ChemPubSoc Europe

DOI: 10.1002/chem.201403989

CHEMISTRY
A European Journal
Communication

Organocatalysis

Intramolecular Anion Effect in Polyoxometalate-Based Organocatalysts: Reactivity Enhancement and Chirality Transfer by a Metal Oxide–Organic Cation Interaction

Christian Brazel,[a] Nathalie Dupré,[a] Max Malacria,[a] Bernold Hasenknopf,*[a] Emmanuel Lacôte,*[a, b] and Serge Thorimbert*[a]

Abstract: An α_1-Dawson polyanion bearing a lateral side chain with a 4-aminopyridine end group was synthesized. This organopolyoxometalate catalyzes the addition of indenyl allyl silanes to cinnamoyl fluorides. The polyanionic framework influences the organocatalyst activity and selectivity. A moderate but nonzero chirality transfer from the chiral inorganic framework to the organic substrate was observed.

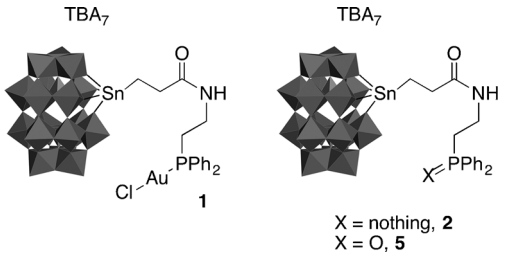


Figure 1. Structures of the starting organo-POMs.

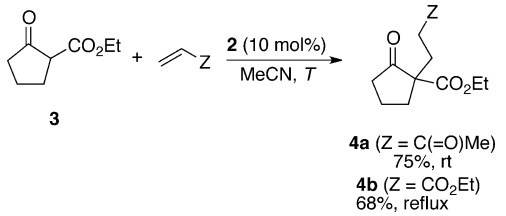
Electrostatic interactions are widespread in polyoxometalate (POM) chemistry. Indeed, POMs are polyanionic molecularly defined clusters of early transition metals and oxygen.[1] They are thus suitable ligands for transition metals,[2] or supports for active species in heterogeneous catalysis, for example, Lewis acidic cations[2b,3] or organic chiral acids.[4] Of particular interest are the reports by the Neumann group, in which a redox active POM supports a metal catalyst by electrostatic interactions and leads to cooperative catalysis.[5]

The same features make POM attractive partners for counterion-directed catalysis,[6] for which the potentially increased electrostatic attraction caused by the high charge of POMs is an appealing key to modulate reactivity. In addition, the development of postfunctionalization methods[7] for preparing complex hybrid structures opens the door to the development of catalysts, in which an intramolecular anionic effect is provided.

We first became aware of this opportunity when we designed the self-buffering Dawson-gold organohybrid **1** (Figure 1).[8] The cluster of **1** allows us to trap any adventitious proton present in solution, thus avoiding acidic degradation of the substrates, and to ease recycling of the noble metal. Interestingly, the conjugate proved superior to other buffer systems, including its non-tethered equivalent. We attributed this effect to the intramolecular capture and delivery of protons that are needed for conversion. This showed us for the first time that the POM surface may actively participate in counterion-directed reactions.

POM-based catalysis has been almost exclusively driven by their redox and/or acidic (including Lewis) properties, but new types of catalysis, for example, basic catalysis has emerged recently.[9] Thus we became interested in using the surface of organo-POMs to change the selectivity of organocatalytic reactions. We report our findings herein and we show the proof of concept that chiral information can be transferred from the inorganic cluster to organic substrates.

We first examined the phosphine-catalyzed Michael addition of keto-ester **3** onto ethyl acrylate and but-3-en-2-one. The hybrid phosphine we chose was **2**, which was the precursor of **1** in our previous study.[8] The reactions proceeded under conditions that are identical to those with the more common triphenylphosphine, but gave slightly lower yields of the expected products (Scheme 1).



Scheme 1. Phosphine-catalyzed Michael addition by using an organo-POM.

