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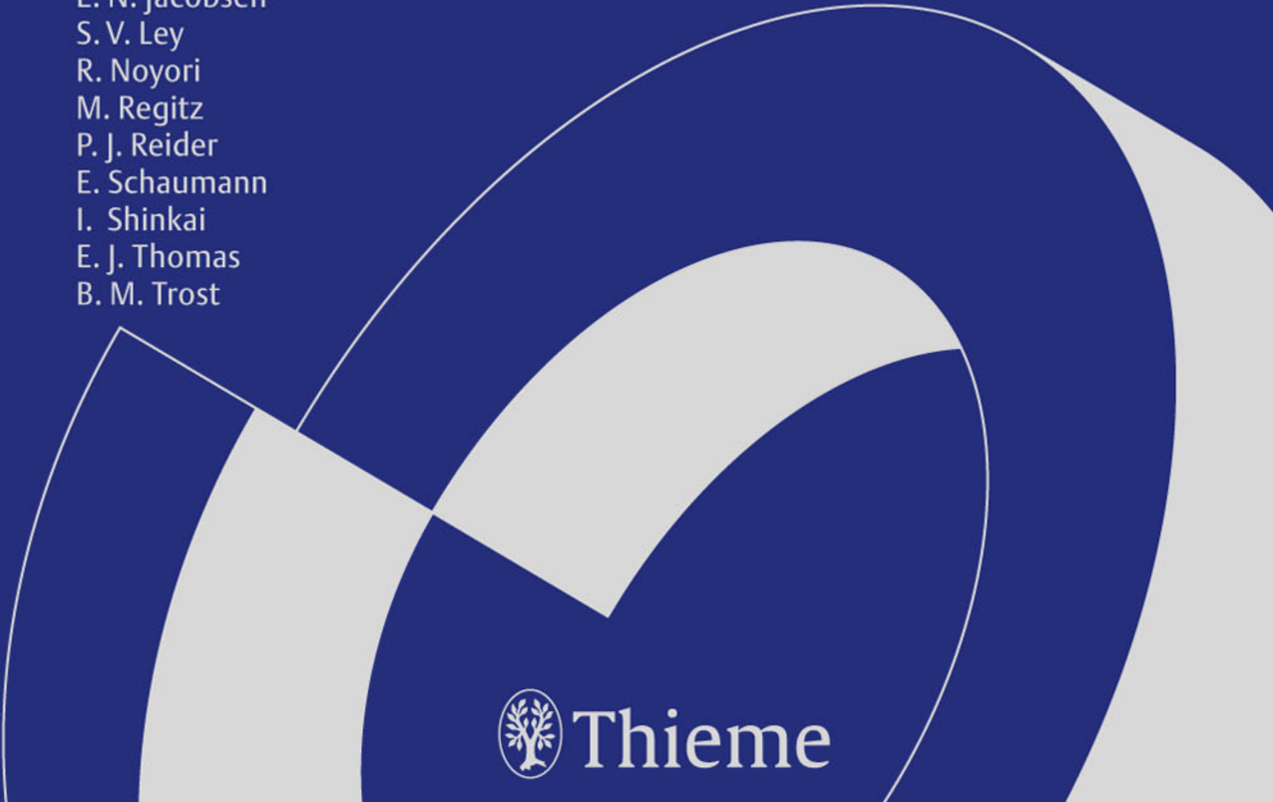
Science of Synthesis

Compounds with Four and Three Carbon—Heteroatom Bonds

Three Carbon—Heteroatom Bonds:
Nitriles, Isocyanides, and Derivatives

Volume Editor
S.-I. Murahashi



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Category 3 **Compounds with Four and Three Carbon—Heteroatom Bonds**

Volume 19 **Three Carbon—Heteroatom Bonds: Nitriles, Isocyanides, and Derivatives**

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2004
Georg Thieme Verlag
Stuttgart · New York

Rüdigerstrasse 14
D-70469 Stuttgart

Printed in Germany

Typesetting: Ziegler + Müller, Kirchentellinsfurt
Printing: Gulde Druck, Tübingen
Binding: J. Spinner, Ottersweier

Bibliographic Information published by
Die Deutsche Bibliothek

Die Deutsche Bibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data is available on the internet at <http://dnb.ddb.de>

Library of Congress Cataloging in Publication Data

Science of synthesis : **Houben–Weyl** methods of molecular transformations.
p. cm.
Includes bibliographical references and index.
Contents: category 3. Compounds with Four and Three Carbon—Heteroatom Bonds. v. 19 Three Carbon—Heteroatom Bonds: Nitriles, Isocyanides, and Derivatives / volume editor, S.-I. Murahashi
ISBN 3-13-118691-7 – ISBN 1-58890-196-3 (v. 19)
1. Organic compounds–Synthesis. I. Title: **Houben–Weyl** methods of molecular transformations.
QD262 .S35 2000
547'.2–dc21
00-061560

