ORGANIC REACTION MECHANISMS

EDITOR
M. G. MOLONEY

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Preface

The present volume, the 55th in the series, surveys research reporting organic reaction mechanisms described in the available literature dated 2019. The general format for ORM 2019 follows the adjustments made for ORM 2018, and I remain grateful to all authors for their continued support and attention to detail, as well as for completing this work during the main global pandemic of 2020.

Interestingly, the challenges of the current pandemic have not directly affected the volume of scientific output relevant to organic reaction mechanisms; the size of this volume is in keeping with those of recent years. Perhaps in the following years, this may become leaner due to laboratory shutdown, which will therefore impact primary research output. It is interesting to see if this is eventually occurs.

M. G. Moloney

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Reactions of Aldehydes and Ketones and Their Derivatives

B. A. Murray

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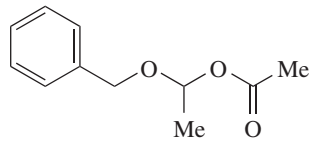
CHAPTER MENU

Organic Reaction Mechanisms 2019, First Edition. Edited by M. G. Moloney.

Formation and Reactions of Acetals and Related Species

A hemiacylal-type species (**1**, from Ph—CH_2—O—CHMe—CO_2H) was formed in a study of photocatalytic decarboxylative acetoxylation of aliphatic carboxylic acids, employing copper(II) catalysis and a hindered acridinium cation in a single electron transfer (SET) process.[1]



(**1**)

Some preliminary results in trithioester exchange with thiols, and in metathesis between trithioesters, have been described. The reactions are discussed in terms of their potential, as tools for dynamic covalent chemistry.[2] Acetal metathesis is also described, particularly in the context of making polyacetals via acetal metathesis polymerization (AMP).[3]

C-Alkynyl-*N*-Boc *N,O*-acetals, R^1—C≡C—CCH(OR^2)NHBoc, have been reacted with oxonium ylides (generated *in situ* from *α*−diazoketones) to give polyfunctional propargyl-amines. A rhodium(III)/chiral Bronsted acid catalyst system gives high yields/*de*s/*ee*s.[4] (ee) (de)

Reactions of Glucosides

A short tutorial/review (55 references) describes advances in stereo- and regio-selective glycosylation with protection-less sugar derivatives.[5] A review (38 references) describes the development of glucose transport inhibitors, which are potentially useful for selective attack on cancer cells (due to their altered metabolism and enhanced glucose demand), and other medical conditions.[6] Synthetic strategies for regio- and stereo-selective fluorinations of sugars have been reviewed (73 references), focusing on reaction mechanisms and biological applications.[7] (de)

The possibility of inosine tautomerism in water has been investigated by computation, including an exploration of relevant conformational space, inosine-water clusters, hydrogen bonding, and comparisons with the gas phase. The 6-enol tautomer appears to be accessible via an asynchronous concerted route.[8]

An unusual 1,5- or 1,6-alkyl transposition has been reported along with acetalization of 3-deoxy glycals, using TMSOTf as Lewis acid. Although the mechanism has not yet been pinned down, the transformation opens up routes to 2-*C*-branched bicyclic acetals of various deoxy-sugars, and to 2-*C*-branched levoglycosans.[9]

In a total synthesis of saffloneoside, an unusual *para*-hydroxycinnamylcyclopentenone *C*-glucoside, a stereospecific acyloin contraction was found to be controlled by the glucose moiety.[10]

A glycosyl fluoride has been activated for glycosylation using indium(III) triflate. This mild, nontoxic catalyst allows the process to occur under ambient conditions, stereoselectively, without pre-activation or additives, and with simple workup.[11] (de)

Unprotected mono- and di-saccharidic carboxamides undergo transamidations with primary and secondary arylic, heterocyclic, and aliphatic amines without solvent or catalyst, producing only ammonia as by-product. A known epimerization at the α−position is a limitation of the method.[12] (ee)

A new route to trifluorinated glucopyranose analogues has been developed, starting from inexpensive levoglucosan and using a Chiron approach. The dominant conformation was established for each. Lipophilicities were then measured, using ^{19}F-NMR spectroscopy to determine log *P*: significant variations were seen, with four isomers varying between −0.64 and −0.18.[13] (de)

β−D-Glycosaminosides have been prepared via a 2,4-nitrobenzenesulfonamide-directed S_N2-type displacement with good stereoselectivity. Examples from the gluco- and galacto-series are reported.[14]

Novel triazole-fused iminocyclitol-δ−lactams have been prepared and tested as glycosidase inhibitors.[15]

Pyrolysis of holocellulose produces carboxylic acids and alcohols. Acetic acid and glycerol were selected as representative compounds in a DFT study of secondary reactions arising from such species during pyrolysis. Glycerol can produce vinyl alcohol, acrolein, acetaldehyde, and acetol by various paths, and can also catalyse reactions of acetic acid.[16]

Such pyrolysis also allows isomerizations between isomers of monosaccharides to occur, and a computational study of the rates and equilibria of such processes indicates that barriers are significantly lowered if a hydroxy group within the monosaccharide participates, or an external R−OH group, including that of water. The equilibrium constants calculated indicate that higher temperatures favour furanoses, and also linear aldehyde forms.[17]

Stereoselectivity in glycosylation with deoxofluorinated glucos- and galactos-azide thiodonors has been investigated by low-temperature NMR for the case of the Tf_2O/Ph_2SO promoter system, with the formation of covalent α−triflate and both anomers of oxosulfonium triflate being observed. The selectivity depends on the configuration of the glycosyl donor and on the reactivity of the acceptor: reactive ones favour 1,2-*trans*-β−glycosides for both D-gluco and D-galacto donors, while poorer acceptors favoured 1,2-*cis*-α−glycosides with D-galacto donors (but were unselective with D-gluco donors).[18] (de)

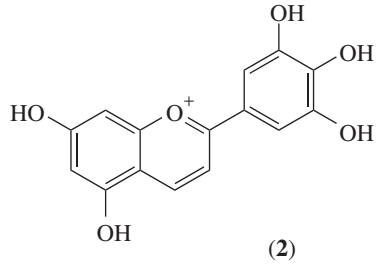
4-*O*-Glycosylated 2-pyrones have been synthesized by a gold(I)-catalysed intermolecular rearrangement of glycosyl alkynoic β−ketoesters.[19]

A pyrrolidine salt converts 2-deoxyribofuranoses to 2-deoxyribofuranosides via a furanosyl oxocarbenium ion, trapped with various alcohols: α−selectivity varies from complete to non-existent, and the reasons are discussed. An unexpected β−selectivity in the case of 2-cyanoethanol is explained in terms of a nitrile effect.[20] (de)

C-Glycosides have been prepared by a carbonylative Negishi-type coupling of 2-iodoglycals and alkyl or aryl halides, using catalysis by palladium and base.[21]

Cascade aldol reactions of aldopentoses with methyl ketones have been studied by QM simulation, using both L- and D-proline as catalysts, and identifying matched and mismatched cases. The mechanism identified includes Mannich, proline hydrolysis, retro aza-Michael, and oxa-Michael steps.[22]

A range of anthocyanidins (e.g. **2**) and anthocyanins (glycosides of anthocyanidins) have been prepared and tested as inhibitors of α−glucosidase. Some proved quite potent: (**2**) exhibits IC_{50} = 14.4 μM, holding out potential application for diabetes. Fluorescence quenching and *in silico* studies have been used to characterize the binding.[23]



