 °C, by modifying a literature protocol by Timmer et al.[23] Notably, the low temperature was found to be crucial to afford the cyclic 5 member phosphate as the only product, since a multitude of undesired phosphorous containing compounds was observed by ^{31}P NMR spectroscopy after reaction of **5a** with $POCl_3$ and triethylamine at room temperature, albeit in anhydrous conditions. Column chromatography was not necessary to isolate cycloglycerophosphate **6a**, which was obtained in pure form in 93% yield and 84% overall yield over 4 steps, starting from **1**. The E factor of this catalyst has been calculated, and the resulting value of 741 is considerably lower than those of axially chiral phosphates.[24] Some attempts of greener phosphorylation with Stawinski reagent[25] (see SI for further details) resulted in a lower conversion of the substrate **5a** and in problematic chromatographic purification (Scheme 4).

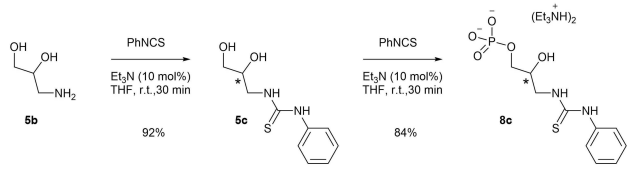
Disappointingly, the acidic treatment of **6a** with both diluted HCl (10^{-2} M to 10^{-6} M) or Dowex-50WX8 ionic exchange resin revealed the instability of the cyclic structure, as highlighted in the ^{31}P-^{1}H coupled NMR spectrum, which shows the presence of equimolar amounts of 1-glycerophosphoric acid **7a** and 2-glycerophosphoric acid **8a**, which correspond to a non regiospecific hydrolysis of the cyclic phosphodiester bonds. Indeed, the peaks in the region between 2.1 and 2.7 ppm are characteristic for open chain phosphoric acid monoesters; furthermore, their multiplicity accounts for a ^{3}J coupling of the phosphorous atom with the proton of the stereogenic centre (compound **7a**, doublet) or with two diastereotopic protons (compound **8a**, double doublet that collapses in a triplet) (Scheme 5).



Scheme 5. Acidic treatment of catalyst **6** and ^{31}P-^{1}H coupled spectrum (600 MHz, MeOD) of the resulting mixture.

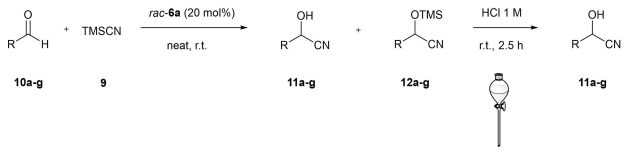
As a further indirect evidence of the acidic instability of the phosphatidic acid scaffold, diol **5c**, bearing a Brønsted acidic phenylthioureidic pendant, was prepared from commercially available 3-amino-1,2-propanediol **5b** and reacted with $POCl_3$ in the same conditions as compound **5a**. However, upon hydrolysis of the intermediate phosphoric acid chloride, an open chain structure (triplet in the ^{31}P-^{1}H coupled NMR spectrum) corresponding to phosphoric acid triethylammonium salt **8c** was isolated (Scheme 6).

Given the challenges associated with the isolation of a 5-member cyclic phosphoric acid, we decided to employ the alkali salt **6a** as the model catalyst. Indeed, it is well known that catalysis from alkali salts of chiral phosphoric acids represents a parallel research field to catalysis from phosphoric acids themselves.[26] As a matter of fact, we found out that, in the presence of 6, the room temperature addition of TMSCN **9** to aldehydes **10** occurs within a few minutes without the necessity of any solvent. This reaction is indeed very important, as the Strecker reaction is a well known protocol for the preparation of synthetic α-amino acids. It must be stressed that some background reactivity has been observed in the absence of catalyst **6a** (silylated cyanohydrin **12a** from aldehyde **10a**, 19% yield); for instance, after 30 minutes partial conversion of benzaldehyde **10a** has been verified by TLC and NMR (spectra in the SI). In any case, it must be stressed that the reaction did not reach complete conversion of the substrate even after 24 hours. Because the reaction affords a mixture of unprotected cyanohydrins **11** and silylated cyanohydrins **12**, after the removal of the catalyst **6a** upon dilution with Et_2O and simple filtration, the crude mixture was treated with 1 M HCl and extracted in EtOAc to afford cyanohydrins **11** without the necessity of any chromatographic purification. In this second step, a catalytic role of hydrochloric acid (desilylation agent) should be excluded. In fact, when substrate **10a** was reacted in the absence of catalyst **6a** for 5 minutes and then treated with diluted HCl for 2.5 hours, NMR spectra of the crude reaction mixture showed the presence of major amount of unreacted **10a**. The E factor of the process is 103; however, to give a more realistic idea of the actual impact of the protocol, the synthesis of the necessary amount of catalyst has been taken into account, thus giving an E_G factor value of 270.[24] It is useful to point out that all the reactions have been carried out on a 1 mmol scale and, therefore, less amount of waste could result from optimisation on a larger scale. A small substrate scope has been performed, and the relative results are summarized in Table 2.



