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Studies on the true catalyst in the phosphate-promoted desymmetrization of *meso*-aziridines with silylated nucleophiles

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ABSTRACT

Significant amounts of metal phosphate impurities have been detected by NMR spectroscopy and ICP-OES analysis of synthetic, as well as purchased, samples of VAPOL hydrogen phosphate purified on silica gel. The previously reported VAPOL hydrogen phosphate-catalyzed desymmetrization of *meso*-aziridines with different silylated compounds, has been re-examined. While metal-free phosphoric acid exhibited low activity and enantioselectivity, calcium and magnesium phosphate salts proved to be the true catalysts in these related processes. Reproducible high enantioselectivities were obtained in the ring-opening of cyclic *meso*-aziridines with Me_3SiX (X=SPh, SePh, N_3) employing a 1:1 mixture of calcium and magnesium VAPOL phosphates. The reaction has been successfully extended to Me_3SiSBn, Me_3SiSMe and Me_3SiNCS, giving ring-opened products in high yield and unprecedented moderate to good enantioselectivities.

1. Introduction

Since the early works of groups of Terada[1] and Akiyama[2] in 2004, phosphoric acids derived from axially chiral biaryls have rapidly emerged as highly efficient and widely applicable enantioselective organocatalysts.[3] The universally recognized mode of action of these catalysts is based on the dual acid/base function of the phosphoric group. In fact, while the acidic OH functionality is able to activate a wide range of electrophiles through the formation of hydrogen bonds or ionic pairs, the P=O basic group has the complementary function of activating protic pronucleophiles.

However, during the last years, chiral phosphoric acids have also been reported to be involved in catalysis with silylated nucleophiles. A highly enantioselective ring opening desymmetrization of activated *meso*-aziridines **2** with Me_3SiN_3, catalyzed by the VAPOL-derived phosphoric acid **1**, was described by Antilla and co-workers.[4] The authors proposed the mechanism depicted in Scheme 1, with the phosphoric acid **1** acting as a Lewis base promoter rather than a proton catalyst. The activation of the silane was suggested to result in the formation of a Lewis acidic intermediate silyl phosphate. During our studies on the desymmetrization of *meso*-aziridines,[5] we developed closely related processes based on the activation of different silylated nucleophiles, such as $PhSSiMe_3$[6] and $PhSeSiMe_3$,[7] with the same phosphoric acid. High enantioselectivities were achieved after appropriate modifications of both the nitrogen activating group and experimental details. In view of the similarity of the reaction with Me_3SiN_3, we believed that the mechanism of Antilla could be involved with different silylated nucleophiles as well. An analogous role for phosphoric acids and other Brønsted acids in the activation of silanes, with the in situ formation of a silylated catalyst, has also been invoked by other groups.[8]

Recent studies indicated that phosphoric acids obtained by previously established synthetic procedures as well as commercially available materials may contain variable amounts of metallic phosphate impurities, mainly produced during purification on silica gel columns.[9–13] However, the acid form can be regenerated by washing with aqueous HCl. These important discoveries have shed new light on the previously reported phosphoric acids promoted processes, since in most of them salt-contaminated catalysts were employed. Since metallic phosphates are known to catalyze a number of asymmetric reactions,[11,12,14–16] it is important to re-evaluate each process in order to verify if these impurities may affect the catalytic activity and the enantioselectivity. To this end, it could be useful to compare the results obtained in reactions catalyzed by phosphoric acids purified on silica gel with those observed by employing the catalyst washed with HCl. In cases where metallic phosphates did not present any appreciable catalytic activity, the treatment with HCl resulted only in improvement of the reaction rate, with no changes in enantioselectivity. In other cases a strong influence of metallic impurities has been observed. For example,

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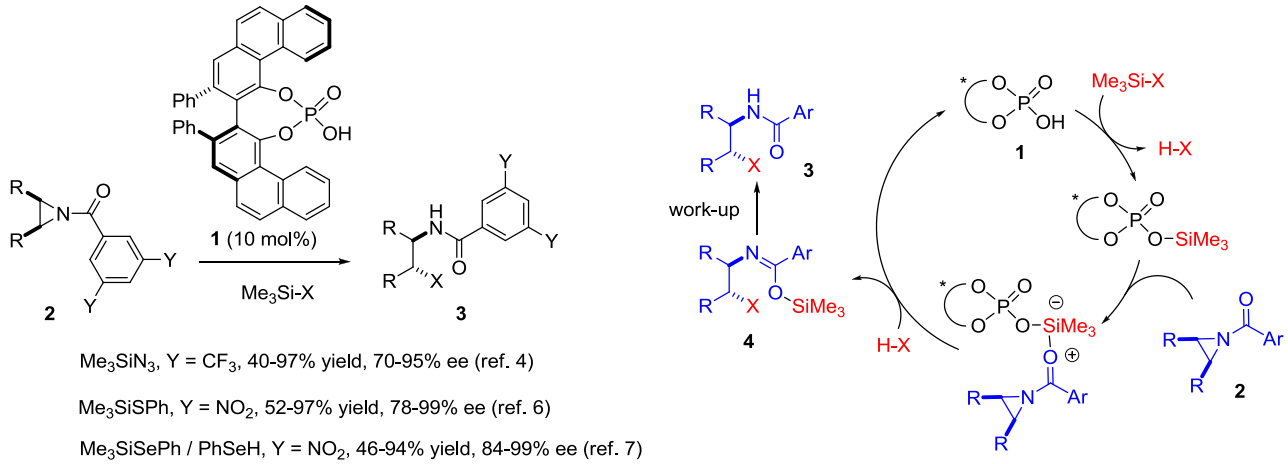


Scheme 1. VAPOL phosphate catalyzed desymmetrization of activated *meso*-aziridines with silylated nucleophiles as described in previous reports. Proposed catalytic cycle.

