Four-membered rings from isocyanides:
Developments since the mid 1980s

Dietrich Moderhack

Institute of Medicinal and Pharmaceutical Chemistry, Technical University of Braunschweig
D-38106 Braunschweig, Germany, Beethovenstraße 55
E-mail: d.moderhack@tu-bs.de

Dedicated to Professor Rosa M. Claramunt on the occasion of her 65th birthday

Abstract
Reactions of isocyanides with open-chain and cyclic substrates leading to four-membered rings are reviewed. The survey is intended to be illustrative rather than encyclopedic.

Keywords: Isocyanides, cyclization, insertion, heterocycles, element-organic rings

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1. Introduction

Within the wide area of cyclizations involving the isocyano group the direct formation of four-membered rings constitutes an especially intriguing process because of elements of serendipity. The first discoveries date back to the 1960s and were summarized at the end of the decade. The period till 1985, however, proved prolific to such an extent as to warrant a second review. Since that time again new results have emerged in great number; this may justify the present survey. Viewing the rich material, two features stand out: (i) The ring-forming principles have almost trebled so as to exclude an introductory graphic of the kind shown in ref.2; (ii) regarding the type of products, a plethora of element-organic rings have arisen.

Adhering to style and format of the earlier review, presentation of all new material will be arranged according to starting compounds rather than to products or actual mechanisms.

2. Reaction of isocyanides with open-chain substrates

2.1. [1+1+2] Cycloaddition of isocyanides to double and triple bond systems

Alkenes: While a methylenemalononitrile bearing two acceptor groups like the derivative 2a reacts with tert-butyl isocyanide to produce the cyclobutanediimine 1 (Scheme 1), benzylidene analogs (even though substituted with a nitro or fluoro group at the phenyl ligand) were shown to take up three molecules of the isocyanide to yield the five-membered ring 3 instead.

Though not being an open-chain substrate, the behavior of the benzocyclobutadiene complex 4 may be compared to that of 2a. When two equivalents of tert-butyl isocyanide were added to 4, the reagent underwent smooth insertion into both Zr–C bonds to eventually afford the Dewarnaphthalene 5, the structure of which was established by X-ray diffraction. Double insertion of tert-butyl isocyanide had been observed before also with the cyclobutene analog of 4, but in that case the carbon atoms of the two isocyanides did not couple to give a four-membered ring.

![Scheme 1](image)

Scheme 1
Alkynes: Open-chain representatives devoid of an acceptor or donor group are usually inert towards isocyanides. As an exception, a [1+1+2] cycloaddition took place very readily when diphenylethynyl was treated with trifluoromethyl isocyanide to afford the cyclobutenediimine 6 (Scheme 2). The structure of this material was determined by an X-ray structure analysis, showing that the imino functions are E and Z configured. Traces of a (mono)ketone arise unless the solvent is rigorously dried. \(^8\) Similar reactions of this isocyanide were reported – but without experimental details – for but-2-yne and ethoxyethyne, whereas hexafluorobutyne and fluoroalkenes were said to be inert. \(^9\)

However, transition metal-induced [1+1+2] cycloadditions are relatively frequent (cf. ref.\(^2\)); more recent examples include the following: (i) When oct-4-yne was heated with tert-butyl isocyanide and a catalytic amount of dicarbonylcyclopentadienylcobalt(I), the cyclobutenediimine 7 was obtained. \(^10\) Yet, on adding – as a fourth component – trimethylsilyl cyanide (which equilibrates with the isocyanide in situ), the pyrrole 8 resulted (or its N-unsubstituted congener if tert-butyl isocyanide was replaced with cyclohexyl isocyanide). (ii) When the cationic molybdenum complex 9 was treated with six equivalents of 2,6-dimethylphenyl isocyanide, alkyne–isocyanide coupling gave rise to the four-membered ring 10. \(^11\) According to the X-ray analysis, the imino groups are configured as observed earlier with the product 6. \(^8\) – For a further example following the formal [1+1+2] cycloaddition pattern, cf. Section 3.2.

Scheme 2

Alkylidene-, imino-, aminoboranes: Compounds of the type 11 and 13 were shown to take up two isocyanide molecules very readily (Scheme 3). Treatment of the allene-type system 11 with tert-butyl isocyanide afforded the boretanediimine 12, even when using less than two equivalents of
the isocyanide. Accordingly, action of 2,6-dimethylphenyl isocyanide on the iminoborane 13 led to the 1,2-azaboretidinediimine 14, the structure of the product was investigated by X-ray diffraction (a study of 12 is lacking). Analogous behavior was shown by the aminoborane 15; the product 16, however, was accompanied by compound 17 which resulted from attack of un-consumed 15 on the four-membered ring; its amount increased as the reaction was prolonged.

\[
\begin{align*}
\text{Scheme 3} \\
\text{Imines, thioimidates: A new example for addition of two isocyanide molecules across the C=N double bond of an imine is represented by the process } 18 \rightarrow 19 \text{ (Scheme 4). The experiment has been carried out along with studies on } \alpha,\beta\text{-unsaturated imines which, however, afforded amino-pyrrole derivatives instead of analogs of 19.}^{15} \text{ The thioimidate unit of the salts 20a,b could be converted into an azetidine using tert-butyl and isopropyl isocyanide (} 20 \rightarrow 21a-c \text{). But a competing reaction gave the 2-aminoimidazoles 22a-e (by involvement of the HC=NR' moiety of 20).}^{16}
\end{align*}
\]

2.2. [1+2] Cycloaddition of isocyanides to double bond systems and subsequent reactions

Diphosphenes: Experiments with this class showed that the resultant ring type depends on the substituents (Scheme 5): 23a reacts with methyl or trifluoromethyl isocyanide to give the stable diphosphiranimines 24a,b, whereas bis[2,4,6-tri-( tert-butyl)phenyl]diphosphene combines with the latter isocyanide in a 1:3 ratio to afford a 1,3-azaphospholidine derivative instead.\(^{17}\) Three-membered rings like 24c,d were also isolated when the metal-substituted diphosphene 23b was reacted with phenyl or trifluoromethyl isocyanide; the same holds for the reaction of the latter component with the analogous substrate (23c → 24e).\(^{18}\) However, treatment of 23c with several
aryl\textsuperscript{18} and alkyl isocyanides\textsuperscript{19} led directly to 1,3-diphosphetanediimines like 25\texttextsubscript{a-f}; the transient compounds 24\texttextsubscript{f-k}, being prone to P–P fission (cf. Section 3.1), were detected spectroscopically.

\[
\begin{align*}
\text{aryl18 and alkyl isocyanides} & \rightarrow 1,3\text{-diphosphetanediimines like 25a-f} \\
\text{transient compounds} & \rightarrow \text{spectroscopic detection (Section 3.1)}
\end{align*}
\]

\[
\begin{align*}
\text{N} & \text{NBu-t} \\
& \text{NMe2} \\
& \text{N[CH2]5} \\
& \text{NMe2} \\
& \text{N[CH2]5} \\
& \text{Ph} \\
& \text{Cl} \\
& \text{H}
\end{align*}
\]

\[
\begin{align*}
\text{Products (yield, %) / from} & \\
21\text{a-c} & 22\text{a-e}
\end{align*}
\]

\[
\begin{align*}
21, 22 & \text{ R} \quad \text{NR}^2_2 \quad \text{X} \quad \text{RNC (mol)} \quad \text{Time} \quad \text{Products (yield, %) / from} \\
\text{a} & \text{t-Bu} \quad \text{NMe2} \quad \text{SMe} \quad 2 \quad 72 \quad 21\text{a (8), 22a (20), 22d (42) / 20a} \\
\text{b} & \text{i-Pr} \quad \text{NMe2} \quad \text{SMe} \quad 5 \quad 18 \quad 21\text{a (18), 22a (55) / 20a} \\
\text{c} & \text{t-Bu} \quad \text{N[CH2]5} \quad \text{SMe} \quad 5 \quad 18 \quad 21\text{b (30), 22b (44) / 20b} \\
\text{d} & \text{t-Bu} \quad \text{NMe2} \quad \text{H} \quad 2 \quad 48 \quad 21\text{e (16), 22e (28), 22e (25) / 20a} \\
\text{e} & \text{t-Bu} \quad \text{N[CH2]5} \quad \text{H} \quad 4 \quad 10 \quad 21\text{c (25), 22c (45) / 20b}
\end{align*}
\]

