ORGANIC REACTION MECHANISMS

EDITOR
M. G. MOLONEY

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Contributors

F. ALONSO	Instituto de Síntesis Orgánica and Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Alicante, Spain
K. K. BANERJI	Department of Chemistry, J.N.V. University, Jodhpur, India
C. T. BEDFORD	Department of Chemistry, University College London, London, UK
M. L. BIRSA	Faculty of Chemistry, "Al. I. Cuza" University of Iasi, Iasi, Romania
S. CHASSAING	Laboratoire de Synthèse, Réactivité Organique et Catalyse, Institut de Chimie, Université de Strasbourg, Strasbourg, France
J. M. COXON	Department of Chemistry, University of Canterbury, Christchurch, New Zealand
M. R. CRAMPTON	Department of Chemistry, University of Durham, Durham, UK
N. DENNIS	3 Camphorlaurel Crt, Stretton, Queensland, Australia
J. C. GONZALEZ-GOMEZ	Instituto de Síntesis Orgánica and Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Alicante, Alicante, Spain
E. GRAS	Laboratoire d'Hétérochimie Fondamentale et Appliquée, Université Toulouse III, Toulouse, France
P. KOČOVSKÝ	Department of Organic Chemistry, Charles University, Prague, Czech Republic *and* Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Prague, Czech Republic
J. G. MOLONEY	Department of Chemistry, University of Oxford, Oxford, UK
M. G. MOLONEY	Department of Chemistry, University of Oxford, Oxford, UK

V. M. MOREIRA Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, Glasgow, UK

and

Laboratory of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Coimbra, Portugal; Center for Neuroscience and Cell Biology, University of Coimbra, Portugal

B. A. MURRAY Department of Science, Technological University of Dublin (TU Dublin), Dublin, Ireland

A. F. PARSONS Department of Chemistry, University of York, York, UK

T. F. PARSONS School of Education and Lifelong Learning, University of East Anglia, Norwich, UK

G. W. WEAVER Department of Chemistry, Loughborough University, Loughborough, UK

Preface

The present volume, the 54th in the series, surveys research reporting organic reaction mechanisms described in the available literature dated 2018. The rapid increase in annual numbers of publications makes the compilation of *Organic Reaction Mechanisms* a challenge in which we seek to achieve comprehensive coverage, but in a defined page limit. While the general format for ORM 2018 is similar to that of recent volumes, I have taken the opportunity to make some adjustments in chapter arrangement and coverage. Firstly, given the amount of material relating to aromatic substitution (electrophilic and nucleophilic), these chapters have been separated, and I am delighted to welcome George Weaver to the author team who has contributed the former chapter, along with our long-standing contributor, Mike Crampton, who has done the latter. Secondly, given the importance ligand coupling processes now have in modern synthetic chemistry, along with their mechanistic variability, we have created a new chapter (Transition-metal Catalyzed Reactions) and I thank Jose Carlos Gonzalez-Gomez and Francisco Alonso for agreeing to take on this significant task. Finally, Radical Reactions are explicitly included as a new chapter and I am delighted that it has been authored by Andy Parsons, very well known in the area, and his son, Thomas. That father and son team is not the only one in this volume, and it is a great pleasure to me to be able to thank my own son, Jonathan, who worked on our own chapter; should any other authors wish to field a family author team in the future, I would be delighted since it would make ORM even more unique! I am also delighted to be able to welcome Vania Moreira to the ORM team, who has contributed the Carbocation chapter. While it is a pleasure to have new members in the ORM author team, it is fully appropriate to celebrate the long-standing service of the other authors, who quietly get on with what is proving to be an ever-expanding task, done under deadline constraints which seek to keep the publication timely, and I offer my thanks to them for their dedication and attention to detail.

M. G. Moloney

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1

Reactions of Aldehydes and Ketones and their Derivatives

B. A. Murray

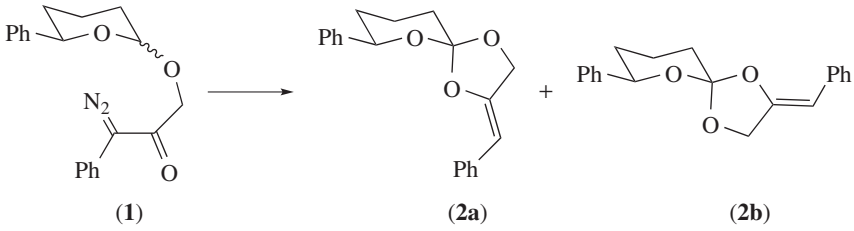
Department of Science, Technological University of Dublin (TU Dublin), Dublin, Ireland

CHAPTER MENU

Formation and Reactions of Acetals and Related Species

Tetrahydropyran acetals [(**1**), both *cis*- and *trans*-isomers] undergo rhodium(II)-catalyzed intramolecular C–H insertions of the proximal diazoketone to give spirocyclic orthoesters (**2a**/**2b**) (Scheme 1).[1] There are anomalous C−O bond-forming insertions, but no trace of the expected C−C product was observed. DFT has been used to explore the factors behind

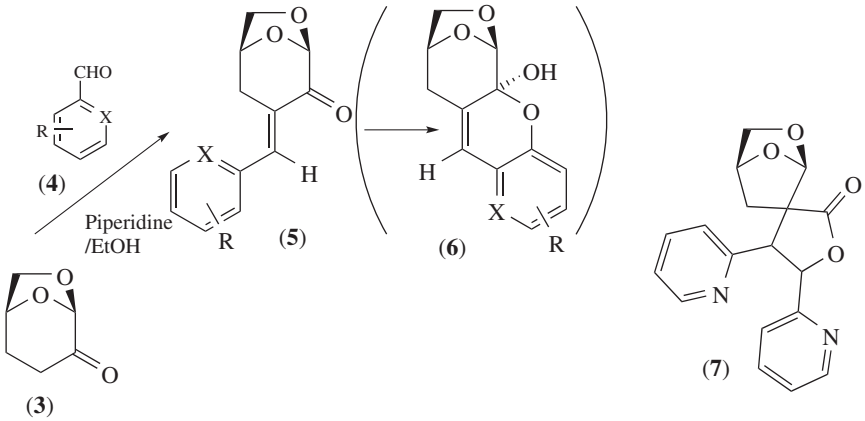
Organic Reaction Mechanisms 2018, First Edition. Edited by M. G. Moloney.



Scheme 1

this unusual selectivity, with C–O bond formation being calculated to be favoured by ca. 3 kcal mol^{-1}.

Dihydrolevoglucosenone [(**3**), cyrene] incorporates the 6,8-dioxabicyclo[3.2.1]octane structure found in several natural products. It undergoes highly diastereoselective aldol condensation with aromatic aldehydes [(**4**); X = CH, R = various 3/4/5-substituents or H] to give exocyclic enones (**5**). With an *ortho*-phenolic benzaldehyde [(**4**) with X = C–OH], further reaction gives a tetracyclic derivative (**6**) with adjacent cyclic acetal and cyclic hemiketal functionality, with the carbon being chiral in both cases. 2-Pyridinecarboxaldehyde [(**4**), X = N] undergoes many additional steps to exclusively give an unexpected spironolactone (**7**) bearing two pendant pyridines (Scheme 2). Mechanisms are discussed in all cases.[2]

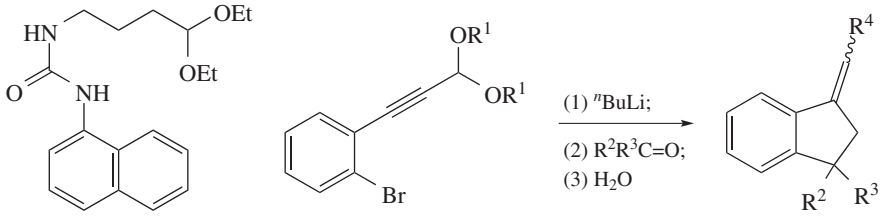


Scheme 2

A urea with a pendant acetal (**8**) has been reacted with nucleophilic aromatics to give a range of heterocyclic products. The acid-catalyzed reaction has a complex mechanistic manifold, with the nature of the product dependent on the nucleophilicity of the arene and the strength of the acid. Possible products included arylpyrrolidines, bispyrroles, or pyrrolidinequinazolines.[3]

