ORGANIC REACTION MECHANISMS

EDITOR
A. C. KNIPE

2015

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An annual survey covering the literature dated January to December 2015

Edited by

A. C. Knipe

University of Ulster

Northern Ireland

WILEY

This edition first published 2019

Registered office
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, United Kingdom

Library of Congress Catalog Card Number 66-23143

British Library Cataloging in Publication Data

A catalogue record for this book is available from the British Library

Print ISBN: 978-1-119-12498-6

Printed and bound by CPI Group (UK) Ltd, Croydon, CR0 4YY

Typeset in 10/12pt TimesLTStd by SPi Global, Chennai, India.

10 9 8 7 6 5 4 3 2 1

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Preface

The present volume, the 51st in the series, surveys research on organic reaction mechanisms described in the available literature dated 2015. In order to limit the size of the volume, it is necessary to exclude or restrict overlap with other publications which review specialist areas (e.g. photochemical reactions, biosynthesis, enzymology, electrochemistry, organometallic chemistry, surface chemistry, and heterogeneous catalysis). In order to minimize duplication, while ensuring a comprehensive coverage, the editor conducts a survey of all relevant literature and allocates publications to appropriate chapters. While a particular reference may be allocated to more than one chapter, it is assumed that readers will be aware of the alternative chapters to which a borderline topic of interest may have been preferentially assigned.

All the chapters have been written by the members of a team of experienced ORM contributors who have submitted authoritative reviews over many years. We are naturally pleased to benefit from such commitment and consequent awareness of developing trends in the title area. Particularly noteworthy in recent years has been a major impact on directed organic synthesis through mechanistic studies which enable optimization of ligand design for highly selective transition metal catalysts.

In view of the considerable interest in the application of stereoselective reactions to organic synthesis, we now provide indication, in the margin, of reactions which occur with significant diastereomeric or enantiomeric excess (*de* or *ee*).

Although every effort was made to reduce the delay between the title year and the publication date, circumstances beyond the editor's control again resulted in the late arrival of a substantial chapter which made it impossible to regain our optimum production schedule. Steps have been taken to reduce the knock-on effect of this occurrence.

I wish to thank the staff of John Wiley & Sons and our expert contributors for their efforts to ensure that the review standards of this series are sustained.

A. C. K.

Contents

CHAPTER 1

Reactions of Aldehydes and Ketones and Their Derivatives

B. A. Murray

Department of Science, Institute of Technology, Tallaght (ITT Dublin), Dublin, Ireland

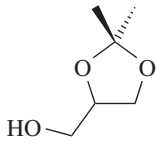
Organic Reaction Mechanisms 2015, First Edition. Edited by A. C. Knipe.

Formation and Reactions of Acetals and Related Species

Lutetium(III) triflate catalyses acetalization of acetone with glycerol, $(HOCH_2)_2$–CH(OH), giving a regioselective preference for the 1,3-dioxolane product (**1**, 'solketal'), as against the six-membered-ring 1,3-dioxane alternative. Density functional theory (DFT) studies have identified a constrained hemiacetal intermediate to explain the selectivity.[1]

To assist in using glycerol by-product from biodiesel manufacturing, a quantum mechanics (QM) study of its acetalization with acetone has been undertaken, using benzenesulfonic acid as catalyst.[2]

Nucleophilic substitutions of acetals such as (**2**) with a remote benzyloxy group can be highly diastereoselective, an effect which *increases* as the reactivity of the nucleophile is increased, in violation of the reactivity/selectivity principle. The result has been explained in terms of multiple conformers of a reactive intermediate leading to the product.[3]



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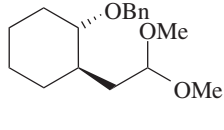

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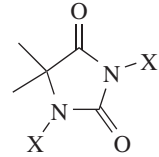
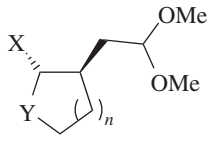


(**3**)

Acetophenones undergo mild one-step α-haloacetalization in ethylene glycol, using 1,3-dihalo-5,5-dimethylhydantoins (**3**; X = Cl or Br). Temperature and solvent effects have been investigated.[4]

A kinetic study of acetal hydrolysis has examined the effect of 4-alkoxy groups, with appropriate control of stereochemistry. For example, several acetal series (**4**) have been prepared with varying ring size ($n = 1$–4), and either endocyclic oxygen (X = H, Y = O) or exocyclic (X = OBn, Y = CH_2), with appropriate non-cyclic controls such as 4-benzyloxy-butanal dimethylacetal. Hydrolysis rate enhancements are of the order of 20-fold, perhaps 200-fold when controlled for inductive destabilization. However, rates of solvolysis of related tosylates show much larger effects, including a factor of nearly



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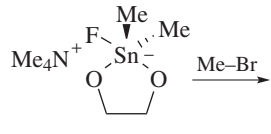


(**5**)

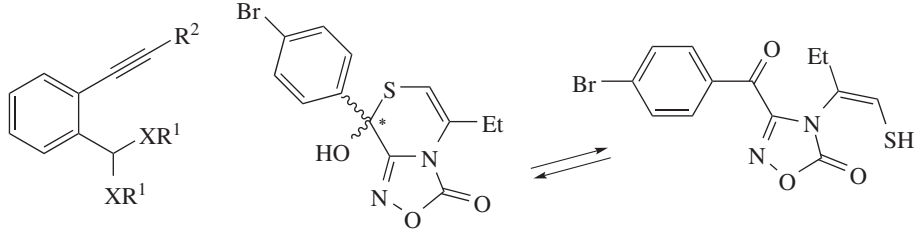
10^6 going from five- to eight-membered rings. It is concluded that neighbouring-group participation operates in the tosylate solvolysis, but not in the acetal hydrolysis.[5]

Using an amine as a nucleophile carrier, $R_2N–CH_2Nu$, a range of progressively more hindered α-cyanoamines, $R_2N–CH_2–C{\equiv}N$ (R = Me, Et, *i*-Pr, and CyHx), have been tested as cyanating agents of acetals. The congested dicyclohexyl compound proved best: using 2 equiv, together with 2 equiv of trichlorosilane triflate in DCM at 0 °C for 30 min, benzaldehyde dimethyl acetal gave 95% yield of PhCH(OMe)CN. Similar results were obtained for a wide range of acetal types, and indeed for orthoesters (to give the cyanoacetal). Investigation by nuclear magnetic resonance (NMR) spectroscopy helped identify an oxocarbenium ion intermediate, $Ph–CH{=}O^+–Me$ (as the triflate), upon addition of Cl_3SiOTf, and addition of $(CyHx)_2N–CH_2–C{\equiv}N$ rapidly gave the product, together with an iminium cation, $(CyHx)_2N^+{=}CH_2$.[6]

