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.*

CONTENTS

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 nitrones[1-13] 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

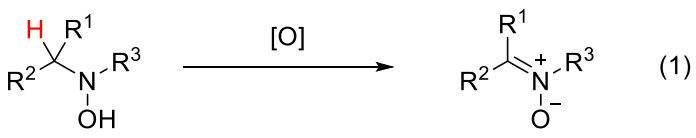
Nitrones are readily obtained by oxidation reactions, condensation reactions of *N*-monosubstituted hydroxylamines, reactions of oximes with electrophiles, and other various methods.

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.

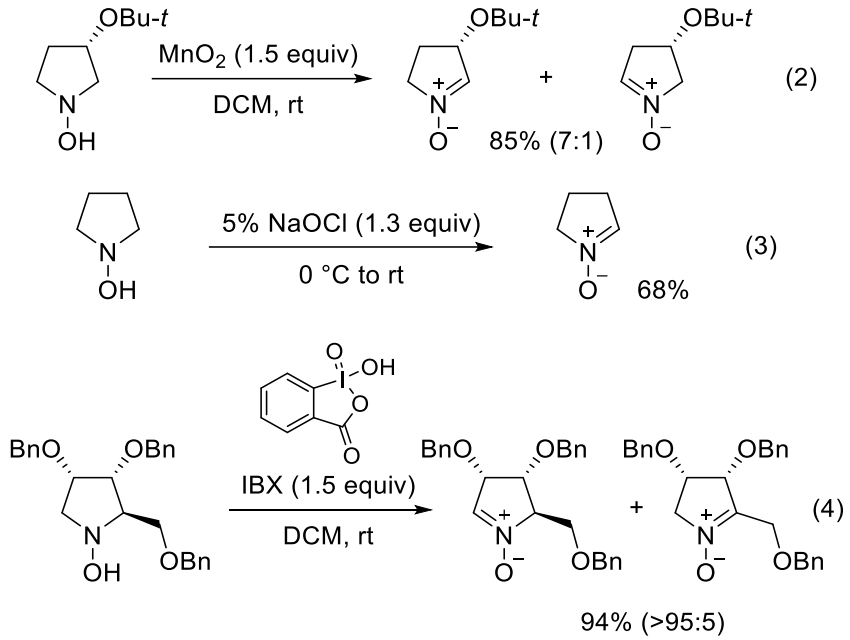
2.1.1. Oxidation of *N*,*N*-Disubstituted Hydroxylamines

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]

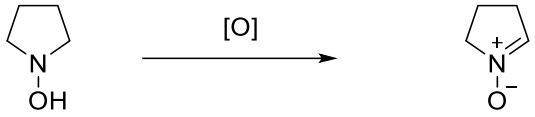
However, HgO is toxic and alternative methods have been explored. Oxidation with MnO_2 is useful and compatible to that of HgO in view of regioselectivity (eq 2).[23] Oxidation with sodium hypochlorite (NaOCl) is a convenient and environmentally friendly; therefore, a large scale production of nitrones 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 carbonate[28] 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/SiO_2)[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-Pr_4NRuO_4, TPAP) catalyst[33] as an environmentally benign extension of the method utilizing TPAP in conjunction with *N*-methylmorpholine *N*-oxide (NMO) as an oxidant.[34]

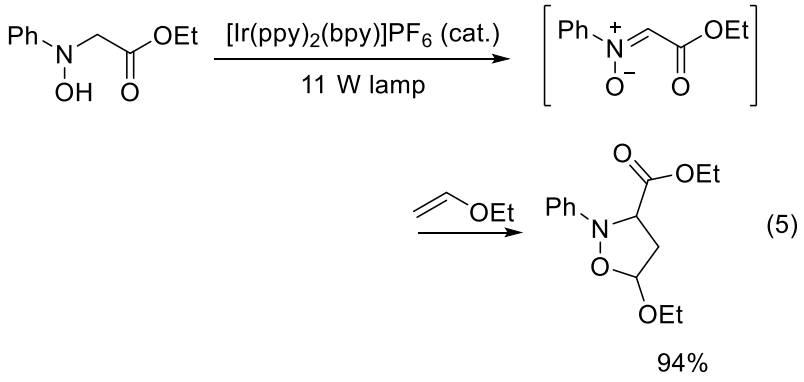
The catalytic oxidation can be also performed using oxidants such as hydrogen peroxide in the presence of methyltrioxorhenium ($MeReO_3$, MTO) catalyst. Complete conversion and high yields were obtained using poly(4-vinylpyridine)—MTO (PVP/MTO) and microencapsulated polystyrene—MTO (PS/MTO) catalysts.[35] The representative examples are summarized in Table 1.

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



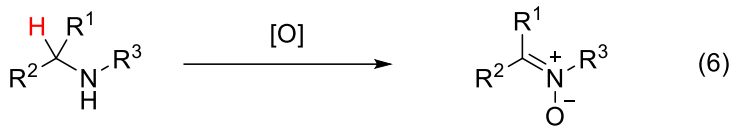
oxidant	catalyst	condn	yield (%)	ref.
air	Pd	H_2O, 80 °C	95	29
air	Au/SiO_2	MeOH, reflux	100	30
air	Rh/CNT	MeOH, rt	89	32
O_2	TPAP	DCM, rt	94	33
NMO	TPAP	MeCN, rt	100	34
H_2O_2	MTO, py	EtOH, rt	98	35
H_2O_2	PS/MTO	EtOH, rt	98	35

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]



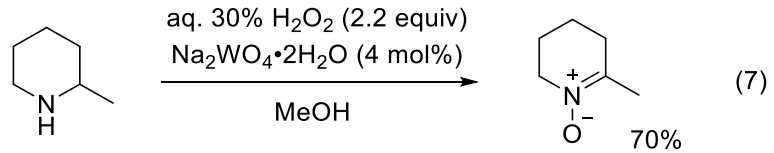
2.1.2. Oxidation of Secondary Amines

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 $Na_2WO_4•2H_2O$ (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.



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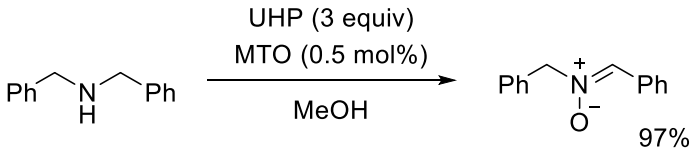

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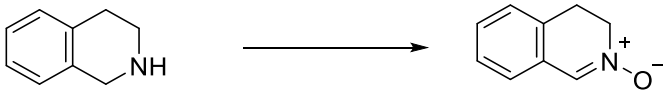
The oxidation reactions can be also carried out with heterogeneous catalysts such as TS-1 (Method I),[49] peroxotungstophsphate ($[C_5H_5N^+(CH_2)_{15}CH_3]_3\{PO_4[W(O)(O_2)_2]_4\}^{3-}$, PCWP) (Method J),[50] Mg–Al–O*t*-Bu hydrotalcite,[51] and $[MoO_3(bipy)][MoO_3(H_2O)]$.[52]

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-methyllumiflavinium perchlorate ($FlEt^+•ClO_4^-$) (Method L).[59-61]

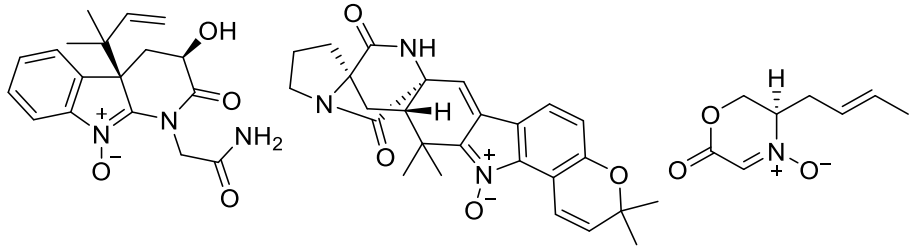
Table 2. Catalytic or Stoichiometric Oxidation of 1,2,3,4-Tetrahydroisoquinoline



method	catalyst	oxidant and conditions	yield (%)	ref

A	Na_2WO_4	aq. 30% H_2O_2, MeOH, 0 °C to rt	85	39
B	Na_2WO_4	UHP, MeOH, rt	80	41
C	SeO_2	aq. 30% H_2O_2, MeOH, 0 °C	89	42
D	MTO	UHP, MeOH, rt	82	43
E	MTO	50% H_2O_2, EtOH, rt	90	44
F	Ti(IV)	aq. 70% H_2O_2, CD_3OD, 60 °C	99	46
G	Pt(II)	aq. 35% H_2O_2, DCM, 50 °C	55	47
H	Ti(IV)	CHP, $CHCl_3$, 60 °C	65	48
I	TS-1	aq. 30% $_2O_2$, MeOH, 60 °C	85	49
J	PCWP	aq. 35% H_2O_2, $CHCl_3$, rt	90	50
K	—	Oxone®, MeCN—THF, 5 °C	79	53
L	$FlEt^+•ClO_4^-$	O_2, $NH_2NH_2•H_2O$, CF_3CH_2OH, 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 SeO_2 catalyst.[62]

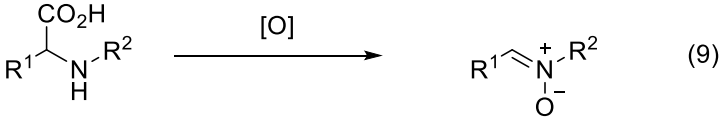


46% (UHP/Na_2WO_4 cat.)[63] | avrainvillamide, 27% (H_2O_2/SeO_2 cat.)[62] | 84% (*m*-CPBA)[57]

Figure 1. Key intermediates for sythsesis 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.



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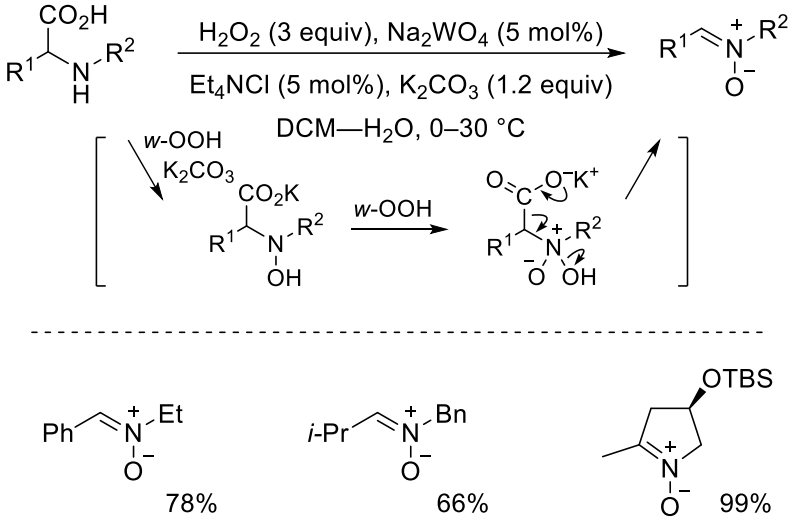
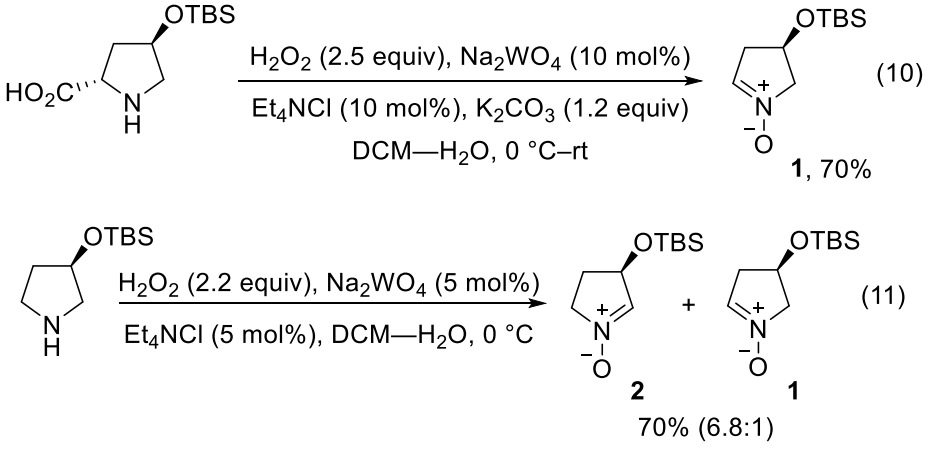
Oxidation of *N*-alkyl-α-amino acids with hydrogen peroxide does not proceed in the presence of Na_2WO_4 or SeO_2 catalyst alone; however, addition of an equivalent of base such as K_2CO_3 and phase transfer catalyst gives nitrones without formation of isomeric nitrones (Scheme 1).[64]

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

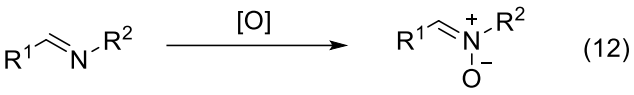


Catalytic oxidation of *trans*-4-(*tert*-butyldimethylsilyloxy)-L-proline under the present conditions gives enantiomerically pure (4*R*)-4-(*tert*-butyldimethylsilyloxy)-1-pyrroline *N*-oxide (**1**) exclusively (eq 10). In contrast, the catalytic oxidation of (3*R*)-3-(*tert*-butyldimethylsilyloxy)pyrrolidine 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]

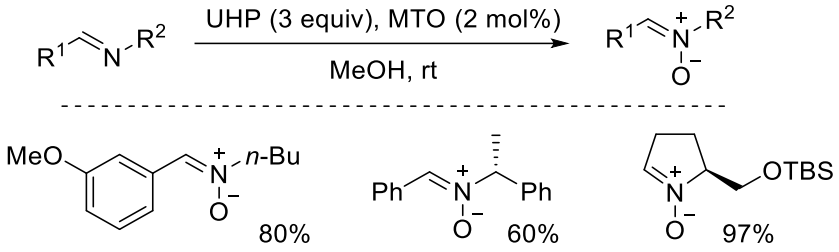


2.1.4. Oxidation of Imines

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]

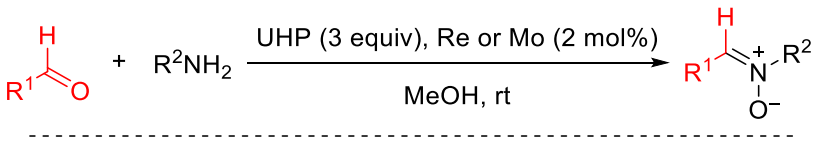


Scheme 2. Catalytic Oxidation of Imines



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 bezaldehyde derivatives are carried out (Scheme 3).

Scheme 3. Synthesis of Nitrones from Benzaldehydes and Primary Amines

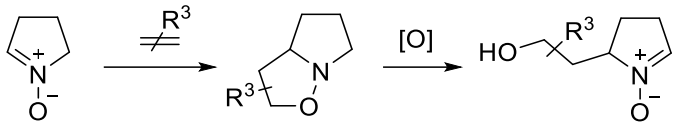


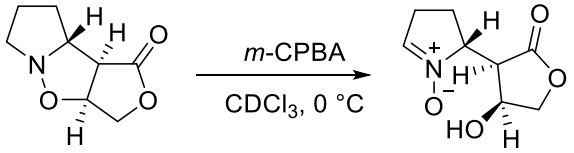
	MTO[69]	Nafion–$MoOCl_4$[70]	silica–$OReO_3$[71]
R^1 = Ph, R^2 = Bn	71%	80%	72%
R^1 = 4-MeO-C_6H_4, R^2 = *n*-Bu	82%	65%	75%
R^1 = 4-NO_2-C_6H_4, R^2 = Bn	67%	70%	74%

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

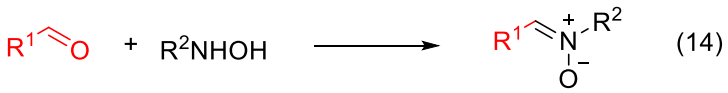




2.2. Reaction of *N*-Monosubstituted Hydroxylamines

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]

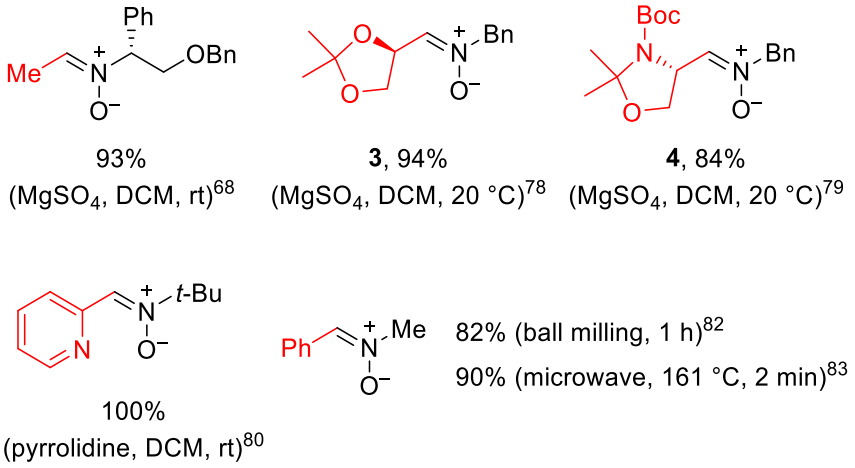
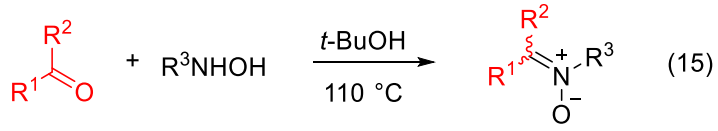
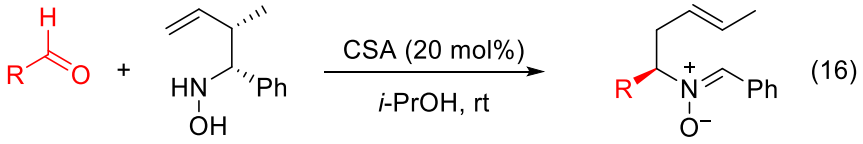


Figure 2. Synthesis of nitrones by condensation reaction

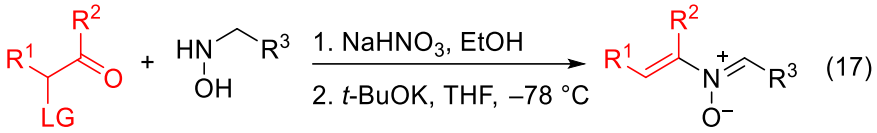
The reaction with cyclic, acyclic, and α,β-unsaturated ketones requires higher temperature (110 °C) (eq 15).[84] Homoallylic nitrones are prepared from homoallylic hydroxylamines and aldehydes upon treatment with (+)-10-camphorsulfonic acid (CSA) catalyst via the 2-oxonia-[3,3]-sigmatropic rearrangement regioselectively (eq 16).[85] *N*-Vinylnitrones have been prepared by a two-step method; the reactions of α-chloroaldehyde or α-phenoxy- or α-acetoxyketone with *N*-benzylhydroxylamines followed by treatment with a base (eq 17).[86] Oxazoline *N*-oxides (eq 18)[87] and imidazoline *N*-oxides[88] are obtained by condensations of heteroatom-substituted hydroxylamines with orthoesters.



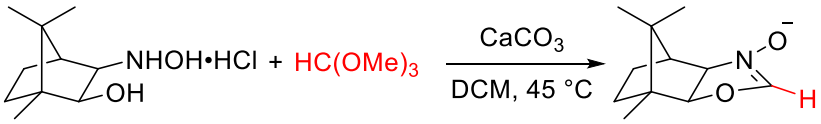
R^1 = *n*-C_6H_{13}, R^2 = Me, R^3 = Bn: 82%
R^1—R^2 = $(CH_2)_5$, R_3 = *c*-C_5H_9: 82%



R = $PhCH_2CH_2$: 80%, 99% ee
R = *c*-C_6H_{11}: 95%, 98% ee



R^1 = Me, R^2 = H, R^3 = 4-NO_2-C_6H_4, LG = Cl: 89%
R^1 = Ph, R^2 = Me, R^3 = Ph, LG = OAc: 49%



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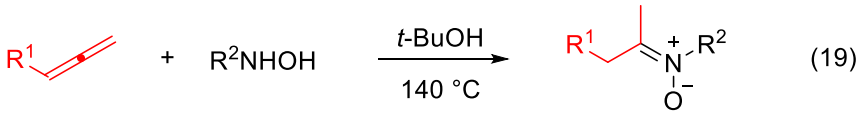
2.2.2. Reaction with Allenes, Acetylenes, and Alkenes

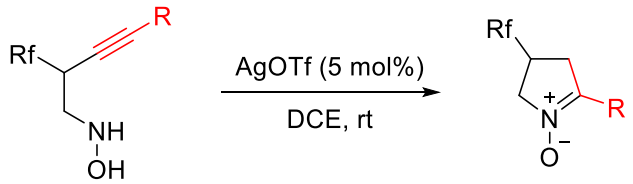
The synthesis of ketonitrones from monosubstituted allenes is performed via a Cope-type hydroamination reaction (eq 19).[89]



(19)

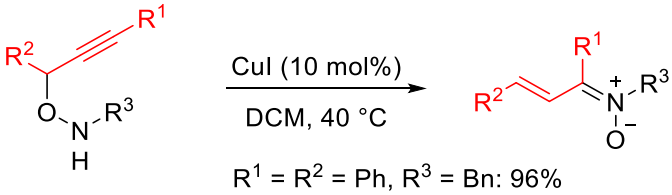
R^1 = *c*-C_6H_{11}, R^2 = Bn: 81%
R^1 = *n*-C_6H_{13}, R^2 = *c*-C_6H_{11}: 81%

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.



(20)

Rf = *n*-C_4F_9, R = Ph: 95%
Rf = CF_3, R = 4-NO_2-C_6H_4: 98%



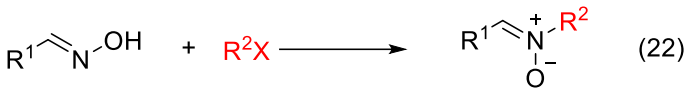
(21)

R^1 = R^2 = Ph, R^3 = Bn: 96%
R^1 = 4-CF_3-C_6H_4, R^2 = Ph, R^3 = Bn: 91%

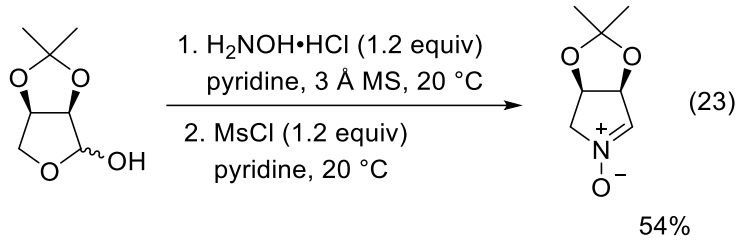
Isoindole nitrones and 3,4-dihydroisoquinoline nitrones are prepared from aryl aldehydes containing ortho-substituted α,β-unsaturated carboxylic acid derivatives and hydroxylamine.[92]

2.3. Reaction of Oximes

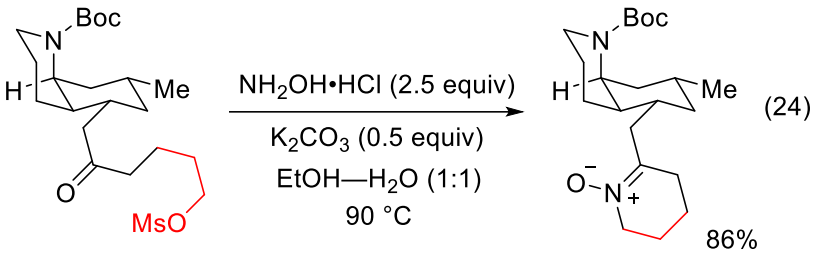
Reaction of oximes with a variety of electrophiles gives nitrones in principle (eq 22).



