Heterocyclic Chemistry

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2009 offered several significant advances in the field of heterocyclic chemistry, with particular highlights including several new approaches to pyrroles, indoles and pyrimidines. Major themes were hydroamination processes, the development of new multi-component reactions and advances in the development of catalytic asymmetric electrocyclisations.

Introduction

This chapter contains a short review of the highlights in the synthesis of heterocycles published in 2009. The main focus is on synthesis rather than reactivity and the review looks at 3-, 4-, 5-, 6-, and 7-membered rings and larger containing nitrogen, oxygen and sulfur. Other elements, as well as polymer and solid supported methodologies and combinatorial approaches are omitted for sake of brevity.

Three-membered rings

The use of surface organometallic chemistry has allowed the production of gold nanoparticles supported on silica, a catalytic system which allows an efficient, high-yielding aerobic liquid-phase epoxidation of trans-stilbene in the presence of a peroxide initiator and hydrocarbon solvent (Scheme 1). 1

Scheme 1

Optically pure epoxides are available via a highly diastereoselective and enantioselective Darzens reaction involving a chiral titanium complex which is generated in situ from titanium isopropanoxide and (R)-binol, as shown in Scheme 2. 2

The range of aldehydes includes aromatic, aliphatic and unsaturated substrates and hence allows access to a wide range of cis-glycidic amides.

Scheme 2

Work by Page has shown that epoxides can be produced in the absence of metal species using the new and highly selective organocatalytic iminium salt shown in Scheme 3. The catalyst works at a relatively low loading, and the process could also
be applied to other alkenes, a selection of which is shown in the Scheme.³

\[
\text{PhI(PhB)}^+ \quad \text{69% yield 91% ee}
\]

\[
\text{PhI(PhB)}^+ \quad \text{66% yield 95% ee}
\]

\[
\text{PhI(PhB)}^+ \quad \text{58% yield 49% ee}
\]

\[
\text{PhI(PhB)}^+ \quad \text{58% yield 20% ee}
\]

**Scheme 3**

The reductive cyclisation of the 1,2-acetoxysulfenyl nitroalkanes shown in Scheme 4 gave trans-aziridines in excellent yields. The starting materials were readily available from the copper catalysed 1,2-acetoxysulfenylation of nitroalkenes generated by an in-situ Henry reaction.⁴

\[
\text{ArNO}_2 + \text{Fe, AcOH} \quad \text{40 - 50 °C} \quad \text{4 examples 79 - 84% yield}
\]

**Scheme 4**

An organocatalytic approach to aziridines using fluoronium ion as the catalyst in the reaction of imines with ethyl diazoacetate has been reported (Scheme 5).⁵ By using N-fluoropyridinium triflate as the F⁺ source, this process allows access to N-aryl systems, species that have attracted relatively few organocatalytic methods. The use of N-(2,4-dimethoxybenzene) or N-TMS substituted imines allowed access to NH aziridines in good yield on large scale.

\[
\text{N-F} \quad \text{OSO}_2 \quad \text{CF}_3 + \text{CH}_2\text{Cl}_2, \text{RT} \quad \text{11 examples 15 - 100% yield cis:trans up to 100%}
\]

**Scheme 5**

The use of the N-amino-tetrahydrophthalimide shown in Scheme 6 in the oxidative aminoaziridation of alkenes was found to give excellent yields of trans-aziridines from trans-alkenes, whereas lower reactivity was observed with cis-alkenes.⁶ This reaction is believed to proceed via an intermediate aminonitrene which arises from the action of the PhI(OAc)₂ upon the N-aminophthalimide.

\[
\text{PhI(OAc)}^2, \text{K}_2\text{CO}_3 \quad \text{CH}_2\text{Cl}_2, \text{RT} \quad \text{13 examples 40 - 76% [trans] 5 examples 19 - 25% [cis]}
\]

**Scheme 6**

The use of 2-azido-1,3-thiazole as a nitrene source has been reported by Racioppi.
with the resulting nitrene giving aziridines upon reaction with enol ethers as shown in Scheme 7, the first time that such a process has been observed (previous reactions of azides with enol ethers proceed via 1,3-dipolar cycloaddition). Aziridine formation via intramolecular 1,3-dipolar cycloaddition and nitrogen extrusion led to the aziridinopyrrolobenzodiazepines shown in Scheme 8, where the products are of interest as DNA-intercalating antitumour antibiotics. Finally, the use of the aza-Darzens reaction (Scheme 9) as an approach to aziridines has been reviewed.

