ORGANIC REACTION MECHANISMS

EDITOR
A. C. KNIPE

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ORGANIC REACTION MECHANISMS · 2010

An annual survey covering the literature dated January to December 2010

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A. C. Knipe
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Contributors

K. K. BANERJI	Faculty of Science, National Law University, Mandore, Jodhpur 342304, India
C. T. BEDFORD	Department of Chemistry, University College London, 20 Gordon Street, London, WC1H 0AJ, UK
M. L. BIRSA	Faculty of Chemistry, "Al. I. Cuza" University of Iasi, Bd. Carol I, 11, Iasi 700506, Romania
A. BRANDI	Dipartimento di Chimica Organica "U. Schiff", Universita' degli Studi di Firenze-Polo Scientifico, Via della Lastruccia 13 1-50019 Sesto Fiorentino (Fl), Italy
J. M. COXON	Department of Chemistry, University of Canterbury, Christchurch, New Zealand
M. R. CRAMPTON	Department of Chemistry, University of Durham, South Road, Durham, DH1 3LE, UK
N. DENNIS	3 Camphor Laurel Court, Stretton, Brisbane, Queensland 4116, Australia
M. GENSINI	Department of Chemistry, Menarini Ricerche S.p.A., Via Sette Santi, 3, 50131 Florence, Italy
E. GRAS	Laboratoire de Chimie de Coordination, CNRS, 205 Route de Narbonne, 31077 Toulouse Cedex 4, France
A. C. KNIPE	Faculty of Life and Health Sciences, University of Ulster, Coleraine, Northern Ireland
P. KOČOVSKÝ	Department of Chemistry, The Joseph Black Building, University of Glasgow, Glasgow G12 8QQ, UK
R. A. McCLELLAND	Department of Chemistry, University of Toronto, 80 St George Street, Toronto, Ontario M5S 1A1, Canada
B. A. MURRAY	Department of Science, Institute of Technology Tallaght (ITT Dublin), Dublin 24, Ireland
K. C. WESTAWAY	Department of Chemistry and Biochemistry, Laurentian University, Sudbury, Ontario P3E 2C6, Canada

Preface

The present volume, the forty-sixth in the series, surveys research on organic reaction mechanisms described in the available literature dated 2010. 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.

In view of the considerable interest in 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*).

Some changes of authorship will be apparent as Sue Armstrong (Molecular Rearrangements: Pericyclic) and Bob Coombes (Electrophilic Aromatic Substitution) have found it necessary to step down, having previously made excellent contributions to ORM for eight and twenty years respectively. Hopefully they will be reassured to find that their chapters are now in the safe hands of continuing members of the team.

Steps taken to reduce progressively the delay between title year and publication date have continued to bear fruit, as evidenced by the publication of recent annual ORM volumes at nine-month intervals. Consequently we hope to regain our optimum production schedule soon.

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, particularly during a period of substantial reorganization of production procedures.

A. C. K.

CONTENTS

CHAPTER 1

Reactions of Aldehydes and Ketones and their Derivatives

B. A. MURRAY

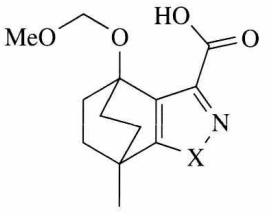
Department of Science, Institute of Technology Tallaght (ITT Dublin), Dublin, Ireland

Organic Reaction Mechanisms 2010, First Edition. Edited by A. C. Knipe.

Formation and Reactions of Acetals and Related Species

A series of pyridinium cations with electron-withdrawing substituents on the ring catalyse acetalization of aldehydes and other protection reactions, such as the formation of dithianes, dithiolanes, dioxanes, and dioxolanes.[1] The best catalyst works at 0.1 mol%, outperforming a Brønsted acid with a pK_a of 2.2.

