*The Nitro Group in Organic Synthesis.* Noboru Ono

ISBNs: 0-471-31611-3 (Hardback); 0-471-22448-0 (Electronic)

# 3

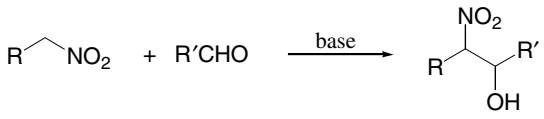
# THE NITRO-ALDOL (HENRY) REACTION

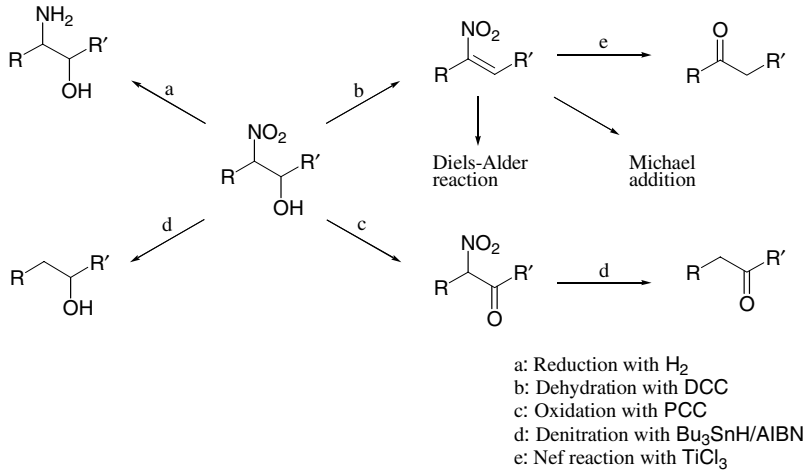
The nitro-aldol reaction between nitroalkanes and carbonyl compounds to yield β-nitro alcohols was discovered in 1895 by Henry.[1] Since then, this reaction has been used extensively in many important syntheses. In view of its significance, there are several reviews on the Henry reaction.[2–5] These reviews cover synthesis of β-nitro alcohols and their applications in organic synthesis. The most comprehensive review is Ref. 3, which summarizes the literature before 1970. More recent reviews are Refs. 4 and 5, which summarize literatures on the Henry reaction published until 1990.

In general, the Henry reaction gives a mixture of diastereomers and enantiomers. The lack of selectivity is due to the reversibility of the reaction and the easy epimerization at the nitro-substituted carbon atom. Existing reviews have hardly mentioned the stereochemistry of the Henry reaction. Recently, Shibasaki has found that the modification of the Henry reaction can control the stereochemistry to give β-nitro alcohols with high diastereo- and enantio-selectivity.[6] In Section 3.3, the progress of the stereoselective Henry reaction and its application to biologically active compounds are discussed.

The β-nitro alcohols are generally obtained in good yield by the reaction of aldehydes with nitroalkanes in the presence of a catalytic amount of base. When aryl aldehydes are used, the β-nitro alcohols formed may undergo elimination of water to give aryl nitroalkenes. Such side reactions are not always disadvantageous, for nitroalkenes are sometimes the ultimate target for the Henry reaction. The choice of reaction conditions is important to stop the reaction at the stage of β-nitro alcohols in aromatic cases.

The synthetic utility of the Henry reaction is shown in Scheme 3.1, where β-nitro alcohols are converted into β-amino alcohols, amino sugars, ketones and other important compounds.

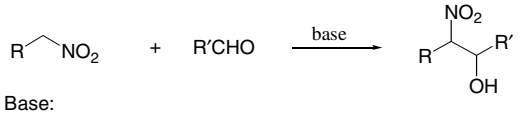




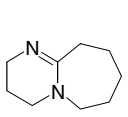

**Scheme 3.1**. Henry reaction and its applications

## 3.1 PREPARATION OF β-NITRO ALCOHOLS

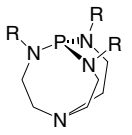
The Henry reaction is catalyzed in homogeneous solution with various catalysts, as shown in Eq. 3.1.




Base:
NaOR, $Et_3N$, DBU, DBN, tetramethylguanidine (TMG),$P(RNCH_2CH_2)_3N$ (PAP), KF, *n*-$Bu_4NF$, $Al_2O_3$, $Al_2O_3$-KF, amberlyst A-21, amberlite IRA-420, NaOH+cetyltrimethylammonium chloride (CTACl)




DBU



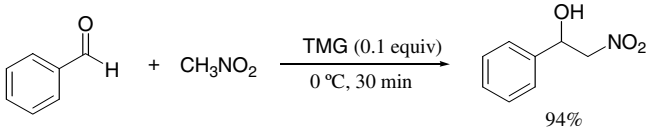

PAP

(3.1)

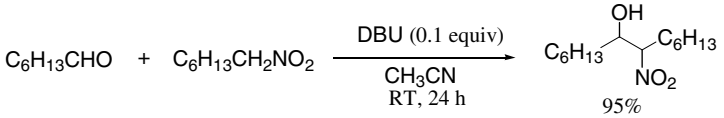
The reaction is generally conducted at room temperature in the presence of about 10 mol% of base to give the desired β-nitro alcohols in good yield. The most popular bases and solvents employed in the Henry reaction are alkali metal hydroxides, carbonates, bicarbonates, and alkoxids in water or ethanol.[7] Recently, powdered KOH in dry medium has been used for this conversion.[7d] This approach is quite simple and inexpensive. It is suitable for the reaction of both aromatic and aliphatic aldehydes with lower nitroalkanes such as nitromethane, nitroethane, and 1-nitropropane. The reaction of aromatic aldehydes with nitromethane using sodium hydroxide (1 equiv) in methanol followed by acidification is a standard method for the preparation of β-nitrostyrenes.[8] Recently, considerable work concerning new reactions mediated by rare earth metal reagents has been reported. The Henry reaction is catalyzed either by rare earth metal alkoxides such as $La_3(O\text{-}t\text{-}Bu)_9$ or rare earth hexamethyldisilazides (HMDS) such as $Sm(HMDS)_3$.[9] Shibasaki and coworkers have developed catalytic asymmetric nitro-aldol reaction using binaphthol (BINOL)-rare earth metal complexes, as discussed in the section of the stereoselective Henry reaction (Section 3.3).

Organic nitrogen bases such as ammonia or various amines are generally effective for the Henry reaction.[10] The reaction between nitromethane and simple aldehydes is particularly simple. Just mixing aldehydes, nitromethane, and amines followed by acidification gives the desired nitro alcohols in good yields. However, the Henry reactions of higher nitroalkanes with aldehydes or ketones proceed very slowly under the conditions using sodium hydroxide or amines. Nonionic strong bases such tetramethylguanidine (TMG),[11] 1,8-diazabicyclo[5.4.0]un-

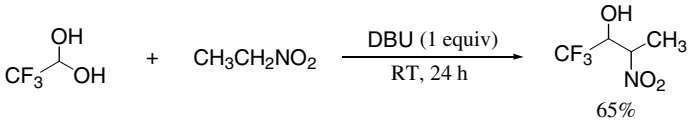
dec-7-ene (DBU), and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN)[12–14] in THF or acetonitrile are more effective catalytic systems than simple amines (see Eqs. 3.2–3.4).




94% (3.2)

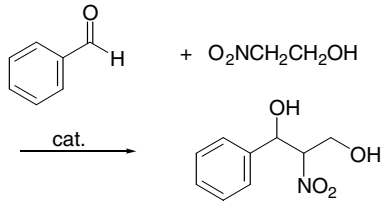


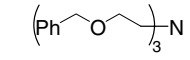

95% (3.3)




65% (3.4)

Dendritic molecules with a single triethylene amine core surrounded by hyperbranched polyether sectors catalyze the nitro-aldol reaction between aromatic aldehydes and nitroalkanes (Eq. 3.5).[15] The activity of the catalysts decreases when the generation number increases. No significant changes in stereo-control are observed on passing from lower- to higher-generation dendrimers.

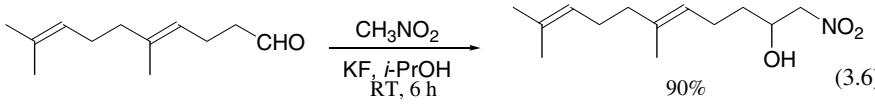



| Catalyst | Time | Yield (%) | *syn:anti* |
|---|---|---|---|
| $Et_3N$ | 0.5 h | 95 | 2:1 |
|  | 4 h | 90 | 2:1 |

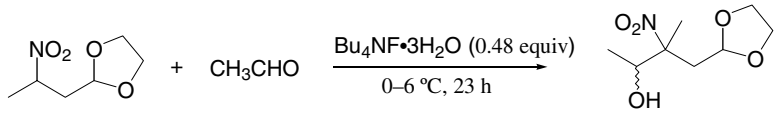


(3.5)

Fluoride ion is effective as a base for the Henry reaction, and potassium fluoride in isopropanol (Eq. 3.6)[16] and tetrabutylammonium fluoride in THF (Eq. 3.7)[17] have been widely used.




90% (3.6)




52% (*anti*/*syn* = 62/38) (3.7)

Thus, various kinds of bases are effective in inducing the Henry reaction. The choice of base and solvent is not crucial to carry out the Henry reaction of simple nitroalkanes with aldehydes, as summarized in Table 3.1. In general, sterically hindered carbonyl or nitro compounds are less reactive not to give the desired nitro-aldol products in good yield. In such cases, self-condensation of the carbonyl compound is a serious side-reaction. Several modified procedures for the Henry reaction have been developed.

**Table 3.1. Preparation of β-nitro alcohol by the Henry reaction**

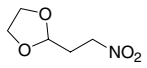
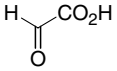
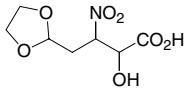
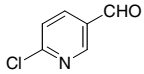
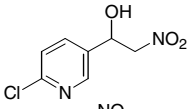
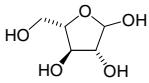
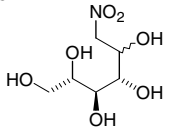
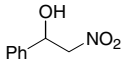
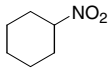
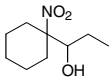
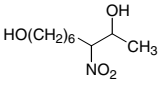
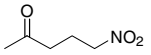
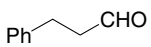
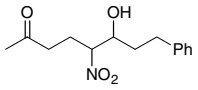
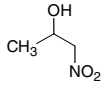
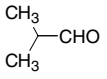
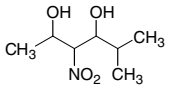
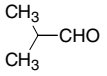
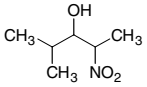
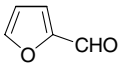
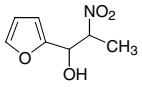
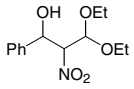
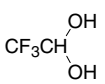
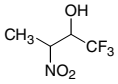
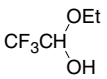
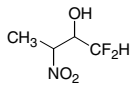
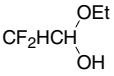
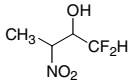
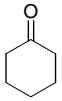
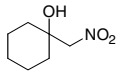
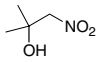
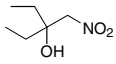
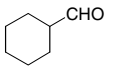
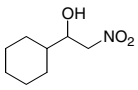
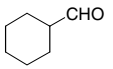
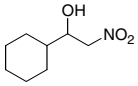
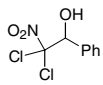
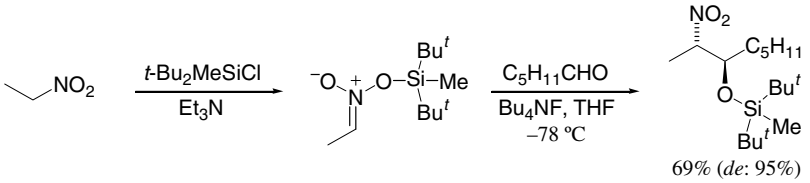
| Nitro compound | Carbonyl compound | Condition | Product | Yield (%) (*syn*/*anti*) | Ref. |
|---|---|---|---|---|---|
|  |  | NaOH EtOH 1 h |  | 100 | 36 |
| $CH_3NO_2$ |  | KF *i*-PrOH |  | 85 | 37 |
| $CH_3NO_2$ |  | $CH_3ONa$ $CH_3OH$ 50 h |  | 61 | 38 |
| $CH_3NO_2$ | PhCHO | TMG 30 min 0 °C |  | 94 | 11 |
| $CH_3CH_2NO_2$ | PhCHO | CTACl NaOH $H_2O$, 2 h |  | 71 | 27 |
|  | $CH_3CH_2CHO$ | CTACl NaOH $H_2O$, 3 h |  | 85 | 27 |
| $HO(CH_2)_6CH_2NO_2$ | $CH_3CHO$ | A-21 20 h |  | 70 | 25 |
|  |  | A-21 5 h |  | 95 | 25 |
|  |  | $Al_2O_3$ 24 h |  | 69 | 22 |
| $CH_3CH_2NO_2$ |  | KF-$Al_2O_3$ 5 h |  | 78 | 23 |
| $CH_3CH_2NO_2$ |  | KF-$Al_2O_3$ 15 h |  | 77 | 23 |
| $(EtO)_2CHCH_2NO_2$ | PhCHO | $Et_3N$ $Bu_4NF{\cdot}3H_2O$ *t*-$BuMe_2SiCl$ THF, 2 h |  | 51 (70/30) | 20 |
| $CH_3CH_2NO_2$ | PhCHO | $Et_3N$ $Bu_4NF{\cdot}3H_2O$ *t*-$BuMe_2SiCl$ THF |  | 95 (47/53) | 20 |
| $CH_3CH_2NO_2$ |  | DBU 24 h |  | 67 | 13 |
| $CH_3CH_2NO_2$ |  | $K_2CO_3$ |  | 60 | 40 |

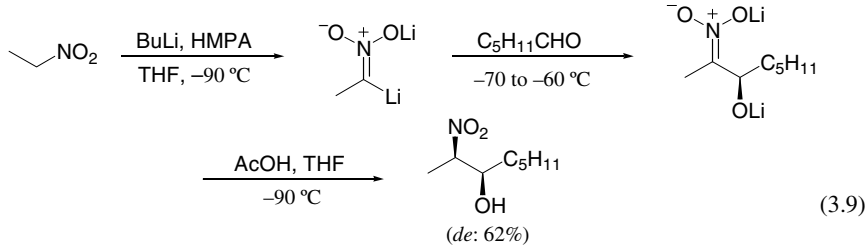
**Table 3.1. Continued**

| Nitro compound | Carbonyl compound | Condition | Product | Yield (%) (*syn*/*anti*) | Ref. |
|---|---|---|---|---|---|
| $CH_3CH_2NO_2$ |  | $K_2CO_3$ |  | 68 (54/46) | 41 |
| $CH_3NO_2$ |  | PAP (see Eq. 3.1, 10 mol%) $MgSO_4$ |  | 95 | 21 |
| $CH_3NO_2$ |  | PAP (10 mol%) $MgSO_4$ |  | 91 | 21 |
| $CH_3NO_2$ |  | PAP (10 mol%) $MgSO_4$ |  | 60 | 21 |
| $CH_3NO_2$ |  | $La_3(O\text{-}t\text{-}Bu_3)_9$ (3.3 mol%) THF, 0 °C |  | 78 | 9 |
| $CH_3NO_2$ |  | $Sm(HMDS)_3$ (10 mol%) RT, 25 h |  | 100 | 9 |
| $Cl_3CNO_2$ | PhCHO | $SnCl_2$ 0 °C |  | 57 | 39 |

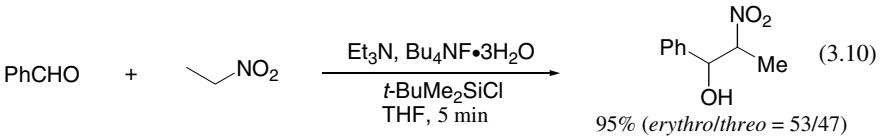
Nitroalkanes are silylated with trialkylsilyl chloride and triethylamine to form stable silyl nitronates, which react with aldehydes to give β-nitro alcohol *O*-silyl ethers in the presence of a catalytic amount of $Bu_4NF{\cdot}3\ H_2O$ at –78 °C in THF. Because the retro nitro-aldol reaction cannot occur, a high diastereoselectivity is observed, as shown in Eq. 3.8.[18] The product is directly reduced to the corresponding β-amino alcohol with retention of the stereochemistry. The dilithium salts of nitroalkanes are formed on treatment with 2 equiv of *n*-butyllithium in THF/HMPA at –90 °C. They react with aldehydes to give β-nitro alcohols with high diastereoselectivity after careful protonation (Eq. 3.9). The dilithium salt is much reactive toward carbonyl compounds than the mono-anion, and this often leads to better yields of β-nitro alcohols than the conventional Henry reaction.[19] The Henry reaction is accelerated by the presence of $Et_3N$, $Bu_4NF{\cdot}3H_2O$ and $^t$BuMe$_2$SiCl (Eq. 3.10).[20] The use of non-ionic strong bases such as the proazaphosphatrane (PAP) is also a good choice for overcoming the low reactivity of the Henry reaction (see Eq. 3.20).[21]




69% (*de*: 95%) (3.8)

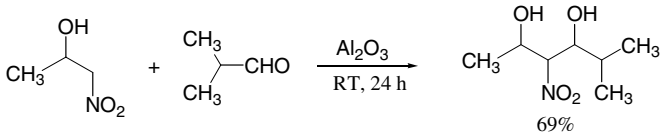



(3.9)

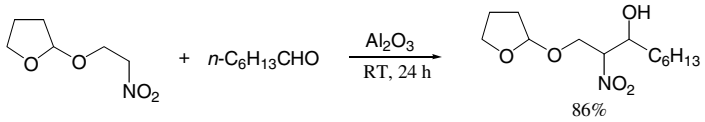



(3.10)

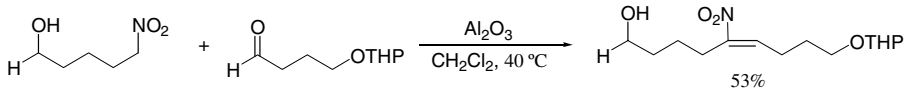
It is inconvenient to remove the base by acidification in the work-up procedure, because acidification may lead to the Nef reaction (Section 6.1). To avoid this inconvenience the reactions catalyzed in heterogeneous systems with $Al_2O_3$, $Al_2O_3$-supported KF, and polymer-supported bases, have been developed. Commercial chromatographic alumina (activity 1 according to Brockmann) is used without solvents for the preparation of functionalized β-nitro alcohols. Acid- or base-sensitive substrates are prepared by this method (Eqs. 3.11 and 3.12).[22] The reactivity is enhanced by a modification using alumina-supported potassium fluoride.[23] Dehydration of β-nitro alcohols is also catalyzed by $Al_2O_3$.[24] One-pot synthesis of nitroalkenes from aldehydes and nitroalkanes using $Al_2O_3$ is convenient (see Section 3.2.1); this process has been applied to a short synthesis of spiro-ethers, (often found in pheromones) involving hydrogenation of the nitroalkene and subsequent Nef reaction (Eq. 3.13).[24b] Importantly, no dehydration is observed when neutral $Al_2O_3$ is employed at room temperature; however, simply warming to 40 °C results in the formation of nitroalkenes.

