

Chemoselective Catalysis with Organosoluble Lewis Acidic Polyoxotungstates

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Abstract: The preparation of new organosoluble Lewis acidic polyoxometalates (POMs) is reported. These complexes were prepared by the incorporation of Zr, Sc, and Y atoms into the corresponding monolacunary Dawson [P₂W₁₇O₆₁]¹⁰⁻ and Keggin [PW₁₁O₃₉]⁷⁻ polyoxotungstates. The catalytic activity of these compounds was evaluated for C–C bond formation in the Diels–Alder, Mannich, and Mukaiyama-type

reactions. Comparisons with previously described Lewis acidic POMs are reported. Competitive reactions between imines and aldehydes or between various imines demonstrated that fine tuning of the reactivity could be reached by varying the metal atom in-

corporated into the polyanionic framework. A series of experiments that employed pyridine derivatives allowed us to distinguish between the Lewis and induced Brønsted acidity of the POMs. These catalysts activate imines in a Lewis acidic way, whereas aldehydes are activated by indirect Brønsted catalysis.

Keywords: aldol reaction • imines • Lewis acids • polyoxometalates

Introduction

Since the beginning of polyoxometalate (POM) chemistry, catalysis and POMs have been closely associated. This connection is largely due to the chemical properties of those early transition-metal–oxo complexes, that is, most commonly V^V, Mo^{VI}, and W^{VI} centers, which are electron acceptors or strong Brønsted acids (in their protonated form).^[1] POMs can also form peroxy complexes and can support highly oxidized metal ions or other catalytically active organometallic groups, which increase their appeal for synthetic chemists.^[2] Yet, because of these properties, catalysis by POMs^[3] has remained mostly confined to oxidation and acid-catalyzed transformations.^[4]

We have introduced Lewis acidic POMs that have opened new options.^[5] Lewis acidity was introduced by modular

grafting Lewis acidic cations onto phosphotungstic backbones, which allowed modulation of the catalytic activities.^[6] Besides, owing to the specific solubilities of POMs, the catalysts were easily recovered. Herein, we give an overview of our contribution to Lewis acidic POM chemistry. Where appropriate, some of our previous results are rediscussed to give a better understanding of the systems.

Results and Discussion

Choice of the catalysts: We surmised that the charges and ionic radii of the cations grafted onto the polyoxotungstic backbone would play a primary role in the reactivity of the POMs. Therefore, we selected a large array of Lewis acidic cations: La³⁺, Eu³⁺, Sm³⁺, and Yb³⁺ ions were chosen as early-, mid-, and late-lanthanide centers. The Sc³⁺ and Y³⁺ ions were logical variations outside the lanthanide group, and Zr⁴⁺ and Hf⁴⁺ ions were chosen as representatives of more charged and smaller Lewis acidic cations.

Because of our previous experiences with the Dawson and Keggin polyoxotungstates,^[7] we selected the α_1 -Dawson lacunary platform to graft the cations onto. The inherent chirality of this platform leaves the door open for potential asymmetric catalysis, should there be a way to obtain an enantiopure form.^[8] Besides, the catalytically active moiety would be embedded in the belt of the POM, thus resulting

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in lower proportions of sandwich POM structures if Lewis acidic atoms with high coordination numbers, such as lanthanide atoms, were used.^[9,10] The reactivity of the catalyst is certainly governed by the available coordination sites on the metal center. To get an idea of the role of the charge of the heteropolyanion, we also considered the Keggin lacunary phosphotungstate as a suitable platform.

The syntheses of the organo-soluble Lewis acids complexes have been reported for lanthanide and hafnium cations. Similar methodologies were used for Zr^{4+} , Sc^{3+} , and Y^{3+} ions (see the Supporting Information). For lanthanide POM derivatives, full control of the pH value has to be taken: under no circumstances it should exceed pH 4.5 to avoid the presence of lacunary species. The addition of aqueous HCl (1 M) was used to maintain the pH value of the reaction mixture under the acceptable limit. The addition of excess tetrabutylammonium bromide (TBABr) causes the precipitation of the TBA salts of the POM derivatives. These complexes generally precipitate with four water molecules bound to the metal center.

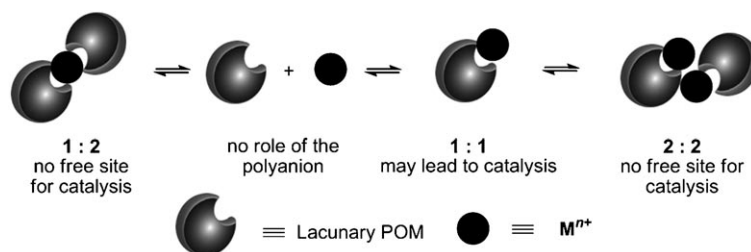
Factors that govern the reactivity of the Lewis acidic POMs:

It was expected that the polyoxometallic backbone would play a significant role in the reactivity. We identified three essential factors in understanding and/or predicting the behavior of the POMs.

