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Selective oxidation of anilines to azobenzenes and azoxybenzenes by a molecular Mo oxide catalyst

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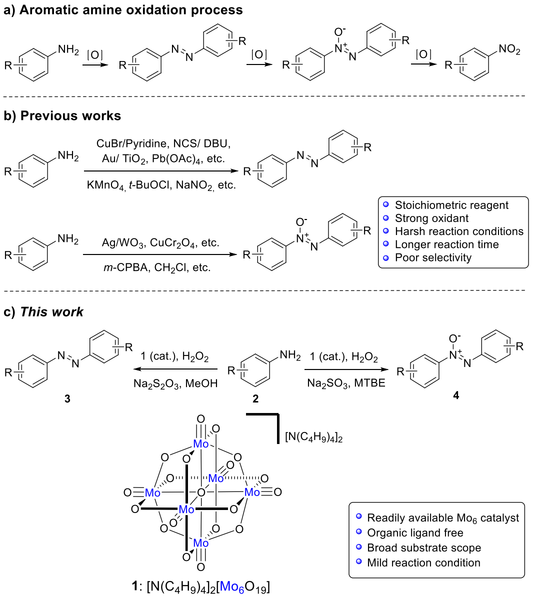
Abstract: Aromatic azo compounds, which play an important role in pharmaceutical and industrial applications, still face great challenges in synthesis. Herein, we report a molybdenum oxide compound, $[N(C_4H_9)_4]_2[Mo_6O_{19}]$ (**1**), catalyzed selective oxidation of anilines with hydrogen peroxide as green oxidant. The oxidation of anilines can be realized in a fully selectively fashion to afford various symmetric/asymmetric azobenzene and azoxybenzene compounds, respectively, by changing additive and solvent, avoiding the use of stoichiometric metal oxidants. Preliminary mechanistic investigations suggest the intermediacy of highly active reactive and elusive Mo imido complexes.

Aromatic azo compounds with the N=N motif are of great interest in modern industry as dyes, pigments, food additives, photochemical switches and therapeutic agents[1]. Therefore, great synthetic efforts have been made to achieve azo compounds from readily available anilines. The oxidation of aromatic amines usually involves stepwise oxidation *via* hydroxylamine, azobenzene, azoxybenzene and nitrobenzene (Scheme 1, a). The challenge lies in controlling the selectivity to a desired product. Classical methods for the synthesis of azobenzenes include reductive coupling of aromatic nitro compounds[2], the coupling of aromatic compounds with aryl diazonium salts[3], the Mills reaction[4], and the Wallach reaction[5]. Specially, direct oxidative dehydrogenative coupling of anilines to azobenzenes has been fully explored (Scheme 1, b). In 2008, Corma's group reported gold nanoparticles supported on titanium dioxide (TiO_2) and nanoparticulated cerium dioxide (CeO_2) catalytic systems to aerobic oxidation of aromatic anilines and gained the corresponding azo compounds with good yield. In 2012, Minakata's group realized oxidative homodimerization of anilines in the presence of *tert*-butyl hypoiodite (*t*BuOI) as the organic oxidant. In 2016, Camargo and co-workers used Ag/Au nanoshells and Au nanoparticles as catalysts for the synthesis of azobenzene in liquid phase. Although various catalysts have been efficiently explored for the oxidative dehydrogenative couplings of anilines' reaction, there are still great challenge such as high catalyst loading, stoichiometric reagents, or the need of strong oxidants. Therefore, a sustainable chemical process for highly selective synthesis of aromatic azo compounds is still high desirable.



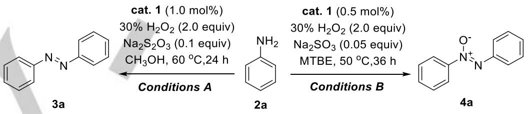
Scheme 1. Mo oxide molecular catalyst system.