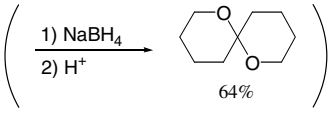



(3.11)




(3.12)

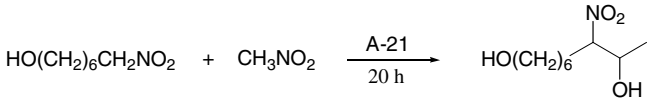


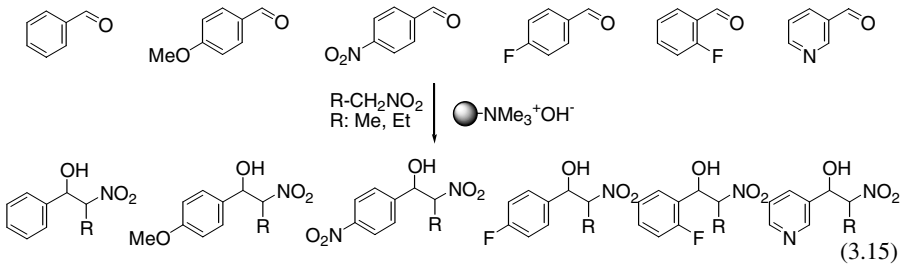

(3.13)

A more effective catalyst for the Henry reaction is a polymer-supported base such as amberlyst A-21. Various β-nitro alcohols can be obtained with the help of amberlyst with or without solvent (Eq. 3.14).[25] A recent report claims that amberlite IRA-420 (OH-form) or DOWEX-1 (OH-form) is more effective for the Henry reaction than amberlyst A-21.[26] Poly-

mer-supported bases are attractive for getting a library of β-nitroalcohols, which are important intermediates for biologically active compounds (Eq. 3.15).

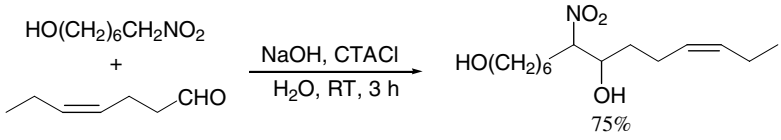



(3.14)



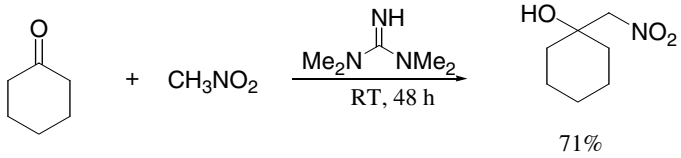

(3.15)

The nitro-aldol reaction can also be carried out in water using NaOH in the presence of cetyltrimethylammonium chloride (CTACl) as a cationic surfactant. CTACl (5 mmol) is added to a mixture of nitroalkane (50 mmol) and aldehyde (50 mmol) in NaOH 0.025 M (150 mL) at room temperature. The mixture is stirred for 2–3 h and worked up to give the product in 70–90% yield. Compared with the classical methods, this procedure has economical and environmental advantages (Eq. 3.16).[27]



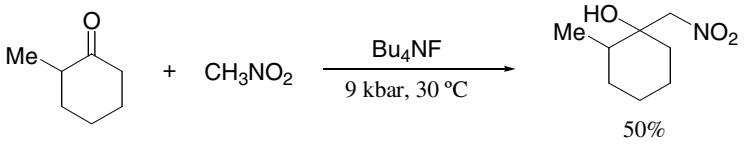

(3.16)

The nitro-aldol reaction with ketones is sensitive to steric factors and generally gives a complex mixture of products depending on the ratio of reactants, base, temperature, and time.[27] Nitromethane is reactive enough toward ketones to give the β-nitro alcohol under various conditions. Cyclohexanone reacts with nitromethane to give 1-(nitromethyl) cyclohexanol in 69–94% yield in the presence of sodium ethoxide in ethanol.[7f] This transformation is more simply carried out using tetramethylguanidine (TMG) as the base (Eq. 3.17).[11] Stronger nonionic bases like proazaphosphatrane (PAP) are more effective in the Henry reaction with ketones (see Eq. 3.20).



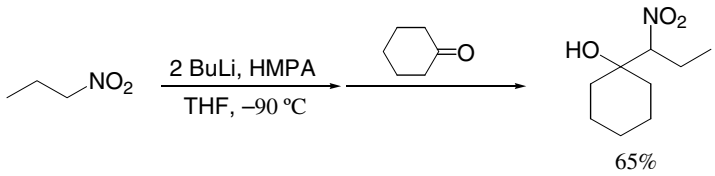

(3.17)

However, 3- or 4-methylcyclohexanone is less reactive to nitromethane than cyclohexanone. Although 2-methylcyclohexanone does not react with nitromethane under the conventional conditions, under high pressure and a fluoride ion catalysis the reaction proceeds to give the β-nitro alcohol in moderate yields (Eq. 3.18).[29]



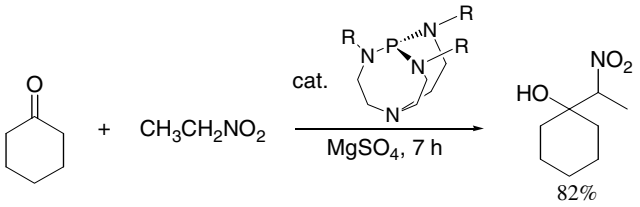

(3.18)

Another method for improving the reactivity of nitro compounds is provided by the double deprotonation of nitroalkanes. In this case, the reaction with ketones affords β-nitro alcohols in 40–60% yield (Eq. 3.19).[30]



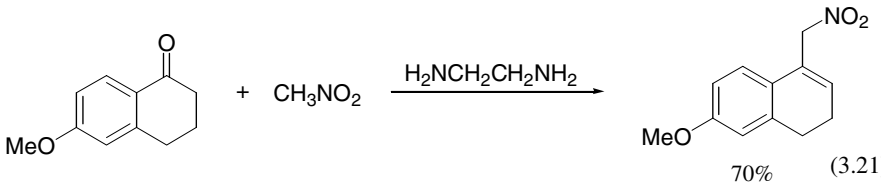

(3.19)

Proazaphosphatrane, $P(RNCH_2CH_2)_3N$, is an efficient catalyst for the Henry reaction, and various ketones give nitro-aldols by the reaction with nitromethane and other nitroalkanes (Eq. 3.20).[21]



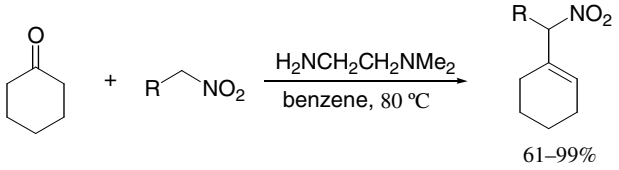

(3.20)

Allylic nitro compounds are obtained by the reaction of cyclic ketones with nitromethane in the presence of 1,2-diaminoethane (1 mol%) as catalyst. Because *exo*-cyclic nitroalkenes are rearranged to the *endo*-cyclic β,γ-nitroalkenes, allylic nitro compounds are selectively produced (Eq. 3.21).[31]

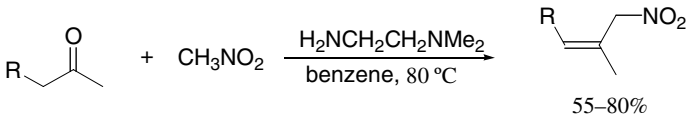



(3.21)

If *N*,*N*-dimethylethylenediamine is used as the base, allylic nitro compounds are obtained in good yields from both acyclic and alicyclic ketones (Eqs. 3.22 and 3.23).[32]

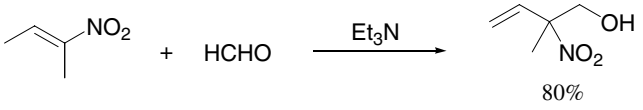



(3.22)



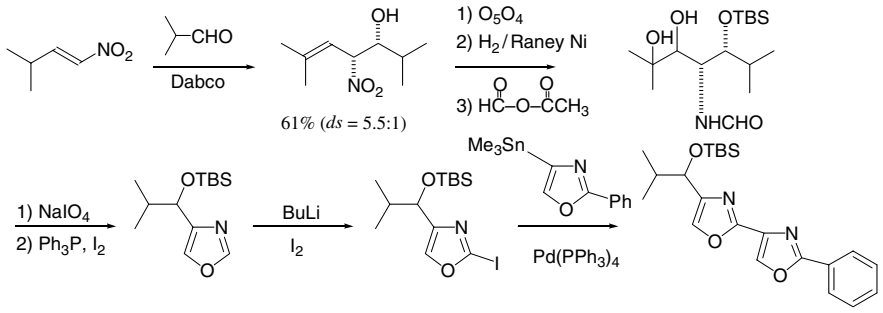

(3.23)

Conjugated nitroalkenes are isomerized to allylic nitro compounds under basic conditions. Reactions of α,β-unsaturated nitro compounds with aldehydes under basic conditions lead directly to γ,δ-unsaturated β-nitro alcohols (Eq. 3.24).[33] This reaction is very useful for preparing allylic nitro compounds.




(3.24)

Barrett and coworkers have used this method for the synthesis of 2,4′-linked bisoxazole, which constitutes a partial structure of hennoxazole A.[34] Condensation of the nitroalkene in Scheme 3.2 with isobutylaldehyde affords the nitro alcohol in 61% yield. Recrystallization gives the pure *syn*-stereoisomer, which is protected as its *tert*-butyldimethylsilyl (TBS) ether and dihydroxylated using osmium tetraoxide as catalyst. Reduction of the nitro group to the amine occurs by hydrogenation over Raney nickel. The subsequent glycol cleavage with $NaIO_4$ followed by cyclization gives the oxazole. Stille coupling of stannyloxazole with iodooxazole using Pd(0) gives the desired bis-oxazole (Scheme 3.2).[35]




**Scheme 3.2.** Model studies on the synthesis of hennoxazole A

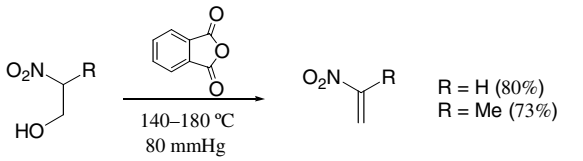
## 3.2 DERIVATIVES FROM β-NITRO ALCOHOLS

### 3.2.1 Nitroalkenes

Dehydration of β-nitro alcohols provides an important method for the preparation of nitroalkenes. Because lower nitroalkenes such as nitroethylene, 1-nitro-1-propene, and 2-nitro-1-propene tend to polymerize, they must be prepared carefully and used immediately after preparation. Dehydration with phthalic anhydride is the most reliable method for such lower nitroalkenes.[42,43] Such lower nitroalkenes have been used as important reagents for Michael acceptors or dienophiles in the Diels-Alder reaction, which will be

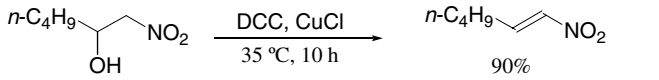
discussed in Chapters 4 and 8. Some typical nitroalkenes which are useful reagents in organic synthesis are presented here.[42]

- **Nitroethylene:** Dehydration of 2-nitroethanol[44] using phthalic anhydride (80%) is the best choice of preparation;[43] bp 38–39 °C/80 mm Hg.
- **1-Nitro-1-propene:** Preparation is accomplished by dehydration of 2-nitro-1-propanol with phthalic anhydride (73%)[45] or acetic anhydride-AcONa[46]; bp 56–57 °C/80 mmHg.
- **2-Nitro-1-propene:** Preparation is accomplished by dehydration of 1-nitro-2-propanol with methanesulfonyl chloride and triethylamine (30% yield),[47] acetic anhydride-AcONa (85% yield),[46] or phthalic anhydride (55%)[45]; bp 58 °C/35 mmHg (Eq. 3.25).

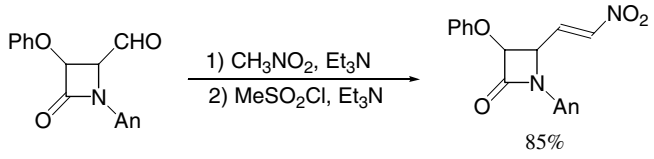



(3.25)

Dehydration of β-nitro alcohols is generally carried out by the following reagents, phthalic anhydride,[44] $CH_3SO_2Cl$-$Et_3N$,[47] dicyclohexylcarbodiimide (DCC),[48] $Ac_2O$-AcONa, $Ph_3P$-$CCl_4$,[49] and TFAA-$Et_3N$,[50] as exemplified in Eqs. 3.26[48] and 3.27[47b].

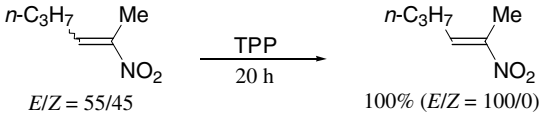



(3.26)

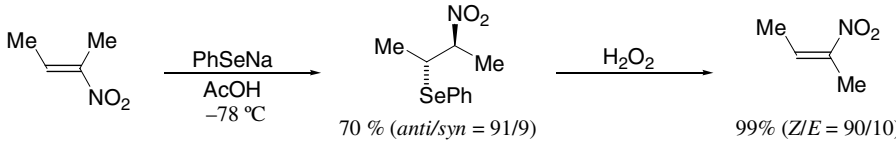



(3.27)

Dehydration of β-nitro alcohols using DCC gives a mixture of *E/Z* nitroalkenes.[48] The pure (*E*)-isomers are obtained on treatment with catalytic amounts of triethylamine or polymer-bound triphenylphosphine (TPP) (Eq. 3.28).[51] When (*Z*) nitroalkenes are desired, the addition of PhSeNa to the *E/Z* mixture and protonation at −78 °C followed by oxidation with $H_2O_2$ gives (*Z*)-nitroalkenes (Eq. 3.29).[52]

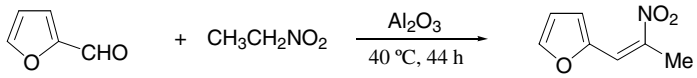



(3.28)



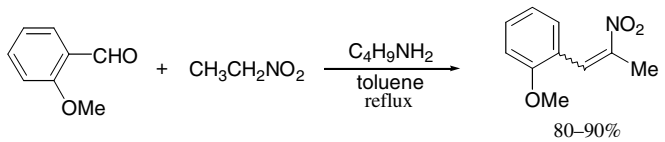

(3.29)

$Al_2O_3$ can be used both as a base for the Henry reaction and as a dehydrating agent. Thus, nitroalkenes are simply prepared by mixing of aldehydes and nitroalkanes with $Al_2O_3$ and subsequent warming at 40 °C (Eq. 3.30).[53]



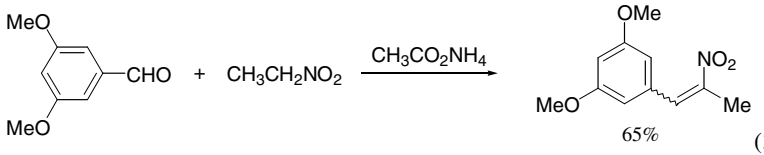

(3.30)

In general, base-catalyzed reactions of aromatic aldehydes with nitroalkanes give nitroalkenes directly (Knoevenagel reaction).[54] The reaction is very simple; heating a mixture of aromatic aldehydes, nitroalkanes, and amines in benzene or toluene for several hours using a Dean-Stark water separator gives the desired nitroalkenes in good yield, as shown in Eqs. 3.31–3.34.[54–58]



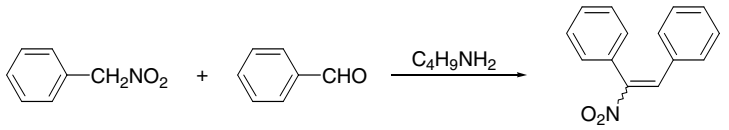

80–90%

(3.31)



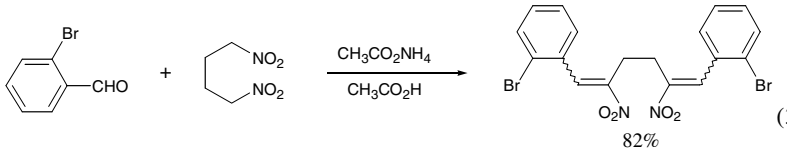

65%

(3.32)




65%

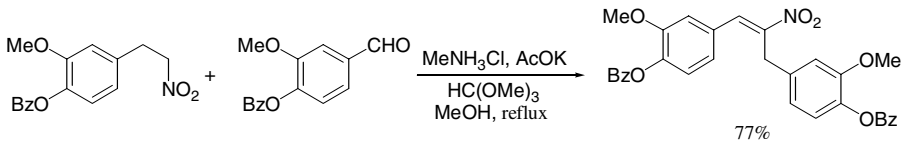
(3.33)




82%

(3.34)

Instead of using the Dean-Stark apparatus, the reaction can be carried out at reflux using $MeNH_3Cl$/AcOK/MeOH with $HC(OMe)_3$ as a water scavenger. A wide variety of nitroalkenes can be prepared in good yields by this method (Eq. 3.35).[59]

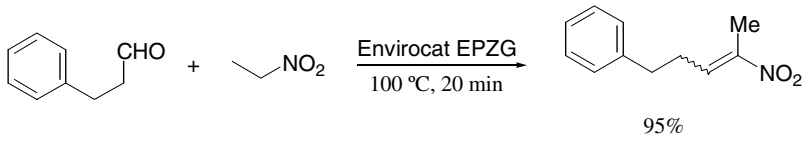



77%

(3.35)

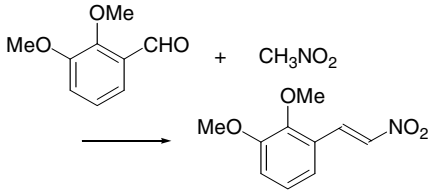
In recent years, there has been a considerable growth of interest in the catalysis of organic reactions by inorganic reagents supported on high surface areas.[60] Envirocat, a new family of supported reagents, which exhibits both Brönstead and Lewis acid character, are ideal for environmentally friendly chemistry. These reagents are non-toxic powders that can be easily

filtered from the reaction mixture and may be reused.[61] With the use of this new heterogeneous catalyst, nitroolefins are prepared directly by heating a mixture of aldehyde and nitroalkane at 100 °C in the absence of solvents (Eq. 3.36).



