Isocyanoacetate Derivatives: Synthesis, Reactivity, and Application

Anton V. Gulevich,[†] Alexander G. Zhdanko,[†] Romano V. A. Orru,[‡] and Valentine G. Nenajdenko*[,†]

Department of Chemistry, Moscow State University, Leninskie Gory, Moscow 119991, Russia, and Department of Chemistry and Pharmaceutical Sciences, Vrije Universiteit Amsterdam, De Boelelaan 1083, 1081 HV Amsterdam, The Netherlands

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* To whom correspondence should be addressed. E-mail: nen@acylium.chem.msu.ru.
[†] Moscow State University.
[‡] Vrije Universiteit Amsterdam.

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1. Introduction

Isocyanide (isonitrile) chemistry began in 1859 when Lieke obtained the first compound of this type.[1] In 1958, isocyanides became generally available by dehydration of formamides prepared from primary amines.[2] At that point, protected amino acids were employed for the first time as precursors for synthesis of the corresponding isocyanides. Thus the first α-isocyano ester (isocyanoacetate) was obtained by Ugi in 1961.[3] Now isocyanoacetates and their derivatives are commonly available compounds.

A molecule of isocyanoacetate, **1**, contains four reaction centers: an isocyanide group, an acidic CH fragment, a substitutent R (which can also handle functional groups), and a carboxylic acid with protecting group (Figure 1). Combination of these potential four reaction centers in the molecule results in exceptional reaction diversity and broad synthetic potential of the isocyanoacetate derivatives, because they can also be obtained in an optically active form from natural amino acids.

Isocyanoacetates and their derivatives are widely used in different branches of organic, inorganic, coordination, polymeric, combinatorial, and medicinal chemistry. Such derivatives are also efficient building blocks for the synthesis of biologically active molecules and in total synthesis of complex natural products. In addition, multicomponent reactions with isocyanoacetate derivatives are used for synthesis of broad varieties of peptides and peptide mimetics. Isocyanoacetates are known as good ligands for transition metals. Therefore, isocyanoacetates and their derivatives can be used in inorganic, coordination, and polymeric chemistry. Among other isocyanides, isocyanoacetate derivatives occupy an important place in the field of synthetic application and reaction diversity, which makes them very attractive objects for investigation.

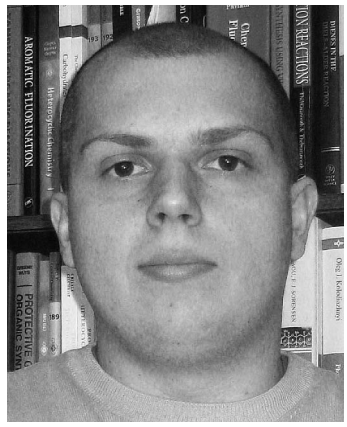
A number of reviews and monographs regarding isocyanides and especially their multicomponent reactions was published.[4,5] However, the chemistry of isocyanoacetate derivatives contains many special features and has not been reviewed comprehensively. This review covers literature from the early 1960s until the beginning of 2010 and describes all aspects of chemistry of isocyanoacetate derivatives but focuses on their unique properties caused by their polyfunctional nature.

2. Synthesis of α-Isocyanoacetate Derivatives

Both methods for direct formation of the isocyanide function as well as methods of insertion of the carboxylic acid group are discussed in this section. Synthesis of substituted derivatives by modification of isocyanoacetates will be reviewed in the corresponding sections.

2.1. Synthesis of Esters and Salts of α-Isocyanoacetic Acid

There are three general synthetic routes to isocyanoacetates **3** (esters of α-isocyanoacetic acid): dehydration of forma-



Anton Gulevich was born in Chelyabinsk, Russia, in 1984. He received his Bachelor's degree in 2006 from Moscow State University. After that he continued his research in the group of Prof. Nenajdenko at the Department of Chemistry. In the end of 2009 he received his Ph.D. degree, working on the development of new polyfunctional reagents for multicomponent reactions. In the beginning of 2010 he joined the group of Prof. Gevorgyan at University of Illinois at Chicago as a postdoctoral fellow. His research interests include multicomponent reactions, synthesis of modified peptides, heterocylic chemistry, transition-metal catalysis, and new methodologies for asymmetric synthesis.

Romano V. A. Orru studied Molecular Sciences at the Agricultural University in Wageningen, The Netherlands, where he obtained his Ph.D. in 1994 on Natural Product Synthesis with Prof. de Groot. From 1996 to 2000, he worked in the group of K. Faber at the Technicaland Karl-Franszens Universities (Graz, Austria). In early 2000 he was appointed assistant professor and later associate professor at the Vrije Universiteit Amsterdam. Since 2007, he has been a full professor of Synthetic and Bioorganic chemistry. His current research focuses on the development of novel, diversity-oriented synthetic methodology for the synthesis of pharmaceutically relevant compounds and natural products.

Alexander G. Zhdanko was born in the town Kletsk, Belarus, in 1985. In 2008, he graduated with honors from Moscow State University. In 2008−2009, he continued working in the research group of Prof. Nenajdenko V. G., where he had been working already for 2 years primarily on isocyanide chemistry and the chemistry of isocyanoacetates in particular. In 2009, he moved to the University of Tuebingen, Germany, for Ph.D. study in the research group of Prof. Dr. Martin E. Maier. His research interests are in the area of total synthesis and new synthetic methods.

Valentine G. Nenajdenko was born in 1967 in Ivanovo, Russia. He graduated from Moscow State University (Lomonosov) in 1991. He received his Ph.D. degree under the supervision of Professor E.S. Balenkova in 1994 researching the synthesis and application of unsaturated CF_3 ketones. In 2000, he received Dr. of Chemistry degree involving the chemistry of sulfonium and iminium salts. In 2003, he became full Professor of Organic Chemistry at the Department of Chemistry of Moscow State University. His scientific interests include organic synthesis, asymmetric catalysis, the chemistry of sulfur- and fluorine-containing compounds, heterocyclic chemistry, and multicomponent reactions. He has been a supervisor of 12 postgraduate studies. Prof. Nenajdenko is head of the Scientific Committee and Jury of International Mendeleev Chemistry Olympiad. He was the winner of the *Academiae Europeae* Award in 1997, the Russian President Award in 1996, the Prize for the best scientific work at the Department of Chemistry of Moscow State University in 2001 and 2007, the Shuvalov Award in 2001, the Russian President Award in 2004, Russian Science Support Foundation in 2005, and Moscow State University Awards in 2006, 2007, and 2008.

mides **2**, carboxylation of isocyanides **4**, and esterification of salts **5** (Scheme 1). Salts of isocyanoacetic acid **5** are easily accessible from isocyanoacetates **3** or by carboxylation of isocyanides **4**.

Thus, alkyl isocyanoacetates **3** can be obtained very easily from amino acids by a three-step approach using a procedure proposed by Ugi.[3] The key stage of synthesis is dehydration of primary formamides **2** (Scheme 2), which can be accomplished by using a number of reagents (phosgene,[6] diphosgene,[7] triphosgene,[8] phosphoryl chloride,[9,10] mesyl chloride, or oxalyl chloride[11]) in combination with bases, in most cases tertiary amines. In the literature, phosgene diphosgene, and triphosgene are acknowledged to give the highest yields, but their application is limited to laboratory scale work due to extreme toxicity and cumbersome handling in the case of phosgene and high costs in the case of diphosgene and triphosgene. Based on our experience, a phosphoryl chloride/triethylamine system is the most convenient for the synthesis of isocyanoacetates due to good yields, simple workup and purification of the reaction product, and applicability for large scale synthesis. However, only racemic isocyanoacetates can be obtained using this synthetic procedure (racemization issues are discussed in section 2.2).

Dehydration methods have also been applied for synthesis of solid-supported isocyanoacetates. For example, α-isocyano

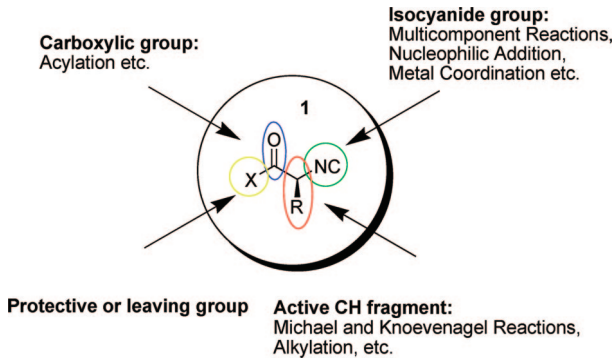
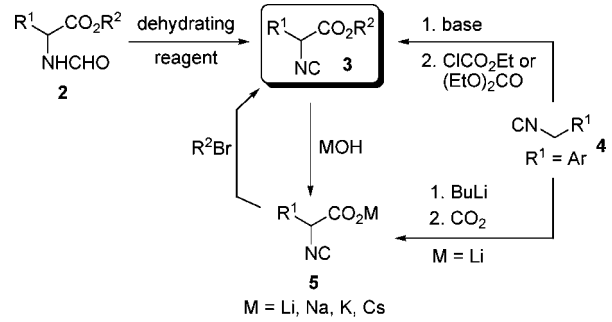
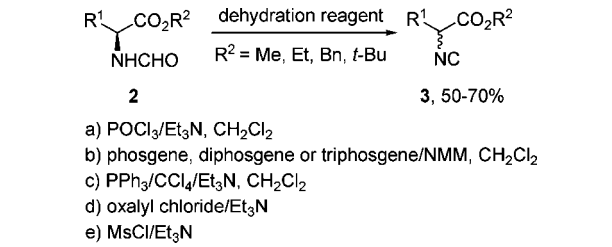


Figure 1. Reactivity profiles of α-isocyanoacetate derivatives **1**.

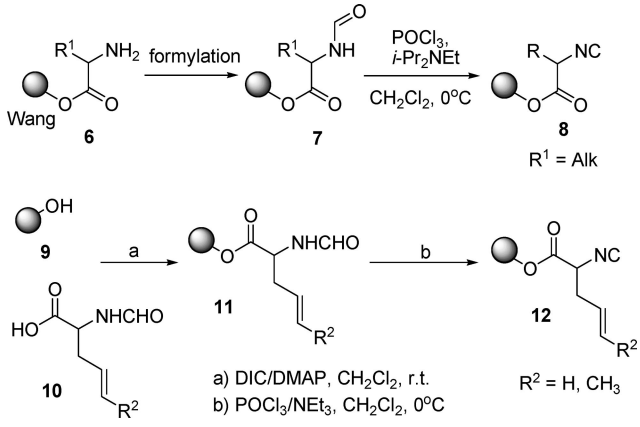
Scheme 1



Scheme 2



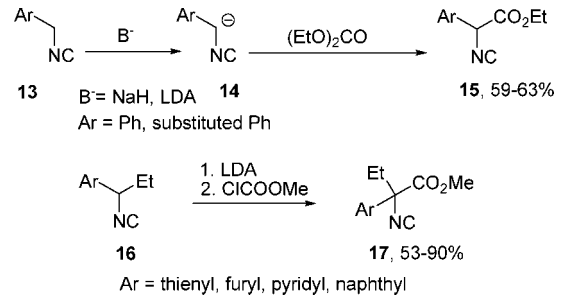
Scheme 3



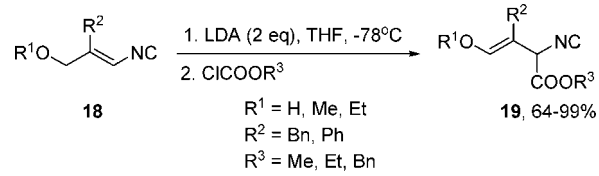
ester resins **8** can be readily synthesized from commercially available α-amino acid **6** that is attached to Wang resin by formylation and subsequent dehydration (Scheme 3).[12] Polymer-supported isocyanides **12** were synthesized from commercial Wang resin **9** by successive coupling with *N*-formylamino acids **10** and standard dehydration methods.[13]

Another method is based on the insertion of a carboxylic acid group at a primary isocyanide. Benzyl isocyanides **13** can be easily deprotonated at the α-position with NaH or BuLi and react smoothly with dialkyl carbonate to afford

Scheme 4



Scheme 5



15 in good yields.[14] Although, the method is not used widely, it can be effective for the synthesis of aryl-substituted isocyanoacetates. Thus, methoxycarbonylation of aryl (or heteroaryl)-substituted isocyanide **16** with methyl chloroformate in the presence of LDA gave α-disubstituted isocyanoacetates **17** in good yields (Scheme 4).[15]

Similarly, α-allyl isocyanoacetates **19** can be obtained by alkoxycarbonylation of α,*β*-unsaturated isocyanides **18** with chloroformates.[16] It should be noted that the reaction is accompanied by migration of the double bond using an additional molar equivalent of LDA, and **19** is formed in a regioselective manner (Scheme 5).

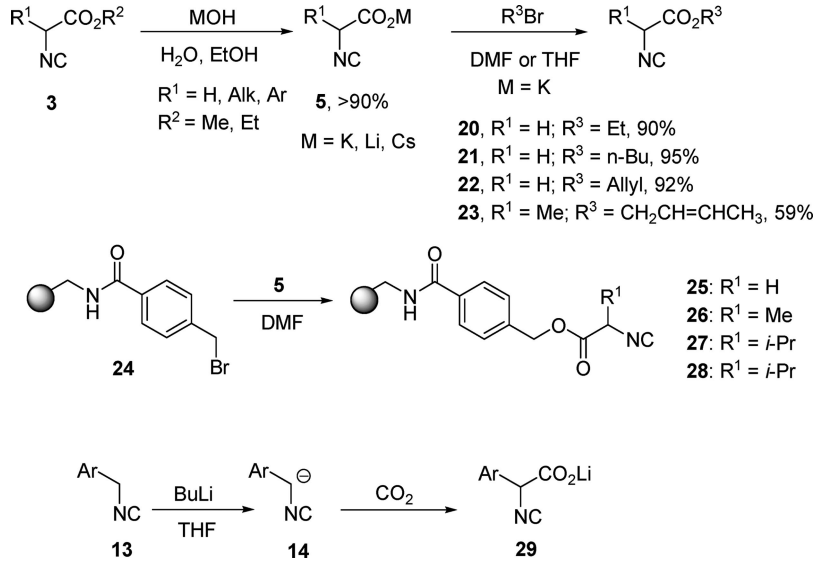
Salts of α-isocyanoacetic acids **5** can be easily obtained from isocyanoacetates **3** by saponification with ethanolic alkali hydroxides (Scheme 6).[17−19] Potassium salts **5** were used for synthesis of other different esters via alkylation. For example, esters **20**−**23**[20,21] or solid-phase-bound isocyanocarboxylic acids **25**−**28**[22] can be obtained by this method. Another approach is based on the deprotonation of benzyl isocyanides **13** with BuLi with subsequent carboxylation with CO_2 to afford a lithium salt **29**.[23]

An interesting complex [K(18-crown-6)](O_2CCH_2NC), **31**, with an O_8-coordinated metal atom was obtained by Fehlhammer et al. from potassium isocyanoacetate **30** and 18-crown-6 (Scheme 7).[24]

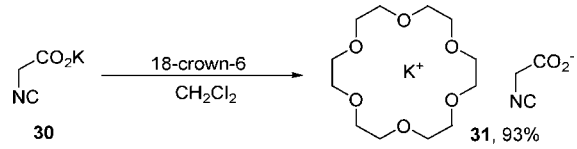
Commercially available diethyl formamidomalonate, **33**, was used as an efficient source of isocyanoacetate fragment for the synthesis of isocyanoacetates **35** and **36**. Thus, substituted formamide **34** can be prepared by alkylation of **33** with benzyl bromide **32**. Malonate **34** was converted to **35** in high yield by selective hydrolysis and decarboxylation of one ester moiety with subsequent dehydration by the $POCl_3/NEt_3$ system.[25] In an analogous fashion diethyl formamidomalonate **33** can be allylated with allyl bromide with subsequent formation of isocyanoacetate **36** containing an additional COOEt group (Scheme 8).[26]

Very interesting are isocyanoacetic acids with a free carboxylic group. However, no reliable literature data have been published on this species because the unprotected isocyanoacetic acid is quite unstable,[18] although one example of an isocyanopeptide with low α-acidity and a free carboxylic acid group was reported (see section 2.3, Scheme 16). It must be mentioned here that free isocyanoacetic acid

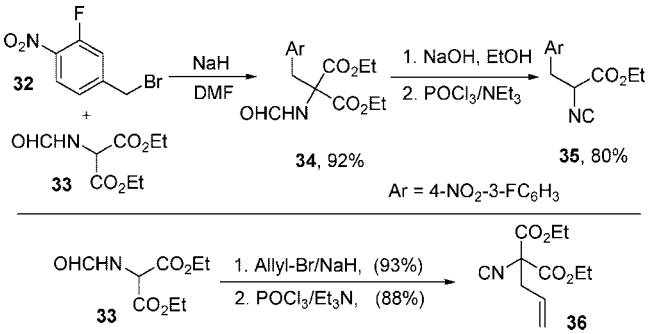
Scheme 6



Scheme 7



Scheme 8



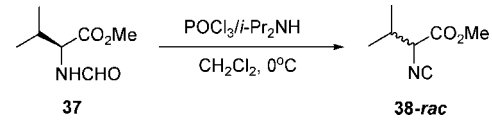
can be obtained as a complex of transition metals, coordinated to the isocyanide group (see section 12).

2.2. Racemization Issue. Synthesis of Chiral Isocyanoacetic Acid Esters

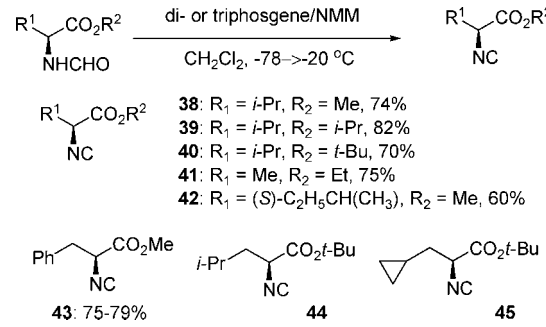
Chiral isocyanoacetates are configurationally unstable under basic conditions due to the relatively high acidity of the α-hydrogen induced by the two strong electron-withdrawing groups: NC and CO_2R. Until now, no quantitative data for the acidity of isocyanoacetates have been reported in the literature but it is well-known they can be deprotonated already by weak bases like amines. As a consequence, isocyanoacetates are racemized easily during preparation by the usual dehydrative methods. Preparation of optically pure substances can be achieved under certain milder conditions. Furthermore, the corresponding isocyanoamides are substantially less acidic and therefore less prone to racemization (see section 2.3).

Unfortunately, racemization of alkyl isocyanoacetates has scarcely been studied, and there are only few papers dealing with selected cases of base-induced racemization. Thus, a diisopropylamine ($pK_a = 10.7$)-containing dehydrating system ($POCl_3/i\text{-}Pr_2NH/CH_2Cl_2$, 0 °C) leads to racemic isocyanide **38**, prepared from optically pure *N*-formyl-L-valine, **37** (Scheme 9).[9]

Scheme 9



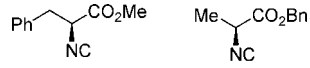
Scheme 10



Isocyanoacetate **43**, obtained from L-phenylalanine, was found to be configurationally unstable in the presence of (*S*)-phenylethylamine ($pK_a = 9.1$).[27] Even a weaker base like *N*-methylmorpholine ($pK_a = 7.4$) in combination with $COCl_2$ at −30 °C affords only in selected cases (synthesis of L-valine isocyanoacetate, er > 99:1) the desired optically active isocyanoacetates. The procedure seems not very reliable since substantial racemization still occurred in some cases, although at *lower* temperatures the method is applicable.[28] The NMM/diphosgene system proved to be more effective and has been used for syntheses of many other optically pure isocyanoacetates derived from L-valine (**38**−**40**), L-alanine (**41**), L-isoleucine (**42**),[29] L-phenylalanine **43**,[27,30] L-leucine **44**, and L-cyclopropylalanine **45**[31] (Scheme 10).

Until recently, there were no reports on quantitative investigations describing the racemization of isocyanoacetates. Only in 2009, a study on the synthesis and racemization of isocyanoacetates was published by the Danishefsky group that provides some insight into this issue. The researchers found that treating the isocyanoacetates **43** and **46** with triethylamine (even at −30 °C) leads to significant

Table 1. Racemization of Chiral Isocyanoacetates

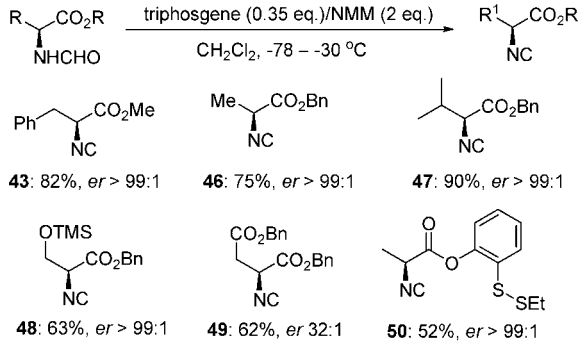


43, >99:1 *er* **46**, >99:1 *er*

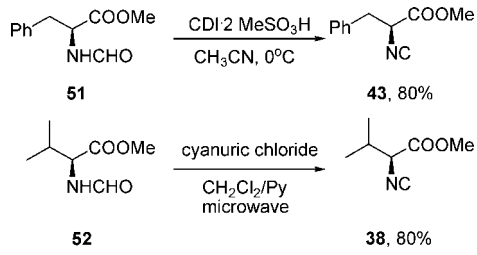
isocyanide	racemization conditions[a]	er[b]
43	Et_3N, CH_2Cl_2, −30 °C, 1.5 h	1.25:1
	Et_3N, CH_2Cl_2, r.t., 20 min	1:1
	NMM, CH_2Cl_2, −30 °C, 1 h	>99:1
	NMM, CH_2Cl_2, r.t., 20 min	7.3:1
46	Et_3N, CH_2Cl_2, −30 °C, 1 h	4.5:1
	Et_3N, CH_2Cl_2, r.t., 20 min	1:1
	NMM, CH_2Cl_2, −30 °C, 1 h	>99:1
	NMM, CH_2Cl_2, r.t., 20 min	13.5:1

[a] One equivalent of a base. [b] Measured by chiral HPLS after treatment by a base.

Scheme 11



Scheme 12



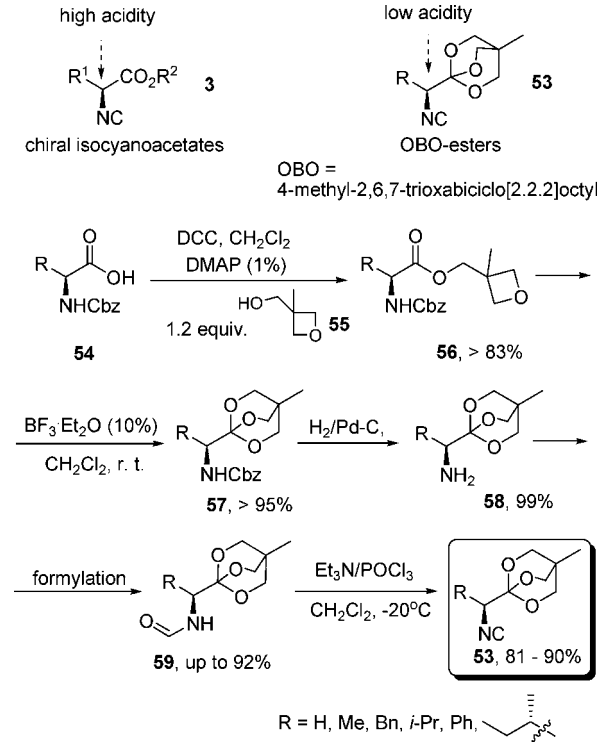
racemization while in the presence of 1.0 equiv of NMM at −30 °C for 1 h the studied isocyanides are rather stable and no detectable racemization takes place (Table 1).[32]

Accordingly, the use of NMM/triphosgene at low temperatures in a range of −78 to −30 °C provides the desired isocyanides **43** and **47**−**51** in high optical purity (Scheme 11).

Further, a nonbasic dehydrating reagent CDI·2MeSO$_3$H was also reported to convert the chiral formamide **51** to isocyanide **43** at 0−5 °C in 80% yield without significant loss of stereochemical integrity.[33] Recently a facile conversion of formamides to isocyanides under microwave irradiation (cyanuric chloride/Py (2 equiv)/CH_2Cl_2) was described. It should be noted that in this case the authors did not observe racemization of **38** even under the quite harsh conditions using pyridine (pK_a = 5.2) under microwave irradiation in sealed vials at 100 °C (Scheme 12).[34]

In conclusion, racemic isocyanoacetates are an easily accessible class of compounds. Optically active chiral α-isocyanoalkyl esters are also available from natural or artificial amino acids under mild weakly basic conditions at low temperature. However, isocyanoacetates were found to be configurationally unstable under the conditions of Ugi multicomponent reaction (while they seem to be stable under

Scheme 13



Passerini conditions; see sections 10.1 and 10.2). Thus, any strategy to avoid their racemization would be highly welcome.

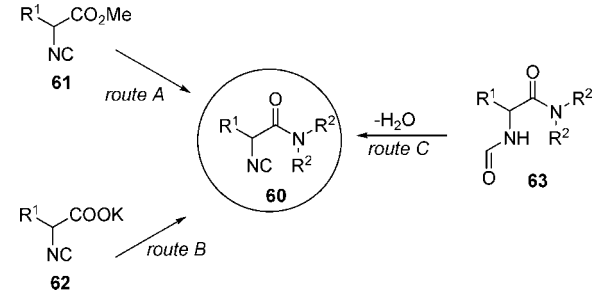
Recently Nenajdenko et al. have developed a new type of α-isocyanoacetic acid **53**, which is stable toward racemization under basic conditions. Transformation of a carboxylic acid group into OBO-ester (4-methyl-2,6,7-trioxabicyclo[2.2.2]octyl derivatives) decreases the α-acidity and avoids racemization. The isocyanoacetate derivatives **53** were synthesized from the corresponding Cbz-protected α-amino acids **54** in high total yields using simple and scalable procedures (Scheme 13). The isocyanides **53** were found to be very stable toward racemization in the presence of different bases and will be useful in isocyanide-based reactions when racemization is an issue, for example, in Ugi reaction (see section 10.2.1).[35] It was also demonstrated that no racemization takes place at the step of deprotection of final Ugi products when OBO-isocyanides **53** are used.

2.3. Synthesis of Isocyanoacetamides

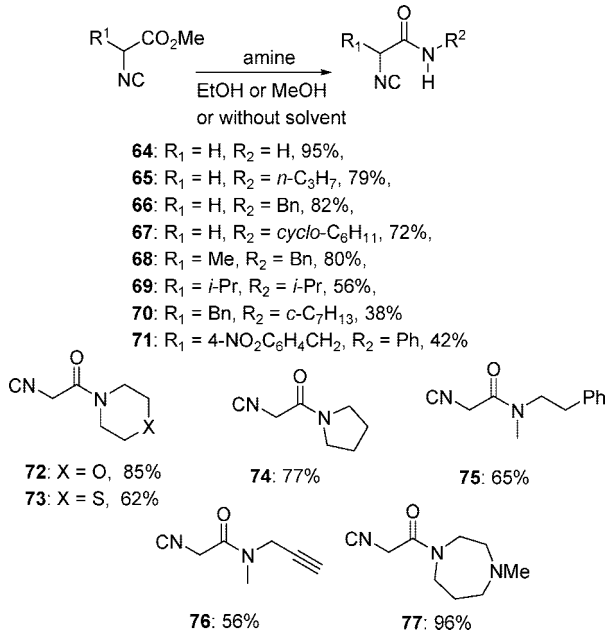
Isocyanoacetamides **60** are easily accessible from the corresponding isocyanoesters **61** (route A), their salts **62** (route B), or the related formamides **63** (route C) (Scheme 14).

It should be noted that isocyanoacetates are somewhat activated substrates (in comparison with alkyl carboxylic acid

Scheme 14

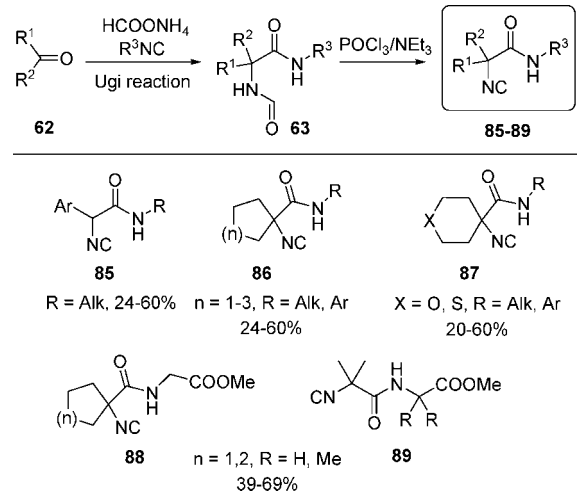


Scheme 15



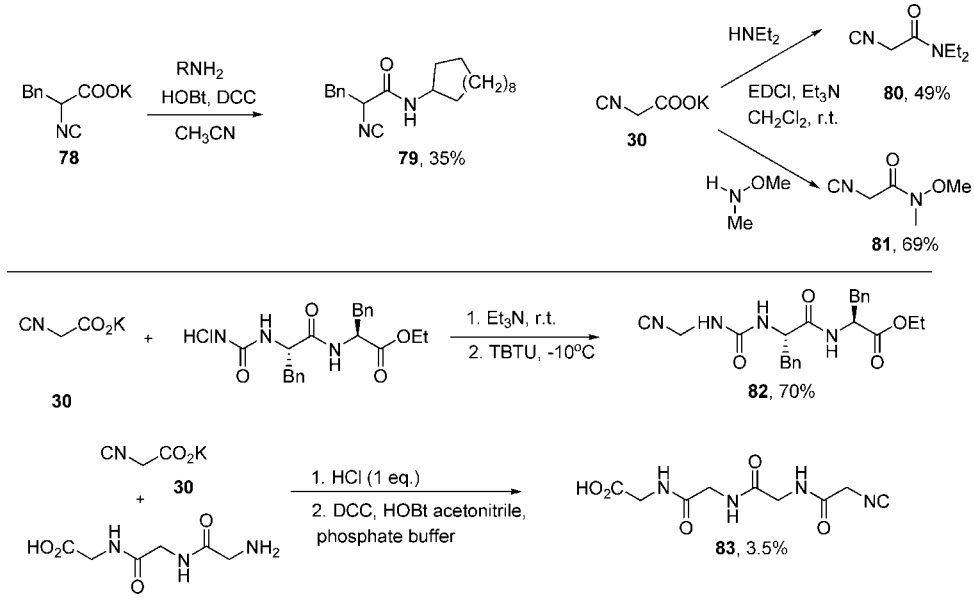
esters) due to the electron-withdrawing effect of the isocyano group and this factor allows aminolysis to occur under rather mild conditions. Reaction of isocyanoacetates **61** with ammonia or amines in ethanol or methanol at room temperature leads to the corresponding amides in good yields. Methyl esters are better starting materials for this procedure compared with the corresponding ethyl esters.[36] Selected examples are shown in Scheme 15. Thus, isocyanoacetamide **64** can be obtained in 95% yield from methyl isocyanoacetate and ammonia in methanol.[37] Secondary amides **65**−**69**[38] and **70** and **71**[39] can be obtained in this way as well. Reaction of isocyanoacetates with secondary amines also gives tertiary amides **72** and **74** in good yields.[40] In general, reaction of isocyanoacetates with amines is most efficient in solventless conditions.[36,41] Thus, for example, isocyanoacetamides **73** and **75**−**77** were prepared by Dömling et al. using aminolysis of the corresponding methyl isocyanoacetates with primary and secondary aliphatic amines.[42] In general, methyl isocyanoacetates **61** react readily with primary or secondary aliphatic amines; however the reaction with anilines gives much lower yields. It should be noted that only racemic isocyanoacetates were involved in the amination reaction. Apparently, chiral isocyanoacetates would be configurationally unstable in the presence of amines.

Scheme 17

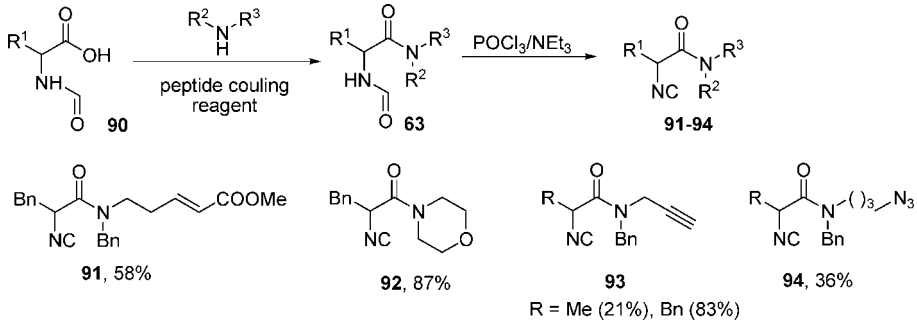


According to route B, isocyanoacetamides can be prepared by reaction of potassium isocyanoacetates and the corresponding amine in the presence of activating agents. Thus, isocyanoacetamide **79** was prepared from salt **78** and a primary amine in the presence of HOBt and DCC.[39] On the other hand, EDCI-mediated coupling of the potassium salt **30** with diethylamine provided the amide **80**. The reaction of **30** with methoxymethylamine afforded Weinreb isocyanoacetamide **81** (Scheme 16).[40] *N*-Isocyanoacetyl-substituted amino acid esters and *N*-isocyanoacetyl di- and tripeptide esters are available by condensation of potassium isocyanoacetate with amino acid esters or peptide esters. Thus, "isocyanopeptide" **82** was obtained from dipeptide by coupling with potassium isocyanoacetate in presence of TBTU (2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate). Longer "isocyanopeptides" can be also prepared by this procedure.[43] Lumpov et al. reported the

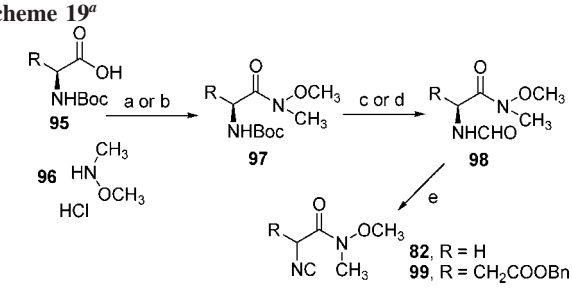
Scheme 16



Scheme 18



Scheme 19[a]



[a] Reagents and conditions: (a) DCC/HOBt/NEt_3; (b) NMM/IBCF; (c) HCO_2H then HCO_2Et, NEt_3; (d) HCOOH/NMM/EDC; (e) $POCl_3$/NEt_3.

synthesis of isocyanopeptide **83** with a free carboxylic acid group, however, the yield was extremely low. Potassium isocyanoacetate **30** initially was neutralized with 1 equiv of HCl and coupled with triglycine in a mixture of acetonitrile and phosphate buffer (Scheme 16).[44]

And finally, according to route C, isocyanoamides can be synthesized by dehydration of formamides **63**, easily accessible by Ugi-MCR (Scheme 17). Monosubstituted isocyanoacetamides **85**,[45] **86**,[46] and **87**[47] and isocyanopeptides **88** and **89**[48] were prepared by dehydration of **63** with $POCl_3$/NEt_3 by Marccacini et al.

Alternatively, formamides **63** can be obtained by coupling of *N*-formyl amino acid **90** and amines in the presence of common reagents used for peptide synthesis (EDCI, HOBt, etc.). Dehydration of formamides **63** lead to disubstituted isocyanoacetamides **91**,[49] **92**,[50] and **93** and **94**[51] (Scheme 18). The α-isocyanoacetanilides can also be prepared from the corresponding formamides in good yields.[41]

Weinreb amides **82**[52] and **99**[53] can be easily prepared from formamides **98**, synthesized from protected amino acids **95** and *N*,*O*-dimethylhydroxylamine (hydrochloride) **96** (Scheme 19). Alternatively, Weinreb amides can be obtained from the salt of isocyanoacetates (Scheme 16).

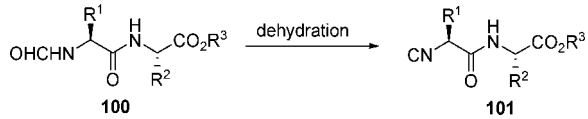
It should be noted that isocyanoacetamides are much more configurationally stable compounds than isocyanoacetates, and can be obtained in optically active form using a variety of reagents. Thus, isocyanopeptides **101** of high optical purity were prepared from formamides **100** with a phosgene/NMM system (Table 2, entries 1−4).[28] Triphosgene in combination with 2,6-lutidine leads to a single diastereomer of **101** exclusively (entries 5 and 6).[32] A range of diastereomerically pure isocyanopeptides of type **101** were prepared from formamides **100** with diphosgene/NMM (entries 7−9).[54−56] The diastereomeric ratio was not affected even when stronger bases were used. For example, the synthesis of diastereomerically pure isocyanopeptides **101** using the $POCl_3$/NEt_3 system for dehydration proceeds smoothly (entries 10–12).[57] Therefore, this system can be successfully used for the dehydratation.[58] It is noteworthy that in these conditions isocyanoacetic esters are usually racemized.

A variety of longer isocyanopeptides were obtained by Nolte et al. and used for subsequent polymerization (see section 13.3). As an example of their procedure, the synthesis of diastereomerically pure isocyanopeptide **103** obtained from the corresponding formamide **102** is depicted in Scheme 20.[59]

2.4. Synthesis of Miscellaneous Isocyanoacetic Acid Derivatives

Very interesting derivatives of isocyanoacetic acids are the isocyanoacetonitriles. In 1975, Schöllkopf reported synthesis of isocyanoacetonitrile **105** by dehydration of the coresponding formamide **104**. Isocyanoacetonitrile **105** was

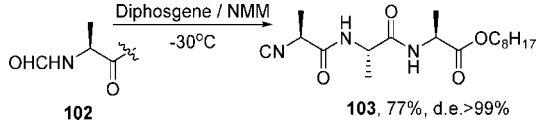
Table 2. Synthesis of Chiral Isocyanoacetamides



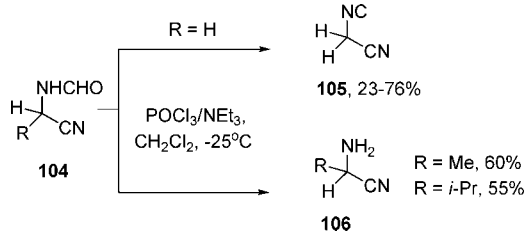
entry	conditions	R^1	R^2	R^3	de, %	yield, %	ref
1	$COCl_2$/NMM/−30 °C	Bn	Bn	Me	95.2	52	28
2	$COCl_2$/NMM/−30 °C	Bn	*i*-Pr	Me	98	42	28
3	$COCl_2$/NMM/−30 °C	*i*-Pr	*i*-Pr	Me	98	52	28
4	$COCl_2$/NMM/−30 °C	Me	Bn	Me	98	32	28
5	triphosgene/2,6-lutidine/−50 °C	Me	Me	Bn	>99	70	32
6	triphosgene/2,6-lutidine/ −50 °C	Me	*i*-Bu	Me	>99	58	32
7	diphosgene/NMM/−30 °C	Me	Me	Me	>99	*a*	54
8	diphosgene/NMM/−30 °C	Me	Me	propargyl	>99	50	55
9	diphosgene/NMM/−30 °C	Me	1-Ts-imidazol-4-yl	Me	>99	70	56
10	$POCl_3$/Et_3N/−40 °C	Me	$HOCH_2$	Bn	>99	63	57
11	$POCl_3$/Et_3N/−40 °C	Me	$HOCH_2$	Bn	>99	75	57
12	$POCl_3$/Et_3N/−40 °C	Me	1-Ts-imidazol-4-yl	Me	>99	70	57

[a] Not determined.

Scheme 20



Scheme 21

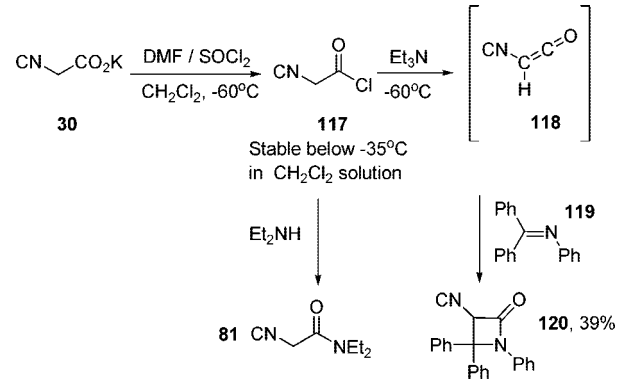


isolated in 23% yield by vacuum distillation and was found to be a very unstable compound that decomposes rapidly above −5 °C. Substituted isocyanoacetates **106** appeared to be much more stable than the parent compound **105** and can be easily isolated by distillation (Scheme 21).[60] Later, Lentz et al. isolated unsubstituted isocyanoacetonitrile **105** in yields up to 76% (by low-temperature high-vacuum condensation) for investigation of ligand properties (see section 12.1).[61]

α-Functionalized isocyanoacetonitriles **111** and **116** were developed by Neidlein et al. (Scheme 22). α-Isocyanoacetonitriles **111** were prepared starting from amines **108** by alkylation of formamides **109** and dehydration of alkylated formamides **110** with diphosgene. However yields on the alkylation step are rather low (8−70%). Amines **108** are easily available by reduction of **107** (prepared by nitrosation of commercially available ethyl cyanoacetate).[62] Synthesis of isocyanoacetonitriles **116**, containing a dialkyl phosphonate group at the α-position is based on the insertion of an amino group into cyanomethyl phosphonates **113** with NH_2Cl. Target compounds **116** were prepared from amines **114** by the usual formylation−dehydration protocol.[63]

An interesting isocyanoacetate derivative, isocyanoketene **118**, was described in 1976 by Hoppe and Schöllkopf. Treatment of potassium salt **30** with thionyl chloride in Vilsmeir-like conditions at −60 °C gave the corresponding

Scheme 23



isocyanoacetyl chloride **117** (Scheme 23), which is stable in solution below −35 °C. The structure of isocyanoacetyl chloride **117** was confirmed by formation of isocyanoacetamide **81** in reaction with diethylamine. Elimination of HCl from **117** with triethylamine gives ketene **118**, which can be trapped with imine **119** to give isocyano-substituted β-lactam **120**.[17]

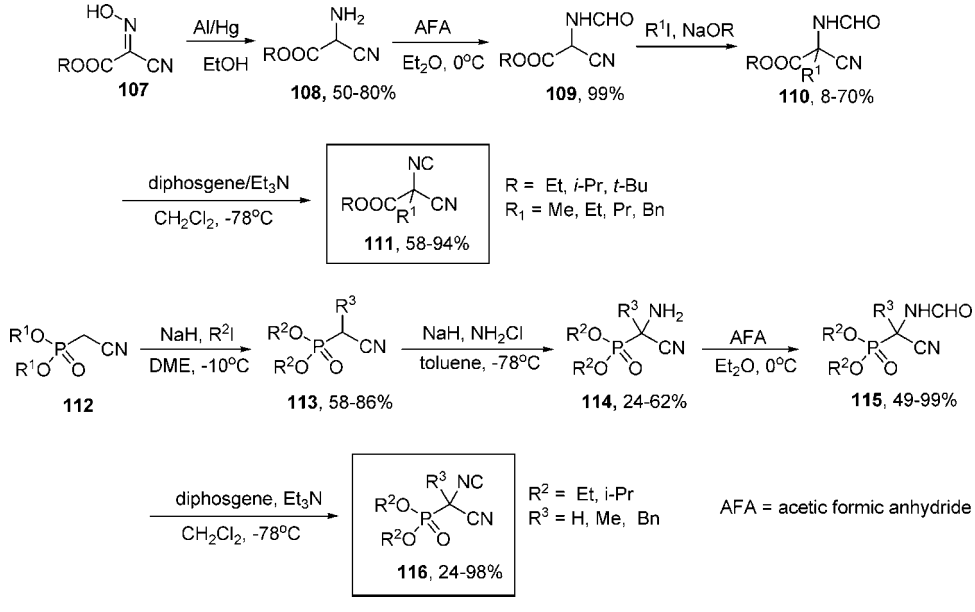
In conclusion, a broad variety of isocyanoacetate derivatives can be prepared by creating a carboxylic acid or more directly an isocyano function. However, the most important approach for the synthesis of isocyanoacetate is based on the formylation of primary amines followed by dehydration of formamides.

3. Alkylation of Isocyanoacetic Acid Derivatives

3.1. Alkylation of α-Isocyanoacetates

α-Isocyanoacetates containing two powerful electron-withdrawing substituents at the α-position, an isocyanide group, and a carboxylic group, can be completely or partially deprotonated by different bases such as potassium *tert*-butoxide, sodium hydride, sodium ethoxide, sodium cyanide, and tertiary amines (Et_3N or DBU).[64] The anion formed can react with various alkylating agents to provide products of C-alkylation, thus representing an approach to substituted isocyanoacetates. In this section, alkylation by alkyl halides,

Scheme 22



Scheme 24

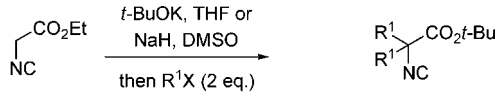
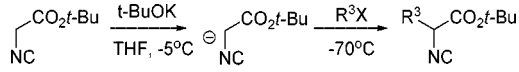
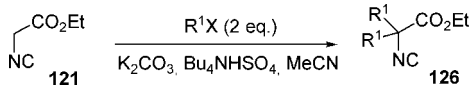


Table 3



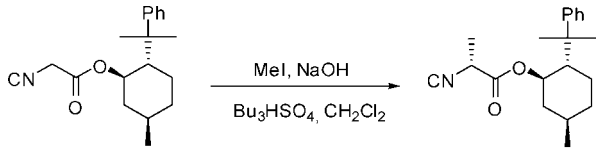
entry	R^3X	yield, %
1	CH_3I	43
2	allyl bromide	76
3	$(CH_3)_2CHI$	35
4	$(CH_3)_2CHCH_2I$	60
5	$C_6H_5CH_2Br$	30

Table 4. Dialkylation of Isocyanoacetate 121 in PTC



entry	R^1X	yield, %	ref
4	propargyl bromide	80	70
5	allyl bromide	88	71
6	$C_6H_5CH_2Br$	88	72
7	2-thienylCH_2Br	33	72

Scheme 25



allylic esters, and oxiranes will be considered. Also the intramolecular Claisen rearrangement of allylic esters of α-isocyanoacetic acids will be discussed here as a method for regioselective allylation of α-isocyanoacetates.

Usually, alkylation of metalated unsubstituted methyl or ethyl isocyanoacetates leads to dialkylation products (in several cases intermediate monoalkylated products can be isolated in 10−20% yields).[65] When 2 equiv of alkylating agent (*n*-alkyl or benzyl halide) is used, dialkylated products **122** can be obtained in yields up to 90% (Scheme 24).[66−69]

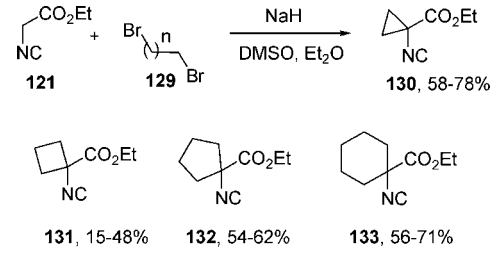
However, monoalkylation of isocyanoacetate can be accomplished with *tert*-butyl ester **123**, since here the bulky ester group prevents attack of the α-anion to a second alkyl halide molecule (Table 3).[66,67]

Initially, alkylation was performed with *t*-BuOK or NaH as a base. In 1997, Kotha et al. proposed phase-transfer conditions (PTC) for dialkylation of isocyanoacetates. Propargyl bromide,[70] allyl bromide,[71] a broad variety of substituted benzyl bromides, and even thienylmethyl bromide are efficient alkylating reagents in this approach (Table 4).[72]

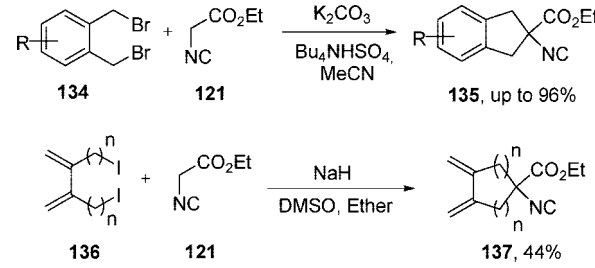
Attempts to alkylate isocyanoacetates bearing a chiral ester moiety, such as the (−)-menthyl or (+)-bornyl esters, in order to achieve asymmetric induction gave unfortunately the desired products only in low selectivity.[73] The use of a (−)-8-phenylmenthyl ester in **127** was found to be the most effective and led to product **128** in a de of up to 48% (Scheme 25).[74]

The alkylation of isocyanoacetates by dihalogen compounds **129** opens broad possibilities for the synthesis of

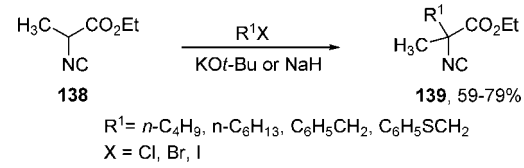
Scheme 26



Scheme 27



Scheme 28



cyclic compounds. Thus, reaction of isocyanoacetate **121** and the appropriate dibromoalkyl derivatives **129** in the presence of NaH afforded 1-isocyanoalkane-1-carboxylates **130**−**133** in good yields (Scheme 26).[66,75−77]

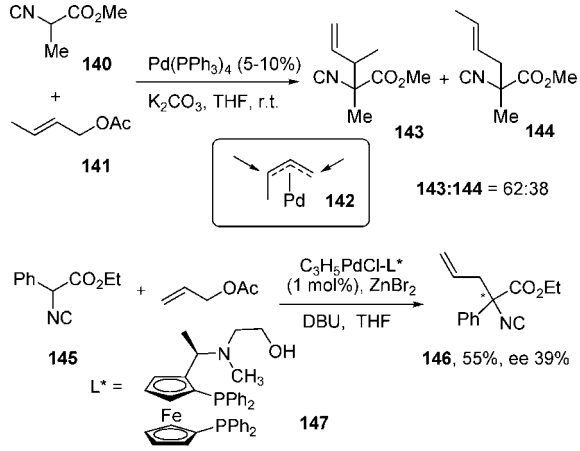
Ethyl isocyanoacetate **121** can be alkylated easily with readily accessible dibromo-*o*-xylene derivatives **134** in good yields. The reaction is an efficient approach to a broad variety of indane−isocyanoacetate derivatives **135**.[78,79] Other alkylating reagents that are activated for nucleophilic substitution, such as **136**, can be used for cyclization to afford isocyano esters of type **137** in moderate yields (Scheme 27).[80]

α-Monosubstituted isocyanoacetates are successfully alkylated by alkyl halides as well. Thus, ethyl α-isocyanopropionate **138** was converted to the corresponding disubstituted isocyanoacetates **139** with alkyl halides in good yields (Scheme 28; see also Scheme 34).[66,67]

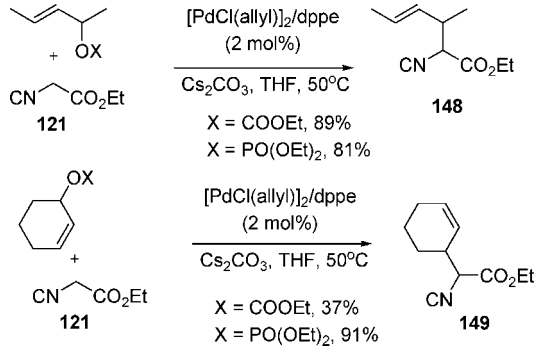
In 1987 Ito, Hayashi, et al. developed a Pd-catalyzed allylation of α-isocyanoacetate esters in the presence of 5−10 mol % palladium catalyst and bases, such as DBU, K_2CO_3, and triethylamine. This reaction proceeds via the palladium complex **142**, which is attacked from two sides leading to formation of regioisomeric mixtures in various ratios. For example, allylation of **140** by 2-butenyl acetate **141** affords a mixture of **143** and **144** in a 62:38 ratio. Therefore, this reaction is only useful for allylation by symmetric "allyl cations" (Scheme 29). An enantioselective variant of the reaction using optically active ferrocenylphosphine ligand **147** in the presence of $ZnBr_2$ as the Lewis acid was found to be ineffective (maximum 39% ee).[81]

In 2003 Kazmaier and Ackerman studied the palladium-catalyzed allylation of unsubstituted α-isocyanoacetates with allylic carbonates and phosphates in the presence of Cs_2CO_3 as a base. They found that the carbonate is an efficient leaving group using linear alkenes as the substrates, whereas the phosphate group works excellently when cyclic substrates

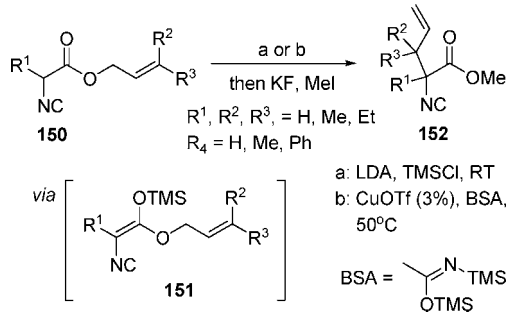
Scheme 29



Scheme 30



Scheme 31

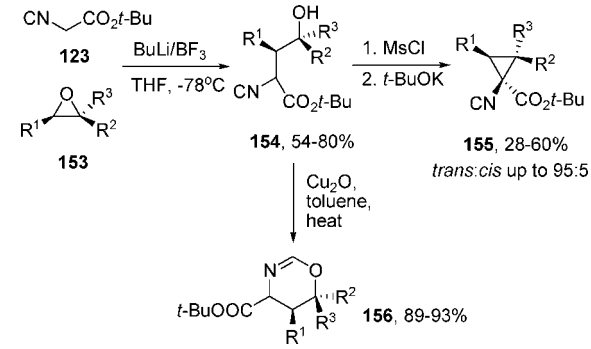


are applied. Phosphates, in contrast to carbonates, are quite unstable compounds, although they can be used directly in the allylation without purification. For example, isocyanoacetates **148** and **149** were obtained from the corresponding allylic carbonates and phosphates in excellent yields (Scheme 30).[82]

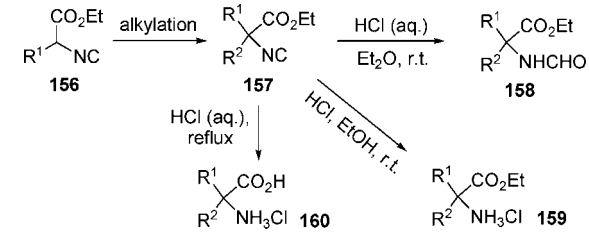
α-Isocyanoallylic esters **150** can undergo intramolecular Ireland−Claisen rearrangement via the corresponding *in situ* generated ketene silylacetals **151**. In contrast to the previous method, the rearrangement of **150** is a regioselective process leading to the formation of only one allylation product, **152** (after KF-mediated transesterification of silyl ester by MeI, Scheme 31). However, the rearrangement did not lead to stereoselective allylation; the corresponding products **152** were isolated as diastereomeric mixtures (1:1−1:2).[21]

In 1973, Schöllkopf et al. described the ring-opening of an oxirane with lithiated 2-isocyanopropionate. In this reaction, the oxirane can be regarded as an alkylating agent.[83] Later, also asymmetric epoxides **153** could be employed using this approach. The optically active epoxides **153** were

Scheme 32



Scheme 33



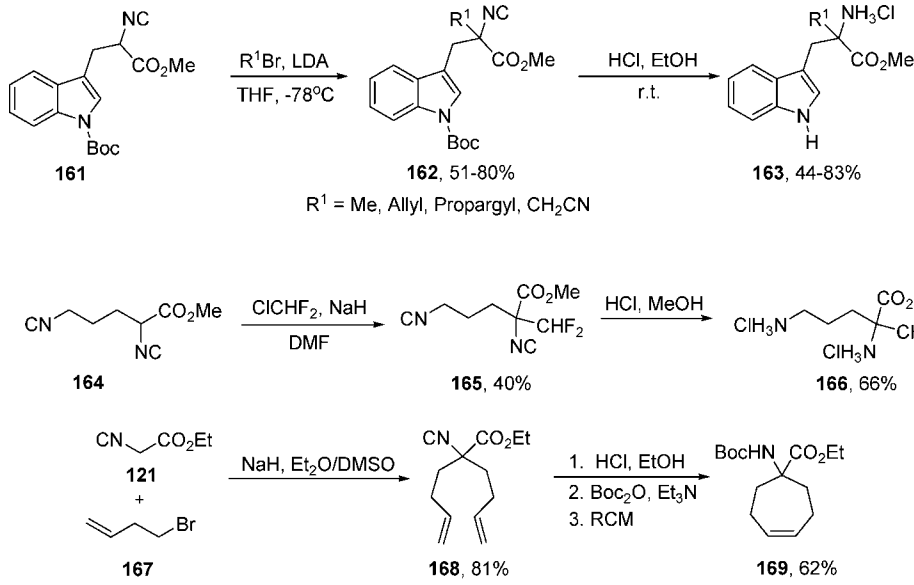
treated with the lithiated *tert*-butyl ester **123** in the presence of boron trifluoride, which afforded γ-hydroxy-isocyanoacetates **154** in good yields. The compounds **154** were converted to the corresponding mesylates, and subsequent treatment with a base gave α-isocyano-cyclopropanecarboxylates **155** in a highly diastereoselective fashion. This can be rationalized by the significant difference in steric bulk between the isocyano group and the *tert*-butoxycarbonyl group. The oxazine derivatives **156**, which are of interest as starting materials for the total synthesis of structural analogues of cephalosporins, are easily obtained from **154** by heating with copper(I) oxide in toluene (Scheme 32).[84]

Alkylation and allylation of α-isocyanoacetic acid derivatives is of interest because its overall effect is the production of longer chain or branched amino acids. α-Isocyanoacetates are used in this case as a glycine anion equivalent. Thus, modified α-isocyanoacetates **157** can be easily converted by ethereal hydrogen chloride at −10 to 0 °C into *N*-formylamino acid esters **158**, by ethanolic hydrogen chloride at room temperature into amino acid ester hydrochlorides **159**, and by hot aqueous hydrochloric acid into the amino acid hydrochlorides **160** themselves (Scheme 33).[66]

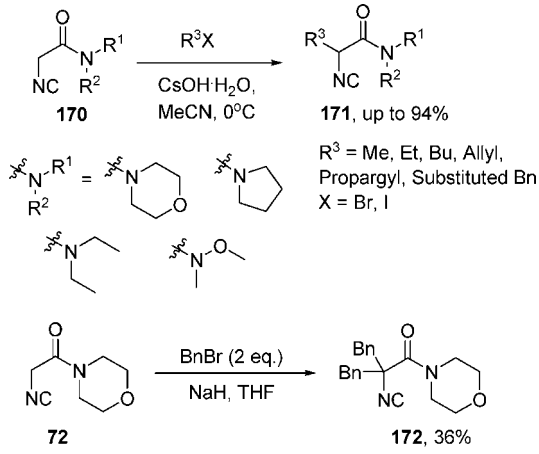
The flexibility of this method for the syntheses of diversely substituted amino acid derivatives was demonstrated by Kotha.[85] As an example, the synthesis of substituted tryptophan derivatives[86] (tryptophan esters **163**,[87] for example), α-difluoromethylornithine **166**,[88] and cyclic amino acid **169**[89] is outlined in Scheme 34.

From a variety of glycine anion equivalents available in the literature, ethyl isocyanoacetate was found to be one of the most effective due to the high α-acidity and its reactivity toward electrophiles. Very recently, Kotha published an excellent review concerning using of isocyanoacetates as glycine equivalents.[90] Moreover, the easy commercial access to ethyl isocyanoacetate combined with the operational simplicity makes this methodology extremely attractive for the preparation of highly functionalized amino acids. However, it should be noted that the achievement of selective monoalkylation remains challenging problem.

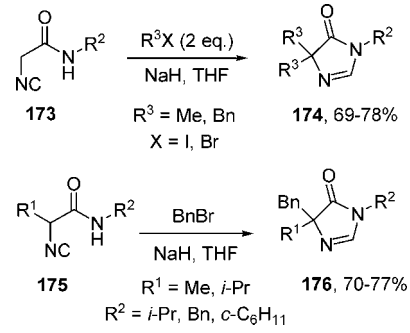
Scheme 34



Scheme 35



Scheme 36



3.2. Alkylation of Isocyanoacetamides

α-Isocyanoacetamides are much less acidic then α-isocyanoacetates, and the reactivity profile was found to be rather different from that of α-isocyanoacetates under mild basic or acidic conditions. Thus, Zhu et al. developed an efficient protocol for monoalkylation of tertiary isocyanoacetamides **171** under mild basic conditions. The monoalkylation of **171** took place smoothly with alkyl and benzyl halides in presence of CsOH.[40] Isocyanoacetamide **72** can be dialkylated with 2 equiv of benzyl bromide in presence of NaH, but the yield is about 36% in this case (Scheme 35).[38]

Remarkable behavior of secondary isocyanoacetamides **173** and **174** in alkylation under basic conditions was observed by Matsumoto et al. They nicely showed that the isocyano group undergoes an intramolecular nucleophilic attack by the amide nitrogen to afford alkylated imidazolinone derivatives **174** and **175** instead of formation of the corresponding alkylated isocyanoamides (Scheme 36).[38] This is in contrast to tertiary amides **170** and **72**, which are unable to cyclize in this manner and therefore afford the expected alkylation products **171** and **172** (Scheme 35).

In conclusion, alkylation is an efficient route to modify isocyanoacetates and access their alkyl derivatives. It is noteworthy that isocyanoacetates are generally more suitable for synthesis of dialkylated products, whereas tertiary isocyanoacetamides can be either mono- or dialkylated effectively.

4. Reaction of Isocyanoacetate Derivatives with Aldehydes and Ketones

The unique reactivity of α-isocyanoacetate derivatives was demonstrated in their reactions with aldehydes and ketones. Due to the multifunctional nature of α-isocyanoacetate derivatives a range of transformations are possible, which can be divided into two large classes by a common mechanistic feature, as schematically outlined in Figure 2. Route 1 transformations, in which the isocyano group attacks a (activated) carbonyl group, are discussed in more detail in sections 10.1.1 and 10.4. In this section, only route 2 transformations are discussed, which are based on a nucleophilic attack of the α-carbanion of an isocyanoacetate to a carbonyl group.

These are all typical base-catalyzed reactions that produce a range of products depending on the reaction conditions such as a solvent, temperature, and the nature of the base or substrates used. Thus, ordinary Knoevenagel and aldol-type reactions, as well as more complex transformations leading

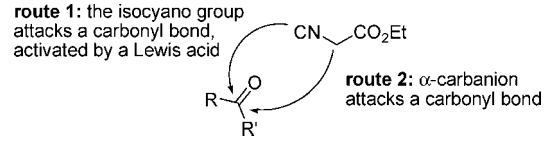
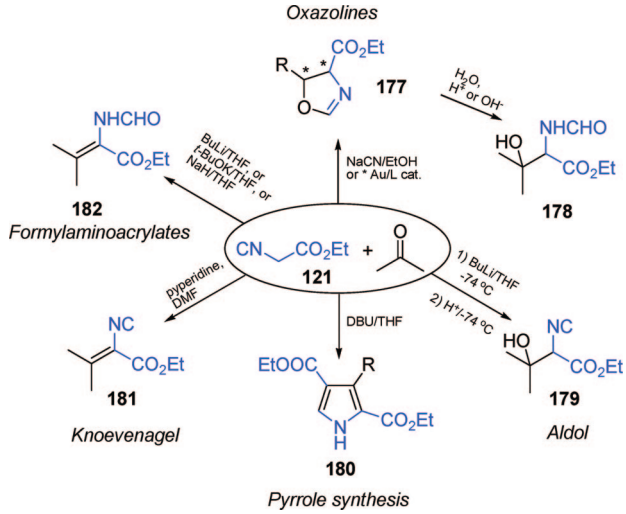
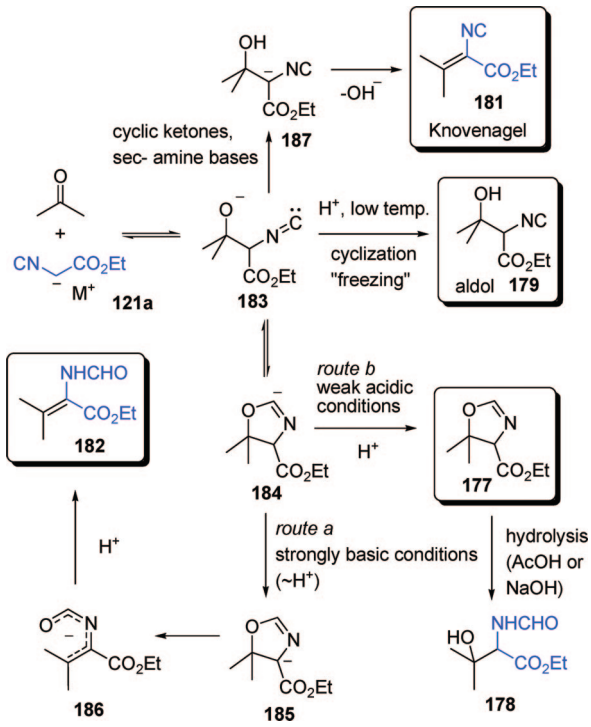


Figure 2.

Scheme 37



Scheme 38



to change of functionality and even formation of heterocycles, have been accomplished. All reported reaction pathways are shown in Scheme 37, and the relevant chemistry is fully discussed here.

All these processes are initiated by the attack of the anion **121a**, arising from isocyanoacetate **121**, onto the carbonyl group of an aldehyde or ketone (Scheme 38). The resulting alkoxide **183** has a strong tendency to cyclize to deliver the oxazoline 2-anion **184**. The further course of reaction is determined primarily by the basicity of reaction media. Under strongly basic conditions in aprotic solvent (route a), the anion undergoes a proton shift and subsequent electrocyclic ring opening to acyclic anion **186**, which yields *N*-formylaminoacrylates **182** upon work up. Under milder alkaline conditions in protic or aprotic solvents, protonation of **184** is easy to give oxazoline **177** before the rearrangement to acyclic anion **186**. Cyclization of alkoxides **183** can be suppressed at low temperature by fast quenching using an acid (usually AcOH). This makes it possible to obtain products of ordinary aldol condensation **179**. It should be noted, however, that quenching of the reaction mixture by a weak acid, like an alcohol or water, can favor cyclization through fast equilibration to give **177**. In certain cases (vide infra), the reaction gives standard Knoevenagel products **181**, but the formation of pyrroles **180** via Knoevenagel-type reactions is also described in this section.

