Amino Group Chemistry

From Synthesis to the Life Sciences

Edited by
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The Editor

Professor Alfredo Ricci
Dipartimento di Chimica Organica
Universita di Bologna
Viale Risorgimento 4
040136 Bologna
Italia

Library of Congress Card No.:
applied for

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek
Die Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <http://dnb.d-nb.de>.

Composition SNP Best-set Typesetter Ltd., Hong Kong

Printing Strauss GmbH, Mörlenbach

Bookbinding Litges & Dopf GmbH, Heppenheim

Cover Design Anne Christine Keßler, Karlsruhe

Printed in the Federal Republic of Germany
Printed on acid-free paper

ISBN: 978-3-527-31741-7

Contents

Preface

The book *Modern Amination Methods*, I edited for Wiley-VCH in 2000, was intended to provide an almost exclusively methodological overview of several research areas in which amination plays a key role and to introduce the reader to new concepts that were at that time developed for generating new C—N bonds. The book was well received by the chemical community and indicated the need for keeping scientists aware of the progress in the field of amino group chemistry. The increasing importance of the amino function, in simple or complex molecular systems, is in fact fully acknowledged by chemists due to the presence of these molecules in the most important areas of basic and applied chemistry, such as pharmaceutical, medicinal, agricultural and natural product chemistry, and even more and more in biochemistry. Far from being exhausted, this topic seeks novel breakthroughs to face the novel challenges of third millennium chemistry. This prompted the writing of a new book, focusing not only on the C—N bond forming methodologies, but also on the role played by the amino function in those processes that are more closely related to the life sciences.

The contributions to this book are organized into interlinked sections and will include several important aspects related to amino group chemistry. The first part of the book deals with several more methodologically addressed chapters. Not only is the use of simple amination reagents and pivotal intermediates disclosed, making thus wider the already rich arsenal of conventional and unconventional amination methods, but also the potential of synthetic strategies like MCR (multicomponent reactions), or the most up-to-date metal- or organo-catalyzed approaches to the assembly of polyfunctional complex nitrogen-containing molecules is highlighted. Throughout each chapter, clear structures, schemes and figures accompany the text. Synthetic procedures, mechanisms, reactivity, selectivity and, especially, stereochemistry are addressed. An emphasis is placed, even at this stage, on target oriented synthesis with the insertion of the generated amino function into N-containing densely functionalized chiral molecules, or precursors therof, of interest in medicinal chemistry.

In the following chapters there is a greater focus on the life sciences. The relevant role played by core units containing a preformed amino functionality, many of them coming from the chiral pool, in the construction of important targets in medicinal chemistry, exhibiting among others anticancer, antibiotic and antiviral

activity, is discussed with a rich series of examples. An even deeper insight into the field of clinically relevant drugs containing amino functionalities is provided by those chapters dealing with the synthesis and biological activity of aminated sugar and with the selective N-modification of aminoglycosides. The primary importance of the amino group in glycol structures, toning the physico-chemical properties, actively participating in recognition phenomena and, in the case of iminosugars, in enzymatic inhibition, and the role of the amino functions in RNA binding are treated in detail.

The last chapter is devoted to the industrial approach to amination reactions via transition metal catalyzed aryl amination. The progress in this field and the transformation of formerly extremely difficult processes into trivial tasks with lots of possibilities for fine tuning apt to the large scale production of modern synthetic targets, are disclosed.

This book is timely and the up-to-date reference sections together with several laboratory protocols would make it immediately useful also for those researchers not familiar with this field. It is aimed at a mixed audience including advanced students, young researchers and, more generally, people working in scientific institutions dealing with chemistry. Industrial chemists looking for a survey of well-tried fundamental concepts as well as for information on modern development in amino group chemistry, are also likely to be interested in this book considering the extensive number of industrially important targets treated.

As far as I know there are no books closely related to or similar to this book. The only exception could be the already mentioned *Modern Amination Methods* published by Wiley-VCH in 2000. This fact, instead of constituting a point of weakness, guarantees that the new book will not give rise to a substantial superimposition with the previous publication but on the contrary will be fully complementary to it.

I would like to thank all the distinguished scientists and their coauthors for their rewarding, timely and well-referenced contributions. Grateful acknowledgements are offered to the Wiley-VCH editorial staff, in particular to Dr. Manfred Koehl for proposing to me this new challenge and to Dr. Waltraud Wuest who was of precious help for the development of this project.

Bologna, July 2007 Alfredo Ricci

List of Contributors

Cristina Airoldi
University of Milano – Bicocca
Department of Biotechnology and Biosciences
Piazza della Scienza 2
20126 Milano
Italy

Roberto Ballini
Università di Camerino
Dipartimento di Scienze Chimiche
Via S. Agostino n. 1
62032 Camerino
Italy

Shunsuke Chiba
Nanyang Technological University
School of Physical and Mathematical Sciences
1 Nanyang Walk, Blk 5 Level 3
Singapore 637616
Singapore

Armando Córdova
Stockholm University
Department of Organic Chemistry
Arrhenius Laboratory
10691 Stockholm
Sweden

Philippe Dauban
CNRS
Institut de Chimie des Substances Naturelles
Avenue de la Terrasse
91198 Gif-sur-Yvette
France

Alexander Doemling
University of Pittsburgh
Department of Pharmaceutical Sciences
10019 BST3
Pittsburgh, PA 15261
USA

Robert H. Dodd
CNRS
Institut de Chimie des Substances Naturelles
Avenue de la Terrasse
91198 Gif-sur-Yvette
France

Barbara La Ferla
University of Milano – Bicocca
Department of Biotechnology and Biosciences
Piazza della Scienza 2
20126 Milano
Italy

André Mann
Laboratoire de Pharmacochimie
de la Communication
Cellulaire-UMR 7081
Faculté de Pharmacie
74, route du Rhin – BP600 24
67400 Ilkirch Cedex
France

Enrico Marcantoni
Università di Camerino
Dipartimento di Scienze
Chimiche
Via S. Agostino n. 1
62032 Camerino
Italy

Koichi Narasaka
Nanyang Technological University
School of Physical and
Mathematical Sciences
1 Nanyang Walk, Blk 5 Level 3
Singapore 637616
Singapore

Francesco Nicotra
University of Milano – Bicocca
Department of Biotechnology and
Biosciences
Piazza della Scienza 2
20126 Milano
Italy

Marino Petrini
Università di Camerino
Dipartimento di Scienze Chimiche
Via S. Agostino n. 1
62032 Camerino
Italy

Ramon Rios
Stockholm University
Department of Organic Chemistry
Arrhenius Laboratory
10691 Stockholm
Sweden

Ulrich Scholz
Boehringer Ingelheim Pharma GmbH
& Co. KG
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

Floris Louis van Delft
Radboud University Nijmegen
Institute for Molecules and Materials
Toernooiveld 1
6525 ED Nijmegen
The Netherlands

1
Simple Molecules, Highly Efficient Amination

Shunsuke Chiba and Koichi Narasaka

1.1
Introduction

In the last two decades, explosive progress has been made in synthetic methods for production of amino compounds, due to their rapidly increasing applications in pharmaceutical and material sciences. Development of amination reagents for the construction of new carbon–nitrogen bonds is one of the most important and basic processes for the synthesis of amino molecules, and this chapter introduces simple and useful amination reagents classified by reaction type, such as electrophilic amination reagents, including transition metal–nitrene and nitrido complexes, radical-mediated amination reagents, and nucleophilic amination (Gabriel-type) reagents.

1.2
Hydroxylamine Derivatives

Hydroxylamine derivatives are one of the most versatile and simple amination reagents, leading the variety of nitrogen-containing compounds. This section mainly focuses on recent advances in electrophilic amination of carbon nucleophiles with various hydroxylamine derivatives.

1.2.1
O-Sulfonylhydroxylamine

Tamura has reported the synthesis of *O*-mesitylsulfonylhydroxylamine (MSH; **1**; Figure 1.1) and related compounds and has examined their reactions with various nucleophiles in detail [1]. With regard to the formation of C—N bonds by the use of MSH, however, the applicable carbanions were quite limited – to stabilized enolates only – and the product yields of the resulting amines were quite low.

The electrophilic amination of organolithium compounds with the methyllithium-methoxyamine system, long recognized as a potentially useful

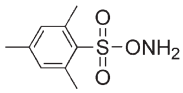

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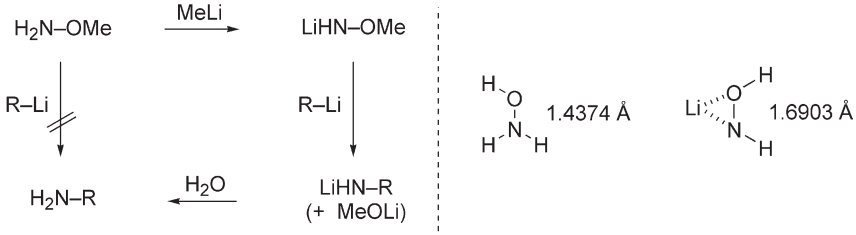
Figure 1.1 Tamura reagent (MSH) **1**.



Scheme 1.1 Electrophilic amination with the methyllithium-methoxyamine system.

