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Nitroso and Azo Compounds in Modern Organic Synthesis: Late Blooming but Very Rich

Hisashi Yamamoto* and Masanori Kawasaki

Department of Chemistry, University of Chicago, Chicago, Illinois, 60637, U.S.A.

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The catalytic enantioselective oxidation is an extremely important process in organic synthesis and numbers of effort to improve this process have been reported so far. Although nitroso and azo compounds are attractive tools for hydroxylation and amination of organic compounds, no reports on a catalytic asymmetric version of these reactions had been reported until recently. The main issues were their high and unique reactivities. In this review, we would like to introduce the recent advances in this area.

1. Introduction

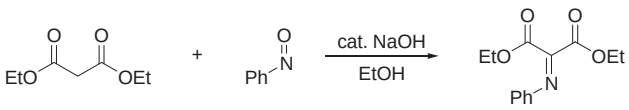
The catalytic enantioselective oxidation, including hydroxylation and amination, is an extremely important process for the pharmaceutical and agrochemical industry.[1] This is clear because the most biologically active compounds have highly functionalized structure. Thus, it is not surprising to know that despite enormous efforts to develop the asymmetric process,[2] more efficient and practical oxidation of organic compounds are still strongly demanded. We recently focus our attention on nitroso and azo compounds to introduce hydroxy and amino groups directly into organic molecules. Nitroso and azo compounds have unique reactivities and react with simple alkenes and carbonyl compounds as electrophiles.[3] Despite their useful reactivity, the chemistry of nitroso and azo compounds have not been intensively studied until recently.[4–6]

In this review, we would like to summarize our recent results of enantioselective *N*-/*O*-nitroso aldol reactions and hetero-Diels–Alder reactions using nitroso and azo compounds.

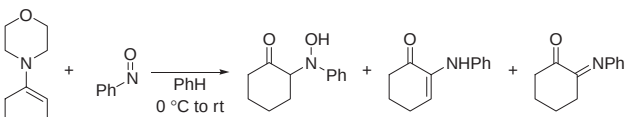
2. Nitroso Aldol Reaction

The reactions of nitrosobenzene with 1,3-dicarbonyl compounds were reported to afford azomethine derivatives (Scheme 1).[7] The first synthesis of α-hydroxyamino ketones using nitrosobenzene as an electrophile was reported in 1972 (Scheme 2).[8] In 1990, Oppolzer et al. described diastereoselective amination reaction with chiral enolates and α-chloro-α-nitroso derivative gave corresponding α-aminooxy ketones which were further transformed (Scheme 3).[9]

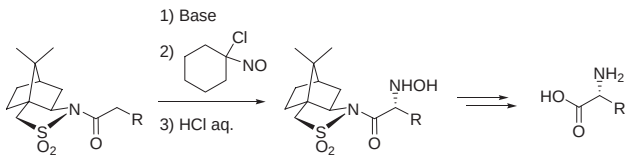
In 2002, we reported a significant contribution in nitroso chemistry. The *O*-regioselective nitroso aldol (NA) reaction with nitrosobenzene and silyl enol ethers promoted by Lewis acids was first reported by us.[10] The reaction was promoted by Lewis acids to afford corresponding α-aminooxy derivatives (Scheme 4). This was a great surprise for us because this is a completely new method to introduce oxygen α- to carbonyl functionality.



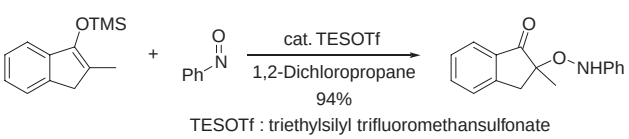
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

After this important finding, we found that α-aminooxy ketones were also obtained using the enamine as a nucleophile (Scheme 5).[11] The reaction of nitrosobenzene with pyrrolidine

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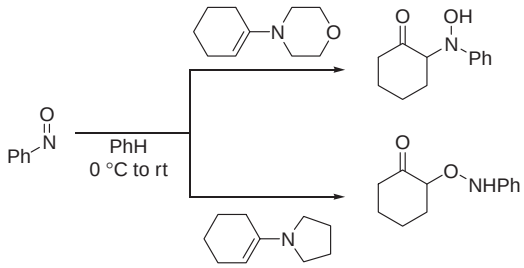
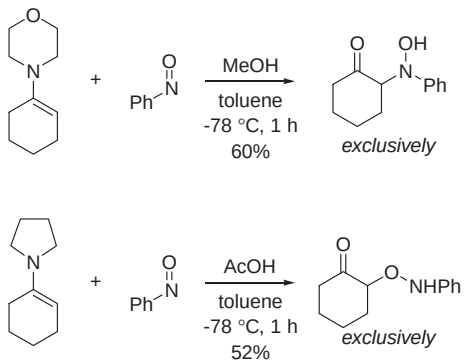


Scheme 5.



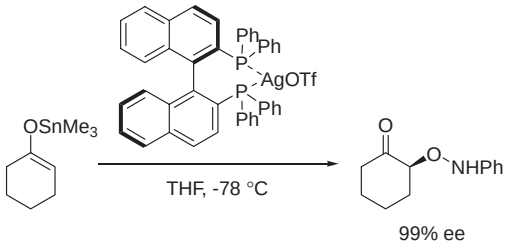
Scheme 6.

enamine afforded α-aminooxy ketone almost exclusively. On the other hand, when morpholine enamine was used instead of pyrrolidine enamine, it gave hydroxyamino ketone exclusively. The observed significant difference of the reaction pathway is still unclear. However, we believe this comes from the different nucleophilicity of enamine and possibly the presence of a small amount of the catalyst in the system. Thus, we studied careful examinations of the effect of Brønsted acids (Scheme 6).[12] The *N*-NA reaction of morpholine enamine in the presence of methanol at $-78\,^{\circ}C$ proceeded smoothly to give hydroxyamino ketone. In sharp contrast, the *O*-NA reaction was accelerated significantly using acetic acid to furnish aminooxy ketone. It is surprising to obtain either *N*- or *O*-NA product simply by changing the acid catalyst and enamine moiety.

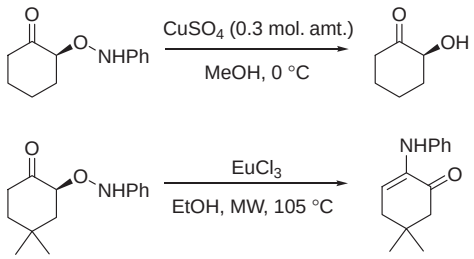
3. Catalytic Enantioselective Nitroso Aldol Reaction

Our previous observations have allowed us to develop a catalytic enantioselective NA reaction for selective introduction of nitrogen or oxygen atoms at α-position of carbonyl groups. The asymmetric NA reaction of nitrosobenzene was initially tested using silver–BINAP catalyst. We found that the 1:1 complex of silver–BINAP was optimal for *O*-NA reaction with high enantioselectivity (Scheme 7).[13] This is the first report of the catalytic enantio- and regioselective process of a nitroso electrophile. The key to this success is efficient generation of trimethylstannyl enolates. The corresponding α-aminooxy ketone was converted to the corresponding α-hydroxy ketone by using $CuSO_4$ without any loss of enantioselectivity. We have also found that α-aminooxy ketone was converted to α-amino enone in the presence of $EuCl_3$ (Scheme 8).[14]

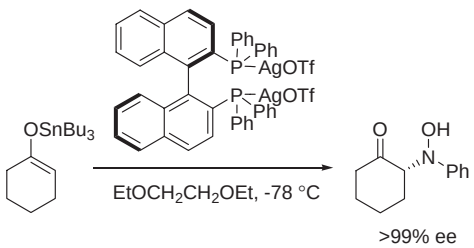
Catalytic enantioselective amination of carbonyl compounds was achieved using nitrosobenzene as an aminating reagent (Scheme 9).[15] This was accomplished by changing the



Scheme 7.



