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Heterocyclic Chemistry

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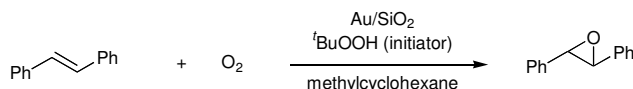
2009 offered several significant advances in the field of heterocyclic chemistry, with particular highlights including several new approaches to pyrroles, indoles and pyrimidines. Major themes were hydroamination
¹⁰ processes, the development of new multi-component reactions and advances in the development 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
¹⁵ 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.

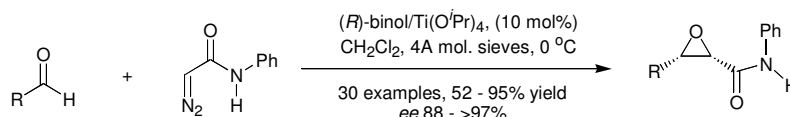
Three-membered rings

The use of surface organometallic chemistry has allowed the production of gold
²⁰ 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



²⁵ Scheme 1

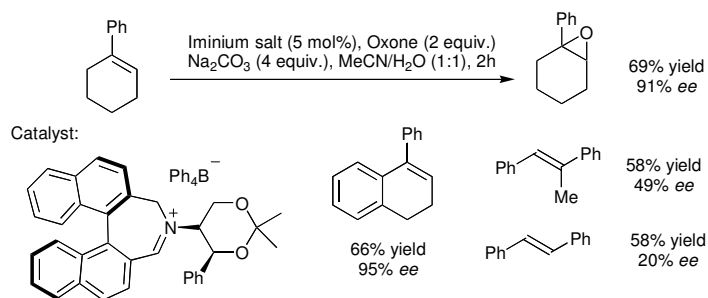
Optically pure epoxides are available *via* a highly diastereoselective and enantioselective Darzens reaction involving a chiral titanium complex which is generated *in situ* from titanium *isopropoxide* and (*R*)-binol, as shown in Scheme 2.²
 The range of aldehydes includes aromatic, aliphatic and unsaturated substrates and
³⁰ hence allows access to a wide range of *cis*-glycidic amides.



Scheme 2

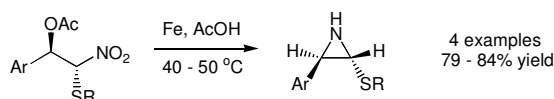
Work by Page has shown that epoxides can be produced in the absence of metal
³⁵ species using the new and highly selective organocatalytic iminium salt shown in Scheme 3. The catalyst works at a relatively low loading, and the process could also

be applied to other alkenes, a selection of which is shown in the Scheme.³



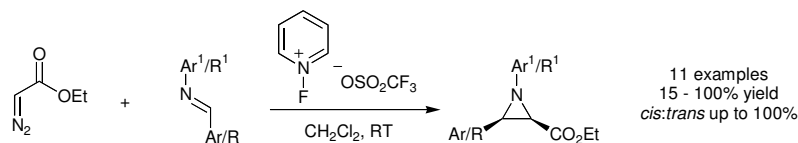
Scheme 3

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



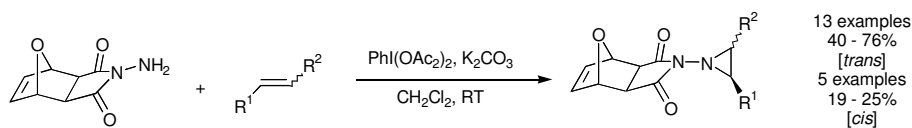
Scheme 4

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.



Scheme 5

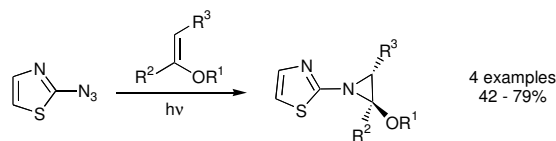
The use of the *N*-amino-tetrahydrophthalimide shown in Scheme 6 in the oxidative aminoaziridation of alkenes was found to give excellent yields of *trans*-aziridines from *trans*-alkenes, whereas lower reactivity was observed with *cis*-alkenes.⁶ This reaction is believed to proceed *via* an intermediate aminonitrene which arises from the action of the $\text{PhI}(\text{OAc})_2$ upon the *N*-aminophthalimide.



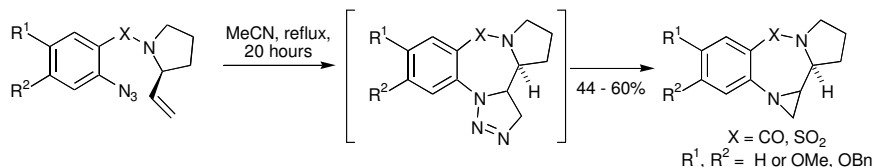
Scheme 6

The use of 2-azido-1,3-thiazole as a nitrene source has been reported by Racioppi,

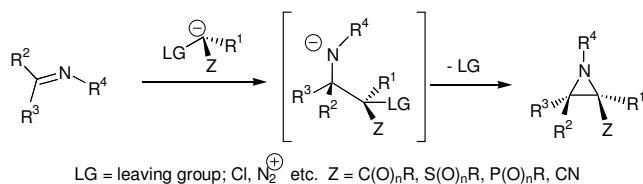
with the resulting nitrene giving aziridines upon reaction with enol ethers as shown in Scheme 7, the first time that such a process has been observed (previous reactions of azides with enol ethers proceed *via* 1,3-dipolar cycloaddition).⁷ Aziridine formation *via* intramolecular 1,3-dipolar cycloaddition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