Charge: The inorganic ligand is anionic and loss of activity of the cation was foreseen. Modulation could arise from tuning of the overall cluster charge, which could be adjusted through synthesis upon appropriate choice of both the polyoxotungstic framework and the embedded Lewis acidic cation.

Ionic radii of the cations: The ionic radii of the cations that we use vary greatly, from Sc^{3+} to La^{3+} ions.^[11] Therefore, the cation is more or less deeply inserted in the lacuna. As a consequence, the stereoelectronic influence of the polyoxometallic backbone should be more or less pronounced. In particular, smaller cations would be less accessible than larger ones, and thus less reactive. Additional bonding of the metal cation to an oxygen atom of the closest phosphate group may develop with small cations that fit better into the lacuna. Larger cations cannot reach deeply enough to allow this bonding. Conceivably, because the POM charge is denser on the inside,^[12] such a bonding pattern should transfer additional electron density to the cation and further decrease its Lewis acidity. On the other hand, smaller and/or more charged cations have higher intrinsic charge densities, which should increase their acidity. These conflicting trends should allow precise fine-tuning of the reactivities.^[13]

Polyoxometalate speciation: Larger cations have high coordination numbers (typically 8 and 9). Several equilibria occur in solution (Scheme 1). In particular, sandwich 1:2 and dimeric 2:2 structures would preclude or decrease catalytic activity—relative to the 1:1 complex—because they have none or less free sites for complexation of the substrates. Thus, the relative ratios of 1:1 versus 1:2/2:2 species should



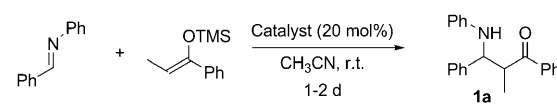
Scheme 1. Speciation equilibria of Lewis acidic polyoxotungstates.

strongly impact the catalytic activity. The speciation depends on the relative steric hindrance and electronic interactions of the polyanionic inorganic ligands. This consideration directed us to consider the α_1 lacunary platform, which was known in the lanthanide series to relatively favor 1:1 complexes over sandwich 1:2 in aqueous solution.^[9] In this context, it is also important to note that ligands that can bind to a POM/lanthanide complex displace the equilibria towards the 1:1 species.^[9d]

Application of imines in the catalysis: We focused on the Lewis acid-catalyzed Mannich reaction between aldimines and silyl enol ethers as a representative benchmark reaction for our catalysts. Acetonitrile was chosen because the TBA salts of our complexes are soluble in polar solvents such as acetonitrile, DMF, or dimethyl sulfoxide (DMSO). A typical reaction was carried out in acetonitrile (0.2 M) at room temperature with benzylideneaniline as the electrophile, a trimethylsilyl enol ether derived from propiophenone, and the substituted POM complex (Table 1). Catalyst POM/La gave β -amino ketone **1a** in 81% yield after two days. As is often the case with lanthanide Lewis acids, the relative configuration of the ketoimine was not controlled (less than 30% *de*). We did not try to improve the diastereoselectivity, but concentrated on the efficiency of the reaction.

The reactions were catalyzed by all the α_1 -[$MP_2W_{17}O_{61}$]ⁿ⁻ complexes (Table 1, entries 1–8), thus confirming our initial hypothesis that Lewis acidic POMs can be obtained through metal substitution. When the lanthanide complexes were used, the reactions took two days to reach completion (Table 1, entries 1–4). The same reaction with $Yb(OTf)_3$ (OTf = triflate) was over in only two hours. This outcome was expected (see above) because the oxo ligands of the lacunary polyanion decrease the overall Lewis acidity of the embedded cations. The activity of the yttrium complex was slightly higher than that of the lanthanide complexes (one day to completion; Table 1, entry 6), whereas the activity of

Table 1. Evaluation of the catalysts in a Lewis acidic POM-catalyzed Mannich reaction.



Entry	Catalyst	(abbreviation)	Yield [%]
1	TBA ₃ H ₂ [α ₁ -La(H ₂ O) ₄ P ₂ W ₁₇ O ₆₁]	(POM/La)	81 ^[a]
2	TBA ₃ H ₂ [α ₁ -Sm(H ₂ O) ₄ P ₂ W ₁₇ O ₆₁]	(POM/Sm)	91 ^[a]
3	TBA ₃ H ₂ [α ₁ -Eu(H ₂ O) ₄ P ₂ W ₁₇ O ₆₁]	(POM/Eu)	71 ^[a]
4	TBA ₃ H ₂ [α ₁ -Yb(H ₂ O) ₄ P ₂ W ₁₇ O ₆₁]	(POM/Yb)	96 ^[a]
5	TBA _{3.5} K _{0.5} Na _{0.5} H _{0.5} [α ₁ -Sc-(H ₂ O) ₄ P ₂ W ₁₇ O ₆₁]	(POM/Sc)	66 ^[b,c]
6	TBA _{4.5} K _{0.5} H ₂ [α ₁ -Y(H ₂ O) ₄ P ₂ W ₁₇ O ₆₁]	(POM/Y)	85 ^[b]
7	TBA ₃ K[α ₁ -Hf(H ₂ O) ₄ P ₂ W ₁₇ O ₆₁]	(POM/Hf)	85 ^[a]
8	TBA ₃ K[α ₁ -Zr(H ₂ O) ₄ P ₂ W ₁₇ O ₆₁]	(POM/Zr)	84 ^[b]
9	TBA ₄ [α-Yb(H ₂ O) ₄ PW ₁₁ O ₃₉]		< 5 ^[d]
10	TBA ₄ [α-Sc(H ₂ O)PW ₁₁ O ₃₉] ^a		55 ^[b]