Ishihara and co-workers, during re-examination of a Mannich reaction previously developed by the Terada group,[1,17] observed for the first time a dramatic difference in the catalytic behavior of a BINOL derived phosphoric acid purified on silica gel with that of the compound successively washed with HCl.[11] Both the chiral phosphoric acid and its calcium phosphate salt, in fact, proved to catalyze the reaction but with the opposite sense of asymmetric induction. Lately, Antilla and co-authors reported marked differences in some reactions catalyzed by HCl washed chiral phosphoric acids and separately prepared metallic phosphates.[12] These findings prompted the group of Terada to re-consider some phosphoric acid catalyzed enantioselective addition to imines.[13] While in aza-Friedel–Crafts and aza-ene-type reactions the metal-free phosphoric acid were shown to be the active catalyst, in substitution of α-diazoacetates, a not-well determined metallic impurity proved to be involved.

In the light of the aforementioned accounts, we felt it useful to re-examine phosphoric acid catalyzed asymmetric reactions with silylated nucleophiles, with a special focus on the desymmetrization of *meso*-aziridines. During our previous studies, in fact, we made use of (*R*)-VAPOL hydrogen phosphate **1** prepared following the reported synthetic procedure,[18] or else the commercially available catalyst. Then, we wondered as to whether the true catalytic species involved in the process is the phosphoric acid itself or some adventitious salt impurity. In this regard, it should be considered that examples of asymmetric metal phosphate salt-catalyzed reactions through activation of silylated nucleophiles, are known.[19] Here, we describe the results of our study on the determination of the actual composition of synthetic phosphoric acid **1** and of the true active catalyst in the ring opening desymmetrization of *meso*-aziridines with different silylated nucleophiles.

2. Results and discussion

2.1. Analysis of VAPOL hydrogen phosphate prepared by the literature procedure

In our previous work on the desymmetrization of *meso*-aziridines[6,7] we used the catalyst **1** prepared according to literature procedures.[18] We observed similar enantioselectivities for products **3**, by using the commercially available catalyst. However, since these reports included the final purification of the product on silica gel, we envisaged the presence of significant amounts of salt impurities. Indeed, Antilla and co-workers recently reported that, in reactions with protic nucleophiles, **1** purified on silica gel showed a different catalytic behavior from the same compound successively washed with HCl.[12a–c]

Recently, List and co-authors demonstrated that basic phosphate impurities in a sample of phosphoric acid TRIP caused a shift of some of the NMR signals. We tried an analogous approach in order to evaluate the possible presence of phosphate salts in our sample of phosphoric acid **1**. The NMR spectrum of **1** in DMSO-d_6 is reported in Fig. 1(a). A nearly indistinguishable spectrum was obtained with a commercially available sample. The addition of 4 N NaOD in D_2O caused only small shifts of the doublet at δ 9.95 and of the singlet at δ 7.53 (Fig. 1(c)). These minor changes were due to the presence of D_2O rather than some acid–base reaction. The same changes, in fact, were observed after addition of the same volume of pure D_2O (Fig. 1(b)). On the other hand, when the solution of **1** in DMSO-d_6 was treated with 4 N DCl in D_2O, a clearly different spectrum resulted. Two especially pronounced shifts could be noticed, namely an upfield shift for a doublet, from δ 9.90 to δ 9.58, and a downfield shift for a singlet, from δ 7.51 to δ 7.65 (compare (b) and (d) in Fig. 1). These observations confirmed that the VAPOL hydrogen phosphate purified on silica gel, as well as the

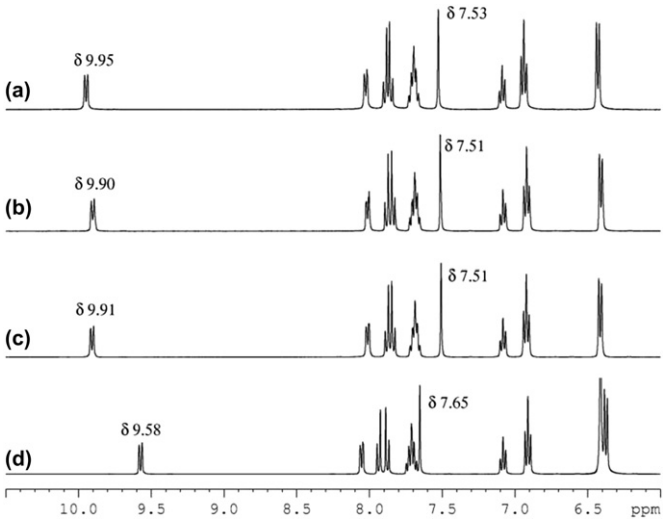


Fig. 1. ^{1}H NMR spectra in DMSO-d_6 of **1** purified on silica gel: (a) without additives; (b) after addition of D_2O; (c) after addition of 4 N NaOD in D_2O; (d) after addition of 4 N DCl in D_2O.

commercially available product, exists mostly in the form of basic phosphate salts. The same conclusion could be drawn from the ^{31}P NMR spectra (Fig. 2). The addition of D_2O to a solution of **1** in DMSO-d_6 caused a sharpening of the ^{31}P NMR signal and a small downfield shift from 1.03 to 1.24 ppm (compare (a) and (b) in Fig. 2). A further downfield shift to 1.65 ppm was observed upon addition of 4 N NaOD in D_2O (Fig. 2(c)), but a much more marked upfield shift to −0.33 ppm, resulted upon addition of 4 N DCl in D_2O (Fig. 2(d)).

