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Advances in
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VOLUME **101**

Editor

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MILESTONE OF 100 VOLUMES OF ADVANCES IN HETEROCYCLIC CHEMISTRY MARKED BY THE PUBLICATION OF VOLUMES 99, 100, AND 101 AS A CELEBRATORY SET

It is hard to believe that it is now 50 years since I conceived the concept of periodical volumes of these "Advances" that would record progress in Heterocyclic Chemistry. In 1960, heterocyclic chemistry was slowly emerging from the dark ages; chemists still depicted purines by the archaic structural designation introduced (was it by Emil Fischer?) 50 years before that. Together with Jeanne Lagowski I had published in 1959 a modern text on heterocyclic chemistry, the first that treated this subject in terms of structure and mechanism and attempted to logically cover significant methods of preparation and reactions of heterocyclic compounds as a whole, all in terms of reactivity.

The first two volumes of Advances contained extensive chapters on the tautomerism of various classes of heterocycles. Despite the great influence the precise structure of heterocyclic compounds has on chemical and biological properties (we only have to remember base pairing of nucleotides to illustrate this), at that time the literature was replete with incorrectly depicted tautomers. The basis for the position of tautomeric equilibria was usually completely misunderstood. Although great progress has been made in the last 50 years, there still exist holdouts even among otherwise reputable chemists who persist in depicting 2-pyridone as ''2-hydroxypyridine'' which is a very minor component of the tautomeric equilibrium under almost all conditions.

Over the years Advances in Heterocyclic Chemistry has indeed monitored many of the advances in the subject: the series is now boosted by "Comprehensive Heterocyclic Chemistry" of which the first edition was published in 1984 in 8 volumes, followed by the second edition in 1996 in 11 volumes and the third in 2008 in 15 volumes. Heterocyclic chemistry

has now taken its place as one of the major branches (by several criteria the most important) of Organic Chemistry.

Chemistry has rapidly become the universal language of molecular interactions; it has essentially taken over biochemistry and is rapidly gaining dominance in zoology, botany, physiology and indeed in many branches of medicine.

Chemical structural formulae are quite basic to this progress and have enabled us to rationalize many natural phenomenon and countless reactions both simple and exotic discovered in the laboratory.

Now we have reached the milestone of 100 volumes of the series. In place of a single volume we are offering the three volume set 99, 100 and 101 which contain a fascinating variety of reviews covering exciting topics in heterocyclic chemistry.

Alan R. Katritzky
Gainesville, Florida

PREFACE TO VOLUME 101

The final volume celebrating the attainment of the century for AHC contains five chapters contributed by heterocyclic chemists from six countries.

Soler, Moorefield, and Newkome (U. Akron, Akron, OH, USA) start with a fascinating account of the Senior Author's work on the construction of hexameric macromolecular architectures in organic chemistry. Patil, Kavthe, and Yamamoto (I.I.C.T., Hyderabad, India, and Tohoku U., Japan) summarize metal catalyzed cyclizations of alkynes bearing a heteroatom attached to a substituent which migrates during the annulation.

The chemistry of the 28 possible isomeric biindolyl structures is covered by Black and Kumar (UNSW, Sydney, Australia), while R.C.F. Jones (Loughborough U., Loughborough, UK) has reviewed his own and others' research on annulation reactions of 2-imidazoline. The volume closes with an upto date account of the chemistry of the Dimroth Rearrangement contributed by E.S.H. El Ashry, S. Nadeem, M.R. Shah, and Y.E. Kilany of Alexandria U. in Egypt.

Alan R. Katritzky
Gainesville, Florida

CHAPTER 1

Hexameric Macrocyclic Architectures in Heterocyclic Chemistry

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1. INTRODUCTION

Peter Stang once noted (97JA4777) that "In nature the hexagon represents the most common pattern throughout biological morphology from the simple diatoms to the bee honeycomb" after reading a treatise by Geoffrey Ozin (97ACR17) describing his investigations into the morphosynthesis of hierarchical inorganic structures, such as that of the radiolaria. The ubiquitous occurrence of the hexagonal motif in nature coupled with Peter Pearce's postulate (78MI1) that "structure in nature is a strategy for design" provides insight and reason to the plethora of diverse hexagonal architectures formed throughout synthetic chemistry. As well, the burgeoning arena of Supramolecular Chemistry, pioneered by Jean-Marie Lehn (78PAC871, 88AGE89, 95MI1), expands the platform for access to self-assembled macrocycles based on the attractive interactions between select metal ions and structurally compatible heterocyclic ligands. Transcending consideration of covalent versus non-covalent bonding, supramolecular chemistry considers building blocks instilled with angles, coordination sites, and affinities that drive their assembly to architectures with utilities and designs not accessed from the starting materials alone. Conjointment of the supramolecular regime with directed and convergent synthetic protocols has facilitated new routes to macrocyclic structures.

In a seminal review of the field of self-assembly of architectures mediated by transition metals Stang et al. (00CRV853) discussed and delineated design strategies or models developed over the years by such notable scientists as Saalfrank (97AGE2482), Lehn (99CEJ102, 99CEJ113), Raymond (99ACR975) ["Symmetry Interaction" Model], Verkade (83JA2494), Fujita (98CSR417), and Stang (97ACR502, 98JCD1707) ["Molecular Library Model"].

The Symmetry Interaction model considers the geometric relationships between ligand coordination sites and metal centers by defining chelate or coordinate vectors, based on the directional orientation of the ligand-binding sites. For example, a bidentate bipyridine ligand coordinated to a metal possesses a vector pointing toward the metal that bisects the chelating group. The Molecular Library model considers the directionality and geometry of multibranched, monodentate ligands and their ramifications on the geometry of the desired molecular architecture. For example, rod-like building blocks with incorporated angles of 90° and end-group coordination sites would generate a tetragonal shape in the presence of a connecting metal that is capable of sustaining 90° coordination.

Herein, we present a brief overview of the current literature dedicated to hexameric macrocyclic architectures predicated on heterocyclic chemistry. We summarize the salient synthetic features of ring construction whereby the participating heterocyclic building blocks, or subunits,

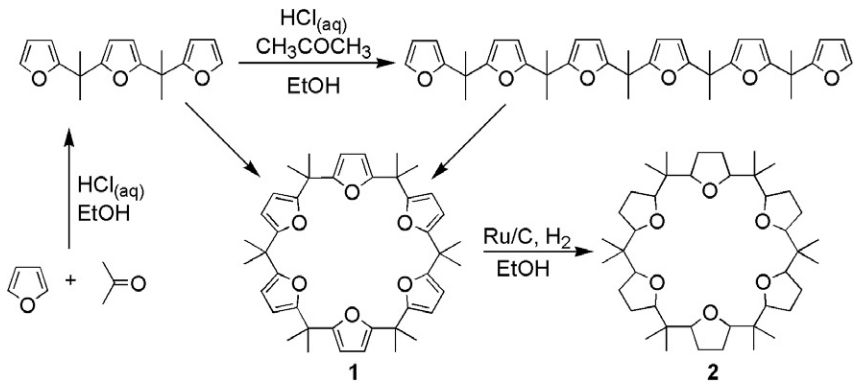
possessing at least one heteroatom, such as nitrogen, oxygen, or sulfur, with the recognition that such a broad subject will necessitate a limitation in scope.

Excluding the "Introduction," this review is organized based on the building blocks used for macrocycle construction into three sections: five-membered heterocyclic subunits, such as furan, furanose, or pyrole; six-membered heterocyclic subunits, such as pyridine, bipyridine, phenanthroline, or glucopyranose; and miscellaneous subunits comprising, for example, a combination of five- and six-membered heterocyclic subunits or larger than six-membered ring subunits. We have sought to include as many pertinent new and classical examples as possible and will endeavor to include examples that have been missed in future manuscripts.

2. MACROCYCLES WITH FIVE-MEMBERED HETEROCYCLIC SUBUNITS

2.1 Furan, tetrahydrofuran, and thiophene

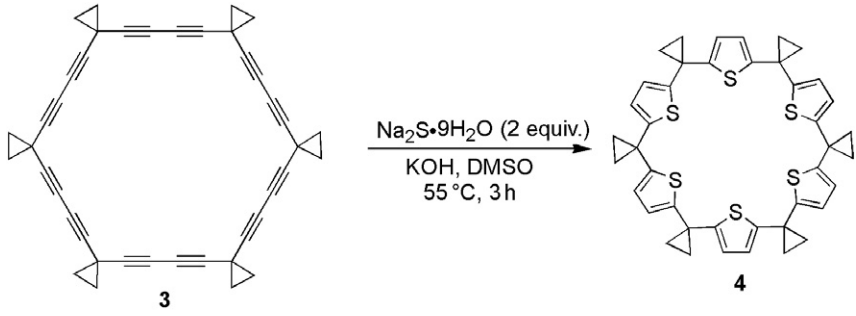
Hexameric macrocycles possessing subunits with oxygen have been reported, of which some of the earliest examples incorporated a series of 18-crown-6 ethers containing one-, two-, or three-furanyl subunits (74JA7159). In 1955, Wright et al. reported (55JOC1147) the first example of calix[6]furan **1**, comprising six furan rings joined by sp^3-hybridized carbons. Such calix[6]furans possess a π-electron-rich cavity with a hydrophilic character similar to crown ethers, but with decreased electron-donating character compared with ethereal analogues (05AHC65). The calix[6]furan **1**, which contains methyl groups in the *meso*-positions, was synthesized following a two-step procedure involving the formation of a three-furan linear oligomer by an acid-catalyzed condensation of furan and acetone. Once the linear trimer was isolated, cyclization was achieved by reaction with acetone in the presence of hydrochloric acid affording (9%) the heterocycle **1** along with linear oligomers (Scheme 1). Kobuke et al. (76JA7414) modified the procedure for **1** by bubbling hydrogen chloride gas into a solution of acetone and linear hexamer to afford **1** in 52% yield. Other modified procedures include the addition of concentrated HCl, acetone, and linear hexamer in ethanol containing Li^+ or Cs^+ ions or no metal, which afforded **1** in ~50% yields (85JCS(P1)973), or slow addition of linear trimer and acetone to a diluted EtOH/HCl mixture with 25% yield (96TL4593). Musau et al. reported (93CC1029, 94JCS(P1)2881) the synthesis of the calix[6]furan with unsubstituted methylene bridges, by cyclization of the corresponding linear hexamer using dimethoxymethane, in the presence of $BF_3{\cdot}Et_2O$, as the catalyst; however, the desired hexamer was isolated in ~1% yield. Kobuke et al.



Scheme 1

(76JA7414) also reported the tetrahydrofuran analogue (Scheme 1) by the hydrogenation of the furan units of **1** using ruthenium/carbon under high pressure conditions to generate an isomeric mixture of the hexamer **2**, which was shown to extract cesium, ammonium, and silver ions from an aqueous to an organic phase. Finally, a larger hexameric macrocycle containing six furan rings joined via acetylene bridges was also reported (69AJC1951).

Three examples of hexameric macrocycles containing thiophene rings have been reported. Meijere et al. described (95AGE781) the novel macrocycle **4**, composed of six thiophene rings linked *via* spirocyclopropane bridges. Reaction of polyalkyne **3** with Na_2S under basic conditions afforded within an hour **4**, which was isolated by recrystallization in chloroform in 59% yield (Scheme 2). The crystal structure (Figure 1) showed a chair-like conformation, in which three sulfur atoms are above and three below the plane of the macrocycle.



Scheme 2

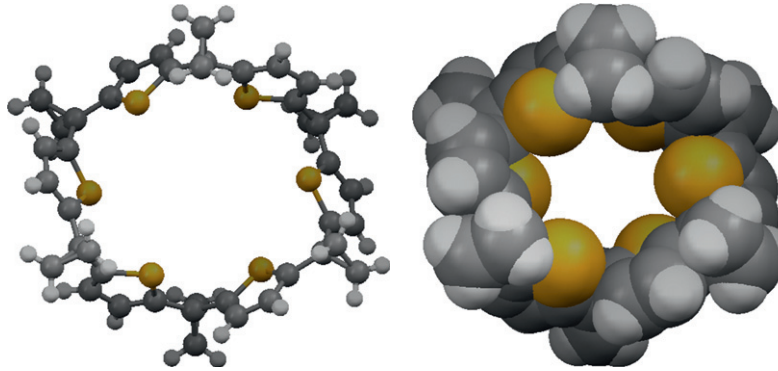
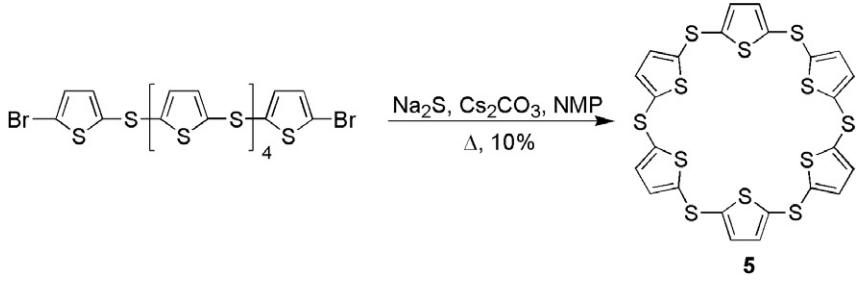


Figure 1 X-ray crystal structure of **4** (95AGE781) (Reproduced by permission from Wiley-VCH).

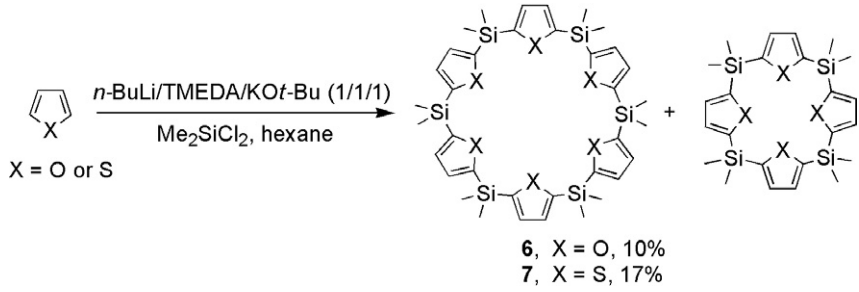
Ishii et al. (97CL897, 98BCJ2695) synthesized a sulfur-bridged thiophene macrocycle **5**. Several different conditions were examined for the preparation of **5** from different oligomers; the best results were obtained (~10%) by heating dibromo oligo(thio-2,5-thienylene) containing six thiophene rings with Na_2S in NMP in the presence of Cs_2CO_3 (Scheme 3). Conditions such as CuI-catalyzed or non-catalyzed reactions also gave the desired product, albeit in slightly lower yields. Sulfur-bridged calixarene-like molecules could function as hosts to soft and heavy metal ion guests.

Another example of a cyclohexathiophene was reported by Kauffmann et al. (75AGE713), composed of six thiophene subunits bound together through the 2,2′- and 3,3′-positions. It was isolated as a by-product in 4% yield, not completely purified, from the reaction designed to obtain cyclotetrathiophene.

Jones et al. (95AGE661) reported the synthesis of silicon-bridged heterocycles containing furan or thiophene subunits. Furan and thiophene were deprotonated at the 2- and 5-positions in hexane, to generate



Scheme 3



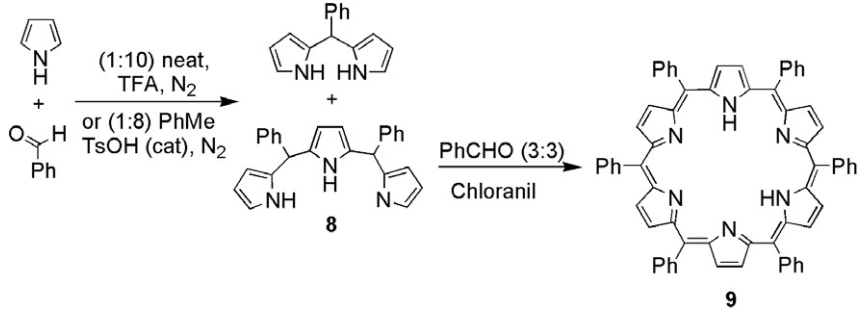
Scheme 4

the organolithium intermediates, followed by slow addition of Me_2SiCl_2 to afford the cyclic hexamer **6** or **7** (Scheme 4), respectively, along with their corresponding cyclic tetramers. Macrocycles comprising other ring sizes were detected in trace amounts by mass spectrometry.

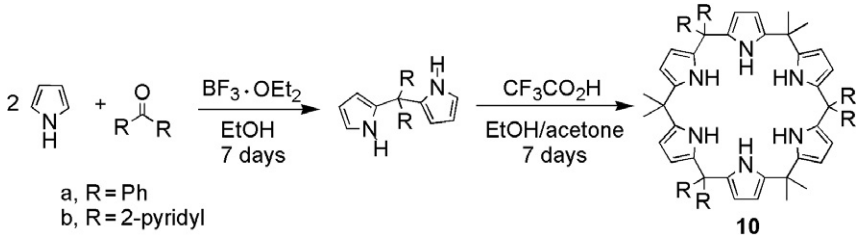
2.2 Pyrrole

Examples of hexameric macrocycles containing pyrrole rings reported in the literature (01CCR57, 08ACR265) include hexaphyrins or expanded porphyrins, calix[6]pyrroles, and cyclo[6]pyrroles.

Hexaphyrins are conjugated macrocycles composed of six pyrrole rings linked via sp^2 hybridized carbon atoms. The first example, *meso*-hexaphenylhexaphyrin (**9**), was prepared by Bruckner et al. (97CC1689) employing 5,10-diphenyltripyrrane (**8**) (Scheme 5), which was isolated as a by-product from a reaction designed to generate 5-phenyldipyrromethane, by the condensation of pyrrole and benzaldehyde in the presence of an acid (94T11427, 94TL2455, 94TL6823). A 3 + 3-type condensation of trimer **8** with benzaldehyde, gave after oxidation and chromatography, the cyclic hexamer **5**. A similar example,



Scheme 5



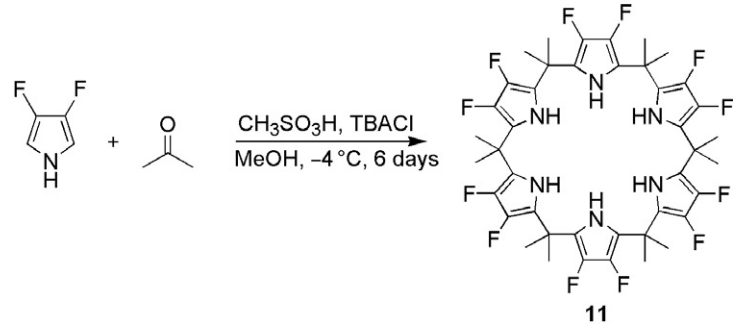
Scheme 6

meso-hexa(pentafluorophenyl)hexaphyrins, was reported by Cavaleiro et al. (99CC385) using a modification of the Rothemund synthesis (39JA2912).

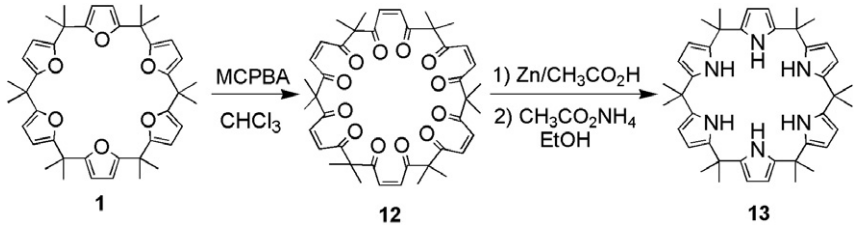
Calix[6]pyrroles are nonconjugated macrocycles composed of six pyrrole rings linked via sp^3 hybridized carbon atoms. A simple and efficient route to calix[6]pyrrole (98AGE2475) involved an acid-catalyzed condensation of dipyrrolemethane with simple ketones that afforded polypyrrole **10** (Scheme 6). X-ray structure determination of **10** revealed that pyrrole units adopted a 1,3,5-alternate conformation in contrast to the more prevalent cone conformation found in calix[6]arenes.

Another example in this family was reported by Sessler et al. (05JOC5982), whereby the dodecafluorocalix[6]pyrrole **11** was constructed (20%) by the condensation of 3,4-difluoro-1H-pyrrole with acetone in the presence of methanesulfonic acid and tetrabutylammonium chloride (Scheme 7).

Calix[6]pyrroles have also been synthesized (00AGE1496) by the conversion of a calix[6]furan to form the dodecaketone **12** via a ring-opening process, as described by Williams and Le Goff (81JOC4143). Subsequent reduction of the olefinic bonds and reaction with ammonium acetate gave **13** in 42% yield (Scheme 8).



Scheme 7

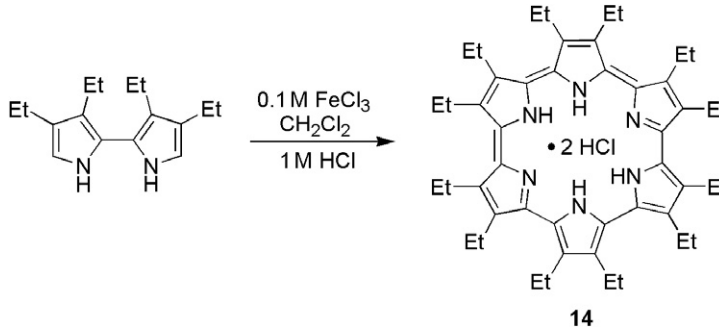


Scheme 8

Host-guest chemistry of calixpyrroles has become an important area of research. Compared to calix[4]pyrroles, which exhibit remarkable selectivity for binding fluoride (96JA5140), calix[6]pyrroles have been shown (01CC13) to form strong complexes with iodine. Other halide ions have shown (00CC1207) strong affinities to trihaloalkanes, such as trifluoroethanol, and electron-deficient aromatic systems, such as nitrobenzene or *p*-nitrotoluene.

Finally, cyclo[6]pyrroles are conjugated pyrrole-based macrocycles that contain no *meso*-carbon bridge. Sessler et al. reported (03JA6872) the preparation of the cyclo[6]pyrrole **14** [HCl salt of [22]hexaphyrin (0.0.0.0.0.0)] (15%) by coupling 3,3′,4,4′-tetraalkylbipyrroles under biphasic oxidative conditions (Scheme 9); cyclo[7]pyrrole and cyclo[8]pyrrole were also isolated. Two crystal structures of **14** were also reported, one containing two TFA^{2-} ions (Figure 2) and the other two chloride ions.

Later, the uranyl cationic complex of **14** was obtained by treatment with $UO_2[N(SiMe_3)_2]_2$ in CH_2Cl_2 under an inert atmosphere (07IC5143). Notably, during this insertion and oxidation process, the initial aromatic ring containing 22 π-electrons was transformed to the 20 π-electron antiaromatic heterocycle.



Scheme 9

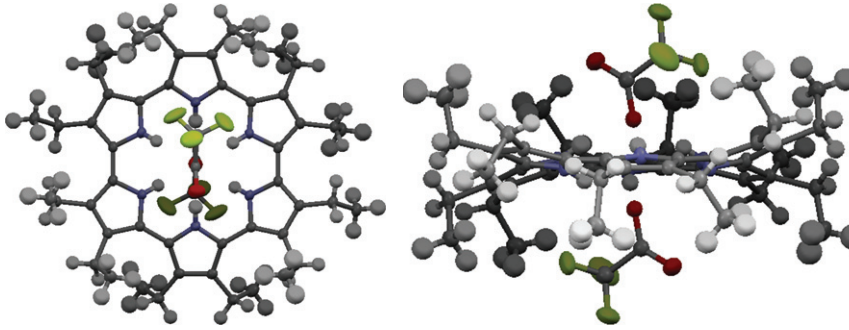
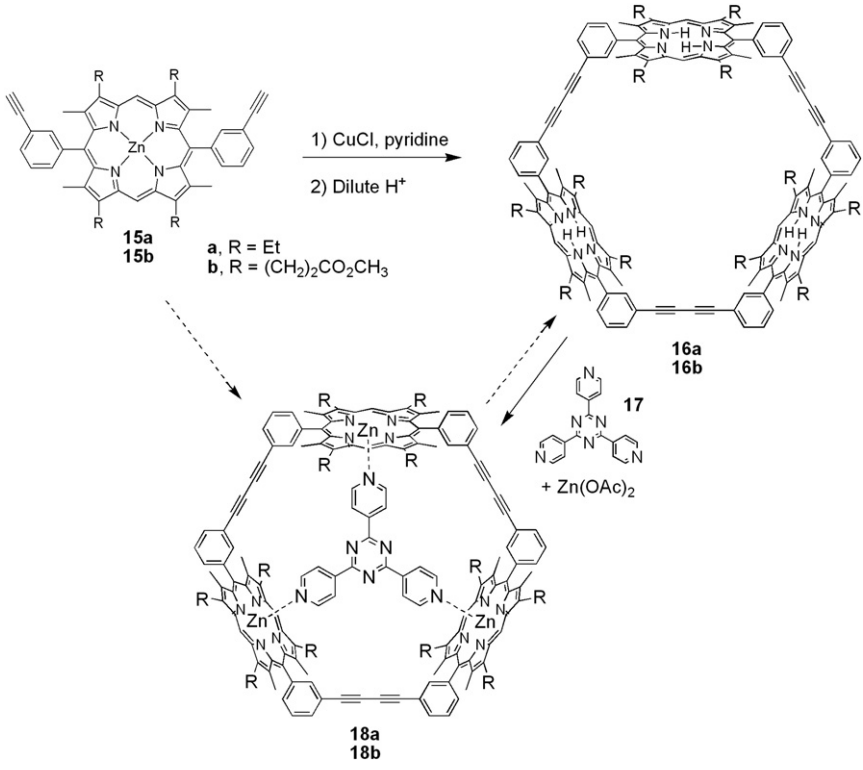


Figure 2 X-ray crystal structure of H_2**14**$^{2+}$2TFA^{2-}, showing top and side views (03JA6872) (Reproduced by permission from American Chemical Society).

2.2.1 Porphyrin

Based on their natural occurrence, physicochemical properties, potential to coordinate numerous metals, and access from readily available starting materials, porphyrins provide ideal building blocks for more complex architectures. Numerous researchers have studied these fascinating materials (09ACR1193, 09CCR2036, 09CSR422, 09CSR2716, 10CCR77).

Anderson and Sanders (89CC1714) have reported the preparation of an hexameric porphyrin-trimer to accommodate organic guests. This cyclic trimer **16a** was synthesized starting from a *bis*-acetylenic porphyrin, obtained by reaction of 3-ethynylbenzaldehyde with 3,3′-diethyl-4,4′-dimethyldipyrromethane, followed by oxidation of the porphyrinogen intermediate with DDQ (81JOC4792, 95JCS(P1)2223). A cyclic Glaser coupling of the *bis*-acetylenic porphyrin Zn adduct **15a** using excess copper(I) chloride in pyridine at 25°C with air afforded the cyclic trimer **16a** (47%), after removing Zn with a dilute acid, along with the cyclic tetramer (20%), cyclic pentamer (traces), and insoluble cyclic dimer (Scheme 10). Addition of 2,4,6-*tris*-4-pyridyl-*s*-triazine (**17**) to the metallated **16a** formed complex **18a**, suggesting that **17** had a complementary shape for the cavity of the host **16a**. Approximately 1 year later, the same group published (90AGE1400) a ligand-templated synthesis (93ACR469) of the cyclic trimer (**16b**) using tripyridine **17**, as a template for directing the assembly, which gave, **16b** in 55% yield (Scheme 10, dash line). The dramatic template effect observed with **17** enhanced the formation of the cyclic trimer **16b** by inhibiting formation of the related dimer. The crystal structure of the porphyrin-trimer Zn adduct of **16a** with three coordinated pyridines to the three Zn ions is presented in Figure 3. It revealed an open, flexible cavity with a mean Zn–Zn distance of ~16 Å



Scheme 10

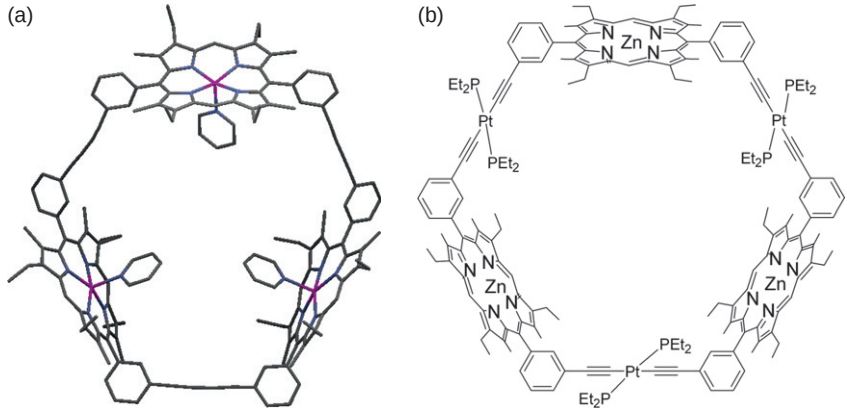
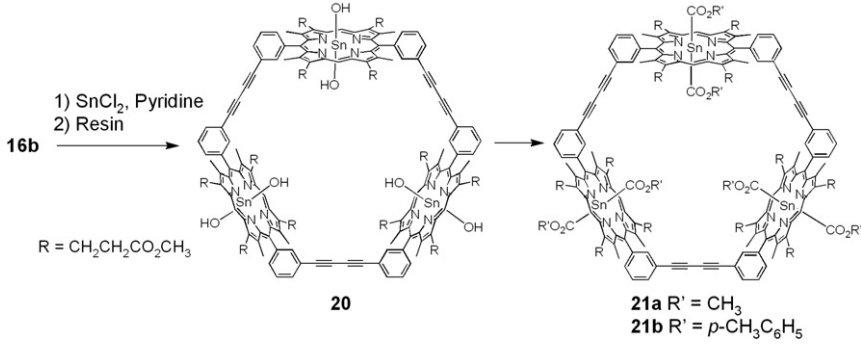


Figure 3 (a) X-ray crystal structure of the porphyrin-trimer Zn adduct **16a** with three coordinated pyridine ligands (94AGE429) (Reproduced by permission from Wiley VCH) and (b) drawing of the Zn adduct of the platinum-linked cyclic porphyrin-trimer **19**.

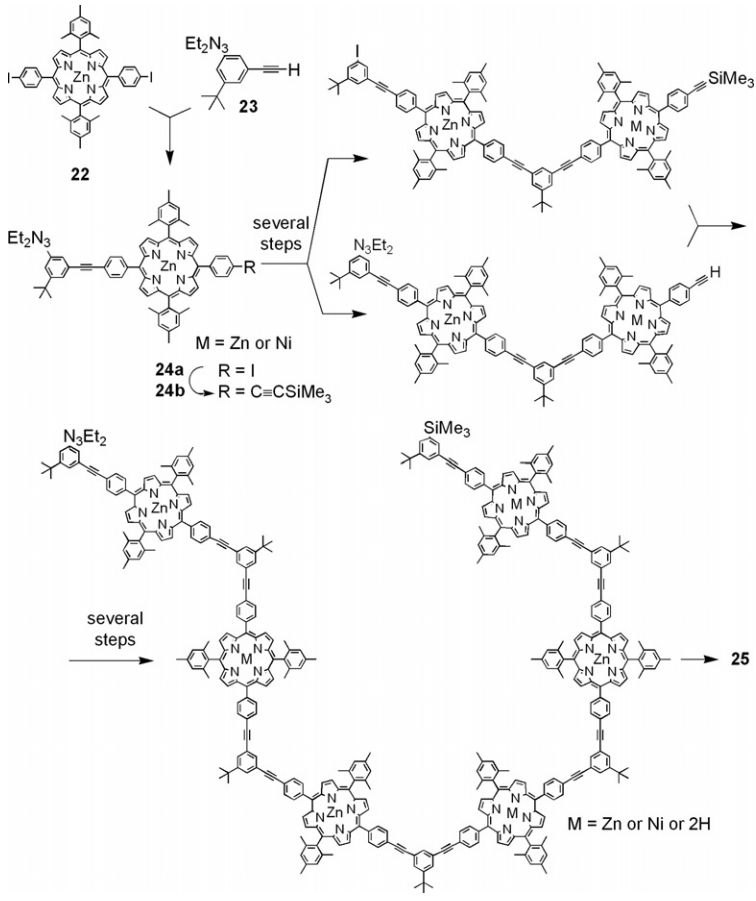
(94AGE429). Another example of a cyclic porphyrin-trimer designed by Sanders et al. (92CC43), with the same topology as **16a** but with a larger 18 Å cavity, was presented by the platinum-linked cyclic porphyrin-trimer **19**. Condensation of *trans*-[$Pt(PEt_3)_2Cl_2$] and **15a** with deoxygenated 10% (v/v) diethylamine in toluene, using Hagihara coupling conditions (78OMC319) with CuI as a catalyst, afforded **19** in 16% yield (drawing Figure 3b), together with expected intermediates. Attempts to increase the yield by templating with $(Pyacac)_3Al$ gave no significant improvement. Sanders et al. (95JCS(P1)2275) further reported the preparation of a cyclic porphyrin-trimer with an increased cavity size using octatetrayne bridges instead of butadiyne bridges.

Sanders et al. also described (03CEJ5211) the formation of a hexameric macrocycle containing three Sn(IV) porphyrins with axial carboxylate ligands generated from the Sn(IV) dihydroxo derivatives, to study the ligand-recognition properties of tin(IV) porphyrins. Tin ion insertion into the cyclic trimer **16b** was performed by refluxing anhydrous tin(II) dichloride in pyridine for 2 h, followed by the quantitative hydrolysis (passing the sample through a weak anion-exchange resin in a water-chloroform mixture) to afford, after recrystallization, trimetallated **20** in 28% yield (Scheme 11). Aliquots of carboxylic acids were then added to **20** in order to study the NMR properties of **21a** and **21b**. A more versatile linear synthesis allowed access to unsymmetrical cyclic trimers with different bridge lengths (ethyne and butadiyne links) (98NJC493) or mixed-metal trimers (97IC6117, 00IC5912).

In 1999, two other cyclic porphyrin families were reported containing six-porphyrin subunits resembling that of the light harvesting supramolecular architectures in photosynthetic bacteria (95NAT517, 96ACR381). Dossauer et al. reported (99TL8347, 01JOC4973, 06JA3396) the construction of the rigid hexameric macrocycle **25**, containing six tetraphenyl-porphyrin rings linked by six *meta*-diethynylphenyl corners, thus forming an internal cavity of 4.6 nm of diameter. The step-by-step method

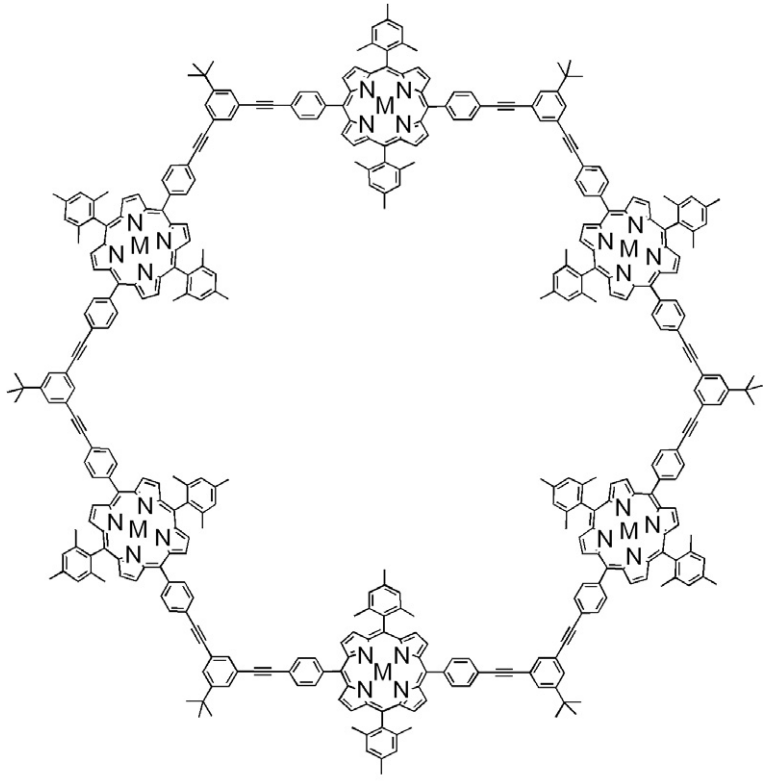


Scheme 11



Scheme 12

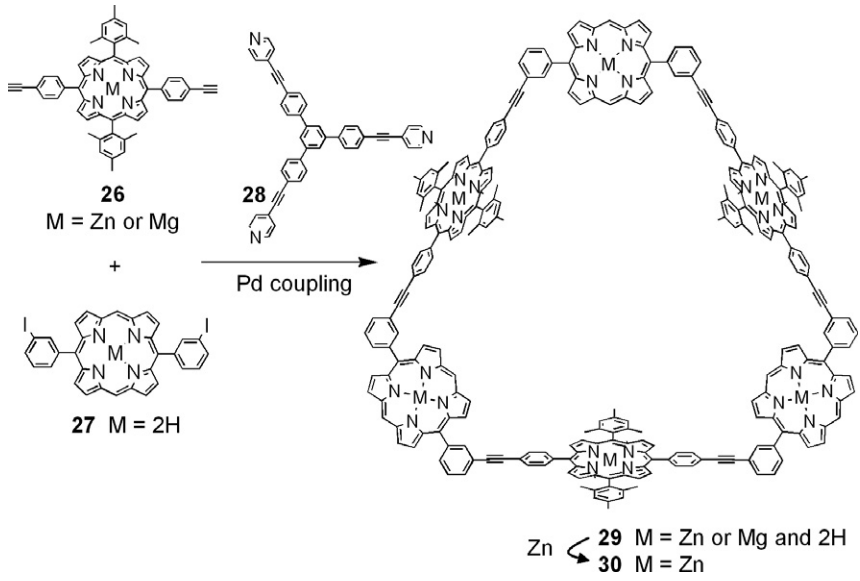
developed by this work enabled the synthesis of these macrocycles with different metallation "'states'," composed of a combination of Zn porphyrin (PZn), Ni porphyrin (PNi), and/or free-base porphyrins (PFB). The synthetic procedure (Scheme 12) started with the reaction of the diiodoporphyrin derivative **22** with **23**, affording a monomeric porphyrin-building block **24b**, with two reactive positions, a protected ethynyl group and a diethyltriazine-substituted phenyl, which could be activated selectively. Employing an interactive divergent–convergent approach (94JA4227, 94AGE1360) to generate the linear precursor, the intramolecular cyclization was effected by a high-dilution, Pd(0)-mediated reaction. The final ring-closure step was the least reproducible affording after chromatographic purification, the product with variable yields (8–31%). Template synthesis of **25** was also attempted (06JA3396), where the yield of the cyclization of the linear precursor was improved to a reproducible yield (52–57%).



25 M = Zn, Ni, or 2H

At about the same time, Lindsey et al. (99JA8927) described the one-flask synthesis of a different family of cyclic hexamers, containing six porphyrins bridged by diphenylethynes. They also synthesized macrocycles with different degrees-of-metallation: one example with six PZn's, and another with an alternating arrangement of three Zn or Mg porphyrins (PZn, PMg) and three free-base porphyrins (PFB). Macrocycle **29** was constructed (Scheme 13) by a Pd-mediated coupling of a Zn-metallated *bis*(4-ethynylphenyl)porphyrin **26** with metal-free *bis*(3-iodophenyl)porphyrin **27** in the presence of a tripyridinyl template **28** affording 5.3% yield after purification (Scheme 13). Treatment of **29** with zinc acetate afforded the all-metallated polyporphyrin **30** that was isolated in 94% yield.

Two years later, (01JOC7402) this family of hexameric architectures was extended with the addition of two more examples, comprising five PZn and one PFB as well as comprising alternating sequence of two PZn and one PFB. Synthesis of these new additions did not follow the one-flask template-directed process, but was achieved by sequential Pd-mediated coupling reactions involving four tetraarylporphyrin-building



Scheme 13

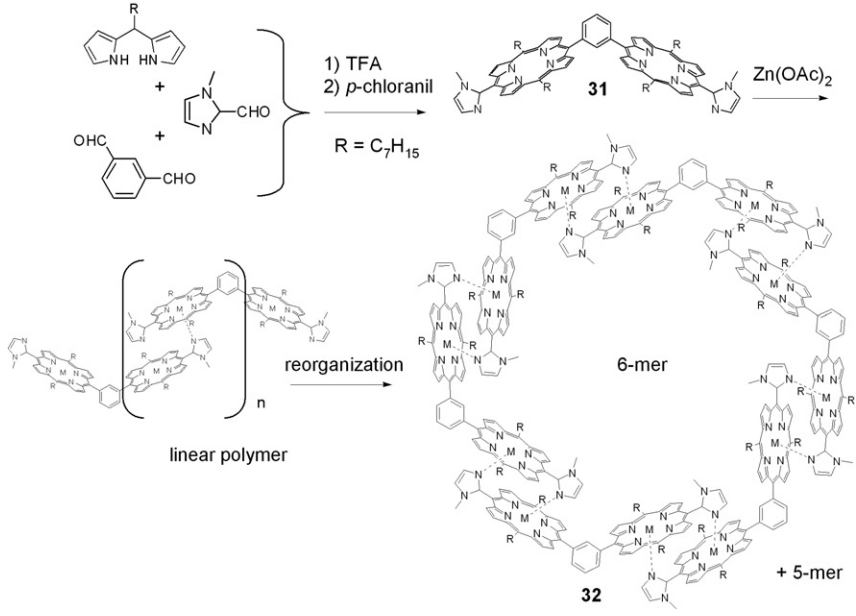
blocks bearing diethynyl, diiodo, bromo/iodo, or iodo/ethynyl groups. The final ring-closure yielding the cyclic construct was performed by the reaction of a porphyrin pentamer and a porphyrin monomer or by joining two porphyrin trimers in the presence of a template. Linsey et al. (03JOC8199) later expanded this family of shape-persistent materials, by generating new derivatives bearing diverse pendant groups, such as thiol moieties, that were used to form self-assembled monolayers (SAMs). Characterization by high-angle X-ray scattering of a host–guest complex with a tripyridyl guest has been reported (04JA14054).

The structures of the light-harvesting complexes (LH) in photosynthetic purple bacteria had been determined by X-ray crystallography studies, electron microscopies, and other analytical methods (95NAT517, 96MI1, 96MI2, 98JMB833, 01B8783). In these complexes, the bacteriochlorophylls (32 in LH1 and 16 in LH2) are arranged in macroring structures, where the key functional unit is composed of bacteriochlorophyll-*a* dimers, which have been described as having a slipped-cofacial juxtaposition, held together by intermolecular forces, specifically the coordination of imidazolyl to the central Mg ion (03JA2372, 03OL4935, 05JOC2745). Kobuke et al. reported (03JA2372) the first example of a hexameric macrocycle **32** composed of six 5,5′-*m*-phenylene-bridged imidazolylporphyrinatozinc(II) dimers (**31**), where coordination of the imidazolyl of one dimer to the zinc of the neighboring one closes the macrocycle. Synthesis of **31** started with the acid-catalyzed condensation

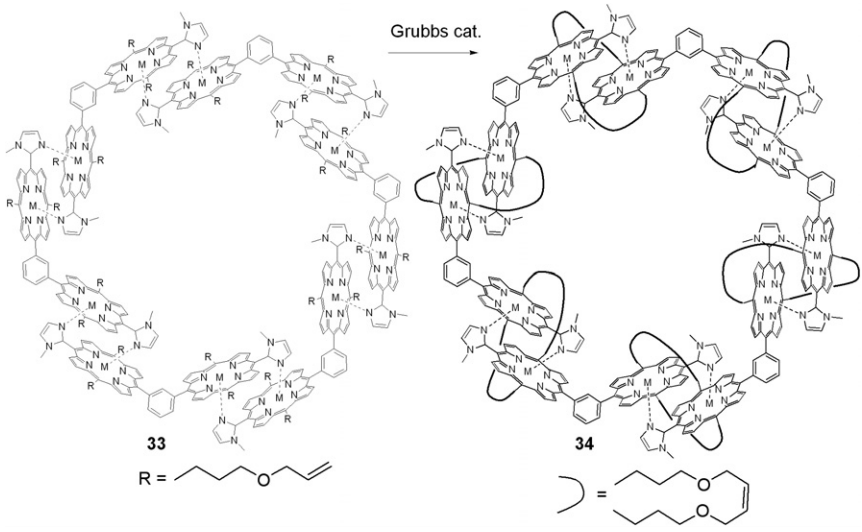
of *meso*-(*n*-heptyl)dipyrromethane with two aldehydes (isophthalaldehyde and 1-methyl-2-imidazolecarbaldehyde), followed by oxidation, which gave a mixture of porphyrin products. Column chromatography afforded 5,5′-*m*-phenylene-bridged gable-porphyrin with 15,15′-*bis*(imidazolyl) groups (**31**) (85JA4192) (Scheme 14) and other products. Addition of zinc acetate converted the free base **31** to polymeric assemblies, which after a reorganization process by cleavage of the coordination bonds upon dilution in more polar solvent (mixture of $CHCl_3$/MeOH), followed by evaporation, afforded a mixture of two components, showing the disappearance of almost all the oligomers. Once these two products were separated, analysis of the first one by small-angle X-ray scattering (SAXS) measurement concluded that it was the hexameric macrocycle **32**.

To further increase the stability, the macrocycle was covalently bound by an olefin metathesis of the allyloxypropyl substituents (the pendant groups in the meso-position of the porphyrin rings) in each dimer (03OL4935) (Scheme 15). This reaction was used to connect each pair of complementary coordinated porphyrins to the other pair. These macrocycles were analyzed by MALDI-TOF MS identifying the hexamer, along with a pentamer.

Previous macrocycles containing gable-porphyrins (**32–34**) showed no π-conjugation between porphyrins since the porphyrin and phenylene planes were orthogonal. In an effort to introduce or increase conjugation,



Scheme 14

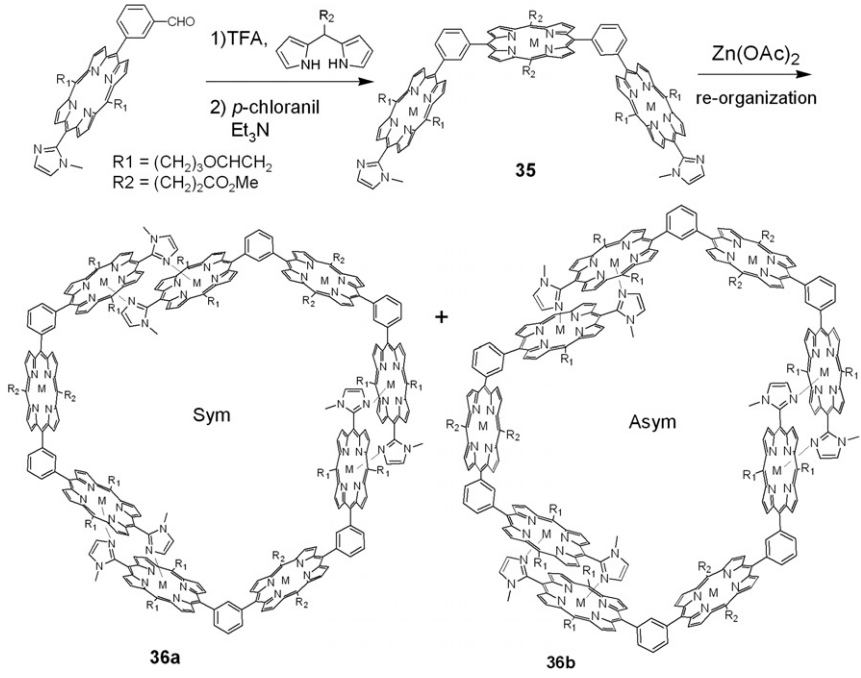


Scheme 15

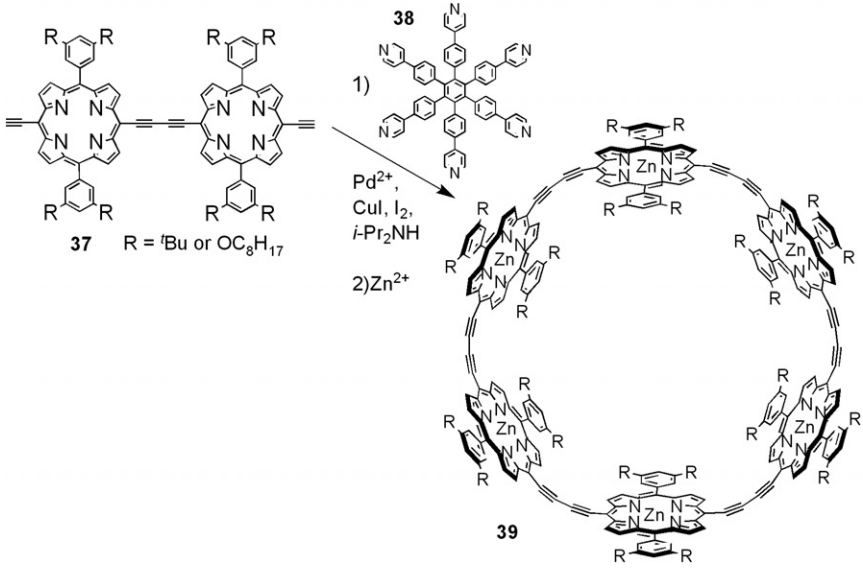
Kobuke et al. (06JA4612) also reported the synthesis of macrocycles using *bis*(zinc-imidazolylporphyrin) linked by a *m-bis*(ethynyl)phenylene spacer, allowing enhanced rotation along the ethyne axis.

A different structure was formed when the repeat unit in the macrocycle was a trimer of porphyrin units instead of a dimer as seen with the gable-porphyrins. Kobuke et al. reported (04JA8668) the hexameric macrocycle **36**, which consisted of three porphyrin-trimer units, containing only nine porphyrin rings instead of twelve as in the precious macrocycles (Scheme 16). The free-base porphyrin-trimer **35** was synthesized by condensation of 5-(1-methylimidazol-2-yl)-10,15-*bis*(3-allyloxypropyl)-20-(3-formylphenyl)porphyrin with *meso*-methoxycarbonyldipyrromethane in 20% yield. Metallation by addition of $Zn(OAc)_2$ and reorganization using $MeOH/CHCl_3$ mixtures afforded the cyclic hexamer **36**. The two terminal porphyrins of each trimer in the hexamer helped in ring formation by coordination to the Zn ions of the terminal imidazole of the other trimer, leaving three noncoordinated porphyrinato-Zn(II) sites that could accommodate a functional molecule. ^{1}H NMR spectra of **36** revealed a mixture of two topological isomers, D_3h-symmetric (**36a**) and D_3h-asymmetric (**36b**).

Anderson et al. reported (08AGE4993) an efficient synthesis of strained, π-conjugated D_6h porphyrin[6]nanoring **39**. A template-directed reaction between the porphyrin dimer **37** and the hexapyridinyl template **38** by an oxidative coupling of **37** under palladium/copper catalysis, using iodine and air, as the oxidants, afforded the cyclic hexamer-templated complex **39** in 30–40% yield (Scheme 17). Size-exclusion chromatography in the presence of 1,4-diazabicyclo[2,2,2]octane gave the template-



Scheme 16



Scheme 17

free hexameric macrocycles **39** in high yields. Comparison between **39** and a similar linear hexamer showed that the π-conjugation was more effective in the macrocycle, probably because of the rigid geometry and lack of end-effects, as well as other contributions.

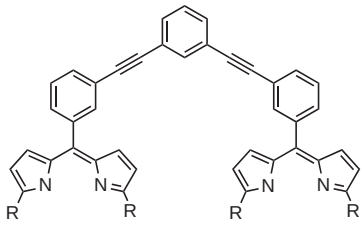
Other interesting polyporphyrins have been reported by Osuka et al. (01CEJ3134). Two linear arrays of three porphyrin each, described as windmill arrays, were connected by a *meso*-*meso*-linked diporphyrin core and examined as light-harvesting devices.

2.2.2 Dipyrrin

In contrast to having porphyrin units in the macrocycle, the use of dipyrrins (dipyrromethenes) (07CEJ7900) can afford flexible metal coordination environments. Dipyrrins (e.g., **40**; Figure 4) (06JA10024) consist of two pyrrole units bridged by a sp^2-*meso* carbon, behaving as a π-conjugated bidentate monoanionic ligand for metal ions, similar to a half-porphyrin unit. Hashimoto et al. reported (07CEJ7900) a family of neutral hexameric architectures composed of two dipyrrin ligands coordinated to two zinc ions forming a hexameric macrocycle in shape. Dipyrrin **40** (03IC6629) was synthesized by a Sonogashira coupling reaction (75TL4467) of 1,3-diethynylbenzene and 3-bromobenzaldehyde, followed by acidic condensation with pyrrole and finally oxidation with DDQ. Refluxing **40** with Zn $(OAc)_2$ in the presence of pyrene, as a templating specie, in chloroform afforded **41** in good yield. Due to the tetrahedral geometry of the Zn(II) ions, complex **41** exhibits two chiral centers and three stereoisomers (one achiral and two chiral), where the chiral isomers are the minor species. The X-ray crystal structure of the major stereoisomer of **40** (Figure 4) showed a distorted hexagonal cavity with a 1.6-nm diagonal, with two THF solvent molecules encapsulated.

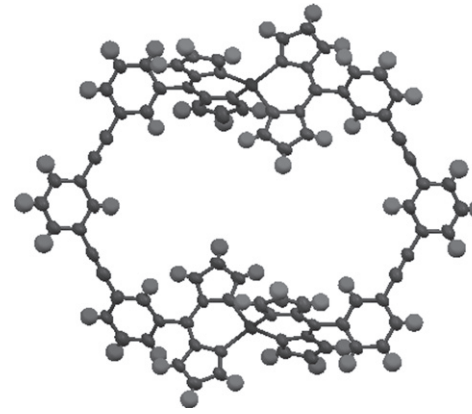
2.3 Cucurbituril

Cucurbituril (**42**) is a cyclic hexamer of dimethanoglycoluril (81JA7367) synthesized from the acidic condensation of glycoluril and excess formaldehyde (Scheme 18a). It was first mentioned in 1905 by Behrend et al. (05LAC1), but it was not until 1981 when Mock et al. (81JA7367) fully characterized its chemical structure and coined the term "Cucurbituril" based on its resemblance to a pumpkin (family Cucurbitaceae). The hexamer **42** (Scheme 18b) possesses an internal cavity diameter of 5.5 Å within the relatively rigid macrocycle to which access is provided by two entrances ringed by carbonyl groups of 4 Å diameter. Extensive studies on the host–guest behavior of **20** have been published by Mock et al. and others (96CSMC477, 96JA9790, 02CSR96). Due to its unique structure and molecular recognition properties, cucurbituril (**20**) has been used in



40

R = H, CH_3 or $C_{16}H_{33}$



41

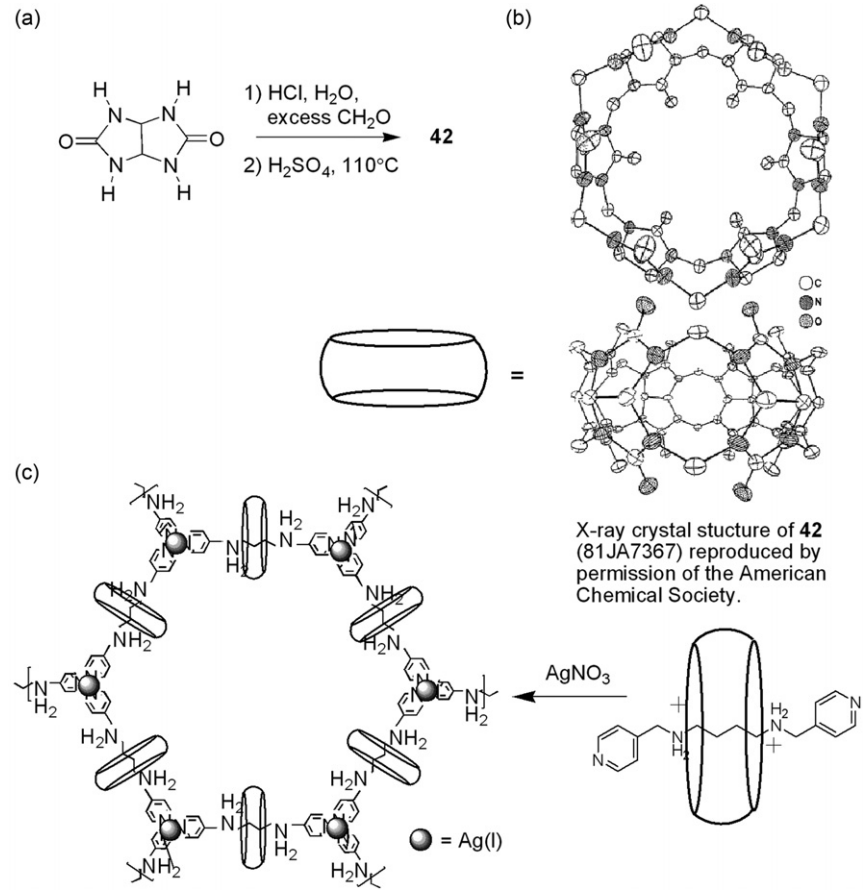
Figure 4 **X-ray** crystal structure of **41** (07CEJ7900) (reproduced by permission from Wiley-VCH) and the dipyrin **40** used in its construction.

numerous supramolecular architectures, as building blocks in rotaxanes, catenanes, or molecular machines (00IEC3419, 02CSR96). Other applications such as catalysis have been demonstrated (89JOC5302, 07CSR267). Scheme 18c illustrates an example of a polyrotaxane network consisting of edge-sharing hexagons, having a silver ion at each corner. Each edge is holding a cucurbituril macrocycle (00IEC3419).

Miyahara et al. reported (04AGE5019) a variation of the cucurbituril (**42**), where the glycoluril unit was equatorially cut-in-half, giving rise to the name hemicucurbituril (**43**). Synthesis was achieved (94%) by the acid-catalyzed condensation of ethyleneurea with formaldehyde. The X-ray crystal structure (Figure 5) shows that **43** assumes an alternate conformation of the heterocyclic subunits and contains a chloride ion in the center of the cavity, *H*-bonded to a H_2O molecule, which in turn is *H*-bonded to an external H_2O molecule, thus creating a rigid hydrogen-bonded network. Along with anions, **43** can also include small molecules, such as propargyl alcohol.

2.4 Cyclofructans

Cyclofructans (94JOC2967) are cyclic oligosaccharides with five-membered ring heterocycles [β-(2→1)-linked-D-fructofuranose units] obtained from inulin with inulin fructotransferase, which catalyzes the formation



Scheme 18

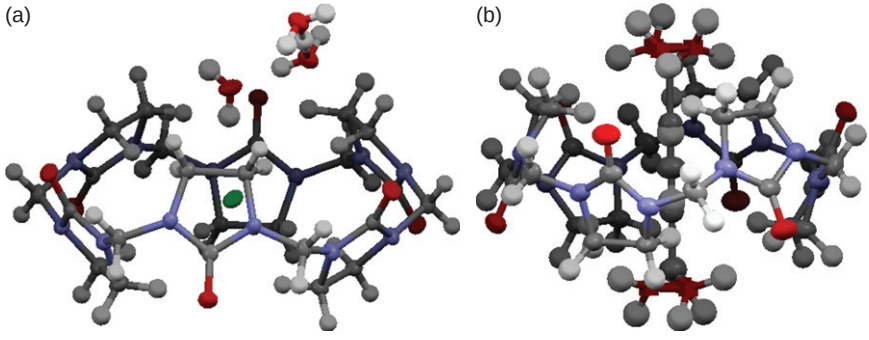
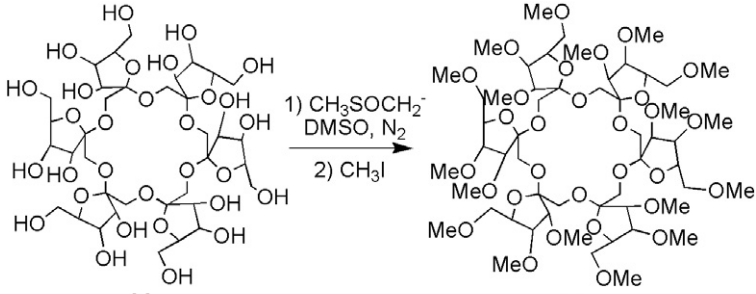


Figure 5 a) X-ray crystal structure of **43** (04AGE5019) containing in the cavity (a) HCl and (b) propargyl alcohol (reproduced by permission from Wiley-VCH).

of the cycloinulohexaose (**44**), cycloinuloheptaose, and cycloinulooctaose. The former **44** displayed a hexameric architecture with a crown ether (18-crown-6) skeleton, which was expected to bind cationic molecules. Several complexation studies have been reported on permethylated cycloinulohexaose **45** in organic solvents (93CC53, 94JOC2967, 01JCS(P2)1306). Permethylated cycloinulohexaose **45** was synthesized following the Hakomori method (64JBT205, 86CAR279, 94JOC2967) starting from dimethylsulfinyl carbanion (Corey's base), prepared from DMSO and NaH. A slight excess of dimethylsulfinyl carbanion was added to **44** in DMSO under N_2, followed by slow addition of methyl iodide to afford **45** in 50% yield (Scheme 19). Complexation studies with **45** revealed lower alkali metal affinities than 18-crown-6 but still possessed the ability to capture K^+ and Ba^{2+} ions by a pocket constructed between the upper MeO-3 rim of the furanose rings and crown ether oxygens.

2.5 Diazole

Two examples of metallomacrocycles containing diazole ligands are noted, a pyrazole- and an imidazole-derivative. Cohen et al. reported (03CC1278) the construction and crystal structure (Figure 6a) of $[(5\text{-methyl-3-phenylpyrazole})_2Zn_2(O(CH_2)_2S)]_6$ (**46**), which was first isolated from thermal decomposition of $[(Tp^{Ph,Me})ZnOH]$ in the presence of 2-mercaptoethanol (02IC5075, 02ICA459). A direct synthesis of metallocycle **46** was later obtained by the reaction of zinc perchlorate with 5-methyl-3-phenylpyrazole and NaOH in hot MeOH, followed by addition of 2-mercaptoethanol in 20% yield after recrystallization. An additional example containing diazole ligands was reported by Mak et al. (01AGE1725), whereby the sodium salt Na(Acntb) [where HAcntb = *N*-[*N*′-(carboxymethyl)benzimidazol-2-yl-methyl]-*N,N-bis* (benzimidazol-2-ylmethyl)amine] was treated with an equal molar amount of $Cu(ClO_4)_2{\cdot}6H_2O$ in ethanol to give $[Cu_6(Acntb)_6](ClO_4)_6{\cdot}nH_2O$ (**47**), as green crystals. In the crystal structure of **47** (Figure 6b), each Cu(II) ion is



44 **45**

Scheme 19

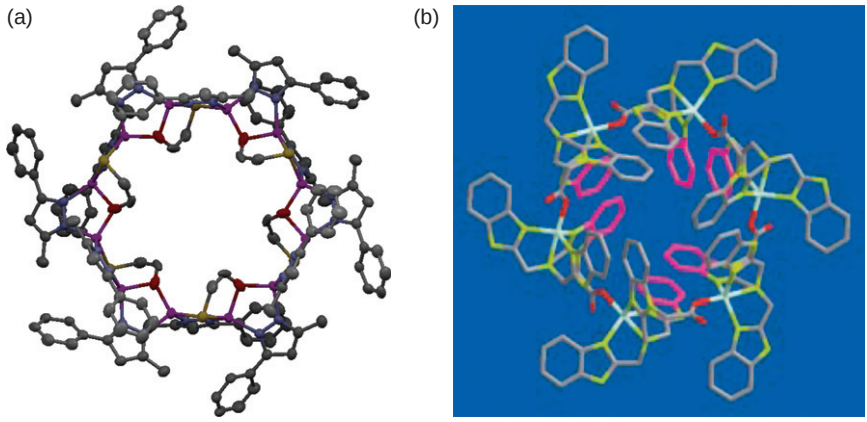


Figure 6 X-ray crystal structure of (a) macrocycle **46** (03CC1278) (reproduced by permission from Royal Society of Chemistry) and (b) macrocycle **47** (01AGE1725) (reproduced by permission from Wiley-VCH).

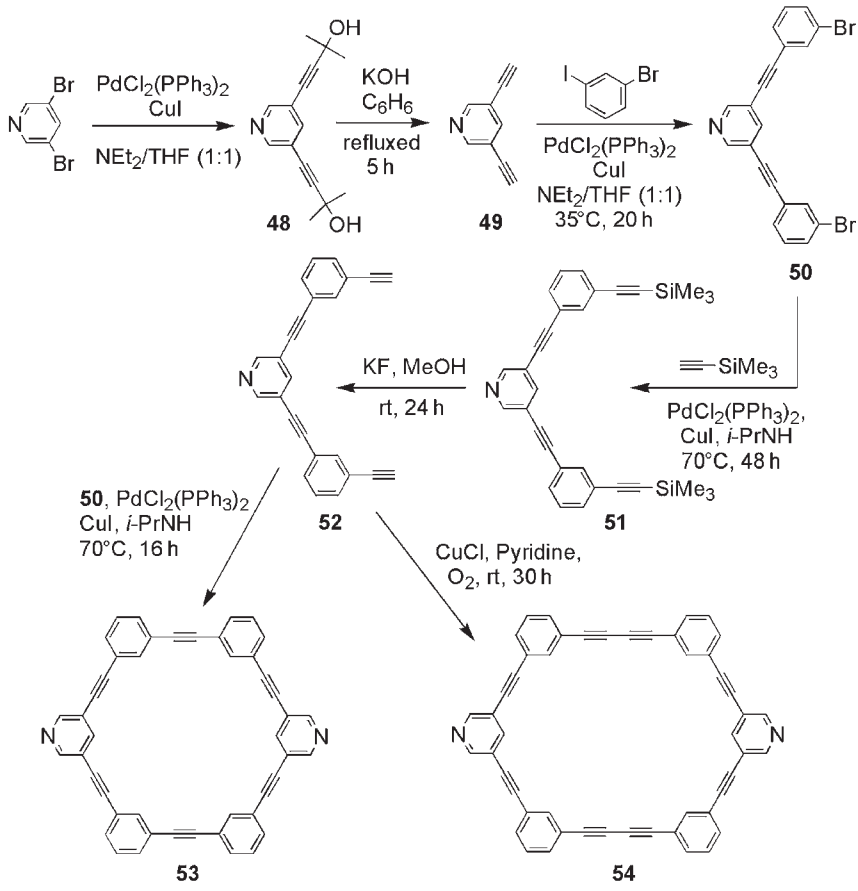
coordinated by the four nitrogen atoms of the ligand, and the branching acetate group functions as a monodentate bridge between adjacent $[Cu(Acnbt)]^+$ units to generate the hexameric motif. Formation of multi-directional hydrogen bonds between the metallamacrocycles generates the 3D network.

3. SIX-MEMBERED RING HETEROCYCLES

3.1 Pyridine

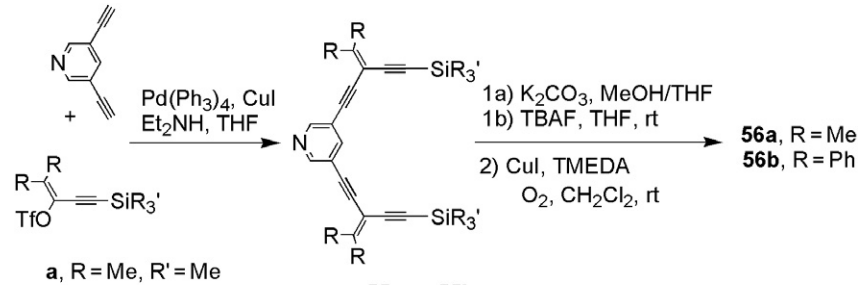
Sun and Lees crafted (01OM2353) two hexagonal phenylacetylenic structures, **53** and **54**, that each contained two pyridine units with the nitrogen atoms directed toward the periphery of the macroring, for the purpose of self-assembling with transition metals. The dinuclear 4,4′-di-*tert*-butyl-2,2′-bipyridine Re(I) tricarbonyl complexes with these ligands were formed and their photophysical properties studied. The stepwise procedure for **53** and **54** (Scheme 20) began by reacting 3,5-dibromopyridine and 2-methyl-3-butyn-2-ol using Sonogashira–Hagihara cross-coupling conditions (75TL4467), followed by deprotection to give 3,5-diethynylpyridine (**49**). Selective coupling with 1-bromo-3-iodobenzene gave the dibromobenzene analog **50**, which was then coupled with trimethylsilylacetylene affording **51**. Deprotection of the trimethylsilyl groups gave tetrayne **52** that was transformed to either the hexagonal macrocycle **53** using a Sonogashira–Hagihara cross-coupling or **54** via Hay coupling (62JOC3320, 93AGE406).

During the same year, Tylwinski et al. reported (01OL1045) two other conjugated macrocycles, **56a** and **56b**, based on 2,6-diethynylpyridine



Scheme 20

subunits, again with the nitrogen atom of the pyridine subunits directed toward the periphery of the macroring. Synthesis of the ligands (Scheme 21) followed a Pd-catalyzed cross-coupling of dimethyl substituted vinyl triflate with 3,5-diethynylpyridine, followed by deprotection and oxidative homocoupling of the tetrayne using Hay conditions under high dilution. In the case of **56a** (R = Me), the reaction afforded a mixture of the desired cyclic ligand as well as linear oligomers possessing limited solubility, which made purification difficult. To circumvent this problem, the combined mixture was treated with two equivalents of a Ru porphyrin complex, which rapidly coordinated the macrocycle, allowing purification by column chromatography, whose crystal structure is shown in Figure 7a. In the case of **56b** (R = Ph), the macrocycle was isolated and coordinated with two Ru porphyrin units. Also, the reaction



Scheme 21

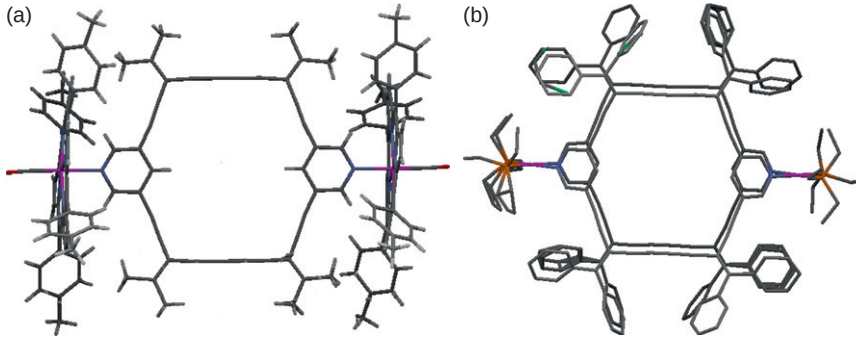
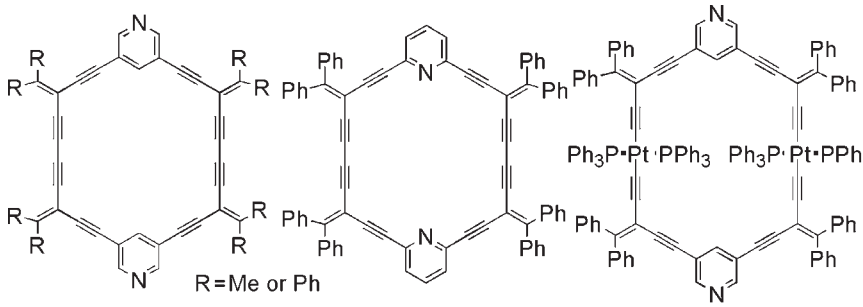


Figure 7 Crystal structure of (a) $[Ru_2(\mathbf{56a})]$ molecule (01OL1045) (reproduced by permission from American Chemical Society) (b) $[Pt_2(\mathbf{56b})_2(PEt_3)_4](OTf)_4$ (02JA7266) (reproduced by permission from American Chemical Society).

of **56b** with *cis*-$(TfO)_2Pt(PEt_3)_2$ (02JA7266) afforded a different coordination arrangement, where each Pt ion was bound to two macrocyclic ligands and each macrocycle to two Pt atoms, forming the complex $[Pt_2L_2(PEt_3)_4](OTf)_4$. The crystal structure is presented in Figure 7b.

