

Recent Advances in the Preparation of Optically Active Hydroxylamines from Nitrones

Rosa Matute,^a Sara García-Viñuales,^b Heather Hayes,^b Mattia Ghirardello,^b Andrea Darù,^b Tomas Tejero,^b Ignacio Delso^{b,c} and Pedro Merino^{*b}

^a Departamento de Ingeniería Química y Tecnologías del Medio Ambiente. Escuela Universitaria de Ingeniería Industrial. Edificio Torres Quevedo. Campus Actur. Zaragoza, Aragón, Spain.

^b Laboratorio de Síntesis Asimétrica. Departamento de Síntesis y Estructura de Biomoléculas. ISQCH. Universidad de Zaragoza. CSIC. Campus San Francisco. Zaragoza, Aragón, Spain.

^c Servicio de Resonancia Magnética Nuclear. CEQMA. Universidad de Zaragoza. CSIC. Campus San Francisco. Zaragoza, Aragón, Spain.

Phone: +34 876 553783. E-mail: pmerino@unizar.es

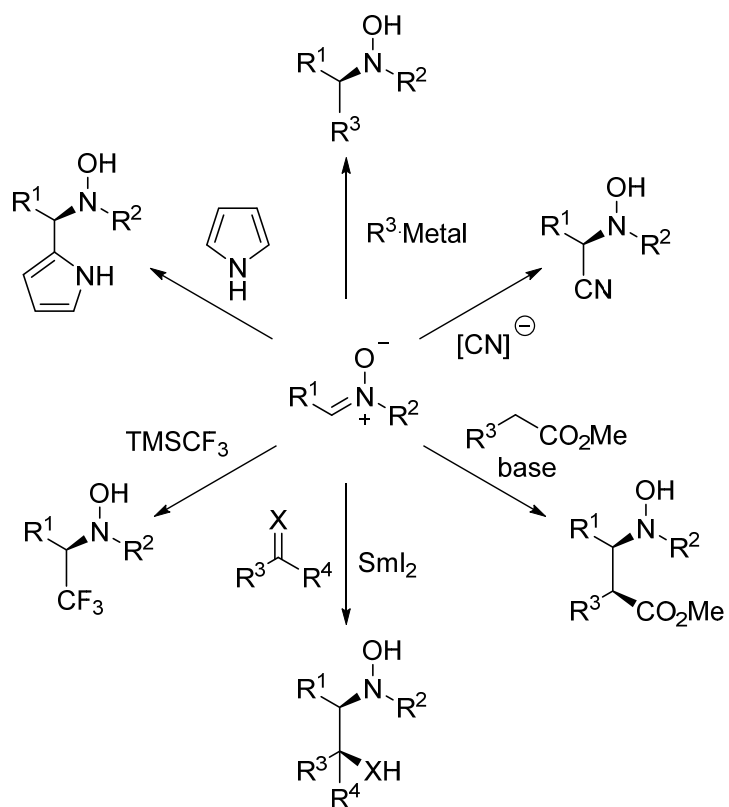
Abstract

This review covers the recent advances in the synthesis of enantiomerically pure hydroxylamines employing nitrones as starting materials. Nucleophilic additions of organometallic reagents to nitrones are the most common way for introducing a hydroxyamino group into carbon skeletons with the concomitant formation of a new carbon-carbon bond. Addition of carbanions derived from enolates, cyanide or fluorinated derivatives allow the preparation of complex structures. Radical additions and, in particular samarium diiodide-mediated reductive coupling of nitrones with carbonyl compounds and α,β -unsaturated esters have also been considered. All these approaches provide efficient methods of preparation of enantiomerically pure hydroxylamines that are valuable synthetic intermediates.

Keywords

Hydroxylamines; Nitrones; Organometallics; Mannich; Reductive coupling

Graphical Abstract



1. INTRODUCTION

Optically active hydroxylamines are important structural components of natural products with important biological properties,[1] which, in addition, are widely used in organic synthesis.[2] Therefore, a great amount of synthetic effort has been spent on the preparation of those compounds from simple starting materials.[3] Though several approaches to hydroxylamines, starting from oximes, [4] nitroso derivatives, [5] and α,β -unsaturated carbonyl compounds[6] have been developed, the use of nitrones as starting materials constitutes the most attractive and efficient alternative. Indeed, nucleophilic additions to nitrones leading to hydroxylamines, including hydride addition (reduction), have been known since the last century, their importance as synthetic reactions being noticed especially by Irvin[7] and Macaluso[8]. Since these early reviews, most new compilations have appeared with emphasis on the addition of organometallic compounds.[9] In 2000 we reviewed, for the first time, the use of chiral non-racemic nitrones in the preparation of enantiomerically pure hydroxylamines through nucleophilic additions[10] and later, we presented some of our own results in the field[11] including Mannich-type reactions[12] and application to the construction of nitrogenated heterocycles.[13] Thus, it is not intended to cover all aspects of stereoselective nucleophilic additions to nitrones but will restrict itself to the most recent studies.

Nitrones can also be used as substrates in radical additions, like samarium-promoted couplings,[14] providing organic structures in which several functional groups (i.e. amino, hydroxy, carbonyl, etc.) are also present in addition to the hydroxyamino moiety. A variety of *C*-nucleophiles, including cyanide, fluorinated substrates and heterocycles (through Friedel-Crafts reactions) can also be used for the synthesis of the target hydroxylamines. (Figure 1).

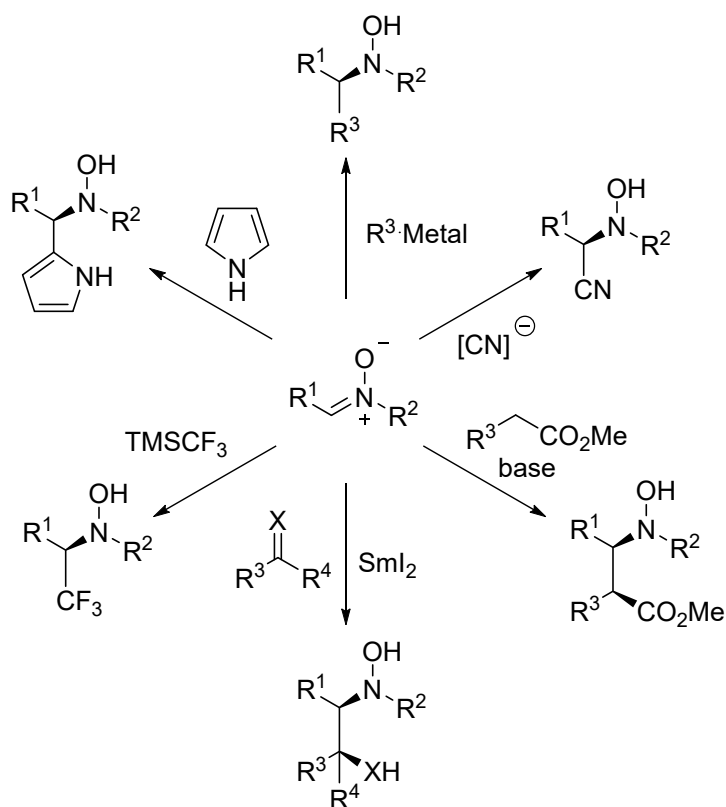


Figure 1. Synthesis of hydroxylamines from Nitrones

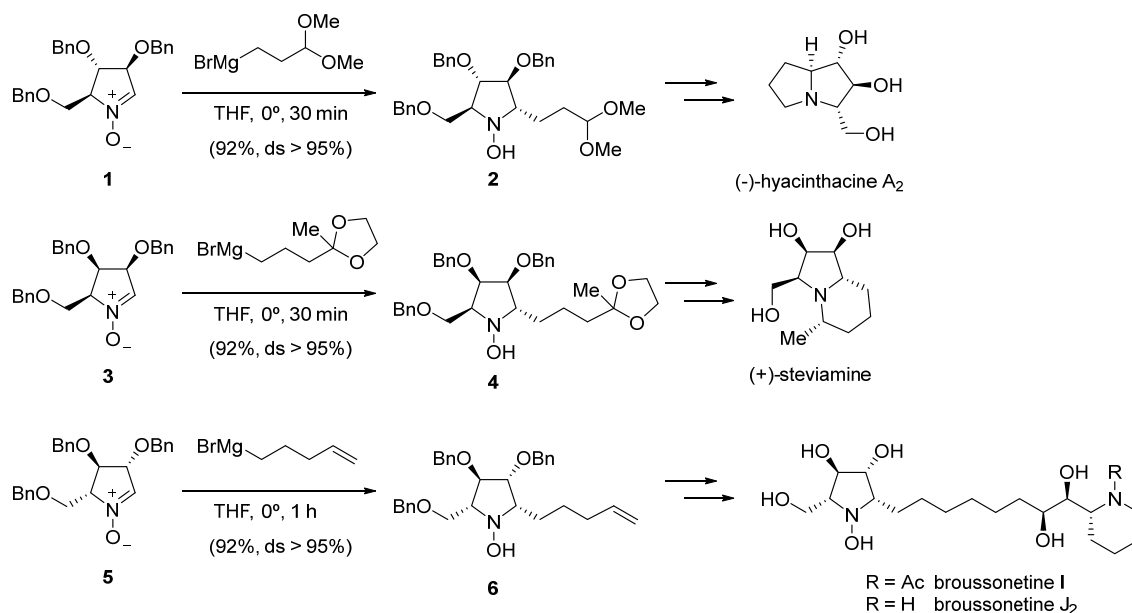
The scope of this review is to present the latest progress in the synthesis of optically active hydroxylamines using nitrones as starting materials in addition reactions in which a new carbon-carbon bond is created (reductions of nitrones are not covered). For the synthesis of nitrones, the reader should refer to recent comprehensive reviews.[15]

