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Synthesis of 1,4-aminoalcohols from substituted dienes and anilines *via* molybdooxaziridine catalysis†

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Herein we report the MoODipic(HMPA)ONAr promoted 1,4-aminohydroxylation of dienes using anilines as the quantitative source of N. The transformation involves the formation of the active catalyst Ar–N-molybdooxaziridine 1a, the formation of Ar–NO, a hetero-Diels–Alder reaction, and then reductive cleavage to obtain 1,4-aminoalcohols. Initial kinetic and mechanistic data indicate that Ar–NO formation is the rate-determining step and provides evidence for the proposed catalytic cycle.

1,4-Aminoalcohols are ubiquitous structural motifs in many natural products and valuable building blocks in organic synthesis.[1] Their applications extend to the development of functional organic materials and their use as ligands in transition-metal catalysis.[2] While the synthesis of aminoalcohols has received a lot of attention, methods for the synthesis of 1,4-aminoalcohols are more limited. Moreover, these often rely on strong acidic conditions and oxidizing agents, which limit their synthetic applicability.[3] On this front, efficient 1,4-aminooxygenation of 1,3-dienes through Pd catalysis has been reported.[4] These can also be accessed through the addition of Grignard's reagent to substituted aminotetrahydrofurans,[5] the Lewis acid-promoted reaction of cyclic N,O-acetals with silyl enol ethers,[6] the Mannich reactions of α-thiocarbonyls,[7] and the addition of amines to substituted hetero-dienes.[8] The sequential nitroso Diels–Alder (NDA), reductive N–O-bond cleavage represents a successful route to the synthesis of 1,4-aminoalcohols.[9] However, the complex nature of nitroso compound cycloadditions and the lack of efficient access to substituted nitroso compounds due to harsh methods, instability and challenging purification have severely limited this approach.[10] Nitroso compounds are also valuable chemical intermediates in various biological metabolic processes and synthetic chemical transformations.[11] Their synthetic applications are often hindered because C-nitroso compounds are unstable and often dimerize to produce azo and/or azoxy arenes through condensation reactions.[12] Therefore, the development of catalytic conditions for the synthesis and cycloaddition of nitroso compounds from simple substrates is of high significance. Metallooxaziridines are organometallic complexes that are derived from the reaction of metal-oxides and N-transfer reagents.[13] These metalloheterocycles have been reported to function as transfer reagents across different π-systems. Early efforts by Sharpless and Nicholas demonstrated that N–Ar molybdooxaziridines achieve N-transfer across alkyl alkenes to produce N–Ar allylic amines.[14] Recently, we have discovered that metallooxaziridines (Zr, V, W, and Mo) can achieve aziridination, amination, oxyamination, and sulfonation reactions across all types of alkenes.[15] Thus, the potential for novel chemical pathways across metallooxaziridines containing other transition metals is of great significance. These complexes can also serve as R–NO precursors, which under specific chemical environments trigger the formation of highly reactive nitroso compounds.[16] Thus, metallooxaziridines can serve as a catalytic source of highly reactive R–NOs and as such exploit their synthetic value.

Thus, we envisioned creating a reaction that achieves the synthesis of 1,4-aminoalcohols from anilines and dienes by designing a well-defined catalytic system for a highly efficient nitrosoarene Diels–Alder cycloaddition, followed by reductive cleavage in a single operation. We started by identifying catalytic reaction conditions for the tandem nitrosoarene Diels–Alder/reductive cleavage process from dienes and anilines (Table 1). The initial discovery with 10 mol% of MoODipic(HMPA)O_2 **1b**, H_2O_2/H_2O, and a 1 : 1 ratio of aniline and cyclohexadiene, followed by treatment with AcOH in H_2O and Zn powder, provided **4a** in good yield as a single diastereomer (84% yield, entry 1). Different solvents showed that polar and non-protic environments enhanced the reaction productivity, with 1,4-dioxane affording an

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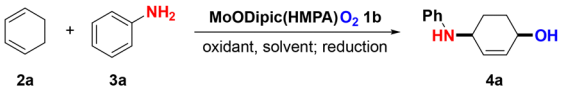
Table 1 Reaction optimization