In 2004, the same group reported (04SL182) the successful synthesis of the fully conjugated macrocycle **57** based on 2,6-diethynylpyridine, where the lone pair of electrons of the pyridine units are directed inward, therefore featuring endotopic binding sites. The synthetic procedure to afford **57** basically followed the same strategy to that of **56**, by a palladium-catalyzed cross-coupling, followed by deprotection with NaOH and finished by a copper-catalyzed homocoupling reaction.

Another example, macrocycle **58**, was reported by Campbell et al. (03JOM379) containing two opposing pyridine units, whereby the two Pt atoms were incorporated in the macrocyclic framework. Construction started from oligomer **55b**, which was desilylated using NaOH in THF-MeOH, and treated with $[(PPh_3)_2PtCl_2]$ under high dilution conditions in the presence of a catalytic amount of CuI at 50°C for 14 h affording the *bis*Pt macrocycle **58**.



56 **57** **58**

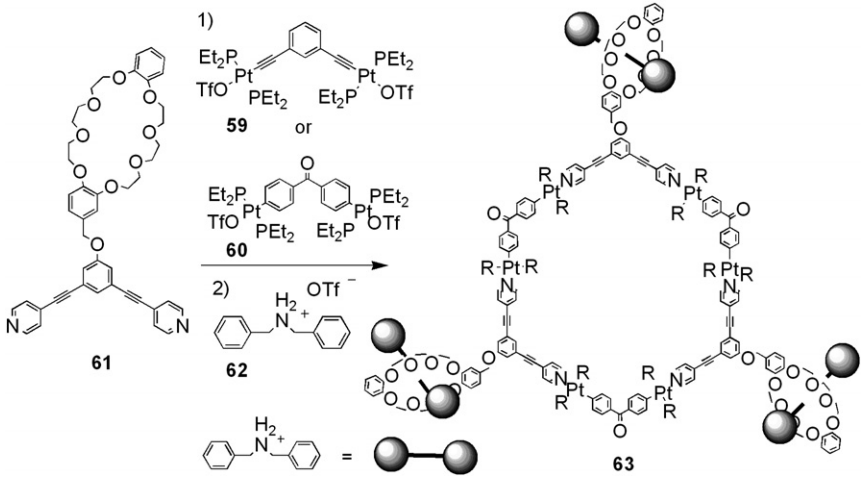
Stang et al. (09ACR249, 09JOC2) have made significant contributions to the self-assembly process. His eloquent use of transition metal hybridization, predesigned, coordinating molecular architectures, and voluminous work to categorize, define, synthesize, and bring to fruition utilitarian building blocks and supramolecular constructs have markedly influenced this burgeoning field.

Toward these ends, Stang et al. has developed a wide range of eloquent architectures with esthetic and utilitarian appeal employing pyridine–metal connectivity for self-assembly. In a report in 1997 (97JA4777), a *bis*pyridinyl ketone (Scheme 22) and a 4,4′-bipyridine (donors) were employed as a corner unit and linear linker units, respectively, in the initial self-assembly of hexameric motifs with *bis*Pt(II) (acceptor) complexes **59** and **60**. Notably, hexamer formation in quantitative yields using these building blocks was observed based on ^{1}H and ^{31}P NMR.

Later, Stang et al. (07JA14187) employed these same *bis*Pt(II) monomers (**59** and **60**, Scheme 22) in conjunction with the 120° juxtaposed bipyridinyl crown ether monomer [**61**, prepared from connection of the crown ether to 3,5-*bis*(pyridine-4-ylethynyl)phenol. Treatment of the angular *bis*Pt(II) bipyridinyl ketone smoothly afforded the desired *tris* (crown ether). Upon addition of the barbell-like bisbenzyl ammonium triflate salt **62** the supramolecular *tris*[2]pseudorotaxane hexamer **63** with a cavity diameter of 2.9 nm was formed.

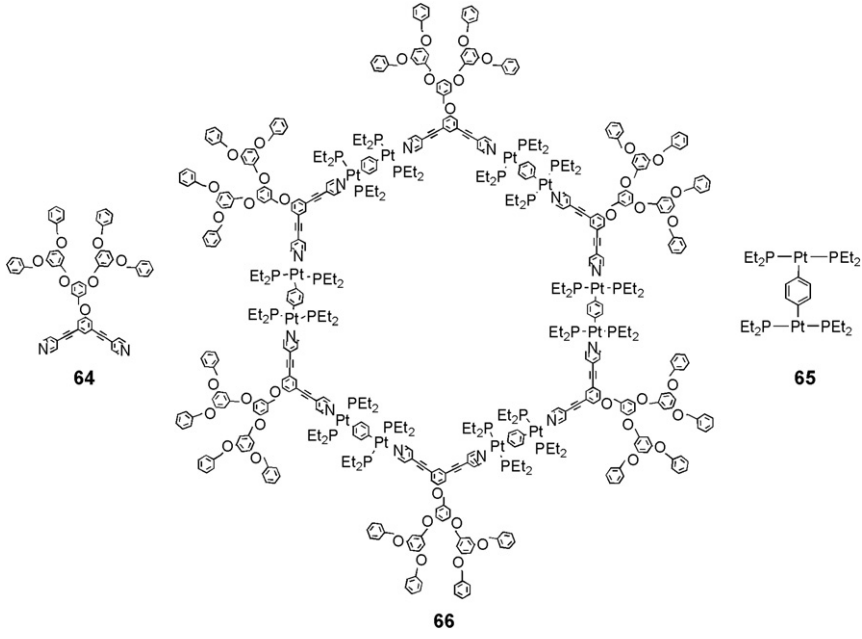
Transformation of the Stang's alkyne-extended, bipyridine crown ether to the corresponding bipyridine benzyl ether dendron **64** [dendrons developed by Fréchet et al. (90JA7638)] and assembly with the linear *bis*Pt(II) monomer **65** gave the dendronized hexamer **66**. Hexamers were prepared using building blocks possessing dendrons constructed through the third generation [G0–G3]. ESI and ESI-FT-ICR mass spectrometry facilitated characterization of these novel materials.

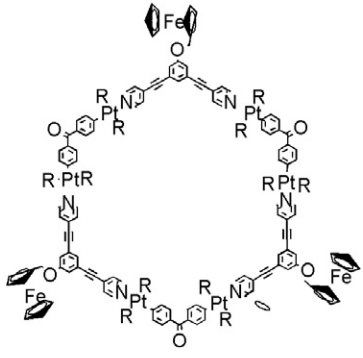
Stang et al. (08JA839) have analogously designed and constructed ferrocene-modified hexamers. Reaction of ferrocene-1-carboxylic acid



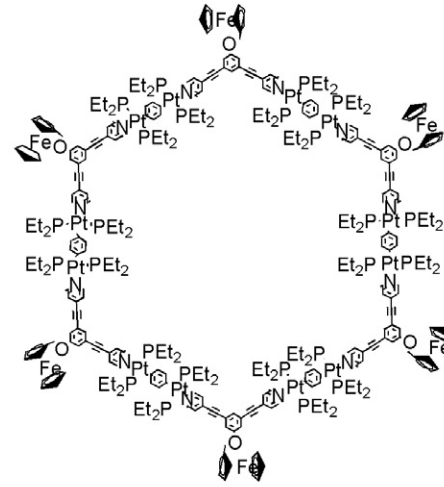
Scheme 22

with 3,5-*bis*(pyridin-4-ylethynyl)phenol generated the bipyridine donor-building block that when treated with either the angular *bis*Pt(II) ketone **60** or the linear *bis*Pt(II) spacer unit **65** gave the *tris*(ferrocene) hexamer **67** (3.3 nm diameter) and the hexa*kis*(ferrocene) hexamer **68** (5.3 nm diameter), respectively. The metallocycles electrochemistry and mass spectroscopy were discussed.





67



68

Attachment of the crown ether moieties to the *bis*Pt(II) diacetylene phenol acceptors to generate poly(crown ether) hexamers and poly[2] pseudorotaxanes has also been reported (08JA5320). As well, a "mix-and-match" approach whereby the crown ether-based, *bis*Pt(II) acceptors and ferrocene-based bipyridine donors or crown ether-based, *bis*Pt(II) donors and ferrocene-based bipyridine acceptors were used to construct heterofunctional macromolecular hexagons was described (09JOC4828). Reviews on coordination-driven metallocycles and metallocages and the requisite geometry of the building blocks necessary to construct them are available (00CRV853, 08CC5896, 08T11495). Metal–carbonyl dipyridine ligands for use in the construction of self-assembled pentagons have also been reported (09IC5590).

Other examples of metallomacrocycles containing metals coordinated to pyridine- or pyrimidine-based ligands exhibiting hexameric architecture are known. Winpenny et al. reported (91CC1453) the formation of the crystalline $[Cu_6(mhp)_{12}Na](NO_3)$ (**69**) from the reaction of hydrated cupric nitrate with the potassium salt of 2-hydroxy-6-methylpyridine (Hmhp). The crystal structure revealed a metallomacrocycle possessing a sodium ion within the cavity, whose source was not identified. A similar structure (Figure 8a) was also reported by Thornton et al. (95POL459), in which $[Co_6(mhp)_{12}Na](O_2CCH_3)$ (**70**) was synthesized by the reaction of the sodium derivative of Hmhp with anhydrous cobalt(II) acetate in MeOH; the structure of **70** shows that the six cobalt atoms form a planar hexagonal ring with a cavity, which accommodates the central sodium atom (Figure 8b).

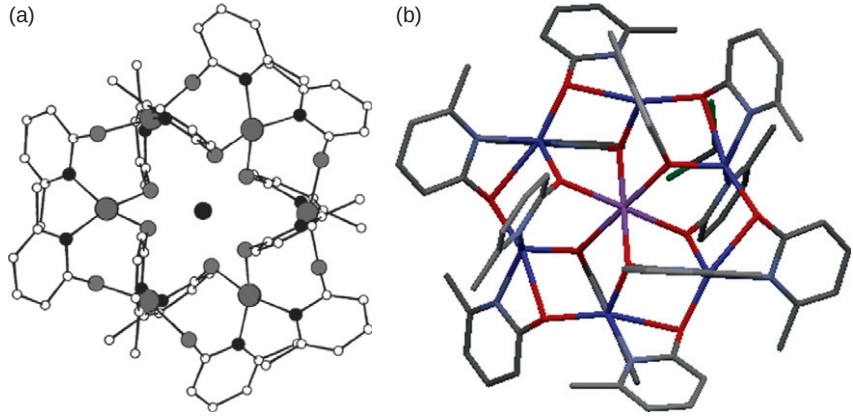


Figure 8 X-ray crystal structure of (a) $[Cu_6(mhp)_{12}Na](NO_3)$ (**69**) (91CC1453) (reproduced by permission from Royal Society of Chemistry), (b) $[Co_6(mhp)_{12}Na](O_2CCH_3)$ (**70**) (95POL459) (reproduced by permission from Elsevier).

A copper-based hexamer with a pyridine-type ligand was also reported by Vittal et al. (03IC5135). The macrocycle $[Cu_6(pgly)_3(spgly)_3]$-$(ClO_4)_6 \cdot 9H_2O$ [**71**, Hspgly = *N*-(2-pyridylidene)glycine] was synthesized from an equimolar reaction of $[Cu(pgly)_2] \cdot 2H_2O$ [Hpgly = *N*-(2-pyridylmethyl)glycine] and $Cu(ClO_4)_2 \cdot 6H_2O$ in MeOH giving dark blue hexagonal crystals. The crystal structure (Figure 9a) shows a hexameric macrocycle composed of two crystallographically independent Cu(II) atoms, a reduced Schiff base ligand (pgly) and a Schiff base ligand (spgly), arranged alternatively in the hexanuclear cation. Cui et al. (08JA4582) reported the metallomacrocycle $[Zn_6L_6]$ (**72**) [H_2L = (R,R)-(−)-*N,N′-bis*(3-*tert*-butyl-5-(4-pyridyl)salicylidene)-1,2-diaminocyclohexane], synthesized by the reaction of $Zn(NO_3)_2$ with the ligand H_2L. The Schiff base ligand (Figure 9b, top) (01IC3222, 01TL2093) was obtained starting with the functionalized salicylaldehyde, which can be prepared by Suzuki coupling between the bromoaldehyde and 3-pyridinylboronic acid. Subsequent condensation of the functionalized salicylaldehyde with 1,2-diaminocyclohexane in refluxing EtOH afforded **72**. The crystal structure of the metallomacrocycle **72** (Figure 9b, bottom) showed that each Zn ion coordinates to the central N_2O_2 donor of the ligand and to a pyridine of another ligand building a hexameric metallocycle, with one uncoordinated pyridine. Noncovalent interactions between the macrocycles directed the packing of the different hexamers into a 3D nanotubular architecture.

3.1.1 Hexapyridine

Newkome and Lee reported (83JA5956) the first successful synthesis of the quintessential, pyridine-based unsubstituted hexamer 77 termed

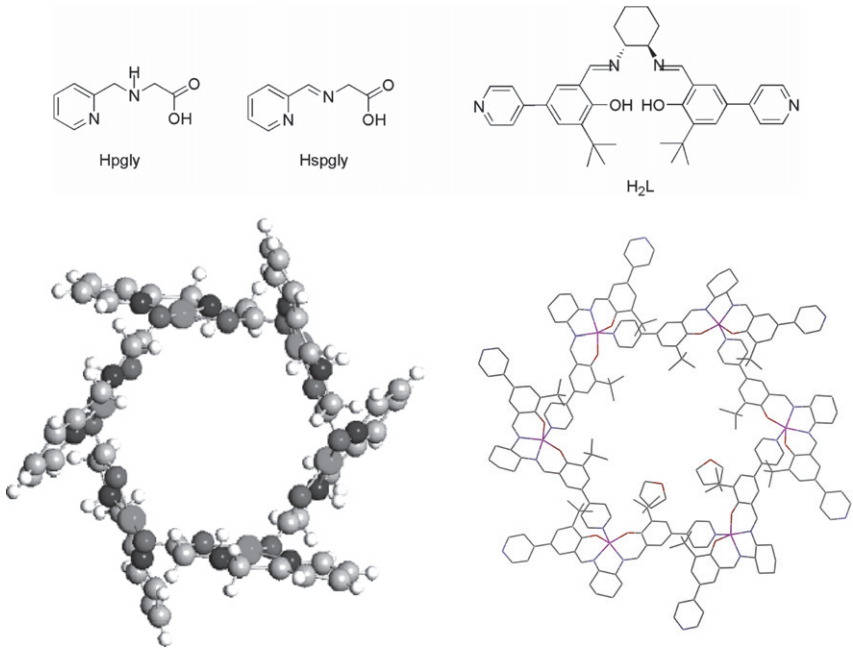
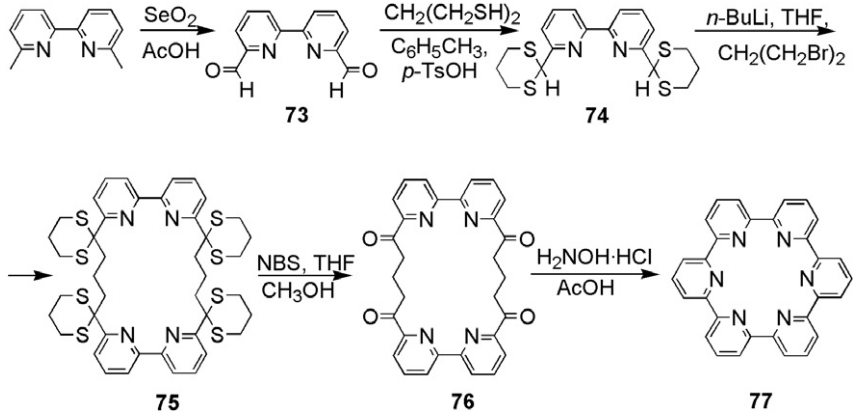


Figure 9 X-ray crystal structure of (a) $[Cu_6(pgly)_3(spgly)_3](ClO_4)_6 \cdot 9H_2O$ (**71**) (03IC5135) (reproduced by permission from American Chemical Society) and (b) $[Zn_6L_6]$ (**72**) (08JA4582) (reproduced by permission from American Chemical Society), along with the corresponding ligand drawings.

"sexipyridine" (Scheme 23) starting from the oxidation of 6,6′-dimethyl-2,2′-bipyridine to the dialdehyde **73.** The aldehyde groups were subsequently protected as thioacetals **74** using a catalytic amount of



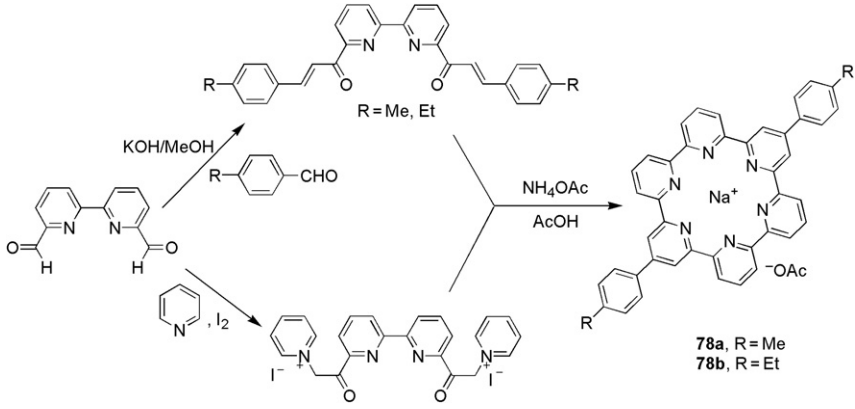
Scheme 23

p-toluenesulfonic acid. Lithiation of the *bis*-dithiane **74**, followed by addition of 1,3-dibromopropane (two equivalents) afforded the cyclic tetradithiane **75**. Deprotection using NBS allowed the isolation of the flexible tetraketone macrocycle **76**, which was finally converted to the desired sexipyridine **77** by treatment with hydroxylamine in refluxing glacial acetic acid for 24 h. A notable attribute of sexipyridine is the nonplanarity of the connected pyridine rings due presumably to crowding of the adjacent lone *N*-electron pairs. Calculations suggest a gas-phase lowest energy D_3 conformation with 'up' and 'down' alternating nitrogens (99JCS(P2)2501).

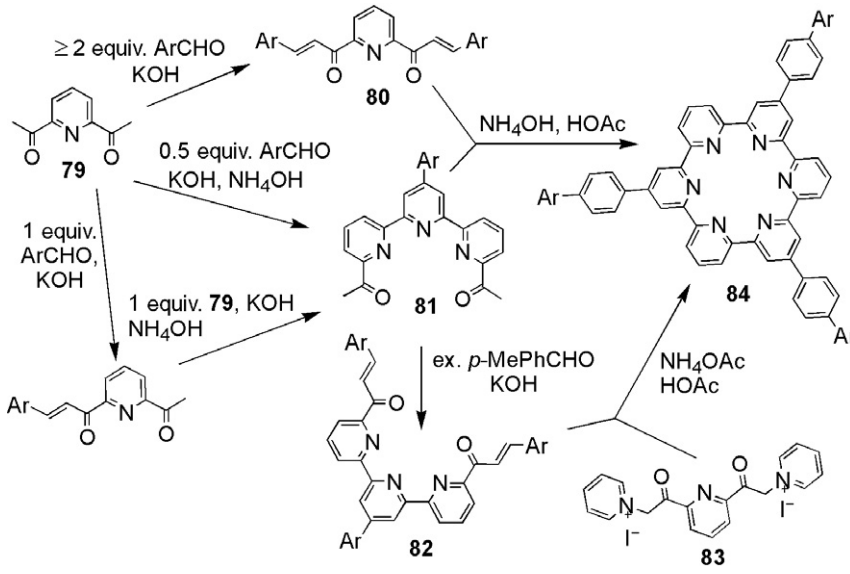
Several derivatives of sexipyridine have since been reported. Toner reported (83TL2707) the synthetic procedure of an aryl derivative **78**, which was formed using a tandom Kröhnke pyridine synthesis (63AG181, 76S1) as the key cyclization step (Scheme 24). The presence of Na^+ in the mass spectrometry and elemental analysis was explained, after attempts to minimize metals during synthesis, with the possibility that the sexipyridine was capable of stripping Na^+ from glass.

Potvin et al. (03CJC209) described the synthesis of the trisubstituted cyclic hexamer **84** that exhibited unexpectedly poor solubility. Two synthetic procedures were described (Scheme 25) to synthesize **84**, coupling of a *bis*-propenone **80** with a diacetylterpyridine **81** in the presence of a source of NH_3 via a dihydropyridine intermediate, or coupling of a more elaborate *bis*propenone **82** with the salt **83** under Kröhnke conditions.

Heterokekulenes, the heteroatomic analogues of kekulene (78AGE372), are classic examples of hexameric molecules composed of fused, cyclized benzenoid rings. Dodecahydro-18,21-dioxoniakekulene (**93**), the first heterokekulene, was reported by Katritzky and Marson (83JA3279), contained two opposing oxygen atoms within the cavity's



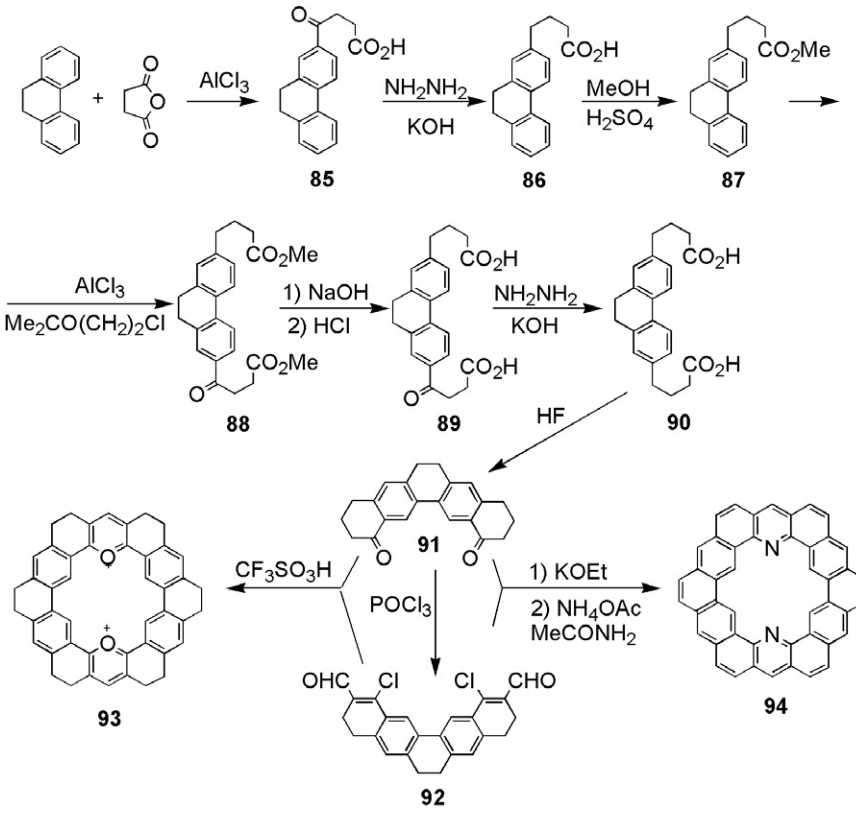
Scheme 24



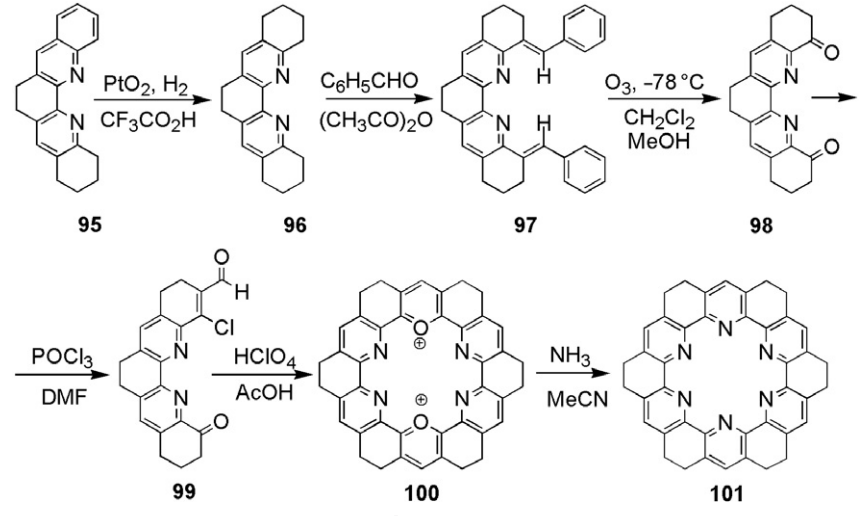
Scheme 25

interior. Synthesis of the heterokekulene **94** containing two opposing nitrogen atoms was also presented (Scheme 26). Acylation of 9,10-dihydrophenanthrene at the 2-position with succinic anhydride gave **85**, which was reduced using a Lock modification of the Wolff–Kishner reduction (48MI1) to afford the acid **86**. Esterification with methanol to give the ester **87**, which was acylated at the 7-position with *β*-(methoxycarbonyl)propionyl chloride to afford monoketone **88**. Saponification of the keto diester, followed again by the Lock modification of the Wolff–Kishner reduction afforded the diacid **90**. Anhydrous hydrogen fluoride was used under mild conditions for the cyclodehydration of the diacid to form the pentaphenedione **91**, which following a Vilsmeier–Haack reaction (76MI1) afforded the required *bis*(β-chlorovinyl) dialdehyde **92**. Condensation of the diketone **91** with the dialdehyde **92** afforded **93** in 87%. Under aldol conditions, the condensation of **91** with **92**, followed by ring-closure afforded a highly insoluble mixture. Mass spectrum detected a peak assigned to the diazakekulene and others assigned to its successive dehydrogenation to afford the fully unsaturated azakekulene **94**.

The first hexaazakekulene was synthesized (Scheme 27) by Staab et al. (85TL6179), which contained six coplanar nitrogen atoms ideally juxtaposed for the complexation of small ions. Catalytic hydrogenation of **95** gave **96**, which was condensed with benzaldehyde to yield the 2,13-dibenzylidene derivative **97** and ozonized at –78°C to produce the



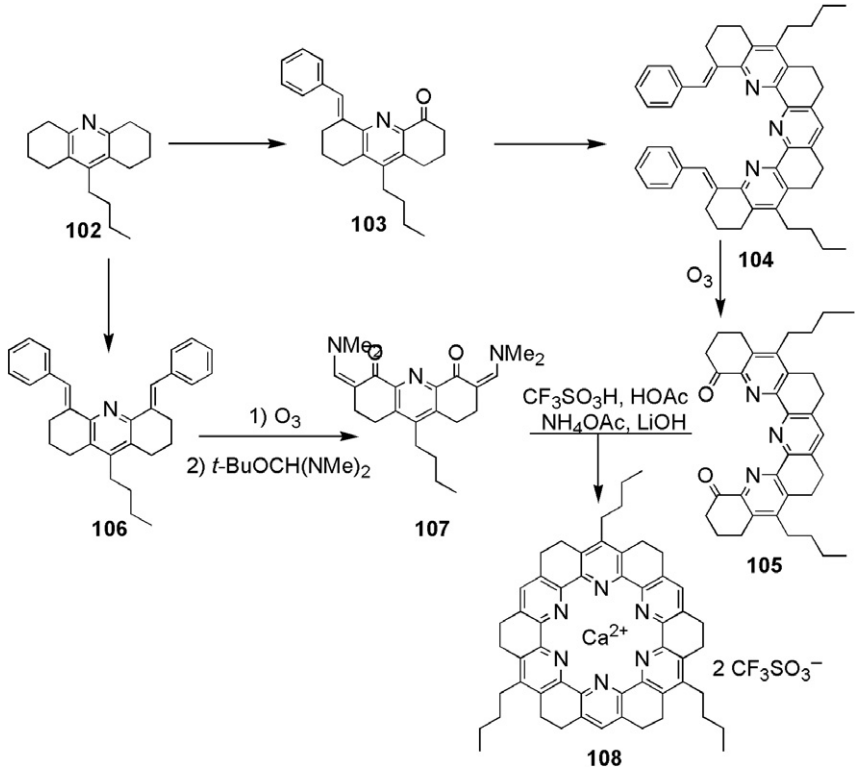
Scheme 26



Scheme 27

diketone **98**. Reaction with $POCl_3$ in DMF [Vilsmeier reaction (76MI1, 92T3659)] afforded β-chlorovinylaldehyde **99**, which when treated with perchloric acid/acetic acids gave dodecahydro-19,20,22,23-tetraaza-21,24-dioxoniakekulene (**100**). Treatment with ammonia in MeCN under reflux conditions gave a yellow powder, assigned by ^{1}H NMR to the D_{6h}-symmetrical dodecahydro-19,20,21,22,23,24-hexaazakekulene (**101**).

In general, the reported heterokekulene rings have shown very low solubility thereby hindering their characterization and study. In an attempt to solve this problem, Bell and Firestone (86JA8109, 87JIP149) synthesized the toroidal dodecahydrohexaazakekulene (**108**) macrocycle, a C_3-symmetric hexaazakekulene derivative with rigidifying ethylene bridges and three *n*-butyl groups to enhance its solubility (Scheme 28). The *n*-butyloctahydroacridine (**102**) was converted in three steps to benzylideneketone **103** and then dimerized by pyrolysis of the trimethylhydrazonium salt, yielding dibenzylideneheptacycle **104**. Ozonolytic cleavage of the benzylidene groups afforded diketone **105**. The complementary segment, *bis*(β-dimethylaminoenone) **107**, was prepared from



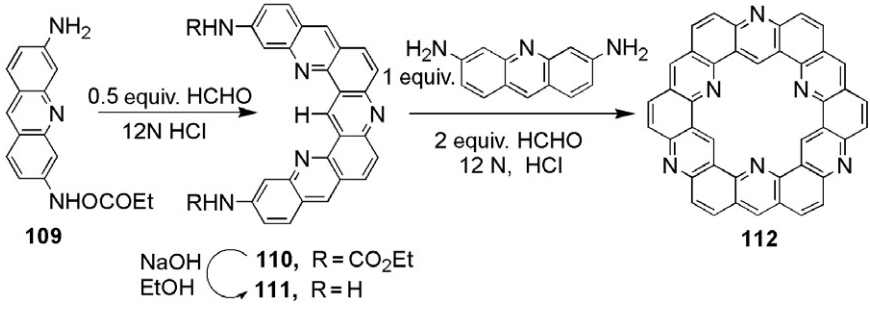
Scheme 28

102 via dibenzylidene derivative **106**, which was ozonized. The resulting ketone was treated with Bredereck's reagent (68CB41) to afford **107**. Macrocyclization was performed by heating **105** and **107** with triflic acid in acetic acid, followed by addition of ammonium acetate, and lastly neutralization with LiOH. The presence of Ca^{2+} ion in the structure was determined to come from a 0.3% impurity of Ca^{2+} in the triflic acid.

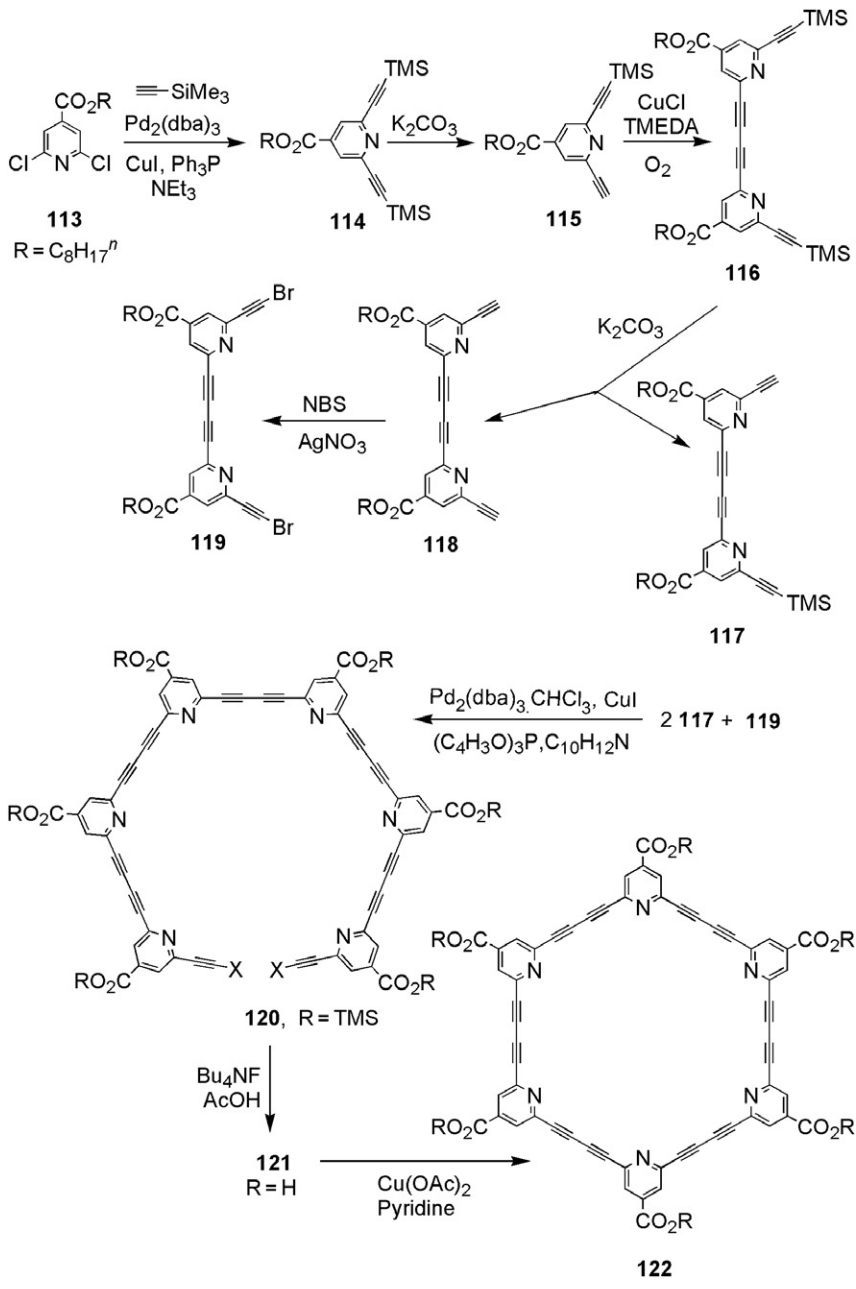
The torand 3,9,15,19,21,23-hexaazakekulene (**112**) with six nitrogen atoms that are alternately located at the inner and outer loci on the cycloarene (Scheme 29) has been reported (97AGE1190). Monoprotected proflavine **109** was reacted slowly with 0.5 equivalent of paraformaldehyde to give tripyridinyl diamine **110**. Removal of ethoxycarbonyl under basic conditions afforded **111**, which produced **112** upon stoichiometric reaction with proflavine and two equivalents of paraformaldehyde.

An analogous shape-persistent cyclic hexamer possessing six pyridine rings connected by triple bonds, the pyridinophane **122** (Scheme 30), has been reported by Tobe et al. (00OL3265). Employing a Sonogashira coupling (75TL4467, 02JOM46, 08JOC6037), the *n*-octyl ester **113** was converted to the *bis*(trimethylsilyl)ethynyl derivative **114**, which was deprotected with K_2CO_3 affording **115** as well as completely deprotected and starting material. Two molecules of **115** were then coupled oxidatively giving **116**. Deprotection of **116** again gave a mixture of partially **117** and completely deprotected **118**, as well as starting material. Purified **118** was brominated with NBS giving **119** and then reacted with two equivalents of **117** to afford the linear hexamer **120**. Deprotection gave the unstable linear hexamer **121**, which was subjected to an intramolecular coupling to form the cyclic hexamer **122**.

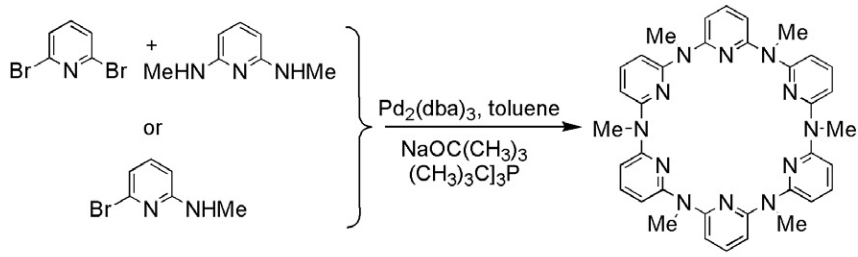
Another example of a heterocyclic macromolecule containing six pyridine subunits reported by Miyazaki et al. (02TL7945) was *N*,*N*′,*N*″,*N*‴,*N*⁗,*N*⁗⁗-hexamethylazacalix[6](2,6)pyridine **123** (Scheme 31), which exhibited more flexibility than previous examples and possessed the pyridine subunits directed towards the ring cavity, able to coordinate



Scheme 29


CO2R
Cl N Cl
SiMe3
Pd2(dba)3
CuI, Ph3P
NEt3
TMS
RO2C N
K2CO3
CuCl
TMEDA
O2
113
R = C8H17n
114
115
116
Br
NBS
AgNO3
119
118
117
Pd2(dba)3.CHCl3, CuI
(C4H3O)3P,C10H12N
2 117 + 119
X
120, R = TMS
Bu4NF
AcOH
121
R = H
Cu(OAc)2
Pyridine
122

Scheme 30



123

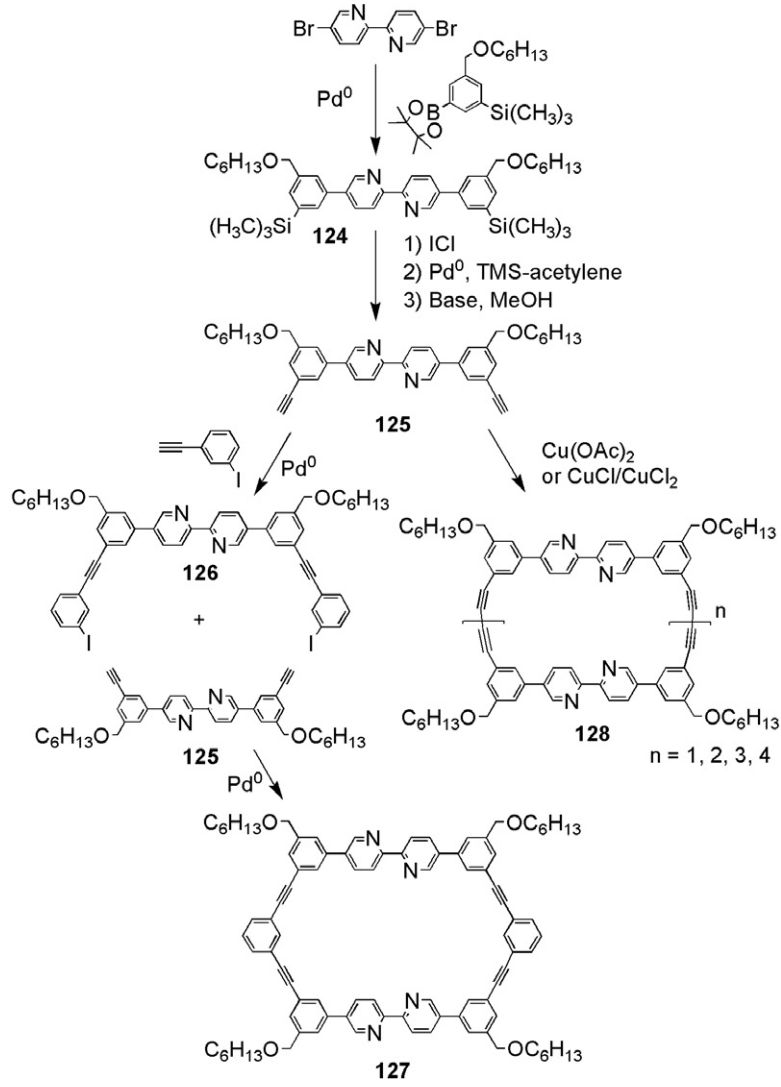
Scheme 31

Zn(II) ion. The Pd-catalyzed aryl amination of 2,6-dibromopyridine with 2,6-*bis*(methylamino)pyridine afforded (10%) the hexameric heterocycle **123**. The cyclization of reaction of 2-bromo-6-(methylamino)pyridine also gave the corresponding macrocycle in 8% yield.

3.1.2 Bipyridine

Routes to hexameric architectures based on bipyridine have been the subject of design by many researchers, including Schlüter, who continues to pioneer synthetic chemistry in numerous areas, including polymer, material science (09AGE1030), and macrocyclic chemistry (07EJO2700). Schlüter et al. have prepared 2,2′-bipyridine-based macrocycles peripherally modified with six hexyloxy groups [as well as others (02EJO3075)] to enhance the ring's solubility and obtained the X-ray structure (00CEJ2362) and also reported on the macrocycles ruthenium complexation and X-ray structure determination (02CEJ357). Illustrative of key transformations employed for the construction of these novel materials is the synthesis of macrocycle **127** (Scheme 32) (05EJO822). Beginning with 5,5′-dibromobipyridine, a Suzuki cross-coupling with a hexyloxybenzyl arylborate afforded the elongated bipyridine **124** that was then transformed (ICl) to the diiodobipyridine and connected to two equivalents of iodophenylacetylene via another cross-coupling reaction to give the extended diiodide **126**. Strategic use of THP protecting groups allowed the incorporation of polymerizable pendant groups, such as methyl methacrylate and norbornene, thereby facilitating their use as macromonomers in free radical and ring-opening metathesis polymerizations. A final coupling with the intermediate *bis*acetylene **125** gave the hexamer **127**. Oxidative treatment [$Cu(OAc)_2$ or $CuCl/CuCl_2$] of the diiodide **125** generated a series of polydiacetylenes **128** (08OL2091).

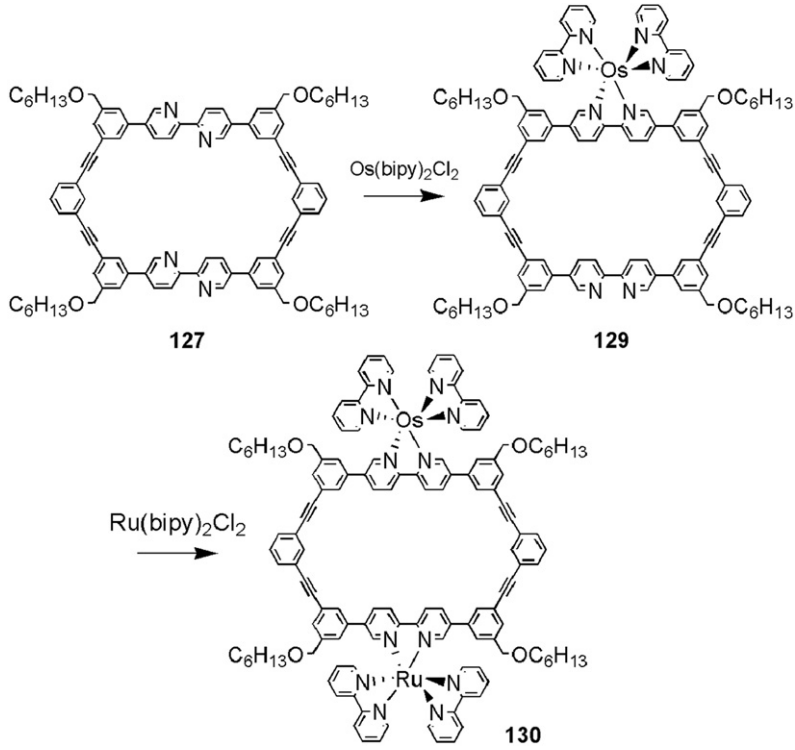
The coordination of osmium and ruthenium as their *tris*bipyridine complexes (Scheme 33) has been reported (06CPC229). Treatment of the macrocycle **127** with $Os(bipy)_2Cl_2$ gave the monometallated specie **129**



Scheme 32

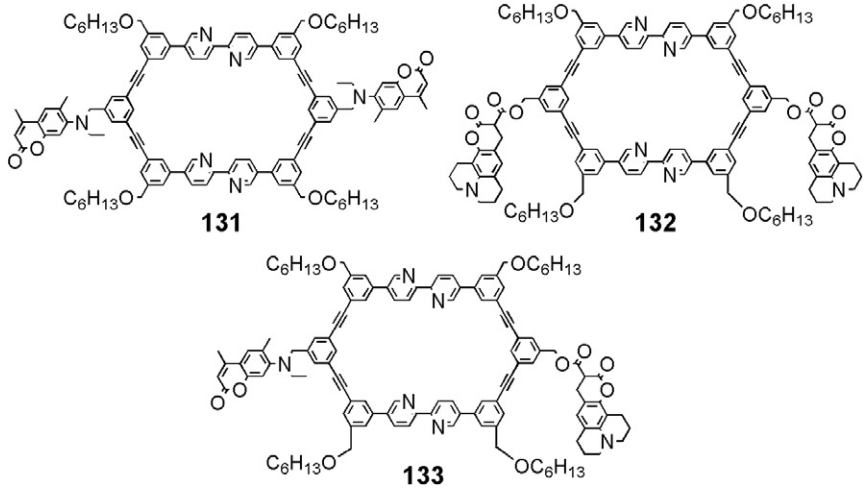
that was then reacted with a second equivalent of the metal adduct $Ru(bipy)_2Cl_2$ to afford the *bis*metallated macrocycle **130**. Photoinduced energy and electron-transfer processes of the Ru(II)–Os(II), Ru(III)–Os(II), and Ru(II)–Os(III) complexes were examined; the macrocyclic ligand was reported to be a "relatively poor conducting bridge."

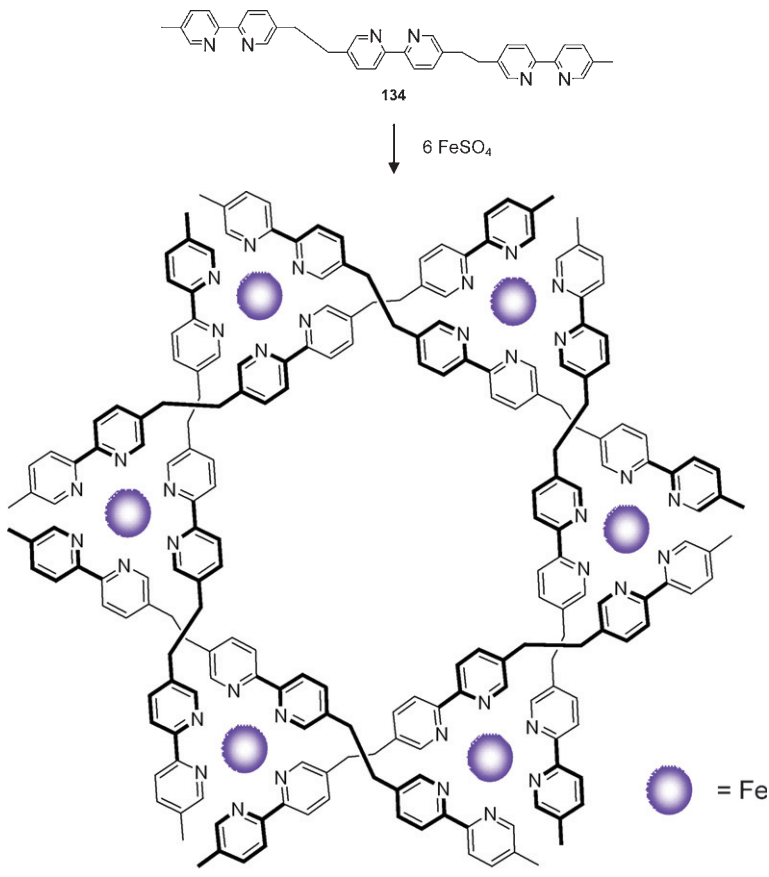
Schlüter et al. (07EJO2700) have also reported the preparation of shape-persistent, 6-sided macrocycles that incorporated site-specific functionalization along with the opposing 2,2′-bipyridine units. Coumarin 2 and 343 dyes



Scheme 33

were attached to the corners as energy-absorbing groups in anticipation of the use of these materials as energy- and electron-transfer devices (**131–133**). Protonation of the coumarin moieties caused significant changes in the



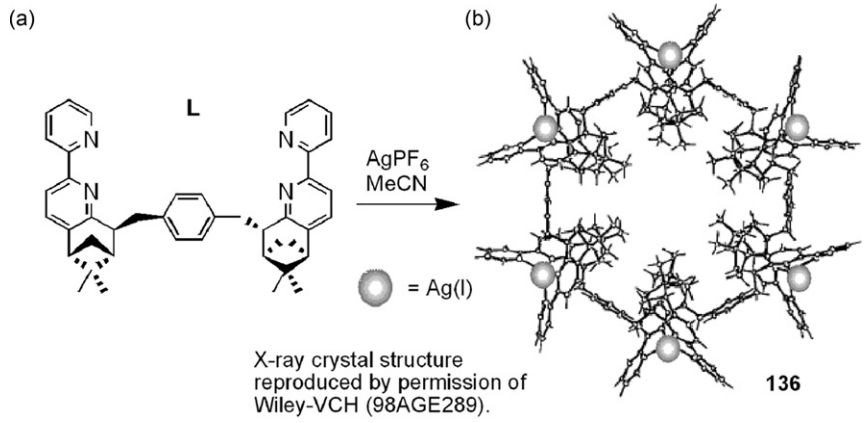


135

Scheme 34

absorption and emission properties due to excited-state order inversion and electron-transfer quenching mechanisms (08CEJ10772).

The research group of Jean-Marie Lehn, who pioneered supramolecular chemistry, (95MI1) has reported the construction of hexanuclear architectures termed helicates (97JA10956) based on the self-assembly of *tris*-2,2′-bipyridine ligands with Fe(II) (Scheme 34). Preparation of the ethylene-bridged ligand **134** (93AGE703) was accomplished by mono-lithiation of 4,4′-dimethyl-2,2′-bipyridine and reaction with 4,4′-dibromomethyl-2,2′-bipyridine. Treatment of these ligands with Ni(II) gave the self-assembled trinuclear helix; whereas, reaction with $FeSO_4$ in ethylene glycol (170°C) afforded the hexameric helicate **135** as a red precipitate in quantitative yield. Similar oligobipyridines employing *bis*methylene(oxy) connectivity have

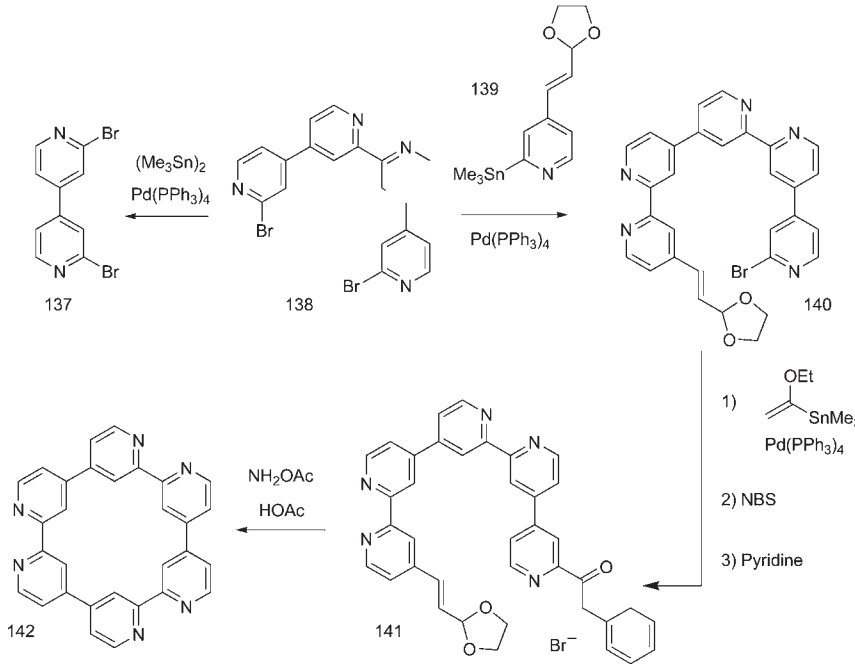


Scheme 35

been reported (91HCA594) and demonstrated to form tetranuclear helicates (97JA10956).

Hexameric helicate **136** was reported by von Zelewsky et al. (98AGE289) using chiral *bis*(pinene-2,2′-bipyridine) ligands for the coordination of six Ag(I) ions; an X-ray structure was also reported (Scheme 35; X-ray crystal structure of **136** (98AGE289), reproduced by permission from Wiley-VCH). Potts et al. (93IC4436, 93IC4450) described the construction of helical, dimeric species by the reaction of an oligomeric septapyridine with Cu(II) and Co(II).

Kelly et al. (97JOC2774) have prepared cyclo-2,2′:4′,4″:2″,2‴:4‴,4⁗:-2⁗,2⁗⁗:4⁗⁗,4-sexipyridine consisting of cyclic-bound bipyridine with the nitrogen lone pair electrons directed *outward* from the periphery of the hexamer. This is in contrast to the sexipyridine constructs prepared by Newkome et al. (83JA5956) and Toner (83TL2707) whereby the nitrogens are directed toward the center of the hexamer. The *tris*-bipyridine hexamer **142** synthesis began (Scheme 36) with 2,2′-dibromo-4,4′-bipyridine [prepared by subjecting 4,4′-bipyridine to the Chichibabin reaction (42MI1) to give the diamine, followed by diazotization (HNO_2, H^+), hydrolysis, and bromination ($POBr_3$)]. The dibromide **137** was subjected to halogen-metal exchange/Stille coupling (06EJO1827) to give the quaterpyridine **138** that was subsequently reacted via another Stille coupling with (trimethyltin)pyridine **139** to generate the quinquepyridine **140**. The sixth and final pyridine ring was constructed by transformation of the arylbromide to a masked acetyl group by Stille coupling with ethylvinyl ether and treatment with NBS to give the bromoacetyl moiety. Addition of pyridine gave the pyridinium bromide **141** that under acidic conditions with added

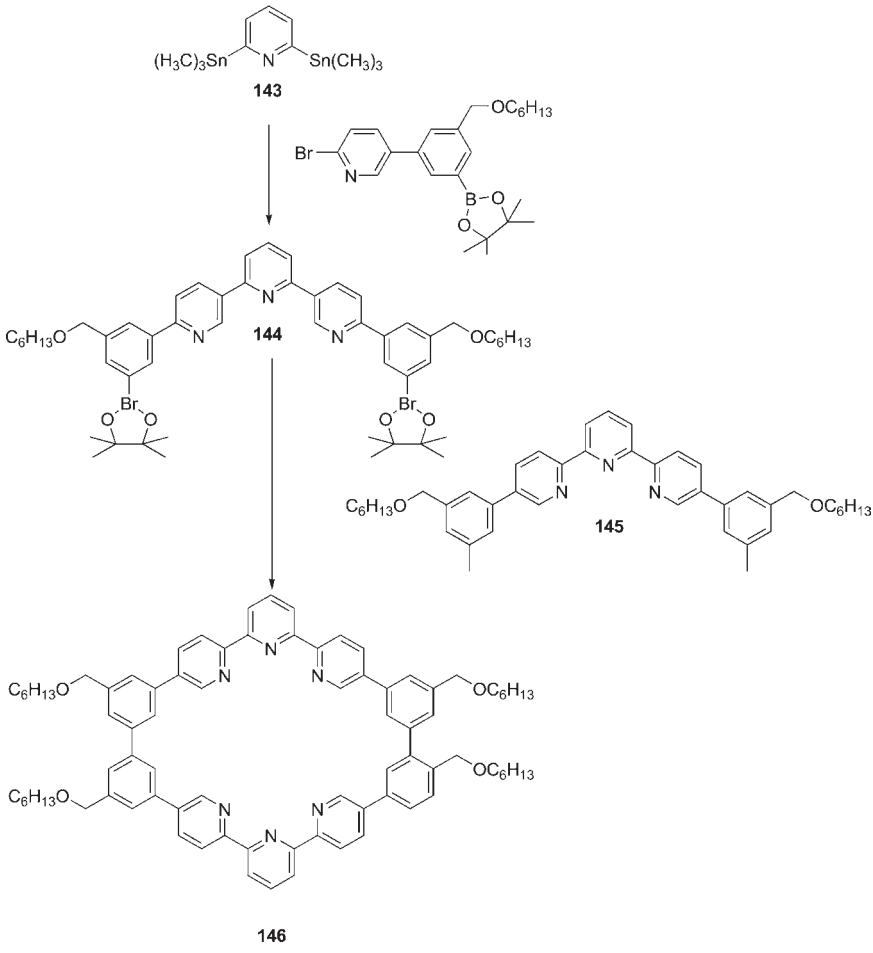


Scheme 36

NH_4OAc underwent a Kröhnke reaction (76S1) to afford the desired hexameric *tris*bipyridine **142**. The authors noted that in some cases the $Pd(PPh_3)_4$-promoted Stille couplings were sensitive to the use of freshly prepared catalyst. As well, Sonogashira coupling of alkyne moieties to 5,5′-dibromo-2,2′-bipyridine in anticipation of generating bipyridine-based hexamers with alkyne spacers was unsuccessful.

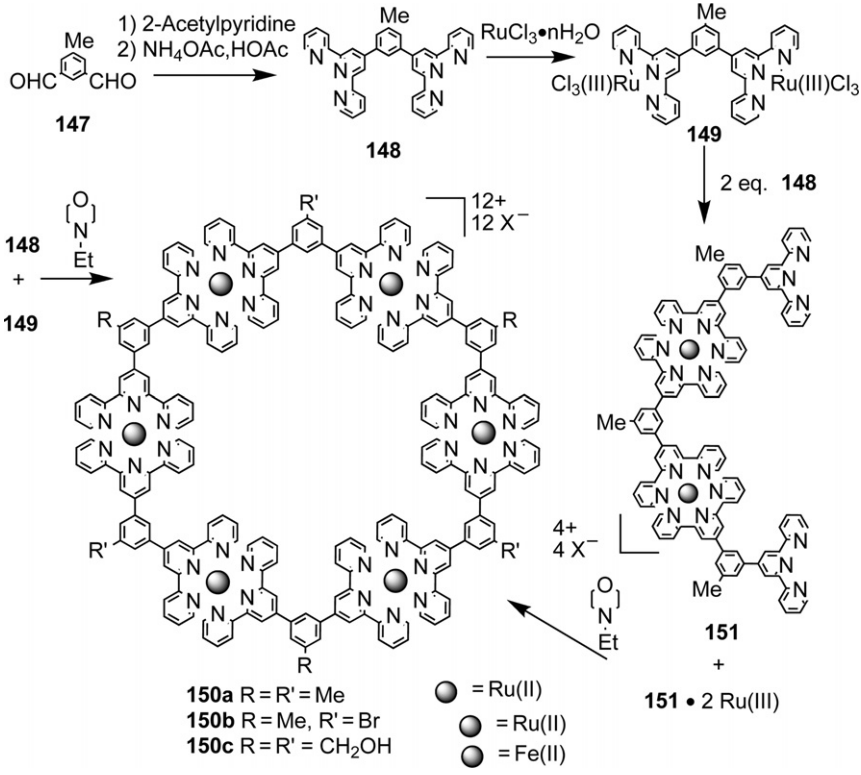
3.1.3 Terpyridine

Schlüter et al. (00EJO3483) have prepared terpyridine-based macrocycles where the polypyridine units are incorporated linearly in the framework. This is analogous to that of their bipyridine-based hexamers (05EJO822, 06CPC229, 08CEJ10772). Construction started with the Pd-catalyzed cross-coupling of the *bis*(trialkyltin)pyridine **143** (Scheme 37) with a bromopyridine to give the *bis*boronated terpyridine **144**. Coupling to the corresponding diiodide **145** generated the macrocycle **146.** Notably, this was the first synthesis of an expanded sexipyridine. Expanded phenylacetylene-modified terpyridine-based macrocycles have been reported (03JA6907) along with the X-ray crystal structure of an alkyl-substituted ring.



Scheme 37

Newkome et al. (99AGE3717) first reported in 1999 the synthesis of hexaruthenium macrocycles based on the self- and directed-assembly of *bis*(terpyridinyl) monomers [based on the 2,2′:6′,2″-terpyridine moiety initially reported by Morgan and Burstall (32JCS20, 37JCS1649)] crafted with a 120° angle between the two coordination sites. This facilitated the positioning of six *bis*terpyridine ligands in the ubiquitous benzenoid motif. Construction of these metallohexamers (Scheme 38) began with the treatment of aryldialdehyde **147** with excess 2-acetylpyridine and base, followed by NH_4OAc and HOAc to give (66%) the requisite *bis*(terpyridine) **148**. Reaction of **148** with $RuCl_3{\cdot}nH_2O$ afforded the corresponding paramagnetic *bis*Ru(III)

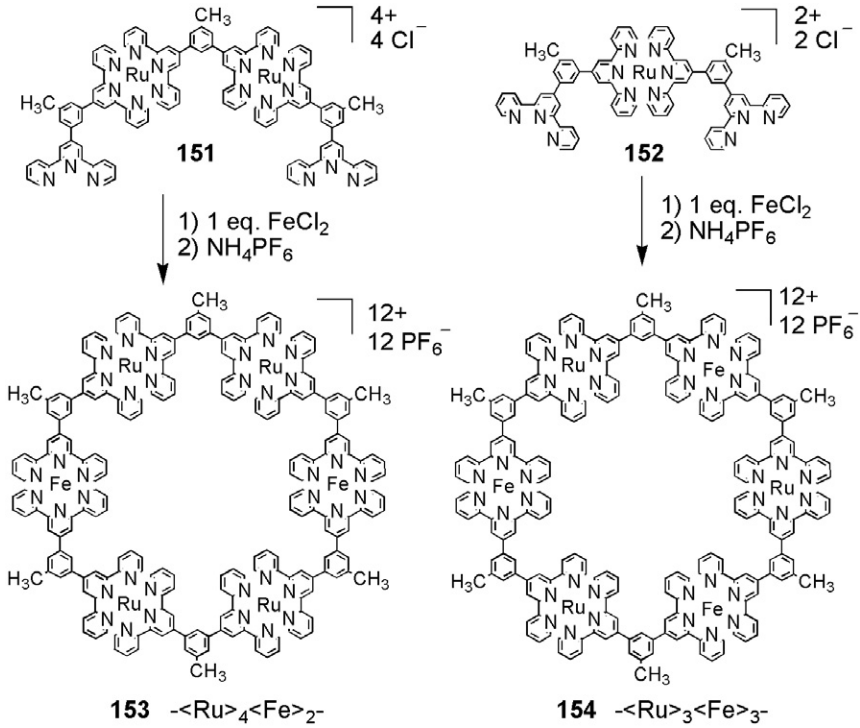


Scheme 38

adduct **149** that was subsequently reacted with **148** under reducing conditions (*N*-ethylmorpholine) in a 1:1 ratio to give the hexaRu(II) metallocycle **150** in ~40% yield after purification. As a proof-of-structure, the identical macrocycle was synthesized by a directed, step-by-step approach that was achieved starting by reacting the *bis*Ru(III) adduct **149** with two equivalents of the ligand **148** to give the *bis*Ru(II) trimer **151**. Upon further conversion to its *bis*Ru(III) adduct (**151**·2Ru(III), not shown) and reaction with the unmetallated trimer **151** (essentially a top-half : bottom-half coupling strategy) the hexamer **150** was obtained. Ultracentrifugation absorption profiles for this macrocycle yielded an average molecular weight for the macrocycle of $M = 5600 \pm 200$ amu, which corresponded well with the calculated value (M 5670 amu with counter ions). A bromodialdehyde was also employed to construct a bromoaryl *bis*terpyridine ligand that gave rise to an alternating methylaryl–bromoaryl substitution pattern on the macrocyclic ring (**150**). These Ru-based metallomacrocycles have been

examined by electrospray ionization (ESI) and matrix-assisted laser desorption ionization (MALDI) mass spectrometry (06IJMS86). Optimal parameters for mass analysis were developed. Traveling wave ion mobility mass spectrometry (TWIM-MS) has been employed for the analysis of similar Cd(II)-based hexamers (09JA16395). It was found that ion mobility separation enhances the resolving power of the mass spectrum by the addition of shape-dependent dispersion thereby facilitating the identification of different conformations in supramolecular assemblies. Transmission electron microscopy of the Fe(II) metallohexamer with hydroxymethyl substituents (**150c**) clearly revealed a hexameric structure that corresponded well with the outer and inner dimensions of 37.5 and 17.5 Å, respectively, obtained by molecular modeling (02CEJ2946).

Incorporation of different metal centers (Scheme 39) within the hexameric framework was also examined (04CEJ1493). Self-assembly of the *bis*Ru(II) trimer **151** with one equivalent of $FeCl_2$ afforded the tetraRu(II)*bis*Fe(II) architecture **153** (–<Ru>$_4$–<Fe>$_2$–); whereas, when the



Scheme 39

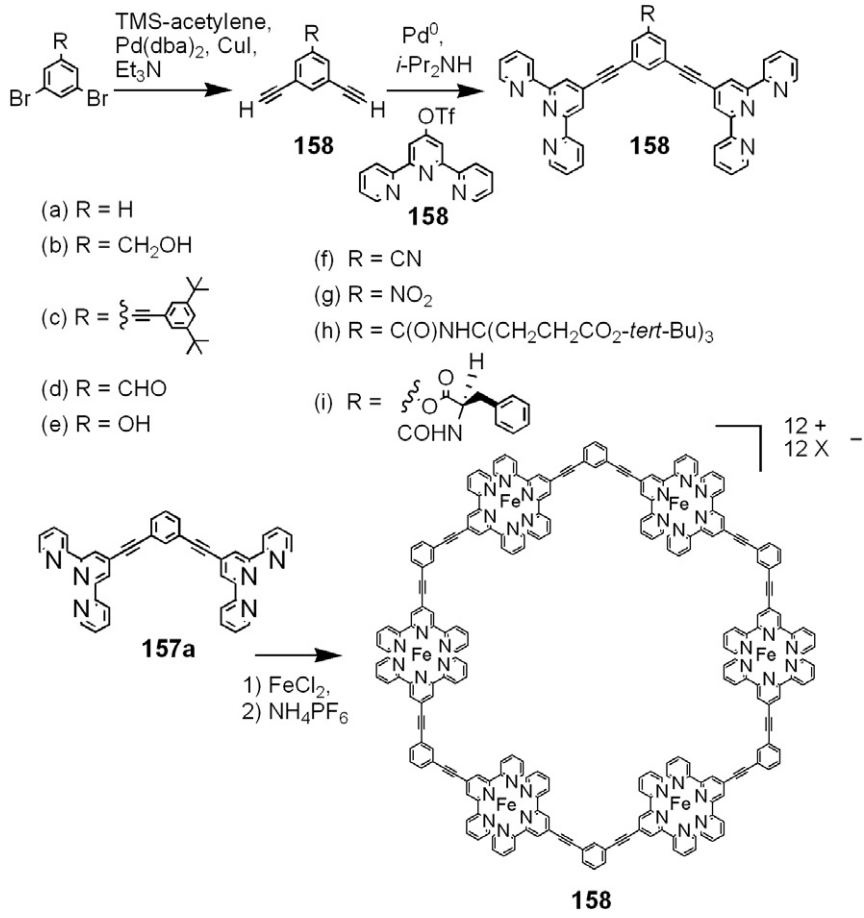
monoRu(II)*bis*terpyridine dimer **152** was treated similarly (1 equiv. $FeCl_2$) the *tris*Ru(II)*tris*Fe(II) motif **154** (–<Ru>$_3$–<Fe>$_3$–) was obtained. A penta*kis*Ru(II)monoFe(II) metallocycle (not shown) was also prepared starting with the monoRu(II)bisterpyridine dimer **152**, the successive addition of two equivalents of $RuCl_3$ followed by two equivalents of *bis*terpyridine ligand, and finally closing the ring with one equivalent of $FeCl_2$. An electrochemical analysis of the Ru-Fe-based structures was reported and compared with that of all the Ru(II) and Fe(II) hexamers; the reversible redox characteristics of this family of metallomacrocycles suggested their suitability for further study as candidates for electron storage devices.

Notably, a series of oligomeric $< \text{tolyl}[bis(\text{terpyridinyl})]_n Ru^{II}_{n-1} >$ complexes, where $n = 2$–6, possessing metal-free terpyridine end groups, was formed and isolated in a single-pot reaction (06EJO4193); UV-Vis, CV, MS, and NMR data for the oligomers are compared and contrasted to that of the corresponding hexamer **150** (Scheme 38) that was also isolated from the reaction.

Other unique *bis*(terpyridine)-building blocks have been reported, such as the 5-substituted 1,3-[*bis*(2,2′:6′,2″-terpyridin-4′-ylethynyl)]benzenes (06DMP413). A Pd-catalyzed cross-coupling procedure was employed to build these elongated, functionalized *bis*(terpyridine) ligands that were readily self-assembled to afford the corresponding hexameric metallomacrocycles possessing an inner void diameter of 24 Å. Starting with the appropriate 1,3-dibromobenzene (Scheme 40), TMS-acetylene was coupled [$Pd(dba)_2$, CuI, Et_3N] to give the diacetylene **155** that was subsequently coupled to terpyridine triflate **156** (91JOC4815) via a Pd(0) cross-coupling procedure to afford the desired elongated *bis*terpyridine monomer **157**. Treatment of the building block **157a** with $FeCl_2$, followed by ion exchange with NH_4PF_6, gave the expanded hexamer **158**.

A terpyridine-based, Zn(II)-hexamer has been reported (06MMRC1809), whereby an *O*-hexyl-3,5-*bis*(terpyridine)phenol ligand was prepared (04OL1197) and subsequently self-assembled. The photo- and electroluminescence properties of the hexamer were investigated in solution and coated onto ITO glass. The HOMO and LUMO energy gap of the Zn-hexamer was determined to be 3.5 eV. Fabrication into an OLED device resulted in green electroluminescent emission at 515 nm with a maximum luminance of 39 cd/m^2 and maximum efficiency of 0.16 cd/A.

A novel use of Newkome's hexameric metallomacrocycles has been their incorporation into dendrimer–hexamer composite materials (08AM1381). Composite fiber formation was effected by the ion-promoted, stoichiometric self-assembly of a structurally rigid hexameric macrocycle and a dodecacarboxylate-terminated, first-generation dendrimer (94MM3464) where the metallocycle and dendrimer function as



Scheme 40

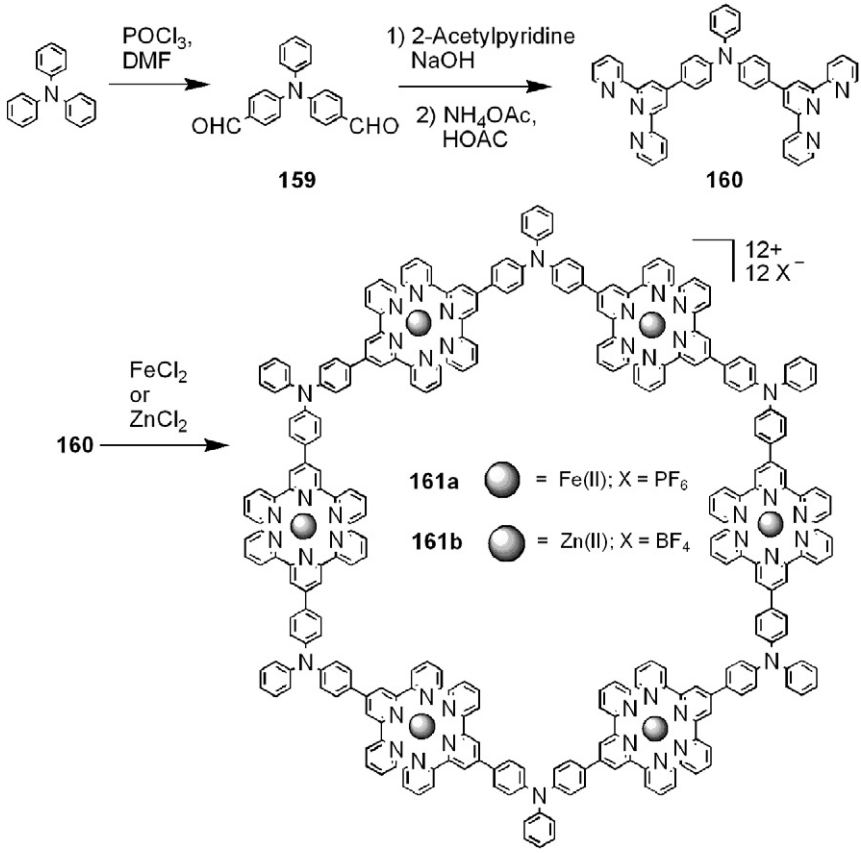
polyionic counter ions. The hexamers were prepared (40–45%) by reacting *O*-hexyl-3,5-*bis*(terpyridinyl)phenol (04OL1197) with one equivalent of $[Ru(Cl)_2(DMSO)_4]$ (88IC4099). The anionic G1 dendrimer (prepared by hydrolysis of the corresponding 12-*tert*-butyl ester with formic acid) possesses a hydrodynamic diameter of 23.6 Å at basic pH, as determined by 2D diffusion-ordered spectroscopy NMR experiments. Notably, this diameter is larger than the internal void region diameter (17.5 Å) of the hexamer that suggests an ordered molecular packing based on a symmetrical association of the dendrimer smoothly fitting above, and not entirely into, the cavity of the hexamer. Fibers were formed by carefully layering a solution of polycarboxylate dendrimer in MeOH and water on top of a deep red MeCN solution of hexamer and allowing the mixture to

set at 25°C for 2 weeks in a sealed vial. The fibers were isolated by filtration and characterized by selected area electron diffraction, which indicated columnar packing of alternating hexamer and dendrimer species with 1.92 nm between hexameric planes and 3.85 nm between the centers of adjacent columns. Fiber formation has also been observed (10CEJ1768) based on the packing of sugar-modified hexamers and the corresponding pentamer upon slow diffusion in a mixed solvent ($CHCl_3$/MeOH/MeCN; 8:3:1). Fiber diameters ranged from 10 to 80 nm and possessed a helical morphology.

