1
Chiral Nonracemic Isocyanides

Luca Banfi, Andrea Basso, and Renata Riva

1.1
Introduction

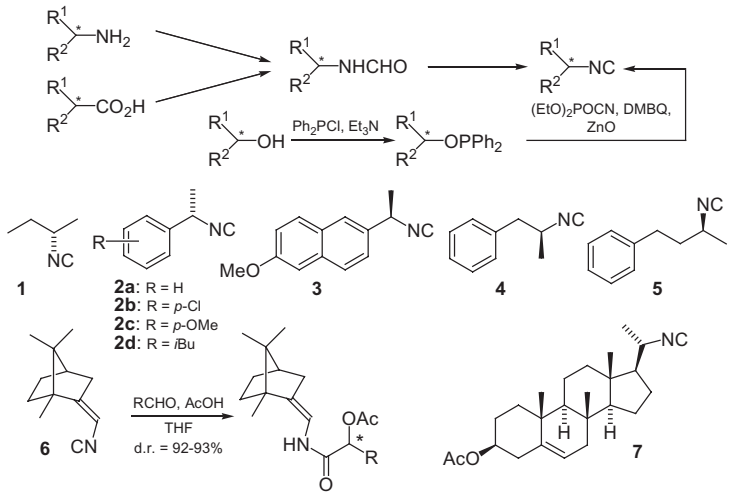
Although isocyanides have proven to be very useful synthetic intermediates – especially in the field of multicomponent reactions – most research investigations performed to date on isocyanides have involved commercially available, unfunctionalized and achiral (or chiral racemic) compounds. Two reasons can be envisioned for the infrequent use of enantiomerically pure isocyanides: (i) the general lack of asymmetric induction produced by them; and (ii) the high tendency to lose stereochemical integrity in some particular classes of isonitriles. However, it is believed that when these drawbacks are overcome, the use of chiral nonracemic isocyanides in multicomponent reactions can be very precious, allowing a more thorough exploration of diversity (in particular stereochemical diversity) in the final products. Recently, several reports have been made describing the preparation and use of new classes of functionalized chiral isocyanides. In fact, several chiral isocyanides may be found in nature, and these will be briefly described in Section 1.5, with attention focused on their total syntheses. Another growing application of chiral isocyanides is in the synthesis of chiral helical polyisocyanides.

It is hoped that this review will encourage chemists first to synthesize a larger number of chiral isocyanides, and subsequently to exploit them in multicomponent reactions, in total synthesis, and in the material sciences.

1.2
Simple Unfunctionalized Isocyanides

The standard method used to prepare chiral isocyanides (whether functionalized, or not) begins from the corresponding amines, and employs a two-step sequence of formylation and dehydration (Scheme 1.1). Many enantiomerically pure amines are easily available from natural sources, classical resolution [1], or asymmetric synthesis. Formylation is commonly achieved via four general

Isocyanide Chemistry: Applications in Synthesis and Material Science, First Edition. Edited by Valentine Nenajdenko.



Scheme 1.1

methods: (i) refluxing the amine in ethyl formate [2]; (ii) reacting the amine with the mixed formic–acetic anhydride [2]; (iii) reacting the amine with formic acid and DCC (dicyclohexylcarbodiimide) [3] or other carbodiimides [4]; and (iv) reacting the amine with an activated formic ester, such as cyanomethyl formate [5], *p*-nitrophenyl formate [6], or 2,4,5-trichlorophenyl formate [7]. For the dehydration step, several reagents are available, with the commonest and mildest methods involving $POCl_3$, diphosgene, or triphosgene at low temperatures in the presence of a tertiary amine [2]. Although less commonly used, Burgess reagent (methyl *N*-(triethylammoniumsulfonyl)carbamate) [8] and the $CCl_4/PPh_3/Et_3N$ system [7] have also been employed.

Alternatively, formamides can be obtained from chiral carboxylic acids, through a stereospecific Curtius rearrangement followed by reduction of the resulting isocyanate [9, 10].

Isocyanides may also be prepared from alcohols, by conversion of the alcohol into a sulfonate or halide, followed by S_N2 substitution with AgCN [11]; however, this method works well only with primary alcohols. In contrast, a series of chiral isocyanides have been synthesized from chiral secondary alcohols via a two-step protocol that involves conversion first into diphenylphosphinite, followed by a stereospecific substitution that proceeds with a complete inversion of configuration [12]. The substitution step is indeed an oxidation–substitution, that employs dimethyl-1,4-benzoquinone (DMBQ) as a stoichiometric oxidant and ZnO as an additive. Alternatively, primary or secondary alcohols can be converted into formamides through the corresponding alkyl azides and amines.

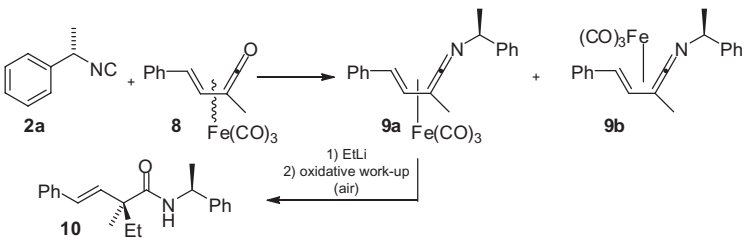
Some examples of simple chiral isocyanides are shown in Scheme 1.1. These materials have all been prepared in a traditional manner, starting from chiral amines; the exception here is **5**, which was synthesized from the secondary alcohol.

The compounds comprise fully aliphatic examples such as **1** [13], α-substituted benzyl isocyanides such as **2** [1, 2, 13, 14] and **3** [14, 15], and α-substituted phenethyl or phenylpropyl isocyanides such as **4** [2] and **5** [12].

Because of the great synthetic importance of isocyanide-based multicomponent reactions, these chiral isocyanides have been often used as inputs in these reactions. The use of enantiomerically pure isocyanides can, in principle, bring about two advantages: (i) the possibility to obtain a stereochemically diverse adduct, controlling the absolute configuration of the starting isonitrile; and (ii) the possibility to induce diastereoselection in the multicomponent reaction. With regards to the second of these benefits, the results have been often disappointing, most likely because of the relative unbulkiness of this functional group. For example, Seebach has screened a series of chiral isocyanides, including **2a** and **4** in the $TiCl_4$-mediated addition to aldehydes, but with no diastereoselection at all [2]. This behavior seems quite general also for the functionalized isocyanides described later, the only exception known to date being represented by the camphor-derived isocyanide **6** [16], which afforded good levels of diastereoselection in Passerini reactions. The same isonitrile gave no asymmetric induction in the corresponding Ugi reaction, however. Steroidal isocyanides have also been reported (i.e., **7**) [17, 18].

Apart from multicomponent reactions, and the synthesis of polyisocyanides (see Section 1.6), chiral unfunctionalized isocyanides have been used as intermediates in the synthesis of chiral nitriles, exploiting the stereospecific (retention) rearrangement of isocyanides into nitriles under flash vacuum pyrolysis conditions (FVP) [14, 19]. This methodology was used for the enantioselective synthesis of the anti-inflammatory drugs ibuprofen and naproxen, from **2d** and **3**, respectively. As isocyanides are usually prepared from amines, the overall sequence represents the homologation of an amine to a carboxylic derivative, and is therefore opposite to the Curtius rearrangement.

Another interesting application of **2a**, as a chiral auxiliary, was reported by Alcock *et al.* (Scheme 1.2). Here, the chiral isocyanide reacts with racemic vinylketene tricarbonyliron(0) complex **8** to produce two diastereomeric (vinylketeneimine) tricarbonyliron complexes **9** that can be separated. Subsequent reaction with an organolithium reagent, followed by an oxidative work-up, was found to be highly diastereoselective, forming only adduct **10**. This represents a useful method for



Scheme 1.2

accessing quaternary stereogenic centers, with the induction being clearly due to the tricarbonyliron group, while the isocyanide chirality serves only as a means of separating the two axial stereoisomers **9a** and **9b** [15].

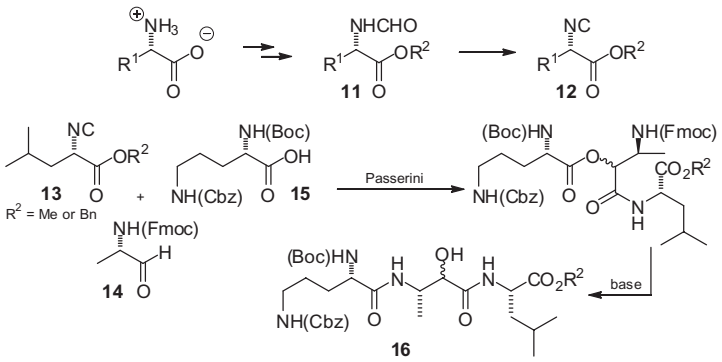
1.3 Isocyanides Containing Carboxylic, Sulfonyl, or Phosphonyl Groups

As the reactivity of α-isocyano esters and amides is reviewed in Chapters 3 and 4 of this book, attention at this point will be focused only on stereochemical issues; reactions exploiting reactivity at the α position will not be described.

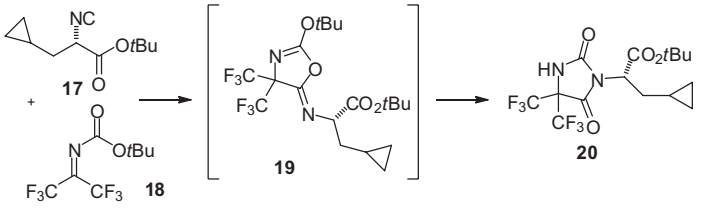
1.3.1 α-Isocyano Esters

Enantiomerically pure α-isocyano esters **12** can be prepared by the dehydration of formamides **11**, which in turn are synthesized in two steps from the corresponding α-amino acids [20, 21] (Scheme 1.3). The most critical step is dehydration, which has been demonstrated in some instances to be partly racemizing. The combination of diphosgene with *N*-methylmorpholine (NMM) at a low (<–25 °C) temperature has been reported in various studies to be able to avoid racemization and to be superior to the use of $POCl_3$ with more basic amines [2, 22–25]. In a recent extensive study, the use of triphosgene/NMM at –30 °C was suggested as the method of choice [26], although a direct comparison of triphosgene with diphosgene was not carried out.

These isocyanides would be very useful in multicomponent reactions, such as the Passerini and Ugi condensations, for the straightforward preparation of depsipetides or peptides, although racemization may be a relevant issue. Under Passerini conditions, these compounds appear to be configurationally stable during reaction with various aldehydes [22, 27–29], and this approach has been used, for



Scheme 1.3



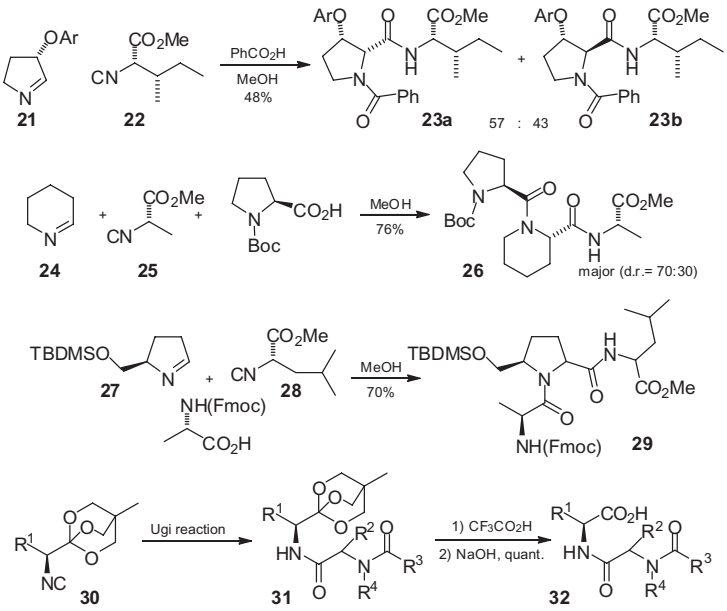
Scheme 1.4

example, in the total synthesis of eurystatin A [22] (Scheme 1.3). The quite complex tripeptide **16** has been assembled in just two steps by using a PADAM (Passerini–Amine Deprotection–Acyl Migration) strategy [30], starting from three enantiomerically pure substrates **13**, **14**, and **15**. Once again, none of the three chiral inputs was able to induce any diastereoselection, but at least three of the four stereogenic centers could be fully controlled by the appropriate substrate configurations. α-Isocyano esters are also configurationally stable during the $TiCl_4$-mediated condensation of isocyanides with aldehydes [2].

