Rich chemistry of nitroso compounds

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Nitrosobenzene or nitrosopyridine are found to be attractive electrophiles in catalytic enantioselective carbon–nitrogen and/or carbon–oxygen bond forming reactions. In the presence of designer Lewis or Brønsted acid catalysts, catalytic enantioselective O- and N-nitroso aldol reaction or nitroso Diels–Alder reaction proceed smoothly. The scope and limitation of new catalytic processes are described.

Introduction

Since Baeyer's first preparation of nitrosobenzene at the end of nineteenth century,[1] the nitroso function has been widely recognized as a useful source to serve nitrogen- and oxygen-containing molecules. In 1899, Ehrlich and Sachs described seminal advances in the utility of nitroso reagent, the so-called Ehrlich–Sachs reaction (Scheme 1).[2] *p*-Nitrosodimethylaniline reacts with active methylene compounds derived from phenylacetonitrile in the presence of a base to afford an azomethine derivative. Since then, the addition of carbanion enolates,[3] ene reactions,[4] and Diels–Alder reactions[5] using nitroso compounds have been reported.

The noteworthy features of the nitroso electrophile are its high reactivity based on the polarization of the nitrogen–oxygen bond and specific structure by the equilibration between monomer and azodioxy dimer (Scheme 2),[6] which results in a unique chemo- and regioselectivity for various transformations using nitroso derivatives. In fact, the careful control of this equilibrium is an essential prerequisite for use of nitroso compounds in organic synthesis. Frequently, however, this unique equilibrium causes various difficulties in developing selective reactions using nitroso compounds.

In this review article, we attempt to summarize the recent developments of nitroso compounds in both aldol-type and hetero-Diels–Alder reaction that have been carried out mainly in our laboratory.[7]

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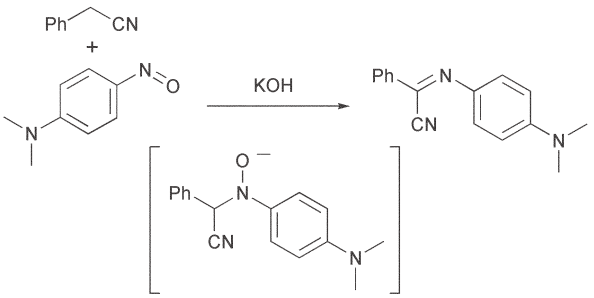
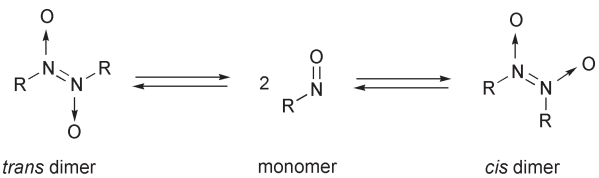
Norie Momiyama was born in Toyokawa, Aichi, Japan, in 1976. She received her BSc in 2000 and MSc in 2002 from Nagoya University under the supervision of Prof. Hisashi Yamamoto. Since 2002, she has started her PhD studies at Nagoya University, and subsequently moved to the University of Chicago. She received the Elizabeth R. Norton Prize for excellence in research in Chemistry, the University of Chicago in 2003 and the Abbott Laboratories Graduate Fellowship in 2005.

Nitroso aldol (NA) reaction

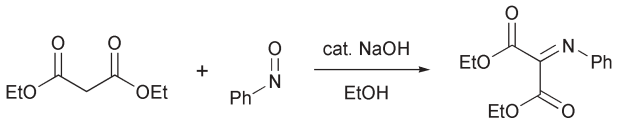
The early study by Mukaiyama and co-workers on the addition of enolates to nitrosobenzene described the transformation to access to azomethine derivatives (Scheme 3).[8] The reaction proceeded through nucleophilic attack at a nitrogen



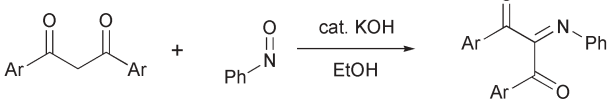
Scheme 1



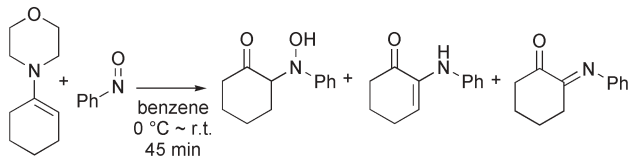
Scheme 2



Scheme 3



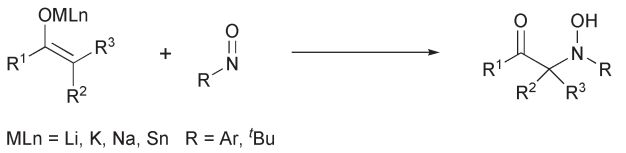
Scheme 4



Scheme 5

atom in nitrosobenzene, followed by dehydration. Subsequent studies by Moskal *et al.* described that the similar condensation of 1,3-diaronlymethanes with nitrosobenzene also served the anil derivatives of vicinal polyketones (Scheme 4).[9]

The first synthesis of α-hydroxyamino ketones from nitrosobenzene was reported by Lewis *et al.* in 1972 (Scheme 5).[10] The reaction was performed in benzene at 0 °C to room temperature with 1-morpholino-1-cyclohexene, yielding corresponding α-hydroxyaminoketone in 30% yield. Later, Sasaki and Ohno implemented this strategy with various silyl enol ethers (Scheme 6).[11] Their study revealed that highly reactive silyl enol ethers, such as aryl and ester derivatives, led to siloxyamino ketones which are further transformed to the heterocyclic derivatives.



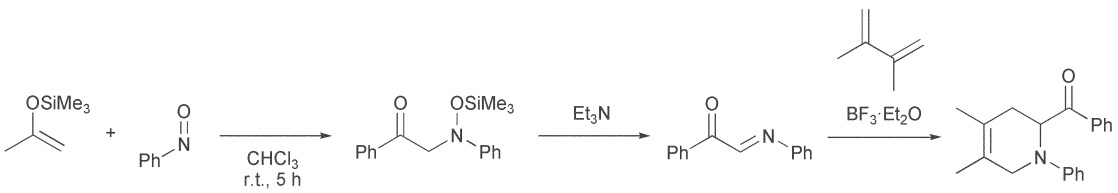
Scheme 9

In 1990, Oppolzer reported that chiral bornansultam-derived enolates undergo diastereoselective amination reaction of α-chloro-α-nitrosocyclohexane (Scheme 7).[12] Later, they developed chiral α-chloro-α-nitroso reagents that were capable of aminating prochiral ketone enolates with high enantiofacial differentiation (Scheme 8).[13] This was the first truly useful reaction based on nitroso compounds and the success of the method heavily depended on the clever use of α-chloronitroso derivatives.