The photophysical properties of similar metallocycles possessing peripheral *tert*-butyl groups have been reported (07ICA1780), whereby the incorporation of alkyne moieties in the framework was studied. It was determined that the ethynyl groups could facilitate electron trapping and enhance molar extinction coefficiency and photocurrent generation.

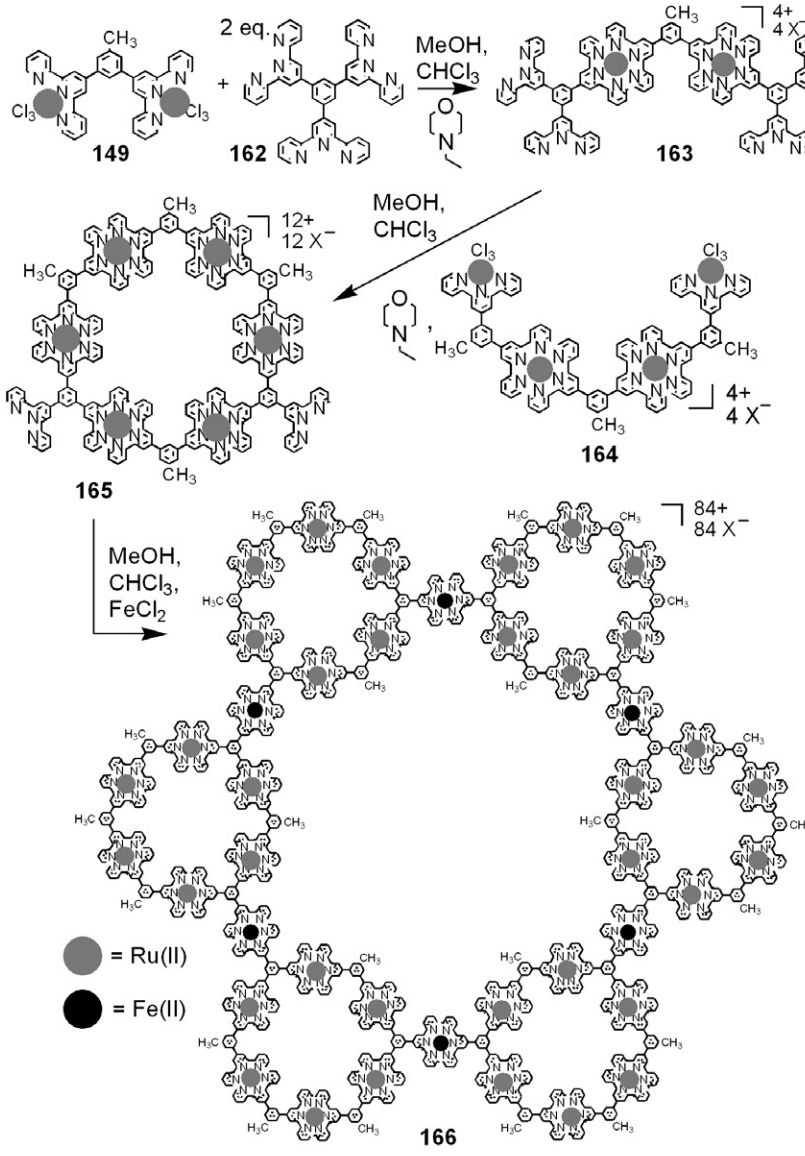
Newkome et al. (06JCD3518) have also prepared metallomacrocycles using triphenylamine as the design element that instills the 120° (or nearly so) required for benzenoid architecture. The terpyridinyl building block was constructed (Scheme 41) by subjecting commercially available triphenylamine to a Vilsmeier–Haak reaction ($POCl_3$, DMF) to generate dialdehyde **159**. Treatment of the dialdehyde with 2-acetylpyridine and base followed by NH_4OH and HOAc afforded the desired 4,4′-*bis*(2,2′:6′,2″-terpyridinyl)triphenylamine **160**. The X-ray crystal structure of this monomer revealed a nearly planar triarylamine group with the terpyridine ligands oriented 119.69° with respect to their coordination sites. Reaction of the *bis*ligand **160** with $FeCl_2$ or $Zn(BF_4)_2$, followed by ion exchange (NH_4PF_6), gave the hexaFe(II) **161a** and hexaZn(II) **161b** macrocycles, respectively. UV-vis absorption and emission spectra for the metallocycles revealed that both metallomer emissions occurred at $\lambda_{max} \cong$ 575 nm with metal-to-ligand charge transfer at $\lambda_{max} \cong 582$ nm suggesting these materials as useful sensitizer components in dye-sensitized solar cells.

The design and synthesis (Scheme 42) of the first non-branched fractal polymer that is the molecular equivalent of a "Sierpinski hexagonal gasket" has been described by Newkome et al. (06SCI1782). Fractal constructs are based on the incorporation of identical motifs that repeat at differing size scales. Thus, this polymer was created based on repeating hexameric architectures incorporated with increasing dimensions at successive higher levels or generations. Based on the Polish mathematician Vaclov Sierpinski's 1915 fractal definition (15CR302) and the collection of equilateral triangles termed the "Sierpinski gasket" by noted mathematician Mandelbrot (82MI1) this non-dendritic, fractal polymer possesses 24 *bis*terpyridine and 12 *tris*terpyridine building blocks (a total of 84 terpyridine moieties) bound together with 42 divalent Ru (36) and Fe (6) metal centers. Preparation began by treatment of 1 equiv. of *bis*[Ru(III)]



Scheme 41

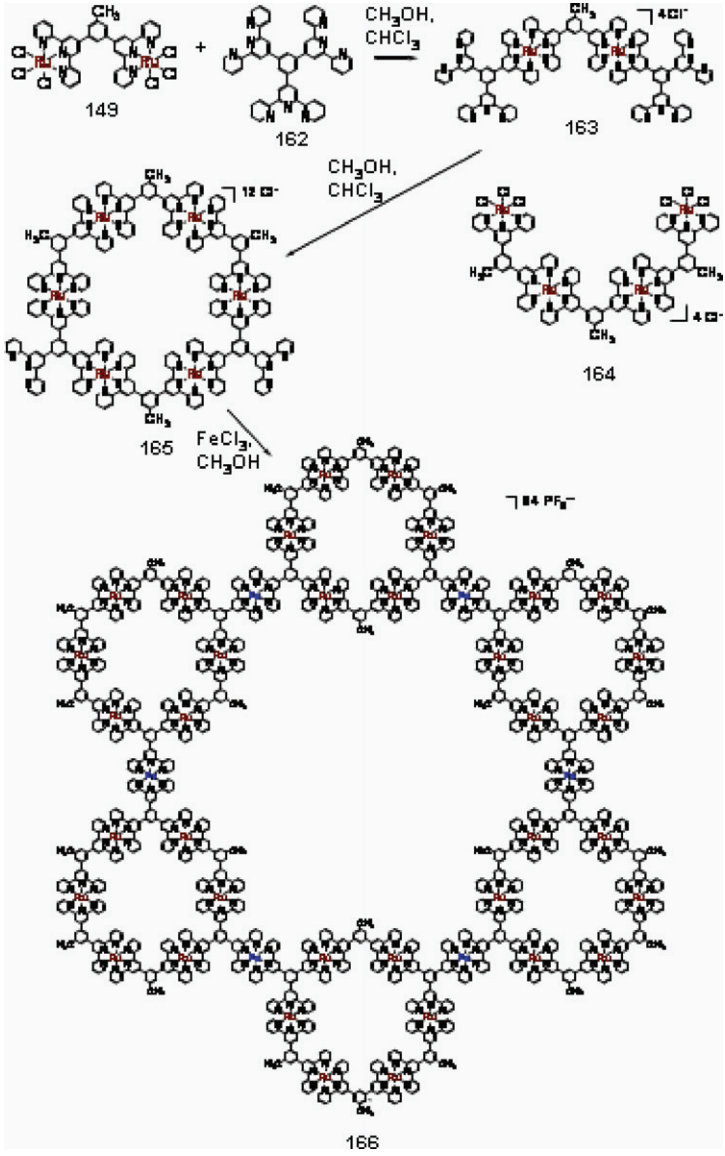
monomer **149** with 4.5 equiv. of *tris*terpyridine **162** [prepared according to the procedure of Constable et al. (92CC617)] ($CHCl_3$/MeOH, cat. *N*-ethylmorpholine) to give (35%) the heterotrimer **163**. Coupling of **163** with homotrimer Ru(III) adduct **164** in the presence of *N*-ethylmorpholine generated (31%) the hexamer **165** possessing the 120° juxtaposed free ligands required for the next stage of hexamer formation; reaction of the building block **165** with $FeCl_2$ afforded the gasket **166** that was isolated as the polyCl^- salt that exhibited good solubility in MeOH, EtOH, DMF, and DMSO and poor solubility in H_2O, CH_2Cl_2, and MeCN; counter ion exchange to the polyPF_6^- salt changed this trend to facilitate solubility in MeCN, DMF, and DMSO and insolubility in MeOH, EtOH, and CH_2Cl_2. Characterization of this novel hexamer included TEM, AFM, and ultrahigh-vacuum low-temperature (8 K) STM, which combined



Scheme 42

with traditional techniques (e.g., NMR, UV-vis) provided a "visual" argument for the formation of the 12-nm diameter hexamer.

A series of shape-persistent hexagonal macrocycles based on trimeric *bis*terpyridine-Fe(II) connectivity (Scheme 43) has been reported (08EJO3328). Differing spacer groups were employed for coordination site

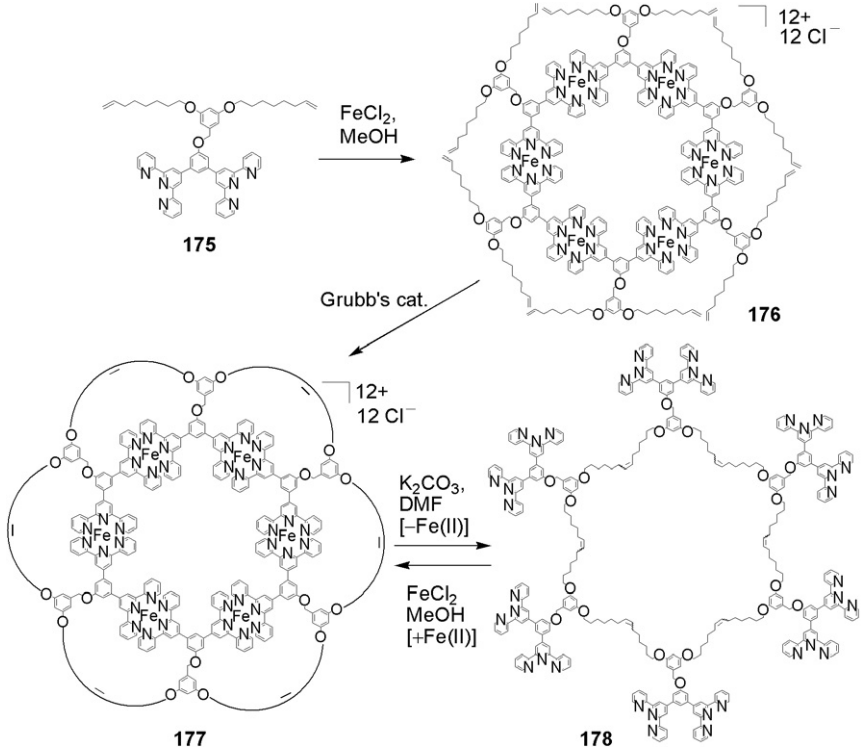


Scheme 43

separation in the *bis*terpyridine building blocks. Construction of the building blocks was effected by coupling terpyridine precursors either with themselves or with the appropriate spacer moiety. Thus, *bis*terpyridine **167** was prepared by treatment of 4′-(3-bromophenyl)-2,2′:6′,2″terpyridine [obtained

by the reaction of the commercially available 3-bromobenzaldehyde with 2-acetylpyridine under basic conditions, followed by the addition of excess NH_4OAc in HOAc (07JCD626)] with *bis*(pinacolato)diboron employing a [$Pd(dppf)_2Cl_2$]-catalyzed coupling (95CR2457). Similar Pd-promoted couplings using the corresponding ethynyl-substituted terpyridine, boron pincolate esters, and aryl alkynes generated the elongated *bis*terpyridine monomers **168**–**170**. Reaction of each monomer with $FeCl_2$, followed by NH_4PF_6 counter ion exchange, gave the desired family of hexamers **171**–**174**. Solubility of the series generally increased as spacer length increased; however, the *bis*terpyridine obtained by coupling of the ethynyl-substituted terpyridine with 1,4-diiodobenzene (i.e. the alkyne-modified homolog of **169**) exhibited poor solubility thereby prompting the synthesis of the alkoxy-modified terpyridine **169** for use in metallocycle construction.

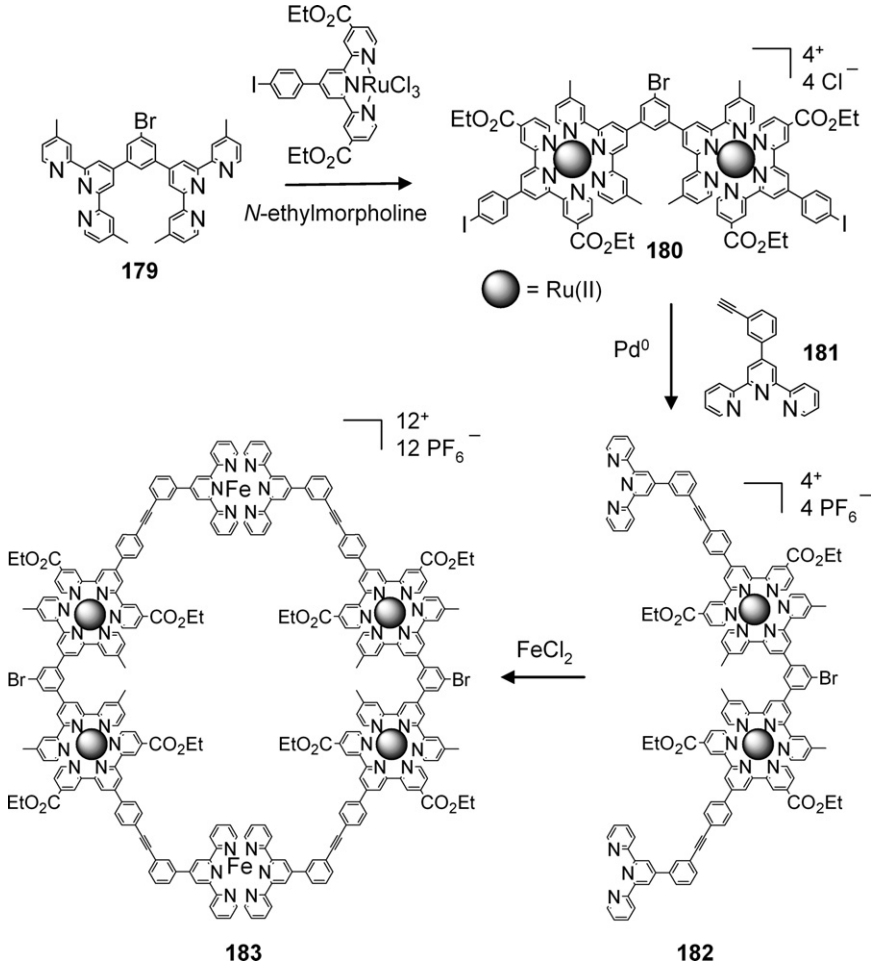
Newkome et al. (05AGE1679) have described a reversible, assembly–disassembly procedure using a *hexa*metallomacrocycle containing twelve terpyridine groups enclosed within a 114-membered macrocyclic structure (Scheme 44). Self-assembly of a *bis*alkene-modified *bis*terpyridine monomer **175** with $FeCl_2$ gave the Fe-based hexamer with peripheral



Scheme 44

alkene groups **176** that were readily connected by use of the Grubb's catalyst to give an imbedded metallocycle **177**. Treatment with base (K_2CO_3, DMF) quantitatively displaced the metal centers to afford a cyclic array of bound *bis*terpyridine ligands **178**. In the presence of more $FeCl_2$, the hexameric motif was readily regenerated. Proof-of-structure included reduction of the alkene moieties and also Pd-mediated hydrogenation of the benzyl ether groups to recover the starting *bis*terpyridine ligands.

Eryazici and Newkome (09NJC345) have reported the synthesis of substituted *bis*terpyridine-building blocks based on a two-step Kröhnke (76S1) procedure. This has allowed the construction of Fe(II)–Ru(II) hexamers (Scheme 45) with terpyridine-based substitution. For



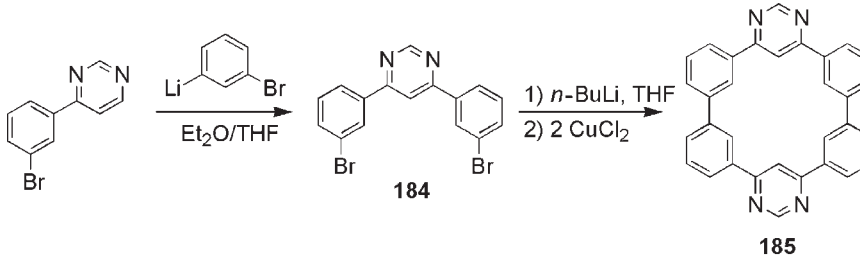
Scheme 45

example, treatment of bromoterpyridine **179** with an iodomonoterpyridineRu(III) adduct gave the diiodo*bis*Ru(II) complex **180**. Pd-promoted coupling of the alkyne-modified terpyridine **181** generated the free ligand intermediate **182** that when treated with $FeCl_2$ gave the desired macrocycle **183.**

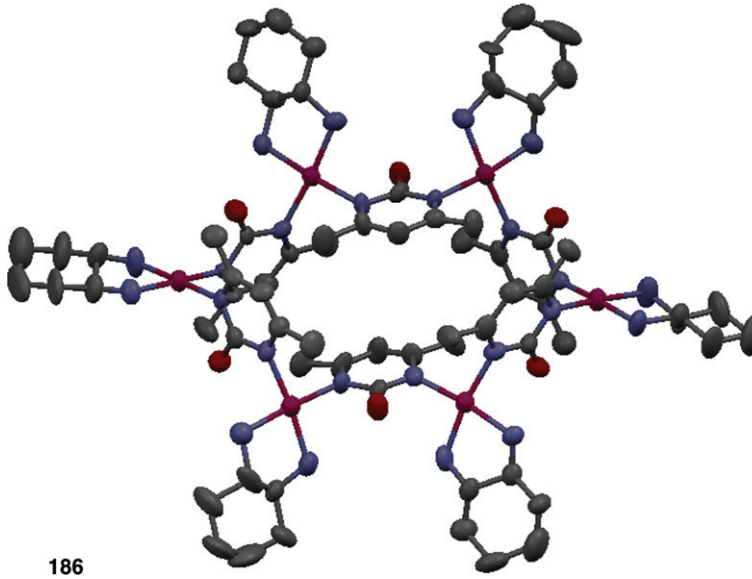
3.2 Pyrimidine

A hexameric macrocycle containing two pyrimidine units has been reported by Kauffmann et al. (75AGE714), where the lone pairs of the pyrimidine ligands are directed toward the periphery of the macrocycle. The macrocycle is aromatic and was synthesized in a two-step reaction (Scheme 46), where 4-(3-bromophenyl)pyrimidine was reacted with (3-bromophenyl) lithium forming **184**, followed by a homocoupling in the presence of $CuCl_2$ to afford **185**.

Examples of cyclic hexamers containing pyrimidine-type ligands have been found in the literature (05JSSC2436), such as with 2-pymoH (2-hydroxypyrimidine) or 2-dmpymoH (4,6-dimethyl-2-hydroxypyridine). Reaction of metals such as Ag and Cu with these ligands formed a combination of macrocycles and 1D polymers. Sironi et al. (97IC5648) showed that addition of Et_3N to a water MeCN solution of $AgNO_3$ and 2-pymoH afforded the cyclic hexamer $[Ag(2\text{-pymo})]_6$. If the same reaction is conducted in water, $[Ag(2\text{-pymo})]_n$ is formed, which can be converted to the more thermodynamically stable cyclic hexamer by heating above 150°C or by suspension at room temperature in anhydrous $HC(OEt)_3$ for 12 h. A similar example was also reported (98AGE3366) where $[Cu(MeCN)_4](BF_4)$ and NEt_3 were reacted to form a microcrystalline precipitate, composed of cyclic hexamers and helical polymers as revealed by crystal structure determination, suggesting a low energy barrier between the two products. Finally, an example of an enantiomeric pure hexamer was reported by Lippert et al. (03CEJ4414) $[(R,R\text{-}/S,S\text{-dach})Pd(2\text{-dmpymo})_6]_6(NO_3)_6$ (**186**) (dach = 1,2-diaminohexane). The self-assembly reaction of *cis*-$[(dach)Pd(H_2O)_2]^{2+}$ and 2-Hdmpymoh in an aqueous solution, followed by concentration of the reaction



Scheme 46



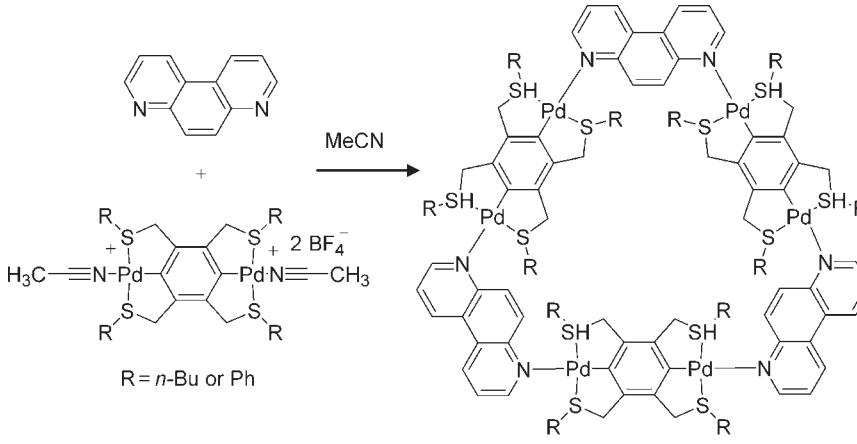
186

Figure 10 X-ray crystal structure of **186** (03CEJ4414) (reproduced by permission from Wiley-VCH).

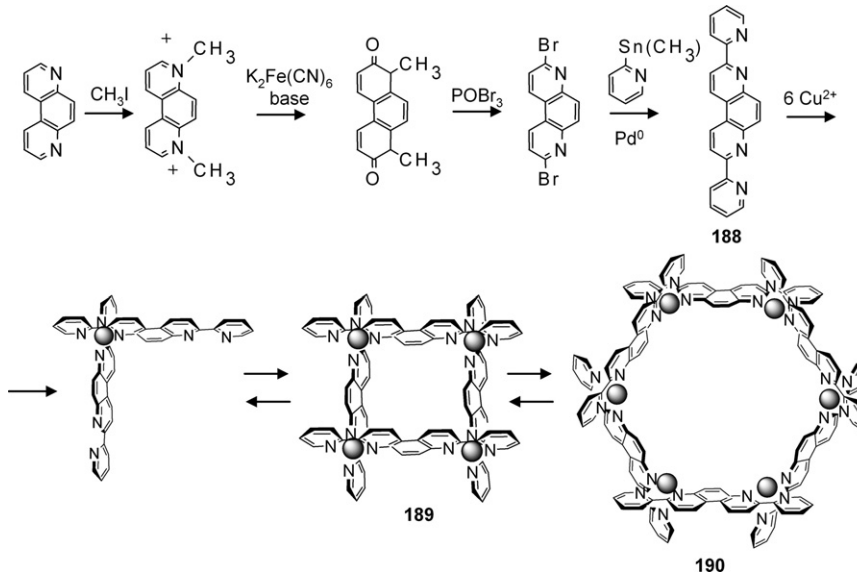
medium by 1/3 afforded, after 7 days, crystals of the cyclic tetramer [(*R*,*R*-/*S*,*S*-dach)Pd(2-dmpymo)$_6$]$_4$(NO$_3$)$_6$. Following the same synthetic procedure, but without concentration, crystals of the cyclic hexamer **186** were isolated after 4 days. The crystal structure (Figure 10) revealed that the Pd binding occurs at the N1 and N3 donor atoms of the pyrimidine ring, where the six Pd centers lie on a plane, and the pyrimidine rings are not coplanar with the Pd$_6$ plane but exhibit a 1,3,5-alternating arrangement.

3.3 Phenanthroline

Loeb et al. (98AGE121) employed commercially available 4,7-phenanthroline, as a bridging ligand, for the construction of a 6-sided, hexaPd macrocycle (Scheme 47). Two hexameric complexes (**187a** and **187b**) were prepared using the *bis*palladium adducts of either 1,2,4,5-tetra*kis*(*n*-butylthiomethyl)benzene or 1,2,4,5-tetra*kis*(phenylthiomethyl)benzene for self-assembly with the phenanthroline ligand. The BF_4^- salts of these materials were isolated as stable, yellow, microcrystalline solids, whose solubility was dependent on the R groups bound to the sulfur centers. The X-ray structure of the *n*-butyl derivative revealed a hexameric structure with a cavity of *ca.* 12 Å in diameter.



Scheme 47



Scheme 48

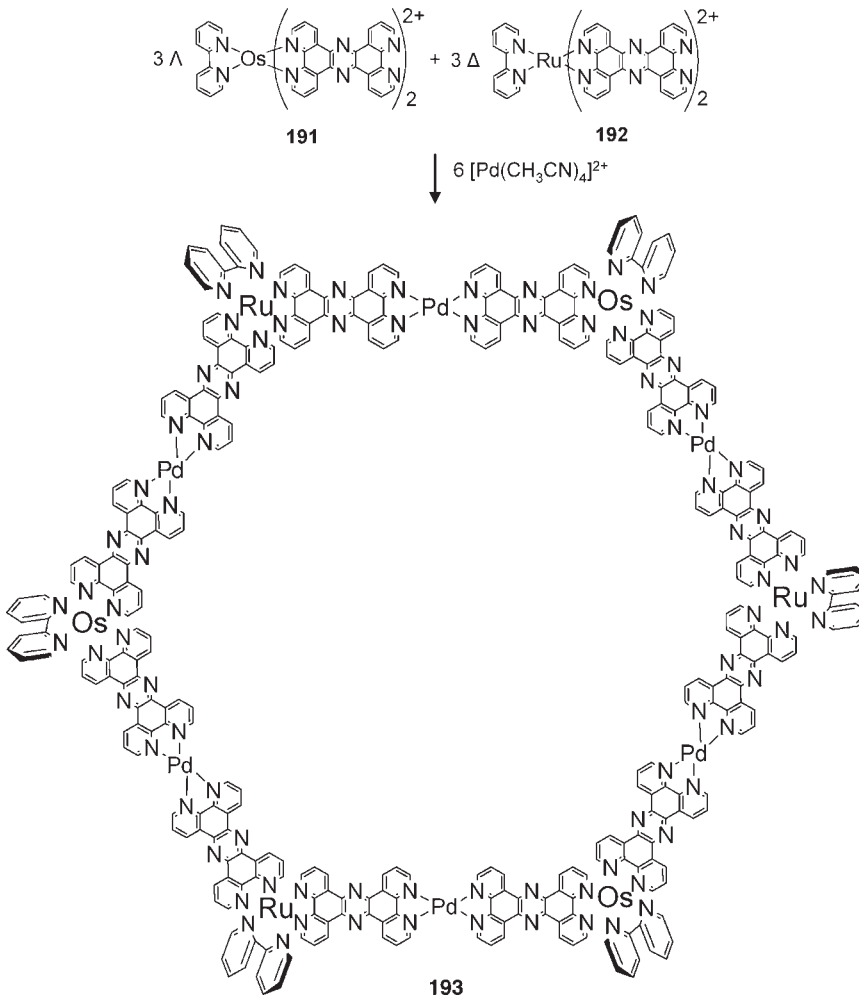
Lehn et al. (00CEJ4140) also described the self-assembly of rigid *bis*(bipyridine) ligands to form hexameric metallocyclophanes (Scheme 48). The key ligand 3,8-*bis*(2-pyridyl)-4,7-phenanthroline **188** was accessed by *N*-methylation of phenanthroline (MeI), Fe-promoted oxidation [aqueous

$K_2Fe(CN)_6$, base], concomitant demethylation and bromination ($POBr_3$), and finally $Pd(PPh_3)_4$ mediated coupling of trimethyltinpyridine. Addition of Cu (II) ions to an MeCN solution of the ditopic ligand **188** gave the hexameric cyclophane **190** that exists in equilibrium with the tetrameric species **189**. Formation of the tetrameric and hexameric species was observed to occur in the [Cu(II)] concentration range of $3.2 \times 10^{-4} - 3.2 \times 10^{-5}$ mol dm^{-3} as evidenced by electrospray mass spectrometry (ES–MS). Notably, the tetramer was favored by lower metal ion concentration and the hexamer favored by higher concentration.

MacDonnell and Ali have described (00JA11527) the construction of mixed-metal hexamers with diameters of 5.5 nm using the elongated bipyridine-based, building block tetrapyrido[3,2-*a*:2′,3′-*c*:3″,2″-*h*:2‴,3‴-*j*] phenazine (tpphz). The stereochemistry of the Λ-$[(bpy)Ru(tpphz)_2]^{2+}$ and Δ-$[(bpy)Os(tpphz)_2]^{2+}$ precursors directed macrocycle ring formation and facilitated the topospecific incorporation of different metals within the hexagon (Scheme 49). Thus, reaction of enantiomeric monomers **191** and **192** with $(MeCN)_4Pd^{II}$ afforded the cyclic hexagonal architecture **193** comprised of alternating Ru(II) and Os(II) metal vertices. A requirement of the planar self-organization of these building blocks is the alternating incorporation of the opposite chirality, as verified and supported by molecular modeling and temperature dependent ^{1}H NMR studies.

3.4 Oligosaccharides

Cyclodextrins, cyclic oligosaccharides made of α-(1→4)-linked *D*-glucopyranose units, are of interest for synthetic chemists from a number of perspectives, including their chemical stability, potential for regioselective modification, and readily availability (94AGE803). Cyclodextrins were first isolated in 1891 by Villiers as degradation products from starch (91CR536), where the cyclodextrin glycosyl transferases (CGTases) enzyme essentially could detach a section of the starch helix and close the two ends of the fragment to form a cyclic molecule (80AGE344). However, CGTases are generally, nonspecific with respect to the fragment ring size, therefore the enzymatic degradation of starch affords a mixture of cyclic and linear maltooligosaccharides. Isolation of a particular cyclodextrin was performed by the addition of selective precipitation agents, which in the case of the hexameric α-cyclodextrin (**194**, α referring to 6 glucose units), included the addition of 1-decanol to afford the macrocycle in 40% yield (94AGE803). Modified synthesis of these ring structures have also been reported (87CAR277) where α-cyclodextrin (**194**) could also be obtained in 0.3% overall yield in 21 steps starting from maltose. Cyclodextrins have been chemically modified in order to change their solubility or in the early literature for purification purposes, as well as for specific applications (80AGE344). Several examples of completely

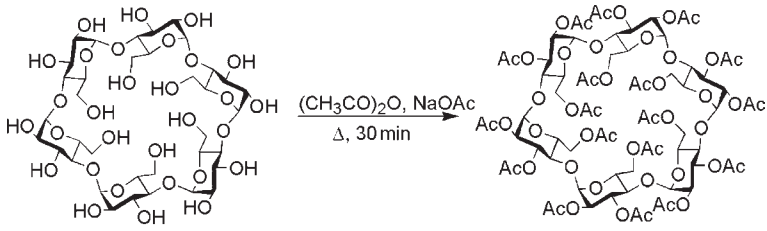


193

Scheme 49

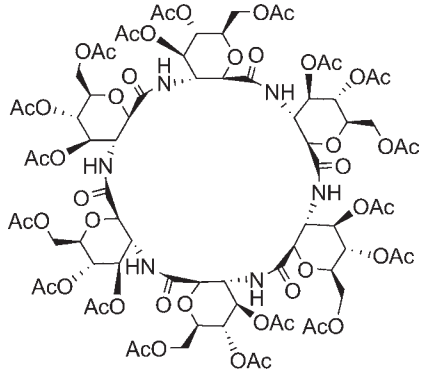
substituted α-cyclodextrins have been reported (83T1417), these include acylated, alkylated, nitrated, silated, boronated, and aminated. Scheme 50 shows the direct acetylation of **194** to afford **195** (49JA353).

Also of interest is the novel cyclic hexa-β-peptide **196** composed of acetylated glycosamino acid (GA). In solution, conformational changes from C_3 to C_6 symmetric structure upon elevation of temperature have been reported (07BPY150). The cyclic hexamer formed rod-shaped crystals with a C_6 symmetric conformation that when examined using electron diffraction analysis demonstrating that the macrocycles stack to form nanotubes.



194 195

Scheme 50



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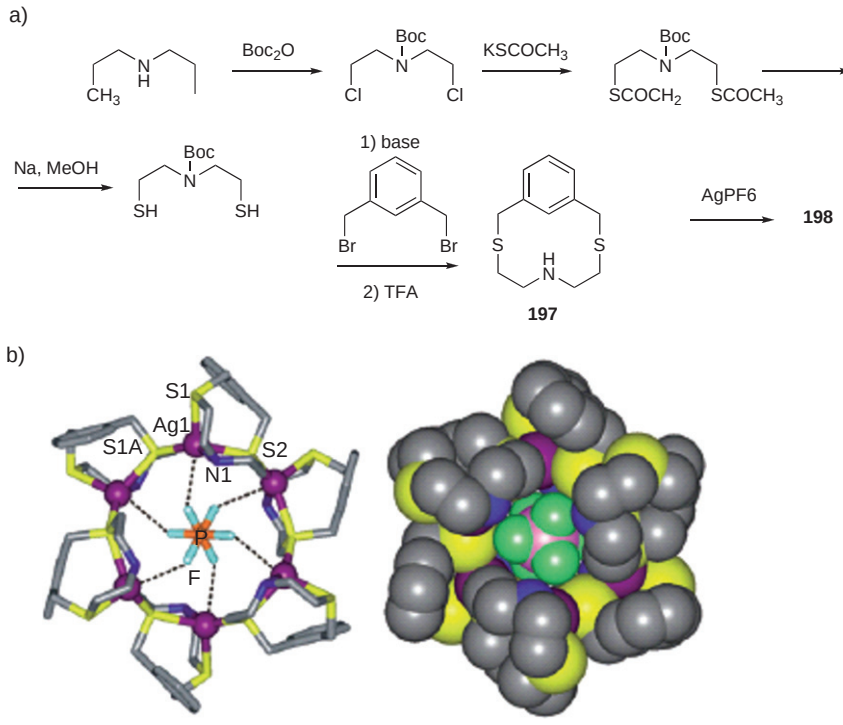
4. MISCELLANEOUS HETEROCYCLIC MATERIALS

4.1 Flexible rings

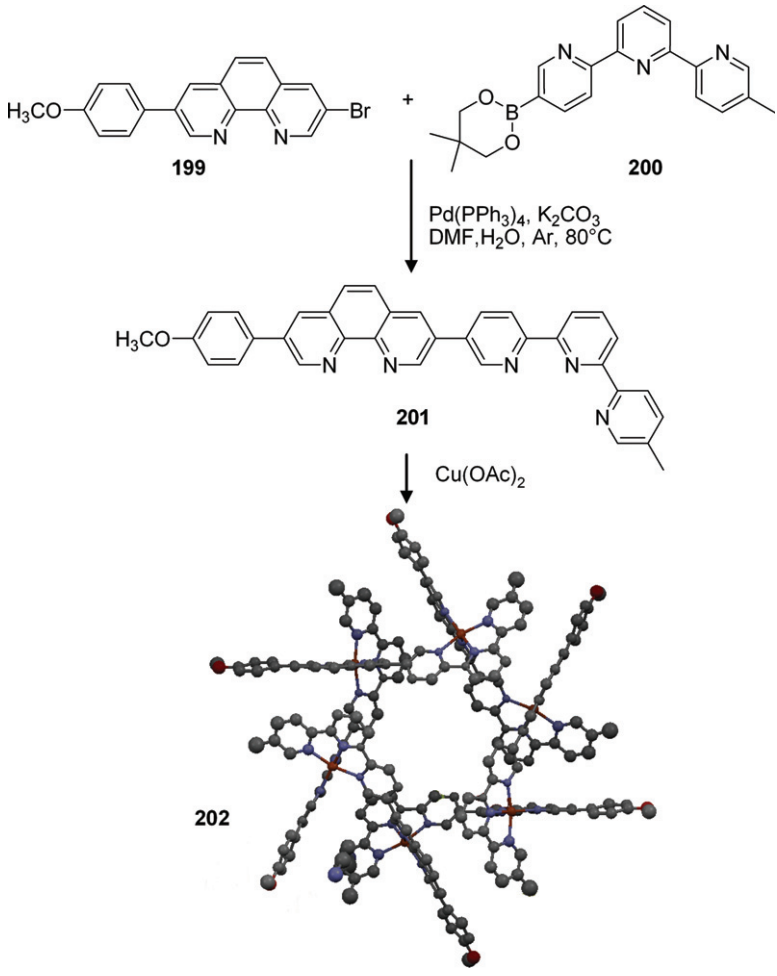
Interest in the structural topologies of metal-organic hybrids as well as in their potential properties led Lee et al. (09CENC43) to construct the flower-shaped cyclic hexameric structure of $[Ag_6(\mathbf{197})_6(PF_6)](PF_6)_5$ (**198**), by the reaction of $AgPF_6$ with the exodentate dithiamacrocycle ligand (**197**) (87JA4328, 92IC203, 00JCA652). Coupling of *N*-Boc-protected dithiol (00JCS(P1)3444) with 1,2-di(bromomethyl)benzene, followed by deprotection of the amine from the macrocycle (Scheme 51a; X-ray crystal structure of **198** (2009CEN43), reproduced by permission from Royal Society of Chemistry) generated the ligand **197**. The crystal structure (Scheme 51b) revealed a flower-shaped cyclic hexamer, formed possibly due to the flexibility of the ligand as well as the stabilization provided by the anion.



Scheme 51

4.2 Terpyridine and phenanthroline

The heteroditopic ligand **201** composed of terpyridine and phenanthroline subunits has been reported by Coronado et al. (08IC5197). The synthesis of **201** (Scheme 52; X-ray crystal structure of **202** (2008IC5197), reproduced by permission from American Chemical Society) relied on the pivotal cross-coupling of 5-(neophenyl glycolatoboron)-5''-methyl-2,2':6',2''-terpyridine (**199**) to 3-bromo-8-(*p*-anisyl)-1,10-phenanthroline (**200**) with $Pd(PPh_3)_4$ in the presence of K_2CO_3 to afford the unique *bis*ligand **201**. Self-assembly with $Cu(OAc)_2$ in MeOH, after recrystallization from MeCN, gave $[Cu_6(\mathbf{201})_6(PF_6)_6](PF_6)_6$ (**202**) as green crystals. The X-ray crystal structure (Figure 11) revealed the cation $[Cu_6(\mathbf{201})_6(PF_6)_6]^{6+}$, where each Cu is coordinated to both a terpyridine and a phenanthroline unit of a different ligand with weakly bound PF_6^- ions completing the octahedral coordination spheres.



Scheme 52

4.3 Five- and six-membered

In 1999, Tuchagues et al. (99IC1165) reported the synthesis and crystal structure (Scheme 53) of the self-assembled macrocycle $[Cu_6(L)_6]^{6+}$ (**204**) (where $L = N$-(2-phenylimidazol-4-ylmethylidene)-2-aminoethylpyridine). The critical tridentate ligand, which was not isolated, was prepared by the addition of 2-aminoethylpyridine to 2-phenyl-4-formylimidazole in MeOH; the mixture was then heated for 1h. After preparation of the mononuclear Cu(II) complex **203**, by reaction with $CuCl_2{\cdot}2H_2O$, addition of triethylamine to a H_2O–MeOH solution of **203** generated further

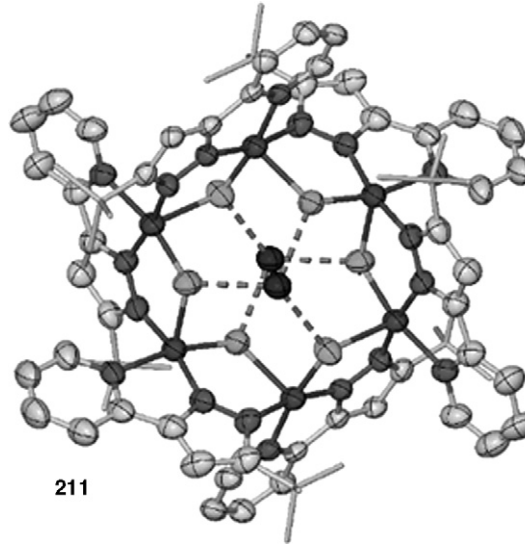
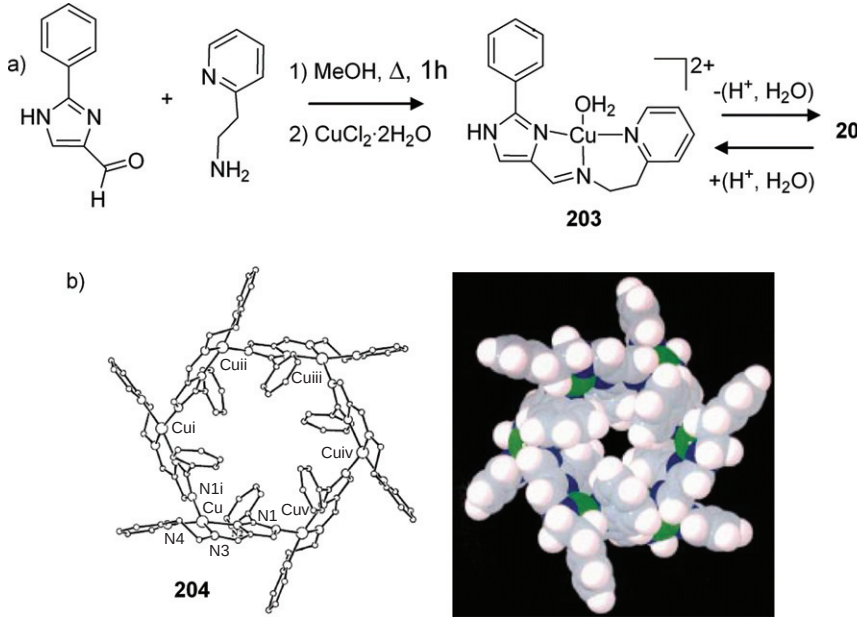


Figure 11 X-ray crystal structure of **211** (07AGE4073) (reproduced by permission from Wiley-VCH).

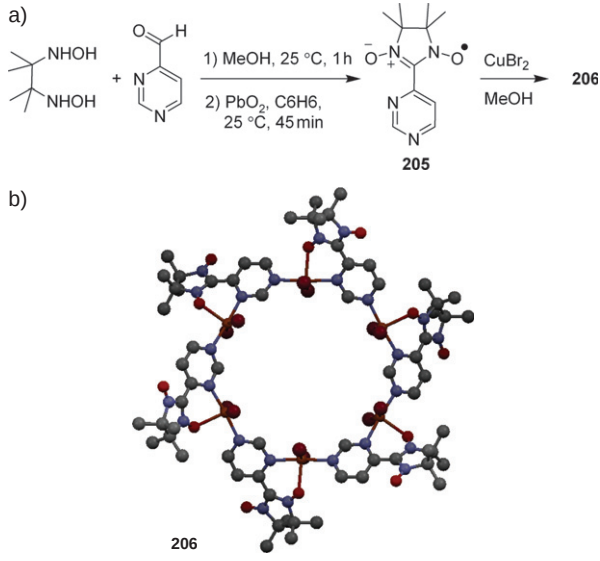


Scheme 53

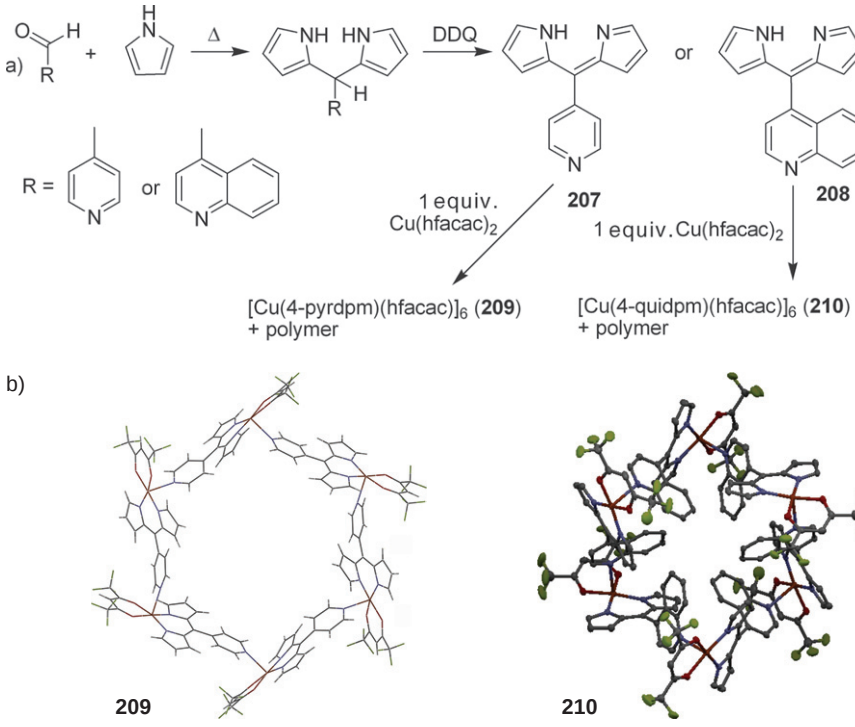
coordination involving the uncomplexed imidazolate nitrogens, to yield the cyclic construct **204**. The crystal structure revealed that each Cu(II) ion was coordinated by three N-donor of the tridentate ligand and an adjacent imidazolate nitrogen. This is a good example of the inherent stability of the hexameric architecture.

Nogami et al. reported (01IC3954) the discrete hexanuclear complex $[CuX_2(4PMNN)]_6$ (**206**) (X = Br, Cl) containing six Cu(II) ions and six 4-pyrimidinyl nitronyl nitroxide (4PMNN, **205**) units. Synthesis of the bridging ligand **205** was achieved starting with 4-pyrimidinecarboxaldehyde, which was converted to the nitronyl nitroxide group by Ullman's method of treatment with 2,3-*bis*(hydroxylamino)-2,3-dimethylbutane (72JA7049) (Scheme 54a; X-ray crystal structure of **206** (2001IC3954), reproduced by permission from American Chemical Society). A mixture of **205** with $CuBr_2$ at room temperature gave, after a week, dark green crystals of the hexamer **206** where each pyrimidine bridges two copper ions, shaping a nanoscale cavity (Scheme 54b). Molecular arrangement in the crystal along the *c*-axis resembled a honeycomb-like channel structure.

Cohen et al. reported (04AGE2385, 05IC4139) two different macrocycles $[Cu(4\text{-pyrdpm})(hfacac)]_6$ (**209**) and $[Cu(4\text{-quidpm})(hfacac)]_6$ (**210**) [where 4-pyrdpm = 5-(4-pyridyl)dipyrromethene and 4-quidpm 5-(4-quinolyl)dipyrromethene] composed of copper with dipyrromethene (dipyrrin) ligands. The reaction of the oxidized ligand with Cu $(hfacac)_2$ afforded **209** and **210**. Ligand synthesis (Scheme 55a; X-ray



Scheme 54



Scheme 55

crystal structure of **209** (2004AGE2385), reproduced by permission from Wiley-VCH) started with the condensation of 4-pyridinecarboxaldehyde or 4-quinolinecarboxaldehyde with pyrrole, followed by oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) to give the heteroditotic ligands 4-pyrdpm **207** and 4-quidpm **208**, respectively. Addition of 1 equivalent of $Cu(hfacac)_2 \cdot H_2O$ (hfacac = hexafluoroacetononate) to the oxidized ligand *in situ* produced the heteroleptic complexes [Cu(4-pyrdm)(hfacac)] and [Cu(4-quindpm)(hfacac)], which were isolated by flash chromatography in modest yield. Crystallization of these complexes revealed surprising structures; each complex self-assembled in two distinct supramolecular motifs: a discrete hexameric ring (**209** and **210**, Scheme 55b; X-ray crystal structure of **210** (2005IC4139), reproduced by permission from American Chemical Society) and a double-helical coordination polymer in the same crystalline lattice. Comparing both, the former has Cu(II) centers in the six-membered rings that are essentially coplanar; while the latter, possesses Cu(II) ions exhibit a cyclohexane-like "chair" conformation.

Halcrow et al. reported (07AGE4073) the synthesis of a fluoro hexameric metallocrown by the reaction of CuF_2 with one equivalent of

3{5}-(pyridin-2-yl)-5-(*tert*-butyl)pyrazole (HL) (03JA10800) and nBu$_4$NOH in MeOH. Evaporation of the solvent and recrystallization afforded [{Cu(μ-F)(HL)}$_6$(H$_2$O)$_2$]·8CH$_2$Cl$_2$ (**211**). Analogous reactions using NaOH or KOH afforded the crystal of **211**, where the crystal structure (Figure 11) shows the same structure as **204**, but with two water molecules complexed by six F donors. Ammonium, alkylammonium and amino acid complexes have also been reported (08CEJ223).

4.4 Nucleobases, nucleosides, and nucleotides

Some cyclic polynuclear metal complexes that include nucleobases have been synthesized, based on self-assembly. Labib et al. reported (88AGE1160) the hexanuclear metallomacrocycle incorporating six d^8 platinum centers and six anions of the pharmacologically active purine base theophylline (Hthp). Reaction of [Me$_3$Pt(H$_2$O)$_3$]$_2$(SO$_4$) and the potassium salt of theophylline in hot water afforded after recrystallization [Me$_3$Pt(thp)]$_6$·12CHCl$_3$ (**212**) in 50% yield. The crystal structure (Figure 12a) revealed an hexameric heterocycle with S$_6$ symmetry, where the Me$_3$Pt moieties are coordinated in a *cis*-fashion by N7 and N9 or neighboring purine ligands.

A hexanuclear platinum complex *cis*-[(PMe$_3$)$_2$Pt(9-MeGu(-H))]$_6$(NO$_3$)$_6$ (**213**) formed with the nucleobase 9-methylguanine [9-MeGu(-H)] was reported by Valle et al. (95IC1745). Synthesis was started by the reaction of the ligand with *cis*-[(PMe$_3$)$_2$Pt(μ-OH)]$_2$(NO$_3$)$_2$

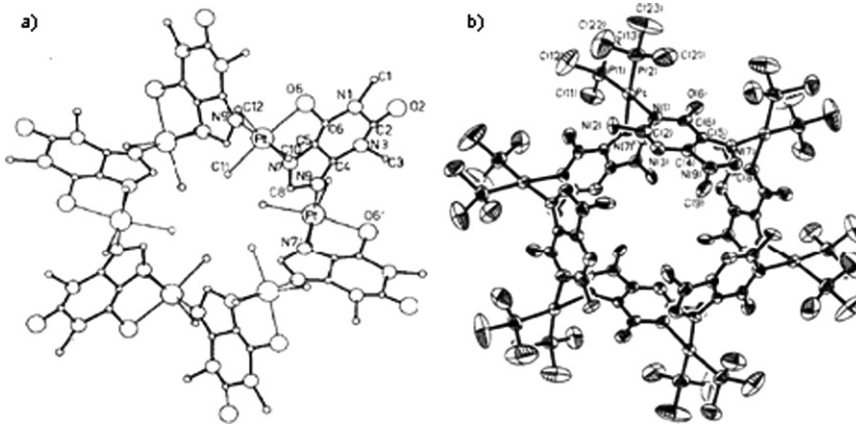
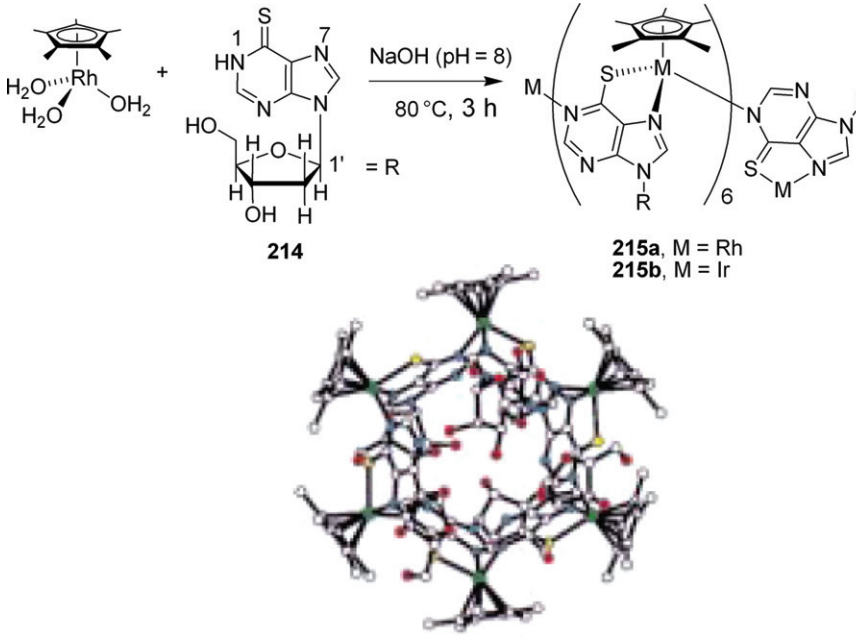


Figure 12 (a) X-ray crystal structure of **212** (88AGE1160) (reproduced by permission from Wiley-VCH) and (b) X-ray crystal structure of **213** (95IC1745) (reproduced by permission from American Chemical Society).

in H_2O at room temperature for 2 h. Concentration of the solution by warming at 60°C for a few minutes, afforded crystals (**213**, Figure 12b) that revealed an hexameric motif with S_3 symmetry where the 9-methylguanines were located alternately above- and below-the-plane of the six Pt(II) centers.

Arakawa et al. reported (01AGE2268) the cyclic hexamer $[Cp^*Rh(6\text{-Putrb-N1;N7,S6})]_6(CF_3SO_3)_6$ (**215**) with the ligand 6-purinethione ribose (6-putrb), which has a similar ligand skeleton as adenosine, except that the NH_2 group in the 6-position is substituted by a thione group. Self-assembly of $[M(Cp^*)(H_2O)_3]^{2+}$ < M = Rh and Ir, isolated from $[\{M(Cp^*)Cl_2\}_2]$ (92IC1745) with $Ag(CF_3SO_3)$ in H_2O> and **214** in H_2O gave $[\{Rh(putrb)(Cp^*)\}_6](CF_3SO_3)_6$ (**215a**) and $[\{Ir(putrb)(Cp^*)\}_6](CF_3SO_3)_6$ (**215b**) in high yield (Scheme 56a; X-ray crystal structure of 215 (2001AGE2268), reproduced by permission from Wiley-VCH). The crystal structure of **215** (Scheme 56b) revealed a cyclic hexanuclear structure, where the ligand coordinates one Rh(III) ion in a bidentate manner [S and N(7) donors] and bridges to another Rh(III) ion through the N(1) donor.

A nucleotide based architecture has been reported by Dalhymple et al. (07IC9945), where the formation of a host complex $[Pd(II)(en)(5'\text{-GMP})]_4$ (5′-GMP = guanosine 5′-monophosphate) was described. Addition of small molecules containing hydrophobic groups resulted in the



Scheme 56

expansion of the tetramer to a cyclic hexamer $[Pd(II)(en)(5'\text{-GMP})]_6$ with an estimated cavity size of 5.2 Å.

5. CONCLUSIONS

The use of heterocyclic species such as furan, pyrrole, thiophene, pyridine, etc., for the preparation of stable, hexameric (macro)molecular architectures has been demonstrated as a logical pathway to functional materials. This is based, in part, on the mature chemistry and ready availability of these versatile building blocks. Step-wise procedures and self-assembly protocols combined with ingenuity and creativity have led to the crafting of architecturally controlled species such as Stang's metal-directed metallocycles, Schlüter's bipyridine phenylacetylenes, Lehn's self-assembling helicates, and Newkome's bisterpyridine-based constructs, to mention but a few. It is clear that the quest for new, utilitarian materials will continue to benefit from the heterocyclic arena.

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CHAPTER 2

Metal-Catalyzed Intramolecular Heteroatom (X) ⟶ Carbon (C) Functional Group Migration Reactions Involving Additions of X–Y Bonds Across Alkynes

Nitin T. Patil,[a] **Rahul D. Kavthe**[a] and **Yoshinori Yamamoto**[b]

Contents

1. INTRODUCTION

In the last two decades many carbon–carbon and carbon–heteroatom bond-forming reactions have evolved as powerful tools in synthetic organic chemistry. Among them, transition metal-catalyzed cyclization

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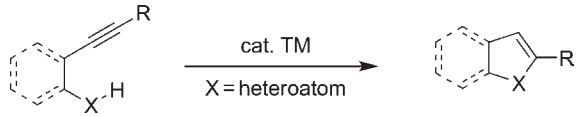
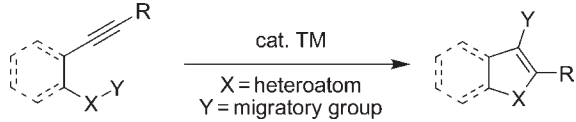


Scheme 1 Addition of X–H bonds across alkynes.



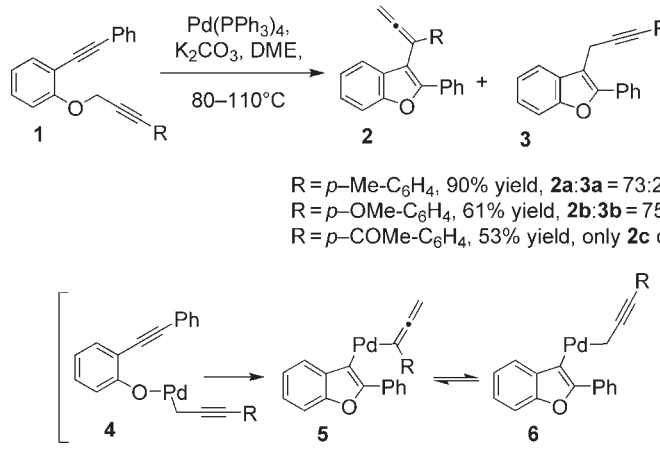
Scheme 2 Cyclizative functional group migration.

reactions are amongst the most valuable (98MI1, 99MI1, 00CRV2963, 00MI1, 04CRV2127, 04CRV2285, 04CRV2199, 04CRV2239, 04CRV3079, 06MI91). A variety of multiply substituted carbocycles and heterocycles can be obtained by these processes. These reactions are very interesting due not only to their ability to construct complex molecules from readily accessible starting materials but also to the fact that they can be carried out under mild conditions and, in some cases, with high atom economy (91SCI1471, 95AGE259, 00PAC1233).

Transition metal-catalyzed annulation of alkynes bearing heteroatoms such as nitrogen, oxygen, and sulfur produces N (88TL1799, 89JOC5856, 89TL2581, 94JOM289, 97TL7687, 98Tl5159, 01JOM149, 02TL1277, 04JOC1126, 04OL1527, 04S610, 05JOC2265, 05OL5437, 05T10958, 06OL3995, 07AGE2074, 07OL627, 07SL1775, 08JOC4160, 09TL2943), O (98TL3017, 99TL431, 00EJO1019, 00JCS775, 03JA15006, 05CEJ5735, 05OL3299, 05OL5409, 06JA3112, 07JOC8559, 07TL1439, 08JOC1620), and S (06AGE1897) containing heterocycles, respectively (Scheme 1). Recently, transition metal-catalyzed cyclizations of alkynes bearing X–Y (X = heteroatom; Y = migratory group) functionality in the proximity have been reported (Scheme 2). The migratory group includes allyl, propargyl, acyl, (α-alkoxy alkyl), (*p*-methoxyphenyl)methyl, etc. These reactions are not only mechanistically new but they also are very important from the synthetic point of view. In this review, we highlight such X → C functional group migration reactions.

2. SYNTHESIS OF *O*-CONTAINING HETEROCYCLES

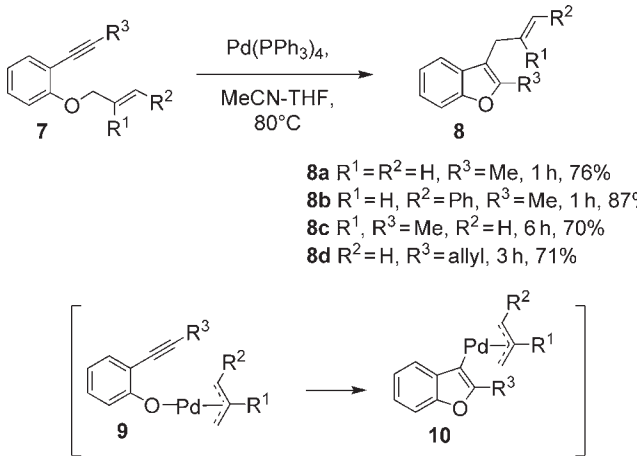
In 1998, Cacchi and coworkers reported the cyclization of propargylic *o*-(alkynyl)phenyl ethers **1** promoted by organopalladium complexes (Scheme 3) (98TL5101, 99JOM42, 02EJO2671). The reaction of *o*-(alkynyl)



Scheme 3 Palladium-catalyzed cyclization of propargylic *o*-(alkynyl)phenyl ethers.

phenyl ethers **1** in the presence of $Pd(PPh_3)_4$ and K_2CO_3 afforded a mixture of 2-substituted-3-allenylbenzo[b]furans **2** and 2-substituted-3-propargylbenzo[b]furans **3** in good yields. When the aromatic ring of **1** contains an electron-withdrawing group such as $COCH_3$, 2-substituted-3-allenylbenzo[b]furans **2** was obtained exclusively. The presence of a substituent on the terminal acetylenic carbon of the propargylic fragment has been found to be mandatory. Mechanistically, Pd(0) adds oxidatively across the C–O bond to form intermediates **4** that can be converted into either **5** or **6** depending on the nature of the R group. Later this approach was extended to the synthesis of 3-allylbenzofurans (98SL741). A seminal work by Balme et al. showed that *o*-alkynylallyloxybenzenes **7** could also undergo an intramolecular carbo-alkoxylation (07SL1994) reaction which is useful for the synthesis of 2-substituted 3-allylbenzo[b]furans **8** (Scheme 4) (98SL746, 03S2115).

In 2000, Fürstner and coworkers reported a platinum-catalyzed intramolecular carbo-alkoxylation reaction of substrates of type **11** (Table 1) (00JA6785), (01JA11863). Various tetrahydrofuran derivatives **12** were obtained in good to high yields. The coordination of $PtCl_2$ to the alkyne (cf. **13**) has been reported to trigger a cascade comprising a 1,4-addition of the ether oxygen onto the complexed alkyne and simultaneous release of an allyl cation as shown in **14**. Union of the allyl cation with the organoplatinum intermediate then leads to product. They carried out a crossover experiment to gain insight: Does the allyl group migrate inter- or intramolecularly? The outcome indicated that no products derived from a crossover of the allyl group were found, thus strongly suggesting an intramolecular delivery of the allyl moieties. This is the first example of an intramolecular carbo-alkoxylation reaction involving an alkyl chain between the alkyne moiety and the heteroatom.

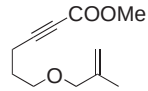
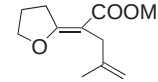
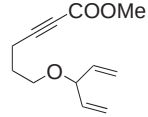
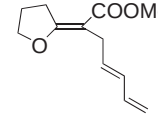
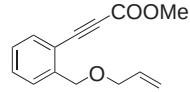
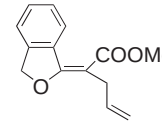
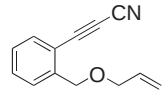
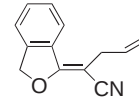
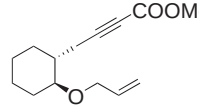
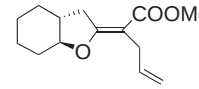
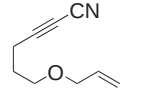
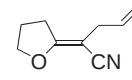
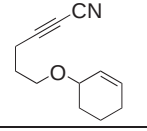
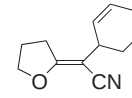


Scheme 4 Palladium-catalyzed cyclization of alkynylallyloxybenzenes.

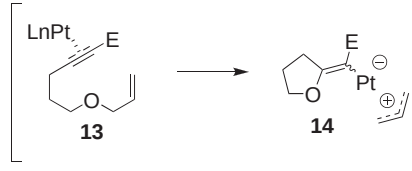
The Yamamoto group reported a $PtCl_2$-catalyzed cyclization reaction of *o*-alkynylphenyl acetals **15** in the presence of COD to give 3-(α-alkoxyalkyl)benzofurans **16** in good yields (Scheme 5) (05JA15022). Electronic and steric effects on the aromatic ring have an influence on the efficiency of this reaction. The use of an olefin as an additive proved to be necessary to facilitate migration. In the absence of an olefin additive such as COD, lower yields were obtained. It is striking to note that commercially available $PtCl_2$(cod) catalyst did not intervene in the reaction. Therefore, the existence of a platinum oligomer was proposed to be the real active species. Mechanistically, nucleophilic attack of the oxygen atom of the phenyl acetal moiety of **15** onto the $PtCl_2$ coordinated alkyne (cf. **17**) occurred to give cyclized intermediate **18** (Figure 1). Migration of the α-alkoxyalkyl group of **18** to the carbon bonded to the platinum atom produced intermediate **19**. Removal of the catalyst gave the desired products **16**. A successful application of this methodology has been demonstrated for the synthesis of the vibsanol (Scheme 6) (05JA15022), (07T8670). An appropriately designed substrate **20** underwent the carboalkoxylation reaction to form substituted furan **21** that on conventional structural manipulation gave vibsanol **22**.

A seminal work in Fürstner's laboratory disclosed the synthesis of C-3-substituted benzofuran **24** by a platinum-catalyzed intramolecular carbo-alkoxylation of **23** (Table 2) (05JA15024). They noticed the necessity of carbon monoxide, which may activate $PtCl_2$. A series of *o*-alkynyl phenols bearing allyl, Bn, PMB, or MOM-acetals underwent efficient carbo-alkoxylation reactions. This method is not limited only to phenolic substrates: in one example they showed the successful cyclization of

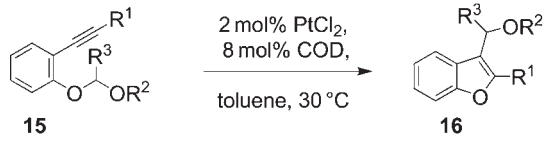
Table 1 Platinum-catalyzed intramolecular carboalkoxylation of alkynes

Entry	Substrate **11**	Product **12**	Yield (%)
1			59[a]
2			73[a]
3			71[b]
4			80[c]
5			56[a,d]
6			86[e]
7			65[e]

Reaction conditions: A reaction mixture was heated in toluene at 80 °C in the presence of 4–10 mol% of $PtCl_2$.
[a] pure (E)-isomer at the exocyclic double bond.
[b] E:Z = 2.4:1.
[c] E:Z = 1:7.9.
[d] With $PtCl_4$ instead of $PtCl_2$.
[e] Pure (Z)-isomer at the exocyclic double bond.



benzoic acid ester **25** to isochromones-1-one **26** (Scheme 7) (After completion of this review Pd-Au catalyzed synthesis of substituted butenolides and isocoumarin was reported) (09JA18022). The potential of this method



15 16

16a $R^1 = {}^n$Hex, R^2 = Et, R^3 = Me, 1 h, 91%
16b $R^1 = {}^t$Bu, R^2 = Et, R^3 = Me, 24 h, trace
16c R^1 = Ph, R^2 = TBS, R^3 = H, 96 h, 61%
16d R^1 = *p*-MeO–C_6H_4, R^2 = Et, R^3 = Me, 24 h, 90%
16e R^1 = *p*-CF_3–C_6H_4, R^2 = Et, R^3 = Me, 96 h, 61%

Scheme 5 Platinum-catalyzed intramolecular cyclization-acetal group transfer.

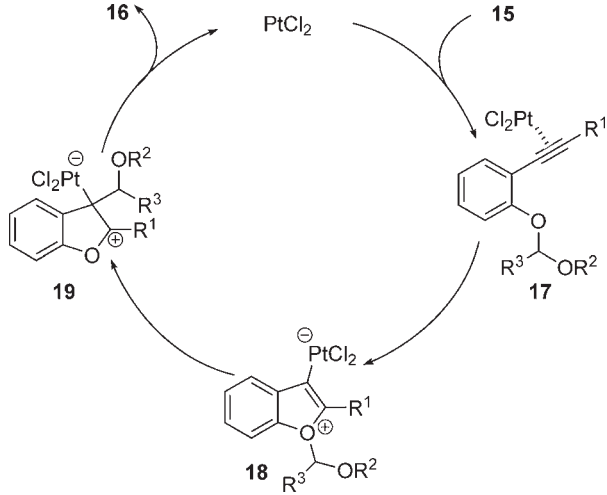
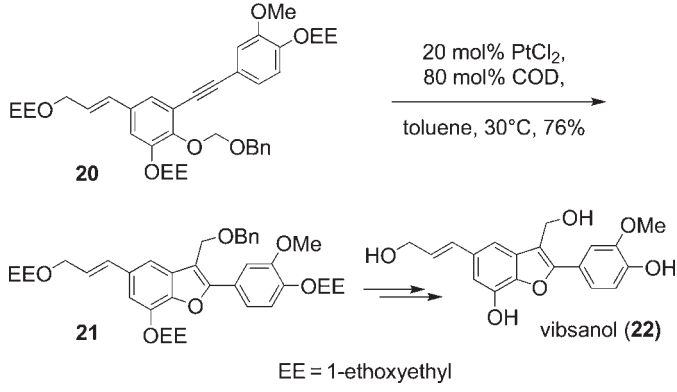


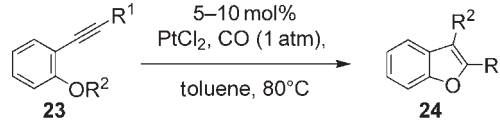
Figure 1 Mechanism for Platinum-catalyzed intramolecular cyclization-acetal group transfer.

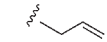
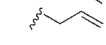
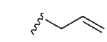
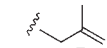
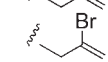


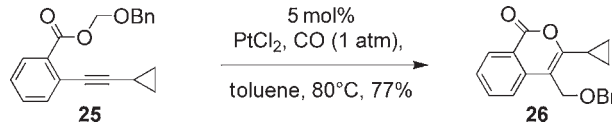
EE = 1-ethoxyethyl

Scheme 6 Synthesis of vibsanol.

