Transition-Metal Catalysis

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With Molecular-Oxygen-Activated Lewis Acids: Dinuclear Molybdenum Complexes for Aza-Diels–Alder Reactions of Acyl Hydrazones**

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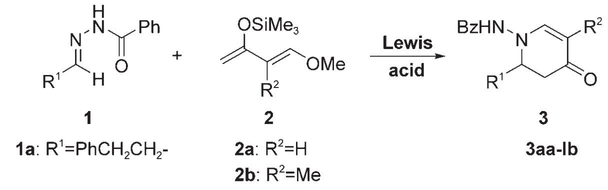
Lewis acids are amongst the most important activating groups in chemistry, and their use is ubiquitous in synthesis. As a result, the last two decades have seen a veritable explosion of interest in the synthesis of Lewis acids based on almost every suitable metal in the Periodic Table and their application as catalysts in a broad range of reactions.[1] In addition to the nature of the metal center, the activity of Lewis acids may be influenced by external factors, such as coordinating additives and variation of the associated counteranion; for example, exchanging a highly coordinating halogen anion for the less nucleophilic triflate anion is frequently used to increase the activity of Lewis acids. Apart from these techniques, however, there are few effective ways of increasing Lewis acidity. We now report a new type of Lewis acid system that is activated by molecular oxygen, which to the best of our knowledge represents the first example of a Lewis acid that is activated in this way. Whilst dinuclear molybdenum compounds [$Mo_2(OAc)_4$] have been investigated as inorganic compounds,[2] their use in synthesis has remained relatively unexplored.[3] Furthermore, we demonstrate that this catalyst mediates the hitherto unknown Diels–Alder reaction of aromatic acyl hydrazones with Danishefsky dienes (Scheme 1).[4]



Scheme 1. Aza-Diels–Alder reaction catalyzed by a Lewis acid.

The aza-Diels–Alder reaction of imines with dienes is an important method for the construction of substituted piper-

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idine derivatives. However, some imines are not suitable for use in these reactions owing to their instability, which leads to low yields of the isolated cyclic products. Hydrazones offer a solution to this problem, as they are known to act as stable imine equivalents and the hydrazone N–N bond can be readily cleaved to give amine functionalities.[5] We have previously demonstrated that acyl hydrazones derived from aliphatic aldehydes can function as electrophiles in allylations and Mannich-type reactions in the presence of Lewis acid catalysts, such as $[Sc(OTf)_3]$ (OTf = trifluoromethanesulfonate).[6] However, when we attempted to extend this methodology to the aza-Diels–Alder reactions of hydrazones with Danishefsky dienes, we found that the reaction proceeded only sluggishly in the presence of conventional Lewis acids such as $[Sc(OTf)_3]$, $[Yb(OTf)_3]$, $BF_3{\cdot}OEt_2$, and $ZnCl_2$ (Table 1, entries 1–4). On further investigation, it was discovered that when the catalyst was switched to $[Mo_2(OAc)_4]$, the reaction proceeded smoothly to afford the desired adduct in good yield (entry 5). A screen of common laboratory solvents revealed that acetonitrile and acetone gave the optimum results. The use of other less polar (toluene, CH_2Cl_2, EtOAc) or more polar solvents ($MeNO_2$, dimethylformamide (DMF)) did not lead to any improvement in yield (26–56 %).

Whilst delighted by these results, we were concerned by the poor reproducibility of the reaction. After careful examination of the reaction conditions, it was found that molecular oxygen present as a contaminant in the system exerted a profound effect on reactivity (entry 6) and that its exclusion led to a dramatic reduction in yield (entry 7).[7] We therefore deliberately sought to introduce molecular oxygen into the reaction by controlled preparation of the catalytic species, thus the catalyst solution was pretreated with O_2 prior to the addition of the diene.