Polyoxometalates (POMs), a unique class of molecular metal-oxide clusters of transition metals, are widely used in catalytic transformations, especially for the catalytic oxidation due to their electron reservoir abilities and the activity of their diverse reduced forms[6]. Recently, our groups have demonstrated that POMs can be used as inorganic ligand-supported metal catalysts in various organic reactions[7]. In 2017, we reported a single-sided iron centered Anderson-type POM, $[N(C_4H_9)_4]_3[FeMo_6O_{18}(OH)_3\{(OCH_2)_3CNH_2\}]$ ($[Fe^{III}Mo_6]$), for the aerobic oxidation of aldehydes in water. Subsequently, other Anderson-type POM with different metals central was successfully used in the oxidation of amines to imines, oxidation of aldehydes to esters or one-step oxidation of alcohols to esters, and *N*-formylation of amines[8]. As part of our ongoing research in developing new applications of POM-based catalysts in organic reactions, we report herein a new preparation protocol of aromatic azo compounds with a molecular molybdenum oxide catalyst $[N(C_4H_9)_4]_2[Mo_6O_{19}]$ (**1**) for the selective oxidation of anilines in the presence of H_2O_2 under mild conditions (Scheme 1, c).

The molecular catalyst $[N(C_4H_9)_4]_2[Mo_6O_{19}]$ (**1**) was prepared from $(NH_4)_6Mo_7O_{24}\bullet 4H_2O$ and $[N(C_4H_9)_4]Br$ according to the published literature reports (Figure S1)[9] and its structure of **1** was confirmed by FT-IR test (Figure S2). We initiated our studies by probing various reaction conditions for the POM catalyzed oxidative dimerization of aromatic amines **2** in an environmentally-friendly way. Phenylamine **2a** was selected as a model substrate for the optimization of reaction conditions. By employing 1.0 mol% of $[N(C_4H_9)_4]_2[Mo_6O_{19}]$ (**1**) in the presence of 2.0 equivalent of H_2O_2 (30% in H_2O_2) in methanol at 50 °C for 24 h, we were delighted to observe the formation of homodimerized azobenzene **3a** as a major product with 49% isolated yield (Table S1, entry 1). Various additives, such as Na_2CO_3, $NaHCO_3$, K_3PO_4, Na_2SO_4, Na_2SO_3 and $Na_2S_2O_3$ were investigated, and $Na_2S_2O_3$ was found to be an ideal additive for this oxidative dimerization reaction (Table S1, entries 2-9). Remarkably, when 0.1 equivalent of $Na_2S_2O_3$ was used, the oxidative homodimerization proceed smoothly to give azobenzene **3a** in 99% yield (Table S1, entry 9). The catalyst loading could be decreased to 1.0 mol% of $[N(C_4H_9)_4]_2[Mo_6O_{19}]$ (**1**) (Table S1, entries 10-12). The reaction worked in a broad range of solvents and wide range of temperatures (Table S2) and with MeOH at 60 °C giving the best reproducibility, highest yield (Table S2, entry 2). Other Mo catalysts, such as $(NH_4)_6Mo_7O_{24}$ and MoO_3, were also found to promote the oxidative dimerization (Table S1, entry 16-17), however with lower efficiency. No desired aromatic azo products were detected in the absence of catalyst **1** (Table 1, entry 4). Moreover, the reaction was completely blocked in an O_2 atmosphere or N_2 atmosphere in replacement of H_2O_2, which indicates the importance of the oxidant in the reaction system. But O_2 is not reactive enough to activate the catalyst (Table 1, entries 5, 6). After extensive optimization with the other reaction parameters (for the detailed conditional screening process, see the Supporting Information, Table S1), we were pleased to find that 1.0 mol% **1**, with 0.1 equivalent of $Na_2S_2O_3$ and 2.0 equivalent of H_2O_2 as oxidant in methanol at 60 °C under air was the most optimized reaction condition (Table 1, entry 1).

Meanwhile, we also detected the production of azoxybenzene **4a** in the reaction system. In the same way, we screened the reaction conditions in order to obtain azoxybenzenes selectively (Table S3-S4). Remarkably, the selections of solvents and additives proved to have a significant influence on the reaction pathway and yield. We can selectively produce azobenzenes or azoxybenzenes by changing solvent and additive, as well as increasing the temperature and extending the reaction time. The highest yield of azoxybenzene can reach to 93%.