[a] Dr. C. Brazel, N. Dupré, Prof. M. Malacria, Prof. B. Hasenknopf, Dr. E. Lacôte, Prof. S. Thorimbert
Institut Parisien de Chimie Moléculaire (UMR CNRS 7201)
UPMC Univ Paris 06
4 Place Jussieu, 75005 Paris (France)
E-mail: bernold.hasenknopf@upmc.fr
serge.thorimbert@upmc.fr

[b] Dr. E. Lacôte
Université de Lyon, Institut de chimie de Lyon
UMR 5265 CNRS-Université Lyon I-ESCPE Lyon
43 Bd du 11 novembre 1918, 69616 Villeurbanne (France)
E-mail: emmanuel.lacote@univ-lyon1.fr

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201403989.

The catalyst could be separated easily from the products. However, in the case of the butenone, the ^{31}P NMR spectrum of the recovered POM showed that the peak at $\delta = -19.3$ ppm, corresponding to the phosphine on the side chain, has disappeared (see Figure S4 in the Supporting Information). Instead, two new peaks appeared in a 3:1 ratio, in addition to the two peaks of the Dawson ion. The major signal was observed at $\delta = 27.8$ ppm, and the minor one at $\delta = 30.1$ ppm. Mass spectrometry of the isolated material showed that the latter signal corresponds to the phosphine oxide **5**, derived from **2** (Figure 1), while the former was the signature of POM **6**, in which the phosphonium moiety replaced one TBA as counterion of the polyanion (Figure 2).

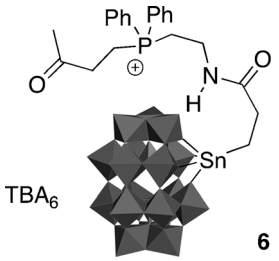


Figure 2. Structure of the new POM **6**.

The previous observations were particularly encouraging for three reasons. Firstly, they showed that organo-POMs are amenable to organocatalysis. Secondly, the catalyst is robust enough to resist the basic intermediates formed during the reaction in an organic medium. The organotin-substituted Dawson structure that is stable only up to pH 7.3 in water[10] did not decompose in the presence of enolates in acetonitrile. Lastly, and most importantly, the presence of the POM allowed the isolation of the phosphonium species **6** formed during the initiation of the reaction, by preventing its final elimination to release the phosphine. POMs can act as hydrogen bond acceptors.[11] So, we believe that the side chain is flexible enough to fold around the cluster allowing both hydrogen-bonding from the amide N–H bond and electrostatic interaction from the quaternary phosphonium with the anionic metal oxide surface.[12] In our view the two stabilizing interactions would prevent the deprotonation necessary for phosphine elimination.

The organocatalyzed [3+2] annulation of allylsilanes and cinnamoyl fluorides[13] appeared a better-suited benchmark reaction to verify our hypothesis that the POM surface could influence reactivity. Indeed, the catalyst introduced by the Fu group is a planar chiral DMAP analogue, which generates a cationic acyl-pyridinium intermediate **8a** upon addition to acylfluoride **7a**. This pyridinium undergoes a stereoselective conjugate addition, eventually leading to the cyclopentane adduct **10a**. The 1,2-addition product **11a** was observed as a minor product (Figure 3).

Since the acylpyridinium intermediates are reactive species with no acidic protons, we assumed that tethering them to the POM would not impair the activity of the catalyst, while hopefully modifying its reactivity (Figure 4). We selected POM

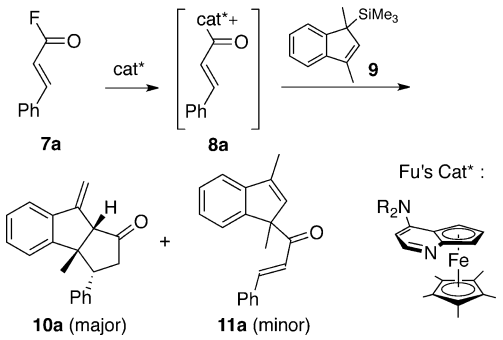


Figure 3. Organocatalyzed reaction of acyl fluorides with indenyl silanes.