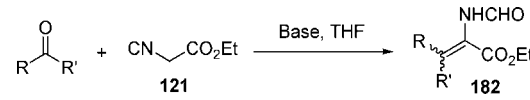
4.1. Synthesis of α-Formylaminoacryl Esters and Amides

α-Formylaminoacrylates **182** are obtained when strong bases like BuLi,[91] *t*-BuOK, or NaH[20,92−94] are used in polar aprotic (usually THF) solvents (Table 5).[95,96] The reaction is applicable to a wide range of aromatic or nonenolizable aldehydes and aromatic and aliphatic ketones and usually proceeds in good yields. This procedure, however, when applied to aliphatic relatively unhindered and enolizable aldehydes, suffers from side reactions and therefore gives the corresponding formylaminoacrylates only in low yield.

Another approach to **182** is based on the ring opening of the corresponding oxazolines **177**, which can be preformed under mild conditions in a high yield. The corresponding one-pot procedure has been recently reported, in which oxazolines are first obtained quantitatively upon Cu(I) catalysis, and then a strong base is added to initiate the ring opening toward **182** (Scheme 39).[97] The oxazoline formation reaction can be affectively catalyzed also by other transition metals (see section 4.2) and has a rather wide scope; therefore this two step approach to **182** probably is more useful than the one step one.

When nonsymmetrically substituted carbonyl compounds are used, formylaminoacrylates are obtained as mixtures of *E*/*Z* isomers, which are usually separable by column chromatography.[94,95,97−99] When aldehydes are applied, *Z*-configured product predominates (Table 5). However, reaction of **121** with trifluoromethyl ketones **188** yields *Z*-isomers

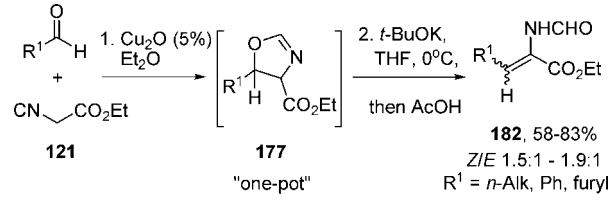
Table 5



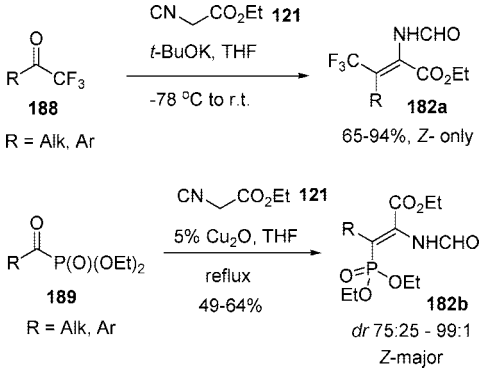
entry	carbonyl	base	yield	*trans*/*cis*[a]
1	PhCHO	*t*-BuOK	85	1:1
2	4-MeOC$_6$H$_4$CHO	*t*-BuOK	71	2:1
3	PhCH=CHCHO	*t*-BuOK	85	*b*
4	PhCOCH$_3$	BuLi	74	1:1
5	fluorenone	BuLi	90	
6	acetone	*t*-BuOK	76	
7	cyclohexanone	BuLi	87	
8	*i*-PrCHO	*t*-BuOK	72	1.4:1
9	*t*-BuCHO	*t*-BuOK	73	3:1
10	CH$_3$CHO	BuLi	13	1.3:1

[a] According to positions of the largest R and CO$_2$Et groups. [b] Not applicable.

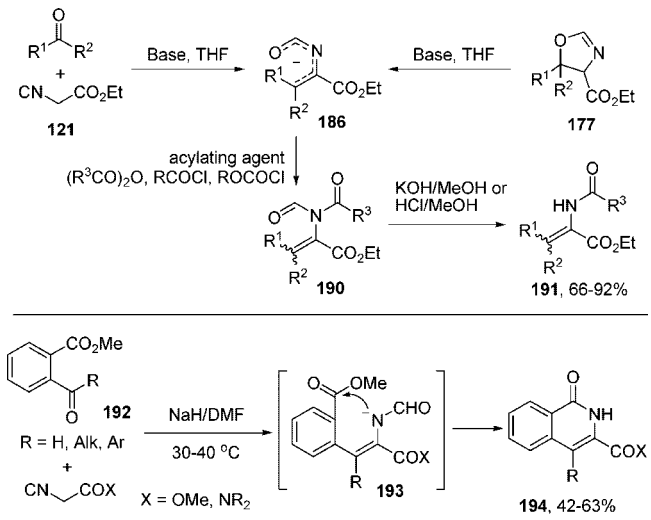
Scheme 39



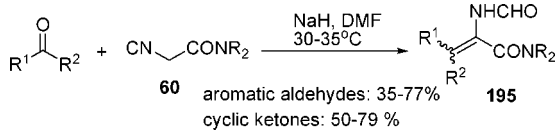
Scheme 40



Scheme 41



Scheme 42



182a exclusively (Scheme 40).[100] Reaction of **121** with 1-oxoalkylphosphonates **189** carried out in the presence of Cu_2O was reported to give formylaminoacrylates **182b** in high diastereoselectivity (that decreases with the bulkiness of the R substituent). Interestingly, the same reaction performed in the presence of NaH showed lower diastereoselectivity (Z/E = 1/3).[101]

The acyclic anion **186** can be scavenged by an acylating agent in a one-pot process to yield α-acylaminoacrylates **191** after deformylation of intermediates **190** by hydrolysis.[102,103] The anion **186** can be obtained directly from isocyanoacetate **121** or indirectly from oxazolines **177**. A similar process accounts for the synthesis of dihydroisoquinolines **194** from aromatic *o*-ketoesters **192** (Scheme 41).[104]

α-Isocyanoacetamides **60** can react with carbonyl compounds by using NaH/DMF in a similar fashion to give α-formylaminoacrylamides **195** (Scheme 42). This reaction has been reported for aromatic aldehydes and cyclic ketones, so its synthetic potential has not been fully exploited yet. α-Formylaminoacrylamides were obtained in moderate to good isolated yield.[20,105,106] Interestingly, application of NaH in THF instead of DMF leads to formation of the corresponding oxazolines of type **177**.[107] This can be ascribed to the lower reactivity of α-hydrogen in the corresponding oxazoline, which causes higher tolerance of an intermediate similar to **184** toward the proton shift and the subsequent ring opening (Scheme 38).

4.2. Synthesis of Oxazolines

In this section, only base-catalyzed oxazoline formation is discussed; for transition metal catalyzed reaction, see section 4.7. Oxazolines **177** can be obtained by the reaction of oxo inputs and α-isocyano ester **121** under weakly basic media. Conditions involving a catalytic amount of NaCN in EtOH at 0 °C or rt conditions are typically used.[108,109] The use of a catalytic amount of sodium ethoxide, fluoride ion,[110] or Et_3N as the base is also reported.[111,112] More recently, strong nonionic bases $P(RNCH_2CH_2)_3N$ (proazaphosphatranes) were employed successfully as catalysts in this reaction as well.[113] The resulting oxazolines can be isolated in good yield or hydrolyzed[114] to β-hydroxy-α-formylamino esters in a one-pot procedure. Several examples are given in Table 6.

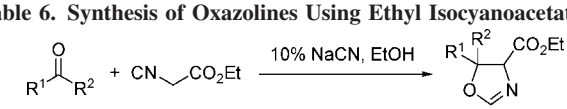
When aldehydes are used as inputs, the reaction proceeds smoothly at 0−30 °C in 1 h and is highly diastereoselective. The *trans*-oxazoline is usually obtained in more than 90% de, which is formed via the thermodynamically controlled process, as alkaline conditions promote epimerization of the *cis* isomer to the thermodynamically more stable *trans*-oxazoline during the reaction. Linear ketones require heating to achieve good yield of a product, whereas sterically hindered or aromatic ketones give sluggish reaction, if at all.

In situ formed thioketones react with isocyanoacetic esters (in tetrahydrofuran at −60 °C in presence of KO*t*-Bu or BuLi) to give 2-thiazoline-4-carboxylic esters, which are useful starting materials for the synthesis of structural variants of penicillin.[115]

Highly enolizable ketones are problematic in the base-catalyzed oxazoline synthesis due to inactivation by deprotonation. On the other hand, reaction of nonenolizable 1,3-diketones is often accompanied by retro-Claisen condensation (see section 4.2.1). Both side processes can be avoided under conditions using a transition metal catalyst (section 4.7).

Stronger alkaline conditions, like KOH in methanol or NaH/THF, are required for the synthesis of the corresponding oxazolines **177** starting from α-isocyanoamides **60** (Scheme 43).[37,107] It should be noted that in the case of secondary amide compounds, X = NHR, there are two possible ways of cyclization of intermediate **183a**. However the present

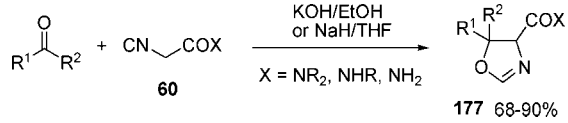
Table 6. Synthesis of Oxazolines Using Ethyl Isocyanoacetate



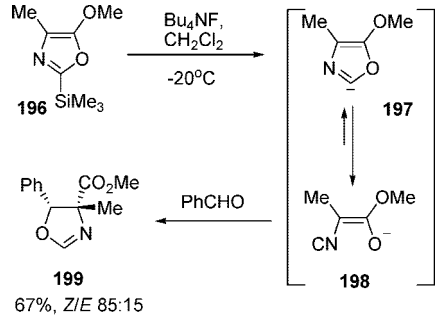
entry	carbonyl compound	*T*, °C	yield	*trans*/*cis*
1	paraformaldehyde	30	53	
2	MeCHO	20	55	>10:1
3	PhCHO	15	72	>20:1
4	*i*-PrCHO	0	78[a]	>10:1
5	cyclohexanone	30	75	
6	acetone	reflux	47	
7[b]	CCl_3CHO, Et_3N/PhH	rt	85	*trans*

[a] *trans* only, ref 116. [b] NaCN is ineffective in this case,probably due to high electrophilicity of the aldehyde, which enhanced a direct nucleophilic attack by CN ion.[112]

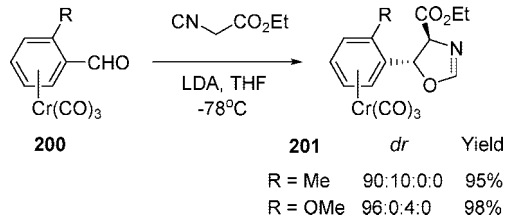
Scheme 43



Scheme 44



Scheme 45



reaction displays a high preference for cyclization on the hydroxy group over the secondary amide. A reaction of a secondary isocyanoacetamide with an alkylating reagent in the presence of sodium hydride gave an imidazolinone compound by the insertion of the isocyano group into the NH group (section 3.2; Scheme 36).

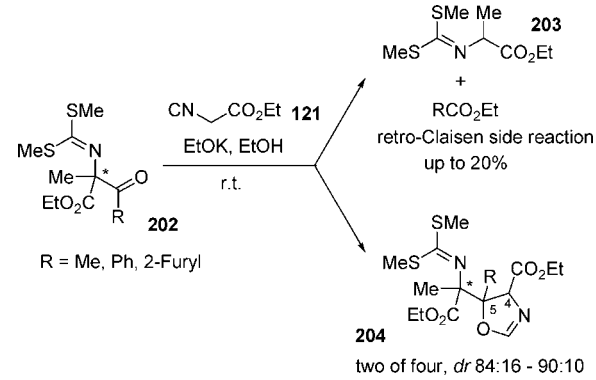
Enolate anions **198** (or **121a**) required for oxazoline synthesis can also be generated from 5-alkoxy-2-silyloxazoles **196** upon treatment with fluoride.[110] This reaction is limited in scope to aromatic aldehydes and probably other nonenolizable substrates because enolizable aldehydes can suffer self-condensation under these conditions (Scheme 44).

4.2.1. Diastereoselective Synthesis Using Chiral Substrate

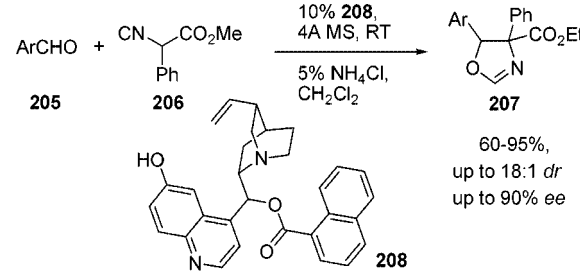
A diastereoselective approach to oxazoline formation using a base-catalyzed reaction of a chiral aldehyde and an isocyanoacetate seems conceivable but currently lacks literature precedents. Only two studies were reported (see also section 4.7.5). In one study, oxazolines **201** were obtained in high yield from chiral chromium π-complexes **200** in ethanol at room temperature with KCN as a base according to Schöllkopf's method and in THF at −78 °C with LDA as well. Interestingly, much higher diastereoselectivity was observed when the reaction was performed with LDA, which supports the idea that efficient diastereoselective oxazoline synthesis with chiral aldehydes should be possible (Scheme 45).[117] Moreover, LDA-assisted oxazoline formation occurring in strongly basic conditions is in contrast to synthesis of formylaminoacrylates, which takes place in the presence of strong bases such as *t*-BuOK or NaH.

The second example describes the reaction of nonenolizable glycine derivatives **202** in the presence of metal alkoxides (Scheme 46). Only two out of four possible diastereomers of **204** were obtained. Optimal diastereomeric excesses were found by using potassium alkoxides. The

Scheme 46



Scheme 47



reaction is accompanied by limited levels of concurrent retro-Claisen condensation.[118,119] It is possible, that carrying out the reaction under less basic conditions in the presence of transition metal catalysts (section 4.7) could diminish this side-process.

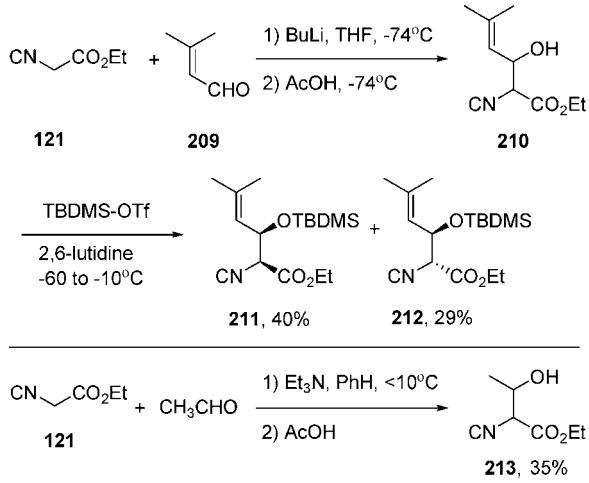
4.2.2. Asymmetric Organocatalytic Synthesis of Oxazolines

An organocatalytic asymmetric variant of oxazoline synthesis involving α-isocyanoactetates has been reported in 2009, which is the only report on the subject.[120] This is in sharp contrast to transition metal catalyzed enantioselective syntheses of oxazolines (section 4.7.2) that were thoroughly investigated for years. In this paper by Xue et al., several derivatives of cinchona alkaloids were discussed that can catalyze the reaction between α-isocyanoactetates **206** and aromatic aldehydes **205** to afford oxazolines **207** in various ee. The best results were obtained using **208** as a catalyst in combination with electron-poor benzaldehydes (Scheme 47). The corresponding oxazolines were prepared in good yield and good dr (4−6:1 up to 18:1), the ee was between 70% and 90% in all cases. The reaction has not been optimized to aliphatic aldehydes: under the reaction conditions, 3-phenylpropanal (the only example reported) gave a 30% yield of oxazoline in low diastereoselectivity (2:1 dr) but high 89% ee.[120]

4.3. Aldol Reaction

The reaction of α-metalated isocyanides and α,β-unsaturated carbonyls yielding an aldol product has been known since 1970.[121,122] To prevent cyclization of alkoxides of type **183** (see Scheme 38), the reaction should be performed at low temperature with subsequent acidification by AcOH. However, alkoxides **183** can also be scavenged by an acylating agent in a one-pot process to yield isocyano esters. This approach has been used for the preparation of protected

Scheme 48



aldols **211** and **212** as a diastereomeric mixture (separable by chromatography).[123] Formation of aldol **213** in Et_3N/PhH conditions has been also reported (Scheme 48).[111]

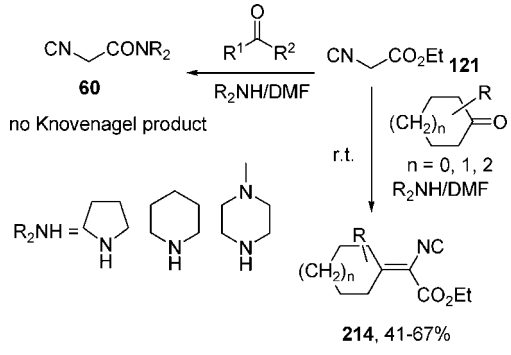
4.4. Knoevenagel Reaction

Due to the strong tendency for alkoxides like **183** to cyclize, the common Knoevenagel reaction is not typical for α-isocyanoacetates and is only known to proceed in specific cases. When cyclic ketones are stirred with secondary amines, which are relatively weak bases (Scheme 49), Knoevenagel-type reactions with α-isocyanoactetates are possible.[20,124] The corresponding α-isocyanoacrylates **214** are thus obtained in moderate to good yield in DMF using 1 equiv of an amine. Acyclic ketones do not give α-isocyanoacrylates under the same conditions; instead α-isocyanoacetamides **60** are formed.

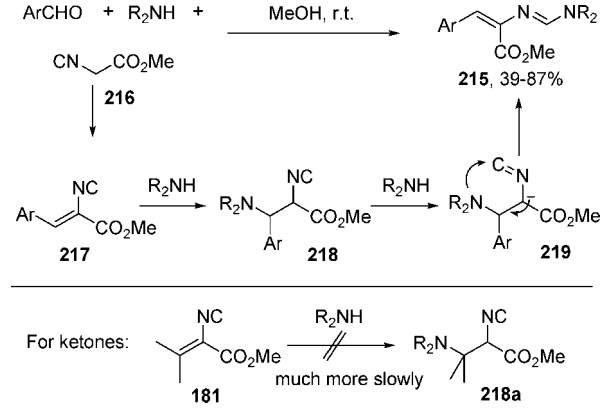
Aromatic aldehydes give amidines **215**, however formation of α-isocyanoacrylates during the reaction is likely to take place as suggested by a mechanistic study. Accordingly, condensation and subsequent Michael addition of a secondary amine to the corresponding Knoevenagel product **217** followed by a base-induced fragmentation leads to the final product **215** (Scheme 50).[94] The stability of ketone-derived Knoevenagel products can be explained by their reluctance to enter the Michael addition step to give **218a**. Attempts to carry out the Knoevenagel reaction with α-isocyanoacetamides under similar conditions (to give α-isocyanoacrylamides) failed due to low reactivity of the substrate. Presumably Knoevenagel adducts are also formed as intermediates in pyrrole synthesis (see section 4.5).

A more convenient route to Knoevenagel adducts **181**, especially in the case of isocyanoacetamides, consists of the

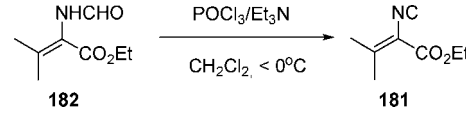
Scheme 49



Scheme 50



Scheme 51



dehydration of α-formylaminoacrylates **182**, which can be easily obtained from isocyanoacetate and a carbonyl compound in the presence of a strong base (see Schemes 51 and 53).

4.5. Pyrrole Synthesis

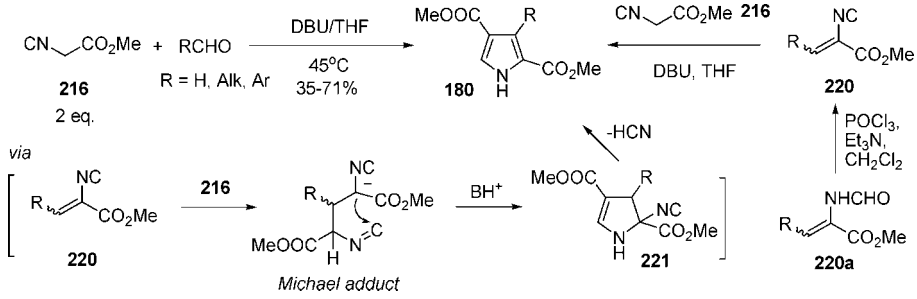
When 2 equiv of α-isocyanoacetate **216** reacts with 1 equiv of aldehyde in the presence of DBU, the formation of pyrroles **180** is observed (Scheme 52).[106,125] This reaction may proceed via the Knoevenagel product **220**, which reacts further via Michael addition of a second molecule of α-isocyanoacetate followed by cyclization to form intermediate **221**. Subsequent elimination of HCN (see also section 9) affords the target pyrroles **180**. This reaction path is supported by the fact that pyrroles can be synthesized from α-isocyanoacrylates **220** using 1 equiv of α-isocyanoacetate under similar conditions, but they cannot be synthesized directly under these conditions from α-formylaminoacrylates **220a**, which would be possible intermediates too.[126] Interestingly, the reaction of 1 equiv of α-isocyanoacetate **216** with an aldehyde in the presence of DBU has not been described. Probably, this leads to the Knoevenagel product **220**, which is normally prepared via dehydration of α-formylaminoacrylates **220a**.[127,126]

The use of α-isocyanoacetamides **60** instead of esters like **216** does not afford pyrroles under these conditions. This is attributed to the lower α-H acidity. The corresponding pyrrolecarboxamides **224** are prepared by the reaction of α-isocyanoacrylamides **223** with 1 equiv of α-isocyanoacetamide **60** in the presence of NaH in DMF (Scheme 53).[106]

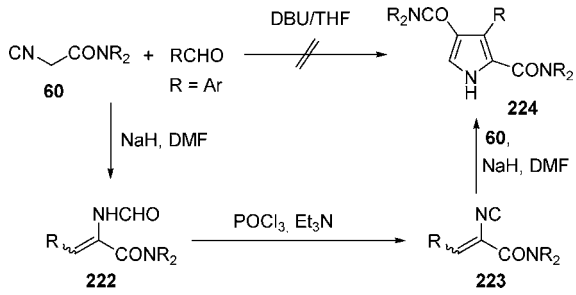
4.6. Reactions with Azole Carboxaldehydes. Synthesis of Fused Pyrimidines

Pyrrole-2-carboxaldehydes **225** react with methyl isocyanoacetate in the presence of DBU to give pyrrolo[1,2-*c*]pyrimidine derivatives **226** (Scheme 54).[128−130] Although this reaction has been known for more than 30 years, it has not received much attention despite that it could serve as a convenient method for preparation of fused heterocycles. Reactions with other azole-2-carboxaldehydes have not been described at all.

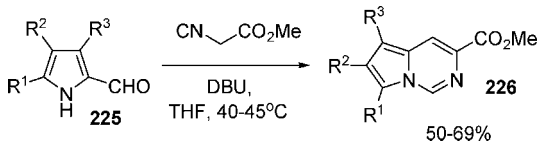
Scheme 52



Scheme 53



Scheme 54



4.7. Transition Metal Catalyzed Aldol Reaction: Oxazoline Formation

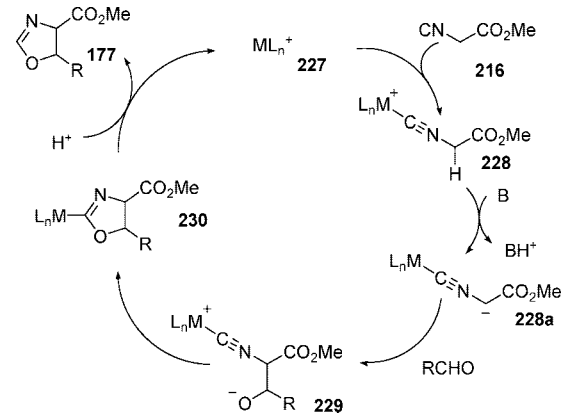
Transition metal catalyzed formation of oxazolines **177** is one of the most studied transformations in the chemistry of α-isocyanoacetate derivatives (Scheme 55).

This reaction is characterized by the ability of a metal ion to form an isocyanide complex **228**, which significantly enhances the acidity of the α-H atom compared with the noncomplexed **216**. This allows smooth formation of a carbanion **228a** by abstracting a proton by a weak base (triethylamine or *i*-Pr_2NEt is usually used). After the subsequent electrophilic attack to a carbonyl compound and intramolecular cyclization of **229**, the 2-oxazoline complex **230** is formed. The low complexing ability of oxazolines allows liberation of free oxazoline **177** and the cationic metal species **227** for a new cycle (Scheme 56). Reaction is usually performed in dichloromethane or 1,2-dichloroethane at room temperature for several hours. Due to the mild conditions, this reaction is virtually free of side processes and in most cases proceeds until complete conversion, so >90% isolated yields are easily accessible.

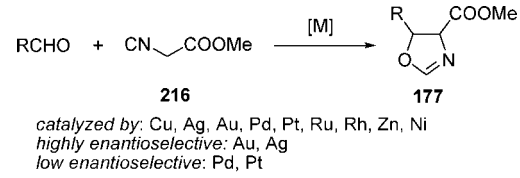
Usually, the formation of *cis*/*trans*-oxazoline diastereomers is observed in this transformation. This suggests that the transition metal catalyzed cyclocondensation proceeds under kinetic control predominantly (vide infra), which is in contrast to the thermodynamic control usually observed under the basic conditions of Schöllkopf. Weak bases like Et_3N

Scheme 55

Scheme 56



Scheme 57



are unable to promote *cis*/*trans* epimerization at room temperature, but they may induce this under reflux conditions in excess of a base. However, the diastereoselectivity of the reaction upon catalysis by a well-designed transition metal catalyst is usually high even under these kinetically controlled conditions.

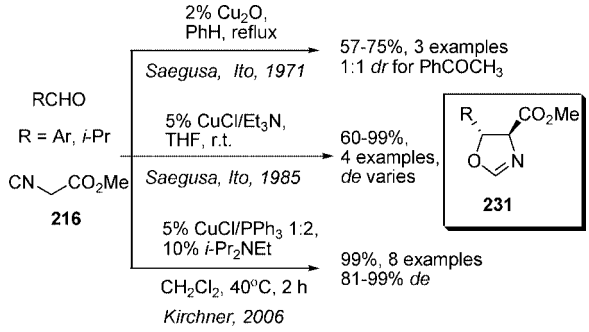
Every soft metal-based Lewis acid that is able to form a complex with isocyano functionality can be used as a catalyst. Indeed, a number of metals were shown to catalyze this reaction (Scheme 57). So far Cu, Ag, Au, and Pd species are most commonly applied. Also several examples using Zn, Ni, Pt, Ru, and Rh catalyzed reactions were reported (Scheme 57).

Highly efficient enantioselective oxazoline formation has been developed using asymmetric gold and silver catalysts (section 4.7.1). Enantioselective Pd and Pt catalyzed reaction has been investigated; however highly efficient catalyst systems were not found.

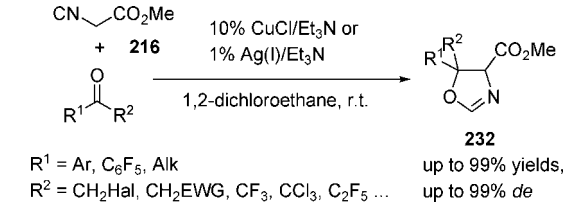
4.7.1. Diastereoselective Cu- and Ag-Catalyzed Aldol Reaction

In 1971, Saegusa and Ito reported initial studies on the Cu_2O catalyzed reaction of ethyl isocyanoacetate with carbonyl compounds to give oxazolines in a moderate to good yield.[131] Few transformations were also performed using a CuCl/Et_3N 1:1 catalyst system.[132] In both cases, the diastereoselectivity highly depends on the substrate. In 2006,

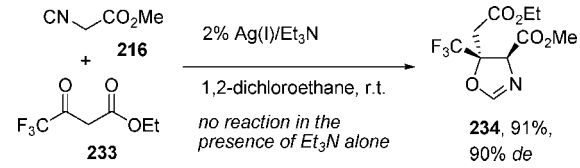
Scheme 58



Scheme 59



Scheme 60



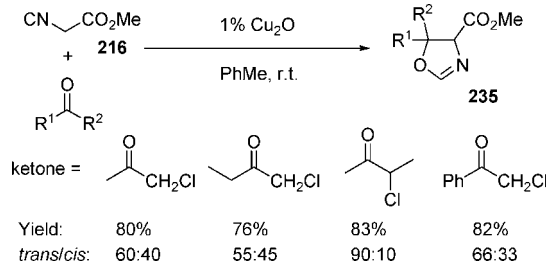
however, a highly efficient CuCl/PPh_3-catalyzed diastereoselective reaction was reported for various aromatic aldehydes and isobutyraldehyde (Scheme 58).[133]

The reaction was also applied to ketones; however their low reactivity imposes some restrictions on the scope of acceptable substrates.[134,135] In all the cases reported, conversions using nonactivated aliphatic and aromatic ketones were less than 50% at room temperature. However, the presence of at least one electron-withdrawing substituent at the α-position of the carbonyl input drastically facilitates the reaction, which then proceeds at room temperature and generally in more than 90% yield. Usually the rate of reaction is higher when the electrophilicity of the ketone increases. Diastereoselectivity depends on several factors, but stereochemical discrimination between the substituents R^1 and R^2 at the carbonyl carbon plays a major role. Electrostatic and electron donor−acceptor interactions, the nature of the amine and the metal also influence the selectivity (Scheme 59). The results suggest that some of the factors, for example, the proper choice of a metal catalyst and a base, could be manipulated to afford synthetically useful diastereoselectivity in these reactions (up to 99% de).

Highly enolizable ketones, which do not usually react as aldol acceptors under basic conditions, can also be involved in this metal-catalyzed synthesis. For example, oxazoline **234** could be successfully prepared from **233** in the presence of 2% Ag(I) (Scheme 60; for another example, see Scheme 75).

A few reactions catalyzed by Cu_2O alone, using α-chloro ketones as the oxo input, have been reported to give 65−83% yield of oxazolines **235** in 55:45 to 90:10 dr (Scheme 61).[136] Enantioselective oxazoline formation using asymmetric Cu complexes has not been reported.

Scheme 61



4.7.2. Enantioselective Aldol Reaction Catalyzed by Au and Ag Chiral Complexes

Enantioselective oxazoline synthesis using well-designed chiral ferrocenylphosphine−gold(I) complexes **237** was first demonstrated by Ito and Hayashi in 1986,[137] since then it has been extensively investigated and has become a valuable methodology for stereoselective C−C bond formation. Chiral ferrocenylphosphine ligands are usually prepared by the method reported by Kumada in 1980.[138]

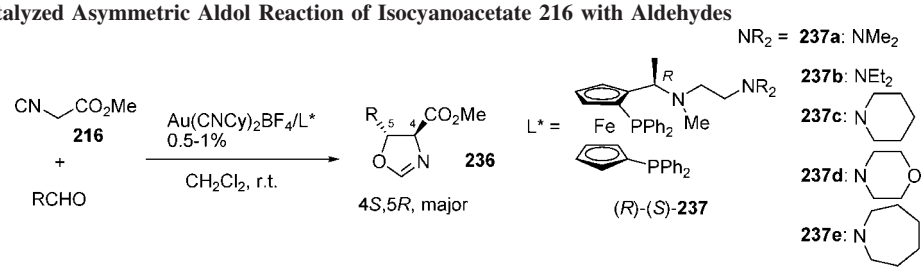
Gold complexes such as **237a**−**e** are effective catalysts for asymmetric oxazoline formation (Table 7). Aldehydes with sterically hindered substituents such as *i*-PrCHO and *t*-BuCHO give the corresponding *trans*-oxazolines almost exclusively with high enantioselectivity (entries 6 and 7). The reaction with α,β-unsaturated aldehydes also proceeds with high stereoselectivity without formation of any byproducts formed by conjugate addition (entries 8 and 9). Various functionalized aromatic aldehydes are tolerated in this highly stereoselective aldol-type reaction. Specific electronic effects may influence stereoselectivity dramatically, for example, both de and ee of *trans*-oxazolines obtained from fluorinated benzaldehydes gradually decreases when the number of fluorine atoms increase (entries 17−19).[139] This phenomenon is rationalized by π−p interaction between the electron-deficient phenyl ring and the negatively charged enolate anion, which favors the formation of the *cis* isomer, but apparently not to such an extent that it dictates the stereoselectivity completely (see also the proposed transition state model in Figure 3). Low enantioselectivity in the reactions of 2-heteroaromatic aldehydes is also attributed to special electronic effects within the transition state (entries 20−22).[140]

Similar Au(I)-catalyzed aldol reactions of isocyanoacetamides are generally even more stereoselective than those of isocyanoacetates (Table 8).[141] Although amides are less reactive, complete conversions are easily achieved in longer reaction times. Remarkably better stereoselectivity is observed for the reactions with highly fluorinated benzaldehydes (entries 4 and 5).[142] The aforementioned effect of π−p interaction is less pronounced in this case.

The asymmetric aldol reaction of α-isocyano Weinreb amide **81** proceeds also with high stereoselectivity (Scheme 62). The corresponding oxazolines **240** can be transformed in excellent yields to various derivatives of optically active β-hydroxy-α-amino aldehydes and ketones **243**−**245**, which are valuable building blocks for asymmetric synthesis.[143]

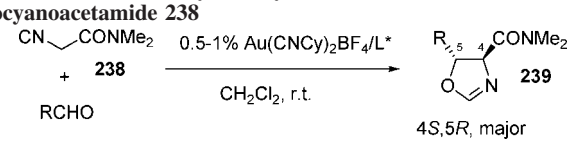
Gold(I) complexes are also applicable to asymmetric aldol reactions of α-substituted isocyanoacetates, although the stereoselectivity is highly depending in these cases on the structures of the substrates. Generally the diastereo preference is gradually reversed toward the *cis* isomer when more bulky substituents R^2 are used (Table 9).[144]

Table 7. Gold(I)-Catalyzed Asymmetric Aldol Reaction of Isocyanoacetate 216 with Aldehydes



entry	R	ligand	yield	*trans*/*cis*	ee_{trans}	ee_{cis}
1	Me	**237a**	94	78/22	37	
2	Me	**237b**	100	84/16	72	
3	Me	**237c**	100	85/15	85	
4	Me	**237d**	99	89/11	89	
5	Me	**237e**	100	86/14	80	
6	*i*-Pr	**237c**	99	99/1	94	
7	*t*-Bu	**237d**	94	100/0	97	
8	(*E*)-*n*-PrCH=CH	**237d**	85	87/13	92	
9	(*E*)-MeCH=C(Me)	**237a**	89	91/9	95	
10	Ph	**237a**	91	90/10	91	
11	Ph	**237d**	93	95/5	95	
12	Ph	**263a**	99	89/11	23	
13	Ph	**263b**	80	68/32	0	
14	2-$MeOC_6H_4$	**237d**	98	92/8	92	
15	4-ClC_6H_4	**237d**	97	94/6	94	
16	4-$NO_2C_6H_4$	**237d**	80	83/17	86	
17	2,4,6-$F_3C_6H_2$	**237c**	96	67/33	73	82
18	2,3,5,6-F_4C_6H	**237c**	90	47/53	48	89
19	C_6F_5	**237c**	99	57/43	36	78
20	2-thienyl	**237a**	90	95/5	33	17
21	2-furyl	**237a**	62	68/32	32	83
22	2-pyridyl	**237a**	45	75/25	6	84

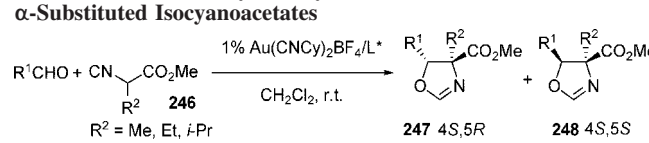
Table 8. Gold(I)-Catalyzed Asymmetric Aldol Reaction of Isocyanoacetamide 238



entry	R	ligand	yield[a]	*trans*/*cis*	ee_{trans}	ee_{cis}
1	Me	**237c**	85	91/9	99	
2	*i*-Bu	**237c**	92	94/6	97	
3	Ph	**237c**	74	94/6	94	
4	C_6F_5	**237c**		77/23	80	20
5	2,3,5,6-F_4C_6H	**237c**		89/11	77	28

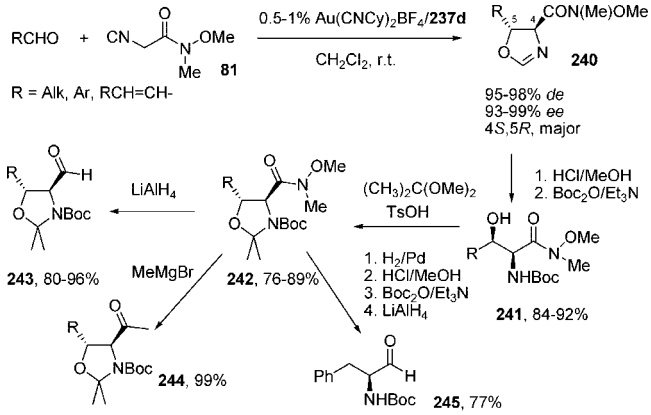
[a] Isolated yield of *trans*-**239** is given.

Table 9. Gold(I)-Catalyzed Asymmetric Aldol Reaction of α-Substituted Isocyanoacetates



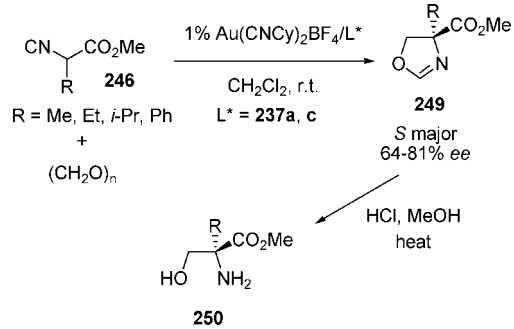
entry	R^1	R^2	ligand	yield	*trans*/*cis*	ee_{trans}	ee_{cis}
1	Ph	Me	**237d**	97	93/7	94	53
2	Ph	*i*-Pr	**237d**	86	62/38	88	17
3	Me	Me	**237d**	86	56/44	86	54
4	Me	Et	**237d**	92	54/46	87	66
5	Me	*i*-Pr	**237d**	100	24/76	26	51

Scheme 62



The enantioselective Au-catalyzed reaction of α-substituted isocyanoacetates **246** with paraformaldehyde yields oxazolines **249**, which can be readily transformed to α-substituted serine analogs **250** (Scheme 63).[145]

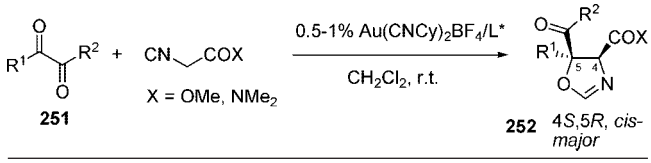
Scheme 63



For the asymmetric aldol reaction of α-isocyanoacetates with ketones, much less detailed studies are available. Few examples involving α-ketoesters and α-diketones **251**, which possess enhanced carbonyl activity, are reported.[146] Isocyanoamides display better stereoselectivities then the corresponding esters; however, in both cases, de's and ee's were not as high as those reported for aldehyde inputs (Table 10).

The Au(I)-catalyzed aldol reactions employing optically active α-isocyano esters or oxo compounds as the inputs have

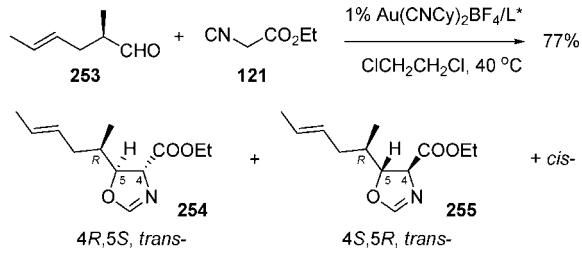
Table 10. Gold(I)-Catalyzed Asymmetric Aldol Reaction of Ketones



entry	R^1	R^2	X	yield	*trans*/*cis*	ee_{trans}	ee_{cis}
1	Me	OMe	OMe	90	27/73	33	82
2	Me	OMe	NMe_2	*a*	12/88	36	90
3	*i*-Bu	OMe	NMe_2	*a*	21/79	84	76
4	Ph	OMe	NMe_2	*a*	20/80	74	42
5	Me	Me	NMe_2	92	49/51	74	75

[a] Almost quantitative yield; crude product was used in a subsequent transformation without purification.

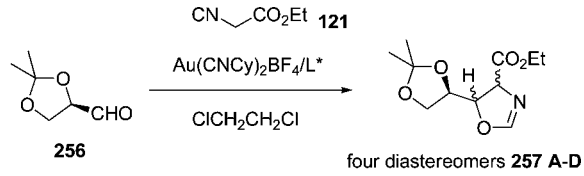
Scheme 64



Stereoisomer distribution (%) according to GLC analysis:

Ligand	4*R*,5*S* (**254**)	4*S*,5*R* (**255**)	total *cis*-
(*R*, *S*)-**237a**	10	85	5
(*S*, *S*)-**237a**	90	6	4

Scheme 65



Diastereomer distribution (%) according to GLC analysis: [a]

Ligand	*trans*-A	*trans*-B	*cis*-C	*cis*-D
R, *S*-**237a**	11	79	7	3
Diphos/Et_3N	22	57	3	18
S, *R*-**237a**	45	44	1	10

[a] absolute configuration was not established

been reported.[140] Chiral induction using isocyano esters derived from optically pure alcohols is not very high, probably because the chiral ester moiety is relatively far away from the bond-forming site.[140] The use of optically active aldehydes, however, has some influence and allows double stereodifferentiation between a chiral substrate and a chiral ferrocenylamine catalyst in the Au(I)-catalyzed aldol reaction (Scheme 64).[147]

An even stronger effect of double stereodifferentiation was observed when the chiral aldehyde **256** bearing a heteroatom at the α-position was used in the Au(I)-catalyzed condensation with **121** (Scheme 65).[140]

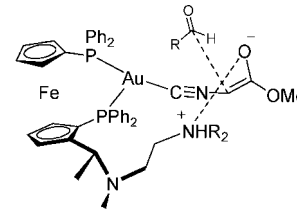
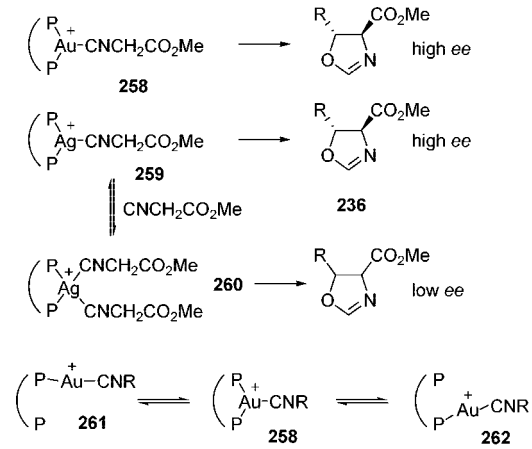


Figure 3.

Scheme 66

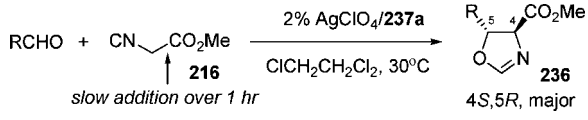


The gold-catalyzed asymmetric aldol synthesis of oxazolines is well suited for scaling up. The [substrate]/[catalyst] ratio can be raised to 10000/1 without significant loss of stereoselectivity. The catalyst can be recovered from the reaction mixture by precipitation with ether or hexanes and displays no loss in stereoselectivity upon recycling.

The high efficiency of the gold catalyst can be explained by the postulated transition state (Figure 3).[137,148] The terminal amino group of the side chain of a catalyst acts as a base to form ammonium enolate. Ionic interaction between the enolate anion and the ammonium cation holds the position of the pendant side chain, which shields the *re*-face of the enolate; therefore aldehydes approach the *si*-face preferentially and precoordination of the carbonyl group to gold is not observed in the process. Such a conformation was confirmed by the NOE measurement structure of the AgOTf/(*R*)-(*S*)-**237a** complex, which coordinated two molecules of **216** in solution.[149]

The use of Au(I) is essential for the high stereoselectivity. The corresponding silver(I) and copper(I) catalysts are much less selective.[137] This is associated with significant differences in coordination properties of these metals, particularly in the number of isocyanide molecules coordinated to the metal. It was shown, that the catalytic gold complex [AuL*]BF_4 adds one molecule of isocyanoacetate to form tricoordinated complexes **258** without formation of species bearing two isocyanides (Scheme 66).[148] The tetracoordinated gold complex was only observed at −95 °C in the presence of 50 equiv of an isocyanide.[149] In contrast, silver has a strong tendency to coordinate one extra isocyanide to form undesirable tetracoordinated species **260**, which are in equilibrium with tricoordinated **259**.[150,151] It is assumed that only species **259** bearing one isocyanide are responsible for high stereoselectivity. Experiments carried out under conditions that hamper formation of tetracoordinated species (slow addition of an isocyanide) resulted in great increase in selectivity (up to 90% ee, in contrast to the low 37% ee when an isocyanide is added in one portion, Table 11).[150] Increased stereoselec-

Table 11. Silver(I)-Catalyzed Asymmetric Aldol Reaction



entry	R	ligand	yield	*trans*/*cis*	ee_{trans}
1	Me	**237c**	90	96	80
2	*i*-Bu	**237c**	90	99	90
3	Ph	**237c**	91	>99	88
4	C_6F_5	**237c**	90	97	87

tivity of the silver-catalyzed reaction was observed at elevated temperature, under conditions favoring dissociation of the tetracoordinated species.[150] Stereoselectivity may further increase by using both slow addition and elevated temperature (e.g., 50−80 °C). It is noteworthy that the structure **258**, showing a three-coordinated metal−isocyanide complex, is, in fact, a simplified model, because this species exists in dynamic equilibrium between **261** and **262**, according to NMR studies.[150,151]

Also, structural differences were demonstrated between Au(I) and Ag(I) catalysts. Coordination of Au(I) with the nitrogen side chain of the ferrocenyl ligands does not occur as was shown by X-ray analysis of $[(AuCl)_3L^*_2]$ species obtained using a $AuCl(Me_2S)$ precursor. In contrast, X-ray analysis of silver trinuclear species $[Ag_3L^*_2](OTf)_3$, which are formed in the $AgClO_4$/L* or AgOTf/L* system, revealed that coordination of silver with the nitrogen side chain does occur. However, these species collapse upon isocyanide addition, and coordination of silver to the nitrogen is lost.[150,151] The behavior of Cu(I) has not been studied in detail, but in this case, formation of undesirable nitrogen-coordinated species is obvious.

The use of ionic Au(I) complexes is preferred over neutral derivatives. It was shown that ionic gold salts such as $Au(CNCy)_2BF_4$ produced a $[AuL^*]BF_4$ complex,[148] which works as a direct catalyst, but the covalent and neutral $AuCl(Me_2S)$ precursor produces trinuclear $[(AuCl)_3L^*_2]$ species, which are somewhat less selective.[152]

Detailed studies of different ferrocenylphosphine ligands in the Au(I)-catalyzed reaction revealed that the most important factors for obtaining good stereoselectivity are (i) the distance between the basic terminal nitrogen and the ferrocenyl moiety and (ii) the stereochemical configuration of the ligand, which possesses both central and planar chirality (Figure 4). Thus, ferrocenylphosphines bearing 3-(dimethylamino)propyl or without a pendant side chain **263** are much less stereoselective, if at all (entries 12 and 13, Table 7).

The planar and central chirality of the ligand may act in either a cooperative or a noncooperative sense, which greatly influences the stereoselectivity, according to Togni and Pastor (Table 12).[153] The best results are obtained when the planar and central chirality are of opposite absolute configurations as depicted for complex **237a**.

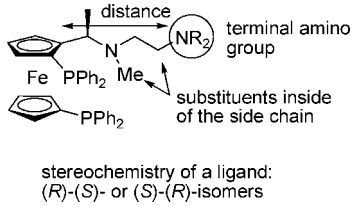


Figure 4. Factors that have been varied in the ligand screening.

Table 12. The Effect of Ligand Chirality upon Product Enantio- and Diastereoselectivity

ligand	yield, %	% *trans* (% ee)	% *cis* (% ee)
R,*S*-**237a**	99	89.6 (91, [4*S*,5*R*])	10.4 (17, [4*S*,5*S*])
S,*S*-**237a**	72	83.5 (41, [4*R*,5*S*])	16.5 (20, [4*S*,5*S*])
S,*R*-**237a**	90	89.6 (90, [4*R*,5*S*])	10.4 (12, [4*R*,5*R*])

The aminoalkyl side chain is an easily variable site, and therefore many ligands of a similar type have been synthesized and tested to further investigate the influence of the side chain on stereoselectivity. It was found that changing the methyl substituent at the *internal* nitrogen to a more bulky benzyl group (compound **266**, Figure 5) influences dramatically both the yield and stereoselectivity.[154] Apparently this is due to steric conflict in the transition state brought about by the bulky substituent. The change of the atom and introduction of two additional substituents at a somewhat distant position (counting from the ferrocenyl core) affects the stereoselectivity depending on the configuration of the side chain (compound **265**).[155]

The change of the methyl group nearest to the ferrocenyl core to a more bulky group should cause more rigidity in the transition state and bring about better selectivity, but such ligands have not been synthesized so far. At present, the ligands of type **237** perform best in terms of availability and effectiveness. Stereoselectivity is also affected by the terminal amino group, but generally not very strongly.[156,157] Only the enantioselectivity of reactions with less sterically demanding aldehydes such as MeCHO is significantly improved by the proper choice of terminal alkyl substituents, whereas for more hindered substrates, the effect is less pronounced. Generally the substituents may be varied broadly without significant effect on the stereoselectivity. For example, additional functional groups can be easily introduced for a specific purpose as in **264**.[158] The ligands bearing a cyclic terminal amino group such as morpholino or piperidino groups are generally superior, **237b**,**c**. The influence of one or two distant chiral centers has also been investigated (general structure **267**), only minor effects of chiral cooperativity having been detected.[159]

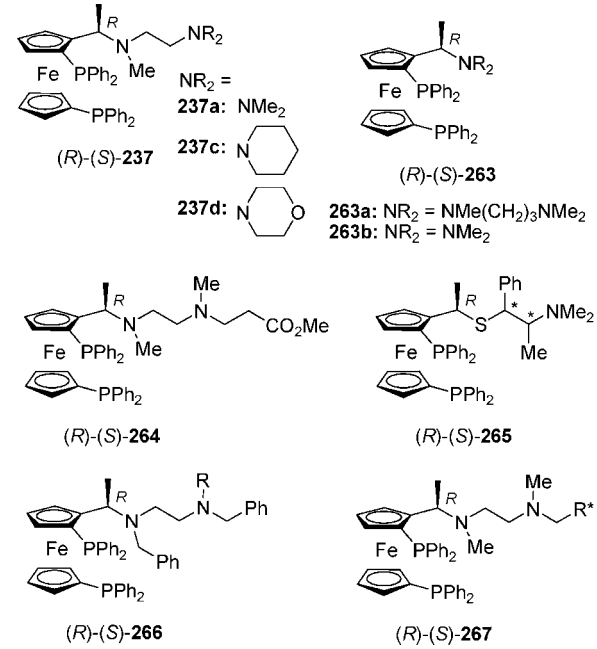


Figure 5.

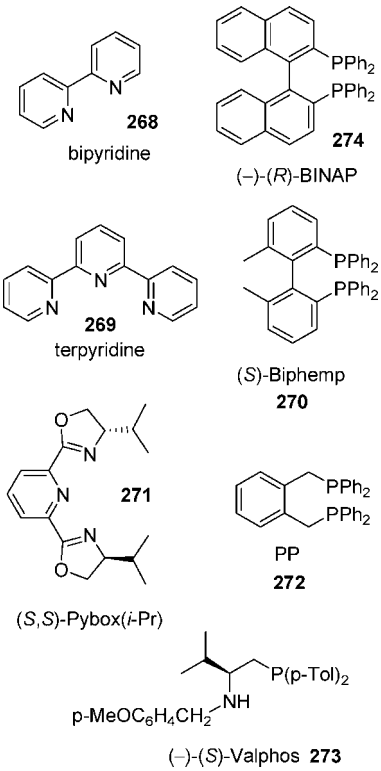


Figure 6.

4.7.3. Aldol Reaction Catalyzed by Palladium and Platinum Complexes

Reaction of **216** with carbonyl compounds catalyzed by palladium and platinum complexes was first reported in 1993 by the Pregosin group.[160] Palladium complexes containing 2,2′-bipyridyl **268**, (−)-(*R*)-BINAP **274**, (*S*)-Biphemp **270**, (−)-(*S*)-Valphos **273**, PP **272**, terpyridyl **269**, or Pybox **271** ligands (Figure 6) and the simplest complex $[Pd(CH_3CN)_4](BF_4)_2$ catalyze effectively the reaction between benzaldehyde and methyl isocyanoacetate yielding >90% of the corresponding oxazoline. However, acceptable levels of stereoselectivity were not achieved. In all cases, *trans*-oxazolines were the major isomers obtained but in rather poor 30−45% de, and with the use of chiral ligands only maximum levels of 10.2% ee using **273** were reported. Platinum NNN-pincer complex [Pt(Pybox)Cl]OTf was also employed as a catalyst to give 95% yield of oxazoline but again with low stereoselectivity.[160]

Since then, several other Pd and Pt pincer complexes of a range of different ligand types (NCN,[161−171] PCP,[172−174] PCS,[175] SCS[175,176]) have been investigated in the catalytic aldol reaction of aldehydes with methyl isocyanoacetate (Table 13).

In all cases, *trans*-oxazolines were formed as the major isomers. The highest deastereoselectivity (94−98% de) was observed when a catalyst complex[174] bearing chiral phosphorus ligand **281** was employed, however, the enantioselectivity was still low (<11% for the *trans*-isomer). Interestingly, a relatively high diastereoselectivity toward the *cis* product was observed for complex **290**.[166] For example, using *o*-methoxybenzaldehyde in the aldol reaction with **216**, the *cis*-oxazoline was formed as the major diastereomer in 70:30% ratio (57% de) and 42% ee. Relatively high ee for *cis*-oxazoline was observed for complex **280a**.[173]

Possibly the poor stereoselectivity is associated with the relative openness of the chiral pocket in these catalyst systems, which cannot sufficiently discriminate between diastereomeric relations in the transition intermediate state. With the Pybox complex (the NNN-type), quantitative ligand substitution in the presence of excess of isocyanide was demonstrated, which accounts for the lack of stereoselectivity using this complex.[177] In contrast, the ferrocenylphosphine complexes were shown to be stable to substitution by an isocyanide, which demonstrates that phosphorus ligands indeed bind palladium much more strongly than nitrogen-based ligands. Therefore, in these systems it is more likely that poor stereoselectivity is caused by unfavorable diastereomeric relations during the course of the reaction rather than by dissociation of the complex. Another interesting observation concerns different behavior of [PCP] complex from that of other [SCS] and [NCN] complexes. It was shown that [SCS] and [NCN] pincer Pd complexes suffer insertion of an isocyanide into the Pd−C bond. The same occurs in mixed [PCS] complexes, while [PCP] complexes are stable toward insertion. This has been ascribed to the stronger P−Pd coordination (Scheme 67).[175,178]

The reaction of benzaldehyde and methyl isocyanoacetate was used as a test reaction to evaluate catalytic performance of Pd pincer complexes immobilized on insoluble supports. Hyperbranched carbosilane,[179] dendronized polymer,[180] mesoporous silica,[178] and fullerene[181] have been used as supports providing covalent bonding to the complex. The use of ionic core−shell dendrimers with an octacationic core as supports for noncovalent bonding has also been reported.[182] Again the catalysts expressed low stereoselectivity but had a positive effect on the reaction course as a whole.

In summary, although over a dozen of Pd and Pt catalysts have been reported and investigated in the asymmetric aldol reaction of isocyanoacetate, a catalyst that delivers oxazolines in high diastereo- and enantioselectivity remains undiscovered.

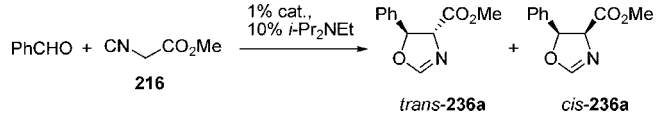
4.7.4. Diastereoselective Oxazoline Formation Catalyzed by Other Metals

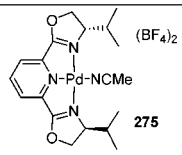
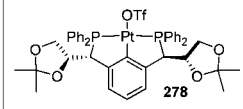
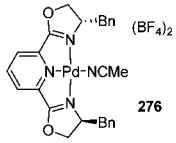
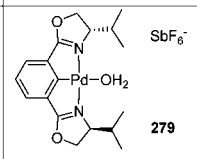
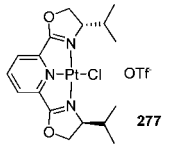
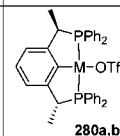
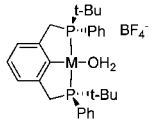
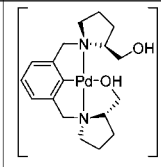
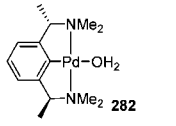
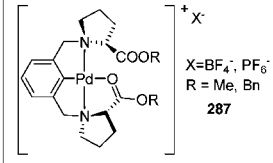
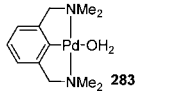
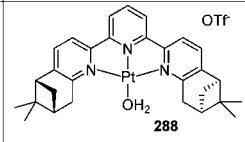
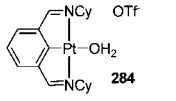
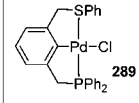
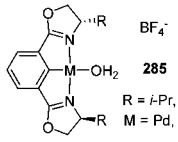
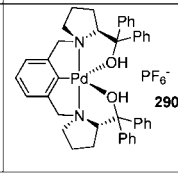
Only a few reports are known for the isocyanoacetate aldol reaction catalyzed by Zn, Ru, and Rh.[135] The zinc-catalyzed reaction was reported as early as 1985 by Saegusa and Ito. The reactions were performed using 1 equiv of $ZnCl_2$ under base-free conditions and yielded the corresponding oxazolines in low to moderate diastereoselectivity.[132] Although it was not thoroughly investigated and optimized, preliminary results suggest that this procedure is only applicable to α,β-unsaturated or aromatic aldehydes, since aliphatic aldehydes gave **177a** in a low yield. Clearly, Zn salts are inferior to other catalysts in efficacy. There is only one example for a Ni-catalyzed reaction reported; oxazoline **177a** was obtained in good yield from acetaldehyde (Scheme 68).[111]

Rhodium-based catalysts can be used successfully in oxazoline synthesis, however their use is not widely investigated and only two examples were reported (Scheme 69).[135]

A completely different behavior was observed in studies using stoichiometric amounts of Rh complexes in the reaction between aldehydes and isocyanides. In the presence of rhodium(III) phebox complexes **292**, it was found that reaction of aldehydes and ethyl isocyanoacetate affords the corresponding aldol adducts as Fischer carbene complexes **294**, some of them being quite unstable. The carbene center in **294** exhibited a high level of π-conjugation with two heteroatoms (Scheme 70).[183] In contrast, a similar reaction

Table 13. Pincer Complexes As Catalysts of Asymmetric Aldol Reaction



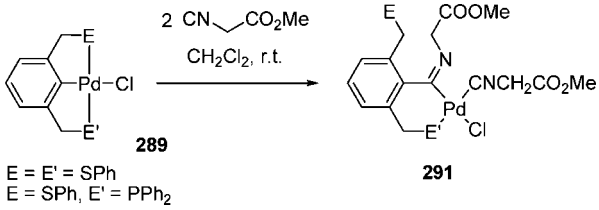
entry	catalyst	Yield	*trans*/*cis* (ee_{trans}/ee_{cis},%)	Ref.	entry	catalyst	Yield	*trans*/*cis* (ee_{trans} /ee_{cis}, %)	Ref.
1	 **275**	91	1/0.7 (1.0/1.7)	160	4	 **278**	96	7/3 (65/3)	172
2	 **276**	91	1/0.7 (5.6/2.8)	160	5	 **279**	95	4:1 (-)	169
3	 **277**	95	1/0.73 (4.7/3.1)	160	6	 **280a,b** M = Pd, Pt	85	78/22 (24/67)	173
7	 **281a,b** M = Pd, Pt	-	94/6 (<11/-)	174	12	 **286**	75 (BF_4), 84 (PF_6)	69/31, 72/28 (<5/-)	164
8	 **282**	-	- (12/-)	168	13	 **287**	-	-	171
9	 **283**	83	62/38 (-)	161	14	 **288**	70	9/1 (21)	165
10	 **284**		4/1	167	15	 **289**	-	57/43 (-)	175
11	 **285** R = *i*-Pr, Bn M = Pd, Pt	>90	80/20–87/13 (3–41/13–20)	170	16	 **290**	92	56/44 (17/42)	166

catalyzed by platinum and palladium phebox complexes was reported to give the corresponding oxazolines in a free form.[170]

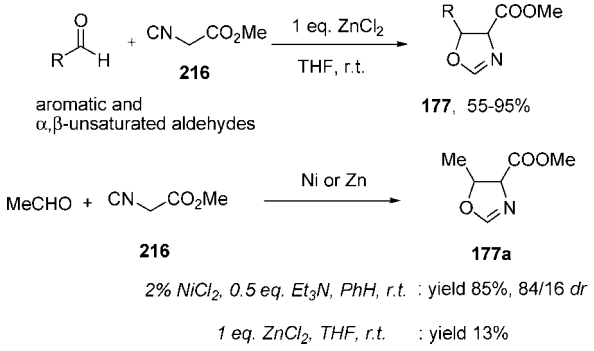
Recently $Rh_4(CO)_{12}$-catalyzed transformation featuring an unusual course of the reaction has been found to give α-formylaminoacrylates **182** (Scheme 71).[184] The reaction involves a C−H activation step and may proceed via oxazolines **177** with subsequent ring-opening.

However, such a behavior of oxazolines is still speculative, since no mechanistic study has been conducted. One may take into consideration the above-mentioned formation of rhodium(III) Fischer carbene complexes **294**. This may provide an alternative mechanistic rationale involving such species as shown in Scheme 72. Thus, Fischer carbene **294** once obtained may undergo further transformations *in situ* under thermal conditions, in contrast to a previously described synthesis of **294** at low temperature. So the C−O bond may dissociate to provide species **301**. Subsequent proton transfer and reductive elimination afford the final compound **182**.[185]

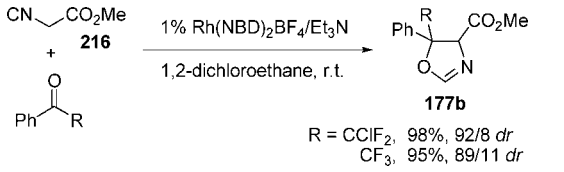
Scheme 67. Insertion of an Isocyanide into a Pd−C Bond



Scheme 68



Scheme 69



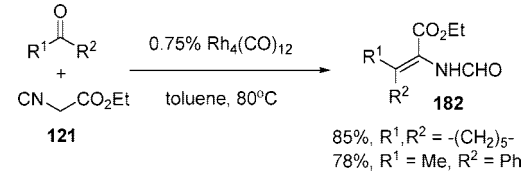
If various 1,3-dicarbonyl compounds **303** are used in the place of ketones, cyclocondensation proceeds to give the corresponding ethyl pyrrole-2-carboxylates **306** regioselectively on the basis of either steric or electronic effects. The reaction proceeds via α-formylaminoacrylates **304**, which undergo decarbonylation and subsequent cyclization (Scheme 73).[185]

Hydroxyapatite-bound ruthenium(III) complex (RuHAP, **307**) has been prepared by the treatment of hydroxyapatite with aqueous $RuCl_3$ and aqueous AgOTf. Excellent catalytic activity of this heterogeneous catalyst was demonstrated in Diels−Alder and aldol reactions, including the aldol reaction of isocyanoacetate. Since no ruthenium leaching in the reaction media was observed, this catalyst is recyclable and well-suited for practical applications (Scheme 74).[185]

4.7.5. Diastereoselective Synthesis Using Chiral Substrate and Achiral Metal Catalyst

Using a carbonyl compound bearing a chiral center as an input for the condensation with α-isocyanoacetates may lead to stereoinduction and preferred formation of one stereoisomer over the others. No systematic study on the potential of this approach has been so far reported, only a few examples being known in literature. For example, the Cu_2O-catalyzed

Scheme 71



reaction of highly enolizable (*S*)-3-fluoro-1-(4-methylpheny1)-sulfinylacetone **308** with methyl isocyanoacetate gave **309** as a mixture of four diastereomers. The major isomer was isolated in an optically pure form by flash chromatography and used for the synthesis of enantiopure monofluoro analog of threonine **310** (Scheme 75).[186]

The reaction of chiral aldehyde **311** with *tert*-butyl isocyanoacetate **123** was used in a recent synthesis of manzacidin B **314**, a natural compound isolated from the Okinawan sponge *Hymeniacidon* sp. (Scheme 76). Only two of four possible oxazoline stereoisomers, **312** and **313**, were obtained in a 7:1 ratio, both with *trans* configuration.[187]

The reaction of **216** with protected optically pure glyceraldehyde **256** performed in the presence of $PdCl_2$ and Et_3N gave also only two diastereomers out of the four possible. Their configurations were established upon conversion to the known 2-amino-2-deoxy-D-arabinose **320** and 2-deoxy-D-ribose **319** derivatives and comparison with authentic samples. In this case, however, another pattern of selectivity was observed, featuring complete facial selectivity of the attack on the aldehyde carbonyl group, so that both diastereomers had the same configuration at the C3 atom (Scheme 77).[188]

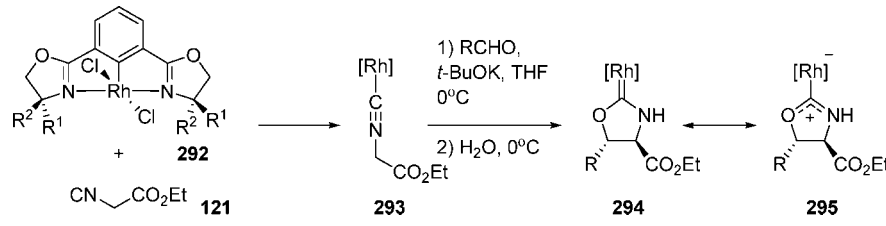
The different selectivity pattern of reactions of **311** and **256** can most likely be attributed to the difference in steric hindrance of the aldehydes, which is usually responsible for the observed *cis*/*trans* ratio, and the difference in facial stereochemical discrimination of the carbonyl groups. The factor is responsible for the observed 3-(*R*)/3-(*S*) ratio, according to numeration given in Scheme 77. For double stereodifferentiation effect in reactions involving a chiral aldehyde and a chiral catalyst, see section 4.7.2.

