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Article

Chiral Sodium Glicerophosphate Catalyst for Enantioselective Michael Reactions of Chalcones.

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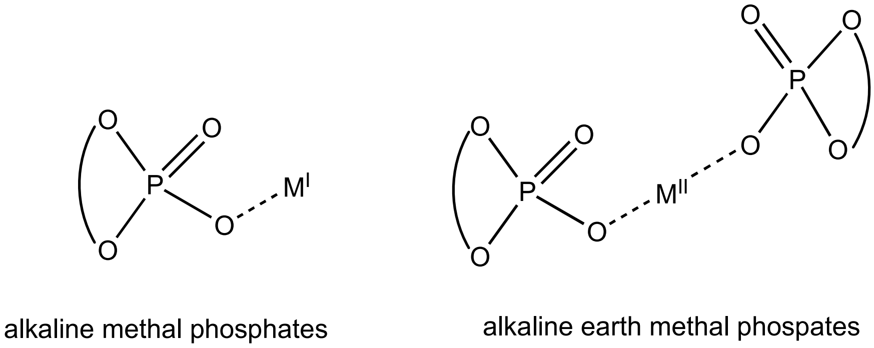
Abstract: A chiral sodium glicerophosphate is successfully exploited as catalyst in Michael addition of methyl malonate to a number of chalcones. The reactions furnished the target adducts in satisfactory yields and good enantiomeric excesses. A tentative of computational study is presented aiming to understand the reaction mechanism.

Keywords: conjugate addition; organocatalyst; chiral catalyst

1. Introduction

The employment of alkali and alkaline earth metal phosphates (Figure 1) in asymmetric catalysis [1–3], even though strictly not classifiable as asymmetric organocatalysts, displays many of its advantages, namely handiness of the catalyst, absence of costly and toxic heavy transition metals and easiness of preparation from the corresponding phosphoric acids [4,5].



alkaline methal phosphates

alkaline earth methal phospates

Figure 1. Methal phosphates.

On this ground, we recently proposed a new class of sodium phosphate catalysts, namely cycloglycerophosphates (Figure 2) prepared from enantiopure solketal (the acetonide of glycerol) [6]. One of these adducts, namely (S)-4-((naphthalen-1-yloxy)methyl)-1,3,2-dioxaphospholan-2-olate 2-oxide sodium (Figure 2; **1**) was employed as catalyst in addition of TMSCN to aldehydes at room temperature, to afford *gem*-cyanohydrins [6]. Unfortunately, no enantioselectivity was observed. This behaviour can be explained with an intrinsically low asymmetric induction exerted by the 5-membered phosphatidic acid scaffold, having the stereogenic center far from the catalyst active site and not supported by steric hindrance effects, because of the free rotation around the exocyclic bond bearing the bulky α-naphthyloxy group. On the other hand, in order to introduce C2-symmetry we prepared adducts **2** and **3** (Figure 2) [7]. They resulted into an outstanding enantiocontrol of the reaction, namely addition of TMSCN to aldehydes and ketones. The reaction mechanism was investigated on a minimal model of the catalyst with a DFT method. A calculation of the most stable conformation of the model catalyst for both *C*2-symmetric cycloglycerodiphosphates instead, accounts for the enantioselectivity, since the two cyclic phosphatidic moieties are *syn*, creating a confined pocket for the reactants through electrostatic interactions involving the sodium cations [7].