Phthalane (1,3-dihydro-2-benzofuran) frequently occurs at the core of natural products and drugs. A range of 1-alkylidenephthalanes (**9**), some bearing additional functionality in substituent R^4, have been prepared from the corresponding *ortho*-bromophenyl-alkyne-acetal (**10**) (Scheme 3), with good deals of predominantly *(Z)*-(**9**).[4]

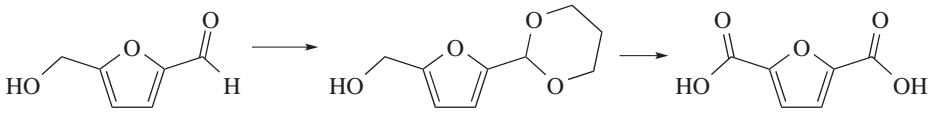
5-Hydroxyfurfural (**11**) is a potentially valuable biofeedstock, but its use is hampered by formation of solid humin by-product during its processing. Now conversion to a cyclic acetal [(**12**),



(**8**) (**10**) (**9**)

Scheme 3

using 1,3-propanediol] sets up a clean aerobic oxidation to give furan-2,5-dicarboxylic acid (**13**) in up to 95% yield, using a gold/CeO_2 catalyst in water at 140 °C/5 atm (Scheme 4). Kinetic studies and DFT calculations support partial hydrolysis of (**12**) and subsequent oxidative dehydrogenation of the *in situ*-generated hemiacetal.[5]



(**11**) (**12**) (**13**)

Scheme 4

The kinetics and mechanism of the formation of the diethyl acetal of furfural (furan-2-carboxaldehyde) have been studied with Ni-Al-layered double-hydroxide catalysts; the nitrate form was efficient via Lewis acid sites, while the carbonate form was not. Calculations probed the relative contribution of Lewis and Bronsted acid sites.[6]

Cs2.5, a heteropoly acid of formula $Cs_{2.5}H_{0.5}PW_{12}O_{40}$, catalyzes acetalization of glycerol with acetone and also with formaldehyde. For acetone, the five-membered cyclic product, solketal, was favoured 98:2 over the six-membered isomer.[7]

The reductive Hosomi–Sakurai reaction of acetals, $R^1–CH_2–CH(OR^2)_2$, with allylsilanes, $TMS–CH_2–C(R^3)=CH_2$, to give alcohols has been carried out as a chemo-, regio-, and diastereo-selective process. As an internal hydrogenation not requiring hydrogenolytic conditions, it is quite tolerant of functional groups. Key to the mechanism is a carbocation (formed by protonation of a homoallylic ether) undergoing a 1,5-hydride transfer. If this cation is sufficiently stabilized, the hydride transfer becomes rate-determining. Consistent with this suggestion, a series of aryl-substituted allylsilanes (R^3 = Ar) show evidence of such a mechanistic switch, as shown by an abrupt break in the Hammett plot of the *de*.[8] (*de*)

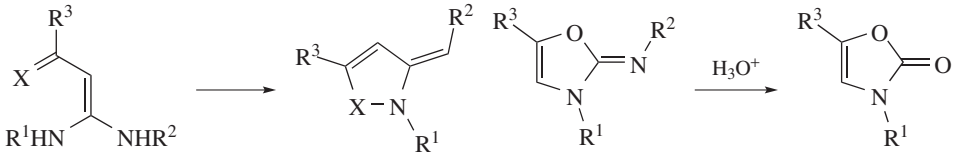
Nanoporous aluminosilicates catalyze direct aldols of acyclic acetals with 1,3-dicarbonyls rather than giving the expected Knoevenagel eliminations.[9]

Frustrated Lewis Pair (FLP) catalysis has been applied to polymerization of renewable cyclic acrylic monomers using silyl ketene acetals and tris(pentafluorophenyl)boron.[10]

A series of bicyclic acetals with a variety of environments—fully saturated, one ring aromatic, or one oxygen part of an enol ether—have undergone chemoselective formation of oxocarbenium ions, depending on hybridization type: sp^3 versus sp^2, with the latter either aromatic or vinylic. Highly efficient synthesis of a range of heterocyclic systems results, with yields/*de*/*ee* up to 93/95/99%.[11] (*ee*) (*de*)

Indoles have been converted to carbazoles, using a three-component reaction; an α-bromoacetaldehyde acetal performs a Friedel–Crafts-type alkylation of the indole [catalyzed by bismuth(III)] with subsequent [4 + 2] annulation with a ketone.[12]

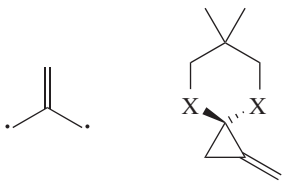
α-Oxo-ketene *N,N*-acetals [(**14**), X = O] undergo formal oxidative C–C bond cleavage and subsequent cyclization to give isoxazolines [(**15**), X = O] using PIDA [phenyliodine(III) diacetate] as oxidant. The corresponding thioxo substrates [(**14**), X = S] give isothiazoline derivatives [(**15**), X = S]. In the oxygen case, the product easily undergoes Baldwin rearrangement to the 2-imino-1,3-oxazoline isomer (**16**), which can be hydrolyzed in acid to the corresponding oxazolone (**17**) (Scheme 5).[13]



(**14**) (**15**) (**16**) (**17**)

Scheme 5

Many studies suggest that trimethylenemethane (TMM, C_4H_6) has a ground-state triplet structure (**18**), together with a low-lying excited singlet state. A DFT study has looked at the generation of TMM structures by ring-opening of dialkoxymethylenecyclopropanes and methylcyclopropane-thioacetals [(**19**), X = O, S] (Scheme 6). A range of resulting ketene-forming reactants and cyclizations are also reported.[14]

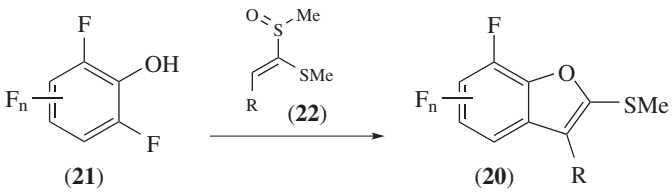


(**18**) (**19**)

Scheme 6

Fluorinated benzofurans (**20**) have been prepared from polyfluorophenols (**21**), using ketene dithioacetal monoxides (**22**), the latter being activated by an acid anhydride (Scheme 7). The sigmatropic de-aromatization/de-fluorination strategy uses (i) an interrupted Pummerer reaction followed by [3,3] sigmatropic rearrangement, (ii) zinc-mediated defluorination, and then (iii) acid-promoted cyclization/aromatization. The 2-methylsulfanyl moiety in the products (**20**) facilitates further functionalization.[15]

Functionalized tetrasubstituted thiophenes (**23**) have been prepared one-pot from ketones (R^1–CH_2COR^2), isothiocyanates (R^3–CNS), and 2-picolyl bromide using potassium carbonate

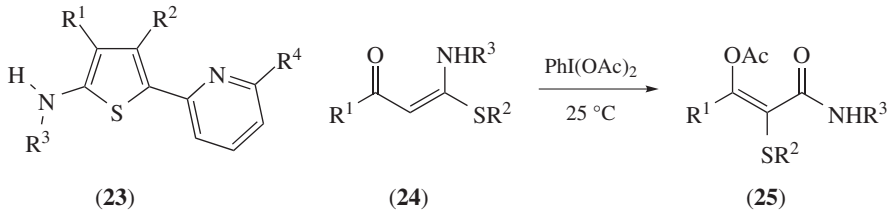


(**21**) (**20**)

Scheme 7

as base in DMF at 60 °C. Sulfur ylide-like intermediates, with stabilization by pyridine, are proposed and supported by ^{1}H–NMR data. A number of five-membered aromatic heterocyclic moieties can replace the 2-pyridyl substituent.[16]

Alkylthio-functionalized enaminones (**24**, α-oxo ketene *N,S*-acetals) have been converted to unsaturated amides (**25**) (Scheme 8) under mild conditions in a metal- and CO-free process involving vicinal alkylthio migration.[17]



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

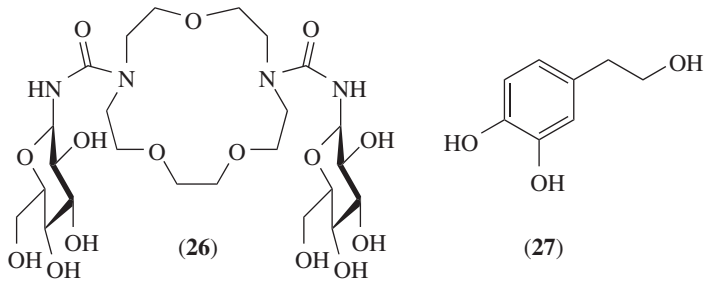
Scheme 8

For carbohydrate-derived lactone acetals undergoing a vinyl Grignard process, see The Wittig and other Olefinations below.

