

Article

Water Tolerant and Atom Economical Amide Bond Formation by Metal-Substituted Polyoxometalate Catalysts

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Abstract

A simple, safe and inexpensive amide bond formation directly from non-activated carboxylic acids and free amines is presented in this work. Readily available Zr(IV)- and Hf(IV)-substituted polyoxometalates (POM) are shown to be catalysts for the amide bond formation reaction under mild conditions, low catalyst loading, and without the use of water scavengers, dry solvents, additives for facilitating the amine attack, or specialized experimental setups commonly employed to remove water. Detailed mechanistic investigations revealed the key role of polyoxometalate scaffolds which act as inorganic ligands to protect Zr(IV) and Hf(IV) Lewis acidic metals against hydrolysis, and preserve their catalytic activity in amide bond formation reactions. The catalysts are compatible with a range of functional groups and heterocycles useful for medicinal, agrochemical and material chemists. The robustness of the Lewis acid-polyoxometalate complexes is further supported by the catalyst reuse without loss of activity. This prolific combination of Zr(IV)/Hf(IV) and polyoxometalates inaugurates a powerful class of catalysts for the amide bond formation, which overcomes key limitations of previously established Zr(IV)/Hf(IV) salts and boron based catalysts.

Keywords

Polyoxometalates, Catalysis, Lewis Acid, Amide bond, Green Chemistry, Atom Economic

Introduction

Environmental and economic sustainability in the production of chemicals is a permanent challenge to process chemists.¹ Among many areas of potential improvement, the development of new catalysts and/or catalytic reactions are the best tools to produce chemicals minimizing waste generation, and decreasing the energy consumption.² To overcome these challenges, many heterogeneous and homogeneous catalysts based on enzymes, metals and/or small organic molecules are intensively researched in industries and universities around the world. Ideally, catalysts should be stable, inexpensive and widely available materials able to efficiently convert starting substrates into products without extra additives, and using more simple experimental protocols. As promising alternatives to meet these challenges, polyoxometalates (POMs), anionic clusters of early transition metals and oxygen, have been widely explored and/or employed as catalysts in academic and industrial settings; however, some catalytic manifolds remain scarcely investigated.³

The development of new catalysts derived from POMs benefits from their well-defined structure which can be modified to tune chemical properties such as solubility, acidity and redox potential. POMs basic structural unit (MO_x)_n resembles the structure of solids commonly used in heterogeneous catalysis (SiO₂, Al₂O₃, Ti₂O...), providing a rare opportunity to develop (equally or more) efficient metal-oxide based catalysts bearing advantages of both soluble molecular catalysts and heterogeneous catalytic materials without the small variations in the catalyst structure often observed among different batches of traditional heterogeneous catalysts.⁴ Despite these exciting features, POM-based catalysts are mostly used in oxidations, reductions and Brønsted acid catalyzed processes while other catalytic modes have been less investigated.⁵ In 2006, Malacria, Lacote and Thorimbert demonstrated that lanthanide-substituted polyoxometalates are catalytically competent Lewis acids in Mannich-like reactions despite being multicharged anions, but this groundbreaking concept remained rather underexplored in synthetic chemistry.⁶ Recently, we expanded the use of such concept by applying Lewis acidic transition-metal substituted POMs in the selective hydrolysis of peptides,⁷ proteins⁸ and other biomolecules.⁹ The great success in this area prompted us to further investigate the catalytic activity of the similar Lewis-acid-POM complexes in other relevant transformations for medicinal and material chemists, such as the formation of amide bonds.