Regioselective monoalkylation of diols is often achieved via dialkylstannylene acetal intermediates. Though slow to form, addition of nucleophiles helps, especially fluoride. The reaction of a fluoride salt (**5**) with bromomethane has now been studied at several levels of theory in the gas phase, and in DMF solution. In solution state most closely related to experiment, fluorinated monomers and monofluorinated dimers showed similar activation energies. A widely considered 'Sn–O bond cleavage first' mechanism did *not* feature, with C–O bond formation actually well advanced over Sn–O cleavage in the TS. Comparing gas phase with DMF, solvation effects significantly lower the energy of fluoride ion to form (**5**), but the tetramethylammonium cation stays close to the F atom.[7]

A series of dialkyl acetals, $Me_2N–CH(OR)_2$, derived from DMF have been screened for their ability to *N*-alkylate 8-oxoadenosine and guanosine at N(7). Comparative kinetic experiments have been used to explore the mechanism and side-reaction possibilities.[8]

ortho-Alkynylbenzaldehyde acetals and thioacetals (**6**) undergo a range of divergent cyclizations catalysed by palladium(II) or platinum(II) halides. While metal-triggered C–X cleavage was previously proposed, DFT calculations now point to electrophilic activation of the alkyne as the initiating step. Terminal and non-terminal alkyne cases are contrasted, and the nature of the heteroatom's effect on the route taken was also studied. The DFT results have led to some literature assignments being challenged, with new experiments reported that validate the new assignments.[9]

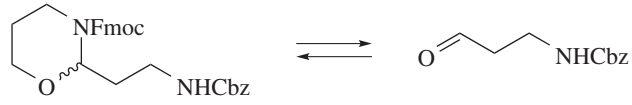


(**6**; X = O or S) (**7**) (**8**)

Hemithioacetal enantiomers (**7**) contain an unstable quaternary chiral centre and can equilibrate through their open-chain ketone–enethiol form (**8**). Variable temperature

and exchange spectroscopy (EXSY) NMR techniques have been used to measure the rates and barriers for the interconversion, in toluene solvent. A DFT study was also undertaken, but the toluene solvent severely constrains the possibilities in terms of acid–base and hydrogen-bonding chemistry. A computed barrier of 40 kcal mol^{-1} is at odds with half that found by NMR. But an alternative path was found to resolve the discrepancy: a 'solvent molecule' *is* available … in the form of another hemithioacetal, which – through a dimer complex – assists the proton transfers.[10]

'Fmox', a 3-Fmoc-(1,3)-oxazinane moiety, has been developed as a base-labile aldehyde-protecting group. For the example of the doubly protected 3-aminopropanal (**9**), deprotection is 100% effected with 1% piperidine in 2 h, while leaving the amine protection intact. The group, like many others, *is* acid-labile to the extent of 6% in 20% acetic acid and 93% in 10% TFA, though it survives in 0.1% TFA for 10 min. Protection of the aldehyde (**10**) requires *N*-Fmoc-3-amino-propanol/Na_2SO_4/HCl(cat.)/50 °C.[11]



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

Enantiomerically enriched β^2-amino acids have been accessed in the form of their *N*,*N*-diprotected esters (**11**) via dual activation of an enal (*trans*-R–CH=CH–CHO) and an *N*,*O*-acetal ($Bn_2N–CH_2–OMe$), the activations being achieved by an *N*-heterocyclic carbene (NHC) and an *in situ*-generated Brønsted acid, respectively. The enal is converted to an azolium enolate, and the acetal to an iminium ion ($Bn_2N^+=CH_2$) and methanol. Typical conditions are mild base at ambient temperature, giving *ee* up to 90%. The essence of the process is an aminomethylation of the enal α-carbon, via an internal redox process.[12] (*ee*)

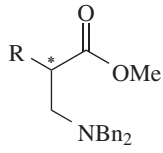
Isatin-derived *N*-Boc imines have been converted to the corresponding *N*,*O*-aminals in up to 96% yield and 92% *ee*, using a cinchonidine–urea catalyst.[13] (*ee*)

Reduction of *O*,*O*-, *N*,*O*-, and *S*,*S*-acetals to ethers has been reviewed.[14]

In a highly diastereoselective synthesis of diaziridines (**12**), an aldehyde or ketone (R^1COR^2) is combined with an amine (R^3NH_2). Compound (**12**) is simultaneously a hydrazine and an aminal, with three chiral centres from achiral reactants: with ring strain and lone pair repulsion, stereochemistry is automatically *anti* at the nitrogens. The reaction is catalysed by hydroxylamine-*O*-sulfonic acid, which exists in zwitterionic form, $H_3N^+–O–S(=O)_2–O^-$. NMR studies at low temperature indicate initial imine formation, and conversion over time to diaziridine. No non-chiral intermediates were observed during the second process, indicating that the diastereoselective step *may* be concerted.[15] (*de*)

Propargylic acetals (e.g. **13**) undergo asymmetric gold(I)-catalysed 3 + 2-cycloaddition with aldehydes to give functionalized 2,5-dihydrofurans in yield/*ee* up to 84/95%. A new gold(I)-catalysed cycloaddition of a secondary propargylic acetal (derived from a ketone) with nitrones is also reported.[16] (*ee*)

An acylrhodium(III) species may be a key intermediate in the rhodium(III)/copper(II)-catalysed cyclization of phthalaldehyde with alcohols to give 3-alkoxyphthalides (**14**). Replacing the alcohol with various 1,3-dicarbonyls gives 3-alkyl-phthalides with side-chain functionality.[17] (*de*)



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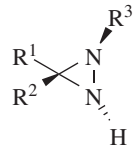

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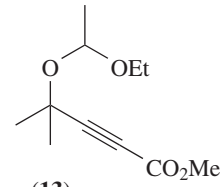

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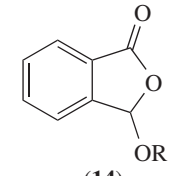
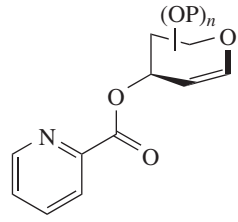


(**14**)

Reactions of Glucosides

A palladium-catalysed reaction of a 3-*O*-picoloyl glucal (**15**) allows α- versus β-selectivity based on the nature of the nucleophile: harder nucleophiles (ROH and ArO^- Na^+) follow an inner-sphere pathway to give β-products, while phenols give α-products, via an outer-sphere route, which is slower.[18] (*de*)



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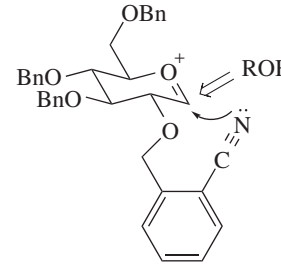


(**16**)

Appropriately *ortho*-substituted benzyl-protecting groups allow control of stereoselective formation of a 1,2-*trans*-glycosidic linkage, essentially acting as armed participating groups. Nitro and cyano are particularly effective: compound (**16**) shows how it sets up the oxocarbenium ion intermediate for β-face attack by the incoming nucleophile. The results and conclusions are supported by DFT calculations.[19] (*ee*)

Gold(III) and gold(I) chlorides both act as powerful catalysts of O-glycosidation with *O*-glycosyl trichloroacetimidates as glycosyl donors. A dual-activation Lewis acid/base mechanism is outlined, with gold forming a catalyst–acceptor adduct which then binds to the donor.[20] (*ee*)