Table 2 Platinum-catalyzed intramolecular carboalkoxylation of alkynes



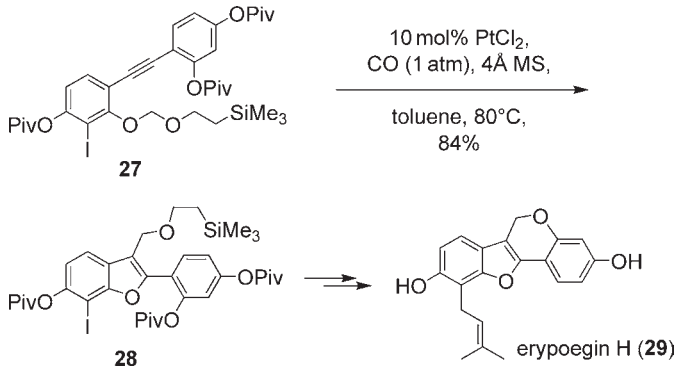
Entry	R^1	R^2	*t* (h)	Yield (%)
1	^{n}Pr		4	88
2	*m*-F_3C–C_6H_4		1	94
3	*m*-MeO–C_6H_4		1	98
4	^{n}Pent		12	73
5	^{n}Pent		5	54
6	^{n}Pent		3	68
7	^{n}Pent	–Bn	4	66
8	*m*-F_3C–C_6H_4	*p*-MeO–(C_6H_4)CH_2–	3	78
9	cyclopropyl	*p*-MeO–(C_6H_4)CH_2–	3	77
10	^{n}Pent	–CH_2OMe	2	91
11	*m*-F_3C–C_6H_4	–CH_2OMe	2	74
12	*m*-F_3C–C_6H_4	–CH_2OBn	0.5	84
13	–CH_2CH_2Ph	–$CH_2OCH_2CH_2SiMe_3$	0.5	81



Scheme 7 Platinum-catalyzed intramolecular carboalkoxylation of benzoate.

has been demonstrated in the synthesis of the natural product erypoegin H. Treatment of an appropriately substituted alkyne **27** with a catalytic amount of $PtCl_2$ under a CO atmosphere furnishes precursor **28** in 84% yield. The precursor **28** was converted into erypoegin H **29** after synthetic structural manipulations (Scheme 8) (07AGE4760).

The Pt(II)-catalyzed processes described by Yamamoto and Fürstner are clearly advantageous compared to Cachhi's palladium-catalyzed protocol. Cachhi's procedure is amenable only to *o*-alkynylphenols bearing an allyl group and is not useful to acetalic substrates as the Pd(0) species is unable to generate a catalytically competent component

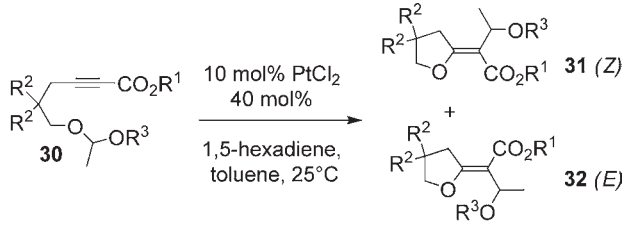


Scheme 8 Synthesis of erypoegin H.

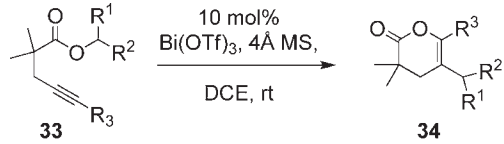
by oxidative addition. Moreover, bromo-substituents are tolerated under Pt(II) catalysis whereas they are not expected to be tolerated under Pd(0) catalysis.

Recently, Nakamura and coworkers reported the synthesis of substituted cyclic enol ethers **31** and **32** via the intramolecular carbo-alkoxylation of alkynes **30** using $PtCl_2$ catalyst in the presence of 1,5-hexadiene (Table 3) (08OL309). The reaction in the absence of 1,5-hexadiene did not proceed at all, and therefore they propose the presence of oligomeric platinum that could be obtained by the disconnection of Pt–Cl bonds in polymeric $PtCl_2$ by the olefin additive. The Z/E

Table 3 Synthesis of substituted cyclic enol ethers via platinum-catalyzed intramolecular carbo-alkoxylation of alkynes



Entry	R^1	R^2	R^3	*t* (h)	Yield (%)	Z/E
1	Cl_3CCH_2	Ph	Et	1.5	84	100:0
2	*p*-NO_2–C_6H_4	Ph	Et	3.5	83	96:4
3	Me	Ph	Et	4.5	54	31:69
4	*p*-MeO–C_6H_4	Ph	Et	24	32	0:100
5	Ph	Ph	Et	48	69	0:100
6	Cl_3CCH_2	Ph	^{i}Bu	3	88	100:0
7	Cl_3CCH_2	H	Et	1	75	78:22
8	Ph	$-(CH_2)_5-$	Et	43	56	0:100
9	Ph	H	Et	1	58	48:52



34a R^1 = Ph, R^2 = Me, R^3 = Ph, 3 h, 60%
34b R^1 = Ph, R^2 = Ph, R^3 = Ph, 7 h, 87%
34c R^1 = Ph, R^2 = Ph, R^3 = *m*-Me-C_6H_4, 2 h, 98%
34d R^1 = *m*-MeO-C_6H_4, R^2 = Me, R^3 = Ph, 1 h, 37%
34e R^1 = *p*-Cl-C_6H_4, R^2 = *p*-Cl-C_6H_4, R^3 = Ph, 3 h, 92%

Scheme 9 Bismuth-catalyzed carbo-oxycarbonylation of alkynes.

selectivity is dependant on the electronic property of the ester group; substrates having an electron-deficient ester group afforded *Z* isomers as major product, while those having a relatively electron-rich ester group gave *E* isomers.

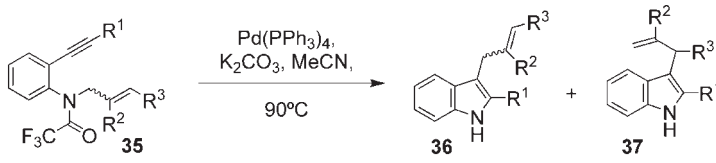
Later, Takaki et al. have shown that not only typical transition metal complexes but also borderline metal complexes have the ability to promote analogous reactions. They reported the synthesis of substituted lactones **34a–e** by a bismuth-catalyzed carbo-oxycarbonylation of alkynyl ester **33** (Scheme 9) (08OL5119). A crossover experiment showed that the reaction is intramolecular, and this observation is in agreement with the results reported by Fürstner et al. (01JA11863).

3. SYNTHESIS OF N-CONTAINING HETEROCYCLES

In 1998, Cacchi et al. reported the synthesis of C-3-substituted indoles via intramolecular carboamination of alkynes. The reaction of *o*-alkynyltrifluoroacetanilides **35** in the presence of catalytic amounts of $Pd(PPh_3)_4$ and excess K_2CO_3 in CH_3CN at 90°C gave C-3-substituted indoles **36** and/or **37** (Table 4) (98JOC1001).

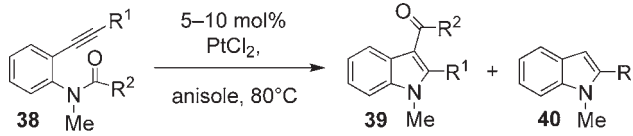
The platinum-catalyzed cyclization of *o*-alkynyl aryl amides **38** provides the synthesis of 3-substituted indoles **39** (Table 5) (04JA10546). In most cases, small amount of 3-unsubstituted indoles **40** was obtained. This reaction is strongly influenced by solvents; aromatic solvents containing an electron-donating group enhanced the rate. Mechanistically, the coordination of $PtCl_2$ to the alkyne increases the electrophilicity of alkynes, which in turn results in the attack of a tethered nitrogen atom to form zwitterionic intermediate **41**. An intramolecular [1,3]-migration of the acyl moiety then yields intermediate **42**, which produces indole **39** and $PtCl_2$ is regenerated. Later, they reported the cyclization of *o*-alkylphenyl ureas **43** and *o*-alkylphenyl carbamates **46** for the synthesis of indoles (**44** and **45**) (Table 6) and indole-3-carboxylates (**47a–b**), respectively (Scheme 10) (09TL2075).

Table 4 Palladium-catalyzed cyclization of *o*-alkynyltrifluoroacetanilides

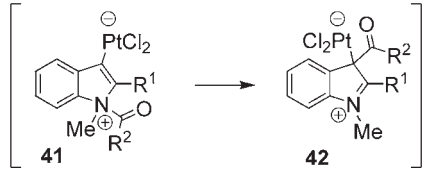


Entry	R^1	R^2	R^3	*t* (h)	Overall yield (%)	**36** Yield (%)	**37** Yield (%)	**36** *E*:*Z* ratio
1	H	H	^{n}Pent	24	38	92	8	89:11
2	H	H	Ph	24	49	100	–	100:0
3	Ph	H	*p*-MeO–C_6H_4	1.5	84	100	–	100:0
4	Ph	H	*p*-Ac–C_6H_4	2	77	100	–	100:0
5	Ph	CH_3	^{n}Pr	5.5	78	100	–	67:33
6	^{n}Pent	H	^{n}Pr	8	66	81	18	81:19
7	*p*-Ac–C_6H_4	H	^{n}Pr	4	83	75	25	78:22
8	*p*-MeO–C_6H_4	H	^{n}Pr	2	81	65	35	88:12

Table 5 Platinum-catalyzed cyclizative carbonyl group migration

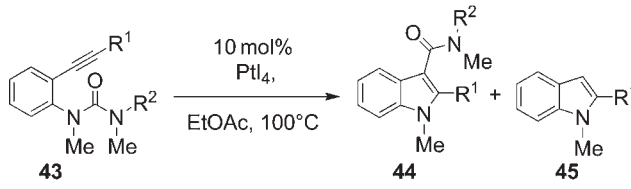


Entry	R^1	R^2	*t* (h)	Yield	**39**:**40**
1	^{n}Pr	Me	0.3	96	9:1
2	^{t}Bu	Me	3	91	2:1
3	*p*–MeO–C_6H_4	Me	0.3	81	3:1
4	*p*–CF_3–C_6H_4	Me	0.7	93	4:1
5	^{n}Pr	Ph	16	75	13:1
6	^{n}Pr	CF_3	3	99%	1:–

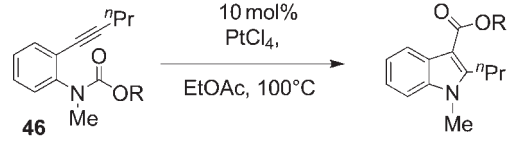


In 2005, Fürstner et al. reported the synthesis of substituted indoles **49a–b** by platinum-catalyzed intramolecular carboamination of alkynes **48** (Scheme 11) (05JA15024). In 2007, Malacria and coworkers designed a

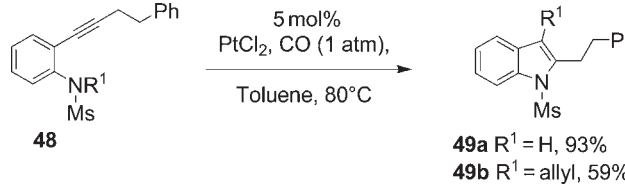
Table 6 Platinum-catalyzed cyclizative amide group migration



Entry	R^1	R^2	*t* (h)	**44** (%)	**45** (%)
1	^{n}Pr	*p*-F_3C-C_6H_4	24	32	56
2	^{n}Pr	*p*-Cl-C_6H_4	4	61	36
3	^{n}Pr	*p*-MeO-C_6H_4	2	46	53
4	Cyclopropyl	Ph	48	32	33
5	Ph	Ph	24	Trace	31
6	H	Ph	4	83	Trace



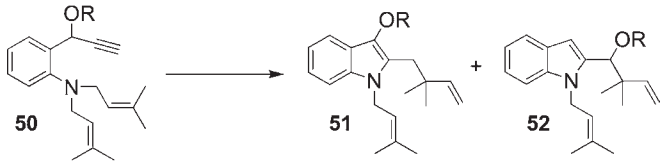
Scheme 10 Platinum-catalyzed cyclizative ester group migration.



Scheme 11 Platinum-catalyzed Intramolecular carboamination of alkynes.

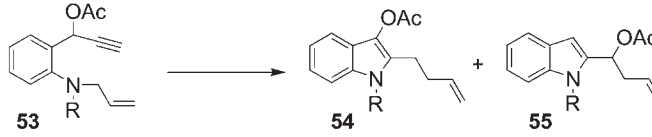
substrate of type **50** for the synthesis of functionalized indoles **51** and **52** (Tables 7 and 8) (07AGE1881). Interestingly, they found that the reaction is not only catalyzed by $PtCl_2$ but also by Brönsted acids such as SiO_2 and *p*-TSA is also equally effective. A ratio of regioisomeric **51**:**52** depends upon the nature of the R group and the reaction temperature. Since Brönsted acids catalyze the reaction (09JCS(CC)5075), a mechanism involving a proton-mediated hydroamination/3-aza-Cope rearrangement cascade was proposed.

Table 7 Synthesis of indoles via intramolecular carboamination of alkynes



Entry	R	Catalyst	Solvent	T (°C)	*t* (h)	**51** (%)	**52** (%)
1	Me	$PtCl_2$(5 mol%)	Toluene	40	1	50	–
2	Me	SiO_2(5 equiv.)	CH_2Cl_2	rt	6	81	–
3	Ac	$PtCl_2$(5 mol%)	Toluene	rt	72	14	38
4	Ac	SiO_2(5 equiv.)	CH_2Cl_2	rt	6	67	–
5	Bn	SiO_2(5 equiv.)	CH_2Cl_2	rt	2	70	–
6	Ac	$PtCl_2$(5 mol%)	Toluene	110	2	–	50

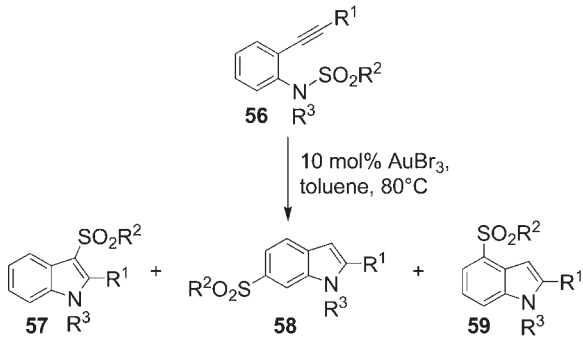
Table 8 Synthesis of indoles via intramolecular carboamination of alkynes



Entry	R	Catalyst	Solvent	T (°C)	*t* (h)	**54** (%)	**55** (%)
1	allyl	$PtCl_2$(5 mol%)	Toluene	rt	1	94	–
2	allyl	$PtCl_2$(5 mol%)	Toluene	80	1	22	57
3	allyl	$PtCl_2$(5 mol%)	Toluene	110	1	–	60
4	allyl	PTSA(1 equiv.)	Toluene	rt	1	54	–
5	Me	$PtCl_2$(5 mol%)	Toluene	110	0.5	19	19
6	Me	SiO_2(5 equiv.)	CH_2Cl_2	rt	0.5	67	–
7	Bn	$PtCl_2$(5 mol%)	Toluene	rt	24	–	45
8	Bn	SiO_2(5 equiv.)	CH_2Cl_2	rt	2	70	–

Nakamura et al. reported the gold-catalyzed intramolecular amino-sulfonylation (formal addition of an N–S bond to a triple bond) for the synthesis of 3-sulfonylindoles **57** (Table 9) (07AGE2284, 08MI285). The procedure involved the treatment of *o*-alkynyl-*N*-sulfonylanilines **56** with $AuBr_3$ catalyst in toluene at 80°C for 1 h. The formation of small amounts of **58** and **59** was also observed. It is interesting to note that the use of $InBr_3$ as a catalyst instead of $AuBr_3$ gave 6-sulfonylindoles **58** as the major products.

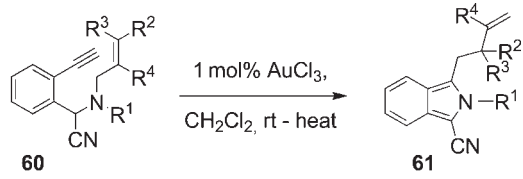
Table 9 Gold-catalyzed cyclizative sulfonyl group migration



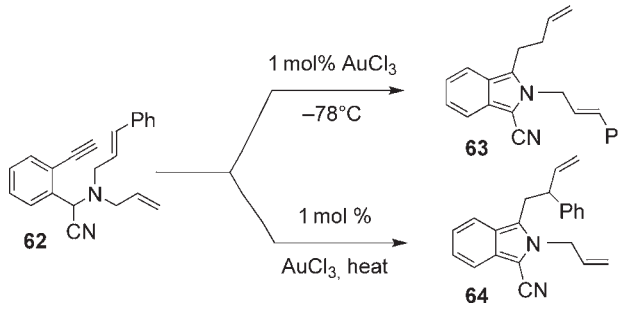
Entry	R^1	R^2	R^3	Yield (%) 57	Yield (%) 58 and 59
1	^{n}Pr	Me	Me	95	–
2	^{t}Bu	Me	Me	38	10
3	*p*–MeO–C_6H_4	Me	Me	81	5
4	*p*–F_3C–C_6H_4	Me	Me	51	20
5	CO_2Et	Me	Me	Decomposition	
6	^{n}Pr	*m*–MeO–C_6H_4	Me	90	4
7	^{n}Pr	CF_3	Me	No reaction	

Stevens and coworkers designed a substrate of type **60** for the synthesis of 1-cyanoisoindole **61**. In the presence of 1 mol% $AuCl_3$, a series of aminonitriles **60** underwent 5-*exo-dig* cyclization followed by 1,3-alkyl group migration (Table 10) (09OL5018). They observed that

Table 10 Synthesis of 1-cyanoisoindole via gold-intramolecular carboamination of alkynes



Entry	R^1	R^2	R^3	R^4	Yield (%)	Condition
1	Bn	H	H	H	95	1 h, 40 min
2	Bn	Me	Me	H	72	22 h
3	^{n}Pr	Ph	H	H	98	2 h, 30 min
4	^{t}Bu	Ph	H	H	99	10 min
5	–CH_2*p*–$MeOC_6H_4$	^{i}Pr	H	H	85	10 min
6	^{n}Pr	Ph	H	Cl	76[b]	8 h, 30 min

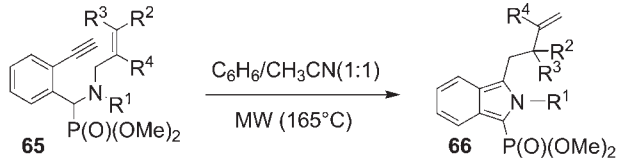


Scheme 12 Kinetic selectivity in gold-catalyzed intramolecular carboamination of alkynes.

differentiation can be made between two migrating groups with different sterical demand, albeit in poor selectivity. At room temperature a 50:50 mixture of **63** and **64** was obtained, while at -78°C a selectivity up to 63% in a favor of **63** was achieved (Scheme 12). The same research group reported the synthesis of phosphonylated substituted isoindoles **66** under a microwave condition from *o*-ethynylbenzyl α-aminophosponates **65** (Table 11) (07OL465). Note that the process is thermally driven and therefore no catalyst was necessary.

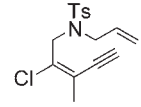
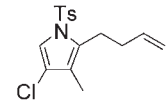
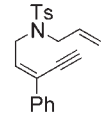
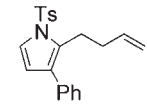
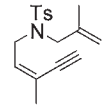
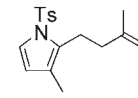
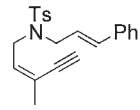
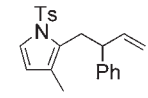
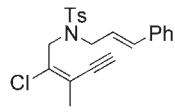
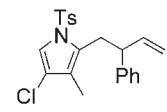
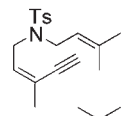
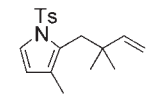
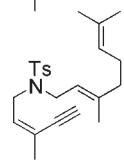
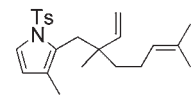
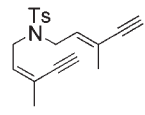
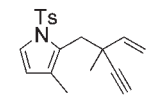
Gagosz and coworkers utilized the carbo-amination process for the synthesis of functionalized pyrroles **68** by using a gold-catalyzed cyclization of allyl tosylamides **67** (Table 12) (07OL3181). The reaction is reported to proceed at room temperature using the air-stable crystalline $Ph_3PAuNTf_2$ catalyst, which was discovered by them (05OL4133).

Table 11 Synthesis of phosphonylated substituted isoindoles under microwave conditions



Entry	R^1	R^2	R^3	R^4	*t* (min)	Yield %
1	Bn	H	Ph	H	90	82
2	^{n}Pr	H	*p*–MeO–C_6H_4	H	90	68
3	*m*–F–C_6H_4	H	H	H	150	63
4	^{n}Bu	CH_3	Ph	H	80	40
5	–CH_2–*p*–Me–Ph	H	CH_3	CH_3	95	47

Table 12 Synthesis of pyrroles via intramolecular carboamination of alkynes

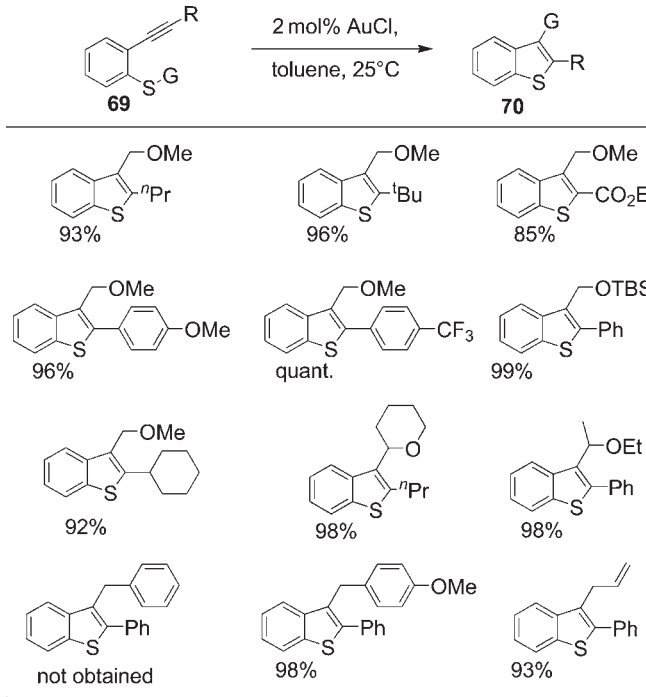
Entry	Substrate **67**	Product **68**	*t* (min)	Yield (%)
1			30	88
2			45	72
3			45	89
4			15	97
5			5	98
6			15	90
7			15	91
8			15	84

Reaction conditions: 2 mol% $(p\mathrm{CF_3Ph})_3\mathrm{PAuNTf_2}$, 0.1 M $\mathrm{CH_2Cl_2}$, rt.

4. SYNTHESIS OF S-CONTAINING HETEROCYCLES

The gold-catalyzed intramolecular carbothiolation of alkynes for the synthesis of 2,3-disubstituted benzothiophene was reported by Nakamura and coworkers (Table 13) (06AGE4473). The reaction involves the migration of groups such as α-alkoxy alkyl, PMB, and allyl from the

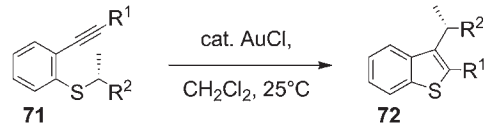
Table 13 Synthesis of thiophenes via intramolecular carbothiolation of alkynes



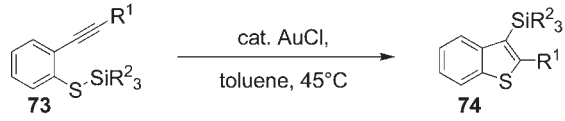
sulfur atom to the alkyne. Various thiophene derivatives **70** were obtained from readily available **69**. Concerning the accessibility of C-3-substituted thiophenes, this method is superior to the known Friedel-Crafts and lithiation/electrophile-trapping reactions. The same groups reported the synthesis of the gold-catalyzed carbothiolation reaction of **71**, which proceeds with 1,3-migration of an aryl ethyl group with retention of configuration at the migrating group to give enantiomerically enriched **72** (Table 14) (08OL2649).

Pioneering work from Nakamura's laboratory revealed the synthesis of 3-silylbenzo[b]thiophenes **74** using gold-catalyzed cyclization of (*o*-alkynylphenylthio)silanes **73**. The reaction proceeds through thiosilylation and 1,3 migration of the silyl group (Scheme 13) (07OL4081). For example, **73** in the presence of 2 mol% AuCl in toluene at 45°C gave 3-silylbenzo[b]thiophene **74a–e** in good to excellent yields. The reaction is reported to proceed through the intramolecular capture of the vinyl gold intermediates by the silicon electrophiles (cf. **75**).

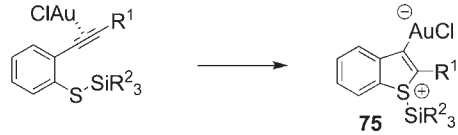
Table 14 Chirality transfer in gold-catalyzed carbothiolation of alkynes



Entry	R^1	R^2	Temp (°C)	Time (h)	Yield %	ee (%)	Chirality transfer (%)
1	*p*–MeO–C_6H_4	Ph	25	0.5	98	88	91
2	*p*–MeO–C_6H_4	Ph	50	0.5	99	79	52
3	*p*–MeO–C_6H_4	Ph	0	4 days	97	69	71
4	*p*–MeO–C_6H_4	*p*-Cl–C_6H_4	25	0.5	97	79	81
5	^{n}Pr	Ph	25	3 days	82	38	38
6	Cyclohexyl	Ph	25	5 days	92	22	23



74a $R^1 = {}^n$Pr, $R^2 = Si({}^i Pr)_3$, 5 h, 98%
74b R^1 = *p*-MeO-C_6H_4, $R^2 = Si({}^i Pr)_3$, 8 h, 44%
74c R^1 = *p*-CF_3-C_6H_4, $R^2 = Si({}^i Pr)_3$, 5 h, 99%
74d R^1 = Cy, $R^2 = Si({}^i Pr)_3$, 21 h, 60%
74e $R^1 = {}^n$Pr, $R^2 = SiPh_3$, 2 h, 40%

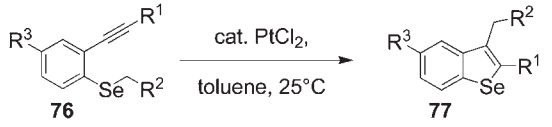


Scheme 13 Synthesis of 3-silylbenzo[b]thiophenes via intramolecular thiosilylation of alkynes.

5. SYNTHESIS OF Se-CONTAINING HETEROCYCLES

Similar to oxygen, nitrogen, and sulfur nucleophiles, selenium can also be used in this type of reaction. Very recently, a platinum-catalyzed carboselenation reaction has been reported. In the presence of 2 mol% $PtCl_2$, alkynes **76** in toluene at 25°C gave 2,3-disubstituted benzo[b]selenophenes **77** (Table 15) (09JOC5509). Table 12 shows that a benzyl group on selenium is reluctant to migrate (entry 7) while a strong cation-stabilizing group is best for migration (entries 1–6).

Table 15 Synthesis of benzo[b]selenophenes via intramolecular carboselenation of alkynes



76 77

Entry	R^1	R^2	R^3	*t* (h)	Yield %
1	Ph	*p*–MeO–C_6H_4	H	1	98
2	Ph	*p*–MeO–C_6H_4	F	1	99
3	^{t}Bu	*p*–MeO–C_6H_4	H	18	99
4	2,6-F_2–C_6H_3	*p*–MeO–C_6H_4	H	48	99
5	Ph	MeO	H	2	77
6	Ph	TIPSO	H	1	77
7	Ph	Ph	H	24	0

6. CONCLUSIONS

In the past decade, alkynes have become attractive starting material for the synthesis of a variety of synthetically useful products. Generally, this type of reaction relies on the interaction of a metal catalyst with the π-bond of the alkynes (07ARK6, 07ARK121, 07AGE3410, 08CRV3239, 08CRV3266, 08CRV3351, 08CRV3395, 08S3183, 09MI1). Most of the reactions involve a single starting material containing various functional groups strategically positioned along a chain, terminating with alkyne functionality. Recent literature revealed that a new type of reactivity is exhibited by the metal catalysts, that is, X→C functional group migration reactions. The results presented herein suggest that a cation-stabilizing group such as allyl, propargyl, acyl, (α-alkoxy alkyl), and (*p*-methoxyphenyl)methyl have an ability to migrate from a heteroatom to a carbon atom.

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CHAPTER 3

Biindolyls

David StC Black and **Naresh Kumar**

Contents

1. INTRODUCTION

The aim of this chapter is to survey the synthesis and reactions of biindolyls, and in doing so, to highlight the significant structural types that have been overlooked or underdeveloped in the past. The connection of indole rings can lead to 28 structural isomers by the variation of linkage possible. Thus the following types can be envisaged, going around the ring in turn.

Linkage at N1: This can give rise to 1,1′-; 1,2′-; 1,3′-; 1,4′-; 1,5′-; 1,6′-; and 1,7′-biindolyls.
Linkage at C2: This can additionally give rise to 2,2′-; 2,3′-; 2,4′-; 2,5′-; 2,6′-; and 2,7′-biindolyls.
Linkage at C3: This can additionally give rise to 3,3′-; 3,4′-; 3,5′-; 3,6′-; and 3,7′-biindolyls.

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Linkage at C4: This can additionally give rise to 4,4′-; 4,5′-; 4,6′-; and 4,7′-biindolyls.
Linkage at C5: This can additionally give rise to 5,5′-; 5,6′-; and 5,7′-biindolyls.
Linkage at C6: This can additionally give rise to 6,6′-; and 6,7′-biindolyls.
Linkage at C7: This can additionally give rise to 7,7′-biindolyls.

The first 7 examples listed contain a C–N linkage and the remaining 21 examples contain C–C linkages.

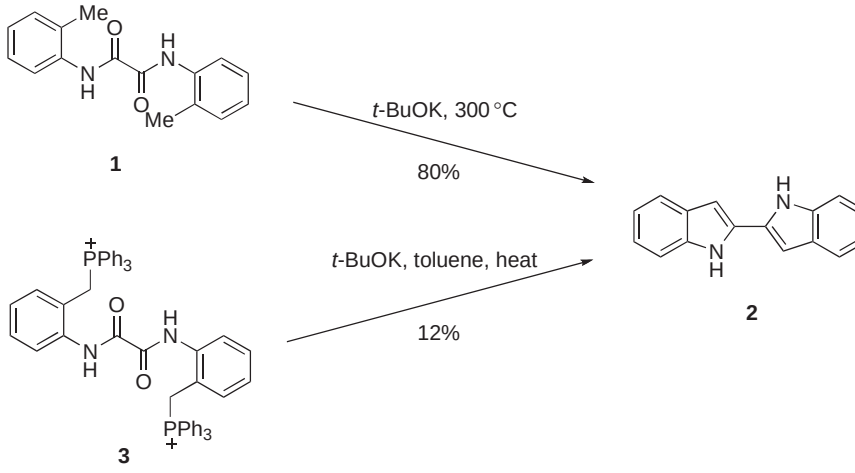
Many of these types of biindolyls are either unknown or poorly known. Also the synthetic methods often lead to mixtures of structural isomers. Consequently the review will not be based on a systematic consideration of each structural isomer, but rather focus on the synthetic routes involved. A following section on some representative reactions of biindolyls will also be included.

2. SYNTHESIS

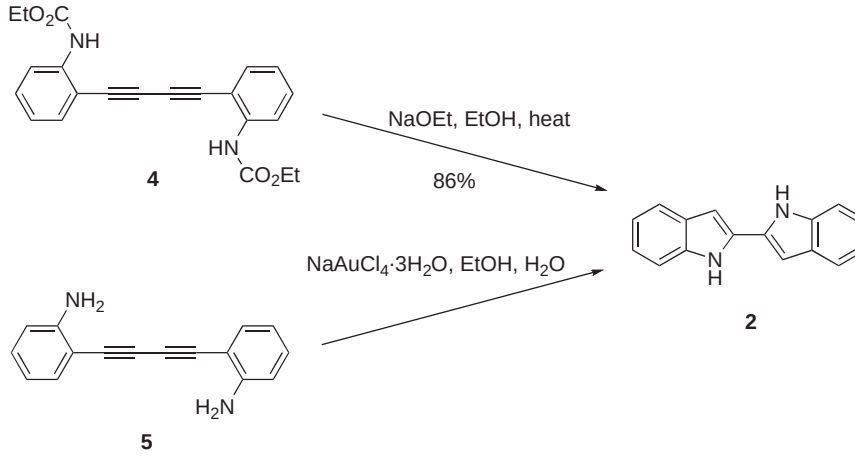
2.1 Formation of two indole rings by cyclization

One of the oldest methods of indole synthesis is the Madelung cyclization of a 2-amidotoluene under conditions of very strong base and high temperature. Because of the harsh conditions, the method is not compatible with sensitive functional groups. However, one of the most successful examples is the cyclization of the oxamide **1** to 2,2′-biindolyl **2** in 80% yield under the precise influence of potassium *tert*-butoxide at 300°C (95T5631). These conditions represent a significant improvement on the original work of Madelung, which achieved a yield of 26% using sodium pentoxide at 360°C (12CB1128, 14LA58). The Madelung type of synthesis can be modified by the introduction of activating influences, as shown by the milder cyclization of the oxamide phosphonium salt **3** with potassium *tert*-butoxide in refluxing toluene: however the yield of the 2,2′-biindolyl **2** in this case is only 12% (84JHC623, 88CB2259) (Scheme 1).

Another standard indole synthesis involves cyclization of a 2-alkynylaniline derivative, and this can be doubled up to generate the parent 2,2′-biindolyl **2**. Treatment of the carbamic ester **4** with sodium ethoxide in refluxing ethanol gives the biindolyl **2** in 86% yield (95SL859), while a gold(III)-catalyzed process converts the diaminodialkyne **5** into biindolyl **2** (04S610) (Scheme 2). More highly functionalized 2,2′-biindolyls have also been successfully prepared by this method (06TL6385).



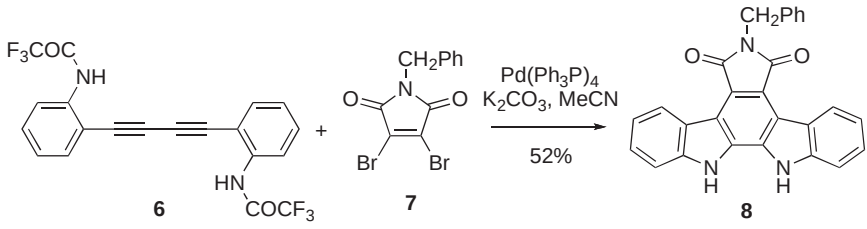
Scheme 1



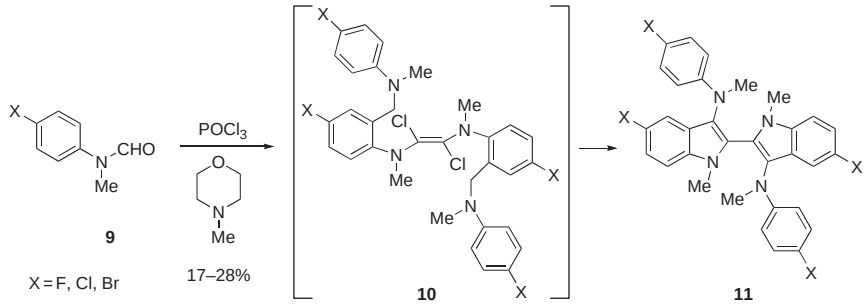
Scheme 2

Simultaneous construction of three rings affords the indolocarbazole **8** by combination of the dialkyne **6** with a dibromomaleimide derivative **7** under the catalytic influence of tetrakis-triphenylphosphinepalladium (95TL7841) (Scheme 3).

In a rather special case, the reaction of *N*-methylformanilides **9** with phosphoryl chloride gives low yields of 3,3′-diarylamino-2,2′-biindolyls **11**, via the cyclization of the double iminium salts **10** (98JCSP(1)1619) (Scheme 4).



Scheme 3



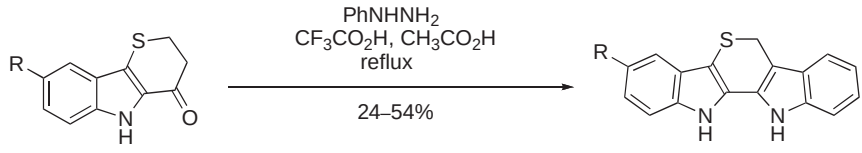
Scheme 4

In principle, any indole synthesis involving a cyclization process can be adapted to the formation of biindolyls, provided that a suitable precursor is readily available. Indeed, 2,5′-, 3,5′-, and 5,5′-biindolyls have been prepared in modest yields by double Fischer syntheses involving the cyclization of bis-hydrazones formed from ethyl pyruvate and bis-hydrazines of biphenyl compounds (78KGS217, 90KGS343, 92KGS1336). Considerable scope remains for the development of this synthetic strategy.

2.2 Formation of one indole ring by cyclization

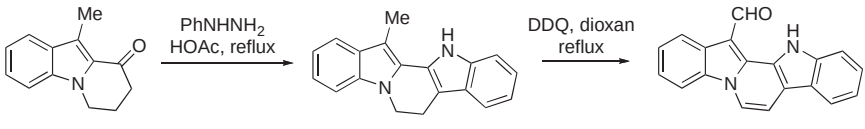
This is a much more popular strategy than the previous one, because indoles can be readily functionalized. Furthermore, this strategy allows for the formation of unsymmetrical biindolyls.

2,2′-Biindolyls can be formed by the Fischer synthesis that combines a 2-acylindole with an arylhydrazone. For example, the cyclic 2-acylindoles **12** react with arylhydrazines in refluxing trifluoroacetic acid and acetic acid to give the pentacyclic heteroaromatic systems **13** containing a 2,2′-biindolyl linkage (98SC1239) (Scheme 5).



12 R = H, MeO, Me, Br, Cl **13**

Scheme 5

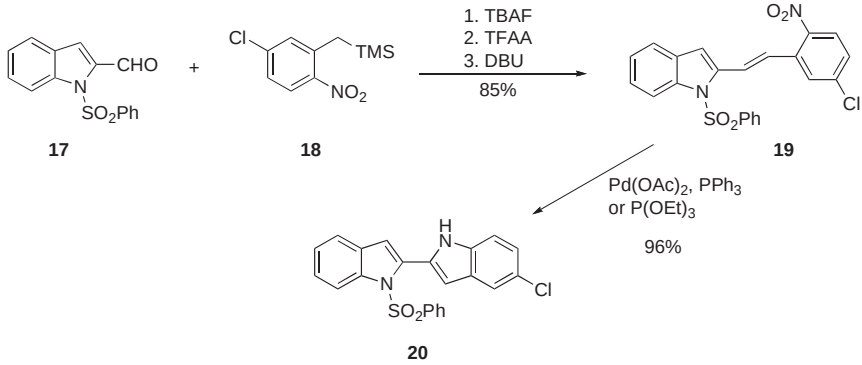


14 **15** **16**

Scheme 6

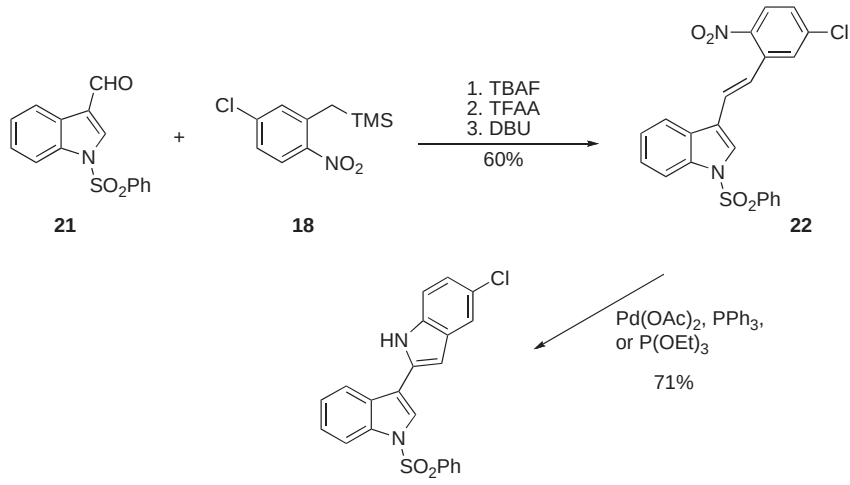
In a related process, a different cyclic 2-acylindole **14** combines with phenylhydrazine in refluxing acetic acid to give a 91% yield of the 2,2′-biindolyl **15**. This compound was subsequently oxidized by dichlorodicyanoquinone to generate the naturally occurring homofascaplysin C **16** (96TL5207) (Scheme 6). A related process gives a modest yield of a fused 2,2′-biindolyl (95T12797).

The reductive cyclization of 2-nitrostyrenes is a useful method for the formation of indoles. When applied to indolyl-2-nitrostyrenes, such as **19**, the 2,2′-biindolyl **20** can be formed (03OL3721) (Scheme 7). The sequence of reactions can be carried out in one pot, by the combination of indole-2-carbaldehyde **17** and the nitrobenzene **18** to generate the intermediate nitrostyrene **19**, which can be reduced by either palladium acetate and



17 **18** **19** **20**

Scheme 7



Scheme 8

triphenylphosphine, or triethylphosphite to give the 2,2′-biindolyl **20** (01T5199). Suitable examples have subsequently been converted into members of the naturally occurring tjipanazole family.

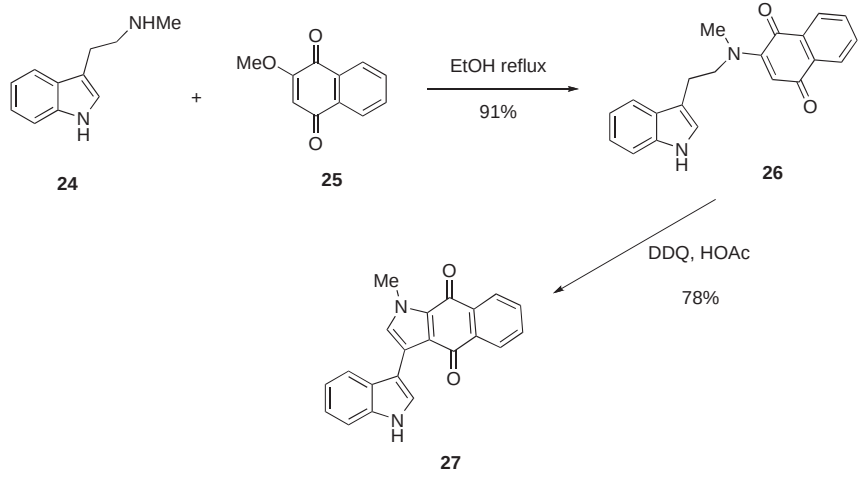
A similar process commencing with the indole-3-carbaldehyde **21** affords the 2,3′-biindolyl **23** via the intermediate **22** (03OL3721) (Scheme 8).

3,3′-Indoloquinones have been formed through an oxidative cyclization process. For example, *N*-methyltryptamine **24** combines with 2-methoxynaphthoquinone **25** to give the intermediate **26**, which on treatment with dichlorodicyanoquinone in acetic acid gives the 3,3′-indoloquinone **27** (98TL7677) (Scheme 9). The *N*-desmethyl analog of intermediate **26** could not be cyclized.

Some 3-arylacetylindoles **28** can be nitrated in the appropriate *ortho* position to give the nitroketones **29**, which undergo reductive cyclization with either stannous chloride in hydrochloric acid or sodium hydrosulfite to afford the 2,3′-biindolyls **30** (62JOC507) (Scheme 10). The sequence is limited by the ability to nitrate in the desired position, so is not widely applicable (64JOC2030).

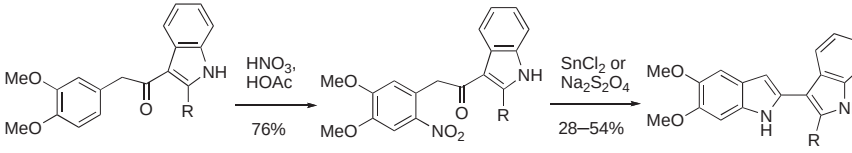
A modified Bischler indole synthesis can be used to prepare 4,6-dimethoxy-3-arylindoles. The 2,3-diphenyl-4,6-dimethoxyindole **31** can be acetylated at C7 and the acetyl compound **32** converted via the bromoketone **33** into an arylaminoketone **34**, which can be cyclized to a 3,7′-biindolyl **35** (94AJC1741) (Scheme 11).

Benzo[b]carbazoles can be synthesized readily and in good yields from the combination of 2,3-unsubstituted indoles and *o*-phthaldialdehyde **37** in the presence of acid catalysts. Use of phosphoryl chloride in



24 25 26 27

Scheme 9



28 29 30

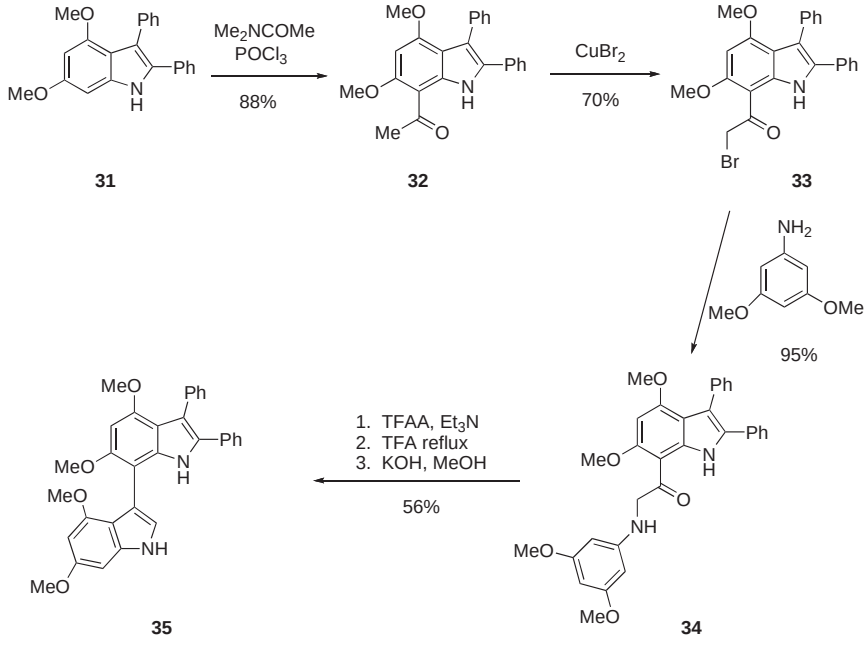
R = H, Me

Scheme 10

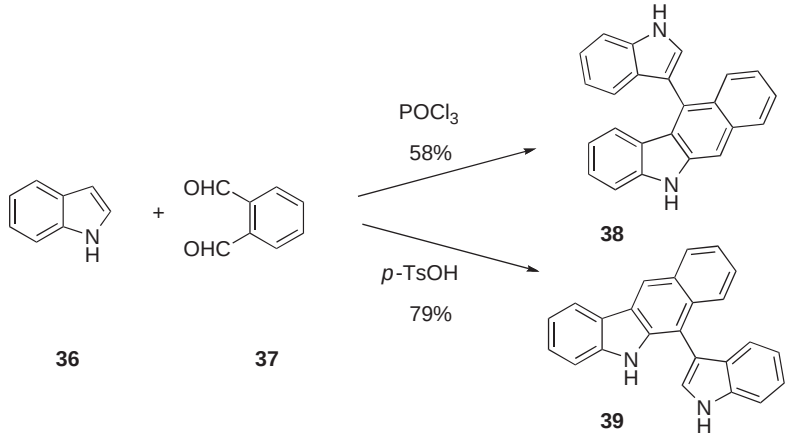
chloroform gives rapid reactions and indole **36** yields 11-(3-indolyl)benzo [b]carbazole **38** (effectively a benzannulated 3,4′-biindolyl), whereas the reaction using *p*-toluenesulfonic acid in methanol proceeds slowly and yields the isomeric 6-(3-indolyl)benzo[b]carbazole **39** (effectively a benzannulated 3,7′-biindolyl) (99TL6653) (Scheme 12).

2.3 Linkage of two indole rings by coupling reactions

Biindolyls can readily be formed by the direct combination of two indoles or related cyclic systems, using a variety of substitution, metal-catalyzed coupling, or oxidative processes. An early example involved the Lewis acid-catalyzed combination of a 3-substituted indole with its singlet oxygen indoline product to give a 2,2′-biindolyl. This is illustrated in the case of tryptophol **40** undergoing conversion to the 3-hydroxyindoline **41**, followed by combination of the two species to give the 2,2′-biindolyl **42** in 52% yield (82JCS(CC)977) (Scheme 13).

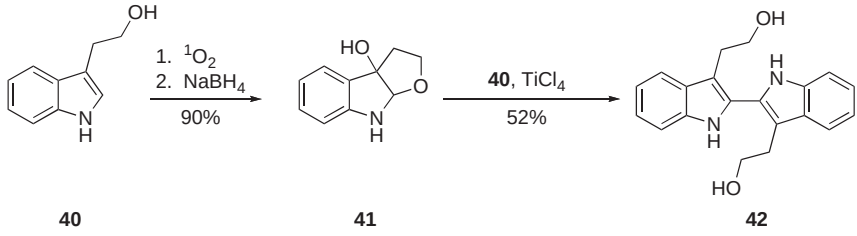


Scheme 11



Scheme 12

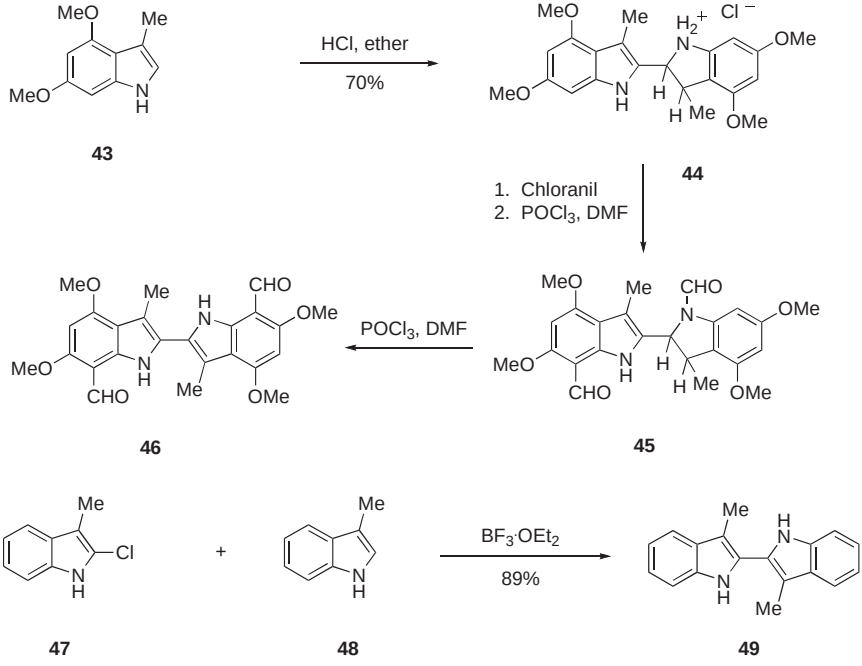
When indole is treated with acid it forms an indoleninium salt, which is electrophilic at C2 and can then be attacked by another indole to give a 3-indolyl-indoline (61JCS940). However, it is not easy to oxidize these compounds to 2,3′-biindolyls. 3-Substituted indoles undergo similar



40 **41** **42**

Scheme 13

acid-catalyzed dimerization to give indolyl-indolines with a 2,2′-linkage, and these can subsequently be converted, with some difficulty, into 2,2′-biindolyls (60TL13; 72JCS(P1)418). For example, 4,6-dimethoxy-3-methylindole **43** on treatment with hydrogen chloride gas in ether yields the 2,2′-indolyl-indoline **44**, which can be formylated using the Vilsmeier reagent to give the formyl-formamide **45** (80TL1883, 83AJC2407). A sequence of chloranil oxidation, amide hydrolysis, and further formylation effectively gave the 2,2′-biindolyl-7,7′-dicarbaldehyde **46** (85JCS(CC)1174, 93SL246) (Scheme 14). However, when 2-chloro-3-methylindole **47** is combined with 3-methylindole **48** in the presence of boron trifluoride etherate, the 2,2′-biindolyl **49** is formed directly in 89% yield (81H1441) (Scheme 14).

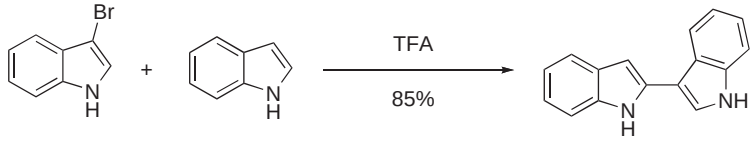


43 **44** **45** **46** **47** **48** **49**

Scheme 14

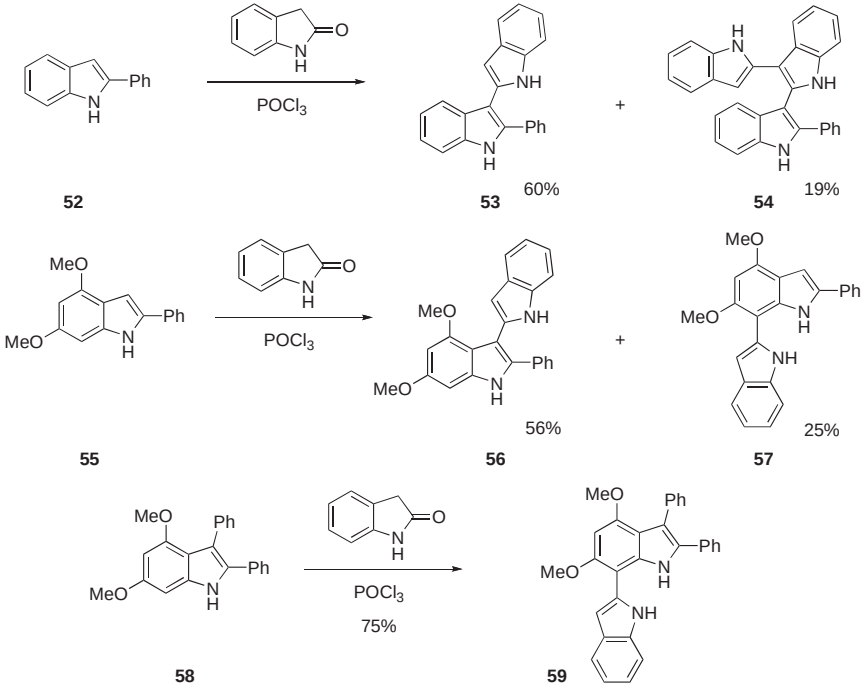
2,3′-Biindolyls can be formed directly by the acid-catalyzed combination of 3-unsubstituted indoles with 3-bromoindoles, as shown by the formation of the parent 2,3′-biindolyl **51** in 85% yield from 3-bromoindole **50** and indole **36** (83JCS(CC)1074, 84T3251) (Scheme 15). The reaction has wide generality and has been extended to the formation of trimeric structures (86T5019, 89JCSR277).

In a modification of the Vilsmeier reagent, phosphoryl chloride and 2-indolinone combine to form an electrophile that can undergo reaction with indoles to yield a wide variety of biindolyl products (80T1445). Reaction of 2-phenylindole **52** with this reagent gives the 2,3′-biindolyl **53** and the 2,3′; 2,3″-terindolyl **54** in 60% and 19% yields, respectively (84JCS(CC)441, 96T4697, 98ANH85) (Scheme 16). The related



50 **36** **51**

Scheme 15

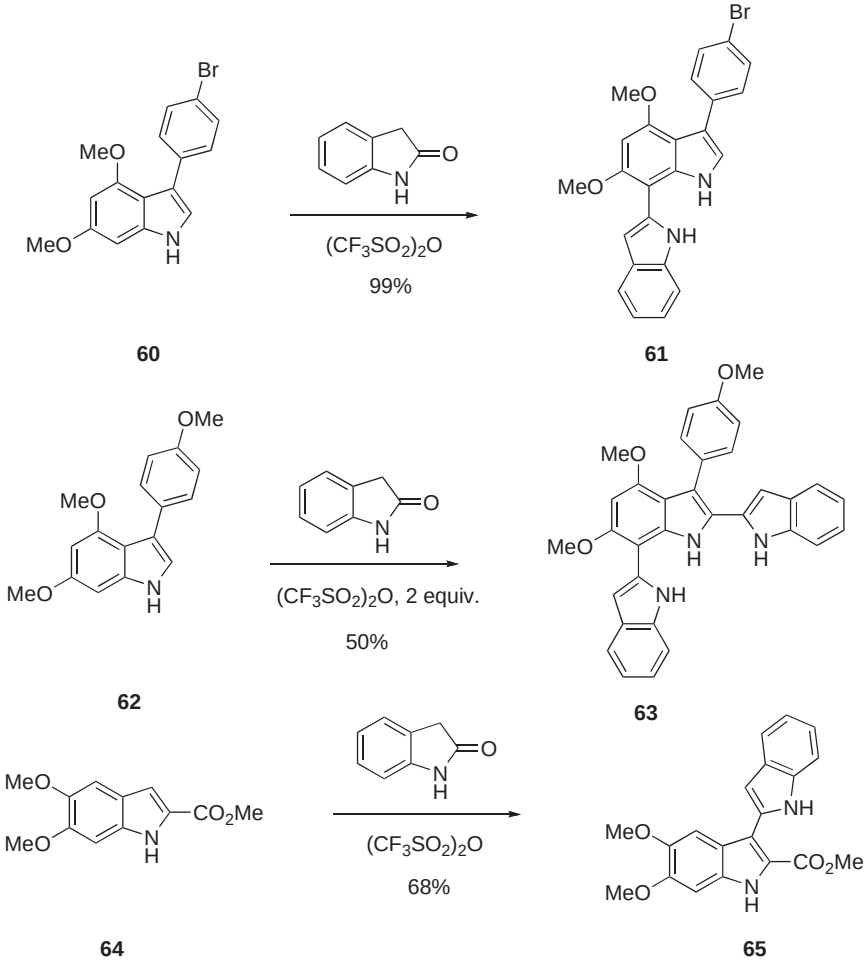


52 **53** **54** **55** **56** **57** **58** **59**

Scheme 16

4,6-dimethoxy-2-phenylindole **55** under similar conditions gave the 2,3′-biindolyl **56** and the 2,7′-biindolyl **57** in respective yields of 56% and 25%. When reactivity at C3 is blocked, as in the case of 4,6-dimethoxy-2,3-diphenylindole **58**, only the 2,7′-biindolyl **59** is obtained in 75% yield.

The situation is a little different with 3-substituted-4,6-dimethoxyindoles. Despite the reactivity of these compounds, mixtures of 2,2′- and 2,7′-biindolyls are formed in only relatively low yields and are dependent on the nature of the 3-substituent. However, the replacement of phosphoryl chloride with triflic anhydride leads to regioselective formation of the 2,7′-biindolyl in high yield, as illustrated by the conversion of the bromophenylindole **60** into the 2,7′-biindolyl **61** in 99% yield (96T4697) (Scheme 17). On the other hand, the corresponding methoxyphenylindole **62**

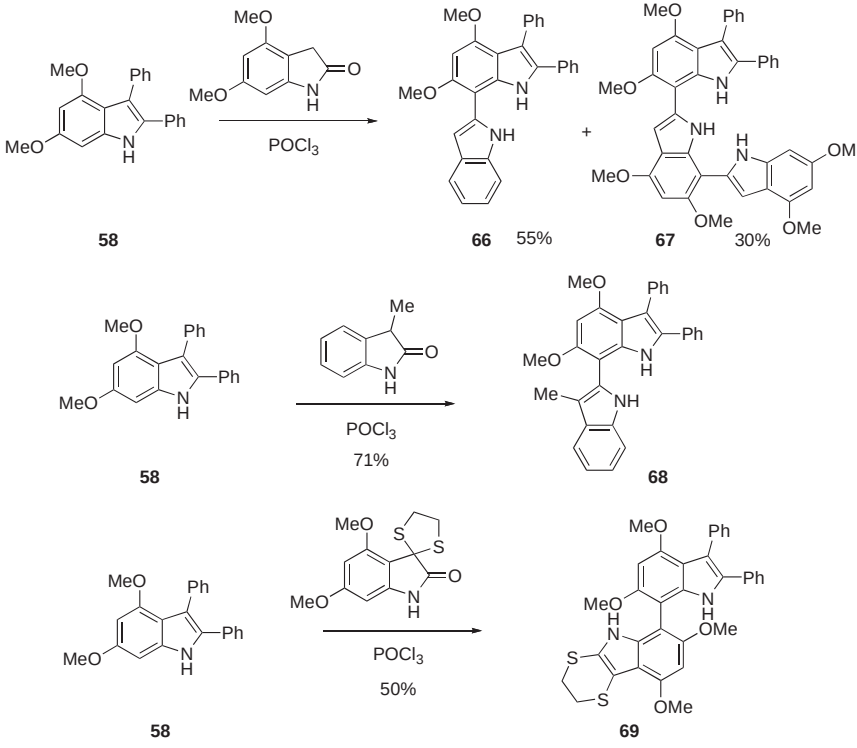


Scheme 17

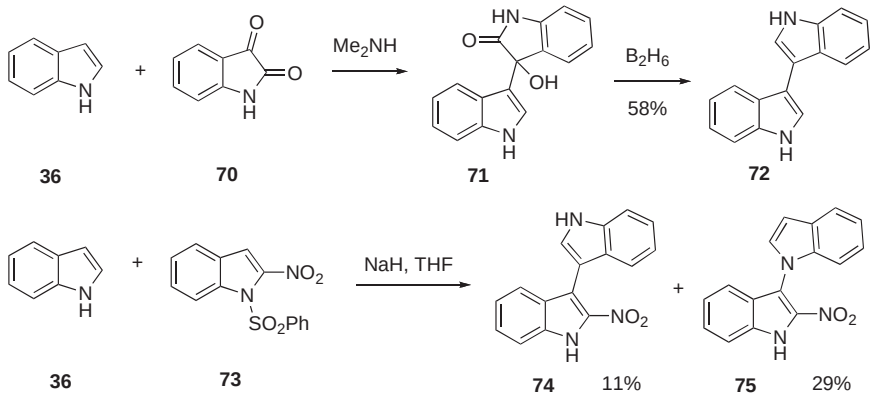
is sufficiently reactive to combine with two equivalents of the reagent to form the 2,2′; 2,7′-terindolyl **63** in 50% yield. Under triflic anhydride conditions, methyl 5,6-dimethoxyindole-2-carboxylate **64**, being 2-substituted, directs the incoming electrophile to C3 to give the 2,3′-biindolyl **65** in 68% yield (04TL7273) (Scheme 17).

Substituted indolones have been investigated in connection with this synthetic strategy, but the results are mixed (96T7003, 04TL7273). For example, when the 2,3-diphenylindole **58** is reacted with 4,6-dimethoxy-2-indolinone and phosphoryl chloride, a 30% yield of the 2,7′; 2,7′-terindolyl **67** is obtained in addition to a 55% yield of the expected 2,7′-biindolyl **66** (96T4697). The corresponding reaction involving 3-methyl-2-indolinone afforded the 2,7′-biindolyl **68** in 71% yield (96T7003). Application of the more complex 4,6-dimethoxy-3-spirodithiolan-2-indolinone gave the 7,7′-biindolyl **69** in 50% yield, following rearrangement of the dithiolan ring (Scheme 18).

Indole **36** readily reacts with isatin **70** in the presence of dimethylamine to give the alcohol **71**, which can be reduced with diborane to 3,3′-biindolyl **72** in 58% yield (96TA285) (Scheme 19). This approach has been



Scheme 18



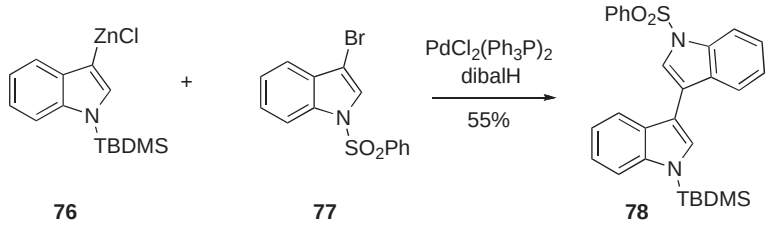
36 **70** **71** **72** **36** **73** **74** **75**

Scheme 19

developed with modest functionality to provide precursors for indolocarbazoles (98JCS(P1)2009). Indole also behaves as a nucleophile in a base-induced Michael addition to the 2-nitroindole **73** to give a mixture of the 3,3′-biindolyl **74** and the 1,3-biindolyl **75** in low yields (99TL7615) (Scheme 19).

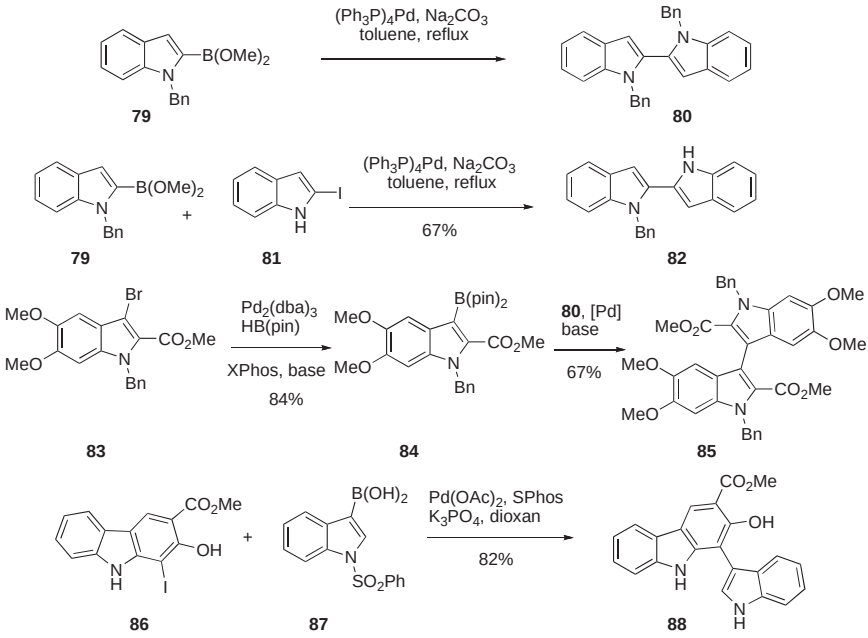
Palladium-catalyzed coupling reactions have been widely used to generate biindolyl systems. The 3-indolylzinc compound **76** can be coupled with the 3-bromoindole **77** to give the 3,3′-biindolyl **78** in 55% yield (94TL793) (Scheme 20). Related indolyl Grignard reagents and iodoindoles can also be used with palladium catalysis (04T3695), but related indolyl copper species react directly with iodoindoles without palladium catalysis (80T1439).

The palladium-catalyzed homocoupling of dimethyl indol-2-ylborates such as **79** generates 2,2′-biindolyls such as **80** (97TL7661, 01T5199) (Scheme 21). Such borate esters can also combine with iodoindoles, and for example, 2-iodoindole **81** gives an unsymmetrical 2,2′-biindolyl **82** in 67% yield. The Suzuki–Miyaura coupling strategy has recently been extended to deliver a wide range of homo- and hetero-biindolyls (08JOC9177, 10H1267). For instance, the 3-bromoindole **83** was converted into the



76 **77** **78**

Scheme 20

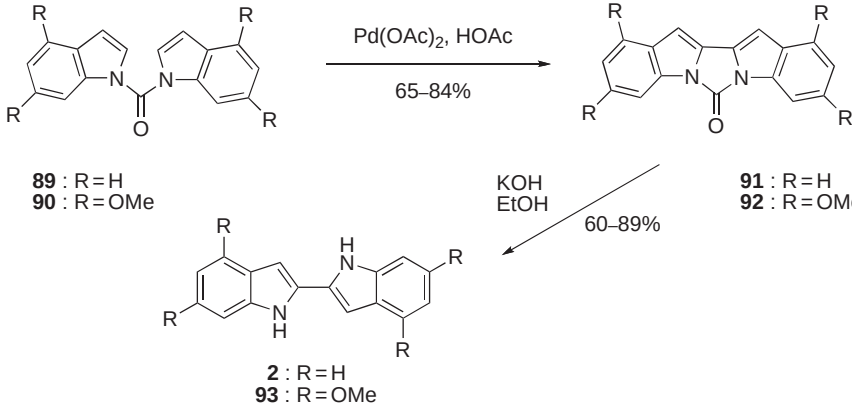


Scheme 21

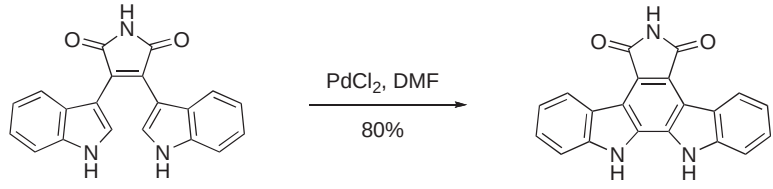
boronate **84** and the two coupled to give the 3.3′-biindolyl **85** (Scheme 21). The application of related 4-bromo- and 7-bromoindoles increases the scope of this strategy, and biindolyls with 3,3′-, 3,4′-, 4,4′-, 3,7′-, 4,7′-, and 7,7′-linkages can be prepared in modest to good overall yields. The Suzuki–Miyaura coupling between an indolyl-3-boronic acid **87** and a 1-iodocarbazole **86** to give a 1-(3-indolyl)carbazole **88** (effectively a benzannulated 3,7′-biindolyl) is a key step in the total synthesis of the yeast metabolite pityriazole (08OBC2481) (Scheme 21).

Another route involving palladium coupling is the intramolecular indole–indole coupling of *N,N*′-carbonyl-bis-indoles **89–90** with palladium (II) acetate in acetic acid to give the biindolyls **91–92** in good yield: base hydrolysis converted these intermediates into the 2,2′-biindolyls **2** and **93** (80T1439, 85JCS(CC)1174) (Scheme 22).

This intramolecular coupling strategy has been used to great effect in the synthesis of indolocarbazoles of biological interest. Two indole units can be coupled at C3 with a succinimide moiety to give compounds such as **94**, which can then be coupled with palladium chloride to give indolocarbazoles such as **95** (93TL8361, 96T8099, 07TL7399) (Scheme 23). Aryl–aryl coupling has been effectively induced in a related di-indolyl succinic anhydride by irradiation with ultraviolet light in the presence of iodine (94S25, 94TL5555).



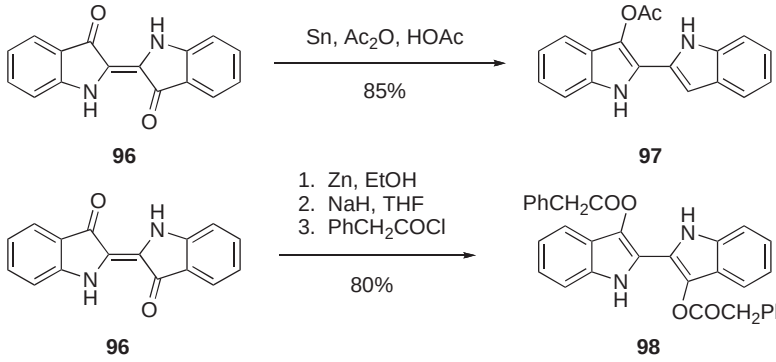
Scheme 22



Scheme 23

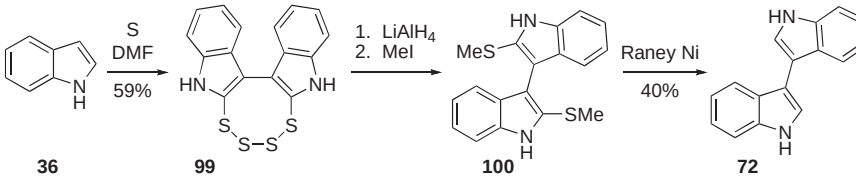
It was found in the course of the above research that a direct oxidative coupling, for example, with dichlorodicyanoquinone gave even higher yields of products. Oxidative coupling has played an important part in the formation of biindolyls, and this strategy will now be considered.

One of the earliest oxidative approaches was to exploit indigo **96**, itself an oxidation product of indoxyl (3-indolinone), with a 2,2′-linkage. In principle, it should then be possible to convert it by a reductive process into a 2,2′-biindolyl. This has proven to be not straightforward. The most effective conditions appear to be the treatment of indigo **96** with tin powder and acetic anhydride in acetic acid at 64–66°C: the product is the monoacetoxylated 2,2′-biindolyl **97** in 85% yield (97H1647, 99H1233, 04H483) (Scheme 24). This product has served as an important starting material for some naturally occurring indolocarbazoles (85TL4015, 07TL231). The related diacyloxy compounds can be prepared via the leucoindigo sodium salt, obtained by reduction of indigo with zinc dust in ethanol, followed by treatment with sodium hydride and phenylacetyl chloride. This method is most effective with bulky acyl halides, such as phenylacetyl chloride, which gives **98** in ~80% yield (84JCS(P1)2305) (Scheme 24).