Scheme 7



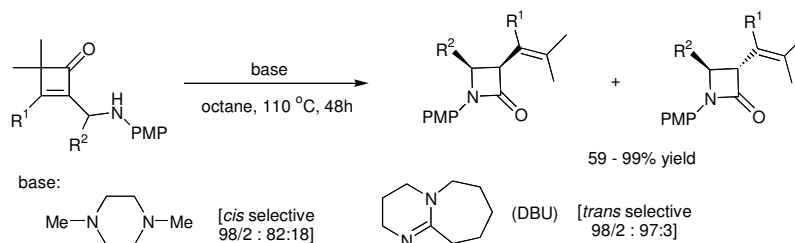
Scheme 8



Scheme 9

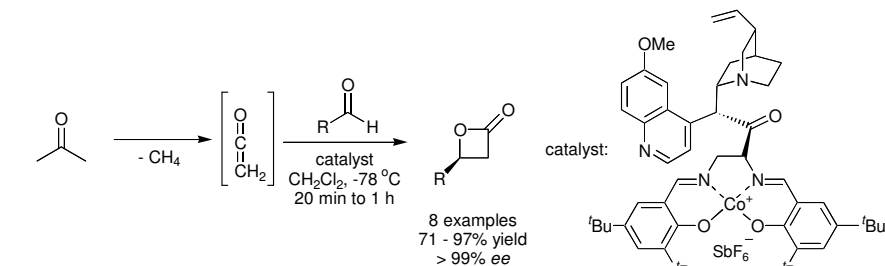
Four-membered rings

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.¹⁰



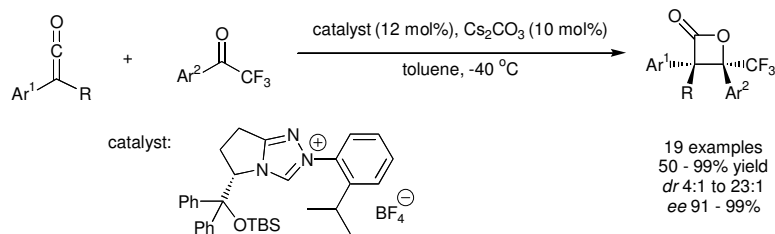
Scheme 10

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 β -lactones with excellent *ees* and high yields. The ease with which the lactones can be converted into β -hydroxy esters makes a valuable alternative to aldol based approaches to these targets.¹¹



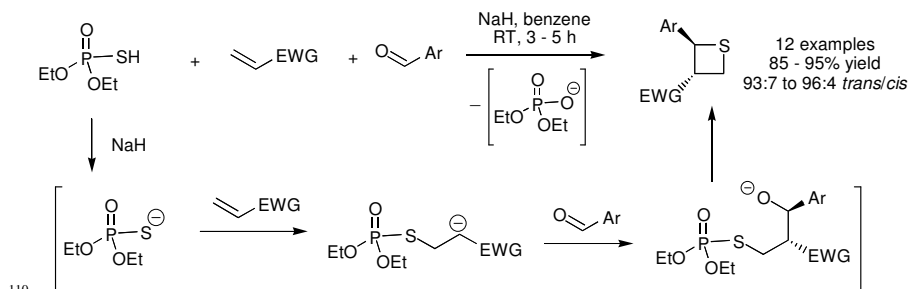
Scheme 11

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- β -lactones shown in Scheme 12, which are typically formed in high yield with good diastereoselectivity and excellent enantioselectivity.¹²



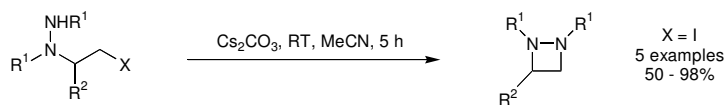
Scheme 12

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.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.



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 R¹ group was a carbonyl. When R¹ was a sulfone, exclusive formation of diazetidines was observed.¹⁴



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Scheme 14

Five-membered rings

Several significant new syntheses of pyrroles appeared in 2009, and these are summarised in Scheme 15. Thus, Anary-Abbasinejad¹⁵ showed that the reaction of phosphoranes with arylglyoxals yields an intermediate dimethyl carboxylate that cyclises to give pyrroles. The phosphoranes were easily formed from the reaction of a Ph₃P-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 *via* a rhodium vinylidene complex.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 -haloalkynols was reported in the same publication, hence avoiding the need to prepare chloroenynes.¹⁷ A titanium(IV) based synthesis has also been reported by Ciez¹⁸ 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,¹⁹ a process also applicable to the synthesis of furans and thiophenes.

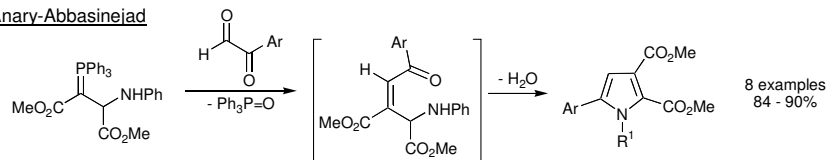
The gold-catalysed cycloisomerisation of acetylene-substituted aziridines reported by Hou²⁰ gave generally high yields of 2,5-disubstituted pyrroles, particularly when carried out in the presence of a protic species. Wilson has reported an uncatalysed Paal-Knoor condensation pyrrole synthesis that utilises microwave irradiation in water, followed by isolation by filtration, an improved and significant 'green' addition to the field.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_1 -pyrrolines (2*H*-pyrroles) which undergo a base-induced loss of HCN to give 2,3,5-trisubstituted pyrroles. Starting from aminoacetonitrile itself (R¹ = H) allowed the Δ_1 -pyrroline-5-carbonitriles to be isolated after reaction in pyridine at reflux.²² The reaction of other α -aminonitriles (R¹ \neq H) with enones in the presence of TiCl₄/triethylamine allowed the isolation of pyrroles. Other new routes to pyrrolines also appeared in 2009. Thus, Wender and Strand²³ used a formal [3+2] cycloaddition between aziridines and non-activated alkynes to give a range of Δ_2 -pyrrolines. The groups of Marinetti²⁴ and Robina²⁵ have also published new routes to Δ_3 -pyrrolines.

