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Recent Advances in Asymmetric Nitroso Diels–Alder Reactions

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During the past decade, the nitroso Diels–Alder (NDA) reaction has become more practical tool for organic synthesis, and a numbers of important compounds have been synthesized using this method. Until recently, no reports on a catalytic asymmetric version of this reaction had been reported; the major issues were the high reactivity of nitroso compounds and their chemical properties. This microreview outlines recent advances in the area of asymmetric NDA reaction following the review by Streith and Defoin in 1994.

Introduction

The chemistry of nitroso compounds has been intensively studied in the past decades, especially in the field of asymmetric synthesis.[1] Significant developments in chiral-auxiliary-mediated asymmetric reactions have been achieved on nitroso Diels–Alder reaction,[2] *N*-nitroso aldol reaction[3] and nitroso ene reaction[4] to serve chiral nitrogen- and oxygen-containing molecules. Most recently, the use of nitrosobenzene as an oxy electrophile was reported and broadened the utility of nitroso compounds.[5]

Nitroso Diels–Alder (NDA) reaction is a useful transformation, which provides easy access to synthetically useful compounds, such as 3,6-dihydro-1,2-oxazines,[6] in a single step. These NDA adducts could serve as 1-amino-4-hydroxy-2-ene derivatives and allow further functionalization, which shows their versatility in organic synthesis.

This useful transformation was first reported by Wichterle and Arbuzov in 1947.[7] After pioneering work by Kresze's group[8] and Kirby's group[9] which opened the door to an asymmetric version of this reaction, several

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Hisashi Yamamoto received his Bachelor's degree from Kyoto University and Ph. D. from Harvard under the mentorship of Professor E. J. Corey. His first academic position was Assistant Professor and lecturer at Kyoto University, and in 1977 he was appointed Associate Professor of Chemistry at the University of Hawaii. In 1980 he moved to Nagoya University where he became Professor in 1983. In 2002, he moved to the United States as Professor at the University of Chicago. He has been honored with the Prelog Medal in 1993, the Chemical Society of Japan Award in 1995, the Max-Tishler Prize in 1998, Le Grand Prix de la Fondation Maison de la Chimie in 2002, National Prize of Purple Medal (Japan) in 2002, and Yamada Prize in 2004. His current interests are mainly the development of new synthetic reactions in the field of acid catalysis including designer Lewis acids, designer Brønsted acids, and combinations of these two acid systems. Recently, he is also interested in a new field on nitroso aldol reactions. He is a member of the International Advisory Board of European Journal of Organic Chemistry.

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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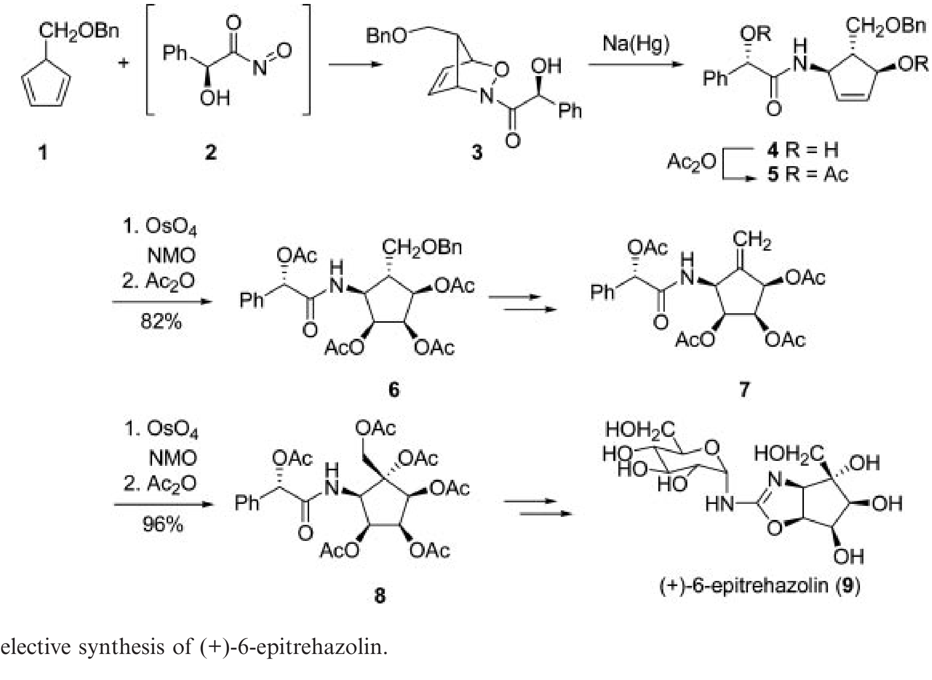
groups have made a great contribution to the development of this transformation. A number of useful chiral nitroso compounds or chiral diene-mediated asymmetric NDA reactions were reported, which have led to the synthesis of many natural products and biologically important compounds. For examples, Ganem and co-workers reported the enantioselective synthesis of Mannostatin A in 1991,[10] and Hudlicky and Olivo showed the efficient synthesis of (+)-lycoricidine in 1992,[11] using this methodology. This microreview discusses recent advances in the area of asymmetric NDA reaction and their synthetic applications, focusing especially on those following Streith and Defoin's review in 1994.[2b]

Total Synthesis with Asymmetric NDA Methodology

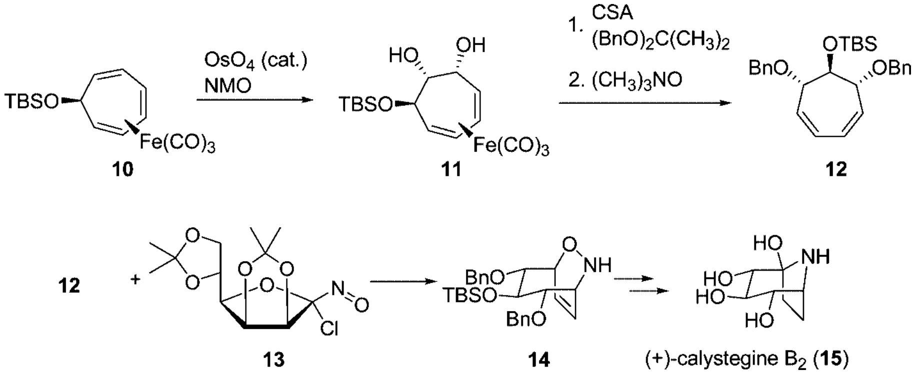
NDA adducts obtained from reactions of nitroso compounds with cyclic 1,3-dienes are an attractive precursor of cyclic polyhydroxylated compounds. For example, Ganem and co-workers applied this methodology for the enantioselective synthesis of (+)-6-epitrehazolin[12] (Scheme 1). The reaction of [(benzyloxy)methyl]cyclopentadiene (**1**) with the (*S*)-mandelic acid derived chiral acylnitroso compound **2**[9,13] afforded the bicyclic adduct **3** with moderate diastereoselectivity. The N–O bond was cleaved by the use of sodium amalgam to afford the pure cyclopentene **4** after silica gel chromatography. Catalytic osmylation of the diacetate **5** proceeded with good facial selectivity (>5:1) which set up two more stereocenters. The diacetate **5** was further transformed to the exocyclic alkene **7**. Flanked by two allyic substituents shielding the top face of the five-membered ring, the exocyclic alkene group in **7** underwent vicinal hydroxylation exclusively from the opposite face using OsO_4 and NMO. Stereoselective introduction of the quaternary center was achieved in this way, and acetylation of this diol afforded the pentaacetate **8** possessing all of the stereocenters required, which was further transformed to (+)-6-epitrehazolin (**9**).

