

The Synthesis and Transformation of Nitrones for Organic Synthesis

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ABSTRACT

Nitrones are important compounds and are highly useful in many aspects. The first part describes the methods for synthesis of nitrones, which are useful and environmentally friendly. Catalytic oxidations, condensations, and other useful reactions are described. The nitrones thus obtained are key intermediates for the synthesis of biologically important nitrogen compounds. The second part describes the fundamental transformations of nitrones, which will provide the strategies and means for the construction of nitrogen compounds. The reactions with nucleophiles or radicals, C—H functionalization, and various addition reactions are described. The last reactions are particularly important for highly selective carbon—carbon bond formations. 1,3-Dipolar cycloaddition reactions are excluded because the size of the review is limited and excellent reviews have been published in *Chem. Rev.*

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1. INTRODUCTION

Nitrones are easily accessible materials and highly useful substrates for selective organic synthesis. Various catalytic, selective, and environmentally friendly methods for the synthesis of nitrones have been developed. In addition to condensation of *N*-monosubstituted hydroxylamines and the reaction of oximes, catalytic oxidations of *N,N*-disubstituted hydroxylamines, secondary amines, imines, and *N*-alkyl-substituted α -amino acids have been established. The nitrones thus obtained are highly useful for the synthesis of biologically

important nitrogen compounds. The unique properties of nitrones reflect fundamental transformation reactions, which include reactions of nitrones with nucleophiles or radicals, C—H functionalization, and various cycloaddition reactions. These reactions are extremely important because selective carbon—carbon bond formations can be carried out diastereo- and enantioselectively, which can be used in various organic syntheses. Nitrones are particularly useful in comparison with the corresponding imines because of ease of handling, usual stability, ready availability, and prompt reactivity. The diastereo- and enantioselective addition reactions to nitrones can be carried out with ease because of the configurational stability of nitrones and in some cases the chelation effect of oxygen. This review provides a brief survey and describes the recent progress in nitrone chemistry and the keys to apply to various fields of science. Several reviews of nitrones¹⁻¹³ were published more than 10 years ago and recent reviews have described special subjects of nitrones.¹⁴⁻¹⁶ 1,3-Dipolar cycloaddition is not described here because the size of the review is limited and excellent reviews have been published in *Chem. Rev.* by K. A. Jørgensen (1998),¹⁷ M. P. Sibi (2008),¹⁸ and K. Maruoka (2011).¹⁹ Recently, a comprehensive account on cycloaddition reactions of cyclic nitrones to alkenes has also been published in *Org. React.*²⁰

2. SYNTHESIS OF NITRONES

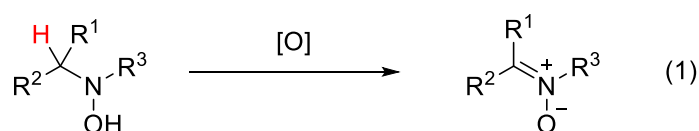
Nitrones are readily obtained by oxidation reactions, condensation reactions of *N*-monosubstituted hydroxylamines, reactions of oximes with electrophiles, and other various methods.

2.1. Oxidation Reaction

Nitrones are readily prepared by the oxidations of *N,N*-disubstituted hydroxylamines, secondary amines, *N*-alkyl- α -amino acids, imines, and isoxazolidines.

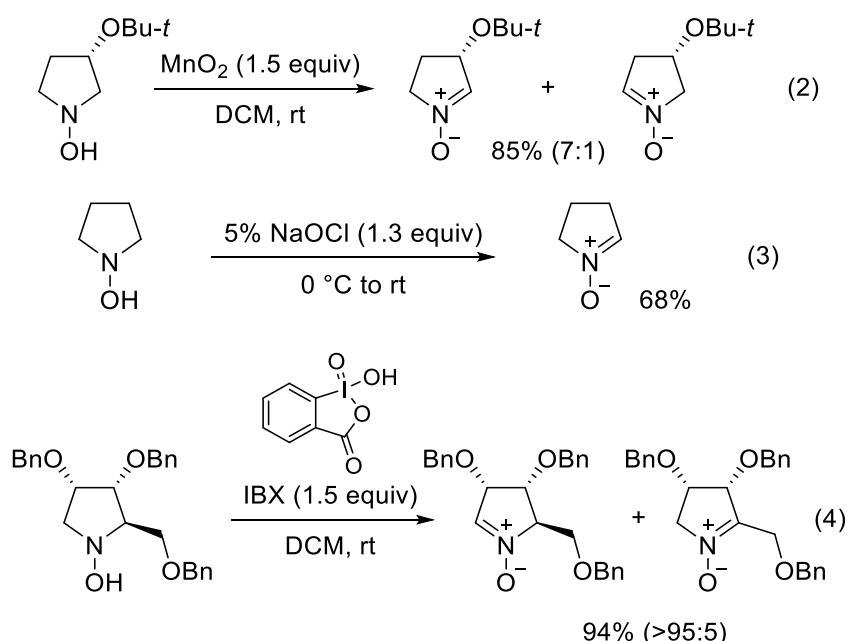
2.1.1. Oxidation of *N,N*-Disubstituted Hydroxylamines

Oxidation of *N,N*-disubstituted hydroxylamines is useful method for synthesis of nitrones (eq 1).



N,N-Disubstituted hydroxylamines are easily oxidized with a variety of oxidizing reagents. An account on methods performed with stoichiometric oxidants has been recently published.²¹ The oxidation with yellow mercuric oxide (HgO) has been utilized for synthesis of natural products because of the high regioselectivity in the presence of appropriate substituents.²²

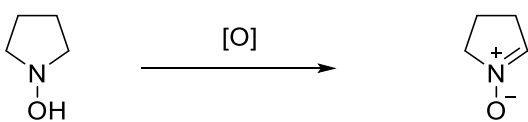
However, HgO is toxic and alternative methods have been explored. Oxidation with MnO₂ is useful and compatible to that of HgO in view of regioselectivity (eq 2).²³ Oxidation with sodium hypochlorite (NaOCl) is a convenient and environmentally friendly; therefore, a large scale production of nitrones can be carried out (eq 3).²⁴ Hypervalent iodine reagent, *o*-iodoxybenzoic acid (IBX), is a highest regioselective oxidant for preparation of aldonitrones in the absence of directing substituents (eq 4).^{25,26} The oxidations with 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO)²⁷ and triphenylbismuth carbonate²⁸ proceed with high efficiency.



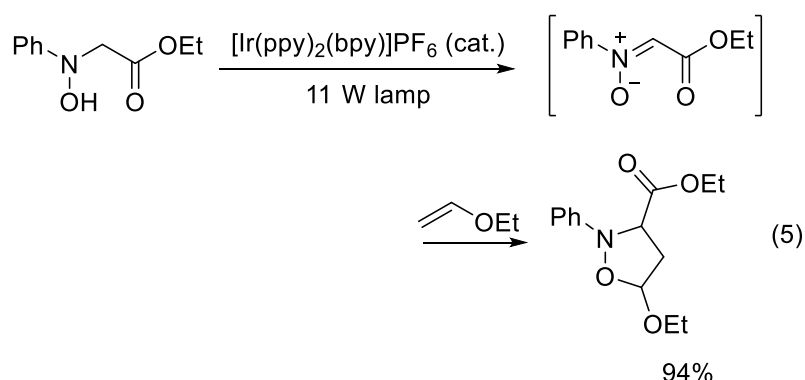
The catalytic oxidation was reported by Murahashi and coworkers for the first time with palladium black catalyst in 1983.²⁹ The aerobic oxidation can be catalyzed by gold nanoparticles supported on silica (Au/SiO₂)³⁰ or unsupported nanoporous gold (AuNPore)³¹ highly efficiently. Similarly, rhodium nanoparticles supported on carbon nanotube (Rh/CNT) catalyze the aerobic oxidation of hydroxylamines.³² Aerobic oxidation of hydroxylamines has also been performed using tetra-*n*-propylammonium perruthenate (*n*-Pr₄NRuO₄, TPAP) catalyst³³ as an environmentally benign extension of the method utilizing TPAP in conjunction with *N*-methylmorpholine *N*-oxide (NMO) as an oxidant.³⁴

The catalytic oxidation can be also performed using oxidants such as hydrogen peroxide in the presence of methyltrioxorhenium (MeReO₃, MTO) catalyst. Complete conversion and high yields were obtained using poly(4-vinylpyridine)—MTO (PVP/MTO) and microencapsulated polystyrene—MTO (PS/MTO) catalysts.³⁵ The representative examples are summarized in Table 1.

Table 1. Catalytic Oxidation of *N,N*-Disubstituted Hydroxylamines

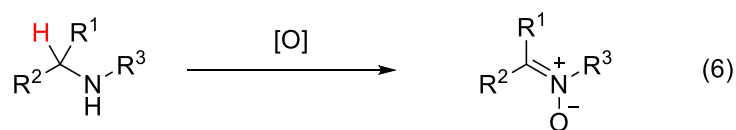
				
oxidant	catalyst	condn	yield (%)	ref.
air	Pd	H ₂ O, 80 °C	95	29
air	Au/SiO ₂	MeOH, reflux	100	30
air	Rh/CNT	MeOH, rt	89	32
O ₂	TPAP	DCM, rt	94	33
NMO	TPAP	MeCN, rt	100	34
H ₂ O ₂	MTO, py	EtOH, rt	98	35
H ₂ O ₂	PS/MTO	EtOH, rt	98	35

An example of asymmetric oxidation has been carried out using Jacobsen catalyst; however, the selectivity was modest.³⁶ Visible-light photoredox-catalyzed oxidation in the presence of water gives nitrones, which are trapped with alkenes (eq 5).³⁷



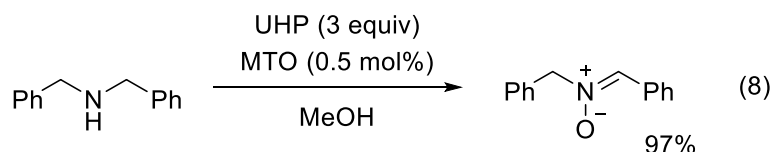
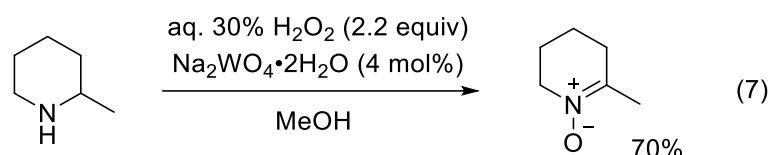
2.1.2. Oxidation of Secondary Amines

Direct oxidation of secondary amines is the most convenient method for synthesis of nitrones (eq 6).



The method was discovered in 1984 by Murahashi and coworkers by catalytic oxidation

with aqueous 30% hydrogen peroxide in methanol in the presence of $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ (Method A).³⁸ This method is very useful and has been used for preparative scale synthesis (eq 7).^{39,40} Aqueous hydrogen peroxide is a cheap and green oxidant; however, separation of water soluble products has a problem. Marcantoni and coworkers demonstrated that in case the urea complex with hydrogen peroxide (UHP) can be used (Method B).⁴¹ Various catalysts such as SeO_2 (Method C),⁴² MTO (Methods D and E) (eq 8),⁴³⁻⁴⁵ (trialkanolamino)titanium(IV) complexes (Method F),⁴⁶ and platinum(II) complex (Method G)⁴⁷ have been used for the oxidation with hydrogen peroxide. Alkyl hydroperoxides such as cumyl hydroperoxide (CHP) and *t*-butyl hydroperoxide can be used as terminal oxidants in combination with (triphenolatoamino)titanium(IV) complexes (Method H).⁴⁸ For comparison of the various methods for the oxidations of 1,2,3,4-tetrahydroisoquinoline are summarized in Table 2.



The oxidation reactions can be also carried out with heterogeneous catalysts such as TS-1 (Method I),⁴⁹ peroxotungstophosphate ($[\text{C}_5\text{H}_5\text{N}^+(\text{CH}_2)_{15}\text{CH}_3]_3\{\text{PO}_4[\text{W}(\text{O})(\text{O}_2)_2]_4\}^{3-}$, PCWP) (Method J),⁵⁰ Mg-Al-Ot-Bu hydrotalcite,⁵¹ and $[\text{MoO}_3(\text{bipy})][\text{MoO}_3(\text{H}_2\text{O})]$.⁵²

As a metal free methodology, Oxone® (Method K)⁵³ in biphasic system and dimethyldioxirane (DMD)⁵⁴ can be used. The method is useful because of tolerance with a variety of functional groups. *C*-Phenyl-*N*-phenylsulfonyloxaziridine (Davis reagent),^{55,56} has also been used; however, the laborious and potentially unsafe Davis oxidation is replaced by a safe, reproducible, and scalable oxidation using *m*-chloroperbenzoic acid (*m*-CPBA).^{57,58}

Biomimetic catalytic oxidation can be performed with molecular oxygen and hydrazine hydrate in 2,2,2-trifluoroethanol with organocatalyst, 3-methylflavinium perchlorate ($\text{FlEt}^+ \cdot \text{ClO}_4^-$) (Method L).⁵⁹⁻⁶¹

Table 2. Catalytic or Stoichiometric Oxidation of 1,2,3,4-Tetrahydroisoquinoline

method	catalyst	oxidant and conditions	yield (%)	ref

A	Na ₂ WO ₄	aq. 30% H ₂ O ₂ , MeOH, 0 °C to rt	85	39
B	Na ₂ WO ₄	UHP, MeOH, rt	80	41
C	SeO ₂	aq. 30% H ₂ O ₂ , MeOH, 0 °C	89	42
D	MTO	UHP, MeOH, rt	82	43
E	MTO	50% H ₂ O ₂ , EtOH, rt	90	44
F	Ti(IV)	aq. 70% H ₂ O ₂ , CD ₃ OD, 60 °C	99	46
G	Pt(II)	aq. 35% H ₂ O ₂ , DCM, 50 °C	55	47
H	Ti(IV)	CHP, CHCl ₃ , 60 °C	65	48
I	TS-1	aq. 30% H ₂ O ₂ , MeOH, 60 °C	85	49
J	PCWP	aq. 35% H ₂ O ₂ , CHCl ₃ , rt	90	50
K	—	Oxone®, MeCN—THF, 5 °C	79	53
L	FlEt ⁺ •ClO ₄ [−]	O ₂ , NH ₂ NH ₂ •H ₂ O, CF ₃ CH ₂ OH, 60 °C	85	59

It is noteworthy that various nitrones have been used as key intermediates for natural product synthesis as shown in Figure 1. Typically, anticancer compound stephacidin B was synthesized by Baran and coworkers by dimerization of avrainvillamide, which was obtained by the oxidation of the corresponding amine with hydrogen peroxide in the presence of SeO₂ catalyst.⁶²

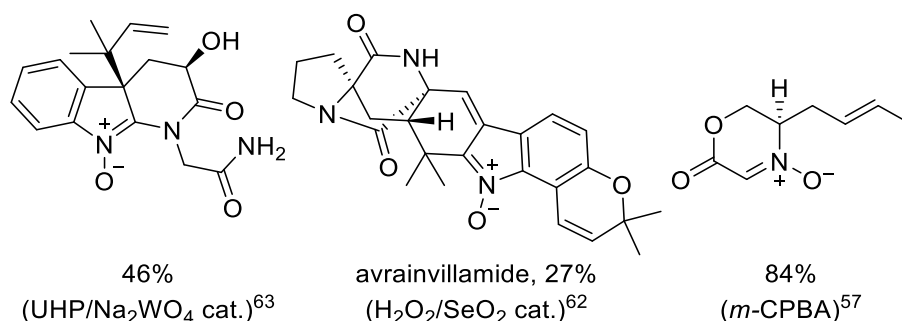
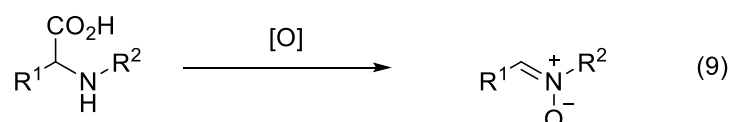


Figure 1. Key intermediates for synthesis of biologically important nitrogen compounds

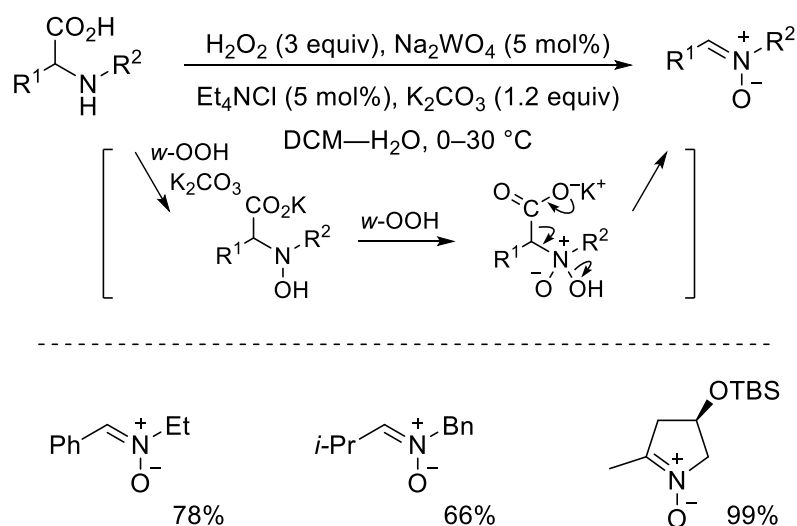
2.1.3. Oxidation of *N*-Alkyl- α -amino Acids

Oxidation of *N*-alkyl- α -amino acids with hydrogen peroxide gives nitrones *via* decarboxylative oxidation regioselectively (eq 9). This single step method is highly useful for regioselective synthesis of nitrones, particularly various chiral nitrones.

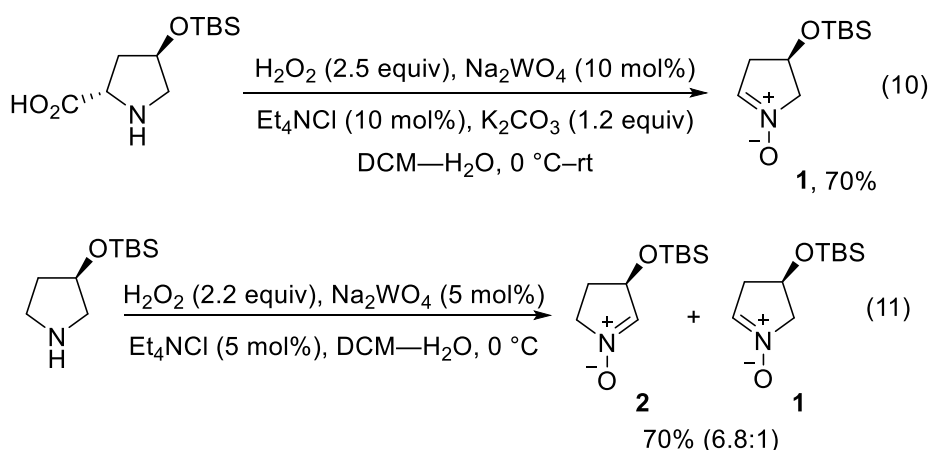


Oxidation of *N*-alkyl- α -amino acids with hydrogen peroxide does not proceed in the presence of Na₂WO₄ or SeO₂ catalyst alone; however, addition of an equivalent of base such as K₂CO₃ and phase transfer catalyst gives nitrones without formation of isomeric nitrones (Scheme 1).⁶⁴

Scheme 1. Decarboxylative Oxidation of *N*-Alkyl- α -amino Acids

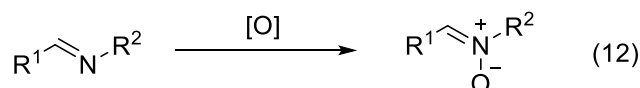


Catalytic oxidation of *trans*-4-(*tert*-butyldimethylsilyloxy)-L-proline under the present conditions gives enantiomerically pure (4*R*)-4-(*tert*-butyldimethylsilyloxy)-1-pyrroline *N*-oxide (**1**) exclusively (eq 10). In contrast, the catalytic oxidation of (3*R*)-3-(*tert*-butyldimethylsilyloxy)pyrrolidine gives (3*R*)-3-(*tert*-butyldimethylsilyloxy)-1-pyrroline *N*-oxide (**2**) along with the isomer **1** (**2**/**1** = 6.8:1) (eq 11),⁶⁵ although enantiomerically pure nitrone **2** was obtained by column chromatography in 61% yield.⁶⁶

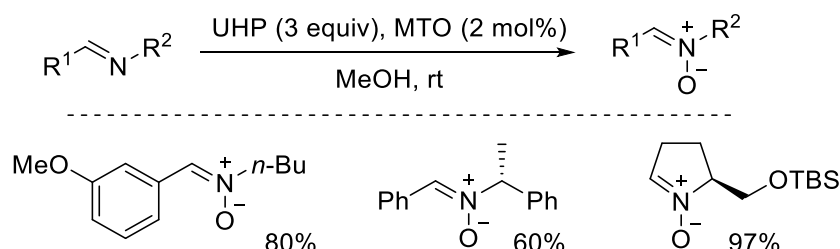


2.1.4. Oxidation of Imines

Imines can be converted into nitrones using an appropriate oxidant (eq 12). Goti and coworkers found convenient method for oxidation of benzylic and cyclic imines into the corresponding nitrones upon treatment with UHP in the presence of catalytic amount of MTO (Scheme 2).⁶⁷ This reaction is general and enantiomerically pure imines can be converted without loss of enantiopurity.⁶⁸

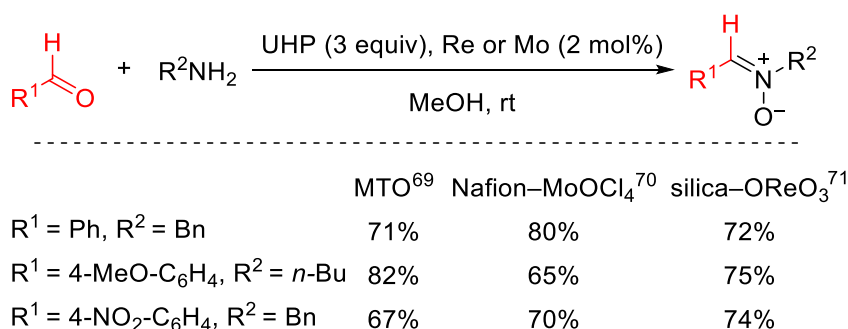


Scheme 2. Catalytic Oxidation of Imines



Goti and coworkers discovered green, direct method for synthesis of nitrones from primary amines and aromatic aldehydes using UHP *via* imines.⁶⁹ Thus, one-pot reaction of a mixture of aromatic aldehydes, primary amines, and UHP with MTO catalyst in methanol gives the corresponding nitrones. Using immobilized catalyst systems such as Nafion-immobilized molybdenum(VI) oxychloride catalyst—UHP,⁷⁰ silica-immobilized oxorhenium catalyst—UHP,⁷¹ and graphite oxide catalyst—Oxone®,⁷² similar direct synthesis of nitrones from primary amines and benzaldehyde derivatives are carried out (Scheme 3).

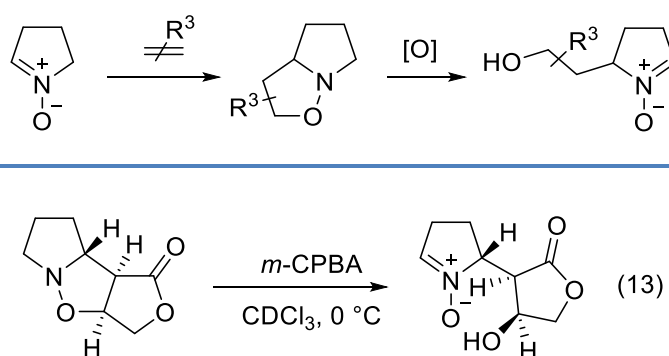
Scheme 3. Synthesis of Nitrones from Benzaldehydes and Primary Amines



2.1.5. Oxidation of Isoxazolidines

Oxidation of isoxazolidines, easily accessible by 1,3-dipolar cycloaddition of nitrones with alkenes, gives nitrones upon treatment with peracids. LeBel demonstrated that the oxidation of tricyclic isoxazolidines with peracids affords the γ -hydroxy ketonitrones.⁷³ This method was extended to regioselective synthesis of substituted nitrones. The oxidation of perhydropyrrolo[1,2-*b*]isoxazoles gives the less substituted aldonitrones regioselectively (Scheme 4),⁷⁴ and also chiral nitrones can be prepared selectively.⁷⁵ The oxidation of bicyclic isoxazolidines with *m*-CPBA gives the corresponding cyclic nitrones (eq 13).⁷⁶

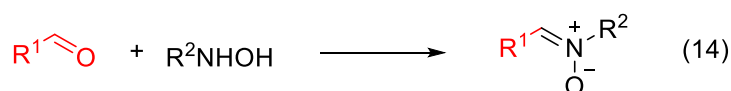
Scheme 4. Synthesis of Nitrones from Isoxazolidines



2.2. Reaction of *N*-Monosubstituted Hydroxylamines

2.2.1. Reaction with Aldehydes and Ketones

The condensation of *N*-monosubstituted hydroxylamines with aldehydes or ketones gives the corresponding nitrones without affecting functional groups (eq 14).



The condensation of *N*-alkyl-, *N*-alkenyl-, *N*-aryl-substituted hydroxylamines with alkyl aldehydes generates nitrones.⁷⁷ The reaction can be carried out in the presence of MgSO_4 to give *Z*-isomers. Typically, *N*-benzyl-2,3-*O*-isopropylidene-D-glyceraldehyde nitrone (**3**) is prepared by condensation of the chiral aldehydes derived from D-mannitol.⁷⁸ Similarly, nitrone **4** is prepared from L-serine.⁷⁹ Nitrones are obtained upon treatment with pyrrolidine by simple filtration through a short pad of silica gel.⁸⁰ Without dehydrating reagent, nitrones are prepared at higher temperature,⁸¹ in a ball-mill without solvent,⁸² or in a microwave apparatus.⁸³

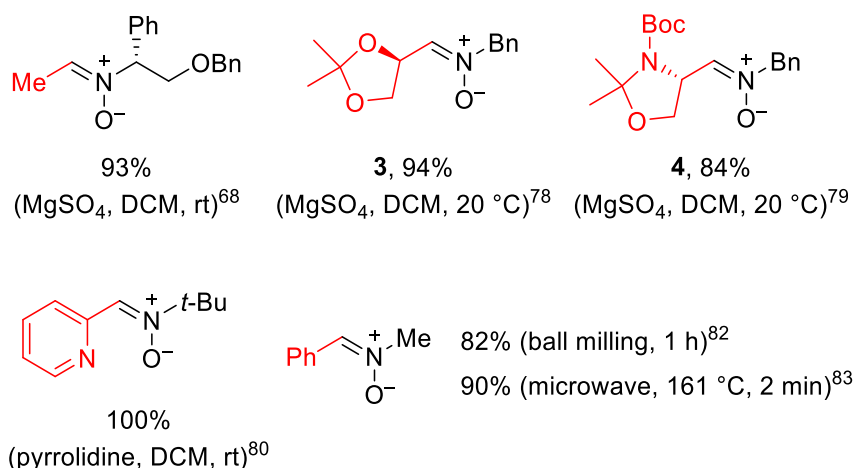
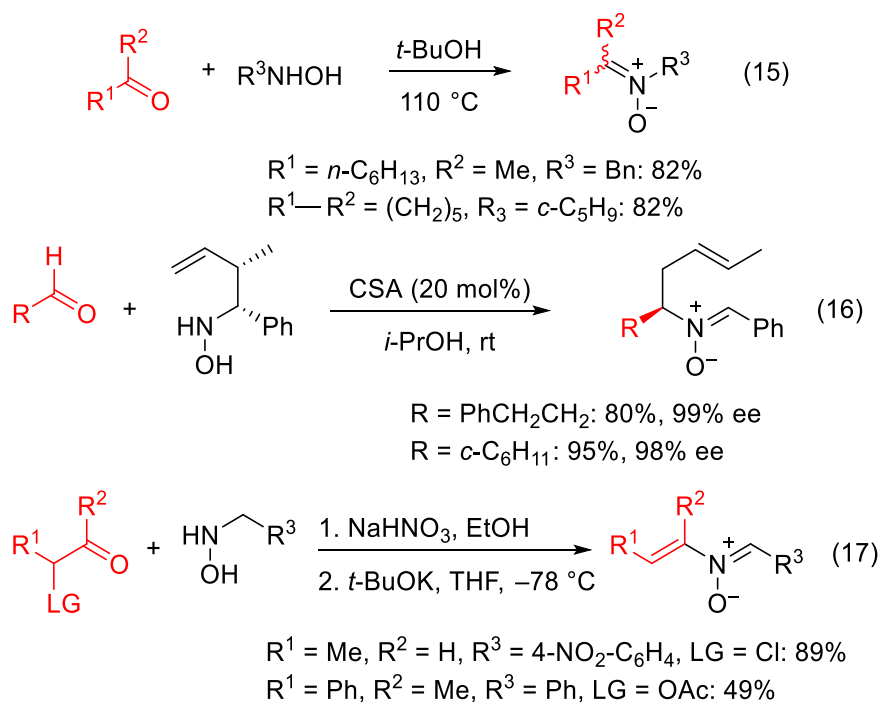
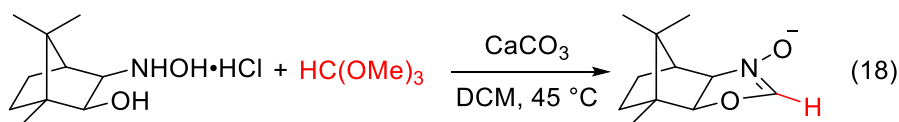


Figure 2. Synthesis of nitrones by condensation reaction

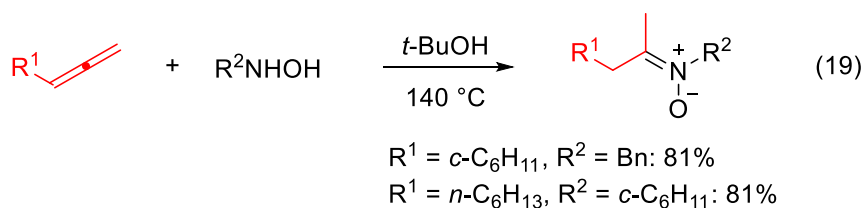
The reaction with cyclic, acyclic, and α,β -unsaturated ketones requires higher temperature (110 °C) (eq 15).⁸⁴ Homoallylic nitrones are prepared from homoallylic hydroxylamines and aldehydes upon treatment with (+)-10-camphorsulfonic acid (CSA) catalyst via the 2-oxonia-[3,3]-sigmatropic rearrangement regioselectively (eq 16).⁸⁵ *N*-Vinyl nitrones have been prepared by a two-step method; the reactions of α -chloroaldehyde or α -phenoxy- or α -acetoxylketone with *N*-benzylhydroxylamines followed by treatment with a base (eq 17).⁸⁶ Oxazoline *N*-oxides (eq 18)⁸⁷ and imidazoline *N*-oxides⁸⁸ are obtained by condensations of heteroatom-substituted hydroxylamines with orthoesters.



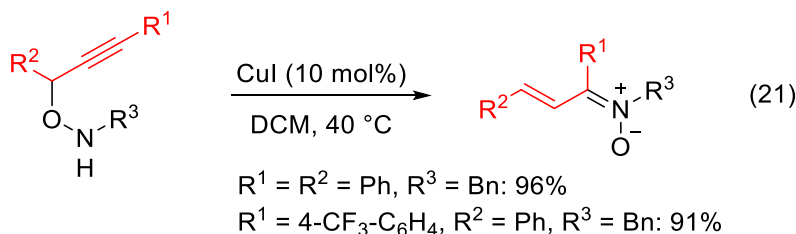
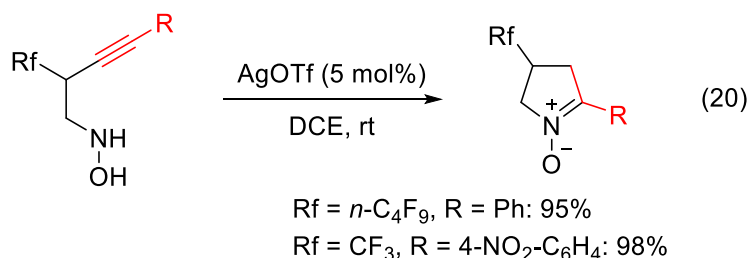


2.2.2. Reaction with Allenes, Acetylenes, and Alkenes

The synthesis of ketonitrones from monosubstituted allenes is performed via a Cope-type hydroamination reaction (eq 19).⁸⁹



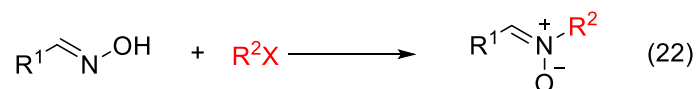
The AgOTf-catalyzed cyclization of *N*-(2-perfluoroalkyl-3-alkynyl) hydroxylamines gives 4-perfluoroalkyl substituted 1-pyrroline *N*-oxides (eq 20).⁹⁰ *N*-Alkylated α,β -unsaturated ketonitrones are synthesized from propargyloxyamines using CuI catalysts (eq 21).⁹¹ This reaction can be rationalized by assuming copper-catalyzed intramolecular hydroamination, followed by electrocyclic ring opening of 3-isoxazoline.



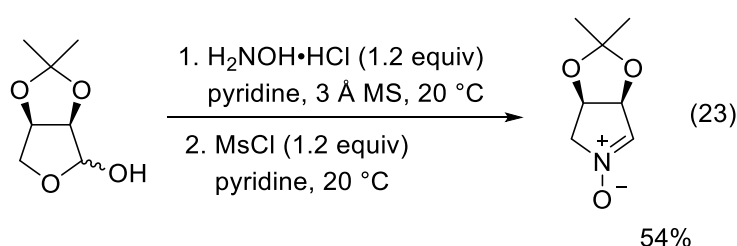
Isoindole nitrones and 3,4-dihydroisoquinoline nitrones are prepared from aryl aldehydes containing ortho-substituted α,β -unsaturated carboxylic acid derivatives and hydroxylamine.⁹²

2.3. Reaction of Oximes

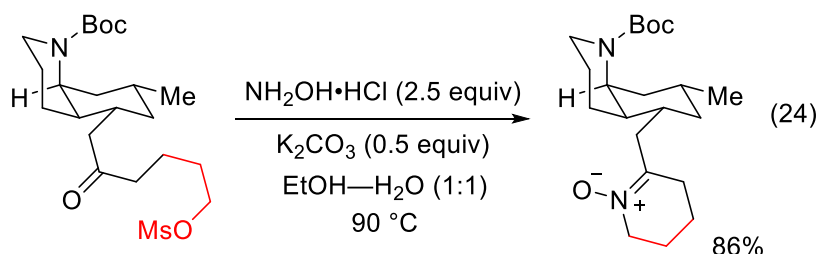
Reaction of oximes with a variety of electrophiles gives nitrones in principle (eq 22).



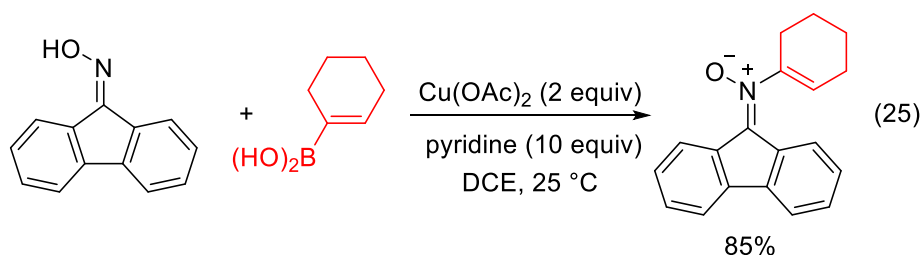
Chiral polyhydroxylated nitrones can be prepared by the intramolecular desilylative cyclizations of carbohydrate-derived ω -iodo-⁹³ or ω -tosyl-*O*-silyloximes.⁹⁴ The procedure was further extended to one-pot processes with in situ formation of silylated⁹⁵ or even free oximes (eq 23).⁹⁶



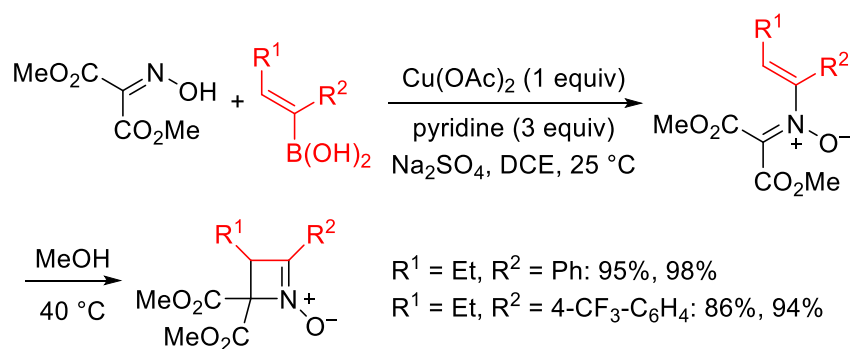
Intramolecular alkylation of oximes has been used for synthesis of natural product of lycoposerramine-Z (eq 24).⁹⁷



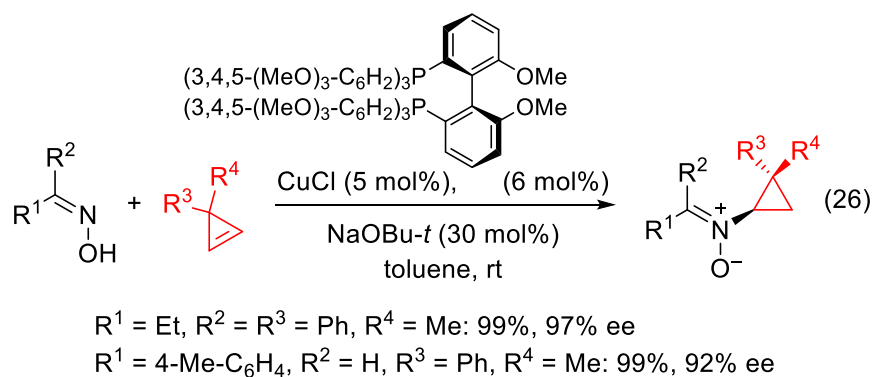
Anderson and coworkers demonstrated that $\text{Cu}(\text{OAc})_2$ -mediated reaction of oximes with alkenylboronic acids gives various types of nitrones. *N*-Vinylnitrones have been prepared from fluorenone oxime by the $\text{Cu}(\text{OAc})_2$ -mediated reactions with alkenylboronic acids (eq 25).^{98,99} Similarly, $\text{Cu}(\text{OAc})_2$ -promoted reactions of malonate-derived oximes with vinylboronic acids give *N*-alkenylnitrones, which undergo 4π -electrocyclization to form azetidine nitrones (Scheme 5).¹⁰⁰



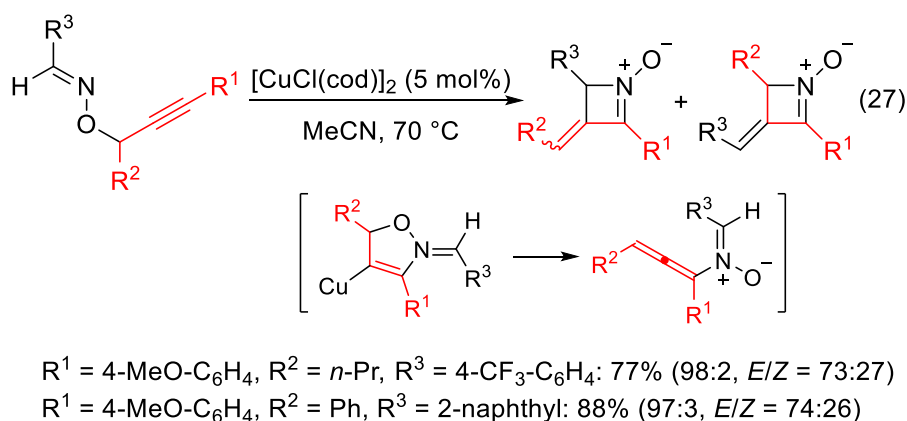
Scheme 5. Preparation of *N*-Alkenylnitrones and Azetidine Nitrones



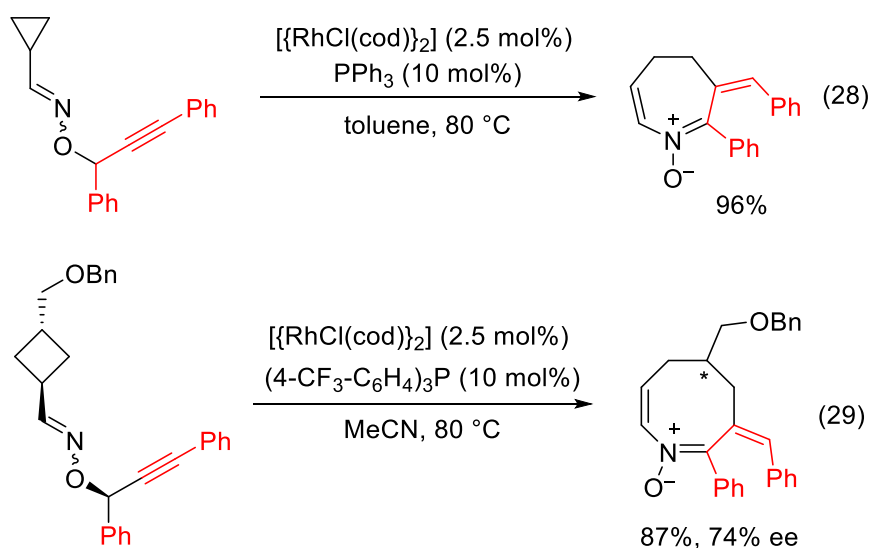
Copper-catalyzed reaction of oximes with cyclopropenes with chiral phosphines gives chiral *N*-cyclopropylnitrones. (eq 26).¹⁰¹



