Addition of carbon nucleophiles to hemiaminals promoted by a Lewis acidic polyoxotungstate

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Abstract : A Lewis acidic hafnium(IV) ion incorporated in a polyoxotungstate (POM/Hf) was successfully employed as recoverable catalyst in the nucleophilic addition of carbon nucleophiles, such as silyl enol ethers, silyl ketene acetals, β-diketones and β-diketoesters, to unprotected hydroxy aminal at room temperature. The corresponding α-substituted heterocycles were obtained in good yields and the recovered POM catalyst could be reused up to three times without significant loss of activity.

In the synthesis of nitrogen-containing heterocycles, *N*-acyliminium ions have been widely used as efficient electrophiles.[1] Most often these stabilized ionic intermediates are generated from precursors such as amino nitrile, N,O acetals in acidic medium in the presence of stoichiometric quantities of Brønsted acids or traditional Lewis acids, such as $BF_3 \cdot OEt_2$, $TiCl_4$, $SnCl_4$, $InCl_3$, $NbCl_5$ and $Zn(OTf)_2$, which are environmentally harmful.[2,3,4] More recently, catalytic versions have been reported that take advantage of the Lewis acidic properties of lanthanides triflates[5] or N-trimethyl silyl-bis-(trifluoromethanesulfonyl)imide derivatives ($HNTf_2$; $Zn(NTf_2)_2$)[6] or Brønsted organocatalysts.[7] Even if those conditions are efficient for synthetic purpose,[8] the need of alkoxy- or acetoxy- aminals lengthen the overall process. Indeed, from the point of view of atom economy and environmental reasons, the direct use of unprotected hemiaminals, which are more easily available, would be better.[9] Some results in this field, including those with activated benzylic alcohols have been reported[9d] but to our knowledge, none of them reports the recovery of the catalyst.

Polyoxometalates (POMs) as rapidly expanding green catalysts, are widely used in oxidation and acid catalyzed transformations.[10] In a previous work, organic soluble Lanthanide complexes of POMs were synthesized by grafting Lewis acidic cations (Y^{3+}, Yb^{3+}, La^{3+}, Hf^{3+}, Sc^{3+} …) onto monolacunary Dawson polyoxotungstates $[P_2W_{17}O_{61}]^{10-}$ and used as Lewis acid catalysts for Mannich type reactions.[11] We demonstrated that the coordination between the metal atoms and water molecules allows an indirect Brønsted acidity useful to catalyze Mukaiyama-aldol reactions.[12] In order to expand the application of those catalysts, the hafnium(IV) complex $TBA_5K[\alpha_1Hf(H_2O)_4P_2W_{17}O_{61}]$ (POM/Hf) (scheme 1) was selected as a representative species and used in the challenging nucleophilic addition reactions to *in situ* generated cyclic *N*-acyliminium ions from 5-*N*-Boc-2-hydroxypyrrolidine **1a** and *N*-Boc-2-hydroxypiperidine **1b** respectively.
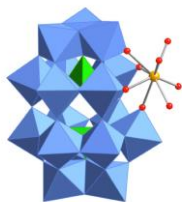
Scheme 1 Representation of the anion of $TBA_5K[\alpha_1\text{-}Hf(H_2O)_4P_2W_{17}O_{61}]$. The phosphotungstic framework is shown as coordination polyhedra (blue W, green P). The Hf^{4+} ion (yellow) is coordinated to four terminal oxo ligands and four water molecules (red).

We report herein our results concerning the POM/Hf-mediated nucleophilic additions of silyl enol ethers, ketene-acetals and activated methylene C-nucleophiles to hemiaminals that provide an easy access to substituted pyrrolidines and piperidines derivatives *via* cyclic *N*-acyliminium ions at room temperature.

We initially chose to examine the addition of 1-Phenyl-1-trimethylsiloxyethylene **2a** to *N*-Boc-2-hydroxypyrrolidine **1a** as a model reaction in the presence of 10 mol % catalyst at room temperature in CH_3CN. The expected product **3a** was isolated in 69 % yield after 20 min. (Table 1, entry 2).

