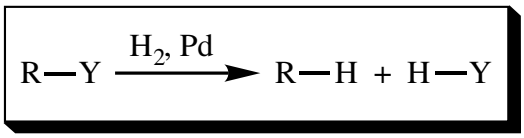

III.3 Palladium-Catalyzed Carbon–Hydrogen and Carbon–Heteroatom Coupling

III.3.1 Palladium-Catalyzed Hydrogenolysis

ANTHONY O. KING and ROBERT D. LARSEN

A. INTRODUCTION

Palladium catalysts are the most widely used catalysts for the hydrogenolysis of organic substrates. Pt and Raney nickel catalysts are also effective for hydrogenolysis in many cases but are used much less frequently than palladium. As shown below in this section, palladium catalysts can catalyze effectively the hydrogenolysis of a wide variety of functional groups. Carbon–carbon, carbon–halogen, carbon–nitrogen, carbon–oxygen, nitrogen–nitrogen, nitrogen–oxygen, and oxygen–oxygen bonds can all be hydrogenolyzed readily under palladium catalysis. The reaction conditions are generally mild and by choosing the appropriate catalysts and reaction conditions, many other functional groups in the substrate can be tolerated. The following presents a summary of Pd-catalyzed hydrogenolysis reactions that have been reported in the literature.

B. HYDROGENOLYSIS OF CYCLOPROPANE

The hydrogenolysis of cyclopropyl derivatives is a convenient method for the introduction of a methyl or methylene group into the substrate. The location of the C—C bond cleavage on the cyclopropyl ring system can be predicted in many cases by the substitution pattern on the ring and the 3-D structure of the substrate.

Hydrogenolysis of tricyclic ketone **1** provided selectively [4.3.0] bicyclic ketone **2** (**Scheme 1**).[1]

The release of the four-membered ring strain is probably the driving force for this regioselective ring opening. In an analogous system, but with even less steric congestion because of the absence of the dimethyl substituents, bicyclo[2.1.0]amino acid **3** still preferably opened at the more substituted C—C bond to give pyrrolidine product **4** (**Scheme 2**).[2]

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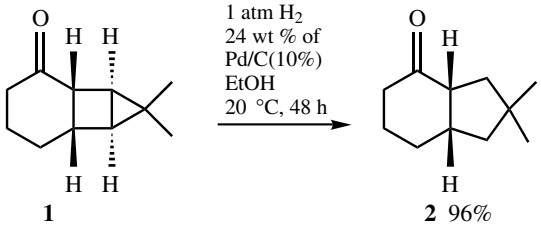
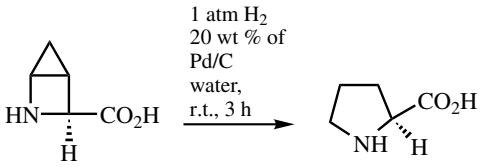


1 **2** 96%

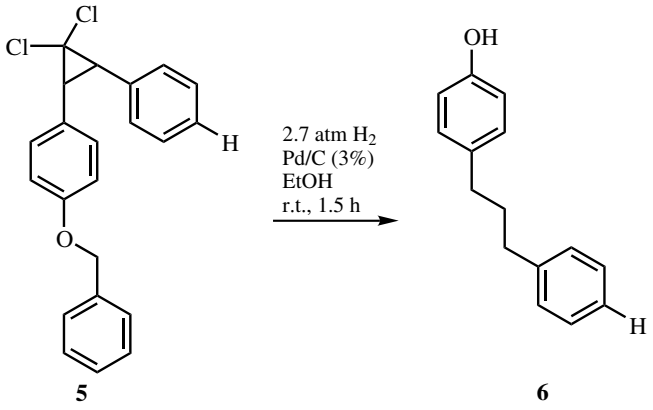
Scheme 1



3 **4**

Scheme 2

Hydrogenolysis of 1,1-dichloro-substituted cyclopropane **5** using 3% Pd/C catalyst proceeded at the C—C bond directly opposite the chloro-substituted carbon to give 1,3-diarylpropane **6** (**Scheme 3**).[3] Lindlar's catalyst was not effective. Dropping the Pd on carbon loading from 3% to 1% gave only dechlorination without ring opening. Therefore, the dechlorination reaction most likely proceeded first before the ring cleavage with the 3% Pd/C catalyst. Although the hydrogenolyzed C—C bond was more hindered, the electronic activation provided by the presence of the two aryl substituents may have overcome the steric factor.

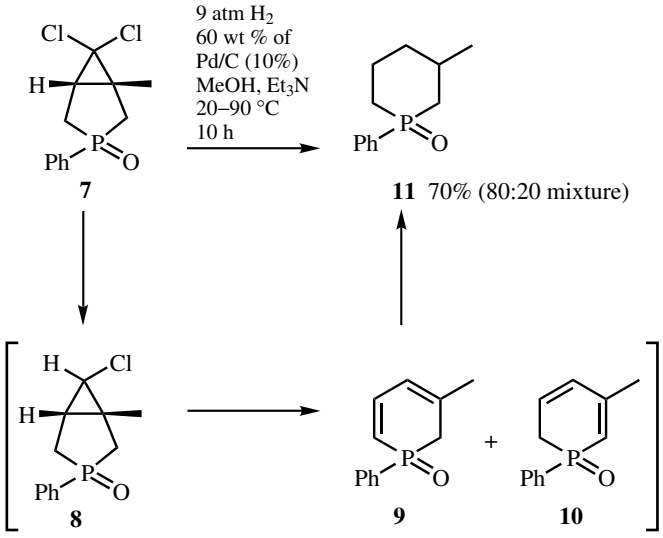


5 **6**

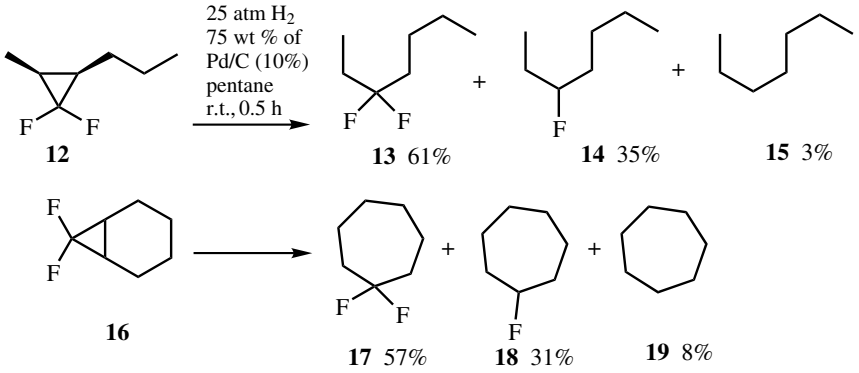
Scheme 3

Bicyclo[3.1.0]phosphine oxide **7** also gave a diastereomeric mixture of the six-membered phosphine oxide **11** in 70% yield and not the five-membered ring product (**Scheme 4**).[4] The hydrogenolysis proceeded through the mixture of dihydrophosphinines.

Similarly, 1,1-difluorinated cyclopropanes **12** and **16** reacted via the cleavage of the C—C bond directly opposite the difluoro-substituted carbon (**Scheme 5**).[5]



Scheme 4



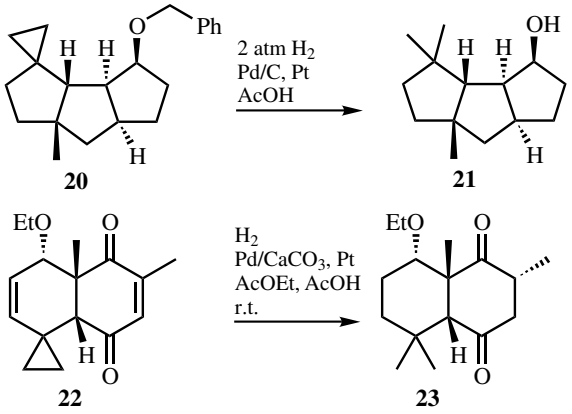
Scheme 5

In fact, *gem*-difluorocyclopropanes undergo hydrogenolysis much faster than monofluorocyclopropanes. Although hydrogenolysis of the C—F bond is usually very difficult, in these instances, loss of one or both of the fluorine atoms was also observed.

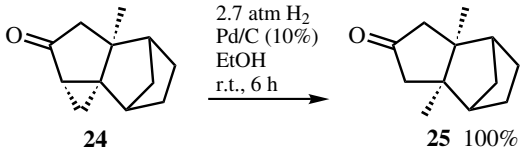
Cyclopropanation of an olefin followed by hydrogenolysis of the resulting cyclopropane is an effective method for the introduction of a methyl group onto a substrate. A *geminal* dimethyl group can be prepared readily in this fashion. However, Pt is a more effective catalyst as shown in these examples. Thus, spiro compounds **20** and **22** were hydrogenolyzed to dimethyl derivatives **21** and **23**, respectively (**Scheme 6**).[6],[7]

Although steric factors may have influenced the regioselective ring opening in **24**, which produced the symmetrical ketone **25** quantitatively, the carbonyl group also directed the cleavage of the C—C bond (**Scheme 7**).[8]

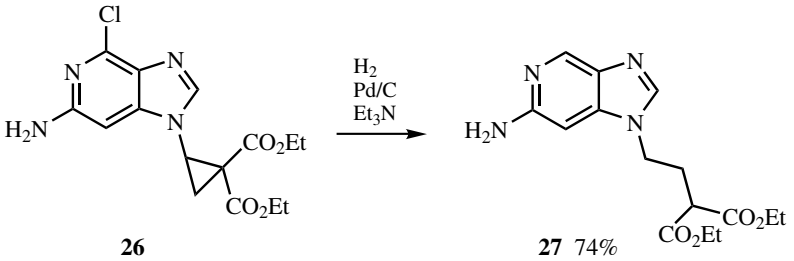
The *geminal* bis-(ethoxycarbonyl)-substituted cyclopropane **26** effectively countered the steric problem to give cleavage at the more highly substituted C—C bond (**Scheme 8**).[9] The nitrogen atom may also have assisted in directing this C—C bond cleavage.



Scheme 6



Scheme 7



Scheme 8

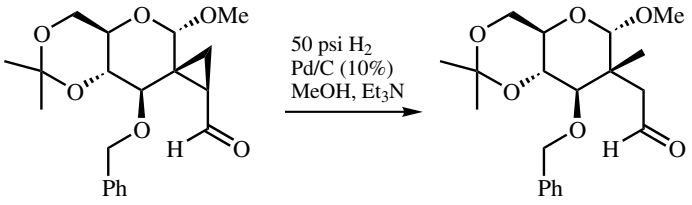
Both steric and electronic effects favored the observed ring opening in **28** producing the β-methyl aldehyde (**Scheme 9**).[10] Addition of Et_3N helped in suppressing the hydrogenolysis of the benzyl ether functional group.

Inversion of configuration at the tertiary carbon center during the hydrogenolysis of **30** was observed (**Scheme 10**).[11] This is a normal mode of reaction with Pd catalysts.

In the absence of any electronic activation, whether the C—C bond in the cyclopropyl ring is approachable by the Pd catalyst is probably the key factor in the observed hydrogenolysis of **32** (**Scheme 11**).[12]

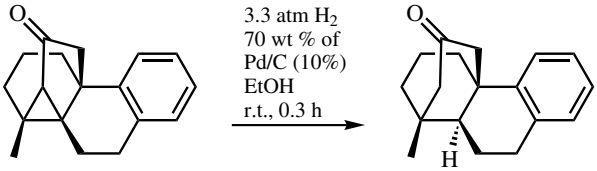
Depending on the substituent R^1 in vinylcyclopropane **34**, the cyclopropyl ring can open to give methyl or straight chain products (**Scheme 12**).[13] Methyl products were obtained when R^1 was an alkyl group and straight chain products were obtained when R^1 was an aryl or acrylate group.

The symmetrical dicyclopropyl **37** hydrogenolyzed to the tetramethylated product **38** in 88% yield.



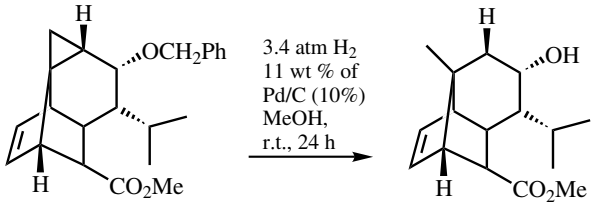
28 **29** 65%

Scheme 9



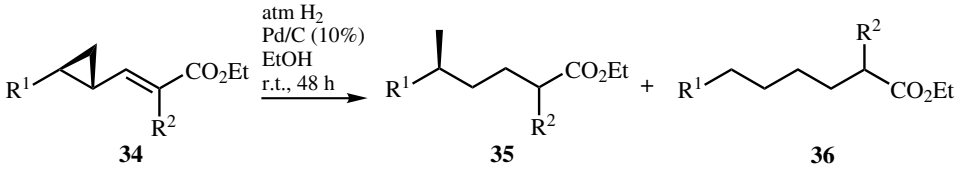
30 **31** 89%

Scheme 10



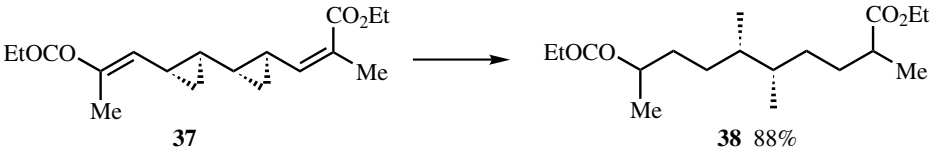
32 **33** 85%

Scheme 11



34 **35** **36**

R^1 = *i*-Pr, R^2 = H	90%	R^1 = Ph, R^2 = H	82%
R^1 = cyclohexyl, R^2 = H	94%	R^1 = Ph, R^2 = Me	80%
R^1 = cyclohexyl, R^2 = Me	96%	R^1 = (*E*)-EtOCOCHCH, R^2 = H	90%



37 **38** 88%

Scheme 12

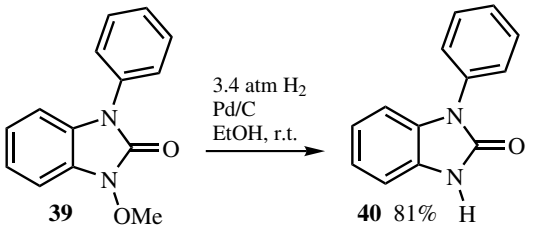
C. HYDROGENOLYSIS OF N—O BOND

The N—O bond can be hydrogenolyzed under mild reaction conditions, generally in a protic solvent with Pd catalyst and H_2. The *N*-methoxy group in imidazolone **39** was cleaved in excellent yield (**Scheme 13**).[14]

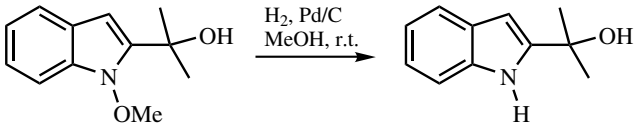
N-Alkoxy indoles were hydrogenolyzed to indoles (**Scheme 14**).[15]

Both primary and secondary amines can be obtained from the hydrogenation of nitrones (**Scheme 15**).[16]

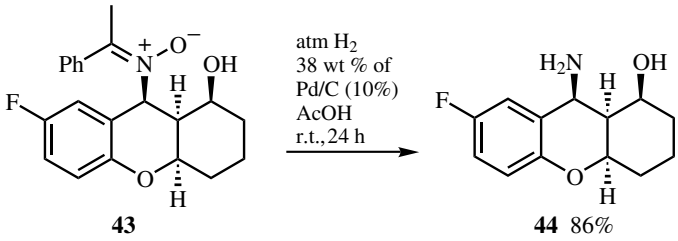
Hydroxylamines derived from the Grignard addition to nitrones were hydrogenolyzed to give primary amines after the *N*-benzyl group on the nitrogen was simultaneously hydrogenolyzed (**Scheme 16**).[17]



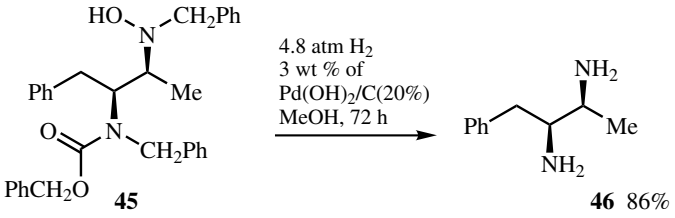
Scheme 13



Scheme 14



Scheme 15



Scheme 16

Amidoxime **47** was reduced to amidine **48** in 94% yield (**Scheme 17**).[18] Use of TFA/TFAA instead of $AcOH/Ac_2O$ was better in one instance.

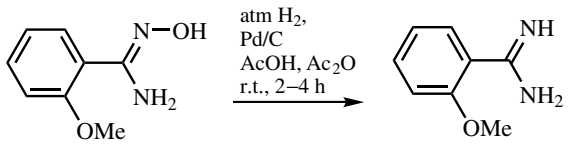
Ring opening of cyclic compounds containing an N—O bond is readily accomplished to give amino alcohols. For isoxazolidines **49** and **51** the *O*-benzyl, *N*-benzyl, and *N*-benzhydryl groups were also cleaved under the reaction conditions (**Scheme 18**).[19],[20]

With isoxazolones **53** and isoxazolidinones **55**, β-amino acids were obtained (**Scheme 19**).[21],[22] Spontaneous decarboxylation was only observed with substitution on C-3 of the isoxazolone ring (**54b**). In these examples, the olefin and the *N*-*p*-methoxybenzyl groups stayed intact.

Instead of alcoholic solvents, THF has also been used for the hydrogenolysis of the N—O bond as in isoxazolidine **57** (**Scheme 20**).[23]

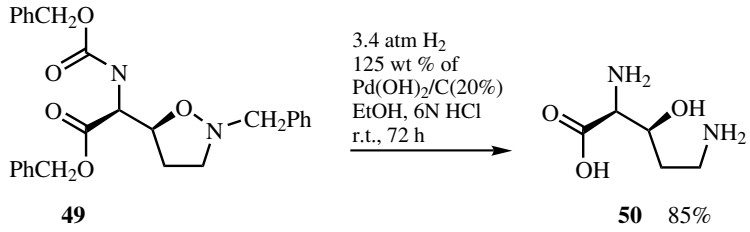
The rate of hydrogenation of *O*-methyloxime was slower than the hydrogenolysis of benzyloxycarbonyl and N—O groups in 1,2-oxazine **59**, which allowed the subsequent reductive amination to take place providing piperidine **60** (**Scheme 21**).[24]

The use of Lindlar's catalyst and aqueous acidic conditions allowed the generation of β-hydroxy ketone **62** from oxazole **61** with the disubstituted olefin remaining intact (**Scheme 22**).[25] A yield of 65% was obtained even when a monosubstituted olefin was present.