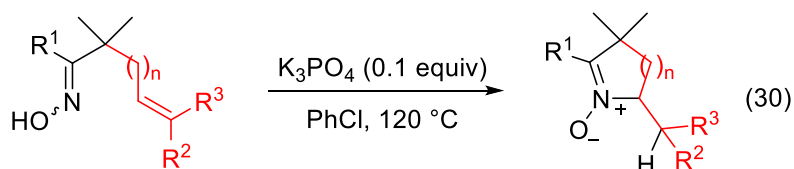
Copper-catalyzed reaction of (*E*)-*O*-propargylic arylaldoximes gives four-membered cyclic nitrones. The reaction involves tandem [2,3]-rearrangement and 4 π electrocyclozation of the *N*-allenynitrones followed by cleavage of the C—N bond (eq 27).^{102,103}



Nakamura and Terada found that rhodium-catalyzed reaction of *O*-propargylic cyclopropylcarbaldoxime gives seven-membered aza-heterocycles under mild conditions (eq 28).¹⁰⁴ Similarly, eight-membered cyclic nitrones can be obtained from *O*-propargylic oximes by rhodium-catalyzed [2,3]-rearrangement/heterocyclization cascade sequence. Optically active oximes undergo the reaction with good levels of chirality transfer (eq 29).¹⁰⁵

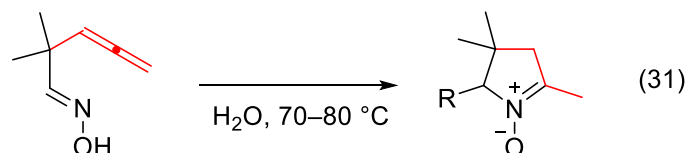


Five-membered cyclic nitrones are prepared simply by hydroamination of alkenyl ketoximes mediated by inorganic base, K_3PO_4 (eq 30).¹⁰⁶ Various five-membered nitrones can be prepared also from allenyl oximes upon treatment of 2,2-dimethylpentane-3,4-dienal oxime with aqueous KOH or with aqueous NH_3 (eq 31).¹⁰⁷ The reaction of oximes with α -ketoacids gives 2,5-dihydrooxazole 3-oxides with an unexpectedly facile and chemoselective annulation (eq 32).¹⁰⁸



$R^1 = 4\text{-MeO-C}_6\text{H}_4$, $R^2 = \text{Ph}$, $R^3 = \text{H}$, $n = 1$: 96%

$R^1 = R^2 = \text{Ph}$, $R^3 = \text{H}$, $n = 2$: 65% (1 equiv of K_3PO_4 at 150 °C)



KOH $R = \text{OH}$: 70%

NH_3 $R = \text{NH}_2$: 73%

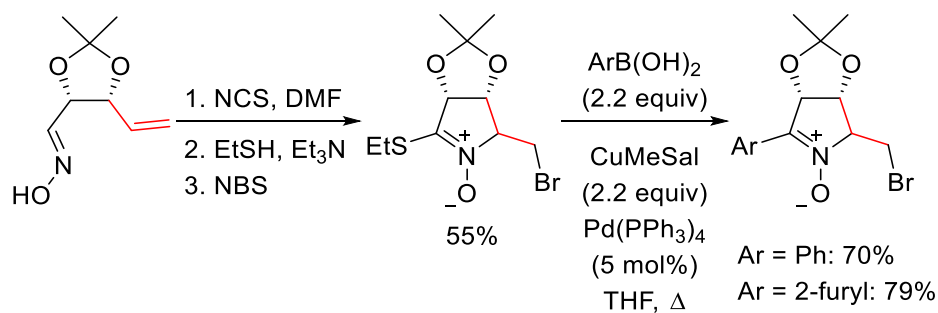


$R^1 = n\text{-C}_7\text{H}_{15}$, $R^2 = \text{Me}$: 92%

$R^1 = n\text{-C}_6\text{H}_{11}$, $R^2 = \text{Ph}$: 73%

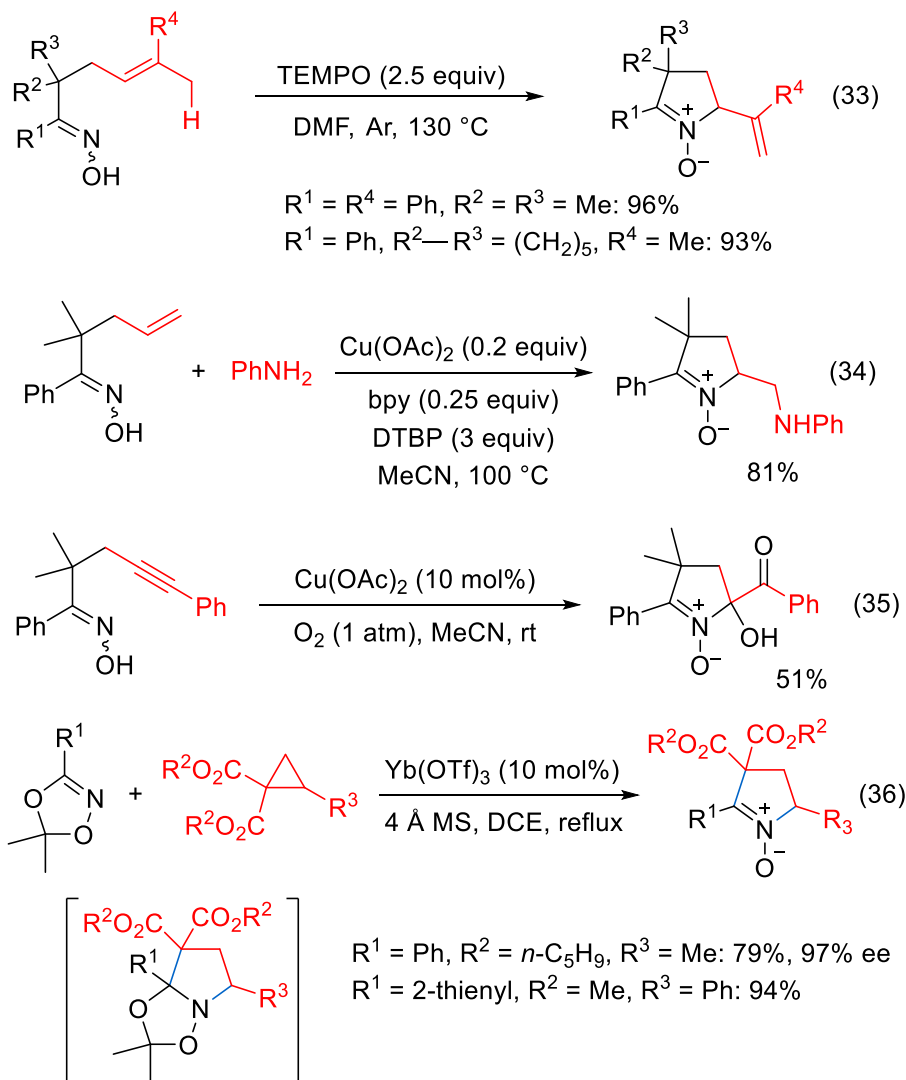
Chiral five-membered cyclic nitrones are prepared from D-ribose. α -Ethylthiooxime undergoes halocyclization upon treatment with NBS to give cyclic nitron, of which ethylthio group can be converted into aryl substituents (Scheme 6).¹⁰⁹

Scheme 6. Preparation of C-Aryl Chiral Cyclic Nitrones

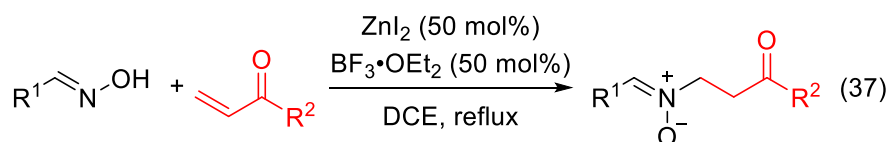


TEMPO-promoted reaction of γ,δ -unsaturated ketoximes gives cyclic nitrones (eq 33). This reaction involves β -hydrogen abstraction and Cope-like elimination.¹¹⁰ Copper-catalyzed oxidative cyclization of γ,δ -unsaturated ketoximes in the presence of aryl amines and di-*tert*-butyl peroxide (DTBP) gives α' -aminomethyl five-membered cyclic nitrones (eq 34).¹¹¹ Similar copper-catalyzed cyclization of internal unactivated alkynes of ketoximes in the presence of molecular oxygen gives cyclic nitrones bearing α -ketols (eq 35).¹¹² The Lewis

acid-catalyzed reaction of donor–acceptor cyclopropanes with 1,4,2-dioxazoles, oxime ether derivatives, gives five-membered cyclic nitrones via stepwise [3 + 2] annulation and the decomposition of the annulation product (eq 36).¹¹³

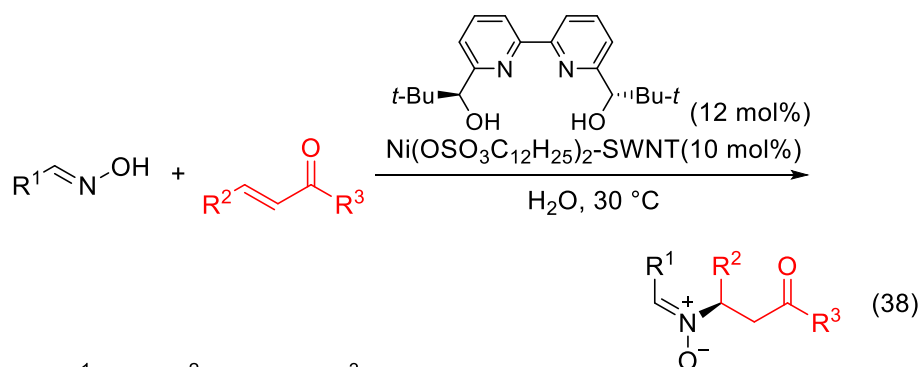


Conjugate addition of oximes to electron deficient alkenes takes place with Lewis acids (eq 37).¹¹⁴ Kobayashi and coworkers discovered very interesting catalytic system that is a homogenized combination of nickel-based Lewis acid–surfactant-combined catalysts and single-walled carbon nanotubes (SWNT). Using this catalyst, asymmetric conjugate addition in water gives optically active nitrones in high yields with excellent enantioselectivities (eq 38).¹¹⁵ *N*-Allylated nitrones are prepared by palladium catalyzed reaction of oximes with allyl acetates under solvent-free conditions (eq 39).¹¹⁶



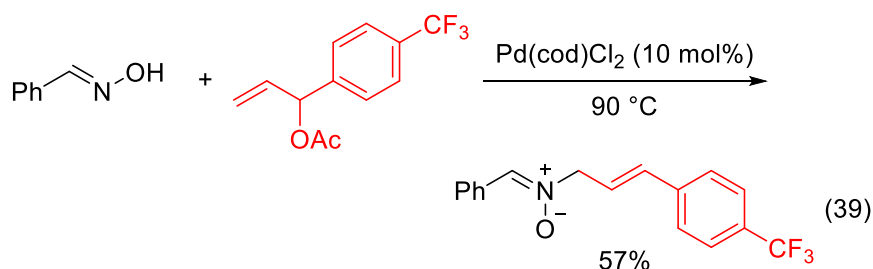
$\text{R}^1 = \text{Ph}, \text{R}^2 = \text{MeO}: 99\%$

$\text{R}^1 = t\text{-Bu}, \text{R}^2 = \text{Me}: 98\% \text{ (rt)}$



$\text{R}^1 = \text{Ph}, \text{R}^2 = n\text{-C}_5\text{H}_9, \text{R}^3 = \text{Me}: 79\%, 97\% \text{ ee}$

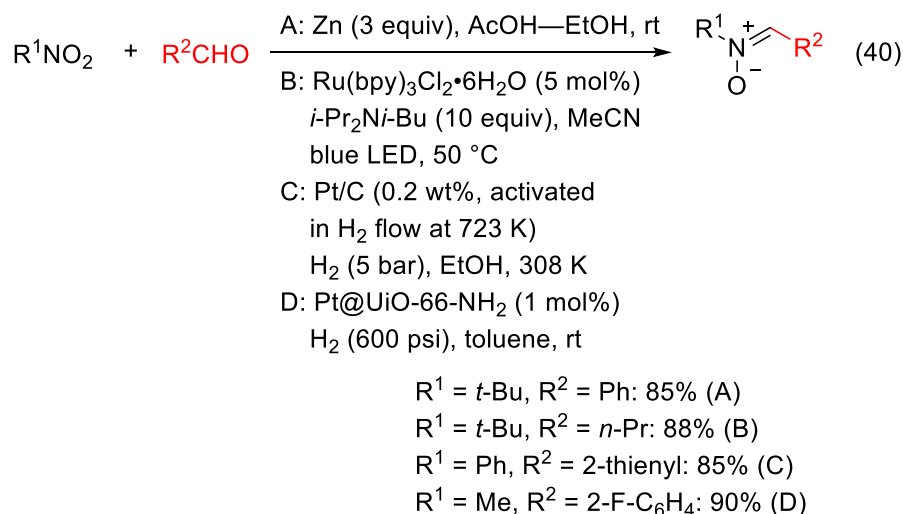
$\text{R}^1 = n\text{-Pr}, \text{R}^2 = \text{Ph}, \text{R}^3 = \text{OEt}: 76\%, 91\% \text{ ee}$



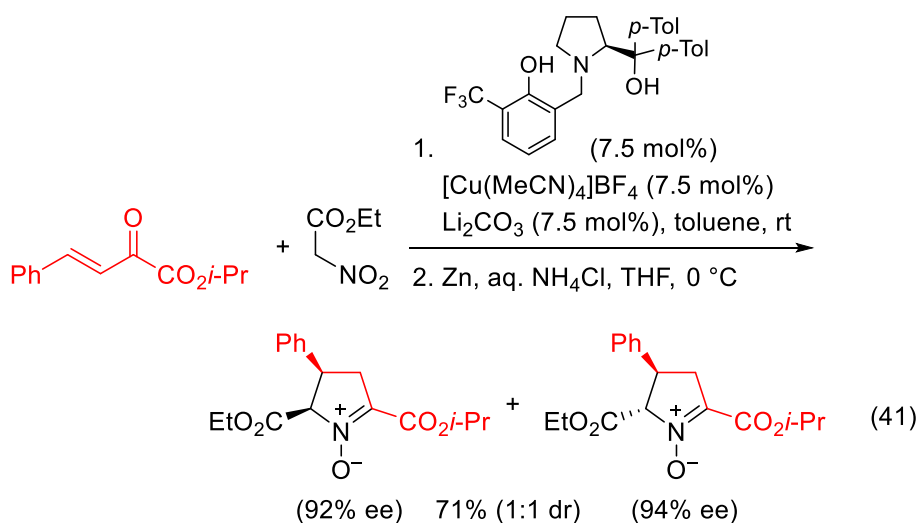
2.4. Other Methods

2.4.1. From Nitro Compounds

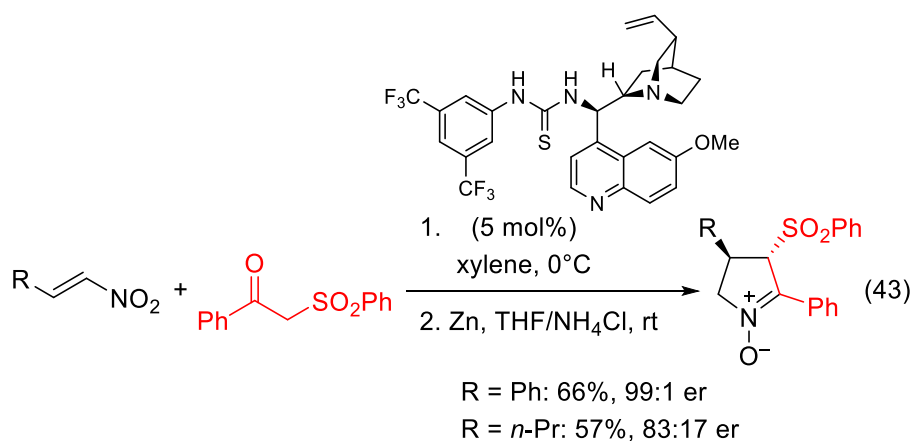
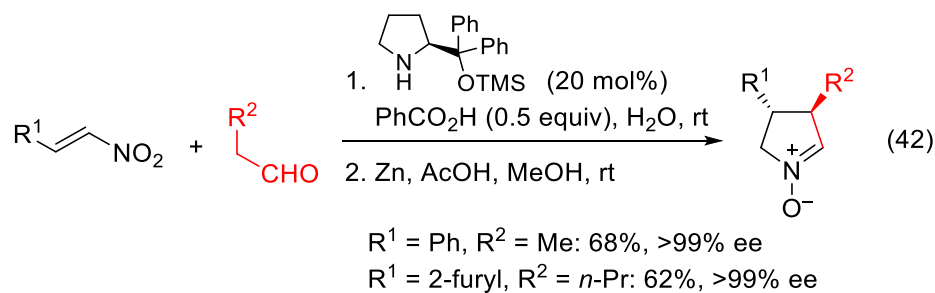
The reaction of nitro compounds with aldehydes under reductive conditions gives nitrones. This method is largely precededented in its intramolecular version for synthesis of cyclic nitrones. The zinc-mediated reduction of nitro compounds in the presence of aldehydes is useful for preparation of aromatic, aliphatic, and highly functionalized sugar-derived nitrones (A, eq 40).¹¹⁷ The reaction with a mixture of a Ru(bpy)₃Cl₂ photoredox catalyst and *i*-Pr₂NEt gives the corresponding nitrones (B, eq 40).¹¹⁸ Furthermore, similar reaction gives nitrones in the presence of H₂ with carbon-decorated platinum nanoparticles (C, eq 40)¹¹⁹ or ultrasmall platinum nanoclusters encapsulated in amine-functionalized Zr-metal-organic framework, Pt@UiO-66-NH₂ (D, eq 40).¹²⁰



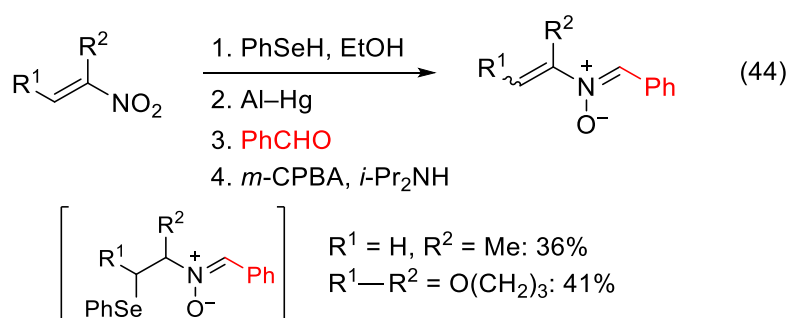
Michael addition of nitro compounds to α,β -unsaturated carbonyl compounds and subsequent reductive cyclization provide a useful procedure for preparation of five-membered cyclic nitrones.¹²¹ Copper-catalyzed Michael addition of nitro esters to β,γ -unsaturated α -ketoesters in the presence of zinc gives cyclic nitrones as a mixture of two separable diastereomers (eq 41).¹²²



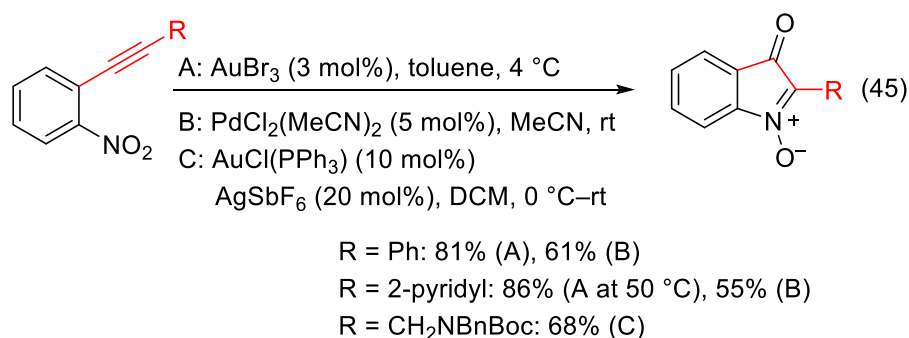
The organocatalytic Michael addition of aldehydes to nitroolefins and in situ reductive cyclization is very convenient method for synthesis of chiral five-membered cyclic nitrones (eq 42).¹²³ Similarly organocatalytic addititon of β -ketosulfones to nitroolefins followed by reductive cyclization gives chiral cyclic nitrones (eq 43).¹²⁴



A general method for synthesis of *N*-vinyl nitrones has been found. Conjugate addition of benzeneselenenol to nitroalkenes followed by reduction gives hydroxylamines, which undergo reaction with aldehydes and subsequent oxidation to provide *N*-vinyl nitrones via *syn*-selenoxide elimination (eq 44).¹²⁵

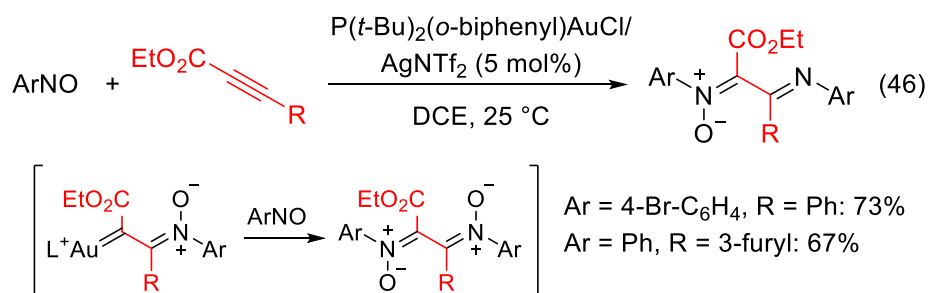


The AuBr₃-catalyzed cyclization of *o*-(alkynyl)nitrobenzenes gives the corresponding isotogens under mild conditions.¹²⁶ This cyclization to isotogens can be also carried out upon treatment with either PdCl₂(MeCN)₂¹²⁷ or AuCl(PPh₃)₃-AgSbF₆¹²⁸ catalyst (eq 45).

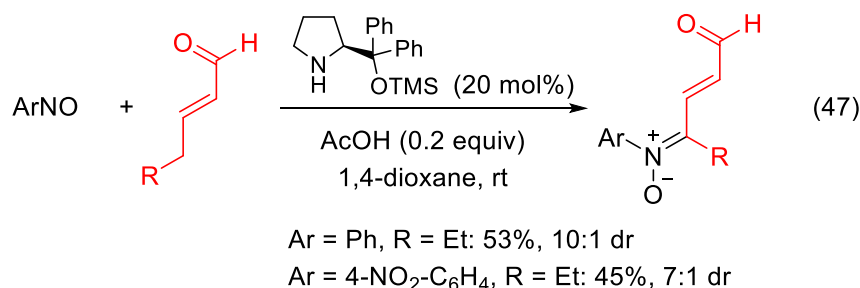


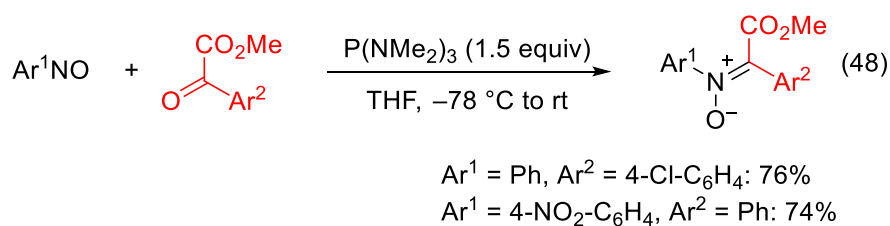
2.4.2. From Nitroso Compounds

Gold-catalyzed reaction of electron-deficient alkynes with nitrosoarenes gives α -imidoylnitrones (eq 46).¹²⁹



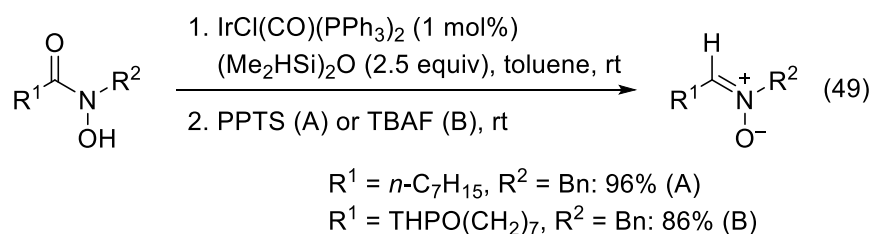
Furthermore, nitron functionality can be introduced directly onto α,β -unsaturated aldehydes at γ -position using nitroso compounds. Thus, the reaction of enal with nitrosobenzene in the presence of a proline-based organocatalyst and AcOH gives the corresponding nitrones (eq 47).¹³⁰ Synthesis of *N*-arylnitrones can be performed by hexamethylphosphorous triamide-mediated addition of 1,2-dicarbonyls to nitroso electrophiles (eq 48).¹³¹





2.4.3. From *N*-Hydroxyamides

Chida and coworkers found a very unique and convenient method for preparation of nitrones. Catalytic reductive transformation of *N*-hydroxyamides in the presence of $\text{IrCl}(\text{CO})(\text{PPh}_3)_2$ and $(\text{Me}_2\text{HSi})_2\text{O}$ followed by addition of pyridinium *p*-toluenesulfonate (PPTS) or tetrabutylammonium fluoride (TBAF) provides nitrones (eq 49). The reaction involves iridium-catalyzed dehydrosilylation, hydrosilylation, and desilylation with sulfonate or fluoride.¹³²



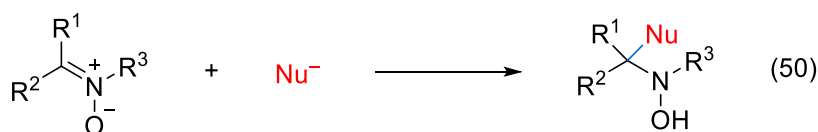
2.4.4. From Aryloxaziridines

Chemoselective ring-opening rearrangement of 3-aryloxaziridines with silver triflate gives nitrones.¹³³ *N-p*-Nitrobenzenesulfonylnitrones are generated by TiCl_4 -catalyzed rearrangement of oxaziridines and undergo cycloaddition with alkenes to give 1,2-isoxazolidines highly diastereoselectively.¹³⁴

3. TRANSFORMATION OF NITRONES

3.1. Reaction with Nucleophiles

Nitrones undergo reactions with a wide range of nucleophiles to give *N,N*-disubstituted hydroxylamines (eq 50).



3.1.1. Reaction with Organometallic Compounds

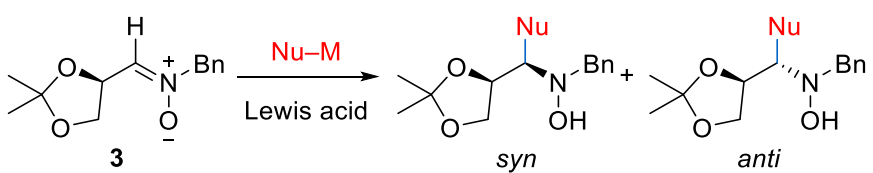
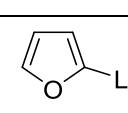
3.1.1.1. Alkylation and Arylation

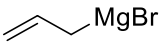
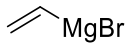
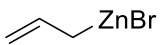
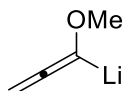
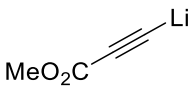
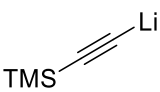
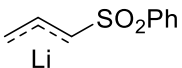
Organometallic reagents such as Grignard reagents and organozinc compounds undergo reaction with nitrones readily to form a carbon—carbon bond at the α -position of nitrogen selectively, and hence, highly useful for synthesis of various compounds, especially biologically important nitrogen compounds.

Diastereoselective reactions of nitrones with organometallic compounds are highly useful, and many key compounds have been prepared. In 2000 Merino and Tejero⁵ and Trombini and coworkers⁶ described excellent reviews on this subject. In 2007 Brandi and Goti described highly valuable review account on asymmetric synthesis using cyclic nitrones.¹⁰

Chiral nitrones are useful for synthesis of nitrogen compounds. Merino and Tejero⁵ demonstrated general routes using α -alkoxy nitrones. This is extremely important, because diastereofacial induction of nucleophiles to chiral nitrones can be controlled effectively. D-Glyceraldehyde-derived nitrone, *N*-benzyl-2,3-*O*-isopropylidene-D-glyceraldehyde nitrone (**3**) led to *syn* adducts, when the nitrone undergoes reaction with a variety of organometallic reagents. The same trend is observed when zinc(II) bromide and trimethylsilyl triflate were used as promoters of the reaction. On the other hand a complete reversal of the stereochemical course of the reaction was observed, when diethylaluminum chloride or boron trifluoride etherate were used as precomplexing agents. In all cases *anti* compounds were obtained preferentially. This method has been applied to various nucleophiles. The representative results are summarized in Table 3. Typically, the reaction of nitrone **3** with 2-furyllithium in THF—Et₂O at $-80\text{ }^{\circ}\text{C}$ gives the *syn* product (*syn/anti* = 96:4) in 92% yield. In contrast, the same reaction in the presence of Et₂AlCl gives the *anti* product (*syn/anti* = 5:95) in 89% yield.¹³⁵

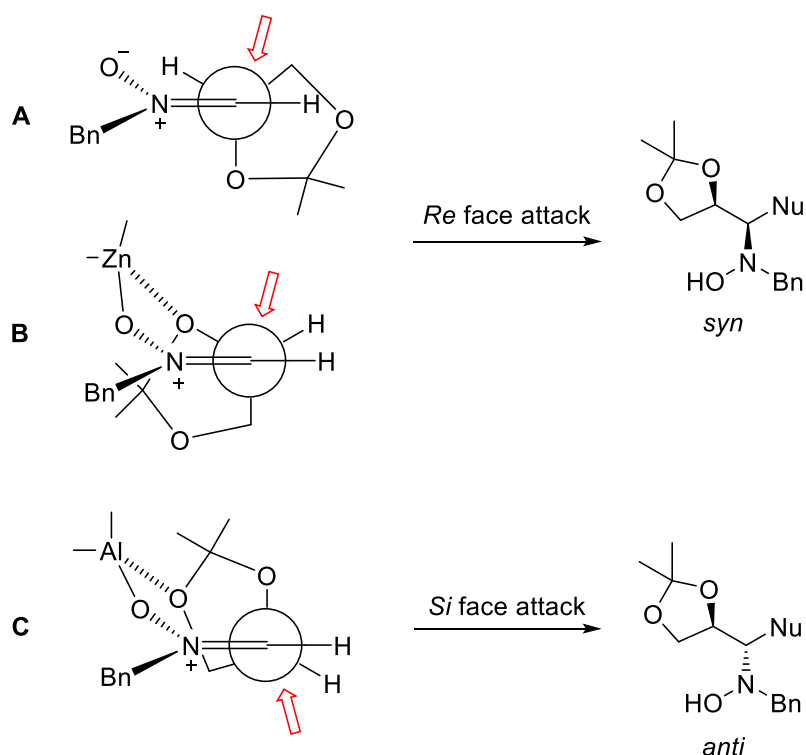
Table 3. Reversal Diastereoselective Reaction of Chiral Nitrone with Various Nucleophiles

					
Nu-M	Lewis acid	condn	<i>syn/anti</i>	yield (%)	ref.
	—	THF, $-60\text{ }^{\circ}\text{C}$	80:20	84	
PhMgBr	ZnBr ₂	Et ₂ O, $-60\text{ }^{\circ}\text{C}$	90:10	86	136
	Et ₂ AlCl	Et ₂ O, $-60\text{ }^{\circ}\text{C}$	5:95	72	
	—	THF—Et ₂ O, $-80\text{ }^{\circ}\text{C}$	96:4	92	135
	Et ₂ AlCl	THF—Et ₂ O, $-80\text{ }^{\circ}\text{C}$	5:95	89	
	ZnBr ₂	Et ₂ O, $-50\text{ }^{\circ}\text{C}$	>95:5	100	137

	BF ₃ •Et ₂ O	THF, -50 °C	5:95	90	
	—	THF, 0 °C	76:24	86	138
	Et ₂ AlCl	Et ₂ O, 0 °C	8:92	86	
	—	THF, 0 °C	25:75	92	139
	Et ₂ AlCl	THF, -40 °C	65:35	80	
	—	THF, -78 °C	98:2	81	140
	Et ₂ AlCl	Et ₂ O, -78 °C	3:97	61	
	—	THF, -80 °C	>95:5	100	141
	Et ₂ AlCl	Et ₂ O, -80 °C	30:70	92	
	—	THF, -80 °C	>95:5	100	142
	Et ₂ AlCl	THF, -80 °C	29:71	96	
	HMPA	THF, -80 °C	98:2	—	143

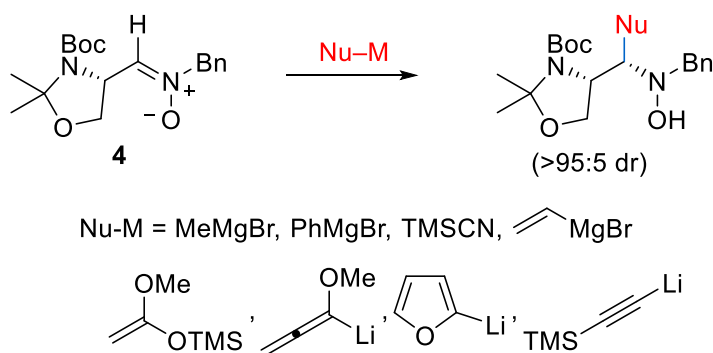
The stereochemical outcome of the reaction of nitrone **3** with PhMgBr is rationalized by assuming Scheme 7. The stereoselection is controlled by diastereoface differentiation of the nitrones. Nucleophilic attack from the less hindered Re face of nitrone in A gives syn hydroxylamines. The precomplexation of nitrones with ZnBr₂ at α-oxygen atom in B leads to the same syn hydroxylamines. In contrast the precomplexation of the nitrones with Et₂AlCl at β-oxygen atom leads to a total reversal of the diastereofacial selectivity in C.¹³⁶

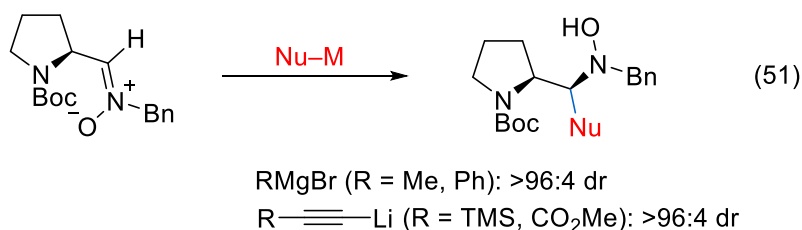
Scheme 7. Reversal Diastereoselectivity in Chiral Nitron.



The stereocontrol of nucleophilic additions to α -aminonitrones does not depend on any Lewis acids, and the reaction to nitronium gives *syn* adducts both in the presence and absence of Lewis acids. The reaction of *N*-benzyl α -aminonitronone **4** derived from L-serine¹⁴⁴ with a variety of nucleophiles gives the corresponding *syn* hydroxylamines as the only detectable diastereoisomers (Scheme 8).⁵ Similarly, L-proline-derived nitronium reacts with Grignard reagents and propargyllithium compounds to give *syn*-hydroxylamines in over 95:5 ratio (eq 51).¹⁴⁵ The diastereoselectivity observed with these α -amino nitrones is much higher than observed in α -alkoxy nitrones.

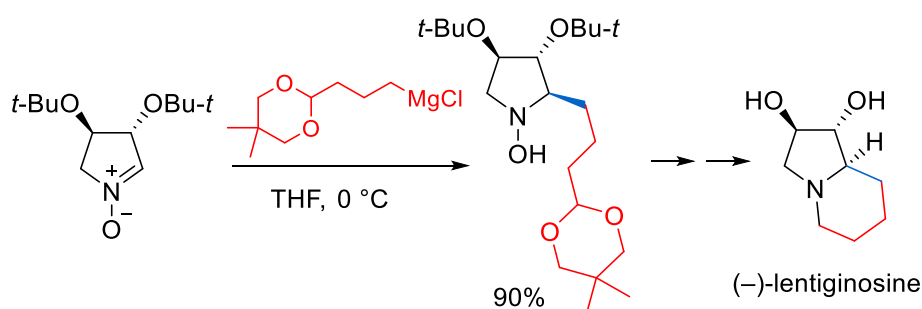
Scheme 8. Diastereoselective Reaction of Chiral α -Aminonitronone with Various Nucleophiles



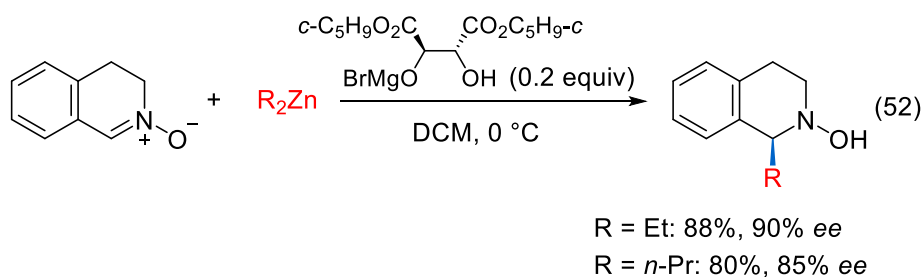


Diastereoselective additions of organometals to 3-alkoxy-substituted cyclic nitrones have been utilized for natural product synthesis.^{146,147} (–)-Lentiginosine was synthesized from the nitronium derived from D-tartaric acid (Scheme 9).¹⁴⁸

Scheme 9. Total Synthesis of (–)-Lentiginosine



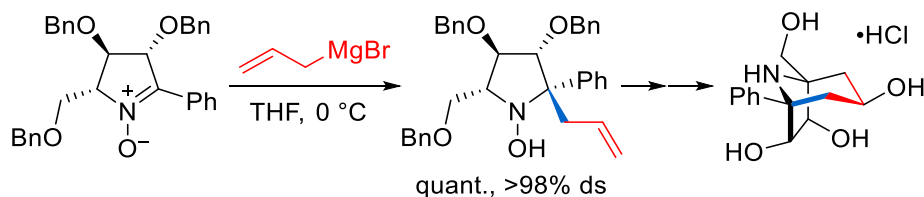
Ukaji and Inomata showed that catalytic asymmetric addition of alkylzinc to 3,4-dihydroisoquinoline *N*-oxides in the presence of magnesium salt of tartaric acid derivatives gives (*S*)-1-alkyl-2-hydroxy-1,2,3,4-tetrahydroisoquinolines with up to 95% ee (eq 52).^{149,150}



3.1.1.2. Allylation

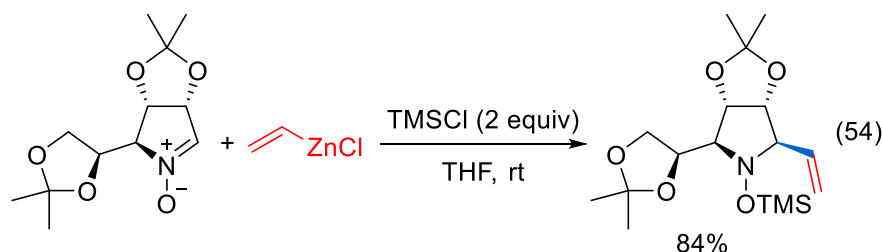
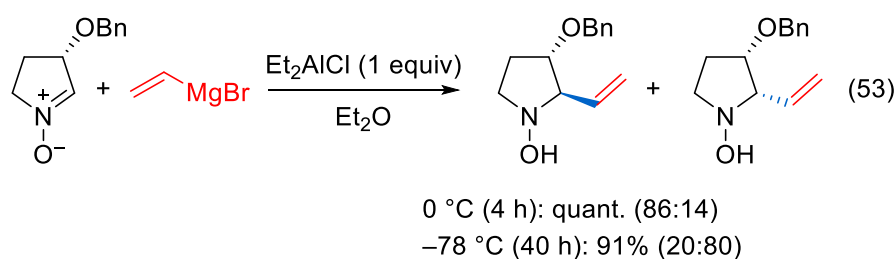
Diastereoselective addition of allylmagnesium bromide is highly useful for the synthesis of polyhydroxynortropane alkaloids (Scheme 10).¹⁵¹

Scheme 10. Sequential Nucleophilic Addition/Cycloaddition



3.1.1.3. Vinylation

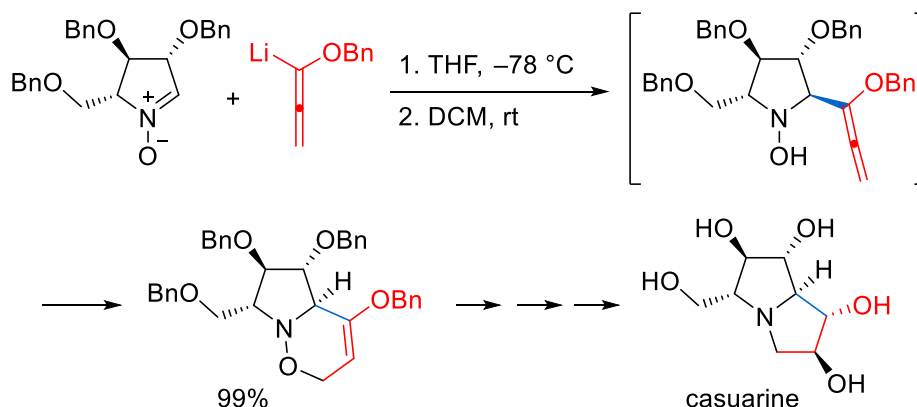
Vinylation is carried out upon treatment with vinylmagnesium bromide. Noteworthy is that a strong dependence on the temperature and the substituent adjacent at the reaction center was observed for the reaction of 3-alkoxy substituted cyclic nitrones in the presence of Et_2AlCl (eq 53).¹⁵² Addition of organozinc halides to nitrones in the presence of trimethylsilyl chloride is very convenient (eq 54). The products can be easily reduced into amines with a zinc–copper couple.¹⁵³