Reactions of Glucosides

Silica-coated silver nanoparticles with acrylate functionality have been used to achieve glucose detection down to 2×10^{-5} L mol^{-1} by a combination of the chain reaction application mechanism (CRAM) with the localized surface plasmon residence (LSPR) effect at the molecular level.[18]

A new *aza*-crown-*bis*-sugar, 1,10-*N*,*N*′-bis(β-D-ureidoglucopyranosyl)-4,7,13-trioxa-1,10-diazacyclopentadecane (**26**) has been shown to complex drugs such as aspirin. A wide range of computational methods have now been brought to bear on elucidation of its low energy conformers *in vacuo* and *in aqua* including computer prediction of the IR and ^{1}H- and ^{13}C-NMR peak positions in both media. The results indicate that the sugar units are energetically favoured being on the same side of the crown, stabilized with hydrogen bonding, whereas a more open structure is much higher in energy (Scheme 9). Simulated spectra have been compared with experimental data, and 1:1 and 2:1 complexes with aspirin have also been characterized.[19]



(**26**) (**27**)

Scheme 9

Experimental thermodynamic data on the interaction of carbohydrates with water, with proteins, and with themselves is not adequately modelled by the CHARMM36 carbohydrate parameter set. A new set has been developed, based on the Kirkwood–Buff-derived alcohol parameters. The correction counteracts CHARMM's overestimation of the self-association of carbohydrates.[20]

Catalytic glycosylations, with a particular focus on synthesis of oligosaccharides, are the subject of a comprehensive review (769 references).[21] The use of glycosyl sulfoxides in glycosylation reactions has been reviewed (130 references), with an emphasis on their applications, but also on how some of the mechanistic details remain to be fully revealed.[22]

Controlling the yield and stereoselectivity of glycosylations depends on the reactivity of both donor and acceptor; that of the donors is relatively well understood but that of the acceptors less so. A simple system has been proposed to screen acceptors, allowing their reactivity to be adjusted to attain stereoselective *cis*-glucosylations.[23]

A mild, direct, metal-free anomeric *O*-arylation of unactivated carbohydrates uses diaryliodonium salts, $[Ar_2I]PF_6$, in toluene at ambient temperature. It has been tested on pyranosyl and furanosyl substrates, and on oligosaccharides.[24] Glycosylations of several flavanoid compounds have been reported.[25]

2° Amine hydrochlorides have been used to activate 2-deoxysugar lactols, using iminium ion catalysis of such masked aldehydes to generate glycosyl oxocarbenium ions. This new organocatalytic, α-selective, direct, dehydrative glycosylation protocol now provides more convenient access to a range of 2-deoxy-glycosides including -pyranoses and -furanoses.[26]

A ceric ammonium nitrate (CAN)-mediated synthesis of 2-hydroxyglucose was unexpectedly discovered to involve glycosyl nitrate intermediates, facilitating a new access route to glucopyranoses differentiated at C(2).[27]

Diterpene glycosyltransferase from *Andrographis Paniculata* has been shown to have broad substrate scope, catalyzing formation of *O*–, *S*–, and *N*–glycosidic bonds.[28]

Protein *O*-GlcNAcylation has been reviewed (73 references). The process involves attachment of a single *O*-linked β-*N*-acetyl-glucosamine to a protein, and the review describes advances involving chemical reporters and their bio-orthogonal reactions for detection and construction of *O*-GlcNAc proteomes.[29]

Hydroxytyrosol (**27**), an olive biophenol, is a 'nutraceutical' with potent anti-oxidant activity (see Scheme 9). It has been fructosylated using the β-fructofuranosidase from a yeast, *Xanthophyllomyces Dendrorhous*, giving products at both alcohol and 4-phenol positions. MS, NMR, and X-ray crystallographic results have helped shed light on the regiospecificity of this enzyme, whose promiscuity for non-sugar hydroxyls may prove to be of wider use.[30]

β-L-Rhamnopyranosylations have been performed in the presence of a glycosyl-acceptor-derived borinic or boronic ester. An S_Ni type mechanism is supported by ^{13}C-KIE measurements and DFT calculations.[31]

Several accounts deal with glucose-to-fructose isomerization, including the use of Lewis-acidic zeolite surfaces to catalyze the reaction, and the subsequent etherification of fructose have also been investigated. The familiar Sn-Beta zeolite catalyzes the first process, but the Sn-SPP material (Self-Pillared Pentasil) catalyzes both, exploiting its Sn-O-Si-OH moiety. DFT and Monte Carlo simulations have been used to identify why fructose ketalization is favoured over glucose acetalization.[32] A metal-organic framework (MOF)-based catalyst incorporating chromium(III) hydroxide and glycine has been developed for this selective isomerization. An alternative to tin-containing Lewis-acidic zeolites, the new catalyst also promotes a different mechanistic route involving mainly proton transfer steps.[33] A zirconium MOF, UiO-66, catalyzes the isomerization in alcohols, with some variation of results by alcohol type. NMR studies helped establish an intramolecular 1,2-hydride transfer mechanism.[34]

Sodium titanate nanotubes have been used as Lewis-base catalysts of the isomerization. While suitable for aqueous use and catalytically efficient initially, leaching of sodium cations and retention of organic material were problematic. Productivity can be regenerated by treatment with sodium hydroxide.[35]

The role of strong Lewis base sites of lanthanide oxides such as La_2O_3, Nd_2O_3, Sm_2O_3, and Pr_6O_{11} on reactions of glucose has been investigated by CO_2-TPD (temperature-programmed desorption) and by DRIFT spectroscopy. Site differentiation allowed identification of functions

that catalyzed glucose-to-fructose isomerization, glucose hydrogenolysis, and retro-aldol processes of fructose to C_3 chemicals.[36]

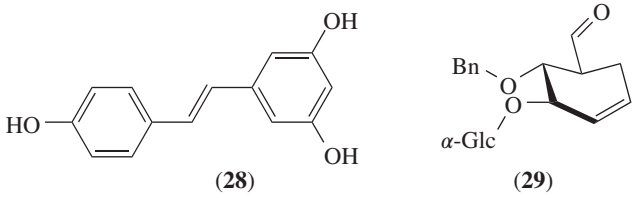
Among several enzymatic reports, β-phosphoglucomutase enzyme catalyzes glucose phosphate isomerization with one of the highest enhancements known; up to a factor of 10^{21}. A variant of the enzyme has been studied to help identify how the native catalyst achieves this, with catalytic efficiency *per se* being balanced with product dissociation.[37]

β-Glucosyl fluoride has been used to identify the acid-base catalytic residue of a glycosyltransferase enzyme.[38]

A kinetic study has characterized the mechanisms of two bacterial cellulose synthase enzymes, from initiation through elongation and termination processes, with kinetic simulation providing further backup. Elongation requires cyclic addition of uridine diphosphate-glucose.[39]

Several investigations into sugar biochemistry focus on diabetic control. The mechanism of glucose-1-phosphate's isomerization to the 6-isomer—as catalyzed by human α-phosphoglucomutase—has been examined via TS calculations and molecular dynamic simulations. The enzyme is a possible target for inhibition by TS analogues in the context of Type 2 diabetes.[40] A similar study used computer simulations of both wild-type and mutant enzymes, helping to pin down the roles of key acid-base catalytic residues and their organization in hydrogen-bonded networks stabilizing the TS.[41]

trans-Resveratrol [(**28**), *trans*-3,5,4′-trihydroxystilbene] is a naturally occurring polyphenol which has shown beneficial effects against Type 2 diabetes, but its low bioavailability and high rate of clearance pose a puzzle as to its mode of action (Scheme 10). Evidence is now presented that it is its primary metabolites, the 3-*O*-glucuronide and the 4-*O*-glucuronide, which are actually acting; they improve glucose uptake by cells and glycogen synthesis, and they block formation of ROS (reactive oxygen species) in cells.[42]