96 **97** **96** **98**

Scheme 24



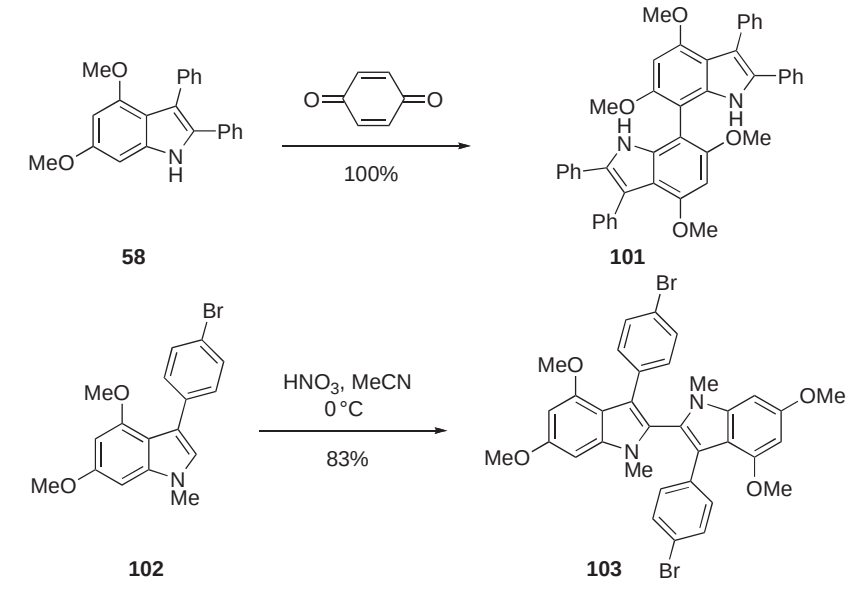
36 **99** **100** **72**

Scheme 25

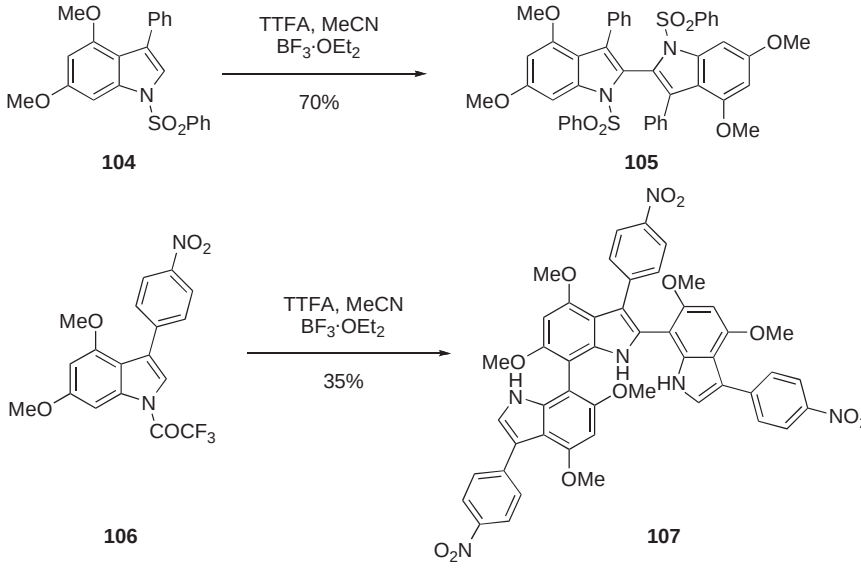
Indole **36** has been reacted with sulfur to give a new cyclic tetrasulfide **99** with a 3,3′-linkage. On treatment with lithium aluminium hydride followed by methyl iodide, the 2,2′-dithiomethyl-3,3′-biindolyl **100** is obtained and the thiomethyl groups can be removed with Raney nickel to yield the parent 3,3′-biindolyl **72** (60JA2739) (Scheme 25).

The activated 4,6-dimethoxyindoles, if substituted at both C2 and C3, undergo ready oxidation at C7 to yield 7,7′-biindolyls: for example, the 2,3-diphenylindole **58** gave a quantitative yield of the 7,7′-biindolyl **101** on oxidation with 1,4-benzoquinone (89JCS(CC)111, 94T10497, 05T10490) (Scheme 26). The related *N*-methylindole failed to dimerize under these conditions, presumably for steric reasons. The 7,7′-biindolyl **101**, and some related 2-methyl-3-phenyl analogs, can be formed by reaction with cold, concentrated nitric acid in acetonitrile. These conditions also generate 2,2′-biindolyls, such as **103** by oxidative coupling of *N*-methylindoles, such as **102**: the *N*-substitution is essential for successful coupling (05T853) (Scheme 26).

Thallium (III) trifluoroacetate is also an effective oxidative coupling reagent, and the *N*-phenylsulfonylindole **104** gives a 70% yield of the 2,2′-biindolyl **105** (08T7787) (Scheme 27). Unfortunately removal of the

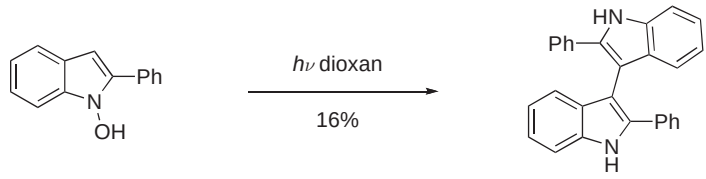


Scheme 26



Scheme 27

N-phenylsulfonyl group is problematic. During the exploration of alternative *N*-protecting groups, it was found that the indole **106** was oxidized to the 7,7′; 2,7′-terindole **107** in 35% yield.

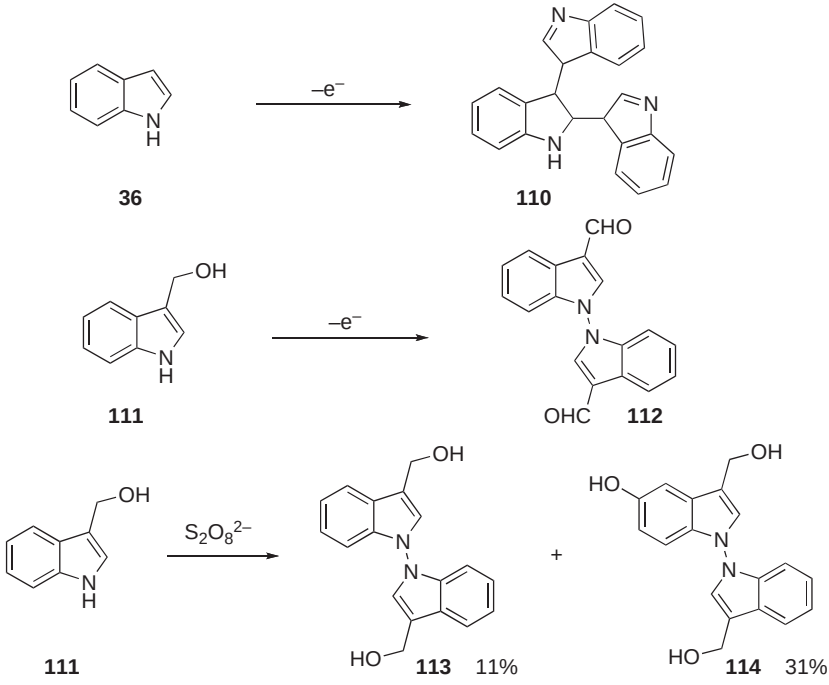


108 **109**

Scheme 28

Photo-irradiation of the *N*-hydroxyindole **108** in dioxane gave a complex mixture of products, of which six were isolated: one of these was the 3,3′-biindolyl **109**, formed in 16% yield (98T5305) (Scheme 28).

Electrochemical oxidation of indoles possibly leads to biindolyls in low yield. The oxidation of indole **36** in a phosphate buffer and using a pyrolytic graphite electrode gives a trimer, with the suggested reduced terindolyl structure **110** (but more likely to be the related 2,3-di(3-indolyl)-2,3-dihydroindole) (98BB47). Similarly the 3-hydroxymethylindole **111** is oxidized to the 1,1′-biindolyl **112**, whereas the comparable chemical oxidation using persulfate gives the simple 1,1-biindolyl **113** together with its hydroxylated analog **114** (01JCS(P2)618) (Scheme 29). It is also



36 **110**

111 **112**

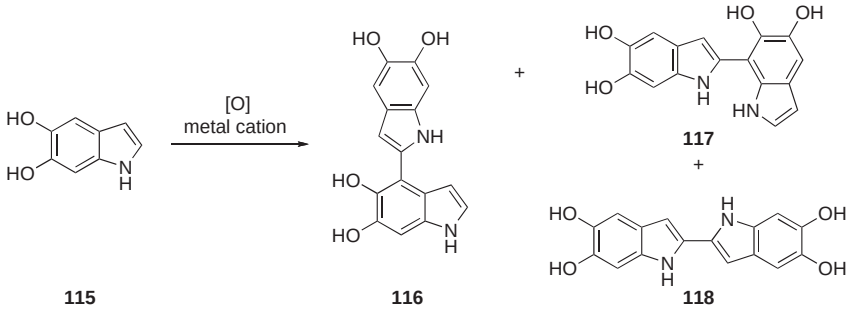
111 **113** 11% **114** 31%

Scheme 29

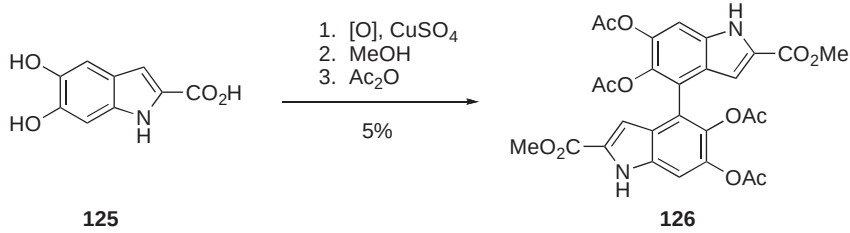
proposed, without evidence, that 1,2-dimethylindole is oxidized electrochemically to the 3,6′-biindolyl (91T737).

The oxidation of 5,6-dihydroxyindoles has been extensively studied because of its relevance to the formation of melanin pigments, and has proven to be a source, albeit in very small yields, of a variety of biindolyls and more complex terindolyls and tetraindolyls (05AHC1). For example, chemical or enzymatic oxidation of 5,6-dihydroxyindole **115** gives initially the 2,4′-biindolyl **116**, the 2,7′-biindolyl **117**, and the 2,2′-biindolyl **118**. Dimers **116** and **117** are subsequently converted into the terindolyls and tetraindolyls **119–121** and **122–124**, respectively (07OL1411, 07JOC9225) (Scheme 30).

The related 2-carboxylic acid **125** undergoes autoxidation with oxygen and copper (II) sulfate to form a 4,4′-dimer, which after methylation and acetylation gives the 4,4′-biindolyl **126**, which can be isolated in 5% yield (87TL467) (Scheme 31). The more reactive 5,6-dihydroxy-2-methylindole



Scheme 30



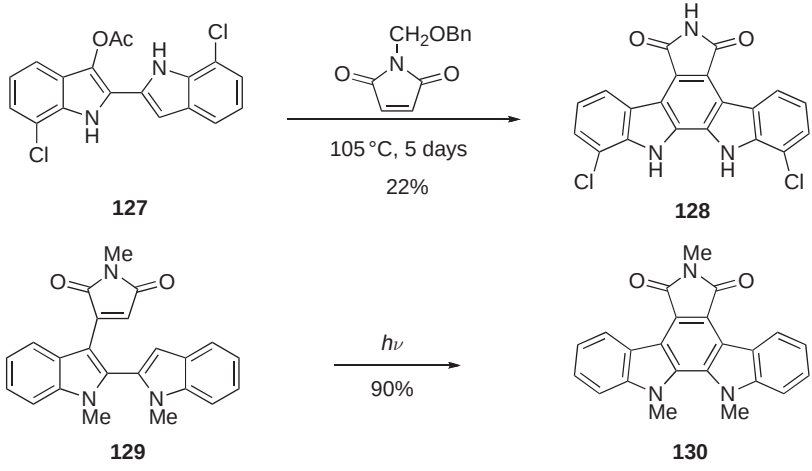
Scheme 31

gives 3,3′-, 3,4′-, 3,7′-, and 7,7′-biindolyls, as well as the 3,3′; 7,2′-terindolyl, again isolated as the acetates in very low yields (93T9143).

3. REACTIONS

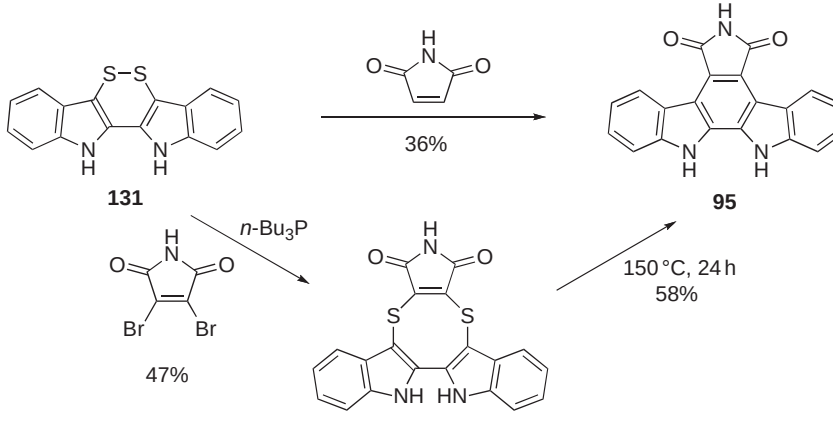
In general, the reactions of biindolyls reflect the reactivity of simple indoles and are therefore not of any particular interest. Therefore, this section will only consider some interesting cyclization reactions. The most important of these are encountered in syntheses of the biologically active indolocarbazoles. For example, the Diels–Alder addition of maleimides to 2,2′-biindolyls has been investigated but generally gives low yields of the desired indolocarbazoles, with Michael addition products being preferred. However, the Michael products can very effectively be cyclized to the indolocarbazoles. For example, when the 2,2′-biindolyl **127** is heated with *N*-benzyloxymaleimide at 105°C for 8 days, the indolocarbazole **128** is produced in 22% yield (85TL4015). In contrast, the Michael adduct **129** undergoes photo-cyclization to the indolocarbazole **130** in 90% yield (93TL5329, 95T12797) (Scheme 32). Similar photo-cyclization of a related pyrrolone is also effective (03TL2577).

A 36% yield of indolocarbazole **95** is obtained from the 2,2′-biindolyl dithiete **131** (99TL3795). Reaction of the dithiete **131** with dibromomaleimide and tri-*n*-butylphosphine gives a 47% yield of the eight-membered ring **132**, which undergoes a sulfur contraction reaction to yield **95** in 58% (00TL9835) (Scheme 33).



127 **128** **129** **130**

Scheme 32



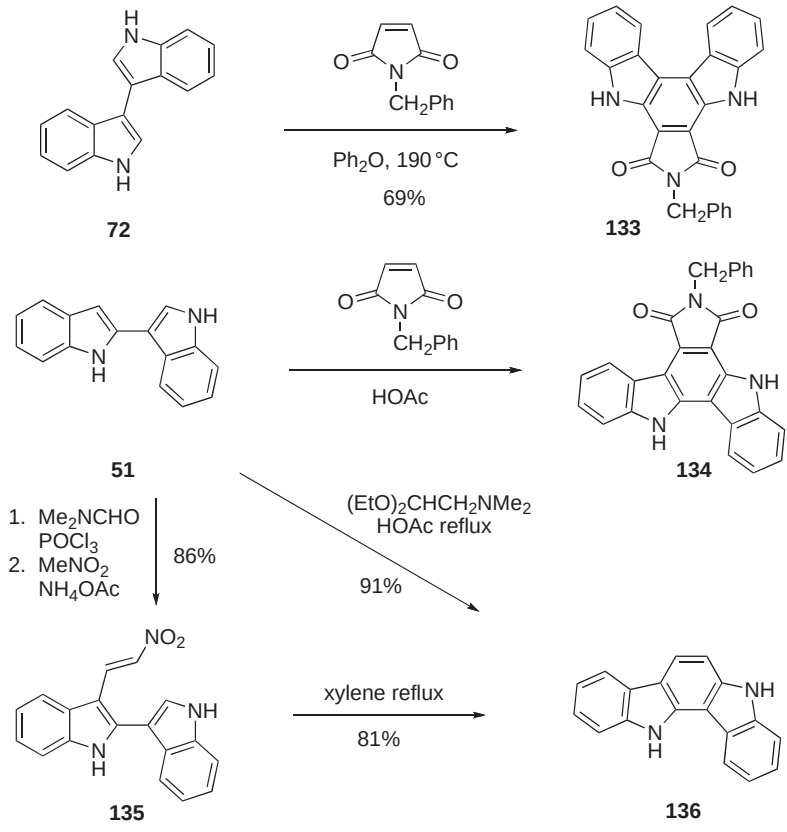
Scheme 33

Cycloaddition reactions are easier to control with 3,3′-biindolyls than with 2,2′-biindolyls. Thus 3,3′-biindolyl **72** forms indolocarbazoles in moderate to good yields on heating under different conditions with dimethyl acetylenedicarboxylate, *N*-substituted maleimides, or maleic anhydride. The reaction of **72** with *N*-benzylmaleimide is illustrated to give indolocarbazole **133** (98JCS(P1)2009) (Scheme 34). A similar cycloaddition of *N*-benzylmaleimide with the 2,3′-biindolyl **51** gave the indolocarbazole **134**, which could also be formed in a stepwise fashion by reaction of **51** with dimethyl acetylenedicarboxylate followed by benzylamine. However, the parent indolocarbazole **136** could be formed by reaction of **51** with dimethylaminoacetaldehyde diethyl acetal in acetic acid or by cyclization of the 3-nitrovinyl derivative **135** of **51** in boiling xylene (99T2363, 99T2371).

The indolocarbazoles **138** and **139** can be formed via a palladium-catalyzed benzannulation of the 3-iodo-2,2′-biindolyl **137** with ethyl phenylpropiolate in 59% and 29% yields, respectively (97TL7661, 01T5199) (Scheme 35).

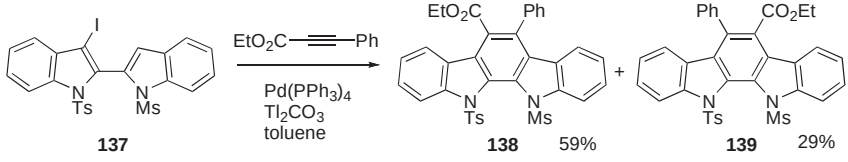
Chromium carbene complexes of 2,2′-biindolyls can be converted to indolocarbazoles by heating with *t*-butylisocyanide or photo-irradiation with carbon monoxide: for example, complex **140** gives the amine **141** and the phenol **142** in 89% and 51% yields, respectively (01T5199) (Scheme 36).

New six-membered rings can be formed in a variety of simple cyclization reactions. For example, the 2,2′-biindolyl **143** can be cyclized to **144** by treatment with base, on the way to a synthesis of calothrixin B (07TL231) (Scheme 37). The 2,3′-biindolyl lactam **146** can be formed by the



72 133 51 134 135 136

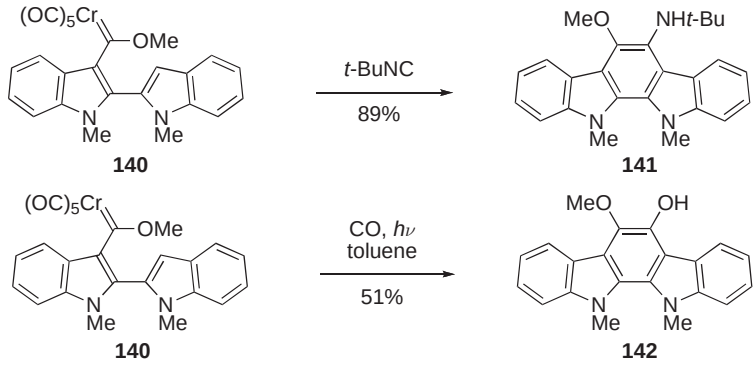
Scheme 34



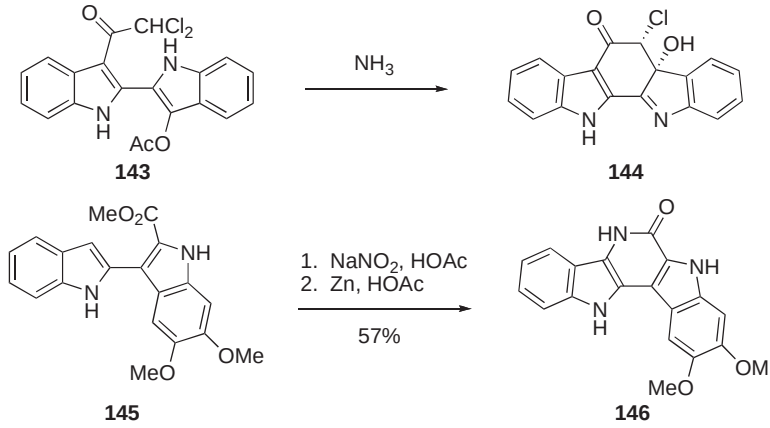
137 138 139

Scheme 35

nitrosation and reduction of the 2,3′-biindolyl ester **145** (04TL7273). A lactam can also be formed when the Suzuki–Miyaura coupling reaction generates a 3,7′-biindolyl in which an indole NH can attack an appropriately located ester function (08JOC9177). Attempted formylation of the 7,7′-biindolyl **66** also leads to cyclization onto an indole nitrogen atom (96T7003).



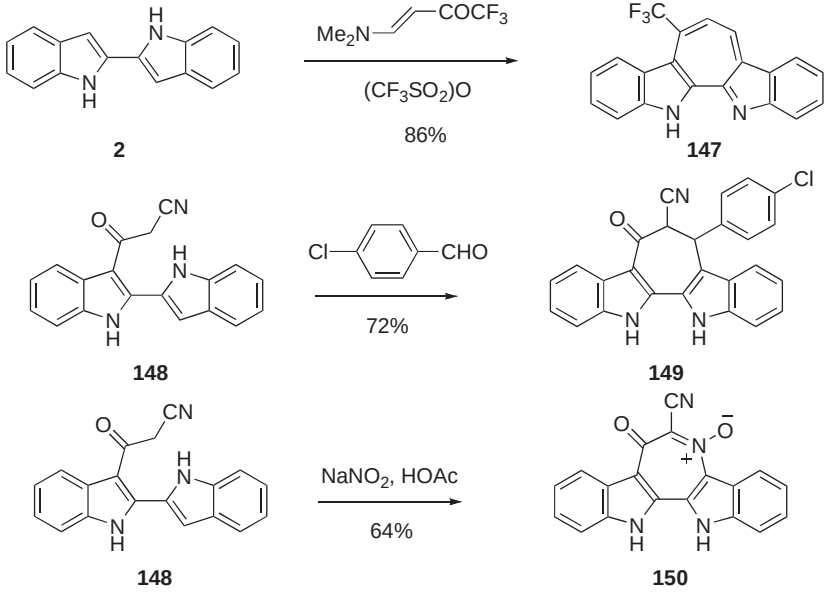
Scheme 36



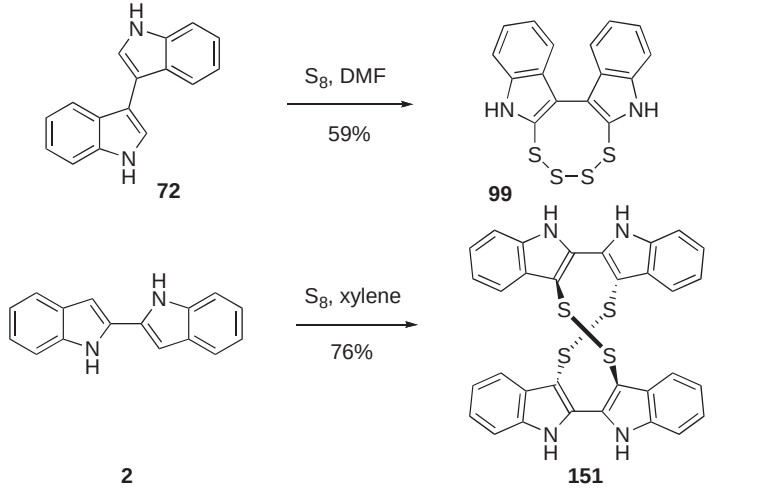
Scheme 37

Examples of seven-membered ring formation have been reported with 2,2′-biindolyls. When the 2,2′-biindolyl **2** is heated with 4-dimethylamino-1,1,1-trifluoro-3-buten-2-one and triflic anhydride, **147** is formed in 86% yield (03CHC776) (Scheme 38). Also the cyanoacetyl **148** reacts with 4-chlorobenzaldehyde to give the cyclized **149** (07JOC5886). An interesting product **150** containing an azepine ring can also be formed by the reaction of **148** with sodium nitrite in acetic acid (Scheme 38).

An eight-membered tetrasulfide **99** is formed in the reaction of 3,3′-biindolyl **72** with sulfur, but the related reaction with 2,2′-biindolyl **2** yields a dimeric structure **151** (02EJOC1392, 02JCS(P1)330) (Scheme 39).



Scheme 38



Scheme 39

4. CONCLUSION

The great majority of the chemistry of biindolyls has focused on those with 2,2′-, 2,3′-, and 3,3′-linkages. There is therefore extensive scope to explore completely new biindolyl systems, and this area of research is likely to be very rewarding in the future.

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CHAPTER 4

The Annulation of 2-Imidazolines

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Contents

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This account is largely a personal view of an area of the author's own research over three decades. It does not set out to be comprehensive, so the author apologizes in advance for any lack of acknowledgment of related work.

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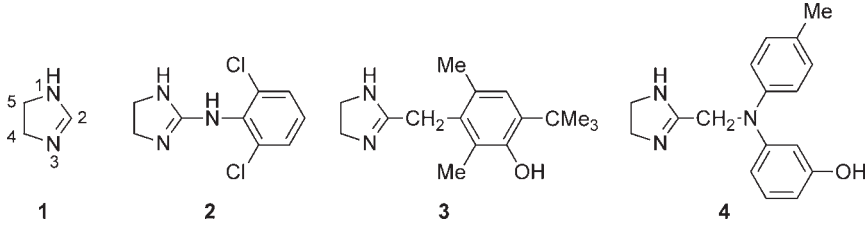
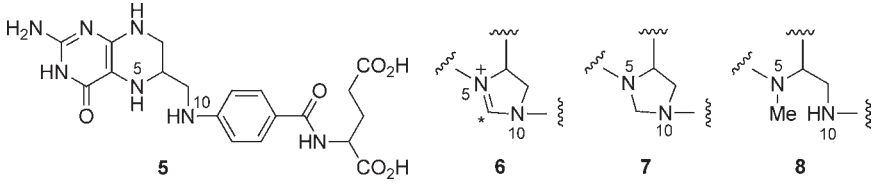
1. INTRODUCTION

The 2-imidazoline (4,5-dihydroimidazole) heterocyclic ring system (**1**) is of interest for a number of reasons. The first is medicinal. There are several imidazoline-based molecules in service in the clinic and several others with significant activity at adrenoreceptors (06MI1). One classic example is clonidine (**2**), which is used as an antihypertensive agent (09MI617), and (as any Internet search will quickly reveal) has found new uses, including treatment of some types of neuropathic pain, opioid detoxification, sleep hyperhidrosis, anesthetic, insomnia relief of menopausal symptoms, and (in conjunction with stimulants) treatment of attention-deficit hyperactivity disorder. Clonidine can be used in the treatment of Tourette syndrome and as a premedication before surgery. Clonidine acts an α_2-adrenoreceptor agonist, with selectivity for presynaptic receptors. It decreases cardiac output and peripheral vascular resistance, lowering blood pressure. Other related imidazolines are oxymetazoline (**3**), a selective α_1-agonist and partial α_2-agonist used as a topical decongestant, and phentolamine (**4**), an α_2-antagonist used for the control of hypertensive emergencies. A family of imidazoline receptors has been defined, known as I_1–I_3 (06MI217). I_3 receptors mediate the sympathoinhibitory actions of imidazolines to lower blood pressure.



Another stimulus for interest in imidazolines is their relationship to Nature's carbon-transfer coenzymes, the family based on tetrahydrofolic acid (FH_4) (**5**) (04MI1112) (10MI3816). N^5,N^{10}-Methenyltetrahydrofolate (**6**) is an intermediate in the transfer of a C-1-unit (the imidazoline C-2 carbon, indicated by an asterisk) at the formate oxidation level, and is an imidazolinium salt. N^{10}- and N^5-Formyl-FH_4, along with N^5-formimino-FH_4, are

also responsible for this transfer. Redox processes connect N^5,N^{10}-methenyl-FH_4 to N^5,N^{10}-methylene-FH_4 (7), the tetrahydroimidazole reduction product, which transfers C-1 units at the formaldehyde oxidation level, and N^5-methyl-FH_4 (8), which operates at the methanol oxidation level. In addition, ylides potentially formed from 2-unsubstituted imidazolines can be regarded as mimics of the thiamine coenzyme thiazole moiety (04MI2176, 05MI1132, 05MI1209, 10MI1566, 10MI2688) and indeed we have exploited the potential of such ylides (90TL1767, 90TL1771).

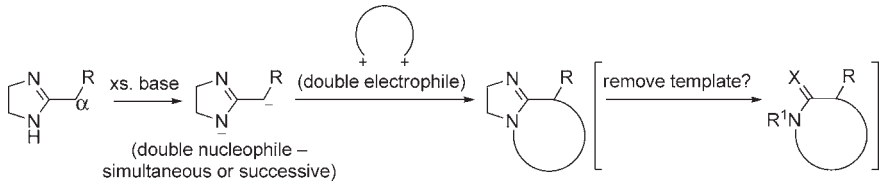


This background provided the motivation to explore imidazoline chemistry, both to produce novel molecules of biological potential and to exemplify the relationship of imidazoline chemistry to coenzyme-mediated chemistry. This chapter will focus in particular on the annulation of imidazolines to produce novel heterocyclic molecules. Our objectives were to use imidazolines in synthesis, and as templates for new rings; to make aza-analogues of biologically significant systems; to develop new routes to 5- and 6-membered rings, and bicyclics; and to contribute to the asymmetric synthesis of heterocycles. This chapter will deal with the chemistry in the achiral molecules first and then show where and how it has been applied to chiral and optically active situations.

2. POLAR ANNULATION STRATEGY

The general strategy for our initial studies was based on the notion that imidazolines substituted with alkyl groups at C-2 should display two sites of nucleophilic reactivity, namely, at N-1 and at C-2(α). The lateral metallation was not known at the start of our endeavors, although related chemistry of 2-oxazolines had been reported; for recent reviews see (05JOC6137, 08CHEC-III(4)510). Such double nucleophilicity would lend itself to annulation via reaction with a range of doubly electrophilic species, to generate varying sizes of fused ring (Scheme 1).

Further on in our studies we also postulated the conversion of imidazolines into 1,3-dipoles by suitable functionalization at N-1, and that this would allow dipolar cycloaddition as an annulation strategy for



Scheme 1

imidazolines with five-membered rings. We have realized both of these approaches and will describe them herein.

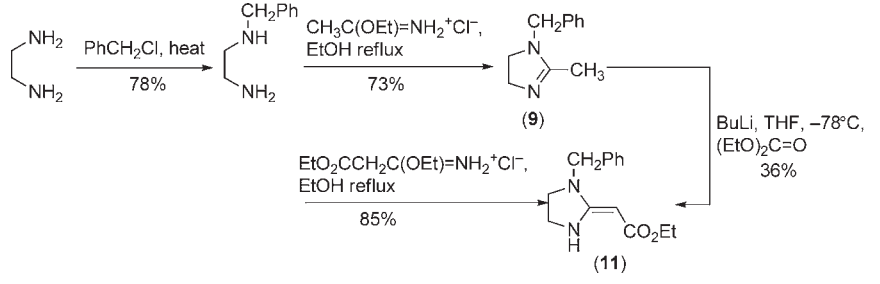
3. IMIDAZOLINES AS DOUBLE NUCLEOPHILES

First, it is necessary to introduce the enabling synthetic methodology underpinning the double nucleophile–double electrophile annulation. Our first steps were to generate suitable imidazoline substrates to establish the C-2(α) nucleophilic reactivity.

3.1 Synthesis of substrates

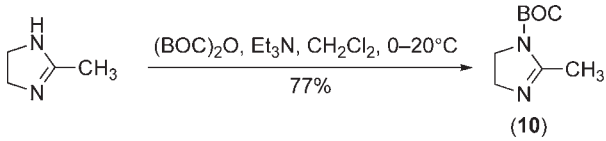
Attempts to demonstrate C-2(α)-anion reactivity by double deprotonation of commercially available 2-methyl-2-imidazoline provided mixed results, and indicated that extra stabilization of the lateral position, for example, by the phenyl group in 2-benzyl-2-imidazoline, was necessary to support a dimetallated species. This was in line with the findings of others (98JOC8107, 98TL8979). It was therefore necessary to seek suitable N-substituted 2-methyl-2-imidazolines.

Much of our early work used N-benzyl derivatives, as a group potentially removable from N-1. Thus we prepared 1-benzyl-2-methylimidazoline (**9**) by straightforward reaction of N-benzyl-1,2-diaminoethane (whose preparation was already reported) with a C-2 unit at the carboxylic oxidation level (Scheme 2) (81TL261, 86JP1205). This latter was the imidate prepared



Scheme 2

from acetonitrile and ethanol in the presence of hydrogen chloride. In later studies discussed below, we used N-*tert*-butyloxycarbonyl-2-methyl-2-imidazoline (**10**), prepared simply from commercial 2-methyl-2-imidazoline (trivially known as lysidine) and di-*tert*-butyl dicarbonate (Equation (1)) (00T2061).



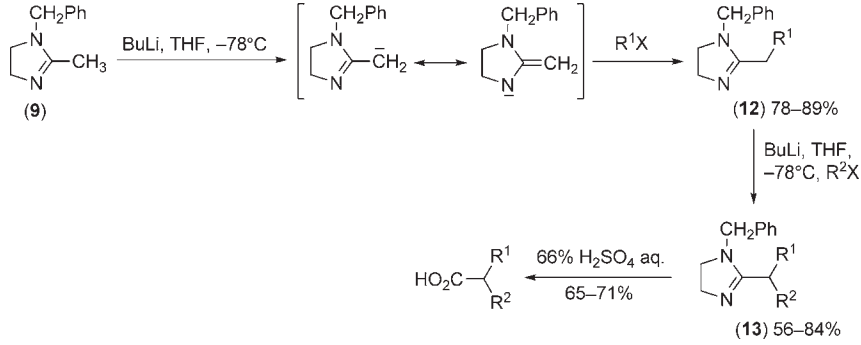
(**10**) (1)

We also prepared a possible alternative substrate for the C-2(α) nucleophilic reactivity, 1-benzyl-2-(ethoxycarbonylmethylene)-1,2,3,4-tetrahydroimidazole (**11**), which may be regarded as an enamino ester or a ketene aminal. This could display the desired nucleophilic potential through its enamine functionality, and the alkoxycarbonyl group regarded as an activating group. This group should be removable, by analogy with acetoacetate/malonate chemistry. The enamino ester was accessed from 1-benzyl-2-imidazoline prepared as above, by metallation and C-acylation with diethyl carbonate, or much more conveniently directly from N-benzyl-1,2-diaminoethane and an imidate prepared from ethyl cyanoacetate and ethanol in the presence of hydrogen chloride (Scheme 2) (84JP12599). Much of our annulation work was performed on this enamino ester as a stable substrate, as will become clear below.

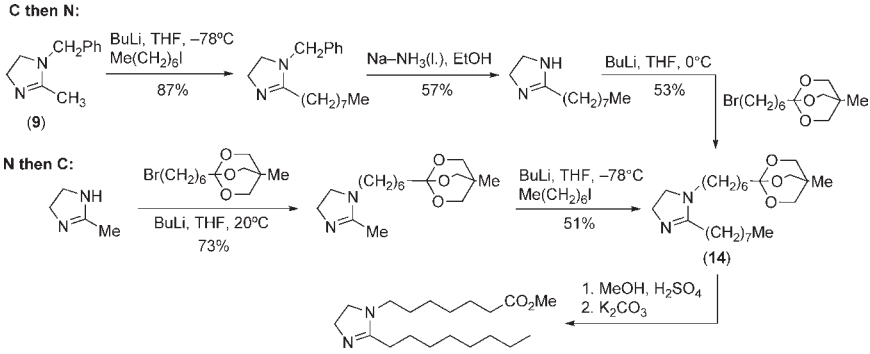
3.2 Lateral metallation at C-2(α)

Lateral metallation of 2-methyl-2-imidazolines was demonstrated by C-2(α)-deprotonation of the N-benzyl compound **9** using *n*-butyllithium (*n*-BuLi) at low temperature and alkylation with alkyl halides (Scheme 3) to afford derivatives **12** (81TL261, 86JP1205). A second deprotonation–alkylation reaction could also be achieved, although a third such successive step was not possible. The α-branched 2-alkyl-2-imidazolines **13** could be hydrolytically cleaved under acidic conditions to realize the potential of the 2-imidazoline system in C-2 transfer: here the 2-methyl-2-imidazoline functions as an ethanoate enolate equivalent.

The C-2(α) nucleophilic property was combined with N-1 nucleophilic potential in two sequences, illustrated by the assembly of some imidazolines that were made as potential aza-analogues of prostaglandins (Scheme 4) (90JP1373). In one sequence, C-alkylation was performed first on 1-benzyl-2-methyl-2-imidazoline (**9**), and the N-benzyl



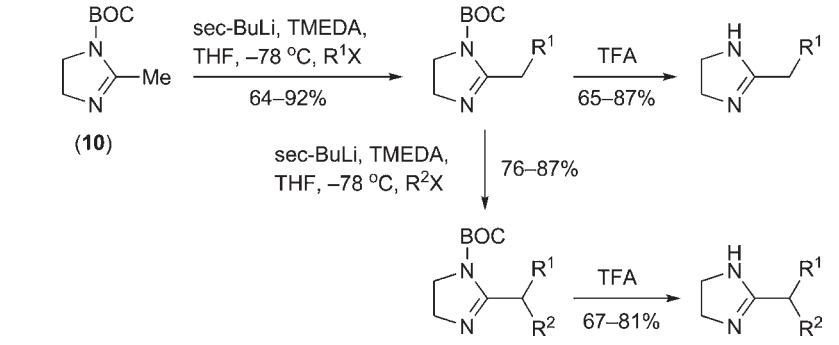
Scheme 3



Scheme 4

group was removed from the C-alkylated product by dissolving metal reduction. The liberated NH function was subsequently alkylated using *n*-BuLi at 0°C and an alkyl halide, which in this case also carried a masked carboxylic acid function that was revealed in a final step. The alternative sequence used commercial 2-methyl-2-imidazoline, which was first N-alkylated at N-1 with the same ω-functionalized alkyl halide introduced in the first sequence (*n*-BuLi at 20°C) and then reacted at C-2(α) as described above to produce the same doubly alkylated material **14**, from which the masked carboxylic acid was revealed as its methyl ester.

In order to avoid the dissolving metal step to remove the N-1 benzyl substituent, we developed an alternative protocol for C-alkylation to give N-1 unsubstituted imidazolines. In this we employed 2-methyl-N-*tert*-butyloxycarbonyl (Boc) imidazoline (**10**) (Scheme 5). Deprotonation–alkylation was now accomplished using sec-BuLi-TMEDA followed by an alkyl halide, and the Boc group was simply removed by trifluoroacetic acid (TFA) treatment (00T2061).



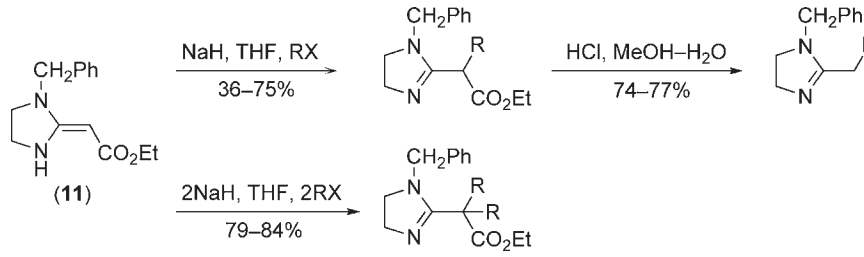
Scheme 5

The C-2(α) metallation reactivity has also been demonstrated on ring-fused imidazolines: 1-benzyl-2-methyl-3a,4,7,7a-tetrahydro-1H-benzimidazole (90JP1373), 3-methyl-1,5,6,10b-tetrahydroimidazo[5,1-*a*] isoquinoline, and 1-methyl-3,3a,4,5-tetrahydroimidazo[1,5-*a*]isoquinoline (90JP1385), the latter designed as mimics of N^5,N^{10}-methenyltetrahydrofolate (**6**).

We have selected to illustrate the nucleophilic reactivity of C-2(α) by alkylation reactions; in addition, the nucleophilic α-lithioalkyl imidazolines also react with carbonyl electrophiles in addition and condensation reactions (88TL5001, 97T1111), some of which will be relevant to the annulation chemistry discussed below.

3.3 Enamine reactivity of the enamino ester 11

Our alternative substrate as a C-2(α) nucleophile, the enamino ester **11**, was also validated by deprotonation–alkylation (Scheme 6). Double alkylation was also successful, although two successive alkylations to produce unsymmetrical dialkylation, was not (91JP1953, 97T11781). Acidic hydrolysis accompanied by the expected decarboxylation was shown to remove the ethoxycarbonyl group and confirmed the enamino ester as an activated synthetic equivalent of the C-2(α) anion.



Scheme 6

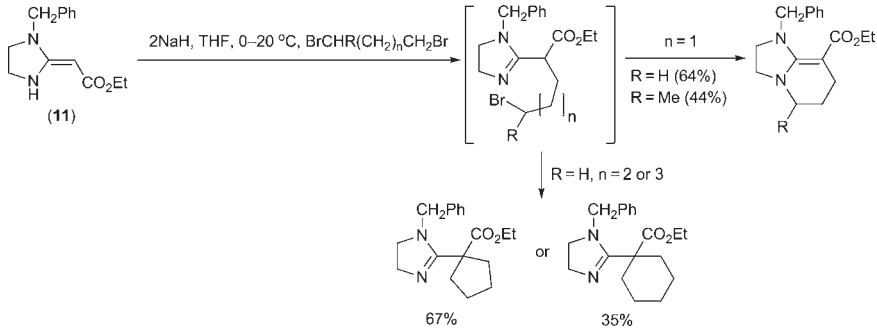
Again, as will become clear from our annulation studies described later, the enamino ester **11** also reacts, as expected, with carbonyl-based electrophiles.

4. ANNULATIONS OF THE ENAMINO ESTER/KETENE AMINAL

As was stated earlier, much of our annulation work was performed on the enamino ester/ketene aminal **11** as a stable activated substrate, and using a range of bis-electrophiles across the spread of potential oxidation levels.

4.1 Dihaloalkane electrophiles

With this enabling chemistry in hand, we were able to embark on annulation studies. Our first forays into this area used the enamino ester **11** and dihaloalkanes. When using a 1,3-dihaloalkane, alkylation under basic conditions was observed at both N-1 and C-2(α), leading to imidazo[1,2-*a*]pyridines (Scheme 7) (91JP1953, 97T11781). The initial alkylation was deduced to be at C-2(α) from the product regiochemistry, which showed the presumably more reactive primary 1-bromo function to become attached at the enamino ester carbon, with the secondary 3-bromo center providing the N-alkylation. This preference for C-alkylation manifested itself again when using 1,4-dibromobutane or 1,5-dibromopentane, when double C-alkylation was observed to give the 1,1-disubstituted cyclopentane and cyclohexane derivatives, rather than ring-fused annulation products. 1,2-Dibromoethane resulted in the recovery of starting material under the same reaction conditions.

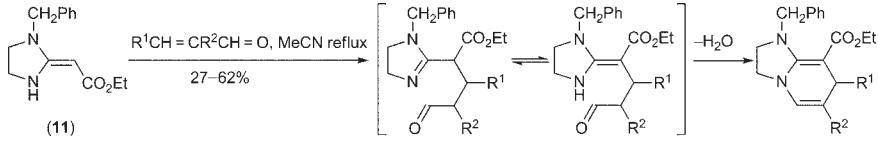


Scheme 7

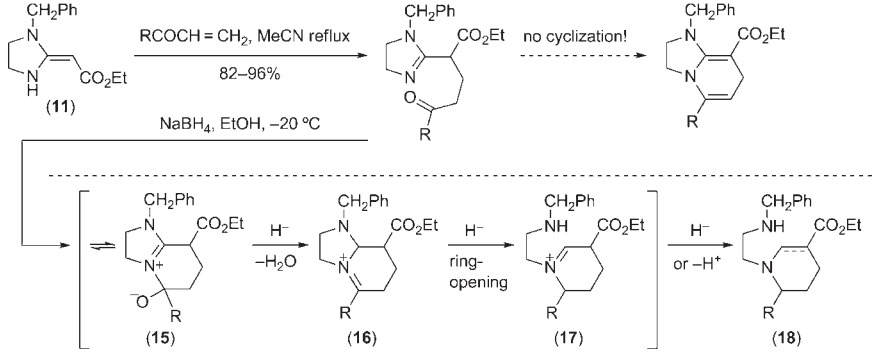
4.2 α,β-Unsaturated aldehyde and ketone electrophiles

Continuing with the enamino ester **11** as substrate, and moving to a bis-electrophile one oxidation level higher than a dihaloalkane, we explored the reactions with conjugated aldehydes (89TL5361, 98T6191). In this case, we found once again the tendency for C-nucleophilicity to lead the annulation. Thus, conjugate C-addition of the enamino ester onto the α,β-unsaturated aldehydes was found, with the presumed initial conjugate adduct undergoing tautomerization to allow N-1(H) cyclization onto the aldehyde group to form an enamine (Scheme 8). The resulting imidazo[1,2-*a*]pyridines can be viewed as unsymmetrical 1,4-dihydropyridines related to the calcium channel blockers such as Nifedipine.

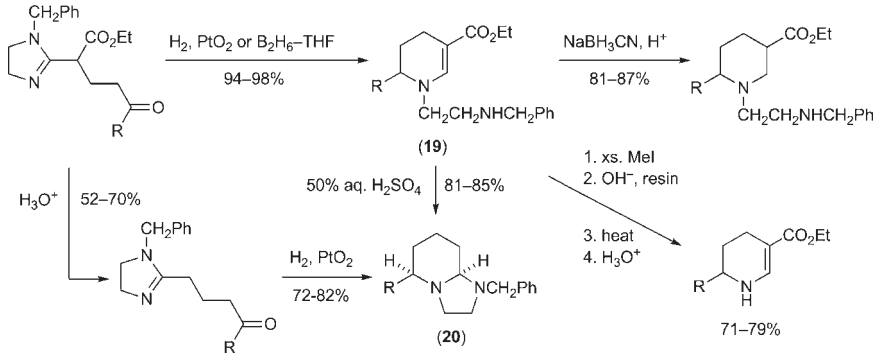
The apparently small change to using α,β-unsaturated ketones as the bis-electrophiles led to a different outcome. The initial conjugate C-addition products could be isolated and resisted the cyclization step (89TL5361, 98T6191). Instead, when they were reduced by sodium borohydride, these adducts underwent a cascade of steps to afford low yields of N(1)-substituted 3-alkoxycarbonyl piperidines or tetrahydropyridines **18** (89TL5365). This is believed to occur via an initial annulation step (Scheme 9). Cyclization of N-1 onto the ketone carbonyl leads to an iminium salt **15**, which can be captured by hydride reduction. Water



Scheme 8



Scheme 9



Scheme 10

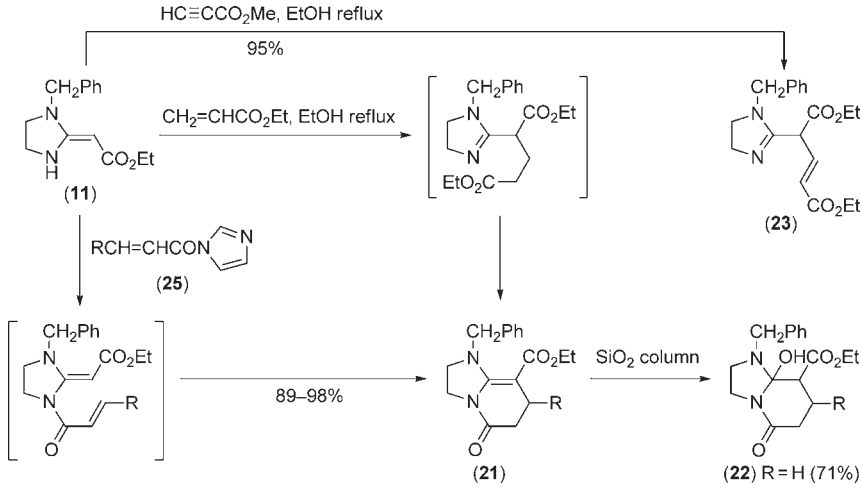
elimination leads to a second iminium salt **16**, which is also reduced by hydride. The aminal produced can ring-open to a third iminium ion **17**, from which hydride reduction or simple proton loss leads to the observed piperidine or tetrahydropyridine products **18**.

This sequence, although mechanistically interesting, did not occur in high yield. If the reducing system applied to the conjugate C-adducts was switched to hydrogen and Adams catalyst, or borane-THF, then an annulation–reduction cascade whose mechanism is not certain but must be related to the hydride-mediated sequence described above, leads to the same N(1)-substituted 3-alkoxycarbonyltetrahydropyridines **19** as with $NaBH_4$ (Scheme 10) (89TL5365). Acid treatment completes hydrolysis–decarboxylation, with cyclization of the intermediate iminium ion to give imidazo[1,2-*a*]pyridines **20**. Hydrolysis–decarboxylation of the initial conjugate addition products before the reductive sequence leads directly to the same imidazopyridines. Some other modifications of the tetrahydropyridines **19** have been achieved.

In all of these [3+3] annulations of the enamino ester **11** to imidazopyridines, the enamino ester is functioning as an acetaldehyde enamine equivalent.

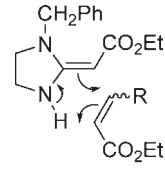
4.3 α,β-Unsaturated acid derivatives as electrophiles

The next set of annulations employed bis-electrophiles one step higher in oxidation level, unsaturated acid derivatives. Treatment of the enamino ester **11** with the α,β-unsaturated ester ethyl propenoate proceeded via a (presumed) imidazo[1,2-*a*]pyridin-5-one **21** (R = H) to afford an isolated cyclol **22** (R = H) by hydration when chromatographed on silica (Scheme 11) (88TL5005, 98T6191). Based on the findings with other bis-electrophiles discussed above, we assume this



Scheme 11

reaction proceeds via conjugate C-addition followed by N-1 acylation. This sequence is supported by the isolation of the conjugate C-addition product **23** from reaction of the enamino ester with ethyl propynoate. An aza-ene proposal (**24**) has been made by others for such conjugate additions (93JP11085, 99JP12087).



24

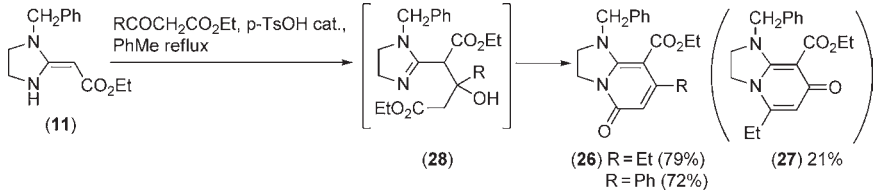
In an attempt to switch the sequence of steps, more activated acid derivatives were selected as electrophiles, and propenoyl chloride gave the same imidazopyridin-5-one **21** (R = H). A more convenient protocol was found based on in situ preparation of α,β-unsaturated acyl imidazolides **25**: thus an α,β-unsaturated acid was pretreated with 1,1′-carbonyldiimidazole before addition of the enamino ester (88TL5005, 98T6191). A simple partition between chloroform and aqueous sodium hydrogen carbonate led to isolation of the imidazopyridin-5-ones **21** in good yield, now presumably via N-acylation followed by conjugate C-addition (Scheme 11). In some cases they were converted into the cyclols **22** if chromatographed on silica,

although the products from phenylpropenoic acid and propynoic acid proved stable toward such chromatography.

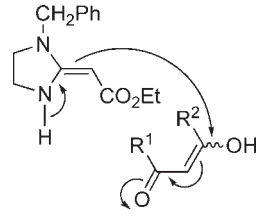
4.4 1,3-Dicarbonyl compounds as electrophiles

1,3-Dicarbonyl compounds would be the next rung up the oxidation ladder. However, attempts to react the enamino ester **11** with 1,3-diketones were unsuccessful, with starting materials recovered. Using 1,3-diesters as the double electrophile gave no reaction with the enamino ester. On the other hand β-keto esters afforded excellent yields of imidazopyridinones: ethyl acetoacetate gave mixtures of imidazopyridin-5-one **26** (R = Et) as major product and the corresponding 7-one **27** (R = Et) as minor product, whereas ethyl benzoylacetate afforded solely the imidazopyridin-5-one **26** (R = Ph) (Scheme 12) (88TL5005, 98T6191). These products arise from competing acylation at N-3 or C-2(α).

Our earlier findings suggest that conjugate C-addition to α,β-unsaturated systems is the preferred reaction of the enamino ester. We therefore rationalize the findings with 1,3-dicarbonyl compounds by proposing a similar pathway of initial conjugate C-addition to the enol of the 1,3-dicarbonyl compound, to give intermediates **28**. This addition, illustrated in **29**, accounts for the preferred regiochemistry of annulation using β-keto esters (98T6191); the lack of reaction with 1,3-diesters may be attributable to their much lower enol content (e.g., diethyl malonate 7.7×10^{-3}% vs. ethyl acetoacetate 8.0% in pure compound). 1,3-Diketones have much higher enol content (pentane-2,4-dione 76.4% neat) and so are proposed to undergo ready conjugate C-addition, but that the primary adduct will resist cyclocondensation (as was observed with α,β-unsaturated ketones (Scheme 9) (89TL5361)). Our experience with 2-(2-hydroxyalkyl)-2-imidazolines, formed from adding 1-benzyl-2-lithiomethyl-2-imidazoline to ketones, when it was found that this addition was readily reversible (88TL5001, 97T1111), suggests that the primary adducts from 1,3-diketones will undergo similar retro-aldol fragmentation (Equation (2)) under the reaction conditions (toluene at reflux, with or without toluene-4-sulfonic acid, or THF–NaH at reflux).



Scheme 12



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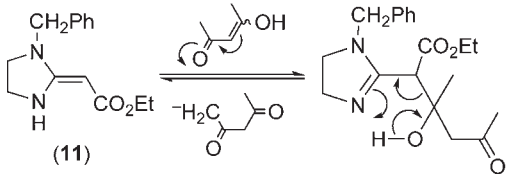
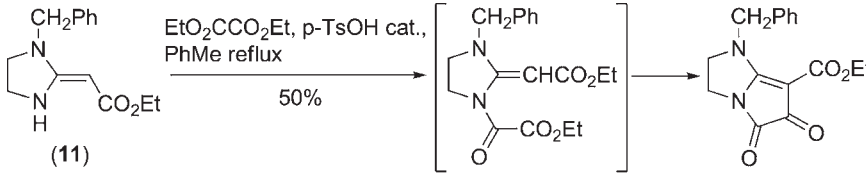


(2)



Scheme 13

As a representative 1,2-bis-electrophile, diethyl oxalate was found to react with the enamino ester **11** under acidic conditions (neutral and basic conditions having produced no reaction) to afford a dioxo-pyrrolo[1,2-*a*]imidazole **30** (Scheme 13) (98T6191). Interrupting the reaction before completion indicated an N-acylated intermediate **31**; arguments about conjugate addition clearly cannot be applied in this case. Taken with the unsuccessful 1,2-dibromoethane result shown earlier, it can be seen that there clearly remains scope for further 1,2-bis-electrophiles at various oxidation levels to be investigated with the enamino ester.

5. ANNULATIONS OF N-UNSUBSTITUTED 2-IMIDAZOLINES

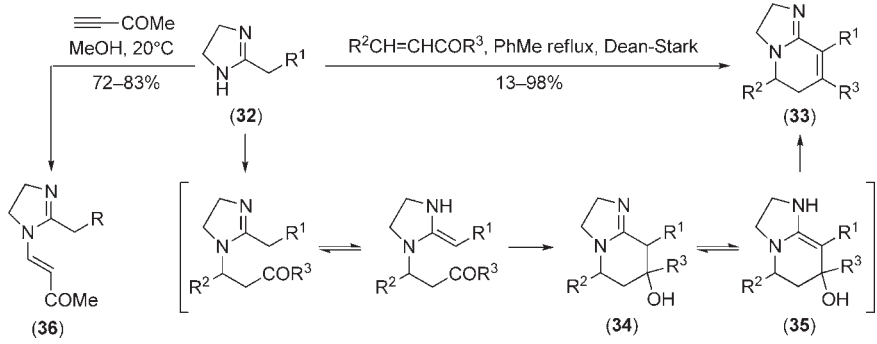
The range of C-2(α)-unactivated, N-unsubstituted 2-alkyl-2-imidazolines made available by our deprotonation–alkylation–deprotection protocol from N-*tert*-butyloxycarbonyl-2-methyl-2-imidazoline (00T2061), opened up further avenues for annulation, and indeed produced some results

distinct from those observed for the enamino ester, detailed in the preceding sections.

5.1 α,β-Unsaturated aldehyde and ketone electrophiles

Heating a variety of 2-alkyl-2-imidazolines **32** with a set of α,β-unsaturated aldehydes & ketones under conditions of water removal, led to a range of tetrahydroimidazo[1,2-*a*]pyridines **33** (Scheme 14) (00JP12331); there was no evidence of enamine formation at N-1. The regiochemistry of the annulation products, as confirmed by NMR studies, is consistent with conjugate N-addition onto the enals and enones, followed by an enamine–aldol reaction of the C-2(α) carbon center as nucleophile with the former enal or enone carbonyl group. Amongst supporting evidence for this pathway were the following observations: isolation of the pre-dehydration intermediate **34** ($R^1 = CH_2CH=CH_2$; $R^2 = Me$; $R^3 = H$) (27%) from reaction of the 2-(prop-2-enyl)-2-imidazoline with but-2-enal at 20°C (CH_2Cl_2, $MgSO_4$); isolation of the tautomeric alcohols **34** and **35** ($R^1 = Ph$; $R^2 = H$; $R^3 = Me$) as a 1:1 mixture (42%), along with the corresponding dehydration product **33** (21%) from reaction of 2-benzyl-2-imidazoline and but-3-en-2-one under the same conditions; and isolation of the enediamine alcohol **35** ($R^1 = Ph$; $R^2 = Me$; $R^3 = H$) (37%) from reaction of the 2-benzyl-2-imidazoline and but-2-enal under the reflux conditions but in more dilute solution. It is possible that the conjugation in alcohols **35** ($R^1 = Ph$) favors the enamine form of the aldol product and inhibits dehydration. When 2-(prop-2-enyl) or 2-benzyl-2-imidazolines were treated at 20°C in MeOH with but-3-yn-2-one, the *E*-enamines **36** were isolated, again the products of conjugate N-addition.

The control of regiochemistry of these annulations by conjugate N-addition is thus in direct contrast to the situation with the activated imidazoline enamino ester, where conjugate C-addition is dominant



Scheme 14

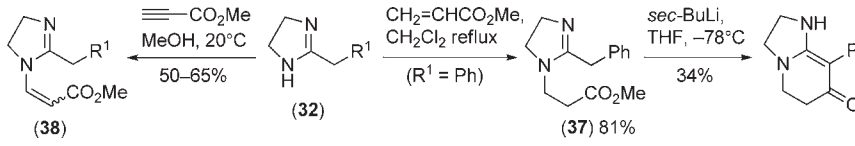
(98T6191). This led us to investigate whether this reversal would extend to other bis-electrophiles.

5.2 α,β-Unsaturated ester electrophiles

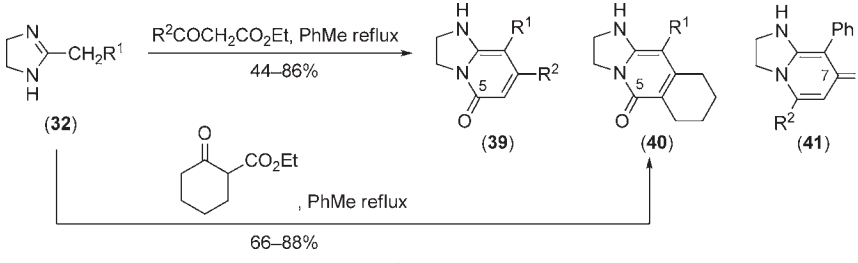
Treatment of 2-benzyl-2-imidazoline (**32**; $R^1 = Ph$) with methyl propenoate afforded the conjugate N-adduct **37**, in support of the preference for this first step with unactivated NH-imidazolines (Scheme 15). Annulation could be completed by C-2(α) metallation and condensation onto the ester function (00JP12331). The conjugate N-adducts were also isolated from reaction of several 2-alkyl-2-imidazolines **32** with methyl propynoate, as separable *Z*:*E* geometric isomer mixtures **38**.

5.3 β-Keto esters as electrophiles

Heating a set of the 2-alkyl-2-imidazolines **32** with ethyl acetoacetate, ethyl benzoylacetate, and ethyl 2-oxocyclohexanecarboxylate afforded the corresponding imidazopyridin-5-one **39** and the imidazoisoquinolin-5-one **40** (Scheme 16) (00JP12331). The regiochemistry is based on NOE studies and secured by an X-ray crystal structure of the imidazoisoquinolinone **40** ($R^1 = Ph$) formed from 2-benzyl-2-imidazoline. Although initial reaction of the imidazoline N-1 at the keto-carbon (either through direct 1,2-addition or through conjugate addition to the enol form) leading to the enamine may be the kinetic product based on the findings above, formation of the more stable amide linkage appears to control the regiochemistry



Scheme 15



Scheme 16

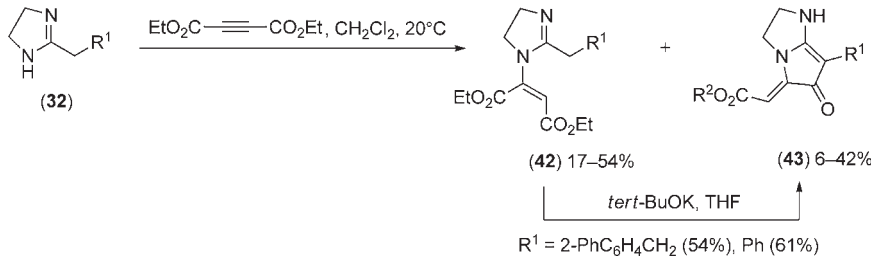
under these reaction conditions. This observed regiochemistry is in contrast to the reported reaction of 2-benzyl-2-imidazoline and β-keto esters to afford products assigned as the regioisomeric imidazopyridin-7-ones **41** (78JHC1021), so that we could conclude the reported structures were misassigned. Indeed our data match those for the reported compounds.

5.4 Diethyl acetylenedicarboxylate as electrophile

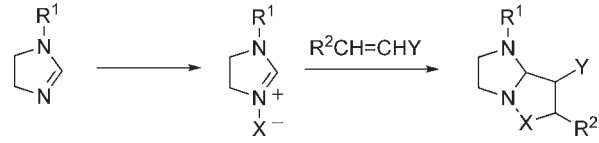
The 2-alkyl-2-imidazolines **32** react under mild conditions with diethyl acetylenedicarboxylate to give (*E*)-conjugate adducts **42** and *Z*-tetrahydropyrrolo[1,2-*a*]imidazol-6-ones **43** (Scheme 17) (00JP12331). Base treatment of the adducts led to the (*Z*)-pyrroloimidazoles and their (*E*)-isomers, and prolonged reaction led to mixtures of the annulation products. The annulation thus once again proceeds via initial conjugate N-addition of the 2-alkyl-2-imidazolines, but the acetylene dicarboxylates function as 1,2- rather than 1,3-bis-electrophiles and the sequence concludes with C-2(α)-acylation rather than with conjugate C-addition and imidazopyridine formation. This reactivity preference is in accord with an X-ray structure of one of the intermediate conjugate N-adducts **42** (from 2-(2-phenylbenzyl)-2-imidazoline), which shows in the solid state that the α-ester group is situated close to the C-2(α) carbon whereas the β-ester is part of a planar conjugated enamino ester system and is deactivated.

6. IMIDAZOLINES AS SOURCES OF 1,3-DIPOLES

The general strategy here was to convert 2-unsubstituted 2-imidazolines into 1,3-dipoles, by appropriate derivatization at N-1 to form a quaternary nitrogen atom carrying a negatively charged atom X, and to react these with dipolarophiles to complete an annulation with a new five-membered ring (Scheme 18). We have realized this with X as carbon fragments, generating azomethine ylides (imidazolinium ylides) and with X as oxygen to create nitrones (imidazolinium N-oxides). Efforts to



Scheme 17



Scheme 18

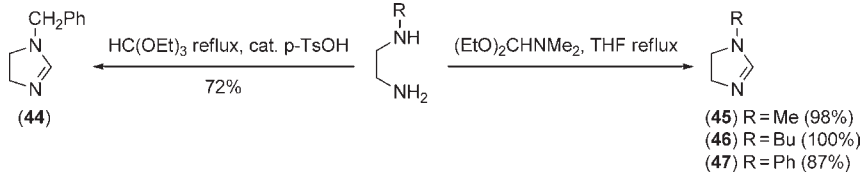
validate this approach with 2-substituted 2-imidazolines were not fruitful so will not be discussed further here.

6.1 Synthesis of substrates

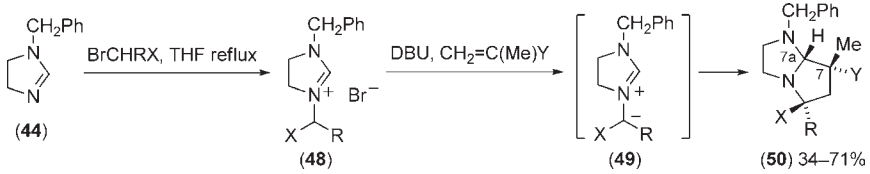
The 2-unsubstituted imidazolines **44–47** required for azomethine ylide formation were very easily prepared by reaction of N-benzyl-1,2-diaminoethane (prepared as Scheme 2) or the commercial N-methyl, N-butyl, and N-phenyl diamines, respectively, with this time a C-1 unit at the carboxylic oxidation level, such as triethyl orthoformate or dimethylformamide dimethyl acetal (Scheme 19) (90TL2333, 98JP12061, 07MI1, 08MI1).

7. AZOMETHINE YLIDES BY ALKYLATION–DEPROTONATION

One classic route to azomethine ylides involves N-alkylation of an imine and deprotonation of an sp^3 carbon atom attached to the iminium carbon. Thus the first approach to imidazolinium ylides involved alkylation of 1-benzyl-2-imidazoline (**44**) with an active halide (bromoacetate esters, chloroacetonitrile) in diethyl ether, removal of solvent from the deposited quaternary salt **48**, replacement of the solvent by THF at reflux containing an excess of the dipolarophile, and then slow addition of 1,8-diazabicycloundec-7-ene (DBU) as base (90TL2333) (98JP12061). Other base systems (e.g., *n*-BuLi, Et_3N, Hünig's base, some phosphazene bases) were unsuccessful. This formed the assumed dipole **49** in low standing concentration, which underwent cycloaddition with the dipolarophile. Suitable dipolarophiles were



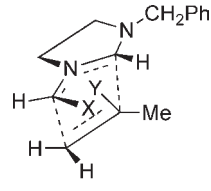
Scheme 19



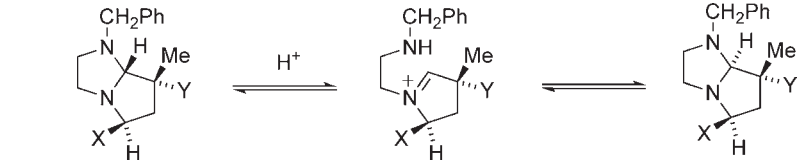
Scheme 20

electron-deficient alkenes, such as 2-methylpropenoate esters. In this way, new pyrrolo[1,2-*a*]imidazoles **50** were formed in diastereoselective fashion (Scheme 20). We subsequently streamlined this procedure to a one-step one-pot protocol by adding, in one portion, the alkylating agent and dipolarophile to the 2-imidazoline in THF at reflux, followed by slow dropwise addition of DBU to the mixture (93JP12391, 98JP12061). This produced effective reaction, even in cases where the alkylation reaction itself was shown to be slow. Dipole formation must therefore occur before alkylation is complete, and this presumably reduces the possibility of intervention of the hydrolytic sensitivity of the imidazolinium quaternary salts, or other side reactions.

The product regiochemistry observed, with the dipolarophile-activating group located at C-7 of the pyrroloimidazole cycloadducts, is as predicted for a stabilized azomethine ylide with an electron-deficient dipolarophile, that is, Sustmann type 1 with HOMO-dipole/LUMO-dipolarophile orbital control (71TL2717). The major (sometimes exclusive) diastereomer of the cycloadducts was as shown in Scheme 20, as secured by extensive NOE studies. Its formation could be rationalized by a transition state **51** involving an anti-dipole (anti referring to the methine-H at the formally negative dipole terminus, and the C-2(H) of the 2-imidazoline) and *endo* approach of dipolarophile to dipole, that is, the activating group on the alkene dipolarophile lying under the ring of the imidazolinium dipole. The anti-dipole has been postulated by other groups to be favored, e.g., (90T6449, 94T895), and H-bonding between the imidazoline C-2(H) and the dipole-activating carbonyl group can be invoked. This model has served well for dipolar cycloadditions in our work. In some cases a minor amount of the *exo* diastereomer (i.e., the C-7 epimer) was observed.



51

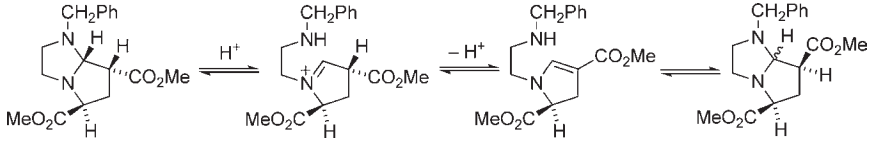


Scheme 21

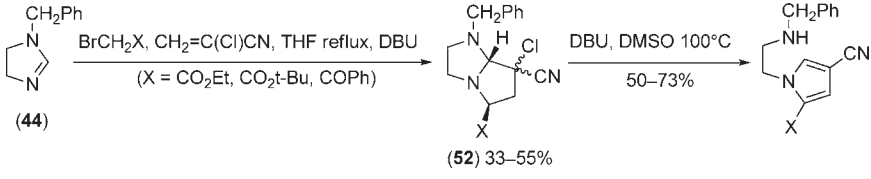
On standing or after chromatography using basic eluents, the cycloadducts underwent partial epimerization at the bridgehead carbon C-7a, presumably via equilibration with an amino-iminium monocyclic intermediate (Scheme 21). This process also intervened when an α-unsubstituted dipolarophile methyl propenoate was employed: after chromatography, a larger proportion of C-7 epimer was observed than might be expected from simple *endo*:*exo* selectivity of the cycloaddition. This was accounted for by reversible deprotonation of the amino-iminium ring-opened intermediate to give an enamino ester that underwent conjugate N-addition with protonation from either face (Scheme 22). Likewise, using methyl (*E*)-but-2-enoate as dipolarophile afforded the expected cycloadduct, which also epimerized at C-7 on standing.

Use of 2-chloropropenonitrile as an alkyne equivalent dipolarophile led to adducts **52** that on further treatment with base underwent a double elimination via a related ring opening and loss of HCl to generate novel N-substituted pyrroles (Scheme 23).