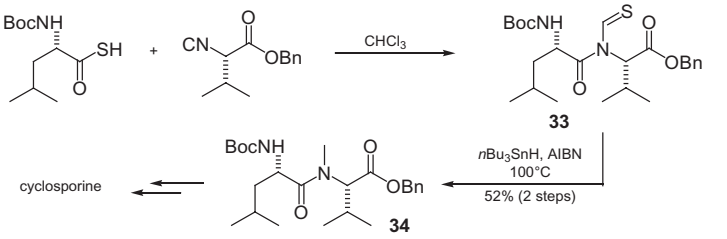
With ketones, the Passerini reaction is slower such that some degree of racemization may occur, depending on the carboxylic acid employed [31]. Chiral α-isocyano esters have been used also in the synthesis of optically active hydantoins such as **20** (Scheme 1.4) [5]; however, the enantiomeric purity was not precisely assessed, and it could not be ascertained if these conditions were racemizing, or not.

In contrast, the conditions of the Ugi reaction are often incompatible with the stereochemical integrity of chiral α-isocyano esters [20, 25, 32]. A careful study of reaction conditions has shown that – at least for the reaction with ketones – racemization can be almost completely suppressed by carrying out the reaction in CH_2Cl_2 with $BF_3 \cdot Et_2O$ as catalyst [25]. In this case, racemization is believed to be provoked by the free amine; in fact, α-isocyano esters will readily racemize when treated with amines at room temperature (r.t.) [2]. On this basis, the use of preformed imines would be expected to be capable of preventing racemization, although such success was stated only in few cases, that always involved preformed cyclic imines (Scheme 1.5). For example, Joullié has reported the formation of only two diastereomers **23** in the condensation of chiral imine **21** with chiral isocyano ester **22** [33]. Similarly, Sello has obtained only two diastereomers in the condensation of achiral imine **24** with chiral isocyanide **25** and Boc-proline. Interestingly, the two diastereomers have been obtained in 70 : 30 ratio [34]; this was unusual since, in most cases, chiral isocyanides and chiral carboxylic acids provide no stereochemical control in Ugi reactions. The absence of racemization in Ugi–Joullié reactions is not general. Rather, the present authors experienced the formation of four diastereomers in the reaction of chiral pyrroline **27** with leucine-derived isocyano ester **28** [24].

An ingenious approach to avoid these racemization issues was recently devised by Nenajdenko and coworkers [35], who employed orthoesters **30** as surrogates of



Scheme 1.5



Scheme 1.6

α-isocyano esters. After the Ugi reaction, which proceeds with no racemization, the free carboxylic acids **32** could be obtained in quantitative yield via a two-step/one-pot methodology.

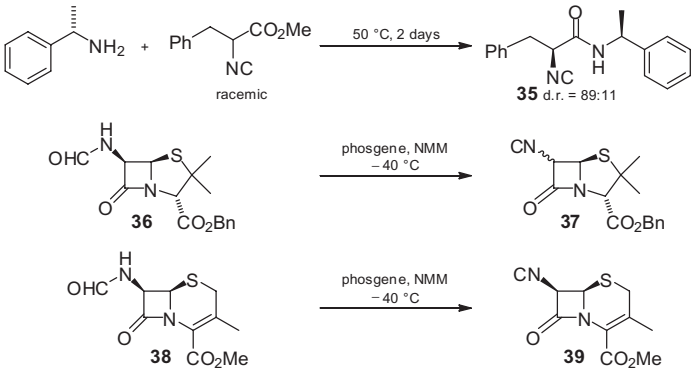
A non-multicomponent application of chiral α-isocyano esters was recently developed by Danishefsky, who created a general method for the synthesis of N-methylated peptides, a moiety which is present in many important natural substances, such as cyclosporine [36] (Scheme 1.6). The coupling of an isocyano ester with a thioacid produces a thioformyl amide that can be conveniently reduced by tributyltin hydride, with the overall sequence taking place without racemization.

α-Isocyano esters can provide a variety of reactions involving enolization at the α positions (these are reviewed in Chapters 3 and 4). Whilst deprotonation clearly brings about the loss of the stereogenic center, if chirality is present elsewhere (e.g., in the alcoholic counterpart of the ester), then asymmetric induction is, in principle, viable. To date, very few α-isocyanoacetates of chiral alcohols have been prepared [37, 38], and their efficient application in asymmetric synthesis has never been reported [21].

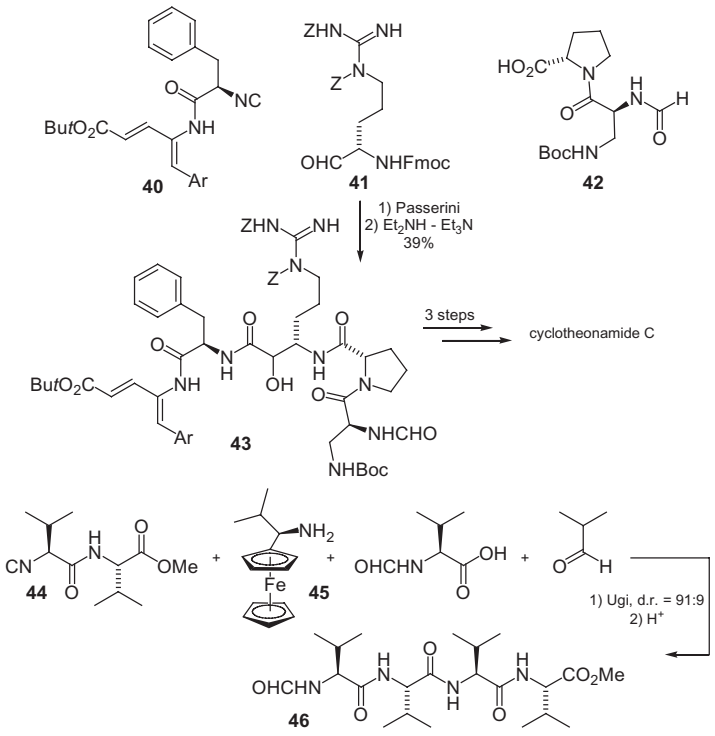
1.3.2
α-Isocyano Amides

Although, in principle, chiral α-isocyano amides can be prepared by the reaction of α-isocyano esters with amines, the easy racemization of the latter compounds under basic conditions makes this approach unfeasible. By using chiral enantiomerically pure amines, it is even possible to realize a dynamic kinetic resolution of racemic α-isocyano esters, obtaining α-isocyanoamides in good diastereomeric ratios, as in the case of compound **35** [2] (Scheme 1.7). Due to the lower α-acidity, the stereoconservative preparation of chiral α-isocyano amides from the corresponding formamides is less problematic than that of the corresponding esters, and combinations of $POCl_3$ with Et_3N may also be used. The only exception here is represented by penicillin- or cephalosporin-derived isocyanides [6]. Cephalosporin-derived isocyanide **39** can be obtained without epimerization, but only when weaker NMM is used as the base (with Et_3N, extensive epimerization takes place). On the other hand, with penicillin-derived formamide **36** a near to 1 : 1 epimeric mixture is obtained, even with NMM.

α-Isocyano amides are also less prone to racemize during multicomponent reactions, although in this case the yields may be impaired by concurrent oxazole formation [24, 39] (see Chapter 3).



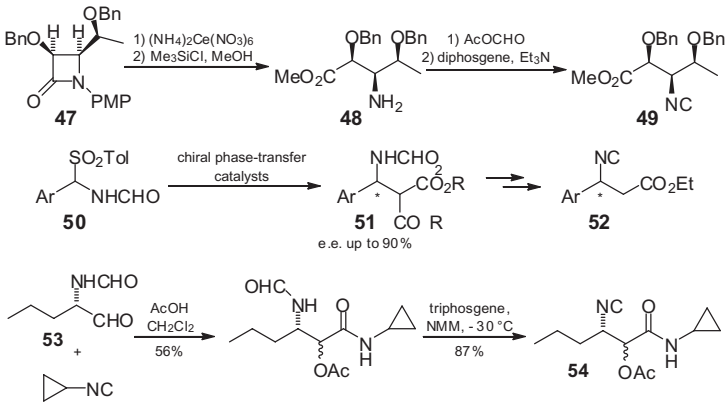
Scheme 1.7



Scheme 1.8

Nonetheless, α-isocyanoamides have been employed successfully in both the Passerini [27, 40] and Ugi reactions [41], some representative examples of which are shown in Scheme 1.8. Aitken and Fauré have accomplished a highly convergent synthesis of cyclotheonamide C by exploiting the above-cited PADAM strategy [30], and using three polyfunctionalized substrates, namely α-isocyano amide **40**, protected α-amino aldehyde **41**, and protected amino acid **42** [40]. Despite none of these three chiral substrates being capable of affording any stereoselection, this is unimportant because the new stereogenic center is later lost by oxidation. Ugi *et al.* have demonstrated the applicability of their reaction in the straightforward synthesis of tetrapeptide **46** [41] although, in this case, two problems had first to be resolved: (i) the poor asymmetric induction provided by both the chiral isocyanide and the carboxylic acid; and (ii) the need for secondary amides (the use of ammonia is often inadequate in Ugi reactions). Ultimately, both issues were resolved by using the chiral ferrocenyl auxiliary **45**, which afforded a good stereoinduction and could easily be removed under acidic conditions.

The α-isocyano amides may also provide a wide variety of stereoselective reactions that involve enolization at the α positions, provided that chirality is present in the amine counterpart. Consequently, various chiral α-isocyano amides have



Scheme 1.9

been prepared [6, 42–46], some of which have provided good levels of diastereoselectivity [6, 42, 45, 46] (these reactions are reviewed in Chapters 3 and 4).

1.3.3
Other Isocyano Esters or Amides

The β-isocyano esters are not expected to suffer from the racemization issues of their α counterparts, and may be very valuable inputs for the multicomponent assembly of peptidomimetics. Somewhat surprisingly, however, very few reports have been made on this class of compound, most likely because of the limited availability of enantiomerically pure β-amino acids (Scheme 1.9). Previously, Palomo *et al.* [47] have successfully prepared β-isocyano esters such as **49** through an opening of the β-lactam **47**, which in turn was stereoselectively accessed by the Staudinger condensation of a lactaldehyde imine. Although this approach may represent a fairly general entry to these isocyanides, its potential has not been further exploited, and the isocyanide **49** has been used simply as an intermediate for deamination procedures.

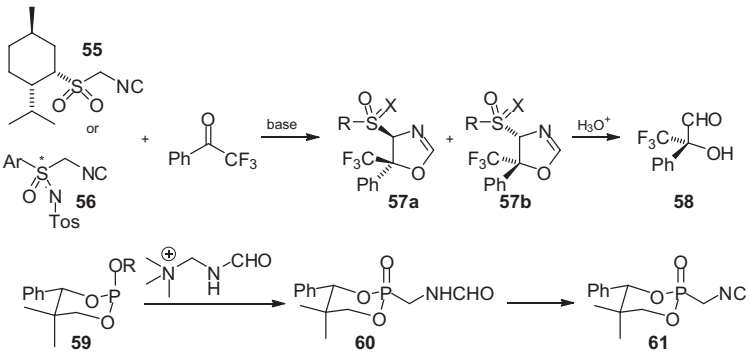
Within the present authors' group, a general organocatalytic entry to β-isocyano esters of general formula **52** in both enantiomeric forms has recently been identified. While *N*-formyl imines have been demonstrated to be unstable, they can be generated *in situ* from sulfonyl derivatives **50** under phase-transfer conditions. Subsequently, the use of quinine- or quinidine-derived catalysts allowed, after careful optimization, malonates **51** to be obtained in both enantiomeric forms, with enantiomeric excess (e.e.) values ranging between 64% and 90%. Moreover, the yields were almost quantitative and the e.e.-values could be brought to 98% by crystallization. Subsequently, malonates **51** have been converted in high yields into isocyanides **52** by decarboxylation and dehydration (F. Morana, *et al.*, unpublished results).

During the total synthesis of the antiviral agent telaprevir, Orru and Ruijter have recently reported an interesting approach (that in principle may be general) for the synthesis of protected α-hydroxy-β-isocyano esters such as **54**, based on the Passerini reaction of a chiral α-formylamino aldehyde **53** [48]. The only drawback of this methodology is the low stereoselection of the Passerini reaction, though this is not influential if the targeted products are peptidomimetic and contain the α-keto-β-amino amide transition state mimic.

1.3.4
Chiral Sulfonylmethyl or Phosphonylmethyl Isocyanides

Sulfonylmethyl isocyanides are synthetic equivalents of formaldehyde mono- or di-anions, and have found several useful applications. Chiral derivatives can, in principle, be used for achieving asymmetric induction, with Van Leusen and colleagues having prepared a series of chiral analogues with either stereocenters in the group attached to sulfur (i.e., **55**) or with a stereogenic sulfur atom (**56**) (Scheme 1.10). These chiral *p*-toluenesulfonylmethyl isocyanide (TosMIC) analogues were tested in the synthesis of cyclobutanones [49] or oxazolines [50]. In the latter case, two *trans* diastereomers (**57a** and **57b**) were usually obtained, and the best results in terms of stereoselectivity were obtained with sulfonimide **56** (diastereomeric excess (d.e.) = 80%). The preparation of enantiomerically pure sulfonimide **56** is not trivial, however. Oxazolines **57** can be hydrolyzed to α-hydroxyaldehydes **58**.