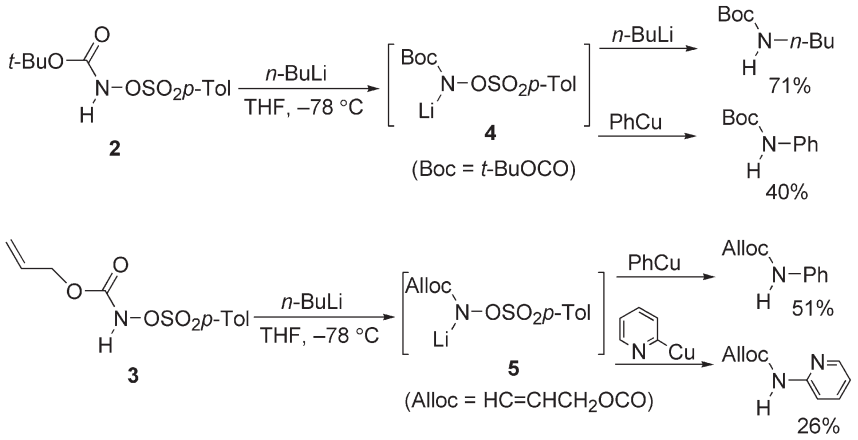
amination method (Scheme 1.1), was discovered by Sheverdina and Kocheskov in 1938 [2]. Overall the process is a formal displacement of the methoxy group of the lithium methoxyamide intermediate with the carbanion. Model calculations performed to provide insight into the electrophilic properties of LiHN—OMe showed that the N—O bond in LiHN—OMe is bridged by Li and is longer than the related bond in H_2N—OMe [3]. This would suggest a particular significance of the nitrenoid-like structure for the facile cleavage of the N—O bond.

These concepts have been translated into the design of some *O*-sulfonylhydroxylamines such as *tert*-butyl-*N*-tosyloxycarbamate (**2**) [4] and allyl-*N*-tosyloxycarbamate (**3**) [5], which can be easily prepared and are stable enough to handle. Actually, Boche et al. reported the crystal structure of lithium *tert*-butyl-*N*-mesityloxycarbamate and revealed that the N—O bond is longer than that in the neutral compound, *tert*-butyl-*N*-mesityloxycarbamate, which supports the calculations mentioned above [6].

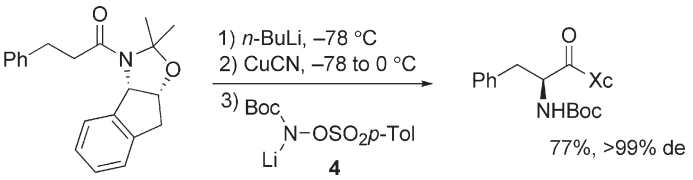
Lithium *tert*-butyl-*N*-tosyloxycarbamate (**4**) and lithium allyl-*N*-tosyloxycarbamate (**5**), generated by treatment of **2** and **3** with butyllithium in THF at –78 °C, are useful for the preparation of *N*-Boc and *N*-Alloc amines. A variety of *N*-protected alkyl, aryl, and heteroaryl primary amines can be synthesized by treatment with the corresponding organolithium and -copper reagents (Schemes 1.2–1.5).

The amination of α-cuproamides and α-cuprophosphonates also proceeds effectively through the use of lithium *tert*-butyl-*N*-tosyloxycarbamate (**4**) and allyl-*N*-tosyloxycarbamate (**5**) to give α-amino acid derivatives. Asymmetric synthesis of α-amino acid derivatives is achieved by the amination of chiral amide cuprates with lithium *tert*-butyl-*N*-tosyloxycarbamate (**4**; Scheme 1.6) [7].

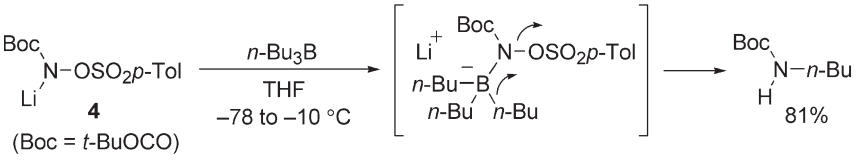
These methods can be applied to the amination of organoboranes [8]. Primary alkyl boranes rapidly react with lithium *tert*-butyl-*N*-tosyloxycarbamate (**4**) in a 1 : 1 molar ratio to give *N*-Boc-protected primary amines in good yield (Scheme 1.7).



Scheme 1.2–1.5



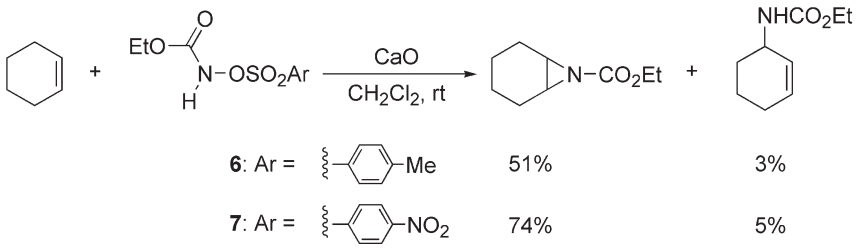
Scheme 1.6



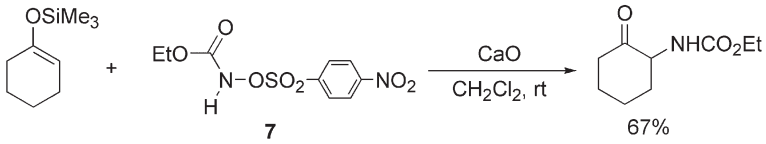
Scheme 1.7

The reaction presumably proceeds through the aniotropic rearrangement of an organoborate complex.

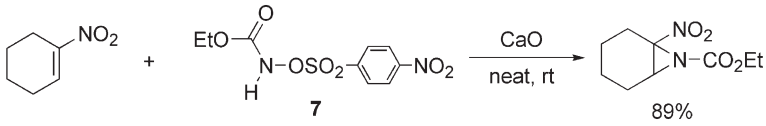
In addition, arylsulfonyloxycarbamates such as **6–8** can be used for aziridination of alkenes by treatment with inorganic bases such as CaO or Cs_2CO_3. The treatment of, for example, cyclohexene with ethyl *N*-arylsulfonyloxycarbamates **6** and **7** in the presence of CaO gives *N*-ethoxycarbonylaziridine along with a small amount of an allylic amination product (Scheme 1.8) [9]. As judged from the formation of an sp^3 C—H amination product, the reactive intermediate of this reaction seems to be ethoxycarbonylnitrene. Silyl enol ethers are aminated by the same procedure to afford α-amino carbonyl compounds, presumably via *N*-ethoxycarbonyl azirines (Scheme 1.9).



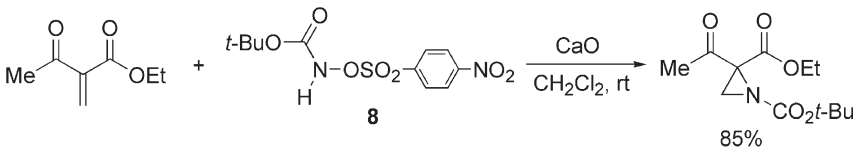
Scheme 1.8



Scheme 1.9



Scheme 1.10



Scheme 1.11

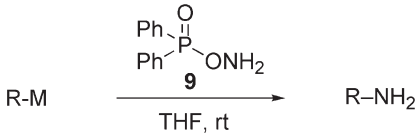
The corresponding reactions with electron-deficient alkenes also afford aziridines, but through some other mechanism, such as an aza-Michael addition–elimination process (Schemes 1.10, 1,11) [10].

1.2.2
O-Phosphinylhydroxylamine

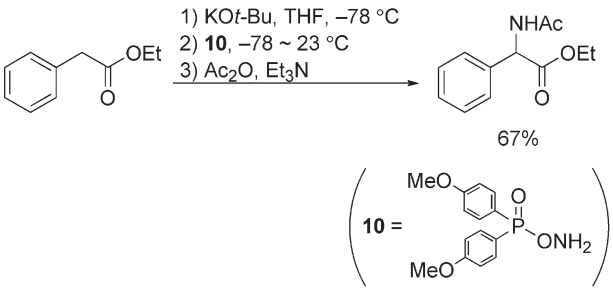
As well as *O*-sulfonyloximes (Section 1.2.1), *O*-(diphenylphosphinyl)hydroxylamine (**9**) has also been utilized for the electrophilic amination of various carbanions to prepare primary amines [11]. Grignard reagents and organolithiums including enolates are aminated with **9** (Table 1.1).

The application of *O*-(diphenylphosphinyl)hydroxylamine (**9**) is limited by its low solubility in most organic solvents. Recently, Vedejs reported that *O*-di-(*p*-methoxyphenylphosphinyl)-hydroxylamine (**10**), which is soluble in THF even at

Table 1.1 Electrophilic amination with *O*-(diphenylphosphinyl)hydroxylamine (**9**).



R-M	$R–NH_2$ (yield / %)		R-M	$R–NH_2$ (yield / %)	
PhMgCl	$Ph–NH_2$	(35)	Ph_3CLi	$Ph_3C–NH_2$	(30)
Ph⌒MgCl	Ph⌒NH_2	(70)	Ph, OLi / OEt	NH2 / Ph⌒CO_2Et	(45)



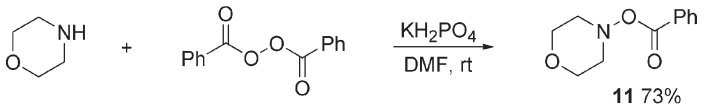
Scheme 1.12

–78 °C, reacts efficiently with stabilized sodium or potassium enolates derived from malonates, phenylacetates, and phenylacetonitrile as shown in Scheme 1.12 [12].

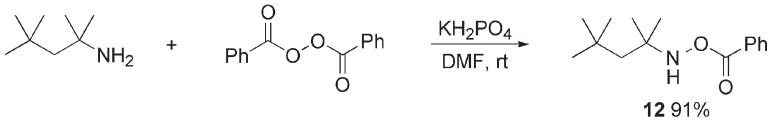
1.2.3 *O*-Acylhydroxylamine

O-Acylhydroxylamines have not been employed for electrophilic amination as extensively as *O*-sulfonyl- and *O*-phosphinylhydroxylamines [13]. Recently, though, J. S. Johnson has developed a mild and widely applicable method for the preparation of various secondary and tertiary amines through the copper-catalyzed electrophilic amination of organozinc reagents with *O*-benzoylhydroxylamines such as **11** or **12** [14]. The *O*-benzoylhydroxylamines, most of which are stable enough to be used in the subsequent amination, are prepared by the oxidation of the corresponding primary and secondary amines with benzoyl peroxide and K_2HPO_4 in DMF (Schemes 1.13 and 1.14).