(**Houben–Weyl methods of organic chemistry**)

British Library Cataloguing in Publication Data

Science of Synthesis : **Houben–Weyl** methods
of molecular transformations.
Category 3: Compounds with Four and Three Carbon—Heteroatom Bonds: Vol. 19: Three Carbon—Heteroatom Bonds: Nitriles, Isocyanides, and Derivatives. –
(**Houben–Weyl methods of organic chemistry**)
1. Organic compounds – Synthesis 2. Organic compounds – Laboratory manuals
I. Murahashi, S.-I., II. Bergsträßer, U.
547.2

ISBN 3-13-118691-7
(Georg Thieme Verlag, Stuttgart)
ISBN 1-58890-196-3
(Thieme New York)

Date of publication: September 22, 2004

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Preface

As our understanding of the natural world increases, we begin to understand complex phenomena at molecular levels. This level of understanding allows for the design of molecular entities for functions ranging from material science to biology. Such design requires synthesis and, as the structures increase in complexity as a necessity for specificity, puts increasing demands on the level of sophistication of the synthetic methods. Such needs stimulate the improvement of existing methods and, more importantly, the development of new methods. As scientists confront the synthetic problems posed by the molecular targets, they require access to a source of reliable synthetic information. Thus, the need for a new, comprehensive, and critical treatment of synthetic chemistry has become apparent. To meet this challenge, an entirely new edition of the esteemed reference work **Houben–Weyl Methods of Organic Chemistry** will be published starting in the year 2000.

To reflect the new broader need and focus, this new edition has a new title, **Science of Synthesis, Houben–Weyl Methods of Molecular Transformations**. **Science of Synthesis** will benefit from more than 90 years of experience and will continue the tradition of excellence in publishing synthetic chemistry reference works. **Science of Synthesis** will be a balanced and critical reference work produced by the collaborative efforts of chemists, from both industry and academia, selected by the editorial board. All published results from journals, books, and patent literature from the early 1800s until the year of publication will be considered by our authors, who are among the leading experts in their field. The 48 volumes of **Science of Synthesis** will provide chemists with the most reliable methods to solve their synthesis problems. **Science of Synthesis** will be updated periodically and will become a prime source of information for chemists in the 21st century.

Science of Synthesis will be organized in a logical hierarchical system based on the target molecule to be synthesized. The critical coverage of methods will be supported by information intended to help the user choose the most suitable method for their application, thus providing a strong foundation from which to develop a successful synthetic route. Within each category of product, illuminating background information such as history, nomenclature, structure, stability, reactivity, properties, safety, and environmental aspects will be discussed along with a detailed selection of reliable methods. Each method and variation will be accompanied by reaction schemes, tables of examples, experimental procedures, and a background discussion of the scope and limitations of the reaction described.

The policy of the editorial board is to make **Science of Synthesis** the ultimate tool for the synthetic chemist in the 21st century.

We would like to thank all of our authors for submitting contributions of such outstanding quality, and, also for the dedication and commitment they have shown throughout the entire editorial process.

The Editorial Board October 2000

Volume 19:
Three Carbon—Heteroatom Bonds:
Nitriles, Isocyanides, and Derivatives

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Introduction

S.-I. Murahashi

This volume covers the synthesis of compounds with three carbon—heteroatom bonds which include nitrile oxides, nitrile sulfides, nitrile imines, nitrilium salts, nitrile ylides, nitriles, phosphaalkynes, and carbon- and heteroatom-bound isocyanides. These are shown in Table 1, together with the sections in which they appear.

Table 1 Structures and Nomenclature for the Three Carbon—Heteroatom Bond Containing Compounds Covered in Volume 19

Product Class	Structural Formula	Section
nitrile oxides	$R^1C{\equiv}N^+{-}O^-$	19.1.1
nitrile sulfides	$R^1C{\equiv}N^+{-}S^-$	19.1.2
nitrile imines	$R^2C{\equiv}N^+{-}N^-R^1$	19.2
nitrilium salts	$R^2C{\equiv}N^+{-}R^1$	19.3
nitrile ylides	$R^2C{\equiv}N^+{-}C^-R^1$	19.4
nitriles	$R^1C{\equiv}N$	19.5
phosphaalkynes	$R^1C{\equiv}P$	19.6
isocyanides	$R^1N{=}C$	19.7.1
heteroatom-bound isocyanides	$YN{=}C$ (Y = N, S, O, P)	19.7.2

References to reviews on these specific functional groups are given in each section. Discussion of each specific group is generally subdivided into methods that have been selected as the most useful for the preparation of the product class or subclass in question. Each method is presented separately as follows:

1. Introduction: comparison with other methods.
2. Presentation of the scope of the method to include background, discussion of representative examples, safety; mechanistic information where relevant to the use of the method in synthesis; a table of examples (for selected methods); reaction schemes.
3. Representative experimental procedures.