Table 1: Aza-Diels–Alder reaction of **1a** with **2a** catalyzed by a Lewis acid.[a]

Entry	Catalyst	Solvent	Yield of **3aa** [%]
1[b]	$[Sc(OTf)_3]$	MeCN	–[c]
2[b]	$[Yb(OTf)_3]$	MeCN	8
3[b]	$BF_3{\cdot}OEt_2$	MeCN	22
4[b]	$ZnCl_2$	MeCN	trace amount
5[b]	$[Mo_2(OAc)_4]$	MeCN	69
6	$[Mo_2(OAc)_4]$	MeCN	70
7[d]	$[Mo_2(OAc)_4]$	MeCN	< 10
8[e]	$[Mo_2(OAc)_4]$	acetone	70
9	$[Mo_2(OCOC_5H_{11})]$	MeCN	64
10	$[Mo_2(OBz)_4]$	MeCN	60
11	$[Mo_2(OCOCF_3)_4]$	MeCN	trace amount
12	$[Mo_2(OTf)_4]{\cdot}4\,AcOEt$	MeCN	no reaction
13[f]	$[Mo_2(OAc)_4]$	MeCN	71
14[g]	$[Mo_2(OAc)_4]$	MeCN	75
15[g,h]	$[Mo_2(OAc)_4]$	MeCN	85
16[h,i]	$[Mo_2(OAc)_4]$	MeCN	55
17[k]	$[MoO_2]$	MeCN	no reaction
18[k]	$[MoO_3]$	MeCN	no reaction

[a] In the case of the Mo_2 catalysts, the Mo_2 species was freshly prepared from $[Mo(CO)_6]$ according to a literature procedure[8] and stored under Ar in a glove box. For the preparation of the catalyst, the Mo_2 salt (10 mol %) and hydrazone were heated under O_2 at 50 °C for 3 h unless otherwise noted. After addition of the diene, the reaction was carried out under Ar at 20 °C for 24 h. [b] Reaction carried out at room temperature using 20 mol % catalyst with no activation. No precautions to exclude oxygen were taken. [c] Complex mixture. [d] Reaction performed under Ar in degassed MeCN. [e] Treated with O_2 at room temperature. [f] Reaction carried out at 40 °C for 24 h. [g] 5 mol % of catalyst was used at 40 °C for 24 h. [h] Powdered 5-Å MS were added (50 mg/0.4 mmol substrate). [i] 2 mol % of catalyst was used at 40 °C for 24 h. [k] Activated by heating under O_2 at 50 °C for 3 h prior to addition of the hydrazone.

The effect of varying the molybdenum source was also investigated. Trials showed that use of dinuclear Mo sources with a counterion that has a similar basicity to acetate, such as $[Mo_2(OCOC_5H_{11})_4]$ and $[Mo_2(OCOPh)_4]$, gave very similar results (entries 9 and 10); however, the use of $[Mo_2(OCOCF_3)]$ or $[Mo_2(OTf)_4]$ resulted in complete shutting down of the reaction (entries 11 and 12). Raising the reaction temperature to 40 °C resulted in a marginal improvement in yield, whereas decreasing the catalyst loading to 5 mol % at 40 °C raised the yield still further to 75 % (entry 14). The addition of dried 5-Å molecular sieves (MS) to the reaction significantly improved the efficiency of the reaction and afforded the desired adduct in 85 % yield (entry 15); however, attempts to decrease the catalyst loading down to 2 mol % resulted in a steep drop in yield (entry 16). It is important to note that use of the mononuclear oxidized molybdenum species (entries 17 and 18) did not promote the reaction at all.[9] This behavior suggests that the catalyst involves a species with at least two metal centers in a well-defined spatial array.[10]

With these results in hand, we turned our attention to the synthetic scope of the reaction (Table 2). Benzoylhydrazones

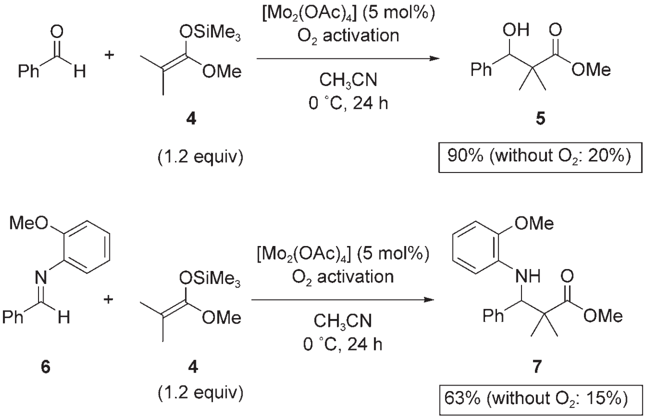
Table 2: Substrate scope in the reaction of hydrazone **1** with Danishefsky diene **2** with nuclear Mo Lewis acid catalysis.[a]