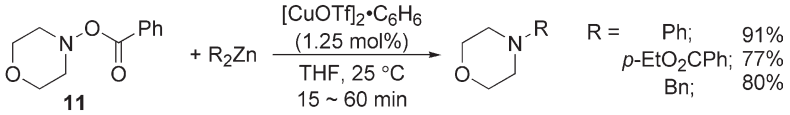
Secondary and tertiary amines are synthesized by treatment of organozincs with *O*-benzoylhydroxylamines **11** and **12** in the presence of catalytic amounts of $[Cu(OTf)]\cdot C_6H_6$ (Schemes 1.15 and 1.16).



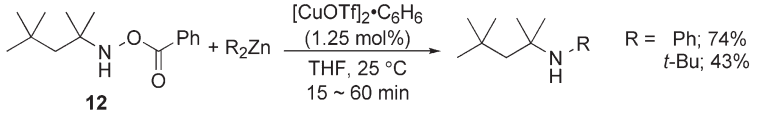
Scheme 1.13



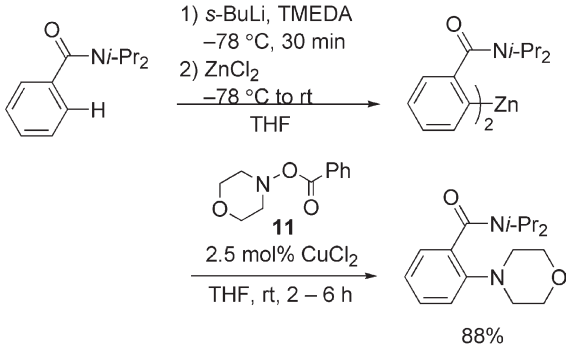
Scheme 1.14



Scheme 1.15



Scheme 1.16

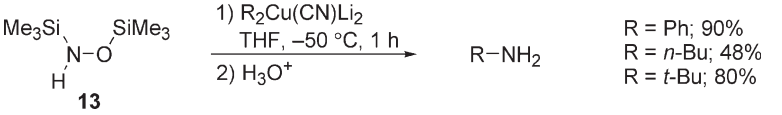


Scheme 1.17

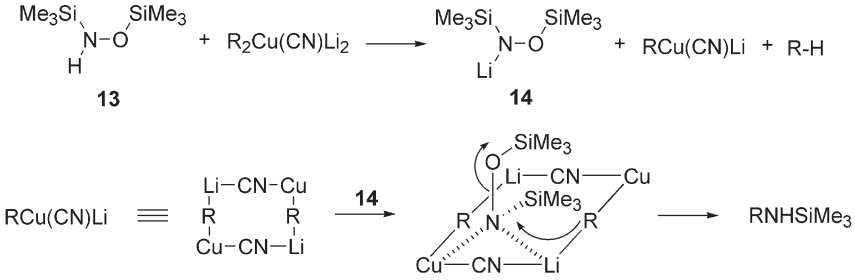
This methodology can be used for aromatic C—H amination by combination with directed *ortho*-lithiation/transmetalation (Scheme 1.17).

1.2.4
O-Trimethylsilylhydroxylamine

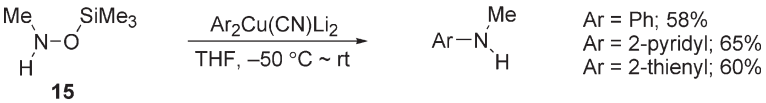
Ricci developed the electrophilic amination of higher-order cyanocuprates with *N,O*-bis(trimethylsilyl)hydroxylamine (**13**), providing a suitable method for the preparation of primary amines (Scheme 1.18) [15].



Scheme 1.18



Scheme 1.19 Electrophilic amination with *N,O*-bis(trimethylsilyl)hydroxylamines (**13**).



Scheme 1.20

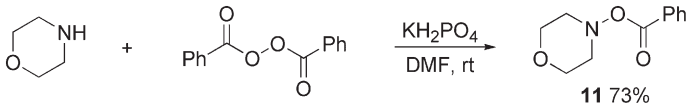
N,O-Bis(trimethylsilyl)hydroxylamine (**13**) first reacts with the higher-order cuprate to generate lithium *N*-silyl-*N*-siloxyamide **14** and monoanionic lower-order cyanocuprate. The new C—N bond may be formed by the interception of lithium amide **14** with the thus formed cuprate via an amide–copper intermediate as shown in Scheme 1.19.

Similarly, by starting from *N*-alkyl-*O*-(trimethylsilyl)hydroxylamines such as **15**, *N*-alkyl aromatic and heteroaromatic amines are prepared by treatment with aryl- and heteroarylcyanocuprates (Scheme 1.20) [16].

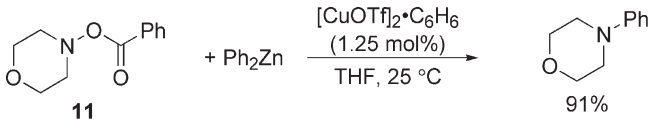
1.2.5
Experimental Procedures

Representative synthesis of O-benzoylhydroxylamines Morpholine (5.2 mL. 60 mmol) was added by syringe in one portion to a mixture of benzoyl peroxide (12.1 g, 50 mmol) and dipotassium hydrogen phosphate (13.1 g, 75 mmol) in DMF (125 mL). The suspension was stirred at ambient temperature for 1 h. Deionized water (200 mL) was added, and the contents were stirred vigorously for several minutes until all solids had dissolved. The organic materials were extracted with ethyl acetate (150 mL) and the combined extracts were washed with saturated aqueous $NaHCO_3$ (100 mL × 2). The aqueous fractions were combined and extracted with ethyl acetate (100 mL × 3), and the organic fractions were combined and washed with deionized water (100 mL × 3) and brine (100 mL), and dried over $MgSO_4$. Volatile materials were removed *in vacuo* and the resulting crude mixture

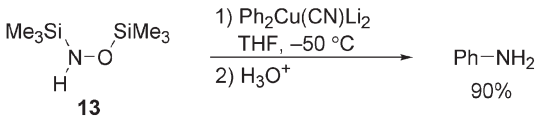
was purified by flash column chromatography, with elution with 50% ethyl acetate/hexane, to afford 4-benzoyloxymorpholine (**11**, 7.71 g, 37 mmol, 74%) of >95% purity by ^{1}H NMR spectroscopy.



Representative electrophilic amination with O-benzoylhydroxylamines A THF solution of diphenylzinc, prepared from an ethereal solution of PhMgBr (1.0 M, 1.1 mL, 1.1 mmol) and $ZnCl_2$ (75 mg, 0.55 mmol) in THF (2.0 mL), was added by cannula in one portion to a mixture of 4-benzoyloxymorpholine (**11**, 103 mg, 0.50 mmol) and $[CuOTf]_2 \cdot C_6H_6$ (3 mg, 0.0056 mmol) in THF (5.0 mL). The resulting solution was stirred at ambient temperature for 1 h. The reaction mixture was diluted with Et_2O (10 mL) and transferred into a separating funnel. The mixture was washed with saturated aq. $NaHCO_3$ (10 mL × 3) and the amino components were extracted with 10% aqueous HCl (10 mL × 3). The aqueous extracts were basified with 10% aq. NaOH and the amino components were extracted with CH_2Cl_2 (10 mL × 3). The organic fraction was washed with brine (10 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford 4-phenylmorpholine as a white solid (80 mg, 0.49 mmol, 98%) of >95% purity by ^{1}H NMR.



Representative electrophilic amination with N,O-bis(trimethylsilyl)hydroxylamine *N, O*-Bis(trimethylsilyl)hydroxylamine (0.426 mL, 2.0 mmol), commercially available from Aldrich Chemical Co., Inc., was added dropwise at –50 °C to a clear brown solution of $Ph_2CuCNLi_2$ (2.0 mmol) in THF After stirring for 1 h, the dark reaction mixture was hydrolyzed with 20% aq. HCl (30 mL). The aqueous layer was basified with NaOH, and aniline was extracted with Et_2O (2 × 20 mL). The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo* and the resulting crude materials were purified by distillation to afford aniline (167 mg, 90%) as a clear liquid.



1.3
Oxime Derivatives

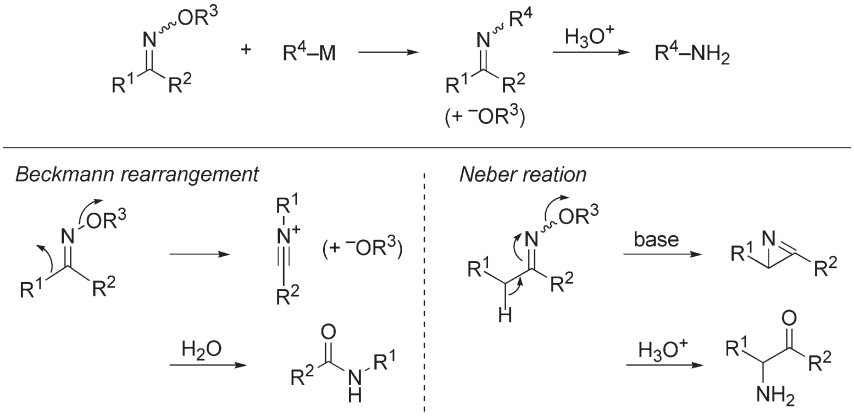
Oxime derivatives are readily converted into a variety of amino compounds through representative reactions such as the Beckmann rearrangement, Beckmann fragmentation, and the Neber reaction [17]. This section mainly focuses on C—N bond formation by electrophilic amination of carbanions with oxime derivatives by substitution on the sp^2 nitrogen atom.