![Scheme 7]

4 examples 42 - 78%

Scheme 7

![Scheme 8]

Scheme 8

![Scheme 9]

LG = leaving group; Cl, N₂ etc. Z = C(O)ₓR, S(O)ₓR, P(O)ₓR, CN

Scheme 9

**Four-membered rings**

The synthesis of β-lactams by thermal rearrangement of aminocyclobutenones leads to cis products in the presence of 1,4-dimethylpiperazine as base, but trans products in the presence of DBU as base, as shown in Scheme 10. The aminocyclobutenones were readily available from the reaction of alkynyl imines with ketene silyl acetals and reduction of the resulting iminocyclobutenones.

![Scheme 10]

Scheme 10
The generation of ketene from acetone and subsequent [2+2] cycloaddition reaction with an aldehyde in the presence of the highly active bifunctional Lewis acid-Lewis base Co(III) catalyst shown in Scheme 11 gave \( \beta \)-lactones with excellent ee's and high yields. The ease with which the lactones can be converted into \( \beta \)-hydroxy esters makes a valuable alternative to aldol based approaches to these targets.\(^\text{11}\)

\[
\begin{align*}
\text{Acetone} + \text{Aldehyde} & \rightarrow \text{\( \beta \)-Lactone} \\
\text{Catalyst:} & \quad \text{Co(III) Lewis acid-Lewis base} \\
\text{Conditions:} & \quad \text{CH}_2\text{C}_6\text{H}_5, -78 °C \text{ for } 20 \text{ min to } 1 \text{ h}
\end{align*}
\]

Scheme 11

The reaction of aryl(alkyl)ketenes with trifluoromethyl ketones in the presence of a triazolium N-heterocyclic carbene has resulted in the asymmetric approach to the 4-trifluoromethyl-\( \beta \)-lactones shown in Scheme 12, which are typically formed in high yield with good diastereoselectivity and excellent enantioselectivity.\(^\text{12}\)

\[
\begin{align*}
\text{Ar} = \text{Ph} \quad & \quad \text{Catalyst:} \\
\text{Catalyst:} & \quad \text{Ph} \quad \text{Pybox} \\
\text{Conditions:} & \quad \text{Toluene, } -40 °C \\
\text{Products:} & \quad \text{Ar}^1 \text{CF}_3 \\
\end{align*}
\]

Scheme 12

A three-component, one pot approach to thietanes has been reported as shown in Scheme 13, giving the products in high yield with high diastereoselectivity.\(^\text{13}\) The process relies upon the treatment of diethyl phosphorodithioate with sodium hydride, addition of the resulting anion to the Michael acceptor and subsequent reaction with an aldehyde to afford the thietane.

\[
\begin{align*}
\text{Diethyl phosphorodithioate} + \text{NaH} + \text{Michael acceptor} + \text{Aldehyde} & \rightarrow \text{Thietane} \\
\text{Conditions:} & \quad \text{RT, } 3 - 5 \text{ h} \\
\text{Yield:} & \quad 85 - 95% \text{ with } 93.7 \text{ to } 96.4 \text{ trans/cis ratio}
\end{align*}
\]

Scheme 13
At the very end of 2009, the formation of highly strained 1,2-diazetidines (see Scheme 14) was reported. This reaction proceeded in good yield when a soft leaving group such as iodide was used. Hard leaving groups tended to result in the formation of almost equal amounts of 6-membered 1,3,4-oxadiazine rings when the R\textsuperscript{1} group was a carbonyl. When R\textsuperscript{1} was a sulfone, exclusive formation of diazetidines was observed.

\[ \text{NHR}^1 \text{N} \text{R}^2 \text{X} \rightarrow \text{Cs}_2\text{CO}_3, \text{RT}, \text{MeCN}, 5 \text{ h} \]

\[ \text{R}^1 \text{N} \text{N} \text{R}^2 \]