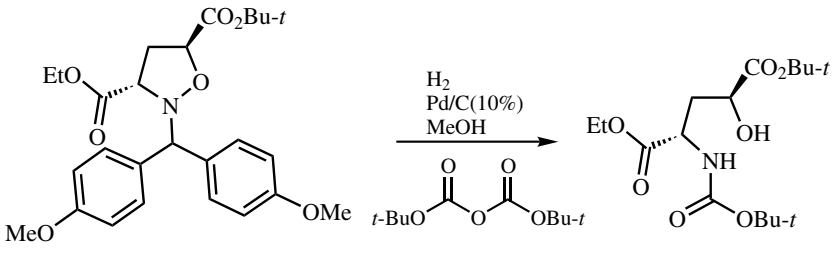


47 **48** 94%

Scheme 17

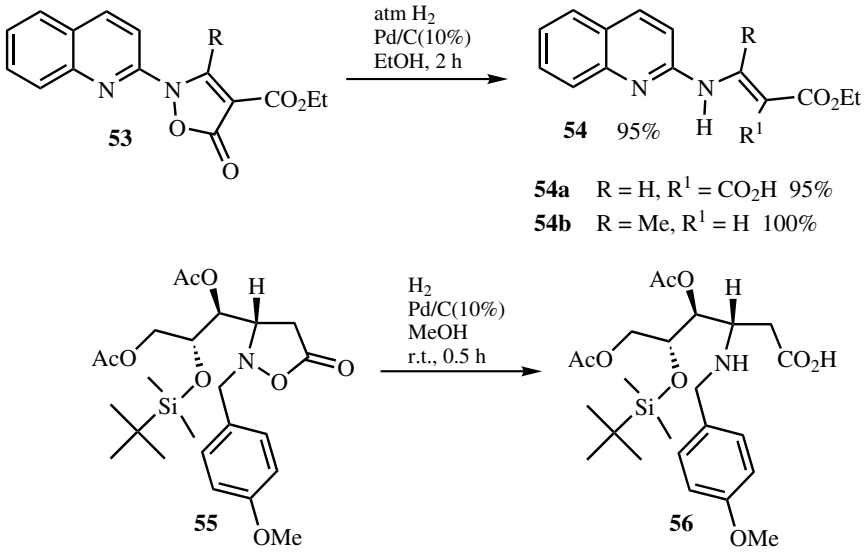


49 **50** 85%

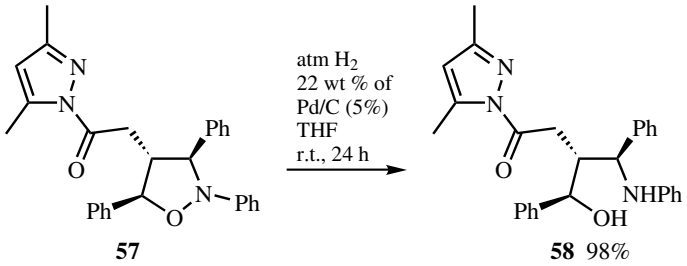


51 **52** 82%

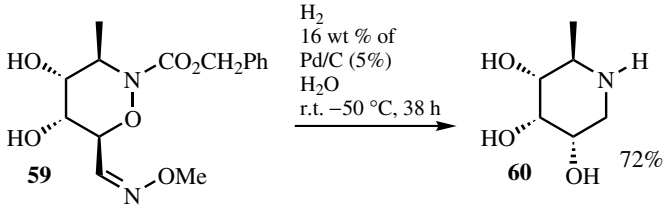
Scheme 18



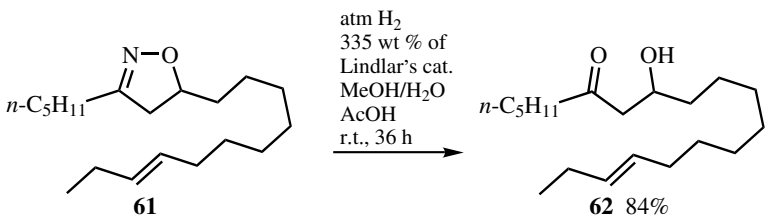
Scheme 19



Scheme 20



Scheme 21



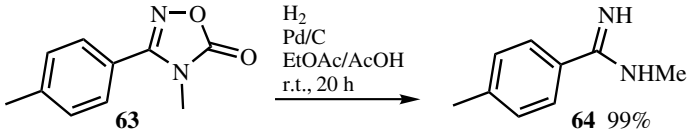
Scheme 22

Hydrogenolysis of oxazolidinone **63** gave amidine **64** in excellent yield (**Scheme 23**).[26]

Primary chloride removal was also slower than N—O bond cleavage. Thus, the newly formed amine from the highly diastereoselective reduction of oxazole **65** was able to further react with the chloro electrophile producing the pyrrole in an overall 96% yield (**Scheme 24**).[27]

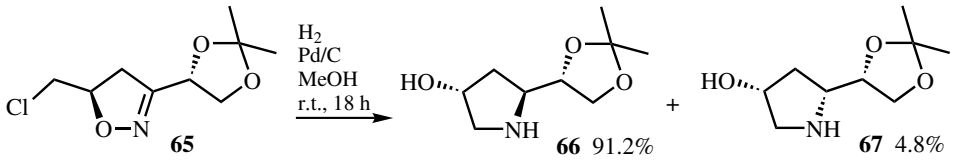
The catalytic reduction proceeded first with the N—O bond cleavage but the sequence of subsequent chemical transformations has not been delineated. Since ketone can be generated from the hydrogenation of oxazine **68**[28] (**Scheme 25**), there is a possibility that reduction of the cyclic imine is the final step of the sequence.

1,4-Reductive nitrogen transposition could be carried out with dihydrooxazine **70**. A diastereoselective version, in which the diacetoneglucose was used as an auxiliary, provided chiral **73** in 80% ee (**Scheme 26**).[29]



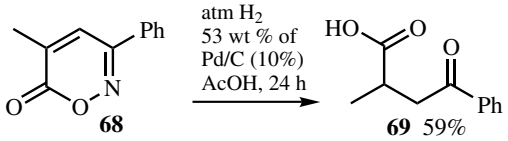
63 **64** 99%

Scheme 23



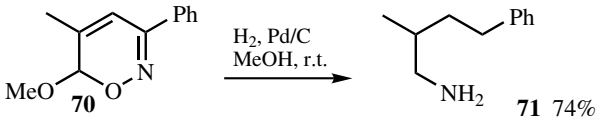
65 **66** 91.2% **67** 4.8%

Scheme 24

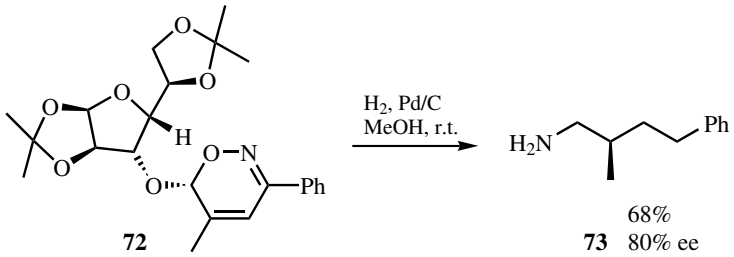


68 **69** 59%

Scheme 25



70 **71** 74%



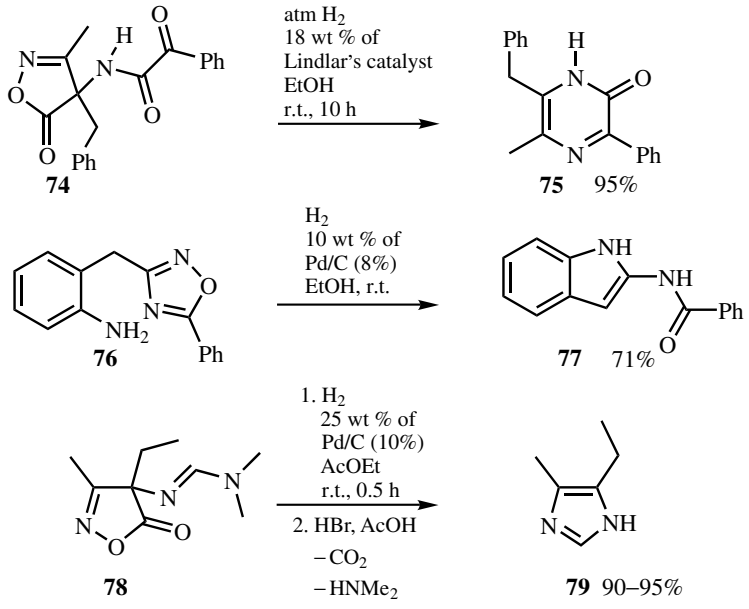
72 **73** 68% 80% ee

Scheme 26

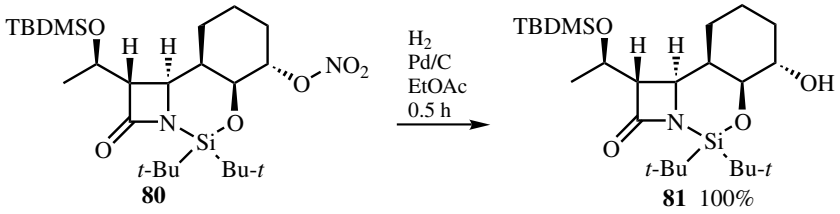
With suitably constructed oxazapyrrolidinones, new heterocycles can also be formed via the hydrogenolysis of the N—O bond followed by a reclosure sequence. The formation of pyrazinone **75** from isoxazolone **74**[30], indole **77** from oxadiazole **76**,[31] and imidazole **79** from isoxazolone **78**[32] have been reported (**Scheme 27**).

Subjecting alkyl nitrates to hydrogenolysis conditions gave alcohols (**Scheme 28**).[33]

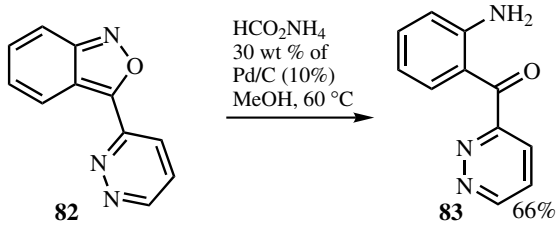
Transfer hydrogenolysis using ammonium formate has also been used for N—O cleavage at 60 °C to give *o*-acylaniline **83** from benzisoxazole **82** in 66% yield (**Scheme 29**).[34]



Scheme 27



Scheme 28



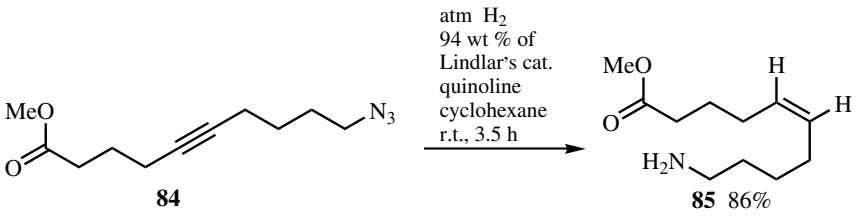
Scheme 29

D. HYDROGENOLYSIS OF N—N BOND

Azide is one of the easiest functional groups to reduce with heterogeneous Pd catalyst and H_2. Thus, even with the less active Lindlar's catalyst, azides can readily be reduced to amines. Reduction of azido alkynoate ester **84** using Lindlar's catalyst produced *cis*-alkenylaminocarboxylic acid ester **85** in 86% yield (**Scheme 30**).[35]

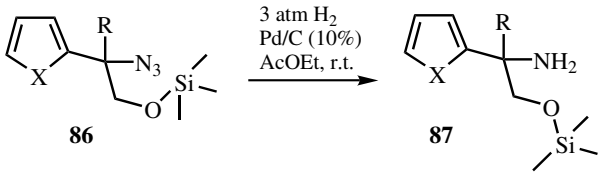
Tertiary azides can be reduced to primary amines under ambient temperature and low hydrogen pressure (**Scheme 31**).[36]

Reduction of alkyl azides can also be accomplished under transfer hydrogenation conditions using cyclohexene[37] and formate[38](**Scheme 32**).



84 **85** 86%

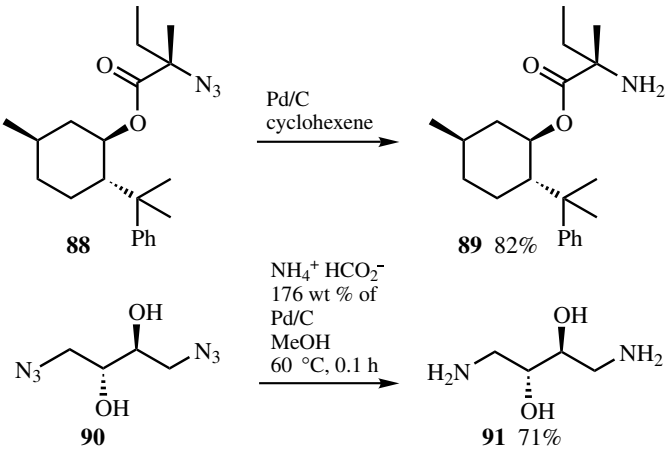
Scheme 30



86 **87**

X = O, R = H 90%
X = S, R = H 90%
X = O, R = Me 75%

Scheme 31



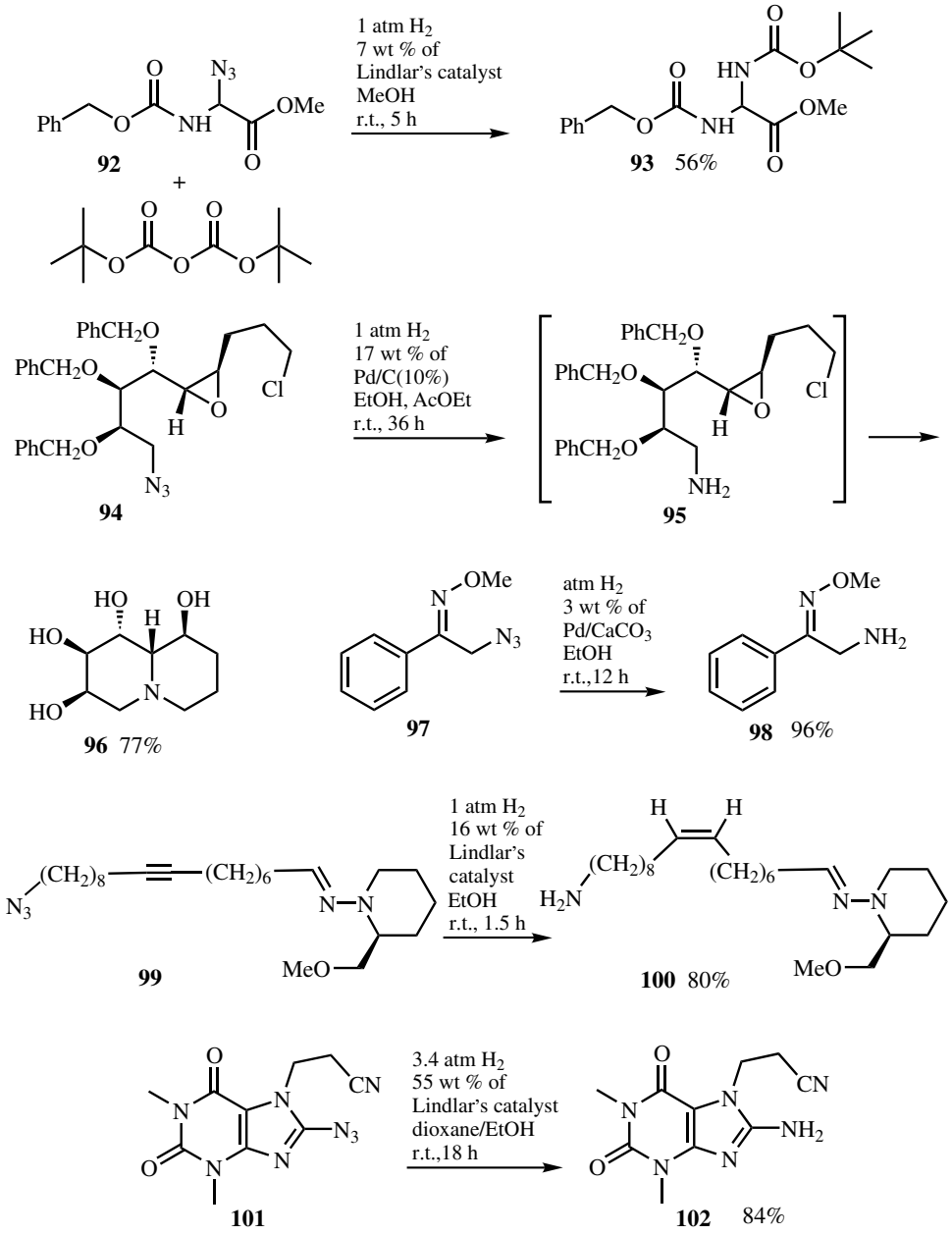
88 **89** 82%

90 **91** 71%

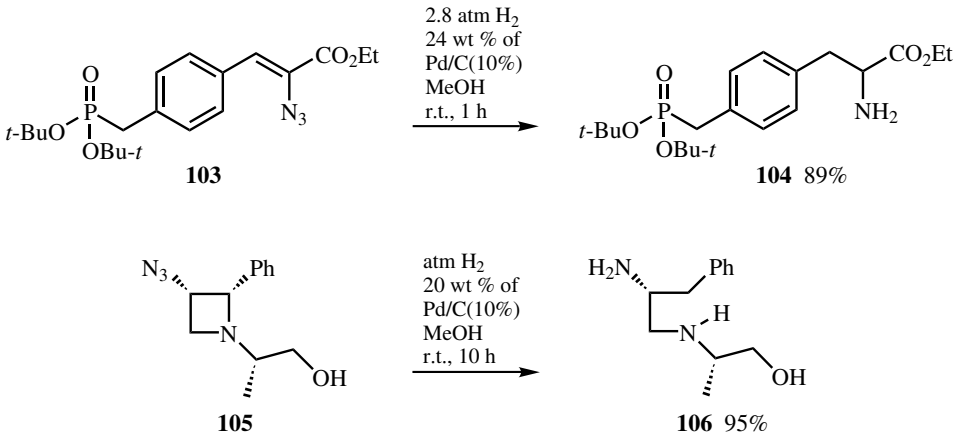
Scheme 32

Functional groups that are stable to reduction during azide hydrogenolysis include benzyl ester, alkyl chloride, benzyl ether, epoxide, alkoxy imine, hydrazone, nitrile, aldehyde, and ketone (**Scheme 33**).[39]–[43]

The above list of functional groups can be made to react along with the azido group under more vigorous conditions or extended reaction time. For example, the olefin and benzylic amine groups were further hydrogenolyzed under these conditions (**Scheme 34**).[44],[45]



Scheme 33



Scheme 34

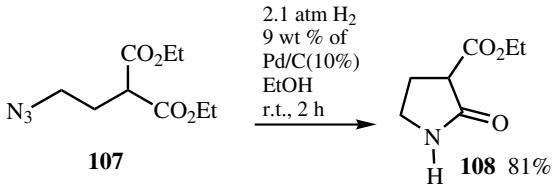
The azide functional group is therefore a convenient precursor to primary amines. The amine formed may further react with other functional groups under the reaction conditions. Thus, the reduction of azido diester **107** provided pyrrolidone **108** after cyclization to the lactam (**Scheme 35**).[46]

In the presence of formaldehyde the initially formed primary amine further underwent a double reductive amination reaction to give the *N*,*N*-dimethylamine product (**Scheme 36**).[47]

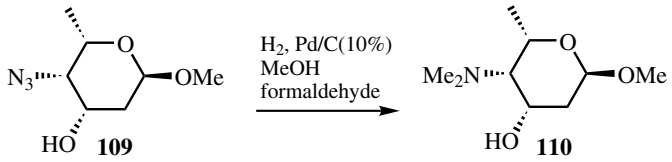
Other examples of intramolecular reductive amination reactions resulting from amines formed from azido compounds are shown below. Excellent diastereoselectivities were observed for the reduction of the intermediate imines in the latter two cases (**Scheme 37**).[48]–[50]

Intramolecular alkylation of the amine formed can also occur to give cyclic compounds. Electrophiles include mesylate,[51] tosylate,[52] epoxide,[53] alkyl bromide,[54] sulfate,[55] and imino ether[56] (**Scheme 38**).