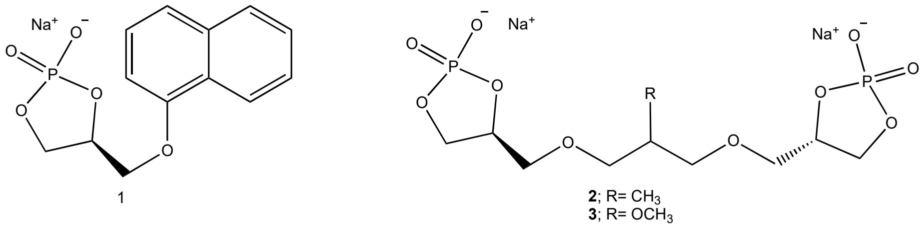
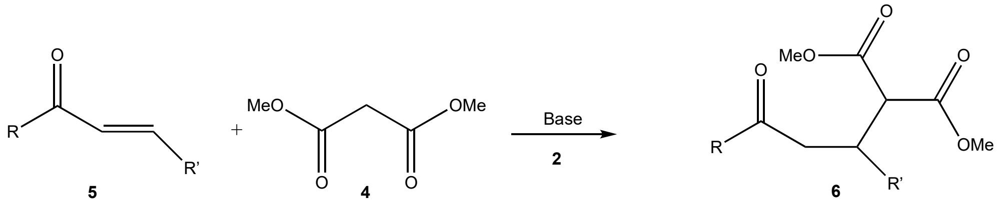


Figure 2. Chiral cycloglycerophosphates.

In light of the interesting results previously obtained and with the aim of expanding the synthetic uses of this class of catalysts, we studied 1,4 addition reactions of methyl malonate (**4**) to a number of chalcones **5** in the presence of **2** as chiral catalyst (Scheme 1). It must be stressed that the catalytic asymmetric conjugate addition of ß,-unsaturated carbonyl compounds is one of the most powerful carbon–carbon bond-forming reactions [8,9]. In fact, its complete atom economy, wide substrate scope, susceptibility to many classes of catalysts, and easily accessible starting materials render it one of the most modern of classical reactions. However, on the other hand, remain difficult to execute via either stoichiometric or catalytic approaches, despite recent advances [10].



Scheme 1. 1,4-Addition of methyl malonate **4** to chalcones **5** in the presence of chiral glycerophosphate **2.**

The chiral catalysts used for this reaction are most varied [11]. However, the literature shows few examples catalysed by chiral phosphates. The most significant are three. In particular, in 2010 Chen reported an enantioselective addition of TMSCN to aromatic enones catalysed by sodium salt of (*R*)-3,3′-di(1-adamantyl)-1,1′-binaphthyl-2,2′-diylphosphoric acid [12] and Antilla in 2011 described a chiral vapol phosphate catalysed Michael reaction of 3-substituted indoles with methyl vinyl ketone [13]. Finally, in 2019 Zhu and Niemeyer reported that heterobifunctional rotaxanes featuring an amine-based thread and a chiral 1,1′-binaphthylphosphoric acid-based macrocycle efficiently catalysed the addition of malonates to Michael acceptors [14].

2. Results and Discussion

As a model reaction, we decided to begin the study by reacting methyl malonate (**4**) with *E*-1,3-diphenylpropen-3-one (**5a**) in the presence of catalyst **2** at room temperature and with a number of solvents (Table 1; entries 8,9,10,11). Only traces of target compound dimethyl 2-(3-oxo-1,3-diphenylpropyl)malonate) **6a** were detected in MeOH (Table 1; entry 2) or 2-MeTHF (Table 1; entry 5) . Also increasing the amount of catalyst to 10 mol% (Table 1; entries 3,6) and carrying out the reaction at 60°C (Table 1; entries 4,7) no appreciable results were obtained. Since the catalyst **2** is not basic enough to deprotonate the malonate and therefore to allow nucleophilic attack to **5a**, in order to transform the malonate into the corresponding more nucleophilic anion, we added an equimolar amount of sodium methoxide to **4** dissolved in methanol.

