Methods for the Cleavage of Allylic and Propargylic C–N Bonds in Amines and Amides – Selected Alternative Applications of the 1,3-Hydrogen Shift

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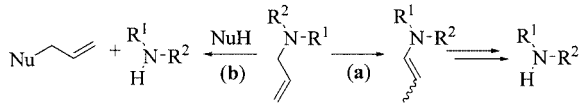
The aim of this article is to provide an updated review on the various methodologies that allow allylic C–N bonds (and by extension propargylic C–N bonds) to be cleaved. Since selectivity is crucial for synthetic planning, as far as possible, the relative reactivity of the various allylic groups is examined, and the discrimination between *O*-allyl and *N*-allyl derivatives is discussed. A special development is devoted to reactions leading to enamines through a 1,3-hydrogen shift, even though some of these reactions were not originally performed for the purpose of cleaving the *N*-allyl bond. Some selected applications are discussed. In addition to preparative deprotection methods, reactions such as the enzyme-mediated cleavage of allylic C–N bonds are also mentioned, although these reactions may not have any practical synthetic interest at the moment.

Introduction

The proper selection and selective cleavage of protecting groups are prerequisites in the synthesis of polyfunctional compounds. The transformation of amines into carbamates, or to a lesser extent into amides, is undoubtedly the most widely spread method for the protection of basic nitrogen atoms. However, in many instances allylation (or propargylation) offers a useful alternative.[1] The essential feature of these protecting groups is their stability towards both acids and bases, although as exemplified later on, they can be cleaved upon basic treatment, but under rather harsh conditions.

Except for a few miscellaneous methods, the above-mentioned methodologies can be roughly classified into two groups according to their mechanistic features. The methods belonging to the first group are based on the isomerization of the allylamine into an enamine, which is generally cleaved upon hydrolysis (Scheme 1, path a). In the second class of procedures, the experimental conditions are such



Scheme 1.

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MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

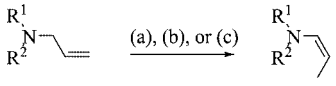
that the amine becomes a leaving group, which is displaced by a nucleophile (Scheme 1, path b).

1. Base-Catalyzed and Transition-Metal-Catalyzed 1,3-Hydrogen Shifts

The rearrangement can be promoted by strong bases, but alternatively, the migration of the double bond can be performed under milder conditions involving transition metals catalysis or free-radical processes. In most cases, the enamine is cleaved upon acidic treatment. Since many of the methodologies discussed below were not necessarily developed with the purpose of cleaving allylic C–N bonds, but rather with the formation of enamines as the goal in itself, any reaction allowing the formal cleavage of the rearranged product through hydrolysis will be discussed.

1.1. Reaction with Strong Bases

The rearrangement of *N*-allylamines to the corresponding enamines has been performed, at –70 °C by treatment with $NaNH_2$ in liquid ammonia or in aprotic solvents.[2] Alternatively, a milder base such as *t*BuOK can be used in HMPA. For the reaction to be efficient it is necessary to use high concentrations of base.[2] The efficacy depends both on the experimental conditions (base, concentration, solvent, etc) and on the stability of the enamine. Quantitative yields are observed in the case of aniline derivatives. Whenever the overlap between the lone pair and the π orbitals is impeded for steric reasons, the migration is slowed down and becomes partial, or even prohibited (Scheme 2).



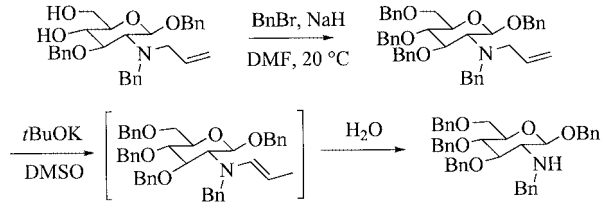
R^1	R^2	Migration (%)	*Z*/*E* ratio	Reaction time (h)
C_6H_4	CH_3	100[a]	85/15	24
–	–	100[b]	43/67	48
–	–	100[c]	98/2	< 1
CH_3	C_2H_5	30[a]	80/20	432
CH_3	CH_3	62[a]	60/40	48
C_6H_{11}	CH_3	0[a]	–	240

[a] $NaNH_2$, liq NH_3, –70 °C; [b] $NaNH_2$ (saturated), HMPA, 20 °C; [c] *t*BuOK (saturated), HMPA, 20 °C

Scheme 2.

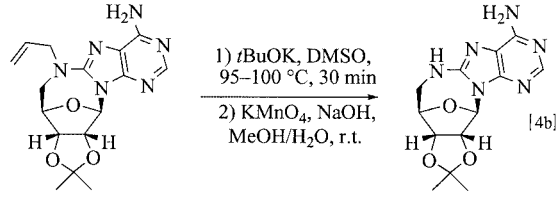
Potassium *tert*-butoxide has also been used in DMSO.[3] *O*-Allyl ethers and *N*-allylamines rearrange at essentially the same rate, whereas *O*-allyl ethers are isomerized faster than *N*-crotylamines. The 1,3-hydrogen shift occurs in half an hour at room temperature for the former, whereas it needs 4 h at 50 °C to isomerize the latter.[3a]

The *N*-allylbenzylamino group is a protected amino function which can be readily converted into the *N*-benzylamino derivative upon the above-mentioned treatment. In the amino sugar series, it is suitable to protect the amino function during the performance of *O*-alkylation, which necessitates vigorous conditions. No quaternization of the amino group was encountered (Scheme 3).[3b]



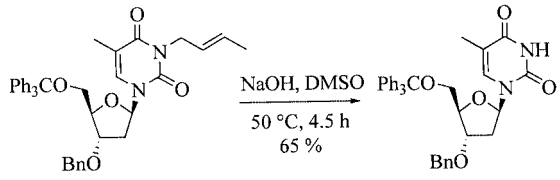
Scheme 3.

This protocol has been applied within a multi-step reaction for the removal of the allyl group used as a convenient blocking group in the synthesis of *N*-substituted purines (Scheme 4).[4]



Scheme 4.

NaOH has been used at 50 °C in DMSO to deprotect the *N*-crotylthymine moiety in carbocyclic analogs of 2′-deoxyribonucleosides (Scheme 5).[5]

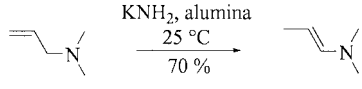


Scheme 5.

Saponification of *N*-(4-acetylaminobutyl)-*N*-(3-methylbut-2-enyl)guanidine with 50% KOH leads to isopropylputrescine in a process where migration of the double bond occurs concomitantly to the hydrolysis of the guanidine and the amide functions.[6]

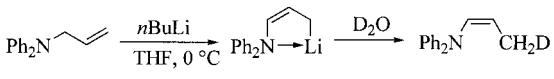
The *N*-propargyl group can also be removed by refluxing in 1 N NaOH.[7] The prototropic rearrangement of secondary propargylic amines upon treatment with *t*BuOK in *t*BuOH at 100 °C affords α,β-unsaturated aldimines in rather moderate yields.[7b]

The formation of *N*,*N*-dimethylpropenylamine from the corresponding allylamine proceeds in good yield in a heterogeneous medium upon treatment with KNH_2 (25 °C) (Scheme 6)[8] or KOH (260–270 °C)[9] supported on Al_2O_3. Heterogeneous catalysis by mean of metallic oxides such as MgO or CaO, carried out at 40 °C, has also been shown to be efficient.[10]



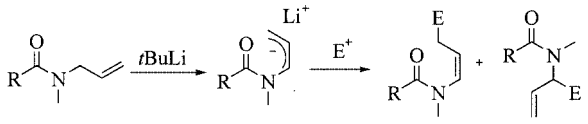
Scheme 6.

The exclusive formation of the (*Z*)-isomer has been reported for the metalation of allyldiphenylamine in the presence of *n*BuLi. This is in agreement with the formulation of the intermediate organolithium species as a five-membered chelate (Scheme 7).[11]



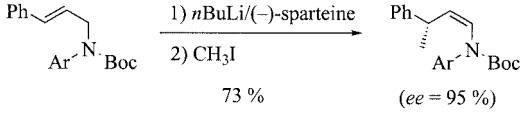
Scheme 7.

Although the aim of these reactions was not the cleavage of the C–N bond, it must be mentioned that the metalation of allyl amides can be performed with RLi[12–14] or LDA.[15] The corresponding lithioallyl amides react regioselectively with electrophiles (Scheme 8).



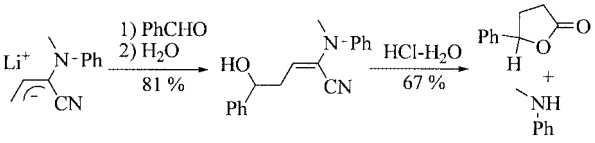
Scheme 8.

In acyclic systems, the γ-alkylated product is generally obtained as the (*Z*)-isomer. Electrophiles such as benzaldehyde, trialkylsilyl chloride, or methyl iodide react preferentially at the γ position. The allyl organolithium species derived from *N*-allyl carbamates that are ligated to (–)-sparteine lead to a high enantiomeric ratio (Scheme 9).[16] They also give rise to Michael addition with high diastereo- and enantioselectivities.[17]



Scheme 9.

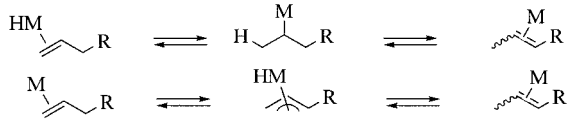
In the following example, the regioselective addition of the delocalized carbanion to benzaldehyde leads, after hydrolysis, to a γ-lactone (Scheme 10).[18]



Scheme 10.

1.2. Methods Involving Transition Metal Catalysts

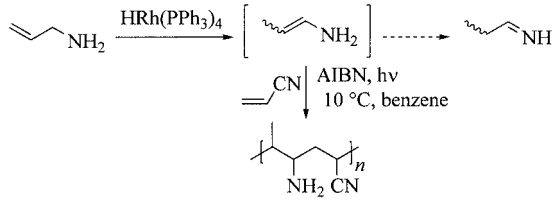
The use of a strong base is restricted to compounds that do not contain base-sensitive functional or protecting groups as it may, in some cases, lead to the cleavage as an undesired side-reaction.[19] This is an argument to claim the superiority of transition-metal-catalyzed processes. Although the reaction mechanisms are not always clear-cut, a tentative classification according to the nature of the active species or the intermediate complex is given here. Two pathways can be distinguished to rationalize the transition-metal-mediated double-bond migration: one is a metal hydride addition/elimination mechanism, and the other is a 1,3-hydrogen shift via a π-allyl intermediate formed by oxidative addition of the allylic C–H bond to the metal (Scheme 11).



Scheme 11.