[a] See ref. [5a]. [b] This study. [c] Six days to reach completion. [d] Dimeric in the solid state.

the scandium complex was much lower, thereby producing **1a** in only 66% yield after six days (Table 1, entry 5). The Sc³⁺ ion is much smaller than the Yb³⁺ ion; therefore, deeper embedding of the cation in the lacuna and the decreased number of available coordination sites are the predominant factors that influence the reactivity. As anticipated, the hafnium and zirconium complexes, which include cations with a formal charge of 4+, seem more reactive than the corresponding lanthanide complexes (Table 1, entries 7 and 8; 85 and 84% yield of the isolated products after less than a day, respectively).

The Keggin series behaved differently (Table 1, entries 9 and 10). First of all, less than 5% conversion was observed after two days with the Yb/Keggin complex (Table 1, entry 9). At first glance, this outcome was surprising because the lacunary Keggin platform is less charged (4-) and might cause a smaller decrease in the Lewis acidic character of the Yb substituent than the lacunary Dawson ion (7-). We attributed this behavior to the persistence of the dimeric 2:2 form in solution, with a resulting decrease in the amount of active 1:1 Yb-substituted Keggin complex. Indeed, X-ray crystallographic studies showed that this complex is a 2:2 [(Yb(H₂O)(PW₁₁O₃₉))₂(μ-H₂O)₂]⁸⁻ dimer in the solid state, in which two {YbPW₁₁O₃₉}⁴⁻ units are bridged by two water molecules.

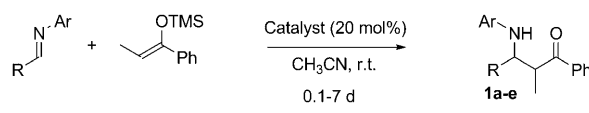
The Sc/Keggin POM led to **1a** in 55% yield after two days (Table 1, entry 10), which is similar to the yield of the parent Sc/Dawson complex. We think this finding may also be explained by the POM speciation. Contrary to the Yb³⁺ ion, the Sc³⁺ ion can only have six ligands in its coordination sphere. Thus, only 1:1 complexes exist in solution, regardless of the POM structure. We can gather from this set of reactions that the POM charge has no strong influence on reactivity. This conclusion matches the one that might have been reached upon considering the model developed by Day and Klemperer of the heteropolyoxotungstates as

neutral inorganic cages with a charged core.^[12a] From this perspective, there is no real difference between the Keggin and Dawson series.

The small changes observed for the scandium complexes may be due to the different geometries and the increased bonding with the internal phosphate group in the Keggin complex relative to the Dawson complex. One should remain cautious in interpreting these results. Some elements of rationalization have been given, but further discussion of the mechanism is developed later. Nonetheless, it was clear at this stage that polyoxometalates could be made Lewis acidic and that subtle variations of the reactivities stemmed from variations not only of the metal cation, but also of the polyoxotungstic backbone.

Various imines were tested to determine the scope of the reaction (Table 2). The reactivity generally reflected the electronic characteristics of the imines. Electron-donating

Table 2. Variation of the imine in a Lewis acidic POM-catalyzed Mannich Reaction.



Entry	R	Ar	Catalyst	Product	Yield [%]
1	Ph	Ph	POM/Yb	1a	96 ^[a]
2	Ph	<i>o</i> -HOC ₆ H ₄	POM/Yb	1b	84 ^[a]
3	Ph	<i>o</i> -HOC ₆ H ₄	POM/Hf	1b	75
4	Ph	<i>p</i> -MeOC ₆ H ₄	POM/Yb	1c	81 ^[a]
5	CO ₂ Et	Ph	POM/Yb	1d	70 ^[a]
6	CO ₂ Et	Ph	POM/Yb	1d	71 ^[b]
7	CO ₂ Et	Ph	POM/Hf	1d	96 ^[c]
8	CO ₂ Et	Ph	POM/Hf	1d	81 ^[b]
9	CO ₂ Et	Ph	POM/Zr	1d	91
10	CO ₂ Et	<i>p</i> -MeOC ₆ H ₄	POM/Y	1e	87
11	CO ₂ Et	<i>p</i> -MeOC ₆ H ₄	POM/Yb	1e	77 ^[a]
12	CO ₂ Et	<i>p</i> -MeOC ₆ H ₄	POM/Hf	1e	99 ^[c]
13	CO ₂ Et	<i>p</i> -MeOC ₆ H ₄	POM/Hf	1e	77 ^[b]
14	CO ₂ Et	<i>p</i> -MeOC ₆ H ₄	POM/Zr	1e	91
15	CO ₂ Et	<i>p</i> -MeOC ₆ H ₄	POM/Zr	1e	64 ^[b]