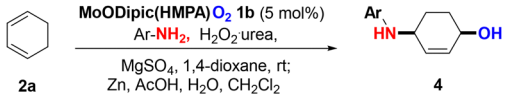


2a 3a 4a

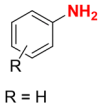
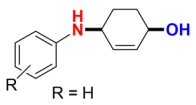
Entry	Catalyst (mol%)	Oxidant	Solvent	Reduction	Yield[ab] (%)
1	10	H_2O_2[c]	CH_3CN	Zn, AcOH, H_2O/CH_2Cl_2	84
2	10	H_2O_2	CH_3CN/H_2O	Zn, AcOH, H_2O/CH_2Cl_2	79
3	10	H_2O_2	Toluene	Zn, AcOH, H_2O/CH_2Cl_2	88
4	10	H_2O_2	Chlorobenzene	Zn, AcOH, H_2O/CH_2Cl_2	80
5	10	H_2O_2	DMA	Zn, AcOH, H_2O/CH_2Cl_2	82
6	10	H_2O_2	1,4-Dioxane	Zn, AcOH, H_2O/CH_2Cl_2	89
7	10	H_2O_2	1,4-Dioxane	Cu/C, Na_2CO_3, H_2O	64
8	10	H_2O_2	1,4-Dioxane	$Mo(CO)_6$, CH_3CN, 70 °C	75
9	10	H_2O_2	1,4-Dioxane	$In(OTf)_3$, CH_3CN, 80 °C	64
10	10	*t*BuOOH	1,4-Dioxane	Zn, AcOH, H_2O/CH_2Cl_2	53
11	10	AcOOH	1,4-Dioxane	Zn, AcOH, H_2O/CH_2Cl_2	64
12	10	H_2O_2·urea[d]	1,4-Dioxane	Zn, AcOH, H_2O/CH_2Cl_2	94
13	5	H_2O_2·urea	1,4-Dioxane	Zn, AcOH, H_2O/CH_2Cl_2	99
14	1	H_2O_2·urea	1,4-Dioxane	Zn, AcOH, H_2O/CH_2Cl_2	71

[a] Isolated yields. [b] $ArNH_2$ (1 equiv.) in 1,4-dioxane was mixed with H_2O_2·urea (2.2 equiv.), $MgSO_4$ (2.2 equiv.), and MoODipic(HMPA)O_2 **1b**, and then stirred at rt for 5 min. Diene (1 equiv.) was added and the reaction mixture was stirred for 16 h. The crude was filtered through Celite and the solvent was removed and reconstituted in CH_2Cl_2, then AcOH (10 equiv.), H_2O and Zn (40 equiv.) were added and the mixture was vigorously stirred for 2 h. Dipic = dipicolinic acid. [c] H_2O_2 30% in H_2O. [d] H_2O_2 35% in urea.

Table 2 Reaction scope



2a 4

Entry	Aniline	Product		Yield[ab] (%)
1	**3a**  R = H	 R = H	**4a**	99
2	**3b**	R = 4-methyl	**4b**	97
3	**3c**	R = 3-methyl	**4c**	98
4	**3d**	R = 2-methyl	**4d**	96
5	**3e**	R = 4-MeO	**4e**	98
6	**3f**	R = 3-MeO	**4f**	95
7	**3g**	R = 2-MeO	**4g**	91
8	**3h**	R = 2-Ph	**4h**	93
9	**3i**	R = 3-ethynyl	**4i**	95
10	**3j**	R = 4-fluoro	**4j**	98
11	**3k**	R = 4-fluoro	**4k**	96
12	**3l**	R = 4-bromo	**4l**	97
13	**3m**	R = 4-iodo[c]	**4m**	93
14	**3n**	R = 3-bromo	**4n**	88
15	**3o**	R = 2-bromo	**4o**	90
16	**3p**	R = 2-iodo	**4p**	89
17	**3q**	R = 3-chloro-4-fluoro	**4q**	95
18	**3r**	R = 4-nitro[c]	**4r**	86
19	**3s**	R = 3-nitro[c]	**4s**	80
20	**3t**	R = 2-nitro[c]	**4t**	82