The use of substituted symmetric diene in NDA reaction provides multiple stereocenters in a single step. Soulié and co-workers took advantage of this property in their total synthesis of (+)-calystegine B_2 (**15**), which is a potent inhibitor of β-glucosidases and α-galactosidases (Scheme 2).[14] The required cycloheptadiene **12** for the NDA reaction was prepared by the method proposed by Pearson and Srinivasan[15] with some modifications. The reaction of this cycloheptadiene **12** with Kresze's sugar derived α-chloronitroso compound **13**[8b] afforded the NDA adduct **14** with complete diastereoselectivity possessing all the stereocenters. Further transformation led to the total synthesis of (+)-calystegine B_2 (**15**) in twelve steps with a satisfactory 13% overall yield.

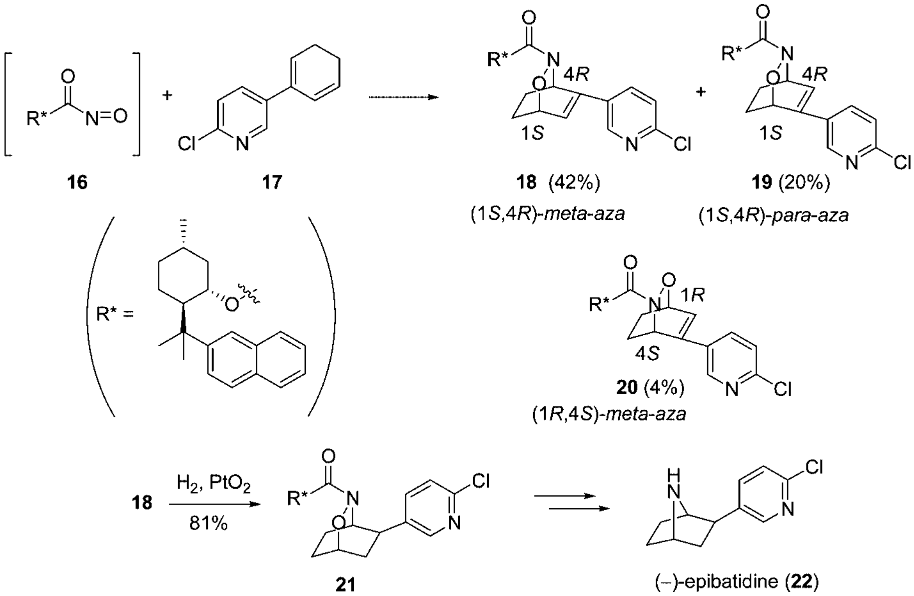
The NDA adduct of the reaction with 1,3-cyclohexadienes is also an attractive precursor for 7-azabicyclo[2.2.1]-heptane derivatives. Kibayashi and co-workers showed the total synthesis of (–)-epibatidine (**22**) by use of an asymmetric NDA reaction with a chiral *N*-acylnitroso dienophile **16** derived from menthol (Scheme 3).[16] The reaction with 2-chloro-5-(1,5-cyclohexadienyl)pyridine (**17**) proceeded with good facial diastereoselectivity, which was consistent with their proposed transition-state model. The regioselectivity was not high, which is often the case for reactions of acyl nitroso compounds with 2-substituted 1,3-cyclohexadienes.[17] The desired NDA adduct **18** was isolated through silica gel chromatography, and hydrogenated over PtO_2 to give the *exo* product **21** (81%) as a single diastereomer. Further conversion led to total synthesis of (–)-epibatidine in ten steps with 5.9% overall yield.



Scheme 1. Enantioselective synthesis of (+)-6-epitrehazolin.

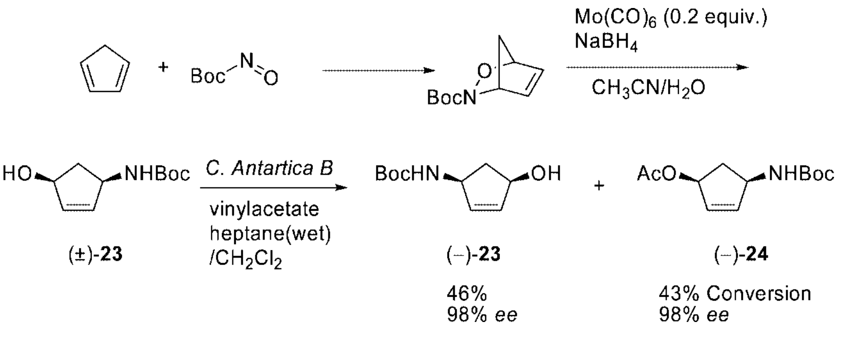


Scheme 2. Total synthesis of (+)-calystegine B_2.

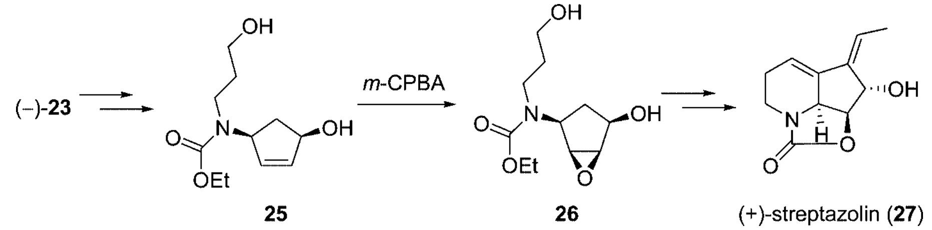


Scheme 3. Total synthesis of (–)-epibatidine.

Miller and co-workers developed an efficient method of enzymatic resolution of acyl nitroso Diels–Alder derived aminocyclopentenols.[18] They accomplished a kinetic resolution of the racemic *cis*-4-aminocyclopent-2-en-1-ol (±)-**23** using commercially available immobilized *C. Antartica B* enzyme (Scheme 4). The enantiopure acetate (–)-**24** and alcohol (–)-**23** were obtained after recrystallization. Importantly, this method worked well on the ten-gram scale, and the resin-bound enzyme could be easily recovered. Synthetic applications of this chiral aminocyclopentenols are demon-



Scheme 4. Kinetic resolution of racemic *cis*-4-aminocyclopent-2-en-1-ol.

