Modern Amination Methods

Edited by
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Preface

The origin of this book can be traced back at least in part to the fact that the importance and practicality of amination reactions as a tool for obtaining target compounds is nowadays fully acknowledged by chemists in synthetic organic, medicinal, agricultural and natural product chemistry, as well as by the pharmaceutical and agricultural industries. This prominence is due to the explosive development during the past decade of novel and more efficient amination methods. These provide a great improvement with respect to the classical methods such as those based on the attack of a nucleophilic nitrogen atom to an electrophilic carbon, which are hampered by the difficult access to the electrophilic precursors – particularly when multifunctional derivatives are taken into consideration – and by the frequently recurring difficult reaction conditions.

This book is intended to provide an overview of several areas of research in which amination plays a key role, and to introduce the reader to new concepts that have been developed quite recently for generating new C – N bonds. As the pharmaceutical and chemical industries move rapidly away from the development of racemic compounds, the access to synthetic routes that lead efficiently to enantiomerically pure materials is becoming increasingly important. For this reason, most of the contributions in this book refer to asymmetric synthesis. However, no attempt has been made to present a comprehensive work, and important areas such as asymmetric hydroxyamination [1] have not been dealt with. Furthermore, it may be worth mentioning that viable, useful and comprehensive sources of information about the methodological approaches to electrophilic amination developed since 1985 have already been reported [2], and that a chapter in Houben-Weyl reviewing several aspects of the asymmetric electrophilic amination [3] compiles important contributions up to 1995.

In order to provide – whenever possible – new perspectives in the different areas treated in the book, the authors have been recruited among internationally recognized experts in their specific fields.

This book is arranged in seven chapters which cover the following aspects of amination – even if the order of the contributions is somewhat arbitrary. Chapter 1 (K. A. Jørgensen) deals with modern aspects of allylic amination reactions for preparing fundamental building blocks which have either distinct important properties or can be used for further transformations in organic synthesis. Two approaches – the

nucleophilic allylic substitution and the direct allylic amination of simple alkenes – are described. Considering the potential importance of electrophilic amination of alkenes, progress and steps being taken to carry out indirect amination of organometallics derived from hydroboration and hydrozirconation of alkenes are also described in Chapter 2 (E. Fernandez and J.H. Brown). In Chapter 3, J.-P. Genet, C. Greck and D. Lavergne provide an exhaustive overview of modern methods (up to 1998) based on the stereoselective electrophilic amination of chiral carbon nucleophiles for making α- and β-amino acid derivatives. Chapter 4 (H. Kunz, H. Tietgen and M. Schultz-Kukula) also addresses the synthesis of α- and β-amino acids with high enantiomeric purity, but a different approach based on the reaction of carbohydrate-derived prochiral imines with nucleophiles is used. More about the use of organometallics is to be found in the following two chapters. Thus, Chapter 5 (E. Carreira, C.S. Tomooka and H. Iikura) focuses on the various methods that have been reported for the synthesis of metal nitride complexes. These complexes have an intriguing array of reactivity and structure, and display a host of desirable properties in material sciences, medicine and chemical synthesis. The nitrogen atom transfer from a nitrido complex is reviewed in Chapter 6 by M. Komatsu and S. Minakata, with special emphasis on enantioselective transformations in aziridination reactions using nitridomanganese complexes. A fairly new approach to C – N bond formation – the transition metal-catalyzed synthesis of arylamines – is the aim of Chapter 7, in which J. F. Hartwig provides an exhaustive account of the palladium-catalyzed amination of aryl halides and sulfonates for use in complex synthetic problems. The breakthrough required to convey efficiency and high performance is the catalyst design, and many new challenges remain for the synthetic chemist in this area.

Complete reference citations have been provided since, as it is increasingly recognized, they are a requirement for manuscripts and proposals.

It is my sincere hope that this book will provide synthetic chemists with new opportunities for achieving their synthetic goals. For those students who are reading the book in order to enhance their synthetic "toolkit", I hope they will enjoy the variety of these new reactions which span from stoichiometric to catalytic, from natural product-based protocols to synthetic strategies employing organometallic complexes.

I gratefully acknowledge the work done by all authors in presenting up-to-date and well-referenced contributions. Without their effort this volume would not have been possible. Furthermore, it was a pleasure to contribute with the Wiley-VCH "crew" in Weinheim, who not only did an excellent job in producing the book, but also helped me in a competent manner in all phases of its preparation. Finally, I am grateful to Dr. Gölitz and to Dr. Eckerle who originally encouraged the idea of creating a book about Modern Amination Methods.

