Chiral Dawson-Type Hybrid Polyoxometalate Catalyzes Enantioselective Diels-Alder Reactions

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Chiral Dawson-type Hybrid Polyoxometalate Catalyzes Enantioselective Diels-Alder Reactions

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Abstract: Can achiral organocatalysts linked to chiral polyanionic metal-oxide clusters provide good selectivity in enantioselective C-C bond formations? We herein answer this question by disclosing a new active hybrid polyoxometalate-based catalyst for asymmetric Diels-Alder reaction. Chirality transfer from the chiral anionic polyoxometalate to the covalently linked achiral imidazolidinone allows us to obtain Diels-Alder cycloaddition products with good yields and high enantioselectivities using cyclopentadiene and acrylaldehydes as partners.

Introduction

Over the past decades, polyoxometalates (POMs)[1] have been the subject of important developments in materials science,[2] in biology[3] and appeared as efficient catalysts due to their acid-base and redox properties.[4] The use of chiral POMs[5] is sparingly developed in these fields, despite the obvious importance of chirality in biology and synthesis. Furthermore, POMs are often considered as molecular models of bulk metal oxides. Thus, chiral POMs represent a model for chiral metal oxide surfaces.[6] Considering the huge importance of metal oxides in catalytic transformations, there is relatively little known on chiral oxide surfaces and their mode of interaction with organic molecules. The chiral recognition on surfaces (of a POM or bulk metal oxide), and the transfer of chirality from a surface to organic substrates are promising fields of investigation for the development of future enantioselective catalysts where the chiral information does no longer rely on chiral organic molecules.[6,7] One should note also that the discrimination on chiral surfaces might have played a major role in prebiotic chemistry, and the occurrence of chiral biomolecules.[8]

Considerable advances in the preparation of chiral POMs have emerged in recent years.[5] The first major approach to obtain enantiopure chiral POM-based frameworks was built on the spontaneous resolution upon crystallization or on supramolecular assemblies.[9] Besides, chiral organic or metallo-organic species can be introduced via ion-pair interaction or direct ligation to POMs to create efficient chiral entities.[10] Most of these homogeneous catalysts are derived from achiral POM platforms and support the chiral information from the organic part *via* electrostatic effects or covalent bonds.[10-11] Some of these architectures have been used to catalyze organic transformations but few of them present efficient transfer of stereochemical information.

The concept of asymmetric catalysis by ion pairing and/or hydrogen bonding which has progressed exponentially in the last decade is mature for original discovery at the interface of organic and inorganic chemistry. The asymmetric catalysis *via* temporary covalent bonding in addition to non-covalent interactions has been exploited and is of prime interest to observe high enantioselectivities. Indeed, the higher the organization in the transition state is, the higher the stereoinduction can be expected.[12] We realized that our POM hybrids could fulfill these requirements. We hypothesized that the polyanionic POM framework could act as a chiral counter ion and thus influence the reaction stereoselectivity.

In line with our research regarding the preparation and use of POM hybrids, we reported very low enantioselectivity in the acylation of indenyl anions. We realized that the chiral POM was at a too long distance from the approaching prochiral nucleophile to efficiently control the configuration of the quaternary carbons during the C-C bond formation (Figure 1 left).[13] Inspired by the known mechanism of imidazolidinone catalyzed reactions in which the transition states involved iminium species,[14] we selected the Diels-Alder reaction between crotonaldehyde and cyclopentadiene as a new benchmark model. We anticipated that the reactive prochiral unsaturated double bond could be closer to the chiral POM giving a better transfer of the chiral information of the inorganic cluster to the created stereogenic centers (Figure 1 right).

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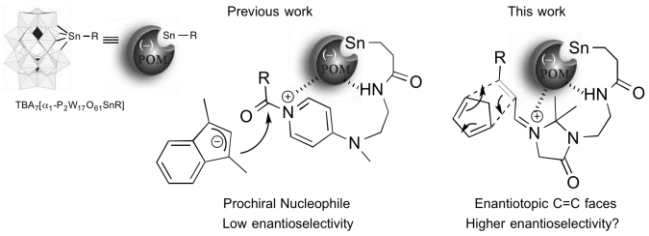
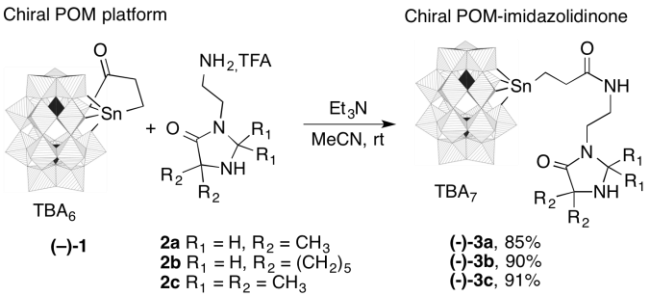


Figure 1. Chiral POM associated to activated reactive functions.