\section*{Scheme 4}

\textit{Silenes}: Photolysis of the acylsilane 26\text{a} using 360-nm radiation generated the silene derivative 27\text{a} (Scheme 6). In the presence of one equivalent of \textit{tert}-butyl isocyanide (a) this compound underwent a [1+2] cycloaddition to give the siliranimine 28\text{a} which in turn rearranged into the azasiliridine 29\text{a}.\textsuperscript{20,21} When a mixture of this material and 2,6-dimethylphenyl isocyanide (b) was photolyzed, the 1,3-azasiletidin-2-imine 30\text{a} resulted.\textsuperscript{22} Extending the experiments to the couples 27\text{a} + (a), 27\text{b} + (a), and 27\text{b} + (b), the expected azasiliridines 29\text{b-d} were formed, but these compounds, while eluding isolation, reacted with unconsumed isocyanide and produced the azasiletidines 30\text{b-d}. However, under nonphotochemical conditions (–70 °C; dark) preformed 27\text{a} and 2,6-dimethylphenyl isocyanide (b) gave rise to a mixture of the compounds 29\text{b} and 30\text{b}; this contrasts with the behavior of 27\text{a} towards alkyl isocyanides (cf. above and ref.\textsuperscript{20}), which leads exclusively to the type 29. – Detailed NMR spectroscopic investigations of the products 30\text{a-d} have shown the occurrence of two stereoisomers each for a and b, but only one for c and d. An X-ray diffraction study of the major isomer of 30\text{b} has revealed a Z / E symmetry (C=N /
C=C group) as depicted; for brevity, this stereo formula was used here for 30a,c,d as well. Yields of 30a-d were not disclosed throughout.22

\[
\begin{align*}
\text{23a-c} & \quad \text{24a-e,[f-k]} & \quad \text{25a-f}
\end{align*}
\]

i: 0 or 20 °C / (n-)pentane (for 24a-d), 2-methylbutane (24e); 20 °C / benzene (for 25a,b), toluene (25d), diethyl ether (25e), neat (25f)

\[
\begin{array}{cccccc}
23 & 24 & 25 & R^1 & R^2 & R^3 & \text{Yield (\%) }^c & E : Z \quad^d \\
a & a & C(SiMe_3)_3 & C(SiMe_3)_3 & Me & 61 \\
b & b & C(SiMe_3)_3 & C(SiMe_3)_3 & CF_3 & 63 \\
c & c & [Fe]^a & C(SiMe_3)_3 & CF_3 & 31 \\
d & d & [Fe] & C(SiMe_3)_3 & Ph & 63 \\
e & e & [Fe] & Mes^b & CF_3 & 54 \\
f & f & [Fe] & Mes^b & Ph & 63 & 2 : 1 \\
g & g & [Fe] & Mes^b & 2-MeC_6H_4 & 48 & 2 : 1 \\
h & h & [Fe] & Mes^b & 2,6-MeC_6H_3 & 58 \\
i & i & [Fe] & Mes^b & C_6F_5 & 46 & 6 : 1 \\
j & j & [Fe] & Mes^b & C_6H_{11} & 57 & 2 : 1 \\
k & k & [Fe] & Mes^b & CH_2Ph & 79 & 2 : 1 \\
\end{array}
\]

\(^a [\text{Fe}] = \text{FeCp}^*(\text{CO})_2. \quad ^b \text{Mes}^* = 2,4,6-(t-Bu)_3C_6H_2. \quad ^c \text{Products 24a-e and 25a-f, respectively (no yield for 25e).} \quad ^d \text{Two Z isomers observed.}

**Scheme 5**

A later example of this kind of conversion constitutes the reaction of the neopentyl-substituted silene 27c. This substrate – prepared from (dimesitylfuorosilyl)ethene and tert-butyllithium – gave the silazetidine 30e on treatment with two equivalents of tert-butyl isocyanide.23

It might be added that azasiliridines related to 29 were obtained very recently from isocyanides and a disilene like \(R_2Si=SiRPh\) \([R = 2,4,6-(t-Pr)_3C_6H_2]\), but, remarkably, these products (which have a semicyclic C=Si bond instead of a C=C bond) did not undergo isocyanide insertion to give four-membered rings, *i.e.* silylidene analogs of 30.24

**Phospa-, arsasilenes:** Unique derivatives of the type 30, *i.e.* compounds like 32a-c, arose quantitatively on exposure of the 'heterosilenes' 31a25 and 31b26 to mesityl and cyclohexyl isocyanide (Scheme 7). The reaction was assumed to follow the pattern of the preceding paragraph. Treatment of the products 32b,c with hydrogen chloride (or fluoride), however, met with surprise in that arsasilete derivatives 33a,b were isolated; X-ray crystallography served to establish the
structures of both \(32c\) and \(33b\).\(^{26}\) Extending their ring forming experiments to 1,6-diisocyanohexane, the authors succeeded in converting \(31a,b\) into the corresponding macroheterocycles; of these new products, the arsa representative has also been studied by X-ray diffraction.\(^{27}\)

\[
\begin{align*}
\text{(Me}_3\text{Si)}_2\text{Si} - C - \text{O} & \xrightarrow{0-10^\circ\text{C}} \text{h} \quad \text{(Me}_3\text{Si)}_2\text{Si} = C - \text{O} \quad \text{SiMe}_3 \\
\text{26a,b} & \quad \text{27a,b} & \quad \text{RN} = \text{C} \\
\text{28a-d} & \quad \text{29a} & \quad \text{R} \quad \text{R}' \\
\text{29b-d} & \quad \text{30a} & \quad \text{R} \quad \text{R}' \\
\text{26, 27} & \quad \text{28, 29} & \quad \text{30} & \quad \text{R} & \quad \text{R}' \\
\text{a a} & \text{a} & \text{a} & \text{a} & \text{1-Adamantyl} \\
\text{b b} & \text{2,6-Me}_2\text{C}_6\text{H}_3 & \text{1-Adamantyl} \\
\text{c c} & \text{t-Bu} & \text{2,4,6-Me}_3\text{C}_6\text{H}_2 \\
\text{d d} & \text{2,6-Me}_2\text{C}_6\text{H}_3 & \text{2,4,6-Me}_3\text{C}_6\text{H}_2 \end{align*}
\]

\(^{27a,b}\) Compound \(30a\) isolated as mixed species of two geometric isomers in about 3:2 proportions.

\[
\begin{align*}
\text{Ar}_2\text{Si} = \text{CHCH}_2\text{Bu-} & \quad \xrightarrow{2 \text{ t-BuN} = \text{C}} \text{ether, r. t.} \quad \text{ArSi} - \text{CHCH}_2\text{Bu-} \\
\text{27e} & \quad \text{30e} & \quad \text{Ar} = \text{2,4,6-Me}_3\text{C}_6\text{H}_2
\end{align*}
\]

Scheme 6
Scheme 7

2.3. [1+3] Cycloaddition of isocyanides to 1,3-dipoles

*Nitrile imines*: Detailed studies on the behavior of N-aryl nitrile imines towards isocyanides\(^{28-32}\) have shown that the title reaction occurred under certain conditions.\(^{29,31,32}\) Best suited are nitrile imines bearing a donor-substituted phenyl group at the terminal nitrogen like \(34\), they gave cycloadducts \(36\) with a wide variety of isocyanides (Scheme 8).\(^{31,32}\) These four-membered rings, however, eluded isolation, but their formation could be inferred from products formed by [2+2] cycloreversion into benzonitrile and a carbodiimide \((37)\), by ring expansion to a quinoxaline \((38)\), and finally by [2+2] cycloreversion of the secondary adduct \(39\) into \(37\) and a 1,2,4-triazole \((40)\).