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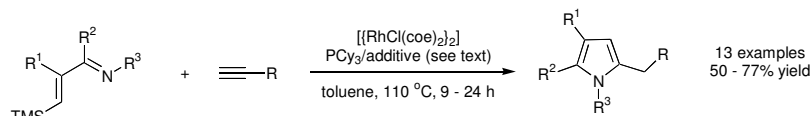
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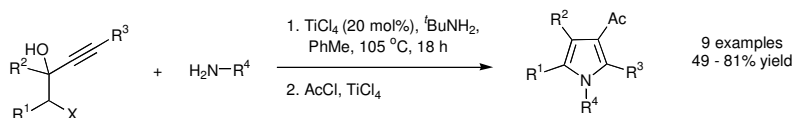
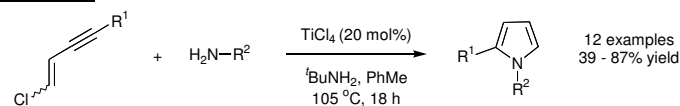
Anary-Abbasinejad



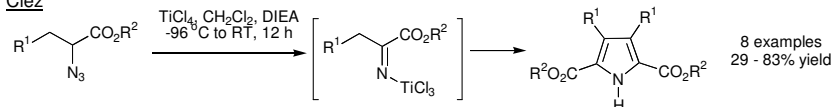
Iwasawa



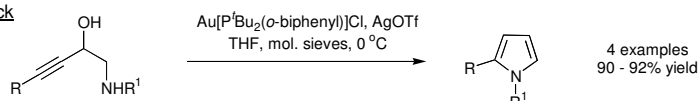
Ackermann



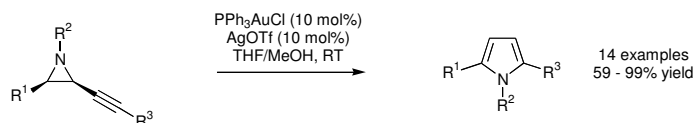
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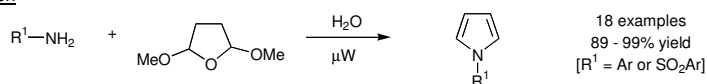
Aponick



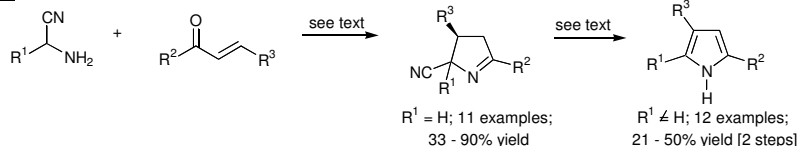
Hou



Wilson



Opatz



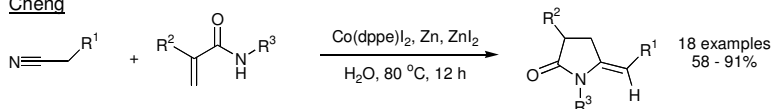
Scheme 15

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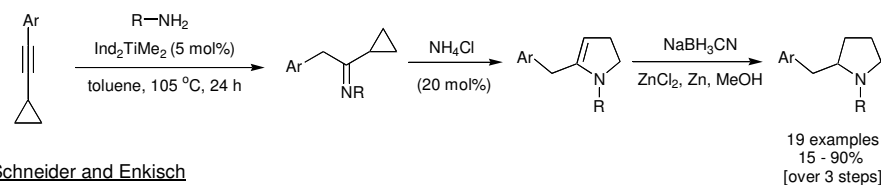
Highlights in the synthesis of the fully saturated pyrrolidine nucleus are shown in Scheme 16. Cheng and co-workers²⁶ showed that pyrrolidinones were available *via* a one-pot, Co-catalysed reductive coupling cyclisation between a nitrile and an

acrylamide. Doye's group reported²⁷ a one-pot synthesis of pyrrolidines from the
 165 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 Δ_2 -pyrroline. Final
 addition of NaBH_3CN , ZnCl_2 and methanol gave the pyrrolidines. A catalyst-free
 170 intramolecular hydroamination/aminocarbonylation of a series of hydrazine
 derivatives also allowed access to pyrrolidines.²⁸ 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.²⁹ Reduction and silylation of the Mannich adducts
 allowed a stereodivergent aza-Michael ring-closure with NaOEt as base giving
 175 excellent yields of 2,5-*trans*-products, whereas KO^tBu 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
 alkynes and amines (including ammonia) in the presence of carbon monoxide and an
 iron carbonyl catalyst.³⁰

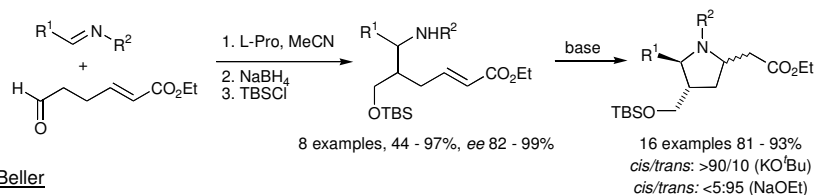
Cheng



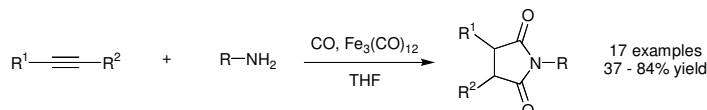
Doye



Schneider and Enkisch

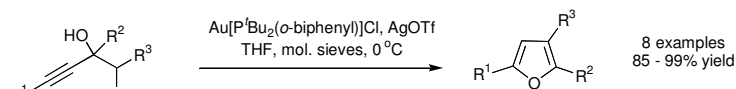


Beller



Scheme 16

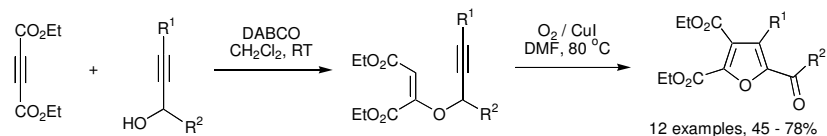
Aponick's gold-catalysed dehydrative cyclisation of pyrroles (previously shown in
 185 Scheme 15) was applied to the synthesis of furans, as shown in Scheme 17.¹⁹



Scheme 17

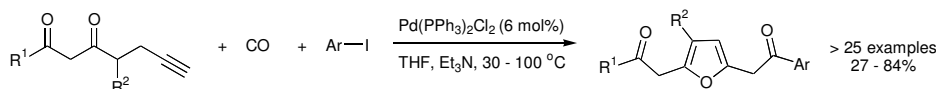
Polysubstituted furans are also available from a Cu(I)-catalysed domino process