Scheme 8.

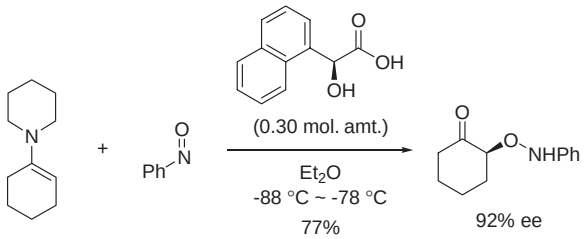


Scheme 9.

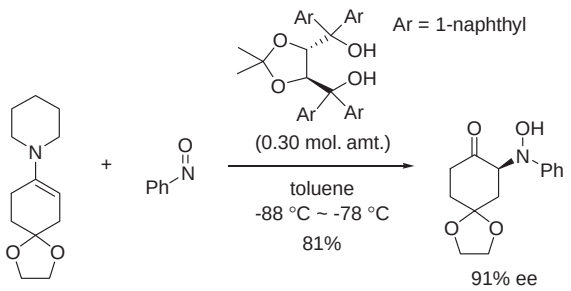
catalyst of the silver–BINAP complex. The reaction of nitrosobenzene and tributylstannyl enolates with the 2:1 complex of silver–BINAP as a catalyst proceeded smoothly to give α-hydroxyamino ketones. The use of ethylene glycol diethyl ether as a solvent was optimal to induce excellent regio- and enantioselectivity.

As we described earlier, the Brønsted acids promote NA reaction of enamines regioselectively. On the basis of these observations, we attempted to develop an asymmetric NA reaction catalyzed by a chiral Brønsted acid. After various chiral carboxylic acids and chiral alcohols were assayed, we found that not only did the use of 1-(1-naphthyl)glycolic acid as a catalyst in Et_2O proceed *O*-NA reaction in excellent enantioselectivity (Scheme 10), but also the use of TADDOL derivative promoted enantioselective *N*-NA reaction (Scheme 11).[16]

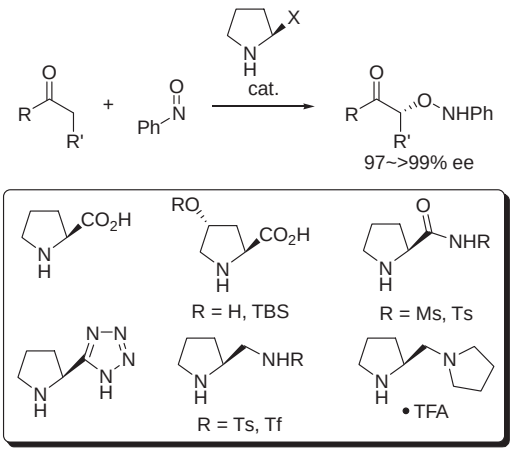
Recent advances of the reactions using proline or its analogs as a catalyst are highlighted in organic chemistry. The asymmetric *O*-NA reaction catalyzed by proline or its analogs has been reported by several groups. Various pyrrolidine-based catalysts were used to give the corresponding α-aminooxy carbonyl compounds with excellent enantio- and regioselectivity (Scheme 12).[17] In contrast, the use of amino alcohols as catalysts promoted *N*-NA reaction enantioselectively: For example, Maruoka and co-workers reported that this catalyst with a binaphthyl framework proceeded the reaction enantioselectively (Scheme 13).[18] These results would be consistent with our previous findings.



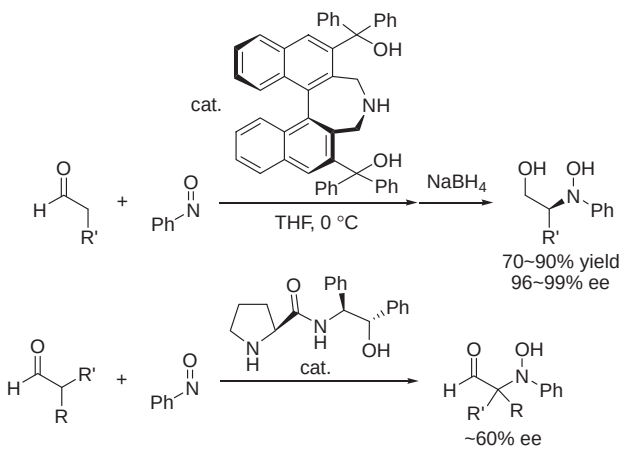
Scheme 10.



Scheme 11.



Scheme 12.



Scheme 13.

After these reports of *O*-NA reaction catalyzed by proline or its analogs, two mechanisms for the catalytic pathway of aldehydes and ketones were reported.[17g,19] In addition, we carefully studied the origin of regioselectivity on this reaction by using calculation and isotope effect. These results strongly suggested *o*-hydrogen of nitrosobenzene coordinates the Lewis basic site of catalyst by hydrogen bonding (Fig. 1). Thus, the proton of carboxylic acid activates nitrogen of nitrosobenzene and carbonyl oxygen of that coordinates *o*-hydrogen to form 8-membered ring. In contrast, two molecules of alcohol participate the activation of nitroso group to form 9- or higher-membered ring because proton of alcohol would coordinate *anti*-lone pair of nitroso group.

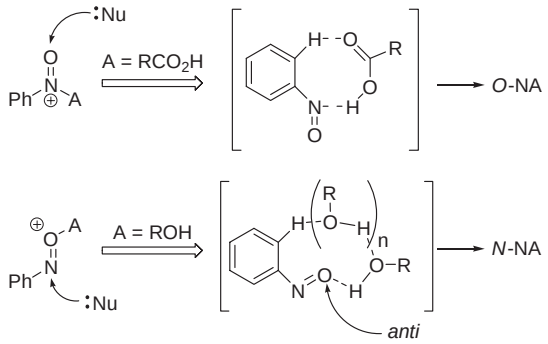
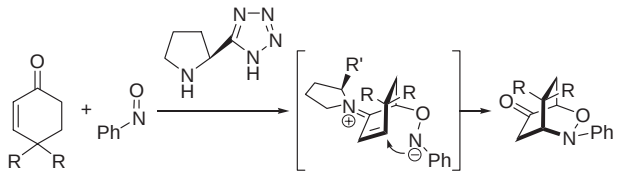
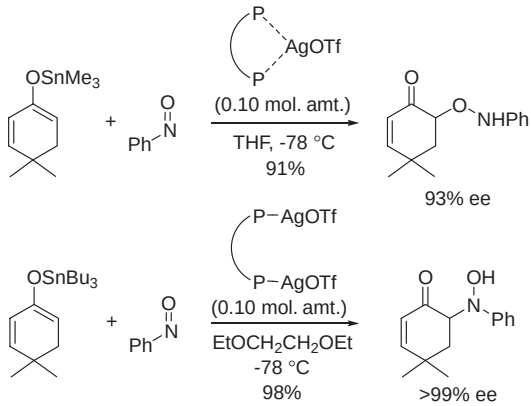


Fig. 1.



Scheme 14.



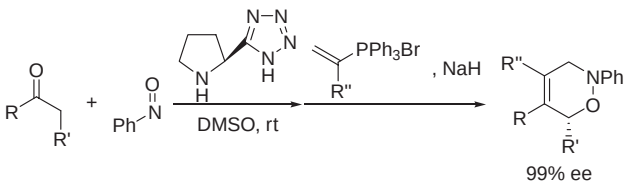
Scheme 15.