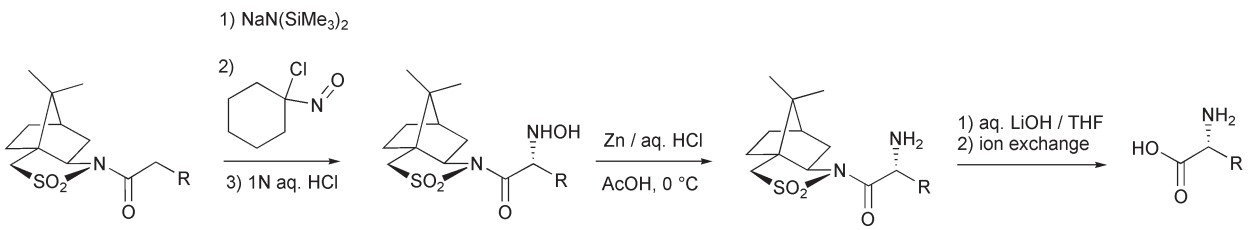
These previous results coupled with our recent interests in the development of new methods for carbon–nitrogen bond formation prompted us to explore the potential use of nitroso compounds for catalytic enantioselective processes.

First, we examined reactions of various aromatic and aliphatic nitroso compounds with several enolate anions to generate α-hydroxyamino ketones (Scheme 9).[14] The *N*-nitroso aldol (*N*-NA) reaction proceeds smoothly using the *in situ* generated or preformed enolates, particularly lithium and tin enolates, to deliver a broad range of *N*-NA products in high yields.

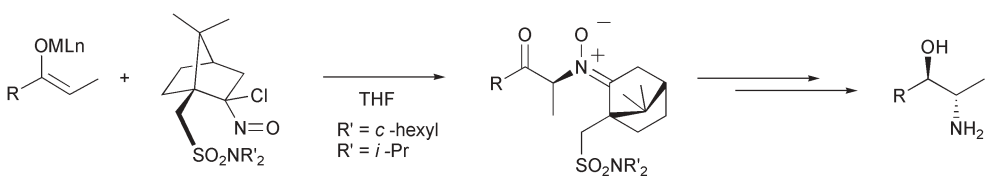
Our first significant contribution to nitroso chemistry was the discovery of O-selective nucleophilic attack of silyl enol



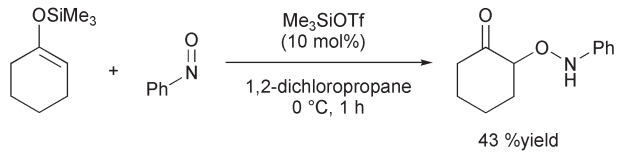
Scheme 6



Scheme 7



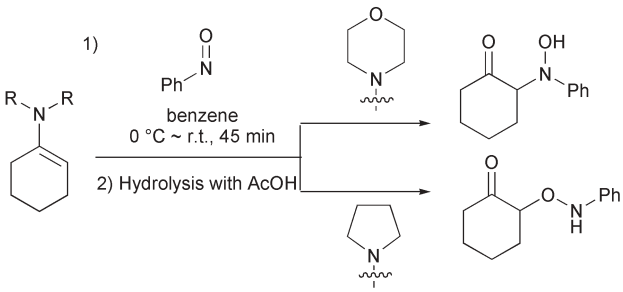
Scheme 8



Scheme 10

ethers to nitrosobenzene promoted by acid catalyst (Scheme 10).[15] Unexpectedly, the α-aminooxy ketone was isolated as a sole product whose structure was identified by X-ray crystallographic analysis. A variety of Lewis acids can induce this unprecedented O-selective nitroso aldol reaction (*O*-NA reaction): for example, a catalytic amount (1–10 mol%) of triethylsilyl triflate which yields the α-aminooxy ketone selectively (Table 1).

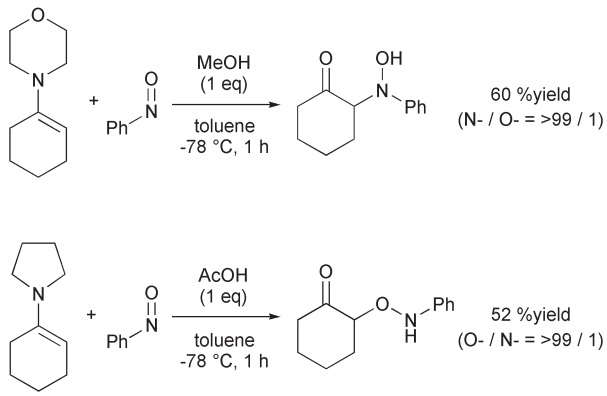
Later, we found that α-aminooxy ketones were also generated using the enamine as a nucleophile (Scheme 11).[16] When the reaction was conducted with 1-pyrrolidin-1-ylcyclohexene followed by treatment with acetic acid, this gave rise to the aminooxy ketone almost exclusively. The observed discrepancies with Lewis's report may have originated from the structural difference of the amino moiety of the enamine. In fact, when the morpholine enamine was used for this reaction, we observed the formation of hydroxyamino ketone exclusively. Recently, the NA reaction of enamine was found to be significantly accelerated in the presence of Brønsted acids (Scheme 12).[17] The rapid generation of the *N*-NA product was realized in the presence of methanol at −78 °C. In contrast, the significant acceleration for the *O*-NA pathway took place in the presence of acetic acid. It is quite surprising to obtain either *N*- or *O*-NA product by simply switching the acid catalyst and the structural motif of the amine moiety in the enamine.



Scheme 11

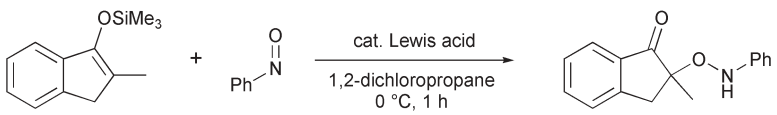
Catalytic enantioselective nitroso aldol reaction

Our observations on acid catalysis of metal enolates and enamines in the *N*- and *O*-NA reaction have provided useful information that has allowed us to develop a catalytic enantioselective process for the introduction of nitrogen or oxygen α to a carbonyl group. The catalytic enantioselective reaction of the nitroso electrophile was initially tested using the (*R*)-BINAP·silver catalyst. The 1:1 silver–(*R*)-BINAP complex was optimal for inducing high enantioselectivity of the *O*-NA reaction (Scheme 13, Fig. 1).[18] This is the first example of a catalytic enantioselective process with nitroso compounds as well as catalytic high enantioselective introduction of oxygen to α-carbonyls. The efficient *in situ* generation of trimethyltin



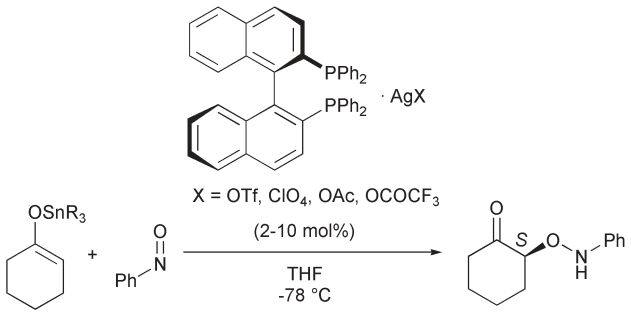
Scheme 12

Table 1 Lewis acid induced O-selective nitroso aldol reaction[a]



Entry	Lewis acid	Equiv. (mol%)	Yield (%)
1	None		<1
2	Me_3SiOTf	5	86
3	Et_3SiOTf	10	94
4	Et_3SiOTf	5	88
5	Et_3SiOTf	1	74
6	tBuMe$_2$SiOTf	5	83
7	Me_2SiNTf_2	5	54
8	$TiCl_4$	5	71
9	$FeCl_3$	5	60
10	AgOTf	5	52
11	$Cu(OTf)_2$	5	58
12	$Sn(OTf)_2$	5	50

[a] The reactions were carried out with 1 equiv. of silyl enol ether and nitrosobenzene in the presence of Lewis acid at 0 °C in 1,2-dichloropropane.