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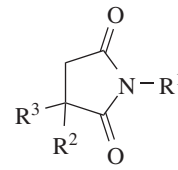


(**3**)

Similar studies have been undertaken for compounds isolated from the bark of *Quercus coccifera*, a folk medicine used to treat diabetes and other conditions. Several are inhibitors of α−glucosidase, and also of tyrosinase.[24]

Another antidiabetic study examined the inhibition of three different α−glucosidases by furofuran lignans: these molecules possess one or two catechol (*ortho*-dihydroxybenzene) moieties.[25]

Gold(III)-catalysed glycosylation has been effected using phenylpropiolate glycosides: the method benefits from phenylpropiolic acid (Ph—C≡C—CO_2H) being an easily separable and reusable leaving group, the reagents are stable and the conditions mild, and good anomeric selectivity was found for mannosyl and rhamnosyl donors.[26]

The significant reactivity difference between hexoses and *N*-acetylhexosamines under the conditions of MS collision-induced dissociation (CID) has been studied by experiment and computation.[27]

Reactions of Ketenes and Related Cumulenes

The reaction of ketene with hydroxyl radical is of growing interest, partly because of its implication in combustion of fuels. A computational study has estimated rate coefficients and their dependence on temperature and pressure: formation of CH_2OH and CO by OH addition to the olefinic carbon is the dominant process under all conditions.[28]

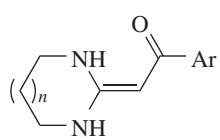
Inline reaction monitoring of the acetylation of benzyl alcohol was conducted using a microfluidic stripline NMR experiment, and—in the case of catalysis by tertiary amines—shows ketene as an intermediate.[29]

The formation of ketene from acetic acid as catalysed by $LaMnO_3$ has been studied for strontium-substituted catalysts, $La_{1-x}Sr_xMnO_3$: Sr substitution accelerates the reaction, apparently by increasing surface oxygen vacancies.[30]

β−Ketothioesters have been prepared by acid-catalysed hydrolysis of ketene *N,S*-acetals with an amine as the leaving group.[31]

Succinimides with *N*- and *C*-substitution (**3**, R^2 typically α−keto) have been prepared by reaction of ketene *N,S*-acetals with glyoxal (ethanedial, as a 40% aqueous solution).[32]

Heterocyclic ketene aminals (**4**, n = 1, 2) undergo a tandem cycloaddition/auto-oxidation with diazo-esters in air to give epoxypyrrolidines in up to 98% *ee*.[33]



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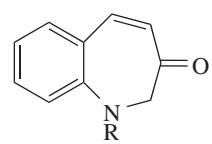

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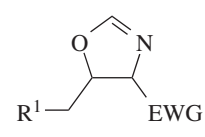


(**6**)

A new metal-free synthesis of benzazepinones (**5**) involves an intramolecular cyclization involving ketene iminium intermediates, starting from an *ortho*-vinyl-anilino-amide. The factors that favour the reaction over a competing formation of a cyclobutaniminium salt were also explored.[34]

α−Chiral esters have been prepared by a photocatalysed Wolff rearrangement of *α*−diazoketones in up to 95% *ee*, with additional catalysis by a chiral benzotetramisole.[35] (ee)

A 3 + 2 cyclization of siloxyalkynes, R^1—C≡C—$OSiR^2_3$, with suitably substituted isocyanides, EWG—CH_2—N^+≡$C:^-$, yields oxazoles (**6**) in good yield, with the siloxyalkyne supplying the C—O unit for ring formation: it is more typically a C≡C contributor. Promoted by tetrabutylammonium fluoride, a ketene intermediate is proposed. However, while fluoride promotes displacement of silicon to yield an ynolate anion, it is not essential that it is stoichiometric: tetrabutylammonium hydroxide can serve as a catalyst for a later step.[36]

A dichloroketene 2 + 2 cycloaddition has been employed in a synthesis of the natural product, Haouamine A.[37]

A scandium phosphonioketene complex has been reported and characterized.[38]

Formation and Reactions of Nitrogen Derivatives

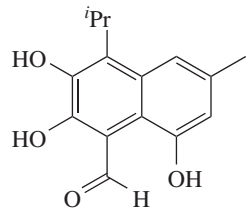
Imines: Synthesis, and General and Iminium Chemistry

A short review (18 references) describes NHC-catalysed umpolung reactions of imines and their role in achieving enantioselectivity.[39] (ee)

The use of benzophenone Schiff bases of glycine derivatives as versatile starting materials for synthesizing amino acids and their derivatives under phase-transfer conditions has been reviewed (115 references). The related use of aldimine derivatives of monosubstituted amino acid esters is also covered.[40] (ee) (de)

DFT has been used to probe the origin of the chemo- and stereo-selectivities of the addition of saturated esters to iminium ions, as catalysed by isothioureas.[41] (ee)

Hemigossypol (**7**) and gossypol (a related 'dimer' diad) are natural products of medicinal interest, as are Schiff bases derived from them. Several of the latter are the subject of a DFT study of their tautomers: for bis-Schiff bases of gossypol, this includes imine-imine, enamine-enamine, and imine-enamine forms.[42]



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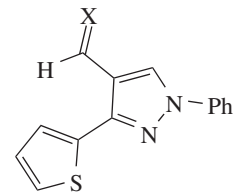

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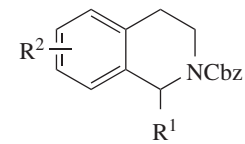


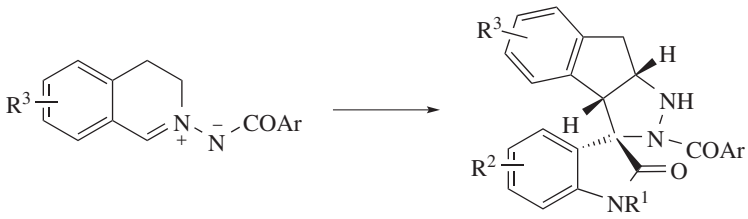
(**9**)

N-Hydroxyanilines (Ar-NHOH) react with diazo compounds ($R^1R^2C{=}N_2$) to give imines, $R^1R^2C{=}N$—Ar, via a 'rebound hydrolysis' mechanism.[43]

As part of a route to produce (thiophenyl)pyrazolyl-*β*−lactams, 2-acetylthiophene has been condensed with phenylhydrazine ($PhNHNH_2$) to give the corresponding hydrazone, 2-thiophenyl-CMe=N—NHPh, which—on reaction with phosphorus oxychloride/DMF—gives 1-phenyl-3-(1′-thiophen-2′-yl)-1*H*-pyrazole-4-carbaldehyde (**8**, X = O). Subsequent treatment with amines, RNH_2, gives a series of corresponding imines (**8**, X = N–R), which can easily be converted to *β*−lactams by cyclization with a suitable ethanoyl chloride.[44]

Protected tetrahydroquinolines (**9**, R^1 = H) react in a transition-metal-free oxidative cross-coupling with triorganoindiums, $(R^1)_3In$, to give 1-substituted products [R^1 = (hetero)aryl, alkyl, and alkynyl]; iminium ion intermediates are implicated, with a ^{1}H-NMR signal being observed at 9.5 ppm for the **H**–C=N^+–Cbz moiety, generated from the starter (**9**) using trityl tetrafluoroborate, Ph_3CBF_4.[45]

