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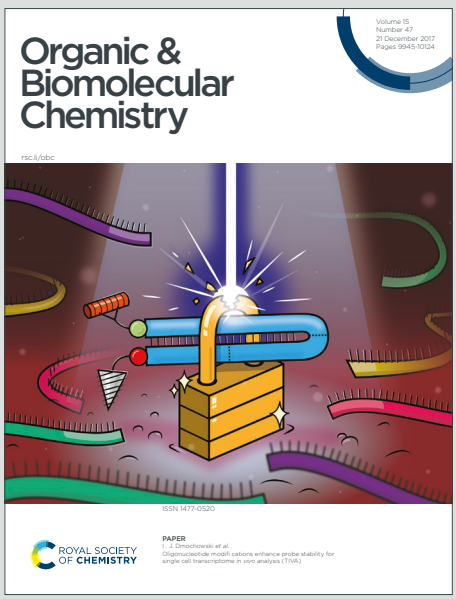

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ARTICLE

Deoxygenation reactions in organic synthesis catalyzed by dioxomolybdenum(VI) complexes

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Dioxomolybdenum(VI) complexes have been applied as efficient, inexpensive and benign catalysts to deoxygenation reactions of a diverse number of compounds in the last two decades. Dioxomolybdenum complexes have demonstrated wide applicability to the deoxygenation of sulfoxides into sulfides and reduction of N–O bonds. Even the challenging nitro functional group was efficiently deoxygenated, affording amines or diverse heterocycles after reductive cyclization reactions. More recently, carbon-based substrates like epoxides, alcohols and ketones have been successfully deoxygenated. Also, dioxomolybdenum complexes accomplished deoxydehydration (DODH) reactions of biomass-derived vicinal 1,2-diols, affording valuable alkenes. The choice of the catalytic systems and reductant is decisive to achieve the desired transformation. Commonly found reducing agents involved phosphorous-based compounds, silanes, molecular hydrogen, or even glycols and other alcohols.

1. Introduction

Molybdenum is a d-block transition metal with atomic number 42. Although not very abundant in Earth's crust, it is the 25th most common element in oceans. Molybdenum possesses different oxidation states varying from –I to +VI, which are the basis of its rich redox chemistry. In addition, molybdenum has been identified as an essential element for life, as it could be found as a component of the active sites and cofactors of several enzymes.[1] Except for nitrogenase in which Mo is present in the FeMoco cofactor (into a $[MoFe_7S_9]$ cluster), molybdenum is bound to a pyranopterin nucleus (also known molybdopterin) in molybdoenzymes by coordination to sulfur atoms. These molybdoenzymes could be classified into three main families DMSO reductase, sulfite oxidase and xanthine oxidase, whose molybdenum centers in oxidized Mo(VI) form are depicted in Figure 1. These enzymes, also called oxotransferases, catalyze electron and oxygen transfer reactions performed on carbon, nitrogen, and sulfur substrates. As its importance in biological systems illustrates, Mo is much less toxic than most other transition metals. In consequence, Mo has been identified as a suitable inexpensive biorelevant metal in sustainable metal catalysis.[2]

In organic synthesis, high-valent molybdenum centers have played an essential role as catalysts in alkene and alkyne metathesis[3] and by mimicking the behavior of molybdoenzimes in oxygen atom transfer reactions. In this latter group, dioxomolybdenum(VI) complexes have been employed as catalysts for the deoxygenation of multiple organic substrates.[4] The deoxygenation of organic compounds is a fundamental reaction extensively used in organic synthesis.

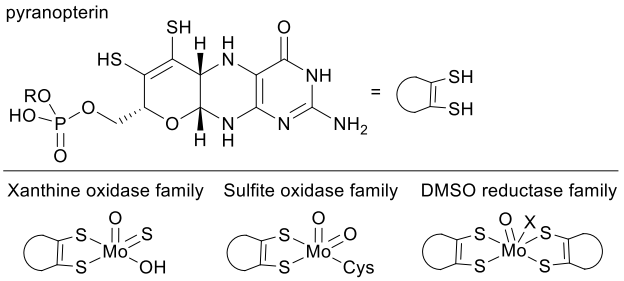

Figure 1 Molybdenum oxotransferases.

This short review intends to summarize recent methodologies developed for the deoxygenation of organic compounds under dioxomolybdenum catalysis. The review focuses mainly on homogeneous catalysis over the last two decades, although heterogeneous catalysts bearing well-defined single-site dioxomolybdenum centers are also covered. Other heterogeneous catalysts are beyond this revision. The methodologies have been classified according to the functional group, which is deoxygenated, and the reducing agent employed.

2. Deoxygenation of S–O bonds

The deoxygenation of sulfoxides to sulfides is a useful transformation in asymmetric synthesis when using chiral sulfoxides as auxiliaries, as they typically require reduction to sulfides prior to their removal. So, the development of flexible and highly selective reductive transformation of sulfoxides to their corresponding sulfides continues to attract considerable attention.[5]

As mentioned above, various metalloenzymes contain high-valent oxo-molybdenum centers. These molybdoenzymes, such as sulfite oxidases, nitrate reductases, or dimethylsulfoxide reductases (DMSOR), are involved in oxygen atom transfer reactions (OAT). For

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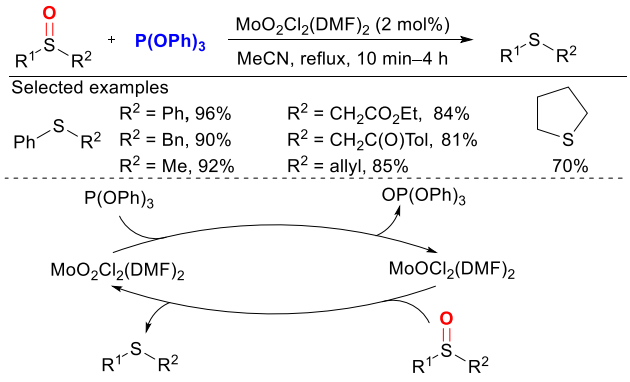
example, DMSOR enzymes catalyze the reduction of dimethylsulfoxide (DMSO) to dimethylsulfide (DMS).[1a] High-valent oxo-molybdenum complexes have been extensively studied to unravel the mechanism of these relevant biological processes.[6] In this sense, numerous research groups have designed and evaluated different model systems of $Mo^{VI}O_2/Mo^{IV}O$ and $Mo^{VI}O/Mo^{IV}$ couples in the oxidation and reduction of various biological substrates.[7] In this context, tertiary phosphines have emerged as convenient and easily modulable alternatives to biological substrates. Interestingly, these studies served as a valuable starting point to design efficient catalytic processes with significant applications in organic synthesis by mimicking the OAT of molybdoenzymes.[6a] In most cases, the reactivity of these synthetic analogs in OAT has been evaluated by the oxidation of tertiary phosphines to form the corresponding phosphine oxide using an excess of DMSO (typically as solvent or cosolvent) as electron acceptor and oxygen atom donor.

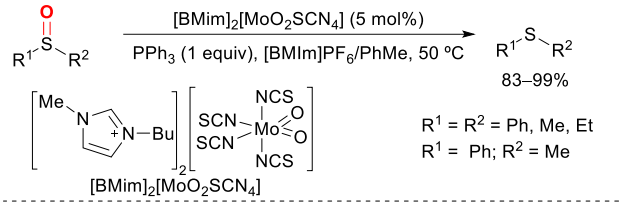
2.1. Phosphorus compounds as reductants

Initially, it was pointed out that OAT reactions could be more easily promoted by dioxomolybdenum complexes attached to *S*-based ligands.[8] However, it was later demonstrated that these ligands were not crucial and could be efficiently replaced by other species such as poly- and bispyrazolylborates.[9] Pioneering work by Arnáiz and co-workers demonstrated that simple, easily accessible *cis*-dihalodioxomolybdenum complexes could be engaged in OAT reactions.[10] Based on these findings, Sanz, Arnáiz and co-workers described the deoxygenation of a wide range of sulfoxides using $MoO_2Cl_2(DMF)_2$ as catalyst and a stoichiometric amount of triphenyl phosphite as reductant (Scheme 1).[11] Although the reaction occurs in different solvents, the reaction rate is faster when performed in MeCN. In addition, the formed $O{=}P(OPh)_3$ byproduct was easily removed, affording the desired sulfides in high yields. This procedure showed excellent chemoselectivity, and esters, ketones, halogens, or C–C multiple bonds are well-tolerated. ^{1}H and ^{31}P-NMR studies suggested that initially the $MoO_2Cl_2(L)_2$ catalyst is reduced by $P(OPh)_3$ affording $O{=}P(OPh)_3$ and $MoOCl_2(L)_2$. The formed Mo(IV) complex promotes the deoxygenation of the sulfoxides regenerating the initial Mo(VI) catalyst and releasing the sulfide.



Scheme 1 $MoO_2Cl_2(DMF)_2$-catalyzed deoxygenation of sulfoxides using $P(OPh)_3$.

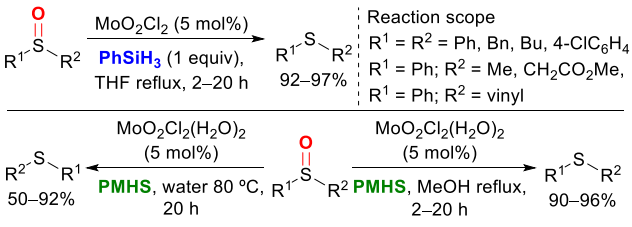
Also, several room-temperature ionic liquids containing tetrathiocyanatodioxomolybdate(VI) anion were designed to act as suitable catalysts for deoxygenation reactions (Scheme 2).[12] A selection of sulfoxides was efficiently reduced to the corresponding sulfides in a biphasic system $[BMIm]PF_6$/toluene under air using equimolecular amounts of PPh_3 as a reducing agent. The addition of the ionic liquid $[BMIm]PF_6$ facilitates the recyclability of the catalyst. Remarkably, no loss of catalytic activity was observed after eight cycles. Also, using triphenylphosphine as a reducing agent, the deoxygenation of several arylsulfoxides into the corresponding sulfides was accomplished by dioxomolybdenum catalysts that were generated in situ by reducing oxo-peroxomolybdenum complexes bearing 2-(2′-hydroxyphenyl)oxazoline (Hphox) ligands.[13]



Scheme 2 $MoO_2(SCN)_4$/ionic liquids-catalyzed deoxygenation of sulfoxides using PPh_3.

2.2. Silanes and boranes as reductants

The reduction of organic compounds catalyzed by dioxomolybdenum and other high-valent oxo-metallic complexes using silanes is a relevant and highly dynamic field in organic synthesis.[14] Inspired by a pioneering report about the hydrosilylation of carbonyl groups by a dioxorhenium catalyst,[15] several strategies for the hydrosilylation of aldehydes and ketones,[16] imines[17], esters[18] and amides[19] have been developed. Rapidly these methods were also applied to different deoxygenation reactions. In this sense, in 2006, Fernandes and Romão reported a protocol for the deoxygenation of sulfoxides using $PhSiH_3$ as the reducing agent and MoO_2Cl_2 as catalyst in refluxing THF (Scheme 3).[20] Sulfoxides bearing both alkyl and aryl substituents were efficiently reduced in excellent yields. The reaction shows good performance even in the presence of other functional groups prone to reduction, like esters or alkenes. The authors also developed a more sustainable attractive approach by using poly(methylhydrosiloxane) (PMHS) as a non-toxic, environmentally friendly, and inexpensive reductant in water or methanol as the solvent, combined with the easily available $MoO_2Cl_2(H_2O)_2$ complex. In general terms, longer reaction times were needed to achieve similar yields under these reaction conditions.



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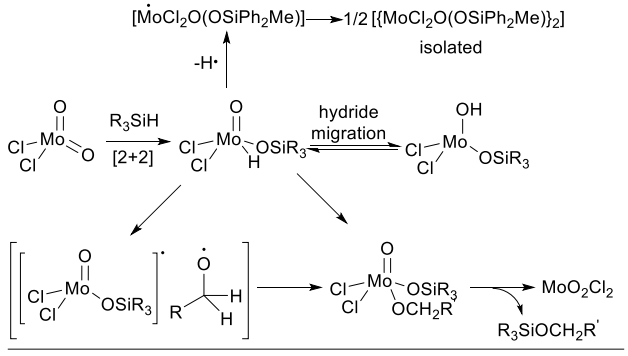
Scheme 3 Deoxygenation of sulfoxides using silanes.

In 2007, the mechanism of these reactions involving silanes under dioxomolybdenum catalysis was studied independently by Calhorda, Strassner and their co-workers through DFT calculations.[21] These studies found that the most plausible mechanism involves an initial [2+2] addition of H–Si to the Mo=O bond. ^{1}H-NMR studies were unable to detect any Mo–H bond. However, in the absence of the carbonyl group, a Mo(V) complex [{$MoCl_2O(OSiR_3)$}$_2$] was isolated, supporting the [2+2] addition path. The formation of this diamagnetic dimer was believed to proceed by the association of two [$MoCl_2O(OSiR_3)$] paramagnetic species generated after homolytic cleavage of Mo–H bond from the [2+2] addition intermediate.