[a] See ref. [5a]. [b] Catalyst loading: 2 mol%. [c] See ref. [5b].

groups on the nitrogen atom decreased the rates of the reactions (Table 2, entries 2–4). The reaction with *para*-methoxyphenylimine was really sluggish (6 days to reach completion; Table 2, entry 4), less so with the *ortho*-hydroxyphenylimine (3 days to reach completion; Table 2, entry 2). On the contrary, electron-withdrawing groups attached to the carbon atom of the imines, such as the glyoxalate derivatives, led to extremely fast reactions (around 1 h), even when the donor groups were simultaneously introduced on the nitrogen atom (Table 2, entries 5–14). This result prompted us to decrease the catalyst loading. Gratifyingly, the reactions of the aniline-derived glyoxalate imine still worked with 2 mol% of catalyst, although the reactions took up to three days to reach completion (Table 2, entries 6, 8, 13, and 15). The Zr and Y complexes compare well with the Hf and Yb catalysts (Table 2, entries 10–14).

Variation of the nucleophile involved in the reaction was examined next (Table 3). A simple silyl enol ether derived from acetophenone worked equally well in less than one

Table 3. Variation of the nucleophile in a Lewis acidic POM-catalyzed Mannich reaction.

Entry	Electrophile	Nucleophile	Product	Catalyst	Yield [%]
1				POM/ Yb	98
2				POM/ Hf	92
3				POM/ Zr	94
4				POM/ Hf	70
5				POM/ Zr	63
6				POM/ Yb	98
7				POM/ Hf	90
8				POM/ Hf	84
9				POM/ Zr	89
10				POM/ Hf	76
11				POM/ Zr	77
12				POM/ Hf	70
13				POM/ Zr	58

hour, whether with diphenylimine (Table 3, entries 1–3) or the pyruvate derivative (Table 3, entries 4 and 5). The reactions could be extended to thioester-derived silyl enol esters with the same efficiency (Table 3, entries 6 and 7). The commercially available (furan-2-yl)trimethylsilane allowed vinylogous Mannich reactions in less than 12 hours (Table 3, entries 8–13). All the reactions that led to products **1f–k** proceeded with rates and yields comparable to those observed for the preceding reactions and seemed to be more sensitive to the nature of the electrophile and the catalyst used rather than the nucleophile.

Encouraged by these results, we looked at other reactions of imines (Table 4). The hetero-Diels–Alder reaction was a logical extension to our investigation. Treated with diphenylimine in the presence of the

POM catalysts, the Danishefsky diene typically delivered the desired heterocycle in good yield (Table 4, entries 1–4). The reaction was very versatile, although the Y complex was surprisingly, yet consistently, less efficient in that case (e.g., **2a** in 67% yield after 24 h versus 88% yield in 5 h for the Zr complex; Table 4, entries 3 and 4). Again, we seemed to be facing very minute modulations of the reactivities of the POMs. As previously noted, the pyruvate derivative reacted faster, but the yield was poor, most probably because of the imine self-condensation (Table 4, entry 14).

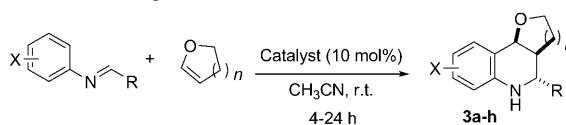
We investigated the aza-Diels–Alder reaction involving the imine as the diene and a cyclic enol ether as the dienophile (Table 5). The tricyclic products that can be obtained thanks to this reaction have three contiguous stereogenic centers. We hoped that the increased strain during the formation of cyclic molecules would lead to more diastereoselective reactions.

Table 4. Aza-Diels–Alder reactions with the Danishefsky diene.

Entry	R	Ar	Catalyst	Product	Yield [%]
1	Ph	Ph	POM/Yb	2a	89 ^[a]
2	Ph	Ph	POM/Hf	2a	84 ^[b]
3	Ph	Ph	POM/Zr	2a	88
4	Ph	Ph	POM/Y	2a	67
5	Ph	<i>p</i> -MeOC ₆ H ₄	POM/Yb	2b	98 ^[a]
6	Ph	<i>p</i> -MeOC ₆ H ₄	POM/Hf	2b	90 ^[b]
7	Ph	<i>p</i> -MeOC ₆ H ₄	POM/Zr	2b	90
8	Ph	<i>p</i> -MeOC ₆ H ₄	POM/Y	2b	81
9	Ph	<i>p</i> -ClC ₆ H ₄	POM/Yb	2c	76 ^[a]
10	Ph	<i>p</i> -ClC ₆ H ₄	POM/Hf	2c	69 ^[b]
11	Ph	<i>p</i> -ClC ₆ H ₄	POM/Y	2c	68
12	Ph	<i>o</i> -HOC ₆ H ₄	POM/Yb	2d	57 ^[a]
13	Ph	<i>o</i> -HOC ₆ H ₄	POM/Y	2d	44
14	CO ₂ Et	<i>p</i> -MeOC ₆ H ₄	POM/Yb	2e	23

[a] See ref. [5a]. [b] See ref. [5b].