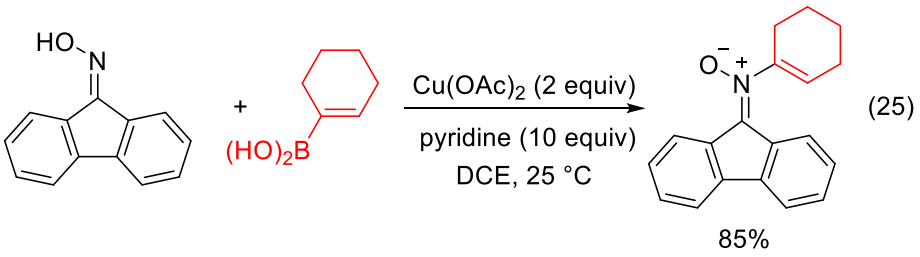
Chiral polyhydroxylated nitrones can be prepared by the intramolecular desilylative cyclizations of carbohydrate-derived ω-iodo-[93] or ω-tosyl-*O*-silyloximes.[94] The procedure was further extended to one-pot processes with in situ formation of silylated[95] or even free oximes (eq 23).[96]



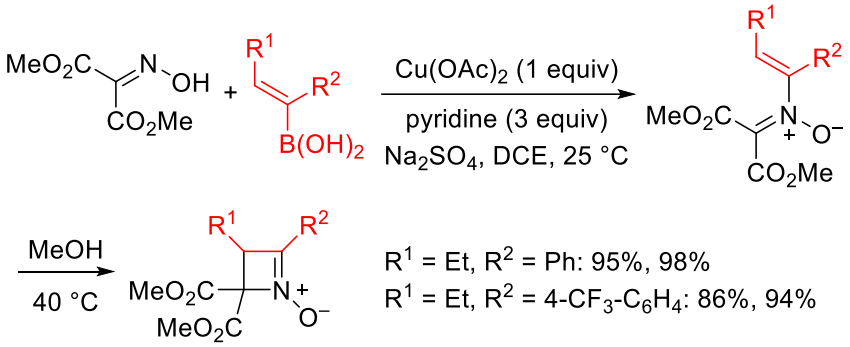
Intramolecular alkylation of oximes has been used for synthesis of natural product of lycoposerramine-Z (eq 24).[97]



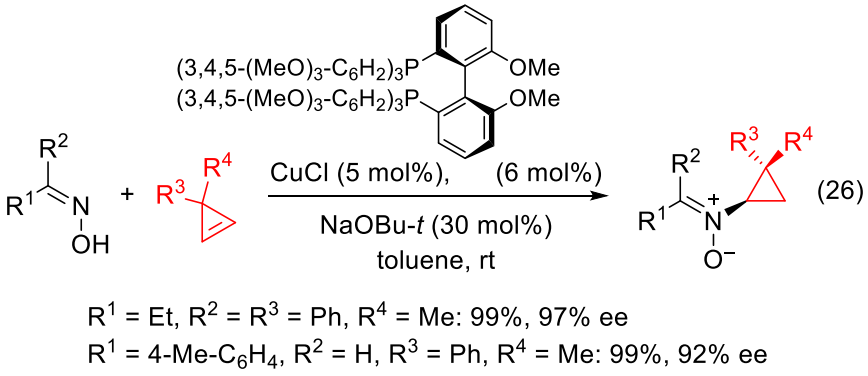
Anderson and coworkers demonstrated that $Cu(OAc)_2$-mediated reaction of oximes with alkenylboronic acids gives various types of nitrones. *N*-Vinylnitrones have been prepared from fluorenone oxime by the $Cu(OAc)_2$-mediated reactions with alkenylboronic acids (eq 25).[98,99] Similarly, $Cu(OAc)_2$-promoted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



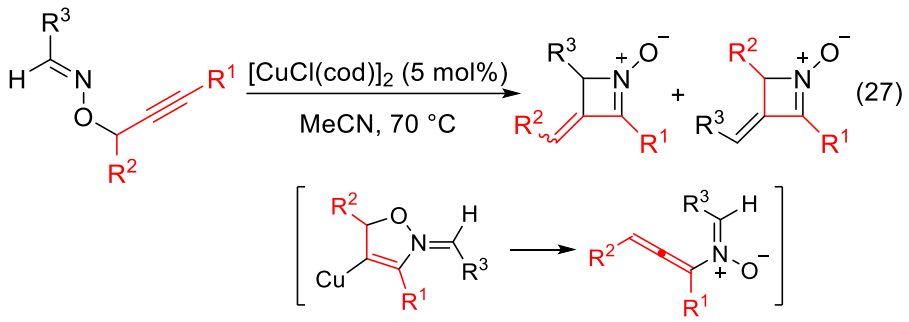
Scheme 5. Preparation of *N*-Alkenylnitrones and Azetidine Nitrones



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

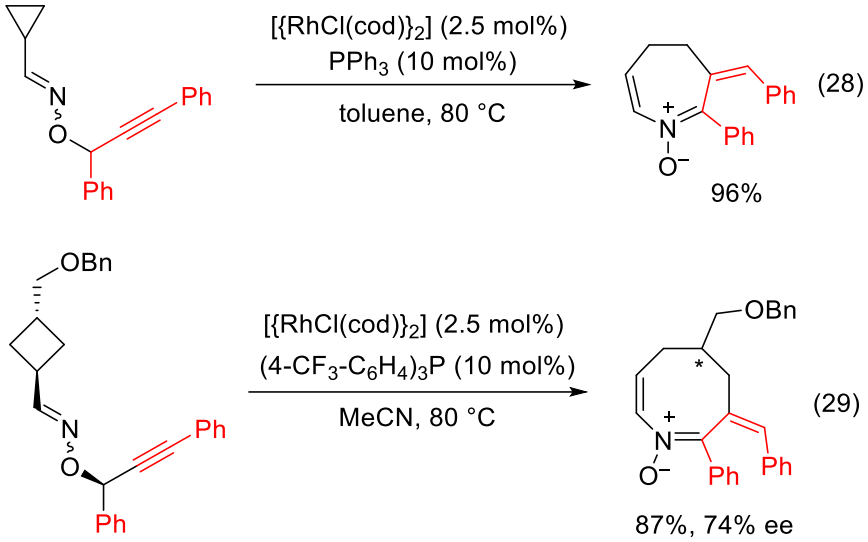


Copper-catalyzed reaction of (*E*)-*O*-propargylic arylaldoximes gives four-membered cyclic nitrones. The reaction involves tandem [2,3]-rearrangement and 4π electrocyclization of the *N*-allenylnitrones followed by cleavage of the C—N bond (eq 27).[102,103]

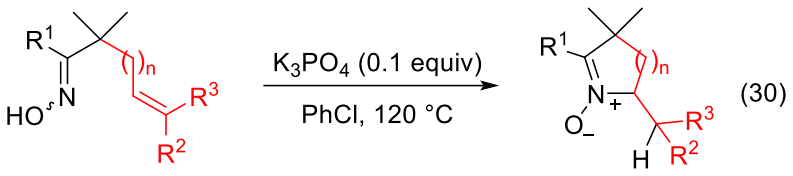


R^1 = 4-MeO-C_6H_4, R^2 = *n*-Pr, R^3 = 4-CF_3-C_6H_4: 77% (98:2, *E*/*Z* = 73:27)
R^1 = 4-MeO-C_6H_4, R^2 = Ph, R^3 = 2-naphthyl: 88% (97:3, *E*/*Z* = 74:26)

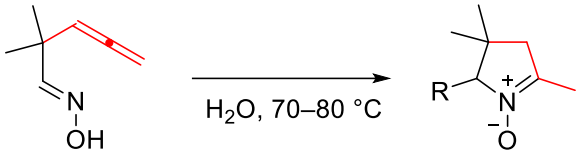
Nakamura and Terada found that rhodium-catalyzed reaction of *O*-propargylic cyclopropylcarbaldoxime gives seven-membered aza-heterocycles under mild conditions (eq 28).[104] Similarly, eight-membered cyclic nitrones can be obtained from *O*-propargylic oximes by rhodium-catalyzed [2,3]-rearrangement/heterocyclization 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-menbered 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-MeO-C_6H_4, R^2 = Ph, R^3 = H, n = 1: 96%
R^1 = R^2 = Ph, R^3 = H, n = 2: 65% (1 equiv of K_3PO_4 at 150 °C)

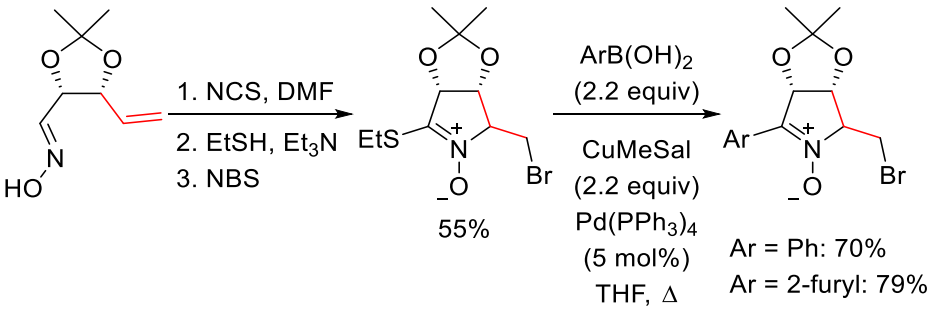


KOH R = OH: 70%
NH_3 R = NH_2: 73%

R^1 = *n*-C_7H_{15}, R^2 = Me: 92%
R^1 = *c*-C_6H_{11}, R_2 = Ph: 73%

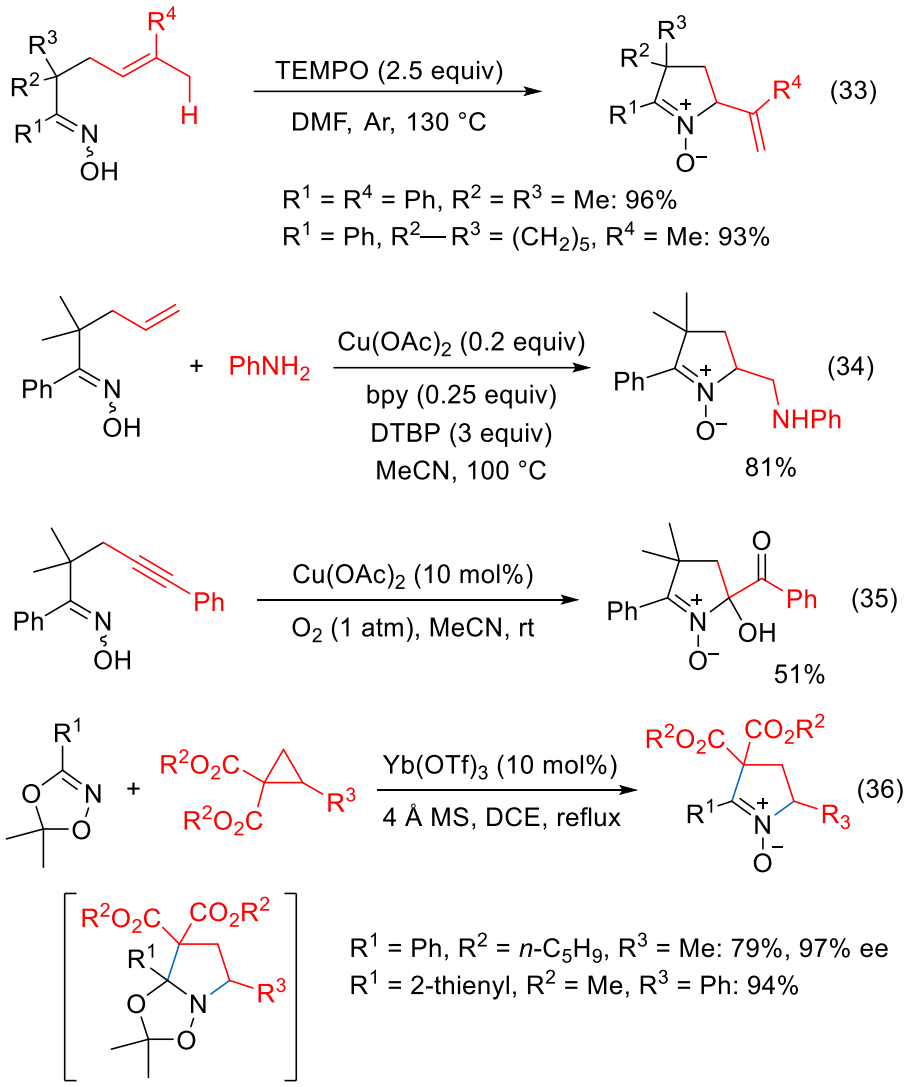
Chiral five-membered cyclic nitrones are prepared from D-ribose. α-Ethylthiooxime undergoes halocyclization upon treatment with NBS to give cyclic nitrone, of which ethylthio group can be converted into aryl substituents (Scheme 6).[109]

Scheme 6. Preparation of *C*-Aryl Chiral Cyclic Nitrones

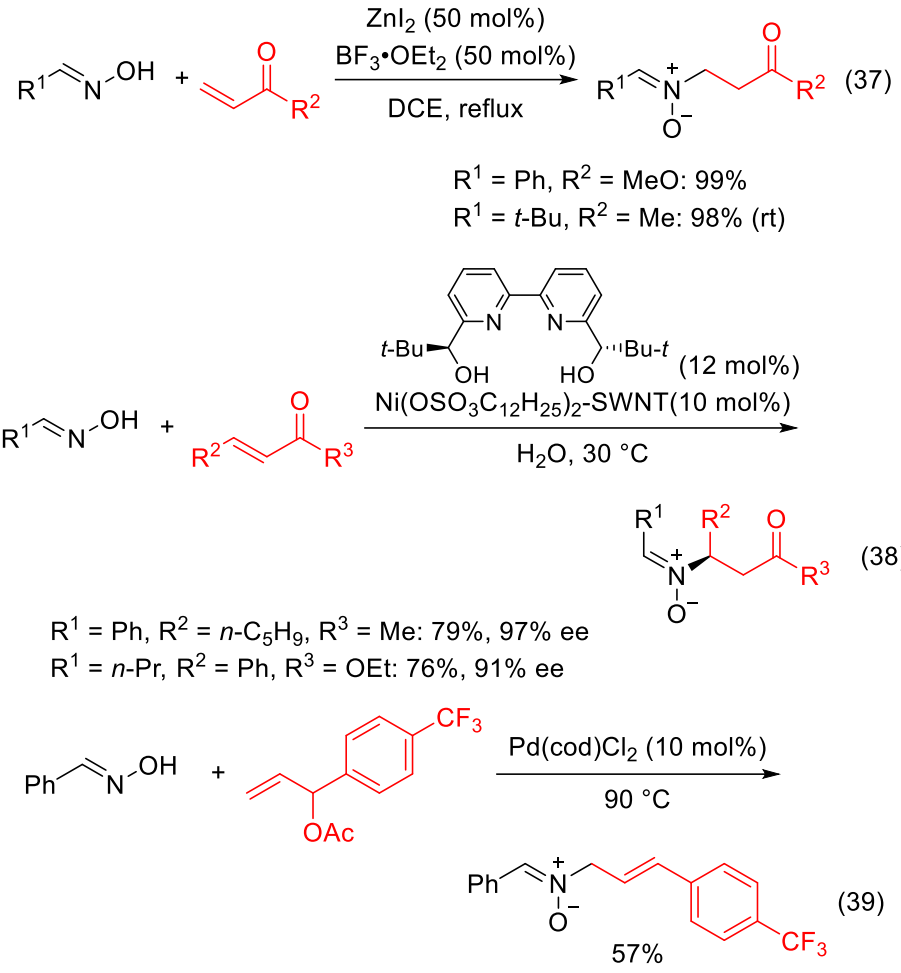


TEMPO-promoted reaction of γ,δ-unsaturated ketoximes gives cyclic nitrones (eq 33). This reaction involves β-hydrogen abstraction and Cope-like elimination.[110] Copper-catalyzed oxidative cyclization of γ,δ-unsaturated ketoximes in the presence of aryl amines and di-*tert*-butyl peroxide (DTBP) gives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



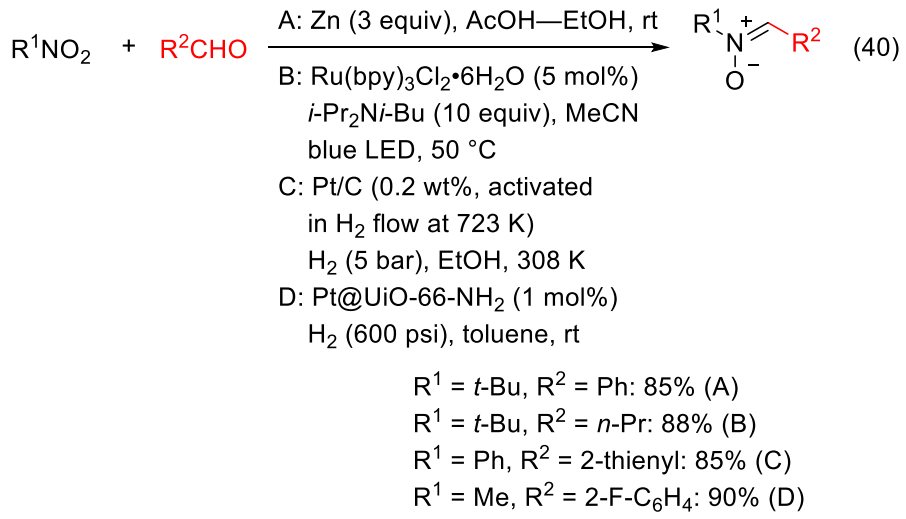
Conjugate addition of oximes to electron deficient alkenes takes place with Lewis acids (eq 37).[114] Kobayashi and coworkers discovered very interesting catalytic system that is a homogenized combination of nickel-based Lewis acid–surfactant-combined catalysts and single-walled carbon nanotubes (SWNT). 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]



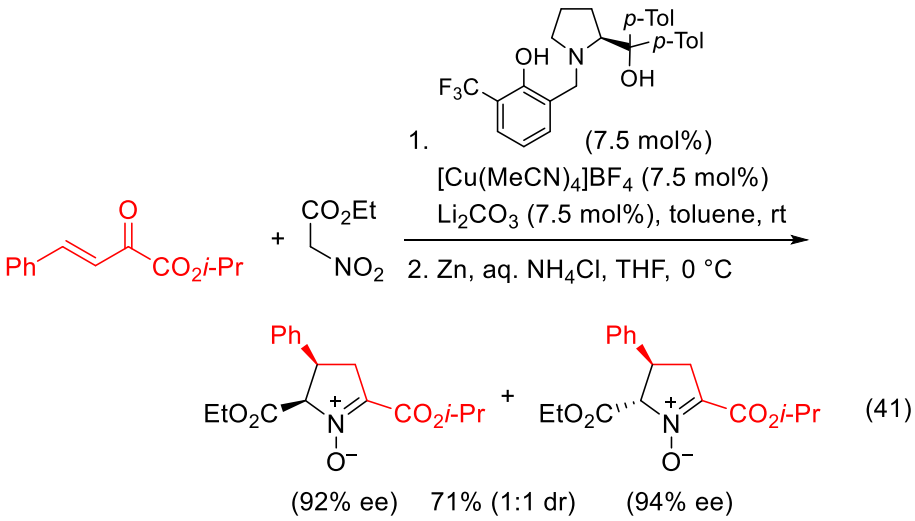
2.4. Other Methods

2.4.1. From Nitro Compounds

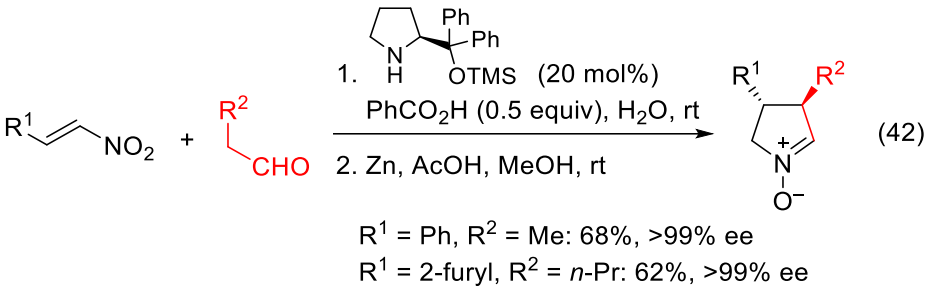
The reaction of nitro compounds with aldehydes under reductive conditions gives nitrones. This method is largely precedented in its intramolecular version for synthesis of cyclic nitrones. The zinc-mediated reduction of nitro compounds in the presence of aldehydes is useful for preparation of aromatic, aliphatic, and highly functionalized sugar-derived nitrones (A, eq 40).[117] The reaction with a mixture of a $Ru(bpy)_3Cl_2$ photoredox catalyst and *i*-Pr_2NEt gives the corresponding nitrones (B, eq 40).[118] Furthermore, similar reaction gives nitrones in the presence of H_2 with carbon-decorated platinum nanoparticles (C, eq 40)[119] or ultrasmall platinum nanoclusters encapsulated in amine-functionalized Zr-metal-organic framework, Pt@UiO-66-NH_2 (D, eq 40).[120]

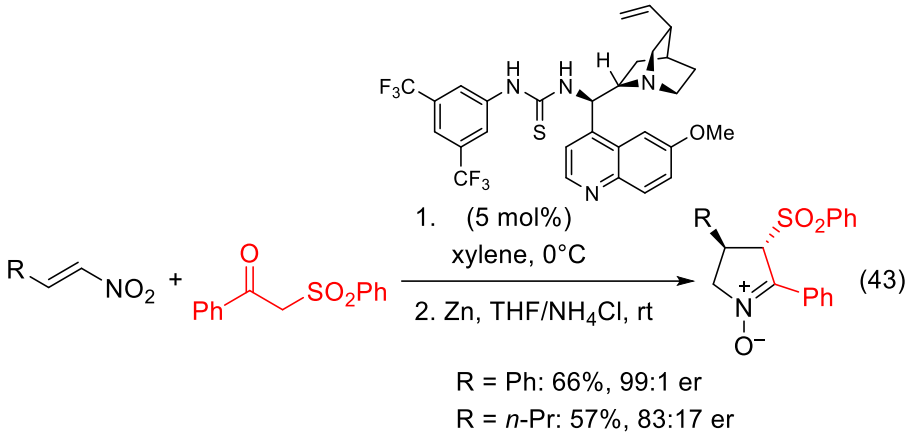


Michael addition of nitro compounds to α,β-unsaturated carbonyl compounds and subsequent reductive cyclization provide a useful procedure for preparation of five-membered cyclic nitrones.[121] Copper-catalyzed Michael addition of nitro esters to β,γ-unsaturated α-ketoesters in the presence of zinc gives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

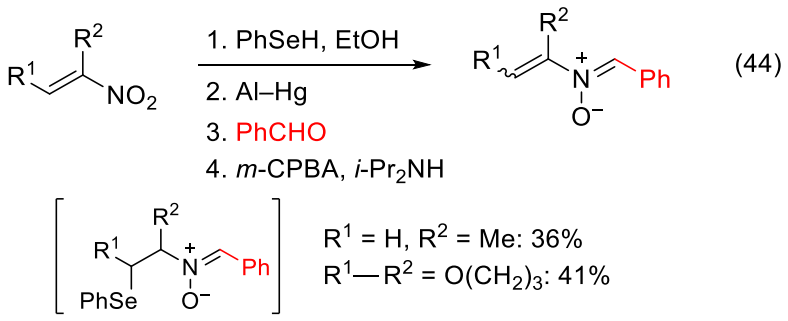


The organocatalytic Michael addition of aldehydes to nitroolefins and in situ reductive cyclization is very convenient method for synthesis of chiral five-membered cyclic nitrones (eq 42).[123] Similarly organocatalytic addititon of β-ketosulfones to nitroolefins followed by reductive cyclization gives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

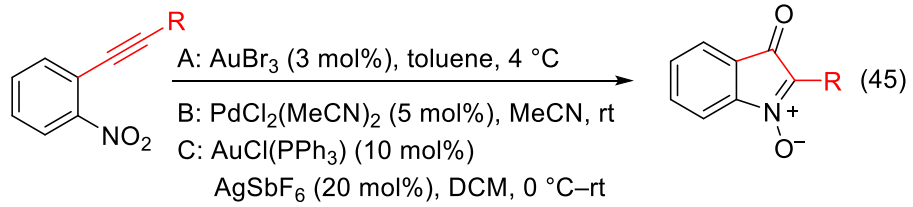




A general method for synthesis of *N*-vinylnitrones has been found. Conjugate addition of benzeneselenol to nitroalkenes followed by reduction gives hydroxylamines, which undergo reaction with aldehydes and subsequent oxidation to provide *N*-vinylnitrones via *syn*-selenoxide elimination (eq 44).[125]



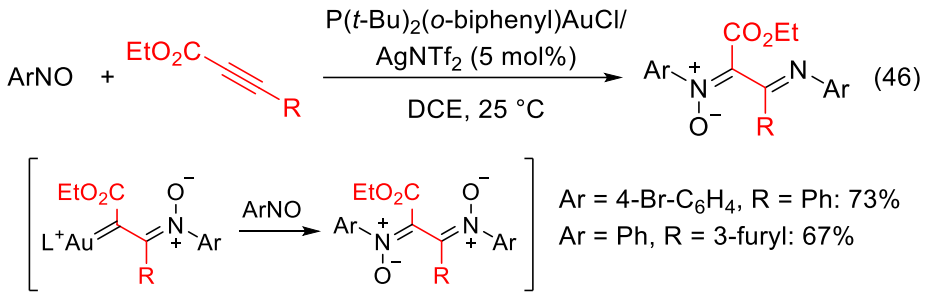
The $AuBr_3$-catalyzed cyclization of *o*-(alkynyl)nitrobenzenes gives the corresponding isatogens under mild conditions.[126] This cyclization to isatogens can be also carried out upon treatment with either $PdCl_2(MeCN)_2$[127] or $AuCl(PPh_3)_3$–$AgSbF_6$[128] catalyst (eq 45).