190 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.³¹



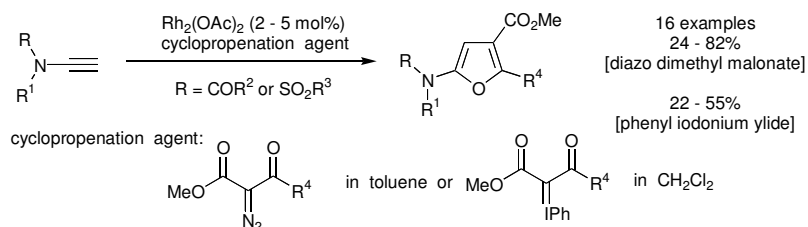
Scheme 18

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



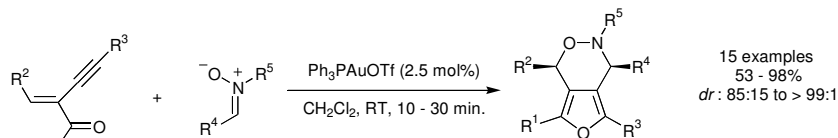
Scheme 19

200 The Rh(II)-catalysed cyclopropanation 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 cyclopropanating agents. In all cases, better yields were observed with
205 diazo dimethyl malonate.³³



Scheme 20

210 Zhang's group³⁴ have accessed furo[3,4-*d*][1,2]oxazines using a gold-catalysed 1,3-dipolar [3+3] cycloaddition between a nitron 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 nitron to the resultant furanyl gold complex. When performed in the presence of asymmetric gold catalysts, moderate enantioselectivities were observed (50 - 71% *ee*).



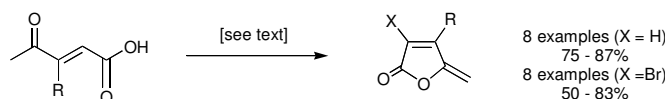
Scheme 21

Furanones have attracted attention,^{35,36,37} and several approaches to these important synthetic building blocks are shown in Scheme 22. Thus, Kumar and co-workers³⁵

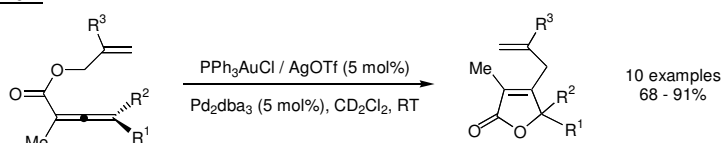
have shown that 4-oxoalkenoic acids yield dihydrofuranones (X = H) under cyclodehydrative conditions. Bromination of the 4-oxoalkenoic acids, cyclodehydration with P₂O₅, and dehydrobromination with DBU allowed the isolation of bromodihydrofuranones (X = Br). Blum and colleagues have shown that a combination of a carbophilic Lewis acid gold catalyst and a Lewis basic palladium catalyst allows the conversion of allenates into furanones (butenolides) through an initial gold-catalysed allenolate rearrangement. Palladium catalysed deallylation, transmetalation and C–C coupling are the other key mechanistic steps.³⁶ Li's group³⁷ 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 22.³⁸

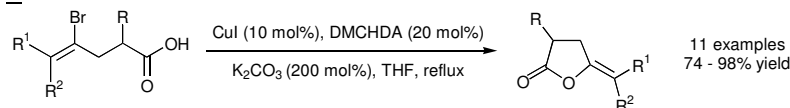
Kumar



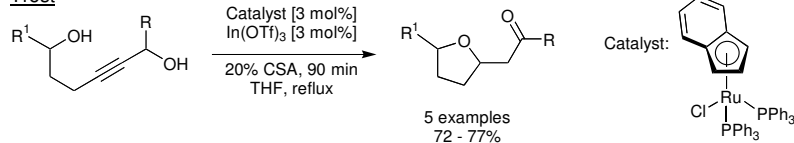
Blum



Li

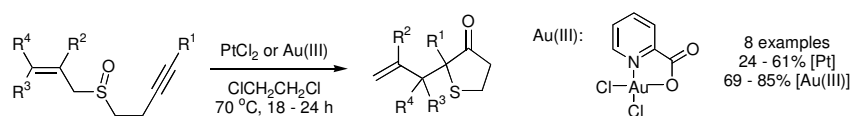


Trost



Scheme 22

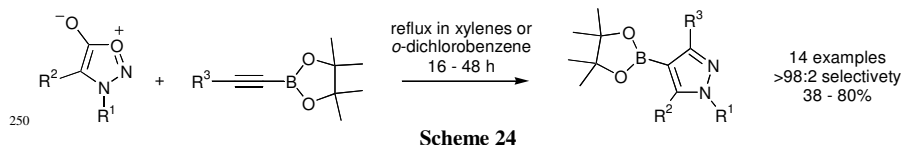
Alkynes can be used to form sulfur ylides from allylic sulfoxides under gold or platinum catalysis. When performed in an intramolecular fashion with a tether of appropriate length, as shown in Scheme 23, these sulfur ylides have been used to generate tetrahydrothiophenes.³⁹



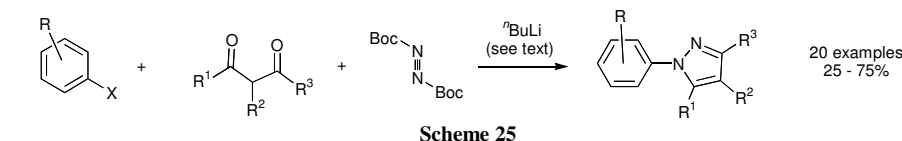
Scheme 23

Pyrazoles, by virtue of their wide range of biological activities, attracted a number

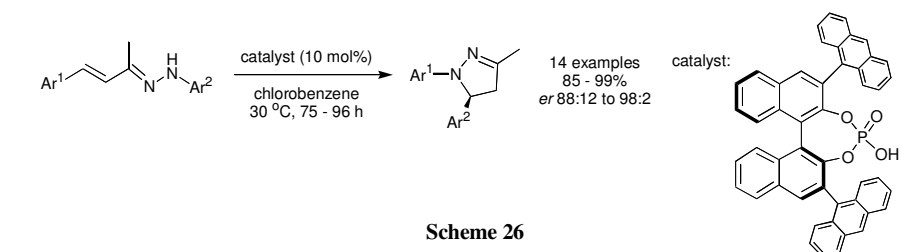
of interesting approaches in 2009. Harrity (Scheme 24)⁴⁰ showed that cycloaddition between a sydnone and an alkynylboronate was highly flexible and regioselective, allowing access to di-, tri- and tetrasubstituted pyrazole boronic esters. The process was extended to three bicyclic sydrones, allowing access to fused pyrazoles. Suzuki coupling of the boronic acids allowed access to further pyrazoles.