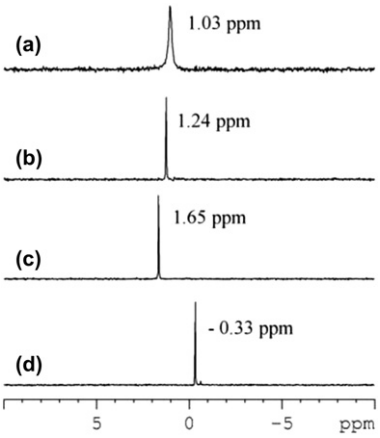


Fig. 2. ^{31}P NMR spectra in DMSO-d_6 of **1** purified on silica gel: (a) without additives; (b) after addition of D_2O; (c) after addition of 4 N NaOD in D_2O; (d) after addition of 4 N DCl in D_2O.

As reported in the literature,[9–13] the pure acidic form of **1**, could be easily regenerated by washing with 6 M HCl.[20] As expected, the elution through a silica gel column led to the formation of a material displaying a ^1H NMR spectrum identical to that of the synthetic compound **1** (Fig. 1(a)). No changes in the ^1H NMR spectrum were noticed after elution through a metal-free silica gel column.[21]

The relative contents of the various metal elements in a sample of phosphoric acid **1** purified on silica gel, were determined by Inductively Coupled Plasma-Optical Emission Spectrometry (ICP-OES). As shown in Table 1, the most abundant metal elements proved to be calcium and magnesium. Much lower levels of sodium were detected, although this element was previously found to be easily captured by purification of phosphoric acids on silica gel. Only traces of other elements could be detected. From the collected data, compound **1** purified on silica gel could be roughly estimated to exist at least in 80% of its amount in the form of metal salts.

Table 1
Trace metal analysis of **1** purified on silica gel, by ICP-OES

Metal element	Na	K	Ca	Mg	Cd	Pb
Content[a,b]	0.288	0.0069	19.36	8.70	0.00078	0.0109

[a] Values are in ppm.
[b] Cr, Fe, Al, Cu, Ni, As, Mn were not detected.

2.2. Determination of the true catalyst in the desymmetrization of *meso*-aziridines with different silylated nucleophiles

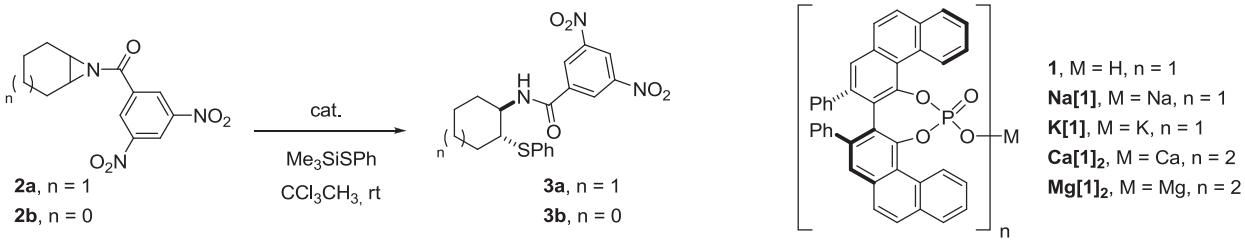
After having established that VAPOL hydrogen phosphate **1** synthesized by literature procedures consists in a mixture of phosphoric acid and metal salts, the next step was to determine, which is the active species in the desymmetrization of *meso*-aziridines with silylated nucleophiles. For this purpose, the desymmetrization of the cyclic six-membered aziridine **2a** with Me_3SiSPh was chosen as the model reaction. First, we used the catalyst **1** washed with 6 N HCl, under the usual reaction conditions previously adopted by us.[6] While the catalyst purified on silica gel readily promoted the highly enantioselective complete conversion of **2a** to (1*R*,2*R*)-**3a** in CCl_3CH_3 at room temperature (Table 2, entry 1), washing with HCl caused the catalytic activity to decrease. The conversion proved to be incomplete after 4 days, and **3a** was recovered in racemic form (entry 2). This finding led us to attribute to phosphate salts, rather than to phosphoric acid, the role of effective catalyst in this process.

Nevertheless, it was still possible to speculate on the mechanism, analogous to that proposed by Antilla, with phosphate ion, in place of phosphoric acid, involved in the activation of silane, with the resulting formation of a chiral Lewis acidic silyl phosphate. In order to assess this hypothesis, we treated a solution of **1** with DIPEA prior to the addition of reagents, to form its ammonium salt. At any rate, only a negligible increase of conversion was accomplished after four days and a racemate was again obtained (entry 3).