Bologna, January 2000 Alfredo Ricci

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[1] (a) G. Li, H.-T. Chang, K. B. Sharpless, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451; (b) G. Li, H. H. Angert, K. B. Sharpless, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2813; (c) H. C. Kolb, K. B. Sharpless, Asymmetric Aminohydroxylation in *Transition Metals for Organic Synthesis*, Vol. 2; M. Beller, C. Bolm (Eds.); WILEY-VCH, Weinheim, **1998**, 243 – 260; (d) G. Schlingloff, K. B. Sharpless, Asymmetric Aminohydroxylation in *Asymmetric Oxidation Reactions: A Practical Approach*; T. Katsuki (Ed.); Oxford University Press, Oxford, in press.

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Contents

Abbreviations

acac	Acetonylacetate
Alloc	Allyloxycarbonyl
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BISBI	2,2'-Bis[(diphenylphosphino)methyl]-1,1'-biphenyl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
CAN	Ceric ammonium nitrate
Cp	η^5-Cyclopentadienyl
Cp*	η^5-Pentamethyl cyclopentadienyl
CT	Chloramine-T
dba	1,5–Diphenylpenta-1,4-dien-3-one
DBAD	Dibenzyl azodicarboxylate
DBU	1,8-Diazabicyclo[5.4.0]undec-1-ene
DCE	1,2-Dichloroethane
de	Diastereomeric excess
DEAD	Azodicarboxylate
DIAD	Diisopropyl azodicarboxylate
DMS	Dimethyl sulfide
DPEphos	Bis(2,2'-diphenylphosphino)diphenylether
DPPBA	2-(Diphenylphosphino)benzoic acid
Dppe	Bis(diphenylphosphino)ethane
DPPF	1,1'-Bis(diphenylphosphino)ferrocene
DPPP	Bis(diphenylphosphino)propane
DTBAD	Di-*tert*-butyl azodicarboxylate
D^{t}BPF	Bis(di-*tert*-butylphosphino)ferrocene
dr	Diastereomeric ratio
ee	Enantiomeric excess
EWG	Electron withdrawing group
GPC	Gel permeation chromatography
Ipc	Isopinocamphenyl
KDO	3-Deoxy-D-manno-octulosonic acid
LDA	Lithium diisopropylamide

LiBTOC	*tert*-Butyl-*N*-lithio-*N*-[(*p*-toluensulfonyl)oxy] carbamate
LiHMDS	Lithium hexamethyldisilazide
LUMO	Lowest unoccupied molecular orbital
MAP	2-Amino-2'-(diphenylphosphino)-1,1'-binaphthyl
Mes	Mesityl
M_n	Number average molecular weight
MOP	2-Methoxy-2'-(diphenylphosphino)-1,1'-binaphthyl
MTPA	*α*-Methoxy-*α*-(trifluoromethyl)phenylacetic acid
M_w	Molecular weight
NBS	*N*-Bromosuccinimide
NMP	*N*-Methylpyrrolidone
NOBIN	2-Amino-2'-hydroxy-1,1'-binaphthyl
NOE	Nuclear Overhauser effect
NPhth	Phthalimide
Ns	4-Nitrobenzylsulfonyl
PHANEPHOS	4,12-Bis(diphenylphosphino)[2.2]-paracyclophane
PTAB	Phenyltrimethylammonium tribromide
Pyr	Pyridine
QUINAP	1-(2-Diarylphosphino-1-naphthyl)isoquinoline
RAMP	(*R*)-(+)-1-Amino-2-(methoxymethyl)pyrrolidine
rt	Room temperature
SAMP	(*S*)-(-)-1-Amino-2-(methoxymethyl)pyrrolidine
TBAF	Tetrabutylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TDCPP	*meso*-Tetra-2,6-dichlorophenylporphyrine
Terpy	Terpyridine
TFAA	Trifluoracetic anhydride
THF	Tetrahydrofuran
tipt	Triisopropyl thiophenol
TMP	5,10,15,20-Tetramesitylporphyrine
TMSCl	Chlorotrimethylsilane
TMSCN	Cyanotrimethylsilane
TMSOTf	Trimethylsilyl trifluorometanesulfonate
Tol	Tolyl
TPD	4,4'-Bis(3-methylphenylphenylamino)biphenyl
TPP	1,5,15,20-Tetraphenylporphyrine anion
Ts	Toluene-*p*-sulfonyl
Ts_2O	Toluene-*p*-sulfonyl anhydride
Xantphos	9,9-Dimethyl-4,6-bis(diphenylphosphino)xanthene