Scheme 10

Human α-glucosidase maltase-glucoamylase (MGAM) enzyme is a target for inhibition in the context of the treatment of diabetes. A QM/MM approach to the mechanism indicates significant differences from other glycosidases.[43]

A Claisen rearrangement of an α-1,4-disaccharide has yielded an α-1,4-glycosyl carbasugar (**29**), an α-aziridine of which can act as an inhibitor of an *endo*-α-mannosidase enzyme, probably via shape mimicry.[44]

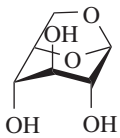
A full QM DFT study of the catalytic mechanism of α-1,4-glucan lyases identifies three phases: (i) glycosylation; (ii) deglycosylation-elimination (rate-determining); and (iii) tautomerization. This final enol-anhydrofructose to keto-anhydrofructose step must occur inside the active site as the overall barrier for the process of 18.3 kcal mol^{-1} determined mainly by step (ii) is much lower than the barrier of 35.8 kcal mol^{-1} calculated for step (iii) if it were to take place in the external aqueous environment.[45]

A computational study has examined the binding of glucose and of galactose to human serum albumin. Glucose binds more strongly than galactose, and—for both monosaccharides (and others in the literature)—a dimer can form in the binding pocket and in some cases one of the monosaccharides may be bound in its open-chain form. How such events trigger glycation/galactation is also investigated, as well as the hydrogen-bonding frameworks.[46]

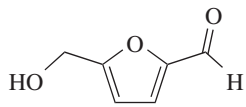
Dihydroxyacetone phosphate (DHAP)-dependent aldolases can use aldehydes as electrophile substrates, but this has been extended to ketones in the case of a bacterial rhamnulose aldolase, leading to branched-chain monosaccharide units with a tertiary alcohol moiety.[47]

The year featured increasing reports of processing of carbohydrate biomass including pyrolysis, other chemical processes, and enzymatic treatments. Upgrading lignocellulosic biomass to energy-intensive fuels and chemicals has been reviewed (469 references), employing carbon-increasing catalytic strategies. A wide variety of relevant reaction types were discussed such as aldol, (hydro)alkylation, oligomerization, ketonization, Diels–Alder, Guerbet, and acylation reactions, as well as hydrolysis, dehydration, oxidation, partial hydrogenation, and hydro-deoxygenation. Other useful derivatives containing C–O, C–N, or C–S bonds were also reviewed.[48]

Levoglucosan (**30**) is formed in thermal degradation of glucose and cellulose and can act as a tracer for the burning of biomass (Scheme 11). Its conformations in the gas phase have been studied using microwave spectroscopy coupled with ultrafast laser vapourization. Three conformers were identified and compared with that found in the crystal. Heavy-atom positions are more or less invariant in all cases but there are significant differences in hydrogen-bonding networks. The axial positions of the hydroxyls contrasts with the equatorial positions found for gas-phase glucose.[49]



(**30**)



(**31**)

Scheme 11

A computational study of fast pyrolysis of glucose has focused on four mechanisms of water loss; Maccoll elimination, pinacol ring contraction, cyclic Grob fragmentation, and alcohol condensation. The latter process, giving levoglucosan (**30**), had the lowest barrier (50.4 kcal mol^{-1}), with the others at least 10 kcal higher. Extension of the study to cellobiose gave similar results.[50]

In a solid substrate/solid catalyst approach to using biomass, lignocellulose has been converted to glucose in up to 88% yield using a mix-milling technique to increase solid-solid contact. The role of weakly acidic sites on mesoporous carbon was investigated by NMR and DFT.[51] Sn-Beta has been used to catalyze glycolysis-like reactions of biomass, with an isotopic NMR study being used to track mechanistic details.[52]

Anatase titania (TiO_2) catalyzes the direct dehydration of glucose to HMF [(**31**), 5-hydroxymethylfurfural] without isomerization to fructose. DFT studies indicate activation of the C(3) hydroxyl to give 3-deoxyglucosone as the start of the reaction. Cooperative Lewis acid-base catalysis leads to simultaneous C–O and C–H activation in glucose. As part of the investigation, chloroform was used as a probe molecule for studying acidic and basic sites on hydrated titania by IR spectroscopy.[53]

The mechanism of hydroxyl-radical-induced depolymerization of cellulose under alkaline conditions in air has been studied by DFT and electron transfer theory, with hydrogen abstraction from C(3) of the pyran ring being found to be rate-determining.[54]

β-Glucosidases from glucoside hydrolase family 3 have industrial applications in biomass degradation but hydrolysis of cellobiose with these enzymes suffers from competing transglycosylation. A QM/MM study on the competing mechanisms finds significant TS differences (despite similar barrier heights), which may be exploitable in engineering β-glucosidases for more efficient hydrolyses.[55]

Glucosyl transferase GTF-SI enzyme, derived from *Streptococcus Mutans*, is a 1,3-1,6-α-glucansucrase implicated in dental caries. A QM/MM study of its mechanism of action in hydrolysis of sucrose has highlighted the structural and stereoelectronic factors involved, which may assist in design of enzyme inhibitors which could prevent bacterial adherence to teeth.[56]

α-C-vinyl or -aryl glycosides have been prepared by nickel-catalyzed cross-electrophile reductive coupling of glycosyl halides with vinyl or aryl halides. High selectivities were achieved with several types of monosaccharides, apparently for steric reasons.[57]

DIPEA (diisopropylethylamine) catalyzes a green and regioselective acylation of carbohydrates and of diols, using acetic anhydride at 40 °C. DIPEA is proposed to react with the anhydride, releasing a carboxylate, leading to selective acylation via hydrogen-bonding interactions.[58]

A heptasaccharide 2-deoxy-2-fluorosugar has been developed as a mechanism-based inhibitor of *endo*-xyloglucanases.[59]

A series of trisaccharide building blocks with orthogonal protection has been prepared using glycosyl phosphates (derived in turn from thioglycosides); they are intended as versatile modules for construction of complex oligosaccharides such as *N*-glycans.[60]

Positional selectivity of hydrosilylative partial deoxygenation of *gluco*-disaccharides has been investigated. Starting with persilylated derivatives, catalytic partial deoxygenation has been carried out using Me_2EtSiH and a Lewis acid, $B(C_6F_5)_3$. For maltose, cellobiose, and trehalose, the kinetically preferred site of reduction and cleavage is the linking anomeric centre, whereas isomaltose differs in having an α-(1′→6′)-linkage which is more resistant to cleavage; it directs reactivity to a ring-opening of the reducing sugar. Selective reduction sequences are largely determined by the first C–O cleavage.[61]

C_2-Symmetric diaminoethanes, $R^1R^2NCH_2CH_2NR^1R^2$, have been prepared by catalytic reductive aminolysis (using R^1R^2NH) of reducing monosaccharides. An amination/dehydration/retro-aldol mechanism is described; kinetics, reactivity studies, and DFT were used to identify it. This useful process for exploiting biomass has been further optimized by study of amine:glucose ratios, and of water and solvent effects.[62]

A 'designer' zirconia sulfonic acid, SO_4^{2-}/ZrO_2–PMO–SO_3H (PMO = Periodic Mesoporous Organosilica), catalyzes direct conversion of glucose to ethyl levulinate (ethyl 4-oxopentanoate) in ethanol solution. The structure of the catalyst facilitates tuning of Bronsted- and Lewis-acidic sites.[63]

For use of the amino-polysaccharide (chitosan) as a catalyst, see under Imines below.