DFT has been used in the development of a general equation relating the activation energy of an intramolecular proton transfer to r (the distance between the reacting centres) and α (the hydrogen-bonding angle).[2] The equation has been applied to intramolecular general acid catalysis of five of Kirby's acetals (e.g. **1**; X = NH, O). Reaction rates correlate with r^2 and sin $(180^\circ - \alpha)$; that is, acetals with short r values and α close to 180° (forming a linear hydrogen bond) are more reactive.[3]



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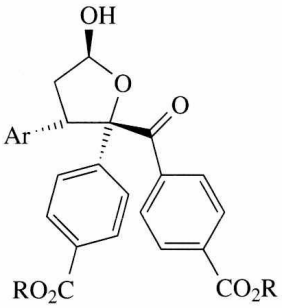

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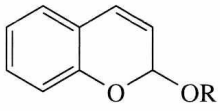


(**3**)

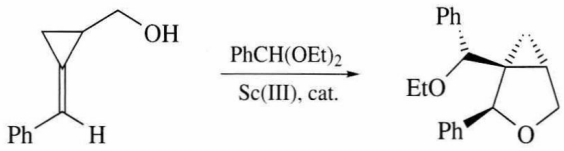
Cyclic hemiacetals (**2**) have been prepared stereoselectively in a 2 : 1 reaction of 4-formylbenzoates and aromatic enals (*trans*-Ar–CH=CH–CHO), using catalysis by *N*-heterocyclic carbenes (NHCs).[4] (de)

A dual acid-catalyst system has been employed for enantioselective addition of alkenyl and aryl boronates to chromene acetals (**3**).[5] The Lewis–Brønsted combination (ee) of a lanthanide triflate and a tartaric acid monoamide gives *ee* up to 97%.

The gas-phase elimination kinetics of several β-substituted acetals have been measured in the range 370–441 °C and in the presence of a radical inhibitor.[6] Two different concerted four-membered transition states are proposed, leading to either the alcohol and vinyl ether (the latter decomposing to alkene and aldehyde) or alkane and alkyl ester.

Methylenecyclopropylcarbinols such as (**4**) react with acetals to give 3-oxabicyclo-[3.1.0]hexanes (**5**); an intramolecular Prins-type mechanism is proposed.[7] (de)

Iron(III) chloride or bromide has been used to catalyse Prins cyclization/halogenation of alkynyl acetals, using an acetyl halide as halogen source.[8]

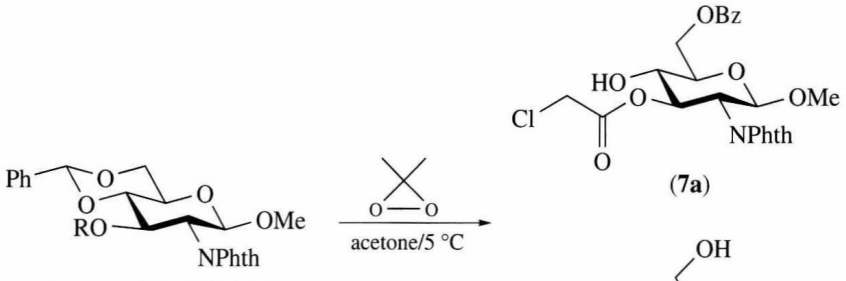


(**4**) (**5**)

Deacetalization of acetals, $R^1CH(OR^2)_2$, in the presence of trifluoroacetic acid has been shown to be viable without water.[9] Although water is a by-product, alcohols are not, and a hemiacetal is not an intermediate. Rather, a hemiacetal TFA ester [R^1–$CH(OR^2)$–$OCOCF_3$] is formed, followed by carbonyl production with two TFA ester byproducts, $F_3CCO_2R^2$. The latter process renders the reaction irreversible. The two esters are produced at separate points in what is essentially a cascade mechanism. All intermediates have been identified by NMR. The new reaction has been dubbed 'acidolysis' to distinguish it from the more familiar acid-catalysed hydrolysis.

Reactions of Glucosides

4,6-*O*-Benzylidene acetals of glycopyranosides (**6**) have been oxidatively cleaved to the corresponding hydroxy-benzoates (**7a/b**) using dimethyldioxirane under mild conditions, and in high yield.[10] Appropriate choice of the neighbouring protecting group gives regioselectivity, with a preponderance of (**7a**) or (**7b**) of >99%, as desired. The balance of electronic and steric effects in the best groups – chloroacetyl and TBS (*t*-butyldimethylsilyl) – is discussed.