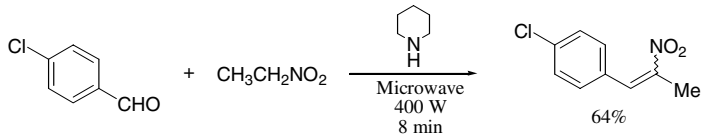

(3.36)

Application of ultrasound[62] or microwave irradiation[63] greatly assists these condensation reactions as shown in Eqs. 3.37 and 3.38, respectively, rendering the use of a Dean-Stark apparatus unnecessary.



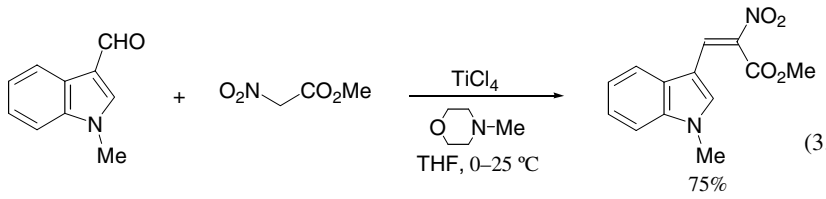

| Condition | Yield (%) |
|---|---|
| $NH_4OAc$/ AcOH 100 ºC, 3 h | 35 |
| $NH_4OAc$/ AcOH 22 ºC, 3 h, ))))) | 99 |

(3.37)




(3.38)

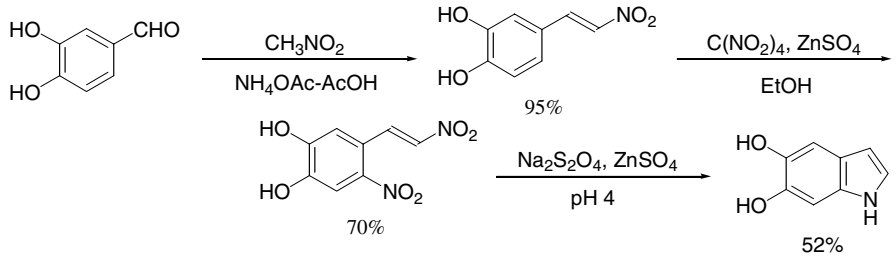
Reactions of methyl nitroacetate with aldehydes are induced by $TiCl_4$ in pyridine. They afford nitroalkenyl-esters,[64] which are used in the preparation of various nonnatural amino acids (Eq. 3.39).[65]



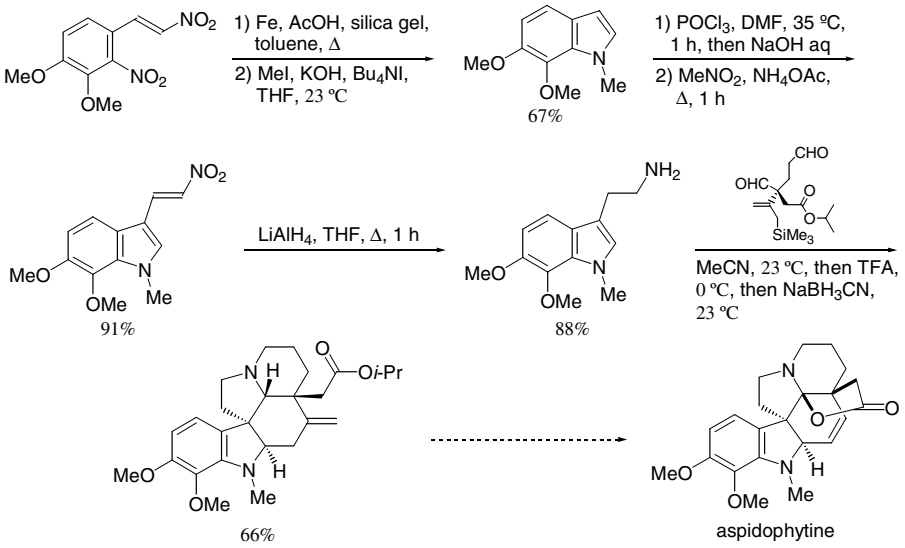

(3.39)

Nitroalkenes prepared from aromatic aldehydes are especially useful for natural product synthesis. For example, the products are directly converted into ketones via the Nef reaction (Section 6.1) or indoles (Section 10.2) via the reduction to phenylethylamines (Section 6.3.2). The application of these transformations are discussed later; here, some examples are presented to emphasize their utility. Schemes 3.3 and 3.4 present a synthesis of 5,6-dihydroxyindole[66] and asperidophytine indole alkaloid,[67] respectively.

Seebach and coworkers have developed the multiple coupling reagent, 2-nitro-2-propenyl 2,2-dimethylpropanoate (NPP). The reaction of nitromethane with formaldehyde gives 1,3-dihydroxy-2-nitropropane in 95% yield. Subsequent acylation with two equivalents of pivaloyl chloride and elimination of pivalic acid affords NPP. The reaction may be run on a 40- to 200-g

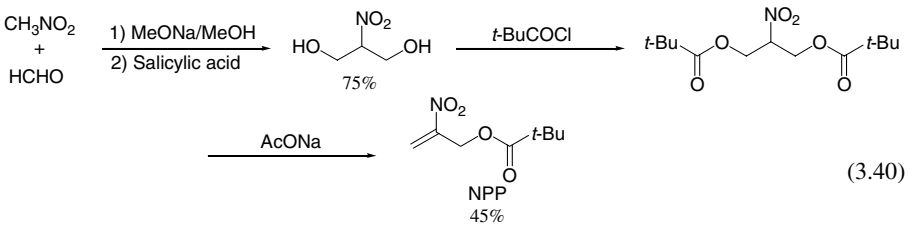



**Scheme 3.3.** Synthesis of 5,6-dihydroxyindole

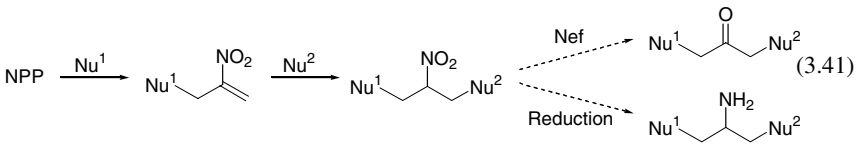



**Scheme 3.4.** Synthesis of aspidophytine

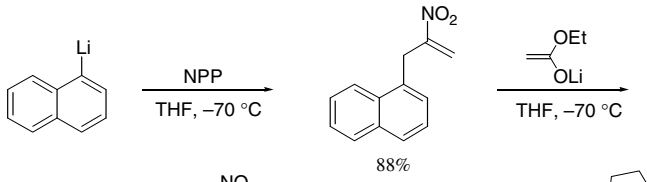
scale without problems (Eq. 3.40).[68] NPP allows successive introduction of two different nucleophiles $Nu^1$ and $Nu^2$ as shown in Eq. 3.41. The conversion of the resulting products via the Nef reaction or reduction into various compounds, makes NPP a useful reagent for convergent syntheses, as demonstrated in Eqs. 3.42 and 3.43.

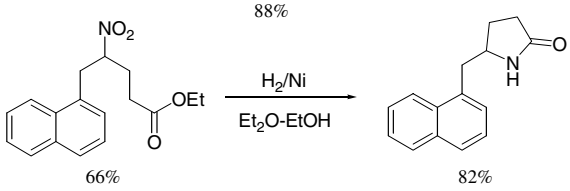



(3.40)

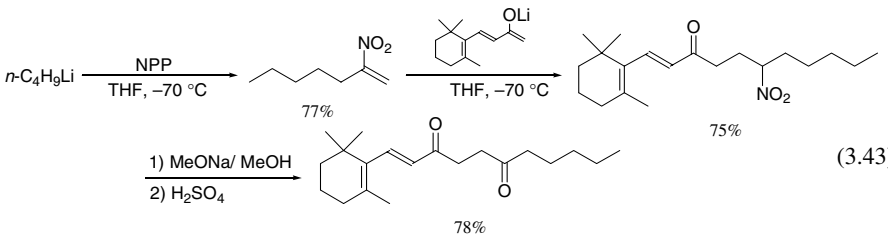



(3.41)



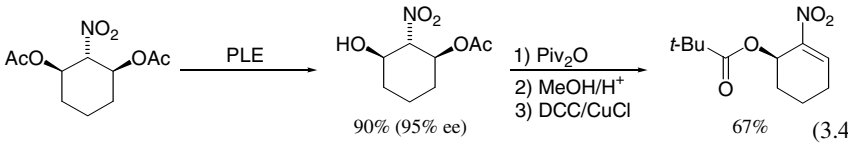




(3.42)



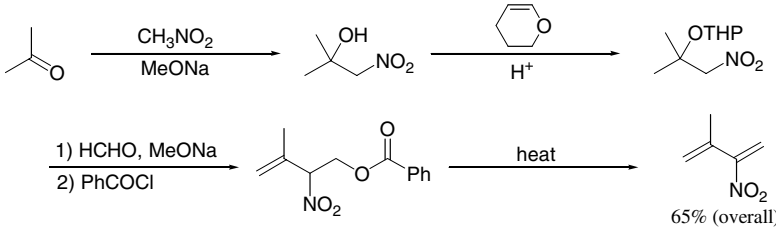

(3.43)

Chiral multiple-coupling reagents have been prepared in enantiomerically pure form by enantio-selective saponification of diesters of meso-2-nitrocyclohexane-1,3-diols (Eq. 3.44) with pig liver esterase (PLE).[69]




(3.44)

The nitro-aldol reaction followed by dehydration gives 2-nitro-1,3-dienes, which are useful reagents for cycloaddition (Eq. 3.45).[70]

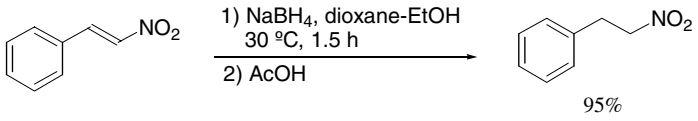



(3.45)

The nitro-aldol approach is impractical for the synthesis of 2,2-disubstituted 1-nitroalkenes due to the reversibility of the reaction when ketones are employed as substrates. Addition-elimination reactions are used for the preparation of such nitroalkenes (see Chapter 4).

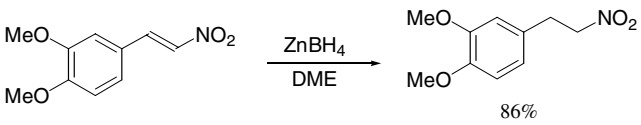
### 3.2.2 Nitroalkanes

Reduction of nitroalkenes with $NaBH_4$ has been widely used for the synthesis of nitroalkanes.[71] In some cases, however, small amounts of dimeric products are also formed, although their formation can be completely suppressed using acidic conditions.[72] Silica gel is also effective in preventing the dimerization of nitrostyrenes. 2-Aryl-1-nitroethanes are obtained in near quantitative yields by the reduction with $NaBH_4$.[73] This route provides a simple route to phenylethylamines of biochemical and pharmacological interest.[74] A simple and efficient method for the large-scale preparation of phenylnitroethanes has been reported, in which solutions of nitrostyrenes in 1,4-dioxane are added to an efficiently stirred suspension of $NaBH_4$ in a mixture of 1,4-dioxane and ethanol (Eq. 3.46).[75] Hydrogenation of nitrostyrene derivatives with bis(triphenylphosphine)rhodium chloride (Wilkinson catalyst) gives also good yields of products.[76]



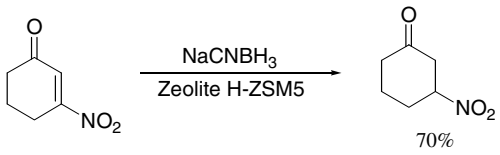

(3.46)

The reduction of nitroalkenes with $ZnBH_4$ in 1,2-dimethoxyethane (DME) gives the corresponding oximes or nitroalkanes depending on the structure of nitroalkenes. α-Substituted nitroalkenes are reduced to the oximes, whereas those having no α-substituents afford the nitroalkanes (Eq. 3.47).[77]




(3.47)

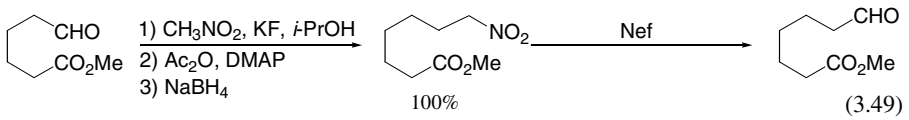
Very selective reduction of nitroalkenes into the corresponding nitroalkanes is achieved using $NaCNBH_3$ in the presence of the zeolite H-ZSM 5 in methanol (Eq. 3.48).[78]




(3.48)

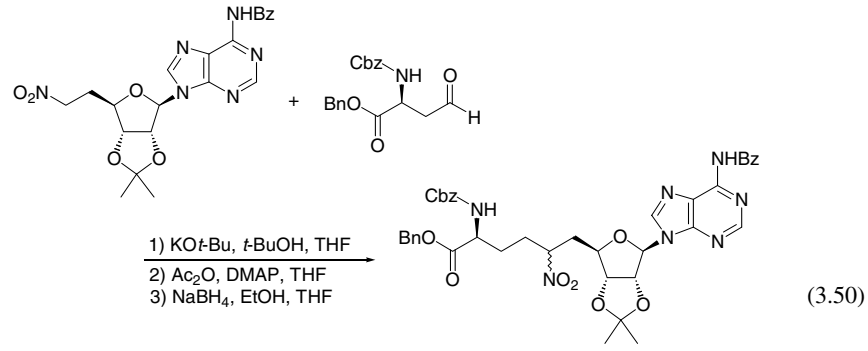
Nitromethylation of aldehydes has been carried out in a one pot procedure consisting of the Henry reaction, acetylation, and reduction with sodium borohydride, which provides a good method for the preparation of 1-nitroalkanes.[16b,79] It has been improved by several modifications. The initial condensation reaction is accelerated by use of KF and 18-crown-6 in isopropanol. Acetylation is effected with acetic anhydride at 25 °C and 4-dimethylaminopyridine (DMAP) as a catalyst. These mild conditions are compatible with various functional groups which are often

present in the synthesis of natural products.[16b] Readily available methyl 6-oxohexanoate has been converted into methyl 7-oxoheptanoate via nitromethylation and subsequent Nef reaction (Eq. 3.49).[79b]

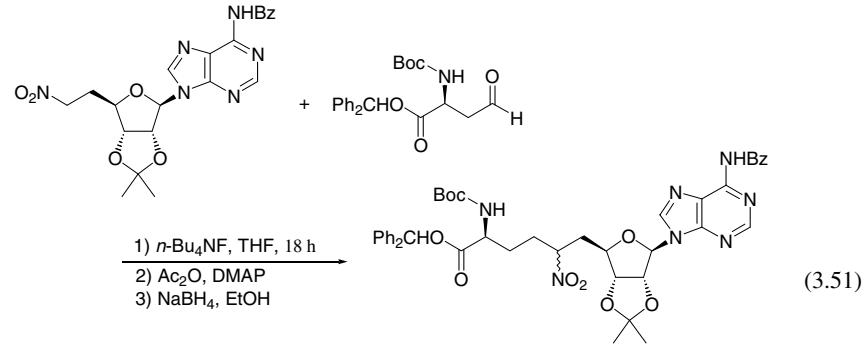



100% (3.49)

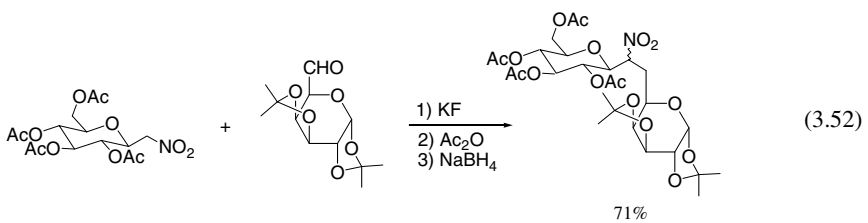
Additional examples of the synthetic utility of this procedure are demonstrated in Eqs. 3.50–3.52.[80] The nitro and nitroalkyl groups in the products are further converted into various functional groups such as carbonyl, amino, and alkyl groups. This is discussed in Chapter 6.




53% (3.50)

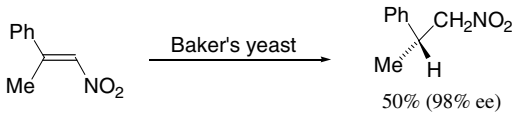



70% (3.51)




71% (3.52)

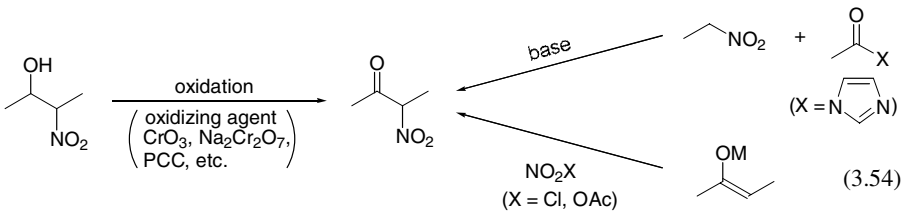
Reduction of 1-nitro-1-alkenes with fermenting Baker's yeast proceeds enantioselectively to give optically active nitroalkanes (Eq. 3.53).[81]




(3.53)

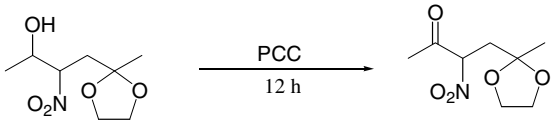
### 3.2.3 α-Nitro Ketones

α-Nitro ketones are useful intermediates in organic synthesis, and they are generally prepared either by nitration of ketones (Chapter 2.1) or by oxidation of β-nitro alcohols. Acylation of nitroalkanes with acylimidazoles or other acylating reagents is also a reliable method for the preparation of α-nitro ketones (see Chapter 5) (Eq. 3.54).