R = Bu	X =	OTf	91 %ee	O- / N- =	>99 / 1
Bu		OAc	87		72 / 28
Me		OTf	99		>99 / 1
Me		OAc	97		>99 / 1

Scheme 13

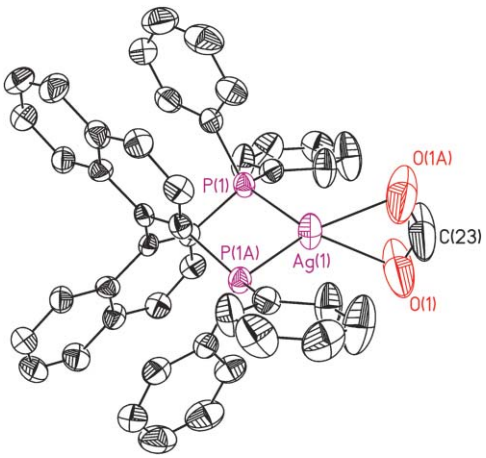
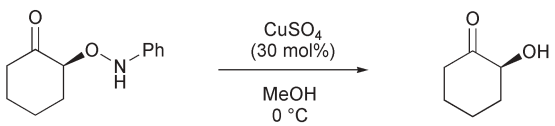


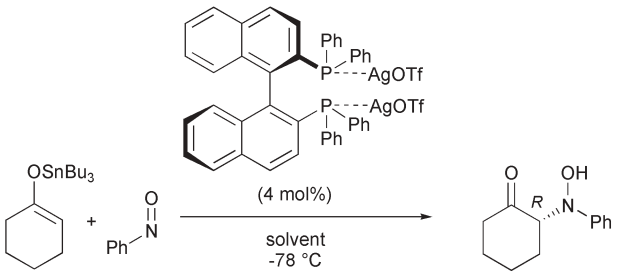
Fig. 1 X-Ray crystal structure of the 1:1 silver–BINAP complex.

enolates was critical to achieving complete O-selectivities. The resulting α-aminooxy carbonyls can be transformed smoothly to the corresponding α-hydroxy carbonyls by treatment of copper sulfate in methanol without any loss of enantioselectivity (Scheme 14).[18a]

The use of nitrosobenzene as an amination reagent in enantioselective reaction was achieved by simply switching the structure of the silver–BINAP complex (Scheme 15).[18b] The 2:1 silver–BINAP complex was generated by preparing it from 2.5 equiv. of AgOTf and 1 equiv. of (*R*)-BINAP (Fig. 2). Variation of the solvent has a pronounced effect on regio- and enantioselectivity, and excellent level of both selectivities was realized in the case of ethylene glycol diethyl ether used as solvent. Importantly, as we described earlier, even though the *N*-NA reaction of tin enolates proceeded rapidly without any promoters, excellent enantioselective *N*-NA reaction was



Scheme 14



Et_2O	90	%ee	N- / O- =	73 / 27
DME	40			92 / 8
$EtOCH_2CH_2OEt$	>99			96 / 4

Scheme 15

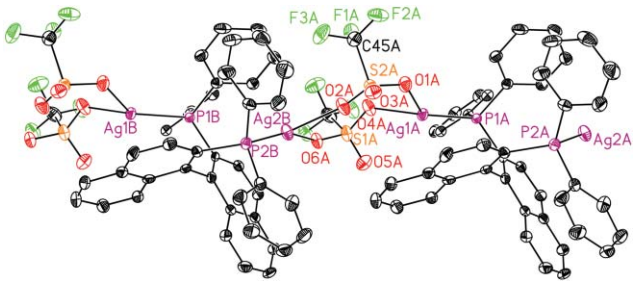
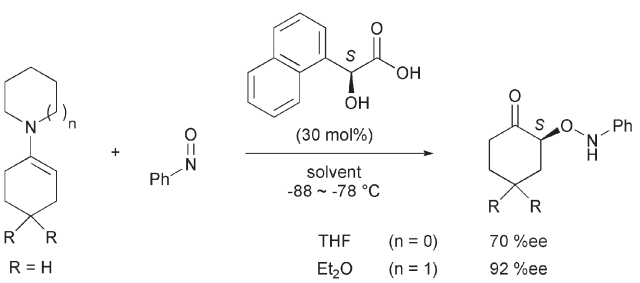


Fig. 2 X-Ray crystal structure of the 2:1 silver–BINAP complex.

observed in the presence of the 2:1 silver–BINAP complex. We are not able to rationalize the surprisingly high activity of the 2:1 silver–BINAP catalyst at this moment, however, we suspect that a highly organized transition state might emerge in ethylene glycol type solvent.

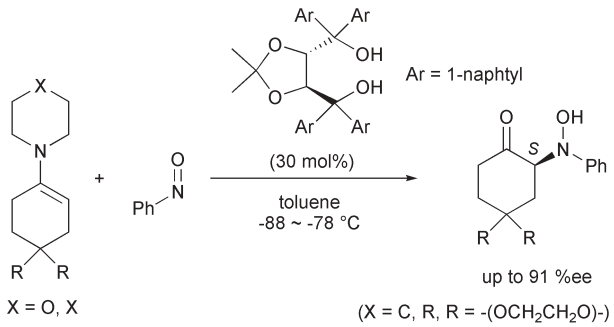
Previously, we described our observation of the Brønsted acid catalyzed NA reaction of enamines that prompted us to extrapolate the possibility to develop chiral Brønsted acid catalysis for enantioselective NA reaction. After examination of various chiral carboxylic acids, 1-aryl glycolic acids were identified as the most successful promoter in enantioselective *O*-NA reaction (Scheme 16).[17] The selectivity was significantly influenced by the choice of solvent. The pipelidine enamine of cyclohexanone reacts with nitrosobenzene with >90% enantioselectivity in diethyl ether. We also found (*S,S*)-TADDOL (Ar = 1-naphthyl) to be a promising chiral promoter for *N*-NA synthesis (Scheme 17).[17]

The absolute configuration of the *N*-NA product can be explained by the hydrogen-bonding activation of nitroso