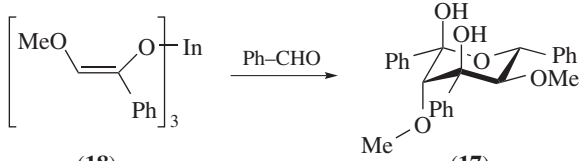
The mechanisms of glycoside bond formation in monosaccharides and glycosides have been reviewed.[21]

Formose chemistry explores plausible prebiotic routes to convert formaldehyde to sugars. Deuterium kinetic isotope effects (KIEs) have been measured for one such reaction: isomerization of glyceraldehyde to dihydroxyacetone, under base catalysis. Evidence for significant quantum-mechanical tunnelling is presented.[22]

Recent advances in the mechanisms of glycosylation have been reviewed.[23]

The reactivity of a series of ring-substituted *S*-glycosyl phenylcarbamothioates has been assessed in comparative glycosidations. Significant differences between *para*-methoxy and *para*-nitro substituents may be exploitable in selective activation strategies for oligosaccharide synthesis.[24]

6-Deoxy-α-D,L-altropyranose derivatives (**17**) have been prepared in up to 99% yield under thermodynamic control, using a domino aldol–aldol–hemiacetal cascade starting from an indium(III) enolate (**18**) and benzaldehyde. The enolate, in turn, is formed from α-methoxy-acetophenone ($PhCOCH_2OMe$) and lithium diisopropylamide (LDA); several other Group 13 metals besides indium also work. A trace of product forms at −20 °C, while at 0 °C, small amounts of 6-deoxy-galactose and -allose by-products show up, plus ca 50% of aldol intermediate. Raising the temperature gives progressively more altrose (**17**), reaching 99% at 67 °C. This switchover from kinetic control was seen as a good test of modern DFT methods, and calculations at the B3LYP/6-31(G)/LANL2DZ level at 25 and 67 °C reproduced the change in experimental behaviour.[25] *de*



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

Molecular dynamics and metadynamics have been used to model hydrolysis of cellulose in two solvents: water and the ionic liquid (IL), 1-ethyl-3-methylimidazolium acetate. The IL makes hydrolysis easier, breaking intramolecular hydrogen bonds and favouring more reactive non-chair conformers.[26]

As part of an investigation of natural selection of nucleobases in ribonucleic acid (RNA) and deoxyribonucleic acid (DNA), rates of hydrolytic deglycosylations of modified, alternative, and native nucleosides were measured at pH 1 over a range of temperatures, allowing extraction of thermodynamic parameters and comparisons of structure at 37 °C. Contemporary nucleosides exhibited the slowest rates, supporting their 'hydrolytic fitness' as nature's selected structures.[27]

As a model for formation of cyclic boronic esters or boronate ions with saccharides, a DFT study examined the rates and mechanisms of reaction of boronic acids with diols.[28]

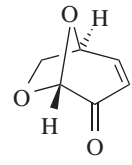
Kinetics of the reaction of D-fructose with diphenylborinic acid, Ph_2BOH, has been studied in aqueous solution.[29]

A DFT study of the Brønsted-acid-catalysed dehydration of glucose has been presented alongside a kinetic and isotopic tracing NMR spectroscopic investigation. The main products are hydroxymethylfurfural, levulinic acid, and formic acid. The rate-limiting step was identified as the first dehydration of protonated glucose with most consumption of glucose proceeding via the furfural. Formic acid is mainly produced at high levels of glucose conversion and/or high temperature, and arises from a retro-aldol at C(6).[30]

In perchloric acid medium, kinetics of oxidation of D-xylose by vanadium(V) is first order in both, with iridium(III) and hydronium ion also being efficient catalysts. A study from 35 to 50 °C afforded thermodynamic parameters.[31] Kinetics of silver(I)-catalysed oxidation of maltose by vanadium(V) in perchloric acid has been studied over a range of temperatures.[32]

Gas-phase oxidation of D-fructose by iodine has been studied by computation.[33]

Levoglucosenone (**19**) is a valuable anhydrosugar derived from pyrolysis of cellulose/biomass. To elucidate the mechanism of formation, DFT was used to study how it forms from both *β*-D-glucopyranose and cellobiose. The results tend to rule out levoglucosan (**20**) as an essential intermediate. The likely pathway from both glucose and cellobiose involves 1,2-dehydration, six-membered hydrogen transfer, and enol–keto steps, the last being rate determining.[34]



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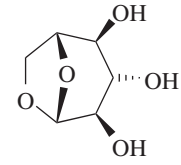
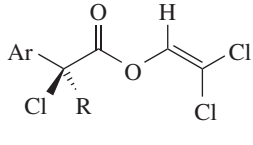


(**20**)

Such fast pyrolysis of biomass can be an efficient route to fuel. Pyrolysis of ^{13}C-labelled cellobioses has been studied by MS. Several products including levoglucosan (**20**) arise from fragmentation of the reducing end, leaving the non-reducing end intact in these products … at variance with previously proposed mechanisms.[35]

Reactions of Ketenes

NHC-catalysed reaction of aryl–alkyl ketenes, Ar(R)C=C=O, with chloral (trichloroacetaldehyde) can give either asymmetric chlorination (in up to 94% *ee*) or formal 2 + 2-cycloaddition to give *β*-lactones in up to 76% *de*/94% *ee*. Steric effects are critical: 2-substitution of the aryl or R = *i*-Pr favours the *α*-chloroester (**21**), while 4-substitution or R = *n*-alkyl yields more lactone (**22**).[36]



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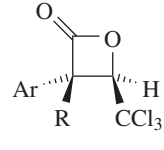

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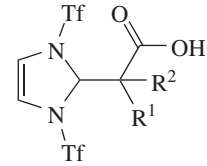


(**23**)

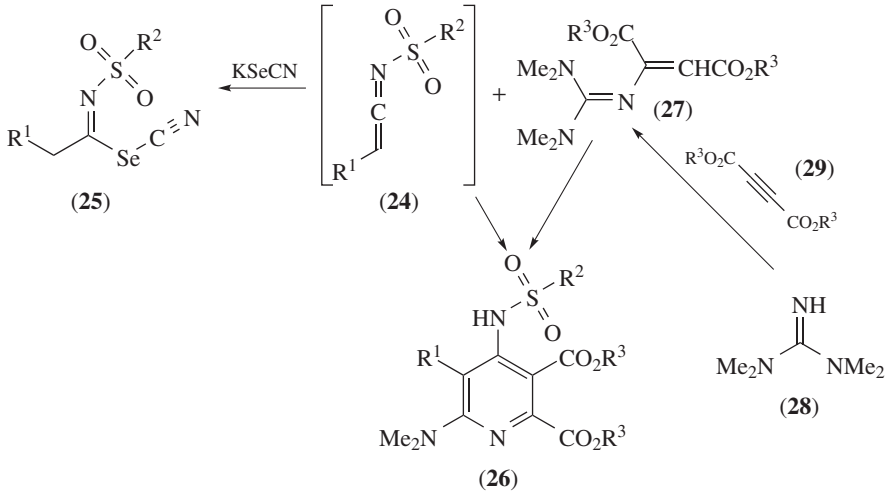
Electro- and nucleo-philicity indices have been used to study the formation of *β*-lactams from 2 + 2-cycloaddition of substituted ketenes and imines.[37]