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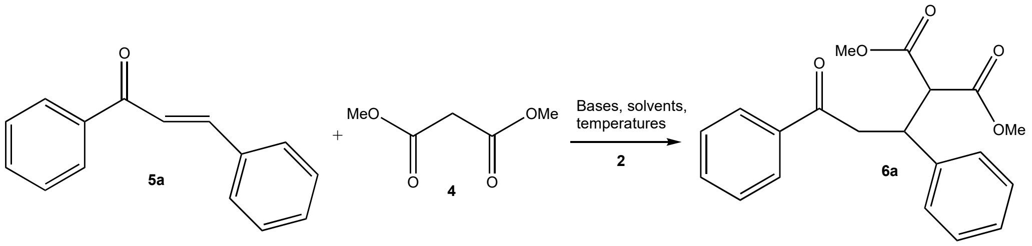
Table 1. Trial reactions.



Entry	Catalyst **2** (mmol%)	Base	Solvent	T (°C)	Time (h)	Yield (%)^{1,2}	*Ee* (%)^{3}
1	-	-	MeOH	rt	24	traces	-
2	5	-	MeOH	rt	24	traces	-
3	10	-	MeOH	rt	24	traces	-
4	10		MeOH	60	24	traces	-
5	5	-	2-MeTHF	rt	24	traces	-
6	10	-	2-MeTHF	rt	24	traces	-
7	10	-	2-MeTHF	60	24	traces	-
8	5	-	Toluene	rt	24	-	-
9	5	-	DCM	rt	24	-	-
10	5	-	DMSO	rt	24	-	-
11	5	-	MeCN	rt	24	-	-
12	5	CH_3ONa	MeOH	rt	8	52	34.3
13	10	CH_3ONa	MeOH	rt	6	51	32.8
14	5	CH_3ONa	Toluene	rt	24	-	-
15	5	NaH	2-MeTHF	rt	3	92	37.5
16	5	NaH	2-MeTHF	0	5	90	57.2
17	5	NaH	2-MeTHF	-20	8	90	91.5
18	5	NaH	2-MeTHF	-45	8	21	90.8
19	-	NaH	2-MeTHF	rt	3	91	-
20	-	NaH	2-MeTHF	-20	8	90	-

[1] Reactants **1c, 2** and MeONa/NaH are in ratio 1:1:1. [2] Yields are referred to pure and isolated **6a,** purified in a short chromatographic column (eluent petroleum ether/diethyl ether 3:2). [3] *Ee* was determined by HPLC analyses on a chiral stationary phase.

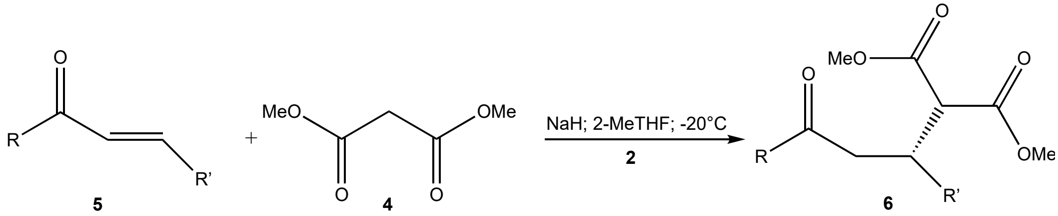
Under these condition (Table 1; entry 12), fairly good yield of target **6a** was obtained (52%), although with low enantiomeric excess (34%). Changing solvent and using 2-MeTHF (Table 1; entry 15) the yield of the target **6a** significantly increased up to 90% but the enantiomeric excess was similar (37%) to that previously obtained. It must be stressed that, in this case (Table 1; entry 15), the anion of malonate was formed adding NaH.

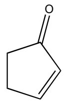
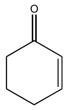
By lowering the temperature to 0°, enantiomeric excess of 57% (Table 1; entry 16) was obtained. By further lowering the temperature to -20°C, to our delight, the enantiomeric excess was 91.5% (Table 1; entry 17). A further lowering of the temperature to -45°C did not lead to changes (Table 1; entry 18). Moreover, this reaction was not completed after 8 hours. On the other hand, it is necessary to underline that the reaction occurred between the anion of **4** and **5a** even in the absence of the catalyst **2** (Table 1; entries 19,20).