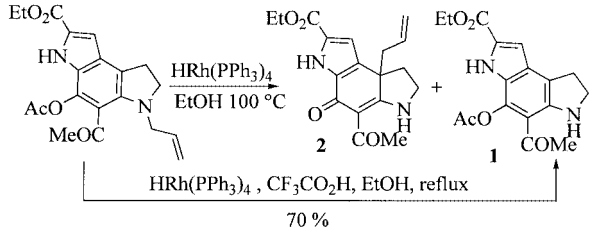
1.2.1. The Active Species is a Metal Hydride

Rhodium hydrides are very active catalysts,[20,21a,22] and the rhodium complex $[HRh(CO)(PPh_3)_3]$[21a] catalyzes the double-bond migration in *N*-methylallylamine and allylamine at 22 °C. It is better than $[HRh(PPh_3)_4]$ in the case of the primary amine because the rate of isomerization is higher than the rate of tautomerization of the intermediate enamine. The tautomerization is not catalyzed by this complex, since the rate of formation of the imine is independent of the concentration of the catalyst. It is therefore possible to copolymerize the primary enamine with acrylonitrile and form a one-to-one alternating copolymer (Scheme 12).[20]



Scheme 12.

As shown in Scheme 13, the use of tetrakis(triphenylphosphane)rhodium hydride at 100 °C in ethanol leads to a mixture of **1** and **2**. The latter is likely to result from a sigmatropic thermal rearrangement after solvolysis of the *O*-acetyl group. Better results can be achieved by use of 0.25 equivalents of the rhodium complex and one equivalent of trifluoroacetic acid in refluxing ethanol.[22]

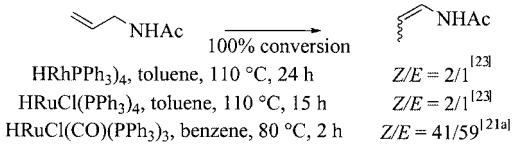


Scheme 13.

Like $[HRh(CO)(PPh_3)_3]$, $[HRuCl(CO)(PPh_3)_3]$[21a] isomerizes *N*-allylamines into the corresponding enamines at temperatures varying between 80 and 120 °C. Whatever the catalyst (Rh or Ru), the (*E*)/(*Z*)-selectivity is 100:1 in most cases. This selectivity is thought to result from steric interactions in the transition state of the β-elimination step.

Rhodium and ruthenium hydrides convert *N*-allyl amides into *N*-propenyl amides.[21,23] As shown below, the reaction

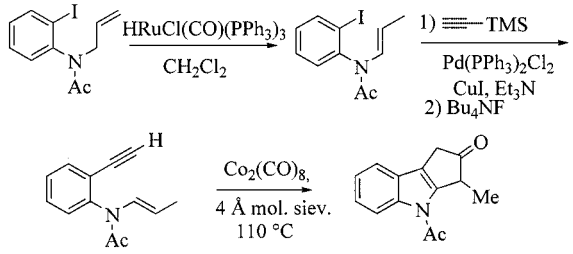
needs 24 h to reach completion with $[HRh(PPh_3)_4]$ and leads to a mixture of (*Z*)- and (*E*)-isomers in a 2:1 ratio (Scheme 14).[23]



Scheme 14.

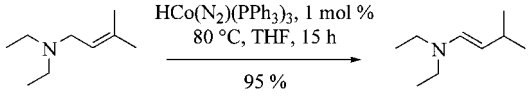
Both $[HRuCl(CO)(PPh_3)_3]$[21b,21c] and $[HRuCl(PPh_3)_4]$[23] also isomerize *N*-allylacetamides to *N*-propenylamides (Scheme 14), although the reaction proceeds faster with the former. It must be underlined that these conditions apply to methallyl derivatives and that *N*-prenyl derivatives fail to isomerize.

The nearly quantitative isomerization of *N*-allyl-2-iodoacetanilide has been used as a key step in the synthesis of cyclopentaindoles by Sonogashira coupling and a subsequent Pauson–Khand reaction (Scheme 15).[24]



Scheme 15.

Cobalt hydrides such as $[HCo(N_2)(PPh_3)_3]$[25] allow the formal cleavage of *N*-prenylamines. A yield as high as 95% of the enamine has been reported (Scheme 16). The cobalt catalyst does not isomerize allylic ethers.

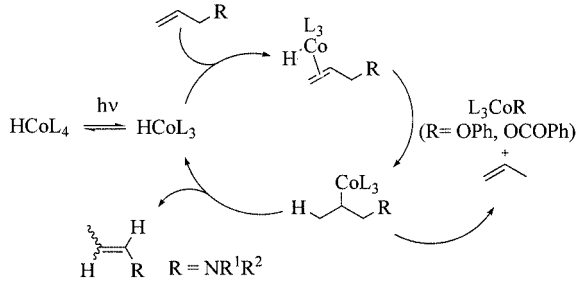


Scheme 16.

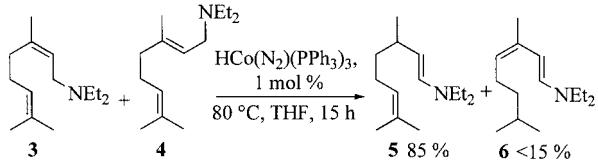
The photo-assisted double-bond migration in *N*-allylamines and *N*-allyl amides can be promoted by $[HCo\{PPh(OEt)_2\}_4]$.[26] Allylbenzoate and allyl phenyl ethers are cleaved under the same conditions, presumably by a β-fragmentation, to give propene and a benzoato- and a phenoxocobalt species, respectively (Scheme 17).

N,*N*-Dialkylgeranylamines and the isomeric *N*,*N*-dialkylnerylamines, such as **3** and **4**, respectively, can be isomerized into citronellal enamine **5**, which is exclusively *E* (Scheme 18). The dienamine **6** is formed as a side product in significant amounts (<15%).[25]

Since the mechanism proceeds by insertion of the double bond into the Co–H bond followed by β-elimination, asymmetric catalysis could reasonably be expected in the first step. Several cobalt(I) hydrides have been prepared by reduction of Co^{II} salts in situ with organoaluminum reagents such as $AlH(iBu)_2$ or $AlEt_3$ in the presence of chiral ligands.



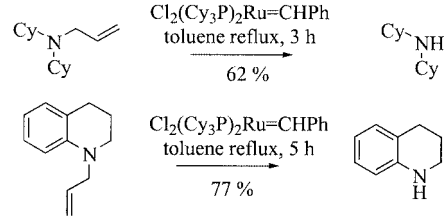
Scheme 17.



Scheme 18.

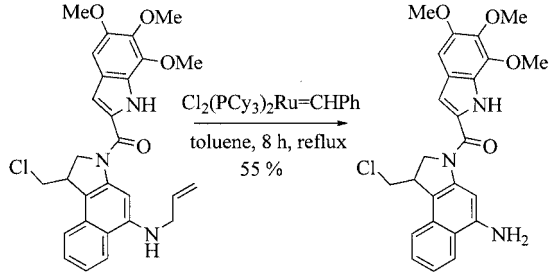
Chiral monodentate phosphanes led to very low *ee*'s (5 to 7%), although bidentate phosphanes led to higher overall yields and higher *ee*'s. As an example, when either **3** or **4** was treated with the cobalt complex in the presence of (+)-DIOP and DIBAL in a 50:1:1:3 ratio in THF at 60 °C for 64–75 h, the reaction led to (3*R*)-**5** and (3*S*)-**5**, respectively, with an *ee* close to 32% and 23%.

As exemplified in Scheme 19, the cleavage of an allyl group in tertiary or secondary amines occurs in refluxing toluene in the presence of a catalytic amount of the Grubbs carbene $[Ru(=CHPh)Cl_2(PCy_3)_2]$.[27]



Scheme 19.

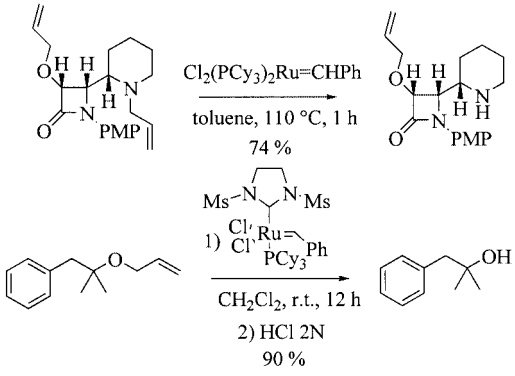
Deblocking the *N*-allyl group, which has proved to be difficult in the synthesis of 5-aminobenzo[*e*]indoles derivatives, can be effected in 55% yield using the above-mentioned Alcaide procedure (Scheme 20).[28]



Scheme 20.

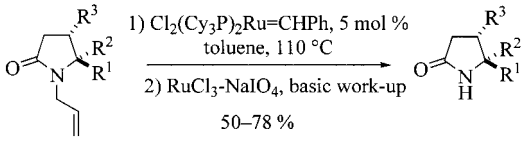
This transformation tolerates various functional groups. It is worth noting that, in the presence of the first-genera-

tion Grubbs carbene, the *N*-allyl group can be cleaved selectively in the presence of the *O*-allyl chain (Scheme 21).[27] The limitation of this method arises when the substrate contains an extra double bond that is capable of giving rise to RCM (ring closing metathesis). The second generation catalysts isomerize *O*-allyl derivatives (with the exception of prenyl ethers) in far higher yields than *N*-allylamines or *N*-allyltosyl amides (Scheme 21).[29]



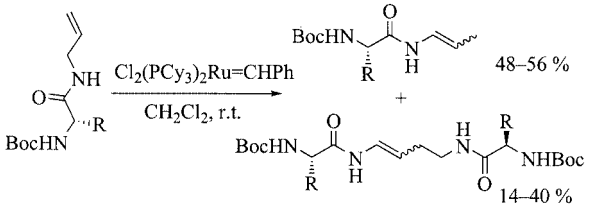
Scheme 21.

The same conditions also apply to the cleavage of *N*-allyl lactams.[30] In the Eighties, a multi-step procedure was reported for the deprotection of *N*-allyl β-lactams,[31] involving reductive ozonolysis of the double bond, transformation of the resulting aldehyde into the corresponding enol acetate, subsequent oxidation with NBS to give a bromohydrin, and final cleavage with hydrazine. Recalling this method enlightens the difficulty of cleaving the allylic C–N bond. A comparison of Alcaide's method[30] with Fukuyama's[31] clearly emphasizes the progress made over the last twenty years (Scheme 22).



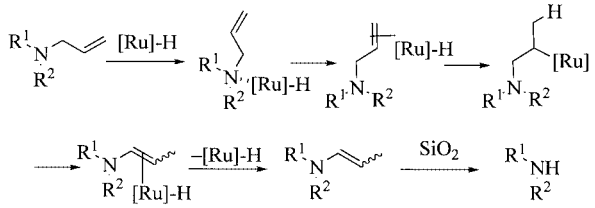
Scheme 22.