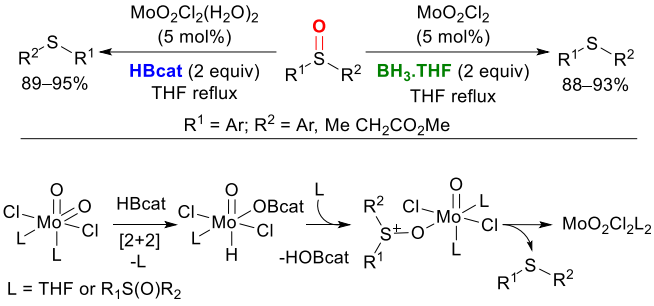
When a carbonyl is present, the hydrosilylation was suggested to proceed after weak coordination of the carbonyl to the intermediate Mo–hydride complex. This intermediate evolves through the stepwise classical mechanism involving the transfer of the H atom to the carbonyl C atom followed by silyl migration to the alkoxide. However, experimental results showed that the addition of radical scavengers inhibited or slowed down the reaction when performed in MeCN. In this sense, Calhorda and co-workers also postulated that an alternative radical path is operative when MeCN is used as the solvent with an energy requirement similar to the classical pathway.



Scheme 4 Proposed mechanism for $[MoO_2]^{2+}$-catalyzed hydrosilylation reactions.

Following the use of hydrides, Fernandes and Romão have also evaluated the deoxygenation of sulfoxides employing boranes (Scheme 5).[22] The authors identified that $MoO_2Cl_2(H_2O)_2$ catalyst combined with catechol borane (HBcat) yielded deoxygenation of sulfoxides. Alternatively, the parent MoO_2Cl_2 catalyst also promotes sulfoxide reduction almost quantitatively when BH_3·THF is employed as a reducing agent. In both cases, the reaction could be performed at room temperature for several hours (16 h) or in refluxing THF in 10 to 35 minutes. The two protocols demonstrated compatibility with esters and were efficiently applied to reduce both aryl alkyl sulfoxides and diaryl sulfoxides.

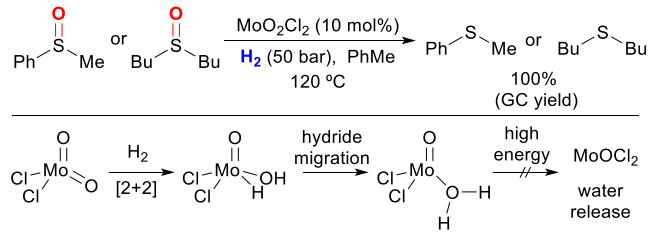
DFT calculations[23] support an analogous mechanism to the reduction with silanes. Initially, the in situ generated $MoO_2Cl_2(R_2SO)_2$ activates the B–H bond by the coordination of one oxo ligand to the empty orbital of the boron. Rapid evolution generates a Mo-hydride complex. Then, the elimination of HOBcat generates a Mo(IV) intermediate. After coordination with the sulfoxide, these Mo(IV) species, commonly invoked in related catalytic cycles for sulfoxide deoxygenation, evolve through thioether liberation, which regenerates the initial dioxomolybdenum complex (Scheme 5). By means of theoretical calculations, the viability of the non-explored hydroboration of carbonyls was also explored. DFT studies supported an ionic outer-sphere mechanism.[23b,24]



Scheme 5 Deoxygenation of sulfoxides using boranes.

2.3. Hydrogen as reductant

In 2008, Royo and co-workers described the activation of H_2 by dioxomolybdenum complexes allowing the reduction of alkynes to alkenes. Additionally, dibutyl and methyl phenyl sulfoxide were efficiently reduced to the corresponding thioethers employing MoO_2Cl_2 as catalyst in toluene at 120 ºC under hydrogen (50 bar) (Scheme 6).[25]



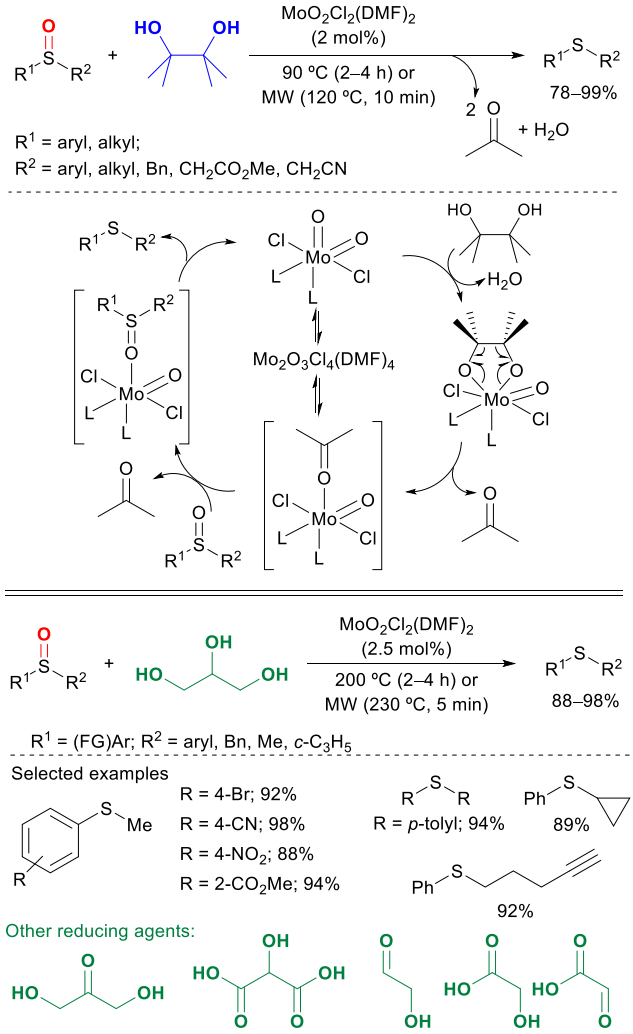
Scheme 6 Deoxygenation of sulfoxides using hydrogen.

Based on DFT calculations, the authors proposed an analogous mechanism to the Si–H bond activation (Scheme 6). Initially, the [2+2] addition of H_2 to Mo=O bond takes place. Then, hydride migration affords an aquo complex. No transition state was found for the elimination of the water molecule from the complex. Considering that sulfoxides are known to act as ligands for $[MoO_2]^{2+}$, it is very likely that a sulfoxide coordinates to the MoO_2Cl_2. The addition complex is also likely to experience a reduction forming an active Mo(IV) species, similar to the deoxygenation reactions using phosphorous compounds.

2.4. Glycols and alcohols as reductants

In 2012, the Sanz group reported pinacol (2,3-dimethyl-2,3-butanediol) as a new environmentally-friendly oxygen acceptor for the deoxygenation of sulfoxides, which only leads to acetone and water as byproducts, in a process catalyzed by $MoO_2Cl_2(DMF)_2$.[26]

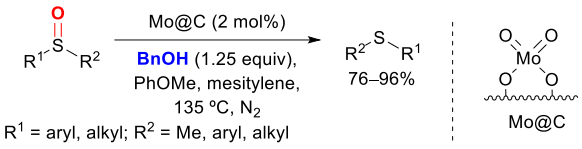
Sulfoxides possessing potentially reducible functional groups such as alkene, carbonyl, cyano, carboxylic acid and nitro were chemoselectively deoxygenated, even on a multigram scale (Scheme 7). In addition, the process is solvent-free and can be carried out under conventional heating or under microwave irradiation with significantly shortened reaction times. The proposed catalytic cycle involved the initial formation of a pinacolate complex with releasing of water. Oxidation of the pinacolate ligand by the molybdenum(VI) center leads to an oxomolybdenum(IV) species $MoOCl_2(DMF)_2(Me_2CO)$, in which the sulfoxide easily displaces the acetone. The resulting unstable adduct $MoOCl_2(DMF)_2(R^1SOR^2)$ rapidly undergoes reoxidation of the metal, releasing the sulfide and recovering the catalyst (Scheme 7). A dinuclear oxomolybdenum(V) complex $Mo_2O_3Cl_4(DMF)_4$,[27] also active as a catalyst for the deoxygenation reaction, was obtained from $MoO_2Cl_2(DMF)_2$ and a slight excess of pinacol, thus supporting the oxomolybdenum(IV) complex as intermediate due to its high tendency to comproportionate with the parent dioxomolybdenum(VI) species.



Scheme 7 Pinacol and glycerol as reducing agents for the deoxygenation of sulfoxides.

In this way, the same authors have reported the use of glycerol, an important biomass-derived feedstock generated as a byproduct in biodiesel production, both as the solvent and reducing agent for the deoxygenation of sulfoxides under the catalysis of the same dioxomolybdenum(VI) complex (Scheme 7).[28] Both refined glycerol and crude glycerine, containing only 5-8% of glycerol, can be used in a process that has also been scaled up. Excellent chemoselectivity, similar to that observed with pinacol, allows exclusive sulfoxide reduction in the presence of different functional groups. In addition, different compounds such as dihydroxyacetone, tartronic acid, glycolaldehyde, glycolic acid and glyoxylic acid, derived from glycerol oxidation, were also checked as suitable reducing agents under molybdenum-catalysis (Scheme 7). Other ditertiary and disecondary aryl- and/or alkyl-substituted 1,2-diols were also demonstrated to achieve the reduction of dioxomolybdenum(VI) to Mo(IV) complexes, being oxidatively cleaved and affording the corresponding carbonyls.[29]

Inspired by glycols as green reducing agents in dioxomolybdenum-catalyzed deoxygenation reactions, Marks, Lohr and co-workers decided to explore other different alcohols employing a heterogeneous catalyst.[30] Although heterogenized dioxomolybdenum catalysts have successfully catalyzed oxidation reactions,[31] scarce examples have been reported in deoxygenation reactions. In this sense, the authors envisioned that single-site dioxomolybdenum species grafted on activated carbon (Mo@C), previously synthesized by the same group,[32] could promote deoxygenation reactions. In this sense, the authors found that Mo@C promotes sulfoxide deoxygenation employing benzyl alcohol as the reductant in anisole at 135 °C (Scheme 8). The reaction proceeds in high yields with sulfoxides bearing alkyl or aryl substituents. Selective reduction of sulfoxides occurs when other compounds bearing potentially reducible functional groups (alkene, alkyne and nitrile) are present in the reaction media. The catalyst could be recycled up to four times without losing catalytic activity.



Scheme 8 Mo@C-catalyzed deoxygenation of sulfoxides.

Kinetic studies revealed that the reaction rate is found to be zero-order in sulfoxide concentration and fractional order in both benzyl alcohol and Mo. On this basis, benzyl alcohol and molybdenum centers may be involved in the turnover-limiting step.

2.5. Thiols as reductants

A convenient sulfoxide deoxygenation reaction using a mercaptopropyl-functionalized silica gel (MPS) as reductant and $MoO_2Cl_2(DMF)_2$ as the catalyst, under microwave irradiation, was described by Sanz and co-workers (Scheme 9).[33] Commercially available Quadrasil™ MP, or easily synthesized MPS, provide similar results. Based on a heterogeneous reagent, this protocol displays similar scope and chemoselectivity to the other processes that use glycols (see Scheme 7). Significantly, the work-up of the reaction is reduced to just a simple filtration of the solid waste. A thiolate

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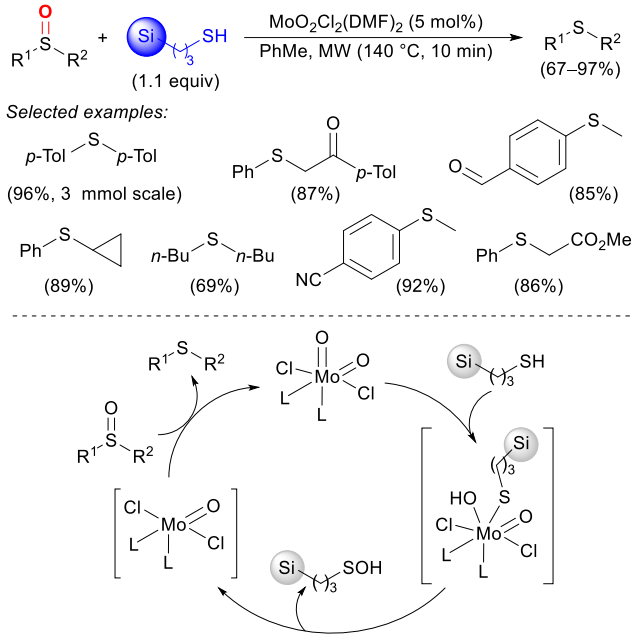
complex was proposed as intermediate, which undergoes reductive elimination of a heterogeneous sulfenic acid derivative leading to a formal oxomolybdenum(IV) species that would be able to deoxygenate the sulfoxide regenerating the catalyst (Scheme 9). An alternative double thiol addition, with subsequent reductive elimination of a disulfide-supported species, would also lead to the key oxomolybdenum(IV) complex after condensation of water.



Scheme 9 Mercaptopropyl-functionalized silica gel (MPS) as reducing agent for the deoxygenation of sulfoxides.

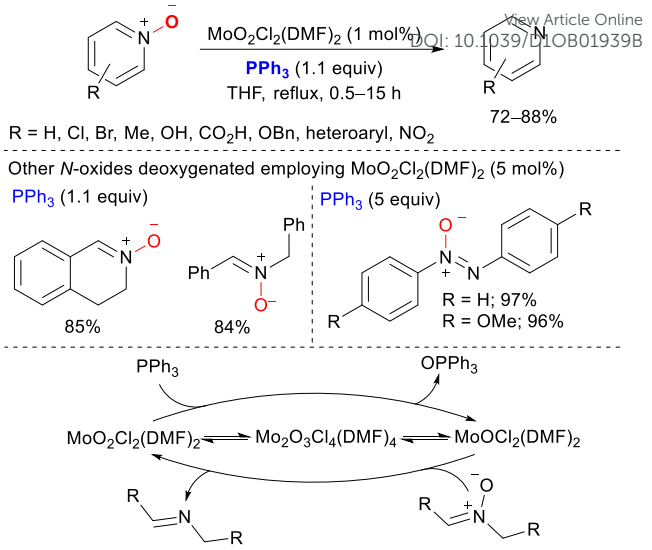
3.-Deoxygenation of N–O bonds

Over the last two decades, dioxomolybdenum complexes have also emerged as suitable catalysts for the deoxygenation of a variety of oxonitrogenated compounds, such as *N*-oxides and even the more challenging nitroarenes, with an exquisite functional group tolerance and selectivity.