Scheme 14

**Five-membered rings**

Several significant new syntheses of pyrroles appeared in 2009, and these are summarised in Scheme 15. Thus, Anary-Abbasinejad\textsuperscript{15} showed that the reaction of phosphoranes with aryglyoxals yields an intermediate dimethyl carboxylate that cyclises to give pyrroles. The phosphoranes were easily formed from the reaction of a Ph\textsubscript{3}P-DMAD zwitterion with aniline. Work by Iwasawa showed that a rhodium(I)-catalysed [4+1] cycloaddition between an aza-diene and an alkyne allows access to substituted pyrroles \textit{via} a rhodium vinylidene complex.\textsuperscript{16} Ackermann reported two related approaches to pyrroles, the first of which was based upon the titanium catalysed hydroamination of chloroenynes. The development of this into a more useful dehydration-hydroamination of α-haloalkynes was reported in the same publication, hence avoiding the need to prepare chloroenynes.\textsuperscript{17} A titanium(IV) based synthesis has also been reported by Ciez\textsuperscript{18} in which symmetric systems, including fused pyrrole derivatives, are available by oxidative dimerisation of α-azido esters. The reaction proceeds through a titanium(IV) enolate which loses nitrogen to generate a titanium-complexed iminoester. The gold-catalysed dehydrative cyclisation of propargyl amino alcohols was shown by Aponick to give pyrroles,\textsuperscript{19} a process also applicable to the synthesis of furans and thiophenes.

The gold-catalysed cycloisomerisation of acetylene-substituted aziridines reported by Hou\textsuperscript{20} gave generally high yields of 2,5-disubstituted pyrroles, particularly when carried out in the presence of a protic species. Wilson has reported an uncatalysed Paal-Knoor condensation pyrrole synthesis that utilises microwave irradiation in water, followed by isolation by filtration, an improved and significant ‘green’ addition to the field.\textsuperscript{21} The final reaction shown in Scheme 15 shows work by Opatz which has shown that α-aminonitriles undergo cyclocondensation with enones to give carbonitrile substituted Δ\textsubscript{1}-pyrrolines (2H-pyrroles) which undergo a base-induced loss of HCN to give 2,3,5-trisubstituted pyrroles. Starting from aminocacetonitrile itself (R\textsuperscript{1} = H) allowed the Δ\textsubscript{1}-pyrrole-5-carbonitriles to be isolated after reaction in pyridine at reflux.\textsuperscript{22} The reaction of other α-aminonitriles (R\textsuperscript{1} ≠ H) with enones in the presence of TiCl\textsubscript{4}/triethylamine allowed the isolation of pyrroles. Other new routes to pyrrolines also appeared in 2009. Thus, Wender and Strand\textsuperscript{23} used a formal [3+2] cycloaddition between aziridines and non-activated alkenes to give a range of Δ\textsubscript{2}-pyrrolines. The groups of Marinetti\textsuperscript{24} and Robina\textsuperscript{25} have also published new routes to Δ\textsubscript{2}-pyrrolines.
Highlights in the synthesis of the fully saturated pyrrolidine nucleus are shown in Scheme 16. Cheng and co-workers\textsuperscript{26} showed that pyrrolidinones were available via a one-pot, Co-catalysed reductive coupling cyclisation between a nitrile and an
acrylamide. Doye’s group reported a one-pot synthesis of pyrrolidines from the reaction of arylcyclopropylalkynes with primary amines. This synthesis proceeds through an initial Ti-catalysed hydroamination to give a cyclopropylimine which rearranges in the presence of ammonium chloride to give a \( \Delta_2 \)-pyrroline. Final addition of NaBH\(_4\), ZnCl\(_2\) and methanol gave the pyrrolidines. A catalyst-free intramolecular hydroamination/aminocarbonylation of a series of hydrazine derivatives also allowed access to pyrrolidines. Schneider and Enkisch showed that a sequential Mannich aza-Michael process gives 2,3,5-trisubstituted pyrrolidines in enantiopure form when the Mannich process was performed in the presence of L-proline as an organocatalyst. Reduction and silylation of the Mannich adducts allowed a stereodivergent aza-Michael ring-closure with NaOEt as base giving excellent yields of 2,5-trans-products, whereas KO\( _t\)Bu gave 2,5-cis-products. Also shown in Scheme 16, Beller and colleagues have developed a convenient one-pot process for the synthesis of succinimides by using commercially available alkenes and amines (including ammonia) in the presence of carbon monoxide and an iron carbonyl catalyst.