Besides these compounds products such as \(41-45\) were found; formally, they derive from the linear adduct \(35\) which in the case \(R = t\)-Bu could be detected spectroscopically.\(^{33}\)

Compared to \(34\), the proclivity of its N-phenyl analog to undergo a [1+3] cycloaddition is low,\(^{29}\) and with \(Ar = 4\)-NO\(_2\)C\(_6\)H\(_4\) there were no indications at all.\(^{32}\) This failure applies also to nitrile imines having an acceptor group at the C-terminus like an acyl\(^{31}\) or a 4-nitrophenyl substituent.\(^{32}\)
Scheme 8

<table>
<thead>
<tr>
<th>37</th>
<th>Yield (%) a</th>
<th>R</th>
<th>38</th>
<th>Yield (%)</th>
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<td>49</td>
<td>i-Pr</td>
<td>a</td>
<td>15</td>
<td>40 / 2, 42a / 8</td>
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<tr>
<td>b</td>
<td>19</td>
<td>i-Bu</td>
<td>b</td>
<td>3</td>
<td>41 b / 27</td>
</tr>
<tr>
<td>c</td>
<td>43</td>
<td>c-C₆H₁₁</td>
<td>c</td>
<td>25</td>
<td>40 / 2, 42b / 10, 43 / 6</td>
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<tr>
<td>d</td>
<td></td>
<td>CH₃CO₂Et</td>
<td>d</td>
<td>18</td>
<td>44 / 31, 45 / 7</td>
</tr>
<tr>
<td>e</td>
<td>37</td>
<td>4-MeOC₆H₄</td>
<td>e</td>
<td>21</td>
<td>40 / 6</td>
</tr>
<tr>
<td>f</td>
<td>62</td>
<td>2,6-Me₂C₆H₃</td>
<td>f</td>
<td>17</td>
<td>40 / 5</td>
</tr>
</tbody>
</table>

a Yield based on the respective urea. b By elimination of isobutene from transient 1-tert-butyl-2-(4-methoxyphenyl)-5-phenyl-2H-1,2,3-triazolium. c Carbodiimide 37d apparently unstable.
Azomethine imines: In contrast to the aryl functionalized CNN moiety in 46a which, using tert-butyl isocyanide, was earlier cyclized to a 1,2-diazetidine ring (47), the acyl group in the congener 46b, as shown recently, confers upon the molecule a 1,5-dipolar character which led to the formation of a 1,3,4-oxadiazine cycle (48) (Scheme 9).^{34}

Scheme 9

Nitrones: The known cyclization^{2} of the nitrone 49 with cyclohexyl isocyanide to give the 1,2-oxazetidin-4-imine 50 has recently been duplicated for mechanistic purposes (Scheme 10).^{35} To rationalize their synthesis of α-oxoamides from N-alkylhydroxylamines and aliphatic aldehydes under the conditions of the Ugi reaction, the authors thought of 50 as one possible intermediate and submitted this model to their procedure. But, being aware of an old observation,^{36} they confirmed that N–O cleavage in 50 occurred with deprotonation of the N-methyl group (→ 51), not at C(3) which would be necessary for the production of an α-oxoamide.

Scheme 10

Diphosphinoketenimines: Although representing no classical 1,3-dipoles, the title substrates 52 were shown to behave as such (Scheme 11). In the presence of water they reacted with isocyanides to give compounds of the type 54 that were proposed to arise via four-membered rings like 53/53'. Labeling experiments demonstrated that the oxygen and ring-attached hydrogen of 54 originate from the external water; in a rigorously dried medium no reaction occurred.^{37}
Scheme 11

(For 1,3-dipolar behavior of metal-coordinated ketenimines, see Section 2.5.)

2.4. Addition of isocyanides to carbenes (including analogs) and subsequent reactions

Carbenes: The phosphino(silyl)carbene \(55a\), generated from the corresponding diazo precursor, reacted with pentafluorophenyl isocyanide to give the dihydro-1,2-azaphosphete \(57a\), which was established by an X-ray analysis (Scheme 12). The process was explained to involve a transient ketenimine \(56a\) that undergoes a \(P/\rightarrow C/\) migration of one \(NR_2\) group, followed by electrolyclization of the resultant 1-aza-4-phosphabutadiene.\(^{38,39}\) When reacting the arylsubstituted carbone \(55b\) with tert-butyl isocyanide, the respective ketenimine \(56b\) could be characterized spectrosopically, but at room temperature it rearranged slowly into the analogous ring system \(57b\).\(^{40}\)

Scheme 12

Silylenes: Photolysis of the trisilirane \(58\) in the presence of isocyanides has been shown to afford disiletedimines of the type \(61\) and \(62\) (Scheme 13). These compounds arose by coupling of the silylene \(59\) with the isocyanide to give the silaketenimine \(60\) which in turn cyclodimerized. The reaction was performed with phenyl\(^{41}\) and sterically crowded aryl isocyanides,\(^ {42}\) but also with isocyanides bearing electron-withdrawing groups.\(^{43}\) As expected, head-to-tail cyclodimerization prevails; only when using 2,6-diisopropylphenyl isocyanide the head-to-head mode occurred too,
giving minor amounts of the derivative 62c.\(^{42}\) While no yield figure was disclosed in that work, it was later detailed that the derivatives 61c and 62c were isolated in a ratio of ca. 10:1 (regardless of the reaction conditions) and that they were not interconverted photochemically.\(^{44}\) The molecular geometry of 61a,c,d and 62c has been determined by X-ray crystallography.\(^{41-43}\)

\[
\begin{align*}
\text{Scheme 13} \\
\text{Surprising behavior was encountered with the (stable) silylene 63. On treatment with cyclohexyl isocyanide two competing reactions occurred (Scheme 14): (i) } \alpha\text{-addition of the CN and } c\text{-C}_6\text{H}_{11} \text{ moieties of the fragmented reagent furnished the carbonitrile 64; (ii) linear coupling of intact isocyanide led to the silaketenimine 65; this intermediate, in contrast to species 60 (cf. Scheme 13), took up another isocyanide to generate a four-membered ring (→ 66); stabilization of its carbene function by uptake of a third isocyanide, followed by hydrogen migration from the cyclohexylimino group, gave the product 67, the structure of which was established by the X-ray method.}^{45}
\end{align*}
\]

\begin{table}
\centering
\begin{tabular}{ll||ll}
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<thead>
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<th>61 / 62</th>
<th>R</th>
<th>Yield (%)</th>
<th>61</th>
<th>R</th>
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<td>d</td>
<td>CF(_3)</td>
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<tr>
<td>b</td>
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<td>C(_6)F(_5)</td>
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<td>76 / minor</td>
<td>f</td>
<td>3,5-(CF(_3))(_2)C(_6)H(_3)</td>
<td>59</td>
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\end{table}

\textit{Borylenes}: An interesting borylene-to-isocyanide transfer resulting in the final formation of the four-membered rings 70a,b happened when the chromium complex 68 was treated with certain aryl isocyanides (Scheme 15). The reaction assumedly involved a [1+2] cycloadduct (69) that was susceptible to isocyanide insertion. The molecular structure of 70a was elucidated by X-ray diffraction.\(^{46}\)
Scheme 14

\[
(Me_3Si)_2N=\overset{\text{B}=\overset{\text{M}}{L_n}}{\text{N}} \quad \overset{\text{RN}=\text{C}}{\text{68}} \quad \overset{\text{RN}=\text{C}}{\text{C_6D_6 \ r.t.}} \quad \overset{\text{RN}=\text{C}}{\text{69}} \quad \overset{\text{RN}=\text{C}}{\text{70a,b}}
\]

\[\text{Ar}^1 = 2,4,6-\text{Me}_3C_6H_2 \quad \text{Ar}^2 = 2,6-(\text{i}-\text{Pr})_2C_6H_3\]

Scheme 15

\[
\overset{\text{71a-d}}{\text{R}_2N^+\text{P}^+\text{R}_2N^-} \quad \overset{\text{R'}N=\text{C}}{\text{72a-g}} \quad \overset{\text{t-BuN=C}}{\text{73a,b}}
\]

\[\text{A} = \text{H}_2\text{C}≡\text{CMe}_2 \quad \text{B} = \text{R}_2\text{NH}_2^+ \text{X}^-\]

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<th>R</th>
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</table>

Scheme 16
**Phospheniums (Addendum):** Carbenoid properties are also exhibited by phosphenium salts like 71a-d (Scheme 16). These substrates couple with alkyl isocyanides to give transient phosphaketenimines (72a-g) which, depending on the substituents, react with a second molecule of isocyanide to afford either dicyanophosphine derivatives (73a,b) or imino-substituted dihydro-1,3-aza-phosphetium salts (74b-g). When the intermediate 72b took up tert-butyl isocyanide, both routes were followed so as to reduce the yield of the product 74b.47,48

2.5. Addition of isocyanides to Fischer carbone complexes and subsequent reactions

Isocyanides combine with Fischer-type carbenes to generate ketenimine complexes of the type A (Scheme 17). The mechanism of the process has recently been studied, showing that A is formed via a metallacyclopropanimine followed by isomerization and 1,2-metallotropic rearrangement.49 Preparatively, these species have turned out to be valuable building blocks for a variety of four-, five-, and six-membered rings (for reviews, see refs. 50,51). Concentrating on the first mentioned class, this section will describe applications of the synthetic principles outlined below. Beyond that, mention will be made of the ring contraction of a single [2+3] cycloadduct obtained from A.