Amide bonds are pivotal structural motifs in biomolecules, drugs and synthetic materials,¹⁰ but the synthesis of amides still faces many challenges.¹¹ From the point of view of sustainable chemical production, the direct formation of amides from non-activated carboxylic acids and free amines would be ideal because it

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generates only water as a by-product, dramatically limiting the amount of waste generated when traditional peptide coupling reagents are used.¹² However, the high energy barrier hampers the widespread use of this reaction. Many other option were considered to improve the synthesis of amides, ^{10, 13} but the catalytic direct amide bond formation from non-activated carboxylic acids and free amines arguably remains one the most promising alternatives. Regrettably, it is also among the least developed ones.^{11a, 14} Considering the limitations still observed in this area, we set out to examine if the transition-metal-substituted POM catalysts that accelerated the hydrolytic cleavage of peptide bonds could also catalyze their formation upon appropriate modification of the reaction conditions. Such reversal in the reactivity observed would be possible if the water could be replaced by an organic solvent shifting the reaction equilibrium toward the amide bond formation instead of its cleavage. Further, as the catalytic hydrolytic activity was observed in aqueous medium, we envisaged the POM framework could prevent hydrolysis of the Lewis acidic metal providing a highly desirable water and air tolerant catalytic reaction. If successful, this approach would provide a new class of cost effective, potentially recyclable, stable, and readily available catalysts for the catalytic formation of amide bond.

Results and Discussion

The metal-substituted POM catalyzed amide bond formation derives from our previous work in the hydrolysis of peptide bonds in the presence of these complexes.^{7a} The formation of minor amounts of the 2,5-diketopiperazine **2a** during the hydrolysis of the glycylglycine (GlyGly) (**1a**) was indicative that it could be formed using the same catalytic system upon appropriate manipulation of the reaction conditions. We started our investigation using this intramolecular reaction to probe the effects of reactions conditions and catalyst structure in the formation of **2a**. Next, we demonstrated the equilibrium shift is not limited only to GlyGly (**1a**), and it is compatible with several functional group in either intra- or intermolecular fashion. Further, a preliminary mechanistic investigation outlined the benefits of combining Lewis acids and POMs in a single catalytic complex.

Perturbing the equilibrium between GlyGly (1a) and c(GlyGly) (2a). Considering the reversibility of the amide bond formation reaction in the presence of water,^{7a} we examined how the equilibrium between **1a** and **2a** would be affected if the water was replaced by other commonly used organic solvents (Scheme 1). Whilst most of the solvents tested resulted in no conversion of **1a**, and pure water and acetonitrile/water mixtures showed a small conversion producing similar amounts hydrolysis and cyclization products of **1a**, dimethylsulfoxide (DMSO) provided a 50% yield of the **2a**. Further, no hydrolysis of **1** was observed in

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DMSO, and all the substrate converted was transformed into the desired product (ratio yield/conversion = 100%). These findings motivated further evaluation of related metal-POM complexes in DMSO to improve the yield of **2a**.

a) Zr:Wells-Dawson POM 2:2 complex is effective to favor 2a



b) Summary of screening observations:

- Solvent: DMSO (50%) >> MeCN:H₂O (12%) \approx H₂O >>> MeCN, MeOH, PhMe...
- *POM structure:* α_2 -Wells-Dawson (100%) > Keggin (38%) > α_1 -Wells-Dawson
- *Metal:* Hf⁴⁺ (75%) > Zr⁴⁺ (36%); Ni²⁺, Cu²⁺, Fe³⁺, Co²⁺, Ce³⁺, Ce⁴⁺ not active
- Metal-POM ratio: 2:2 (100%) > 1:2 (40%) > 1:1 (3%)

c) Generic structures of the POM catalysts tested



Scheme 1: a) Best conditions, b) trends, c) and general structure of the metal-POM complexes tested to favor the formation of **2a**. $[Zr(\alpha_2-P_2W_{17})]_2 = (Me_2NH_2)_{14}[Zr(\mu-O)(H_2O)(\alpha_2-P_2W_{17}O_{61})]_2$