Aponick’s gold-catalysed dehydrative cyclisation of pyroles (previously shown in Scheme 15) was applied to the synthesis of furans, as shown in Scheme 17. Polysubstituted furans are also available from a Cu(I)-catalysed domino process...
involving the rearrangement/dehydration oxidation/carbene oxidation cascade shown in Scheme 18. The process starts with diethyl acetylenedicarboxylate and an alkynol, and proceeds through an intermediate 1,5-enyne.\textsuperscript{31}

\[
\begin{align*}
\text{CO}_2\text{Et} + \text{HO R^2} \rightarrow \text{O}_2\text{Et} \rightarrow \text{EtO}_2\text{C} \rightarrow \text{O}_2\text{C} \rightarrow \text{EtO}_2\text{C} & \rightarrow \text{R^1} \rightarrow \text{R^2} \\
\text{DABCO} & \rightarrow \text{CH}_2\text{Cl}_2, \text{RT} \rightarrow \text{EtO}_2\text{C} \rightarrow \text{DABCO} \rightarrow \text{O}_2\text{Et}
\end{align*}
\]

Scheme 18

Scheme 19 shows that di- and tri-substituted furans can be accessed through a palladium(II)-catalysed intramolecular carboxylation of an aryl iodide followed by cycloisomerisation of an activated alkyne-substituted 1,3-diketone.\textsuperscript{32}

\[
\begin{align*}
\text{R^1} & \rightarrow \text{CO} \rightarrow \text{CO} \rightarrow \text{Ar I} \rightarrow \text{Pd(PPh}_3\text{)}_2\text{Cl}_2 (6 \text{ mol%}) \rightarrow \text{THF, Et}_3\text{N, 30 - 100 °C} \rightarrow \text{Ar} \rightarrow \text{Ar} \rightarrow \text{Ar} \rightarrow \text{Ar} \\
\text{R^1} & \rightarrow \text{CO} \rightarrow \text{CO} \rightarrow \text{Ar I} \rightarrow \text{Pd(PPh}_3\text{)}_2\text{Cl}_2 (6 \text{ mol%}) \rightarrow \text{THF, Et}_3\text{N, 30 - 100 °C} \rightarrow \text{Ar} \rightarrow \text{Ar} \rightarrow \text{Ar} \rightarrow \text{Ar}
\end{align*}
\]

Scheme 19

The Rh(II)-catalysed cyclopropenation of a range of ynamides and sulfonamides results in a formal [3+2] cycloaddition, leading to a series of 2-amido/sulfonamido-furans when diazo dimethyl malonate or a phenyl iodonium ylide (see Scheme 20) were used as cyclopropenating agents. In all cases, better yields were observed with diazo dimethyl malonate.\textsuperscript{33}

\[
\begin{align*}
\text{Rh}_2(\text{OAc})_2 (2 - 5 \text{ mol%}) \rightarrow \text{R = CO R^2 or SO}_2 \rightarrow \text{R^3} \rightarrow \text{R^4} \rightarrow \text{N} \rightarrow \text{Ph} \rightarrow \text{3PAuOTf (2.5 mol%)} \rightarrow \text{CH}_2\text{Cl}_2, \text{RT, 10 - 30 min.} \\
\text{R^1} & \rightarrow \text{R^2} \rightarrow \text{R^3} \rightarrow \text{R^4} \rightarrow \text{N} \rightarrow \text{Ph} \rightarrow \text{3PAuOTf (2.5 mol%)} \rightarrow \text{CH}_2\text{Cl}_2, \text{RT, 10 - 30 min.}
\end{align*}
\]

Scheme 20

Zhang’s group\textsuperscript{34} have accessed furo[3,4-d][1,2]oxazines using a gold-catalysed 1,3-dipolar [3+3] cycloaddition between a nitrone and a 2-(1-alkynyl)-2-alken-1-one, as shown in Scheme 21. This reaction probably proceeds through a gold-catalysed cyclisation of the 2-(1-alkynyl)-2-alken-1-one, followed by addition of the nitrone to the resultant furanyl gold complex. When performed in the presence of asymmetric gold catalysts, moderate enantioselectivities were observed (50 – 71% ee).