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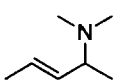
1 Modern Allylic Amination Methods

Karl Anker Jørgensen

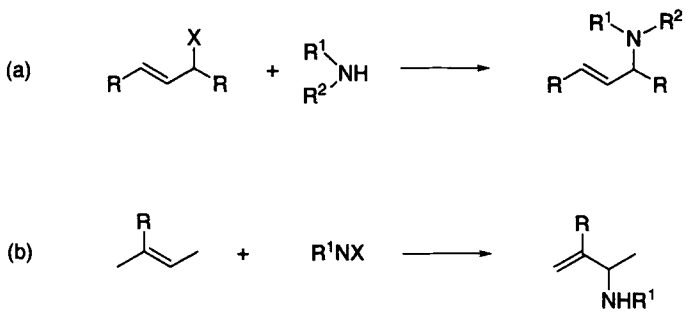
1.1 Introduction

One of the challenges in organic chemistry is to prepare fundamental molecular building blocks which either have distinct important properties, or can be used for further transformations in organic synthesis. Allyl amines **1** can be used as fundamental building blocks in organic chemistry, and their synthesis is an important industrial and synthetic goal. They can be incorporated in natural products, but often the allyl amine moiety is transformed to a range of products by functionalization, reduction or oxidation of the double bond.



1

The synthetic methods for the preparation of allyl amines can be divided into several types of reactions [1]. In the present chapter, the focus will be on the formation of allyl amines by reaction of substrates having an allylic bond which can be broken. Two approaches will be covered and these are outlined in Scheme 1: the first method (a) is the synthesis of allyl amines by nucleophilic allylic substitution of compounds having an allyl functionality; the second method (b) is the direct allylic amination of simple alkenes.



Scheme 1

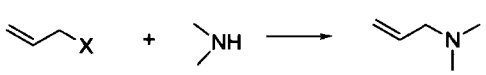
Other types of allylic amination reactions include a variety of indirect approaches such as reduction of α,β-unsaturated imines and oximes, rearrangement of aziridines, and elimination of water from vicinal amino alcohols. However, these reactions will not be considered in this chapter [2].

The present chapter on modern allylic amination methods will be restricted mainly to an overview of some of the major developments for the transformation of allylic compounds into allyl amines according to reaction types (a) and (b) in Scheme 1, and an attempt is made to cover the literature up to August 1999.

The reaction type (a) in Scheme 1 for the allylic amination reaction uses substrates which have an allylic C–X (X = heteroatom, halide) bond and is mainly nucleophilic amination of functionalized alkenes, whereas reaction type (b) is a direct allylic amination of an alkene, based on electrophilic amination of nonfunctionalized alkenes and involves a cleavage of a C–H bond.

1.2 Nucleophilic Amination of Functionalized Alkenes

Nucleophilic amination of alkenes functionalized by an allylic C–X (x = heteroatoms, halides) as outlined in Eq. (1) is a simple and direct procedure for the synthesis of allyl amines, since very efficient methods for the selective allylic functionalization of alkenes are available.

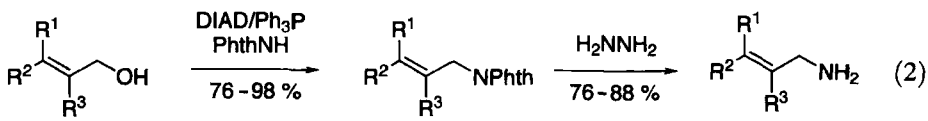


(1)

X = heteroatom, halide

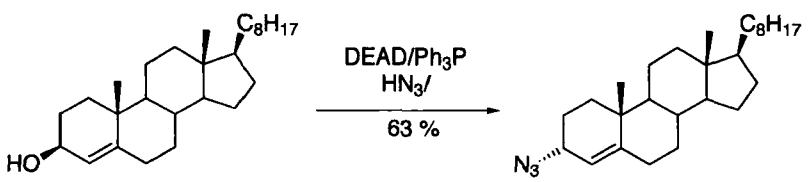
1.2.1 Amination of Allyl Alcohols

The Mitsunobu reaction is an attractive procedure for the transformation of an allyl alcohol into an allyl amine [3]. The reaction can be carried out under very mild conditions with a variety of amine nucleophiles. Recently, this method has been used for the preparation of configurationally pure primary allyl amine **4** (Eq. 2) by the reaction of allyl alcohols **2** with diisopropyl azodicarboxylate (DIAD) and triphenyl phosphine, followed by phthalimide (PhthNH) as the ammonia synthon giving **3** [4]. Reaction of **3** with hydrazine or methyl amine gave allyl amine **4**. An advantage of this reaction sequence is the almost complete conservation of alkene geometry, both under the Mitsunobu coupling conditions and after the deprotection of the amino group. Use of iminocarbonate as the nitrogen nucleophile donor gives a mixture of *trans*- and *cis*-products.