Based on these results of proline-catalyzed *O*-NA reaction, we developed the tandem *O*-NA/Michael reaction to afford cyclized products starting from enones (Scheme 14).[20] The *O*-NA reaction of nitrosobenzene with enones in the presence of pyrrolidine-based catalyst followed by intramolecular hetero-Michael reaction afforded cyclized products with high enantioselectivity and complete regioselectivity. This reaction would proceed via a stepwise mechanism since the reaction of nitrosobenzene with stannyloxy diene in the presence of silver catalyst gave *N*- or *O*-NA adduct without any cyclized product (Scheme 15).[21]

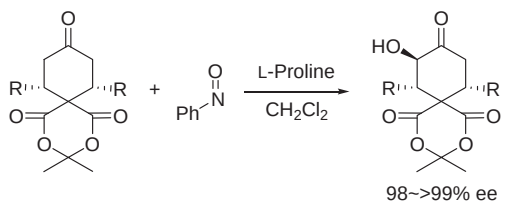
After our report of *O*-NA reaction catalyzed by organocatalyst, similar reaction catalyzed by different organocatalysts was reported by several groups. For example, Ley and coworkers reported the synthesis of chiral 3,6-dihydro-2*H*-oxazines starting from aldehydes or ketones by using *O*-NA and sequential Wittig reactions (Scheme 16).[22] The reaction of ketones with nitrosobenzene in the presence of pyrrolidine-based tetrazole catalyst afforded *O*-NA adducts. The resulting solution was treated with Wittig reagents to give 3,6-dihydro-2*H*-oxazines with excellent enantioselectivity. These compounds which are regarded as nitroso hetero-Diels–Alder (HDA) adducts were converted to *cis*-1,4-amino alcohols. Barbas and Ramachary reported asymmetric α-hydroxylation of *meso*-ketones in a single step (Scheme 17).[23] The excess amount of PhNO was used as a reducing agent. Since the reaction was conducted with *meso*-ketones and PhNO in the presence of proline, α-hydroxy ketones were obtained with excellent enantioselectivity. This is a fine example of desymmetrization reaction.

4. Nitroso Hetero-Diels–Alder Reaction

The nitroso compounds also undergo hetero-Diels–Alder (HDA) reaction with dienes. The nitroso HDA reaction provides 1,4-aminoalcohols which are useful building blocks in the synthesis of natural products and drugs. This useful reaction was first reported by Wichterle and Arbuzov in 1947.[24] After this important finding, Kresze et al. and Kirby and Nazeer extended nitroso HDA reaction to an asymmetric version using chiral nitroso compounds or dienes.[25] This powerful tool was applied for a number of natural product syntheses. The utilities of this method are summarized in several reviews.[5,26] We would like to introduce several excellent applications in this field.



Scheme 16.



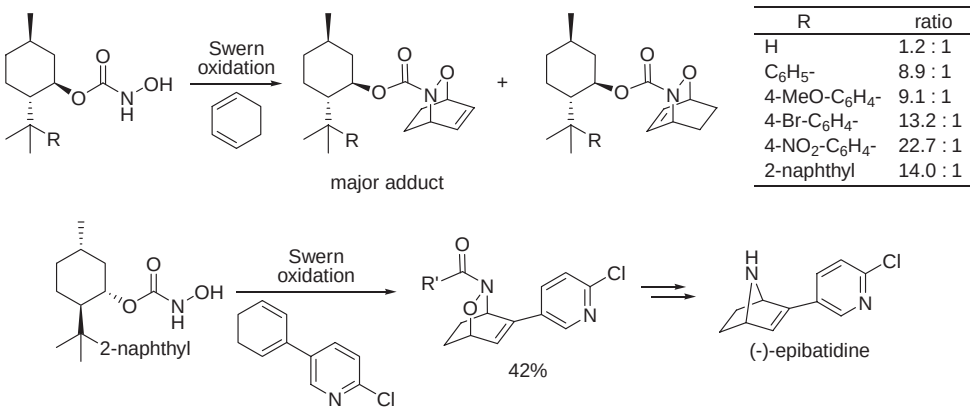
Scheme 17.

5. Diastereoselective Nitroso Hetero-Diels–Alder Reaction

Since nitroso HDA adducts are attractive building blocks toward the synthesis of polyhydroxylated molecules, several excellent reports on nitroso HDA reactions using chiral nitroso compounds were reported. Miller and Ritter reported that the reaction of chiral acylnitroso compounds derived from amino acids with 1,3-dienes afforded chiral cycloadducts.[27] They also demonstrated further manipulation of these adducts to useful building blocks such as 1,2- or 1,3-amino alcohols.[28] For example, the reaction was conducted with adducts and Grignard reagent in the presence of copper catalyst to give 1,2-amino alcohols. In addition, Kibayashi and co-workers reported total synthesis of (−)-epibatidine using asymmetric nitroso HDA reaction as a key reaction (Scheme 18).[29] They used a chiral acylnitroso compound which has a menthol derivative as a chiral auxiliary and investigated the relationship between diastereoselectivity and substituents of menthol derivatives. The Swern oxidation of chiral hydroxamic acids at low temperature generated chiral acylnitroso compounds which were trapped with 1,3-cyclohexadiene to give adducts with good diastereoselectivity.

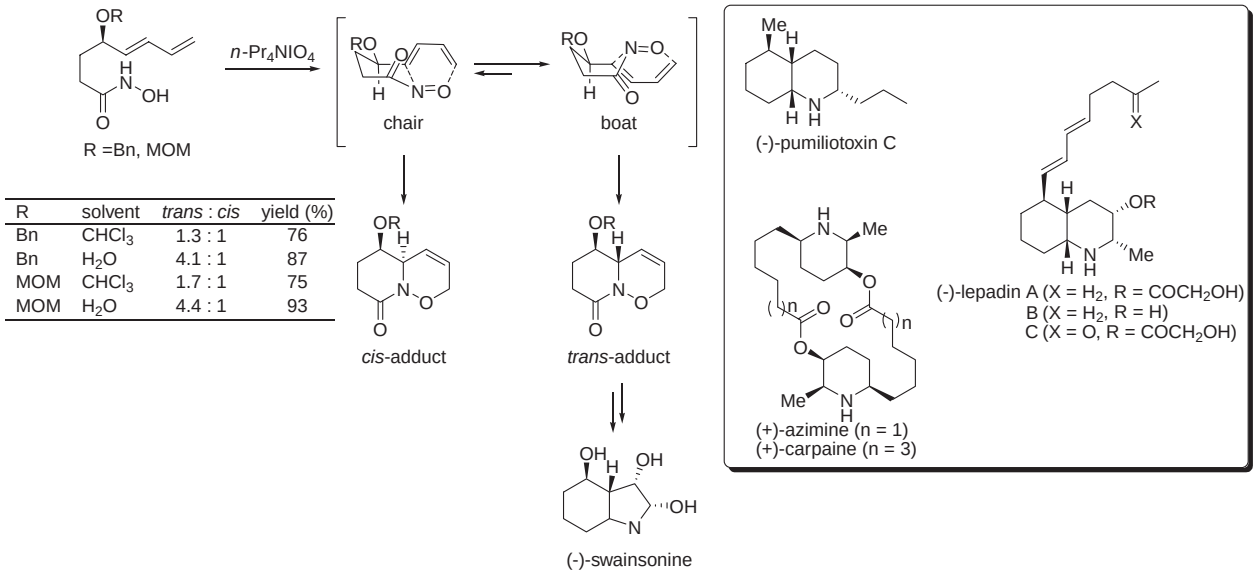
Intramolecular nitroso HDA reaction has been recognized as an efficient method to construct cyclic amino compounds with several stereocenters. Despite many synthetic efforts for diastereoselective intramolecular nitroso HDA reaction, the diastereoselectivities are typically low.[30] Kibayashi and co-workers accomplished highly diastereoselective nitroso HDA reaction in aqueous media. They found that intramolecular nitroso HDA reaction of 4-substituted 5,7-alkadienohydroxamic acid in aqueous media proceeded with high diastereoselectivity. This interesting finding was applied for total synthesis of (−)-swainsonine,[31] (−)-pumiliotoxin C,[32] (+)-azimine,[33] (+)-carpaine,[33] and (−)-lepadins[30d] (Scheme 19).