R = Ph: 81% (A), 61% (B)
R = 2-pyridyl: 86% (A at 50 °C), 55% (B)
R = $CH_2NBnBoc$: 68% (C)

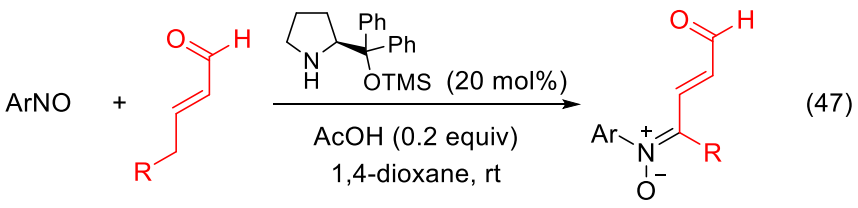
2.4.2. From Nitroso Compounds

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

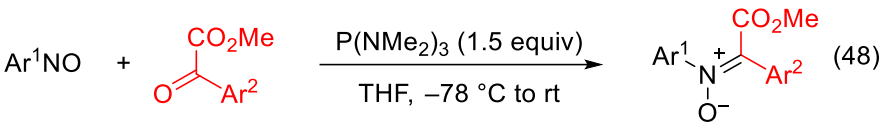


Ar = 4-Br-C_6H_4, R = Ph: 73%
Ar = Ph, R = 3-furyl: 67%

Furthermore, nitrone 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]



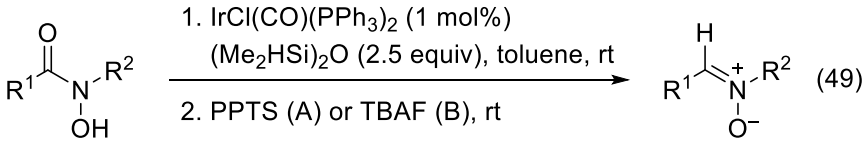
Ar = Ph, R = Et: 53%, 10:1 dr
Ar = 4-NO_2-C_6H_4, R = Et: 45%, 7:1 dr



Ar^1 = Ph, Ar^2 = 4-Cl-C_6H_4: 76%
Ar^1 = 4-NO_2-C_6H_4, Ar^2 = Ph: 74%

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 $IrCl(CO)(PPh_3)_2$ and $(Me_2HSi)_2O$ 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]



R^1 = *n*-C_7H_{15}, R^2 = Bn: 96% (A)
R^1 = THPO$(CH_2)_7$, R^2 = Bn: 86% (B)

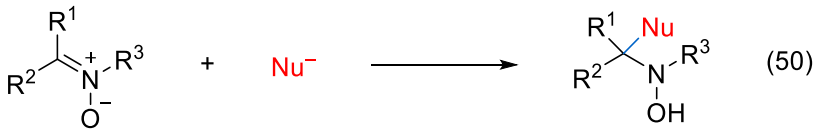
2.4.4. From Aryloxaziridines

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

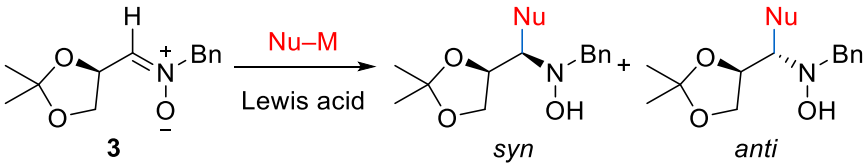
3.1.1.1. Alkylation and Arylation

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.

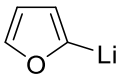
Diastereoselective reactions of nitrones with organometallic compounds are highly useful, and many key compounds have been prepared. In 2000 Merino and Tejero[5] and Trombini and coworkers[6] described excellent reviews on this subject. In 2007 Brandi and Goti described highly valuable review account on asymmetric synthesis using cyclic nitrones.[10]

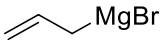
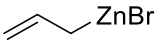
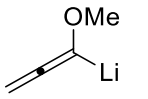
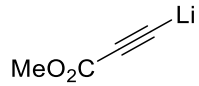
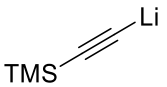
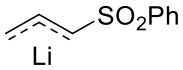
Chiral nitrones are useful for synthesis of nitrogen compounds. Merino and Tejero[5] demonstrated general routes using α-alkoxy nitrones. This is extremely important, because diastereofacial induction of nucleophiles to chiral nitrones can be controlled effectively. D-Glycaraldehyde-derived nitrone, *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—Et_2O at –80 °C gives the *syn* product (*syn*/*anti* = 96:4) in 92% yield. In contrast, the same reaction in the presence of Et_2AlCl gives the *anti* product (*syn*/*anti*= 5:95) in 89% yield.[135]

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



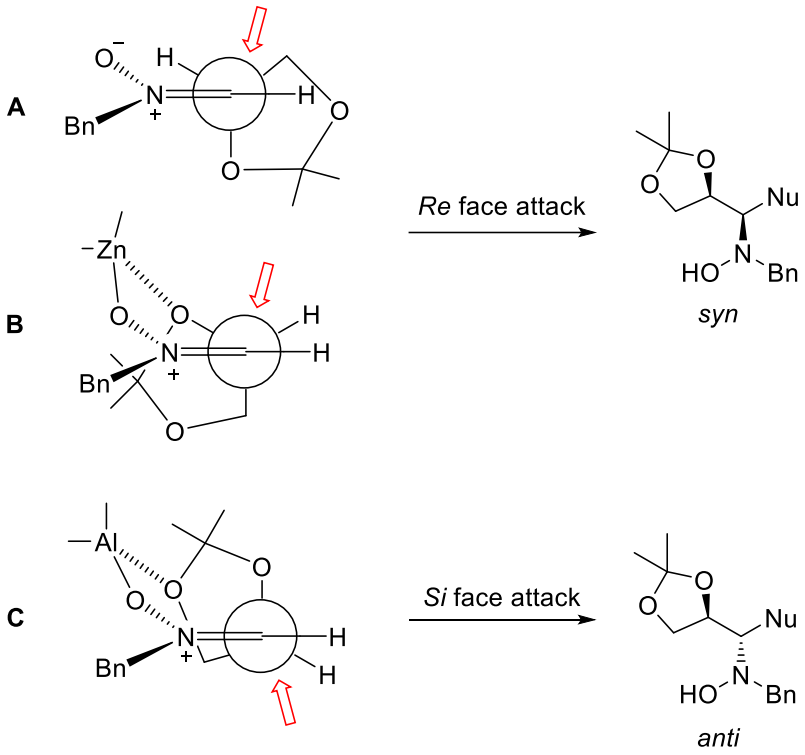
3 *syn* *anti*

Nu–M	Lewis acid	condn	*syn*/*anti*	yield (%)	ref.
PhMgBr	—	THF, –60 °C	80:20	84	136
	$ZnBr_2$	Et_2O, –60 °C	90:10	86	
	Et_2AlCl	Et_2O, –60 °C	5:95	72	
	—	THF—Et_2O, –80 °C	96:4	92	135
	Et_2AlCl	THF—Et_2O, –80 °C	5:95	89	
	$ZnBr_2$	Et_2O, –50 °C	>95:5	100	137

	$BF_3•Et_2O$	THF, –50 °C	5:95	90	
	—	THF, 0 °C	76:24	86	138
	Et_2AlCl	Et_2O, 0 °C	8:92	86	
	—	THF, 0 °C	25:75	92	139
	Et_2AlCl	THF, –40 °C	65:35	80	
	—	THF, –78 °C	98:2	81	140
	Et_2AlCl	Et_2O, –78 °C	3:97	61	
	—	THF, –80 °C	>95:5	100	141
	Et_2AlCl	Et_2O, –80 °C	30:70	92	
	—	THF, –80 °C	>95:5	100	142
	Et_2AlCl	THF, –80 °C	29:71	96	
	HMPA	THF, –80 °C	98:2	—	143

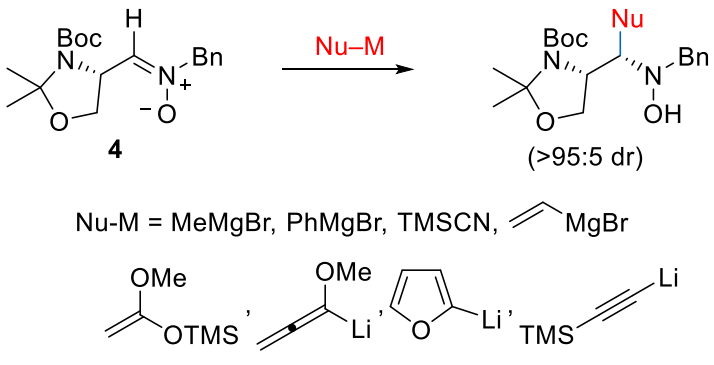
The stereochemical outcome of the reaction of nitrone **3** with PhMgBr is rationalized by assuming Scheme 7. The stereoselection is controlled by diastereoface differentiation of the nitrones. Nucleophilic attack from the less hindered Re face of nitrone in A gives syn hydroxylamines. The precomplexation of nitrones with $ZnBr_2$ at α-oxygen atom in B leads to the same syn hydroxylamines. In contrast the precomplexation of the nitrones with Et_2AlCl at β-oxygen atom leads to a total reversal of the diastereofacial selectivity in C.[136]

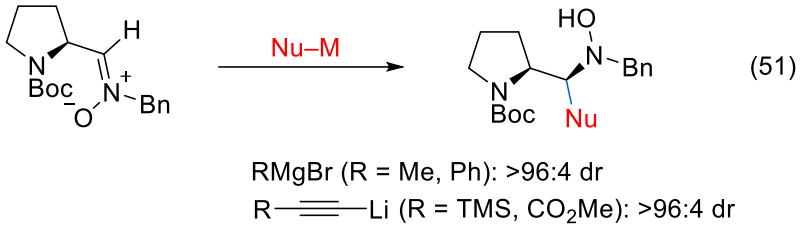
Scheme 7. Reversal Diastereoselectivity in Chiral Nitrone.



The stereocontrol of nucleophilic additions to α-aminonitrones does not depend on any Lewis acids, and the reaction to nitrone gives *syn* adducts both in the presence and absence of Lewis acids. The reaction of *N*-benzyl α-aminonitrone **4** derived from L-serine[144] with a variety of nucleophiles gives the corresponding *syn* hydroxylamines as the only detectable diastereoisomers (Scheme 8).[5] Similarly, L-proline-derived nitrone 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.

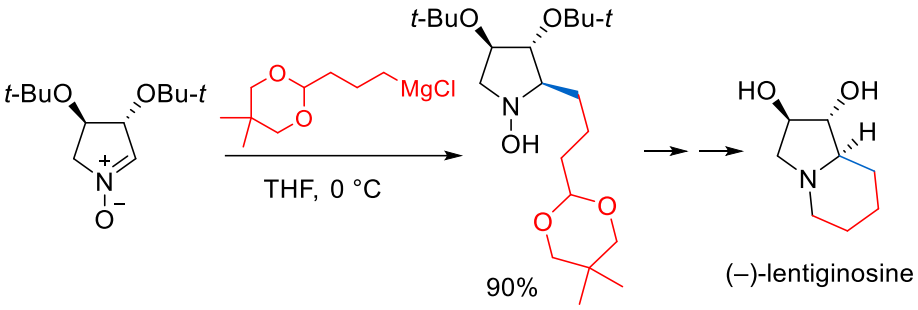
Scheme 8. Diastereoselective Reaction of Chiral α-Aminonitrone with Various Nucleophiles



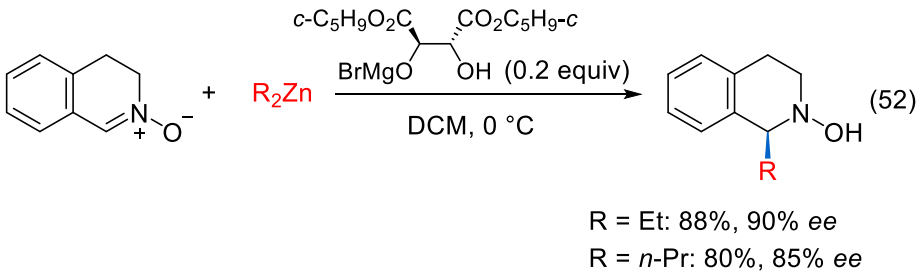


Diastereoselective additions of organometals to 3-alkoxy-substituted cyclic nitrones have been utilized for natural product synthesis.[146,147] (–)-Lentiginosine was synthesized from the nitrone derived from D-tartaric acid (Scheme 9).[148]

Scheme 9. Total Synthesis of (–)-Lentiginosine



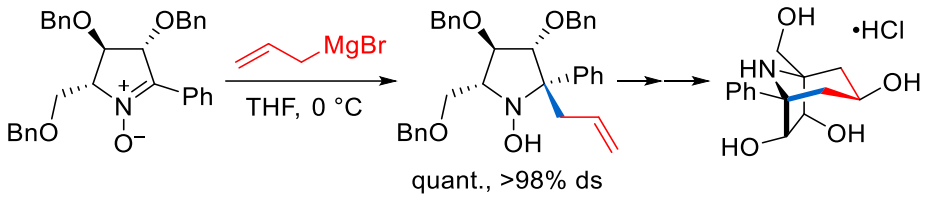
Ukaji and Inomata showed that catalytic asymmetric addition of alkylzinc to 3,4-dihydroisoquinoline *N*-oxides in the presence of magnesium salt of tartaric acid derivatives gives (*S*)-1-alkyl-2-hydroxy-1,2,3,4-tetrahydroisoquinolines with up to 95% ee (eq 52).[149,150]



3.1.1.2. Allylation

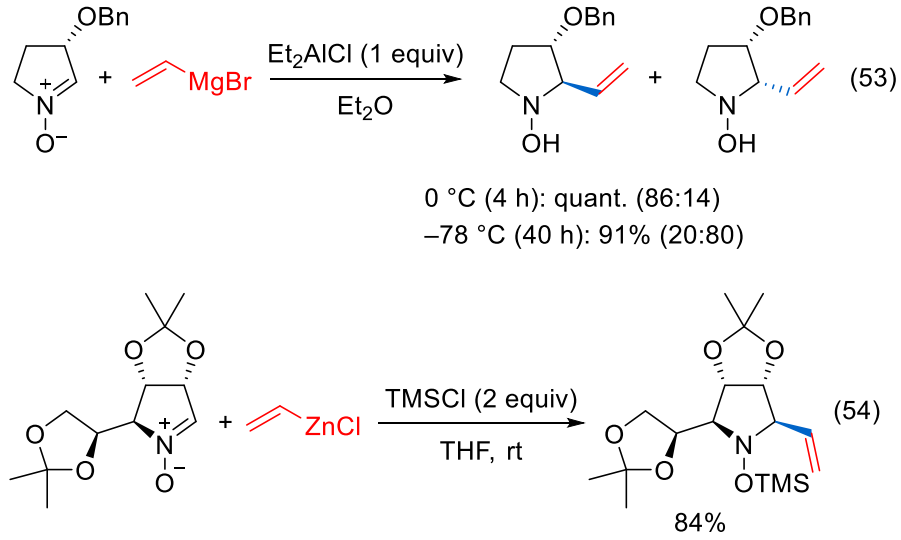
Diastereoselective addition of allylmagnesium bromide is highly useful for the synthesis of polyhydroxynortropane alkaloids (Scheme 10).[151]

Scheme 10. Sequential Nucleophilic Addition/Cycloaddition



3.1.1.3. Vinylation

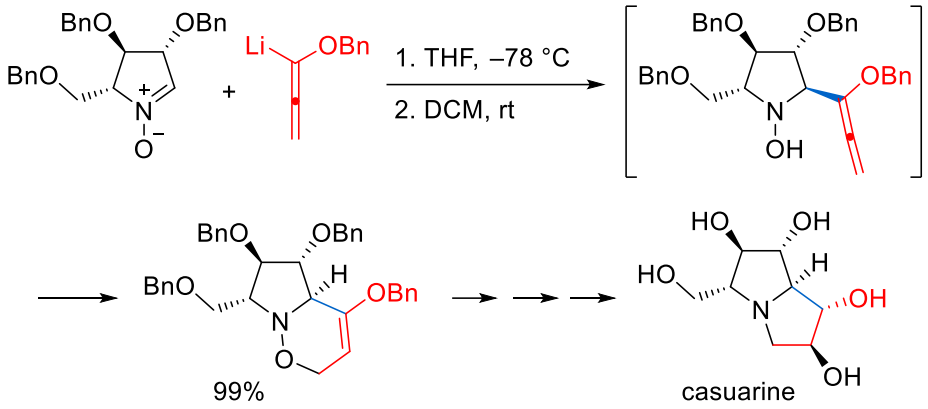
Vinylation is carried out upon treatment with vinylmagnesium bromide. Noteworthy is that a strong dependence on the temperature and the substituent adjacent at the reaction center was observed for the reaction of 3-alkoxy substituted cyclic nitrones in the presence of Et_2AlCl (eq 53).[152] Addition 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

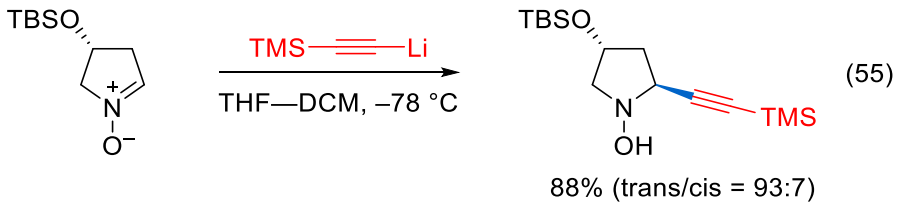
Reissig and coworkers reported that the reaction of lithiated 1-methoxylallene to D-glyceraldehyde-derived chiral nitrone **3** in the presence of Et_2AlCl gives the corresponding *anti* product (*anti*/*syn* = 97:3) in 61% yield (Table 3).[140] Goti and Reissig reported the diastereoselective addition of D-arabinose-derived nitrone 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 B_4 using lithiated 3-methylsubstituted benzyloxyallene.[155]

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

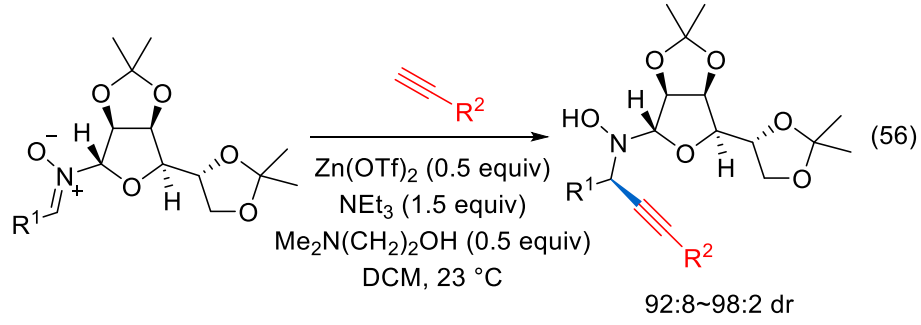


3.1.1.5. Ethynylation

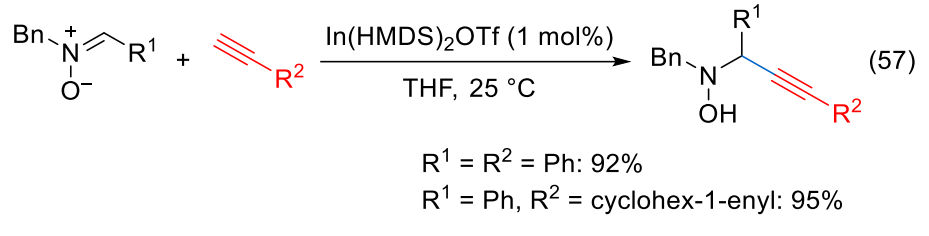
Merino and coworkers reported that the reaction of chiral nitrone **3** with ethynyllithium gives *syn* products, while the reaction in the presence of Et_2AlCl gives *anti*-isomers (Table 3).[141,142] Ohtake and Murahashi demonstrated diastereoselective ethynylation of cyclic nitrone upon treatment with lithium acetylide to give trans adduct with high preference (eq 55).[65]

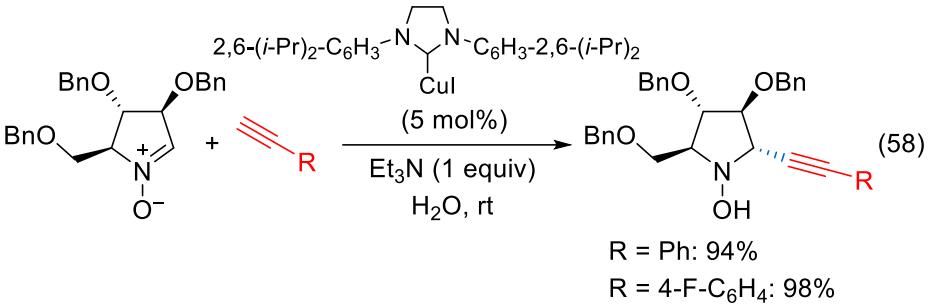


Carreira and coworkers explored the first catalytic method for the preparation of propargylic *N*-hydroxylamines.[156] Addition of terminal alkynes to chiral nitrones, prepared from mannose-derived glycoside *N*-hydroxylamine, in the presence of $Zn(OTf)_2$, 2-(dimethylamino)ethanol, and NEt_3 gives adducts in high diastereoselectivities and yields (eq 56).[157] Deprotection with aqueous acid yields *N*-hydroxy propargylamines.[158]



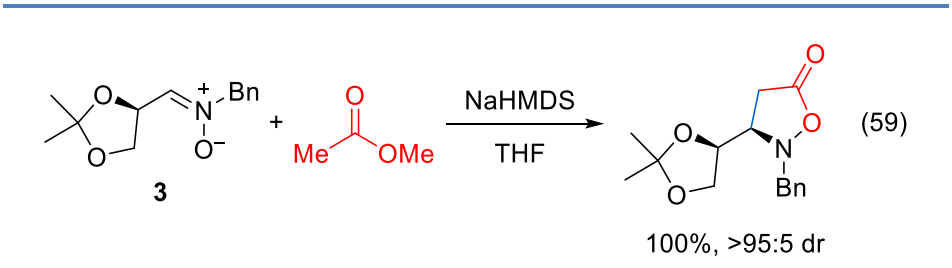
Reaction of nitrones with terminal alkynes takes place in the presence of Et_2Zn in toluene in excellent yields.[159] Kobayashi and coworkers demonstrated that zinc bis[bis(trimethylsilyl)amide] ($Zn(HMDS)_2$) is an efficient Lewis acid/Brønsted base cooperative catalyst for these reactions.[160] It was also reported that the combination of $InBr_3$ and *i*-Pr_2NEt is an alternative catalytic system for ethynylation.[161] $In(HMDS)_2OTf$ 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]





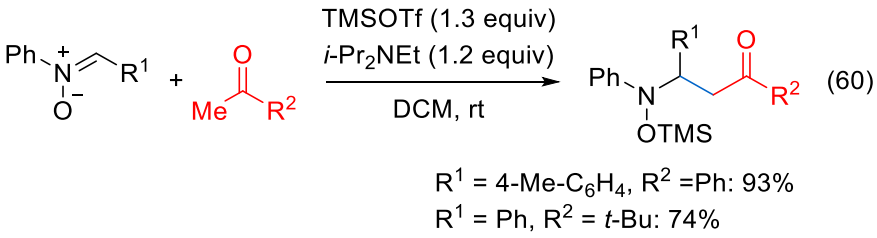
3.1.2. Reaction with Carbonyl Compounds and Related Compounds