Van Leusen has also prepared the chiral phosphonylmethyl isocyanide **61** (as well as its *trans* epimer), starting from enantiomerically pure dioxaphosphorinane **59** [51]. Here, the key step is an Arbuzov reaction of **59** with a *N*-methylformamide equipped with a good leaving group. It is worth noting that this represents an unconventional formamide synthesis, that does not proceed through a primary amine.



Scheme 1.10

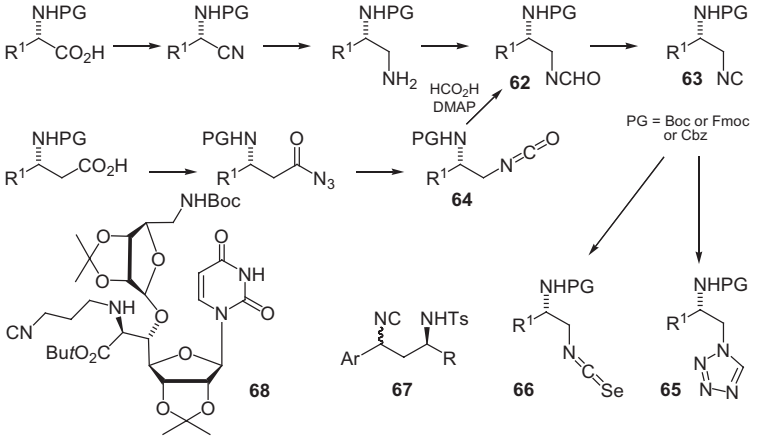
1.4
Isocyanides Containing Amino or Alcoholic Functionalities

1.4.1
Chiral Amino or Azido Isocyanides

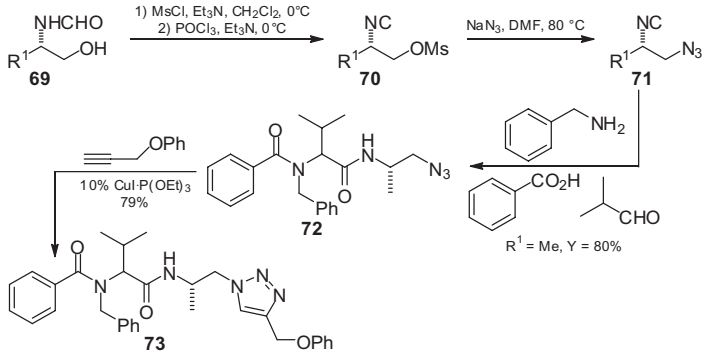
A series of protected chiral β-amino isocyanides of general formula **63** has been prepared in enantiomerically pure form via two general strategies (Scheme 1.11). The first strategy begins with protected α-amino acids and involves transformation into the nitriles, reduction, formylation, and dehydration [52]. The second strategy [10] is considerably shorter, but starts from less readily available β-amino acids that are converted in a one-pot reaction, via a Curtius rearrangement, into the same formamides **62**. These isocyanides have been used in the cycloaddition with trimethylsilyl azide to produce tetrazoles **65** [10], and also in the synthesis of isoselenocyanates **66** and selenoureas [52].

A few chiral γ-isocyano amines are also known [10]. For example, compounds **67** have been obtained by the reaction of chiral *N*-tosyl aziridines with α-lithiated benzyl isocyanides [53], though the reaction is poorly stereoselective and two separable diastereomers were obtained. Likewise, the complex nucleosidic γ-amino isocyanide **68** has been prepared as an advanced intermediate in the convergent total synthesis of muraymicyn D2, and used as input in an Ugi reaction with a chiral carboxylic acid and achiral aldehyde and amine [54]. No asymmetric induction was observed, however.

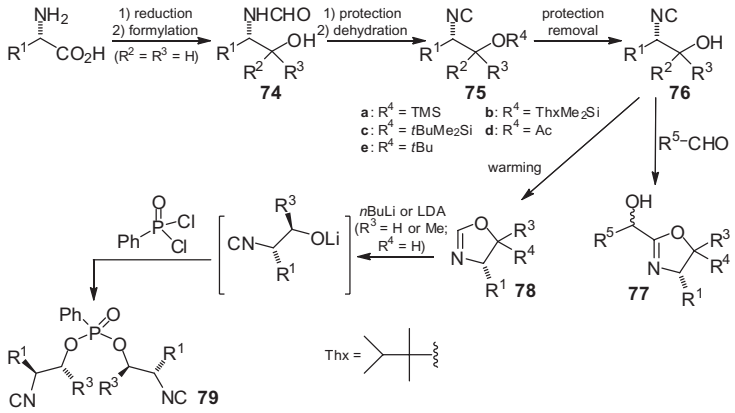
Whereas, the use of isocyanides in the Ugi reactions leads to peptide-like structures, the Huisgen cycloaddition of azides and alkynes produces triazoles, which are also deemed as peptide surrogates. Consequently, the incorporation of both an isocyanide and an azide into the same building block represents a valuable



Scheme 1.11



Scheme 1.12



Scheme 1.13

strategy to build up peptidomimetics in a very convergent manner [55]. Compounds **71** (Scheme 1.12) have been prepared from β-formamido alcohols **69**, in turn obtained from α-amino acids; in this case, a one-pot mesylation–dehydration step provided the sulfonate **70**, which was then substituted by sodium azide. These isocyanides are configurationally stable under either Ugi or Passerini conditions. An example of an application featuring a tandem Ugi–Huisgen protocol is shown in Scheme 1.12 where, as usual, no asymmetric induction by the chiral isocyanide was noted in the Ugi step.

1.4.2 Chiral Hydroxy Isocyanides

β-Hydroxy isocyanides **76** or their protected derivatives **75** represent very useful synthons for the synthesis of peptidomimetic structures through multicomponent reactions (Scheme 1.13). Compounds **76** have also been prepared as potential

anti-AIDS drugs (i.e., nucleoside mimics with reverse transcriptase inhibitory activity) [56]. For $R^2 = R^3 = H$, the alcoholic function can be later oxidized, making **75–76** synthetically equivalent to easily racemizable α-isocyano esters or the likely unstable α-isocyano aldehydes [57].

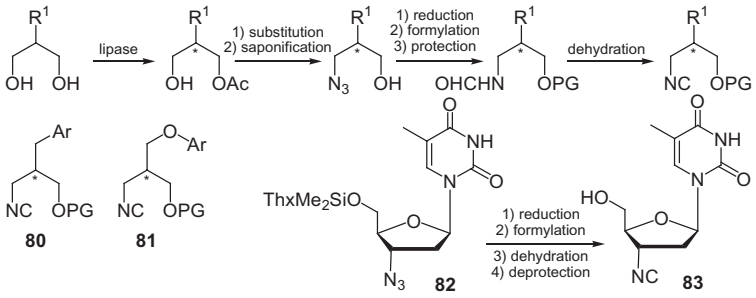
For $R^2 = R^3 = H$, formamides **74** can be easily obtained in two steps from α-amino acids, whereas α- or α,α′-substituted derivatives have been obtained through longer routes [58, 59]. As the direct conversion of **74** into isocyanides **76** was reported to be troublesome [59], the best route seems to involve a temporary protection of **74** to produce **75a** or **75b**, followed by dehydration and finally deprotection with $BF_3 \cdot Et_2O$ (**75a**) [59] or nBu$_4$NF (**75b**) [56]. However, when R^2 and R^3 are different from hydrogen [59], or if the Burgess reagent is employed [8], then dehydration to **76** can be carried out directly on **74**. One of the main uses of compounds **76** is the two-component synthesis of oxazolines **77** by reaction with aldehydes. This reaction displays no stereoselectivity, and consequently oxazolines **77** are obtained as a 1:1 separable mixture of diastereomers that have been used as bidentate chiral ligands in the asymmetric diethylzinc addition to aldehydes [60].

In contrast, the protected isocyano alcohols **75c** and **75d** have been employed in classical Passerini [61] and Ugi reactions [57, 62] although, again, no stereoselection was observed. Compounds **75d** have also been submitted to the isocyanide–cyanide rearrangement under FVP conditions to produce β-acetoxy nitriles [19]. Finally, **75e** has been employed in the synthesis of formamidines which have, in turn, been used as chiral auxiliaries [63].

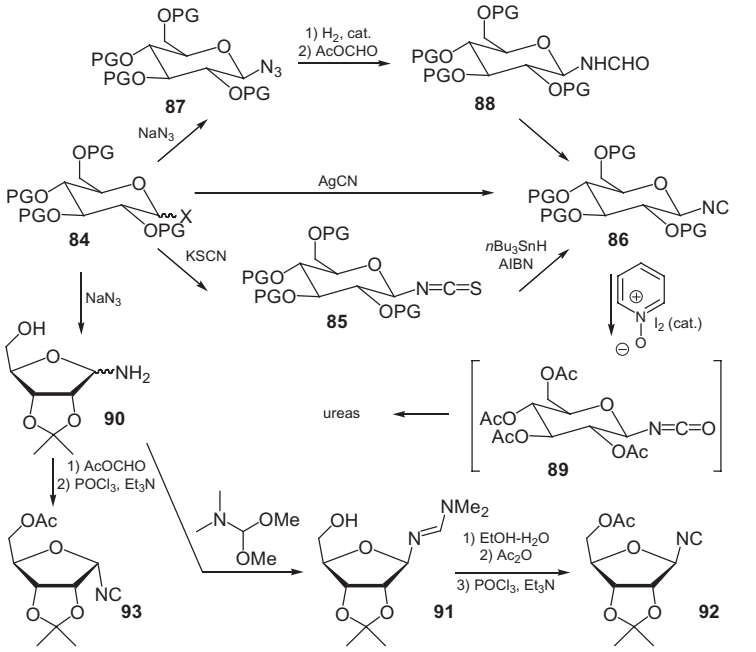
Alcohols **76** are not very stable, and must be conserved at low temperatures or used immediately after their preparation, because they tend to be converted into unsubstituted oxazolines **78**. This cyclization may be reverted under strong basic conditions to produce the conjugate bases of **76**, that have been exploited for the preparation of *pseudo*-C_2-symmetric ligands **79** [58, 64]. These ligands have found various applications in organometal catalysis; for example, iron(II) complexes have recently been used in the asymmetric transfer hydrogenations of aromatic and heteroaromatic ketones [58].

A general approach to γ-isocyano alcohols is represented by the biocatalytic desymmetrization of 2-substituted 1,3-propanediols, followed by the substitution of one of the two hydroxy functions with the isocyanide, through the corresponding azides and formamides (Scheme 1.14). The synthetic equivalence of the two hydroxymethyl arms allows the enantiodivergent synthesis of both enantiomeric isocyanides, starting from the same monoacetate. The present authors' group has recently prepared both enantiomers of a series of isocyanides **80** and **81** by this strategy, and used them in stereoselective Ugi–Joullié coupling with chiral imines [65]. The nucleosidic γ-isocyano alcohol **83** has been prepared, again by reduction, formylation, and dehydration from azido alcohol **82**, in an attempt to identify potential anti-AIDS drugs, such as azidothymidine (AZT) analogues [7].

Previously, several isocyano sugars have been synthesized, with the isocyanide either being bound to the anomeric positions, or not. Glycosyl isocyanides, such as **86** (Scheme 1.15), may be prepared starting from fully benzylated glycosyl halides **84** by reaction with silver cyanide [66], with the β-anomer usually being



Scheme 1.14



Scheme 1.15

favored. A more efficient methodology, that is also more compatible with fully acetylated glycosyl halides, involves the initial transformation into the isothiocyanate **85**, followed by a controlled radical reduction with nBu$_3$SnH initiated by azo-*bis*-isobutyronitrile (AIBN) [67].

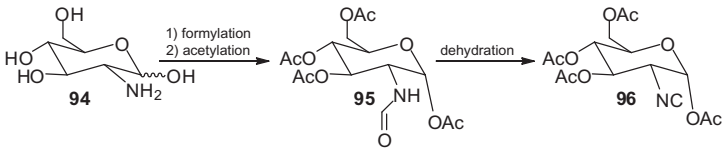
Alternatively, glycosyl isocyanides may be prepared by a longer (but often more stereoselective) route that involves the formation of a glycosyl azide **87**, followed by reduction, formylation, and dehydration [68, 69]. A shorter route, which allows the preparation of both anomers, has been developed in the field of pentofuranoses

(ribosyl isocyanides are shown as an example) [70]. The treatment of protected ribofuranosylamine **90** with the mixed acetic formic anhydride affords directly the α formamide, with concomitant acetylation of the 5-OH; dehydration then yields α isocyanide **93**. In contrast, when **90** is converted into the amidine **91**, only the β-anomer is formed. A careful hydrolysis produces a β-formamide that, upon acetylation and dehydration, leads to the β-isocyanide **92**.