1.3.1
Synthesis of Primary Amines by Electrophilic Amination of Carbanions

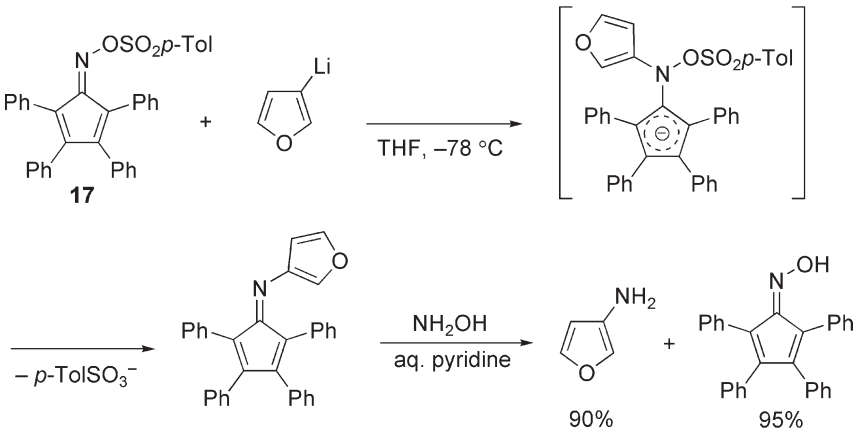
Oxime sp^2 nitrogen atoms possessing suitable leaving groups (OR^1) react with organometallic reagents (R^3–M) to afford the corresponding *N*-alkyl- or *N*-arylimines, which are readily hydrolyzed to primary amines (Scheme 1.21). To make this substitution reaction efficient, competing side reactions such as the Beckmann rearrangement and the Neber reaction have to be suppressed by suitably masking the oxime derivatives.

Murdoch reported that treatment of tetraphenylcyclopentadienone *O*-tosyloxime (**17**) with excess amounts of aryllithium and aryl Grignard reagents gives *N*-arylimines, which can be converted into primary amines and cyclopentadienone oxime by treatment with excess hydroxylamine in aqueous pyridine (Scheme 1.22) [18]. The formation of the imines probably proceeds through nucleophilic addition to the nitrogen atom of oxime **17** to generate stabilized cyclopentadienyl anions, which undergo elimination of tosylate.

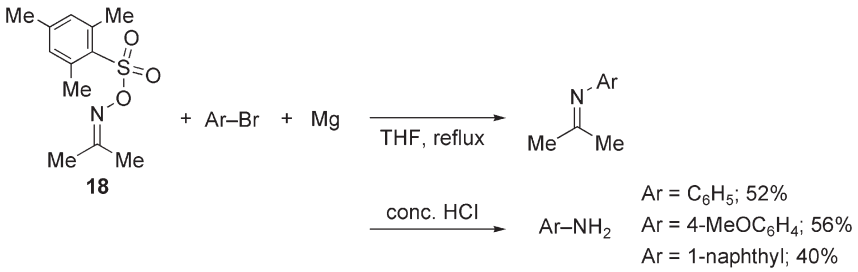
Acetone *O*-(2,4,6-trimethylphenylsulfonyl)oxime (**18**) can be applied in the amination of arylmagnesium and arylzinc reagents [19]. Treatment of oxime **18** under Barbier conditions (i.e., treatment of aryl bromide with **18** and magnesium in THF at reflux temperature), followed by the hydrolysis of the resulting imines under



Scheme 1.21 Synthesis of primary amines by use of oxime derivatives.



Scheme 1.22 Electrophilic amination with tetraphenylcyclopentadienone *O*-tosyloxime (**17**).



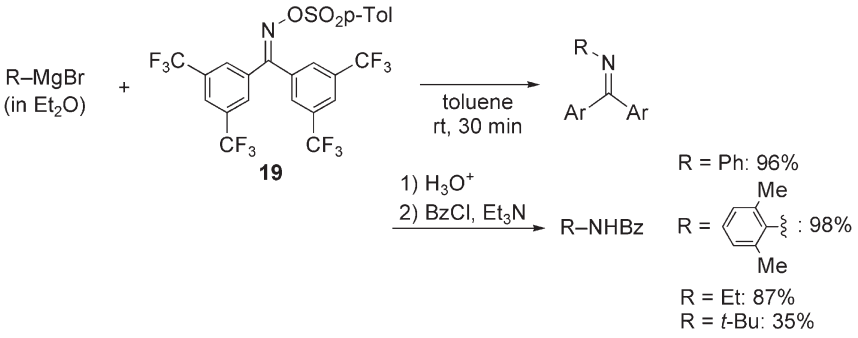
Scheme 1.23 Electrophilic amination with acetone *O*-(2,4,6-trimethylphenylsulfonyl)oxime (**18**).

acidic conditions, afforded *N*-aryl primary amines, although the yields were moderate (40–56%) (Scheme 1.23) [20].

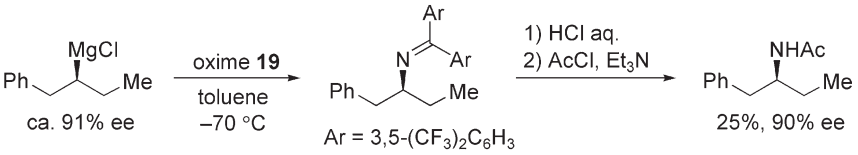
Narasaka developed the amination of Grignard reagents with bis[3,5-bis(trifluoromethyl)phenyl] ketone *O*-tosyloxime (**19**) [21], the introduction of the electron-withdrawing trifluoromethyl groups suppressing the competing Beckmann rearrangements. Various primary amine derivatives are synthesized by the reaction with aryl and alkyl Grignard reagents, except in the case of tertiary alkyl reagents (Scheme 1.24).

A chiral secondary amine is prepared without loss of optical purity by treatment of a chiral Grignard reagent with oxime **19** (Scheme 1.25) [22]. This means that the reaction proceeds not through an electron-transfer mechanism but by nucleophilic substitution at the oxime nitrogen.

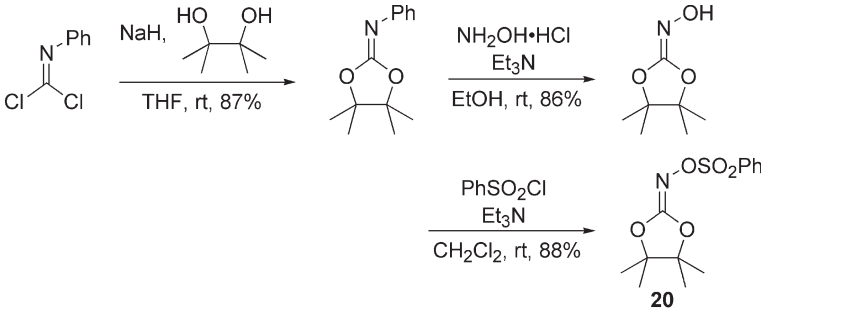
The employment of *O*-sulfonyl oximes of cyclic ureas and carbonates [23, 24] works effectively for the electrophilic amination of Grignard reagents, because they never undergo Beckmann rearrangements or Neber reactions. Among them, 4,4,5,5-tetramethyl-1,3-dioxolan-2-one *O*-(phenylsulfonyl)oxime (**20**), which can be



Scheme 1.24 Electrophilic amination with bis[3,5-bis(trifluoromethyl)phenyl] ketone *O*-tosyloxime (**19**).



Scheme 1.25 Synthesis of a chiral secondary amine with oxime **19**.

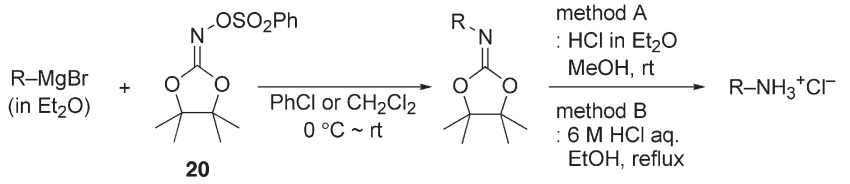


Scheme 1.26 Synthesis of 4,4,5,5-tetramethyl-1,3-dioxolan-2-one *O*-(phenylsulfonyl)oxime (**20**).

prepared easily from commercially available phenylcarbonimidic dichloride (Scheme 1.26), was found to be most suitable [25]. The imidic dichloride was treated with pinacol and NaH to give 2-phenylimino-1,3-dioxolane, which was transformed into *O*-(phenylsulfonyl)oxime **20** by imino-exchange by treatment with hydroxylamine followed by *O*-sulfonylation of the resulting oxime.

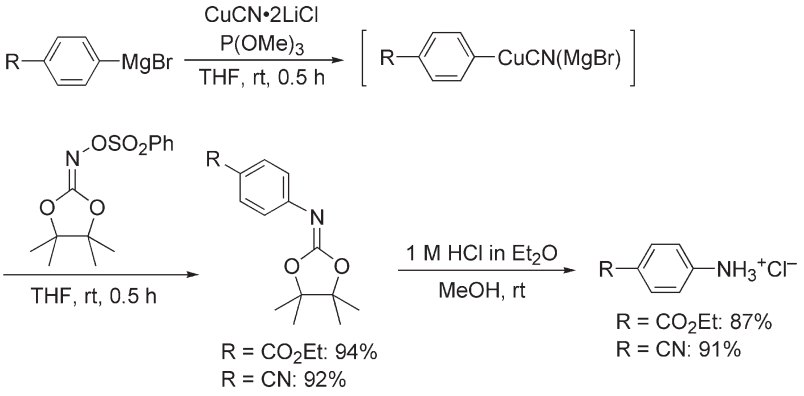
Various Grignard reagents react with oxime **20** in nonpolar solvents to afford the corresponding imines, which are easily converted into primary amines under mild acidic conditions (Table 1.2). Aryl Grignard reagents, regardless of steric congestion and the electronic effects of the substituents on the aryl group, are smoothly aminated with **20**, and anilines are obtained after hydrolysis or solvolysis of the resulting *N*-aryl imines. Primary, secondary, and tertiary alkylamines are

Table 1.2 Synthesis of primary amines by the electrophilic amination of Grignard reagents with *O*-(phenylsulfonyl)oxime (**20**).