When employing dipolarophiles with a sulfone- or sulfoxide-activating group, we were surprised to find that *exo* cycloadducts were the major products (Equation (3)), that is, epimeric at C-7 to those illustrated in Scheme 20 (10CAJ461). The relative stereochemistry was secured by X-ray crystallographic analyses. We speculate that the extra steric requirement of the tetrahedral sulfone moiety may overcome any secondary

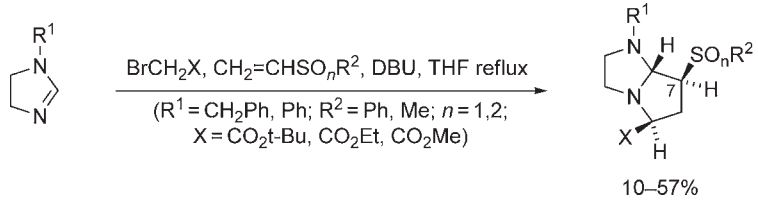


Scheme 22



Scheme 23

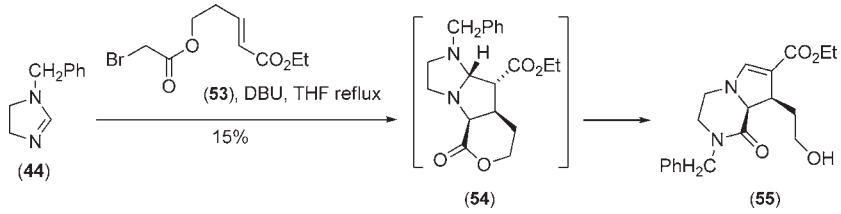
orbital interactions that favor an *endo* approach for the planar sp^2 (carbonyl)-activating groups discussed above. Some secondary products were also observed in low yield when methyl bromoacetate was the alkylating agent, from quaternization of the bridgehead nitrogen atom and eliminative ring-opening.



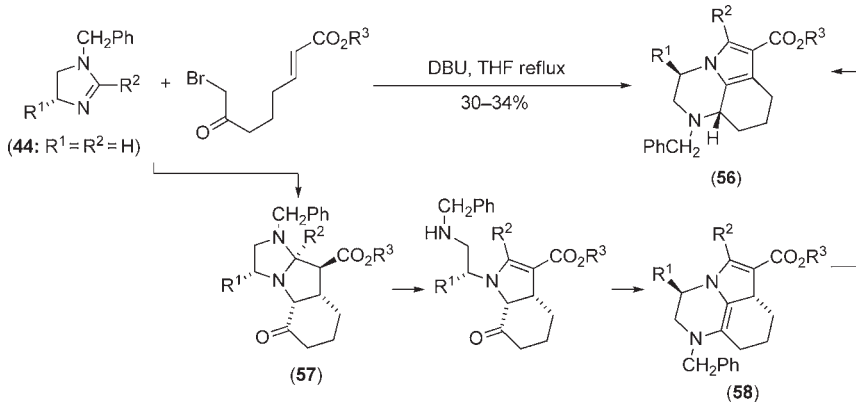
(3)

We were also interested to examine an intramolecular variant of the process, in which the reaction was reduced to a two-component process by tethering the alkylating agent and dipolarophile. Ethyl 5-(bromoacetoxy)pent-2-enoate (**53**) was thus reacted with 1-benzyl-2-imidazoline (**44**) under the usual conditions, when the expected cycloadduct **54** was not isolated, but instead the pyrrolo[1,2-*a*]pyrazine transformation product **55** was isolated in low yield, from the same eliminative ring-opening, followed by lactone–lactam exchange between the liberated amine and the ester tether (Scheme 24) (98JP12061).

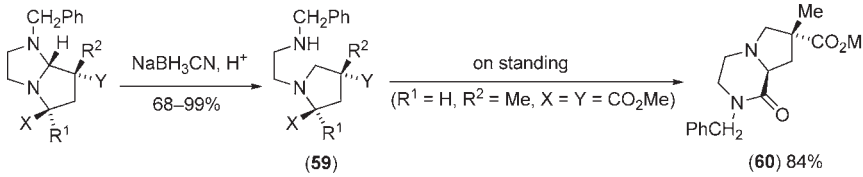
When attempting to extend the intramolecular cycloaddition to molecules in which the alkylating agent tethered to a dipolarophile is a bromoketone rather than a bromoester, we observed an unexpected result: the formation of pyrrolo[1,2,3-*de*]quinoxalines **56** from imidazolines such as 1-benzyl-2-imidazoline (**44**) (Scheme 25) (01TL3951, 06OBC3155). This was rationalized by assuming initial formation of the expected primary dipolar cycloadduct **57**, which then underwent the eliminative ring-opening, formation of enamine **58** (or its regioisomer) from the liberated amine, and subsequent prototropic shifts to generate the pyrrole subunit. This mechanism was supported by the isolation in one case of the primary cycloadduct (**57**; $R^1 = Ph$, $R^2 = H$, $R^3 = tert$-Bu; 31%) using a chiral starting imidazoline (see later for the



Scheme 24



Scheme 25

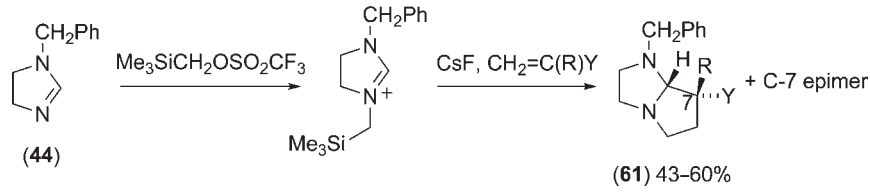


Scheme 26

chiral series). The relative stereochemistry (secured by an X-ray crystallographic determination) was as expected from our transition state model.

Reductive cleavage ($NaBH_3CN$ in acidic medium) of the aminal function in the pyrroloimidazole cycloadducts revealed new N-substituted pyrrolidines **59** that had been formed in diastereoselective fashion (90TL2333, 93JP12391, 98JP12061) (Scheme 26). The pyrrolidine-2,4-dicarboxylic acid derivatives **59** (X, Y = carboxylate esters) so produced were of interest as mimics of the neurotransmitter glutamic acid. If the C-2 ester was unhindered, then the secondary amine liberated on cleavage of the imidazoline ring recyclized on standing to form bicyclic lactams, hexahydropyrrolo[1,2-*a*]pyrazines, e.g., **60**.

A variant on the alkylation–deprotonation generation of the ylides was observed when the alkylating agent was trimethylsilyl trifluoromethanesulfonate and CsF was used as desilylating agent. The cycloadducts formed with propenoate derivatives were observed as diastereomer mixtures assumed to be from *endo* **(61)** and *exo* reaction modes (Scheme 27) (90TL2333, 98JP12061).

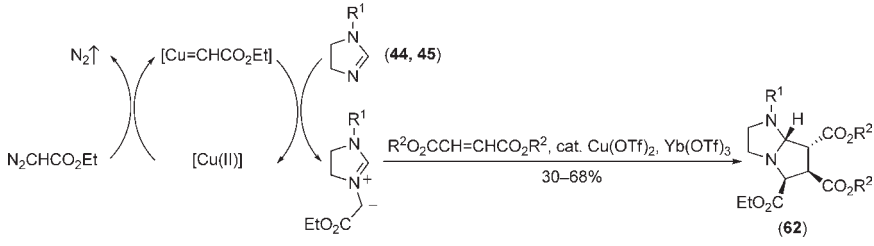


Scheme 27

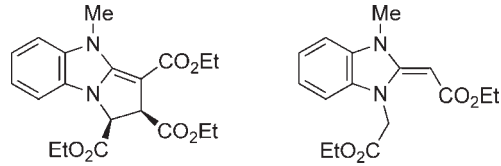
8. AZOMETHINE YLIDES BY CARBENE INSERTION IN A CATALYTIC CYCLE

Most recently, to make the azomethine ylide generation catalytic, and to avoid the need to add base as an additional reagent, we proposed a "cleaner" process, a catalytic cycle (Scheme 28) wherein the active halide-alkylating agent is replaced by a diazo ester and the ylide is formed by insertion of a metal carbenoid onto the imine lone pair of the 2-imidazoline. This proved successful via simultaneous addition of ethyl diazoacetate and fumarate esters (as illustrated) or nitriles as dipolarophiles to solutions of 1-benzyl (**44**) or 1-methyl-2-imidazoline (**45**) with 10 mol% $Cu(OTf)_2$ as catalyst for carbenoid formation, and in the presence of 10 mol% $Yb(OTf)_3$ (09TL3577). We speculate that the latter component can complex the imine function of the dipole, but its role may also be to activate the dipolarophile. Cycloadducts **62** were isolated from 1-benzyl-2-imidazoline, which were *endo* adducts that followed our transition state model **51**; the N-methyl series also afforded the *exo* adducts as minor products.

Double activation of the dipolarophiles seems to be necessary, as ethyl propenoate did not give the expected cycloadduct but rather a fumarate adduct derived from dimerization of the diazoester. A cycloadduct **63**, which had unexpectedly undergone oxidation, was observed using N-methylbenzimidazole in this protocol, along with a by-product **64** from proton transfer within the dipole to give an N-heterocyclic carbene (NHC), which couples to the diazo ester-derived



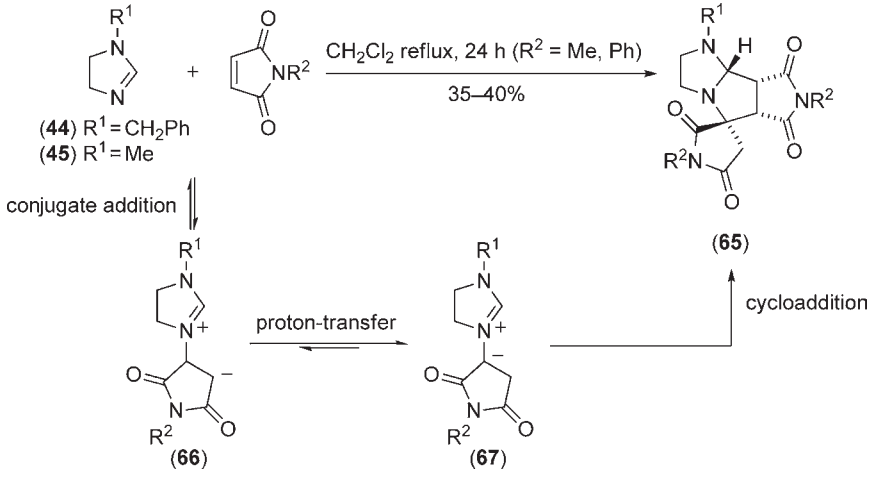
Scheme 28



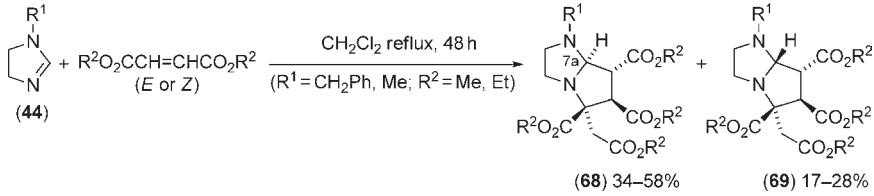
carbenoid. Further scoping of this catalytic alternative to the alkylation–deprotonation protocol for ylide generation is desirable.

9. AZOMETHINE YLIDES BY CONJUGATE ADDITION-PROTON TRANSFER

We made a serendipitous discovery when reacting 2-imidazolines **44** and **45** with doubly-activated alkenes such as N-phenyl and N-methylmaleimides. Novel cycloadducts **65** were isolated that proved to be 2:1 combinations of maleimide and imidazoline (Scheme 29) (06MI3, 07MI1). Their formation is rationalized by invoking a (reversible) conjugate addition of the imidazoline imine nitrogen atom onto the alkene to form adduct **66**, followed by transfer of a proton from the methine group attached to N-3 to the adjacent enolate carbon resulting from the conjugate addition. This forms a more stable formal anionic center and generates the imidazolinium dipole **67**, which can then undergo cycloaddition with a second molecule of the doubly activated alkene. The alkene thus functions as



Scheme 29



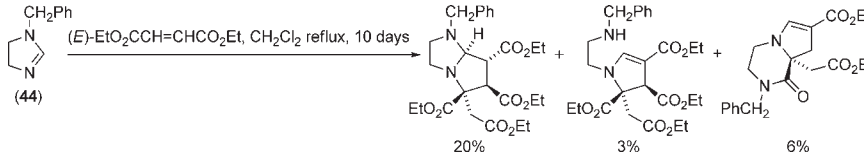
Scheme 30

both Michael acceptor and dipolarophile. The stereochemistry of the 2:1 adducts matches expectation from our transition state model (as in structure **51**), with the nonactivating dipole substituent anti to the imidazoline C-2(H) and an *endo* mode of approach of dipole and dipolarophile. Minor amounts of *exo* 2:1 adducts were found. The relative stereochemistries of all these products followed from NOE studies and some X-ray crystallographic analyses.

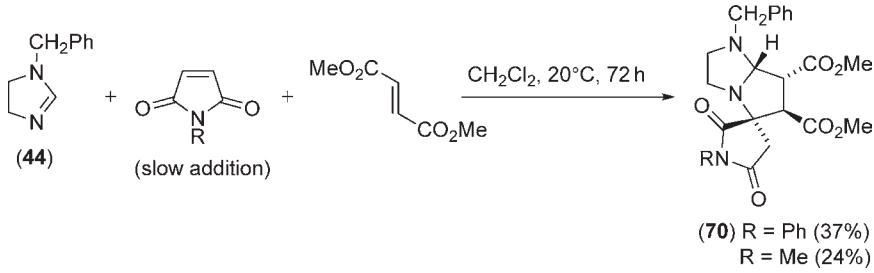
These results were mirrored using other doubly activated alkenes. With fumarate esters, major and minor 2:1 products (**68** and **69**, respectively) were isolated (Scheme 30); the minor products had the expected relative stereochemistry based on the transition state model, but the major products were C-7a epimers, presumably formed by an amino-imine ring-opening equilibrium, as postulated earlier for other cycloadducts (Scheme 20) (98JP12061). Again, NOE studies and crystallographic analyses substantiated the stereochemical assignments. The separated diastereomers underwent re-equilibration in slightly acidic $CDCl_3$ as observed by NMR spectroscopy, so we proposed that the transition state model (as **51**) predicts the kinetic product, but that in this instance the thermodynamic product is the C-7a epimer. When maleate esters were used, the same products were found as from fumarate esters, consistent with interconversion of maleate and fumarate, mediated by the reversible initial conjugate addition step.

The fumarate/maleate reactions were slower than the maleimide examples, e.g., 48 h vs. 24 h in CH_2Cl_2 at reflux. Extended reaction times (e.g., 10 days) with fumarates afforded secondary transformation products of the 2:1 cycloadducts, of the type discussed already (98JP12061), such as ring-opening to give enamino esters, and subsequent lactamization to form pyrrolo[1,2-*a*]pyrazines (Scheme 31).

The conjugate addition-proton transfer mechanism is supported further by the use of different alkenes as conjugate addition acceptors and dipolarophiles, to form 1:1:1 adducts (e.g., Scheme 32) (06MI3). The slower reaction with fumarates than maleimides suggested an experiment where 1-benzyl-2-imidazoline (**44**) and dimethyl fumarate were mixed at 20°C and an N-substituted maleimide was added slowly. Presuming that the conjugate addition is rate determining, the maleimide



Scheme 31



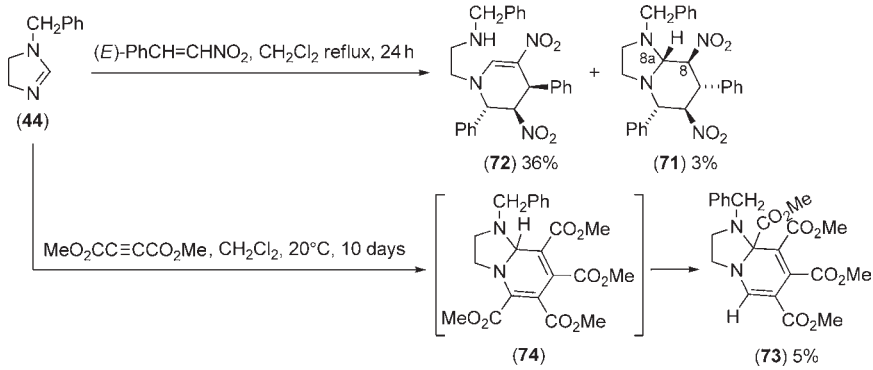
Scheme 32

undergoes addition fastest, followed by proton transfer to produce a dipole in the presence of a relative excess of fumarate, which acts as dipolarophile. The stereochemistry of these three-component adducts **70** conforms to the standard transition state model. Trace amounts of the 2:1 *endo* and *exo* adducts of the maleimide and of the fumarate were, not surprisingly, also isolated.

Using fumaronitrile as the "slow" acceptor with 1-benzyl-2-imidazoline and the maleimides in the same procedure produced related 2:1 adducts, and a further three-component experiment using fumarate esters and fumaronitrile illustrated that fumaronitrile is the poorer conjugate addition acceptor, since the major 1:1:1 adducts had the diester in the dipole portion and the dinitrile in the dipolarophile position.

9.1 Annulation via the conjugate addition route with singly activated alkenes and with alkynes

Whilst investigating the conjugate addition-proton transfer approach for 1,3-dipole generation, singly activated acceptors were investigated with only limited success (06MI3). (2-Nitroethenyl)benzene (nitrostyrene) afforded a minor 6-membered annulation product **71**, plus a major enamino ester elimination product **72** (Scheme 33). It is assumed that nitrostyrene underwent the conjugate addition but not the proton transfer, and that the initial 1,4-dipole added to a second nitrostyrene molecule, with closure onto the imidazolinium C-2 position, to give the



Scheme 33

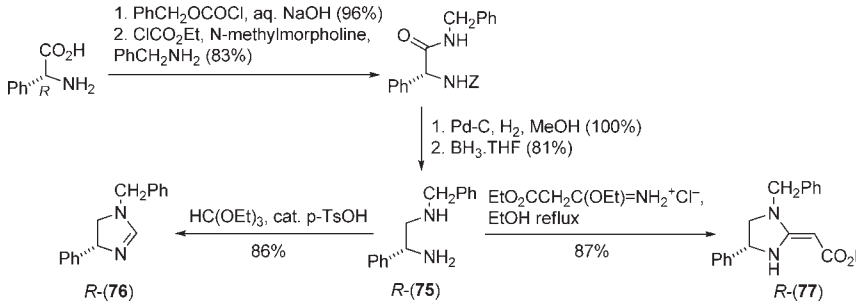
annulation product and possibly its diastereoisomer in which the opposite stereoface of the second nitrostyrene molecule has been attacked. Clearly, when the annulation product has the bond to C-8(H) anti to the C–N bond at C-8a, the β-elimination is favored. Using dimethylacetylene dicarboxylate as acceptor gives no possibility of proton transfer, so again annulation to a 6-membered ring in **73** was observed in very low yield (Scheme 33). Interestingly, the new 6-membered ring was of the opposite regiochemistry to that expected, suggesting again a ring-opening/ring-closing transformation from a primary annulation product **74**. Despite the low yields, these results all lend support to the mechanism proposed for 2:1 adduct formation (cf. Scheme 29).

10. ANNULATIONS USING CHIRAL IMIDAZOLINES

Several parts of the methodologies introduced previously, in particular the dipolar cycloaddition chemistry, have been applied to the synthesis of chiral optically active heterocycles. For this, chiral 2-imidazolines had to be prepared as starting materials, and the 4-phenyl-2-imidazolines were the selected series. Initially this was applied to the 1-benzyl compounds and then also to other N-substituted derivatives via an improved route.

10.1 Synthesis of substrates

The commercial starting point was phenylglycine, readily available as both enantiomers. In the first synthesis, the optically pure amino acid was N-protected as its benzyloxycarbonyl (Z) derivative, then coupled with benzylamine to form benzylamide, using a mixed anhydride method (93TL6329, 96TL1707). Removal of the Z group followed by borane



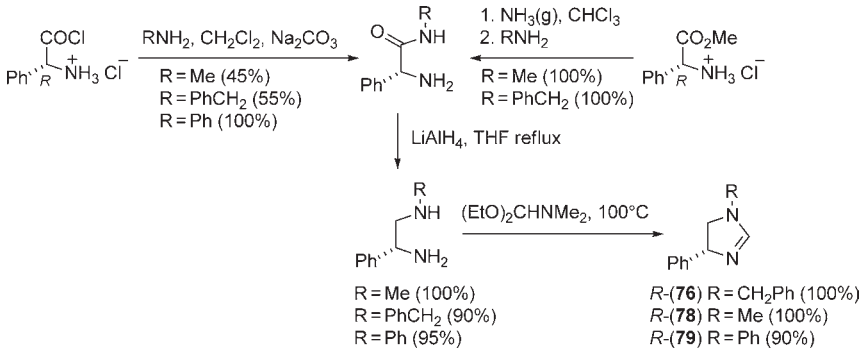
Scheme 34

reduction of the amide afforded the enantiomers of 2-benzylamino-1-phenylethanamine (**75**) corresponding to the enantiomer of the phenylglycine starting material that had been used. The diamine enantiomers were separately converted into enantiomerically pure 1-benzyl-4-phenyl-2-imidazoline (**76**) using triethyl orthoformate as the C1 source (Scheme 34; *R*-series illustrated) (96TL1707). In addition, reaction of this diamine in optically active form with the imidate prepared from ethyl cyanoacetate and ethanol–hydrogen chloride afforded the two enantiomeric 4-phenyl derivatives **77** of the enamino ester **11** used as the starting point for many of our earlier annulation sequences (93TL6329).

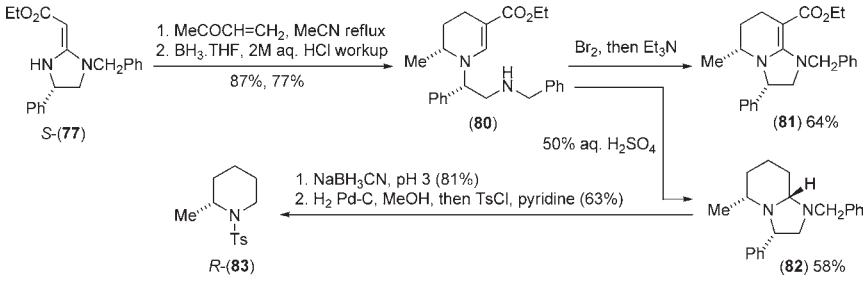
Later improvements to the route included starting with phenylglycyl chloride hydrochloride, now commercially available for the (*R*)-series, and reacting with methylamine, benzylamine, or aniline to form the corresponding amides. The methylamide and benzylamide could also be formed by reaction of commercial methyl phenylglycinate hydrochloride (after neutralization) with the relevant amine. Reduction of the amides with lithium aluminum hydride afforded the corresponding N-substituted diaminoethanes that were converted into the 4-phenyl-2-imidazolines, N-benzyl (**76**), N-methyl (**78**), and N-phenyl **(79)**, using dimethyl formamide diethyl acetal (Scheme 35) (08MI1).

11. OPTICALLY ACTIVE PIPERIDINES VIA ENAMINO ESTER ANNULATION

The sequence developed earlier for annulation of the imidazoline enamino ester **11** with α,β-unsaturated ketones (Scheme 9) was applied to the optically active 4-phenyl enamino ester enantiomers **77**. Thus conjugate C-addition to but-3-en-2-one was followed by borane reduction to give optically active piperidine enamino esters **80**, from which imidazo[1,2-*a*] pyridines **81** and **82** could be formed oxidatively (Br_2–Et_3N) or on acid treatment, respectively (Scheme 36; *S*-enamino ester illustrated)



Scheme 35



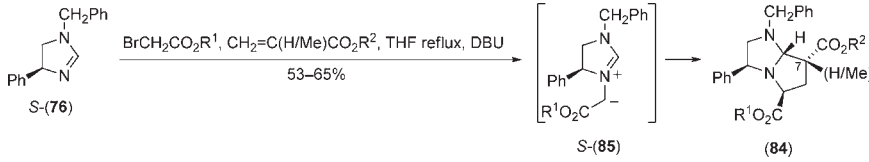
Scheme 36

(93TL6329). The latter product could also be obtained directly from the conjugate adducts by completing the borane reduction with a sulfuric acid workup rather than the hydrochloric acid workup. Further aminal reduction of **82** by sodium cyanoborohydride and removal of the secondary benzylic N-substituent (the residue from the imidazoline ring!) by hydrogenolysis gave the optically active 2-methylpiperidines isolated as N-tosyl derivatives **83**. Pent-1-en-3-one afforded (*R*)-2-ethylpiperidine in similar fashion from the (*S*)-enamino ester.

We have also reported preliminary studies using a chiral (but racemic) 4,5-diphenyl enamino ester analogous to the 4-phenyl compound **77**, to produce a piperidine enamino ester, cf. **80** (03ARK(ii)133).

12. DIPOLAR CYCLOADDITION OF OPTICALLY ACTIVE IMIDAZOLINIUM YLIDES

When either enantiomer of the optically active 1-benzyl-4-phenyl-2-imidazoline (**76**) was employed in the alkylation–deprotonation sequence for imidazolinium ylide generation and cycloaddition, using the one-pot



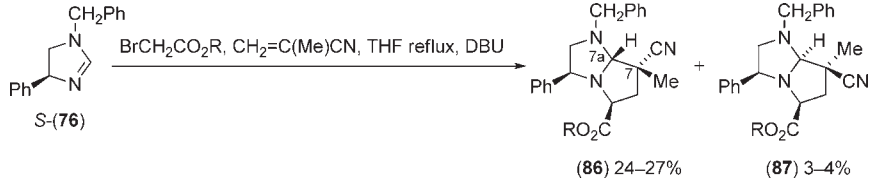
Scheme 37

protocol described earlier, optically active hexahydropyrrolo[1,2-*a*]imidazoles **84** were prepared (96TL1707) (Scheme 37; *S*-dipole series illustrated). Alkylating agents used were methyl and *tert*-butyl bromoacetates, and suitable dipolarophiles were 2-methylpropenoate and propenoate methyl esters. Reactions using *tert*-butyl bromoacetate ($R^2 =$ *tert*-butyl) as alkylating agent gave the highest yields observed to date. The cycloadducts were found to derive from an *endo* diastereoselective reaction mode, with an anti-dipole, as predicted from our transition state model **51**, and additional facial selectivity was provided by the 4-phenyl substituent: cycloaddition took place exclusively from the face opposite to the phenyl substituent of the dipole **85**.

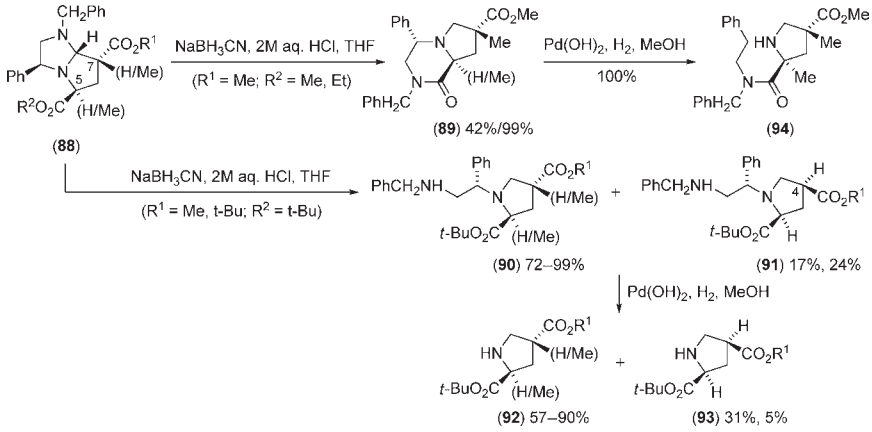
With *tert*-butyl propenoate or 2-methylpropenonitrile as dipolarophile, some *exo* cycloaddition (to give the C-7 epimers of the cycloadducts) was also observed as minor products. In these cases, epimerization at C-7a also took place, as had been observed in the achiral series (cf. Schemes 21 and 22). This is illustrated for 2-methylpropenonitrile, which afforded major products **86** and minor products **87** (Scheme 38) (96TL1707).

To place substituents at C-6 of the pyrroloimidazole, methyl but-2-enoate proved to be a suitable dipolarophile, and to generate a quaternary center at C-5, ethyl 2-bromopropionate could be used as an alkylating agent, although yields were lower. As usual, relative stereochemistry was secured by NOE studies and X-ray crystal structure determinations.

Using a sulfone- or sulfoxide-activated dipolarophile, optically active *endo* cycloadducts were observed (with just one exception from the examples studied) as expected from the transition state model, in contrast to the situation discussed earlier (Equation (3)) with achiral imidazoline substrates (10CAJ461).



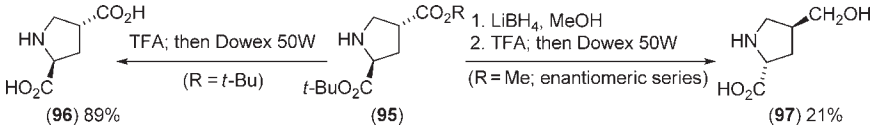
Scheme 38



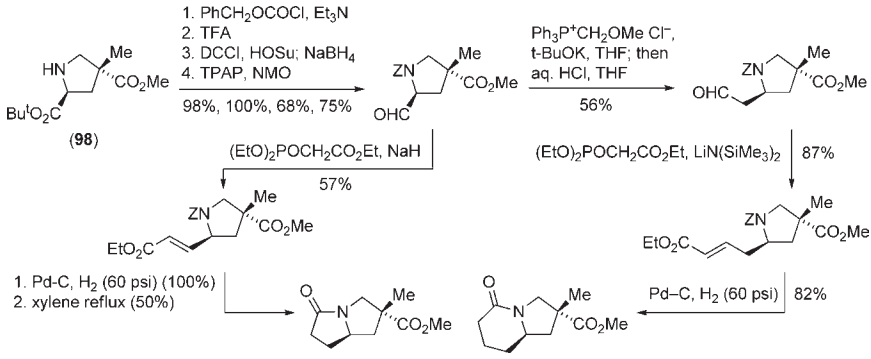
Scheme 39

We have utilized the pyrroloimidazole annulation products as sources of optically active pyrrolidines. Thus sodium cyanoborohydride under acidic conditions afforded aminal reduction of cycloadducts **88** (Scheme 39); when the C-5 ester was ethyl or methyl, the liberated secondary amine cyclized to produce pyrrolopyrazine lactams **89**, but when the ester was more hindered, that is, *tert*-butyl, N-substituted pyrrolidines **90** were isolated (96TL1711). An unexpected difficulty was encountered in this reduction when pyrrolimidazoles mono-substituted at C-7 were reduced, as this gave pyrrolidines **91** partially epimerized at C-4. This could be minimized by use of excess acid and exactly one equivalent of hydride reagent to afford acceptable ratios in favor of 2,4-*trans* isomers. The N-substituted pyrrolidines were not easy to purify, so were directly hydrogenolyzed ($Pd(OH)_2$, H_2 at 60 psi, MeOH–TFA) to cleave the benzylic C–N bond and reveal the homochiral pyrrolidines **92, 93**. When the C-4 epimer mixtures **90/91** were subjected to hydrogenolysis, some improvement in epimer ratio was observed, implying that 2,4-*cis*-substituted pyrrolidines are less stable toward the reaction conditions than the 2,4-*trans* diastereoisomers. Similar hydrogenolysis of a pyrazine **89** gave pyrrolidine-2-carboxamide **94**.

Deprotection of pyrrolidine diesters such as **95**, prepared as above, was easily accomplished, to give 2,4-dicarboxylic acid **96**, which is a naturally occurring potent competitive glutamate transport inhibitor (Scheme 40); our synthesis is shorter than the reported route and also can easily provide analogues. The 2-*tert*-butyl, 4-methyl ester (**95**; R = Me, enantiomeric series) undergoes selective reduction at the less-hindered ester and then *tert*-butyl ester cleavage to give another natural product **97** (Scheme 40). Comparison of our data to the natural materials confirms the stereochemical assignments. Selective manipulation of pyrrolidine



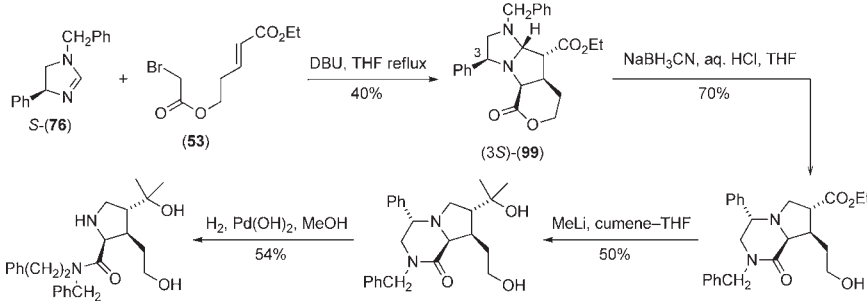
Scheme 40



Scheme 41

diester **98** at C-2 via the acid and aldehyde, on C-2 or C3 chain extensions, led to an optically active pyrrolizidine and indolizidine, respectively (Scheme 41) (96TL1711).

The intramolecular mode of cycloaddition was extended into the chiral arena, by the reaction of the 1-benzyl-4-phenyl-2-imidazoline enantiomers (**76**) with the alkylating agent/dipolarophile **53** described earlier in Scheme 24 (Scheme 42; *S*-series illustrated). Single enantiomers of the tricyclic adduct **99** were isolated in moderate yield (97TL1647). The stereochemistry was confirmed by X-ray crystallographic analysis and once again conforms to our transition state



Scheme 42

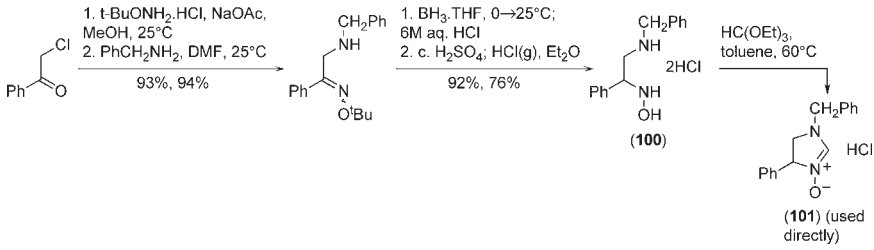
model. Manipulations of the (*S*)-imidazoline-derived cycloadduct were accomplished to reveal highly functionalized optically active pyrrolidines.

Using the bromoketone-linked dipolarophiles in intramolecular cycloadditions with chiral imidazolines led to optically active pyrrolo [1,2,3-*de*]quinoxalines **56** as secondary products formed from the expected dipolar cycloadducts **57**, as described earlier (Scheme 25).

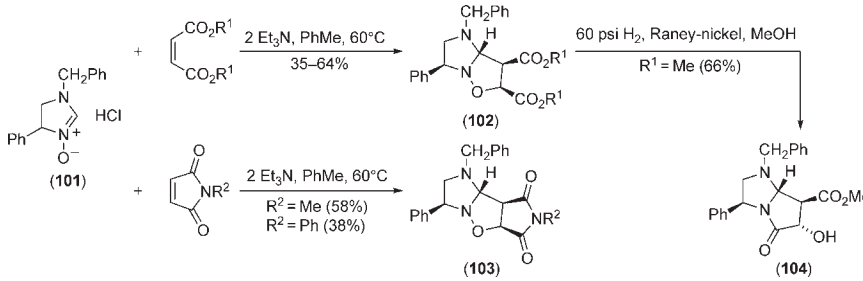
13. CHIRAL IMIDAZOLINE NITRONES IN CYCLOADDITIONS

Imidazolinium oxides (imidazoline nitrones) were prepared in the chiral series. To date these are racemic materials but clearly the potential exists for asymmetric synthesis. Unlike the other 2-imidazolines featured thus far, the nitrones were not prepared from N-substituted-1,2-diaminoethanes, since attempts to directly oxidize 1-benzyl-2-imidazoline were unproductive. Instead, 2-chloroacetophenone was converted into its *tert*-butyl oxime ether followed by chloride substitution with benzylamine. The oxime function was reduced using borane with acidic workup to destroy amine–borane complexes, and the *tert*-butyl group removed by strong acid to afford a hydroxylaminoamine **100** that was stored as its bishydrochloride. Warming the salt with triethyl orthoformate in toluene afforded the 2-imidazoline nitrone salt **101** that was used directly (Scheme 43) (00JHC481, 00SL967). Oxime formation with an optically active O-alkyl hydroxylamine, and/or reduction with an optically active borane-reducing agent, presents two opportunities for future asymmetric synthesis.

Treatment of the nitrone salt **101** with base and alkene dipolarophiles such as maleate esters and maleimides led to imidazo[1,2-*b*]isoxazole cycloadducts **102** and **103**, respectively, whose stereochemistry was as usual determined by NOE studies and an X-ray crystal structure (Scheme 44) (00JHC481, 00SL967). The relative stereochemistry observed corresponded to an *exo* approach mode, with facial selectivity (as



Scheme 43

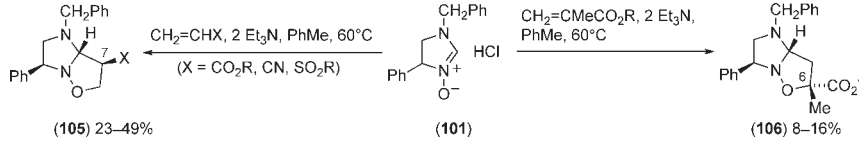


Scheme 44

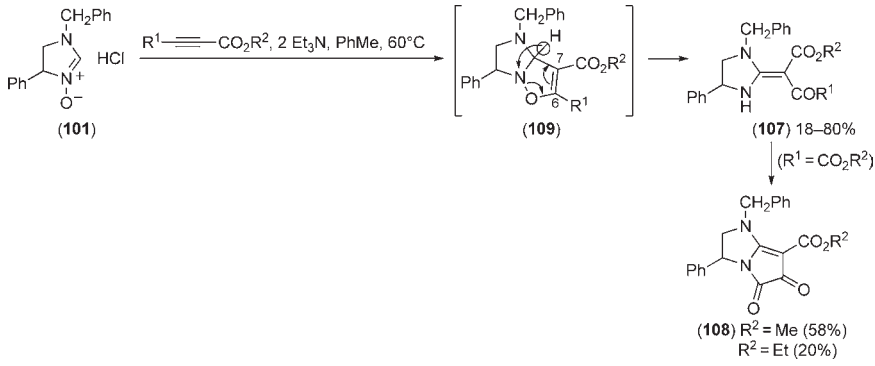
expected) controlled by, and anti to, the 4-phenyl substituent. The *exo* mode contrasts with the predominant observations with imidazolinium ylides. Cleavage-recyclization of isoxazolidine rings is a well-known synthetic strategy, and this was demonstrated with the cycloadduct (**102**; $R^1 = Me$) derived from dimethyl maleate: hydrogenolysis afforded a pyrrolo[1,2-*a*]imidazole **104** by N–O bond breaking and lactamization with a new 5-membered ring favored over the alternative β-lactam. A crystal structure determination confirmed retention of stereochemistry during this sequence.

When singly activated alkenes were used as dipolarophiles, the derived cycloadducts **105** displayed the activating group at C-7 (C-4 of the isoxazolidine ring), regiochemistry consistent with FMO control in a Sustmann type 1 reaction, and with an *exo* orientation mode (Scheme 45). However, in the case of α-disubstituted alkenes, the C-6 substituted cycloadducts **106** were observed, albeit in lower yield, and with the activating group *endo* (00JHC481, 00SL967).

Alkynes as dipolarophiles with the imidazoline nitrones afforded different products that could be explained as secondary transformation products of primary cycloaddition products. Thus, with 2-alkynoate esters, acyl alkoxycarbonyl enediamines **107** were formed, whereas with alkyne-1,2-dicarboxylates, pyrrolo[1,2-*a*]imidazoles **108** were the isolated products (Scheme 46) (00CC1949, 00JHC481). The enediamines in solution presented the enaminoketone tautomer as illustrated; however, studies of two examples in the solid state showed one to exist in an enaminoketone tautomer with NH–ketone H-bonding, whereas the

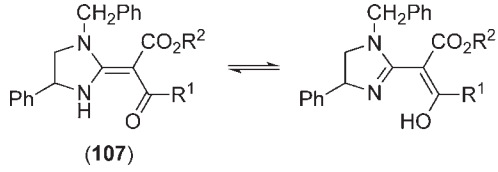


Scheme 45



Scheme 46

other demonstrated an apparent imino-enol tautomer (Equation (4)). These secondary products can be rationalized by loss of the bridgehead H-atom and N–O cleavage in the initial imidazo[1,2-*b*]isoxazole cycloadducts **109**, either by a 1,5-sigmatropic H-shift that is not available to cycloaddition products from alkene dipolarophiles (illustrated in Scheme 46) or by an alternative elimination–enolate reprotonation pathway. This provides the enediamines **107**, and in the case of doubly activated alkynes, an ester group is then positioned for cyclization to produce the pyrroloimidazoles **108**.



(4)

14. SUMMARY

Our studies have demonstrated various methods of annulation of 2-imidazolines, using both the double nucleophile strategy and the dipolar cycloaddition strategy. Several of the routes have been extended into the realm of chiral and optically active synthesis. In addition many of the annulation products have been demonstrated to be building blocks for onward transformations in heterocyclic synthesis. We contend that further variations, and extended scope, are possible, and that applications of these methodologies will be forthcoming. The author thanks the

researchers who have contributed to this work (and are acknowledged in the cited references) and the range of funding bodies and pharmaceutical companies who have made this adventure possible.

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CHAPTER 5

Recent Advances in the Dimroth Rearrangement: A Valuable Tool for the Synthesis of Heterocycles

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1. INTRODUCTION

The Dimroth rearrangement (DR) is a translocation of two heteroatoms in a heterocyclic system, with or without changing its ring structure. Such a rearrangement is also known as an amidine rearrangement. The conversion of a heterocycle to a rearranged isomeric product can give one or two isomers via an intermediate, which selectively or specifically forms one of them as the major one. The stability of the rearranged product is the driving force for its formation, which may lead to the preference of one isomer. The heteroatoms which exchange positions in the rearrangement are S, N, O, and Se.

The DR can be generalized to give products resulting from "ring opening, ring closing" (RORC) processes leading to the rearrangement. Different authors have suggested mechanistic aspects, either proposed or based on isotopic labeling; when the rearrangement is initiated by the attack of a nucleophile, it is termed ANRORC (addition of nucleophile, RORC), while in the case of an attack with an electrophile it is termed AERORC (addition of electrophile, RORC). Most cases proceed through the ANRORC mechanism.

The DR is typically a reversible process (71JHC643, 73JHC755, 99AHC79, 05JOC6034, 01JOC6576, 07TL2041), leading to the thermodynamically most stable product (96H2607). The isomerization mechanism depends not only on the pH of the solution but also on the number of atoms or bulkiness of the substituents (06RCB2247). The imidazopyrimidines with an aryl substituent at the 2-position are thermodynamically more favored than those with the substituent at the 3-position (99AHC79). When a carbonyl group is present in a pyrimidine ring, the rearrangement process is hampered due to its ability to form hydrogen bonds, hence stabilizing the molecule and retarding the rearrangement (06RJO1403).

The DR is usually performed under heat, light, acidic, or basic conditions and yields a varied ratio of the two possible regioisomers (99AHC79, 07TL2041). The rearrangement takes place even in neutral solvents such as ethyl acetate, ethanol, dimethyl sulfoxide (DMSO), or dimethylformamide (DMF) such as in the isomerization of the 5-oxo-1,2,4-triazolo[4,3-c]-pyrimidines, which were rapidly isomerized to the oxo-1,2,4-triazolo-[1,5-c]pyrimidines (02H631).

DR can be divided into two types based on the position of the translocating heteroatom(s): either both in the ring or one in the ring and the other located in an exocyclic position of that ring. These two types can be generalized in the two schemes DR-Type 1 and DR-Type 2, respectively. The DR can take place in any step of a synthetic scheme when the structure of the molecule and the reaction conditions are suitable (97JOC4085, 05JME5728, 06M1543).

The DR has been recognized as a general phenomenon in heterocyclic chemistry (55JC4035, 55JC1858, 99AHC79), although the rearrangement was noticed in earlier works (88BCG867, 09AC183). The rearrangement was termed the DR in the early 1960s (63JC1276). Reviews have included

some aspects of the DR of particular heterocycles (74AHC33, 98AHC57, 99AHC127, 06RJO1403), and a review from our group has compiled the literature to 1995 (99AHC79). This review covers the literature during 1996 to 2008. Some of the old references have been included when needed to emphasize the phenomenon.

This review consists of two main sections as in the former review (99AHC79). Thus, the first one includes the translocation of heteroatoms between rings in fused heterocycles, whereas the second one includes the translocation of exo- and endoheteroatoms within a heterocyclic ring. Further division under each section is based on the number and arrangement of heteroatoms.

1.1 General schemes for type 1

1.1.1 Translocation of Heteroatoms in Fused Heterocycles

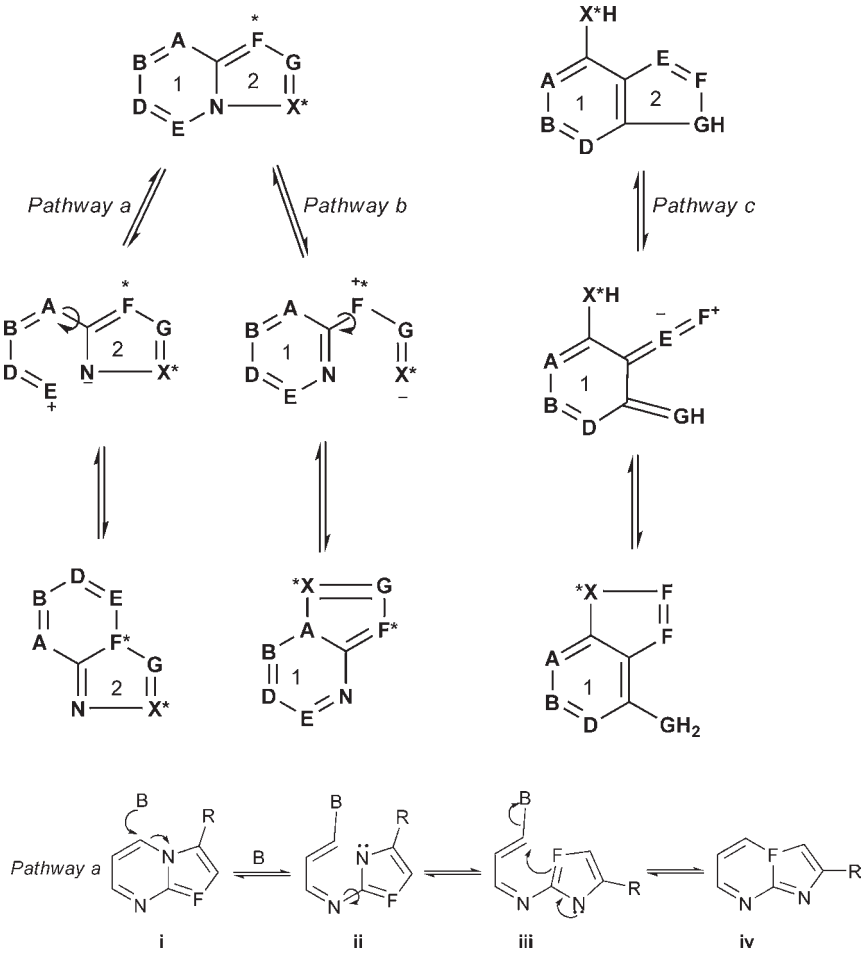
In this type of rearrangement the translocated heteroatom(s) are part of the ring. The translocation process changes the position of the heteroatom or substituent on that ring leading to either a retained or a changed ring structure. The presence of a heteroatom within a five-membered ring and also at an exocyclic position of the adjacent ring is a promoting factor for the rearrangement. The translocation of heteroatoms can take place between two rings of a fused system by three possible pathways, including the opening of the fused heterocycles via a six-membered or a five-membered ring.

Pathway a: ring-1 opens at the **N–E** bond, followed by rotation of the single bond linked to ring-2 and ultimately **E** closes with **F**, thus shifting the ring-1 exocyclic heteroatom **F*** to be endocyclic in the ring.

Pathway b: ring-2 opens at the **N–X*** bond, followed by rotation of the single bond linked to ring-1 and then **X*** closes with **A**, thus the exocyclic heteroatom **X*** on ring-1 becomes exocyclic to the same ring but at another position.

Pathway c: ring-2 opens at the **F–G** bond, and then **F** closes with **X***. The heteroatom **G**, in the five-membered ring-2, becomes a substituent on ring-1 whereas the other two heteroatoms of ring-2 become a part of the newly formed five-membered ring on cyclization. The rearrangement is promoted by the presence of an amino, hydroxyl, or thiol group (**X*****H**) at the ortho position of heterocyclic ring-2; this group can then be incorporated in the new ring on recyclization after ring fission.

Examples of *pathway a*, mostly proceed through the ANRORC mechanism. Nucleophilic attack on C1 of **i** leads to the cleavage of the C–N bond to form **ii**, which can reversibly be reconverted to **i** or undergo rotation around the single bond to give **iii** whose cyclization produces DR product **iv**. The R group may be alkyl, aryl, amine, thiol, or halide. Thus, an imidazopyrimidine follows this pathway by the action of OH^- as a nucleophile to give the rearranged products (01JOC6576, 07TL2041).

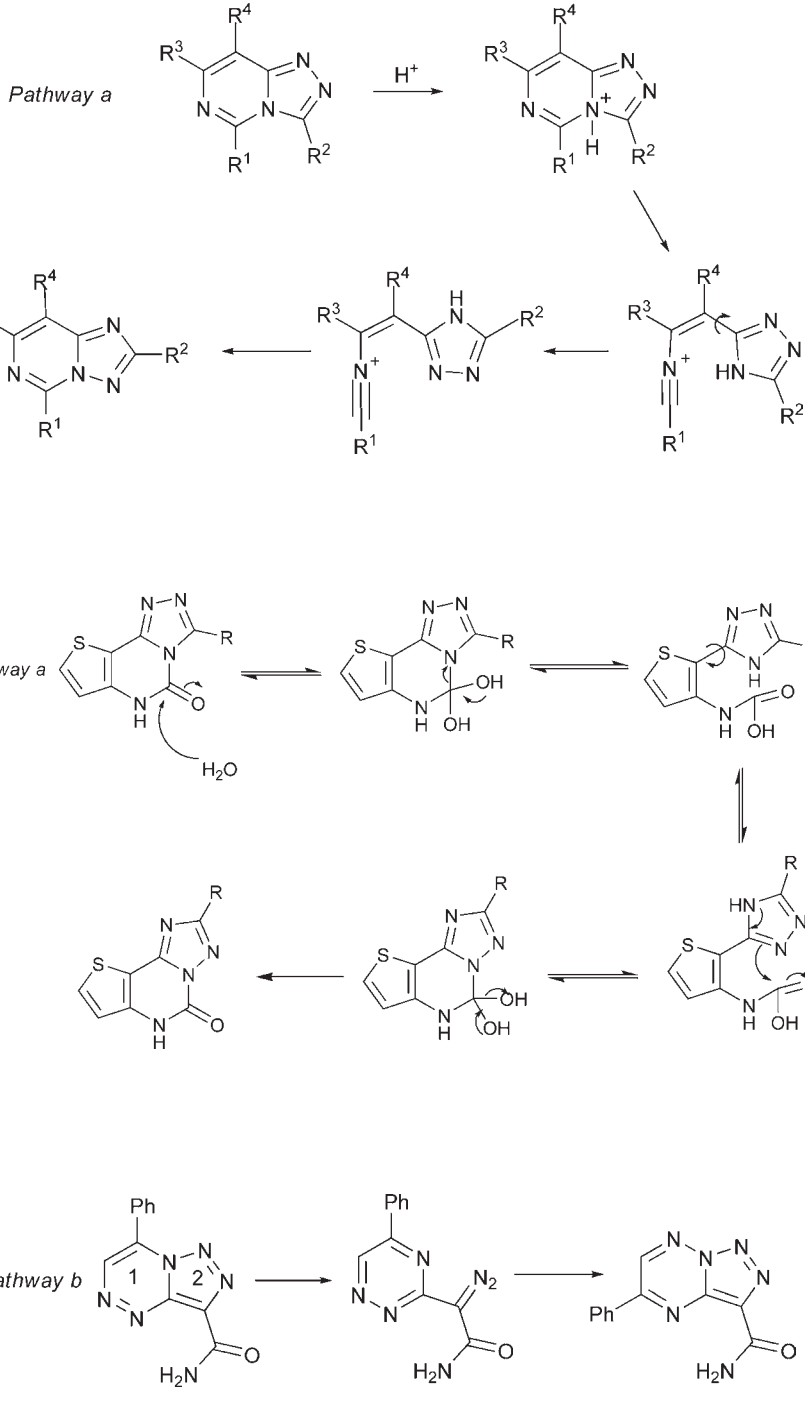


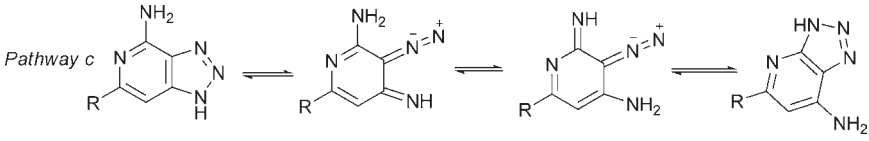
Acid can catalyze the DR leading to RORC, such as in the synthesis of triazolo[1,5-c]pyrimidines obtained from their triazolo[4,3-c] isomers (06RCB2247, 05ACSV429).

The instability of a substituted thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-5(6*H*)-one has promoted its rearrangement to the isomeric thieno-[2,3-*e*][1,2,4]triazolo[1,5-*c*]pyrimidin-5(6*H*)-ones under neutral conditions at room temperature (05H2683).

In *pathway b*, opening of ring-2 in a phenyl-triazolotriazine led to a diazo-type intermediate that upon cyclization gave the isomeric phenyl-triazolotriazine.

An example of *pathway c* is represented by the rearrangement of mono- and diaminotriazolopyridines in ethanolic ammonia (99AHC79, 04MC76).

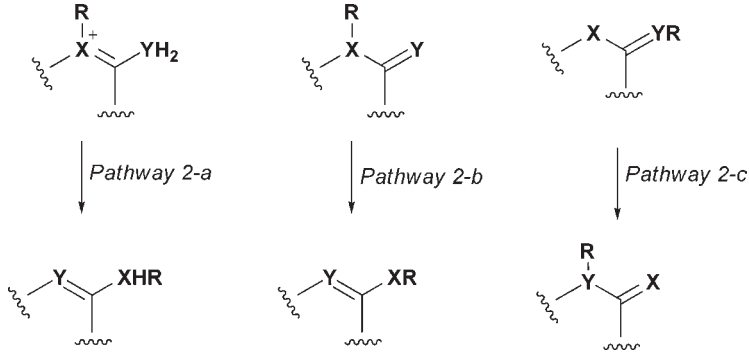

Pathway a
H+
Pathway a
H2O
Pathway b



1.2 General schemes for type 2

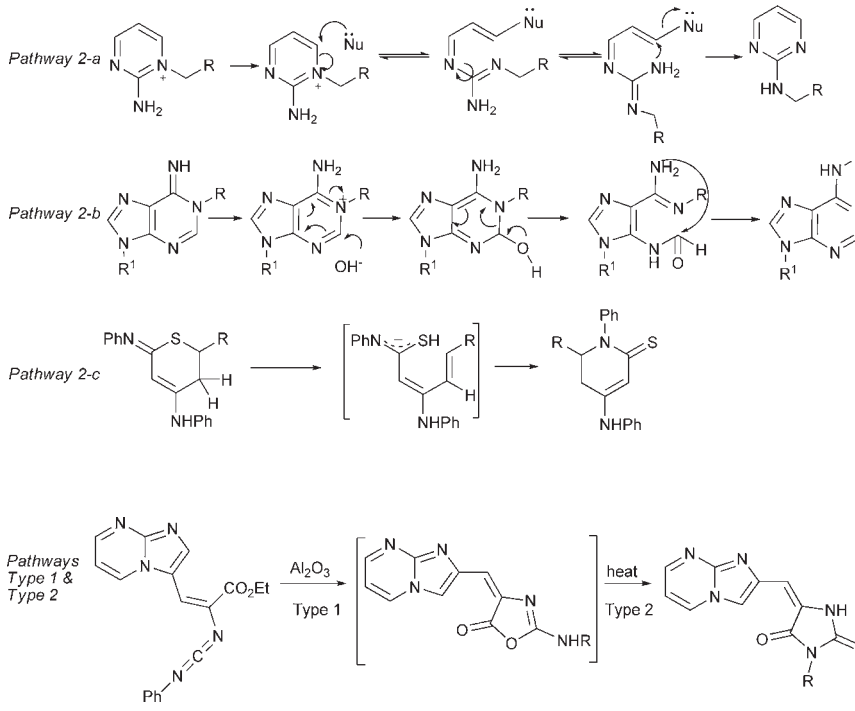
1.2.1 Translocation of exo- and endocyclic heteroatoms in heterocyclic rings

In this type the translocation of heteroatom X (endocyclic in the ring) and Y (exocyclic to the ring) takes place during the rearrangement. A bulky substituent on the endo heteroatom prefers to be at the exo position after the isomerization. The exocyclic heteroatom Y can be singly bonded and X can have a substituent and a positive charge or be double bonded where either the double bond can move into the ring to adopt aromaticity or it may remain exocyclic but be translocated with respect to X. All the processes are driven by the stability of the product, solvent, aromaticity of the ring, heteroatom valence, and bulkiness of the substituent.



Pathway 2-a is favorable when X is a nitrogen atom. The reaction proceeds in the presence of a base, heat, or even neutral conditions (03MOL467). If both X and Y are nitrogens and R is any substituent, then the rearrangement follows *pathway 2-b* to form the thermodynamically stable product. *Pathway 2-c* is adopted when oxygen or sulfur are endocyclic and nitrogen is exocyclic. In these cases the DR leads to thermodynamically stable amides or thioamides (99JOC9493, 01T8305). This type is common in both five- and six-membered heterocycles.

The DR can occur in the absence of nucleophile but heating can induce it. Thus, two DR processes of type 1 and type 2 took place on heating bicyclic heterocumulenes to yield imidazole-dione ring via an oxazole one (97JOC4085).

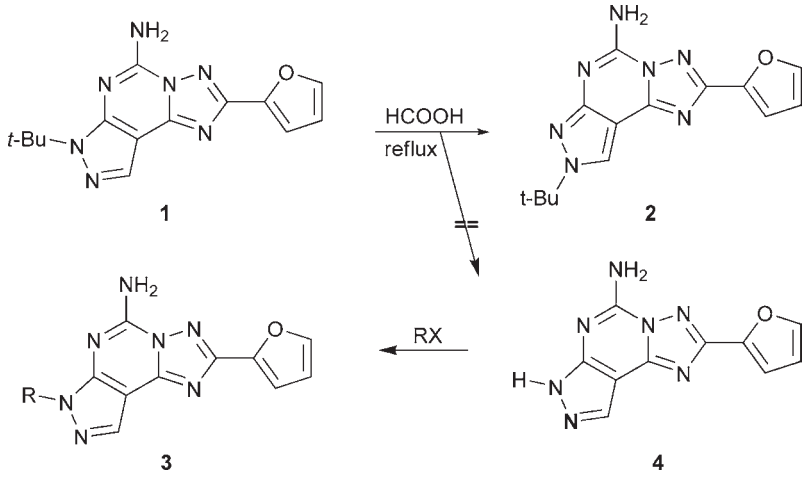


2. TRANSLOCATION OF HETEROATOMS IN FUSED HETEROCYCLES (TYPE 1)

This kind of rearrangement has been found mostly in five-membered nitrogen heterocycles. It is classified according to the number of nitrogen atoms and their positions in the ring, for example, pyrazolo (Section II.A), imidazo (Section II.B), triazolo (Section II.C), and triazino (Section II.D) heterocycles. Triazolo compounds are extensively studied and are classified according to the fused ring attached with the triazine ring, for example, triazolopyridines (Section II.C.1), triazolopyrimidines (Section II.C.2), triazoloquinazolines (Section II.C.3), and triazolotriazines (Sections II.C.4 and II.C.5).

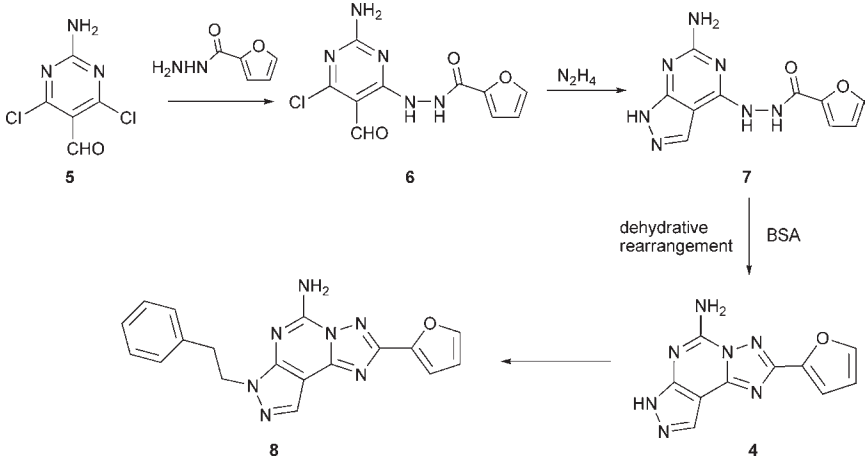
2.1 Rearrangement of pyrazoloheterocycles

The attempted deblocking of the *t*-butyl group from pyrazole **1** gave **2**, instead of the expected product **4** required for the synthesis of **3**. Compound **2** was formed from **1** through a DR type 1-*pathway **a*** (Scheme 1) (07BML1376).



Scheme 1

An alternative route for **4** was started by the conversion of **5** to **6** whose reaction with hydrazine gave **7**. Dehydrative cyclization of **7** with N,O-bis(trimethylsilyl)acetamide afforded **4**, via a DR by the formation of a nitrile imine-like species that underwent 1,5-electrocyclic cyclization (07BML1376). This rearrangement was followed by alkylation of **4** to afford **8** (Scheme 2) (96JME1164).



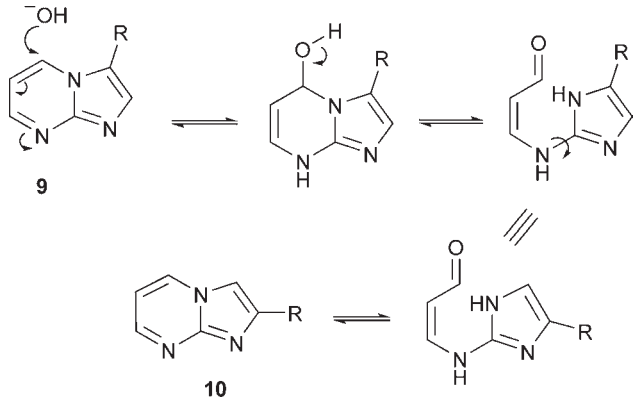
Scheme 2

2.2 Rearrangement of imidazoheterocycles

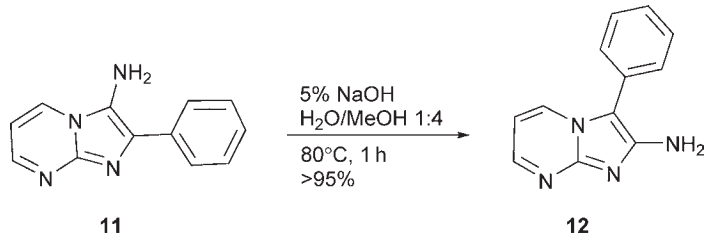
The DR plays a key role for the regioselective synthesis of 3-substituted-2-aminoimidazo[1,2-*a*]pyrimidines that led to a combinatorial approach. Thus treatment of **9** with NaOH/H_2O at 100°C for 24 h yielded a ratio 95:5 of **9** and **10**, respectively (07TL2041) (Scheme 3) and no byproducts were detected by liquid chromatography-mass spectrometry (LCMS), and ^{1}H nuclear magnetic resonance (NMR). The insolubility of the products was a main problem. The use of H_2O/MeOH was critical to reverse ratio to 5:95. Changing the base did not afford better result but an increase in the concentration of the base significantly reduced the reaction time. Mild conditions were necessary to avoid possible decomposition of the intermediates (71JHC643).

The reaction was applied to **11** to give **12** quantitatively as the only regioisomer. Selectivity in the cyclization step was not only driven by steric effects but also by the different electronic patterns of the imidazole intermediates due to the presence of an amino group at C-3 (Scheme 4) (07TL2041). Similar treatment of **13** with aqueous sodium carbonate afforded **14** in 55% yield, where a DR of the 3-bromoimidazole moiety occured in addition to the transformation of the —$CHBr_2$ to an aldehyde group (Scheme 4) (01JOC6576).

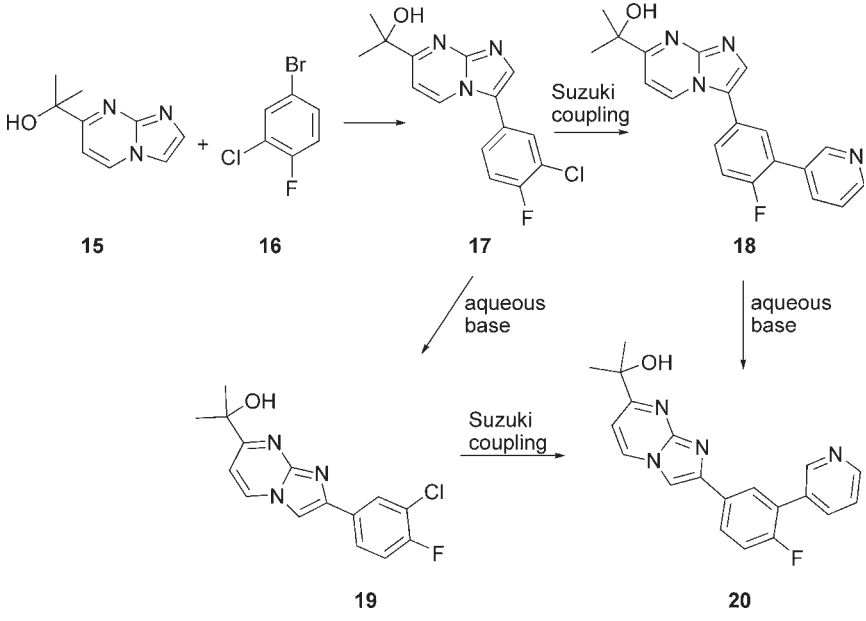
Suzuki coupling of substituted imidazopyrimidines **15** with **16** produced **17** whose further arylation gave **18**. The reactions have taken place without rearrangement due to the anhydrous conditions. On the other hand, a DR of both **17** and **18** yielded **19** and **20**, respectively. The rearranged product **19** subsequently underwent a Suzuki coupling to provide **20** (Scheme 5) (05JOC6034). While the DR is typically a reversible process, presence of an aryl group at the 2-position thermodynamically favors that at the 3-position. In compounds **19** and **20**, the aryl



Scheme 3



Scheme 4



Scheme 5

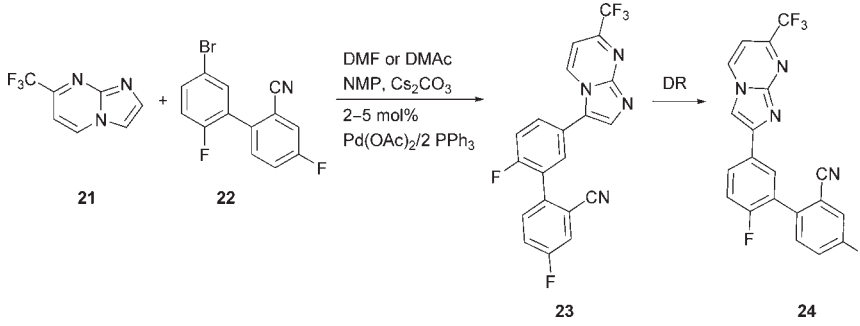
rings are coplanar and thus conjugated with the imidazopyrimidine ring as supported by UV and molecular modeling calculations. However, such conjugation was not possible with **17** and **18** due to steric interactions between the ortho hydrogens of the aryl ring and the

5-hydrogen of the pyrimidine ring. This explained the exclusive formation of **19** and **20**.

Coupling 7-(trifluoromethyl)imidazo[1,2-a]pyrimidine **21** with aryl-halides **22**, in polar aprotic solvents such as DMF, DMAc, and NMP in the presence of Cs_2CO_3 and $Pd(OAc)_2/2PPh_3$, gave 3-aryl-7-(trifluoromethyl)imidazo[1,2-*a*]pyrimidine **23**. However, during the course of the reaction, its concentration decreased and isomerization via a DR occurred to give the regioisomer 2-aryl-7-(trifluoromethyl)imidazo[1,2-*a*]pyrimidine **24** (Scheme 6) (06OPD398).

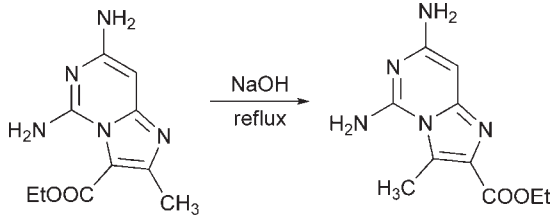
The action of alkali on ethyl 5-amino-2-methylimidazo[1,2-*c*]pyrimidine-3-carboxylate **25** caused its conversion to ethyl 5-amino-3-methylimidazo[1,2-*c*]pyrimidine-2-carboxylate **26** (Scheme 7) (99JOC634).

3-Substituted 6H-imidazo[1,2-*c*]quinazolin-5-ones **27** underwent a DR to the thermodynamically more stable 2-substituted 6H-imidazo [1,2-*c*]quinazolin-5-ones **28** by the action of HCl in methanol. This stability was said to be due to the presence of the carbonyl group in an eclipsed position to the large substituent on the imidazole ring in **27** but only with a hydrogen atom in **28** (Scheme 8) (96H2607).



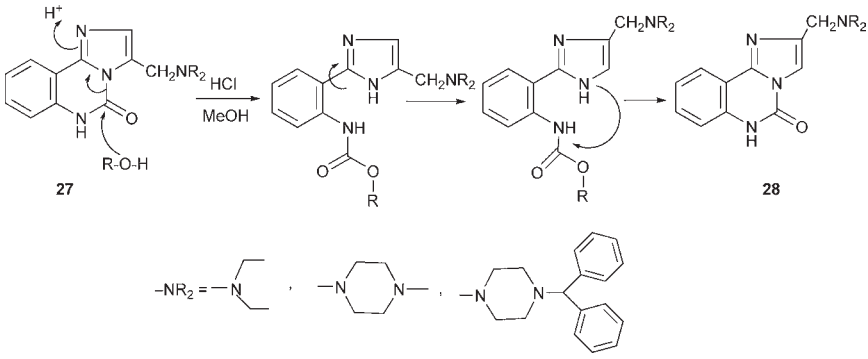
21 **22** **23** **24**

Scheme 6



25 **26**

Scheme 7



Scheme 8

2.3 Rearrangement of 1,2,4-triazoloheterocycles

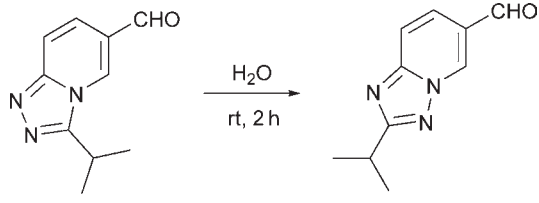
2.3.1 1,2,4-Triazolopyridines

Treatment of 1,2,4-triazolo[4,3-a]pyridine **29** with an acid yielded 1,2,4-triazolo[1,5-a]pyridine **30** (Scheme 9) (05JME5728).