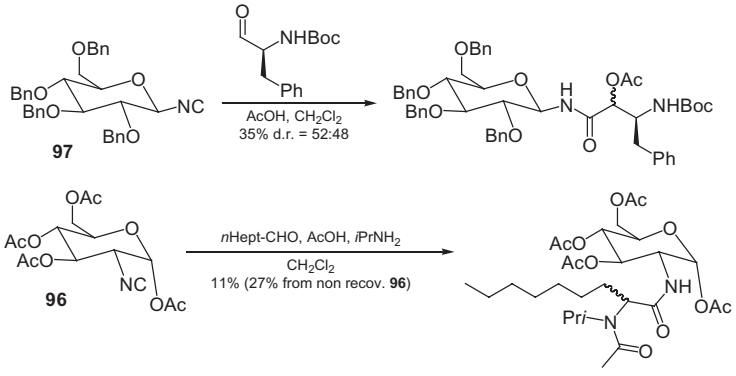
The main application of glycosyl isocyanides relies on their transformation into isocyanates such as **89**, *en route* to ureido-linked disaccharides or sugar-amino acid conjugates [68, 71, 72]. These isocyanides have also been converted into amidines [73].

In contrast, 2-deoxy-2-isocyano sugars have been synthesized starting from the corresponding 2-deoxy-2-aminosugars (glucosamine, galactosamine) (Scheme 1.16) [74]. Thus, glucosamine **94** was formylated to produce (after peracetylation of the hydroxy groups) formamide **95**, which was then either directly dehydrated to **96** or first activated and coupled with various glycosyl acceptors, and later dehydrated, affording isocyano disaccharides [75, 76]. In each of these cases the isocyano group was finally reductively (nBu$_3$SnH) removed. Thus, its ultimate function was simply an elimination of the amino group in order to obtain 2-deoxysugars.

Surprisingly, despite the excellent chemistry that has been developed for their synthesis, these sugar isocyanides have to date been employed only very rarely in multicomponent reactions (some examples are depicted in Scheme 1.17). Ziegler



Scheme 1.16



Scheme 1.17

has reported a series of Ugi and Passerini reactions of glycosyl isocyanides such as **97** [69], while Beau and again Ziegler have reported Ugi and Passerini reactions of 2-isocyano sugars such as **96** [77]. The yields of these reactions are not very high although, in general, glycosyl isocyanides behave better than 2-isocyano sugars. Among the latter compounds the bulkier α-anomers function worse, often giving rise to sluggish reactions. Finally, the Passerini condensations afford better yields than their Ugi counterparts, and in all cases – even when chiral aldehydes have been used – the stereoselectivity was very poor; that is, the diastereomeric ratio (d.r.) never was >60 : 40).

1.5
Natural Isocyanides

1.5.1
Isolation and Natural Sources

This topic has been widely examined, and information obtained up to mid 2003 has been included in three excellent reviews [78–80]. Interestingly, the first naturally occurring isocyanide, xanthocillin **98** (Figure 1.1), was isolated only in 1957 from a culture of *Penicillium notatum*, but this is not a chiral compound. The first enantiomerically pure isocyanide, axisonitrile-1 **99**, was isolated and characterized only in 1973 [81]. In general, these compounds have been identified in marine invertebrates, such as sponges and nudibranch mollusks, and less frequently in fungi or cyanobacteria (blue-green algae). Natural isocyanides are often accompanied by the corresponding isothiocyanates and formamides – compounds that have been shown as being biogenetically related. In natural chiral isonitriles, the isocyano group is in most cases attached directly to the stereogenic center which is, in turn, a tertiary or often a quaternary carbon.

Marine derivatives display almost exclusively a terpene-derived skeleton (sesqui- or diterpenes) and, in some cases, also interesting biological properties, such as anti-malarial activity, antibiotic properties, and cytotoxicity. On the contrary, com-

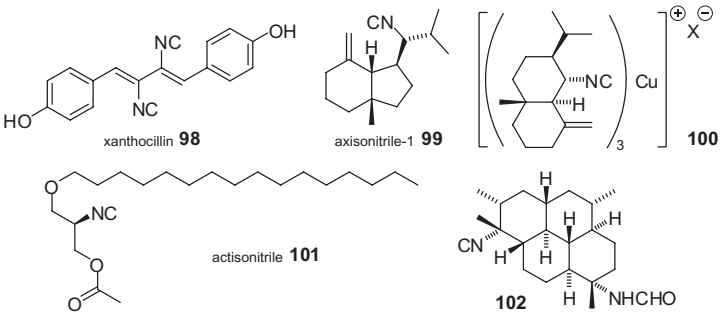


Figure 1.1 Examples of natural isocyanides.

pounds isolated from cyanobacteria have rather complex alkaloid structures, whereas to date very few examples of natural isocyanides in the field of macrolides or carbohydrates have been reported [82, 83].

During the past eight years, only a limited number of new isocyanides have been isolated, among which three compounds are worthy of mention: **100**, a copper(I) complex [84]; **101**, with a unique lipidic arrangement [85]; and **102**, one of the few examples of structures which bear simultaneously an isocyanide and a formamide function [86].

1.5.2
Synthesis of Naturally Occurring Isocyanides

Among the plethora of total syntheses that have been reported to date, to the best of the present authors' knowledge only a few dozen are related to the total synthesis of chiral natural isocyanides. These syntheses typically afford enantiomerically pure molecules, although in some instances they may be either enantiomers [87, 88] or epimers [11] of the actual natural compounds. In addition, efficient – but racemic – syntheses have been reported, including the preparation of racemic **99** [89, 90], **103** [91], **104** and its diastereoisomer [92], and **105** [93]. The anti-malarial β-lactam **106** was prepared via a semi-synthesis from another natural substance [94], whereas in the case of **107** only a synthetic approach to the racemic target was reported [95] (Figure 1.2). Those compounds which seem to have attracted the most synthetic efforts are the complex hapalindole alkaloids, for which an exhaustive collection of references is available [96]. In essentially all of the synthesized compounds, however, the isocyanide moiety is bound to a stereogenic center (often quaternary), with the exception of **105** [93] and **108–109** [11].

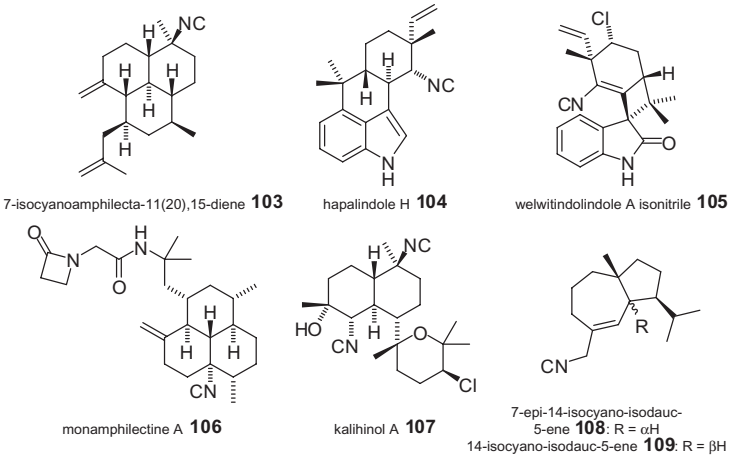
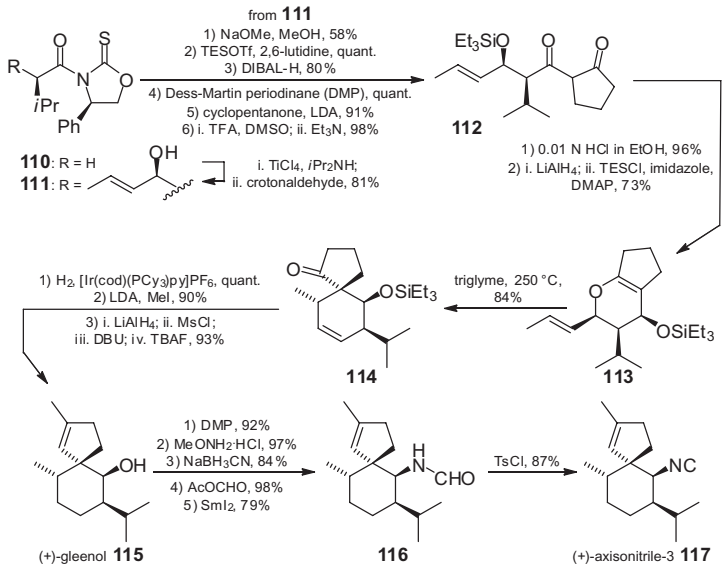


Figure 1.2 Examples of natural isocyanides that have been the targets of total syntheses.

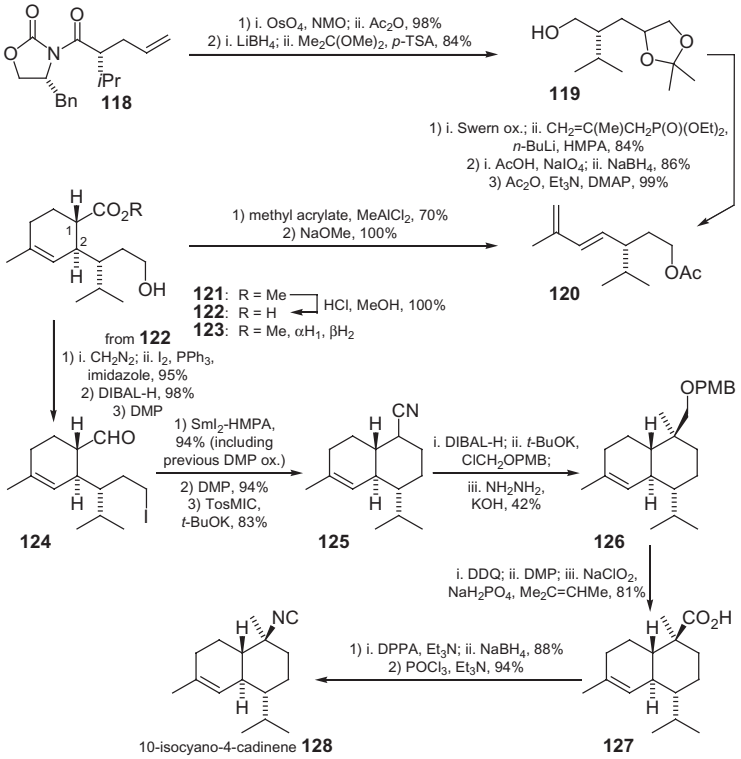


Scheme 1.18

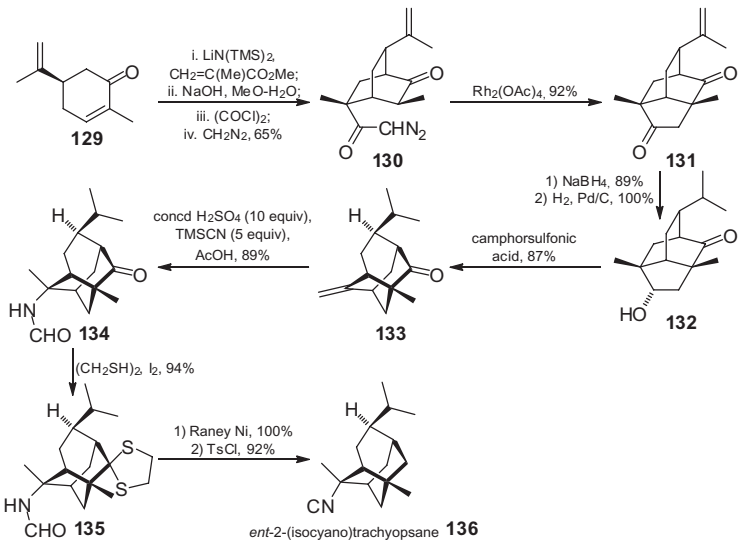
Typically, the introduction of the isocyanide moiety has been performed as the final step, by dehydration of the corresponding formamide. The only exceptions to this are compounds **106**, in which an advanced intermediate already bearing the isocyanide group (**146**) was used [94], and **108** in which a nucleophilic substitution of an allylic iodide by means of AgCN has been performed at the end of the synthesis (see Schemes 1.22 and 1.21, respectively) [11]. Other exceptions are represented by the syntheses of hapaindole derivatives, where often the formation of an isocyanide group is not the last transformation [97]. Hence, on this basis, more attention will be dedicated to these compounds.

A brief survey of the syntheses of enantiomerically pure sesquiterpenes [11, 87, 88, 90, 98, 99] and diterpenoids [91, 94, 95] is reported in Schemes 1.18–1.22.