To overcome these problems, Shea and co-workers applied



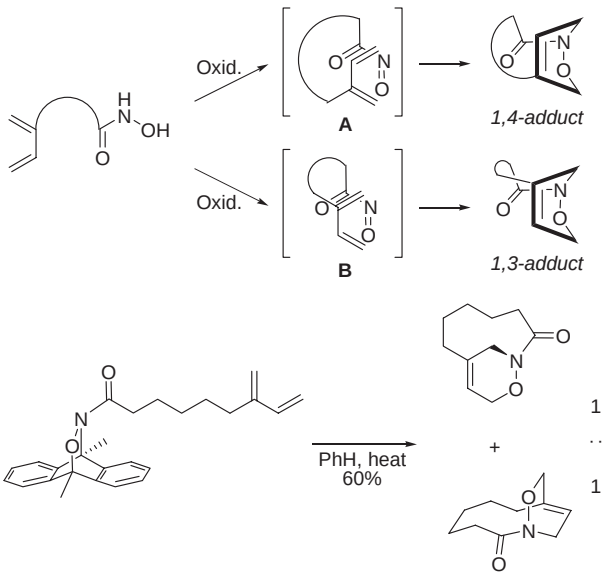
R	ratio
H	1.2 : 1
C_6H_5-	8.9 : 1
4-MeO-C_6H_4-	9.1 : 1
4-Br-C_6H_4-	13.2 : 1
4-NO_2-C_6H_4-	22.7 : 1
2-naphthyl	14.0 : 1

Scheme 18.

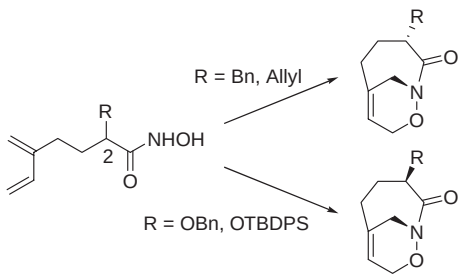


R	solvent	*trans* : *cis*	yield (%)
Bn	$CHCl_3$	1.3 : 1	76
Bn	H_2O	4.1 : 1	87
MOM	$CHCl_3$	1.7 : 1	75
MOM	H_2O	4.4 : 1	93

Scheme 19.



Scheme 20.



Scheme 21.

their "type 2 intramolecular Diels–Alder reaction" methodology for intramolecular nitroso HDA reaction.[34]

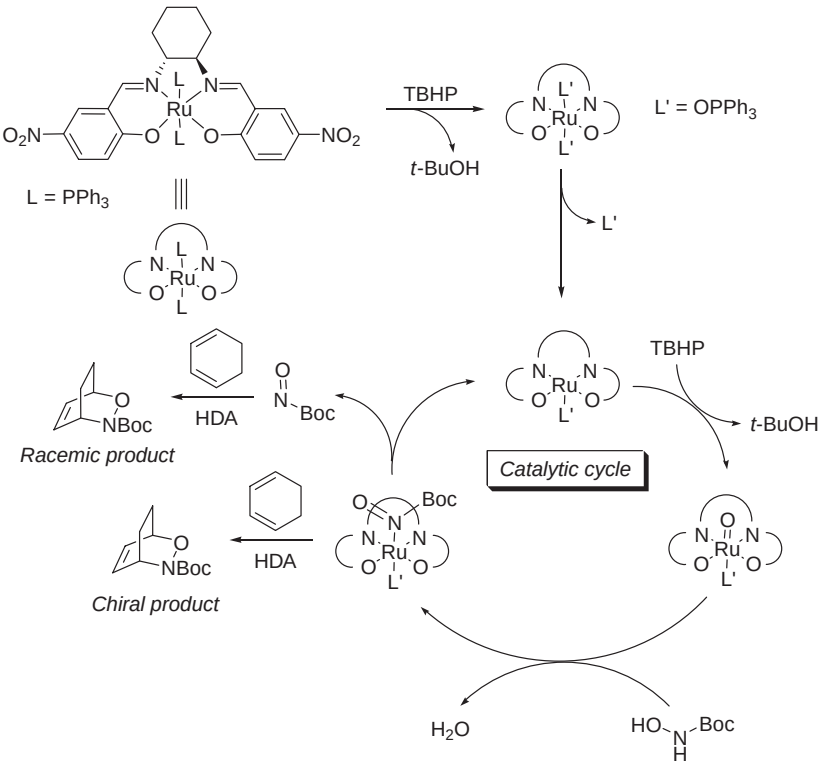
The reaction of dienes for formation of bicyclo[4.3.1]oxazinolactams and bicyclo[5.3.1]oxazinolactams proceeded with complete diastereoselectivity. These products would be formed from intermediate **A**. With dienes containing longer chains, the energetics for HDA reaction in conformation **A** and **B** are equivalent (Scheme 20).[34b] This would be consistent with low selectivity of intramolecular nitroso HDA reaction with 2-substituted 1,3-dienes. Detailed studies on the relationship between C2 substituents and π-facial selectivity indicated that diastereoselectivity of the reaction relies on steric and electronic effects on C2 substituent (Scheme 21).[34c]

6. Enantioselective Nitroso Hetero-Diels–Alder Reaction

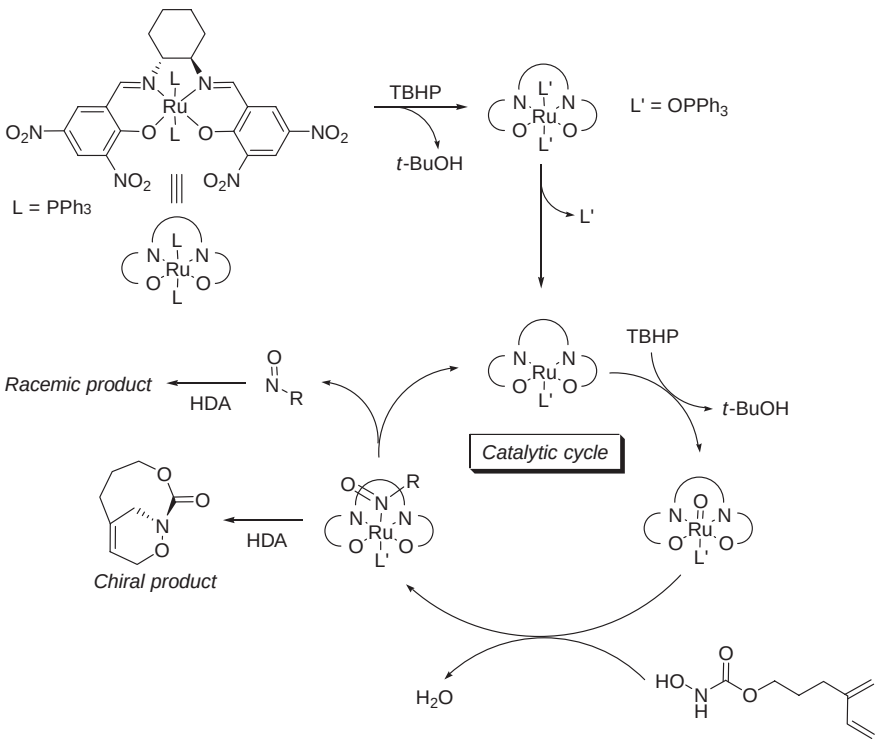
Enantioselective nitroso HDA reaction has been regarded as a difficult process due to the unique reactivities of nitroso compounds. These compounds are quite reactive as electrophiles and smoothly proceed the HDA reaction with dienes without any promoters. Carboxamide *N*-oxide (acyl nitroso) compounds are particularly reactive nitroso compounds which are usually generated and directly trapped by dienes.[35]