(**6**; R = $ClCH_2CO$, TBS) (**7a**) (**7b**)

The stereo- and regio-selectivity of Lewis-acid-catalysed reductive ring-opening of 4,6-*O*-benzylidene acetals have been studied by kinetics, including primary and secondary isotope effects, leading to identification of a range of mechanisms in solvents of varying polarity, and in protocols with Brønsted acid additives.[11] It is hoped that this will lead to new reducing agents, where reactivity and selectivity can be fine-tuned by choice of borane, solvent, Lewis acid, and temperature.

Glycoside hydrolases can give 10^{17}-fold rate enhancements, and estimates of their dissociation constants from their transition states are as low as 10^{-22} mol dm^{-3}. Such affinity has encouraged mimicry, and a number of criteria have now been advanced to assess whether a natural or man-made glycosidase inhibitor is a true TS mimic.[12]

A new dicyanohydrin-β-cyclodextrin acts as an artificial glycosidase, hydrolyzing aryl glycosides up to 5500 times faster than the uncatalysed reaction.[13] Michaelis–Menten parameters are reported and compared with other modified cyclodextrins.

An investigation of nucleophilic substitutions of 2-deoxyglycosyl donors indicates that the more nucleophilic the oxygen nucleophile used, the less stereo-selective the reaction becomes.[14] This erosion of stereo-chemical control is attributed to the rate (de) of the stereochemistry-determining step approaching the diffusion limit, when the two faces of the prochiral oxocarbenium ion are subject to nucleophilic addition to afford a statistical mixture of diastereomers.

Recent advances in understanding mechanisms of chemical *O*-glycosylation have been reviewed.[15] pH-rate profiles have been constructed and analysed for glycosylation reactions of a range of aromatic amines.[16]

Oxime formation from sugars can be slow, but nucleophilic catalysis by aniline (at 100 mM) can increase rates up to 20-fold, and glycosylamine formation has to be watched.[17]

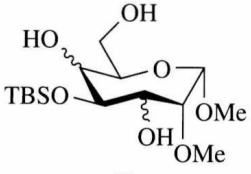
A DFT method has been applied to scan the potential energy surface of furanosyl oxocarbenium ions.[18] The results suggest that the preferred oxocarbenium ion (de) conformation is *not* a consistent predictor of product stereochemistry.

A chiral Brønsted acid, a BINOL-phosphoric acid, activates trichloroacetimidate glycosyl donors with β-selectivity.[19] (de)

An account describes the mechanistic investigations that have led to a fuller understanding of the use of the 4,6-*O*-benzylidene acetal as a control element in glycosylation, giving direct access to β-mannopyranosides in high yield and selectivity.[20] (ee) (de)

A rhodium(II)-carbene-promoted activation of the anomeric C–H bond of carbohydrates has been used to provide a stereospecific entry to α- and β-ketopyranosides.[21] (de)

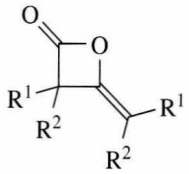
Three unnatural methyl α-septanosides (**8**), with the 3- and 5-hydroxyls *ax–eq*, *eq–ax*, and *eq–eq* have been synthesized, and their rates of hydrolysis measured by ^{1}H NMR at 50 °C in 0.5 mol dm^{-3} DCl.[22] The hydroxyl orientation affects the rate, (de) with equatorial being more electron withdrawing than axial. Comparison with rates for analogous methyl α-pyranoside structures shows that, while the inherently less stable seven-membered sugars react about two orders of magnitude faster, the rank ordering is the same.



(**8**)

Reactions of Ketenes

Keto-ketenes ($R^1R^2C{=}C{=}O$) homodimerize to β-lactones (e.g. **9**), thereby providing an important way of accessing such compounds. Catalysis by tributylphosphine has been investigated by NMR, and evidence for tetravalent phosphonium enolate intermediates (**10**) is presented: they can be trapped as their TMS ethers or by reaction with 4-chlorobenzaldehyde (to give a β-lactone). Such enolates may prove useful in other synthetic methodologies. There was no evidence for pentacovalent phosphorus intermediates.[23] (de)



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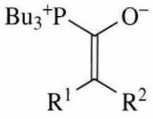


(**10**)