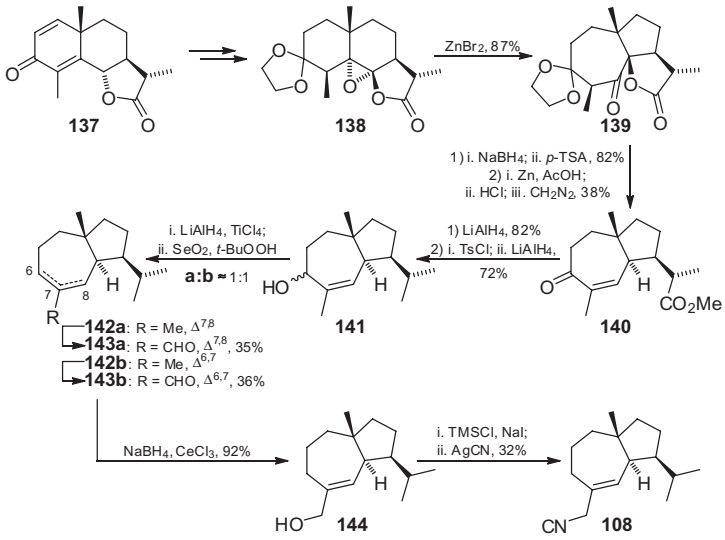
(+)-Axisonitrile-3 **117**, an anti-malarial compound isolated from the marine sponge *Axinella cannabina*, was synthesized from chiral oxazolidinethione **110** by exploiting a non-Evans *syn*-aldol reaction to produce **111** (Scheme 1.18) [99]. After several steps, the key spiranic intermediate (+)-gleenol **115** was obtained through a Claisen rearrangement of dihydropyran **113** to **114**, followed by methylation and other simple transformations. The stereoselective conversion of the hydroxy group of **115** into the isocyanide required the oxidation to a ketone, and the introduction of the nitrogen function through a highly diastereoselective reduction of the corresponding *O*-methyl oxime. The resulting hydroxylamine was formylated, while a reductive cleavage of the N–O bond produced formamide **116** which, eventually, was dehydrated.



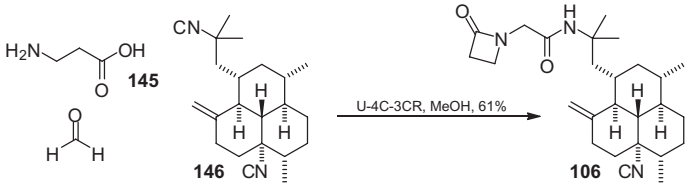
Scheme 1.19



Scheme 1.20



Scheme 1.21



Scheme 1.22

10-Isocyano-4-cadinene **128**, a marine sesquiterpene with anti-fouling activity isolated from nudibranchs of the family *Phyllidiidae*, was prepared from a known allylated oxazolidinone **118**, which was the precursor of diene **120** (Scheme 1.19). Here, the key step is the formation of the cyclohexene moiety with a *trans* relationship of the 1,2-substituents. The Diels–Alder reaction of diene **120** with methyl acrylate afforded the expected products **121**, but as a mixture of four diastereomers. However, equilibration with NaOMe/MeOH gave (apart from cleavage of the acetate) only the *trans* ester **121** and its *trans* isomer **123** in a 2 : 1 ratio. The desired acid **122** was finally obtained in pure form by the slow addition of 1 M HCl, followed by selective precipitation; **122** was then transformed into decaline **125** and, via a rather lengthy route, into the carboxylic acid **127**. Finally, a Curtius rearrangement (see Section 1.2) allowed production of the formamide precursor of **128**, with the isocyanide on a quaternary carbon [98].

The biomimetic synthesis of *ent*-2-(isocyano)trachyopsane **136**, the enantiomer of a complex tricyclo[4.3.1.$0^{3,8}$]decane which was extracted from the nudibranch

Phyllidia varicosa and displayed anti-fouling activity, was achieved from carvone **129** (Scheme 1.20), which was first transformed into diazoketone **130** by a double Michael reaction, followed by functional group transformations. Isotwistane dione **131**, bearing a neopupukeanane skeleton, was obtained through a known regioselective C–H insertion of the corresponding Rh carbenoid. Regioselective and stereoselective reduction to **132**, followed by treatment with camphorsulfonic acid, promoted the rearrangement affording trachyopsane **133**, an advanced precursor of **136** [88]. The required nitrogen function was introduced stereoselectively through a Ritter reaction, using cyanotrimethylsilane and H_2SO_4 to yield **134**.

7-Epi-14-isocyano-isodauc-5-ene **108**, the epimer of natural **109** extracted from the marine sponge *Acantkella acuta*, was prepared from natural α-(–)-santonin **137**, which was converted into eudesmane derivative **138** by a reported procedure (Scheme 1.21). This intermediate was submitted to a $ZnBr_2$-mediated rearrangement to give the typical isodaucane skeleton of **139**, while subsequent functional group manipulation afforded **141**. The reductive removal of allylic hydroxy group afforded an inseparable mixture of the regioisomeric alkenes **142a,b**, after which selective oxidation of the allylic methyl group gave alcohols **143a,b**. Following separation of the two regioisomers, **143a** was finally converted (in moderate yield) into isocyanide **108** by substitution of the corresponding iodide with AgCN [11].

Monamphilectine A **106** is a diterpenoid β-lactam alkaloid that has recently been extracted from the marine sponge *Hymeniacidon* sp. and shows a potent antimalarial activity. The synthesis of **106** is the only one in which a multicomponent reaction was employed for a semi-synthetic approach (Scheme 1.22) [94], whereby the β-lactam moiety was introduced through a Ugi four-center, three-component reaction (U-4C-3CR) reacting together β-alanine **145**, formaldehyde, and *bis*isocyanide **146**. Interestingly, only one isocyanide group (probably the less-hindered) takes part in the multicomponent reaction.

Hapalindole-type natural compounds form a family of over 60 biogenetically related structures that have been isolated from blue-green algae (cyanobacteria) since 1984, and which are characterized by a broad range of biological activities. Typically, they have an indole (and in few cases a fragment derived from the oxidative degradation of the indole) with a monoterpene unit bonded to C_3. Most of these compounds have an isocyanide or an isothiocyanate bound (with few exceptions) to a stereogenic carbon that is part of a cyclohexane; moreover, they present in the vicinal position an all-carbon quaternary center (with methyl and vinyl substituents). The tricyclic framework of hapalindole may become either tetracyclic (some hapalindoles, fischerindoles, and some ambiguines) or even pentacyclic (more complex ambiguines). Welwitindolinones may be tetracyclic with a spirocyclic cyclobutanone centered around C_3, or they can be characterized by a [4.3.1] bicyclononanone moiety. Some representative examples of their structures are shown in Figure 1.2 (compounds **104** and **105**) and Figure 1.3 (compounds **147–151**) [96, 97, 100].

Apart from an early report on the synthesis of a hapalindole [101], the most impressive syntheses of these alkaloids in enantiomerically pure form are those reported by Baran's group [96, 97, 100]. Each of these syntheses is based on a very

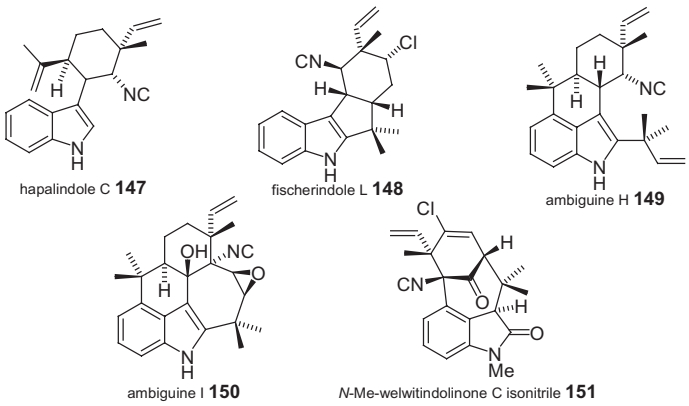
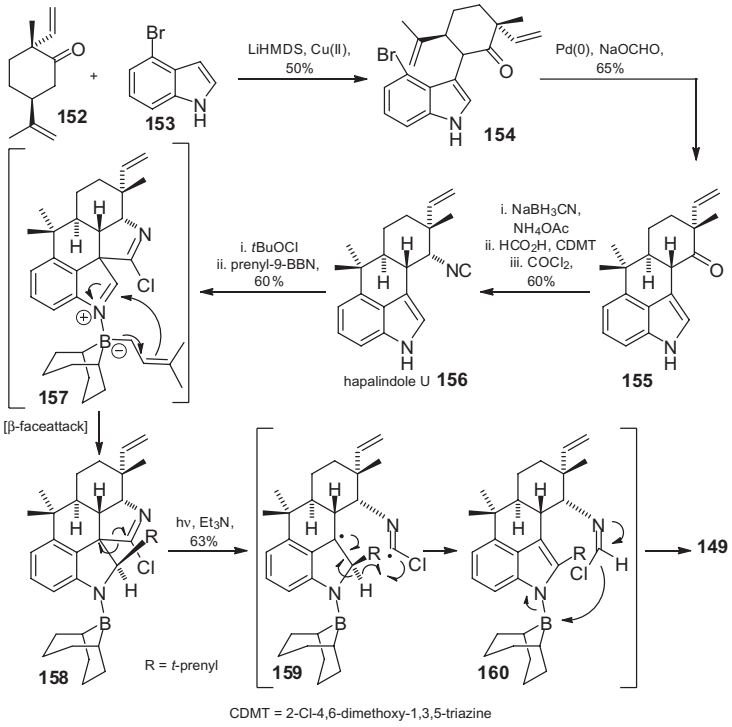


Figure 1.3 Structures of some hapalindoles.

simple principle: maximize "atom", "step," and "redox-economy", where the latter term indicates a minimization of the superfluous redox manipulations. In this way, the preparation of the target molecule avoids the use of protecting groups and also exploits the natural reactivity of functional groups, such that the basic skeleton can be built on the gram scale.

An example of this, the synthesis of ambiguine H **149** and of hapalindole U **156**, the precursor of **147** lacking the prenyl unit at C_2, is shown in Scheme 1.23 [97]. Here, the intermediate **152**, which is readily available from commercial *p*-menth-1-en-9-ol, was coupled with 4-bromoindole **153** to produce **154**, without any need to protect the NH group. The direct Friedel–Crafts annulation on the analogue of **154** (having H instead of Br) was unsuccessful because it was sitoselective on C_2 instead of on C_4; hence, a switch was made to **154**, which allowed the possibility of forcing a formation of the fourth ring in the appropriate position. The desired 6-*exo-trig* cyclization (reductive Heck) onto C_4 to afford **155** was effective when promoted by Hermann's catalyst. Subsequently, transformation into hapalindole U **156** was accomplished by a reductive amination under microwave heating, followed by conventional introduction of the isocyanide group.

Introduction of the prenyl unit, leading to **149**, was the most critical step because direct C–C bond formation was impossible, due to the unusual reactivity of the indole moiety, and to an incompatibility of the isocyanide with acids and transition metals. However, instead of resolving the problem by means of protective groups, the high reactivity of both the indole and the isocyanide was exploited simultaneously by the treatment of **156** with *t*BuOCl followed by prenyl 9-borabicyclononane (BBN). The electrophilic chlorination of the isocyanide is presumably followed by an addition of the chloronitrilium ion to C_3 of the indole, and by coupling of the borane to the indolenine nitrogen to produce **157**. Finally, B → C migration yields the crystalline chlorimidate **158**, with the *t*-prenyl group correctly bound at C_2. The following Norrish-type homolytic cleavage, promoted by irradiation,



Scheme 1.23

furnished eventually ambiguine H **149**, most likely through the fragmentation cascade depicted in Scheme 1.23. Hence, the synthesis of **149** was achieved via a very rapid strategy which fits perfectly with the initial assumptions quoted above.

1.6
Isocyanides Used in the Synthesis of Chiral Polyisocyanides

Atropisomerism, a stereochemical property that is well known in organic chemistry but very rare in polymer chemistry, was first demonstrated in 1974 in polymers of isocyanides [102] (Figure 1.4a). In this case, it was shown that poly(*tert*-butyl isocyanide) could be resolved chromatographically into separate fractions that displayed positive and negative optical rotations. Subsequent investigations [13] revealed that the optical rotation was due to a helical configuration of the polymer backbone. Remarkably, these helices did not undergo racemization, even at elevated temperatures, due to the presence of bulky substituents which prevented the kinetically formed helical polymer from unfolding. (For reviews on the subject of polyisocyanides, see Refs [104–105] and Chapter 16.)

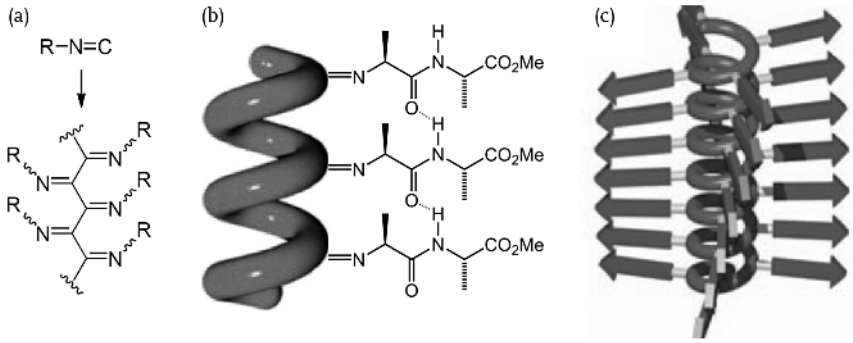


Figure 1.4 Structure of polyisocyanides. Reproduced in part, with permission from Prof. Dr R. J. M. Nolte, from Ref. [103]; © 2010, Wiley.