3.1.1.4. Allenylation

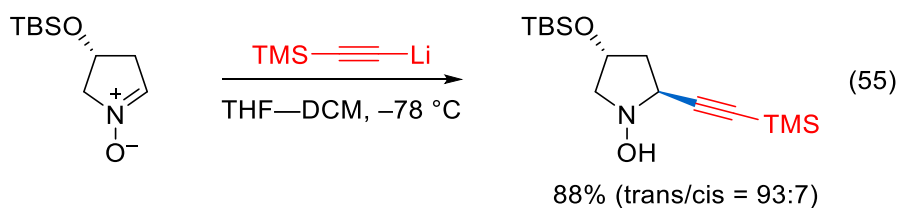
Reissig and coworkers reported that the reaction of lithiated 1-methoxyallene to D-glyceraldehyde-derived chiral nitronium **3** in the presence of Et_2AlCl gives the corresponding *anti* product (*anti/syn* = 97:3) in 61% yield (Table 3).¹⁴⁰ Goti and Reissig reported the diastereoselective addition of D-arabinose-derived nitronium with lithiated 1-benzyloxyallene provides adduct, which is a precursor of casuarine (Scheme 11).¹⁵⁴ Furthermore, they extended this approach to the synthesis of (–)-hyacinthacine B₄ using lithiated 3-methylsubstituted benzyloxyallene.¹⁵⁵

Scheme 11. Nucleophilic Addition of Lithiated 1-Benzyloxyallene and Total Synthesis of Casuarine

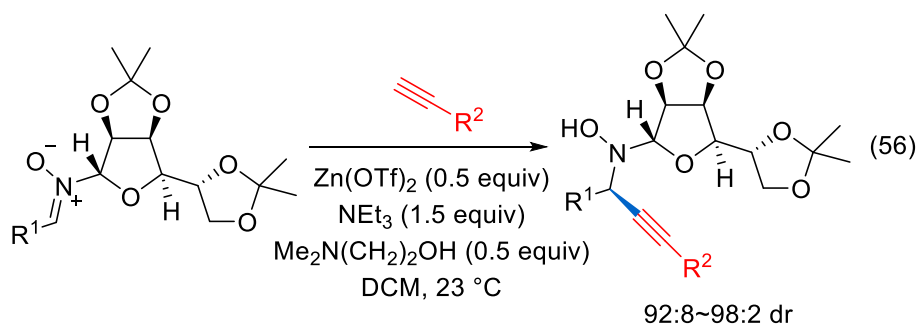


3.1.1.5. Ethynylation

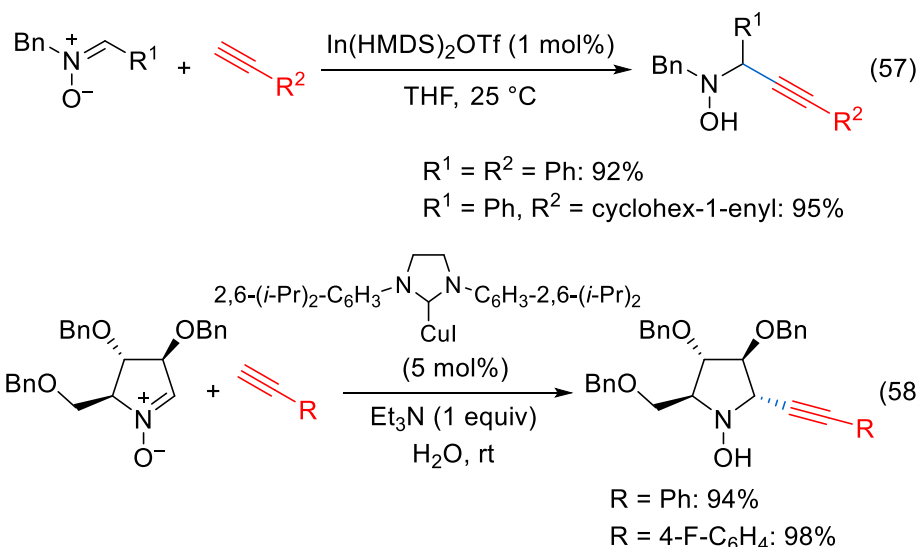
Merino and coworkers reported that the reaction of chiral nitron **3** with ethynyllithium gives *syn* products, while the reaction in the presence of Et₂AlCl gives *anti*-isomers (Table 3).^{141,142} Ohtake and Murahashi demonstrated diastereoselective ethynylation of cyclic nitron upon treatment with lithium acetylide to give *trans* adduct with high preference (eq 55).⁶⁵



Carreira and coworkers explored the first catalytic method for the preparation of propargylic *N*-hydroxylamines.¹⁵⁶ Addition of terminal alkynes to chiral nitrones, prepared from mannose-derived glycoside *N*-hydroxylamine, in the presence of Zn(OTf)₂, 2-(dimethylamino)ethanol, and NEt₃ gives adducts in high diastereoselectivities and yields (eq 56).¹⁵⁷ Deprotection with aqueous acid yields *N*-hydroxy propargylamines.¹⁵⁸

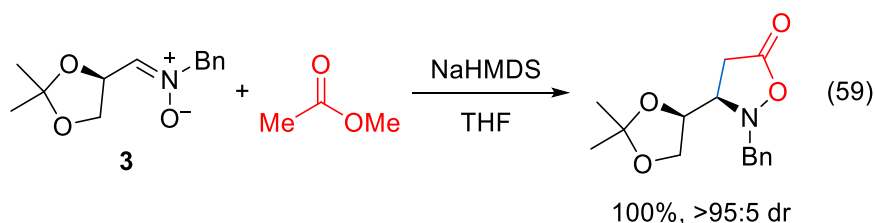


Reaction of nitrones with terminal alkynes takes place in the presence of Et_2Zn in toluene in excellent yields.¹⁵⁹ Kobayashi and coworkers demonstrated that zinc bis[bis(trimethylsilyl)amide] ($\text{Zn}(\text{HMDS})_2$) is an efficient Lewis acid/Brønsted base cooperative catalyst for these reactions.¹⁶⁰ It was also reported that the combination of InBr_3 and $i\text{-Pr}_2\text{NEt}$ is an alternative catalytic system for ethynylation.¹⁶¹ $\text{In}(\text{HMDS})_2\text{OTf}$ shows an excellent catalytic activities with lower amounts of catalysts (eq 57).¹⁶² The *N*-heterocyclic carbene–copper-catalyzed reaction of terminal alkynes with chiral nitrones in water provides propargylic hydroxylamines with up to 97% stereoselectivity. It is claimed that the reaction is easy to be handled because the catalytic system is not sensitive to moisture (eq 58).¹⁶³



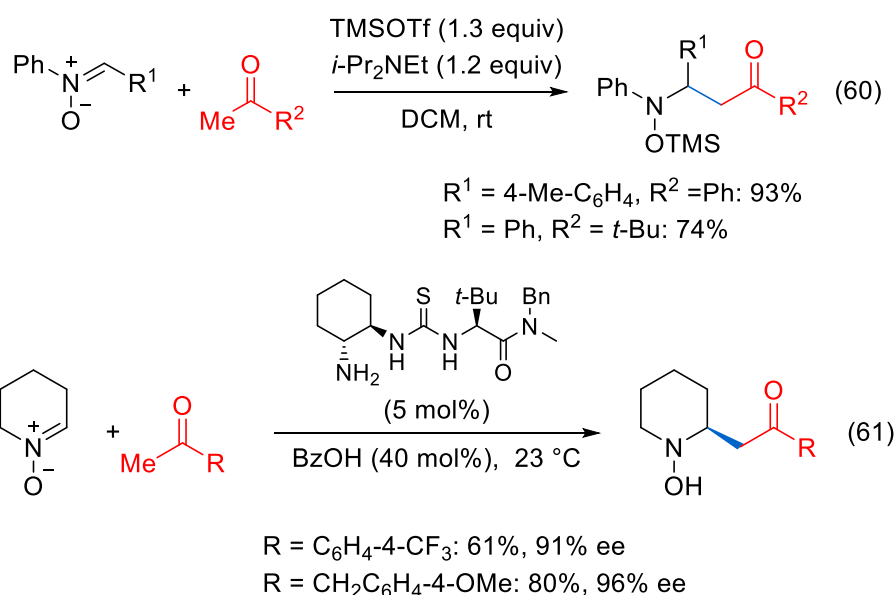
3.1.2. Reaction with Carbonyl Compounds and Related Compounds

Mannich-type reaction of nitrones with metal enolates of esters and amides has been reviewed by Merino and Tejero.¹³ The first example of stereocontrolled nucleophilic addition of sodium enolate, prepared from methyl acetate and NaHMDS , has been reported to give D-glyceraldehyde-derived nitrone **3** in a completely *syn*-selective manner (eq 59).¹⁶⁴



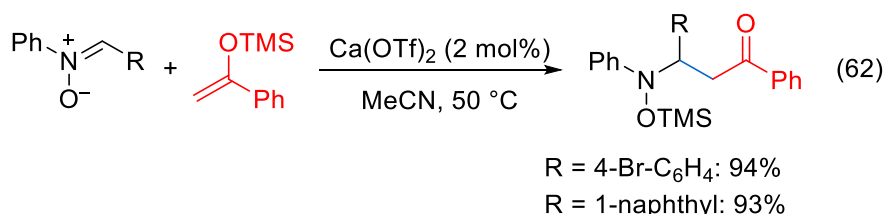
Ketones form enol silanes and add to *N*-phenylnitrones in the presence of TMSOTf and trialkylamine (eq 60).¹⁶⁵ The reaction is general to amides and thioesters. Importantly,

asymmetric Mannich-type reaction of cyclic nitrones with methyl ketones gives β -*N*-hydroxylaminoketones with high enantioselectivities using chiral thiourea catalyst (eq 61).¹⁶⁶ The reaction of nitrones with enolizable 1,3-dicarbonyls affords highly functionalized β -enamino diones by initial self-catalyzed reaction of 1,3-dicarbonyls to nitrones followed by a spontaneous intramolecular reorganization of the resulting non isolated hydroxylamine to enamino derivatives.¹⁶⁷ Aliphatic nitriles undergo cyanomethylation with aldonitrones in the presence of triethylsilyl trifluoromethanesulfonate (TESOTf) and triethylamine. The reaction involves formation of *N*-silyl ketene imine followed by Mannich-type reaction.¹⁶⁸



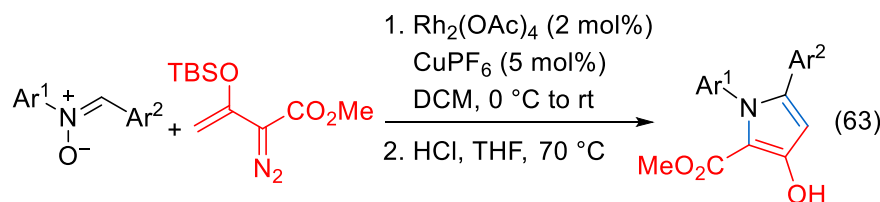
3.1.2.1. Reaction with Enolates

Reactions of nitrones with enolates are useful for synthesis of β -amino carbonyl compounds. Calcium(II)-catalyzed reaction of *N*-phenylnitrones with ketone-derived enol ethers gives β -(silyloxy)amino carbonyls (eq 62).¹⁶⁹



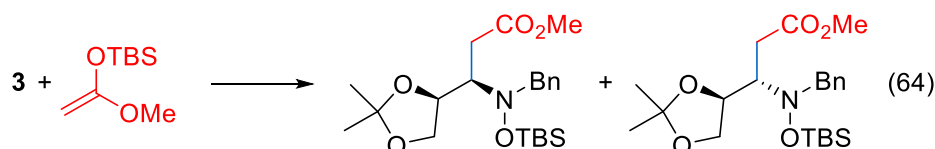
Doyle and coworkers reported that the copper-catalyzed reaction of nitrones with a TBSO-substituted vinyl diazoacetate gives *N*-aryl-2-carboxyl-3-hydroxy-5-arylpyrroles. The reaction involves the Mannich addition, dirhodium-catalyzed dinitrogen extrusion, insertion into N—

OTBS bond, and acid-promoted elimination–aromatization (eq 63).¹⁷⁰



3.1.2.2. Reaction with Silyl Ketene Acetals

The ZnI_2 -promoted reaction of nitrones with silyl ketene acetal gives adducts (A, eq 64).¹⁷¹ Merino and Tejero demonstrated that high stereocontrol of the reaction for syn or anti isomer can be accomplished by using appropriate Lewis acids (B and C, eq 64).¹⁷²



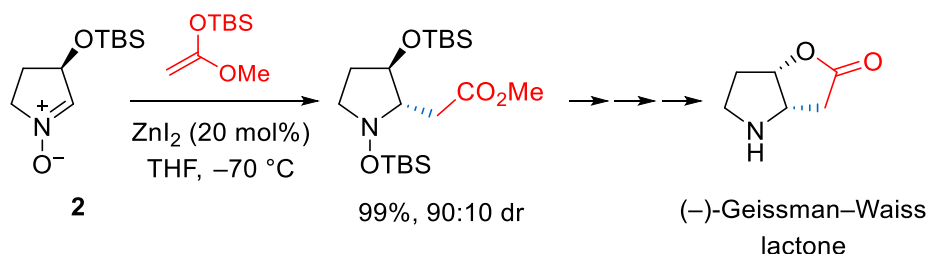
A: ZnI_2 (10 mol%), MeCN–DCM, –78 °C: 100%, 89:11 dr

B: TBSOTf (1 equiv), THF, –80 °C: 94% 70:30 dr

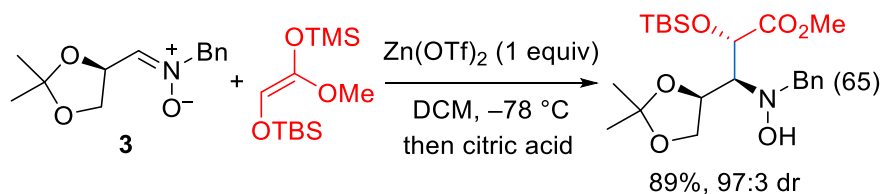
C: $\text{BF}_3 \cdot \text{OEt}_2$ (1 equiv), DCM, –80 °C: 91%, 7:93 dr

The ZnI_2 -catalyzed reaction of chiral nitrone **2** with silyl ketene acetal gives methyl (2*S*,3*R*)-[1,3-bis(*tert*-butyldimethylsilyloxy)pyrrolidin-2-yl]acetate, which is a precursor of (–)-Geissman–Waiss lactone, in a 90:10 *trans/cis* ratio (Scheme 12).⁶⁶ Enhanced *trans* selectivity was achieved by the use of silyl ketene acetal derived from *tert*-butyl acetate, affording *trans* and *cis* adduct in a 96:4 ratio.⁶⁵

Scheme 12. Reaction of Chiral Nitrone with Silyl Ketene Acetal

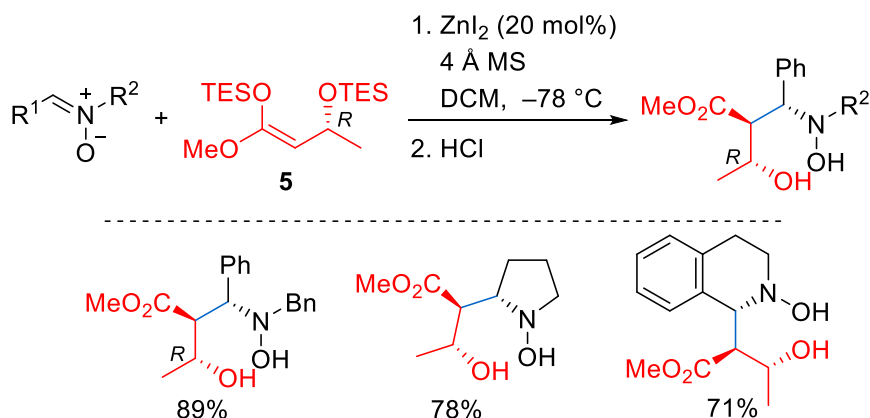


Reaction of substituted silyl ketene acetal with nitrone **3** in the presence of $\text{Zn}(\text{OTf})_2$ affords the key intermediate for synthesis of D- and L-*erythro*-sphingosine (eq 65).¹⁷³



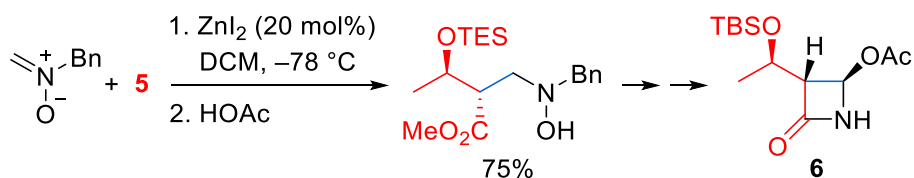
Murahashi and coworkers have developed a convenient method for synthesis of chiral β -amino acids by ZnI_2 -catalyzed reaction with (*Z*)-(*R*)-1,3-bis(triethylsilyloxy)-1-methyl-1-butane (**5**) readily derived from methyl (*R*)-3-hydroxybutanone.¹⁷⁴ Typically, the reaction of acyclic (*Z*)-nitrones gives the adducts with α,β -*anti*- β,γ -*anti* selectivity (Scheme 13). Hydrogenation of these *N*-hydroxylamines gives the corresponding β -amino acids selectively.

Scheme 13. Reaction with Chiral Silyl Ketene Acetal



The zinc-catalyzed reaction of *N*-benzylmethanimine *N*-oxide with chiral silyl ketene acetal **5** gives *N*-hydroxy- β -amino acid ester as a single stereoisomer. The compound is converted to β -lactam, and selective oxidation¹⁷⁵ gives the key intermediate **6** (Scheme 14).¹⁷⁴

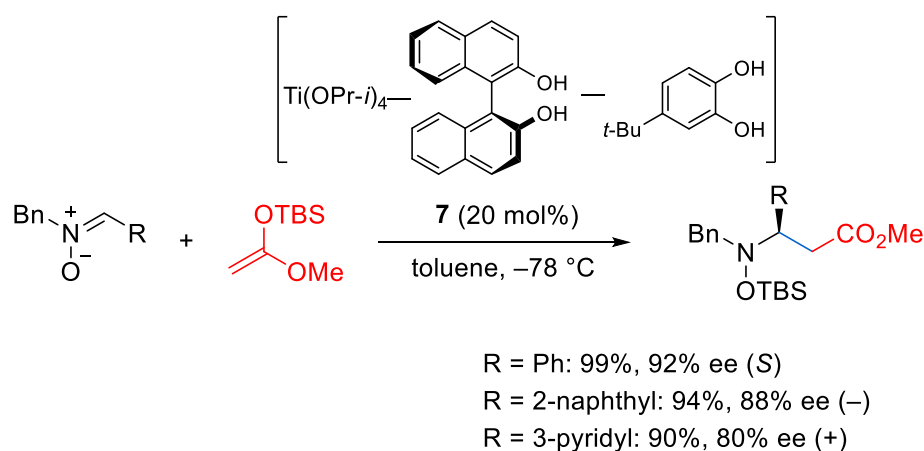
Scheme 14. Synthesis of Azetidinone Derivatives



Murahashi and coworkers found the first enantioselective addition of silyl ketene acetals to nitrones.¹⁷⁶ This method is very attractive for synthesis of β -amino acids derivatives, and is superior to the asymmetric Mannich-type addition to imines because of the configurational stability of nitrones, ease of handling, and readiness of preparation.

Titanium catalyst prepared from $\text{Ti}(\text{O}i\text{-Pr})_4$ and (*S*)-BINOL is an excellent catalyst for the formation (*R*)- β -amino acid ester; however, the enantioselectivity is not high. However, addition of phenol derivatives to the catalyst increased the enantioselectivity dramatically. The titanium complex **7** exhibited high enantioselectivity to give the adduct in 99% yield with 92% *ee*. Using this catalytic reaction, various β -amino acid derivatives are obtained (Scheme 15). Treatment with $\text{Zn}/\text{H}_2\text{SO}_4$ and hydrogenation over palladium on charcoal catalyst provides esters of β -amino acids. Similar reaction by replacement of the catechol unit in the catalyst by D-mannitol derivatives afforded *R*-enantiomer of the adduct preferentially.¹⁷⁷

Scheme 15. Enantioselective Reaction with Silyl Ketene Acetal

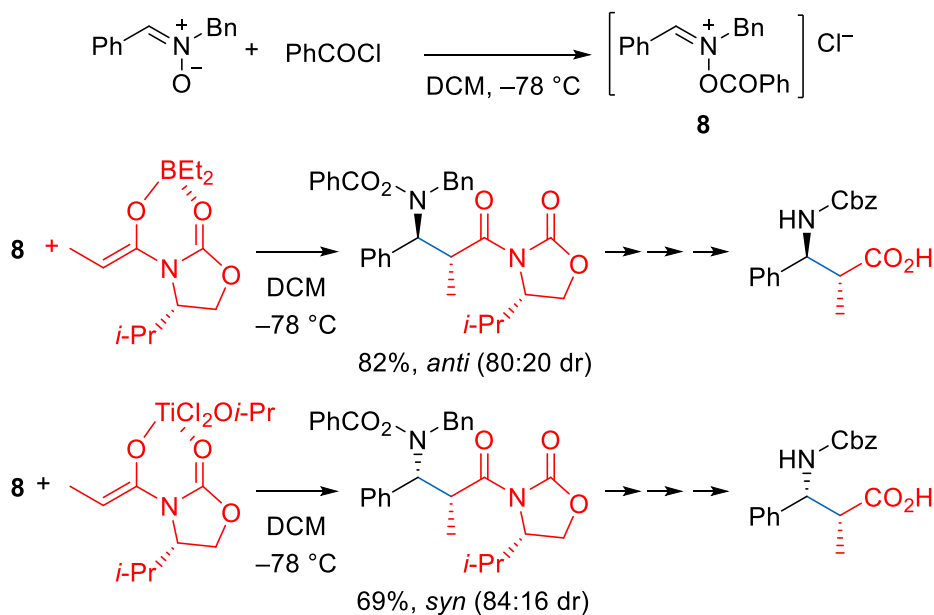


3.1.2.3. Reaction of *N*-Acyloxyiminium Ions Derived from Nitrones

Hard carbon nucleophiles such as Grignard reagents and cyanide anions undergo reaction with nitrones easily; however, soft carbon nucleophiles such as enolates do not undergo reaction with nitrones directly. Lewis acids have been used to promote these reactions. Murahashi and coworkers have succeeded in generation of highly reactive *N*-acyloxyiminium species upon treatment of nitrones with acyl halides. *N*-Acyloxyiminium species undergo rearrangement to give the corresponding amide at room temperature; however, it can be used at $-78\text{ }^\circ\text{C}$ before rearrangement for the reaction with various soft nucleophiles. This method provides an attractive method for syntheses of chiral β -amino acids and chiral nitrogen compounds.¹⁷⁸

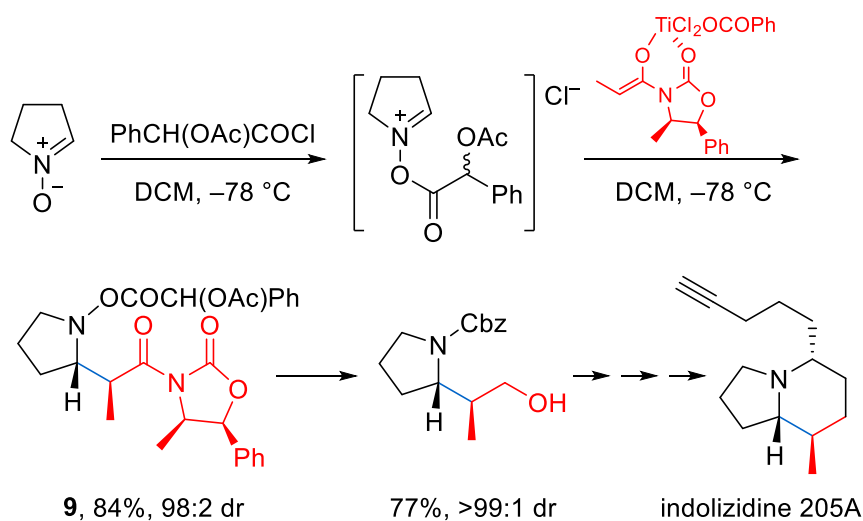
The reaction of *N*-acyloxyiminium species **8** with chiral boron enolate and chiral titanium enolate gives *anti*- and *syn*-isomers, respectively. Interestingly, the chelating effect of the boron enolate and the titanium enolate are opposite, and reversal diastereoselectivity was observed. Thus, four stereoisomeric β -amino acids have been obtained selectively (The examples of two amino acids, Scheme 16).¹⁷⁹

Scheme 16. Reaction of Acyloxyiminium Ion 8 with Boron and Titanium(IV) Enolates



This method can be applied for asymmetric synthesis of cyclic compounds. The stereocontrol at the α -position of pyrrolidines is very difficult because of five-membered planar structure. However, the adduct **9** was obtained from racemic *N*-(acetylmandelyloxy)iminium ion and titanium enolate, prepared from (4*R*,5*S*)-4-methyl-5-phenyl-3-propanoxyloxazolidine, in 84% yield in extremely high diastereoselectivity (2'*S*,2''*S*)/(2'*S*,2''*R*) = 98:2. Reductive cleavage followed by *N*-protection and reduction gives (2*S*,2'*S*)-2-(1-hydroxyprop-2-yl)pyrrolidine in 77% yield as a single diastereoisomer, which is a key intermediate for synthesis of indolizidine alkaloids such as indolizidine 205A (Scheme 17).¹⁸⁰

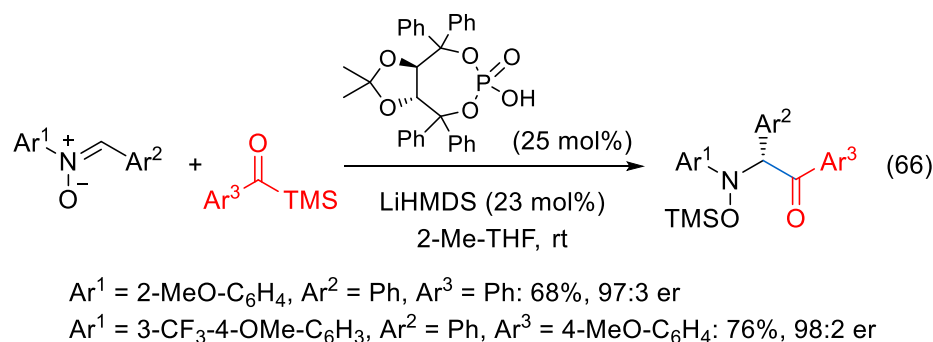
Scheme 17. Synthesis of Indolizidine Alkaloid via Acyloxyiminium Ion



3.1.2.4. Reaction with Acyl Moiety

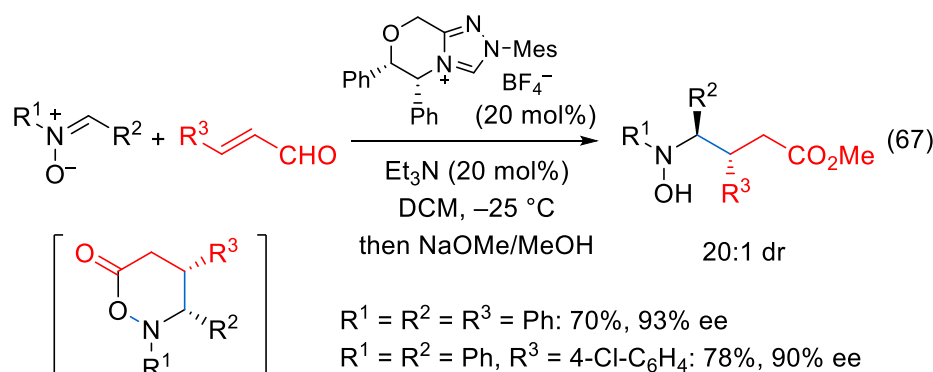
The diastereoselective reaction of carbamoyl anions derived from *N,N*-disubstituted formamides and LDA provides a direct route to α -(*N*-hydroxyl)amino amides.¹⁸¹

Enantioselective additions of acyl silanes to nitrones gives protected α -aryl amino ketones. Thus, the reaction of nitrones with acylsilane in the presence of catalyst (*R,R*)-TADDOL-phosphite gives α -aryl amino ketones. (eq 66).¹⁸²



3.1.2.5. Addition of Homo-enolates

The reaction of α,β -unsaturated aldehydes with nitrones catalyzed by NHC affords γ -amino esters enantioselectively (eq 67). The reaction involves addition of the homo-enolate equivalent formed in situ from the combination of the NHC and unsaturated aldehyde to the nitrones and subsequent tautomerization and intramolecular acylation generates the six-membered heterocycles.¹⁸³ Similarly, NHC-catalyzed cross-coupling of sugar-derived chiral cyclic nitrones with an enal gives γ -hydroxyamino esters.¹⁸⁴

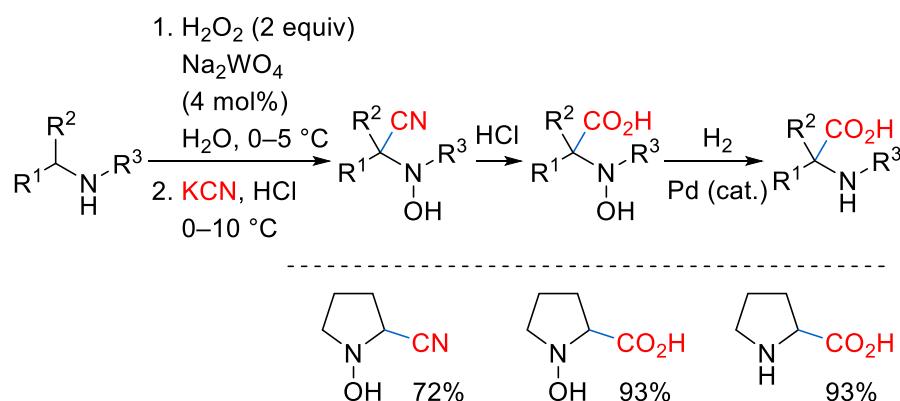


3.1.3. Cyanation

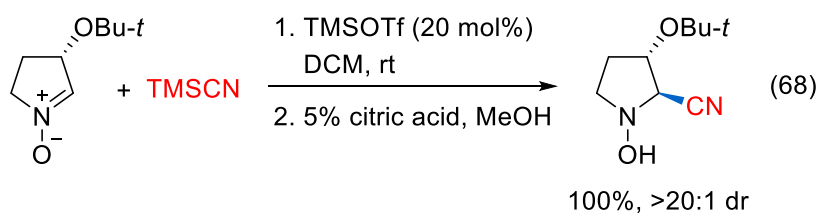
Murahashi and coworkers found that α -cyanohydroxylamines are generally prepared by the

oxidation of secondary amines with hydrogen peroxide in the presence of $\text{Na}_2\text{WO}_4 \cdot 2\text{H}_2\text{O}$ catalyst followed by treatment with potassium cyanide and 4 N hydrogen chloride in water. Hydrogen chloride is used to adjust to pH 7–8. If hydrogen chloride is not used, elimination of HCN takes place, giving the corresponding nitrones. Hydrolysis of α -cyanohydroxylamines under acidic conditions gives *N*-hydroxyamino acids. Further, palladium-catalyzed hydrogenation of *N*-hydroxyamino acids gives the corresponding amino acids (Scheme 18).¹⁸⁵

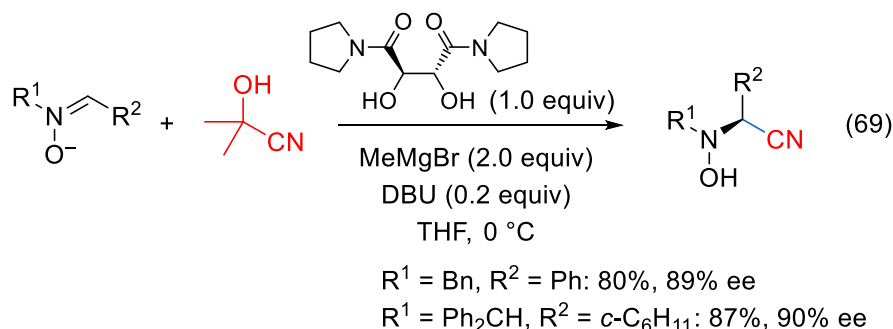
Scheme 18. Synthesis of α -Cyanohydroxylamines, *N*-Hydroxyamino Acids, and Amino Acids



Merino and Goti demonstrated that the stereoselective cyanation of chiral nitron with TMSCN proceeds in the presence of TMSOTf catalyst (eq 68).¹⁸⁶ Similar cyanation to chiral cyclic nitron derived from D-ribose can be applied to the synthesis of (–)-pochonicine and its stereoisomers.¹⁸⁷



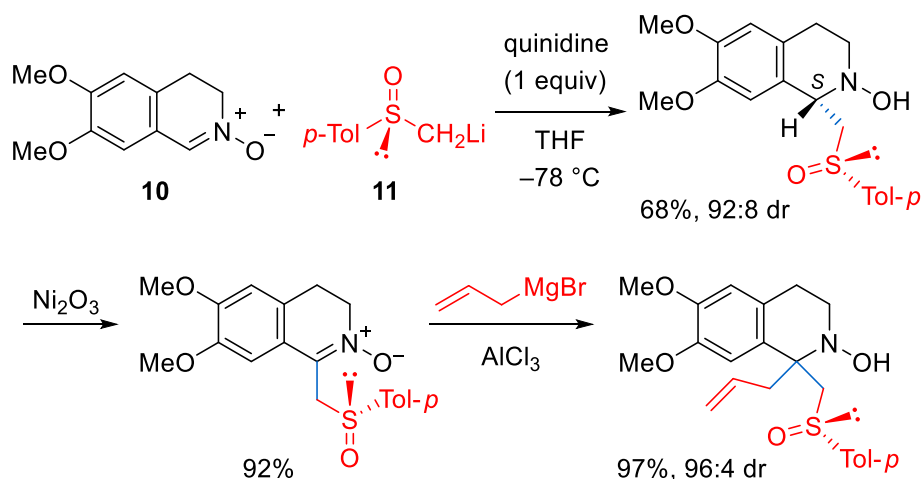
Ukaji and coworkers found that enantioselective synthesis of (*S*)- α -(hydroxyamino)nitrile derivatives upon treatment of nitrones with acetone cyanohydrin in the presence of a magnesium—tetramide complex, generated from (*R,R*)-2,3-dihydroxy-1,4-di(pyrrolidin-1-yl)butane-1,4-dione and MeMgBr , and catalytic amount of DBU (eq 69). The reaction is applicable to various nitrones.¹⁸⁸



3.1.4. Reaction with Other Unique Carbon Nucleophiles

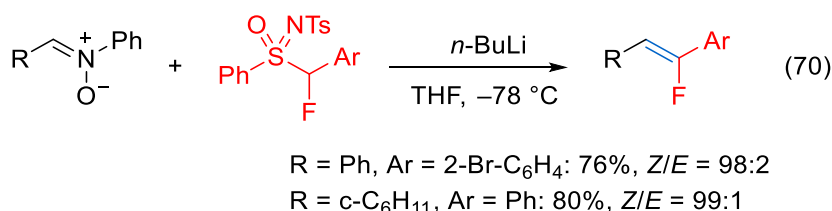
The method for introduction of an asymmetric quaternary carbon α to the nitrogen of secondary amines has been developed. The reaction of nitron **10** with lithiated (*R*)-(+)-methyl *p*-tolyl sulfoxide **11** followed by oxidation with nickel(III) oxide provides enantiopure β -sulfinylketonitrone. Diastereoselective addition of organometallic compounds gives chiral α,α -disubstituted hydroxylamines, which are versatile precursors of α,α -disubstituted secondary amines. Typically, α -allyl hydroxylamine with stereogenic quaternary carbon center has been obtained upon treatment with allylmagnesium bromide in the presence of AlCl_3 (Scheme 19).¹⁸⁹ Various alkaloids such as (+)-euphococcinine are prepared.¹⁹⁰

Scheme 19. Asymmetric Introduction of Quaternary Carbon Center

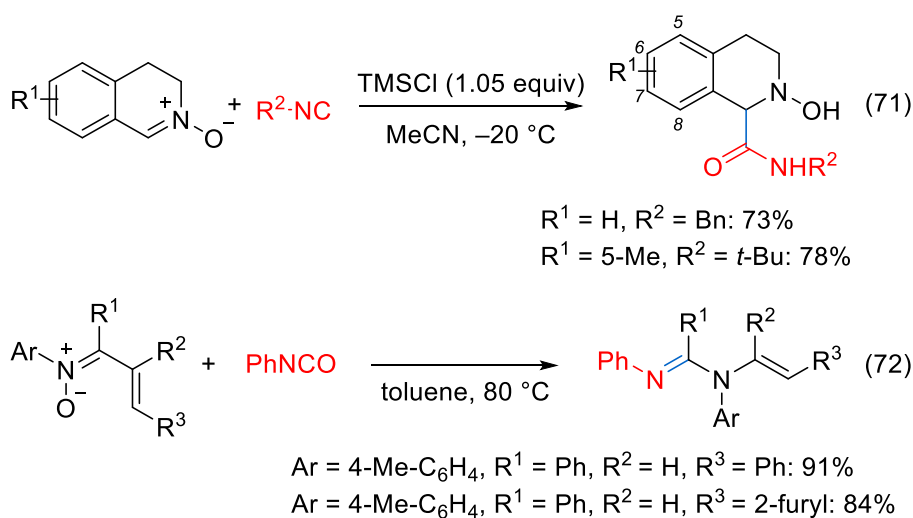


Introduction of polyhalomethyl group such as CF_3 , CF_2H , and CCl_2H at the α -position of *N*-hydroxylamines can be performed efficiently. Trifluoromethylation of nitrones upon treatment of TMSCF_3 with *t*-BuOK gives the corresponding hydroxylamines.¹⁹¹ Fluorine-catalyzed nucleophilic reaction of chiral pyrroline *N*-oxides with TMSCF_2SPh and subsequent reductive cleavage of $-\text{OTMS}$ and $-\text{SPh}$ groups provides asymmetric synthesis of α -

difluoromethylated polyhydroxypyrrolidines.¹⁹² α -Dichloromethylation of nitrones can be performed upon treatment with TMSCF_3 and tetramethylammonium fluoride (TMAF) in DCM, where highly basic $[\text{CF}_3^-]$ generates dichloromethide from DCM, followed by *O*-desilylation with TBAF.¹⁹³ The reaction of nitrones with carbanions generated by the reaction of α -fluorosulfoxylimines with *n*-BuLi provides stereoselective method for preparation of monofluoroalkenes (eq 70).¹⁹⁴

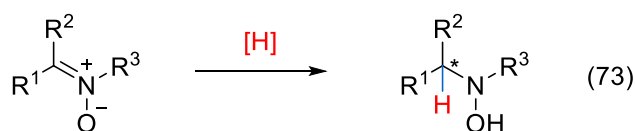


The reaction of isocyanides with 3,4-dihydroisoquinoline *N*-oxide in the presence of TMSCl gives the corresponding 1,2,3,4-tetrahydroisoquinoline-1-carboxylamides (eq 71).¹⁹⁵ The reaction of isocyanates with *N*-aryl- α,β -unsaturated nitrones gives *N*-styrenyl amidines by initial formation of an oxadiazolidinone intermediate that undergoes CO₂ elimination and styrenyl migration (eq 72).¹⁹⁶



3.1.5. Reduction of Nitrones

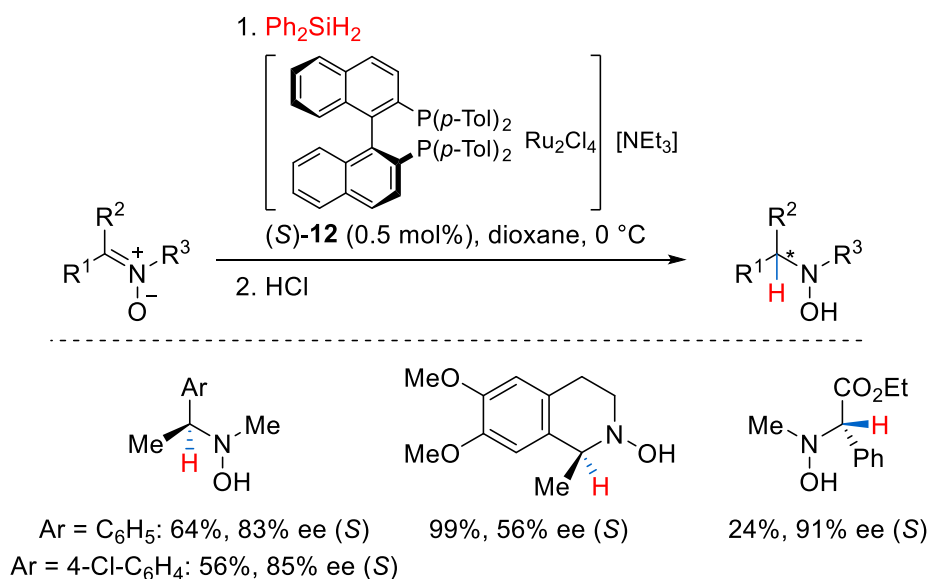
Reduction of nitrones gives *N*-hydroxylamines. Typically, the reductions with NaBH₄ occurs readily giving *N*-hydroxylamines,¹⁹⁷ and catalytic hydrogenation under high pressure directly furnishes amines.¹⁹⁸ Synthetically most important reduction is the catalytic asymmetric reduction of ketonitrones with hydrogen sources such as hydrosilanes and molecular hydrogen (eq 73).