DFT investigation of Staudinger 2 + 2-cycloaddition of a ketene and an imine, catalysed by NHCs, favour the 'ketene-first' mechanism, that is, it is the ketene that is initially activated by the NHC. This mechanism persists even when variation in the electrophilicity of the imine leads to stereodivergence in the experimental results.[24] NHCs also promote the chlorination of unsymmetrically disubstituted ketenes, $R^1R^2C{=}C{=}O$; the products are typically α-halo esters [$R^1R^2C^*(Cl)–CO_2R^3$] under the conditions employed. With chiral NHCs, modest *ee*s of up to 61% are seen.[25] (ee)

Dimerization and trimerization reactions of thioformaldehyde and dimerization of thioketene have been studied by computation.[26]

Formation and Reactions of Nitrogen Derivatives

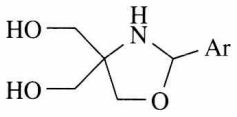
Synthesis of Imines

The affinities of a wide-ranging array of imines for hydride, proton, and electron have been measured by titration colorimetry and by electrochemical methods, in acetonitrile.[27] Thermodynamic 'characteristic graphs' are then introduced, linking the energies of the processes for each imine: each graph is intended to give the 'molecular ID' of the imine, facilitating prediction of likely reactions and mechanisms thereof.

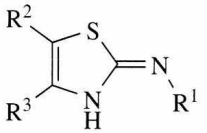
The mechanism of Schiff base formation between pyridoxal analogues and aldehydes has been studied by DFT.[28]

P–N–P 'pincer' complexes of ruthenium catalyse a new imine synthesis, from an alcohol and an amine, with evolution of hydrogen.[29]

Formylpyridines react with tris(hydroxymethyl)aminomethane [$(HOCH_2)_3CNH_2$, 'TRIS'], to give 1,3-oxazolidines (e.g. **11**), which can equilibrate with their acyclic tautomers, that is, Schiff bases. Anomeric and hydrogen-bonding effects have been studied in these systems, including the adduct derived from pyridoxal.[30] Oxazolidines such as (**12**) – derived from TRIS and a benzaldehyde – have been prepared and then



(**11**; Ar = 4-Py;
12; Ar = Ph-X)



(**13**)

ring-opened under acetylating conditions. X-ray crystal data and computations indicate a strong *endo* anomeric effect stabilizing a conformation that leads to regioselective ring opening to give imine (rather than *N*-acetyloxazolidine). Imine-oxazolidine equilibria are also reported, and a per-*O*-acetylated imine, $(AcOCH_2)_3$–C–N=CHAr, in the *para*-nitro case.[31]

An alkyl or aryl group, R^1, in a 2-iminothiazole (**13**) can be exchanged with that in an isothiocyanate, R^4–N=C=S, in toluene at 105 °C.[32] The position of equilibrium in this reversible reaction is mainly dependent on the electronic properties of the exchanging groups (i.e. R^1 and R^4) and has been used to empirically compare the electrophilicity of various isothiocyanates.

2-Substituted benzimidazoles have been prepared by condensation of various aldehydes with 1,2-phenylenediamine, using copper(II) triflate catalyst, in refluxing acetonitrile.[33]

The Mannich Reaction

Organocatalytic asymmetric Mannich reactions have been reviewed, focussing on proline derivatives,[34] as have Mannich preparations of alkyl- and cycloalkyl-amines.[35] (*ee*) (*de*)

The autocatalysis previously seen in enantioselective Mannich reactions catalysed by L-proline and related species has been reinvestigated, using both the products themselves and close structural mimics.[36] (*ee*) (*de*)

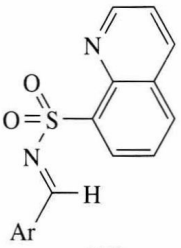
The 1-ethyl-3-methylimidazolium salt of (*S*)-proline acts as an ionic liquid (IL), which gives 'three 99s' performance (yield/*de*/*ee*) in a one-pot three-component Mannich reaction.[37] The reaction shows excellent chemo- and regio-selectivities, the precursors are cheap, the process tolerates moisture, and it can often be conducted at −20 °C. (*ee*) (*de*)