On the basis of these experiments we deduced that the presence of some metal species is essential to achieve high levels of activity and enantioselectivity. Then, we pursued the determination of the metal phosphate actually responsible for our best results. The most common alkali and alkaline earth metal salts of phosphoric acid **1** were prepared and screened against catalyst purified on silica gel. Interestingly the various salts exhibited a completely different behavior, suggesting the active involvement of the metal center in the reaction mechanism. Sodium and potassium salts **Na**[**1**] and **K**[**1**], catalyzed the ring-opening with low levels of enantioselectivity favoring the opposite enantiomer of **3a** (1*S*,2*S*) (entries 4 and 5). The alkaline earth metal phosphates **Ca**[**1**]$_2$ and **Mg**[**1**]$_2$ were more enantioselective, affording the same enantiomer obtained with the catalyst purified on silica gel (entries 6 and 7). The two salts showed a complementary effectiveness, being **Ca**[**1**]$_2$ less enantioselective but more active compared with **Mg**[**1**]$_2$. Unfortunately, even with these salts, the % ee values did not reach the high level obtained with **1** purified on silica gel. Then, we speculated that in the latter, actually a mixture of different VAPOL phosphate species, a cooperative effect of two or more catalysts might be working. The presence of the calcium salt looked to be essential, otherwise the reaction was too slow. In view of this, mixtures of two phosphate constituents were tested. A 2:1 mixture of **Ca**[**1**]$_2$ and the phosphoric acid **1** washed with HCl, afforded the product with a lower % ee (entry 8). To our delight a 1:1 mixture of **Ca**[**1**]$_2$ and **Mg**[**1**]$_2$ worked much better than single salts, furnishing a reaction rate and an enantioselectivity very close to those observed with **1** purified on silica gel (entry 9). Apparently, the properties of the two salts complement each other, so as to maximize the catalytic activity and the stereoselectivity. We performed analogous experiments with the five-membered *meso*-aziridine **2b**. The ring-opening desymmetrization promoted by **Ca**[**1**]$_2$ was incomplete after 23 h leading to **3b** with poor enantioselectivity (entry 10). The mixture **Ca**[**1**]$_2$/**Mg**[**1**]$_2$ 1:1, conversely, led to the same product in 4 h and with very high levels of enantioselectivity (entry 11), as previously reported by us with the catalyst purified on silica gel.[6]

We next diverted our attention to the efficiency of the phosphate catalysts with different silylated nucleophiles (Table 3). The desymmetrization of **2a** with Me_3SiSBn and Me_3SiSMe in CCl_3CH_3 at room temperature, promoted by **Ca**[**1**]$_2$/**Mg**[**1**]$_2$ 1:1, proceeded with good enantioselectivity (entries 1 and 2), even if the latter reagent gave better results when used in larger excess. These results are especially noteworthy since low enantioselectivities have so far been reported in the few examples of desymmetrization of *meso*-aziridines with benzylthiols and alkylthiols.[22] Moreover, acylated β-amino(benzyl)sulfides are very interesting from a synthetic point of view, because the removal of the benzyl group, furnished useful β-aminothiols.[23] Me_3SiNCS proved to be a remarkably more active silane. Under the usual conditions, the ring-

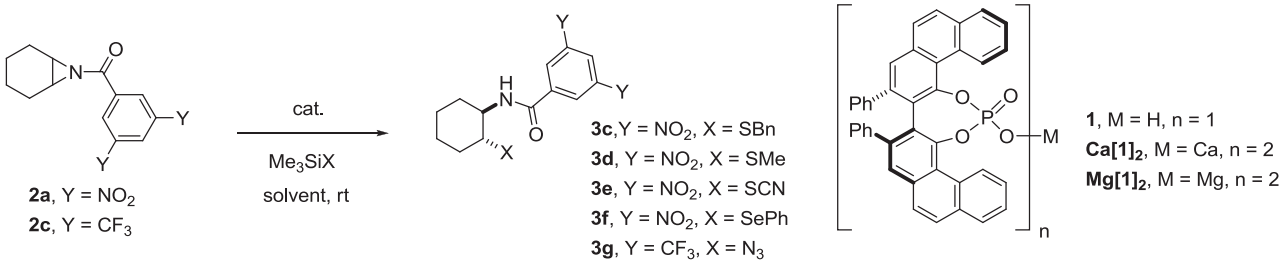
Table 2
Comparison of the efficiency of different VAPOL phosphates in the desymmetrization of aziridines **2a**,**b** with Me_3SiSPh[a]



Entry	Catalyst	Substrate **2**	Time/h	Yield[b]/%	ee[c]/% (absolute configuration)
1	**1** purified on silica gel	**2a**	2	100	92 (1*R*,2*R*)
2	**1** washed with HCl	**2a**	96	72	0
3	**1** washed with HCl, DIPEA	**2a**	96	77	0
4	**Na[1]**	**2a**	12	95	40 (1*S*,2*S*)
5	**K[1]**	**2a**	3	100	7 (1*S*,2*S*)
6	**Ca[1]$_2$**	**2a**	1	100	72 (1*R*,2*R*)
7	**Mg[1]$_2$**	**2a**	24	97	80 (1*R*,2*R*)
8	**Ca[1]$_2$/1** 2:1	**2a**	3	90	56 (1*R*,2*R*)
9	**Ca[1]$_2$/Mg[1]$_2$** 1:1	**2a**	3	94	90 (1*R*,2*R*)
10	**Ca[1]$_2$**	**2b**	23	84	37 (1*R*,2*R*)
11	**Ca[1]$_2$/Mg[1]$_2$** 1:1	**2b**	4	98	92 (1*R*,2*R*)

[a] Reactions performed at 0.08 mmol scale using **2** (1 equiv), Me_3SiSPh (1.5 equiv), and catalyst (0.10 equiv for **1**, **Na[1]** and **K[1]**; 0.05 equiv for metal phosphate salts **Ca[1]$_2$** and **Mg[1]$_2$**) in CCl_3CH_3 (0.1 M concentration), at room temperature, unless otherwise stated.
[b] Isolated yields.
[c] Determined by chiral HPLC.