![Scheme 17](image)

**Scheme 17**

**Dimerization:** Carbene complexes such as 75 react with alkyl isocyanides to give the corresponding ketenimine complexes 76 (Scheme 18). On being heated in an inert solvent, these coupling products slowly dimerize to afford the metal-coordinated cyclobutadiimines 78.52–54 The symmetrical [2+2] cycloaddition which is unusual for free ketenimines is template-induced and thought to proceed through an intermediate like 77. Part of this remarkable reaction has been reviewed earlier.2
Intramolecular cycloaddition: Ketenimine complexes bearing an alk-3-enyl moiety at the carbon atom like the derivatives 80a-c undergo, once generated from the precursor 79, an intramolecular \([2s+2a]\) cycloaddition (Scheme 18). Owing to the involvement of the cycloheptatrienyl ligand, the cyclobutanimine unit becomes part of a tricyclic system, as illustrated by the products 81a-c. Of these materials, two stereoisomers were found; the structure of anti-81c has been determined by X-ray crystallography. Attempts to demetalate this derivative with pyridine caused fragmentation of the four-membered ring.55

\[
\text{MeO} C = M(CO)_5 + RN=C \xrightarrow{\Delta} \text{MeO} C = C = N \xrightarrow{\Delta} \text{MeO} C = C = N \text{M(CO)}_4
\]

R' = Me, Ph, 2-thienyl, naphthyl (unspecified); M = Cr, Mo, W; R = Me, \(t\)-Bu, \(c\)-C\(_6\)H\(_{11}\)

Scheme 18

Addition of isocyanides: Ketenimine complexes exhibit 1,3-dipolaroid properties. Using isocyanides as dipolarophiles, 4-iminoazetidin-2-ylidene complexes can arise (Scheme 19). Success and extent of this reaction depend primarily on the metal. Thus, starting from the iron carbene complex 82a, the desired products, e.g. 84a-d, were obtained in high yield regardless of the nature of the isocyanide; the intermediary ketenimine complexes 83a-d were not observed.56,57 Yet, in the
case of the tungsten complex 82b, the [1+3] cycloaddition became a side reaction: Employing benzyl isocyanide, 84e was accompanied by the indanedione 86a and the complex 87a.57 and using alkenyl isocyanides, relatively high quantities of the 2H-pyrroles 88a,b were isolated besides the azetidinylidene complexes 84f,g.58 As the compounds 84 readily undergo oxidative demetalation, they are useful precursors to functionalized β-lactams (→ 85a-c,f).56,58

\[
\begin{align*}
\text{EtO} & \quad \text{Ph} \\
C & \quad \text{M(CO)}_n \\
\text{C} & \quad \text{Ph} \\
\text{RN} & \quad \text{C} \\
\text{Ph} & \quad \text{C} \\
\text{EtO} & \quad \text{Ph} \\
\text{M(CO)}_n & \quad \text{R} \\
\end{align*}
\]

i: light petroleum, r. t. (for a-d,g) or hexane, 0 °C (for e,f)
ii: KMnO₄, H₂O / C₆D₆, r. t. (for a-c) or pyridine N-oxide, toluene, Δ (for f)

<table>
<thead>
<tr>
<th>82</th>
<th>M</th>
<th>n</th>
<th>R</th>
<th>83–85</th>
<th>Yield (%)</th>
<th>84</th>
<th>85</th>
<th>Other / Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Fe</td>
<td>4</td>
<td>Me</td>
<td>94</td>
<td>95</td>
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<td></td>
<td></td>
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<tr>
<td>b</td>
<td>Fe</td>
<td>4</td>
<td>Ph</td>
<td>96a / 76b</td>
<td></td>
<td>86a</td>
<td>10</td>
<td>87a / 14</td>
</tr>
<tr>
<td>c</td>
<td>Fe</td>
<td>4</td>
<td>c-C₆H₁₁</td>
<td>94b / 77b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d</td>
<td>Fe</td>
<td>4</td>
<td>CH₂Ph</td>
<td>80b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e</td>
<td>W</td>
<td>5</td>
<td>CH₂Ph</td>
<td>7</td>
<td>86a</td>
<td>10</td>
<td>87a</td>
<td>14</td>
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<tr>
<td>f</td>
<td>W</td>
<td>5</td>
<td>CH=CH₂</td>
<td>20</td>
<td>88</td>
<td>(Z)-88a / 50, (E)-88a / 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>g</td>
<td>W</td>
<td>5</td>
<td>CH=CHR</td>
<td>31</td>
<td>(Z)-88b / 52, (E)-88b / 10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ref.56 b Ref.51 c No yield figures for 85b,e (formed without side materials).56

Scheme 19

Further derivatives 84 could be prepared from the manganese complex 82c (Scheme 20).59 This species is less reactive towards isocyanides than the substrates 82a,b. Moreover, the excess isocyanide which is necessary for ring closure tends to displace the metal from the ketenimine complex 83 to leave a mixture of the isocyanide complex 87 and the free ketenimine 89. As a
consequence of this competing process, the 'regular' products 84h-j were accompanied by [2+2] cycloadducts like 90a-c; the proportions varied with the conditions and the kind of isocyanide. Since the conversion 83 → 84 proceeds more slowly than the step 82c → 83, it was also possible to construct azetidinylidene complexes 84 (including the type 90) from two different isocyanides; this is exemplified by the couples 84k / 90d and 84l / 90e. Representatives of both ring series such as 84h,i and 90a,b could be demetalated with permanganate salt to give the β-lactams 85a,b and 91a,b, respectively.59

\[
\begin{align*}
\text{83h-j} & \quad \xrightarrow{\text{RN=C}} \quad \text{84h-j} \\
\text{83h,i} & \quad \xrightarrow{\text{RN=C}} \quad \text{84k} \quad \text{841} \\
\text{84h,i} & \quad \xrightarrow{\text{RN=C}} \quad \text{90a,b} \\
\text{i: toluene, } & \quad \text{ii: KMnO}_4, \text{ diethyl ether / } H_2O, \text{ r. t.}
\end{align*}
\]

<table>
<thead>
<tr>
<th>(83, 84)</th>
<th>(R)</th>
<th>(87)</th>
<th>(89 - 91)</th>
<th>Yield (%(84 / 90))</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>(h)</td>
<td>Me</td>
<td>b</td>
<td>a</td>
<td>30 [4] / 15 [25]</td>
<td>60 °C (4 h) → 100 °C (3 h) [100 °C (4 h)]</td>
</tr>
<tr>
<td>(i)</td>
<td>Ph</td>
<td>c</td>
<td>b</td>
<td>67 [37] / 4 [10]</td>
<td>60 °C (4 h) → 100 °C (3 h) [100 °C (4 h)]</td>
</tr>
<tr>
<td>(j)</td>
<td>CH(_2)Ph</td>
<td>d</td>
<td>c</td>
<td>29 / trace</td>
<td>100 °C (3.5 h)</td>
</tr>
</tbody>
</table>

Scheme 20
In contrast to the ketenimine complexes 83a-j dealt with above, analogs prepared from the chromium complexes 82d,e did not undergo [1+3] cycloadditions with isocyanides (Scheme 21). After 83k,l have taken up methyl and phenyl isocyanide, respectively, cyclization engaged the C- and N-attached aryl groups to give the indane-2,3-diimine 86b60 and – through hydrolysis of the enol ether – the 3-aminoindole 92.54,61 However, in the case of 4-nitrophenyl isocyanide, i.e. with the intermediary 1:1 adduct formed from 83m, generation of an indole is impeded because of the electron-withdrawal exerted by the nitro group; hence, a further isocyanide molecule will attack to eventually afford the azetidine-2,3-diimine 93 – formally a [1+1+2] cycloadduct of two isocyanides and one ketenimine (for another rare example, cf. ref.2).