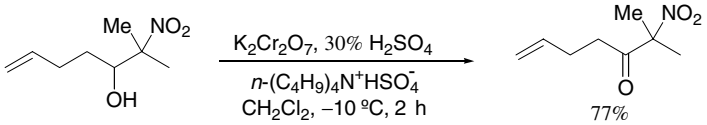



(3.54)

In this chapter the synthesis of α-nitro ketones by the hydroxyalkylation of nitroalkanes (Henry reaction) followed by oxidation is discussed. The oxidation is normally carried out by treating the nitro alcohols with $CrO_3$ or $Na_2Cr_2O_7$ in strong acidic media.[82] To avoid acidic conditions, pyridinum chlorochromate (PCC)[83] or $K_2Cr_2O_7$ under phase-transfer conditions [84a] has been used. Acid labile groups are retained under these conditions as shown in Eqs. 3.55 and 3.56. Recently, Ballini and coworkers established a one-pot, solvent-free synthesis of acyclic α-nitro ketones (by using neutral alumina) in the Henry reaction followed by in situ oxidation of the nitro alcohol using wet alumina supported with $CrO_3$. [84b]



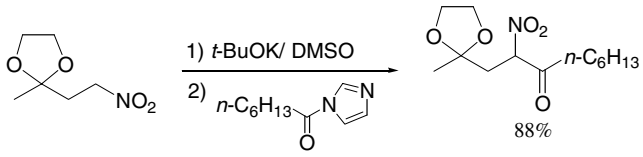

(3.55)




(3.56)

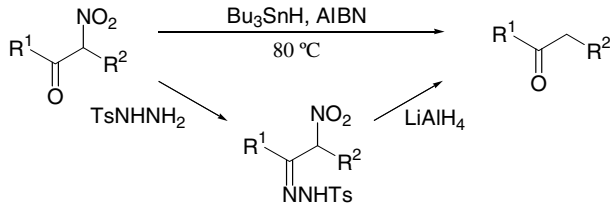
In general, alkylation or acylation of nitronate ions takes place at the oxygen to yield the O-alkylated or O-acylated products. However, the choice of alkylating or acylating reagents can alter the reaction course to give the C-alkylated or acylated products. The acylation of primary nitroalkane salts with acyl cyanides gives the O-acylated product in 30–70% yield.[85] A combination of diethyl phosphorocyanidate and triethylamine allows the direct C-acylation of nitromethane by aromatic carboxylic acids to give α-nitro ketones.[86] Acyl imidazoles are more effective as C-acylating agents of nitroalkane salts, and α-nitro ketones are obtained in good

yields.[87] Although the isolated lithium salts of nitroalkanes are used in the original paper, the potassium salt prepared in situ by treatment of nitro compounds with *t*-BuOK in DMSO is reactive enough with acyl imidazoles to give α-nitro ketones in 60–90% yield (see Section 5.2, Acylation of Nitro Compounds) (Eq. 3.57).[88]



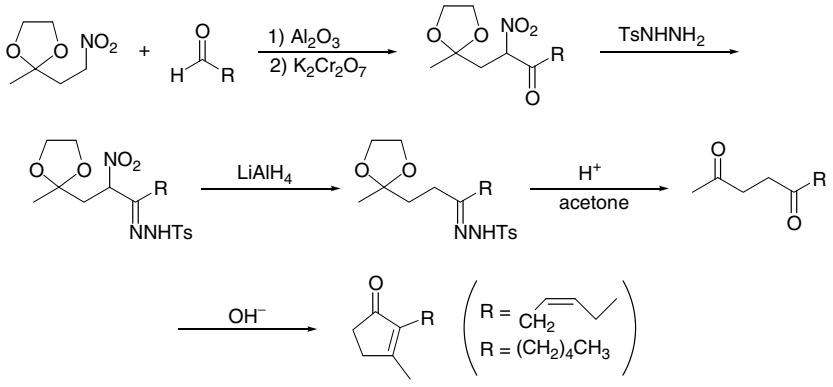

(3.57)

The nitro group of α-nitro ketones is readily removed either by treatment with $Bu_3SnH$[89] or reduction with $LiAlH_4$ of the corresponding tosylhydrazones (Eq. 3.58).[90] Details of denitration are discussed in Section 7.2, and some applications of this process are shown in Schemes 3.5–3.7.

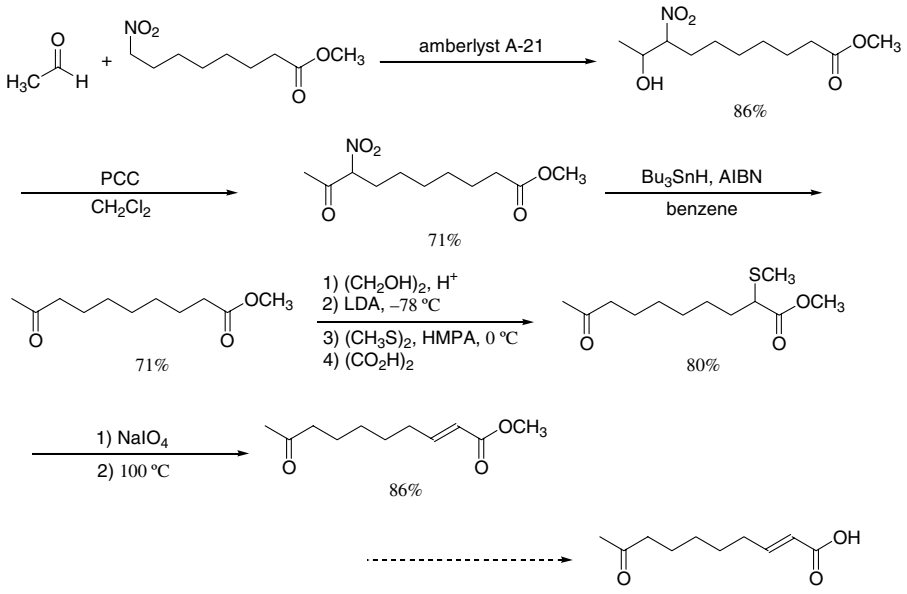



(3.58)

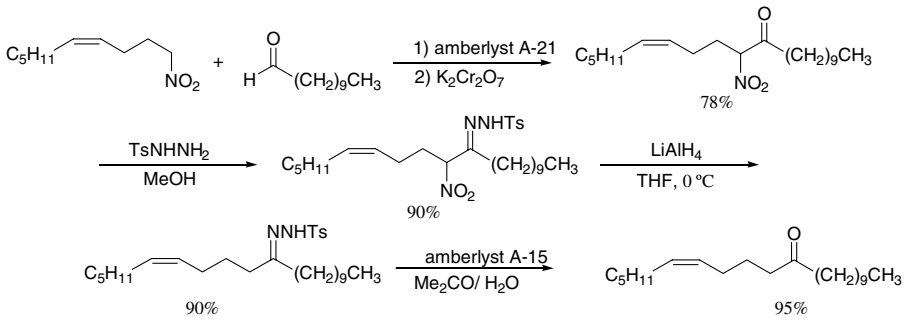
Construction of the carbon frameworks by using the activating property of the nitro group followed by denitration provides a useful tool for the preparation of various natural products as shown in Schemes 3.5–3.7. For example, (*Z*)-jasmone and dihydrojasmone, constituents of the essential oil of jasmone flowers, have been prepared as shown in Scheme 3.5.[91] Schemes 3.6 and 3.7 present a synthesis of pheromones via denitration of α-nitro ketones.[92,93]




**Scheme 3.5.**




**Scheme 3.6.**




**Scheme 3.7.**

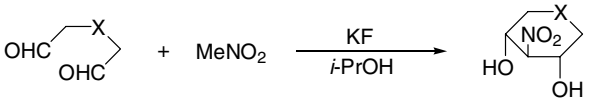
### 3.2.4 β-Amino Alcohols

β-Nitro alcohols prepared by the Henry reaction are important precursors for β-amino alcohols. The reduction of the nitro group to the amino function is commonly carried out by hydrogenation in the presence of Raney Ni in EtOH or Pd/C in THF and MeOH (see Section 4.2). The conversion into β-amino alcohols is also described in the Sections 3.2.5 and 3.3.

### 3.2.5 Nitro Sugars and Amino Sugars

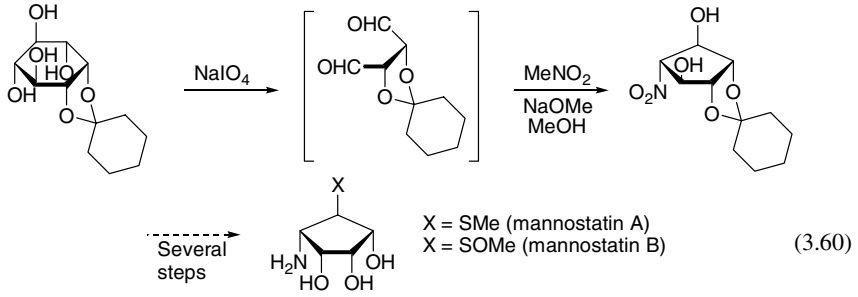
The chemistry and biochemistry of nitro sugars and amino sugars have stimulated extensive research. They are the components of various antibiotics, which show important biological

activities.[94] Synthesis of nitro and amino sugars is one of the most important applications of nitro-aldol condensation. Synthesis of nitro sugars has been well reviewed by Wade and Giuliano,[95] also there are many other excellent reviews on this topic.[96] Only selected recent papers are described here to show the importance of nitro-aldol reaction in carbohydrate chemistry. The Baer-Fisher procedure is one of the simplest and shortest methods for obtaining 3-deoxy-3-nitrohexopyranosides and 3-amino-3-deoxyhexose derivatives by means of the Henry reaction with sugar dialdehydes. Sugar dialdehydes are obtained by glycol cleavage of glycosides.[95,96] The reaction of nitromethane with sugar dialdehydes as shown in Eq. 3.59 is catalyzed with KF in isopropanol to give one isomer. If this reaction is carried out with sodium methoxide, the stereoselective becomes poor.[97]



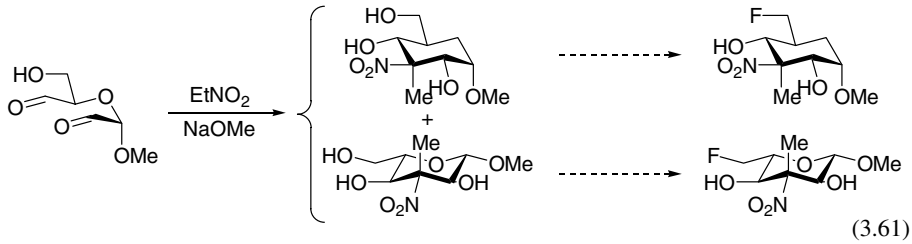

(3.59)

Base-catalyzed nitromethane cyclization of the dialdehyde generated by periodate oxidation of 1,2-*O*-cyclohexylidene-*myo*-inositol affords the nitrodiol with 1,4/2,3,5-configuration. This is converted into the α-mannosidase inhibitor, mannostatin A (Eq. 3.60).[98]



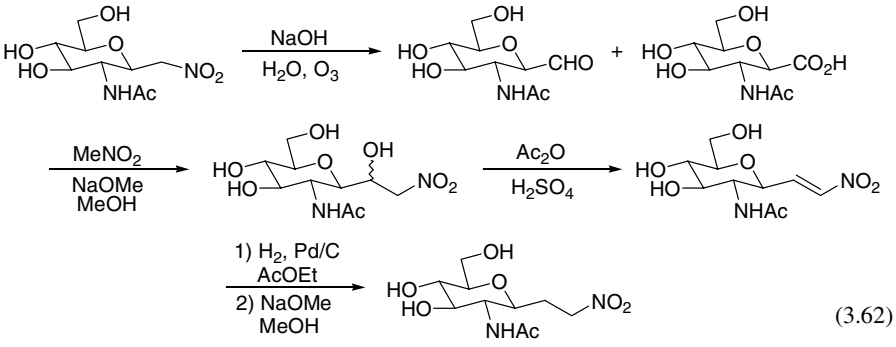

(3.60)

A mixture of methyl 3-deoxy-3-C-methyl-3-nitro-α-D- and β-L-glucopyranosides (1:1) is formed by the reaction of nitroethane with the sugar dialdehyde obtained from D-glucose. The products are separated and converted into branched-chain fluoro nitro D- and L-sugars (Eq. 3.61).[99]



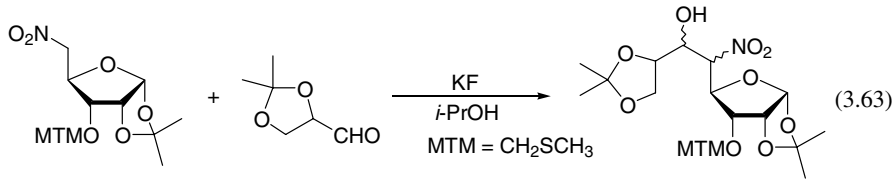

(3.61)

The anion of nitromethane adds easily to the carbonyl functions of sugars. This is a useful strategy for extension of the carbon chain.[100] 2-Acetamido-2-deoxy-β-D-glucose (*N*-acetyl-D-glucosamine) is the carbohydrate unit of glycoproteins that occurs most often. The nitromethylation method provides a straightforward route to a series of *C*-glycosyl compounds with the acetamido functionality (Eq. 3.62).[101]




(3.62)

If a carbohydrate already contains a nitro group, the nitro-bearing carbon atom can become the nucleophilic center for the coupling of two monosaccharide units (see Section 3.2.2). Suami and coworkers have used this method for the synthesis of antibiotics bearing sugars.[102] A typical example is presented in Eq. 3.63.[102b]

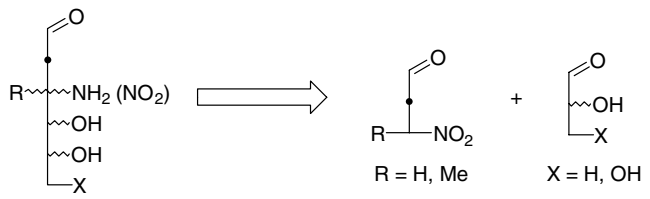



(3.63)

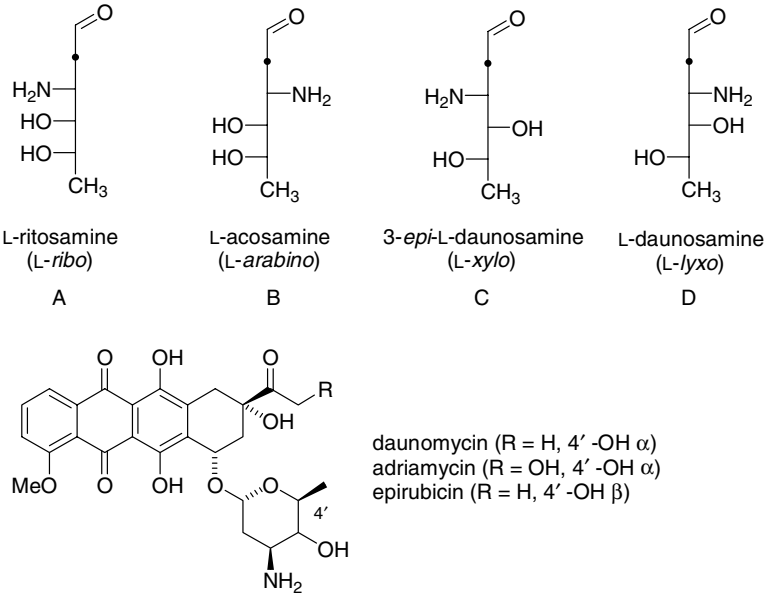
3-Nitro and 3-amino sugars have been prepared via stepwise construction from acyclic precursors by the nitro-aldol strategy as shown in Scheme 3.8.[103]

3-Amino-2,3,6-trideoxy-L-hexoses (A-D in Scheme 3.9) occur naturally, forming the glycone part of anthracyclinone antibiotics, important in anti-tumor treatment.[104]

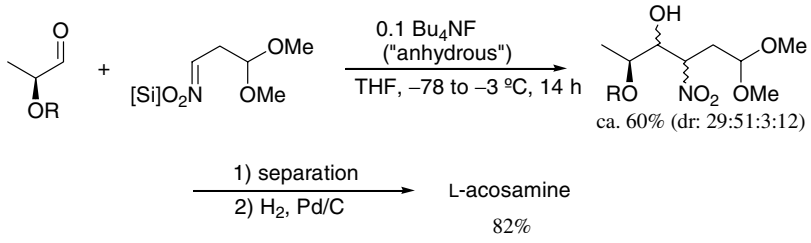
Several approaches based on nitro-aldol for the synthesis of amino sugars have been reported. Alumina-catalyzed reaction of methyl 3-nitropropanoate with *O*-benzyl-D-lactaldehyde gives the D-ribo-nitro-aldol (anti, anti isomer) in 63% yield, which is converted into L-daunosamine[17b,105] (see Section 3.3). Jager and coworkers have reported a short synthesis of L-acosamine based on the stereoselective nitro-aldol reaction of 2-*O*-benzyl-L-lactaldehyde with 3-nitropropanal dimethyl acetal as shown in Scheme 3.10.[106] The stereoselective nitro-aldol reaction is carried out by the silyl nitronate approach as discussed in Section 3.3.