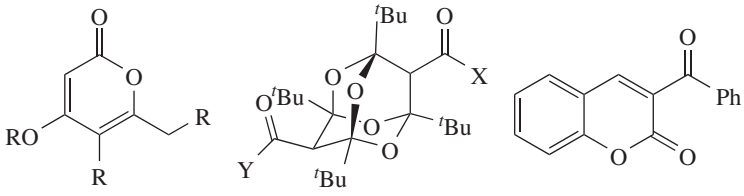
Reactions of Ketenes and Related Cumulenes

The role of ketenes in zeolite chemistry and catalysis has been reviewed (21 references).[64]

Highly functionalized derivatives of 2-pyranone have been accessed via preparation of a trisilylated derivative [(**32**), TBDPS, R = $SiPh_2{}^tBu$] from the *tert*-butyldiphenylsilyl ketene, R–CH=C=O, via a thermally induced rearrangement employing an alkoxide catalyst. NMR, MS, and X-ray characterization of intermediates helped clarify the mechanism.[65]

Dipivaloylketene, $({}^tBu–CO)_2$–C=C=O can be converted to functionalized 2,4,6,8-tetra-*oxa*-adamantanes [(**33**); X, Y = various Nu] with a rich range of intermediate functionality such as bisdioxines, via the addition of nucleophiles (Scheme 12). The preparation and reactions of dipivaloylketene, and their mechanisms, are the subject of a short review (43 references).[66]

Chiral *N*-heterocyclic carbenes (NHC's) catalyze enantioselective cycloaddition of ketenes to 3-aroylcoumarins (**34**) to give dihydrocoumarin-fused dihydropyranones. A DFT study has considered ketene-first versus coumarin-first mechanistic alternatives, similar to the options



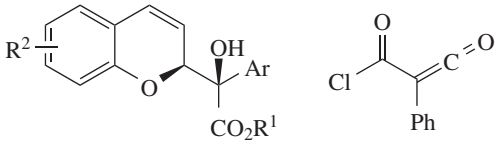
(**32**) (**33**) (**34**)

Scheme 12

possible in reactions of ketenes with other classes such as imines and diazenes. The ketene-first mechanism is found to be operative, and the calculations also reproduce experimental enantioselectivities quite well.[67] (ee)

QM calculations have been used to investigate the scope for formation of acetamide from ketene and ammonia in the troposphere. While ammonia could add across either double bond, the results indicate almost exclusive addition to the carbonyl. In a comparison with hydration (to acetic acid), the rate coefficient for ammonia addition is estimated to be at least one million times greater.[68]

2*H*-Chromenes (**35**) with a quaternary carbon have been synthesized by formal carbene insertion into the C=O bond of *E*-2-hydroxycinnamaldehydes (Scheme 13). Aryl diazoacetates are used as carbene precursors in a rhodium-catalyzed process with good yields and *de(syn)* typically >95%.[69] (de)



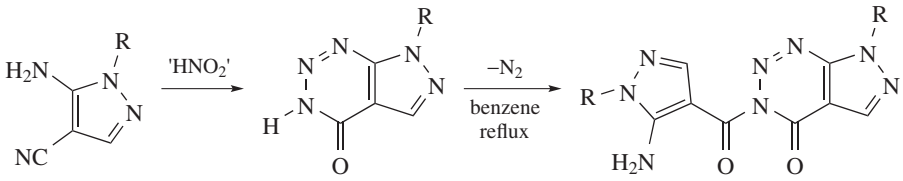
(**35**) (**36**)

Scheme 13

Acyl ketenes such as chlorocarbonylphenylketene (**36**) undergo a range of cycloaddition reactions with 1° amides which have been investigated synthetically and theoretically.[70]

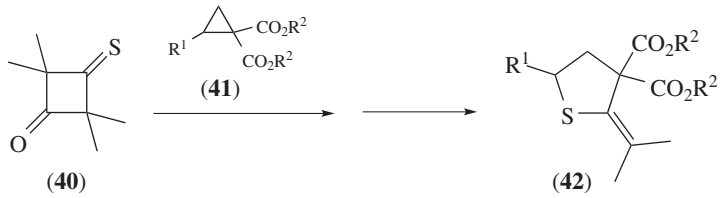
5-Amino-1*H*-pyrazole-4-carbonitriles (**37**), under diazotization conditions, yield pyrazolo [3,4-*d*][1,2,3]triazin-4-ones (**38**), thermal treatment of which gives new 3-(5-aminopyrazol-4-yl-carbonyl) derivatives (**39**) (Scheme 14). Tautomeric forms of the bicyclic systems have been characterized by NMR. Ring-opening reactions of the six-membered ring may involve cyclic bisiminoketene intermediates of the form (*cyclo*-R–N=C)$_2$–C=C=O.[71]

3-Thioxocyclobutanones (**40**), acting as surrogates for disubstituted thioketenes, have been formally inserted into donor-acceptor cyclopropanes [(**41**); R^1 = Ph, Ar; R^2 = alkyl] to give 2-substituted tetrahydrothiophenes with an *exo*cyclic double bond (**42**) (Scheme 15),



(**37**) (**38**) (**39**)

Scheme 14



Scheme 15

accompanied by the extrusion of a ketene, $Me_2C{=}C{=}O$. Lewis acid catalysis by scandium(III) triflate is proposed to involve a formal [3 + 2] cycloaddition.[72]

The photo-dissociation dynamics of acetone have been studied by time-resolved ion imaging and by photo-fragment excitation (PHOFEX) spectroscopy, with considerable detail provided on dissociation to methyl and acetyl radicals (and the latter's further dissociation), and on formation of ketene.[73]

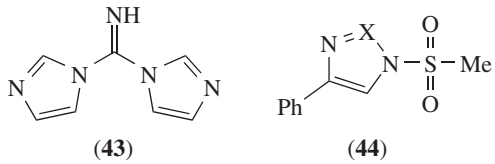
A variety of references to ketene acetals, including *S,S*-, *N,S*-, and *N,N*-cases, are described under Formation and Reactions of Acetals and Related Species above. Ketene (and imine) intermediates are implicated in a new mechanism of the Kinugasa reaction; see under Other 'Name' Reactions of Imines below. *N,O*- and *N,N*-acetal derivatives have been prepared from imines, described under Other Reactions of Imines below. Uses of α-oxoketenes, $R^1{-}C(=O){-}(R^2)C{=}C{=}O$, are listed under The Wittig Reaction below.

Formation and Reactions of Nitrogen Derivatives

Imines: Synthesis, and General and Iminium Chemistry

Mechanistic approaches to oxidative coupling of primary amines to give imines has been reviewed (72 references), with a focus on removing adverse factors such as cost, harsh conditions, and toxicity.[74]

Ribonucleoside 5′-monophosphates have been activated with imidazole to give their 5′-phosphorimidazolides, using diimidazole imine (**43**), prepared in turn from reaction of cyanogen chloride (N≡C–Cl) with two imidazoles (Scheme 16). Cyanogen chloride, in turn, is conveniently generated *in situ* from cyanide anion and hypochlorous acid, HOCl.[75]



Scheme 16

Eosin Y-mediated photo-oxidation of *N*-allylbenzylamine yields the corresponding imine, $Ph{-}CH{=}N{-}CH_2{-}CH{=}CH_2$, and benzaldehyde after long reaction times. The reaction, which requires inputs of light and air, is a good demonstrator of online monitoring by FlowNMR under realistic conditions, whereas NMR monitoring of photochemical reactions is more typically done offline.[76]

A variety of amine types have been dehydrogenated to imines—acyclic, cyclic, conjugated, and aromatic—using photocatalytic conditions at near-ambient temperature and with catalysis by carbon dioxide (1 atm). A wide range of other functional groups are tolerated. Eosin Y is again employed as photocatalyst, with DBN (1,5-diaza-bicyclo[4.3.0]non-5-ene) as trapping agent, and DMSO as solvent. A radical mechanism is proposed, with the hydroxycarbonyl radical ($\cdot CO_2H$) being detected by EPR.[77]

Primary amines, $R^1R^2CHNH_2$, undergo facile oxidative coupling in water in the presence of air at 35–40 °C to give imines, using a cobalt(II) complex as catalyst. A wide range of amines are tolerated with R^1 = H or Me, and R^2 can be alkyl, aryl, or heteroaryl. In some cases, two different primary amines give one major product. A cobalt(II/III) cycling mechanism is proposed, with one likely cobalt(III) intermediate being isolated. Addition of butylated hydroxytoluene (BHT) causes a drastic drop in yield, supporting a radical route.[78]

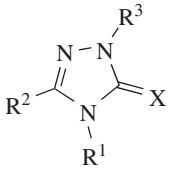
Phenazine radical cations catalyze aerobic oxidative homo- and cross-coupling of primary amines to give aldimines. UV-visible absorbance and fluorescence spectroscopy and EPR techniques have been used to characterize the mechanism as SET-based.[79]