A diastereoselectivity switch has been engineered in the direct Mannich reaction of glycine imines, R^1O_2C–CH_2–N=CR^2R^3, with *N*-(8-quinolyl)sulfonyl imines (**14**).[38] Steric and electronic tuning of the R groups of the glycine imine switches the selectivity from *syn*-α,β-diamino acids (for benzophenone-type imines) to *anti*- (for electron-rich aldimines). An Fe-sulfos-Cu(I) chiral catalyst gives *ee*s of 99% in many cases. (*ee*) (*de*)

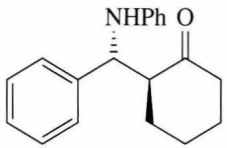
An *anti*-selective reaction of aldehydes with *N*-sulfonyl imines exploits hydrogen bonding involving a 4-hydroxypyrrolidine catalyst and an external Brønsted acid.[39] (*de*)

DFT methods have been used to study diastereoselective reactions of ketimine with aldehyde, using both L-proline and (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine, catalysts that give opposite diastereoselectivities.[40] (*ee*) (*de*)

Ferrocenyl cation, as its PF_6^- salt, catalyses Mannich reaction of benzaldehyde, aniline, and cyclohexanone to give β-aminoketone (**15**), with some *anti*-preference,



(**14**)



(**15**)

under solvent-free conditions.[41] Tests of two-reactant combinations indicate that the reaction proceeds initially via imine rather than aldol formation. (de)

Bench-stable α-amido sulfones have been used to generate *N*-Boc amino-protected imines, which then undergo *in situ* Mannich reactions with glycine Schiff-bases, using a cinchonidine–thiourea catalyst, to give α,β-diamino acid derivatives with *ee*/*de* close to 100%.[42] In a similar strategy, a highly diastereo- and enantio-selective aminocatalytic Mannich reaction of aldehydes with *N*-carbamoyl imines involves their generation *in situ* from such α-amido sulfones.[43] (ee) (de) (ee) (de)

DFT-calculated *ee*s and *de*s compare well with observed values for *anti*-Mannich and *syn*-aldol reactions catalysed by axially chiral amino sulfonamides.[44] (ee) (de)

While chiral phosphoric acids such as 3,3′-disubstituted BINOLs have been known to catalyse direct Mannich-type reaction of aldimines with 1,3-dicarbonyls, such catalysts can be contaminated by group I/II metal cations. Deliberate introduction of such cations, especially calcium, confirms that the metal salts may be the 'true' catalysts, giving higher yields and *ee*s in some cases.[45] (ee)

Enantioselective Mannich reactions of diethyl fluoromalonate with *N*-Boc aldimines using chiral bifunctional organocatalysts give (β-aminoalkyl)fluoromalonates in 93–97% *ee*,[46] and bifunctional amine–thiourea catalysts derived from rosin give high *ee* and *de* in reaction of lactones with such imines.[47] (ee) (ee) (de)

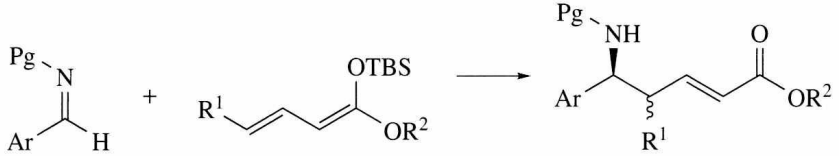
N-Sulfonylcarboxamides of proline catalyse Mannich reaction of cyclic ketones with *N*-protected iminoglyoxylate, with *de*/*ee* up to 94/99%. Enamine intermediates have been examined by DFT.[48] (ee) (de)

The first catalytic, enantioselective vinylogous Mannich reaction of acyclic silyl dienolates (**17**) has been reported. Using protected imines (**16**), *ee*s up to 98% have been achieved (R^1 = H), and more highly substituted products (**18**, R^1 = Me) can be prepared diastereoselectively. A second-generation BINOL-based phosphoric acid catalyst developed for the process has been studied by NMR, and a crystal structure of the imine-bound catalyst was obtained, shedding light on the facial selectivity of the reaction.[49] (ee) (de)

A Yb/K heterobimetallic catalyst and a chiral amide ligand promote nitro-Mannich (aza-Henry) reactions in up to 86% *ee*.[50] (ee)