C,N-Cyclic azomethine imines (**10**) undergo a (3+1) annulation/rearrangement cascade with 3-chloro-oxindoles to give hexahydro-indeno[2,1-*c*]pyrazole spiro-oxindoles (**11**). Modest *des* were obtained, but racemization was observed over time, possibly due to the process being reversible.[46] (*ee*) (*de*)

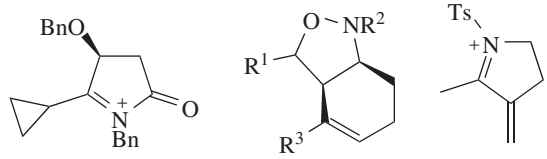


(**10**) (**11**)

The reaction of an *α*−cyclopropyl *N*-acyliminium ion (**12**), derived from the hemiaminal, with indoles can involve 1,2-addition or homoconjugate addition. A synthetic and DFT study has probed the factors involved, finding the 1,2-addition to be kinetically controlled: destabilizing the 1,2-adduct makes its formation reversible and allows the thermodynamically preferred homoconjugate addition to predominate. Other electron-rich arenes were also tested.[47] (*de*)

An intramolecular iminium cyclization features simultaneous generation of planar, central, and axial chiralities on a ferrocene backbone, as confirmed by NOESY, variable-temperature NMR, and X-ray diffraction.[48] (*ee*) (*de*)

Bicyclic isoxazolidines (**13**) have been accessed in good *de* and up to 99% yield via 3 + 2 cycloaddition of oxaziridines and cyclic allylic alcohols, apparently via a carbonyl imine intermediate [R^2—N^-—$^+$O=CH—R^1] derived from the oxaziridine, and an allyl cation.[49] (*de*)



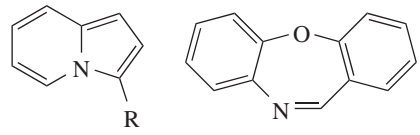
(**12**) (**13**) (**14**)

To improve our understanding of rhodium-organic cooperative catalysis, DFT has been used to estimate Rh—C bond dissociation enthalpies of (iminoacyl)rhodium(III)hydride and (iminoacyl)rhodium(III)alkyl.[50]

Novel-five-membered *N*-tosyl cyclic *α,β*−unsaturated iminium ions (**14**) have been generated from stable precursors, and applied in iminium Diels–Alder cycloadditions, Mukaiyama–Michael reactions, and intramolecular cyclizations.[51] (*de*)

Mannich and Mannich-type Reactions

A new and unusual route to indolizines (**15**) reacts 2-mercaptopyridine with a nitroallylic acetate in the presence of base, via a domino S_N2/Michael addition sequence followed by removal of the sulfur moiety.[52]



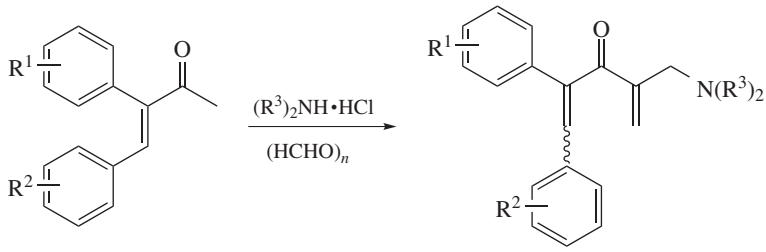
(**15**) (**16**)

An organocatalytic asymmetric Mannich addition of 3-fluoro-oxindoles to dibenzo[*b,f*][1,4] oxazepines (**16**) allows a highly enantioselective synthesis of quaternary C–F stereocentres. (*ee*) Using a bifunctional thiourea catalyst derived from a *Cinchona* alkaloid, yields/*ee*/*de* of up to 88/99/95% were obtained.[53] (*de*)

An investigation of labile imino-substituted ethano Tröger bases has identified a reversible Mannich reaction as the cause of the racemization.[54] (*ee*)

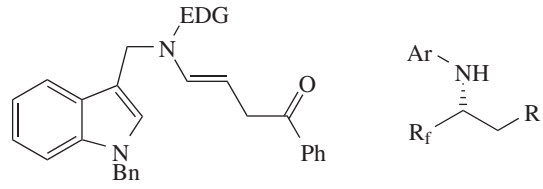
A Mannich reaction between an *O*-triethylsilylated hemiaminal, $Et_3SiOCH_2NMe_2$, and a substituted aniline can generate a wide variety of diamine, triamine, imine, or 1,3,5-triazine products, depending on the nature of the aniline's substituent(s).[55]

Enone (**17**) has been converted to a *β*–amino diaryldienone (**18**) by reaction with a secondary amine and paraformaldehyde, via a double Mannich/*β*–elimination sequence.[56]



(**17**) (**18**)

Spiro-indolenines, acting as *ω*–indol-3-yl *α,β*–unsaturated ketones (**19**), have been (*ee*) employed for enantio- and diastereo-selective synthesis of 3-(indolyl)-pyrrolidines via a Michael/retro-Mannich/Mannich sequence, employing a BINOL-derived chiral phosphoric acid (CPA).[57] (*de*)



(**19**) (**20**)

Such CPAs are often buttressed and electronically modified with 3,3′-substituents. The structural space around such catalysts and the effect of such substituents on the CPA's Bronsted acid catalysis have been investigated by NMR and DFT studies for the case of CPA/imine complexes.[58]

Stereoselective Hydrogenation of Imines, and Other Reductive Processes

Chiral *β*–fluoroalkyl *β*–amino acid derivatives (**20**, $R_f = CF_3$ or CF_2H, R = ester or amide) have been prepared in excellent *ee* from the corresponding enamines (which may tautomerize

to the imines), using palladium(II) catalysis with chiral ligands. Deuterium labelling and NMR experiments support the route via the imine tautomer.[59] (ee)

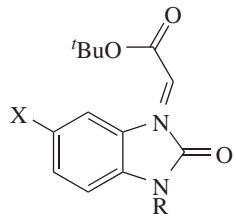
Aryl imines, activated with *N*-diphenylphosphinoyl (or *N*-tosyl) groups, have been enantioselectively hydrogenated using an unsymmetrical iron(II)–P–NH–P′ catalyst, with DFT calculations suggesting that the NH of the catalyst plays a key role: it activates and orients the imine towards hydride attack by hydrogen bonding to the PO (or SO) group on the imine nitrogen, rather than to the imine nitrogen itself.[60] (ee)

A DFT investigation of the reduction of quinoline by the Hantzsch ester with iodoimidazolinium catalysis seeks to tease out contributions of halogen bond catalysis versus Bronsted acid catalysis, noting the complication that such a catalyst can itself be reduced by the Hantzsch ester, generating a Bronsted acid as a by-product![61]

n-Butyllithium catalyses hydroboration of aldimines with HBpin (pinacolborane) at ambient temperature, a method which also works for hydroboration of alkynes (with *trans*-selectivity), though there is a high selectivity for the imine function over the alkyne. For the imine product, treatment with silica at 50 °C removes boron to give free secondary amine.[62]

Cyclizations of Imines

Enantioselective copper(II)-BOX-catalysed spiroannulation of *N*-Boc-imino-oxindoles (**21**) with allylsilanes shows a nonlinear effect (NLE): the significantly positive effect observed has been explained in terms of a heterochiral ML_2 species detected by ESR.[63] (ee) (de)



