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Synthetic Methods

Isocyanides in the Synthesis of Nitrogen Heterocycles

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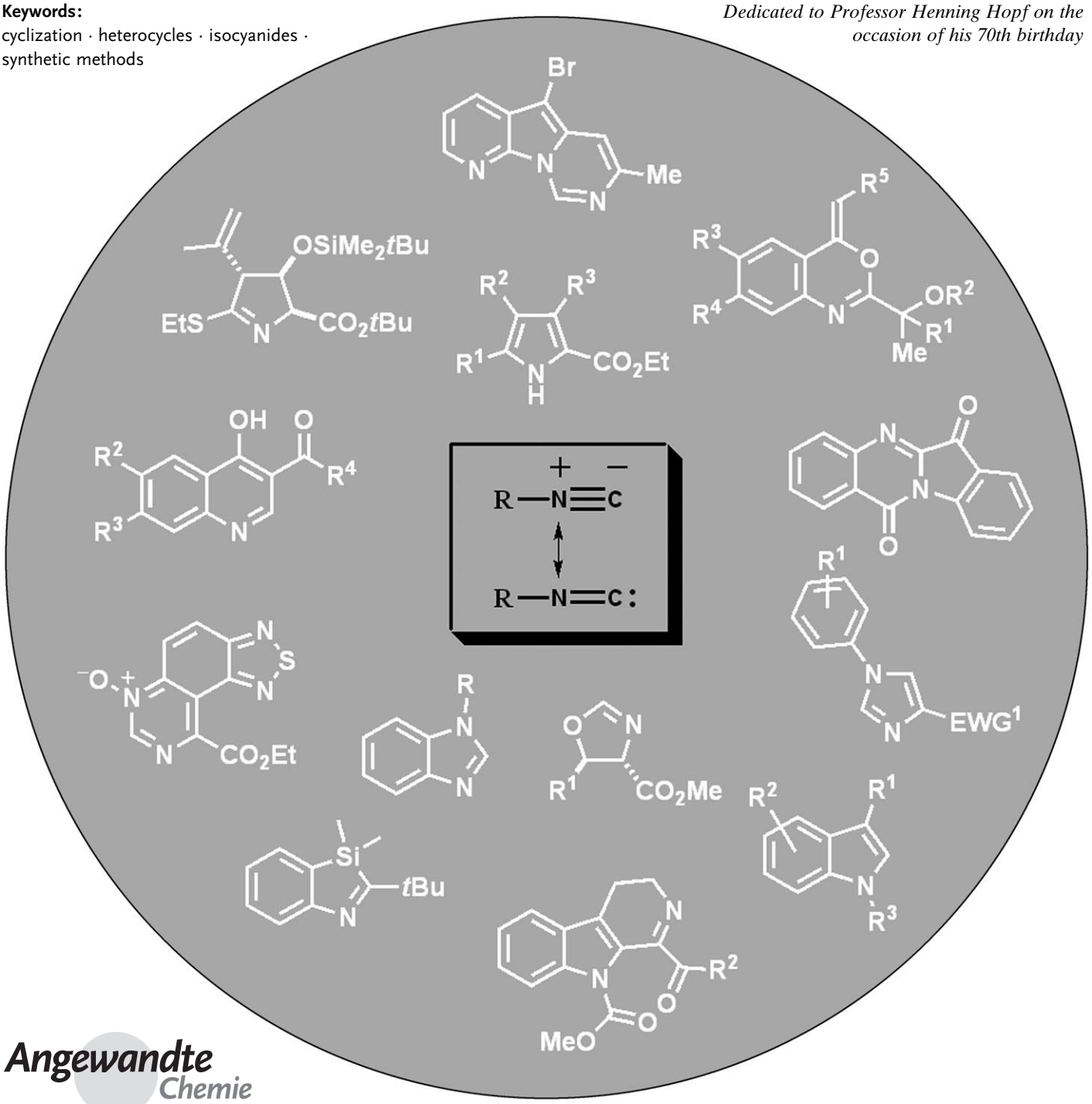
Keywords:
cyclization · heterocycles · isocyanides · synthetic methods

Dedicated to Professor Henning Hopf on the occasion of his 70th birthday



Isocyanides have long proved themselves to be irreplaceable building blocks in modern organic chemistry. The unique features of the isocyano group make isocyanides particularly useful for the synthesis of a number of important classes of nitrogen heterocycles, such as pyrroles, indoles, and quinolines. Several cocyclizations of isocyanides via zwitterions and radical intermediates as well as transition-metal-catalyzed syntheses of different types of heterocycles have recently been developed. Methods starting from isocyanides often have distinct advantages over alternative approaches to the same heterocycles because of their enhanced convergence, the great simplicity of most of the operations with them, and the great variety of isocyanides readily available for use. Isocyanides have also been used in some enantioselective syntheses of chiral heterocyclic compounds, including natural products as well as precursors thereof.

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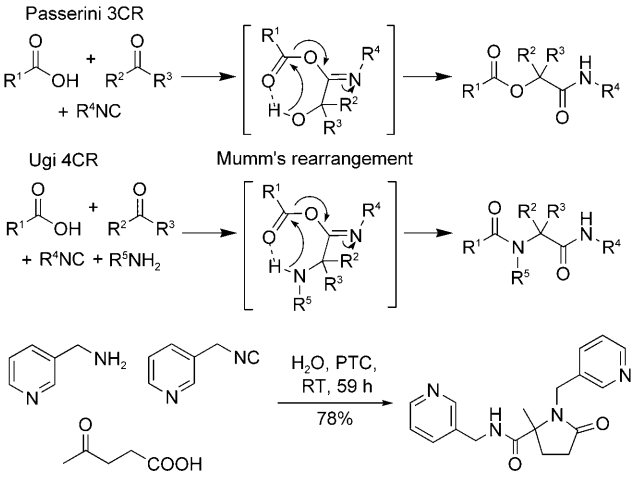
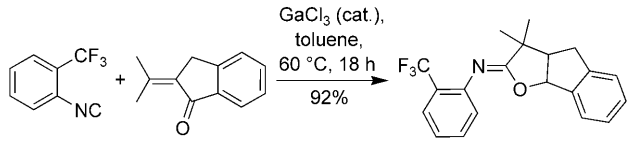
1. Introduction

Isocyanides were first described[1] as isomers of cyanides independently by Gautier[2] and Hofmann,[3] when they observed their formation in the reaction of silver cyanide with alkyl iodides, and on treatment of aniline with chloroform in the presence of potassium hydroxide (the so-called carbylamine reaction), respectively. To a certain extent, the extremely unpleasant odor of the simplest and the most volatile isocyanides discouraged chemists from developing efficient methods for their synthesis, and therefore these compounds remained under-investigated for a long time. However, the chemistry of isocyanides received a significant boost when the dehydration of formamides[4] and the carbylamine reaction of amines in the presence of phase-transfer catalysts[5] appeared in the literature as reliable synthetic routes with wide scope. The unique properties of the isocyano group, which may function both as an electrophile and as a nucleophile, have since turned these compounds into indispensable building blocks for organic synthesis.[6]

The diversity of transformations which isocyanides can undergo include the previously reviewed multicomponent reactions,[7,8] their transition-metal-catalyzed insertions,[9,10] as well as their oligo- and polymerizations.[11] Arguably, the most important applications of isocyanides are toward the synthesis of various heterocycles, and yet no comprehensive up to date review on this topic has appeared in recent years.[12] The present Review, therefore, is intended to cover the most important cocyclization reactions of isocyanides that lead to heterocycles, no matter whether they are transition-metal-catalyzed (or mediated), organo-catalyzed, or uncatalyzed. The classical syntheses of heterocycles, such as the Barton–Zard and the van Leusen pyrrole syntheses, the Ito and the Fukuyama indole syntheses, as well as less well-known applications of isocyanides are discussed. However, the Ugi- and Passerini-type reactions and related multicomponent processes (Scheme 1),[7] as well as insertions of isocyanides and other cocyclizations utilizing isocyanides as C_1 donors (Scheme 2)[13] are beyond the intended scope of the present Review. The main goal of this Review is to show the great



Scheme 1. Mechanisms of the three-component Passerini reaction and the four-component Ugi reaction[7] as well as an example of a heterocycle synthesis by the Ugi reaction.[14] PTC = phase-transfer catalysis.



Scheme 2. An example of a formal [4+1] cycloaddition of an α,β-unsaturated carbonyl compound with an isocyanide.[13f]

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diversity in the possible types of transformations that lead from isocyanides to different heterocycles. The Review consists of three major parts that reflect the three major possible mechanisms of heterocycle formation from isocyanides: a) the initial step of the process is metalation of the isocyanide, b) an addition to the isocyano group is followed by immediate cyclization, and c) the cyclization is a radical reaction.

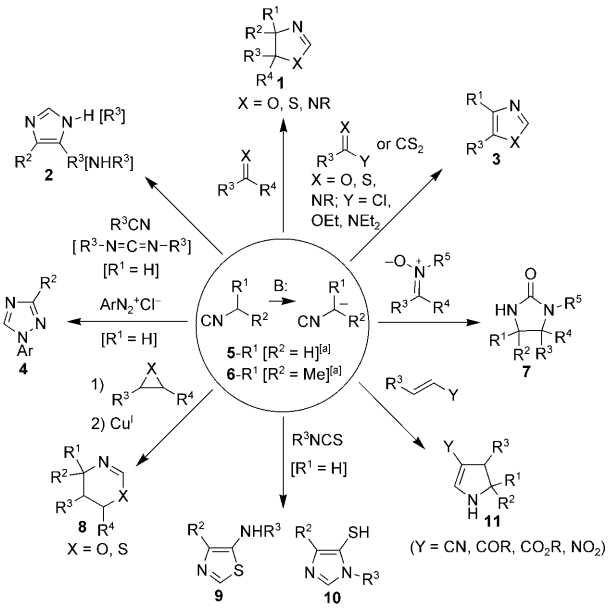
2. Cocyclizations of Metalated Isocyanides

2.1. Applications of α-Metalated Isocyanides

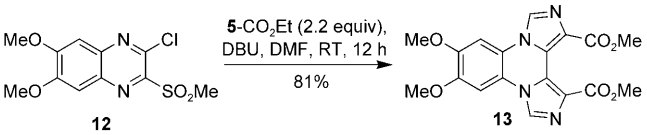
The electron-withdrawing effect of the isocyano group enhances the acidity of α-C–H bonds, and this was first exploited by Schöllkopf and Gerhart[15] in 1968. Since then, α-metalated methyl isocyanides of type **5**-R^1 (mostly deprotonated isocyanoacetates) have been shown to participate in various types of cocyclizations leading to different nitrogen-containing heterocycles. Several reviews on this topic had appeared by 1985.[16] The main types of transformations reported therein are depicted in Scheme 3 and include syntheses of 1,3-azoles **2**, **3**, **9**, **10** and azolines **1**, pyrroles and pyrrolines **11**, 1,2,4-triazoles **4**, 2-imidazolidinones **7**, and 5,6-dihydro-4*H*-1,3-oxazines and -thiazines **8**.[16] Some important updates on these reactions are also presented in the current Review.

Many conventional methods for the preparation of heterocycles have been improved to better meet the demands of modern combinatorial synthesis and medicinal chemistry. Thus, a very convenient synthesis of oxazoles (**3**, X = O) from acid chlorides and isocyanoacetates induced by a polymer-supported base in a miniflow reactor has been reported recently.[17] Imines can also be generated in situ from amines and aldehydes and used as cyclization partners for **5**-R^1, thus providing 2-imidazolines (**1**; X = NR) in a one-pot three-component reaction.[18,19]

Well-known subunits such as azoles can be installed into more sophisticated heterocyclic structures by employing other more complex substrates for cocyclization with **5**-R^1. Thus, in analogy to reactions of **5**-R^1 with acid chlorides or imidoyl chlorides, acceptor-substituted methyl isocyanides react with some nitrogen heterocycles containing an activated leaving group adjacent to the nitrogen atom, such as in **12**, to provide new heterooligocyclic systems such as **13** with fused imidazole rings (Scheme 4).[20]



Scheme 3. Various applications of α-metalated substituted methyl isocyanides **5**-R^1 and **6**-R^1 reviewed previously.[16] [a] **5**-R^1: R^1 = CO_2Alk, CON(Alk)$_2$, Ts (*p*-toluenesulfonyl), PO(OEt)$_2$, CN, STol, Ph; **6**-R^1: R^1 = CN, Ts.



Scheme 4. Synthesis of the heterotetracycle **13** with two fused imidazole rings.[20] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMF = dimethylformamide.

One of the most important applications of α-metalated methyl isocyanides is undoubtedly their reaction with nitroalkenes to generate 1,2-disubstituted pyrroles.[21,22] In this so-called Barton–Zard pyrrole synthesis the nitro group on the

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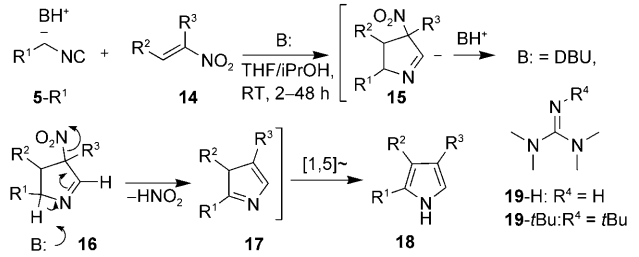
Armin de Meijere, born 1939, studied chemistry in Freiburg and Göttingen, and completed his PhD in 1966 in Göttingen. After postdoctoral research at Yale University, he completed his Habilitation in 1971 in Göttingen. He was full professor of organic chemistry in Hamburg from 1977 to 1989, and since then professor in Göttingen. His research interests include the development of new small-ring systems as building blocks in the syntheses of natural and non-natural compounds as well as the preparation and study of highly strained polycyclic compounds, and organometallic complexes with applications in catalysis.

alkene serves two purposes, namely 1) to activate the double bond toward Michael addition of the isocyanide and 2) to provide a leaving group for the conversion of the initially formed 2-pyrroline **16** into a 1*H*-pyrrole **18** by overall elimination of nitrous acid and a subsequent 1,5-sigmatropic hydrogen shift of the 3*H*-pyrrole **17** (Table 1).

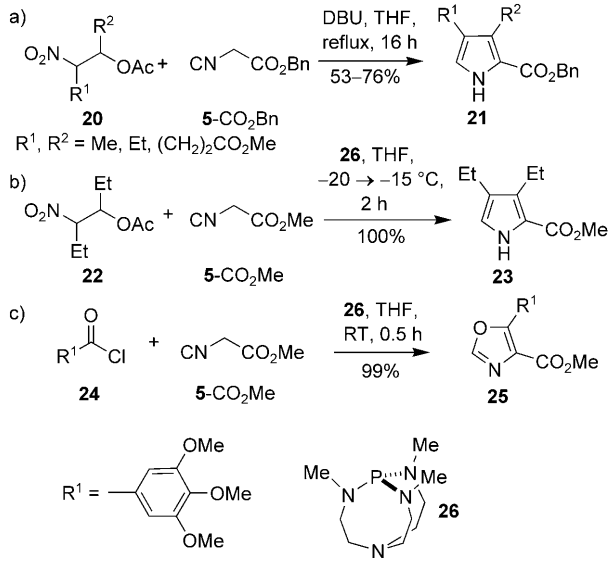
Table 1: The Barton–Zard pyrrole synthesis.[21]



R^1	R^2	R^3	Base	**18** [%]	Ref.
CO_2tBu	4-MeOC_6H_4	Me	**19**-*t*Bu	90	[21]
CO_2tBu	4-MeOC_6H_4	Me	DBU	80	[21]
CO_2Et	$(CH_2)_4$		DBU	80	[21]
CO_2tBu	H	Me	**19**-*t*Bu	48	[21]
CO_2tBu	H	Me	**19**-*t*Bu	70[a]	[21]
Ts	4-MeOC_6H_4	Me	DBU	52	[21]
$CONMe_2$	Me	Et	**19**-H	77[a]	[21]
CON(OMe)Me	Ph	Ph	DBU	71	[23]

[a] The nitroalkene was generated in situ from an *O*-acetyl-β-hydroxynitroalkane **20** (see Scheme 5).

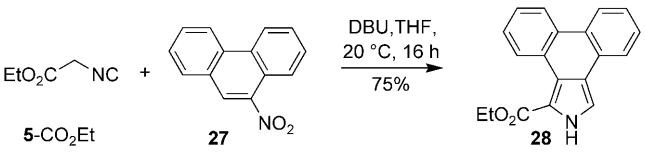
The nitroalkenes required for this synthesis are easily accessible by an aldol-type condensation of nitroalkanes with aldehydes; they can also be generated in situ from *O*-acetyl-β-hydroxynitroalkanes (Scheme 5a).[24] When a non-ionic superbase such as **26**, which is about 10^{17} times more basic than 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), is employed instead of DBU, the respective pyrroles are obtained in excellent yields (Scheme 5b).[25] The same base **26** has also been shown to be superior to DBU in the synthesis of oxazoles **25** by the reaction of acid chlorides **24** and anhydrides with methyl isocyanoacetate (**5**-CO_2Me), thereby providing the products quickly and in almost quantitative yields (Scheme 5c).[25]



Scheme 5. In situ generated nitroalkenes in the Barton–Zard pyrrole synthesis; applications of the superbase **26**.[24,25]

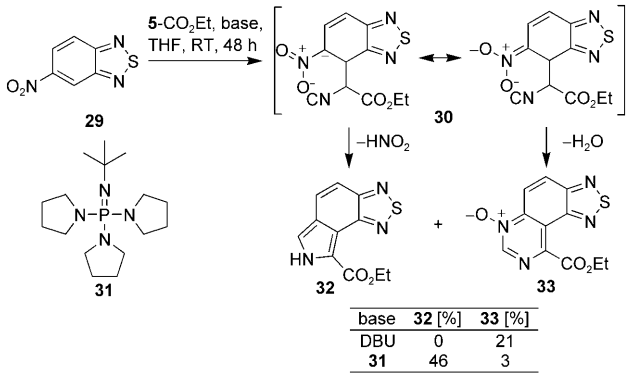
The quality and the type of the solvent, particularly the absence of radical inhibitors such as 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT), which is routinely present in commercial THF, have been shown to influence the rate of the reaction as well as the yields of the pyrroles.[26] *tert*-Butyl methyl ether (MTBE) has been found to be better than THF for this reaction.

The reaction of ethyl isocyanoacetate (**5**-CO_2Et) with certain nitroaromatic compounds, for example, 9-nitrophenanthrene (**27**), also provided the corresponding phenanthrene-annelated pyrrole **28** (Scheme 6).[27] Polycyclic aromatic nitro compounds with decreased aromaticity per ring gave the corresponding arene-annelated pyrroles in good yields, while simple nitroarenes such as nitronaphthalene and nitrobenzene turned out to be less efficient or even failed in this reaction.[27]



Scheme 6. Synthesis of a phenanthrene-annelated pyrrole **28**.[27]

Interestingly, in some cases, such as with 5-nitrobenzo[*c*]-[1,2,5]thiadiazole (**29**) in the presence of DBU, the ring-fused pyrimidine *N*-oxide **33** was formed. This product apparently arises, albeit in low yield, from the ionic intermediate **30** by attack of the nitrogen center of the nitro group onto the isocyano group, (Scheme 7).[28] The preferential formation of pyrroles or pyrimidine *N*-oxides or their ratio turned out to depend on the type of substrate and the base used. The formation of the more sterically demanding pyrimidine *N*-



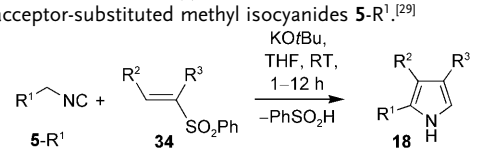
base	**32** [%]	**33** [%]
DBU	0	21
31	46	3

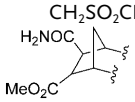
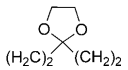
Scheme 7. Competitive formation of pyrrole **32** and pyrimidine *N*-oxide **33**.[28]

oxides requires coplanarity of the nitro group and the aromatic ring. Consequently, this reaction mode is disfavored by the use of bulky bases and particular substrates in which the nitro group is rotated out of coplanarity, so that pyrroles are formed preferentially.