2. NUCLEOPHILIC ADDITIONS TO NITRONES

2.1. Organometallic Reagents

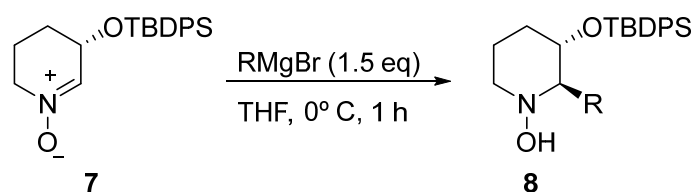
2.1.1. Grignard reagents

Much attention has been focused on the stereoselective addition of Grignard reagents to chiral non-racemic nitrones and a number of reports including alkyl, aryl, allyl and vinyl additions have appeared in the past few years. Nucleophilic addition reactions of alkyl Grignard reagents to diastereomeric cyclic nitrones **1**, **3** and **5** (the enantiomer of **1**) have been used for preparing a variety of alkaloids like (-)-hyacinthacine A₂,[16] (+)-steviamine[17] and brossusetines I and J₂. [18] In all cases, the Grignard reagent was prepared *in situ* and the reaction took place with excellent chemical yield and complete diastereoselectivity. The stereoselectivity is governed by the α -substituent to the nitrone carbon, the isomer corresponding to the attack by the opposite less hindered face being obtained (Scheme 1).



Scheme 1

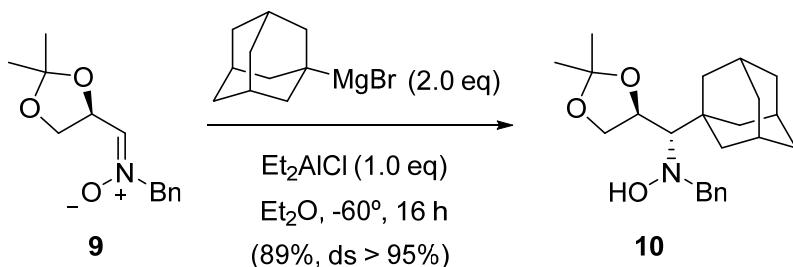
A variety of alkyl Grignard reagents (e.g. methyl, benzyl, isopropyl magnesium halides, etc.) added to polyhydroxylated cyclic nitrones of five,[19] six[20] and seven[21] members to provide the corresponding cyclic hydroxylamines in very good yields and selectivities. As an example, nitrone **7** reacted with alkyl Grignard reagents in a complete stereoselective fashion (Scheme 2).[22]



R	Yield (%)	ds (%)
Me	81	>95
Et	81	>95
<i>i</i> -Pr	73	>95
Bn	92	>95

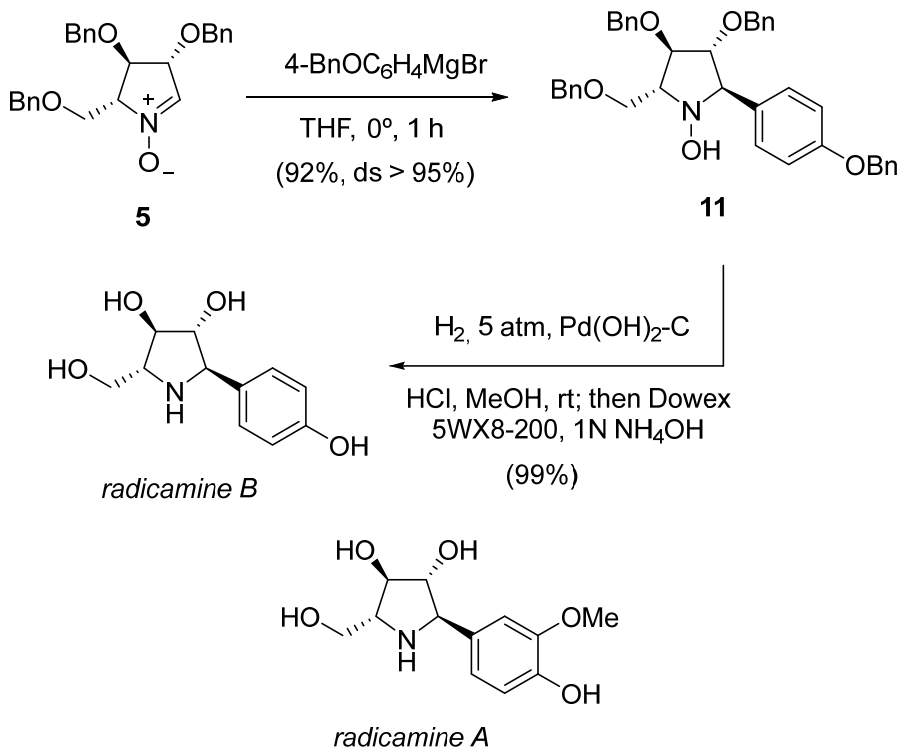
Scheme 2

With more hindered alkyl Grignard reagents excellent results were also obtained. Cyclopropyl magnesium bromide added quantitatively and with total selectivity to *C*-galactosyl-*N*-benzyl nitron. [23] On the other hand, the addition of adamantyl magnesium bromide to *D*-glyceraldehyde derived nitron **9** gave a 42:58 mixture of diastereomeric hydroxylamines in 52% yield. Upon addition of an equimolar amount of diethylaluminium chloride, following the methodology initially developed in our group, [24] the *anti* isomer **10** was obtained as the only product of the reaction (Scheme 3). [25] On the other hand, acyclic *C*-(trifluoromethyl)nitrones with chiral substituents at the nitron nitrogen underwent additions of Grignard reagents in very good yields but moderate selectivities. [26] Propargyl Grignard bromide led to mixtures of propargyl and allenyl derivatives as it was predicted by theoretical calculations; [27] however, when the alkyne was substituted at the terminal position only propargyl derivatives were obtained.



Scheme 3

The addition of aryl Grignard reagents has mainly been focused on the preparation of radicamines A and B, two polyhydroxylated pyrrolidines isolated from natural sources. [28] The addition of the corresponding aryl Grignard reagent to nitron **5**, easily available from *D*-arabinose, provided cyclic hydroxylamine **11**, which was used as an advanced intermediate in the synthesis of Radicamine B (Scheme 4). [29]

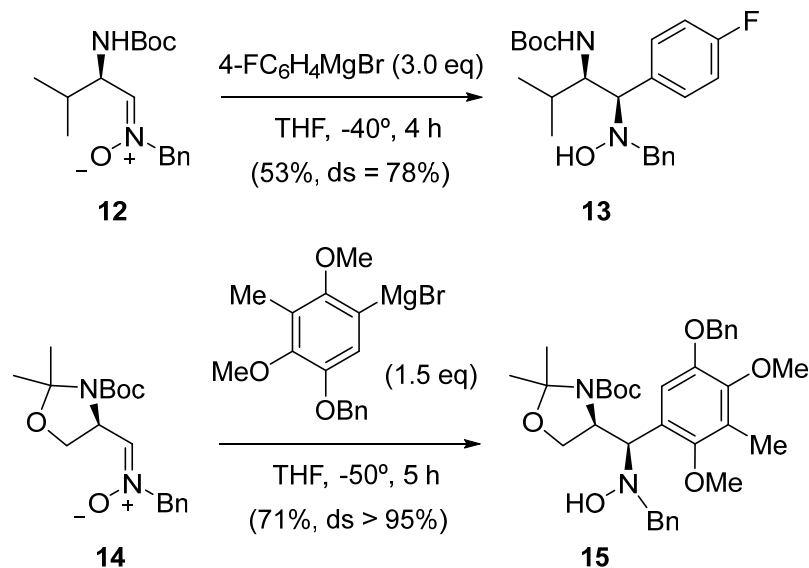


Scheme 4

Actually, only Radicamine B has been prepared in the correct enantiomeric form. [19a] Starting from nitron **1**, derived from *D*-xylose, the corresponding enantiomers of both Radicamine A and B have been