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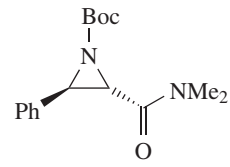
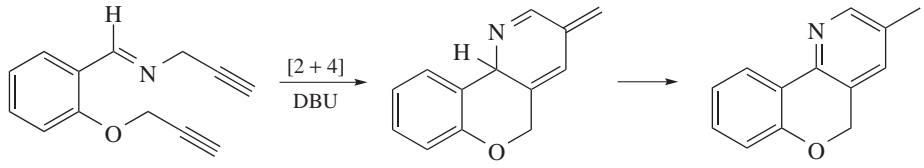


(**22**)

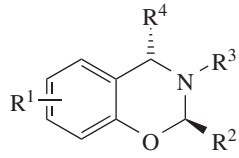
A computational study has probed the mechanism of the mild, caesium carbonate-catalysed reaction of a simple *N*-protected aldimine, Ph—CH=N—Boc, with a quaternary ammonium amide, $Me_3N^+–CH_2CONMe_2\ Br^–$, to give the *trans*-aziridine (**22**). The ammonium salt is deprotonated to the ylide, and this is then proposed to react with the imine to give a betaine-like intermediate, which subsequently loses trimethylamine.[64]

Pyridine-fused heterocycles have been prepared via a 6π-aza-electrocyclization of imino-alkyne derivatives. For example, *N,O*-dipropargylaldimine (**23**, prepared from the corresponding aldehyde and propargyl amine) undergoes a 2 + 4 cycloaddition (the 6π-aza-electrocyclization) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give tricycle (**24**), which aromatizes via a 1,5-hydrogen shift to chromenopyridine (**25**). If an *ortho*-hydroxy group is included in the imine, (benz)oxazepane derivatives can be prepared. Several other heterocycles are similarly described.[65]

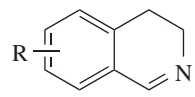


(**23**) (**24**) (**25**)

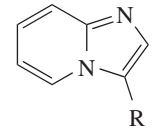
3,4-Dihydro-2*H*-1,3-benzoxazines (**26**) have been prepared via a one-pot, three-component cyclization of an *O*-Boc salicylaldehyde, an aldimine (R^2—CH=N—R^3), and a Grignard (R^4MgCl). An *ortho*-quinone methide intermediate has been implicated.[66] (*de*)



(**26**)



(**27**)

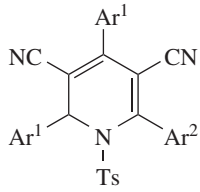


(**28**)

3,4-Dihydroquinolines (**27**) undergo aza-Navarov cyclizations with *α,β*−unsaturated acid chlorides to give *α*−methylene-*γ*−lactams as single diastereomers.[67] (*de*)

Imidazopyridines (**28**) have been prepared from formimidamide pyridinium salts (made from 2-aminopyridine starters) in a new alternative to classical *α*−haloketone chemistry.[68]

Arylcyanoacetylenes, Ar^1—C≡C—CN, undergo highly regioselective phosphine-catalysed 2 + 2 + 2 annulations with *N*-tosylaldimines, Ar^2—CH=N—Ts, to give 1,2-dihydropyridine-3,5-dicarbonitriles (**29**); the closely related '1,6'-isomer (**30**) was not observed.[69]



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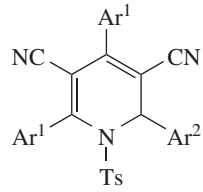
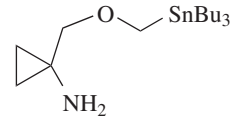
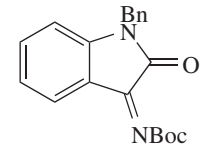


(**30**)



(**31**)



(**32**)

SnAP [tin (Sn) amine protocol) reactions involve an aminocyclopropane with pendant ether and tin atoms (**31**) undergoing imine formation with aldehydes (or ketones), followed by copper(II)-catalysed cyclization to give *N,O*-heterocycles. Detailed investigations tend to confirm the initial assignment of the cyclization mechanism as being radical-based.[70]

A diastereoselective aziridination of olefins via an organocatalytic nitrene transfer from [*N*-(*p*-toluenesulfonyl]imino]phenyliodinane (PhINTs) is catalysed by an iminium salt.[71] (*de*)

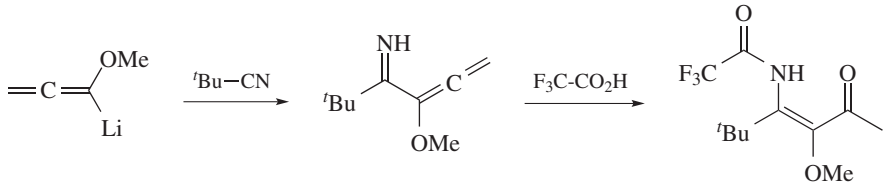
DFT has been used to probe the mechanism of an NHC-catalysed oxidative *α*−C(sp^3)-H activation of aliphatic aldehydes and subsequent cascade 2 + 2 cycloaddition with ketimines (e.g. **32**). In the example, the cycloaddition involves an azolium enolate intermediate reacting with the C=N bond of (**32**) rather than with the C=O bond.[72] (*de*)

Sulfamate-derived cyclic imines undergo phosphine-catalysed 3 + 2 cycloaddition with *β*−sulfonamido-substituted enones, to give imidazoline derivatives in high *de*.[73]

Cyclic enamides have been prepared in up to 99% *ee* via a chemo- and regio-selective catalytic umpolung cascade reaction of *α*−imino-amides with enals.[74]

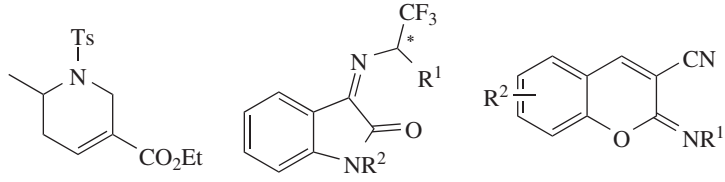
Other Reactions of Imines

A review deals with the development of a three-component reaction to yield highly substituted *β*−keto-enamides (**33**). Dubbed 'LANCA' after the components, it features a **l**ithiated methoxy**a**llene (**34**, 'LA') reacting with pivalo**n**itrile ('N') to give an intermediate allenyl-imine (**35**), which reacts with a **c**arboxylic **a**cid ('CA', TFA), under very mild conditions (−78 °C, then 0 °C → RT). The resulting *β*−keto-enamides (**33**) are very useful for making functionalized pyridines, pyrimidines, oxazoles, and quinoxalines.[75]



(**34**) (**35**) (**33**)

The mechanism of the tributylphosphine-catalysed 1,4-dipolar addition of an allene ester, $H_2C{=}C{=}CMe{-}CO_2Et$, and an imine, *trans*-Me—CH=N—Ts, to give a tetrahydropyridine (**36**) has been investigated at the M06-2X/6-311++G(d,p) level of theory.[76]



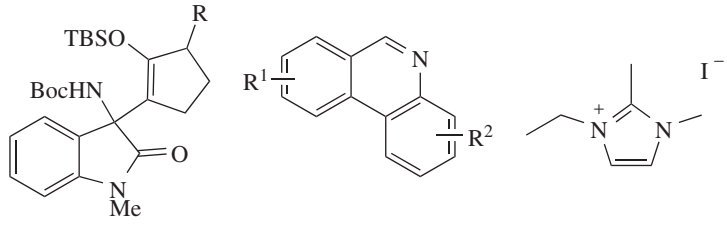
(**36**) (**37**) (**38**)