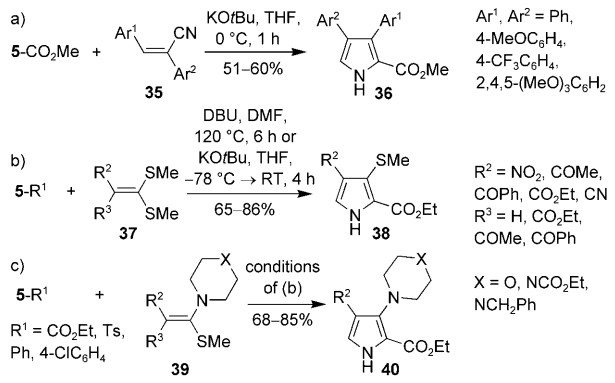
Alternatively to nitroalkenes, α,β-unsaturated phenylsulfones **34** can be employed in the reaction with acceptor-substituted methyl isocyanides **5**-R^1 to furnish pyrroles **18** with the same substitution pattern as in the Barton–Zard synthesis (Table 2).[29] This reaction is often referred to as the Montforts pyrrole synthesis.

Table 2: 2,3,4-Trisubstituted pyrroles **18** from α,β-unsaturated sulfones **34** and acceptor-substituted methyl isocyanides **5**-R^1.[29]



R^1	R^2	R^3	**18** [%]	Ref.
CO_2Bn	$CH_2SO_2CH_2$		60	[29g]
CO_2tBu			84	
CN			86[29g]	[29g]
CO_2tBu			92	
CN			77[29g]	[29g]
CO_2Et	$(CH_2)_2CO(CH_2)_2$		41	[29g]

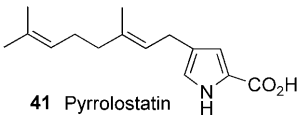
These formal cycloadditions onto **34** proceed with elimination of phenylsulfinic acid. The alkenylphenylsulfones of type **34** are easily accessible, for example, by sulfenohalogenation of alkenes with subsequent β elimination of hydrogen halide from the resulting adducts. 2,3-Diarylacrylonitriles **35**, which can conveniently be prepared by condensation of substituted arylacetonitriles with aromatic aldehydes, in turn have been shown to react with methyl isocyanoacetate (**5**-CO_2Me) to provide, with elimination of cyanide, 3,4-diarylpyrrole-2-carboxylates **36** in moderate yields (51–60%; Scheme 8a).[30] Acceptor-substituted ketene *S*,*S*-acetals of type **37** and *N*,*S*-acetals **39** represent further suitable substrates for reactions with acceptor-activated methyl isocyanides **5**-R^1 to yield 2,3,4-trisubstituted pyrroles **38** and **40**,



Scheme 8. 2,3,4-Trisubstituted pyrroles **36**, **38**, and **40** from acceptor-substituted alkenes.[30,31]

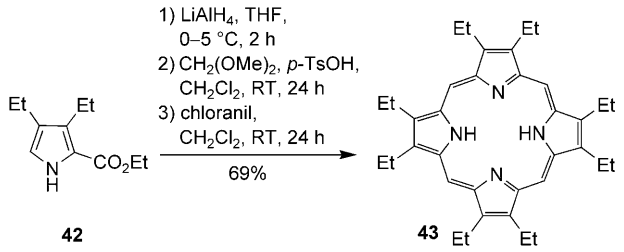
respectively (Scheme 8b,c).[31] These base-induced reactions proceed with elimination of methanethiol and loss of the respective substituent R^3 (H, COR, or CO_2Et).[31]

The Barton–Zard method has been employed in various natural products syntheses, such as those of pyrrolostatin (**41**)



41 Pyrrolostatin

and its analogues[32] as well as chromophores for the plant photoreceptor protein phytochrome, which consists of open-chain tetrapyrroles.[33] Importantly, the pyrroles synthesized from α,β-unsaturated nitroalkenes or alkenylphenylsulfones have a substitution pattern that is perfect for the construction of porphyrines.[27,29d–f,34] Thus, the reduction of the ester group in the pyrrole **42**, followed by an acid-catalyzed cyclizing condensation in the presence of an excess of formaldehyde dimethylacetal, and subsequent dehydrogenation with chloranil led to octaethylporphyrin (**43**) in 69% yield over the three steps (Scheme 9).[25,34]

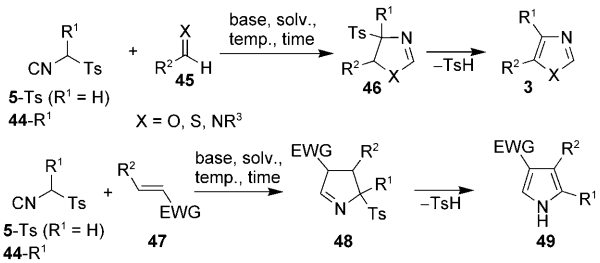


Scheme 9. Synthesis of the octaethylporphyrin (**43**) from pyrrole **42**.[25]

The most frequently used α-isocyanoalkanoic acid derivatives contain electron-withdrawing alkoxycarbonyl groups and are easily accessible from the corresponding α-amino acids. Some other acceptor-substituted methyl isocyanides have found a wide range of applications in the synthesis of heterocycles because of their ability to undergo both an α metalation and an eventual elimination of this electron-withdrawing leaving group from the initially formed adduct. Tosylmethyl isocyanide (TosMIC, **5**-Ts), first introduced into organic synthesis and employed for various purposes by van Leusen et al.,[35] has become a classical reagent for the construction of 1,3-azoles and pyrroles.[36] Thus, under basic conditions it reacts (with elimination of *p*-toluenesulfinic acid) with aldehydes to provide oxazoles (**3**, X = O),[37] with aldimines to give imidazoles (**3**, X = NR^3),[38–40] and with acceptor-substituted alkenes to furnish pyrroles **49** (Table 3).[41] The last reaction, known as the van Leusen pyrrole synthesis, is of particular importance, as pyrroles are widespread among naturally occurring biologically active compounds and their synthetic analogues.

Pyrroles prepared from tosylmethyl isocyanide **5**-Ts and derivatives **44**-Ts can be further elaborated. Thus, the application of α-trimethylstannyl-substituted analogues **44**-$SnMe_3$ in this reaction provided 2-(trimethylstannyl)pyrroles,

Table 3: Synthesis of 1,3-azoles **3** and pyrroles **49** from tosylmethyl isocyanide (TosMIC, **5**-Ts) and its phenyl derivative **44**-Ph.[37,41]



R^1	R^2	X or EWG	Base	LM	*T* [°C]	*t* [h]	Yield of **3** or **49** [%]	Ref.
H	Ph	O	K_2CO_3	MeOH	65	2	91	[37a]
H	4-ClC_6H_4	O	K_2CO_3	MeOH	65	2	91	[37a]
H	4-$NO_2C_6H_4$	O	K_2CO_3	MeOH	65	2	57	[37a]
H	4-$NO_2C_6H_4$	NPh	K_2CO_3	MeOH/DME	20	16	82	[38a]
Ph	Ph	NMe	K_2CO_3	MeOH	20	16	90	[38a]
Ph	Me	N*t*Bu	*t*BuNH$_2$	MeOH	20	0.5	89	[38a]
H	Me	CN	NaH	Et_2O/DMSO	36	0.25	50	[41a]
H	Ph	COMe	NaH	Et_2O/DMSO	36	0.25	70	[41a]
Ph	Ph	CO_2Me	NaH	Et_2O/DMSO	36	0.25	23	[41a]

which could be further transformed by Stille cross-coupling with aryl bromides[42] or can undergo oxidative dimerization in the presence of copper(II) nitrate.[43] Mono- and 1,2-disubstituted arylalkenes (preferably electron deficient) have also been shown to provide 3-aryl- or 3,4-diaryl-substituted pyrroles, respectively, in moderate to good yields upon reaction with TosMIC in the presence of sodium *tert*-butoxide in DMSO.[44]

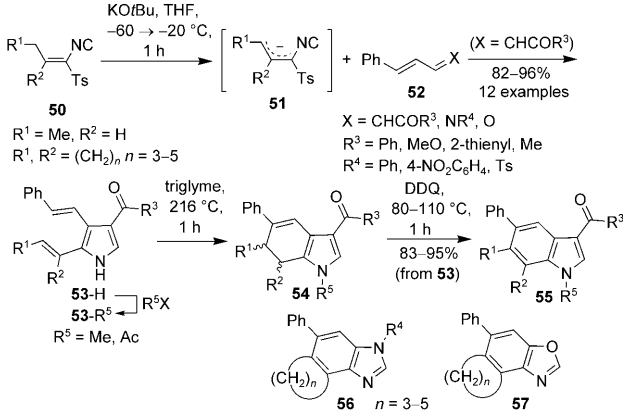
The acceptor-substituted alkenes required for the van Leusen pyrrole synthesis can be generated in situ by a Horner–Wadsworth–Emmons reaction of aldehydes with phosphonates. Both the formation of the alkene and of the pyrrole in this case occur in toluene with sodium amylate as a base. Conveniently, the product usually crystallizes from the reaction mixture, which makes the whole procedure extremely useful for the synthesis of 3,4-disubstituted pyrroles.[45] A one-pot van Leusen synthesis and subsequent N-arylation of pyrroles was recently reported to provide 1,3,4-trisubstituted pyrroles in moderate to good yields.[46]

A base-induced reaction of 1-isocyano-1-tosyl-1-alkenes **50** with activated dienes **52** and α,β-unsaturated aldehydes or aldimines furnished 2,3-dialkenyl-substituted azoles and pyrroles **53**-H, respectively, which are capable of undergoing a subsequent 6π electrocyclization. The cyclohexene-annelated compounds of type **54** are finally dehydrogenated by treatment with DDQ to give the corresponding benzoannelated heterocycles, namely indoles **55**, benzimidazoles **56**, and benzoxazoles **57** (Scheme 10).[47] Apparently, the α,β-unsaturated isocyanide **50** is deprotonated at the allylic position, and the resulting allyl anion **51** reacts selectively with aldehydes, imines, and acceptor-substituted alkenes **52**.

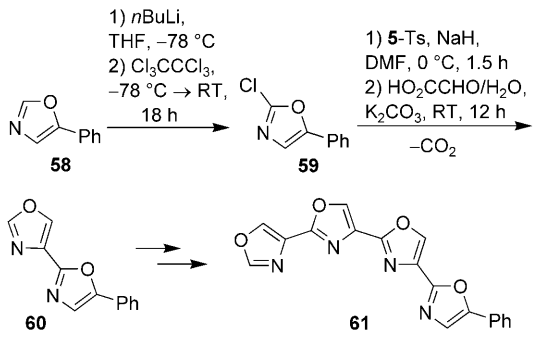
Recently, the synthesis of 4,5-disubstituted oxazoles from TosMIC in environmentally benign ionic liquids has been reported.[48] Iterative chlorination of oxazoles and substitution of the resulting 2-chlorooxazoles by deprotonated TosMIC followed by subsequent reaction with glyoxalic acid allowed the efficient construction of oligooxazoles of type **61** (Scheme 11).[49]

Oxazoline-substituted potassium organotrifluoroborates of type **63**, produced by the van Leusen oxazoline synthesis, have been shown to undergo subsequent Suzuki–Miyaura cross-coupling reactions with aryl bromides to provide the correspondingly substituted oxazoles of type **64** in moderate to good yields (44–73%; Scheme 12).[50]

TosMIC has also been employed in reactions with 2-pyrrolcarbaldehydes **66** to provide various pyrrolo[1,2-*c*]pyrimidines **67** in good yields (Table 4, reaction a).[51] In this transformation, an aldol-

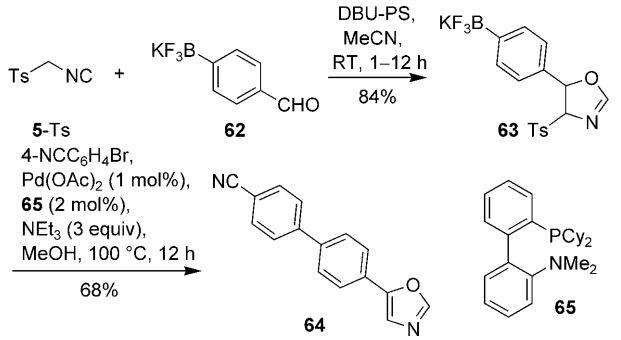


Scheme 10. Indoles **55**, benzimidazoles **56**, and benzoxazoles **57** by sequential construction of the heterocycle and the benzene ring.[47]



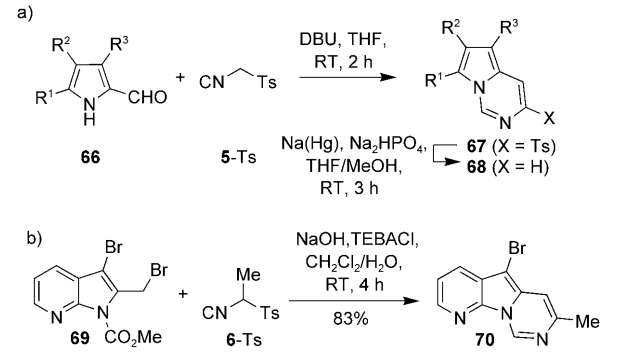
Scheme 11. Synthesis of tetraoxazole **61**.[49]

type condensation of the aldehyde with TosMIC is followed by an attack of the deprotonated pyrrole-NH group on the isocyano group. Subsequent reductive removal of the *p*-toluenesulfonyl group was achieved with a 6% sodium amalgam and Na_2HPO_4 in THF/MeOH solution. The same



Scheme 12. Synthesis of the substituted oxazole **64** by Suzuki–Miyaura coupling of **63**.[50]

Table 4: Construction of ring-annelated pyrimidine derivatives **67**, **68**, and **70**.[51,53]



R^1	R^2	R^3	**67** [%]	**68** [%]
H	H	H	82	51
Me	Et	Me	69	83
	H	H	80	55
H	CO_2Me	H	69	12
H	allyl	H	61	46

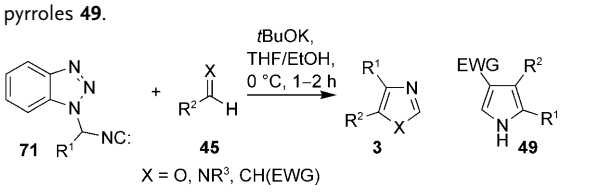
[a] TEBA = tetrabutylammonium.

reaction with isocyanoacetates (**5**-CO_2R) instead of TosMIC had been reported previously.[52] The reaction of the pyridine-annelated 2-bromomethyl-3-bromopyrrole derivative **69** with 1-tosylethyl isocyanide **6**-Ts and related cocyclizations lead to oligoheterocycles of type **70** with a fused pyrimidine ring. In this sequential reaction, alkylation of **6**-Ts in the basic medium under the phase-transfer catalysis conditions with subsequent in situ deprotection of the pyrrole moiety is followed by cyclization and elimination of TsH to provide the trisheterocycle **70** in a single operation in 83% yield (Table 4, reaction b).[53]

Another example of an acceptor-substituted methyl isocyanide with a good leaving group is (benzotriazol-1-yl)methyl isocyanide **71** (BetMIC, Table 5), which was reported by Katritzky et al. to frequently be comparable or superior to TosMIC in the synthesis of oxazoles,[54] imidazoles, and pyrroles.[55]

In addition to base-mediated formal cycloadditions of substituted methyl isocyanides to unsaturated compounds, catalytic versions have also been intensively investigated.

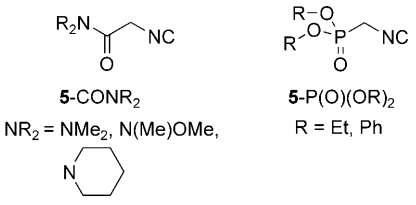
Table 5: Comparison of BetMIC with TosMIC in the synthesis of azoles **3** and pyrroles **49**.



R^1	R^2	X	Yield of **3** or **49** with TosMIC [%]	Ref.	Yield of **3** or **49** with BetMIC [%]	Ref.
H	Ph	NPh	56	[38a]	85	[55]
Bn	4-$MeOC_6H_4$	NPh	0	[56]	73	[55]
H	H	$CHCO_2Me$	33	[41a]	45	[55]
Me	H	$CHCO_2Me$	0	[56]	30	[55]
H	Me	CHCN	50	[41a]	92	[55]
H	Ph	O	91	[37a]	69	[54]

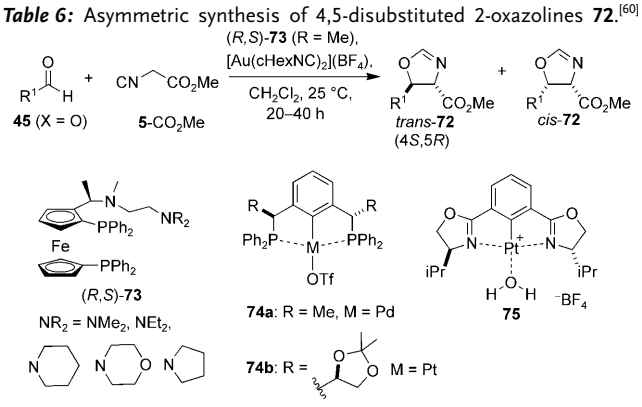
Copper(I), silver(I), and gold(I) salts are the most frequently used catalysts for the aforementioned syntheses of heterocycles. Thus, copper(I)-, silver(I)-, and gold(I)-catalyzed reactions of substituted methyl isocyanides with aldehydes (ketones),[57] imines,[58] as well as various Michael acceptors[59] have been reported. Such catalytic variants have some advantages over conventional methods, for example, the possibility to obtain the respective products diastereo- or even enantioselectively. An asymmetric synthesis of synthetically useful 4,5-disubstituted 2-oxazolines **72** by an aldol-type condensation of aldehydes **45** (X = O) with acceptor-substituted methyl isocyanides **5** was first reported by Ito et al. in 1986.[60a] Thus, the reaction of methyl isocyanoacetate (**5**-CO_2Me) with aldehydes in the presence of 1 mol% of an Au^I complex with chiral bis(diphenylphosphino)ferrocene ligands of type **73** gave the respective oxazolines, *trans*- and *cis*-**74**, in high yields (83–100%) as well as diastereo- (up to 100%) and enantioselectively (up to 97% *ee* for the major diastereomer; Table 6).[60]

Isocyanomethylcarboxamides (**5**-$CONR_2$),[61a,d] and -phosphonates (**5**-$P(O)(OR)_2$)[61b] have also been employed successfully. The reactions with α-substituted methyl isocyanoacetates proceeded notably more slowly than those with



methyl isocyanoacetate (**5**-CO_2Me) itself, and some of them with decreased stereo- and enantioselectivity.[60c,d] Silver complexes with ligands of type **73** were found to be superior to gold(I) analogues in the reactions of aldehydes with TosMIC,[61c] with the corresponding (4*R*,5*R*)-5-alkyl-4-tosyl-2-oxazolines generated in excellent yields and with high

Table 6: Asymmetric synthesis of 4,5-disubstituted 2-oxazolines **72**.[60]



R^1 in **45**	*trans*/*cis*	Yield of **72** [%]	*ee* (4*S*,5*R*)-**72** [%]
(*E*)-*n*PrCH=CH	81:19	83	84
Ph	89:11	98	96
Me	84:16	100	72
*t*Bu	100:0	100	97
cHex	97:3	95	90
	91:9	89	95

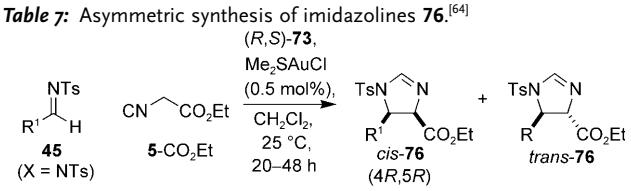
degrees of diastereo- (up to 100%) and enantioselectivity (up to 86% *ee* for the major diastereomer).