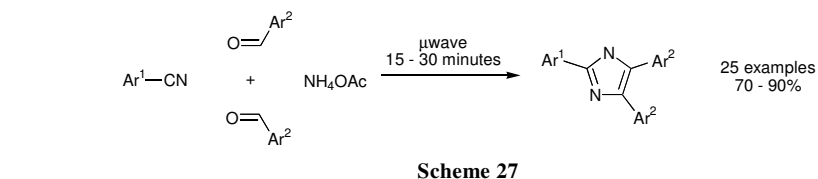
A simple one-pot route to *N*-arylpyrazoles from di-*tert*-butylazodicarboxylate (DBAD), aryl nucleophiles (derived from aryl halides in the presence of *n*-BuLi) and 1,3-dicarbonyls has been reported (Scheme 25). The process requires generation of the nucleophile, addition of DBAD, and then addition of the carbonyl, and can be adapted to allow access to halogenated pyrazoles and to indazoles.⁴¹



List and Müller⁴² have developed an asymmetric synthesis of highly sought after 2-pyrazolines (e.g. as COX-2 inhibitors) using a chiral Brønsted 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.

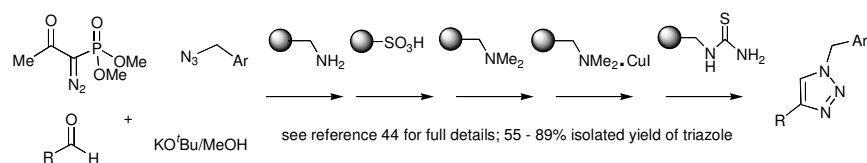


A notable advance in imidazole chemistry, shown in Scheme 27, has been described whereby a four-component domino reaction gives excellent yields in short reaction times. The reaction is proposed to occur through an interesting condensation, nucleophilic addition, umpolung, intramolecular addition, dehydration sequence.⁴³

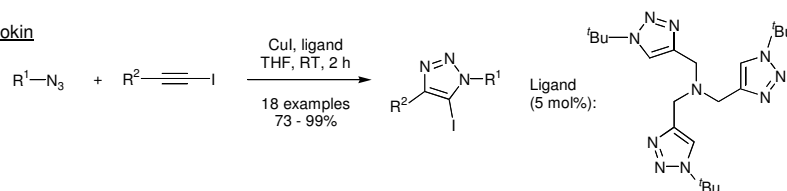


The major advances in the synthesis of 1,2,3-triazoles are shown in Scheme 28. Ley's group used modular flow reactors in which alkynes are delivered by the use of the Bestmann–Ohira reagent. Excess aldehyde was removed using an amine resin, excess base was removed using a sulfonic acid resin, and acidic 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 alkyne to react with an azide to produce 1,2,3-triazoles.⁴⁴ Work by Fokin showed that 5-iodo-1,4-substituted-1,2,3-triazoles were available from the reaction of 1-iodoalkynes with azides in the presence of Cu(I) and a tris(triazole) catalyst. The products are excellent substrates for further couplings.⁴⁵ 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 alkyl bromides is a process that is significant in avoiding the manipulation of organic azides.⁴⁶ The synthesis of 1-substituted triazoles under an atmosphere of acetylene gas⁴⁷ or by the use of calcium carbide⁴⁸ 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,⁴⁹ and by Fast and co-workers⁵⁰ are notable in this respect.