Addition of Organometallics

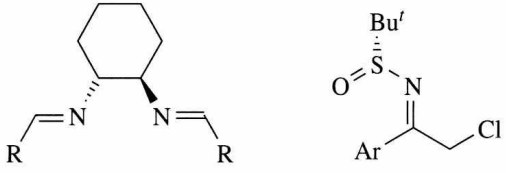
Advances in copper-catalysed enantioselective addition of dialkylzincs to imines have been reviewed back to 2000.[51] (ee)



(**16**) (**17**) (**18**)

Nickel(II) and a spiro-chiral phosphine catalyse the three-component coupling of imines, diethylzinc, and aromatic alkynes with *ee* up to 98%, and with good chemoselectivity, to give useful allylic amines.[52] (*ee*)

Diimines (**19**; R = Ph, 2-pyrrolyl, 2- and 4-pyridinyl, 2,2′-bithiophen-5-yl) have been prepared from (*R*,*R*)-1,2-diaminocyclohexane and aromatic aldehydes.[53] Addition of organolithiums and allylzinc proceeds in high yield and *de* (except for the 2-pyridine case), giving diamines with four chiral centres. The latter have also been tested as enantioselective catalysts for the Henry reaction. (*de*)



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

Quantitative structure–reactivity relationships (QSSR) have been used to examine enantioselectivity in the addition of organolithiums to imines.[54] (*ee*)

Chiral α-chloro *N*-*t*-butanesulfinyl ketimines (**20**) react with Grignards to give chiral aziridines with *de*/*ee* up to 96/98%; the stereoselectivity is opposite to that found for imines without the α-chloro substituents, presumably due to chlorine coordination of the incoming Grignard.[55] (*ee*) (*de*)

The reactions of Grignard reagents with imines have been contrasted for catalytic and stoichiometric amounts of titanium alkoxide reagents.[56] The former favours alkylation, while the latter gives reductive coupling, with distinctive mechanisms for each, as shown by studies using deuterium-labelled substrates.

Chiral phosphinoylimines have been prepared in high yield and good *de* by addition of Grignards to new *P*-chirogenic *N*-phosphinoylimines.[57] (*de*)

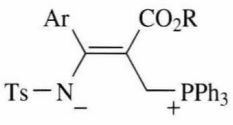
For more references to Grignards and imines, *see* under 'Addition of Other Organometallics, Including Grignards' *below*.

Other Arylations, Alkenylations, and Allylations of Imines

Rhodium-diene complexes catalyse arylation of *N*-tosyl ketimines by addition of sodium tetraarylborates. Using a chiral diene renders the process highly enantioselective.[58] (*ee*)

Enantioselective formal alkenylations of imines, catalysed by axially chiral BINAP dicarboxylic acids, have been carried out using vinylogous aza-enamines.[59] As the latter can be oxidized to nitriles, the route can allow access to enantiomerically enriched γ-amino α,β-unsaturated nitriles, and thus to synthetically useful chiral γ-amino acids. (*ee*)

In the triphenylphosphine-catalysed reaction of alkyl propiolates with *N*-tosylimines, a stable phosphonium-enamine zwitterion (**21**) of proven importance in the mechanism has been isolated and characterized by X-ray crystallography.[60] Deuterium-labelling experiments have identified several hydrogen-specific processes, none of which limit turnover, but they are highly medium dependent.



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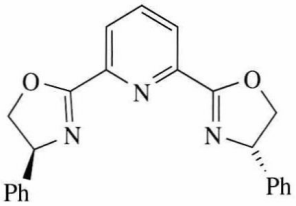

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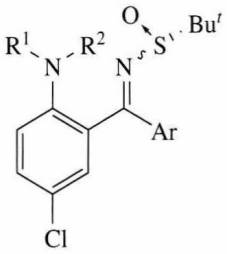

(**23**)

N-protected α-imino esters, for example, Pg-N=CH–CO_2Et, have been alkynylated with terminal alkenes using copper(I) triflate and a PYBOX ligand (**22**).[61] Surprisingly, excess ligand does *not* raise the *ee*, but excess copper does, and a switch in metal-to-ligand ratio alone can reverse the *ee*. A modest positive non-linear effect was observed, and it is suggested that changing the metal-to-ligand stoichiometry may alter the coordination geometry at copper, and thus the transition state. (*ee*)