Results and Discussion

An intrinsically chiral POM framework can be obtained by the formation of a lacuna followed by the replacement with other metals.[5] We employ herein the α_1-tin-substituted Dawson oxo-acyl anhydride **1** (ee > 99%), $(TBA)_6[\alpha_1\text{-}P_2W_{17}O_{61}\{SnCH_2CH_2C(=O)\}]$ (TBA = tetra-*n*-butyl ammonium), as an inherently chiral platform.[15] Since it can be further functionalized by amide bond formation, it is a convenient and easily prepared starting material to study the transfer of stereochemical information from inorganic metal oxide surface to organic molecules. Moreover, the polyanionic structure of POMs is relevant for supramolecular contacts with organics by hydrogen bonding or electrostatic interactions.[15c]

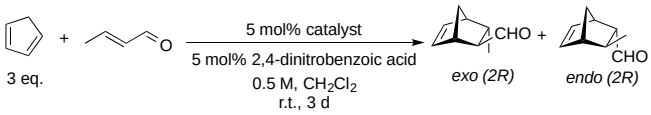
Three kinds of achiral amino ethyl imidazolidinones **2** were prepared following known procedures[16] whereas catalysts **3a-c** were prepared without special precautions as follows:[15b] the chiral activated POM platform (**1**) was reacted with amines **2a-c** in the presence of Et_3N to afford after precipitation with Et_2O the corresponding hybrids **3a-c** in high yields (150-300 mg; 85-91 %) (Scheme 1). They showed the expected signals for the organic and inorganic moieties in ^1H, ^{13}C and ^{31}P NMR spectroscopy, and ESI-MS further confirmed their composition (see SI).



Scheme 1. Synthesis of chiral polyoxometalate-imidazolidinone hybrids.

The cycloaddition between crotonaldehyde and cyclopentadiene is efficiently promoted by a combination of **3a** (5 mol%) and 2,4-dinitrobenzoic acid (DNBA) (5 mol%) for three days at room temperature in DCM (Table 1, entry 1). Satisfyingly, we isolated the cycloadduct in 95% yields as a mixture of *endo* and *exo* bicyclic products with enantiomeric excess of 54 and 46 % respectively. A 2 day reaction time slightly diminished the yield to 87% but did not modify the overall stereoselectivity (entry 2). Interestingly, our homogeneous catalyst favors the formation of the *exo* cycloadduct. It is well known that, for steric reasons, (supported) imidazolidinones-catalyzed Diels Alder reactions between unsaturated aldehydes and cyclopentadiene are giving *exo/endo* ratio close to 50/50.[14a, 17] In our experiments, the observed 67/33 *exo/endo* ratio highlight that our bulky hybrid POM is close to the reactive centers. A drop in both reactivity and enantioselectivity was observed when the more sterically constrained catalysts **3b** and **3c** were applied (Table 1, entries 3, 4).[18] Besides, control experiments were conducted by either omitting hybrid catalyst **3** or using simple N-Boc protected amino imidazolidinone **2a** revealing an expected low and non enantioselective reactivity (Table 1, entries 5 and 6). We also tested activated POM **(-)-1** as catalyst but no enantioselectivity was detected in the products. Consequently, catalyst **3a** was selected to further optimize the reaction conditions. Among the different solvents we tested, DCM and CH_3CN were the most efficient with slightly better yields observed for DCM. THF, mixture of THF/H_2O, or polar solvents (*t*-BuOH, *i*-PrOH) gave either lower conversion or enantioselectivities.

Table 1. Diels-Alder reaction between cyclopentadiene and crotonaldehyde with POM-Imidazolidinone catalysts **3**.[a]

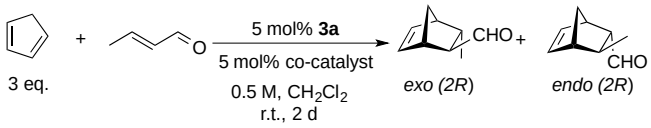


Entry	Cat.	Yield (%) [b]	*exo* : *endo* [c]	*exo ee* (%) [d]	*endo ee* (%) [d]
1	**3a**	95	67 : 33	54	46
2[e]	**3a**	87	69 : 31	55	46
3	**3b**	19	46 : 54	0	< 5
4	**3c**	45	59 : 41	0	8
5	**Boc-2a**	58	57 : 43	0	0
6	—	29	25 : 75	0	0

[a] Absolute configuration assigned by chemical correlation to a known compound (SI). [b] Yields of isolated *exo* and *endo* isomers. [c] Diastereoselectivity determined by ^{1}H NMR of the crude. [d] The *ee* values were determined by GC analysis on a chiral phase. [e] Reaction stopped after 2 days

We next turned our attention to the acid co-catalyst effect. The presence of the acid co-catalyst is required and found to have a positive effect on both yield and enantioselectivity. (Table 2, entries 1, 2). The reaction gave higher yields but lower enantioselectivities in the presence of a stronger acid such as TFA (Table 2, entry 3). HCl had a negative effect on both yields and *ee*. (Table 2, entry 4). Interestingly, the chiral (*S*)-10-camphorsulfonic acid (CSA) gave the Diels-Alder adduct in comparable stereoselectivities but in lower yields (Table 2, entry 5). It should be noted that CSA alone without POM **3a** catalyzes the reaction but does not lead to any enantioselectivity.