3.1.5.1. Asymmetric Hydrosilylation

Asymmetric synthesis of *N,N*-disubstituted hydroxylamines by catalytic hydrosilylation of nitrones can be performed. Hydrosilylation of (*Z*)-*N*-[1-(4-chlorophenyl)ethylidene]methanimine *N*-oxide with diphenylsilane in the presence of $\text{Ru}_2\text{Cl}_4[(S)-(-)-p\text{-tolbinap}]_2(\text{NEt}_3)$ ((*S*)-**12**) catalyst followed by hydrolysis with aqueous diluted hydrogen chloride solution gives the corresponding (*S*)-(-)-hydroxylamine with 85% ee. The (*R*)-enantiomer was obtained with a similar ee, when $\text{Ru}_2\text{Cl}_4[(R)-(+)-p\text{-tolbinap}]_2(\text{NEt}_3)$ ((*R*)-**12**) was used as a catalyst. When (*S*)-BINAP ruthenium(II) complex catalyst (*S*)-**12** was used (*S*)-hydroxylamines are obtained from (*E*)-nitrones, while (*R*)-hydroxylamines are obtained from (*Z*) isomers (Scheme 20).¹⁹⁹

Scheme 20. Asymmetric Hydrosilylation of Nitrones

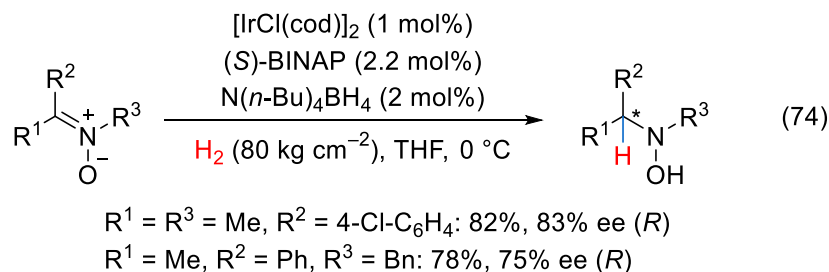


3.1.5.2. Asymmetric Hydrogenation

Catalytic asymmetric hydrogenation of nitrones can be performed easier in comparison with the hydrogenation of imines because of the configurational stability of nitrones, ease of handling, and readiness of preparation.

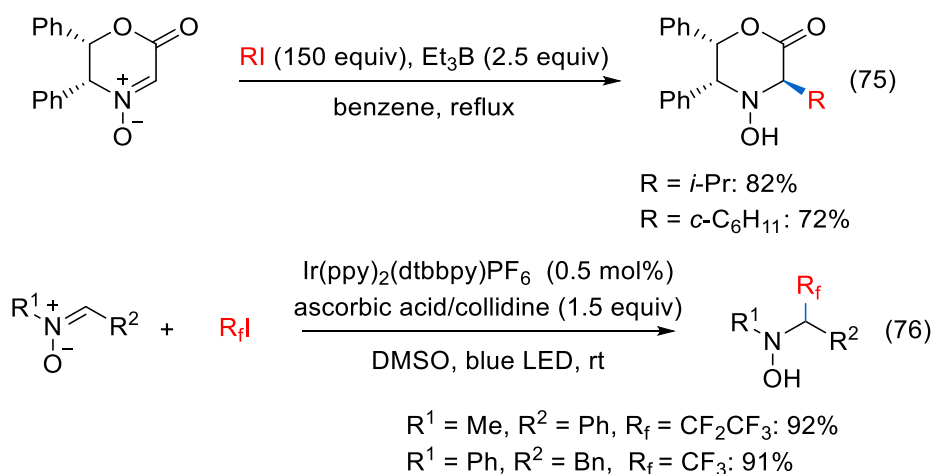
Murahashi and Tsuji demonstrated hydrogenation of nitrones with molecular hydrogen (80 kg cm⁻²) in the presence of the iridium catalyst, prepared from $[\text{IrCl}(\text{cod})]_2$ (1 mol%), (*S*)-

BINAP (2.2 mol%), and $N(n\text{-Bu})_4\text{BH}_4$ (2.0 mol%), gives (*R*)-*N*-hydroxylamine in 82% yield with 83% ee.²⁰⁰ Furthermore, nitrones can be hydrogenated enantioselectively with the $[\text{IrCl}(\text{cod})]_2/(\text{S})\text{-BINAP}/N(n\text{-Bu})_4\text{BH}_4$ catalyst system (eq 74).



3.2. Reaction with Radicals

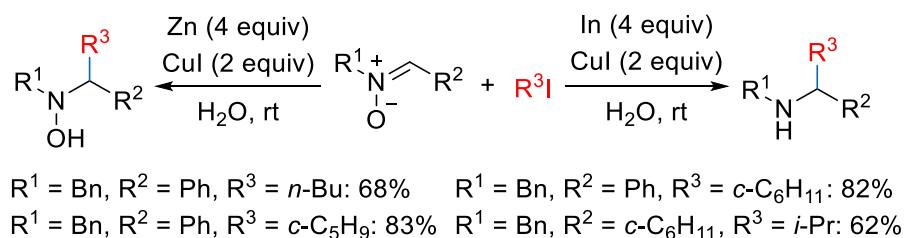
Nitrones undergo reactions with various radicals. Addition of alkyl radicals to chiral nitrones gives carbon—carbon bond formation with a high degree of stereocontrol.^{201,202} This provides a method for asymmetric synthesis of α -amino acids. Typically, the reaction of chiral cyclic glyoxylic nitrone, prepared by oxidation of 5,6-diphenylmorpholin-2-one, with alkyl iodides in the presence of Et_3B gives the products highly diastereoselectively (eq 75).²⁰² The products can be converted to the corresponding pure (*R*)-*N*-Cbz amino acids by reductive cleavage with $\text{Mo}(\text{CO})_6$ and subsequent palladium-catalyzed hydrogenation. The addition of fluorinated groups to nitrones using iridium photocatalyst and ascorbic acid as a stoichiometric reducing agent can be performed. The reaction involves single-electron reduction of fluorinated alkyl iodides with photo-activated iridium complex to give fluorinated radicals (eq 76).²⁰³



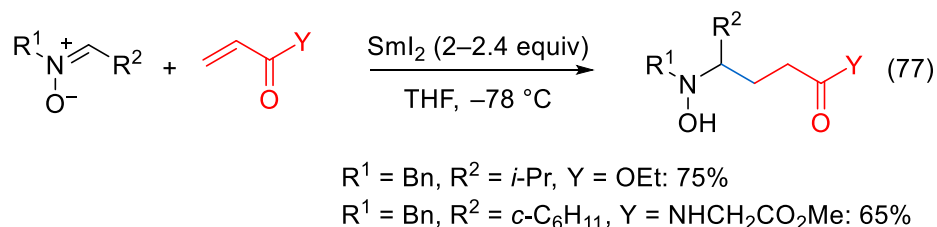
Loh and coworkers reported Barbier-type alkylation of nitrones (including chiral version) with alkyl halides in water to give α -alkylated amines or α -alkylated *N*-hydroxylamines, depending on the choice of the metal complexes. Thus, the reaction of nitrones with alkyl

iodides in the presence of Zn/CuI in water gives *N*-hydroxylamines. In contrast, the reaction with In/CuI in water gives amines (Scheme 21).²⁰⁴ The latter reaction involves single-electron transfer (SET) from indium to alkyl iodide to generate alkyl radical. Subsequent indium-promoted reduction followed by quenching with water affords hydroxylamine, which is reduced via indium-mediated SET process to give amine.

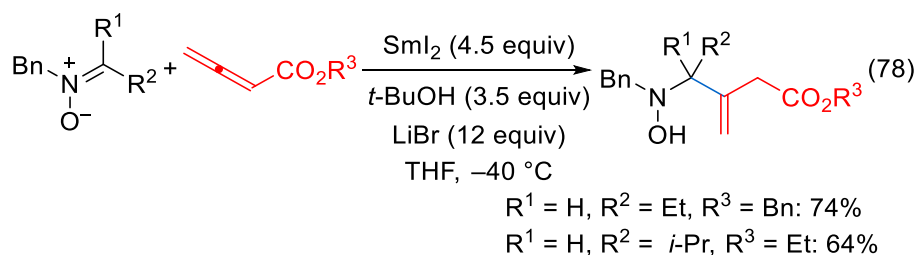
Scheme 21. Barbier-Type Alkylation of Nitrones



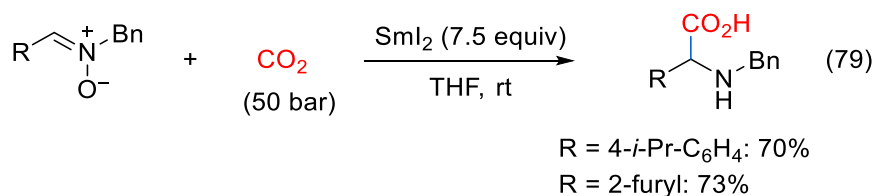
Aliphatic nitrones undergo radical reaction with α,β -unsaturated esters²⁰⁵ and amides²⁰⁶ in the presence of two equivalents of SmI₂ to give γ -*N*-hydroxyamino esters or amides (eq 77). A single-electron transfer from SmI₂ to the nitron and subsequent radical coupling has been proposed. However, electron transfer from 2 equivalents of SmI₂, followed by nucleophilic attack of the generated carbanion cannot be ruled out.



Nitrones undergo conjugate addition to alkyl allenates under SmI₂-mediated reductive conditions using *t*-BuOH as a proton source to produce β -methylene-substituted γ -amino esters (eq 78).²⁰⁷ Similar SmI₂-mediated reductive coupling of nitrones with β -silyl- α,β -unsaturated esters, followed by zinc reduction, gives β -silyl lactams diastereoselectively.²⁰⁸ The SmI₂-induced reductive cross-coupling of nitrones with chiral *N*-*tert*-butanesulfinyl imines gives optically pure unsymmetrical vicinal diamines.²⁰⁹

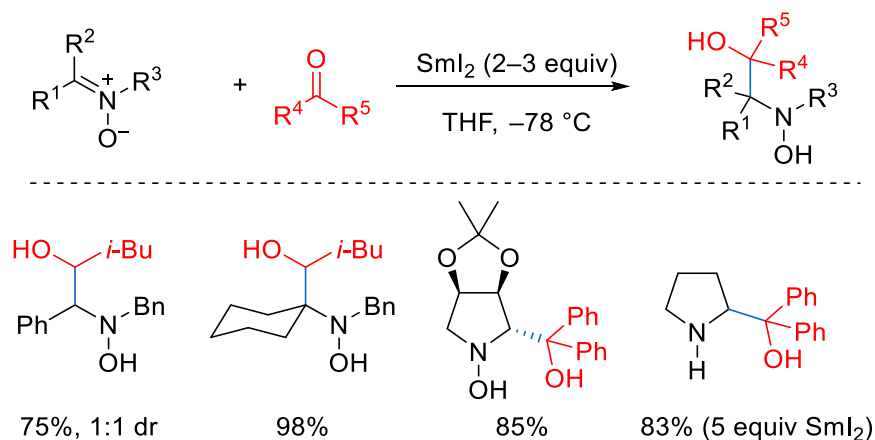


The α -amino acids are obtained upon treatment of *N*-benzyl nitrones with CO₂ in the presence of SmI₂ by reductive C—C coupling (eq 79).²¹⁰



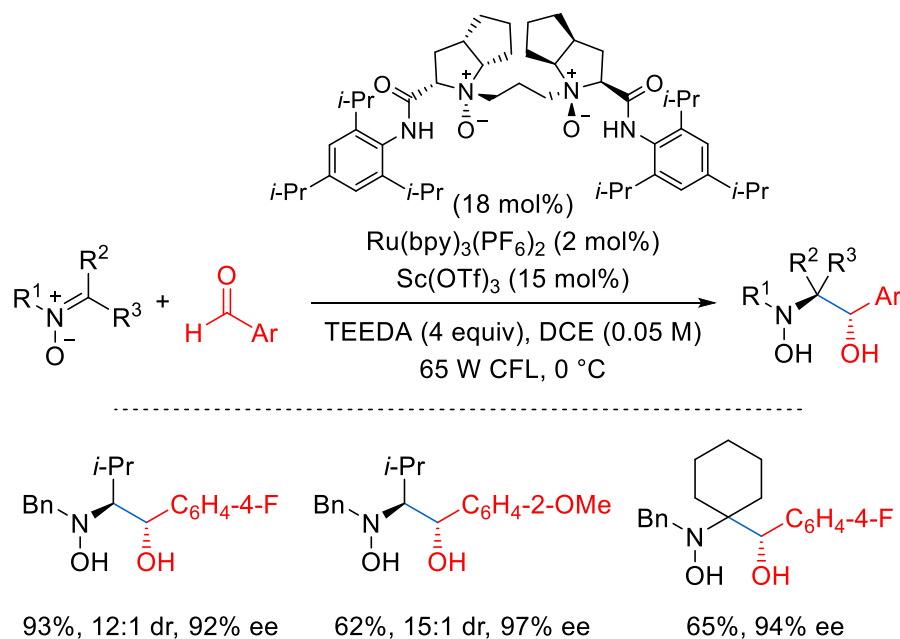
SmI₂-induced reductive cross-coupling of nitrones with aldehydes and ketones provides a method to prepare highly substituted and unsymmetrical vicinal *N*-hydroxyamino alcohols (Scheme 22).^{211,212} Increasing the amount of SmI₂ allows direct access to the corresponding amines. The *N*-hydroxy- α,α -diphenyl-2-pyrrolidinylmethanol is also easily prepared and resolved.²¹³

Scheme 22. Reductive Cross-Coupling of Nitrones with Carbonyl Compounds

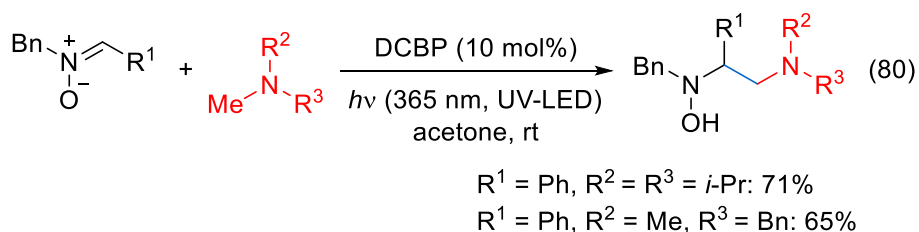


Enantioselective reductive cross-coupling of nitrones with aldehydes can be carried out under photocatalytic conditions in the presence of ruthenium photoredox catalyst, rare earth Lewis acid catalyst, and a chiral *N,N'*-dioxide ligand (Scheme 23).²¹⁴

Scheme 23. Photocatalytic Enantioselective Reductive Cross-coupling with Aldehydes



Irradiation of a mixture of nitrones and tertiary amines in the presence of a sensitizer of 4,4'-dichlorobenzophenone (DCBP) gives β -amino hydroxylamines (eq 80).²¹⁵ The photo-excited nitrones serve as excellent electron acceptors as well as radical acceptors, and photochemically-induced direct sp^3 C—H functionalization of tertiary amines takes place.

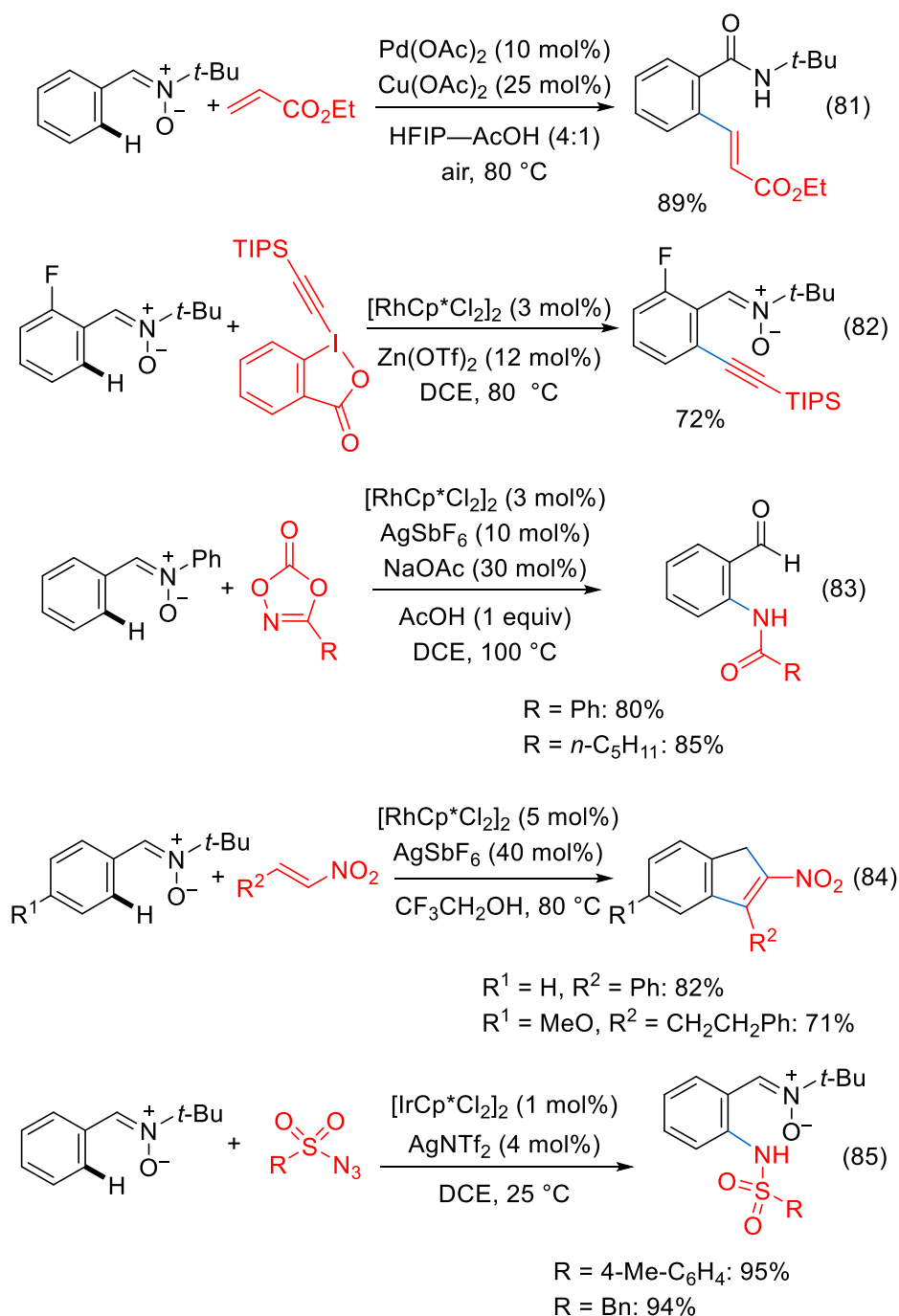


3.3. C—H Functionalization of Nitrones

Transition-metal-catalyzed direct C—H bond functionalization of nitrones has emerged as a powerful protocol to synthetic innovation. There has been extensive study of sp^2 C—H activation induced by directing-groups of nitrones.

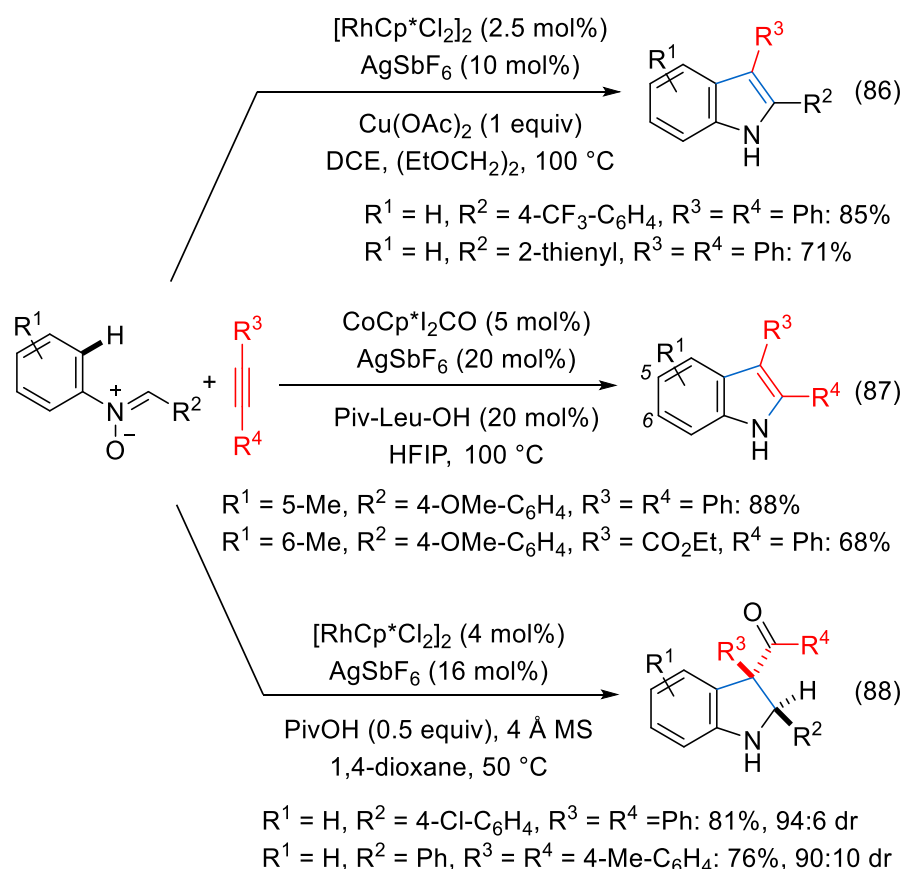
Palladium-catalyzed alkenylation of *C*-arylnitrones with ethyl acrylate gives *ortho*-alkenylated benzamide derivatives (eq 81).²¹⁶ Rhodium-catalyzed C—H alkenylation of *N*-*tert*-butyl-*C*-arylnitrones is developed. The reaction with 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3-(1*H*)-one affords the alkynylation products (eq 82).²¹⁷ Rhodium-catalyzed C—H activation with 1,4,2-dioxazol-5-ones gives *o*-amido-substituted benzaldehydes. The significance of the amidation is highlighted by late-stage transformation of the formed

aldehydes (eq 83).²¹⁸ Synthesis of nitro-functionalized indenes has been realized via rhodium-catalyzed C—H activation and annulation with nitroolefins (eq 84).²¹⁹ The reaction of nitrones with *p*-toluenesulfonyl azide in the presence of [IrCp*Cl₂]₂ and AgNTf₂ gives *O*-sulfonylamino nitrones with excellent regioselectivity via direct C—H annulation. (eq 85).²²⁰

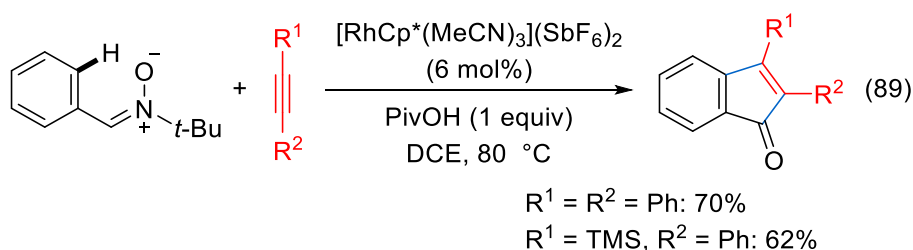


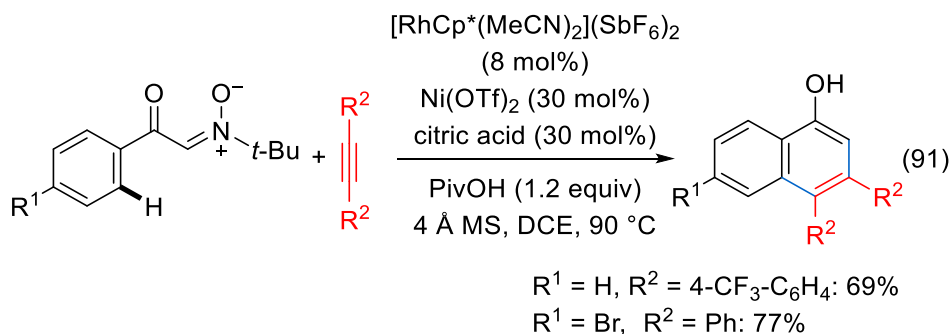
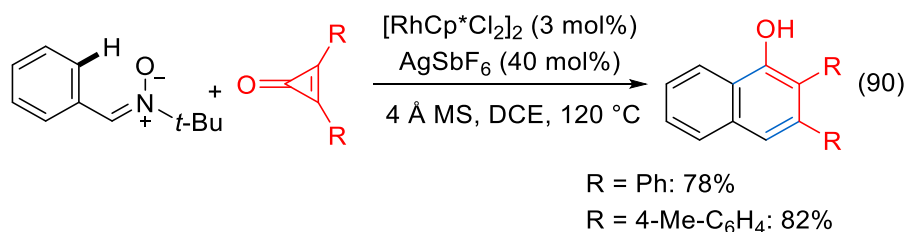
Transition-metal-catalyzed C—H annulation of *N*-arylnitrones with acetylenes gives indoles, indolines, and indenones depending on the catalysts used. Thus, rhodium-catalyzed C—H annulation of *N*-arylnitrones with symmetrical diarylalkynes gives 2,3-diaryl-substituted

N-unprotected indoles (eq 86).²²¹ Cobalt-catalyzed C—H/N—O functionalization of *N*-arylnitrones gives indoles. This is a step-economical access to indoles and displays in excellent site- and regioselectivity with unsymmetrical nitrones and alkynes (eq 87).²²² Rhodium-catalyzed C—H activation of *N*-arylnitrones with alkynes in the presence of pivalic acid (PivOH) gives indolines. The imino moiety is incorporated into the indoline ring in a stereoselective manner (eq 88).²²³

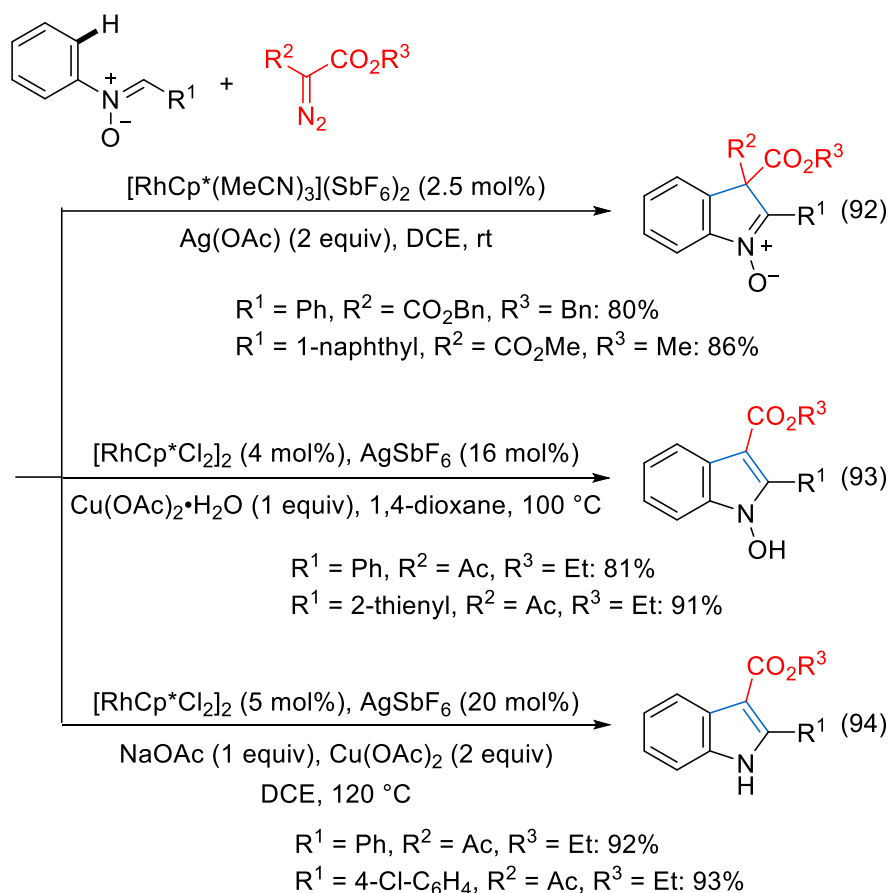


The reaction of *N*-*tert*-butyl-*C*-arylnitrones with alkynes in the presence of $[RhCp^*(MeCN)_3](SbF_6)_2$ catalyst and pivalic acid gives indenones with good functional group tolerance (eq 89).²²⁴ Rhodium-catalyzed reaction of aryl nitrones with cyclopropanones affords 1-naphthols (eq 90).²²⁵ Similar rhodium-catalyzed reaction of *C*-benzoylnitrones with alkynes provides a redox-neutral naphthol synthesis (eq 91).²²⁶

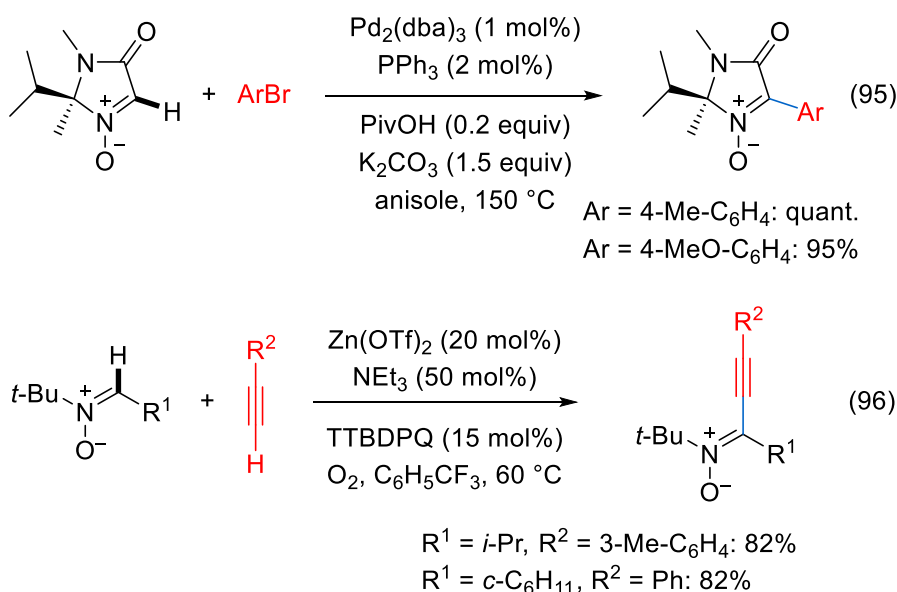




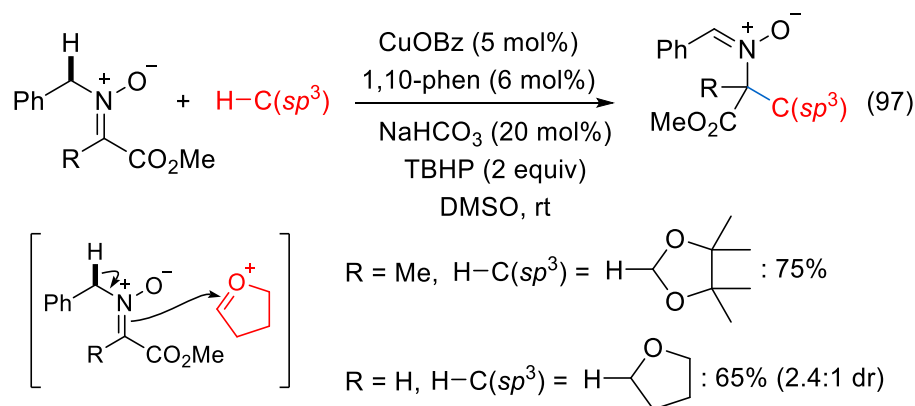
Rhodium-catalyzed C—H activation of *N*-arylnitrones and coupling with diazo compounds affords different indole derivatives depending on the additives. Nitrone is introduced as a directing group to trigger a new [4 + 1] cyclization capture approach wherein diazo compounds undergo migratory insertion to afford 3*H*-indole *N*-oxides. Thus, treatment of nitrones with diazo compounds in the presence of $[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$ catalyst and AgOAc gives 3*H*-indole *N*-oxides (eq 92).²²⁷ The Rh(III) catalyst with $\text{Cu}(\text{OAc})_2$ gives *N*-hydroxyindole derivatives, which are unique structural motif with various biological activities (eq 93).²²⁸ The reaction with Rh(III) catalyst, $\text{Cu}(\text{OAc})_2$, and NaOAc provides regioselective synthesis of 2,3-disubstitued 1*H*-indole derivatives (eq 94).²²⁹



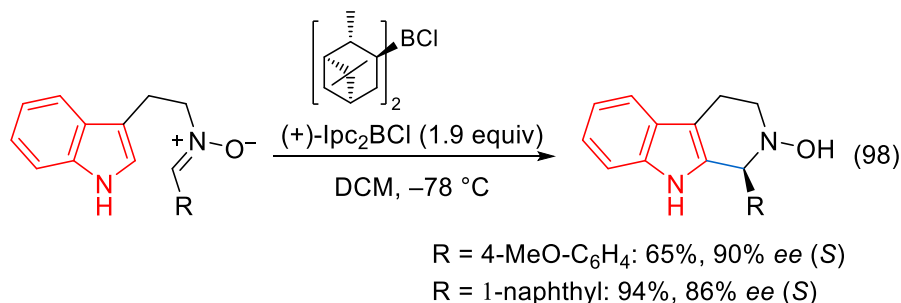
Palladium-catalyzed direct cross-coupling of cyclic nitrones occurs readily to give aryl substituted cyclic nitrones (eq 95).²³⁰ Similarly, cross-dehydrogenative-coupling between nitrones and terminal alkynes can be carried out by using cheap, readily available 3,3',5,5'-tetra-*tert*-butyldiphenylquinone (TTBDPQ) and molecular oxygen (eq 96).²³¹



Kanai and coworkers reported that CuOBz-catalyzed migratory oxidative coupling between nitrones and heterocycles or methylamines with *tert*-butyl hydroperoxide (TBHP) proceeds through cleavage of two sp^3 C—H bonds concomitant with C—N double bonds-migration (eq 97).^{232,233}

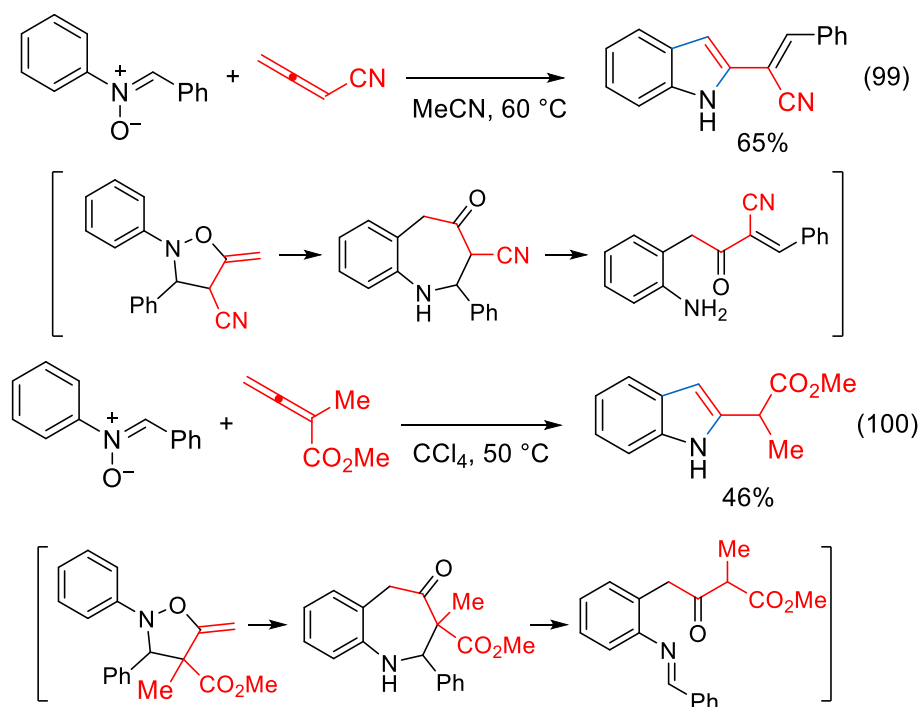


The Pictet–Spengler reaction of nitrones in the presence of $\text{Yb}(\text{OTf})_3$ — TMSCl gives tetrahydro- β -carboline.²³⁴ Enantioselective version with chiral (+)-diisopinocampheylchloroborane ((+)-Ipc₂BCl) gives 2-hydroxytetrahydro- β -carboline in up to 90% *ee* (eq 98).²³⁵

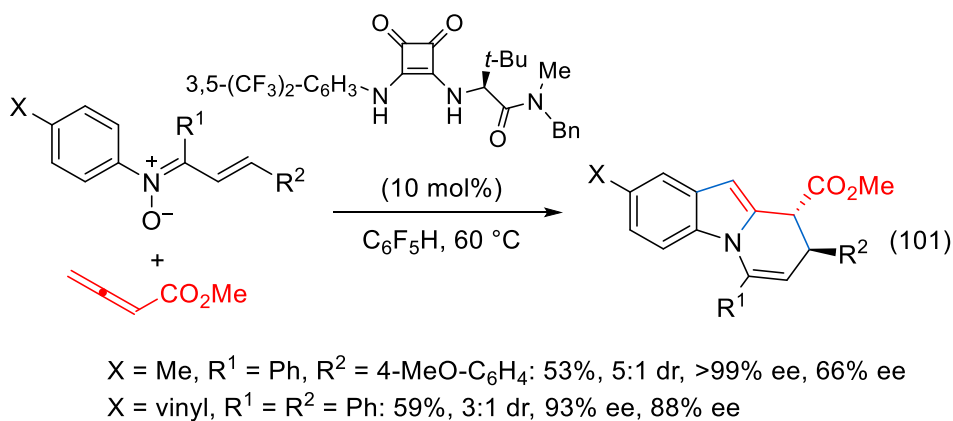


3.4. Reaction with Allenes

The addition and rearrangement reactivity of nitrones with allenes has been studied for the synthesis of a variety of different heterocycles. Blechert and coworkers²³⁶ and Padwa and coworkers²³⁷ independently reported that the treatment of *N*-arylnitrones with allenoate derivatives can provide access to benzazepin intermediates that undergo either retro-Michael or retro-Mannich ring opening to give 2-vinylindole (eq 99) or 2-alkylindole products (eq 100), respectively, depending on the substitution pattern of the allenes.

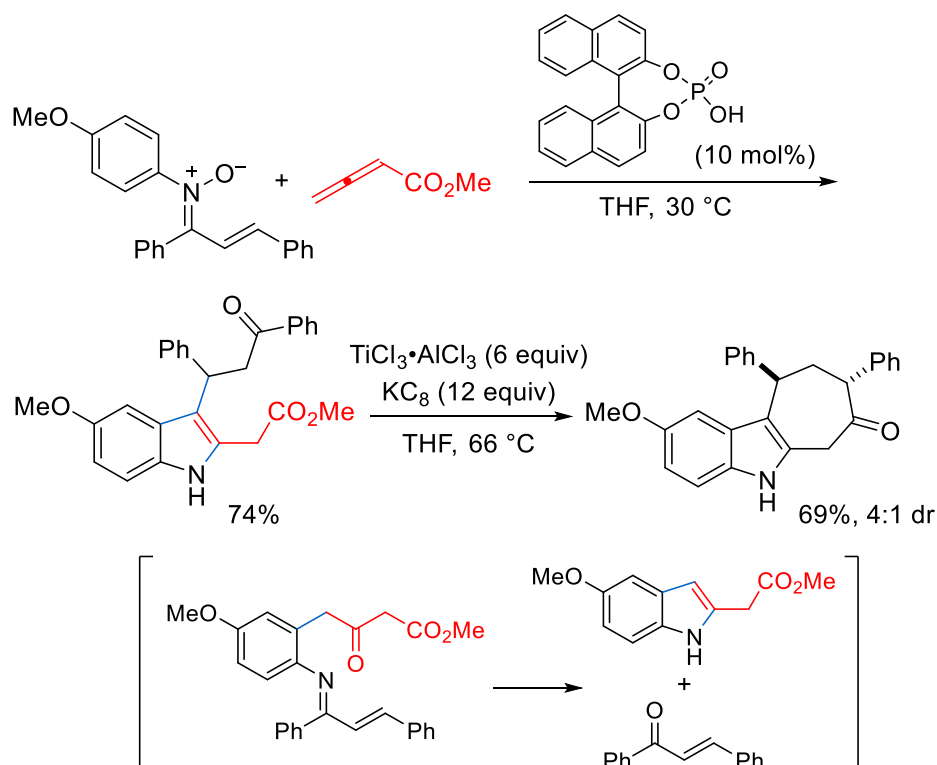


These formation of indoles have been extended to prepare dihydrocarbazole or dihydropyridoindole products.^{238,239} Anderson and coworkers discovered the first catalytic asymmetric version of these cascade reactions providing dihydropyrido[1,2-*a*]indoles with high diastereoselection and excellent enantioselectivity (eq 101).²⁴⁰

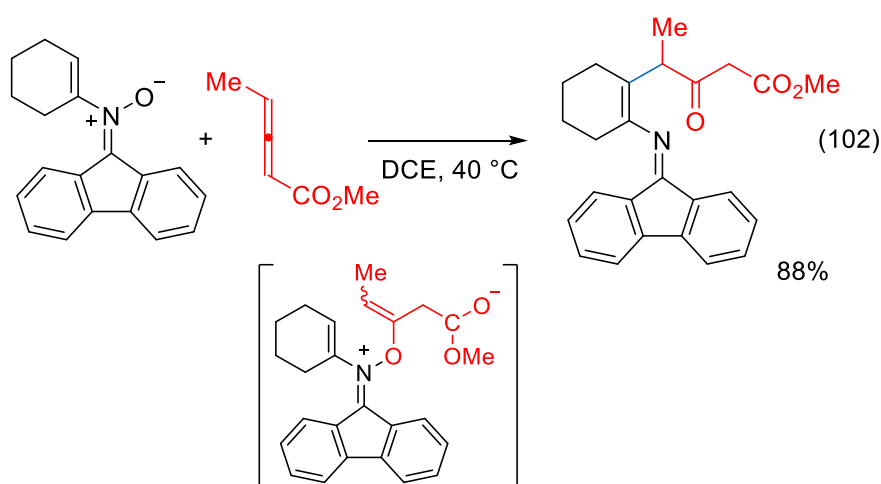


The reaction of *N*-aryl- α,β -unsaturated nitrones with electron-deficient allenes in the presence of phosphoric acid catalyst gives 3-functionalized indoles. The heterocycles prepared from the cascade synthesis undergo a McMurry coupling to form cycloheptanone-fused indoles (Scheme 24).²⁴¹

Scheme 24. Synthesis of Cycloheptanone-Fused Indoles



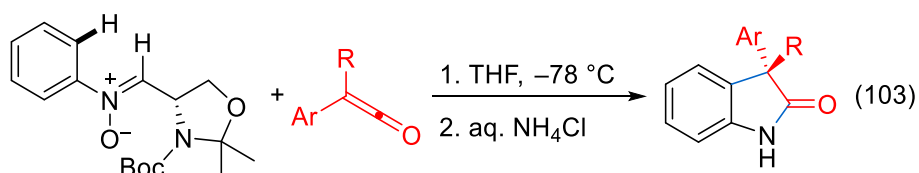
The reaction of fluorenylnitrones with electron-deficient allenes gives the corresponding 1,4-enamino ketones (eq 102).²⁴² The reaction proceeds through the [3,3]-rearrangement of dialkenylhydroxylamines generated from the addition of *N*-alkenylnitrones to electron-deficient allenes.