\[
\begin{align*}
\text{R^1} & \rightarrow \text{R^2} \rightarrow \text{R^3} \rightarrow \text{N} \rightarrow \text{Ph} \rightarrow \text{3PAuOTf (2.5 mol%)} \rightarrow \text{CH}_2\text{Cl}_2, \text{RT, 10 - 30 min.}
\end{align*}
\]

Scheme 21

Furanones have attracted attention,\textsuperscript{35,36,37} and several approaches to these important synthetic building blocks are shown in Scheme 22. Thus, Kumar and co-workers\textsuperscript{35}
have shown that 4-oxoalkenoic acids yield dihydrofuranones ($X = H$) under cyclodehydrative conditions. Bromination of the 4-oxoalkenoic acids, cyclodehydration with $P_2O_5$, and dehydrobromination with DBU allowed the isolation of bromodihydrofuranones ($X = Br$). Blum and colleagues have shown that a combination of a carbophilic Lewis acid gold catalyst and a Lewis basic palladium catalyst allows the conversion of allenoates into furanones (butenolides) through an initial gold-catalysed allenoate rearrangement. Palladium catalysed deallylation, transmetalation and C–C coupling are the other key mechanistic steps. Li’s group have demonstrated that the Cu(I)-catalysed $O$-vinylation of a series of vinylcarboxylic acids gave furanones after an Ullmann coupling process. Trost and co-workers have shown that a Ru/In-catalysed redox cycloisomerisation–$O$-conjugate addition process can be used for the atom efficient formation of tetrahydrofurans starting from the propargyl alcohols, also shown in Scheme 22.

Alkynes can be used to form sulfur ylides from allylic sulfoxides under gold or platinum catalysis. When performed in an intramolecular fashion with a tether of appropriate length, as shown in Scheme 23, these sulfur ylides have been used to generate tetrahydrothiophenes.

Pyrazoles, by virtue of their wide range of biological activities, attracted a number
of interesting approaches in 2009. Harrity (Scheme 24) showed that cycloaddition between a sydnone and an alkynylboronate was highly flexible and regioselective, allowing access to di-, tri- and tetrasubstituted pyrazole boronic esters. The process was extended to three bicyclic sydnone, allowing access to fused pyrazoles. Suzuki coupling of the boronic acids allowed access to further pyrazoles.

A simple one-pot route to N-arylpyrazoles from di-tert-butylazodicarboxylate (DBAD), aryl nucleophiles (derived from aryl halides in the presence of n-BuLi) and 1,3-dicarboxyls has been reported (Scheme 25). The process requires generation of the nucleophile, addition of DBAD, and then addition of the carbonyl, and can be adapted to allow access to halogenated pyrazoles and to indazoles.

List and Müller have developed an asymmetric synthesis of highly sought after 2-pyrazolines (e.g. as COX-2 inhibitors) using a chiral Bronsted acid (Scheme 26) to catalyse the cycloisomerisation of α,β-unsaturated hydrazones, the first example of a catalytic asymmetric 6π-electrocyclisation. The process was modified to allow the enantioselective synthesis of 2-pyrazolines starting from an unsaturated ketone and phenylhydrazine, thus removing the need to isolate the hydrazone.

A notable advance in imidazole chemistry, shown in Scheme 27, has been described whereby a four-component domino reaction gives excellent yields in short reaction times. The reaction is proposed to occur through an interesting condensation, nucleophilic addition, umpolung, intramolecular addition, dehydration sequence.
The major advances in the synthesis of 1,2,3-triazoles are shown in Scheme 28. Ley’s group used modular flow reactors in which alkynes are delivered by the use of the Bestmann-Ohira reagent. Excess aldehyde was removed using an amine resin, excess base was removed using a sulfonic acid resin, and acidic impurities were removed using a dimethylamine resin. The use of an immobilised copper(I) catalyst, followed by removal of excess copper by a thiourea resin allowed the alkene to react with an azide to produce 1,2,3-triazoles. Work by Fokin showed that 5-iodo-1,4-substituted-1,2,3-triazoles were available from the reaction of 1-iodoacetylenes with azides in the presence of Cu(I) and a tris(triazole) catalyst. The products are excellent substrates for further couplings. The use of a tris(triazolyl)methanol catalyst by Pericàs (see Scheme) for the ‘on water’ synthesis of 1,4-disubstituted-1,2,3-triazoles starting from benzyl or alkylbromides is a process that is significant in avoiding the manipulation of organic azides. The synthesis of 1-substituted triazoles under an atmosphere of acetylene gas or by the use of calcium carbide have been reported. Click processes have continued to offer significant advances in molecular biology, and the selective labeling of living or intact cells by Popik and Boons and co-workers, and by Fast and co-workers are notable in this respect.