Table 3
Desymmetrization of aziridines **2a**,**c** catalyzed by VAPOL phosphate salts with different silylated nucleophiles[a]



Entry	Nucleophile	Catalyst	Substrate **2**	Product **3**	Solvent	Time/h	Yield[b]/%	ee[c]/%
1	Me_3SiSBn	**Ca[1]$_2$/Mg[1]$_2$** 1:1	**2a**	**3c**	CCl_3CH_3	24	53	85
2[d]	Me_3SiSMe	**Ca[1]$_2$/Mg[1]$_2$** 1:1	**2a**	**3d**	CCl_3CH_3	48	67	82
3[e]	Me_3SiNCS	**Ca[1]$_2$/Mg[1]$_2$** 1:1	**2a**	**3e**	CCl_3CH_3	8	100	42
4[f]	$Me_3SiSePh$/PhSeH	**1** purified on silica gel	**2a**	**3f**	toluene	0.5	93	92
5[f]	$Me_3SiSePh$/PhSeH	**1** washed with HCl	**2a**	**3f**	toluene	96	35	0
6[f]	$Me_3SiSePh$/PhSeH	**Ca[1]$_2$/Mg[1]$_2$** 1:1	**2a**	**3f**	toluene	0.5	90	96
7[g,h]	Me_3SiN_3	**1** purified on silica gel	**2c**	**3g**	DCE	21	97	95
8[g]	Me_3SiN_3	**1** washed with HCl	**2c**	**3g**	DCE	72	49	6
9[g]	Me_3SiN_3	**Ca[1]$_2$/Mg[1]$_2$** 1:1	**2c**	**3g**	DCE	24	94	91

[a] Reactions performed at 0.08 mmol scale using catalyst (0.10 equiv for **1**; 0.05 equiv for metal phosphate salts), **2a**,**c** (1.0 equiv) and silylated nucleophile (1.5 equiv) in the appropriate solvent (0.1 M concentration) at room temperature, unless otherwise stated.
[b] Isolated yields.
[c] Determined by chiral HPLC.
[d] Me_3SiSMe (5.0 equiv) was used.
[e] Reaction performed at −20 °C.
[f] $Me_3SiSePh$ (0.5 equiv) and PhSeH (1.0 equiv) were used.
[g] Compound **2c** (1.5 equiv) and Me_3SiN_3 (1.0 equiv) were used.
[h] Ref. 4.

opening catalyzed with **Ca[1]$_2$/Mg[1]$_2$** 1:1 was very fast, and lowering of the temperature to −20 °C was found to be useful. The nucleophile reacted cleanly at the sulfur atom giving the β-aminothiocyanate **3e** in high yield and moderate enantioselectivity (entry 3). The result obtained, even if not fully satisfactory, is worth considering as the aziridine opening with thiocyanate nucleophiles has been extensively described,[24] but the only reported attempt of *meso*-aziridine desymmetrization promoted by a chiral catalyst afforded a racemic product.[25]

Based on the results described above, we intended to re-evaluate the desymmetrization of *meso*-aziridines with silylated selenium nucleophiles previously described by our group.[7] Ring-opening of **2a** with a 1:2 mixture of $Me_3SiSePh$ and PhSeH in toluene at room temperature, catalyzed by **1** purified on silica gel, was accomplished in 30 min with 92% ee (entry 4). As expected, the outcome changed dramatically when **1** washed with HCl was employed. Indeed, the reaction proved to be very slow, and was far from being complete after four days. Many byproducts were

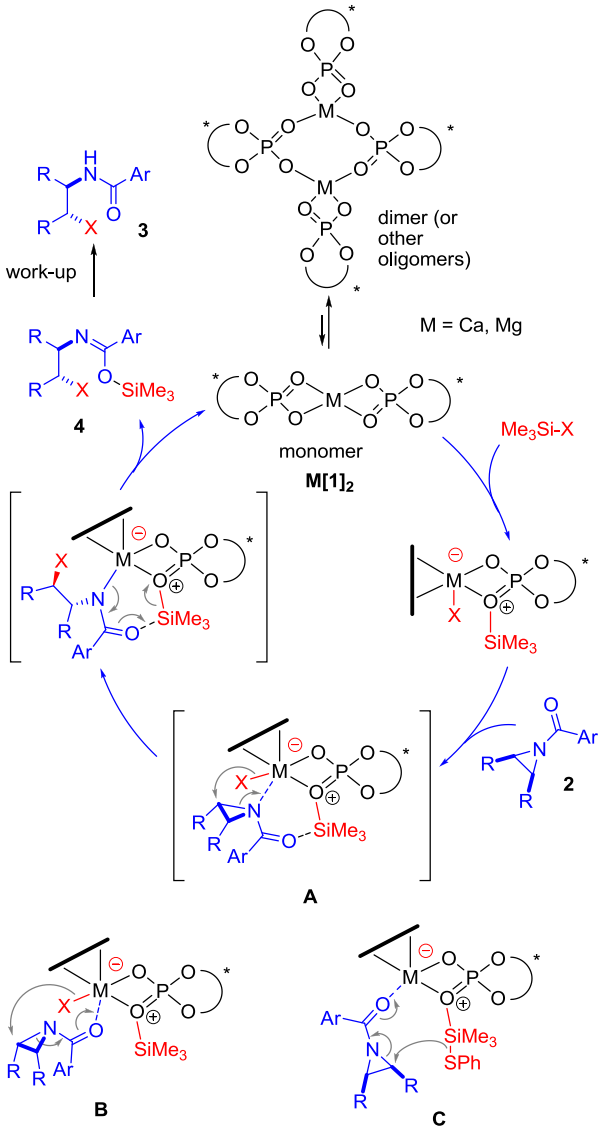
formed, and product **3a** was recovered as a racemate in poor yield (entry 5). Fortunately, as observed with sulfur nucleophiles, the former high enantioselectivity was reproduced by using the mixture of phosphate salts **Ca[1]$_2$/Mg[1]$_2$** 1:1 (entry 6).