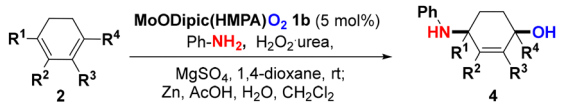
[a] Conditions: $ArNH_2$ (1 equiv.) in 1,4-dioxane was mixed with H_2O_2·urea (2.2 equiv.), $MgSO_4$ (2.2 equiv.), and MoODipic((HMPA)O_2 **1b** (5 mol%) and stirred for 5 min. Diene (1 equiv.) was added and the reaction mixture was stirred for 16 h. The crude was filtered through Celite and the solvent was removed and reconstituted in CH_2Cl_2, then AcOH (10 equiv.), H_2O and Zn (40 equiv.) were added and stirred for **2 h**. [b] Isolated yields without silica gel purification. [c] The crude reaction mixture from NDA was dissolved in CH_3CN/H_2O (4 : 1) and $Mo(CO)_6$ (1.1 equiv.) was heated at 80 °C for **4 h**.

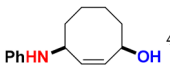
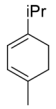
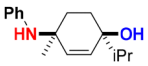
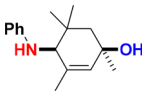
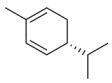
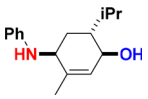
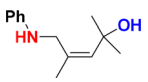
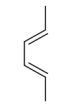
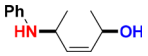
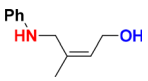
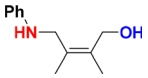
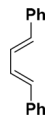
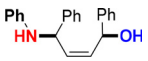
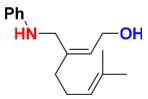
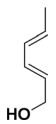
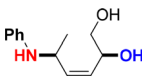
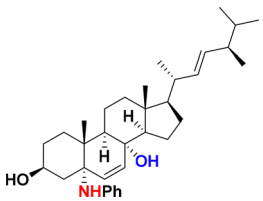
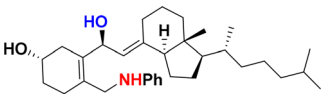
89% yield (entries 2–6). Due to the biphasic nature of the reductive cleavage, we attempted to employ homogenous conditions, but none provided equally high yields (entries 7–9). We were concerned that the high equivalency of water hindered the overall productivity due to competing oxidative pathways, and we tested different terminal oxidants without much improvement (entries 10 and 11). Eventually, we found that H_2O_2·urea elevated the productivity, and we were able to obtain **4a** in 94% (entry 12). The product still required a final purification step, but at 5 mol% trace impurities from competing oxidative pathways disappeared, and the yield increased to 99% without a final purification step (entry 13).

Based on the results observed for aniline and 1,3-cyclohexadiene, we then focused on investigating the generality across anilines with electron-donating groups (EDGs) and electron-withdrawing groups (EWGs) as a means of activating or deactivating the reaction pathway (Table 2). 4-Methyl-aniline afforded a similar yield at a faster observable rate for the cycloaddition (97%, 6 h, entry 2). Moreover, 3-methyl and 2-methyl provided the corresponding 1,4-aminoalcohols in very good yields, but the yield was slightly slower in the case of 2-methyl (entries 3 and 4). 4-OMe, 3-OMe, and 2-OMe reacted very fast (~4 h for both) with very good productivities (entries 5–7). Efforts to expand the scope with other EDGs found that 2-phenyl and 3-ethynyl aniline reacted in great yields and at slightly slower reaction rates (10 and 12 h, entries 8 and 9). To our surprise, the EDG ability in 2-phenyl aniline completely overrode any potential steric hindrance on the reaction kinetics. We anticipated that halogenated anilines would react with equal efficiencies but at slower rates and we found that 4-fluoro, 4-chloro, 4-bromo, and 4-iodo reacted with high yields but slower observable rates (24 h, 26 h, 25 h, and 25 h, respectively; entries 10–13). 3-Bromo, 2-bromo, 2-iodo, and 3-chloro-4-fluoro all proceeded with high yields and similar reaction rates (~32 h, entries 14–17).