The mechanism of this reaction has been studied extensively to understand the mode of action of the catalyst and the reason why it induces this selectivity.[62] It has been shown, that the "internal cooperativity" of both the central and planar chirality of the ligand **73** plays a crucial role in the high diastereo- and enantioselectivity observed in the reaction. Other combinations of both types of chirality have been shown to be less efficient. Secondary interactions between the pendant amine and the substrate are also crucial, as metal complexes with other chiral bidentate phosphine ligands, for example, chiraphos, diop, and binap, give almost racemic oxazolines. A mechanistic rationalization of this observation is that enolates derived from isocyanoactetate in this aldol-type reaction are placed too far away from the chiral pocket formed by such ligands to allow them to control the stereoselectivity of the reaction.

Some Pd^{II}, Pt^{II}, and Pt^{IV} complexes of chiral PCP and PNP pincer-type ligands with a deeper chiral pocket around the metal center have indeed been employed successfully in the asymmetric synthesis of oxazolines, although with inferior results when compared with the above-mentioned Au^{I} complexes with **73**.[63] Among them, complexes of type **74a** gave the best diastereo- and enantioselectivity (**74a**: *trans*/*cis* 45:55 to 91:9; *trans*: low *ee* (<30%); *cis* (4*S*,5*S*): 42–77% *ee*;[63b] **74b**: *trans*/*cis* 56:44–93:7; *cis*: low *ee*; *trans*: 13–65% *ee*).[63c] The use of ligand **75** in the reaction of aldehydes with TosMIC provided the corresponding products with >98% excess of the *trans* diastereomer and with an enantiomeric excesses of 25–75%, whereas the stereoselectivities were low in the reaction of aldehydes with methyl isocyanoacetate (**5**-CO_2Me) in the presence of **75**.[63d]

The gold(I)-catalyzed reaction of isocyanoacetates (**5**-CO_2R) with *N*-tosylimines **45** (X = NTs) in the presence of the ligand (*R*,*S*)-**73** afforded the respective *cis*-(4*R*,5*R*)-2-imidazolines *cis*-**76** enantioselectively (in contrast to reactions with aldehydes; Table 7).[64]

Table 7: Asymmetric synthesis of imidazolines **76**.[64]



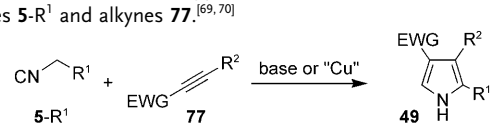
R^1	*cis*/*trans*	Yield of *cis*-**76** [%]	*ee* (4*R*,5*R*)-**76** [%]
Ph	92:8	85	61
4-$MeOC_6H_4$	96:4	89	58
4-$NO_2C_6H_4$	94:6	84	62
4-MeC_6H_4	96:4	88	47
4-IC_6H_4	96:4	86	88
α-naphthyl	92:8	79	58

cis-Disubstituted 2-imidazolines were also obtained diastereoselectively when achiral $[RuH_2(PPh_3)_4]$[65] was used as a catalyst as well as diastereo-[66] and enantioselectively when some chiral palladium(II)-pincer complexes were used.[67] The *trans*-stereoselective synthesies of *N*-sulfonyl-2-imidazolines by a copper(I)-catalyzed reaction of *N*-tosylimines with aldehydes has also been reported.[68]

The possibility of using low catalyst loadings and achieving high degrees of diastereo- and enantioselectivity make such aldol-type reactions (especially their silver(I)- and gold(I)-catalyzed variants with ligands of type **73** discussed above) extremely valuable.

The efficient synthesis of oligosubstituted pyrroles **49** by a formal cycloaddition of substituted methyl isocyanides **5**-R^1 across the triple bond of electron-deficient alkynes **77** was reported independently by the research groups of Yamamoto[69] and de Meijere. (Table 8).[70] The latter group per-

Table 8: 2,3,4-Trisubstituted pyrroles **49** from substituted methyl isocyanides **5**-R^1 and alkynes **77**.[69,70]

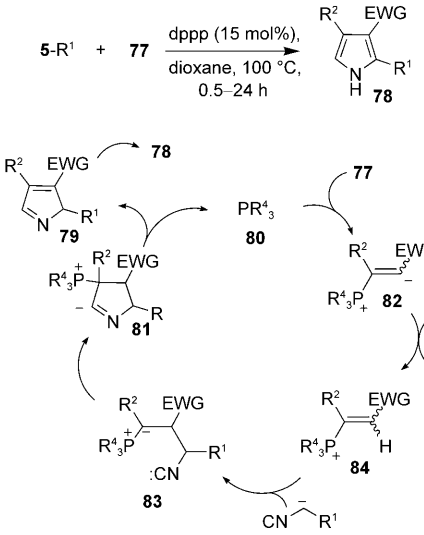


R^1	R^2	EWG	Base or cat.	**49** [%]	Ref.
CO_2Et	Ph	CO_2Et	Cu_2O/phen	79	[69]
CO_2*t*Bu	Ph	CO_2Et	Cu-NP	78	[70]
CO_2Me	cPr	CO_2Me	KO*t*Bu	91	[70]
CO_2Et	$HO(CH_2)_4$	CO_2Et	Cu_2O/phen	65	[69]
CN	cPr	CO_2*t*Bu	KHMDS	83	[70]
$P(O)(OEt)_2$	Me	CO_2Et	Cu_2O/phen	59	[69]
Ph	cPr	CO_2*t*Bu	CsO*t*Bu	87	[70]
Ts	cPr	CO_2 *t*Bu	CuSPh	91	[70]
CO_2Me	CH_2OMe	$PO(OEt)_2$	KO*t*Bu	53	[70]
$CONEt_2$	Me	CO_2Et	Cu_2O/phen	75	[69]
CO_2Et	Ph	CN	Cu_2O/phen	22	[69]
Ts		CO_2Me	KO*t*Bu	45	[70]

formed this transformation both in the presence of bases such as KO*t*Bu or KHMDS and under copper catalysis, with CuSPh, Cu_2O, and metallic Cu nanoparticles providing the best results. It is noteworthy that only the base-induced variant allows substituted methyl isocyanides **5**-R^1 even without electron-withdrawing groups, for example, benzyl isocyanide (**5**-Ph) to be used efficiently for the synthesis of the corresponding phenyl-substituted pyrroles. Yamamoto and co-workers reported similar results for the formation of pyrroles **49** catalyzed by Cu_2O in the presence of 1,10-phenanthroline. A broad range of isocyanides **5**-R^1 and acetylenes **77** have been tested in these catalyzed reactions (Table 8).

Yamamoto and co-workers have also reported a phosphine-catalyzed regioselective formation of pyrroles **78**, which are regioisomers of **49**, from the same starting materials **5**-R^1 and **77** as above (Table 9).[69,71] This interesting organo-

Table 9: Phosphine-catalyzed formation of pyrroles **78** and a plausible mechanism for this reaction.[69,71]



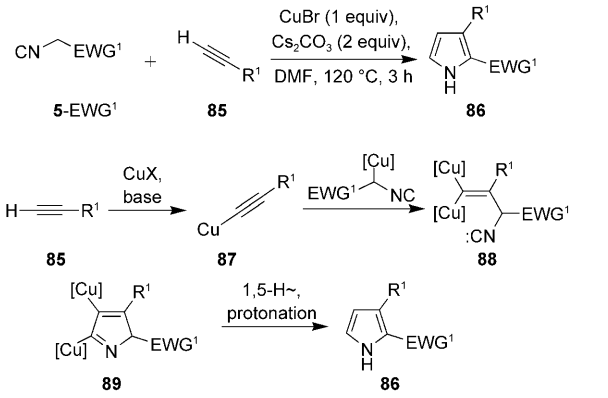
R^1	R^2	EWG	**78** [%]
CO_2Et	Me	CO_2Et	60
CO_2Et	cHex	CO_2Et	66
CO_2Et	Ph	CO_2Et	79
CO_2Et	Ph	COMe	77
CO_2Et	Ph	CN	35
Ts	Ph	CO_2Et	20
$CONEt_2$	Ph	CO_2Et	27
$PO(OEt)_2$	Ph	CO_2Et	18

catalytic transformation has been found to proceed best in dioxane at 100 °C with bidentate phosphanes such as dppp used as catalysts. The proposed mechanism includes the addition of the phosphine **80** onto the activated triple bond of the alkyne to form a zwitterionic intermediate **82**, which in turn deprotonates the isocyanide **5**-R^1 to furnish the alkenylphosphonium ion **84**. This species, because of the strongly electron-withdrawing phosphonium substituent on its double bond, has a reversed reactivity, and is thus subject to nucleophilic attack of the deprotonated methyl isocyanide **5**-R^1 with subsequent cyclization of the resulting phosphonium ylide **83**. This formal cycloaddition of **5**-R^1 onto the double bond of **84** to give **81** is followed by elimination of the phosphine and a [1,5]-hydrogen shift, which finally converts the intermediate **79** into the pyrrole **78**. This method thus supplements the synthesis of the regioisomeric pyrroles **49** discussed above, although it proved to be applicable only to methyl isocyanides with electron-withdrawing substituents.

More recently, a Cu_2O-catalyzed solid-phase synthesis of 2,3,4-trisubstituted pyrroles **49** by the reaction of polymer-supported acetylenic sulfones with methyl isocyanoacetate (**5**-CO_2Me) was reported.[72]

Both of the pyrrole syntheses (Tables 8 and 9) discussed above employ activated acetylenes as indispensable reaction partners for the substituted methyl isocyanides. Under the same reaction conditions, *unactivated* internal acetylenes did not provide the respective pyrroles at all or at best only traces of them.[70b] On the other hand, a copper(I)-mediated approach to 2,3-disubstituted pyrroles **86** from acceptor-substituted methyl isocyanides (**5**-EWG^1) and unactivated terminal acetylenes **85** has recently been reported by de Meijere and co-workers (Table 10).[70b] The 11 examples of such

Table 10: 2,3-Disubstituted pyrroles **86** from isocyanides **5**-EWG^1 and unactivated terminal acetylenes **85** and proposed mechanism for this reaction.[70b]

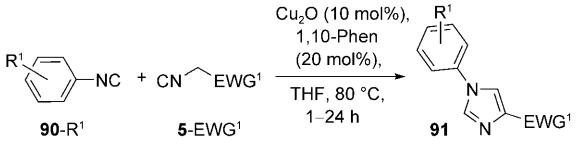


EWG^1	R^1	**86** [%]
CO_2Et	*n*Bu	70
CO_2Et	*sec*Bu	58
CO_2Et	Ph	40
CO_2Et	cPr	88
CO_2tBu	*n*Bu	47
4-$NO_2C_6H_4$	*n*Bu	20

pyrroles were obtained in low to good yields depending on the nature and size of the substituents on the isocyanide and the alkyne. Terminal acetylenes are presumed to form the respective copper acetylenides **87** in the reaction mixture. Carbocupration[73] of **87** by the deprotonated isocyanide **5**-EWG^1 followed by cyclization of the thus formed intermediate **88** would yield the 2*H*-pyrrolenline-4,5-dicopper derivative **89**, which by 1,5-hydrogen shift and twofold protonation would furnish the pyrrole **86**.

Substituted methyl isocyanides, such as methyl isocyanoacetate (**5**-CO_2Me), have been observed to efficiently undergo dimerization under Ag(I), Au(I), or Cu(I) catalysis to give imidazoles.[59,70] Yamamoto and co-workers developed a catalyzed cocyclization of two different isocyanides **90**-R^1 and **5**-EWG^1 to provide various 1,4-disubstituted imidazoles **91** mostly in high yields (Table 11).[74] The most efficient

Table 11: Cu_2O-catalyzed cocyclization of two different isocyanides to yield imidazoles **91**.[74]

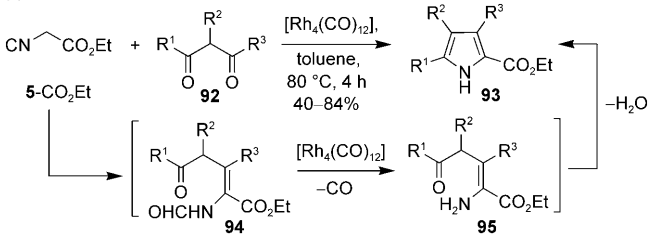


R^1	EWG^1	**91** [%]
H	CO_2Et	93
4-OMe	CO_2Et	93
4-CO_2Me	CO_2Et	98
2,6-dimethyl	CO_2Et	92
H	$P(O)(OEt)_2$	62
H	$CONEt_2$	71

catalytic system tested was Cu_2O/1,10-phenanthroline. Combinations of aryl isocyanides **90**-R^1 with various substituents and several acceptor-substituted methyl isocyanides (**5**-EWG^1) were successfully employed in this cocyclization, but the attempted reaction of isocyanobenzene with benzyl isocyanide (**5**-Ph) afforded only traces of the corresponding imidazole **91**.

The $[Rh_4(CO)_{12}]$-catalyzed condensation of ethyl isocyanoacetate (**5**-CO_2Et) with 1,3-dicarbonyl compounds **92** (in a twofold excess) represents another approach towards substituted pyrroles **93** (Table 12).[75] In the presence of a stoichiometric amount of a base such as BuLi or NaH, ethyl isocyanoacetate (**5**-CO_2Et) reacts with simple carbonyl compounds to produce α,β-unsaturated formamides of type **94**.[76] The same condensations occur when $[Rh_4(CO)_{12}]$ is used as a catalyst at 80 °C. When 1,3-dicarbonyl compounds **92** are employed, the rhodium catalyst causes a decarbonylation of the initially formed *N*-formylenamine **94** to give an enamine **95**, which immediately undergoes intramolecular condensation with cyclization to give the corresponding pyrrole **93**. The cyclocondensation of **5**-CO_2Et with nonsymmetric 1,3-dicarbonyl compounds **92** ($R^1 \neq R^3$) provides the respective pyrroles **93**, regioselectively, when the substituents have significantly different steric demands or electronic effects (for example, R^1 = Me, R^3 = *t*Bu or R^1 = Me, $R^3 = CO_2Et$; see Table 12).

Table 12: Rhodium-catalyzed cyclocondensation of ethyl isocyanoacetate (**5**-CO_2Et) with 1,3-dicarbonyl compounds **92** to yield tetrasubstituted pyrroles **93**.[75]

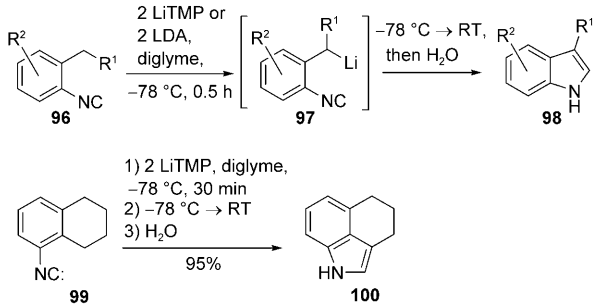


R^1	R^2	R^3	**93** [%]
Me	H	Me	84
Me	Me	Me	68
Me	$(CH_2)_2CN$	Me	52
Me	H	Ph	52
*t*Bu	H	Me	65
Me	H	CO_2Et	76
Me	F	Me	40
*t*Bu	H	nC_3F_7	70

2.2. Applications of γ-Metalated ortho-Methylphenyl Isocyanides

Ito, Saegusa et al. were the first to report the selective deprotonation of *o*-methylphenyl isocyanides **96** by means of lithium dialkylamides in diglyme and the utilization of the thus obtained lithiated isocyanides **97** for the versatile syntheses of various substituted indoles **98** (Table 13).[77,78]

Table 13: Formation of indoles **98** from lithiated *o*-methylphenyl isocyanides **97**.[77]



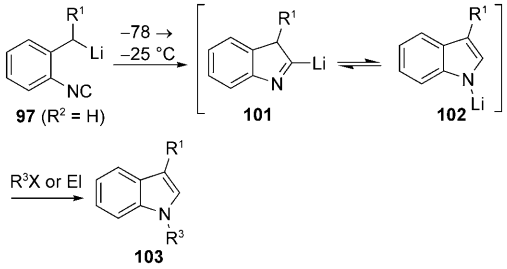
R^2	R^1	**98** [%]
H	H	100
4-MeO	H	91
5-Me	H	82
H	Me	95
H	$SiMe_3$	90
H	*i*Pr	65
H	*i*Bu	78

When the reaction was carried out in THF or Et_2O, the addition of the lithium dialkylamide onto the isocyano group became a competing process, thereby lowering the yield of the indole. The methyl group is deprotonated selectively in the presence of larger alkyl groups. Thus, *o*-methylphenyl isocyanides **96** with R^1 = H afforded the respective 3-unsubstituted indoles **98** (R^1 = H) in high yields (82–100%) when lithium diisopropylamide (LDA) was used as a base, whereas lithium 2,2,6,6-tetramethylpiperidide (LiTMP) turned out to be the base of choice for such isocyanides substituted at the benzylic positions (for example, **96**, $R^1 \neq$ H) to provide 3-substituted indoles in good yields (62–95%). The use of a twofold excess of the base dramatically improved the yields of

indoles, which suggests that the deprotonation of the starting material **96** must be reversible. Under such conditions the tricyclic 1,3,4,5-tetrahydrobenz[*c*,*d*]indole (**100**) was obtained from 1-isocyano-5,6,7,8-tetrahydronaphthalene (**99**; Table 13).