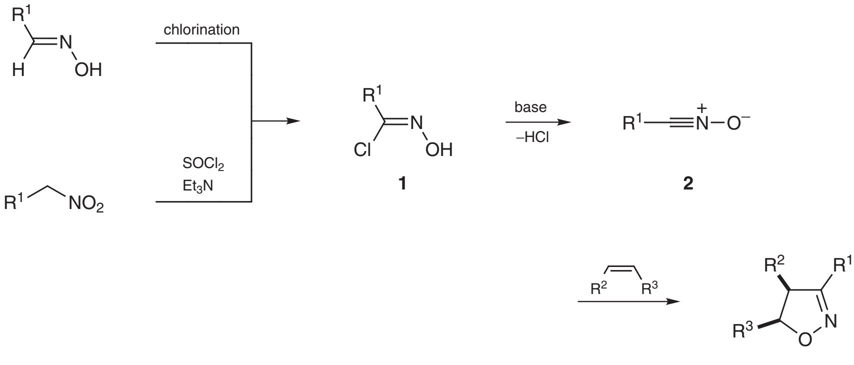
In some cases, methods are further subdivided into variations on a method, each variation being presented according to the above format.

The coverage is not exhaustive, rather the most useful and reliable methods for the synthesis of each functional group have been selected. In some cases, methods that are recommended for limited use, or that have not yet been fully developed, are listed at the end of a section for reference. Tables and representative experimental procedures are given to illustrate the applicability of each approach.

This introduction will outline the individual product classes together with highlighted synthetic methods.

Nitrile oxides are 1,3-dipoles containing the same array of atoms in the functional group as nitrones, but at one oxidation level higher. Nitrile oxides **2** are readily prepared, mainly from hydroximoyl halides **1**, which are obtained through the halogenation of aldoximes with a variety of halogenating reagents[1] or by treatment of activated nitroalkanes with thionyl chloride in the presence of triethylamine (Scheme 1).[2] As they are difficult to isolate and store, nitrile oxides are normally generated in the presence of a reactive dipolarophile, giving the appropriate adduct directly; however, some nitrile oxides with bulky substituents are stable. Cycloaddition to a substituted ethene proceeds regioselectively, and the products are highly useful as precursors for a variety of other compounds and their functionality is readily unmasked. Typically, metal ion promoted cycloadditions to give dihydroisoxazoles **3** are highly useful reactions (Scheme 1). Stereospecific syntheses of dihydroisoxazoles can be achieved using effective chiral auxiliaries and metal ions. Typically, in the presence of magnesium ions the cycloaddition of nitrile oxides to allylic alcohols proceeds in a highly *syn*-selective manner when α-chiral dipolarophiles are used.[3]

Scheme 1 Synthesis of Nitrile Oxides from Hydroximoyl Halides and Stereospecific 1,3-Dipolar Addition to Alkenes[2–4]



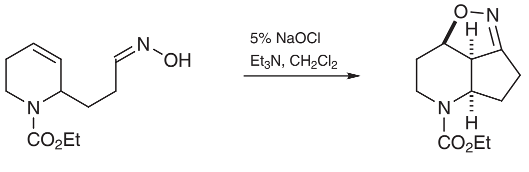
1

2

3

Nitrile oxides can also be prepared directly by oxidation of aldoximes with sodium hypochlorite or *N*-bromosuccinimide in the presence of a base such as triethylamine. Such oxidations are normally combined with cycloaddition reactions with a suitable dipolarophile already present in the same pot. One typical example is the intramolecular cycloaddition of an aldoxime to give tricycle **4**, which contains the ring skeleton of natural product streptazolin (Scheme 2).[5]

Scheme 2 Direct Synthesis of a Nitrile Oxide and Its Application in the Partial Synthesis of Streptazolin[5]

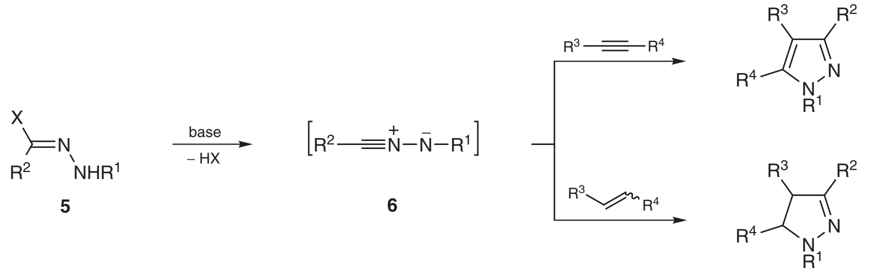


4

Nitrile sulfides are unstable and it is impossible to isolate them. Nitrile sulfides are generated by the thermal decomposition of five-membered heterocyclic compounds, such as 1,3,4-oxathiazol-2-one, and trapped immediately with a suitable dipolarophile, thereby providing access to several classes of heterocycles that are obtained only with difficulty by other means.