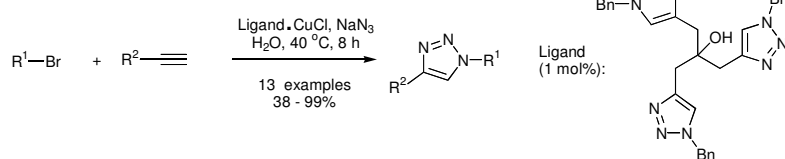
Ley



Fokin



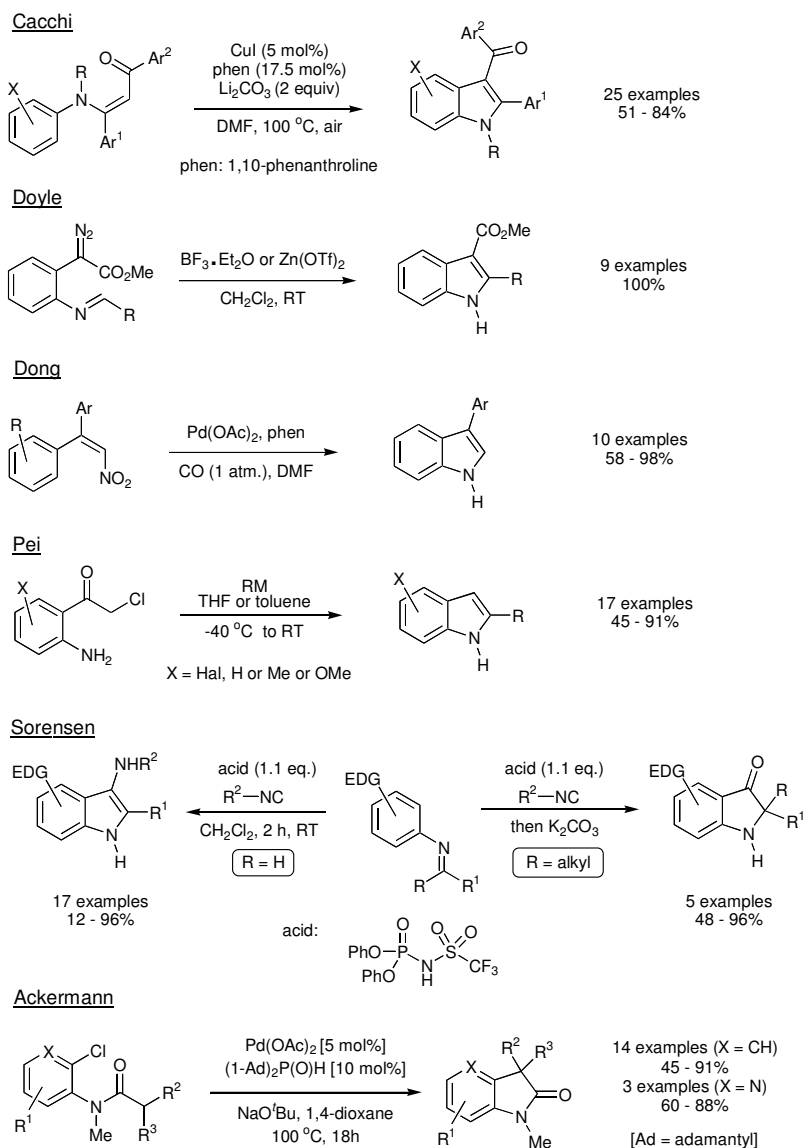
Pericàs



Scheme 28

The major highlights in indole synthesis are summarised in Scheme 29.⁵¹⁻⁵⁶ Cacchi's approach uses a copper-catalysed C–H functionalisation of readily available *N*-aryl enaminones.⁵¹ Doyle⁵² has shown that intramolecular nucleophilic attack of imines by aryldiazoacetates 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.⁵³ Pei and colleagues at Merck have shown that carbon nucleophiles add readily to a series of α -chloro acetophenones to give 2-substituted indoles after a [1,2]-aryl rearrangement.⁵⁴ 2-Substituted indoles are also available

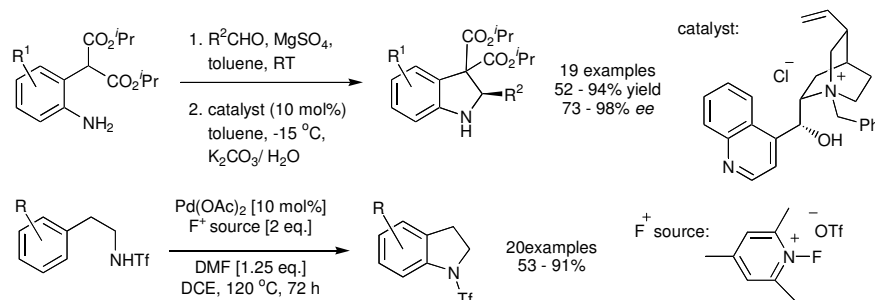
305 from the reduction/hydroamination of (2-nitroaryl)alkynes using iron oxide
supported gold nanoparticles.⁵⁵ Sorensen⁵⁶ has shown that an interrupted Ugi
process allows cyclisation to give 3-aminoindoles when an aldimine is reacted with
an isocyanide, and indoxyls when a ketimine is reacted. The triflyl phosphoramidate
shown in Scheme 29 was found to be the optimal acid. Oxindoles are recurrent
310 motifs in natural products and Ackermann⁵⁷ 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.



315

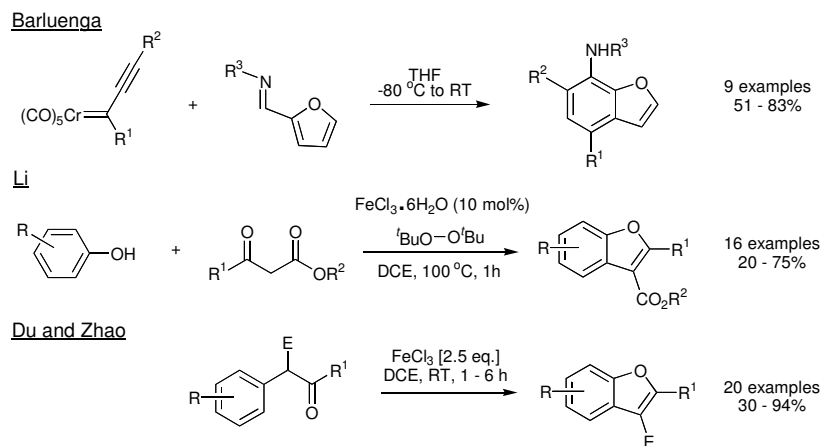
Scheme 29

A catalytic asymmetric electrocycloisatation for the generation of indolines has been developed and relies upon the use of the cinchona-derived ammonium salt shown in Scheme 30.⁵⁸ Indolines are also available from a palladium-catalysed C–H amination using 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.⁵⁹



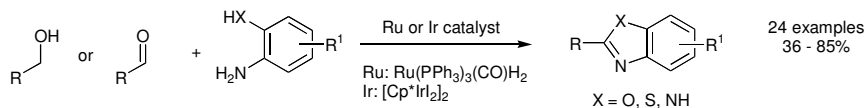
Scheme 30

New approaches to benzofurans are summarised in Scheme 31. Barluenga's group⁶⁰ showed that a non-heteroatom stabilised carbene complex underwent regioselective [3+3] benzannulation in the presence of 2-imino furans. Li's group⁶¹ 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 Zhao⁶² used an Fe-mediated intramolecular cyclisation of electron-rich α -aryl ketones in which direct oxidative aromatic C–O bond formation occurs.