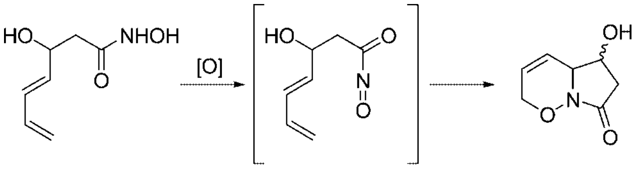


Scheme 5. Total synthesis of (+)-streptazolin.

strated by their group. For example, concise total synthesis of (+)-streptazolin (**27**) was accomplished starting from the aminocyclopentenol (–)-**23** (Scheme 5).[18b]

Intramolecular NDA Reaction

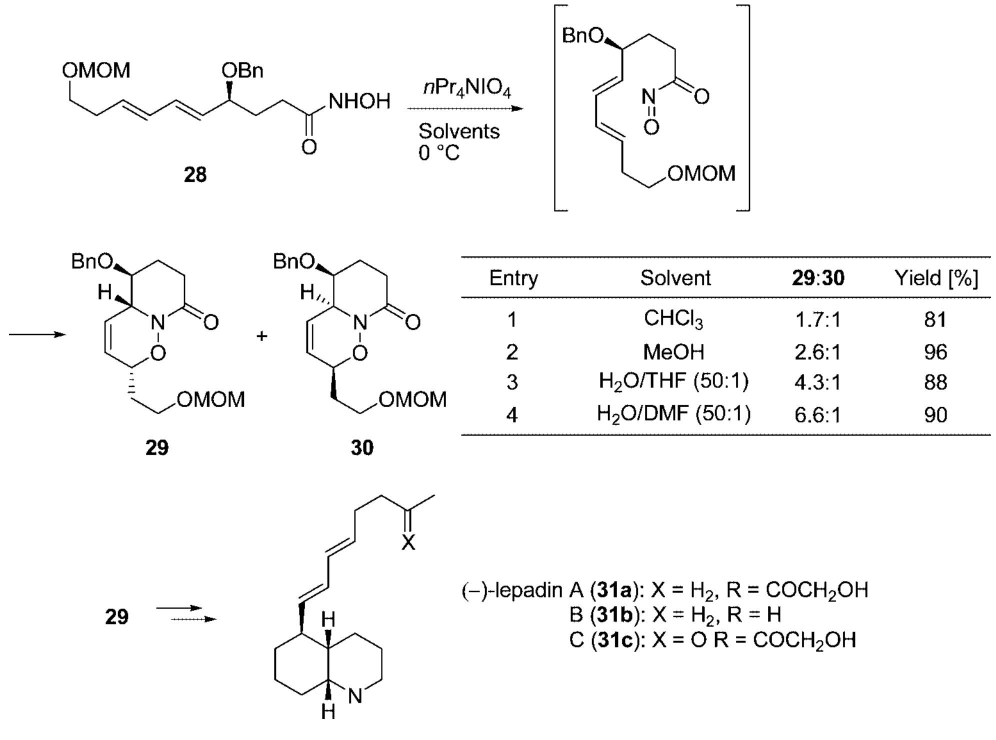
After the first report by Keck in 1978,[19] intramolecular NDA reaction has been recognized to be an efficient method for the construction of compounds containing a piperidine or pyrrolidine ring with stereocenters (Scheme 6).



Scheme 6. Intramolecular NDA reaction.

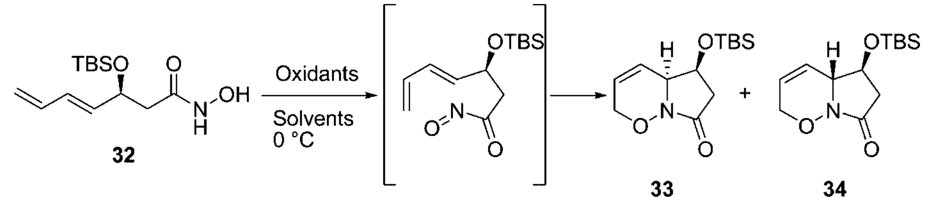
Although there are a number of reports using chiral substrates in the asymmetric synthesis of natural products and related compounds,[20] the diastereoselectivities are generally low. Only Kibayshi's group succeeded in a highly diastereoselective intramolecular NDA reaction, which was conducted in aqueous media.[20c–20e] Their finding was that intramolecular NDA reaction of 4-substituted 5,7-dienohydroxamic acid in aqueous media would proceed with high diastereoselectivity. Their highest diastereoselectivity (6.6:1) was observed during their total synthesis of (–)-lepadins A, B and C (Scheme 7).[20d] They employed the chiral compound **28** to afford their desired bicyclo[4.4.0]1,2-oxazine **29** with good yield and diasteroselectivity. When the reaction was conducted in organic solvents like $CHCl_3$, only poor selectivity was observed.

This enhanced diastereoselectivity was not observed when White and co-workers applied the intramolecular NDA reaction toward the total synthesis of (+)-loline (Scheme 8).[21] The reaction of the 3-substituted 4,6-dienohydroxamic acid **32** to afford the bicyclo[4.3.0]1,2-oxazine

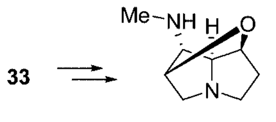


Entry	Solvent	**29**:**30**	Yield [%]
1	$CHCl_3$	1.7:1	81
2	MeOH	2.6:1	96
3	H_2O/THF (50:1)	4.3:1	88
4	H_2O/DMF (50:1)	6.6:1	90

Scheme 7. Diastereoselective intramolecular NDA reaction for total synthesis of (–)-lepadins.

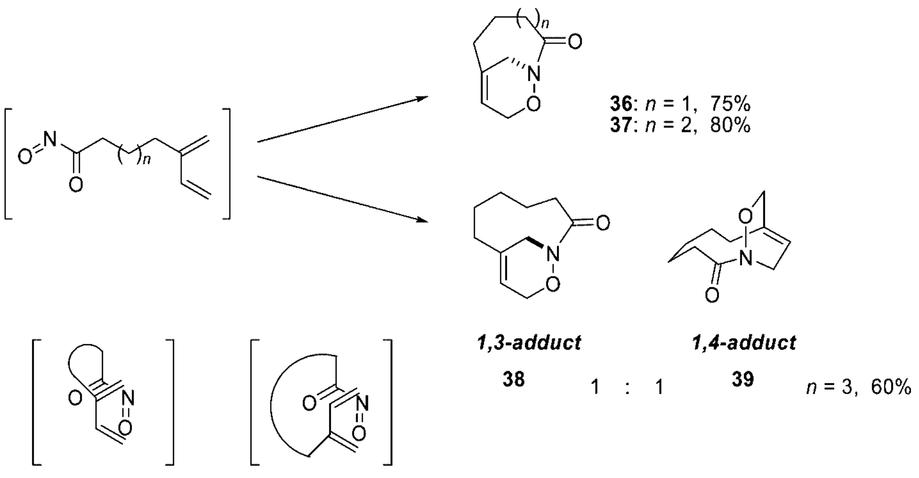


Entry	Oxidant	Temp. [°C]	Solvent	**33**:**34**	Yield [%]
1	nBuNIO$_4$	0	benzene	71:29	60
2	nBuNIO$_4$	– 78	CH$_2$Cl$_2$	50:50	86
3	nBuNIO$_4$	22	CHCl$_3$	55:45	91
4	NaIO$_4$	0	H$_2$O/DMF (1:1)	27:73	97



(+)-loline (**35**)

Scheme 8. Intramolecular NDA reaction for total synthesis of (+)-loline.