Table 5. Aza-Diels–Alder reaction using an imine as the diene.



Entry	R	Ar	<i>n</i>	Catalyst	3	Yield [%] ^[a]	d.r. ^[a]
1	Ph	Ph	1	POM/Yb	3a	67 (80)	60:40 (50:50) ^[b]
2	Ph	Ph	1	POM/Hf	3a	48	60:40
3	Ph	Ph	2	POM/Yb	3b	79 (89)	80:20 (50:50) ^[b]
4	Ph	Ph	2	POM/Hf	3b	0 ^[c]	–
5	Ph	<i>o</i> -HOC ₆ H ₄	1	POM/Yb	3c	63 ^[d] (74)	90:10 (55:45) ^[b]
6	Ph	<i>o</i> -HOC ₆ H ₄	1	POM/Y	3c	48 ^[d]	80:20
7	Ph	<i>o</i> -HOC ₆ H ₄	1	POM/Hf	3c	87 ^[d]	60:40
8	Ph	<i>o</i> -HOC ₆ H ₄	2	POM/Yb	3d	39 (64)	80:20 (50:50) ^[b]
9	CO ₂ Et	Ph	1	POM/Yb	3e	39	50:50 ^[b]
10	CO ₂ Et	Ph	2	POM/Yb	3f	< 40	50:50 ^[b]
11	CO ₂ Et	<i>p</i> -MeOC ₆ H ₄	1	POM/Yb	3g	67 (48)	50:50 (50:50) ^[b]
12	CO ₂ Et	<i>p</i> -MeOC ₆ H ₄	2	POM/Yb	3h	62 (< 20)	50:50 (50:50) ^[b]

[a] Values in brackets correspond to the reaction with Yb(OTf)₃ as the catalyst. [b] See ref. [5a]. [c] Only degradation was observed. [d] Reaction stopped after 24 hours.

The reactions between various imines and either dihydrofuran or dihydropyran were efficiently catalyzed by 10 mol% of our Yb or Y complexes and afforded the expected cyclic adducts in acceptable-to-good yields. The POM/Hf complex was too harsh, thus leading sometimes to sharp drops in the yield (Table 5, entries 1–4). Highly activated aryl imines also gave moderate yields (Table 5, entries 9–12). The more reactive the imine, the more degradation we observed (Table 5, compare entries 9 and 10 to entries 11 and 12). However, the more active metal triflate salts gave even lower yields or no products at all. Hence, lowering the activity of the catalyst can prevent degradation of the substrates.

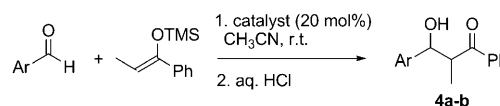
Parallel reactions were set up to compare the activities of the POMs for less sensitive *ortho*-hydroxy substrates (Table 5, entries 5–7). All three reactions were stopped after 24 hours: the POM/Hf-catalyzed reaction reached completion (87% yield), but the conversions for the POM/Yb and POM/Y catalysts (63 and 48% yield of the isolated products, respectively) were not complete. For this reaction and substrate, POM/Y was less active than POM/Yb and POM/Hf, which shows that we should remain cautious in issuing absolute ranking of the reactivities of the POM complexes (see also below).

Interestingly, a sharp increase in the diastereoselectivity (up to 90:10 d.r.) was observed when using $\text{TBA}_5\text{H}_2[\alpha_1\text{-YbP}_2\text{W}_{17}\text{O}_{61}]$ and an *ortho*-hydroxy substrate (Table 5, entry 5). The same reaction with the Yb triflate compound was not diastereoselective. This trend was more or less observed for all the *ortho*-hydroxy substrates and might be due to hydrogen-bonding of the latter to the polyoxotungstic backbone. This diastereoselectivity boost is an additional important specific feature of the POMs with regard to traditional Lewis acidic triflates, at least for Yb ions and to some extent Y ions.

Application of aldehydes in the catalysis: For the Mukaiyama–aldol reaction, benzaldehyde was chosen as a representative aldehyde (Table 6). It soon appeared that no reaction took place when POM/Yb or standard heteropolyacids (HPAs: $\text{H}_3\text{PW}_{12}\text{O}_{40}$ and $\text{H}_4\text{SiW}_{12}\text{O}_{40}$) were used.^[14] On the contrary, both POM/Hf and POM/Zr gave good conversions and yields of the desired Mukaiyama–aldol products. This outcome supported our initial assumption that metallic cations with a higher charge would lead to increased Lewis acidity.