Various sequential reactions, including an in situ modification of the cyclized *o*-methylphenyl isocyanides in the presence of different electrophiles, have also been reported by the same authors. Thus, the cyclization of **97** ($R^2 = H$) at temperatures below −25 °C, followed by trapping of the reaction mixture with various electrophiles such as alkyl halides, acid chlorides, epoxides, etc. provides *N*-substituted indoles exclusively in good yields (Table 14).[77]

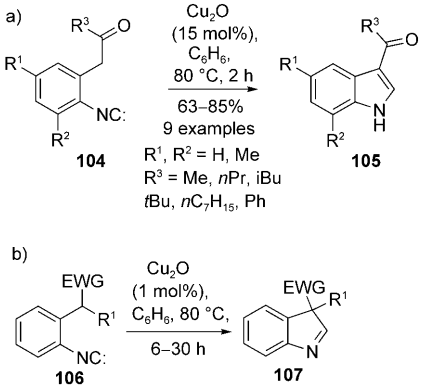
Table 14: Synthesis of 1,3-disubstituted indoles **103**.[77]



R^1	R^3X or El	R^3 in **103**	**103** [%]
H	MeI	Me	82
Me	*n*BuBr	*n*Bu	65
H	$MeOCOCH_2Br$	$MeOCOCH_2$	52
H	Me_3SiCl	Me_3Si	87
H	EtCOCl	EtCO	76
H			84

Ito, Saegusa et al. also found that acceptor-substituted *o*-methylphenyl isocyanides of type **104** can conveniently be converted into the corresponding 3-substituted indoles **105** under Cu^I catalysis (Table 15, reaction a).[79,80] This method nicely supplements the lithium amide induced formation of substituted indoles from *o*-methylphenyl isocyanides. Thus, the catalytic conditions used tolerate some functionalities such as keto-carbonyl groups as, for example, in **104** to yield 3-acylindoles of type **105**, which could not be prepared under basic conditions.[80] On the other hand, the base-mediated variant does not require an acceptor substituent in the side chain of the aryl isocyanide.[77] The key intermediate in the copper-catalyzed process is presumed to be a γ-copper-substituted (acylmethyl)phenyl isocyanide, which undergoes an intramolecular insertion of the isocyano group into the carbon–copper bond with subsequent isomerization and protonation to provide the indoles of type **105**. Evidence of the intermolecular insertion of isocyanides into copper(I) derivatives of C,H-acidic compounds such as acetylacetone and dialkyl malonates[81] support this assumption. γ,γ-Disubstituted *o*-methylphenyl isocyanides of type **106** with at least one acceptor substituent furnished the corresponding 3,3-disubstituted 3*H*-indoles **107** in moderate to high yields under similar conditions (Table 15, reaction b).[79]

Table 15: Cu_2O-catalyzed formation of 3-acceptor-substituted 1*H*-indoles **105** and 3*H*-indoles **107**.[79,80]

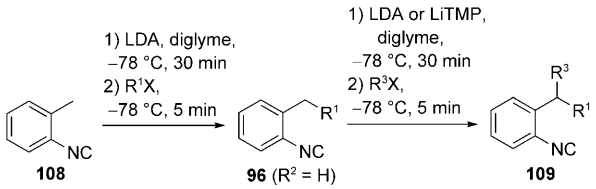


EWG	R^1	**107** [%]
CN	Me	71
CN	*i*Pr	61
CN	$CH_2{=}CHCH_2$	60
CN	$MeCO_2CH_2$	43
CO_2Me	Me	80
CO_2Me	*n*Bu	88

Various γ-substituted *o*-methylphenyl isocyanides could be prepared from *o*-(lithiomethyl)phenyl isocyanides by alkylation with alkyl halides and by reaction with other electrophiles such as trimethylsilyl chloride, dimethyl disulfide,[77b] aldehydes, ketones, epoxides,[82] isocyanates, or isothiocyanates (Table 16).[83,84]

The thus obtained isocyanides can subsequently undergo base-promoted or copper(I)-catalyzed cyclizations to furnish indoles (Tables 13–15) and other benzoannelated hetero-

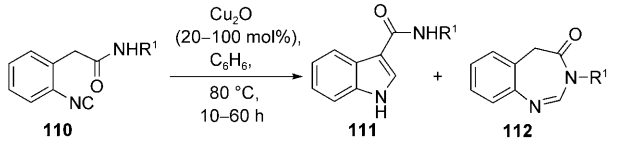
Table 16: Synthesis of γ-substituted *o*-methylphenyl isocyanides **96** and **109**.[77]



R^1X or ElX	R^1 in **96**	Yield of **96** [%]	R^3X	R^3 in **109**	Yield of **109** [%]	Ref.
MeI	Me	95	*n*BuBr	*n*Bu	72	[77b]
Me_3SiCl	Me_3Si	95	MeI	Me	88	[77b]
$(MeS)_2$	MeS	67	$(MeS)_2$	MeS	65	[77b]
$(EtO)_2CHCH_2Br$	$(EtO)_2CHCH_2$	68				[77b]
MeCOCl	MeCO	92	MeI	Me	84	[77b]
*t*BuCOCl	*t*BuCO	86	$NCCH_2I$	$NCCH_2$	89	[77b]
MeO_2CCl	MeO_2C	69	allylBr	allyl	57	[79]
EtCHO	CH(OH)Et	93				[82]
		91				[82]
*n*BuNCO	CONH*n*Bu	70				[83]
cHexNCS	CONHcHex	96				[83]

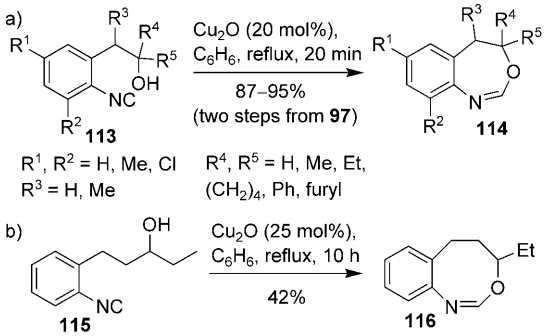
cycles (Table 17 and Schemes 13 and 14). Thus, *N*-substituted *o*-isocyanophenylacetamides of type **110**, which are obtained by reaction of *o*-lithiophenylmethyl isocyanide with isocyanates, can undergo two types of cyclizations under Cu_2O catalysis to provide 3-substituted indoles **111** and/or benzodiazepine-4-ones **112**, depending on the substituents present (Table 17). Under basic conditions, however, *N*-substituted *o*-isocyanophenylacetamides **110** and analogous thioacetamides furnish indoles of type **111** exclusively.[83]

Table 17: Cu_2O-catalyzed cyclization of *N*-substituted *o*-isocyanophenylacetamides **110**.[83]



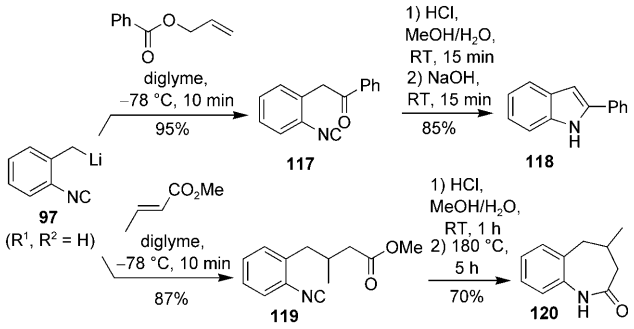
R^1	**111** [%]	**112** [%]
nC_4H_9	0	85
cC_6H_{11}	25	58
tC_4H_9	20	0
Ph	75	0

Reaction of *o*-(lithiomethyl)phenyl isocyanides **97** with aldehydes and ketones at −78 °C followed by hydrolysis of the reaction mixtures at the same temperature and subsequent Cu_2O-catalyzed cyclization of the resulting isocyanoalcohols **113** furnished 4,5-dihydro-3,1-benzoxazepines **114** in high overall yields (Scheme 13a). An analogous cyclization of the adduct **115** of *o*-lithiomethylphenyl isocyanide (**108**) and 1-butene epoxide provided 4*H*-5,6-dihydro-3,1-benzoxacine **116** in 42% yield (Scheme 13b).[82]



Scheme 13. Synthesis of 4,5-dihydro-3,1-benzoxazepines **114** and 4*H*-5,6-dihydro-3,1-benzoxacine **116**.[82]

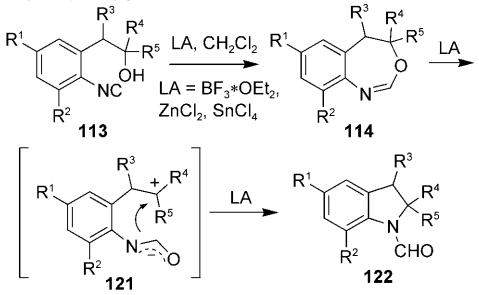
γ-Substituted *o*-methylphenyl isocyanides prepared by functionalization of *o*-lithiomethylphenyl isocyanide **97** (R^1,R^2 = H) can undergo hydrolysis to provide anilines. Subsequent cyclization of the latter by reaction with an adjacent keto or ester group provides 2-substituted indoles **118**[80] or 1,3,4,5-tetrahydro-2*H*-benzazepine-2-ones **120**, respectively (Scheme 14).[85] These examples show how efficiently isocyanides can function as masked amines in some cases.



Scheme 14. Synthesis of 2-phenylindole **118** and the benzocaprolactame **120**.[80,85]

On the other hand, the adducts of **97** with aldehydes (ketones), namely 2-(2′-isocyanophenyl)ethanol derivatives of type **113**, have been reported to undergo an overall rearrangement under Lewis acid catalysis to give *N*-formylindolines **122** (Table 18).[86] The reaction is presumed to

Table 18: *N*-Formylindolines **122** by a Lewis acid catalyzed isomerization of 2-(2′-isocyanophenyl)ethanol derivatives **113**.[86]

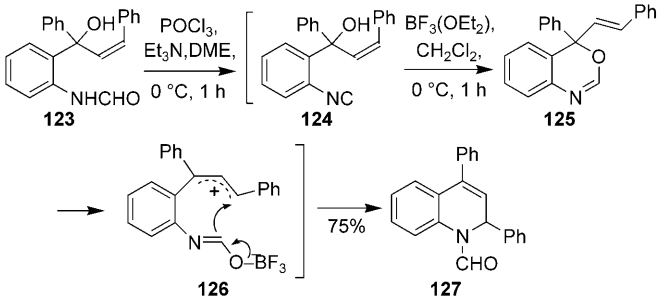


R^1	R^2	R^3	R^4	R^5	Method[a]	**122** [%]
H	H	H	Me		A	80
H	H	H	Me	Me	D	32
H	H	H	Me	2-naphthyl	B	70
Me	H	H	Me		A	63
H	Me	H	Me		C	66
H	H	Me	Me	Ph	B	73
H	H	MeS	H		C	70

[a] Method A: 0.1 equiv $BF_3{\cdot}OEt_2$, 0 °C, 1 h. Method B: 0.1 equiv $BF_3{\cdot}OEt_2$, RT, overnight. Method C: 1 equiv $ZnCl_2$, RT, overnight. Method D: 1 equiv $SnCl_4$, RT, overnight.

proceed via initial formation of dihydro-3,1-benzoxazepine **114** by a Lewis acid catalyzed insertion of the isocyano group into the O–H bond. The latter species then undergoes heterolytic cleavage and recyclization via a zwitterionic intermediate of type **121** to eventually yield the *N*-formylindoline **122**. Dihydro-3,1-benzoxazepines **114** prepared separately indeed rearrange under Lewis acid catalysis to provide **122**.[86]

A mechanistically related Lewis acid catalyzed rearrangement of *o*-(hydroxymethyl)-substituted phenylisocyanides of type **124** provides 1-formyl-1,2-dihydroquinolines **127** (Scheme 15).[87] Mixtures of such isocyanides **124** with cyclic



Scheme 15. Synthesis of 1-formyl-2,4-diphenyl-1,2-dihydroquinoline (**127**).[87]

products of type **125** were obtained upon treatment of 1-(2′-formylaminophenyl)allyl alcohol **123** and its analogues with phosphoryl chloride. Subsequent treatment of these mixtures with $BF_3(Et_2O)$ induced complete cyclization of, for example, **124** (from **123**) to 4*H*-3,1-benzoxazine **125**, which apparently underwent cleavage and recyclization via the zwitterionic intermediate **126** to provide 1-formyl-2,4-diphenyl-1,2-dihydroquinoline (**127**) in 75% yield (from **123**).

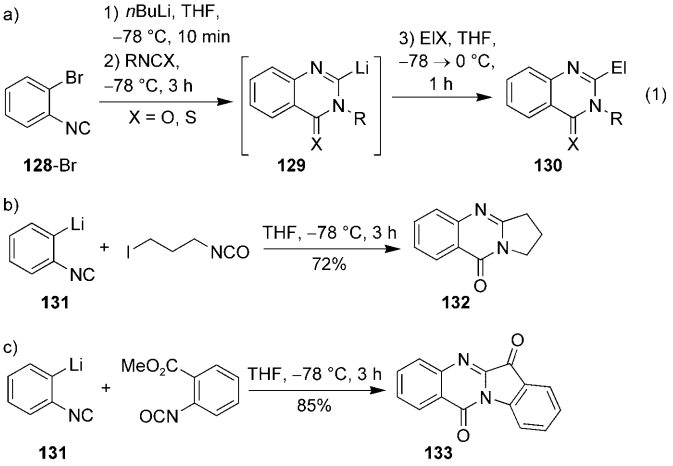
2.3. Applications of ortho-Lithiophenyl Isocyanides

It was recently found that previously unknown *ortho*-lithiophenyl isocyanides can also be versatile precursors for certain types of heterocycles.[88] A bromine–lithium exchange on *ortho*-bromophenyl isocyanide (**128**-Br), best performed with *n*BuLi in THF at −78 °C, allows the smooth generation of the parent *ortho*-lithiophenyl isocyanide (**131**). This species could be trapped with various electrophiles. Thus, the reaction of **131** with isocyanates or isothiocyanates initially lead to lithiated 3*H*-quinazolin-4-ones (-thiones) **129**, which provide cyclic 3*H*-quinazolin-4-ones (-thiones) **130** in good to high yields (54–91%) after trapping with a second electrophile (Table 19, reaction a). The naturally occurring alkaloids deoxyvasicinone **132** and tryptanthrine **133** could be synthesized in this way by employing cyclizing intramolecular substitutions of appropriately *N*-functionalized intermediates of type **129** (Table 19, reactions b and c).

The reaction of *ortho*-lithiophenyl isocyanide (**131**) with aldehydes and ketones (**134**) proceeds via the corresponding 2-lithiated 4*H*-3,1-benzoxazines **136**, which equilibrate at −78 °C with the respective acyclic *ortho*-isocyanobenzyl alkoxides **135** (Table 20).[89] Treatment of **131** with aldehydes at −78 °C followed by hydrolysis of the reaction mixture at the same temperature led to *ortho*-isocyanobenzyl alcohols **137** (El = H) rather than the corresponding 4*H*-3,1-benzoxazines **138**, which were obtained in the analogous reactions with ketones. The adducts of *ortho*-lithiophenyl isocyanide (**131**) with carbonyl compounds **134** could also be trapped with electrophiles other than water (methyl chloroformate, iodine, ethyl bromoacetate) to provide functionally substituted phenyl isocyanides **137** or benzoxazines **138** (Table 20).[90]

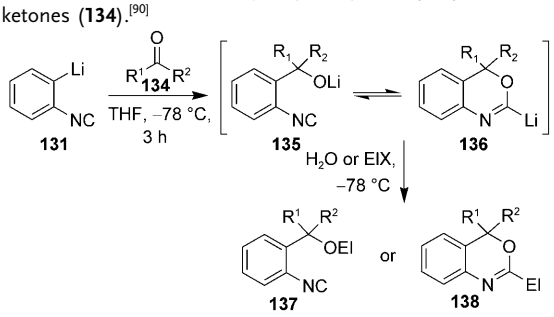
The lithiated benzoxazine intermediates of type **136** have been found to undergo two types of rearrangements to give the correspondingly substituted isobenzofuran-1(3*H*)-imines **139** or indoline-2-ones (oxoindoles) **140**. As far as the mechanism is concerned, the intermediate **136** is considered to undergo a pericyclic ring opening to yield **141**. Intramolecular 1,4-addition to **141** would furnish the lithiated indolin-2-one **143**, or an intramolecular 1,2-addition and

Table 19: Synthesis of 3*H*-quinazolin-4-ones and 3*H*-quinazolin-4-thiones **130**.[88]



R	X	ElX	El	**130** [%]
Ph	O	H_2O	H	91
*i*Pr	O	H_2O	H	81
cPr	S	H_2O	H	71
cHex	S	H_2O	H	78
Ph	O	TsCN	CN	54
Ph	O	PhSSPh	PhS	77
Bn	O	I_2	I	75

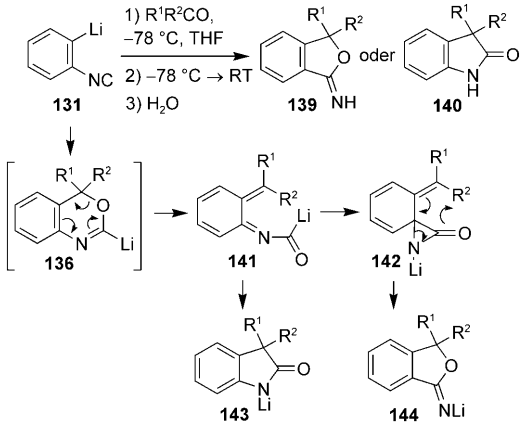
Table 20: Reaction of *ortho*-lithiophenyl isocyanide (**131**) with aldehydes and ketones (**134**).[90]



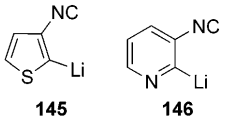
R^1	R^2	El	**137** [%]	**138** [%]
Ph	H	H	84	
4-pyridyl	H	H	82	
4-pyridyl	H	MeO_2C	56	
	H	H	88	
*t*Bu	H	H	80	
*i*Pr	H	H	36	
	H	H	70	
Ph	Ph	H		48
Ph	CF_3	H		78
Ph	CF_3	MeO_2C		45
Ph	CF_3	EtO_2CCH_2		47
Me	Me	H		52

subsequent 6π-pericyclic reaction of the resulting lithiated aziridinone **142** would provide the lithiated isobenzofuranimines **144** (Table 21).[90]

Table 21: Reaction of *ortho*-lithiophenyl isocyanide (**131**) with carbonyl compounds and a mechanistic rationalization.[90]



R^1	R^2	**143** [%]	**144** [%]
2-pyridyl	H		79
CF_3	Me	58	
Ph	Ph		42

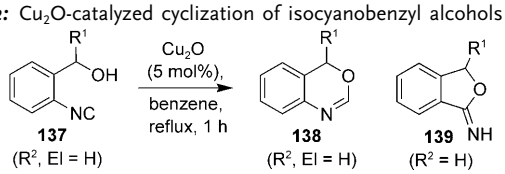


Analogous transformations have been observed for other *o*-lithioaryl isocyanides such as 2-lithio-3-isocyanothiophene (**145**) and 2-lithio-3-isocyanopyridine (**146**).

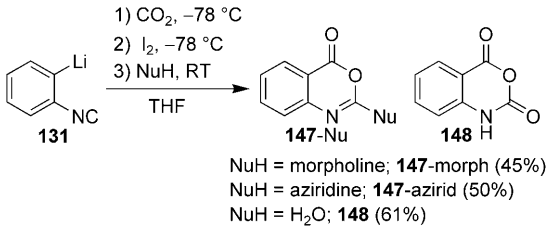
The isolated isocyanobenzyl alcohols of type **137** (El = H) have been shown to undergo a Cu_2O-catalyzed cyclization that also leads to 4*H*-3,1-benzoxazines **138** or isobenzofuran-1(3*H*)-imines **139** depending on the substituents R^1 and R^2 present (Table 22).[90]

Treatment of *ortho*-lithiophenyl isocyanide (**131**) with carbon dioxide at −78 °C and then with iodine at the same temperature furnished 2-iodobenzoxazin-4-one (**147**-I). The in situ substitution of this compound by nucleophiles, such as morpholine, aziridine, and water, provided the correspondingly substituted 4-*H*-benzo[3,1]oxazin-4-ones **147**-Nu and isatoic anhydride (**148**), respectively, in a one-pot four-step procedure in moderate yields (Scheme 16).[90]

Table 22: Cu_2O-catalyzed cyclization of isocyanobenzyl alcohols **137**.[90]



R^1	**138** [%]	**139** [%]
Ph	86	
4-$MeOC_6H_4$	74	
4-ClC_6H_4	75	
4-pyridyl	73	
*t*Bu	83	
2-(5-methylfuryl)		66
*i*Pr		68

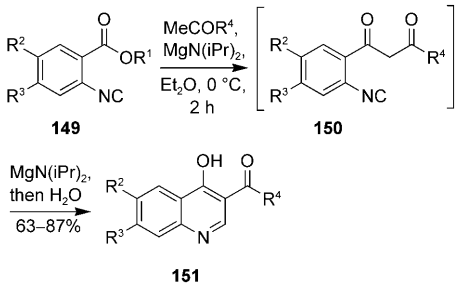


Scheme 16. Synthesis of 2-substituted 4*H*-benzo[*d*][1,3]oxazin-4-ones (**147**-Nu) and isatoic anhydride (**148**).[90]

2.4. Cyclizations of Other Metalated Isocyanides

Kobayashi et al. reported the facile formation of 4-hydroxyquinolines **151** by a magnesium bis(diisopropylamide)-induced cyclization of 3-(2'-isocyanoaryl)-3-oxocarboxylates (or amides) **150**. The latter species were generated by Claisen condensation of *ortho*-isocyanobenzoates **149** with magnesium enolates of alkyl acetates or *N*,*N*-dimethylacetamide and underwent in situ transformation to the quinolines **151** (Table 23).[91]

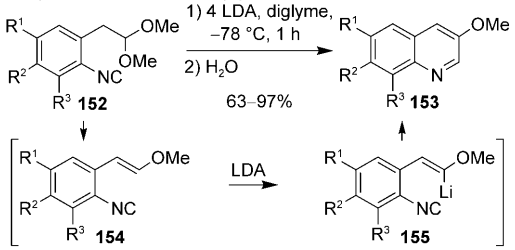
Table 23: Synthesis of 4-hydroxy-3-quinolinecarboxylic acid derivatives **151**.[91]



R^1	R^2	R^3	R^4	**151** [%]
Et	H	H	OEt	79
*n*Pr	H	H	O*n*Pr	80
*n*Bu	H	H	O*n*Bu	75
*n*Pr	Cl	H	O*n*Pr	71
*n*Pr	OMe	OMe	O*n*Pr	87
Me	H	H	O*t*Bu	74
Me	H	H	NMe_2	63

2-(2′-Isocyanophenyl)acetaldehyde dimethyl acetals of type **152**, when treated with an excess of lithium diisopropylamide at −78 °C in diglyme, furnish 3-methoxyquinolines **153** in good to high yields (Table 24).[92] The key intermediate is believed to be the δ-lithiated aryl isocyanide **155** arising from deprotonation of the corresponding *ortho*-isocyano-β-methoxystyrene **154**, which is evidently a product of benzylic deprotonation of the acetal **152** and subsequent elimination of lithium methoxide.