3.1. Deoxygenation of N–O single bonds: *N*-oxides and related compounds.

3.1.1. Phosphorus compounds as reductants

Triphenylphosphine was also found to be a highly efficient reducing agent for deoxygenation of *N*-oxides. In 2005, Sanz, Arnáiz and co-workers described the deoxygenation reaction of pyridine and quinoline *N*-oxides, nitrones and azoxyarenes (Scheme 10).[34] Even employing $MoO_2Cl_2(DMF)_2$ in low catalyst loadings (up to 1 mol%) together with a slight excess of PPh_3, deoxygenation proceeds in excellent yields in various solvents. However, the reaction progresses faster in THF. Halogens, alkoxy, free hydroxyl and carboxylic acid functional groups are well-tolerated. Even nitro groups remained unaltered under the described reaction conditions, affording the corresponding pyridines and quinolines in high yields.

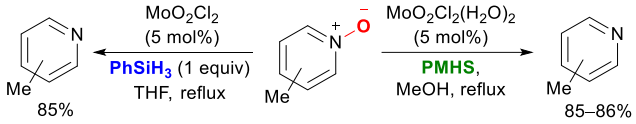


Scheme 10 [MoO_2]-catalyzed deoxygenation of *N*-oxides using PPh_3.

Nevertheless, deoxygenation of nitrones and azoxyarenes required higher catalyst loadings. The authors proposed a similar simplified catalytic cycle based on their previous work on the deoxygenation of sulfoxides. Also, Mo(IV) and Mo(VI) species were found to be in equilibrium with a dinuclear μ-oxomolybdenum(V) $Mo_2O_3Cl_4(DMF)_4$ complex (Scheme 10).[27] Theoretically, a wide variety of oxomolybdenum chloro complexes may be active catalysts in these oxo-transfer processes.

3.1.2. Silanes as reductants

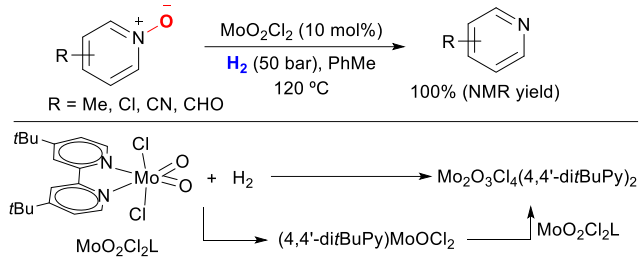
Also, while studying the deoxygenation of sulfoxides, Fernandes and Romão reported the deoxygenation of picoline *N*-oxides.[20] Interestingly, both previously reported catalytic systems based on $PhSiH_3$ and PMHS as reducing agents provided high yields of the corresponding pyridines (Scheme 11). However, when PMHS was employed in water, no reaction was observed, differing from the reaction with sulfoxides.



Scheme 11[[MoO_2]-catalyzed deoxygenation of *N*-oxides using silanes.

3.1.3. Hydrogen as reductant

The combination of MoO_2Cl_2 catalyst and H_2 was also reported to be a suitable method for the deoxygenation of several pyridines and quinoline *N*-oxides.[35] Relatedly to the deoxygenation of sulfoxides, the reaction occurs in toluene at 120 °C under H_2 pressure (50 bar) (Scheme 12). Interestingly the method is compatible with other potentially reducible functional groups like aldehydes or nitriles. With azoxybenzene as starting substrate, only a moderated yield of deoxygenated product was afforded.

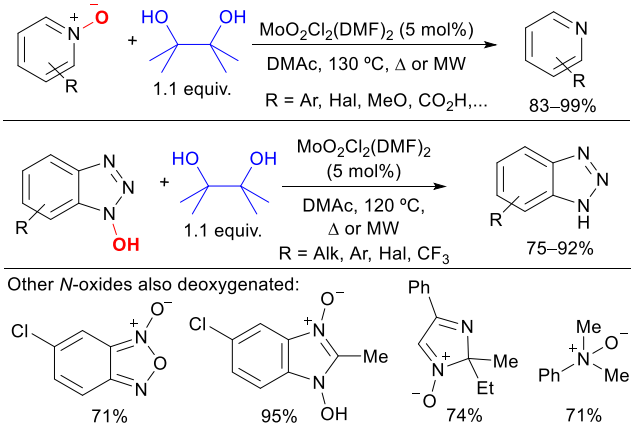


Scheme 12 [MoO_2]-catalyzed deoxygenation of *N*-oxides using H_2.

When MoO_2Cl_2(*t*BuBipy) complex bearing a 2,2′-bipyridine ligand was subjected to reaction with H_2, Mo(V) μ-oxo dimer $Mo_2O_3Cl_4$(Bipy)$_2$ adduct was isolated, similarly to previous reports (Scheme 12).

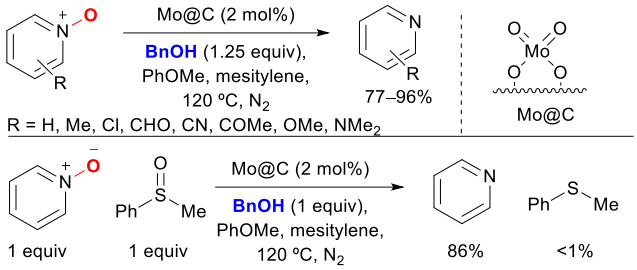
3.1.4. Glycols and alcohols as reductants

In an analogous way to the deoxygenation of sulfoxides, pinacol was evaluated as a green and sustainable reagent for the deoxygenation of *N*-oxides and *N*-hydroxy compounds under dioxomolybdenum catalysis.[36] Various pyridine, quinoline, isoquinoline *N*-oxides, benzofuroxans, 2*H*-imidazole 1-oxides, triazole *N*-oxides, and even aniline *N*-oxides were efficiently reduced with the combination of $MoO_2Cl_2(DMF)_2$ catalyst and pinacol, under conventional or microwave heating (Scheme 13). In addition, heteroaromatics were generally isolated by simple extraction without requiring further purification by column chromatography. Interestingly, *N*-hydroxybenzotriazoles, which are easily accessed from 1-halo-2-nitroaromatics, were also positively reduced with the pinacol/$MoO_2Cl_2(DMF)_2$ system affording benzotriazoles in high yields (Scheme 13). The successful N–OH bond reduction with these substrates is likely achieved due to a prototropy that generates an *N*-oxide tautomer. Under these reaction conditions, diverse functional groups, such as halogens, alkoxy, carbonyl, ester, carboxylic acid, and nitro, remained unaltered during the course of the reaction. Only sulfoxide groups compete moderately with the reduction of the *N*-oxide. The reaction time was considerably shortened under microwave irradiation.



Scheme 13 $MoO_2Cl_2(DMF)_2$-catalyzed deoxygenation of *N*-oxides with pinacol.

Marks, Lohr and co-workers also examined the performance of single-site dioxomolybdenum catalyst grafted on activated carbon (Mo@C) for sustainable deoxygenation of *N*-oxides (Scheme 14).[30] Several pyridine and quinoline *N*-oxides were efficiently reduced in anisole employing mesitylene as an internal standard with a slight excess of benzyl alcohol as the reducing agent employing low catalyst loadings.



Scheme 14 Mo@C-catalyzed deoxygenation of *N*-oxides using benzyl alcohol.

The reaction shows good compatibility with other reducible functional groups like nitriles, aldehydes, ketones. Interestingly, competition reaction between pyridine *N*-oxide and methyl phenyl sulfoxide with one equivalent of benzyl alcohol afforded selectively almost complete conversion of the pyridine *N*-oxide leaving the sulfoxide unaltered (Scheme 14). The catalyst displays high stability, as shown from XPS and PXRD analysis before and after deoxygenation reactions. Also, leaching studies determined by ICP analysis of the supernatant revealed insignificant amounts of Mo. Interestingly Mo@C was efficiently recycled four times without significant loss of the catalytic activity.

3.2. Deoxygenation of N–O multiple bonds: nitro compounds

3.2.1. Phosphorus compounds as reductants

The Cadogan reaction, a reductive cyclization of nitroaromatics, is a precious synthetic tool that enables a straightforward construction of indoles and carbazoles, common structural motifs in biologically relevant molecules and material science.[37] The classical Cadogan reaction, which causes the deoxygenation and the subsequent reductive cyclization of *o*-nitroarenes, is commonly conducted using an excess of triethyl phosphite (also used as solvent) typically at reflux above 150 °C. Under these conditions, *N*-alkylation byproducts derived from triethyl phosphate are frequently observed. Alternative Cadogan cyclization reactions using triphenylphosphine as the reducing agent in *o*-dichlorobenzene or DMAc have been developed to avoid the formation of these side products.[38] Nevertheless, these procedures require higher temperatures (over 180 °C), longer reaction times, or the use of a highly toxic solvent like *o*-dichlorobenzene. The development of alternative Cadogan cyclizations that enable reactions to proceed under milder reaction conditions has attracted much attention.[39] In this field, Sanz has developed the Mo-catalyzed Cadogan reaction using $MoO_2Cl_2(DMF)_2$ as an efficient catalyst in the reductive cyclization of *o*-nitrobiphenyls and *o*-nitrostyrenes with PPh_3 under reflux in toluene (Scheme 15a and 15b),[40] affording a diverse range of functionalized carbazole and

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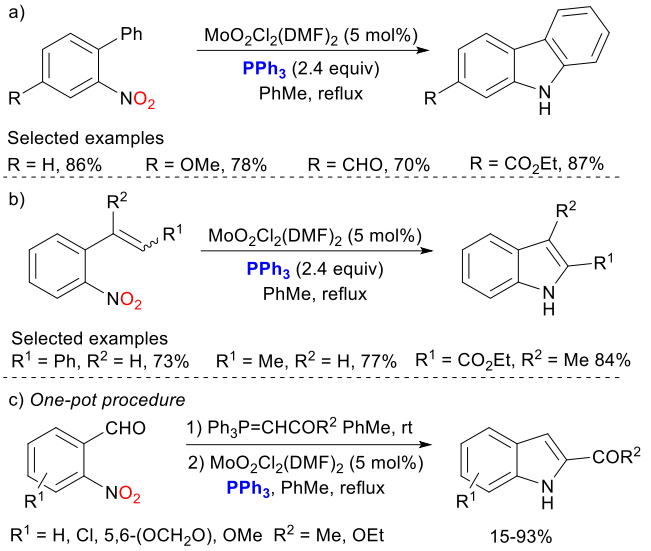
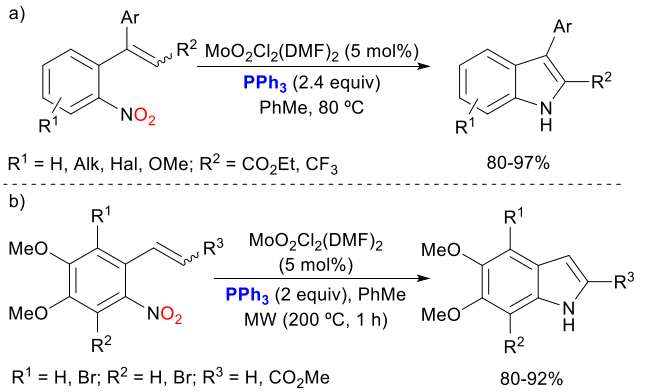
indole cores. In addition, also 2-nitrobenzaldehydes were reported to be suitable starting materials through a one-pot procedure involving an initial Wittig reaction followed by the Mo-catalyzed reductive cyclization, affording 2-acylindoles and indole 2-carboxylates (Scheme 15c).



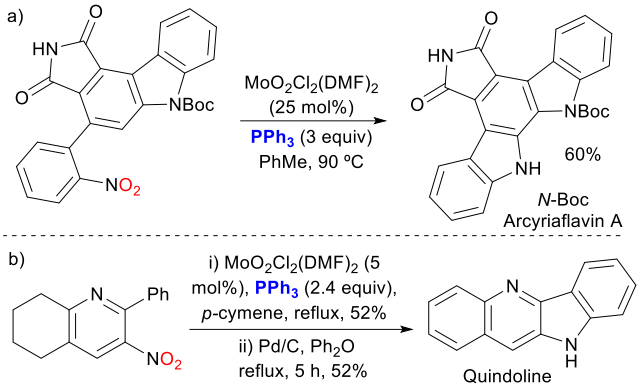
Scheme 15 $MoO_2Cl_2(DMF)_2$-catalyzed Cadogan reductive cyclization.