**Table 1** Optimization of the amount of catalyst for the reaction between *N*-Boc-2-hydroxypyrrolidine **1a** and 1-Phenyl-1-trimethyl-siloxyethylene **2a**.
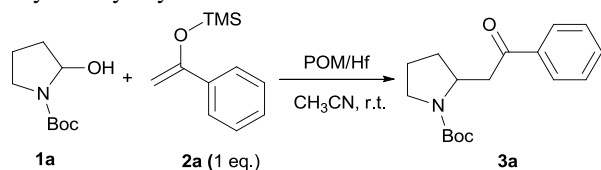
Entry	POM/Hf (mol%)	Time	Yield (%)
1	-	24 h	-
2	10	20 min	69
3	1	1 h	72
5	0.25	17 h	80

It is possible to decrease the loading of catalyst down to 0.25 mol% albeit the reaction time should be increased up to 17 h to achieve a similar yield (Table 1, entry 4). However, the amount of 1 mol% of POM/Hf was chosen to extend the scope of the nucleophilic addition as well as the use of *N*-Boc-2-hydroxypiperidine **1b** as electrophile..
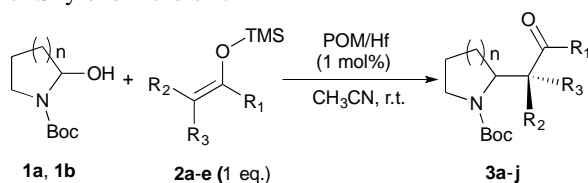
Unfortunately, the reaction of 1-Phenyl-1-trimethylsiloxy-ethylene **2a** with *N*-Boc-2-hydroxypiperidine **1b** was not as efficient as for **1a**. Indeed, in the previous conditions a low yield of the expected product **3b** together with a total consumption of the starting material was observed (Table 2, entry 2), a pattern that results from the elimination of water from the corresponding iminium. Actually, the *in-situ* formed *N*-acyliminium intermediate resulting from the interaction of the *N*-Boc-2-hydroxypiperidine **1b** and POM/Hf can lead to the relatively stable enecarbamate by-product **4b**, or can undergo self-condensation to further form the "dimeric" enecarbamate **5b** which were proved to be inert to the nucleophile **2a**.[13,14] Both forms of enecarbamate cause the competitive loss of starting materials, which can explain the relatively low yield for all the 2-substituted *N*-piperidines.
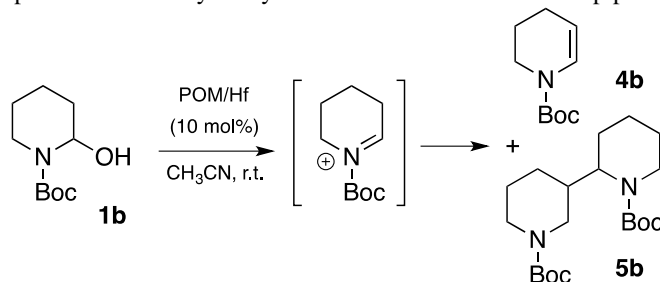
Scheme 2 Competitive elimination and dimerization of *N*-Boc-2-hydroxypiperidine **1b** *via* N-acyliminium.

Thereafter, the scope of the reaction was investigated with different substrates N-Boc pyrrolidine **1a** and N-Boc piperidine **1b** and a series of nucleophiles such as silyl enol ethers or ketene-acetals. The 1-(trimethylsiloxy)-cyclohexene **2c** acts as a good nucleophile with **1a** and gives the corresponding 2-substituted *N*-Boc pyrrolidine **3e**, in 63% yield after 4h. Interestingly, an excellent yield of 98% as a 70:30 mixtures of diastereomers could be obtained by the used of 10 mol % of catalyst (Table 2, entry 5). Both 1- and 2-(trimethylsilyloxy) butadiene **2d** and **2e** reacted moderately with pyrrolidine **1a** (Table 2, entries 7 and 9).

Attempts to employ methyl trimethylsilyl dimethylketene acetal **2b** and 1-(trimethylsiloxy)-cyclohexene **2c** as nucleophiles with *N*-Boc-2-hydroxypiperidine **1b** failed, which might be attributed to the relative steric hindrance of the secondary or tertiary reactive C-atom whereas the less substituted nucleophiles **2d-e** reacted in low yields. The competitive elimination of water on **1b** (vide supra) simultaneously to the partial hydrolysis of the nucleophiles should be responsible of these unproductive results. In conclusion, our investigation on the addition of trimethylsilyl enol ethers to the 5-membered *N*-acyliminium precursor **1a** under Lewis acidic POM/Hf revealed that moderate to high yields of the corresponding 2-substituted *N*-Boc pyrrolidines were obtained. Lower yields were observed for the reaction between the same nucleophiles and the 6-membered precursor **1b**.