The results obtained on a series of acyclic *N*-allylamides derived from Boc-protected amino acids[32] are consistent with Alcaide's reports,[27,30] although, even though double-bond migration was the major outcome, metathesis products were also formed (Scheme 23).



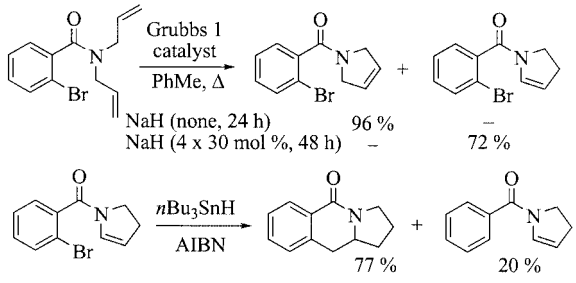
Scheme 23.

The authors speculate that a ruthenium hydride that would result from the decomposition of the Grubbs catalyst is the active species (Scheme 24).[27b,33,34]



Scheme 24.

The discovery that double-bond migration and metathesis could interfere has led to sequences that combine carbene chemistry and a ruthenium hydride mediated hydrogen shift.[33] Schmidt has shown that allyl ethers can be converted to enol ethers through such a sequence. The addition of a hydride source such as NaH or $NaBH_4$ activates the double-bond migration.[33b,33c] RCM and subsequent double-bond migration have been used by Piva et al. to prepare precursors of tricyclic lactams (Scheme 25).[35]

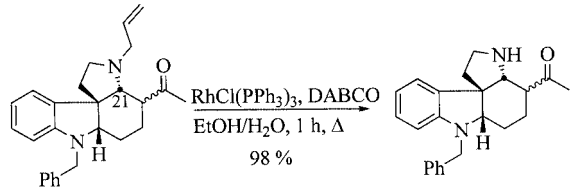


Scheme 25.

1.2.2. Reactions Proceeding via π-Allyl Intermediates

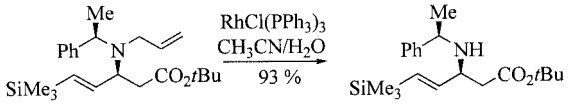
Rhodium catalysts give good results. Wilkinson's catalyst[36] was used first under experimental conditions similar to those used by Corey for allylic ethers, i.e., in the presence of DABCO.[37] When $[RhCl(PPh_3)_3]$ is used in a mixture of ethanol and water as solvent, the reduction of the double bond may occur as a side reaction. Since ethanol is a hydride donor, the side reaction can be avoided by using dioxane or *tert*-butanol, or even a benzene/water mixture as solvent. The major drawback is that the rate of the process is considerably lowered (50 h is needed for completion instead of 3 h).[36a]

The selective removal of the *N*-allyl protecting group has been achieved with $[RhCl(PPh_3)_3]$ in the synthesis of unnatural *aspidosperma* alkaloids (Scheme 26).[38] It should be noted that the same reaction failed when performed with the C-21 epimer.



Scheme 26.

Very good results have been reported when using Wilkinson's catalyst in aqueous acetonitrile (Scheme 27).[36b,39,40]

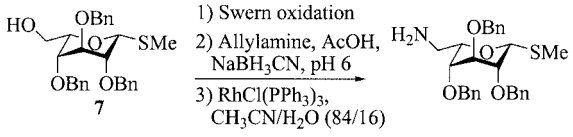


Scheme 27.

The number of referenced articles clearly demonstrates the efficacy of the method, which is probably among the most frequently used. The ability to differentiate between different protecting groups is of special interest with respect to the synthetic planning of complex molecules. As shown below, it is possible to deprotect the *N*-allyl group in the presence of an α-branched allylic chain and in the presence of *N*-benzyl nitrogen protecting groups.[39,89]

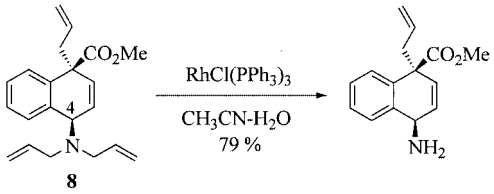
The need for a variety of selectively removable protecting groups is of special importance in the chemistry of carbohydrates. Examples are given in recent syntheses of glycosidases inhibitors[41] and aminoglycoside antibiotics.[42]

When the amino group cannot be introduced by displacement of a mesylate by an azide, as is the case for compound **7** owing to intramolecular participation of the anomeric sulfide, the introduction of the amino substituent can be achieved by Swern oxidation followed by reductive elimination with allylamine and subsequent deallylation (Scheme 28).[42]



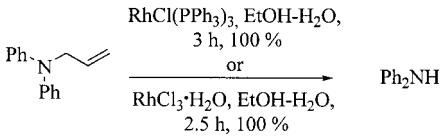
Scheme 28.

The successful removal of two allyl groups to give the corresponding primary amine from **8** occurred without any migration of the two additional double bonds. This is remarkable, since the C-4 position should be very reactive as it is both allylic and benzylic (Scheme 29).[43]



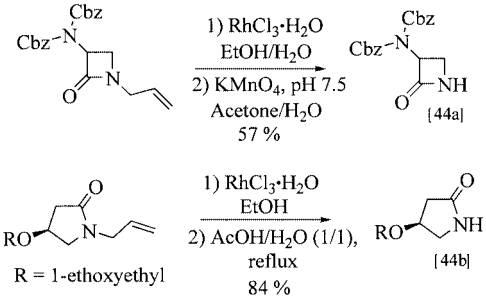
Scheme 29.

In some cases, $RhCl_3 \cdot H_2O$, used under the same conditions as Wilkinson's catalyst, leads to very good results, and this procedure has been claimed to be superior because of its better reproducibility (Scheme 30).[36a]



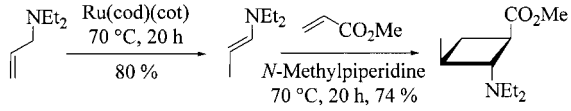
Scheme 30.

$RhCl_3 \cdot H_2O$ is efficient for the deprotection of *N*-allyl lactams via a two-step procedure (Scheme 31).[44]



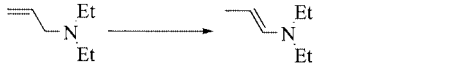
Scheme 31.

Ruthenium complexes give similar results. The isomerization of *N*,*N*-diethyl allylamine catalyzed by [Ru(cod)(cot)][45] leads to *trans*-1-diethylamino-1-propene in 80% yield (Scheme 32). The enamine can be trapped by methyl acrylate to give the corresponding cycloadduct in 74% yield.



Scheme 32.

The migration of the double bond in allylamines can be promoted by *trans*-$[Mo(N_2)_2(Ph_2PCH_2CH_2PPh_2)_2]$.[46] The same complex also catalyzes a 1,3-hydrogen shift in allylic alcohols and allylic ethers. When *N*,*N*-diethylallylamine was heated for 2 h in the presence of the molybdenum catalyst, *N*-*trans*-propenyldiethylamine was obtained in quantitative yield. Another molybdenum catalyst prepared in situ from $Mo(acac)_3$, dppe ($Ph_2PCH_2CH_2PPh_2$), and triethylaluminum led to the same result. In comparison, the reaction catalyzed by $[MoH_4(dppe)_2]$ under UV irradiation gave only 50% yield (Scheme 33). The molybdenum complex does not catalyze a 1,3-hydrogen shift in *N*-prenyl, *N*-crotyl, or even *N*-methallyl derivatives.



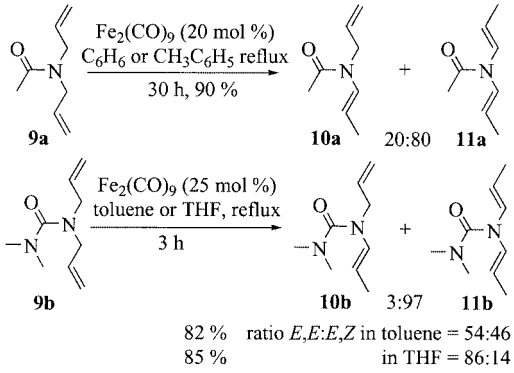
1. *trans*-$Mo(N_2)_2(dppe)_2$, 100 °C, 2 h, 100 %.
2. $MoH_4(dppe)_2$, irradiation UV, 100 °C, 4 h, 50 %.
3. $Mo(acac)_3$, dppe, Et_3Al (1:2:10), 100 °C, 5 h, 100 %.

Scheme 33.

$[RuCl_2(PPh_3)_3]$ promotes the irreversible migration of the double bond in *N*-allylphthalimides at 150 °C to give the corresponding *n*-propenyl derivatives. Under these conditions methallyl derivatives are inert, although their isomerization can be performed by prolonged heating (100 h) in the presence of $[H_4Ru_4(CO)_{12}]$.[47]

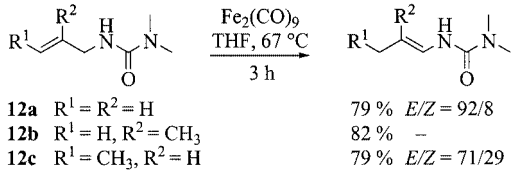
N-Allylsuccinimide can be isomerized to *N*-propenylsuccinimide in the presence of $[Fe(CO)_5]$. The activation of the catalyst was performed either by heating in refluxing xylene or by irradiating at room temperature.[48] $[Fe_2(CO)_9]$[49] isomerizes *N*,*N*-diallyl amide (**9a**) in a mixture of *N*-allyl-*N*-vinyl amide (**10a**) and *N*,*N*-divinyl acetamide (**11a**) (Scheme 34). The same conditions apply to the urea **9b**. The

stereoselectivity is influenced by the nature of the solvent; in THF, the (*E*,*E*)-isomer of **11b** becomes largely predominant.



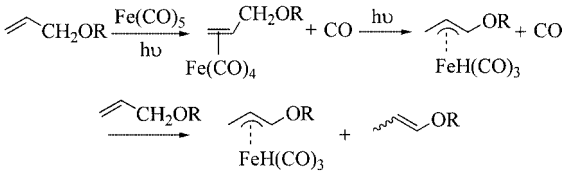
Scheme 34.

A larger amount of catalyst is needed to isomerize the crotyl and methallyl derivatives **12b** and **12c** compared to the *N*-allyl analog **12a**. The rate of the reaction is not only sensitive to the nature of the allylic chain but also to the structure of the other amine residue. When *N*-allyl *N*′,*N*′-diethylurea was treated with [$Fe_2(CO)_9$] (0.5 mol%) in THF, no isomerization occurred, which clearly demonstrates the importance of the *N*,*N*-dimethylcarbamoyl moiety (Scheme 35).