The first catalytic asymmetric alkenylation of isatin imines has been reported.[77] An *N*-trifluoroethyl imine derived from isatin (**37**, R^1 = H) reacts with cinnamyl methyl carbonate (Ph—CH=CH—CH_2—OCO_2Me) in a formal net *C*-alkenylation to give chiral imine derivatives (**37**, R^1 = CH_2—CH=CH—Ph) in high yield and *ee*. The iridium-catalysed reaction involves an umpolung allylation followed by a 2-aza-Cope rearrangement.[78]

An *ortho*-nitrosobenzaldimine intermediate is critical to a photochemical Davis–Beirut synthesis of *N*-aryl 2*H*-indazoles: previously generated under basic conditions, a new method uses a Bronsted acid catalyst.[79]

A one-pot Knoevenagel–Chan–Evans–Lam coupling of a salicylaldehyde with malononitrile (NC—CH_2—CN) in the presence of triethylamine produces, initially, an unsubstituted 2-imino-2*H*-chromene-3-carbonitrile (**38**, R^1 = H), which—on the addition of an arylboronic acid and copper(II)—converts to the *N*-aryl derivative (**38**, R^1 = Ar).[80]

A cyclic silyl enol ether undergoes an α−alkenyl addition to an isatin-derived *N*-Boc imine to give a protected amine retaining the silyl enol ether moiety (**39**). A silyl shift had been expected after the addition (to give the protected amine with pendant cyclopentanone, i.e. the Mukaiyama–Mannich product), but a proton shift intervened. Control experiments suggest that the Si- and H-shifts are in competition. Using a chiral zinc(II) catalyst, the tandem addition/shift process is rendered enantioselective. The product is easily converted to give a β−fluoroamine with two vicinal tetrasubstituted carbons.[81]



(**39**) (**40**) (**41**)

2-Aryl benzenesulfonimides, *ortho*-Ar^2—Ar^1—CH=N—SO_2—Ph, undergo a mild tandem annulation/aromatization to yield 6*H*-phenanthridines (**40**) in a process catalysed by copper(0) and Selectfluor.[82]

2-Cyano-*N*-benzylidene-imine has been reacted with a thiol in the presence of *Cinchona*-based alkaloids to desymmetrize it; a dynamic kinetic resolution is achieved via an organocatalytic heterocyclization. Mechanistic investigations clearly show how hydrogen bonding effects can explain the enantioselectivity, and the route provides an enantiopure tertiary isoindolinone *N,S*-acetal for the first time.[83] (*ee*)

A polarity-reversed addition of enol ethers to glyoxalate aldimines in the presence of TMS-azide yields γ−azido amino acids. The redox-neutral, metal-free process is activated by visible light, and likely involves an oxyalkyl radical intermediate.[84]

Michael addition of 2-chloromalonate esters to conjugated imines gives chiral α,β−dehydro-α−aminoesters enantioselectively. The configuration of the double bond in these enamines can be chosen by the catalyst, and in particular, its metal: $La(OTf)_3$ gives *Z*-, while $Ca(OTf)_2$ gives *E*-.[85] (*ee*) (*de*)

A DFT study has examined the imine-type intermediates implicated in the addition of organometallics to nitriles.[86]

A catalytic asymmetric synthesis of γ−lactams has been developed, using cycloaddition between enolizable anhydrides (such as succinic anhydride) and imines, with a simple bisurea catalyst. A DFT-generated model shows how the enolate and iminium components are likely to bind.[87] (*ee*) (*de*)

Intramolecular cyclization of iminyl radicals has been investigated by QM and a numerical simulation for evidence of a neophyl-like (ring contraction) rearrangement.[88]

Chiral oxazaborolidinium ions catalyse enantioselective Strecker and allylation reactions of *N*-aryl aldimines in yields/*ee* up to 98/99%, allowing access to α-aminonitriles and homoallylic amines.[89]

A magnesium-aluminium hydroxide acts as a heterogeneous catalyst for preparation of azetidine-2-ones from aldimines as acid chlorides in a greener approach to this reaction. However, an unexpected C—N cleavage of the azetidine-2-ones was detected in some cases, giving an enamide. The catalyst was characterized by N_2-adsorption/desorption, X-ray diffraction, SEM, and high-resolution transmission electron microscopy (HR-TEM).[90] (*ee*)

Rhodium(III) catalyses formation of 3-amino-4-arylisoquinolinones from 4-diazo-isochroman-3-imines and *N*-methoxybenzamides.[91]

The bicyclic amidines, DBU and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), undergo ring-opening reactions with benzaldehydes, to yield the corresponding benzaldimines with a γ−pendant lactam, using 1,2-dimethyl-3-ethylimidazolium iodide (**41**) as catalyst, an 'NHO' species (*N*-heterocyclic olefin).[92]

A fluorinated iminoyl chloride, Ar—N=C(CF_3)—Cl, acts as a four-atom building block, facilitating construction of benzazepines via 4 + 3 annulation with MBH (Morita–Baylis–Hillman) carbonates.[93]

DFT has been used to examine hydrogen bond bifunctional catalysis in the dipolar cycloaddition of azamethylene imines to nitroalkenes catalysed by Takemoto's catalyst, with a particular focus on activation by intramolecular hydrogen bonds and its effects on reactivity and enantioselectivity.[94] (*ee*)

Chiral cyclic ureas such as *trans*-2-imidazolinones have been prepared from a range of nitrones, Ph—N^+(—O^-)=CHR, and isocyano-acetate esters in good yields, fair *de*, and up to 99% *ee*, using as catalysts a chiral bifunctional Bronsted acid and Ag^+ as a Lewis base.[95] (*ee*) (*de*)

Carbodiimides, RN=C=NR, have been monohydroborated with pinacol borane (HBpin), using commercial 9-borabicyclo[3.3.1]nonane dimer (H-BBN dimer) as a metal-free catalyst.

Based on studies of stoichiometry and kinetics, and DFT calculations, a heterocyclic amidinate intermediate is proposed.[96]

Oximes, Oxime Ethers, and Oxime Esters

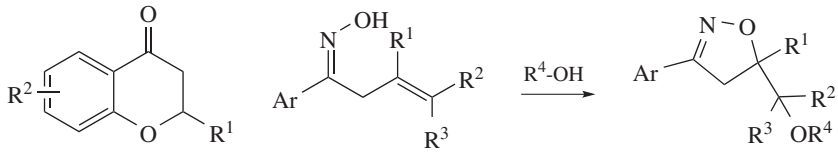
Hydrogen bonding effects in the Beckmann rearrangement of diphenyl-ketoxime on protonated amino-functional mesoporous silica have been studied in a range of solvents.[97]

In a new enamide synthesis, a simple oxime such as that of acetophenone is converted to its acetate ester (with acetic anhydride), and then reduced by $KI/Na_2S_2O_4$ with iron(II) catalysis to give the *N*-acetyl enamide, Ph—C(=CH)—NHAc, possibly via the intermediate radical, Ph—C(Me)=N$^{\bullet}$.[98]