Table 24: Synthesis of 3-methoxyquinolines **153**.[92]



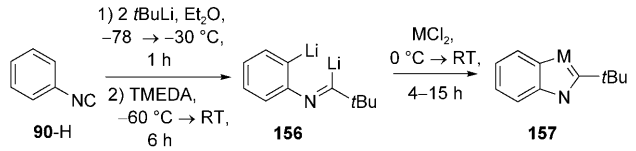
R^1	R^2	R^3	**153** [%]
H	H	H	79
H	Me	H	72
H	H	Me	63
H	*i*Pr	H	71
H	H	OMe	47
		H	97

3. Additions to an Isocyano Group Followed by Cyclization

3.1. Uncatalyzed Processes

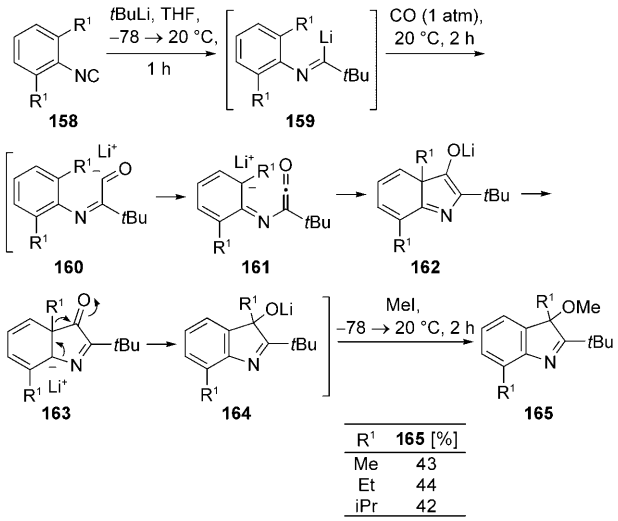
Organolithium[93] as well as organomagnesium[94] reagents have been found to undergo α addition to isocyanides to give metalated aldimines, which provide an opportunity for cyclization to N-heterocycles if an appropriate adjacent functional group is established or present in the same molecule. For example, the addition of *tert*-butyllithium to phenyl isocyanide (**90**-H) and subsequent TMEDA-assisted *ortho*-lithiation has been reported to lead to the dilithiated aldimine **156**, which in turn can be trapped with various element dichlorides to provide the corresponding benzelementazoles **157** in moderate to good yields (Table 25).[95] The use of an excess of the sterically demanding *tert*-butyllithium (2 equiv) as well as adding the isocyanide to the organolithium reagent has been found to be crucial for the effective formation of the intermediate **156**. In this way conventional benzazoles such as benzothiazole as well as less well known benzoazosiloles, benzoazogermoles etc. have been prepared, and their degree of aromaticity has been investigated.

Table 25: Addition of *tert*-butyllithium to phenyl isocyanide and subsequent *ortho*-lithiation as well as synthesis of benzoannelated azoles **157**.[95]



M	**157** [%]
PPh	52
S	65
AsMe	55
$GeMe_2$	68
$SnMe_2$	41
$SiMe_2$	53
$SiPh_2$	63

Murai and co-workers have used 2,6-dialkylsubstituted phenyl isocyanides **158** to prevent *ortho*-metalation after the addition of *tert*-butyllithium to the isocyano group (Scheme 17). The resulting deprotonated aldimines **159** were then trapped with carbon monoxide to induce a multistep cascade of transformations, which led, after treatment with methyl iodide, to 3-methoxy-3*H*-indoles **165**.[96] According to the proposed mechanism, the lithiated aldimine **159** initially forms the reactive acyllithium intermediate **160** which cyclizes by way of its tautomeric form, the non-aromatic ketene **161**, to furnish **162**. This species tautomerizes to the ketone **163**, in which a 1,2-migration of an alkyl group can occur to afford the deprotonated 3*H*-indole **164**, that finally reacts with methyl iodide to give the observed product **165** (Scheme 17).[96]

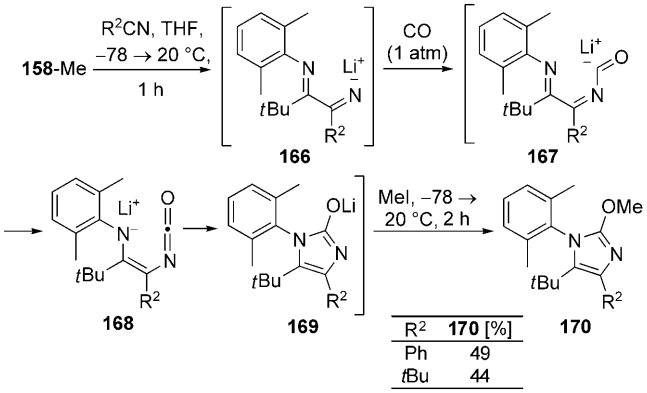


R^1	**165** [%]
Me	43
Et	44
iPr	42

Scheme 17. 3*H*-Indoles **165** from 2,6-dialkylphenyl isocyanides.[96]

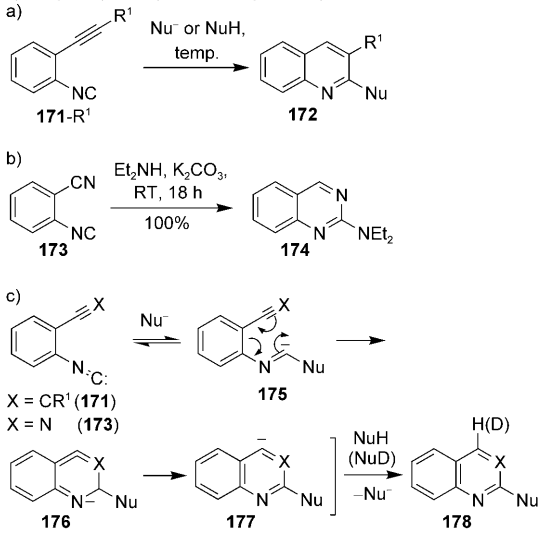
Treatment of the lithiated aldimine of type **159** in situ with a nitrile, before exposing the reaction mixture to CO, and then adding methyl iodide afforded 1-aryl-2-methoxy-imidazoles **170** in a four-step one-pot procedure in moderate yields (Scheme 18).[96] This sequential reaction, just like the previous one, is presumed to proceed through a reactive acyllithium intermediate **167**, which cyclizes by way of its tautomer, the isocyanate **168**, and the resulting deprotonated 2-hydroxy-imidazole **169** is finally trapped with methyl iodide to yield the methoxyimidazole **170**.

The reaction of *ortho*-alkynylphenyl isocyanides **171** with nucleophiles such as alcohols, amines, and the sodium enolate of diethyl malonate, as reported by Ito and co-workers, constitutes a convenient and efficient synthesis of 2,3-disubstituted quinolines **172** (Table 26, reaction a).[97] The related diethylamine-induced 6-*endo*-dig cyclization of *ortho*-isocyanobenzonitrile **173** afforded 2-diethylaminoquinazoline (**174**) in quantitative yield (Table 26, reaction b).[97] In the crucial step of both of these transformations, the imidoyl



Scheme 18. 1-(2,6-Dimethylphenyl)-2-methoxyimidazoles **170** from 2,6-dimethylphenyl isocyanide.[96]

Table 26: Formation of 2,3-disubstituted quinolines **172** as well as 2-diethylaminoquinazoline **174** from *ortho*-alkynylphenyl isocyanide and *ortho*-cyanophenyl isocyanide, respectively.[97]

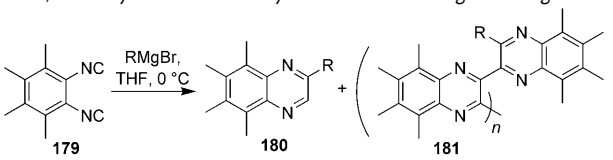


R^1	NuH or Nu	*T*	**172** [%]
Ph	MeOH	50 °C	86
CH_2OMe	MeOH	50 °C	66
$SiMe_3$	Et_2NH	RT	92
cHex	Et_2NH	RT	80
1-cyclohexenyl	Et_2NH	RT	86
*t*Bu	$(EtO_2C)CH^-$	RT	87

anion **175**, formed initially upon addition of a nucleophile to the isocyano group, is presumed to undergo a 6π electrocyclization to provide the intermediate **176** with cumulated double bonds. Protonation (or deuteration) of its valence tautomer **177** leads to **178** (Table 26, reaction c).[97]

Other interesting substrates that could lead to the formation of heterocycles on reaction with nucleophiles are 1,2-diisocyanoarenes of type **179**. They have been found to react with alkylmagnesium halides to furnish, after hydrolysis of the reaction mixture, quinoxalines **180** along with oligomers **181**, the polymerization degree of which depends on the number and types of substituents (Table 27).[98] These products apparently arise by successive insertions of the isocyano groups into magnesium–carbon bonds.

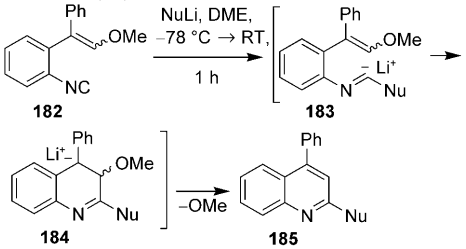
Table 27: Formation of substituted oligo- and polymeric quinoxalines from 1,2-diisocyanoarenes **179** by treatment with Grignard reagents.[98]



R	**180** [%]	**181**, *n* = 1 [%]	2 [%]	3 [%]	4 [%]	5 [%]
*i*Pr	5	3	7	5	8	3
*n*Bu	2	4	8	10	10	–
*i*Bu	5	6	6	4	6	3
*t*Bu	12	3	3	3	4	–

Kobayashi et al. have shown that *o*-isocyano-β-methoxystyrenes such as **182**, can be employed for the preparation of 2,4-disubstituted quinolines **185** (Table 28).[99] Nucleophiles such as organolithium reagents, lithium dialkylamides, and lithium thiophenolate undergo α addition to the isocyano group to provide an imidoyl anion **183**. Cyclization of **183** and subsequent elimination of lithium methoxide furnishes the quinolines **185**.

Table 28: Preparation of quinolines **185** by addition of nucleophiles to *o*-isocyano-β-methoxystyrenes **182**.[99]

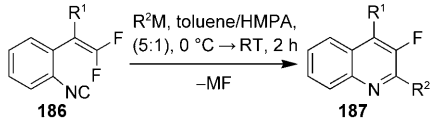


NuLi	**185** [%]	NuLi	**185** [%]
*n*BuLi	79	Et_2NLi	60
	74		72
PhLi	91	PhSLi	32

Independently, Ichikawa et al. developed a similar reaction of organometallic reagents with β,β-difluoro-*ortho*-isocyanostyrenes **186** to produce 2,4-disubstituted 3-fluoroquinolines **187** by 6-*endo*-*trig* cyclization of the initially formed imidoyl anions with subsequent elimination of fluoride (Table 29).[100] The use of *n*-butyllithium in this reaction furnished a complex mixture of products, whereas treatment with the sterically encumbered *tert*-butyllithium smoothly led to the corresponding quinoline **187** in 78% yield. Some organomagnesium reagents as well as triethylgermyllithium, which are less reactive than organolithium compounds, have also been employed successfully in this reaction.[100]

In contrast to all these organometallic reagents, treatment of **186** with tributylstannyllithium and subsequent hydrolysis

Table 29: Synthesis of 2,4-disubstituted 3-fluoroquinolines **187** by addition of organometallic reagents to β,β-difluoro-*ortho*-isocyanostyrenes **186**.[100]

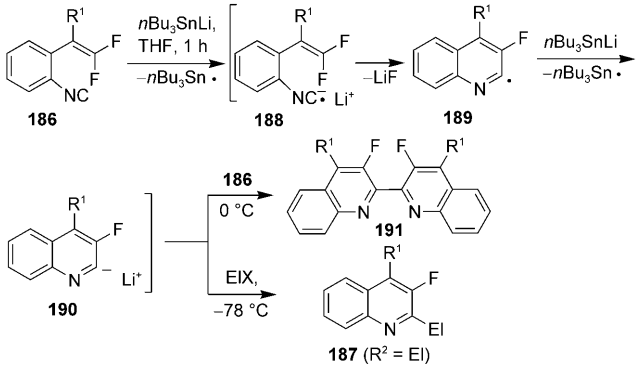


186 **187**

R^1	R^2M	**187** [%]
*n*Bu	*n*BuMgBr	69
secBu	*n*BuMgBr	60
*n*Bu	EtMgBr	59
*n*Bu	*i*PrMgBr	64
*n*Bu	*t*BuLi	78
*n*Bu	Et_3GeLi	61

provided quinolines **187** ($R^2 = H$) along with bisquinolines **191** (Table 30).[101] In the latter case, tributylstannyllithium plays the role of a one-electron reducing agent, which reduces the *ortho*-isocyano-β,β-difluorostyrene **186** to the radical anion **188**, which in turn undergoes cyclization to give the quinolyl radical **189**. Further reduction of this radical yields the 2-lithiated quinoline **190**, which may react with the starting material **186** to eventually furnish the bisquinoline **191**. The organolithium intermediate **190**, when generated at −78 °C, can be trapped at the same temperature by various electrophiles to provide the corresponding 2,3,4-trisubstituted quinolines **187**, or after transmetalation with zinc chloride can be subjected to a subsequent Negishi cross-coupling reaction with aryl iodides.[101]

Table 30: Reaction of *ortho*-isocyano-β,β-difluorostyrene **186** with tributylstannyllithium.[101]

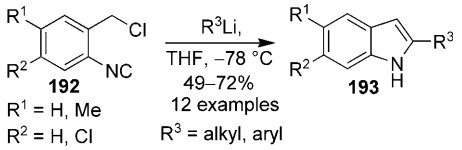


187 (R^2 = EI)

R^1	Method	E	E	**187** [%]	**191** [%]
*n*Bu	A[a]	H_2O	H	80	–
Et	A[a]	H_2O	H	77	–
*sec*Bu	A[a]	H_2O	H	65	–
*n*Bu	B[b]	H_2O	H	4	59
Et	B[b]	H_2O	H	12	42
*sec*Bu	B[b]	H_2O	H	–	42
*n*Bu	A[c]	PhCHO		78	–
*n*Bu	A[c]	I_2	I	52	–
*n*Bu	A[c]	DMF	CHO	70	–
*n*Bu	A[d]	ArI	4-$MeOC_6H_4$	87	–
*n*Bu	A[d]	ArI	4-$NO_2C_6H_4$	74	–

[a] Method A: Substrate **186** was added to nBu_3SnLi at −78 °C. [b] Method B: nBu_3SnLi was added to substrate **186** at 0 °C, then RT. [c] Electrophile EI was added at −78 °C. [d] $ZnCl_2$ (2.5 equiv), −78 °C, then $[Pd_2(dba)_3]$ (4 mol%), PPh_3 (16 mol%), ArI, RT, 3.5 h.