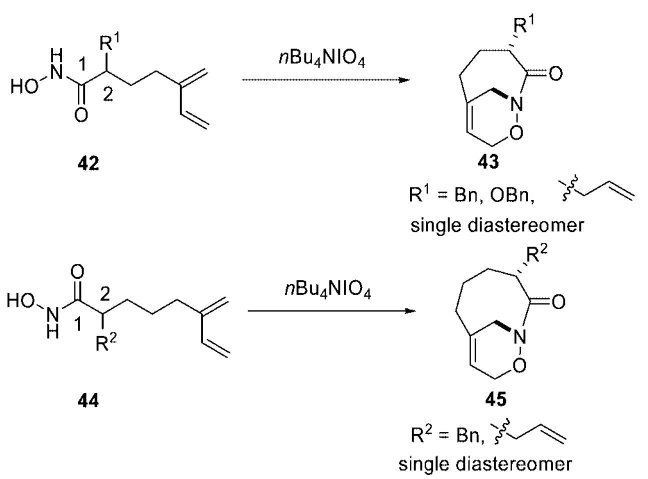


40 **41**

Scheme 9. Type 2 intramolecular NDA reaction.

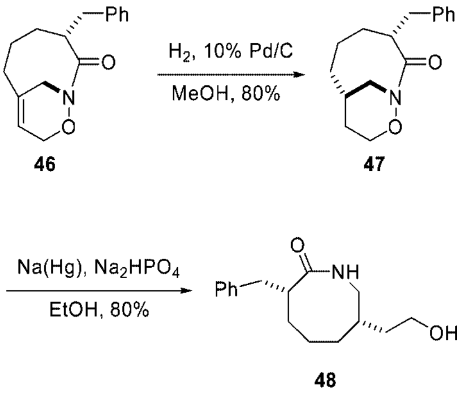
33 resulted in poor diastereoselectivity. Instead of obtaining high diastereoselectivity, reversed selectivity was observed when the reaction was conducted in aqueous media. The reason is still unclear.

Recently, Shea and co-workers expanded their "type 2 intramolecular Diels–Alder reaction" methodology[22] to the intramolecular NDA reaction (Scheme 9).[23] The reaction of dienes for formation of bicyclo[4.3.1]-oxazinolactams and bicyclo[5.3.1]-oxazinolactams proceeded with complete regioselectivity which is a product from conformation **40**. With dienes containing longer tethers, the energetics for the cycloaddition in conformations **40** and **41** are equivalent and both cycloadducts **38** and **39** were found in equal amounts, where their low selectivity is consistent with the intermolecular reaction of *N*-acyl nitroso compounds with 2-substituted 1,3-dienes.[17] Detailed studies on the relationship between substituents on alkyl group and π-facial



Scheme 10. Diastereoselective type 2 intramolecular NDA reaction.

selectivity of the reaction revealed that the selectivity heavily relies on steric and electronics on C2 carbon (Scheme 10). Indeed, complete diastereoselectivity was observed when the C2-substituted hydroxamic acids **42** and **44** were used, which led to the formation of an *anti*-substituted oxazinolactam **43** and **45**. Elaboration of **46** led to the formation of a *cis*-3,7-disubstituted azocin-2-one **48** after catalytic hydrogenation of the double bond followed by cleavage of the N–O bond by Na(Hg) amalgam (Scheme 11).



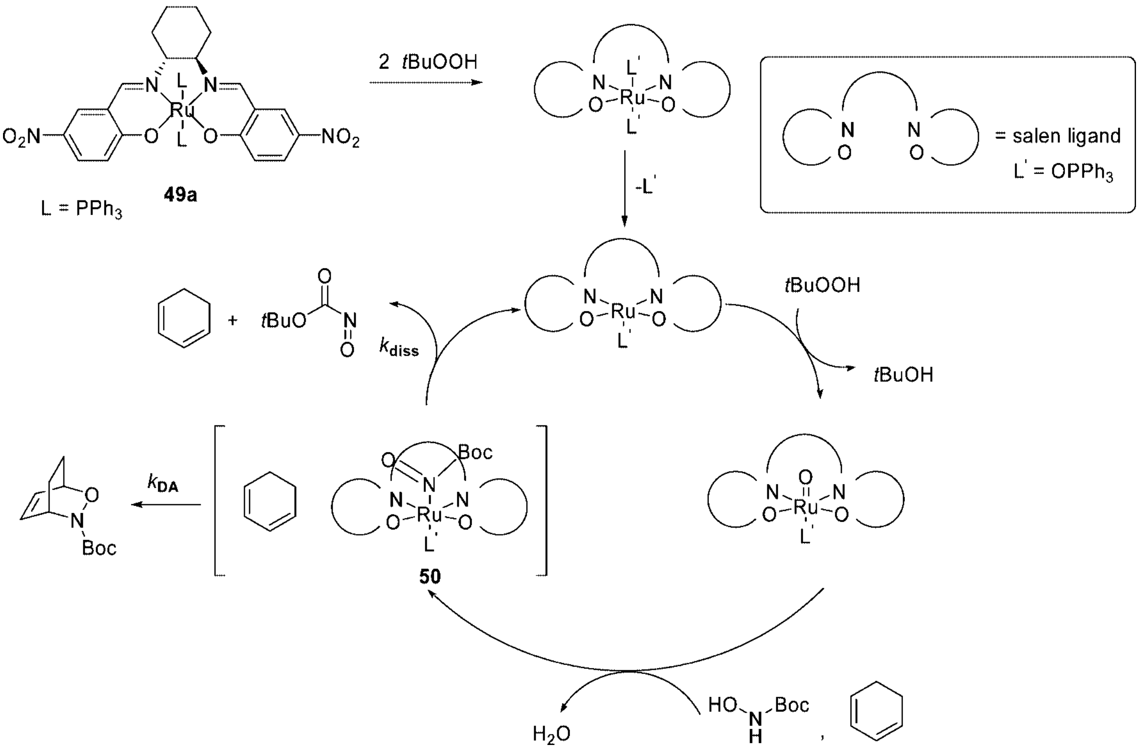
Scheme 11. Conversion to *cis*-3,7-disubstituted azocin-2-one.