The use of oximes and hydroxamic acids as α−nucleophile compounds which can act as catalytic scavengers of toxic organophosphates is described in an account which focuses in particular on *N*-methylpyridinium oximes (2-, 3-, and 4-isomers).[99]

α−Sulfonyl ketones, R^1—CO—CH_2—SO_2Tol, undergo α−methylsulfonylation by DMSO, to give the α,α−bis-derivatives, R^1—CO—CH(SO_2Me)—SO_2Tol. This substitution is achieved using hydroxylamine/HCl, i.e. an umpolung route via the oxime.[100]

Chromones (**42**, X = CH or N) have been prepared from *ortho*-bromoaryl ynones and benzaldoxime via sequential C—O bond formation. The oxime acts as a source of hydroxide, with this oxygen ending up in the ring, and 1,3-diketone intermediates are implicated.[101]

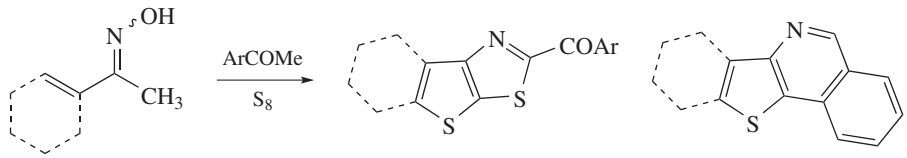


(**42**) (**43**) (**44**)

In a new green protocol for nitrile oxides, R—C≡N^+—O^-, they have been generated from aldoximes (RCH=NOH) using Oxone (potassium peroxymonosulfate) and sodium chloride to first form the hydroximoyl chloride [RC(Cl)=NOH]. Both of these species are isolable and observable by NMR, and a base (sodium carbonate) is required to perform the dehydrochlorination. To test the usefulness of the method, an alkene was added to allow 1,3-dipolar cycloaddition to give isoxazolines. Indeed, the whole protocol was successfully converted to a one-pot, three-component reaction by mixing aldehyde, hydroxylamine, and alkene, with addition of NaCl, Oxone, and Na_2CO_3 in acetonitrile for comparable yields.[102]

Allyloximes (**43**) undergo an alkoxy-oxygenation in a reaction promoted by iodosobenzene diacetate, Ph-I$(OAc)_2$, to give isoxazoline products (**44**).[103]

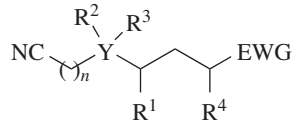
2-Aroylthienothiazoles (**46**) have been prepared via C—H/N—O bond functionalization of α,β−unsaturated ketoximes (**45**), using an acetophenone (or heterocyclic analogue) and octasulfur. Evidence for a radical process is presented, and for the intermediacy of 3-aminobenzothiophene (from the oxime and S_8) and of phenylglyoxal (ArCOCHO, from acetophenone forming a carbon radical, which gets oxidized).[104]



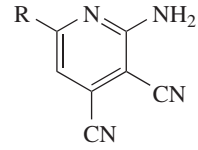
(**45**) (**46**) (**47**)

In a similar process, vinyl or aryl methylketoxime acetates participate in a three-component bis-heteroannulation with *ortho*-chloro or -bromobenzaldehydes and octasulfur to give thieno[3,2-*c*]isoquinolines or benzo[4,5]thieno[3,2-*c*]isoquinolines (**47**). The reaction is catalysed by copper(I) and requires lithium carbonate as base in DMSO at 140 °C.[105]

para-Methoxybenzyl cycloketoxime ethers (PMB oxime ethers) ring-open in reaction with electron-deficient terminal alkenes, $H_2C{=}CR^4$-EWG, to give nitriles (**48**, $n = 1, 2$; Y = C, O, N), via a radical C—C bond cleavage/addition cascade. The reaction is promoted by photogenerated iminyl radicals under metal-free conditions.[106]



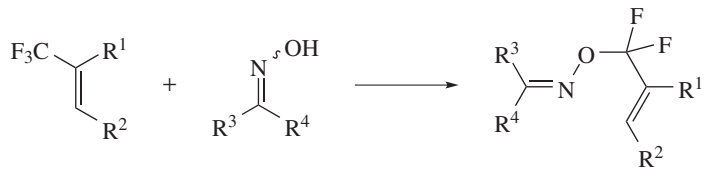
(**48**)



(**49**)

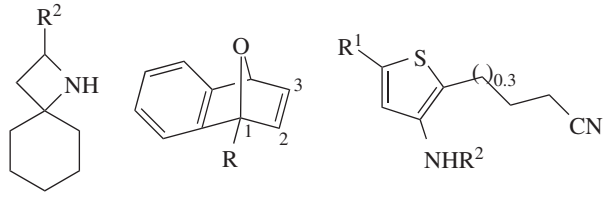
The 2-aminopyridine moiety features in many drugs and is also a starting point for many more elaborated heterocycles. A new synthesis cyclizes a simple ketoxime, R—CMe=NOH, with tetracyanoethene (TCNE) to yield 3,4-dicyano-substituted 2-aminopyridines (**49**) using copper(I) chloride as catalyst in toluene at 120 °C. A radical mechanism is proposed, and addition of TEMPO is found to completely kill the reaction.[107]

A defluorinative *ipso*-functionalization of (trifluoromethyl)alkenes (**50**) is reported, in which an oxime (**51**) reacts to give an *O*-(1,1-difluoroallyl) oxime ether (**52**) via a single C(sp^3)—F bond activation in a CF_3 group. The reaction is carried out in DMF with caesium carbonate as base, under nitrogen at 90 °C for 12 hours. The γ−selective product (i.e. reaction at the other end of the alkene) is not observed. Radical traps have no effect, but oxime ethers are unreactive, suggesting the need to deprotonate the oxime OH. Indeed, the mechanism is proposed to involve the conjugate base of the oxime reacting in an S_N2-like process with the CF_3 carbon.[108]



(**50**) (**51**) (**52**)

Spirocyclic *NH*-azetidines (e.g. 2-substituted-1-azaspiro[3.5]nonanes, **53**) have been synthesized from oxime ethers (in this case, from CyHx=NOR[1]) using a Grignard reagent, $R_2—CH_2—CH_2—MgBr$, and titanium(IV) mediation. A Kulinkovich-type reaction is proposed, with a titanacyclopropane intermediate acting as a 1,2-dianion equivalent which inserts into the 1,2-dielectrophilic oxime ether. An alternative route, using a terminal alkene instead of the Grignard, is also explored.[109]



(**53**) (**54**) (**55**)

C_1-Substituted unsymmetrical oxabenzonobornadienes (**54**) undergo ring-opening reactions with oximes to give either naphthols (if R is donating) or 1,2-dihydronaphthols (diastereoselectively), the latter arising from oxime addition at C(2), but the isomer arising from reaction at C(3) is not observed. Palladium(II)/Lewis acid co-catalysis is employed.[110] (de)

Aromatic ketoxime ethers, Ar—C(R)=N—OMe, undergo C—H amination in the *ortho*-position in rhodium(III)-catalysed reaction with benzenesulfonamides. Potassium acetate was found to be essential for the process.[111]

In another reaction of aromatic ketoxime ethers, Ar—C(Me)=N—OMe, a pendant ketone can be placed in the *ortho*-position via rhodium(III)-catalysed oxidative coupling with a cyclopropanol. DFT studies indicate that ring-opening of the cyclopropanol occurs first, followed by C—H activation, with an outer-sphere mechanism involving N→Rh binding to set up the oxime's directing role and concerted metallation–deprotonation.[112]