R		yield / %	R		yield / %
Ph	A	93	$PhCH_2CH_2$	B	90
p-CF_3-C_6H_4	A	94	$PhCH_2CH(CH_3)$	B	89
2,4-$(MeO)_2$-C_6H_3	A	91	1-adamantyl	B	89
2,6-Me_2-C_6H_3	B	90	CH_2=$CH(CH_3)$	—	93[a]

a) Yield of 2-aza-1,3-diene.



Scheme 1.27 Electrophilic amination of arylcopper reagents with *O*-(phenylsulfonyl)oxime (**20**).

prepared in high yield from the corresponding alkyl Grignard reagents, and even alkenyl Grignard reagents reacted with **20** to give 2-aza-1,3-dienes.

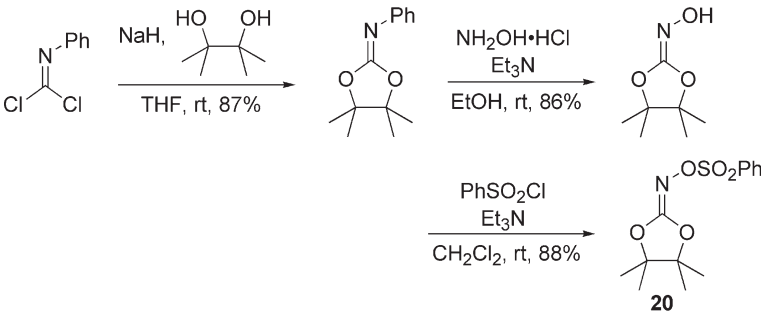
Aryl Grignard reagents bearing a cyano or an alkoxy carbonyl group, prepared by iodine–magnesium exchange [26], cannot be used directly for this amination procedure, because of their instability at temperatures higher than 0 °C. Arylcopper reagents generated by transmetalation of such arylmagnesium compounds with $CuCN \cdot 2LiCl$ in the presence of trimethyl phosphite [27] react with 4,4,5,5-tetramethyl-1,3-dioxolan-2-one *O*-(phenylsulfonyl)oxime (**20**) to afford the corresponding *N*-arylimines, which are hydrolyzed to anilines (Scheme 1.27) [28].

1.3.2
Experimental Procedures

Procedure for the preparation of 4,4,5,5-tetramethyl-1,3-dioxolan-2-one O-phenylsulfonyloxime Pinacol (15.2 g, 128 mmol) in THF (60 mL) was slowly added under argon at 0 °C to a suspension of NaH (6.36 g, 264 mmol) in THF (250 mL), after which phenylcarbonimidic dichloride (20.5 g, 128 mmol) in THF (40 mL) was added over 15 min. This mixture was stirred at room temperature for 30 min, after which the reaction was quenched with a pH 9 ammonium buffer and the mixture was extracted three times with ethyl acetate. The combined extracts were washed with brine and dried over Na_2SO_4, and the ethyl acetate was removed *in vacuo* to give an 87% yield of 4,4,5,5-tetramethyl-2-phenylimino-1,3-dioxolane (22.5 g, 111 mmol), which was used without further purification.

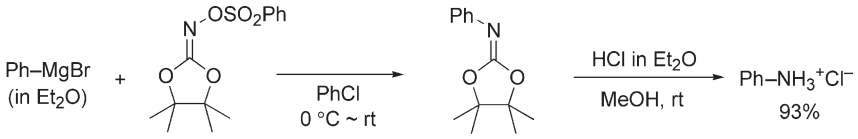
Triethylamine (61.7 g, 611 mmol) and $NH_2OH \cdot HCl$ (34.1 g, 491 mmol) were added to a solution of 4,4,5,5-tetramethyl-2-phenylimino-1,3-dioxolane (26.7 g, 122 mmol) in ethanol (300 mL), and this mixture was stirred at room temperature for 24 h. After the reaction had been quenched with pH 9 ammonium buffer, the mixture was extracted three times with ethyl acetate. The combined extracts were washed with water and brine and dried over Na_2SO_4, the ethyl acetate was removed *in vacuo*, and the crude materials were purified by flash column chromatography (hexane/ethyl acetate 1 : 1 to 1 : 4) to give 4,4,5,5-tetramethyl-1,3-dioxolan-2-one oxime (16.7 g, 105 mmol) in 86% yield.

Benzenesulfonyl chloride (5.59 g, 31.6 mmol) in dichloromethane (15 mL) was slowly added under argon at 0 °C to a solution of 4,4,5,5-tetramethyl-1,3-dioxolan-2-one oxime (4.49 g, 22.8 mmol) and triethylamine (5.90 mL, 42.3 mmol) in dichloromethane (100 mL), and the mixture was stirred at room temperature for 1 h. After the reaction had been quenched with ice water, the mixture was extracted three times with ethyl acetate, the combined extracts were washed with brine and dried over anhydrous sodium sulfate, the ethyl acetate was removed *in vacuo*, and the crude materials were purified by recrystallization (hexane/ethyl acetate) to give 4,4,5,5-tetramethyl-1,3-dioxolan-2-one *O*-phenylsulfonyloxime (**20**, 7.40 g, 25.9 mmol) in 88% yield.

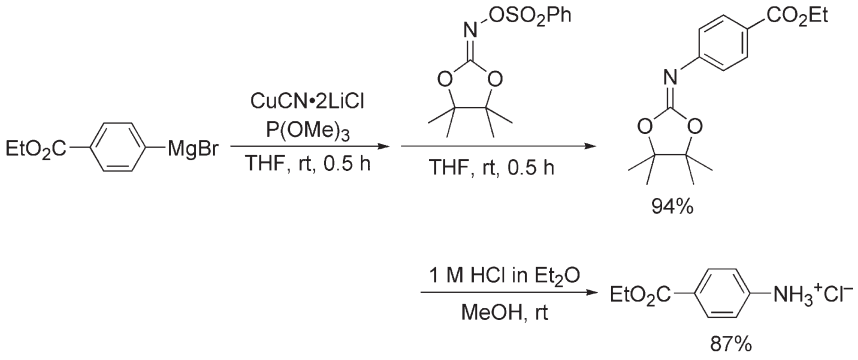


20

Representative procedure for the preparation of primary amine hydrochlorides by treatment of 4,4,5,5-tetramethyl-1,3-dioxolan-2-one O-phenylsulfonyloxime with Grignard reagents An ether solution of phenylmagnesium bromide (0.96 M, 2.3 mL, 2.2 mmol) was added dropwise under argon at 0 °C to a solution of 4,4,5,5-tetramethyl-1,3-dioxolan-2-one *O*-phenylsulfonyloxime (**20**, 593 mg, 1.98 mmol) in chlorobenzene (15 mL), and this mixture was stirred at the same temperature for 30 min. The reaction was then quenched with pH 9 ammonium buffer at 0 °C, and the mixture was extracted three times with ethyl acetate. The combined extracts were washed with brine and dried over Na_2SO_4, and the ethyl acetate was removed under vacuum. Hydrogen chloride in ether (1.0 M, 4.0 mL) was added at 0 °C to the crude imine in methanol (10 mL), and this mixture was stirred at room temperature for 1.5 h. Volatile materials were removed *in vacuo*, and anhydrous ether (40 mL) was added. The insoluble materials were collected by filtration to give aniline hydrochloride (239 mg, 1.84 mmol) in 93% yield.



Representative procedure for the preparation of primary arylamines possessing electron-withdrawing groups by use of 4,4,5,5-tetramethyl-1,3-dioxolan-2-one O-phenylsulfonyloxime A THF solution of isopropylmagnesium bromide (1.15 M, 0.96 mL, 1.1 mmol) was slowly added under argon at –20 °C to a solution of ethyl 4-iodobenzoate (278 mg, 1.01 mmol) in THF, and this mixture was stirred at the same temperature for 30 min. A THF solution of CuCN · 2LiCl (0.50 M, 2.0 mL, 1.0 mmol) was then added, the temperature again being kept below –20 °C. After completion of the addition, the reaction mixture was allowed to warm to room temperature over 30 min. Trimethyl phosphate (128 mg, 2.0 mmol) was then added and the clear solution was stirred for an additional 5 min. 4,4,5,5-Tetramethyl-1,3-dioxolan-2-one *O*-phenylsulfonyloxime (**20**, 290 mg, 0.969 mmol) in THF (3 mL)



was then added dropwise and the reaction mixture was stirred at this temperature for 15 min. After the reaction had been quenched with a pH 9 buffer at 0 °C, the mixture was extracted three times with ethyl acetate, and the combined extracts were washed with brine and dried over anhydrous sodium sulfate. The ethyl acetate was removed under vacuum and the crude materials were purified by flash column chromatography (silica gel, hexane/ethyl acetate 8 : 2) to give 2-(4-ethoxycarbonylphenyl)imino-4,4,5,5-tetramethyl-1,3-dioxolane (266 mg, 0.913 mmol) in 94% yield. The resulting imine was converted into aniline by the same procedure as described in Section 1.3.2.