THF	(n = 0)	70 %ee
Et_2O	(n = 1)	92 %ee

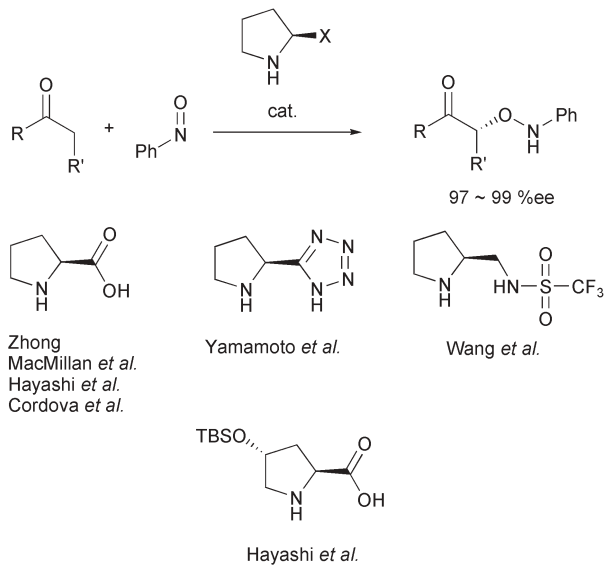
Scheme 16



Scheme 17

derivative by (*R*,*R*)-TADDOL (Ar = phenyl) reported by Po½oński and co-workers (Fig. 3).[19] An X-ray crystal structure of the nitrosoamine-(*R*,*R*)-TADDOL (Ar = phenyl) complex suggested that the *Si* nitrosobenzene enantioface is masked by the catalyst diphenyl group exposing the *Re* enantioface to nucleophilic attack of the enamines. When the reaction proceeds *via* the acyclic transition state, the *N*-NA product should be of *R* configuration, that is also consistent with the finding in our experiments of the *N*-NA reaction catalyzed by (*R*,*R*)-TADDOL (Ar = phenyl) (Scheme 18).

The recent reports of enamine catalysis highlight the attractive attributes of proline or its analogs, especially *in situ* formed chiral enamines from ketones or aldehydes and chiral pyrrolidine for intermolecular reaction. Enantioselective *O*-NA reaction was thus reported by several groups almost simultaneously (Scheme 19).[20] The reaction was performed



Scheme 19

with the illustrated pyrrolidine-based catalysts, yielding the α-aminooxy carbonyl compounds with 97–99% ee. The appropriate Brønsted acidity in each catalyst may contribute to provide both high enantioselectivity and O-selectivity in catalytic reaction.

The resulting highly reactive aminooxy aldehyde was used in sequential *in situ* transformations by Zhong. For example, the *O*-NA reaction followed by allylation reaction (Scheme 20)[21]

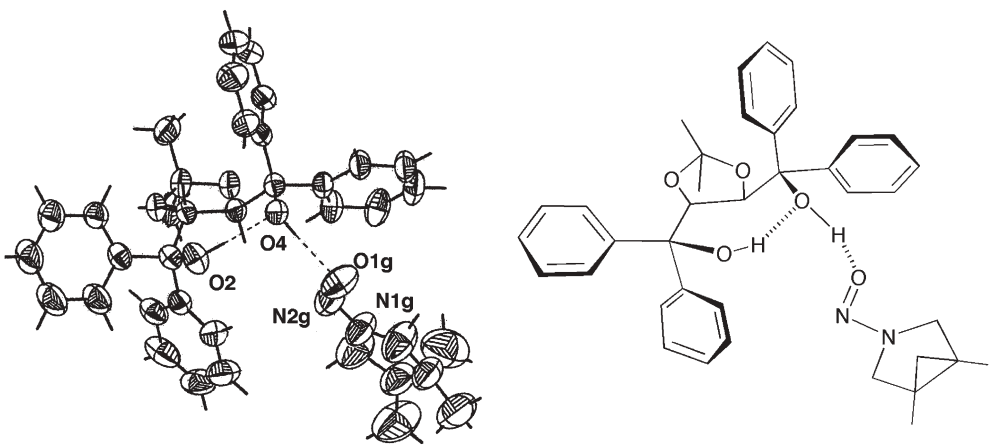
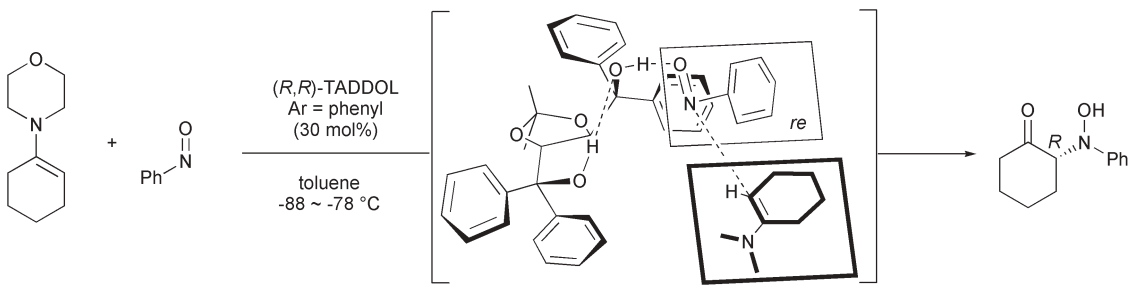
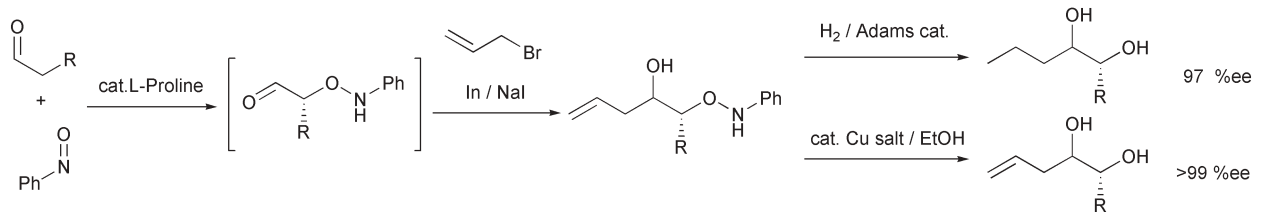


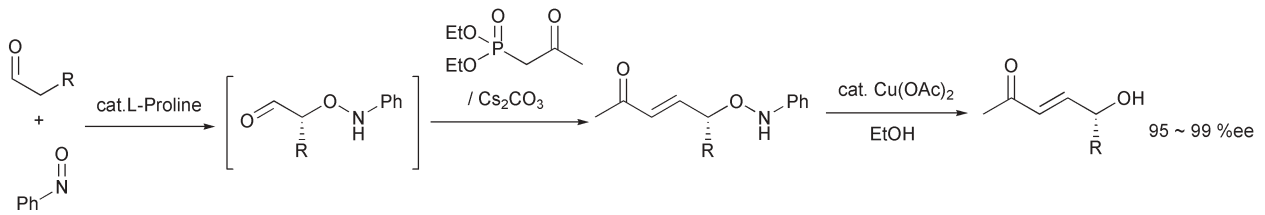
Fig. 3 Crystal structure of (*R*,*R*)-TADDOL·nitrosoamine.