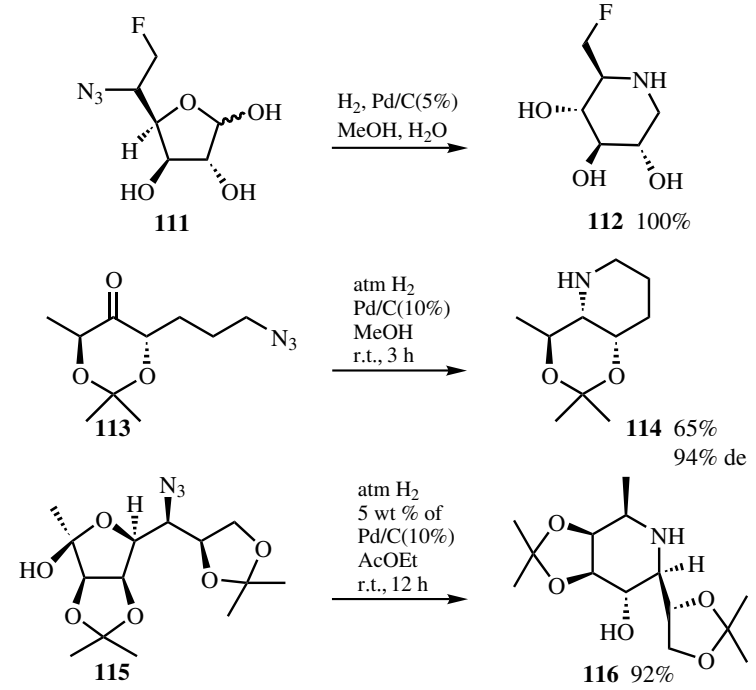
Other N—N bonds such as those in hydrazone **129**,[57] azine **131**,[58] and tetrazolopyrimidinone **133**[59] can readily be hydrogenolyzed (**Scheme 39**).



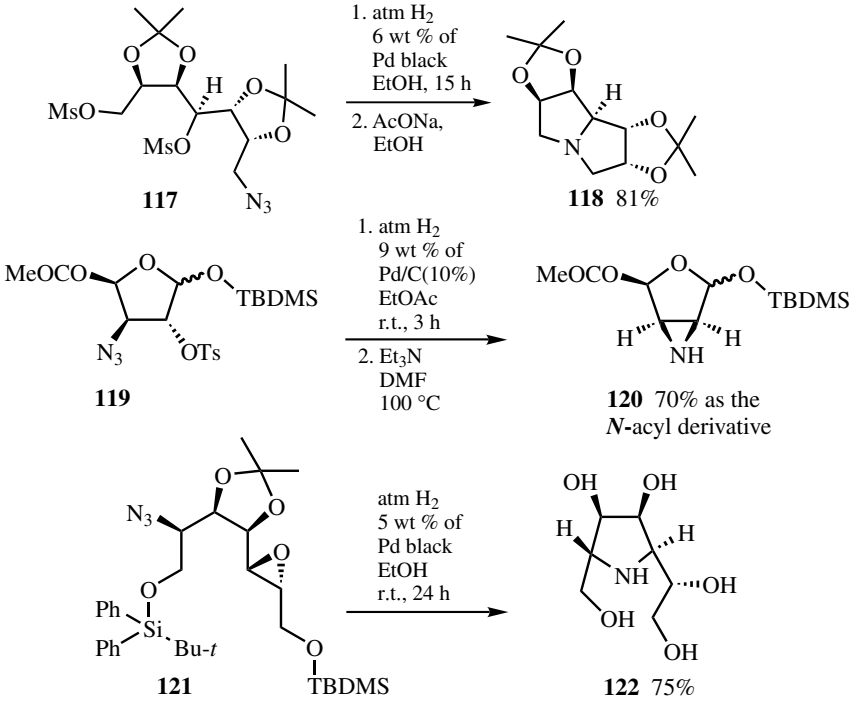
Scheme 35



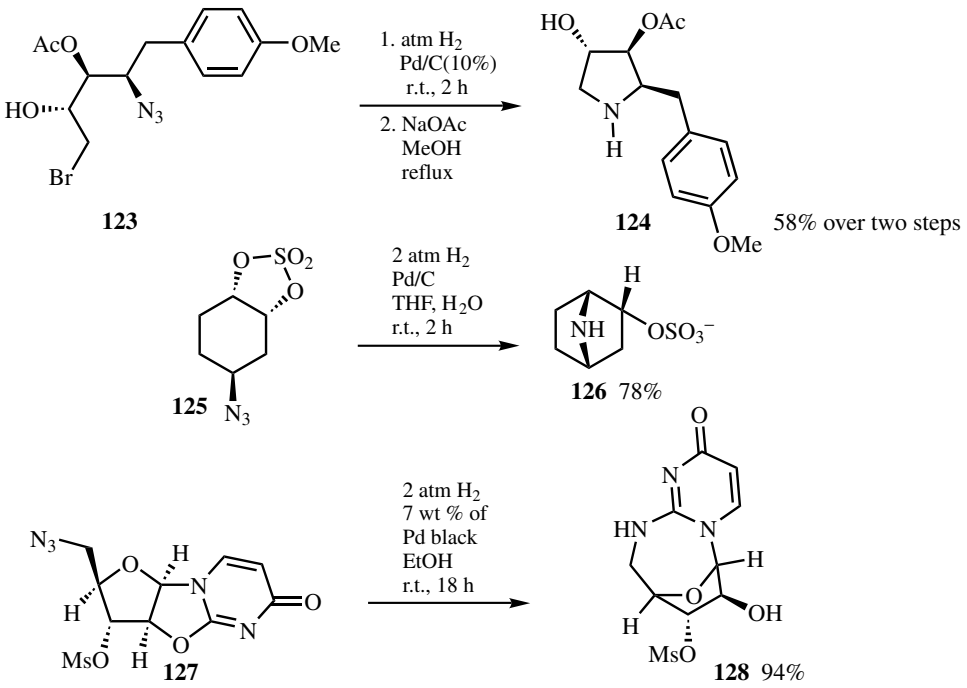
Scheme 36



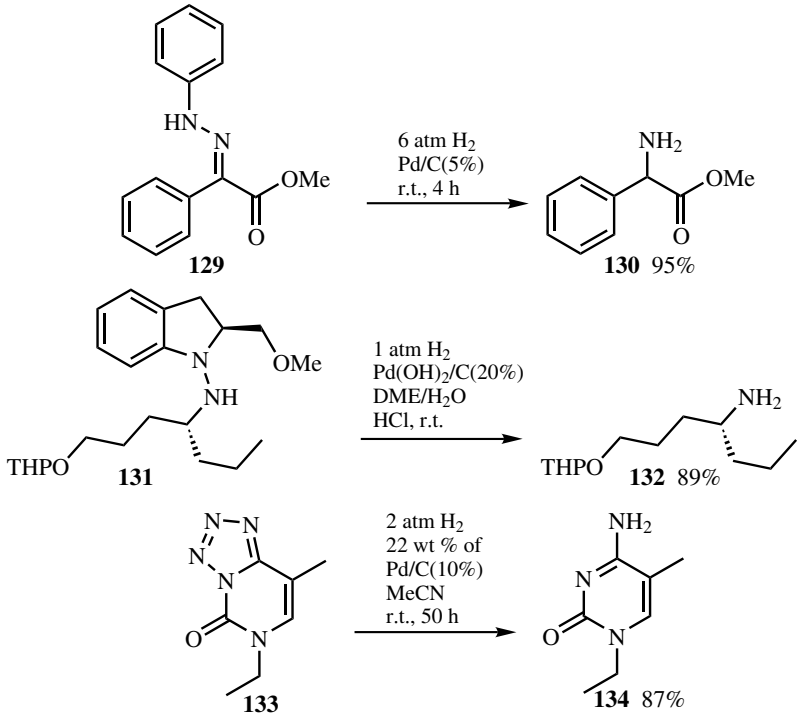
Scheme 37



Scheme 38



Scheme 38 (*Continued*)



Scheme 39

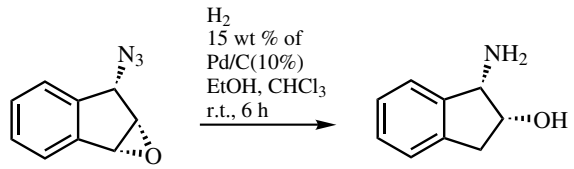
E. HYDROGENOLYSIS OF EPOXIDE

Regioselectivity in the epoxide ring opening is also controlled by similar factors affecting the opening of cyclopropanes, with aryl substituent providing the greatest influence. When an aryl substituent is on the epoxide ring, the benzylic C—O bond is always hydrogenolyzed (**Scheme 40**).[60]

Since azide is reduced so easily, it is reduced first under the reaction conditions before the epoxide ring hydrogenolysis. Because the epoxide ring opening is quite regioselective, the initially formed amine must not have influenced the regioselectivity of the epoxide ring opening. Similarly, the presence of the hydroxymethyl substituent and steric hindrance around the benzylic position in **137** were not able to prevent the benzylic C—O bond cleavage (**Scheme 41**).[61] The hydrogenolysis proceeded with inversion of configuration, which is the predominant occurrence with Pd catalysts.

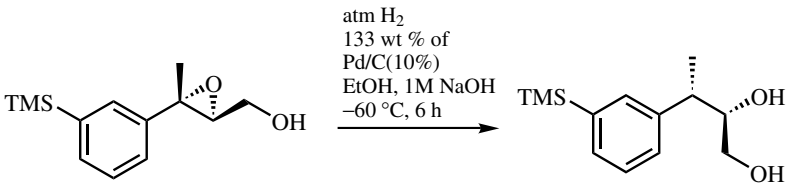
The ester carbonyl also did not exert any influence on the epoxide opening of **139** (**Scheme 42**).[62] Steric control leads to the exclusive formation of the tertiary alcohol **140**.

Under the hydrogenolysis conditions used for the opening of epoxide, other benzylic C—O bonds may also react. For example, the benzylic C—O bond of the acetonide **141** was cleaved to an extent of 80% (**Scheme 43**).[63]



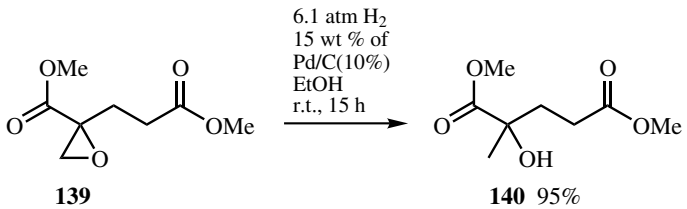
135 **136** 69%

Scheme 40



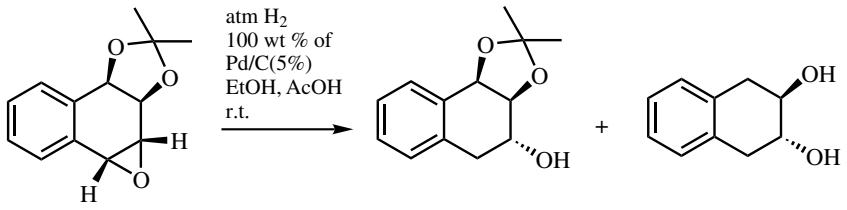
137 **138** 97%

Scheme 41



139 **140** 95%

Scheme 42



141 **142** 12% **143** 80%

Scheme 43

Further reduction completed the hydrogenolysis to the diol. In this case a lower catalyst charge or the use of a less reactive Pd catalyst, such as $Pd/CaCO_3$ or $Pd/BaSO_4$, and a neutral solvent may help to control the overreduction. Transfer hydrogenation conditions using 1,4-cyclohexadiene as the hydrogen source gave **142** in 76% yield along with 16% of the deprotected triol.

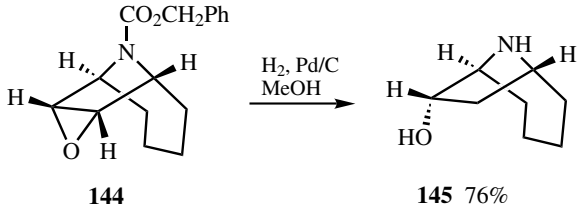
Effective reaction conditions to prevent the benzylcarbamate functional group from hydrogenolysis is probably impossible during the epoxide ring opening of **144** due to the higher reactivity of the Cbz group (**Scheme 44**).[64] The corresponding *exo*-epoxide was more reactive toward hydrogenolysis and gave the aminol in 86% yield.

Besides aryl-directed ring opening, regioselective opening via allylic activation has also been reported for **146** (**Scheme 45**).[65] The olefin was not reduced under the reaction conditions.

The use of $Pd/CaCO_3$ provided diol **149** from **148** in high yield without the loss of the benzylic hydroxy group (**Scheme 46**).[66] Hydrogenolysis of the benzylic hydroxy group, if necessary, can be accomplished with Pd/C at 75 °C.

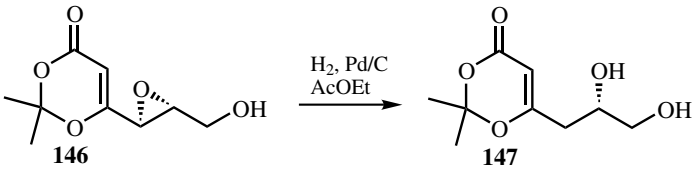
Mesylate and tosylate functional groups are usually not cleaved under Pd-catalyzed hydrogenolysis conditions. Thus, it was possible to prepare hydroxy tosylate **152** from **151** in good yield (**Scheme 47**).

Pd-catalyzed transfer hydrogenolysis conditions have also been applied to epoxide opening. Hydrogenolysis of representative examples with ammonium formate are presented in **Scheme 48**.[67]



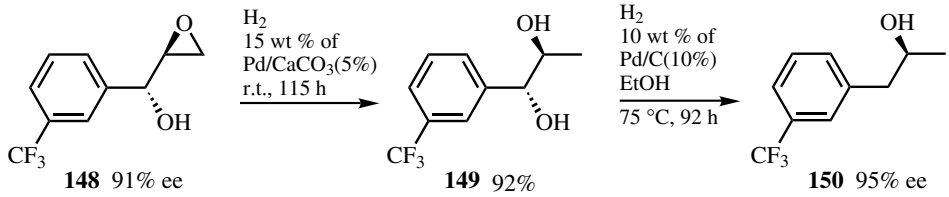
144 **145** 76%

Scheme 44

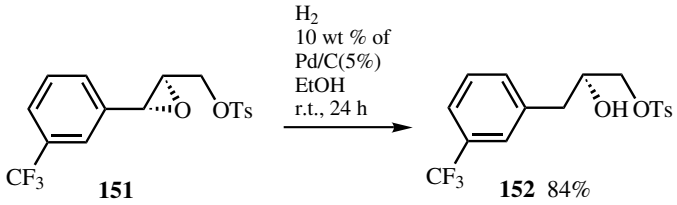


146 **147**

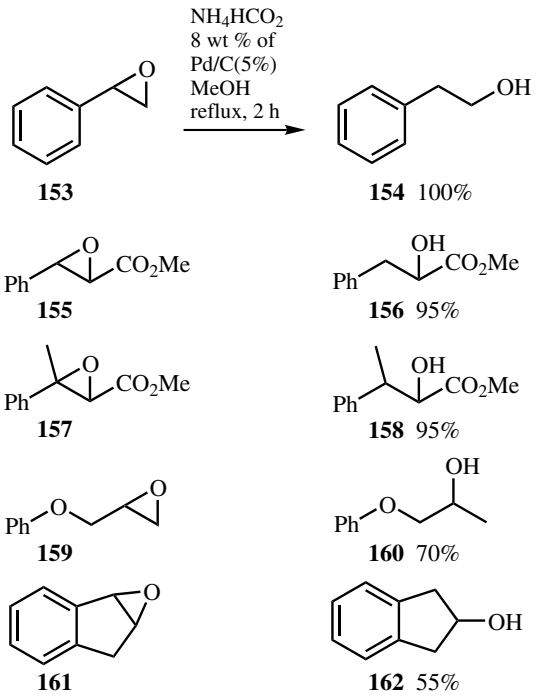
Scheme 45



Scheme 46



Scheme 47



Scheme 48

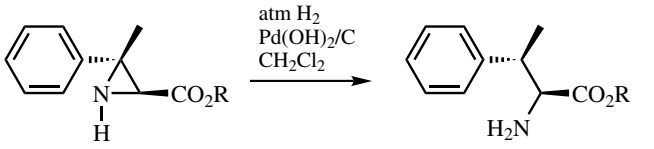
F. HYDROGENOLYSIS OF AZIRIDINE

Again, aryl substituent has the greatest directing effect on the regioselectivity of aziridine ring opening. Both inversion and retention of configurations at the carbon center have been observed. Extensive loss of chirality was observed during the cleavage of the C—N

bond in methyl ester **163** (**Scheme 49**).[68] Better stereoselectivity was observed when the *t*-Bu ester was used.

The stereochemistry of hydrogenolysis of 2-methyl-2-phenylaziridine with $Pd(OH)_2/C$ catalyst can favor either retention or inversion of configuration depending on the solvent used.[69] Under neutral reaction conditions, retention of configuration (68%) was observed in benzene whereas inversion of configuration occurred to an extent of 88% in EtOH. With *N*-acyl-2-methyl-2-phenylaziridine, both benzene and EtOH solvents gave inversion of configuration as the major reaction pathway in 93% and 88% yields, respectively. The stereoselectivity observed in EtOH could be completely reversed with the addition of NaOH and KI. Under these basic conditions, 100% retention was observed with 2-methyl-2-phenylaziridine. Although this reversal was not observed with *N*-acyl-2-methyl-2-phenylaziridine, under the basic conditions but in the absence of KI the stereochemistry of hydrogenolysis did improve to 97%. These results were explained based on the affinity of Pd for the neutral nitrogen (in neutral pH) and anionic nitrogen (in basic conditions). With the Pd preferably complexed with the anionic nitrogen because of the nitrogen's increased electron-donating character and also with the phenyl ring, retention of configuration was observed. Since Pd has a low affinity for the neutral nitrogen, complexation with the Pd occurs primarily with the phenyl ring only and from the backside of the C—N bond, resulting in the observed inversion of configuration.

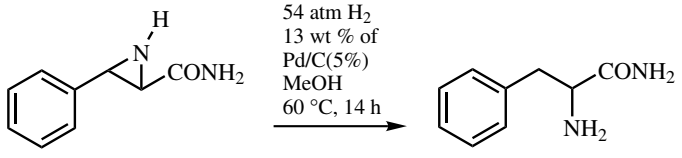
Neither the amide carbonyl in **165**[70] nor the hydroxymethyl group in **167**[71] influenced the out come of the hydrogenolysis (**Scheme 50**).