An intriguing concept for enantioselective nitroso HDA reaction was reported by Whiting and co-workers. They found that the oxidation of hydroxamic acids catalyzed by the oxoruthenium complex afforded corresponding acyl nitroso compounds which reacted with dienes simultaneously. On the basis of their observations, they expected that the use of a chiral ligand could lead to a chiral induction on an intermolecular nitroso HDA reaction. They envisioned that the acyl nitroso species which are generated by oxidation of hydroxamic acids would remain in the chiral environment of an oxoruthenium catalyst when they react with dienes (Scheme 22).[36] However, the reaction of the acyl nitroso compound generated from *tert*-butyl *N*-hydroxycarbamate with 1,3-cyclohexadiene produced the corresponding adduct in high yield without enantioselectivity. This result indicates that dissociation of the acyl nitroso compound from the catalyst proceeds rapidly before HDA reaction on the catalyst take place and is supported by an intramolecular version of this reaction.

Chow and Shea reported an intramolecular version of this reaction. They expected that such a version of the reaction would make acquisition of enantioselectivity easier, since the HDA reaction would take place while the acyl nitroso com-



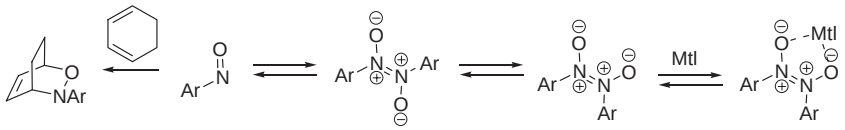
Scheme 22.



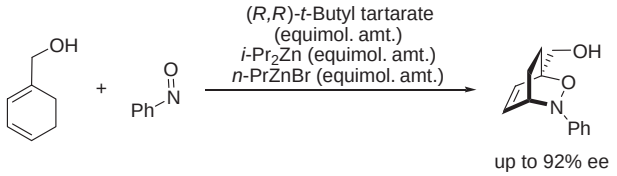
Scheme 23.

pound still coordinates a catalyst. In fact, the reaction was conducted with *N*-hydroxycarbamate derivative in the presence of the chiral ruthenium catalyst and afforded the product with 75% ee (Scheme 23).[37] This result was rationalized by the hypothesis of their group and Whiting's group. Namely, the acyl nitroso compound coordinates the chiral catalyst while the HDA reaction proceeds.

In contrast to the acyl nitroso compounds, the aryl nitroso compounds are more stable. Whiting and co-workers reported that the reaction of nitrosobenzene or *ortho*-methoxynitroso-



Scheme 24.



Scheme 25.

benzene with 1,3-cyclohexadiene in the presence of chiral Lewis acids afforded the product without any asymmetric induction.[38] As we described earlier, this result is rationalized by a unique property of nitroso compounds. The dimers of nitroso compounds act as bidentate ligands for transition metals (Scheme 24). Moreover, Whiting et al. also revealed that this complex neither promotes nor inhibits the nitroso HDA reaction. These results suggested that hard and/or bidentate Lewis acids would also not accelerate the reaction.

The first highly enantioselective nitroso HDA reaction was reported by Ukaji, Inomata, et al. (Scheme 25).[39] The reaction was conducted with nitrosobenzene and diene having an alcohol group in the presence of stoichiometric amount of *tert*-butyl tartarate to give the corresponding adduct with complete regioselectivity and 92% ee. Key to the success is coordination of a hydroxy group of a diene to obtain a high enantioselectivity.

As described earlier, we have developed catalytic enantio- and regioselective nitroso aldol reaction catalyzed by various silver–BINAP complexes.[13,15] In these cases, silver might coordinate nitrosobenzene via a monodentate mode. In spite of the attraction of a monodentate coordination mode, the formation of a stable dimer–metal complex is also possible. The bidentate coordination with an additional site should afford a more rigid and stable monomer–metal complex which should be reactive. The complexes of metals and nitroso compounds via an oxygen atom or a nitrogen atom (**1** and **2**) are well known.[40] These complexes are attractive for asymmetric reactions while the resonance structures of these complexes could lead to deactivate the nitroso compounds. However, if the complexation increases the reactivity of nitroso group, this would be a nice tool for asymmetric synthesis. The choice of moiety X has numerous possibilities as shown in Fig. 2. The complex **4** would be the effective for asymmetric synthesis using nitroso compounds since this complex might not lead to deactivate through resonance structure.

On the basis of this hypothesis, we developed the first catalytic enantioselective nitroso HDA reaction using 2-nitrosopyridine derivative as a dienophile and a chiral copper as a catalyst.[41] The reaction of 2-nitrosopyridine and 1,3-cyclohexadiene gave the corresponding adduct with 59% ee. Gratifyingly, the copper catalyst increases the reactivity of nitroso HDA reaction significantly and successfully minimizes the back ground non-catalyzed HDA reaction. The enantioselectivity of the reaction is sensitive to the substituents of 6-position and to the dihedral angle of the phosphine ligand (Scheme 26).

The alkyl group at 6-position would force a bidentate coordination between oxygen and pyridine. However, the much bulkiness such as isopropyl group also would cause monodentate coordination for oxygen. The combination of 6-methyl-2-nitrosopyridine and $CuPF_6(CH_3CN)_4$-SEGPHOS was optimal, producing the HDA adducts with excellent enantioselectivity and yield in a completely regioselective manner (Scheme 27).

The nitroso HDA adduct was easily converted to the protected amino alcohol (Scheme 28).[41] The cleavage of N–O bond followed by protection of the resulting amine and alcohol afforded the protected amino alcohol. Quaternization of pyridine ring with MeOTf followed by hydrolysis with NaOH gave the protected amino alcohol without any loss of enantioselectivity.