Enantioselective NDA Reaction

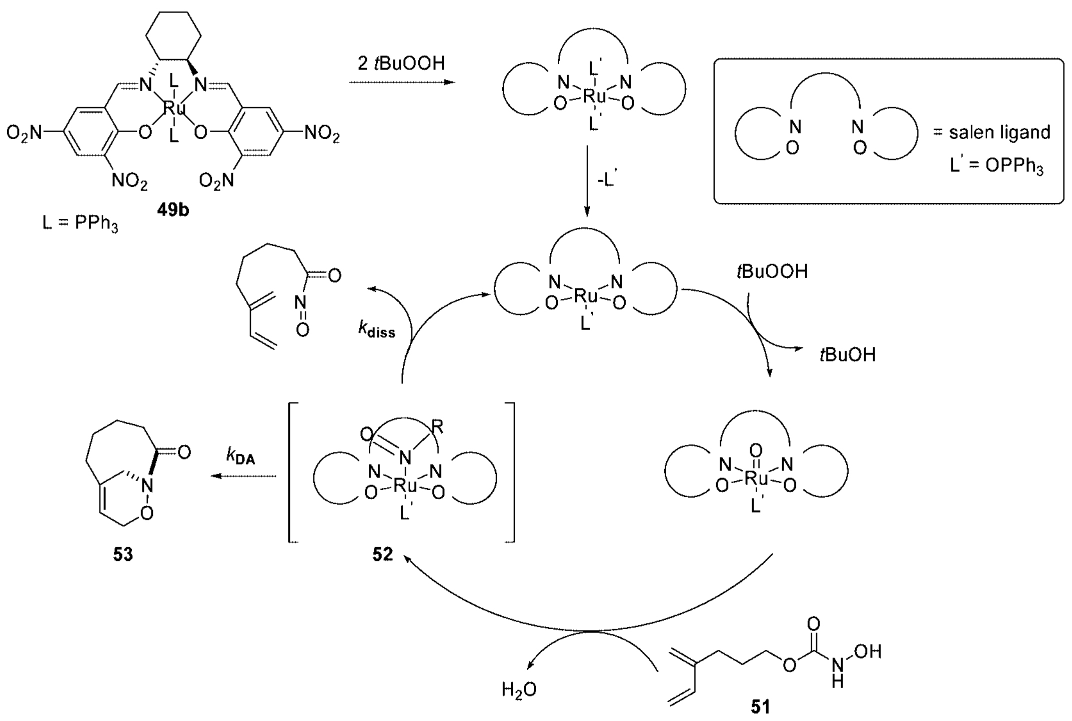
Enantioselective NDA reaction has long been regarded as a difficult process. One major reason is the high reactivity of nitroso compounds: they readily undergo [4+2] cycloaddition with dienes without activation. Acyl nitroso compounds, for example, are very reactive species and have a relatively short lifetime.[24] As the isolation of acyl nitroso compounds is an almost impossible process, the formation is usually achieved by an in situ oxidation of hydroxamic acids, which are directly trapped by 1,3-diene.[25]

An interesting concept for induction of asymmetry using this in situ *generated* acyl nitroso compound was reported by Whiting and co-workers. As they previously found that the oxoruthenium(IV) complex catalyzed the oxidation of hydroxamic acids to the corresponding acyl nitroso compounds, which then immediately undergo NDA reaction,[26] they expected that the use of a chiral ligand would lead to a chiral induction on this NDA reaction step.[27] They envisioned that the acyl nitroso compound formed after the oxidation step would stay in the coordination sphere of the chiral ruthenium catalyst when it reacts with 1,3-cyclohexadiene (Scheme 12). The ruthenium-salen type ligand **49a** was chosen because all the equatorial ligand positions are fixed and the ligand is enantiomerically pure. This catalyst was prepared using procedures reported by Zheng et al.,[28] from $RuCl_2(PPh_3)_2$ and the salen ligand. Unfortunately, the reaction of *tert*-butyl *N*-hydroxycarbamate with 1,3-cyclohexadiene proceeded with no enantioselectivity, in spite of high yield. Considering this result, it is most likely that the formed acyl nitroso compound rapidly dissociates from ruthenium and undergoes thermal Diels–Alder reaction ($k_{diss} >> k_{DA}$).

Although Whiting and his co-workers' *intermolecular* process had no asymmetric induction, Chow and Shea proposed that an *intramolecular* version of this reaction would



Scheme 12. Proposed mechanism for ruthenium catalyzed oxidation of a hydroxamic acid and in situ NDA reaction.



Scheme 13. Proposed mechanism for ruthenium catalyzed oxidation of a hydroxamic acid and in situ intramolecular NDA reaction.

have a higher probability of taking place while the intermediate is still in the coordination sphere of the ruthenium. They proved this hypothesis by applying their type-2 *intramolecular* NDA reaction. Thus, the reaction was conducted with 4-methylene-5-hexenyl *N*-hydroxycarbamate (**51**) in the presence of the chiral ruthenium-salen catalyst **49b**, which gave the product **53** with 75% *ee* (Scheme 13).[29] This result could be rationalized by the proposal of their group and Whiting's group that acyl nitroso compound stays in the coordination sphere of ruthenium catalyst after the oxidation step. In fact, *N*-binding nitrosoruthenium complexes [Ru^{II}(RN=O)(L)] (R = alkyl, aryl) have been reported and characterized by X-ray structure analysis.[30] Rapid dissociation from ruthenium (k_{diss}) might be a result of the electron deficiency of acyl nitroso compounds. Because this dissociation is dependent on the reoxidation process, which is a bimolecular reaction, the importance of *intramolecularity* for asymmetric induction is clear. Indeed, concentration impacted the enantioselectivity, whereas a diluted condition gave better enantioselectivity than the concentrated one.

Aryl nitroso compounds are much more stable than acyl nitroso compounds, which should make them amenable to activation by chiral Lewis acids. Interesting results were reported by Whiting and his co-workers as they tried to activate nitrosobenzene or *ortho*-methoxynitrosobenzene with various chiral Lewis acids.[31] They reported that reactions of these nitroso compounds with 1,3-cyclohexadiene in the presence of various series of Lewis acid metals, ligands and solvents led to no chiral induction. The rational explanation for this result is connected with a well-known property of nitroso compounds. Nitroso compounds exist in rapid equilibrium with their dimer counterparts **55**,[32] which in turn are reasonable bidentate ligands for transition metals.[31,33] Indeed, Whiting and his colleagues isolated and identified the structure of the Sc(OTf)$_3$-*o*-methoxynitrosobenzene dimer complex by X-ray analysis (Figure 1) and showed that this complex neither promotes nor inhibits the NDA reaction (Scheme 14). These results suggested that hard and/or bidentate Lewis acids will neither cause rate acceleration nor will they be applicable in obtaining asymmetric induction. They described that possible solutions are the use of softer Lewis acids or Lewis acids which are only capable of monodentate coordination.

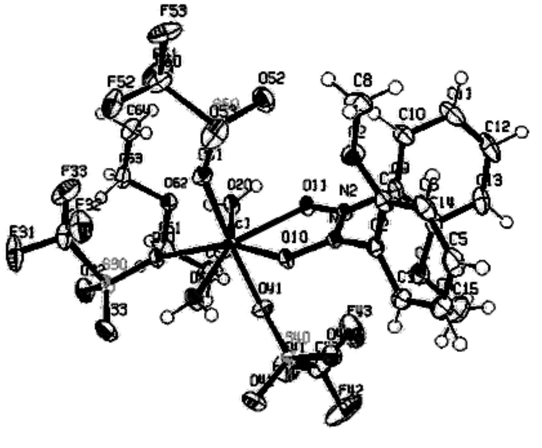
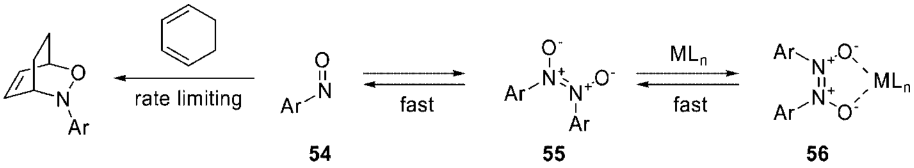


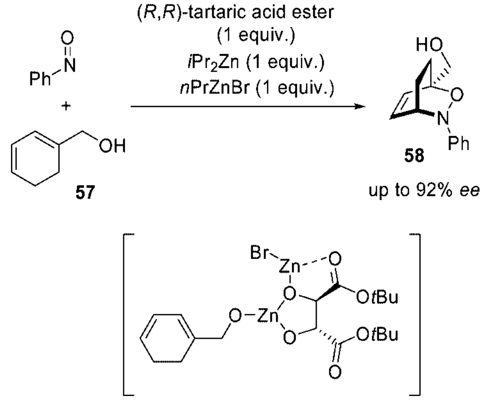
Figure 1. X-ray structure of the Sc(OTf)$_3$-*o*-methoxynitrosobenzene dimer complex.