DFT methods have been used to explore the mechanism of the ketene–imine Staudinger reaction, identifying an initial attack of the imine lone pair on the central carbon of the ketene (generating a zwitterionic intermediate), followed by a rate- and stereo-selectivity-determining ring closure.[38]

N-Ditriflylimidazole reacts with bis-(TMS)ketene acetals, $R^1R^2C{=}C(OTMS)_2$, to give 2,3-dihydroimidazolylcarboxylic acids (**23**) in DCM at −78 °C. New bicyclic *δ*-lactones can then be formed by bromolactonization with NBS.[39]

Torquoselective effects have been investigated in Nazarov reactions of allenyl-vinyl ketones, mediated by boron trifluoride etherate.[40]

Sulfonyl-ketimines (**24**) are proposed as key intermediates in the preparation of selenocyanates (**25**) from nitriles (R^1–CN) and sulfonyl azides (N_3–SO_2–R^2). This three-component coupling reaction is catalysed by copper(I) iodide via the copper acetylide, which presumably reacts with the azide to form a triazole, the ring opening of which gives (**24**) after loss of dinitrogen. Trapping by KSeCN yields the *N*-(alkyl- or aryl-sulfonyl)alkaneimidoyl selenocyanate derivative (**25**). The whole sequence occurs at ambient temperature in DMF, using Et_3N base.[41]



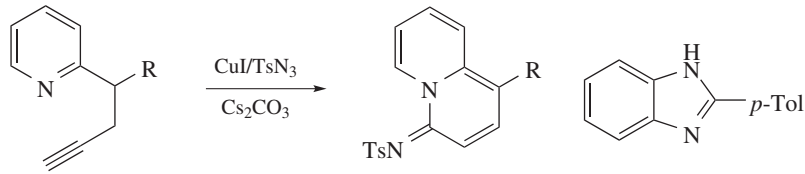
Pentasubstituted pyridines (**26**) have been prepared regioselectively in up to 88% yield at ambient temperature, using CuI/Et_3N in acetonitrile. In a four-component one-pot reaction, sulfonyl-ketenimine (**24**) is reacted with a conjugated guanidine adduct [(**27**), generated from tetramethylguanidine (**28**) and a dialkyl acetylenedicarboxylate (**29**)] to give dialkyl 5-aryl(alkyl)-4-[aryl(alkyl)sulfonamide]-6-(dimethylamino)pyridine (**26**).[42]

Formation and Reactions of Nitrogen Derivatives

Imines: Synthesis, and General and Iminium Chemistry

N-Tosyl-4-iminoquinolizines (**31**) have been prepared from pyridyl alkynes (**30**) in a process that requires air. A copper(I)-catalysed azide–alkyne cycloaddition (CuAAC) route is proposed, with tosyl azide converting the alkyne group to give an *N*-sulfonyl ketenimine *in situ*. Attack on the pyridine nitrogen closes the ring, and subsequent base-promoted oxidation gives the *N*-tosyl-4-iminoquinolizines (**31**).[43]

DFT has been used to study the mechanism of the one-pot preparation of 2-(*para*-tolyl)-1*H*-benzo[*d*]imidazole (**32**) from *ortho*-phenylenediamine, isothiocyanatomethane, and *para*-methylbenzaldehyde.[44]

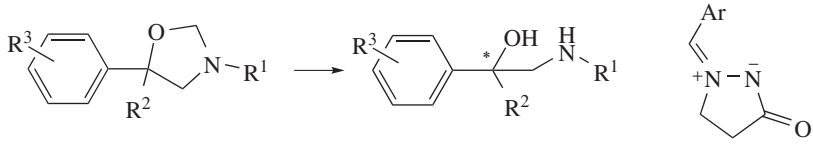


(**30**; R = CN, CO_2Me/Et, COMe, CH_2O-PG) (**31**) (**32**)

A computational investigation of Paal–Knorr syntheses of furan, pyrrole, and thiophene has identified specific mechanisms involving water assistance.[45] The mechanism of Schiff base formation from glycine and formaldehyde has been studied by a variety of computational approaches.[46] Solvent(water)-catalysed reactions of phenylpropanone and ethylamine have been studied by a variety of computational methods.[47]

Mechanisms of imine exchange reactions in organic solvents have been reviewed, especially imine formation, transimination, and imine metathesis.[48]

Non-stabilized azomethine ylides, $^{-}$**:**CH_2–$N^{+}(R^1)$=CH_2, generated *in situ* from *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine, $MeOCH_2N(Bn)$–CH_2SiMe_3, or (methylamino)acetic acid, react with aromatic ketones (R^3–C_6H_4–COR^2) to give 5-aryloxazolines (**33**). HCl treatment ring opens (**33**) to give 2-alkylamino-1-arylethanols (**34**), via demethylenation.[49]

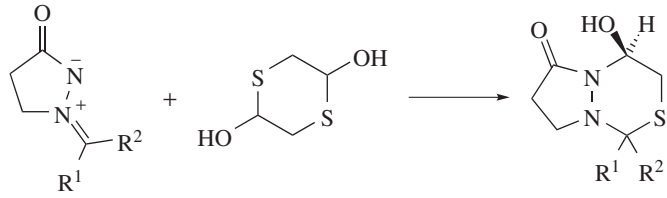


(**33**; R = Bn, Me) (**34**) (**35**)

Stable *N,N′*- and *C,N*-cyclic azomethine imines based on pyrazolidine-3-one (e.g. **35**) and 3,4-dihydroisoquinoline undergo 1,3-dipolar addition to give *N*-arylitaconimides regioselectively.[50] (*de*)

The cycloaddition of 1,4-dithiane-2,5-diol (**36**) with cyclic azomethine imines (**37**) in the presence of DABCO in methanol has been studied by B3LYP and M06-2X functionals. The domino process consists of cleavage of (**36**) to give free mercaptoacetaldehyde, followed by 3 + 3-cycloaddition with imine (**37**). The first step is catalysed by a methanol dimer-mediating proton transfer. Calculations then suggest that DABCO deprotonates the free thiol, followed by nucleophile attack of the thiolate anion on the imine (**37**), and intramolecular cyclization to produce diastereomeric products (**38**), with *de* being mainly determined by hydrogen-bonding effects.[51] (*de*)

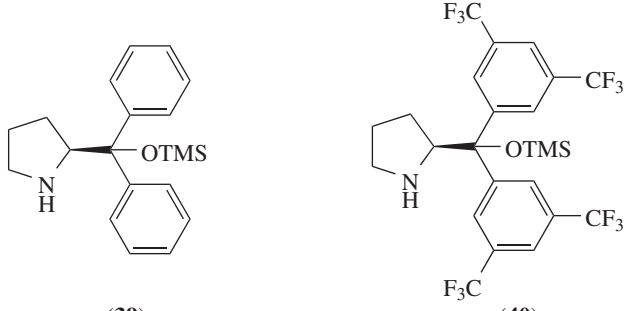
Pyrazolidinones have been prepared via a formal 1,3-dipolar cycloaddition of azomethine imines with mixed anhydrides. The Lewis-base-catalysed process exhibits high *de* and *ee*.[52] (*de*) In a study of iminium ion activation, addition of uncharged nucleophiles to iminium salts derived from MacMillan's first-generation catalyst has been examined (*ee*)