Scheme 28

The major highlights in indole synthesis are summarised in Scheme 29. Cacchi’s approach uses a copper-catalysed C–H functionalisation of readily available N-aryl enamiones. Doyle has shown that intramolecular nucleophilic attack of imines by aryldiazooacetates is catalysed by Lewis acids, facilitating the formation of 2,3-disubstituted indoles in quantitative yields. Work from Dong’s laboratory has exploited the reactivity of nitroalkenes which were shown to undergo a Pd-catalysed reductive cyclisation using carbon monoxide as the reductant during a novel C–H amination process. Pei and colleagues at Merck have shown that carbon nucleophiles add readily to a series of α-chloro aceto phenones to give 2-substituted indoles after a [1,2]-aryl rearrangement. 2-Substituted indoles are also available

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from the reduction/hydroamination of (2-nitroaryl)alkynes using iron oxide supported gold nanoparticles. Sorensen has shown that an interrupted Ugi process allows cyclisation to give 3-aminoindoles when an aldimine is reacted with an isocyanide, and indoxyls when a ketimine is reacted. The triflyl phosphoramid shown in Scheme 29 was found to be the optimal acid. Oxindoles are recurrent motifs in natural products and Ackermann has developed a new approach that uses an air-stable secondary phosphine oxide to catalyse the arylation of acidic C–H compounds, a process that also allowed the synthesis of azaoxindoles.

Scheme 29
A catalytic asymmetric electrocyclisation for the generation of indolines has been developed and relies upon the use of the cinchona-derived ammonium salt shown in Scheme 30.\textsuperscript{58} Indolines are also available from a palladium-catalysed C–H amination using $\text{F}^+$, the role of which is to ensure the oxidation of a C–H insertion intermediate up to a Pd(IV) species whilst still allowing reductive elimination of the aminated product. The use of DMF as labile ligand was crucial to the process.\textsuperscript{59}

![Scheme 30](image)

New approaches to benzofurans are summarised in Scheme 31. Barluenga’s group\textsuperscript{60} showed that a non-heteroatom stabilised carbene complex underwent regioselective [3+3] benzannelation in the presence of 2-imino furans. Li’s group\textsuperscript{61} have used a Fe-catalysed oxidative Pechmann-type condensation to generate benzofurans rather than coumarins from the reaction of phenols with β-keto esters. The group of Du and Zhao\textsuperscript{62} used an Fe-mediated intramolecular cyclisation of electron-rich α-aryl ketones in which direct oxidative aromatic C–O bond formation occurs.

![Scheme 31](image)

A wide range of benzazoles has been made available using the transition-metal-catalysed hydrogen-transfer reactions shown in Scheme 32. Thus, benzimidazoles were synthesised from 1,2-aminoanilines and alcohols using crotononitrile as the hydride acceptor, a Ru catalyst, Xantphos and piperidinium acetate; benzoxazoles and benzothiazoles were synthesised using no acceptor, an aldehyde, a 1,2-aminophenol/thiophenol and an Ir catalyst with no further additives.\textsuperscript{63}
Six-membered rings

Notable syntheses of pyridines are shown in Scheme 33. Chiba and Wang have developed a Mn(III)-induced reaction between vinyl azides and cyclopropanols. The initial product is a tetrahydropyridine, but this undergoes dehydration and oxidation in the presence of excess Mn(III), AcOH and oxygen to give the pyridines. Beauchemin and colleagues were able to access pyridines from an intramolecular Cope-type hydroamination, isomerisation, aromatisation sequence starting with the alkynyl oximes shown in Scheme 33. It is of interest to note that the process was also adaptable to enable the synthesis of pyrazines, also shown in Scheme 33. Banerjee and Sereda used silica nanoparticles under mild, near neutral conditions to catalyse the formation of pyridines from aldehydes, malononitrile and thiols.