The addition of alkyl- or aryllithium reagents to the isocyano group of *ortho*-(chloromethyl)phenyl isocyanides **192** followed by intramolecular nucleophilic substitution has been reported to provide substituted indoles **193** in moderate to good yields (Scheme 19).[102]



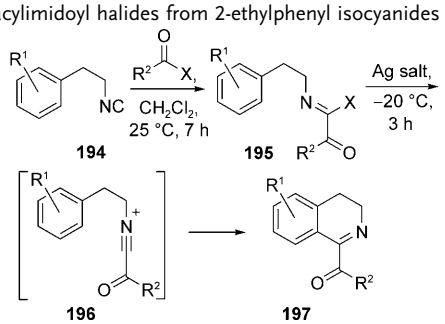
192 **193**

R^1 = H, Me
R^2 = H, Cl

Scheme 19. 2-Substituted indoles **193** from *ortho*-(chloromethyl)phenyl isocyanides **192**.[102]

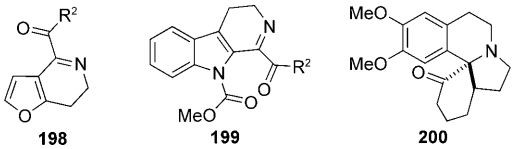
For more than a century isocyanides have been known to react with acyl halides to provide the corresponding α-ketoimidoyl halides.[103] The products of such insertions such as **195** derived from 2-phenylethyl isocyanides of type **194** have been found to undergo silver(I)-mediated cyclizations to form 1-acyl-3,4-dihydroisoquinolines **197** in moderate to good yields (Table 31).[104,105] Transient acylnitrilium cations of type **196** are presumed to be the key intermediates in these reactions under ionizing conditions (with Ag salts), whereas Lewis ($SnCl_4$) or Brønsted acids (CF_3SO_3H), which also induce such cyclizations, would coordinate or protonate **195** to form the corresponding haloiminium derivatives, which then play the same role as **196**.[104]

Table 31: 1-Acyl-3,4-dihydroisoquinolines by silver(I)-mediated cyclization of acylimidoyl halides from 2-ethylphenyl isocyanides **194**.[104]



194 **195**

196 **197**



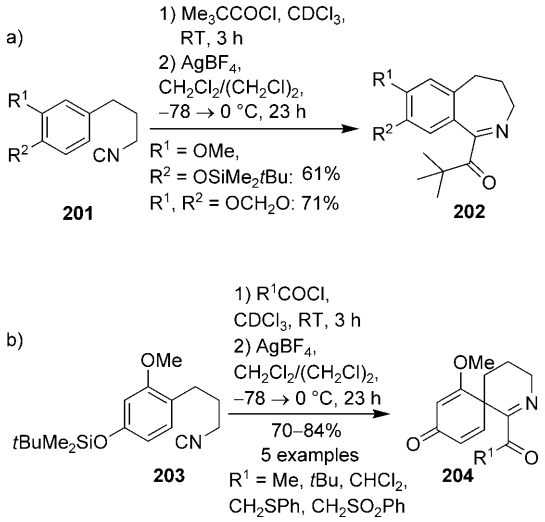
198 **199** **200**

63% (R^2 = *t*Bu)
49% (R^2 = Ph)

67% (R^2 = *t*Bu)
60% ($R^2 = MeO_2C(CH_2)_2$)

R^1	R^2	X	Ag salt	**197** [%]
3,4-$(MeO)_2$	*t*Bu	Br	AgOTf	82
3,4-$(MeO)_2$	SEt	Cl	AgOTf	57
3,4-$(MeO)_2$	$(CH_2)_3CH{=}CH_2$	Cl	AgOTf	87
4-Me	*i*Pr	Cl	$AgBF_4$	62

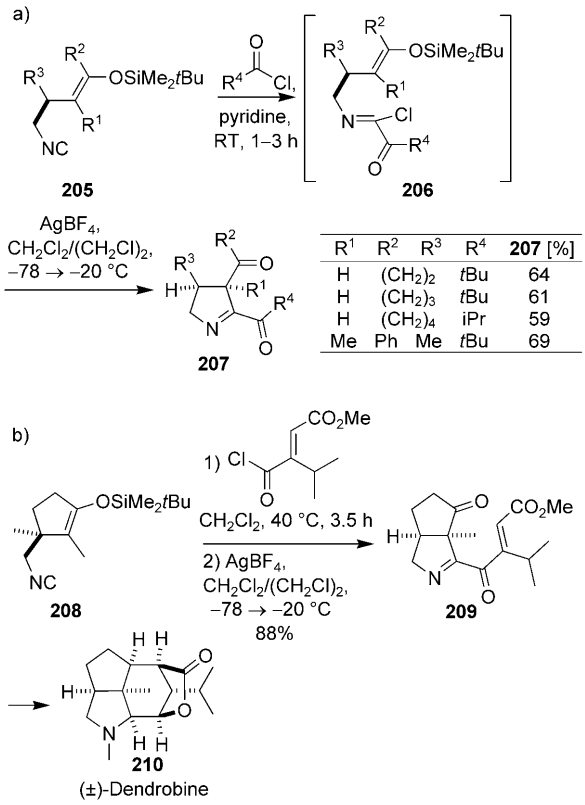
Analogously to the dihydroisoquinolines **197**, the furan- and indole-annelated dihydropyridines of types **198** and **199**, respectively (Table 31), have been synthesized in good yields from the corresponding 2-arylethyl isocyanides. The generality and very mild conditions of this method make it a useful supplement to the classical Bischler–Napiralski synthesis of 3,4-dihydroisoquinolines (and the corresponding isoquinolines). The tetracyclic compound **200**, which resembles the skeleton of the alkaloid erythrinane, has been conveniently prepared in a two-step one-pot procedure from an appropriately substituted 3,4-dihydroisoquinoline **197** prepared by this route.[104b] 3,4-Bisdonor-disubstituted 3-phenylpropyl isocyanides of type **201**, which are homologues of the previously discussed isocyanides **194**, also undergo smooth addition of acid chlorides with subsequent silver(I)-promoted cyclization to furnish 2-acylbenzazepines **202** (Scheme 20, reaction a).[106]



Scheme 20. Cyclizations of 3-arylpropyl isocyanides **201** and **203** after reaction with acid chlorides.[106,107]

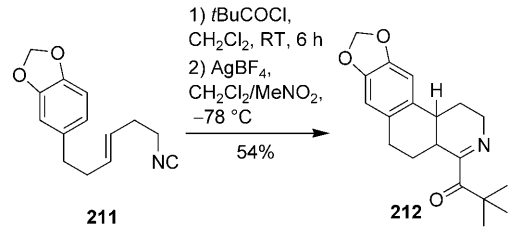
However, similar isocyanides, such as **203**, with a different substitution pattern do not form the correspondingly substituted benzazepines **202**, but instead afford the spiroannelated tetrahydropyridines **204** exclusively by *ipso* attack of the intermediate acylnitrilium cation of type **196** with subsequent in situ desilylation and tautomerization in good yields (Scheme 20, reaction b).[106,107]

Westling and Livinghouse reported an approach to 2-acyl-Δ^1-pyrrolines **207** which involved cyclization of acylnitrilium ions by a 5-*exo-trig* attack on a γ-positioned silyl enol ether moiety (Scheme 21, reaction a).[108] The key intermediate **206** was produced by addition of an acid chloride to the isocyano group of the homoallyl isocyanide **205** followed by $AgBF_4$-mediated cyclization and subsequent desilylation. No intermediates were isolated or purified and the 2-acylpyrrolines **207** were obtained in moderate to good yields. This method was employed successfully by the same research group in the synthesis of the bicyclic Δ^1-pyrroline **209**, the key precursor in a total synthesis of the alkaloid (±)-dendrobine (**210**; Scheme 21, reaction b).[109]



Scheme 21. 2-Acylpyrrolines **207** by $AgBF_4$-mediated cyclization of imidoyl chlorides **206** and application in the total synthesis of (±)-dendrobine **210**.[108,109]

As a kind of extension of the previously described cases, the adduct of pivaloyl chloride to the isocyano group of the homoallyl isocyanide **211** upon treatment with $AgBF_4$ undergoes a cascade cyclization involving both the unactivated double bond and an aromatic ring to provide the tricyclic compound **212**, a benzoannelated hexahydroisoquinoline, in 54% yield over two steps (Scheme 22).[108]

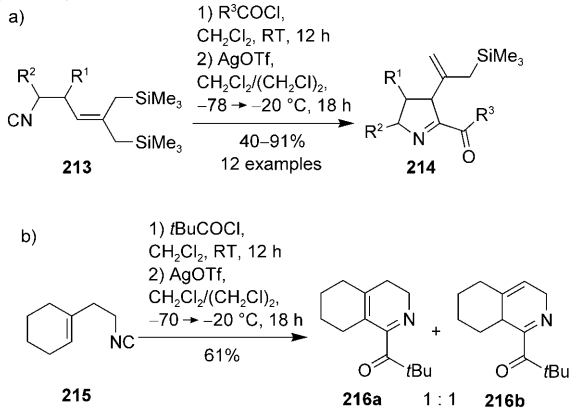


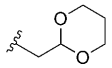
Scheme 22. Synthesis of the benzoannelated hexahydroisoquinoline **212** by $AgBF_4$-mediated cascade cyclization of the adduct obtained from the homoallyl isocyanide **211** and pivaloyl chloride.[108]

Some particular alkenes such as **213** and **215** were later employed in similar silver(I)-mediated cyclizations to provide the corresponding 3,4-dihydro-2*H*-pyrroles **214** and dihydropyridines **216**, respectively (Table 32).[110]

The acylimidoyl chlorides **218** generated by the addition of acyl chlorides to cyclohexyl isocyanide (**217**) have recently been shown to react in situ with the tetrazole **219** to provide

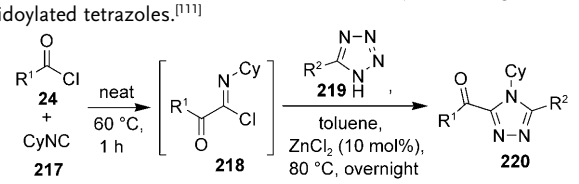
Table 32: 3,4-Dihydro-2*H*-pyrroles **214** and dihydropyridines **216a**/**216b** by AgOTf-mediated cocyclizations of alkenyl isocyanides **213** and **215**, respectively, with acid chlorides.



R^1	R^2	R^3	**214** [%]
H	H	*t*Bu	82
H	H		91
Me	H	Et	40
H	CH_2OMe_2tBu	*t*Bu	87
H	Me	Et	78

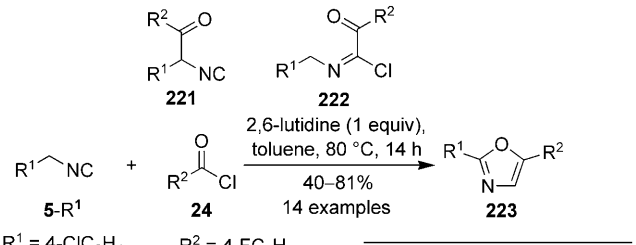
1,2,4-triazoles **220**.[111] These compounds are apparently formed by the rearrangement of the intermediate imidoylated tetrazole, as previously reported by Huisgen et al. (Table 33).[112]

Table 33: Substituted 1,2,4-triazoles **220** by rearrangement of imidoylated tetrazoles.[111]



R^1	R^2	**220** [%]
$4\text{-}FC_6H_4$	Ph	79
$4\text{-}FC_6H_4$	$4\text{-}FC_6H_4$	61
$4\text{-}FC_6H_4$	$4\text{-}MeOC_6H_4$	63
$Ph(CH_2)_2$	Ph	42
*i*Pr	$4\text{-}MeOC_6H_4$	39
$4\text{-}FC_6H_4$		53

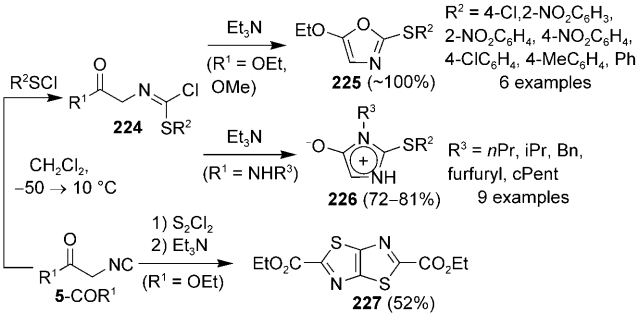
As has been mentioned above, methyl isocyanides **5**-R^1 deprotonated with a strong base such as *n*-butyllithium react with acyl chlorides **24** to provide 4,5-disubstituted oxazoles **3** (X = O).[16] The intermediates in this transformation are α-acylmethyl isocyanides of type **221**. Conversely, in the presence of a relatively weak base such as 2,6-lutidine, acyl chlorides undergo α addition to the isocyano group to furnish acylimidoyl chlorides **222**, and the latter species subsequently cyclize to provide 2,5-disubstituted oxazoles **223** regioselectively (Scheme 23).[113]



R^1	R^2	**223** [%]
$4\text{-}ClC_6H_4$	cPr	81
$4\text{-}ClC_6H_4$	$4\text{-}FC_6H_4$	79
3-pyridyl	Ph	50
2-furyl	$4\text{-}FC_6H_4$	40
2-styryl	iPr	48

Scheme 23. Regioselective synthesis of 2,5-disubstituted oxazoles **223**.[113]

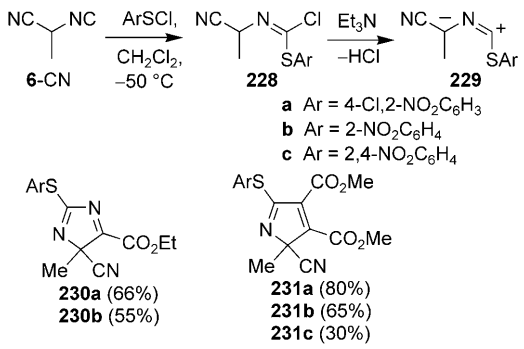
Similarly to acid chlorides, arylsulfenyl chlorides react with isocyanides to furnish unstable thioimidoyl chlorides such as **224**, which are capable of reacting further with cyclization if an appropriate adjacent functionality is present. Thus, the adducts of isocyanides **5**-COR^1 with ester or amide moieties have been shown to undergo cyclizations to 2-arylthio-5-alkoxyoxazoles **225**[114] and 3-alkyl-2-arylthio-1,3-diazolium-4-olates **226**,[115] respectively, when treated with triethylamine (Scheme 24). Similarly, dichlorosulfane SCl_2



Scheme 24. Reactions of isocyanoacetates and isocyanoacetamides **5**-COR^1 with arylsulfenyl chlorides or dichlorodisulfane with subsequent Et_3N-induced cyclizations of the adduct.[114,117]

reacts with two equivalents of the isocyanide **5**-COR^1, and the twofold adduct, after amine-induced cyclization, generates the corresponding 2,2'-bis(oxazolyl) sulfide.[116] The reaction of two equivalents of ethyl isocyanoacetate (**5**-CO_2Et) with dichlorodisulfane S_2Cl_2 unexpectedly led to diethyl thiazolo[5,4-*d*]thiazole-2,5-dicarboxylate (**227**; Scheme 24). The mechanism of this complex transformation, as proposed by the authors, includes cleavage of the S–S bond in the primary bisadduct followed by a cascade of further reaction steps.[117]

The reaction of cyanoethyl isocyanide (**6**-CN) with arylsulfenyl chlorides and subsequent treatment of the thus formed adduct **228** with triethylamine led to the 1,3-dipolar compounds **229** (Scheme 25), which were subjected in situ to cycloadditions with ethyl cyanoformate and dimethyl acety-

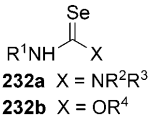


Scheme 25. The formation of 1,3-dipolar compounds **229** and their cycloadditions to yield 4*H*-imidazoles **230** and 2*H*-pyrroles **231**.[118]

lenedicarboxylate to provide the 4*H*-imidazoles **230** and 2*H*-pyrroles **231**, respectively.[118] Analogously, 1*H*-pyrroles and 1*H*-imidazoles have been synthesized by employing 4-(nitrobenzyl)methyl isocyanide **5**-(4-$NO_2C_6H_4$) instead of **6**-CN.[119]

3.2. Transition-Metal-Catalyzed Processes

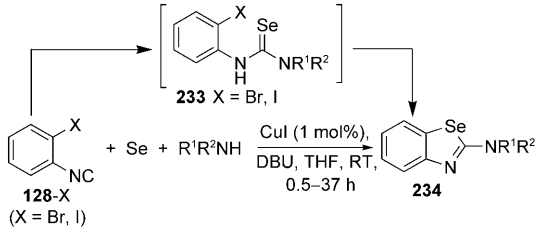
Aryl isocyanides have been shown to react with elemental selenium to form isoselenocyanates.[120] Analogous reactions with alkyl isocyanides in the presence of a base, and subsequent reactions of the thus-formed isoselenocyanates with amines and alcohols to give selenoureas **232a** and selenocarbamates **232b**, respectively, were later reported.[121]



When *o*-halophenyl isocyanides **128**-X were used as substrates in this reaction, the resulting selenoureas **233** could be transformed efficiently into the corresponding benzoselenazoles **234** in a copper(I)-catalyzed one-pot process (Table 34).[122] Secondary alkyl- and arylamines, *n*-butylamine, as well as imidazole furnished the corresponding 2-amino-substituted benzoselenazoles **234** in high yields.

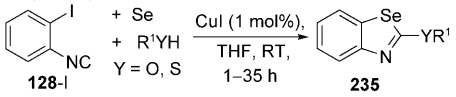
The use of alcohols or thiols instead of amines under essentially the same conditions as above, but without a base, afforded 2-alkoxy- (aryloxy-) and 2-alkylthiobenzoselenazoles **235** in high yields (Table 35).[122] Aliphatic alcohols and phenols with electron-donating substituents gave much higher yields than 4-methoxycarbonylphenol (48%), while all the thiols tested, both aliphatic and aromatic, provided the corresponding products **235** in high yields. As further investigations revealed, treatment of *ortho*-bromophenyl isocyanide (**128**-Br) with selenium and an amine can lead to 2-aminobenzoselenazoles **234**, even without a copper catalyst, although more slowly and only at an elevated temperature (100 °C), while *ortho*-iodophenyl isocyanide **128**-I undergoes this transformation even at ambient temperature. This finding led the authors to propose that mechanistically the cyclization might proceed as an intramolecular nucleophilic aromatic substitution of an initially formed selenolate **236** via an intermediate of type **237**. The role of copper iodide in facilitating this process remains unclear, but it may act as in a typical cross-coupling reaction and undergo oxidative addition to yield **238** with subsequent reductive elimination (Scheme 26).[123]

Table 34: Copper(I)-catalyzed formation of benzoselenazoles **234** from *ortho*-halophenyl isocyanides **128**-X.[122]

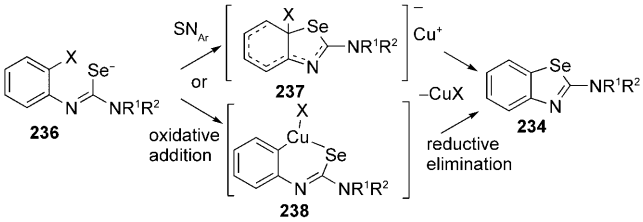


X	R^1	R^2	**234** [%]
Br	Et	Et	99
Br	Et	Ph	97
I	*n*Bu	H	71
I			97

Table 35: Copper(I)-catalyzed formation of benzoselenazoles **235** from *ortho*-iodphenyl isocyanide **128**-I.[122]



R^1	Y	**235** [%]
Bn	O	87
4-$MeOC_6H_4$	O	98
4-$MeO_2CC_6H_4$	O	48
n-$C_{12}H_{25}$	S	92

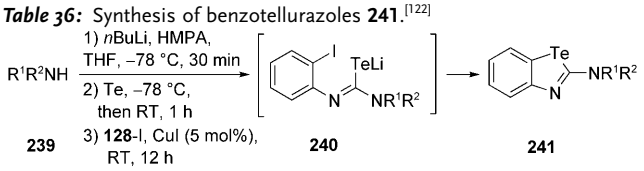


Scheme 26. Mechanistic rationalization of the formation of benzoselenazoles **234** from *ortho*-halophenyl isocyanides, selenium, and amines.[122]

The same authors have also extended their previously developed tellurium-assisted imidoylation of amines with isocyanides[124] and employed the thus formed intermediates **240,** such as in the syntheses of benzoselenazoles shown above, in a copper(I)-catalyzed one-pot synthesis of 2-amino-1,3-benzotellurazoles **241** (Table 36).[122]

Isocyanides are known to react with amines in the presence of copper[125] as well as other metal salts[126] to furnish formamidines in excellent yield. Amidines formed from *ortho*-bromophenyl isocyanide **128**-Br in this way have been found to undergo an intramolecular copper-catalyzed N-

Table 36: Synthesis of benzotellurazoles **241**.[122]

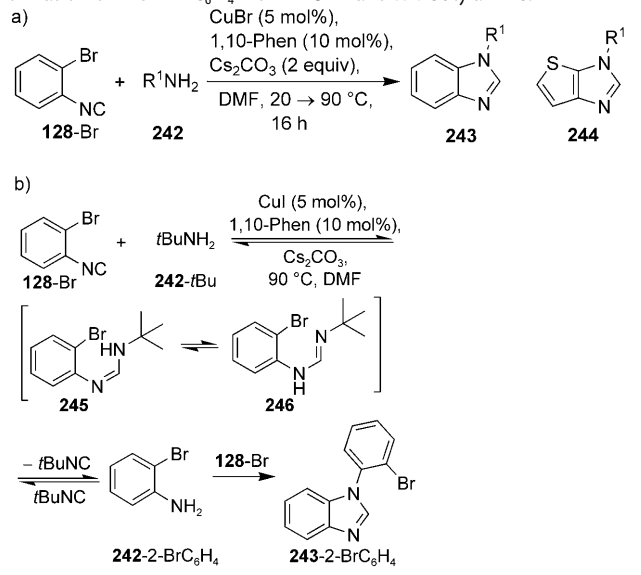


R^1	R^2	**241** [%]
$(CH_2)_5$		75
Et	Et	31
Et	Ph	53
Ph	Ph	65

arylation to give benzimidazoles **243** in moderate to good yields (38–70%; Table 37a).[127] Three examples of the related 3-substituted 3*H*-thieno[2,3-*d*]imidazoles **244** have been synthesized from 2-bromo-3-isocyanothiophene in the same way (44–49%). *n*-Alkylamines in general gave slightly better yields of benzimidazoles **243** than *sec*-alkylamines or amines with decreased nucleophilicity, such as 4-trifluoromethylbenzylamine and 4-methylaniline. The sterically demanding *tert*-butylamine did not afford the respective benzimidazole **243**-*t*Bu at all, but led to the formation of the 1-(2-bromophenyl)-substituted benzimidazole **243**-2-BrC_6H_4 in 38% yield.[127]