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

for evidence of cation-π interactions. Calculated quadrupole moments were found to linearly correlate with enantioselectivity.[53] *ee*

A computational and kinetic study of the mechanism of prolinol-silyl-ether catalysis of the reaction of α,β-unsaturated aldehydes with cyclopentadiene has highlighted subtle differences between the diphenyl catalyst (**39**) and its trifluoromethyl-substituted analogue (**40**). Proceeding via iminium ions, the reactions can be Michael type, or cycloaddition. The LUMO of the iminium ion derived from (**40**) is lower in energy than that derived from (**39**), favouring the Diels–Alder cycloaddition type. In contrast, the Michael type is favoured for (**39**) as it forms the iminium ion quicker. While acid promotes iminium ion formation, it also protonates anionic nucleophiles, so Michael reaction requires careful choice of appropriate acid.[54] *de* *ee*

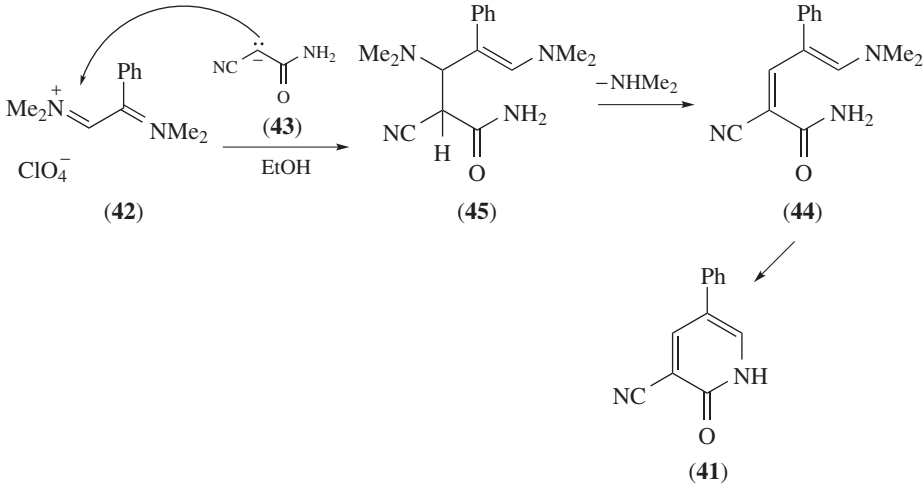


(**39**) (**40**)

An investigation of the formation of pyridine-2(1*H*)-one (**41**) from a vinamidinium salt (**42**) and cyanoacetamide (**43**, shown as its conjugate base) has identified, isolated, and characterized 2-cyano-5-(dimethylamino)-4-phenylpenta-2,4-dienamide (**44**) as an intermediate, formed by loss of dimethylamine from the initially formed adduct (**45**).[55]

A review has examined the progress in green transition-metal-catalysed C–H and C–C activation for the case of propargylic amines, that is C(sp^3)–H and C(sp^3)–C(sp) activation, typically via iminium intermediates.[56]

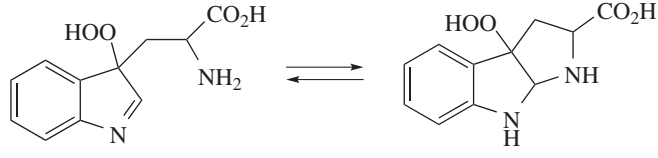
A formal C(sp^3)–H activation seen in rhodium(I)-catalysed direct C–H alkylation of benzylic amines with alkenes has been shown to be a C(sp^2)–H mechanism, that is via an imine intermediate. A benzylic aminopyridine, 2-Py–NH–CH_2–Ph, reacts with an alkene, H_2C=CHR, to give C-alkylated product, 2-Py–NH–CH(CH_2–CH_2–R)–Ph. A primary KIE of 4.3 is seen at the benzylic C–H, together with reversible H–D exchange.[57]



A review of guanylation reactions of amines and carbodiimides discusses four types of mechanisms that have been well characterized.[58] A short review highlights the unique properties of hafnium(IV) triflate as a Lewis acid, focussing on its applications in Friedel–Crafts acylation, and in Mannich-type reactions of imines, hydrazones, and *N,O*-acetals.[59]

E,Z-Isomerization of imines, $(R^1)_2C{=}NR^2$, has been investigated by DFT for a wide range of *C*- and *N*-substituents.[60]

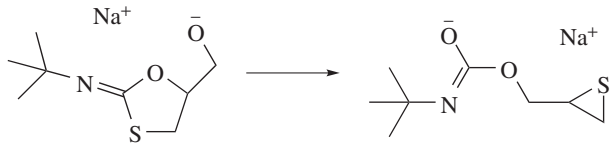
3a-Hydroperoxitryptophan, an intermediate in photodynamic cancer treatment, can exist in an indolenine form (**46**) or the tautomeric pyrroloindoline structure (**47**). Computation has identified two mechanisms of interconversion close to the isoelectric point, one involving protonation of the side-chain nitrogen and proton transfer to the other nitrogen, with the second starting with attack of the side-chain amino on the C(2) of the indole. The former predominates at low pH, and the latter at high pH.[61]



Rearrangement of 5-oxymethyl-1,3-oxathiolane-2-imine (**48**) to thiiran-2-ylmethyl-carbonate (**49**) was modelled by DFT.[62]

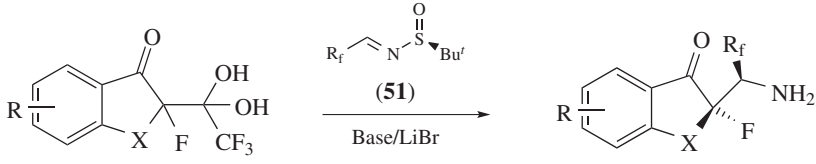
Mannich, Mannich-type, and Nitro-Mannich Reactions

Asymmetric detrifluoroacetylative Mannich addition reactions between 2-fluoro-1,3-diketones (or their hydrates, e.g. **50**) and chiral *N*-sulfinylimines (**51**) give C–F quaternary α-fluoro-β-ketoamines (**52**) in high yields and *de*. Many ring types work (X = CH_2,



(**48**) (**49**)

CH_2CH_2, O, O–CH_2), and a range of fluoroalkyl substituents (R_f) have been used in the imine. (Not shown is the deprotecting step to give free amine, but this is mild, high-yielding, and shows *ee* > 99.5%).[63] *de* *ee*