5. Reactions with Imines: Imidazoline Formation

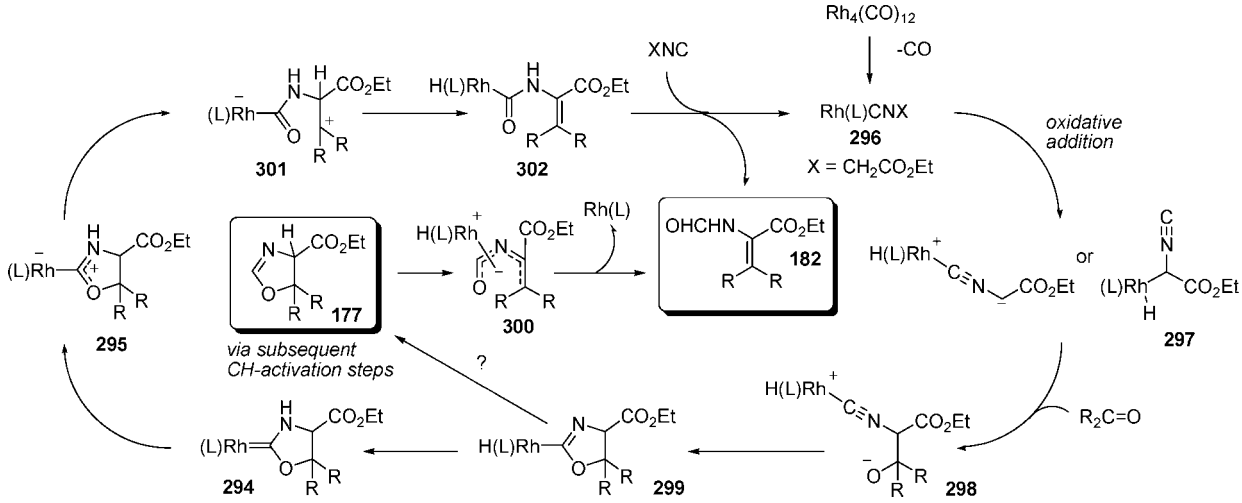
The reaction of ethyl isocyanoacetate with imines was first described by Schöllkopf et al. in 1977, is similar to that for aldehydes and ketones in many ways, and represents a convenient method for imidazoline preparation. In general, reactions are usually base- or metal-catalyzed and in many cases proceed in a quantitative yield. Reaction with aliphatic imines **321** proceeds even without addition of a base in an excellent yield; however, traces of an amine in the starting substrate may act as the base (Scheme 78).[189]

As might be expected, transition metal catalysts can greatly enhance reactivity of the substrate via metal coordination to the isocyano group. In 1996 Hayashi reported the use of

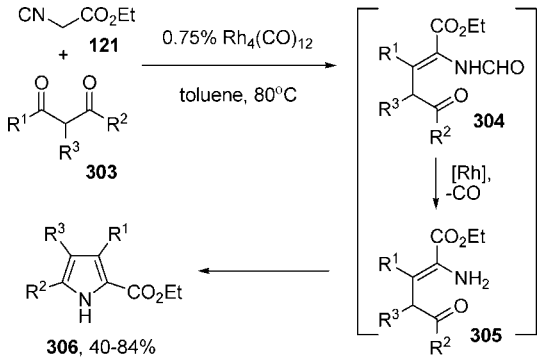
Scheme 70



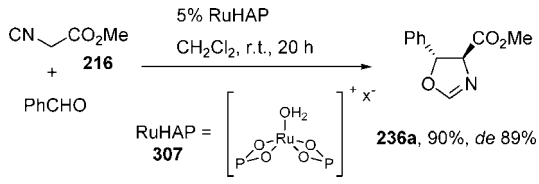
Scheme 72



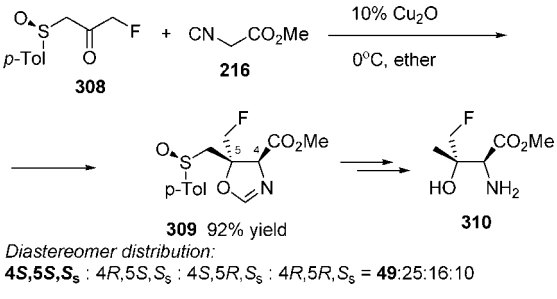
Scheme 73



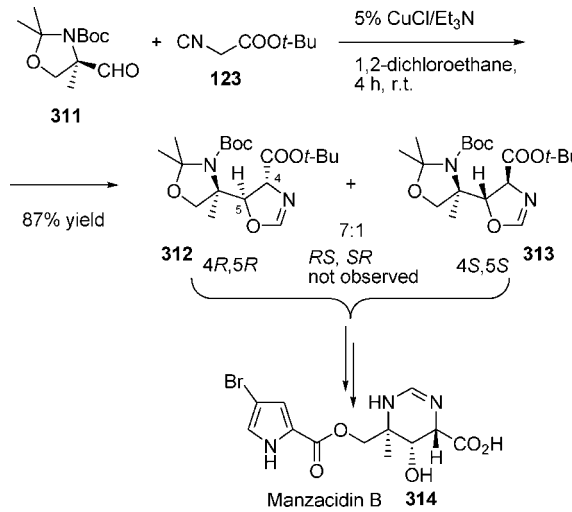
Scheme 74



Scheme 75



Scheme 76



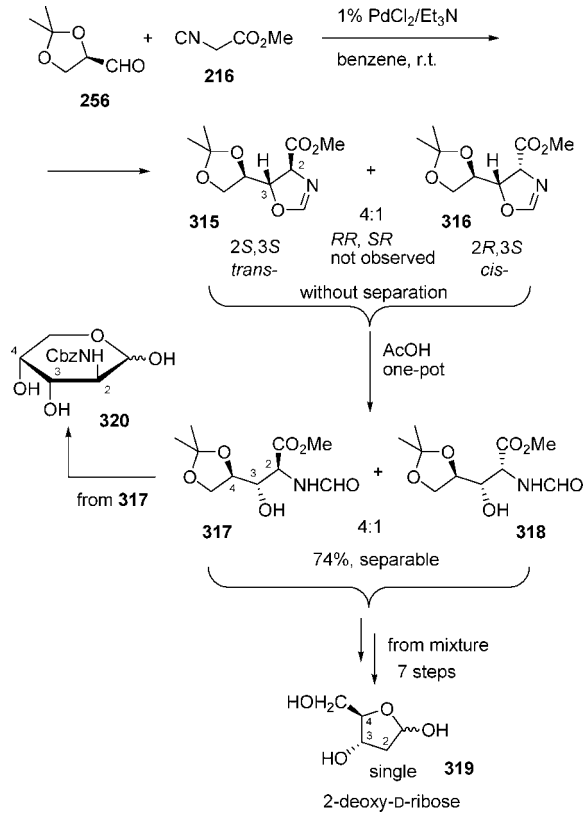
several Cu, Ag, Au, Pd, Ni, and Rh complexes in the base-free reaction of several *N*-sulfonylaldimines **323** with methyl isocyanoacetate.[190] Less electrophilic imines derived from aromatic aldehydes and anilines or $Ph_2P(O)NH_2$ were unreactive under the conditions reported. In these experiments, $AuCl(CNCy)_2$ demonstrated the best diastereoselectivity, furnishing *cis* isomers **324** in high de despite the fact that *trans* isomers are more thermodynamically stable. Correspondingly, *trans* isomers **325** can be obtained from *cis* isomers **324** by epimerization in the presence of Et_3N in high de (Scheme 79).

An interesting peculiarity of the metal-catalyzed reaction of isocyanoacetates with imines is that configuration of the major isomer (*trans* or *cis*) can be dramatically dependent on the catalyst choice. Thus, in 1997 Lin reported highly efficient *trans*-imidazoline synthesis using $RuH_2(PPh_3)_4$ catalyst. $IrH_5(i\text{-}Pr_3P)_2$, $FeH_2(dppe)_2$, and some simple palladium complexes also exhibited *trans* selectivity in catalysis, but less efficiently than ruthenium (Scheme 80).[191]

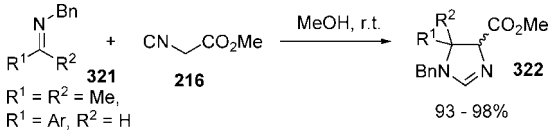
The catalytic cycle proposed for this reaction is similar to that described above for the aldol reaction but involves a C−H activation step (a similar aldol reaction of nitriles has been reported).[192] Thus, the starting isocyanoacetate is supposed to give complex **326**, which undergoes intramolecular oxidative addition or C−H insertion to give intermediate **327**. A subsequent aldol-type reaction with imine and cyclization yields the final imidazoline **324** (Scheme 81).

Recently, the reaction catalyzed by different [PCP], [SCS], [SeCSe], and [NCN] pincer palladium complexes has been reported.[193] All the complexes studied showed excellent catalytic ability but different diastereoselectivity depending on the ligand. Thus, electron-deficient phosphine complex **330** displayed optimal *cis* selectivity, while electron-rich selenide complexes **331** showed a reversal of selectivity toward the *trans* isomer (Scheme 82). The [SCS] and [NCN] complexes also exhibited *trans* selectivity but in lower de. These differences in stereodirecting performance may be

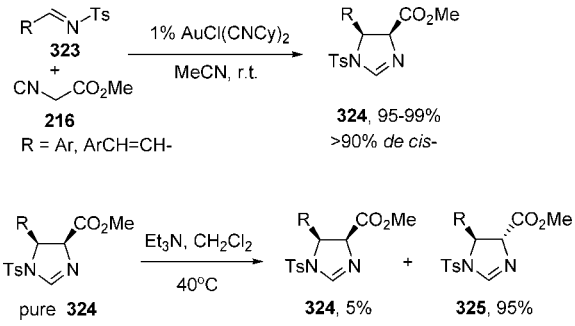
Scheme 77



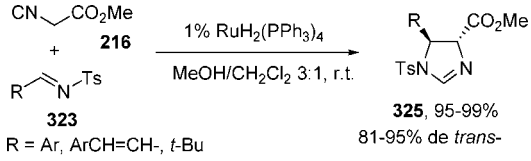
Scheme 78



Scheme 79

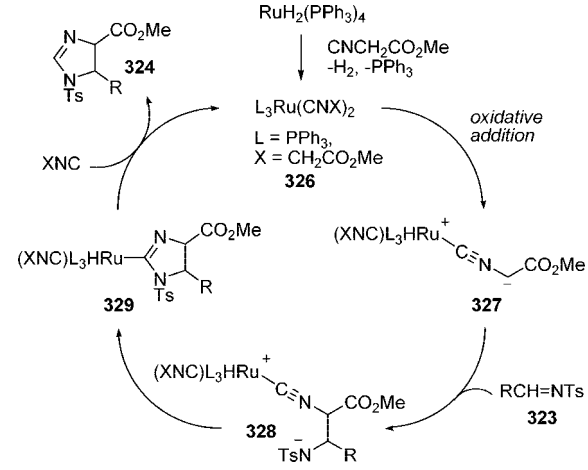


Scheme 80

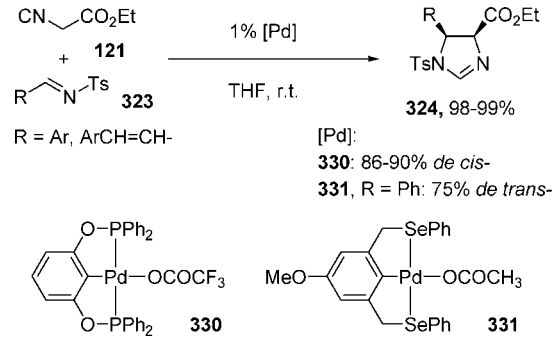


explained by their different behavior in the catalytic cycle rather than by electronic properties of the ligand. It was shown that [SCS] and [NCN] pincer Pd complexes can undergo insertion of an isocyanide into the C−Pd bond. In contrast, [PCP] complexes are stable toward insertion (see section 4.7.3, Scheme 67).[175,178] Therefore, the species that actually enter the catalytic cycle are different in these cases, which apparently accounts for differences in diastereoselectivity.

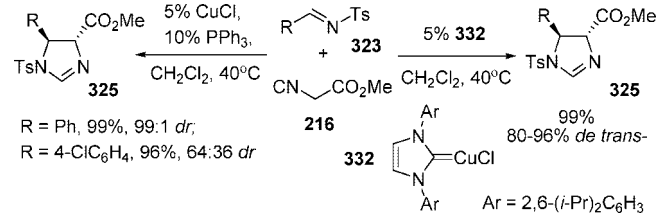
Scheme 81



Scheme 82



Scheme 83

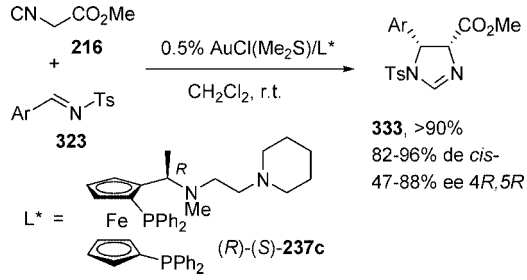


Copper catalysts would be especially attractive due to the low cost; however in the initial studies, highly selective catalysis was not observed. In 2006, it was reported by Kirchner that a de up to 99% could be achieved using the $CuCl/PPh_3$ catalyst, although the diastereoselectivity was highly dependent on the substrate. The copper carbene complex **332** proved to be more suitable, showing excellent *trans* selectivity in the reaction of methyl isocyanoacetate with *N*-tosylaldimines obtained from benzaldehydes pivalaldehyde (Scheme 83).[133]

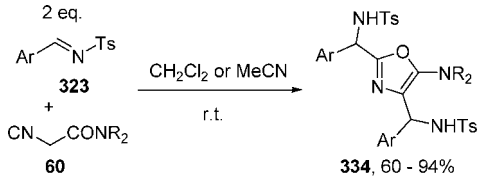
An enantioselective variant was accomplished using ferrocenylphosphine gold(I) complexes **237**, analogous to those used in the asymmetric aldol reaction (section 4.7.2). However, whereas ionic complexes $[AuL^*]BF_4$ formed in the $Au(CNCy)_2BF_4/L^*$ system exhibited better diastereo- and enantioselectivity in oxazoline formation, the use of the neutral complex $(AuCl)_3L^*_2$ formed from $AuCl(Me_2S)$ precursor proved to be more effective in the present reaction (Scheme 84).[194,195]

Until recently, metal-catalyzed reactions with imines were reported on electrophilic *N*-sulfonylimines **323** only. Imines bearing an aryl substituent at the nitrogen were considered to be not reactive. Metal-catalyzed reaction of simple

Scheme 84



Scheme 85



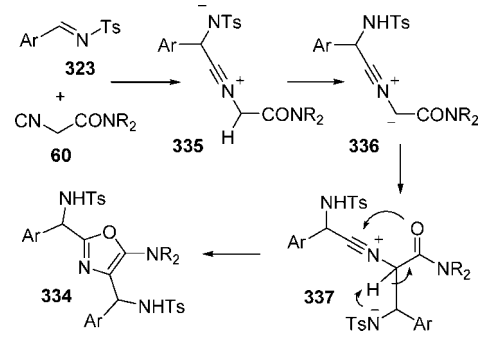
aliphatic imines was not investigated either, although, the corresponding noncatalytic variant of the reaction was described by Schöllkopf long before, as early as 1977. As can be realized from recent works reported by Orru et al. (see section 10.3.3), the metal-catalyzed reaction with imines is indeed not limited in scope only to highly electrophilic tosyl imines. Thus, AgOAc was shown to be a very effective catalyst for this reaction and a wide range of alkyl imines is applicable. It may be concluded that both electron-deficient and electron-rich imines are suitable substrates for the reaction. While in the former case they apparently do not need any further activation for nucleophilic attack, in the second case, activation by protonation (in a protic solvent) may be essential. In this respect, imines bearing an aromatic substituent at nitrogen are less reactive.

Attempts to prepare imidazolines from isocyanoacetamides **60** have led to the observation of completely different chemistry. It was found that isocyanoacetamides react with *N*-sulfonylimines **323** under neutral conditions without using an additive, a base, or another catalyst to give 2,4,5-trisubstituted oxazoles **334** in good yields (Scheme 85). In this reaction, 2 mol of an *N*-sulfonylimine per mole of isocyanide is employed. Substrates bearing electron donor substituents at the aromatic ring are less reactive.[196]

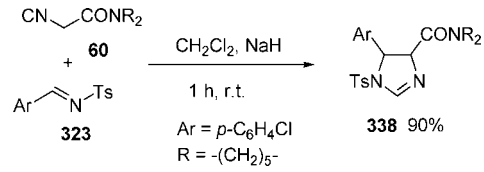
A detailed study revealed that the key step in the mechanism of this transformation is a nucleophilic attack of the isocyano group on the electrophilic C═N bond to generate intermediate **335**. When methyl isocyanoacetate or tosylmethyl isocyanide were used, no reaction took place under the same conditions. This is attributed to the reduced nucleophilicity of the isocyano carbon atom due to the strong electron-withdrawing effect of the CO_2R or tosyl group in comparison to the $CONR_2$ group (Scheme 86). It should be noted here, that under suitable conditions a similar nucleophilic attack of the isocyano group on activated C═O and C═N bonds also occurs with subsequent cyclization to form an oxazole ring; the corresponding reactions are described in sections 10.3 and 10.4.

The formation of imidazolines can occur competitively in the presence of a metal catalyst. Finally, oxazole formation can be completely avoided in favor of imidazoline **338** under strongly basic conditions (Scheme 87).

Scheme 86



Scheme 87



6. Reaction with Acylating Agents

In this section, we will discuss reactions of various acylating agents with isocyanoacetates and isocyanoacetamides. All reactions can be rationalized by one of the two pathways (routes 1 and 2) schematically outlined in Figure 7. Reactions with several types of acylating agents will be considered in this section.

6.1. Reaction with Acylating Agents of Type RC(═O)X: Synthesis of Oxazoles

It is well-known that acyl chlorides react with isocyanides to afford the corresponding α-addition products, the acyl imidoyl chlorides, also known as the Nef reaction. With isocyanoacetate, the reaction proceeds smoothly with aliphatic acyl chlorides to give **339**,[197,198] but aromatic acyl chlorides may stay unreactive even at elevated temperature.[198] Only electron-deficient aromatic acyl chlorides react smoothly. This is ascribed to the reduced nucleophilicity of the isocyano group. Imidoyl chlorides **339** are obtained in high yield and can be transformed into 2,5-disubstituted oxazoles **341** without purification upon addition on Et_3N (Scheme 88).[198,199] The generally accepted mechanism of such a cyclization involves formation of nitrilium ylides **340**. When this reaction was performed in the presence of methyl acrylate, the corresponding product of 1,3-dipolar addition was not observed, which means that the cyclization to **341** could be much faster, but in another similar reaction, trapping of such an intermediate was possible (see section 7). Formation of nitrilium ylides by nucleophilic attack of an isocyano group onto an electrophile in the presence of a base is a typical process in isocyanoacetate chemistry, and similar mechanistic elements are also found in many other reactions throughout

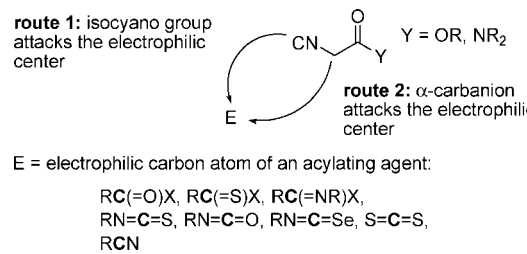
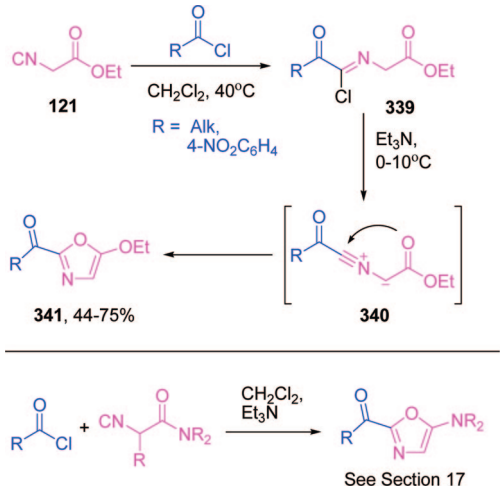
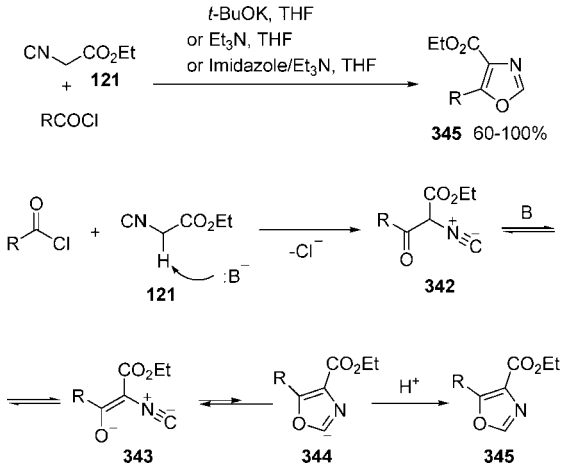


Figure 7.

Scheme 88



Scheme 89



the review (sections 7 and 10). Very recently, reaction with acyl chlorides was applied to α-isocyanoacetamides, see section 17 for discussion.

Another pathway involves the attack of the α-anion to the acylating agent. The initial attack of the α-carbon atom forms an unstable intermediate **342**, which is cyclized spontaneously to 4,5-disubstituted oxazole **345** as shown in Scheme 89. This chemistry is known as Schöllkopf oxazole synthesis and is described below in full detail together with known modifications. This reaction was reported for the first time in 1971 by Schöllkopf, who studied reactions of various metalated isocyanides with acyl chlorides, esters, and amides as electrophiles.[200,201] Shortly after that, this reaction was independently reported by Matsumoto et al, who used amine bases (see below).[202] The mechanism of this transformation has not been studied in detail, but it most likely involves an attack of the isocyanoacetate enolate anion to an electrophilic carbon atom of an acylating agent. Generally, oxazoles **345** are obtained in good to high yield by this method (Scheme 89).

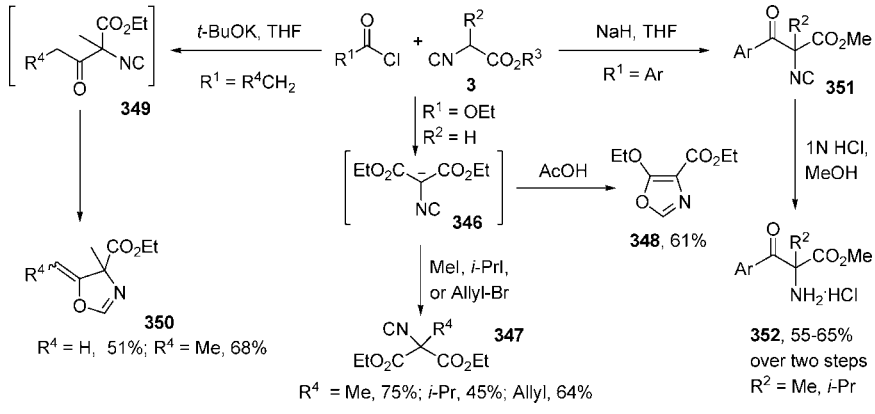
Metalated isocyanoacetates are able to react smoothly only with active acylating agents such as acyl chlorides. Due to the relatively high stability and low reactivity of the enolate anion of isocyanoacetate, this species does not react with esters and amides (however, less CH-acidic isocyanides do react, for exampel, MeNC). To generate the isocyanoacetate enolates, Schöllkopf used strong metallic bases such as *t*-BuOK, but this method required 2 equiv of both an isocyanide and a base to achieve a good yield of an oxazole. When the reagents were used in a 1:1:1 ratio, the reaction was accompanied by several side processes.

The ease of the cyclization of **342** is ascribed to the high CH acidity of the intermediate. In the reaction of ethyl chloroformate, it was possible to capture the α-isocyanomalonic ester enolate **346** by an alkyl halide under reflux conditions to give esters **347** as shown in Scheme 90. This supports the idea that the equilibrium between **343** and **344** is shifted to the uncyclized anion **343** unless the reaction mixture is quenched by an acid. In contrast, quenching by AcOH yielded the corresponding oxazole **348** in 61% yield. Attempts to capture anion **343** (R = Alk) have not been reported.

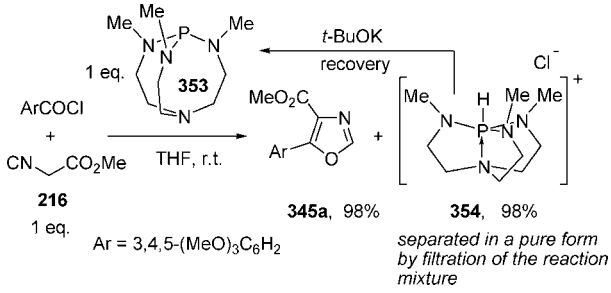
Matsumoto used organic bases to synthesize oxazoles, and this method can be considered advantageous because it does not require the excess of an isocyanoacetate and affords oxazoles **345** in a good yield.[202−205] Success of this reaction is presumably due to equilibrium formation of the enolate species rather than stoichiometric as in Schollköpf's procedure. Matsumoto used Et_3N in reactions with acyl chlorides and DBU for acid anhydrides.

α-Substituted isocyanoacetates **3** react with acylating agents to give similar initial products of C acylation, **349** or **351**; however they are unable to form an oxazole aromatic ring and their fate depends on the nature of the acylating agent used (Scheme 90). In the case of an α-hydrogen atom containing substrate, the intermediate **349** suffers enolization and cyclization to give oxazolines **350** containing an *exo*-C=C double bond.[201] If an aromatic substrate is used, C-acylation product **351** does not enter any subsequent

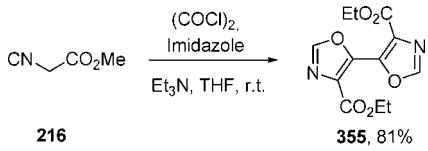
Scheme 90



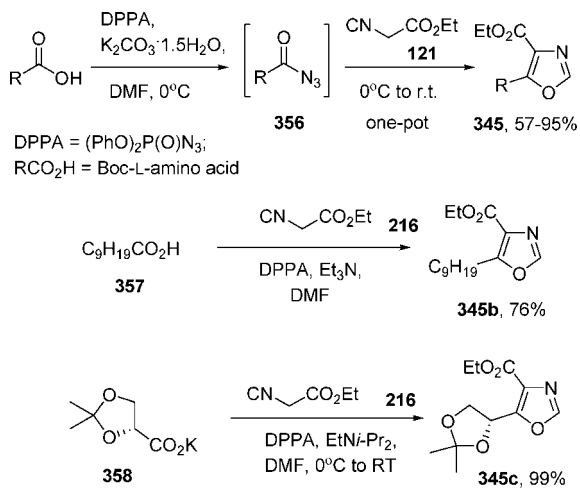
Scheme 91



Scheme 92



Scheme 93



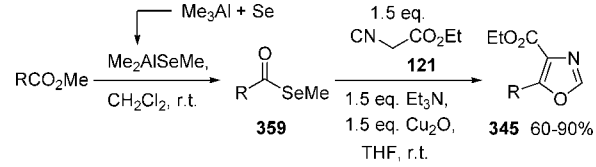
transformation and can be isolated successfully and used for synthesis of α-acyl-α-amino acids **352**.[202]

In 1994, Verkade et al. revealed a highly efficient method for the conversion of an acyl chloride or anhydride and methyl isocyanoacetate into oxazole **345a** by using a nonionic superbase **353** (2,8,9-trimethyl-2,5,8,9-tetraaza-1-phosphabicyclo[3.3.3]undecane). Outstanding results were demonstrated for aromatic substrates (Scheme 91); however its applicability for aliphatic substrates has not been investigated. Nevertheless, the method deserves attention due to the clean and complete conversion of starting materials and the ability to recover the superbase **353** almost quantitatively by a simple procedure (from **354**).[206]

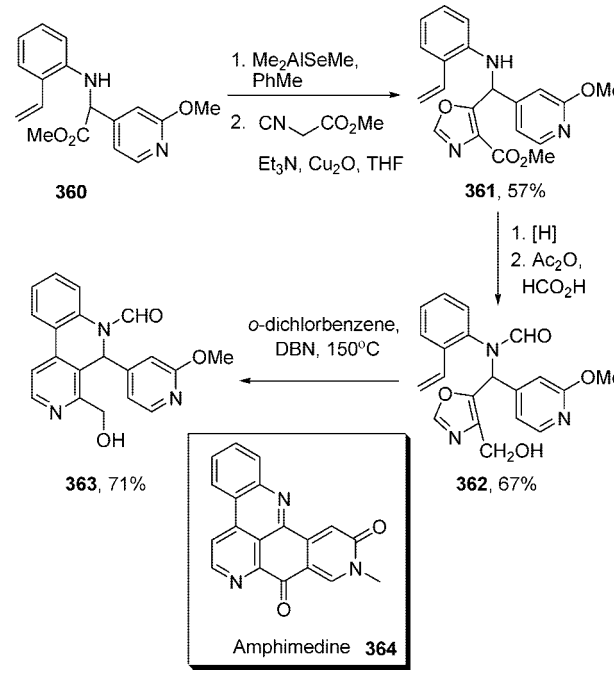
Some other acylating agents next to acyl chlorides can be used in reactions with isocyanoacetates, for example, carboxylic acid anhydrides and acylimidazoles; the latter are synthesized *in situ* using the reaction of acyl chloride with a stoichiometric amount of imidazole. The method is also useful for synthesis of bisoxazoles from dicarboxylic acid chlorides; for example, **355** was synthesized from oxalyl chloride in high yield (Scheme 92).[207]

Several modifications are based on the *in situ* activation of free carboxylic acids or their salts. Diphenyl phosphoryl azide (DPPA) is the most popular activator so far (Scheme 93).[208−210] This method has some advantages over those previously described. Thus, the direct use of a carboxylic acid is possible, which eliminates the acyl chloride preparation step. More importantly, this method can be efficiently applied to aliphatic acids, including chiral ones. A few examples are shown in Scheme 93. In this way, oxazoles **345**,[211] **345b**,[212] and **345c**[213] were successfully prepared. Oxazole syntheses based on acylation of isocyanoacetate using other methods of carboxylic acid activation have not been described.

Scheme 94



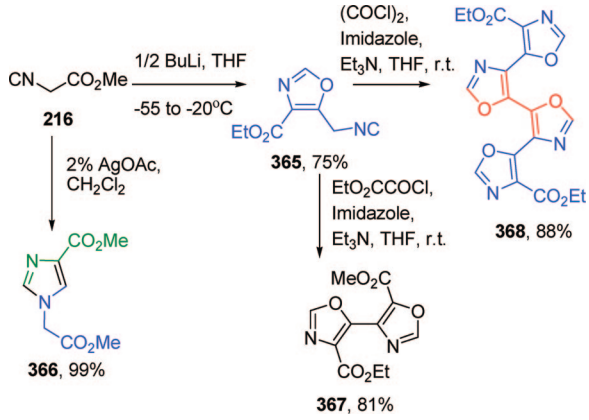
Scheme 95



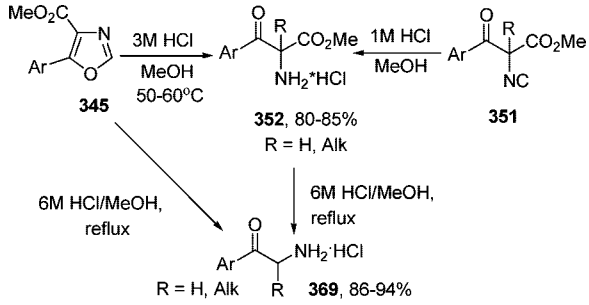
An interesting modification was reported in 1980 by Kozikowski, which consists of the use of selenoesters as acylating agents in a combination with a soft Lewis acid (Scheme 94). Thus, various methyl selenoesters **359** react with isocyanoacetates in the presence of 1.5 equiv of Cu_2O and triethylamine. The role of Cu_2O is to activate a selenoester **359** toward nucleophilic attack, while triethylamine is responsible for generating the enolate anion of **121**.[214,215]

On the other hand, Cu_2O can also coordinate to the isocyano group facilitating proton abstraction from the α-position, a well-known fact, see section 4.7. The starting selenoesters are easily prepared in high yield from carboxylic esters and the $Me_2AlSeMe$ reagent at room temperature.[215] Due to this, this modification in question can be especially useful in cases when other carboxylic acid derivatives are not easily accessible or when mild reaction conditions are required. For example, this methodology was used in an attempt to access the alkaloid amphimedine, **364**, by Weinreb et al. (Scheme 95). The authors prepared ester **360**, which should be hydrolyzed into an acid that could then be activated and used in oxazole synthesis. But the corresponding acid is decarboxylated rapidly and quantitatively, so the authors achieved only oxazole **361** in good overall yield employing selenol esters. Another interesting feature of this synthesis

Scheme 96



Scheme 97



is application of this oxazole in an intramolecular pyridine core construction by the Kondrat'eva method. Since the oxazole ester **361** is electron-deficient, it is inactive in this intramolecular Diels−Alder reaction (at least with donor alkenes, as is the case of **361**). However, the required transformation was successfully accomplished using alcohol **362** and yielded pyridine **363** in a good overall yield. In the end, amphimedine, **364**, could not be synthesized because the next steps of the synthesis failed.[216] More recently, Zhu has developed a number of versatile multicomponent reactions of isocyanoacetates employing a similar intramolecular Diels−Alder reaction to prepare various heterocyclic scaffolds, see section 10.3.2.

In the absence of any acylating agent but in the presence of 0.5 equiv of a strong base, methyl isocyanoacetate **216** condenses with itself to give isocyanomethyl oxazole **365**. A similar reaction carried out under different conditions to give *N*-substituted imidazole **366** will be discussed in the section 14.1. Oxazole **365** can also be applied in reactions with acylating agents to give bi- and quateroxazoles **367** and **368** (Scheme 96).[207]

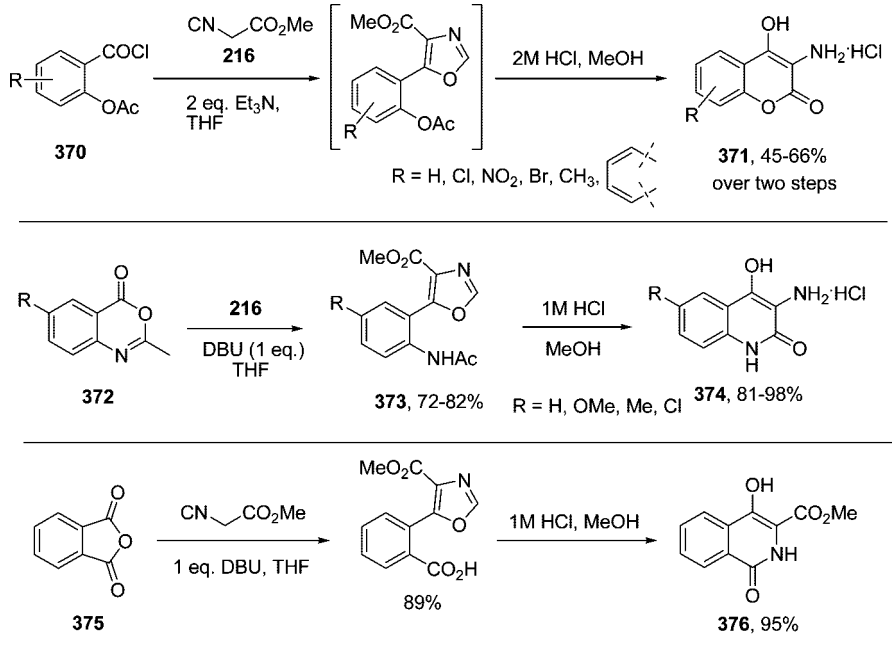
It is known that soft Lewis acids can coordinate to an isocyanide to enhance the acidity of the α-H atom. This property plays a key role in the catalytic oxazoline formation in reactions of isocyanoacetate with carbonyl compounds, which is a well established and efficient methodology. The analogous catalytic procedure for oxazole formation has not been developed. We envisage such a methodology to extend the scope of this reaction and make it even more efficient.

Oxazoles **345** or isocyano esters **351** prepared using the acylation of isocyanoacetates can be used for subsequent modification and synthesis of valuable synthetic products. Thus, **345** and **351** hydrolyzed in acidic media to afford α-keto-α-amino acids **352** or α-amino ketones **369** upon simultaneous decarboxylation (Scheme 97).[207]

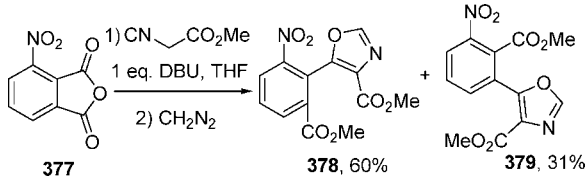
Matsumoto et al. developed a synthesis of various cumarine and quinoline heterocyclic systems by reaction of isocyanoacetates with acylating agents. Thus, *o*-acetoxybenzoyl chlorides **370**, 4-oxo-4*H*-3,1-benzoxazines **372**, and phthalic anhydride **375** in the reaction with isocyanoacetates gave 3-amino-4-hydroxycoumarines **371**,[217] 3-amino-4-hydroxy-2-oxo-1,2-dihydroquinoline **374**,[218] and 1,2-dihydro-1-oxoisoquinoline **376**[219] derivatives in good overall yields (Scheme 98).

When substituted phthalic anhydrides were used, two oxazole regioisomers were obtained in a good combined yield but usually in almost equal quantities; examples of complete regioselectivity are rare. For example, 3-nitrophthalic anhydride **377** yields a 2:1 mixture of oxazoles **378** and **379**. The regioselectivity in this case is governed by two major factors: the difference in electrophilicity between the two carboxyl groups and the difference in their acidity as a factor defining the better leaving group (Scheme 99). This is associated with steric rather than electronic factors.[220]

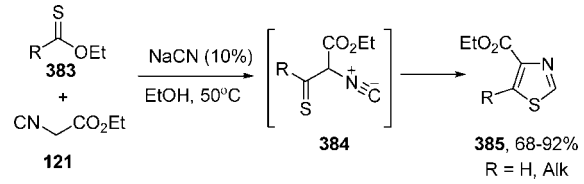
Scheme 98



Scheme 99



Scheme 100



Isocyanoacetamides have not been systematically investigated in base-catalyzed reaction with acyl chlorides, but according to one study they should produce oxazoles as well.[41]

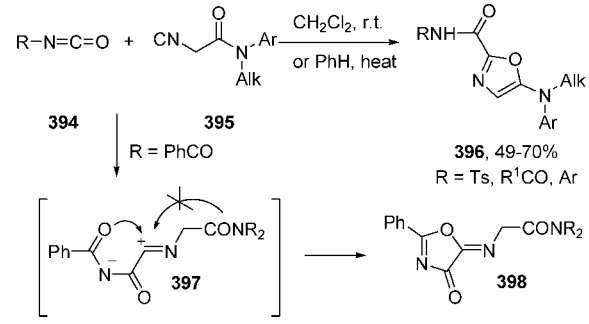
6.2. Reactions with Thionoesters RC(═S)OEt: Synthesis of Thiazoles

Aliphatic thionoesters **383** exothermically react with ethyl isocyanoacetate **121** in the presence of 10% NaCN to afford thiazole derivatives **385** (Scheme 100). Aromatic thionoesters are less susceptible; for example, PhC(S)OEt gives only 22% yield of the corresponding thiazole. Reaction proceeds via an acyclic intermediate **384** through a similar pathway as was described above for the oxazole synthesis.[221]

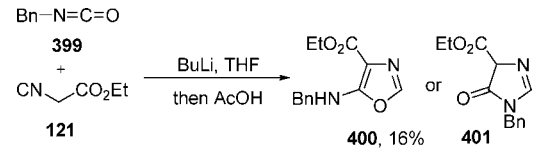
6.3. Reactions with Heterocumulenes, RN═C═X and CS_2: Synthesis of Five-Membered Heterocycles

Reactions of isocyanoacetate derivatives with heterocumulenes **386** have been scarcely investigated. Heterocumulenes **386** can react with isocyanoacetates according to two routes (Scheme 101). Nucleophilic attack of the isocyanide carbon of isocyanoacetate onto **386** (route 1) leads to the formation of the intermediates **387**, which finally afford 5-methoxyoxazole derivatives **388** via the dipolar species **387a**. In the presence of base, the reaction proceeds via route 2 with nucleophilic attack of **386** by the C enolate of the isocyanoacetate to produce the intermediate **389**, which then

Scheme 102



Scheme 103



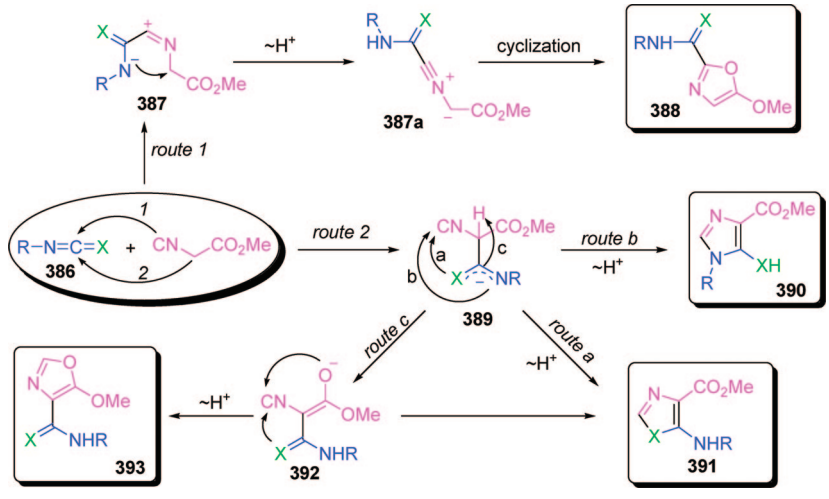
enters a number of subsequent transformations (routes a−c) to the final products **390**−**393**.[222]

Following route 1, electron-deficient isocyanates **394** react with tertiary *N*-alkyl-*N*-aryl isocyanoacetamides **395** under neutral conditions to afford 2-substituted oxazoles **396** (Scheme 102). The reaction proceeds via an initial nucleophilic attack of **394** by the isocyano carbon; the application of electron-deficient isocyanates (such as aryl, sulfonyl-, or acylisocyanates) seems crucial. Reaction with acylisocyanates was shown to give a variety of products. As an example, benzoyl isocyanate yields oxazolone **398** via intermediate **397**.[223]

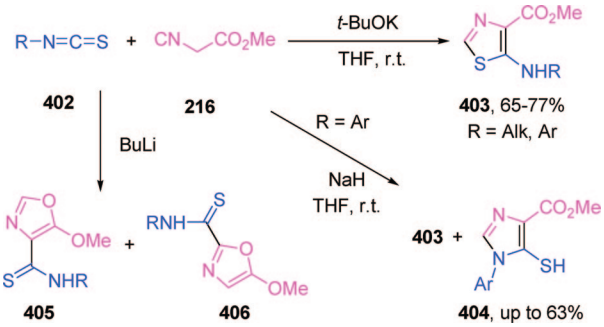
Reactions of isocyanoacetate **216** with isocyanates under basic conditions should proceed via route 2 (Scheme 101). Although such a base-catalyzed reaction was not systematically investigated, either 5-aminooxazoles **400** or imidazolones **401** can be expected as the products. For example, Solomon and Kaminski could obtain oxazole **400** in a reaction of ethyl isocyanoacetate with benzyl isocyanate **399** in 16% unoptimized yield (Scheme 103).[222]

Isothiocyanates also can undergo base-induced cyclizations with isocyanoacetates (Scheme 104). Thus, reaction of methyl isocyanoacetate **216** with various isothiocyanates **402** in the presence of potassium *tert*-butoxide affords thiazole derivatives **403** (according to route 2a, Scheme 101) in good

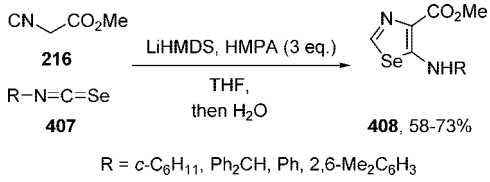
Scheme 101



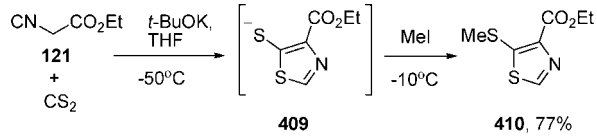
Scheme 104



Scheme 105



Scheme 106



yields.[224] If NaH was used as a base in the reaction of phenyl isothiocyanate (**402**, R = Ph) with isocyanoacetates, formation of imidazole byproduct **404** was observed (corresponding to route 2b).[224] Change of the base to *n*-BuLi drives the reaction to the other pathway with a mixture of oxazole derivatives **405** and **406** as the major outcome. Obviously, the nature of cation strongly influences the reaction pathway. This can be explained by the specific nature of a lithium enolate, which is less reactive and more prone to react at the oxygen center.[224] Although formation of imidazole byproduct in small amounts cannot be excluded, the method is rather selective and suitable for preparation of thiazoles of type **403**. Hovewer, a method for the synthesis of thiazoles **403** and imidazoles **404** as distinct regioisomeric products using a modular flow microreactor was recently developed by Ley et al.[225]

Selenazoles **408** can be prepared in good yields by the same method using isoselenocyanates **407** (Scheme 105). In this synthesis, strong lithium base (LiHMDS) and 3 equiv of hexamethylphosphoric triamide (HMPA) were used, probably with the aim to solvate the lithium cation and render the isocyanoacetate anion more reactive. Other bases have not been studied.[226]

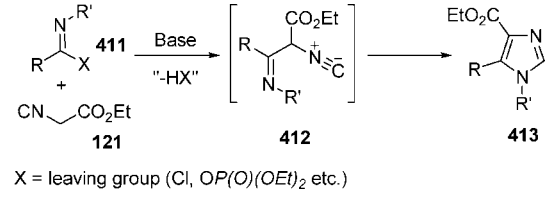
Carbon disulfide also can serve as electrophile in base-induced reactions with isocyanoacetate **121** to give thiazole derivative **410**. In this reaction, the intermediate thiazolethiolate **409** could be trapped with methyl iodide to give the corresponding product **410** (Scheme 106).[227]

6.4. Reactions with Acylating Agents of Type RC(=NR)X and RCN: Synthesis of Imidazoles

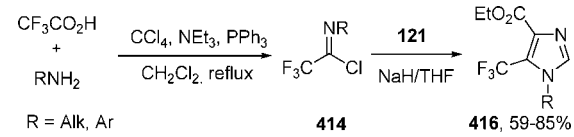
Reaction of acylating agents **411** with isocyanoacetates gives rise to imidazoles **413** via a similar mechanism as that described for oxazoles (Scheme 107).

Trifluoromethyl imidoyl chlorides are an easily accessible class of compounds (from trifluoroacetic acid, amine, carbon

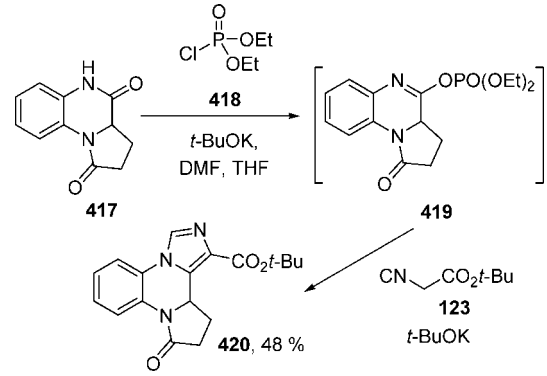
Scheme 107



Scheme 108



Scheme 109



tetrachloride, and PPh_3). Trifluoroimidoyl chlorides **414** were found to react with ethyl isocyanoacetate **121** to give N-substituted imidazoles **416** in good yield via cyclization of the intermediate product **414**. The method is convenient for the synthesis of N-substituted 5-CF_3-imidazoles, especially *N*-aryl derivatives, which are not easily accessible otherwise (Scheme 108).[228] An alternative strategy consists of activation of secondary amides leading to *in situ* formation of the required electrophilic agent, which enters the subsequent reaction with isocyanoacetate in one pot.

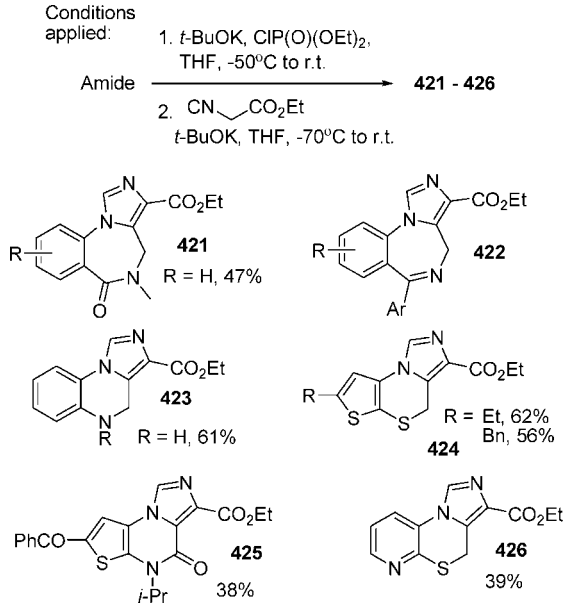
In situ formed imidoyl phosphonates **419**, prepared from starting amide **417** and diethyl chlorophosphate **418** under basic conditions, react with isocyanoacetate **123** and another equivalent of a base to afford the corresponding fused imidazoles **420** in moderate yield (Scheme 109).[229]

This approach was used by Erker et al. for the annulation of an imidazole core to different heterocyclic systems. The reaction opens a route to fused imidazole scaffolds, for example, **421**, **422**,[230–232] **423**,[229,233] **424**,[234,235] **425**,[236] or **426**,[237] as potential receptor ligands (Scheme 110). Reaction proceeds usually in moderate yield. Despite its potential for fused imidazole syntheses, no systematic study of this reaction on simple substrates has been reported to establish the optimal conditions and scope of the method.

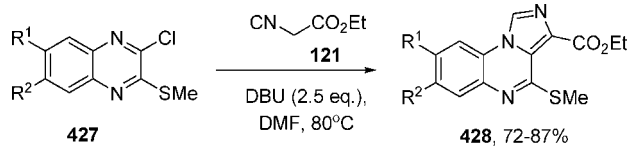
Recently annulation of an imidazole ring to substituted 3-chloro-2-(methylsulfanyl)quinoxalines **427** (Scheme 111) and 3-chloro-2-(methylsulfonyl)quinoxalines **429** has been reported (Scheme 112).[238] Such heterocyclic systems activated for nucleophiles can be regarded as imidoyl chloride analogs.

Reactions of 3-chloro-2-(methylsulfonyl)quinoxalines **429** are interesting because they have two electrophilic reaction sites and can annulate one or two imidazole cores. In practice, the annulation of one imidazole core can be accomplished

Scheme 110

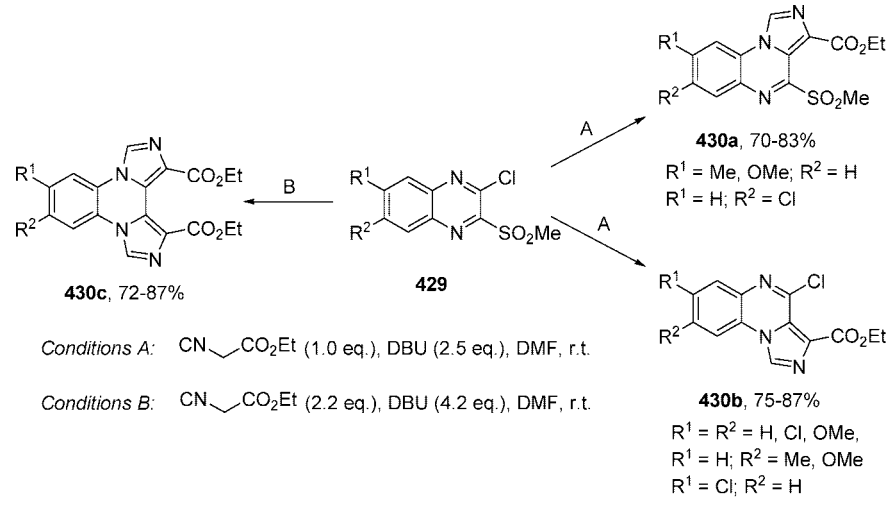


Scheme 111

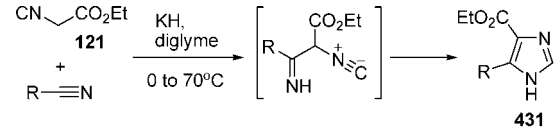


highly regioselectively either to the N=C−SO_2Me or to the N=C−Cl bond depending on the electronic effects of other substituents. Thus, in the case of unsubstituted or symmetrically substituted quinoxalines, the 2-(methylsulfonyl) group directs the annulation to afford compounds of type **430b**.[238] In the monosubstituted substrate, the direction of the attack of the ethyl isocyanoacetate anion is very effectively governed by the electronic effect of the substituent at the benzene ring, to deliver products of type **430a** or **430b** selectively. Double annulation to give **430c** is also possible when 2 equiv of isocyanoacetate is used. Although quinoxaline derivatives have been the only type of heterocycles studied in this reaction, this approach may be effective to synthesize various imidazole-containing heterocyclic scaffolds using appropriately substituted activated heterocycles of other types as well.[238]

Scheme 112



Scheme 113



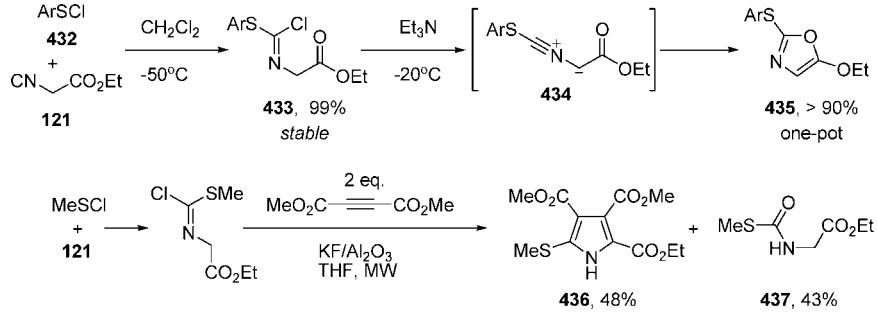
Nitriles can be also regarded as leaving group free acylating agents; however they are weak electrophiles, and if they are not sufficiently activated, reaction with the isocyanoacetate enolate anion does not occur. The reaction is possible only for nitriles activated by inductive or resonance effects of the diethoxyethyl or an aryl group, and the corresponding imidazoles **431** were obtained in good yields (Scheme 113).[239] The reaction strongly depends on the bases and solvents employed. Thus, the Li enolate is not reactive toward even activated nitriles due to strong binding of Li cation to oxygen. NaH and KH can be used, but their efficiency is highly depending on the solvent: good yields are obtained in diglyme but not in DMF or THF. Potassium hydride in diglyme is most effective providing reactive "naked" enolates. Other bases have not been investigated in this reaction.

7. Reactions with Sulfur Electrophiles

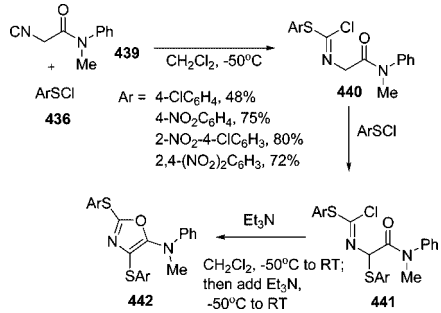
Since 1955, it has been known that sulfenyl chlorides exhibit high reactivity toward isocyanides and easily form primary α-addition products.[240] Application of isocyanoacetate derivatives instead of aliphatic isocyanides allows interesting reactivity profiles due to the multifunctional nature of the substrate. Most reactions discussed in this section were investigated by Marcaccini et al. in 1980s.

Reaction of ethyl isocyanoacetate **121** with arenesulfenyl chlorides **436** proceeds easily even at low temperature to give the corresponding α-addition products **437**, which can be isolated in quantitative yield but gives cyclization upon addition of triethylamine to yield oxazole derivatives **438** quantitatively (Scheme 114).[241a] The latter process involves formation of thiocyanate ylides **434**, which suffer 1,5-cyclozation to oxazole. Direct evidence for the formation of ylides like **434** was provided by trapping them with dimethyl acetonedicarboxylate in heterogeneous medium to yield

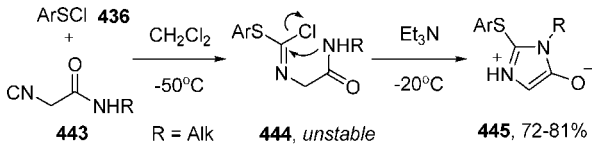
Scheme 114



Scheme 115



Scheme 116



pyrole **436** in moderate yield, along with methyl thioimidate **437**, which might result from hydrolysis of oxazole of type **435**.[241b]

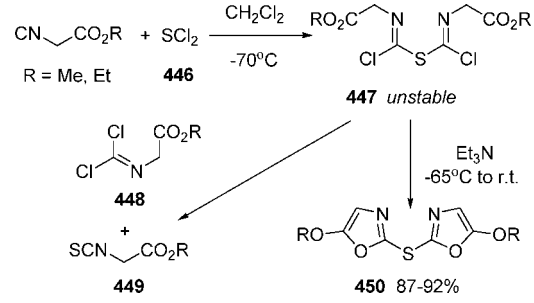
In contrast to isocyanoacetates, another interesting behavior was observed for aryl substituted tertiary isocyanoacetamides **439**.[242] Primary α-addition products **440** appeared to be more prone to electrophilic attack on the α-position and easily reacted with another equivalent of sulfenyl chloride **436** before cyclization. Sulfenylated intermediates **441** cyclized then to trisubstituted oxazoles **442** similarly as described for **438** (Scheme 115).

Even different behavior was observed for alkyl-substituted secondary isocyanoacetamides **443**. Primary α-addition products **444** are unstable and suffer smooth cyclization upon addition of triethylamine (Scheme 116); however a nucleophilic attack occurs in this case by the nitrogen rather than the oxygen to afford mesoionic 5-hydroxy imidazole derivatives **445** (as was confirmed by spectroscopic methods including X-ray analysis).[36]

Reaction of ethyl isocyanoacetate **121** with sulfur dichloride **446** proceeds at low temperature via double α-addition to the isocyano group. The initial product **447** is unstable and fragmentation at elevated temperatures gives **448** and **449**. Cyclization of **447** upon addition of triethylamine yields bis-oxazole **450** in high yield (Scheme 117).[243]

Attempts to prepare a similar bis-oxazole using S_2Cl_2 have led to the discovery of yet another reaction, which yielded thiazolo[5,4-*d*]thiazole **458** (confirmed by X-ray analysis). As usual, α-addition occurred initially to give the unstable intermediate **452**, which after fragmentation to isothiocyanate **453** and sulfocarboimidoyl chloride **454** and subsequent transformations of the latter in the presence of triethylamine

Scheme 117



yielded **458** in 52% yield. A plausible mechanism includes a number of unusual intermediates on the way to the final compound **458** as summarized in Scheme 118.[244]

Replacement of sulfenyl chlorides with sulfenyl thiocyanates **459** leads to even more interesting chemistry. Thus, the simple mixing of **459** with secondary isocyanoacetamides **460** at low temperature leads initially to formation of α-addition products **461**, which enter a series of transformations that finally afford 2,5-dihydro-1*H*-imidazole-2-thione derivatives **465** (confirmed by X-ray analysis).[245] In this transformation, a thiocyanato group plays the role of a leaving group, a nucleophile, and an electrophile! Nonenolizable cycloalkyl-based isocyanoacetamides **466** afforded the corresponding spiro compounds **467** in good yields (Scheme 119).[46] It is worth noting that α-methylene group is not involved in this transformation.

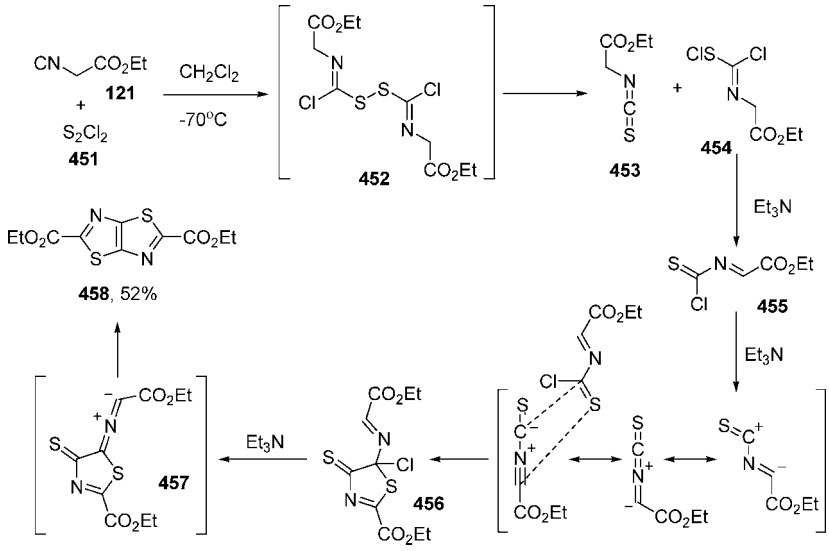
Isocyanoacetates react with sulfenyl thiocyanates **459** to give α-addition products **468**, which are supposed to be stable toward intermolecular cyclization but enter a series of transformations upon addition of triethylamine to yield 2-mercaptoimidazo[5,1-*b*][1,3,5]thiadiazine derivatives **471** (a possible mechanism is shown in Scheme 120).[246] Salts **471** can be transformed into a neutral form **472** in quantitative yield; subsequent reaction of **472** with diazomethane yields *S*-methyl ester **473** quantitatively.

Few examples of sulfenamide reactions are known.[247] Ethyl isocyanoacetate **121** in reaction with *N*-(alkylthio)-phtalimide **474** produces **475**, whereas isocyanoacetamide **476** gives a mixture of both α-addition product **479** and oxazole **480** (due to the enhanced nucleophilicity of amide oxygen). Compound **481** yields the corresponding oxazole **482** exclusively (Scheme 121). This fact supports that a nitrogen anion may act as a base abstracting a proton from **477** and favoring the cyclization.