This reaction can be applied for acyclic dienes (Scheme 29). The reaction was conducted with 2-silyloxy-1,3-dienes and 6-methyl-2-nitrosopyridine in the presence of copper catalyst to afford the corresponding adducts enantioselectively.[42] The bulkiness of the silyl group significantly impacted on the enantioselectivity. Their role is to force the diene to form an *s-cis* configuration which favors the concerted [4 + 2] cycloaddition reaction. In this case, compete back ground reaction is ene-

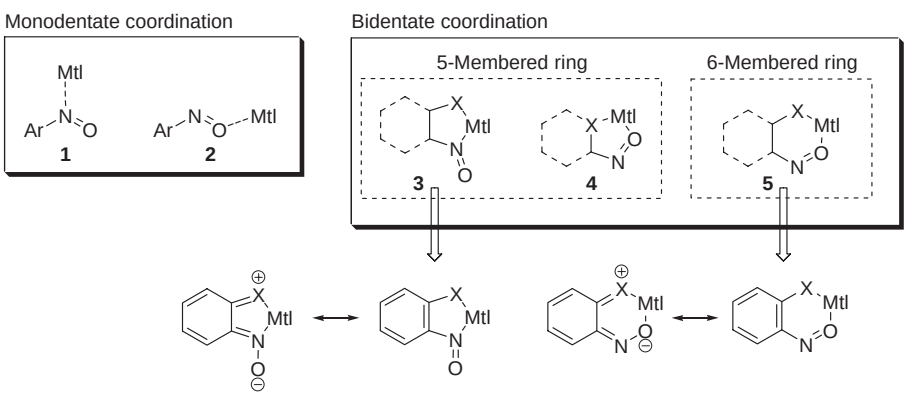
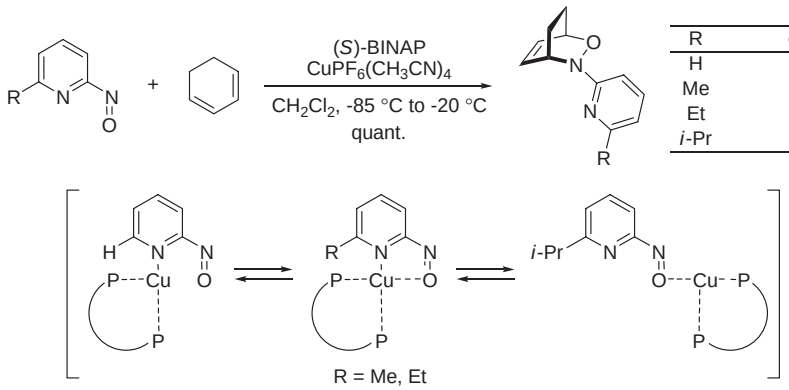
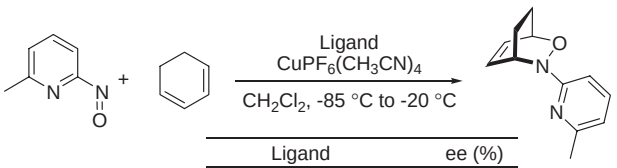


Fig. 2.



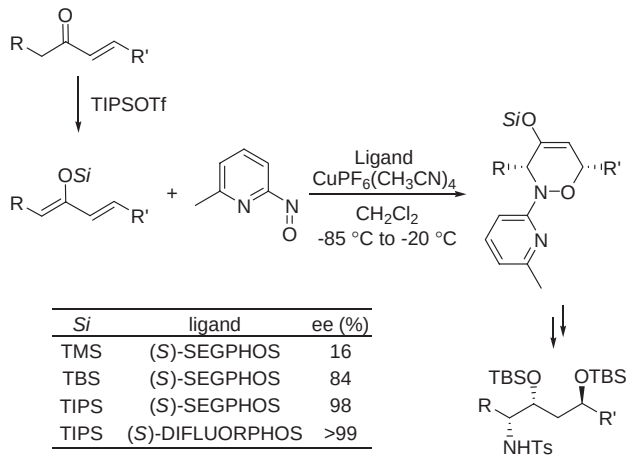
R	ee (%)
H	59
Me	86
Et	87
i-Pr	77

Scheme 26.



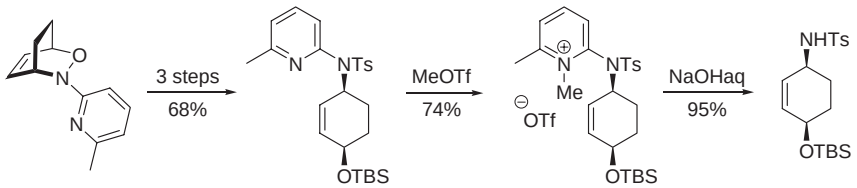
Ligand	ee (%)
(*R*)-BINAP	87
(*R*)-Tol-BINAP	86
(*R*)-H_8-BINAP	67
(*R*)-MeO-BIPHEP	90
(*S*)-SEGPHOS	92

Scheme 27.



Si	ligand	ee (%)
TMS	(*S*)-SEGPHOS	16
TBS	(*S*)-SEGPHOS	84
TIPS	(*S*)-SEGPHOS	98
TIPS	(*S*)-DIFLUORPHOS	>99

Scheme 29.



Scheme 28.

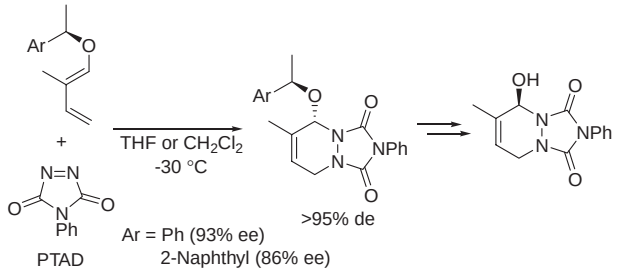
type reaction which is not enantioselective. The triisopropylsilyl (TIPS) group was optimal, obtaining excellent enantioselectivity. The reaction was conducted with 6-methyl-2-nitrosopyridine and 2-TIPSO-1,3-diene in the presence of $CuPF_6$-$(CH_3CN)_4$-DIFLUORPHOS as a catalyst to give an adduct with excellent enantioselectivity in complete regioselectivity. The adduct was transformed to the corresponding amino alcohol in the same manner as described earlier. This catalytic reaction can be applied to a wide range of functionalized substrates, proceeding the adduct with complete regioselectivity and good to excellent enantioselectivity. This method provides an easy access to protected amino alcohols with three stereocenters enantioselectively.

7. Azo Hetero-Diels–Alder Reaction

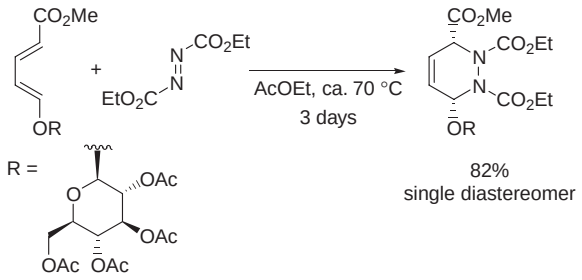
The optically active 1,4-diamines are important building blocks in natural product synthesis and drug discovery. The hetero-Diels–Alder (HDA) reaction of azo compounds with dienes is an attractive route toward chiral 1,4-diamines.[43] It is well known that the azodicarboxylate undergoes HDA reaction (azo HDA reaction) to give 1,4-diamines in a single step. Diastereoselective versions of this process are well studied; however, there are no reports of highly enantioselective azo HDA reaction. We recently reported catalytic highly enantioselective azo HDA reaction using the designed azo compound based on nitroso HDA reaction.[44]

8. Diastereoselective Azo Hetero-Diels–Alder Reaction

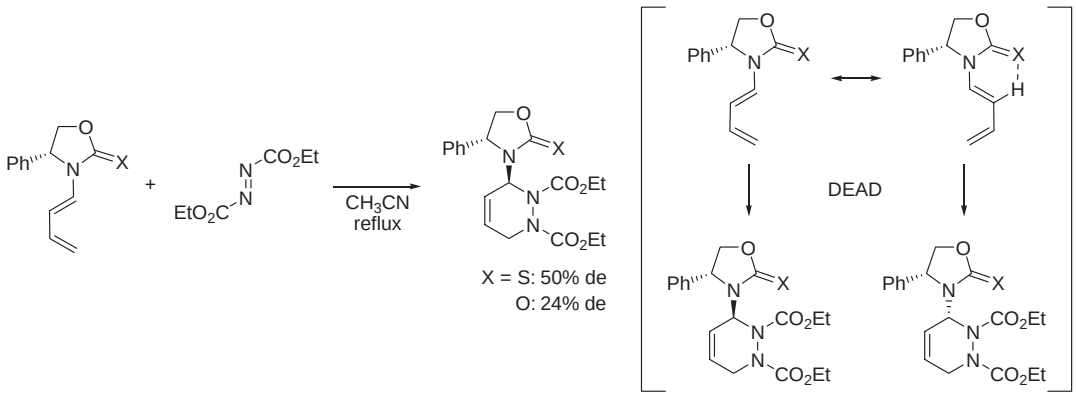
Several diastereoselective azo HDA reactions have been reported. They have mainly been accomplished using achiral azodicarboxylates with chiral dienes. In 1990, Breitmaier and Rieger reported that the reaction of 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione (PTAD), which is one of the most reactive azo dienophile, with chiral dienes which have a chiral secondary alcohol gave the corresponding adducts diastereoselectively (Scheme 30).[45] These adducts were converted to alco-