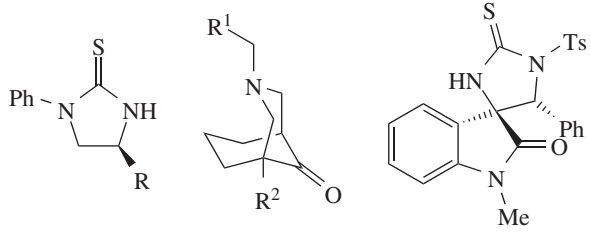
(**50**) (**52**)

β-Amino nitriles with congested vicinal tetrasubstituted stereocentres have been obtained from Mannich reaction of silyl ketene imines with isatin-derived ketimines. Using a chiral *N,N*-dioxide/Zn(II) catalyst, yields/*des*/*ee*s of up to 98/90/99% were achieved.[64] 3-Substituted benzofuran-2(3*H*)-ones undergo Mannich reaction with isatin *N*-Boc ketimines with yield/*de*/*ee* up to 99/90/98%, using a biscinchona catalyst.[65] *de* *ee*

A range of imidazolidine-2-thiones (**53**) derived from L-amino acids have been investigated as chiral auxiliaries in titanium-mediated Mannich reactions, using triphenylphosphine as an additive. The high *de* and *anti*-stereochemistry of the products are explained in terms of a non-chelated TS with the titanium enolate bound to the phosphine. Methanolysis can then be used to cleave (and recover) the auxiliary.[66] *de*

An asymmetric synthesis of azabicyclo[3.3.1]nonanes (**54**) reacts chiral derivatives of 2-oxocyclohexanecarboxylic acid with bis(aminol) ethers, R–$CH_2N(CH_2OEt)_2$, in a double-Mannich process.[67] *de*

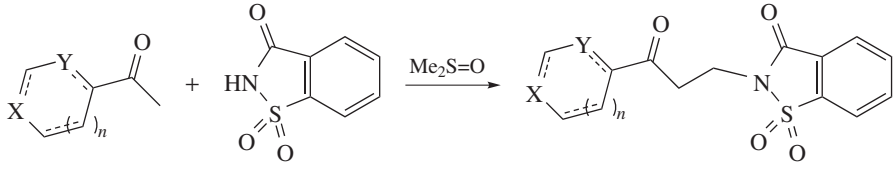
Structurally diverse chiral spiro[imidazolidine-2-thione-4,3′-oxindole] derivatives (e.g. **55**) have been prepared via a domino-Mannich/cyclization of the corresponding 3-isothiocyanate oxindoles with *N*-tosyl aldimines, R–CH=NTs. Commercially available quinine catalysts give yields/*des*/*ee*s up to 99/98/97%.[68] *de* *ee*



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

N-(Benzothiazolyl)imines undergo an NHC-catalysed domino-Mannich/lactamization with α-chloroaldehydes, giving pyrimidinones in yield/*de*/*ee* up to 78/95/99%.[69] (*de*) (*ee*)

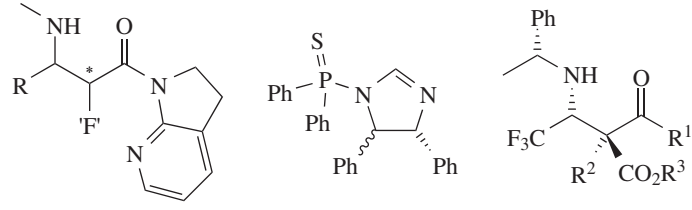
Inspired by classic three-component Mannich syntheses of β-aminoketones, a novel Mannich-type reaction combines an imide source (saccharin, **56**) and acetophenone or acetylheteroarene (**57**), using DMSO as solvent and also as a 'carbon bridge' … in some ways, a formaldehyde surrogate. Selectfluor™ was essential, and – although transition metallic species were not required – best yields of the β-aroyl saccharin products (**58**) were achieved with an $RuCl_3/Na_2CO_3$ combination. Evidence for initial reaction of saccharin (**56**) with DMSO, and for C–S bond cleavage as the rate-limiting step ($k_H/k_D = 4.0$), has helped narrow down the likely mechanisms.[70]



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

Mannich-type reactions of the addition of lithium enolates derived from esters, ketones, and aldehydes to nitrones have been studied by DFT. α-Methoxy and α-methyl enolates react stepwise, with initial nucleophilic attack of the enolate on the carbon of the nitrone followed by nucleophile attack of the oxygen of the nitrone to the formed carbonyl group. However, the calculations show α-unsubstituted enolates reacting in a highly asynchronous one-step process, with C–O bond formation lagging well behind the formation of the (first) C–C bond.[71]

Fluorinated β-amino acid derivatives (**59**; 'F' = F, CF_3, and other R_f) have been made by Mannich-type reaction of appropriately fluorinated 7-azaindoline amides with aldimines, RCH=N–PG, with yield/*de*/*ee* up to 96/95/99%, using a chiral diphosphine catalyst.[72] (*de*) (*ee*)



(**59**) (**60**) (**61**)

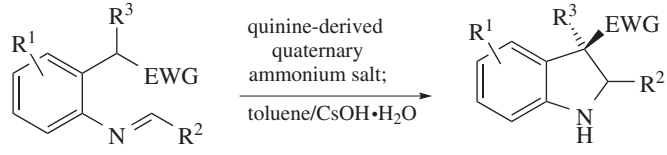
N-(Diphenylthiophosphinoyl)imines, Ph–CH=N–P(=S)Ph_2, undergo direct catalytic Mannich-type reactions with benzyl isocyanide (Ph–CH_2–$N^+\equiv C{:}^-$), using a copper(I) catalyst as soft Lewis acid, a chiral phosphine ligand, and potassium *t*-butoxide in toluene at ambient temperature. The 1,2-diphenyl products (**60**) were obtained in good yield, fair *ee*, and moderate *de* (predominantly *trans*-). To access free 1,2-diarylethylenediamines

requires aqueous $HClO_4$ at 65 °C (to remove the thiophenylphosphine), followed by basic hydrolysis of the imidazoline with aqueous $Ba(OH)_2$ at 80 °C.[73] (de) (ee)

β-Keto esters (R^1–CO–CHR^2–CO_2R^3) undergo diastereoselective Mannich-type reactions with chiral trifluoromethyl aldimines [e.g. F_3C–CH=N–CH(Ph)–Me], catalysed by zirconium tetrachloride. The reaction proceeds at ambient temperature in <30 min, without solvent, producing a highly functionalized product (**61**) with three chiral centres as a single *anti*-diastereomer, in 68–80% yield.[74] (de)

Asymmetric Mannich-type reactions of *N*-Boc imines use an alkyl ketone as an enolate equivalent. A zinc phenolate catalyst with diphenylprolinol ligands pendant in the *ortho*-positions gives yield/*de*/*ee* performance of up to 99/95/99% in THF.[75] (de) (ee)

