ORGANIC REACTION MECHANISMS

EDITORS
A. C. KNIPE
M. G. MOLONEY

Organic Reaction Mechanisms • 2017

Organic Reaction Mechanisms · 2017

An annual survey covering the literature dated
January to December 2017

Edited by

A. C. Knipe
University of Ulster
Northern Ireland, UK

M. G. Moloney
University of Oxford
England, UK

WILEY

This edition first published 2020

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 Cataloguing in Publication Data

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

Print ISBN: 978-1-119-42619-6

Set in 10/12pt WarnockPro by SPi Global, Chennai, India

10 9 8 7 6 5 4 3 2 1

Contributors

P. ANGELOV	Faculty of Chemistry, Plovdiv University Paisii Hilendarski, Plovdiv, Bulgaria
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 Camphor Laurel Court, Stretton, Queensland, Australia
S. R. HUSSAINI	Department of Chemistry and Biochemistry, The University of Tulsa, Tulsa, OK, United States
E. GRAS	Laboratoire de Chimie de Coordination & Institut des Technologies Avancées en sciences du Vivant, Centre National de la Recherche Scientifique (CNRS), Université de Toulouse, Toulouse, France
P. KOČOVSKÝ	Department of Organic Chemistry, Charles University, and Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Prague, Czech Republic
R. N. MEHROTRA	Department of Chemistry, Jai Narayan Vyas University, Jodhpur, India
J. G. MOLONEY	Department of Chemistry, University of Oxford, Oxford, UK
M. G. MOLONEY	Department of Chemistry, University of Oxford, Oxford, UK

Preface

The present volume, the 53rd in the series, surveys research on organic reaction mechanisms described in the available literature dated 2017. The general format remains as defined in the preface for recent volumes.

This year represents the start of some change for *Organic Reaction Mechanisms* (ORM); Chris Knipe, long-time Editor and Author over a 50-year career, is retiring, and it is appropriate to acknowledge here his outstanding contribution over this period which has firmly established the reputation of *Organic Reaction Mechanisms* as an authoritative and highly respected series providing an annual mechanistic overview of the organic chemical literature. This success comes in particular from a cohort of meticulous and expert chapter authors, most of whom have also made regular contributions over many years. As incoming Editor, I am mindful of the need to maintain these standards which have been so clearly elaborated, but also to ensure that ORM reflects modern practice and meets modern needs. I am aware that there is much to learn! Appropriate subject coverage is difficult, and especially so at a time when new reactions are being developed and discovered at an unprecedented rate, and new technology is opening new opportunities. Rapid developments in (chiral) catalysis mediated by ligands and metals, and photomediated processes, are examples. Of further interest is the development of what might be called classical mechanisms with a distinctly modern twist – direct S_N processes on alcohols, unreactive in a classical context, provide an example. A key question in my mind is becoming: What constitutes a valid mechanism? Computational approaches offer detailed insights undreamt of previously, but should ORM only include experimentally validated mechanistic schemes? Is a plausible but unverified (or even unverifiable) mechanism worthy of inclusion? These questions, coupled with my own learning to grapple with the breadth of subject coverage in a tight page limit, create some interesting challenges, but nonetheless it is my hope and expectation that ORM will continue to meet the needs of readers as a useful resource for teaching, research, and scholarship. If the analysis and insight that ORM provides continues to inform mechanistic considerations in the effective development of organic syntheses, and in the training and education of next-generation chemists, feeding the upward development of our subject, that would surely be a major success. As for this particular volume, I thank Chris for so generously passing on his experience and wisdom, along with our regular and newer authors, whose work is so critical to the success of the volume as a whole.

M.G.M.

Having assumed editorship of ORM in 1977, following experience as an author since 1970, my commitment to the series has been both demanding and fulfilling. Fortunately I was able to recruit expert contributors who, benefitting from the annual allocation of relevant references for their respective chapters, were enabled to apply their reviewing skills to the series for many

consecutive years. I am therefore delighted to learn that Mark Moloney, following this year as co-editor, is likely to retain such support as he applies his considerable mechanistic experience to gradually adjust coverage in line with developing trends.

I particularly wish to thank the dedicated staff of John Wiley & Sons who throughout my editorship worked cooperatively to ensure that the presentation standards of the series were sustained.

A.C.K.

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Reactions of Aldehydes and Ketones and their Derivatives

S. R. Hussaini

Department of Chemistry and Biochemistry, The University of Tulsa, Tulsa, OK, United States

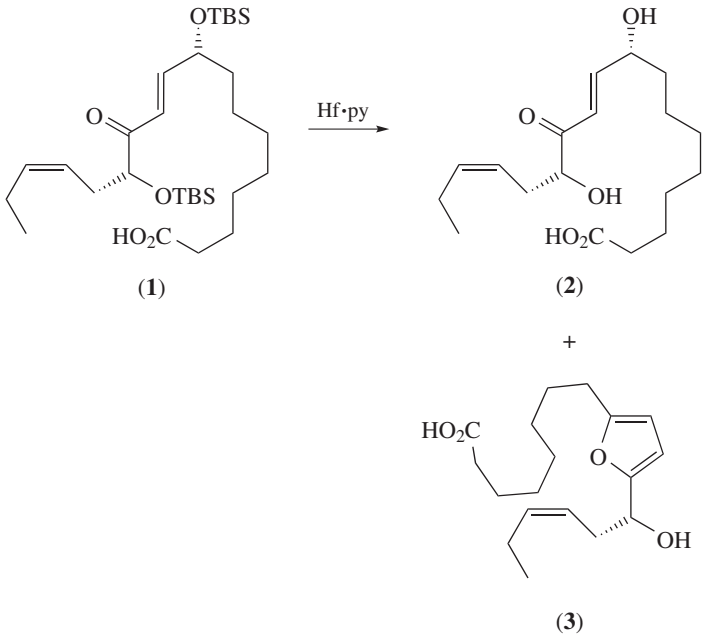
CHAPTER MENU

Organic Reaction Mechanisms 2017, First Edition. Edited by A. C. Knipe and M. G. Moloney.