Enantioselective addition of terminal alkynes to imines and their derivatives has been reviewed, including *in situ* examples, that is, three-component reactions of terminal alkynes, aldehydes, and amines.[62] (*ee*)

Chiral phosphinoylimines undergo highly diastereoselective alkynylation with aluminium acetylides, but lithium or magnesium alkynes give poor results.[63] (*de*)

An alkylzinc-mediated enantioselective synthesis of *N*-tosyl-(*E*)-(2-en-3-ynyl)-amines has been developed, working well with various *N*-tosylaldimines.[64] (*ee*)

A review covers diastereo- and enantio-selective alkynylation of imines and iminium ions.[65] (*ee*) (*de*)

Reduction of Imines

Chiral 1,3-diamines have been accessed by diastereoselective reduction of enantiopure *N*-*t*-butanesulfinylketimines (**23**, prepared from the corresponding diaryl ketone).[66] The reduction can be 99 : 1 diastereoselective in either direction, depending on substrate and conditions. X-ray crystallography of reactants and products and NOESY-NMR studies point to unusual directing effects of the *ortho*-substituent in controlling the selectivity. (*de*)

A chiral phosphoramidite ligand has been used to achieve good enantioselectivity in iridium-promoted hydrogenation of benzophenone *N*–H imines, Ar–C(=NH)–Ph, affording chiral diarlmethylamines without the need for *N*-protection.[67] Several *ortho*-substituted substrates gave particularly high *ee*. (ee)

Advances in enantioselective reduction of C=N bonds have been reviewed, focussing on the use of metal-free chiral organocatalysts with Hantzsch esters as hydride source.[68] (ee)

Reductive amination of carbonyl compounds – via transfer hydrogenation of their imine derivatives – has been achieved with cyclometalated iridium complexes.[69] (ee)

Ammonia–borane (H_3N–BH_3) has been employed in a mild, metal-free transfer hydrogenation of imines.[70] A concerted double-hydrogen-transfer mechanism is proposed, backed up by deuterium kinetic isotope effects, Hammett correlations, and *ab initio* calculations. Hydrogenation of other unsaturated systems is being followed up.

Iminium Species

Kinetics of the reactions of iminium ions (pre-generated from cinnamaldehyde and secondary amines) with cyclic ketene acetals were studied by UV–visible spectroscopy.[71] Second-order rate constants have been used to derive values of the electrophilicity parameter, E ($-10 < E < -7$), and these have been analysed using a correlation equation, $\log_{10}k = S(E + N)$, where S and N are nucleophilicity parameters. The equation is then found to predict rate constants for reactions of the iminium ions with a range of other species, such as pyrroles, indoles, and sulfur ylides.

The intermediacy of an iminium ion, $Me_2N^+{=}CH_2$, in the nitrosative cleavage of triethylamine to *N*-nitrosodimethylamine (Me_2N–NO) has been explored in a DFT study designed to elucidate how carcinogenic *N*-nitrosamines form from tertiary amines.[72]

Reaction of dimethyl sulphate with DMF gives methoxymethylene-*N*,*N*-dimethyliminium salt, $Me_2N^+{=}CH(OMe)\ {}^-O_4S$–Me.[73] It acts as an acid promoter of Staudinger synthesis of 2-azetidinones (β-lactams) from imines and substituted acetic acids. Under base catalysis, the carboxylate is proposed to react with the iminium salt to produce an activated ester, which breaks down (again with base catalysis) to yield the corresponding ketene, which is the immediate reactant with the imine.

A review surveys the development and potential of iminium ion catalysis, using ions formed by the condensation of chiral secondary or primary amines with α,β-unsaturated aldehydes or ketones, in a variety of cyclo- and conjugate-addition reactions.[74] (ee) (de)

Other Reactions of Imines

Palladium(II) and rhodium(I) catalysts and chiral disphosphane ligands allow addition of phenylboronic acid, and of phenylboroxine, to *N*-tosylimines, in up to 99% *ee*.[75] (ee)

Azomethine imines (**24**) undergo 1,3-dipolar cycloaddition to homoallylic alcohols, giving *trans*-pyrazolidines (**25**) with excellent regio-, diastereo-, and enantioselectivities and good yields.[76] A tartrate auxiliary and a Grignard in excess complete (ee)