The metal, the POM structure and the metal:POM ratio also affected the ratio between **1a** and **2a** (Scheme 1). Using metal-Wells-Dawson POM complexes with the ratio metal:POM = 1:2 in DMSO, only Zr⁴⁺ and Hf⁴⁺ formed **2** (40% and 75% of yield, respectively), while Fe³⁺, Ni²⁺, Co²⁺, Cu²⁺, Ce³⁺ and Ce⁴⁺-substituted POMs did not provide product **2**. The change in POM structure from α_2 -Wells-Dawson to Keggin or to a α_1 -Wells Dawson isomer provided slower conversions of **1a** to **2a** (28% and 3% of **2a** observed,

respectively). On the other hand, more **2a** was formed when a Zr(IV)-Wells-Dawson 2:2 complex was used instead of the original Zr:POM 1:2 complex. The Zr-Wells-Dawson 2:2 complex completed shifted the equilibrium, and only **2a** was observed after 24 h. Of note, no hydrolysis of **1a** was observed in any of these reactions.

Other dipeptides and amino acid substrates were also cyclized in the presence of Zr-Wells-Dawson 2:2 complex in DMSO, showing this new lactamization reaction is compatible with challenging substrates without the need of using protecting groups. (Table 1). To probe the generality of the intramolecular bond formation observed, other dipeptides were submitted to the same conditions, and the cyclized products were generally observed in good to excellent yields. Notably, tryptophan, histidine, serine and aspartic acid containing dipeptides were cyclized without the use of any protecting groups in high yields demonstrating the excellent compatibility of this catalytic system with (functional) groups widely present in drug candidates and biomolecules.¹⁵ Moreover, the reaction provided similar yields of cyclized products regardless if Glv-X or X-Gly dipeptides were used as starting materials, even when a secondary amine was used (Pro-Gly, product 2f). The low yield observed for the Asp-Gly substrate is not fully understood at the moment but it could be attributed to a preferential coordination of side-chain carboxylic acid group of the aspartate instead of the one from the glycine moiety generating a stable complex that decreases the catalyst availability. Further, the cyclization of Phe-Phe (11) demonstrates the cyclization is not limited to glycine containing dipeptides, and the formation of **2i**, **k** in excellent yields from non-peptide amino acids shows the reaction is no limited to the formation of diketopiperazines or products containing six-membered rings. We isolated products 2b and 2c to check if the substrates epimerized during the reaction, but no change in the optical purity was detected, highlighting the smoothness of this catalytic reaction (see Supporting Information for details).





Conditions: **1b-k** (0.100 – 0.500 mmol), 5.0 mol% [$Zr(\alpha_2 - P_2W_{17}O_{61})$]₂, DMSO (0.10 mol L⁻¹), 70 °C, 24 h. ¹H NMR yields (isolated yields). [$Zr(\alpha_2 - P_2W_{17}O_{61})$]₂ = (Me₂NH₂)₁₄[$Zr(\mu - O)(H_2O)(\alpha_2 - P_2W_{17}O_{61})$]₂

Intermolecular amide bond formation. The successful conversion of the dipeptide hydrolysis reaction into an intramolecular amide bond formation reaction under smooth and open-flask conditions prompted us to investigate the analogous intermolecular coupling. Using phenylacetic acid (**3a**) and benzylamine (**4a**) as model substrates, an optimization based on the intramolecular reaction conditions was carried out, and the new conditions afforded amide products in good to excellent yields without the use of water scavengers, dry solvents or any other additives. As observed for the intramolecular reaction, the POM structure was found to be essential to the catalytic activity, but also the reaction concentration, and the stoichiometry between the amine and the acid were important.

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Initial screening of the POM structure and the metal:POM ratio showed that metal-Wells-Dawson POM 2:2 complexes were superior catalysts, but only moderate yields of the desired product were observed. Employing Zr(IV) as the metal, Wells-Dawson and Keggin POM complexes with the ratio metal:POM 1:2 provided the desired product in 14% and 10%, respectively. Changing the ratio metal:POM from 1:2 to 2:2 slightly increased the yields to 29% for the Wells-Dawson complex and 16% for the Keggin complex. Previously, metal complexes of α_1 -Wells-Dawson lacunary POMs complex were suggested to be better Lewis acids,^{6b} but a Zr:[α_1 -Wells-Dawson] 1:1 complex was ineffective for the formation of the amide **5** (8% yield). While small improvements were obtained using different POM structures, better yields were observed when Zr(IV) was replaced with Hf(IV) in the metal:POM 2:2 complex. In this case, the desired product was obtained in 47% yield (Table S3 of Supporting Information).