3.5. Reaction with Ketenes

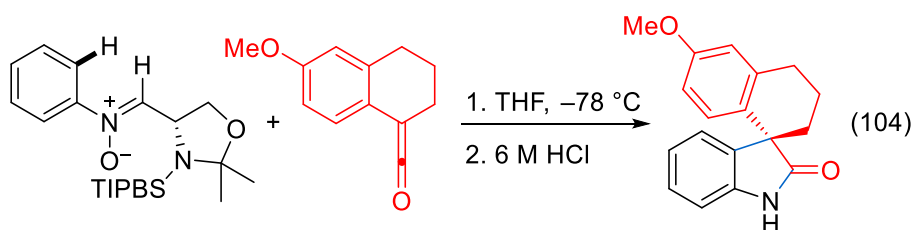
Smith and coworkers discovered an asymmetric synthesis of 3,3-disubstituted oxindoles. The reaction of the chiral *N*-arylnitrones with disubstituted ketenes gives 3,3-disubstituted

oxindoles (eq 103).²⁴³ This methodology has been extended to the asymmetric construction of 3,3-spirocarbocyclic oxindoles (eq 104).²⁴⁴ The reaction seems to involve a [3 + 2] cycloaddition across the ketene C=O bond, with preferential *anti*-addition with respect to the aryl portion of the ketene.²⁴⁵ This method has been applied to the synthesis of a Roche anti-cancer agent.



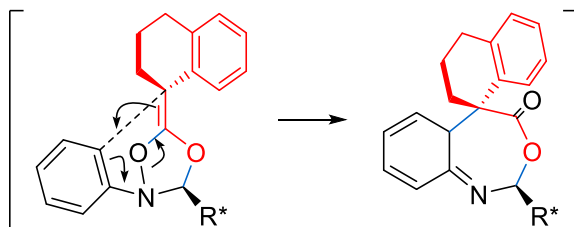
Ar = Ph, R = Me: 85%, 87% ee

Ar = 4-MeO-C₆H₄, R = Et: 88%, 90% ee



TIPBS = 2,4,6-triisopropylbenzenesulfonyl

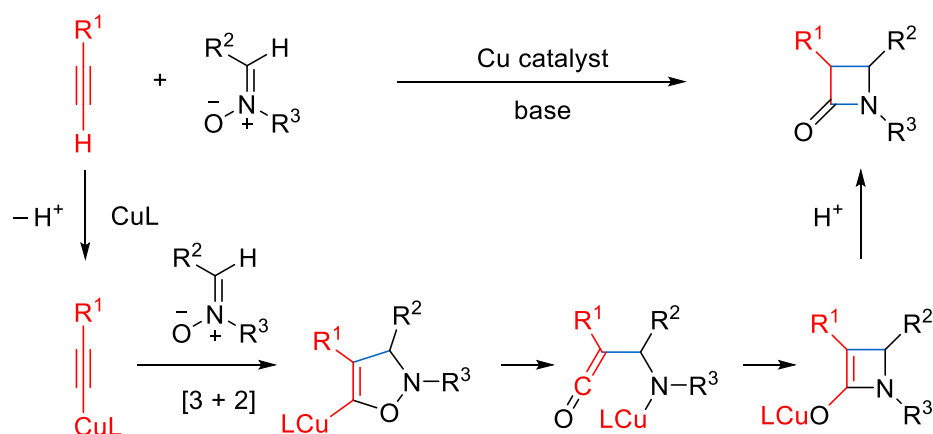
98%, 97% ee



3.6. Reaction with Terminal Alkynes (Kinugasa Reaction)

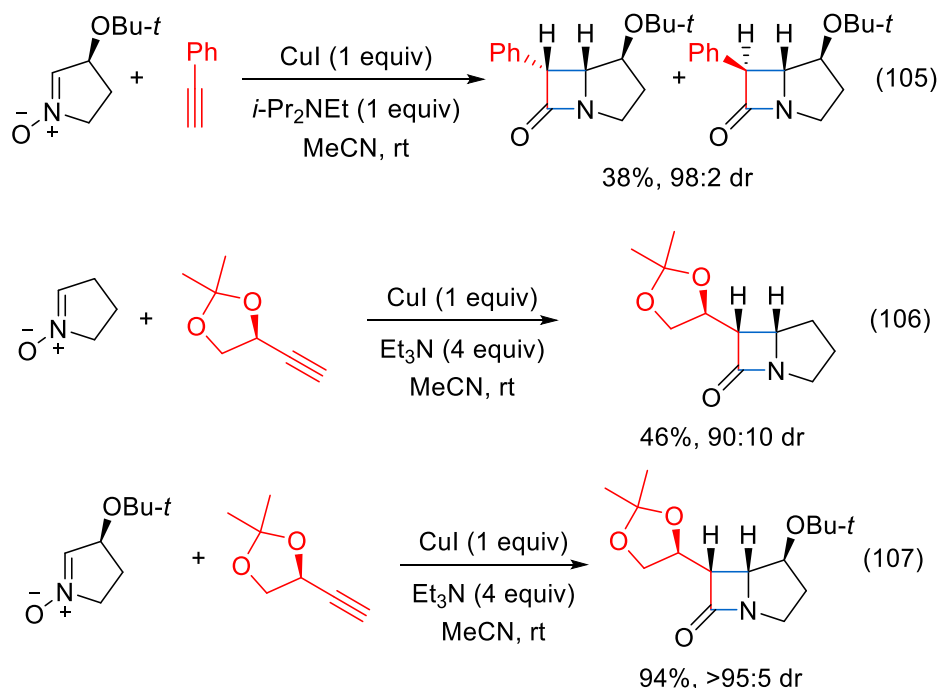
In 1972, Kinugasa and Hashimoto reported that the copper-promoted reaction of nitrones with phenylacetylide gives β -lactams.²⁴⁶ This reaction is highly useful for synthesis of β -lactams, which are key structure for biologically important antibiotics and has been received much attentions.²⁴⁷⁻²⁵⁰ This reaction involves a 1,3-dipolar cycloaddition–rearrangement cascade process catalyzed by copper ions and treatment with an organic base (Scheme 25).

Scheme 25. Kinugasa Reaction



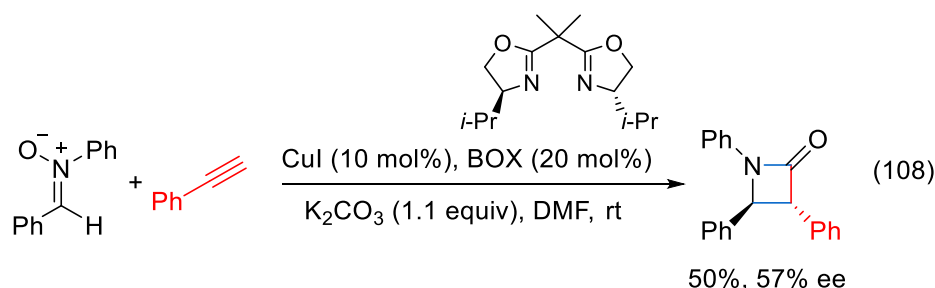
Diastereoselective reactions have been reported by two methods; the reaction of chiral nitrones with acetylenes and the reaction of achiral nitrones with chiral acetylenes. Diastereoselective reaction of chiral nitrone with phenylacetylene gives *cis*-azetidinones predominantly (eq 105).²⁵¹ The geometry of the carbapenam skeleton depends on the first step of the 1,3-dipolar cycloaddition. The major product displays the relative *cis*-orientation of protons in the four-membered β -lactam ring.

On the other hand, diastereoselective reaction of achiral nitrone with chiral alkyne proceeds to give chiral β -lactam (eq 106). The reaction of chiral nitrone with chiral alkyne gives the product through double asymmetric induction (eq 107).²⁵²

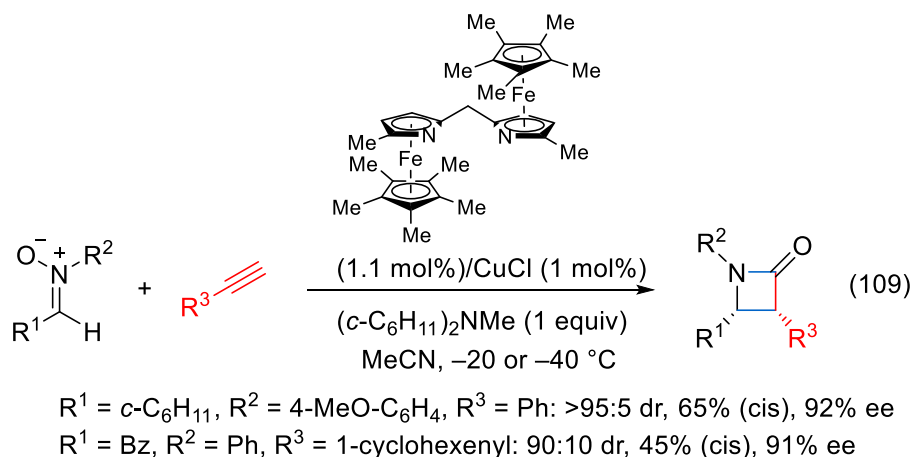


The first catalytic modification of Kinugasa reaction was reported by Miura and Nomura

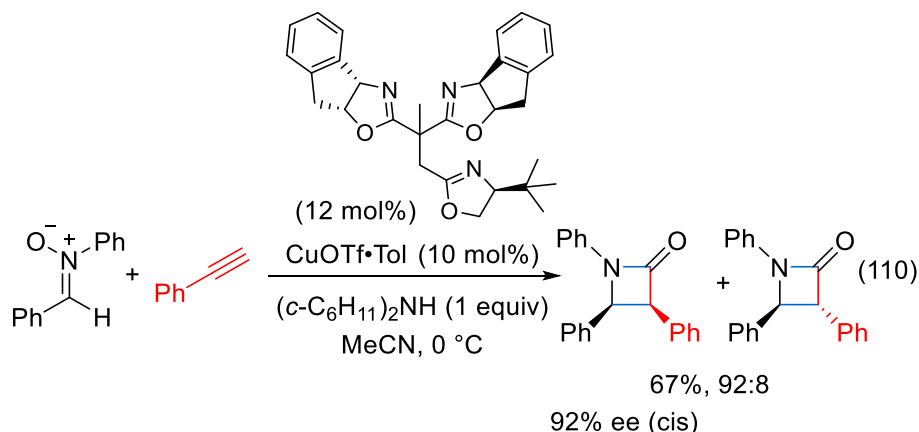
in 1993,²⁵³ and asymmetric version was reported by the same research group in 1995.²⁵⁴ The reaction of phenyl substituted nitron with phenylacetylene in the presence of CuI and bisoxazoline ligand (BOX) gives the β -lactam (cis/trans=66:34, for the trans-diastereomer up to 57% ee) (eq 108).



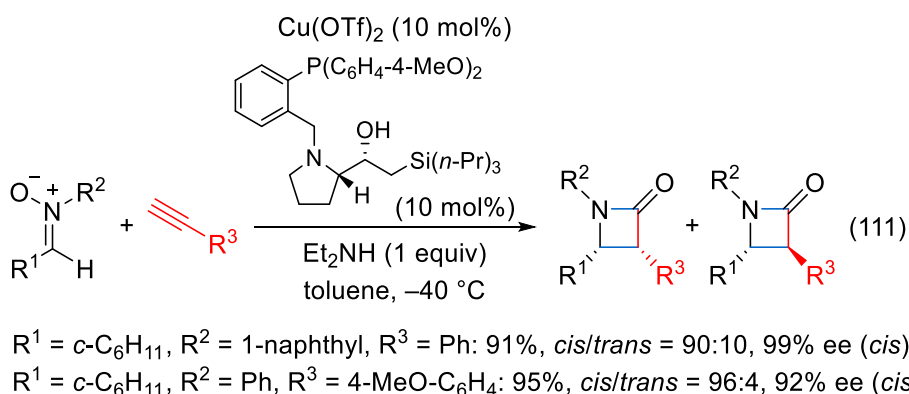
The first diastereo- and enantioselective catalytic variant was reported by Fu and coworkers in 2002. The reactions of nitrones with terminal alkynes afford cis β -lactams selectively using a CuCl catalyst and a C_2 -symmetric planar chiral bis(azaferrocene) ligand in the presence of dicyclohexylmethylamine. This method can be applied to various substituted alkynes. The cis products are obtained in very high diastereoselectivity, good enantioselectivity, and modest to high isolated yields (eq 109).²⁵⁵



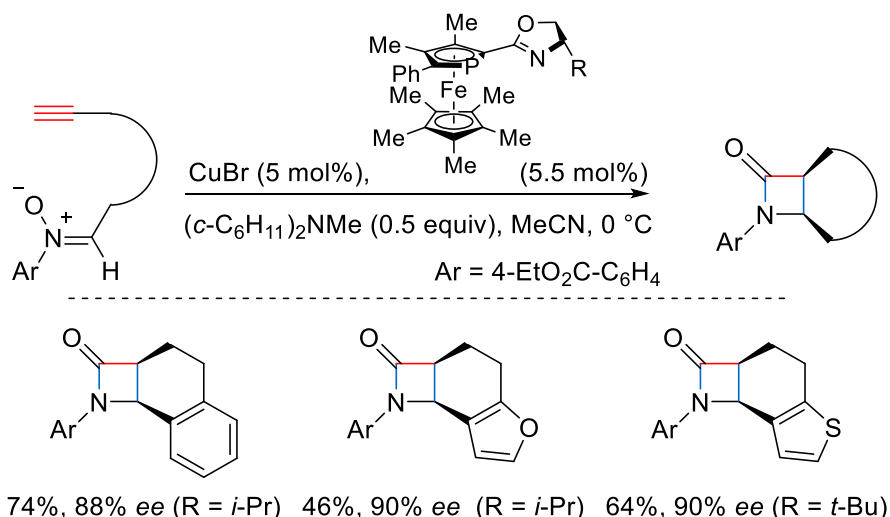
Tang and coworkers found that the use of Cu(OTf)₂•Tol catalyst with tris(oxazoline) ligand gives cis β -lactams with high enantioselectivity (eq 110).²⁵⁶



Sawamura and coworkers reported that copper-catalyzed reaction with prolinol–phosphine chiral ligand gives 1,3,4-trisubstituted chiral β-lactams with high enantioselectivity. Catalytic reaction with the unique ligand seems to involve two-point hydrogen bonding between the chiral ligand and the nitronium oxyanion and C(sp³)—H...O hydrogen bonds (eq 111).²⁵⁷ Using atropisomeric monophosphine *N*-PINAP ligand developed by Carreira and coworkers, the catalytic Kinugasa reaction was investigated, while the results are not as good as those obtained using Fu ligand.²⁵⁸ Fu and Shintani extended to the catalytic intramolecular reaction. Using planar chiral phosphaferrrocene-oxazoline ligand with CuBr and dicyclohexylmethylamine, tricyclic β-lactams were obtained in high enantioselectivity (85–91% ee) (Scheme 26).²⁵⁹ Theoretical study of the mechanism including stereoselectivity has been reported.²⁶⁰

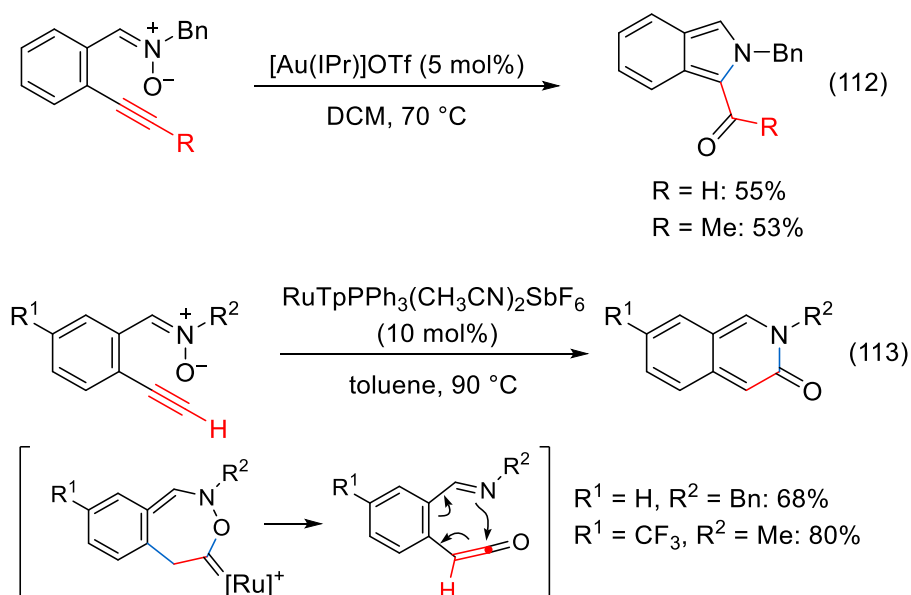


Scheme 26. Intramolecular Enantioselective Kinugasa Reaction



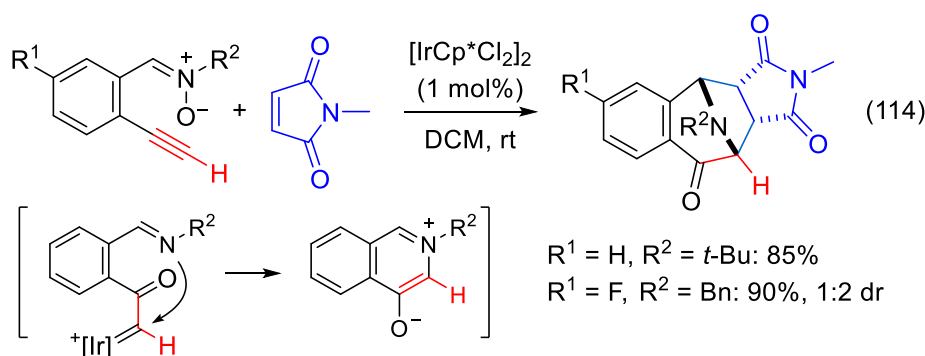
3.7. Reaction of Nitrone-Functionalized Terminal Alkynes

Catalytic cyclization of *C*-(*o*-alkynylaryl)nitrones provides various cyclic products depending on the catalysts used. The gold-catalyzed redox-cyclization affords isoindoles with the intermediacy of both an α -oxo carbenoid and a five-membered azomethine gold species.²⁶¹ Thus, the reaction of these nitrones in the presence of [Au(IPr)]OTf [IPr = *N,N'*-bis(2,6-diisopropylphenyl)imidazole-2-ylidene] catalyst provides isoindoles (eq 112). In contrast, RuTpPPh₃L₂X-catalyzed [Tp = tris(1-pyrazolyl)borate] cyclization of these nitrones yields 3-isoquinolones (eq 113).²⁶²

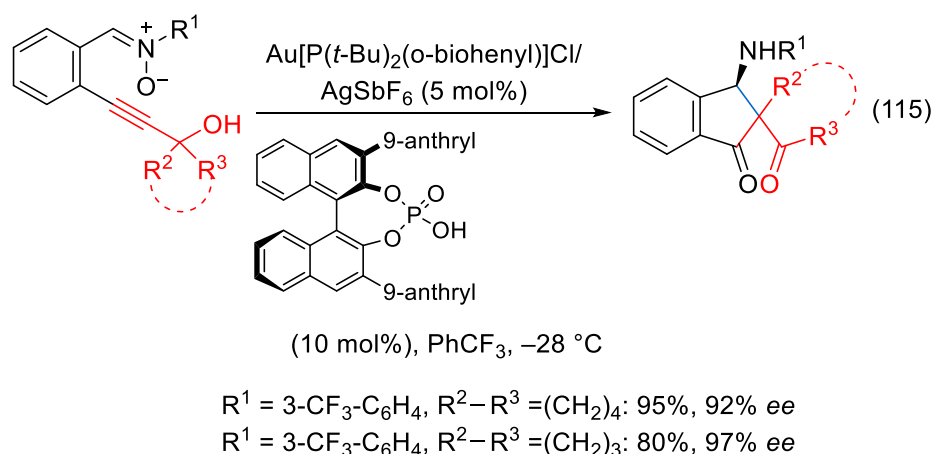


Iridium catalyzed internal redox cyclization of similar substrates gives unusual azomethine ylides, which are highly useful for [3 + 2] dipolar cycloaddition reaction with activated alkynes

and alkenes (eq 114).²⁶³



A gold-catalyzed reaction of hydroxy-alkyne substituted nitrones provides the efficient redox–pinacol–Mannich–Michael cascade to give aminoindanone derivatives.²⁶⁴ Using chiral phosphine ligand and chiral Brønsted acid catalyst, chiral α -amino spirocyclic and quaternary diketone derivatives are obtained with up to 99% ee (eq 115).²⁶⁵

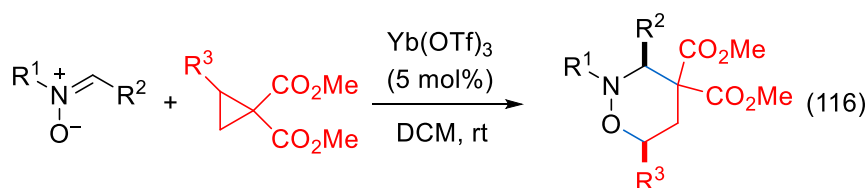


3.8. Cycloaddition Reaction

3.8.1. [3 + 3] Cycloaddition Reaction

For the formal [3 + 3] cycloaddition reactions of nitrones, there would be four types of reactions which include additions of cyclopropanes, trimethylenemethanes, vinyl diazoacetate, and alkenylgold complex metal carbenoids generated through cycloisomerization. These reactions are highly useful for synthesis of heterocyclic compounds and have been received much attention as shown in reviews and accounts.^{14,16}

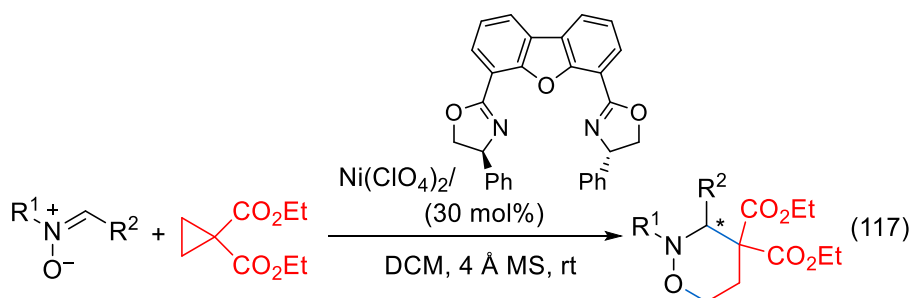
Kerr and coworkers found that nitrones react with cyclopropanes in the presence of Yb(OTf)₃ to give the 3,5-disubstituted cis isomer of [3 + 3] adduct regio- and diastereoselectively (eq 116).²⁶⁶ MgI₂²⁶⁷ and Ca(OTf)₂²⁶⁸ show similar catalytic activity.



$R^1 = p\text{-Tol}$, $R^2 = R^3 = \text{Ph}$: 94%

$R^1 = p\text{-Tol}$, $R^2 = \text{Ph}$, $R^3 = (E)\text{-PhCH=CH}$: 95%

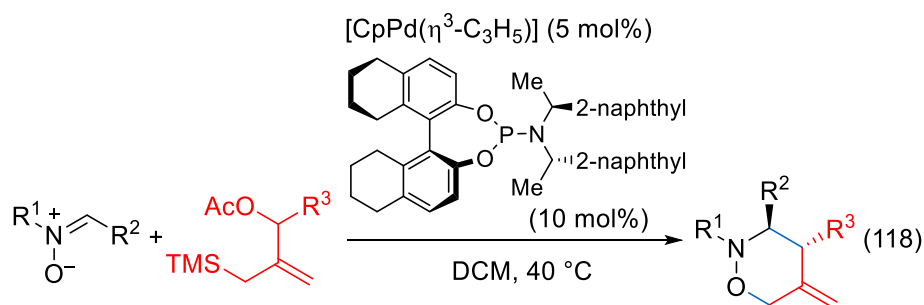
Sibi and coworkers reported the first example of chiral Lewis acid catalysis in the formation of the tetrahydro-1,2-oxazines from the addition of nitrones to cyclopropanes with very high enantioselectivity.²⁶⁹ Thus, the reaction of achiral cyclopropanes with nitrones in the presence of $Ni(ClO_4)_2$ /ligand gives the [3 + 3] adducts in excellent yields with high ee (eq 117). The reaction with substituted cyclopropanone dicarboxylates resulted in moderate diastereoselectivity, while enantioselectivities of both isomers are high. Similar nickel(II)-catalyzed [3 + 3] cycloaddition of racemic 2-substituted cyclopropane-1,1-dicarboxylates with nitrones occurs with efficient kinetic resolution providing optically active tetrahydro-1,2-oxazine derivatives with high diastereoselectivity and enantioselectivity.²⁷⁰



$R^1 = \text{Me}$, $R^2 = \text{Ph}$: 99%, 92% ee

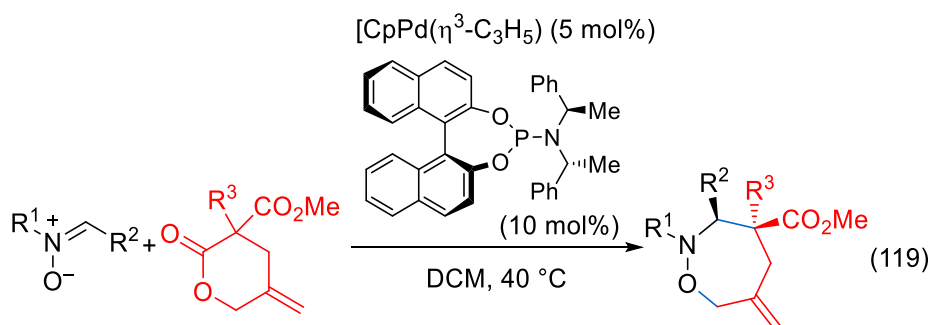
$R^1 = \text{Bn}$, $R^2 = \text{Ph}$: 99%, 93% ee

Hayashi and coworkers demonstrated that palladium-catalyzed asymmetric [3 + 3] cycloaddition of trimethylenemethane derivatives with nitrones gives 1,2-oxazines. Using a modified phosphoramidite ligand, these compounds were obtained with high stereoselectivity (eq 118).²⁷¹ The palladium-catalyzed system has been extended to γ -methylene- δ -valerolactones to give tetrahydro-1,2-oxazepines (eq 119) by a [3 + 4] formal cycloaddition.²⁷²



$R^1 = 4\text{-EtO}_2\text{C-C}_6\text{H}_4$, $R^2 = 4\text{-CF}_3\text{-C}_6\text{H}_4$, $R^3 = \text{Ph}$: 95%, 89:11 dr, 92% ee (trans)

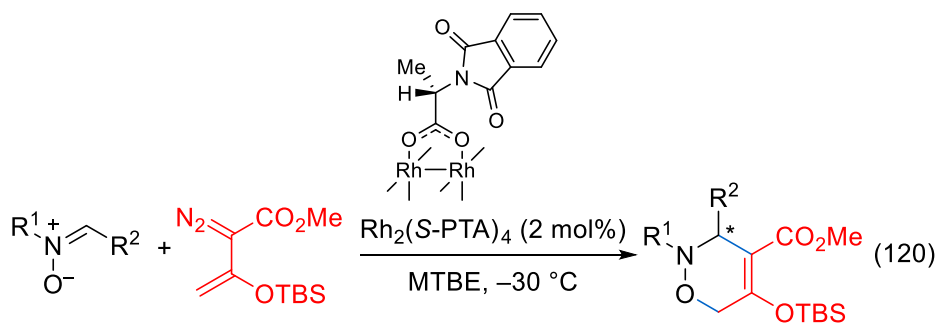
$R^1 = 4\text{-EtO}_2\text{C-C}_6\text{H}_4$, $R^2 = \text{Ph}$, $R^3 = \text{Ph}$: 92%, 85:15 dr, 92% ee (trans)



$R^1 = 4\text{-EtO}_2\text{C-C}_6\text{H}_4$, $R^2 = 4\text{-CF}_3\text{-C}_6\text{H}_4$, $R^3 = \text{Ph}$: 98%, 81:19 dr, 83% ee
(major diastereomer)

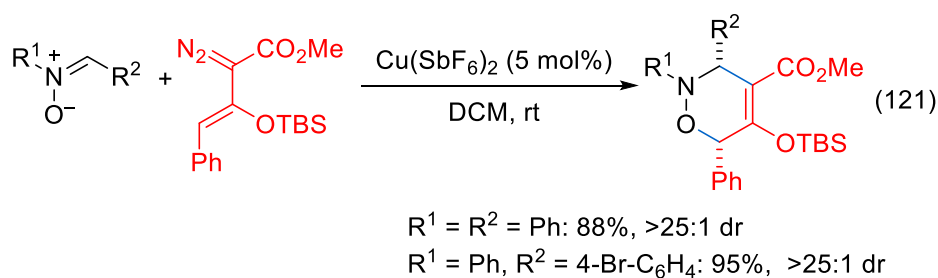
$R^1 = 4\text{-EtO}_2\text{C-C}_6\text{H}_4$, $R^2 = 4\text{-CF}_3\text{-C}_6\text{H}_4$, $R^3 = 1\text{-naphthyl}$: 98%, 80:20 dr, 96% ee
(major diastereomer)

Doyle and coworkers discovered that dirhodium(II) carboxylate-catalyzed [3 + 3] cycloaddition reactions of nitrones with a β -TBSO-substituted vinyl diazoacetate occur to give 3,6-dihydro-1,2-oxazines. High enantiocontrol occurs with catalysis of (*S*)-*N*-phthaloylamino acid-ligated dirhodium carboxylates [Rh₂(*S*-PTA)₄] for [3 + 3] cycloaddition reaction (eq 120).²⁷³ Changing the substituent at the vinylogous position can inhibit this cycloaddition pathway. It is noteworthy that catalysis by Cu(SbF₆)₂ gives the [3 + 3] cycloaddition product selectively to favor the cis isomer (eq 121).²⁷⁴

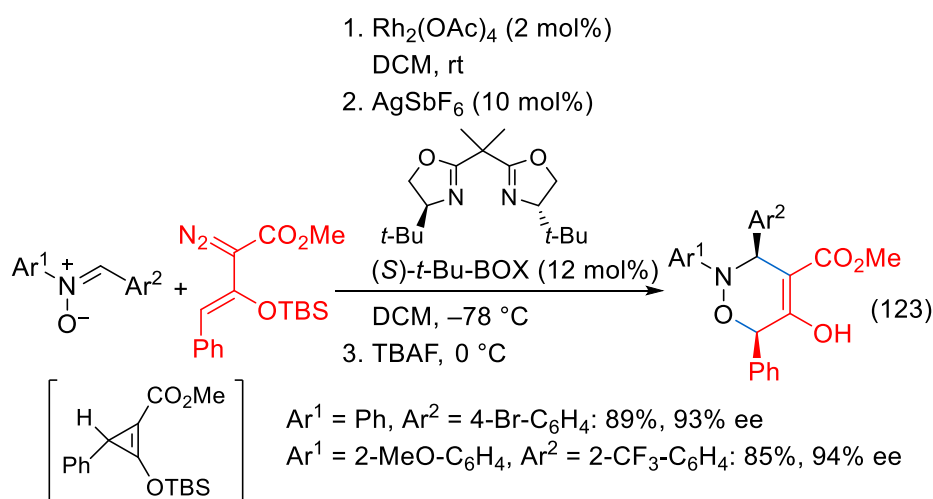
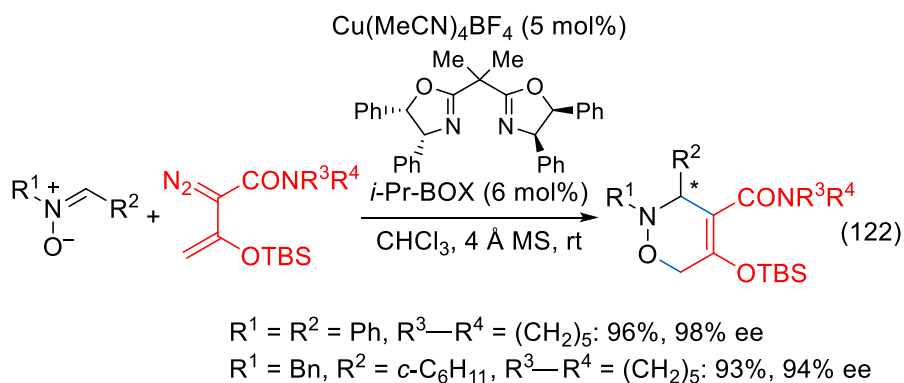


$R^1 = R^2 = \text{Ph}$: 95%, 93% ee

$R^1 = \text{Ph}$, $R^2 = c\text{-C}_6\text{H}_{11}$: 85%, 77% ee

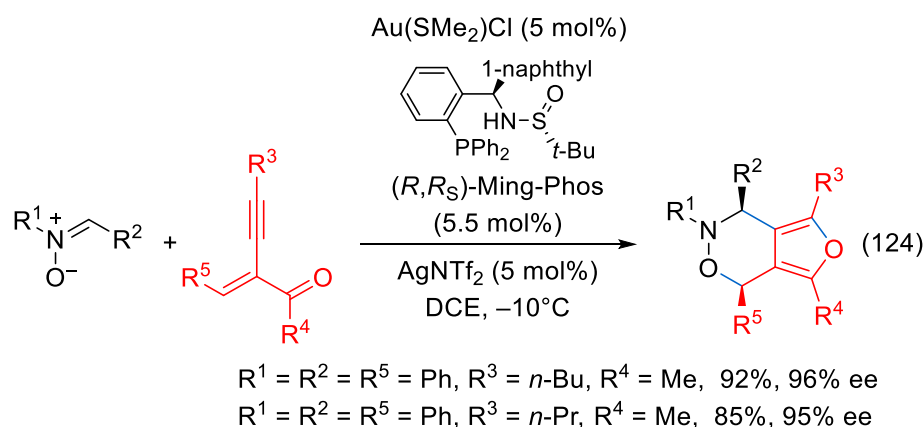


Doyle extended this reaction to asymmetric synthesis of [3 + 3] cycloadducts using copper tetrafluoroborate/bisoxazoline complex catalyst (eq 122).^{275,276} Silver-catalyzed asymmetric [3 + 3] cycloaddition of nitrones gives 3,6-dihydro-1,2-oxazine derivatives with exceptional stereocontrol. The reaction involves formation of donor–acceptor cyclopropane by dirhodium acetate-catalyzed dinitrogen extrusion followed by intramolecular cyclization of enoldiazoacetates (eq 123).²⁷⁷



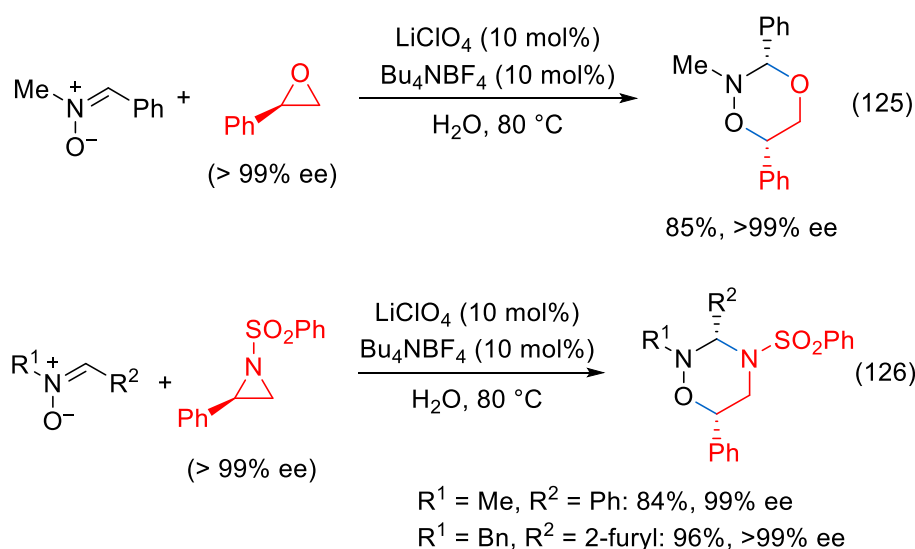
Zhang and coworkers reported that asymmetric gold-catalyzed reaction of 2-(1-alkynyl)-alk-2-en-1-ones with nitrones proceeds with excellent diastereo- and enantioselectivity with concomitant furan ring formation. Importantly, using two sets of diastereomeric (R,R_S)- and

(*S,R*_S)-Ming-Phos ligands, both enantiomers can be obtained easily (eq 124).²⁷⁸



Lewis acid-catalyzed reaction of three-membered heterocycles, such as oxiranes, aziridines, and thiiranes, with nitrones gives six-membered heterocycles. A broad substrate scope was obtained for aluminum or indium catalysts.²⁷⁹

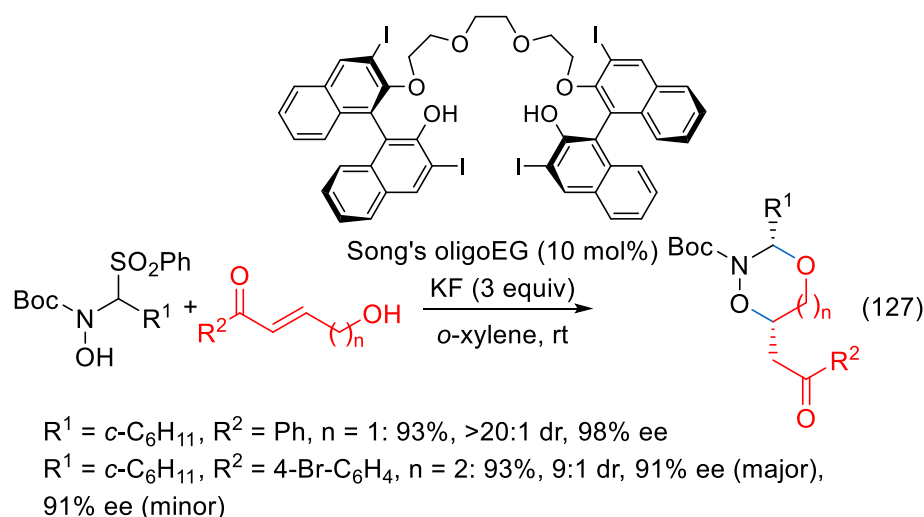
Efficient and regio- and stereoselective synthetic routes to chiral 1,4,2-dioxazinanes (eq 125) and 1,2,4-oxadiazinanes (eq 126) with excellent de/ee (>99%) have been developed via the domino ring-opening cyclization of epoxides and *N*-activated aziridines with nitrones using a $\text{LiClO}_4/\text{Bu}_4\text{NBF}_4$ dual catalyst system.²⁸⁰



4-Dimethylaminopyridine²⁸¹ or Na_2CO_3 ²⁸²-mediated [3 + 3] cycloaddition reaction of nitrones with aza-oxyallyl cation proceeds to give 1,2,4-oxadiazinan-5-ones under metal-free conditions.