Scheme 31

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.⁶³

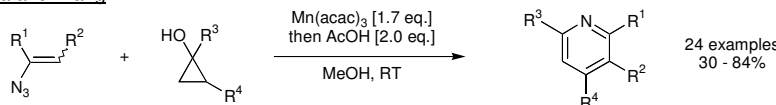


Scheme 32

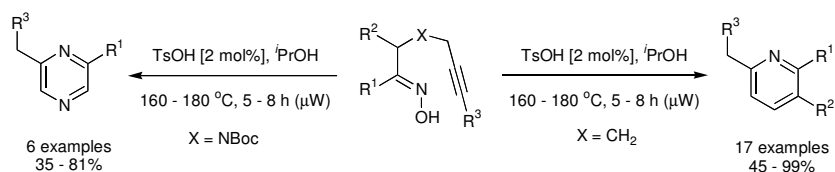
Six-membered rings

345 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.⁶⁴ Beauchemin and colleagues⁶⁵ 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 33.⁶⁵ Banerjee and Sereda used silica nanoparticles under mild, near neutral conditions to catalyse the formation of pyridines from aldehydes, malononitrile and thiols.⁶⁶

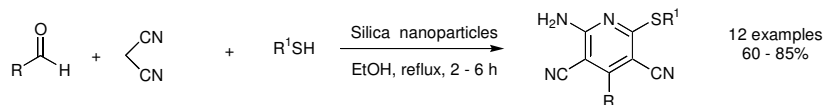
Chiba and Wang



Beauchemin

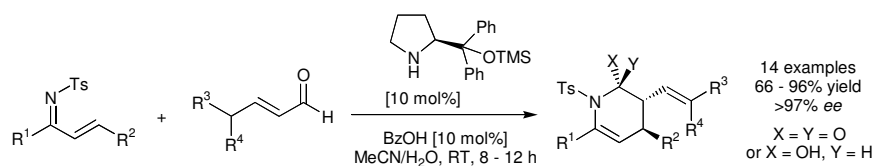


Banerjee and Sereda



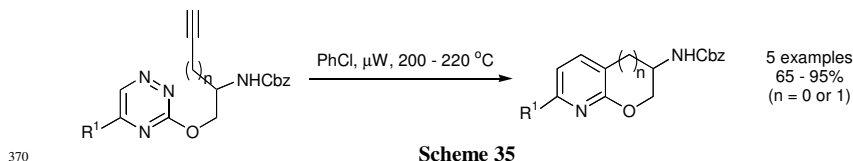
Scheme 33

360 Chen and colleagues (Scheme 34) 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.⁶⁷

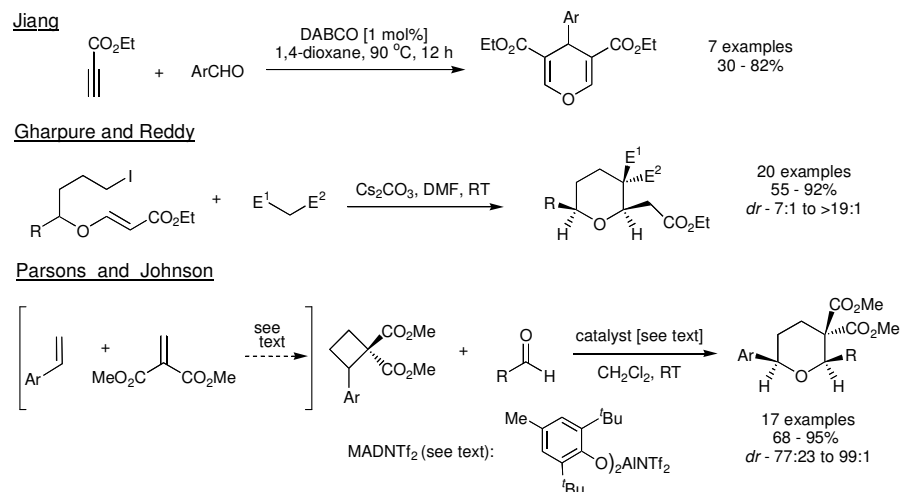


Scheme 34

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 azachomans and azabenzofurans, as shown in Scheme 35.⁶⁸



Advances in the synthesis of pyrans are shown in Scheme 36. Jiang⁶⁹ used a DABCO-induced [2+2+2]-cycloaddition cascade to synthesise 4-aryl-4*H*-pyrans from ethyl propiolate and aryl aldehydes. Gharpure and Reddy used a tandem S_N2 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 MADNTf₂ (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 methylenemalonate and a styrene in the presence of Sc(OTf)₃.⁷¹



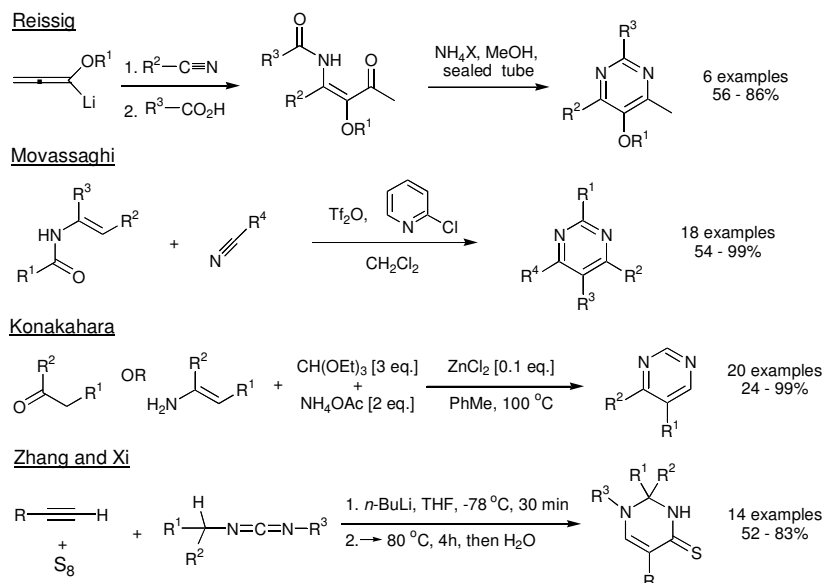
385

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 group⁷³ synthesised pyrimidines and quinazolines from the reaction of cyanic acid derivatives with *N*-vinyl or *N*-aryl amides in the presence of 2-chloropyridine and trifluoromethanesulfonic anhydride as electrophilic amide activators. Konakahara and colleagues⁷⁴ used a ZnCl₂-catalysed three-component coupling reaction in which