Molecular iodine promotes the conversion of benzaldehydes to *N*-sulfonyl aldimines using a hypervalent iodine reagent, Ph-I$(OAc)_2$ (PIDA, or iodobenzene diacetate), and an arylsulfonamide. Subsequent reduction by sodium borohydride in one pot yields benzylic *N*-alkylsulfonamides. The reaction is catalyzed by visible light and requires at least two equivalents of aldehyde. Evidence for radical-initiated activation of a sacrificial equivalent of aldehyde is presented.[80]

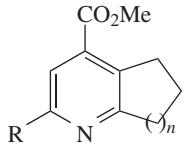
An *N*-sulfonyl-1,2,3-triazole [(**44**), X = N] undergoes denitrogenative transannulation to give an imidazole [(**44**), X = C–Me] (see Scheme 16). Reactions of this type, previously achieved with metal-based agents, have been performed using boron trifluoride etherate under acetonitrile reflux, with the X moiety being derived from the solvent. Ring-chain isomerization of the triazole is proposed as the first step, giving the α-diazo-imine, Ph–C(=N_2)–CH=N–SO_2Me, followed by reaction of the (imine) nitrogen with BF_3, with a number of possibilities for subsequent extrusion of dinitrogen and incorporation of the nitrile.[81]

S-Chiral sulfinyl imines, Ph–CH=N–*S(=O)–^{t}Bu, have been formed from benzaldehyde and *tert*-butanesulfinamide via acid catalysis by tetrafluoroboric acid diethyl etherate (HBF_4·OEt_2) under very mild conditions; DCM solvent, ambient temperature, and a mild desiccant, $MgSO_4$, in 2 hours.[82]

N-H 1,2,4-Triazolylimines [(**45**), X = NH] have been prepared by a formal 1,3-dipolar cycloaddition of organo-cyanamide ions, R^1–N^-–C≡N (from the tosylates), to hydrazonoyl chlorides, R^2–C(Cl)=N–NHR^3. Hydrolysis then yields the 1,2,4-triazol-5-one [(**45**), X = O] (Scheme 17). The tosylate precursor is activated by fluoride and the hydrazonoyl chloride acts as a precursor of a nitrile imine, R^1–C≡N^+–N^-–R^3.[83]



(**45**)



(**46**; *n* = 1–4)

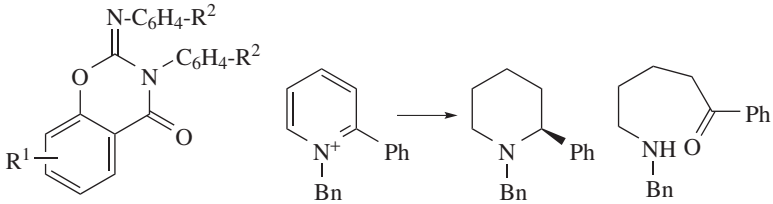
Scheme 17

A systematic synthesis of alicyclic fused[*b*]-pyridines [(**46**); e.g. 5,6,7,8-tetrahydro-quinolines for n = 2] have been prepared from an α,γ-diketoester, $RCOCH_2COCO_2Me$, ammonium acetate (as solid/buffered *N*-source) and cycloalkanones. In a regioselective metal-free green protocol, the amino-polysaccharide chitosan is used as catalyst, a wide range of R groups are tolerated (including aryl and heteroaryl), and the starting materials do not require pre-functionalization nor protection. The Guareschi–Thorpe-type process involves imine-enamine cascades and gives high yields in dioxane at 80 °C in a few hours using ca. 1 monomer equivalent of chitosan.[84]

2-Imino benzo[*e*]-1,3-oxazin-4-ones (**47**) have been synthesized from a salicylic acid and 2 equivalents of an aniline, the central carbon deriving from HATU {1-*bis*(dimethylamino)-methylene-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxide hexafluorophosphate}, the latter being better known as a peptide coupling agent. HATU reacts with an initially formed salicylanilide, converting—via a series of isouronium intermediates and an imine-iminium exchange—to give oxazinones (**47**). The novel synthesis was discovered when HATU-catalyzed coupling of salicylic acid and aniline was being attempted.[85]

Hydride-metal iminium addicts have been implicated in hydrogen-transfer reactions of internal alkenes with tertiary amines as hydrogen donors.[86]

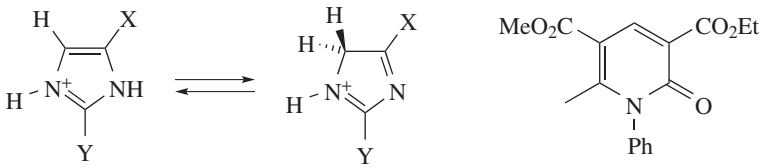
N-Protected chiral pyrrolidines (**48**) have been prepared by iridium(I)-catalyzed hydrogenation of pyridinium cations (**49**), using a chiral bisphosphine ligand. A detailed investigation has led to a mechanistic description of the successive hydrogenations involved, including several tautomeric steps. Before the last double bond is reduced, a side-equilibrium can operate to produce the non-cyclic ketone intermediate (**50**), supported by ^{13}C-NMR spectroscopy. 1- and 2-D NMR, MS, and kinetic studies informed the results (Scheme 18).[87]



(**47**) (**49**) (**48**) (**50**)

Scheme 18

Aromatic/non-aromatic tautomerism in protonated imidazoles [(**51** ⇌ **52**); X, Y = H, NH_2, NMe_2, and others] has been studied computationally. Tautomer (**52**) is favoured by electron-donating groups due to π-π repulsive effects in structure (**51**) (Scheme 19). Solvent effects have been explored, with hydrogen-bonding networks in water significantly facilitating proton transfers.[88]



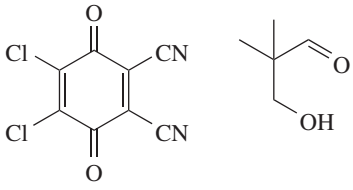
(**51**) (**52**) (**53**)

Scheme 19

Highly substituted and functionalized 2-pyridones (**53**) have been prepared from four components—methyl acetoacetate, diethyl malonate, triethyl orthoformate, and aniline—in a branched domino reaction. The green credentials include microwave irradiation under solvent- and catalyst-free conditions, with water and ethanol as by-products. Yields are high and the process is proposed to be self-sorting. The mechanism is suggested to include condensation, an *aza*–ene reaction, *N*-nucleophilic addition, imine-enamine tautomerization, cyclization, and loss-of-ethanol steps.[89]

Aliphatic nitriles undergo α-deuteration by D_2O under basic conditions ($K^+ {}^-O^tBu$) using a PNP-ruthenium(I) catalyst, with an imine-enamine tautomeric route implicated.[90]

2,3-Dichloro-5,6-dicyanobenzoquinone (**54**) has been employed to assist phosphonation and cyanation of secondary *N*-alkylanilines via dehydrogenative imine formation involving single-electron-transfer (SET) to the quinone (**54**), followed by nucleophilic attack of phosphate and cyanide anion (Scheme 20).[91]



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

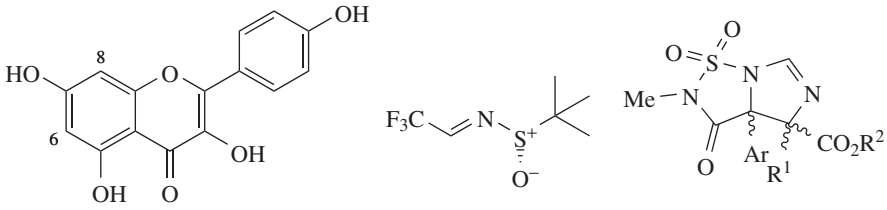
Scheme 20

Aerobic β-hydroxylation of aliphatic aldehydes has been achieved using an imine clip-and-cleave methodology. For example, trimethylacetaldehyde is converted to 3-hydroxy-2,2-dimethylpropanal (**55**). Use of *N,N*-diethyl-ethylenediamine ($H_2N–CH_2–CH_2–NEt_2$) converts the aldehyde to an imine, and the amino-imine product is then complexed to copper(I). Exposure to O_2 and aqueous workup gives the β-hydroxy aldehyde (**55**). Low-temperature stopped-flow measurements suggest a *bis*(μ-oxido)dicopper complex as intermediate.[92]

For an *aza*-Morita–Baylis–Hilman reaction, see under The Morita–Baylis–Hilman Reaction and its *Aza*-variants below.