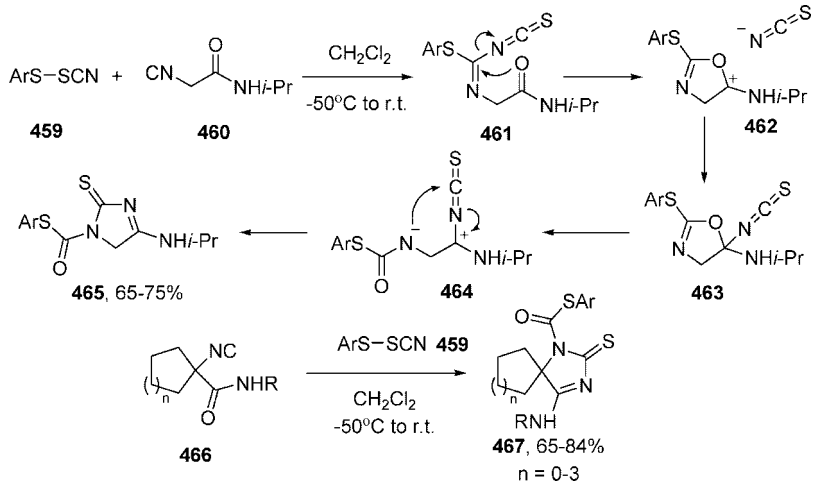
8. α-Isocyanoacetates as a Michael Donors

In 1970, Schöllkopf et al. observed for the first time the Michael addition of ethyl isocyanoacetate **121** to acrylates **483** and their derivatives. The reaction took place in ethanol

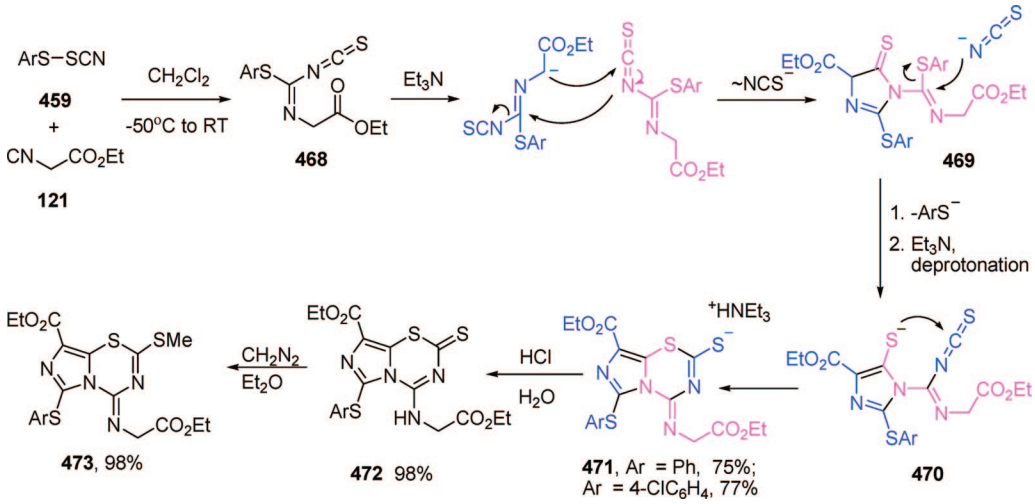
Scheme 118



Scheme 119



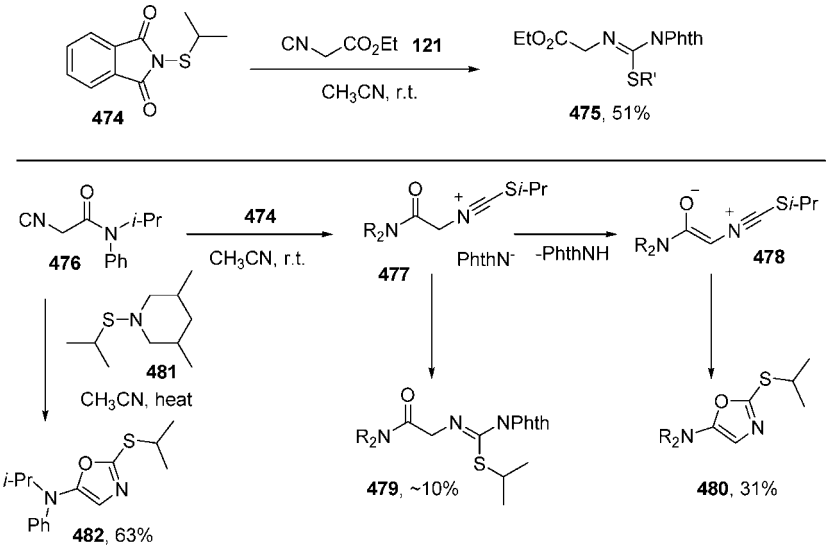
Scheme 120



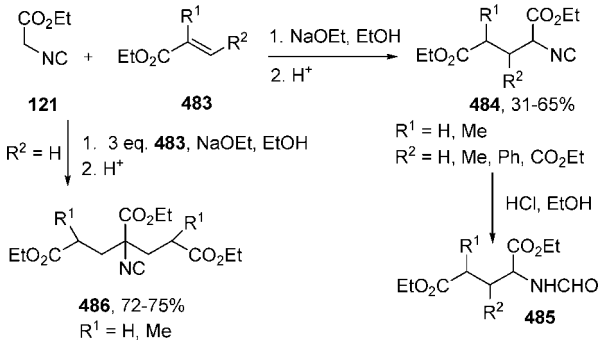
containing catalytic amounts of sodium ethoxide and led to formation of Michael adducts **484** in moderate yields. Formation of bis-adducts **486** is a serious issue and becomes the main process when isocyanoacetate **121** is treated with 3 equiv of acrylic ester **483** in the presence of the base. Derivatives **484** can be converted to glutamic acid derivatives **485** by acid hydrolysis (Scheme 122).[248]

Other activated olefins such as acrylonitriles[249] and α,β-unsaturated ketones[250] can be used as a Michael acceptors. Particularly reactive Michael components such as acryloni-

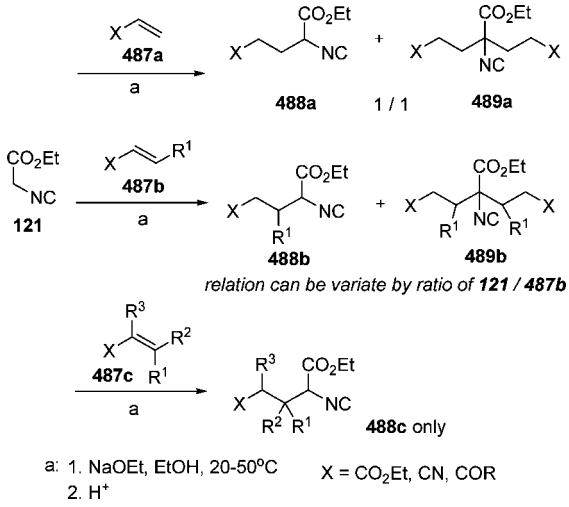
Scheme 121



Scheme 122



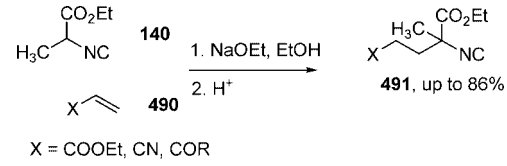
Scheme 123



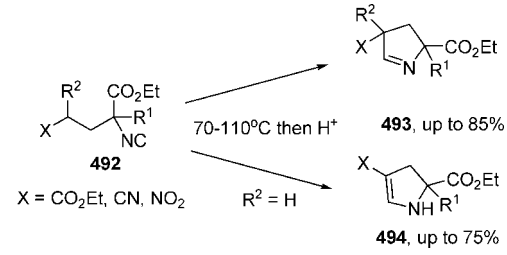
trile, ethyl acrylate, and α,β-unsaturated carbonyls **487a** gave mono- and bis-adducts in a ~1:1 ratio. Therefore, the method is not very convenient for the selective synthesis of mono- or di-Michael adducts **488a** and **489a**. β-Monosubstituted Michael acceptors **487b** can be selectively converted to mono- or bis-adducts **488b** and **489b**, respectively, by varying the molar ratio of the reactants. α,β-Disubstituted and β,β-disubstituted olefins **487c** and those stabilized by a phenyl group give only the monoadduct **488c** (Scheme 123).

Apparently, the more sterically hindered *tert*-butyl isocyanoacetate or the less acidic isocyanoacetamides could favor

Scheme 124



Scheme 125

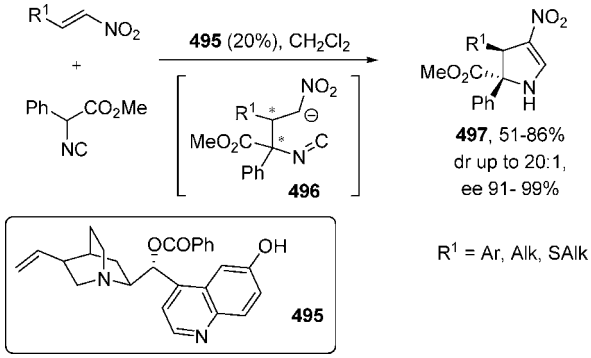


monoaddition, like monoalkylation of *tert*-butyl isocyanoacetate and isocyanoacetamides (section 3). For activated alkenes, with good leaving groups, such as nitroolefins, α,β-unsaturated sulfones, and sulfides, the initially formed Michael adducts spontaneously cyclize to form pyrroles as the single product (see section 9.1). α-Substituted isocyanoacetates, for example, **140**, react with all types of activated alkenes to form monoadducts **491** in good yields (Scheme 124).[249]

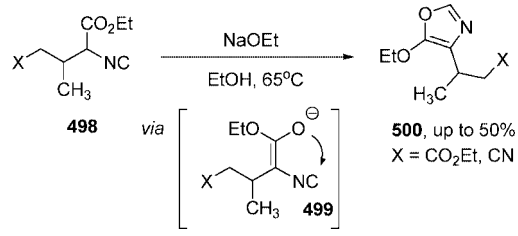
The combination of a Michael addition with a subsequent thermal cyclization via insertion of an isocyanide into the activated C−H bond leads to a variety of heterocyclic compounds. Thus, monoadducts of type **492**, which can be generated *in situ* or obtained after isolation, can be cyclized to 1- and 2-pyrrolines **493** or **494** by heating with sodium ethoxide at 70−110 °C, thanks to the stabilization of the generated carbanion α to the electron-withdrawing X group.[249−251] The cyclization also takes place efficiently in the presence of catalytic amounts of Cu_2O.[131] The position of the double bond (formation of 1- or 2-pyrrolines) is determined by the structure of the starting adduct. Thus, when $R^2 = H$, 2-pyrrolines **494** are formed; otherwise 1-pyrrolines **493** are the main products (Scheme 125).

Recently, Gong et. al developed an organocatalytic tandem Michael−CH insertion process (formal [3 + 2] cycloaddi-

Scheme 126



Scheme 127



tion) for the synthesis of dihydropyrroles in an asymmetric manner. The reaction of nitroolefins with α-aryl isocyanoacetates catalized by cinchona alkaloid **495** (20% mol.) yields chiral 2-pyrrolines **497**. High enantioselectivity (91−99% ee) and synthetically useful diastereoselectivity were observed for alkyl- and aryl-substituted nitroolefins. The best results (dr up to 20:1) were obtained with electron-deficient aryl substituents. The reaction runs through the formation of chiral Michael adducts **496** (Scheme 126).[252]

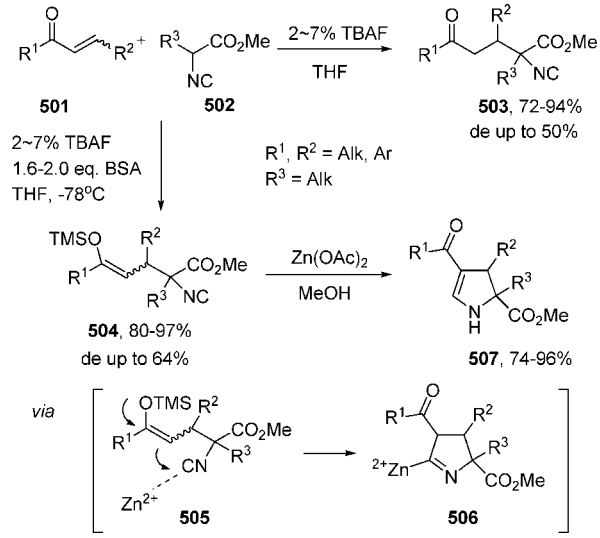
The *β*-substituted Michael adducts **498** containing an α-hydrogen atom undergo thermal cyclization under basic conditions via the ester enolate **499** to give 5-alkoxyoxazoles **500** bearing an ester group (X = COOEt)[250] or a cyano group (X = CN)[251] in moderate yields (Scheme 127).

In 1989, Ito et al. found that the Michael reaction of α-isocyanoesters **502** with α,*β*-unsaturated carbonyl compounds **501** can be efficiently promoted by a catalytic amount of tetrabutylammonium fluoride to produce α-isocyano-*δ*-ketoesters **503** in high yields. Next to this, they found a remarkable acceleration of the Michael reaction by employing *N*,*O*-bis(trimethylsilyl)acetamide (BSA) to give silyl enolates **504** under mild conditions.[253] Activation of the isocyanide group through coordination by a Lewis acid promotes different types of nucleophilic cyclizations. Thus, silylated Michael adducts **504** were cyclized successfully to pyrroline-2-carboxylic acids derivatives **507** using $Zn(OAc)_2$. The reaction runs via cyclization of complex **505** after coordination of Zn(II) to the isocyano group (Scheme 128).[254]

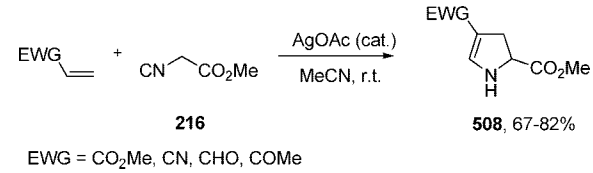
As another example, the Michael/cyclization reaction (formal [3 + 2] cycloaddition) of methyl isocyanoacetate **216** with activated alkenes catalyzed by silver acetate gives pyrrolines **508** in good yields. This Ag-catalyzed reaction proceeds smoothly with acrylates, acrylonitriles, α,*β*-unsaturated aldehydes, and ketones (Scheme 129).[255]

Very recently, Xu and Liu et al. disclosed that unsubstituted isocyanoacetates containing an activated CH_2 group can be involved in two successive Michael reactions to form cyclic products. Thus, it was found that isocyanoacetate **121** reacts with divinyl ketones **509**, under DBU catalysis, to afford 1-amino-cyclohexanecarboxylic acid derivatives **510**

Scheme 128



Scheme 129



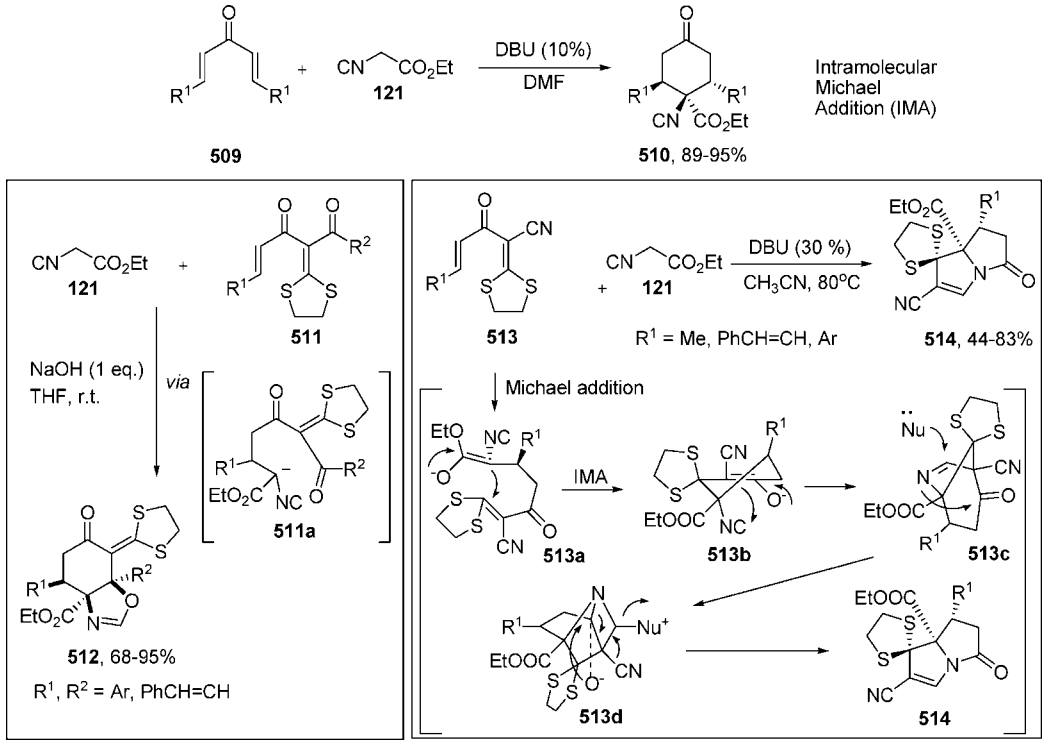
as a product of [5 + 1] annulation reaction. It should be noted that reaction proceeds in diastereoselective manner and only one diastereomer of double-Michael adduct **510** is formed (Scheme 130).[256]

Insertion of additional functional groups in the molecule of divinyl ketone opens broad possibilities for tandem Michael additions or heterocyclizations. Thus divenyl ketones **511** with a carbonyl group in the α-position can be involved in the Michael addition−intramolecular [3 + 2] isocyanide cycloaddition reaction to give fused oxazoles **512**. The reaction takes place in a highly diastereoselective manner and yields a single diastereomer of **512**.[257]

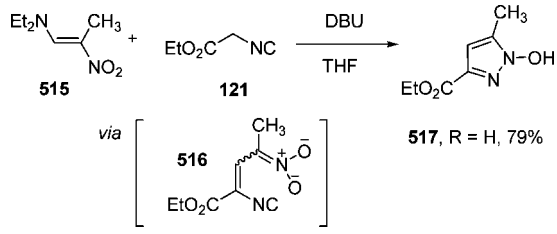
It has been found that α-cyano-divinylketones **513** and ethyl isocyanoacetate **121** undergoes tandem double-Michael addition/cyclization/acyl migration. The reaction afforded pyrrolizidine derivatives **514** in good yields with formation of one C−N and three C−C bonds in a regio- and diastereoselective manner. The overall process involves a Michael addition and intramolecular Michael addition (IMA) to provide intermediate **513b**, an intramolecular cyclization to form intermediate **513c**, and then a transannular attack of the imine nitrogen atom to the carbonyl atom in **513c**, followed by breaking of the C−C bond, to afford pyrrolizidines **514** (Scheme 130). This new strategy excels by the formation of one C−N and three C−C bonds in a regio- and diasetereoselective maner from the achiral starting materials. The method is useful for the synthesis of several pyrrolizidines from the corresponding 1,4-dien-3-ones of type **509**, **511**, or **513** (Scheme 130).[258]

An interesting cyclization was described by Ono et al. The reaction of 1-diethylamino-2-nitroalkenes **515** (containing a good leaving group in the *β*-position) with ethyl isocyanoacetate **121** in the presence of DBU at room temperature followed by quenching with HCl leads to 1-hydroxypyrazoles **517** in good yield (Scheme 131). The mechanism of this transformation is not entirely understood; however, it probably proceeds via the Michael adduct **516**.[259]

Scheme 130



Scheme 131



9. Reaction of Isocyanoacetate with Activated Alkenes and Alkynes: Synthesis of Pyrroles

Reaction of isocyanoacetates with activated alkenes followed by cyclization affords pyrrolines, as discussed above. When the alkenes are activated by an electron-withdrawing group that is also a leaving group, pyrroles are formed instead. The same aromatic heterocycles are also formed when using activated alkynes. Therefore, formation of a pyrrole ring by the reaction of isocyanoacetates with nitroolefins via a nucleophilic attack of an isocyanoacetate anion with subsequent cyclization is discussed in this section. Moreover, pyrrole syntheses by reaction of isocyanoacetate with other activated alkenes and particularly alkynes (the modern and perspective field) and some miscellaneous syntheses are discussed.

9.1. Barton−Zard Reaction

Generally, Barton−Zard pyrrole synthesis involves the reaction of isocyanoacetates with activated alkenes bearing a group prone to elimination. On the Barton−Zard pyrrole synthesis, a review[260] and a number of book chapters[261,262] covered the literature up to 2004. In this section, the Barton−Zard reaction is discussed in the context of the polyfunctionality of isocyanoacetates and includes the most recent publications up to the end of 2009.

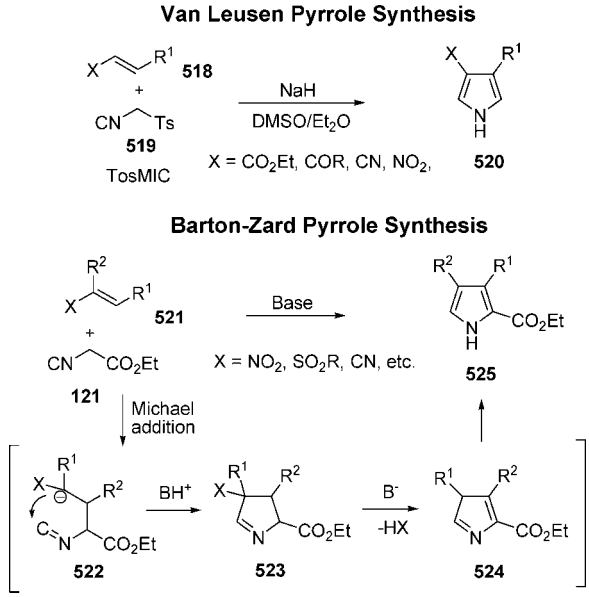
Van Leusen and co-workers demonstrated that α-acidic tosylmethylisocyanide (TosMIC) **519** reacts with Michael acceptors (nitroolefins, acrylic acid derivatives, etc.) in the presence of a non-nucleophilic base to produce pyrroles **518** with a broad variety of substituents.[263] The Barton−Zard (BZ) reaction is another efficient method for pyrrole synthesis based on the Michael addition of acidic α-isocyanoacetates to electron-deficient alkenes **521**, such as α,*β*-unsaturated nitroalkenes, sulfones, nitriles, and sulfides. The reaction provides 3,4-disubstituted-2-pyrrolecarboxylates **525**, and the mechanism most likely involves a base-induced formation of the isocyanoacetate anion followed by Michael addition to the alkene and subsequent cyclization of intermediate **522** to pyrroline **523** after protonation. Elimination of X from **523** led to 3*H*-pyrroles **524**, which after aromatization gave 1*H*-pyrrole derivatives **525** (Scheme 132).

9.1.1. Reaction of Isocyanoacetates with Activated Nitroolefins

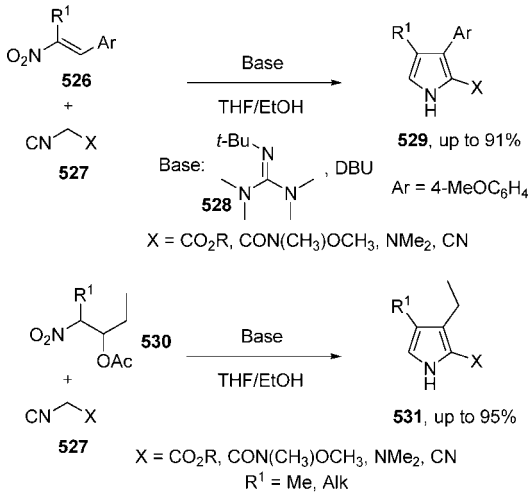
In 1985, Barton and Zard reported the base-catalyzed reaction of nitroalkenes with α-isocyanoacetate derivatives leading to pyrroles (Scheme 133).[264] The reaction is generally performed in THF or alcohols in presence of 1.5−3 equiv of nonionic strong bases such as guanidine derivative **528** or DBU. Potassium carbonate can be also used as a base for the BZ reaction with *β*-nitroacetoxy derivatives.[265] Recently the yields of the BZ reaction could be considerably improved by using MTBE as a solvent.[266]

Aliphatic nitroalkanes can be conveniently generated *in situ* from *β*-nitroacetoxy derivatives **530**. Pyrroles **531** with aliphatic substituents (R^1 = Alk) are generally obtained in excellent yields. The nature of the isocyanoacetate derivative **527** has no significant influence on the reaction. The transformation takes place efficiently with various isocyanoesters (Me, Et, *t*-Bu, Bn[267]), Weinreb isocyanoamides,[268] tertiary isocyanoacetamides, and isocyanonitriles.[269] Starting

Scheme 132



Scheme 133



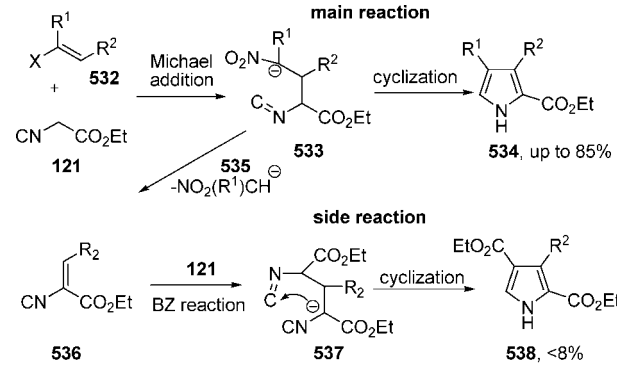
nitroolefins **526** and **530** are available by Henry reaction of a nitro compound with a carbonyl compound.[270]

In 1989, Ono et al. observed the formation of 2,4-dialkoxycarbonyl pyrroles **538** as byproducts (usually <10% yields) along with formation of the expected pyrroles **534**. A feasible pathway for the formation of **538** includes as the key step elimination of the nitroalkane anion **535** to afford isocyanoacrylate **536**, attack of which by anion of **121** gives the intermediate **537** which evolves to the final product via cyclization and HCN elimination (Scheme 134).[271] In this case, one isocyanide group acts as the leaving group, expelling cyanide; the driving force is formation of the aromatic pyrrole system.

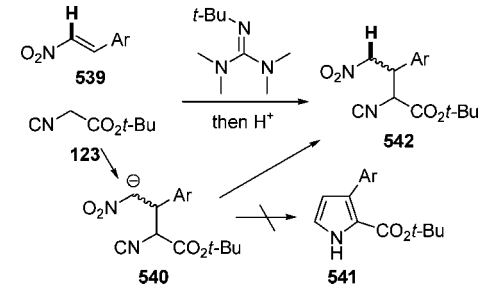
α-Unsubstituted nitroolefins **539** react with α-isocyanoacetate **123** under similar conditions giving a complex mixture of products in which none of the expected pyrroles **541** were found. The Michael adduct **542** could be isolated when the reaction was conducted at −70 °C and the mixture was neutralized at low temperature. In this case, the cyclization step is much slower due to the lower nucleophilicity of the primary nitronate anion **540**, and the expected 4-unsubstituted pyrrole **541** is not formed (Scheme 135).[264,270]

Generally, the reaction is very convenient for the synthesis of 2-pyrrolecarboxylates with various substituents at the 3-

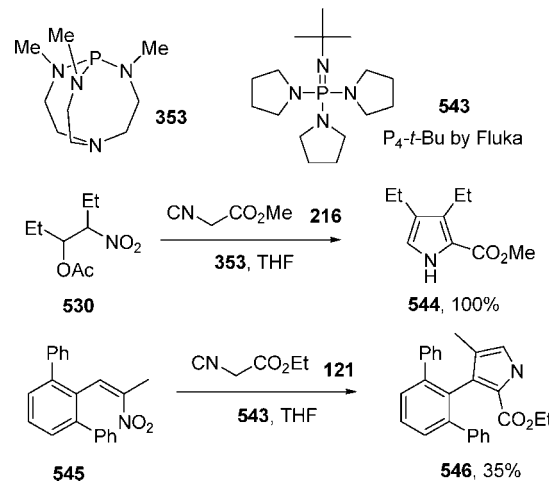
Scheme 134



Scheme 135



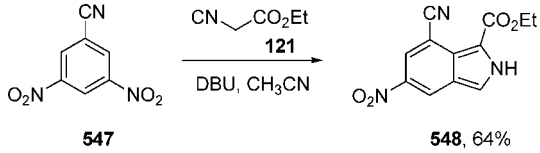
Scheme 136



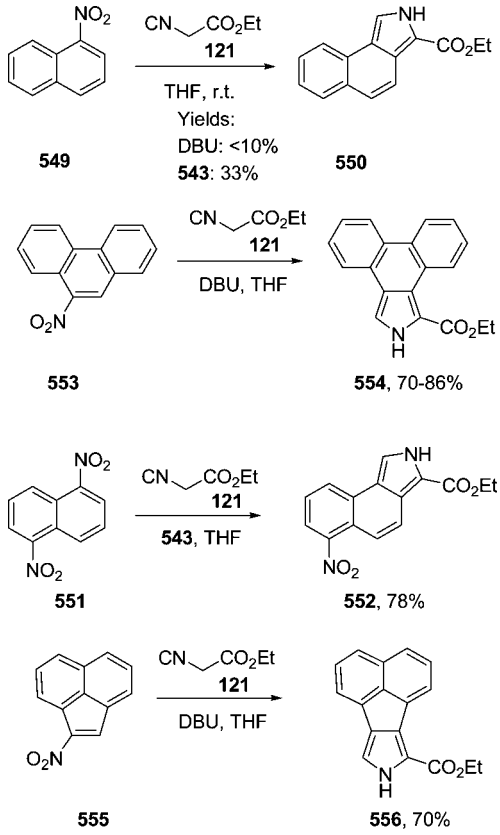
and 4-positions of pyrrole ring. The target pyrroles bearing 3-alkyl, 3,4-dialkyl,[272] and 3,4-diaryl,[273] as well as β-CF_3 groups,[274] were prepared in this manner. DBU is the most widely used base in the BZ reaction and is effective for highly reactive starting materials. Stronger nonionic superbases, such as **353** and the phosphazene **543** (P_4-*t*-Bu, supplied by Fluka) are, however, more effective and produce the pyrroles in higher yields even when less reactive substrates are employed (Scheme 136). Thus, simple pyrroles (**544**, for example) can be obtained in quantitative yields using superbase **353**, the formation of byproduct **538** (Scheme 134) not being observed at all in this case.[206] On the other hand, sterically hindered nitroalkene **545** was converted to the corresponding pyrrole **546** using P_4-*t*-Bu, while DBU was found not effective in this reaction.[275]

The reaction tolerates a broad variety of nitro compounds including nitroarenes. However, the starting nitroarene must have a partially localized π-system to allow nucleophilic attack by the isocyanoacetate enolate. Not surprisingly, nitrobenzene fails to react with ethyl isocyanoacetate to give

Scheme 137



Scheme 138



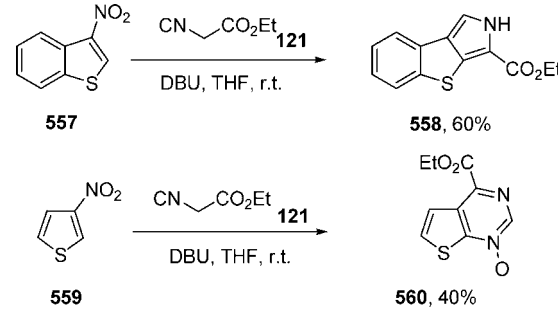
an isoindole product. However, more activated 3,5-dinitrobenzonitrile **547** reacts with isocyanoacetate **121** in the presence of DBU to afford the corresponding isoindole **548** in 64% yield (Scheme 137).[276]

Bi- and polycyclic aromatic nitro compounds are generally more reactive, due to the lower aromaticity, toward the anion of ethyl isocyanoacetate and give fused pyrroles. Thus, 1-nitronaphthalene **549** gave the corresponding pyrrole **550** in 33% yield in the presence of phosphazene superbase **543**. More active 1,5-dinitronaphthalene **551** gave the product **552** in higher yields.[277] Polycyclic nitroarenes, for example, 9-nitrophenanthrene **553** and 1-nitroacenaphthylene **555**, gave the corresponding fused pyrroles **554**[278] and **556**[279] in good yields in the presence of DBU (Scheme 138).

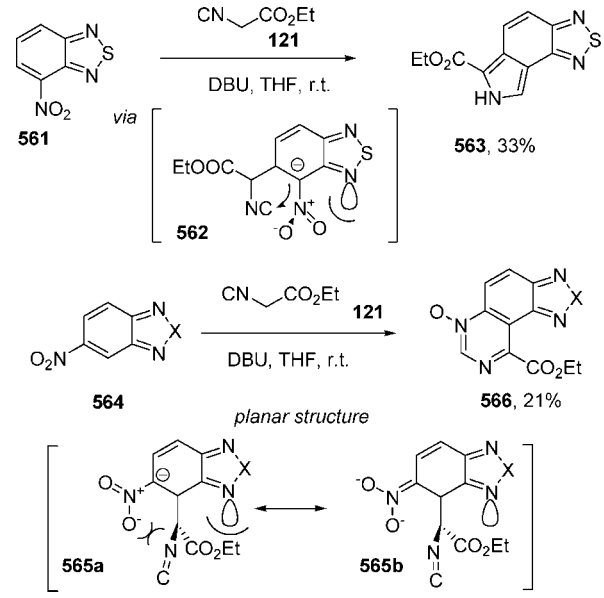
Extending this isoindole synthesis to nitroheteroarenes provides many pyrro-fused heteroarenes. Less aromatic heteroarenes are expected to be more reactive to nucleophilic reagents. However, heterocyclic nitro compounds react with isocyanoacetate derivatives following alternative pathways. For example, 3-nitrobenzothiophene **557** was converted into the corresponding pyrrole **558** in good yields, whereas 3-nitrothiophene **559** gave *N*-oxide **560** as the only isolable product (Scheme 139).[280]

Moreover, it was found that 4-nitrobenzo[*c*][1,2,5]-thiadiazol **561** reacts with ethyl isocyanoacetate **121** to give the expected pyrrole **563**, while a similar reaction with 5-nitrobenzo[*c*][1,2,5]thiadiazol **564** gave the corresponding

Scheme 139



Scheme 140



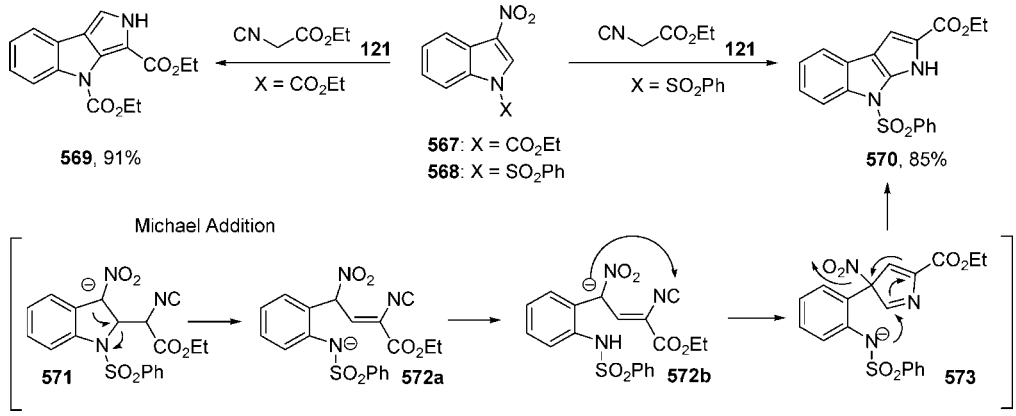
N-oxide **566** as the sole product. A viable mechanism for the alternative formation of pyrroles or pyrimidine *N*-oxides includes the initial attack of ethyl isocyanoacetate anion to the β-position of the nitro groups to form the corresponding anionic intermediates **562** and **565**.

When the nitro group is coplanar with the aromatic ring, as in **565**, the intermediate can be represented by two resonance structures **565a** and **565b**; subsequent cyclization gives the annulated pyrimidine *N*-oxide **566**. In contrast, the intermediate **562**, derived from **561**, is twisted (which favors elimination of NO_2), and the corresponding pyrrole **563** is obtained instead (Scheme 140). The same arguments may explain the different behavior of **567** and **569**.[281]

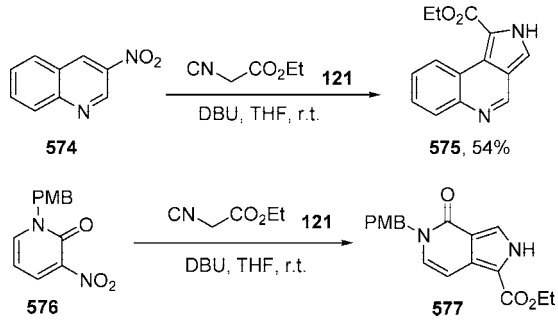
Remarkable behavior of 1-protected 3-nitroindoles in the Barton−Zard reaction was observed by Gribble et al. Thus, the use of 1-alkoxycarbonyl indole **567** gives the expected product **569**,[282] whereas 1-(phenylsulfonyl)-3-nitroindole **568** undergoes a transformation leading to the derivative **570**, with an unusual pyrrolo[2,3-*b*]indole ring system. The mechanism proposed for this abnormal Barton−Zard reaction involves Michael addition of the isocyanoacetate and then a fragmentation of the 2,3-dihydroindole ring system **571**. This can be rationalized by the presence of a good leaving group (arenesulfonamide anion). Subsequent cyclization of **573** followed by NO_2^- elimination leads to the target product **570** (Scheme 141).[283]

In contrast to the above-mentioned examples, 3-nitroquinoline **574** and nitropyridone **576** gave the expected pyrroles **575** and **577** in good yields (Scheme 142). However,

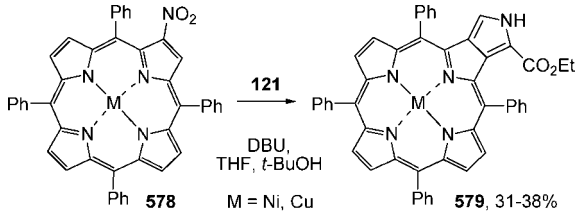
Scheme 141



Scheme 142



Scheme 143



3- and 4-nitropyridines proved not suitable as a precursor for the synthesis of the corresponding pyrrolopyridines.[284]

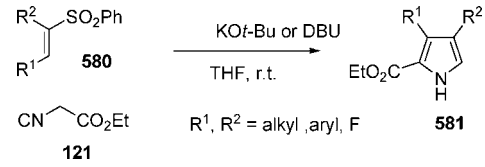
Even metal−nitroporphyrin complexes **578** (M = Ni, Cu) were successfully employed in the condensation to afford pyrroloporphyrins **579** (Scheme 143).[285]

In summary, it should be noted that not all nitroheteroarenes give fused pyrroles by a base-induced reaction with ethyl isocyanoacetate. However, the reaction can be carried out with a broad variety of nitroalkenes and some nitroarenes.

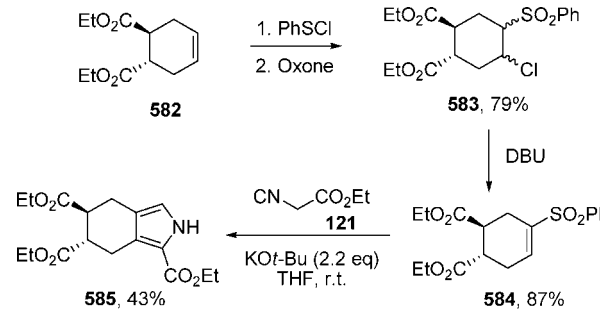
9.1.2. Reaction of Isocyanoacetates with α,β-Unsaturated Sulfones

α,β-Unsaturated sulfones can also be used as activated alkenes for pyrrole synthesis. The first example of pyrrole formation from α,β-unsaturated sulfones **580** and isocyanoacetates was described by Magnus et al. in 1984 (the first example of BZ-type pyrrole synthesis)[286] and further studied in detail by Montforts et al.[287] When sulfones **580** are used, elimination of sulfinic acid leads to formation of the pyrroles **581**. Alkenes bearing electron-withdrawing groups (α-trifluoromethyl, α-cyano, α-ethoxycarbonyl) gave 4-substituted pyrrole-2-carboxylates in moderate to good yields in the presence of 1 equiv of DBU.[288] This method can be used for the synthesis of 3-CF_3-pyrroles[289] and 3-F substituted pyrroles.[290] Generally, application of aryl- and alkyl-substituted sulfones results in good yields (Scheme 144).[291]

Scheme 144



Scheme 145



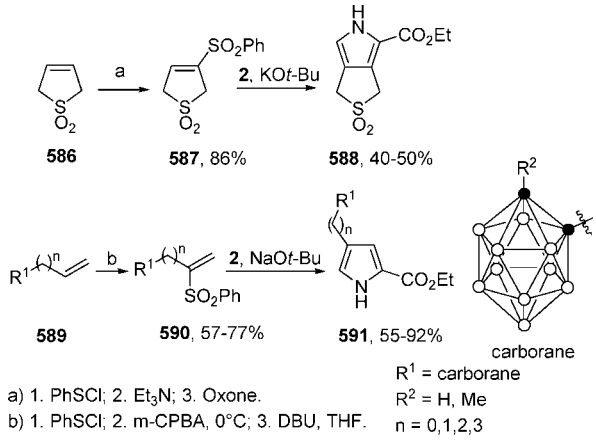
A clear advantage of this protocol is that, α,β-unsaturated sulfones are readily available from a broad range of alkenes. The phenylsulfonyl group is conveniently introduced via addition of phenylsulfenyl chloride to olefins, followed by elimination of HCl and oxidation of α,β-unsaturated sulfides to the sulfones. Thus, for example, fused pyrrole **585** was obtained from alkene **582** in only four synthetic steps (Scheme 145).[287,292]

α,β-Unsaturated sulfone **587** is readily available from the corresponding alkene 2,5-dihydrothiophene-1,1-dioxide **586** and gave pyrrole-fused 3-sulfolene **588** in good yield.[293] The same approach was also used for the synthesis of carboranyl-substituted pyrroles **591** from the corresponding alkenes **589** (Scheme 146).[294]

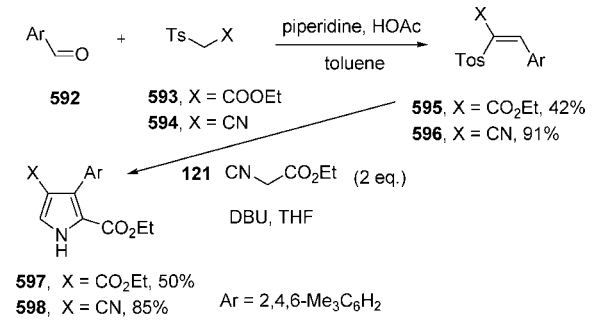
On the other hand, starting sulfones can be obtained from benzaldehydes and ethyl tosylacetate **593** or tosylacetonitrile **594** in good yields. Thus, pyrroles **597** and **598** were synthesized in this manner from 2,4,6-trimethylbenzaldehyde **592**.[295] Terephthalaldehyde was also used in this approach for the synthesis of a molecule with two pyrole moieties (Scheme 147).[296]

The combination of a Diels−Alder reaction of β-sulfonylnitroethylene and the BZ reaction provides a new synthesis of pyrroles fused with polycyclic skeletons. For example, synthesis of pyrrole **601** was achieved by BZ reaction of **600** with ethyl isocyanoaceatate **121**. Precursors for the pyrrole synthesis have been prepared from **599** and 1,3-cyclohexadiene **598**.[297] The reaction proceeds likely

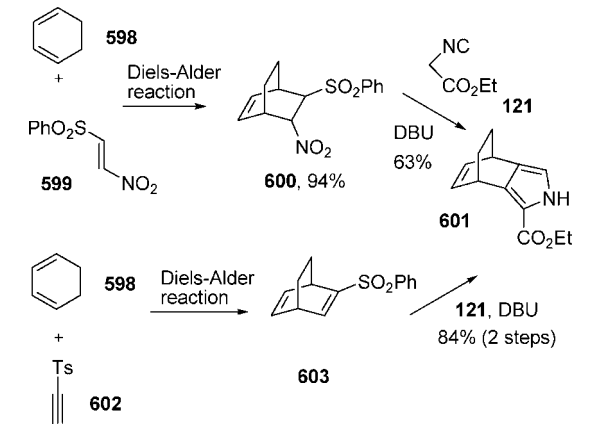
Scheme 146



Scheme 147

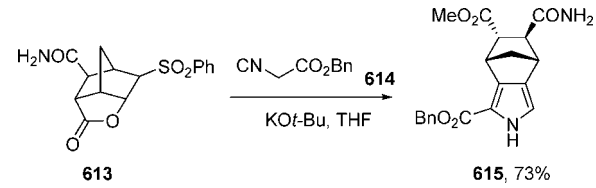


Scheme 148



through elimination product **603**. This methodology was also applied starting from cyclopentadiene[298] and substituted 1,3-cyclohexadienes[299] as inputs. The synthesis of fused pyrroles **601** was recently more efficiently achieved starting from the Diels−Alder reaction of 1,3-cyclohexadiene **598** with tosylacetylene **602** and proceeding through the same intermediate **603** (Scheme 148).[300]

Scheme 150



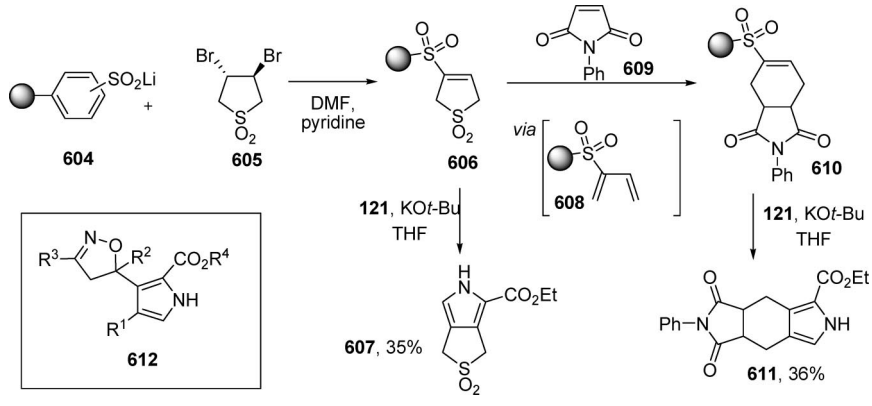
Kurth et al. developed a traceless solid-phase sulfone linker strategy for the BZ pyrrole synthesis. For example, polymer-supported sulfolene **606** was prepared from resin-bound lithium phenylsulfinate **604** and dibromide **605**. Subsequent BZ reaction afforded **607** in moderate yield. Alternatively, heating of **606** leads to extrusion of SO_2 to form intermediate diene **608**. Diels−Alder reaction of diene **608** with various alkenes opens broad possibilities for modification of the sulfone and synthesis of various fused pyrroles, for example, **611** (Scheme 149).[301] Solid-phase BZ reaction was also used several times for the synthesis of 2-isoxazoline-pyrrole derivatives **612**.[302] However, application of solid-phase sulfones does not give significant advantages in comparison with solution-phase synthesis.

As an example of unusual BZ-type transformations, Montforts et al. reported that tricyclic lactone carboxamide **613** gives directly the pyrrole derivative **615** by treatment with benzyl isocyanoacetate **614**. Apparently, the reaction took place through formation of an α,β-unsaturated sulfone required for BZ-pyrrole-ring formation (Scheme 150).[303]

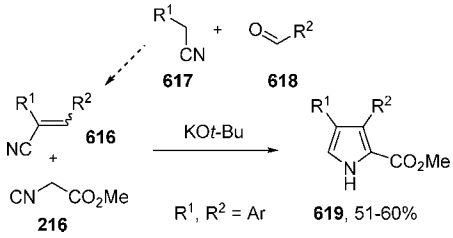
9.1.3. Reaction of Isocyanoacetates with α,β-Unsaturated Nitriles

α,β-Unsaturated nitriles also can be used as precursors for regioselective synthesis of 2-substituted 3,4-diarylpyrroles **619**. The cyano group plays the role of leaving group, and HCN is eliminated in this reaction (see general mechanism of BZ reaction). α,β-Unsaturated nitriles **616** can be easily obtained from the appropriate benzaldehydes **618** and phenylacetonitriles **619** in the presence of base. The ease of preparation of α,β-unsaturated nitriles **616** allows the rapid synthesis of pyrroles **619** with various aryl substituents. Yields are typically between 50% and 60% regardless of the electron-withdrawing or electron-releasing substitutions on each of the aromatic rings (Scheme 151).[304]

Scheme 149



Scheme 151

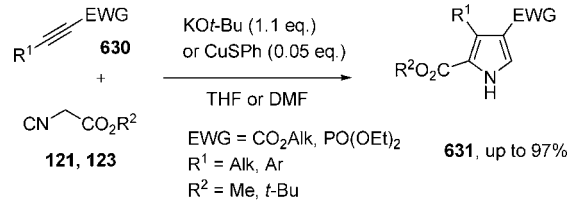


9.2. Reaction of Isocyanoacetates with Activated Alkynes

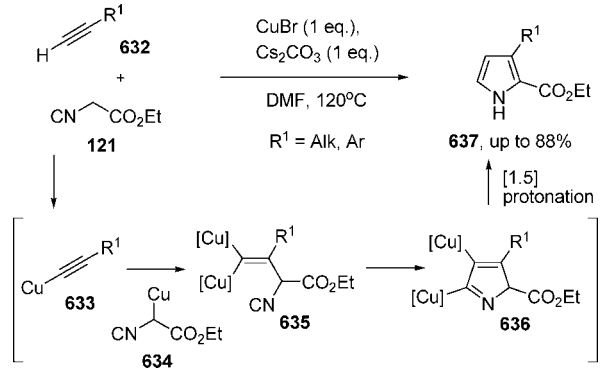
Direct access to pyrroles from acetylenes is an important goal in organic synthesis. In 2005, Yamamoto et al. developed new synthetic procedures for the regiocontrolled formation of pyrroles via a formal [3 + 2] cycloaddition of isocyanoacetate derivatives **621** and electron-deficient alkynes **620**. The heteroaromatization proceeds smoothly under either a copper or an organophosphine catalyst. The reaction gives pyrroles **622** (path a) under the catalysis of Cu_2O, by means of the ordinary Michael addition of the metalated isocyanide **624** to the β-carbon of **620**. On the other hand, under dppp (1,3-bis(diphenylphosphino)propane) catalysis, pyrroles **623** are formed instead (path b), through a formal attack of the nucleophilic isocyanide to the α-carbon of **620**. The proposed mechanism is depicted in Scheme 152. The reactions take place with broad variety of aliphatic and aromatic compounds and appeared to be an efficient approach to trisubstituted pyrroles (Scheme 152).[305]

It was also found by de Meijere et al. that pyrroles **631** can be obtained from acetylenes **630** and isocyanoacetates **121** or **123** by CuSPh catalysis or using 1.1 equiv of a strong base.[306] The reaction takes place via ordinary Michael addition of the isocyanide anion (path a). Under optimized conditions, the corresponding pyrroles could be obtained in yields up to 97% (Scheme 153). This condensation can also be performed in MTBE with KH as a base.[266]

Scheme 153



Scheme 154

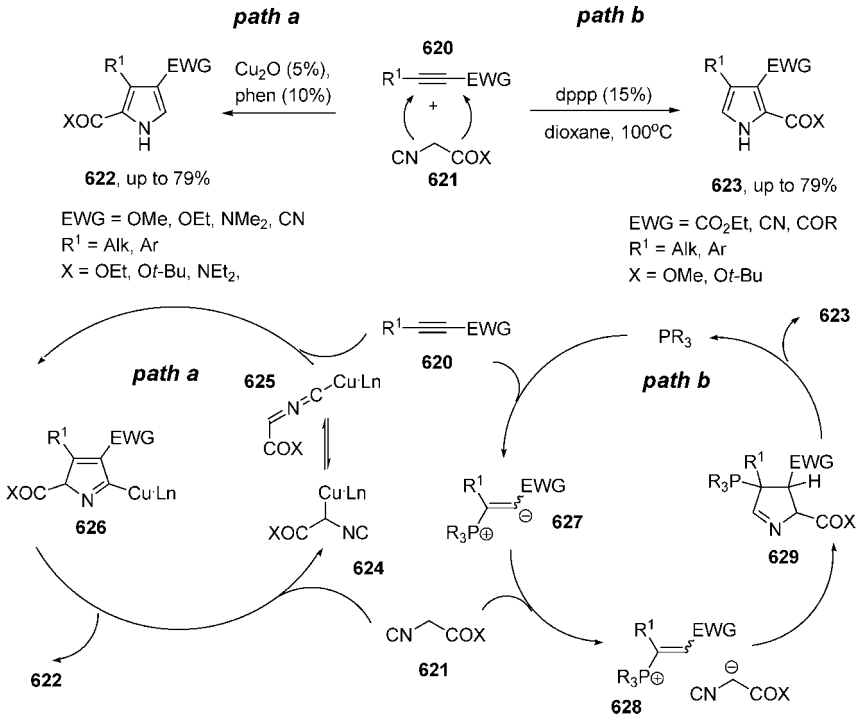


In 2009, this methodology was extended to terminal alkynes as the inputs. The reaction between substituted ethyl isocyanoacetate **121** and nonactivated terminal acetylide **632** afforded 2,3-disubstituted pyrroles **637** in the presence of 1 equiv of CuI and base. The proposed mechanism includes carbocupration of the copper acetylenide **633** by the deprotonated isocyanide **634** followed by cyclization of thus-formed intermediate **635**. The formed 2*H*-pyrrole-4,5-dicopper derivative **636** gives the pyrrole **637** after spontaneous aromatization and metal removal (Scheme 154).[307]

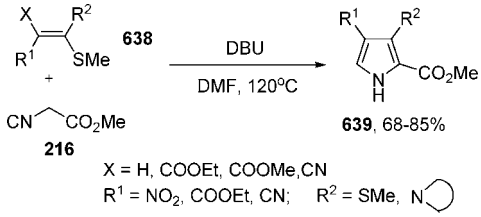
9.3. Miscellaneous Synthesis of Pyrroles

Recently various interesting modifications of the BZ methodology appeared in literature. In 2007, Ila et al.

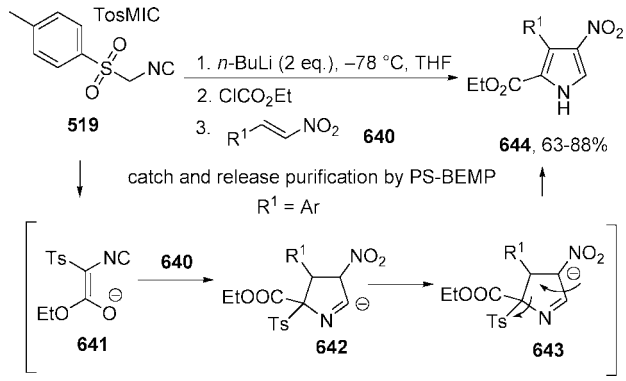
Scheme 152



Scheme 155



Scheme 156



developed a concise and efficient protocol for regioselective synthesis of 2,3,4-trisubstituted pyrroles **639** from readily available polarized ketene *S*,*S*- and *N*,*S*-acetals **638** and isocyanoacetates. The methodology allows precise control over the introduction of a number of substituents and functionalities (ester, cyano, nitro, cyclic amines, etc.) on the pyrrole ring. The reported reaction is the first example of the BZ reaction in which a nitro group can be retained in the 4-position of the pyrrole ring (Scheme 155).[308]

Very recently, Ley et al. developed an interesting hybrid of the classical van Leusen and Barton−Zard pyrrole syntheses leading to 4-nitroindoles **644**. Thus, treatment of TosMIC **519** with ethyl chloroformate in the presence of strong base leads to intermediate isocyanoacetate **641**, which easily attacks nitroalkene **640** to form cyclic compound **642**. Subsequent elimination of *p*-toluenesulfinate from **643** and [1,5] proton shift provides the corresponding nitropyrroles **644**. Isocyanoacetates **641** already contain a good leaving group; therefore, the NO_2 group is retained in the target molecule **644**. The products were isolated in good yields using a polymer-assisted catch-and-release workup and purification protocol using PS-BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine on polystyrene 2%). In general, under usual workup and column chromatography conditions, the yields do not exceed 40% (Scheme 156).[309]

9.4. Application of Pyrroles Obtained by Isocyanoacetate−Alkene Reaction

9.4.1. Synthesis of Porphyrins and Oligopyrroles

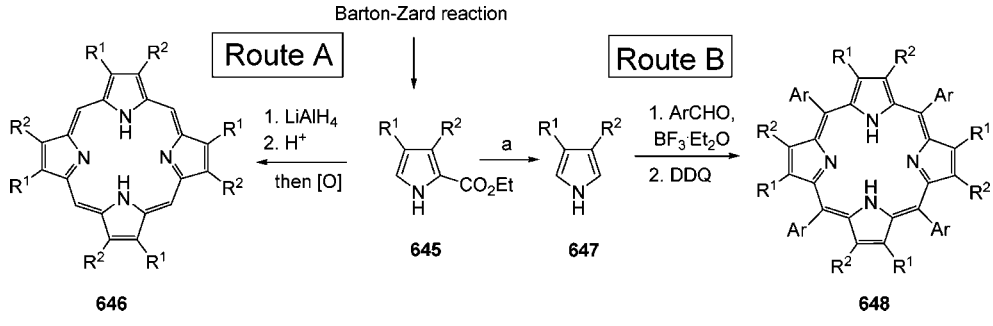
Porphyrins show remarkable and highly important functions in nature (heme, chlorophylls, etc.) and have many unusual structural and chemical properties. Porphyrins can be easily prepared from pyrroles available via Barton−Zard synthesis, using different approaches (Scheme 157). Thus, in 1988, Ono and Maruyama discovered a very simple synthesis of porphyrins **646** by reduction of the carboxylic groups in pyrrole **645** followed by oxidative macrocyclizations (route A).[310] This method was extensively used for the synthesis of symmetric porphyrins bearing different fragments, for example, long chain alkyl and aryl group,[311] various EWGs,[312] trifluoromethylated porphyrins,[274] porphyrins with mono-[293] or polycyclic arene units[280,313,314] or polycyclic ring systems.[299,315] Carboranyl porphyrins for boron neutron capture therapy (BNCT) of tumors could be synthesized,[294] and a synthesis of a chiral atropoisomeric porphyrin was also demonstrated following route A.[316] On the other hand, the ester group at the 2-position is readily removed under basic conditions to give α-unsubstituted pyrroles **647**, which were used for the preparation of porphyrins **648** by Lash et al. (route B).[314] This approach was used for the synthesis of symmetric meso-tetraarylporphyrins.[273,317]

2,5-Unsubstituted pyrroles **647** can also be used for the synthesis of oligopyrroles, for example, 9-unsubstituted dipyrrindione **651**[318] and tripyrrindione **653**,[319] which are useful precursors for the synthesis of bile pigments (Scheme 158). Cyclic oligopyrroles, for example, cyclo[8]pyrrole, an efficient supramolecular liquid crystal, were also prepared using the BZ reaction.[320] Moreover, pyrroles **647** are useful for the synthesis of unsymmetrical porphyrins **657** with different substituents (route C, Scheme 158). A so-called "3 + 1" variant of the MacDonald condensation, where a dialdehyde **656** is condensed with a tripyrrolic compound **655** (tripyrrane), easily accessible from pyrrole **647**, was developed by Lash et al.[321] This approach is widely used for the synthesis of porphyrins with exocyclic rings,[322] "geoporphyrins"[323] and bicyclo[2.2.2]octadiene-bridged porphyrin oligomers.[324]

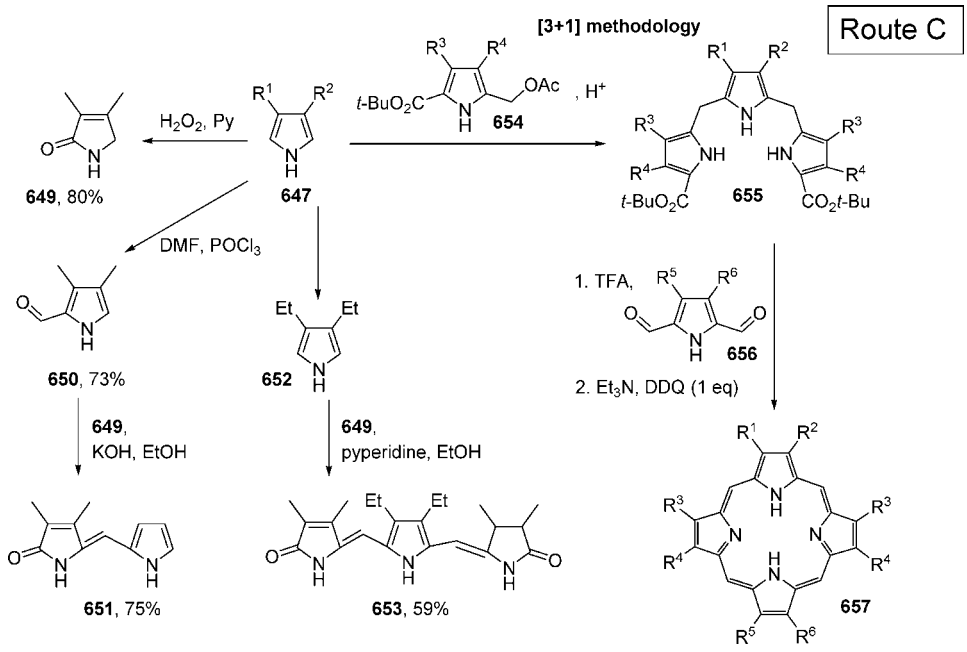
9.4.2. Miscellaneous Applications

1,10-Phenanthrolinopyrrole (php) **660**, prepared by BZ reaction and subsequent decarboxylation of **659**, exhibits rich coordination chemistry, for example, as an efficient ligand for the formation of Ru complexes **661**−**663**, showing interesting photochemistry (Scheme 159).[325]

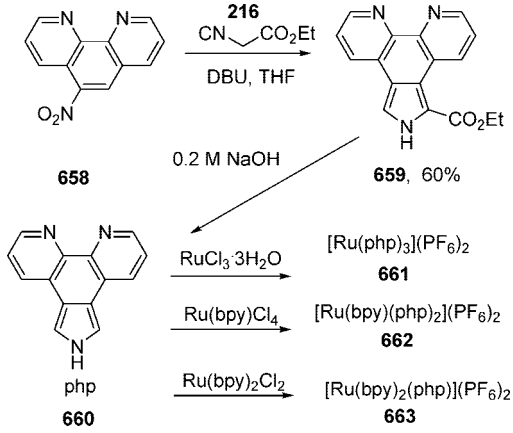
Scheme 157



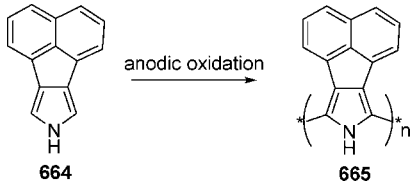
Scheme 158



Scheme 159



Scheme 160



Another type of application of pyrroles, for example **664**, is the preparation of polypyrroles **665**, showing good conducting properties (Scheme 160).[279,326]

Application of BZ reaction in synthesis of biologically active and drug-like molecules and in total synthesis of natural products is discussed in the corresponding sections.

10. Multicomponent Reactions of Isocyanoacetates and Isocyanoacetamides

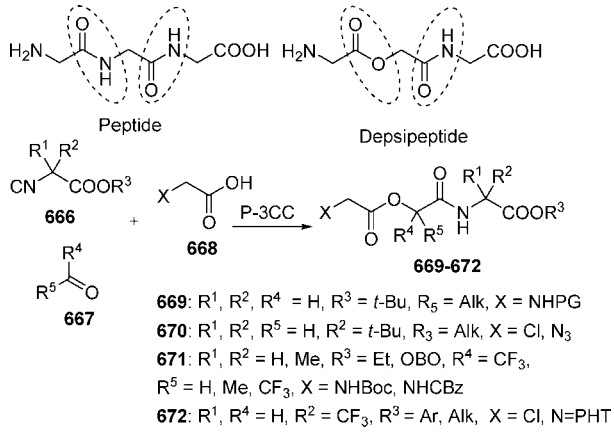
Multicomponent reactions (MCRs) are powerful tools in modern organic synthesis having excellent diversity and complexity generating ability.[3−5] Isocyanide-based multicomponent reactions, such as the Passerini and Ugi reactions, are exciting methods for the synthesis of amino acids, peptides, and peptide-like molecules, as well as heterocycles. The presence of an isocyanide group in isocyanoacetic acid derivatives make them very attractive for Passerini and Ugi reactions (sections 10.1 and 10.2). On the other hand, the polyfunctionality of isocyanoacetates opens many synthetic routes to obtain diverse sets of heterocyclic species such as oxazoles, imidazoles, etc. (sections 10.3 and 10.4). These products, in turn, can undergo different postcondensation modifications increasing the number of accessible structures enormously (section 10.5).

10.1. Passerini Reaction

The classic Passerini three-component reaction (P-3CC) was discovered in 1921 by Mario Passerini.[327] It is one of the oldest multicomponent reactions and the first that was based on isocyanides. The P-3CC combines carboxylic acids, carbonyl compounds, and isocyanides to access α-acyloxycarboxamides in one step. α-Isocyanoacetates were used in the Passerini reaction for the first time by Ugi in 1962.[328] His group demonstrated that the reaction is a most convergent approach to depsipeptides, which are an important family of antitumor agents (a depsipeptide bears a COO function instead of a CONH in normal peptides). Chloroacetic acid, azidoacetic acid, or glycine derivatives **668** treated with simple aldehydes **667** and isocyanoacetates **666** give depsipeptide precursors, such as **669** and **670** (Scheme 161). After suitable functional group manipulation, the resulting depsipeptides have been used again for subsequent Passerini reactions, allowing preparation of yet longer peptides.[328] Recently Nenajdenko et al. developed the Passerini reaction with CF_3-carbonyl compounds and used them for the synthesis of internal CF_3-depsipeptides **671**.[329] C-terminal CF_3-depsipeptide molecules **672** can be readily prepared using α-CF_3 isocyanoacetates (Scheme 161).[330,331]

Chiral isocyanoacetates were also used in the P-3CC. Interestingly, no racemization of the isocyanoacetate chiral center was observed in reactions with aldehydes and carboxylic acids.[332] For example, solid-supported chiral isocyanoacetates **673** (R_1 = Me, *i*-Bu) were prepared from the corresponding amino acids, bound to the Lantern resin by

Scheme 161

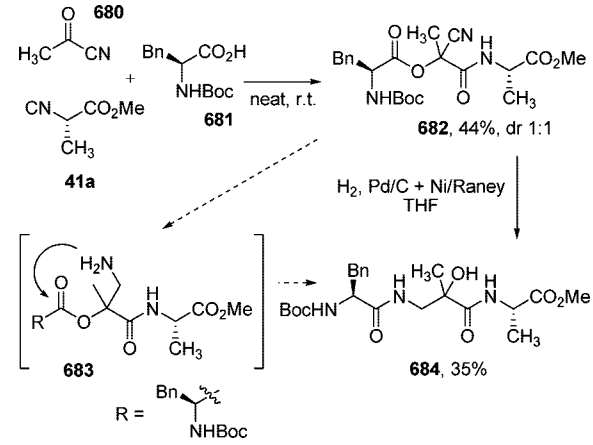


standard formylation/dehydration procedure with diphosgene/NMM as a dehydrating system. Supported depsipeptide molecules **676** prepared by the Passerini reaction gave derivatives **678** after removal of Fmoc-protective group and O→N acyl migration (Scheme 22). Further oxidation and cleavage from the resin led to compounds **679**, potential protease inhibitors, without racemization of the former α-isocyanide center (Scheme 162).[333,334] It should be noted that this strategy, Passerini reaction−amine deprotection−acyl migration (PADAM), is highly efficient for solid-phase preparation of peptides and peptidomimetics.[335] (See section 16.3, Scheme 304).

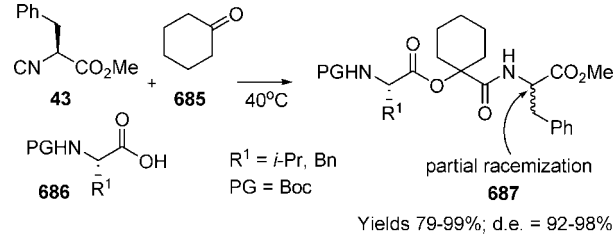
In 2004, Ganem et al. developed the synthesis of peptide molecules **684** based on postcondensation modification of Passerini-type products **682** containing a nitrile fragment. A mixture of acetyl cyanide **680** and Boc-L-phenylalanine **681** reacted with chiral isocyanoacetate **41a** to form α-cyanoamide **682** (dr 1:1; no racemization of isocyanoacetate center was observed). No solvents were necessary for optimal performance. Subsequent hydrogenation of **682** leads to the *β*-peptide analog **684** via intramolecular acylation of intermediate amine **683**. It was also possible to synthesize **684** in a one-pot process directly from the starting materials with comparable overall yields (Scheme 163).[336]

On the other hand, the Passerini reaction of chiral isocyanoacetate **43** with protected amino acids **686** and cyclohexanone **685** leads to partial racemization of the isocyanide chiral center in the Passerini product **687** (Scheme 164).[337] The authors studied the dependence of the diastereoselectivity in relation to the structure of the protective group of amino acids **686**. Boc-protected amino acids gave the best yields and selectivity (de 92−98%). Other protective groups like Bz, Trt, Cbz, Phth, and Ac proved less effective.