1.6.1 Properties

One special characteristic of polyisocyanides (also known as polyiminomethylenes or polycarbonimidoyls) is the fact that every carbon atom in the polymer backbone bears a substituent and, as a consequence, the side chains experience sufficient steric hindrance that causes the polymer to adopt a nonplanar conformation. The polymers fold into a 4_1-helical conformation containing four repeat units per turn and a helical pitch of 4.1–4.2 Å [106] (Figure 1.4b). Both, left- (M) and right-handed (P) helices can be distinguished, with absolute helic sense being determined by using circular dichroism (CD) spectroscopy or X-ray diffraction analyses on liquid crystalline phases [107].

Besides the helical conformation, a so-called "*syndio*" conformation was discussed by Clericuzio and Alagona [108] on the basis of *ab initio* calculations, while Green [109], relying on comprehensive measurements such as viscosity, light scattering and nuclear magnetic resonance (NMR) spectroscopy, suggested an alternative irregular conformation, in which the stereo irregularity is associated with a *syn–anti* isomerism about the imine bond.

The helical conformation of the polyisocyanide backbone can be effectively stabilized if a well-defined hydrogen bonded network is present between the side chains at positions n and $n + 4$. This additional stabilization increases the persistence length of these types of macromolecule, which were found to be even more rigid than DNA [110]. As in biomolecules, the disruption of these hydrogen-bonding arrays is a cooperative effect. When the pendant side chains are peptidic fragments, they are stacked above each other at a distance of approximately 4.6 Å, with a general structure as depicted in Figure 1.4b,c [103]. Analogously to the denaturation of proteins, such secondary structure can be irreversibly disrupted by treatment with strong acids or heating.

1.6.2 Synthesis

Polyisocyanides are prepared by the polymerization of isocyanides. Shortly after their discovery, it was realized that the isonitriles readily polymerize, the driving force being the conversion of a formally divalent carbon atom in the monomer to a tetravalent carbon in the polymer, which yields a heat of polymerization of around 81 kJ mol^{-1} [111]. The polymerization process may be either acid-mediated or catalyzed by transition metal complexes based on Ni(II), Rh(III), or Pd(II)/Pt(II) couples. The latter approach has been more widely used, with the Pd–Pt heteronuclear complex mainly being used for the polymerization of aryl isocyanides, while the Rh catalysts were effectively employed where the isonitrile monomer displayed bulky substituents [112, 113]. In contrast, the acid-mediated polymerizations can offer polymers with exceptionally long lengths and high stereospecificities [114].

Based on kinetic measurements and experiments with optically active isocyanides, a so-called "merry-go-round" mechanism has been proposed for the Ni(II) catalyzed polymerization and extensively reviewed by Cornelissen and Nolte [104]. The polymerization is initiated by a nucleophile (an amine or an alcohol), and the isocyanide monomers coordinate to the Ni center and are incorporated into the growing chain by a series of consecutive α-insertions. When achiral isocyanides are used, the intermediate formed after attack of the nucleophile on one of the four coordinated isocyanide molecules has no preference to attack either the left or the right neighboring isocyanide and, as a consequence, an equal amount of M and P helices are formed. A preferred helical handedness can be achieved when a chiral initiator or a chiral isocyanide is used; some of the chiral isocyanides that have been successfully employed are shown in Figure 1.5. Remarkably, isocyanides bearing a remote chiral group are also capable of chirality transfer onto the ongrowing polymer chain.

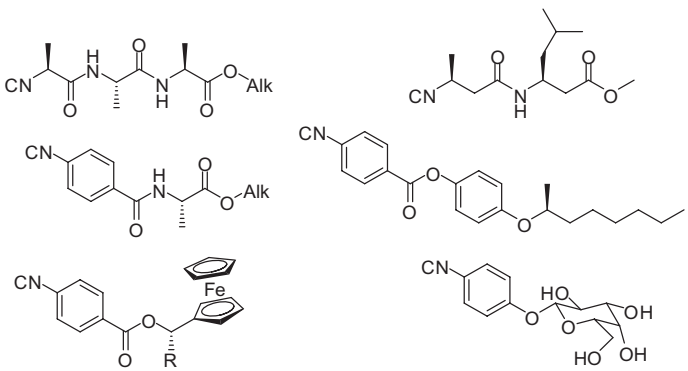


Figure 1.5 Chiral isocyanides used in the diastereoselective synthesis of polyisocyanides.

The many factors that can influence the helix-sense of the polymer may include not only the nature of the isocyanide, but also the solvent, the temperature, and the metal catalyst employed in the polymerization process. For example it has been found, as a consequence, that the same isocyanide can fold to a preferred P or M helix, depending on the specific reaction conditions [115]. The assignment of the preferred helical sense by CD spectroscopy is, however, often hampered by an overlap of the signals that arise from the polymer backbone and the side chains, thus rendering determination of the helical sense excess a difficult task. In fact, high-resolution atomic force microscopy (AFM) has often been the only method used to determine such helical sense [116].

1.6.3 Applications

Stable helical polymers with a preferred handedness are materials that offer intriguing characteristics which might be exploited in the fields of electronics, biosensing, and catalysis. For example, the group of Gomar-Nadal has developed polyisocyanides bearing chiral tetrathiafulvalene derivatives to be used as multistate redox-switchable organic materials in molecular devices [117]. Redox-active polyisocyanides have been reported also by Takahashi, by employing chiral ferrocenyl isocyanide monomers [118], sugar polyisocyanides have been synthesized to study the effect of saccharide arrays along the backbone on molecular recognition phenomena [119], and cholesterol-containing isocyanides have been polymerized to obtain liquid-crystalline polymers [120]. Of particular benefit have been the bioinspired polyisocyanides bearing peptidic appendages; for example, imidazole-containing polyisocyanides have been used in enantioselective ester hydrolysis [121], while cysteine-based polyisocyanides have been synthesized and preliminary experiments performed with the aim of exploiting thio-specific "click" reactions to obtain multichromophoric scaffolding, platforms for nucleation of proteins, or for the binding of metal ions [103]. Dipeptide-derived polyisocyanides have also been used as probes to prove the Davydov hypothesis, that energy-transport in proteins and enzymes occurs via a vibrational soliton mechanism [122]. Finally, giant vesicles (employed as simple model systems for living cells) have been electroformed from diblock copolymers of styrene and isocyanoalanine-2-(thiophen-3-ylethyl)amide [123].

References

1 Saegusa, T., Ito, Y., Kinoshita, H., and Tomita, S. (1971) Synthetic reactions by complex catalysts. XIX. Copper-catalyzed cycloaddition reactions of isocyanides. Novel synthesis of δ-1-pyrroline and δ-2-oxazoline. *J. Org. Chem.*, **36**, 3316–3323.

2 Seebach, D., Adam, G., Gees, T., Schiess, M., and Weigand, W. (1988) Scope and limitations of the $TiCl_4$-mediated additions of isocyanides to aldehydes and ketones with formation of α-hydroxycarboxylic acid amides. *Chem. Ber.*, **121**, 507–517.

3 Waki, M. and Meienhofer, J. (1977) Efficient preparation of *N*-α-formylamino acid tert-butyl esters. *J. Org. Chem.*, **42**, 2019–2020.

4 Zhang, X., Zou, X., and Xu, P. (2005) Template synthesis of peptidomimetics composed of aspartic acid moiety by Ugi four-component condensation reaction. *Synth. Commun.*, **35**, 1881–1888.

5 Wehner, V., Stilz, H.-U., Osipov, S.N., Golubev, A.S., Sieler, J., and Burger, K. (2004) Trifluoromethyl-substituted hydantoins, versatile building blocks for rational drug design. *Tetrahedron*, **60**, 4295–4302.

6 Bentley, P.H., Clayton, J.P., Boles, M.O., and Girven, R.J. (1979) Transformations using benzyl 6-isocyanopenicillanate. *J. Chem. Soc., Perkin Trans. 1*, 2455–2467.

7 Maillard, M., Faraj, A., Frappier, F., Florent, J.-C., Grierson, D.S., and Monneret, C. (1989) Synthesis of 3′-substituted-2′,3′-dideoxynucleoside analogs as potential anti-AIDS drugs. *Tetrahedron Lett.*, **30**, 1955–1958.

8 Creedon, S.M., Crowley, H.K., and McCarthy, D.G. (1998) Dehydration of formamides using the Burgess reagent: a new route to isocyanides. *J. Chem. Soc., Perkin Trans. 1*, 1015–1018.

9 Walborsky, H.M. and Niznik, G.E. (1972) Synthesis of isonitriles. *J. Org. Chem.*, **37**, 187–190.

10 Sureshbabu, V.V., Narendra, N., and Nagendra, G. (2009) Chiral *N*-Fmoc-β-amino alkyl isonitriles derived from amino acids: first synthesis and application in 1-substituted tetrazole synthesis. *J. Org. Chem.*, **74**, 153–157.

11 Li, D.R., Xia, W.J., Shi, L., and Tu, Y.Q. (2003) A general approach from eudesmane to isodaucane sesquiterpenes: synthesis of 7-epi-14-isocyanato-isodauc-5-ene from α-(–)-santonin. *Synthesis*, 41–44.

12 Masutani, K., Minowa, T., Hagiwara, Y., and Mukaiyama, T. (2006) Cyanation of alcohols with diethyl cyanophosphonate and 2,6-dimethyl-1,4-benzoquinone by a new type of oxidation-reduction condensation. *Bull. Chem. Soc. Jpn*, **79**, 1106–1117.

13 Kamer, P.C.J., Cleij, M.C., Nolte, R.J.M., Harada, T., Hezemans, A.M.F., and Drenth, W. (1988) Atropisomerism in polymers. Screw-sense selective polymerization of isocyanides by inhibiting the growth of one enantiomer of a racemic pair of helices. *J. Am. Chem. Soc.*, **110**, 1581–1587.

14 Wolber, E.K.A. and Rüchardt, C. (1991) Neue synthesen für Ibuprofen und Naproxen. *Chem. Ber.*, **124**, 1667–1672.

15 Alcock, N.W., Pike, G.A., Richards, C.J., and Thomas, S.E. (1990) Generation of homochiral quaternary carbon centres from (vinylketenimine)tricarbonyliron(0) complexes. *Tetrahedron: Asymmetry*, **1**, 531–534.

16 Bock, H. and Ugi, I. (1997) Multicomponent reactions 2. Stereoselective synthesis of 1(*S*)-camphor-2-cis-methylidene-isocyanide and its application in Passerini- and Ugi-reaction. *J. Prakt. Chem.*, **339**, 385–389.

17 Hertler, W., and Corey, E. (1958) Notes. A novel preparation of isonitriles. *J. Org. Chem.*, **23**, 1221–1222.

18 Stoelwinder, J., Van Zoest, W.J., and Van Leusen, A.M. (1992) Chemistry of N,P-acetals: application to the synthesis of 20-ketosteroids. *J. Org. Chem.*, **57**, 2249–2252.

19 Rüchardt, C., Meier, M., Haaf, K., Pakusch, J., Wolber, E.K.A., and Müller, B. (1991) The isocyanide–cyanide rearrangement; mechanism and preparative applications. *Angew. Chem. Int. Ed. Engl.*, **30**, 893–901.

20 Failli, A., Nelson, V., Immer, H., and Goetz, M. (1973) Model experiments directed towards the synthesis of N-aminopeptides. *Can. J. Chem.*, **51**, 2769–2775.

21 Gulevich, A.V., Zhdanko, A.G., Orru, R.V.A., and Nenajdenko, V.G. (2010) Isocyanoacetate derivatives: synthesis, reactivity, and application. *Chem. Rev.*, **110**, 5235–5331.

22 Owens, T.D., Araldi, G.-A., Nutt, R.F., and Semple, J.E. (2001) Concise total synthesis of the prolyl endopeptidase inhibitor eurystatin A via a novel Passerini reaction–deprotection–acyl migration strategy. *Tetrahedron Lett.*, **42**, 6271–6274.

23 Skorna, G. and Ugi, I. (1977) Isocyanide synthesis with diphosgene. *Angew. Chem. Int. Ed. Engl.*, **16**, 259–260.

24 Banfi, L., Basso, A., Guanti, G., Merlo, S., Repetto, C., and Riva, R. (2008) A convergent synthesis of enantiopure bicyclic scaffolds through multicomponent Ugi reaction. *Tetrahedron*, **64**, 1114–1134.

25 Berlozecki, S., Szymanski, W., and Ostaszewski, R. (2008) Application of isocyanides derived from α-amino acids as substrates for the Ugi reaction. *Synth. Commun.*, **38**, 2714–2721.