Addition of alkynes: a) Alk-1-ynes: Two types of 4-ylideneazetidin-2-ylidene complexes arise, when the second isocyanide that effects ring closure to 84 and 90 (cf. Scheme 19, 20) is replaced with a 1-unsubstituted alk-1-yne (94) (Scheme 22). Heating an equimolar mixture of 82b, cyclohexyl isocyanide, and (trimethylsilyl)ethyne (94a), the four-membered rings 95a and 97a were formed (isolated as the silicon-free derivatives b). While the process leading to 95 can be compared to that giving 84, the formation of 97 resembles the route to series 90; the vinylidene complexes 96 – putative intermediates – may arise directly from 82b. Using alkynes like 94b,c, only the derivatives 97c,d were found, with the Z isomer predominating.62
b) Ynamines: The reaction of the ketenimine complexes 83 with the electron-rich diethyl-(prop-1-ynyl)amine took an unexpected course: Treatment of 83n,o (isolated pure) furnished the 2,3-dihydroazete complexes 99a,b (Scheme 22). Here four atoms of the original ketenimine unit were incorporated into the product (the structure of 99b was studied by X-ray crystallography).

\[ \text{Scheme 22} \]

\[ \text{b) Ynamines: The reaction of the ketenimine complexes 83 with the electron-rich diethyl-(prop-1-ynyl)amine took an unexpected course: Treatment of 83n,o (isolated pure) furnished the 2,3-dihydroazete complexes 99a,b (Scheme 22). Here four atoms of the original ketenimine unit were incorporated into the product (the structure of 99b was studied by X-ray crystallography).} \]
Mechanistically, the reaction was understood as proceeding through an adduct of the type 98; in this species a hydrogen transfer from the CHR2 group to the central keteniminium carbon took place to generate the intermediate 98' which underwent electrolycclization. In the case of 98b, a second mode was operative, i.e. intramolecular [2+2] cycloaddition to the 1,4-dihydroazetidine complex 100 which on work-up was hydrolyzed to the β-lactam 101 (no yield).63

Ring contraction (Addendum): An unexpected formation of a four-membered ring was encountered when the [2+3] cycloadduct 102 from the ketenimine complex 83h (for preparation, see Scheme 20) and carbon disulfide was oxidized with aqueous permanganate (Scheme 23). Besides the regular product – the thiazolidin-5-one 103 – small amounts of the 3-iminothietane-2-thione 104 were detected; formally, this material arose through ring contraction of 'deoxygenated' 103. Both compounds were formed in a 20:1 ratio with a total yield of 96% (crude).64

Scheme 23

2.6. Miscellaneous

Functionalized phosphino(phosphonio)carbene: Treatment of the salt 105 with two equivalents of tert-butyl isocyanide gave rise to the 1,3-diphosphetanium ring as in 108 (no yield); employment of only one equivalent led to the recovery of 50% of the starting substrate (Scheme 24).65 The reaction commenced with formation of the ketenimine 106; but, while stable when unprotonated (cf. ref.66), this species rapidly inserts the second isocyanide into the P–H bond to give an intermediate like 107 which underwent ring closure through elimination of diisopropylamine.

Butynedioic acid ester: It is known that reactions of isocyanides with dimethyl butynedioate (DMAD) do not follow the pattern of Section 2.1, i.e. giving cyclobutenediimines.2 However, a four-membered ring may arise from that reagent by another route. Indeed, a more recent study using cyclohexyl isocyanide has shown that – besides the cyclopenta[h]pyridine 109 (including minor quantities of an isomer and a 1-azaspiro[4.4]nonatriene) – the cyclohepta-anellated azetidinimine 110 was formed (Scheme 25).67,68 As a direct precursor the 3:1 cycloadduct of DMAD and the isocyanide, i.e. the cycloheptatrienimine 111, has been invoked.67 To rationalize its conversion into 110, a transient species like 112 is added here tentatively. Ensuing work of other
authors concentrated on the preparation of 109 (including an X-ray study of the product); additional compounds were not reported.69

\[
\begin{align*}
\text{CF}_3\text{SO}_3^- & \quad \text{NF}_2 \\
\text{t-BuN} & \quad \text{C} + \\
\text{R}_2\text{N} & \quad \text{H} \\
\text{CF}_3\text{SO}_3^- & \quad \text{R}_2\text{N} \\
\text{105} & \\
\text{R} = \text{i-Pr} \\
\text{i: CH}_2\text{Cl}_2, -78^\circ \text{C} \to \text{r. t.}
\end{align*}
\]

**Scheme 24**

\[
\begin{align*}
\text{E} & \quad \text{R-N=CH}_2 \\
\text{R} & \quad \text{E} \\
\text{NR} & \quad \text{E} \\
\text{109 (28\%)} & \\
\text{R} = \text{i-C}_6\text{H}_{11} \\
\text{E} = \text{CO}_2\text{Me}
\end{align*}
\]

**Scheme 25**

*Oligosilanes:* Insertion of isocyanides into the Si–Si bond involving a unique skeletal rearrangement has been encountered when the tetrasilanes 113a-c and the hexasilane 113d were reacted with certain aryl isocyanides in the presence of a palladium catalyst and 1,1,3,3-tetramethylbutyl isocyanide (115) (Scheme 26). This procedure gave the 1,2,4-azadisiletanes 114a-g and 114h, respectively.70,71 The structures of 114c70 and 114h71 have been elucidated by X-ray crystallography. Regarding the tert-alkyl isocyanide 115, this additive, without entering the four-membered ring, has proved an effective promotor in most cases as evidenced by comparison of the yields.71
Organoauminum compounds: tert-Butyl isocyanide was found to undergo double insertion into one Al–C bond of tris(tetramethylcyclopentadienyl)aluminum (116) to form the four-membered ring 117 (Scheme 27). The cyclic structure has been elucidated by X-ray diffraction. The strong Al–N linkage seems to be the driving force behind the twofold insertion which is favored to such an extent as to leave unreacted 116 when working with less than two equivalents of isocyanide.72

Insertion of isocyanides into the Al–Al bond of the dialane 118 resulted in the formation of a three- or four-membered ring, depending on the reagent and conditions. Using one equivalent of tert-butyl isocyanide, compound 119a was obtained as the single product. However, phenyl isocyanide not only afforded the expected derivative 119b, but also gave 17% of the product of double insertion, i.e. the bicyclic system 120. Hence, on repeating the experiment with two equivalents of this isocyanide, compound 120 was isolated exclusively. An analogous run with tert-butyl isocyanide was not reported.73

The aluminum(I) complex 121 (dealt with in this section for practical reasons) was found to react very readily with two equivalents of 2,6-diisopropylphenyl isocyanide. When this reagent was added neat to a suspension of 121 in a minimum amount of solvent, the remarkable compound 122 was isolated. Its formation was thought to proceed through consecutive coupling of both isocyanides leaving a four-membered ring, the carbenic C(4) of which interfered with the adjacent isopropyl group to give the stable product 122. When working in a dilute medium, compound 123 arose, possibly via insertion of the two isocyanides into one of the Al–C bonds to be followed by a skeletal rearrangement of the resultant eight-membered ring. The structures of 122 and 123 have been determined by X-ray crystallography.74
Scheme 27

(Diaminoboryl)silanes: Insertion of an aryl isocyanide into the Si–B bond of the borylsilanes 124 generates (boryl)(silyliminomethanes (125) (Scheme 28). Compounds of this type, e.g. 125a (R= Me, Ar = 3,5-Me₂C₆H₃), are obtained in high yield when working at room temperature. However, in refluxing toluene an unexpected rearrangement took place, consisting in a 1,2-shift of the silyl group to leave an (amino)(boryl)carbene species which engaged an adjacent isopropyl group to form the 1,2-azaboretidine 126a. The reaction was shown to be limited to isocyanides having a free ortho-position. Thus, while the reaction of 124a with 2,6-dimethylphenyl isocyanide even at 110 °C did not go beyond the stage of insertion (125), four-membered rings like 126b-d were formed readily from a range of 2-alkynylphenyl isocyanides. Extending the experiments to 1,2-disiocyanobenzenes, only one –N=C group reacted with the substrate to give the benzimidazolyl substituted azaboretidines 127a-c; the two derivatives a,b having R" = H were obtained at room temperature. X-ray crystallographic data are available for the products 126d and 127a.
**Tris(trimethylsilyl)silyllithium:** The silyllithium substrate 128 was found to react smoothly with two molecules of 2,6-dimethylphenyl isocyanide to form, in the presence of \(N,N,N',N'\)-tetramethylethlenediamine (tmeda), the 1,2-dihydro-1,2-azasilete derivative 129 (Scheme 29).\(^{76}\) The process assumedly started with the formation of a lithioaldimine followed by migration of one silyl group to generate a silene species which incorporated the second isocyanide via electron cyclization. Quenching of 129 with trimethylsilyl triflate afforded the derivate 130,\(^{76}\) while treatment with cyclopentadiene yielded the conjugated acid 131.\(^{77}\) Moreover, reacting 128 in the presence of the soft 1,2-bis(dimethylphosphino)ethane gave a product 129 having THF instead of tmeda.\(^{77}\) Detailed X-ray diffraction studies have been conducted with both 129 and 131.\(^{76,77}\)

\[
\text{PhR}_2\text{Si} + \text{ArN} \rightarrow \text{PhR}_2\text{Si} + \text{ArN} \rightarrow \text{PhR}_2\text{Si} + \text{ArN} \rightarrow \text{PhR}_2\text{Si} + \text{ArN}
\]

\[
\text{Scheme 28}
\]