In order to explore the applicability of this optimized procedure, we tested other reactions between aromatic or heteroaromatic chalcones, variously substituted with electron withdrawing or electron donating substituents (Table 2; entries 1–20). The yields were always good and good enantiomeric excesses were obtained, always between 87 and 94%. The average enantiomeric excess for 20 examples was 90.2%.

Moving on to examine the reactivity of aliphatic chalcones (or similar compounds), quite surprisingly, no reactions occurred with methyl vinyl ketone (**5x**; Table 2, entry 23) methyl acrylate (**5y**; Table 2, entry 24) or acrylaldehyde (**5z**; Table 2, entry 25). We believe that, due to the lack of an electron-donating and activating group linked to the C atom in ß of CO, the nucleophilic attack of malonate cannot occur. Instead, the compounds **5u**, **5v**, **5w** showed the same reactivity as the corresponding aromatic ones (Table 2; entries 21–23) even if the enantiomeric excesses obtained were lower (average enantiomeric excess for tree examples was about 83.2%)

Table 2. Synthesis of adducts **6.**



Entry	R in **5,6**	R′ in **5,6**	Time (h)	Yield (%) of **6** ^{1,2,3}	*Ee* (%)^4
1	C_6H_5	C_6H_5	8	**6a**; 90	91.5
2	C_6H_5	4-$NO_2C_6H_4$	10	**6b;** 87	88.9
3	C_6H_5	4-ClC_6H_4	6	**6c;** 89	92.9
4	C_6H_5	4-MeC_6H_4	4	**6d;** 92	90.0
5	C_6H_5	4-CNC_6H_4	10	**6e;** 92	90.3
6	C_6H_5	2-$NO_2C_6H_4$	12	**6f;** 77	90.5
7	C_6H_5	3-$NO_2C_6H_4$	8	**6g;** 90	89.9
8	C_6H_5	Thiophen-2-yl	6	**6h;** 82	89.6
9	C_6H_5	Furan-2-yl	6	**6i;** 77	89.3
10	Me	C_6H_5	6	**6j**; 82	92.5
11	Me	2-MeC_6H_4	8	**6k**; 90	94.4
12	Me	3-$MeOC_6H_4$	6	**6l**; 85	88.8
13	C_6H_5	Me	4	**6m**; 87	89.5
14	4-$CF_3C_6H_4$	C_6H_5	6	**6n**; 92	89.7
15	2-$MeOC_6H_4$	C_6H_5	6	**6o;** 79	87.0
16	3-MeC_6H_4	4-ClC_6H_4	8	**6p;** 82	89.9
17	3-MeC_6H_4	4-$NO_2C_6H_4$	10	**6q;** 91	87.0
18	4-$CF_3C_6H_4$	4-MeC_6H_4	6	**6r;** 90	92.4
19	4-ClC_6H_4	C_6H_5	6	**6s;** 85	89.0
20	4-$NO_2C_6H_4$	C_6H_5	6	**6t;** 85	90.5
21	Et	Me	4	**6u;** 85	81.8
22			6	**6v;** 83	87.5
23			6	**6w;** 91	70.2
24	CH_3	H	8	**6x;** -	-
25	OCH_3	H	8	**6y;** -	-
26	H	H	8	**6z;** -	-

[1] Reactants **1c**, **2** and NaH are in ratio 1:1:1.[2] Temperature was -20°C. [3] Yields are referred to pure and isolated **6**, purified in a short chromatographic column (eluent petroleum ether/diethyl ether 3:2). [4] *Ee* was determined by HPLC analyses on a chiral stationary phase.

In an attempt to rationalize the experimental outcomes, we performed a computational study on the reaction with chalcone **5a** (see SI-CD for details on the method and a more extended discussion). In the transition structure (**TS**) for the nucleophilic addition (Figure 3), the catalyst is depicted on the upper part of the figure; the upper sodium cation is fully solvated by the oxygen atoms (in red) of the catalyst while the second on the lower part interacts also with the oxygen atoms of the malonate (in the middle) and of the chalcone (in the lower part).