Formation and Reactions of Acetals and Related Species

Novel nitrated [6,6,6]-tricyclic acetal or ketals are prepared by an intramolecular annulation of *o*-carbonyl allylbenzenes. The proposed mechanism involves olefinic nitration, bis-cyclization, and tautomerization, followed by another nitration. Further tautomerization and dehydration give the product. Non-cyclic products are obtained when the deoxygenated groups are at 4,5-position rather than 3,4-position on the benzaldehyde skeleton.[1]

During the synthesis of sacrolide A, attempted deprotection of (**1**) gave the desired product (**2**) along with an unexpected contaminant (**3**) in substantial amounts. Formation of (**3**) was speculated to be the result of *E*/*Z* isomerization of the conjugated double bond and subsequent cyclic hemiacetal formation followed by dehydration (Scheme 1).[2]

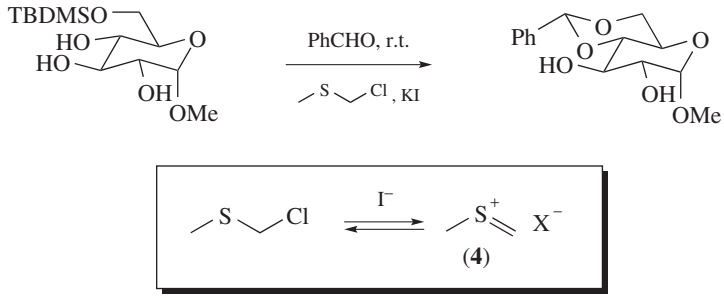


Scheme 1

Chloromethyl methyl sulfide/KI catalyses desilylation and acetal formation. The reaction also works with a combination of (ethylthio)methanol and TBDMSCl or TMSCl, but fails when only (ethylthio)methanol is used. On the basis of this information, and reactivity trends of aldehydes (electron-deficient aldehydes react faster), it is proposed that the active catalyst is methylene sulfonium halide (**4**), which activates the aldehyde and converts the OH group on the aldehyde into a better leaving group (Scheme 2).[3]

Acetal configuration interconversion is observed by ^{1}H NMR spectroscopy for the six-membered ring phenyl-substituted acetal during its formation from the corresponding diol. These diastereomers are hypothesized to interconvert as a result of acid catalysis under the reaction conditions.[4]

A gold(I)-catalysed ring opening of cyclic acetals and ketals by trimethylsilyl alkynes was achieved, which exploits the use of gold(I)-silicon catalysis. The reaction benefits from *in situ* and simultaneous generation of small amounts of a silicon-based super acid and a gold



Scheme 2

alkynylide. The Lewis acid activates the electrophilic cyclic acetal or the ketal, while the *in situ* formed gold alkynylide, which is more nucleophilic than the parent alkynylsilane, attacks the acetal.[5]

Removal of the acetonide group from (**5**) does not result in the formation of expected product (**6**), and instead (**7**) is formed.[6] A plausible mechanism involves an acid-catalysed ring opening of acetonide via deprotonation. Finally, the acid-catalysed removal of hemiketal provides (**7**) (Scheme 3).

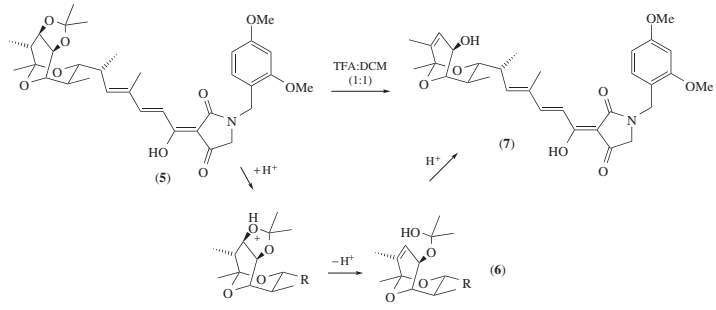
Substituted enaminoesters and acetal groups undergo an intramolecular cyclization with Lewis acids. The reaction probably undergoes a [1,5]-hydride shift after activation of the alkene by the Lewis acid. The zwitterionic intermediate undergoes the cyclization process, providing spirocycles. Density function theory calculations were performed to validate the proposed mechanism. Partial racemization observed in the process is explained using density functional theory (DFT) calculations.[7]