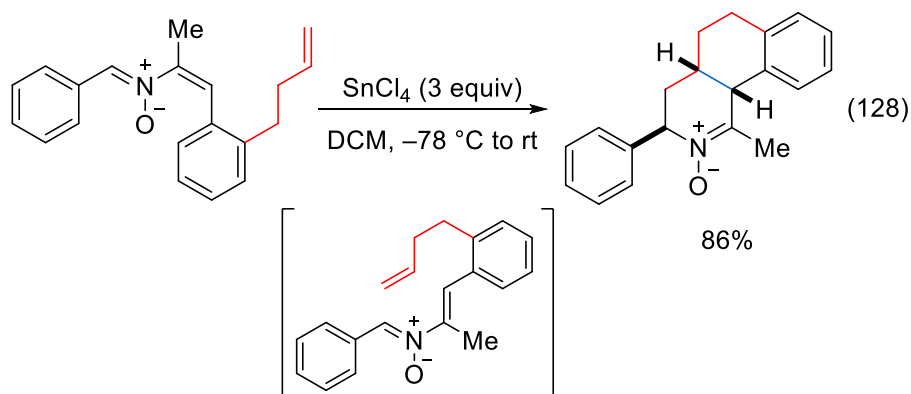
The reaction of *N*-Boc-*N*-hydroxy amido sulfones with allylic and homoallylic hydroxy-substituted α,β -unsaturated carbonyls in the presence of Song's chiral oligo(ethylene glycol)

and KF gives six or seven-membered heterocycles. The reaction seems to occur through a tandem pathway sequence of oxa-Mannich/oxa-Michael/tautomerization/protonation (eq 127).²⁸³

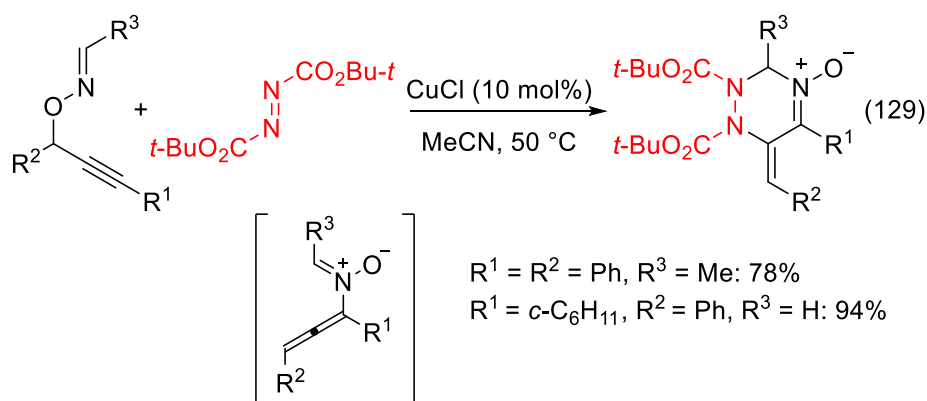


3.8.2. Other Cycloaddition Reactions

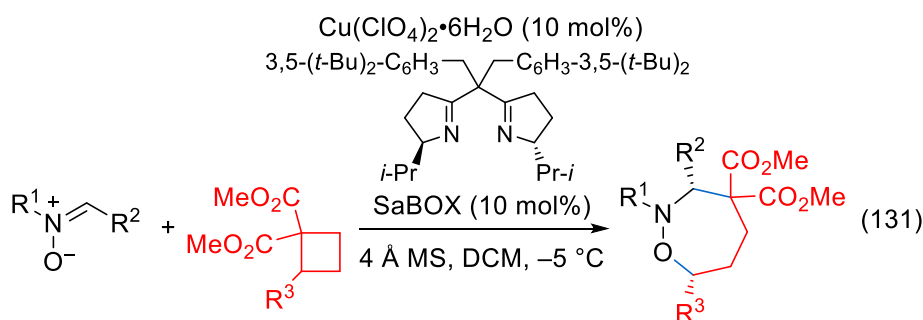
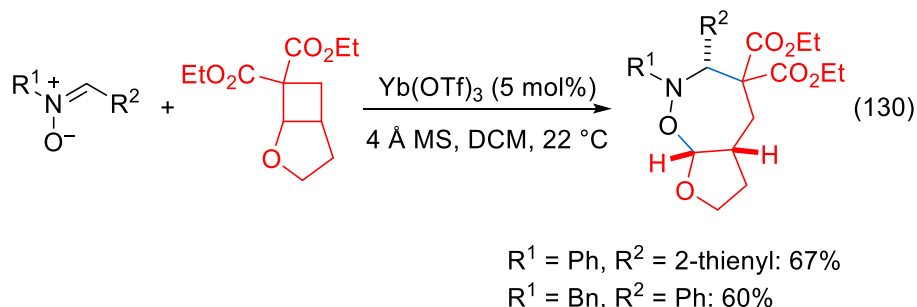
Denmark and coworkers have first reported intramolecular [4 + 2] cycloaddition of *N*-vinyl nitrones bearing a tethered dienophile upon treatment with SnCl_4 to give tetrahydropyridine *N*-oxide (eq 128).¹²⁵



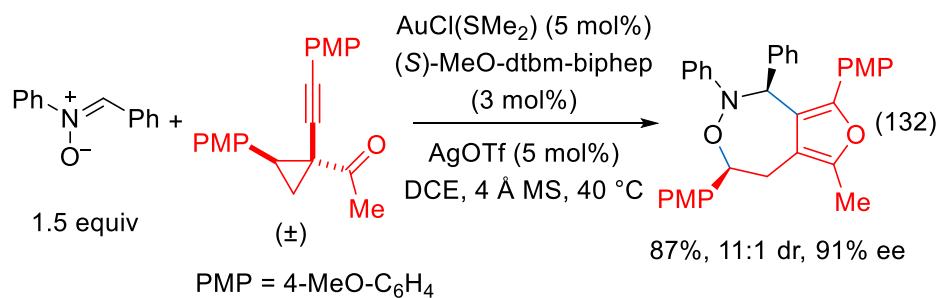
N-Allenyl nitrones act as 2-azadienes in the copper-catalyzed cascade reaction of *O*-propargylic oximes with azodicarboxylates to undergo [4 + 2] cycloaddition affording 1,2,4-triazine oxides (eq 129).²⁸⁴



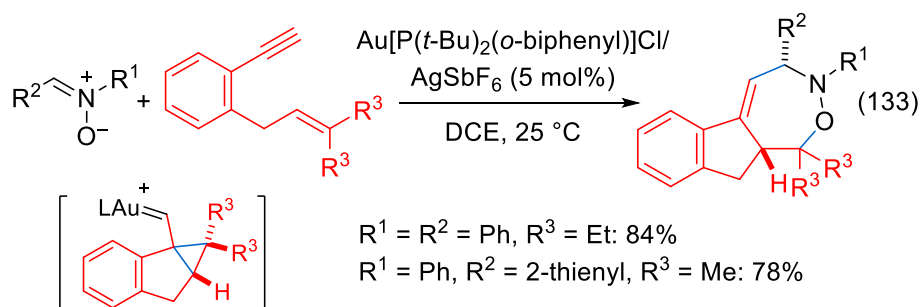
The ytterbium-catalyzed [4 + 3] cycloaddition of 2-alkoxy-1,1-dicarboxylate, activated donor–acceptor cyclobutanes, with nitrones gives seven-membered 1,2-oxazepane derivatives (eq 130).²⁸⁵ Using chiral SaBOX/Cu(II) catalyst the similar reaction occurs to give multifunctionalized optically active 1,2-oxazepanes with excellent stereocontrol (eq 131).²⁸⁶ The [4 + 3] cycloaddition of α -halogeno hydrazones with nitrones gives 2,3,4,7-tetrahydro-1,2,4,5-oxatriazepines in the presence of sodium carbonate.²⁸⁷ Copper or gold-catalyzed [4 + 3] cycloadditions of nitrones with 1-(1-alkynyl)cyclopropyl ketones give seven-membered heterocyclic compounds selectively.²⁸⁸ Optically active adducts can be obtained via dynamic kinetic resolution process using gold complex with a chiral phosphine ligand (eq 132).²⁸⁹



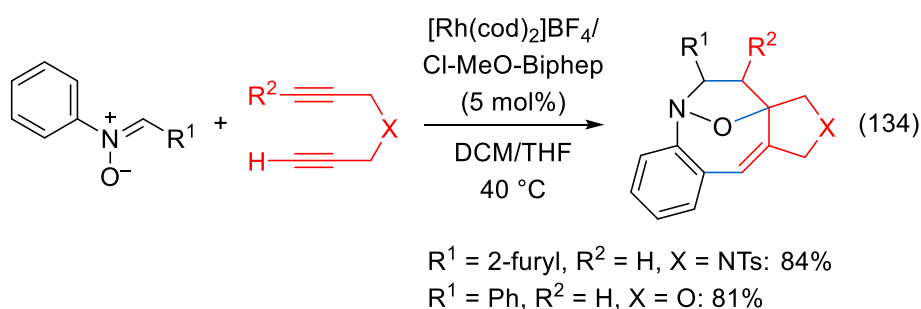
$R^1 = 4\text{-MeO-C}_6\text{H}_4, R^2 = 4\text{-Cl-C}_6\text{H}_4, R^3 = 2\text{-thienyl}: 66\%, >99:1 \text{ dr}, 96\% \text{ ee}$
 $R^1 = \text{Ph}, R^2 = 4\text{-Cl-C}_6\text{H}_4, R^3 = 4\text{-MeO-C}_6\text{H}_4: 96\%, 97:3 \text{ dr}, 95\% \text{ ee}$



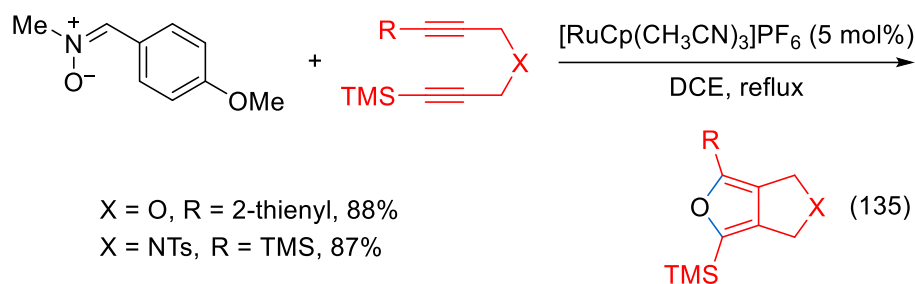
Gold-catalyzed cyclization/[2 + 2 + 3] cycloaddition cascade between nitrones and 1,6-enynes gives 1,2-oxazepane derivatives. (eq 133).²⁹⁰ The importance of this reaction is the occurrence of 1,2-oxazepane moieties in several bioactive molecules.



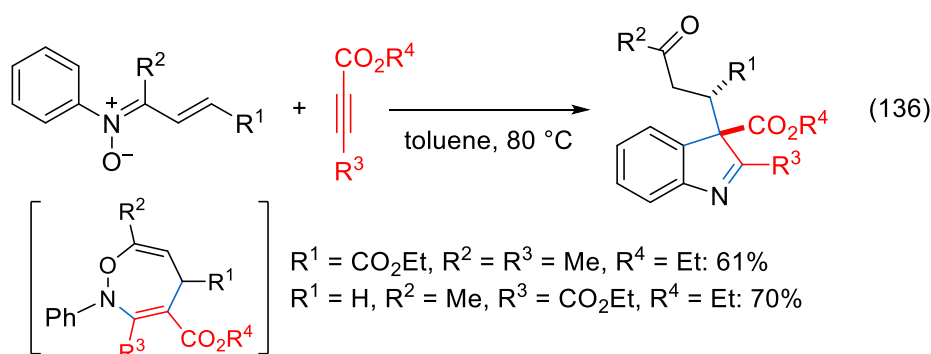
The rhodium-catalyzed reaction of *N*-aryl-substituted nitrones with diynes gives bridged eight-membered heterocycles. This reaction involves catalytic C—H activation of the *N*-aryl ring and [2 + 2 + 5] cycloaddition (eq 134).²⁹¹



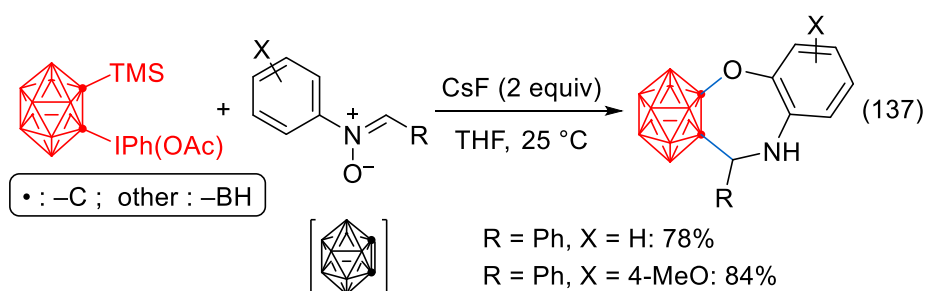
The ruthenium-catalyzed transfer oxygenative [2 + 2 + 1] cycloaddition of silyldiynes produces bicyclic 2-silylfurans. Nitrones are used as adjustable oxygen atom donors (eq 135).²⁹²



The reaction of α,β -unsaturated *N*-aryl ketonitrones with activated alkynes gives C3-quaternary indolenines without transition metal catalysis via [5 + 2] cyclization (eq 136).²⁹³



The reaction of nitrones with *o*-carboryne affords carborane-fused seven-membered heterocycles via formal [5 + 2] cycloaddition. The [3 + 2] cycloaddition, N—O bond cleavage, oxygen migration, and rearomatization seems to be involved (eq 137). The nitronone moieties seem to serve as five-atom coupling partners.²⁹⁴

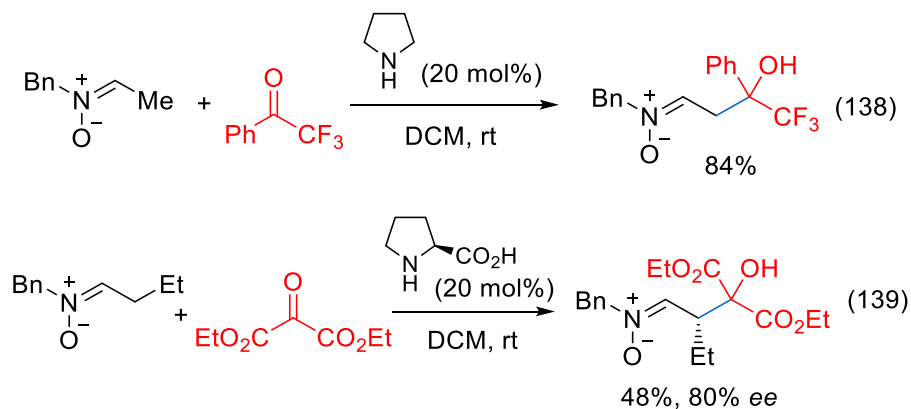


3.9. Other Reactions

3.9.1. Aldol-Type Reaction

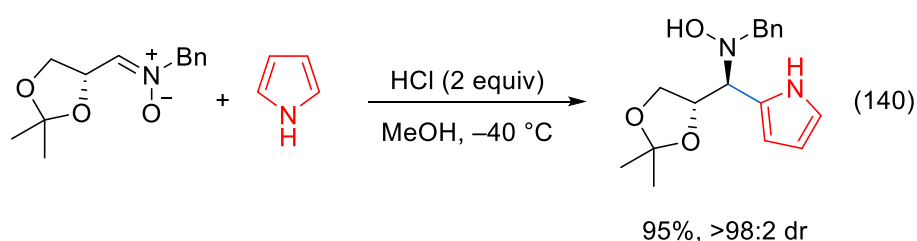
The aldol-type reaction of nitrones with carbonyl compounds gives functionalized β -hydroxynitrones. The α -carbon atom of the nitronone react with electron-deficient ketones (eq

138).²⁹⁵ The use of L-proline leads to optically active β -hydroxynitrones (eq 139).²⁹⁵ Jørgensen and coworkers proposed the mechanism, which was confirmed using density functional theory at B3LYP/6-31G.²⁹⁶ Merino and coworkers reported that the reaction of azomethine ylide *N*-oxides derived from nitrones with aldehydes in the presence of *n*-butyllithium catalyst gives 3-oxazolines.²⁹⁷



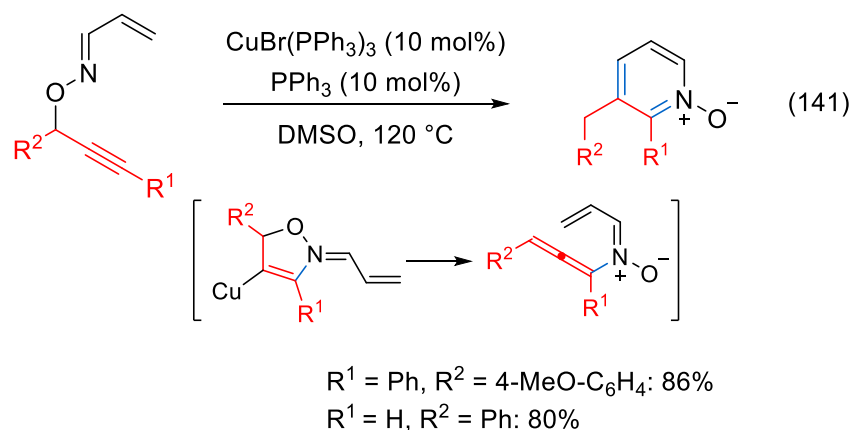
3.9.2. Friedel-Crafts-Type Reaction

Friedel-Craft type reaction of nitrones to electron rich arenes such as indoles takes place in the presence of HCl to give 3-indolylhydroxylamines.²⁹⁸ Regioselective additions of pyrroles to optically active nitrones give chiral pyrrolic *N*-hydroxylamines (eq 140).²⁹⁹ Similarly, the reaction of polyhydroxylated cyclic nitrones with aromatic compounds catalyzed by Brønsted acid gives 2-aryl-substituted polyhydroxylated pyrrolidines.³⁰⁰

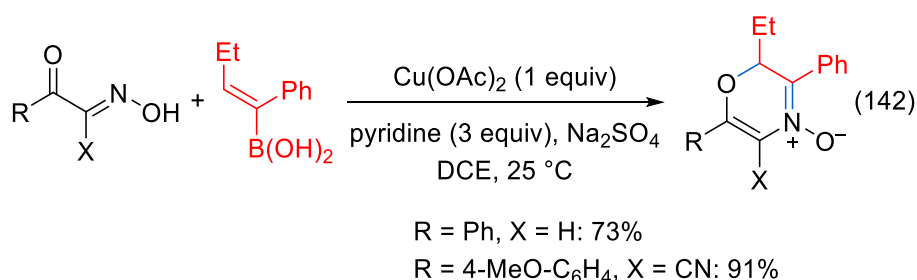


3.9.3. Electrocyclization Reaction

Nakamura and Terada reported the copper-catalyzed reactions of (*E*)-*O*-propargylic α,β -unsaturated oximes. This reaction involves [2,3]-rearrangement to the *N*-allenynitrones followed by 6 π -3-azatriene electrocyclization affording polysubstituted pyridine *N*-oxides (eq 141).³⁰¹



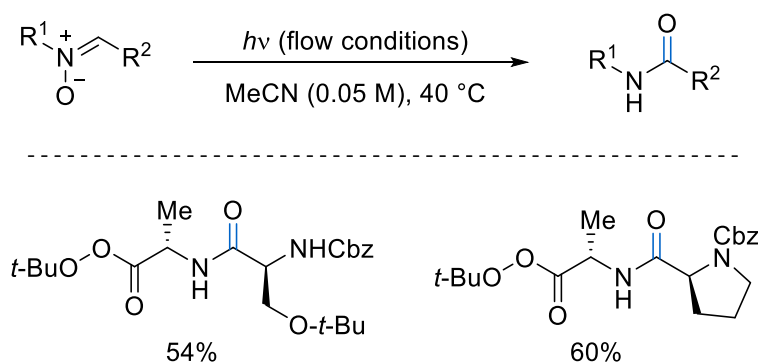
As described in section 2.3, *N*-alkenylnitrones formed by coupling of oximes and alkenyl boronic acids undergo a variety of novel rearrangements, as well as addition and rearrangement reactions. Anderson and coworkers found a single-flask procedure for the generation of α -keto-*N*-alkenylnitrones and subsequent 6π electrocyclicization for synthesis of 2*H*-1,4-oxazine *N*-oxides (eq 142).³⁰² This method is highly useful for synthesis of diverse novel heterocycles. It is noteworthy that *N*-alkenyl- α,β -unsaturated nitrones undergo thermal rearrangement to give tri- and tetrasubstituted pyridines.⁹⁹



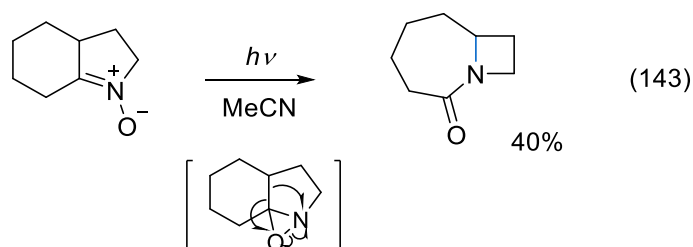
3.9.4. Rearrangement Reaction

Photochemical rearrangements of nitrones to oxaziridines³⁰³ and oxaziridines to amides³⁰⁴ have been documented. However, there are only sporadic reports of photochemical rearrangement of nitrones to amides. Jamison and coworkers found a general and versatile approach for amide bond formation using a continuous flow photochemical rearrangement of nitrones. This one-pot photochemical process using straight-forward, easily accessible, flow reaction system is highly efficient to provide simple amides and complex peptides without using activating agents. Importantly, this transformation represents a novel approach for peptide fragment coupling and expands the current scope of protein synthesis. (Scheme 27).³⁰⁵

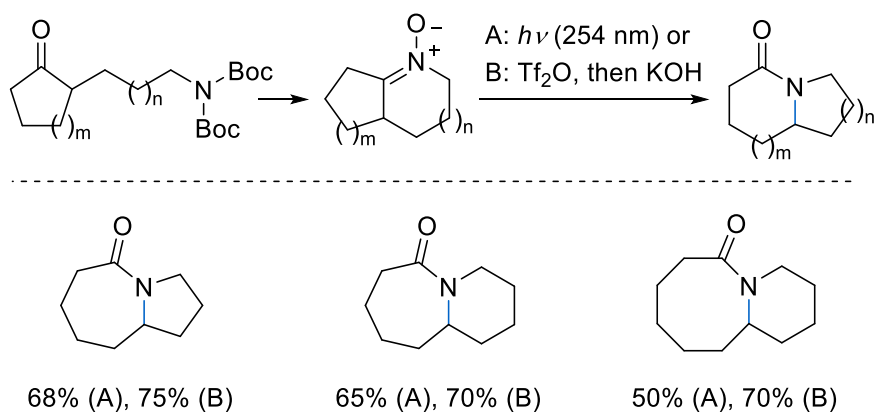
Scheme 27. Continuous-Flow Photochemical Rearrangement of

Nitrones

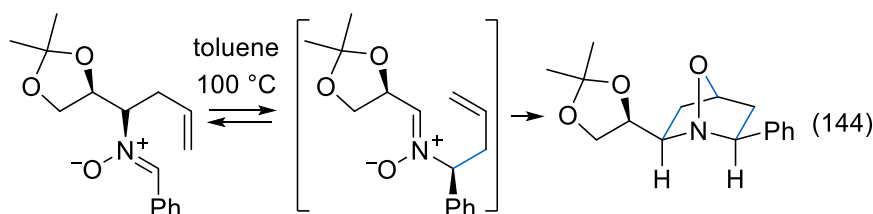
Photolysis of adequately substituted nitrones provides a convenient method for synthesis of fused bicyclic lactam scaffolds for mimicking conformationally constrained β -turn peptides as in the tripeptide RGD signaling motif of fibronectin. UV irradiation of 6/5-fused bicyclic nitronone gives the corresponding 7/4-fused bicyclic lactam (eq 143).³⁰⁶



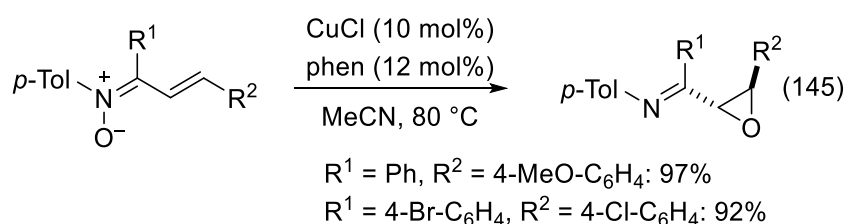
The rearrangement of nitrones to lactams can be carried out by photochemical activation or by treatment with TiF_2O followed by KOH -promoted rearrangement. Photochemical rearrangement of nitrones affords good yields of lactams. Two-step nonphotochemical process provides slightly better yields of the same targets (Scheme 28).³⁰⁷

Scheme 28. Photochemical and Base-Induced Rearrangement of Fused Nitrones

Merino demonstrated the intramolecular cycloaddition of diastereomeric enantiopure *N*-alkenylnitrones, and the corresponding theoretical calculations using DFT and ab initio methods provide evidences for a thermal sigmatropic rearrangement of the nitrones with chirality transfer (eq 144).³⁰⁸

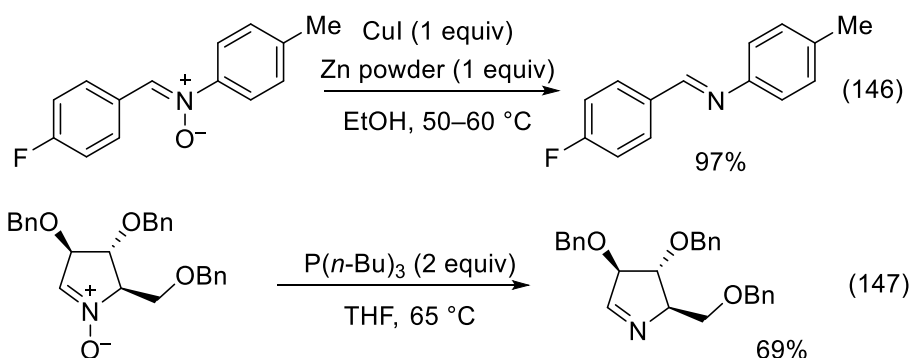


α,β -Epoxyketimines can be synthesized with excellent diastereoselectivity from α,β -unsaturated nitrones through a copper-catalyzed oxygen-atom transfer. This transformation is used in combination with a copper-catalyzed boric acid coupling for the preparation of α,β -unsaturated nitrones (eq 145).³⁰⁹



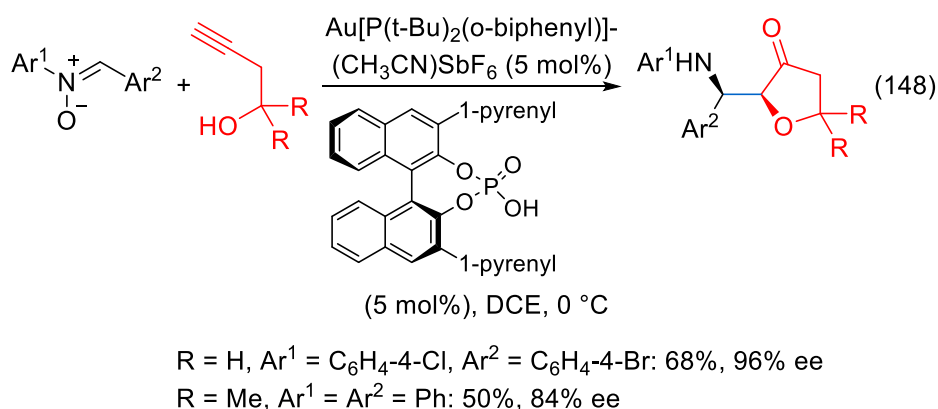
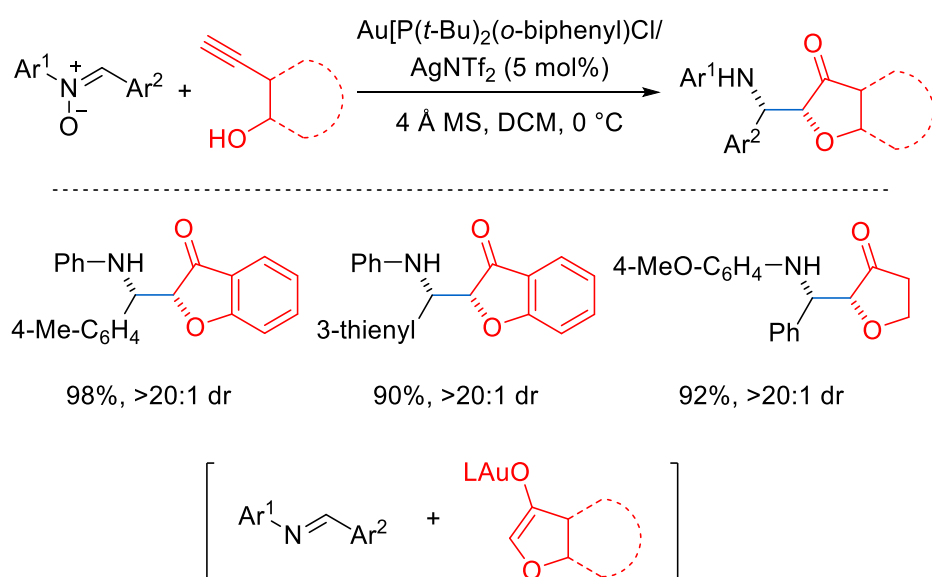
3.9.5. Reductive Deoxygenation of Nitrones to Imines

Deoxygenation of nitrones to imines is useful, and various methods have been developed. A mild and highly efficient deoxygenation of nitrones to imines is carried out upon treatment with CuI and Zn powder in ethanol (eq 146).³¹⁰ For the preparation of highly water-soluble imines, aqueous work-up should be avoided. Carbohydrate-derived cyclic nitrones are deoxygenated to form imines using tributylphosphine (eq 147).³¹¹



Gold-catalyzed reactions of 1-alkyne-4-ols and 2-ethynylphenols affords *N*-containing dihydrofuran-3(2*H*)-ones with *syn* selectivity (Scheme 29). The mechanism involves the Mannich reactions of gold enolates with imines, both of which are obtained by the oxidation of alkynes with oxygen atom of nitrones followed by cyclization.³¹² Gold-catalyzed enantioselective Mannich-type reactions proceed with the assistance of chiral phosphoric acid (eq 148).³¹³

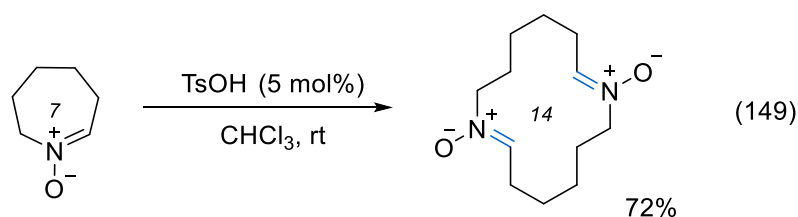
Scheme 29. Gold-Catalyzed Reaction of 3-Alkyn-1-ols with Nitrones



3.9.6. Ring Expansion Metathesis Oligomerization

Imada and coworkers found unique ring-expanding dimerization/oligomerization of medium-sized cyclic nitrones upon treatment with organic or inorganic acids. An unprecedented ring-size-dependent specificity was observed; that is, cyclic nitrones with odd number-membered

rings are converted to dimers selectively, while even number-membered rings affords macrocyclic oligonitrones (eq 149).³¹⁴



4. CONCLUSION AND OUTLOOK

This review describes the synthesis and transformation of nitrones for organic synthesis. Nitrones are important compounds, which are highly useful in many respects. Methods of synthesizing nitrones are still being explored from the viewpoint of useful, practical, and environmentally friendly standpoints. The transformation of nitrones, which include the addition of nucleophiles or radicals, C—H functionalization, and various addition reactions, provides a strategy and means for construction of highly selective and unique carbon—carbon bond formations, which are useful for the synthesis of various biologically important nitrogen compounds. Although many aspects of the transformation of nitrones are established, it is still attracting considerable interest, particularly from synthetic viewpoints. In this regard, we believe that there is a considerable potential to synthesize important key compounds, which include biologically active nitrogen compounds, heterocyclic compounds, and compounds that are attractive to material science. Nitron chemistry is still expanding and has enormous possibility to give deep impact of science.

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Notes

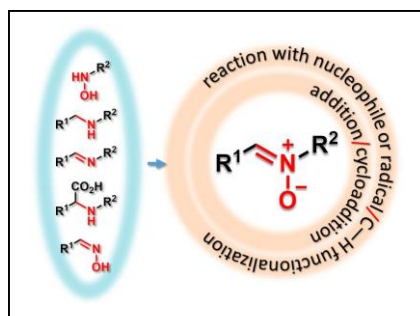
The authors declare no competing financial interest.

Biographies

Shun-Ichi Murahashi received Ph.D. degree from Osaka University (1969) under the direction of Professor Ichiro Moritani. He worked as a postdoctoral fellow with Professor Ronald Breslow at Columbia University (1968–1970). He joined the faculty of Osaka University as an Assistant Professor in 1963 and was promoted to Associate Professor in 1972, and subsequently to Professor in 1979. In 2001, he retired from Osaka University and became Professor Emeritus. He was a Visiting Professor of Okayama University of Science (2001-2014). He received the Chemical Society of Japan Award in 1995, Docteur Honoris Causa, Universite de Rennes in 1995, the Merck-Schuchardt Lecture Award in 1996, a Humboldt Research Award in 2002, the Special Award in Synthetic Organic Chemistry Japan in 2005, The Japan Academy Prize in 2010, and The Order of the Sacred Treasure Gold Rays with Neck-Ribbon in 2012. He was the president of Chemical Society of Japan (2001). His research interests are the structure and reactivity of carbenes, palladium- and ruthenium-catalyzed reactions, biomimetic catalytic oxidation reactions, and C—H bond activation.

Yasushi Imada received his BEng (1981), MEng (1983) and Ph.D. (1991) degrees from Osaka University under the direction of Professor Shun-Ichi Murahashi. He worked with Professor Howard Alper at the University of Ottawa as a postdoctoral fellow (1995–1996). He joined Osaka University as an Assistant Professor in 1985 and was promoted to Associate Professor in 1997. He has been a Professor at Tokushima University since 2012. His research interests are the development of novel environmentally benign synthetic methods, in particular those focused on organocatalytic oxidation and catalytic asymmetric synthesis.

TOC graphics



REFERENCES

- (1) Hamer, J.; Macaluso, A. Nitrones. *Chem. Rev.* **1964**, *64*, 473-495.
- (2) Torssell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis: Novel Strategies in Synthesis*; VCH Publishers: New York, 1988.
- (3) Breuer, E.; Aurich, H. G.; Nielsen, A. Nitrones and Nitric Acid Derivatives. In *Nitrones, Nitronates and Nitroxides*; John Wiley & Sons, 1989, pp. 139-312.

- (4) Murahashi, S.-I. Synthetic Aspects of Metal-Catalyzed Oxidations of Amines and Related Reactions. *Angew. Chem. Int. Ed.* **1995**, *34*, 2443-2465.
- (5) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. Nucleophilic Additions of Chiral Nitrones: New Approaches to Nitrogenated Compounds. *Synlett* **2000**, 442-454.
- (6) Lombardo, M.; Trombini, C. Nucleophilic Additions to Nitrones. *Synthesis* **2000**, 759-774.
- (7) Merino, P. Product Class 13: Nitrones and Cyclic Analogues. In *Science of Synthesis, Vol 27, Heteroatom Analogues of Aldehydes and Ketones*; Padwa, A., Ed.; Thieme, 2004, pp. 511-580.
- (8) Merino, P. New Developments in Nucleophilic Additions to Nitrones. *C. R. Chimie* **2005**, *8*, 775-788.
- (9) Cardona, F.; Goti, A. The Discovery of Novel Metal-Induced Reactions of Nitrones: Not Only Electrophiles and Reagents for [3 + 2] Cycloadditions. *Angew. Chem. Int. Ed.* **2005**, *44*, 7832-7835.
- (10) Revuelta, J.; Cicchi, S.; Goti, A.; Brandi, A. Enantiopure Cyclic Nitrones: A Useful Class of Building Blocks for Asymmetric Syntheses. *Synthesis* **2007**, 485-504.
- (11) Grigor'ev, I. A. Nitrones: Novel Strategies in Synthesis. In *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis: Novel Strategies in Synthesis, 2nd Ed.*; Feuer, H., Ed.; John Wiley & Sons: Hoboken, 2007, pp. 129-434.
- (12) Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. Stereocontrolled Cyclic Nitronone Cycloaddition Strategy for the Synthesis of Pyrrolizidine and Indolizidine Alkaloids. *Chem. Eur. J.* **2009**, *15*, 7808-7821.
- (13) Merino, P.; Tejero, T. Mannich-Type Reactions of Nitrones, Oximes, and Hydrazones. *Synlett* **2011**, 22, 1965-1977.
- (14) Xu, X.; Doyle, M. P. The [3 + 3]-Cycloaddition Alternative for Heterocycle Syntheses: Catalytically Generated Metalloenolcarbenes as Dipolar Adducts. *Acc. Chem. Res.* **2014**, *47*, 1396-1405.
- (15) Cheng, Q.-Q.; Deng, Y.; Lankelma, M.; Doyle, M. P. Cycloaddition reactions of enoldiazo compounds. *Chem. Soc. Rev.* **2017**, *46*, 5425-5445.
- (16) Anderson, L. L. Diverse Applications of Nitrones for the Synthesis of Heterocyclic Compounds. *Asian J. Org. Chem.* **2016**, *5*, 9-30.
- (17) Gothelf, K. V.; Jørgensen, K. A. Asymmetric 1,3-Dipolar Cycloaddition Reactions. *Chem. Rev.* **1998**, *98*, 863-910.
- (18) Stanley, L. M.; Sibi, M. P. Enantioselective Copper-Catalyzed 1,3-Dipolar Cycloadditions. *Chem. Rev.* **2008**, *108*, 2887-2902.
- (19) Hashimoto, T.; Maruoka, K. Recent Advances of Catalytic Asymmetric 1,3-Dipolar Cycloadditions. *Chem. Rev.* **2015**, *115*, 5366-5412.
- (20) Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. [3 + 2] Dipolar

- Cycloadditions of Cyclic Nitrones with Alkenes. *Org. React.* **2017**, *94*, 1-529.
- (21) Matassini, C.; Cardona, F. Oxidation of *N,N*-Disubstituted Hydroxylamines to Nitrones: The Search for More Sustainable Selective and Practical Stoichiometric Oxidants. *Chimia* **2017**, *71*, 558-561.
 - (22) Goti, A.; Cicchi, S.; Fedi, V.; Nannelli, L.; Brandi, A. Synthesis of Enantiopure 3-Substituted Pyrroline *N*-Oxides by Highly Regioselective Oxidation of the Parent Hydroxylamines: A Mechanistic Rationale. *J. Org. Chem.* **1997**, *62*, 3119-3125.
 - (23) Cicchi, S.; Marradi, M.; Goti, A.; Brandi, A. Manganese Dioxide Oxidation of Hydroxylamines to Nitrones. *Tetrahedron Lett.* **2001**, *42*, 6503-6505.
 - (24) Cicchi, S.; Corsi, M.; Goti, A. Inexpensive and Environmentally Friendly Oxidation of Hydroxylamines to Nitrones with Bleach. *J. Org. Chem.* **1999**, *64*, 7243-7245.
 - (25) Matassini, C.; Parmeggiani, C.; Cardona, F.; Goti, A. Oxidation of *N,N*-Disubstituted Hydroxylamines to Nitrones with Hypervalent Iodine Reagents. *Org. Lett.* **2015**, *17*, 4082-4085.
 - (26) Parmeggiani, C.; Matassini, C.; Cardona, F.; Goti, A. On the Oxidation of Hydroxylamines with *o*-Iodoxybenzoic Acid (IBX). *Synthesis* **2017**, *49*, 2890-2900.
 - (27) Merino, P.; Delso, I.; Tejero, T.; Cardona, F.; Goti, A. Nucleophilic Additions and Redox Reactions of Polyhydroxypyrroline *N*-Oxides on the Way to Pyrrolidine Alkaloids: Total Synthesis of Radicamine B. *Synlett* **2007**, 2651-2654.
 - (28) Nguyen, D.-V.; Prakash, P.; Gravel, E.; Doris, E. Triphenylbismuth Carbonate-mediated Oxidation of Hydroxylamines to Nitrones and in situ 1,3-Dipolar Cycloaddition. *RSC Adv.* **2016**, *6*, 89238-89241.
 - (29) Murahashi, S.-I.; Mitsui, H.; Watanabe, T.; Zenki, S.-i. The Reaction of *N*-Mono and *N,N*-Disubstituted Hydroxylamines with Palladium Catalyst. *Tetrahedron Lett.* **1983**, *24*, 1049-1052.
 - (30) D'Adamio, G.; Parmeggiani, C.; Goti, A.; Cardona, F. Gold Supported on Silica Catalyzes the Aerobic Oxidation of *N,N*-Disubstituted Hydroxylamines to Nitrones. *Eur. J. Org. Chem.* **2015**, 6541-6546.
 - (31) Yudha S, S.; Kusuma, I.; Asao, N. Aerobic Oxidation of Hydroxylamines with Nanoporous Gold Catalyst as an Efficient Synthetic Method of Nitrones. *Tetrahedron* **2015**, *71*, 6459-6462.
 - (32) Prakash, P.; Gravel, E.; Nguyen, D.-V.; Namboothiri, I. N. N.; Doris, E. Direct and Co-catalytic Oxidation of Hydroxylamines to Nitrones Promoted by Rhodium Nanoparticles Supported on Carbon Nanotubes. *ChemCatChem* **2017**, *9*, 2091-2094.
 - (33) Cardona, F.; Gorini, L.; Goti, A. Tetra-*n*-propylammonium Perruthenate (TPAP) Catalyzed Aerobic Oxidation of Hydroxylamines to Nitrones. *Lett. Org. Chem.* **2006**, *3*, 118-120.
 - (34) Goti, A.; De Sarlo, F.; Romani, M. Highly Efficient and Mild Synthesis of Nitrones by