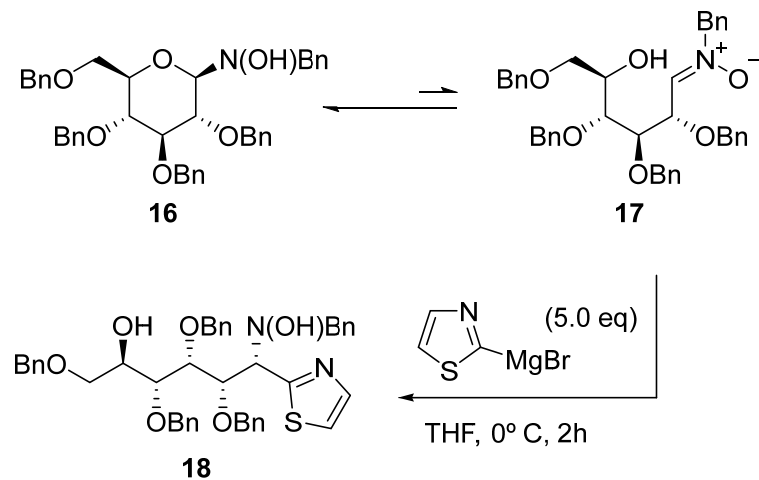
prepared.[30] A library of radicamine analogues has also been synthesized following the same approach.[31]

The addition of 4-fluorophenylmagnesium bromide to acyclic α -amino nitrone **12** afforded hydroxylamine **13** in 53% yield and moderate selectivity. This compound was used in the preparation of diamine ligands used in cytotoxic platinum(II) complexes with antitumoral activity. [32] The stereoselective synthesis of diamines from α -amino nitrones through the addition of Grignard reagents had been previously reported in our group.[33] The addition of a highly substituted aryl Grignard reagent to the serine-derived nitrone **14** gave rise to hydroxylamine **15** with complete *syn* selectivity (Scheme 5).[34]



Scheme 5

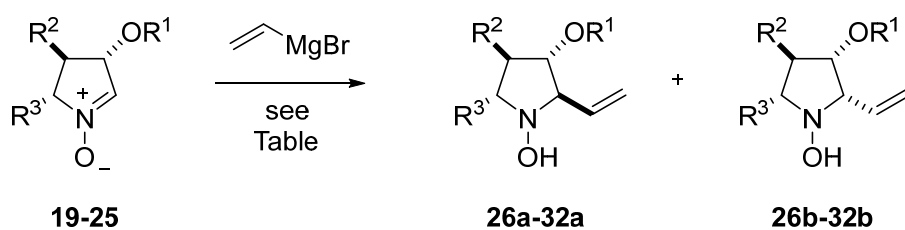
N-glycosyl hydroxylamines are actually masked nitrones.[35] Those derived from pyranoses underwent addition of thiazolylmagnesium bromide to give open-chain α -(2-thiazolyl) hydroxylamines (Scheme 6).[36] The addition of a second Grignard reagent was possible by applying a sequential addition-oxidation-addition protocol.[37] Starting from *N*-glycosyl nitrones, easily accessible from the parent *N*-glycosyl hydroxylamines, and using 3.0 equivalents of Grignard reagent allowed a double addition, but mixtures of diastereomers were obtained.[38] These protocols were applicable for any sort of Grignard reagent, i.e. alkyl, (het)aryl, allyl, vinyl, and ethynyl.



Scheme 6

The addition of vinylmagnesium bromide to polyhydroxylated cyclic nitrones was the starting point for the synthesis of variety of alkaloids such as 4-azatriquinanes,[39] DMDP,[40] hyacinthacine A₂ [41]and (+)-lentiginosine,[42]and other substituted polyhydroxylated pyrrolidines with biological activity as chaperones for Gaucher disease.[43]

In general, the addition took place with excellent trans-selectivity with respect to the substituent placed at α -position of the nitron carbon to form the corresponding *N*-hydroxypyrrolidines **26a-32a** (Scheme 7). When the reaction was carried out in the presence of a Lewis acid such as diethylaluminium chloride (DEAC), an anomalous behaviour was observed[44] and whereas a high selectivity was obtained even at 0°C, in the presence of DEAC, a trend to invert the stereochemical course of the reaction was observed at lower temperatures (Scheme 7, Table 1).[45] This behavior and difference in selectivity was due to the high conformational barriers of the initially formed complex between nitron, DEAC and vinylmagnesium bromide.[45]



nitron	hydroxylamine	R ¹	R ²	R ³
19	26	Bn	OBn	H
20	27	^t Bu	H	H
21	28	MOM	H	H
22	29	Bn	H	H
23	30	Me	H	H
24	31	^t Bu	O ^t Bu	H
25	32	Bn	OBn	CH ₂ OBn

Scheme 7

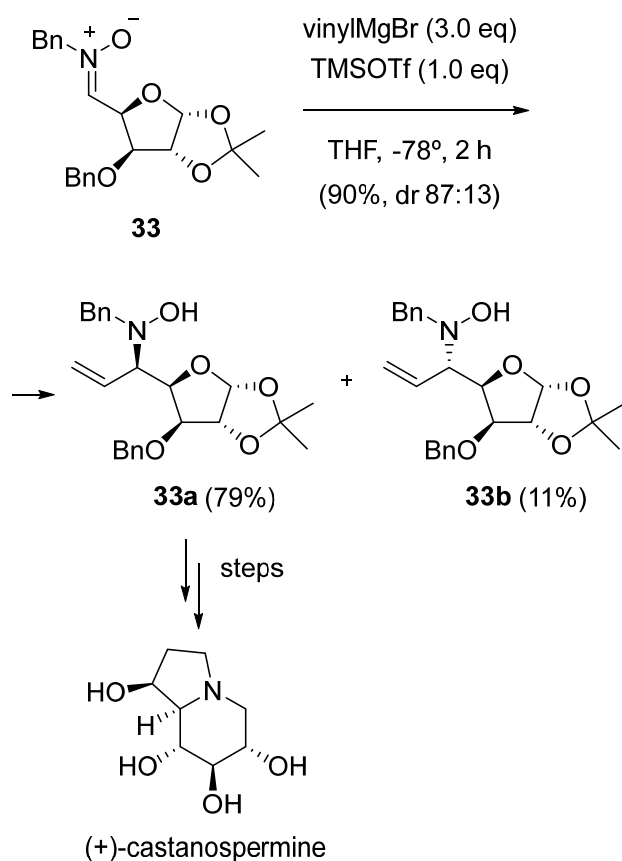
Table 1. Nucleophilic addition of vinylmagnesium bromide to nitrones **19-25**

e ntry	nitron	T(°C)	without DEAC			with DEAC (1.0 eq)			ref.
			t (h)	a:b	yield	t (h)	a:b	yield	
1	11	0	1	93 : 7	90	n.g.	93 : 7	n.g.	[44]
2	11	-30	4	93 : 7	90	n.g.	86 : 14	n.g.	[44]
3	11	-78	1 2	93 : 7	90	n.g.	55 : 45	n.g.	[44]
4	12	0	1	>98 : 2	quant.	4	>98 : 2	quant.	[45]
5	12	-30	4	>98 : 2	quant.	12	>98 : 2	91	[45]
6	12	-78	1 2	>98 : 2	quant.	48	>98 : 2	96	[45]
7	13	0	1	88 :	96	3	92 : 8	qua	[45]

				12				nt.	
8	13	- 30	4	87 : 13	90	10	65 : 35	93	[45]
9	13	- 78	1 2	89 : 11	92	36	52 : 48	90	[45]
1 0	14	0	1	88 : 12	qua nt.	3	87 : 13	96	[45]
1 1	14	- 30	4	91 : 9	94	10	70 : 30	94	[45]
1 2	14	- 78	1 2	93 : 7	93	36	31 : 69	92	[45]
1 3	15	0	1	55 : 45	96	36	92 : 8	93	[45]
1 4	15	- 30	4	60 : 40	94	2	56 : 44	92	[45]
1 5	15	- 78	1 2	67 : 33	90	8	55 : 45	88	[45]
1 6	16	0	1	>98 : 2	92	24	14 : 86	86	[45]
1 7	16	- 30	4	>98 : 2	93	4	>98 : 2	90	[45]
1 8	16	- 78	1 2	>98 : 2	91	12	>98 : 2	91	[45]
1 9	17	0	1	87 : 13	qua nt.	48	>98 : 2	91	[45]
2 0	17	- 30	4	89 : 11	94	3	93 : 7	98	[45]
2 1	17	- 78	1 2	91 : 9	96	10	70 : 30	96	[45]
2 2	17	0	1	>98 : 2	qua nt.	36	55 : 45	91	[45]

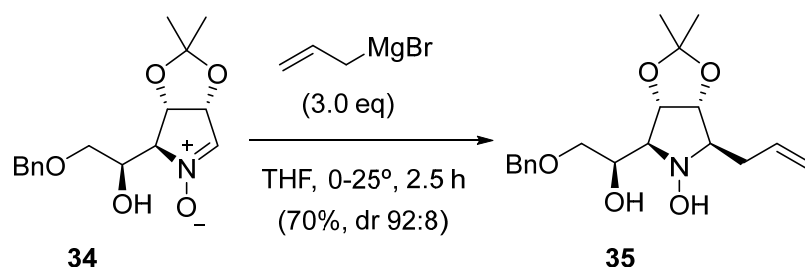
n.g.: not given

The addition of vinylmagnesium bromide to acyclic *C*-furanosyl *N*-benzyl nitrones took place with good selectivity[46] to provide hydroxylamines which have been used as advanced intermediates in the synthesis of castanospermine,[47] uniflorine A[48] and derivatives of calystegine B₂. [49] The selectivity could be enhanced by activating the nitrone with TMSOTf and carrying out the reaction at -78°C (Scheme 8).