Table 1. Optimal reaction conditions

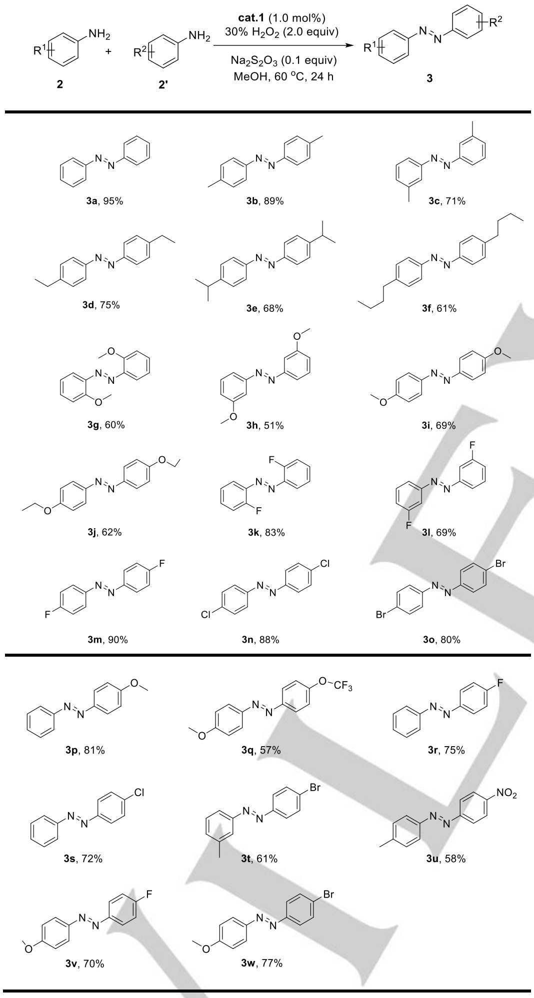


Entry	Deviations from standard conditions A[a] and B[b]	Yield **3a** (%)[c]	Yield **4a** (%)[c]
1	None	99	93
2	$(NH_4)_6Mo_7O_{24}$	35	52
3	MoO_3	39	34
4	-	-	<8
5	O_2 replacement H_2O_2	-	-
6	N_2 replacement H_2O_2	-	-

[a] **1** (1.0 mol%), **2a** (1.0 mmol), methanol (2.0 mL), 30% H_2O_2 (2.0 equiv), $Na_2S_2O_3$ (0.1 equiv), 60 ºC, 24 h. [b] **1** (0.5 mol%), **2a** (1.0 mmol), MTBE (2.0 mL), 30% H_2O_2 (2.0 equiv), Na_2SO_3 (0.05 equiv), 50 ºC, 36 h. [c] Yield determined by GC-MS.

With these optimized reaction conditions in hand, we sought to examine the substrate scope of the Mo-catalysed oxidative dehydrogenation reaction (Table 2). Anilines with both electron-rich and electron-deficient substitutions were readily dimerized to afford the corresponding symmetric azobenzenes in excellent yields. Various substituents including Me, Et, *i*Pr, *n*-Bu, OMe, OEt, F, Cl and Br were well tolerated (Table 2, **3b-o**). It showed that the substrates with an electron-withdrawing group are better than those with the electron-donating group, maybe due to the existence of the electron-withdrawing group, which reduces the electron cloud density of the benzene ring and thus promotes the reaction process. Moreover, we also explored the effect of steric hindrance on the reaction. The yield of *para*-substituted for electron-withdrawing groups products was significantly higher than that of *ortho*- and *meta*-substituted products (Table 2, **3k-m**). The same experimental results were obtained for the substrate of the electron donor product (Table 2, **3b-c**, **3g-i**). That means that *para*-substituted products are easier to convert to corresponded azo compounds. The conversion to azobenzene can be achieved even if the phenylamine compound is substituted by *n*-butyl with 61% yield. Furthermore, the aniline oxidative cross-dimerization was also examined to give the corresponding asymmetric azobenzenes in good to excellent yields (Table 2, **3p-w**). Benzylamine can react with 4-methoxyaniline, 4-fluorobenzeneamine or 4-chlorophenylamine under the same condition, affording the corresponding 4-methoxyazobenzene, 4-fluoroazobenzene and 4-chloroazobenzene with 81%, 75% and 72% yield, respectively (Table 2, **3p, 3r-s**). Even (*p*-nitrophenylazo)toluene can be generated in 58% yield (Table 2, **3u**).