As **243**-2-BrC_6H_4 can also be prepared directly from **128**-Br with *ortho*-bromoaniline (42% yield), its formation in the reaction of **128**-Br with *tert*-butylamine is rationalized by a reversible release in the reaction mixture of 2-bromoaniline

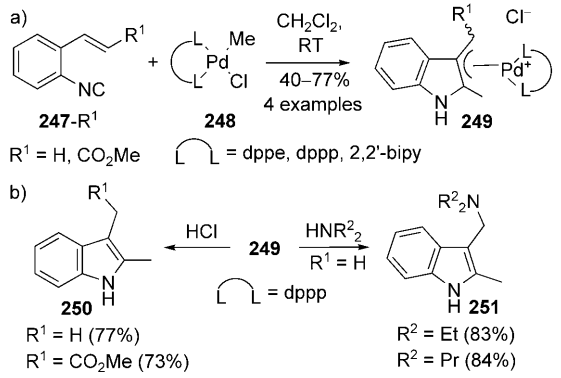
Table 37: Synthesis of 1-substituted benzimidazoles **243** as well as related heterocycles **244** and a mechanistic rationalization of the formation of **243**-2-BrC_6H_4 from **128**-Br and *tert*-butylamine.[127]



R^1	**243** [%]	**244** [%]
CH_2Ph	70	49
3-indolyl$(CH_2)_2$	59	44
$PhCH_2O(CH_2)_3$	66	44
Pr	65	
cHex	46	
4-MeC_6H_4	41	
2-BrC_6H_4	42	

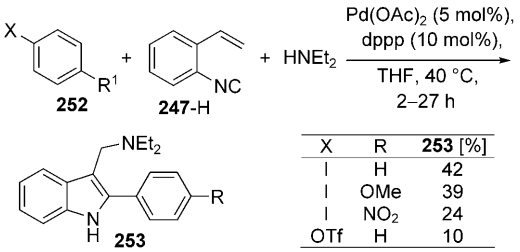
(**242**-2BrC_6H_4) from the initially formed formamidine **245**, which equilibrates with the formamidine **246** under the basic conditions (Table 37b).[127]

Takahashi and co-workers have shown that some methylpalladium chloride complexes of type **248** react stoichiometrically with *o*-alkenylphenyl isocyanides **247** to provide (η^3-indolylmethyl)palladium complexes **249** in moderate to good yields (Scheme 27, reaction a).[128] These isolated and fully characterized complexes could be converted into 2-methyl-3-(aminomethyl)indoles **251** by treatment with secondary amines and to 2,3-dimethylindoles **250** by protonation with HCl (Scheme 27, reaction b).[128]



Scheme 27. Palladium(II)-mediated cyclization of *ortho*-alkenylphenyl isocyanides **247**.[128]

The same research group reported somewhat later that 2,3-disubstituted indole derivatives **253** can be prepared by a palladium-catalyzed three-component reaction of *ortho*-ethenylphenyl isocyanide **247**-H with aryl iodides, aryl triflates, and diethylamine (Scheme 28).[129] It is clear in this case that



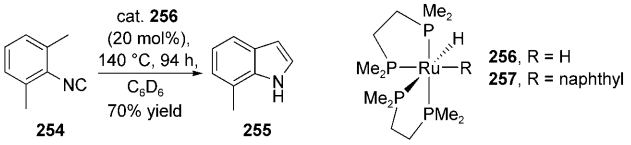
X	R	**253** [%]
I	H	42
I	OMe	39
I	NO_2	24
OTf	H	10

Scheme 28. Palladium-catalyzed formation of 2,3-disubstituted indoles **253** from *ortho*-ethenylphenyl isocyanide.[129]

arylpalladium iodide (triflates) complexes generated in situ by the oxidative addition of aryl iodides (triflates) to a Pd(0) species play the same role as methylpalladium complexes **248** used stoichiometrically in the case above. However, the reaction conditions in the latter case lead the palladium complexes of type **249** to release the indoles **253**, thus regenerating the catalytically active Pd(0) species and completing the catalytic cycle. This catalytic method afforded the 2,3-disubstituted indoles **253** only from the unsubstituted

ortho-ethenylphenyl isocyanide **247**-H and only in low yields, while the substituted isocyanide **247**-CO_2Me did not afford any of the corresponding indole under the same reaction conditions.[129]

Jones et al. reported that indoles **255** could also be obtained by treatment of 2,6-dimethylphenyl isocyanide (**254**) and some other *ortho*-methylphenyl isocyanides with ruthenium complexes **256** and **257** (Scheme 29).[130] This transformation was one of the earliest examples of a catalytic



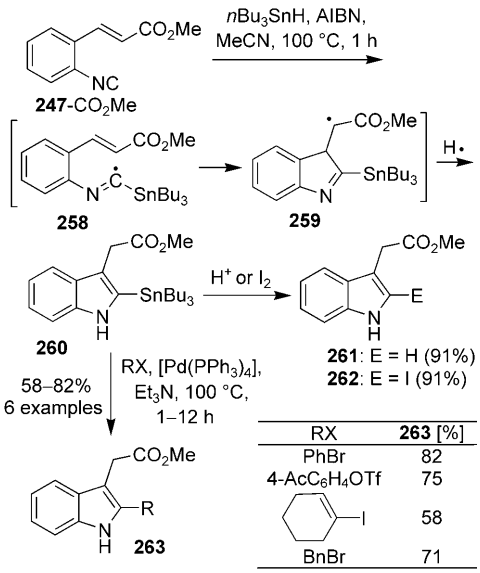
Scheme 29. Ruthenium-catalyzed formation of 7-methylindole **255** from 2,6-dimethylphenyl isocyanide.[130]

C,H activation with interesting mechanistic implications.[130b] Unfortunately, the harsh reaction conditions (140 °C, 94 h) and the limited number of possible applications prevent this method from being preparatively useful. Moreover, the thermal instability of *ortho*-methylphenyl isocyanides as well as the reversible insertion of a second isocyanide molecule into the N–H bond of the newly formed indole contribute to a lowering of the yields of the desired products.

4. Radical Cocyclizations

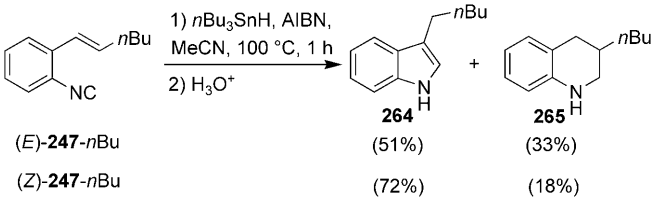
Isocyanides have also been reported to participate in various types of radical-initiated reactions. Once generated, radicals readily add to the isocyano group to produce the corresponding imidoyl radicals, which in certain cases are able to undergo subsequent cyclizations to give heterocyclic compounds. One of the most well-known and important processes of this type is the synthesis of indoles from *ortho*-isocyanostyrenes **247** and tri-*n*-butyltin hydride in the presence of a radical initiator, as developed by Fukuyama et al. (Scheme 30).[78,131]

The tri-*n*-butyltin radical reacts in situ with the *ortho*-isocyanostyrene **247**-CO_2Me to furnish a stannoimidoyl radical **258**, which readily undergoes a 5-*exo*-*trig* cyclization to give a 3*H*-indolyl radical (**259**). This in turn abstracts a hydrogen atom from tri-*n*-butyltin hydride, thereby leading, after tautomerization, to the 2-(tributylstannyl)indole **260**, which can be protio-destannylated to the 3-substituted indole **261** simply by acidic work-up. More importantly, **260** provides convenient access to various 2,3-disubstituted indoles of type **263** by Stille coupling reactions. The stannyl derivative **260** also reacts smoothly with electrophiles other than water; for example, with iodine it provides the 2-iodoindole **262**, which is another useful substrate for various cross-coupling reactions.[131] A clean formation of indoles has been found experimentally for substrates such as **247**-CO_2Me with radical-stabilizing substituents, whereas tetrahydroquinolines **265** were observed as side products (apparently arising from



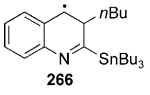
Scheme 30. The Fukuyama indole synthesis.[131] AIBN = azobisisobutyronitrile.

reduction of an imine with tributyltin hydride) for substrates such as **247**-*n*Bu bearing primary alkyl groups (Scheme 31).[131]



Scheme 31. Competitive formation of indoles and tetrahydroquinolines in the tributyltin-radical-initiated cyclization of *ortho*-alkenylphenyl isocyanides.[131]

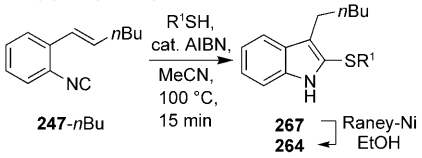
Apparently, in the case of **247**-*n*Bu, the intermediate imidoyl radical of type **258** can also undergo a 6-*endo*-*trig* cyclization to provide a dihydroquinoline radical of type **266**, although such a process is in general kinetically less favorable than a 5-*exo*-*trig* cyclization.[132]



The selective formation of indoles was achieved by using a large excess (typically 5 equiv) of alkylthio radicals generated from alkanethiols instead of tri-*n*-butyltin radicals. The thus formed 2-indolyl sulfides **267**-SR^1 could be smoothly desulfurized immediately after the rapid radical reaction to give the respective 3-substituted indole **267**-H. This one-pot procedure gave better overall yields than the sequential desulfurization after isolation of **267**-SR^1, presumably because of its instability in air (Table 38).

The strategy employed initially for the synthesis of *o*-alkenylphenyl isocyanides **247**-R^1 included dehydration of the corresponding formanilides, which were prepared by Heck coupling of *o*-iodoformanilides with alkenes. The Horner–

Table 38: Alkylthio radical induced formation of indoles **267**-SR[1] and **264** from *ortho*-alkenylphenyl isocyanides **247**.[133]



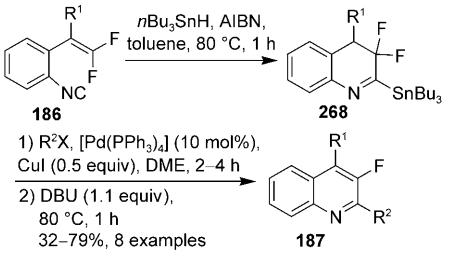
R^1	R^1SH (equiv)	Yield [%] **247** to **267**	Yield [%] **247** to **264**
Et	1.5	31	29
Et	5.0	71	67 (83)[a]
Ph	5.0	50	40
$HO(CH_2)_2$	5.0	79	60

[a] **267**-SEt was desulfurized immediately after removal of the solvent.

Wadsworth–Emmons reaction of diethyl *o*-isocyanobenzyl phosphonates with aldehydes and ketones provides another convenient access to the starting materials **247**-R[1].[133] Suitable products from Fukuyama indole syntheses have been employed in the total syntheses of several natural products,[131b–d] including the alkaloids (−)-aspidophytine,[134] (±)-vincadifformine, (−)-tabersonine,[135] and paullones.[136]

The selective formation of 3,3-difluorodihydroquinoline derivatives **187** by 6-*endo-trig* cyclizations of the corresponding imidoyl radicals generated from β,β-difluoro-*o*-isocyanostyrenes **186** and tri-*n*-butyltin hydride under conditions similar to those employed by Fukuyama et al. was observed by Mori and Ichikawa (Table 39).[137] The initially formed α-

Table 39: Tributyltin hydride induced formation of 2-stannylated dehydroquinolines **268** and subsequent synthesis of 2,4-disubstituted 3-fluoroquinolines **187**.[137]

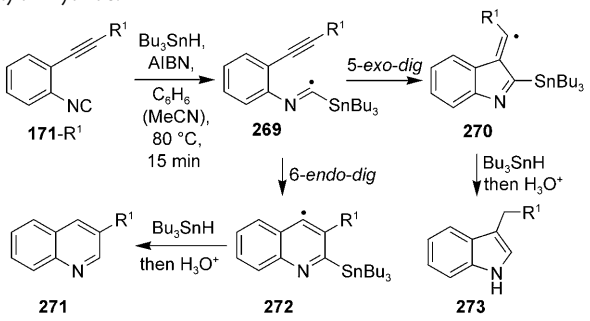


R^1	R^2X	**187** [%]
*n*Bu	PhI	70
*n*Bu	(*E*)-PhCH=CHBr	51
*i*Pr	2-$BocNHC_6H_4I$	61
H	PhI	32

stannylimidoyl radicals are presumed to have, in general, a nucleophilic character and, therefore, undergo a 6-*endo-trig* cyclization selectively because of the polarization of the *gem*-difluoro-substituted C–C double bond. The dihydroquinolines **268** thus obtained from **186** can undergo various modifications in situ, for example, Stille cross-coupling with aryl or alkenyl halides followed by base-induced dehydrofluorination to give the corresponding 3-fluoroquinolines **187**.

A strategy similar to that of the Fukuyama indole synthesis but employing tri-*n*-butyltin and alkylthio free-radical-mediated cyclizations of *o*-alkynylphenyl isocyanides **171**-R[1] was developed a short time later for the synthesis of indoles and quinolines (Table 40).[138]

Table 40: Reaction of *ortho*-alkynylphenyl isocyanides (**171**-R[1]) with tri-*n*-butyltin hydride.[138]



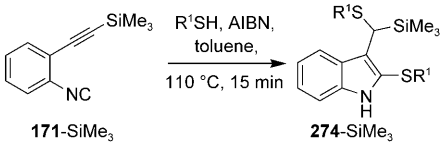
R^1	**271**/**273**	Total yield [%]
$SiMe_3$	0:1	82
Ph	1:2.2	41
*n*Bu	5.3:1	63
*t*Bu	1:14	60
CH_2OBn	1:2	11
H	1:0	18

In these transformations, the initially formed imidoyl radicals **269** are apparently able to undergo either a 5-*exo-dig* cyclization to give indolenine radicals **270** or a 6-*endo-dig* cyclization to provide the corresponding quinoline radicals **272**. Both radicals subsequently abstract hydrogen from tri-*n*-butyltin hydride and the resulting tri-*n*-butyl derivatives are eventually protio-destannylated during acid work-up to yield the 3-substituted indoles **273** and 3-substituted quinolines **271**, respectively (Table 40). The ratio of these two products and their total yield depend significantly on the nature of the alkynyl substituent on the isocyanide. Thus, sterically demanding substituents such as $SiMe_3$ and *t*Bu on the acetylene terminus favored the 5-*exo-dig* over the 6-*endo-dig* cyclization mode, since in the latter case the two bulky substituents (R^1 and Bu_3Sn) would be placed close to each over. The reaction was not as selective with other substituents on **171**-R[1], and provided both indoles **273** and quinolines **271** in comparable quantities.[138]

By using the isocyanide **171**-$SiMe_3$ and an excess of an alkanethiol in the presence of a free-radical initiator, the same authors also succeeded in the selective synthesis of 2-alkylthioindoles **274**, which are equipped for further elaboration (Table 41).[138] In both the described cases of alkylthio radical induced indole formation (Tables 38 and 41) the process is terminated by thiol itself, either by transfer of a hydrogen (Table 38) or an alkylthio radical (Table 41). All attempts to use external nucleophiles, such as alcohols or amines, in the reaction of **171**-$SiMe_3$ with tri-*n*-butyltin hydride were unsuccessful and provided only the starting material **171**-$SiMe_3$ along with the indole **274**-$SiMe_3$.[138]

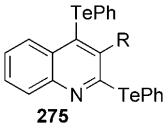
Interestingly, *ortho*-alkynylphenyl isocyanides **171**-R[1], upon treatment with diphenyl ditelluride or a mixture of diphenyl disulfide and diphenyl ditelluride under irradiation

Table 41: Reaction of *ortho*-(trimethylsilylethynyl)phenyl isocyanide (**171**-SiMe3) with thiols under free-radical conditions.[138]



171-SiMe$_3$ **274**-SiMe$_3$

R^1	**274** [%]
Et	86
*n*Bu	66
Ph	49
$(CH_2)_2OH$	94
$(CH_2)_2OSiMe_2tBu$	60
$(CH_2)CO_2Me$	72



275

with visible light, undergo cyclization to provide the corresponding 2,4-di(tellurophenyl) quinolines **275**.[139] *ortho*-Alkenylphenyl isocyanides (**247**-R^1) have been reported to undergo cyclizations under the same conditions to furnish indoles **274**-R^1.[140]

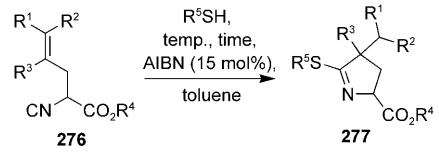
In close analogy to the formation of indoles from *ortho*-alkenylphenyl isocyanides (**247**-R), aliphatic homoallyl isocyanides of type **276** generate 2-alkylthiopyrrolines **277** in a radical-initiated reaction with alkanethiols (Table 42).[141] The free radical may lower the yield of the pyrroline **277** when a thiol with a radical-stabilizing group is used (for example, $R^5 = CH_2CO_2Me$). In such cases, the reaction was shown to proceed more selectively at lower temperatures (down to −60 °C) upon photochemical initiation, and provided pyrrolines **277** almost exclusively.[141b]

Mercaptoethanol, in principle, reacts with the unsubstituted 2-allylisocyanoacetate **276** in the same way under radical initiation, but eventually yields the pyrrolidin-2-one **279**, which supposedly arises via the intermediate thioacetal **278**,[141b] which in turn must be formed by intramolecular addition of the hydroxy group to the imine double bond of the initial cyclization product of type **277** (Table 42, reaction b).[141b]

Alkenylisocyanoacetates of type **281** with a phenylthio substituent in the second allylic position have been found to undergo a cycloisomerization to 3-ethylidene-2-phenylthio-$\triangle^1$-pyrrolinecarboxylates **280** in the presence of catalytic amounts of a thiol and a radical initiator. The initial addition of a phenylthiyl radical (**282**) to the isocyano group of **281** is considered to furnish the thioimidoyl radical **284**, which in turn undergoes a *5-exo-dig* cyclization to provide **285**. Compound **285** again releases a phenylthiyl radical (**282**) by β elimination to provide the 3-ethenyl-2-thiophenylpyrroline **283**, which isomerizes to the finally isolated **280** (Scheme 32).[141b]

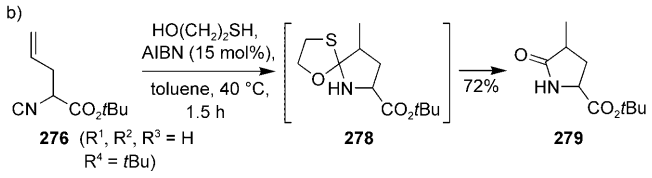
Table 42: 5-(Alkylthio)-$\triangle^1$-thiopyrrolines **277** and pyrrolidinone **279** from homoallylic isocyanides **276**.[141]

a)



276 **277**

b)