**Dilithium tert-butylarsinide and -phosphinide:** Action of the arsenic compound 132a on cyclohexyl isocyanide caused trimerization of the latter to form the product 133 which was isolated after addition of cyclohexane and diglyme (Scheme 30). By contrast, usage of the phosphorus analog 133b led to an engagement of six equivalents of the isocyanide to generate the more complicated structure 134 and, as a side product, an open-chain material originating from cyclohexynitrile. The constitution of both cyclic products has been established by X-ray analyses.\(^{78}\)
\[ \text{[LiSiR}_3(\text{THF})_3] } \rightarrow \begin{array}{c} \text{ArN} = \text{C} \\
\text{Li} \end{array} \quad \left[ \begin{array}{c}
\frac{\text{ArN} = \text{C}}{= \text{SiR}_3} \\
\frac{\text{Li}}{= \text{SiR}_2} \end{array} \right] \rightarrow \begin{array}{c} \text{ArN} = \text{C} \\
\text{(tmeda) Li} \end{array} \]

\[ \text{i: pentane, tmeda, } -80 \degree \text{C r. t. ii: pentane, } -40 \degree \text{C r. t. iii: pentane, } -60 \degree \text{C r. t.} \]

Scheme 29

\[ \text{t-Bu}=\text{As} \rightarrow \text{Li} + 3 \text{RN} = \text{C} \rightarrow \frac{1}{2} \]

\[ \text{R} = \text{c-C}_6\text{H}_{11} \]

Scheme 30

\text{Tetragermabutadiene:} Studies on the behavior towards the heavy chalcogens selenium and tellurium have revealed that the title substrate 135 (Scheme 31) is capable of undergoing [1+4] cycloadditions or Ge–Ge bond scissions, depending on the reagents. The former mode was followed by selenium, whereas treatment with tellurium caused fragmentation of the substrate. In this context the reaction with 2-methoxyphenyl isocyanide was probed too, showing that one Ge–Ge bond was broken: while the extruded germylene dimerized, the residual Ge 3 chain cyclized to the 1,4-dihydrotrigermet-4-imine 136 which was characterized by X-ray crystallography.79
3. Reaction of isocyanides with cyclic substrates

3.1. Insertion of isocyanides into three-membered rings

**Triafulvenes**: In a fashion similar to the behavior of cyclopropenones towards isocyanides, the triafulvenes 137a-c underwent ring expansion to the 2-ylidenecyclobutenimines 138a-h when treated with the respective isocyanides in an aprotic medium (Scheme 32).80 From the substrates 137d,e, however, four-membered rings such as 138i-m could not be obtained. In this instance two equivalents of the isocyanide were engaged to afford, depending on the substituents R1, R2, and R3, (i) the cyclopentenediimine 139 or the azapentalenes 140a,b (which were formed through intramolecular dehydrogenation of a precursor like 139 having CH2Ph and CH2CO2Et instead of t-Bu), and (ii) the furo[b]pyridine derivatives 141a,b when reacting the benzoyl-containing triafulvene 137e.

**Cyclopropenylioborates**: Studies on this class led to the discovery of another insertion of an isocyanide into a cyclopropene ring (Scheme 33): Compound 143 – easily prepared from 142 – or its product of hydrolysis (144) reacted with tert-butyl isocyanide to give the cyclobutenimine 145 in good or reasonable yield. The molecular geometry was determined by X-ray diffraction.83

**Cyclopropanedicarboxylic acid esters**: A lanthanide-catalyzed insertion of aryl isocyanides into bis-acceptor activated cyclopropanes like 146 has been reported to lead directly to the cyclopentene derivatives 148 (Scheme 34). Substrates devoid of the Ar1 ligand (which functions as an additional activator) failed to react. The conversion was viewed as proceeding via four-membered rings like 147, but these species could not be observed for their high proclivity to insert an isocyanide themselves (as exemplified for Ar1 = Ph / Ar2 = 4-MeOC6H4).84 Hence, the reaction of 146 parallels the behavior of oxiranes, viz. the occurrence of double isocyanide insertion, with the failure to detect a four-membered ring, which belies the quotation made in ref.84.
Scheme 32
Scheme 33

E = CO₂Me/Et  \[\text{ML}_2 = \text{Pr(CF}_3\text{SO}_3)_2\text{ (20 mol\%)} \]

Ar¹ = Ph, 4-Me/MeOC₆H₄, 2-furyl/-thienyl  \[\text{Ar}² = 4-\text{MeO/MeSC}_6\text{H}_₄, 3-\text{Cl-4-MeOC}_6\text{H}_₃\]

Scheme 34

**1H-Aluminirene:** tert-Butyl isocyanide was found to insert under very mild conditions into the aluminirene unit of the spiro substrate 149 to form the unique molecule 150. Of this compound stable \(E\) and \(Z\) isomers were detected by NMR spectroscopy. Crystallization gave a solid in 57% yield that, according to X-ray diffraction, represented the \(Z\) configured form. It may be added by analogy that carbon monoxide transformed 149 into the corresponding aluminetimine.⁸⁶
**Scheme 35**

α-Lactams: The conversion of this class into imino-substituted β-lactams through reaction with isocyanides is well established. In a more recent work a stereochemical aspect was investigated (Scheme 36). Heating the enantiomer (R)-151 with tert-butyl isocyanide gave rise to a β-lactam like (E,R*)-153 of unknown absolute configuration (low enantiomeric excess), i.e. the stereochemical information got almost lost (if not fully). This was rationalized by considering the behavior of the zwitterionic intermediate (R)-152: this species, formed with inversion at C(3), did not cyclize directly [which must have led to (E,R)-153], but in a competing step it underwent a 1→3/hydrogen shift to generate the ketenimine 154 which would yield racemic (E)-153.

![Scheme 35](image)

**Scheme 36**

Siliranes: The insertion of isocyanides into siliranes was found to affect the Si–C bond. The first known examples originated from experiments with substrates like 155a-c and aryl isocyanides which gave the siletan-2-imines 156a-c (Scheme 37). Of these products the derivative 156b has been studied by X-ray diffraction, showing a practically planar four-membered ring with elongated Si–C and C–C bonds and a Z configured imine function. Soon thereafter other authors investigated regioselectivity and stereospecificity: (i) Studying the behavior of the monosubstituted
siliranes 155d-f towards tert-buty isocyanide, they found that insertion occurred at the more substituted Si–C bond (→ 156d-f), but this regioselectivity was gradually eroded as the substituent R1 became bulkier. (ii) Reactions of cis- and trans-155g with p-tolyl and tert-buty isocyanide revealed that the formation of the respective siletan-2-imines 156g,h proceeded with stereospecific retention of configuration. As for the reactivity of these compounds, it was observed inter alia that both cis- and trans-156g,h tautomerase to 2-amino-1,4-dihydrosiletanes on heating.89

Scheme 37

_Thiirene S-oxides:_ Isocyanide insertion into the thiirene half-ring of 157 has been accomplished with 4-nitrophenyl isocyanide (Scheme 38).90 However, as observed with the cyclopropane derivative 146 (cf. Scheme 34), the reaction did not stop at the four-membered ring (158), but proceeded with double insertion to give a thiophenediimine 159 which, depending on the conditions,
was obtained as S-oxide (n=1) or deoxygenated (n = 0). Since four equivalents of the isocyanide were applied in both experiments, it is open whether 158 constitutes an elusive species.