The scope was completed with the study of anilines with EWGs: 4-nitro, 3-nitro, and 2-nitro aniline provided the expected 1,4-aminoalcohols in lower yields with a required final purification step (entries 18–20). The initial cycloaddition required heat for 24 h (60 °C) to achieve full conversion and under reductive conditions ($Mo(CO)_6$ in CH_3CN at 80 °C to avoid NO_2 group reduction) the respective 1,4-aminoalcohols were obtained. These results provide a clear indication that the rate-determining step may involve the initial molybdooxaziridine-mediated nitrosoarene formation. The reaction across different

Table 3 Reaction scope



Entry		Aniline	Product		Yield[a] (%)
1	**2b**			**4u**	91[b]
2	**2c**			**4v**	88
3	**2d**			**4w**	89
4	**2e**			**4x**	79
5	**2f**			**4y**	90[b]
6	**2g**			**4z**	95[b]
7	**2h**			**4aa**	96[b]
8	**2i**			**4ab**	91[b]
9	**2j**			**4ac**	82
10	**2k**			**4ad**	84
11	**2l**			**4ae**	88
12	**2m**			**4af**	71[c]
14	**2n**			**4ag**	64[c]

[a] Conditions: $ArNH_2$ (1 equiv.) in 1,4-dioxane was mixed with H_2O_2·urea (2.2 equiv.), $MgSO_4$ (2.2 equiv.), and MoODipic((HMPA)O_2 **1b** (5 mol%), and stirred for 5 min. Diene (1 equiv.) was added and the reaction mixture was stirred for 24 h. The crude was filtered through Celite and the solvent was removed and reconstituted in CH_2Cl_2, then AcOH (10 equiv.), H_2O and Zn (40 equiv.) were added and stirred for **2 h**. [b] Isolated yields without silica gel purification. [c] The crude reaction mixture from NDA was dissolved in CH_3CN/H_2O (4 : 1) and $Mo(CO)_6$ (1.1 equiv.) was heated at 80 °C for **4 h**.

anilines proved to be very successful and kinetic data indicate a clear reaction acceleration with EDGs and reaction deceleration with EWGs. While the reactions with EDG-bound anilines afforded great yields without requiring purification, nitroanilines provided more complex mixtures and required a purification step.

We then set out to test different dienes, with special emphasis on non-symmetrical dienes (Table 3). NDA reactions have shown different degrees of regioselectivity; while these reactions are known to proceed through a concerted but asynchronous mechanism, the regioselectivity trends are less well-understood.[17] 1-Substituted dienes are expected to have proximal-selectivity, while 2-substituted dienes are expected to provide the distal isomer. 1,3-Cyclooctadiene provided the corresponding 1,4-aminoalcohol in great yield (entry 1). We aimed to investigate the steric biases across polysubstituted dienes and found that α-terpinene and 1,3,5,5-tetramethyl-1,3-cyclohexadiene reacted with complete regioselectivity to produce the proximal-regioisomers with the N–Ph group on the least hindered side (entries 2 and 3).

Moreover, optically pure α-phellandrene also reacted with high regioselectivity, but 1,4-aminoalcohols were obtained as a mixture of diastereomers (7 : 1, entry 4). 1,3-Pentadiene was also successful in providing the expected *proximal*-isomer (entry 5). 1,3-Hexadiene, 2-methyl-1,3-butadiene (selective for the *distal*-isomer), and 2,3-dimethylbutadiene all reacted in great yields without final purification (entries 6–8). 1,4-Diphenyl-1,3-butadiene reacted with great efficiency, thus proving that highly sterically demanding dienes do not affect NDA reaction kinetics (entry 9). Myrcene also reacted selectively to provide the distal-regioisomer (entry 10), while 1,3-hexadienol provided 1,4-aminoalcohols **4ae** and **4ae′** as a 55 : 45 mixture of regioisomers (entry 11). Dienes are also recurrent among some naturally occurring steroids. We found that ergosterol and vitamin D3 reacted with high efficiencies to provide the corresponding 1,4-aminoalcohols as single isomers in very good yields (these two required purifications post reductive cleavage; entries 12 and 13). Ergosterol reacted with surprisingly high selectivity for the proximal-isomer (71% yield), with no other identifiable cycloadduct impurities.[18] Moreover, the vitamin D3 NDA reactivity pattern displays a clear preference for its terminal diene. Although a complex mixture was obtained, no other NDA products were isolated.