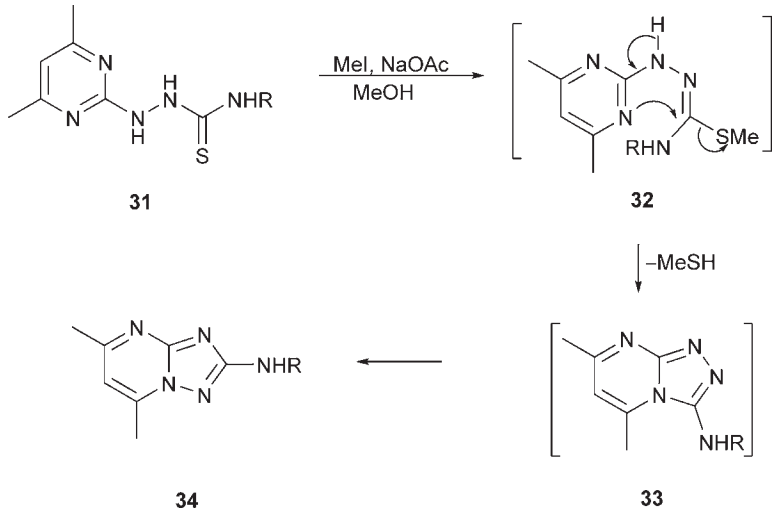
2.3.2 1,2,4-Triazolopyrimidines

When 4-aryl(alkyl)-1-(4,6-dimethylpyrimidin-2-yl)thiosemicarbazides **31** reacted with methyl iodide in boiling methanol in the presence of sodium acetate, they gave 2-R-amino-5,7-di-methyl[1,2,4]triazolo[1,5-*a*]pyrimidines **34** in high yield. The first step could be the alkylation of the sulfur atom with the formation of **32** followed by intramolecular cyclization with elimination of methanethiol to give **33**. The subsequent DR of **33** gave **34** (Scheme 10) (06RJO1403).

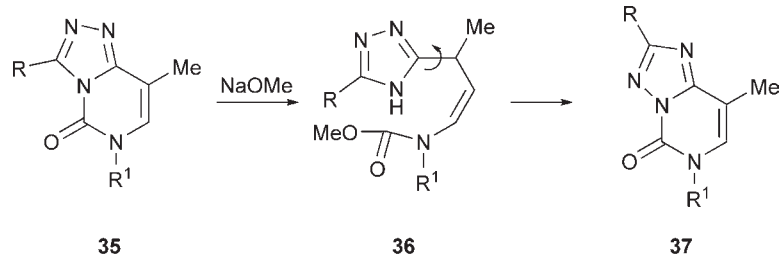
Treatment of 1,2,4-triazolo[4,3-*c*]pyrimidin-5(*6H*)-ones **35** with base gave [1,2,4]triazolo[1,5-*c*]pyrimidin-5(6H)-ones **37** via a DR, whereby the pyrimidine ring in **35** was cleaved to give the triazole ester intermediate **36** that survived under these conditions (Scheme 11) (99JCS(P1) 1333). But in aqueous sodium hydroxide, the DR did not occur and a



Scheme 9



Scheme 10

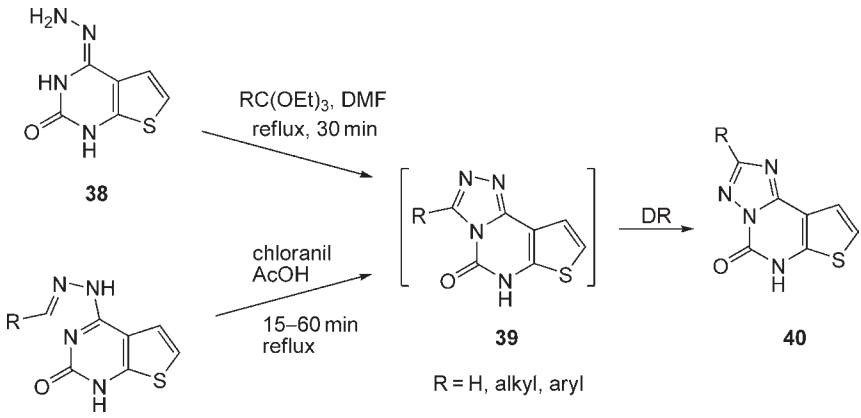


Scheme 11

decarboxylation presumably took place, which led to degradation of products. In neutral solvents, such as ethyl acetate, ethanol, DMSO, or DMF, the DR took place. On the other hand, **35** at room temperature was quite stable for several days in trifluoroacetic acid (TFA) or concentrated HCl, but gradually were isomerized in glacial acetic acid within one day (02H631). Thus, the synthesis of **35** encountered confusing results due to rearrangement. The occurrence of a DR was supported by the crystal structure of **37**.

An unexpected participation of the cyano group has been reported during the DR of 6-cyano-7-phenyl-1,2,4-triazole[4,3-a]pyrimidin-5(8H)-one to give 7-imino-5-phenyl-1,2,4-triazolo[1,5-a]pyrimidine (98ZN1203).

The thieno[2,3-*e*][1,2,4]triazolo[4,3-*c*]pyrimidin-5(6*H*)-ones **39** were too unstable to be isolated even in neutral solution at room temperature

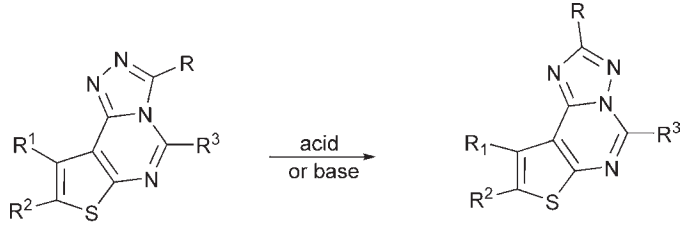


Scheme 12

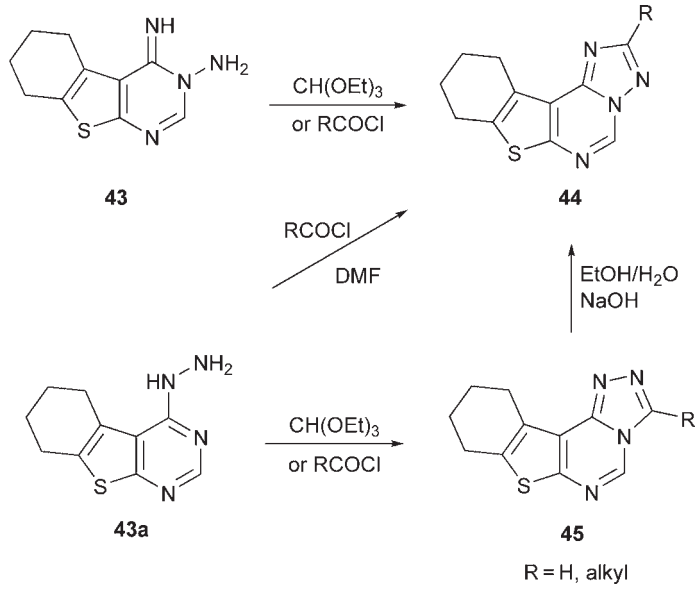
but rearranged directly to the 2-substituted thieno[2,3-*e*][1,2,4]triazolo [1,5-*c*]pyrimidin-5(6*H*)-ones **40** (Scheme 12) (05H2683). The two pathways for **40**, from the hydrazine **38** on refluxing with triethoxy alkane or from its hydrazone by reflux in the presence of chloranil, never led to the isolation of the expected product **39** but each time led to the isomerization to **40** through a DR (Scheme 12) (08H777).

The cyclization of 4-hydrazino-2-methylthio-thieno[2,3-d]primidines with one carbon-inserting agent gave the triazolo[4,3-c]pyrimidines **41**. They resist the isomerization in acid, but undergo a DR to the [1,5-c] isomers **42** under basic conditions using NaOMe or hydrazine; the DR product was confirmed by X-ray analysis (08JCR336). The rearrangement of analogs of **41** to **42** can take place in both alkaline and acidic media (Scheme 13) (06RCB2247).

Heating aminoimine **43** and hydrazino-pyrimidine **43a** with acid chlorides (R = H, CH_3, Et, Pr, or Bu) in cholorobenzene and catalytic amount of DMF gave **44** and **45**, but by refluxing **45** in an aqueous ethanolic solution of NaOH afforded **44** via a DR. The rearrangement



Scheme 13



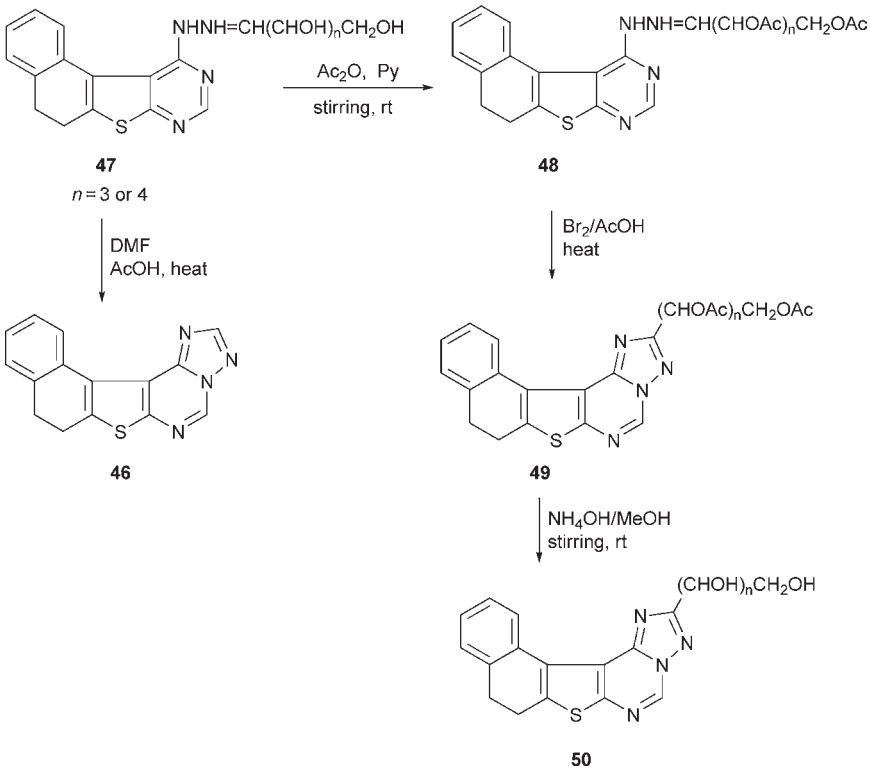
Scheme 14

also occurred in acidic media through an ANRORC mechanism, confirmed by quantum chemical calculations. Substituents on the triazole ring were found to play the principal role in the rearrangement (Scheme 14) (06RCB2247).

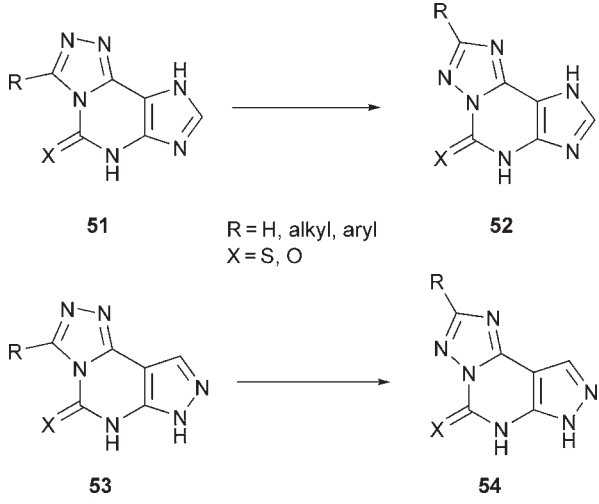
The triazolo[1,5-*c*]pyrimidine **46** and **49** were obtained directly via the DR of their respective triazolo[4,3-*c*]pyrimidines, formed by cyclization of the hydrazone **47** and its acetate **48**, which upon deacetylation afforded **50** (05ACSV429). The DR product **46** was verified with X-ray diffraction, and its formation was said to be due to hydrolysis of the hydrazine residue followed by cyclization of the resulting hydrazone with DMF in boiling acetic acid (Scheme 15) (05HAC226).

The tricyclic 1,2,4-triazolopurin-5(6*H*)-ones **51** (R = H, Alkyl, or Aryl, X = O or S) and pyrazolo-1,2,4-triazolo[4,3-*c*]pyrimidin-5(6*H*)-ones **53** were easily rearranged into **52** and **54**, respectively (Scheme 16) (02H631). The DR can be induced thermally in acid, alkali, and neutral media (78AJC2505).

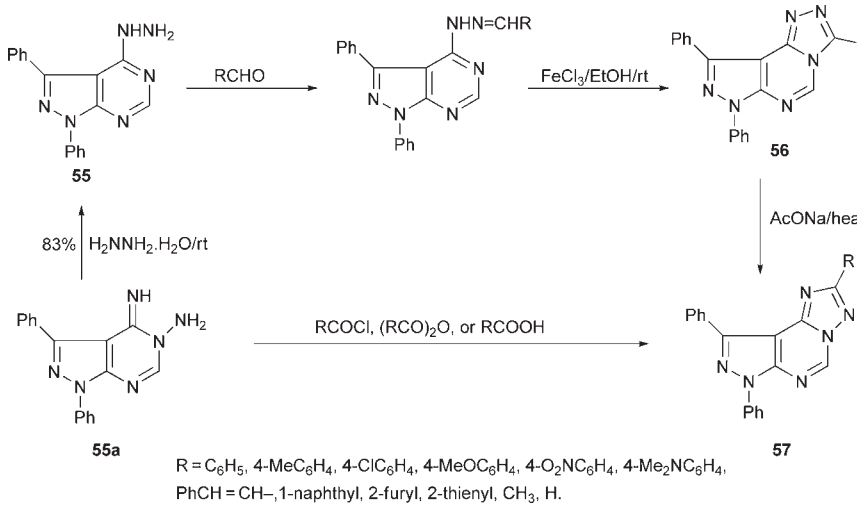
When compound **55a** reacted with excess hydrazine hydrate at room temperature, it underwent a DR to give 1,3-diphenyl-4-hydrazino-pyrazolo [3,4-d]-pyrimidine **55**. The respective N-(1,3-diphenylpyrazolo[3,4-d]pyrimidin-4-yl)hydrazones were prepared by condensation with aldehydes. Treatment of the hydrazones with iron(III) chloride in ethanol gave as a single product 3-substituted-7,9-diphenylpyrazolo[4,3-e][1,2,4]triazolo [4,3-c]pyrimidines **56** (Scheme 17). The conversion is similar to other related



Scheme 15



Scheme 16



Scheme 17

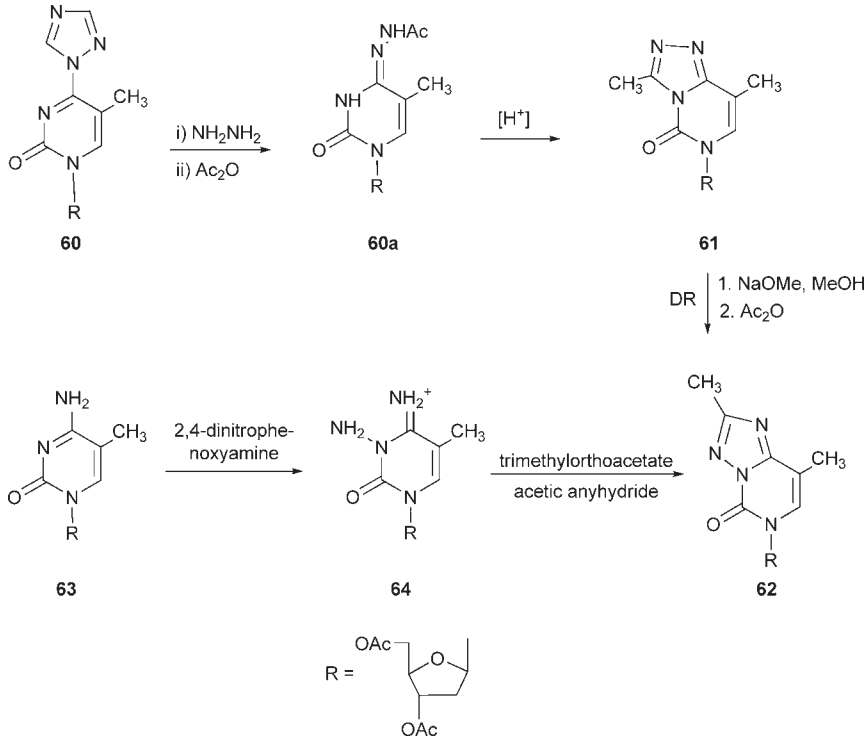
oxidative cyclization of aldehyde N-heteroarylhydrazones with iron(III) chloride, which have been reported to proceed via the generation of their respective nitrilimines, which then through an *in situ* 1,5 electrocyclization afforded the respective fused heterocycles. When **56** were heated in ethanol and sodium acetate, they isomerized to the thermodynamically more stable pyrazolo[4,3-e][1,2,4] [1,5-c]pyrimidine derivative **57** through tandem ring opening and ring closure reactions (08T10339).

Derivatives of the pyrazolo[3,4-d][1,2,3]triazolo[1,5-a]pyrimidines **59** were synthesized from the corresponding angular isomers **58** through a DR, in quantitative yields (Scheme 18) (08TL5125).

The 1,2,4-triazolo[4,3-*c*]pyrimidinone nucleoside **61** was prepared from **60** by hydrazinolysis and subsequent acetylation to give N^4-acetylamino-2′-deoxycytidine **60a** where acid promoted its cyclization to give **61**. The basic conditions required for the deprotection of **61** caused its rearrangement to its

R = Ph, CN, $CONH_2$; R^1 = Ph, Me; X = NH, O

Scheme 18



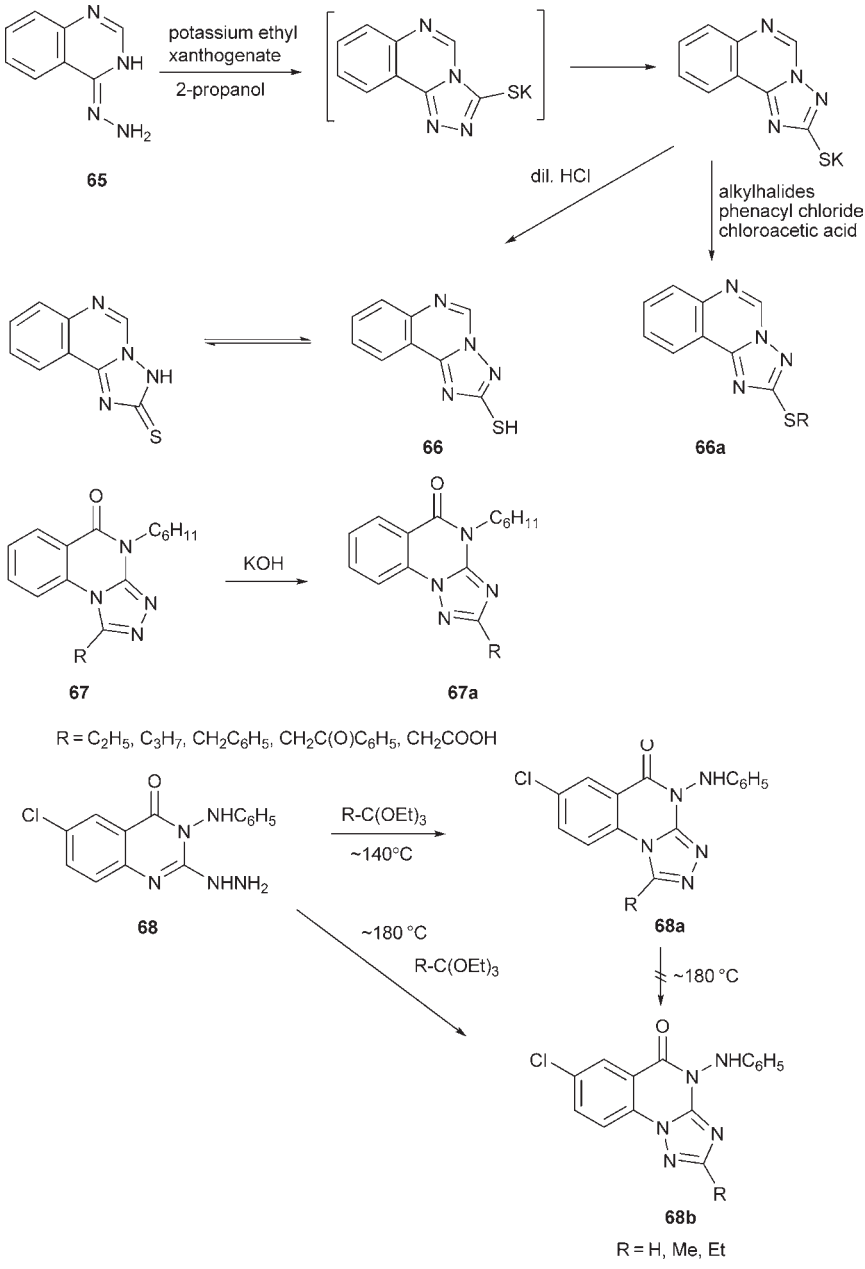
60 60a 61 63 64 62

Scheme 19

isomer 6-(4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2,8-dimethyl-[1,2,4]triazolo[1,5-*c*]pyrimidin-5(6H)-one **62** (R = H). Alternatively, the latter isomer **62** was prepared by the amination of diacetyl-5-methyl-deoxycytidine **63** using 2,4-dinitrophenoxyamine to give the 3,4-diaminopyrimidinone **64** whose reaction with trimethylorthoacetate or acetic anhydride led to the triazolopyrimidinone **62** (R = Ac) (75CPB844). Interestingly, acetyl **60** did not rearrange or cyclize under basic conditions with methoxide ion (Scheme 19) (99JCS(P1)1333, 98TL3865).

2.3.3 1,2,4-Triazoloquinazolines

The 2-thio[1,2,4]triazolo[1,5-*c*]quinazoline **66** was obtained by treatment of 4-hydrazinoquinazoline **65** with potassium ethyl xanthogenate via a facile *in situ* DR of the expected triazolo[4,3-*c*]quinazoline. The potassium salt that converted to **66** with dilute HCl has an ^{1}H NMR spectrum in DMSO-d_6 solution indicating its existence in equilibrium with the thione tautomer. Its structure was established by X-ray diffraction and confirmed by an independent synthesis (Scheme 20) (06M1543). When the potassium salt was treated with alkylhalides, phenacyl chloride, or


potassium ethyl xanthogenate
2-propanol
65
dil. HCl
alkylhalides
phenacyl chloride
chloroacetic acid
66
66a
KOH
67
67a
R = C2H5, C3H7, CH2C6H5, CH2C(O)C6H5, CH2COOH
R-C(OEt)3
~140°C
68
68a
~180 °C
R-C(OEt)3
~180 °C
68b
R = H, Me, Et

Scheme 20

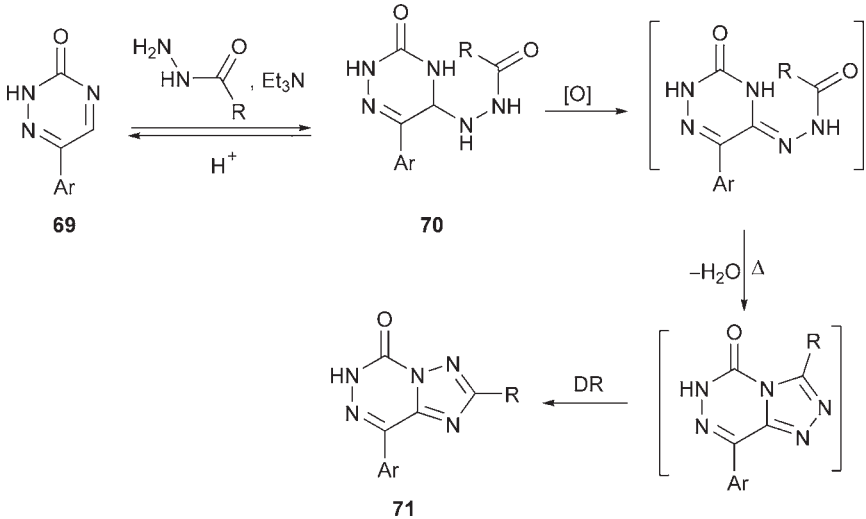
chloroacetic acid under mild conditions, the alkylation was found to proceed smoothly at the sulfur atom to give **66a** (06M1543). A series of 4-cyclohexyl-1-substituted 1,2,4-triazolo[4,3-*a*]quinazolin-5-(4*H*)-ones **67** were treated with potassium hydroxide in boiling ethanol to yield the DR product **67a** (Scheme 20) (08H1479). The reaction of **68** with triethyl orthoformate under reflux at 140°C gave 7-chloro-4-phenylamino[1,2,4] triazolo[4,3-*a*]quinazolin-5(4*H*)-ones **68a**, which were heated in pyridine and xylene at 180°C but no isomerization occurred. Careful investigations revealed that the reaction of **68** directly with the orthoformate at 180°C afforded **68b** suggesting that DR occurred under these reaction conditions (Scheme 20) (08H2421).

2.3.4 1,2,4-Triazolo-1,2,4-triazines

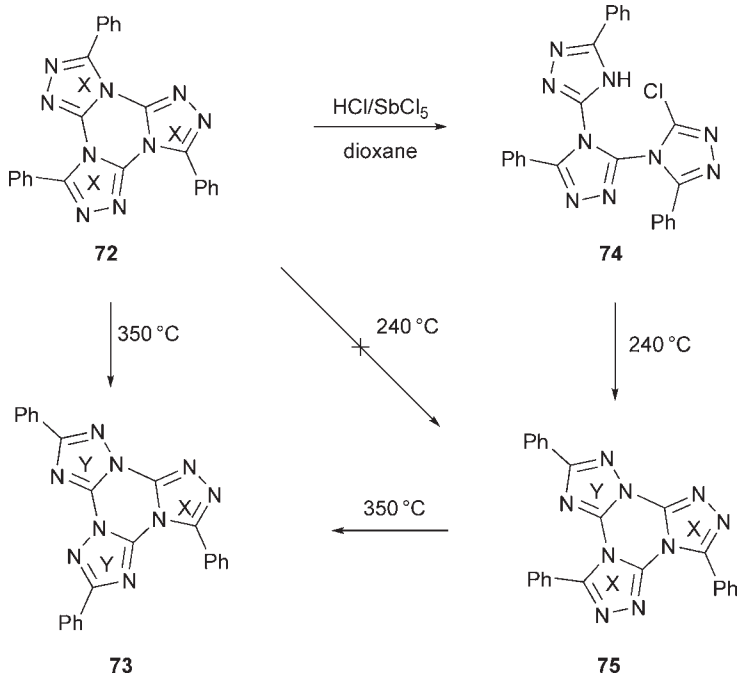
Heating 6-aryl-1,2,4-triazin-3(2H)-ones **69** with carboxylic acid hydrazides in nitrobenzene-containing triethylamine gave 1,2,4-triazolo[1,5-*d*] [1,2,4]triazin-5(6H)-ones **71** (Scheme 21). During the course of the reaction several intermediates including **70** were formed (04RJOC85). This rearrangement readily occurred either under basic conditions (77AJC2515) or thermally in boiling nitrobenzene (66JC2031).

2.3.5 1,2,4-Triazolo-1,3,5-triazines

Thermolysis of both **72** and **75** at 350°C was accompanied by a DR to yield 3,6,10-triphenyl-tris[1,2,4]triazolo[1,5-*a*:1′,5′-*c*:4″,3″-*e*][1,3,5]triazine **73.** However, thermolysis of **72** at 240°C did not give **75**, but its ring-



Scheme 21



Scheme 22

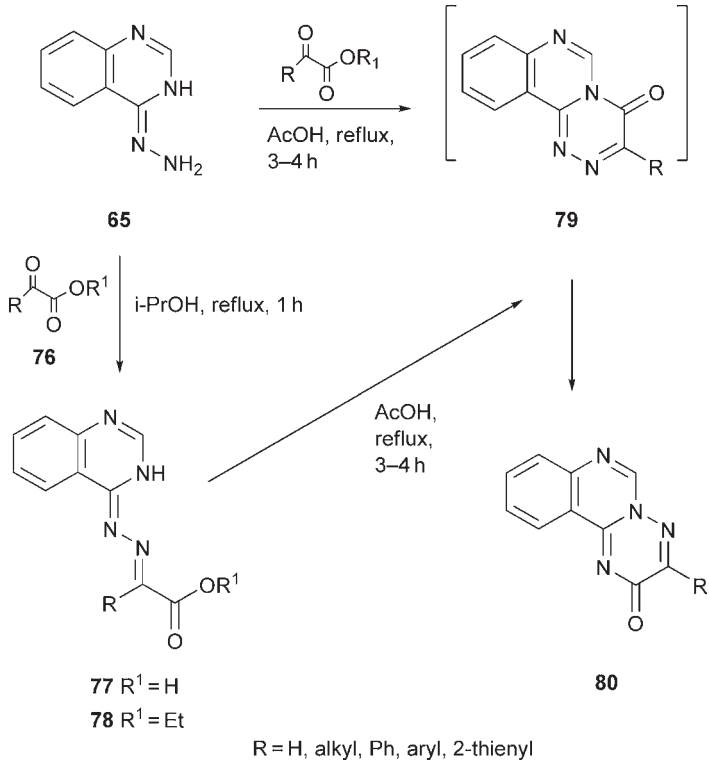
opened product **74** gave **75** under thermolysis at the same temperature (Scheme 22) (05RCB719).

2.4 Rearrangement of 1,2,4-Triazinoheterocycles

When 4-hydrazinoquinazoline **65** was allowed to react with α-keto-carboxylic acids or their esters **76** in 2-propanol, the corresponding hydrazones **77** ($R^1 = H$) and **78** ($R^1 = Et$) were isolated in good yields. Their cyclocondensations in acetic acid afforded the 3-substituted 2-oxo-2*H*-1,2,4-triazino[2,3-*c*]quinazolines **80** ($R = CH_3$, Ph, 2-thienyl) apparently through facile DR intermediates, triazino[4,3-*c*]quinazolines **79** (Scheme 23) (07H619).

3. TRANSLOCATION OF EXO- AND ENDOCYCLIC HETEROATOMS IN HETEROCYCLES (TYPE 2)

This type of DR is versatile in both five- and six-membered heterocycles. The heteroatoms are not restricted to nitrogen but may also be sulfur, oxygen, or selenium. Two heteroatoms are involved; one must be



Scheme 23

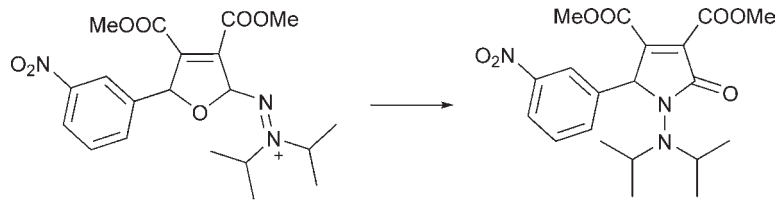
exocyclic at the ortho position of the endo heteroatom-containing heterocycle. This type can be classified according to the number of heteroatoms, from one to four heteroatoms in the ring. The DR also occurrs in natural compounds like DNA and other nitrogenous bases, such as pyrimidines and purines. This part is divided according to the heteroatom(s) present in the ring where translocation occurs.

3.1 Heterocycles with one heteroatom in the ring

Heterocycles with one heteroatom include furans, isoquinolines, pyrans, and thiopyrans that will be discussed here.

3.1.1 Furans

Functionalized furans can undergo a DR as such or after their presumable formation as intermediates. Thus, the furans **81**, which are rarely used

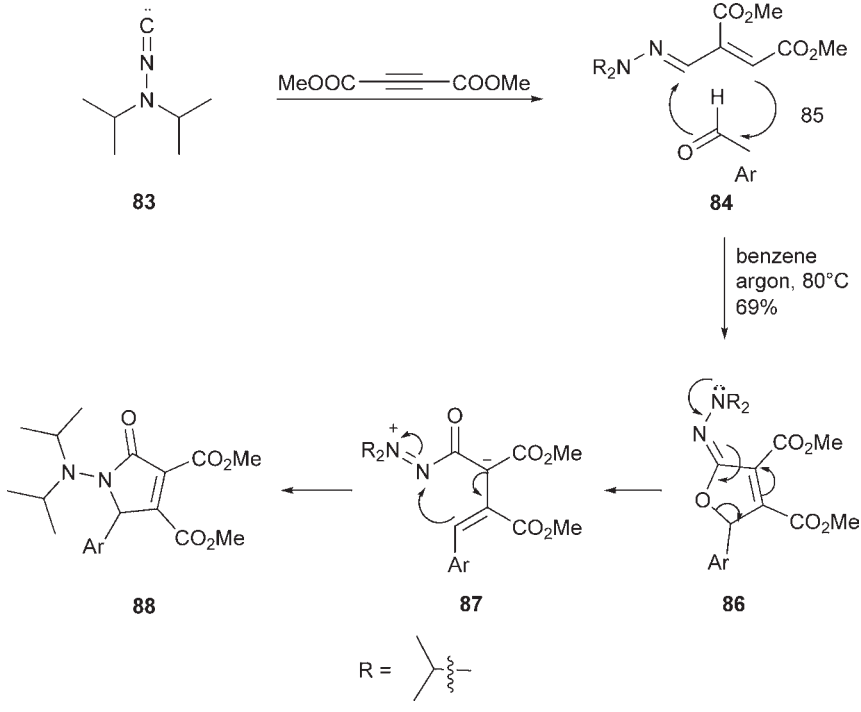


81 **82**

Scheme 24

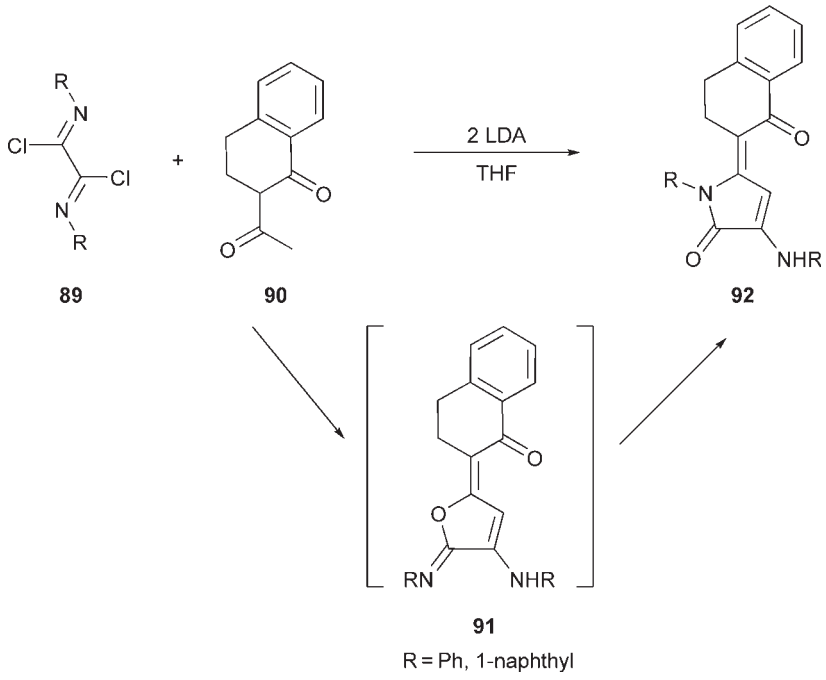
but are accessible species, allow a facile synthesis of substituted 3(5*H*)-pyrrolin-2-ones **82** via a DR (Scheme 24) (01CL738).

A domino cycloaddition-DR sequence takes place during the synthesis of pyrrolin-2-ones from N-isocyanides. Thus, methyl acetylene dicarboxlate with isocyanide **83** and aromatic aldehyde **84** gave furans **86** via intermediate **85**. Rearrangement of **86** gave **88** via the open chain intermediate **87** (Scheme 25) (03ACR899).



83 **84** **86** **87** **88**

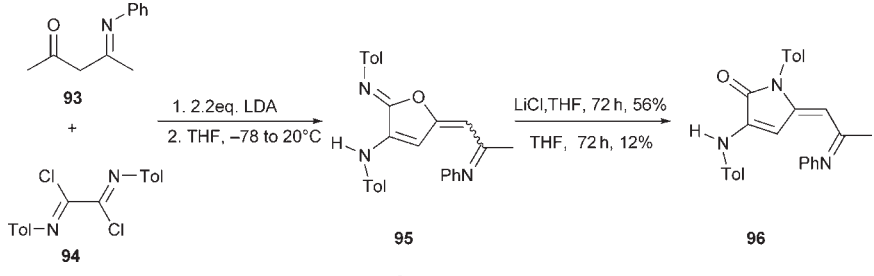
Scheme 25



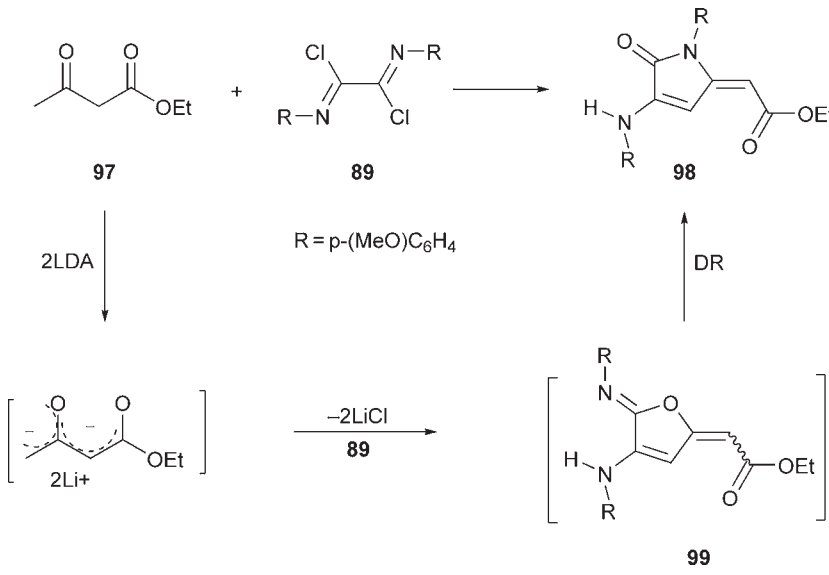
Scheme 26

Regioselective cyclization of oxalic acid-bis(imidoyl)dichloride **89** and the dianion derived from 2-acetyltetralone **90** led to intermediate **91**, which subsequently rearranged to **92** by the translocation of N and O atoms (Scheme 26) (04SL2779).

Dilithiated 4-(phenylimino)pentan-2-one, generated from **93**, with oxalic acid bis(imidoyl)dichloride **94** resulted in regioselective cyclization and formation of **95** as an inseparable 1:1 mixture of E/Z isomers. On standing, the yellow-colored solution of **95** changed slowly into the red-colored isomer 5-alkylidene-2,5-dihydropyrrol-2-one **96** (12%, low conversion) formed by a DR (Scheme 27) (04EJO1897). The yield of **96** was



Scheme 27



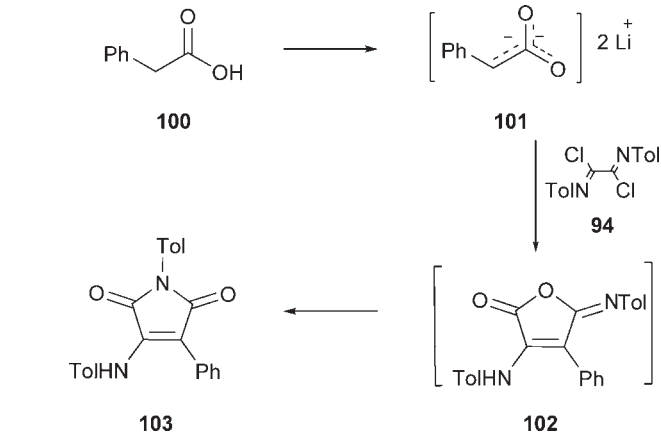
Scheme 28

improved (56%) by the addition of two equivalents of lithium chloride to the reaction. The rearrangement proceeded sterioselectively and afforded the E-isomer exclusively.

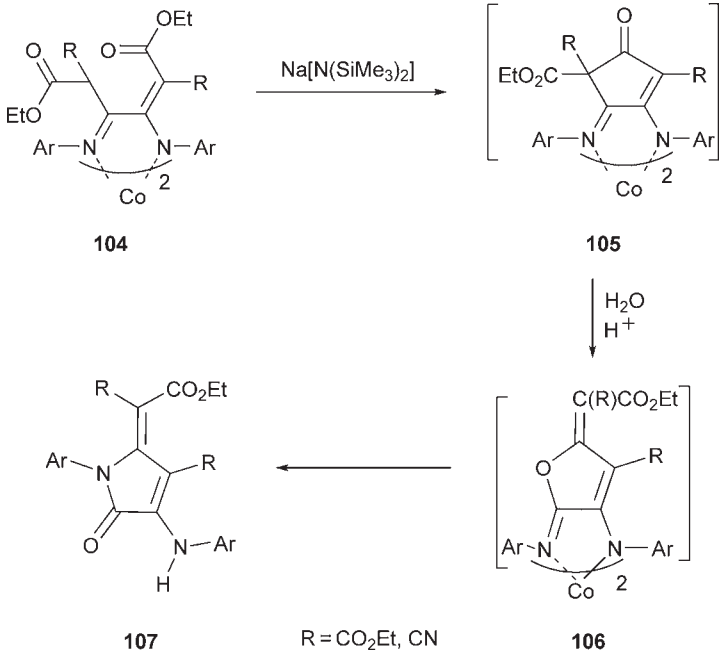
Ethyl acetoacetate **97** with oxalic acid bis(imidoyl)chloride **89** (R = p–MeO–C_6H_4) gave the 5-alkylidene-5*H*-pyrrolin-2-one **98** (Scheme 28) (01SL1437, 04EJO1897). The reaction can be explained by a regioselective attack of the terminal carbon atom of the dianion of **97** onto the dielectrophile **89** and cyclization mediated by the oxygen atom to give intermediate **99**, which then underwent a DR to **98**. The domino cyclization/DR proceeded with excellent E/Z diastereoselectivity due to the stereodirecting effect of the substitituent attached to the pyrrole nitrogen atom, which is present in **96** and **98** but not in **95** and intermediate **99**. The rate of the DR was enhanced by the Lewis acid LiCl formed during the cyclization.

The cyclization of the dianion of phenylacetic acid **100** with oxalic acid-bis(*p*-tolylimidoyl)dichloride **94** afforded maleic imide **103** by an initial cyclization to give intermediate **102** and subsequent DR (Scheme 29) (98SL399, 01CEJ2617, 04CRV4125).

The 3-amino-1-azadiene complex **104** underwent a ring-closure reaction to give the unstable intermediate **105** that rearranged to **106**. A subsequent DR either before or after decomplexation afforded 5-ylidene-pyrrol-2(5*H*)-ones **107** (Scheme 30) (99JOC365).

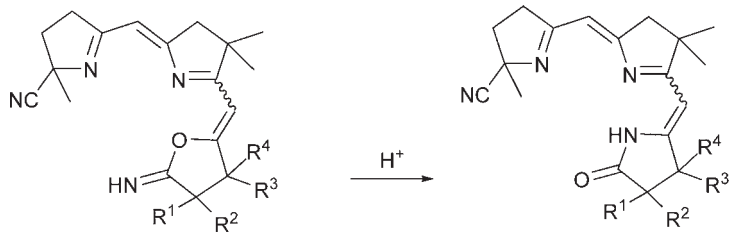


Scheme 29



Scheme 30

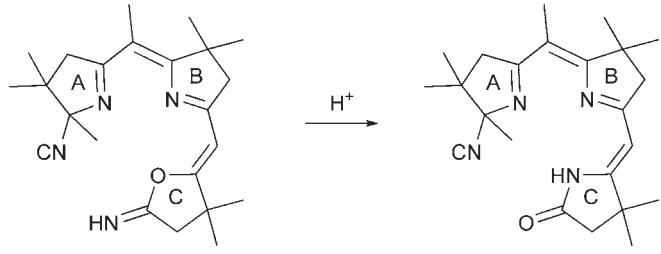
Acid-catalyzed DR of **108** in the presence of $TsOH/H_2O/CHCl_3$ gave 65% yield of tripyrroline **109** (Scheme 31) (99JA1958) as an inseparable mixture of *E*- and *Z*-isomers (84CHEC94). Similarly, Pd(0)/CuI-mediated coupling of semicorrin with an alkyne amide formed tricyclic



108 $R^1 = R^2 = CH_3$, $R^3 = R^4 = H$
110 $R^1 = R^2 = H$, $R^3 = R^4 = CH_3$

109 $R^1 = R^2 = CH_3$, $R^3 = R^4 = H$
111 $R^1 = R^2 = H$, $R^3 = R^4 = CH_3$

Scheme 31



112 **113**

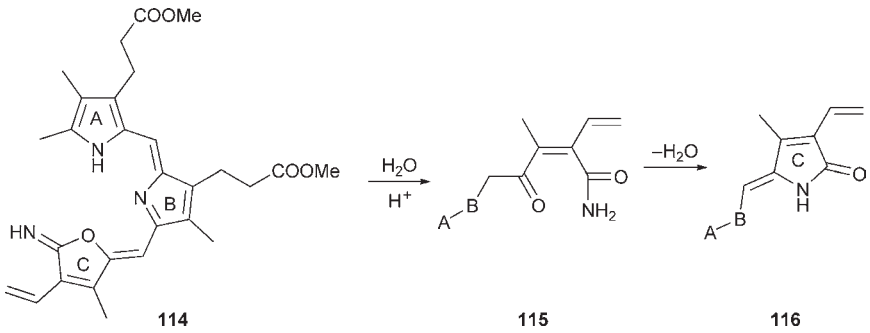
Scheme 32

iminolactone **110** in 60% yield. Analogous to **108**, iminolactone **110** was converted to the tripyrroline **111** (60%; *Z*:*E* = 3:1) on acid-catalyzed isomerization.

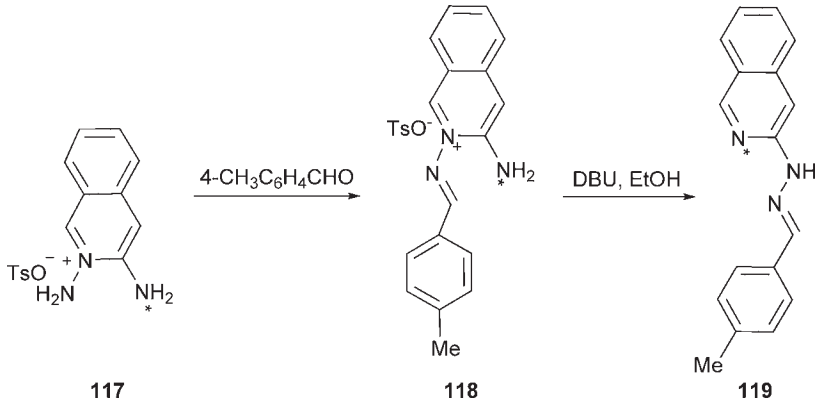
Similarly, furamine **112** was converted with acid to the pyrrolidines **113** via a DR (Scheme 32) (99JOC1778). Also, **114** gave **116** via ring opening to the keto-amide **115**, which was followed by cyclodehydration to yield **116** (Scheme 33) (00JOC205).

3.1.2 Isoquinolines

Reaction of **117** labeled with an ^{15}N isotope in the amino group and 4-methylbenzaldehyde yielded hydrazone **119** where the ^{15}N atom was found in the ring. The change in the position of the isotopic label supported the idea that the reaction proceeded through a DR. As further proof **117** was reacted with the aldehyde in acetonitrile in the absence of base in order to hinder the rearrangement. After a 5-h reflux postulated intermediate **118** was obtained in considerable yield. Treatment of this compound with DBU in ethanol then afforded **119** revealing that the azomethine salt was most probably an intermediate during the rearrangement of **117** to **119** (Scheme 34) (08T1101).



Scheme 33

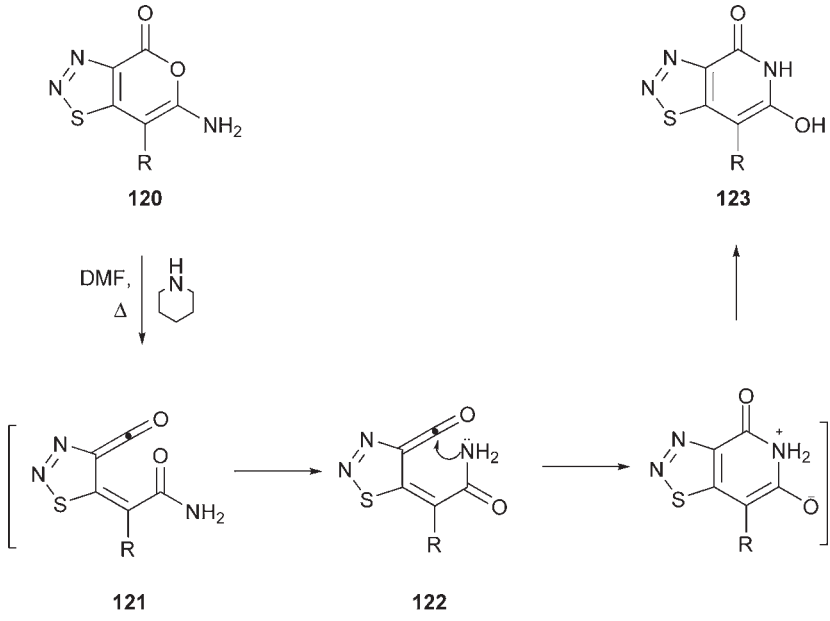


Scheme 34

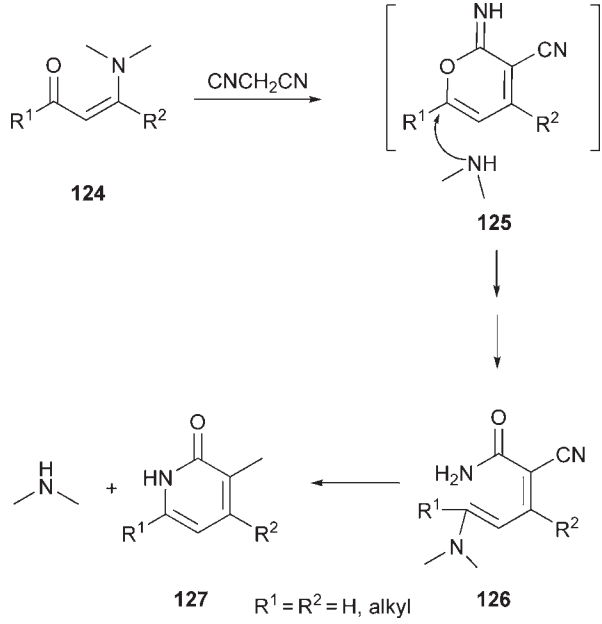
3.1.3 Pyrans

A DR of 6-amino-4-oxopyrano[3,4-*d*][1,2,3]thiadiazoles **120** gave 6-hydroxy-4-oxo-[1,2,3]thiadiazolo[4,5-*c*]pyridines **123** under thermal conditions. The rearrangement proceeded by the opening of the pyran ring to the ketene intermediate (s-*cis*) **121** followed by simultaneous rotational isomerization to **122** (s-*trans*) and then recyclization to form the pyridin-2-one **123**. The calculated energy barriers [B3LYP/6-31G(d)] were used to support the experimental results (Scheme 35) (05EJOC2914).

The intermediate of 2*H*-pyran-2-imine **125** was identified by spectroscopic methods during the synthesis of 2(1*H*)-pyridones from β-enaminones **124** by a reaction with malononitrile. Ring opening by action of a nucleophile afforded **126** that cyclized to 2(1*H*)-pyridone **127**. The transformation via **126** was considered to be a DR (Scheme 36) (99JOC9493).



Scheme 35



Scheme 36

3.1.4 Thiapyrans

The conversion of 5,6-dihydro-*N*-phenyl-2-(phenylimino)-2*H*-thiopyran-4-amine **128** (R = iPr or Ph) to 1,2,5,6-tetrahydro-2-methylene-*N*,1-diphenyl-4-pyridinamine **130** occurs by a DR under thermal conditions through intermediate **129** (Scheme 37) (01T8305).

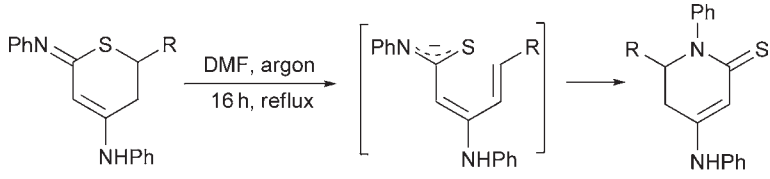
3.2 Heterocycles with two heteroatoms in the ring

3.2.1 Pyrimidines

The presence of a DR in pyrimidine rings again has attracted much attention as shown earlier (99AHC79). The synthesis and reactions of purines and their nucleosides, as well as kinetic studies of the DR, have been reviewed (96YZ355).

The reaction of 2-amino pyrimidine with ethyl bromoacetate gave a mixture containing **132** presumably as a product from a DR (Scheme 38) (03MOL467).

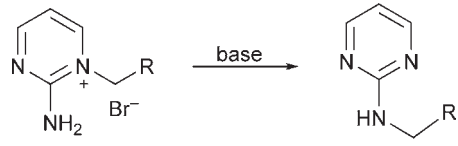
Protonated cytosine and 5-hydroxy as well as 5-hydroxymethylcytosine, but not its 5-formyl-substituted analog, undergo a DR in the gas phase. The loss of HNCO from the $[M+H]^+$ ion of [1,3-^{15}N]cytosine required a rearrangement of the cytosine component before the elimination (06JAM1335). Adenosine can undergo a DR to exchange the exocyclic N^6 and endocyclic N^1 atoms. Theoretical predictions and experimental data unequivocally supported ring cleavage between N^1 and C2 followed by



128 **129** **130**

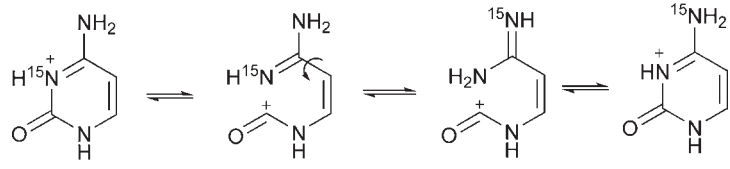
R = alkyl, aryl

Scheme 37



131 **132**

Scheme 38



133 134

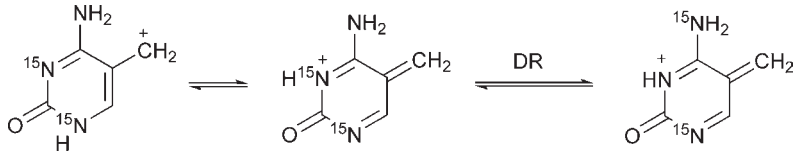
Scheme 39

rotation about the C4–C5 bond, ring closure, and proton migration (75BBR581, 05JAM1713). Although the literature is varied in the case of a DR of unmodified cytosine, or cytidine, the rearrangement of N^3-substituted cytosine during acetylation has been observed (64JOC1770, 65JOC2766). Moreover, this type of rearrangement has been employed for the synthesis of $^{15}N^3$-labeled uridine (65B54) and cytidine (04JOC8148) from the $^{15}N^4$-substituted cytidine N^3-oxide. Protonated cytosine underwent a similar rearrangement, which allowed the switching of N^3 and N^4 in the gas phase and facilitated the loss of unlabeled HNCO from [1,3-^{15}N] cytosine (**133** to **134**). In this regard, a proton on cytosine at N^3 resembles to some extent a substituent at N^3, which results in weakening of the N^3–C2 bond that facilitates the rearrangement (Scheme 39) (06JAM1335).

Semi-empirical calculations at the AM1 level predict that the gas-phase proton affinities of N^3 in 2′-deoxycytidine-5′-monophosphate and 2′-deoxycytidine-3′-monophosphate are higher than those of O^2 in the corresponding nucleotides by 2.5 and 3.9 kcal/mol (00JAM24). On the other hand, high-level *ab initio* calculations with the inclusion of correlation effects at the Møller–Plesset level predicted that three atoms (N^1, N^3, O^2) in neutral cytosine are susceptible to protonation within a range of 1 kcal/mol (96JA6811). Furthermore, recent calculations suggested that the transition-state energies for proton migrations between O^2 and N^3 of 1-methylcytosine are much smaller than the energy required for the major cleavage reactions (05JMP1417).

Similar to the dissociation of uracil (94JAM339), ammonia can be lost from N^3 of cytosine. Alternatively, ammonia can originate from the N^4 nitrogen. The percentage of the product resulting from a DR can be estimated to be ~25% from the relative abundances of the product ions derived from the loss of HNCO. On the other hand, ~40% of the lost ammonia does not bear the ^{15}N label. Therefore, a DR cannot account completely for the elimination of unlabeled NH_3 from [1,3-^{15}N]cytosine; a small fraction of the ammonia, therefore, must be lost from N^4. Thus the DR made it somewhat complicated to ascertain the origin of the site of loss of NH_3.

The collisional activation of the $[M + H]^+$ of 5-hydroxymethyl-2-deoxycytidine (5-HmC) led to the facile cleavage of the glycosidic bond. Further fragmentation of the protonated 5-HmC resulted in the



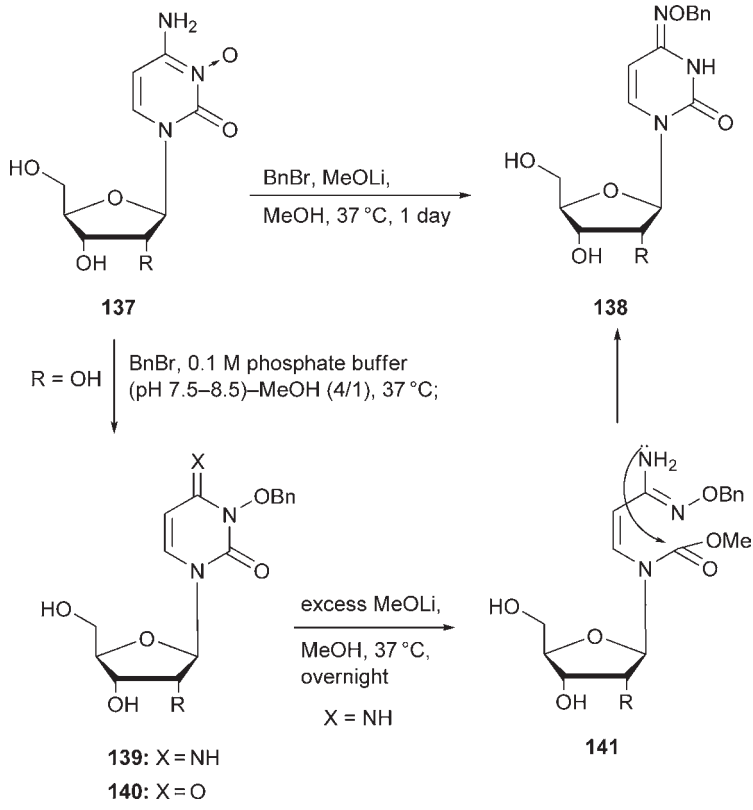
Scheme 40

predominant loss of a H_2O molecule, and the resulting ion can readily eliminate a HNCO component upon further collisional activation. The loss of both HNCO and $H^{15}NCO$ from the $[M–H_2O]^+$ ion of **135** or **136** can be attributed to a Dimroth-like rearrangement (Scheme 40) (06JAM1335). The relative abundances of these two ions may show that ~40% of the ion of *m/z* 124 has undergone such a rearrangement, which was higher than that found for the protonated deoxycytidine.

A DR was largely prohibited for protonated 5-formyl-methylcytidine (5-FmC), which necessitated protonation of N^3 because the presence of a 5-formyl group rendered protonation of N^3 most unlikely. Intramolecular hydrogen bonding led to facile protonation on the exocyclic 5-carbonyl group. The difficulty in protonating N^3 prevents the elimination of NH_3 from the $[M+H]^+$ of 5-FmC. Further fragmentation resulted in a facile loss of CO, though the expulsion of HCN constituted a minor fragmentation pathway. The fragmentation demonstrated the loss of only $HC^{15}N$, supporting that HCN was selectively eliminated from the N^1 position (06JAM1335).

$^{15}N^4$-Labeled cytidine N^3-oxide **137** (R = OH) was treated with a slight excess of benzyl bromide in the presence of lithium methoxide to give the DR product $^{15}N^4$-labeled uridine 4-O-benzyloxime **138** (R = OH) in 95% yield (Scheme 41) (04JOC8148). The key intermediates are **139** and **140**. Their ring opening gave **141** that recyclized to **138**. Similarily, [3-^{15}N,4-$^{15}NH_2$]cytidine was synthesized from the 4-oxo of uridine or N^3-activated uridine followed by a DR (00JOC2827).

When **142** was treated with 1-amino-2-hydroxypropane **143** in ethanol, the expected product of the DR via ring opening was 6-amino-3-methyl-5-(N-2-hydroxypropyl)iminomethyl)-1-(4-nitrophenyl) uracil **144** in 51% yield (Scheme 42) (04TL8007). To establish the influence of solvent on the outcome, the reaction was conducted in 2-hydroxypropane and t-butanol. A mixture of DR product **144** and ANRORC product **145** was obtained in molar ratios of 3:1 and 4:1, respectively (total yield 90%). However, the opposite ratio 1:5 (total yield 96%) of DR/ANRORC products was obtained using DMF containing 10% of water. Apparently after the addition of the amino group to C6 of the uracil and ring opening in protic solvents, addition of a proton to the nitrile nitrogen atom made the

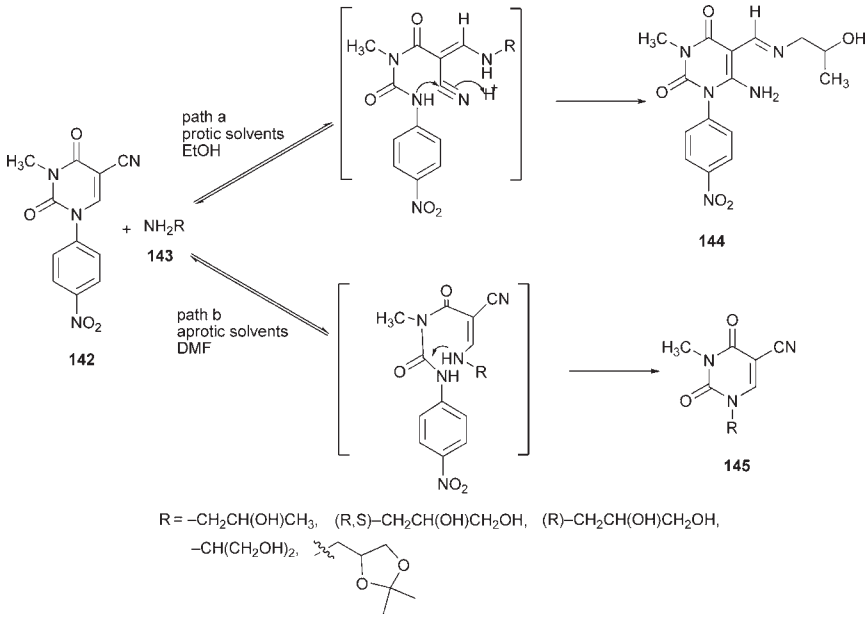


Scheme 41

latter more susceptible to attack by the NH-nitrogen leading to **144** (Scheme 42, path a). But when an aprotic solvent was used, attack of the nucleophile on the carbonyl gave the ANRORC product **145** (Scheme 42, path b) (04TL8007).

3.2.2 Pyrrolopyrimidines

Heating 3-(3-chlorophenyl)-5,6-dimethyl-4H-pyrrolo[2,3-*d*]pyrimidine-4-imine **146** in ethylene glycol, ethanol, or water gave 4-(3-chlorophenylamino)-5,6-dimethyl-7H-pyrolo-[2,3-*d*]pyrimidine **147** in 92% yield via a DR (Scheme 43) (01OPD581). 3-Amino-4-imino 7*H*-pyrrolo[3,2-*e*][1,2,4]triazolo[1,5-*c*]pyrimidine **148** was synthesized from 2-ethoxymethyleneamino-1*H*-pyrrole-3-carbonitrile and hydrazine hydrate transformed by alkali into hydrazinopyrimidine **149** via a DR. Reaction of **149** with acid chlorides gave pyrrolotriazolopyrimidines **150** (R = H, Me, or Et) that underwent a DR to give **151** on heating for several hours in aqueous ethanolic alkali. Under similar conditions, **150** with bulkier



Scheme 42

substituents R very easily rearranged into isomers **151**. The steric pressure of bulky substituents decreases the energy required for a DR of **150** to **151** (Scheme 43) (06RCB1492).

3.2.3 Thienopyrimidines

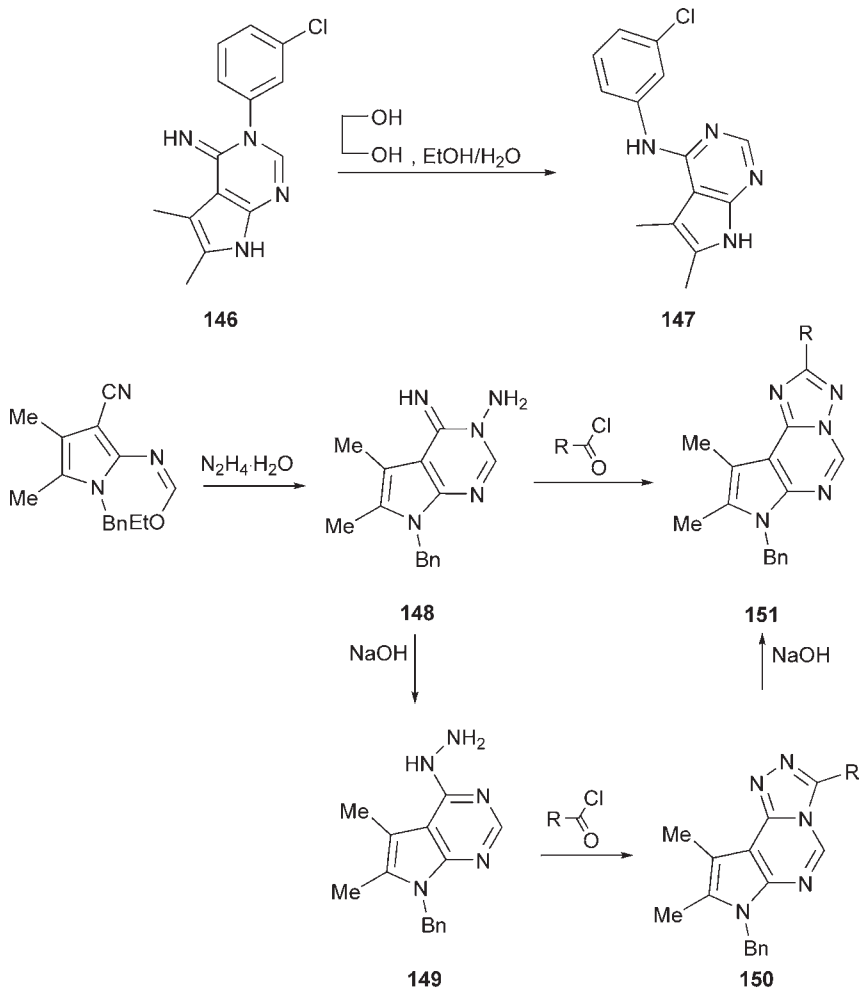
7-Amino-4-[(4-methylphenyl)amino]pyrido-thieno[3,2-*d*]pyrimidine-8-carbonitriles **153** were synthesized from **152** via a DR (Scheme 44) (07HTC405).

3.2.4 Pyrazolopyrimidines

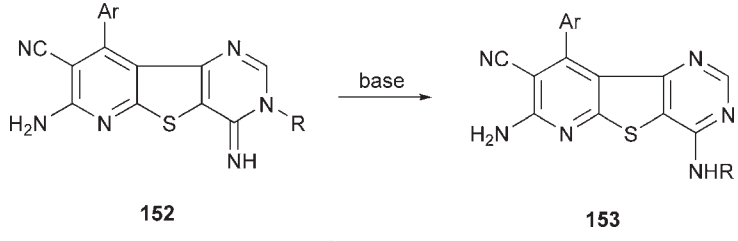
Monosubstituted hydrazines reacted with ethyl *N*-4-cyano-1-(4-substituted)-1*H*-pyrazol-5-ylformimidate **154** to afford a mixture including the DR product **155**. Similarly, **154** with *m*-anisidine afforded only the DR product **156** (Scheme 45) (07ARK92).

3.2.5 Imidazopyrimidines

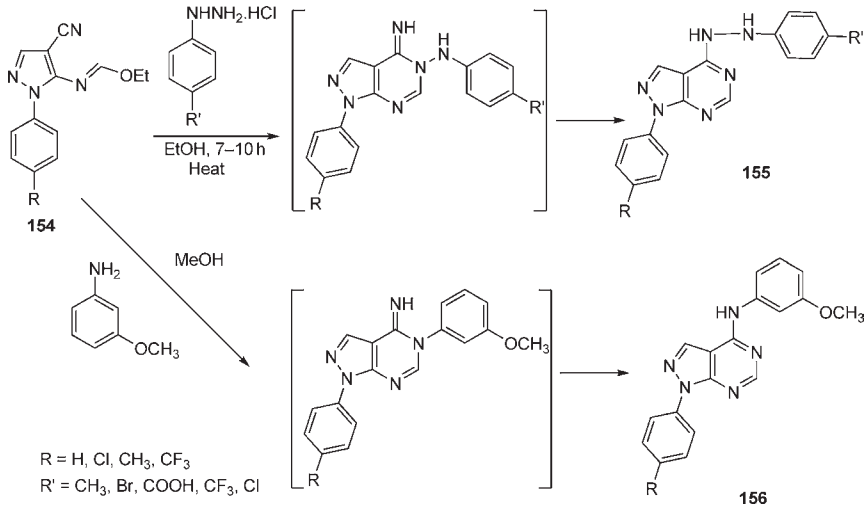
The alkylation of imidazopyrimidines may involve initial attack at N^1 that on a DR gave the N^6 adduct. Thus, the base-catalyzed cleavage of the six-membered ring in **157** gave a ring-opened intermediate that upon recyclization interchanged the locations of the endo- and exocyclic



Scheme 43



Scheme 44



Scheme 45

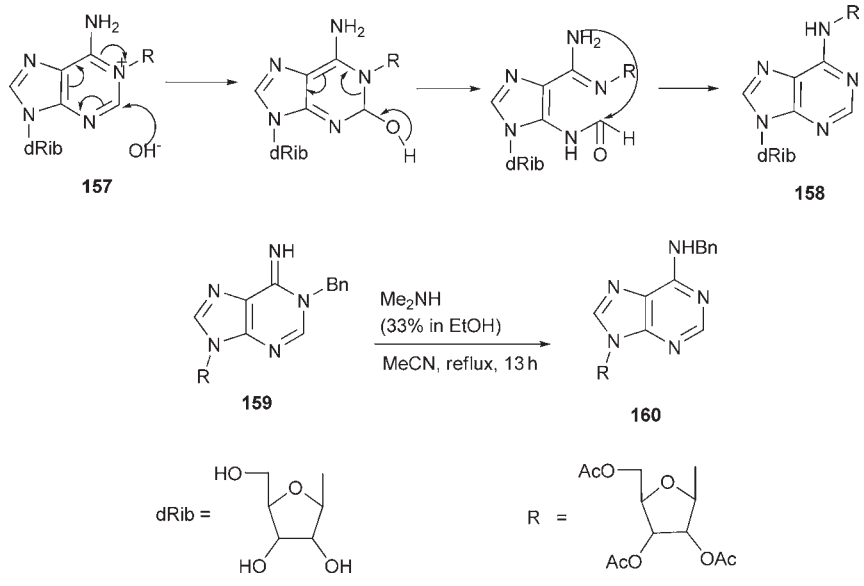
nitrogens to give **158** (00CRT625). A DR of **159** took place under harsh conditions using Me_2NH to give **160** (Scheme 46) (05CC3968).

When DNA was treated *in vitro* with styrene oxide, significant quantities of deaminated products were detected. The initial alkylation on the N^1 and N^6 positions of adenine in DNA was difficult to estimate due to the instability of the styrene oxide-induced N^1 adducts. The N^1 adducts were prone to either a DR to the corresponding N^6-adenines or deamination to the corresponding hypoxanthine adducts (00CRT18, 00CRT625, 07CRT790). Under alkaline conditions, a DR was the sole pathway, whereas deamination prevailed at pH 6.

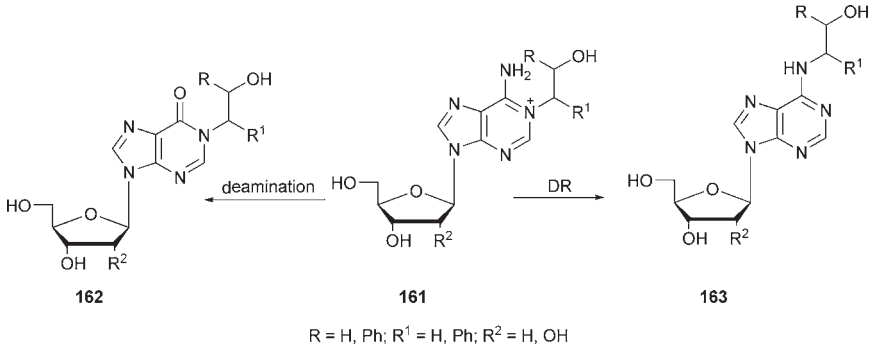
The rate of DR of 1-substituted deoxyadenosine-styrene oxide adducts was slower than that of the riboside analogs resulting in greater yields of the deaminated compounds. The DR from **161** to **163** has a competing deamination process to give **162** (Scheme 47) (92JBC23427, 98CRT838).