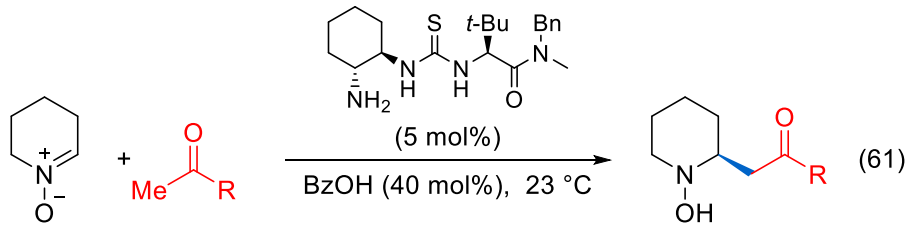
Mannich-type reaction of nitrones with metal enolates of esters and amides has been reviewed by Merino and Tejero.[13] The first example of stereocontrolled nucleophilic addition of sodium enolate, prepared from methyl acetate and NaHMDS, has been reported to give D-glyceraldehyde-derived nitrone **3** 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,

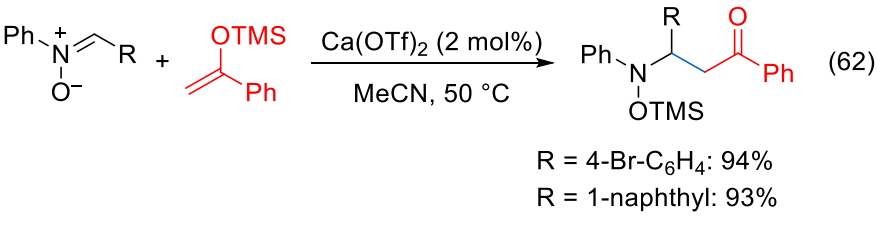
asymmetric Mannich-type reaction of cyclic nitrones with methyl ketones gives β-*N*-hydroxylaminoketones with high enantioselectivities using chiral thiourea catalyst (eq 61).[166] The reaction of nitrones with enolizable 1,3-dicarbonyls affords highly functionalized β-enamino diones by initial self-catalyzed 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]





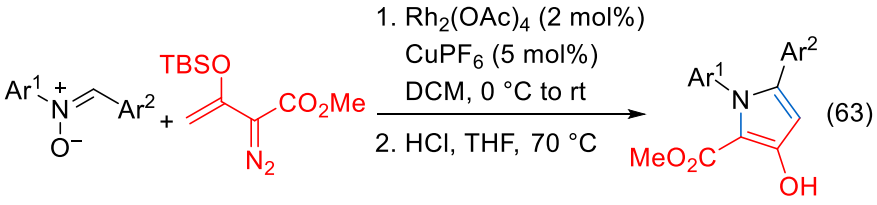
3.1.2.1.Reaction with Enolates

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]



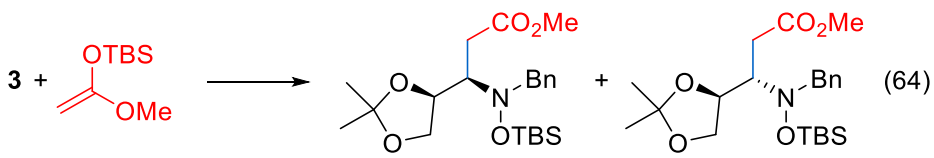
Doyle and coworkers reported that the copper-catalyzed reaction of nitrones with a TBSO-substituted vinyldiazoacetate gives *N*-aryl-2-carboxyl-3-hydroxy-5-arylpyrroles. The reaction involves the Mannich addition, dirhodium-catalyzed dinitrogen extrusion, insertion into N—

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



3.1.2.2. Reaction with Silyl Ketene Acetals

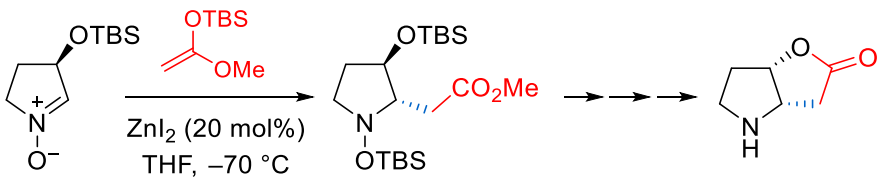
The ZnI_2-promoted reaction of nitrones with silyl ketene acetal gives adducts (A, eq 64).[171] Merino and Tejero demonstrated that high stereocontrol of the reaction for syn or anti isomer can be accomplished by using appropriate Lewis acids (B and C, eq 64).[172]



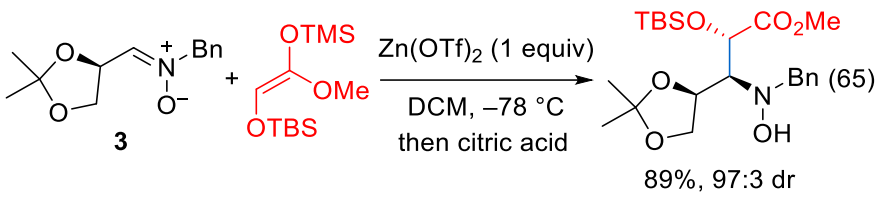
A: ZnI_2 (10 mol%), MeCN—DCM, –78 °C: 100%, 89:11 dr
B: TBSOTf (1 equiv), THF, –80 °C: 94% 70:30 dr
C: BF_3•OEt_2 (1 equiv), DCM, –80 °C: 91%, 7:93 dr

The ZnI_2-catalyzed reaction of chiral nitorone **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

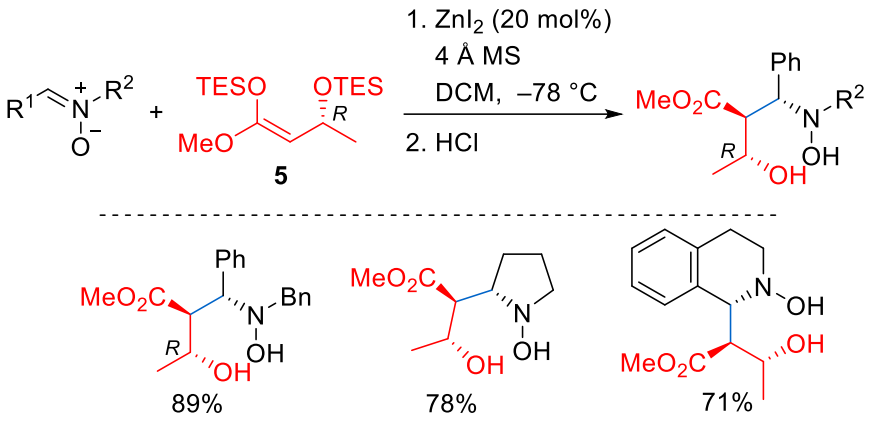


Reaction of substituted silyl ketene acetal with nitrone **3** in the presence of $Zn(OTf)_2$ affords the key intermediate for synthesis of D- and L-*erythro*-sphingosine (eq 65).[173]



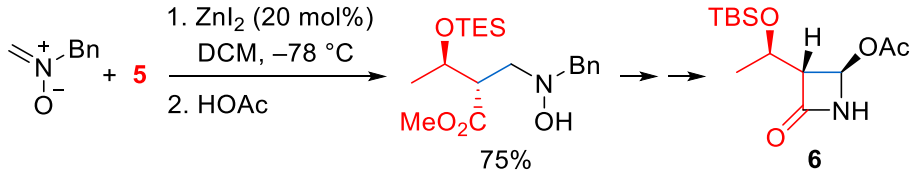
Murahashi and coworkers have developed a convenient method for synthesis of chiral β-amino acids by ZnI_2-catalyzed reaction with (*Z*)-(*R*)-1,3-bis(triethylsilyloxy)-1-methyl-1-butane (**5**) readily derived from methyl (*R*)-3-hydroxybutanone.[174] Tipically, the reaction of acyclic (*Z*)-nitrones 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 oxidation[175] gives the key intermediate **6** (Scheme 14).[174]

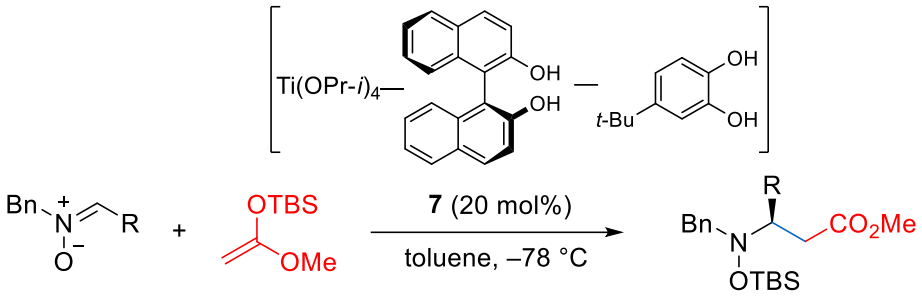
Scheme 14. Synthesis of Azetidinone Derivatives



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 Ti(O*i*-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 Zn/H_2SO_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



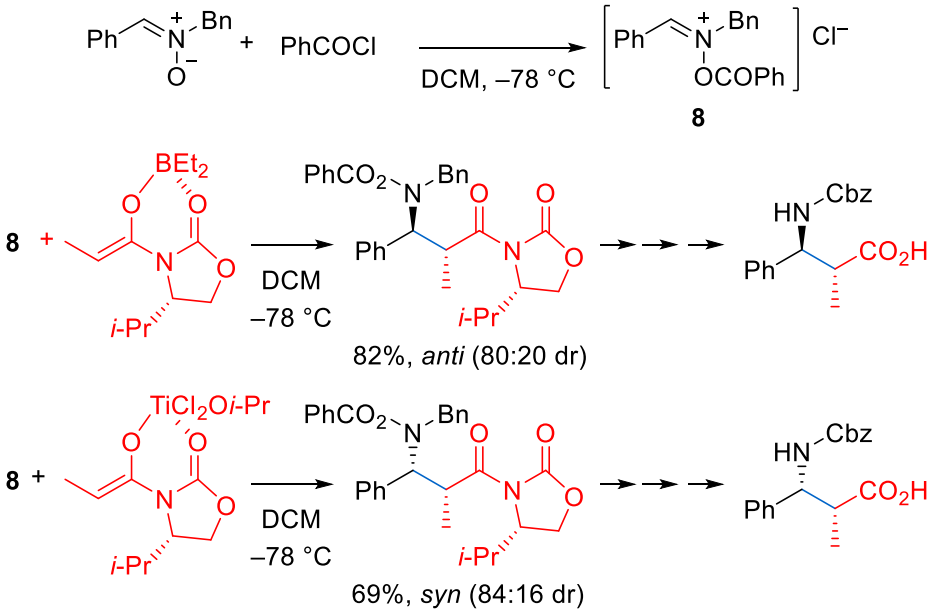
R = Ph: 99%, 92% ee (*S*)
R = 2-naphthyl: 94%, 88% ee (–)
R = 3-pyridyl: 90%, 80% ee (+)

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 °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]

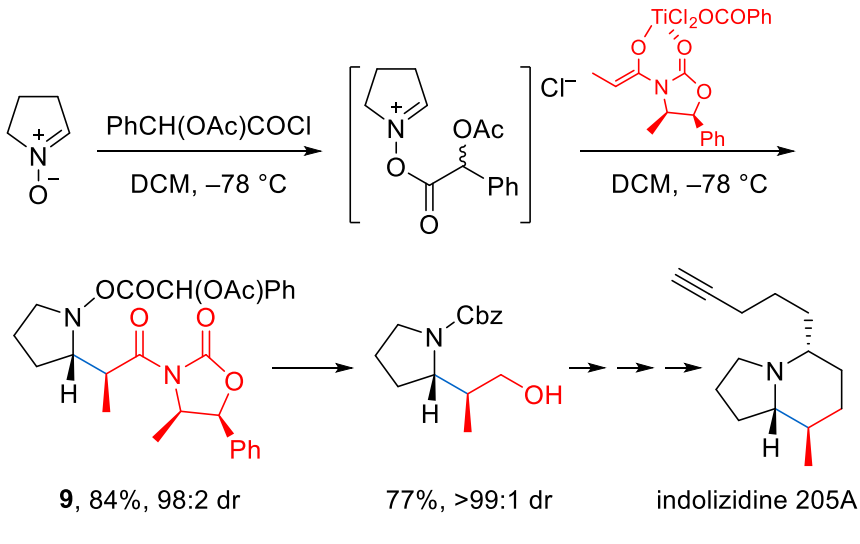
The reaction of *N*-acyloxyiminium species **8** with chiral boron enolate and chiral titanium enolate gives *anti*- and *syn*-isomers, respectively. Interestingly, the chelating effect of the boron enolate and the titanium enolate are opposite, and reversal diastereoselectivity was observed. Thus, four 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]

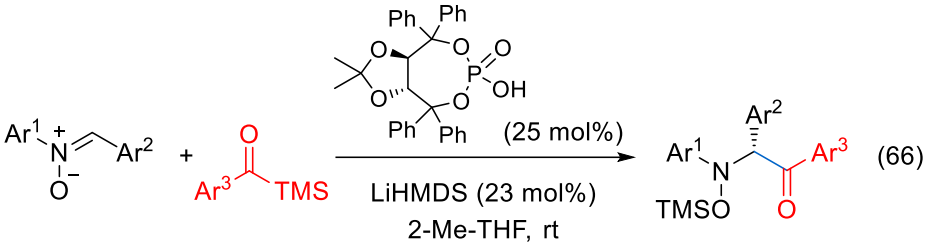
Scheme 17. Synthesis of Indolizidine Alkaloid via Acyloxyiminium Ion



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]

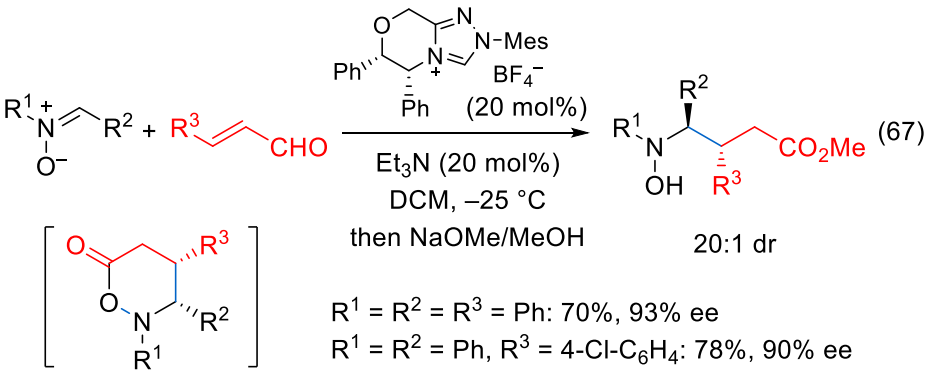
Enantioselective additions of acyl silanes to nitrones gives protected α-arylamino ketones. Thus, the reaction of nitrones with acylsilane in the presence of catalyst (*R*,*R*)-TADDOL-phosphite gives α-arylamino ketones. (eq 66).[182]



Ar^1 = 2-MeO-C_6H_4, Ar^2 = Ph, Ar^3 = Ph: 68%, 97:3 er
Ar^1 = 3-CF_3-4-OMe-C_6H_3, Ar^2 = Ph, Ar^3 = 4-MeO-C_6H_4: 76%, 98:2 er

3.1.2.5. Addition of Homoenolates

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 homoenolate 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]



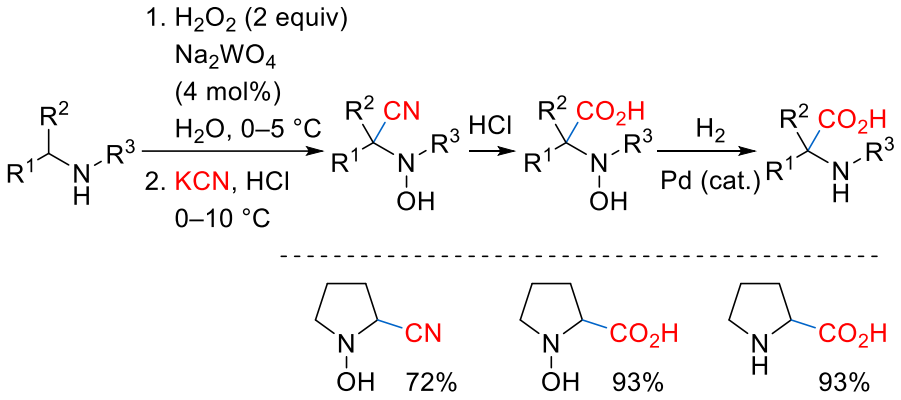
R^1 = R^2 = R^3 = Ph: 70%, 93% ee
R^1 = R^2 = Ph, R^3 = 4-Cl-C_6H_4: 78%, 90% ee

3.1.3. Cyanation

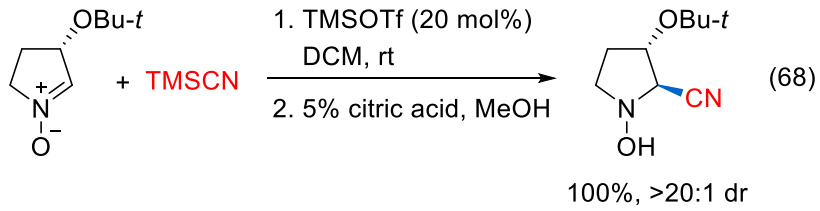
Murahashi and coworkers found that α-cyanohydroxylamines are generally prepared by the

oxidation of secondary amines with hydrogen peroxide in the presence of $Na_2WO_4•2H_2O$ 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]

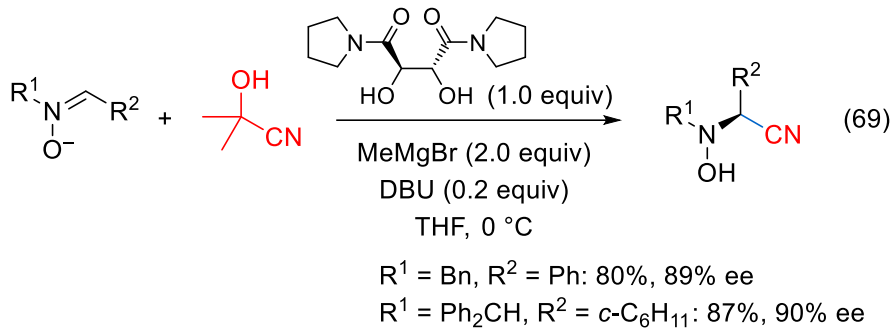
Scheme 18. Synthesis of α-Cyanohydroxylamines, *N*-Hydroxyamino Acids, and Amino Acids



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



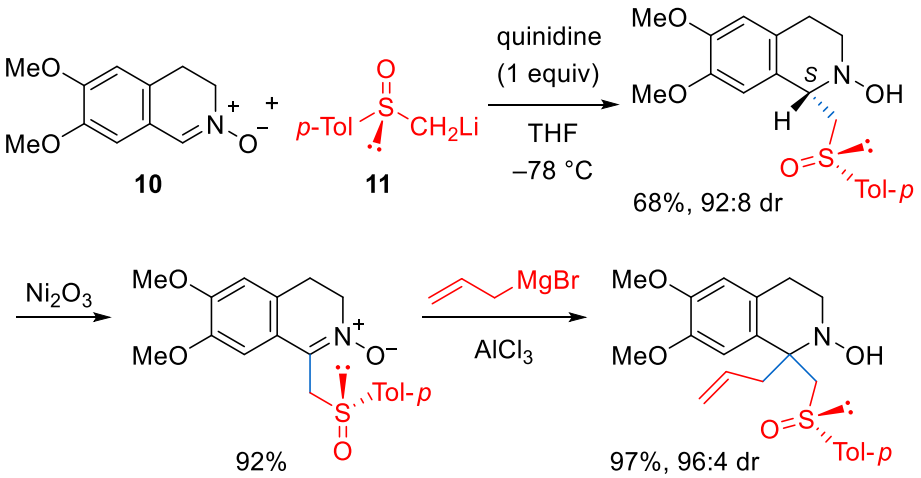
Ukaji and coworkers found that enantioselective synthesis of (*S*)-α-(hydroxyamino)nitrile derivatives upon treatment of nitrones with acetone cyanohydrin in the presence of a magnesium—tetramide complex, generated from (*R*,*R*)-2,3-dihydroxy-1,4-di(pyrrolidin-1-yl)butane-1,4-dione and MeMgBr, and catalytic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



3.1.4. Reaction with Other Unique Carbon Nucleophiles

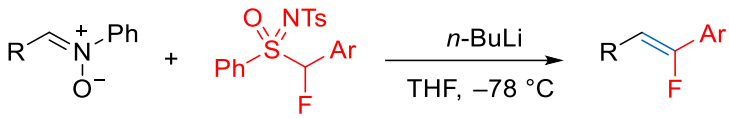
The method for introduction of an asymmetric quaternary carbon α to the nitrogen of secondary amines has been developed. The reaction of nitrone **10** with lithiated (*R*)-(+)-methyl *p*-tolyl sulfoxide **11** followed by oxidation with nickel(III) oxide provides enantiopure β-sulfinylketonitrone. Diastereoselective 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 –OTMS and –SPh groups provides asymmetric synthesis of α-

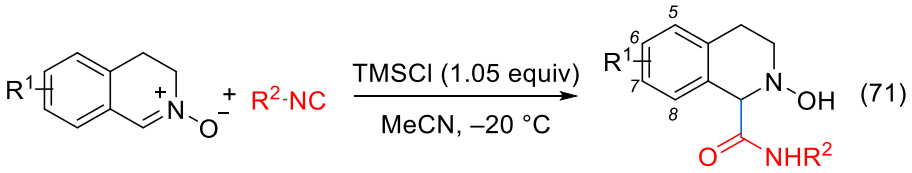
difluoromethylated polyhydroxypyrrolidines.[192] α-Dichloromethylation of nitrones can be performed upon treatment with $TMSCF_3$ and tetramethylammonium fluoride (TMAF) in DCM, where highly basic [CF_3^-] generates dichloromethide from DCM, followed by *O*-desilylation with TBAF.[193] The reaction of nitrones with carbanions generated by the reaction of α-fluorosulfoxylimines with *n*-BuLi provides stereoselective method for preparation of monofluoroalkenes (eq 70).[194]



(70)

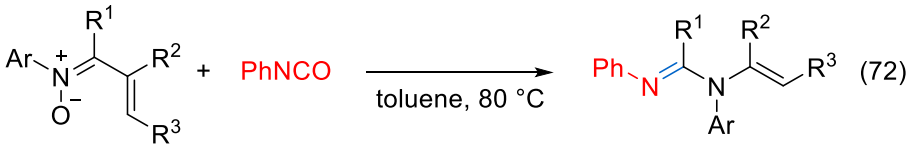
R = Ph, Ar = 2-Br-C_6H_4: 76%, *Z*/*E* = 98:2
R = c-C_6H_{11}, Ar = Ph: 80%, *Z*/*E* = 99:1

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 CO_2 elimination and styrenyl migration (eq 72).[196]



(71)

R^1 = H, R^2 = Bn: 73%
R^1 = 5-Me, R^2 = *t*-Bu: 78%

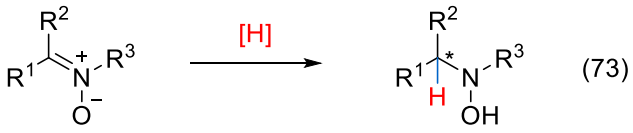


(72)

Ar = 4-Me-C_6H_4, R^1 = Ph, R^2 = H, R^3 = Ph: 91%
Ar = 4-Me-C_6H_4, R^1 = Ph, R^2 = H, R^3 = 2-furyl: 84%

3.1.5. Reduction of Nitrones

Reduction of nitrones gives *N*-hydroxylamines. Typically, the reductions with $NaBH_4$ 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).