Scheme 32

\[
\text{Ru or Ir catalyst}
\]

\[
\text{Ru: Ru(PPh}_3)_3(CO)H}_2
\]

\[
\text{Ir: [Cp*IrI}_2
\]

\[
X = O, S, NH
\]

Scheme 33

Chen and colleagues have disclosed an inverse-demand aza-Diels-Alder reaction in which N-tosyl-1-aza-1,3-butadienes react with α,β-unsaturated aldehydes in the presence of a dienamine catalyst, generated from the reaction of a chiral amine with the aldehyde. The products are enantiomerically pure piperidines which can be isolated as hemiaminals or, after PCC oxidation, as lactams.

Scheme 34
The formation of a pyridine ring from the intramolecular inverse-demand Diels-Alder reaction of an alkyne with a 1,2,4-triazine has been used to make azachromans and azabenzo furans, as shown in Scheme 35.\(^{68}\)

![Scheme 35](image)

Advances in the synthesis of pyrans are shown in Scheme 36. Jiang\(^{69}\) used a DABCO-induced [2+2+2]-cycloaddition cascade to synthesise 4-aryl-4H-pyrans from ethyl propiolate and aryl aldehydes. Gharpure and Reddy used a tandem S$_2$2 alkylation-Michael addition to make tetrahydropyrans from the iodides shown and active methylene compounds.\(^{70}\) This process was easily adapted to allow access to trans-fused bicyclic tetrahydropyrans. Johnson and Parsons have developed a formal [4+2] cycloaddition using donor-acceptor cyclobutanes and aldehydes. Sc(OTf)$_3$ was shown to be a useful catalyst for aryl aldehydes; alkyl aldehydes required the use of MADNTf$_2$ (see Scheme) as catalyst. The methodology could be streamlined into a [2+2+2] process so that some of the cyclobutanes were constructed in situ from dimethyl methylidene malonate and a styrene in the presence of Sc(OTf)$_3$.\(^{71}\)

Pyrimidines attracted several notable new syntheses in 2009, and these are summarised in Scheme 37. Reissig’s group reported a three-component approach using lithiated alkoxyallenes, nitriles and carboxylic acids as precursors. The reaction proceeds via an intermediate enamide which could be ring-closed with ammonium salts to give the pyrimidine.\(^{72}\) Work from the Movassaghi group\(^{73}\) synthesised pyrimidines and quinazolines from the reaction of cyanoic acid derivatives with N-vinyl or N-aryl amides in the presence of 2-chloropyridine and trifluoromethanesulfonic anhydride as electrophilic amide activators. Konakahara and colleagues\(^{74}\) used a ZnCl$_2$-catalysed three-component coupling reaction in which...
a range of enamines were reacted with triethyl orthoformate and ammonium acetate to give 4,5-disubstituted pyrimidines. Ketones can be used in the place of the enamine, allowing access to 4-monosubstituted pyrimidines. Zhang, Xi and co-workers have shown that an organolithium-promoted three-component reaction between terminal alkynes, elemental sulfur and carbodiimides gives an easy route through to 2,3-dihydropyrimidinthiones.\(^7^9\)

\[
\begin{align*}
& \text{Reissig} \\
& 1. \text{R}^1\text{C}==\text{N} \quad 2. \text{R}^2\text{COOH} \\
& \text{NH}_2\text{X}, \text{MeOH}, \text{sealed tube} \\
& 6 \text{ examples } 56 - 86%
\end{align*}
\]

\[
\begin{align*}
& \text{Movassaghi} \\
& \text{NH}_2\text{Cl} + \text{TsO} \quad \text{CH}_2\text{Cl}_2 \\
& 18 \text{ examples } 54 - 99%
\end{align*}
\]

\[
\begin{align*}
& \text{Konakahara} \\
& \text{CH(OEt)}_3 [3 \text{ eq.}] + \text{ZnCl}_2 [0.1 \text{ eq.}] \quad \text{PhMe, } 100^\circ\text{C} \\
& 20 \text{ examples } 24 - 99%
\end{align*}
\]

\[
\begin{align*}
& \text{Zhang and Xi} \\
& 1. \text{n-BuLi, THF, } -78^\circ\text{C}, 30 \text{ min} \\
& 2. \text{H}_2\text{O} \quad \text{7 examples } 30 - 35% \\
& 12 \text{ examples } 67 - 87% \quad \text{dr } >20:1
\end{align*}
\]