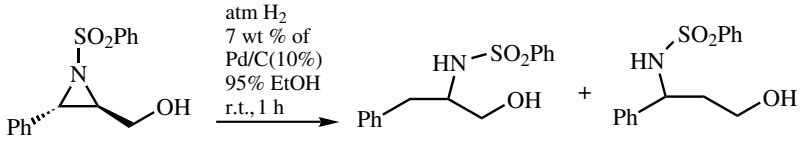
163 **164**

R = Me 88% yield, 72% de
R = Bu-*t* 84% yield, 92% de

Scheme 49



165 **166** 90%
at 90% conversion



167 **168** 99% **169** 1%

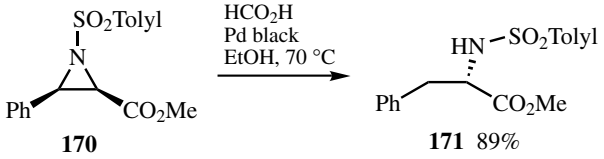
Scheme 50

In the latter case, only 1% of benzylic sulfonamide **169** was observed resulting from the cleavage of the nonbenzylic C—N bond. A similar substrate **170** was hydrogenolyzed in 99% yield using transfer hydrogenation conditions with formic acid as the hydrogen source (**Scheme 51**).[72],[73]

In the absence of benzylic electronic effect, the ester group on aziridines **172**[74] and **174**[75] directed the C—N bond cleavage effectively to give β-amino esters (**Scheme 52**).

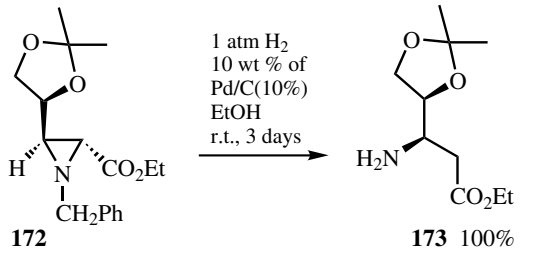
For comparison, the hydrogenolysis of the hydroxymethyl derivative proceeded at the less hindered C—N bond (**Scheme 53**).

For **172**, the removal of the *N*-benzyl group occurred within the first 30 min of the reaction followed by the hydrogenolysis of the aziridine ring, whereas the *N*-methylbenzyl protecting group remained attached throughout the reaction for **174**. Removal of the *N*-methylbenzyl group can be accomplished at a higher temperature and in an acidic solvent as reported for the hydrogenolysis of **178** (**Scheme 54**).[76]



170 **171** 89%

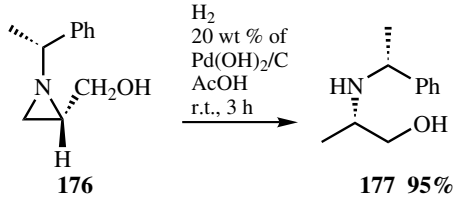
Scheme 51



172 **173** 100%

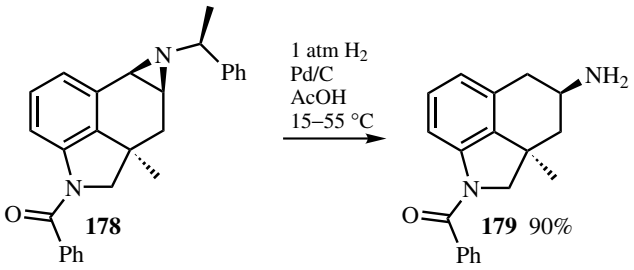
174 **175** 80%

Scheme 52



176 **177** **95%**

Scheme 53



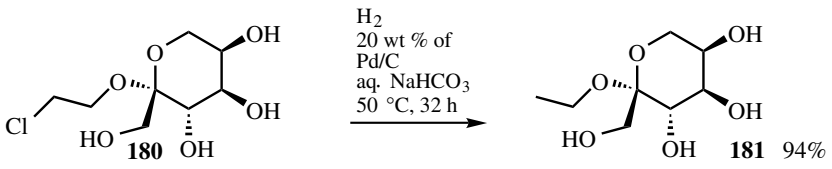
Scheme 54

G. HYDROGENOLYSIS OF HALIDES

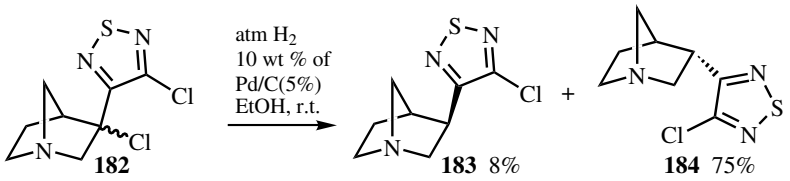
Pd-catalyzed hydrodehalogenation of halides is a useful method for the removal of halogen atoms. Since other metals are usually not as effective for this reaction (there are exceptions), Pd is therefore the metal of choice. In fact, in order to preserve halogen on a substrate, other metals such as Pt, Rh, and Raney nickel are used in the hydrogenation of other functional groups. In general, the order of reactivity for halide removal is F $<<$ Cl $<$ Br $<$I. Fluoride is usually not hydrogenolyzed except in a limited number of cases. Unless the substrate contains a basic functional group, it is beneficial to add one or more equivalents of a base to neutralize the hydrogen halide formed in order to minimize its poisonous effect on the catalyst. In the absence of a base, rapid slowing down of the reaction may sometimes occur, resulting in incomplete reaction. The following are common bases used in hydrodehalogenation reactions: MgO, carbonates, bicarbonates, hydroxides, acetates, alkoxides, R_3N, and DABCO. The useful hydrodehalogenation of acyl halides to aldehydes, the Rosenmund reduction, will not be covered here but will be covered in **Sect. VI.2.4**.

Besides carrying out dehydrohalogenation in organic solvents, the reaction can also be carried out in water. 1°-Chloride **180** was dehalogenated in an aqueous bicarbonate solution in 94% yield (**Scheme 55**).[77] Reduction of the corresponding bromide gave an 81% yield.

3°-Chloride **182** was also removed to give **184** as the major diastereomeric product in 83% combined yield (**Scheme 56**).[78]



Scheme 55



Scheme 56

The imino chloride in **185** was completely reduced but the bridgehead chloride was not touched. Surprisingly, when the bridgehead chloride was replaced with a methyl group, only 10% of the imino chloride reduced product was observed and the major product was the bislactam from hydrolysis (**Scheme 57**).[79]

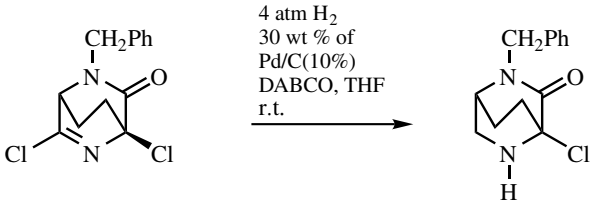
The selective removal of the chloride in the presence of a readily hydrogenated aromatic nitro group was also reported (**Scheme 58**).[80] Acetonitrile was used as the solvent along with triethylamine as the base for the hydrogenolysis of the chloro group in chloronitrobenzene derivative **187**. In EtOAc, however, the nitro group was concomitantly reduced to give aniline **189** in 80% yield.

It was interesting to note that in the process of removing the bromide in **190**[81] and **193**,[82] the hydroxy and acetoxy groups were also lost (**Scheme 59**). The primary bromide in **191** was removed in a separate step.

At 75% conversion, selectivity was observed in the reduction of bromoepoxysulfone **195** to give desbromo **196** in 79% yield with only 5% of the epoxide opened product **197** formed (**Scheme 60**).[83] On prolonged reaction time (15 h) hydroxysulfone **197** was obtained in 72% yield.

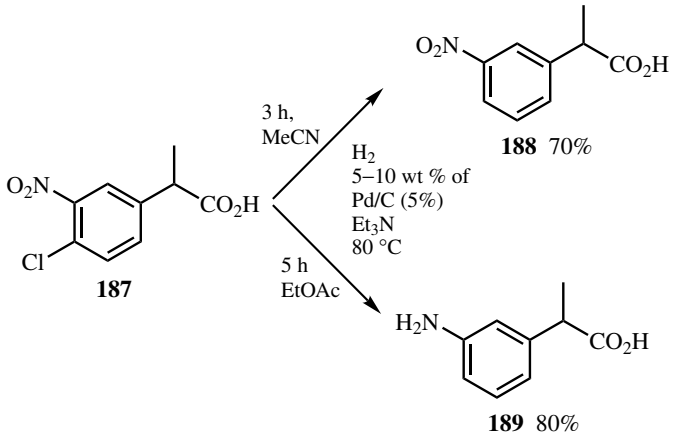
The multiple chloro-substituted substrate **198** underwent complete hydrodechlorination in good yield by passing the substrate over Pd/C at 250 °C and atmospheric hydrogen pressure (**Scheme 61**).[84]

In the hydrogenolysis of the Cbz group in **200**, monodechlorination of the trichloroacetamide was also observed to give **201** in excellent yield (**Scheme 62**).[85]



185 **186** 64%

Scheme 57

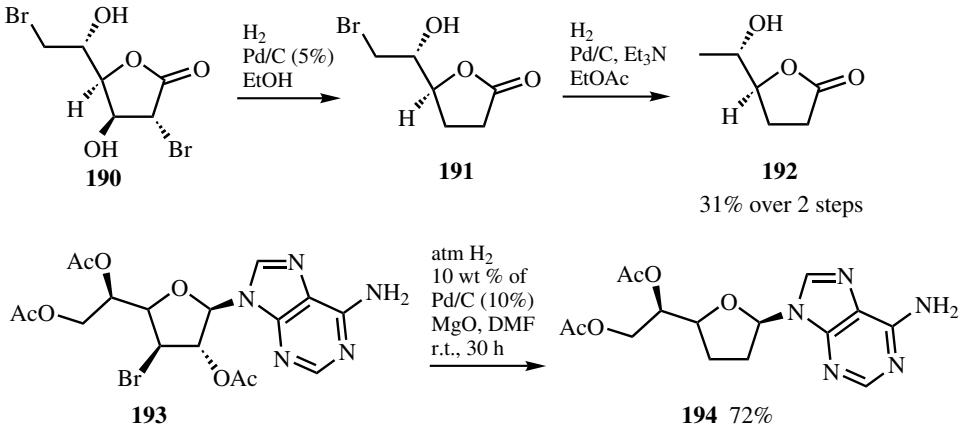


188 70%

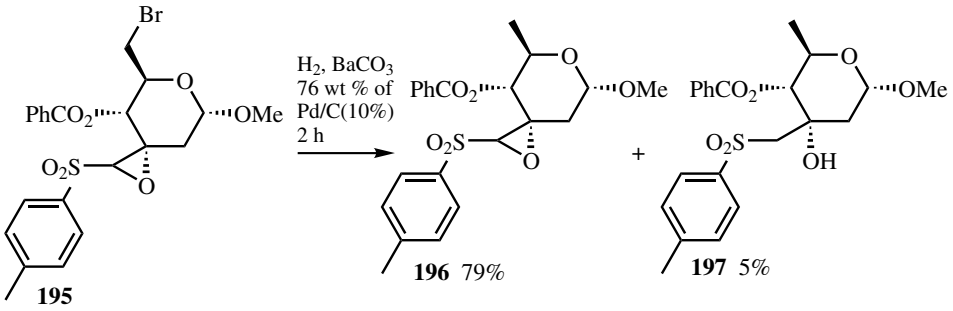
187

189 80%

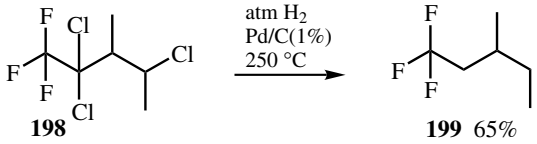
Scheme 58



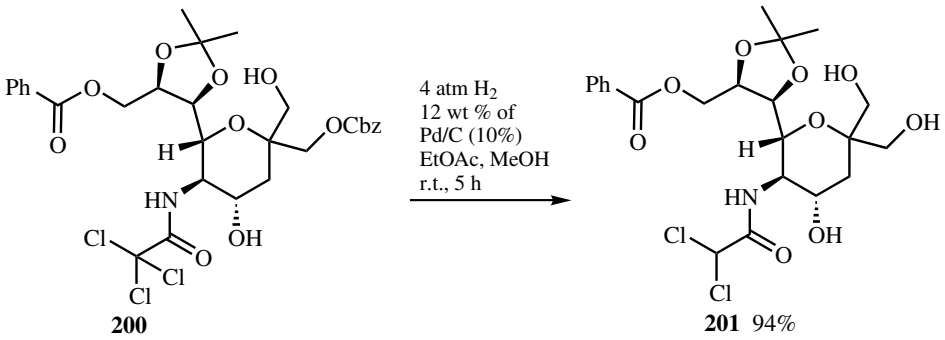
Scheme 59



Scheme 60



Scheme 61



Scheme 62

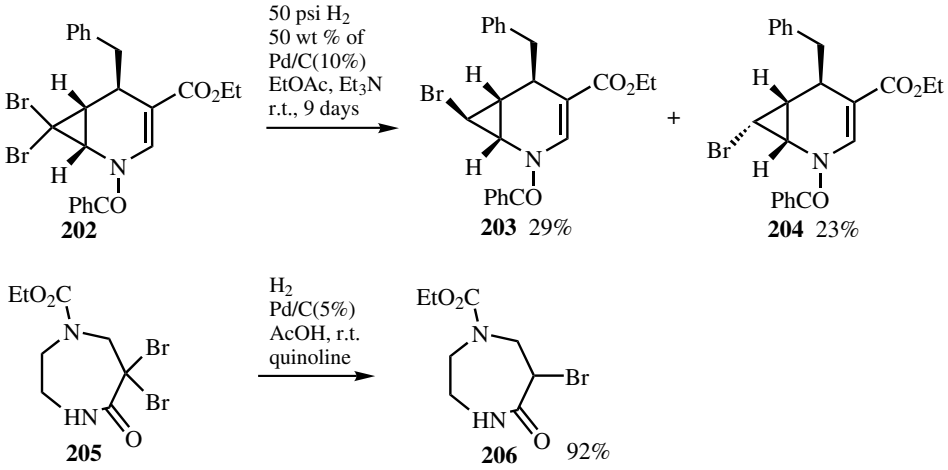
The selective monodebromination of *geminal*-substituted dibromopropane **202**[86] was realized in only fair yield, whereas an excellent yield was obtained in the monodebromination of α,α-dibromolactam **205**[87] (**Scheme 63**).

Dichlorolactam **207** behaved similarly to give the monochlorolactam in 98% yield (**Scheme 64**).[88]

More interestingly, 50% enantioselectivity was observed in the monodechlorination of α,α-dichlorolactam **209** using a cinchonine modified Pd catalyst (**Scheme 65**).[89]

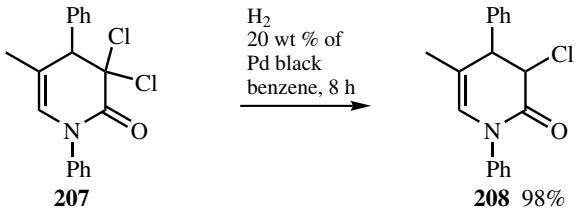
In some cases alkenyl halides can be hydrodehalogenated without the reduction of the resulting olefins. Some examples are presented below (**Scheme 66**).[90]–[92] These olefinic products can and should eventually be reduced on prolonged reaction time or under more vigorous hydrogenation conditions.

Iodobutadiene **218** was also dehalogenated selectively (**Scheme 67**).[93]



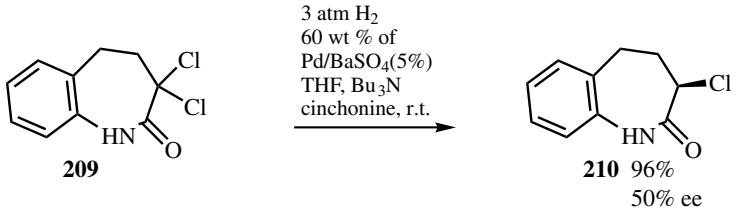
202 **203** 29% **204** 23% **205** **206** 92%

Scheme 63



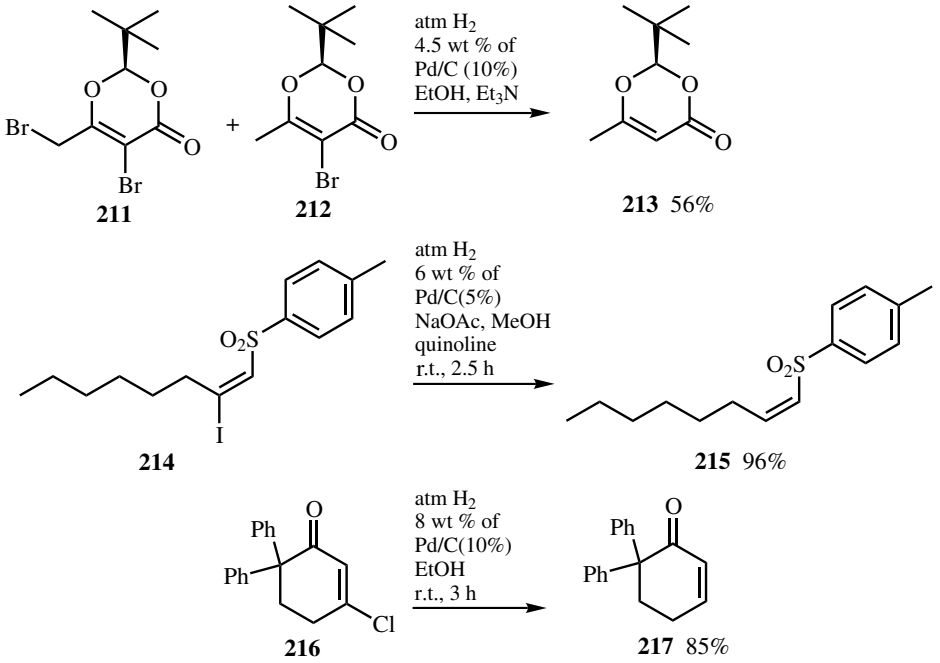
207 **208** 98%

Scheme 64

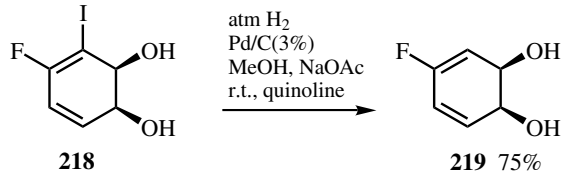


209 **210** 96%
50% ee

Scheme 65



Scheme 66



Scheme 67

Under catalytic hydrogenolysis conditions, (*Z*)-*N*-methoxyarenecarboximidoyl halides **220** gave oximes **221** as the major if not exclusive product. The corresponding (*E*)-*N*-methoxyarenecarboximidoyl halides **223** gave nitriles **222** as the major or exclusive product instead (**Scheme 68**).[94]

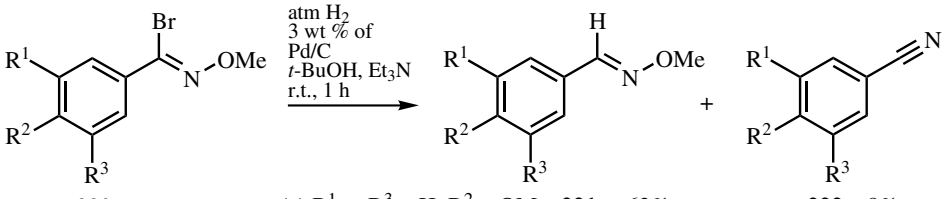
With a variety of *N*-methoxyalkanimidoyl halides **225**, good yields of oximes **226** were obtained exclusively.