Nitrile imines **6**, which can be generated by the base-induced dehydrohalogenation of stable hydrazonoyl halides **5**, are trapped by a variety of 1,3-dipolarophiles such as alkenes and alkynes to afford 4,5-dihydropyrazoles and pyrazoles, respectively (Scheme 3).[6,7]

Scheme 3 Generation of Nitrile Imines from Hydrazonoyl Halides and Entrapment with Alkenes and Alkynes[6,7]



Nitrilium salts are intermediates in a number of reactions that include the Beckmann rearrangement producing amides from oximes,[8,9] the Ritter reaction producing amides from alcohols and nitriles,[10–12] the von Braun amide degradation reaction producing alkyl halides and nitriles,[13] the Bischler–Napieralski reaction producing dihydroisoquinolines and related ring-fused imines from amides and arenes,[13] the Hoesch acylation reaction from arenes and nitriles,[14] the Gattermann formylation reaction of arenes and hetarenes,[15] and the Schmidt reaction producing amides from ketones and hydrazoic acid.[16] In most cases, the nitrilium ions are formed and reacted instantly, but stable nitrilium salts can be isolated. The acid-mediated dehydration of oximes is better known as the Beckmann rearrangement. N-Alkylation of nitriles provides one of the most convenient and direct routes to nitrilium salts. Nitrilium salts are also prepared by the interaction of alkyl chloroformates with Lewis acid complexes of nitriles.

Nitrile ylides are 1,3-dipoles and can be prepared by several methods[7,17] including the elimination of hydrogen chloride from imidoyl chlorides, the reaction of carbenes and carbenoids with nitriles, and the photochemical ring opening of aziridines. Pyrroles and dihydropyrroles are obtained by the 1,3-dipolar cycloaddition of nitriles ylides with alkynes and alkenes.

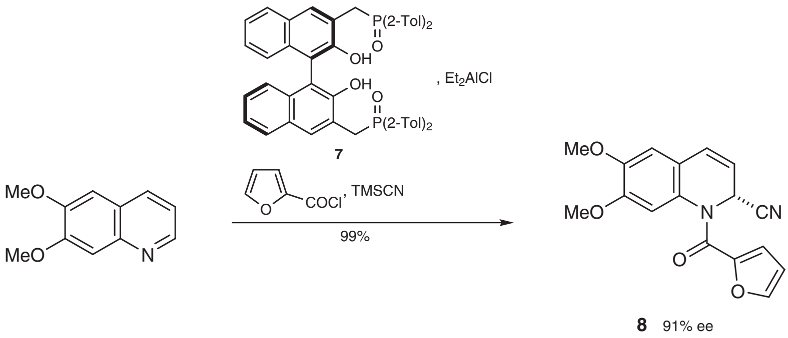
Nitriles are an extremely important class of compounds in organic synthesis. Nitriles have a strong dipole, oriented with the negative end toward the nitrogen, and the cyano group is recognized as a powerful electron-withdrawing substituent. Nitriles have unique properties, and thus various reactions for the synthesis and the unique transformations of nitriles have been developed.

A typical method for the synthesis of nitriles is the construction of the cyano group by functional group transformation from various starting materials, such as aldehydes, carboxylic acids and their derivatives, hydrazones, aldoximes, carboxamides, and thioamides.[18–20]

The oxidation of hydrazones and aldoximes are important synthetic routes to nitriles, although the direct conversion of aldehydes in a one-pot reaction can be carried out by oxidation of the in situ formed aldimines. One of the most typical transformations is the preparation of nitriles by nucleophilic substitution of alkyl, allyl, and benzyl halides (at the sp^3-carbon—halogen bonds) with various cyanide reagents.[21,22] Substitution at the sp^2-carbon—halogen bonds is very difficult; however, the palladium-catalyzed coupling reaction of *Z*- and *E*-vinyl halides with sodium cyanide in the presence of 18-crown-6 was introduced in 1977 as the first transition-metal-catalyzed cyanation reaction of sp^2-carbon—halogen bonds to give *Z*- and *E*-vinyl cyanides stereospecifically.[23] This reaction led to the discovery of palladium- and nickel-catalyzed cyanations of aryl halides and vinyl and aryl trifluoromethanesulfonates. The conversion of the aryl chlorides into aryl cyanides is very convenient.[24]

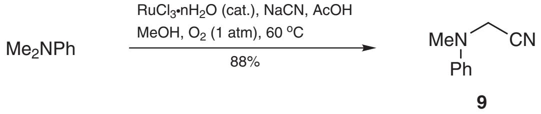
Aromatic and heteroaromatic nitriles can be prepared by direct cyanation of aromatic and heteroaromatic compounds with cyanogen bromide or trichloroacetonitrile in the presence of Friedel–Crafts catalysts.[25] Heterocyclic *N*-oxides such as pyridine, quinone, pyrazine, pyrimidine, quinoxaline, or isoquinoline *N*-oxide undergo reaction with trimethylsilyl cyanide in the presence of a base to give the cyanation products directly. The reactions of pyridine 1-oxide with dimethylcarbamoyl chloride and trimethylsilyl cyanide give the corresponding carbonitriles in excellent yields (modified Reissert–Henze reaction).[26] Catalytic asymmetric Reissert-type reactions of quinoline and isoquinoline derivatives using a Lewis acid–Lewis base bifunctional catalyst are highly useful; for example, with a catalyst obtained from ligand **7** and diethylaluminum chloride,[27] 1-(2-furylcarbonyl)-6,7-dimethoxy-1,2-dihydroquinoline-2-carbonitrile (**8**) is obtained in 91% ee (Scheme 4).