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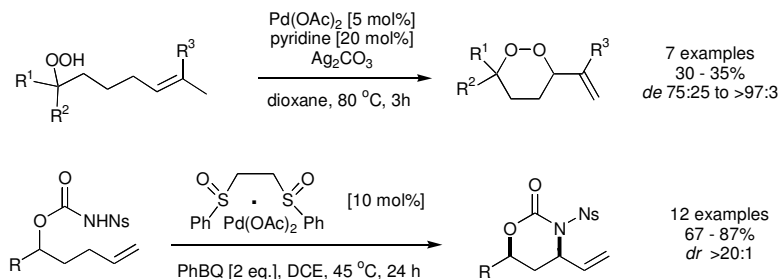
395

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
400 between terminal alkynes, elemental sulfur and carbodiimides gives an easy route through to 2,3-dihydropyrimidinthiones.⁷⁵



Scheme 37

Looking at other non-benzo-fused systems, a significant new synthesis of potentially
405 antimalarial 1,2-dioxanes through the Pd(II)-catalysed cyclisation of readily available unsaturated hydroperoxides has appeared (Scheme 38).⁷⁶ White and Rice (also Scheme 38) have developed a Pd(II)-sulfoxide-catalysed allylic C–H amination that allows the synthesis of *syn*-oxazinanones.⁷⁷ The products are valuable intermediates for the synthesis of *syn*-1,3-amino alcohols.

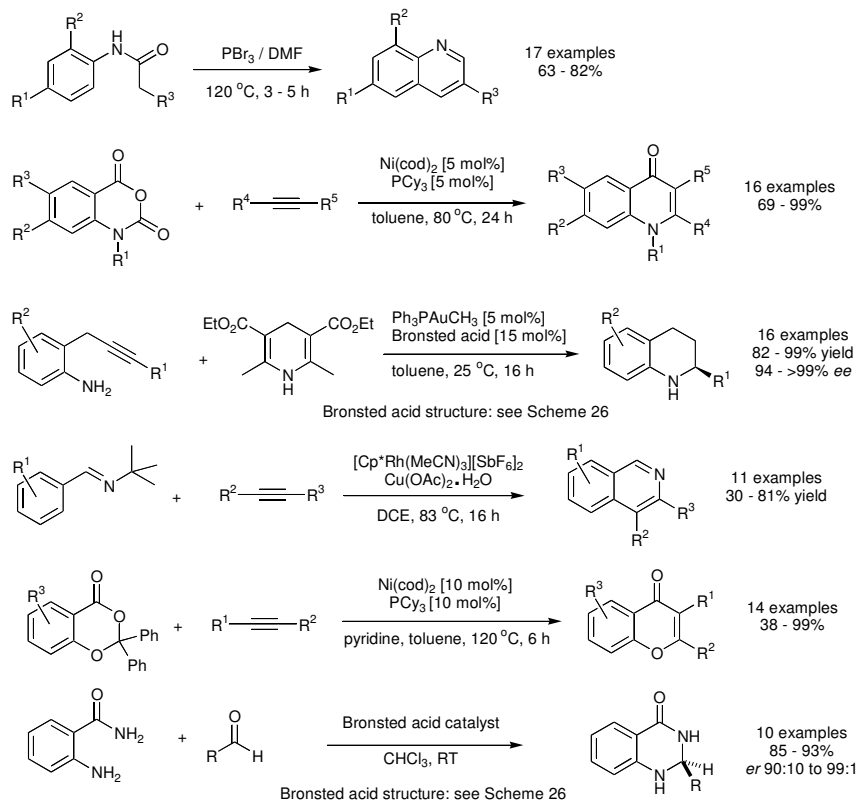


Ns - nosyl; PBQ - phenylbenzoquinone

Scheme 38

Approaches to benzo-fused six-membered heterocycles are shown in Scheme 39. Thus, Dong and Lin⁷⁸ have developed a Vilsmeier-Haack, cyclisation, aromatisation

approach to quinolines by reacting α -arylamino ketones with PBr_3 in DMF. A nickel-catalysed decarboxylative carboamination of alkynes using isatoic anhydrides was shown by Matsubara and Kurahashi to give quinolones.⁷⁹ 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.⁸⁰ Guimond and Fagnou used a Rh(III)-catalysed oxidative cross-coupling, cyclisation process to form isoquinolines in a regioselective manner from aldimines and alkynes. Rh species were shown to catalyse C–H bond-breaking and C–C and C–N bond-formation.⁸¹ Further work from Matsubara and Kurahashi⁸² 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.⁸³

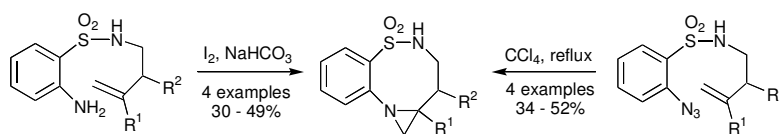


Scheme 39

Seven-membered rings and larger

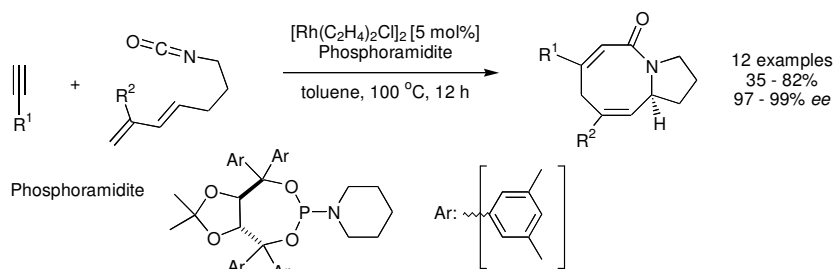
An unexpected benzothiadiazocine formation occurred when the amino alkenes shown in Scheme 40 were subjected to iodocyclisation conditions. The identical

products were obtained from the corresponding azides upon intramolecular 1,3-dipolar cycloaddition and nitrogen extrusion from the intermediate triazoline.⁸



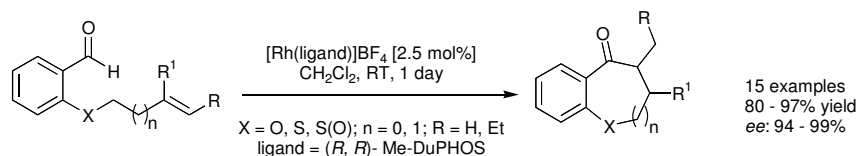
Scheme 40

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 41.⁸⁴



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).⁸⁵



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.

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