To complete our study we became interested in re-examining the highly enantioselective desymmetrization reaction with Me_3SiN_3 previously reported by Antilla and co-workers.[4] In fact, although these authors did not clearly state if the phosphoric acid **1** had been purified or not on silica gel, we hypothesized, given the close similarities with the process developed by us, that the catalyst used might contain phosphate salts impurities as well. In our hands, ring-opening of the aziridine **2c**, promoted by **1** washed with HCl, in 1,2-dichloroethane (DCE) at room temperature, occurred in a strikingly different way from that described. A low conversion was achieved after long reaction time, many byproducts were formed, and the product **3g** was recovered in a nearly racemic form (cfr. entries 7 and 8). Once more, we were able to achieve high enantioselectivities and a clean transformation, by employing the mixture of catalysts **Ca[1]$_2$/Mg[1]$_2$** 1:1 (cfr. entries 7 and 9).

The data collected during our study demonstrated that phosphoric acids are not able to promote efficiently the ring-opening desymmetrization of *meso*-aziridines with silylated nucleophiles. The catalytic cycle proposed by the group of Antilla and later quoted by us (Scheme 1), must be ruled out. The actual mechanism should take into account that calcium and magnesium phosphate salts are indeed the catalytic active species. Although further investigations are necessary to propose an exact mechanism, the Lewis acidity of the metal center and the Lewis basicity of the phosphate ligands are likely to be involved. In this regard, Ishihara and co-authors, postulated the Lewis-base catalytic ability of lithium phosphate salts is in the cyanosilylation of ketones with Me_3SiCN.[19b] Along these lines we suggest the catalytic cycle depicted in Scheme 2 as a possible working hypothesis.

Recently, earth alkaline metal bis(phosphate) salts have been found to exist mainly as dimers or more complex oligomers, in equilibrium with the catalytic active monomer.[11,16b] The reaction of monomer with silane, is supposed to force the equilibrium away from the oligomers. We, in fact, observed that the sparingly soluble phosphate salts were dissolved completely in CCl_3CH_3 after addition of silanes. The metal phosphate/Me_3SiX activated complex presents two Lewis acidic sites on metal and silicon atoms. The *N*-acyl aziridine **2** might be activated by coordination to one of these Lewis acidic centers (alternative transition states B and C, Scheme 1) or even to both of them (transition state A), acting as a bidentate ligand. Then, the thiolate may conduct the nucleophilic attack either from inside or outside the coordination sphere of the metal. At any rate, the involvement of a hypervalent silicon intermediate cannot be ruled out (alternative transition state C). Finally, a silylation step has to occur, accordingly to the isolation of **4** reported by Antilla and co-workers.[4]

The rough mechanistic model outlined above, does not clarify the higher performance of the Ca/Mg combined catalyst compared to the single salts. Nevertheless, one may speculate that both metals play a key role in the catalytic cycle, whether as part of a bimetallic species, or as distinct monometallic molecules; one metal center might act as a Lewis acid, activating the aziridine, while the ligand attached to the other generates the reactive nucleophile. In this regard, some examples of aziridine desymmetrizations with silylated nucleophiles, promoted by bimetallic complexes, are known.[26]



Scheme 2. Proposed catalytic cycle, and alternative transition state models, for the earth alkaline metal VAPOL phosphate catalyzed desymmetrization of *meso*-aziridines.

3. Conclusions

In summary, we have clearly demonstrated that metal-free phosphoric acid **1** is not able to promote efficiently the ring-opening desymmetrization of *meso*-aziridines with silylated nucleophiles. The activity and enantioselectivity previously observed by us and others can actually be ascribable to the combined action of calcium and magnesium phosphate salts, present as adventitious impurities in the phosphoric acid purified on silica gel. Reproducible results could be obtained by using a 1:1 mixture of calcium and magnesium VAPOL phosphate salts as the catalyst. This process has been extended to a broad range of silylated nucleophiles. We suggest metal phosphates might operate through a dual Lewis acid–base activation mechanism. We believe that our findings may offer valuable clues in the study of processes with silylated nucleophiles promoted by phosphoric acid and other Brønsted acids. Specific experiments will be required, addressed to confirm the capacity of these compounds in activating the nucleophile, and precluding significant involvement of metal salt impurities. Further studies along these lines are currently under way in our laboratory.