Halogen-substituted aryl and heterocyclic compounds can also be hydrodehalogenated as easily. With NaOAc as the base, iodopyrrole was deiodinated in quantitative yield (**Scheme 69**).[95]

Chlorinated acetophenones and benzophenones were hydrodechlorinated selectively under phase transfer conditions without the hydrogenation of the ketone (**Scheme 70**).[96]

The hydrodehalogenation of *o*-bromonitrobenzene with Pd and H_2 to give nitrobenzene is usually unsatisfactory, but under transfer hydrogenation conditions with triethylammonium formate a 91% yield of nitrobenzene was obtained.[97]

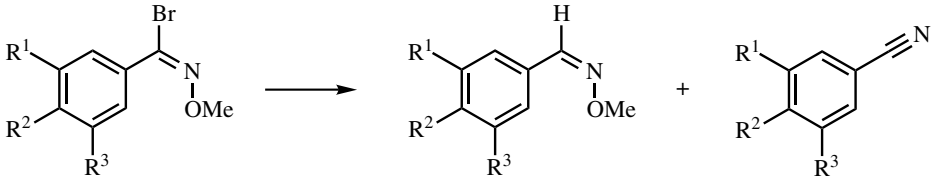
Transfer hydrogenation with cyclohexene also removed the chloride in chlorodinitroaniline **233** but one of the two nitro groups was also reduced (**Scheme 71**).[98]



220

(a) $R^1 = R^3 = H$, $R^2 = OMe$ **221a** 63% **222a** 8%

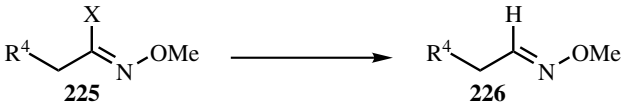
(b) $R^1 = R^2 = R^3 = OMe$ **221b** 70% **222b** 0%



223

(a) $R^1 = R^3 = H$, $R^2 = OMe$ **224a** 11% **222a** 69%

(b) $R^1 = R^2 = R^3 = OMe$ **224b** 0% **222b** 88%



225 **226**

(a) R = 2-naphthyl, X = Br 76%

(b) R = $PhCH_2$, X = Br 78%

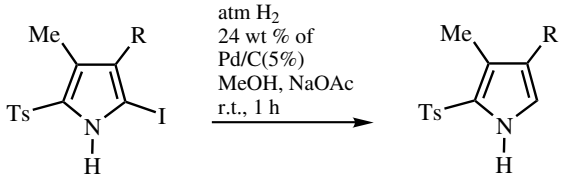
(c) R = 4-$AcC_6H_4CH_2$, X = Br 84%

(d) R = 4-$MeOC_6H_4$, X = Br 85%

(e) R = $NC(CH_2)_9$, X = Br 69%

(f) R = $PhCH_2$, X = Cl 64%

Scheme 68



227 **228** 100%

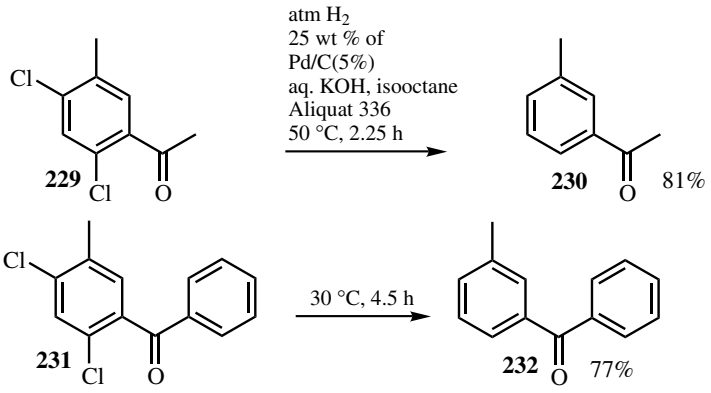
R = *p*-$CH_3C_6H_4$

R = $C_6H_5(CH_2)_2$

R = Et

R = *t*-Bu

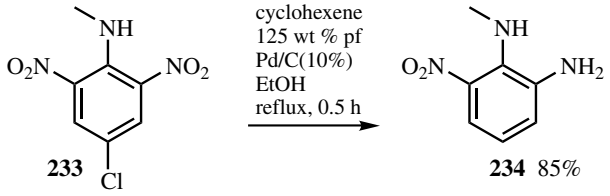
Scheme 69



229 **230** 81%

231 **232** 77%

Scheme 70



233 **234** 85%

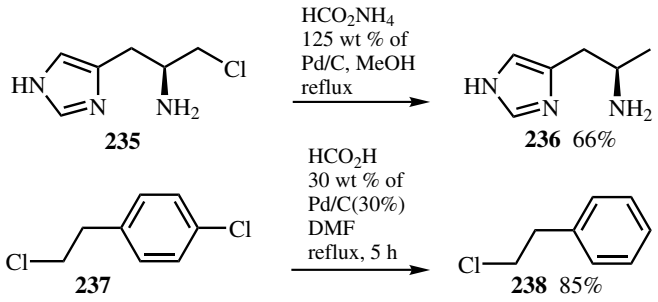
Scheme 71

Although transfer hydrogenolysis conditions can be used to remove a 1°-chloride such as **235**,[99] modification of the reaction conditions also allowed the selective removal of the aryl chloride in **237**[100] while leaving the alkyl chloride untouched (**Scheme 72**).

Other monohalogen transfer hydrogenolysis was seen with trichloroanilide **239**[101] and dibromo steroidal derivative **241**[102] (**Scheme 73**).

The hydrogenation of benzaldehyde to the alcohol is usually facile with Pd, but even under the refluxing temperature of the transfer hydrogen conditions, hydrodehalogenation of bromoformylimidazole **243** still provided the formylimidazole in 70% yield (**Scheme 74**).[103]

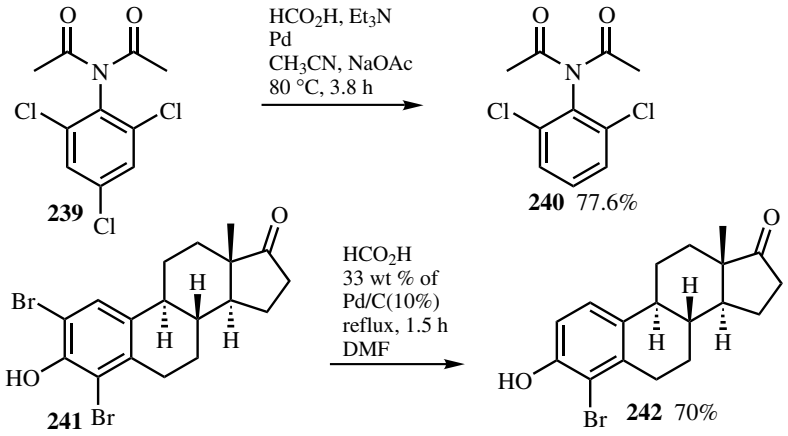
Besides observing hydrodehalogenation of aryl bromides under transfer hydrogen conditions, in some cases biaryl coupling is observed. Bromopyridine **245** was homocoupled to give the bipyridyl **246** in 68% yield (**Scheme 75**).[104]



235 **236** 66%

237 **238** 85%

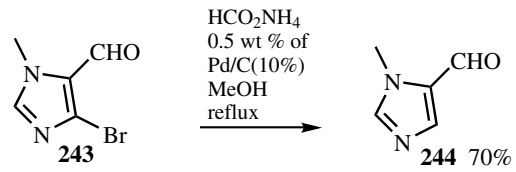
Scheme 72



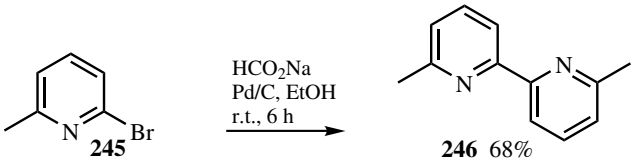
239 **240** 77.6%

241 **242** 70%

Scheme 73



Scheme 74

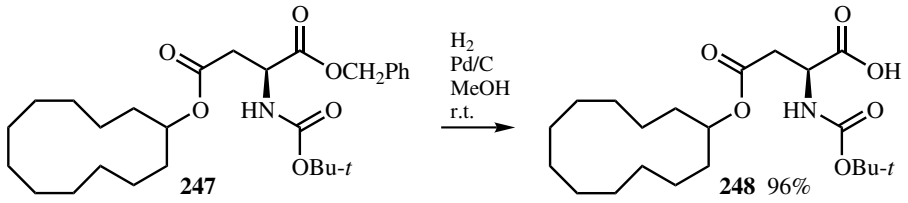


Scheme 75

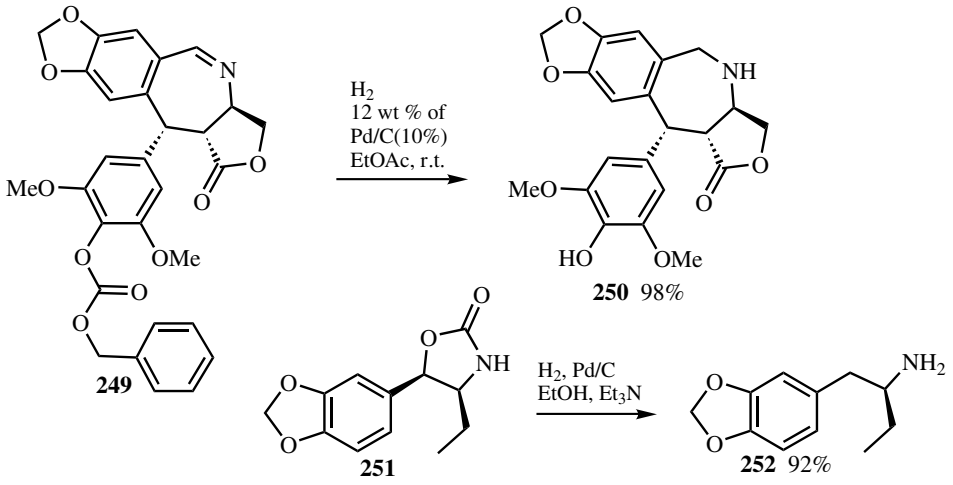
H. HYDROGENOLYSIS OF BENZYLIC AND OTHER C—O BONDS

Of all the heterogeneous Pd-catalyzed C—O bond hydrogenolysis reactions, cleavage of benzyl esters is the most facile (**Scheme 76**).[105]

Benzyl carbonates[106] and carbamates[107] can be hydrogenolyzed as readily with the concomitant release of CO_2 (**Scheme 77**).



Scheme 76



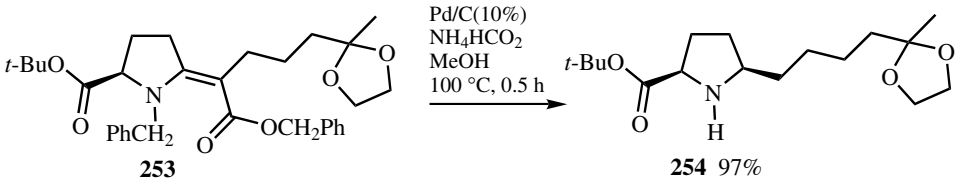
Scheme 77

Debenzylation of esters has been carried out under transfer hydrogenation conditions with ammonium formate as the hydrogen source (**Scheme 78**).[108],[109] Under transfer hydrogenolysis conditions, the vinylogous carbamate **253** also underwent decarboxylation. The *N*-benzyl was also hydrogenolyzed.

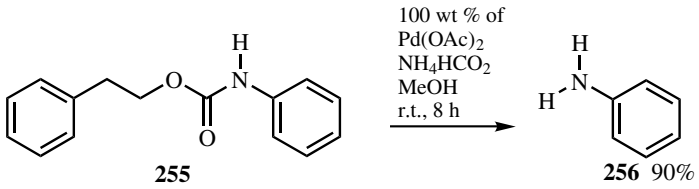
Even 2-phenylethylcarbamate ("homobenzyloxycarbonyl") can be hydrogenolyzed (**Scheme 79**).[110]

Although hydrogenolysis of benzyl ethers is slower than benzyloxycarbonyl derivatives, especially when an amine is used as an additive,[111] they are still readily reduced in a variety of solvents (**Scheme 80**).[112],[113]

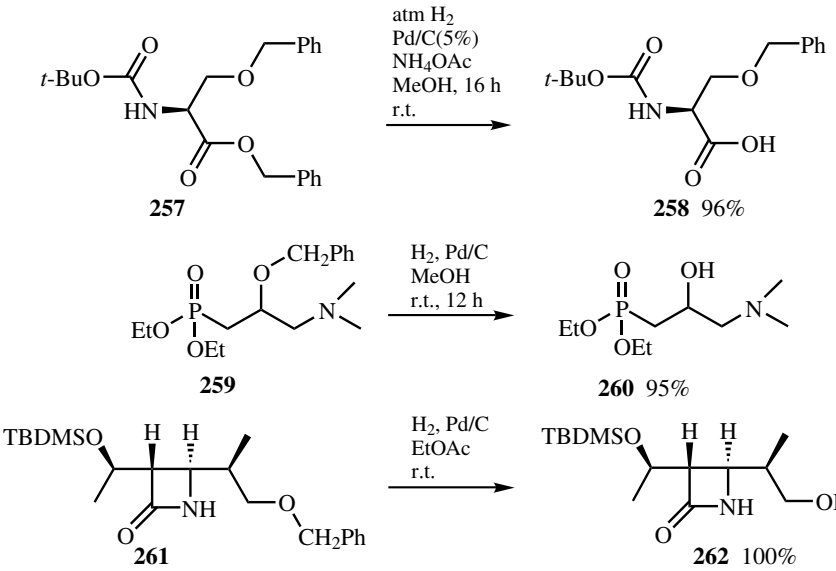
In the case of binaphthyl ether **263**, the secondary C—O bonds were hydrogenolyzed exclusively to provide the desired binaphthyl diol **264** (**Scheme 81**).[114]



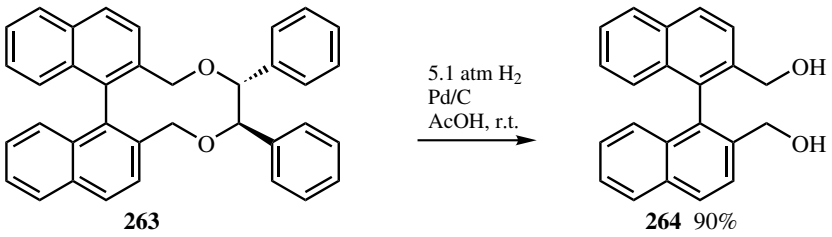
Scheme 78



Scheme 79



Scheme 80



263 **264** 90%

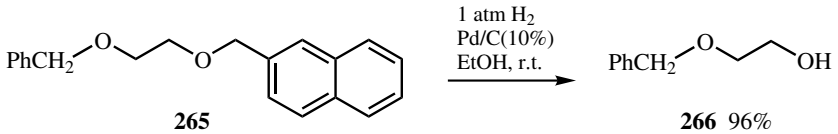
Scheme 81

Benzyl ethers can be cleaved under hydrogen transfer conditions with many commonly used hydrogen donors such as ammonium formate,[115] 2-propanol,[116] and cyclohexene.[117]

Although the hydrogenolysis of benzyl protecting groups is faster than many other hydrogenolyzable groups, hydrogenolysis of benzyl ethers has been found to be inhibited by 2-methylnaphthalene. In the competitive hydrogenolysis of diether **265**, only the naphthylmethyl ether group was cleaved to give the benzyloxy alcohol **266** (**Scheme 82**).[118] The 2-methylnaphthalene formed continued to inhibit the deprotection of the benzyl group. In fact, the addition of 2-methylnaphthalene alone inhibited the hydrogenolysis of benzyl ethers.

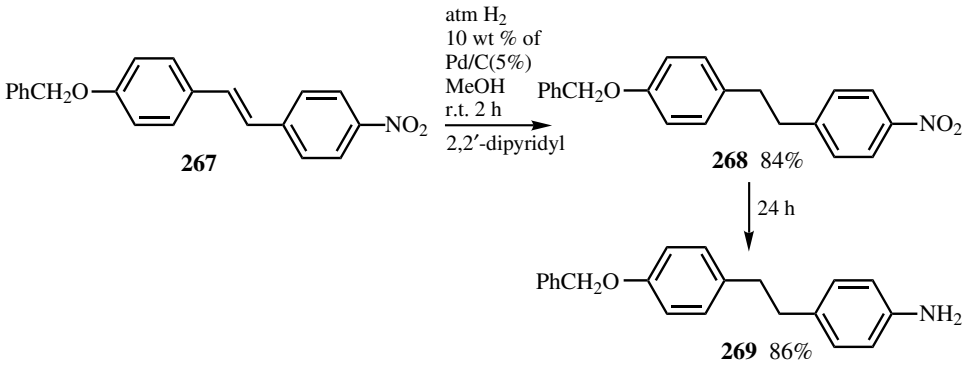
In addition, a catalytic amount of pyridine or ammonium acetate also suppresses the hydrogenolysis of aliphatic *O*-benzyl protective group.[111],[119] Cleavage of phenolic benzyl ethers, which are more labile than alkyl benzyl ethers, can also be prevented by the addition of 2,2′-dipyridyl (**Scheme 83**).[120]

The reduction of the stilbene olefin in **267** occurred selectively first while the aromatic nitro group was reduced with longer reaction time. Even prolonged reaction time did not further hydrogenolyze the phenolic benzyl ether.