1.4 Azo Compounds

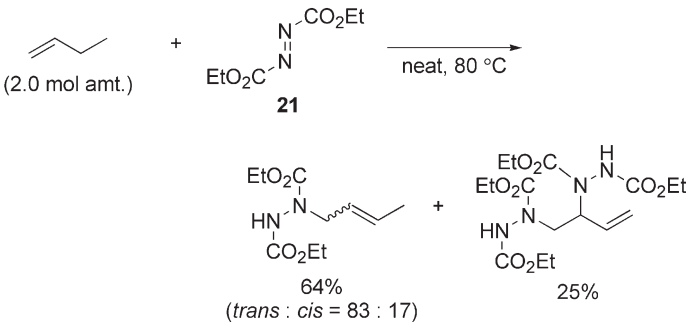
In this section some amination reactions utilizing azodicarboxylates (Section 1.4.1) and arylazo sulfones (Section 1.4.2) as nitrogen sources are illustrated. In the azodicarboxylate section, amination reactions of alkenes are discussed, because there are some reviews on the electrophilic amination of carbanions leading various hydrazine dicarboxylates [29].

1.4.1 Azodicarboxylates

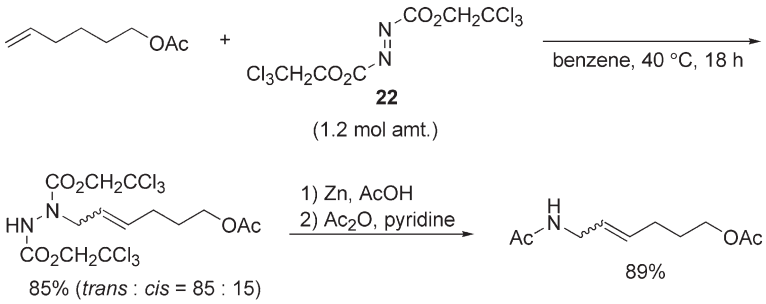
1.4.1.1 Allylic Amination through Ene-Type Reactions

Ene reactions play an important role in organic transformations, and the use of azo compounds such as diethyl azodicarboxylate (DEAD; **21**) as enophiles provides a useful method for amination of alkenes (aza-ene reaction) to give allyllic hydrazines (Scheme 1.28). Although thermal aza-ene reactions of various alkenes with DEAD have been reported, such reactions generally require high temperatures and are difficult to control because of the formation of bis-adducts [30].

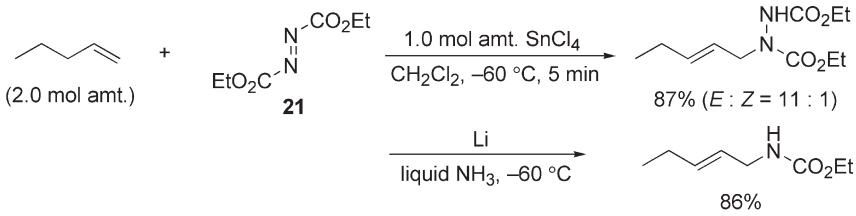
Leblanc improved this thermal aza-ene reaction by use of bis-(2,2,2-trichloroethyl) azodicarboxylate (**22**) [31]. Reactions between alkenes and **22**



Scheme 1.28



Scheme 1.29 The aza-ene reaction with bis(2,2,2-trichloroethyl) azodicarboxylate (**22**).



Scheme 1.30 Lewis acid-mediated allylic amination of alkenes with DEAD (**21**).

proceed under milder conditions to give the corresponding ene adducts in good yield without the formation of bis-adducts (Scheme 1.29). In addition, by treatment with Zn dust and acetic acid, the reductive cleavage of the N—N bonds in the resulting allyllic hydrazines proceeds to give allylic amine derivatives.

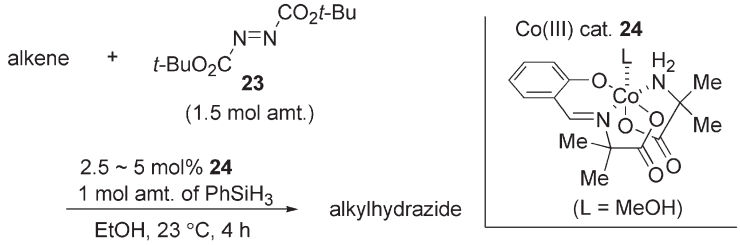
Heathcock developed Lewis acid-mediated allylic amination of alkenes with DEAD (Scheme 1.30) [32]. The use of $SnCl_4$ in dichloromethane promotes the reaction at –60 °C, affording the ene adducts in good yield with excellent selectivity for the formation of (*E*)-alkenes. The allylic hydrazines can be converted into carbamates by treatment with lithium in liquid ammonia. In addition, $LiClO_4$ was also able to catalyze aza-ene reactions of azodicarboxylate derivatives [33].

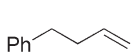
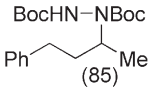
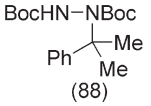
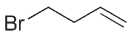
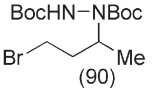
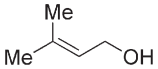
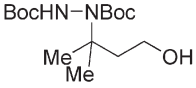
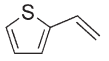
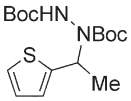
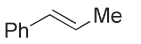
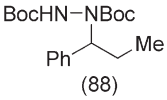
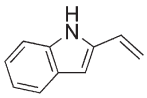
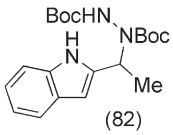
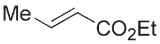
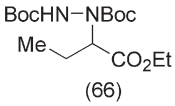
1.4.1.2 **Hydrohydrazination of Alkenes**

Carreira has recently developed the Co- and Mn-catalyzed hydrohydrazination of alkenes with azodicarboxylates, which enables the preparation of various alkylhydrazines from a broad range of alkenes [34].

Mono-, di-, and trisubstituted alkenes, including vinyl heterocycles, react with azodicarboxylates such as **23** in the presence of phenylsilane and the Co(III) catalyst **24**, bearing Schiff base ligands, to give alkylhydrazines in good yields (Table 1.3). Monosubstituted, 1,1-disubstituted, and trisubstituted alkenes give exclusively the Markovnikov-type hydrohydrazination products with broad functional group tolerance. In the reaction behavior of 1,2-disubstituted alkenes, the selectivity is governed by electronic effects. Phenyl substitution results in the formation of the benzylic hydrazine, while the presence of an ethoxycarbonyl group produces an α-hydrazinyl ester.

Table 1.3 Co-catalyzed hydrohydrazination of alkenes with azodicarboxylate **23**.



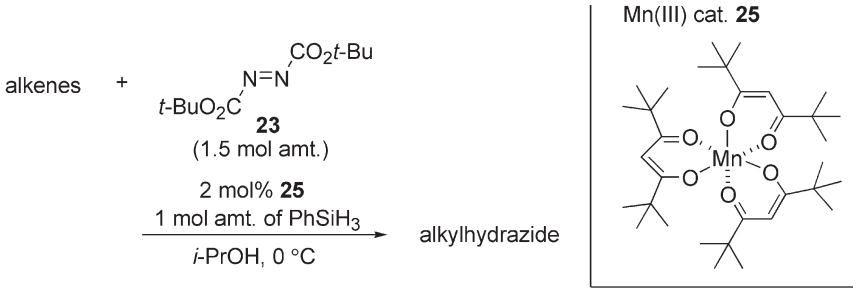
alkene	product (yield / %)	alkene	product (yield / %)
	 (85)		 (88)
	 (90)		 (70)
	 (84)		 (88)
	 (82)		 (66)

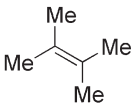
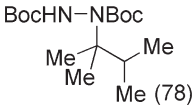
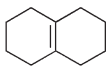
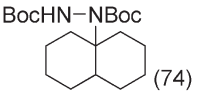
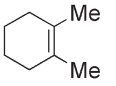
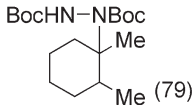
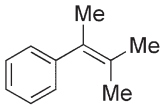
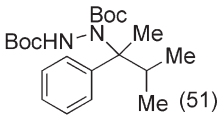
The above cobalt catalyst could not be employed for the hydrohydrazination of tetrasubstituted alkenes. As an alternative, Mn(III) complex **25** exhibits high catalytic reactivity even for the hydrohydrazination of hindered alkenes such as tetrasubstituted ones (Table 1.4).

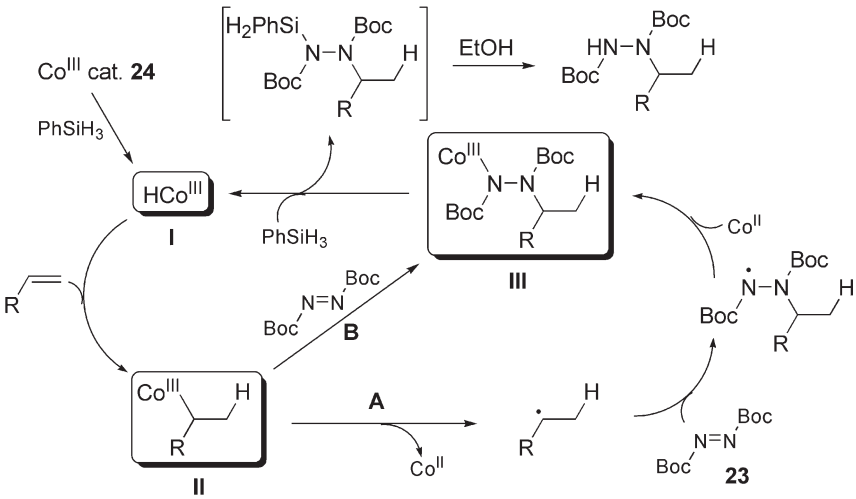
The proposed mechanism of the Co-catalyzed reaction is shown in Scheme 1.31. The first step is the formation of the active Co(III)-hydride complex **I**. From **I**, hydrocobaltation of an alkene proceeds to form Co-alkyl complex **II**. It is believed that this step is rate-determining, whereas the following amination step is fast. The crucial amination step from **II** to **III** could proceed either by radical addition to the N=N double bond (path A) or by direct insertion of the N=N double bond into the Co-alkyl complex **II** (path B). The thus generated Co-hydrazido complex **III** reacts with a silane to regenerate Co-hydride complex **I** with the formation of silylated hydrazine derivatives, which are readily transformed into the alkylated hydrazines after ethanolysis.