Table 2. Mo-catalysed oxidative dimerization of anilines to azobenzenes.[a,b]

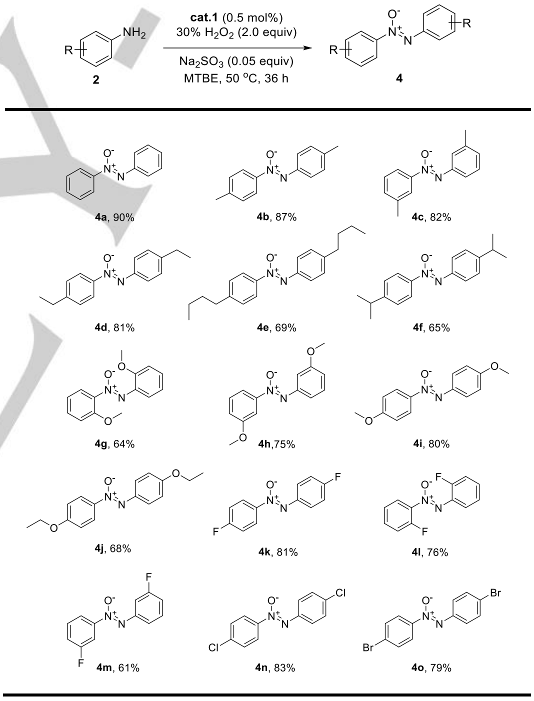


[a] Reaction conditions: cat. **1** (1.0 mol%), $ArNH_2$ (1.0 mmol), MeOH (2.0 mL), 30% H_2O_2 (2.0 equiv), $Na_2S_2O_3$ (0.1 equiv), 60 ºC, 24 h; [b] isolated yields.

In parallel, we have examined the scope of the Mo-catalyzed oxidation of anilines to azoxybenzenes with the optimal conditions by employing aniline **2** in the presence of 0.5 mol% of **1** as the catalyst, 0.05 equivalent of Na_2SO_3 as the additive and methyl *tert*-butyl ether (MTBE) (2.0 mL) as the solvent and 2.0 equivalents of 30% H_2O_2 at 50 ℃ for 36 h (Table 3). Initially, the oxidation was carried out with phenylamine **2a** leading to azoxybenzene **4a** in high yield (90% isolated yield). In addition, homodimerization products were also detected in minor quantities. Anilines bearing electron-donating groups tolerated well, and gave the corresponding azoxybenzene **4b-j** in slightly lower yields. Anilines bearing electron-withdrawing groups, such as F, Cl and Br, were also tolerated well and gave azoxybenzenes in relative lower yields (Table 3, **4k-o**). In addition, *para*-substituted anilines can be converted more efficiently to the corresponding azoxybenzenes in higher yield than *ortho*- and *meta*-substituted anilines due to steric effects.

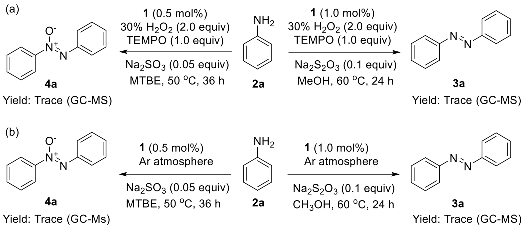
The scalability of the method was validated by oxidizing compound **2a** on a six-gram scale (Scheme S1 and S2), affording the desired azobenzene **3a** and azoxybenzene **4a** in 90% and 85% isolated yield respectively.

Table 3. Mo-catalysed oxidation of anilines to azoxybenzenes.[a,b]



[a] Reaction conditions: cat. **1** (0.5 mol%), $ArNH_2$ (1.0 mmol), MTBE (2.0 mL), 30% H_2O_2 (2.0 equiv), Na_2SO_3 (0.05 equiv), 50 ºC, 36 h; [b] isolated yields.

To gain insight into the reaction mechanism, several control experiments were performed as shown in Scheme 1. When stoichiometric amounts of TEMPO were added as the radical scavenger in the reaction under the optimized conditions, the oxidative dimerization reactions were retarded dramatically with trace amounts of oxidative products detected (Scheme 2, a). Furthermore, when the reaction was performed under inert atmosphere (Ar) without the addition of hydrogen peroxide, there were no desired products formed (Scheme 2, b). These results indicate that the presence of an appropriate oxidant is the key to the reaction, and the reaction involves some free radical intermediates.



Scheme 2. Control experiments.