**Scheme 3.8.**




**Scheme 3.9.**

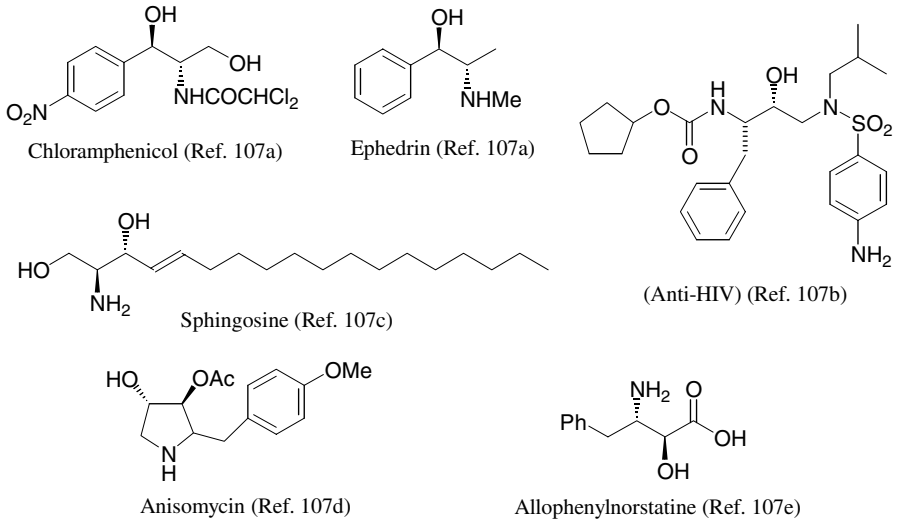



**Scheme 3.10.**

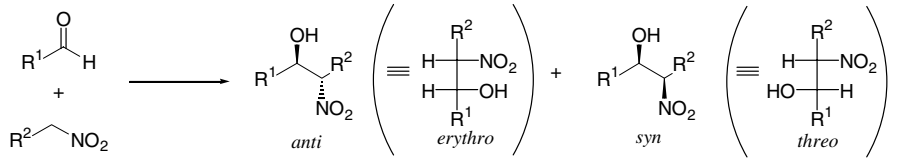
## 3.3 STEREOSELECTIVE HENRY REACTIONS AND APPLICATIONS TO ORGANIC SYNTHESIS

β-Nitro alcohols can be hydrogenated to the corresponding amino alcohols with retention of configuration; the stereoselective Henry reaction is a useful tool in the elaboration of pharmacologically important β-amino alcohol derivatives including chloramphenicol, ephedrine, norephedrine, and others. Some important β-amino alcohols are listed in Scheme 3.11.[107]

In general, the Henry reaction proceeds in a non-selective way to give a mixture of *anti (erythro)* and *syn (threo)* isomers. Ab initio calculations on the Henry reaction suggest that free nitronate anions (not influenced by cations) react with aldehydes via transition states in which the nitro and carbonyl dipoles are antiperiplanar to each other. This kind of reaction yields *anti*-nitro alcohols. The Henry reaction between lithium nitronates and aldehydes is predicted to occur via cyclic transition states yielding *syn*-nitro alcohols as major products (Eq. 3.64).[108]




**Scheme 3.11** Biological active β-amino alcohol derivatives



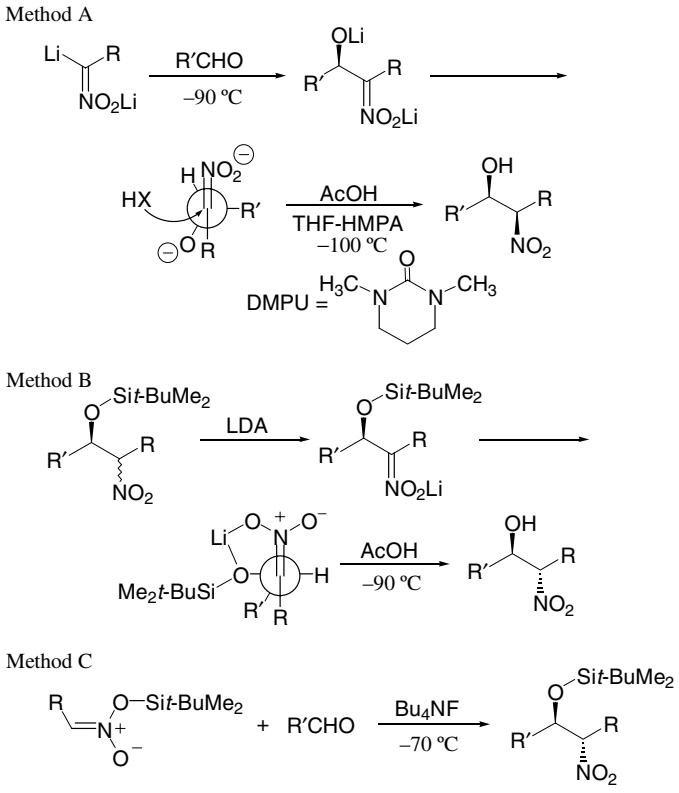

(3.64)

Seebach and co-workers have developed complementary protocols for stereocontrol of the Henry reaction (Scheme 3.12).[18,19]

- Method A: α,α-Doubly deprotonated nitroalkanes react with aldehydes to give intermediate nitronate alkoxides, which afford *syn*-nitroalcohols as major products (18:7–47:3) by kinetic protonation at −100 °C in THF-HMPA. The carcinogenic hexamethylphosphorous triamide (HMPA) can be replaced by the urea derivative (DMPU).
- Method B: In contrast, reprotonation of the *tert*-butyldimethylsilyl-protected nitronate anions gives *anti*-isomers selectively (41:9–19:1).
- Method C: High *anti*-selectivity is also observed in the fluoride-catalyzed reaction of silyl nitronates with aldehydes. Trialkyl silyl nitronates are prepared in good yield from primary nitroalkanes by consecutive treatment with lithium diisopropylamide and trialkylsilyl chloride at −78 °C in THF.

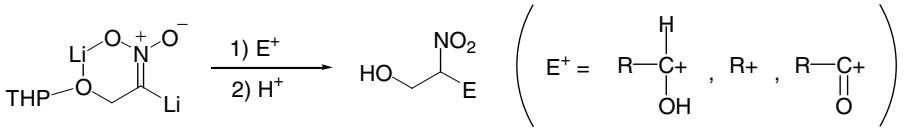
They react with a wide range of aliphatic and aromatic aldehydes in the presence of catalytic amounts of tetrabutylammonium fluoride (TBAF) to give the trialkylsilyl ethers of β-nitro alcohols with high *anti*-selectivity (98%). The diastereoselective Henry reaction is summarized in Table 3.2. The products are reduced to β-amino alcohols using Raney Ni-$H_2$ with retention of the configuration of β-nitro alcohols (Scheme 3.12).

Tetrahydropyranyl (THP)-protected nitroethanol can be doubly deprotonated to lithium α-lithionitronate, which is stable to react with various electrophiles. Higher β-nitro alcohols,

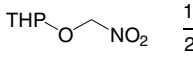



**Scheme 3.12.**

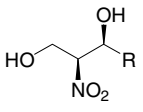
hydroxynitro ketones, and nitrodiols are prepared in good yields after deprotection of THP with an acidic ion-exchange resin in methanol. The nitrodiols are formed with high *syn*-diastereoselectivity (ds 75 to >95%). Because the nitro diols crystallize eventually, pure samples of single diastereomers can easily be prepared (Eqs. 3.65 and 3.66).[109]




(3.65)

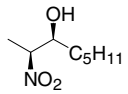
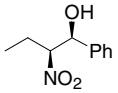
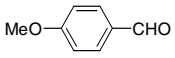
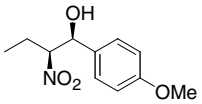
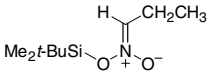
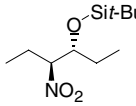
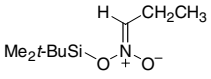
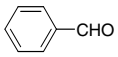
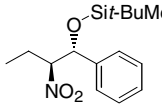
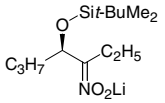
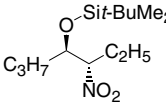
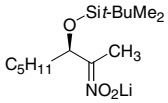
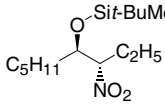
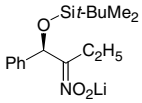
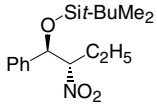



| R | Overall yield (%) | ds (%) |
|---|---|---|
| $Me_2CH$- | 68 | 93 |
| Ph- | 75 | >95 |
| *p*-$MeOC_6H_4$- | 79 | 80 |
| $C_{12}H_{25}$–C≡C– | 74 | 91 |

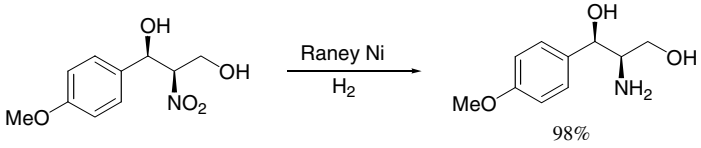


(3.66)

**Table 3.2. Stereoselective Henry reaction**

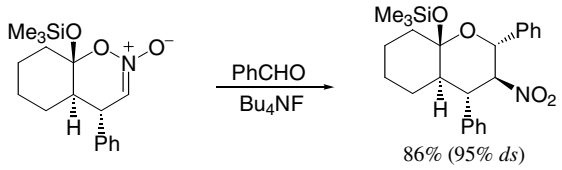
| Nitro compound | Aldehyde | Condition | Product | *syn*/*anti* |
|---|---|---|---|---|
| $CH_3CH_2NO_2$ | $C_5H_{11}CHO$ | 1) 2 *n*-BuLi in THF-HMPA<br>2) AcOH, –100 °C<br>(Method A) |  | 81/19 |
| $CH_3CH_2CH_2NO_2$ | PhCHO | 1) 2 *n*-BuLi in THF-HMPA<br>2) AcOH, –100 °C |  | 90/10 |
| $CH_3CH_2CH_2NO_2$ |  | 1) 2 *n*-BuLi in THF-HMPA<br>2) AcOH, –100 °C |  | 94/6 |
|  | $C_2H_5CHO$ | $Bu_4NF$<br>(Method C) |  | 5/95 |
|  |  | $Bu_4NF$ |  | 22/78 |
|  | | AcOH<br>(Method B) |  | 10/90 |
|  | | AcOH |  | 5/95 |
|  | | AcOH |  | 18/82 |

The products are reduced to amino diols with $H_2$-Raney Ni in ethanol without loss of configurational purity (Eq. 3.67).[109]



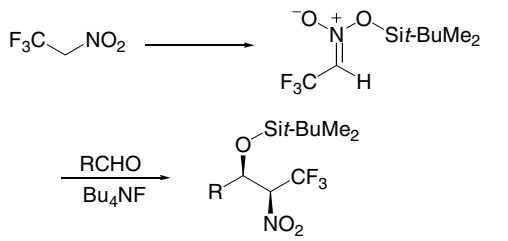

98% (3.67)

Bicyclic trimethylsilyl nitronates undergo stereoselective Henry reactions with benzaldehyde in the presence of fluoride ion to give cyclic hemiacetals in good yield with high diastereo-selectivity (95% ds) (Eq. 3.68).[110]



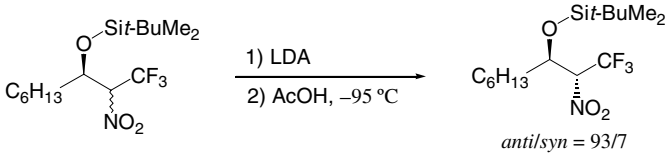

(3.68)

Silyl nitronates of 2,2,2-trifluoronitroethane react with aldehydes in the presence of $Bu_4NF$ in THF to give the *syn*-diastereomers of β-nitro alcohol, as shown in Eq. 3.69. This is in sharp contrast with the results of *anti*-isomers prevailing for non-fluorinated analogues. This is due to the *syn*/*anti* equilibrium of $CF_3$-substituted *O*-silyl nitro aldols. The *anti*-epimer in the trifluoromethyl series can be prepared by diastereoselective protonation of the corresponding *O*-silyl lithium nitronates (Eq. 3.70).[111]



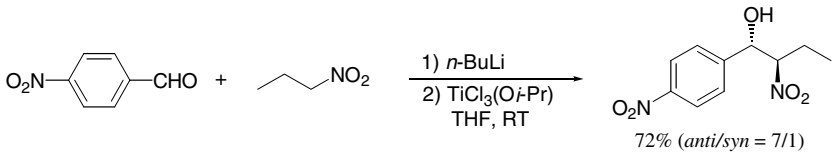

| R | Yield (%) | *syn*/*anti* |
|---|---|---|
| *i*-Pr- | 52 | 76/24 |
| Ph- | 72 | 75/ 25 |
| *p*-$MeOC_6H_4$- | 72 | 73/ 27 |

(3.69)




(3.70)

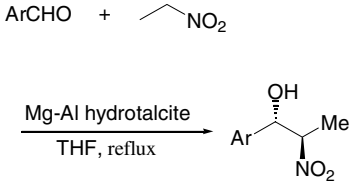
An experimentally simple procedure for stereoselectively preparing β-nitro alcohols has been developed. The alkyl nitronates, formed by the action of *n*-butyllithium on nitroalkanes in THF solution, react with aldehydes in the presence of isopropoxytitanium trichloride at room temperature to give the β-nitro alcohols enriched in the *anti*-diastereoisomers (Eq. 3.71).[112]




(3.71)

This method is particularly useful for electron-deficient aromatic aldehydes, but it is not efficient with aliphatic aldehydes, probably a consequence of competitive aldol reaction.

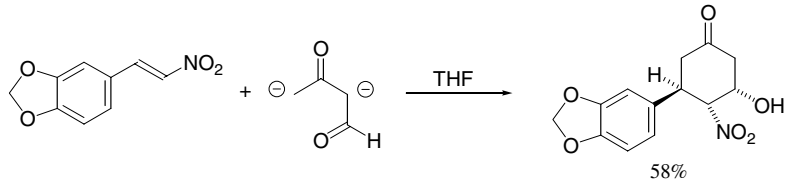
A new heterogeneous catalyst exists that uses Mg-Al hydrotalcites for the diastereoselective synthesis of β-nitro alcohols. The positively charged Mg-Al double hydroxide sheets are charge-balanced by the carbonate anions residing in the interlayer section of the clay structure. Both aromatic and aliphatic aldehydes react with nitroalkanes using this catalyst to give β-nitro alcohols in good yields. Diastereoselectivity depends on the structure of the aldehydes, 4-nitrobenzaldehyde and 2-chlorobenzaldehyde react with nitroethane to give the corresponding nitro alcohols in 100% *anti*-selectivity.[113] However, the reaction with aliphatic aldehydes exhibits low selectivity (Eq. 3.72).



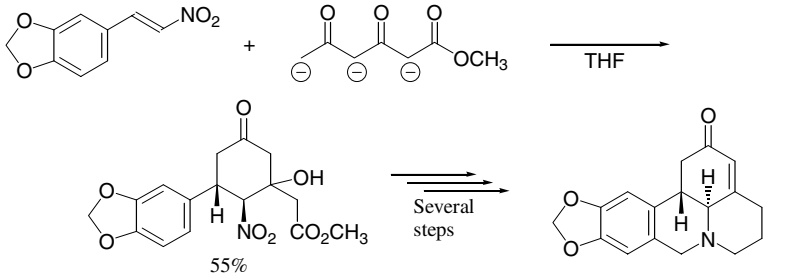

| Ar | Yield (%) | *anti*/*syn* |
|---|---|---|
| Ph- | 87 | 3.75/ 1 |
| *p*-$O_2NC_6H_4$- | 84 | 100/ 0 |
| *p*-$ClC_6H_4$- | 82 | 100/ 0 |
| *p*-$MeOC_6H_4$- | 62 | 1.23/1 |

(3.72)

The stereoselective intramolecular Henry reactions have been reported by Seebach. The Michael addition of doubly deprotonated acetyl acetaldehyde to 1-methylenedioxyphenyl-2-nitroethene followed by subsequent intramolecular nitro-aldol cyclization leads to the diastereomerically pure cyclohexanone derivative, where the nitro and OH groups are *cis* as shown in Eq. 3.73.[114] This reaction is applied to the synthesis of 1-desoxy-2-lycorinone as shown in Eq. 3.74.[115]




(3.73)

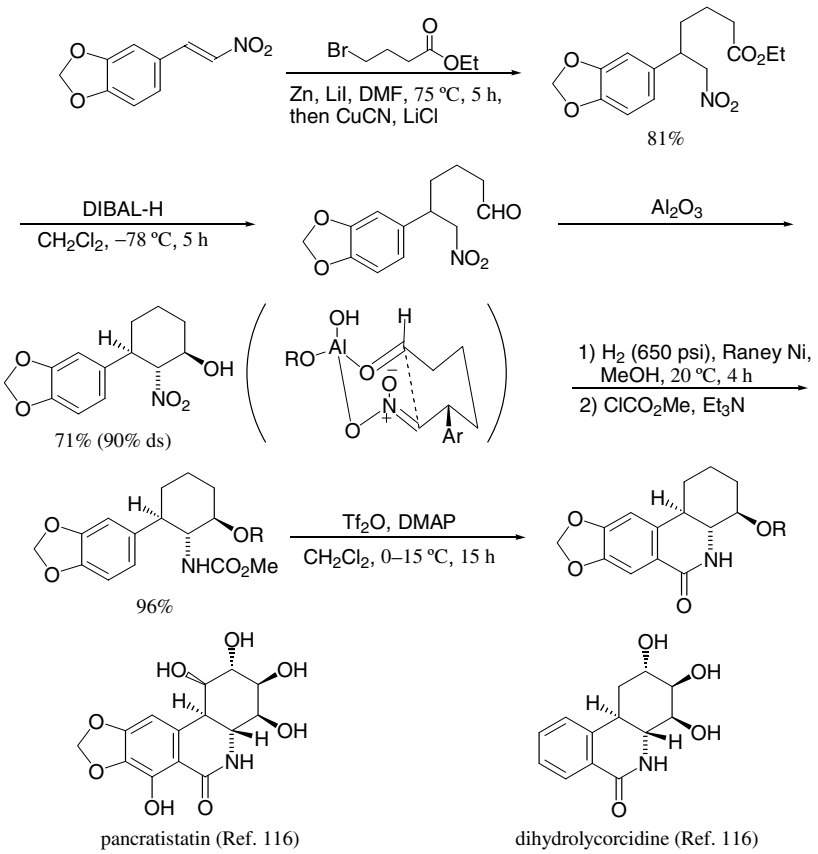



(3.74)

In consideration of the structure of the valuable anticancer alkaloids pancratistatin and *trans*-dihydrolycorcidine,[116] the development of an intramolecular nitro-aldol cyclization exhibiting alternative diastereoselectivity to that of Eq. 3.74 has been achieved. In contrast to cyclization of Eq. 3.74, a neutral alumina-promoted nitro-aldol cyclization provides the desired diastereoselectivity. Scheme 3.13 shows key steps of the total synthesis of lycoricidine alkaloids. Michael addition of the copper-zinc reagent derived from ethyl 4-bromobutanoate to nitroalkene[117] followed by the reduction with diisobutylaluminum hydride (DIBAL-H) gives the requisite nitro-aldehyde, which is the key substrate for the intramolecular nitro-aldol reaction. The alumina-promoted 6-*exo*-trig intramolecular nitro-aldol cyclization proceeds in a highly diastereoselective way via a chelation-controlled chair-like transition state. The major isomer has the correct relative configuration at three stereoisomers, as observed in the pancratistatin series of anti-tumor agents.[118]

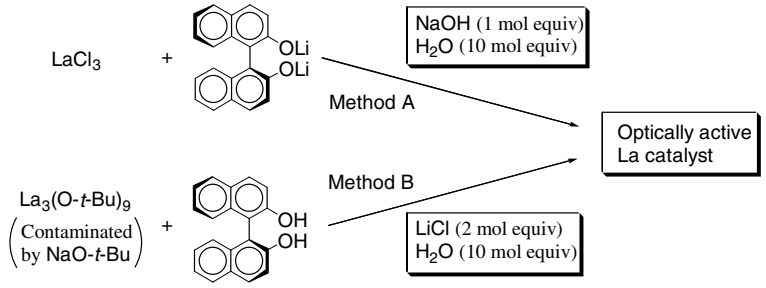
Over the last few years several examples have been reported in the field of asymmetric catalysis that are based on the interaction of two centers.[6,119] Recently, Shibasaki and coworkers have developed an asymmetric two-center catalyst. Scheme 3.14 shows preparation of optically active La binaphthol (BINOL). This catalyst is effective in inducing the asymmetric nitro-aldol reaction, as shown in Scheme 3.15.