26 Zhu, J.L., Wu, X.Y., and Danishefsky, S.J. (2009) On the preparation of enantiomerically pure isonitriles from amino acid esters and peptides. *Tetrahedron Lett.*, **50**, 577–579.

27 Banfi, L., Guanti, G., Riva, R., Basso, A., and Calcagno, E. (2002) Short synthesis of protease inhibitors via modified Passerini condensation of N-Boc-α-aminoaldehydes. *Tetrahedron Lett.*, **43**, 4067–4069.

28 Basso, A., Banfi, L., Riva, R., Piaggio, P., and Guanti, G. (2003) Solid-phase synthesis of modified oligopeptides via Passerini multicomponent reaction. *Tetrahedron Lett.*, **44**, 2367–2370.

29 Oaksmith, J.M., Peters, U., and Ganem, B. (2004) Three-component condensation leading to β-amino acid diamides: convergent assembly of β-peptide analogues. *J. Am. Chem. Soc.*, **126**, 13606–13607.

30 Banfi, L., Guanti, G., and Riva, R. (2000) Passerini multicomponent reaction of protected α-aminoaldehydes as a tool for combinatorial synthesis of enzyme inhibitors. *Chem. Commun.*, 985–986.

31 Berlozecki, S., Szymanski, W., and Ostaszewski, R. (2008) α-Amino acids as acid components in the Passerini reaction: influence of N-protection on the yield and stereoselectivity. *Tetrahedron*, **64**, 9780–9783.

32 Immer, H., Nelson, V., Robinson, W., and Goetz, M. (1973) Anwendung der Ugi-reaktion zur synthese modifizierter eledoisin-teilsequenzen. *Liebigs Ann. Chem.*, 1789.

33 Bowers, M.M., Carroll, P., and Joullié, M.M. (1989) Model studies directed toward the total synthesis of 14-membered cyclopeptide alkaloids: synthesis of prolyl peptides via a four-component condensation. *J. Chem. Soc., Perkin Trans. 1*, 857–865.

34 Socha, A.M., Tan, N.Y., LaPlante, K.L., and Sello, J.K. (2010) Diversity-oriented synthesis of cyclic acyldepsipeptides leads to the discovery of a potent antibacterial agent. *Bioorg. Med. Chem.*, **18**, 7193–7202.

35 Zhdanko, A.G., and Nenajdenko, V.G. (2009) Nonracemizable isocyanoacetates for multicomponent reactions. *J. Org. Chem.*, **74**, 884–887.

36 Wu, X.Y., Stockdill, J.L., Wang, P., and Danishefsky, S.J. (2010) Total synthesis of cyclosporine: access to N-methylated peptides via isonitrile coupling reactions. *J. Am. Chem. Soc.*, **132**, 4098–4100.

37 Solladié-Cavallo, A. and Quazzotti, S. (1992) An efficient synthesis of (+)-8-phenylmenthyl isocyanoacetate. *Tetrahedron: Asymmetry*, **3**, 39–42.

38 Ilankumaran, P., Kisanga, P., and Verkade, J.G. (2001) Facile synthesis of a chiral auxiliary bearing the isocyanide group. *Heteroat. Chem.*, **12**, 561–562.

39 Bughin, C., Zhao, G., Bienaymé, H., and Zhu, J.P. (2006) 5-aminooxazole as an internal traceless activator of C-terminal carboxylic acid: rapid access to diversely functionalized cyclodepsipeptides. *Chem. Eur. J.*, **12**, 1174–1184.

40 Fauré, S., Hjelmgaard, T., Roche, S.P., and Aitken, D.J. (2009) Passerini reaction-amine deprotection-acyl migration peptide assembly: efficient formal synthesis of cyclotheonamide C. *Org. Lett.*, **11**, 1167–1170.

41 Urban, R., Eberle, G., Marquarding, D., Rehn, D., Rehn, H., and Ugi, I. (1976) Synthesis of an isomer-free tetravaline derivative by stereoselective four-component condensation and exponential multiplication of selectivity. *Angew. Chem. Int. Ed. Engl.*, **15**, 627–628.

42 Schoellkopf, U., Hausberg, H.-H., Segal, M., Reiter, U., Hoppe, I., Saenger, W., and Lindner, K. (1981) Asymmetric syntheses via heterocyclic intermediates, IV. Asymmetric synthesis of α-

methylphenylalanine and its analogues by alkylation of 1-chiral substituted 4-methyl-2-imidazoline-5-one. *Liebigs Ann. Chem.*, 439–458.

43 Yamamoto, Y., Kirihata, M., Ichimoto, I., and Ueda, H. (1985) Asymmetric synthesis of α-methylglutamic acid and α-methylornithine by a chiral isocyano amide reagent. *Agric. Biol. Chem.*, **49**, 1761–1766.

44 Tang, J.S. and Verkade, J.G. (1996) Chiral auxiliary-bearing isocyanides as synthons: synthesis of strongly fluorescent (+)-5-(3,4-dimethoxyphenyl)-4-[[*N*-[(4*S*)-2-oxo-4-(phenylmethyl)-2-oxazolidinyl]]carbonyl]oxazole and its enantiomer. *J. Org. Chem.*, **61**, 8750–8754.

45 Aratani, M., Hirai, H., Sawada, K., Yamada, A., and Hashimoto, M. (1985) Synthetic studies on carbapenem antibiotics from penicillins. III. Stereoselective radical reduction of a chiral 3-isocyanoazetidinone: a total synthesis of optically active carpetimycins. *Tetrahedron Lett.*, **26**, 223–226.

46 John, D.I., Tyrrell, N.D., and Thomas, E.J. (1983) Stereoselective preparation of 6β-substituted penicillanates: tri-organotin hydride reduction of 6-isocyano-, 6-phenylselenenyl-, 6-halo-, and 6-isothiocyanato-penicillanates. *Tetrahedron*, **39**, 2477–2484.

47 Palomo, C., Aizpurua, J.M., Urchegui, R., and Garcia, J.M. (1993) A new entry to 1,3-polyols, 2-amino 1,3-polyols, and β-(1-hydroxyalkyl)isoserines using azetidinone frameworks as chiral templates via iterative asymmetric [2+2] cycloaddition reactions. *J. Org. Chem.*, **58**, 1646–1648.

48 Znabet, A., Polak, M.M., Janssen, E., de Kanter, F.J.J., Turner, N.J., Orru, R.V.A., and Ruijter, E. (2010) A highly efficient synthesis of telaprevir by strategic use of biocatalysis and multicomponent reactions. *Chem. Commun.*, **46**, 7918–7920.

49 van Leusen, D., Rouwette, P.H.F.H., and van Leusen, A.M. (1981) Synthesis of (+)-(neomenthylsulfonyl)methyl isocyanide. Synthesis and absolute configuration of (*R*)-(+)-2-methylcyclobutanone and (*S*)-(−)-2-methylcyclobutanone. *J. Org. Chem.*, **46**, 5159–5163.

50 Hundscheid, F.J.A., Tandon, V.K., Rouwette, P.H.F.M., and van Leusen, A.M. (1987) Synthesis of chiral sulfonylmethyl isocyanides, and comparison of their propensities in asymmetric induction reactions with acetophenones. *Tetrahedron*, **43**, 5073–5088.

51 Weener, J.-W., Versleijen, J.P.G., Meetsma, A., ten Hoeve, W., and van Leusen, A.M. (1998) *Cis*- and *trans*-2-(isocyanomethyl)-5,5-dimethyl-2-oxo-4-phenyl-1,3,2-dioxaphosphorinane– synthesis and structure of the first chiral isocyanomethylphosphonate synthons. *Eur. J. Org. Chem.*, **1998**, 1511–1516.

52 Chennakrishnareddy, G., Nagendra, G., Hemantha, H.P., Das, U., Guru Row, T.N., and Sureshbabu, V.V. (2010) Isoselenocyanates derived from Boc/Z-amino acids: synthesis, isolation, characterization, and application to the efficient synthesis of unsymmetrical selenoureas and selenoureidopeptidomimetics. *Tetrahedron*, **66**, 6718–6724.

53 Kaiser, A. and Balbi, M. (1999) Chiral 1,3-diamines from a lithiated isocyanide and chiral aziridines. *Tetrahedron: Asymmetry*, **10**, 1001–1014.

54 Tanino, T., Ichikawa, S., Shiro, M., and Matsuda, A. (2010) Total synthesis of (−)-muraymycin D2 and its epimer. *J. Org. Chem.*, **75**, 1366–1377.

55 Nenajdenko, V.G., Gulevich, A.V., Sokolova, N.V., Mironov, A.V., and Balenkova, E.S. (2010) Chiral isocyanoazides: efficient bifunctional reagents for bioconjugation. *Eur. J. Org. Chem.*, **2010**, 1445–1449.

56 Genevois-Borella, A., Florent, J.-C., Monneret, C., and Grierson, D.S. (1990) Synthesis of 1-(3-*R*-amino-4-hydroxy butyl)thymine acyclonucleoside analogs as potential anti-aids drugs. *Tetrahedron Lett.*, **31**, 4879–4882.

57 Mroczkiewicz, M. and Ostaszewski, R. (2009) A new and general method for the synthesis of tripeptide aldehydes

based on the multi-component Ugi reaction. *Tetrahedron*, **65**, 4025–4034.

58 Naik, A., Maji, T., and Reiser, O. (2010) Iron(II)-bis(isonitrile) complexes: novel catalysts in asymmetric transfer hydrogenations of aromatic and heteroaromatic ketones. *Chem. Commun.*, **46**, 4475–4477.

59 Bauer, M. and Kazmaier, U. (2009) Straightforward synthesis of chiral hydroxy isocyanides. *Eur. J. Org. Chem.*, **2009**, 2360–2366.

60 Bauer, M. and Kazmaier, U. (2006) A new, modular approach towards 2-(1-hydroxyalkyl)oxazolines, effective bidentate chiral ligands. *J. Organomet. Chem.*, **691**, 2155–2158.

61 Soeta, T., Kojima, Y., Ukaji, Y., and Inomata, K. (2010) O-Silylative Passerini reaction: a new one-pot synthesis of α-siloxyamides. *Org. Lett.*, **12**, 4341–4343.

62 Mroczkiewicz, M., Winkler, K., Nowis, D., Placha, G., Golab, J., and Ostaszewski, R. (2010) Studies of the synthesis of all stereoisomers of MG-132 proteasome inhibitors in the tumor targeting approach. *J. Med. Chem.*, **53**, 1509–1518.

63 Meyers, A.I. and Bailey, T.R. (1986) An asymmetric synthesis of (+)-morphinans in high enantiomeric purity. *J. Org. Chem.*, **51**, 872–875.

64 Naik, A., Meina, L., Zabel, M., and Reiser, O. (2010) Efficient aerobic Wacker oxidation of styrenes using palladium bis(isonitrile) catalysts. *Chem. Eur. J.*, **16**, 1624–1628.

65 Cerulli, V., Banfi, L., Basso, A., Rocca, V., and Riva, R. (2012) Diversity oriented and chemoenzymatic synthesis of densely functionalized pyrrolidines through a highly diastereoselective Ugi multicomponent reaction. *Org. Biomol. Chem.*, **10**, 1255–1274.

66 Boullanger, P., Marmet, D., and Descotes, G. (1979) Synthesis of glycosyl isocyanides. *Tetrahedron*, **35**, 163–167.

67 Witczak, Z.J. (1986) Desulfurization of glycosyl isothiocyanates with tributyltin hybrid. *Tetrahedron Lett.*, **27**, 155–158.

68 Ichikawa, Y., Ohara, F., Kotsuki, H., and Nakano, K. (2006) A new approach to the neoglycopeptides: synthesis of urea- and carbamate-tethered N-acetyl-D-glucosamine amino acid conjugates. *Org. Lett.*, **8**, 5009–5012.

69 Ziegler, T., Kaisers, H.-J., Schlömer, R., and Koch, C. (1999) Passerini and Ugi reactions of benzyl and acetyl protected isocyanoglucoses. *Tetrahedron*, **55**, 8397–8408.

70 Ewing, D.F., Hiebl, J., Humble, R.W., Mackenzie, G., Raynor, A., and Zbiral, E. (1993) Stereoselective synthesis of *N*-(α- and β-ribofuranosyl)-formamides and related glycosyl formamides – precursors for sugar isocyanides. *J. Carbohydr. Chem.*, **12**, 923–932.

71 Nishiyama, T., Kusumoto, Y., Okumura, K., Hara, K., Kusaba, S., Hirata, K., Kamiya, Y., Isobe, M., Nakano, K., Kotsuki, H., and Ichikawa, Y. (2010) Synthesis of glycocinnasperimicin D. *Chem. Eur. J.*, **16**, 600–610.

72 Prosperi, D., Ronchi, S., Lay, L., Rencurosi, A., and Russo, G. (2004) Efficient synthesis of unsymmetrical ureido-linked disaccharides. *Eur. J. Org. Chem.*, **2004**, 395–405.