Samarium(II) iodide promotes reductive cleavage of the N—O bond in oxime ethers to produce an iminyl radical. If the oxime ether has an appropriately placed pendant bromine, intramolecular cyclization provides a five-membered cyclic imine.[113]

A photoredox benzyl activation involving C(sp^3)—C(sp^3) bond dissociation of 1-aryl acetone oxime esters, Ar—CHR—C(Me)=N—OPG, under irradiation by visible light has been developed: subsequent benzyl C—O and C—N formation via coupling with alcohols or amines yields useful ether and amine derivatives, Ar—CHR—X (X = O, N). Control experiments, electrochemical investigations, and *in situ* NMR spectroscopy have been used to probe the mechanistic manifold.[114]

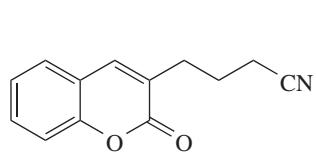
Amino-oxygenation of alkenes has been achieved using *O*-acylhydroxylamines, with catalysis by copper(II): the method can be applied to the use of oximes, carbonyls, thio-carboxylic acids, and alcohols as nucleophiles, which have broad functional group tolerance.[115]

Cycloketone oxime esters with ring sizes of 4–7 react in DMF at 70 °C with enaminothiones, R^1—C(=S)—CH=C(NHR^2)–SMe (*α*−thioxo ketene *N,S*-acetals), to give 2-cyanoalkyl-3-aminothiophenes (**55**). The copper(I)-catalysed process involves radical C—C bond cleavage and 4 + 1 annulation.[116]

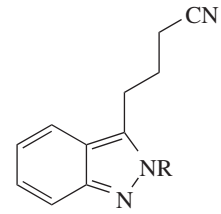
A similar C(sp^3)–N cross-coupling reaction of cyclobutanone oxime esters with anilines—again catalysed by copper(I)—yields 4-(arylamino)butanenitriles,[117] and *O*-Boc cyclobutane- and cyclopentane-ketoximes yield *ω*−trifluoromethyl nitriles on treatment with a $Zn(CF_3)_2$ complex.[118]

Cyclobutylketoxime aryl esters react with anilines in a SET-induced C(sp^3)–N coupling via a C—C bond cleavage catalysed by copper(II) triflate, with loss of the ester functionality, yielding an aniline with an *ω*−cyano function, Ar—NH—$(CH_2)_3$—CN. In some cases, the product's secondary aniline can react again. A radical pathway is indicated, and photoredox catalysis is also effective.[119] Another report describes a similar cyclobutylketoxime aryl ester substituting a cyanopropyl group on the 3-position of a coumarin (**56**), on carbon in (2*H*)-indazoles (**57**),[120] and also on carbon in quinoxal-2(1*H*)-ones (in this case, for an oxime *ether*, and with photocatalysis).[121]

Acetophenone *O*-acetyl oximes have been annulated via a redox-neutral *ortho*-C—H activation with allenoates to produce isoquinolines, using rhodium(III) catalysis.[122]

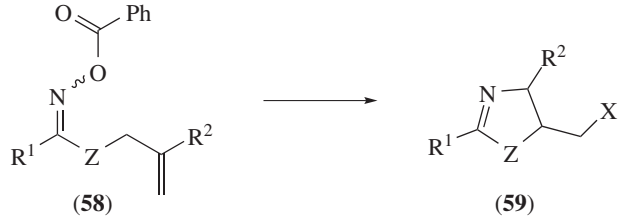


(**56**)



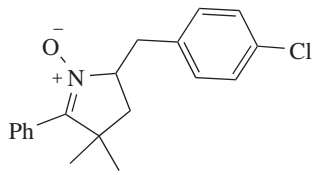
(**57**, R = Me, Ph)

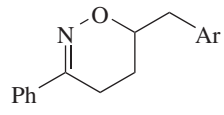
A copper-catalysed iminohalogenation of unactivated alkenes of γ,δ−unsaturated oxime esters (**58**, Z = CH_2, CMe_2, NR) was achieved using copper(I) and halide salts (KX), yielding functionalized 2-halomethyl pyrrolines (**59**, X = I, Br, or Cl). Iminyl radical intermediates are proposed.[123] The method has been extended to imino-sulfonylation, imino-cyanogenation, and imino-thiocyanation to give the corresponding pyrrolines.[124]

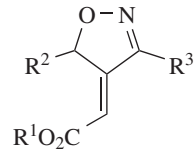


(**58**) (**59**)

The ester derivative is not essential for such processes: the simple γ,δ−unsaturated ketoxime, Ph—C(=NOH)—CR_2—CH_2—CH=CH_2, reacts with *para*-iodochlorobenzene to give in some cases a carbonitronylation product, the 5-membered cyclic nitrone (**60**, R = Me), or in other cases a carboetherification product, the 5,6-dihydro-4*H*-oxazine (**61**, R = H).[125]





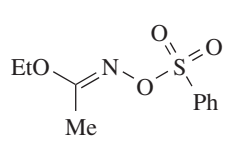


(**60**) (**61**) (**62**)

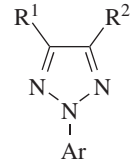
Oxime acetates undergo a copper(I)-catalysed 3 + 3 cycloaddition with fluorinated enones, *trans*-F_5C_2—CH=CH—COR, to yield 4-(pentafluoroethyl)pyridines in a mild, redox-neutral process. A copper(II)-enamine intermediate is proposed.[126]

O-Propargylic glyoxylate-derived oximes, *trans*-R^1O_2C—CH=N—O—CH(R^2)—C≡C—R^3, are cyclized and rearranged to give 2-isoxazolines (**62**), using gold(I) catalysis.[127]

An oxime reagent (**63**) brings about a remarkable one-pot deacetylative amination, converting acetophenones (Ar–Ac) and aliphatic methyl ketones (R–Ac) to primary amines (Ar–NH_2, R–NH_2). The domino transoximation/Beckmann rearrangement/Pinner process is catalysed by a Bronsted acid in methanol solvent. Ambient temperature works for the arenes, while the alkyl cases require reflux.[128]



(**63**)



(**64**)

Hydrazones and Related Species

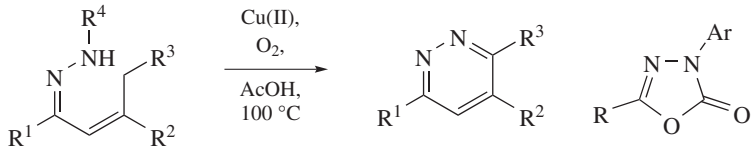
While exchange at hydrazones via transamination processes has been exploited in dynamic combinatorial chemistry, the fact that the optimal rate occurs at c. pH 4.5 limits their use for biological targets. A DFT study has been undertaken with a view to identifying suitable substitutions that could nudge this towards pH 7. One strategy identified is to place N- or O-hydrogen-bond acceptors on the 'carbonyl' side. The use of a benzodihydropyran substituent looks promising.[129]

Regioselective syntheses of 1,3-disubstituted and 1,3,4-trisubstituted pyrazoles have been reported, using copper(II)-catalysed cascade reactions of saturated ketones with hydrazines or aldehyde hydrazones. An enone intermediate is proposed to undergo 3 + 2 annulation.[130]