Reactions of Glucosides

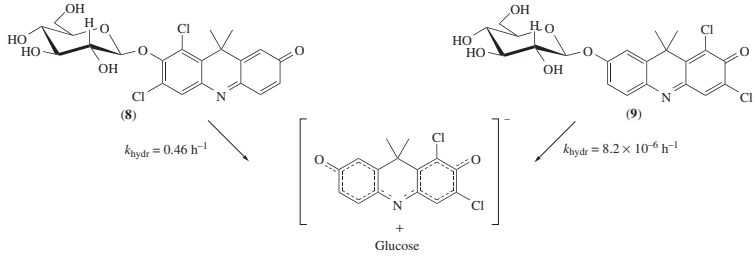
Two isomeric glucosides hydrolyse at rates differing by 10^6-fold, despite the fact that they both give the same hydrolysed products (Scheme 4). Experimental and quantum chemical calculations revealed that ground-state destabilization and transition-state stabilizing effects are responsible for the observed reactivity differences. The ground-state destabilization in (**8**) is due to a longer glycosidic bond length because of a negative inductive effect of the proximal chlorine atom. Compared to (**9**), the transition state for the hydrolysis of (**8**) has better stabilization of the charge at the leaving group oxygen due to the presence of proximal chlorines.[8]

A Pd-catalysed decarboxylative Wittig reaction furnishes *c*-vinyl glycosides diastereoselectively. The Tsuji–Trost reaction, followed by the Wittig reaction, is the proposed reaction pathway. For non-pyridyl groups, *Z*-selectivity is observed as the oxaphosphetane is formed via the Newman projection (**10**), which allows for minimal gauche interactions between the sugar moiety and the aldehydic substituent (Scheme 5). The *E*-selectivity of the pyridyl group is a result of Pd–M coordination that brings the P-ylide and aldehyde into close proximity, overcoming the opposing steric factors.[9]

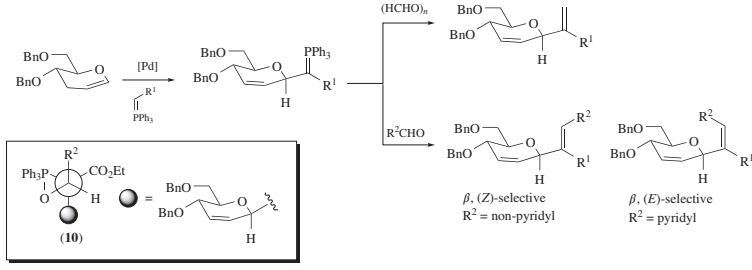
Sugars are introduced at the C3, C5, and C11 positions of macrolactones in a regiodivergent manner by selecting an appropriate chiral phosphoric acid catalyst or through the introduction of stoichiometric boronic acid–base additives. Mechanistic studies suggest that the reactive intermediates involved in the reaction are covalently linked anomeric phosphates rather than oxocarbenium ion pairs.[10]



Scheme 3



Scheme 4

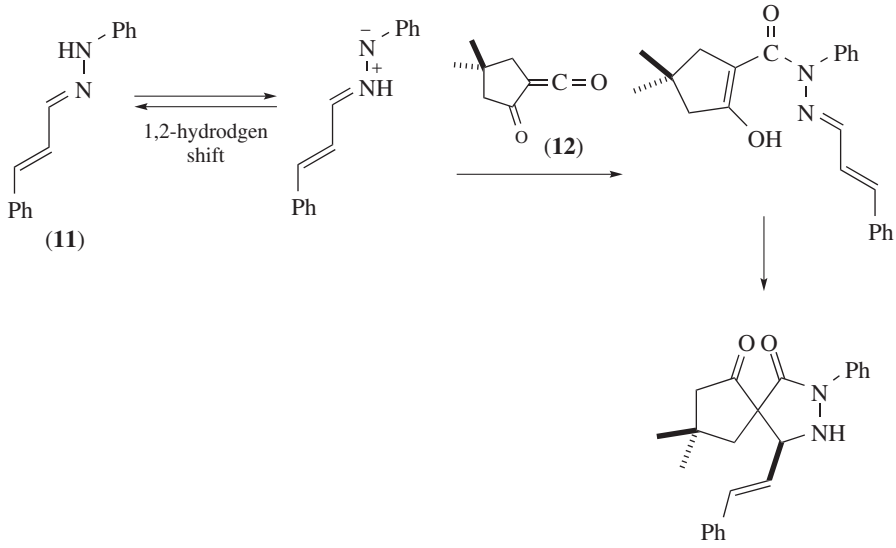

BnO
BnO
O
[Pd]
R1
PPh3
PPh3
R1
H
(HCHO)n
R2CHO
R1
R2
β, (Z)-selective
R2 = non-pyridyl
β, (E)-selective
R2 = pyridyl
Ph3P
CO2Et
(10)

Scheme 5

Glycosylation of 4,6-tethered glucosides with a panel of nucleophiles reveals that decreasing electron density on glucosides or increasing electron density of nucleophilic atoms results in increasing β-selectivity. It is proposed that when the glucoside is electron deficient and the nucleophile is strong, β-selectivity occurs because the β-triflate is in equilibrium with the α-triflate which is less stable, leading to β-products. When the nucleophile is weak and the glucoside is electron rich, the triflate dissociates to form an oxocarbenium species. Nucleophilic attack from the bottom face leads to α-products through a chair-like transition state.[11]

Reactions of Ketenes

DFT calculations have been performed at the B3LYP/6-311+G(d,p) and M)6-2X/6-31(d,p) levels to understand the experimental outcome of the reaction between hydrazone (**11**) and α-oxo-ketene (**12**) (Scheme 6). Among the three possible pathways, leading to different products, the 1,3-dipolar cycloaddition is the most favoured. The mechanism is speculated to involve a 1,2-hydrogen shift that proceeds via quantum mechanical tunnelling. Without this 1,2-hydrogen shift, the other two Diels–Alder product pathways are expected to be favoured.[12]