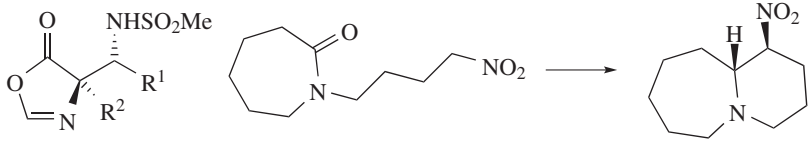
Indolines (**63**) have been prepared in good to excellent yields with *de*/*ee* up to 95/99% from appropriate aldimines (**62**). The process is auto-inductive, and is phase-transfer *initiated* (as against phase-transfer-catalysed), with most steps occurring in the organic phase. The cyclization is a kinetically controlled 5-*endo*-trig process. The mechanistic conclusions are supported by kinetic, NMR, and DFT studies.[76] (de) (ee)



(**62**) (**63**)

In situ-generated *N*-Boc imines have been prepared under both acidic and basic conditions from *N*-Boc-aminals, R–$CH(NHBoc)_2$, with a wide variety of R groups: aryl, alkyl, *E*- and *Z*-alkenyl, and alkynyl. The novel precursors have been demonstrated in asymmetric Mannich-type reactions under phase-transfer conditions.[77] (de) (ee)

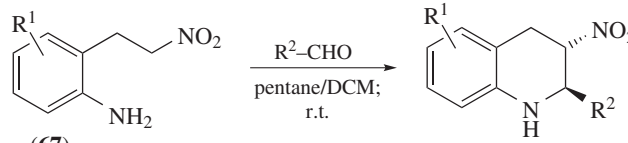
Azlactones undergo Mannich-type reaction with aldimines, R^1–CH=N–SO_2Me, to give azlactone derivatives (**64**) with two contiguous chiral centres. Using a buttressed BINOL-phosphoric acid catalyst, yield/*de*/*ee* up to 74/90/98% was achieved.[78] (de) (ee)



(**64**) (**65**) (**66**)

In an unusual reductive nitro-Mannich cyclization, an 'unreactive' lactam with a tethered nitro group (**65**) undergoes chemoselective partial reduction to a 'reactive' iminium, followed by a diastereoselective nitro-Mannich cyclization to bicyclic product (**66**). Two equivalents of a silane [$(Me_2HSi)_2O$] and Vaska's catalyst [$IrCl(Co)(PPh_3)_2$] followed by HCl give yields/*de*s up to 80/94% in toluene at ambient temperature. NMR evidence for an enamine is presented, followed by iminium ion on addition of HCl.[79] (de)

trans-2-Aryl- or *trans*-2-alkyl-3-nitro-tetrahydroquinolines (**68**) with two contiguous chiral centres have been prepared from *ortho*-(*β*-nitroethyl)anilines (**67**) via an intramolecular aza-Henry (nitro-Mannich) reaction. Using a chiral thiourea catalyst derived from a quinine alkaloid, good yields, *de*s, and *ee*s were obtained across a wide range of aldehydes and aniline substituents.[80] (de) (ee)



(**67**) (**68**)

α-Substituted vinylogous nitronates have been generated catalytically from *α*,*β*-unsaturated nitroolefins, setting up a highly stereoselective aza-Henry reaction with *N*-Boc aldimines.[81] (de) (ee)

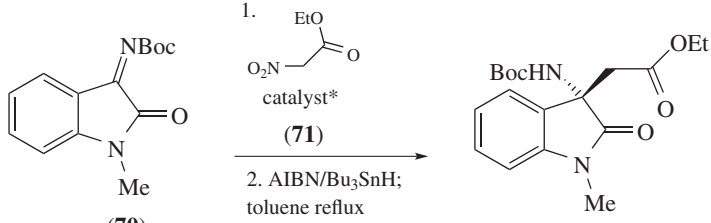
Inexpensive cinchonidinium acetate catalyses aza-Henry reaction of an *N*-Boc imine (Ph–CH=N–Boc) with arylnitromethanes to give *cis*-stilbenediamines (in masked form) in good *de* and *ee*. Key to the catalysis is the formation of the kinetic *syn*-product without causing epimerization of the highly acidic *α*-nitro stereocentre.[82] (de) (ee)

In a similar vein, aryl *N*-Boc imines, Ar^1–CH=N–Boc, undergo highly stereoselective aza-Henry reactions with *α*-aryl nitromethanes, Ar^2–CH_2NO_2, using chiral BINAP-betaine catalysts. The *β*-nitro-*N*-Boc-amine products, after reduction and deprotection, yield non-racemic *anti*-1,2-diarylethylenediamines, *anti*-Ar^1–*CH(NH_2)–*CH(NH_2)–Ar^2.[83] (de) (ee)

A chiral 1,2-cyclohexyldiamine bearing quinolyl groups catalyses aza-Henry reaction of nitromethane and *N*-Boc phenylaldimine. DFT studies have identified deprotection of the nitromethane as rate-limiting step, while C–C bond formation is enantiodetermining. As well as being a Brønsted base, the catalyst activates both nucleophile and electrophile via hydrogen bonding.[84] (ee)

3-Ethylacetate-substituted 3-amino-2-oxindoles (**69**) have been prepared in high *ee* using a cinchona-alkaloid catalyst. Starting with isatin-derived *N*-Boc imine (**70**), a Mannich reaction is carried out with ethyl nitroacetate (**71**), followed by denitration. The nitro group thus acts as a traceless activating and directing group.[85] (ee)

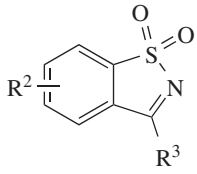
Malonic acid half thioesters ('MAHT's, HO_2C–CH_2–$COSR^1$) undergo enantioselective decarboxylative Mannich reaction with cyclic *N*-sulfonyl ketimines (**72**).



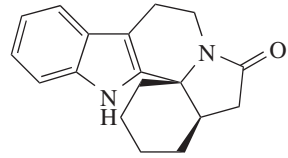
(**70**) (**69**)

Using cinchona-alkaloid catalysts, yields/*ee* of up to 99/92% are reported. NMR evidence points to the initial nucleophilic addition of (**72**) to the MAHT, followed by decarboxylation.[86] *ee*

An MS charge-tag strategy has revealed key intermediates in the Petasis Borono-Mannich multi-component reaction. One such intermediate was isolated and characterized by single crystal X-ray diffraction.[87]



(**72**)



(**73**)

A BINOL-derived phosphoric acid catalyses asymmetric Pictet–Spengler reaction of tryptamine with (2-oxocyclohexyl)acetic acid to give a *β*-carboline (**73**). DFT and hybrid quantum mechanics/molecular mechanics (QM/MM) calculations have now been employed to explain the *de*/*ee* observed.[88] *de*

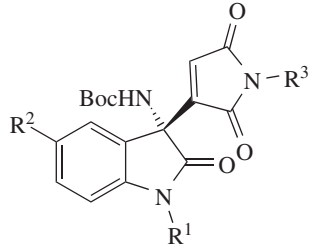
A Mukaiyama–Mannich reaction of *N*-Boc isatin ketimines[185] is described in the 'Aldols' section.