The POMs are air and water stable, which is an improvement over the standard Hf^{IV} and Zr^{IV} Lewis acids generally used in catalysis.^[15] The amount of silyl enol ether strongly influenced the efficiency of the reactions (Table 6, entries 1–4). Indeed, the hydrated water molecules of the POM slowly hydrolyzed the silyl enol ether. The use of an excess of nucleophile (3–5 equiv) was the best compromise found. It allowed fast enough reactions and reproducible results independent of the POM dryness. Activated electrophiles led to good yields with both POM/Hf and POM/Zr (Table 6, entries 5 and 6), but aliphatic aldehydes gave low conversions.

Table 6. POM-catalyzed Mukaiyama–aldol reaction



Entry	Ar	Nucleophile [equiv]	Catalyst	<i>t</i>	Product	Yield [%]	Conv. [%]
1	Ph	1.5	POM/Hf	1 day	4a	85	100
2	Ph	3	POM/Hf	7 h	4a	n.d.	98
3	Ph	3	POM/Zr	3 day	4a	n.d.	78
4	Ph	5	POM/Zr	1 day	4a	92	100
5	<i>p</i> -NO ₂ C ₆ H ₄	2	POM/Hf	12 h	4b	95	>95
6	<i>p</i> -NO ₂ C ₆ H ₄	2	POM/Zr	12 h	4b	89	96

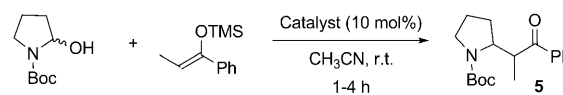
Finally, the diastereoselectivities remained poor for all the reactions. The use of POMs suffers some limitations as well. In particular, no reaction has been observed so far for the allylation of benzaldehyde, whether with allylsilanes or with allylstannanes.

Application of amins in the catalysis: Amins reacted very rapidly with silyl enol ether under POM catalysis, and acceptable yields of the desired products were obtained (Table 7). The reaction times (1–4 h) were generally shorter than those of the Mannich reactions; however, the scandium complex was an exception that required 3 days to give 79% yield (40% yield after 4 h). As before, the diastereoselectivities were poor. A related hemiketal did not react at all and was recovered after several days.

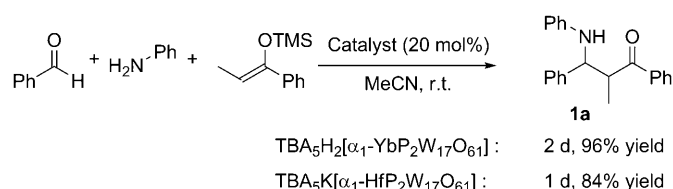
Chemoselectivity: To test the scope of our catalysts further, we extended the Mannich reaction to its three-component version (Scheme 2). Direct mixing of benzaldehyde, aniline, and the silyl enol ether in acetonitrile in the presence of the catalyst delivered aminoketone **1a** in high yields. Water is released upon formation of the imine, thus confirming again the water stability of our complexes.^[5b]

Interestingly, benzaldehyde did not react in the presence of the POM/Hf in this case due, certainly, to the very rapid formation of the imine, which consumed the aldehyde too

Table 7. Reaction of amins.



Entry	Catalyst	Yield [%]
1	POM/Yb	64
2	POM/Sc	79
3	POM/Y	82
4	POM/Hf	78
5	POM/Zr	73



Scheme 2. Three-component Mannich reaction.

quickly for the catalyst to compete. Nonetheless, this attracted our attention to the potential offered by our catalysts for chemoselective reactions. We reasoned that their lower activity could be turned into an advantage because they would not catalyze reactions with higher activation energies. Weaker Lewis acids might also coordinate better Lewis bases with increased selectivity.

First, we focused on the imine/aldehyde competition. In a typical experiment, one equivalent of silyl enol ether was treated simultaneously with one equivalent of diphenylimine and one equivalent of benzaldehyde in the presence of a catalytic amount of the Lewis acid in acetonitrile at room temperature. The standard commercial Lewis and Brønsted acids led to varied results (see the Supporting Information).^[16] To our pleasure, all the POM-based Lewis acids were extremely chemoselective (Table 8). The POM complexes were superior both for the metal atoms that generally favor addition onto imines, in which case they led to increased chemoselectivities, and for the more oxophilic metals, in which case the chemoselectivities were reversed. The complex POM/Sc proved again to be less reactive (Table 8, entry 5).

We turned our attention to the competition between the imines. We started with two diarylimines that differed only in the electron density on the nitrogen atom: diphenylimine and benzylidene(4-methoxyphenyl)amine (see the Supporting Information). However, the chemoselectivities were modest in favor of diphenylimine with the POM Lewis acids but did not change significantly with the traditional Lewis acids. Thus, we examined more electronically different imines, for example, a diarylimine and a pyruvate-derived

Table 8. Imine/aldehyde competition with Lewis acidic POMs.