4. Experimental section

4.1. General information

All the aziridine desymmetrizations were performed in flame-dried Schlenk tubes, under a dry nitrogen atmosphere and with

magnetic stirring. Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel plates (0.25 mm) and visualized by UV light or by phosphomolybdic acid/ethanol spray test. Flash chromatography was performed on Merck silica gel (60, particle size: 0.040–0.063 mm). ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra were recorded on Bruker DRX 400 and 300 spectrometers at room temperature in $CDCl_3$, DMSO-d_6 or acetone-d_6 as solvents. Chemical shifts for protons are reported using residual $CHCl_3$ (δ=7.26), CD_3SOCHD_2 (δ=2.50) or CD_3COCHD_2 (δ=2.04) as internal references. Carbon spectra are referenced to the shift of the ^{13}C signal of $CDCl_3$ (δ=77.0) or acetone-d_6 (δ=206.7). ^{13}P NMR spectra were recorded using H_3PO_4 as an external standard. Optical rotation measurements were performed on a Jasco DIP-1000 digital polarimeter using the Na lamp. FT-IR spectra were recorded on a Bruker Vertex 70 spectrophotometer. ESI-MS was performed using a Bio-Q triple quadrupole mass spectrometer (Micromass, Manchester, UK) equipped with an electrospray ion source. Optical Emission Spectrometry (ICP-OES) analysis was performed using an Optima 7000DV (Perkin–Elmer) instrument. Elemental analyses were carried out by using Flash EA 1112 (Thermo Electron Corporation) analyzer. Enantiomeric excesses were measured by HPLC (Jasco PU-2089 quaternary gradient pump equipped with an MD-2010 plus adsorbance detector) using Daicel Chiralcel AD-H and AS-H chiral columns.

All the solvents used in moisture sensitive reactions were distilled over calcium hydride and stored over activated molecular sieves, except for anhydrous 1,2-dichloroethane, which was purchased from Aldrich. (*R*)-VAPOL hydrogen phosphate **1** purified on silica gel,[18] **1** washed with HCl,[12a–c] as well as salts **Na**[**1**], **K**[**1**], **Ca**[**1**]$_2$, and **Mg**[**1**]$_2$,[12a–c] were prepared as described in literature. The nucleophiles (phenylthio)trimethylsilane, (methylthio)trimethylsilane, trimethylsilyl isothiocyanate, and azidotrimethylsilane, were purchased from Aldrich and used without further purification. (Benzylthio)trimethylsilane[27] and (phenylseleno)trimethylsilane[28] were prepared according to literature procedures. The acylaziridines **2a**–**c** were synthesized as described in literature, by opening of epoxides with sodium azide, followed by Staudinger rearrangement of azido alcohols and then in situ acylation of unsubstituted aziridines with aroyl chlorides and triethyl amine.[4,29]

4.2. NMR analysis of VAPOL hydrogen phosphate purified on silica gel, after treatment with acid or base (Figs. 1 and 2)

The sample for the reference ^{1}H and ^{31}P NMR spectra was prepared by dissolving **1** purified on silica gel (5 mg) in DMSO-d_6 (0.5 mL). The other spectra were recorded after treatment of this sample with D_2O, 4 N NaOD in D_2O and 4 N DCl in D_2O (40 μL), respectively.

4.3. Preparation of the sample for trace element analysis (ICP-OES)

A solution of VAPOL hydrogen phosphate **1** purified on silica gel (21.5 mg) in CH_2Cl_2 (1.0 mL) was treated with 3.7 M aqueous HNO_3 (10.0 mL), and the mixture was stirred overnight. An aliquot of the aqueous phase (2.45 mL) was removed and diluted with deionized H_2O (up to 5.0 mL). The resulting solution was submitted to ICP-OES analysis.

4.4. General procedure for the desymmetrization of *meso*-aziridines 2a–c with silylated nucleophiles catalyzed by Ca[1]$_2$/Mg[1]$_2$ 1:1

To a solution of phosphates **Ca**[**1**]$_2$ (2.5 mg, 0.0020 mmol) and **Mg**[**1**]$_2$ (2.5 mg, 0.0020 mmol) in the appropriate anhydrous solvent (0.8 mL), the silane was added (0.080–0.40 mmol). The mixture was stirred for 10 min and then the aziridine **2a**–**c** was added (0.080–0.120 mmol). After stirring for the appropriate time (see Tables 2 and 3), CH_2Cl_2 was added until dissolution of the precipitate, and then the solution was passed through a plug of silica gel eluting with CH_2Cl_2 (3 mL) and then ethyl acetate (3 mL). The solvent was removed under reduced pressure and the residue was purified by FC (silica gel, eluent: $CHCl_3$ for **3a**,**b**; petroleum ether/ethyl acetate mixtures from 95:5 to 70:30 for **3c**,**d**,**g**; CH_2Cl_2/acetone mixtures from 100:0 to 98:2 for **3e**). The characterization data of the opening products **3a**,**b**[6] and **3g**[4] were identical to those previously reported and the enantiomeric purity was determined by chiral HPLC as therein described.