Scheme 4 Aluminum-Catalyzed Asymmetric Reissert-Type Reaction of a Quinoline[27]



Direct cyanation of the sp-C—H bond of acetylenes is performed by treatment with copper(I) cyanide and chlorotrimethylsilane,[28] or butyllithium and phenyl cyanate.[29] Direct cyanation of the sp^3-C—H bond is extremely difficult; however, aerobic oxidative cyanation of tertiary amines with sodium cyanide has been demonstrated. Thus, the treatment of *N*,*N*-dimethylaniline with catalytic ruthenium(III) chloride hydrate and sodium cyanide under molecular oxygen (1 atm) gives α-cyanated amine **9** (Scheme 5), which is the precursor of amino acids and 1,2-diamines, in excellent yields. The direct C—H activation of an amine α to nitrogen with a ruthenium catalyst forms the intermediate iminium ion and this is the key step of this interesting reaction.[30]

Scheme 5 Aerobic Ruthenium-Catalyzed Oxidative Cyanation of a Tertiary Amine with Sodium Cyanide[30]



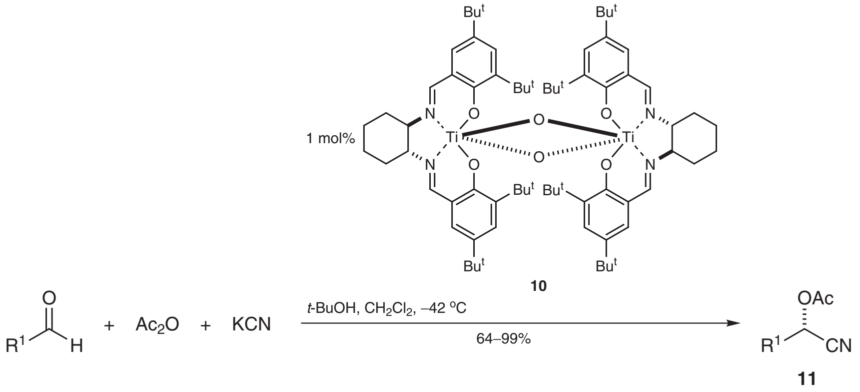
Introduction of the cyano group by substitution of the metals in organometallic compounds can also be used for nitrile synthesis. Typically, the substitution reaction of organozinc or copper compounds with tosyl cyanide is highly useful.[31]

Nitriles can also be synthesized by the transformation of other substrates such as amines, alcohols, and nitro compounds. The oxidative transformation of primary amines to nitriles is performed by aerobic oxidation of primary amines in the presence of a hydroxyapatite-bound ruthenium complex [Ru-HAP(II)], which is prepared by mixing calcium hydroxyapatite [$Ca_{10}(PO_4)_6(OH)_2$] with aqueous ruthenium(III) chloride.[32]

The synthesis of cyanohydrins and especially the asymmetric synthesis of these compounds are extremely important; therefore, many methods have been developed.[33] The cyanohydrins of aldehydes are prepared upon treatment with potassium or sodium cyanide/18-crown-6, acetone cyanohydrins with a metal complex catalyst, and trimethylsilyl cyanide with a catalyst. The most significant advances in the area of cyanohydrin chemistry since 1985 have been the development of catalysts for the asymmetric addition of cyanide to aldehydes. The reaction can be induced by a variety of catalysts, of which enzymes, synthetic peptides, and chiral metal complexes are the three most common.[34–38]

The cyclic dipeptide containing histidine residue catalyzes the asymmetric addition of hydrogen cyanide to benzaldehyde, giving optically active mandelonitrile with up to 90% ee.[39] A number of organometallic reagents based on chiral complexes of titanium,[40–42] aluminum, lanthanide,[41,43,44] and other metals[45] have been found to catalyze the asymmetric addition of hydrogen cyanide or trimethylsilyl cyanide to aldehydes. Typically, the chiral titanium–salen complex **10** catalyzes the asymmetric addition of potassium cyanide and acetic anhydride to aldehydes affording the cyanohydrin acetates **11** with high enantioselectivities (Scheme 6).