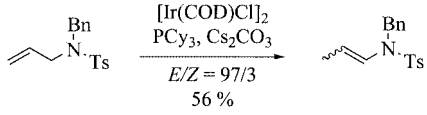
Scheme 35.

The catalytic procedure is also effective in more polar solvents such as methanol or acetone.[50] The mechanism admitted for the related [$Fe(CO)_5$]-mediated isomerization of *O*-allyl ethers is shown in Scheme 36.[50] According to the authors, the π complex formed by ligand exchange stimulated by UV irradiation is the precursor of the π-allyl complex. Reductive elimination, followed immediately by complexation of another molecule of substrate, gives the enol ether (Scheme 36).



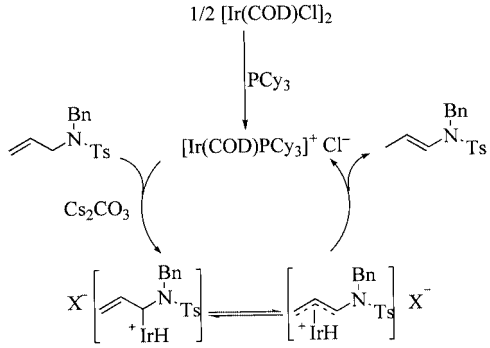
Scheme 36.

The migration of the double bond in *N*-allyl tosylamides, imides, and carbamates can be catalyzed by [IrCl(COD)]$_2$[51] in the presence of tricyclohexylphosphane and cesium carbonate (Scheme 37). It is worth noting that, again, the yield depends strongly on the nature of the allylic chain. Methallyl and crotyl derivatives are not reactive at all, which provides a chemoselective entry to the synthesis of enamides that can be cleaved under oxidative[107] or standard hydrolysis conditions.[114]



Scheme 37.

The mechanism is summarized in Scheme 38. The first step in the catalytic cycle is the base-catalyzed oxidative addition of the allylic C–H bond to Ir^I, which leads to the η^1-allyl intermediate. The η^3 complex then gives the enamine by reductive elimination.

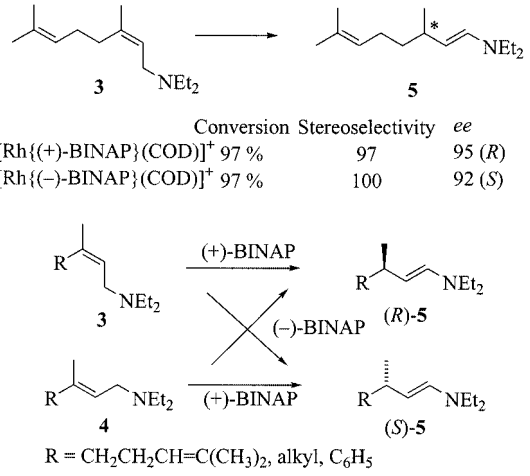


Scheme 38.

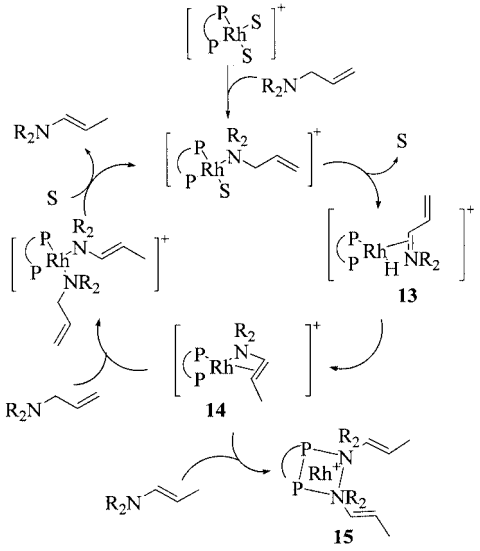
Although their aim was not the release of the amino group from the enamine, but rather the recovery of the aldehyde moiety, the following paragraph is devoted to enantioselective processes. As already mentioned in Section 1.2.1., the synthesis of optically pure citronellal from the readily available racemic geranyl- and nerylamines is a goal of economic importance.[52] Chiral rhodium catalysts have been used to investigate the enantioselectivity of the reaction. A catalyst such as [Rh{(±)-BINAP}(COD)]$^+$, which is more stable but less reactive than [Rh{(±)-BINAP}(solvent)$_n$]$^+$, is efficient for the isomerization of **3** into the (*E*)-enamine **5** with a stereoselectivity exceeding 95% and an *ee* of 92 or 95% depending on the enantiomer of the ligand (Scheme 39).[52] A correlation was established between the configuration of the double bond in the starting material, the configuration of the chiral bidentate ligand, and the configuration of the chiral center in the product (Scheme 39). BIPHEMP[53] (6,6′-dimethylbiphenyl-2,2′-diyl)bis(diphenylphosphane) has been shown to be as efficient as BINAP for the isomerization of *N*,*N*-diethylgeranylamine.[54]

In the first step, the amine coordinates to the metal. Owing to the basic character of nitrogen, oxidative addition of the C–H bond to the metal leads formally to a complexed iminium salt (**13**)[55] (Scheme 40).

Insertion of the C=C bond into the Rh–H bond leads to the complexed enamine **14**. A change in hapticity is accompanied by the coordination of a molecule of the starting amine before the enamine is replaced by a molecule of solvent. It is worth noting that the coordination of a second



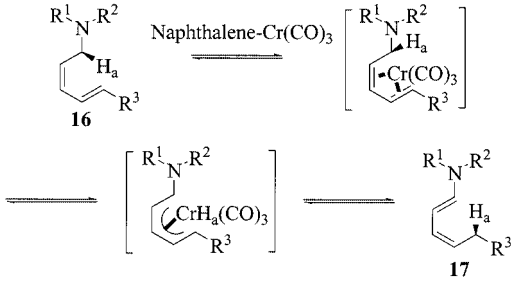
Scheme 39.



Scheme 40.

molecule of enamine to **14** leads to **15**, which slows down or even stops the catalytic process. The transition-metal-catalyzed stereospecific isomerization with the aid of an immobilized chiral ligand has been patented.[56]

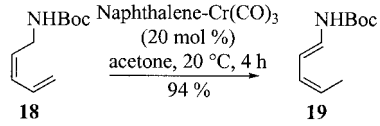
The isomerization of dienic amines of type **16** to dienamines **17** is catalyzed by a chromium naphthalene carbonyl complex,[57] and the reaction proceeds via an intermediate η^5 complex formed, as previously, by oxidative addition of



Scheme 41.

the C–H bond to the metal. Subsequent reductive elimination leads to **17** (Scheme 41).

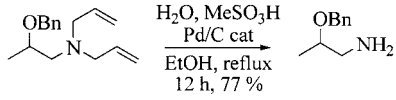
When carbamate **18** was allowed to react with the above-mentioned complex for 2 h in acetone at 20 °C, **19** was isolated in 94% yield (Scheme 42). Adequately *N*-substituted dienamines have also been used in intramolecular Diels–Alder reactions to form octahydroquinoline derivatives.[57]



Scheme 42.

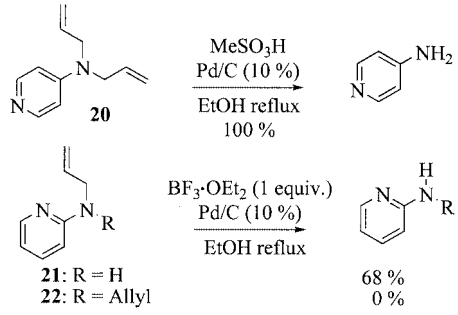
1.2.3. Heterogeneous Conditions

The cleavage of C–N allylic bonds in *N*-allyl- and *N*,*N*′-diallylamines can be performed in good yields by refluxing the substrate in ethanol in the presence of one equivalent of methanesulfonic acid and a catalytic amount of Pd/C.[58,59] The mechanism proceeds as with allyl ethers by migration of the double bond.[60] The heterogeneous catalyst can also be used in water, which allows the concomitant hydrolysis of the enamine (Scheme 43).[58] Basic conditions ($NaHCO_3$) have also been successfully employed.[58e]



Scheme 43.

Methanesulfonic acid can be replaced by $BF_3{\cdot}OEt_2$,[61] as shown in Scheme 44 for a series of aminopyridines and pyrimidines. It should be noted that the reaction failed for diallyl derivatives **22** where the *N*,*N*-diallylamino moiety is adjacent to one or more nitrogen atoms. However, monoallylamines are deallylated in the presence of $BF_3{\cdot}OEt_2$.

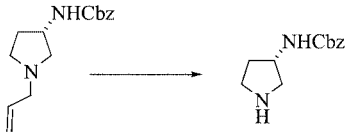


Scheme 44.

The cleavage of an allylic C–N bond catalyzed by Pd/C proceeds in 1.5 h in aqueous solution, in the presence of 2.2 equivalents of AcOH.[62,63]

Comparative data obtained with different catalysts for 3-aminopyrrolidines,[62] either homogeneous or heterogeneous, are given in Scheme 45. Among Rh and Ru catalysts, only $RhCl_3{\cdot}3H_2O$ did not give the expected pyrrolidine. It is interesting to note again that all these methodolo-

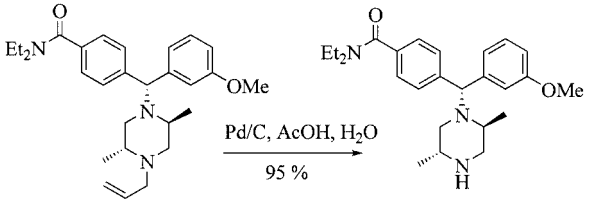
gies allow the allylic C–N bond to be cleaved selectively in the presence of the benzyl carbamate moiety.



- 10 % Pd/C, 2.2 equiv. AcOH, H_2O, 100 °C, 1.5 h, 92 %.
- $RhCl(PPh_3)_3$, H_2O/EtOH (1:1), 80 °C, 2 h, 83 %.
- $RhCl_3{\cdot}3H_2O$, H_2O/EtOH (1:1), 80 °C, 1 h, traces
- $RuCl_2(PPh_3)_3$, H_2O/EtOH (1:1), 80 °C, 5 h, 91 %

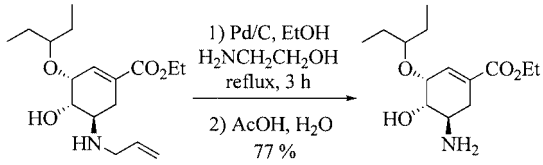
Scheme 45.