Our previous studies on the functionalization of alkenes *via* metallooxaziridine catalysis has helped design the mechanistic experiments for this new transformation. The proposed catalytic cycle (Fig. 1) starts with fast addition of aniline to molybdodioxirane **1b** to form molybdooxaziridine **1a**. This step is followed by fast diene–HMPA exchange and then the H_2O_2-mediated rate-determining step nitrosoarene extrusion. The resulting DipicMoO_2-(diene) complex undergoes NDA with nitrosoarene and the resulting DipicMoO_2(HMPA) **1c** undergoes H_2O_2-mediated oxidation to molybdodioxirane **1b**. The oxazine intermediate is then quantitatively reduced to the corresponding 1,4-aminoalcohol **4**. Based on the observed conversion rates and selectivities, the reaction exhibits first order kinetics on aniline, zeroth order kinetics for diene and saturation kinetics for H_2O_2 (details in the ESI†). Control experiments show that the reaction has no conversion in the absence of **1b**. However, the stoichiometric reaction with **1a** provides very low

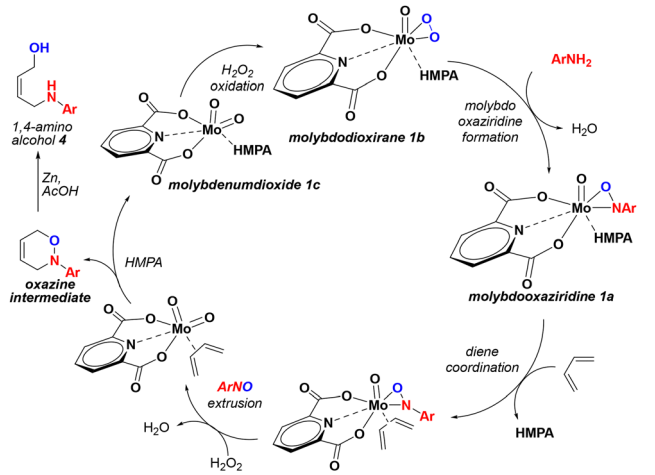


Fig. 1 Proposed catalytic cycle.

conversion at rt, but the presence of 1 equivalent of H_2O_2 enables full conversion. Moreover, the stoichiometric reaction with **1a** and an equivalent of DipicMoO$_2$(HMPA) **1c** at 50 °C also achieves conversion, highlighting the high rate of molybdenum oxide dimerization.[19] The lack of biradical intermediates up to the NDA step was also confirmed when reaction conversion to the oxazine intermediate was not hindered in the presence of radical scavengers.

The proposed catalytic cycle is further supported by a Hammett correlation study employing 4-substituted anilines (**3a, b, j, k, l**). The results show a ρ-value of −1.62 and hence demonstrate enhanced reactivity for anilines with EDGs as a positive charge develops on the nitrosoarene N atom in the transition state (details in the ESI†). Moreover, these results are also in agreement with a nitrosoarene extrusion as the rate-determining step for this catalytic cycle.

In summary, this work reports a novel method to selectively access 1,4-aminoalcohols from substituted anilines and dienes. The reaction works with high efficiency and stereoselectivity for dienes with diverse substitution patterns and for anilines with a variety of functional groups. The proposed catalytic cycle involves the formation of the active catalyst molybdooxaziridine **1a**, which releases nitrosoarene for the highly selective NDA to form an oxazine intermediate that then undergoes quantitative reductive cleavage to provide 1,4-aminoalcohol **4**. Further experiments to better understand and fully characterize all mechanism intermediates are ongoing, and a follow-up manuscript is in preparation.

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Conflicts of interest

There are no conflicts to declare.

Data availability

The data (including the experimental protocols, kinetic studies, and spectroscopic characterization of the catalysts and 1,4-aminoalcohols) supporting this article have been included as part of the ESI.†

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19 The reaction also works very well on a large scale (100 mmol of aniline) to produce **4a** in 99% yield (18.711 g).