This strategy, based on Mo-catalyzed Cadogan cyclizations, has been subsequently used by other groups demonstrating a broad versatility in synthesizing different indole, carbazole and related heterocyclic scaffolds. For instance, Yamamoto has ideated a two-step strategy to obtain 3-aryl-2-ethoxycarbonyl and 3-aryl-2-trifluoromethyl indoles in almost quantitative yields.[41] After copper-catalyzed alkyne hydroarylation with boronic acids, a variety of *o*-nitrostyrenes were formed. Subsequent $MoO_2Cl_2(DMF)_2$-catalyzed Cadogan cyclization afforded the desired indoles (Scheme 16a). Versatile bromo-5,6-dimethoxyindole building blocks were competently synthesized by a similar Mo-catalyzed Cadogan reaction, although required from microwave irradiation at 200 °C for one hour to achieve the corresponding indoles (Scheme 16b).[42]



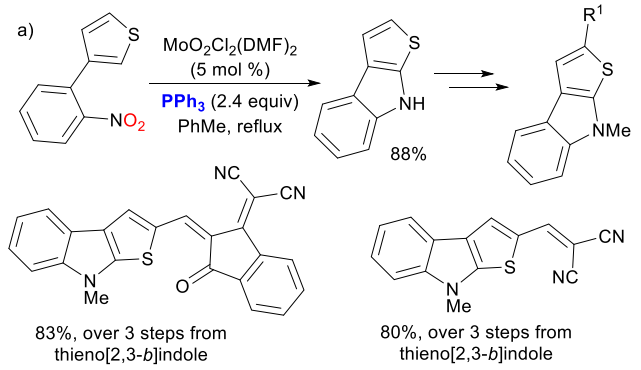
Scheme 16 $MoO_2Cl_2(DMF)_2$-catalyzed Cadogan reductive cyclization to synthesize *a*) 3-aryl-2-ethoxycarbonyl and 3-aryl-2-trifluoromethyl indoles; *b*) bromo-5,6-dimethoxyindoles.

The enhanced reactivity and functional group tolerance achieved with the Mo-catalyzed Cadogan reaction make this method suitable for synthesizing biologically relevant indoles and carbazoles. In this sense, Aponick reported the synthesis of *N*-Boc monoprotected Arcyriaflavin A.[43] Where other methods failed, an increase in the $MoO_2Cl_2(DMF)_2$ catalyst loading was decisive to achieve the reductive cyclization at 90 °C in toluene (Scheme 17a). Similarly, novel potent aromatase inhibitors based on a substituted indole moiety were efficiently prepared by reductive cyclization using triphenylphosphine and ($MoO_2Cl_2(DMF)_2$) as the catalyst.[44] Recently, a related protocol was applied to the synthesis of different carbolines, including the natural product quindoline, a precursor for the synthesis of the antimalarial drug cryptolepine (Scheme 17b).[45]



Scheme 17 Mo-catalyzed Cadogan reaction applied to the total synthesis of natural products.

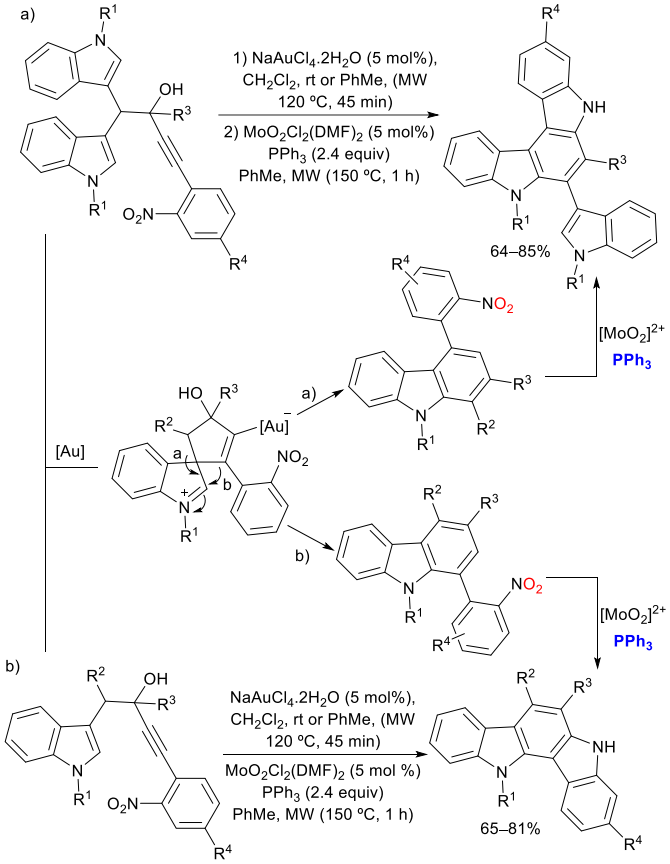
The Mo-catalyzed Cadogan reaction was also extended to the synthesis of polycyclic structures with valuable photophysical properties. In this sense, Blanchard, Leriche and co-workers synthesized thieno[2,3-*b*]indole by applying previously disclosed reductive cyclization conditions (Scheme 18).[46] Further modification of this electron-donating core afforded small push-pull molecules by connecting directly to a 2,2-dicyanovinyl or (1-(dicyanomethylene)-3-oxo-1-inden-2-ylidene)methyl electron-withdrawing groups that showed potential application in organic electronics and nonlinear optics.



Scheme 18 Mo-catalyzed synthesis of thieno[2,3-*b*]indoles.

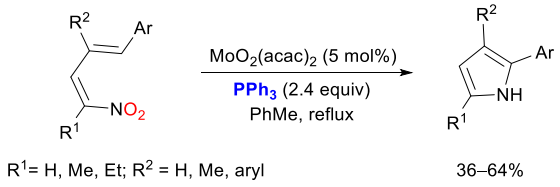
Also, angular indolo[2,3-*c*]carbazole and indolo[3,2-*a*]carbazole derivatives were easily accessed by combining a gold-catalyzed regioselective cyclization and the dioxomolybdenum-catalyzed

reductive Cadogan cyclization with PPh_3 (Scheme 19).[47] Interestingly, when the gold-catalyzed reaction is performed in toluene, the indolocarbazoles could be obtained directly in a one-pot two-step procedure. The preferential 1,2-alkyl (pathway a) or 1,2-alkenyl migration (pathway b) in the key spirocyclic intermediate originated in the gold-catalyzed cyclization step determines which indolocarbazole is formed.[48] The nature of the R^2 substituent is decisive in favoring one migration over the other. When an indole is located at position R^2, highly fluorescent indolo[2,3-*c*]carbazoles were obtained, whereas indolo[3,2-*a*]carbazole derivatives were formed when R^2 is an alkyl or aryl group.



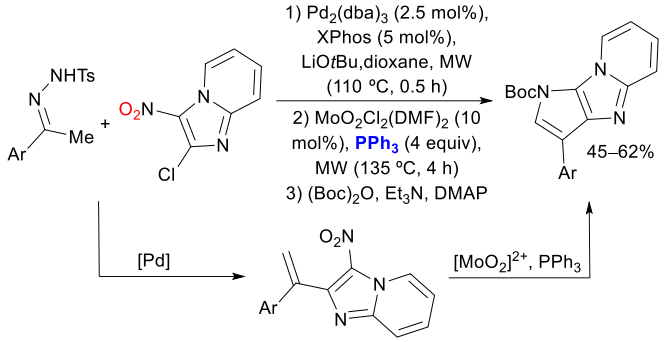
Scheme 19 Combined gold- and molybdenum-catalyzed synthesis of indolocarbazoles.

Interestingly, pyrroles could also be accessed by the reductive cyclization of nitrodienes using $MoO_2(acac)_2$ catalyst with PPh_3 (Scheme 20).[49] Employing PPh_3 or $P(OEt)_3$ as a reducing agent, but in the absence of the molybdenum catalyst, pyrroles were obtained in very poor yields (12–14%). The method was later applied to the synthesis of bimetopyrol and pseudilin derivatives.[50]



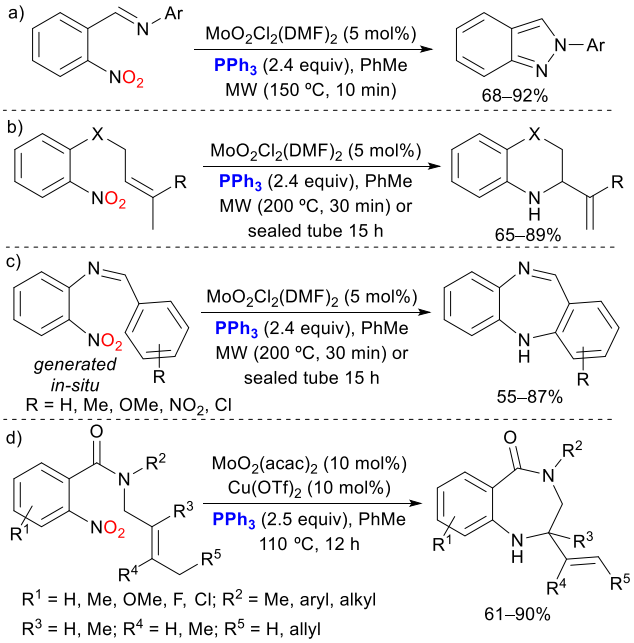
Scheme 20 $MoO_2(acac)_2$-catalyzed synthesis of pyrroles.

Recently, novel pyrrolo-imidazo[1,2-*a*]pyridine scaffolds were also synthesized by applying the Mo-catalyzed Cadogan reaction.[51] In this case, higher loadings of both $MoO_2Cl_2(DMF)_2$ catalyst (10 mol%) and PPh_3 (4 equiv), in combination with microwave heating at 135 °C in dioxane, were decisive to achieve high yields. Remarkably, the authors have also designed a one-pot synthesis of pyrrolo-imidazo[1,2-*a*]pyridines combining Mo-catalyzed Cadogan reaction with Pd-catalyzed cross-coupling of tosylhydrazones and aryl chlorides (Scheme 21).



Scheme 21 One-pot [Pd] and $[MoO_2]^{2+}$-catalyzed synthesis of pyrrolo-imidazo[1,2-*a*]pyridines.

Beifuss and co-workers have successfully extended the dioxomolybdenum-catalyzed reductive cyclization of nitroarenes to synthesize other different heterocycles such as 2-aryl-2*H*-indazoles,[52] (Scheme 22a) or even 6-membered ring heterocycles such as 3,4-dihydro-2*H*-1,4-benzoxazines or -benzothiazines[53] using PPh_3 as a reducing agent (Scheme 22b). Similarly, Malakar and co-workers have described the synthesis of 1-hydroxyphenazines and quinoxalines by reductive cyclization of β-(*N*-2-nitroaryl)-α,β-unsaturated ketones using a $MoO_2Cl_2(DMF)_2$ catalyst and PPh_3, followed by aromatization under air atmosphere.[54]



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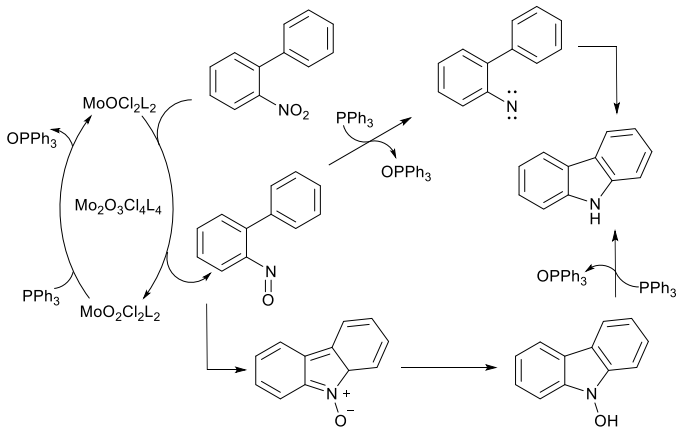
Scheme 22 Mo-catalyzed synthesis of indazoles, benzoxazines, benzothiazines and benzodiazepines.

Seven-membered ring heterocycles like biologically relevant benzodiazepines were also accessible by related Mo-catalyzed reductive cyclization (Scheme 22c and 22d).[55] Imines generated in-situ by condensation of 2-nitroaniline with different benzaldehydes experienced reductive cyclization when treated with catalytic amounts of $MoO_2Cl_2(DMF)_2$ and an excess of PPh_3, affording dibenzodiazepines (Scheme 22c). Similarly, benzodiazepines were obtained by reductive cyclization of the derivatives of *N*-(3-methylbut-2-en-1-yl)-2-nitrobenzamide. In this case, a copper co-catalyst was required combined with $MoO_2(acac)_2$ complex. The addition of the Cu(II) salt increased the benzodiazepine yields.

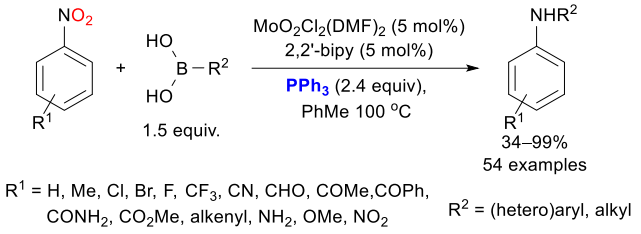
These types of Mo-catalyzed reductive cyclization reactions were proposed to proceed through an initial reduction of the dioxomolybdenum(VI) catalyst after an attack of triphenylphosphine. The formed oxomolybdenum(IV) complex, as well as the likely dinuclear μ-oxomolybdenum(V) dimer generated from comproportionation of molybdenum(IV) and (VI) species, are capable of causing the deoxygenation of the nitroarene to the corresponding nitroso derivative (Scheme 23).[40] Theoretical calculations suggest that the molybdenum(VI) catalyst behaves similarly to that proposed for molybdoenzymes.[56] Then, the more reactive nitrosoarene intermediate could evolve through two previously postulated reaction pathways, even in the absence of the Mo-catalyst. The attack of the second equivalent of phosphine produced exhaustive deoxygenation of the nitroso compound, generating a single nitrene,[57] which evolves through a formal C–H insertion affording the nitrogenated heterocycle. Recent mechanistic studies have also suggested the formation of a nitrenoid oxazaphosphirane (2 + 1) adduct between the phosphine and the nitrosoarene, which progresses through loss of phosphine oxide generating the nitrene.[58]



Scheme 23 Mechanistic proposal for the $[MoO_2]^{2+}$-catalyzed reductive cyclization of nitroarenes.