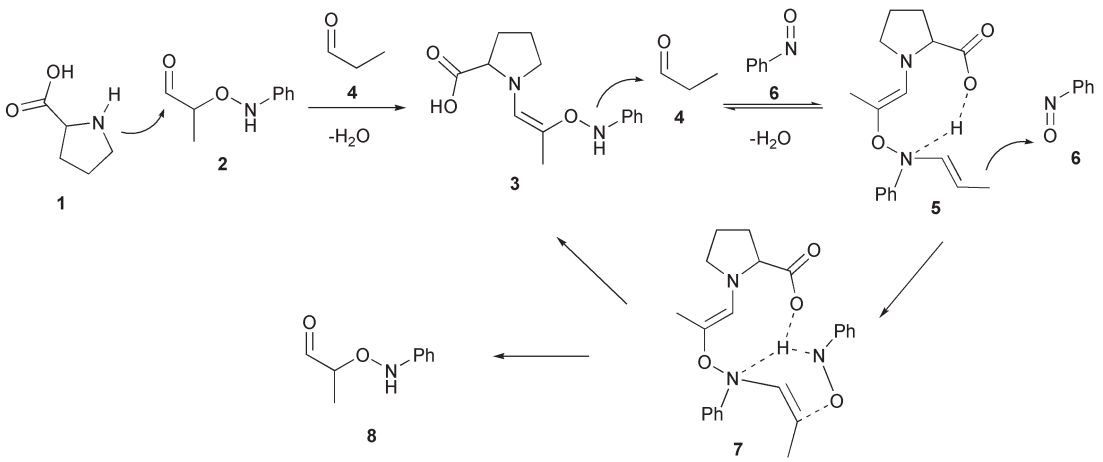
Scheme 18



Scheme 20



Scheme 21



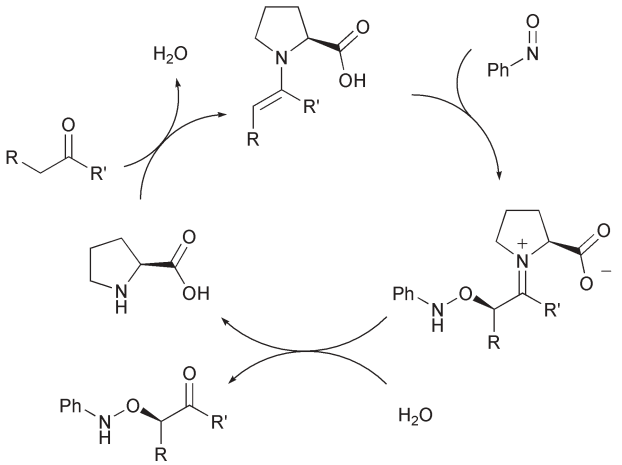
Scheme 22

and the *O*-NA reaction followed by Wadsworth–Emmons–Horner olefination reaction (Scheme 21).[22] The aminooxy aldehyde as intermediate reacted with *in situ* activated allylation reagent by indium or oxopropyl phosphonate in the presence of cesium carbonate. The resulting products were further converted to enantiopure alcohols after cleavage of N–O bonds.

After these proline catalyzed *O*-NA reports, two contrasting mechanisms for the catalytic cycles were proposed. Blackmond and co-workers showed the possibility of a selectivity-enhancing autoinductive process on the basis of their calorimetry and kinetic study for the *O*-NA reaction of aldehydes (Scheme 22).[23] They observed that when the *O*-NA product was added to the crude reaction mixture containing the original proline catalyst and the reaction product in the first reaction, the initial rate at the outset of second reaction was as high as that at the end of the first. Based on their observation, they proposed a mechanism in which the proline **1** may attack the carbonyl group of the *O*-NA product **2** to form a new catalyst **3**, followed by nucleophilic attack of the nitrogen atom in the aminooxy group to aldehyde **4** to form a new enamine **5**. The generated new enamine **5** may be competent to attack nitrosobenzene **6**, forming a transition state **7**: this leading to production of *O*-NA product **8** and regeneration of an improved catalyst **3**.

In contrast to the report by Brackmond and co-workers on aldehydes, Cordova *et al*. described the absence of a non-linear effect in the case of *O*-NA reaction of ketones. It is suggested that a single proline molecule is involved as catalyst (Scheme 23).[20g] Accordingly, the ketone reacts with proline, yielding chiral proline enamine. O-Selective nucleophilic attack of enamine to nitrosobenzene provides the *O*-NA product after hydrolysis. If both mechanistic studies are correct, the *O*-NA reaction of ketones and aldehydes proceeds through two different pathways.

Several types of transition states were also independently proposed, which are consistent with results of O-selectivity (Fig. 4). These are classified into the following different transition states: (i) carboxylic acid-activated proton transfer,[20c] (ii) both proline amine- and carboxylic acid-activation proton transfer,[20a] (iii) enaminium-mediated ene-like zwitterion,[20b] and (iv) amine–nitroso complex.[20f] It was considered



Scheme 23

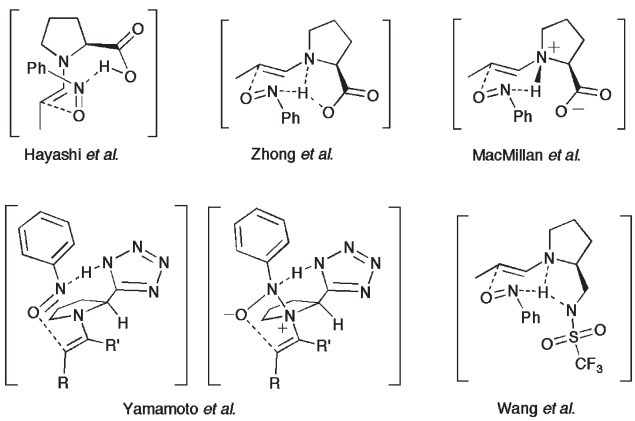


Fig. 4 Possible transition states in pyrrolidine-based organic catalysts.

that O-selectivity may possibly be originated from the nitroso dimer. However, ^{1}H and ^{13}C NMR studies in our laboratory confirmed that monomer nitrosobenzene was mainly observed during the reaction in Brønsted acid catalysis.[17] Thus, initial formation of the azodioxy dimer may be unlikely except for the rapid equilibrium of a small amount of the highly reactive dimer.

Additional study regarding the transition states and selectivity in *O*-NA reaction *via* an enamine intermediate was subsequently provided in the computational study reported by Houk[24] (and Cordova *et al.*[20g]) (Fig. 5). They calculated the energy in each transition state. The lowest-energy transition structure was shown to involve an (*E*)-*anti* proline enamine adopting the axial position of phenyl group in nitrosobenzene.

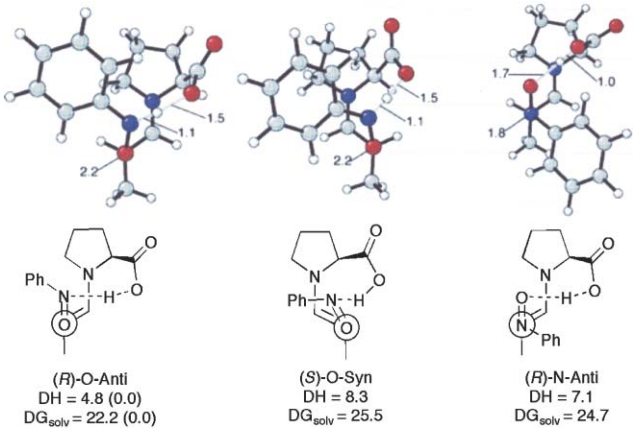


Fig. 5 Calculation for possible transition states.