Scheme 6

The 3 + 2-cycloaddition between nitrones and ketenes has been studied using DFT and molecular electron density (MEDT). The reaction takes place in one kinetic step, but in a non-concerted mechanism. The study predicts a switch to a two-step mechanism with electrophilic ketenes.[13]

DFT methods have been used to understand the mechanism and stereochemical outcome of trimethylsilylquinine (TMSQ) or methylquinidine (MeQd)-catalysed 2 + 2-cycloaddition between methylketene (MK) and methylphenylketene (MPK). With TMSQ, *R–E* isomer is predominantly formed, while with MeQd, *S–Z* isomer is the major product. Formation of lactone occurs via a stepwise process. The enantio- and diastereo-selectivities are controlled by lower distortion of the reactants in the most preferred transition state. With $LiClO_4$ as the additive, the stereochemical outcome (*S–E* with MeQd and *R–E* with TMSQ) is due to more effective noncovalent interactions among the catalyst, substrate, and $LiClO_4$ in the transition state of the rate-determining step.[14]

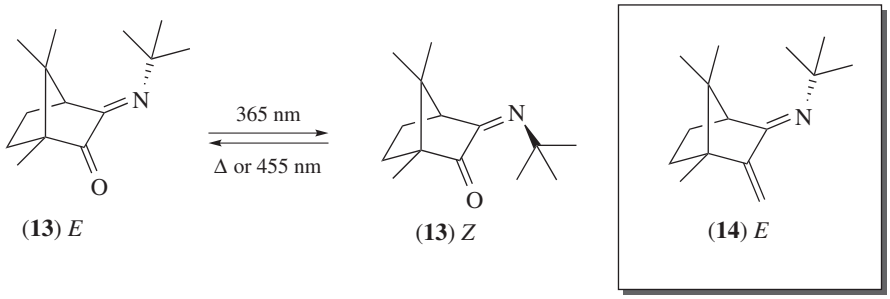
ee
de

Formation and Reactions of Nitrogen Derivatives

Imines: General, Synthesis, and Iminium Chemistry

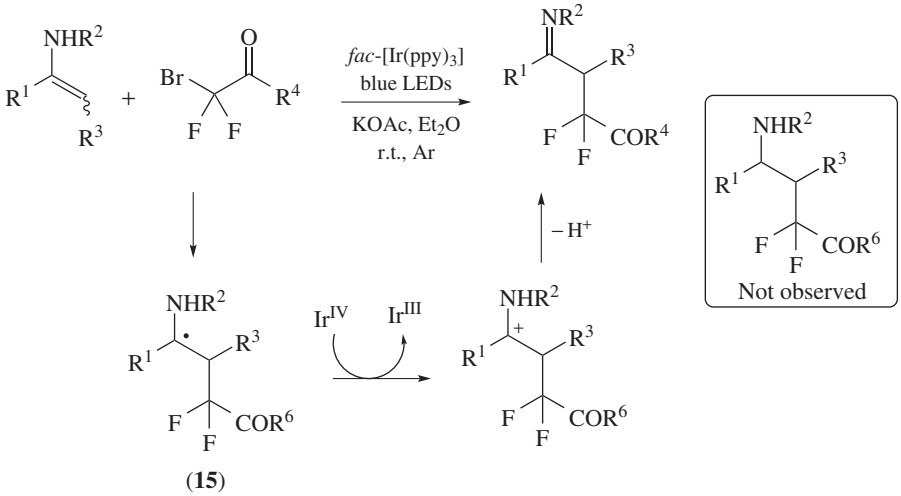
The amphiphilic imines aggregate to micelles in water. This was judged by diffusion-ordered NMR spectroscopy, dynamic light scattering, and interferometric scattering microscopy. These imines do not undergo autocatalysis and instead hydrolyse in a neutral aqueous solution.[15]

DFT (time-dependent)//CASPT2 (active space second-order perturbation theory) and CASPT2//CASSCF (complete active space-consistent field) studies shed light onto the mechanism of imine photoswitches (**13**) and (**14**) (Scheme 7). A mild energy barrier exists for $E \rightarrow Z$ and $Z \rightarrow E$ isomerization of (**13**). The photoisomerization of (**14**) is barrierless.[16]