Mannich and Mannich-type Reactions

The flavonoid, kaempferol (**56**), undergoes aminomethylations at the 8-position (and also at the 6-) to give primary aminomethyl derivatives via a Mannich/S_N2 sequence, with the intermolecular hydrogen bonding of the amino and phenolic groups playing a key role, as supported by DFT calculations (Scheme 21). A wide variety of primary amine reactant types included diamines and ethanolamine, as well as thiosemicarbazides. Semicarbazine, glycine, and glycinamide were unsuccessful due to their decreased nucleophilicity at nitrogen. A number of the products showed anti-cancer activity.[93]



(**56**) (**57**) (**58**)

Scheme 21

Gold(I) enolates derived from the reaction of alkoxy- or aryl-alkynes with aryl nitrones, $Ar^1–CH=N^+(–O^-)–Ar^2$, undergo a range of Mannich reactions to give nitrogen-containing dihydrofuran-3(2*H*)-ones.[94]

Among reports of asymmetric Mannich reactions, copper(I)-catalyzed 1,3-dipolar cycloaddition between azomethine ylides and fluorinated aldimines gives imidazolidines stereospecifically via a stepwise Mannich/cyclization process.[95]

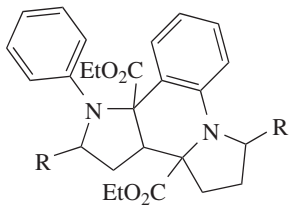
Mannich-type addition of β-diketones to *(S_S)-N-tert*-butanesulfinyltrifluoro-acetaldimine (**57**) gives different stereochemical outcomes when carried out without solvent or catalyst at 70 °C, compared to the DBU-catalyzed reaction in DCM at –10 °C.[96]

Isocyanoacetates, R^1–CH(–$^+$N≡C$^-$)–CO_2R^2, react with cyclic sulfamide ketimines to give optically active 4-aryl-3-carbonyl-1,2,5-thiadiazole-1,1-dioxides (**58**) (see Scheme 21). Using cooperative catalysis by a *Cinchona* alkaloid squaramide derivative and silver acetate, yields/*de*/*ee* of up to 99/95/94% were obtained. A Mannich/cyclization cascade is described.[97] (ee) (de)

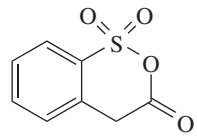
A Lewis-acidic gold(I) complex, constructed from Ph_3PAuCl and a chiral BINAP, catalyzes enantioselective synthesis of β-amino-α-diazoesters via a Mannich reaction of α-diazocarbonyls and *N*-sulfonyl cyclic ketimines. Control experiments and MS/NMR/operando IR studies have been used to characterize the mechanism.[98] (ee)

The enantioselectivity observed in Mannich reactions of acetylacetone and benzaldimine using chiral BINOL-phosphoric acids is both increased *and* reversed when the calcium or magnesium salt of the phosphoric acid is employed. A QM/MM study has identified the true catalytic species and has explained the superior behaviour of Ca^{2+} over Mg^{2+} in terms of the former's higher coordination number.[99] (ee)

Octahydro[1,2-*a*][3′,2′-*c*]dipyrroloquinoline diesters (**59**) have been prepared in one pot, involving the generation of eight σ-bonds and five stereogenic centres. A benzaldimine, PhN=CHR (generated from aniline and an aldehyde) is reacted with a *bis*(silyl) dienediolate, H_2C=CH–C(OTMS)=C(OTMS)–OEt, under Lewis acid catalysis, with a second imine completing the process under Bronsted acid catalysis (Scheme 22). Predominantly two diastereomers are formed, readily separable by chromatography. The first step constitutes a vinylogous Mukaiyama–Mannich reaction, and a Mannich/Pictet–Spengler cascade follows; DFT and MS results support the mechanism.[100] (de)



(**59**)



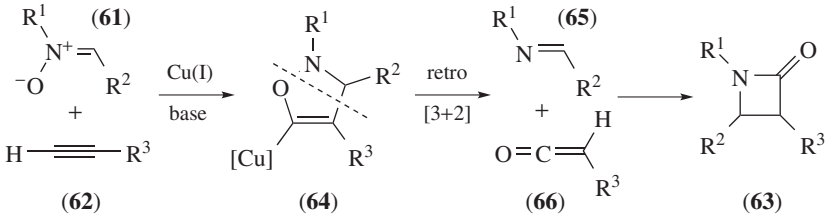
(**60**)

Scheme 22

Other 'Name' Reactions of Imines

Benzo[*c*][1,2]oxathiin-3(4*H*)-one 1,1-dioxide (**60**) is an isostere of homophthalic anhydride (HPA), and can be considered as a mixed cyclic carboxylic-sulfonic anhydride. HPA may react with aryl aldimines to give either δ-lactam adducts (the Castagnoli–Cushman [4 + 2] cycloaddition process), or via [2 + 2] Staudinger-type reaction to give β-lactams. Using mixed anhydride, only the β-lactam is produced, using very mild conditions; triethylamine as base, THF solvent, and 0 → 20 °C. While the base is not essential, it facilitates purification, yielding the product β-lactam-benzenesulfonates as their ammonium salts, which are highly water-soluble drug candidates.[101]

Kinugasa reaction of a nitrone (**61**) and an acetylene (**62**) to give a β-lactam (**63**) is catalyzed by copper(I) and base, but it suffers from multiple by-products, and aspects of its kinetics are both internally inconsistent and inconsistent with the accepted mechanism. A new analysis suggests: (i) a [3 + 2] cycloaddition of the nitrone (**61**) and copper acetylide (**62-Cu**) to give the copper-dihydroisoxazolide (**64**); (ii) followed by [2 + 2] cyclo-reversion to imine (**65**) and ketene (**66**); and finally (iii) [2 + 2] cycloaddition to give the β-lactam (**63**). Second-order dependence

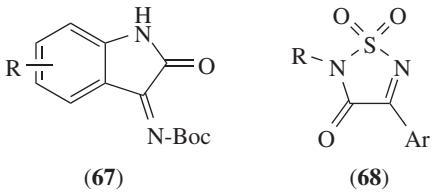


Scheme 23

on catalyst is consistent with copper complexation of the copper acetylide (i.e. formation of **Cu→62-Cu**) and the new mechanism accounts better for by-products. Ketene (**66**) intermediacy was also confirmed by a cross-over experiment (Scheme 23). The Kinugasa reaction can now be considered a 'disguised Staudinger' and the improved understanding should lead to widened and cleaner use of the reaction.[102]

In an *aza*-Morita–Baylis–Hilman reaction catalyzed by phosphenes (PAr_3), alkynones have been used as nucleophilic synthons of dienones, R^1–CH=CH–CH=CH–C(=O)–Me, via an α,β-zwitterionic intermediate, $^-$:CH_2–CH=C($^+PAr_3$)–CH_2–C(=O)–Me, with the process completed with a ketimine, R^2R^3C=NPG. The product retains a protected amino group.[103]

A chiral copper(II)-salen catalyst allows nitro-amines to be formed with yield/*ee* up to 88/99% from isatin *N*-protected imines (**67**) and nitromethane (Scheme 24). This asymmetric *aza*-Henry reaction is complete in a few hours in DCM at ambient temperature. DFT and kinetic studies suggest a rapid interaction between the imine and catalyst, as the reaction showed zero-order dependence on imine, but was first-order with respect to catalyst, and also with respect to nitromethane. Nitroethane and nitropropane proved to be markedly less reactive.[104] (ee)