Scheme 8

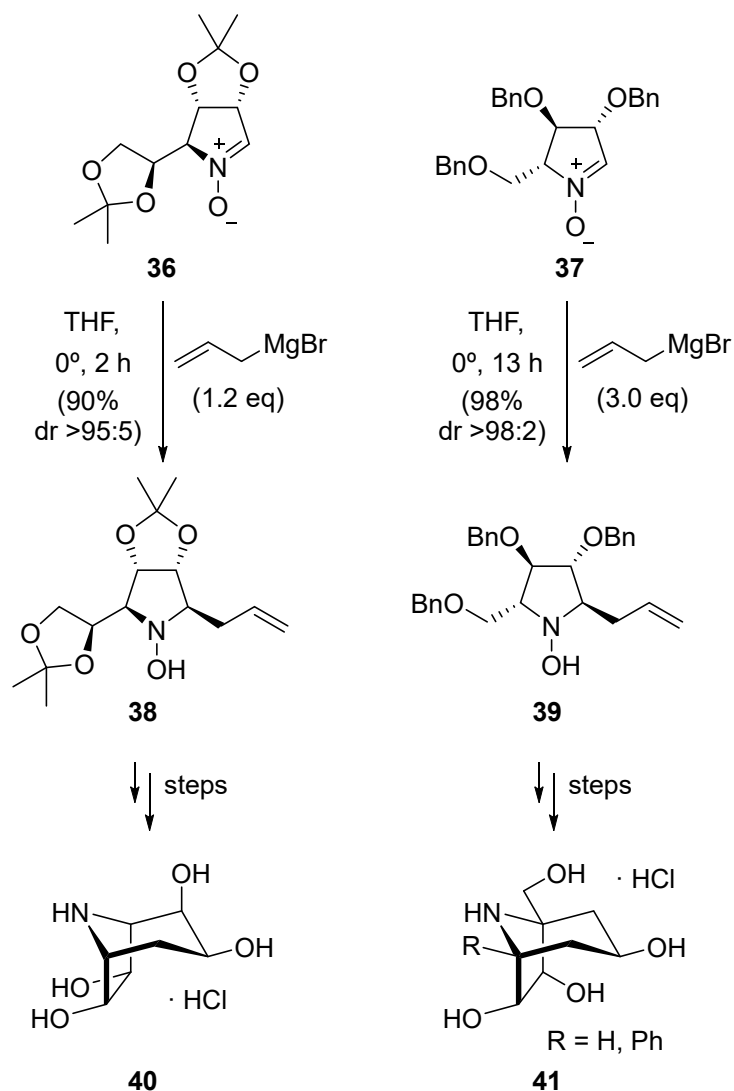
The addition of allylmagnesium bromide to chiral non-racemic acyclic nitrones took place with lower selectivity for both aldo-[50] and ketonitrones,[51] presumably because of the possibility of α - and γ -addition. In the case of *C*-glycosyl nitrones some differences in the selectivity was achieved by carrying out the reaction in the presence of Lewis acids as additives but a general behaviour could not be deduced.[52] It was the sugar residue at the nitrone carbon which mainly governed the stereochemical induction. Again, for nitrone **33** an enhancement of the diastereoselectivity was observed by activating the nitrone with TMSOTf which allowed to perform the reaction at -78°C;[53] otherwise, the reaction needed to be conducted at higher temperatures and lower selectivities were observed. Cyclic nitrone **34** showed a higher selectivity leading to hydroxylamine **35** in 70% and 92% ds (Scheme 9).[54]



Scheme 9

The addition of allylmagnesium bromide to cyclic nitrones **36** and **37** has been used in the synthesis of calystegines [55] and closely related nortropane alkaloids [56]. In these cases, excellent selectivities were observed with the employed substrates (Scheme 10); in general very good diastereofacial selectivities

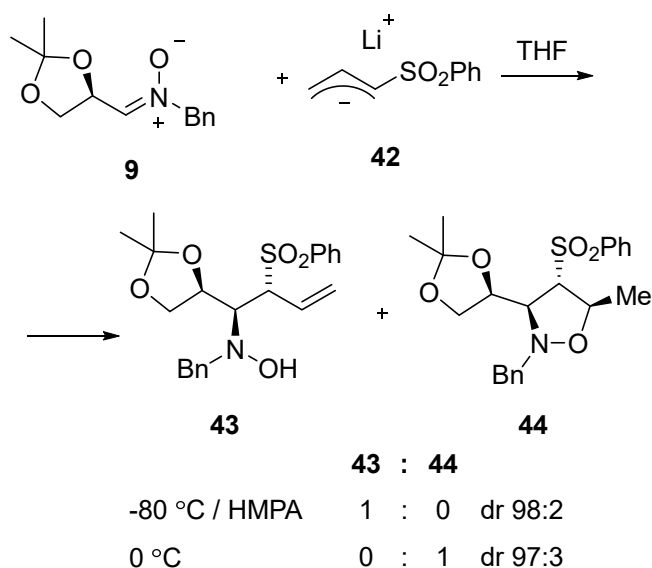
were obtained in the allylation of ppolyhydroxylated cyclic nitrones.[57] Hydroxylamine **39** has also been employed in the synthesis of iminosugars inhibitors of trehalase.[58]



Scheme 10

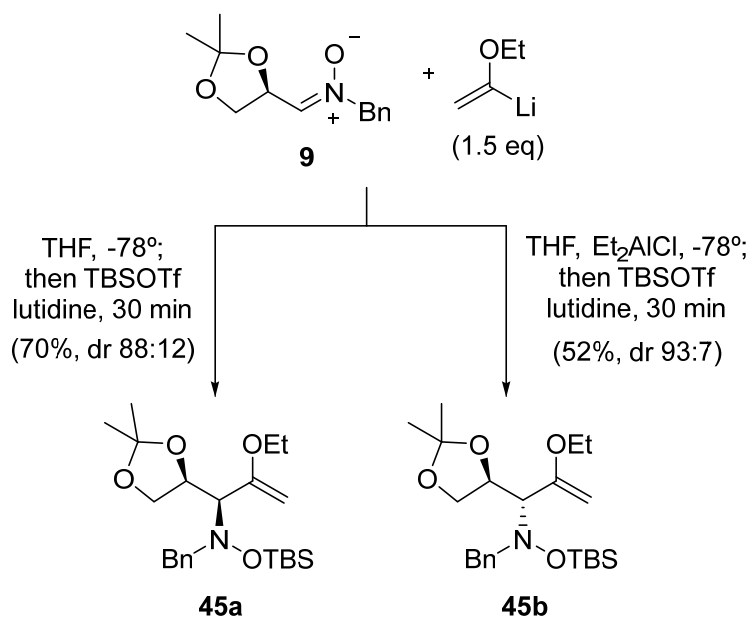
2.1.2. Organolithium compounds

The addition of allyllithium has been used as an alternative to the addition of the Grignard reagent when low selectivities are obtained with the latter. In general, the use of the lithium derivative afforded higher selectivities, particularly when Lewis acids were employed as additives.[50] The allylsulfonylation of nitrone **42** at -80°C and in the presence of HMPA afforded hydroxylamine **43** in an excellent diastereoselectivity. At higher temperature and in the absence of HMPA, only isoxazolidine **44** was obtained. The formation of compound **44** was explained on the basis of double bond isomerization in **43** to form a vinylsulfone followed by an intramolecular Michael addition (Scheme 11). [59]