The Pd/C/AcOH methodology has been successfully applied to the synthesis of δ-opioid receptor agonists (Scheme 46).[64]



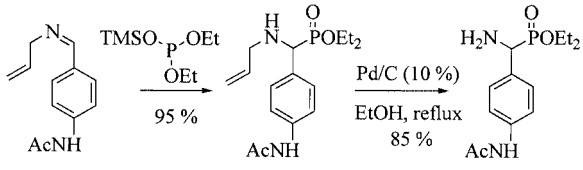
Scheme 46.

The reaction can also be performed in ethanol in a neutral medium, followed by acidic hydrolysis (Scheme 47),[65] or by direct chromatographic purification of the product.[66]



Scheme 47.

Due to the selective cleavage of the allylic C–N bond with Pd/C in the presence of benzylic C–N bonds, the use of *N*-allylimines is particularly interesting compared to *N*-benzylimines for the synthesis of α-aminophosphonic acids by addition of phosphorus reagents to benzaldimines (Scheme 48).[66]



Scheme 48.

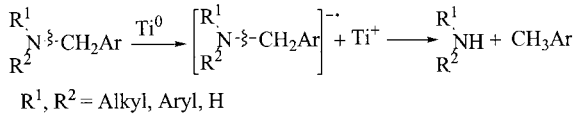
The catalytic dealkylation of tertiary amines has been performed with palladium on charcoal in the presence of air, in methanol at 0 °C.[67] Under these oxidative conditions methyl and ethyl groups are cleaved, and no dealkylation occurs for saturated alkyl groups containing more than two carbons. However, the allyl group and cinnamyl group are oxidized in preference to methyl groups. It should be noted that the propargyl group does not react and apparently inhibits the catalytic oxidation of the methyl group in *N*-methyl and *N*-propargyl derivatives.

2. Radical Reactions

Radical processes make a sort of link between Sections 1 and 3, since the different reactions described hereafter involve either a 1,3-hydrogen shift mediated by radicals or reductive and oxidative pathways where the amine behaves as a leaving group.

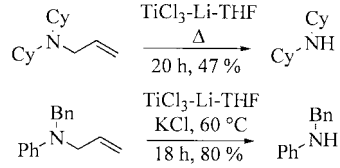
2.1. Reductive Cleavage

Electron transfer from low-valent titanium (LVT) is known to cleave C–O bonds. This methodology, which allows allyl-oxygen, benzyl-oxygen, and propargyl-oxygen bonds to be cleaved,[68] also applies to the corresponding amines.[69] According to the authors, the reaction might proceed through two subsequent single electron transfer steps. For instance, benzyl radical might be reduced by Ti^0 to a benzyltitanium derivative, which is protonated upon hydrolysis. Alternatively, it might undergo hydrogen atom transfer from the solvent (Scheme 49).



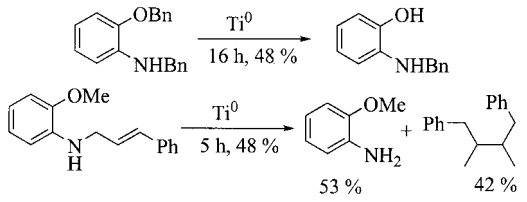
Scheme 49.

The allyl chain is cleaved faster than the benzyl group under such conditions, although yields are moderate. As shown in Scheme 50, when *N*,*N*-dicyclohexylallylamine is heated in the presence of LVT, formed in situ by reduction of $TiCl_3$ with lithium in THF, the cleavage is complete within 20 h in 47% yield. Substantial improvement of the yield can be achieved by adding an inorganic salt such as KCl to the reaction medium.[69b]



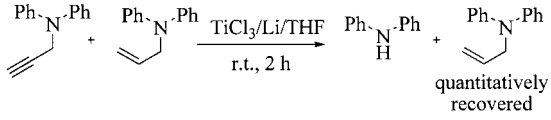
Scheme 50.

The cleavage of allyl- and benzylamines is slower than the cleavage of the corresponding ethers (20 h is needed to reach completion instead of 2.5 h). This is readily explained if one considers the oxophilic character of titanium. Due to the higher stability of the radical, the cleavage of the cinnamylamines proceeds faster (5 h, 53% yield) (Scheme 51).[69a]



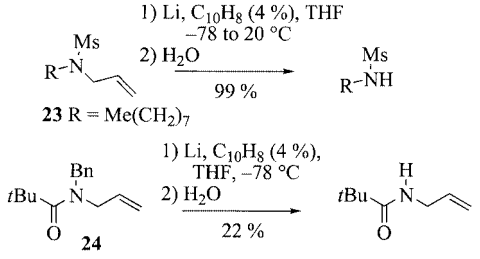
Scheme 51.

The yields were substantially improved when cleaving propargylamines. As exemplified in Scheme 52, in contrast to the cleavage of *N*-allyl derivatives, the reaction occurs (with a few exceptions) within less than 1 h. Thus, the selective cleavage of a propargyl group can be carried out in the presence of *N*-allyl or *N*-benzyl groups and other reducible functionalities.[70]



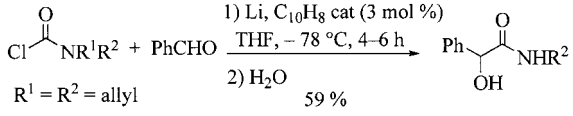
Scheme 52.

The reductive deprotection of alcohol, amines, and amides can be performed with Li and a catalytic amount of naphthalene.[71] *O*-Allyl and *O*-benzyl groups are easily removed. However, the selective cleavage of the *O*-benzyl group can also be performed in the presence of an allyl ether. Two amides are of special interest with respect to the purpose of the present article (Scheme 53). Whereas sulfonyl groups are usually cleaved easily compared to benzyl or allyl protecting groups, the cleavage of the *N*-allyl bond is preferred to the cleavage of the *N*–Ms bond in **23**. The preferential removal of the benzyl group has been observed with the nonenolizable amide **24**, although the yields are rather low.



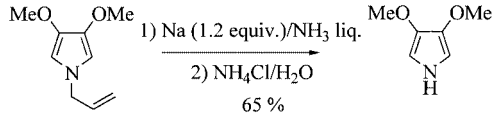
Scheme 53.

As exemplified in Scheme 54, mono-deallylation (and similarly debenzylation) has been observed concomitantly with the reaction of carbamoyl chlorides and aldehydes (or imines) in the presence of lithium powder and a catalytic amount of naphthalene.[72]



Scheme 54.

The Birch reduction of *N*-allylpyrrole derivatives has also been reported (Scheme 55).[73] It should be noted that *O*-allyl, *O*-benzyl, and *N*-benzyl derivatives are all cleaved under these conditions.



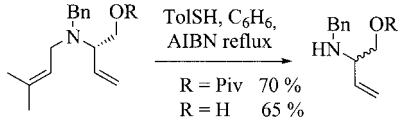
Scheme 55.

It is interesting to note that in the reductive decyanation of cyclopropanic α-aminonitriles, the *N*,*N*-dibenzyl protecting group is resistant to treatment with sodium in liquid ammonia, whereas the *N*,*N*-diallyl protecting group is not.[74]

2.2. Thiol-Mediated Radical Processes

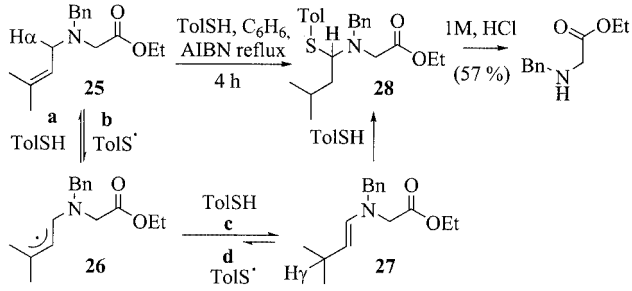
A 1,3-hydrogen shift leading to an enamine can be promoted by the thiyl radical.[75] Subsequent hydrolytic treatment allows primary or secondary amines to be released. The reaction can be performed in the presence of either a stoichiometric or a catalytic amount of thiol. These conditions apply to allyl, crotyl, prenyl, and cinnamyl derivatives, although prenyl groups are cleaved slightly faster.

The prenyl group can be removed selectively in the presence of α-branched allylic groups (Scheme 56).



Scheme 56.

Evidence for the formation of the enamine has been obtained in the case of catalytic reactions by NMR analysis of the crude reaction mixture before treatment. Additional evidence for the formation of intermediate thioaminal and imine (in the case of primary amines) has led to the proposal of the mechanism shown in Scheme 57.



Scheme 57.

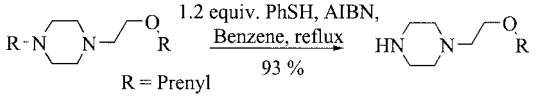
This process is likely to involve two subsequent hydrogen transfer steps: the *p*-TolS· radical would abstract an allylic hydrogen atom from **25** to form radical **26**, which is stabilized by the delocalization of both the π-system and the nitrogen lone pair (step a); the subsequent reverse transfer of a hydrogen atom from the thiol back to the carbon-centered radical would lead to the most stable olefin, i.e., enamine **27**. Addition of the thiol to the enamine leads to

the corresponding thioaminal **28**, which is hydrolyzed upon treatment with aqueous HCl.

The two hydrogen-atom transfers involved in the above mechanism benefit from favorable polar effects since the electrophilic sulfur-centered radical generates a nucleophilic carbon-centered radical in step (a), and vice versa in step (c). The efficacy of the reaction is sensitive to the nature of the thiol. Correlations were established between C–H and S–H bond dissociation energies (BDEs). In an ideal situation, the S–H bond should be stronger than the C–H_α bond but weaker than the C–H_γ bond.[76]

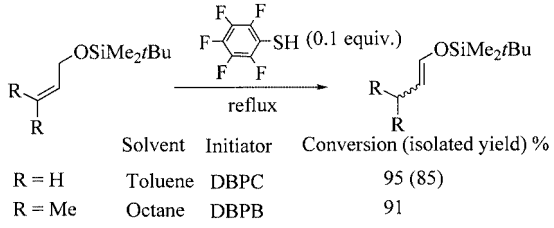
It should be noted that the reaction does not work with aniline derivatives. An additional interesting feature is that carbamates, amides, and sulfonamides do not rearrange under these conditions, even in the presence of thiols having a stronger S–H bond, like *n*-OctSH.

Allyl ethers are also not cleaved under the same conditions. Therefore, it is possible to selectively release the amine in the presence of a prenyl ether (Scheme 58).



Scheme 58.