Scheme 6. Phosphorylation of diol **5c**, bearing an acidic pendant, affords open chain glycerophosphate **8c**.

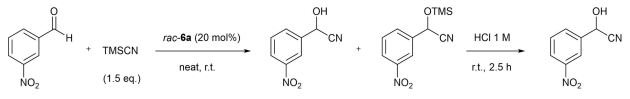
Table 2. Substrate scope of the solventless addition of TMSCN to aldehydes catalysed by *rac*-**6a**.



Entry	R	TMSCN [eq.]	Time [min]	Product	Yield [%]
1	C_6H_5	1.5	5	**11a**	99
2	3-NO_2-C_6H_4	1.5	5	**11b**	99
3	4-Cl-C_6H_4	1.5	5	**11c**	99
4	2-Thienyl	1.5	5	**11d**	99
5	4-CH_3-C_6H_4	1.5	5	**11e**	99
6	4-OCH_3-C_6H_4	1.5	60	**11f**	99
7	*n*-C_9H_{19}	1.5	10	**11g**	99
8	2-OCH_3-C_6H_4	1.5	120	**11h**	99
9	2-NO_2-C_6H_4	1.5	5	**11i**	99
10	2-Ph-C_2H_5	1.5	30	**11j**	99[a]

[a] Mixture of diastereomers in 1.69:1.00 ratio.

Table 3. Recycling of catalyst *rac*-**6a** in the solventless addition of TMSCN to aldehyde **10b**.



Entry	Cycle n.	Time [min]	Yield [%]	Cat. recovery [%]
1	1	5	99	82
2	2	5	99	80
3	3	5	99	80
4	4	5	99	83
5	5	5	99	88

It must be stressed that, differently from substrates indicated in Table 2, the above described protocol did not prove suitable for 4-pyridinecarboxaldehyde **10k**, which underwent decomposition, or 4-hydroxybenzaldehyde **10l**, which gave no conversion over 4 hours. The catalyst could be recycled without any significative loss in the reaction yield (Table 3); given the very fast reaction time, it was not possible to assess any impact on the catalyst activity, *e.g.*: stopping the reaction at a timepoint equivalent to 50% conversion on the first cycle to show that it doesn't change throughout the recycles.

No enantiomeric excess was observed when catalyst **6a** was tested as an enantioselective catalyst (Table SI1). In order to develop enantioselective competent catalysts, the design of novel cGPAs decorated with bulkier or coordinating pendants and C_2-symmetric cGPAs is currently under investigation in our laboratory.

3. Conclusion

Herein the first member of a novel class of chiral phosphates to be employed for catalytic purposes, namely cycloglycerophosphates (cGPAs), has been presented. Both the enantiomers of

cGPAs are easily accessible from inexpensive reagents of the chiral pool. Particularly, desymmetrization of glycerol offers the possibility of realizing their synthesis from glycerol, one of the cheapest renewable sources currently available for organic synthesis. The main part of our synthetic route, starting from inexpensive chiral glycerol derivative solketal **1**, is compliant to some of the 12 principles of green chemistry and involves a single chromatographic purification, while the green optimization of the final phosphorylation step is currently underway. The novel catalyst, employed in the neat addition of TMSCN to aldehydes, showed quantitative conversion of the substrates in extremely short reaction times, albeit no enantiomeric excess could be induced at this stage. We envision that the design of more bulky or C_2-symmetric cGPAs, as well as the choice of different substrates, will help in the improvement of the enantioselectivity outcomes and it represents our next goal for this research.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: green chemistry · catalyst design · chiral phosphate salt catalysis · Strecker reaction · chiral pool

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