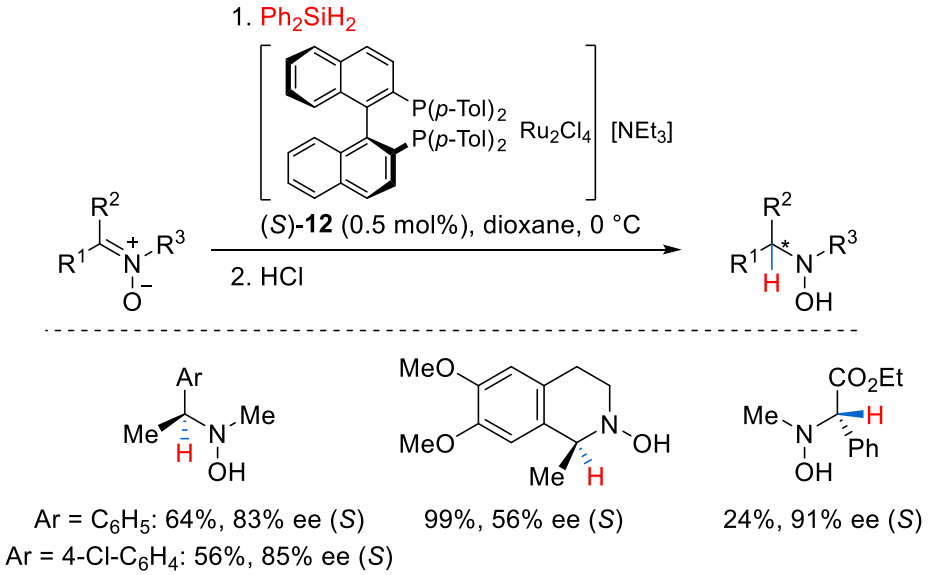


(73)

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]methylamine *N*-oxide with diphenylsilane in the presence of Ru_2Cl_4[(*S*)-(–)-*p*-tolbinap]$_2$(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 Ru_2Cl_4[(*R*)-(+)-*p*-tolbinap]$_2$(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

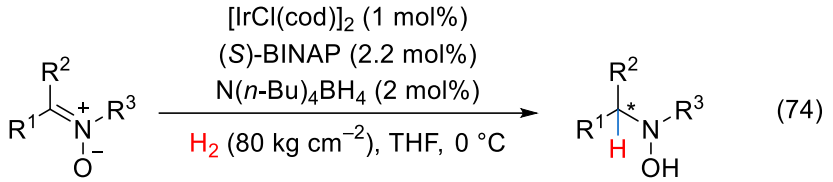


3.1.5.2. Asymmetric Hydrogenation

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 [IrCl(cod)]$_2$ (1 mol%), (*S*)-

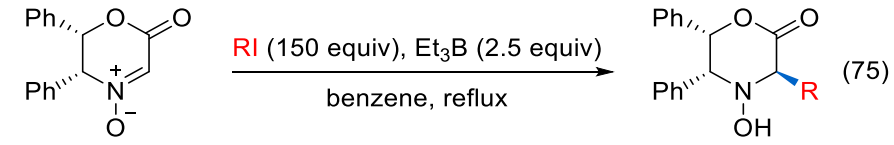
BINAP (2.2 mol%), and N(*n*-Bu)$_4$BH$_4$ (2.0 mol%), gives (*R*)-*N*-hydroxylamine in 82% yield with 83% ee.[200] Furthermore, nitrones can be hydrogenated enantioselectively with the [IrCl(cod)]$_2$/(*S*)-BINAP/N(*n*-Bu)$_4$BH$_4$ catalyst system (eq 74).



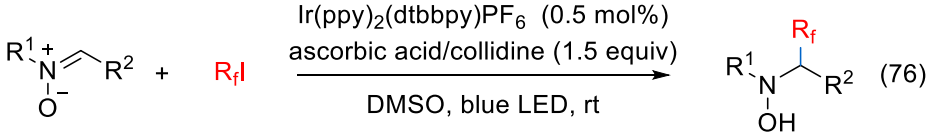
R^1 = R^3 = Me, R^2 = 4-Cl-C_6H_4: 82%, 83% ee (*R*)
R^1 = Me, R^2 = Ph, R^3 = Bn: 78%, 75% ee (*R*)

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$_3$B 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 Mo(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]



R = *i*-Pr: 82%
R = *c*-C_6H_{11}: 72%

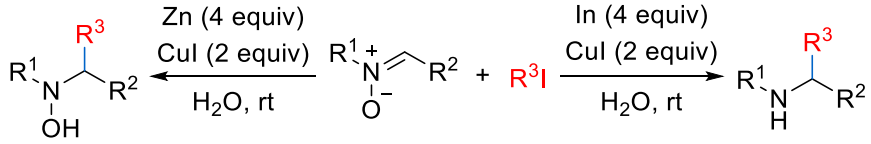


R^1 = Me, R^2 = Ph, R_f = CF_2CF_3: 92%
R^1 = Ph, R^2 = Bn, R_f = CF_3: 91%

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

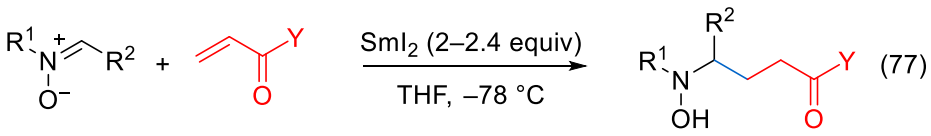
iodides in the presence of Zn/CuI in water gives *N*-hydroxylamines. In contrast, the reaction with In/CuI in water gives amines (Scheme 21).[204] The latter reaction involves single-electron transfer (SET) from indium to alkyl iodide to generate alkyl radical. Subsequent indium-promoted reduction followed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

Scheme 21. Barbier-Type Alkylation of Nitrones



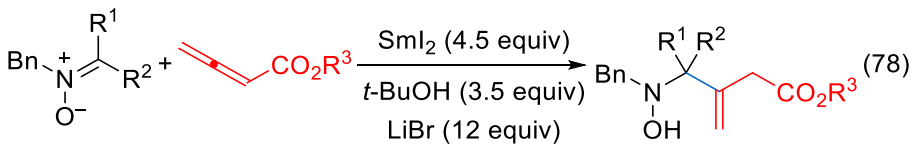
R^1 = Bn, R^2 = Ph, R^3 = *n*-Bu: 68% R^1 = Bn, R^2 = Ph, R^3 = *c*-C_6H_{11}: 82%
R^1 = Bn, R^2 = Ph, R^3 = *c*-C_5H_9: 83% R^1 = Bn, R^2 = *c*-C_6H_{11}, R^3 = *i*-Pr: 62%

Aliphatic nitrones undergo radical reaction with α,β-unsaturated esters[205] and amides[206] in the presence of two equivalents of SmI_2 to give γ-*N*-hydroxyamino esters or amides (eq 77). A single-electron transfer from SmI_2 to the nitrone and subsequent radical coupling has been proposed. However, electron transfer from 2 equivalents of SmI_2, followed by nucleophilic attack of the generated carbanion cannot be ruled out.



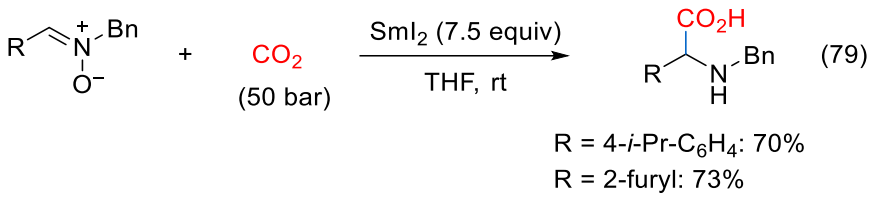
R^1 = Bn, R^2 = *i*-Pr, Y = OEt: 75%
R^1 = Bn, R^2 = *c*-C_6H_{11}, Y = $NHCH_2CO_2Me$: 65%

Nitrones undergo conjugate addition to alkyl allenoates under SmI_2-mediated reductive conditions using *t*-BuOH as a proton source to produce β-methylene-substituted γ-amino esters (eq 78).[207] Similar SmI_2-mediated reductive coupling of nitrones with β-silyl-α,β-unsaturated esters, followed by zinc reduction, gives β-silyl lactams diastereoselectively.[208] The SmI_2-induced reductive cross-coupling of nitrones with chiral *N*-*tert*-butanesulfinyl imines gives optically pure unsymmetrical vicinal diamines.[209]



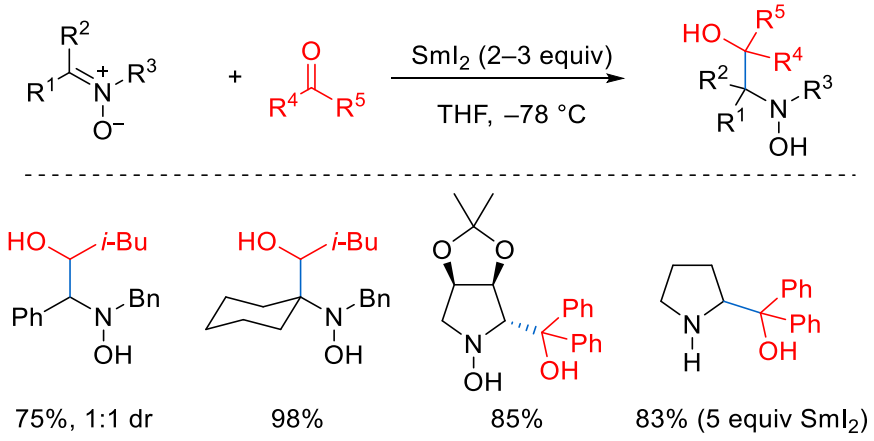
R^1 = H, R^2 = Et, R^3 = Bn: 74%
R^1 = H, R^2 = *i*-Pr, R^3 = Et: 64%

The α-amino acids are obtained upon treatment of *N*-benzylnitrones with CO_2 in the presence of SmI_2 by reductive C—C coupling (eq 79).[210]



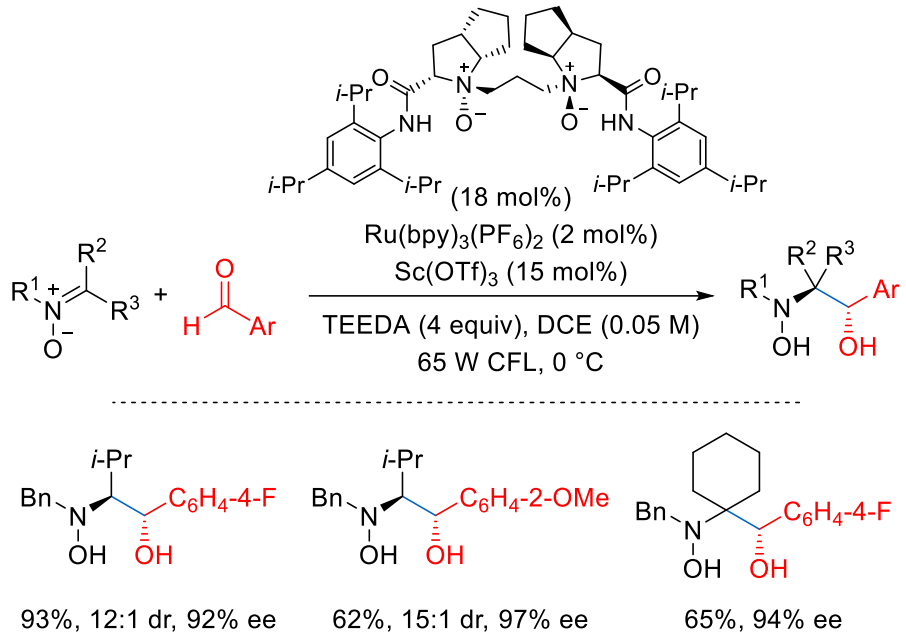
SmI_2-induced reductive cross-coupling of nitrones with aldehydes and ketones provides a method to prepare highly substituted and unsymmetrical vicinal *N*-hydroxyamino alcohols (Scheme 22).[211,212] Increasing the amount of SmI_2 allows direct access to the corresponding amines. The *N*-hydroxy-α,α-diphenyl-2-pyrrolidinylmethanol is also easily prepared and resolved.[213]

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

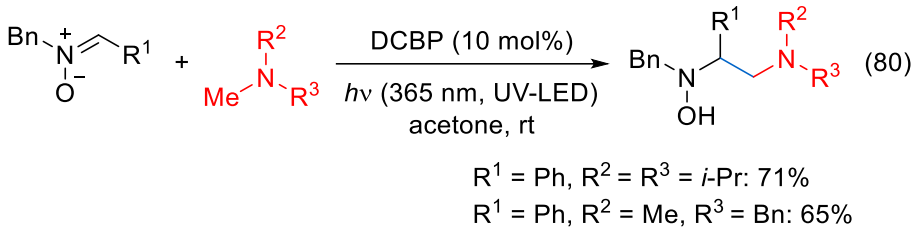


Enantioselective reductive cross-coupling of nitrones with aldehydes can be carried out under photocatalytic conditions in the presence of ruthenium photoredox catalyst, rare earth Lewis acid catalyst, and a chiral *N*,*N*'-dioxide ligand (Scheme 23). [214]

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.

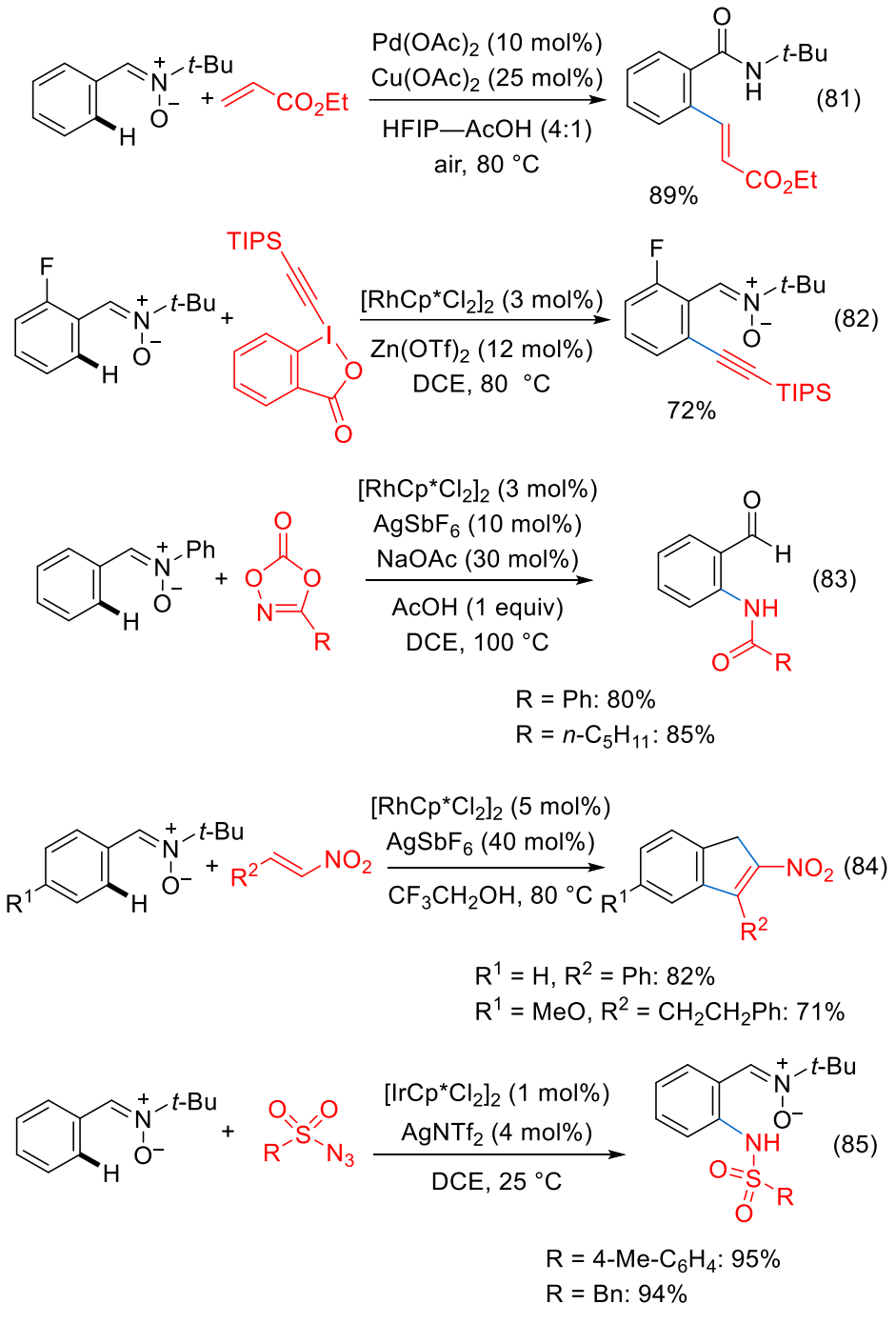


3.3. C—H Functionalization of Nitrones

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.

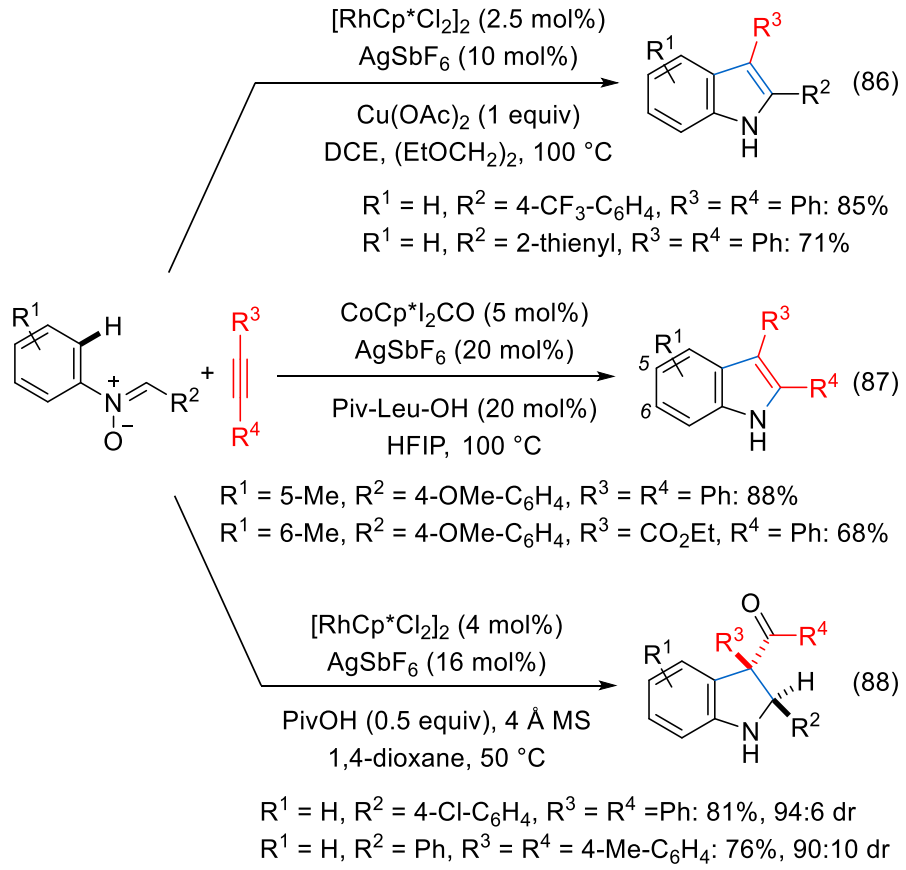
Palladium-catalyzed alkenylation of *C*-arylnitrones with ethyl acrylate gives *ortho*-alkenylated benzamide derivatives (eq 81).[216] Rhodium-catalyzed C—H alkenylation of *N*-*tert*-butyl-*C*-arylnitrones is developed. The reaction with 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3-(1*H*)-one affords 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 $[IrCp^*Cl_2]_2$ and $AgNTf_2$ gives *O*-sulfonylamino nitrones with excellent regioselectivity via direct C—H annulation. (eq 85).[220]

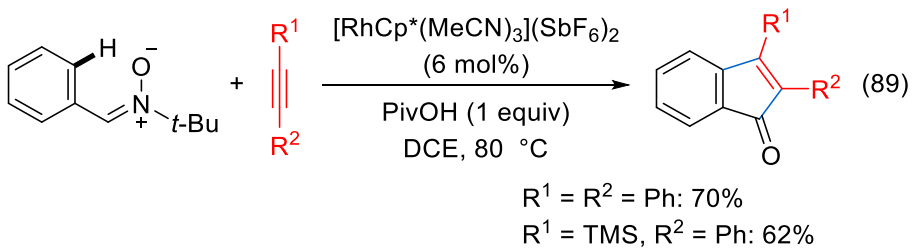


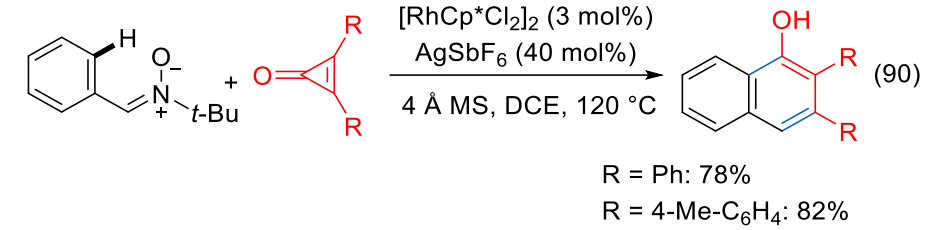
Transition-metal-catalyzed C—H annulation of *N*-arylnitrones with acetylenes gives indoles, indolines, and indenones depending on the catalysts used. Thus, rhodium-catalyzed C—H annulation of *N*-arylnitrones with symmetrical diarylalkynes gives 2,3-diaryl-substituted

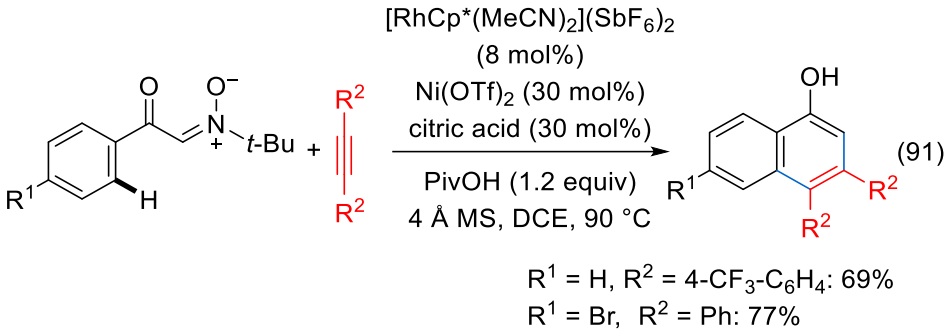
N-unprotected indoles (eq 86).[221] Cobalt-catalyzed C—H/N—O functionalization of *N*-arylnitrones gives indoles. This is a step-economical access to indoles and displays in excellent site- and regioselectivity with unsymmetrical nitrones and alkynes (eq 87).[222] Rhodium-catalyzed C—H activation of *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]



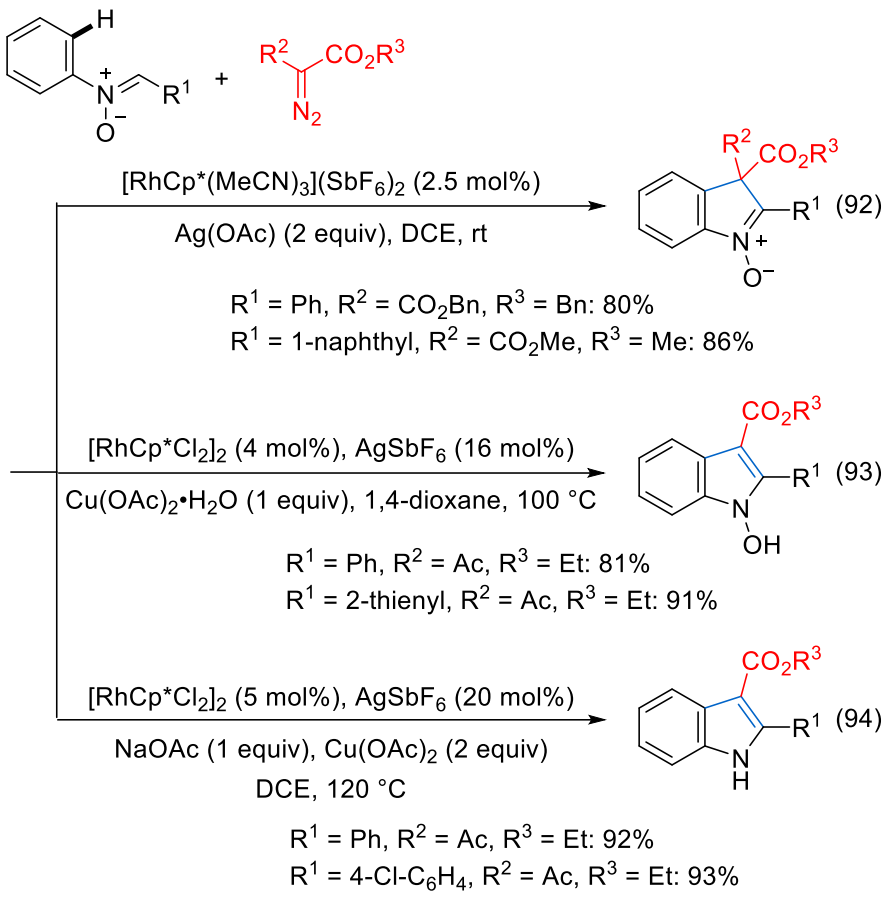
The reaction of *N*-*tert*-butyl-*C*-arylnitrones with alkynes in the presence of [RhCp*(MeCN)$_3$](SbF$_6$)$_2$ catalyst and pivalic acid gives indenones with good functional group tolerance (eq 89).[224] Rhodium-catalyzed reaction of arylnitrones with cyclopropenones affords 1-naphthols (eq 90).[225] Similar rhodium-catalyzed reaction of *C*-benzoylnitrones with alkynes provides a redox-neutral naphthol synthesis (eq 91).[226]