- Catalytic Oxidation of Hydroxylamines with Tetra-*n*-propylammonium Perruthenate. *Tetrahedron Lett.* **1994**, *35*, 6571-6574.
- (35) Saladino, R.; Neri, V.; Cardona, F.; Goti, A. Oxidation of *N,N*-Disubstituted Hydroxylamines to Nitrones with Hydrogen Peroxide Catalyzed by Polymer-Supported Methylrhenium Trioxide Systems. *Adv. Synth. Catal.* **2004**, *346*, 639-647.
- (36) Cicchi, S.; Cardona, F.; Brandi, A.; Corsi, M.; Goti, A. Oxidation of Hydroxylamines to Nitrones Catalyzed by (Salen)Mn(III) Complexes. Enantioselective Synthesis of a Protected *cis*-Dihydroxypyrroline *N*-Oxide with Jacobsen Catalyst. *Tetrahedron Lett.* **1999**, *40*, 1989-1992.
- (37) Hou, H.; Zhu, S.; Pan, F.; Rueping, M. Visible-Light Photoredox-Catalyzed Synthesis of Nitrones: Unexpected Rate Acceleration by Water in the Synthesis of Isoxazolidines. *Org. Lett.* **2014**, *14*, 2872-2875.
- (38) Mitsui, H.; Zenki, S.; Shiota, T.; Murahashi, S.-I. Tungstate Catalysed Oxidation of Secondary Amines with Hydrogen Peroxide. A Novel Transformation of Secondary Amines into Nitrones. *J. Chem. Soc., Chem. Commun.* **1984**, 874-875.
- (39) Murahashi, S.-I.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. Tungstate-Catalyzed Oxidation of Secondary Amines to Nitrones. α -Substitution of Secondary Amines via Nitrones. *J. Org. Chem.* **1990**, *55*, 1736-1744.
- (40) Murahashi, S.-I.; Shiota, T.; Imada, Y. Oxidation of Secondary Amines to Nitrones: 6-Methyl-2,3,4,5-tetrahydropyridine *N*-Oxide. *Org. Synth.* **1992**, *70*, 265-271.
- (41) Marcantoni, E.; Petrini, M.; Polimanti, O. Oxidation of Secondary Amines to Nitrones Using Urea-Hydrogen Peroxide Complex (UHP) and Metal Catalysts. *Tetrahedron Lett.* **1995**, *36*, 3561-3562.
- (42) Murahashi, S.-I.; Shiota, T. Selenium Dioxide Catalyzed Oxidation of Secondary Amines with Hydrogen Peroxide. Simple Synthesis of Nitrones from Secondary Amines. *Tetrahedron Lett.* **1987**, *28*, 2383-2386.
- (43) Goti, A.; Nannelli, L. Synthesis of Nitrones by Methyltrioxorhenium Catalyzed Direct Oxidation of Secondary Amines. *Tetrahedron Lett.* **1996**, *37*, 6025-6028.
- (44) Murray, R. W.; Iyanar, K.; Chen, J.; Wearing, J. T. Synthesis of Nitrones Using the Methyltrioxorhenium/Hydrogen Peroxide System. *J. Org. Chem.* **1996**, *61*, 8099-8102.
- (45) Goti, A.; Cardona, F.; Soldaini, G. Methyltrioxorhenium Catalyzed Oxidation of Secondary Amines to Nitrones: *N*-Benzylidenebenzylamine *N*-Oxide. *Org. Synth.* **2005**, *81*, 204-212.
- (46) Zonta, C.; Cazzola, E.; Mba, M.; Licini, G. *C*₃-Symmetric Titanium(IV) Triphenolate Amino Complexes for a Fast and Effective Oxidation of Secondary Amines to Nitrones with Hydrogen Peroxide. *Adv. Synth. Catal.* **2008**, *350*, 2503-2506.
- (47) Colladon, M.; Scarso, A.; Strukul, G. Mild Catalytic Oxidation of Secondary and

- Tertiary Amines to Nitrones and *N*-Oxides with H₂O₂ Mediated by Pt(II) Catalysts. *Green Chem.* **2008**, *10*, 793-798.
- (48) Forcato, M.; Mba, M.; Nugent, W. A.; Licini, G. Effective Oxidation of Secondary Amines to Nitrones with Alkyl Hydroperoxides Catalysed by (Trialkanolaminato)titanium(IV) Complexes. *Eur. J. Org. Chem.* **2010**, 740-748.
- (49) Joseph, R.; Sudalai, A.; Ravindranathan, T. Catalytic Oxidation of Secondary Amines with H₂O₂ over Molecular Sieves: A High Yield and Single Step Preparation of Nitrones. *Synlett* **1995**, 1177-1178.
- (50) Sakaue, S.; Sakata, Y.; Nishiyama, Y.; Ishii, Y. Oxidation of Aliphatic and Aromatic Amines with Hydrogen Peroxide Catalyzed by Peroxoheteropoly Oxometalates. *Chem. Lett.* **1992**, *21*, 289-292.
- (51) Choudary, B. M.; Reddy, C. V.; Prakash, B. V.; Bharathi, B.; Kantam, M. L. Oxidation of Secondary and Tertiary Amines by a Solid Base Catalyst. *J. Mol. Catal. A: Chem.* **2004**, *217*, 81-85.
- (52) Abrantes, M.; Gonçalves, I. S.; Pillinger, M.; Vurchio, C.; Cordero, F. M.; Brandi, A. Molybdenum Oxide/Bipyridine Hybrid Material {[MoO₃(bipy)][MoO₃(H₂O)]}_n as Catalyst for the Oxidation of Secondary Amines to Nitrones. *Tetrahedron Lett.* **2011**, *52*, 7079-7082.
- (53) Gella, C.; Ferrer, È.; Alibés, R.; Busqué, F.; de March, P.; Figueredo, M.; Font, J. A Metal-Free General Procedure for Oxidation of Secondary Amines to Nitrones. *J. Org. Chem.* **2009**, *74*, 6365-6367.
- (54) Murray, R. W.; Singh, M. Chemistry of Dioxiranes. 16. A Facile One-Step Synthesis of *C*-Arylnitrones Using Dimethyldioxirane. *J. Org. Chem.* **1990**, *55*, 2954-2957.
- (55) Zajac Jr., W. W.; Walters, T. R.; Darcy, M. G. Oxidation of amines with 2-sulfonyloxaziridines (Davis' reagents). *J. Org. Chem.* **1988**, *53*, 5856-5860.
- (56) Brandi, A.; Cicchi, S.; Paschetta, V.; Pardo, D. G.; Cossy, J. A New Nitrone from *C*₂ Symmetric Piperidine for the Synthesis of Hydroxylated Indolizidinone. *Tetrahedron Lett.* **2002**, *43*, 9357-9359.
- (57) Looper, R. E.; Williams, R. M. A Concise Asymmetric Synthesis of the Marine Hepatotoxin 7-Epicylindrospermopsin. *Angew. Chem. Int. Ed.* **2004**, *43*, 2930-2933.
- (58) Tokuyama, H.; Kuboyama, T.; Fukuyama, T. Transformation of Primary Amines to *N*-Monoalkylhydroxylamines: *N*-Hydroxy-(*S*)-1-phenylethylamine Oxalate. *Org. Synth.* **2003**, *80*, 207-218.
- (59) Imada, Y.; Iida, H.; Ono, S.; Murahashi, S.-I. Flavin Catalyzed Oxidations of Sulfides and Amines with Molecular Oxygen. *J. Am. Chem. Soc.* **2003**, *125*, 2868-2869.
- (60) Imada, Y.; Iida, H.; Ono, S.; Masui, Y.; Murahashi, S.-I. Flavin-Catalyzed Oxidation of Amines and Sulfides with Molecular Oxygen: Biomimetic Green Oxidation. *Chem. Asian J.* **2006**, *1*, 136-147.

- (61) Iida, H.; Imada, Y.; Murahashi, S.-I. Biomimetic flavin-catalysed reactions for organic synthesis. *Org. Biomol. Chem.* **2015**, *13*, 7599-7613.
- (62) Baran, P. S.; Hafensteiner, B. D.; Ambhaikar, N. B.; Guerrero, C. A.; Gallagher, J. D. Enantioselective Total Synthesis of Avrainvillamide and the Stephacidins. *J. Am. Chem. Soc.* **2006**, *128*, 8678-8693.
- (63) Sunazuka, T.; Shirahata, T.; Tsuchiya, S.; Hirose, T.; Mori, R.; Harigaya, Y.; Kuwajima, I.; Ōmura, S. A Concise Stereoselective Route to the Indoline Spiroaminal Framework of Neoxaline and Oxaline. *Org. Lett.* **2005**, *7*, 941-943.
- (64) Murahashi, S.-I.; Imada, Y.; Ohtake, H. Tungstate-Catalyzed Decarboxylative Oxidation of *N*-Alkyl- α -amino Acids: An Efficient Method for Regioselective Synthesis of Nitrones. *J. Org. Chem.* **1994**, *59*, 6170-6172.
- (65) Ohtake, H.; Imada, Y.; Murahashi, S.-I. Regioselective Synthesis of Nitrones by Decarboxylative Oxidation of *N*-Alkyl- α -amino Acids and Application to the Synthesis of 1-Azabicyclic Alkaloids. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2737-2754.
- (66) Murahashi, S.-I.; Ohtake, H.; Imada, Y. Synthesis of (*R*)- and (*S*)-3-(*tert*-Butyldimethylsilyloxy)-1-pyrroline *N*-Oxides — Chiral Nitrones for Synthesis of Biologically Active Pyrrolidine Derivative, Geissman-Waiss Lactone. *Tetrahedron Lett.* **1998**, *39*, 2765-2766.
- (67) Soldaini, G.; Cardona, F.; Goti, A. Catalytic Oxidation of Imines Based on Methyltrioxorhenium/Urea Hydrogen Peroxide: A Mild and Easy Chemo- and Regioselective Entry to Nitrones. *Org. Lett.* **2007**, *9*, 473-476.
- (68) Diez-Martinez, A.; Gultekin, Z.; Delso, I.; Tejero, T.; Merino, P. Synthesis of *N*-(Benzyloxyethyl)- and *N*-(Alkoxy carbonylmethyl)nitrones. *Synthesis* **2010**, 678-688.
- (69) Cardona, F.; Bonanni, M.; Soldaini, G.; Goti, A. One-Pot Synthesis of Nitrones from Primary Amines and Aldehydes Catalyzed by Methyltrioxorhenium. *ChemSusChem*. **2008**, *1*, 327-332.
- (70) Singh, B.; Jain, S. L.; Khatri, P. K.; Sain, B. Nafion Supported Molybdenum Oxychloride: Recyclable Catalyst for One-Pot Synthesis of Nitrones via Direct Condensation/Oxidation of Primary Amines and Aldehydes Using UHP as Oxidant. *Green Chem.* **2009**, *11*, 1941-1944.
- (71) Singh, B.; Jain, S. L.; Rana, B. S.; Khatri, P. K.; Sinha, A. K.; Sain, B. Silica-Immobilized Highly Dispersed Oxo-Rhenium and its Catalytic Activity for the Direct Synthesis of Nitrones. *ChemCatChem* **2010**, *2*, 1260-1264.
- (72) Mirza-Aghayan, M.; Tavana, M. M.; Boukherroub, R. Direct Oxidative Synthesis of Nitrones from Aldehydes and Primary Anilines Using Graphite Oxide and Oxone. *Tetrahedron Lett.* **2014**, *55*, 5471-5474.
- (73) LeBel, N. A.; Spurlock, L. A. The Epimeric *syn*-Bicyclo[3.2.1]octane-2,8-diols. *J. Org. Chem.* **1964**, *29*, 1337-1339.

- (74) Tufariello, J. J.; Mullen, G. B.; Tegeler, J. J.; Trybulski, E. J.; Wong, S. C.; Ali, S. A. Synthesis in the Tropane Class of Alkaloids. Pseudotropine and *dl*-Cocaine. *J. Am. Chem. Soc.* **1979**, *101*, 2435-2442.
- (75) Morozov, D. A.; Kirilyuk, I. A.; Komarov, D. A.; Goti, A.; Bagryanskaya, I. Y.; Kuratieva, N. V.; Grigor'ev, I. A. Synthesis of a Chiral C₂-Symmetric Sterically Hindered Pyrrolidine Nitroxide Radical via Combined Iterative Nucleophilic Additions and Intramolecular 1,3-Dipolar Cycloadditions to Cyclic Nitrones. *J. Org. Chem.* **2012**, *77*, 10688-10698.
- (76) de March, P.; Figueredo, M.; Font, J.; Milán, S.; Alvarez-Larena, A.; Piniella, J. F.; Molins, E. First Example of a Third Generation Nitrone Cycloaddition. *Tetrahedron* **1997**, *53*, 2979-2988.
- (77) LeBel, N. A.; Banucci, E. G. Intramolecular Nitrone-Olefin Cycloadditions. The Stereochemistry of Hexahydro-2,1-benzisoxazoline Formation. *J. Org. Chem.* **1971**, *36*, 2440-2448.
- (78) Degiorgis, F.; Lombardo, M.; Trombini, C. Synthesis of Four Stereoisomers of 5-Amino-2,5-dideoxy-heptono-1,5-lactams. *Tetrahedron* **1997**, *53*, 11721-11730.
- (79) Merino, P.; Lanaspa, A.; Merchan, F. L.; Tejero, T. Totally Stereocontrolled Synthesis of α,β -Diamino Acids by Addition of Grignard Reagents to Nitrones Derived from L-Serine. *Tetrahedron: Asymmetry* **1998**, *9*, 629-646.
- (80) Morales, S.; Guijarro, F. G.; Alonso, I.; Ruano, J. L. G.; Cid, M. B. Dual Role of Pyrrolidine and Cooperative Pyrrolidine/Pyrrolidinium Effect in Nitrone Formation. *ACS Catal.* **2016**, *6*, 84-91.
- (81) Wielechowska, M.; Dąbrowska, P.; Plenkiewicz, J. Lipase-Catalyzed Separation of the Enantiomers of 1-Arylideneamino-3-aryloxypropan-2-ol-*N*-oxides. Preparation of Optically Active Nitrones. *Tetrahedron: Asymmetry* **2006**, *17*, 1786-1792.
- (82) Colacino, E.; Nun, P.; Colacino, F. M.; Martinez, J.; Lamaty, F. Solvent-Free Synthesis of Nitrones in a Ball-Mill. *Tetrahedron* **2008**, *64*, 5569-5576.
- (83) Andrade, M. M.; Barros, M. T.; Pinto, R. C. Exploiting Microwave-Assisted Neat Procedures: Synthesis of *N*-Aryl and *N*-Alkyl nitrones and Their Cycloaddition en Route for Isoxazolidines. *Tetrahedron* **2008**, *64*, 10521-10530.
- (84) Pfeiffer, J. Y.; Beauchemin, A. M. Simple Reaction Conditions for the Formation of Ketonitrones from Ketones and Hydroxylamines. *J. Org. Chem.* **2009**, *74*, 8381-8383.
- (85) Cheng, H.-S.; Seow, A.-H.; Loh, T.-P. Homoallylic Nitrone Isomerization: Convenient Enantioselective Synthesis of Homoallylic Nitrones and Homoallylic Hydroxylamines. *Org. Lett.* **2008**, *10*, 2805-2807.
- (86) Michael, R. E.; Chando, K. M.; Sammakia, T. Synthesis of *N*-Vinyl Nitrones via 1,4-Conjugate Elimination. *J. Org. Chem.* **2015**, *80*, 6930-6935.
- (87) Kouklovsky, C.; Dirat, O.; Berranger, T.; Langlois, Y.; Tran-Huu-Dau, M. E.; Riche,

- C. [3 + 2] Cycloadditions between α,β -Unsaturated Esters or Nitroalkenes and Camphor-Derived Oxazoline *N*-Oxides: Experimental and Theoretical Study. *J. Org. Chem.* **1998**, *63*, 5123-5128.
- (88) Jones, R. C. F.; Martin, J. N.; Smith, P. A Chiral Imidazoline Nitron; A Cycloaddition Route to Imidazoisoxazoles and Pyrroloimidazoles. *Synlett* **2000**, 967-970.
- (89) Moran, J.; Pfeiffer, J. Y.; Gorelsky, S. I.; Beauchemin, A. M. Ketonitrones via Cope-Type Hydroamination of Allenes. *Org. Lett.* **2009**, *11*, 1895-1898.
- (90) Zeng, Q.; Zhang, L.; Yang, J.; Xu, B.; Xiao, Y.; Zhang, J. Pyrroles *versus* Cyclic Nitrones: Catalyst-Controlled Divergent Cyclization of *N*-(2-Perfluoroalkyl-3-alkynyl) Hydroxylamines. *Chem. Commun.* **2014**, *50*, 4203-4206.
- (91) Nakamura, I.; Onuma, T.; Kanazawa, R.; Nishigai, Y.; Terada, M. Efficient Synthesis of *N*-Alkylated α,β -Unsaturated Ketonitrones via Cu-Catalyzed Rearrangement. *Org. Lett.* **2014**, *16*, 4198-4200.
- (92) Peacock, L. R.; Chapman, R. S. L.; Sedgwick, A. C.; Mahon, M. F.; Amans, D.; Bull, S. D. Simple *Aza*-Conjugate Addition Methodology for the Synthesis of Isoindole Nitrones and 3,4-Dihydroisoquinoline Nitrones. *Org. Lett.* **2015**, *17*, 994-997.
- (93) Holzapfel, C. W.; Crous, R. Synthesis and Reactions of Chiral Cyclic Nitrones Derived from D-Ribose. *Heterocycles* **1998**, *48*, 1337-1342.
- (94) Peer, A.; Vasella, A. Synthesis of an L-Fucose-Derived Cyclic Nitron and its Conversion to α -L-Fucosidase Inhibitors. *Helv. Chim. Acta* **1999**, *82*, 1044-1065.
- (95) Cicchi, S.; Corsi, M.; Brandi, A.; Goti, A. Straightforward Synthesis of Enantiomerically Pure (3*S*,4*R*)- and (3*R*,4*S*)-3,4-Isopropylidenedioxypyrroline 1-Oxide, Precursors of Functionalized *cis*-Dihydroxy Azaheterocycles, by a Novel "One-Pot" Procedure. *J. Org. Chem.* **2002**, *67*, 1678-1681.
- (96) Cicchi, S.; Marradi, M.; Vogel, P.; Goti, A. One-Pot Synthesis of Cyclic Nitrones and Their Conversion to Pyrrolizidines: 7*a*-*epi*-Crotanecine Inhibits α -Mannosidases. *J. Org. Chem.* **2006**, *71*, 1614-1619.
- (97) Zhang, L.-D.; Zhong, L.-R.; Xi, J.; Yang, X.-L.; Yao, Z.-J. Enantioselective Total Synthesis of Lycoposerramine-Z Using Chiral Phosphoric Acid Catalyzed Intramolecular Michael Addition. *J. Org. Chem.* **2016**, *81*, 1899-1904.
- (98) Mo, D.-L.; Wink, D. A.; Anderson, L. L. Preparation and Rearrangement of *N*-Vinyl Nitrones: Synthesis of Spiroisoxazolines and Fluorene-Tethered Isoxazoles. *Org. Lett.* **2012**, *14*, 5180-5183.
- (99) Kontokosta, D.; Mueller, D. S.; Mo, D.-L.; Pace, W. H.; Simpson, R. A.; Anderson, L. L. Copper-mediated Synthesis of *N*-Alkenyl- α,β -unsaturated Nitrones and Their Conversion to Tri- and Tetrasubstituted Pyridines. *Beilstein J. Org. Chem.* **2015**, *11*, 2097-2104.
- (100) Reidl, T. W.; Son, J.; Wink, D. J.; Anderson, L. L. Facile Synthesis of Azetidine

- Nitrones and Diastereoselective Conversion into Densely Substituted Azetidines. *Angew. Chem. Int. Ed.* **2017**, *56*, 11579-11583.
- (101) Li, Z.; Zhao, J.; Sun, B.; Zhou, T.; Liu, M.; Liu, S.; Zhang, M.; Zhang, Q. Asymmetric Nitrone Synthesis via Ligand-Enabled Copper-Catalyzed Cope-Type Hydroamination of Cyclopropene with Oxime. *J. Am. Chem. Soc.* **2017**, *139*, 11702-11705.
- (102) Nakamura, I.; Araki, T.; Zhang, D.; Kudo, Y.; Kwon, E.; Terada, M. Regioselective Transformation of *O*-Propargylic Arylaldoximes to Four-Membered Cyclic Nitrones by Copper-Catalyzed Skeletal Rearrangement. *Org. Lett.* **2011**, *13*, 3616-3619.
- (103) Nakamura, I.; Kudo, Y.; Araki, T.; Zhang, D.; Kwon, E.; Terada, M. Copper-Catalyzed Skeletal Rearrangement of *O*-Propargylic Aryloximes into Four-Membered Cyclic Nitrones – Chirality Transfer and Mechanistic Insight. *Synthesis* **2012**, *44*, 1542-1550.
- (104) Nakamura, I.; Okamoto, M.; Sato, Y.; Terada, M. Synthesis of Azepine Derivatives by Rhodium-Catalyzed Tandem 2,3-Rearrangement/Heterocyclization. *Angew. Chem. Int. Ed.* **2012**, *51*, 10816-10819.
- (105) Nakamura, I.; Sato, Y.; Takeda, K.; Terada, M. Efficient Synthesis of Eight-Membered Nitrogen Heterocycles from *O*-Propargylic Oximes by Rhodium-Catalyzed Cascade Reactions. *Chem. Eur. J.* **2014**, *20*, 10214-10219.
- (106) Peng, X.; Tong, B. M. K.; Hirao, H.; Chiba, S. Inorganic-Base-Mediated Hydroamination of Alkenyl Oximes for the Synthesis of Cyclic Nitrones. *Angew. Chem. Int. Ed.* **2014**, *53*, 1959-1962.
- (107) Buchlovič, M.; Man, S.; Potáček, M. Allenyloxime—A New Source of Heterocyclizations to Stable Cyclic Nitrones. *Tetrahedron* **2008**, *64*, 9953-9961.
- (108) Flores, M. A.; Bode, J. W. Chemoselective Protection of α -Ketoacids by Direct Annulations with Oximes. *Org. Lett.* **2010**, *12*, 1924-1927.
- (109) Schleiss, J.; Rollin, P.; Tatibouët, A. Palladium-Catalyzed Coupling Reactions of Thioimide *N*-Oxides: Access to α -Alkenyl- and α -Aryl-Functionalized Cyclic Nitrones. *Angew. Chem. Int. Ed.* **2010**, *49*, 577-580.
- (110) Chen, F.; Yang, X.-L.; Wu, Z.-W.; Han, B. Synthesis of Isoxazoline/Cyclic Nitrone-Featured Methylene Using Unsaturated Ketoximes: A Dual Role of TEMPO. *J. Org. Chem.* **2016**, *81*, 3042-3050.
- (111) Liu, R.-H.; Wei, D.; Han, B.; Yu, W. Copper-Catalyzed Oxidative Oxyamination/Diamination of Internal Alkenes of Unsaturated Oximes with Simple Amines. *ACS Catal.* **2016**, *6*, 6525-6530.
- (112) Peng, X.-X.; Wei, D.; Han, W.-J.; Chen, F.; Yu, W.; Han, B. Dioxygen Activation via Cu-Catalyzed Cascade Radical Reaction: An Approach to Isoxazoline/Cyclic Nitrone-Featured α -Ketols. *ACS Catal.* **2017**, *7*, 7830-7834.
- (113) Wang, Z.-H.; Zhang, H.-H.; Xu, P.-F.; Luo, Y.-C. Synthesis of five-membered cyclic nitrones based on the Lewis acid-catalysed [3 + 2]-annulation reaction of

- donor–acceptor cyclopropanes with 1,4,2-dioxazoles. *Chem. Commun.* **2018**, *54*, 10128-10131.
- (114) Nakama, K.; Seki, S.; Kanemasa, S. A New Synthetic Access to *N*-Alkylated Nitrones through Lewis Acid-Catalyzed Conjugate Additions of Aldoximes. *Tetrahedron Lett.* **2001**, *42*, 6719-6722.
- (115) Kitanosono, T.; Xu, P.; Kobayashi, S. Chiral Lewis acids integrated with single-walled carbon nanotubes for asymmetric catalysis in water. *Science* **2018**, *362*, 311-315.
- (116) Miyabe, H.; Yoshida, K.; Reddy, V. K.; Matsumura, A.; Takemoto, Y. Selective Synthesis of Allylated Oxime Ethers and Nitrones Based on Palladium-Catalyzed Allylic Substitution of Oximes. *J. Org. Chem.* **2005**, *70*, 5630-5635.
- (117) Gautheron-Chapoulaud, V.; Pandya, S. U.; Cividino, P.; Masson, G.; Py, S.; Vallée, Y. One-Pot Synthesis of Functionalized Nitrones from Nitro Compounds. *Synlett* **2001**, 1281-1283.
- (118) Lin, C.-W.; Hong, B.-C.; Chang, W.-C.; Lee, G.-H. A New Approach to Nitrones through Cascade Reaction of Nitro Compounds Enabled by Visible Light Photoredox Catalysis. *Org. Lett.* **2015**, *17*, 2314-2317.
- (119) Cisneros, L.; Serna, P.; Corma, A. Selective Reductive Coupling of Nitro Compounds with Aldehydes to Nitrones in H₂ Using Carbon-Supported and -Decorated Platinum Nanoparticles. *Angew. Chem. Int. Ed.* **2014**, *53*, 9306-9310.
- (120) Li, X.; Zhang, B.; Tang, L.; Goh, T. W.; Qi, S.; Volkov, A.; Pei, Y.; Qi, Z.; Tsung, C.-K.; Stanley, L.; Huang, W. Cooperative Multifunctional Catalysts for Nitrone Synthesis: Platinum Nanoclusters in Amine-Functionalized Metal–Organic Frameworks. *Angew. Chem. Int. Ed.* **2017**, *56*, 16371-16375.
- (121) Duvall, J. R.; Wu, F.; Snider, B. B. Structure Reassignment and Synthesis of Jenamidines A₁/A₂, Synthesis of (+)-NP25302, and Formal Synthesis of SB-311009 Analogues. *J. Org. Chem.* **2006**, *71*, 8579-8590.
- (122) Zhang, S.; Xu, K.; Guo, F.; Hu, Y.; Zha, Z.; Wang, Z. Enantioselective Copper(I/II)-Catalyzed Conjugate Addition of Nitro Esters to β,γ -Unsaturated α -Ketoesters. *Chem. Eur. J.* **2014**, *20*, 979-982.
- (123) Sádaba, D.; Delso, I.; Tejero, T.; Merino, P. Water-Compatible One-Pot Organocatalytic Asymmetric Synthesis of Cyclic Nitrones. Application in Intramolecular 1,3-Dipolar Cycloadditions. *Tetrahedron Lett.* **2011**, *52*, 5976-5979.
- (124) Mancheño, O. G.; Tangen, P.; Rohlmann, R.; Fröhlich, R.; Alemán, J. Synthesis of Chiral Cyclic Nitrones by Asymmetric Addition of β -Ketosulfones to Nitroalkenes followed by Reductive Cyclization. *Chem. Eur. J.* **2011**, *9*, 984-992.
- (125) Denmark, S. E.; Montgomery, J. I. A General Synthesis of *N*-Vinyl Nitrones. *J. Org. Chem.* **2006**, *71*, 6211-6220.
- (126) Asao, N.; Sato, K.; Yamamoto, Y. AuBr₃-Catalyzed Cyclization of *o*-

- (Alkynyl)nitrobenzenes. Efficient Synthesis of Isatogens and Anthranils. *Tetrahedron Lett.* **2003**, *44*, 5675-5677.
- (127) Ramana, C. V.; Patel, P.; Vanka, K.; Miao, B.; Degterev, A. A Combined Experimental and Density Functional Theory Study on the Pd-Mediated Cycloisomerization of *o*-Alkynylnitrobenzenes – Synthesis of Isatogens and Their Evaluation as Modulators of ROS-Mediated Cell Death. *Eur. J. Org. Chem.* **2010**, 5955-5966.
- (128) Kumar, C. V. S.; Ramana, C. V. Tuning the Regioselectivity of Gold-Catalyzed Internal Nitroalkyne Redox: A Cycloisomerization and [3 + 2]-Cycloaddition Cascade for the Construction of *spiro*-Pseudoindoxyl Skeleton. *Org. Lett.* **2014**, *16*, 4766-4769.
- (129) Singh, R. R.; Liu, R.-S. Gold-Catalyzed 1,2-Iminonitronation of Electron-Deficient Alkynes with Nitrosoarenes to Afford α -Imidoyl Nitrones. *Chem. Commun.* **2014**, *50*, 15864-15866.
- (130) Fraboni, A. J.; Brenner-Moyer, S. E. Dienamine-Catalyzed Nitron Formation via Redox Reaction. *Org. Lett.* **2016**, *18*, 2146-2149.
- (131) Chavannavar, A. P.; Oliver, A. G.; Ashfeld, B. L. An Umpolung Approach toward *N*-Aryl Nitron Construction: A Phosphine-Mediated Addition of 1,2-Dicarbonyls to Nitroso Electrophiles. *Chem. Commun.* **2014**, *50*, 10853-10856.
- (132) Katahara, S.; Kobayashi, S.; Fujita, K.; Matsumoto, T.; Sato, T.; Chida, N. An Iridium-Catalyzed Reductive Approach to Nitrones from *N*-Hydroxyamides. *J. Am. Chem. Soc.* **2016**, *138*, 5246-5249.
- (133) Xing, D.; Xu, X.; Yang, L. Highly Chemoselective Rearrangement of 3-Aryloxaziridines to Nitrones or Amides. *Synlett* **2009**, 3399-3404.
- (134) Partridge, K. M.; Anzovino, M. E.; Yoon, T. P. Cycloadditions of *N*-Sulfonyl Nitrones Generated by Lewis Acid Catalyzed Rearrangement of Oxaziridines. *J. Am. Chem. Soc.* **2008**, *130*, 2920-2921.
- (135) Dondoni, A.; Franco, S.; Merchán, F. L.; Merino, P.; Tejero, T. Stereocontrol by Diethylaluminum Chloride in the Addition of 2-Lithiofuran and *N*-Methyl-2-Lithioimidazole to α -Alkoxy Nitrones. Total Synthesis of 5-*O*-Carbamoylpolyoxamic Acid. *Tetrahedron Lett.* **1993**, *34*, 5479-5482.
- (136) Merino, P.; Castillo, E.; Franco, S.; Merchán, F. L.; Tejero, T. Nucleophilic Additions of Grignard Reagents to *N*-Benzyl-2,3-*O*-isopropylidene-D-glyceraldehyde Nitron (BIGN). Synthesis of (2*S*,3*R*) and (2*S*,3*S*)-3-Phenylisoserine. *Tetrahedron* **1998**, *54*, 12301-12322.
- (137) Merino, P.; Mannucci, V.; Tejero, T. Exploring Nitron Chemistry: Towards the Enantiodivergent Synthesis of 6-Substituted 4-Hydroxypipericolic Acid Derivatives. *Eur. J. Org. Chem.* **2008**, 3943-3959.
- (138) Merino, P.; Anoro, S.; Castillo, E.; Merchán, F.; Tejero, T. Direct Vinylation and

- Ethynylation of Nitrones. Stereodivergent Synthesis of Allyl and Propargyl Amines. *Tetrahedron: Asymmetry* **1996**, 7, 1887-1890.
- (139) Fiumana, A.; Lombardo, M.; Trombini, C. Synthesis and Iodocyclization of Homoallylic Hydroxylamines. *J. Org. Chem.* **1997**, 62, 5623-5626.
- (140) Schade, W.; Reissig, H.-U. A New Diastereoselective Synthesis of Enantiomerically Pure 1,2-Oxazine Derivatives by Addition of Lithiated Methoxyallene to Chiral Nitrones. *Synlett* **1999**, 632-534.
- (141) Merino, P.; Castillo, E.; Franco, S.; Merchan, F. L.; Tejero, T. Ready Access to Enantiopure 5-Substituted-3-pyrrolin-2-ones from *N*-Benzyl-2,3-*O*-isopropylidene-D-glyceraldehyde Nitron (BIGN). *Tetrahedron: Asymmetry* **1998**, 9, 1759-1769.
- (142) Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. Diastereoselective Nucleophilic Addition of Acetylide to *N*-Benzyl-2,3-*O*-isopropylidene-D-glyceraldehyde Nitron (BIGN). Stereodivergent Synthesis of β -Hydroxy- α -(hydroxyamino)- and β -Hydroxy- α -amino Acids. *Tetrahedron: Asymmetry* **1997**, 8, 3489-3496.
- (143) Merino, P.; Mannucci, V.; Tejero, T. Nucleophilic Additions of Lithiated Allylphenylsulfone to Nitrones: Experimental and Theoretical Investigations. *Tetrahedron* **2005**, 61, 3335-3347.
- (144) Dondoni, A.; Franco, S.; Junquera, F.; Merchán, F. L.; Merino, P.; Tejero, T. Synthesis of *N*-Benzyl Nitrones. *Synth. Commun.* **1994**, 24, 2537-2550.
- (145) Merino, P.; Franco, S.; Gascon, J. M.; Merchan, F. L.; Tejero, T. Highly Diastereoselective Nucleophilic Addition of Organometallic Reagents to 2-Pyrrolidinyl Nitrones: A Semiempirical Approach. *Tetrahedron: Asymmetry* **1999**, 10, 1867-1871.
- (146) Merino, P.; Revuelta, J.; Tejero, T.; Cicchi, S.; Goti, A. Fully Stereoselective Nucleophilic Addition to a Novel Chiral Pyrroline *N*-Oxide: Total Syntheses of (2*S*,3*R*)-3-Hydroxy-3-methylproline and Its (2*R*)-Epimer. *Eur. J. Org. Chem.* **2004**, 776-782.
- (147) Zhao, H.; Kato, A.; Sato, K.; Jia, Y.-M.; Yu, C.-Y. Total Synthesis and Glycosidase Inhibition of Broussonetine I and J₂. *J. Org. Chem.* **2013**, 78, 7896-7902.
- (148) Cordero, F. M.; Vurchio, C.; Brandi, A. A Stereoselective Synthesis of Lentiginosine. *J. Org. Chem.* **2016**, 81, 1661-1664.
- (149) Ukaji, Y.; Shimizu, Y.; Kenmoku, Y.; Ahmed, A.; Inomata, K. Catalytic Asymmetric Addition of Dialkylzinc to 3,4-Dihydroisoquinoline *N*-Oxides Utilizing Tartaric Acid Ester as a Chiral Auxiliary. *Bull. Chem. Soc. Jpn.* **2000**, 73, 447-452.
- (150) Ukaji, Y.; Inomata, K. Development of New Asymmetric Reactions Utilizing Tartaric Acid Esters as Chiral Auxiliaries. The Design of an Efficient Chiral Multinucleating System. *Synlett* **2003**, 1075-1087.
- (151) Delso, I.; Tejero, T.; Goti, A.; Merino, P. Sequential Nucleophilic

- Addition/Intramolecular Cycloaddition to Chiral Nonracemic Cyclic Nitrones: A Highly Stereoselective Approach to Polyhydroxynortropane Alkaloids. *J. Org. Chem.* **2011**, *76*, 4139-4143.
- (152) Delso, I.; Marca, E.; Mannucci, V.; Tejero, T.; Goti, A.; Merino, P. Tunable Diastereoselection of Biased Rigid Systems by Lewis Acid Induced Conformational Effects: A Rationalization of the Vinylation of Cyclic Nitrones En Route to Polyhydroxylated Pyrrolidines. *Chem. Eur. J.* **2010**, *16*, 9910-9919.
- (153) Fu, Y.; Liu, Y.; Chen, Y.; Hgel, H. M.; Wang, M.; Huang, D.; Hu, Y. Trimethylsilyl Chloride Promoted Synthesis of α -Branched Amines by Nucleophilic Addition of Organozinc Halides to Nitrones. *Org. Biomol. Chem.* **2012**, *10*, 7669-7672.
- (154) Parmeggiani, C.; Cardona, F.; Giusti, L.; Reissig, H.-U.; Goti, A. Stereocomplementary Routes to Hydroxylated Nitrogen Heterocycles: Total Syntheses of Casuarine, Australine, and 7-*epi*-Australine. *Chem. Eur. J.* **2013**, *19*, 10595-10604.
- (155) Pecchioli, T.; Cardona, F.; Reissig, H.-U.; Zimmer, R.; Goti, A. Alkoxyallene-Based Stereodivergent Syntheses of (–)-Hyacinthacine B₄ and of Putative Hyacinthacine C₅ Epimers: Proposal of Hyacinthacine C₅ Structure. *J. Org. Chem.* **2017**, *82*, 5835-5844.
- (156) Frantz, D. E.; Fssler, R.; Carreira, E. M. Catalytic in Situ Generation of Zn(II)-Alkynilides under Mild Conditions: A Novel C=N Addition Process Utilizing Terminal Acetylenes. *J. Am. Chem. Soc.* **1999**, *121*, 11245-11246.
- (157) Fssler, R.; Frantz, D. E.; Oetiker, J.; Carreira, E. M. First Synthesis of Optically Pure Propargylic *N*-Hydroxylamines by Direct, Highly Diastereoselective Addition of Terminal Alkynes to Nitrones. *Angew. Chem. Int. Ed.* **2002**, *41*, 3054-3056.
- (158) Downey, C. W.; Maxwell, E. N.; Confair, D. N. Silyl Triflate-Accelerated Additions of Catalytically Generated Zinc Acetylides to *N*-Phenyl Nitrones. *Tetrahedron Lett.* **2014**, *55*, 4959-4961.
- (159) Pinet, S.; Pandya, S. U.; Chavant, P. Y.; Ayling, A.; Valle, Y. Dialkylzinc-Assisted Alkynylation of Nitrones. *Org. Lett.* **2002**, *4*, 1463-1466.
- (160) Saito, Y.; Yamashita, Y.; Kobayashi, S. Zinc Bis[bis(trimethylsilyl)amide] as an Efficient Lewis Acid/Brnsted Base Cooperative Catalyst for the Direct Alkynylation of Nitrones. *Chem. Lett.* **2015**, *44*, 976-977.
- (161) Ji, D.-M.; Xu, M.-H. InBr₃-Catalyzed Direct Alkynylation of Nitrones with Terminal Alkynes: An Efficient Synthesis of *N*-Hydroxy-Propargyl Amines. *Tetrahedron Lett.* **2009**, *50*, 2952-2955.
- (162) Yamashita, Y.; Saito, Y.; Imaizumi, T.; Kobayashi, S. A Lewis Acid/Metal Amide Hybrid as an Efficient Catalyst for Carbon—Carbon Bond Formation. *Chem. Sci.* **2014**, *5*, 3958-3962.
- (163) Woniak, Ł.; Staszewska-Krajewska, O.; Michalak, M. Diastereoselective Synthesis

- of Propargylic *N*-Hydroxylamines via NHC–Copper(I) Halide-Catalyzed Reaction of Terminal Alkynes with Chiral Nitrones on Water. *Chem. Commun.* **2015**, *51*, 1933-1936.
- (164) Merino, P.; Franco, S.; Garces, N.; Merchan, F. L.; Tejero, T. Modified Nucleosides from Nitrones: A New and Efficient Stereoselective Approach to Isoxazolidinyl Thymidine Derivatives. *Chem. Commun.* **1998**, 493-494.
- (165) Downey, C. W.; Dombrowski, C. M.; Maxwell, E. N.; Safran, C. L.; Akomah, O. A. One-Pot Enol Silane Formation/Mukaiyama–Mannich Addition of Ketones, Amides, and Thioesters to Nitrones in the Presence of Trialkylsilyl Trifluoromethanesulfonates. *Eur. J. Org. Chem.* **2013**, 5716-5720.
- (166) Lisnyak, V. G.; Lynch-Colameta, T.; Snyder, S. A. Mannich-type Reactions of Cyclic Nitrones: Effective Methods for the Enantioselective Synthesis of Piperidine-containing Alkaloids. *Angew. Chem. Int. Ed.* **2018**, *57*, 15162-15166.
- (167) Cordaro, M.; Risitano, F.; Scala, A.; Rescifina, A.; Chiacchio, U.; Grassi, G. Self-Catalyzed Mannich-Type Reaction of Enolizable Cyclic 1,3-Dicarbonyls to Acyclic Nitrones: An Entry to Functionalized β -Enamino Diones. *J. Org. Chem.* **2013**, *78*, 3972-3979.
- (168) Yoshimura, F.; Abe, T.; Tanino, K. Nucleophilic Addition Reactions of Nitriles to Nitrones under Mild Silylation Conditions. *Synlett* **2014**, *25*, 1863-1868.
- (169) Congdon, E. A.; Nolin, K. A. Calcium Catalyzed Mukaiyama–Mannich Addition of Silyl Enol Ethers to Nitrones. *Catal. Commun.* **2016**, *79*, 35-38.
- (170) Xu, X.; Ratnikov, M. O.; Zavalij, P. Y.; Doyle, M. P. Multifunctionalized 3-Hydroxypyrroles in a Three-Step, One-Pot Cascade Process from Methyl 3-TBSO-2-diazo-3-butenate and Nitrones. *Org. Lett.* **2011**, *13*, 6122-6125.
- (171) Kita, Y.; Tamura, O.; Itoh, F.; Kishino, H.; Miki, T.; Kohno, M.; Tamura, Y. Chemistry of *O*-Silylated Ketene Acetals: Stereocontrolled Synthesis of 3-Benzoylamino-2,3-dideoxypentoses by a 1,3-Addition to Chiral Nitrones. *Chem. Pharm. Bull.* **1989**, *37*, 2002-2007.
- (172) Merino, P.; del Alamo, E. M.; Bona, M.; Franco, S.; Merchan, F. L.; Tejero, T.; Vieceli, O. Lewis Acid Stereocontrolled Additions of a Silyl Ketene Acetal to 2,3-Di-*O*-isopropylidene-D-glyceraldehyde Nitrones. Synthesis of L-Isoxazolidinyl Nucleosides. *Tetrahedron Lett.* **2000**, *41*, 9239-9243.
- (173) Merino, P.; Jimenez, P.; Tejero, T. Enantiodivergent Synthesis of D- and L-*erythro*-Sphingosines through Mannich-Type Reactions of *N*-Benzyl-2,3-*O*-isopropylidene-D-glyceraldehyde Nitron. *J. Org. Chem.* **2006**, *71*, 4685-4688.
- (174) Ohtake, H.; Imada, Y.; Murahashi, S.-I. Highly Diastereoselective Addition of a Chiral Ketene Silyl Acetal to Nitrones: Asymmetric Synthesis of β -Amino Acids and Key Intermediates of β -Lactam Antibiotics. *J. Org. Chem.* **1999**, *64*, 3970-3971.