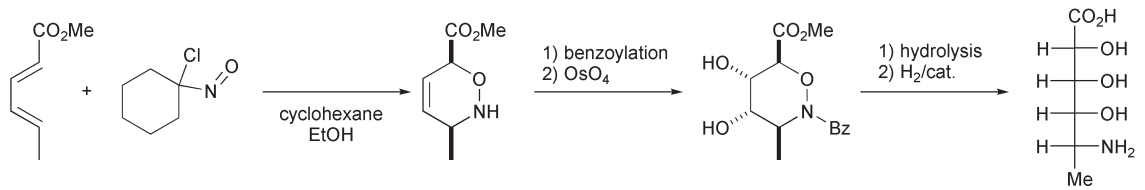
Scheme 24

Cordova *et al.* also reported a similar calculation study of the transition state.

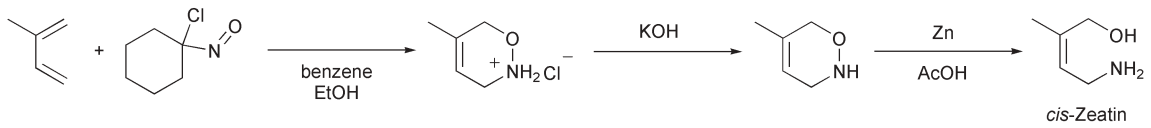
Nitroso Diels–Alder (NDA) reaction

The nitroso Diels–Alder (NDA) reaction is a remarkable synthetic transformation which produces a 1,4-amino-oxo group in a single step. This useful reaction was first reported by Wichterle and Arbuzov in 1947 (Scheme 24).[25] Their findings were later confirmed and extended as a general tool to synthesize a number of natural products and biologically active compounds. For example, the reaction of methyl *trans*,*trans*-sorbate with 1-chloro-1-nitrosocyclohexane gave an NDA product that was further converted to an amino acid of the glucose series in four steps (Scheme 25).[26] Similarly obtained NDA product from isoprene is the key for success in the synthesis of *cis*-zeatin (Scheme 26).[27]

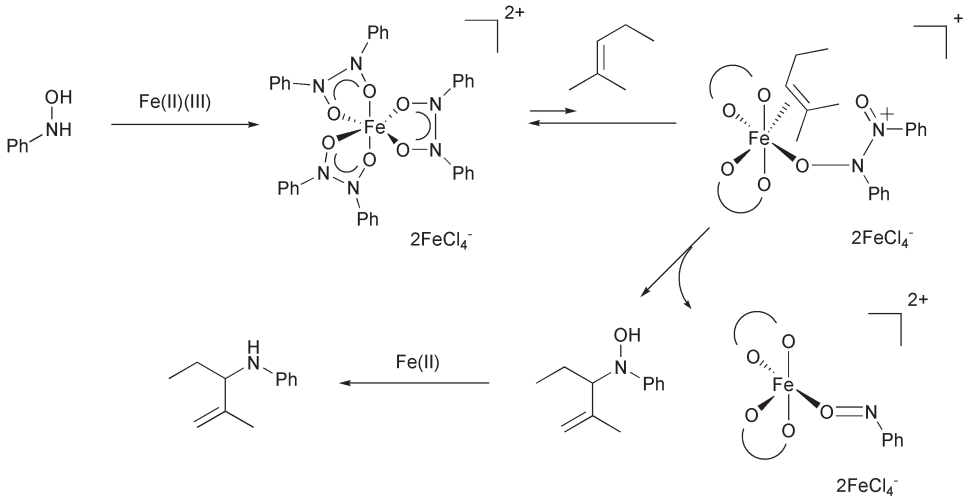
During the reaction of a nitroso electrophile, a Lewis acid can act as a pivotal element in terms of reactivity and controlling selectivity. Several metal catalyst–substrate complexes have been determined by X-ray analysis.[28] Nicholas and co-workers reported a structurally verified iron complex of a nitroso dimer and its unprecedented reactivity and selectivity in the allylic amination of olefins (Scheme 27).[29] The reaction of $FeCl_{2,3}$ with nitrosobenzene or phenyl hydroxy amine produced an azo dioxide iron complex (Fig. 6). Further, the treatment of the iron complex of a *C*-nitroso dimer with



Scheme 25



Scheme 26



Scheme 27

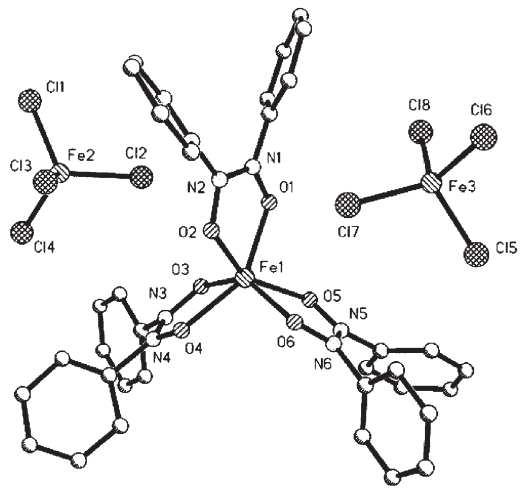


Fig. 6 X-Ray structure of the azo dioxide iron complex.

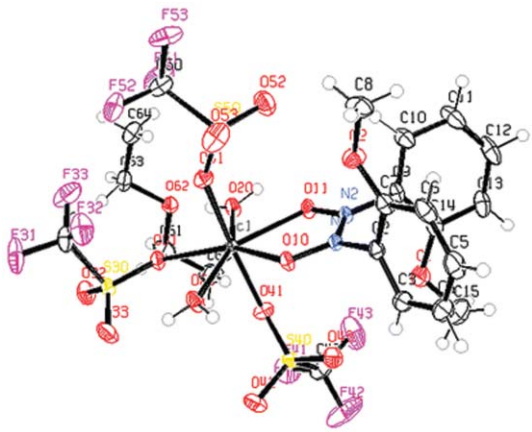
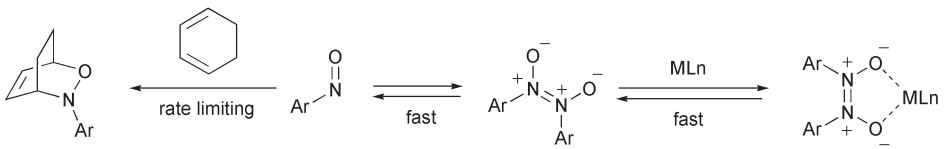


Fig. 7 X-Ray structure of the $Sc(OTf)_3$–*o*-methoxynitrosobenzene complex.

2-methyl-2-pentene in dioxane resulted in smooth conversion to the corresponding allylic amino alcohol at room temperature. These results indicated that nitrosobenzene dimer iron complex is the active aminating agent in iron salt-catalyzed reaction.

On the other hand, the strong binding of aryl nitroso compounds with Lewis acid frequently causes the loss of its ability as a catalyst. Whiting and co-workers identified the structure of the $Sc(OTf)_3$–*o*-methoxynitrosobenzene complex by X-ray analysis (Fig. 7) and showed that this complex neither promotes nor inhibits the NDA reaction (Scheme 28).[30]



Scheme 28

While the use of Lewis-acid catalyst did not affect the reaction rate significantly, it enhanced the stereoselectivity in NAD reaction for the synthesis of a steroidal product (Scheme 29).[31] The presence of Lewis acids increased the amount of the 16β-H derivatives compared to the reaction without catalyst.