265 **266** 96%

Scheme 82



267 **268** 84% **269** 86%

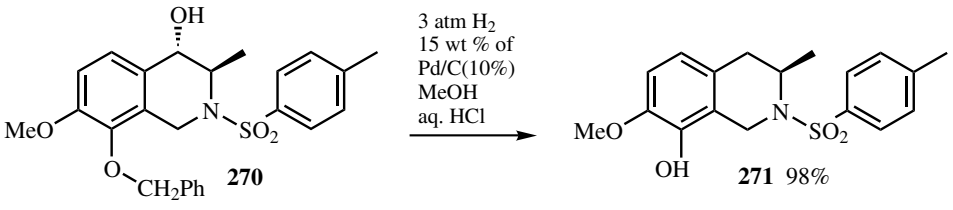
Scheme 83

The hydrogenolysis of benzylic alcohols in many cases can benefit from the use of an acid to provide faster or more satisfactory reaction rates (**Scheme 84**).[121]

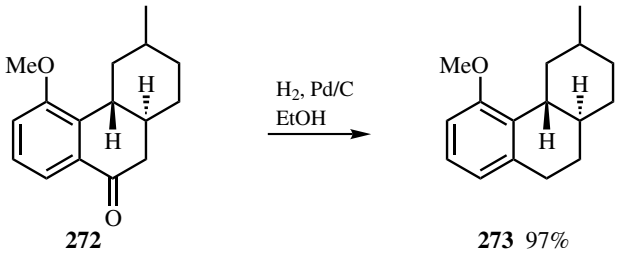
Commonly used acids include hydrochloric, sulfuric, perchloric, and acetic. Although aliphatic ketones are generally resistant to Pd-catalyzed hydrogenation, benzylic ketones readily hydrogenolyze to aryl alkanes via hydroxy intermediates (**Scheme 85**).[122]

3-Acyltetronic acids, which carry a nonbenzylic ketone function, can also be hydrogenolyzed to give 3-alkyltetronic acids (**Scheme 86**).[123]

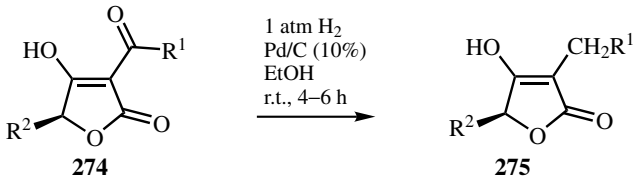
Interestingly, in the presence of KOH and aliquat 336, the Pd-catalyzed hydrogenolysis of (4′-chlorophenyl)-1-propanol in hydrocarbon solvents gave propylbenzene in 96% yield along with 4% of 1-phenyl-1-propanol (**Scheme 87**).[124] With nonhalogenated aryl alcohols, such as 1-phenyl-1-propanol, the hydrogenolysis did not proceed unless an aryl halide was also added. Thus, in the presence of *o*-dichlorobenzene even *t*-benzylic alcohol **278** was hydrogenolyzed quite rapidly. The reason for this selectivity is unknown at this time.



Scheme 84

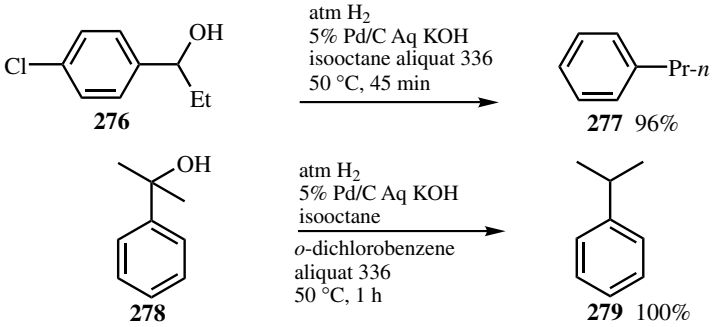


Scheme 85



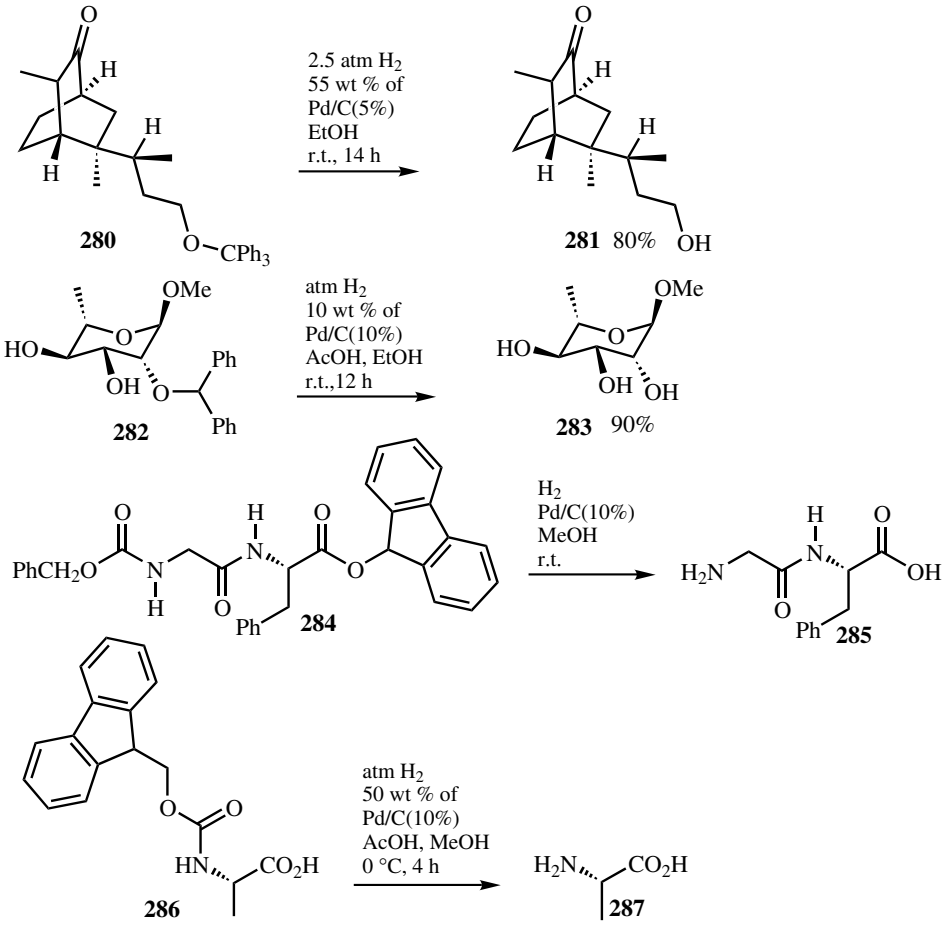
R^1	R^2 = H	R^2 = Me
CH_3	96%	95%
Et	86%	86%
n-Pr	84%	93%
Benzyl	93%	

Scheme 86



Scheme 87

Other commonly encountered hydrogenolyzable *O*-protecting groups are shown below. These include triphenylmethyl,[125] diphenylmethyl,[126] 9-fluorenyl,[127] and 9-fluorenylmethyl[128] (**Scheme 88**). The 9-fluorenylmethyl protecting group has also been hydrogenolyzed under transfer hydrogenolysis conditions using freshly precipitated Pd



Scheme 88

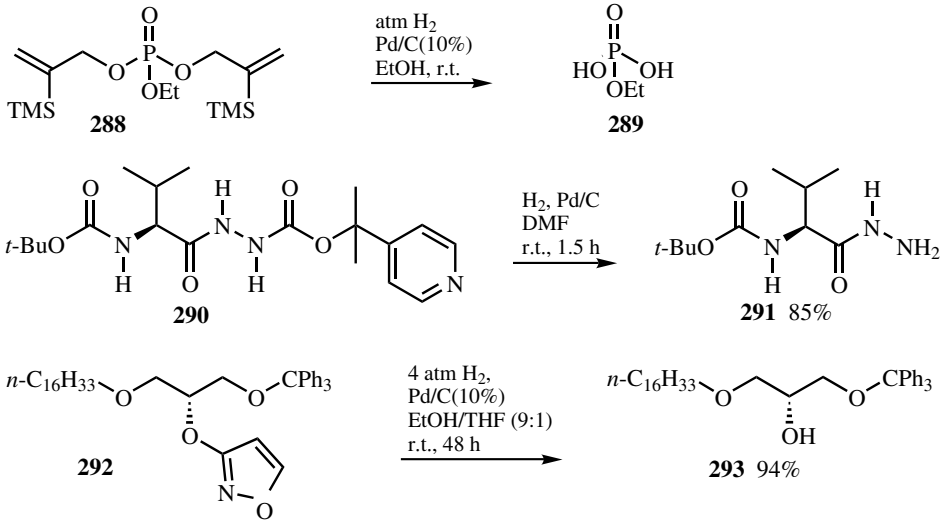
[from $Pd(OAc)_2$] on Pd/C and ammonium formate as the hydrogen source.[129] The catalyst prepared in this manner was more active in the hydrogenolysis reaction.

Several less commonly utilized protecting groups include 2-trimethylsilylpropenyl,[130] dimethylpicolinyl,[131] and 3-alkoxyisoxazole[132] (**Scheme 89**).

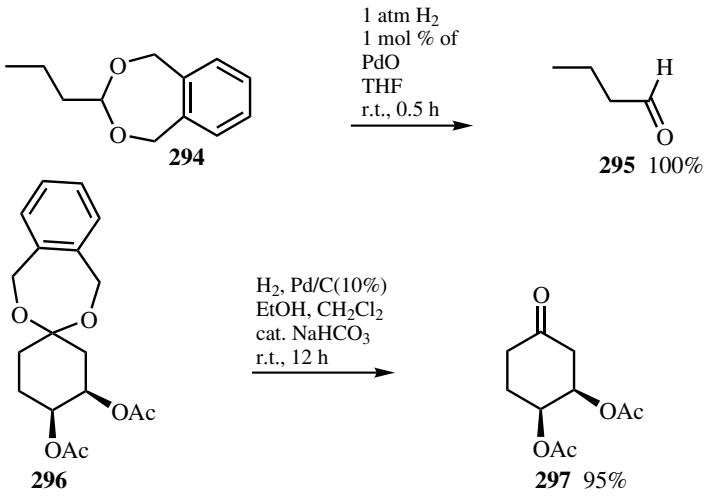
The frequently used protecting group for carbonyl protection is 1,2-bis(hydroxymethyl)benzene. It has been used for the protection of both aldehyde[133] and ketone[134] functional groups (**Scheme 90**).

This diol has also been used to protect boronic acids[135] and phosphates[136] (**Scheme 91**).

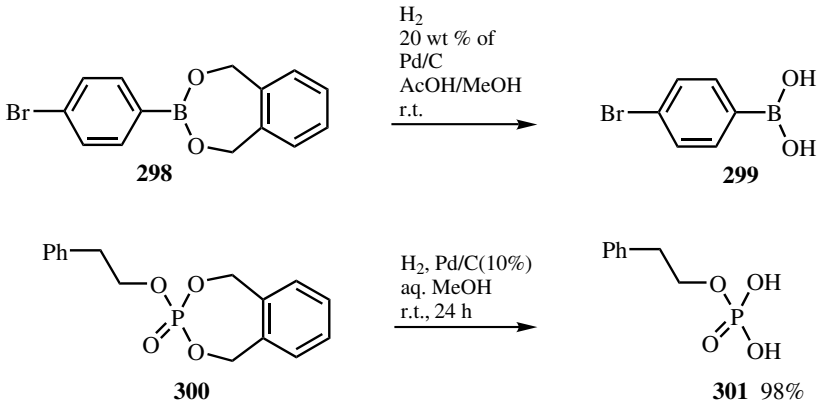
Another protecting group for aliphatic aldo and keto carbonyl groups is phenylethandiol (**Scheme 92**).[137]



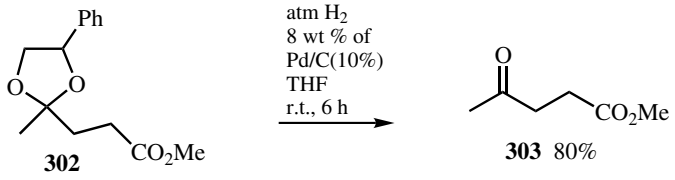
Scheme 89



Scheme 90



Scheme 91



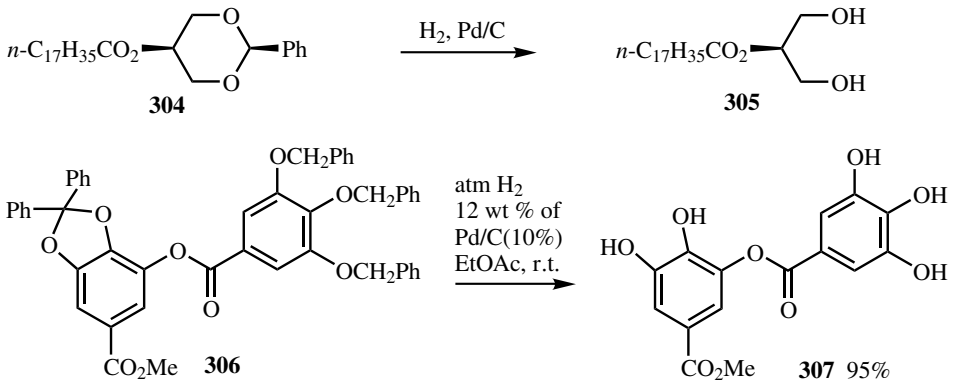
Scheme 92

Diols, on the other hand, can be protected as the benzaldehyde acetal or the benzophenone ketal, which are readily deprotected again under Pd-catalyzed hydrogenolysis conditions (**Scheme 93**).[138],[139]

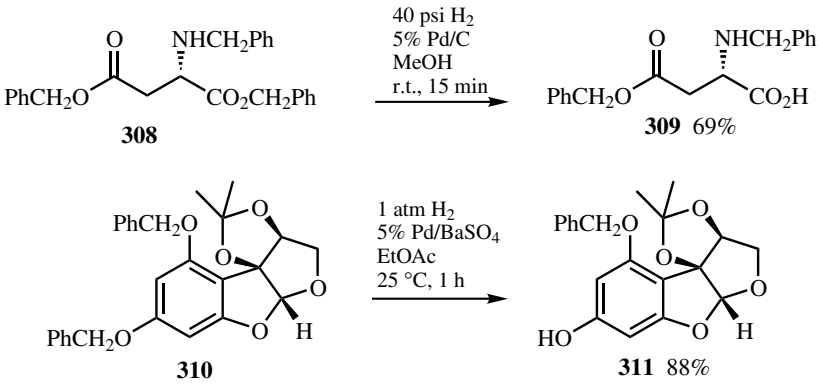
Although similar hydrogenolyzable groups are in the same molecule, the selective removal of one may sometimes be carried out (**Scheme 94**).[140],[141]

In a competitive hydrogenolysis reaction, the benzyl protecting group was selectively removed leaving the dimethylbenzyl ether intact (**Scheme 95**).[142] The dimethylbenzyl ether could be removed after 15 h under 4 atm of hydrogen.

The parent benzyl group was also selectively removed in the presence of the 4-methoxy-substituted benzyl (**Scheme 96**).[143]

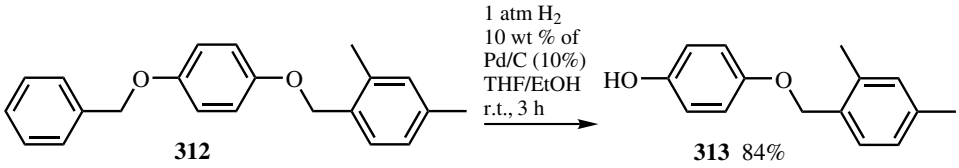


Scheme 93



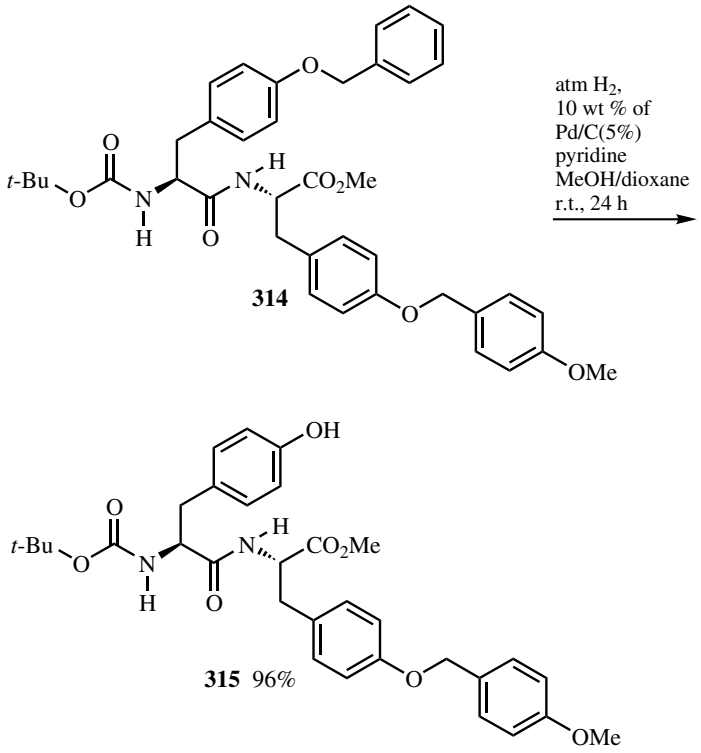
308 **309** 69% **310** **311** 88%

Scheme 94



312 **313** 84%

Scheme 95



314 **315** 96%

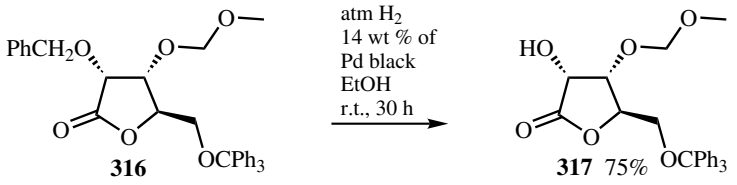
Scheme 96

As expected, certain hydrogenolyzable protecting groups are more readily removed than others. For example, the benzyl ether was removed faster than the trityl protecting group (**Scheme 97**).[144]

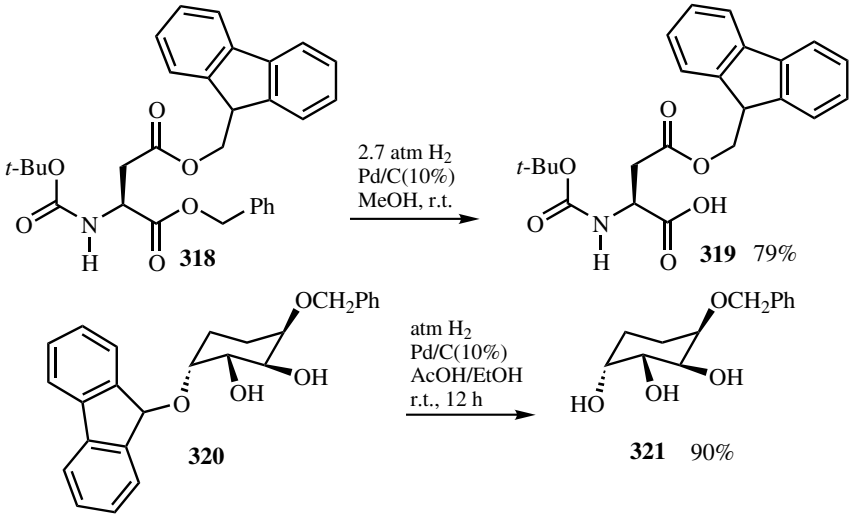
Similarly, the benzyl protected ester was selectively hydrogenolyzed in the presence of the 9-fluorenylmethyl protecting group,[145] but the benzyl group was slower to hydrogenolyze than the 9-fluorenyl protecting group[146] (**Scheme 98**).