Scheme 11

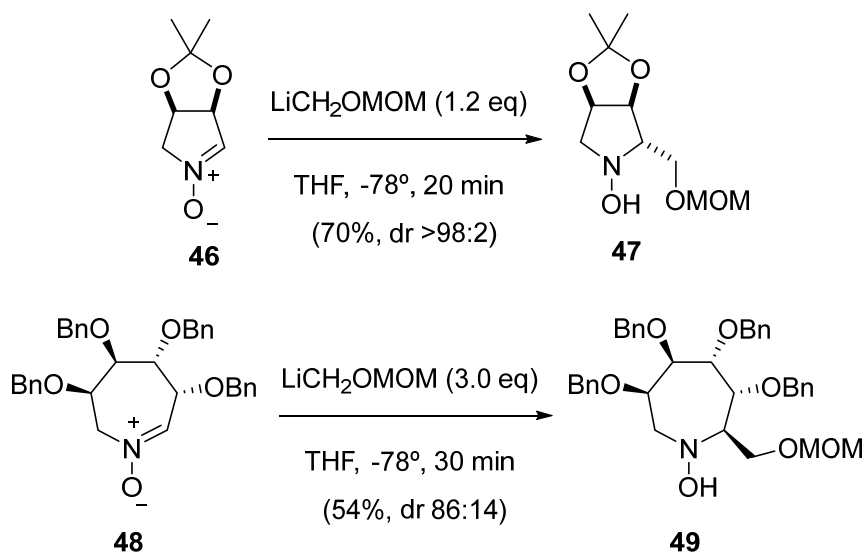
Alkyl and aryl organolithium compounds added to nitrones with good yields at -80°C.[26] In the case of acyclic α -alkoxy nitrones the selectivity could be modulated by the use of Lewis acids as additives.[51] Vinyl lithium derivatives, including lithiated enol ethers added to nitron **42** in a complete sterecontrolled way depending on the use of Lewis acids[60] as previously reported (Scheme 12).[10]



Scheme 12

Lithium α -diazoacetates underwent nucleophilic addition to **42** with moderate selectivity (dr 3:1). Similar results were observed with *C*-furanosyl nitrones (dr 3:2).[61] On the other hand, the addition to cyclic nitrones proceeded quantitatively and with complete selectivity, only one isomer being isolated from the reaction mixture.[62] The addition of a lithiated purine to cyclic nitrones also proceeded with total selectivity. The resulting hydroxylamine was used for the preparation of analogs of forodesine, a human purine nucleoside phosphorylase inhibitor.[63] The total synthesis of (-)-hyacinthacine C₅ and its epimers at C6 and C7 was achieved by means of a nucleophilic addition of a dithiane to a cyclic nitron followed by a Cope-House cyclization as a key step.[64] Polyhydroxylated pyrrolidines were prepared in quantitative yield and complete diastereofacial selectivity through the addition of the Still's reagent[65] (a

carbinyl carbanion) to polyhydroxylated five-membered cyclic nitrones like **46** (Scheme 13).[19a,66] The same reaction was done with azepane nitron **47** to give hydroxylamine **48** but with moderate yield and selectivity.[21]

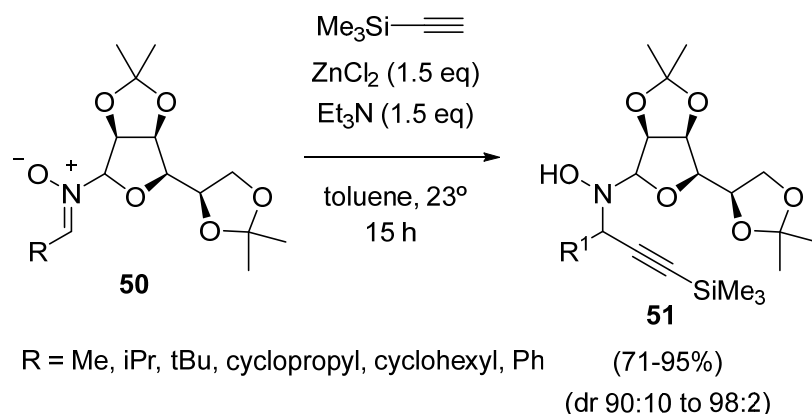


Scheme 13

Polysubstituted β,γ -epoxyhydroxylamines are easily accessible by means of the addition of α -lithiated aryloxiranes. The reaction proceeded with good yields and selectivities (Scheme 13).[67] The resulting hydroxylamines **48** were easily transformed into 1,2-oxazetidines through a basic treatment. By using more complex substrates spirocyclic compounds were also accessible.[68]

2.1.3. Organozinc derivatives

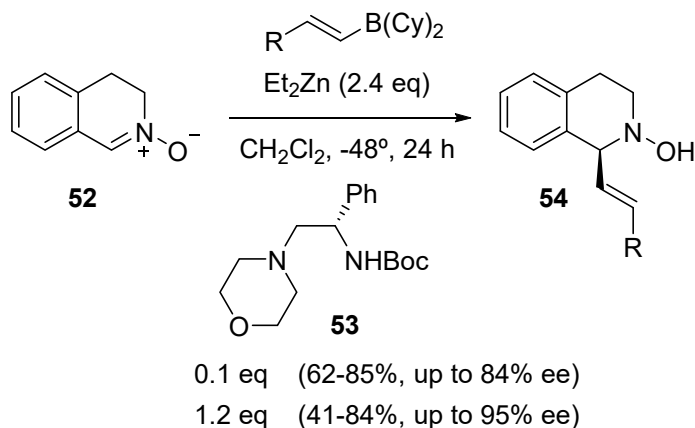
Enantioselective alkynylations of *N*-glycosyl nitrones by alkynylzinc reagents formed *in situ* afforded the corresponding hydroxylamines in very good yields and excellent diastereomeric ratios (Scheme 14).[69] This methodology was amenable to be used for the preparation of disaccharide mimics.[70]



Scheme 14

Asymmetric addition of diphenylzinc to *C*-alkynyl nitrones to afford optically pure hydroxylamines was achieved by using di(*t*-butyl) (*R,R*)-tartrate as a chiral auxiliary. By employing a mixed zinc reagent, PhZnMe, the enantioselection increased up to 92% ee.[71] Boron derivatives are good precursors of arylzinc reagents. Thus, the diethylzinc-mediated addition of alkoxyboronates to chiral nitrones afforded

hydroxylamines in high diastereomeric ratios.[71] The reaction could also be promoted by chiral ligands (used in an excess of 1.3 eq) to give enantioselectivities up to 97-99%ee.[72] An enantioselective addition of substituted vinylzinc reagents (also prepared from the corresponding boranes) was achieved by using ligand **53**. While 0.1 eq of ligand afforded 84% ee, the use of 1.2 eq gave rise to an enhanced enantioselectivity of 95% (Scheme 15).[73]

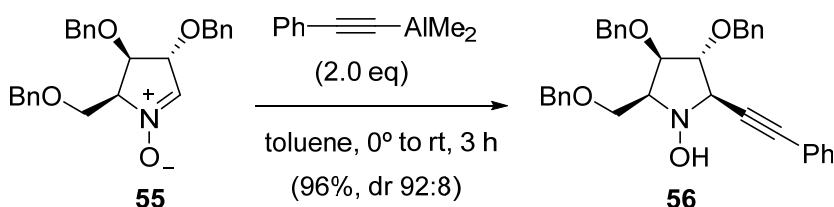


R = tBu, nBu, cyclopropyl, cyclohexyl, Ph, $PhCH_2CH_2$, 4-MeOC₆H₄

Scheme 15

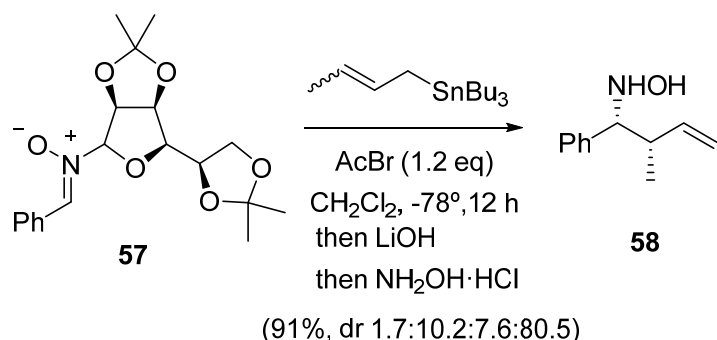
2.1.4. Other organometallic compounds

The direct ethynylation of cyclic nitrones with organoaluminium reagents (alanes) provided the corresponding hydroxylamines with high diastereoselectivity, the best results being obtained with 2.0 equivalents of organometallic derivative (Scheme 16).[74] The addition of either an excess of alane or DEAC as additive caused a notable decreasing of the diastereoselectivity (from 92% to 65%), presumably due to the same effect observed for the addition of vinylmagnesium bromide.[75]