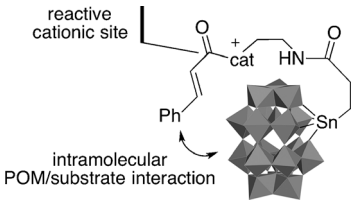
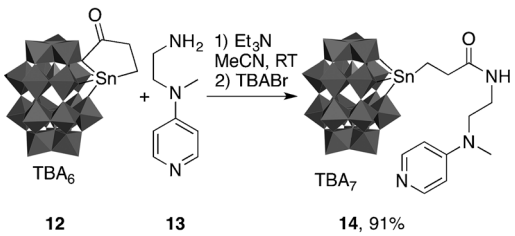


Figure 4. General approach for the organo-POM catalyzed reactions.

14 as the catalyst for the following reasons: 1) its structural similarity to **2** allows the side chain to fold around the cluster; 2) a direct comparison of **14** with 4-dimethylaminopyridine (DMAP) shows the role of the POM surface; 3) compound **14** is available in an enantiopure form.[12b] The latter would provide insight on the challenging concept of chirality transfer from a chiral metal-oxide surface to organic substrates,[14] which has never been examined for POMs thus far.

Catalyst **14** was prepared as follows:[15] Oxo-acyl organo-POM $(TBA)_6[\alpha_1\text{-}P_2W_{17}O_{61}\{SnCH_2CH_2C(=O)\}]$ **12** was reacted with amine **13**[16] at room temperature, leading to DMAP-hybrid **14** in 91% yield (Scheme 2). The ^{13}C and ^{1}H NMR spectra showed



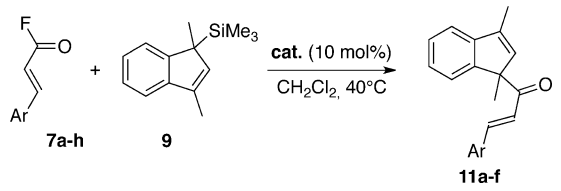
Scheme 2. Preparation of catalyst **14**.

the expected signals for the organic moiety. The ^{1}H triplet at $\delta = 7.49$ ppm was characteristic for the NH of the created amide bond. The two ^{31}P NMR spectroscopic signals at $\delta = -12.1$ and -6.6 ppm (the latter is the sum of a singlet and a doublet exhibiting a $J_{Sn\text{-}P}$ coupling constant of $J = 176.6$ Hz) indicated the integrity of the POM structure. This was definitively confirmed by ESI-MS, which showed exclusively the expected signals for this polyanion at m/z: 946.3 (calcd: 946.2)

for $\{TBA_1H[P_2W_{17}C_{11}H_{16}\ N_3O_{63}]\}^{5-}$, *m/z*: 1243.5 (calcd: 1243.6) for $\{TBA_2H[P_2W_{17}C_{11}H_{16}N_3O_{63}]\}^{4-}$, and *m/z*: 1303.9 (calcd: 1303.9) for $\{TBA_3[P_2W_{17}C_{11}H_{16}N_3O_{63}]\}^{4-}$.

In a typical experiment, silyl-indene **9** was reacted for 22 h with acryloyl fluoride **7a** in the presence of 10 mol% of organo-POM **14** at 40 °C in dichloromethane (Table 1, entry 1).

Table 1. Organo-POM catalyzed 1,2-additions of allylindenes to acyl fluorides.



Entry[a]	Ar, substrate	Cat.	Product, Yield [%]
1	Ph, **7a**	**14**	**11a**, 56
2	Ph, **7a**	DMAP	**11a**, 11
3	Ph, **7a**	DMAP[a]	**11a**, 9
4	Ph, **7a**	$POMSn(CH_2)_2CO_2H$	–[b]
5	*o*-Me-C_6H_4, **7b**	**14**	**11b**, 66
6	*o*-OMe-C_6H_4, **7c**	**14**	**11c**, 76
7	*m*,*m*-di(OMe)(C_6H_3), **7d**	**14**	**11d**, 65
8	*o*,*p*-di(OMe)(C_6H_3), **7e**	**14**	**11e**, 89
9	*o*,*p*-di(OMe)(C_6H_3), **7e**	**14**[c]	**11e**, 76
10	2-furyl, **7f**	**14**	**11f**, 64
11	*o*-F-C_6H_4, **7g**	**14**	–[d]
12	*m*-F-C_6H_4, **7h**	**14**	–[d]
13	Ph, **7a**	(+)-**14**	**11a**, 50[e]

[a] 20 mol% of DMAP was used. [b] Only starting material was recovered by using 10 mol% of $TBA_6H[\alpha_1P_2W_{17}O_{61}Sn(CH_2)_2CO_2H]$. [c] The reaction was performed with a recycled catalyst. [d] Complex mixture. [e] *ee* = 8%.