Increasing of reaction concentration improved the yield of the desired amide product **5** (Scheme 2). To perturb the equilibrium coordination of the substrates to the catalyst and tune their concentration nearby the catalytic active site, different reaction concentrations were evaluated. Using the Hf(IV)-Wells-Dawson POM 2:2 complex, we varied the reaction concentration from 0.10 mol L⁻¹ to 3.33 mol L⁻¹. A direct correlation between the concentration and the yield was observed, and **5** was formed in 99% yield at the highest concentration (3.33 mol L⁻¹). Remarkably, at this highest concentration, the catalyst loading can be reduced to as low as 0.25 mol% without affecting the yield (Table S6 of Supporting Information). The same trend was observed for the analogous Zr(IV)-Wells-Dawson 2:2 complex, and this catalyst afforded the desired product **5** in 82% yield at 1.67 mol L⁻¹ concentration (Table S4 of Supporting Information).



Scheme 2. Yield of 5 improves upon increasing reaction concentration *Conditions:* 3a (0.500 mmol), 4a (1.2 equiv.), 1.0 mol% [Hf(α_2 -P₂W₁₇O₆₁)]₂, DMSO (0.15 – 5.0 mL), 70 °C. [Hf(α_2 -P₂W₁₇O₆₁)]₂ = (Me₂NH₂)₁₄[Hf(μ -O)(H₂O)(α_2 -P₂W₁₇O₆₁)]₂

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Considering the excellent yield of amide product 5 observed upon increasing reaction concentration, we briefly probed the scope of the transformation regarding different amines and carboxylic acids (Table 2). Primary aliphatic amines efficiently provided the desired amides in good to excellent yields, even bearing electron-donating or withdrawing groups (5, 6 - 10). The reaction showed sensitivity to steric hindrance and an increase in the temperature and amine equivalents were needed to achieve good vields with orthosubstituted benzyl amines (7 - 8) and α -methyl benzylamine (9). Remarkably, the reaction is compatible with fully unprotected tryptamine providing the desired product 10 in 70% yield. Moreover, 1methylpiperazine, i.e., a secondary amine, provided product 11 in 75% yield. Several carboxylic acid substrates were also efficiently converted to the desired amide products. Products 12 and 13 with extra substituents at the carbon α were formed in 44% and 79% yield, respectively. The benzyl *p*-nitrobenzamide 14 was obtained in 95% yield showcasing the compatibility of benzoic acid derivatives. In addition, the catalyst showed exceptional compatibility with N, S and O-heterocycles. The pyridine-containing nicotinic acid, a valuable moiety in drug discovery, afforded the desired amide **15** in quantitative yield. Moreover, the electro-rich and prone to oxidation furan and thiophene substrates were not affected by the well-known oxidative properties of the POM framework, and the products were obtained high yields without any special care (16 - 17).^{5d} Similarly, the reaction was also suitable for the formation of amide bonds with Bocprotected amino acids in excellent yields (18 and 19). Of note, most of the products could be isolated by a simple acid-base extraction in satisfactory purity to further transformations (>90%) due to the clean reaction conditions containing only the reactants and a small amount of catalyst, highlighting the simplicity of the method. The effectiveness of the metal-POM catalyst was also evident from the gram-scale reaction using 41.2 mmol of the acid **3a**, in which 8.37 g of amide **5** were produced from a single experiment, without any modification to the experimental procedure (Scheme 3). The efficiency of this catalyst was further evidenced by its low Product Mass Intensity¹⁶ (PMI) compared to conventional amide coupling reactions (see Supporting Information for details).^{11b}



Table 2. Intermolecular bond formation from free amines and non-activated carboxylic acids