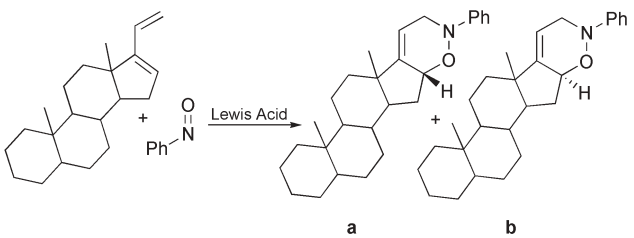
Kouklovsky and co-workers reported that Lewis acids could coordinate both nitrogen of nitroso and oxygen of acetoxy group in α-acetoxynitroso dienophiles.[32] Thus, the reactivity was effectively enhanced in the presence of Lewis acids. Furthermore, the generated NDA product was directly converted to the amino alcohol derivative (Scheme 30).

Enantioselective nitroso Diels–Alder reaction

The catalytic enantioselective [4 + 2] cycloaddition of achiral dienes is one of the exciting challenges among hetero-Diels–Alder reactions. Major difficulties are due to issues of aforementioned dimerization in the presence of acid catalyst and high reactivity for diene without any promoter.

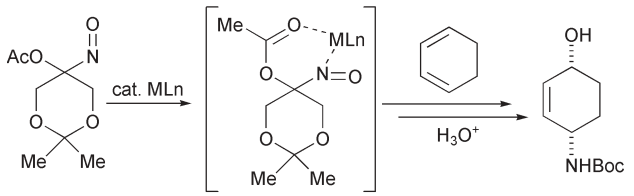
A reagent-controlled enantioselective nitroso Diels–Alder reaction was reported by Ukaji and Inomata (Scheme 31).[33] In the presence of one equivalent of zinc catalyst, NDA reaction of hydroxyl diene and nitrosobenzene proceeded smoothly to give the cycloadduct in up to 91% ee. The attached hydroxyl group in diene played an important role in generating the unique transition state for inducing enantioselectivity.

Whiting and co-workers proposed that a chiral ruthenium(IV) oxo complex catalytically oxidizes hydroxamic acid to the corresponding nitroso dienophile and stayed bound to the nitroso dienophile. Subsequent reaction with diene could result in the induction for the NDA adduct



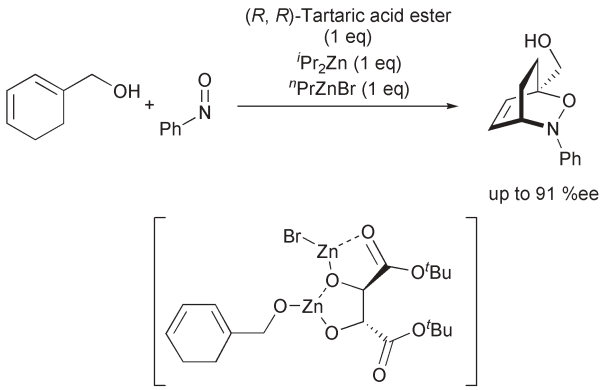
Lewis Acid	conversion, %	a / b
none	88	68 / 32
$AlCl_3$	69	75 / 25
$ZnCl_2$	85	87 / 13

Scheme 29



MLn: $Mg(OTf)_2$, $CrCl_3$, $Cu(OTf)_2$

Scheme 30



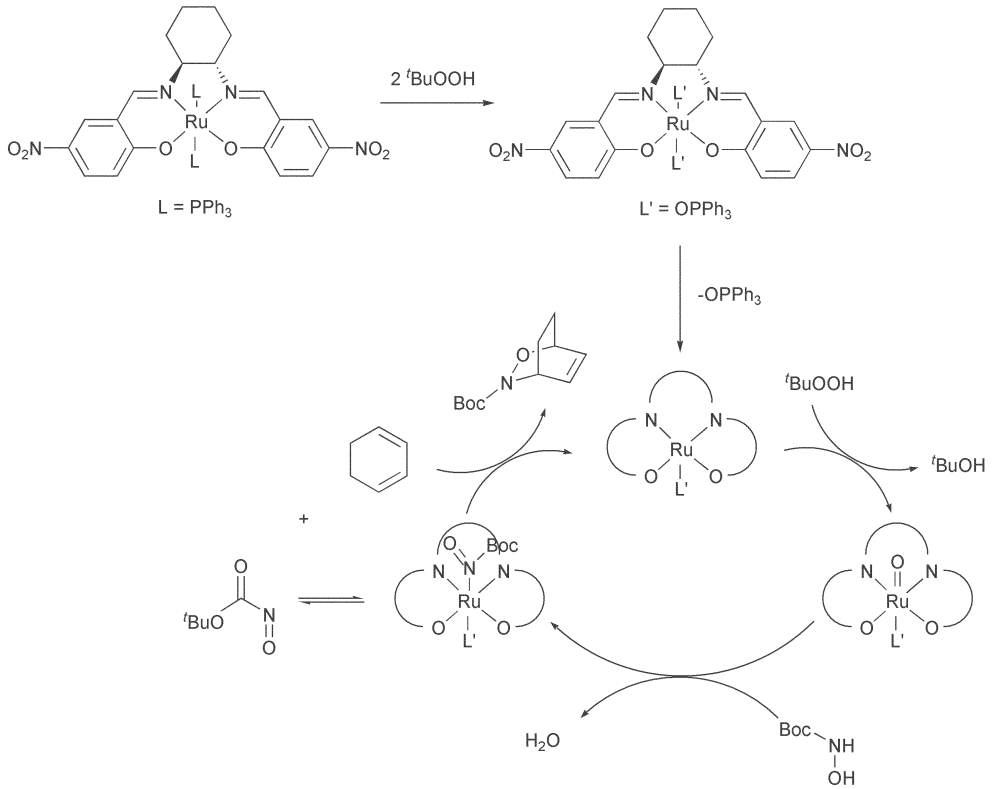
Scheme 31

(Scheme 32).[34] Although their hypothesis did not lead to success for intermolecular reaction between acylnitroso compounds and dienes, significant enantioselectivity was reported in the intramolecular reaction by Chow and Shea. The intramolecular reaction of *N*-hydroxy formate ester in the presence of a ruthenium–salen catalyst and TBHP proceeded involving the production of acylnitroso formate to afford a cycloadduct in up to 75% ee (Scheme 33).[35]