Entry	Catalyst	1a/4a	Yield [%]
1	POM/La ^[a]	100:0	82
2	POM/Sm ^[a]	100:0	97
3	POM/Eu ^[a]	100:0	96
4	POM/Yb ^[a]	100:0	97
5	POM/Sc	100:0	55
6	POM/Hf ^[b]	98:2	84
7	POM/Zr	100:0	86
8	POM/Y	100:0	87

[a] See ref. [5a]. [b] See ref. [5b].

imine (see the Supporting Information). The reactions with all the traditional Lewis acids tested were already quite chemoselective. Nonetheless, the POMs compared very well to more common catalysts. The yields were generally higher and the reactions equally or more selective, especially for the POM/Zr catalyst.

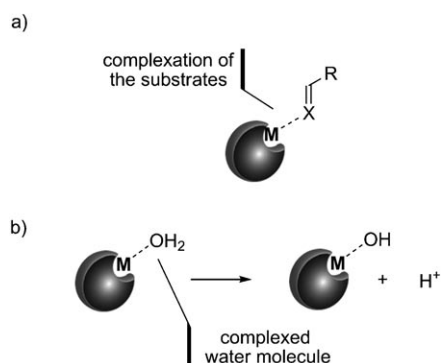
Catalyst recovery and recycling: As stated in the introduction, POMs have very narrow solubility properties, which opened the way to catalyst recycling. The addition of a mixture of acetone/ethanol/diethyl ether (1:1:20) precipitated the POM, while keeping all the organic species in solution. Centrifugation allowed complete recovery of the catalysts. Given the molecular nature of the recovered material, its purity could be assessed by IR and ³¹P NMR spectroscopic analysis. The Mannich reaction could be repeated up to ten times with no loss in yield with the POM/Yb catalyst.

We have already shown that no leaching from the POM/Yb complex took place. Previous work indicated that the complexation constants for the Ln complexes of POMs in water are extremely high^[9c] and are presumably higher in less polar organic solvents.

In this study, no trace of lacunary POM was found in the precipitated solids. Besides, the Yb³⁺ ion is paramagnetic and the leached material would influence the NMR spectra of the organic phase. As no paramagnetic shift or line broadening was observed, it was deduced that no free Yb³⁺ ions remained in solution. This reasoning was further supported by the fact that the filtrate showed no catalytic activity. Thus, we excluded catalysis by decomplexed lanthanide ions. No evidence for dissociation of the other POM complexes could be found either.

Mechanistical considerations: We wished to obtain a clear picture of the exact mechanism of our reactions. We initially excluded direct Brønsted catalysis by protons around the POM. Indeed, even if the lanthanide complexes featured two protons (e.g., TBA₅H₂[α₁-YbP₂W₁₇O₆₁]), the lacunary Dawson (TBA)₆H₄[α₁-P₂W₁₇O₆₁] did not catalyze the Mannich reactions and the Hf and Zr complexes have no proton available (e.g., TBA₅K[α₁-MP₂W₁₇O₆₁]). We also excluded catalysis by the decomplexed metal cations for the same reasons as above. In the lanthanide series, the complexation constants in water are already extremely high and are presumably higher in less polar organic solvents.^[9c]

Two possibilities should be considered. The first obvious option was the traditional Lewis acid activation of the substrates at the metal cornerstone of the POM (Scheme 3a). In the second path, a water molecule might bind to the metal center and become activated toward deprotonation (Scheme 3b).^[17] We label this pathway as indirect Brønsted catalysis because it is triggered by the initial coordination of water to the Lewis acidic POM. Indeed, thermogravimetric analysis (TGA) shows water associated to the POMs, so water molecules are always present in the catalytic reaction mixtures.



Scheme 3. Possible pathways for catalysis by Lewis acidic POMs.

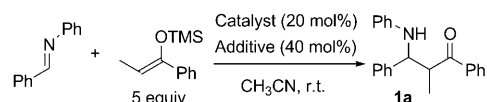
In both cases, catalysis would originate from Lewis acidity. Yet, discrimination between the two hypotheses was required to predict reactivities and devise potential further applications in asymmetric catalysis.

Mizuno and co-workers reported a way of discriminating between Lewis and Brønsted acid catalysis by protonated Lewis acidic γ -Keggin dialuminum- and dihafnium-substituted silicotungstates.^[5c,d] It appeared to us that such a method could also apply to the problem in hand, even if no protons of the POMs were considered. Thus, we ran two sets of reaction in the presence or absence of pyridine and 2,6-di-*tert*-butylpyridine. Both bases are strong enough to capture protons and should inhibit any Brønsted acid-catalyzed reaction. On the other hand, pyridine also binds to metal centers, thus inhibiting Lewis acid-catalyzed reactions. However, 2,6-di-*tert*-butylpyridine is highly hindered and should coordinate less to the Lewis acid corners located in our bulky POMs, and its effect on Lewis acid catalysis is expected to be weak.^[18]