The first enantioselective NDA reaction was reported by Ukaji and Inomata using one equivalent of tartaric acid



Scheme 14.

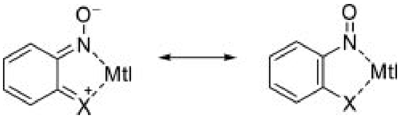
ester (Scheme 15).[34] Instead of activating nitrosobenzene, they generated an unique chelating transition state of (cyclohex-1,3-dienyl)methanol (**57**) with zinc–tartaric acid complex to induce enantioselectivity. This reaction gave the NDA adduct **58** with complete regioselectivity in 94% yield with 92% *ee*.



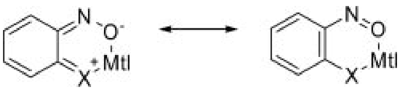
Scheme 15. Enantioselective NDA reaction utilizing tartaric acid ester chiral auxiliary.

Connected with our recent results on the catalytic enantioselective O-selective-[5b] and N-selective[35] nitroso aldol reaction of metal enolate with nitrosobenzene in the presence of various silver-BINAP complexes, we were interested in activating nitroso compounds with chiral Lewis acid. Interactions of nitroso compounds with metals are well studied,[36] and Figure 2 represents the binding modes with metals which should be amenable for activation. Sole N-binding (**i**) is the most common mode of RN=O binding observed to date in crystallography characterized metal–RN=O compounds, whereas sole O-binding (**ii**) is less common.[37] Metal–RN=O compounds with an additional coordinating site on nitroso compounds are also known, and most of them are N-binding (**iii**). O-binding modes (**iv**, **v**) are also rare in this case.

Activation by single-bond coordination (**i**, **ii**) is attractive, but the possibility of forming stable dimer–metal complex cannot be excluded (Scheme 14). Coordination with an additional site should give a more rigid complex, which could avoid the formation of a dimer–metal complex. N-binding and O-binding metal–RN=O complex (**iii**, **v**) have precedents, and are suitable for this purpose, but the existence of the resonance form [shown at the left in Equation (1) and Equation (2)] can possibly deactivate the nitroso compound. Although there were no precedents, activation via chelate intermediate (**iv**) was the most reasonable approach for us, and our interest in this chemistry drove us to explore the use of strategy.[38]



(1)



(2)

We recently accomplished the first catalytic asymmetric NDA reaction using 2-nitrosopyridine derivatives in the presence of a chiral phosphane–copper catalyst.[39] We expected that the coordination of pyridine would generate a monomeric nitrosopyridine–catalyst complex, which would immediately react with dienes. As expected, the reaction of

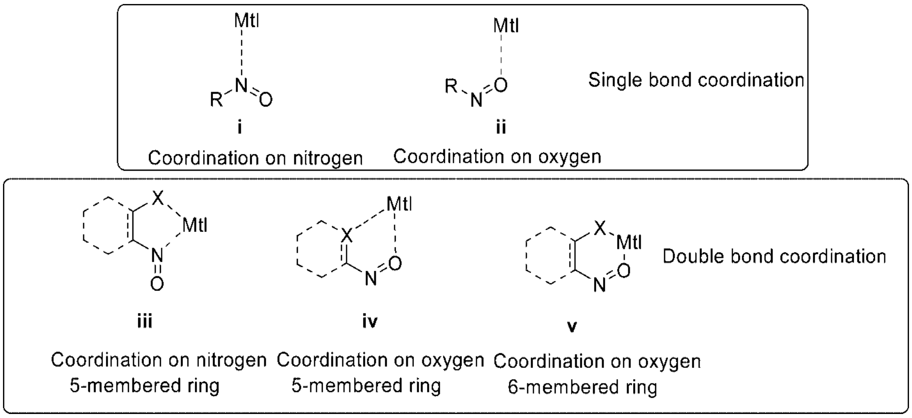


Figure 2. Binding modes of metal–RNO complexes.

2-nitrosopyridine (**59a**) with 1,3-cyclohexadiene afforded NDA adduct **61a** with excellent yield and good enantioselectivity. Our proposed reaction model (Figure 3) is consistent with the absolute configuration obtained from the reaction. Furthermore, the enantioselectivity is sensitive to the substituent at 6-position of 2-nitrosopyridine (Scheme 16), and to the dihedral angle of the phosphane ligand (Scheme 17),[40] which further indicates that the reaction proceeds via this highly organized transition state.

Our best result was obtained with 6-methyl-2-nitrosopyridine (**59b**) in the presence of [Cu(MeCN$_4$)-segphos]PF$_6$ complex, and worked well for a wide range of substrates. Especially, the reaction with 2-substituted 1,3-cyclohexadienes proceeded in a completely regioselective manner, which is normally difficult using acyl nitroso compounds (Scheme 18).[17]