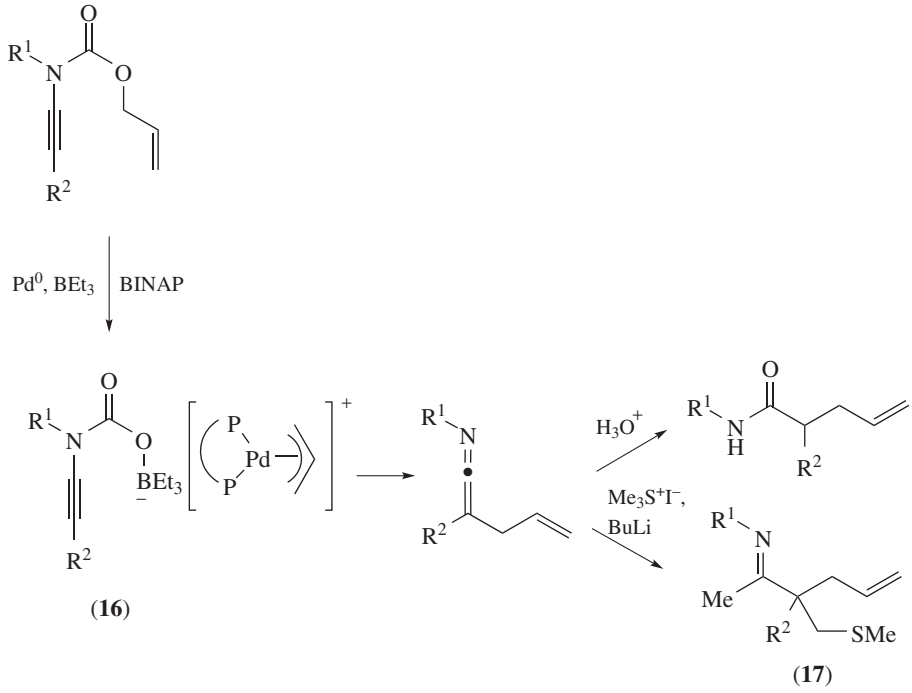
Scheme 7

Photoredox-catalysed cross-coupling of enamides and bromodifluoro compounds provides *gem*-difluoromethylenated γ-imines (Scheme 8). The mechanistic hypothesis involves a radical/SET pathway, and NMR and LC–MS analysis of the crude reaction failed to detect the H atom abstraction product of (**15**), indicating the formation of a carbocation. The radical reduces Ir(IV) into Ir(III), thus regenerating the catalyst.[17]



Scheme 8

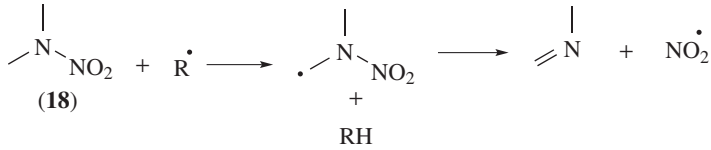
Formation of ketenimines has been achieved via a decarboxylative allylic rearrangement pathway that does not require strong stabilizing or protecting groups (Scheme 9). A crossover experiment concluded that the products were formed via a dissociative solvent-separated



Scheme 9

ion pair (**16**). Kinetic studies and the presence of the bidentate ligand on the Pd alongside the allylic intermediate suggested that the reaction goes through an outer-sphere process in which reductive alkylation is rate limiting. Owing to the labile nature of ketenimines, they were immediately hydrolysed to amides or reacted with sulfur ylides to form imines. Formation of imine (**17**) is proposed via nucleophilic addition to the central carbon of the ketenimine, followed by C-to-N proton transfer, [2,3]-Wittig rearrangement, and subsequent tautomerization.[18]

DFT calculations indicate that H abstraction from (**18**) by most radicals is the lowest-barrier mechanism (Scheme 10). A subsequent N–N β-scission leads to the formation of the imine.[19]



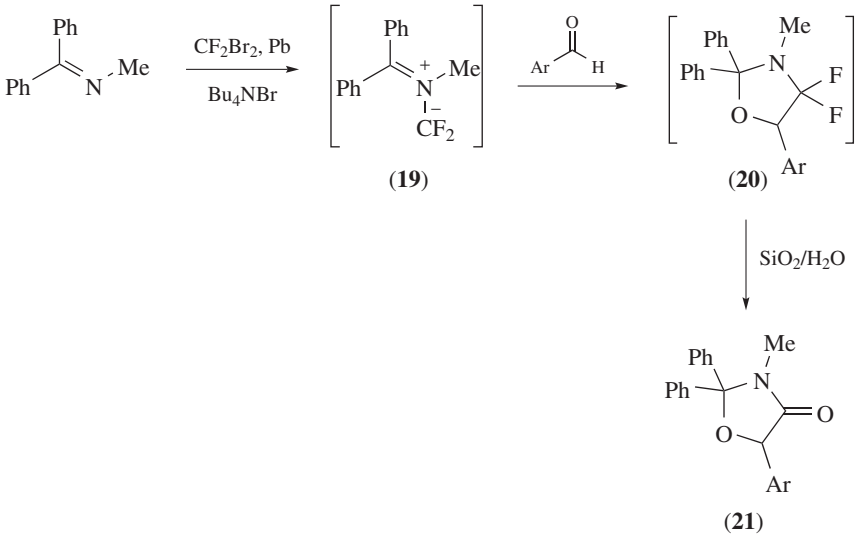
Scheme 10

DFT is used to study the regio- and diastereo-selectivity of Rh(III)-catalysed cyclization reactions of *N*-arylnitrones. The regioselectivity is controlled by the electronic effect in alkyne insertion. The diastereoselectivity is controlled by the imine insertion step.[20]

Active transition states in the (*R*)-TRIP-catalysed reactions of imines are identified by determining the impact of photoisomerization of double bonds on the rate and the *ee* of the reaction. The method, named decrypting transition state by light (DTS–*hν*), identified Type I *Z* and Type II *Z* (Type I = bottom nucleophilic attack; Type II = top nucleophilic attack; *E* and *Z* are the diastereomers of imines) pathways to be competing in the asymmetric transfer

hydrogenation of ketimines. Type I *E* and Type II *E* pathways are active in the nucleophilic addition of acetylacetone to *N*-Boc-protected aldimines. Quantum chemical calculations and noncovalent interaction analysis support these experimental findings.[21] (de)