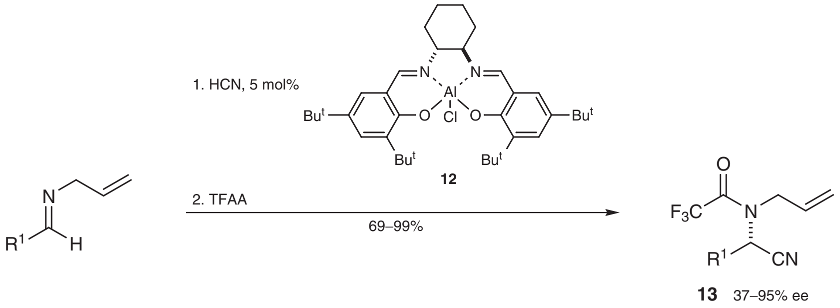
Scheme 6 Titanium-Catalyzed Asymmetric Addition of Potassium Cyanide and Acetic Anhydride to Aldehydes[43,44]



The Strecker reaction is a three-component condensation reaction between a carbonyl compound, an amine, and a cyanide to produce an α-aminonitrile. The reaction proceeds via in situ formation of an imine, followed by addition of cyanide to the imine.

The asymmetric addition of cyanide to imines is important in organic synthesis.[46–50] The enantioselective addition of hydrogen cyanide or trimethylsilyl cyanide to imines in the presence of a chiral catalyst such as a cyclic dipeptide,[51] or an aluminum,[52,53] titanium,[54] or zirconium[55] complex is very important in the synthesis of optically active α-aminonitriles. Typically, enantioselective addition of hydrogen cyanide to imines gives aminonitriles **13** using 5 mol% of the chiral aluminum–salen complex **12** (Scheme 7).[52]

Scheme 7 Enantioselective Addition of Hydrogen Cyanide to Imines Catalyzed by a Chiral Aluminum–Salen Complex[52]

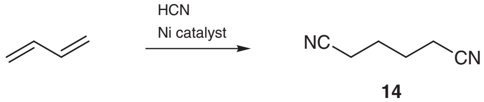


Hydrocyanation of α,β-unsaturated carbonyl compounds and related compounds is performed upon treatment with diethylaluminum cyanide (prepared from HCN and Et_3Al), trimethylsilyl cyanide and a Lewis acid, or acetone cyanohydrin. Hydrogen cyanide itself is normally incapable of adding to Michael acceptors.

The hydrocyanation of alkynes is a very important and useful process since it generates highly versatile α,β-unsaturated nitriles from easily accessible starting materials. The tetrakis(triphenyl phosphite)nickel(II)-catalyzed hydrocyanation of diphenylacetylene gives 1,2-diphenylethanenitrile selectively.[56,57]

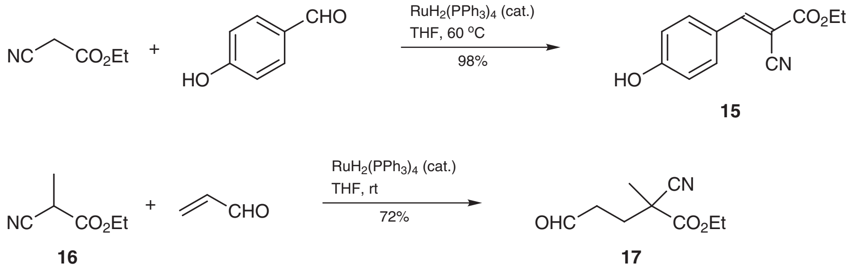
The Dupont process for the synthesis of adiponitrile (hexanedinitrile, **14**) from buta-1,3-diene is the most important application of hydrocyanation. The overall reaction consists of three stages, the first being the synthesis of a mixture of pent-3-enenitrile and 2-methylbut-3-enenitrile (7:3) by the nickel-catalyzed addition of 1 equivalent of hydrogen cyanide to buta-1,3-diene. The isomeric nitriles are separated by distillation, and the unwanted branched product is isomerized in a second step using a similar nickel(0) catalytic system in the presence of a Lewis acid. In the final part of the process, the mixture of unbranched pentenenitriles is isomerized and concomitantly hydrocyanated resulting in the product adiponitrile (**14**) with selectivities of up to 90% (Scheme 8).[58–60]

Scheme 8 Nickel-Catalyzed Hydrocyanation of Buta-1,3-diene To Give Adiponitrile[58–60]