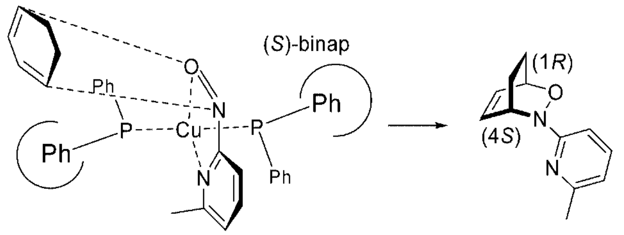
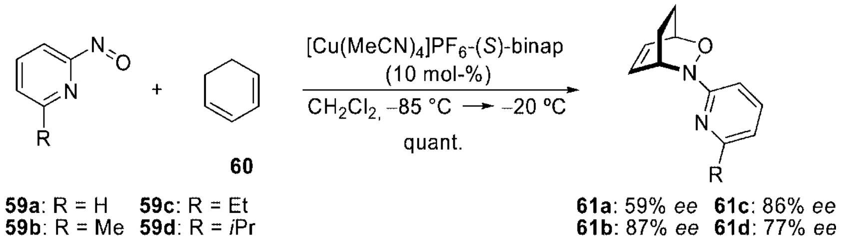
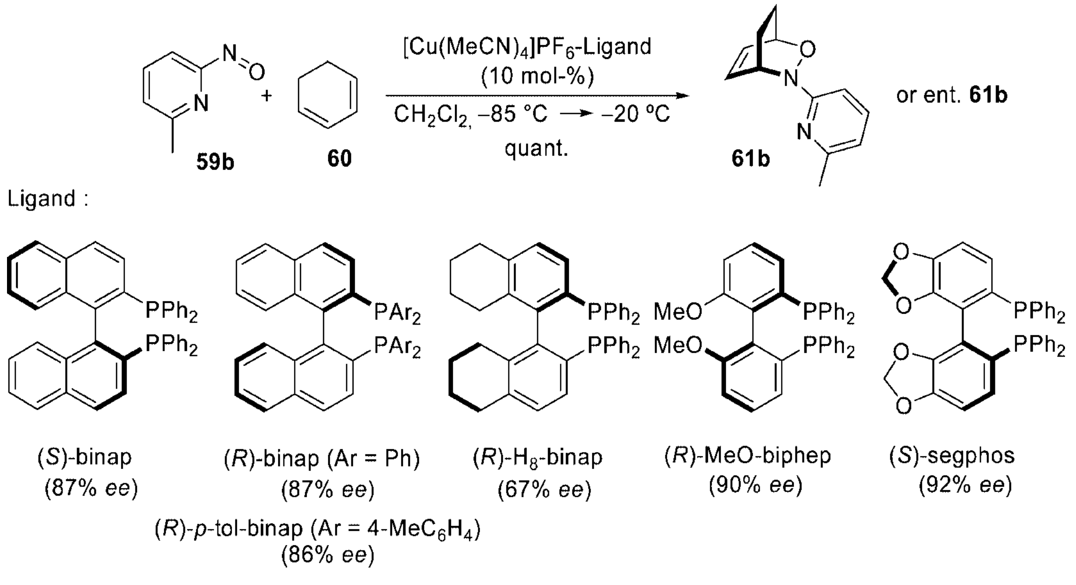


Figure 3. Plausible chelate intermediate.

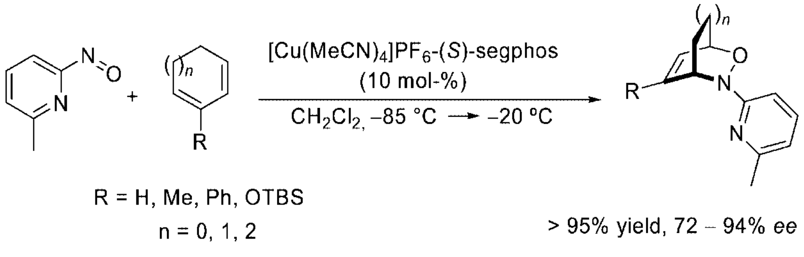
The Diels–Alder adduct was easily transformed to a protected amino alcohol (Scheme 19). After cleavage of the N–O bond, the resulting alcohol and amine were protected by TBS and tosyl group, respectively. Quaternization of pyridine followed by treatment of NaOH afforded the protected amino alcohol **64** in good yield without loss of enantioselectivity.



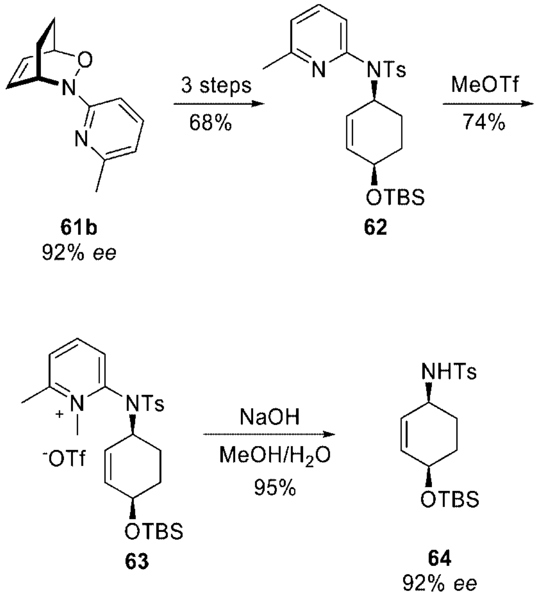
Scheme 16. Reaction with various 2-nitrosopyridines.



Scheme 17. Effects of ligand on enantioselectivity.

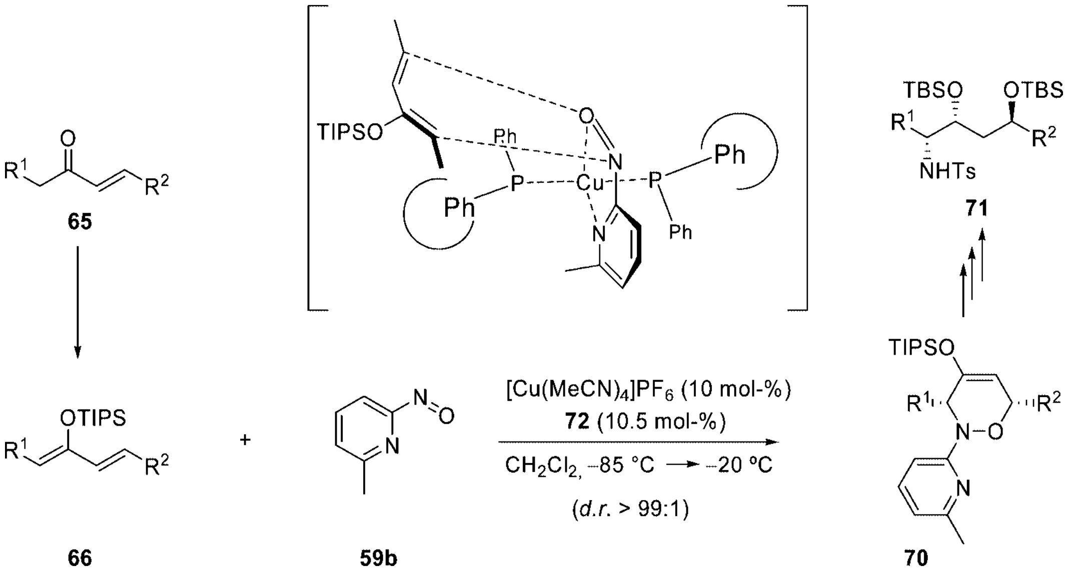


Scheme 18. Reaction with substituted 1,3-dienes.

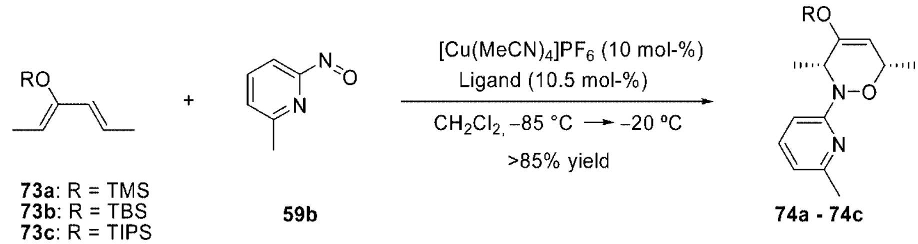


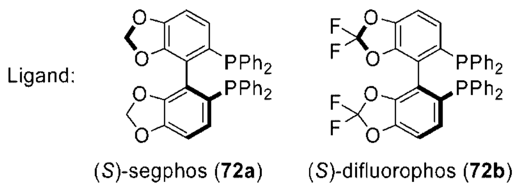
Scheme 19. Conversion to protected amino alcohol.