2 **3** **4** (2)

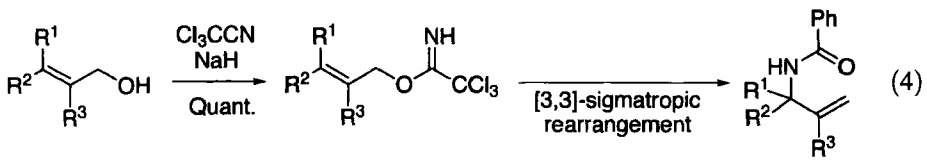
Several examples of reactions of allyl alcohols under Mitsunobu reaction conditions using diethyl azodicarboxylate (DEAD) and triphenyl phosphine giving allyl amines are known. An example is the reaction of the steroid **5** with azide nucleophiles under Mitsunobu reaction conditions, giving the corresponding azide **6** in 63 % yield (Eq. (3)) [5]. The reaction is regioselective with inversion of the configuration and no $S_N2\prime$ substitution is observed.



5 **6** (3)

The nucleophilic addition to allyl alcohols under Mitsunobu reaction conditions is normally regioselective with no allylic rearrangement during the reaction [6].

The Overman rearrangement, a thermal [3,3]-sigmatropic rearrangement of allylic trichloroacetimidates, is an attractive procedure for the preparation of allyl amines from allyl alcohols (Eq. (4)) [7].

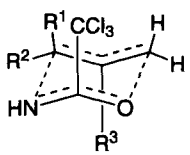


(4)

3 **8** **9**

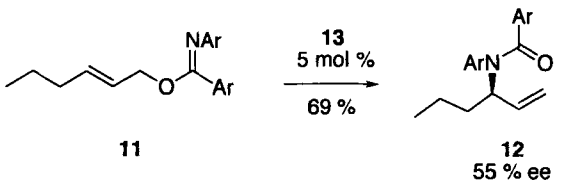
The first step in this reaction is formation of the allyl trichloroacetimide **8** formed from allyl alcohol **3** by reaction with trichloroacetonitrile. The allyl amides **9** are formed by the [3,3]-sigmatropic rearrangement of **8**, followed by hydrolysis. The reaction proceeds with good yield for primary and secondary amides; however, for products where the amide nitrogen is bound to a tertiary carbon atom the yields are generally low.

Overman has suggested a cyclic six-membered transition state **10** for the reaction [8]. The experimental result for the formation of substituted alkenes is similar to that observed for other [3,3]-sigmatropic rearrangements. Furthermore, the preferred formation of the *trans*-isomer of the di- and trisubstituted alkenes is consistent with transition state **10**. The activation parameters for the [3,3]-sigmatropic rearrangements are similar to related rearrangement reactions.

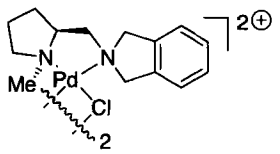


10

The rearrangement reaction can be catalyzed by various metal salts, and salts such as homogeneous solutions of palladium(II) and mercury(II) complexes have emerged as relatively good catalysts [9]. Based on the catalytic properties of soluble palladium(II) salts, attempts to perform enantioselective rearrangement reactions were performed. The used of a cationic palladium catalyst with a chiral nitrogen ligand led to the first enantioselective version of the Overman rearrangement (Eq. (5)) [9]. The [3,3]-sigmatropic rearrangement of **11** catalyzed by the chiral palladium complex **13** gave **12** in 69 % yield and up to 55 % enantiomeric excess (ee).