Scheme 163



Scheme 164



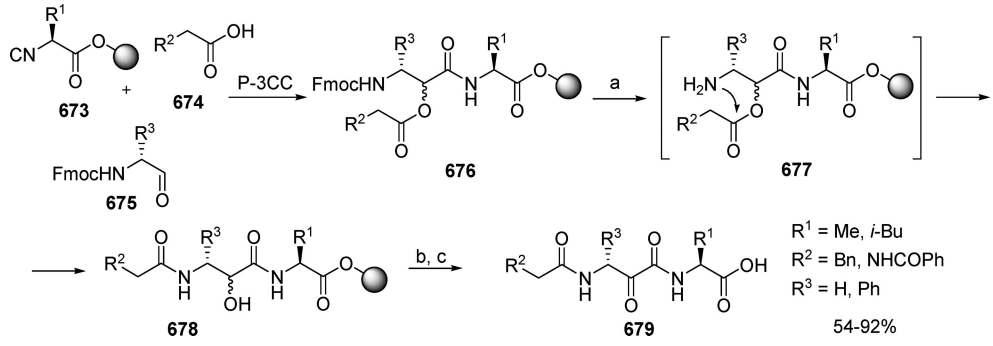
Possibly, in these cases, the Passerini reaction runs into difficulty with less reactive ketones, and side reactions including racemization occur.

Recently, a Passerini approach to chiral tripeptides **692** was developed by Ostaszewski (Scheme 165). The crucial step of the approach was a chemoenzymatic stereoselective hydrolysis of racemic Passerini products **689**, which was performed by wheat germ lipase (WGL) in good yields and high stereopurity of hydroxy compounds **690**. The nonhydrolized starting material **689** can be easily separated. Subsequent transformations lead to unprotected dipeptides **691**, which were converted to tripeptides **692** by standard peptide synthesis procedures.[338]

The Passerini reaction with trifluoroacetic acid in the presence of pyridine affords the corresponding α-hydroxy amides **693** instead of α-trifluoracetoxyamides (Scheme 166). A possible explanation for α-hydroxy amide formation is that the intermediate α-trifluoroacetoxyamide is hydrolyzed during the workup. Action of pyridine as the nucleophile, instead of trifluoroacetate, is also discussed.[339]

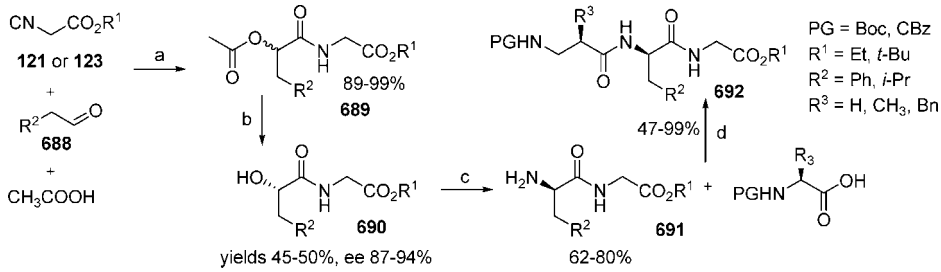
In general, isocyanoacetates are less reactive then other isocyanides (alkyl isocyanides for example), but in most

Scheme 162[a]



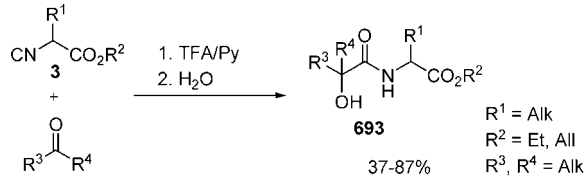
[a] Reagents and conditions: (a) piperidine, DMF; (b) IBX/DMSO; (c) TFA, CH_2Cl_2.

Scheme 165[a]

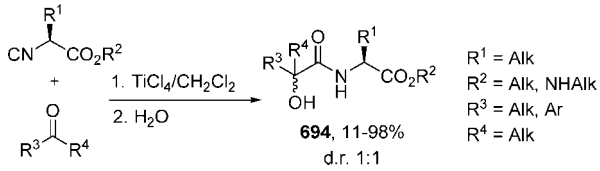


[a] Reagents and conditions: (a) CH_2Cl_2, rt; (b) WGL (wheat germ lipase); (c) MsCl, Et_3N, DMAP, CH_2Cl_2, rt, then NaN_3, DABCO, DMAP, benzo-15-crown-5, CH_2Cl_2, then H_2, Pd/C, methanol, 4 h; (d) EDC, HOBt, CH_2Cl_2, rt.

Scheme 166



Scheme 167



cases, isocyanoacetates react in the classic Passerini reaction smoothly and give the products in good yields.[340] Recently, a new solvent-free methodology for the Passerini reaction with aromatic aldehydes was established and proved more effective than the original protocol.[341] It was found that addition of nucleophilic additives[342] and use of water as a solvent[343] also can have a beneficial influence on the Passerini reaction.

10.1.1. Passerini-Type Reactions in the Presence of Lewis Acids

The reaction between a carbonyl compound and an isocyanide in the presence of a Lewis acid can afford several types of products including α-hydroxyamides and other compounds. The reaction is based on the activation of the carbonyl group with Lewis acid followed by nucleophilic attack of isocyanide. Thus, the reactions of an aldehyde or a ketone with an isocyanide in the presence of $TiCl_4$ afford α-hydroxyamides **694** in variable yields (Scheme 167). The method is efficient for synthesis of α-hydroxyamides containing amino acid residue **694**. However, it should be noted that there was no stereoinduction observed originating from isocyanoacetate derivatives.[27]

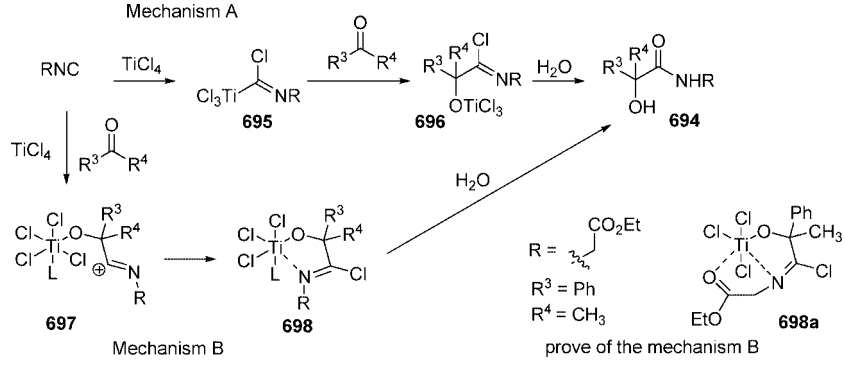
Two mechanisms for this type of Passerini reaction have been proposed. The initially discussed mechanism A[344] involves the insertion of the isocyanide carbon into the Ti−Cl bond giving intermediate **695** and subsequent reaction with the carbonyl compound and hydrolysis of formed titanate **696**. Mechanism A was later ruled out because the simple complex ($TiCl_4$·RNC) **697** was detected rather than insertion products such as **695**. Thus mechanism B, with the intervention of hexacoordinated titanium complexes **698**, was suggested and indeed confirmed. Hexacoordinated intermediate complex **698a**, the adduct of ethyl isocyanoacetate and acetophenone stabilized by the additional coordination of Ti with the carboxylate group from ethyl isocyanoacetate, was isolated in 76% yield and characterized by X-ray analysis.[345] Intermediate **698** is hydrolyzed giving α-hydroxy amides **694** on workup (Scheme 168).

A three-component Passerini-type reaction with an epoxide **699** instead of a carbonyl compound in presence of LiOTf has been described by Kern and Motherwell. The reaction included S_N1-like ring-opening of the epoxide followed by hydride migration and subsequent Passerini-type reaction of the resulting carbonyl compound. The reaction provided the depsipeptide-type product **701** in good yield when ethyl isocyanoacetate **121**, styrene oxide **699**, and Fmoc-L-lysine **700** were used (Scheme 169).[346]

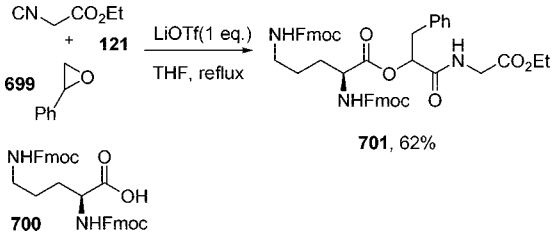
10.2. Ugi Reaction

Many papers describe Ugi reactions with isocyanoacetates as the isocyanide component. For a complete overview of such reactions, the reader is referred to reviews or books on multicomponent reactions.[3−5] The Ugi reaction allows construction of a broad variety of amino acid and peptide molecules. Use of isocyanoacetate derivatives, containing an

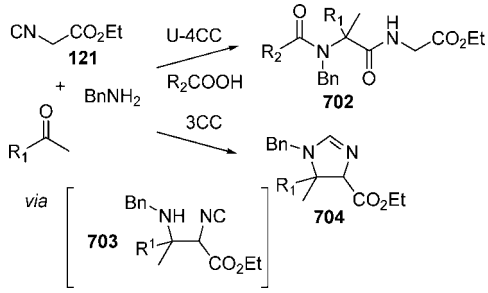
Scheme 168



Scheme 169



Scheme 170



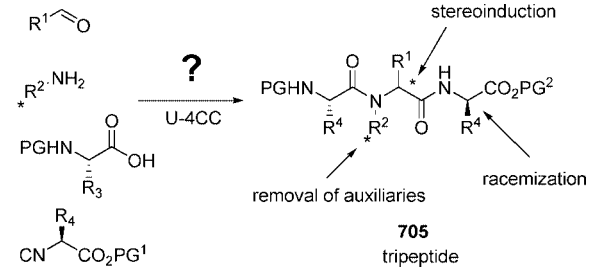
amino acid skeleton, opens an efficient multicomponent approach to small peptides. At the beginning of this section general reactivity issues of isocyanoacetic acid derivatives and application in peptide synthesis is discussed. Then, selected examples of peptide syntheses by the Ugi reaction are presented.

Isocyanoacetic acid derivatives contain an electron-withdrawing ester group and, in this connection, generally, show lower nucleophilicity in comparison with alkyl isocyanides containing no additional functional groups. This causes reduced reactivity in reactions that involve a nucleophilic addition of isocyanide, such as the Passerini reaction (see previous chapter) and the Ugi reaction. However, isocyanoacetates can successfully react in multicomponent reactions in most cases, although yields are slightly lower than those for alkyl isocyanides.

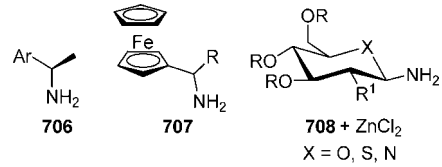
Thus, isocyanoacetates generally react straightforwardly in four-component Ugi reactions with aldehydes as carbonyl inputs. However, reactions with ketones rarely deliver yields higher than 50%. Indeed, this is due to reduced nucleophilicity of isocyanide coupled with lower reactivity of ketones. But moreover, in 2009 formation of side products **704** along with the corresponding Ugi products **702** in the four-component variant with ketones was observed, which further explains reduced yields of Ugi products (Scheme 170). Due to the relatively high α-acidity of isocyanoacetates, the corresponding anions can be generated even by weak bases such as benzyl amine. Subsequent formation of adduct **703** and cyclization affords imidazolines **704** as the main side products. This three-component reaction was recently published by Orru et al. as a separate synthetic method (see section 10.3.3). Although, imidazoline formation from imines and iscyanoacetates, in principle, has been known since the 1970s (works of Schöllkopf), their competitive formation in Ugi reaction has not been described until 2009.[347]

Imidazolines are formed in a three-component reaction (3CR) taking place under Ugi conditions competitively. The results obtained by us suggest that in the case of aldehydes, the Ugi reaction is faster and imidazolines are not formed. But the Ugi reaction with ketones is slower; therefore both processes occur with comparable rates. It is noteworthy that imidazoline formation in Ugi four-component condensation

Scheme 171



Scheme 172



with ketones can be efficiently suppressed by simply performing the reaction in trifluoroethanol rather than methanol or by using imines as inputs.

10.2.1. Synthesis of Peptides and Peptide Molecules

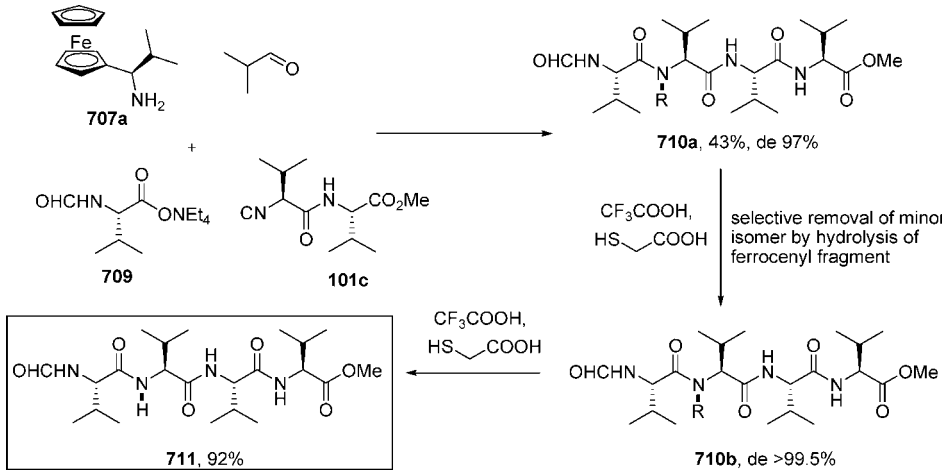
The first example of an Ugi four-component reaction (U-4CR) with isocyanoacetates was described by Ugi in 1961.[348] Initially, the four-component reaction of carbonyl compounds, chiral amine, protected amino acids, and chiral isocyanoacetates was conceived as a novel approach to tripeptides **705**. However, a major difficulty connected to this approach is the facile racemization of the α-center in many isocyanoacetates. Consequently, it proved difficult to develop direct stereoselective methodology and also indirect methods are not general because truly efficient and removable amine auxiliaries for the application in diastereoselective Ugi reactions are still not available (Scheme 171).

Chiral isocyanoacetates were found to be configurationally unstable in the Ugi reaction in the presence of amines.[11,349] However, reaction of chiral isocyanoacetates with less basic preformed cyclic imines has been carried out without racemization,[350] although this behavior is not general.[351] More configurationally stable isocyanoacetamides **60**,[352] as well as OBO−isocyano esters **53**,[35] undergo Ugi reaction without significant racemization.

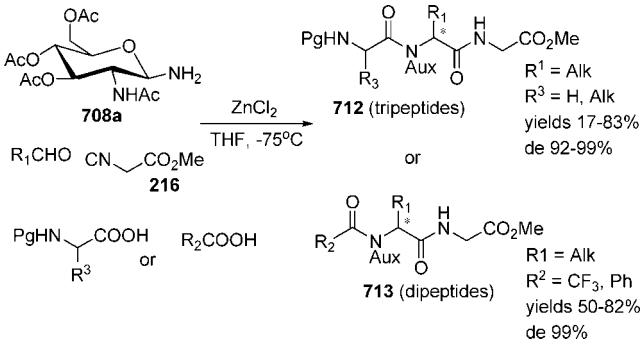
Effective chiral auxiliaries ($*R^2NH_2$) have been reported for the synthesis of peptides to prepare **705** in good yields and high optical purity. A number of chiral auxiliaries **706**−**708** were tested in the Ugi reaction (Scheme 172), and a number of critical reviews concerning this field were published.[353] However, the amine auxiliaries used have significant disadvantages, and a universal chiral amine has not been found until now. Thus, phenylethylamines **706** gave low selectivity, whereas ferrocenyl ethyl amines **707** and glycosylamines **708** are not easily accessible. Moreover, they all have limitations with respect to the carbonyl input tolerated. Especially, aromatic aldehydes react less efficiently than the aliphatic ones.

Therefore, synthesis of optically pure tripeptides **705** by U-4CC is difficult. It is not surprising that only two examples of asymmetric synthesis of such optically pure tripeptides were described. Thus, the ferrocenyl ethyl amine **707a** (R = *i*-Pr) was used for synthesis of tetravaline **711**. The configurationally stable chiral isocyanoacetamide **101c** was used as the isocyanide component to avoid racemization.

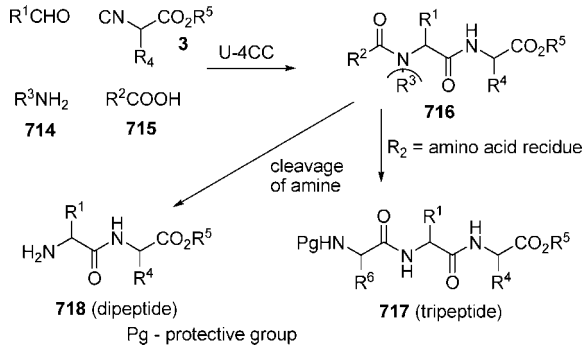
Scheme 173



Scheme 174



Scheme 175

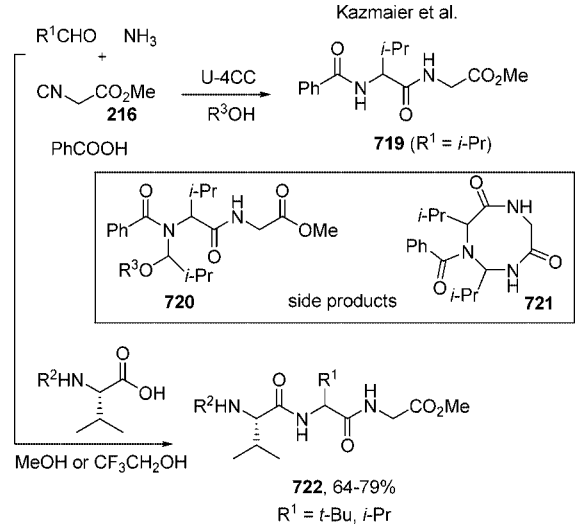


Protected tetrapeptide **710a** was obtained in 43% yield and 97% de. Preparation of pure tetrapeptide **710b** can be accomplished by selective acidolysis and removal of the ferrocenyl group from of the mixture. The minor isomer was cleaved some 230 times faster and the thus obtained enriched peptide **710b** was deprotected easily to afford diastereopure tetravaline **711** in 92% yield (Scheme 173).[354] Diastereopure glutathione also was synthesized in this manner by Urban in 1979.[355]

Glucopyranosyl amine **708a** has been used to prepare protected tripeptides **712** and dipeptides **713** in high diastereopurity (Scheme 174).[356] However, the auxiliary could not easily be removed under sufficiently mild conditions.

Thus, synthesis of optically pure peptides by Ugi reaction is not trivial problem so far. However, a significant number of racemic peptides, peptidomimetics, and peptide structures have been synthesized using isocyanoacetates (Scheme 175). Suitable amines **714** and carboxylic acids **715** should be chosen in order to allow removal of R^3 and R^2CO groups in

Scheme 176

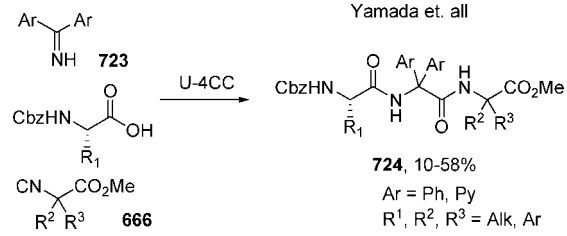


peptides **716**. The amine residue (R^3) should be easily removable for synthesis of tripeptides **717**, whereas both amine and carboxylic acid residues should be removable for synthesis of dipeptides **718**.

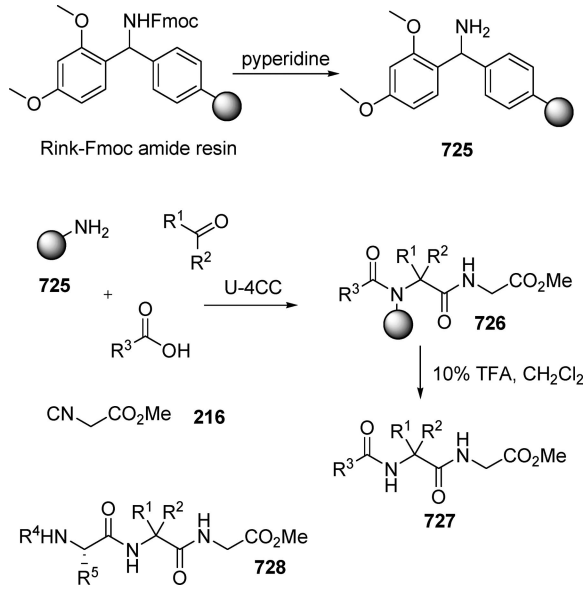
The simplest variant of amine, ammonia, can undergo Ugi reaction with isocyanoacetates to afford dipeptides with variable success (Scheme 176). Thus, reaction of aldehydes, ammonia, isocyanoacetate, and benzoic acid in methanol led to formation of side products **720** and **721** along with the Ugi product **719**. If methanol was replaced by the much less nucleophilic trifluoroethanol, the side reactions could be suppressed, and **719** was obtained in 45% yield. Based on this knowledge, a number of peptides **722** were obtained. However, the reaction was performed only with sterically demanding aldehydes (*t*-BuCHO and *i*-PrCHO) and acids (L-valine derivatives).[357] Therefore, the Ugi reaction with ammonia is less predictable than that with other amines and is not widely used for the synthesis of N-unprotected peptides.[358]

Ammonia-derived imines of diarylketones **723** were found to be useful for the synthesis of various crowded peptides containing α,α-diphenylglycine residues. In several cases, the reaction was carried out under high pressure to afford congested tripeptides **724** containing the α,α-diphenylglycine fragment together with other very bulky α,α-disubstituted glycines (Scheme 177).[359]

Scheme 177



Scheme 178



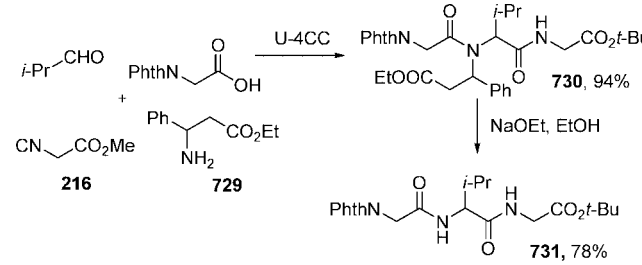
Solid-supported amines were also used as a cleavable amine component in Ugi peptide synthesis. Commercial Rink-Fmoc amide resin can be deprotected to afford solid-supported amine **725**. The amine **725** was used in Ugi reaction for the solid-phase synthesis of dipeptides **727**[360] and tripeptides **728**[361] (Scheme 178). Although yields were below 50%, purification of products is quite simple, and this approach is a powerful tool for the preparation of combinatorial libraries of small peptides.[362]

The cleavage of the amino component was first proposed by Ugi and Offermann, who used stabilized enamines (such as enaminoesters, enaminoketones, and enaminonitriles) as cleavable amino components, but the results were unsatisfactory because of low nucleophilic strength of the enamino group. With enaminoketones and enaminonitriles, the Passerini product is predominant. A great improvement was accomplished by using β-amino esters **729** as the amino input. The amide function in the resulting Ugi product **730** (generally obtained in high yields) was easily liberated with sodium ethoxide in ethanol to give the final product **731** in high yield. Thus, β-amino esters can be considered as synthetic equivalents of ammonia (Scheme 179).[363]

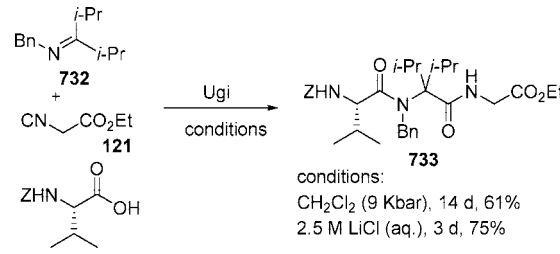
2-Aminomethylfluorene has been successfully employed as a cleavable amine. Liberation of the amide was achieved in excellent yields with DBU in pyridine.[364] Nitroveratryl-type amine (4,5-dimethoxy-2-nitro-benzylamine) was also used as a mild photolytically cleavable *N*-alkyl residue for synthesis of peptides.[365]

Benzyl amine is widely was used as amine component[366] for the synthesis of dipeptides. Thus, bulky α,α-disubstituted glycine tripeptide **733** was obtained in 61% yield from a dichloromethane solution at 9 kbar after 14 days.[367] Significant acceleration of this reaction was observed when the reaction was carried out in water, especially in LiCl aqueous solutions. Thus, **733** can be obtained in 75% yield after 72 h reaction in 2.5 M aqueous LiCl at atmospheric pressure (Scheme 180).[343] Unfortunately, removal of the benzyl group from the Ugi product is often problematic.[368]

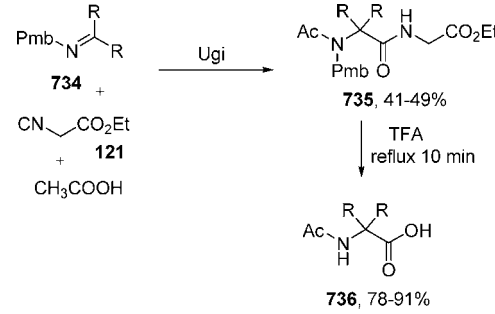
Scheme 179



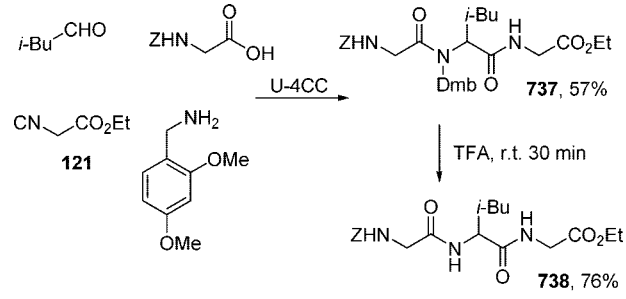
Scheme 180



Scheme 181



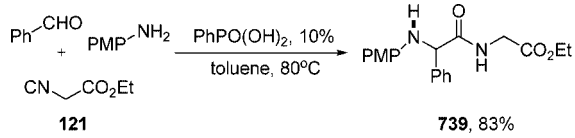
Scheme 182



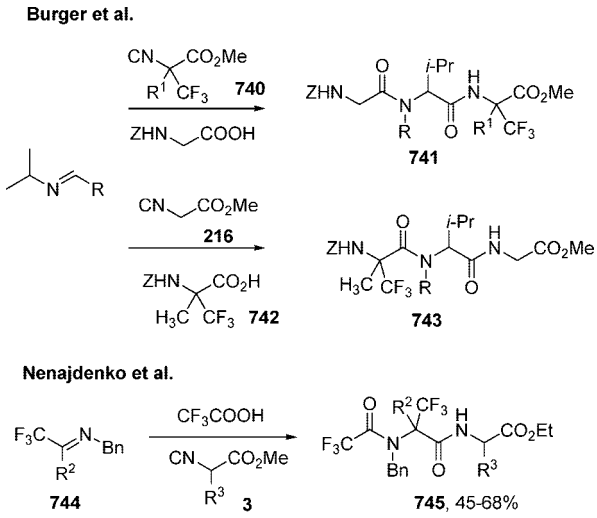
4-Methoxy benzyl amine is more convenient and can be removed by treatment with TFA. As an example, Ugi products **735** were converted to the α,α-diphenylglycine derivatives **736**, while the glycine fragment is also removed under these conditions (TFA, reflux).[369] Consequently, isocyanoacetate can be used as a cleavable isocyanide component in the synthesis of amino acids **736** (Scheme 181).

The more labile 2,4-dimethoxybenzyl (Dmb) protecting group can be also used.[370] Recently, N-protected tripeptide **737** was synthesized and converted to **738** with TFA at room temperature (Scheme 182). It should be noted that the glycine fragment remains in **738** under these conditions (TFA, room

Scheme 183



Scheme 184



temperature).[371] The 4-methoxybenzyl group can also be easily removed from the Ugi products by CAN oxidation.[372]

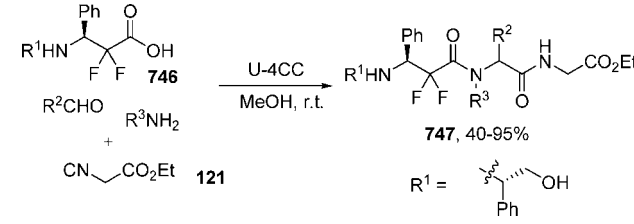
A broad variety of acids, such as formic, acetic, benzoic, and others can be used for the multicomponent synthesis of peptides. Trifluoroacetic acid seems to be more convenient and can be easily cleaved under mild reductive conditions. But the most promising approach was recently developed by List et al. The reaction of various carbonyl compounds, amines, and isocyanides, in the presence of phenylphosphinic acid (0.1 equiv), led directly to formation of N-unprotected Ugi products in good yields. As an example, the reaction with ethyl isocyanoacetate to obtain dipeptide **739** in good yield is depicted in Scheme 183.[373] The broad scope, operational simplicity, practicability, and mild reaction conditions make this reaction promising for the direct, atom-economic synthesis of dipeptides.

10.2.2. Selected Multicomponent Peptide Syntheses

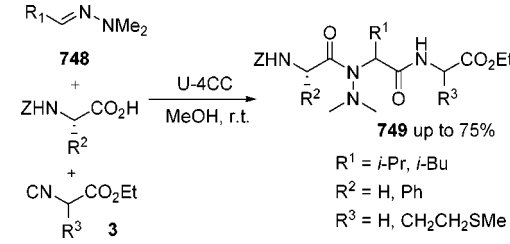
Fluorine-containing peptides have found a wide range of applications in enzymology, pharmaceutical, medicinal, and agricultural chemistry. However, the classic condensation approach can be ineffective in the synthesis of fluorinated peptides, especially peptides containing a CF_3 group. Therefore, the Ugi reaction with CF_3-isocyanoacetates **740** and CF_3-amino acid **742** was studied by Burger et al. Peptides containing C-terminal α-CF_3-amino acid **741** and N-terminal α-CF_3-amino acid **743** can be prepared efficiently using this approach.[331] Recently, CF_3-imines **744** were used by Nenajdenko et al. as a source of CF_3-group for Ugi-MCR construction of dipeptides **745**, containing N-terminal α-CF_3-amino acid. Unfortunately, tripeptides cannot be prepared using this procedure, because only strong acids (such as CF_3COOH) gave the corresponding Ugi products (Scheme 184).[374] Dipeptides containing polyfluoro-substituted proline and its homologues can be also obtained from the perfluorinated cyclic imines (see Scheme 190).

Chiral α,α-difluorocarboxylic acids **746** were synthesized and tested in the Ugi reaction, which then leads to difluorinated pseudopeptides **747** in moderate to good yields (Scheme 185).[375]

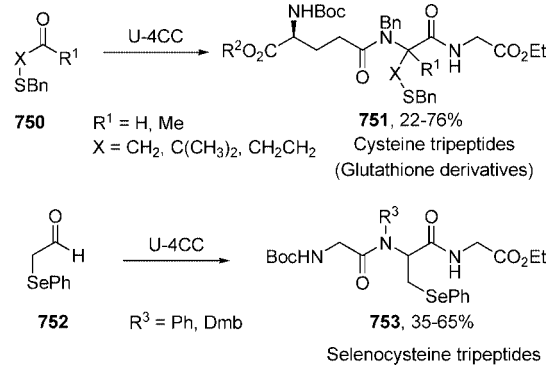
Scheme 185



Scheme 186



Scheme 187

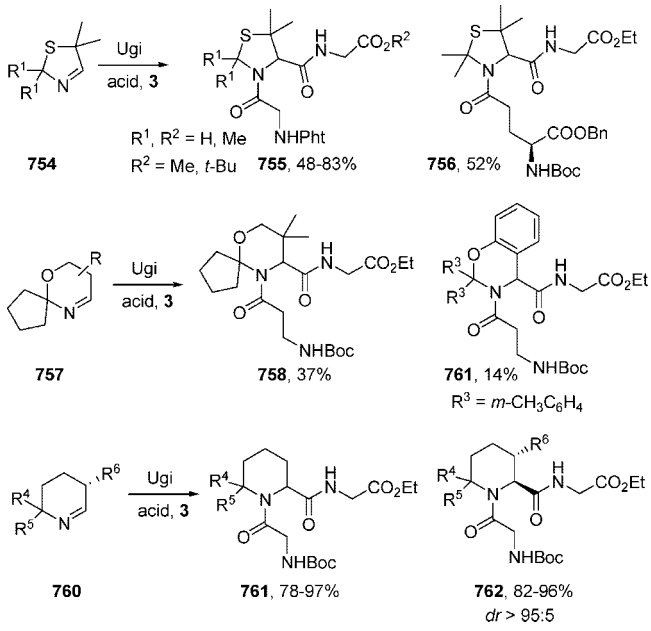


Hydrazones **748** prepared from aldehydes and *N*,*N*-dimethylhydrazine have been used in Ugi reaction with isocyanoacetates. The protected *N*-aminopeptides **749** containing *N*-dimethylaminovaline or *N*-dimethylaminoleucinol as unnatural building blocks were synthesized using this approach (Scheme 186).[376,349]

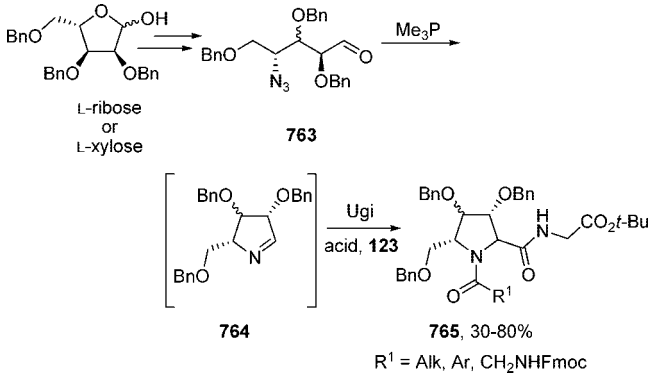
Peptides containing cysteine or selenocysteine units can be obtained by the Ugi reaction with α-methylthio- or α-methylseleno carbonyl compounds **750** and **752**. Thus, fully protected substituted glutathione derivatives **751** were synthesized by Ugi four-component reaction using various benzylthio aldehydes and ketones **750** as carbonyl building blocks.[347] Selenocysteine-containing peptides **753** were also synthesized by Ugi-MCR with selenylaldehydes **752** in water (Scheme 187).[377]

The Ugi reaction with cyclic aldimines is an effective route to peptides containing a cyclic amino acid residue, namely, proline, homoproline (pipecolinic acid), and azepan carboxylic acid. A number of cyclic imines containing five- or six-membered rings were subjected to Ugi reaction with isocyanoacetate **2** by Martens et al. Indeed a broad variety of tripeptides, including cysteine derivatives **755** (3-thiazolidine derivatives)[378] and glutathione derivatives **756**, can be obtained by such an Ugi reaction with **754**.[379] Imines **757** were also used for the Ugi multicomponent synthesis of the corresponding peptides **758** and **759**.[380] Tripeptides **761** and **762** with a central pipecolinic acid derivative were obtained via Ugi-MCR with imines of type **760**. This one-pot

Scheme 188



Scheme 189



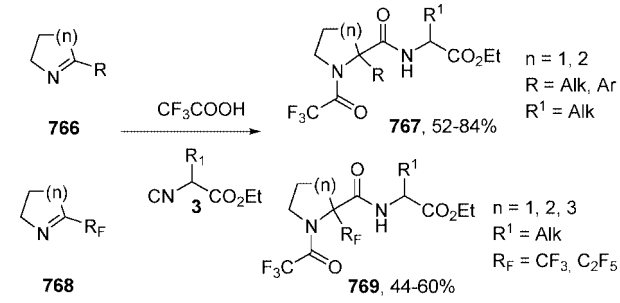
procedure leads to the diastereoselective formation of tripeptides **762** if chiral tetrahydropyridines **760** were used as reactants (Scheme 188).[381]

Recently, Overkleeft et al. reported the synthesis of highly functionalized pyrrolidines by a tandem Staudinger/aza-Wittig/Ugi three-component reaction (SAWU-3CR). Aldehyde **763** forms imine **764**, which reacts *in situ* in an Ugi reaction, which affords peptide-like products **765** in good yields (Scheme 189).[382]

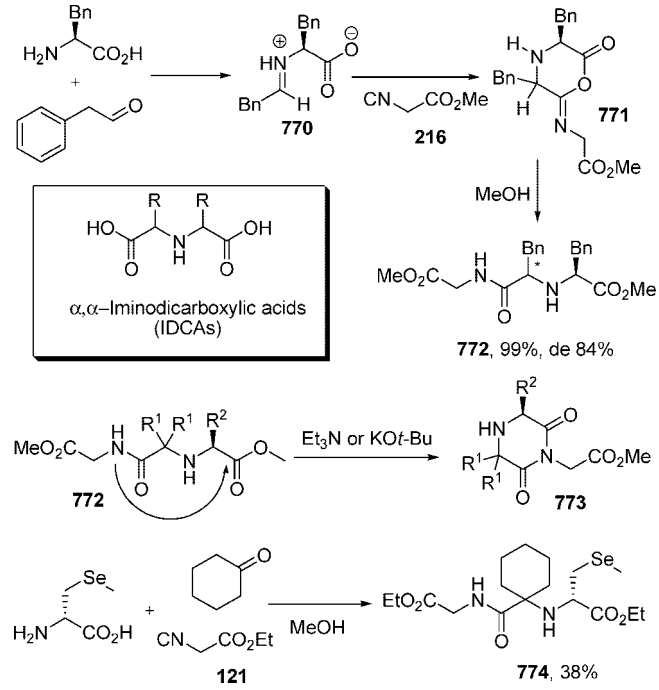
Recently, Nenajdenko et al. described a synthesis of dipeptides containing α-substituted cyclic amino acid residues based on the Ugi reaction with 2-substituted cyclic imines. Substituted imines are less reactive than nonsubstituted ones, and the reaction can be carried out only with strong acids such as CF_3COOH; thus, tripeptides cannot be prepared using this reaction. However, dipeptides **767**, containing proline and homoproline residues, can be efficiently prepared from imines **766** by an Ugi reaction with TFA and isocyanoacetates.[383] CF_3-[384] and C_2F_5-substituted[385] imines **768** also react readily under Ugi conditions and lead to the dipeptides **769** containing polfluorosubstituted cyclic amino acids. Polyfluorosubstituted derivatives of proline, homoproline, and azepan carboxylic acid were prepared in good yields by Ugi reaction (Scheme 190).[386]

Peptides containing α,α-iminodicarboxylic acid (IDCA) are a thoroughly investigated group of natural substances.

Scheme 190



Scheme 191

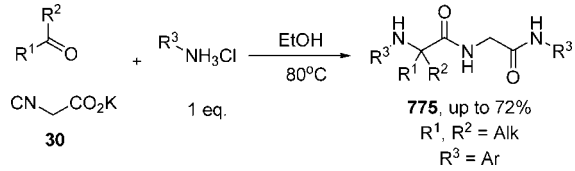


They can be obtained using a very effective variation of the Ugi five-center four-component reaction (U-5C-4CR), which involves four components (4CR) and five functional groups (5C) (Scheme 191).[387] Thus, L-phenylalanine condenses with aldehyde to form the imine **770**. Cyclic **771** is formed after α-addition of isocyanoacetate **216**. Finally, peptide **772** containing the IDCA residue is formed after reaction with methanol. This product was obtained selectively and in high yield.[388] These peptides **772** can be converted to a 2,6-piperazinedione **773** *in situ* or after subsequent cyclization in the presence of a base.[389] Highly functionalized selenopeptide derivative **774** also can be obtained in this manner from the corresponding selenyl-substituted amino acid (Scheme 191).[390]

In 1994, Bossio, Marcaccini, and Pepino developed a three-component condensation of potassium isocyanoacetate **30**, an amine salt, and a ketone in refluxing ethanol. The reaction afforded the corresponding peptides **775** in yields up to 72%. The reaction was found to be limited in scope and was applicable only to anilines and ketones. When aliphatic aldehydes were used as carbonyl input, a very complex reaction mixture was produced under these conditions (Scheme 192).[391]

In 2004, Zhu et al. enlarged the scope of the reaction using 2 equiv of secondary amine (morpholine) in toluene in the presence of NH_4Cl. A plausible reaction mechanism involves formation of the iminium intermediate **777** and trapping of

Scheme 192



the latter by the internal carboxylate oxygen to form oxazolone **778**. Further nucleophilic attack of the amine on the oxazolone **778** would produce **779**, which can undergo fragmentation to afford the observed dipeptides **780**. The reaction runs efficiently with aliphatic and aromatic aldehydes and aliphatic ketones and affords peptides **780** in good yields (Scheme 193).[18]

In summary, despite the difficulties for the synthesis of diastereopure compounds, some limitations and several side reactions, the Ugi reaction with isocyanoacetates is a very simple and straightforward method to access large varieties of different peptides and peptide-like products.

10.3. Ugi-Type Heterocyclizations of Isocyanoacetate Derivatives

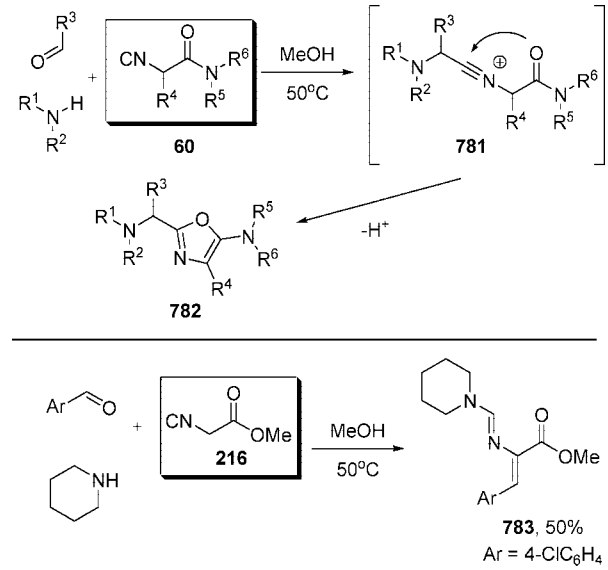
The multifarious reactivity of isocyanoacetate derivatives provides a broad range of opportunities for the multicomponent synthesis of heterocycles. In general, Ugi-type heterocyclizations are based on the reaction of an isocyanoacetate derivative with imines (prepared or formed *in situ*) to afford an initial nitrilium ion, which then cyclizes through interaction with the carboxylic moiety. In this chapter, a range of MCRs based on isocyanoacetates or -amides leading to a plethora of heterocyclic structures are discussed in detail.

10.3.1. Multicomponent Oxazole Synthesis

In 2001, Zhu et al. reported a three-component Ugi-type synthesis of 5-aminooxazoles from α-isocyanoacetamides and imines. Thus, simply heating a methanol solution of an aldehyde, an amine, and isocyanoacetamide **60** provided 5-aminooxazoles **782** through formation of the iminium intermediate **781** (Scheme 194).[392] The condensation was performed with approximately equimolar quantities of the three components, simplifying the purification step.[50]

The use of an α-isocyanoacetamide in the place of an isocyanoacetate is crucial. Matsumoto and co-workers reported already in 1978 that simply heating a solution of 4-chlorobenzaldehyde, methyl isocyanoacetate **216**, and piperidine in MeOH led to the formation of amidine **783** in 50% yield.[94] The reaction is most likely initiated by a Knoevenagel condensation followed by a formal α-addition

Scheme 194

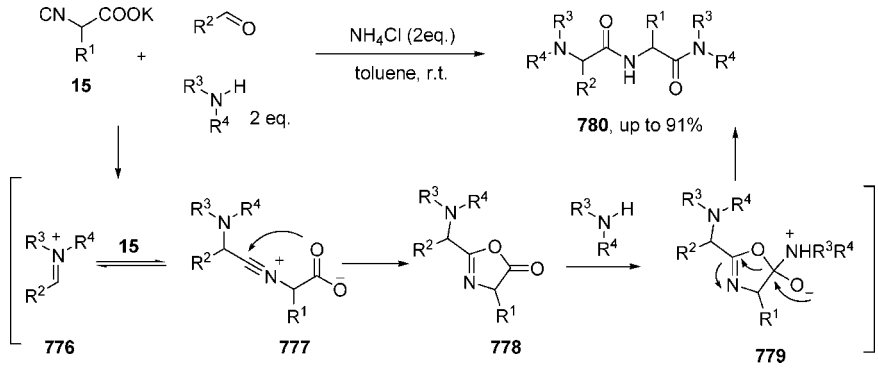


of the secondary amine onto the isocyano group. The following characteristics of α-isocyanoacetamides in comparison to α-isocyanoacetates are responsible for this behavior. First, the pK_a of an amide is 2−4 units lower than that of an ester. Consequently, the α-methylene proton of an amide should be less easily deprotonated, and the isonitrile carbon is slightly more nucleophilic. Second, the higher Lewis basicity of the amide oxygen compared with that of the corresponding ester should kinetically favor the ring-forming process. Since oxazole formation is irreversible, the increased reaction rate of this step should provide the overall driving force to the desired transformation.

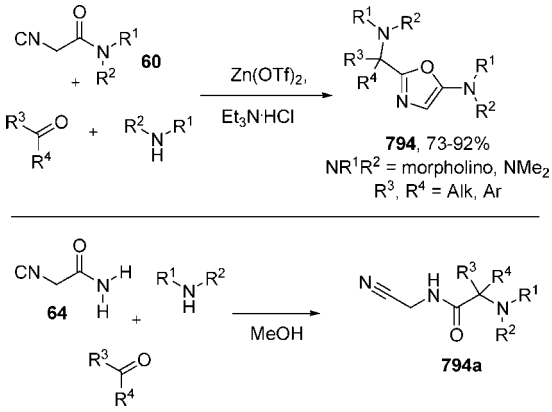
A variety of amines, aldehydes, and isocyanoacetamides have been used for the preparation of the corresponding oxazoles **782**. No racemization was detected when enantiomerically pure amino esters were used as amine component. The reaction initially was performed in methanol. It was found that in the presence of a weak Lewis acid (LiBr) or protic acid (NH_4Cl, CSA), the condensation took place efficiently in toluene.[393]

In 2003, Ganem et al. found that α-unsubstituted isocyanoacetamides **60** can react with carbonyl compounds and amines in the presence of $Zn(OTf)_2$ and $Et_3N\cdot HCl$ leading to 2-aminoalkyl oxazole derivatives **794** in good yields with a broad variety of aliphatic or aromatic carbonyl compounds (Scheme 195).[394] The same reaction with N-unsubstituted isocyanoacetamide (for example, **64**) leads to formation of

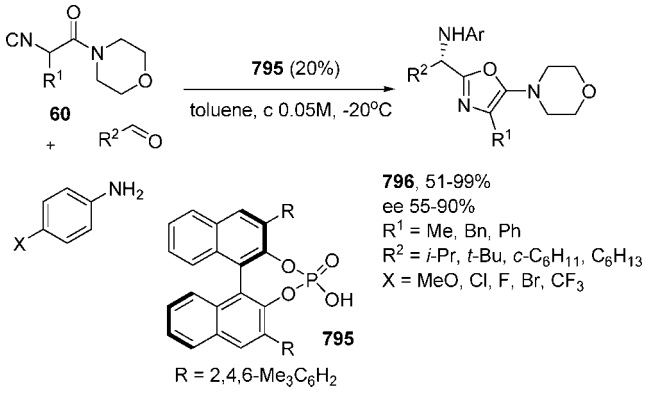
Scheme 193



Scheme 195



Scheme 196



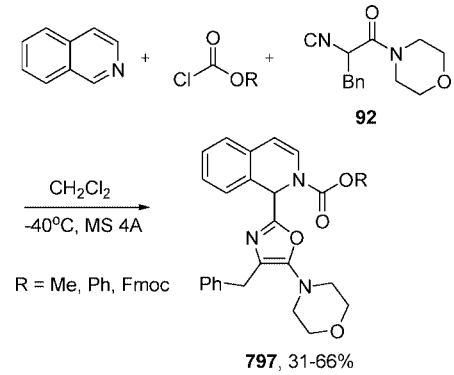
N-(cyanomethyl) amides **794a** instead of oxazoles, representing a new multicomponent reaction (see section 10.6, Scheme 237).[395]

Very recently, an enantioselective variant of the oxazole MCR was developed by Zhu et al. The reaction of aldehydes, anilines, and isocyanoacetamides in the presence of 20% chiral phosphoric acid diester **795** afforded optically enriched oxazole derivatives **796** in excellent yields and moderate to good enantiomeric excess (Scheme 196). The best results (90% ee) were observed with sterically hindered pivalaldehyde ($R^2 = t$-Bu) and 4-trifluoromethyl aniline ($X = CF_3$).[396]

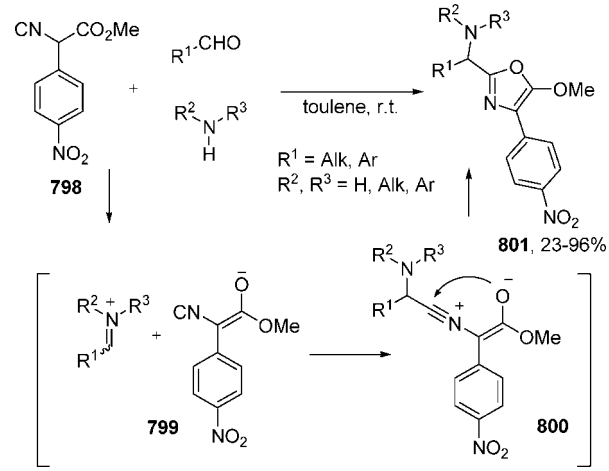
The three-component reaction of isoquinoline, chloroformates, and isocyanoacetamide **92** (CH_2Cl_2, −40 °C, 4 Å molecular sieves) provided the (1,3-oxazol-2-yl)-1,2-dihydroisoquinolines **797** in good yields. A variety of chloroformates such as ClCOOMe, ClCOOPh, and FmocCl can be used in the reaction to provide the corresponding N-acylated derivatives (Scheme 197).[397]

In 2007, Zhu et al. also reported on the application of methyl 2-isocyano-2-(4-nitro)phenylacetate **798** in the three-component synthesis of 5-methoxyoxazoles **801**. The nitro group is strategically incorporated into the phenyl ring to render the α-C−H bond even more acidic, so that it can be deprotonated by weaker bases. Moreover, nucleophilicity of the isocyanide group increased due to easy formation of enolate **798a**. The reaction was performed with an approximately equimolar amount of the three components in toluene at room temperature and gave the corresponding 5-methoxyoxazoles **801** in good or excellent yields. Various aliphatic and aromatic aldehydes, including formaldehyde, were found to be good substrates. Both aliphatic and aromatic amines participated in the reaction. Cyclic secondary amines generally afforded the oxazole product in higher yield than

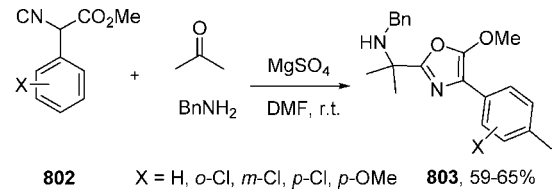
Scheme 197



Scheme 198



Scheme 199



primary amines. The formation of the iminium enolates **799** is favored by the high acidity of the enol tautomeric form of the isocyanoester **798**. Evolution of **799** to the dipoles **800** followed by 1,5 dipolar cyclization affords the final oxazoles **801** (Scheme 198). Consequently, the reactivity profile of **798** is completely different from that of usual isocyanoacetates and more like that of α-isocyanoacetamides.[398]

Orru et al. extended the scope of this reaction by using various less acidic aryl isocyanoacetates **802** by tuning of reaction conditions (DMF was used as a solvent in presence of $MgSO_4$ or other additives). When the pK_a of the α-proton of **802** becomes too high ($X = 2,4\text{-}(CH_3O)_2C_6H_3$, for example), no reaction is observed. In the cases of other isocyanoacetates **802**, 5-methoxy oxazoles **803** can be obtained in good yields (Scheme 199).[399]

10.3.2. Multicomponent Oxazole Synthesis and in Situ Tandem Reactions

5-Aminooxazole has an electron-rich 2-azadiene fragment, which can undergo Diels−Alder reaction with electron-poor dienophiles. The use of amines containing double or triple bonds sets the stage for intermolecular Diels−Alder reactions

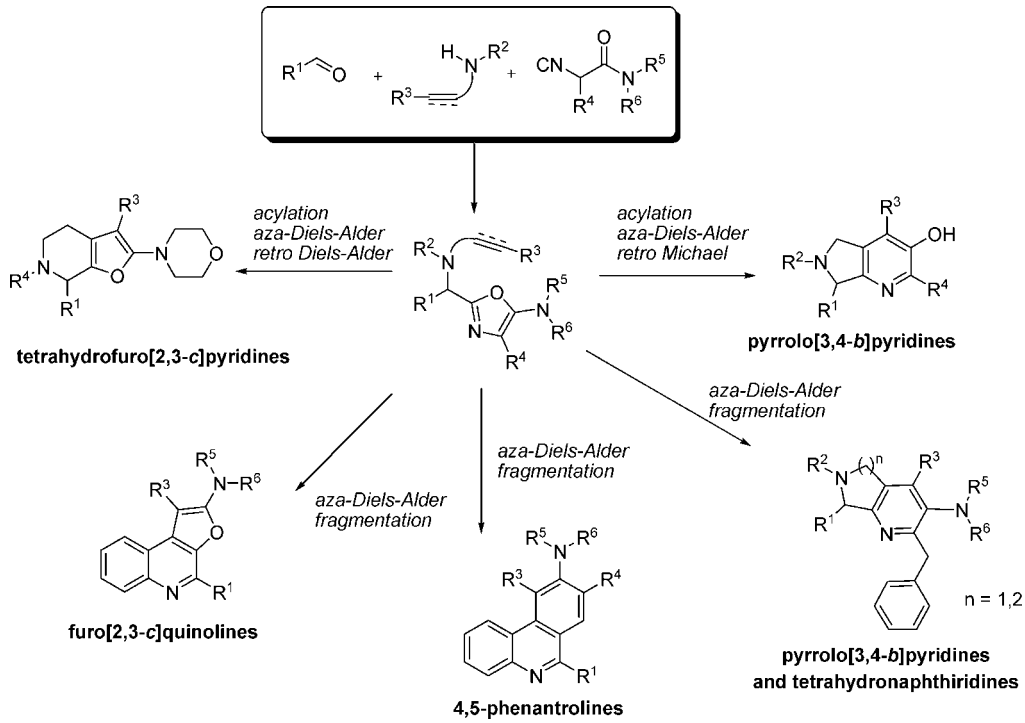
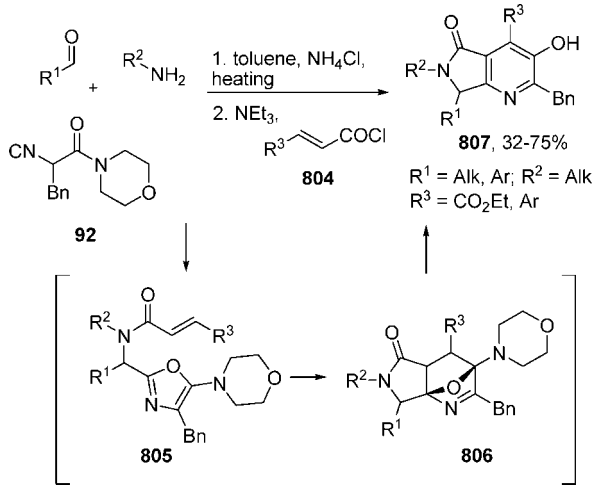
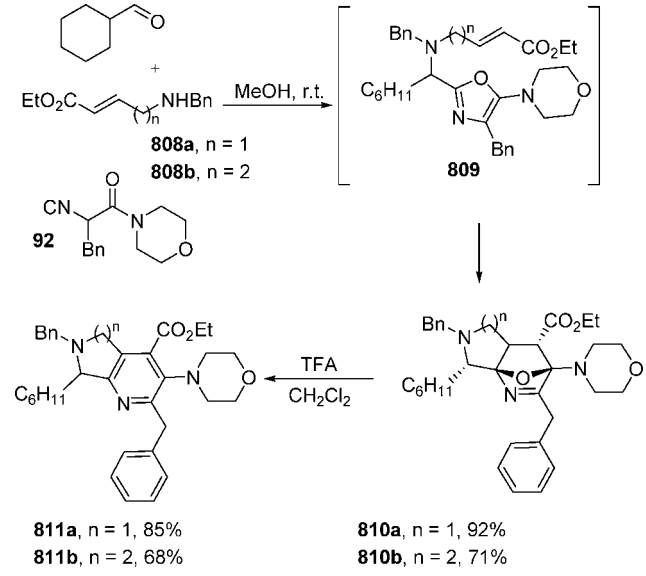


Figure 8.

Scheme 200



Scheme 201



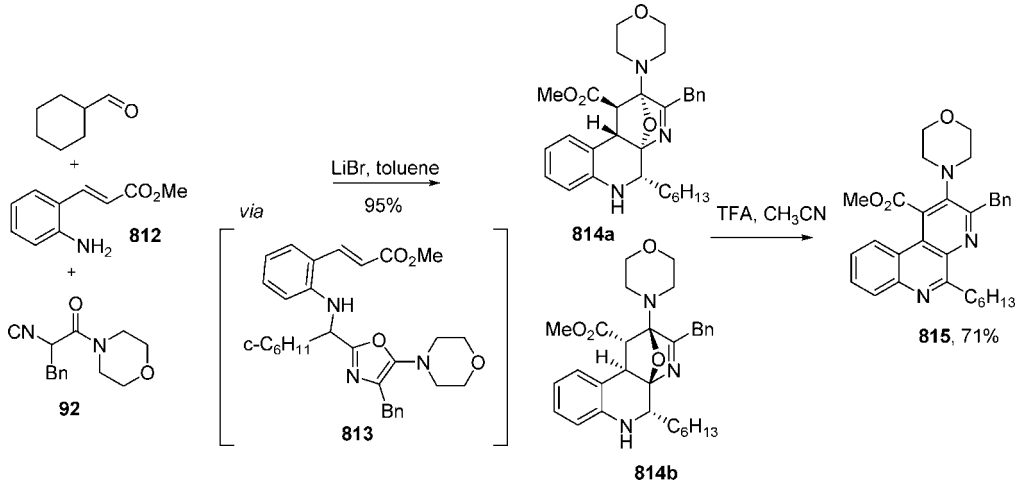
and subsequent tandem transformations, which offer opportunities for the synthesis of a broad range of heterocyclic systems. (Figure 8).

Zhu et al. described a novel four-component synthesis of pyrrolo[3,4-*b*]pyridine-5-ones **807**. In the first step, the three-component reaction between aldehydes, amines, and isocyanoacetamide **92** affords oxazoles, which are acylated with the appropriate α,*β*-unsaturated acyl chloride in the presence of triethylamine to give the intermediates **805**, which can undergo intramolecular Diels−Alder reaction to generate **806**. Subsequent retro-Michael reaction produces pyrrolo[3,4-*b*]pyridine-5-ones **807** in good yields. This domino-type reaction involves a three-component condensation, an acylation, an intramolecular cycloaddition, and a retro-Michael cycloreversion. Both aromatic and aliphatic aldehydes participated readily in this reaction (Scheme 200).[393]

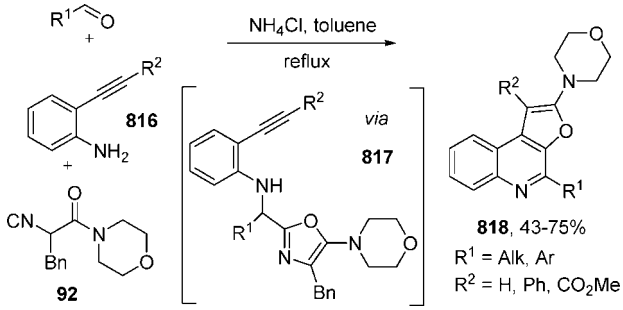
An alternative three-component synthesis of pyrrolo[3,4-*b*]pyridines **811a** and 5,6,7,8-tetrahydro-1,7-naphthyridines **811b** was described tethering an amine and a dienophile into a single component. The reaction between **808**, an aldehyde, and isocyanoacetamide **92** in methanol at room temperature provided oxa-briged tricycles **810** as single diastereomers in good yields. It is worth noting that one C−N, one C−O, and three C−C bonds were formed with concomitant creation of five asymmetric centers in this one-pot multicomponent process. Compound **810a** is readily fragmented to pyrrolo[3,4-*b*]pyridine **811a**,[400] while **810b** gave 5,6,7,8-tetrahydro-1,7-naphthyridines **811b**[401] in good yields after acidic treatment (Scheme 201).

Also, a three-component synthesis of tetracyclic tetrahydroquinolines based on the *ortho*-aminocinnamate **812** (amine and dienophile in a single component) was described. The approach is based on the reaction of an aldehyde, an amine, and an α-isocyanoacetamide **92** in toluene using a stoichiometric amount of LiBr as promoter. Under these conditions, two pairs of diastereomers **814** were produced

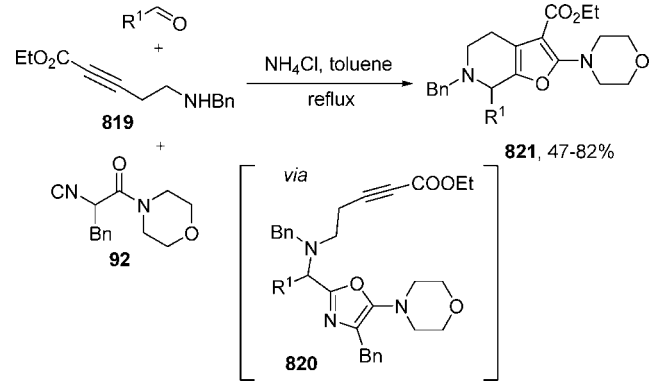
Scheme 202



Scheme 203



Scheme 204



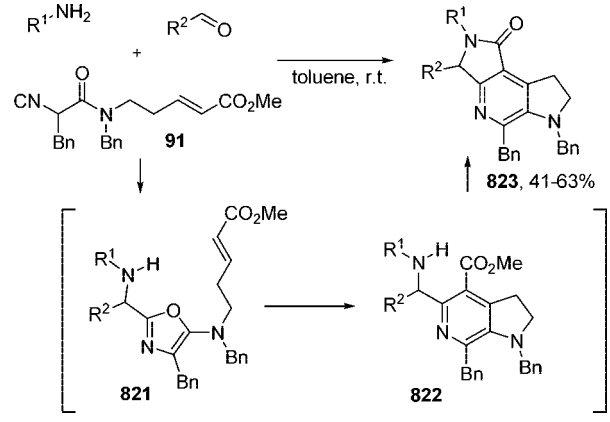
out of 16 possible isomers in 95% yield.[402] Under carefully controlled conditions, the mixture of **814** was cleanly converted to 4,5-phenanthroline **815** in 71% yield (Scheme 202).[403]

Bifunctional *ortho*-alkynyl aniline **816**, which contains an amine and a dienophile, was used for a three-component synthesis of polysubstituted furoquinolines **818**. These furoquinolines **818** were obtained by heating of **816**, an aliphatic or aromatic aldehyde, and isocyanoacetamide **92** in toluene in the presence of ammonium chloride. The initially formed oxazoles **817** underwent an intramolecular hetero-Diels−Alder cycloaddition followed by a fragmentation to afford **818**. Acetylenes bearing both electron-poor and neutral substituents participated in the reaction. Incorporation of various substituted amino functions was easily achieved by varying the isocyanoacetamide input (Scheme 203).[404]

When aminopentynoate **819**, a bifunctional acetylene-containing amine, was applied in this domino reaction, a novel three-component synthesis of tetrahydrofuro[2,3-*c*]pyridines **821** was found. Upon heating a toluene solution of an aldehyde, the aminopentynoate **819**, and α-isocyanoacetamide **92** in the presence of ammonium chloride, the corresponding products **821** were obtained in good to excellent yield. The fused ring system is produced in this one-pot process by the concomitant formation of five chemical bonds. A possible reaction sequence includes oxazole **820** formation, intramolecular Diels−Alder cycloaddition, and fragmentation by a retro-Diels−Alder process (Scheme 204).[405]

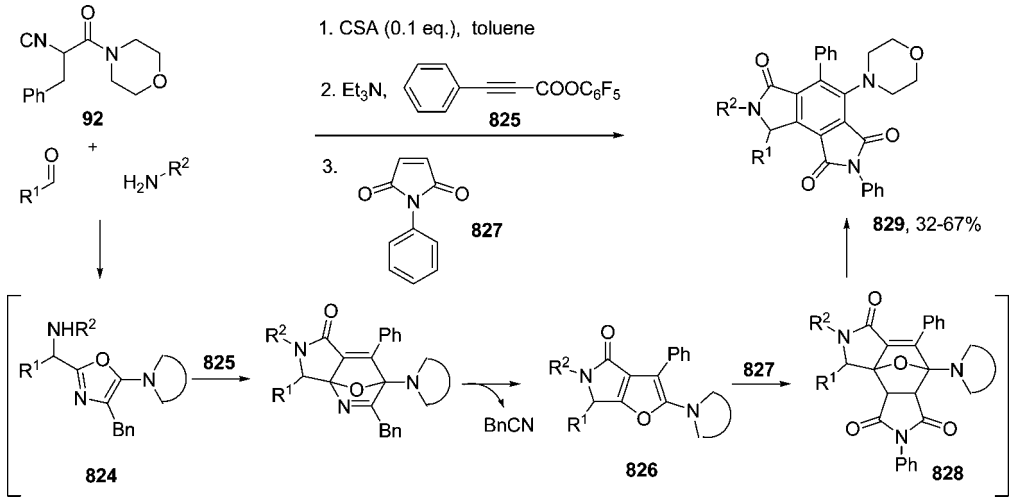
Isocyanoacetamides containing a double bond can be used for intramolecular Diels−Alder reaction as well. Thus, isocyanoacetamide **91** was used for a domino multicomponent synthesis of tricyclic derivatives of 6-azaindoles **823** in good yields. The reaction takes place with various aldehydes and amines in an ecologic and atom-economic route (Scheme 205).[49]

Scheme 205

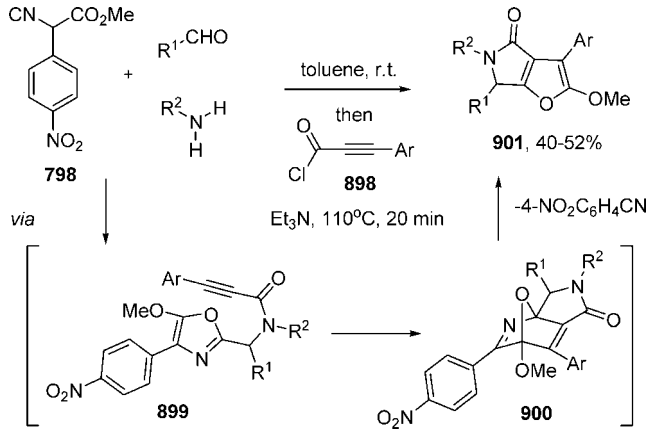


Recently, a conceptually new strategy for the synthesis of hexasubstituted benzenes **829** based on a one-pot multicomponent domino process was described. The reaction scenario includes a three-component oxazole **824** formation and subsequent reaction with acetylene **825** to deliver the furopyrroles **826**. This may be rationalized by a sequence consisting of acylation, intramolecular Diels−Alder cycloaddition, and retro-Diels−Alder cycloreversion to form **826**. Subsequent cycloaddition react of **826** with maleimide **827** followed by fragmentation of the oxa-briged derivative **828** would then provide the observed hexasubstituted benzene

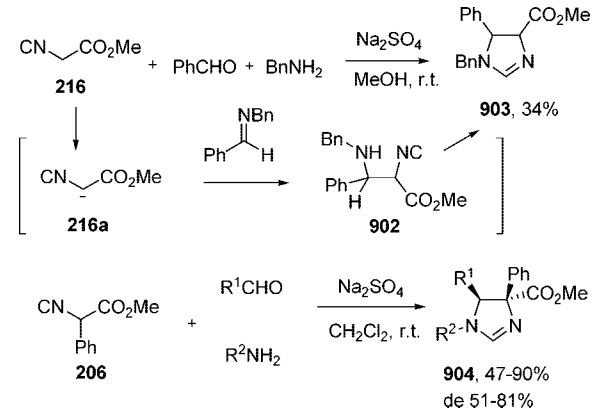
Scheme 206



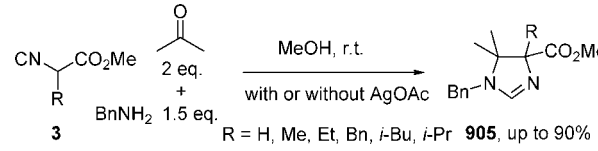
Scheme 207



Scheme 208



Scheme 209



829. The overall process leads to the creation of seven chemical bonds and delivers five elements of diversity into the polyheterocycle, thus providing a large increase in molecular complexity (Scheme 206).[406]

The same transformation was successfully carried out with isocyanoacetate **798** and acyl chloride **898**, containing an acetylene fragment. Diels−Alder reaction and subsequent fragmentation of **900** leads to formation of the corresponding furopyrrolones **901** in moderate to good yields (Scheme 207).[398]

In summary, the MCR-based oxazole synthesis with subsequent tandem reactions (Diels−Alder reaction, particularly) as discussed here is a highly productive route that allows preparation of new complex heterocyclic systems in an efficient step- and atom-economic manner.