These heterobimetallic $M^1$-$M^2$-binol complexes constitute a new class of widely applicable chiral catalysts as shown in Scheme 3.16. The new catalysts consist of a central metal ion (e.g., $La^{3+}$, $Al^{3+}$, $Sm^{3+}$, $Ga^{3+}$), three alkali metal ions (e.g., $Li^+$, $Na^+$, $K^+$), and three chiral diphenol

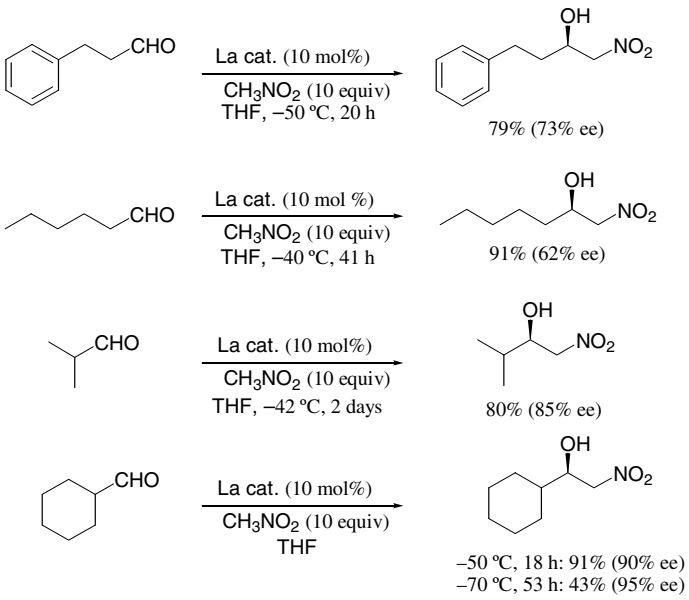



**Scheme 3.13.**

[1,1′-(*R*)- or 1,1′-(*S*)-binaphthol]. These catalysts exhibit basic as well as Lewis acid properties. They are easily prepared, stable to air and moisture, and nontoxic. By careful choice of the metal centers, various types of organic reactions are catalyzed. Asymmetric nitro-aldol reactions are catalyzed by lanthanoid-lithium-BINOL (LLB),[9,120] asymmetric Michael reactions are catalyzed by lanthanoid-sodium BINOL (LSB),[122] asymmetric hydrophosphonylation of imines is catalyzed by lanthanoid-potassium-BINOL (LPB),[121] and asymmetric Michael-aldol reactions




**Scheme 3.14.** Preparation of the optically active La-BINOL complex

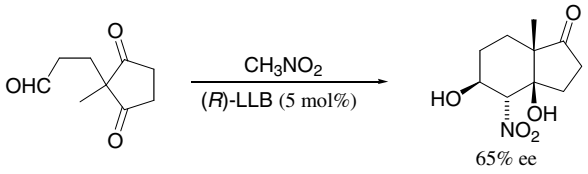



**Scheme 3.15.** La-BINOL complex-catalyzed asymmetric nitro-aldol reactions

and hydrophosphonylation of aldehydes are catalyzed by aluminum-lithium-BINOL (ALB).[122] The nitro-aldol reactions catalyzed by these catalysts are summarized here.

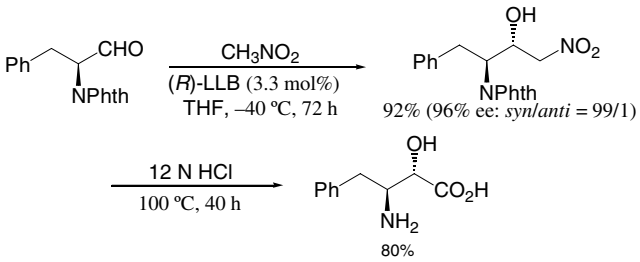
The enantioselective nitro-aldol reaction catalyzed by (*R*)-LLB is effectively applied to the synthesis of three kinds of optically active β-receptor blocking drugs (*S*)-metoprolol,[123a] (*S*)-propanolol,[123b] and (*S*)-pindolol[123c] (Scheme 3.17).

Shibasaki has also extended the use of LLB catalyst to tandem nitro-aldol reactions providing bicyclic adducts with 65% ee (Eq. 3.75).[124]

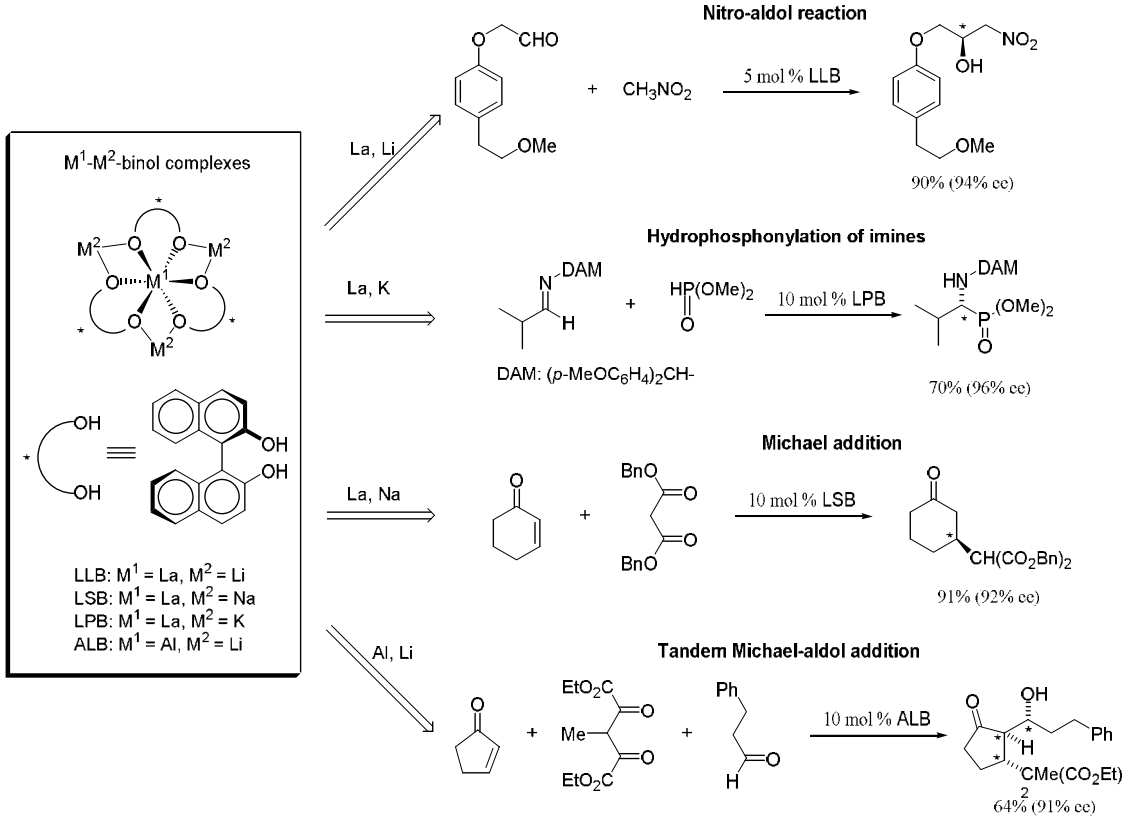



(3.75)

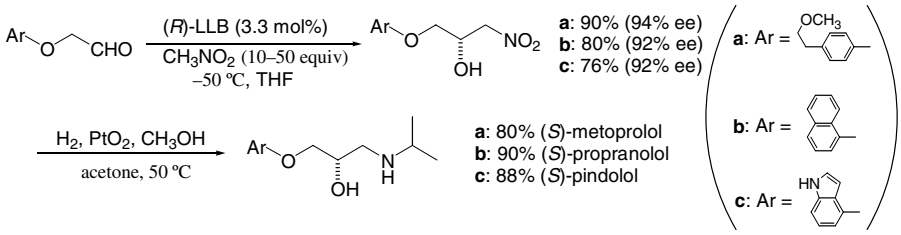
Diastereoselective catalytic nitro-aldol reactions of optically active *N*-phthaloyl-L-phenylalanal with nitromethane in the presence of LLB proceed with high diastereoselectivity (*anti*:*syn* = 99:1) as shown in Eq. 3.76.[125] The product is converted via the Nef reaction into (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid, which is a subunit of the HIV-protease inhibitor




(3.76)


M1-M2-binol complexes
LLB: M1 = La, M2 = Li
LSB: M1 = La, M2 = Na
LPB: M1 = La, M2 = K
ALB: M1 = Al, M2 = Li
La, Li
Nitro-aldol reaction
5 mol % LLB
90% (94% ee)
La, K
Hydrophosphonylation of imines
DAM: (p-MeOC6H4)2CH-
10 mol % LPB
70% (96% ee)
La, Na
Michael addition
10 mol % LSB
91% (92% ee)
Al, Li
Tandem Michael-aldol addition
10 mol % ALB
64% (91% ee)

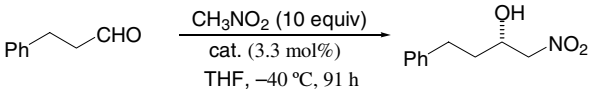
Scheme 3.16.




**Scheme 3.17.** Asymmetric syntheses of β-blockers with (R)-LLB as catalyst

KNI-272. The reaction of the same aldehyde with nitromethane using (*S*)-LLB leads to the reduced diastereoselectivity (74:26).

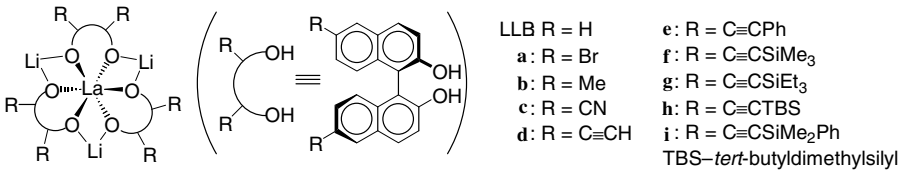
LLB-type catalysts are able to promote diastereo-selective and enantio-selective nitro-aldol reactions from prochiral materials. However, LLB gives unsatisfactory results in terms of both diastereoselectivity (Syn:Anti: 63:37 ~ 77:23) and enantioselectivity (<78% ee) in many cases (Scheme 3.15).[120a] A number of complexes **a**,**b**,**c**,**d**,**e**,**f**,**g**,**h**, and **i** are prepared, as shown in Scheme 3.18, in which BINOL rings are substituted by alkyl, alkenyl, alkynyl, and cyano groups. The effect of substituents on the BINOL rings is tested by the reaction of Eq. 3.77. Thus, stereoselectivity is affected by the substituents of BINOL, and alkynyl-substituted BINOLs, such as **f**–**i**, give the better optical activity of the product than LLB.[126] Another advantage is conferred by introducing 6,6′-substituents to BINOL.




(3.77)

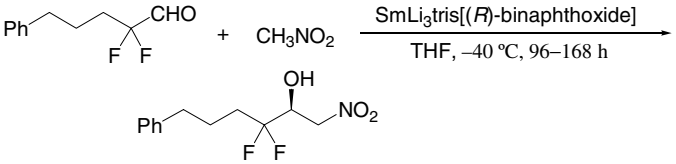
| Entry | Catalyst | Yield (%) | ee (%) |
|---|---|---|---|
| 1 | LLB | 79 | 73 |
| 2 | **a** | 80 | 67 |
| 3 | **b** | 84 | 63 |
| 4 | **c** | 67 | 55[a] |
| 5 | **d** | 69 | 71 |
| 6 | **e** | 74 | 79 |
| 7 | **f** | 85 | 88 |
| 8 | **g** | 84 | 85 |
| 9 | **h** | 59 | 85 |
| 10 | **i** | 54 | 86 |

[a] 6,6′-Dicyano-BINOL with 93% ee was used.



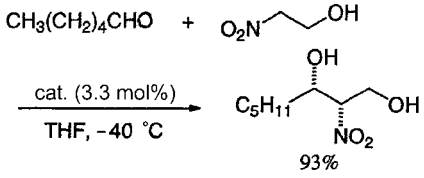

**Scheme 3.18.** Structural modification of LLB

The heterobimetallic asymmetric catalyst, Sm-Li-(*R*)-BINOL, catalyzes the nitro-aldol reaction of α,α-difluoroaldehydes with nitromethane in a good enantioselective manner, as shown in Eq. 3.78. In general, catalytic asymmetric syntheses of fluorine containing compounds have been rather difficult. The *S* configuration of the nitro-aldol adduct of Eq. 3.78 shows that the nitronate reacts preferentially on the *Si* face of aldehydes in the presence of (*R*)-LLB. In general, (*R*)-LLB causes attack on the *Re* face. Thus, enantiotopic face selection for α,α-difluoroaldehydes is opposite to that for nonfluorinated aldehydes. The stereoselectivity for α,α-difluoroaldehydes is identical to that of β-alkoxyaldehydes, as shown in Scheme 3.19, suggesting that the fluorine atoms at the α-position have a great influence on enantioface selection.

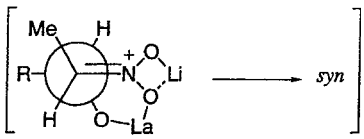


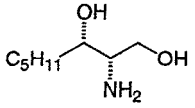

74% (87% ee) (3.78)

A *syn*-selective asymmetric nitro-aldol reaction has been reported for structurally simple aldehydes using a new catalyst generated from 6,6-bis[(triethylsilyl)ethynyl]BINOL (**g** in Scheme 3.18).[126] The *syn* selectivity in the nitro-aldol reaction can be explained by steric hindrance in the bicyclic transition state as can be seen in Newman projection. In the favored transition state, the catalyst acts as a Lewis acid and as a Lewis base at different sites. In contrast, the nonchelation-controlled transition state affords anti product with lower ee. This stereoselective nitro-aldol reaction has been applied to simple synthesis of *threo*-dihydrosphingosine by the reduction of the nitro-aldol product with $H_2$ and Pd-C (Eq. 3.79).




| Catalyst | Yield (%) | *syn*/*anti* | *ee* of *syn* |
|---|---|---|---|
| LLB | 79 | 87/13 | 78 |
| **g** (**Scheme 3.18**) | 96 | 92/8 | 95 |



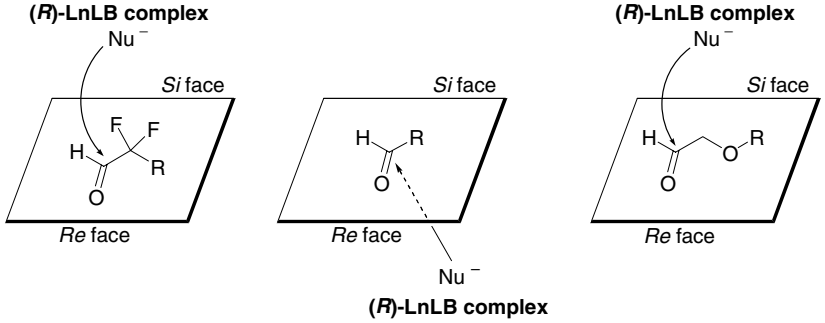




*threo*-dihydrosphingosine

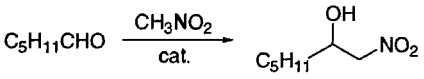
(3.79)

The LLB catalysts requires at least 3.3 mol% of asymmetric catalyst for efficient nitro-aldol reactions, and the reactions are rather slow (first generation). Second-generation LLB catalysts are prepared by addition of 1 equiv of $H_2O$ and 0.9 equiv of *n*-BuLi. The second-generation-catalysts are more reactive than the first generation LLB as shown in Eq. 3.80. The proposed mechanism of asymmetric nitro-aldol reaction using these catalysts is presented in Scheme 3.20.[128]

The diastereoselectivity is observed in the Henry reaction using optical active nitro compounds or α-heteroatom substituted aldehydes. For example, the reaction of O-benzyl-D-lactaldehyde with methyl 3-nitropropionate in the presence of neutral alumina leads to a mixture of three nitro-aldol products from which D-ribo isomer is isolated by direct crystallization. D-Ribo