Scheme 16

Allyltin added smoothly to chiral nitrones when activated with a Lewis acid such as boron trifluoride etherate and trimethylsilyl triflate, best selectivities being obtained with the former.[50a] The addition of substituted allyltin derivatives in the presence of acetyl bromide took place at α -position without migration of the double bond (Scheme 17).[76]



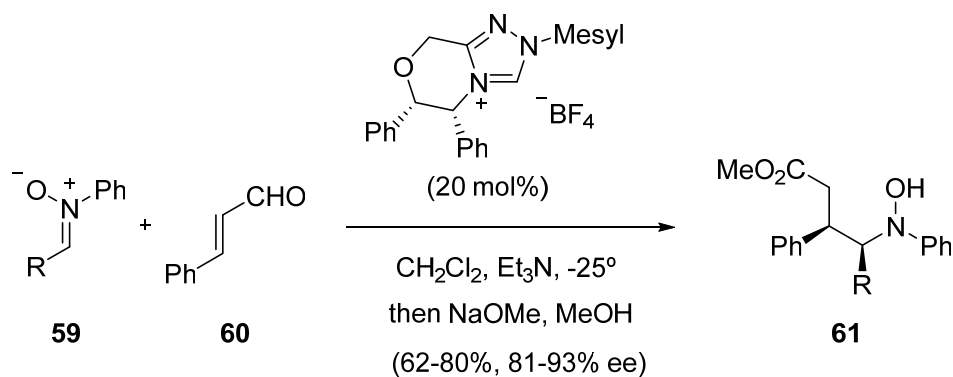
Scheme 17

2.2. Carbanions

2.2.1. Enolates (Mannich-type reactions) and related compounds

The addition of enolates to nitrones has been recently reviewed[77] and the reader is referred to such a report for publications prior to 2011. Very recently, the mechanism of the Mannich reactions with nitrones has been elucidated[78] and it is observed a change of mechanism from stepwise to concerted (actually, one kinetic step but two stages) on passing from α -substituted enolates (derived from esters and ketones) to α -unsubstituted enolates (derived from aldehydes). Thus, the reaction between nitrones and enolates derived from aldehydes, unreported until now, is predicted to be concerted in a rather similar way to that between nitrones and lithium ynoates.[79]

Highly diastereo- and enantioselective additions of homoenolates to nitrones have been achieved under organocatalysis with *N*-heterocyclic carbenes. The reaction, a formal [3+3] cycloaddition, gave rise γ -hydroxyamino ester derivatives after treatment with methanol (Scheme 18).[80] Application of this methodology to cyclic nitrones lead to the synthesis of polyhydroxylated pyrrolizidines and indolizidines.[81]

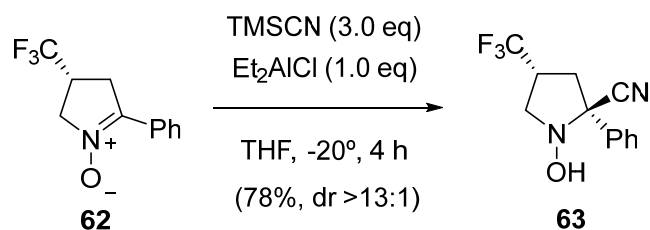


R = Ph, 4-MeC₆H₄, 4-MeOC₆H₄, 4-BrC₆H₄, 2-naphthyl

Scheme 18

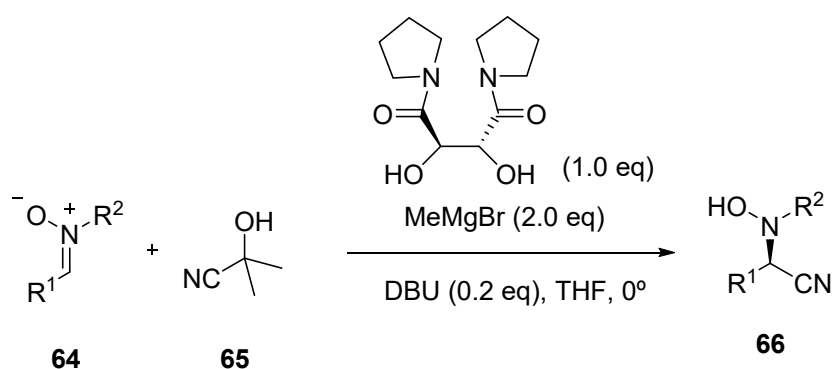
2.2.2. Cyanides (Hydrocyanation)

The stereoselective hydrocyanation of nitrones is known since 1995.[82] More recently, the hydrocyanation of polyhydroxylated five-membered cyclic nitrones has been used for preparing enantiopure 2-aminomethyl pyrrolidines of synthetic and biological interest[19a,66] such as nitrogenated analogues of glycosidase inhibitor DMDP[83] and stereoisomers of pochonicine inhibitors of β -*N*-acetylhexosaminidases. [84] The addition of trimethylsilylcyanide to cyclic ketonitrones provided an entry to pyrrolidines bearing quaternary centers (Scheme 19).[85]



Scheme 19

A magnesium-tartramide complex promoted the asymmetric hydrocyanation reaction of nitrones using acetone cyanohydrin as a source of cyanide. A catalytic amount of base was required and the chiral promoter should be used in stoichiometric amounts; very good enantioselectivities were observed for both C-alkyl and C-aryl nitrones (Scheme 20, Table 2). [86]



Scheme 20

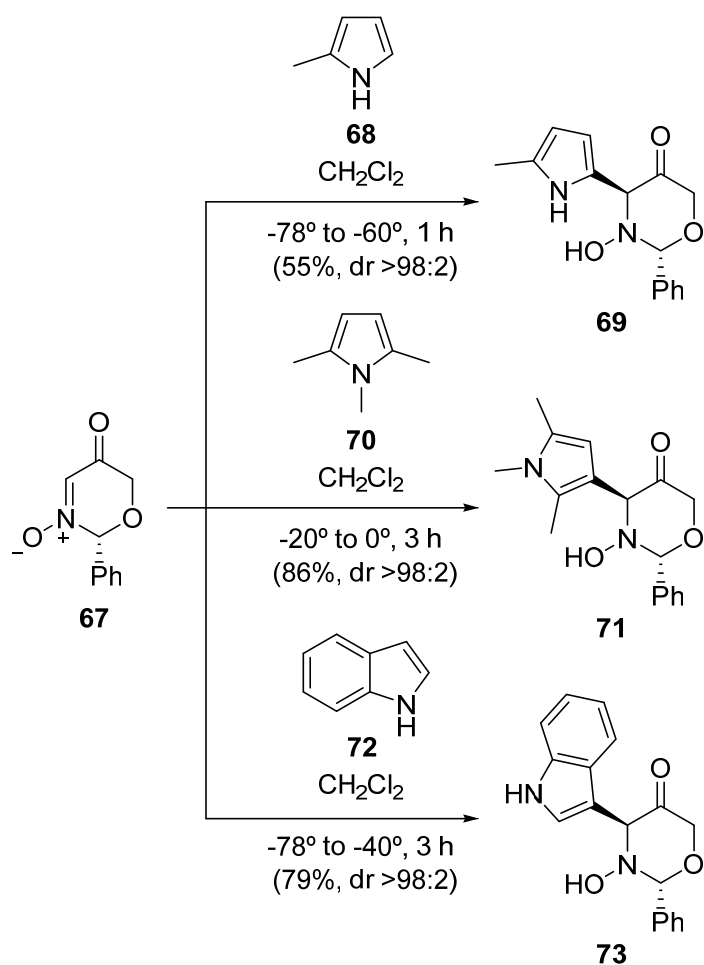
Table 2. Asymmetric hydrocyanation of nitrones (Scheme 20). [86]

entry	R ¹	R ²	t(h)	yield (%)	ee (%)
1	Ph	Bn	22	80	89
2	Ph	Me	21	47	72
3	Ph	Ph	21	6	63
4	Ph	Ph ₂ CH	21	58	96
5	4-MeOC ₆ H ₄	Bn	21	72	90
6	4-ClC ₆ H ₄	Bn	21	75	96
7	4-BrC ₆ H ₄	Bn	23	63	96
8	1-naphthyl	Bn	41	89	85
9	2-naphthyl	Bn	41	73	96
10	Me	Bn	4	95	79
11	Me	Ph ₂ CH	2	94	97

1 2	cyclohexy l	Bn	6	97	73
1 3	cyclohexy l	Ph ₂ CH	21	87	90
1 4	tBu	Bn	22	90	87
1 5	tBu	Ph ₂ CH	21	88	93