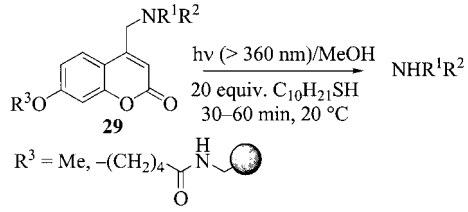
In agreement with the importance of the relative value of the C–H and S–H BDEs, the rearrangement of allyl silyl ethers to silyl enol ethers can only be performed in the presence of a thiol having a better suited BDE like pentafluorophenol (Scheme 59).[77,78]



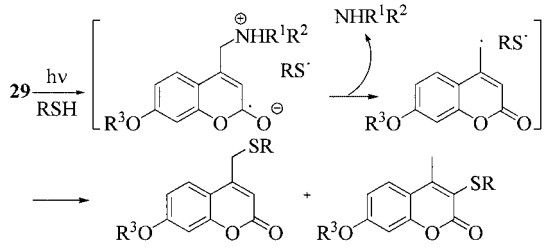
Scheme 59.

An original methodology for the photochemically induced release of primary and secondary amines has been reported by Giese.[79] The cleavage of tertiary and secondary aminocoumarins **29** leading to aliphatic and aromatic amines, including amino acid derivatives, was performed at 20 °C upon irradiation in the presence of a hydrogen donor. The best yields were obtained when using *n*-dodecanethiol. The reaction has been extended to the solid phase by attaching the amine to a TentaGel-supported coumarin moiety (Scheme 60).

A mechanism involving electron transfer from the thiol to the coumarin system and subsequent proton transfer, followed by elimination of the amine, has been proposed. This mechanism, which proceeds through the formation of a delocalized carbon-centered radical, is supported by the isolation of recombination products (Scheme 61).



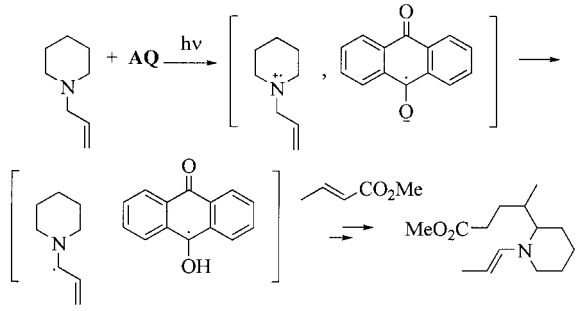
Scheme 60.



Scheme 61.

2.3. Electron-Transfer Oxidative Pathway

In a very specific study, anthraquinone (AQ) has been reported to mediate the formation of the α-amino conjugated radical through electron transfer followed by deprotonation (Scheme 62).[80] An intramolecular hydrogen transfer would then lead to the enamine. Since *O*-allyl ethers are cleaved under related conditions in the presence of DDQ,[81] this reaction, that occurs in a rather complex multi-step pathway, has not been developed further into a method of synthetic interest for the cleavage of allylic C–N bonds.

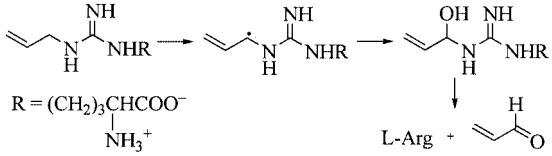


Scheme 62.

2.4. Enzymatic Cleavage

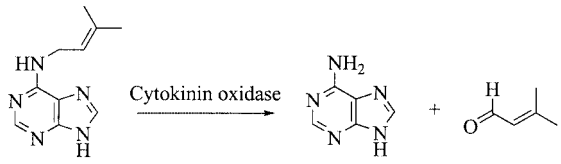
Enzymatic cleavage is worth noting, even though none of the following enzymatic reactions can reasonably be expected to ever give rise to a synthetic method.

The design of nitric oxide synthase (NOS) inhibitors is of special interest since overproduction of nitric oxide is a factor responsible in numerous diseases. Recent mechanistic studies have shown that *N*-allyl-L-arginine acts as a substrate for neuronal NOS.[82] A mechanism involving initial hydrogen-atom abstraction followed by oxygen rebound has been proposed to explain the formation of acroleine, water, and L-arginine (Scheme 63).



Scheme 63.

Cytokinin oxidase has been shown to cleave the side chain of *N*-prenyladenosine, but the mechanism of the oxidative cleavage leading to 3-methyl-2-butenal is not known (Scheme 64).[83]



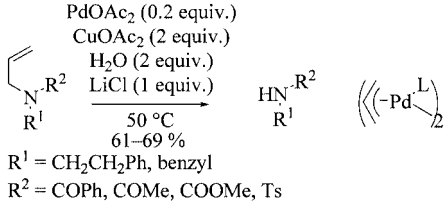
Scheme 64.

3. Procedures where the Amine Plays the Role of the Leaving Group in Organometallic and Polar Processes

3.1. Nucleophilic Displacement at Allylic Amines

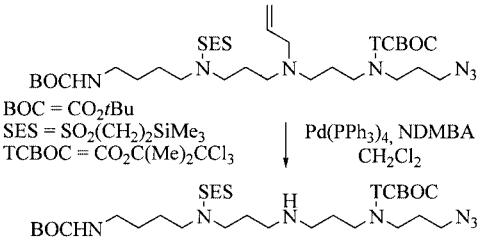
3.1.1. Transition Metal Catalysis

Again, most of the recorded methods are catalyzed by transition metals. The removal of *N*-allylic chains may compete with Wacker oxidation.[84] Mori and Ban[85] have reported that *N*-acyl allylamines are cleaved in the presence of Pd^{II} with Cu^{II} as the reoxidant. Under the experimental conditions summarized in Scheme 65, i.e., heating at 50 °C in the presence of a catalytic amount of Pd^{II} and a stoichiometric amount of Cu^{II} and LiCl, deallylation proceeds in 61–69% yield. The reaction involves the formation of a dimeric π-allyl complex that could lead to Pd^0 either by reductive elimination or nucleophilic attack by AcO^- (Scheme 65).



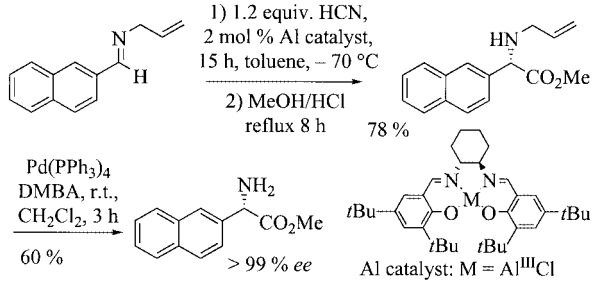
Scheme 65.

Guibé has developed a very efficient method for the deprotection of monoallylamines and diallylamines based on a Pd^0 catalyst and *N*,*N*′-dimethylbarbituric acid[86] (NDMBA; Schemes 66 to 70). The number of recorded examples suggests that this is probably the most efficient and widely employed procedure.[74,87,88] As exemplified in Scheme 66, five independent amino protecting groups, including the azido group, that could be selectively deprotected were needed to achieve the synthesis of polyamine toxins. The removal of the allyl group was efficiently performed using Guibé's procedure.[87a]



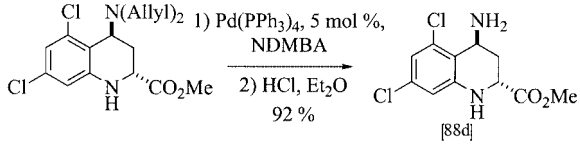
Scheme 66.

As already noted in Section 1.2.3. for Cadogan's synthesis of α-aryl-α-aminophosphonic acids,[66] the use of allyl imines is useful in the asymmetric Strecker reaction combining, successively, addition of HCN to aryl aldimine, methanolysis, and selective cleavage of the *N*-allyl bond (Scheme 67).[87c]



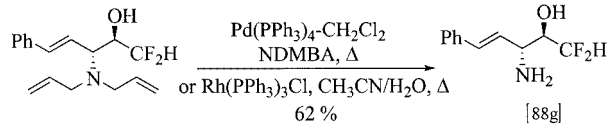
Scheme 67.

As exemplified in Scheme 68, bis-allylation is frequently used to protect primary amines.[88]



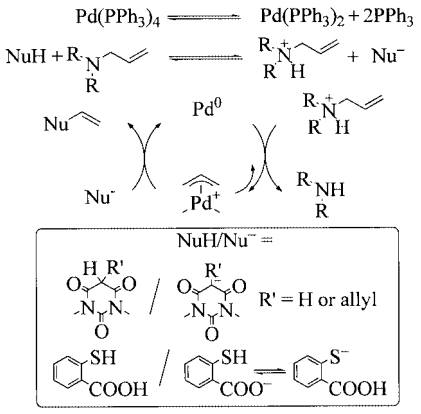
Scheme 68.

As previously mentioned for Wilkinson's catalyst, it is possible to cleave the *N*-allyl group selectively in the presence of an α-branched allylic chain (Scheme 27, Scheme 69).[88g,89]



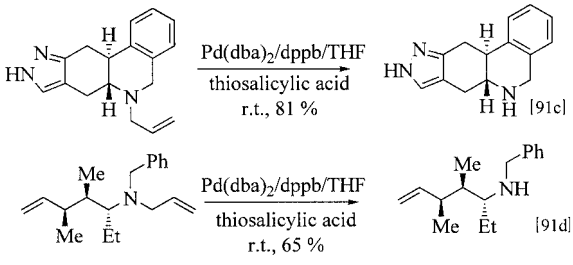
Scheme 69.

An extension to aminomethyl resin-supported *N*-propylbarbituric acid has been reported recently.[90] Protonation, which makes the allylamine electrophilic enough, allows the formation of the π-allyl complex. Then, the conjugated base of the acid acts as the allyl scavenger and is allylated according to Scheme 70.



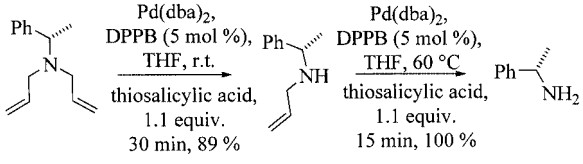
Scheme 70.

The best related reagent is 2-mercaptobenzoic acid (Scheme 71) and Pd^0 in the presence of 1,4-bis(diphenylphosphanyl)butane (dppb).[87f,91] The mechanism of the reaction is strictly identical to that proposed for barbituric acid. The π-allyl complex is trapped by the thiolate, which regenerates Pd^0. The whole process results in the transfer of the allyl group from the protonated amine to the nucleophile. The co-product and the catalyst can be readily separated by acid/base treatment, which leads to the crude product in satisfactory purity; there is no need for further purification.



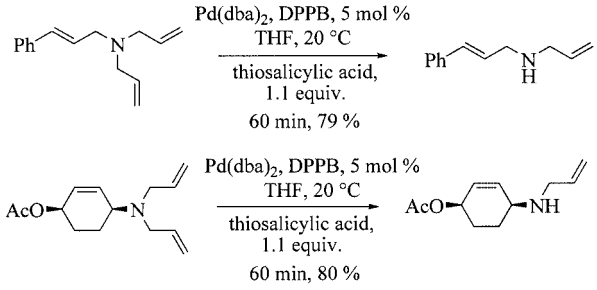
Scheme 71.