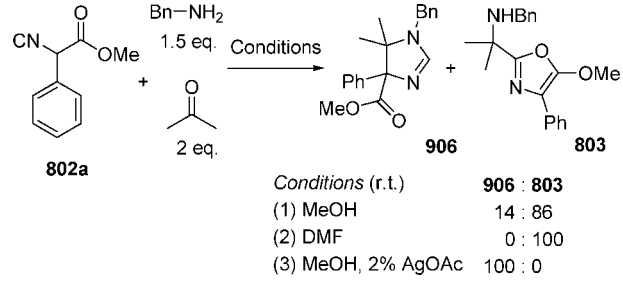
10.3.3. Multicomponent Imidazoline Synthesis

In 2003, Orru et al. observed the formation of imidazoline **903** (yield 34%) in the reaction of benzaldehyde, benzyl amine, and methyl isocyanoacetate **216**. The reaction proceeds via initial addition of isocyanoacetate anion **216a** to the *in situ* generated imine with subsequent cyclization of adduct **902**. The more α-acidic isocyanide **206** proved a more suitable substrate, which reacts in a smooth fashion to the corresponding imidazolines **904**. One-pot reaction of **206** with functionalized aliphatic, aromatic, or benzylic amines and aliphatic, (hetero)aromatic, or α,β-unsaturated aldehydes provides a range of imidazolines **904** in moderate to good isolated yield and in moderate diastereoselectivity (Scheme 208). The reaction is sensitive to steric factors (Ph_2CHNH_2 gave the corresponding imidazoline only in 13% yield).[407]

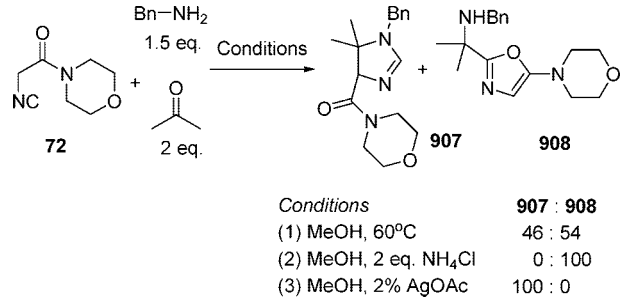
In a more recent study (2007), the scope of the reaction was broadened toward less α-acidic isocyanoacetates.[408] The reaction between acetone, benzylamine, and methyl isocyanoacetates was shown to proceed in various solvents, MeOH being most practical and effective. This MCR is virtually free of side processes and is therefore well-suited for effective imidazoline **905** synthesis. For less reactive substrates, the reaction may require quite a long period of time (up to 2 weeks). Silver(I) acetate was found to accelerate the reaction, probably by coordination of the isocyanide carbon to Ag, which increases the α-acidity and NC electrophilicity (Scheme 209).[408,409]

In addition to formation of 2-imidazolines **906**, a different MCR yielding 2-substituted oxazoles **803** is reported that involves essentially the same components (section 10.3.1, Scheme 199). Consequently, under certain conditions both processes may take place competitively. For example, reaction of α-phenyl isocyanoacetate **802a** with benzyl amine and acetone yields a 14:86 mixture of imidazoline **906** and

Scheme 210



Scheme 211



oxazole **803** upon mixing in methanol. Addition of AgOAc leads to exclusive formation of imidazoline **906** whereas the use of DMF as a solvent provides oxazole **803** as the sole product (Scheme 210). It should be noted, however, that the formation of oxazoles **803** is typical only for isocyano esters with enhanced CH acidity (e.g., isocyanoacetates containing a α-substituent stabilizing a negative charge), whereas in the other cases imidazolines are obtained as major products.

If isocyanoamides are used in the place of isocyano esters, the regioselectivity of formation of imidazolines and oxazoles also can be directed by choosing suitable reaction conditions. For example, reaction of isocyanoacetamide **72** with benzyl amine and acetone yields a nearly 1:1 mixture of imidazoline **907** and oxazole **908** in methanol. The reaction can, however, be completely directed to either the imidazole or the oxazole by using AgOAc or NH_4Cl, respectively (Scheme 211).[399] In a similar experimental setup, it was shown that primary isocyanoamides afford in high yields *N*-(cyanomethyl)amides (section 10.6, Scheme 237).

Due to the high functional group tolerance and high conversions generally observed (>90%), the 2-imidazoline MCR could be combined with other MCRs in the same pot, generating higher order multicomponent reactions (union of MCRs). In addition, the broad solvent compatibility observed for the 2-imidazoline MCR allows selection of the optimal solvent for the follow-up MCR. The most straightforward approach to such combinations of MCRs is the incorporation of a functional group in one of the inputs of the primary MCR that does not participate in the reaction but does react as one of the components in the secondary MCR (Figure 9).[410]

For example, using an amino acid as amine input ($R^5 = CHR^6CO_2H$) in the 2-imidazoline MCR under basic conditions resulted in the formation of an imidazoline **909a** bearing a carboxylic group ($R^5 = CHR^6CO_2^-$). This salt can be used as carboxylic acid component in a subsequent Ugi-4CR after protonation. The resulting 2-imidazoline Ugi products **910** generated by this formal 6CR could be isolated in 38−62% (93% yield per bond formation). Moreover, this approach allows variation on no less than nine positions in a single reaction step. The same approach turned out to be successful using levulinic acid allowing formation of 2-imidazoline **909b** ($R^3 = Me$, $R^4 = (CH_2)_2CO_2H$). One-pot combination with Ugi-4CRs or a Passerini-3CR affords **911** and **912**, respectively (32−58%). Introduction of an aliphatic isocyanide functional group by using a diisocyanide ($R^2 = (CH_2)_3NC$) allowed the union with Ugi, Passerini, and other isocyanide-based MCRs at the position 4 of the 2-imidazoline **909c**, which gave **913**−**916** in 41−78% yield (Scheme 212).[410]

The MCR affords highly substituted imidazolines, which are not functionalized at the C2 position and thus can be used for further modification. Thus, imidazolines **917** prepared by this MCR have been used in versatile syntheses of Rh and Ir *N*-heterocyclic carbene complexes **918**[411] and nutlin (tumor suppressor p53−mdm2 interactions antagonist) analogues **919** (Scheme 213).[412] Dömling et al. also used 2-imidazoline MCR for synthesis of library of potential p53−mdm2 interaction inhibitors.[413]

Potent antiplasmodial and antitrypanosomal imidazolines **921** were prepared by this 3CR from amine **920** and various aldehydes (Scheme 214).[414]

In conclusion, the Orru-3CR for 2-imidazolines is a highly efficient method to generate a broad variety of functionalized imidazolines for application in bioorganic and medicinal chemistry. Application of this 3CR in the union of MCRs makes it a very attractive platform for combinatorial chemistry and synthesis of libraries of pharmaceutically interesting compounds.

10.3.4. Miscellaneous Ugi-Type Heterocyclizations

A new three-component synthesis of 5-iminooxazolines starting from aldehydes, amines, and α,α-disubstituted isocyanopetides was developed by Zhu et al. Thus, for example, reaction of an α,α-disubstituted α-isocyanoacetamide **89**, an aldehyde, and a functionalized amine **922** afforded the 5-iminooxazoline **925** in 50% yield (Scheme 215). The reaction proceeds with complete conversion of the substrates. The low isolated yields are caused by partial degradation during purification. The obtained iminoxazolines were engaged without purification in a subsequent macrocyclization (see next section).[48]

The Ugi-type reaction of cyclic isocyanoacetamide **926** (see Scheme 238 for the synthesis) with amines and carbonyl compounds allows the construction of a very broad range of dihydrooxazolopyridines **927**, an unexplored class of bicyclic compounds, in good yields. This interesting new scaffold has high potential for drug discovery (Scheme 216).[415]

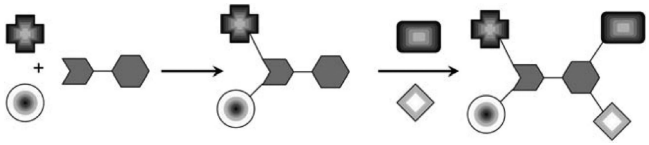
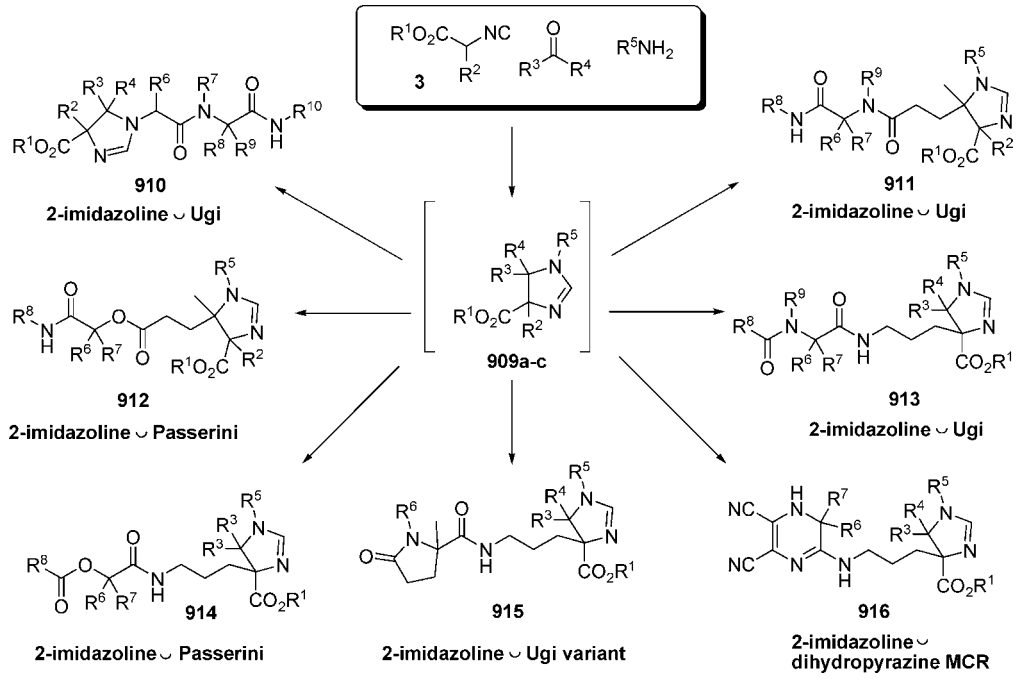


Figure 9. Union of MCR. Reprinted with permission from ref 410. Copyright 2009 WILEY-VCH Verlag GmbH & Co. KGaA.

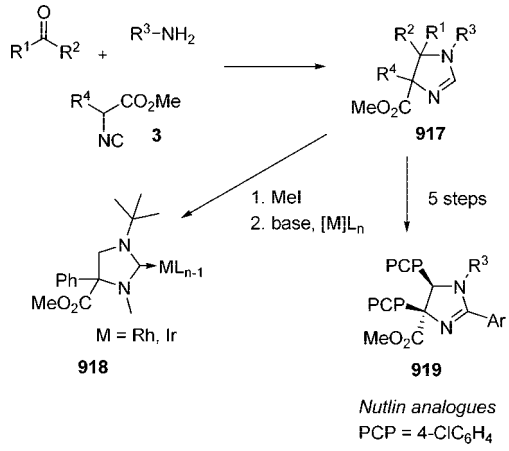
10.4. Passerini-type Heterocyclizations of Isocyanoacetate Derivatives

It was found that isocyanoacetic acid derivatives can undergo Passerini-type heterocyclizations with carbonyl compounds activated by Lewis acids. Thus, activation of carbonyl compound with Zn^{2+} in a reaction with isocyanoac-

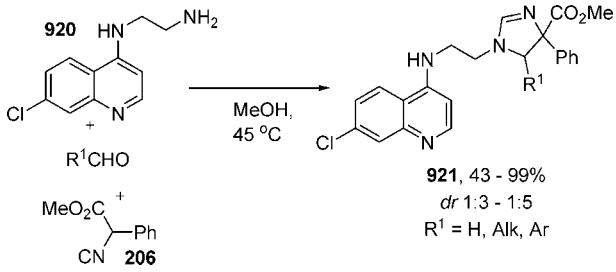
Scheme 212



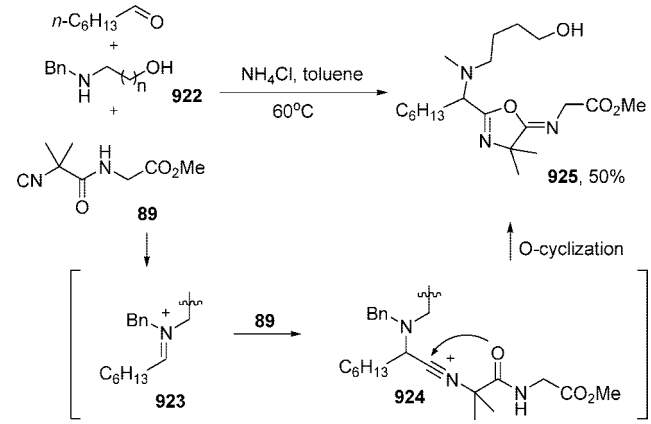
Scheme 213



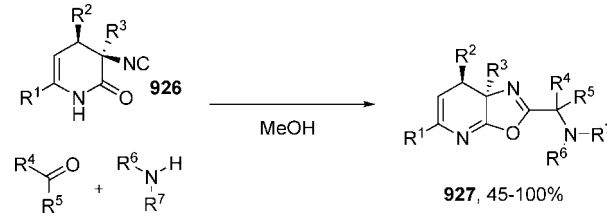
Scheme 214



Scheme 215



Scheme 216

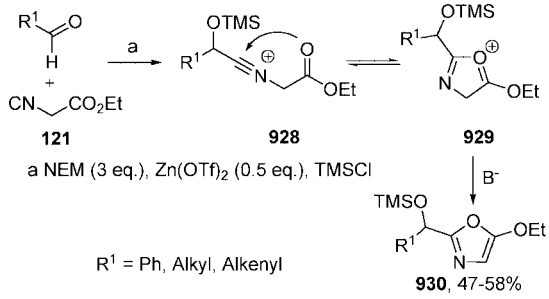


etates was examined by Ganem et al. Ethyl isocyanoacetate **121** reacts with aldehydes and afforded oxazoles **930** in the presence of 0.5 equiv of $Zn(OTf)_2$ and 3 equiv of *N*-ethylmorpholine (NEM). A plausible mechanism involves a neighboring group effect, leading to stabilization of the initial nitrilium ion **928** as oxonium ion **929**. Deprotonation of **929** gives oxazole **930** in good yield (Scheme 217).[416]

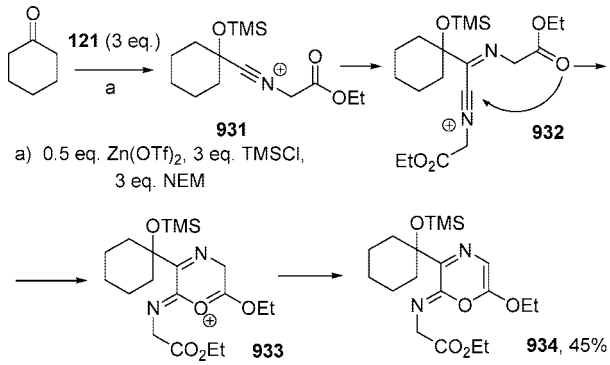
By using cyclohexanone as the carbonyl component, the formation of oxazoles of type **930** (64% yield) was accompanied by an unusual substituted 2*H*-1,4-oxazin-2-one **934**. The formation of **934** involves trapping of the initially formed nitrilium ion **931** with a second molecule of isocyanide leading to **932**. Cyclization of the ethoxycarbonyl group in **932** gives **933**. Subsequent deprotonation affords **934**. The yield of **934** could be increased up to 45% when 3 equiv of isocyanoacetate was used (Scheme 218).[416]

Isocyanoacetamides also can be involved in these Passerini-type heterocyclizations. Thus, isocyanoacetamides **60** react smoothly with aliphatic carbonyl compounds in the presence of R_3SiCl and $Zn(OTf)_2$ as the Lewis acid to give protected 2-hydroxyalkyl oxazole derivatives **935** in good yields.[394] Benzaldehyde gave, along with **935a**, a significant amount of **936a**, which is the product of a second condensation of benzaldehyde at the 4-position of oxazole. As expected, **936a** became the dominant products (yield 61%)

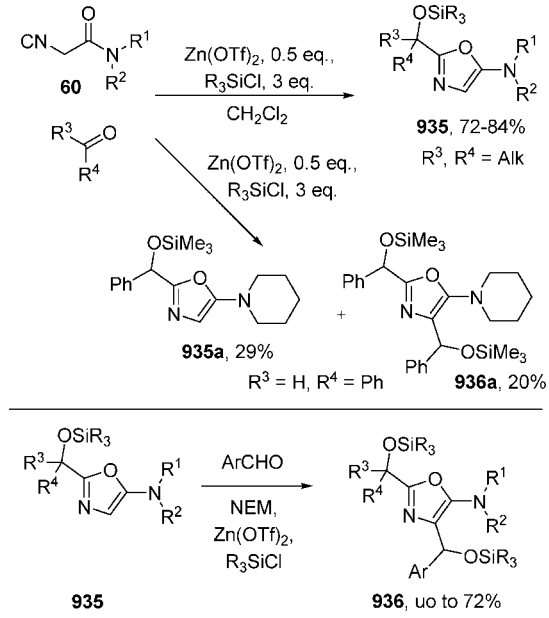
Scheme 217



Scheme 218



Scheme 219

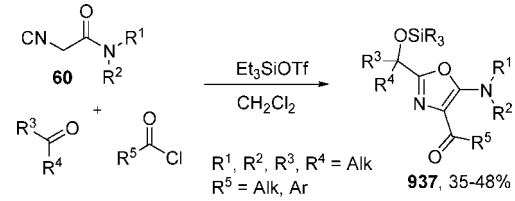


when 2 equiv of benzaldehyde was used. The high reactivity of the 4-position in oxazoles toward electrophilic attack can offer useful opportunities for further modifications. Thus, oxazoles **935** can undergo subsequent electrophilic reaction with a variety of benzaldehydes to afford trisubstituted oxazole derivatives **936** in good yields (Scheme 219).[417]

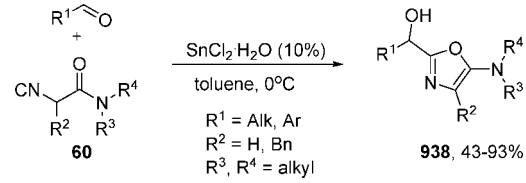
The use of acyl chlorides as electrophiles allows formation of 2,4,5-trisubstituted oxazoles **937**. The reaction can be carried out as a postcondensational modification of oxazoles **935** or as a one-pot, four-component condensation of carbonyl compounds, silyltriflates, isocyanoacetamides **60**, and acyl chlorides. The reaction can be successfully carried out with a range of a acyl chlorides (Scheme 220).[417]

In 2007, Zhu et al. developed a catalytic Passerini-type heterocyclization based on the addition of substituted isocyanoacetamides **60** to aldehydes in the presence of Lewis acids ($ZnCl_2$, $SnCl_2 \cdot 2H_2O$, $SnCl_4$, $Sn(OTf)_2$). They found that the reaction performed optimally in toluene in the presence of 0.1 equiv of $SnCl_2 \cdot 2H_2O$. In general, aliphatic aldehydes, either linear or α-branched, gave the corresponding oxazoles in higher than 80% yield. Less reactive aromatic aldehydes furnish the oxazoles **938** in 40−60% yields (Scheme 221).[418]

Scheme 220



Scheme 221



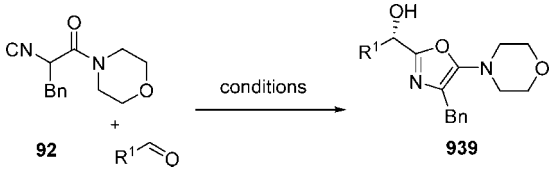
An enantioselective variant of this reaction using catalyst **940** and **941** was also reported. The reaction of isocyanoacetamide **92** and aldehydes in the presense of (salen)Al(III)Cl complex **940** led to enantioenriched 5-amino-2-(1-hydroxyalkyl)oxazoles **939** in good yields and moderate selectivity. The conditions are applicable to both aliphatic and aromatic aldehydes. In general, the ee is higher for aliphatic than for aromatic inputs.[419] The phosphoric acid **941**−aluminum complex was also used for enantioselective catalysis of this reaction. The approach is effective only for aliphatic carbonyl compounds and gave the same results as mentioned (excellent yields, ee up to 87%).[420] Very recently, Matsunaga, Shibasaki, et al. used a heterobimetallic Ga/Yb−Schiff base **942** complex for catalytic asymmetric α-addition of isocyanoacetamide **92** to aldehydes. The condition works efficiently for aryl, heteroaryl, alkyl, and alkenyl aldehydes and gives the corresponding oxazoles **939** in excellent yields and selectivity (Table 14).[421] Finally, the organocatalytic variant of this transformation catalyzed by chiral phosphoric acid was described very recently (see section 17).

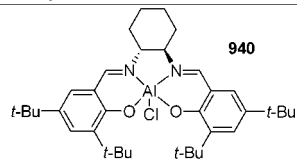
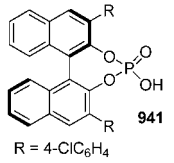
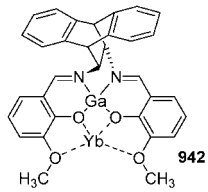
In conclusion, the polyfunctional nature of isocyanoacetic acid derivatives opens broad possibilities for various multicomponent heterocyclizations. The great advance of this chemistry is a simple modulation reactivity profile of isocyanoacetic acid derivatives by variation of substituents in the molecule.

10.5. Postcondensation Modification of the Multicomponent Reactions with Isocyanoacetate Derivatives

Multicomponent reactions with isocyanoacetic acid derivatives are extremely powerful synthetic tools for preparation of structurally diverse and complex molecules as well as for the easy access to combinatorial libraries of compounds. The synthetic possibilities of MCRs can be further increased by postcondensation transformations, especially, due to the presence of a range of functional groups in the products of MCRs. These modifications are usually accomplished by

Table 14



Entry	Catalyst and conditions	R^1 / Yield (ee)
1	 **940** (10%), toluene, -20 °C	Alk, Ar / 35-90% (up to 80%)
2	 **941** (10%), Et_2AlCl (5%), toluene, c 0.07M, -40 °C	Alk / 75-95% (up to 87%)
3	 **942** (10%), MS 4Å, CH_2Cl_2, -20 °C	Ar, HetAr, Alk, Alkenyl / 75-95% (88-98%)

employing suitable functionalized or protected components and take place spontaneously or upon treatment with additional reagents.

10.5.1. Intramolecular Amide Formation

Recently, a diversity-oriented macrocyclization strategy termed multiple multicomponent macrocyclization including bifunctional building blocks (MiBs) was developed that allows the synthesis of constitutionally diverse and complex macrocycles from simple building blocks in one pot.[422] The Ugi reaction with isocyanoacetates as isocyanide component and protected amino acid as an acid component, after deprotection, leads to peptide-like molecules, containing a carboxylic and an amino group on opposing sides of the molecule. This is useful for subsequent build-up of the molecule or for cyclization to macrocycles via a multiple multicomponent Ugi reaction. Thus an efficient approach to cyclic peptoids based on the repetitive Ugi reaction was described by Wessjohann et al. As an example, synthesis of cyclic peptides **947** was realized with sequential Ugi reaction with isocyanoacetate **121** and paraformaldehyde followed by deprotection. At the last stage peptide, **946** was cyclized to **947** again by an Ugi reaction (Scheme 222).[423]

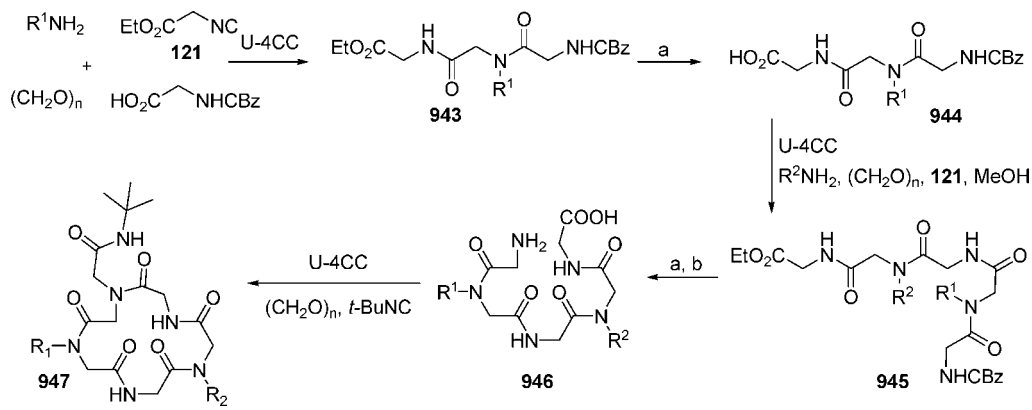
A novel application of the $TMSN_3$-modified Ugi four-component reaction was disclosed for a solution-phase synthesis of fused tetrazole libraries. Thus, Ugi reaction of an amine, an isocyanoacetate, trimethylsilylazide, and a carbonyl compound in methanol afforded tetrazoles **948**, which gave fused tetrazolo-ketopiperazines **949** after subsequent cyclization. The Ugi reaction of a *N*-Boc-amino aldehyde, followed by acid treatment of the product **950**, affords bicyclic azepine-tetrazoles **951** in good yields. This efficient protocol, producing products with three diversity points, can be used to generate arrays of biologically relevant small molecules for general and targeted screening (Scheme 223).[424]

10.5.2. Postcondensation Modification of Oxazoles

The rich chemistry of oxazoles opens broad possibilities for postcondensation modifications of the products. The reaction of aldehydes (2 equiv), diamine **952**, and diisocyanide **953** delivers at least three elements of diversity into the final 18-member macrocycle **954**. Various diamines and aldehydes were successfully used for synthesis of macrocyclic compounds type **954**. The overall process leads to the creation of six chemical bonds with the concomitant formation of two oxazole residues as part of a new macrocycle. Although compound **954** is already of considerable interest as, for example, a pincer ligand for metal complexation, it may also serve as a useful chemical platform for the production of new structures by taking advantage of the oxazole MCR/follow-up chemistry depicted in Scheme 224. Thus, hydrolysis of **954** under acidic conditions (THF/H_2O/TFA, 8/2/1) afforded the corresponding macrocyclic amide **955** (all six possible diastereomers were readily separated and identified by LC/MS).[425]

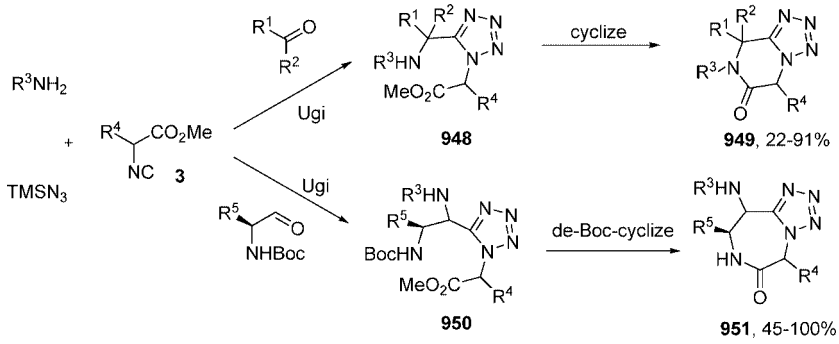
A new concept for the construction of macrocyclodepsipeptides **960**−**962** from aldehydes, amino alcohols, and isocyanopeptides is based on the synthesis of oxazoles **957**. The process involves a subsequent domino reaction with activation of the terminal carboxylic acid function of **957**

Scheme 222[a]

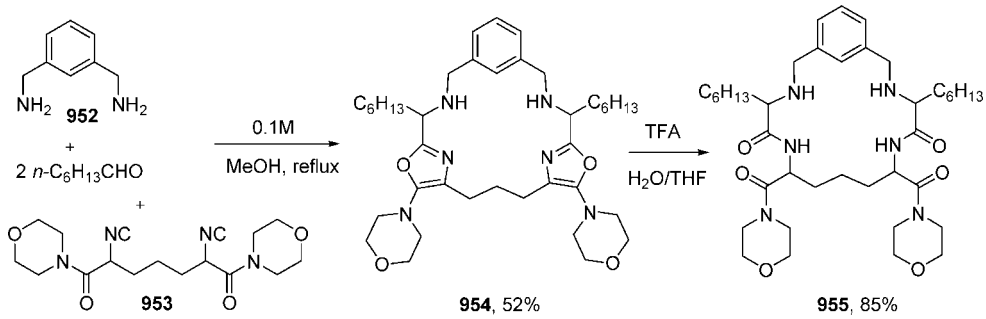


[a] Reagents and conditions: (a) LiOH, THF-H_2O, 0 °C; (b) H_2, Pd/C, MeOH.

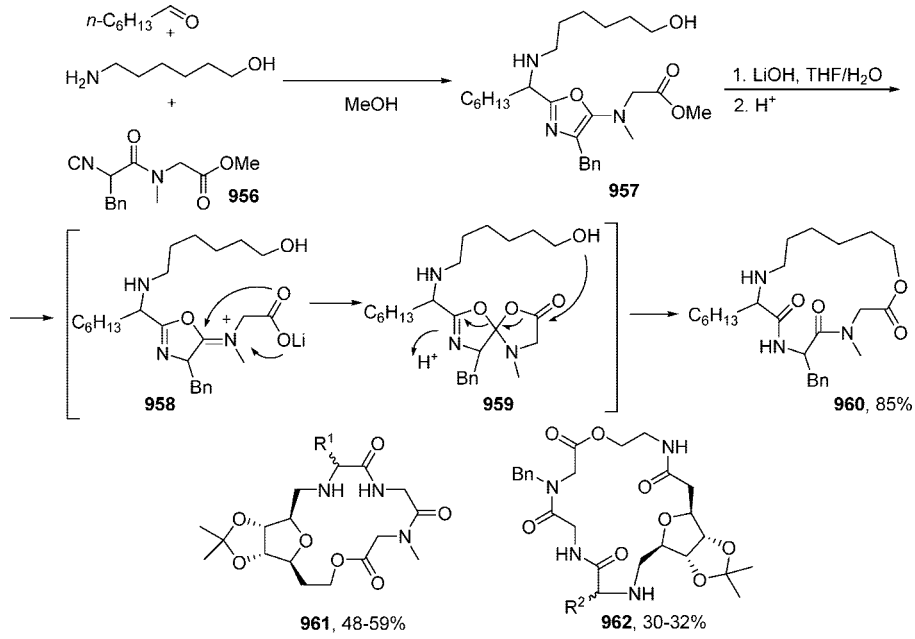
Scheme 223



Scheme 224



Scheme 225



followed by macrocyclization of **959** under acidic conditions.[426] Iminooxazolidines **925** (Scheme 215) can also cyclize in this manner.[48] The same methodology was used for the synthesis of macrocyclic sugar amino acids (SAAs) **961** and **962** (Scheme 225).[427]

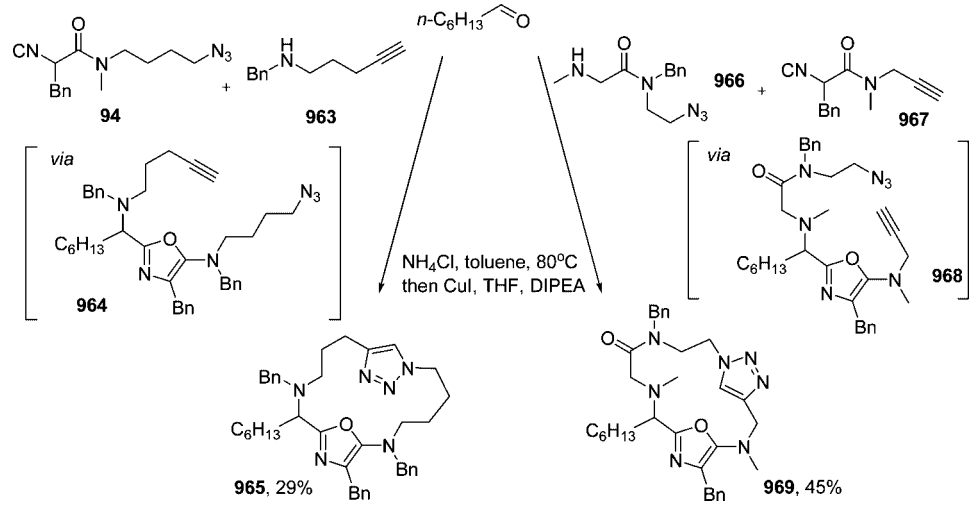
A broad variety of macrocycles were obtained via click chemistry using bifunctional aldehyde, isocyanoacetamide, or amine, bearing azide or alkyne. The multicomponent synthesis of oxazoles **964** and **968** and subsequent intramolecular Huisgen 1,3-dipolar cycloaddition reaction of azides and alkynes leads to 14-, 15-, and 16-membered macrocycles (**965** and **969**, for example). The oxazole core of compounds **964** and **968** induces preorganization for macrocyclization (Scheme 226).[51]

10.5.3. MCR and Ring-Closing Metathesis

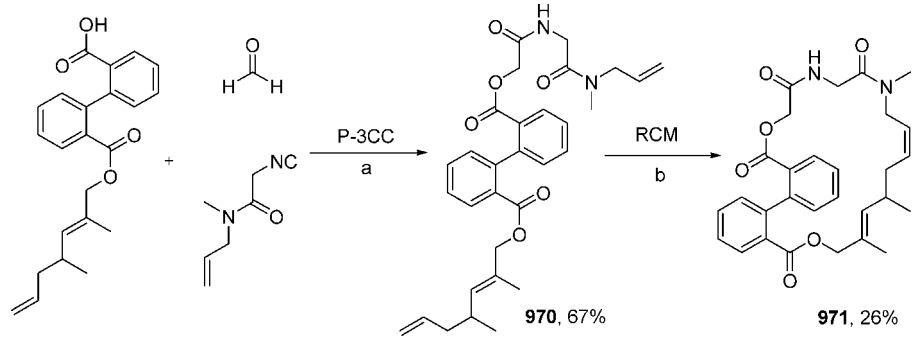
The ring-closing metathesis (RCM) of bis-olefins arising from isocyanide-based MCR has been employed by Dömling and co-workers to achieve ready access to macrocyclic lactones similar to natural compounds. Thus, the reaction of ω-olefinic carboxylic acid, double bond-containing isocyanoamide, and carbonyl compounds afforded the expected Passerini adduct **970**, which was ideally suited for a ring-closing metathesis reaction to give natural product-like macrocyclic lactone **971** (Scheme 227).[428]

A simple approach to several cyclic peptidomimetics containing an N-alkylated amino acid was described by Kazmaier et al. Linear natural and unnatural tripeptide allylic

Scheme 226

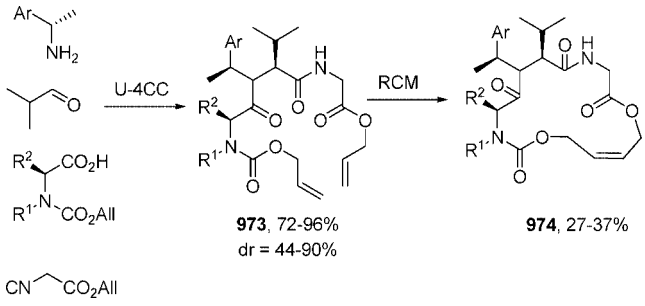


Scheme 227[a]

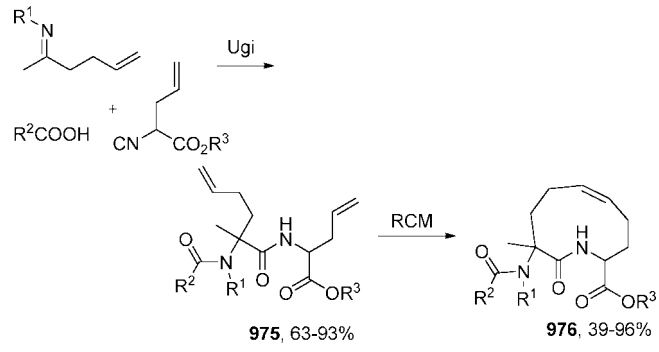


[a] Reagents and conditions: (a) Et_2O, 20 °C, 3 days, 67%; (b) Grubbs catalyst, Ti(O*i*-Pr)$_4$, DCM, reflux, 2 days, 26%.

Scheme 228



Scheme 229



esters **973** can be obtained in one step by Ugi reaction with excellent yields and in a stereoselective manner. Subsequent RCM opens a very flexible approach to cyclic peptides **974** (Scheme 228).[429]

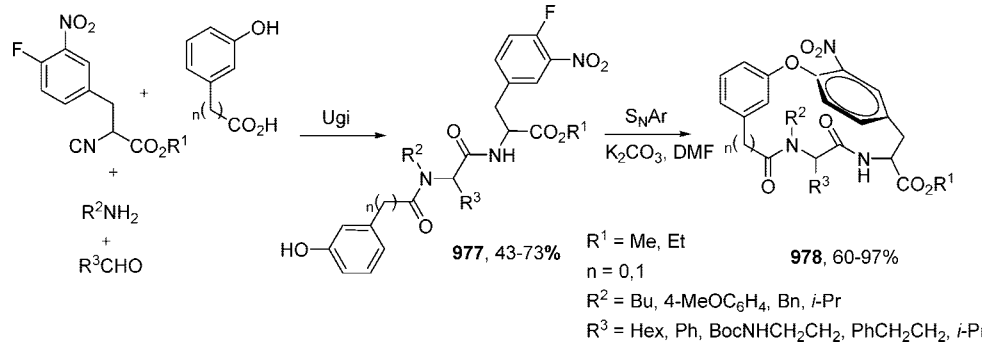
Banfi and co-workers applied the tandem Ugi reaction/ring-closing metathesis to the synthesis of unsaturated nine-membered lactams as potential reverse-turn inducers. Thus, Ugi reaction of racemic allyl-substituted isocyanoacetates with imines bearing a double bond gave adducts **975** that lead to nine-membered lactams **976** in the presence of first generation Grubbs catalyst (Scheme 229).[430]

10.5.4. Ugi−S_NAr Reactions and Ugi Cross-Coupling

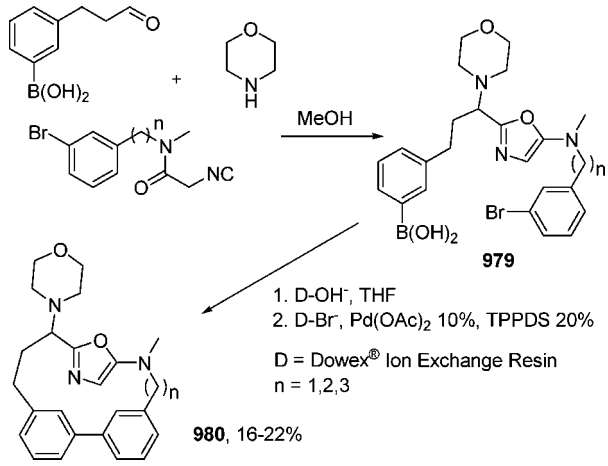
Zhu et al. reported a facile access to biologically relevant macrocycles bearing a diaryl ether fragment by means of a tandem Ugi-4CR/S_NAr. The reaction between hydroxy acid, aldehydes, amines, and benzyl isocyanoacetate gave the expected dipeptide derivatives **977** as a 1:1 mixture of diastereoisomers. The cycloetherification of **977** took place easily in DMF in the presence of potassium carbonate to give the macrocyclic diaryl ethers **978** in good yields. The presence of the nitro group in **978** allowed further transformations such as the reduction to amines and their transformations into amides, ureas, and sulfonylamides and deamination via diazonium salts (Scheme 230).[431]

A "resin-capture−release" hybrid technique for macrocyclization via intramolecular Suzuki−Miyaura coupling was described by Bienaymé. Oxazoles **979**, containing arylboronic and aryl bromide residues, were prepared by three-component reaction from the corresponding aldehyde, morpholine, and isocyanoacetamide. Products **979** could be isolated from the reaction mixture using the amine resin and

Scheme 230

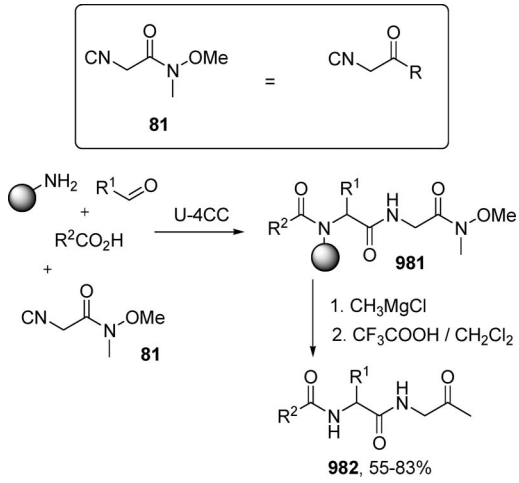


Scheme 231



transformed to target macrocycles **980** by ring-closure coupling (Scheme 231).[432]

Scheme 232



10.5.5. Miscellaneous Postcondensational Modifications

Weinreb isocyanoacetamide **81** opens broad possibilities for postcondensational modification of the Ugi products by reactions with organometallic compounds. In general, Weinreb-type amide **81** can be used as a synthetic equivalent of carbonyl compounds. Thus, compounds **981** prepared on solid support were subjected to further modification with a Grignard reagent. After removal from the resin, a library of compounds **982** was isolated in reasonable yields and purity suitable for biological testing (Scheme 232).[52]

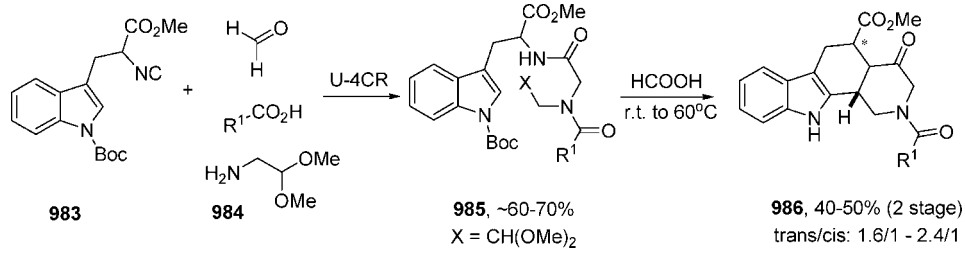
Very recently, Dömling et al. developed the efficient synthesis of indole derivatives via Ugi/Pictet−Spengler reaction with isocyanoacetate **983**. The Ugi reaction of protected isocyanoacetate **983** prepared from tryptophan, formaldehyde, carboxylic acid, and amine **984**, containing a protected carbonyl group, afforded indole derivatives **985** in good yields. Subsequent acid-mediated intramolecular Pictet−Spengler reaction leads to formation of indole derivatives **986** in good yield and moderate stereoselectivity (Scheme 233).[433]

10.6. Miscellaneous Multicomponent Reactions with Isocyanoacetate Derivatives

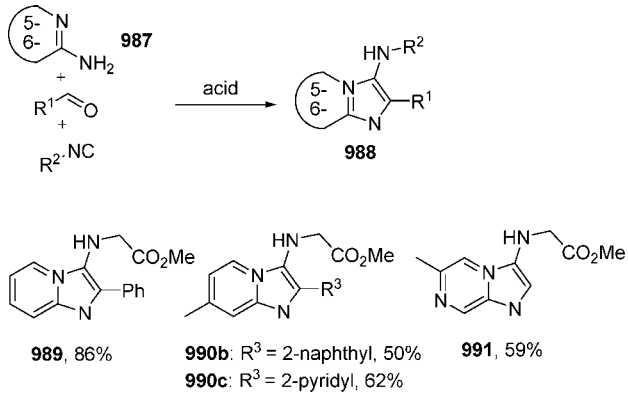
A recently discovered variation of the Ugi three-component reaction reported by Blackburn,[434] Groebcke,[435] and Bienaymé[436] employs 2-aminoazines (or 2-aminoazoles) **987**, isocyanides, and aldehydes in the presence of a variety of Lewis or Brønsted acids and generates fused imidazo[1,2-*a*]heterocycles **988** in a one-pot. The industrial application of this powerful 3-CC transformation is significant because imidazo[1,2-*a*]heterocycles have received great attention in drug discovery. Isocyanoacetates readily participate in this reaction and give the target products **989**,[436] **990**,[437] and **991**[438] in good yields (Scheme 234).

The multicomponent synthesis of imidazo[1,2-*a*] annulated heterocycles **988** was performed on the α-isocyano Wang resin

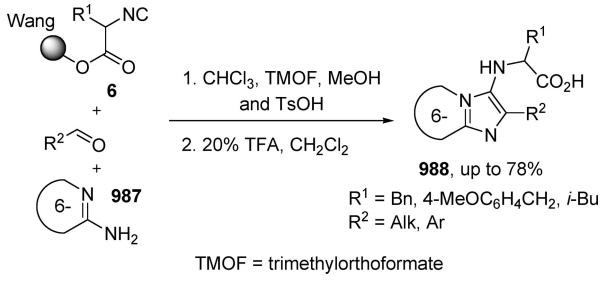
Scheme 233



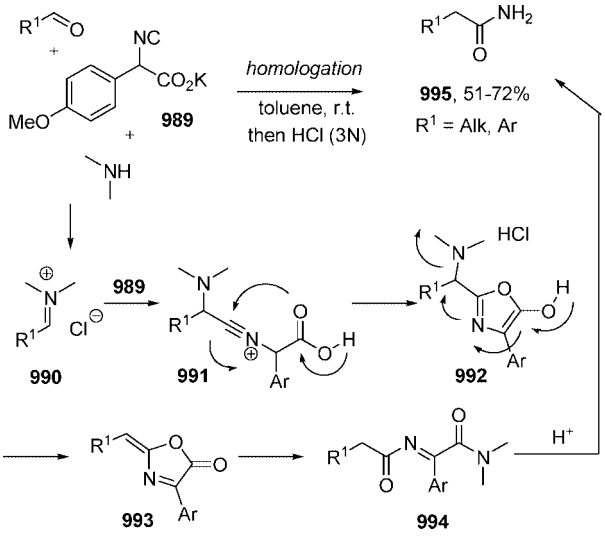
Scheme 234



Scheme 235



Scheme 236



6 by Chen et al. 3-CC and subsequent removal from solid support leads directly to the corresponding fused heterocycles **988**, containing a free carboxylic group (Scheme 235).[12]

Zhu et al. developed a novel method for oxidative homologation of aldehydes to amides **995**. The reaction is realized under very mild conditions using potassium isocyanoacetate **989**. *p*-Methoxyphenyl-α-isocyanoacetic acid **989** serves as reducing agent and donor of the $CONH_2$ function to the aldehyde via of oxazole **992** formation. The scope of the reaction is quite broad, and the yields are quite good (Scheme 236).[19] Thus, MCRs are effective not only for creating structural complexity and diversity but also for discovery of new fundamental transformations.

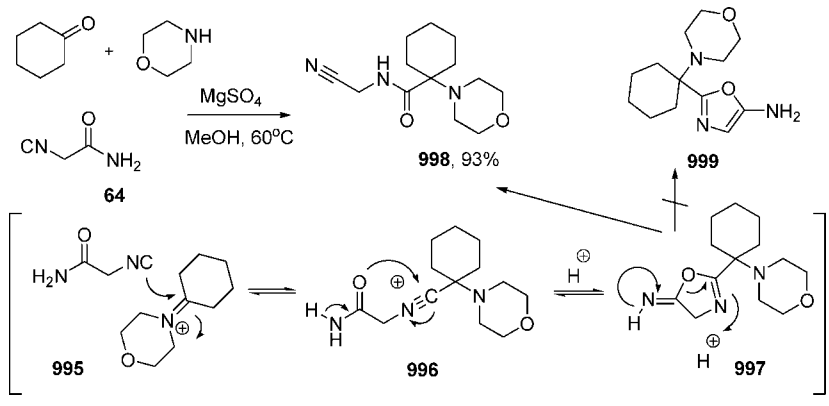
A new multicomponent reaction toward *N*-(cyanomethyl) amides was developed by Orru et al. The reaction of α-isocyanoacetamides, amines, and carbonyl compounds afforded *N*-(cyanomethyl) amides instead of the expected oxazoles. As an example, *N*-(cyanomethyl) amide **998** was obtained in excellent yield whereas formation of the corresponding oxazole **999** was not observed. In the observed process, proton abstraction and subsequent ring-opening of **997** and formation of **998** takes place instead of tautomerization and aromatization to form the oxazole **999**. The reaction proceeds smoothly with substituted or unsubstituted isocyanoacetamides, primary or secondary amines, and aldehydes or ketones (Scheme 237).[395] It is noteworthy that this "*N*-(cyanometyl) amide" MCR also can be involved in the union of MCRs (just like the imidazoline MCR (see Scheme 212) affording a record-holding eight-component reaction.

In 2006, Orru et al. developed a new diastereoselective four-component reaction in which a phosphonate, nitriles, aldehydes, and isocyanoacetates combine to afford functionalized *cis*-3-isocyano-3,4-dihydro-2-pyridones **926**. Aromatic, heteroaromatic, and α,β-unsaturated aldehydes and nitriles gave the expected products **926** in reasonable to excellent yields. However, primary aliphatic nitriles should be avoided because they are known to be less efficient in the generation of the azadiene **1000** (Scheme 238).[439]

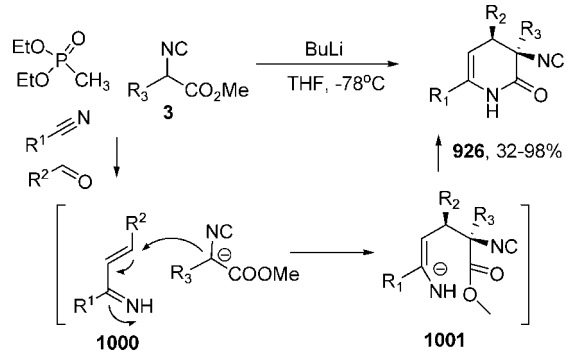
Isocyanides **926** open broad possibilities for follow-up Passerini-3CR and Ugi-4CR reaction and lead to a series of complex DHP-2-one based conformationally constrained peptides **1002**[440] and depsipeptides **1003** (Scheme 239).[441] Very recently, scope and limitations of synthesis of **926** and subsequent MCRs were studied by Orru et al.[442]

In conclusion, isocyanoacetate derivatives are widely used in multicomponent reactions for synthesis of peptides and peptide molecules as well as for heterocyclic synthesis. Rich polyfunctionality and many reactions are available now, which allow controlling the reactivity profile of isocyanoacetate derivatives and driving the reaction path to the formation of desired products.

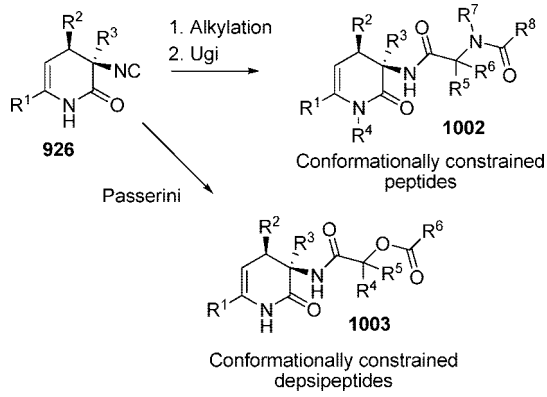
Scheme 237



Scheme 238



Scheme 239



11. Chemistry of Isocyanoacetates Bearing an Additional Functional Group

The synthesis and properties of β-dialkylamino-α-isocyanoacrylates, β-bromo-α-isocyanoacrylates, α-cyano-α-isocyanoacetates, 1-cyano-1-isocyanoalkylphosphonic acid esters will be discussed in this section (Figure 10).

11.1. β-Dialkylamino-α-isocyanoacrylates

The simplest representative of this class of compounds, β-dimethylamino-α-isocyanoacrylate **1006**, was first described by Schöllkopf in 1979. The corresponding methyl and ethyl esters are stable compounds, which can be prepared in good yield by a reaction between isocyanoacetate **1004** and dimethylformamide dimethylacetal **1005** in ethanol.[443] For the preparation of other dialkylamino analogs of **1006**, a versatile three-component reaction can be used. The method combines a secondary amine, *N*-formylimidazole diethylacetal **1007** and isocyanoacetate **1004** (Scheme 240).[444]

This procedure works well for sterically unhindered secondary amines only. Aromatic, primary, and sterically hindered secondary amines either are not reactive or do not give the desired compounds. It is interesting to note that all β-dialkylamino-α-isocyanoacrylates were prepared via this approach as single *Z*-isomers, most likely because then steric interactions between CO_2R and NR_2 groups in the same plane are minimized. More recently, resin-bound

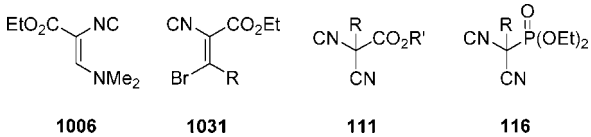
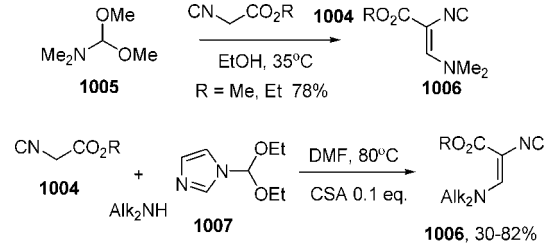
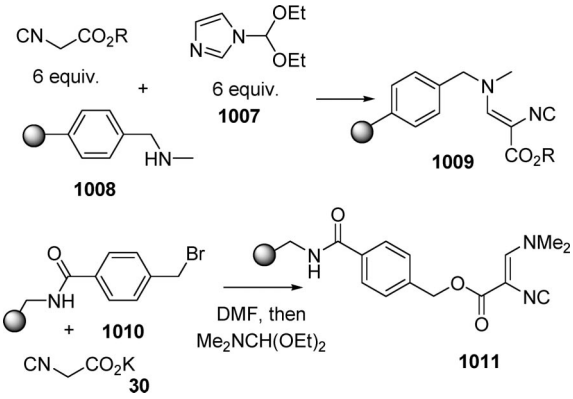


Figure 10.

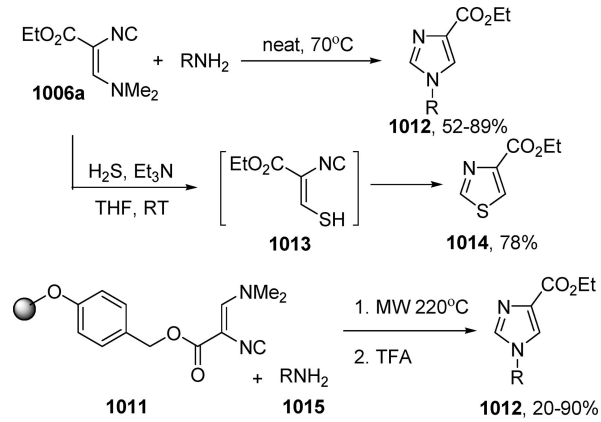
Scheme 240



Scheme 241



Scheme 242

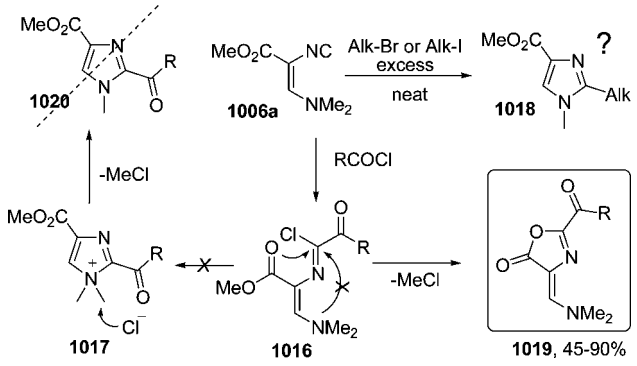


analogs have been prepared; they involve attachment of either the dialkylamino group (**1009**) or the ester group (**1011**) (Scheme 241).[445]

β-Dimethylamino-α-isocyanoacrylates are interesting substances that bear an isocyano functionality, a Michael acceptor, and dimethylamine as a leaving group in one molecule! This set of functionalities makes them especially interesting and valuable reagents. For example, **1006a** reacts with hydrogen sulfide to yield ethyl thiazole-4-carboxylate **1014** in a good yield (Scheme 242).[443] This reaction proceeds via initial Michael addition and dimethyl amine elimination, the intermediate product **1013** cyclizing spontaneously.

A similar reaction using primary amines occurs upon heating,[446] which provides a valuable and regioselective method for the preparation of 1-substituted imidazole-4-carboxylates **1012**. The reaction proceeds smoothly using primary amines bearing primary or secondary alkyl substituents. However, anilines or amines bearing tertiary groups are less reactive and require prolonged heating to achieve only moderate yields of the corresponding imidazoles. Recently a solid-phase microwave-assisted synthesis of

Scheme 243



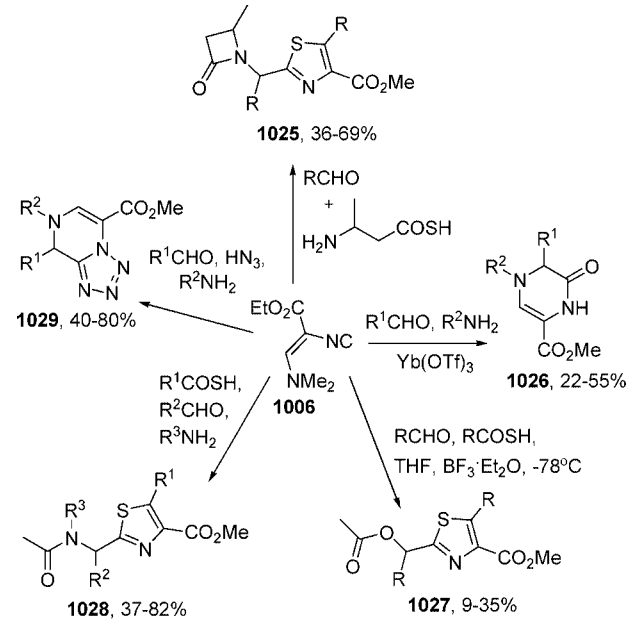
imidazoles **1012** using resin-bound reagent has been described by Henkel.[447] Primary alkylamines and several aromatic amines were successfully employed, some synthetically useful functionalities, such as OH, being tolerated in this reaction setup (Scheme 242).

On the other hand, reactions using electrophilic reagents have been scarcely studied. In 1982, Schöllkopf reported reactions with alkyl bromides and iodides and acyl halides to give imidazole derivatives **1018** and **1020**, respectively.[448] Some 10 years later Marcaccini reinvestigated the reaction with acyl halides, and he found that the product had a different structure than originally reported, namely, it appeared to be the 5-oxazolone derivative **1019** (instead of **1020**),[449] as independently confirmed by X-ray analysis (Scheme 243). The reaction with alkyl halides has not been revised, so it is not excluded that the structure of product **1018** in this reaction is the same as that in **1019**.

Marcaccini also studied reactions of **1006a** with arenesulfenyl chlorides and found that the structure of the products obtained differs depending on the electrophilicity of starting arylsulfenyl chloride. Thus, when strongly electrophilic reagents, such as nitro-substituted benzenesulfenyl chloride, are used, 5-oxazolone derivatives **1022** are obtained in good yield.[449] Less electrophilic substrates bearing an electron-donating substituent at the aromatic ring led to 2-imidazolyl-5-oxazolone derivatives **1024** (confirmed by X-ray analysis). The reaction proceeds via cyclizaton of **1023** and subsequent reaction with a second molecule of **1021** (Scheme 244).[450]

β-Dimethylamino-α-isocyanoacrylates **1006** show even more interesting reactivity in multicomponent reactions. This opens potential routes for the diversity-oriented synthesis of multiple scaffolds and their libraries, such as thiazoles **1025**, **1027**, and **1028**, ketopiperazines **1026**, and bicyclic tetrazolopiperazines **1029**. This multiarmed

Scheme 245



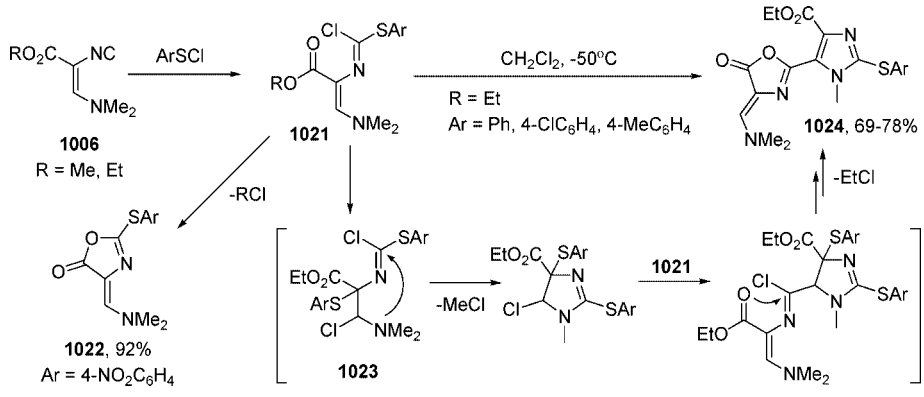
chemistry has been developed by the groups of Dömling, Bienaymé, and Illgen since 2000 and has been recently reviewed (Scheme 245).[451]

11.2. β-Bromo-α-isocyanoacrylates (BICA)

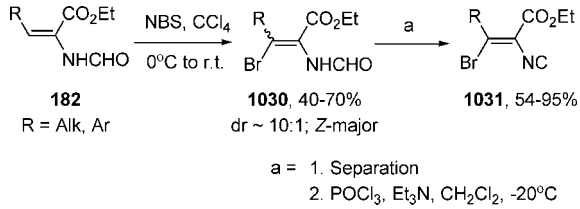
β-Bromo-α-isocyanoacrylates **1031** (BICA) are interesting polyfunctional building blocks. In many respects, they are quite similar to β-dialkylamino-α-isocyanoacrylates **1006** as described above. These BICAs are usually prepared in two steps from α-formylaminoacrylates **182**, which are easily accessible from α-isocyanoacetate and aldehydes (see section 4.1). The geometric isomers of β-bromo-α-formylaminoacrylates **1030** obtained after the first step can be easily separated by column chromatography to obtain pure isomers. The *Z*-isomer generally is the predominant isomer formed. Subsequent dehydration occurs under classic conditions usually in high yield and without significant isomerization enabling preparation of BICA **1031** in diastereopure form (Scheme 246).[98,452]

Like β-dialkylamino-α-isocyanoacrylates, BICAs also possess a rich set of functionalities. However, BICAs have an extra diversity point because they contain an additional substituent (R), which can be easily varied depending on the aldehyde used for synthesis of the starting α-formylaminoacrylates. The corresponding β-dialkylamino analogs have

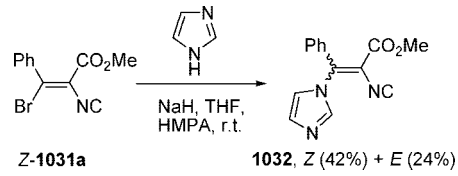
Scheme 244



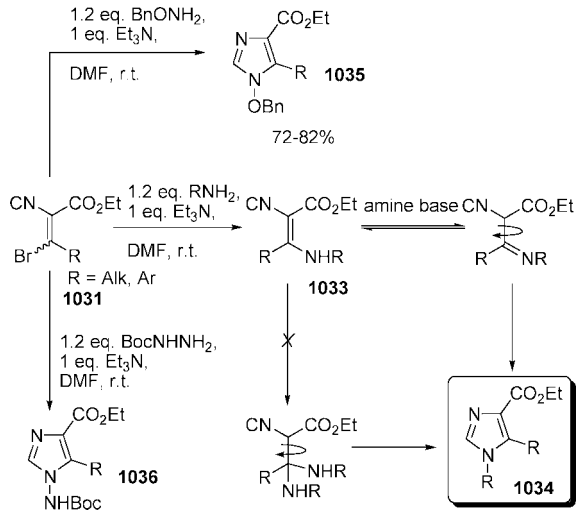
Scheme 246



Scheme 247



Scheme 248

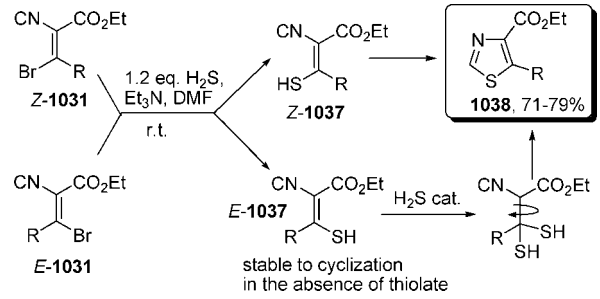


not been described, although they may be prepared from BICA by reaction with a secondary amine. In this respect, it is interesting to note that β-imidazolyl-α-isocyanoacrylate **1032** was prepared as a mixture of separable *E*/*Z* isomers by the reaction of *Z*-**1031a** with imidazole in the presence of NaH (Scheme 247). Though BICAs and their precursors can be isolated as single geometric isomers, most reactions of BICAs (including MCR) can be performed on the *E*/*Z* mixtures, since often cyclizations to form an aromatic cycle occur subsequently (vide infra) and the initial *E*/*Z* configuration does not matter.