This Co(III) catalyst was successfully applied to the hydrohydrazination of dienes and enynes. Although a simple reaction between di-*tert*-butyl

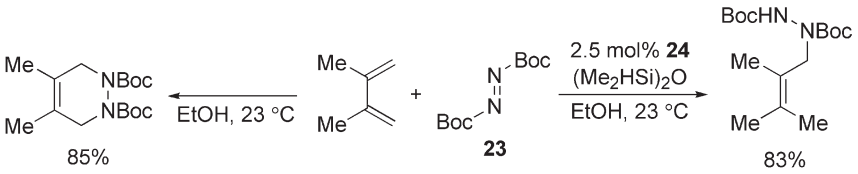
Table 1.4 Mn-catalyzed hydrohydrazination of tetrasubstituted alkenes with azodicarboxylate **23**.



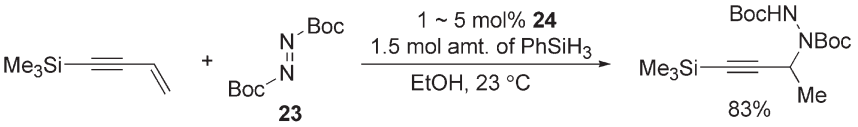
alkene	product (yield / %)	alkene	product (yield / %)
			
			



Scheme 1.31 Proposed mechanism of the hydrohydrazination of alkenes catalyzed by the Co(III) catalyst **24**.



Scheme 1.32 Hydrohydrazination of dienes catalyzed by the Co(III) catalyst **24**.



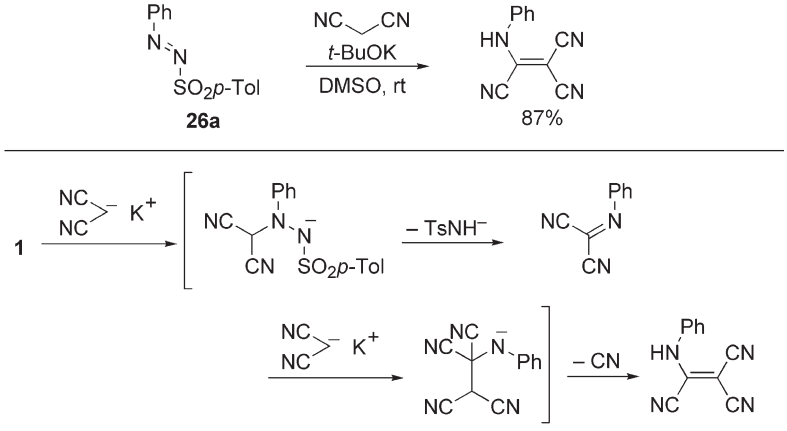
Scheme 1.33

azodicarboxylate (**23**) and 2,3-dimethyl-1,3-butadiene results in the formation of a [4+2] adduct in 85% yield at ambient temperature [35], the reaction in the presence of Co(III) catalyst **24** and tetramethyldisiloxane results in the preferential formation of allylic hydrazine in 83% yield (Scheme 1.32). The selective formation of the primary hydrazine derivative contrasts with the same reaction with alkenes, in which the formation of Markovnikov-type products was observed.

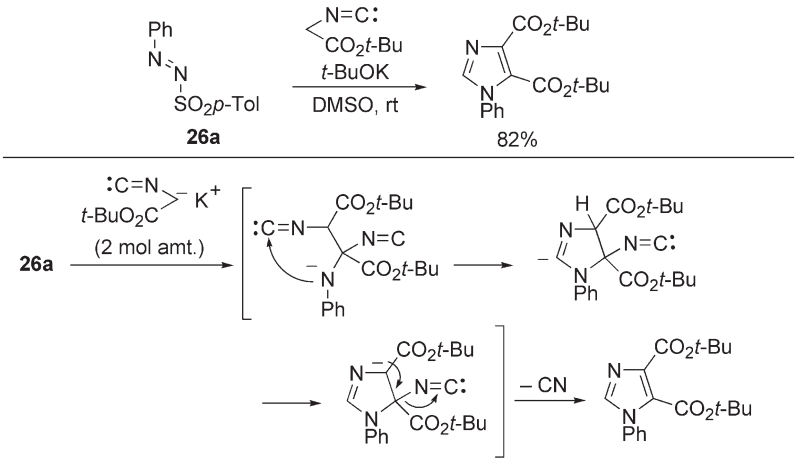
Propargylic hydrazines can be obtained from enynes through the selective amination of the double bonds (Scheme 1.33).

1.4.2
Arylazo Sulfones

Arylazo *p*-tolyl sulfones **26** (Scheme 1.34) are readily prepared from aromatic amines in a two-step sequence consisting of the formation of the corresponding



Scheme 1.34 Synthesis of tetrasubstituted ethylenes.



Scheme 1.35 Synthesis of tetrasubstituted 1-arylimidazoles.

arene diazonium salts and subsequent treatment with sodium *p*-tolyl sulfinate [36]. There are some reports on the synthesis of amino compounds by treatment of **26** with carbanions.

Potassium salts of active methylene compounds such as malononitrile react with phenylazo *p*-tolyl sulfones (**26a**) in DMSO to afford tetrasubstituted ethylenes bearing arylamino moieties (Scheme 1.34) [37]. Nucleophilic attack of the carbanion at the N=N double bond of **26a** and subsequent elimination of a tosylamide anion gives *N*-arylimines, on which a second nucleophilic attack by the carbanion proceeds to give tetrasubstituted ethylenes.

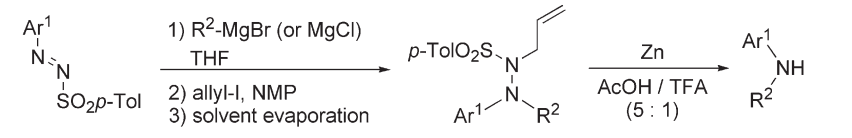
Substituted 1-arylimidazoles can be synthesized by treatment of phenylazo *p*-tolylsulfone (**26a**) with (*tert*-butoxycarbonyl)methyl isocyanides (Scheme 1.35) [38]. After double attack of the nucleophiles as described above (Scheme 1.34), intramolecular attack at the electrophilic isocyano group carbon, aromatization through proton transfer, and elimination of cyanide ion proceed successively to give imidazoles.

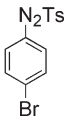
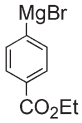
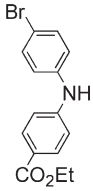
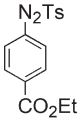
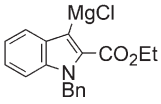
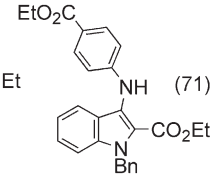
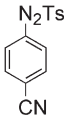
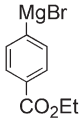
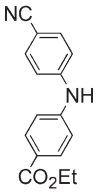
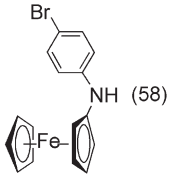
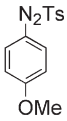
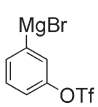
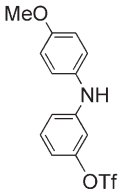
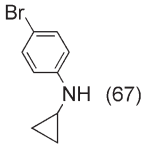
Knochel identified the utility of various arylazo *p*-tolyl sulfones **26** as synthetic equivalents of *N*-positively charged arylamine synthons. Arylazo *p*-tolyl sulfones **26** react under mild conditions with various polyfunctional arylmagnesium halides, and allylation of the resulting addition products, followed by treatment with zinc, provides polyfunctionalized diarylamines in good yield as shown in Table 1.5. Aliphatic magnesium halides are also aminated [39].

1.4.3
Experimental Procedures

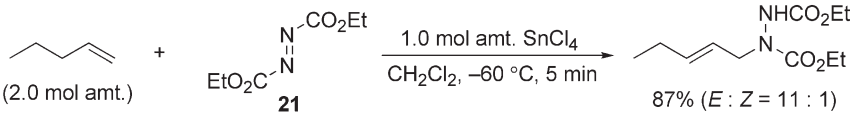
Representative procedure for the Lewis acid-mediated allylic amination of alkenes with DEAD $SnCl_4$ (0.41 mL, 3.56 mmol) was added at –60 °C to a solution of DEAD (**21**, 620 mg, 3.56 mmol) and pent-1-ene (0.78 mL, 7.12 mmol) in CH_2Cl_2. After

Table 1.5 Synthesis of diarylamines by treatment of organomagnesium compounds with aryl *p*-tolyl sulfones **26**.