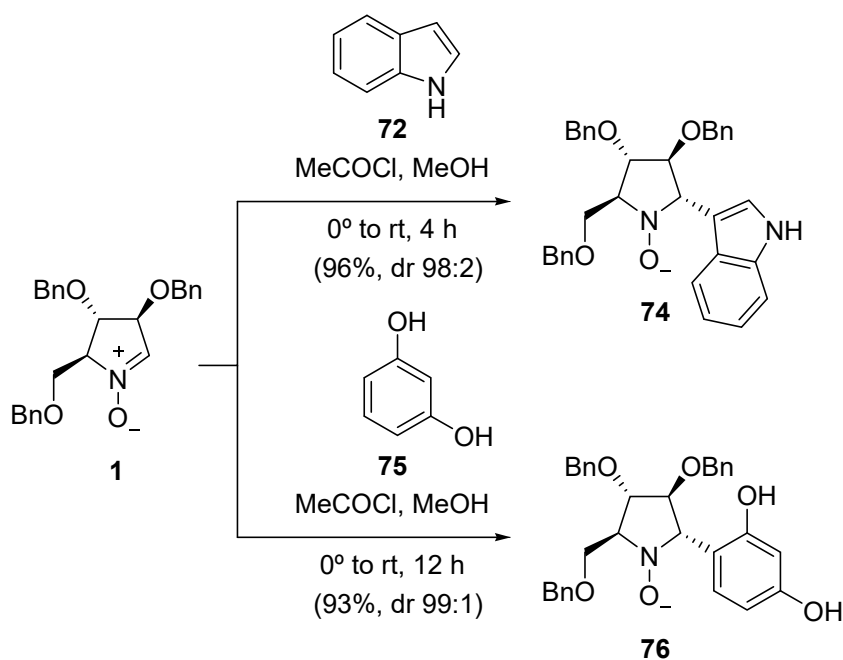
2.2.3. Heterocycles (Friedel-Crafts reaction)

Nitrones react with electron-rich aromatics in a typical Friedel-Crafts reaction, firstly reported in 1982[87] and further investigated by Vallee and co-workers. [88] The addition of pyrrole **68** onto the chiral cyclic nitrone **67**, promoted by hydrochloric acid, provided hydroxylamine **69** as the unique regio- and diastereoisomer. According to the expected reactivity for the heterocyclic nucleus, the addition to pyrrole took place at C-2. On the other hand, when such a position is occupied, as in **70**, the addition required higher temperature and it took place at C-3, hydroxylamine **71** being obtained. The reaction with indole **72** also occurred at C-3 in good agreement with the expected reactivity giving rise to hydroxylamine **73** (Scheme 21).[89] In the case of the reaction with *N*-triisopropylpyrrole treatment with MeOH *in situ* provided the corresponding open-chain α -hydroxyamino ester [90]



Scheme 22

The reaction proceeds via the activated nitron (becoming an electrophilic *N*-oxyiminium ion) and it can also be extended to cyclic nitrones and indole; in this case the addition took place at C-3 of the heterocyclic system. Activation of the nitron was carried out with acetyl chloride and very good diastereomeric ratios were obtained in agreement with an attack by the less hindered face of the nitron. The reaction with electron-rich benzene rings is also possible. As an example, Scheme 23 illustrates the reaction of nitron **1** with indole **70** and 3,5-dihydroxybenzene **72**.^[91]

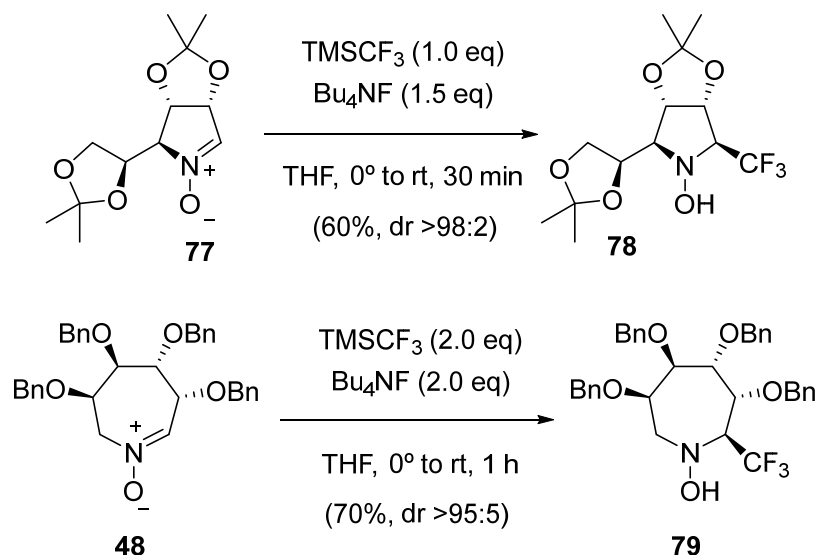


Scheme 23

Activation of the reaction can also be exerted by microwave irradiation. Under these conditions pyrroles and indoles added with good chemical yields and excellent diastereoselectivities. ^[92]

2.2.4. Fluorinated nucleophiles

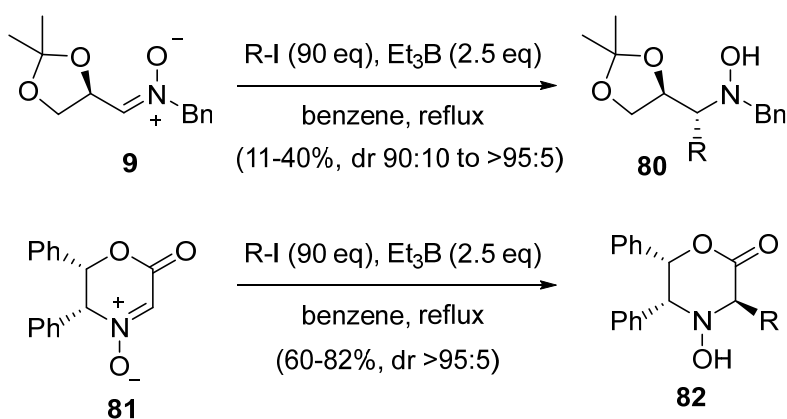
Trifluoromethylated analogues of polyhydroxylated alkaloids can easily be prepared by the nucleophilic addition of trimethyl(trifluoromethyl)silane to sugar-derived cyclic nitrones. Complete diastereoselectivities have been observed for both five-^[93] and seven-membered^[21] cyclic nitrones (Scheme 24). In a similar way, the difluoro(phenylsulfanyl)methyl group, generated *in situ* from PhSCF₂SiMe, could be added to cyclic nitrones with high diastereoselectivity.^[94]



Scheme 24

3. Radical Reactions

Nitrones are excellent radical acceptors for carbon-carbon forming bond radical reactions. Several types of nitrones including cyclic and acyclic ones underwent radical additions with good diastereoselectivities (Scheme 25). [95] However, whereas low yields were observed for D-glyceraldehyde-derived nitrone **9**, nitrone **81** showed higher reactivity. In all cases some by-products were obtained in minor amounts.

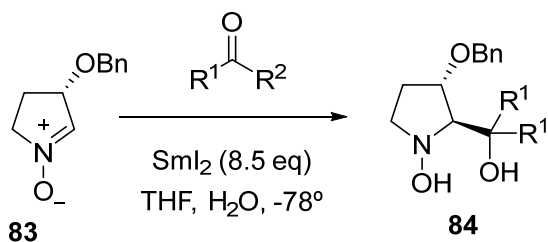


R = *i*Pr, cyclohexyl, cyclopentyl

Scheme 25

Nitrones are able to undergo reductive samarium diiodide-induced coupling with both carbonyl derivatives[96] and α,β -unsaturated esters.[97] Direct coupling between 1-pyrroline *N*-oxide and ketones afforded racemic *N*-hydroxy- α,α -disubstituted 2-pyrrolidylmethanols that could be resolved by chemical resolution and crystallization.[98] Starting from chiral nitrones like **83**, optically active substrates were obtained. The reaction, which can be done with aldehydes and ketones, required a proton source, usually water, although alcohols can also be used. (Scheme 26).[99] For aromatic ketones (Table 3, entries 1-2) and aldehydes (Table 3, entries 3-7), the obtained compound corresponded to the attack by the less hindered face of the nitrone, the different diastereomeric ratios corresponding to the different substituents

of the carbonyl compound. On the other hand, for aliphatic aldehydes (Table 3, entries 8-10) mixtures of several diastereomers were obtained.