The regioselective cycloaddition of aromatic aldehydes and *gem*-difluoro azomethine ylides (**19**) provides difluoropyrrolidine cycloadducts (**20**) that hydrolyse under the reaction conditions to give oxazolidin-4-ones (**21**) (Scheme 11). Correlation analysis and DFT calculations reveal a stepwise mechanism. Exchange of germinal fluorines with hydrogen results in the mechanism becoming pericyclic. The stability of cycloadducts can be increased, and fluorinated products could be isolated if the aldehydes are replaced with trifluoroacetophenone.[22]

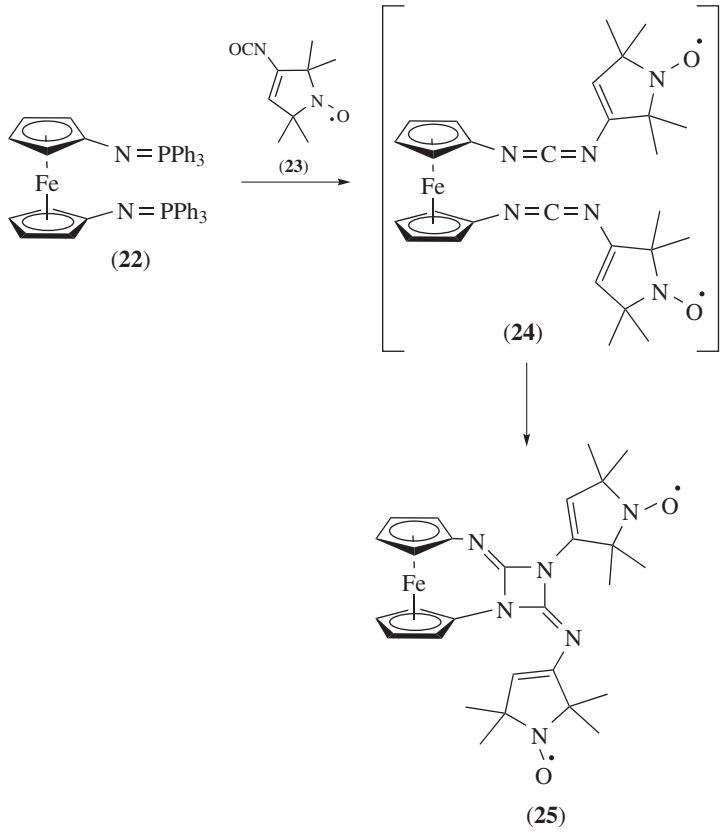


Scheme 11

Kinetic *anti*-*β*-aminonitriles can be prepared by deprotonation of secondary alkane nitriles with BuLi and addition to aryl imines. Thermodynamic *syn*-*β*-aminonitriles can be prepared by replacing BuLi with LHMDS. Use of LHMDS results in a reversible protonation of the reaction intermediate, giving *syn* product. Crossover and additional mechanistic experiments suggest that the reversible protonation mechanism is operative at −78 °C, while a (with both bases) retro- then re-addition pathway is present at rt. The later pathway results in a mixture of diastereomers.[23] (de)

Instead of the expected 3 + 2-dipolar cycloaddition, the Lewis acid-catalysed reaction of azomethine imines and nitrones to *N*-vinylpyrroles proceeds by a formal 3 + 3-cycloaddition. It is proposed that the 1,3-dipole reacts as an electrophile as a result of Lewis acid coordination. Nucleophilic attack by pyrrole, [1,7]-H-shift, followed by cyclization, leads to the final products.[24]

A rare 2 + 2-cycloaddition of carbodiimides is speculated to be operative for the synthesis of (**25**) bearing two radical groups (Scheme 12). First, the aza-Wittig reaction of bis(iminophosphorane) (**22**) with paramagnetic isocyanate (**23**) produces the intermediate (**24**). The bis(carbodiimide) intermediate (**24**) undergoes cycloaddition reaction producing (**25**).[25]



Scheme 12

Mannich, Mannich-type, and nitro-Mannich Reactions

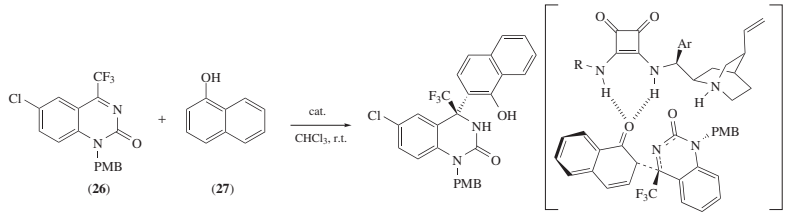
A cascade of Staudinger/aza-Wittig/Mannich reactions of substituted oxindoles provides spiro[pyrrolidine-3,3′-oxindoles]. The stereochemical outcome is hypothesized to be due to pseudoequatorial location of C2′ and C5′ groups in the Mannich step transition state.[26]