Based on our experimental results and related literature reports[10], a plausible mechanism was proposed to explain the catalytic cycle as depicted in Figure 1. For the cycle of synthesis of azobenzene compounds, initially, in the presence of amine, cat. **1** can be converted to intermediate *via* a Mo≡N triple bond[11], which can generate radical of nitrogen **III**. Then **III** can be combined with excess aromatic amine to obtain hydrazobenzene radical **IV**, which can generate **V**. Next when hydrogen peroxide is used as an oxidant, **V** can be oxidized to generate azobenzene compound **3a** and completing catalytic cycle back to **1**. The mechanism follows a simple redox-coupled sequence to furnish self-supported solids that behave as efficient acid, redox and acid/redox heterogeneous catalysts for different C-H and C-C activation reactions.

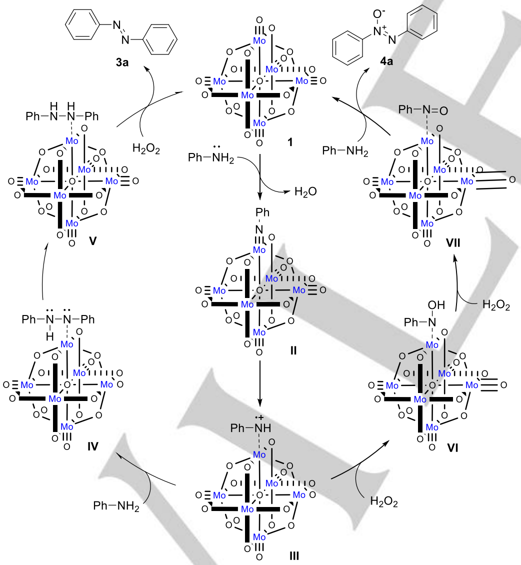


Figure 1. The proposed mechanism for the oxidation of aniline.

For the cycle of synthesis of azoxybenzene compounds, it has the same first step with the process of synthesis of azobenzene compounds to generate radical of nitrogen **III**. Then, in the presence of hydrogen peroxide, **III** can be converted to *N*-phenylhydroxylamine **VI**, which can be further oxidized to produce nitrosobenzene **VII**. Next, because of the presence of phenylamine, **VII** can generate azoxybenzene compound **4a** and completing catalytic cycle back to **1**.

In conclusion, we have demonstrated the capacity of polyoxometalate-based molecular molybdenum oxide catalyst $[N(C_4H_9)_4]_2[Mo_6O_{19}]$ for the oxidation of anilines to achieve various azobenzene and azoxybenzene compounds, respectively. This protocol works with a wide range of substrates and tolerates a series of functional groups on the anilines. Both symmetric and asymmetric azobenzenes, as well as azoxybenzenes can be facilely prepared in excellent yields by utilizing H_2O_2 as an environmentally benign oxidant. Preliminary mechanistic investigations suggest the intermediacy of highly active reactive and elusive Mo imido complexes.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: anilines • azo compounds • azoxy compounds • molybdenum • oxidation

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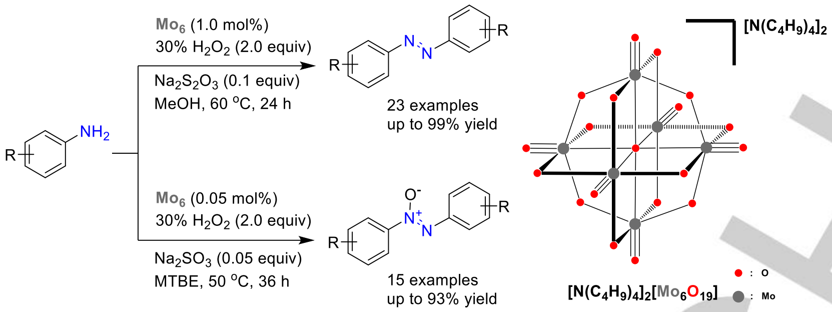

An effective approach was performed to selectively synthesize of azobenzene compounds and azoxybenzene compounds with N=N bond by a molecular molybdenum oxide compound $[N(C_4H_9)_4]_2[Mo_6O_{19}]$ (simplified as Mo_6) under mild conditions. A series of symmetric and asymmetric azobenzene and azoxybenzene compounds were produced by changing additive and solvent in high yield and selectivity. Moreover, the catalytic mechanism of the reaction system was also assumed appropriately.