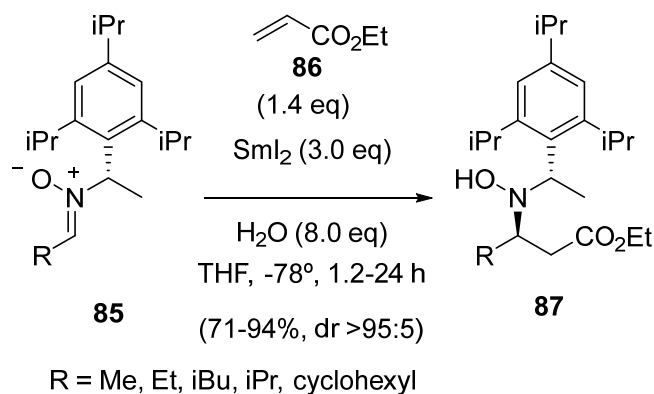
Scheme 26

Table 3. Coupling of nitrone **83** with carbonyls (Scheme 26).[99]

entry	R ¹	R ²	t(h)	yield (%)	dr
1	Me	Ph	1.5	84	79:21
2	Ph	Ph	1.2	83	-----
3	Ph	H	1.2	93	61:39
4	4-MeOC ₆ H ₄	H	1.5	95	62:38
5	2-ClC ₆ H ₄	H	1.2	72	67:33
6	4-ClC ₆ H ₄	H	1.3	95	63:37
7	2,4-Cl ₂ C ₆ H ₃	H	1.2	93	61:39
8	nBu	H	1.2	80	43:36:11:10
9	iBu	H	1.5	88	45:36:19
10	nHex	H	0.8	88	40:35:10:15

The same reaction can be extended to other polyhydroxylated cyclic nitrones with similar results.[100] Coupling has been also reported with acyl chlorides but in that case moderate diastereofacial selectivities are observed.[101]

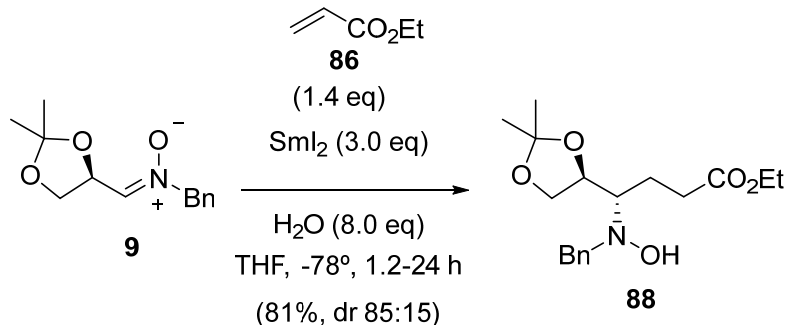
Excellent diastereoselectivities were found in the reductive coupling of nitrones **85** bearing a chiral auxiliary and ethyl acrylate (Scheme 27).[102]



Scheme 27

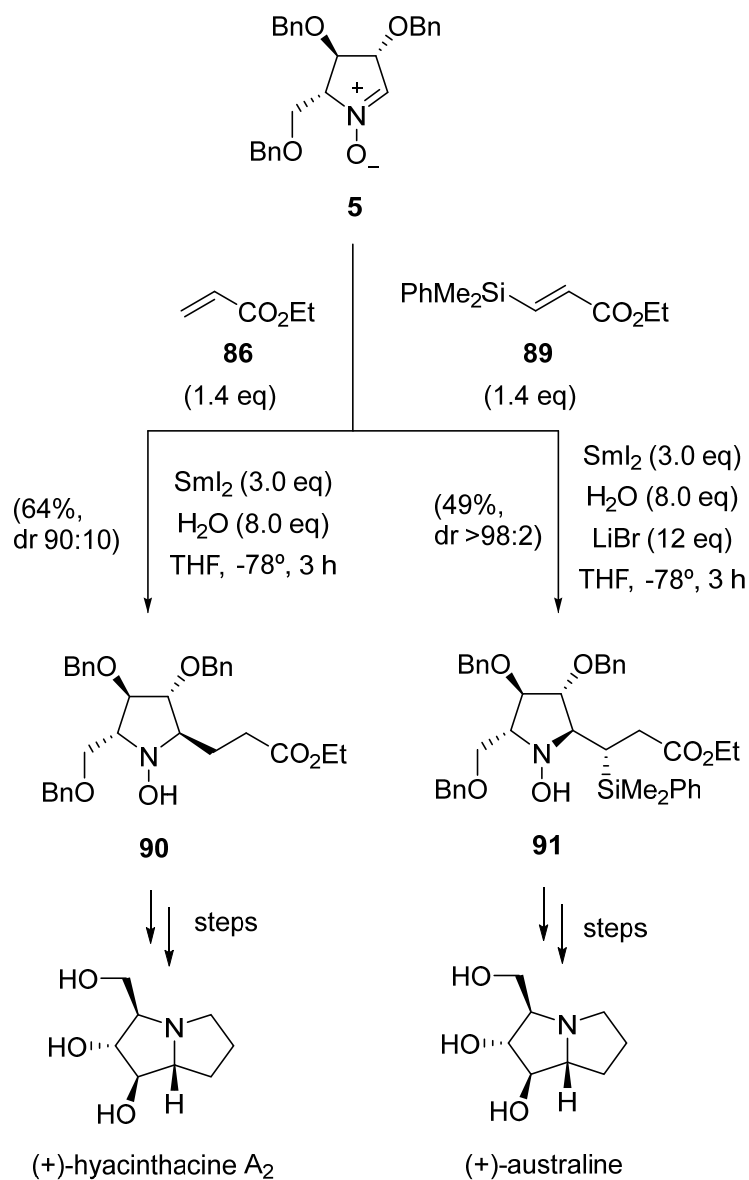
Optically active cyclopropyl nitrones have been tested in the coupling with ethyl acrylate and the corresponding α -cyclopropyl carbinylamine derivatives have been obtained in good chemical yields and diastereoselectivities. [103]

α -Alkoxy acyclic nitrones also underwent samarium diiodide-mediated coupling with ethyl acrylate. The reaction course strongly depends on the structure of the starting chiral nitron. For instance, nitron **9** derived from D-glyceraldehyde afforded the corresponding hydroxylamine in good yield and acceptable diastereoselectivity (Scheme 28).[104] On the other hand, whereas similar results were obtained with a C-furanosyl nitron derived from D-ribose, very low yield was observed with a nitron derived from D-xylose which underwent undesired reductive deoxygenation of the starting nitron. However, an epimeric acyclic nitron derived from D-ribose provided the expected product in excellent yield and selectivity.[105]



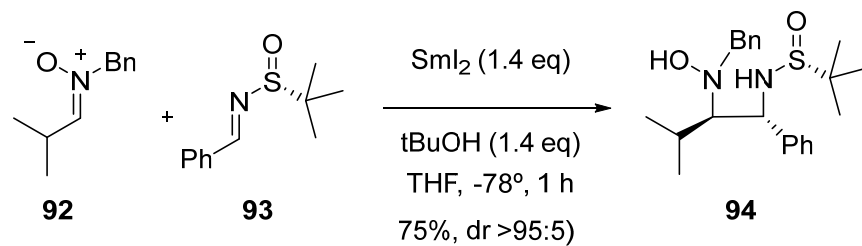
Scheme 28

Coupling of five-membered cyclic nitron **5** with ethyl acrylate afforded hydroxylamine **90** in 64% yield and 90% ds. Compound **90** was used for the synthesis of (+)-hyacinthacine A₂ (Scheme 29).[106] The same reaction with substituted ethyl acrylate **89**, but in the presence of 12 equiv. of lithium bromide, afforded hydroxylamine **91** which was reduced *in situ* en route to (+)-australine. [107] This synthetic strategy was applied to other polyhydroxylated nitrones and the resulting hydroxylamines were used as valuable synthetic intermediates in the preparation of compounds of biological interest such as 1,4-imino-D-galactitols.[108]



Scheme 29

The reductive coupling of nitrones mediated by samarium diiodide can be extended to chiral sulfonylimines (Scheme 30).^[109] The methodology is of a great synthetic utility in the preparation of unsymmetrical vicinal diamines.



Scheme 30

5. CONCLUDING REMARKS

Nitrones are excellent starting materials for the synthesis of hydroxylamines by means of nucleophilic additions and radical coupling processes. Hydroxylamines are valuable synthetic intermediates which possess a nitrogen atom in an intermediate oxidation state that allows i) easy reduction to the amine function and ii) to transfer the oxygen atom to a different position in the molecule through further chemical elaborations. The synthetic utility of hydroxylamines has been amply demonstrated through their use in a variety of synthesis of products of interest. The use of chiral nitrones allows the obtention of enantiomerically pure hydroxylamines increasing their added value as synthetic intermediates. Excellent values of diastereoselectivities can be achieved, particularly with cyclic nitrones. However, there are so few asymmetric catalytic processes involving nitrones and directed to the enantioselective preparation of optically active hydroxylamines. Undoubtedly, the future in the synthesis of chiral non-racemic hydroxylamines should be focus on the development of new efficient catalytic procedures that provide high enantioselectivities.

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