Entry	R^1	Diene	Product	Yield [%][b]
1	$PhCH_2CH_2$ (**1a**)	**2a**	**3aa**	85
2	$PhCH_2CH_2$ (**1a**)	**2b**	**3ab**	86
3	CH_3– (**1b**)	**2a**	**3ba**	88
4	CH_3– (**1b**)	**2b**	**3bb**	77
5	C_3H_7– (**1c**)	**2a**	**3ca**	85
6	C_3H_7– (**1c**)	**2b**	**3cb**	76
7	C_5H_{11}– (**1d**)	**2a**	**3da**	85
8	C_5H_{11}– (**1d**)	**2b**	**3db**	82
9	C_7H_{15}– (**1e**)	**2a**	**3ea**	81
10	C_7H_{15}– (**1e**)	**2b**	**3eb**	70
11	C_9H_{19}– (**1f**)	**2a**	**3fa**	70
12	C_9H_{19}– (**1f**)	**2b**	**3fb**	50
13	c-C_6H_{10}– (**1g**)	**2a**	**3ga**	16
14	$(CH_3)_2CHCH_2$– (**1h**)	**2a**	**3ha**	62
15	$(CH_3)_2CHCH_2$– (**1h**)	**2b**	**3hb**	73
16	$TBSOCH_2CH_2$– (**1i**)	**2a**	**3ia**	86
17	$TBSOCH_2CH_2$– (**1i**)	**2b**	**3ib**	68
18	$TIPSC{\equiv}C$– (**1j**)	**2a**	**3ja**	84
19	$TIPSC{\equiv}C$– (**1j**)	**2b**	**3jb**	61
20c	C_6H_5– (**1k**)	**2a**	**3ka**	65
21	C_6H_5– (**1k**)	**2b**	**3kb**	72
22c	p-ClC_6H_4– (**1l**)	**2a**	**3la**	64
23	p-ClC_6H_4– (**1l**)	**2b**	**3lb**	42

[a] $[Mo_2(OAc)_4]$ (5 mol %), the hydrazone substrate, and 5-Å MS were mixed in dry MeCN and heated to 50 °C under O_2 atmosphere for 3 h. After addition of the diene in MeCN (final reaction mixture concentration = 0.2 mM), the reaction was carried out at 40 °C under Ar for 24 h. [b] Yield of the isolated product analysis. [c] Conditions: 10 mol % catalyst, reaction time = 72 h. TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

prepared from non-branched aldehydes performed well in the reaction, thus affording the corresponding 4-piperidenone products in good yields (entries 1–12). However, the introduction of α- or β-branching had a detrimental effect on the efficiency of the reaction (entries 13–15). The mild nature of the procedure was attested to by the observation that a benzylhydrazone bearing a silyloxy functionality could be employed in the reaction without significant deprotection (entries 16 and 17). Additionally, alkynyl hydrazones worked well as they gave the desired adducts in good yields (entries 18 and 19). It should be noted that aryl hydrazones also functioned well in the reaction, although longer reaction times were required to achieve good yields (entries 20–23).

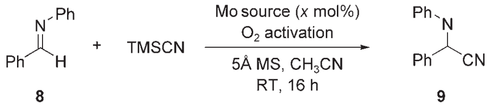
The molecular-oxygen-activated molybdenum catalyst was also found to be effective in other Lewis acid mediated reactions (Scheme 2). Gratifyingly, the Mukaiyama aldol reaction between benzaldehyde and silyl enol ether **4** proceeded smoothly in the presence of 5 mol% $[Mo_2(OAc)_4]$ to afford the desired β-hydroxy ester **5** in excellent yield. Similarly, the corresponding Mannich-type addition of **4** to *N*-*o*-methoxyphenyl imine **6** was also catalyzed by the oxidized molybdenum system to give β-imino ester **7** cleanly and efficiently. In both cases, it was found that activation of the catalyst by pretreatment with molecular oxygen was essential for an efficient reaction: the corresponding reactions carried out without O_2 activation proceeded to give the products in much lower yields than those observed under the oxygen-activated conditions.