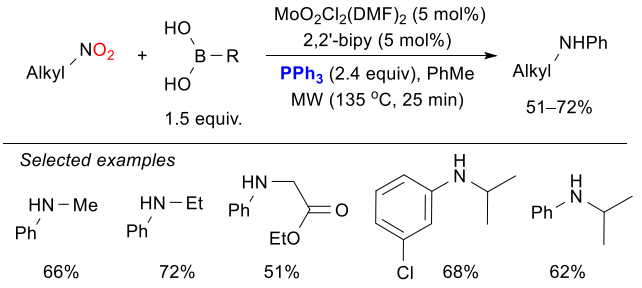
An alternative competitive mechanism involves pericyclic reactions.[59] The nitroso intermediate evolves through a 6π-electron 5-atom electrocyclization leading to a nitrone. Then, a 1,5-H shift provides a more stable nitrone that, after tautomerization, delivers the *N*-hydroxy heterocycle. Its final reduction with the second equivalent of PPh_3 allows the formation of the *N*-heterocycle. Both mechanistic proposals are suggested and supported by different authors and, therefore, the activation barriers for both types of processes can be different depending on the substrate and reaction conditions.

Related intermolecular reductive amination to afford anilines in one single operational step has proved to be more challenging. Dioxomolybdenum catalysts combined with a 2,2'-bipyridine ligand and PPh_3 as reductant were decisive in achieving the direct amination of boronic acids with nitro compounds to yield secondary (hetero)arylamines (Scheme 24).[60] Various nitro(hetero)arenes were efficiently coupled with both aryl and alkyl boronic acids. Moreover, the method has proven to be scalable, air and moisture tolerant, and highly chemoselective, allowing the presence of aldehydes, ketones, amides, halogens, alkenes, esters, nitriles, methoxy and free amino functional groups. In this latter case, C–N bond-forming reaction occurs selectively with the nitro group. When two equivalent nitro substituents are placed on the arene moiety, only one of the nitro groups is selectively reduced.



Scheme 24 $MoO_2Cl_2(DMF)_2$-catalyzed reductive amination of boronic acids with nitroarenes.

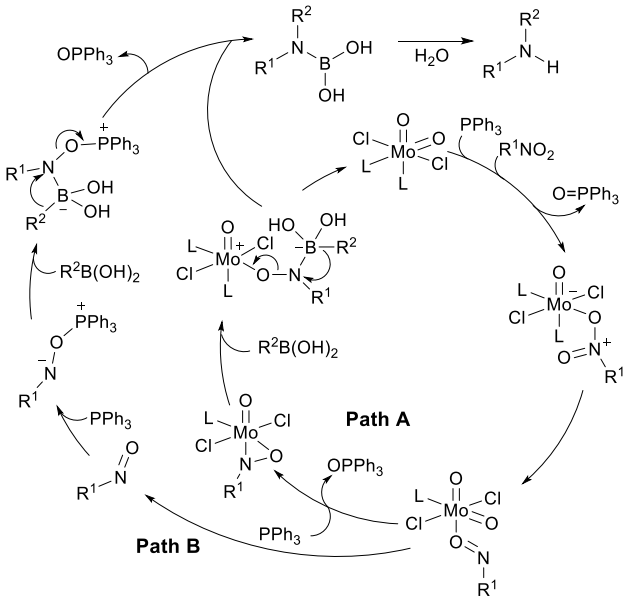
Remarkably, more challenging nitroalkanes were also engaged in this transformation, although required from microwave irradiation at 135 °C (Scheme 25). This report supposes the first example of reduction of nitroalkanes to amino functional group under dioxomolybdenum catalysis.



Scheme 25 $MoO_2Cl_2(DMF)_2$-catalyzed reductive amination of boronic acids with nitroalkanes.

The authors proposed a mechanism involving a MoO_2(VI) species bearing a nitroso ligand and two different pathways, which both end with the migration of the nucleophilic R^2 group. Path A proceeds via a molybdooxaziridine species after reducing the nitroso ligand and reoxidation of the metal center, leading to a nitrenoid intermediate whose subsequent rearrangement would generate an aminoboronic acid. Alternatively, Path B would involve releasing a free nitroso

compound, which would deliver a reduced adduct after subsequent deoxygenation. Its interaction with the boronic acid would afford a nitrenoid borate that would release O=PPh$_3$ and the aminoboronic acid through 1,2-migration of the R^2 group (Scheme 26).[60]

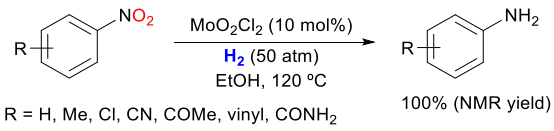


Scheme 26 Mechanistic proposal for the Mo-catalyzed reductive amination of boronic acids with nitro compounds.

Recently, a heterogeneous version of this coupling has been developed employing a well-shaped catalyst obtained by nanoporous MoO_3 confinement in mesoporous silica that generates single-site MoO_2 centers.[61] The catalyst achieved higher turnover number values for the coupling of nitroarenes. Moreover, the catalyst was recycled up to 5 times without loss of the catalytic activity.

3.2.2.Hydrogen as reductant

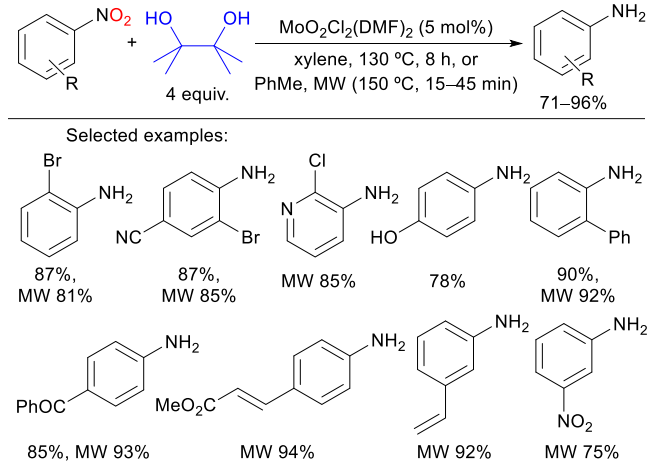
Also, Royo described the reduction of selected nitroarenes with H_2 under dioxomolybdenum catalysis.[35] Best results were obtained using ethanol as solvent at 120 ºC under H_2 pressure (50 atm) with MoO_2Cl_2 as the catalyst (Scheme 27). Functional groups susceptible to reduction (ketones, nitriles, vinyl, amides) are well tolerated and the desired anilines were obtained in high yields.



Scheme 27 Mo-catalyzed deoxygenation of nitroarenes under H_2 pressure.

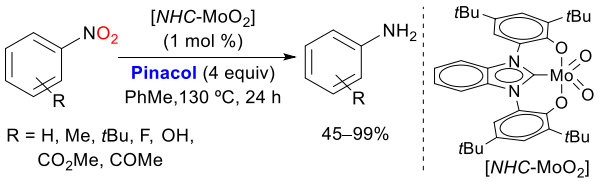
3.2.3. Glycols and alcohols as reductants

Similar to the deoxygenation of sulfoxides using glycols, Sanz and co-workers described the use of pinacol as a green, reducing agent for the conversion of nitroaromatic compounds into anilines under $[MoO_2]^{2+}$ catalysis (Scheme 28).[26b] However, the reduction of nitroarenes compared to sulfoxides is required from slightly higher catalyst loadings and temperatures. The protocol was efficiently scaled up to multigram amounts. Interestingly, the reaction time was considerably shortened to 15–45 minutes under microwave heating. Remarkably, the reduction of the nitro moiety takes place selectively over other potentially reducible functional groups such as C=C, ester, amide, carbonyl, halogen, cyano, and hydroxyl. Also, 2-nitrobiphenyl was selectively reduced to 2-aminobiphenyl using pinacol, whereas when PPh_3 was used as a reducing agent, the only formation of carbazole was observed.



Scheme 28 $MoO_2Cl_2(DMF)_2$-catalyzed reduction of nitroarenes into anilines using pinacol.

Hohloch, Maron and co-workers have designed novel dioxomolybdenum complexes bearing *NHC*-ligands that were applied to the reduction of nitroaromatics with pinacol (Scheme 29).[62] Remarkably, in some cases, the authors found that only 0.25 mol% catalyst loading was needed to reduce nitroaromatics in high yields. More challenging substrates are required from up to 1 mol% catalyst loading. Inspired by the previous reports, the authors also demonstrated that dinuclear μ-oxo molybdenum complexes bearing *NHC*-ligands generated in-situ could be involved in these transformations.



Scheme 29 [*NHC*-MoO_2]-catalyzed reduction of nitroarenes into anilines using pinacol.

The Sanz group described several domino reactions to synthesize different heterocyclic scaffolds, taking advantage of the shown broad functional group tolerance using pinacol as the reductant and the wide availability of inexpensive nitroaromatics. In 2017, this group reported the synthesis of pyrrolo(indolo)[1,2-*a*]quinoxalines and

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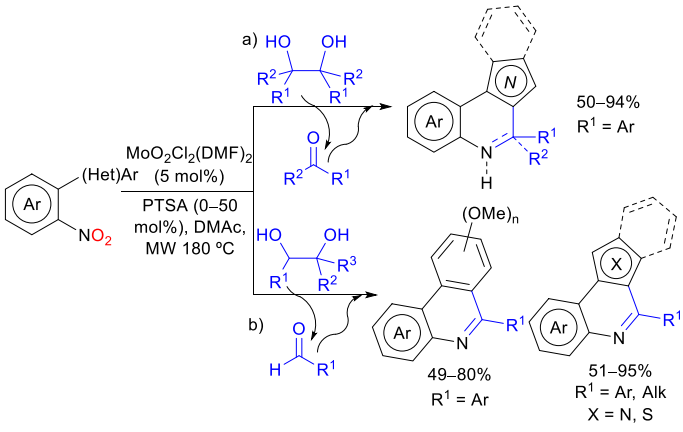
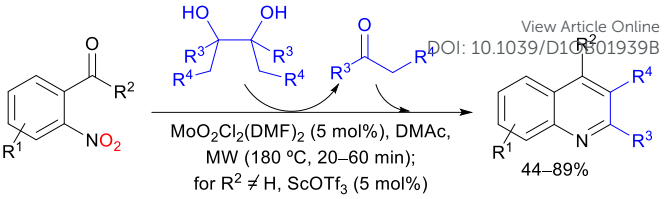
pyrrolo(indolo)[3,2-*c*]-quinolines from appropriately *ortho*-substituted nitroarenes and different symmetrical glycols employing a cascade sequence involving reduction, imine formation, intramolecular cyclization and oxidation (Scheme 30a).[63] Interestingly, the generated carbonyl waste byproduct derived from the initial dioxomolybdenum(VI)-catalyzed reduction of the nitroaromatic was utilized as a reagent for the imine generation. Depending on the substrate, substoichiometric quantities of *p*-toluenesulfonic acid are needed to favor cyclization and further oxidation. When 1,2-diaryl substituted diols were used, aromatization occurs after cyclization. Alternatively, if tertiary tetrasubstituted glycols are employed, α,α-disubstituted 1,2-hydroquinolines are obtained as no final oxidation step is possible. This methodology represents the first example of recycling a waste byproduct as a reagent that is embodied into the final compound.



Scheme 30 $[MoO_2]^{2+}$-catalyzed synthesis of *N*-polyheterocycles from 2-(hetero)arylnitroarenes with recycling of the waste byproduct.

More recently, the same group has expanded this methodology by using non-symmetrical glycols, mixed secondary-tertiary 1,2-diols, as reducing agents (Scheme 30b).[64] This enhanced protocol enables the introduction of alkyl substituents at C-4 position (R^1 = Alk) of the pyrrolo(indolo)quinoxaline cores that otherwise were inaccessible with the previous methodology. In addition, a wide variety of pyrrolo- and indolo-fused quinoxalines and quinolines, as well as thienoquinolines and phenanthridines, were synthesized by applying this strategy that reuses the waste reduction byproduct, which is ultimately incorporated into the target compounds.

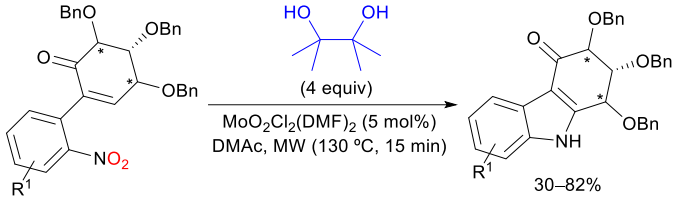
The strategy of recycling the waste byproduct was also applied to a sustainable Friedländer synthesis of quinolines (Scheme 31).[65] Easily available 2-nitrophenyl aldehydes or ketones reacted with ditertiary glycols under dioxomolybdenum catalysis affording a wide variety of polysubstituted quinolines. Interestingly, the waste byproduct of the initial reduction is used as a reactant for the next step of the domino process and incorporated into the final product. More reactive 2-nitrobenzaldehydes delivered the quinolines in high yields, whereas 2-nitrophenyl ketones were required from an additional Lewis acid co-catalyst, such as $Sc(OTf)_3$, to achieve the condensation reaction (Scheme 31).



R^1 = H, Cl, CO_2Me, CF_3, OMe, NMe_2; R^2 = H, Me, CF_3
R^3 = Me, Alkyl, Ph, (Het)Aryl; R^4 = H, Me, Alkyl

Scheme 31 $[MoO_2]^{2+}$-catalyzed Friedländer synthesis of quinolines with recycling of the waste byproduct.