3,5-Substituted pyrazoles have been prepared from phenylethyne, hydrazine, and O_2 as oxidant, via a cascade of Glaser coupling and annulation. Promoted by visible light, the mechanism is proposed to include hydrogen atom abstraction and enamine-imine tautomerization.[131]

2-Aryl-1,2,3-triazoles (**64**) have been prepared from bis-hydrazones via intramolecular N—N bond formation.[132]

β,γ−Unsaturated hydrazones (**65**) undergo a copper(II)-catalysed aerobic 6-*endo-trig* cyclization to yield pyridazines (**66**). Changing the conditions to somewhat milder acetonitrile reflux gives the corresponding 1,6-dihydropyridazine, suggesting that the latter is an intermediate in the formation of the aromatic (**66**) in the acetic acid condition.[133]

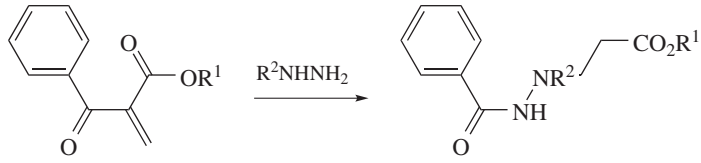


(**65**) (**66**) (**67**)

While *E*-oxime ether azatrienes are inert to 6*π*-electrocyclization (to give pyridine derivatives), their *Z*-isomers proved inert. Switching to the more geometrically labile hydrazones solved the problem.[134]

1,3,4-Oxadiazol-2(3*H*)-ones (**67**, R = alkyl or aryl) have been prepared from aldehydes (R–CHO), arylhydrazines, and carbon dioxide, in a reaction promoted by hypoiodite generated *in situ*. The first step is presumed to be formation of the hydrazone, which is then iodinated at carbon, followed by base-catalysed ring closure.[135]

N′-Alkyl benzohydrazides (**68**) have been obtained by a hydrazine insertion route via an unexpected C—C bond cleavage in benzoyl acrylates (**69**) under mild conditions: triethylamine in cold acetonitrile. Preliminary mechanistic investigation suggests a cyclic hemiaminal intermediate. The reaction works for both aromatic and aliphatic hydrazines.[136]

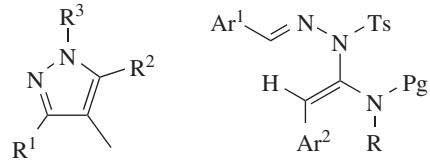


(**69**) (**68**)

Guanylhydrazones can exist as such (**70**), but the azine tautomeric form (**71**) is more stable. This affects reactions such as the I_2-induced tandem oxidative cyclocondensation to give a 1,2,4-triazole, where a shift from intra- to inter-molecular reaction can occur.[137]

(**70**) (**71**)

Borylated pyrazoles (**72**) have been prepared regioselectively by aminoboration of alkynylhydrazones, $R^2—C{\equiv}C—C(R^1){=}N—NHR^3$, with subsequent cyclization catalysed by copper(II) triflate. The products can be further functionalized by Suzuki coupling.[138]



(**72**) (**73**)

α−Amino alkenyl-substituted hydrazone derivatives (**73**) have been stereoselectively prepared from sulfonyl hydrazones, $Ar^1—CH{=}N—NHTs$, and ynamides, $Ar^2—C{\equiv}C—N(Me)—Ts$, with catalysis by silver triflate and potassium carbonate; a keteniminium intermediate is proposed.[139]

In the asymmetric aldol addition of chiral *N*-amino cyclic carbamate hydrazones, an experimental and computational study presents evidence for non-Curtin–Hammett behaviour, comparing the stereoselectivity at −78 °C with that at ambient temperature.[140] (*de*)

N-Acylsubstituted hydrazides with a bithiophene core have potential as excited-state intramolecular proton transfer (ESIPT) species and can exist in keto, enol, and double enol forms, with the keto-enol tautomerism being significantly affected by photo-excitation. A theoretical approach explores the potential for double proton transfer in such systems.[141]

C—C Bond Formation and Fission: Aldol and Related Reactions

Reviews of Aldols, and General Reviews of Asymmetric Catalysis

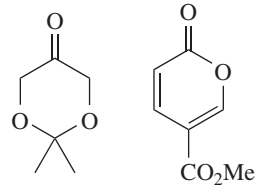
A review of asymmetric organocatalytic C—C bond-forming reactions with organoboron compounds (61 references) focuses on the range of mechanisms in operation, and covers additions to enones, aldehydes, ketones, imines, dienes, and related systems, as well as the various organoboron types, and the typical chiral organocatalysts employed.[142] (*ee*)

A critical review (107 references) focuses on enantioselective catalysed multicomponent reactions, and in particular on the need for sufficient knowledge of both the mechanism and non-covalent interactions if one wishes to design successfully in this field. Several salient examples (Biginelli, Ugi, Strecker) are dissected to emphasize these points.[143] (ee)

In an approach to the problem of synthesizing a disfavoured diastereomer, a polyfunctional catalyst has been designed in an attempt to mimic nature's high specificity. The particular example is the direct 1,4-addition of 1,3-dicarbonyls to *β*−substituted nitro-olefins, and a combined imidazolium aryloxide betaine/Lewis acid/copper(II) design is described and tested. Yields/*ee*s/*de*s of up to 99/98/99% were achieved.[144] (ee) (de)

The Asymmetric Aldol

Keto-acetal (**74**), a protected version of dihydroxyacetone, undergoes enantio- and diastereo-selective aldol reaction with *para*-nitrobenzaldehyde, using as catalysts chiral zinc(II) complexes that mimic a class II aldolase, carboxypeptidase A, and serine protease giving *ee*/*de* of up to 98/98%. ESI-HRMS and pH titrations have been used to characterize the catalysts and their action.[145] (ee) (de)



(**74**) (**75**) (**76**)

An intramolecular aldol has been developed for an unusual class of cyclopentanoids: *α*−substituted dienones tethered with ketones yield a variety of 3-hydroxy-3-dienyl-cyclopentanones fused to arenes or heteroarenes in the presence of tributylphosphine and water. The role of water was probed through deuterium and ^{18}O-labelling experiments.[146]

Porphyrin-catalysed regioselective carbonylation of 2,2-disubstituted epoxides gives *β,β*−disubstituted lactones, which—upon hydrolysis—yield ketone-based aldol products: the method provides an alternative to the Mukaiyama route.[147] (ee)

The Morita–Baylis–Hillman Reaction

A catalytic enantioselective transannular Morita–Baylis–Hilman (MBH) reaction has been reported, featuring bicyclic products, both carbo- and hetero-cyclic, via multifunctional phosphine catalysis.[148] (ee)

MBH carbonates undergo a palladium(0)-phosphine-catalysed reaction with allylic alcohols in a process which exhibits auto-tandem cooperative catalysis (ATCC), via an allylic alkylation and a cascade intramolecular Heck-type process.[149]

An MBH reaction of the bio-based feedstock, methyl coumalate (**75**), has been developed, triggered by a novel 1,6-conjugated addition.[150]

Other Aldol and Aldol-Type Reactions

The 'on water' mechanism of the heterogeneous catalytic aldol has been studied for the case of isatins reacting with acetophenones, to give 3-hydroxy-2-oxindoles, using polyetheramine as catalyst: the enamine mechanism operates, with interfacial hydrogen bonding identified via NMR titrations.[151]