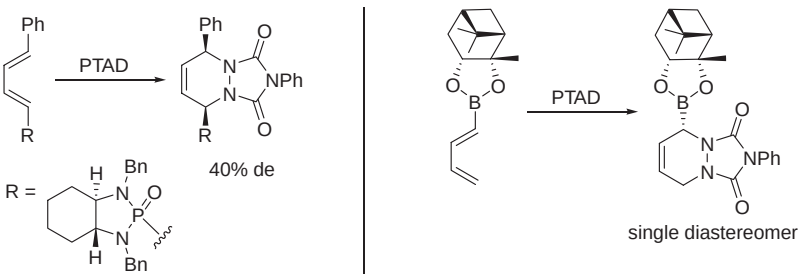
Scheme 30.



Scheme 33.



Scheme 31.



Scheme 32.

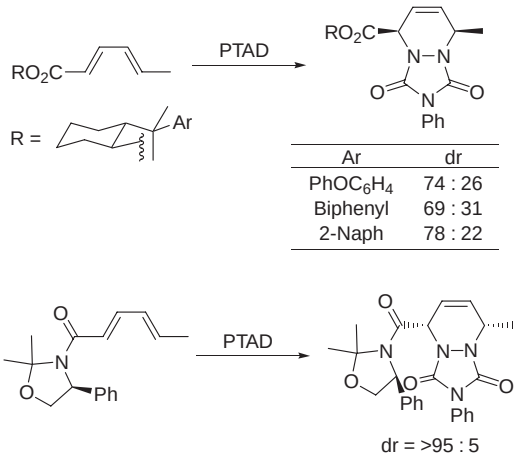
hols with inversion of stereochemistry of alcohol. In addition, the reaction of an amino alcohol derived chiral amino diene was conducted with DEAD as a dienophile to afford an adduct (Scheme 31).[46] The diastereoselectivity of thiooxazolidinone derived diene was higher than that of oxazolidinone derived diene. This selectivity would be explained by the *syn* conformer of diene being less stable than the *anti* conformer, since the *syn* conformer of oxazolidinone derived diene is stabilized by hydrogen bonding.

Dienes which have diazaphospholidine or boronate as a chiral auxiliary have been tried for diastereoselective azo HDA reactions (Scheme 32).[47] While the reaction of chiral diene with diazaphospholidine as a chiral auxiliary and PTAD gave an adduct with 40% de, the reaction of a chiral boronate derived diene and PTAD afforded an adduct as a single diastereomer.[48]

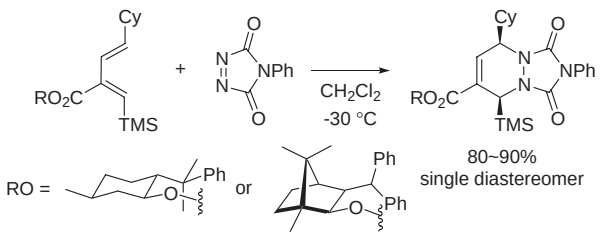
The use of D-glucopyranose derivative as a chiral auxiliary was reported by Stoodley et al. The reaction was conducted with DEAD and a chiral diene which has D-glucopyranose derivative to afford an adduct in 82% yield (Scheme 33).[49] This reaction proceeded slowly even at 70 °C in ethyl acetate, since diene has a conjugated ester group which causes a lower HOMO level of diene. Meanwhile, Adam and co-workers reported that the reaction of dienes with esters or an amide and PTAD gave adducts in good diastereoselectivity. These dienes were installed various chiral alcohols and an amine as esters or an amide groups (Scheme 34).[50] The reaction of a diene having an amide group with PTAD gave better selectivity than those having ester groups.

Moreover, tri-substituted diene can be used in this reaction. Sato and co-workers reported that the reaction of PTAD or azodicarboxylate with chiral tri-substituted dienes gave adducts as a single diastereomer in high yield (Scheme 35).[51]

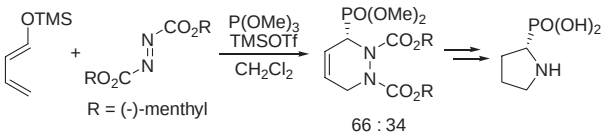
The use of a chiral azodicarboxylate was also reported in 2001 (Scheme 36).[52] Di-(−)-menthyl azodicarboxylate reacted with silyloxydiene in the presence of trimethyl phosphite and TMSOTf to afford an adduct in quantitative yield. The diastereoselectivity of this reaction was 66:34. These mixtures were separated and were converted into pyrrolidine-2-phosphonic acid in several steps.



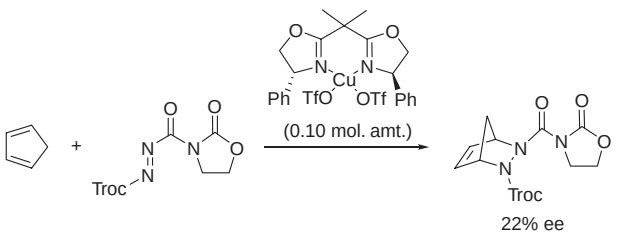
Scheme 34.



Scheme 35.



Scheme 36.



Scheme 37.

9. Enantioselective Azo Hetero-Diels–Alder Reaction

Despite the many reports of diastereoselective azo HDA reaction, only one paper on enantioselective azo HDA has been reported and that by Jørgensen and co-workers (Scheme 37).[53] They described that the use of an azodicarboxylate with an oxazolidinone moiety was as a chelation auxiliary for enantioselective azo HDA reaction. The reaction of the azodicarboxylate derivative with cyclopentadiene in the presence of chiral copper catalyst afforded the corresponding adduct with 22% ee.

We recently accomplished the first highly enantioselective azo HDA reaction using 2-azopyridine as a dienophile in the presence of a silver catalyst.[44] As described earlier, we have reported nitroso HDA reaction using 2-nitrosopyridine derivative. The key to this success is the formation of a rigid five-membered ring between pyridine and oxygen of a nitroso group. Based on this successful design, we envisioned that the formation of the same rigid transition state in azo HDA reaction would lead to a high enantioselectivity (Fig. 3). However, contrary to our expectation, the reaction of 2-azopyridine with 3-TIPSO-2,4-hexadiene in the presence of $CuPF_6$-$(CH_3CN)_4$-BINAP catalyst afforded the corresponding adduct without any chiral induction. Surprisingly, the reaction in the presence of silver–BINAP catalyst proceeded smoothly to give an adduct with good enantioselectivity and complete regioselectivity. The solvent and ratio of silver to ligand were checked, since we had found three types of silver–BINAP complex (Table 1). The use of EtCN as a solvent and 2:1 of silver to BINAP was optimal, producing an adduct with >99% ee. It is noted that the use of ligands with a narrow dihedral angle led to lower enantioselectivity. Although the transition state of this reaction is not clear, it seems that 2:1 complex of silver–BINAP is an active catalyst, because ligands with a narrow dihedral angle form 1:1 complex of silver–BINAP preferentially.