The use of pinacol as a reducing agent was also applied to synthesize five-membered ring heterocycles through a reductive cyclization. Sagar and co-workers reported the synthesis of functionalized chirally enriched tetrahydrocarbazolones using an excess of pinacol and $MoO_2Cl_2(DMF)_2$ catalyst under microwave irradiation (Scheme 32).[66] Several functional groups over the nitroaromatic moiety are well-tolerated and the stereocenters remained unaffected. The chiral non-racemic 2'-nitro-4,5-dihydro-[1,1'-biphenyl]-2(3*H*)-one starting materials were obtained from Pd-catalyzed Ullmann coupling of nitroaromatics and 2-iodo-2-cyclohexenones derived from D-glucose, D-galactose and D-mannose. Also, pinacol has replaced PPh_3 as the reducing agent in other dioxomolybdenum catalyzed reductive cyclizations previously described using phosphorous reagents, such as the synthesis of 1-hydroxyphenazines and quinoxalines,[67] and 2-aryl-2*H*-indazoles.[68]



R^1 = H, Me, F, Cl, Br, CO_2Me, CF_3, COMe, NO_2, OMe

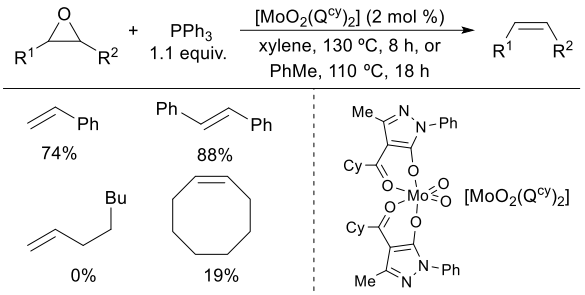
Scheme 32 $[MoO_2]^{2+}$-catalyzed synthesis of tetrahydrocarbazolones.

4.-Deoxygenation of C–O bonds

4.1.-Deoxygenation of C–O single bonds: epoxides, alcohols and related compounds.

4.1.1. Phosphorus compounds as reductants

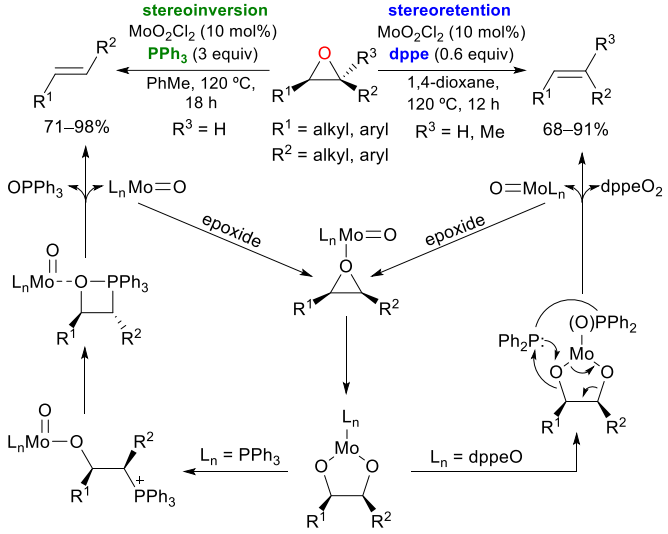
Although dioxomolybdenum complexes were known to promote the deoxygenation of epoxides upon reaction with PPh_3 since 1988,[69] it was not until recently when the first catalytic process was described. In 2013, Galindo, Montilla and colleagues developed novel dioxomolybdenum complexes bearing acylpyrazolonate ligands.[70] Then, these complexes were demonstrated to be competent catalysts in the deoxygenation reaction of oxiranes (Scheme 33). Only four different epoxides were tested. Whereas aryl-substituted oxiranes gave rise to the corresponding alkenes in high yields determined by GC-MS analysis, alkyl-substituted epoxides were proven to be more challenging substrates.



Scheme 33 Mo-catalyzed deoxygenation of epoxides to alkenes.

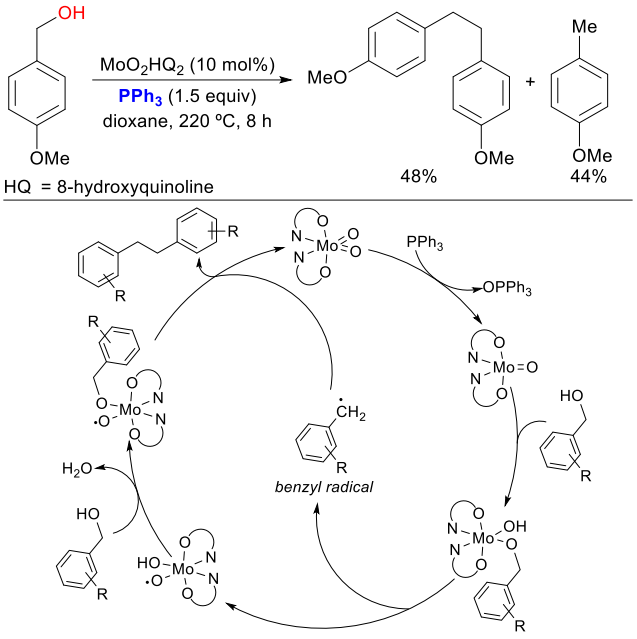
In 2016, Takai, Asako, and co-workers reported a more general and stereospecific approach to deoxygenating epoxides using MoO_2Cl_2 as the catalyst. Interestingly, the nature of the phosphine determines the stereochemistry of the final alkene product.[71] Whereas 1,2-bis(diphenylphosphino)ethane (dppe) favors retention of the stereochemistry of the alkene from di- and trisubstituted epoxides, the use of PPh_3 affords inversion products from disubstituted epoxides (Scheme 34). Concerning the chemoselectivity of the process, while functional groups such as ester, ketone, nitrile, alkyne, or alcohol did not affect the stereoselectivity, other groups like carboxylic acid, aldehyde, and phenol had a negative influence. However, with PPh_3, the scope was more limited and only selected *cis*-disubstituted epoxides provided good results.

Regarding the mechanism, the authors suggest that after the initial reduction of Mo(VI) complex, the newly formed Mo(IV) species reacts with the epoxide affording a molybdenum diolate (molybda-2,5-dioxolane) intermediate. The stereoretentive deoxygenation with dppe (0.6 equiv) implies an intermediate in which the dppe monoxide acts as a ligand and an oxygen acceptor. By contrast, inversion alkenes are obtained after PPh_3 attack to the diolate complex, followed by rapid reorganization into an oxaphosphenate. Finally, retro [2+2] releases the olefin and the phosphine oxide (Scheme 34).



Scheme 34 Phosphine effect in the deoxygenation of epoxides to alkenes catalyzed by MoO_2Cl_2.

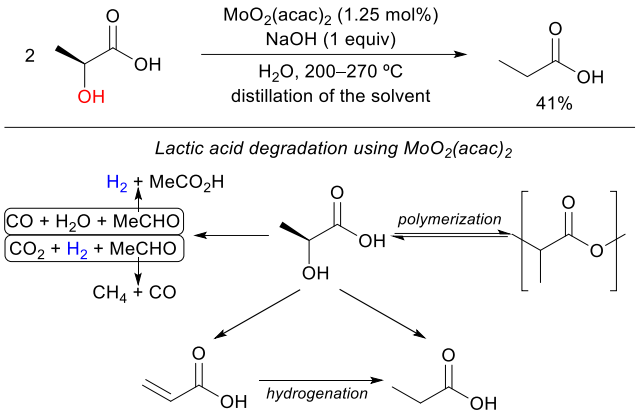
Also employing PPh_3, the group of Lu and co-workers reported the deoxygenation of several benzylic alcohols derived from lignin like anisyl alcohol.[72] Two main products were obtained: one derived from homocoupling, which gave rise to 1,2-diarylethanes, and another that was generated from the reduction into methyl-substituted arenes (Scheme 35). Traces of the corresponding aldehydes were also observed. Although the nature of the starting alcohol determines the proportion of products obtained, $[MoO_2]^{2+}$ complexes bearing 8-hydroxyquinoline ligands were essential to achieve high conversion of starting alcohols. The reaction was postulated to proceed by an initial reduction of Mo(VI) complex to a Mo(IV) compound (Scheme 35). Then condensation with the benzylic alcohol generated a Mo-alkoxide, that evolves through C–O bond cleavage, producing a benzyl radical. Hydrogen atom transfer from the solvent afforded the methyl-substituted arene, whereas coupling of two benzyl radicals delivered the 1,2-diarylethane product.



Scheme 35 $[MoO_2]^{2+}$-catalyzed homocoupling of lignin-derived alcohols.

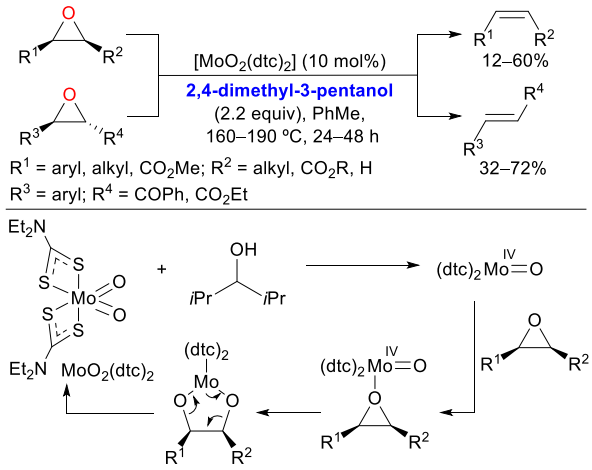
4.1.2. Alcohols as reductants

In 2013, Gebbink described an innovative production of propionic acid from lactic acid, an inexpensive renewable feedstock employing a $MoO_2(acac)_2$ as catalyst (Scheme 36).[73] The addition of NaOH (1 equiv) converts the initial lactic acid into the sodium lactate, which facilitates the complete distillation of the solvent by raising the temperature to 270 ºC. The higher temperatures achieved during the distillation enable the deoxygenation and the sodium lactate is transformed into sodium propionate at a multigram scale. Interestingly, the authors found that adding industrially relevant 44% (w/v) lactic acid solution in water to the hot solution of the dioxomolydenum catalyst provided the best results. By NMR analysis of the reaction, other different byproducts were detected like lactide, oligo- and polylactide, as well as small amounts of acetic acid.



Scheme 36 Lactic acid degradation under $[MoO_2]^{2+}$-catalysis.

The formation of several gases such as H_2, CO, CO_2 and CH_4 were detected by GC-MS analysis. According to these results, decarbonylation and the decarboxylation reactions operate during the process. Based on these findings, the authors considered two main reaction pathways for the deoxygenation of lactic acid. On the one hand, direct deoxygenation of lactic acid could be achieved under $[MoO_2]^{2+}$-catalysis using the generated H_2 as the reductant. Alternatively, initial dehydration of lactic acid to acrylic acid may also happen, and subsequent hydrogenation will afford propionic acid. Deuterium-labeled experiments employing D_2 revealed that although deuteration at α- and β-carbon positions of generated propionic acid occurred, a considerably higher deuteration proportion at the α position was observed. This result suggests that although both pathways operate in the process, dehydration/hydrogenation takes place in lesser extension than direct deoxygenation and cannot be completely ruled out. Relatedly, dioxomolybdenum complexes were also reported to catalyze dehydration of alcohols. In this sense, the same group has described a convenient protocol for dehydration of alcohols under catalysis employing dioxomolybdenum complexes bearing bulky 1,3-diketone ligands.[74] In addition, other dioxomolybdenum catalysts like $MoO_2Cl_2(H_2O)_2$ were also found to catalyze dehydration reactions of carbohydrates to afford 5-hydroxymethylfurfural.[75]



View Article Online DOI: 10.1039/D1OB01939B

Scheme 37 Mo-catalyzed deoxygenation of epoxides to alkenes using 2,4-dimethyl-3-pentanol as reducing agent.

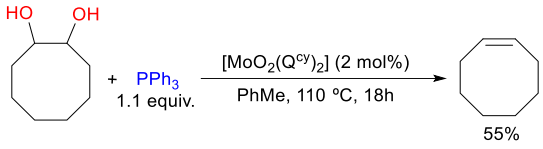
In 2017, Srivastasa and Robertson reported the deoxygenation of epoxides employing an alcohol as a sacrificial reducing agent on the basis of the recent advances about deoxygenation and deoxydehydration using alcohols as reductants.[76] Best results were achieved employing a dioxomolybdenum catalyst bearing diethyl dithiocarbamate (dtc) ligands and an excess of 2,4-dimethyl-3-pentanol as reductant (Scheme 37). Other alcohols like MeOH, EtOH, *n*PrOH, 1-butanol, 1-octanol, 1-hexanol, 2-methyl-2-butanol, isoamyl alcohol, and 3-methyl-1-butanol were proven to be inefficient and the alkene was obtained in poor yields. Several mono- and/or 1,2-disubstituted epoxides were efficiently deoxygenated in a range of 160–190 °C in toluene in a sealed tube. In all cases, the deoxygenation reaction proceeds in a stereoretentive manner. After the initial reduction of Mo(VI) catalyst to Mo(IV) species, condensation with the epoxide generates a molybdenum diolate that, after alkene extrusion, regenerates the initial Mo(VI) catalyst.