- (175) Murahashi, S.-I.; Naota, T.; Kuwabara, T.; Saito, T.; Kumobayashi, H.; Akutagawa, S. Ruthenium-Catalyzed Oxidation of Amides and Lactams with Peroxide. *J. Am. Chem. Soc.* **1990**, *112*, 7820-7822.
- (176) Murahashi, S.-I.; Imada, Y.; Kawakami, T.; Harada, K.; Yonemushi, Y.; Tomita, N. Enantioselective Addition of Ketene Silyl Acetals to Nitrones Catalyzed by Chiral Titanium Complexes. Synthesis of Optically Active β -Amino Acids. *J. Am. Chem. Soc.* **2002**, *124*, 2888-2889.
- (177) Merino, P.; Franco, S.; Jimenez, P.; Tejero, T.; Chiacchio, M. A. Effect of Additional Chiral Ligands in Catalytic Enantioselective Addition of Ketene Silyl Acetals to Nitrones. *Lett. Org. Chem.* **2005**, *2*, 302-305.
- (178) Kawakami, T.; Ohtake, H.; Arakawa, H.; Okachi, T.; Imada, Y.; Murahashi, S.-I. Asymmetric Synthesis of β -Amino Acids by Addition of Chiral Enolates to Nitrones via *N*-Acyloxyiminium Ions. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2423-2444.
- (179) Kawakami, T.; Ohtake, H.; Arakawa, H.; Okachi, T.; Imada, Y.; Murahashi, S.-I. Reversal of Diastereoselectivity of the Reaction of Chiral Boron and Titanium Enolates with Nitrones via *N*-Acyloxyiminium Intermediates. Asymmetric Synthesis of Diastereomeric α -Substituted β -Amino Acids. *Chem. Lett.* **1999**, *28*, 795-796.
- (180) Kawakami, T.; Ohtake, H.; Arakawa, H.; Okachi, T.; Imada, Y.; Murahashi, S.-I. Asymmetric Synthesis of β -Amino Acids by Addition of Chiral Enolates to *N*-Acyloxyiminium Ions and Application for Synthesis of Optically Active 5-Substituted 8-Methylindolizidines. *Org. Lett.* **1999**, *1*, 107-110.
- (181) Reeves, J. T.; Lorenc, C.; Camara, K.; Li, Z.; Lee, H.; Busacca, C. A.; Senanayake, C. H. Carbamoyl Anion Addition to Nitrones. *J. Org. Chem.* **2014**, *79*, 5895-5902.
- (182) Garrett, M. R.; Tarr, J. C.; Johnson, J. S. Enantioselective Metallophosphite-Catalyzed *C*-Acylation of Nitrones. *J. Am. Chem. Soc.* **2007**, *129*, 12944-12945.
- (183) Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. Highly Diastereo- and Enantioselective Additions of Homo-enolates to Nitrones Catalyzed by *N*-Heterocyclic Carbenes. *J. Am. Chem. Soc.* **2008**, *130*, 2416-2417.
- (184) Xu, W.-Y.; Iwaki, R.; Jia, Y.-M.; Zhang, W.; Kato, A.; Yu, C.-Y. NHC-Mediated Cross-Coupling of Sugar-Derived Cyclic Nitrones with Enals: General and Efficient Synthesis of Polyhydroxylated Pyrrolizidines and Indolizidines. *Org. Biomol. Chem.* **2013**, *11*, 4622-4639.
- (185) Murahashi, S.-I.; Shiota, T. Short-step synthesis of amino acids and *N*-hydroxyamino acids from amines. *Tetrahedron Lett.* **1987**, *28*, 6469-6472.
- (186) Merino, P.; Tejero, T.; Revuelta, J.; Romero, P.; Cicchi, S.; Mannucci, V.; Brandi, A.; Goti, A. A Comparative Study of the Stereoselective Addition of Trimethylsilyl Cyanide and Diethylaluminum Cyanide to Chiral Cyclic Nitrones. *Tetrahedron: Asymmetry* **2003**, *14*, 367-379.

- (187) Zhu, J.-S.; Nakagawa, S.; Chen, W.; Adachi, I.; Jia, Y.-M.; Hu, X.-G.; Fleet, G. W. J.; Wilson, F. X.; Nitoda, T.; Horne, G.; van Well, R.; Kato, A.; Yu, C.-Y. Synthesis of Eight Stereoisomers of Pochonicine: Nanomolar Inhibition of β -N-Acetylhexosaminidases. *J. Org. Chem.* **2013**, *78*, 10298-10309.
- (188) Sakai, T.; Soeta, T.; Endo, K.; Fujinami, S.; Ukaji, Y. Magnesium–Tartramide Complex Mediated Asymmetric Strecker-Type Reaction of Nitrones Using Cyanohydrin. *Org. Lett.* **2013**, *15*, 2422-2425.
- (189) Murahashi, S.-I.; Sun, J.; Tsuda, T. The Reaction of Nitrones with (*R*)-(+)-Methyl *p*-Tolyl Sulfoxide Anion; Asymmetric Synthesis of Optically Active Secondary Amines. *Tetrahedron Lett.* **1993**, *34*, 2645-2648.
- (190) Murahashi, S.-I.; Sun, J.; Kurosawa, H.; Imada, Y. Synthesis of Homochiral β -Sulfinyl Nitrones and Their Application for Enantioselective Synthesis of (+)-Euphococcinine. *Heterocycles* **2000**, *52*, 557-561.
- (191) Nelson, D. W.; Owens, J.; Hiraldo, D. α -(Trifluoromethyl)amine Derivatives via Nucleophilic Trifluoromethylation of Nitrones. *J. Org. Chem.* **2001**, *66*, 2572-2582.
- (192) Korvorapun, K.; Soorukram, D.; Kuhakarn, C.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. Stereoselective Nucleophilic Addition of PhSCF₂SiMe₃ to Chiral Cyclic Nitrones: Asymmetric Synthesis of *gem*-Difluoromethylenated Polyhydroxypyrrolizidines and -indolizidines. *Chem. Asian J.* **2015**, *10*, 948-968.
- (193) Behr, J.-B.; Chavaria, D.; Plantier-Royon, R. Trifluoromethide as a Strong Base: [CF₃⁻] Mediates Dichloromethylation of Nitrones by Proton Abstraction from the Solvent. *J. Org. Chem.* **2013**, *78*, 11477-11482.
- (194) Zhang, W.; Huang, W.; Hu, J. Highly Stereoselective Synthesis of Monofluoroalkenes from α -Fluorosulfoximines and Nitrones. *Angew. Chem. Int. Ed.* **2009**, *48*, 9858-9861.
- (195) Soeta, T.; Fujinami, S.; Ukaji, Y. Chlorosilane-Promoted Addition Reaction of Isocyanides to 3,4-Dihydroisoquinoline *N*-Oxides. *J. Org. Chem.* **2012**, *77*, 9878-9883.
- (196) Mo, D.-L.; Pecak, W. H.; Zhao, M.; Wink, D. J.; Anderson, L. L. Synthesis of *N*-Styrenyl Amidines from α,β -Unsaturated Nitrones and Isocyanates through CO₂ Elimination and Styrenyl Migration. *Org. Lett.* **2014**, *16*, 3696-3699.
- (197) Palmer, A. M.; Jäger, V. Pyrrolidine *N*-Oxides by Stereoselective Addition of Grignard and Lithium Compounds to 4,5-Dideoxy-2,3-*O*-isopropylidene-D-*erythro*-4-pentenose *N*-Benzyl Nitron and Subsequent Cope-House Cyclization. *Eur. J. Org. Chem.* **2001**, 1293-1308.
- (198) Marradi, M.; Cicchi, S.; Delso, J. I.; Rosi, L.; Tejero, T.; Merino, P.; Goti, A. Straightforward Synthesis of Enantiopure 2-Aminomethyl and 2-Hydroxymethyl Pyrrolidines with Complete Stereocontrol. *Tetrahedron Lett.* **2005**, *46*, 1287-1290.

- (199) Murahashi, S.-I.; Watanabe, S.; Shiota, T. Asymmetric Hydrosilylation of Nitrones using Ruthenium(II) Phosphine Complex Catalysts; Syntheses of Optically Active *N,N*-Disubstituted Hydroxylamines and Secondary Amines. *J. Chem. Soc., Chem. Commun.* **1994**, 725-726.
- (200) Murahashi, S.-I.; Tsuji, T.; Ito, S. Synthesis of Optically Active *N*-Hydroxylamines by Asymmetric Hydrogenation of Nitrones with Iridium Catalysts. *Chem. Commun.* **2000**, 409-410.
- (201) Ueda, M.; Miyabe, H.; Teramachi, M.; Miyata, O.; Naito, T. Novel Intermolecular Carbon Radical Addition to a Nitrone: Asymmetric Synthesis of α -Amino Acids. *Chem. Commun.* **2003**, 426-427.
- (202) Ueda, M.; Miyabe, H.; Teramachi, M.; Miyata, O.; Naito, T. Diastereoselective Intermolecular Radical Addition to Nitrones. *J. Org. Chem.* **2005**, 70, 6653-6660.
- (203) Supranovich, V. I.; Levin, V. V.; Struchkova, M. I.; Dilman, A. D. Photocatalytic Reductive Fluoroalkylation of Nitrones. *Org. Lett.* **2018**, 20, 840-843.
- (204) Yang, Y.-S.; Shen, Z.-L.; Loh, T.-P. Indium (Zinc)-Copper-Mediated Barbier-Type Alkylation Reaction of Nitrones in Water: Synthesis of Amines and Hydroxylamines. *Org. Lett.* **2009**, 11, 1209-1212.
- (205) Masson, G.; Cividino, P.; Py, S.; Vallée, Y. SmI₂-Induced Umpolung of the C=N Bond: First Reductive Conjugate Addition of Nitrones to α,β -Unsaturated Esters. *Angew. Chem. Int. Ed.* **2003**, 42, 2265-2268.
- (206) Riber, D.; Skrydstrup, T. SmI₂-Promoted Radical Addition of Nitrones to α,β -Unsaturated Amides and Esters: Synthesis of γ -Amino Acids via a Nitrogen Equivalent to the Ketyl Radical. *Org. Lett.* **2003**, 5, 229-231.
- (207) Xu, C.-P.; Huang, P.-Q.; Py, S. SmI₂-Mediated Coupling of Nitrones and *tert*-Butanesulfinyl Imines with Allenates: Synthesis of β -Methylenyl- γ -lactams and Tetramic Acids. *Org. Lett.* **2012**, 14, 2034-2037.
- (208) Gilles, P.; Py, S. SmI₂-Mediated Cross-Coupling of Nitrones with β -Silyl Acrylates: Synthesis of (+)-Australine. *Org. Lett.* **2012**, 14, 1042-1045.
- (209) Zhong, Y.-W.; Xu, M.-H.; Lin, G.-Q. Samarium Diiodide-Induced Asymmetric Synthesis of Optically Pure Unsymmetrical Vicinal Diamines by Reductive Cross-Coupling of Nitrones with *N-tert*-Butanesulfinyl Imines. *Org. Lett.* **2004**, 6, 3953-3956.
- (210) Prikhod'ko, A.; Walter, O.; Zevaco, T. A.; Garcia-Rodriguez, J.; Mouhtady, O.; Py, S. Synthesis of α -Amino Acids through Samarium(II) Iodide Promoted Reductive Coupling of Nitrones with CO₂. *Eur. J. Org. Chem.* **2012**, 2012, 3742-3746.
- (211) Masson, G.; Py, S.; Vallée, Y. Samarium Diiodide-Induced Reductive Cross-Coupling of Nitrones with Aldehydes and Ketones. *Angew. Chem. Int. Ed.* **2002**, 41, 1772-1775.
- (212) Zhang, H.-K.; Xu, S.-Q.; Zhuang, J.-J.; Ye, J.-L.; Huang, P.-Q. A Flexible

- Enantioselective Approach to 3,4-Dihydroxyprolinol Derivatives by SmI₂-Mediated Reductive Coupling of Chiral Nitronone with Ketones/Aldehydes. *Tetrahedron* **2012**, *68*, 6656-6664.
- (213) Burchak, O. N.; Philouze, C.; Chavant, P. Y.; Py, S. A Direct and Versatile Access to α,α -Disubstituted 2-Pyrrolidinylmethanols by SmI₂-Mediated Reductive Coupling. *Org. Lett.* **2008**, *10*, 3021-3024.
- (214) Ye, C.-X.; Melcamu, Y. Y.; Li, H.-H.; Cheng, J.-T.; Zhang, T.-T.; Ruan, Y.-P.; Zheng, X.; Lu, X.; Huang, P.-Q. Dual catalysis for enantioselective convergent synthesis of enantiopure vicinal amino alcohols. *Nature Commun.* **2018**, *9*, 410.
- (215) Itoh, K.; Kato, R.; Kinugawa, D.; Kamiya, H.; Kudo, R.; Hasegawa, M.; Fujii, H.; Suga, H. Photochemically-Induced C–C Bond Formation between Tertiary Amines and Nitrones. *Org. Biomol. Chem.* **2015**, *13*, 8919-8924.
- (216) Hasegawa, M.; Nomoto, A.; Suga, T.; Soeta, T.; Ukaji, Y. Palladium-catalyzed C–H Alkenylation of *C*-Aryl Nitrones. *Chem. Lett.* **2017**, *46*, 45-47.
- (217) Xie, F.; Qi, Z.; Yu, S.; Li, X. Rh(III)- and Ir(III)-Catalyzed C–H Alkynylation of Arenes under Chelation Assistance. *J. Am. Chem. Soc.* **2014**, *136*, 4780-4787.
- (218) Deng, H.; Li, H.; Zhang, W.; Wang, L. Rh^{III}-Catalyzed Site-Selective Amidation with Nitronone as a Traceless Directing Group: An Approach to Functionalized Arylaldehydes. *Chem. Commun.* **2017**, *53*, 10322-10325.
- (219) Bai, D.; Jia, Q.; Xu, T.; Zhang, Q.; Wu, F.; Ma, C.; Liu, B.; Chang, J.; Li, X. Rhodium(III)-Catalyzed C–H Activation of Nitrones and Annulative Coupling with Nitroalkenes. *J. Org. Chem.* **2017**, *82*, 9877-9884.
- (220) Pi, C.; Cui, X.; Wu, Y. Iridium-Catalyzed Direct C–H Sulfamidation of Aryl Nitrones with Sulfonyl Azides at Room Temperature. *J. Org. Chem.* **2015**, *80*, 7333-7339.
- (221) Yan, H.; Wang, H.; Li, X.; Xin, X.; Wang, C.; Wan, B. Rhodium-Catalyzed C–H Annulation of Nitrones with Alkynes: A Regiospecific Route to Unsymmetrical 2,3-Diaryl-Substituted Indoles. *Angew. Chem. Int. Ed.* **2015**, *54*, 10613-10617.
- (222) Wang, H.; Moselage, M.; González, M. J.; Ackermann, L. Selective Synthesis of Indoles by Cobalt(III)-Catalyzed C–H/N–O Functionalization with Nitrones. *ACS Catal.* **2016**, *6*, 2705-2727.
- (223) Dateer, R. B.; Chang, S. Selective Cyclization of Arylnitrones to Indolines under External Oxidant-Free Conditions: Dual Role of Rh(III) Catalyst in the C–H Activation and Oxygen Atom Transfer. *J. Am. Chem. Soc.* **2015**, *137*, 4908-4911.
- (224) Qi, Z.; Wang, M.; Li, X. Access to Indenones by Rhodium(III)-Catalyzed C–H Annulation of Arylnitrones with Internal Alkynes. *Org. Lett.* **2013**, *15*, 5440-5443.
- (225) Xie, F.; Yu, S.; Qi, Z.; Li, X. Nitronone Directing Groups in Rhodium(III)-Catalyzed C–H Activation of Arenes: 1,3-Dipoles versus Traceless Directing Groups. *Angew. Chem. Int. Ed.* **2016**, *55*, 15351-15355.

- (226) Wang, Q.; Xu, Y.; Yang, X.; Li, Y.; Li, X. Naphthol Synthesis: Annulation of Nitrones with Alkynes via Rhodium(III)-Catalyzed C–H Activation. *Chem. Commun.* **2017**, 53, 9640-9643.
- (227) Yang, Y.; Wang, X.; Li, Y.; Zhou, B. A [4 + 1] Cyclative Capture Approach to 3*H*-Indole-*N*-oxides at Room Temperature by Rhodium(III)-Catalyzed C—H Activation. *Angew. Chem. Int. Ed.* **2015**, 54, 15400-15404.
- (228) Li, Y.; Li, J.; Wu, X.; Zhou, Y.; Liu, H. Rh(III)-Catalyzed C–H Cyclization of Arylnitrones with Diazo Compounds: Access to 3-Carboxylate Substituted *N*-Hydroxyindoles. *J. Org. Chem.* **2017**, 82, 8984-8994.
- (229) Guo, X.; Han, J.; Liu, Y.; Qin, M.; Zhang, X.; Chen, B. Synthesis of 2,3-Disubstituted *NH* Indoles via Rhodium(III)-Catalyzed C–H Activation of Arylnitrones and Coupling with Diazo Compounds. *J. Org. Chem.* **2017**, 82, 11505-11511.
- (230) Demory, E.; Farran, D.; Baptiste, B.; Chavant, P. Y.; Blandin, V. Fast Pd- and Pd/Cu-Catalyzed Direct C–H Arylation of Cyclic Nitrones. Application to the Synthesis of Enantiopure Quaternary α -Amino Esters. *J. Org. Chem.* **2012**, 77, 7901-7912.
- (231) Murarka, S.; Studer, A. Zinc Triflate Catalyzed Aerobic Cross-Dehydrogenative Coupling (CDC) of Alkynes with Nitrones: A New Entry to Isoxazoles. *Org. Lett.* **2011**, 13, 2746-2749.
- (232) Hashizume, S.; Oisaki, K.; Kanai, M. Catalytic Migratory Oxidative Coupling of Nitrones. *Org. Lett.* **2011**, 13, 4288-4291.
- (233) Hashizume, S.; Oisaki, K.; Kanai, M. Functional-Group-Tolerant Catalytic Migratory Oxidative Coupling of Nitrones. *Chem. Asian J.* **2012**, 7, 2600-2606.
- (234) Tsuji, R.; Yamanaka, M.; Nishida, A.; Nakagawa, M. Pictet–Spengler Reaction of Nitrones and Imines Catalyzed by Yb(OTf)₃–TMSCl. *Chem. Lett.* **2002**, 31, 428-429.
- (235) Yamada, H.; Kawate, T.; Matsumizu, M.; Nishida, A.; Yamaguchi, K.; Nakagawa, M. Chiral Lewis Acid-Mediated Enantioselective Pictet–Spengler Reaction of *N*_b-Hydroxytryptamine with Aldehydes. *J. Org. Chem.* **1998**, 63, 6348-6354.
- (236) Wilkens, J.; Kühling, A.; Blechert, S. Hetero-Cope Rearrangements - VI: Short and Stereoselective Syntheses of 2-Vinylindoles by a Tandem-Process. *Tetrahedron* **1987**, 43, 3237-3246.
- (237) Padwa, A.; Bullock, W. H.; Kline, D. N.; Perumattam, J. Heterocyclic Synthesis via the Reaction of Nitrones and Hydroxylamines with Substituted Allenes. *J. Org. Chem.* **1989**, 54, 2862-2869.
- (238) Mo, D.-L.; Wink, D. J.; Anderson, L. L. Solvent-Controlled Bifurcated Cascade Process for the Selective Preparation of Dihydrocarbazoles or Dihydropyridoindoles. *Chem. Eur. J.* **2014**, 20, 13217-13225.
- (239) Anderson, L. L.; Kroc, M. A.; Reidl, T. W.; Son, J. Cascade Reactions of Nitrones and Allenes for the Synthesis of Indole Derivatives. *J. Org. Chem.* **2016**, 81, 9521-9529.

- (240) Pace, W. H.; Mo, D.-L.; Reidl, T. W.; Wink, D. J.; Anderson, L. L. Catalytic Asymmetric Synthesis of Dihydropyrido[1,2-*a*]indoles from Nitrones and Allenates. *Angew. Chem. Int. Ed.* **2016**, *55*, 9183-9186.
- (241) Kroc, M. A.; Prajapati, A.; Wink, D. J.; Anderson, L. L. Cascade Synthesis of 3-Functionalized Indoles from Nitrones and Their Conversion to Cycloheptanone-Fused Indoles. *J. Org. Chem.* **2018**, *83*, 1085-1094.
- (242) Pecak, W. H.; Son, J.; Burnstine, A. J.; Anderson, L. L. Synthesis of 1,4-Enamino Ketones by [3,3]-Rearrangements of Dialkenylhydroxylamines. *Org. Lett.* **2014**, *16*, 3440-3443.
- (243) Duguet, N.; Slawin, A. M. Z.; Smith, A. D. An Asymmetric Hetero-Claisen Approach to 3-Alkyl-3-aryloxindoles. *Org. Lett.* **2009**, *11*, 3858-3861.
- (244) Richmond, E.; Duguet, N.; Slawin, A. M. Z.; Lébl, T.; Smith, A. D. Asymmetric Pericyclic Cascade Approach to Spirocyclic Oxindoles. *Org. Lett.* **2012**, *14*, 2762-2765.
- (245) Çelebi-Ölçüm, N.; Lam, Y.-h.; Richmond, E.; Ling, K. B.; Smith, A. D.; Houk, K. N. Pericyclic Cascade with Chirality Transfer: Reaction Pathway and Origin of Enantioselectivity of the Hetero-Claisen Approach to Oxindoles. *Angew. Chem. Int. Ed.* **2011**, *50*, 11478-11482.
- (246) Kinugasa, M.; Hashimoto, S. The Reaction of Copper(I) Phenylacetylide with Nitrones. *J. Chem. Soc., Chem. Commun.* **1972**, 466-467.
- (247) Marco-Contelles, J. β -Lactam Synthesis by the Kinugasa Reaction. *Angew. Chem. Int. Ed.* **2004**, *43*, 2198-2200.
- (248) Pal, R.; Ghosh, S. C.; Chandra, K.; Basak, A. Synthesis of β -Lactams Using the Kinugasa Reaction. *Synlett* **2007**, 2321-2330.
- (249) Maciejko, M.; Stecko, S.; Staszewska-Krajewska, O.; Jurczak, M.; Furman, B.; Chmielewski, M. An Entry to the Carbapenem Antibiotic Scaffold via the Asymmetric Kinugasa Reaction. *Synthesis* **2012**, *44*, 2825-2839.
- (250) Pitts, C. R.; Lectka, T. Chemical Synthesis of β -Lactams: Asymmetric Catalysis and Other Recent Advances. *Chem. Rev.* **2014**, *114*, 7930-7953.
- (251) Stecko, S.; Mames, A.; Furman, B.; Chmielewski, M. Diastereoselective Synthesis of Carbapenams via Kinugasa Reaction. *J. Org. Chem.* **2008**, *73*, 7402-7404.
- (252) Stecko, S.; Mames, A.; Furman, B.; Chmielewski, M. Asymmetric Kinugasa Reaction of Cyclic Nitrones and Nonracemic Acetylenes. *J. Org. Chem.* **2009**, *74*, 3094-3100.
- (253) Okuro, K.; Enna, M.; Miura, M.; Nomura, M. Copper-Catalysed Reaction of Arylacetylenes with *C,N*-Diarylnitrones. *J. Chem. Soc., Chem. Commun.* **1993**, 1107-1108.
- (254) Miura, M.; Enna, M.; Okuro, K.; Nomura, M. Copper-Catalyzed Reaction of Terminal Alkynes with Nitrones. Selective Synthesis of 1-Aza-1-buten-3-yne and 2-

- Azetidinone Derivatives. *J. Org. Chem.* **1995**, *60*, 4999-5004.
- (255) Lo, M. M.-C.; Fu, G. C. Cu(I)/Bis(azaferrocene)-Catalyzed Enantioselective Synthesis of β -Lactams via Couplings of Alkynes with Nitrones. *J. Am. Chem. Soc.* **2002**, *124*, 4572-4573.
- (256) Chen, J.-H.; Liao, S.-H.; Sun, X.-L.; Shen, Q.; Tang, Y. Tris(oxazoline)/Copper-Catalyzed Coupling of Alkynes with Nitrones: A Highly Enantioselective Access to β -Lactams. *Tetrahedron* **2012**, *68*, 5042-5045.
- (257) Takayama, Y.; Ishii, T.; Ohmiya, H.; Iwai, T.; Schwarzer, M. C.; Mori, S.; Taniguchi, T.; Monde, K.; Sawamura, M. Asymmetric Synthesis of β -Lactams through Copper-Catalyzed Alkyne–Nitron Coupling with a Prolinol–Phosphine Chiral Ligand. *Chem. Eur. J.* **2017**, *23*, 8400-8404.
- (258) Wolosewicz, K.; Michalak, M.; Adamek, J.; Furman, B. Studies on the Enantioselective Kinugasa Reaction: Efficient Synthesis of β -Lactams Catalyzed by *N*-PINAP/CuX Complexes. *Eur. J. Org. Chem.* **2016**, 2212-2219.
- (259) Shintani, R.; Fu, G. C. Catalytic Enantioselective Synthesis of β -Lactams: Intramolecular Kinugasa Reactions and Interception of an Intermediate in the Reaction Cascade. *Angew. Chem. Int. Ed.* **2003**, *42*, 4082-4085.
- (260) Santoro, S.; Liao, R.-Z.; Marcelli, T.; Hammar, P.; Himo, F. Theoretical Study of Mechanism and Stereoselectivity of Catalytic Kinugasa Reaction. *J. Org. Chem.* **2015**, *80*, 2649-2660.
- (261) Yeom, H.-S.; Lee, J.-E.; Shin, S. Gold-Catalyzed Waste-Free Generation and Reaction of Azomethine Ylides: Internal Redox/Dipolar Cycloaddition Cascade. *Angew. Chem. Int. Ed.* **2008**, *47*, 7040-7043.
- (262) Pati, K.; Liu, R.-S. Efficient Syntheses of α -Pyridones and 3(2*H*)-Isoquinolones through Ruthenium-Catalyzed Cycloisomerization of 3-En-5-ynyl and *o*-Alkynylphenyl Nitrones. *Chem. Commun.* **2009**, 5233-5235.
- (263) Song, G.; Chen, D.; Su, Y.; Han, K.; Pan, C.-L.; Jia, A.; Li, X. Isolation of Azomethine Ylides and Their Complexes: Iridium(III)-Mediated Cyclization of Nitron Substrates Containing Alkynes. *Angew. Chem. Int. Ed.* **2011**, *50*, 7791-7796.
- (264) Yeom, H.-S.; Lee, Y.; Jeong, J.; So, E.; Hwang, S.; Lee, J.-E.; Lee, S. S.; Shin, S. Stereoselective One-Pot Synthesis of 1-Aminoindanes and 5,6-Fused Azacycles Using a Gold-Catalyzed Redox-Pinacol-Mannich-Michael Cascade. *Angew. Chem. Int. Ed.* **2010**, *49*, 1611-1614.
- (265) Qian, D.; Zhang, J. Gold/Brønsted Acid Relay Catalysis for Enantioselective Construction of Spirocyclic Diketones. *Chem. Eur. J.* **2013**, *19*, 6984-6988.
- (266) Young, I. S.; Kerr, M. A. A Homo [3 + 2] Dipolar Cycloaddition: The Reaction of Nitrones with Cyclopropanes. *Angew. Chem. Int. Ed.* **2003**, *42*, 3023-3026.
- (267) Ganton, M. D.; Kerr, M. A. Magnesium Iodide Promoted Reactions of Nitrones with

- Cyclopropanes: A Synthesis of Tetrahydro-1,2-oxazines. *J. Org. Chem.* **2004**, *69*, 8554-8557.
- (268) Braun, C. M.; Congdon, E. A.; Nolin, K. A. Diastereoselective 1,3-Dipolar Cycloaddition of Nitrones to Donor–Acceptor Cyclopropanes Catalyzed by a Calcium(II) Complex. *J. Org. Chem.* **2015**, *80*, 1979-1984.
- (269) Sibi, M. P.; Ma, Z.; Jasperse, C. P. Enantioselective Addition of Nitrones to Activated Cyclopropanes. *J. Am. Chem. Soc.* **2005**, *127*, 5764-5765.
- (270) Kang, Y.-B.; Sun, X.-L.; Tang, Y. Highly Enantioselective and Diastereoselective Cycloaddition of Cyclopropanes with Nitrones and Its Application in the Kinetic Resolution of 2-Substituted Cyclopropane-1,1-dicarboxylates. *Angew. Chem. Int. Ed.* **2007**, *46*, 3918-3921.
- (271) Shintani, R.; Park, S.; Duan, W.-L.; Hayashi, T. Palladium-Catalyzed Asymmetric [3 + 3] Cycloaddition of Trimethylenemethane Derivatives with Nitrones. *Angew. Chem. Int. Ed.* **2007**, *46*, 5901-5903.
- (272) Shintani, R.; Murakami, M.; Hayashi, T. γ -Methylidene- δ -valerolactones as a Coupling Partner for Cycloaddition: Palladium-Catalyzed [4 + 3] Cycloaddition with Nitrones. *J. Am. Chem. Soc.* **2007**, *129*, 12356-12357.
- (273) Wang, X.; Xu, X.; Zavalij, P. Y.; Doyle, M. P. Asymmetric Formal [3 + 3]-Cycloaddition Reactions of Nitrones with Electrophilic Vinylcarbene Intermediates. *J. Am. Chem. Soc.* **2011**, *133*, 16402-16405.
- (274) Qian, Y.; Xu, X.; Wang, X.; Zavalij, P. J.; Hu, W.; Doyle, M. P. Rhodium(II)- and Copper(II)-Catalyzed Reactions of Enol Diazoacetates with Nitrones: Metal Carbene versus Lewis Acid Directed Pathways. *Angew. Chem. Int. Ed.* **2012**, *51*, 5900-5903.
- (275) Cheng, Q.-Q.; Yedoyan, J.; Arman, H.; Doyle, M. P. Copper-Catalyzed Divergent Addition Reactions of Enoldiazoacetamides with Nitrones. *J. Am. Chem. Soc.* **2016**, *138*, 44-47.
- (276) Marichev, K. O.; Adly, F. G.; Carranco, A. M.; Garcia, E. C.; Arman, H.; Doyle, M. P. Catalyst Choice for Highly Enantioselective [3 + 3]-Cycloaddition of Enoldiazocarbonyl Compounds. *ACS Catal.* **2018**, *8*, 10392-10400.
- (277) Xu, X.; Zavalij, P. J.; Doyle, M. P. A Donor–Acceptor Cyclopropene as a Dipole Source for a Silver(I) Catalyzed Asymmetric Catalytic [3 + 3]-Cycloaddition with Nitrones. *Chem. Commun.* **2013**, *49*, 10287-10289.
- (278) Zhang, Z.-M.; Chen, P.; Li, W.; Niu, Y.; Zhao, X.-L.; Zhang, J. A New Type of Chiral Sulfinamide Monophosphine Ligands: Stereodivergent Synthesis and Application in Enantioselective Gold(I)-Catalyzed Cycloaddition Reactions. *Angew. Chem. Int. Ed.* **2014**, *53*, 4350-4354.
- (279) Pathipati, S. R.; Singh, V.; Eriksson, L.; Selander, N. Lewis Acid Catalyzed Annulation of Nitrones with Oxiranes, Aziridines, and Thiiranes. *Org. Lett.* **2015**, *17*,

- 4506-4509.
- (280) Wani, I. A.; Sayyad, M.; Ghorai, M. K. Domino Ring-Opening Cyclization (DROC) of Activated Aziridines and Epoxides with Nitrones via Dual-Catalysis "On Water". *Chem. Commun.* **2017**, 53, 4386-4389.
- (281) Jia, Q.; Li, D.; Lang, M.; Zhang, K.; Wang, J. 4-Dimethylaminopyridine-Mediated [3 + 3] Cycloaddition of Aza-oxyallyl Cations and Nitrones. *Adv. Synth. Catal.* **2017**, 359, 3837-3842.
- (282) Zhao, H.-W.; Zhao, Y.-D.; Liu, Y.-Y.; Zhao, L.-J.; Feng, N.-N.; Pang, H.-L.; Chen, X.-Q.; Song, X.-Q.; Du, J. Facile Access to Novel 1,2,4-Oxadiazinan-5-ones via [3 + 3] Cycloaddition of *in situ* Generated Azaoxyallyl Cations with Nitrones. *RSC Adv.* **2017**, 7, 12916-12922.
- (283) Liu, Y.; Ao, J.; Paladhi, S.; Song, C. E.; Yan, H. Organocatalytic Asymmetric Synthesis of Chiral Dioxazinanes and Dioxazepanes with *in Situ* Generated Nitrones via a Tandem Reaction Pathway Using a Cooperative Cation Binding Catalyst. *J. Am. Chem. Soc.* **2016**, 138, 16486-16492.
- (284) Nakamura, I.; Jo, T.; Zhang, D.; Terada, M. *N*-Allenynitronone Acts as 2-Azadiene in the Cu-catalyzed Cascade Reaction of *O*-Propargylic Oximes with Azodicarboxylates. *Org. Chem. Front.* **2014**, 1, 914-918.
- (285) Stevens, A. C.; Palmer, C.; Pagenkopf, B. L. The Formal [4 + 3] Cycloaddition between Donor–Acceptor Cyclobutanes and Nitrones. *Org. Lett.* **2011**, 13, 1528-1531.
- (286) Hu, J.-L.; Wang, L.; Xu, H.; Xie, Z.; Tang, Y. Highly Diastereoselective and Enantioselective Formal [4 + 3] Cycloaddition of Donor–Acceptor Cyclobutanes with Nitrones. *Org. Lett.* **2015**, 17, 2680-2683.
- (287) Zhao, H.-W.; Pang, H.-L.; Tian, T.; Li, B.; Chen, X.-Q.; Song, X.-Q.; Meng, W.; Yang, Z.; Liu, Y.-Y.; Zhao, Y.-D. Construction of 2,3,4,7-Tetrahydro-1,2,4,5-oxatriazepines via [4 + 3] Cycloadditions of α -Halogeno Hydrazones with Nitrones. *Adv. Synth. Catal.* **2016**, 358, 1826-1832.
- (288) Bai, Y.; Fang, J.; Ren, J.; Wang, Z. Highly Diastereoselective Gold- or Copper-Catalyzed Formal [4 + 3] Cycloaddition of 1-(1-Alkynyl) Cyclopropyl Ketones and Nitrones. *Chem. Eur. J.* **2009**, 15, 8975–8978.
- (289) Zhang, Y.; Zhang, J. Kinetic Resolution of 1-(1-Alkynyl)cyclopropyl Ketones by Gold(I)-Catalyzed Asymmetric [4 + 3]Cycloaddition with Nitrones: Scope, Mechanism and Applications. *Chem. Commun.* **2012**, 48, 4710-4712.
- (290) Gawade, S. A.; Bhunia, S.; Liu, R.-S. Intermolecular Gold-Catalyzed Diastereo- and Enantioselective [2 + 2 + 3] Cycloadditions of 1,6-Enynes with Nitrones. *Angew. Chem. Int. Ed.* **2012**, 51, 7835-7838.
- (291) Wang, C.; Wang, D.; Yan, H.; Wang, H.; Pan, B.; Xin, X.; Li, X.; Wu, F.; Wan, B. Rhodium-Catalyzed Cyclization of Diynes with Nitrones: A Formal [2 + 2 + 5]

- Approach to Bridged Eight-Membered Heterocycles. *Angew. Chem. Int. Ed.* **2014**, *53*, 11940-11943.
- (292) Matsui, K.; Shibuya, M.; Yamamoto, Y. Ruthenium-Catalyzed Transfer Oxygenative [2 + 2 + 1] Cycloaddition of Silyldiynes Using Nitrones as Adjustable Oxygen Atom Donors. Synthesis of Bicyclic 2-Silylfurans. *ACS Catal.* **2015**, *5*, 6468-6472.
- (293) Huehls, C. B.; Hood, T. S.; Yang, J. Diastereoselective Synthesis of C3-Quaternary Indolenines Using α,β -Unsaturated *N*-Aryl Ketonitrones and Activated Alkynes. *Angew. Chem. Int. Ed.* **2012**, *51*, 5110-5113.
- (294) Zhao, D.; Zhang, J.; Xie, Z. An Unprecedented Formal [5 + 2] Cycloaddition of Nitrones with *o*-Carboryne via Tandem [3 + 2] Cycloaddition/Oxygen Migration/Aromatization Sequence. *J. Am. Chem. Soc.* **2015**, *137*, 13938-13942.
- (295) Bøgevig, A.; Gothelf, K. V.; Jørgensen, K. A. Nucleophilic Addition of Nitrones to Ketones: Development of a New Catalytic Asymmetric Nitrone-Aldol Reaction. *Chem. Eur. J.* **2002**, *8*, 5652-5661.
- (296) Arnó, M.; Zaragoza, R. J.; Domingo, L. R. The Nucleophilic Addition of Nitrones to Carbonyl Compounds: Insights on the Nature of the Mechanism of the L-Proline Induced Asymmetric Reaction from a DFT Analysis. *Tetrahedron: Asymmetry* **2004**, *15*, 1541-1549.
- (297) Juste-Navarro, V.; Delso, I.; Tejero, T.; Merino, P. Azomethine Ylides from Nitrones: Using Catalytic *n*BuLi for the Totally Stereoselective Synthesis of *trans*-2-Alkyl-3-oxazolines. *Chem. Eur. J.* **2016**, *22*, 11527-11532.
- (298) Chalaye-Mauger, H.; Denis, J.-N.; Averbuch-Pouchot, M.-T.; Vallée, Y. The Reactions of Nitrones with Indoles. *Tetrahedron* **2000**, *56*, 791-804.
- (299) Berini, C.; Minassian, F.; Pelloux-Léon, N.; Denis, J.-N.; Vallée, Y.; Philouze, C. Efficient Stereoselective Nucleophilic Addition of Pyrroles to Chiral Nitrones. *Org. Biomol. Chem.* **2008**, *6*, 2574-2586.
- (300) Su, J.-K.; Jia, Y.-M.; He, R.; Rui, P.-X.; Han, N.; He, X.; Xiang, J.; Chen, X.; Zhu, J.; Yu, C.-Y. A Rapid Synthesis of 2-Aryl Polyhydroxylated Pyrrolidines. *Synlett* **2010**, 1609-1616.
- (301) Nakamura, I.; Zhang, D.; Terada, M. Copper-Catalyzed Tandem [2,3]-Rearrangement and 6π -3-Azatatriene Electrocyclization in (*E*)-*O*-Propargylic α,β -Unsaturated Oximes. *J. Am. Chem. Soc.* **2010**, *132*, 7884-7886.
- (302) Son, J.; Kim, K. H.; Mo, D. L.; Wink, D. J.; Anderson, L. L. Single-Step Modular Synthesis of Unsaturated Morpholine *N*-Oxides and Their Cycloaddition Reactions. *Angew. Chem. Int. Ed.* **2017**, *56*, 3059-3063.
- (303) Splitter, J.; Calvin, M. Preparation of Oxaziranes by Irradiation of Nitrones. *J. Org. Chem.* **1958**, *23*, 651-651.
- (304) Splitter, J. S.; Calvin, M. Oxaziridines. I. The Irradiation Products of Several

- Nitrones. *J. Org. Chem.* **1965**, *30*, 3427-3436.
- (305) Zhang, Y.; Blackman, M. L.; Leduc, A. B.; Jamison, T. F. Peptide Fragment Coupling Using a Continuous-Flow Photochemical Rearrangement of Nitrones. *Angew. Chem. Int. Ed.* **2013**, *52*, 4251-4255.
- (306) Bourguet, E.; Baneres, J.-L.; Girard, J.-P.; Parello, J.; Vidal, J.-P.; Lusinchi, X.; Declercq, J.-P. Photochemical Rearrangement of Oxaziridines and Nitrones in the Hexahydroindole Series: A Convenient Synthetic Route to 1-Azabicyclo[5.2.0]nonan-2-ones as Novel RGD Mimetics. *Org. Lett.* **2001**, *3*, 3067-3070.
- (307) Zeng, Y.; Smith, B. T.; Hersherberger, J.; Aubé, J. Rearrangements of Bicyclic Nitrones to Lactams: Comparison of Photochemical and Modified Barton Conditions. *J. Org. Chem.* **2003**, *68*, 8065-8067.
- (308) Merino, P.; Tejero, T.; Mannucci, V. Experimental and Theoretical Evidences of 2-Aza-Cope Rearrangement of Nitrones. *Tetrahedron Lett.* **2007**, *48*, 3385-3388.
- (309) Mo, D.-L.; Anderson, L. L. Copper-Catalyzed Rearrangement of *N*-Aryl Nitrones into Epoxyketimines. *Angew. Chem. Int. Ed.* **2013**, *52*, 6722-6725.
- (310) Singh, S. K.; Reddy, M. S.; Mangle, M.; Ganesh, K. R. Cu(I)-mediated Deoxygenation of *N*-Oxides to Amines. *Tetrahedron* **2007**, *63*, 126-130.
- (311) Cividino, P.; Dheu-Andries, M.-L.; Ou, J.; Milet, A.; Py, S.; Toy, P. H. Mechanistic Investigations of the Phosphine-Mediated Nitron Deoxygenation Reaction and Its Application in Cyclic Imine Synthesis. *Tetrahedron Lett.* **2009**, *50*, 7038-7042.
- (312) Sahani, R. L.; Patil, M. D.; Wagh, S. B.; Liu, R.-S. Catalytic Transformations of Alkynes into either α -Alkoxy or α -Aryl Enolates: Mannich Reactions by Cooperative Catalysis and Evidence for Nucleophile-Directed Chemoselectivity. *Angew. Chem. Int. Ed.* **2018**, *57*, 14878-14882.
- (313) Wei, H.; Bao, M.; Dong, K.; Qiu, L.; Wu, B.; Hu, W.; Xu, X. Enantioselective Oxidative Cyclization/Mannich Addition Enabled by Gold(I)/Chiral Phosphoric Acid Cooperative Catalysis. *Angew. Chem. Int. Ed.* **2018**, *57*, 17200-17204.
- (314) Imada, Y.; Okita, C.; Maeda, H.; Kishimoto, M.; Sugano, Y.; Kaneshiro, H.; Nishida, Y.; Kawamorita, S.; Komiya, N.; Naota, T. Ring-Expanding Metathesis Oligomerization of Cyclic Nitrones. *Eur. J. Org. Chem.* **2014**, 5670-5674.