To test the Mannich reaction, we selected diphenylamine, which was treated with an excess of silyl enol ether (5 equiv) in the presence of 20 mol% of several POM catalysts with or without the pyridine derivatives (Table 9). The excess silyl enol ether ensured a rapid enough conversion and avoided artifacts that arise from hydrolysis of the reagents. The reactions were stopped after one (Hf, Zr) or two days (Yb). The 2,6-di-*tert*-butylpyridine did not influence any of the reaction outcomes, regardless of the metal center (Table 9, entries 2, 6, and 10). From the opposite view, pyridine significantly decreased the overall rate of all the reactions (Table 9, entries 3, 7, and 11), but without totally inhibiting the catalyst (Table 9, entries 4 and 8). Thus, the Mannich reaction proceeds through substrate complexation.

It has been reported that α_2 -[HfP₂W₁₇O₆₁]⁶⁻ dimerizes with increasing pH value.^[19] As stated above, such dimers are expected to be less active Lewis acids because of the fewer available coordination sites. In our case, the addition of the basic additive 2,6-di-*tert*-butylpyridine did not impact reactivity. Furthermore, in the case of the Hf catalyst, ³¹P NMR spectra and mass spectra of the resulting solution were not modified upon the addition of 2,6-di-*tert*-butylpyri-

Table 9. Inhibition of the Mannich reaction.

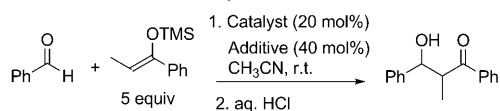


Entry	Catalyst	Additive	Time [days]	Yield [%]
1	POM/Yb	–	2	78
2	POM/Yb	2,6-di- <i>tert</i> -butylpyridine	2	77
3	POM/Yb	pyridine	2	0
4	POM/Yb	pyridine	8	16
5	POM/Hf	–	1	92
6	POM/Hf	2,6-di- <i>tert</i> -butylpyridine	1	94
7	POM/Hf	pyridine	1	37
8	POM/Hf	pyridine	5	95
9	POM/Zr	–	1	73
10	POM/Zr	2,6-di- <i>tert</i> -butylpyridine	1	68
11	POM/Zr	pyridine	1	14

dine. This outcome supports our conclusion that dimerization of the Hf^{IV} and Zr^{IV} α_1 -Dawson polyoxometalates under our reaction conditions is negligible and that the reactions are blocked by the additives not by an increase in pH value.

The Mukaiyama–aldol reaction was examined (Table 10), and again the substrate (benzaldehyde) was mixed with enough silyl enol ether (5 equiv) to ensure smooth reactions. The POM/Yb complex was omitted because it did not cata-

Table 10. Inhibition of the Mukaiyama–aldol reaction.



Entry	Catalyst	Additive	Time [days]	Yield [%]
1	POM/Hf	–	1	100
2	POM/Hf	2,6-di- <i>tert</i> -butylpyridine	1	6
3	POM/Hf	pyridine	1	5
4	POM/Zr	–	1	92
5	POM/Zr	2,6-di- <i>tert</i> -butylpyridine	1	0
6	POM/Zr	pyridine	1	16

lyze the reactions with aldehydes. Nearly complete inhibition of the reaction was observed in all the cases in which an additive was included. This finding tends to prove that the reactions follow the indirect pathway and is in good agreement with our DFT calculations, which indicated an easy deprotonation of a complexed water molecule in the POM/Hf complexes, but not in the POM/Yb catalysts.^[20] Thus, we conclude that both the POM/Hf and POM/Zr complexes act as indirect Brønsted catalysts in the aldol reaction.

To sum up, we propose that all the Mannich reactions proceed through the direct Lewis acid pathway, regardless of the POM complexes used, whereas the POM/Hf and

POM/Zr complexes catalyze the Mukaiyama–aldol reactions through an indirect Brønsted mechanism. This mechanistic difference may also account for the high chemoselectivity, which constitutes the most important feature of our Lewis acidic POMs.

Conclusion

Organosoluble α_1 -substituted Dawson polyoxotungstates incorporating Ln, Sc, Y, Hf, or Zr metal cations are air- and water-stable Lewis acids and were used in several organic reactions. Grafting Lewis acidity onto the inorganic backbone of POMs led to catalysts with high chemoselectivities, thus favoring activation of imines over aldehydes. The poly-anionic framework also enhanced diastereoselectivities in some cases, thus indicating that secondary interactions between the substrates and the POM skeleton take place.^[21] The Lewis acidity of the catalysts allows direct complexation of organic substrates and exaltation of the acidity of water molecules coordinated to the catalytic cornerstone; furthermore, both pathways are accessible, depending on the substrates. These findings provide new and growing opportunities for POM catalysis.^[5] Future developments will focus on new Lewis acidic POM structures, investigation of the influence of the central group,^[22] and extension to asymmetric catalysis with chiral structures.

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