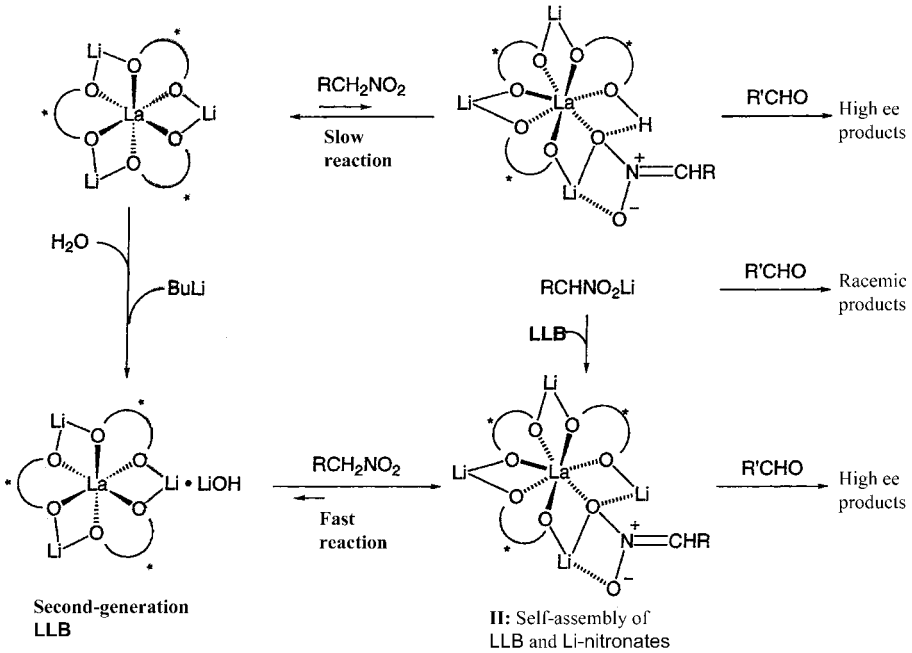

**Scheme 3.19.**




(3.80)

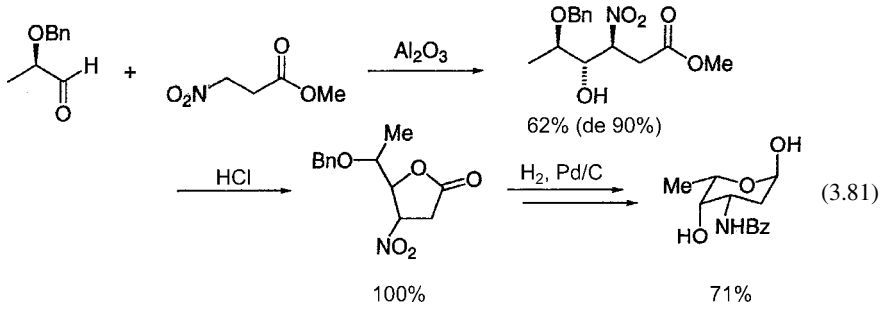
| Catalyst | Condition | Yield(%) | ee (%) |
|---|---|---|---|
| LLB (1 mol%) | −50 °C, 24 h | 56 | 88 |
| | −50 °C, 24 h | 73 | 89 |
| LLB-II | −50 °C, 4 h | 70 | 90 |

LLB-II = LLB + $H_2O$ (1 equiv) + BuLi (0.9 equiv).



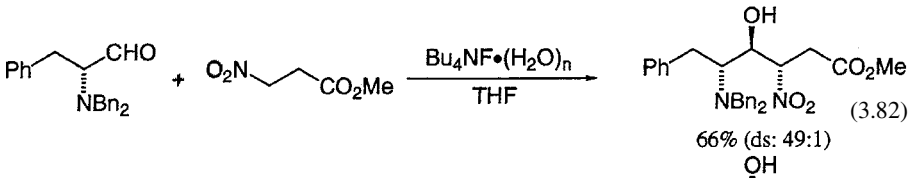

**Scheme 3.20.** Proposed mechanism of asymmetric nitro-aldol reactions catalyzed by LLB, LLB-II, or LLB-Li nitronate

isomer is the thermodynamic product, which is converted into *N*-benzoyl-L-daunosamine, as shown in Eq. 3.81.[129]

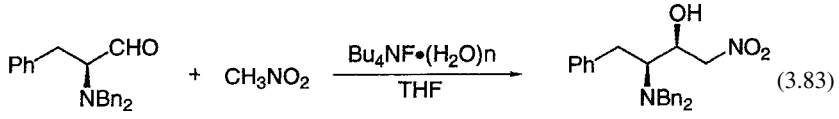


(3.81)

The Henry reactions of *N*,*N*-dibenzyl-L-phenylalaninal with nitroalkanes using 1.2 equiv of tetrabutylammonium fluoride (TBAF) as the catalyst proceed in a highly stereoselective manner, as shown in Eqs. 3.82 and 3.83.[130] This reaction provides rapid and stereoselective access to important molecules containing 1,3-diamino-2-hydroxypropyl segments, which are central structural subunit of the HIV protease inhibitor amprenavir (in Scheme 3.21).



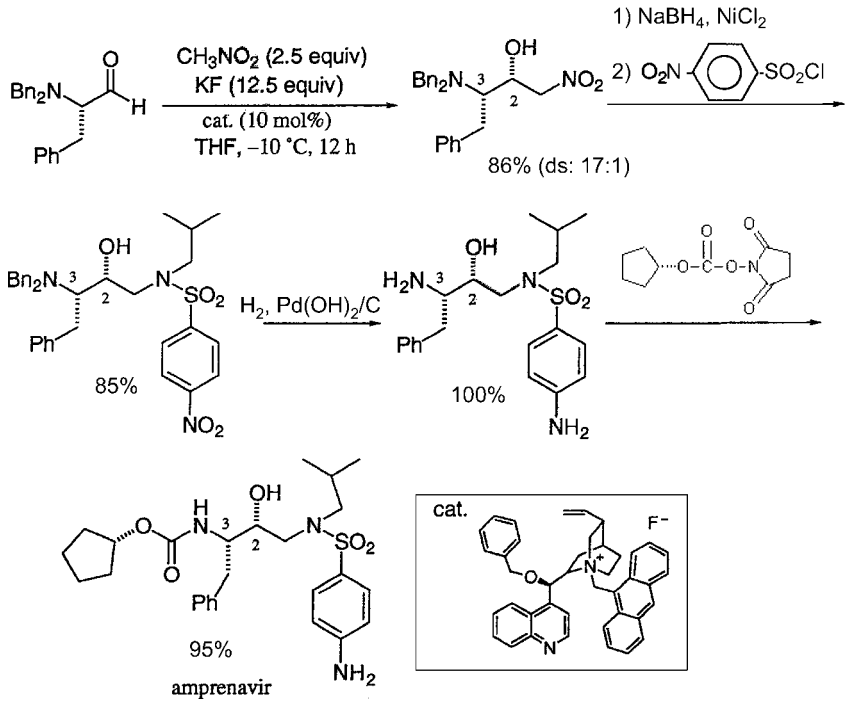
(3.82)
66% (ds: 49:1)



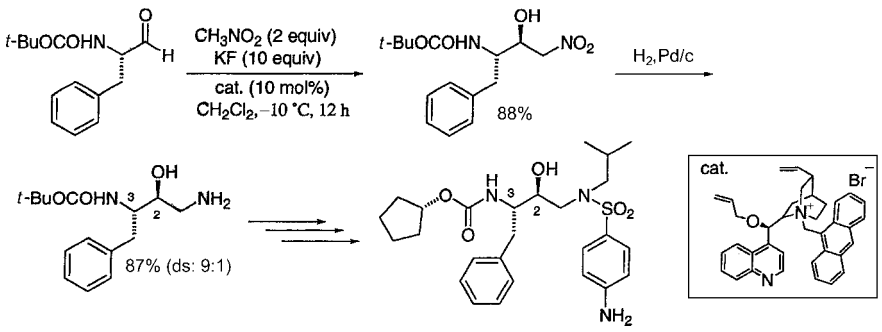
(3.83)
63% (ds: 8:1)

Corey has discovered that chiral quaternary ammonium salts shown in Schemes 3.21 and 3.22 are more effective for inducing *re*- and *si*-face-selective nitro-aldol reactions than TBAF.[131] The sequence utilized for the synthesis of amprenavir is shown in Scheme 3.21. The reaction of *N*,*N*-dibenzyl-(*S*)-phenylalanial with nitromethane gives the desired *syn*-nitro alcohol with a 17:1 diastereoselectivity. The diastereoselectivity is only 4:1 when TBAF is used. This nitro alcohol is reduced to the corresponding amino alcohol with $NaBH_4$ in the presence of $NiCl_2$ in 85% yield. The reductive alkylation with isobutyraldehyde followed by sulfonylation with *p*-nitrobenzenesulfonyl chloride, deprotection with $H_2$-Pd/C, and acylation with (*S*)-3-tetrahydrofuranyl-*N*-oxysuccinimidyl carbonate gives amprenavir in 50% overall yield from the starting amino aldehyde. The (2*S*,3*S*) isomer of amprenavir is prepared from *N*-*tert*-butoxycarbonyl derivative of (*S*)-phenyalaninal as shown in Scheme 3.22. The use of rigid chiral quaternary ammonium cations as shown in Schemes 3.21 and 3.22 control the face selectivity in nucleophilic addition of nitromethyl anion to aldehydes, *re*- or *si*-face selectivity depending on the *N*-protecting group of the *S*-phenylalaninal moiety. This provides a new strategy for stereocontrol of the Henry reaction.

Jager and coworkers have used the TBAF catalyzed-stereoselective nitro-aldol reaction for the synthesis of cyclic amino alcohols such as iminopolyols, imino sugars, and cyclic amino acids. They are important classes of compounds and have the potential utility as *anti*-diabetic,

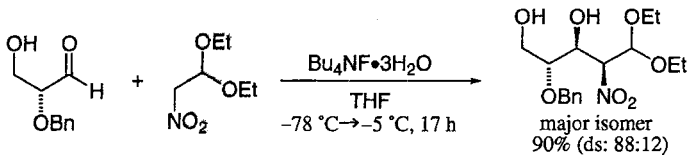



**Scheme 3.21.**



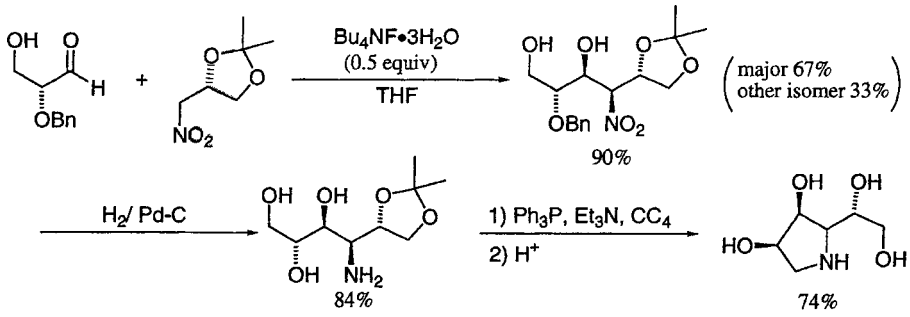

**Scheme 3.22.**

*anti*-viral, or *anti*-tumor agents.[132] TBAF-catalyzed reaction of α-alkoxy aldehydes with nitroacetaldehyde diethylacetal yields *anti-syn* diastereomers as predominant thermodynamic products (Eq. 3.84).[133] The products are good precursors of cyclic amino alcohols.



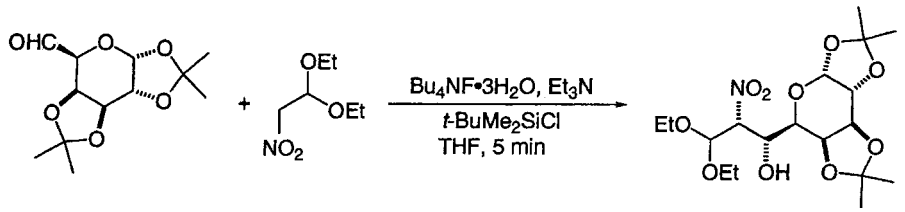

(3.84)

Another application of diastereoselective nitro-aldol reactions catalyzed by $Bu_4NF{\cdot}3H_2O$ is demonstrated in a simple synthesis of 1,4-dideoxy-1,4-imino-D-mannitol (DIM) and amino analogues (Eq. 3.85).[134] The nitro-aldol reaction of nitro compounds bearing α-oxy or α-amino function with glyceraldehyde leads to nitrohexitols, which can be reduced to the corresponding amino compounds. Cyclization gives iminopolyols, as shown in Eq. 3.85.




(3.85)

The nitro-aldol reaction using 1,1-diethoxy-2-nitroethane is useful for lengthening of the carbon chain of carbohydrates. The reaction of Eq. 3.86 proceeds in a stereoselective way (ds 75%) to give the *syn*-nitro alcohol in 58% isolated yield.[135] The product is converted into 2-amino-2-deoxyaldoses by reaction with $H_2$/Raney Ni.




(3.86)

## REFERENCES


1. Henry, L., and C. R. H. Seances. *Acad. Sci.*, **120**, 1265 (1895).
2. Baer, H. H., and L. Urbas, *The Chemistry of the Nitro and Nitroso Groups*, ed. by H. Feuer, Interscience, New York, Vol. 2, 1970.
3. Houben-weyl, *Methoden der Organischen Chemie*, 4th Ed., ed. by E. Muller, Vol. X/I, Georg Thieme Verlag, Stuttgart, 1971.
4. Rosini, G. *Comprehensive Organic Synthesis*, ed. by B. M. Trost, Vol. 2, Pergamon, New York, 1992.
5. Shvekhgeimer, M. C. A. *Russian Chemical Reviews*, **67**, 35 (1998).
6. Shibasaki, M., H. Sasai, and T. Arai. *Angew. Chem. Int. Ed. Engl.*, **36**, 1236 (1997).

7a. Vanderbilt, B. M., and H. B. Hass. *Industrial and Engineering Chemistry*, **32**, 34 (1940).
7b. Herman, L. W., and J. W. ApSimon. *Tetrahedron Lett.*, **26**, 1423 (1985).
7c. Simaneck, V., V. Preininger, A. Klasek, and J. Jurina, *Heterocycles*, **4**, 1263 (1976).
7d. Cavallo, A. S., H. Lapitais, P. Buchert, A. Klein, and S. Colonna, *J. Organomet. Chem.*, **330**, 357 (1987).
7e. Ballini, R., G. Bosica, and M. Petrini. *Chem. Lett.*, 1105 (1999).
7f. Dauben, H. J., Jr, H. J. Ringold, R. W. Wade, D. L. Pearson, and A. G. Anderson, Jr. *Org. Synth*, **4**, 221 (1963).

8. Worrall, D. E. *Org. Synth.* **1**, 413 (1941).

9a. Sasai, H., S. Arai, and M. Shibasaki. *J. Org. Chem.*, **59**, 2661 (1994).

9b. Sasai, H., T. Suzuki, S. Arai, T. Arai, and M. Shibasaki. *J. Am. Chem. Soc.*, **114**, 4418 (1992).
10. Torssell, K., and O. Zeuthen. *Acta Chem. Scand*., **B32**, 118 (1978).
11. Simoni, D., F. P. Invidiata, S. Manfredini, R. Ferroni, H. Lampronti, M. Roberti, and G. P. Po llini. *Tetrahedron Lett*., **38**, 2749 (1997).
12. Ono, N., H. Katayama, S. Nishiyama, and T. Ogawa. *J. Heterocyclic Chem.*, **31**, 707 (1994).
13. Ono, N., H. Kawamura and K. Maruyama. *Bull. Chem. Soc. Jpn.*, **62**, 3386 (1989).
14. Ono, N., and K. Maruyama. *Bull. Chem. Soc. Jpn.*, **61**, 4470 (1988).
15. Morao, I., and F. P. Cossio. *Tetrahedron Lett.*, **38**, 6461 (1997).
16a. Kambe, S., and H. Yasuda. *Bull. Chem. Soc. Jpn.*, **41**, 1444 (1968).
16b. Wollenburg, R. H., and S. J. Miller. *Tetrahedron Lett.*, 3219 (1978).
17a. Clark, J. H., and J. M. Miller. *J. Chem. Soc. Perkin Trans 1*, 940 (1978).
17b. Ohrlein, R., and V. Jager. *Tetrahedron Lett*., **29**, 6083 (1988).
18. Seebach, D., A. K. Beck, F. Lehr, T. Weller, and E. Colvin. *Angew. Chem. Int. Ed. Engl*., **20**, 397 (1981).
19. Seebach, D., A. K. Beck, T. Mukhopadhyay, and E. Thomas. *Helv. Chim Acta*, **65**, 1101 (1982).
20. Fernandez, R., C. Gasch, A. G-Sanchez, and J. E. Vichezz. *Tetrahedron Lett.*, **32**, 3225 (1991).
21. Kisanga, P. B., and J. G. Verkade. *J. Org. Chem*., **64**, 4298 (1999).
22. Rosini, G., R. Ballini, and P. Sorrenti. *Synthesis*, 1014 (1983).
23. Melot, J. M., F. Texier-Boullet, and A. Foucaud. *Tetrahedron Lett.*, **27**, 493 (1986).
24a. Rosini, G., R. Ballini, and M. Petrini. *Synthesis*, 46 (1986).
24b. B. Ballini and M. Petrini, *J. Chem. Soc. Perkin Trans 1*, 3159 (1992).
25. Ballini, R., G. Bosica, and P. Forconi. *Tetrahedron*, **52**, 1677 (1996).
26. Caldarelli, M., J. Habermann, and S. V. Ley. *J. Chem. Soc. Perkin Trans 1*, 107 (1999).
27. Ballini, R., and G. Boscia. *J. Org. Chem.*, **62**, 425 (1997).
28. Torssell, K. B. G., and K. V. Gothelf. Nitromethane and nitroethane, in *Encyclopedia of Reagents for Organic Synthesis*, ed. by L. Paquette, Wiley, New York, 1996.
29. Matsumoto, K. *Angew. Chem. Int. Ed. Engl*., **23**, 617 (1984).
30. Seebach, D., and L. Lehr. *Angew. Chem. Int. Ed. Engl*., **15**, 505 (1976).
31a. Barton, D. H. R., W. B. Motherwell, and S. Z. Zard. *J. Chem. Soc. Chem. Commun*., 551 (1982).
31b. Barton, D. H. R., W. B. Motherwell, and S. Z. Zard, *Bull. Soc. Chim. Fr., II*, 61 (1983).
32. Tamura, R., M. Sato, and D. Oda. *J. Org. Chem*., **51**, 4368 (1986).
33. Ono, N., I. Hamamoto, A. Kamimura, A. Kaji, and R. Tamura. *Synthesis*, 259 (1987).
34. Wipf, P., and S. Lin. *J. Am. Chem. Soc*., **117**, 558 (1995).
35. Barrett, A. G. M., and J. T. Kohrt. *Synlet*, 415 (1995).
36. Williams, T. M., R. Crumbie, and H. S. Mosher. *J. Org. Chem*., **50**, 91 (1985).
37. Pandey, G., T. D. Bagul, and A. K. Sahoo. *J. Org. Chem.*, **63**, 760 (1998).
38. Grethe, G., T. Mitt, T. H. Williams, and M. R. Uskokovic. *J. Org. Chem*., **48**, 5309 (1983).
39. Demir, A. S., C. Tanyeli, A. S. Mahasneh, and H. Aksoy. *Synthesis*, 155 (1994).
40. Poupart, M. A., G. Fazal, S. Goulet, and L. T. Mar. *J. Org. Chem*., **64**, 1356 (1999).
41. Kaneko, S., T. Yamazaki, and T. Kitazume. *J. Org. Chem*., **58**, 2302 (1993).
42. Nitroethylene, 1-nitro-1-propene and 2-nitro-1-propene, see *Encyclopedia of Reagents for Organic Synthesis*, ed. by L. Paquette, Wiley, New York, 1996.
43. Ranganathan, D., C. B. Rao, S. Ranganathan, A. K. Mehrotra, and R. Iyengar. *J. Org. Chem*., **45**, 1185 (1980).
44. Noland, W. E. *Org. Synth.*, **5**, 833 (1973).
45. Miyashita, M., T. Yanami, and A. Yoshikoshi. *Org. Synth.* **7**, 396 (1990).
46. Hass, H. B., A. G. Susie, and R. Heider. *J. Org. Chem.*, **15**, 8, (1950).
47a. Melton, J., and J. E. McMurry. *J. Org. Chem*., **40**, 2138 (1975).
47b. Palomo, C., J. M. Aizpurua, F. P. Cossio, J. M. Garcia, M. C. Lopez, and M. Oiarbide. *J. Org. Chem*., **55**, 2070 (1990).
48. Knochel, P., and D. Seebach. *Synthesis*, 1017 (1982).
49. Saikia, A. K., N. C. Barua, R. P. Sharma, and A. C. Ghosh. *Synthesis*, 685 (1994).
50. Denmark, S. E., and L. R. Marcin. *J. Org. Chem.*, **58**, 3850 (1993).
51. Stanetty, P., and M. Kremslehner. *Tetrahedron Lett.*, **39**, 811 (1998).
52. Ono, N., A. Kamimura, T. Kawai, and A. Kaji. *J. Chem. Soc., Chem. Commun*., 1550 (1987).
53a. Ballini, R., R. Castagnani, and M. Petrini. *J. Org. Chem*., **57**, 2160 (1992).