In contrast to the results of the Fu group, however, no [3+2]-cycloadduct was observed. Instead, 56% of the direct acylation product **11a** was isolated as the sole identifiable product. When DMAP was used as catalyst instead of the organo-POM **14**, the reaction failed (11% of **11a** was obtained, entry 2). Increasing the amount of DMAP to 20 mol% resulted in an equally poor yield (9%, entry 3). In the absence of any nucleophile, but with a simple organohybrid $[P_2W_{17}O_{61}Sn(CH_2)_2CO_2H]^{7-}$ the reaction did not proceed (entry 4).

The 1,2-addition proceeded also with electron-rich aromatic acryloyl fluorides, such as methyl- or methoxy-substituted derivatives **7b–e**, leading to indenes **11b–e** in yields ranging from 66 to 89% (Table 1, entries 5–8). A similar outcome was observed with furyl substrate **7f** (64% yield of **11f**, entry 10). In contrast, electron-deficient fluoro-substituted acryloyl fluorides gave complex mixtures (entries 11–12).

The organo-POM catalyst **14** could be recovered in good yields (>96%) by precipitation of the crude mixture in Et_2O containing a few drops of ethanol (5% in volume). The solid obtained after filtration was treated with a TBA resin. The recovered DMAP-hybrid **14** is still catalytically active and does not show significant loss of activity (Table 1, entry 9).

The results reported above are the first examples of organocatalytic reactions catalyzed with an organo-POM. Most interestingly, the POM surface and the pyridine moiety act synergistically, since neither DMAP nor $[P_2W_{18}O_{62}]^{6-}$ alone leads to appreciable catalysis. The reactivity is changed compared to Fu's ferrocenyl DMAP catalyst, since no [3+2]-cycloaddition was observed.[13]

Both the reactivity and selectivity depend on the combination of electronic and steric properties of the nucleophilic catalysts. Compared to Fu's DMAP catalyst, the DMAP-hybrid **14** is less sterically hindered (like a DMAP), and probably less nucleophilic. However, **14** is more reactive compared to DMAP. As it is unlikely that these effects are due to through-bond electronic influence of the POM, because of the many σ bonds separating the POM from the pyridine, we deduce that the POM surface interacts with the cationic reactive intermediates, which enhances the catalytic efficiency.

Since the α_1-hybrids are available in an enantiopure form,[12b] we decided to investigate the employment of POMs in asymmetric counteranion-directed catalysis.[6] Asymmetric catalysis involving chiral POMs is scarce and no example exists to date in which the chiral source is the inorganic cluster itself, as opposed to the counterions[4,17] or the organic chains of hybrid POMs.[18]

The reaction of **7a** in the presence of enantiopure (+)-**14** led to **11a** in 50% yield and a modest 8% *ee* determined by HPLC analysis (Table 1, entry 13; see also the Supporting Information, Figure S15). Even if the observed *ee* is much too low to qualify **14** as a synthetically useful asymmetric catalyst in this reaction, it nonetheless establishes the possibility of chirality transfer from a POM to an organic substrate.[19] We have previously reported the kinetic resolution of a chiral POM with peptides.[12b] This is the first example of the reverse path, that is, the chirality transfer from the inorganic cluster to an organic molecule.

In conclusion, we report the first example of organocatalyzed reactions by an organo-polyoxometalate. In the phosphine-catalyzed Michael addition, the POM does not show the desired turnover because the phosphonium cation interacts with the POM surface. However a similar interaction is beneficial in the pyridine-catalyzed acylation reaction, where the hybrid catalyst is more efficient than its two separate components. This synergistic effect shows that organo-POMs have their own specific chemistry. In both cases, reactivity is driven by interaction of the cationic reactive intermediates with the POMs. Finally, we established the proof of principle that chirality on the inorganic structure could be transferred to organic molecules during reactions, opening the way to use POMs as chiral anions in asymmetric catalysis.