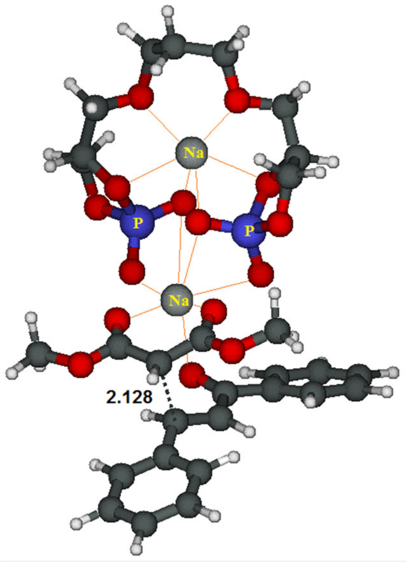
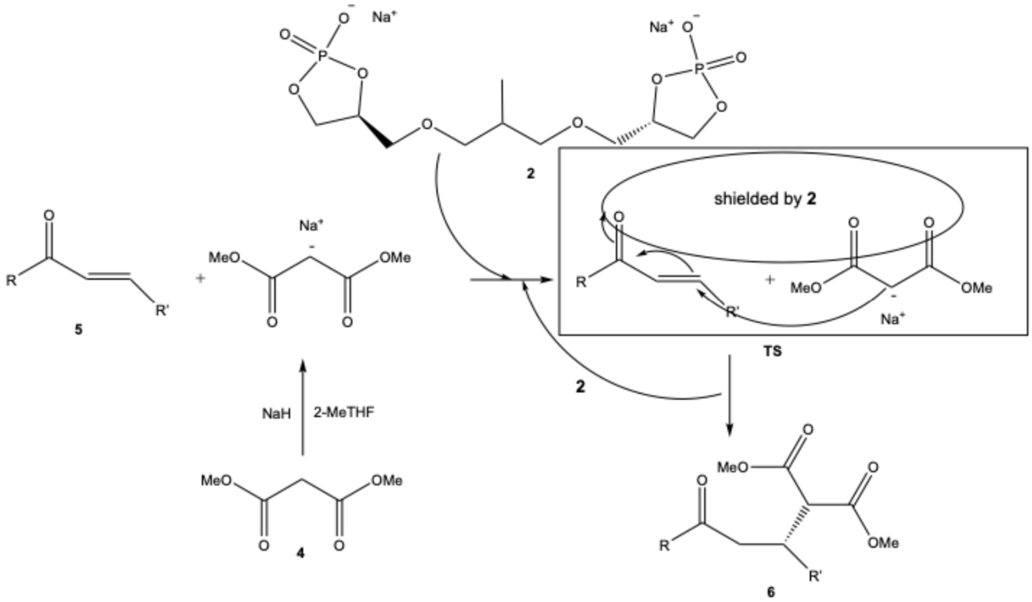


Figure 3. Transition structure (**TS**) for the nucleophilic addition.

We believe that, thanks to these interactions in **TS**, one of the prochiral faces of the chalcone is shielded. So, the nucleophilic attack of the anion of **4** on **5** can occur mainly from a single direction, allowing **6** to be obtained with a good enantiomeric, as depicted in Scheme **2** and qualitatively reproduced by the calculation. As already mentioned previously (Table 1, entry 19), the reaction occurs even in the absence of **2**. Therefore, its essential function is to create a chiral fashion.



Scheme 2. Hypothesized mechanism.

We also tried to model the effect of the catalyst on the kinetics of the reaction. A small increase in the catalyzed reaction rate was observed, but the computations failed to fully reproduce it. However, the computed energy difference between the non-catalyzed and the catalyzed reactions was very small (0.5 kcal mol^{-1}) and strongly dependent on the solvent effects which are very difficult to fully reproduce.