Even though aliphatic mesylates are difficult to hydrogenolyze, no difficulty was encountered in the cleavage of benzylic mesylate **322** (**Scheme 99**).[147]

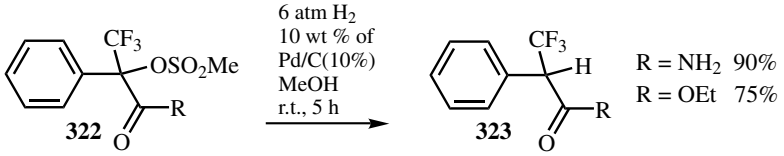
Marinating Pd/C with (1*R*,3*S*)-3-aminoborneol, (*S*)-2-hydroxymethylazetidine, and (1*R*,2*S*)-ephedrine produced useful chiral heterogeneous catalysts. These catalysts have been used for the asymmetric hydrogenolysis of benzyl β-keto esters and benzyl enol carbonates to give chiral ketones in fair to good yield (ee) (**Scheme 100**).[148]–[151] These



Scheme 97



Scheme 98



Scheme 99

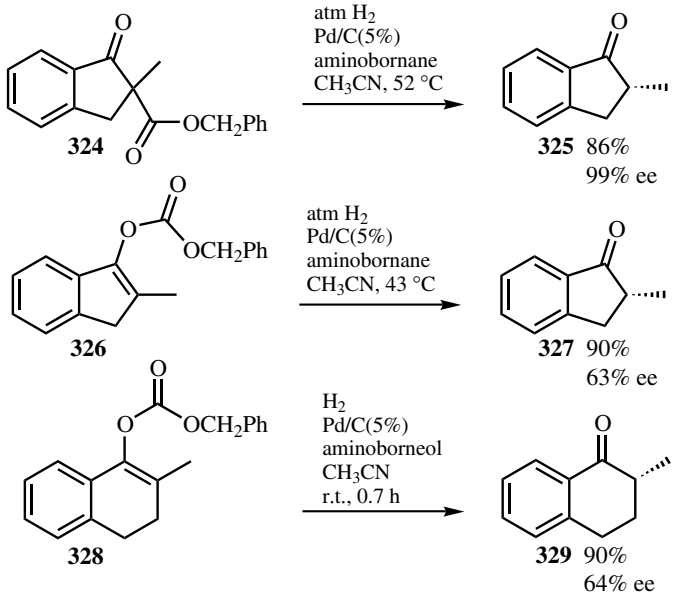
transformations have also been accomplished under homogeneous transfer hydrogenolysis conditions with phosphinated palladium complexes (see **Sects. V.2.3.1** and **V.2.3.2**).

Hydrogenolysis of a nonbenzylic mesylate group on an sp^3 carbon is generally sluggish, but the trifluoromethanesulfonate seems to be easier. Thus, the α-triflate leaving group in lactone **330** was cleaved under mild hydrogenolysis conditions (**Scheme 101**).[152] Even enol triflate **332** was hydrogenolyzed along with the hydrogenation of the olefin, but very high loading of catalyst was used.[153]

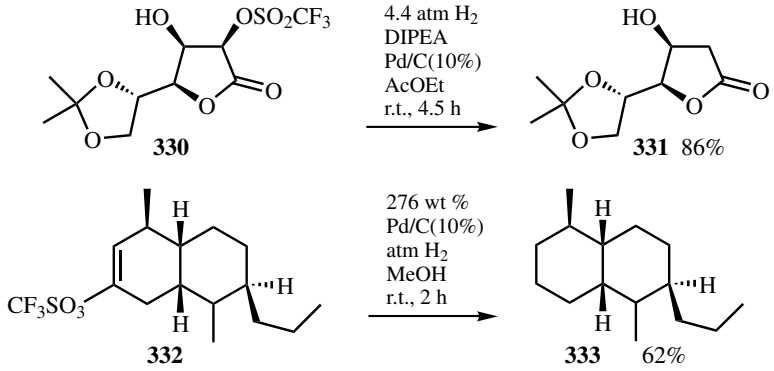
Trichloroethyl phosphate and phosphonate esters are hydrogenolyzed to give phosphate and phosphonate acids, respectively (**Scheme 102**).[154],[155]

Phenolic hydroxy group can be hydrogenolyzed via the diethylisourea (**Scheme 103**).[156]

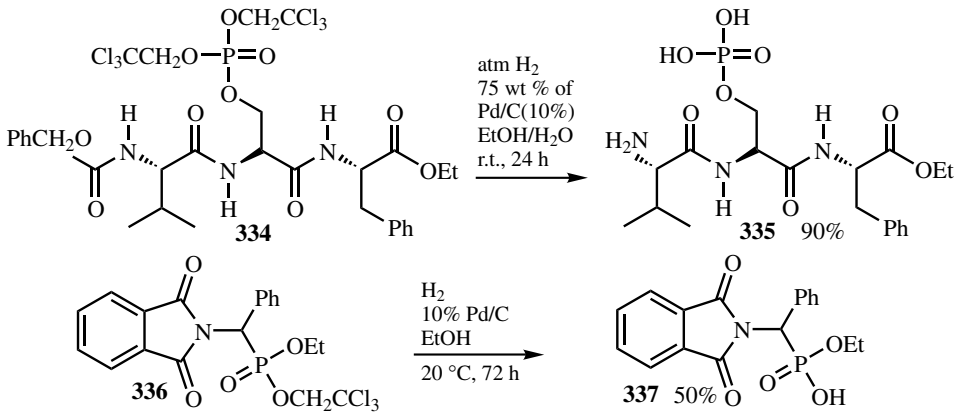
Under either hydrogenation[157] or transfer hydrogenation[158] conditions, the 5-oxytetrazole fragment can be hydrogenolyzed in fair to good yields (**Scheme 104**).



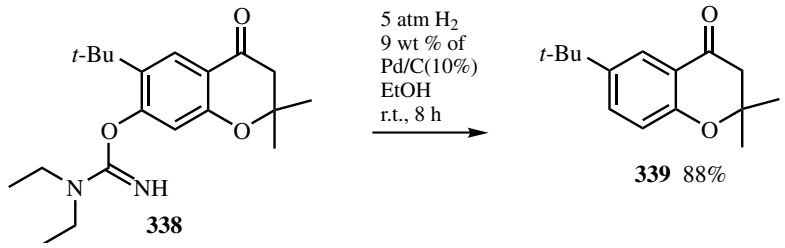
Scheme 100



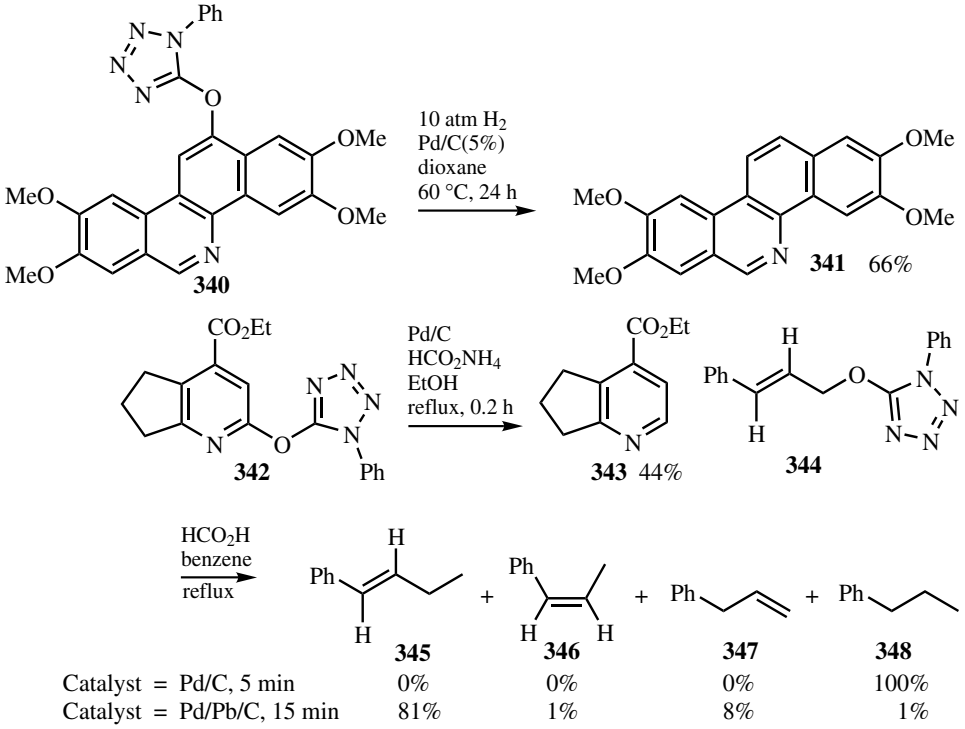
Scheme 101



Scheme 102



Scheme 103



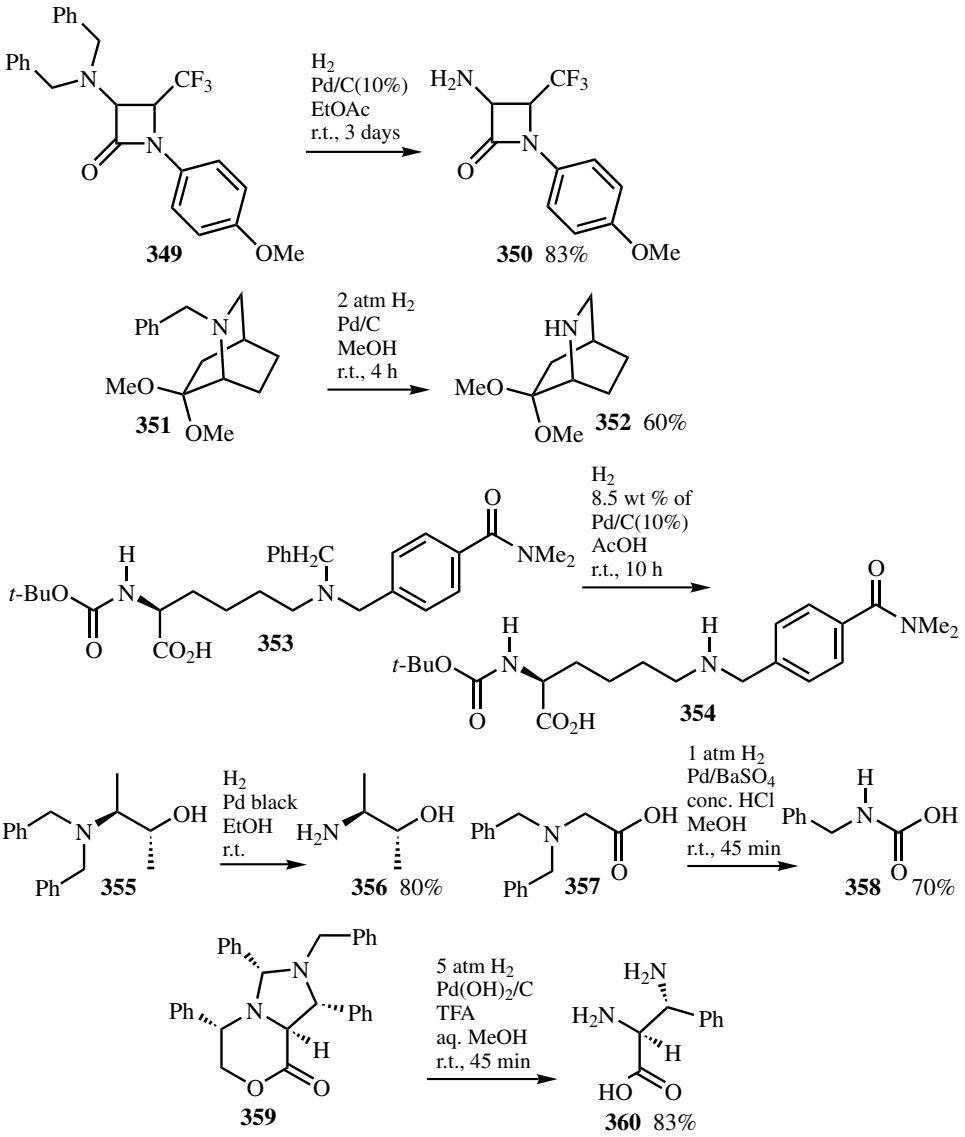
Catalyst = Pd/C, 5 min	0%	0%	0%	100%
Catalyst = Pd/Pb/C, 15 min	81%	1%	8%	1%

Scheme 104

To preserve the olefin in **344**, Pb-doped Pd/C was required. Some olefin isomerization products were also formed.

I. HYDROGENOLYSIS OF C—N BONDS

Many hydrogenolyzable protecting groups used for *O*-protection can also be used for *N*-protection. Again, benzyl is the most common protecting group used for *N*-protection. As shown by the examples in **Scheme 105**, many different reaction conditions and Pd catalysts have been used successfully to accomplish the hydrogenolysis of the *N*-benzyl



Scheme 105

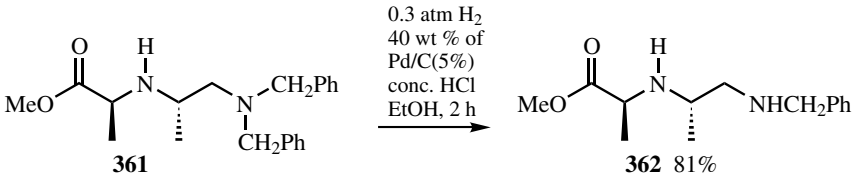
group.[159]–[164] Acidic conditions in conjunction with $Pd(OH)_2/C$ (this catalyst has been used especially for hydrogenolysis reactions) are used favorably in many instances.

In some cases the selective monodebenzylation of *N*,*N*-dibenzylamine has been accomplished (**Scheme 106**).[165]

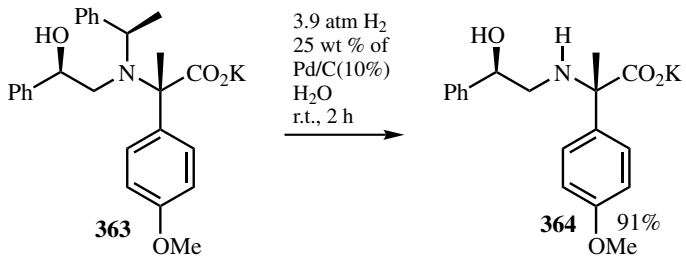
Chiral α-methylbenzylamine has frequently been used as a chiral auxiliary for diastereoselective synthesis. This protecting group does not present any problem during its hydrogenolysis (**Scheme 107**).[166]

The *N*-methylbenzyl and *N*-benzyl protecting groups have been selectively removed in the presence of benzylic hydroxy[167] and *N*-nitrosoamine[168] functional groups, respectively (**Scheme 108**).

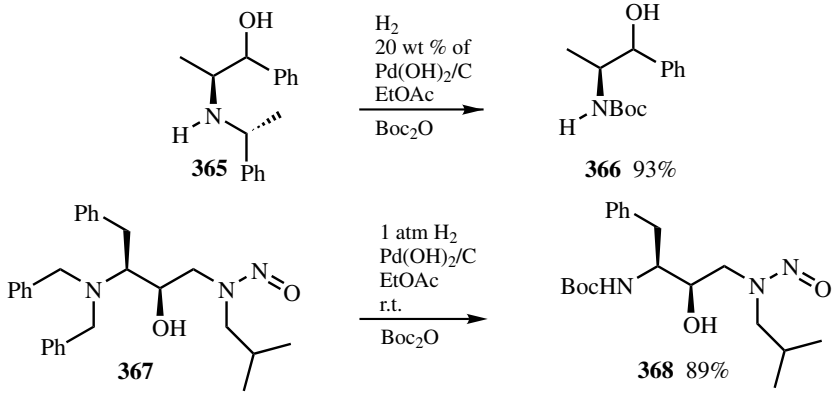
In a competitive hydrogenolysis reaction between *O*-benzyl ether and *N*-benzylamine groups, the latter was preferably hydrogenolyzed. Amines have been shown to have an inhibitory effect on the hydrogenolysis of benzyl ether.[111],[119],[169]



Scheme 106



Scheme 107



Scheme 108

The selective hydrogenolysis of *N*-benzylamine in the presence of a trityl ether was also carried out in 60% yield (**Scheme 109**).[170]

Benzhydryl group has been used for protecting alcohols as well as amines and amides. The protected imide was hydrogenolyzed at 65 °C in 75 min (**Scheme 110**).[171]

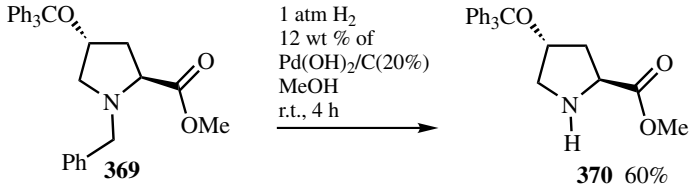
The imine derived from benzophenone was also hydrogenolyzed after the initial reduction of the C═N double bond (**Scheme 111**).[172]

Trityl,[173] 9-phenyl-9-fluorenyl,[174] and dibenzosubery[175] groups have also been used for amine protection and they can also be removed quite readily (**Scheme 112**).

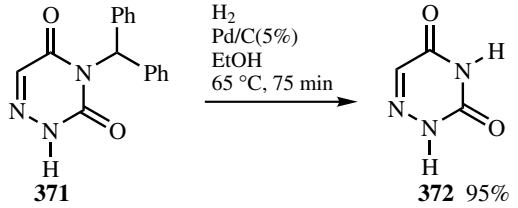
N-Benzylamide is usually difficult to hydrogenolyze. Surprisingly, even the relatively more difficult to hydrogenolyze *p*-methoxybenzyl on an amide nitrogen was removed under acidic conditions and $PdCl_2$ to give lactam **382** in excellent yield (**Scheme 113**).[176]

N-Benzylpyridone **383**[177] and *N*-benzylurea **385**[178] were also hydrogenolyzed in good yields using AcOH and $Pd(OH)_2/C$ (**Scheme 114**).

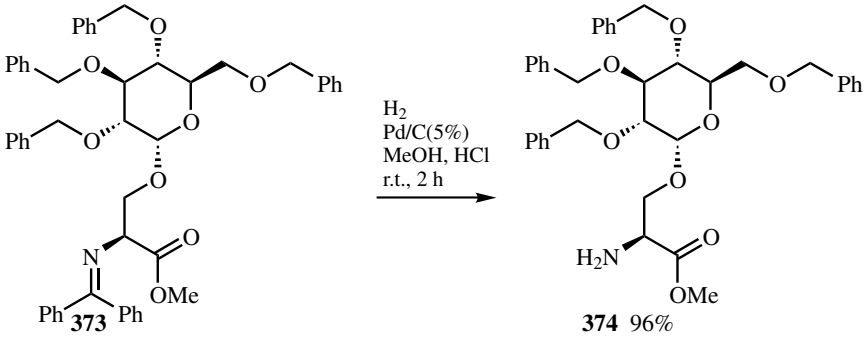
Dibenzylpyrimidine **387** was monodebenzylated under transfer hydrogenolysis conditions to give **388** in 60% yield (**Scheme 115**).[179] The imide benzyl group was slower to react but did get removed after 48 h at reflux and 300 wt % catalyst loading to give the completely debenzylated product in 78% yield.