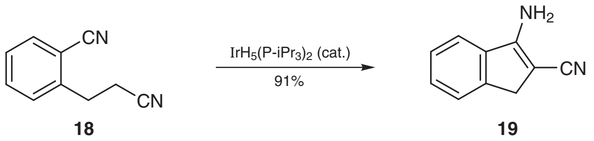
There are many methods for the synthesis of nitriles from other nitriles with retention of the cyano group. The reactions of α-cyano carbanions with electrophiles are one of the fundamental synthetic routes to nitriles, which include reaction with alkyl halides, epoxides, the aldol reaction, the Knoevenagal reaction, the Michael reaction, and the Thorpe–Ziegler reaction. Usually α-cyano carbanions can be generated upon treatement of nitriles with strong bases such as lithium diisopropylamide and potassium *tert*-butoxide; however, C—H activation α to the nitrogen of nitriles with a low-valent transition-metal catalyst such as dihydridotetrakis(triphenylphosphine)ruthenium(II) is highly useful. The aldol reaction, the Knoevenagel reaction, and the Michael reaction of nitriles can be carried out in a highly selective manner with low-valent transition-metal complexes such as dihydridotetrakis(triphenylphosphine)ruthenium(II) as the redox Lewis acid catalyst under neutral and mild reaction conditions.[61,62] Typically, the reaction of ethyl cyanoacetate with 4-hydroxybenzaldehyde gives the product **15** in 98% yield (Scheme 9). The reaction can be carried out under neutral conditions and acidic substrates are tolerated in the reaction. Another example is the Michael addition of ethyl 2-cyanopropanoate (**16**) to a base-sensitive substrate of prop-2-enal to give **17** (Scheme 9). These reactions provide nonsalt processes that are environmentally benign.[63]

Scheme 9 Ruthenium-Catalyzed Aldol Condensation and Michael Addition[61,62]



The Thorpe–Ziegler reaction has been carried out using a stoichiometric amount of a strong base, such as sodium hydride, to give aminonitriles from dinitriles; however, pentahydridobis(triisopropylphosphine)iridium(V) can be used instead of a strong base, and the catalytic reaction of **18** can be carried out to give **19** under neutral conditions (Scheme 10).[64]

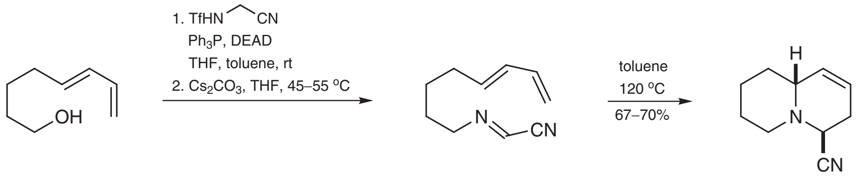
Scheme 10 Iridium-Catalyzed Thorpe–Ziegler Condensation of a Nitrile[64]



Conjugate additions of reactive nucleophiles to alkenes or alkynes are important C—C and carbon—heteroatom bond-forming reactions for making a variety of nitriles.[65,66] Various nucleophiles such as oxo enolates, ester enolates, enamines, metalated nitriles, metalated nitroalkanes, organometallic compounds, allylsilanes, thiols, and amines add to alkenenitriles selectively to give numerous nitrile compounds.

[2+2] Cycloaddition, 1,3-dipolar cycloaddition, and the Diels–Alder reaction are convenient for the stereoselective synthesis of cyclic compounds bearing a nitrile. Iminoacetonitriles, which are readily prepared from alcohols, are useful azodienophiles for intramolecular hetero-Diels–Alder reactions (Scheme 11).[67]

Scheme 11 Aza-Diels–Alder Reaction of an Iminoacetonitrile[67]

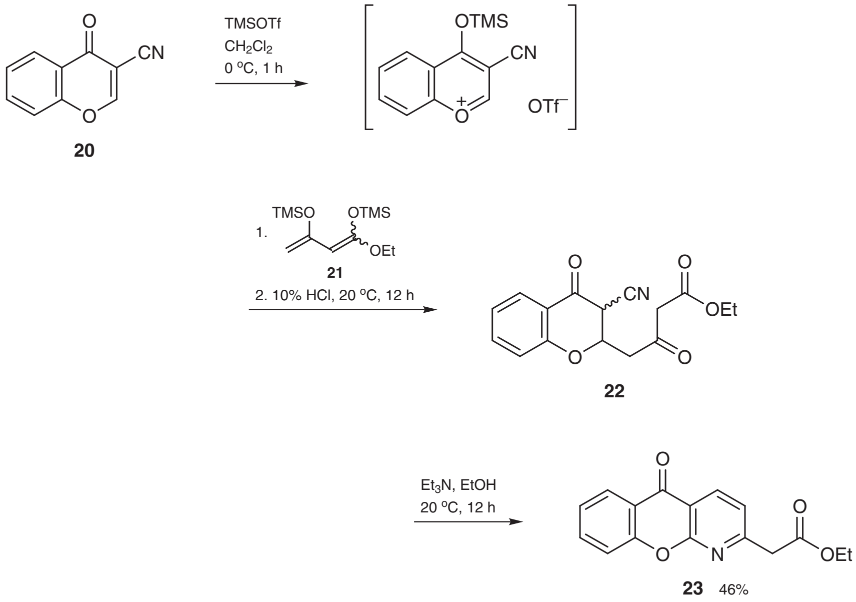


The Heck–Mizoroki reaction, palladium- and nickel-catalyzed cross-coupling reactions with various organometallic compounds, and palladium-catalyzed reactions of allyl esters are extremely useful for the synthesis of nitrile compounds, especially alkenenitriles.