Significant broadening in the scope of the reaction was achieved by the use of the 2-silyloxy-1,3-diene **66** as diene, which allowed us to apply this transformation to acyclic dienes (Scheme 20).[41] The bulkiness of the substituents on the silicon atom played a crucial role in achieving high enantioselectivity, where their role is to force the diene to form a *s-cis* configuration in favor of the concerted [4+2] cycloaddition reaction (Scheme 21). The OTIPS group proved to be the best among the silyloxy groups we tried, and together with copper(I)-(*S*)-difluorophos catalyst, complete enantioselectivity was observed. Importantly, the reaction proceeded with complete regioselectivity giving the 4-triisopropylsilyloxy-3,6-dihydro-1,2-oxazine derivatives **70** in a single step. The product was further efficiently transformed to the protected chiral amino alcohol **71**. Wide ranges of substrates were applicable to this method, and functionalized dienes containing protected alcohol, heteroaromatics and esters proceeded with good enantioselectivity. This method provides an easy access to protected chiral amino alcohols with three stereocenters starting from simple enones **65**.



Scheme 20. Catalytic asymmetric nitroso Diels–Alder reaction with acyclic dienes.





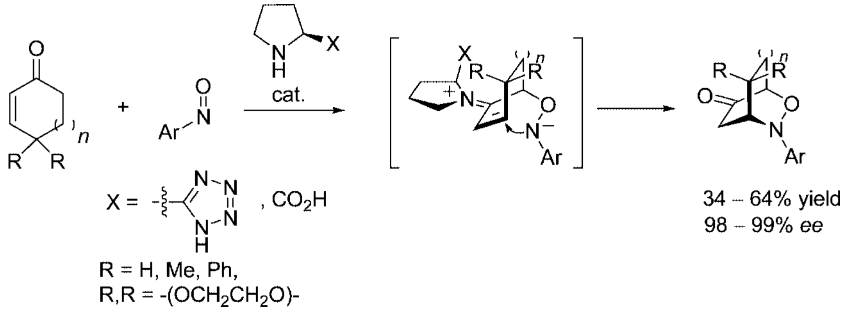
Silyloxydiene	ligand	*ee* [%]
73a	**72a**	16
73b	**72a**	84
73c	**72a**	98
73c	**72b**	>99

Scheme 21. Effect of size of silicon group on enantioselectivity.

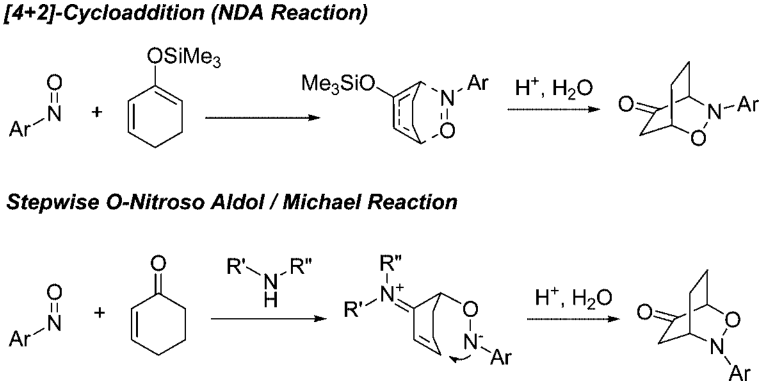
Enantioselective Tandem *O*-Nitroso Aldol/Michael Reaction

Recently, many groups almost simultaneously reported the enantioselective *O*-selective nitroso aldol reaction using amine-based catalyst.[1,42] On the basis of this reaction, we designed and developed a new pathway to NDA-type bicyclic products (Scheme 22).[43] Two roles were expected for the amine catalyst. One was the formation of enamine for enantioselective *O*-nitroso aldol reaction and the other was activation of the enone through an iminium intermediate to facilitate the Michael reaction of aminooxy anion.[44] The reaction was performed with enone with aryl nitroso compounds in the presence of pyrrolidine-based catalyst to give the formal NDA adducts in moderate yields with complete enantioselectivities. An interesting fact is that the regioselectivity of the product is opposite from that of the NDA adduct from the "normal" concerted [4+2] pathway (Scheme 23).

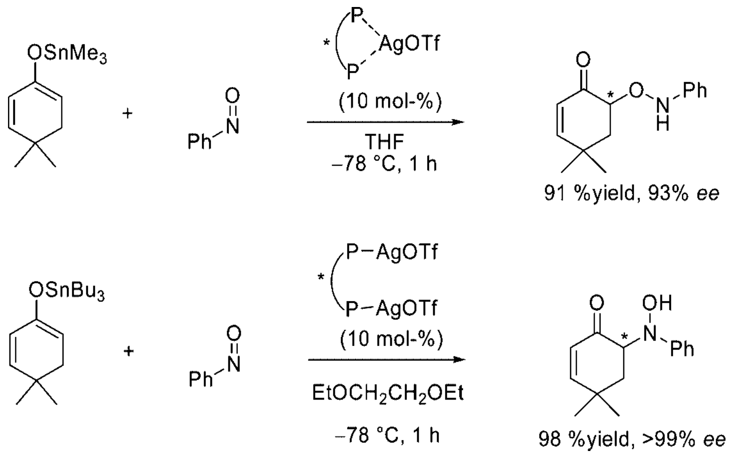
We also found that the reactions of stanyloxy diene with nitrosobenzene in the presence of selectively prepared silver-BINAP complexes gave *O*- or *N*-nitroso aldol adducts, respectively, with high enantioselectivities (Scheme 24). Considering that no cyclized product was obtained from this reaction, and attempts to cyclize these products proceeded without success, the smooth cyclization depicted in



Scheme 22. Enantioselective tandem *O*-nitroso aldol/Michael reaction.



Scheme 23. Regioselectivity of NDA reaction and tandem *O*-nitroso aldol/Michael reaction.



Scheme 24. Enantioselective *O*- or *N*-nitroso aldol reaction in the presence of silver-BINAP complexes.

Scheme 22 must have originated from the steric requirements of enamine and/or the electronic effect of the intermediate ion pair.

Conclusion

The asymmetric NDA reaction has been used as a key reaction in the synthesis of natural products and biologically important products. Until very recently, steady improvements in this methodology were focused only on developing new chiral nitroso compounds to achieve a diastereoselective version of this reaction. The enantioselective NDA reaction is a great challenge to chemists as nitroso compounds are highly reactive and have some special properties. Many new aspects in nitroso chemistry have recently been found along with the advances in enantioselective nitroso chemistry. A chiral ruthenium catalyst which catalyzes the oxidation of hydroxamic acid can, in turn, accelerate the cyclization step to induce enantioselectivity. The chiral induction is also possible with a chiral Lewis acid when an appropriate nitroso compound is used to form a chelate monomer complex.

Catalytic asymmetric NDA reaction has just gotten started, and we feel fortunate that we have a chance to contribute to this chemical field. We hope and believe that the next decade will see great development in this interesting chemistry.

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