4.5. Spectral data of products 3c–e

*4.5.1. (1R,2R)-1-Benzylthio-2-[N-(3,5-dinitrobenzoyl)amino] cyclohexane (**3c**).* White solid; mp 152–157 °C (dec); $[\alpha]_D^{20}$ −40.4 (*c* 0.8, $CHCl_3$, 85% ee); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.14 (t, *J*=1.9 Hz, 1H), 8.84 (d, *J*=1.9 Hz, 2H), 7.33–7.22 (m, 4H), 7.19 (m, 1H), 6.22 (d, *J*=6.8 Hz, 1H), 3.87 (m, 1H), 3.81–3.66 (m, 2H), 2.52 (dt, *J*=11.2, 3.4 Hz, 1H), 2.40–2.19 (m, 21H), 1.91–1.72 (m, 2H), 1.64 (m, 1H), 1.45 (m, 1H), 1.37–1.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4, 148.6, 138.6, 138.3, 128.8, 128.7, 127.3, 127.2, 120.9, 52.9, 48.4, 33.8, 33.6, 33.4, 26.0, 24.6; FT-IR (KBr): ν/cm^{-1}: 3272, 3106, 3086, 2922, 2855, 1648, 1539, 1343, 915, 730, 706; MS (ESI): *m*/*z*: 454 $[M+K]^+$; elemental analysis calcd (%) for $C_{20}H_{21}N_3O_5S$: C 57.82, H 5.09, N 10.11, S 7.72; found: C 58.12, H 5.37, N 9.97, S 7.63; HPLC (Chiralcel AD-H, hexane/^{i}PrOH 80:20, λ=220 nm, 1.0 mL min^{-1}): t_{minor}=11.6 min, t_{major}=13.1 min.

*4.5.2. (1R,2R)-1-Methylthio-2-[N-(3,5-dinitrobenzoyl)amino] cyclohexane (**3d**).* White solid; mp 173–175 °C; $[\alpha]_D^{20}$ −80.2 (*c* 0.8, $CHCl_3$, 82% ee); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.16 (t, *J*=2.1 Hz, 1H), 8.96 (d, *J*=2.1 Hz, 2H), 6.54 (d, *J*=6.9 Hz, 1H), 3.92 (m, 1H), 2.57 (dt, *J*=11.2, 3.7 Hz, 1H), 2.39 (m, 1H), 2.20 (m, 1H), 2.06 (s, 3H), 1.91–1.75 (m, 2H), 1.70–1.55 (m, 1H), 1.54–1.17 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4, 148.6, 138.3, 127.2, 121.0, 52.4, 48.9, 33.5, 32.4, 26.0, 24.7; FT-IR (KBr): ν/cm^{-1}: 3320, 3097, 2930, 2858, 1644, 1543, 1341, 1076, 917, 730, 722; MS (ESI): *m*/*z*: 378 $[M+K]^+$; elemental analysis calcd (%) for $C_{14}H_{17}N_3O_5S$: C 49.55, H 5.05, N 12.38, S 9.45; found: C 49.81, H 5.24, N 12.29, S 9.54; HPLC (Chiralcel AD-H, hexane/^{i}PrOH 90:10, λ=220 nm, 1.0 mL min^{-1}): t_{major}=17.3 min, t_{minor}=20.1 min.

*4.5.3. (1R,2R)-3,5-Dinitro-N-(2-thiocyanatocyclohexyl) benzamide (**3e**).* White solid; mp 167–168; $[\alpha]_D^{20}$ −82.4 (*c* 0.6, acetone, 42% ee); ^{1}H NMR (400 MHz, acetone-d_6): δ 9.08 (app. s, 3H), 8.66 (d, *J*=7.8 Hz, 1H), 4.18 (m, 1H), 3.54 (dt, *J*=11.5, 4.0 Hz, 1H), 2.37 (m, 1H), 2.18 (m, 1H), 1.93–1.75 (m, 3H), 1.74–1.61 (m, 1H), 1.60–1.39 (m, 2H); ^{13}C NMR (100 MHz, acetone-d_6): δ 163.5, 150.1, 138.8, 128.8, 122.3, 112.0, 54.7, 53.9, 35.0, 34.5, 27.1, 25.8; FT-IR (KBr): ν/cm^{-1}: 3379, 3333, 3110, 3092, 2944, 2925, 2859, 2153, 1662, 1592, 1345, 1074, 916, 730, 721; MS (ESI): *m*/*z*: 373 $[M+Na]^+$; elemental analysis calcd (%) for $C_{14}H_{14}N_4O_5S$: C 47.99, H 4.03, N 15.99, S 9.15; found: C 48.05, H 4.14, N 15.91, S 9.06; HPLC (Chiralcel AD-H, hexane/^{i}PrOH 90:10, λ=220 nm, 1.0 mL min^{-1}): t_{major}=23.8 min, t_{minor}=31.1 min.

4.6. Desymmetrization of *meso*-aziridine 2a with Me$_3$SiSePh/PhSeH catalyzed by Ca[1]$_2$/Mg[1]$_2$ 1:1

To a suspension of phosphates **Ca**[**1**]$_2$ (2.5 mg, 0.0020 mmol) and **Mg**[**1**]$_2$ (2.5 mg, 0.0020 mmol) in anhydrous toluene (0.8 mL), $Me_3SiSePh$ was added (9.1 mg, 0.040 mmol). The mixture was stirred for 10 min, after which the solid dissolved. Then PhSeH (12.7 mg, 0.080 mmol) and the aziridine **2a** (23.2 mg, 0.080 mmol) were added. After stirring for 30 min, CH_2Cl_2 was added until

dissolution of the precipitate, and then the solution was passed through a plug of silica gel eluting with CH_2Cl_2 (3 mL) and then ethyl acetate (3 mL). The solvent was removed under reduced pressure and the residue was purified by FC (silica gel, eluent: $CHCl_3$). The characterization data of the opening product **3f** were identical to those previously reported and the enantiomeric purity was determined by chiral HPLC as therein described.[7]

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Supplementary data

Copies of ^{1}H NMR and ^{13}C NMR spectra for the unreported products. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.10.068.

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