Table 2. POM-catalyzed Reaction with Silylenol Ethers **2**.

Entry	**1**	Nucleophile	Time (h)	Product	Yield (%)
1	**1a**	**2a** (O-TMS, Ph)	1	**3a**	72
2	**1b**		0.3	**3b**	16
3	**1a**	**2b** (O-TMS, O-Me)	18	**3c**	58[a]
4	**1b**		16	**3d**	-
5	**1a**	**2c** (cyclohexenyl O-TMS)	4	**3e**	63[b], 98[c]
6	**1b**		4	**3f**	-
7	**1a**	**2d** (O-TMS diene)	24	**3g**	69[d], 62[d]
8	**1b**		1.5	**3h**	24[e]
9	**1a**	**2e** (O-TMS diene)	4	**3i**	45[a]
10	**1b**		4	**3j**	10[a]

[a] 10 mol% catalyst was used. [b] Diastereomeric ratio of **3e** (70 : 30). [c] After 18 min. with 10 mol% catalyst. [d] After 100 min. with 10 mol% cat. [e] 4 mol% catalyst was used.

To further expand the scope of the reaction, the use of 1,3-dicarbonyl compounds **6** as nucleophiles was also investigated. Such enolizable C-nucleophiles are expected to react smoothly in such slightly acidic conditions. In the presence of POM/Hf, they provided the corresponding 2-substituted pyrrolidine adduct **7** in moderate to good yields as illustrated by the representative examples in Table 3. Acyclic diketones or keto esters reacted with electrophile **1a** in yields ranging from 49 to 64% (Table 3 entries 1-6). Excellent yields were achieved in the reactions with 1,3-cyclopentanedione **6e** or 1,3-cyclohexanedione **6f**. The 2-substituted *N*-Boc-pyrrolidines **7i** and **7k** were isolated in 96 and 85 % yields respectively with 1 mol% of POM/Hf as catalyst (Table 3, entries 9 and 11). The desired products **7i-k** exist mainly in their corresponding enolic form as indicated from the inspection of the corresponding ^{1}H and ^{13}C NMR spectra (see SI). The products **7c**, **7e** and **7g** were formed as difficultly separable mixture of diastereoisomers. While the purification of **7d** allowed its isolation as a single, analytically pure diastereomer, **7h** and **7l** could not be obtained as pure products. Besides, the attempt to employ diethyl malonate as nucleophile failed so far. As previously observed with silylenol ethers as nucleophyles, lower yields were noticed with hydroxypiperidine **1b** in comparison to hydroxypyrrolidine **1a** (Table 3, compare entries 1,3,5,9 *vs* 2,4,6,10). The lower reactivity of the 6-membered iminium in comparison to the 5-membered one, should be responsible for the presence of elimination products.[13-16]

Table 3. POM-catalyzed Reaction with 1,3-dicarbonyls (β-diketones or β-ketoesters).

Entry	1	Nucleophile	Time (h)	Product	Yield (%)
1	**1a**	**6a**	3	**7a**	63
2	**1b**	**6a**	1	**7b**	57
3	**1a**	**6b** (Ph)	20	**7c**	64
4	**1b**	**6b**	39	**7d**	8[a]
5	**1a**	**6c** (OEt)	6.5	**7e**	55
6	**1b**	**6c**	22	**7f**	35
7	**1a**	**6d** (Cl, OMe)	5.5	**7g**	49
8	**1b**	**6d**	5.5	**7h**	-
9	**1a**	**6e**	5.5	**7i**	96[b]
10	**1b**	**6e**	4	**7j**	83[b]
11	**1a**	**6f**	2	**7k**	85[b]
12	**1b**	**6f**	2	**7l**	-

[a] only one diastereomer was successfully separated. [b] 1 mol% catalyst was used. [c] Diastereomer ratio of **7c** (76 : 24), **7e** (66 : 34) and **7g** (55 :45)

In our previous work, the POM/Hf has been used for its Lewis acidity in Mannich reactions and its induced Brønsted acidity for Mukaiyama-aldol reactions. We thus decided to explore the acidity involved in the present activation of hemiaminals **1a,b**.