Conditions: **3a-i** (0.500 mmol), **4a-g** (1.2 – 2.0 equiv.), 1.0 mol% $[Hf(\alpha_2-P_2W_{17}O_{61})]_2$, DMSO (0.15 mL), 70 – 90 °C. Isolated yields (crude yields with purity >90%). $[Hf(\alpha_2-P_2W_{17}O_{61})]_2 = (Me_2NH_2)_{14}[Hf(\mu-O)(H_2O)(\alpha_2-P_2W_{17}O_{61})]_2$

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Scheme 3. Gram-scale synthesis of amide **5** catalyzed by $(Me_2NH_2)_{14}[Hf(\mu-O)(H_2O)(\alpha_2-P_2W_{17}O_{61})]_2$. PMI = Product Mass Intensity (see Supporting Information for details)

Mechanistic investigations. The catalytic cycle depicted on Scheme 4 featuring a general Lewis acid catalysis, is likely the general pathway followed by the reaction, as observed previously in other Zrcatalyzed amidation reactions¹⁷. Based on our previous work,¹⁸ we propose a monomeric metal-POM 1:1 complex (A) as the catalytically active species in this reaction. This monomeric form A derives from the solvent and/or amine induced dissociation of the dimeric metal-POM 2:2 complex added to the reaction. After dissociation, the carboxylic acid binds A at its metal center, and the carboxylate group is activated to the amine nucleophilic attack, which forms key tetrahedral intermediate C. At this point, it is not clear if amine attack occurs through an inner or outer sphere mechanism in the intermolecular reactions. In contrast to the previous proposals,¹⁷ the high concentration of the intermolecular reaction and the concomitant availability of coordination sites at the metal could indicate that an inner sphere C–N bond formation event is favored. This is also consistent with our previous studies on the dipeptide hydrolysis where the dipeptide coordination through both the amine and carboxylate groups were necessary to enable water attack.^{7a, 18} At last, release of water from C leads to product formation, and regenerates the catalyst. The catalyst tolerance to the water formed in the last step of the reaction is attributed to the increased resistance of the metal center to hydrolytic decomposition when complexed to the POM framework. This proposed pathway and the water tolerance observed are consistent with the trends observed during reaction development, and several mechanistic experiments, such as control reactions, kinetic experiments, and ³¹P NMR investigations conducted using the intermolecular reaction between 3a and 4a as a model.



Scheme 4. Metal-POM complex catalyzed amidation reaction likely follows a general Lewis acid catalysis pathway

Control experiments. The combination of POM with the Lewis acidic metal in a single complex is essential to promote the amide bond formation in good yields. Using zirconium as a representative metal, we probed the catalytic activity of the different components of the catalyst (Table 3, and Tables S9 and S10 of Supporting Information). In the absence of any catalyst or in the presence of monomeric tungstates (Li₂WO₄ and Na₂WO₄) or the lacunary POM (K₇P₂W₁₇O₆₁) minimal yields were observed. On the other hand, the Lewis acidity of Zr(IV) salts alone led to the formation of both intra- and intermolecular amide bonds with limited efficiency as shown by the control experiments done with diverse Zr(IV) salts (Table S10 of Supporting Information). A potential mechanism involving the lixiviation of the Zr(IV) metal from the POM framework was disfavored by the low yield of **5** observed when $ZrCl_4$ and $K_7P_2W_{17}O_{61}$ were used together.

Thus, the synergistic actuation of the Zr(IV) Lewis acid and the POM framework in a single compound was pivotal to the catalytic activity observed.