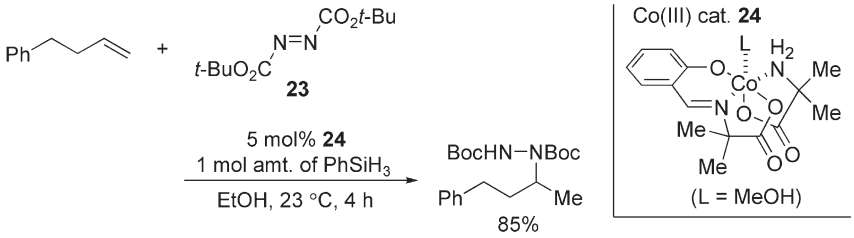
diazo reagent	R^2-MgX	product (yield / %)	diazo reagent	R^2-MgX	product (yield / %)
 **26b**		 (83)	 **26e**		 (71)
 **26c**		 (64)	**26b**		 (58)
 **26d**		 (83)	**26b**		 (67)

stirring for 5 min, the yellow solution had turned colorless and water (15 mL) was added. The organic materials were extracted with CH_2Cl_2 (3 × 50 mL), and the combined extracts were dried over Na_2SO_4. The solvents were concentrated under vacuum to afford crude materials, which were purified by flash column chromatography (silica gel, hexane/ethyl acetate 2 : 1) to give *N*-(pent-2-enyl)-*N*′-(ethoxycar bonyl)hydrazinecarboxylic acid ethyl ester (760 mg, 3.11 mmol) in 87% yield.

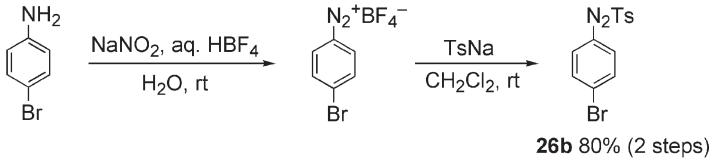


Representative procedure for the Co-catalyzed hydrohydrazination of alkenes The alkene (75 µL, 0.5 mmol) and phenylsilane (65 µL, 0.52 mmol) were added under

argon at 23 °C to the Co catalyst **24** (10 mg, 0.025 mmol) in ethanol (2.5 mL). Di-*tert*-butyl azodicarboxylate (**23**, 0.17 g, 0.75 mmol) was then added in one portion, and the resulting solution was stirred at 23 °C for 4 h. The reaction mixture was quenched with water (1 mL) and brine (5 mL) and extracted with ethyl acetate (3 × 10 mL). The solvents were removed *in vacuo* to afford crude materials, which were purified by flash column chromatography (silica gel, hexane/ethyl acetate 10 : 1) to give *N*-(3-phenyl-1-methylpropyl)-*N*′-(*tert*-butoxycarbonyl)hydrazinecarboxylic acid *tert*-butyl ester (155 mg, 0.425 mmol) in 85% yield.



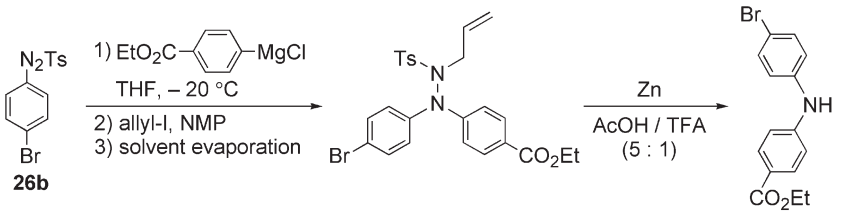
Representative preparation of arylazo tosylates: 4-bromophenylazo p-tolyl sulfone 4-Bromoaniline (1.72 g, 10 mmol) was dissolved in an aqueous HBF_4 solution (50% in water, 15 mL) and cooled to 0 °C, and then a solution of $NaNO_2$ (760 mg, 11 mmol) in water (5 mL) was added dropwise. After stirring for 30 min, the reaction mixture was allowed to warm to room temperature. The resulting white precipitate was filtered off and washed with aqueous HBF_4 solution (10 mL), ethanol (10 mL), and Et_2O (20 mL). The white crystalline powder was dissolved in CH_2Cl_2, TsNa (2.14 g, 12 mmol) was then added, the mixture was stirred overnight, and the resulting salts were removed by filtration. The solvent was removed under vacuum, and the resulting crude materials were purified by crystallization from ethanol to give 4-bromophenylazo *p*-tolyl sulfone (**26b**; 2.71 g, 8.0 mmol) in 80% yield (Scheme 1.36).



Scheme 1.36

Representative procedure for the amination of arylmagnesium reagents with arylazo tosylates A THF solution of *i*-PrMgCl (0.95 M, 1.15 mL, 1.1 mmol) was added dropwise at –20 °C to a solution of ethyl 4-iodobenzoate (306 mg, 1.1 mmol) in THF (5 mL). After the mixture had been stirred for 30 min, a solution of 4-bromophenylazo tosylate (**26b**, 339 mg, 1 mmol) in THF (3 mL) was added dropwise to the solution of the Grignard reagent, and the reaction mixture was stirred for 1 h at –20 °C. The mixture was treated with allyl iodide (510 mg, 3 mmol) and NMP

(*N*-methyl-2-pyrrolidone; 2 mL), and stirred for 2 h at room temperature. After the solvent had been removed under vacuum, the resulting residue was dissolved in glacial acetic acid (10 mL). Zn powder (10 mmol) and trifluoroacetic acid (2 mL) were added to the mixture, which was then heated at 75 °C until no starting material was evident by TLC analysis (2 h). After cooling to room temperature, the mixture was poured into crushed ice (ca. 30 g) and aqueous NaOH (2 M, 20 mL). The organic materials were extracted three times with Et_2O (30 mL) and the combined extracts were washed with saturated aqueous $NaHCO_3$ and brine. The solvent was removed *in vacuo*, and the resulting residue was purified by flash column chromatography (silica gel, pentane/Et_2O 9 : 1) to give ethyl 4-(4-bromoph enylamino)benzoate (265 mg, 0.83 mmol) in 83% yield as a colorless solid.



1.5 Oxaziridine Derivatives

Oxaziridines exhibit unique reactivity as a result of their ring strain and their relatively weak N—O bonds. They are utilized either as amination or as oxygenation reagents of nucleophiles. The site of nucleophilic attack (at the N or the O atom) in an oxaziridine is governed by the substituent at the nitrogen [40, 41].

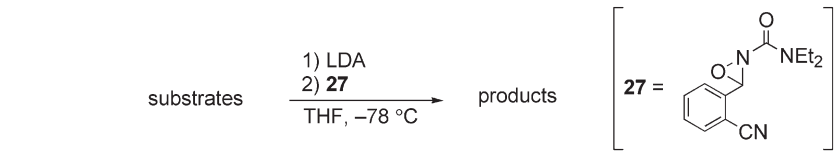
1.5.1 Electrophilic Amination of Carbon Nucleophiles

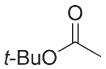
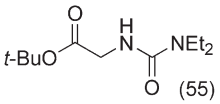
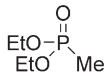
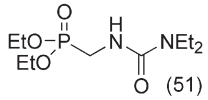
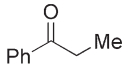
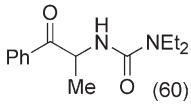
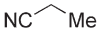
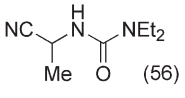
N-Alkoxy- or -aminocarbonyl oxaziridines, easily prepared by treatment of the corresponding imines with *m*CPBA/*n*-BuLi, are used as aminating reagents of enolate anions [42]. *N*-Carboxamide oxaziridine **27**, for example, is used for the α-amination of various enolate anions in good to moderate yields (Table 1.6) [43]. These *N*-transfer reactions contrast sharply with those of *N*-sulfonyloxaziridines, which give α-hydroxylated product exclusively [40].

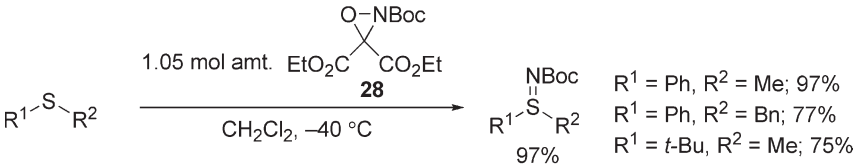
1.5.2 Amination of Allylic and Propargylic Sulfides by Use of a Ketomalonate-Derived Oxaziridine

Armstrong found that amination of sulfides proceeded with the oxaziridine **28**, derived from 2-oxomalonate, to afford a wide range of sulfimides (Scheme 1.37) [44].

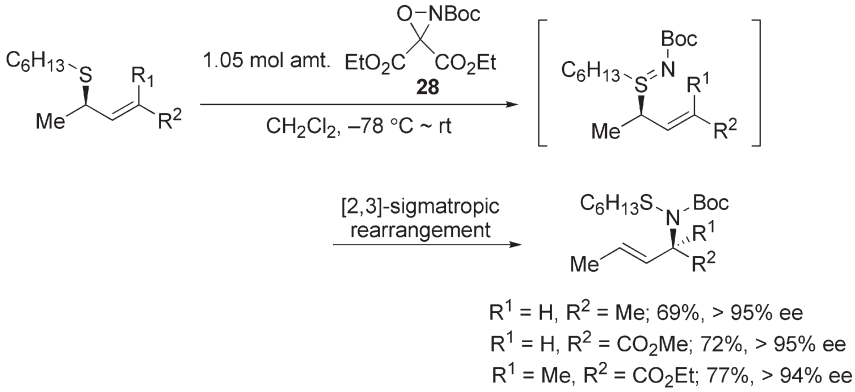
Table 1.6 Electrophilic amination of lithium enolates with oxaziridine **27**.



substrates	products (yield / %)	substrates	products (yield / %)
	 (55)		 (51)
	 (60)		 (56)



Scheme 1.37



Scheme 1.38 Synthesis of allylic amine derivatives by the [2,3]-sigmatopic rearrangement of allylic sulfides.

By this method, allyl amine derivatives are prepared from allylic sulfides through the rapid [2,3]-sigmatropic rearrangement of the resulting sulfimides (Scheme 1.38). A high level of chirality transfer is observed in this rearrangement and a quaternary stereocenter is successfully constructed [45].