4.2. Deoxygenation and deoxydehydration of C–O single bonds: vicinal diols.

The over-exhaustion of fossil fuels has caused a continuous search for more efficient processes to obtain valued chemicals from biorenewable resources.[77] In this sense, deoxydehydration (DODH) processes to synthesize olefins from biomass-derived polyols and vicinal diols have attracted much interest.[78] In recent years, dioxomolybdenum complexes have emerged as an inexpensive alternative to oxo-rhenium catalysts, which have been frequently employed in DODH reactions.[4d,14,79]

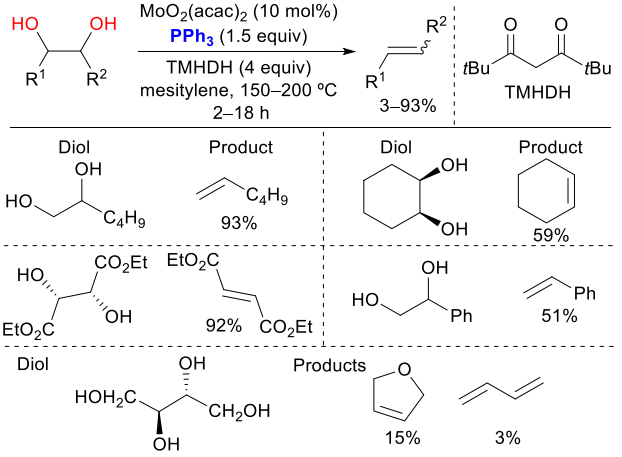
4.2.1. Phosphorus compounds as reductants

The first example of deoxydehydration reaction (DODH) catalyzed by dioxomolybdenum complexes was also reported by the group of Montilla and Galindo in 2013 using PPh_3 as the reducing agent.[70] In this case, molybdenum catalysts bearing acylpyrazolonate ligands (see Scheme 33) promote deoxydehydration of 1,2-cyclooctanediol, affording the cyclic alkene (Scheme 38).



Scheme 38 DODH of 1,2-cyclooctanediol catalyzed by dioxomolybdenum complexes and using PPh_3 as reducing agent.

Triphenylphosphine was utilized as a model reductant in related DODH transformations. In 2018, De Vos and Stalpaert studied the DODH reaction employing dioxomolybdenum catalysts in the presence of 1,3-diketones ligand precursors having different steric and electronic properties (Scheme 39).[80]

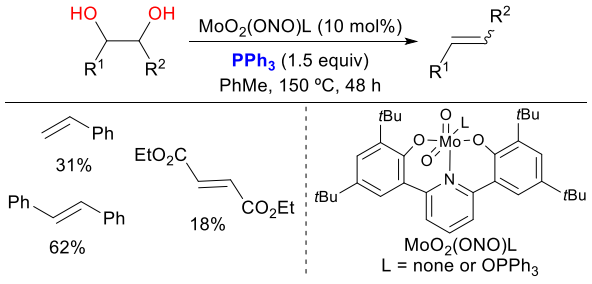


Scheme 39 $MoO_2(acac)_2$-catalyzed DODH of vicinal diols using PPh_3 as reductant.

The authors found that electron-donating and sterically bulky ligands enhanced the catalytic activity of the molybdenum center towards DODH reactions considerably. Whereas commercially available $MoO_2(acac)_2$ catalyst in the absence of additional ligands provided low conversion of vicinal diols into desired alkenes, the addition of 2,2,6,6-tetramethylheptanedione increased yields significantly (Scheme 39). Best results were obtained when 1,2-hexanediol and biobased (+)-diethyl L-tartrate were subjected to the reaction at 200 °C in mesitylene. By contrast, biobased erythritol afforded 2,5-dihydrofurane and 1,3-butadiene in low yields.

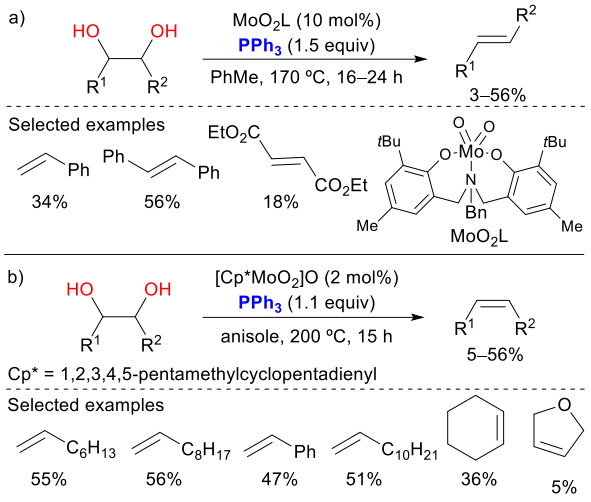
After ESI-MS analysis of centrifuged reaction samples, the authors observed that when enough 2,2,6,6-tetramethylheptanedionate (TMHD) ligand is present only monomeric and oligomeric Mo could be detected. This observation supports that the TMHDH ligand plays a crucial role in stabilizing Mo-catalyst, diminishing or avoiding catalyst precipitation.

Recently, other dioxomolybdenum complexes bearing bulky ligands have been designed and evaluated in DODH with PPh_3, aiming to achieve a more efficient and active catalyst that may compete with oxorhenium catalysts. In this sense, Kilyanek and Tran developed dioxomolybdenum complexes coordinated to a dianonic pincer ONO ligand (Scheme 40).[81] The catalyst achieved moderate to low yields in the DODH of 1-phenyl-1,2-ethanediol, (*R*,*R*)-(+)-hydrobenzoin, and (+)-diethyl L-tartrate. DODH of 1,2-octanediol was also accomplished at 200 °C in chlorobenzene, obtaining up to 62% yield of 1-octene.



Scheme 40 DODH reaction catalyzed by dioxomolybdenum complexes bearing pincer ligands and using PPh_3 as reducing agent.

Similarly, John and co-workers described dioxomolybdenum complexes with aminobisphenolate ligands bearing a pendant arm.[82] The authors also tested their catalytic activity with several model substrates affording similar results to those reported by Kilyanek with the pincer ONO ligand (Scheme 41a).



Scheme 41 DODH reaction catalyzed by dioxomolybdenum complexes bearing bulky ligands and using PPh_3 as reducing agent.

More broad applicability to diverse substrates was described by the Gebbink group employing μ-oxo dioxomolybdenum dimer with 1,2,3,4,5-pentamethylcyclopentadienyl (Cp^*) ligands (Scheme 41b).[83] Interestingly, alkyl and aryl-substituted 1,2-diols as well cyclic 1,2-diols were converted into the desired olefins in a sustainable solvent like anisole, although moderate yields were achieved. Biobased 1,4-anhydroerythritol was also tested with this $[Cp^*MoO_2]_2O$ catalyst affording a 5% yield of alkene probably due to poor solubility of 1,4-anhydroerythritol in anisole. Similarly, glycerol generated a biphasic mixture, and no allyl alcohol was detected. Intriguingly, with 1,2-diphenyl 1,2-ethanediols, no DODH reaction occurred and only products derived from oxidative cleavage were observed.[26,28]

4.2.2.-Deoxydehydration reactions with alcohols

To implement efficient industrially attractive DODH processes from biomass, not only sustainable and affordable catalysts are essential, but also greener and cheaper reductants are required. Pursuing these goals, in 2014, Fristrup and co-workers reported a pioneering use of alcohols as suitable reducing agents in DODH reactions catalyzed by dioxomolybdenum complexes.[84] After testing several different molybdenum catalysts like $Mo(CO)_6$, $Mo(CO)_4$(bipy), MoO_2Cl_2(bipy), MoO_2Br_2(bipy), $MoO_2(CH_3)_2$(bipy), $(NH_4)_6Mo_7O_{24}$, Na_2MoO_4, and $H_3PMo_{12}O_{40}$, the authors found that most of the complexes catalyzed the DODH of 1,2-tetradecanediol in similar yield (27–43%) without adding any additional reductant in dodecane as solvent at 190–220 °C. Best results were obtained with the cheap and readily available $(NH_4)_6Mo_7O_{24}$ (AMH) catalyst (Scheme 42). Diols bearing smaller aliphatic chains were insoluble in the alkane solvent. Replacing dodecane by 1,5-pentanediol, DODH of 1,2-hexanediol

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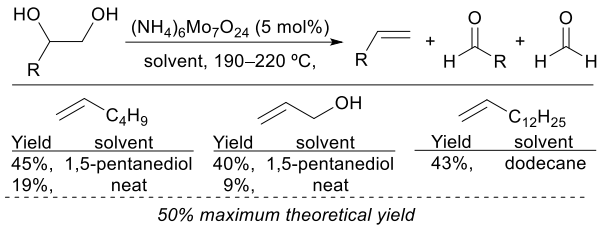
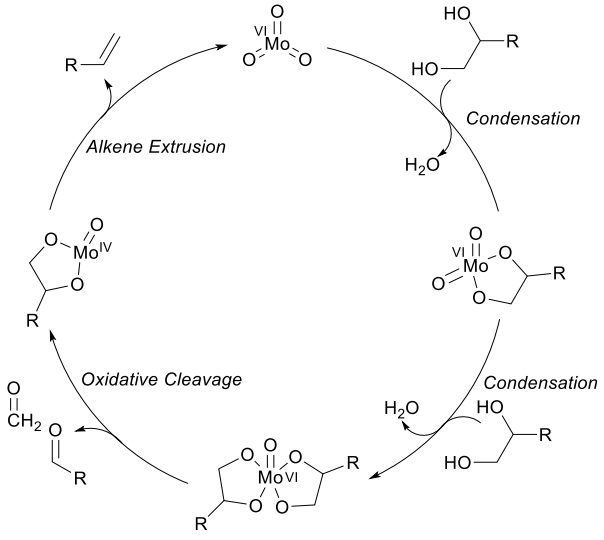
and biomass-derived glycerol was accomplished in a similar extension of the model substrate (Scheme 42). The authors also checked neat conditions with these two diols, although yields dropped considerably, affording byproducts derived from the condensation of diols with the in situ generated carbonyls. Mechanistic studies revealed that diol acts as both substrate and reducing agent. One-half of the diol undergoes DODH into the corresponding alkene while the other half evolves through oxidative cleavage. Actually, the alkene yield is as high as 90% for 1-hexene and 80% for allyl alcohol employing 1,5-pentanediol as the solvent, and 86% for 1-tetradecene in dodecane solvent considering the stoichiometry of the process.



Scheme 42 DODH reaction of 1,2-diols catalyzed by ammonium heptamolybdate in the absence of an additional reductant. Disproportionation of 1,2-diols.

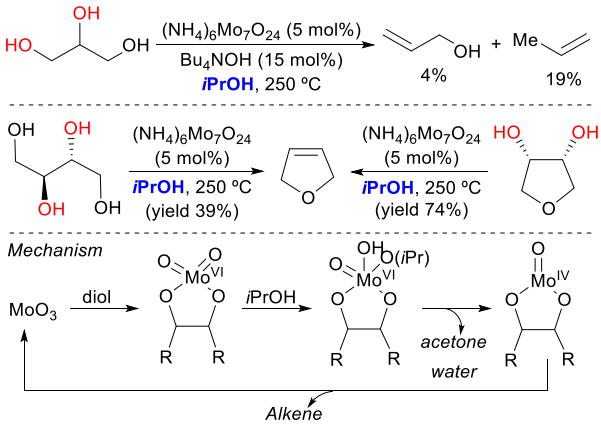
The same group studied the reaction mechanism by DFT calculations (Scheme 43). Initially, condensation of starting molybdenum oxide with a molecule of 1,2-diol generates a dioxomolybdenum diolate intermediate, liberating a water molecule. A second condensation with another 1,2-diol molecule affords another Mo(VI) complex bearing two diolate ligands. Then, one of the diolate ligands evolved through oxidative cleavage, releasing formaldehyde and an aldehyde. At the same time, the molybdenum center experiences reduction forming a Mo(IV) diolate complex. This oxomolybdenum diolate evolves through alkene extrusion, regenerating the initial molybdenum catalyst and releasing a molecule of the desired olefin.



Scheme 43 Proposed mechanism for the DODH using 1,2-diols as both substrate and reductant.

Intrigued why pinacol causes deoxygenation of sulfoxides exclusively without competitive DODH reactions with dichlorodioxomolybdenum catalysts,[26] Fristrup and co-workers performed DFT calculations of this process. After the initial formation of a Mo(VI) pinacolate complex, the authors found that the energy barrier for the cleavage of pinacol is significantly lower than the corresponding one for the propane-1,2-diol cleavage. Interestingly, substantial differences between molybdenum catalysts were observed. In contrast, oxidative diol cleavage requires very low activation energies (2.1 kcal mol^{-1}) with monodiolate dichloride complexes. The activation energy increases significantly with a pure oxomolybdenum catalyst without chlorine ligands. In addition, DODH processes with alkene extrusion require the formation of a Mo(IV) pinacolate intermediate whose energy barrier is considerably high ~40 kcal/mol^{-1} for oxochloromolybdenum complexes.

Further studies exploring alternative reductants achieved promising results employing isopropanol in DODH processes. Interestingly, affordable and green *i*PrOH could also be used as the reaction solvent, although the reaction could no longer be conducted in an open system and temperatures over 240 °C were required (Scheme 44).[85] In most cases, the addition of Bu_4NOH to the reaction media allowed higher yields of the desired alkene. In this sense, 1-hexene from 1,2-hexanediol was obtained in 77%, whereas in the absence of Bu_4NOH the yield dropped to 46%. Biomass-derived diols were also tested. Glycerol afforded small amounts of allyl alcohol and propylene (Scheme 44). Both erythritol and 1,4-anhydroerythritol delivered 2,5-dihydrofuran in 39% and 74% yield, respectively (Scheme 44). Surprisingly, the addition of Bu_4NOH produced lower yields.