Looking at other non-benzo-fused systems, a significant new synthesis of potentially antimalarial 1,2-dioxanes through the Pd(II)-catalysed cyclisation of readily available unsaturated hydroperoxides has appeared (Scheme 38).\(^7^6\) White and Rice (also Scheme 38) have developed a Pd(II)-sulfoxide-catalysed allylic C–H amination that allows the synthesis of syn-oxazinanones.\(^7^7\) The products are valuable intermediates for the synthesis of syn-1,3-amino alcohols.

\[
\begin{align*}
& \text{Pd(OAc)}_2 [5 \text{ mol%}] + \text{pyridine [20 mol%]} \\
& \text{dioxane, } 80^\circ\text{C}, 3 \text{h} \\
& 7 \text{ examples } 30 - 35% \quad \text{de } 75:25 \text{ to } >97:3
\end{align*}
\]

\[
\begin{align*}
& \text{Ns - nosyl; PBQ - phenylbenzoquinone}
\end{align*}
\]

\[
\begin{align*}
& \text{Scheme 37}
\end{align*}
\]

\[
\begin{align*}
& \text{Approaches to benzo-fused six-membered heterocycles are shown in Scheme 39. Thus, Dong and Lin}\(^7^8\) \text{ have developed a Vilsmeier-Haack, cyclisation, aromatisation}
\end{align*}
\]
approach to quinolines by reacting α-arylaminoketones with PBr₃ in DMF. A nickel-catalysed decarboxylative carboxamination of alkynes using isatoic anhydrides was shown by Matsubara and Kurahashi to give quinolones.²⁹ Gong has developed an enantioselective synthesis of tetrahydroquinolines starting from 2-(2-propynyl)anilines using a gold-catalysed hydroamination and Brønsted acid catalysed transfer hydrogenation.³⁰ Guimond and Fagnou used a Rh(III)-catalysed oxidative cross-coupling, cyclisation process to form isoquinolines in a regioselective manner from aldmines and alkynes. Rh species were shown to catalyse C–H bond-breaking and C–C and C–N bond-formation.³¹ Further work from Matsubara and Kurahashi³² showed that chromones are available from the nickel-catalysed cycloaddition of salicylic acid ketals with alkynes, a process which was shown to involve the β-elimination of a ketone. Rueping’s group used asymmetric Brønsted acid catalysis to synthesise dihydroquinazolinones from aldehydes and 2-aminobenzamide.³³

Scheme 39

**Seven-membered rings and larger**

An unexpected benzothiadiazocine formation occurred when the amino alkenes shown in Scheme 40 were subjected to iodocyclisation conditions. The identical
products were obtained from the corresponding azides upon intramolecular 1,3-dipolar cycloaddition and nitrogen extrusion from the intermediate triazoline.\(^8\)

![Scheme 40](image)

**Scheme 40**

An enantioselective Rh-catalysed \( [4+2+2] \) cycloaddition between terminal alkynes and dienyl isocyanates gave bicyclo[6.3.0]azocines in the presence of a phosphoramidite ligand as shown in Scheme 41.\(^{44}\)

![Scheme 41](image)

**Scheme 41**

A variety of seven- and eight-membered heterocyclic rings is available in highly asymmetric fashion from the Rh-catalysed intramolecular hydroacylation of alkenals, a rare example of transition-metal-catalysed asymmetric medium ring formation (Scheme 42).\(^{45}\)

![Scheme 42](image)

**Scheme 42**

To conclude, the central role of heterocycles in medicinal chemistry and natural product chemistry, and the huge interest in C–heteroatom bond synthesis, have ensured that 2009 was a productive year with many novel and useful contributions to this most important field of organic chemistry.

**References**