Table 3. Synergistic combination of Lewis acid and POM framework is evidenced by control experiments

/ CO2	² H 1–5 mol% Cat.		0	
``NH2	DMSO, 70 °C	0 NH		h
		2a	5	
_	Catalyst	Yield 2a (%)	Yield 5 (%)	
	no catalyst	0%	3%	
	Li ₂ WO ₄ or Na ₂ WO ₄	0%		
K ₇ (P ₂ W ₁₇ O ₆₁)		0%	5%	
ZrCl ₄		32%	27%	
ZrCl ₄ + K ₇ (P ₂ W ₁₇ O ₆₁)			26%	
$[Zr(\alpha_2 - P_2W_{17}O_{61})]_2$		99%	82%	

Behavior of the metal-POM catalyst in solution. The behavior of the metal-POM 2:2 complexes in solution is influenced by the concentration, and the presence of substrates as evidenced by ³¹P NMR. Using DMSO solutions of metal-POM complexes reproducing the same nominal concentrations of catalyst used in the reactions, e.g., a solution of 0.02 mmol of metal-POM 2:2 complex in 0.60 mL of DMSO reproduces the reaction conducted at a 3.33 mol L^{-1} concentration of **3a** (see Supporting Information for details), we observed a concentration dependent equilibrium between two species for both the Zr(IV)- and Hf(IV)-Wells-Dawson POM 2:2 complex (Figures S3 and S4 of Supporting Information, respectively). These two species are likely the monomeric and the dimeric forms of the complexes, based on Le Chatelier's principle and previous reports for similar metal-POM systems.¹⁸⁻¹⁹ At the highest concentration, the equilibrium heavily favors the dimeric species. Upon addition of acid or amine substrates (100 equivalents to reproduce reaction stoichiometry) to the most concentrated solution of Hf-POM complex (0.03 mol L⁻¹ of catalyst), different species are formed (Figure S5 of Supporting Information). While benzylamine induces the formation of a monomeric species like the one observed upon dilution, the addition of acid generates a new species that could be either monomeric or dimeric in nature. As the excess of carboxylic acid substrate negatively impacts the initial reaction rate (Figure S6 of Supporting Information), this species is presumably an off-cycle resting state of the catalyst similarly to previously proposed in a similar Zr(IV)-catalyzed amidation reaction.^{17b} Interestingly, addition of 0.5 equivalent of benzylamine to this acid solution reverted this species back to the putative monomeric one (Figure S5 of Supporting Information). Considering the beneficial effect of an excess of amine in the initial rate of reaction (Figure S6 of Supporting Information), these equilibria observed for the Hf(IV)-POM in the presence of substrates are consistent with a monomeric complex, i.e., Hf(IV)-POM 1:1 complex, as the active catalyst.^{18, 20}

Tolerance to water. The reaction tolerates the addition of water up to 13% of the reaction volume without a significant decrease in the yield of **5** (Table 4). Early on in the optimization of both the intra- and intermolecular reactions, we realized the presence of molecular sieves was not improving the yield, in sharp contrast with the sensitivity to water reported previously in the literature, ^{10, 13} including Zr(IV) and Hf(IV) catalyzed reactions.^{17b, 21} To better understand this unique feature, we performed control and kinetic experiments using external water additions under controlled conditions to evaluate the effect of water in the product yield and reaction kinetics. The reaction tolerated the addition of water up to 13% of the reaction volume (a >220 molar excess of water) before a significant drop in the product yield was observed (entries 3 - 4, Table 4), thus explaining why the water formed in the reaction does not affect the yield. The yield decrease due to the addition of external water might derive from the slower reaction kinetics, as observed through the initial reaction rates (Figure S7 of Supporting Information), showing the water is tolerated by the reaction,²² as opposed to being part of the active catalytic species.^{21b, 23}

Table 4. POM framework preserves the high activity of the catalyst in the presence of up to a >220 molar excess of water

	0			
Ph´ `CO ₂ H + 3a 0.5 mmol	H ₂ N´ `Ph · 4a (1.2 equiv.)	DMSO [3.33 M], 7 <i>H₂O (table)</i>	— ➤ Ph、_ 0 °C	N Ph H 5
Entry	H ₂ O (mmol)	n _{H2O} / n _{Cat} c	Yield 5 (%)	
1	0	0	>99%	
2	0.55	110	94	
3	1.11	222	90	
4	1.39	278	69	
5	1.67	334	71	
6	4.17	834	46	
7 ^b	1.67	334	76	

Conditions: **3a** (0.500 mmol), **4a** (1.2 equiv.), 1.0 mol% $[Hf(\alpha_2-P_2W_{17}O_{61})]_2$, DMSO (0.15 mL), 70 °C (GC yields). *^a* $[Hf(\alpha_2-P_2W_{17}O_{61})]_2 = (Me_2NH_2)_{14}[Hf(\mu-O)(H_2O)(\alpha_2-P_2W_{17}O_{61})]^{b}$ 0.12 mL DMSO as solvent (reaction concentration ~3.33 M), *^c* nH₂O / nCat = mmol H₂O / mmol Catalyst.