Nitriles have unique properties, and, therefore, various transformations of nitriles have been developed. Functional group transformations of nitriles to amines, imines, aldehydes, ketones, amides, amidines, amidrazones, imidates, and carboxylic acids are widely known, and these transformations have been described in sections of other volumes within *Science of Synthesis*.

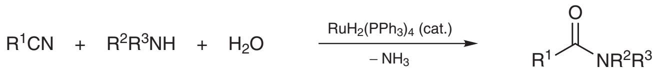
The applications of nitriles in the construction of more complex molecules are also described in this volume. Three-component reactions, one-pot cyclization, cycloaddition, and domino reactions are often used for the synthesis of various heterocyclic compounds. Typically, the reaction of **20** with trimethylsilyl trifluoromethanesulfonate, followed by disiloxydiene **21** affords the open-chain product **22**. Treatment of **22** with triethylamine affords the benzopyrano[2,3-*b*]pyridine **23** (Scheme 12).[68]

Scheme 12 Reaction of 4-Oxo-4*H*-1-benzopyran-3-carbonitrile with a Disiloxy-1,3-diene[68]



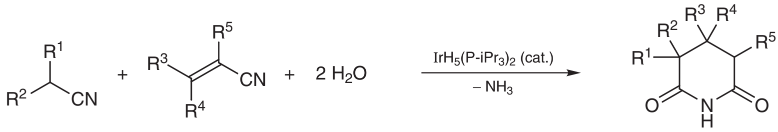
One of the unique properties of nitriles is their ability to strongly coordinate to metals. Using this property, new types of practical catalytic reactions of nitriles have been developed. Typically, the ruthenium-catalyzed reaction of amines, nitriles, and water under neutral reaction conditions to give amides and ammonia is an extremely useful reaction which can also be applied to the synthesis of polyamides from diamines and dinitriles (Scheme 13).[63,69]

Scheme 13 Ruthenium-Catalyzed Amidation of Nitriles with Amines and Water[69]



A novel three-component reaction involving nitriles, alkenenitriles, and water in the presence of pentahydridobis(triisopropylphosphine)iridium(V) as a Lewis acid and base ambiphilic catalyst affords glutarimides **24**, which are versatile intermediates in the synthesis of biologically active compounds (Scheme 14).[64]

Scheme 14 Iridium-Catalyzed Three-Component Reaction of Nitriles, Alkenenitriles, and Water To Give Glutarimides[64]

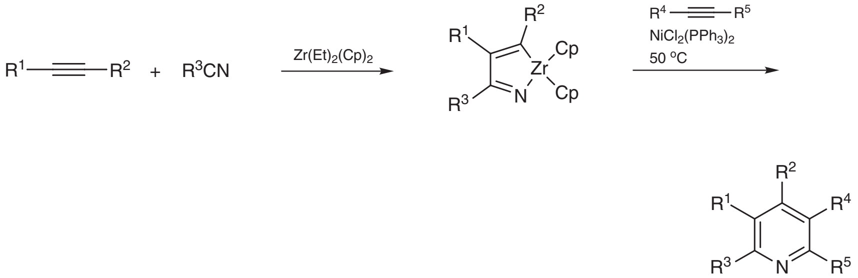


24

A wide range of pyridines have been prepared by the [2+2+2] cyclotrimerization of nitriles and alkynes. Cobalt complexes are the most common catalysts.[70] The complex fused heterocycles can be prepared using cobalt-catalyzed cycloaddition reactions.[71]

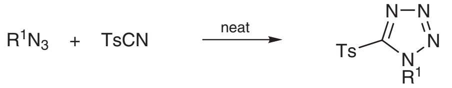
Two alternative approaches to the cyclotrimerization were reported, although both result in the formation of a stoichiometric transition-metal species. Thus, titanium(II) alkoxide [prepared in situ from $Ti(OiPr)_4$ and iPrMgCl][72] and bis(η^5-cyclopentadienyl)(diethyl)zirconium(IV)[73] promote this type of reaction (Scheme 15).

Scheme 15 Zirconium-Mediated Pyridine Synthesis[73]



Demko and Sharpless demonstrated the formation of substituted tetrazoles from nitriles and azides by heating neat tosyl cyanide with an unhindered azide, giving quantitative conversion into the 1-substituted 5-tosyltetrazole **25** (Scheme 16), which can be readily elaborated by nucleophilic substitution of the tosyl group.[74] This is a "click chemistry" transformation in that no solvent is required.

Scheme 16 The "Click Chemistry" Approach to Tetrazoles[74]



25

Phosphaalkynes are unstable molecules, and their chemistry resembles that of alkynes rather than nitriles. The P≡C bond system shows a pronounced tendency to undergo cycloaddition and cyclooligomerization reactions.

Methylidynephosphine (**26**), ethylidynephosphine (**27**), and fluoromethylidynephosphine (**28**) (Scheme 17) can be generated and characterized, but must be stored under dry argon at low temperature.[75]