![Scheme 38](image)

**Scheme 38**

**Azoniaboranuidacyclopropane:** The title substrate 160 was found to react readily with tosyl and benzyl isocyanide to give in excellent yield the 1-azonia-3-boranuidacyclobutanimines 161a and b, respectively (Scheme 39). The structure of 161a has been elucidated by X-ray diffraction.91

![Scheme 39](image)

**Scheme 39**

**Azasiliridines:** For preparative reasons this class of compounds is dealt with in Section 2.2.

**2H-Azaphosphirene:** In the presence of a stoichiometric amount of triflic acid the azaphosphirene complex 162 underwent rapid insertion of cyclohexyl isocyanide (Scheme 40). When the reaction was quenched with triethylamine after five minutes, the dihydro-1,3-azaphosphate complex 163 was obtained in high yield. Its structural parameters have been determined by the X-ray method. Interestingly, the 3-(2-thienyl)-substituted analog of 162 did not form the corresponding product 163 (2-thienyl instead of Ph), but was converted into a 2H-azaphosphole derivative.92

**Diphosphiranes, diphosphirenium:** The insertion of isocyanides into the P–P bond of diphosphiranes appears as a consequence of decomposition rather than representing a preparative concept (Scheme 40).93 Substrates like 164a-d (made from isocyanide dichlorides and alkali diphosph-
ides) proved partially labile, depending on the Ar substituent: The derivatives a and b having sterically less demanding ligands released isocyanide within a few hours that reacted with residual 164a,b to give mixtures of the E- and Z-configured 1,3-diphosphetane-2,4-diimines 165a,b; in the case of the derivatives 164c,d, the bulkier substituents caused the respective conversion (→ 165c,d) to occur much more slowly.93

Another example of P–P bond breaking by an isocyanide was observed on treatment of the diphosphirenium salt 166 with tert-butyl isocyanide. As the product of insertion the 1,2-dihydro-1,3-diphosphetium derivative 167 resulted, which was characterized also by X-ray diffraction.94

\[ \text{Ph} \quad (\text{CO})_5W \quad \text{c-C}_6\text{H}_{11}\text{N}=\text{C} \]  
\[ \text{R} = \text{CH(SiMe}_3)_2 \]  
\[ \text{i: CF}_3\text{SO}_2\text{H, CH}_2\text{Cl}_2, -30 \degree\text{C} ; \text{then NEt}_3 \]

\[ 163 \quad (81\%) \]

\[ \text{t-Bu} \quad \text{Ar}=2\text{-MeC}_6\text{H}_4 (\text{a}), 2\text{-Me-4-ClC}_6\text{H}_3 (\text{b}), 2,4-(\text{t-Bu})_2\text{C}_6\text{H}_3 (\text{c}), 2-(\text{t-Bu})\text{C}_6\text{H}_4 (\text{d}) \]

\[ 164a-d \]

\[ 165a-d \]

\[ 166 \quad (70\%) \]

\[ 167 \]

Scheme 40

**Azadiboriridine:** Isocyanides were found capable of breaking the B–B bond of the azadiboridine 168 (Scheme 41). The nature of the products depends on the R ligand of the reagent: Usage of the sterically demanding 2,6-dimethylphenyl isocyanide (one equivalent only!) gave rise to the 1,2,4-azadiboretidin-3-imine 169a, whereas the analogous products from methyl and ethyl isocyanide, i.e. 169b,c, eluded isolation by undergoing a [3+3] cyclodimerization which led to the tricycles 170b,c. Of these derivatives, 170b has been submitted to an X-ray diffraction study.95

**Trisilirane, trigermirane:** Three-membered cycles having silicon or germanium as the sole ring atoms readily incorporate isocyanides (Scheme 42). Thus, on heating 171 with an aryl isocyanide
the trisiletanimines 172a-d\textsuperscript{96} and 172e-g\textsuperscript{97} were formed. Regarding 1,4-diisocyanobenzene, less than one equivalent led to the 'bis' derivative 173 which is also accessible stepwise via 172c; this product\textsuperscript{96} as well as compound 172f\textsuperscript{97} has been studied by X-ray diffraction. The same kind of conversion occurred with the trigermirane 174 when treated with phenyl isocyanide (→ 175).\textsuperscript{98}

\[
\begin{array}{cccc}
169, 170 & R & \text{solvent} & \text{Yield (\%)} \\
\hline
a & \text{2,6-Me}_2C_6H_3 & \text{CH}_2\text{Cl}_2 & 61 (169a) \\
b & \text{Me} & \text{pentane} & 89 (170b) \\
c & \text{Et} & \text{hexane} & 92 (170c) \\
\end{array}
\]

**Scheme 41**

\[
\begin{align*}
& \begin{array}{ccc}
\text{t-Bu} & \text{Bu} & \text{t-Bu} \\
\text{Bu} & \text{t-Bu} & \text{t-Bu} \\
\text{t-Bu} & \text{Si} & \text{Si} \\
\text{t-Bu} & \text{Si} & \text{Si} \\
\text{t-Bu} & \text{Si} & \text{Si} \\
\text{t-Bu} & \text{Si} & \text{Si} \\
\text{t-Bu} & \text{Si} & \text{Si} \\
\text{t-Bu} & \text{Si} & \text{Si} \\
\text{t-Bu} & \text{Si} & \text{Si} \\
\text{t-Bu} & \text{Si} & \text{Si} \\
\end{array} \\
& + \text{ArN=C} \\
& \xrightarrow{\Delta} \text{n-hexane} \\
& \text{NAr} \\
& \text{172a-g} \\
\end{align*}
\]

**Scheme 42**

\[
\begin{align*}
172 & \quad \text{Ar} & \quad \text{Yield (\%)} \\
\hline
a & \text{Ph} & 75 \\
b & 4\text{-O}_2\text{NC}_6\text{H}_4 & 68 \\
c & 4\text{-CNC}_6\text{H}_4 & 61 \\
d & 2\text{-MeC}_{6}\text{H}_4 & 46 \\
e & 2,6\text{-MeC}_{6}\text{H}_3 & 18 \\
f & 2,6\text{-}\text{t-PrC}_{6}\text{H}_3 & 30 \\
g & 1\text{-naphthyl} & 78 \\
\end{align*}
\]
Trisilirennes: The behavior of this class of compounds towards isocyanides is characterized by two competing reaction modes, i.e. insertion into the three-membered ring and [1+2] cycloaddition across the double bond.\(^9\) Starting from the substrates 176a,b, the trisilimines 177a,b and the trisilabicyclo[1.1.1]butanes 178a-c were prepared (Scheme 43). According to a DFT study on the models 177 and 178 having R = SiMe\(_3\) / R' = c-C\(_8\)H\(_{11}\) and 2,6-Me\(_2\)C\(_6\)H\(_3\), the derivatives 178 were found higher in energy by 2.4 and 5.1 kcal/mol, showing that they arise under kinetic control. This is best demonstrated by the reaction of 176a with tert-butyl isocyanide: At room temperature a mixture of 177a and 178a was formed immediately; on standing, the latter component slowly rearranged to 177a; yet, working at \(-94^\circ C\), only compound 178a was observed. – X-ray diffraction studies have been performed with 177a,b and 178b,c (b: adduct with hexane).\(^9\)

In certain cases the isocyanide opened the Si–Si bridge in 178 to give a trisilabicyclo[1.1.1]-pentane 179. This occurred on prolonged treatment of 176b with two equivalents of cyclohexyl isocyanide (\(\rightarrow 179a\)); using 2,6-dimethylphenyl isocyanide, the formation of 179b took place even in five minutes, the intermediate 178d being undetectable.\(^9\)

![Scheme 43](image)

### Table 1

<table>
<thead>
<tr>
<th>176</th>
<th>177</th>
<th>178</th>
<th>179</th>
<th>R</th>
<th>R'</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>a</td>
<td>a</td>
<td>2,4,6-((i\text{-Pr})_3\text{C}_6\text{H}_2)</td>
<td>t-Bu</td>
<td>57</td>
<td>77</td>
</tr>
<tr>
<td>b</td>
<td>b</td>
<td>2,4,6-((i\text{-Pr})_3\text{C}_6\text{H}_2)</td>
<td>2,6-Me(_2)C(_6)H(_3)</td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>b</td>
<td>c</td>
<td>a</td>
<td>SiMe((t\text{-Bu})_2)</td>
<td>c-C(<em>8)H(</em>{11})</td>
<td>58</td>
<td>81</td>
</tr>
<tr>
<td>b</td>
<td>d</td>
<td>b</td>
<td>SiMe((t\text{-Bu})_2)</td>
<td>2,6-Me(_2)C(_6)H(_3)</td>
<td>48</td>
<td>39</td>
</tr>
</tbody>
</table>

**Scheme 43**

### 3.2. Migratory insertion of isocyanides into metallacycles

Titanacyclobutanes: A synthetically useful synthesis of cyclobutanimines has been developed by starting from the titanacycles 180 and 183a-d (Scheme 44).\(^10\) Treatment of compound 180 with...
tert-butyl and cyclohexyl isocyanide gave, respectively, the titanacyclopentanimines 181a and b in ≥ 90% yield. Moderate heating of the latter induced ring contraction with demetalation to afford the cyclobutanimine 182 in 72% yield (or 94% when working in the presence of ethene).