73 Marmet, D., Boullanger, P., and Descotes, G. (1981) Reaction des glycosyl isonitriles avec les amines et les alcools. *Can. J. Chem.*, **59**, 373–378.

74 Barton, D.H.R., Bringmann, G., Lamotte, G., Motherwell, W.B., Motherwell, R.S.H., and Porter, A.E.A. (1980) Reactions of relevance to the chemistry of aminoglycoside antibiotics. Part 14. A useful radical-deamination reaction. *J. Chem. Soc., Perkin Trans. 1*, 2657–2664.

75 Tavecchia, P., Trumtel, M., Veyrières, A., and Sinaÿ, P. (1989) Glycosylations with N-formylamino sugars: a new approach to 2′-deoxy-β-disaccharides. *Tetrahedron Lett.*, **30**, 2533–2536.

76 Trumtel, M., Tavecchia, P., Veyrières, A., and Sinaÿ, P. (1989) The synthesis of 2′-deoxy-β-disaccharides: novel approaches. *Carbohydr. Res.*, **191**, 29–52.

77 Grenouillat, N., Vauzeilles, B., and Beau, J.-M. (2007) Lipid analogs of the nodulation factors using the Ugi/Passerini multicomponent reactions: preliminary studies on the carbohydrate monomer. *Heterocycles*, **73**, 891–901.

78 Garson, M.J. and Simpson, J.S. (2004) Marine isocyanides and related natural products–structure, biosynthesis and ecology. *Nat. Prod. Rep.*, **21**, 164–179.

79 Scheuer, P.J. (1992) Isocyanides and cyanides as natural products. *Acc. Chem. Res.*, **25**, 433–439.

80 Edenborough, M.S. and Herbert, R.B. (1988) Naturally occurring isocyanides. *Nat. Prod. Rep.*, **5**, 229–245.

81 Cafieri, F., Fattorusso, E., Magno, S., Santacroce, C., and Sica, D. (1973) Isolation and structure of axisonitrile-1 and axisothiocyanate-1 two unusual sesquiterpenoids from the marine sponge *Axinella cannabina*. *Tetrahedron*, **29**, 4259–4262.

82 Carmeli, S., Moore, R.E., Patterson, G.M.L., Mori, Y., and Suzuki, M. (1990) Isonitriles from the blue-green alga *Scytonema mirabile*. *J. Org. Chem.*, **55**, 4431–4438.

83 Gloer, J.B., Poch, G.K., Short, D.M., and McCloskey, D.V. (1988) Structure of brassicicolin A: a novel isocyanide antibiotic from the phylloplane fungus *Alternaria brassicicola*. *J. Org. Chem.*, **53**, 3758–3761.

84 Ishiyama, H., Kozawa, S., Aoyama, K., Mikami, Y., Fromont, J., and Kobayashi, J.-I. (2008) Halichonadin F and the Cu(I) complex of halichonadin C from the sponge *Halichondria* sp. *J. Nat. Prod.*, **71**, 1301–1303.

85 Manzo, E., Carbone, M., Mollo, E., Irace, C., Di Pascale, A., Li, Y., Ciavatta, M.L., Cimino, G., Guo, Y.-W., and Gavagnin, M. (2011) Structure and synthesis of a unique isonitrile lipid isolated from the marine mollusk *Actinocyclus papillatus*. *Org. Lett.*, **8**, 1897–1899.

86 Wright, A.D. and Lang-Unnasch, N. (2009) Diterpene formamides from the tropical marine sponge *Cymbastela hooperi* and their antimalarial activity *in vitro*. *J. Nat. Prod.*, **72**, 492–495.

87 Caine, D. and Deutsch, H. (1978) Total synthesis of (–)-axisonitrile-3. An application of the reductive ring opening of vinylcyclopropanes. *J. Am. Chem. Soc.*, **100**, 8030–8031.

88 Srikrishna, A., Ravi, G., and Venkata Subbaiah, D.R.C. (2009) Enantioselective first total syntheses of 2-(formylamino) trachyopsane and ent-2-(isocyano) trachyopsane via a biomimetic approach. *Synlett*, 32–34.

89 Piers, E., Yeung, B.W.A., and Rettig, S.J. (1987) Methylenecyclohexane annulation. Total synthesis of (±)-axamide-1, (±)-axisonitrile-1, and the corresponding C-10 epimers. *Tetrahedron*, **43**, 5521–5535.

90 Kuo, Y.-L., Dhanasekaran, M., and Sha, C.-K. (2009) Total syntheses of (±)-axamide-1 and (±)-axisonitrile-1 via 6-*exo-dig* radical cyclization. *J. Org. Chem.*, **74**, 2033–2038.

91 Miyaoka, H. and Okubo, Y. (2011) Total synthesis of amphilectane-type diterpenoid (±)-7-isocyanoamphilecta-11(20),15-diene. *Synlett*, 547–550.

92 Muratake, H., Kumagami, H., and Natsume, M. (1990) Synthetic studies of marine alkaloids hapalindoles. Part 3. Total synthesis of (±)-hapalindoles H and U. *Tetrahedron*, **46**, 6351–6360.

93 Reisman, S.E., Ready, J.M., Weiss, M.M., Hasuoka, A., Hirata, M., Tamaki, K., Ovaska, T.V., Smith, C.J., and Wood, J.L. (2008) Evolution of a synthetic strategy: total synthesis of (±)-welwitindolinone A isonitrile. *J. Am. Chem. Soc.*, **130**, 2087–2100.

94 Avíles, E. and Rodríguez, A.D. (2010) Monamphilectine A, a potent antimalarial β-lactam from marine sponge Hymeniacidon sp: isolation, structure, semisynthesis, and bioactivity. *Org. Lett.*, **12**, 5290–5293.

95 White, R.D. and Wood, J.L. (2001) Progress toward the total synthesis of kalihinane diterpenoids. *Org. Lett.*, **3**, 1825–1827.

96 Richter, J.M., Ishihara, Y., Masuda, T., Whitefield, B.W., Llamas, T., Pohjakallio, A., and Baran, P.S. (2008) Enantiospecific total synthesis of the hapalindoles, fischerindoles, and welwitindolinones via a redox economic approach. *J. Am. Chem. Soc.*, **130**, 17938–17954.

97 Baran, P.S., Maimone, T.J., and Richter, J.M. (2007) Total synthesis of marine natural products without using protecting groups. *Nature*, **446**, 404–408.

98 Nishikawa, K., Nakahara, H., Shirokura, Y., Nogata, Y., Yoshimura, E., Umezawa, T., Okino, T., and Matsuda, F. (2010) Total synthesis of 10-isocyano-4-cadinene and determination of its absolute configuration. *Org. Lett.*, **12**, 904–907.

99 Tamura, K., Nakazaki, A., and Kobayashi, S. (2009) Stereocontrolled total synthesis of antimalarial (+)-axisonitrile-3. *Synlett*, 2449–2452.

100 Baran, P.S. and Richter, J.M. (2005) Enantioselective total syntheses of welwitindolinone A and fischerindoles I and G. *J. Am. Chem. Soc.*, **127**, 15394–15396.

101 Fukuyama, T. and Chen, X. (1994) Stereocontrolled synthesis of (–)-hapalindole G. *J. Am. Chem. Soc.*, **116**, 3125–3126.

102 Nolte, R.J.M., van Beijnen, A.J.M., and Drenth, W. (1974) Chirality in polyisocyanides. *J. Am. Chem. Soc.*, **96**, 5932–5933.

103 Le Gac, S., Schwartz, E., Koepf, M., Cornelissen, J.J.L.M., Rowan, A.E., and Nolte, R.J.M. (2010) Cysteine-containing polyisocyanides as versatile nanoplatforms for chromophoric and bioscaffolding. *Chem. Eur. J.*, **16**, 6176–6186.

104 Cornelissen, J., Rowan, A.E., Nolte, R.J.M., and Sommerdijk, N. (2001) Chiral architectures from macromolecular building blocks. *Chem. Rev.*, **101**, 4039–4070.

105 Schwartz, E., Koepf, M., Kitto, H.J., Nolte, R.J.M., and Rowan, A.E. (2011) Helical poly(isocyanides): past, present and future. *Polym. Chem.*, **2**, 33–47.

106 Van Beijnen, A.J.M., Nolte, R.J.M., Drenth, W., and Hezemans, A.M.F. (1976) Screw sense of polyisocyanides. *Tetrahedron*, **32**, 2017–2019.

107 Hase, Y., Nagai, K., Iida, H., Maeda, K., Ochi, N., Sawabe, K., Sakajiri, K., Okoshi, K., and Yashima, E. (2009) Mechanism of helix induction in poly(4-carboxyphenyl isocyanide) with chiral amines and memory of the macromolecular helicity and its helical structures. *J. Am. Chem. Soc.*, **131**, 10719–10732.

108 Clericuzio, M., Alagona, G., Ghio, C., and Salvadori, P. (1997) Theoretical investigations on the structure of poly(iminomethylenes) with aliphatic side chains. Conformational studies and comparison with experimental spectroscopic data. *J. Am. Chem. Soc.*, **119**, 1059–1071.

109 Green, M.M., Gross, R.A., Schilling, F.C., Zero, K., and Crosby, C. (1988) Macromolecular stereochemistry–effect of pendant group-structure on the conformational properties of polyisocyanides. *Macromolecules*, **21**, 1839–1846.

110 Cornelissen, J., Donners, J., de Gelder, R., Graswinckel, W.S., Metselaar, G.A., Rowan, A.E., Sommerdijk, N., and Nolte, R.J.M. (2001) β-Helical polymers from isocyanopeptides. *Science*, **293**, 676–680.

111 Nolte, R.J.M. (1994) Helical poly(isocyanides). *Chem. Soc. Rev.*, **23**, 11–19.

112 Onitsuka, K., Mori, T., Yamamoto, M., Takei, F., and Takahashi, S. (2006) Helical sense selective polymerization of bulky aryl isocyanide possessing chiral ester or amide groups initiated by arylrhodium complexes. *Macromolecules*, **39**, 7224–7231.

113 Onitsuka, K., Yamamoto, M., Mori, T., Takei, F., and Takahashi, S. (2006) Living polymerization of bulky aryl isocyanide with arylrhodium complexes. *Organometallics*, **25**, 1270–1278.

114 Metselaar, G.A., Cornelissen, J., Rowan, A.E., and Nolte, R.J.M. (2005) Acid-initiated stereospecific polymerization of isocyanopeptides. *Angew. Chem. Int. Ed.*, **44**, 1990–1993.

115 Kajitani, T., Okoshi, K., and Yashima, E. (2008) Helix-sense-controlled polymerization of optically active phenyl isocyanides. *Macromolecules*, **41**, 1601–1611.

116 Onouchi, H., Okoshi, K., Kajitani, T., Sakurai, S.I., Nagai, K., Kumaki, J., Onitsuka, K., and Yashima, E. (2008) Two- and three-dimensional smectic ordering of single-handed helical polymers. *J. Am. Chem. Soc.*, **130**, 229–236.

117 Gomar-Nadal, E., Veciana, J., Rovira, C., and Amabilino, D.B. (2005) Chiral teleinduction in the formation of a macromolecular multistate chiroptical redox switch. *Adv. Mater.*, **17**, 2095–2098.

118 Hida, N., Takei, F., Onitsuka, K., Shiga, K., Asaoka, S., Iyoda, T., and Takahashi, S. (2003) Helical, chiral polyisocyanides bearing ferrocenyl groups as pendants: synthesis and properties. *Angew. Chem. Int. Ed.*, **42**, 4349–4352.

119 Hasegawa, T., Matsuura, K., Ariga, K., and Kobayashi, K. (2000) Multilayer adsorption and molecular organization of rigid cylindrical glycoconjugate poly(phenylisocyanide) on hydrophilic surfaces. *Macromolecules*, **33**, 2772–2775.

120 van Walree, C.A., van der Pol, J.F., and Zwikker, J.W. (1990) A liquid-crystalline poly(iminomethylene) with cholesterol-containing pendant groups. *Rec. Trav. Chem. Pays-Bas*, **109**, 561–565.

121 van der Eijk, J.M., Nolte, R.J.M., Richters, V.E.M., and Drenth, W. (1981) Activity and enantioselectivity in the hydrolysis of substituted phenyl esters catalysed by imidazole-containing poly(iminomethylenes). *Rec. Trav. Chem. Pays-Bas*, **100**, 222–226.

122 Schwartz, E., Bodis, P., Koepf, M., Cornelissen, J.J.L.M., Rowan, A.E., Woutersen, S., and Nolte, R.J.M. (2009) Self-trapped vibrational states in synthetic β-sheet helices. *Chem. Commun.*, 4675–4677.

123 Vriezema, D.M., Kros, A., de Gelder, R., Cornelissen, J.J.L.M., Rowan, A.E., and Nolte, R.J.M. (2004) Electroformed giant vesicles from thiophene-containing rod-coil diblock copolymers. *Macromolecules*, **37**, 4736–4739.