Acknowledgements

We thank CNRS, UPMC, and ANR (grant 08-PCVI-0005 to E.L., S.T., and B.H.) for funding. FR2769 is acknowledged for technical assistance. The experimental work has been carried out at UPMC. C.B. thanks the Deutsche Forschungsgemeinschaft for a post-doc fellowship.

Keywords: acylation · chirality · organocatalysis · polyanions · polyoxometalates

[1] a) C. L. Hill, in *Comprehensive Coordination Chemistry II*, Vol. 4 (Ed.: A. G. Wedd), Elsevier, Oxford, **2004**, pp. 679 – 759; b) M. T. Pope, in *Comprehensive Coordination Chemistry II, Vol. 4* (Ed.: A. G. Wedd), Elsevier, Oxford, **2004**, pp. 635 – 678; c) D.-L. Long, E. Burkholder, L. Cronin, *Chem. Soc. Rev.* **2007**, *36*, 105.

[2] a) C. J. Besecker, V. W. Day, W. G. Klemperer, M. R. Thompson, *J. Am. Chem. Soc.* **1984**, *106*, 4125; b) D. Hueber, M. Hoffmann, B. Louis, P. Pale, A. Blanc, *Chem. Eur. J.* **2014**, *20*, 3903; c) M. Egi, M. Umemura, T. Kawai, S. Akai, *Angew. Chem. Int. Ed.* **2011**, *50*, 12197; *Angew. Chem.* **2011**, *123*, 12405.

[3] a) C. Boglio, G. Lemière, B. Hasenknopf, S. Thorimbert, E. Lacôte, M. Malacria, *Angew. Chem. Int. Ed.* **2006**, *45*, 3324; *Angew. Chem.* **2006**, *118*, 3402; b) Y. Kikukawa, S. Yamaguchi, Y. Nakagawa, K. Uehara, S. Uchida, K. Yamaguchi, N. Mizuno, *J. Am. Chem. Soc.* **2008**, *130*, 15872; c) G. Absillis, T. N. Parac-Vogt, *Inorg. Chem.* **2012**, *51*, 9902; d) H. El Moll, *Chem. Eur. J.* **2011**, *17*, 14129.

[4] a) S. Luo, J. Li, H. Xu, L. Zhang, J.-P. Cheng, *Org. Lett.* **2007**, *9*, 3675; b) J. Li, X. Li, P. Zhou, L. Zhang, S. Luo, J.-P. Cheng, *Eur. J. Org. Chem.* **2009**, *26*, 4486.

[5] a) J. Ettedgui, R. Neumann, *J. Am. Chem. Soc.* **2009**, *131*, 4; b) J. Ettedgui, Y. Diskin-Posner, L. Weiner, R. Neumann, *J. Am. Chem. Soc.* **2011**, *133*, 188.

[6] M. Mahlau, B. List, *Angew. Chem. Int. Ed.* **2013**, *52*, 518; *Angew. Chem.* **2013**, *125*, 540.

[7] a) D.-L. Long, R. Tsunashima, L. Cronin, *Angew. Chem. Int. Ed.* **2010**, *49*, 1736; *Angew. Chem.* **2010**, *122*, 1780; b) A. Dolbecq, E. Dumas, C. R. Mayer, P. Mialane, *Chem. Rev.* **2010**, *110*, 6009; c) A. Proust, B. Matt, R. Villaneau, G. Guillemot, P. Gouzerh, G. Izzet, *Chem. Soc. Rev.* **2012**, *41*, 7605; d) S. Thorimbert, B. Hasenknopf, E. Lacôte, *Isr. J. Chem.* **2011**, *51*, 275.

[8] N. Dupré, C. Brazel, L. Fensterbank, M. Malacria, S. Thorimbert, B. Hasenknopf, E. Lacôte, *Chem. Eur. J.* **2012**, *18*, 12962.

[9] a) T. Minato, K. Suzuki, K. Kamata, N. Mizuno, *Chem. Eur. J.* **2014**, *20*, 5946; b) K. Sugahara, T. Kimura, K. Kamata, K. Yamaguchi, N. Mizuno, *Chem. Commun.* **2012**, *48*, 8422.