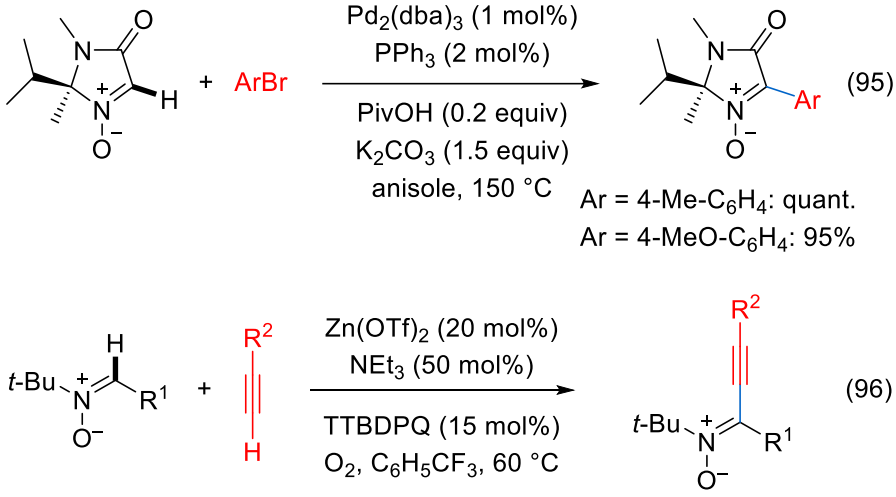




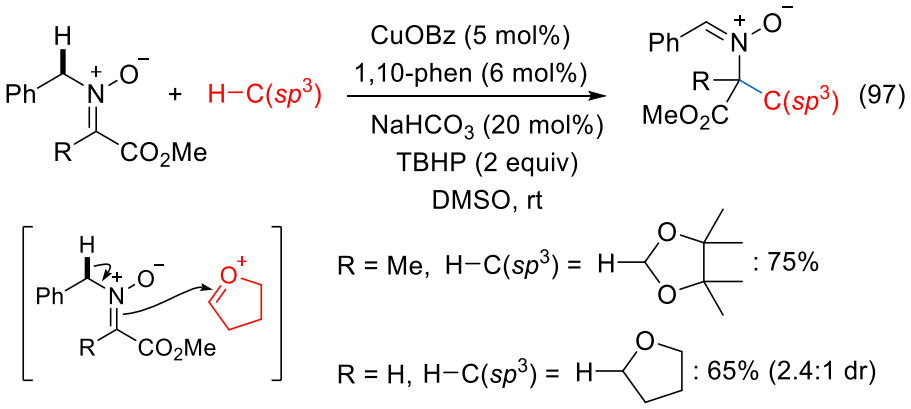
Rhodium-catalyzed C—H activation of *N*-arylnitrones and coupling with diazo compounds affords different indole derivatives depending on the additives. Nitrone is introduced as a directing group to trigger a new [4 + 1] cyclization capture approach wherein diazo compounds undergo migratory insertion to afford 3*H*-indole *N*-oxides. Thus, treatment of nitrones with diazo compounds in the presence of $[Cp^*Rh(MeCN)_3](SbF_6)_2$ catalyst and AgOAc gives 3*H*-indole *N*-oxides (eq 92).[227] The Rh(III) catalyst with $Cu(OAc)_2$ gives *N*-hydroxyindole derivatives, which are unique structural motif with various biological activities (eq 93).[228] The reaction with Rh(III) catalyst, $Cu(OAc)_2$, and NaOAc provides regioselective synthesis of 2,3-disubstitued 1*H*-indole derivatives (eq 94).[229]



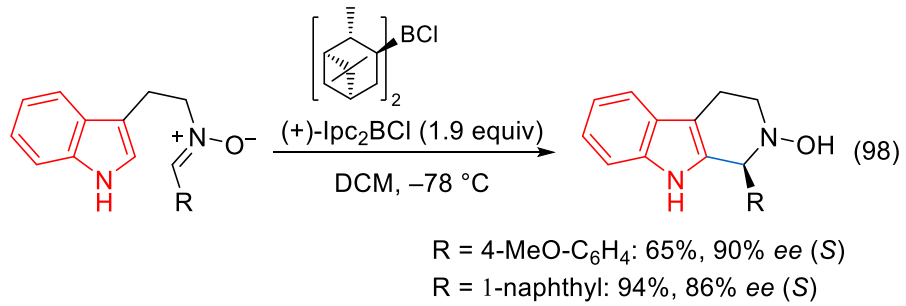
Palladium-catalyzed direct cross-coupling of cyclic nitrones occurs readily to give aryl substituted cyclic nitrones (eq 95).[230] Similarly, cross-dehydrogenative-coupling between nitrones and terminal alkynes can be carried out by using cheap, readily available 3,3',5,5'-tetra-*tert*-butyldiphenoquinone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

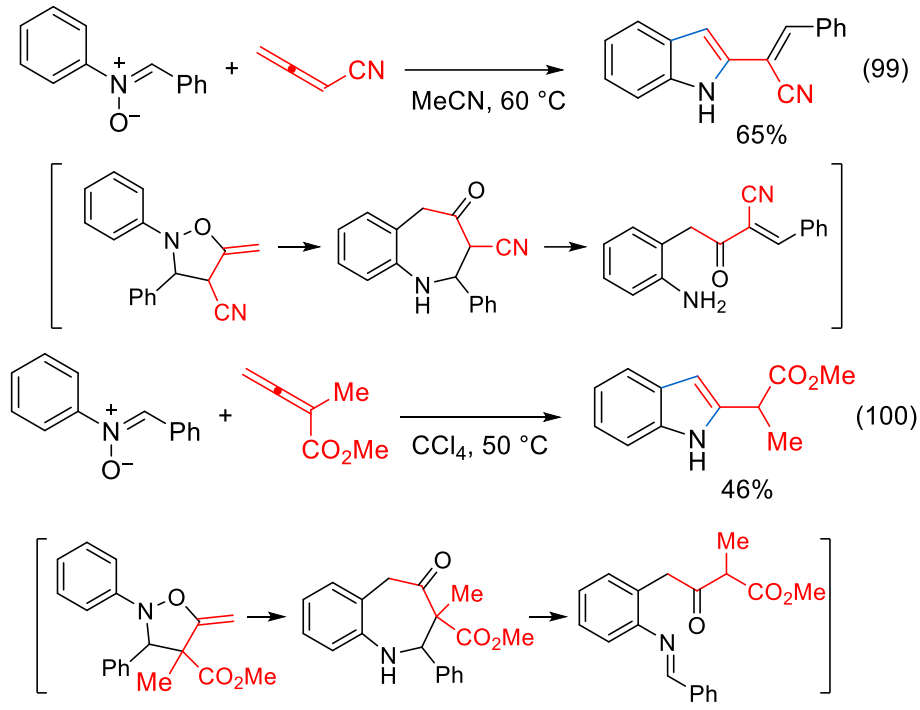


The Pictet–Spengler reaction of nitrones in the presence of $Yb(OTf)_3$—TMSCl gives tetrahydro-β-carbolines.[234] Enantioselective version with chiral (+)-diisopinocampheylchloroborane ((+)-Ipc_2BCl) gives 2-hydroxytetrahydro-β-carbolines in up to 90% *ee* (eq 98).[235]

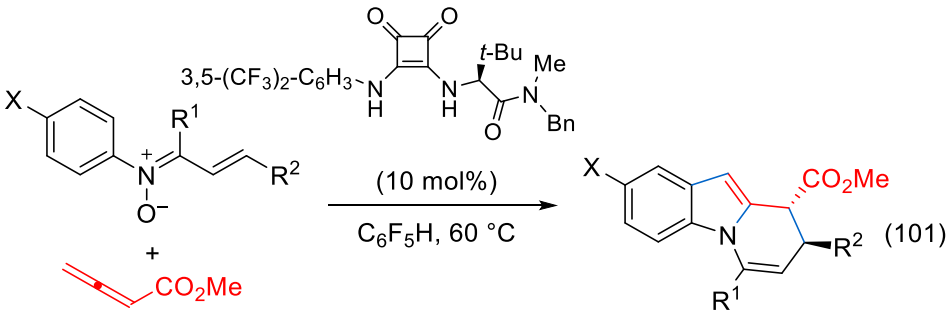


3.4. Reaction with Allenes

The addition and rearrangement reactivity of nitrones with allenes has been studied for the synthesis of a variety of different heterocycles. Blechert and coworkers[236] and Padwa and coworkers[237] 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.



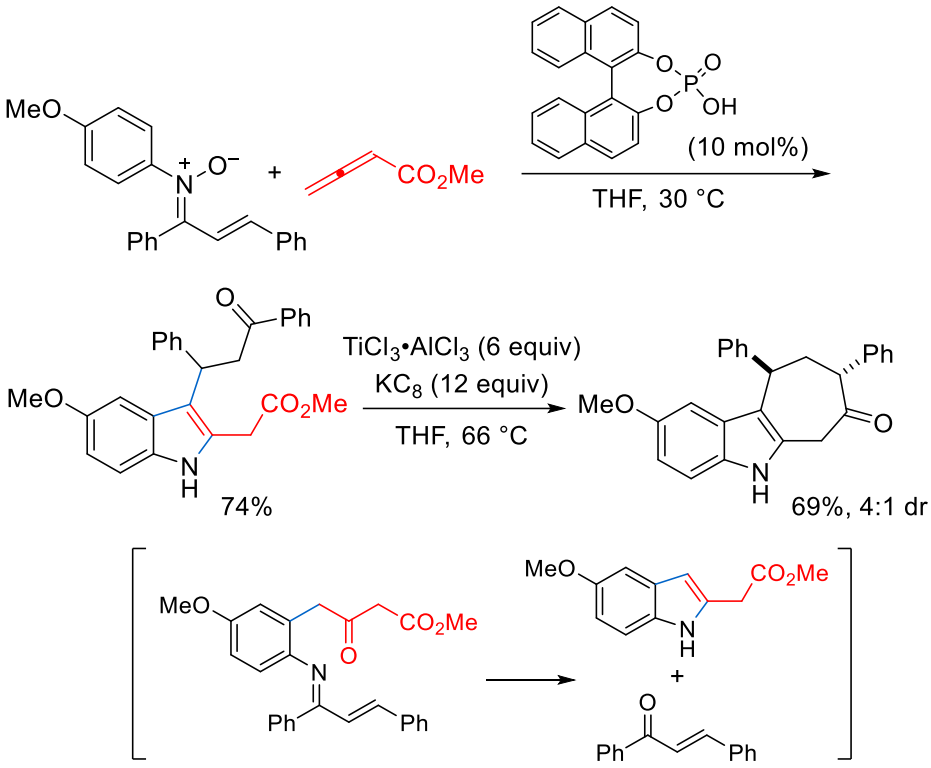
These formation of indoles have been extended to prepare dihydrocarbazole or dihydropyridoindole products.[238,239] Anderson and coworkers discovered the first catalytic asymmetric version of these cascade reactions providing dihydropyrido[1,2-*a*]indoles with high diastereoselection and excellent enantioselectivity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



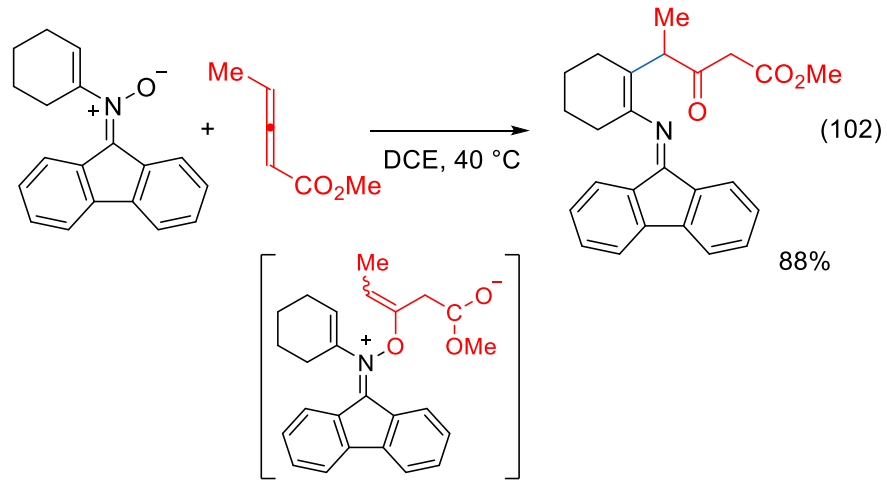
X = Me, R^1 = Ph, R^2 = 4-MeO-C_6H_4: 53%, 5:1 dr, >99% ee, 66% ee
X = vinyl, R^1 = R^2 = Ph: 59%, 3:1 dr, 93% ee, 88% ee

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



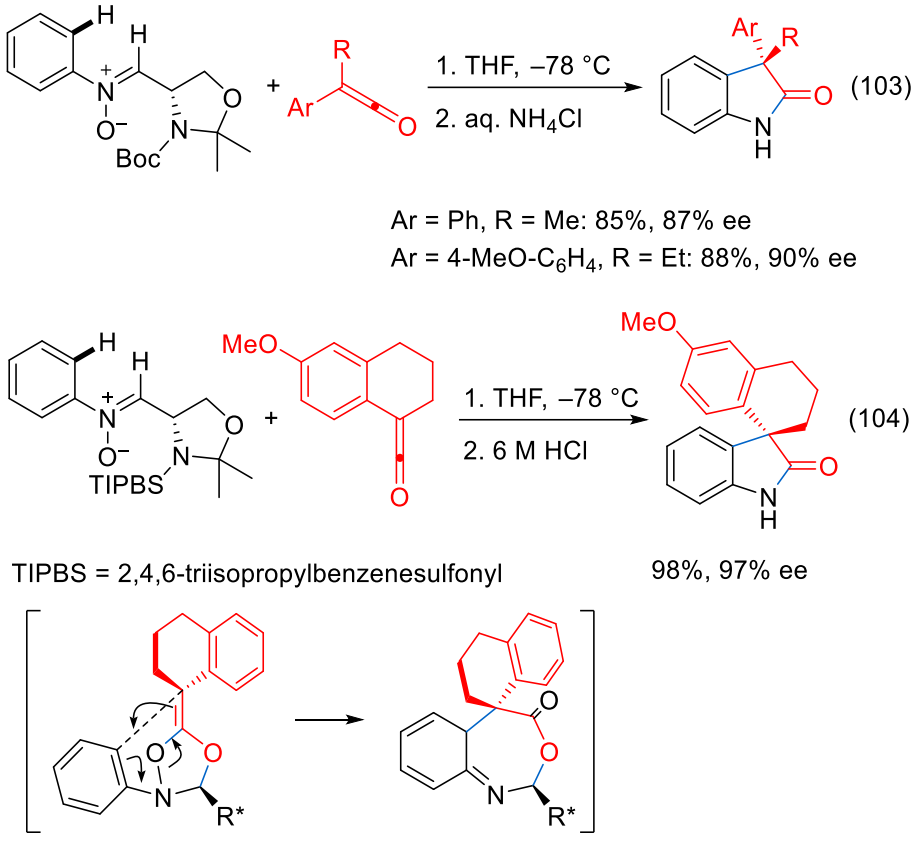
The reaction of fluorenylnitrones with electron-deficient allenes gives the corresponding 1,4-enamino ketones (eq 102).[242] The reaction proceeds through the [3.3]-rearrangement of dialkenylhydroxylamines generated from the addition of *N*-alkenylnitrones to electron-deficient allenes.



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

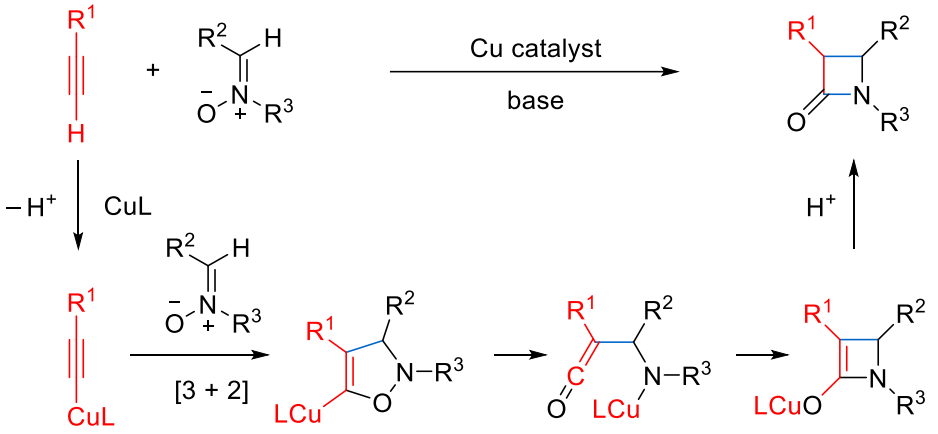
oxindoles (eq 103).[243] This methodology has been extended to the asymmetric construction of 3,3-spirocarbocyclic oxindoles (eq 104).[244] The reaction seems to involve a [3 + 2] cycloaddition across the ketene C=O bond, with preferential *anti*-addition with respect to the aryl portion of the ketene.[245]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



3.6. Reaction with Terminal Alkynes (Kinugasa Reaction)

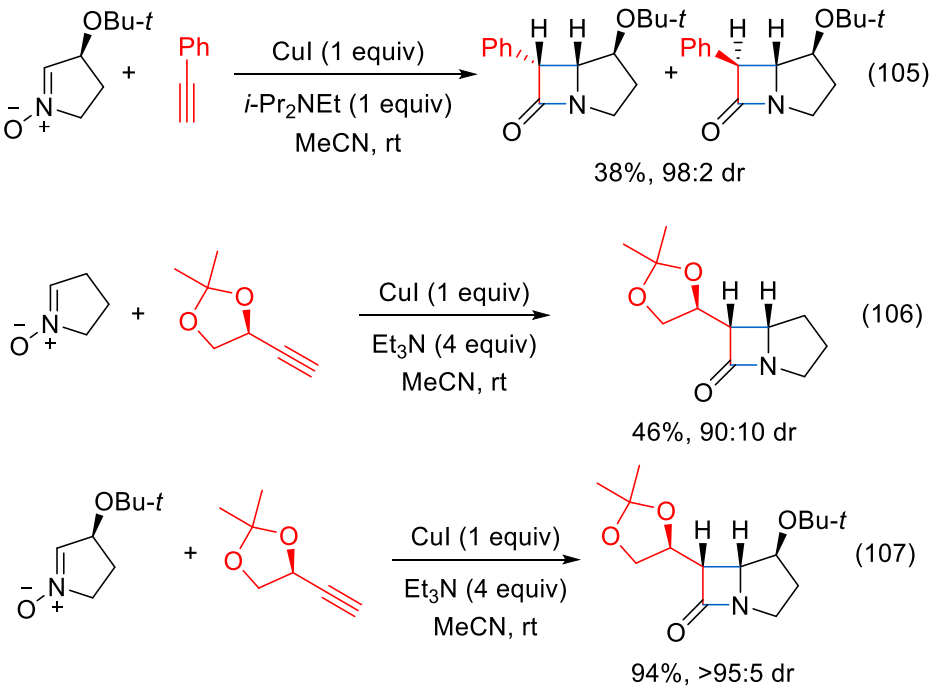
In 1972, Kinugasa and Hashimoto reported that the copper-promoted reaction of nitrones with phenylacetylide gives β-lactams.[246] This reaction is highly useful for synthesis of β-lactams, which are key structure for biologically important antibiotics and has been received much attentions.[247-250] This 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



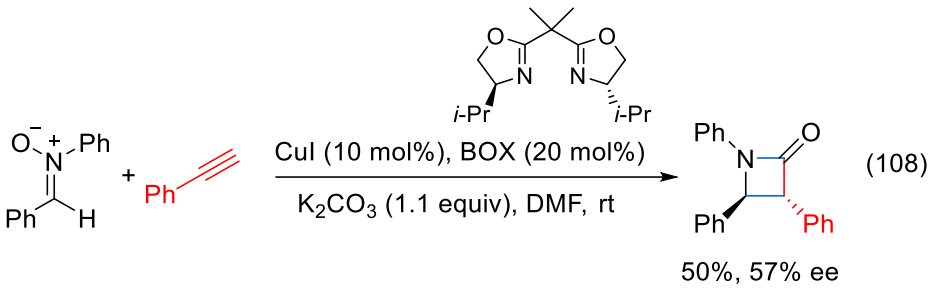
Diastereoselective reactions have been reported by two methods; the reaction of chiral nitrones with acetylenes and the reaction of achiral nitrones with chiral acetylenes. Diastereoselective reaction of chiral nitrone with phenylacetylene gives cis-azetidinones predominantly (eq 105).[251] The geometry 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]



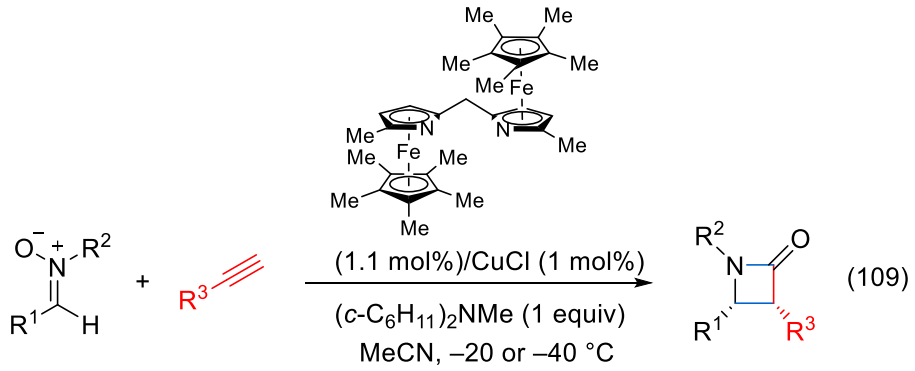
The first catalytic modification of Kinugasa reaction was reported by Miura and Nomura

in 1993,[253] and asymmetric version was reported by the same research group in 1995.[254] The reaction of phenyl substituted nitrone with phenylacetylene in the presence of CuI and bisoxazoline lingand (BOX) gives the β-lactam (cis/trans=66:34, for the trans-diastereomer up to 57% *ee*) (eq 108).