3. Materials and Methods

3.1. General

Catalyst **2** [7] and chalcones **5** [15] were prepared as reported in the literature. Analytical grade reagents and solvents (purchased from Merck, Carlo Erba, Alfa Aesar and Fluorochem) were used and reactions were monitored by GC, GC-MS. Column chromatography and TLC were performed on Merck silica gel 60 (70-230 mesh ASTM) and GF 254, respectively. Petroleum ether (PE) refers to the fraction boiling in the range 40–70 °C. GC analyses were performed on a PerkinElmer AutoSystem XL GC with a methylsilicone capillary column. Mass spectra were recorded on an HP5989B mass selective detector connected to an HP 5890 GC with a cross-linked methyl silicone capillary column. Chiral analyses were performed on a HPLC using a Daicel CHIRALPAK-IG (250 x 4.6 mm, 5 mm) on Essential LC- 16 series and eluting with i-PrOH and n-hexane. For the determination of optical rotation a Jasco P-2000 polarimeter was used. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Brucker spectrometer at 400 and 100 MHz respectively. IR spectra were recorded on a IR Perkin-Elmer UATR-two spectrometer. Structures and purity of all the adducts **6** obtained in this research were confirmed by their spectral (NMR, GC-MS, IR) data. Satisfactory microanalyses were obtained for all new compounds.

3.2. As a Catalyst in Michael Reactions. Typical Procedure: Synthesis of (R)(-)-Dimethyl 2-(3-oxo-1,3-diphenylpropyl)Malonate (6a)

NaH (60% dispersion in paraffin liquid; 44 mg, 1.1 mmol) was added as to a stirring solution of methyl malonate (**4**; 132 mg, 1 mmol) in 2-MeTHF (5 mL). A white suspension was immediately formed. After 10 min of further stirring, the mixture was cooled to -20°C. At this point, chiral catalyst (**2**; 5 mol%, 21 mg, 0.05 mmol) and *E*- 1,3-diphenylprop-2-en-1-one (**5a**; 208 mg, 1 mmol) were added. The mixture was stirred for 8 h, until TLC (eluent PE/EE 4:1) GC and GC-MS analyses showed the complete disappearance of **4** and **5a** and the complete formation of dimethyl 2-(3-oxo-1,3-diphenylpropyl)malonate (**6a**; MS (70eV) *m/z* : 340 (37) $[M]^+$). Then, H_2O (5 mL) was added to the reaction mixture, which was extracted with Et_2O (10 mL). The organic phase was washed with H_2O (5 mL) and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The crude residue was purified in a short chromatographic column (eluent: PE/EE 4:1). The resulting white solid was virtually pure title compound (**6a**; 305 mg; 90% yield). After the above work-up, *Ee* was measured.

4. Conclusions

We have reported the enantioselective conjugate addition of methyl malonate (**4**) to chalcones **5** catalyzed by a C2-symmetric cycloglycerodiphosphate **2**. The target adducts **6** were obtained in satisfactory yields with good enantiomeric excess. In light of this and in light of its ease of preparation and purification, this catalyst turns to be very competitive for this type of asymmetric protocol since results comparable to those obtained with other catalytic systems dedicated to this purpose and already cited in the literature were obtained.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Physical data of malonates **6**: page S-2; NMR Spectra and chiral analyses of malonates **6**: page S-7; Computational method: page S-54; Schemes, tables, pictures and Cartesian coordinates for the uncatalyzed reaction: page S-56; for the catalyzed reaction: page S-67.

Author Contributions: Conceptualization, S.D. and G.G.; methodology, S.D.; software, G.G.; validation, S.D. and G.G.; formal analysis, S.D.; investigation, S.D., G.G., J.R. and A.R.B.; resources, S.D.; data curation, S.D.; writing—original draft preparation, S.D and G.G.; writing—review and editing, S.D and G.G.; visualization, S.D.; supervision, S.D.; project administration, S.D.; funding acquisition, S.D. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflicts of interest.

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