[10] a) G. S. Chorghade, M. T. Pope, *J. Am. Chem. Soc.* **1987**, *109*, 5134; b) S. Bareyt, S. Piligkos, B. Hasenknopf, P. Gouzerh, E. Lacôte, S. Thorimbert, M. Malacria, *Angew. Chem. Int. Ed.* **2003**, *42*, 3404; *Angew. Chem.* **2003**, *115*, 3526.

[11] B. J. S. Johnson, R. C. Schroden, C. Zhu, V. G. Young Jr., A. Stein, *Inorg. Chem.* **2002**, *41*, 2213.

[12] a) S. Bareyt, S. Piligkos, B. Hasenknopf, P. Gouzerh, E. Lacôte, S. Thorimbert, M. Malacria, *J. Am. Chem. Soc.* **2005**, *127*, 6788; b) K. Micoine, B. Hasenknopf, S. Thorimbert, E. Lacôte, M. Malacria, *Angew. Chem. Int. Ed.* **2009**, *48*, 3466; *Angew. Chem.* **2009**, *121*, 3518.

[13] a) E. Bappert, P. Müller, G. C. Fu, *Chem. Commun.* **2006**, 2604; b) see also R. P. Wurz, *Chem. Rev.* **2007**, *107*, 5570.

[14] a) T. Yasukawa, H. Miyamura, S. Kobayashi, *Chem. Soc. Rev.* **2014**, *43*, 1450; b) L. L. Chng, N. Erathodiyil, J. Y. Ying, *Acc. Chem. Res.* **2013**, *46*, 1825; c) E. Guyonnet Bilé, A. Denicourt-Nowicki, R. Sassine, P. Beaunier, F. Launay, A. Roucoux, *ChemSusChem* **2010**, *3*, 1276; d) L. Durán Pachón, I. Yosaf, T. Z. Markus, R. Naaman, D. Avnir, G. Rothenberg, *Nat. Chem.* **2009**, *1*, 160; e) E. Schmidt, A. Vargas, T. Mallat, A. Baiker, *J. Am. Chem. Soc.* **2009**, *131*, 12358; f) M. Heitbaum, F. Glorius, I. Escher, *Angew. Chem. Int. Ed.* **2006**, *45*, 4732; *Angew. Chem.* **2006**, *118*, 4850.

[15] C. Boglio, K. Micoine, E. Derat, R. Thouvenot, B. Hasenknopf, S. Thorimbert, E. Lacôte, M. Malacria, *J. Am. Chem. Soc.* **2008**, *130*, 4553.

[16] B. Helms, C. O. Liang, C. J. Hawker, J. M. J. Fréchet, *Macromolecules* **2005**, *38*, 5411.

[17] a) C. Jahier, M. Cantuel, N. D. McClenaghan, T. Buffeteau, D. Cavagnat, F. Agbossou, M. Carraro, M. Bonchio, S. Nlate, *Chem. Eur. J.* **2009**, *15*, 8703; b) C. Jahier, M.-F. Coustou, M. Cantuel, N. D. McClenaghan, T. Buffeteau, D. Cavagnat, M. Carraro, S. Nlate, *Eur. J. Inorg. Chem.* **2011**, *5*, 72; c) C. Jahier, S. Nlate, *Eur. J. Inorg. Chem.* **2012**, *5*, 833; d) Y. Wang, H. Li, W. Qi, Y. Yang, Y. Yan, B. Li, L. Wu, *J. Mater. Chem.* **2012**, *22*, 9181; e) Q. Han, C. He, M. Zhao, B. Qi, J. Niu, C. Duan, *J. Am. Chem. Soc.* **2013**, *135*, 10186.

[18] M. Carraro, G. Modugno, A. Sartorel, G. Scorrano, M. Bonchio, *Eur. J. Inorg. Chem.* **2009**, *34*, 5164.

[19] Fu's ferrocenyl derivative led to only 13% *ee* for the same product, see ref. 12. The POM can also become temporarily chiral when reacting with chiral substrates. See: W. Adam, P. L. Alsters, R. Neumann, C. R. Saha-Moeller, D. Seebach, A. K. Beck, R. Zhang, *J. Org. Chem.* **2003**, *68*, 8222.

Received: June 16, 2014
Published online on October 24, 2014