(108)

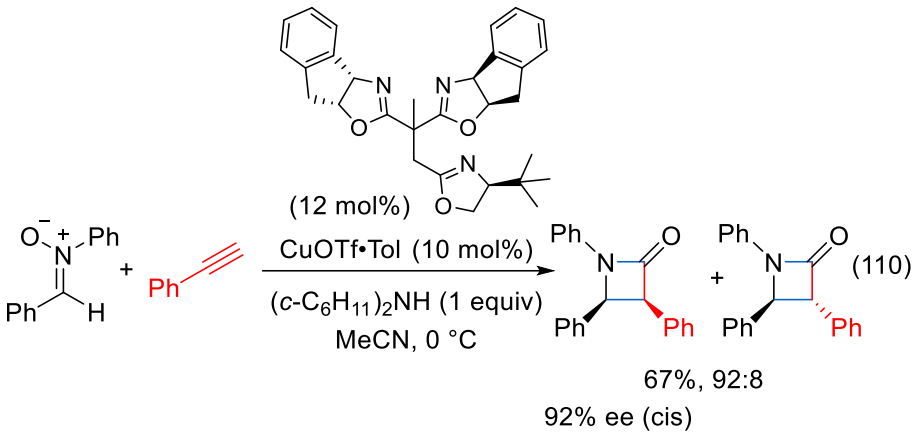
The first diastereo- and enantioselective catalytic variant was reported by Fu and coworkers in 2002. The reactions of nitrones with terminal alkynes afford cis β-lactams selectively using a CuCl catalyst and a C_2-symmetric planar chiral bis(azaferrocene) ligand in the presence of dicyclohexylmethylamine. 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]



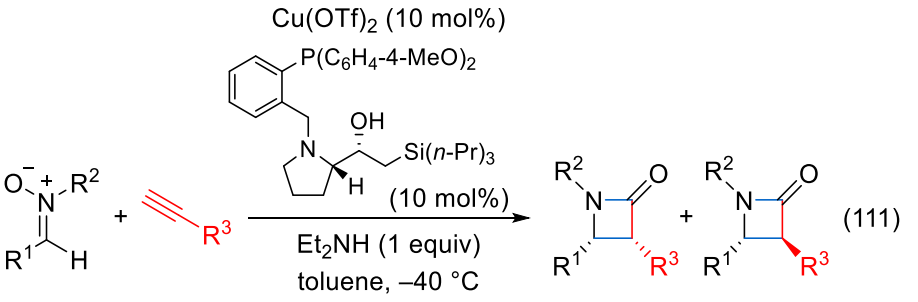
(109)

R^1 = *c*-C_6H_{11}, R^2 = 4-MeO-C_6H_4, R^3 = Ph: >95:5 dr, 65% (cis), 92% ee
R^1 = Bz, R^2 = Ph, R^3 = 1-cyclohexenyl: 90:10 dr, 45% (cis), 91% ee

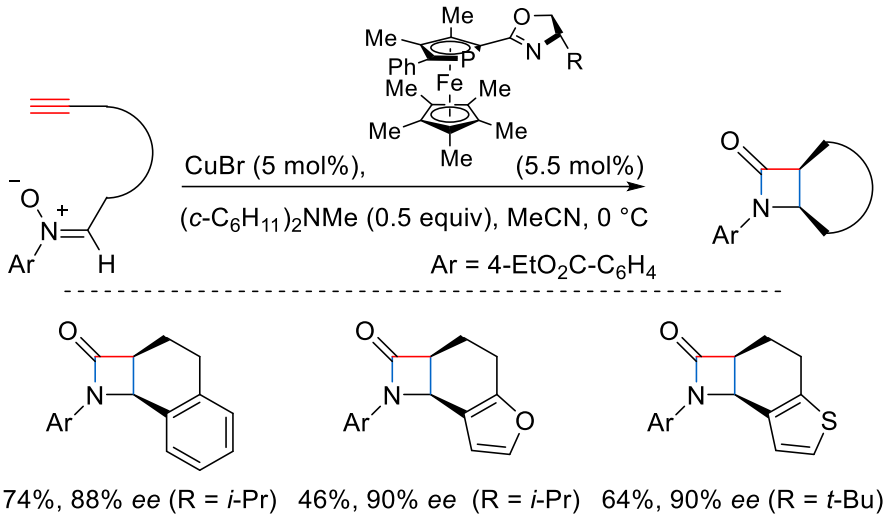
Tang and coworkers found that the use of $Cu(OTf)_2$•Tol catalyst with tris(oxazoline) ligand gives cis β-lactams with high enantioselectivity (eq 110)[256]



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 nitrone oxyanion and C(sp^3)—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 phosphaferrocene-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]

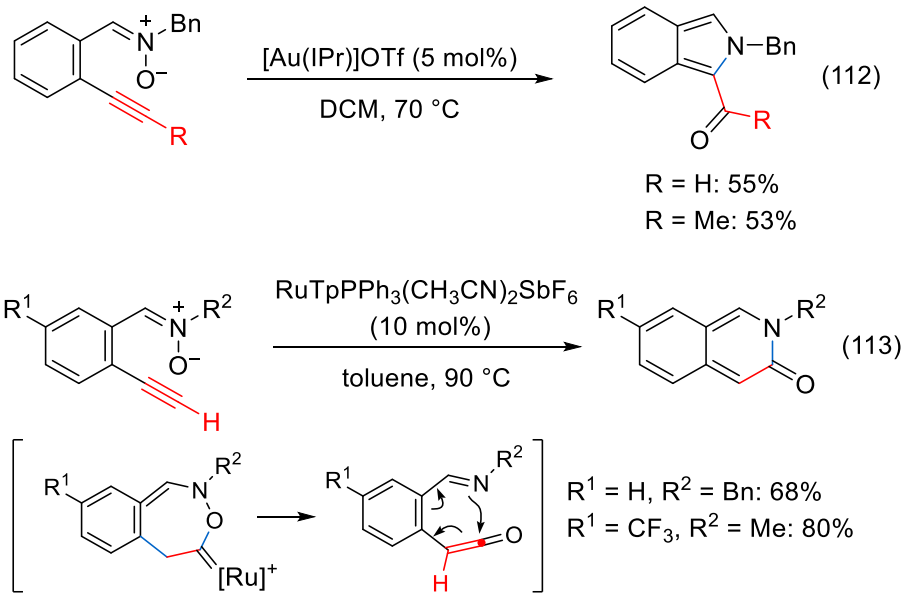


Scheme 26. Intramolecular Enantioselective Kinugasa Reaction



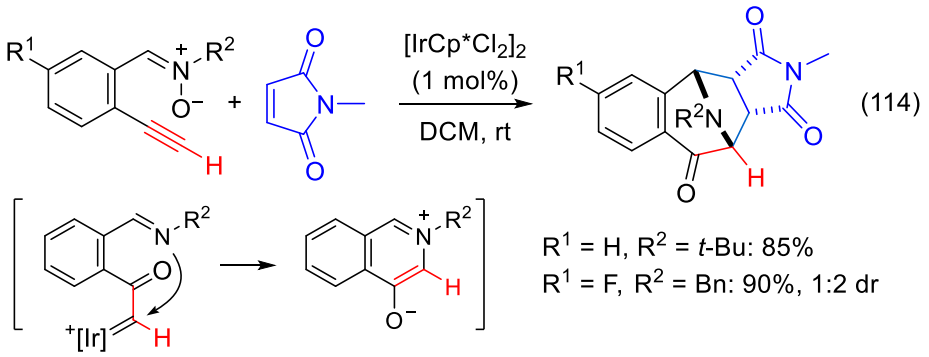
3.7. Reaction of Nitrone-Functionalized Terminal Alkynes

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, RuTpPPh$_3$L$_2$X-catalyzed [Tp = tris(1-pyrazolyl)borate)] cyclization of these nitrones yields 3-isoquinolones (eq 113).[262]

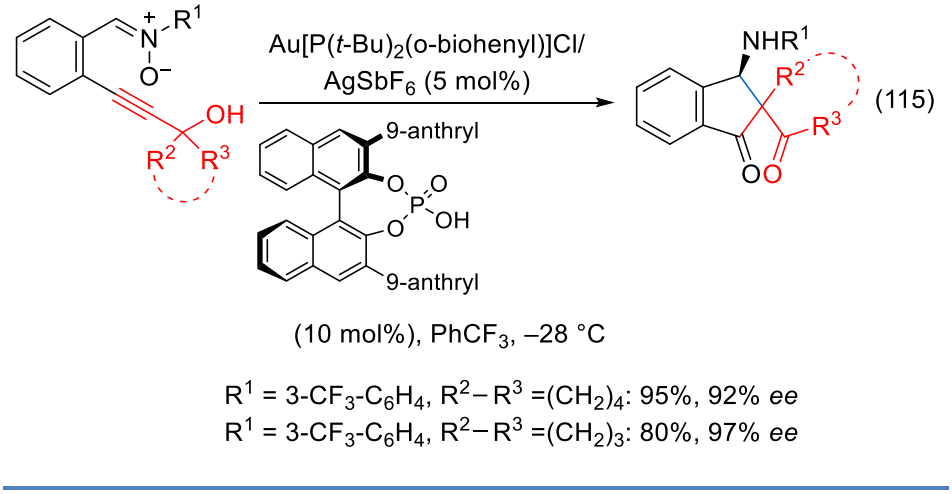


Iridium catalyzed internal redox cyclization of similar substrates gives unusual azomethine ylides, which are highly useful for [3 + 2] dipolar cycloaddition reaction with activated alkynes

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]

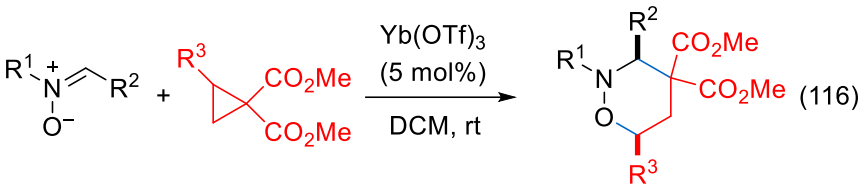


3.8. Cycloaddition Reaction

3.8.1. [3 + 3] Cycloaddition Reaction

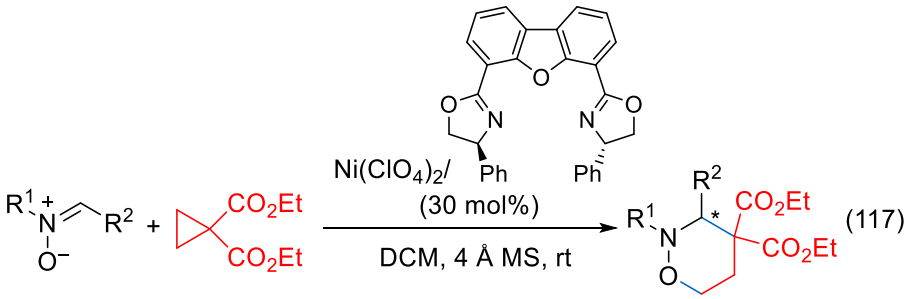
For the formal [3 + 3] cycloaddition reactions of nitrones, there would be four types of reactions which include additions of cyclopropanes, trimethylenemethanes, vinyldiazoacetate, and alkenylgold complex metal carbenoids generated through cycloisomerization. These reactions are highly useful for synthesis 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] MgI_2[267] and $Ca(OTf)_2$[268] show similar catalytic activity.



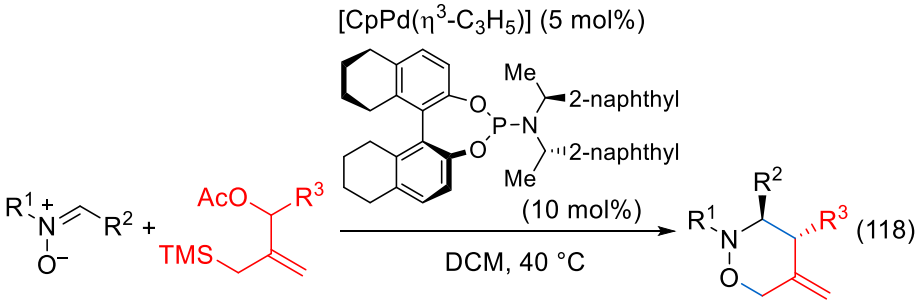
R^1 = *p*-Tol, R^2 = R^3 = Ph: 94%
R^1 = *p*-Tol, R^2 = Ph, R^3 = (*E*)-PhCH=CH: 95%

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]

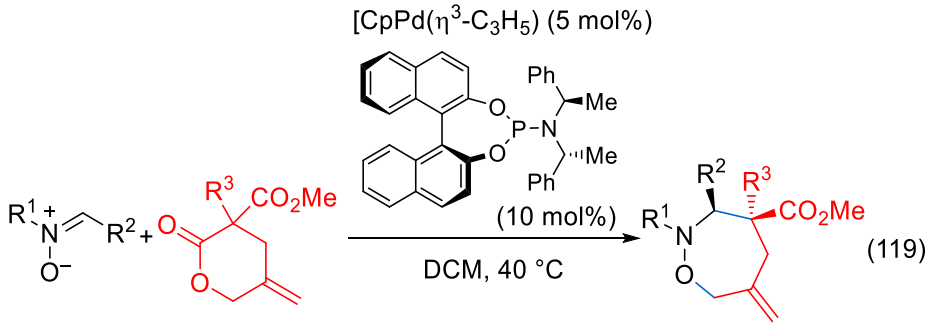


R^1 = Me, R^2 = Ph: 99%, 92% ee
R^1 = Bn, R^2 = Ph: 99%, 93% ee

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 syetem has been extended to γ-methylene-δ-valerolactones to give tetrahydro-1,2-oxazepines (eq 119) by a [3 + 4] formal cycloaddition.[272]

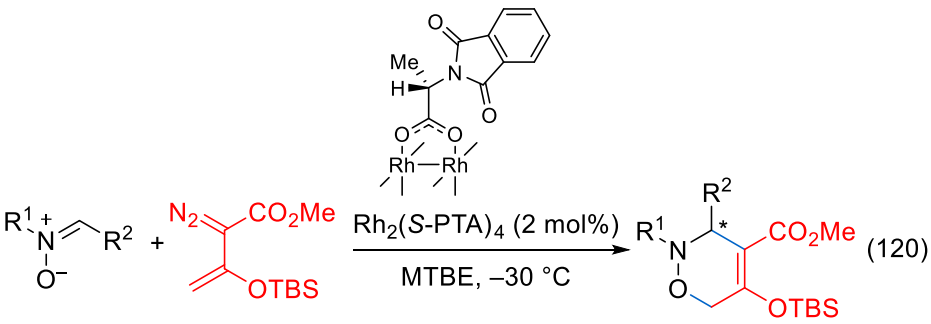


R^1 = 4-EtO_2C-C_6H_4, R^2 = 4-CF_3-C_6H_4, R^3 = Ph: 95%, 89:11 dr, 92% ee (trans)
R^1 = 4-EtO_2C-C_6H_4, R^2 = Ph, R^3 = Ph: 92%, 85:15 dr, 92% ee (trans)



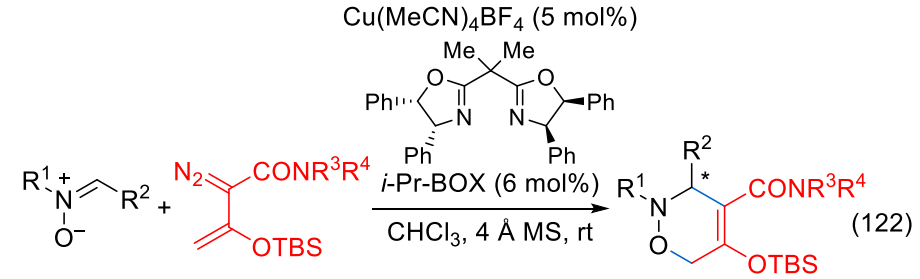
R^1 = 4-EtO_2C-C_6H_4, R^2 = 4-CF_3-C_6H_4, R^3 = Ph: 98%, 81:19 dr, 83% ee (major diastereomer)
R^1 = 4-EtO_2C-C_6H_4, R^2 = 4-CF_3-C_6H_4, R^3 = 1-naphthyl: 98%, 80:20 dr, 96% ee (major diastereomer)

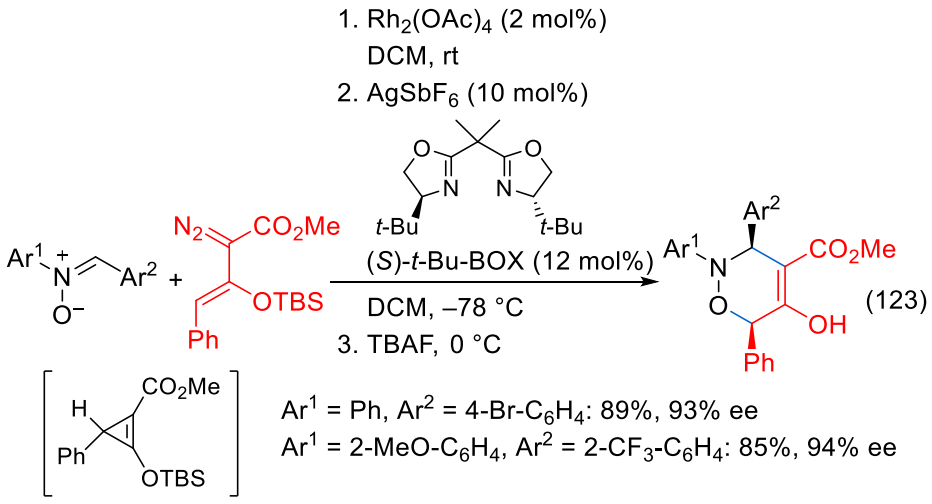
Doyle and coworkers discovered that dirhodium(II) carboxylate-catalyzed [3 + 3] cycloaddition reactions of nitrones with a β-TBSO-substituted vinyldiazoacetate occur to give 3,6-dihydro-1,2-oxazines. High enantiocontrol occurs with catalysis of (*S*)-*N*-phthaloylamino acid-ligated dirhodium carboxylates [Rh_2(*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 $Cu(SbF_6)_2$ gives the [3 + 3] cycloaddition product selectively to favor the cis isomer (eq 121).[274]



R^1 = R^2 = Ph: 95%, 93% ee
R^1 = Ph, R^2 = *c*-C_6H_{11}: 85%, 77% ee

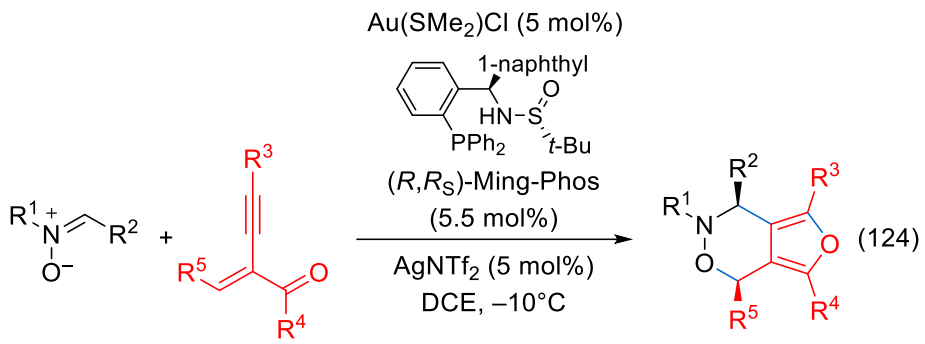
Doyle extended this reaction to asymmetric synthesis of [3 + 3] cycloadducts using copper tetrafluoroborate/bisoxazoline complex catalyst (eq 122).[275,276] Silver-catalyzed asymmetric [3 + 3] cycloaddition of nitrones gives 3,6-dihydro-1,2-ozazine derivatives with exceptional stereocontrol. The reaction 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

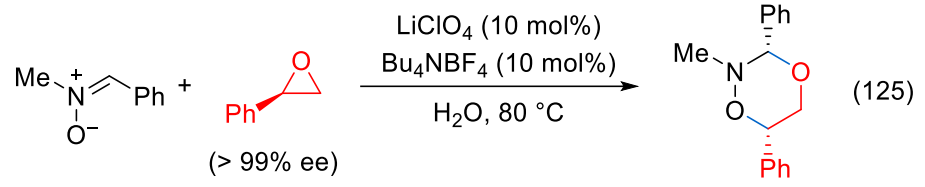
(*S*,R_S)-Ming-Phos ligands, both enantiomers can be obtained easily (eq 124).[278]



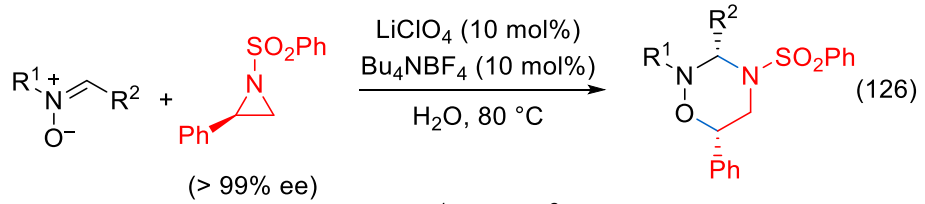
$R^1 = R^2 = R^5 = Ph$, $R^3 = n$-Bu, $R^4 = Me$, 92%, 96% ee
$R^1 = R^2 = R^5 = Ph$, $R^3 = n$-Pr, $R^4 = Me$, 85%, 95% ee

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 $LiClO_4/Bu_4NBF_4$ dual catalyst system.[280]



85%, >99% ee

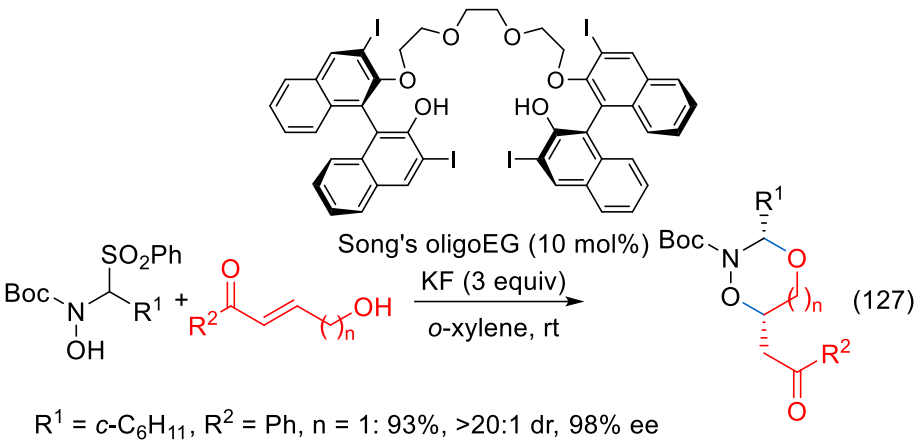


R^1 = Me, R^2 = Ph: 84%, 99% ee
R^1 = Bn, R^2 = 2-furyl: 96%, >99% ee

4-Dimethylaminopyridine[281] 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)

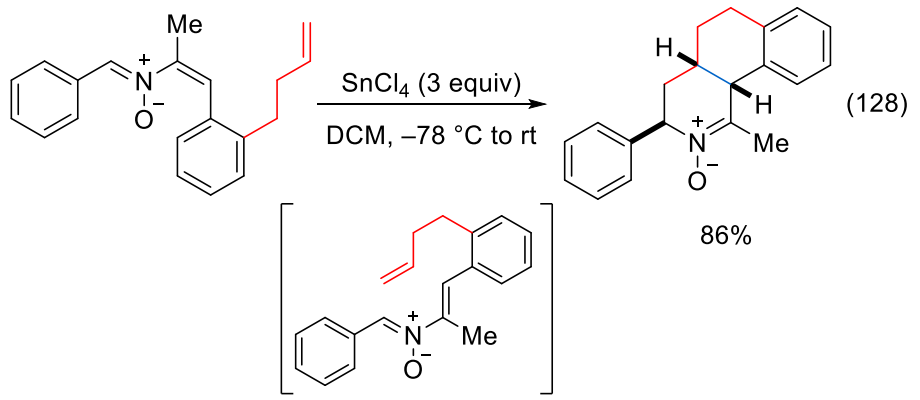
and KF gives six or seven-membered heterocycles. The reaction seems to occur through a tandem pathway sequence of oxa-Mannich/oxa-Michael/tautomerization/protonation (eq 127).[283]



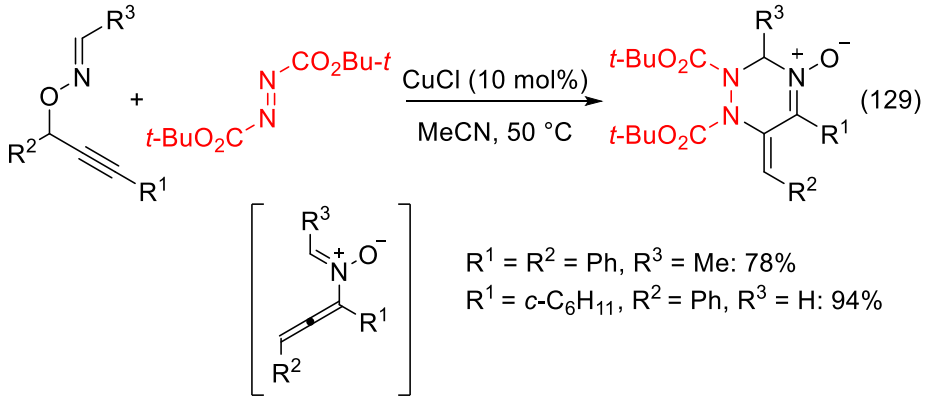
R^1 = *c*-C_6H_{11}, R^2 = Ph, n = 1: 93%, >20:1 dr, 98% ee
R^1 = *c*-C_6H_{11}, R^2 = 4-Br-C_6H_4, n = 2: 93%, 9:1 dr, 91% ee (major), 91% ee (minor)