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The POM framework likely act as a "molecular shield" to protect the catalytic metal center from the water formed in the reaction preventing its hydrolysis and stabilizing the catalytic complex against decomposition. It is well known that Zr(IV) and Hf(IV) salts hydrolyze in aqueous medium to form many species, some of which are in the form of extended polymeric chains that hinder experimental handling and product isolation.²⁴ To probe the effect of water in the Hf(IV)-POM 2:2 complex behavior in DMSO, stepwise addition of water was done to the most concentrated solution of Hf(IV)-POM complex (0.03 mol L⁻¹ of catalyst) used in the NMR study (vide supra). Upon gradual addition of water, the putative Hf(IV)-POM 2:2 dimer complex forms a monomeric species similar to what is observed upon addition of benzylamine (Figure S8 of Supporting Information). However, this water induced dissociation was not observed when the carboxylic acid and amine substrates were present, thus water is a labile ligand compared to the substrates, and its influence on the catalyst monomer-dimer equilibrium is probably not relevant for the reaction outcome (Figure S9 of Supporting Information). On the other side, Zr(IV) and Hf(IV) can coordinate up to 8 ligands, and the transient coordination of water molecules to the metal center is not enough to account for the water tolerance observed. The crystallographic structures of the catalyst,²⁵ the behavior of metal-substituted POM complexes,^{7a, 18, 20} and the hygroscopic properties of polyoxometalates²⁶ strongly suggest that part of the water is also trapped/adsorbed by the POM through H-bonding/polar interactions, thus decreasing the amount of water available to interfere with the reaction. Further attempts to correlate the amount of water with the catalyst loading revealed a non-linear relationship, indicating the complexity in the equilibria present in solution enabling this 'shielding effect'. Finally, the POM-conferred robustness of the catalyst to the water formed in the reaction was further supported by the catalyst recycle for three times without a decrease in the reaction efficiency. ³¹P NMR analysis of the recovered catalysts showed the catalyst did not decompose or changed its structure after the reaction, underlining the robustness of the metal-POM combination (see Supporting Information for details).

Conclusion

In summary, a new class of robust catalysts based on the synergic combination of Zr(IV) or Hf(IV) and Wells-Dawson POM frameworks for the direct formation of amide bonds from non-activated acids and free amines are reported. Products bearing a range of functional groups and heterocycles useful for medicinal, agrochemical and material chemists deriving from intra- and intermolecular reactions were obtained in good to excellent yields. Remarkably, water scavengers or specialized experimental setups employed to remove water, dry solvents, additives, and inert atmosphere were not necessary to observe high yields. Moreover, the catalyst could be recycled without loss of efficiency due to the robustness conferred to the Lewis acid

by the POM framework. Mechanistic experiments showed the POM framework likely inhibits the hydrolysis of the Lewis acidic metal by the water formed in the reaction, and a high catalytic activity is obtained even in the presence of a >220 molar excess of externally added water. This ligand induced robustness without impacting the reactivity is strikingly different from previous protocols in which the rigorous exclusion of water was necessary to achieve high conversions. Given the diversity of POMs known, along with its structural versatility, ready availability and low cost, the water tolerance observed in the amide bond formation strongly suggests the POMs are promising ligands to develop many other safer, greener and robust homogeneous catalytic processes.

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ASSOCIATED CONTENT

Supporting Information. Experimental procedures, supplementary experiments and copy of NMR spectra. This information is available free of charge on the ACS Publications website.

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