For that purpose, pyridine and 2,6-di-*tert*-butylpyridine were used as additives during the POM/Hf catalyzed nucleophilic addition.[17] Both bases are strong enough to capture protons and should inhibit any Brønsted acid-catalyzed reaction. While pyridine can also bind to metal centers, thus inhibiting strongly Lewis acid-catalyzed reactions, 2,6-di-*tert*-butylpyridine is highly hindered and should less coordinate to the Lewis acidic Hafnium ion located in our bulky POM. Therefore its effect on Lewis acid catalysis is expected to be weak. In our experiments, when pyridine (20 mol%) was added, the reaction between 1-phenylvinyl trimethylsilyl ether **2a** (5 equiv.) and *N*-Boc-2-hydroxypyrrolidine **1a** was totally halted, while no influence was observed in the presence of 2,6-di-*tert*-butylpyridine (Table 4). We thus conclude that the reaction is catalyzed in a Lewis acidic manner by the coordination of the substrates **1a,b** to the Hf^{4+} ion incorporated in the POM.

**Table 4**. Mechanism Consideration, Inhibition with Pyridine Derivatives as Additive
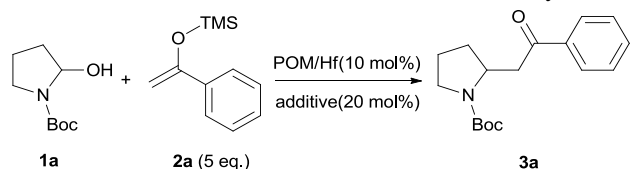
Entry	Additive	Time (h)	Yield (%)
1	-	1	69
2	2,6-di-*tert*-butylpyridine	1	72
3	pyridine	1	-

We also examined the possible recovery of our catalyst. Due to the specific solubility of POMs, the catalyst should be easily recovered. Indeed, at the end of the reaction the addition of a solvent mixture of acetone/ethanol/diethyl ether (1/1/20) resulted in the precipitation of the POM/Hf as a white powder (with a recovery of >95% yield). In this study, the recyclability of catalyst has been tested on the 1 mol% scale, and its purity was checked by ^{31}P NMR after each round. The catalyst can be reused at least for three times without losing its reactivity. Slow decrease was then observed due to the few mg handled as well as probable slow decomposition and/or dimerization of the catalyst as time going.[18]

Table 5 Recyclability of the Catalyst.
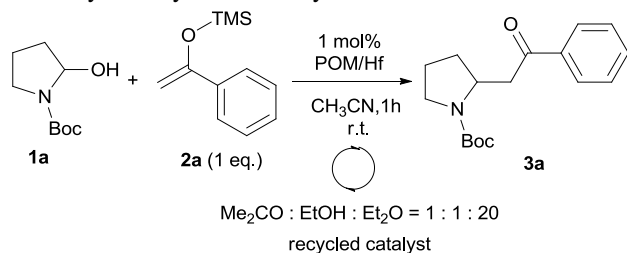
Cycle	1	2	3	4
Yield (%)	72	74	69	49

Finally, we also examined the addition of allyltrimethylsilane to the reagent **1a**. By using 20 mol% of POM/Hf catalyst, a 17% yield of the expected 2-allyl carbamate product **8a** was obtained after 120 h. Although the yield is relatively low, this is the first time such kind of polyoxometalate complex (POM/Hf) allows the nucleophilic addition of allyltrimethylsilane onto emiaminal via the *in situ* formation of *N*-acyliminium ions.
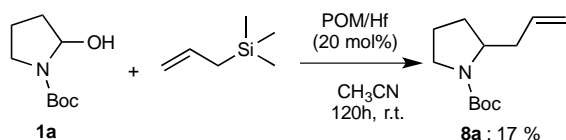
Scheme 3 : Reaction with allyl silane

In summary, we used a Hafnium containing Dawson polyoxometalate as soluble catalyst for the carbon nucleophilic addition of silyl ether and methylene activated pro-nucleophiles to cyclic hemiaminals. The *in-situ* formed *N*-acyliminium ions reacted smoothly at room temperature giving the desired pyrrolidine and piperidine products in moderate to good yields. The POM/Hf has been proved to catalyze the reaction in a Lewis acidic pathway. It can be easily precipitated and removed taking advantage of its specific solubility. Recycling of the catalyst is possible for a limited number of cycles. Studies are still underway for its further application in other organic reactions and its asymmetric versions.

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