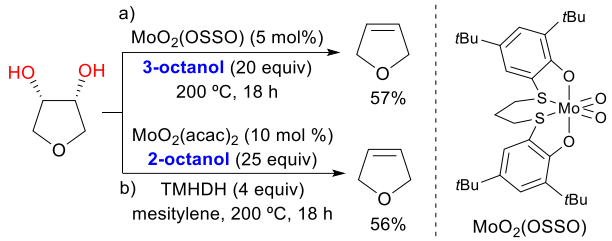


Scheme 44 DODH reaction of 1,2-diols catalyzed by ammonium heptamolybdate using *i*PrOH as reductant.

The mechanism supported by DFT calculations again involves the formation of a dioxomolybdenum diolate complex. After condensation with *i*PrOH, this intermediate experiences reduction by hydrogen transfer reaction, which generates a Mo(IV) diolate complex and releases a water molecule. Finally, alkene extrusion regenerates the initial catalyst.

These promising results on DODH of 1,2-diols employing alcohols as reductants have served as the basis for further investigations. In this sense, other authors have explored alternative catalytic systems in

combination with different alcohols. In 2016, Okuda and co-workers obtained good results in the DODH reaction of 1,4-anhydroerythritol employing a molybdenum complex bearing (OSSO)-type bis(phenolate) ligand and 3-octanol as the reducing agent (Scheme 45a).[86] De Vos and Stalpaert obtained similar results employing $MoO_2(acac)_2$ in the presence of 2,2,6,6-tetramethylheptane-3,5-dione ligand and 2-octanol as the reductant (Scheme 45b).[80] Supported $(NH_4)_6Mo_7O_{24}{\cdot}4\,H_2O$ catalysts on TiO_2 performed readily well in the DODH of 1,4-anhydroerythritol with 3-octanol at 200 °C affording 2,5-dihydrofuran in high yield (76%).[87]

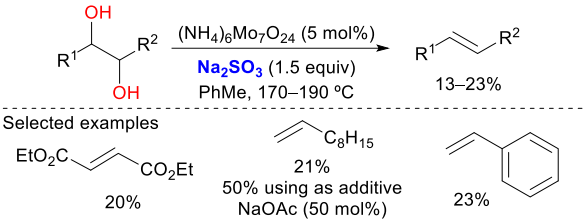


Scheme 45 DODH reaction of 1,2-diols catalyzed by dioxomolybdenum complexes bearing an (OSSO)-ligand and using 3-octanol as reductant.

Kilyanek and Tran achieved the DODH of (+) diethyl-L-tartrate into diethyl fumarate in 18% yield when applying isopropanol as the reductant with dioxomolybdenum complexes supported by ONO pincer ligands.[81]

In 2019, Lu and co-workers reported DODH of tartaric acid employing powder single-site $[MoO_2]^{2+}$ complexes supported by 8-hydroxyquinoline ligands.[88] In this case, 1-butanol acted as both reductant and solvent, which delivered dibutyl fumarate in high yields up to 86% at 160 °C. Interestingly, the solid catalyst could be recovered after the reaction, although its catalytic activity was shown to be lower in a second cycle.

4.2.3. Deoxydehydration reactions using other reductants



Scheme 46 DODH reaction of 1,2-diols catalyzed by ammonium heptamolybdate using sodium sulfite as reductant.

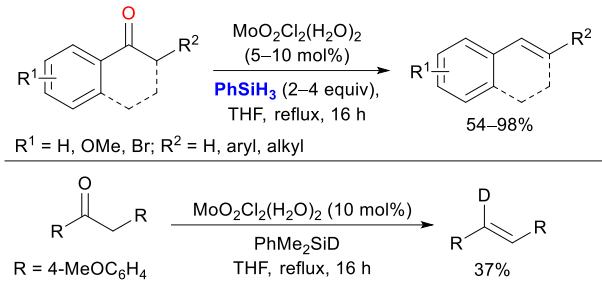
Dioxomolybdenum-catalyzed DODH reactions of vicinal diols are not limited to the utilization of PPh_3 and alcohols as reducing agents. Other reductants such as zinc, carbon, sodium sulfite, and potassium iodide were also investigated, although generally lower yields were obtained than when alcohols or triphenylphosphine were used as reductants.[81,82,89]

Interestingly, inexpensive sodium sulfite combined with ammonium heptamolybdate (AHM) as catalyst achieved higher yields for the DODH of (+) diethyl-L-tartrate into diethyl fumarate than when PPh_3 was used as the reducing agent (Scheme 46). The addition of NaOAc (50 mol%) was beneficial. For example, the DODH of 1,2-decanediol into 1-decene produced the desired alkene in 50% yield, whereas without additive, only 21% yield was achieved.[89]

4.3. Deoxygenation of C–O multiple bonds

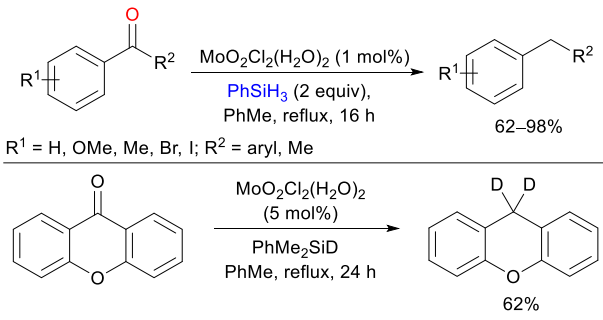
4.3.1. Silanes as reductants

As mentioned previously, dioxomolybdenum complexes have emerged as suitable catalysts for the hydrosilylation of aldehydes and ketones,[16] imines[17,90], as well as for the reduction of esters[18] and amides[19] into ethers and amines, respectively. Based on these findings, the Fernandes group has reported the deoxygenation of arylketones to arylalkenes[91] and alkanes.[92] The choice of solvent was decisive to achieve the deoxygenation of arylketones with $MoO_2Cl_2(H_2O)_2$ catalyst and $PhSiH_3$ as the reductant (Scheme 47).[91] Incorporation of deuterium at the carbon bearing the initial carbonyl moiety was observed when the catalytic reaction was performed with deuterated silanes (Scheme 47). A plausible mechanism is based on an initial hydrosilylation reaction followed by dehydration of the generated alcohol or silyl ether, achieving a formal deoxygenation process.



Scheme 47 $MoO_2Cl_2(H_2O)_2$-catalyzed deoxygenation of aryl ketones to alkenes.

Switching the reaction conditions by employing refluxing toluene, the arylketones are efficiently transformed into arylalkanes instead of the arylalkenes mentioned above when THF was used as the solvent (Scheme 48).[92] Interestingly, the catalyst loading was reduced down to 1 mol% without observing any deleterious effect. This process also holds a similar group tolerance, although iodoarenes are well tolerated in this case.



Scheme 48 $MoO_2Cl_2(H_2O)_2$-catalyzed deoxygenation of aryl ketones to alkanes.

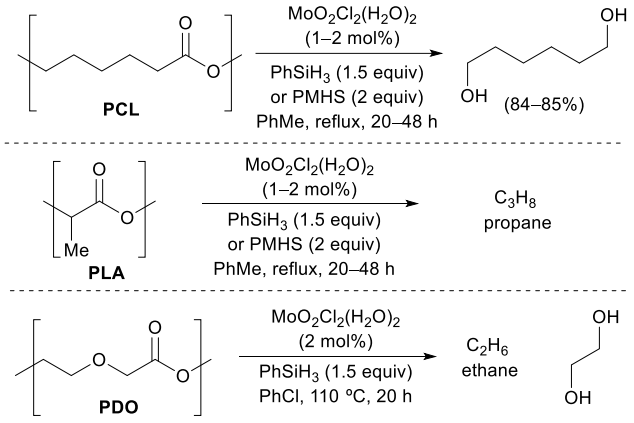
DOI: 10.1039/D1OB01939B

The authors performed again deuterium-labeled experiments employing a deuterated silane. Under standard reaction conditions using higher catalyst loadings, the arylalkanes incorporated two deuterium atoms at the carbon of the initial carbonyl position.

4.4. Deoxygenation in depolymerization of plastic waste

The continuous waste plastic accumulation has negative consequences on the environment and human health. Moreover, in most cases, plastics are obtained from non-renewable resources. Aiming to achieve a circular economy, depolymerization and recycling of plastic waste have emerged as relevant, sustainable strategies to deal with plastic waste accumulation.[93]

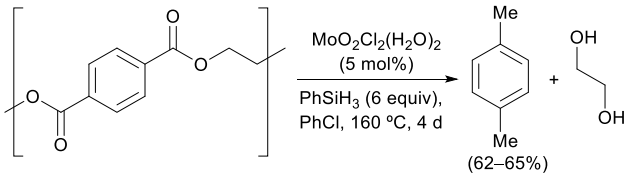
Several methods for depolymerization of plastic have been developed, but it was not until 2020 when the first example of plastic waste depolymerization by employing dioxomolybdenum catalysts was reported.[94] Based on their previous experience in deoxygenation with silanes with $[MoO_2]^{2+}$ catalysts, the Fernandes group ideated a convenient scalable method for depolymerizing different plastic polymers into value-added compounds and fuels.



Scheme 49 $MoO_2Cl_2(H_2O)_2$-catalyzed depolymerization of PCL, PLA and PDO.

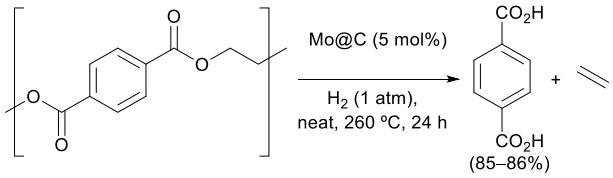
Initially, the authors studied the depolymerization of polymers based on aliphatic monomers such as polycaprolactone (PCL), polylactic acid (PLA) and (PDO) (Scheme 49). PCL experienced hydrosilylation giving rise to 1,6-hexanediol, whereas PLA and PDO were depolymerized into light weight alkanes like ethane and propane, which implies deoxygenation reactions. In all cases, high conversion was obtained by employing $MoO_2Cl_2(H_2O)_2$ in low catalyst loading combined with an excess of $PhSiH_3$ reductant under heating at 110 °C. Reductive depolymerization of PCL generated high yields 1,2-hexanediol. Under similar reaction conditions, depolymerization of PLA and PDO proceeds in full conversion. In these two cases, deoxygenation of the aliphatic monomers was observed, affording propane from PLA and ethane and small amounts of ethylene glycol in the depolymerization of PDO. Remarkable, cheap, environmentally friendly PMHS could be used for the depolymerization of PCL and PLA.

This strategy successfully achieved the deoxygenative depolymerization of more challenging thermoplastic polymers based on terephthalic acid monomers. Nevertheless, harsher reaction conditions were required to depolymerize polyethylene terephthalate (PET) and polybutylene terephthalate (PBT), which are highly resistant and widely used polymers. Best results were obtained by increasing reaction temperature (160 °C), the catalyst loading (5 mol%), and excess of $PhSiH_3$ (6 equiv). Fernandes and co-workers also demonstrated that PET waste from water bottles, synthetic pillows, or clothes could be efficiently depolymerized into xylene (62–65% yield) and ethylene glycol (Scheme 50). A prolonged reaction time of 7 days caused the deoxygenation of the glycol into ethane. Depolymerization of PBT was achieved under the same reaction conditions achieving higher amounts of *p*-xylene (86%).



Scheme 50 $MoO_2Cl_2(H_2O)_2$-catalyzed depolymerization of PET.

Also, in 2020, Marks, Gao and co-workers described a promising alternative approach to the depolymerization of PET that enables the recuperation of terephthalic acid.[95] To this aim, the authors employed the carbon grafted Mo@C catalyst bearing single site $[MoO_2]^{2+}$ centers combined with molecular hydrogen as the reductant at 260 °C without any solvent (Scheme 51). In this case, the depolymerization process involves a DODH reaction of ethylene glycol monomer into ethylene, allowing the terephthalic acid regeneration. Both commercial and bottle waste plastic samples of PET were efficiently depolymerized, achieving terephthalic acid in high yields from both sources.



Scheme 51 Mo@C-catalyzed depolymerization of PET.

Conclusions

Over the last two decades, deoxygenation reactions under dioxomolybdenum catalysis have experienced significant development. Numerous structurally different carbon-, nitrogen-, and sulfur-based substrates were efficiently deoxygenated. Environmentally friendly and easily available dioxomolybdenum complexes have demonstrated wide applicability to the deoxygenation of sulfoxides into sulfides and, more interestingly, from a synthetic point of view to the reduction of the nitro functional group that leads to the synthesis of value-added nitrogen-containing compounds. Remarkably, Mo-catalyzed reductive cyclizations and related cascade reactions are a fruitful research area. This strategy allows the synthesis of highly attractive N-heterocyclic cores

such as indole, carbazole, benzopyrazole, quinoline, benzodiazepine, among many others, from readily available and inexpensive nitro compounds. Moreover, in the last decade, dioxomolybdenum complexes were successfully applied to deoxygenation of epoxides, alcohols and ketones, and also to deoxydehydration of biomass-derived 1,2-vicinal diols, which is a research area that is experiencing significant progress. The improvement of the catalytic systems and the emergence of new reductants have contributed decisively to this development. Particularly, the rise of green and sustainable reducing agents has attracted much attention.

The development of strategies for efficient deoxygenation reactions catalyzed by dioxomolybdenum(VI) complexes has enormous growth potential. The future directions on this field will probably focus on the use of more efficient and sustainable reductants, especially to those methodologies applied to biomass and waste valorization. Furthermore, the design of more efficient catalysts that will increase the efficiency of the processes is another area that will experience considerable expansion. In this sense, supported molybdenum complexes have been experienced significant progress in recent years, although more advances in the field could be expected.

Conflicts of interest

There are no conflicts to declare.

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Biographic Sketch

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