53b. Rosini, G., R. Ballini, M. Oetrini, and P. Sorrenti. *Synthesis*, 515 (1985).
54. Mathieu, J., and J. Weill-Raynal. *Formation of C-C Bonds*, Vol. II, George Thieme, Stuttgart, 1975, pp 576–577.
55. Heinzelman, R. V. *Org. Synth.*, **4**, 573 (1963).
56. Ahmad, S., W. B. Whaley, and D. F. Jones. *J. Chem. Soc. (C)*, 3590 (1971).
57. Drehal, G., and H. Ehrhardt, *Chem. Ber.*, **93**, 500 (1960).
58. Remberz, G., and M. Schwill. *J. Prakt. Chem.*, [4] **31**, 127 (1966).
59a. McDonald, E., and R. T. Martin. *Tetrahedron Lett.*, 1317 (1977).
59b. Ono, N., H. Kawamura, M. Bougauchi, and K. Maruyama. *Tetrahedron*, **46**, 7483 (1990).
60a. Clark, J. H., A. P. Kybett, and D. J. Macquarrie. *Supported Reagents*, VCH, New York, 1992.
60b. Clark, J. H., and D. J. Macquarrie. *Chem. Soc. Reviews*, 303 (1996).
61. Bandgar, B. P., M. B. Zirange, and P. P. Wadgaonkar. *Synlett.*, 149 (1996).
62a. McMulty, J., J. A. Steere, and S. Wolf. *Tetrahedron Lett.*, **39**, 8013 (1998).
62b. Ayoubi, S. A. E., F. T. Boullet, and J. Hamelin. *Synthesis*, 258 (1994).
63. Valma, R. S., R. Dahiya, and S. Kumar. *Tetrahedron Lett.*, **38**, 5131 (1997).
64a. Lahnert, W. *Tetrahedron*, **28**, 663 (1972).
64b. Dauzonne, D., and R. Royer. *Synthesis*, 399 (1987).
65a. Fornicola, R. S., E. Oblinger, and J. Montogomery. *J. Org. Chem.*, **63**, 3528 (1998).
65b. Rodrigues, R., A. Diez, M. Rubiralta, and E. Giralt. *Heterocycles*, **43**, 513 (1996).
66. Novellino, L., M. d'Ischia, and G. Prota. *Synthesis*, 793 (1999).
67. He, F., Y. Bo, J. D. Altom, and E. J. Corey. *J. Am. Chem. Soc.*, **121**, 6771 (1999).
68a. Seebach, D., and P. Knochel. *Helv. Chim. Acta*, **67**, 261 (1984).
68b. Knochel, P., and D. Seebach. *Tetrahedron Lett.*, **23**, 3897 (1982).
69. Eberle, M., M. Egli, and D. Seebach. *Helv. Chim. Acta*, **71**, 1 (1988).
70a. Barco, A., S. Benetti, G. P. Pollini, G. Spalluto, and V. Zanirato. *Tetrahedron Lett.*, **32**, 2517 (1991).
70b. Barco, A., S. Benetti, C. De-Risi, C. F. Morelli, G. P. Pollini, and V. Zenirato. *Tetrahedron*, **52**, 9275 (1996).
71a. Schechter, H., D. E. Ley, and E. B. Robertson, Jr. *J. Am. Chem. Soc.*, **78**, 4984 (1956).
71b. Nair, V., and A. K. Sinhababu. *J. Org. Chem.*, **45**, 1893 (1980).
71c. Hassner, A., and C. Heathcock. *J. Org. Chem.*, **29**, 1350 (1964).
72. Meyers, A. I., and J. C. Sircar. *J. Org. Chem.*, **32**, 4134 (1967).
73. Sinhababu, A. K., and R. T. Borchardt. *Tetrahedron Lett.*, **24**, 227 (1983).
74. Nagatsu, T. *Biochemistry of Catecholamines*, Univ. of Tokyo Press, 1973.
75a. Bhattachariya, A., R. Mukhopadhyay, and S. C. Pakrashi. *Synthesis*, 886 (1985).
75b. Dauzonne, D., and R. Royer, 1054 (1984).
76. Mahboobi, S., and K. Bernauer. *Helv. Chim. Acta*, **71**, 2034 (1988).
77a. Ranu, B. C., and R. Charkraborty. *Tetrahedron Lett.*, **32**, 3579 (1991).
77b. Ranu, B. C. *Synthesis*, 885 (1983).
78. Gupta, A., A. Hasque, and Y. D. Vankar. *Chem. Commun.*, 1653 (1996).
79a. Bachman, G. B., and R. J. Maleski. *J. Org. Chem.*, **37**, 3810 (1972).
79b. Bosone, E., P. Farina, G. Guazzi, S. Innocenti, V. Marottaand, and U. Valcavi. *Synthesis*, 942 (1983).
80a. Mock, G. A., and J. G. Moffatt. *Nucleic Acids Res.*, **10**, 6223 (1982).
80b. Buchanan, J. G., A. Flinn, P. H. C. Mundill, and R. H. Wightman. *Nucleosides Nucleotides*, **5**, 136 (1986).
80c. Martin, O. R., and W. Lai. *J. Org. Chem.*, **58**, 176 (1993).
81a. Ohta, H., N. Kobayashi, and K. Ozaki. *J. Org. Chem.*, **54**, 1802 (1989).
81b. Kawai, Y., M. Hayashi, Y. Inaba, K. Saitou, and A. Ohno. *Tetrahedron Lett.*, **39**, 5225 (1999).
82. Hurd, C. D., and M. E. Nilson. *J. Org. Chem.*, **20**, 927 (1955).
83. Rosini, G., and R. Ballini. *Synthesis*, 543 (1983).
84a. Rosini, G., R. Ballini, P. Sorrenti, and M. Petrini. *Synthesis*, 607 (1984).
84b. Ballini, R., G. Bosica, and M. Oarrini. *Tetrahedron Lett.*, **39**, 7963 (1998).
85. Bachman, G. B., and T. Hokoma. *J. Am. Chem. Soc.*, **81**, 4882 (1959).
86. Hamada, Y., K. Ando, and T. Shioiri. *Chem. Pharm. Bull.*, **29**, 259 (1981).
87. Crumbie, R. L., J. S. Nimitz, and H. S. Mosher. *J. Org. Chem.*, **47**, 4040 (1982).
88. Ono, N., M. Fujii, and A. Kaji. *Synthesis*, 532 (1987).

89. Ono, N., and A. Kaji. *Synthesis*, 693 (1986).
90. Rosini, G., and R. Ballini. *Synthesis*, 833 (1988).
91. Rosini, G., R. Ballini, and P. Sorrenti. *Tetrahedron*, **39**, 4127 (1983).
92. Rosini, R., R. Ballini, and M. Petrini. *Synthesis*, 269 (1985).
93. Ballini, R. *J. Chem. Soc. Perkin Trans 1*, 1419 (1991).
94a. Hauser, F. M., and S. Ellenberger, *Chem. Rev*., **86**, 35 (1986).
94b. Rinhalt, K. L., and T. Suami. *Aminocyclitol Antibiotics*, American Chemical Society, Washington DC, 1980.
95. Wade, P. W., and R. M. Giuliano. *Nitro Compounds Recent Advances in Synthesis and Chemistry*, ed. by H. Feuer and A. T. Nielsen, VCH, New York, 1990.
96a. Baer, H. H. *Adv. Carbohyd. Chem. Biochem.* **24**, 67 (1969).
96b. Lichtentaler, F. W., Fortsch. *Chem. Forsch*, **14**, 556 (1970).
96c. Gonzalev, F. S., and F. H. Mateo. *Synlett*, 715 (1990) and references therein.
97. Gonzalez, F. S., and B. A. Vargas. *Tetrahedron*, **46**, 4083 (1990).
98. Ogawa, S., and Y. Yuming. *J. Chem. Soc., Chem. Commun.*, 890 (1991).
99. Carmona, A. T., P. Borrachero, F. C. Escribano, M. J. Dianez, M. D. Estrada, A. L. Castro, R. Ojeda, M. G. Guillen, and S. P. Garrido. *Tetrahedron Asymmetry*, **10**, 1751 (1999).
100a. Thronchet, J. M. J., K. D. Pallie, and F. B. Rey. *J. Carbohydr. Chem.*, **4**, 29 (1985).
100b. Binkley, R. W., and J. C. Fan. *J. Carbohydr. Chem.*, **2**, 213 (1982).
101. Petrusova, M., J. N. BeMiller, and L. Petrus. *Tetrahedron Lett.*, **37**, 2341 (1996).
102a. Fukuda, Y., H. Kasai, and T. Suami. *Bull. Chem. Soc. Jpn.*, **54**, 1830 (1981).
102b. Sakanaka, O., T. Ohmori, S. Kozaki, T. Suami, T. Ishii, S. Ohba, and Y. Saito. *Bull. Chem. Soc. Jpn*., **59**, 1753 (1986).
102c. Sakanaka, S., T. Ohmori, S. Kozaki, and T. Suami. *Bull. Chem. Soc. Jpn.*, **60**, 1057 (1987).
102d. Kanai, K., J. Nishigaki, S. Ogawa, and T. Suami. *Bull. Chem. Soc. Jpn.*, **60**, 261 (1987).
102e. Maguire, M. P., P. L. Feldman, and H. Rapoport. *J. Org. Chem.*, **55**, 948 (1990).
103. Hauser, F. M., and S. R. Ellenberger. *Chem. Rev.*, 86, 35 (1986).
104a. Hanessian, S., and J. Klose. *Tetrahedron Lett.*, **26**, 1261 (1985).
104b. Hanessian, S., and P. V. Decasthale. *Tetrahedron Lett.* **37**, 987 (1996).
105a. Jager, V., and V. Wehner. *Angew. Chem. Int. Ed. Engl.*, **28**, 469 (1989).
105b. Kies, F. M., P. Poggendorf, S. Picasso, and V. Jager. *Chem. Commun.*, 119 (1998).
106. Menzel, A., R. Ohrlein, H. Griesser, V. Wehner, and V. Jager. *Synthesis*, 1691 (1999).
107a. Lednicer, D. A., and L. A. Mitscher. *The Organic Chemistry of Drug Synthesis*, John Wiley and Sons, New York, 1975.
107b. Shibata, N., T. Katoh, and S. Terashima. *Tetrahedron Lett.*, **38**, 619 (1997).
107c. Koskinen, P. M., and M. P. Koskinen. *Synthesis*, 1075 (1998).
107d. Veith, U., O. Schwardt, and V. Jager. *Synlett*., 1181 (1996).
107e. Bunnage, M. E., S. G. Davis, C. J. Goodwin, and O. Ichihara. *Tetrahedron*, **50**, 3975 (1994).
108. Lecca, B., A. Arrieta, I. Morao, and F. P. Cossio, *Chem. Eur. J.*, **3**, 20 (1997).
109. Eyer, M., and D. Seebach. *J. Am. Chem. Soc.*, **107**, 3601 (1985).
110. Brook, M. A., and D. Seebach. *Can. J. Chem.*, **65**, 836 (1987).
111. Marti, R. E., J. Heinzer, and D. Seebach. *Liebigs Ann*., 1193 (1995).
112. Barrett, A. G. M., C. Robyr, and C. D. Spilling. *J. Org. Chem.*, **54**, 1233 (1989).
113. Bulbule, V. J., V. H. Deshpande, S. Velu, A. Sudalai, S. Sivasankar, and V. T. Sathe. *Tetrahedron*, **55**, 925 (1999).
114. Ehrig, V., and D. Seebach. *Chem. Ber.*, **108**, 1961 (1975).
115. Weller, T., and D. Seebach. *Tetrahedron Lett.*, **23**, 935 (1982).
116. Pettit, G. R., G. R. Pettit III, R. A. Backhaus, M. R. Boyd, and A. W. Meerow. *J. Nat. Prod.*, **56**, 1682 (1993).
117. Jubert, C., and P. Knochel. *J. Org. Chem.*, **57**, 5431 (1992).
118. McNulty, J., and R. Mo. *Chem. Commun.*, 933 (1998).
119. Steinhagen, H., and G. Helmchen. *Angew. Chem. Int. Ed. Engl.*, **35**, 2239 (1996).
120a. Sasai, H., T. Suzuki, N. Itoh, K. Tanaka, T. Date, K. Okamura, and M. Shibasaki. *J. Am. Chem. Soc*., **115**, 10372 (1993).
120b. Sasai, H., T. Arai, Y. Satow, K. N. Houk, and M. Shibasaki. *J. Am. Chem. Soc.*, **117**, 6194 (1995).
121. Sasai, H., S. Arai, Y. Tahara, and M. Shibasaki. *J. Org. Chem.*, **60**, 6656 (1995).

122. Arai, T., H. Sasai, K. Aoe, K. Okamura, T. Date, and M. Shibasaki. *Angew. Chem. Int. Ed. Engl.*, **35**, 104 (1996).
123a. Sasai, H., T. Suzuki, N. Itoh, S. Arai, and M. Shibasaki, *Tetrahedron Lett.*, **34**, 2657 (1983).
123b. Sasai, H., N. Itoh, T. Suzuki, and M. Shibasaki. *Tetrahedron Lett.*, **34**, 855 (1983).
123c. Sasai, H., Y. M. A. Yamada, T. Suzuki, and M. Shibasaki. *Tetrahedron*, **50**, 12313 (1994).
124. Sasai, H., M. Hiroi, Y. M. A. Yamada, and M. Shibasaki. *Tetrahedron Lett.*, **38**, 6031 (1997).
125. Sasai, H., W. S. Kim, T. Suzuki, and M. Shibasaki. *Tetrahedron Lett.*, **33**, 6123 (1994).
126. Sasai, H., T. Tokunaga, S. Watanabe, T. Suzuki, N. Itoh, and M. Shibasaki. *J. Org. Chem.*, **60**, 7388 (1995).
127. Iseki, K., S. Oishi, H. Sasai, and M. Shibasaki. *Tetrahedron Lett.*, **37**, 9081 (1996).
128. Arai, T., Y. M. A. Yamada, N. Yamamoto, H. Sasai, and M. Shibasaki. *Chem. Eur. J.*, **2**, 1368 (1996).
129. Hanessian, S., and J. Kloss. *Tetrahedron Lett.*, **26**, 1261 (1985).
130. Hanessian, S., and P. V. Devasthale. *Tetrahedron Lett.*, **37**, 987 (1996).
131. Corey, E. J., and F. Y. Zhang. *Angew. Chem. Int. Ed. Engl.*, **38**, 1931 (1999).
132a. Gasiraghi, G., F. Zanardi, G. Rassu, and P. Spanu. *Chem. Rev.*, **95**, 1677 (1995).
132b. Hudlicky, T., D. A. Entwistle, K. K. Pitzer, and A. J. Thorpe. *Chem. Rev.*, **96**, 1195 (1996).
133. Wehner, V., and V. Jager. *Angew. Chem. Int. Ed. Engl.*, **29**, 1169 (1990).
134. Kiess, F. M., P. Poggendorf, S. Picasso, and V. Jager. *Chem. Commun.*, 119 (1998).
135. Fernandez, R., C. Gasch, A. G. Sanchez, J. E. Vilchez, A. L. Castro, M. J. Dianez, M. D. Estra da, and S. P. Garrido. *Carbohydrate Research*, **247**, 239 (1993).