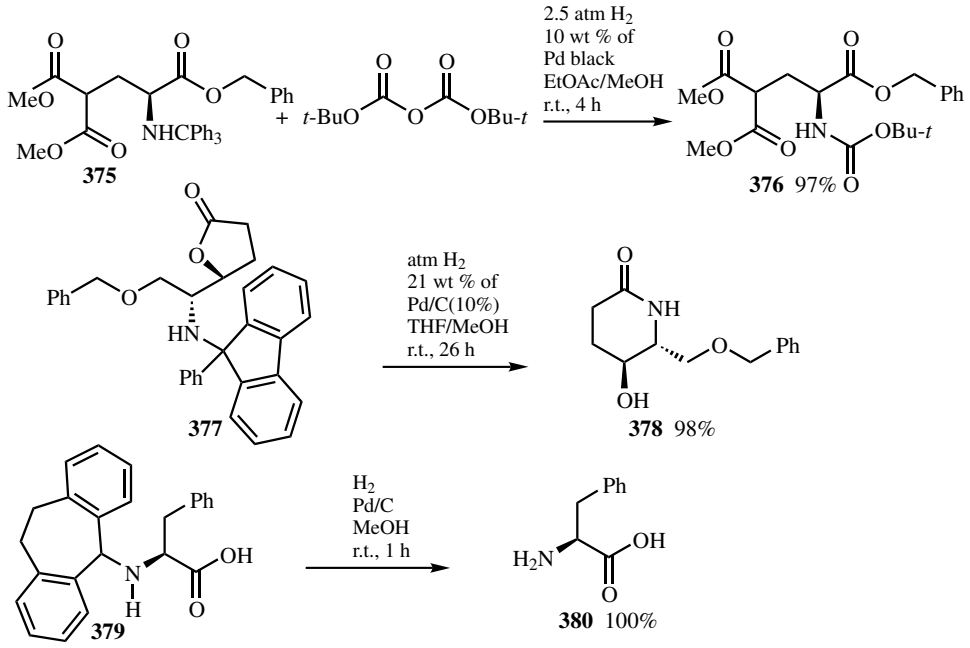
Scheme 109



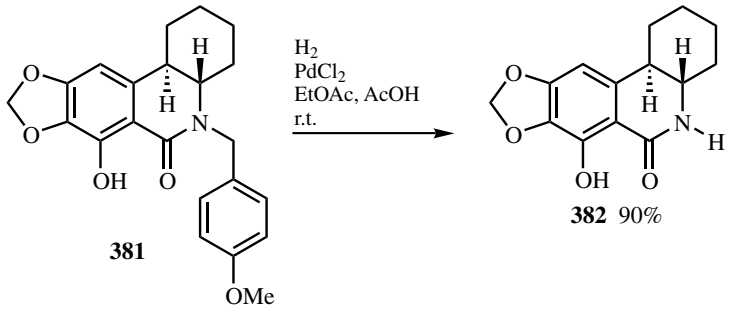
Scheme 110



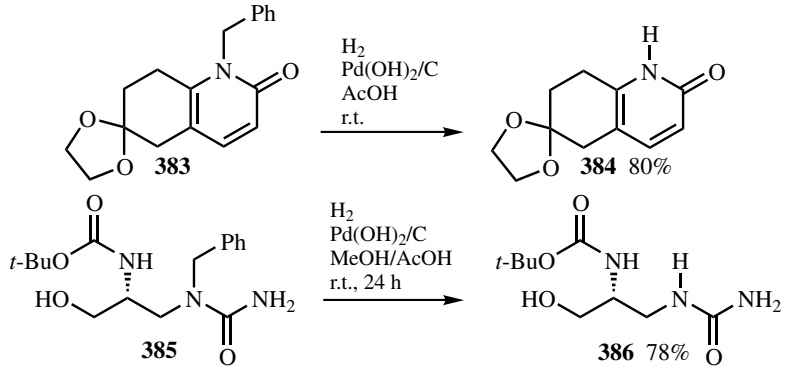
Scheme 111



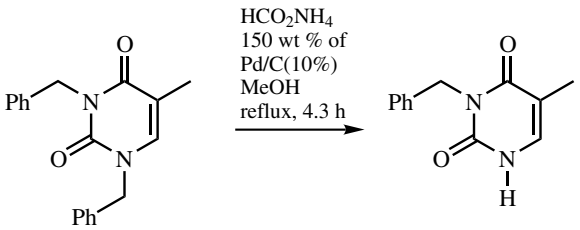
Scheme 112



Scheme 113



Scheme 114



387 **388** 60%

Scheme 115

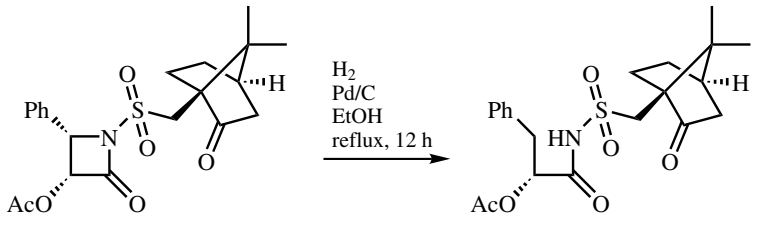
Benzylic C—N bonds of sulfonamides **389**[180] and **391**[181] are more readily hydrogenolyzed than *N*-benzylamide protecting group (**Scheme 116**). Hydrogenolysis of **389** under neutral conditions resulted in the opening of the β-lactam ring. Both the benzhydryl and benzyl groups were removed in the hydrogenolysis of **391** to give the primary sulfonamide in excellent yield.

Nitrone **393**,[182] oxazapyrrolidinone **395**,[183] and dienone **397**[184] were hydrogenolyzed to give primary amines (**Scheme 117**).

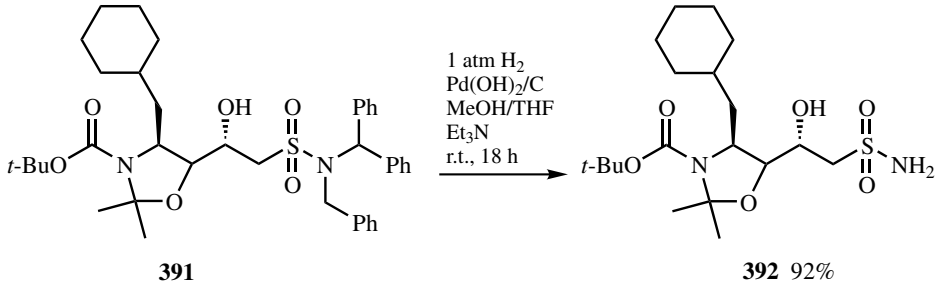
Nitrogen on heterocycles has frequently been protected as the *N*-benzyl derivative. Thus, 2-benzylimidazole **399** was successfully debenzylated to **400** in excellent yield (**Scheme 118**).[185] It should be noted that the benzylic ketone in **399** was not hydrogenated. Transfer hydrogenolysis with ammonium formate was also effective for the removal of the benzyl group in *N*-benzyl-2-methylimidazole.

The *p*-methoxybenzyl protecting group in tetrazole **401** was hydrogenolyzed without the cleavage of the hydroxy group (**Scheme 119**).[186]

Diazo compounds are also easily hydrogenolyzed (**Scheme 120**).[187]

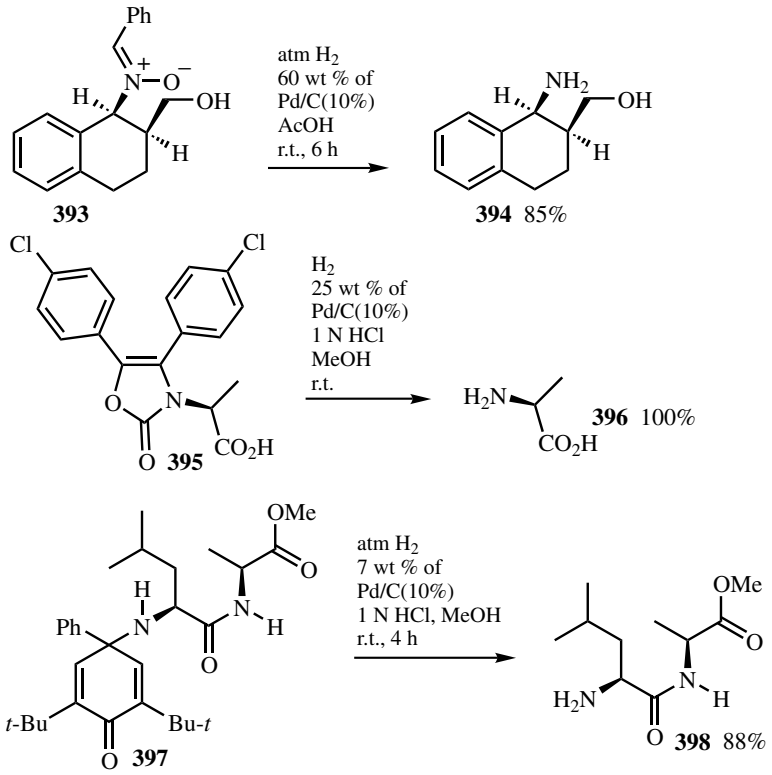


389 **390** 65%

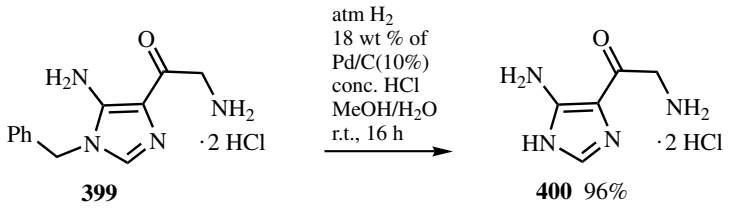


391 **392** 92%

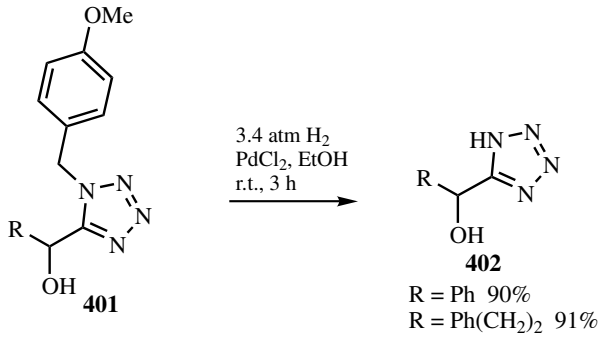
Scheme 116



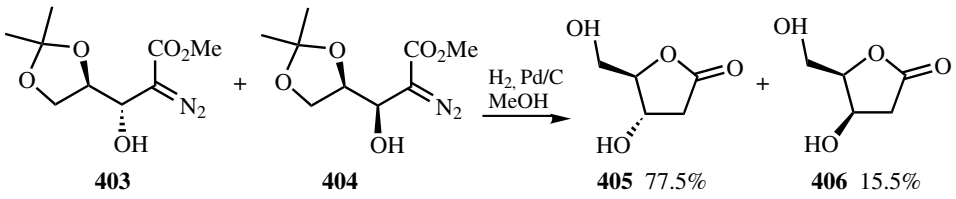
Scheme 117



Scheme 118



Scheme 119

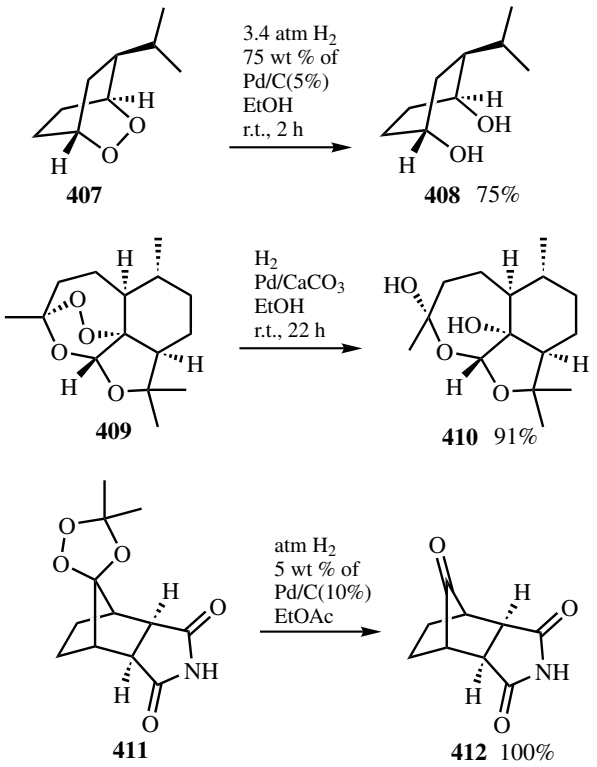


Scheme 120

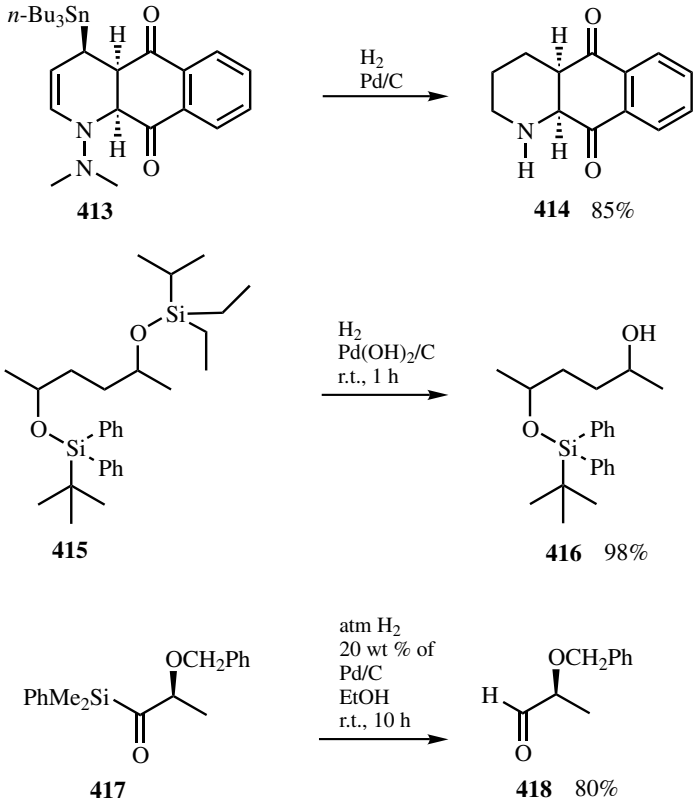
J. OTHER HYDROGENOLYSIS

The oxygen–oxygen bonds of peroxides and ozonides (resulting from the ozonolysis of alkenes) can easily be cleaved under Pd-catalyzed hydrogenation conditions (**Scheme 121**).[188]–[190]

Interestingly, even carbon–tin[191] and oxygen–silicon bonds[192] can be hydrogenolyzed (**Scheme 122**). The Si—O bond can be hydrogenolyzed with interesting selectivity. The diethylisopropylsilyl group in **415** was selectively removed while the *t*-butyldiphenylsilyl was untouched. In a competitive hydrogenolysis experiment between benzyl ether and diethylisopropylsilyl ether in dioxane, only the benzyl group was hydrogenolyzed in 98%. Acylsilane **417** was hydrogenolyzed to aldehyde **418**.[193] The phenyl substituent on silicon is crucial in the acceleration of the hydrogenolysis rate.



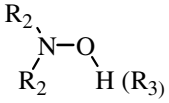
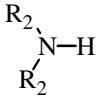
Scheme 121



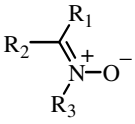
Scheme 122

K. SUMMARY

This section summarizes the different hydrogenolyzable functional groups discussed in previous sections.

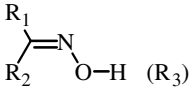
Reaction Number	Substrates	Products
Sect. B *Carbon–Carbon Bonds (Cyclopropane)*		
1.		
Sect. C *Nitrogen–Oxygen Bonds*		
2.		

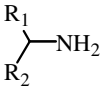
3.



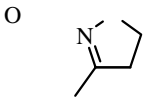
$R_3—NH_2$

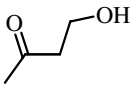
4.





5.

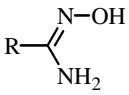


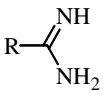


6.

$R—ONO_2$ $R—OH$

7.



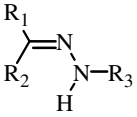


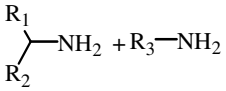
Sect. D *Nitrogen–Nitrogen Bonds*

8.

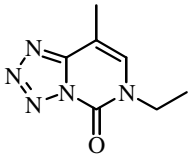
$R—N_3$ $R—NH_2$

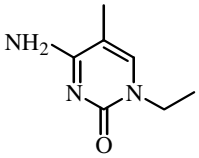
9.





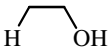
10.





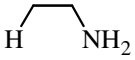
Sect. E *Carbon–Oxygen Bonds (Epoxide)*

11.



Sect. F *Carbon–Nitrogen Bonds (Aziridine)*

12.

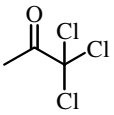
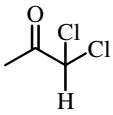


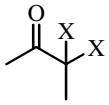
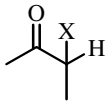
Sect. G *Carbon–Halogen Bond (I, Br, Cl)*

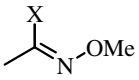
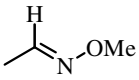
13. R—X → R—H

14.  → 

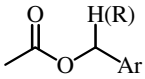
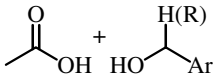
15. Ar—X → Ar—H

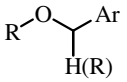
16.  → 

17.  → 

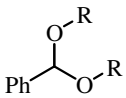
18.  → 

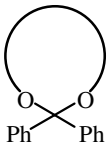
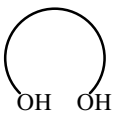
Sect. H *Carbon–Oxygen Bond (Benzylic and Others)*

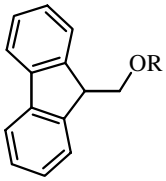
19.  → 

20.  → R—OH

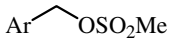
21.  → 

22.  → 2 R—OH

23.  → 

24.  → R—OH

25.



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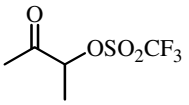
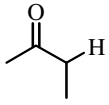
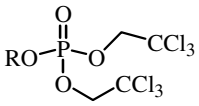
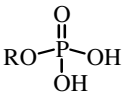


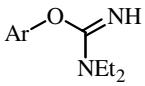


27.



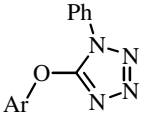


28.



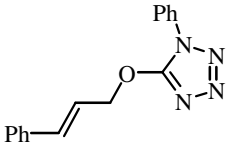
Ar—H

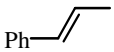
29.



Ar—H

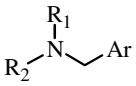
30.





Sect. I *Carbon–Nitrogen Bond (Benzylic)*

31.



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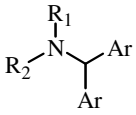
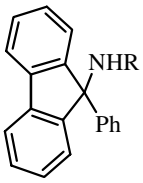


33.

34.



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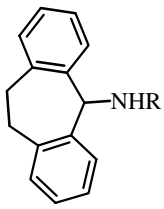
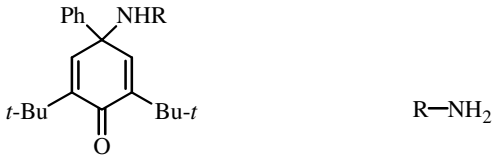


36.

37.



38.

39.

40.

Sect. J *Other Bond Cleavage*

41.

42.

43.

44.

45.

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