The *N*-allyl bond in tertiary amines is efficiently cleaved at room temperature, but a higher temperature (60 °C) is needed for the cleavage of secondary amines, as shown in Scheme 72.[91a,91b] This influence of the temperature allows the cleavage of only one allyl chain from diallylamines at room temperature.



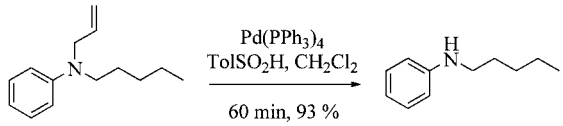
Scheme 72.

Interestingly, the *N*-allyl group can be removed selectively in the presence of an *N*-cinnamyl or a functionalized cyclohexenyl group (Scheme 73).[91a,91b]



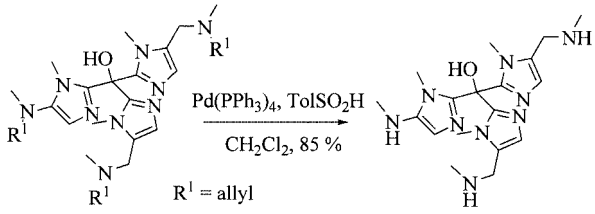
Scheme 73.

In a slightly modified protocol, sulfinic acids or their salts[92] have been used in the presence of a catalytic amount of $[Pd(PPh_3)_4]$ (Scheme 74). This procedure is efficient to cleave both C–N and C–O allylic bonds. The procedure involving $[Pd(PPh_3)_4]$ in dichloromethane or in a THF/MeOH mixture in the presence of $ArSO_2Na$ allows the cleavage of allyl, methallyl, crotyl, and cinnamyl ethers, and the cleavage of allyloxycarbonyl (alloc) derivatives and allyl esters as well.



Scheme 74.

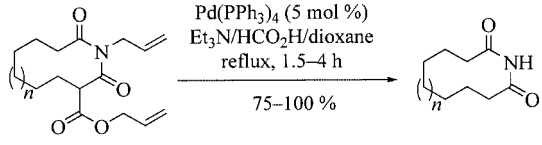
N-Allyl protecting groups have been found to be efficient in the synthesis of imidazole-based tripodal ligands (Scheme 75).[92b]



Scheme 75.

All these related methods need the simultaneous presence of the Pd catalyst, a Lewis acid activator, and an efficient nucleophile to trap the allyl moiety.[93] The reaction can also be performed in the presence of a hydride donor.[93,94]

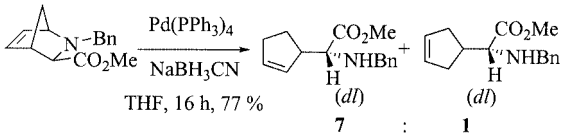
The method using Pd^0 in the presence of formic acid as both the acid and the hydride donor has been successfully applied to the cleavage of *N*-allyl imides.[95] As illustrated in Scheme 76, both the *O*-allyl and *N*-allyl groups are removed.



Scheme 76.

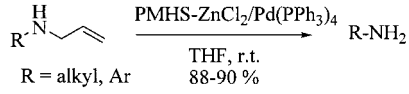
Hydrogenolysis with $NaBH_3CN$ has been found to be more efficient than formic acid in the synthesis of cyclopen-

tenylglycine by ring opening of the *exo*-Diels–Alder adduct between cyclopentadiene and *N*-benzyl glyoxylic imines (Scheme 77).[96]



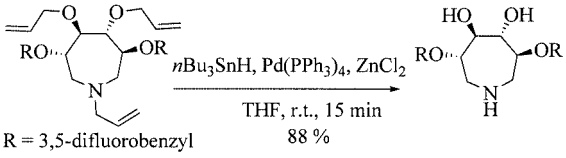
Scheme 77.

The association of $[Pd(PPh_3)_4]$ with poly(methylhydrosiloxane) (PMHS) in the presence of $ZnCl_2$ has recently been shown to cleave allyl ethers, allyl esters, and allylamines.[97] *N*-Benzyl, *N*-Boc, and *N*-Cbz derivatives were found to be stable under these reaction conditions (Scheme 78).



Scheme 78.

A related method using tributyltin hydride instead of PHMS had previously been applied to the cleavage of *N*-allyl and *O*-allyl groups in C_2-symmetrical tetrahydroxytetrazepanes (Scheme 79).[98]

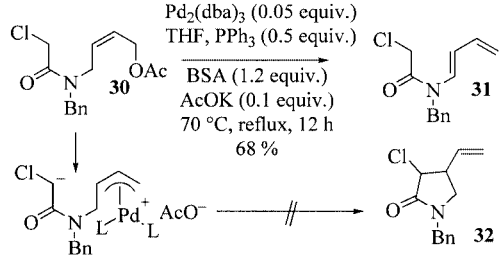


Scheme 79.

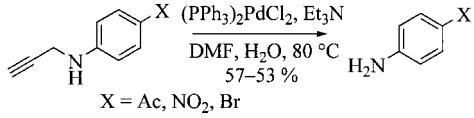
The last example in this section is related to the previous ones in the sense that a π-allyl intermediate is involved, but the leaving group is not the amido group. In the following reaction, Bäckvall's amino acetoxy palladation provides a formal method for protecting amides, since **30** leads to dienyl amide **31** in 68% yield upon treatment with Pd^0. Attempts to perform Pd^0-mediated cyclization of chloroacetamide **30** failed as the intermediate π-allyl complex underwent an unexpected β-elimination. In all likelihood the combination of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate is not basic enough to form the enolate anion that would lead to vinyl pyrrolidone **32** through 5-*exo* ring closure (Scheme 80).[99]

A variety of aryl propargylamines and ethers can be deprotected in the presence of $[PdCl_2(PPh_3)_2]$ or $[Pd(PPh_3)_4]$ (Scheme 81).[100a]

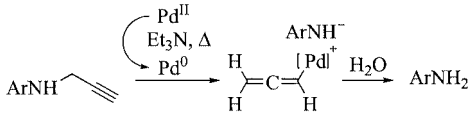
The reaction is carried out in DMF/H_2O (2:1) in the presence of a base. NEt_3 is employed in most cases; $NaHCO_3$ can also be used but longer periods of time are needed. The presence of water appears to play a crucial role in the depropargylation. Although the mechanism is not clear yet, Pd^0 is supposed to be the active species. The reaction proceeds presumably through an intermediate allenylpalladium species (Scheme 82).



Scheme 80.



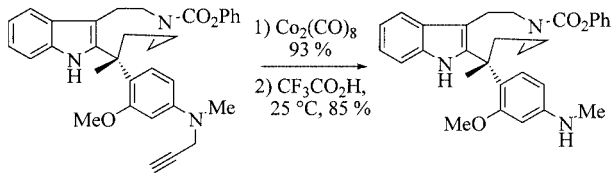
Scheme 81.



Scheme 82.

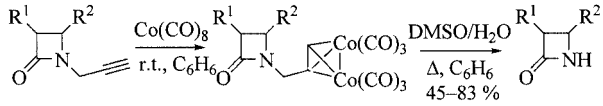
In a recent report, Pd^0 was used to synthesize allenes from propargylic diisopropylamines.[100b] In this catalytic process a hydride is supposed to be transferred from the isopropyl carbon to Pd^0. Migration of the hydride to the alkyne moiety would break the C–N bond and generate an allene by displacement of an imine (thus the amine moiety is not recovered unchanged).

The Nicholas reaction offers a very specific methodology for the deprotection of *N*-propargylamines and amides.[101] In the Magnus approach to vinblastine alkaloids, the *N*-propargyl group is removed upon exposure to trifluoroacetic acid after complexation with dicobalt octacarbonyl (Scheme 83).[102]



Scheme 83.

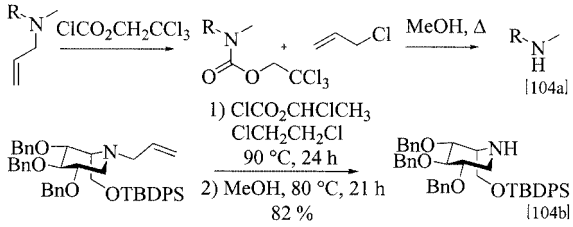
Alcaide et al.[103] have devised a new approach to azetidones using a Staudinger reaction between *N*-propargyl imines and ketenes. The removal of the propargyl group can be performed by complexation of the triple bond with $Co_2(CO)_8$; the thus-formed alkyne dicobalt hexacarbonyl complexes are readily hydrolyzed in situ upon treatment with DMSO/H_2O in boiling benzene (Scheme 84). Owing to the smooth and neutral conditions employed, the method is compatible with labile functional groups.



Scheme 84.

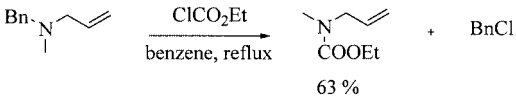
3.1.2. Noncatalyzed Displacement

Deallylation upon treatment with chloroformate provides a two-step procedure to release secondary amines.[104] The first step leads to a carbamate, which is cleaved upon heating at reflux in methanol (Scheme 85). Vinyl and trichloroethyl chloroformates are among the best reagents for this purpose since their oxygenated moieties are very good leaving groups.



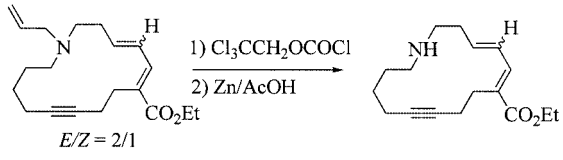
Scheme 85.

It should be noted that *N*-debenzylation is faster under these experimental conditions than *N*-deallylation, which itself is faster than demethylation (Scheme 86). However, when the allyl group is sterically hindered, preferential cleavage at the alkyl group may occur. In such a case, metal-catalyzed isomerization gives better results.[22]



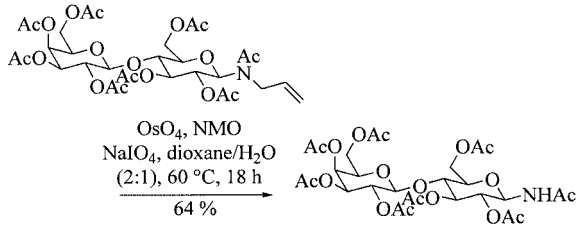
Scheme 86.