Other 'Name' Reactions of Imines

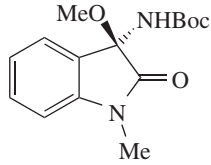
An organocatalysed asymmetric tandem reaction of cyclic *N*-sulfonylimines with *α,β*-unsaturated aldehydes yields tricyclic piperidines with yield/*de*/*ee* up to 93/95/99.7% via a Michael-type process.[89] *de* *ee*

The use of *N*-substituted maleimides as nucleophiles in aza-Morita–Baylis–Hillman (MBH) reactions of ketimines derived from isatin has been described, giving 3-substituted-3-amino-oxindoles (**74**) in up to 99% *ee*.[90] *ee*

ortho-Diphenylphosphinobenzaldehyde reacts with *N*-tosyl-1,2-phenylenediamine to give the product of intramolecular Wittig reaction, *N*-[2-{2-(diphenylphosphoryl)-benzylamino}phenyl]-4-methyl-benzenesulfonamide. The product was characterized by NMR and IR, and the mechanism was explored using DFT.[91]



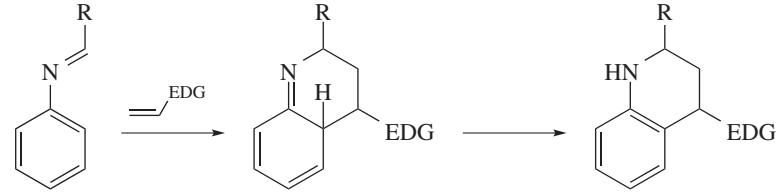
(**74**)



(**75**)

Nickel(II) complexed with a chiral bis(imidazolidine)pyridine catalyses addition of methanol or organic peroxides to an isatin-derived *N*-Boc imine to give chiral quaternary *N,O*-acetals (e.g. **75**) in high yields and *ee*s.[92] (*ee*)

The Povarov reaction combines an *N*-aryl imine (**76**) with an electron-rich alkene to give a formal [4 + 2] cycloadduct (**77**), followed by an aromatizing 1,3-hydrogen shift to a tetrahydroquinoline (**78**). The first step, an aza-Diels–Alder, is traditionally catalysed by Lewis acid, but more recently Brønsted acids have been used to activate the imine. Such a reaction between *N*-phenyl-*C*-methoxycarbonyl imine (Ph–N=CH–CO_2Me) and diphenyl-methylene–cyclopropane has now been studied by DFT. Protonation of the imine allows it to react with the alkene in an intramolecular Friedel–Crafts-type reaction.[93]



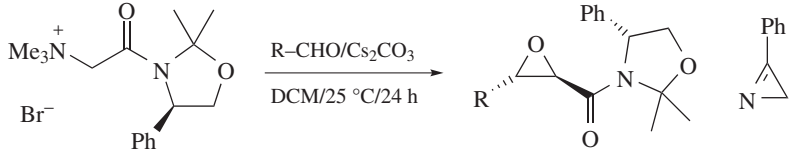
(**76**) (**77**) (**78**)

Whether Staudinger reactions of chloro-cyano-ketene with unsaturated imines give δ- or β-lactones has been studied by DFT; the former product is favoured in the absence of countervailing steric effects.[94]

Synthesis of Azacyclopropanes and Azirines

Nucleophilic addition to >C=O and >C=N bonds to produce epoxides and aziridines has been reviewed from 1991 to date.[95]

Chiral ammonium ylide precursor (**79**) undergoes epoxidation under mild conditions in good yields with *de* typically >98% for a range of R groups: aromatic, aliphatic, and alicylic. Replacement of the aldehyde with an *N*-protected aldimine gives the corresponding aziridine.[96] (*de*)



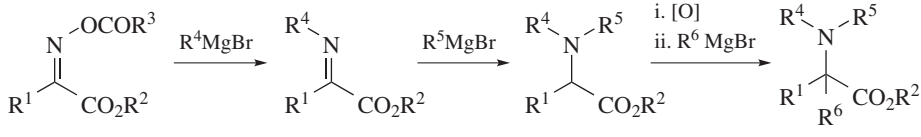
(**79**) (**80**) (**81**)

UV methods and DFT have been used to examine the reaction of a simple imine, MeCH=NEt, with R–NHBr to give 1,2,3-trialkyldiaziridines.[97]

3-Phenylazirine (**81**) reacts with butane-1,2,4-tricarbonyls to give functionalized pyrroles via transition-metal-catalysed reactions, yielding mixtures of the 3-(1,2-dioxyethyl) and 2,3-dicarbonyl products via an azirine–metal complex intermediate.[98]

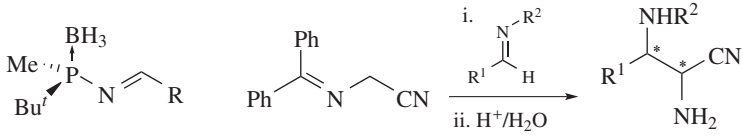
Alkylations, Arylations, Allylations, and Additions of Other C-Nucleophiles

α-N-Acyloxyiminoesters (**82**) have proved to be highly versatile precursors to a wide range of substituted *α*-amino esters (**84**, **85**). Attack by Grignard reagent gives *N*-substituted imino-ester (**83**, previously inferred, now isolated). Another Grignard can react again at nitrogen (to give **84**), and subsequent oxidation and a further Grignard gives (**85**). So the starting material allows access to *N*-alkyl, *N,N*-dialkyl, and *N,N,C*-trialkyl products.[99]



(**82**) (**83**) (**84**) (**85**)

Borane has been used as a directing group for addition of organolithiums to *N*-phosphanylimines. Coordination of a *P*-stereogenic *N*-phosphanylimine with borane (e.g. **86**), followed by 1,2-addition of R^2–Li, gives the corresponding phosphanylamine in up to 98% *de*. Changing from non-coordinating DCM to THF reverses the selectivity.[100] (*de*)



(**86**) (**87**) (**88**)

α-Aminoacetonitriles, protected as their diphenylmethylidene derivatives (**87**), undergo enantioselective reaction with aromatic aldimines to give highly functionalized diastereomeric products (**88**), using chiral palladium catalysts and silver(I) co-catalyst. Yields/*des*/*ee*s of up to 95/98/99% were obtained. A palladium ketenimide intermediate, $Ph_2C{=}N{-}CH{=}C{=}N{-}Pd^*$, is proposed, which then reacts with the aldimine; MS and DFT evidence is provided.[101] (*de*) (*ee*)

α,α-Diaryl-*α*-amino acid esters, $Ar^1Ar^2C^*(NH_2){-}CO_2R$, have been accessed via a rhodium-catalysed asymmetric addition of arylboronic acids to cyclic aromatic *N*-sulfonyl ketimines, followed by deprotection.[102] (*ee*)

A new mechanism has been proposed for the enantioselective phenylation of (*E*)-*N*-propylidene–tosylsulfonimide, (*E*)-Et–CH=N–Ts, catalysed by a rhodium(I) species, $Rh(OH)(diene^*)_2$. Phenylboronic acid is found to play a dual role as aryl source and proton donor. The DFT study rules out a role for water and indicates that the phenylboronic acid–phenylboroxin equilibrium is not relevant.[103]

A chiral ferrocenyl-palladacycle catalyses enantioselective arylation of *N*-sulfonylimines by arylboroxines.[104] (*ee*)