Other 'Name' Reactions of Imines

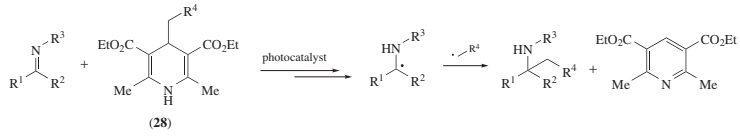
The mechanism of a quinine-squaramide-catalysed enantioselective aza-Friedel–Crafts reaction between (**26**) and (**27**) is studied using DFT (Scheme 13). The C–C bond-forming step is the rate-determining step. The *R*-configuration adduct is energetically and kinetically favoured. The nucleophile is activated by the squaramide N–H groups and the electrophile binds to the protonated amine of the catalyst.[27]

Alkylations

A photoredox/Brønsted acid cocatalysis enables radical alkylation of imines with 4-alkyl-1,4-dihydropyridine (**28**) (Scheme 14). The reaction is terminated by the addition of TEMPO, and the TEMPO-trapped product is identified by LC–MS. In one experiment, a dimeric product is isolated. Stern–Volmer quenching experiments show significant quench of one photocatalyst's fluorescence by (**28**) and a much lower effect by the imine. On the basis of these observations,


CF3
Cl
N
O
N
PMB
(26)
+
OH
(27)
cat.
CHCl3, r.t.
F3C
OH
Cl
NH
N
O
PMB
O
O
R
N
H
N
H
Ar
N
H
O
O
N
N
PMB
F3C
‡

Scheme 13


R4
R3
N
R1
R2
+
EtO2C
CO2Et
Me
N
H
Me
(28)
photocatalyst
HN
R3
R1
R2
R4
HN
R3
R1
R2
R4
+
EtO2C
CO2Et
Me
N
Me

Scheme 14

a mechanistic cycle is proposed, which involves the formation of an alkyl radical from and its reaction with the alkylamine radical.[28]

Miscellaneous Additions to Imines

Thermal intramolecular cyclization of *N*-aryloxyacrylate aldimines (**29**) leads to the synthesis of functionalized dihydrobenzoxazoles (**30**) (Scheme 15). An intramolecular attack on the conjugated double bond, followed by the ring opening and closure, leads to the product formation. Mechanistic studies exclude the possibility of (**31**) an aza-Michael addition to the α,β-unsaturated ester. A crossover experiment confirms the intramolecular nature of the rearrangement. The successful formation of (**30**) in the presence of TEMPO is used to exclude the participation of radicals in this reaction.[29]

Electrochemical, spectroscopic, computational, and kinetic studies provide understanding of the factors governing the iminium ion-mediated enantioselective radical conjugate addition to β,β-disubstituted cyclic enones. The investigation revealed that the turnover-limiting step is the single-electron transfer reaction (SET).[30]

Propylphosphonic anhydride (T3P®) mediates a three-component Ugi-type reaction, providing α-amino amides. The anhydride T3P® is speculated to promote the formation of the imine, its protonation, and the formation of (**32**) (Scheme 16).[31]

A Ugi/Staudinger/aza-Wittig sequence provides a 3,4-dihydroquinazoline (**34**). It is proposed that the Ugi-type reaction of isocyanide, acid, aldehyde, and amine produces an azide intermediate, which reacts with PPh_3 by a Staudinger reaction generating the intermediate (**33**) (Scheme 17). The iminophosphorane intermediate (**33**) undergoes an aza-Wittig reaction, producing (**34**). The observed regioselectivity is attributed to be a result of greater reactivity of the sterically less-hindered carbonyl group.[32]

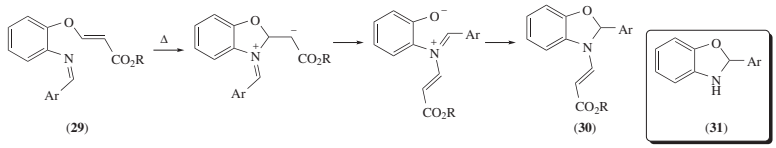
A one-pot Ugi-3CR/Wittig sequence provides indoles (Scheme 18). This is first time isocyanide-substituted phosphonium salts are used in the Ugi reaction. Although no intermediates are isolated, intermediate (**35**) is expected to be involved in the reaction mechanism.[33]

Acetaldehyde and ammonia react to form 2,4,6-trimethyl-1,3,5-hexahydrotiazine trihydrate. DFT calculations suggest that the most favourable pathway for the formation of the cyclic triazine product is a result of the repetition of the following stages: addition of a primary amine acetaldehyde, dehydration to produce imine, and the addition of ammonia to form the germinal diamine.[34]

Oxidation and Reduction of Imines

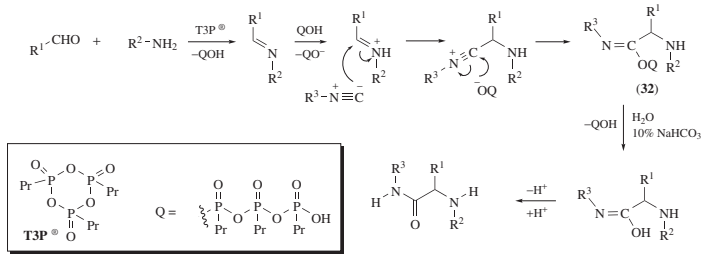
DFT and ONIOM (B3LYP/6-31G**: UFF) calculations show that the presence of an *ortho*-hydroxyl group on the imine results in the transfer hydrogenation reaction to proceed through a 14-membered bifunctional mechanism. On the basis of the transition state, a qualitative model is proposed for predicting the stereoinduction in this reaction. Contrary to conventional models, the new model predicts a minimal increase in steric repulsion between the large group on the imine nitrogen and the $SiPh_3$ group on the catalyst.[35]