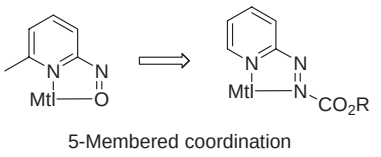
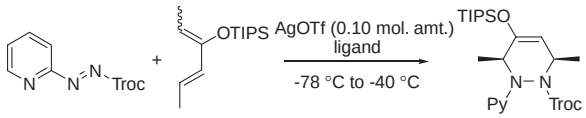


Fig. 3.

Table 1.

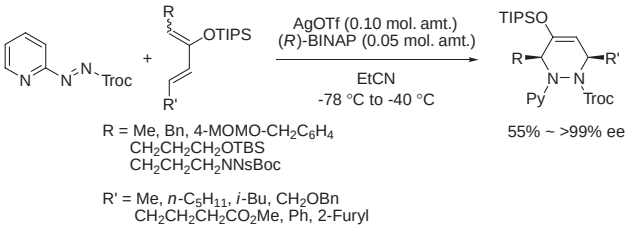


Entry	Ligand	Solvent	Yield /%	ee /%
1	(*R*)-BINAP (0.10 mol. amt.)	THF	73	55
2	(*R*)-BINAP (0.10 mol. amt.)	Et_2O	74	56
3	(*R*)-BINAP (0.10 mol. amt.)	Toluene	63	67
4	(*R*)-BINAP (0.10 mol. amt.)	CH_2Cl_2	72	80
5[a)]	(*R*)-BINAP (0.10 mol. amt.)	CH_3CN	61	94
6	(*R*)-BINAP (0.10 mol. amt.)	EtCN	62	94
7	(*R*)-Difluorphos (0.10 mol. amt.)	EtCN	76	30
8	(*R*)-Segphos (0.10 mol. amt.)	EtCN	71	20
9	(*R*)-BINAP (0.05 mol. amt.)	EtCN	87	>99
10	(*R*)-BINAP (0.20 mol. amt.)	EtCN	26	0

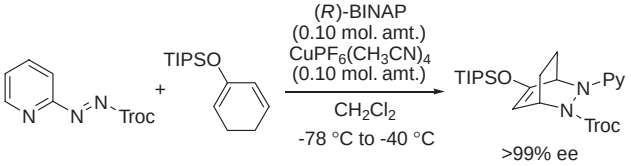
a) Reaction was conducted at −40 °C.

This reaction can be applied for various dienes including ester, ether, and protected amine, producing the corresponding adducts with high enantioselectivity (Scheme 38). However, when silyloxydiene with a phenyl group was used, the enantioselectivity was decreased dramatically. This result might be explained by the reaction having proceeded with low endo/exo selectivity.

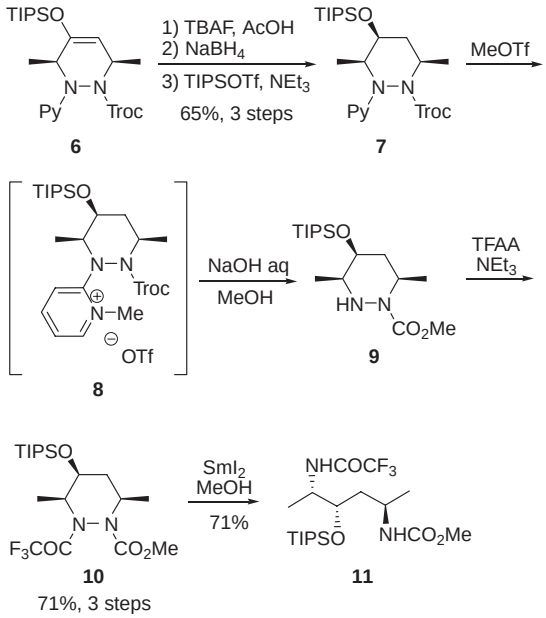
In contrast to these results, when 2-TIPSO-1,3-cyclohexadiene was used as a diene in the presence of chiral copper catalyst, the corresponding adduct was obtained with >99% ee (Scheme 39).



Scheme 38.



Scheme 39.



Scheme 40.

The resulting adducts can be converted to diamino alcohols (Scheme 40). For example, deprotection of TIPS group followed by reduction and protection of the resulting alcohol gave **7** as a single diastereomer. As described earlier, removal of the pyridine ring was cleanly achieved, accompanied by the conversion of 2,2,2-trichloroethoxycarbonyl group to methoxycarbonyl group. The reaction of **7** with MeOTf gave pyridinium salt which was identified by ^{1}H NMR and LRMS. Continuously, **8** was treated with NaOHaq in MeOH to afford an amine and to convert Troc group to methoxycarbonyl group. Protection of the resulting amine **9** with trifluoroacetyl group followed by treatment with SmI_2 afforded the diamino alcohol **11** in good yield. Thus, two amino groups were differentiated for further transformation.

10. Conclusion

The nitroso and azo compounds are attractive reagents to introduce hydroxy and amino groups into organic molecules. Needless to say, these functionalized molecules are important building blocks in organic synthesis. The demand for synthesis of chiral-functionalized molecules from simple achiral molecules is increasing day by day. Although the chiral technology has advanced greatly in past decade, the asymmetric reactions with nitroso and azo compounds are difficult issues due to their unique properties.

We have summarized herein recent advances in catalytic enantioselective reactions with nitroso compounds and enantioselective hetero-Diels–Alder reaction of an azo compound. In nitroso aldol reaction, the structurally defined silver–BINAP complex has led to a clear solution of enantioselective nitroso aldol reaction with high *N*/*O*-selectivity. Moreover, the utility of chiral Brønsted acids and pyrrolidine-based organocatalyst in nitroso chemistry has been demonstrated. In nitroso HDA reaction, the appropriate and efficient design of the substrates such as 2-nitrosopyridine derivatives has led to significant solutions in this field. This substrate design has also been applied for development of catalytic enantioselective azo HDA reaction.

The door to catalytic enantioselective reactions with nitroso and azo compounds has just been opened and we feel fortunate that we have contributed to this interesting and important field. It is our hope that this fascinating chemistry will see strong development and make the organic synthesis of chiral molecules more facile.

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Hisashi Yamamoto received his B.Sc. from Kyoto University and his Ph.D. from Harvard University (Prof. E. J. Corey). He held academic positions at Kyoto University and at the University of Hawaii, before he moved to Nagoya in 1980, where he became Professor (1983). In 2002, he was appointed Professor at the University of Chicago. He has been honored with the Prelog Medal (1993), the Chemical Society of Japan Award (1995), the Max-Tishler Prize (1998), Le Grand Prix de la Fondation Maison de la Chimie (2002), the National Prize of the Purple Medal (Japan) (2002), the Yamada Prize (2004), and the Tetrahedron Prize (2006).

Masanori Kawasaki was born in Nara, Japan, in 1977. He received his B.Sc. in 2000, M.Sc. in 2001, and Ph.D. in 2005 from Osaka City University under the guidance of Professor Yasufumi Ohfune. In 2005, he joined the research group of Professor Hisashi Yamamoto at University of Chicago and is currently working to develop the catalytic asymmetric reaction using nitroso and azo compounds. He awarded the Graduate Student Fellowship from Ono Pharmaceutical Co., Ltd. (2002–2003), the Student Presentation Award from Japan Chemical Society (2004), and Postdoctoral Fellowship from the Uehara Memorial Foundation (2007).