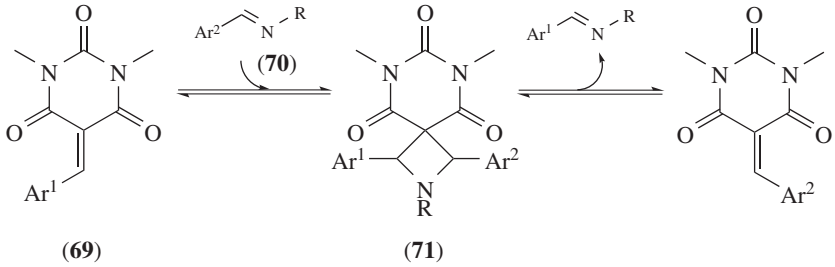
Scheme 24

Enantioselective Friedel–Crafts reaction of the *N*-tosylimide of benzaldehyde at the 3-position of indole is catalyzed by a variety of chiral phosphoric acids, and has been much studied via qualitative reaction models that seek to predict the sense and degree of the *ee* as reactants are varied. However, a QM/MM study has pointed out the limitations of such predictive guides, failing as they do to take into account many pertinent factors such as relative conformational stabilities of reagents, and hydrogen-bonding networks seen in some cases and not in others.[105] (ee)

Similarly, cyclic ketimines (**68**) (see Scheme 24) undergo an enantioselective *aza*-Friedel–Crafts reaction with indoles at the 3-position using chiral imidazoline-phosphoric acid catalysts.[106] (ee)

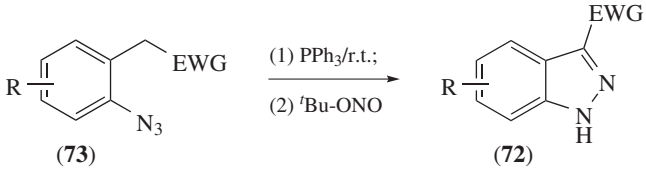
The aryl group of the barbiturate-derived Knoevenagel compound (**69**) and an araldimine (**70**) can be swapped via fast and reversible dynamic covalent C=C/C=N exchange in non-polar solvents in the absence of catalyst. An associative organo-metathesis yields an azetidine intermediate (**71**) which was trappable at low temperature (Scheme 25). An alternative dissociative mechanism proceeding via hydrolysis of one or both reactants followed by re-condensation was ruled out.[107]

Functionalized 1*H*-indazoles [(**72**), EWG = H, NO_2, C≡N, CO_2Me, $CONEt_2$, SO_2Tol] have been prepared from aryl azides (**73**) through an iminophosphorane (Scheme 26). Control



(**69**) (**71**)

Scheme 25



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

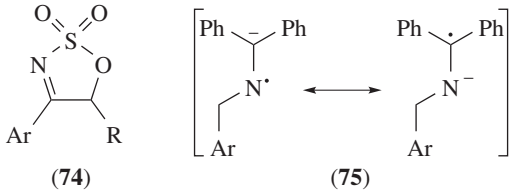
Scheme 26

experiments point to a new Staudinger/*aza*-Wittig mechanism. The wide range of functional groups, mild conditions, and simple reagents suggest a useful future for the conversion which has already been extended to yield 1*H*-benzo- and 1*H*-*aza*-indazoles.[108]

Stereoselective Hydrogenation of Imines, and other Reductive Processes

Iridium-catalyzed asymmetric hydrogenation of prochiral imines is very useful for preparing chiral amines. While an iridium phosphine oxazoline was recently identified as the active catalyst, mechanistic details remain controversial. A DFT study has now identified an outer-sphere pathway, with experimental studies supporting spontaneous formation of an iridacycle. Although the mechanism lacks direct interaction points, the high stereoselectivity appears to be linked to aromatic stacking interactions.[109]

Racemic 4-aryl-5-alkyl cyclic sulfamidate imines (**74**) undergo dynamic kinetic resolution (DKR) during asymmetric transfer hydrogenation catalyzed by a chiral rhodium catalyst using a formic acid/base/acetonitrile medium at 25 °C. With conversions and *ee* regularly above 99% (*de*) and *de* >95%, the reaction was optimized with DBU as base. Stereoselective ring-opening of (**74**) leads to chiral 1,2-amino alcohols (Scheme 27).[110] (*ee*)



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

Scheme 27

Imine iridacycle complexes have been isolated and characterized by X-ray crystallography as part of an investigation into the origin of the enantioselectivity in asymmetric hydrogenation of *N*-aryl imines catalyzed by an iridium(I)-P,N-2-oxazoline catalyst, Ir-MaxPHOX.[111] (*ee*)

N-Sulfonylimines undergo asymmetric transfer hydrogenation using alcohols as hydrogen source and palladium/zinc co-catalysis. The chiral amines are obtained with yields/*ee* of up to 93/99% and a palladium-hydride route is discussed.[112] (*ee*)

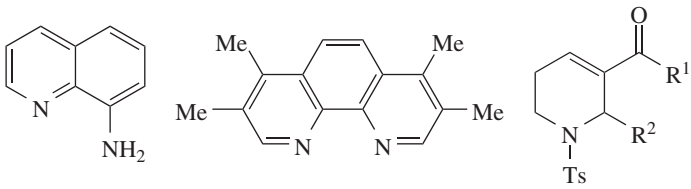
A carbanionic reactivity of imines has been demonstrated using photoredox catalysis. In this umpolung process, benzophenone ketimines, $Ph_2C{=}NCH_2{-}Ar$, are converted to radical anions (**75**) which—rather than reacting with a radical species—can abstract a proton from water and give amines (see Scheme 27). The process is carried out in aqueous acetonitrile at ambient temperature using an iridium(I) photocatalyst, a blue LED, and an aliphatic 3° amine as sacrificial electron donor. Use of D_2O gives efficient α-deuteration; this proves that water supplies this proton and is also a convenient way of introducing deuterium into an imine.[113]

Simple imines have been hydrogenated using lithium aluminium hydride employed catalytically rather than stoichiometrically. The process can be run at 85 °C, typically without organic solvent, using H_2 as reductant at ambient or slightly higher pressures. Evidence for cooperative Li–Al catalysis is reported.[114]

Olefin-stabilized cobalt nanoparticles show considerable promise as user-friendly catalysts for hydrogenation of alkenes, carbonyls, and imines. The material is easily prepared from cobalt(II) bromide, lithium triethyl borohydride ($LiEt_3BH$), and anthracene, and can be used *in situ*, or separated magnetically.[115]

Synthesis of chiral α-amino acid derivatives by asymmetric addition to α-imino esters has been reviewed (65 references), including coverage of Mannich reactions, allylations, arylations, alkenylations, alkynylations, and alkylations.[116]

Iridium-catalyzed C(sp^2)–H borylation of the aromatic ring of a prototypical araldimine, Ph–CH=N–^{t}Bu, features ligand control of regioselectivity: with 8-aminoquinoline (**76**), *ortho*-borylation dominates; whereas TMP [(**77**); 3,4,7,8-tetramethyl-1,10-phenanthroline] favours *meta*-borylation. A computational study of the mechanism identifies an Ir(I)–Ir(III) catalytic cycle, and has also clarified the ligand roles, with (**76**) favouring the *ortho*-position due to its electron-donating effect and lack of steric hindrance, whereas the bulk of TMP (**77**) switches the reaction to the *meta*-position (Scheme 28). The results should be very useful for design of ligands of even higher selectivity.[117]



(**76**) (**77**) (**78**)

Scheme 28

A novel chiral spiro monophosphate-olefin (SMPO) ligand gives *ee*'s of up to 99% in rhodium(I)-catalyzed 1,2-addition of organo-boronic acids to acyclic and cyclic *N*-sulfonyl aldimines, yielding chiral amines.[118]

The borrowing hydrogen strategy has been used to reductively *N*-ethylate *N*-aryl aldimines. An air-stable iron complex acts as pre-catalyst, and the reaction is completely selective for ethanol. A one-pot MCR approach, starting from aldehyde and amine, was also successful.[119]

A nickel(0) species catalyzes hydroalkenylation of imines by styrene, to give allylic amines in up to 95% yield. The approach avoids alkenyl-metallic reagents.[120]

Cyclizations of Imines

1,3-Dipolar cycloadditions of enamines and azides have been reviewed (95 references).[121]

In an unusual [5 + 1] annulation of δ-sulfonamido-chalcones, $TsNH{-}C{-}C{-}C{=}C{-}COR^1$, and aldimines, $R^2{-}CH{=}N{-}PG$, 1,2,3,6-tetrahydropyridyl ketones (**78**) have been prepared under mild conditions with a simple phosphine catalyst (see Scheme 28).[122]