Table 2. Co-catalyst effects on the Diels-Alder reaction.[a]



Entry	Co-cat.	Yield (%)[b]	*exo* : *endo*[c]	*exo ee* (%)[d]	*endo ee* (%)[d]
1	–	9	65 : 35	39	22
2	DNBA	87	69 : 31	55	46
3	TFA	97	68 : 32	22	9
4	HCl	46	69 : 31	48	32
5	(*S*)-CSA	38	68 : 32	59	41
6	Cat **4**	41	66 : 34	58	29

[a] Absolute configuration assigned by chemical correlation to a known compound (SI). [b] Yields of isolated *exo* and *endo* isomers. [c] Diastereoselectivity determined by ^{1}H NMR of the crude. [d] The *ee* values were determined by GC analysis on a chiral phase.

These experiments performed so far revealed some trends on the active catalytic species. Indeed, the relative acidity seems to be less important than the nature of the corresponding conjugated base. We speculate that the strong influence of the acid co-catalyst on both reactivity and enantioselectivity is due to a competitive association of its conjugated base with either iminium or TBA counter ions.[19]

In order to go deeper into the understanding of this ion pairing effect, we prepared and isolated a POM-imidazolidinium **4** by mixing POM **3a** with TFA in a THF/CH_3CN solution and precipitation by adding Et_2O (Figure 2). The solid was characterized as the expected hybrid POM **4** whereas the filtrate, after evaporation of the solvents, afforded $CF_3COO{\cdot}TBA$ as the unique residue (see SI). By using 5 mol% of **4** to catalyze the studied Diels-Alder reaction, the enantioselectivities for both *endo* and *exo* products were significantly higher than those obtained by simply mixing **3a** with TFA (Table 2, entries 3, 6). The selectivity of the reaction reached the same level as in the DNBA case. However the yield of the reaction dropped to 41% revealing a decrease of the efficiency of the catalyst due to possible partial decomposition. We thus confirmed that the nature of the anion associated to the catalytically active intermediate is

essential for modulating both the reactivity as well as the stereoselectivity of the reaction.[20]

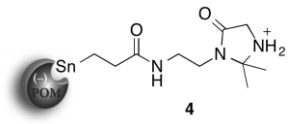
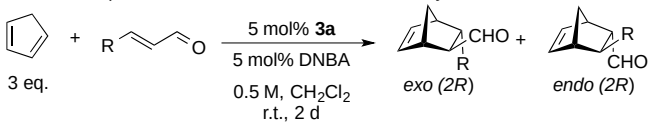


Figure 2. Proposed structure of POM-imidazolidinium **4**.

Experiments that probe the scope of the dienophiles are summarized in Table 3. The POM-imidazolidinone-catalyzed cycloaddition tolerates a range of β-substituted dienophiles. Alkylated β-substituted dienophiles are sensitive to steric hindrance with lower reactivity but almost without loss in enantioselectivity (Table 3, entries 1, 2). However, the reactions of the less constrained and more reactive unsubstituted α, β-unsaturated aldehydes, provide the desired product in good yields but without enantioselectivities. This is due to the proton-catalyzed background reaction, which can now compete (Table 3, entries 3-5). As for other homogeneous imidazolidinones organocatalyzed reactions, the catalyst **3a** is not efficient with α-methyl-substituted α, β-unsaturated aldehydes, like methacrolein (low conversion, no enantioselectivity) and tiglic aldehyde (no conversion). Finally, β-aryl-substituted dienophiles provided somewhat higher dia- and enantioselectivities with moderate to excellent yields (Table 3, entries 6, 7). By decreasing the catalyst loading to 2.5 mol%, the reactive 4-nitrophenylacrylaldehyde reacted with the same high efficiency giving quantitatively after 2 days, the cycloadduct in a 84/16 *exo/endo* ratio and enantioselectivities reaching to 86 and 78% respectively (Table 3, entry 8).