Alkylation of the adenine N^1 **164** with the oxirane **165** can occur at both the carbon atoms anchoring the ring. Reaction at the internal carbon resulted in the formation of stereoisomeric N^1-(1-hydroxy-3-buten-2-yl)-2′-deoxyadenosine adduct **166** (Scheme 48) (05B3327), which can subsequently undergo deamination to the corresponding deoxyinosine adduct **167**, or a DR to the corresponding N^6-adducts **168** (96CRT875, 99IARC123, 00EMM48).

Reaction of adenine N^1 **169** at the terminal epoxide of **165** gave an unstable intermediate **170** (06CRV607), which underwent deamination to **171** (96CRT875) or DR to **172** (Scheme 49) (95CRT389).

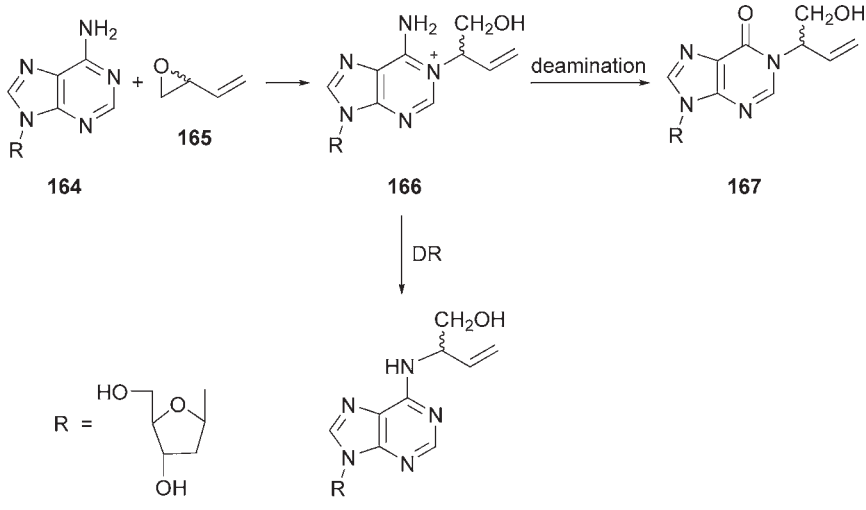


Scheme 46



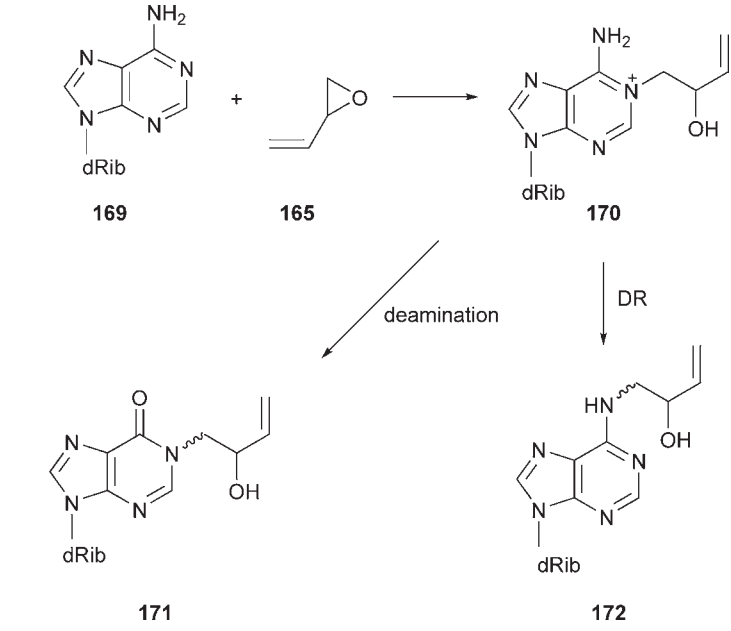
Scheme 47

The incubation of **174a** that tautomerizes with **173** gave products which by high-performance liquid chromatography analysis were found to be **175a** resulting from a DR (Scheme 50) (99OL1233, 00B924). Adenine N^1-adducts **174b** from butadiene diol epoxides formed from human metabolism of butadiene diol (99CRT566, 05CRT145) gave N^1 adducts **175b** (95CRT389, 00CRT625) and **174c** gave **175c** (99B13338). Similarly, **174d** formed **175d** under alkaline conditions, whereas at pH 6 deamination prevailed (95CRT389, 98CRT838, 00CRT421, 01B9780).



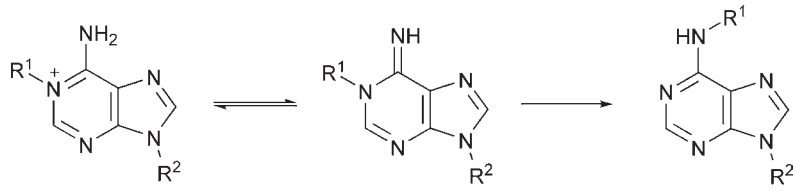
164 165 166 167 168

Scheme 48



169 165 170 171 172

Scheme 49



174 **173** **175**

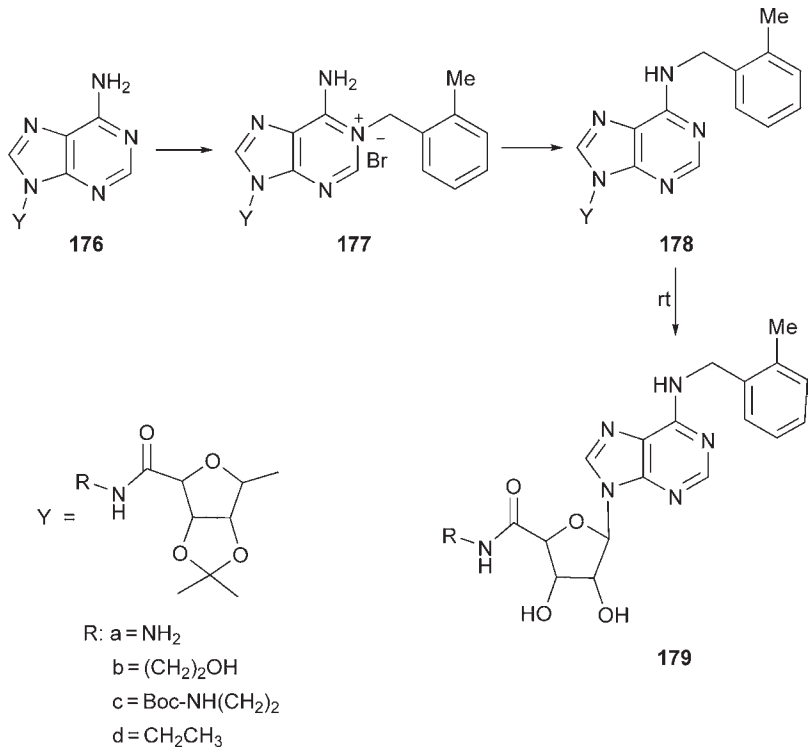
a = R^1 = 1-phenylethanol, R^2 = H
b = R^1= butadiene triol, R^2 = H
c = R^1 = CH_3, R^2 = H
d = R_1 = styrene oxide, R^2 = ribose
e = R^1=butadiene triol, R^2 = deoxyribose
f = R^1 = isopropyl, R^2 = H
g = R^1 = styrene oxide, R^2 = ribofuranosyl/deoxyfuranosyl
h = R^1 = 3,4-epoxy-1-butene
i = R^1 = $-(CH_2)_2NH_2$, or $-(CH_2)_2NH-(CH_2)_2NH_2$
j = R^2 = ribose, N^6 = 3-iodobenzyl
k = R^2 = ribose, R^1 = OCH_3
l = R^1 = 3-chloro-2-hydroxy-3-buten-1-yl, R^2 = deoxyribose
m = R^2 = carbocylic ribose, R^1 = benzyl

Scheme 50

The deoxyadenosyl-N^6-butadiene triol **175e** adduct identified in Chinese hamster ovary cells (94CG1903) resulted from a DR of **174e**. Analogous chemistry was described for the reactions of styrene oxide with adenine N^1 (97CRT1247, 04CRT1007). 1-Isopropyladenine **174f** gave **175f** under basic conditions (04CRT1531). The N^1-adenine **174g** gave **175g**, or a deamination to N^1-hypoxanthine (98CRT838). Adenine underwent a DR even at neutral conditions (95CRT389). The N^1-3,4-epoxy-1-butene adenine **174h** adducts detected as precursors of previously reported N^6-adenine **175h** adducts (95CG2999) formed through a DR (97CG137). Under mild conditions (50°C, pH range 6–7) 15-N^6-labeled adenosine **174i** was converted to N^6-adenosine **175i** (95H1399). An N^6-(3-iodobenzyl) group was introduced in aristeromycin **174j** to give **175j** (00JME2196).

Oxidizing and then O-alkylating the N^1 position of adenosine gave **174k**. Subsequent base-mediated ring-opening hydrolysis and then ring closure swaps the positions of the N^6-exocyclic amine and the derivatized N^1 nitrogen, thereby installing the *N*-alkoxy functionality at the N^6 in **175k** (07CB299).

2-Deoxyadenosine with recemic (1-chloroethenyl)oxirane gave the initial adduct **174l**, which hydrolyzed to **175l** (02CRT1549). Similar results



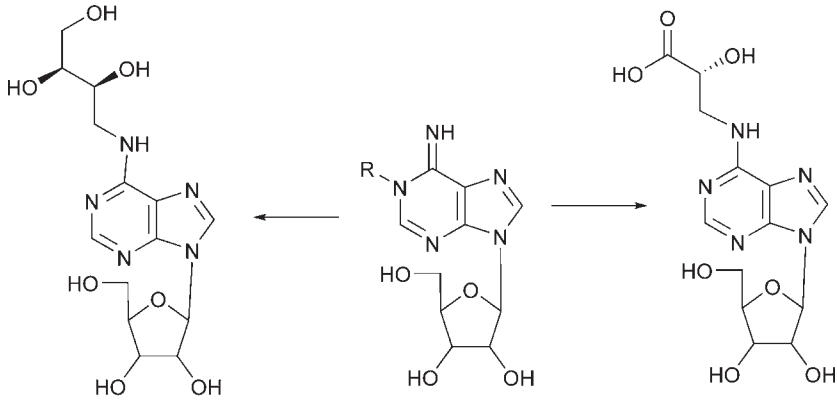
Scheme 51

have been reported for the N^1 adducts of ethenyloxirane (96CRT875), styreneoxide (98CRT838), and ethyleneoxide (92MI35). Under basic conditions **174m** gave **175m** quantitatively (01JA8750).

The N^6-(2-methylbenzyl) derivatives **179a–d** were synthesized by the alkylation of **176c** at N^1 by 2-methylbenzyl bromide to give **177**, which rearranged under basic conditions to **178a–d** whose deprotection gave **179a–d** (Scheme 51) (95CRT389, 98CRT838, 00CBI201, 01CBI111, 04MI379, 05CAB237).

Treatment of $^{15}N^4$-labeled cytidine N^3-oxide and $^{15}N^4$-labeled 2-deoxycytidine N^3-oxide, prepared from the appropriate unprotected uridines in three steps, with benzyl bromide in the presence of excess lithium methoxide allowed a smooth DR even under mild conditions leading to $^{15}N^3$-labeled uridine 4-O-benzyloximes, which easily underwent reductive N–O bond cleavage to give $^{15}N^3$-labeled cytosine nucleosides in high yields (04MI379).

The nucleoside analogs **180** undergo rearrangement at pH 13 to chromophores consistent with N^6-substituted adenosines **181** and **182** (03CRT1328, 04CRT717).

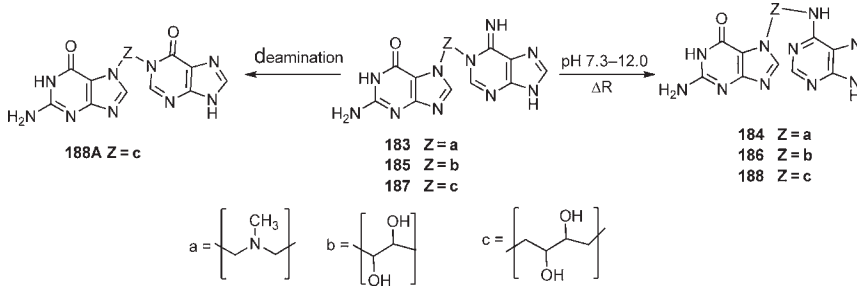


182 180 181

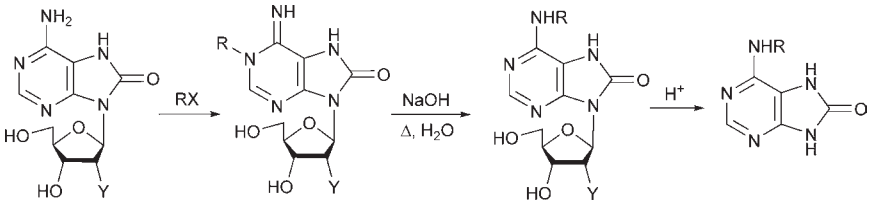
Scheme 52

A DR of N^1-alkyladenines **183**, isolated from calf thymus DNA, was quantitatively converted to **184** at basic pH (Scheme 52) (04CRT950). When **185** was heated at pH 12 overnight, it gave **186** (04CRT1638). 1,3-Butadiene (BD) is classified as a known human carcinogen based on epidemiological evidence in occupationally exposed workers and its ability to induce tumors in laboratory animals. Under physiological conditions, the BD-adduct 1-(guan-7-yl)-4-(aden-1-yl)-2,3-butanediol **187** afforded **188** along with its deaminated product **188A** via a DR (Scheme 53) (08CRT1163).

The marine ascidian purine aplidiamine and its 9-β-D-ribofuranoside, a derivative of naturally occurring 8-oxadenine, were synthesized by alkylation of 8-oxadenosine **189** (Y = OH) with 4-benzyloxy-3,5-dibromobenzyl bromide to give the N-alkylated analog. A subsequent DR by heating in boiling NaOH produced product in 58% overall yield. Further acid hydrolysis gave **190** (Scheme 54) (98TL4695).



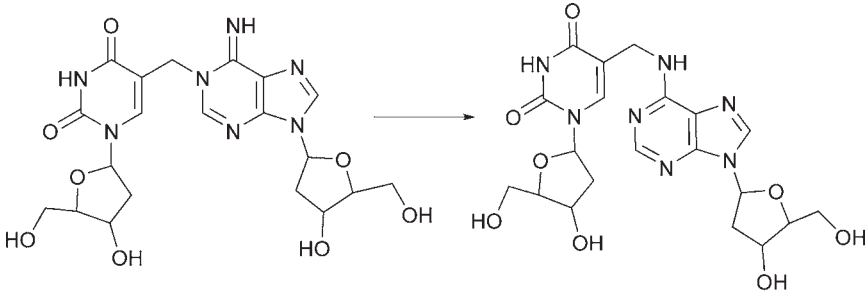
Scheme 53



189 190

R = 4-benzyloxy-3,5-dibromobenzyl bromide

Scheme 54



191 192

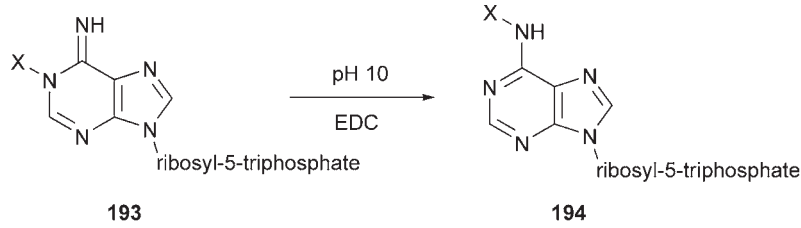
Scheme 55

A DR of the N^1-adduct **191** to **192** was noticed during its isolation (98H359). The rearrangement was consistent with a slight change in gel mobility of the interstrand cross-link that was observed on piperidine treatment (Scheme 55) (05JA3692).

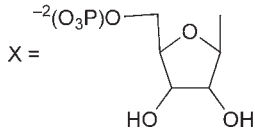
Matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometry could not determine whether oligonucleotide conversion had taken place during storage or under genome construction conditions (04PNA14051). The nucleotide **194** was formed by treating **193** with 1-ethyl-3-(3-dimethy-lamino)propyl carbodiimide hydrochloride (EDC) at pH 10 (94JA7481). (Scheme 56)

The labeled N^1-oxide nucleoside was methylated with methyl iodide or dimethyl sulfate and then followed by treatment with dimethylamine to afford the stable intermediate 6-amino-N^1-methoxy-2-(N,N-dimethylamino) **197** via **196**. A DR was accomplished by heating in the presence of a dimethylammonium hydrohalide salt to give the 6-N-methoxy nucleosides **198** in high yield. In the absence of heating, **197** did not rearrange. The rearrangement can be carried out without isolation of **197** simply by refluxing in methanol (Scheme 57) (98JOC3213).

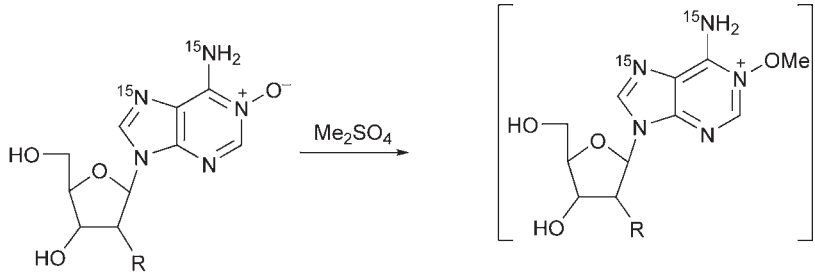
When tricyclic **199** was stored in an aqueous solution at neutral pH it rearranged to **201** by a ring opening of **199** to yield an N^1-propanal



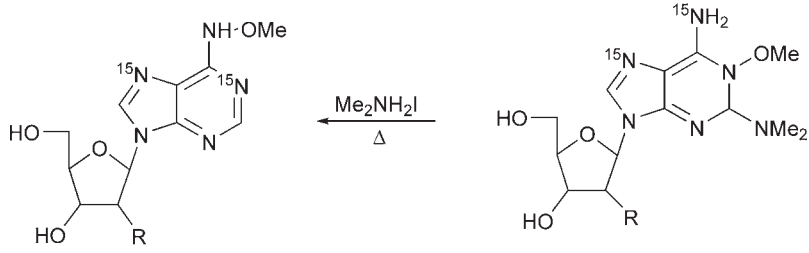
193 194



Scheme 56



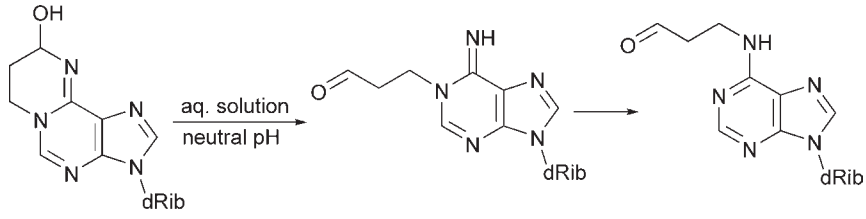
195 196



198 R = H, OH 197

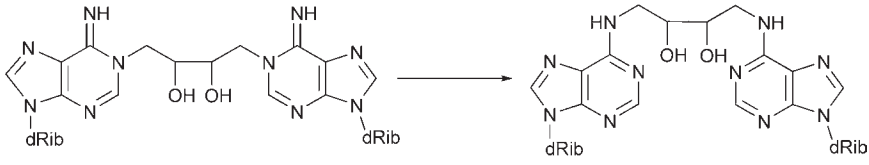
Scheme 57

adduct **200**, which underwent the DR to the N^6-propanal adduct **201** (Scheme 58) (68B3453, 73JOC2247, 88MI275, 99CG2025, 06CRT571). The N^1-deoxyadenosine adducts **202** underwent a DR to N^6 adducts **203** (Scheme 59) (02CRT1572).



199 200 201

Scheme 58



202 203

Scheme 59

^{15}N-labeled adenosine [6-^{15}N] **204** and deoxyadenosine generated the N^6 adduct with **205** to form **206**, which hydrolyzed to **207**. The N^1 adduct of **207** was isomerized to its N^6 derivatives **210** at pH 13 through a DR involving ring opening to **208** and recyclization to **209**, which dehydrates to **210** (Scheme 60) (98H359, 99JA6773, 01JA11126).

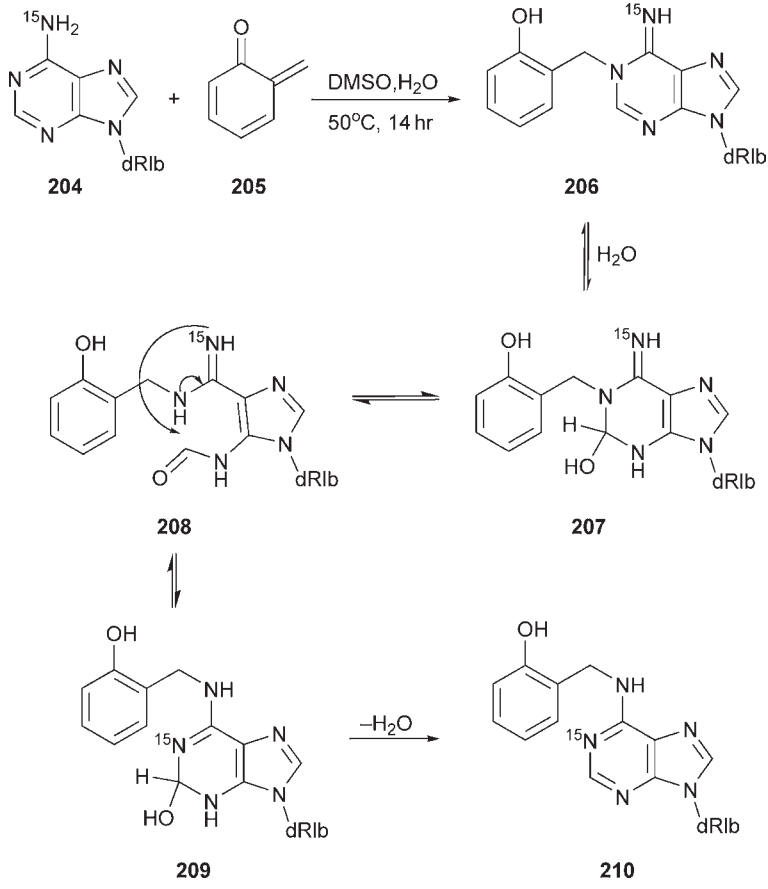
N,N-bis(2-chloroethyl)-p-aminophenylbutyric acid **212** (chlorambucil) reacts with deoxyadenosine **211** in a non-nucleophilic buffer (0.2M cacodylic acid, 50% base) at 37°C to give **213** that rearranged to **214** when treated with aqueous base. Although the rearrangement under basic conditions was quantitative, the rate was slow (90CRT587) and under neutral conditions still slower (Scheme 61) (03CRT403).

The DR of **215** gave **216** whose purification on ion-exchange chromatography afforded triethylammonium salt **217** in 70% yield (Scheme 62) (01JA8750).

Hydrolytic cleavage of 1-alkoxy-7-alkyladenines **218** produced imidazol-5-carboxyamidines **219** in 53–60% yields then followed by a DR to give N^6-alkoxy-7-alkyladenine **220** (Scheme 63) (97CPB832).

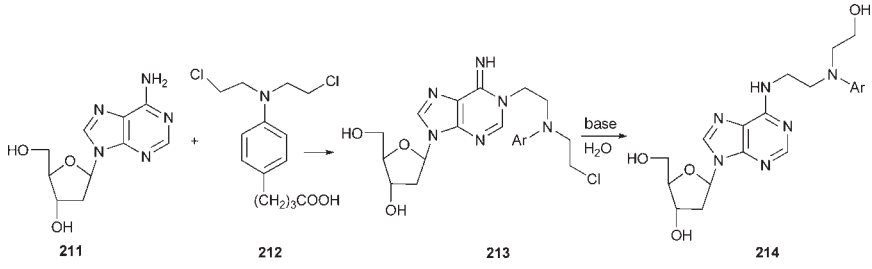
Oxidation of N^6-benzyladenine (R = Bn) **221** afforded the N^1-oxides **222** whose structure was established by conversion to N^6-methoxyadenine **225** through O-methylated **223** followed by a DR to **224** and then a non-reductive debenzylation (Scheme 64) (96CPB967).

1-Benzyladenine-7-oxide **226** was converted by a DR to N^6-benzyladenine-7-oxide **227** on heating with alkali (Scheme 65) (95CPB325).



204 205 206 208 207 209 210

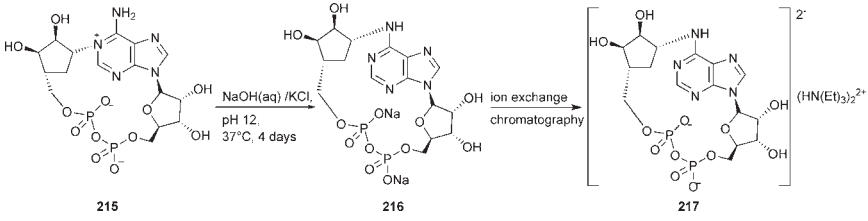
Scheme 60



211 212 213 214

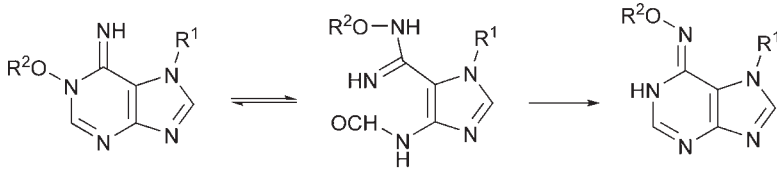
Scheme 61

DR isomerization of [N^1-methyl-5′-deoxyadenosylcobaltamine]Cl **228** in water and ethylene glycol gave N^6-methyl-deoxyadenosylcobaltamine **229** (Scheme 66) (97CB373, 98JIB45).



215 216 217

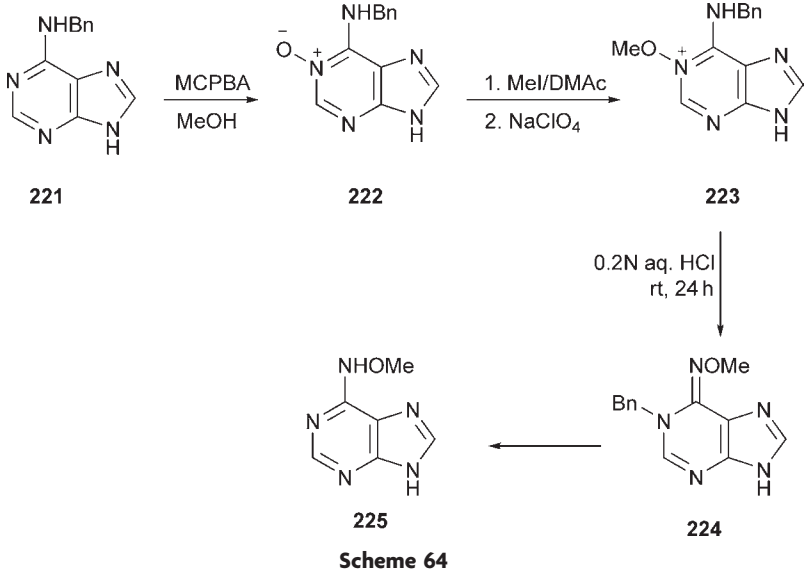
Scheme 62



218 219 220

$R^1 = R^2$ = Me, Et, Bn

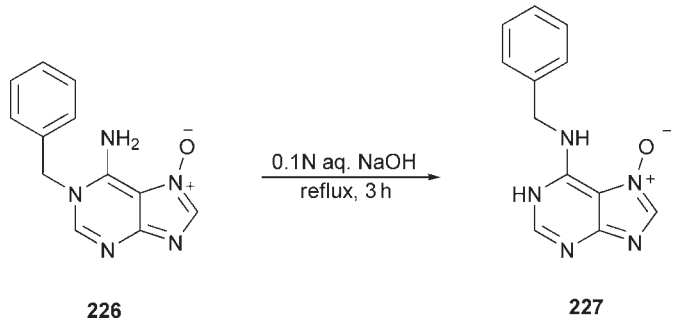
Scheme 63



221 222 223 224 225

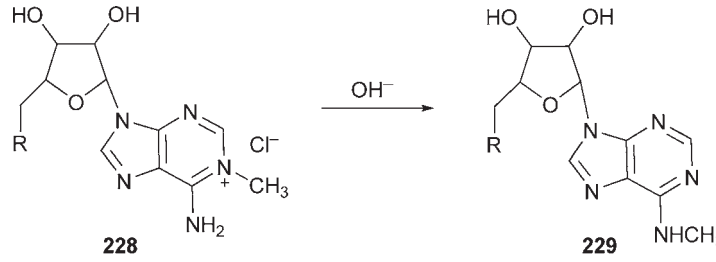
Scheme 64

The DR was implemented with dimethylsulfate-modified RNA to explore which position was modified within *Escherichia coli* ribosomes. Selective DR of a 1-methyladenosine adduct could provide a means to



226 **227**

Scheme 65



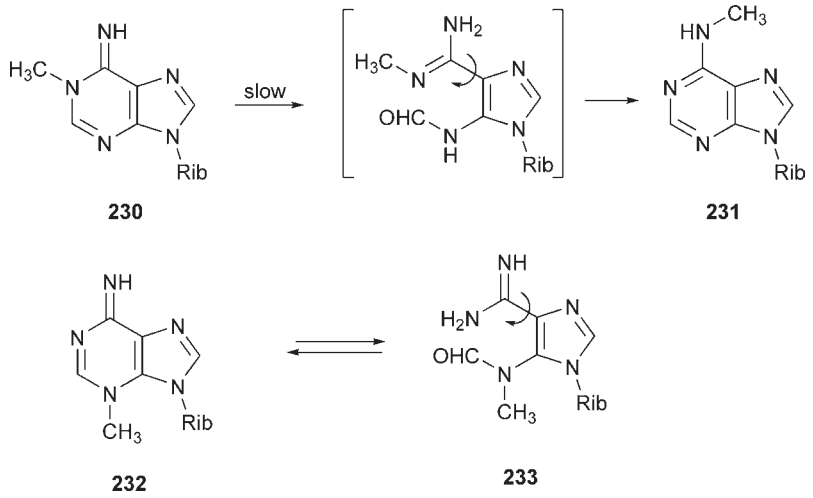
228 **229**

R = Cobalt B_{12} complex

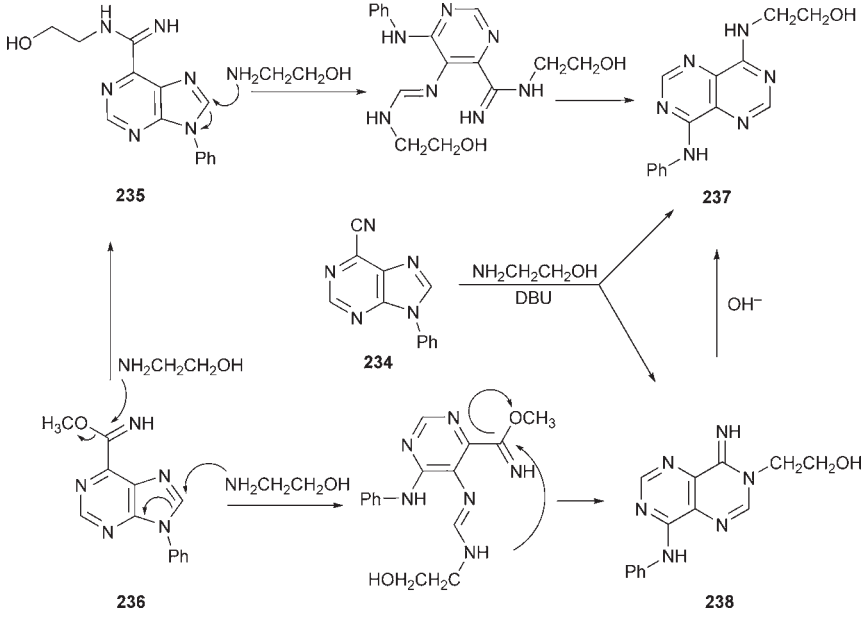
Scheme 66

distinguish between the different methylated derivatives **230** and **232**. Both modifications resulted in opening of the six-membered ring at neutral to slightly alkaline pHs. This process was quite slow for 1-methyladenosine at neutral pH, but at pH 9 and 25°C it occurred with a 1-day half-life and once the ring was opened, it rapidly underwent a DR to produce the highly stable 6-methyladenosine **231** (Scheme 67). The N^3-methylated **232** adduct also underwent a ring opening to form the N-methylformamido-imidazole **233** at neutral to alkaline pH, but it recyclized back to 3-methyladenosine **232**. These results offer an approach to determine which nitrogen of a given adenosine was methylated within an RNA sequence because mild base treatment of modified RNA can result in migration of methyl groups from N^1 to N^6 (01RNA1403). Modified oligonucleotides also easily undergo a DR (07HCA928).

When purines **234** and ethanolamine (2.5 molar equivalent) were heated under reflux in methanol containing a catalytic amount of DBU, a mixture of DR isomers pyrimido[5,4-*d*]pyrimidines **237** and **238** in a 1:2 ratio was obtained. Also, **235** gave **237** (Scheme 68) (07EJO1324).

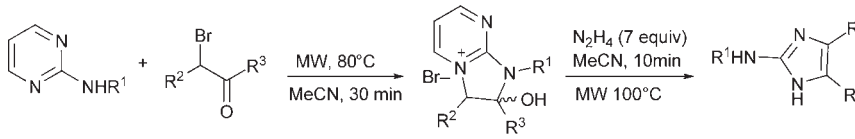


Scheme 67



Scheme 68

Similarily, **236** was converted to a mixture of **237** and **238** in 1:4 ratio. The transformation of **238** into **237** arises by a DR. A nucleophile caused ring opening of the pyrimidine ring in **238** that has an exocyclic double bond, and subsequent ring-closure afforded the more stable **237**.



$R^1 = R^2 = R^3$ = H, alkyl, aryl

Scheme 69

Structure **238** arises from nucleophilic attack of ethanolamine on C8 of purine **236** followed by ring opening and ring closure (Scheme 68) (07EJO1324).

A divergent synthesis of substituted 2-aminoimidazoles **240** starts from 2-aminopyrimidines and α-bromocarbonyl compounds. Conventional heating or microwave irradiation affords 2-hydroxy-2,3-dihydro-1H-imidazo[1,2-*a*]pyrimidin-4-ium salts **239**. Their hydrazinolysis gave 2-amino-1H-imidazoles **240** via a DR (Scheme 69) (08JOC6691).

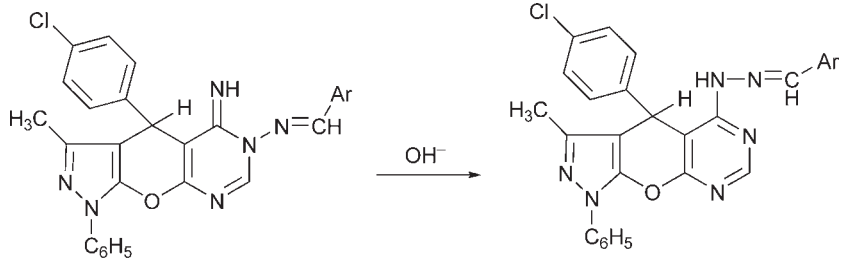
3.2.6 Pyranopyrimidines

The functionalized azolopyrano-pyrimidine **241** was converted to **242** under basic conditions via a DR (Scheme 70) (98MOL71).

3.2.7 Pyridopyrimidines

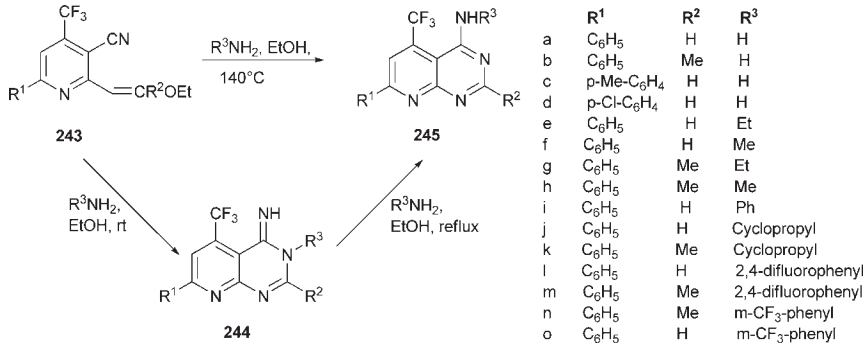
Pyrido[2,3-*d*]pyrimidines **245** are prepared directly by amination of **243** with amines at 140°C whereas at room temperature imine **244** forms. But subsequent heating with the same reagent gives **245** via a DR (Scheme 71) (06EJM1011).

6-Amino-4-(4-methoxyphenyl)-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitril **246** and phenyl isothiocyanate in pyridine gave 2,7-dimercapto-5-(4-methoxyphenyl)-4-phenylaminopyrido[2,3-*d*]pyrimidine **247** as a result of a DR (Scheme 72) (05JS381).



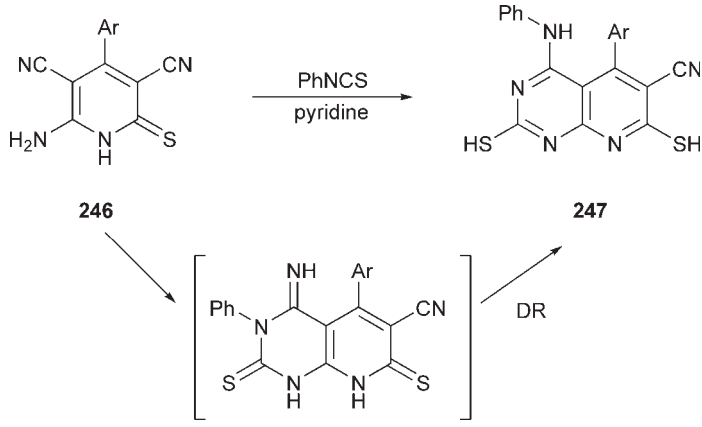
241 **242**

Scheme 70



	R^1	R^2	R^3
a	C_6H_5	H	H
b	C_6H_5	Me	H
c	p-Me-C_6H_4	H	H
d	p-Cl-C_6H_4	H	H
e	C_6H_5	H	Et
f	C_6H_5	H	Me
g	C_6H_5	Me	Et
h	C_6H_5	Me	Me
i	C_6H_5	H	Ph
j	C_6H_5	H	Cyclopropyl
k	C_6H_5	Me	Cyclopropyl
l	C_6H_5	H	2,4-difluorophenyl
m	C_6H_5	Me	2,4-difluorophenyl
n	C_6H_5	Me	m-CF_3-phenyl
o	C_6H_5	H	m-CF_3-phenyl

Scheme 71



Scheme 72

3.2.8 Quinazolines

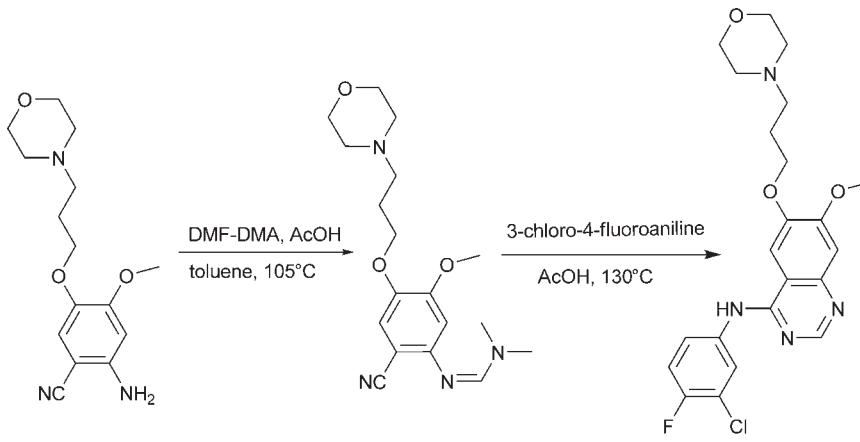
Quinazoline **250** began as amino nitrile **248** by conversion to **249** and then reaction with 3-chloro-4-fluoroaniline via cyclization and then a DR (Scheme 73) (01OPD581, 07OPD813).

Similarly, amino nitrile **251** was treated with DMF–DMA in toluene to yield formamidine **252** that was reacted with 3-ethynylaniline to give **253** by a DR (Scheme 74) (07OPD813).

Amino nitrile **254** with **255** led to the selenourea **256**, which underwent a ring closure to give **257** (Scheme 75) (04HCA1873). An isomerization via ring opening to **258** and ring closing led to **259** via a DR (97CPB832, 98H359).

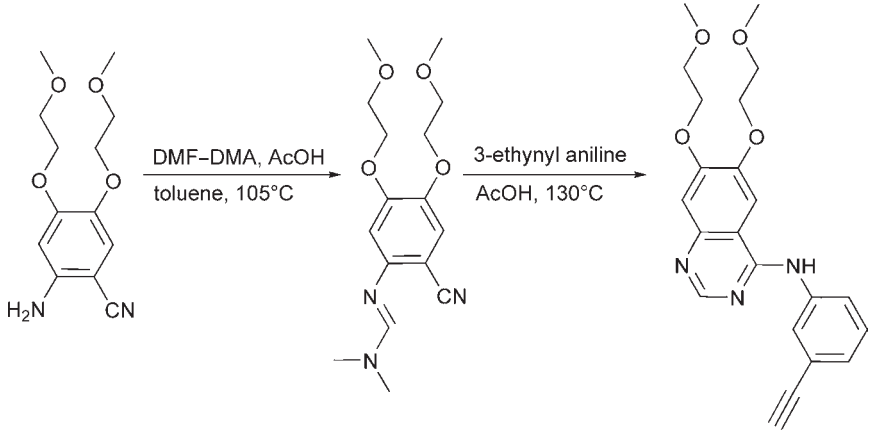
Iminoquinazoline **260** ($R^1 = CH_3$, $R^2 = H$, $R^3 = CH_2Ph$) in 1 M sodium hydroxide yielded 4-alkylaminoquinazoline **261** (Scheme 76) (05T5778).

Iminoquinazolines **262** readily underwent a DR under basic conditions to quinazolines **263** (Scheme 77) (06JME955).



248 249 250

Scheme 73

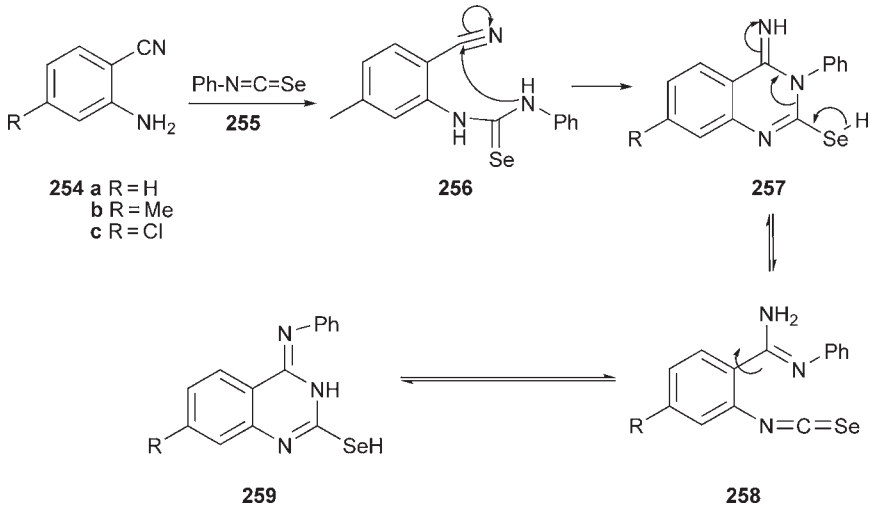


251 252 253

Scheme 74

Iminoquinazolines **265** from **264** underwent a DR to afford 1-(2-phenylquinazolin-4-yl)-3-substituted thioureas **266**. The tautomerization of **266** involving the proton of the N^1 substituted thioureas and N^3 of the quinazoline ring gave either **267** or **268**, stabilized by hydrogen bond interactions (Scheme 78) (01MOL574, 01MOL588).

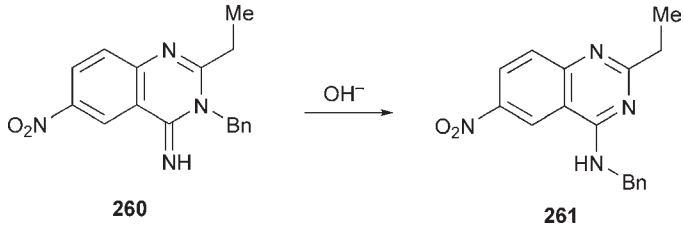
Attack of the amino group in **270** onto the isothiocyanate group in **269** gave **271** that cyclized to **272**. Subsequent attack of the imino nitrogen onto the carbonyl group afforded **273**. A DR did not take place (Scheme 79) (07T11287).



254 a R = H
b R = Me
c R = Cl

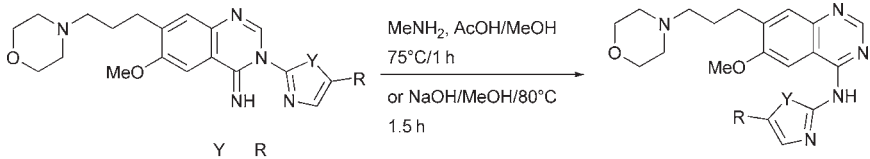
256 **257** **259** **258**

Scheme 75



260 **261**

Scheme 76



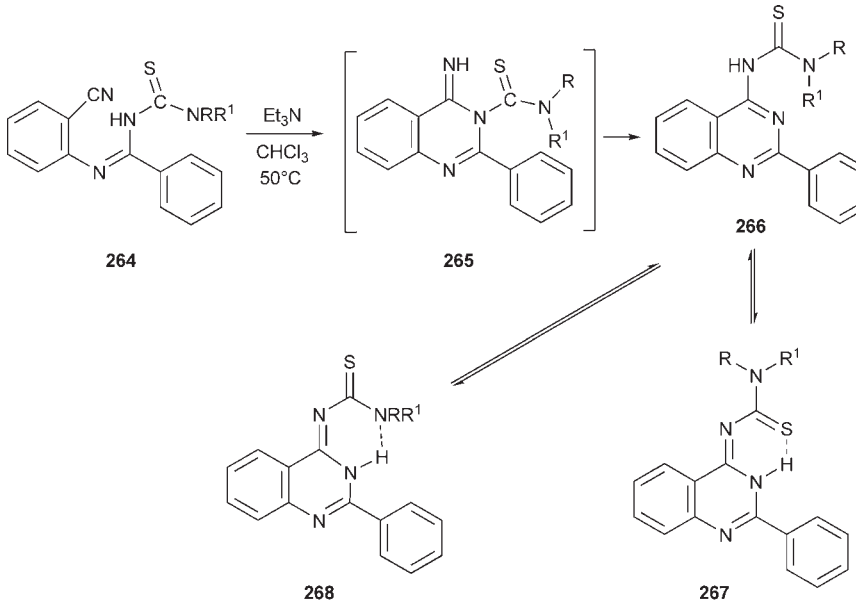
	Y	R
262 a	S	Me
b	S	nBu
c	NH	COOEt

263

Scheme 77

3.2.9 Thiazines

A library of functionalized 2-amino-1,3-thiazines **274** was reported (04AGE621, 05QC364). They underwent a thermal uncatalyzed DR to the thermodynamically more stable pyrimidine-2-thiones **275** (75M1469, 06QC509) under microwave irradiation in a batch or continuous flow



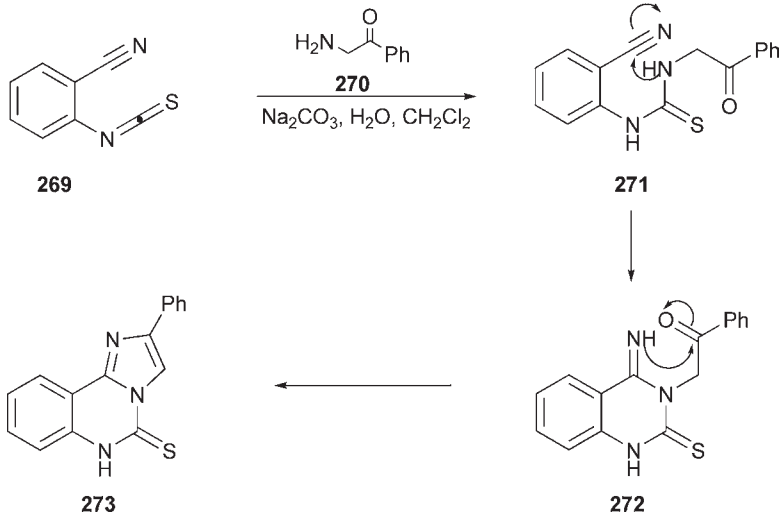
R, R^1 = morpholine, N-methylpiperazine, piperidine, dibutylamine, pyrrolidine, diphenylamine

Scheme 78

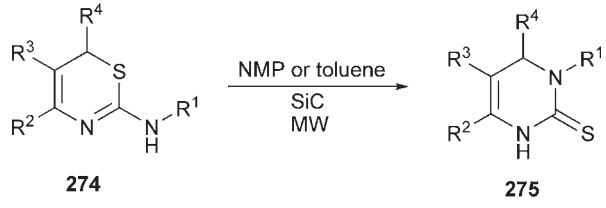
format, employing either toluene or 1-methyl-2-pyrrolidone solvent. Thiazines bearing an ester group at the C5 position rearranged at a considerably higher temperature than derivatives without substituents at this position. This thermal rearrangement was studied in detail using differential scanning calorimetry and density functional theory computational methods. The reaction pathway involved a zwitterionic intermediate (06QC509). The optimized conditions involved heating **274** in toluene together with a silicon carbide at 220°C for 30 min to provide a 68% yield (Scheme 80) (06JOC4651).

3.2.10 Benzo and Pyrido-oxazines

A one-pot three-component synthesis of benzo[1,3]oxazine **280** (X = H) from 2-hydroxybenzonitril **276** with 1,1′-carbonyldiimidazole and hydroxylamine gave **278** via **277**. Cyclization of **278** with triethylamine gave benzo[4,3]oxazine **279**, which readily rearranged under basic conditions via a DR to 4-methoxy (aralkoxy)iminobenzo[1,3]oxazine-2-ones **280** (Scheme 81) (04S1987). Similarly, 2-cyano-3-hydroxy-pyridine **276** (X = N) was converted to **280** (X = N) (Scheme 81) (05T3091). Amino nitrile **281** with formic acid gave the DR product spiro{6H-indeno [2′,1′:5,6]pyrano[2,3-*d*]pyrimidine-5,3′-indoline} **283** via **282**. The same



Scheme 79



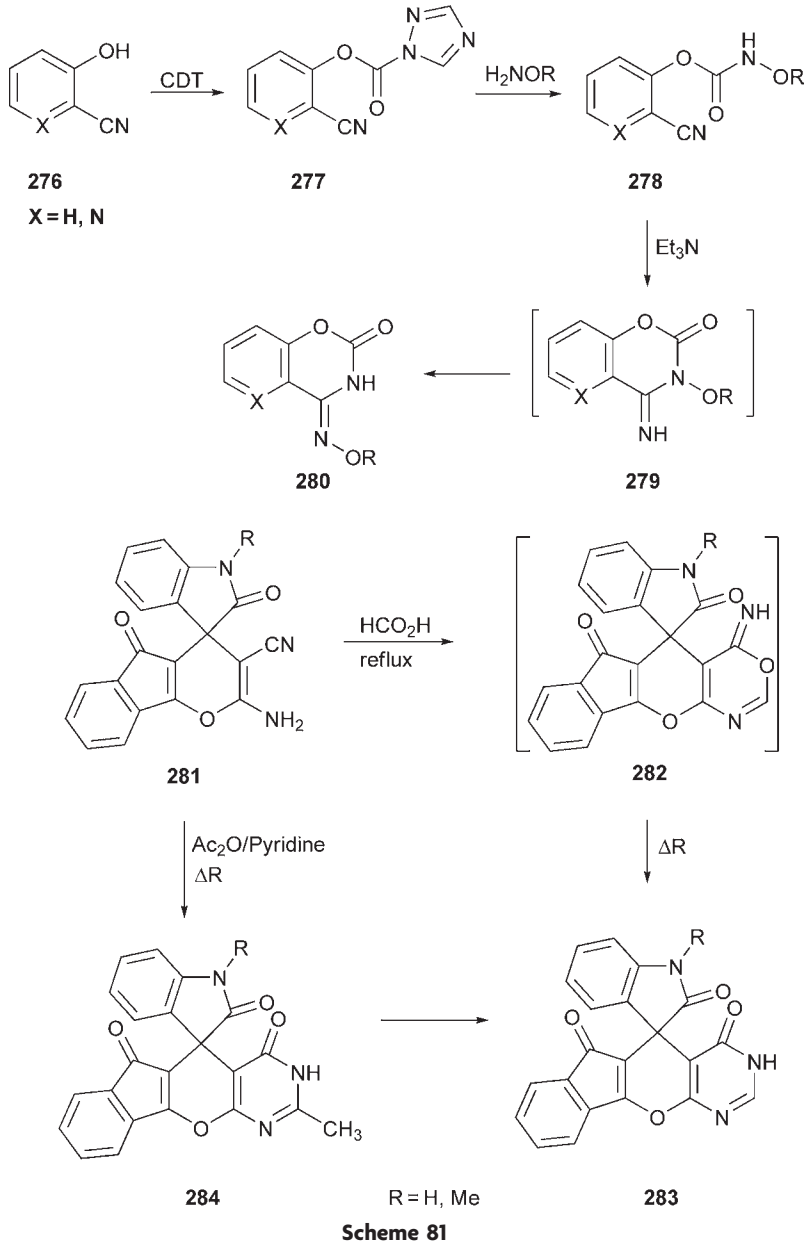
$R^1 = H$, $R^2 = Me$, $R^3 = CO_2Et$, $R^4 = Ph$

Scheme 80

281 with an acetic anhydride/pyridine mixture afforded 1′,2-dimethyl-spiro{6H-indeno[2′,1′: 5:6]pyrano[2,3-*d*]pyrimidine-5,3′-indoline}-2′, 2, 6 (3H)-trione **284** via a DR (Scheme 81) (08H955).

3.2.11 Thiazolidines

The DR of the thiazolidine ring into the imidazolidine ring occurs under basic conditions. Alkylation of **285** with diiodomethane containing sodium hydride gave imidazolidino[1,5-*a*]piprazin-4-one **287** via **286**. The imidazolidino[1,5-*a*]perhydroquinoxalin-4-one **289** was similarly prepared from **288** via a DR of the intermediate thiazolidines (Scheme 82) (04S2169).



276
X = H, N

277

278

279

280

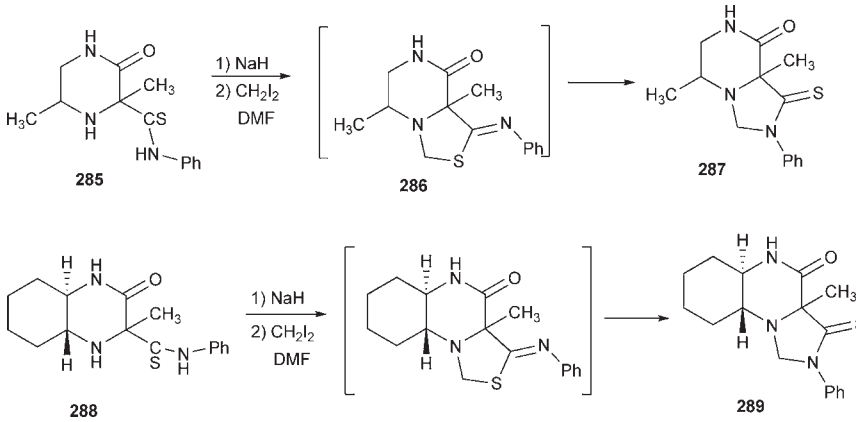
281

282

283

284

Scheme 81



Scheme 82

3.2.12 Imidazolidines

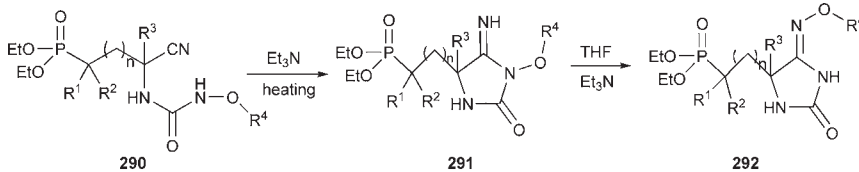
When **290** was heated in the presence of a base such as triethylamine it furnished 4-alkoxy(aralkoxy)-iminoimidazolidin-2-ones **292** by a base-catalyzed DR of the cyclized **291** (Scheme 83) (04T2409).

3.2.13 Oxazolidines

Successive treatment of cyanohydrins with 1,1′-carbonyldiimidazole and O-substituted hydroxylamines furnished **293**, which with Et_3N underwent a DR to **294** in 70–80% yield (Scheme 84) (04OBC2023, 04S1340).

The reaction of **295** with equimolar amounts of sodium methoxide in boiling methanol furnished the rearranged **296** in 51–72% yields (Scheme 85) (06S1803).

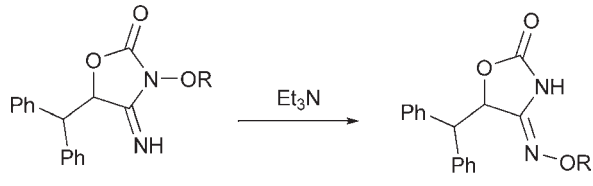
Thermal reaction of pyridoimidazole heterocumulenes **297** yielded, via a DR intermediate, the pyridoimidazole-linked imidazoledione **298** (Scheme 86) (97JOC4085).



R^1, R^2, R^3 = H, Me;

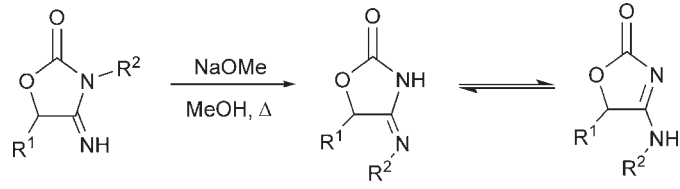
R^4 = Bn, Ph, 4-Me-$C_6H_4CH_2$, Me, 4-Br-$C_6H_4CH_2$

Scheme 83



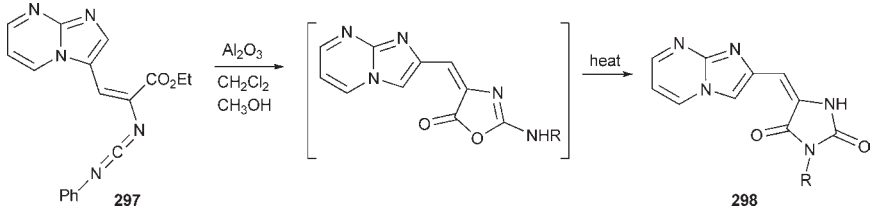
293 294

Scheme 84



295 296

Scheme 85



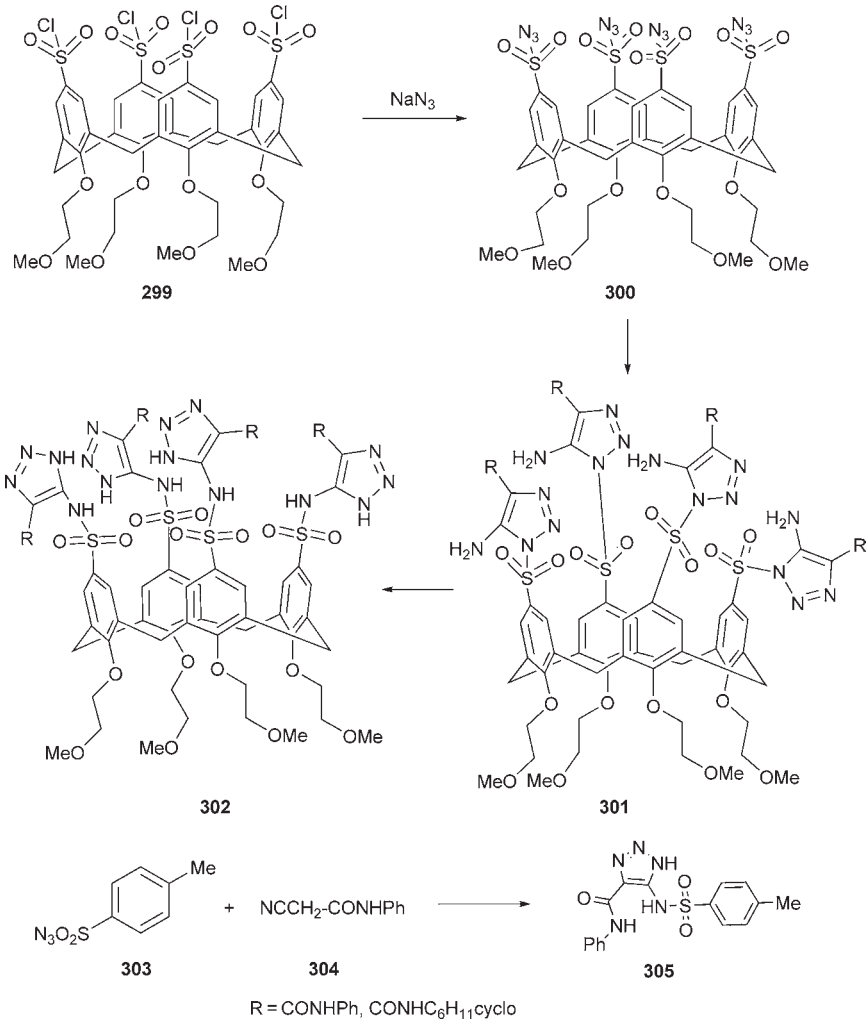
297 298

Scheme 86

3.3 Heterocycles with three heteroatoms in the ring

3.3.1 Triazoles

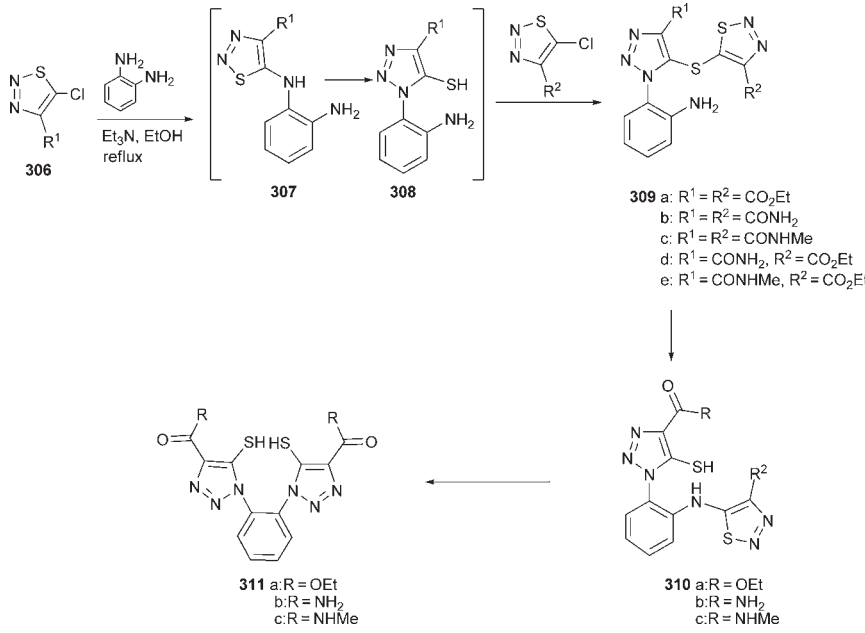
The azidosulfonylcalixarene **300** was obtained in 55% yield from chlorosulfonylcalix[4]arene **299** (cone conformation) with sodium azide. Their cycloaddition to N-phenyl- and N-cyclohexyl-2-cyanoacetamides in the presence of EtONa gave the tetrakis((1H-1,2,3-triazol-5-amine)sulfonyl) calix[4]arenes **302** in 38–60% via **301**. A simple analog was prepared from tosyl azide **302** with N-phenyl-2-cyanoacetamide **304** to give the DR product, 1H-5-tosylamino-1,2,3-triazole-4-N-phenylcarboxamide **305** (Scheme 87) (04ARK31).



Scheme 87

3.3.2 Thiadiazoles

5-Halo-1,2,3-thiadiazoles **306**, having at the 4-position an electron-withdrawing group, with amines gave **307**, which were not isolated but immediately reacted with a second equivalent of 5-chlorothiadiazoles **306** to afford **310** via **309** (84JHC627, 89JHC1811, 94KGS554). The 1,2,3-thiadiazole rings of **310** underwent DR to dithiols **311** (Scheme 88) (99CC2273). The ester group in triazole **308** ($R^1 = CO_2Et$) was unstable in acid (pH > 1) and caused a partial reverse DR, whereas **308** ($R^1 = CONH_2$, $CONHCH_3$) with amide groups were stable even in a



Scheme 88

strong acidic medium. 1-(*o*-Aminophenyl)-1,2,3-triazolo-5-thiols **308** was obtained via a DR by heating 5-arylamino-1,2,3-thiazoles **307** (R = COOEt, CONHMe, $CONH_2$) in ethanol in the presence of triethylamine, followed by acidification (04RJOC870).

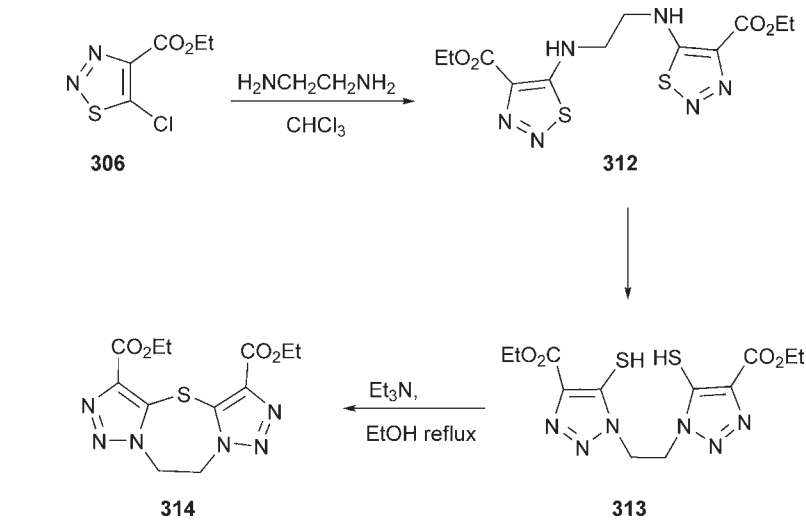
Similarily, **306** with aliphatic diamines gave bisthiols **313** via **312**. Hydrogen sulfide was lost from dithiols **313** by an intramolecular nucleophilic substitution, yielding thiadiazepines **314** (Scheme 89) (99CC2273).

3.3.3 Oxadiazoles

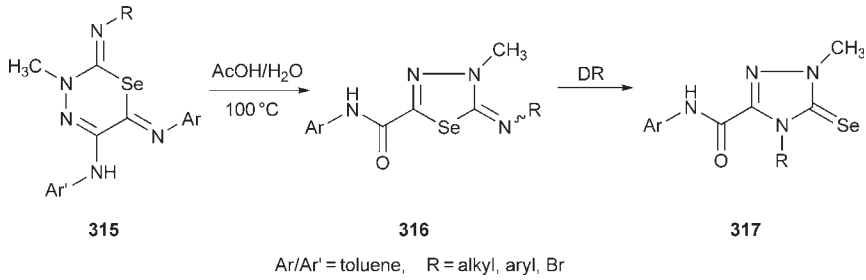
The cycloaddition of 4-amino-3-azido-1,2,5-oxadiazole to nitriles with activated methylene groups gave 3-amino-4-(5-amino-1*H*-1,2,3-triazol-1-yl)-1,2,5-oxadiazoles whose DR gave *N*-(4-R-1*H*-1,2,3-triazol-5-yl)-1,2,5-oxadiazole-3,4-diamines (04MC76).

3.3.4 Selenadiazines

When selenadiazines **315** was subjected to acid hydrolysis at 100°C a ring contraction occurred to form **316**, which underwent a DR to form 4-aryl-1-methyl-5-selenoxo-1,2,4-triazole-3-carboxamide **317** (Scheme 90) (08ZN415).



Scheme 89



Ar/Ar' = toluene, R = alkyl, aryl, Br

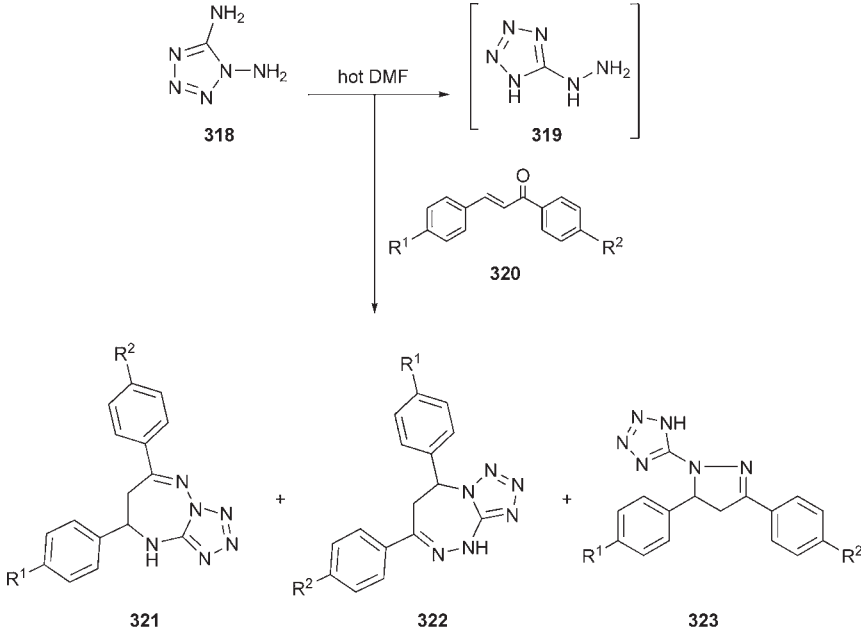
Scheme 90

3.4 Heterocycles with four heteroatoms in the ring

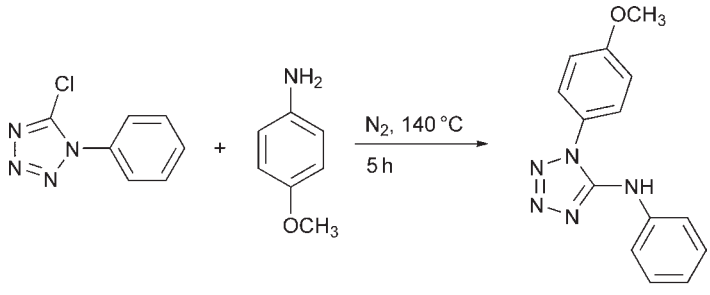
3.4.1 Tetrazoles

Thermal isomerization of 1,5-diaminotetrazole **318** to tetrazolohydrazine **319** took place via a DR (90CB1575). The possibility of rearrangement of **318** caused the participation of its isomeric structures during the reaction with 1,3-diphenylpropenone **320** to give three isomeric products, the seven-membered triazepines **321** and **322** in addition to 1-(5-tetrazolyl)-3,5-diaryl-Δ^2-pyrazolines **323** (Scheme 91) (06JST114).

Fusion of 5-chloro-1-phenyl-1*H*-tetrazole **324** with 4-methoxyaniline gave *N*-[1-(4-Methoxyphenyl)-1H-tetrazol-5-yl]aniline **325**. X-ray crystallographic diffraction analysis showed that, as a result of a DR, structure **325** was correct and it is not that expected of a simple substitution of chlorine in 5-chloro-1-phenyl-1H-tetrazole by aniline (Scheme 92) (01JCS(P2)1315).



Scheme 91



Scheme 92

ACKNOWLEDGMENTS

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