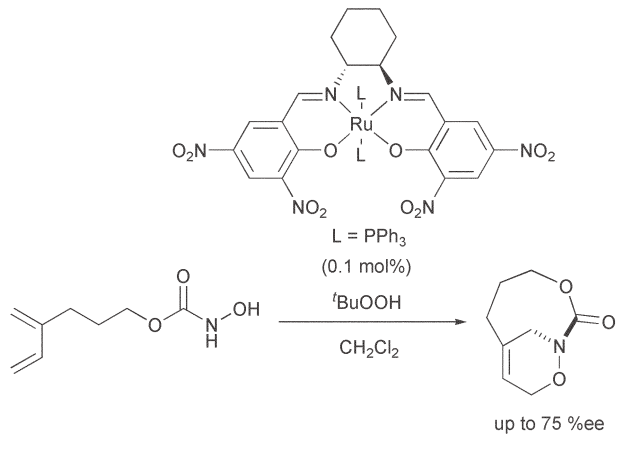
We are interested in generating chelated monomeric nitroso derivatives with suitable Lewis-acid catalysts. This idea is focused on the specific case of a 2-nitrosopyridine derivative in the presence of a chiral phosphine–copper catalyst (Scheme 34).[36] The success of the first catalytic enantioselective NDA reaction heavily relied on chelation control to well-organized catalyst–substrate complexes. High enantioselectivity was obtained using a $Cu(PF_6)(MeCN)_4$–(*S*)-SEGPHOS complex for broad range of cyclic dienes. The provided NAD product can be easily transformed to the protected optically active amino alcohols (Scheme 35). After cleavage of the N–O bond, the resulting alcohol and amine were protected by TBS and tosyl groups, respectively. Quaternization of pyridine, followed by treatment of NaOH afforded protected amino alcohol in good yields without loss of enantioselectivities.

The sense of asymmetric induction and its absolute configuration is consistent with the intervention of a chelation controlled monomeric nitrosopyridine-catalyst complex (Fig. 8). It is evident that the first and third quadrants are more congested than the second and fourth quadrants for (*S*)-BINAP transition-metal complexes. Thus, the reaction preceded to completion though the access of diene from the sterically uncrowded site to nitrosopyridine positioning of the pyridine ring at another uncrowded site.

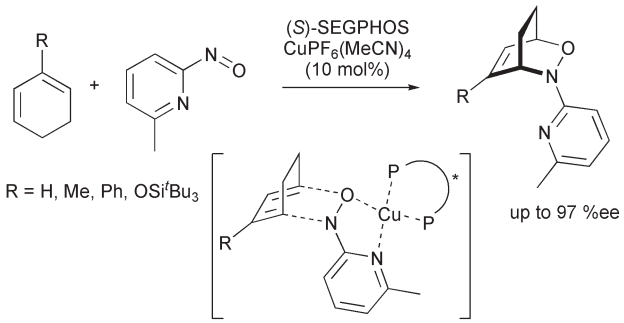
In the integration of the enantioselective *O*-NA reaction with *in situ* generated dienamines, followed by intramolecular Michael reaction, the pyrrolidine-based catalyst opened a new enantioselective route to NDA-type bicyclic products (Scheme 36).[37] The reaction was performed with enone as diene precursor in delivering NDA adducts with complete enantioselectivities and in moderate yields. It may be worth noting that the tandem *O*-NA–Michael reaction affords the regioisomer of the "normal" enantioselective NDA reaction.



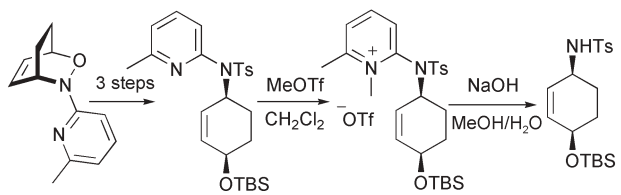
Scheme 32



Scheme 33



Scheme 34



Scheme 35

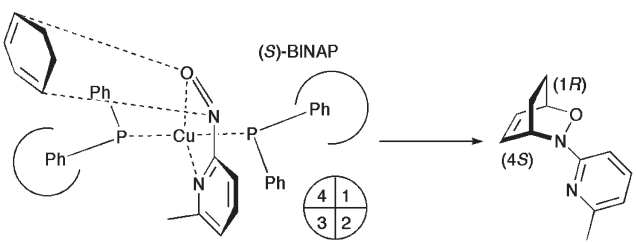
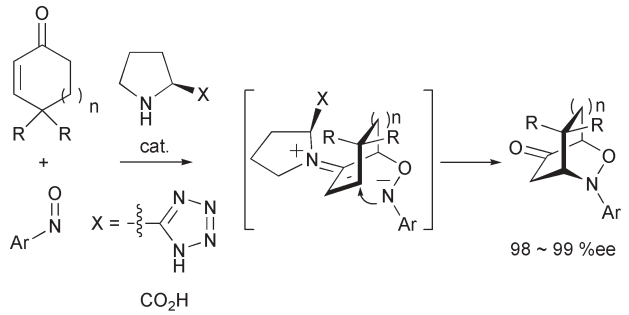
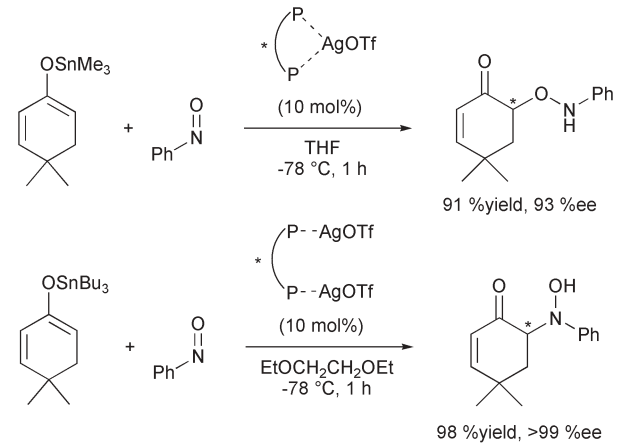


Fig. 8 Possible chelation controlled intermediate.

We also found that the aminooxy unsaturated carbonyl derivatives can be synthesized from the stanyloxy diene as substrate. The use of selective prepared silver–BINAP complexes was again critical to achieving high enantioselective either *O*- or *N*-NA reaction without the production of NDA adduct (Scheme 37).[37] Attempts at cyclization of these products proceeded without success. Therefore, the smooth cyclization of Scheme 36 must originate from the steric



Scheme 36



Scheme 37

requirements of enamine and/or the electronic effect of the intermediate ion pair.

Conclusion

The ongoing efforts in our laboratory toward asymmetric synthesis by acid catalysts are providing the impetus for the development of new entries to the enantioselective reaction of nitroso electrophiles. While the latent ability of nitroso electrophiles has barely emerged and there has been steady progress in recent years, only a part of these advances have been described herein.

Not only its utility as an amino electrophile but also its newly recognized ability as an oxy electrophile has further established nitrosobenzene as an attractive reagent in synthetic organic chemistry. The structurally defined BINAP–silver complexes provide an enantioselective avenue for both *O*- and *N*-NA products with high yields and high enantioselectivities. Reaction of achiral enamines catalyzed by chiral Brønsted acids has advanced to a new level of applicability and generality. Furthermore, the use of pyrrolidine-based catalysts has realized quite a practical *O*-NA reaction. This concept has been applied to tandem *O*-NA–Michael reaction using enones for the synthesis of NDA-type products.

The structural motif of nitrosopyridine for the efficient binding ability of a copper Lewis acid has led to the first catalytic enantioselective NDA reaction.

Enantioselective nitroso chemistry has just got started and we feel fortunate to have played a part in opening the door to this rich chemistry. We believe the development of general, fundamental and applicable enantioselective reaction of nitroso electrophiles may be just around the corner – if so, it will be a great contribution to organic synthesis.

Acknowledgements

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