11 12
55 % ee (5)



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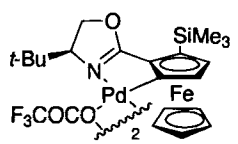
The enantioselectivity of the rearrangement reaction of allylic imidates has been improved significantly by the introduction of chiral ferrocenyl oxazoline catalysts such as **14** [10]. The use of **14** as catalyst for the reaction of a series of different *Z*- and *E*-imidates similar to **11** gave the amides in good yield and with ees higher than 90 % for several of the substrates studied and the chiral ferrocenyl oxazoline catalysts are until know the best catalysts for this rearrangement reaction. It is notable that an exchange of the bridging trifluoroacetate group with an iodine-bridging complex leads to a complex which is inactive, while the chloride-bridging complex is a poor catalyst in terms of reaction rate, but gives the same enantioselectivity as **14** [10a]. Furthermore, it should be pointed out that the ferrocenyl trimethylsilyl substituent is also of utmost importance for the enantioselectivity as the ee of the reaction is reduced significantly by removal of this substituent [10a]. Overman et al. have also investigated other planar–chiral cyclopalladated ferrcenyl amines and imines as chiral catalyst for the allylic imindate rearrangement reactions [10b].

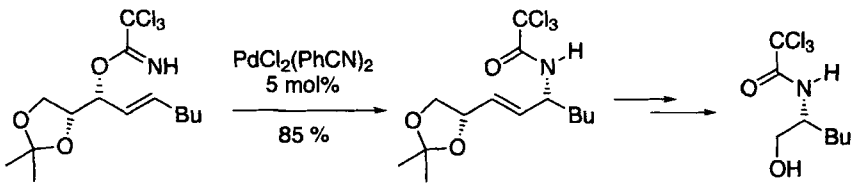


14

Several other chiral ligands have also been introduced for the rearrangement reaction [11]. The use of a tridenate ligand containing an (*R*)-phenyloxazoline as the chiral unit gave in combination with palladium(II) up to 83 % ee for one substrate [11a], while Hayashi et al. have investigated the rearrangement reaction catalyzed by a series of different chiral palladium complexes including bisoxazolines and P,N chelating ligands ((*S*)-(+)-2-(2-diphenylphosphino)phenyl)-4-(benzyl)oxazoline) with the latter giving up to 81 % ee of the allyl amide; however, the yields were often low [11b].

One problem with the metal-catalyzed Overman reaction is the basicity of the imidates. However, this problem has also been solved be Overman et al. by the introduction of the less basic allylic N-benzoylbenzimidates. The application of these allylic *N*-benzoylbenzimidates and palladium(II) chloride as the catalyst improved both the yield, selectivity and rate for the formation of the allyl amines [9].

The palladium(II)-catalyzed rearrangement of allyl imidates for the formation of allyl amines has also been investigated for chiral imidates (Eq. (6)) [12]. The chiral imidate **15** undergoes a palladium(II)-catalyzed rearrangement to **16**, which was applied for the synthesis of (*R*)-*N*-(trichloracetyl)norleucinol **17** as presented in Eq. (6).



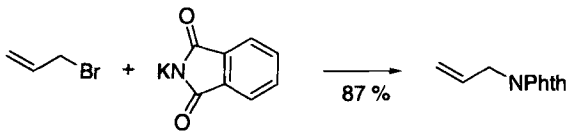
15 **16** **17** (6)

Several applications of the Overman rearrangement for different type of substrates have been published and some examples can be found in [13].

1.2.2 Amination of Allyl Halides

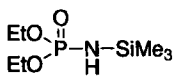
The second approach for the nucleophilic amination reactions to be considered here will be reactions of allyl halides and allyl acetates leading to allyl amines. Allyl halides are normally very reactive in S_N2 reactions, but the direct coupling of allyl halides with nitrogen nucleophiles has been performed with limited success [4], as di- and trialkylated by products often predominate. The application of the Gabriel synthesis can to a certain extent eliminate the problem with polyalkylation of amines using, e.g., the stabilized phthalimide anion **19** as the nucleophile. The allyl amine **20**

can thus be prepared in good yield from alkyl halides **18** by reaction with potassium phthalimide **19** (Eq. (7)) [14].

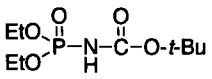


18 **19** **20** (7)

A problem with the use of the phthalimide anion as the nucleophile is the removal of phthaloyl group from the product [15]. Therefore, several attempts have been made to develop reagents with a more labile protecting group than the phthalimide. Compounds **21** and **22** are among some of the reagents investigated. By application of **21** and **22**, better yields of some primary allyl amines were obtained, compared to the traditional method using the phthalimide [16.] The advantage of **21** and **22** as the nitrogen donor for the formation of allyl amines is that the substituents at the nitrogen atom can easily be removed with gaseous hydrogen chloride after alkylation. However, the substrate tolerance is low, and the reagents are somewhat exotic.