![Diagram](https://example.com/diagram.png)

i: toluene, 78 °C r. t.  
ii: toluene, 65 °C  
iii: C₂H₄ (10 psi), toluene, 65 °C  
iv: THF, 35 °C r. t.

Ti₂L₂  
RN=C  
i or iii (a)  
−t-BuN=C

180

181a: R = i-Bu  
b: R = c-C₆H₁₁

182  
(72 or 94%)

R¹

R²

L = Cp*  
L’ = C₂H₄  
L” = 2-(dimethylamino)indenide

i: toluene, −78 °C → r. t.  
ii: toluene, 65 °C  
iii: C₂H₄ (10 psi), toluene, 65 °C  
iv: THF, −35 °C → r. t.

<table>
<thead>
<tr>
<th>183, 184</th>
<th>R¹</th>
<th>R²</th>
<th>Yield (%)</th>
<th>E : Z ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Me</td>
<td>CH₂Ph</td>
<td>quant</td>
<td>6 : 1</td>
</tr>
<tr>
<td>b</td>
<td>Me</td>
<td>i-Pr</td>
<td>90</td>
<td>&gt;99 : &lt;1</td>
</tr>
<tr>
<td>c</td>
<td>Ph</td>
<td>CH₂Ph</td>
<td>quant</td>
<td>6 : 1</td>
</tr>
<tr>
<td>d</td>
<td>Ph</td>
<td>i-Pr</td>
<td>86</td>
<td>10 : 1</td>
</tr>
</tbody>
</table>

Scheme 44

The tert-butyl analog 181a, however, reverted to the starting ring 180 when submitted to either procedure. In a second series of experiments the authors reacted the disubstituted (trans-configured) substrates 183a-d with a threefold excess of 2,6-dimethylphenyl isocyanide. Here the intermediary five-membered rings were not isolated, but in a stereocontrolled manner directly converted into the cyclobutanimines 184a-d.¹⁰⁰
1-Zirconacyclopent-3-ynes: Another, rather unexpected migratory insertion of an isocyanide was observed with the zirconacycles 185a-c (Scheme 45). At slightly elevated temperature two equivalents of tert-butyl isocyanide were inserted into the β-Zr–C bonds, followed by a skeletal rearrangement to form the bicyclic compounds 186a-c with a four-membered half-ring. Methanolation of the derivative 186c gave the monocycle 187 which, like the products 186b,c, was studied by X-ray crystallography.101 – The mechanism was the subject of extensive speculations, among which the assumption of an equilibrium between structure 185 and the isomeric butatriene complex placed the reaction into the neighborhood of the process $4 \rightarrow 5$ shown in Scheme 1.101

\[
\begin{array}{ccc}
185, 186 & \text{Cp}’_2 & \text{Yield (\%)} \\
\text{a} & \text{Cp}_2 & 85 \\
\text{b} & [\eta^5-(t-Bu)C_5H_4]_2 & 44 \\
\text{c} & \text{Me}_2\text{Si}(\eta^5-C_5H_4)_2 & 56 \\
\end{array}
\]

Scheme 45

3H-1,2-Dithiole-3-thiones: Under mild conditions dithiolethiones like 188a-h were transformed into the 1,3-dithietan-2-imines 189a-h on treatment with the respective isocyanides (Scheme 46). The reaction was shown to be reversible, especially at elevated temperature. Studying the scope, the authors found that substrates 188 lacking electron-withdrawing substituents were unreactive, nor did a reagent like benzyl isocyanide enter the process.102 The same kind of reaction occurred with the fused systems 190a-h to give the derivatives 191a-h.102,103 These examples demonstrate that a dithiolone moiety (as present in 190a-e) is not affected and, second, that in the case of the bis(thioxodithiolo) fused thiazines 190f-h only one of the two five-membered anellands will be involved. Moreover, replacement of the central thiazine ring in 190 with a 6π cycle like pyrrole (which on ring transformation would lose its aromaticity) resulted in total loss of reactivity.102
3H-1,2-Dithiol-3-ones, -3-imines: Modifying the above conditions, it was found that also the hitherto unreactive 3-oxo-substituted 1,2-dithiole moiety is convertible. Experiments with both fused and monocyclic substrates revealed that a 1:2 reaction occurred to give a thiophene derivative besides an isothiocyanate, as illustrated by the process \(192a,b \rightarrow 193a,b\) (Scheme 47)\(^{104,105}\). To rationalize this finding, the authors invoked a transient 1,3-oxathietane (194) which via [2+2] cycloreversion generates an \(\alpha\)-thioxoketene that is ring-closed by the second isocyanide\(^{104}\).

Quite different from substrates of the type 192, imino congeners like 195a,b yielded isolable four-membered rings (196a,b) when heated with the same isocyanide\(^{106}\).

### Scheme 46

<table>
<thead>
<tr>
<th></th>
<th>R'</th>
<th>R</th>
<th>Yield (%)</th>
<th></th>
<th>X</th>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Cl / SPh</td>
<td>CH₂Ts</td>
<td>92 / 84</td>
<td>a</td>
<td>O / S</td>
<td>CH₂Ts</td>
<td>64 / 61</td>
</tr>
<tr>
<td>b</td>
<td>Cl / SPh</td>
<td>Ph</td>
<td>72 / 73</td>
<td>b</td>
<td>O / S</td>
<td>Ph</td>
<td>38 / 42</td>
</tr>
<tr>
<td>c</td>
<td>Cl / SPh</td>
<td>4-MeOC₆H₄</td>
<td>72 / 68</td>
<td>c</td>
<td>O</td>
<td>4-MeOC₆H₄</td>
<td>74</td>
</tr>
<tr>
<td>d</td>
<td>Cl / SPh</td>
<td>4-NO₂C₆H₄</td>
<td>85 / 84</td>
<td>d</td>
<td>O</td>
<td>4-NO₂C₆H₄</td>
<td>77</td>
</tr>
<tr>
<td>e</td>
<td>O / S</td>
<td>CH₂CO₂Et</td>
<td>41 / 39</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

i: benzene, r. t.
4. Conclusions

In the preceding pages we have tried to demonstrate the growing importance of isocyanides for the construction of four-membered rings. Meanwhile their diversity has gained an imposing width, as summarized below (Chart 1). Quite a number of these rings are formed with exceptional ease and are difficult to obtain by other methods. Yet, the synthetic potential of several reactions has not been fully exploited; certain transformations wait for mechanistic studies. An additional target might be the cyclic tetramerization of isocyanides to give tetraaza[4]radialenes – a pattern that is formally present in the 'four-over-one' helix (41) of poly(isocyanides).107
Chart 1. Ring systems from isocyanides (numerals indicate relevant sections).

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Author's Biography

Dietrich Moderhack, born 1940 in Berlin, graduated from Technical University Braunschweig, Germany, where he took his PhD in 1968 (mentor: Prof. G. Zinner). From October 1974 to September 1975 he held a DFG scholarship for joining Prof. Katritzky's group at the University of East Anglia in Norwich, UK. After his Habilitation in Braunschweig (1978), he became a full Professor (1982); since October 2005, he has been retired. His major interests include triazole and tetrazole chemistry, but azapentalenes, four-membered rings with two adjacent heteroatoms and isocyanides are being looked at as well.