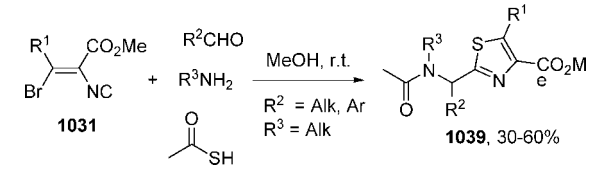
BICAs have been used to synthesize various heterocycles such as imidazoles and thiazoles. Thus, imidazoles **1034** are formed from the reaction with primary amines in the presence of a base (Et_3N).[452,453] The reaction proceeds via initial substitution at the C═C double bond to furnish predominantly *E* isomers of β-alkylamino-α-isocyanoacrylate **1033**. While the minor *Z* isomer cyclizes spontaneously into the final imidazole, its *E* counterpart requires a little excess amine to isomerize and cyclize. When no excess amine base is present, **1033** can be isolated along with imidazoles **1034** in only moderate yield.[452] Analogously, reactions of **1031** with hydroxylamine and hydrazine derivatives lead to *N*-hydroxy and *N*-aminoimidazole derivatives **1035** and **1036** (Scheme 248).[454]

Similar reactions using hydrogen sulfide give thiazole derivatives, albeit via a slightly different mechanism. Initially, *Z*- and *E*-**1031** undergo substitution to furnish *Z*- and *E*-thiols

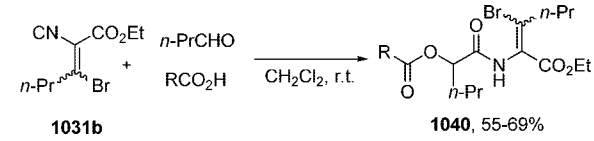
Scheme 249



Scheme 250



Scheme 251



1037. The *Z* isomer cyclizes spontaneously, but for *E*-**1037** to cyclize an isomerization is needed first. This occurs easily in the presence of excess H_2S via an addition−rotation−elimination process (Scheme 249).[455] Despite differences in mechanisms of reactions of separate BICA stereoisomers, these syntheses of imidazole and thiazole can truly be performed on *E*/*Z* mixtures without concerns.

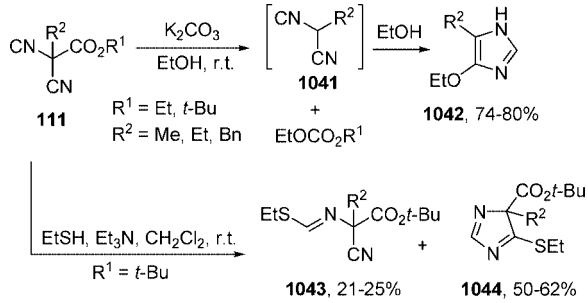
Also, a multicomponent synthesis of thiazoles **1039** has been described recently. The reaction can be applied for aliphatic and aromatic aldehydes and aliphatic ketones (lower yield), as well as aliphatic or benzyl amines. In contrast to the method described for β-dimethylamino-α-isocyanoacrylate **1006**, the BICA-based method permits further introduction of diversity points in the final molecule by an additional substituent at the 5-position of the thiazole system (Scheme 250).[456]

Ordinary Passerini reaction of BICA **1031b** has been reported. Several depsipeptides **1040** were obtained in moderate yield without affecting the bromoalkene moiety (Scheme 251).[457]

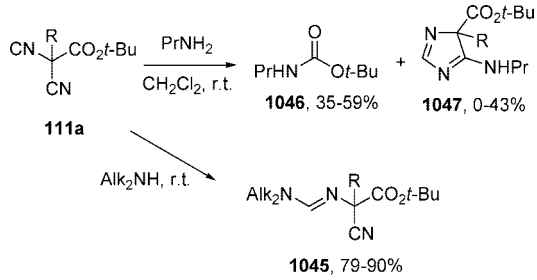
11.3. α-Cyano-α-isocyanoacetates

Unsubstituted isocyanoacetonitrile was obtained for the first time by Schöllkopf in 1975 and was found to be a very unstable compound (see Scheme 21). Functionalized isocyanoacetonitriles were developed by Neidlein in 1996. Their synthesis was described in section 2.4, Scheme 22. α-Cyano-α-isocyanoacetates **111** contain three centers that are susceptible to nucleophilic attack. They contain an isocyano, a cyano, and an ester group. The selectivity of the nucleophilic attack depends on the nature of the nucleophile used. α-Cyano-α-isocyanoacetates **111** react selectively with alkoxides at the ester group, which leads to fragmentation and loss of a carbonate, which can be isolated as byproduct. The intermediate α-isocyanonitrile **1041** is unstable under the reaction conditions and reacts further with the alkoxide to give 4-alkoxyimidazole **1042** in good yield.[458] In contrast to

Scheme 252



Scheme 253



hard alkoxide nucleophiles, the softer thiolates prefer to react with the isocyano and cyano groups rather than the ester one. The reaction yields two compounds, **1043** and **1044**, in low selectivity. The thioformimidate **1043** is formed by nucleophilic attack on the isocyano group and 4*H*-imidazole **1044** is the product of attack on the cyano group and subsequent ring closure involving the isocyano C-atom (Scheme 252).[458] The mixture of **1043** and **1044** is easily separated by column chromatography.

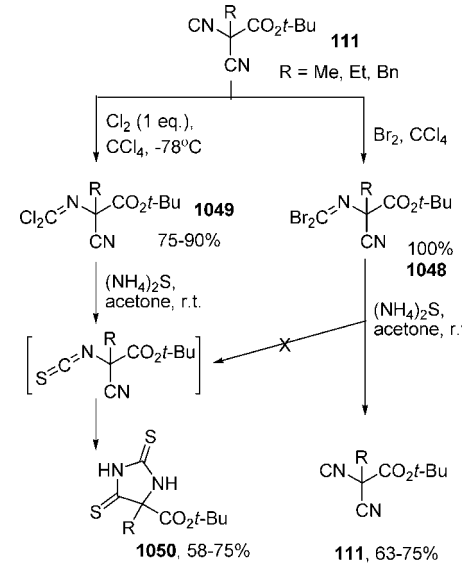
Secondary alkyl amines react selectively with the isocyano group of **111a** to yield formimidates **1045** in high yield.[458] However, primary amines attack both the cyano and the ester groups to yield carbamate **1046**, which is the product arising from the reaction of the amine with the ester group, while the 4*H*-imidazole **1047** is the product of attack to the cyano group and subsequent ring closure (Scheme 253).[458]

α-Cyano-α-isocyanoacetates react smoothly with electrophilic reagents like bromine, chlorine, and acyl isocyanates. Thus, reaction with bromine proceeds cleanly at 0 °C and yields the corresponding dibromides **1048** quantitatively, even with excess bromine. In contrast to this, chlorination of **111** should be performed more carefully at lower temperature because the use of excess chlorine leads to the formation of additional chlorination products. Nevertheless, the desired dichlorides **1049** can be obtained in high yield.[459] The dichlorides **1049** can be transformed into 2,4-dithiohydantoins **1050** in good yield upon treatment with ammonium sulfide. However the dibromides **1048**, under the same conditions, are reversed to **111** instead of forming the corresponding 2,4-dithiohydantoins (Scheme 254).

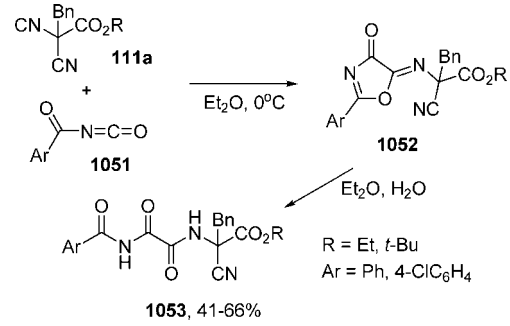
Upon treatment with highly electrophilic acyl isocyanates **1051**, α-cyano-α-isocyanoacetates **111a** react at the isocyano group. The products **1052** are highly susceptible to hydrolysis, which results in oxamides **1053** (Scheme 255).[458]

Multicomponent Passerini and Ugi reactions with α-cyano-α-isocyanoacetates were also investigated. The corresponding depsipeptides or peptides **1054** or **1055** are obtained in only moderate yield. This may be attributed to the strong electron-withdrawing effect of both the CN and COOR substituents, which make the isocyano group less nucleophilic. Attempts

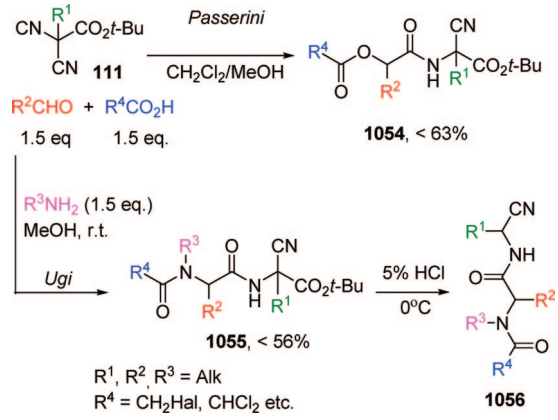
Scheme 254



Scheme 255



Scheme 256

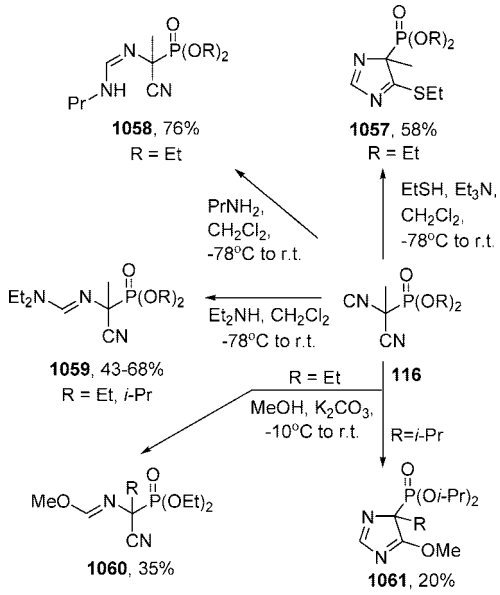


to hydrolyze ester **1055** were unsuccessful because decarboxylation occurs easily even under mild conditions to afford **1056** (Scheme 256).[460]

11.4. 1-Cyano-1-isocyanoalkylphosphonates

1-Cyano-1-isocyanoalkylphosphonates **116** were prepared in 2000 by a four-step procedure (Scheme 22, section 2.4). These versatile reagents are suitable for the preparation of several phosphorus-containing compounds **1057**−**1061** (Scheme 257). Reactions with nucleophilic agents have been described by Simon in 2001, who showed that they react either by the isocyano or by the cyano group to yield addition or cyclization products,

Scheme 257

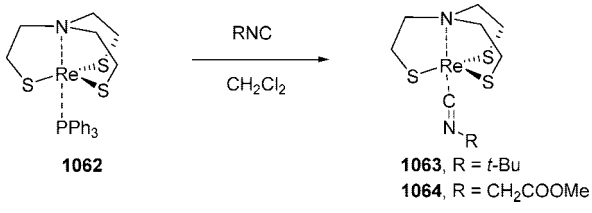


respectively, albeit with various success.[461] Multicomponent reactions of this class of isocyanoacetonitriles have not been investigated so far.

12. Synthesis and Application of Metal−Isocyanoacetate Complexes

Isocyanides, which are isoelectronic to CO, are widely used as ligands for transition metals, for example, Cu,[462] Au(I), Pd(II), Pt(II), Fe(0),[463] and others.[464] In general, isocyanoacetate derivatives show superior π-acceptor properties compared with other isocyanides. For example, trigonal-bypyramidal Re(III) complexes of *tert*-butyl isocyanide **1063** and isocyanoacetate **1064** were obtained from the corresponding triphenylphosphine complex **1062** (Scheme 258). The isocyanoacetate in **1064** is a better π-acceptor than *tert*-butyl isocyanide in **1063**. This was demonstrated by the difference in the IR absorption for the CN stretching vibration (1949 cm^{-1} for **1064**, 1976 cm^{-1} for **1063**) together with other bond parameters. For example, the Re−C7 bond in **1064** (1.905 Å) is significantly shorter than the Re−C7 bond in **1063** (1.949 Å) and the N2−C7 bond in **1064** is longer than that in **1063**. Moreover, another indication for strong backbonding from the electron-rich atom to the isocyanide carbon atoms is the bond angle at the isocyanide nitrogen atom N2 (Figure 11). For **1064** and **1063**, C7−N2−C8 angles of 150.8(9)° and 154.0(10)° have been found respectively. The smaller values for the angles in **1064** correspond to the better π-acceptor character of isocyanide group.[465] The same trends were observed for other *trans*-[$ReCl_3(CNCH_2CO_2Me)(PPh_3)_2$] complexes.[466]

Scheme 258



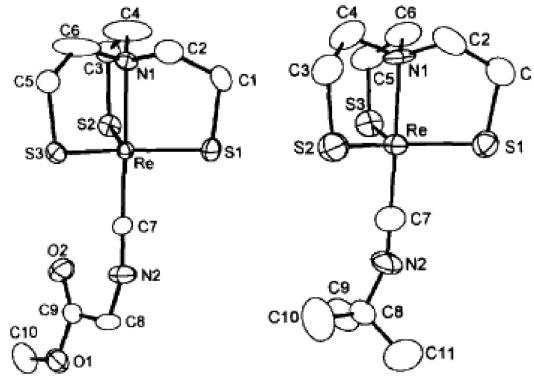


Figure 11. Molecular structure of **1064** (left) and **1063** (right). Reprinted with permission from ref 465b. Copyright 1995 Elsevier Science S.A.

12.1. Protection of Isocyanide Group by Coordination: Synthesis of Isocyanoacetic Acid Complexes

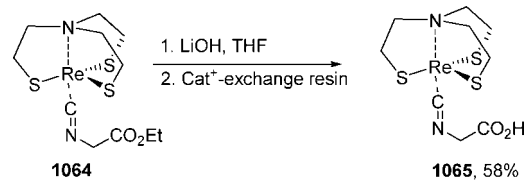
As mentioned above, free isocyanoacetic acids and their selected derivatives (such as isocyanoacetyl chloride) are unstable compounds. However, they can be obtained when the isocyanide group is stabilized in complexes with transition metals. This "protection" of the isocyanide group opens possibilities for the modification of isocyanoacetate derivatives and the synthesis of interesting compounds based on them. For example, trigonal-bipyramidal rhenium complex **1064** with the isocyanide group strongly bound to the Re atom was transformed to the corresponding lithium salt, which was converted without isolation and purification into isocyanoacetic acid complex **1065** via a cation-exchange resin in good yield (Scheme 259).[467]

On the other hand, Re(III) complex **1066** gave the product of isocyanide hydrolysis **1067** after treatment with base (NaOH(aq) 1 M in CH_2Cl_2; Scheme 260).[468]

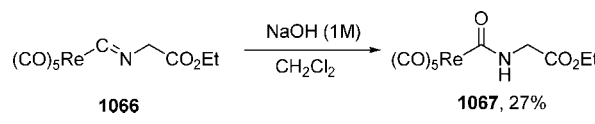
Complexes **1068** and **1069** were obtained from isocyanoacetate and pentacarbonyl chromium and tungsten in excellent yields.[469] The saponification of **1068** and **1069** affords the isocyanoacetate complexes **1070** and **1072**, which can be protonated to give the sublimable isocyanoacetic acid complexes **1071** and **1073** in which the functional isocyanide is stabilized by the metal atom. Triethylamine salt **1074** can be obtained from isocyanoacetic acid complex **1073** in excellent yield. The synthesis of a unique isocyanoacetyl chloride complex **1075** was described by Fehlhammer et al. Reaction of salt **1070** with oxalyl chloride gives the isocyanoacetyl chloride **1075**, which can be purified by sublimation and isolated in 15% yield (Scheme 261).[470]

Complex **1075** can be used for coupling with amines to form an amide bond and opens a new approach to peptidic

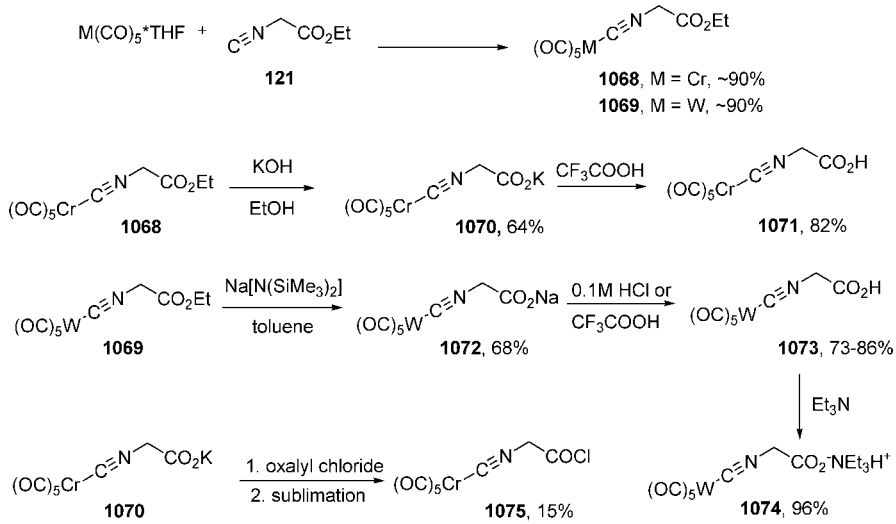
Scheme 259



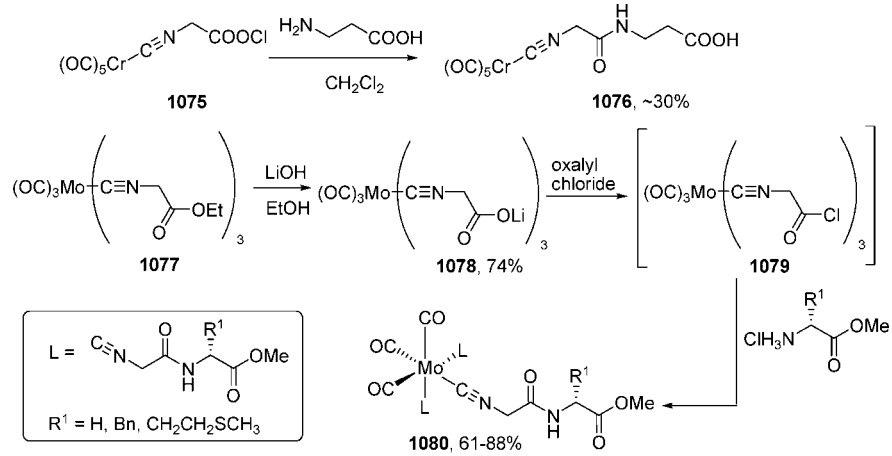
Scheme 260



Scheme 261



Scheme 262



structures. For example, **1075** reacts with β-alanine to afford isocyanopeptide complex **1076** in moderate yield. Mo−isocyanopeptide complexes **1080** were also efficiently obtained in this manner from Mo-complex **1077**. Longer isocyanopeptides, stabilized by the molybdenum atom, were also synthesized using N-unprotected peptides instead of amino acid esters (Scheme 262).[470]

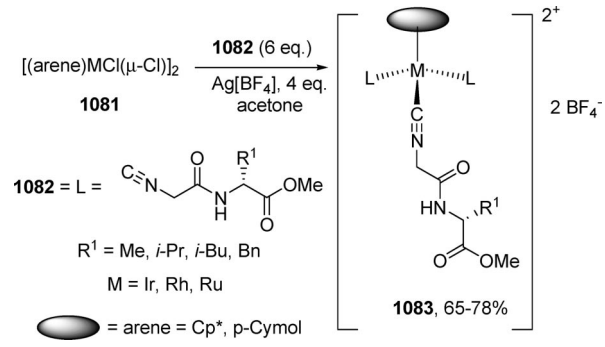
Another type of isocyanopeptide complex was described by Beck et al. Isocyanopeptides **1082**, as well as longer isocyanopeptides, react with chloro-bridged complexes of Ir, Rh, or Pt in the presence of $Ag[BF_4]$ to form the cationic half-sandwich complexes **1083** in good yields (Scheme 263).[43]

Isocyanoacetonitrile shows the exclusive coordination of the isocyanide group to metals like Cr and W (Scheme 264). Thus, complexes **1084**, **1085**, and **1086** were obtained from the corresponding starting materials.[61,471]

A very interesting approach to organometallic isocyanoacetate complexes was described by Lin et al. The nitrogen of a cyanide group in [Ru]CN complexes **1087** was alkylated by bromoacetonitrile or methyl bromoacetate to afford the corresponding complexes **1088** and **1089** in good yields (Scheme 265).[472,473]

Substitution of one chloro ligand in a $Pt[(Cl)_2(PPh_3)_2]$ complex by potassium isocyanoacetate results in the Δ^2-oxazolin-5-on-2-ato complex **1090**. In contrast, the open chain form of the functional isocyanide is retained in Fe-

Scheme 263

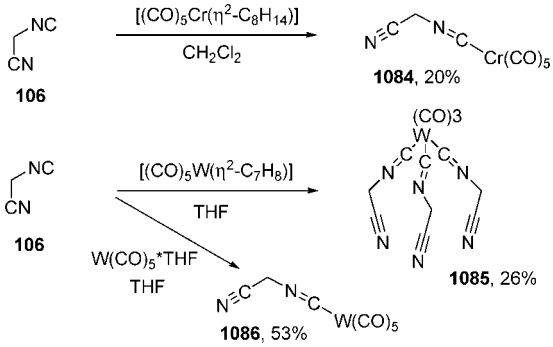


[K(18-crown-6)] complex **1092**, in which it occupies a terminal position. Protonation of the platinum complex **1090** proceeds with ring cleavage and formation of isocyanoacetic acid **1091** stabilized by metal ion coordination. Protonation of **1092** requires 2 equiv of acid to yield the aminocarbyne-bridged complex **1093** as the only isolable product (Scheme 266).[474]

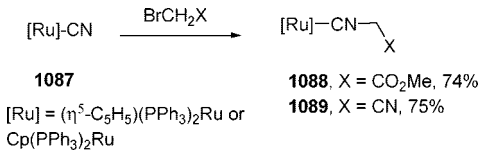
In addition, several examples of rhodium,[475] platinum,[476] and palladium[477] complexes of isocyanoacetates were also obtained.

Despite the number of isocyanoacetate complexes described, no examples of destruction of isocyanoacetate−metal

Scheme 264



Scheme 265



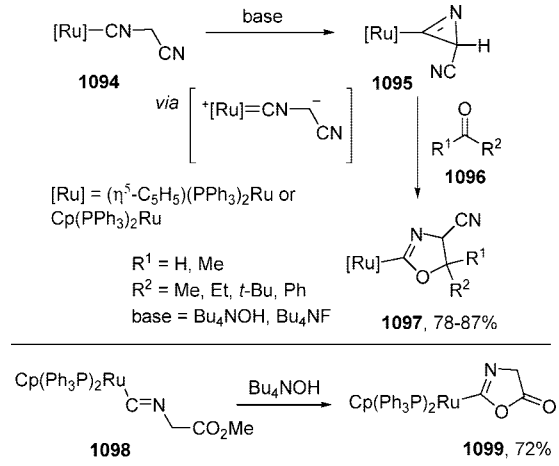
complexes (to recover isocyanoacetate derivative), to the best of our knowledge, was published.

12.2. Cyclization of Metal−Isocyanoacetate Complexes

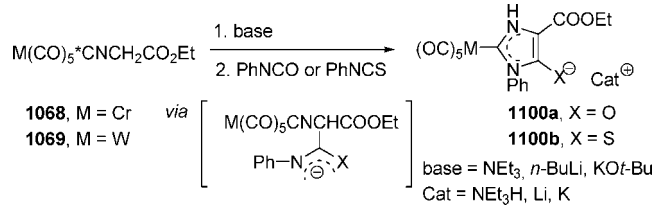
Metal complexes of isocyanoacetates can undergo different types of cyclization due to the high α-acidity and due to strong bonding of the isocyanide carbon to the metal atom. Thus, deprotonation of ruthenium isocyanoacetonitrile complexes **1094** affords metal azirinyl complexes **1095**. Subsequent insertion of a carbonyl group of a ketone or an aldehyde into the ruthenium−carbon bond of the azirinyl ring gives oxazoline complexes **1097** in a regioselective manner (Scheme 267). It is noteworthy that the ruthenium bound azirinyl ring **1095** gives oxazoline complexes **1097** with regioselectivity opposite to that observed in the photolytic reaction of carbonyl compounds with usual azirines (without metal).[472,473] Reaction of the methyl isocyanoacetate complex **1098** with *n*-Bu_4NOH hydrolyzes the ester group to give the ruthenium oxazolone complex **1099** (Scheme 267).[473]

Chromium and tungsten complexes of ethyl isocyanoacetate **1068** and **1069** react with heteroallenes PhNCO and PhNCS in a regio- and site-selective fashion to give the heterocyclic carbenoids **1100**. Oxygen and sulfur in these compounds can be easily alkylated and acylated. Thiocompound **1100b** can also be oxidized to give the disulfide.

Scheme 267



Scheme 268



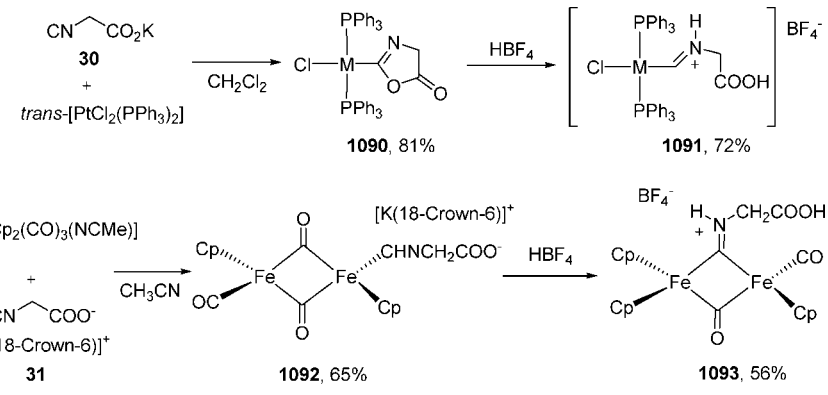
Moreover, the thiolate function in **1100b** can act as a monodentate ligand coordinating to platinum (Scheme 268).[469]

12.3. Application of Metal−Isocyanoacetic Acid Complexes

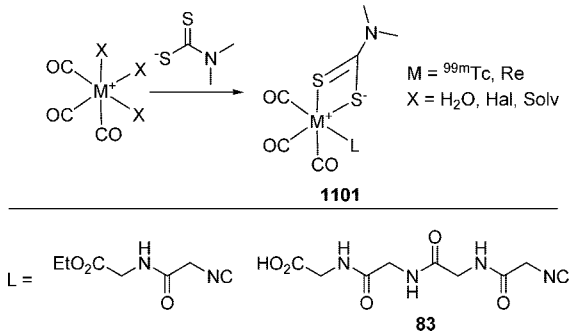
Isocyanopeptides are important molecules that connect a peptide part with the isocyanide function, which can be a strong ligand. The presence of the isocyanide group in isocyanopeptides may be used to label these peptides with transition metals, especially lanthanides. For example, isocyanopeptides were labeled with $M(CO)_3^+$ (M = ^{99m}Tc and Re) atoms by "2 + 1" dithiocarbamate−isocyanide chelating systems (Scheme 269).[44] In this way, peptides can be labeled with $^{99m}Tc(CO)_3^+$ by insertion of an isocyanide group, which can be used in radiopharmacology. This approach can also be used for modification of various biomolecules containing free amino groups (e.g., steroids, small peptides).

A new method for easy removal of ruthenium from metathesis reactions, which is often a significant problem, was reported by Diver et al. They reported the addition of

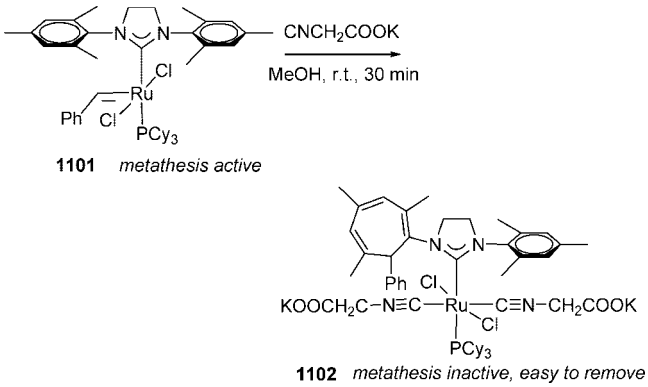
Scheme 266



Scheme 269



Scheme 270



potassium isocyanoacetate to a crude metathesis reaction mixture that "quenches" the metal carbene by triggering a bond insertion into the mesityl group forming **1102**. It was found that the quench is effective for a variety of metatheses including for the commonly used first- and second-generation Grubbs' carbene complexes. Potassium isocyanoacetate is an odorless solid that is easily obtained and easily handled and thus is a very efficient reagent for removal of Ru from metathesis reactions (Scheme 270).[478]

In conclusion, complexation with transitition metals is a very important aspect of isocyanoacetic acid chemistry. Complexation is an efficient method to increase nucleophilicity of the isocyanide group in order to activate reactions involving nucleophilic isocyanide attack: metal-catalyzed aldol reaction for synthesis of oxazoline (section 4.7), metal-catalyzed reaction with imines for synthesis of imidazoles (sections 5 and 10.3.3), metal-catalyzed multicomponent heterocyclizations (section 10.3), etc. On the other hand, complexation can "protect" isocyanide groups. As a result, complexes of isocyanoacetic acid and even isocyanoacetyl chloride were successfully prepared (section 12.1).

13. Polymerization of Isocyanoacetates

The divalent, carbene-like electronic structure of isocyanides opens broad possibilities for different electrophilic, nucleophilic, and radical reactions (see above). Moreover, isocyanides are able to undergo homopolymerization giving rise to the formation of polyisocyanides, a new type of polymeric material. In this section, general features of polymerization of isocyanides are briefly outlined to introduce the reader to the topic. Then, polymerization of isocyanoacetic acid derivatives and isocyanopeptides is considered.

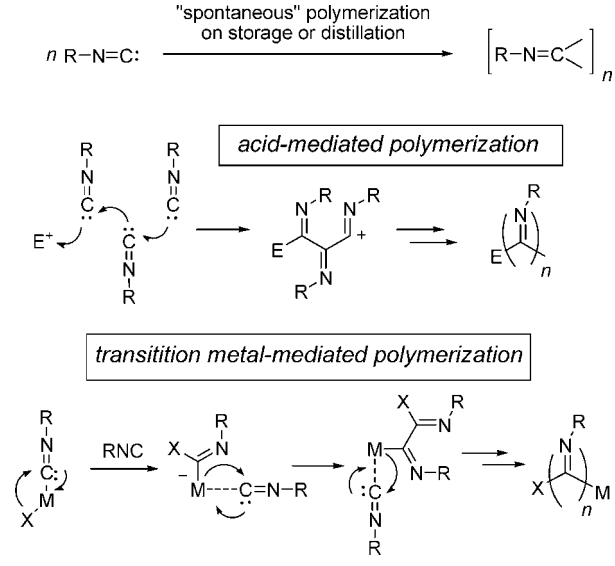
13.1. Polymerization of Isocyanides: General Features

Initially, it was found that isocyanides that lack bulky N-substituents tend to form polyisocyanides on storage or distillation. However, this "spontaneous" polymerization (or resinification) strongly depended upon the conditions and, therefore, was poorly reproducible and uncontrollable. Much effort has been expended to realize the efficient polymerization of isocyanides using promoters or catalysts. Polymerization via radical intermediates and via anionic intermediates was found to be ineffective. The synthesis of polyisocyanides can be successfully achieved via acid-mediated polymerization and transition-mediated polymerization (Scheme 271).

Recent progress in isocyanide polymerization has largely relied on the use of transition metal complexes (Pd, Rh, Co, and, particularly, Ni complexes) acting as initiators. The isocyanide activated on the transition metal via coordination then undergoes migratory insertion reactions, which lead to the formation of high molecular weight polymers. Nickel systems are still the most common synthetic access to polyisocyanides. More details can be found in the excellent reviews of Millich,[479] Nolte,[480] Sommerdijk et al.,[481] Suginome et al.,[482] and Yashima et al.[483]

In the beginning of 1970, Millich and Nolte demonstrated that poly(*tert*-butylisocyanide), R = *t*-Bu, prepared by Ni-catalyzed polymerization, exists as a 1:1 mixture of right- and left-handed helices and can be resolved into left-handed and right-handed helices, which do not racemize even at elevated temperatures.[484] The helical structure of a poly(isocyanide) is the result of restricted rotation around the single bonds that connect the carbon atoms (atropisomerism). The polymers are highly isotactic and possess a large angle of polarized light rotation, attributed to helical superstructures. These experiments stated the important stereochemical features of polyisocyanides. First, racemic polyisocyanides consisting of achiral repeating units exist as a 1:1 mixture of right- and left-handed helices. Second, the right- or left-handed helical conformations are stable enough to exist as either enantiomer at ambient temperature in solution, although the stability may depend upon the substituent linked to the isocyanide group as well as the degree of polymerization. In general, helices are stable when the side chain

Scheme 271



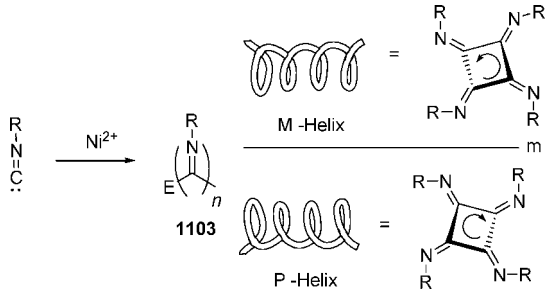


Figure 12.

contains bulky groups or groups that can form intramolecular hydrogen bonds (see polymerization of isocyanopeptides). It is also commonly known that polyisocyanides have a well-defined 4_1 helical conformation (i.e., four repeat units per helical turn; Figure 12).

Simplistically, for the polymerization catalyzed by $NiCl_2$, a so-called "*merry-go-round*" mechanism was proposed (Scheme 272). The first step consists of the formation of square-planar nickel complex **1105**, spectroscopically characterized in solution (in some occasions can be isolated when bulky isocyanides are used). Subsequent nucleophilic attack gives complex **1105** in which the amine migrates to form complex **1106** with a carbene ligand. This nucleophile may already be presented in solution (for example, molecule of water or the counterion of Ni^{2+}) or may be added as a promoter, for example, an amine R^1NH_2. Further reaction route influence on the configuration of target polymer. The first C−C bond is formed when the carbon atom of the carbine ligand attacks one of the neighbor isocyanide ligands. Thus, attack of counterclockwise isocyanide lead to formation of P-helixes whereas attack of clockwise isocyanide (as shown at Scheme 272) afford M-helix poly(isocyanide). After this step, the free coordination position is occupied by an isocyanide from solution, the reaction sequence continues in the direction of the initial step (i.e., one particular helical sense is formed), and each rotation around the nickel adds one turn to the helix. In the absence of a chiral bias, there is an equal probability of attack of the carbene-like carbon atom on both neighboring ligands (route a or b), leading to a racemic mixture of helical polymers. In the presence of a chiral species (introduced in the monomer, Ni-complex, or nucleophile), there is a preference for reacting with specifically one of the two neighboring isocyanide monomers on

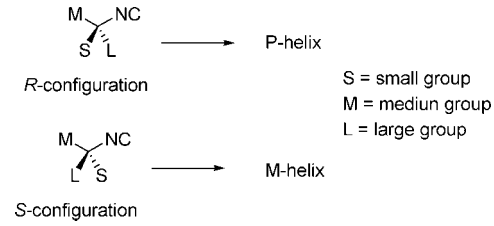


Figure 13.

the nickel. This can be successfully used for the synthesis of chiral polymer.

As mentioned, polymers with an excess of one type of helix can be prepared by chromatographic resolution using an optically active column. This method has proven to be successful for poly(*tert*-butyl isocyanide) but has turned out to be less applicable to other polymers of isocyanides Therefore other procedures for preparing optically active helical polyisocyanides were developed.

Thus, three distinct approaches can be used for the helix-sense selective polymerization. One, the use of chiral catalyst, was employed in numerous cases; however, it was found to be ineffective (ee up to 70%, low polymerization degree).[485] Addition of chiral initiator (chiral amine) also can be used for stereoselective polymerization of achiral isocyanides with stereoselectivity up to 85% de.[486]

The most effective approach to chiral polyisocyanides is based on the polymerization of chiral isocyanides or use of bulky chiral isocyanide as a copolymer with achiral isocyanide. Thus, chiral isocyanides are polymerized stereoselectively to afford one type of helix. An empirical rule for the prediction of screw-sense induction in the polymerization of optically active isocyanides was proposed. Thus, chiral isocyanide (S)(M)(L)C-NC, where S, M, and L stand for the smallest, medium, and the largest organic groups (typically, (*R*)-isocyanide), which have no coordinating substituents, polymerizes to P-screw (right-handed helix, Figure 13). For (*S*)-isocyanides, M-screw (left-handed helix) polymerization is supposed to be preferred.[487]

13.2. Transition-Metal Catalyzed Polymerization of Isocyanoacetates

Chiral isocyanoacetates were extensively used as chiral homo- and copolymers for the synthesis of chiral (poly)iso-

Scheme 272

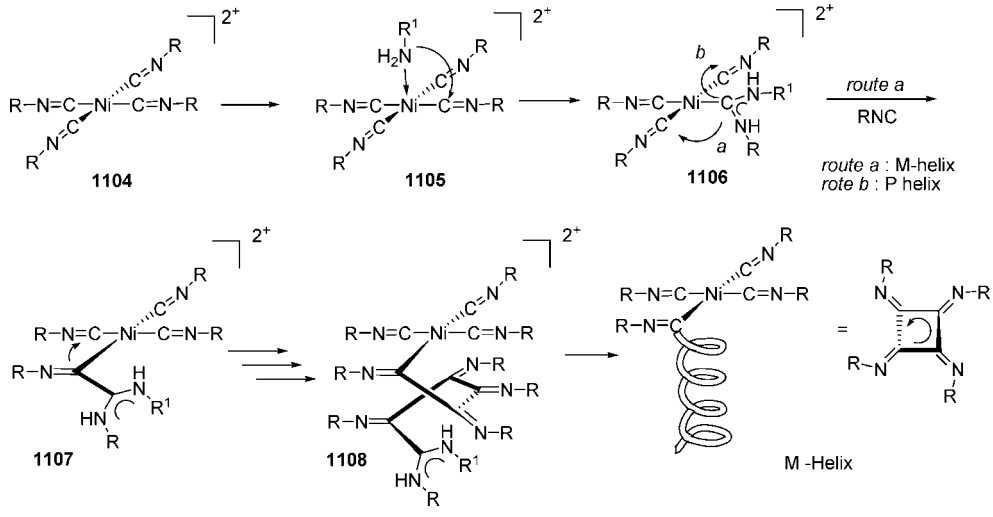
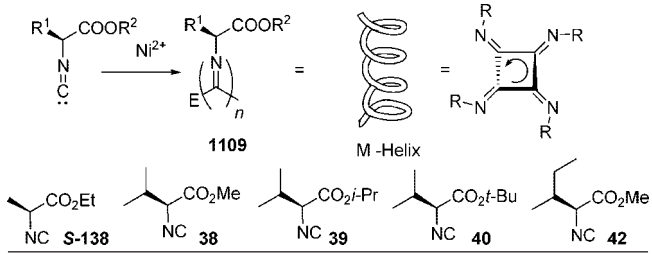


Table 15



entry	isocyanide	rotation of monomer, deg	rotation of polymer, deg	screw sense	M_w
1	***S*-138**	+16.7	−280	*a*	71 700
2	**38**	+5.5	−110	M	*a*
3	**39**	+32.7	−24	M	14 400
4	**40**	+29.5	+32.5	M	*a*
5	**41**	+35	−32.2	M	32 500

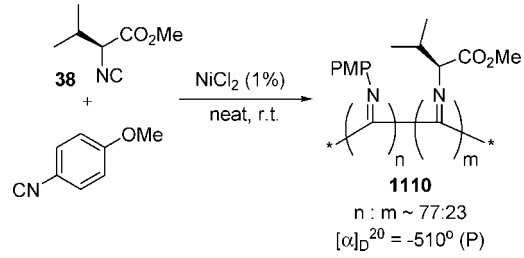
[a] Not determined.

cyanides. Thus, nickel-catalyzed polymerization of optically active isocyanoacetates studied with particular attention being paid to the screw-sense induction to the polymer main chain.[29,487,488] For all polymerizations listed in Table 15, the preferential formation of one helical sense is suggested by a comparison of the specific rotations of the starting isocyanide with the resulting polymer. More precisely, the CD spectra can be used to estimate the sense and degree of asymmetric induction. In general, it has been suggested that a positive couplet (a negative-to-positive transition with an increase in wavelength) corresponds to M-helical conformation.[489]

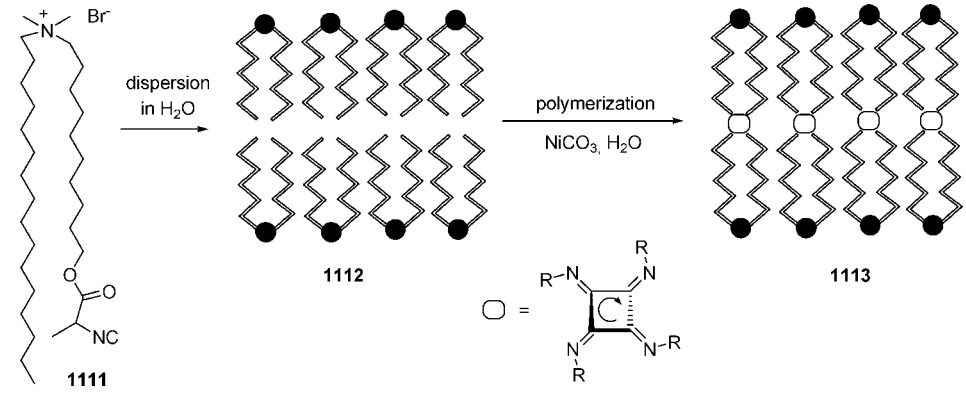
Another efficient approach to enantiomerically enriched polyisocyanides is based on the copolymerization of slow-reacting chiral isocyanides and fast-reacting achiral isocyanides. Thus, chiral isocyanoacetate **38** slowly copolymerizes with 4-methoxyphenylisocyanide (1:1) in the presence of $NiCl_2$ to give homopolymer **1110** with predominantly left-handed helices. Polymer **1110** contains achiral and chiral monomer units in a ratio of ~3:1 (Scheme 273).[29,490] The formation of the P-helix is in sharp contrast to the formation of M-helical polymer in the homopolymerization of **38** (Table 15).[491]

Isocyanoacetate **1111** bearing ammonium side chains was polymerized in the presence of nickel catalyst to construct microreactors. On dispersal in water, **1111** forms closed vesicles **1112** with diameters of approximately 250 nm. These vesicle bilayers can be stabilized by polymerization of the isocyanide group in the bilayers with nickel carbonate to form polymerized vesicles **1113** (Scheme 274).[492]

Scheme 273



Scheme 274



13.3. Polymerization of Isocyanopeptides

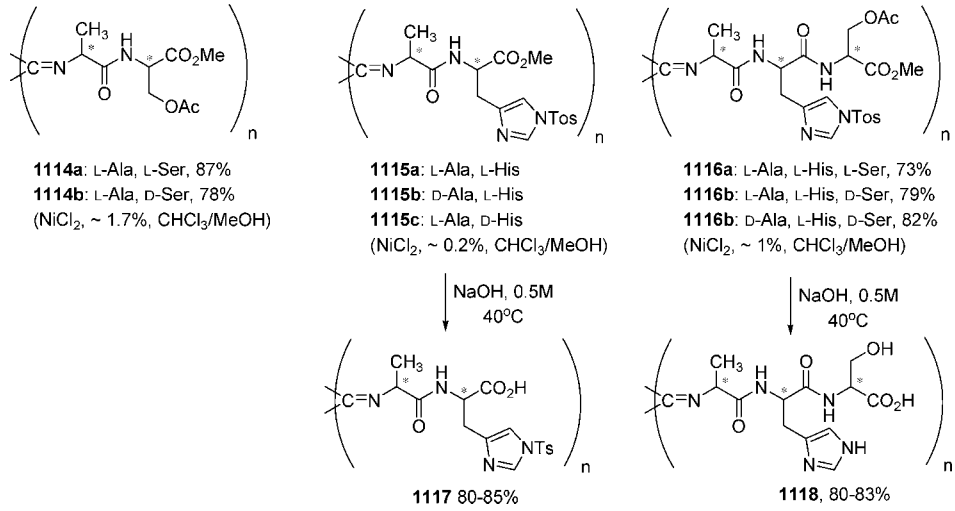
Isocyanopeptides, along with the usual isocyanoacetates, can be easily polymerized by means of transition metals or acidic catalysis. Substituted polyisocyanopeptides are a recently developed class of "supramolecular" materials that fold like a protein. As an example, optically active polymers **1114**,[493] **1115**,[56] and **1116**[57] built from di- and tri-isocyanopeptides were synthesized. These polymers contain imidazolyl, carboxy, and hydroxymethyl functional groups (these functions are also present in chymotrypsin). By these means, polymers **1114**−**1116** were tested as protease mimetics and exhibit markedly higher activities than the corresponding low molecular weight compounds in the hydrolysis of nitrophenyl and dinitrophenyl esters.[494] These polymeric materials can be easily deprotected to afford polymeric materials **1117**, **1118** with free carboxylic groups (Scheme 275).

13.3.1. Formation of β-Sheets in Polyisocyanopeptides

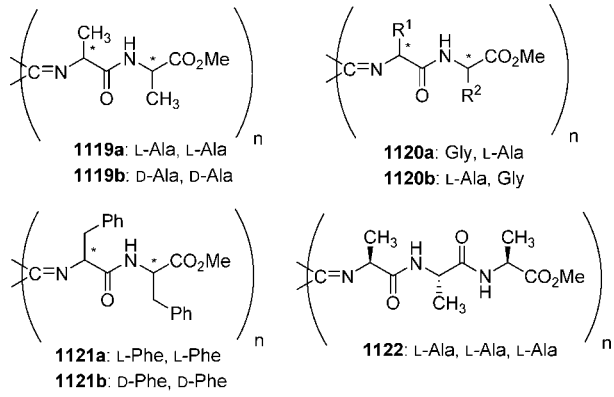
As mentioned, stability of helical structure of isocyanopeptides depends on the volume of isocyanide substituents. Additional interactions between polyisocyanide chains (for example, hydrogen bonds) also can stabilize helixes. Thus, isocyanopeptides **1119**, **1120**,[495] **1121**,[30] and **1122**[496] were synthesized to investigate the effect of hydrogen bonding between side chains (Scheme 276).[497] It was found that polymerization of these isocyanopeptides results in the formation of high molecular weight polymers that fold in a protein-like fashion to give helical strands in which the peptide chains are arranged in β-sheets. The β-helical polymers retain their structure in water and unfold in a cooperative process at elevated temperatures (Figures 14 and 15).

The peptide architecture in these polymers is a different form of the β-helix motif found in proteins. Unlike their natural counterparts, which contain arrays of large β-sheets stacked in a helical fashion, the isocyanopeptide polymers have a central helical core that acts as a director for the

Scheme 275



Scheme 276



β-sheet-like arrangement of the peptide side arms. The helical structure of these isocyanopeptide polymers has the potential to be controlled through tailoring of the side branches and the hydrogen-bonding network present in the β-sheets.

The hydrogen bonds are formed between the amide carbonyl groups in side chains n and the amide NH groups in side chains $n + 4$ (4_1 helix). The presence of well-defined arrays of hydrogen bonds along the polymeric backbone was confirmed by ^{1}H NMR, IR, CD, UV, and other studies.[498]

Obtained isocyanopeptides can be used, for example, to create new liquid crystals. Thus, rigid, helical polyisocyanodipeptides derived from alanine **1019** were found to form lyotropic liquid-crystalline (LC) phases in tetrachloroethane.[499]

13.3.2. Synthesis of Functionalized Polyisocyanopeptides

Introduction of various functional groups in the starting isocyanopeptides and subsequent polymerization lead to dramatic modification of target polymer properties and open broad possibilities for synthesis of new polymeric materials. The polymerization gives two variants for the synthesis of modified polymers: use of functionalized initiator (amine, for example) and introduction of functional groups into the monomeric isocyanopeptide.

13.3.3. Copolymerization of Isocyanopeptides with Other Isocyanides

Isocyanopepties, along with usual isocyanoacetates, can be copolymerized with other isocyanides. The presence of amine initiator (see polymerization mechanism, Scheme 272) led to formation of polymer with the amine residue on the end of tails. Thus, amphiphilic copolymers **1126** and **1127**, having a hydrophobic polystyrene tail with a charged helical poly(isocyanide) headgroup, were prepared by polymerization of the corresponding peptide-derived isocyanide **1125a** and **1125b** with the macromolecular nickel initiator **1124**.

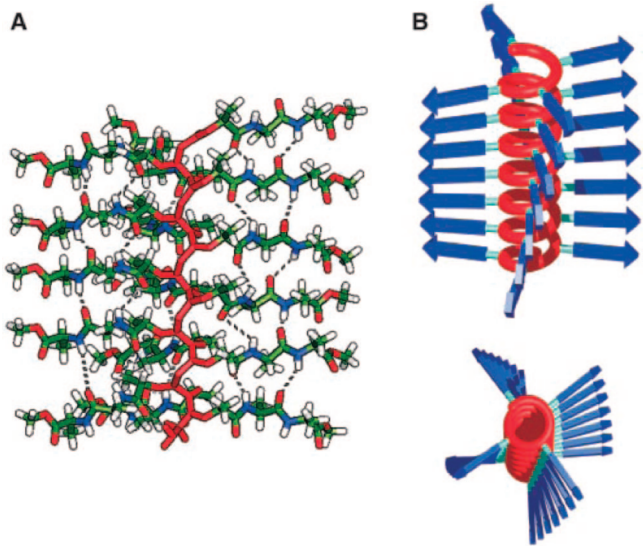


Figure 14. Structure of (poly)isocyanopeptide **1122**. Reprinted with permission from ref 496. Copyright 2003 American Association for the Advancement of Science.

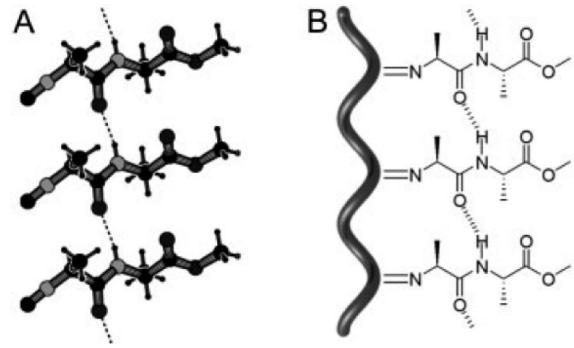
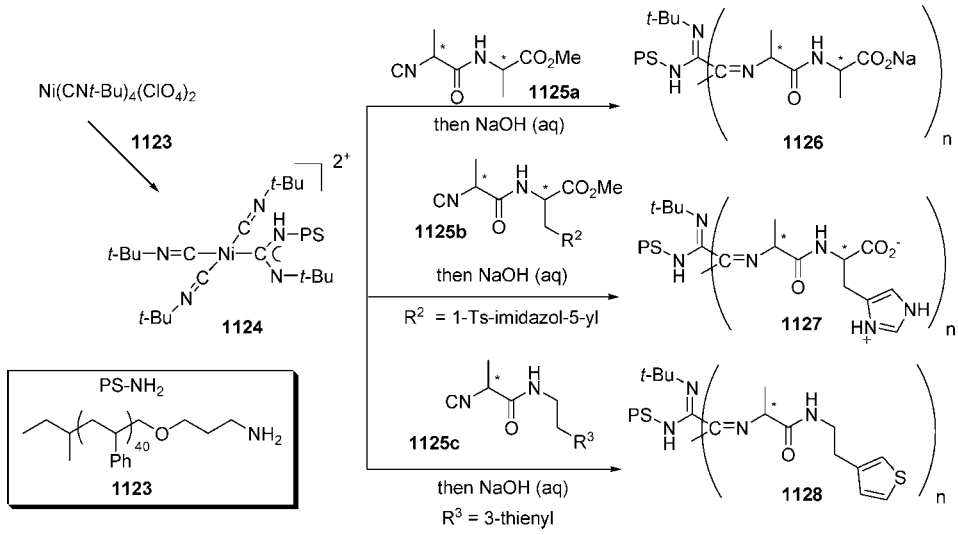


Figure 15. Structure of polyisocyanopeptide **1119a**. Reprinted with permission from ref 497. Copyright 2003 Wiley Periodicals, Inc.

Scheme 277



Macromolecular nickel initiator **1124**, which is end-capped with an amino group, was prepared by reaction of (*tert*-BuNC)$_4$Ni(ClO$_4$)$_2$ with polystyrene **1123**. The block copolymers **1126** and **1127** thus obtained exhibited a variety of morphologies, which depended upon the length of the polystyrene block, the pH of the solution, and the anion−headgroup interactions. These morphologies were supposed to arise from aggregation of the polystyrene block via hydrophobic interactions. Interestingly, the aggregation of the nonracemic helical copolymer resulted in the formation of helical superstructures, the screw-sense of which was opposite to that of the copolymer (Scheme 276).[500] Thiophene-containing diblock copolymer **1128** is uniquely able to form aggregates in both water and organic solvents. The thiophene groups located in the skin of the aggregates can be coupled to give polymerized vesicles, capable of including enzymes, thus resulting in catalytically active microreactors. The presence of the thiophene moieties in the diblock copolymers additionally enables the construction of conducting vesicles with potentially tunable properties (Scheme 277).[501]

Carbosilane amine dendrimers were used for copolymerization of isocyanopeptides with *tert*-butyl isocyanide and synthesis of block copolymers **1129**, containing flexible carbosilane dendrimers and a rigid polyisocyanide part. In chloroform, these block copolymers respond to the addition of silver ions by the generation of nanowires.[502] Even surface-bound amine initiator can be used for copolymerization of isocyanopeptide with *tert*-butyl isocyanide. Thus, synthesis of surface-initiated helical polyisocyanopeptide **1130** brushes (up to 200 nm) was also obtained by means of copolymerization. The polymer growth was studied as a function of reaction time, monomer concentration, and growth conditions (Figure 16).[503]

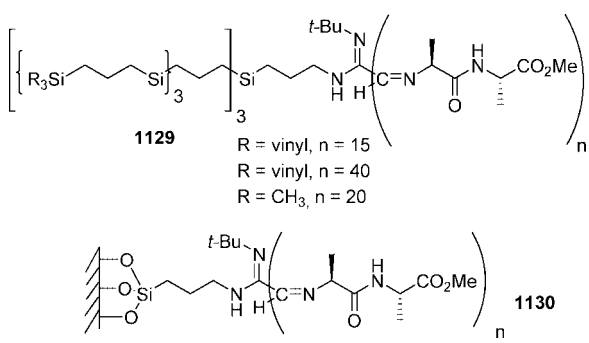


Figure 16.

13.3.4. Perylene-Substituted Polyisocyanides

Recently, a new class of multichromophoric polymers, namely, perylene polyisocyanides **1131** and **1132** was developed. Thus, **1131a** shows interesting fluorescence properties.[504] Polyisocyanopeptides **1331** functionalized with perylene units are able to interact with each other by $\pi-\pi$ stacking. In general, the $\pi-\pi$ interactions are responsible for stronger intermolecular interactions, producing formations of continuous networks of bundles on surfaces and efficient charge transport in thin-film transistors (Figure 17).[505] Later, a careful study on perylene-based polyisocyanopeptides **1131** and **1132** performed using various experimental and computational methodologies shows that these ultrastiff polymers are ideal scaffolds for precisely organizing chromophoric arrays into functional 2D wires.[506] Perylene-substituted polyisocyanide materials were also found to be effective for development of new photovoltaic devices.[507]

13.3.5. Synthesis of "Clickable" Polyisocyanopeptides

The utility of click chemistry and, especially, Huisgen Cu-catalized alkyne−azide cycloaddition to prepare novel materials has received wide attention in different fields in recent years.[508] Therefore, introduction of alkyne or azide groups in the starting isocyanoacetates open access to clickable polymeric materials, which can be easily modified by click chemistry. Thus, acetylene-containing polymer **1134**

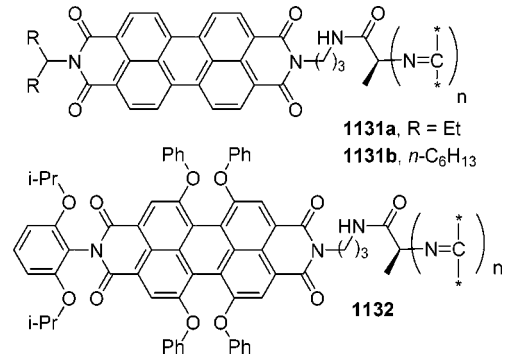
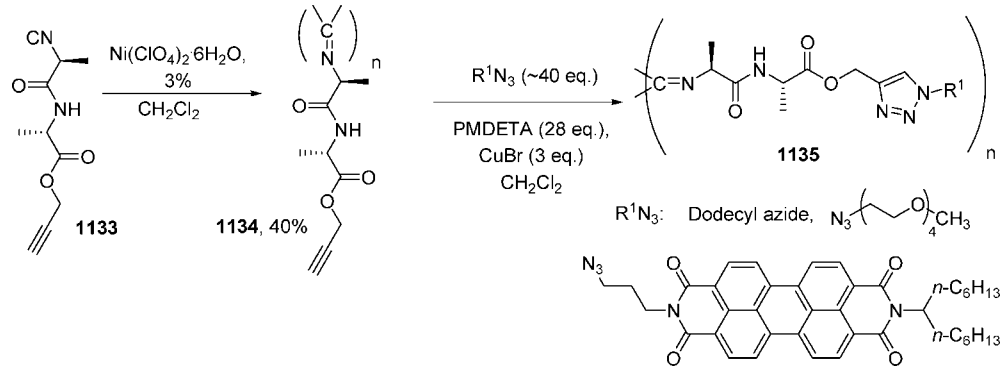
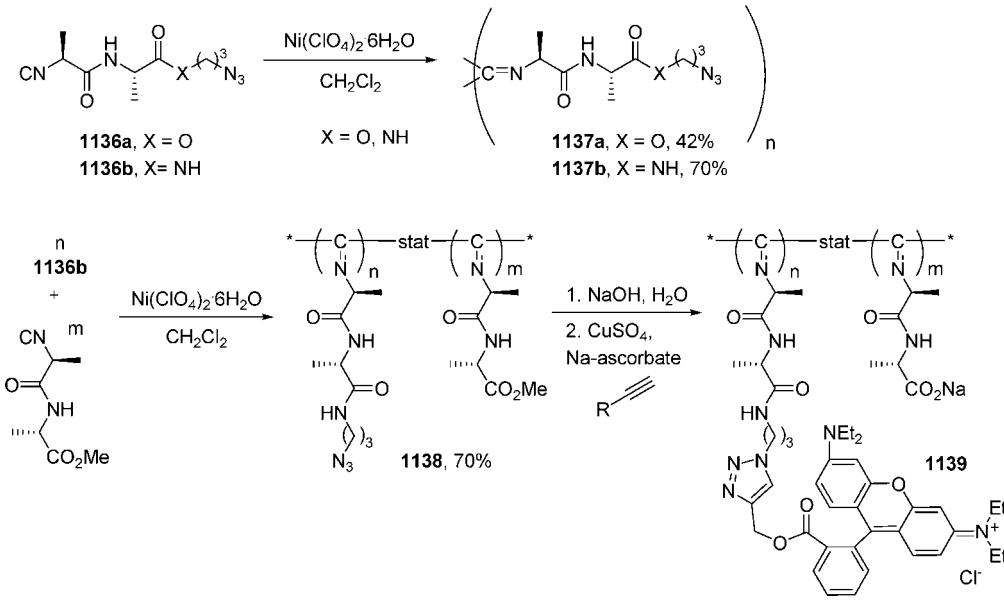


Figure 17.

Scheme 278



Scheme 279



was synthesized from the corresponding isocyanopeptide **1133** by Ni-catalyzed polymerization. The click reaction of the polymer scaffold **1134** with the azides was performed in presence of PMDETA and CuBr. The copper salts were removed from solution by complexation with EDTA and the clicked polymers **1135** were subjected to size-exclusion chromatography to remove unreacted starting materials. Perylene-containing polyisocyanopeptide can also be synthesized using this synthetic procedure (Scheme 278).[55,509]

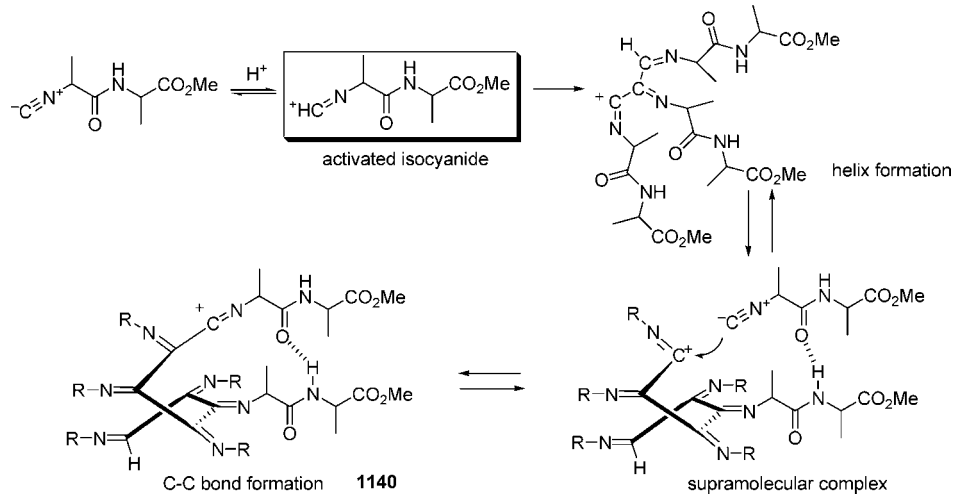
Another type of clickable polyisocyanopeptide bearing azide functionalities, **1137**, has been successfully synthesized by means of polymerization of the corresponding azide-containing isocyanopeptides **1136**. However, these polymers disappointingly do not display the characteristics of a well-defined hydrogen-bonding network. The polymer with a well-defined architecture **1138** can be obtained by copolymerization of **1136b** with another isocyanide monomer. Methyl esters in **1138** can be saponified to give a water-soluble polymer possessing azido groups, which can be postmodified by click chemistry. The modification of the water-soluble polymer scaffold was achieved using an acetylene-functionalized rhodamine dye to form **1139**. This route opens the way to use the polyisocyanides as effective water-soluble scaffolds to which a variety of acetylene-functionalized biomolecules can be added (Scheme 279).[510] Very recently Nolte et al. developed cysteine-containing (poly)isocyanopeptides which can be modified by thio-specific "click" reactions (see section 17).

13.3.6. Acid-Mediated Polymerization of Isocyanopeptides

It was shown that isocyanodipeptides can be polymerized by a proton-initiated process; however, the success of this method of polymerization is very sensitive to temperature, solvent, acid concentration, and, in particular, the stereochemistry of the monomer. The preorganization effect of amide bonds in isocyanopeptides plays a crucial role in this reaction. Initially, a reaction mechanism was proposed with an initial helical oligomer stabilized by hydrogen bonds. During the propagation of the polymerization reaction, this helical prepolymer acts as a template in which the monomer is "docked" at the reactive chain end of the polymer by attractive hydrogen-bonding forces between the amide function of the monomer and the hydrogen-bonded array already present in the peptide side chains of the polymer. In this supramolecular complex, thus "immobilized" monomer can readily react to form a new carbon−carbon bond, thereby extending the helical polymer **1140** (Scheme 280).[511,512] In general, acid-mediated polymerization of isocyanopeptides is not as effective as a transition-metal-catalyzed process for synthesis of polyisocyanopeptides.

In conclusion, metal-catalyzed polymerization of isocyanoacetates results in the formation of polyisocyanides that fold in a protein-like fashion. Isocyanopeptides give polymers in which the peptide chains are arranged in β-sheets. It is also noteworthy that polymerization of functionalized isocyanoacetic acid permits control of properties of the target

Scheme 280



polymers. These polymers seem to be important for the development of new functional materials.

14. Miscellaneous Reactions

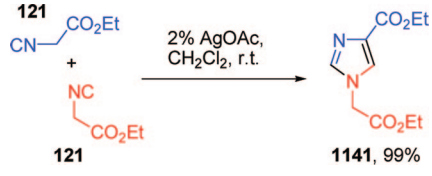
In this section, reactions not included in the previous sections are discussed. This especially concerns reactions when isocyanoacetate derivatives act just like ordinary isocyanides and do not enter any subsequent transformation affecting other functionalities of them. However such reactions will not be considered in full in this review, and the reader is referred to reading on general isocyanide chemistry. Only a few more recent and relatively unknown examples will be mentioned, but the material will not pretend to full coverage of the corresponding literature. All other reactions involving not only the isocyano group and making accent on a polyfunctional nature of isocyanoacetates will be discussed in full.