3.8.2. Other Cycloaddition Reactions

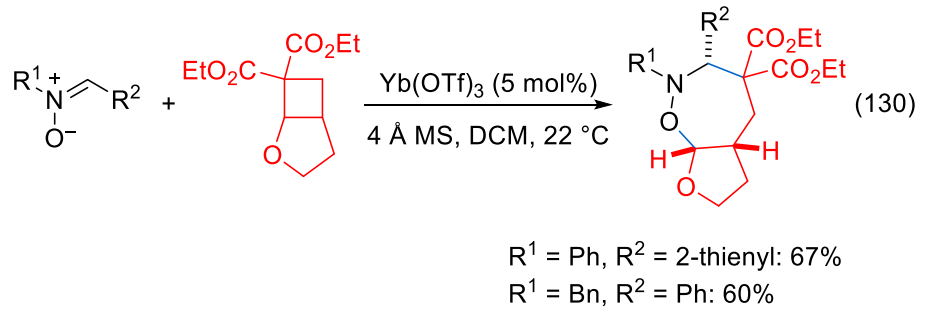
Denmark and coworkers have first reported intramolecular [4 + 2] cycloaddition of *N*-vinylnitrones bearing a tethered dienophile upon treatment with $SnCl_4$ to give tetrahydropyridine *N*-oxide (eq 128).[125]

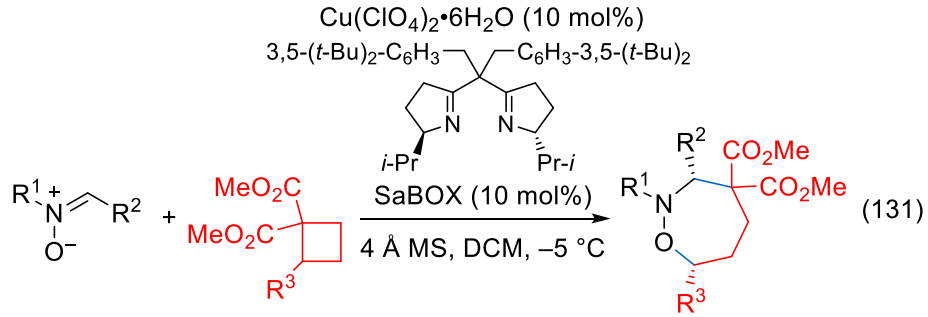


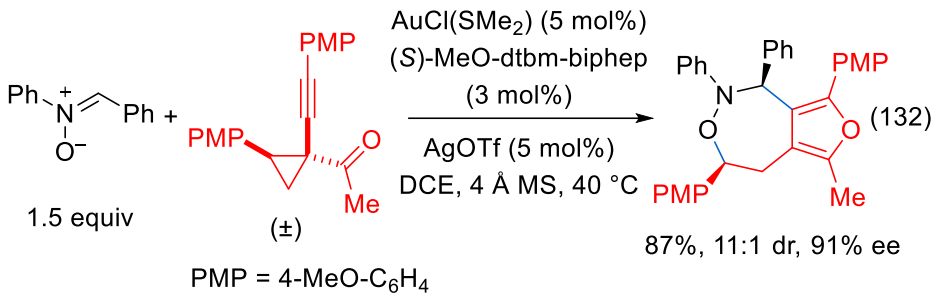
N-Allenylnitrones act as 2-azadienes in the copper-catalyzed cascade reaction of *O*-propargylic oximes with azodicarboxylates to undergo [4 + 2] cycloaddition affording 1,2,4-triazine oxides (eq 129).[284]



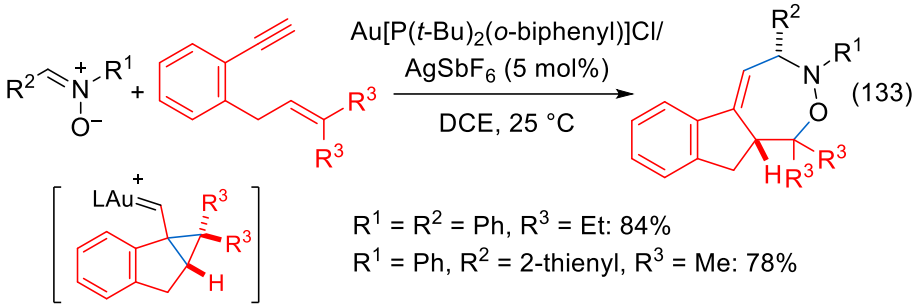
The ytterbium-catalyzed [4 + 3] cycloaddition of 2-alkoxy-1,1-dicarboxylate, activated donor–acceptor cyclobutanes, with nitrones gives seven-membered 1,2-oxazepane derivatives (eq 130).[285] Using chiral SaBOX/Cu(II) catalyst the similar reaction occurs to give multifunctionalized optically active 1,2-oxazepanes 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]



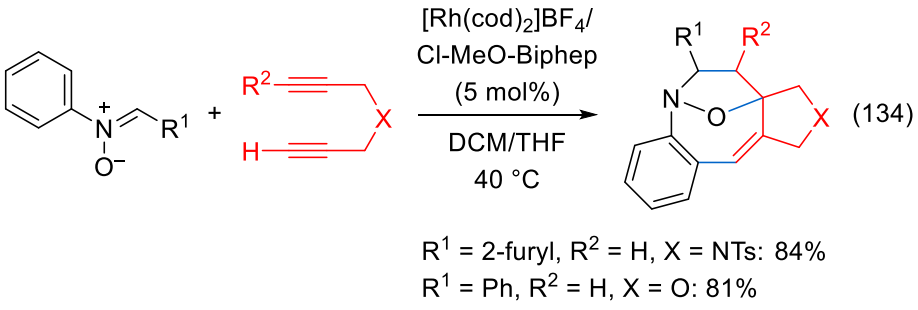




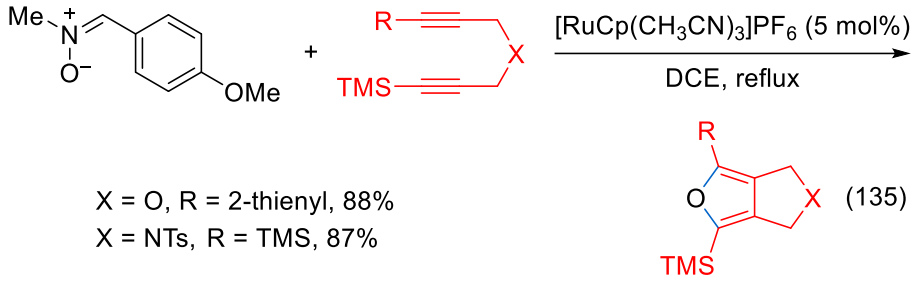
Gold-catalyzed cyclization/[2 + 2 + 3] cycloaddition cascade between nitrones and 1,6-enynes gives 1,2-oxazepane derivatives. (eq 133).[290] The importance of this reaction is the occurrence of 1,2-oxazepane moieties in several bioactive molecules.



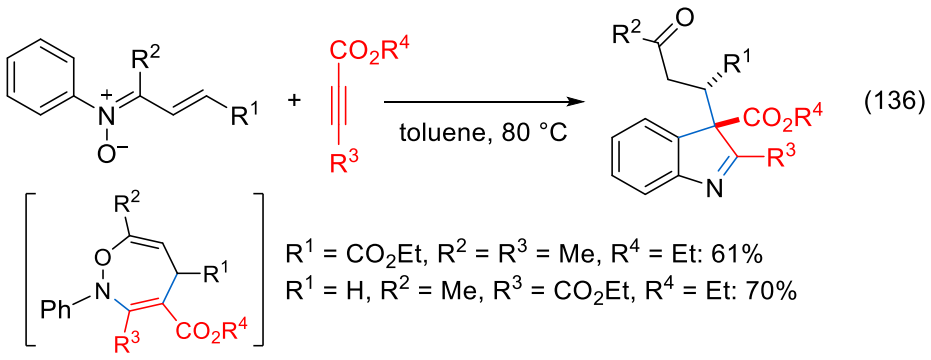
The rhodium-catalyzed reaction of *N*-aryl-substituted nitrones with diynes gives bridged eight-membered heterocycles. This reaction involves catalytic C—H activation of the *N*-aryl ring and [2 + 2 + 5] cycloaddition (eq 134).[291]



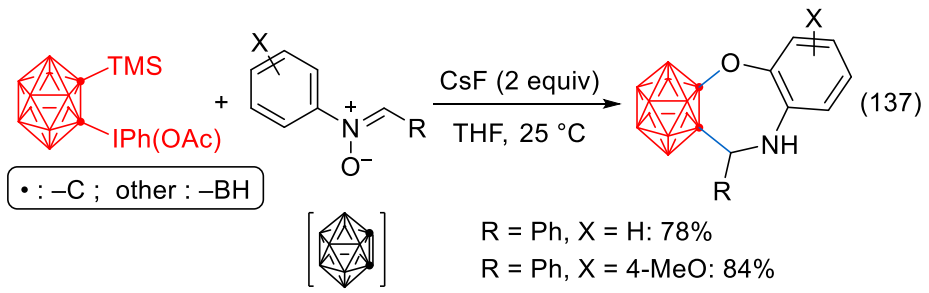
The ruthenium-catalyzed transfer oxygenative [2 + 2 + 1] cycloaddition of silyldiynes produces bicyclic 2-silylfurans. Nitrones are used as adjustable oxygen atom donors (eq 135).[292]



The reaction of α,β-unsaturated *N*-aryl ketonitrones with activated alkynes gives C3-quaternary inodolenines 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 nitrone moieties seem to serve as five-atom coupling partners.[294]

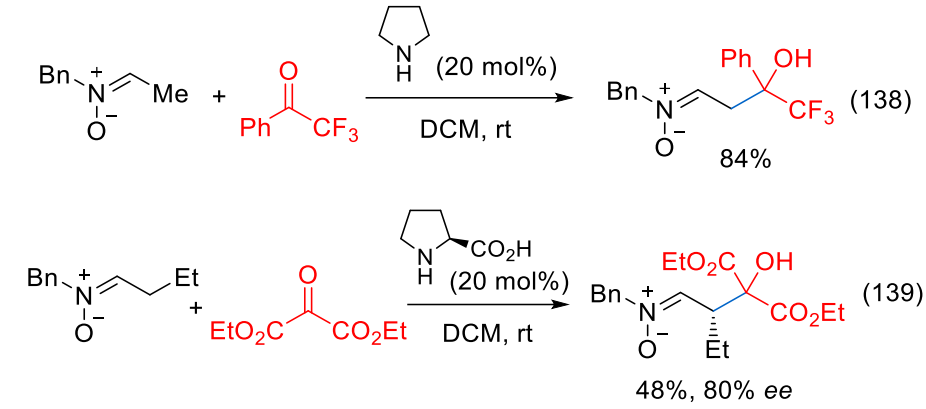


3.9. Other Reactions

3.9.1. Aldol-Type Reaction

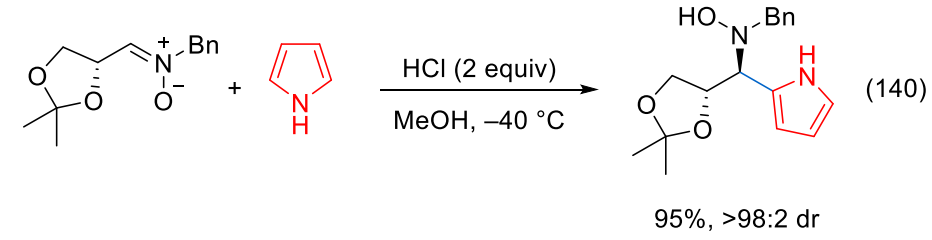
The aldol-type reaction of nitrones with carbonyl compounds gives functionalized β-hydroxynitrones. The α-carbon atom of the nitrone react with electron-deficient ketones (eq

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]



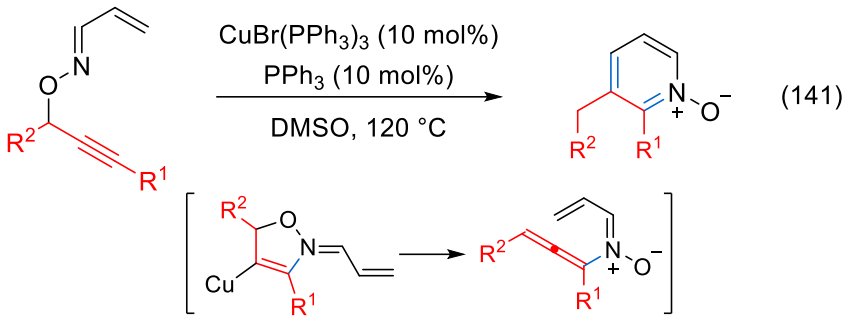
3.9.2. Friedel-Crafts-Type Reaction

Fridel-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]

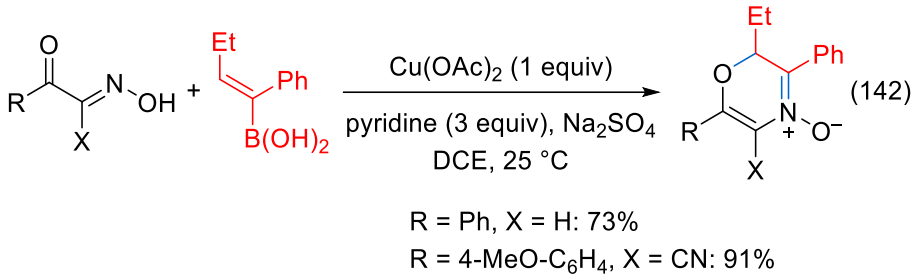


3.9.3. Electrocyclization Reaction

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*-allenylnitrones followed by 6π-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 electrocyclization 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]

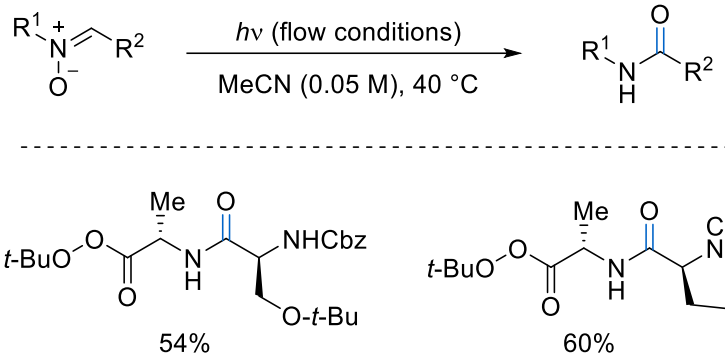


3.9.4. Rearrangement Reaction

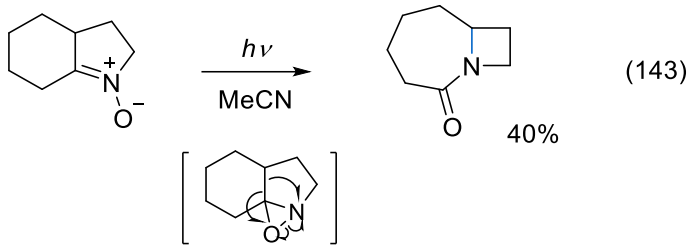
Photochemical rearrangements of nitrones to oxaziridines[303] and oxaziridines to amides[304] have been documented. However, there are only sporadic reports of photochemical rearrangement of nitrones to amides. Jamison and coworkers found a general and versatile approach for amide bond formation using 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

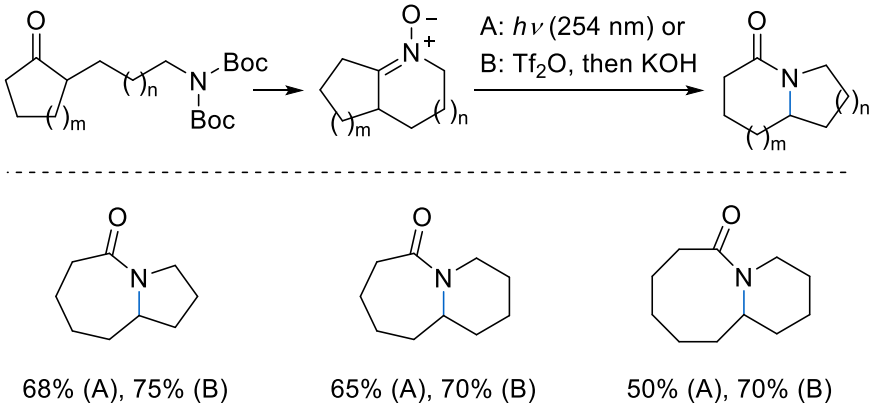


Photolysis of adequately substituted nitrones provides a convenient method for synthesis of fused bicyclic lactam scaffolds for mimicking conformationally constrained β-turn peptides as in the tripeptide RGD signaling motif of fibronectin. UV irradiation of 6/5-fused bicyclic nitrone gives the corresponding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

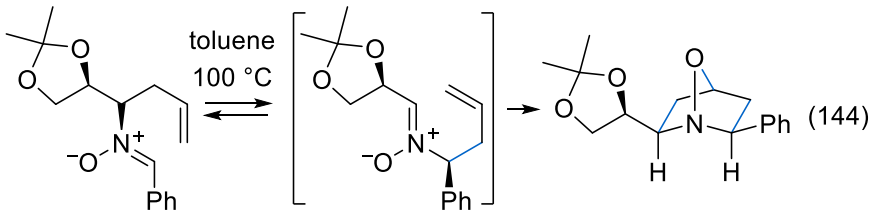


The rearrangement of nitrones to lactams can be carried out by photochemical activation or by treatment with Tf_2O followed by KOH-promoted rearrangement. Photochemical rearrangement of nitrones affords good yields of lactams. Two-step nonphotochemical process provides slightly better yields of the same targets (Scheme 28).[307]

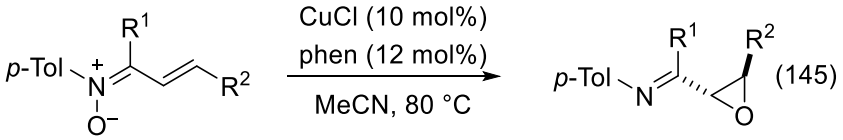
Scheme 28. Photochemical and Base-Induced Rearrangement of Fused Nitrones



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]



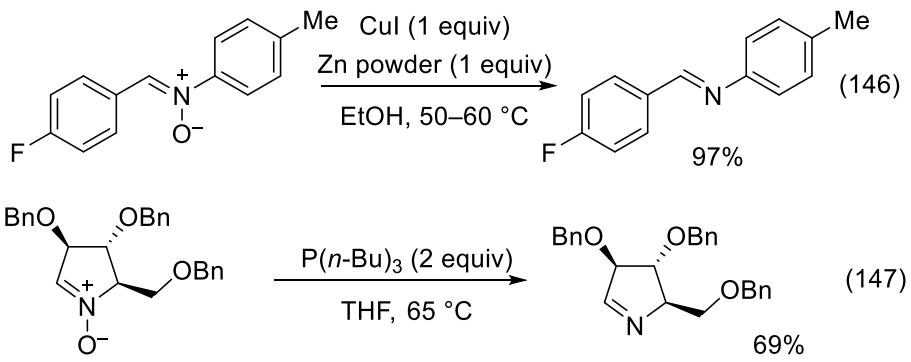
α,β-Epoxyketimines can be synthesized with excellent diastereoselectivity from α,β-unsaturated nitrones through a copper-catalyzed oxygen-atom transfer. This transformation is used in combination with a copper-catalyzed boric acid coupling for the preparation of α,β-unsaturated nitrones (eq 145).[309]



R^1 = Ph, R^2 = 4-MeO-C_6H_4: 97%
R^1 = 4-Br-C_6H_4, R^2 = 4-Cl-C_6H_4: 92%

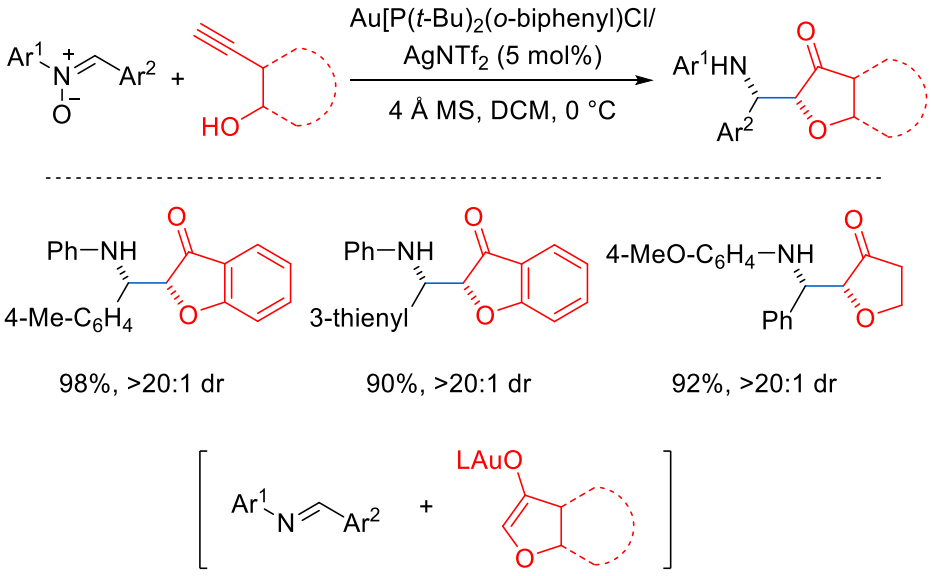
3.9.5. Reductive Deoxygenation of Nitrones to Imines

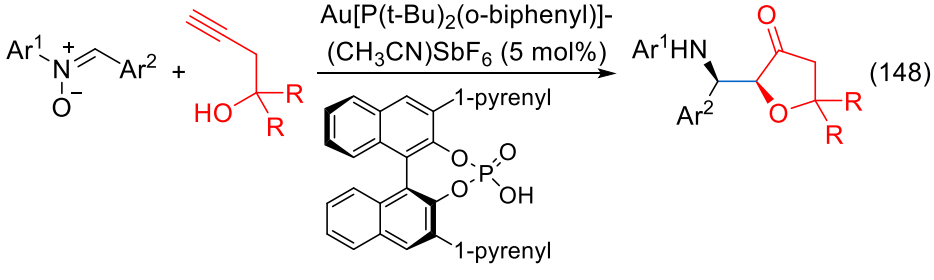
Deoxygenation of nitrones to imines is useful, and various methods have been developed. A mild and highly efficient deoxygenation of nitrones to imines is carried out upon treatment with CuI and Zn powder in ethanol (eq 146).[310] For the preparation of highly water-soluble imines, aqueous work-up should 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



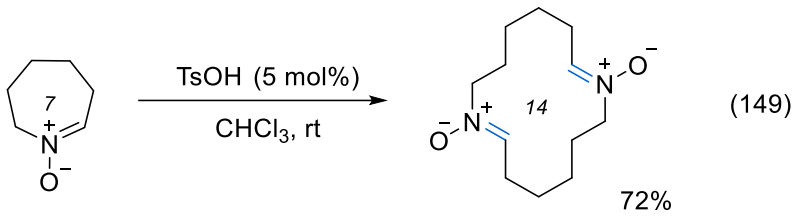


R = H, Ar^1 = C_6H_4-4-Cl, Ar^2 = C_6H_4-4-Br: 68%, 96% ee
R = Me, Ar^1 = Ar^2 = Ph: 50%, 84% ee

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. Nitrone 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.

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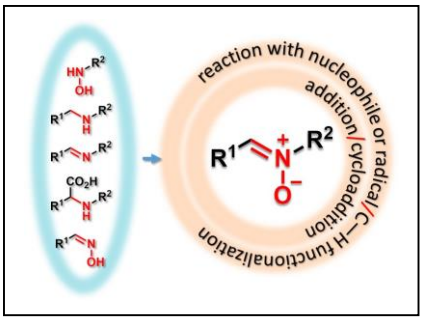
Yasushi Imada received his BEng (1981), MEng (1983) and Ph.D. (1991) degrees from Osaka University under the direction of Professor Shun-Ichi Murahashi. He worked with Professor Howard Alper at the University of Ottawa as a postdoctoral fellow (1995–1996). He joined Osaka University as an Assistant Professor 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



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