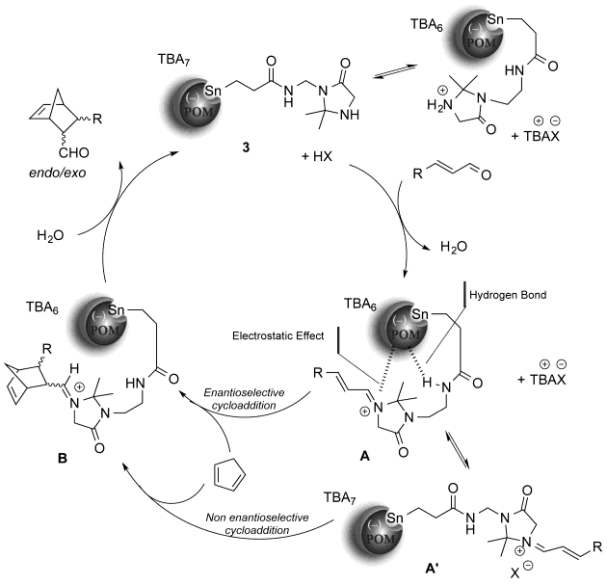
Table 3. Scope of the POM-Imidazolidinone **3a** catalyzed Diels-Alder reaction.[a]



Entry	R	Yield (%)[b]	*exo* : *endo*[c]	*exo ee* (%)[d]	*endo ee* (%)[d]
1	Me	87	69 : 31	55 (2*R*)	46 (2*R*)
2	Pr	29	72 : 28	55 (2*R*)	49 (2*R*)
3	H	96	32 : 68	0	0
4	CO_2Et	100	45 : 55	0	0
5[e]	CO_2Et	86	42 : 58	0	0
6	Ph	38	80 : 20	88 (2*S*)	72 (2*S*)
7	4-NO_2-Ph	100	84 : 16	86 (2*S*)	64 (2*S*)
8[f]	4-NO_2-Ph	100	84 : 16	84 (2*S*)	78 (2*S*)

[a] Absolute configuration assigned by chemical correlation to a known compound (SI). [b] Yields of isolated products as mixture of *exo* and *endo* isomers. [c] Determined by ^{1}H NMR of the crude. [d] The *ee* values were determined by GC or HPLC on a chiral phase. [e] reaction run without cat **3a**. [f] 2.5 mol% of catalyst were used.

The origin for this unique chirality transfer from the chiral POM to the new organic molecule is assumed to involve a commonly accepted iminium intermediate.[21] The protonation of the hybrid POM **3** by the acid co-catalyst leads to an equilibrium that determines the overall reactivity with the unsaturated aldehydes. After formation of the usual conjugated iminium species **A** (ESI-MS proof, see SI),[22] the electrostatic interaction and the hydrogen bonding between the amide NH and the oxido ligands,[15a] hold the organic chain close to the inorganic surface. Because of the chirality of the POM, one sense for the wrapping of the organic chain around the POM is preferred to the other. This helical orientation might justify the origin of the enantioselectivities observed during the formation of **B**. Indeed, only one face of the unsaturated iminium in **A** should be accessible to the diene. The unfolded conformation **A'** is certainly more reactive but should not be productive for enantioselectivity as both faces of the prochiral unsaturated iminium **A'** are reactive. The affinity of the iminium for the oxide surface *versus* the conjugated base of the acid co-catalyst (X^-) is crucial for the equilibrium between **A** and **A'**. Finally, after cycloaddition with cyclopentadiene, hydrolysis of iminium intermediate **B** liberates the bicyclic product and regenerates the catalyst/co-catalyst system.



Scheme 2. Mechanism and origin of enantioselectivity in studied reaction.

Conclusions

In summary, a new type of chiral hybrid POM-imidazolidinone catalyst was synthesized and used to perform the first efficient chirality transfer from an intrinsically chiral inorganic oxide surface, represented by the POM cluster, to organic molecules. As for the mechanism, competitive ion pairing between positive iminium side chain and either anionic POM surface or co-catalyst anion seems essential to affect the reaction rate and enantioselectivity. This study opens an entry to the challenging fields of asymmetric catalysis using POMs, or more generally speaking for using inorganic oxides as source for chiral information. Further studies to address the scope of this new catalytic strategy will be forthcoming.

Experimental Section

Typical experimental procedure: Catalyst **3a** (60 mg, 5 mol%) and DNBA (5 mol%) were stirred in DCM (0.4 mL) for 5 minutes, followed by addition of crotonaldehyde (0.19 mmol, 16 µL) then cyclopentadiene (0.58 mmol, 49 µL). After 2 days, the POM was precipitated upon addition of EtOH/Et_2O (0.4 mL/ 8 mL) and removed by centrifugation and filtration. The filtrate was concentrated and purified by flash chromatography on a silica column to furnish the product (23 mg, 87 % yield). Preparation of catalysts, GC, HPLC and ESI-/MS studies and other full characterization are included in SI.

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Keywords: Polyoxometalates • Chirality • Cycloaddition • Organocatalysis

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