14.1. Self-Condensation and Reactions with Aromatic Isocyanides: Synthesis of Imidazoles

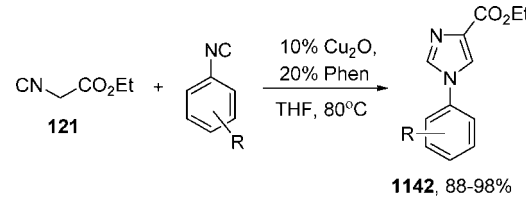
Ethyl isocyanoacetate **121** undergoes self-condensation in the presence of AgOAc as a catalyst to afford ethyl 1-ethoxycarbonylimidazole-4-carboxylate **1141** in quantitative yield (Scheme 281).[255] This reaction may also take place in other reactions of isocyanoacetate competitively when AgOAc is used as a catalyst and can become predominant if other partners are not sufficiently reactive.

Another very similar reaction has been reported in 2006 by Yamamoto. It was found that ethyl isocyanoacetate **121** reacts with aryl isocyanides to afford ethyl 1-arylimidazole-4-carboxylates **1142** at 80 °C in THF in the presence of a catalyst (10% Cu_2O/20% phenanthroline). Various aromatic isocyanides bearing either EWG or EDG and even sterically hindered 2,6-substituted substrates are acceptable and a series of imidazoles **1142** were obtained in excellent yields (Scheme 282). However, attempts to perform the reaction on aliphatic

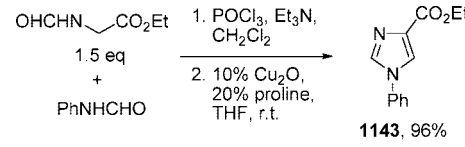
Scheme 281



Scheme 282



Scheme 283



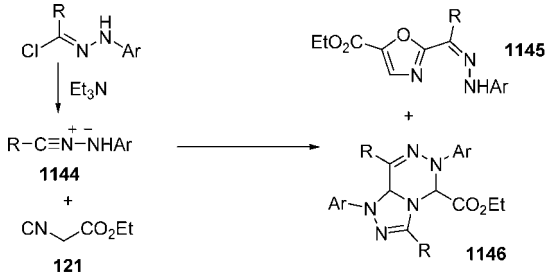
isocyanides were unsuccessful (the desired imidazoles were obtained only in approximately 10% yields; the major product was the homocycloadduct **1141**; see Scheme 281). Isocyanoacetamide gave the corresponding imidazole in a moderate yield.[513]

The method was extended by Roy in 2007, who described a direct catalytic synthesis of 1-arylimidazole-4-carboxylates, such as **1143**, starting from the corresponding *N*-arylformamides and *N*-formylglycine esters. At first, a mixture of two formamides is transformed into a crude mixture of two isocyanides followed by transformation in the presence of a catalyst to the final imidazole. Importantly, the authors found a new catalytic system 10% Cu_2O/20% proline which allowed reaction to proceed at room temperature with great efficiency (Scheme 283).[514] Generally, the method described is efficient for synthesis of alkyl 1-arylimidazole-4-carboxylates.

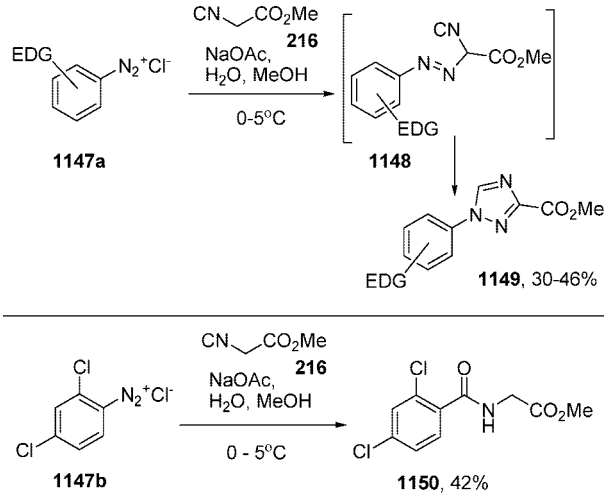
14.2. Reaction with Nitrilimines

Reaction of ethyl isocyanoacetate with nitrilimines **1144**, which can be generated *in situ* from hydrazonoyl chlorides in the presence of triethylamine, gives a diverse set of products (Scheme 284). In most reported cases, the reaction was rather unselective, but the products were isolable in a pure form. It seems that only hydrazonoyl chlorides bearing an EWG are able to react selectively to afford oxazoles.[515]

Scheme 284



Scheme 285



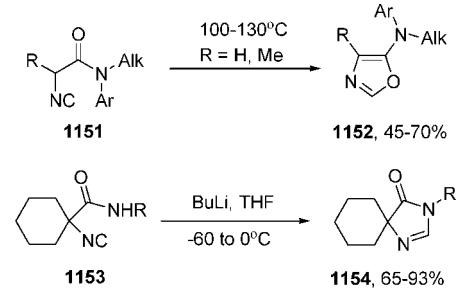
14.3. Reaction with Diazonium Salts: Synthesis of 1,2,4-Triazoles

Depending on the nature of substituents at the aromatic ring, the reaction of arenediazonium salts with ethyl isocyanoacetate affords two types of products. With an electron-rich aromatic ring in **1147a**, initial Japp−Klingemann reaction occurs to yield azo-compounds **1148**, which undergo spontaneous cyclization to form 1,2,4-triazole derivatives **1149** in moderate to good yields. When electron-withdrawing groups are present as in **1147b**, a nucleophilic attack by the isocyano group occurs at the ipso-position to form benzamide **1150** (Scheme 285).[516,517]

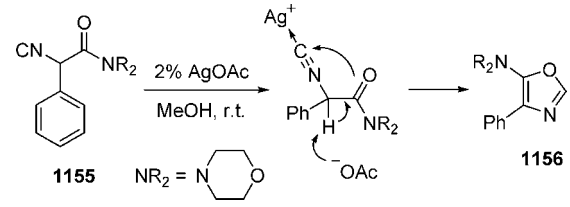
14.4. Base- or Thermal-Induced Cyclization of N-Substituted Isocyanoacetamides

Under certain conditions, N-substituted isocyanoacetamides are able to cyclize via either the nitrogen or the oxygen atom to give imidazolinones or 5-aminooxazoles, respectively. Thus, tertiary *N*-alkyl-*N*-aryl isocyanoacetamides **1151** undergo thermal rearrangement to oxazoles **1152**, which in certain cases may already occur upon vacuum distillation.[41] This is a reversible process, and the equilibrium mixture consists of 97−98% of the corresponding 5-aminooxazole. Attempts to isomerize secondary α,α-unsubstituted *N*-alkylisocyanoacetamides were unsuccessful due to decomposition.[41] Behavior of secondary *N*-aryl amides was not investigated. However, *N*-substituted 1-isocyano-1-cyclohexanecarboxamides **1153** (which can be regarded as α,α-disubstituted isocyanoacetates) undergo smooth cyclization to **1154** upon treatment with butyllithium at low temperature (Scheme 286).[46]

Scheme 286



Scheme 287



This base-induced rearrangement occurs by alkylation of secondary isocyanoacetamides, as was described in section 3.2, Scheme 36. The intermediate imidazolyl anions can be alkylated *in situ* as described in section 15.1, Scheme 296. More recently, the cyclization to isocyanoacetamides to oxazoles **1056** was found to be promoted by AgOAc catalysis, but the scope of the method was not investigated (Scheme 287).[399]

14.5. Coupling of Isocyanoacetates with Carboxylic Acids

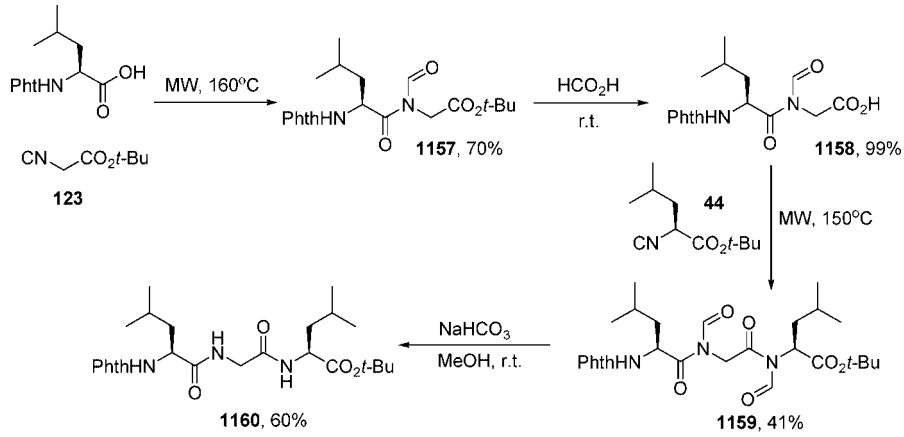
Very recently, Danishefsky et al. developed a synthesis of *N*-formyl amides by a two-component microwave-assisted coupling (2CC) of an isocyanide and a carboxylic acid.[518] Based on the reaction of amino acids with isocyanoacetates, a new route to construct peptides was described. Thus, as an example, reaction of protected L-leucine with isocyanoacetate **123** afforded *N*-formyl peptide **1157** in good yield. Subsequent deprotection and second 2CC of **1158** with chiral isocyanoacetate **44** produces the bis-formylamide **1159** in 41% yield. It is noteworthy that the configuration of the isocyanide center is fully retained. Subsequent mild deprotection leads to peptide **1160**. While the yield of peptides is rather modest, the method is promising for synthesis of chiral polypeptides (Scheme 288).[519]

The same reaction with thioacids proceeds without irradiation at room temperature. As an example, 2CC of protected thio L-valine and chiral isocyanoacetate **48** forms **1161** in 60% yield (Scheme 289). The reaction takes place in a straightforward fashion with a variety of thioacids, whereas yields of desired products were increased with ascending isocyanoacetate steric hindrance.[520] Application of these isocyanide-mediated peptide couplings has been recently demonstrated in elegant total synthesis of cyclosporine A by Danishefsky et al. (see section 16.11).

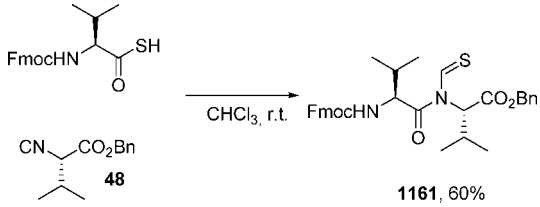
14.6. Cu-Catalyzed Reaction with 2-Halo Aryl Aldehydes and Ketones

Very recently, a straightforward synthesis of indole-2-carboxylic esters was developed through a ligand-free copper-catalyzed condensation/coupling/deformylation cascade process from 2-haloaryl aldehydes or ketones **1162** with

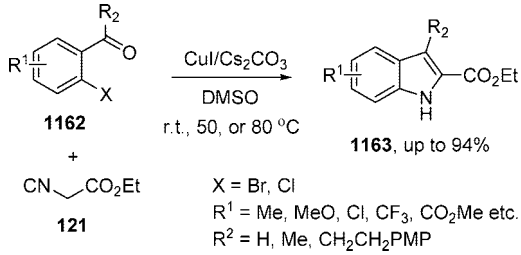
Scheme 288



Scheme 289



Scheme 290



ethyl isocyanoacetate. The reactions proceeded well for most of the 2-iodo-, bromo-, and chlorosubtrates under mild conditions (rt to 80 °C). The reaction displayed excellent functional group compatibility and high chemical selectivity in the presence of a broad range of functional groups (Scheme 290).[521]

15. Applications in the Synthesis of Biologically Active Compounds

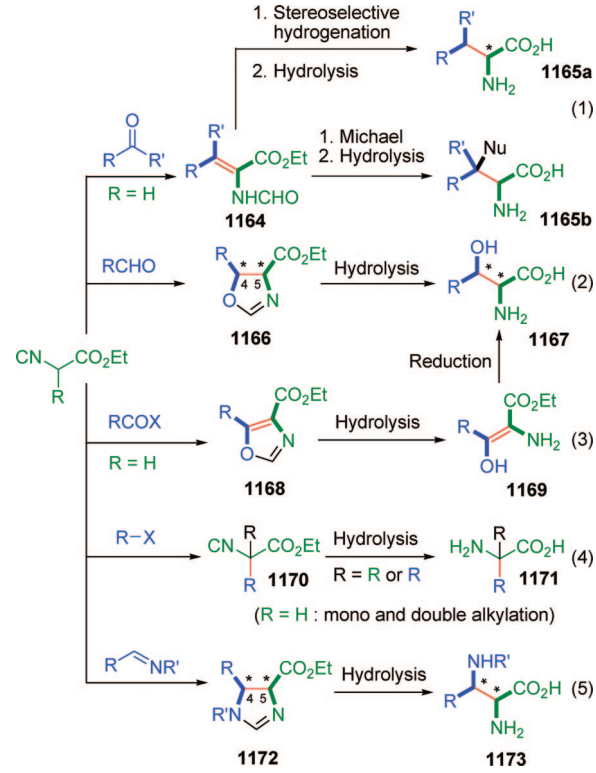
15.1. Synthesis of Amino Acid Derivatives

As has been put forward in the preceding sections, the unique properties of the isocyano group effectively stabilize a negative charge on the adjacent carbon. Another characteristic of the isocyano group is that it can be easily transformed into an amino group. Consequently, isocyanoacetates and isocyanoacetamides serve as convenient synthetic equivalents for a glycine carbanion and are widely applied as building blocks for the synthesis of amino acids.[90]

Five major strategies can be identified from literature that are most commonly used for the synthesis of different kinds of amino acids, as briefly summarized in Scheme 291. All are based on reactions with carbonyl compounds, imines, acylating agents, and alkylating agents.

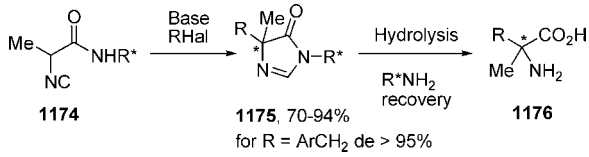
The first strategy is based on a Knoevenagel-type reaction as was already discussed in detail in section 4.4. Formylaminoacrylates **1164** thus obtained can be further transformed into amino acids in several ways. For example, stereoselective hydrogenation[97] of **1164** gives access to optically pure α-amino acids **1165a**, whereas Michael reaction of **1164** with nucleophiles yields functionalized α-amino acids **1165b**. In principle, a diastereoselective Michael reaction may be conceived too, but to the best of our knowledge, such a process has not been described on formylaminoacrylates.

Scheme 291



The second strategy is based on oxazoline formation as was also summarized in depth in section 4.2. Oxazolines **1166** can be obtained from isocyanoacetates in high yield and under very mild conditions. Subsequent hydrolysis gives amino acids **1167**. Moreover, asymmetric synthesis of oxazolines by means of gold-catalyzed reaction is well-developed. This strategy is especially suitable for the synthesis of optically pure β-substituted serine derivatives, because reaction of α-unsubstituted isocyanoacetates with aldehydes proceeds with high stereoselectivity (both de and ee). Higher substituted amino acids can be obtained from

Scheme 292



ketones and α-monosubstituted isocyanoacetates, but good stereoselectivity is often not observed. Nevertheless, this strategy is regarded as a valuable alternative to other methods for the synthesis of amino acids.

The next strategy (eq 3 in Scheme 291) exploits the application of acylating agents as a key step. Oxazoles **1168** prepared by this route can be transformed into olefinic amino acids **1169**, which can be reduced to give **1167**. With an appropriate reduction methodology, this method is also suitable for the synthesis of optically active amino acids. The synthesis of oxazoles is reviewed in section 6.1.

The fourth strategy (eq 4 in Scheme 291) is based on an alkylation reaction (for more details, see also section 3.1). Since formation of monoalkylated products from α-substituted isocyanoacetates is not widely applicable, this approach is more suitable for the synthesis of symmetrically substituted α,α-dialkyl amino acids **1170**. For monoalkylation, isocyanoacetamides should be used (section 3.2). The corresponding amino acids **1171** bearing different substituents at the α-position can also be obtained from α-monosubstituted isocyanoacetates but only in racemic form.

The final strategy (eq 5 in Scheme 291) is based on reactions with imines, which are discussed in more detail in section 5. *In situ* generation of the imine results in a three-component reaction (see section 10.3.3), and this approach was applied to access of wide range of α,*β*-diamino acids **1173**, including the N^{β}-substituted derivatives. In many cases, this method is applicable for the stereoselective synthesis of α,*β*-diamino acids.

In general, these methods employ isocyanoacetates as the input, but often isocyanoacetamides can be used as starting material too. However, for isocyanoacetamides an additional strategy for the synthesis of amino acids is worthy of note. The method is based on the diastereoselective alkylation of *N*-alkylisocyanoacetamides bearing a chiral alkyl substituent at the nitrogen (see also section 3.2). The alkylation is accompanied by cyclization, which affords imidazolinones diastereoselectively, but high de is observed only for benzyl halogenides (Scheme 292). The corresponding amino acids are obtained upon hydrolysis (see Scheme 296 for examples). The chiral amine auxiliary can be recovered.[522]

Although the chemistry relevant to this section has been described in detail in the corresponding sections above, we wish to discuss some additional syntheses of natural and unnatural amino acids to further demonstrate the synthetic utility of isocyanoacetates. Thus, (−)-(2*R*,3*S*)-3-hydroxylysine **1178**, a naturally occurring amino acid, was synthesized using a gold-catalyzed asymmetric aldol reaction. The intermediate oxazoline **1177** was formed in high yield, de, and ee.[523]

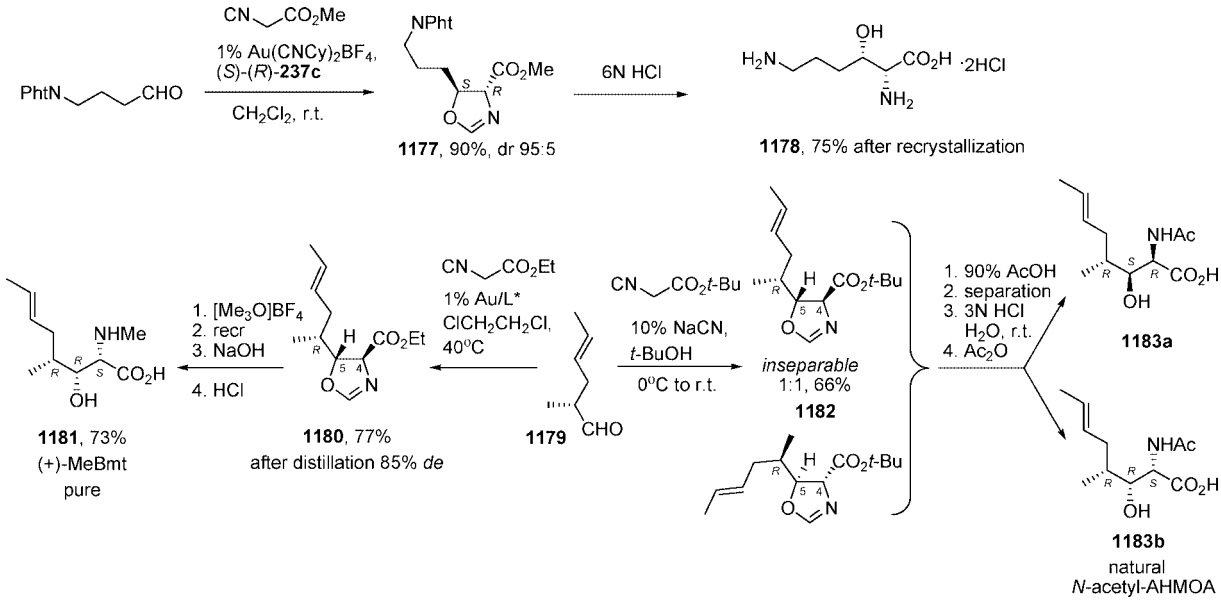
(4*R*)-4-[(*E*)-But-2-enyl]-4,*N*-dimethyl-L-threonine, MeBmt, the unusual amino acid in the immunosuppressive undecapeptide cyclosporine, was obtained from the corresponding aldehyde **1179**.[147] The optically pure species was obtained from **1180** after a single recrystallization step and further transformed into the desired amino acid **1181**.

The octenoic acid derivative **1183b** (*N*-acetyl-AHMOA), a analogue of **1181** isolated from a culture broth of *Neocosmospora vasonfecta*, was synthesized from the same starting aldehyde **1179**. Sodium cyanide catalyzed aldol reaction afforded an inseparable mixture of two diastereoisomers **1182** (out of four possible) in 1:1 ratio, both having *trans*-configuration at C4−C5. The mixture was separated by flash chromatography after the ring cleavage in the next step, which finally led to preparation of two stereoisomers of *N*-acetyl-AHMOA **1183**, including the natural one **1183b** (Scheme 293).[524]

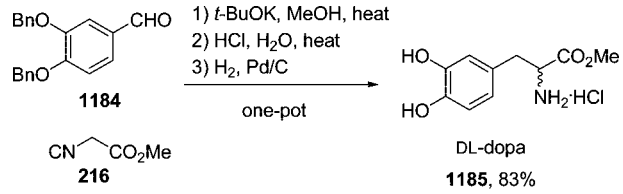
Another interesting example of this chemistry involves the synthesis of DL-dopa **1185**, which was achieved starting from aldehyde **1184** using the oxazoline method. All three steps were successively accomplished in one pot (Scheme 294).[525]

Carborane-containing amino acids are used for boron neutron capture therapy. The boron-containing phenylalanine[526] **1187** analog was synthesized using a formylaminoacrylate synthesis (section 4.1) as a key step. Catalytic

Scheme 293



Scheme 294



hydrogenation on Pd/C with subsequent hydrolysis afforded the racemic DL-amino acid. Next to this method, a stereoselective variant of formylaminoacrylate hydrogenation has also been reported.[97] Phenylserine **1198**[527] and β-hydroxy tyrosine **1191**[528] analogs were synthesized using NaCN-catalyzed aldol reaction. The corresponding oxazolines **1188** and **1190** were formed as mixtures of *cis*/*trans* diastereomers, which were separated before or after ring opening in the next step (Scheme 295).

Several optically pure phenylalanine analogs **1194** were prepared by Schöllkopf almost three decades ago (Scheme 296). He found that alkylation of *N*-[(*S*)-phenetyl]-2-isocyanopropionamides **1192** by benzyl halides proceeds with high diastereoselectivity, whereas with nonbenzylic alkyl halides, the de is much lower.[522]

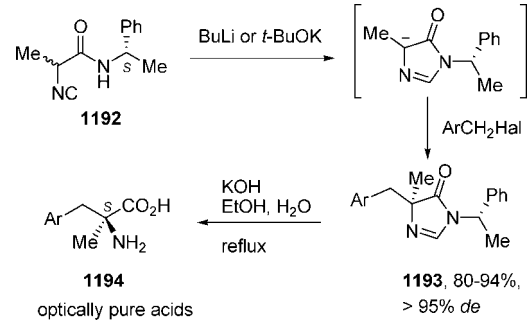
Furthermore, Schöllkopf has described the cyclopropanation of formylaminoacrylates **1195a** and isocyanoacrylates **1195b** by dimethylsulfoxonium methylide,[529] a method used for the preparation of aminocyclopropane carboxylic acid (ACC) derivatives **1196** (Scheme 297).[530,531]

15.2. Synthesis of Amino Sugar Compounds

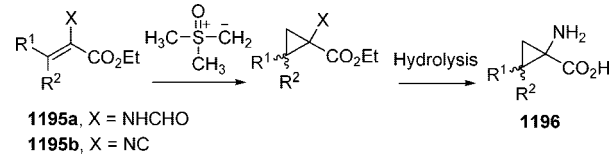
Oxazolines and oxazoles, which are accessible by reaction of isocyanoacetate with carbonyl compounds and carboxylic acid derivatives (sections 3 and 4), are convenient starting materials for the synthesis of polyfunctionalized hydroxyamino compounds. This approach links the C-4−C-5 bond during the reaction, which allows quick assembly of complex structures from simpler precursors. Importantly, this approach can be used for the synthesis of optically pure stereoisomers via enantioselective oxazoline synthesis or stereoselective reduction, thus complementing the olefination/aminohydroxylation strategy (Scheme 298). This method is particularly well suited for the synthesis of amino sugar derivatives from low molecular weight precursors, thus constituting an alternative to standard methods in carbohydrate chemistry. Therefore, it is not surprising to find numerous applications of this method in the total syntheses of natural products containing amino sugar moieties.

Besides the syntheses of 2-amino-2-deoxy-D-arabinose derivative **320** and 2-deoxy-D-ribose **319**, which were mentioned in section 4.7.5, isocyanoacetate was used to

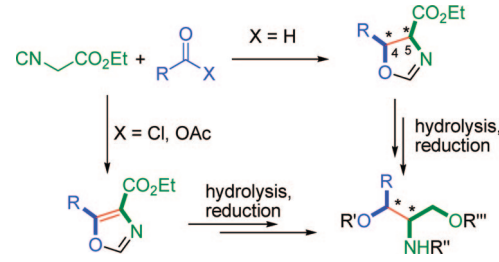
Scheme 296



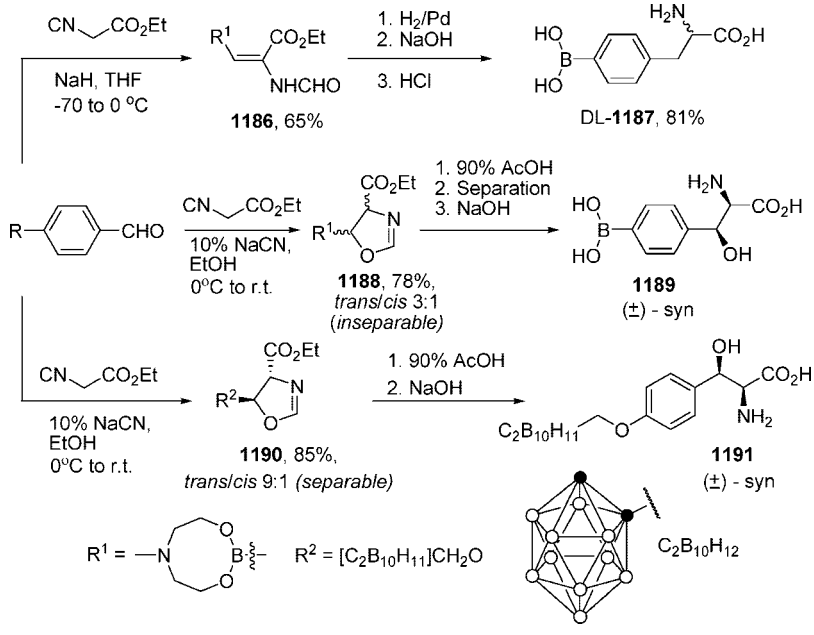
Scheme 297



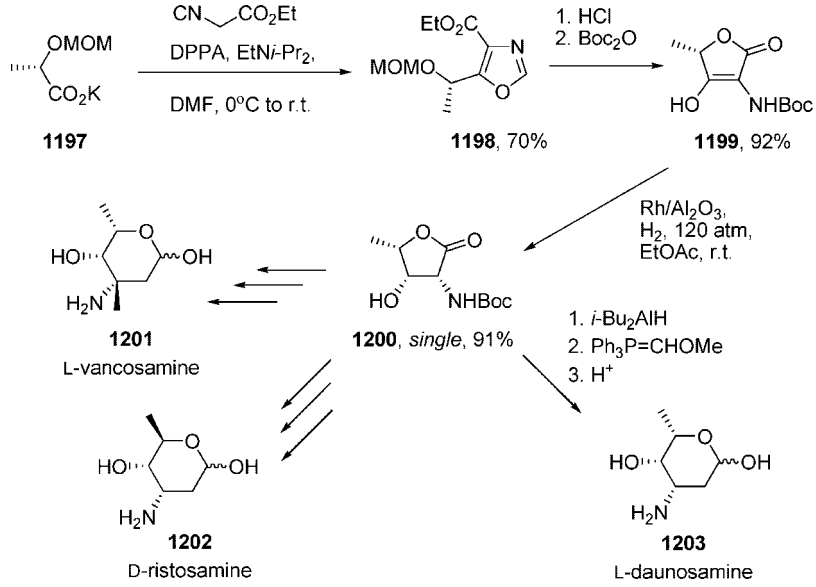
Scheme 298



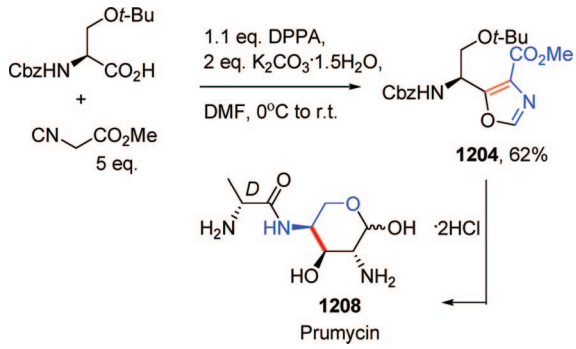
Scheme 295



Scheme 299



Scheme 300



assemble amino sugar moieties of L-vancosamine **1201** (a carbohydrate component of the antibiotics vancomycin and sporaviridin), D-ristosamine **1202** (the enantiomer of the carbohydrate component of the antibiotic ristomycin), L-daunosamine **1203** (the carbohydrate constituent of the important anthracycline antitumor agents, daunorubicin, adriamycin, and their congeners) by Shioiri et al. L-Vancosamine, D-ristosamine, and L-daunosamine were prepared from a common lactone precursor **1200**, which was synthesized starting from lactate **1199**.[213] Two additional stereocenters in **1200** were introduced by hydrogenation, which in this case proceeded highly stereoselectively on rhodium catalyst to afford **1200** as single diastereomer (Scheme 299).

Prumycin **1208** (4-(D-alanylamino)-2-amino-2,4-dideoxy-L-arabinose) is an antifungal antibiotic with interesting antitumor activity. The amino sugar skeleton was assembled also using isocyanoacetate oxazole synthesis as shown in Scheme 300.[208]

There are many applications of isocyanoacetate derivatives in synthesis of various drug-like molecules that were evaluated for biological activity. Some examples were already mentioned in the relevant chapters.

16. Application in Synthesis of Natural Products

Isocyanoacetate derivatives have been used in the total syntheses of numerous natural products. Some examples of natural products synthesis, such as manzacidin B (section 4.7.5, Scheme 75) and amphimedine (section 6.1, Scheme 95) were already mentioned above. Other examples are classified by a common type of transformation involving the isocyanoacetate and are discussed below to exemplify the versatility of these reactive building blocks in synthesis. We have ordered the summary below in analogy to the corresponding transformations as discussed in the preceding text.

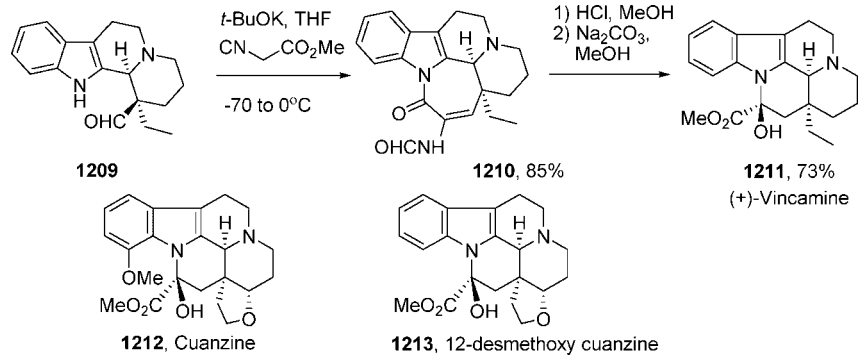
16.1. (+)-Vincamine and (±)-Cuanzine

(+)-Vincamine (the major alkaloid of *Vinca minor* L.) is a therapeutically widely used compound because of its cerebral vasodilatory effects. Synthesis of racemic (±)-vincamine was reported by Langlois et al. in 1987, who used ethyl isocyanoacetate in the last steps to incorporate the final ring into the molecule.[96] Synthesis of enantiomerically pure natural (+)-vincamine **1211** was achieved by Rappoport et al. in 1990 via the same sequence starting from the optically pure aldehyde **1209** (Scheme 297).[532] The same strategy was used in syntheses of (−)-cuanzine **1212**, a hexacyclic indole alkaloid, which was isolated from the roots of *Voacanga chalotiana* (Apocynaceae) and intensively studied for its vasodilating, antihypertensive, and antiarrhythmic activities.[533,534] Its desmethoxy analog **1213** also was obtained in this manner (Scheme 301).[535]

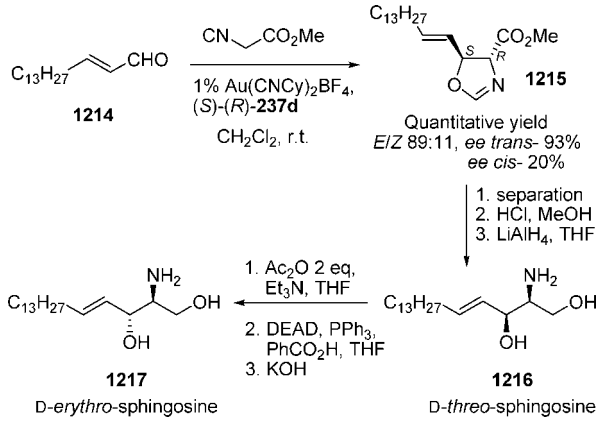
16.2. D-*erythro*- and D-*threo*-Sphingosines

The sphingolipid bases, D-*erythro*- and D-*threo*-sphingosines, are the target molecules that have been synthesized to demonstrate the efficiency of a new methodology to control both absolute and relative configurations in acyclic systems. A short synthesis of D-sphingosines has been attained by using the gold(I)-catalyzed asymmetric aldol reaction of aldehydes with the use of isocyanoacetate in the key step. The corresponding oxazoline mixture **1215** was obtained in quantitative yield from aldehyde **1214**. The major diastereomer was isolated by silica gel MPLC and after methanolysis and reduction gave D-*threo*-sphingosine **1216**. The D-*erythro* isomer **1217** was obtained from **1216** using a Mitsunobu reaction (Scheme 302).[536]

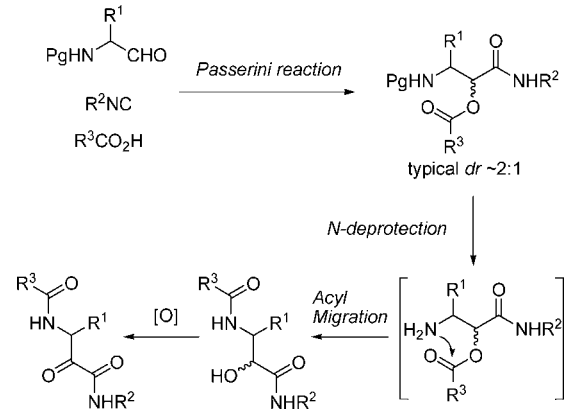
Scheme 301



Scheme 302



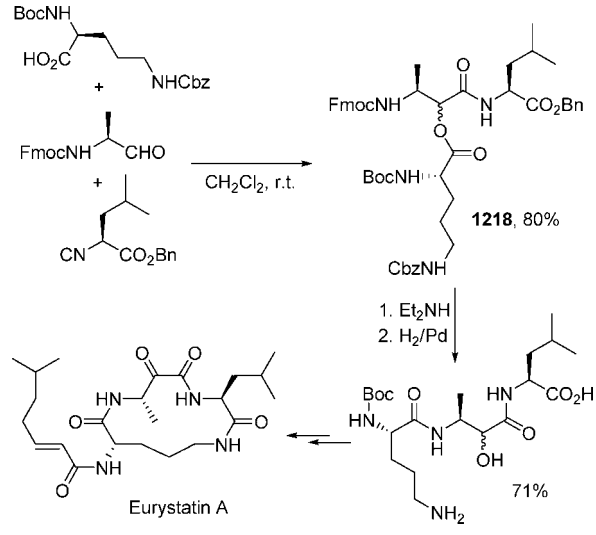
Scheme 304



16.3. Eurystatin A and Cyclotheonamide C

Eurystatins A and B are 13-membered macrocyclic natural products isolated from *Streptomyces eurythermus* R353-21 featuring leucine, ornithine, and α-ketohomoalanine subunits. They are reported as potent inhibitors of the serine protease prolyl endopeptidase. Due to their relative structural simplicity, they serve as attractive targets for the development of new methodologies for synthesis of α-hydroxy-β-amino amides and α-ketoamides. For the first time eurystatin A was synthesized by Schmidt in 1993.[537] But in 2001 an improved synthesis was reported by Semple.[332] Both syntheses employed the Passerini reaction, but Semple's synthesis features a highly efficient and atom-economic Passerini reaction/deprotection/acyl migration (PADAM) strategy that was employed for rapid construction of the key intermediate **1218** to construct the acyclic skeleton of eurystatins (Scheme 303). Just a few steps were required from there to complete the synthesis.

Scheme 303



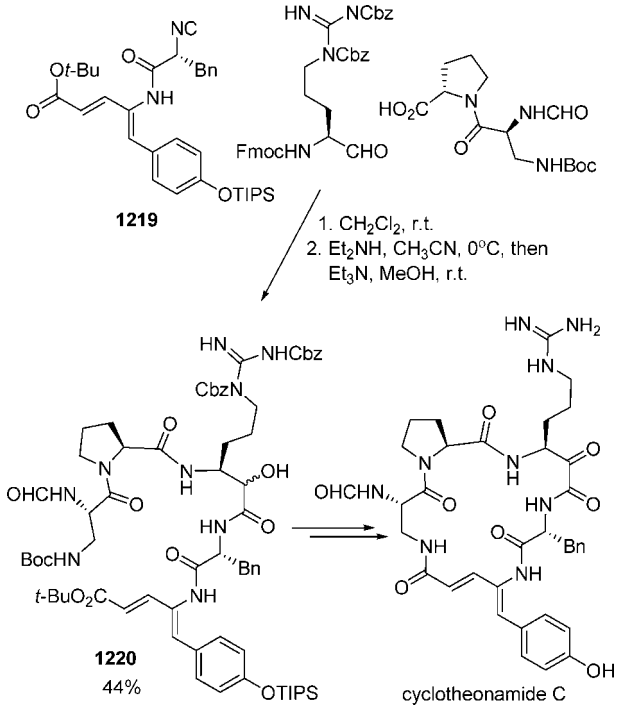
PADAM strategy, initially described by Banfi et al., appears to be a valuable supplement to the classic Passerini reaction since it allows an easy combinatorial entry to peptide-like molecules with two new amide bonds (Scheme 304).[334,335]

Recently, this has been applied in a short formal total synthesis of cyclotheonamide C, a member of a family of cyclic pentapeptides, inhibitors of serine proteases, isolated from the marine sponges *Theonella swinhoei* and *Theonella ircinia*. The key intermediate **1220** was assembled in moderate yield from three components, including chiral isocyanoacetamide **1219**, using a PADAM sequence (Scheme 305).[538]

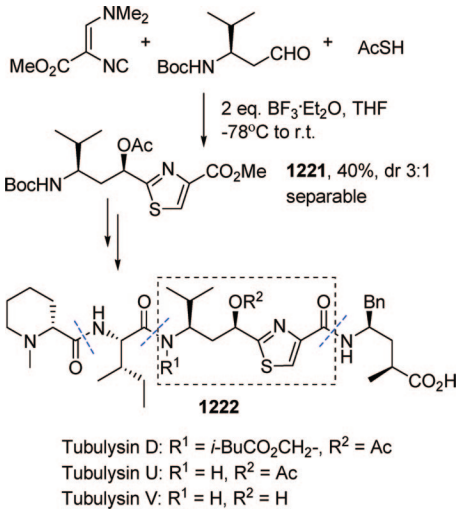
16.4. Tubulysin U and V

Tubulysins are compounds of extraordinary potency, rapidly degrading the tubulin cytoskeleton, with tubulysin D being the most active tubulin-modifier known so far. Semisynthetic tubulysins, derived from isolated material, show promising *in vivo* anticancer properties and are candidates for antibody conjugates. Two members of the tubulysin family, tubulysin U and V, were synthesized by Dömling and Wessjohann et al. in 2006.[539] The synthesis of a complex central amino acid building block **1221** was achieved using a convergent and stereoselective thiazole multicomponent reaction in 40% yield and in dr of 3:1 favoring the desired diastereomer (Scheme 306).

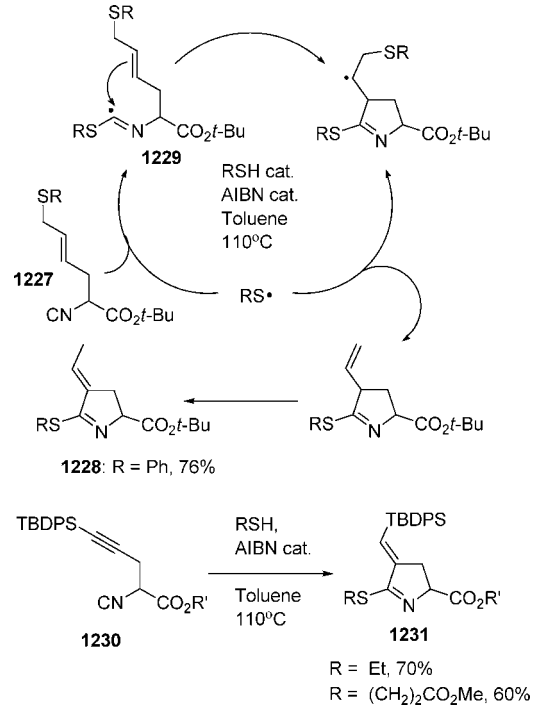
Scheme 305



Scheme 306



Scheme 308

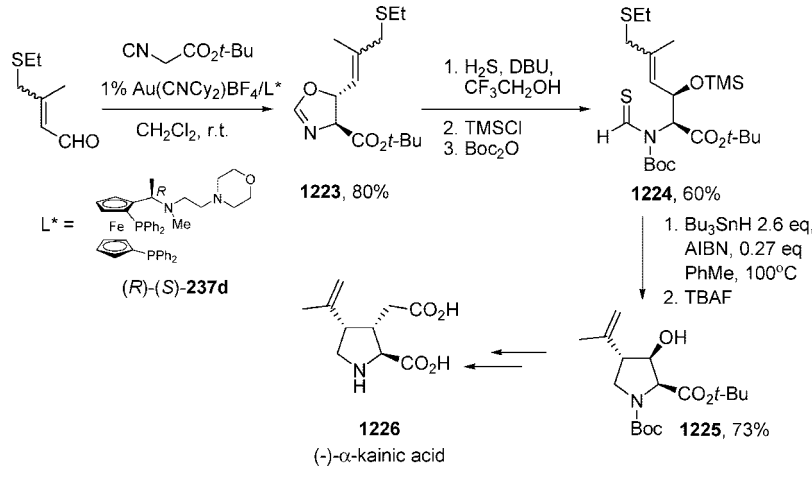


16.5. Kainic Acid

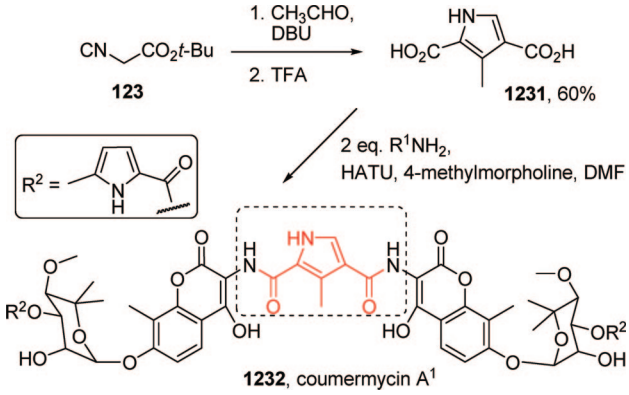
(−)-α-Kainic acid is the prototype of a group of neuroexcitatory amino acids that activate particular subtypes of glutamic acid receptors. These amino acids are important substrates for physiological and pharmacological studies of the central nervous system. Enantioselective synthesis of (−)-α-kainic acid was reported by Bachi et al. in 1997.[540] In the first step of their synthesis, a highly stereoselective gold-catalyzed asymmetric aldol reaction was utilized to prepare oxazoline **1223** as a pure stereoisomer. This is the key intermediate since it secures stereocontrol in the following steps. Further, **1223** was transformed into thioformamide **1224**, which was subjected to radical cyclization and deprotection to afford pyrrolidine **1225**. Subsequent transformations led to (−)-α-kainic acid **1226** (Scheme 307).

Thiol-mediated radical cyclizations of alkenyl and alkynyl isocyanides **1227** and **1230** to the cyclic imines **1228** and **1231**[541,123] were also used for the synthesis of intermediate compounds in the synthesis of racemic kainic acid (Scheme 308).[542,543] They are initiated by radical cyclization of thiyl

Scheme 307



Scheme 309



radical on the isocyano group to provide species **1229**, which enter subsequent transformations to a final product. These reactions can be efficiently promoted using flash-heating by microwave irradiation,[544] according to Kilburn et al., who also described microwave-assisted radical cyclization of isocyanides on solid support.[13]

16.6. Coumermycin A_1

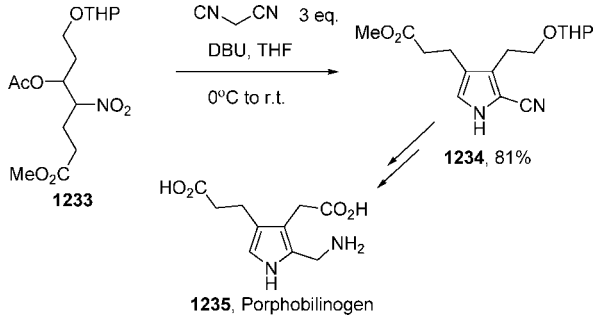
Coumermycin A_1 **1232** is a potent antibiotic isolated from *Streptomyces* that binds reversibly and with high affinity to the amino-terminal 24K subdomain of the B subunit of bacterial DNA gyrase (GyrB). It was synthesized recently by coupling of 3-methyl-1*H*-pyrrole-2,4-dicarboxylic acid **1231** with 2 equiv of the appropriate amine (Scheme 309).[545] The starting acid **1231** was prepared from *tert*-butyl isocyanoacetate and acetaldehyde by the Matsumoto procedure (section 4.5).

16.7. Porphobilinogen and (+)-Deoxypyrrololine

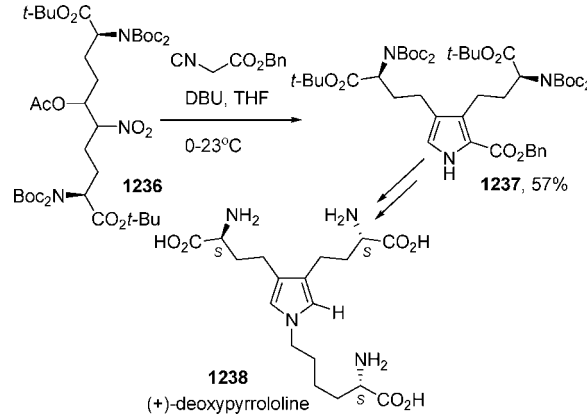
Porphobilinogen (PBG) **1235** was isolated by Westall in 1952 from the urine of patients with acute porphyria. PBG is the key building block in the biosynthesis of tetrapyrrolic natural products such as porphyrins, chlorophylls, corrins, and vitamin B_{12}. One of several syntheses of PBG utilizes a Barton−Zard reaction to prepare the pyrrole fragment as a key intermediate compound **1234**. The conversion of **1234** into the final product **1235** required just a few consecutive functional group transformations (Scheme 310).[546]

(+)-Deoxypyrrololine **1238** is a potential biochemical marker for diagnosis of osteoporosis. Its synthesis also includes a Barton−Zard reaction (section 9.1) as the key step (Scheme 311).[547,548]

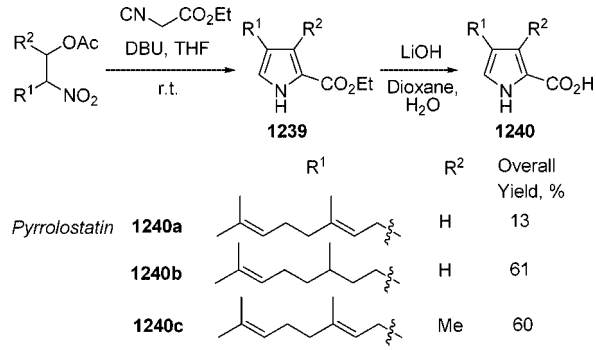
Scheme 310



Scheme 311



Scheme 312



16.8. Pyrrolostatin

Pyrrolostatin is a peroxidation inhibitor isolated from *Streptomyces chrestomyceticus*, it consists of a pyrrole-2-carboxylic acid with a geranyl group at the 4-position. This pyrrole derivative shows *in vitro* inhibitory activity against lipid peroxidation comparable to that of vitamin E (α-tocopherol), a well-known antioxidant. Pyrrolostatin **1240a** and its analogs **1240b**,**c** were synthesized using the Barton−Zard reaction. However, this method appeared inefficient for the synthesis of pyrrolostatin **1240a** itself (yield 13% only). Nevertheless, pyrrolostatin analogs **1240b**,**c** can be prepared by this method in good yields (Scheme 312).[549]

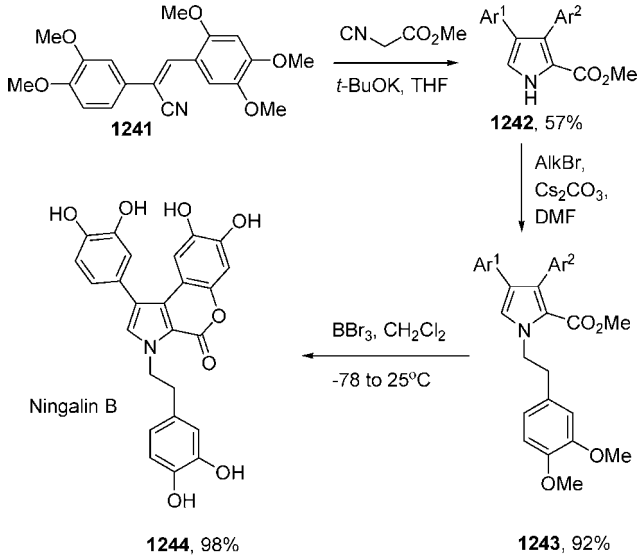
16.9. Ningalin B

The marine natural product ningalin B **1257** was synthesized just in three steps from **1254**. The key feature of this synthesis utilizes the leaving group ability of the nitrile group (see also section 9.1.3, Scheme 151). Since this reaction demonstrates good tolerance to electronic changes for both aromatic rings, it is very amenable for the synthesis of a variety of analogues of these natural products and 3,4-diarylsubstituted pyrroles in general (Scheme 313).[304]

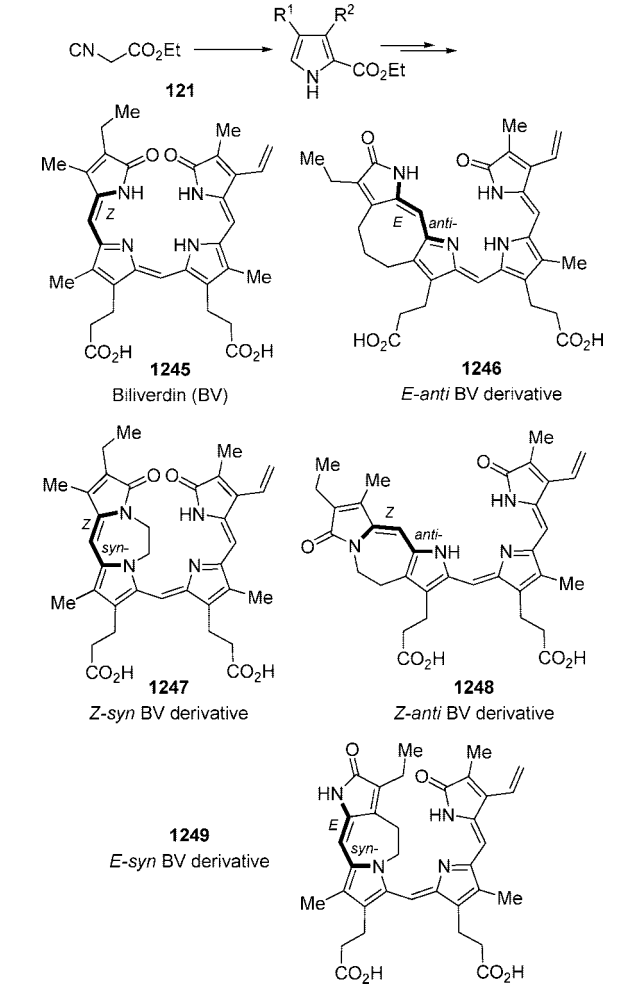
16.10. Porphyrin- and Polymethylenepyrrole-Based Natural Products

3,4-Disubstituted pyrrole-2-carboxylic acid derivatives **525** are easily accessible by the Barton−Zard method. They are useful building blocks for the synthesis of various porphyrin-like natural compounds and analogs (see section 9.4.1). For example, by this method the pyrrole rings of sterically locked *E-anti*, *E-syn*, *Z-anti*, and *Z-syn* derivatives of biliverdin (BV)

Scheme 313



Scheme 314



1245−**1249** were assembled, which are natural chromophores of bacterial phytochromes (Scheme 314).[550,551]

16.11. Cyclosporine A

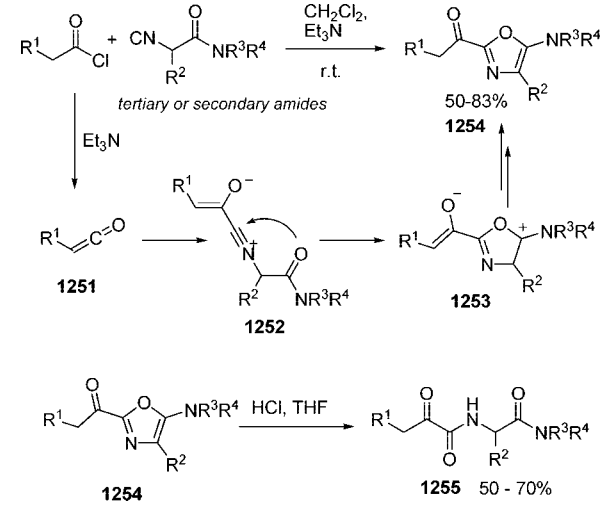
Cyclosporine A is a reversible inhibitor of cytokines in T helper cells that was isolated from the fungus *Tolypocladium inflatum* gams. In 2010, Danishefsky reported an elegant total synthesis of cyclosporine A **1250** in which six out of eleven amide bonds of this macrocyclic peptide (including the last macrolactamization step) were constructed using different isonitrile chemistry.[552] This is briefly summarized in Figure 18. The relevant chemistry was discussed in section 14.5. With respect to isocyanoacetates used in this synthesis, it is important to note that no racemization occurred in the corresponding steps. The synthesis of cyclosporine A by Danishefsky is an outstanding example of using versatile and powerful isonitrile chemistry for constructing polyamide structures.

17. Supplement

In 2010, Zhu reported a reaction of aliphatic acyl chlorides and isocyanoacetamides in the presence of triethyl amine leading to 2-acyl-5-aminooxazoles **1254**.[553] The title compounds were obtained in good yields. Both α-unsubstituted and α-substituted α-isocyanoacetamides participated in the reaction. It is remarkable that compared with the related multicomponent reaction between aldehydes, amines, and isocyanoacetamides (section 10.3.1), this method works well not only with tertiary α-isocyanoacetamides but also with secondary ones. Optically active α-substituted acyl chloride led to racemized product, which could imply formation of ketene intermediate **1251** during the reaction. Formation of ketene is also supported by the fact that benzoyl chloride does not react under the reaction conditions. Additionally, in reaction of acyl chlorides and α-isocyanoacetamides without TEA, only the α-ketoimidoyl chloride was formed; this intermediate could not be transformed to the corresponding 2-acyl-5-aminooxazole because addition of the base gave rise to a complex mixture (which is in contrast to behavior of isocyanoacetates under similar conditions, see section 6). So a plausible reaction scenario involves formation of ketene **1251**. The isocyanide attacks the electrophilic carbon atom to produce the nitrilium ion **1252**. This latter intermediate cyclizes and, after proton transfer, gives the 2-acyl-5-aminooxazole **1254** (Scheme 315). Oxazoles **1254** were hydrolyzed into open-chain α-ketoamides **1255**.

A substantially similar method was reported in 2010 by Yongping Yu et al. They found that tertiary α-isocyanoacetamides react with α-diazocarbonyl compounds **1256** under thermal conditions without any additives to yield oxazole derivatives **1258** in good yields.[554] It is supposed that initially thermal Wolff rearrangement occurs to generate ketene **1257**,

Scheme 315



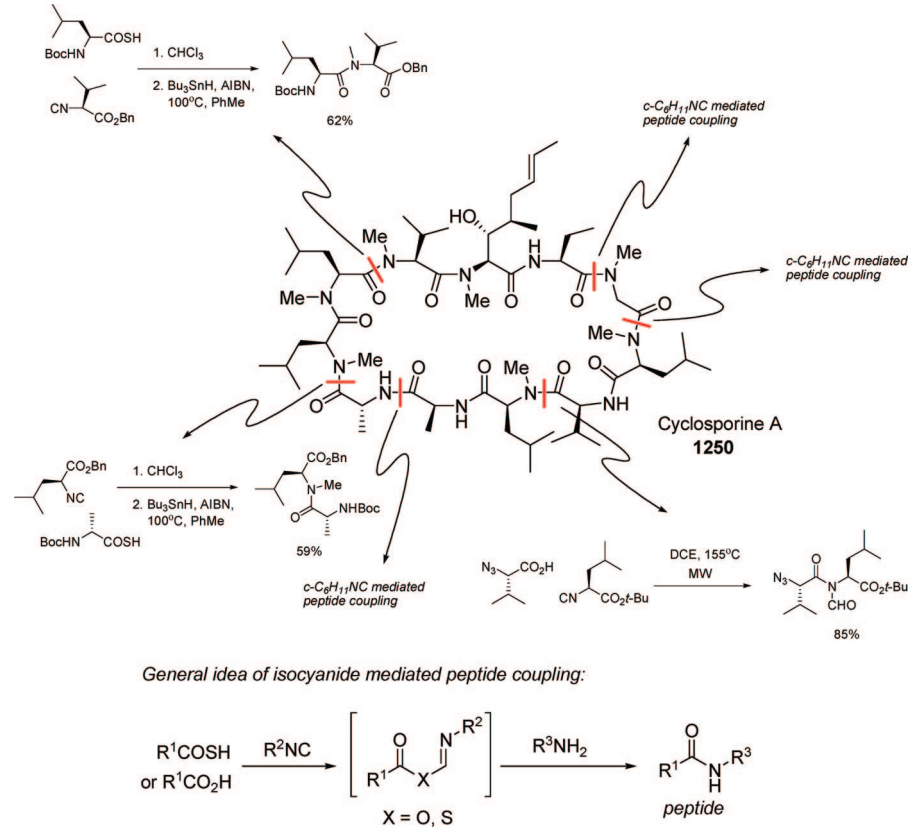
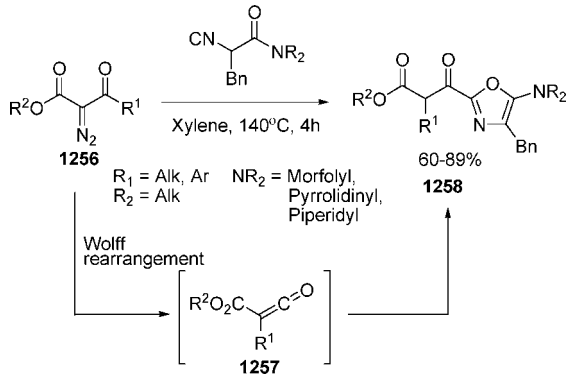
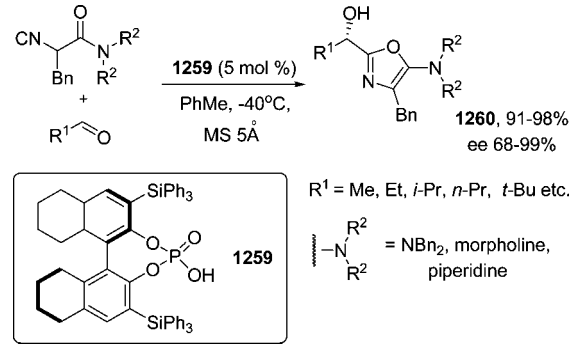


Figure 18.

Scheme 316



Scheme 317



which enters similar transformations as those described above (Scheme 316).

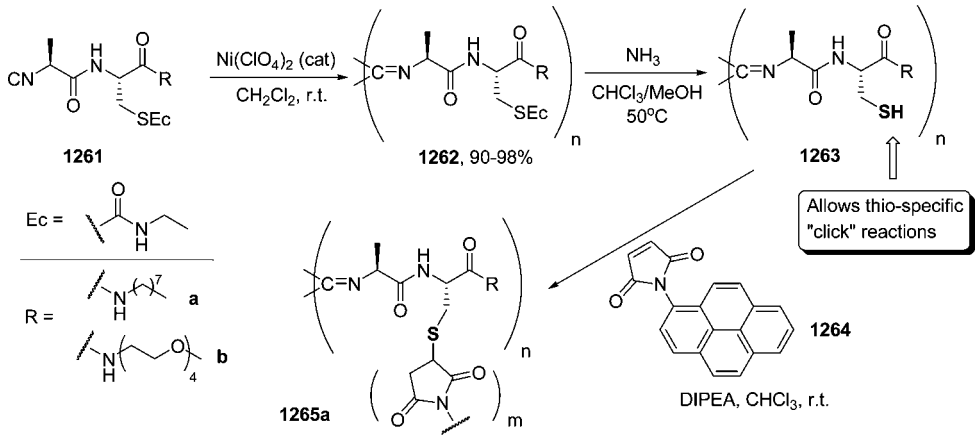
Very recently organocatalytic enantioselective α-addition of aldehydes to α-isocyanoacetamides was developed by Zhong et al. (for metal-catalyzed examples see section 10.4, Table 14). The reaction takes place in mild conditions and affords the desired oxazoles **1260** in excellent yields and good to excellent enantioselectivity (up to 99% ee). However, only aliphatic aldehydes can be employed by the described procedure, whereas aromatic aldehydes failed to react (Scheme 317).[555] Therefore, this efficient organocatalytic approach can compete with metal-catalyzed transformations in the case of aliphatic aldehydes, whereas in the case of aromatic carbonyl compounds metal-catalyzed reaction is without a rival (see Table 14).

In 2010 polyisocyanides **1262** containing the alanine–cysteine fragment were obtained from the corresponding isocyanopeptides **1261** (for the synthesis of "clickable" polyisocyanopeptides, see section 13.3.5). These protected polymeric compounds **1262**, containing a cysteine sulfur atom, allow efficient postmodification by using deprotection/thio-specific click reactions. After deprotection, in situ formed polymers **1263** with a free thio-group can be subjected to reaction with a variety of reagents, such as maleimides, iodoacetamides, etc. Thus, as an example, reaction with pyrene-maleimide **1264** yields polymer **1265a**, modified with a polyfluorescent pyrene moiety (Scheme 318). Thereby, cysteine-containing (poly)isocyanopeptides **1162** can serve as a molecular platform for postcondensational modification with a variety of different entities, which can be useful in the fields of material science and biohybrid systems.[556]

18. Concluding Remarks

Among other isonitriles, isocyanoacetate derivatives occupy an important place in the field of synthetic application and reaction diversity, which makes them strongly attractive objects for investigation. The unique multifunctional nature of isocyanoacetic acid derivatives opens up a range of

Scheme 318



exciting reactions, especially tandem/cascade processes for the synthesis of complex cyclic and macrocyclic systems. Multicomponent chemistry of isocyanoacetates is also a powerful instrument to access different classes of biochemically relevant compounds such as peptides, peptide molecules, and nitrogen heterocycles. This might be promising from the point of view of atom-economy and protecting group free strategies. The literature data collected in this review demonstrate the high synthetic utility of isocyanoacetate derivatives in modern organic, combinatorial, and medicinal chemistry. Such derivatives are efficient building blocks for synthesis of biologically active molecules and for total synthesis. It was also shown that isocyanoacetates and their derivatives are widely used in inorganic, coordination, and polymer chemistry. Thus, isocyanoacetates and isocyanopeptides are perspective monomers for creation of new polymer materials modified with functional groups. The unique combination of isocyanide and carboxylic group makes isocyanoacetic acid derivatives extremely important for synthesis of transition metal complexes. Therefore, further exploration of isocyanoacetic acid derivatives will open new frontiers in organic, inorganic, coordination, and polymer chemistry as well as medicinal chemistry and total synthesis of natural products.

19. List of Abbreviations

AFA	acetic formic anhydride
BICA	β-bromo-α-isocyanoacrylates
BNCT	boron neutron capture therapy
bpy	2,2′-bipyridyl
BZ	Barton−Zard
CDI	1,1′-carbonyldiimidazole
Cp	cyclopentadiene
CSA	camphorsulfonic acid
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicycloundec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DMAP	4-dimethylaminopyridine
Dmb	2,4-dimethoxybenzyl
DMP	Dess−Martin periodinane
DPPA	diphenylphosphoryl azide
dppp	1,3-bis(diphenylphosphino)propane
EDC	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
Fmoc	9-fluorenylmethyl carbamate
HMPA	hexamethylphosphoramide
HOBt	*N*-hydroxybenzotriazole
IBCF	isobutyl chloroformate
IBX	2-iodoxybenzoic acid
IDCA	α,α-iminodicarboxylic acid
MCR	multicomponent reaction
MTBE	methyl *tert*-butyl ether
NBD	norbornadiene
NMM	*N*-methylmorpholine
OBO	4-methyl-2,6,7-trioxabiciclo[2.2.2]octyl
Pg	protective groups
php	1,10-phenanthrolinopyrrole
phen	1,10-phenantroline
Pmb	4-methoxybenzyl
PMEDTA	*N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine
Py	pyridine
RCM	ring-closing metathesis
SAAs	sugar amino acids
TBDMS	*tert*-butyldimethylsilyl ethers
TBTU	2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate
TFA	Trifluoroacetic acid
TosMIC	toluenesulfonylmethyl isocyanide

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21. References

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