Scheme 2. Mukaiyama aldol and Mannich-type reactions catalyzed by the $[Mo_2(OAc)_4]/O_2$ system.

In addition, it was found that the $[Mo_2(OAc)_4]/O_2$ system could also be applied to the catalysis of the Strecker reaction of imine **8** with trimethylsilyl cyanide (TMSCN) to give the corresponding α-cyano imine **9** (Table 3). In these cases as well, the controlled introduction of molecular oxygen was found to be essential for an efficient reaction. Oxidation of freshly prepared $[Mo_2(OAc)_4]$[8] prior to use afforded the desired addition product in very high yield (entry 1), whereas omission of the oxidative conditioning step resulted in a drastic decrease in the efficiency of the reaction (entry 2). Interestingly, the reaction proceeded only very sluggishly in the presence of molecular oxygen and the mononuclear $[MoO_x]$ species (entries 3 and 4). This observation further reinforces the hypothesis that a binuclear array of molybdenum centers is responsible for the efficient action of the novel catalyst.

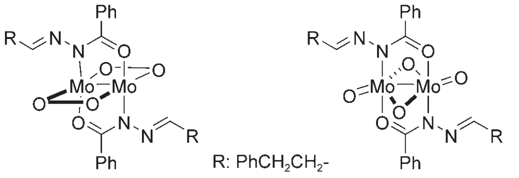
Table 3: Strecker reaction of (*E*)-*N*-benzylidenebenzenamine (**8**) with TMSCN.



Entry	Mo source	Mo loading [mol%]	O_2 activation[a]	Yield [%][b]
1[c]	$[Mo_2(OAc)_4]$	5	yes	96
2[c]	$[Mo_2(OAc)_4]$	5	no	24
3	$[MoO_2]$	10	yes	18
4	$[MoO_3]$	10	yes	21

[a] Mo source, imine, and MS heated under O_2 for 3 h prior to the addition of TMSCN. [b] Yields of the isolated products. [c] Freshly prepared $[Mo_2(OAc)_4]$ (bright yellow).

Next, we gave consideration to the structure of the active catalyst species. Our working hypothesis involves an oxidized dinuclear molybdenum species; therefore, as molybdenum complexes are readily oxidized and Cotton et al. reported[10] the preparation and X-ray crystallographic characterization of $[Mo_2(\eta_2\text{-}O_2CCH_3)_2(\mu_2\text{-}DXylF^{2,6})_2(\mu_2\text{-}O_2)]$ (**10**; DXylF = *N,N*,′-di(2,6-xylylformamidine)), a dinuclear molybdenum complex in which a diamidinate ligand is coordinated to the metal centers and has two bridging oxygen atoms that span the Mo–Mo bond, we examined the species obtained by heating $[Mo_2(OAc)_4]$ with hydrazone **1a** in MeCN by electrospray ionization mass spectroscopy (ESI MS; solvent: MeCN, negative mode). A major peak at *m*/*z* 758 was observed, which corresponds to a molecular formula of $C_{32}H_{30}Mo_2N_4O_6$. By analogy with complex **10**, we tentatively assigned this species as having one of the two possible structures shown in Scheme 3. Moreover, the aza-Diels–Alder reaction proceeded in quite low yield (< 10%) in the presence of 50 mol% $[Mo_2(OAc)_4]$. This result provided further circumstantial evidence for our hypothesis and indicated that the two hydrazone molecules that coordinate to the Mo_2 species were less reactive and that the dimolybdenum–hydrazone complex activates free the hydrazone towards cyclization.



Scheme 3. Plausible structures for the catalytic species formed from $[Mo_2(OAc)_4]$ and hydrazone **1a** under O_2 in MeCN.

In summary, we have discovered a new type of Lewis acid catalyst based on molybdenum, which relies on activation by molecular oxygen for its function. The novel complex catalyzes the aza-Diels–Alder reaction of a range of acyl hydrazones with Danishefsky dienes to afford 4-piperidinones in good yields. Additionally, the same catalyst efficiently mediates Mukaiyama aldol and Mannich-type reactions as well as the addition of TMSCN to imines. In all cases, activation by molecular oxygen was found to be crucial for high catalytic activity; the absence of such activation resulted in a dramatic decrease in efficiency and yield. Further investigations into the synthetic scope of the reaction and catalyst structure are in progress.

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