Methyl α-chloroethyl chloroformate (ACE-Cl) was used by Magnus for the deprotection of *N*-allyl group in the synthesis of a navelbine analog.[105] In the two-step procedure using trichloroethyl chloroformates, methanolysis can be replaced by reduction with Zn/AcOH (Scheme 87).[106]



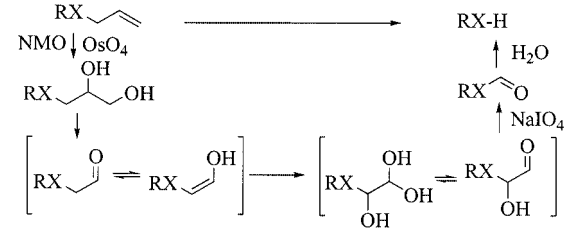
Scheme 87.

The multi-step oxidative cleavage, upon catalytic dihydroxylation and subsequent periodate scission, is a new one-pot method that allows *O*-allyl ethers and *N*-allylacetamides to be cleaved (Scheme 88).[107]



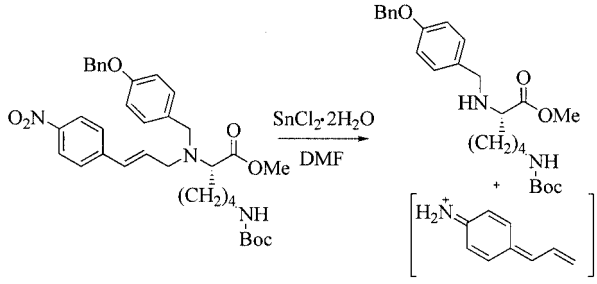
Scheme 88.

The mechanism is supposed to involve the repetition of a dihydroxylation/cleavage sequence followed by hydrolysis of the resulting formate (Scheme 89).



Scheme 89.

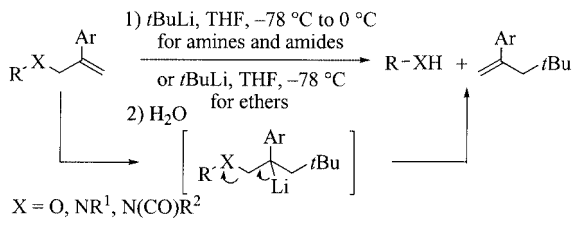
The acid-catalyzed solvolysis of 4-aminocinnamyl dialkylamine has been observed by accident during the reduction of the 4-nitrocinnamyl group. Protonation would stimulate nucleophilic displacement of the amine (Scheme 90).[108]



Scheme 90.

3.2. The Amine is Released by β-Elimination

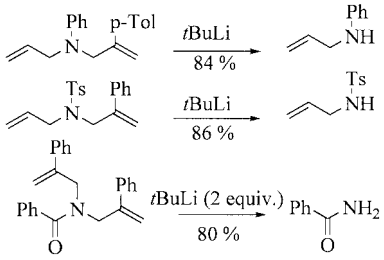
Ethers, amines, and amides containing 2-arylallyl groups are readily deprotected upon treatment with *t*BuLi in THF from –78 to 0 °C.[109] The transformation probably involves the carbolithiation of the styrene moiety, followed by a β-elimination process (Scheme 91).



Scheme 91.

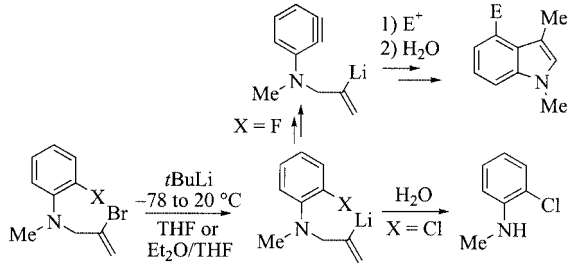
The reaction is highly selective and the 2-arylallyl group is removed even in the presence of allyl or benzyl groups. It

should be noted that the reaction can be applied to secondary amines provided two equivalents of *t*BuLi are used, since one equivalent is consumed to deprotonate the acidic N–H. Moreover, the removal of two 2-arylallyl groups leads to primary amides under the same conditions (Scheme 92).



Scheme 92.

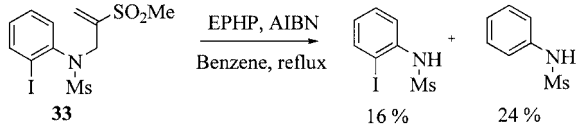
Barluenga et al. have reported the cleavage of *N*-(2-bromoallyl)-*N*-methyl-2-chloroanilines upon treatment with *t*BuLi.[110] The authors were looking for precursors of benzyne intermediates capable of giving rise to indoles by cyclization (Scheme 93). Whereas 2-fluoroanilines behaved as expected, in the case of their chlorinated analogs a bromine–lithium exchange promoted the release of the amine through β-elimination. The same process was observed with 3-chloro derivatives.



Scheme 93.

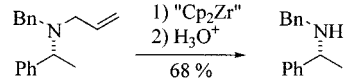
This procedure is not suitable for secondary aliphatic 2-bromoallylamines, which were shown to undergo an original cleavage that leads to acetylene and saturated amines, in which the organic group of the organolithium reagent is incorporated at the α carbon, via intermediate lithium propargylamides.[111]

An unexpected cleavage of the allylic C–N bond in *N*-methylsulfonylamide (**33**) occurs upon treatment with *N*-ethylpiperidine hypophosphite (EPHP) in the presence of AIBN. It was suggested that this side reaction might be rationalized either as an S_N2' or an S_H2' process (Scheme 94).[112]



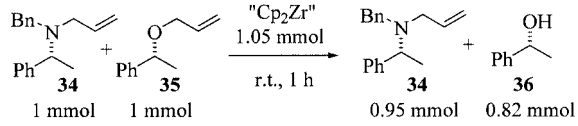
Scheme 94.

N-Allylamines can be cleaved upon treatment with one equivalent of zirconocene[113] at room temperature (Scheme 95).



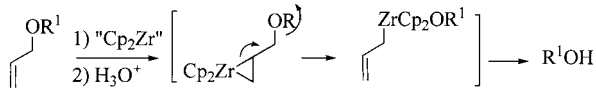
Scheme 95.

Both allyl ethers and allylamines are cleaved under these peculiar conditions, but since the rate constants for the two processes are quite different, it is possible to cleave the C–O bond selectively without breaking the C–N bond (Scheme 96). When equimolar amounts (1 mmol) of **34** and **35** are submitted to the action of zirconocene (0.95 mmol) at room temperature, amine **34** remains unchanged, whereas after 1 h, alcohol **36** (0.82 mmol) is formed.[113]



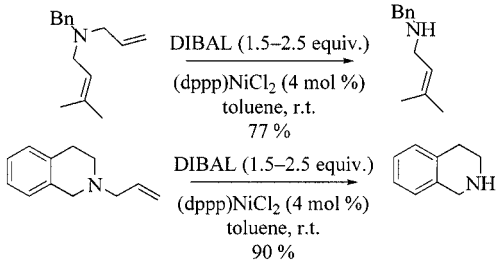
Scheme 96.

The following mechanism has been proposed for the cleavage of the allylic C–O bonds (Scheme 97). "Cp_2Zr" is prepared from dichlorozirconocene by treatment with *n*BuLi in THF at –78 °C.



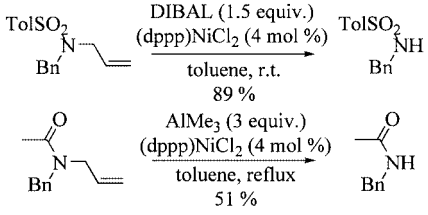
Scheme 97.

The deprotection of a series of allylic tertiary amines, including aliphatic, benzylic, aromatic, and heteroaromatic compounds, is catalyzed by dichlorobis(diphenylphosphanyl)propanenickel [$NiCl_2$(dppp)][114] in the presence of DIBAL (1.5 equivalents for a tertiary amine; 2.5 equivalents for a secondary amine), at 0 °C in toluene (Scheme 98). It is worth noting that the reaction is chemoselective. The allyl group is removed selectively and the prenyl group is recovered unchanged.



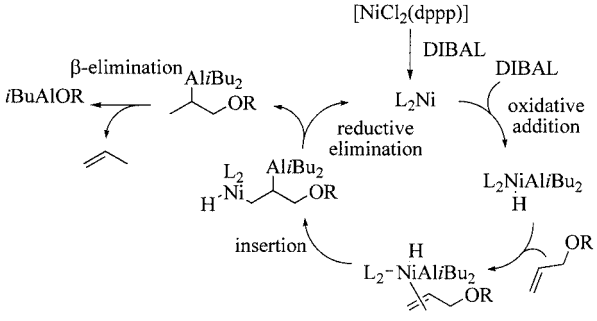
Scheme 98.

Similar experimental conditions apply also to the cleavage of the corresponding *N*-allyl amides and sulfonamides (Scheme 99). In the case of *N*-allylamides, DIBAL is replaced by trimethylaluminum (3 equiv.) in order to avoid the reduction of the carbonyl group.



Scheme 99.

A mechanism has been proposed for the related cleavage of allylic ethers. Although a hydride complex is involved, and since no enol ether intermediates could be detected, the reaction likely proceeds by the insertion of the double bond into the Ni–Al bond and subsequent reductive elimination of Ni^0. The deprotected alcohol would be formed as an aluminum alkoxide[115] (Scheme 100). Therefore, these protocols were rather classified as processes involving the amine as the leaving group in a β-elimination step than with those involving a metal hydride-mediated 1,3-hydrogen shift (cf. Section 1.2.1).



Scheme 100.

In a very recent article, a slightly different mechanism has been proposed to account for the closely related catalytic deallylation of allyl- and diallyl malonates.[116] This reaction might also be connected to the Ni^{II}-catalyzed cleavage of *N*-allyl indole with phenylmagnesium bromide[117] and to reactions involving π-allylnickel complexes being therefore more related to Section 2.1.1.

Conclusion

The use of allyl or propargyl chains as protecting groups for primary or secondary amines offers an alternative to the widely spread transformation of basic nitrogen atoms into carbamates. Early reports demonstrated that allylamines can be isomerized into enamines (and therefore can be cleaved by hydrolysis of the enamine) upon treatment with strong bases. However, basic conditions are rather tough and generally cannot be used under catalytic conditions. The use of a stoichiometric amount of a strong base is incompatible with base-sensitive functional groups. Processes that are catalyzed by transition metals (essentially Pd and Rh) have been developed. Among the latter, new procedures involving Grubbs-type catalysts have emerged. It is undeniable that transition-metal-catalyzed methods are the most widely spread methods, but selectivity can still be a problem, since *O*-allyl derivatives are cleaved faster than *N*-allyl derivatives in most cases. Reductive metals are not selective either. Selectivity is also a problem with chloroformate-mediated processes, which are capable of cleaving different types of N–C bonds. New methods that satisfy the criteria of selectivity and proceed under mild conditions have been reported in recent years. Thiyl radical-mediated pathways are among the latter. Regarding the cleavage of *N*-propargyl groups, Nicholas's reaction can be considered as the most convenient specific method.

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