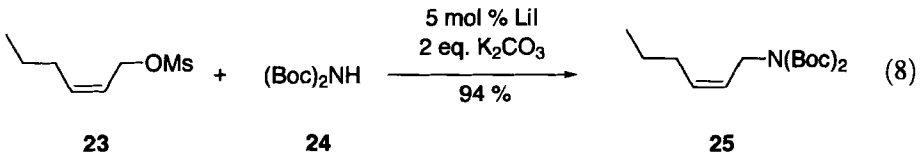


21



22

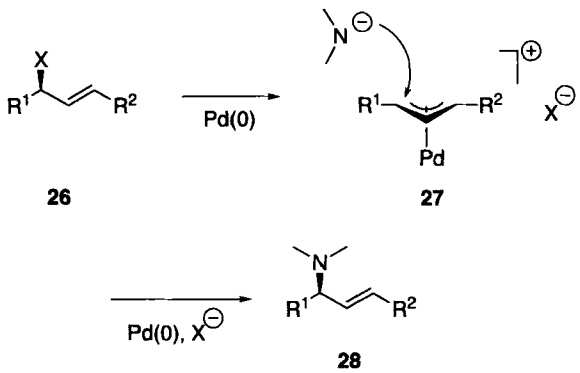
The use of the stabilized anion of di-*t*-butyl iminocarbonate ($(Boc)_2NH$) **24** is more promising in allylic amination reaction. It reacts under mild conditions with a variety of primary and secondary halides and mesylates **23**, giving the allyl amines **25** in high yields (Eq. (8)) [17]. The use of **24** as the nitrogen donor in the amination reaction has the great advantage compared to the palladium-catalyzed amination with the same reagent, that *cis*-alkenes react without scrambling of the double bond, an important aspect considering the isomerization sometimes observed using palladium-catalyzed substitution.



1.2.2.1 Amination of Allyl Halides, Acetates, etc. Catalyzed by Metal Complexes

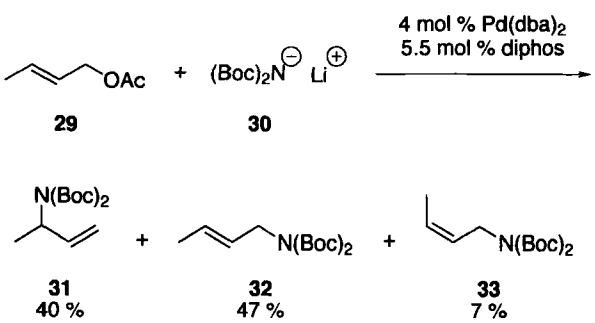
In 1965, Tsuji et al. observed that palladium could catalyze the allylic alkylation reaction [18]. This discovery, which is a very attractive way to expand the scope of the allylic amination reactions mentioned above, has stimulated an intense research in this field, and even though complexes of nickel, platinum, rhodium, iron, ruthenium, molybdenum, cobalt, and tungsten have been found also to catalyze the alkylation, palladium complexes have received by far the greatest attention [19].

As a spin off, the allylic alkylation reaction, allylic amination reactions can now be carried out in high yield and selectivity and the palladium-catalyzed allylic amination reaction is now a cornerstone reaction in organic chemistry [1a,19]. The palladium-catalyzed allylic amination is generally accepted to proceed via a palladium π-allyl complex **27** (Scheme 2). The π-allyl complex intermediate **27** is formed by a nucleophilic attack on **26** by palladium and in a second step the amine attacks directly the allylic ligand leading to retention of configuration in the product **28** [19c,d]. It has been observed that the unsymmetrical allyl systems are attacked by the amine nucleophile at the less substituted carbon atom, although there have been observations of reactions on nonsymmetrical substrates with low regioselectivity.



Scheme 2

In the palladium-catalyzed allylic amination reaction, primary and secondary amines can be used as nucleophiles, whereas ammonia does not react. Therefore, many ammonia synthons have been developed, and a variety of protected primary allyl amines can now be prepared using azide, sulphonamide, phthalimide, di-*t*-butyl iminocarbonate ($(Boc)_2NLi$), and dialkyl *N*-(*tert*-butoxycarbonyl)phosphoramide anions as the nucleophile [20]. An example of the use of ($(Boc)_2NLi$) **30** as the amine nucleophile in the palladium-catalyzed allylic amination reaction is shown in Eq. (9). This reaction also illustrates the problem with the regioselectivity in the reaction as a mixture of the products **31–33** are obtained [21].



(9)