Phosphorus triamide (**36**) reacts with pinacolborane via B–H bond activation, providing (**37**) (Scheme 19). P-Hydrido-1,3,2-diazaphospholene (**37**) shows hydridic reactivity and it reacts with imines. The intermediates (**38**) eliminate the *N*-borylamine product via an intramolecular boryl transfer. The proposed mechanism is verified by kinetic experiments and by independently verified stoichiometric steps.[36]

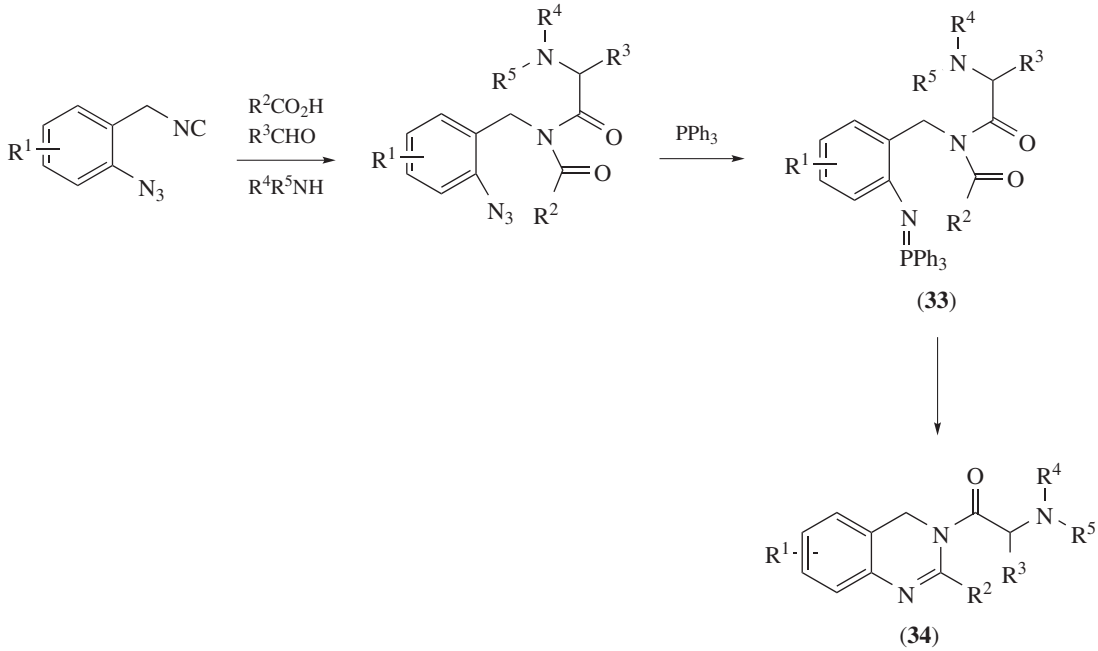


(**29**) (**30**) (**31**)

Scheme 15



Scheme 16



Scheme 17

Catalytic activity of 1,2,4,3-triazaphospholenes (TAPs) is evaluated in the hydroboration of imines and α,β unsaturated aldehydes. DFT supports a mechanism in which the transition state of the rate-determining step involves a triazaphospholene cation that interacts with the substrate.[37]

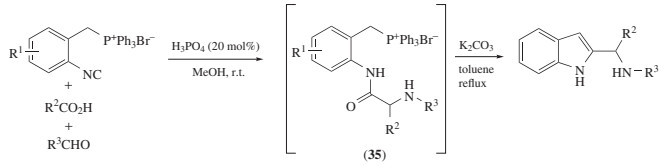
Amides are prepared from aldimines via an aerobic oxidative NHC catalysis, which also involves the use of LiCl as a cooperative Lewis acid catalyst (Scheme 20). The mechanism involves the aza-Breslow intermediate (**39**), which was isolated under inert conditions. The intermediate could be converted into the corresponding amide under the reaction conditions.[38]

A Cu(II)/O_2-catalytic system provides oxidative N-dealkylation of *N*-(2-pyridylmethyl)phenylamine and its derivatives. Mechanistic studies show that the imine and amide species are possible precursors, leading to the carboxylate.[39]

Other Reactions of Imines

Reaction of 2-picolylamine and benzaldehyde gives cyclized product (**40**) (Scheme 21). The unexpected formation of (**40**) is explained as a result of transamination/transimination (TATI), which provides (**41**). Condensation of benzaldehyde with (**41**) provides (**42**). As a result of lability of the pyridine ligand, (**42**) is converted into the (**43**), which upon cyclization provides (**44**). Tautomerization of (**44**) gives (**45**) which, owing to steric repulsion between hydrogen atoms of the pyridine units, loses the metal, forming (**40**).[40]

A mechanistic model, based on steric effects, is proposed to rationalize the observed diastereoselectivity in thioketene–imine cycloaddition. However, it is shown that epimerization of products is facile under the reaction conditions. Therefore, it is unclear if the model has any use in predicting the outcome of a reaction.[41]


R1
P+Ph3Br−
NC
+
R2CO2H
+
R3CHO
H3PO4 (20 mol%)
MeOH, r.t.
NH
O
H
N
R3
R2
(35)
K2CO3
toluene
reflux
R2
N
H
HN − R3

Scheme 18