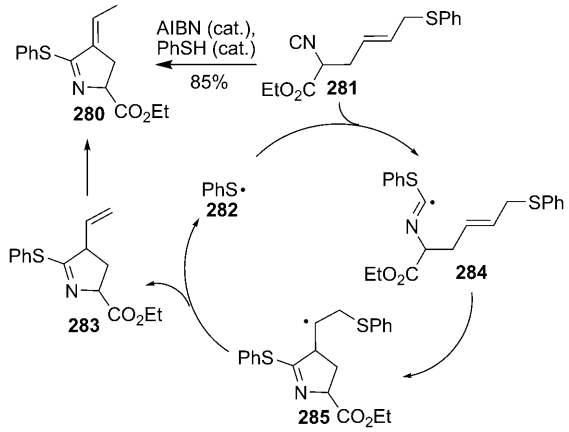


276 (R^1, R^2, R^3 = H, R^4 = *t*Bu) **278** **279**

R^1	R^2	R^3	R^4	R^5	*T* [°C]	*t* [h]	**277** [%]
H	H	H	*t*Bu	Ph	110	1.0	74
H	H	H	Et	Et	40	1.5	85
H	Me	Me	Et	$(CH_2)_3CO_2Me$	85	2.0	84
Me	H	H	*t*Bu	Ph	110	1.5	30
H	Me	Me	Et	CH_2CO_2Me	45	3.0	38
H	Me	Me	Et	CH_2CO_2Me	−60[a]	8.5	78

[a] Irradiation with a Hanovia E-H4 lamp.

yields of such 5-*exo-trig* cyclization products are high (74–85 %) when $R^1 = H$ (see Table 42, reaction a), but decrease significantly for substrates that contain substituents larger than hydrogen at these positions, since the attack of the initially formed thioimidoyl radical on the double bond is hampered. A competing degradation of this initial thioimidoyl radical by its β fragmentation to isothiocyanate and a

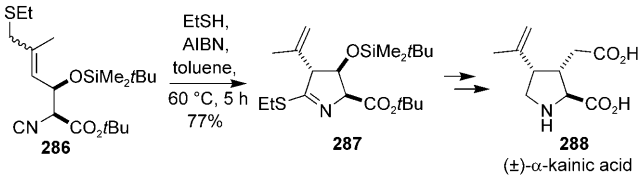


280 **281** **282** **283** **284** **285**

Scheme 32. Phenylthio radical catalyzed isomerization of ethyl 2-(4-phenylthiobut-2-ene-1-yl)isocyanoacetate (**281**) to ethyl 3-ethylidene-2-phenylthio-$\triangle^1$-pyrrolinecarboxylate (**280**).[141b]

Importantly, these thiol-mediated and -catalyzed radical cyclizations have been shown to proceed stereoselectively with appropriate substrates.[142] Thus, the ethanethiol-catalyzed isomerization of the isocyano-substituted *tert*-butyl ester **286** led to a single diastereomer of the 2-ethylthiopyrroline **287** in 77 % yield. Pyrroline **287** has successfully served as the key intermediate in a total synthesis of (±)-α-kainic acid **288** (Scheme 33).[143]

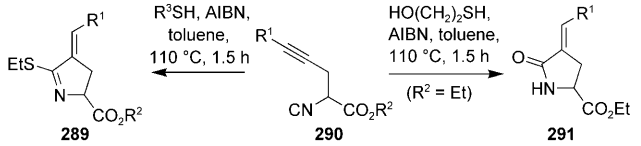
Analogously to allyl isocyanoacetates **276**, propargyl isocyanoacetates of type **290** react with thiols under radical initiation to provide 3-alkylidenepyrrolines of type **289**, and



Scheme 33. Ethylthio radical catalyzed cyclization of a 2-(4-ethylthio-but-2-en-1-yl)isocyanoacetate to the key intermediate **287** in a total synthesis of (±)-α-kainic acid **288**.[143]

with mercaptoethanol to yield 3-alkylidenepyrrolidin-2-ones of type **291** by 5-*exo-trig* cyclizations (Table 43).[141b]

Table 43: Alkylthio radical initiated cyclizations of a propargyl isocyanoacetate **290**.[141b]



R^1	R^2	R^3	**289** [%]	R^1	**291** [%]
$SiMe_2tBu$	*t*Bu	Et	72	$SiMe_2tBu$	81
$SiMe_2tBu$	Et	$(CH_2)_2CO_2Me$	60	$SiPh_2tBu$	84
$SiPh_2tBu$	Et	Et	90		

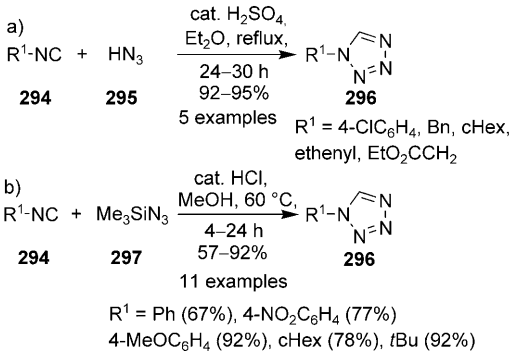
Microwave flash-heating technology has been shown to reduce reaction times of such alkanethiol-mediated (-catalyzed) cyclizations of allyl and propargyl isocyanoacetates dramatically, and to afford the final products in higher yields.[144] Recently, the same types of transformations have also been performed successfully on a solid phase with polymer-supported allyl isocyanoacetates.[145]

Diverse radical-initiated cascade cocyclizations with isocyanides, a representative example of which concerns a synthesis of the antitumor agent (20*S*)-camptothecin (**293**)[146] as depicted in Scheme 34, have previously been reviewed by Curran and co-workers,[147] and are considered to go beyond the scope of the present article.[148]

Scheme 34. An example of a radical-initiated cascade cocyclization involving phenyl isocyanide to yield (20*S*)-camptothecine (**293**).[146]

5. Other Cocyclizations

The reaction of isocyanides **294** with hydrazoic acid (**295**) has been known for almost a century as a route to 1-substituted tetrazoles **296** (Scheme 35, reaction a). These products are obtained in high yields when this reaction is carried out in diethyl ether under reflux in the presence of



Scheme 35. 1-Substituted tetrazoles **296** from isocyanides **294**.[149c,150a]

sulfuric acid as a catalyst and a large excess (6 equiv) of the hydrazoic acid.[149] Alternatively, trimethylsilylazide (1.5 equiv) may be used to generate hydrazoic acid in methanol and then used in situ at 60 °C. A variety of substituted isocyanides have been employed to provide the 1-substituted tetrazoles **296** mostly in high yields (Scheme 35, reaction b).[150]

α,β-Unsaturated isocyanides of type **298** are other versatile building blocks for the construction of N-heterocycles. Nucleophiles can add across the double bond of these Michael acceptors, and certain adducts thus formed are capable of undergoing subsequent cyclization by intramolecular addition to the isocyano group. Thus, 1-isocyano-1-tosyl-1-alkenes **299**, which are conveniently prepared by the condensation of aldehydes with TosMIC,[151] have been shown to react with nitromethane in the presence of potassium *tert*-butoxide to furnish 3-nitropyrroles **300** in high yields

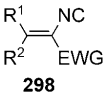
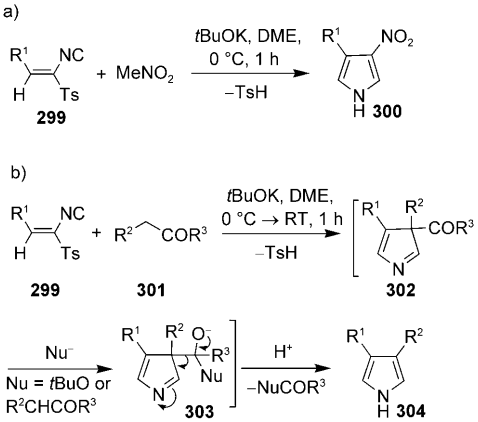


Table 44: 3,4-Disubstituted pyrroles **300** and **304** by Michael addition of carbanions to 1-isocyano-1-tosyl-1-alkenes **299** and subsequent ring closure.[152,153]



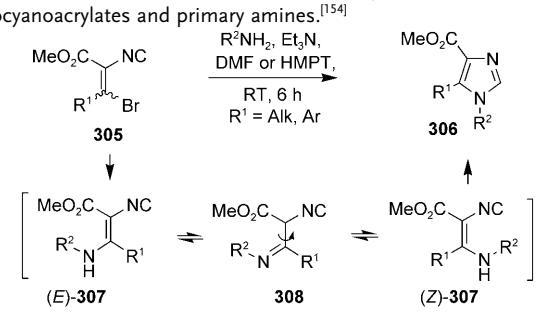
R^1	**300** [%]	R^1	R^2	R^3	**304** [%]
Ph	94	Ph	CN	OEt	99
4-ClC_6H_4	86	Ph	CO_2Et	OEt	70
4-$MeOC_6H_4$	88	*n*Bu	CO_2Et	Me	62
*t*Bu	91	Ph	PhCO	Ph	61
		Ph	Me	Ph	73
		Ph	Ph	Ph	57

(Table 44, reaction a).[152] However, acetonitrile and ethyl acetate did not react under the same conditions, presumably because of their lower C,H acidity.[153]

Some other carbanions of C,H-acidic compounds of type **301**, such as deprotonated ethyl cyanoacetate, diethyl malonate, and ethyl acetoacetate, have been employed successfully in reactions with **299** to yield 3,4-disubstituted pyrroles **304** (Table 44, reaction b).[153] On the one hand, an additional ester or ketone carbonyl group increases the C,H acidity of the adjacent methylene group to the required level, while on the other hand they are subsequently smoothly cleaved off by attack of the nucleophiles present in the mixture, and do not remain in the final product.

3-Bromo-2-isocyanoacrylates **305** (BICA) react in an analogous way with primary amines to furnish 1,5-disubstituted imidazole-4-carboxylates **306** (Table 45).[154] Aliphatic

Table 45: 1,5-Disubstituted imidazole-4-carboxylates **306** from 3-bromo-2-isocyanoacrylates and primary amines.[154]

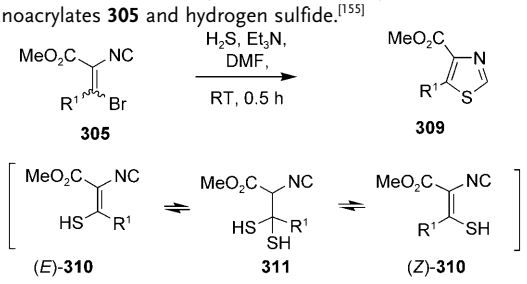


R^1	R^2	**306** [%]
Ph	$PhCH_2$	80
Ph	Ph	52
Ph	4-$MeOC_6H_4$	62
*i*Pr	Ph	63
Et_2CH	Ph	34

amines gave good yields, while those with anilines were substantially lower, and anilines with acceptor substituents such as methyl *para*-aminobenzoate did not react at all. The transformation is considered to proceed by an initial Michael addition of the amine to the double bond and subsequent elimination of bromide to furnish the equilibrating enamines (*E*)-**307** and (*Z*)-**307**. (*Z*)-**307** then undergoes a base-catalyzed cyclization by intramolecular addition of the amino to the isocyano group to provide the imidazoles **306** (Table 45).[154]

5-Substituted methyl thiazole-4-carboxylates **309** can be obtained in good yields by the reaction of 3-bromo-2-isocyanoacrylates **305** with hydrogen sulfide (Table 46).[155] On the basis of additional mechanistic investigations on this transformation, the authors propose that initially the bromine in the two diastereomeric **305** is formally substituted by a thiol group with retention of the double bond configuration. The thus formed 3-hydrothio-2-isocyanoacrylates (*E*)- and (*Z*)-**310** undergo reversible isomerization via the dithiol **311**, which is formed by Michael addition of hydrogen sulfide, but the *Z* isomer (*Z*)-**310** undergoes irreversible cyclization to **309**.

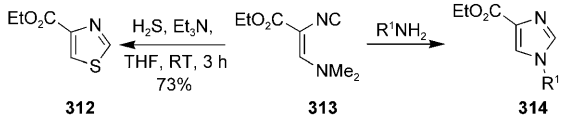
Table 46: 5-Substituted methyl thiazole-4-carboxylates from 3-bromo-2-isocyanoacrylates **305** and hydrogen sulfide.[155]



R^1	**309** [%]
$CH_2CH(CH_3)_2$	89
$CH(C_2H_5)_2$	71
C_6H_{13}	73
Ph	83
4-ClC_6H_4	82

3-(Dimethylamino)-2-isocyanoacrylates of type **313** have found various applications in isocyanide-based multicomponent reactions and syntheses of heterocycles.[156] In a similar manner as the 3-bromo-2-isocyanoacrylates **305**, treatment of **313** with hydrogen sulfide and primary amines resulted in Michael addition and subsequent elimination of dimethylamine as well as ensuing cyclization to afford thiazolecarboxylates **312** and imidazolecarboxylates **314**, respectively (Table 47).[157,158a,b] 3-(Dimethylamino)-2-isocyanoacrylates

Table 47: Reactions of ethyl 3-*N*,*N*-(dimethylamino)-2-isocyanoacrylate **313** with hydrogen sulfide[157] and amines.[158]



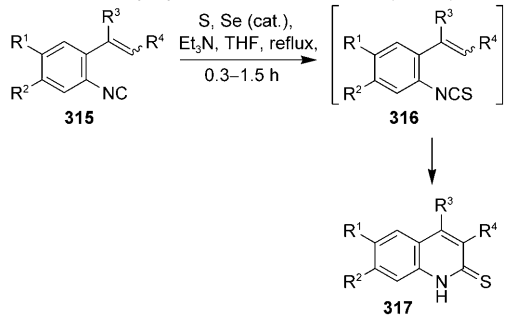
R^2	*T* [°C]	*t* [h]	**314** [%]
$Ph(CH_2)_2$	70	1.5	74
$PhCH_2$	70	2	80
cC_5H_{11}	70	2	89
*t*Bu	140	48	62
Ph	70	72	31

bound to Wang resin were later employed for the solid-phase synthesis of imidazole-4-carboxylic acids.[158c]

Kobayashi et al. have shown that isocyanostyrenes **315** undergo selenium-catalyzed addition of sulfur to furnish unstable isothiocyanostyrenes **316**, which immediately cyclize to form quinoline-2(1*H*)-thiones **317** in moderate to good yields (Table 48).[160] The same research group had previously reported on the analogous synthesis of quinoline-2(1*H*)-ones by in situ oxidation of isocyanostyrenes **315** to form transient isocyanatostyrenes that then underwent an ensuing cyclization.[159]

Aryl isothiocyanates with an *ortho*-acetyl or an *ortho*-acetoxy function **319** generated in situ from the corresponding isocyanides **318** under similar conditions as the styrenes

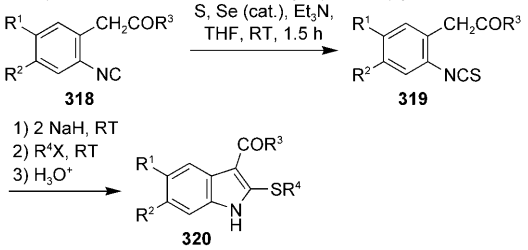
Table 48: Quinoline-2(1*H*)-thiones **317** from 2-isocyanostyrenes **315**.[160]



R^1	R^2	R^3	R^4	**317** [%]
H	H	*p*-Tol	H	79
H	H	3,4-$(MeO)_2C_6H_3$	H	91
H	H	Me	H	37
OMe	OMe	Ph	H	58
H	H	Ph	Me	74

316 have been found to undergo cyclization to yield 3-substituted 2-(alkylsulfanyl)indoles **320** upon treatment with sodium hydride and subsequent trapping with an alkyl halide (Table 49).[161]

Table 49: Synthesis of 3-substituted 2-(alkylsulfanyl)indoles **320**.[161]

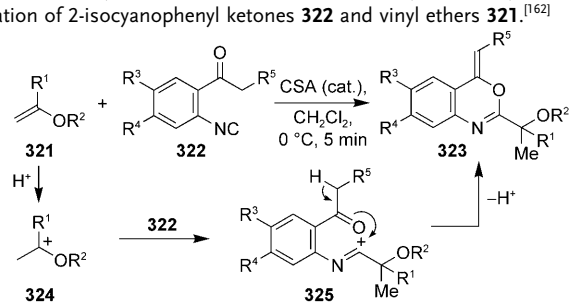


R^1	R^2	R^3	R^4X	**319** [%]
H	H	Me	MeI	71
H	H	Ph	BnBr	64
Cl	H	Et	$NCCH_2Br$	91
OMe	H	OEt	MeI	88
H	Me	OEt	MeI	82

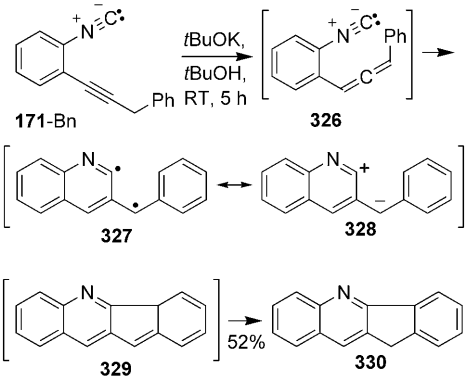
2-Isocyanophenyl ketones of type **322** have been shown to undergo cocyclizations with vinyl ethers **321** in the presence of a camphor-10-sulfonic acid (CSA) catalyst to provide 4-alkylidene-4*H*-3,1-benzoxazines **323** in moderate to good yields (Table 50).[162] The carbocation **324** generated by protonation of the vinyl ether **321** is presumed to be trapped by the isocyano group in **322** to furnish a transient imidoyl cation **325**. In the intermediate, the carbonyl oxygen atom attacks the electrophilic carbon center intramolecularly, and a subsequent deprotonation provides the product **323**.

An interesting example of a formal intramolecular [4 + 1] cycloaddition of the *ortho*-allenylphenyl isocyanide **326** generated in situ by base-induced isomerization of the alkynyl derivative **171**-Bn has recently been reported (Scheme 36).[163] The authors propose that the reaction proceeds via the

Table 50: 4-Alkylidene-4*H*-3,1-benzoxazines **323** by acid-catalyzed cocyclization of 2-isocyanophenyl ketones **322** and vinyl ethers **321**.[162]



R^1	R^2	R^3	R^4	R^5	**323** [%]
H	Et	H	H	H	61
H	Et	Cl	H	Me	54
Me	Me	H	Cl	Me	85
Me	Me	OMe	OMe	Me	49



Scheme 36. Formal intramolecular [4 + 1] cycloaddition of the *ortho*-allenylphenyl isocyanide **326** and formation of an indene-annelated quinoline **330**.[163]

transient biradical intermediate **327**, which is formed by a Myers–Saito cyclization. A subsequent intramolecular radical–radical coupling in **327** or intramolecular electrophilic substitution in the zwitterionic form **328**, which would be followed by a prototropic rearrangement of **329**, then gives the indene-annelated quinoline **330**.[163]

6. Summary and Outlook

The spectrum of transformations which isocyanides can undergo en route to different N-heterocycles is almost as diverse and multifaceted as organic chemistry as a whole. The reactions exemplified in this Review include only those cases in which both the carbon and the nitrogen atom of the isocyano group are incorporated in the heterocyclic product. The major proportion of such catalyzed or base-induced processes proceed along one of two possible routes: Either an initial deprotonation of the isocyanide is followed by addition of the deprotonated isocyanide to an appropriate functional group along with or followed by cyclization, or an addition of a suitable reagent to the isocyano group (or its insertion into another functional group as, for example, an acyl halide) is

followed by cyclization of the thus formed reactive intermediate. Base-induced anionic cyclizations are complemented by several radical-initiated (-catalyzed) processes, some transition-metal-catalyzed (-mediated) reactions, as well as organocatalyzed transformations. Some cyclizations have been found to proceed with high stereo- and enantioselectivity. The versatility and simplicity of such processes is reflected in their use in the synthesis of various natural products or at least their precursors. Although a substantial part of isocyanide chemistry, particularly in the synthesis of N heterocycles, has been explored in the last 30 – -40 years, it is foreseeable that many more new applications will be uncovered in the future. It is already evident that interest in new metal-catalyzed processes is growing steadily.

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