ORGANIC REACTION MECHANISMS

EDITOR
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M. G. Moloney
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Preface

The present volume, 57th in the series, surveys research reporting organic reaction mechanisms described in the available literature dated 2021. The format of this volume follows the usual arrangement. Of interest is that this year's volume is down by 25%, probably reflecting the full impact of COVID lockdowns on research output. It also marks, however, a significant change in the type of outputs, noticeable to me as an editor, responsible for the selection and inclusion of references in each volume. Since 2018, there has been not only a change in emphasis of publications, which now often include some elements of computational analysis, but also an equally significant change in the rising level of numbers of photo-mediated processes, either by activation or by catalysis. A common outcome of both changes has been a challenge to existing norms of thinking about what reactions and mechanisms are possible.

I acknowledge that this year marks the final contribution from Jim Coxon, a very long-standing contributor, and offer sincere thanks for his long service and submission of high-quality chapters on rearrangements.

University of Oxford, Oxford, UK
19 January 2024

M. G. Moloney

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1

Reactions of Aldehydes and Ketones and Their Derivatives

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CHAPTER MENU

Aldehydes and Ketones

A study on the formation and real-space distribution of acetophenone dimers on an H-containing Pt(111) surface using scanning tunneling microscopy and infrared reflected absorption spectroscopy shows that different types of acetophenone dimers (**1–4**) were found, depending on the coverage of H species at the surface (Figure 1).[1] A combined experimental and theoretical study of the twisted intramolecular charge transfer process in hemithioindigo photoswitches with picosecond time resolution has been reported.[2] The gas-phase decomposition of aluminum acetylacetonate between 325 and 1273 K proceeds by initial formation of the $Al(C_5H_7O_2)_2^+$ ion, and then formation of up to 49 species, including aluminum bis(diketo)acetylacetonate-H, $Al(C_5H_7O_2)C_5H_6O_2$, acetylacetone ($C_5H_8O_2$), $Al(OH)_2(C_5H_7O_2)$, a substituted pentalene ring species ($C_{10}H_{12}O_2$), acetylallene (C_5H_6O), acetone (C_3H_6O), and ketene ($H_2C{=}C{=}O$). Arrhenius parameters have been determined for the gas-phase decomposition kinetics of $Al(C_5H_7O_2)_3$.[3]

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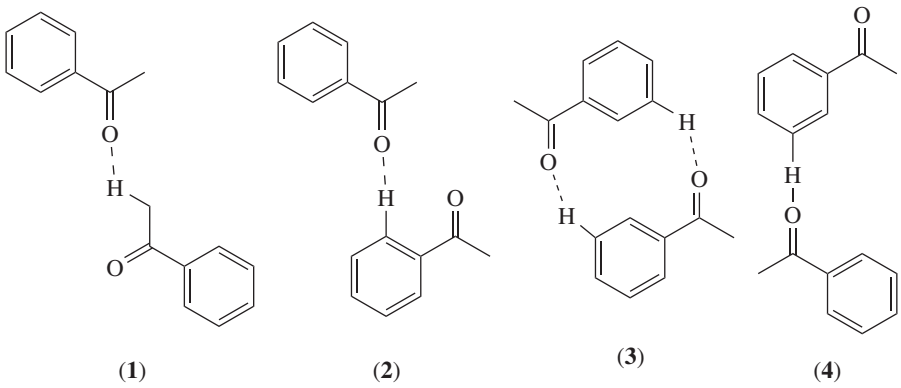
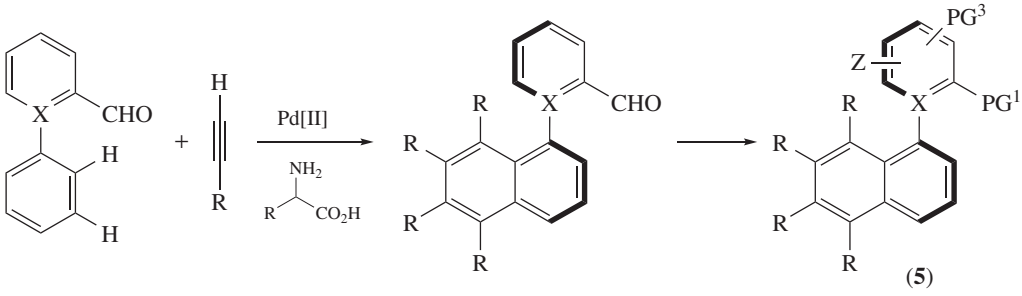


Figure 1

The preparation of deuterated aldehydes via a hydrogen-isotope exchange reaction on an aldehyde starting material (ArCH=O ⇒ ArCD=O) using a rationally engineered mutant thiamine diphosphate (ThDP)-dependent enzyme has been reported.[4] In this process, the ThDP cofactor activates aldehyde C—H bonds via a Breslow-type intermediate, enabling deuteration in the presence of D_2O, even though a benzoin condensation is kinetically favored under the same conditions. The desired selectivity was achieved by the incorporation of suitable binding pockets favoring the formation of the desired deuterated aldehydes. The reaction mechanism of 2-succinyl-5-enolpyruvyl-6-hydroxy-3-cyclohexene-1-carboxylic-acid (SEPHCHC) synthase (known as MenD), a thiamin diphosphate-dependent decarboxylase that catalyzes the formation of SEPHCHC from 2-ketoglutarate and isochorismate, has been studied using X-ray data and computational analysis. This enzyme is involved in the menaquinone biosynthesis pathway in *Mycobacterium tuberculosis* and is proposed as a potential drug target for antituberculosis therapeutics. The structure and role of the tetrahedral post-decarboxylation intermediate are discussed.[5]

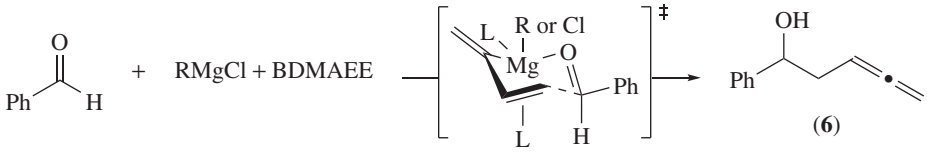
The transition-metal-catalyzed sp^2 C–H functionalization of arenes directed by aldehydes has been reviewed.[6] An axially chiral aldehyde (**5**) is formed by a Pd(II)-catalyzed atroposelective dual C–H activation using leucine as the chirality source in good yields (up to 95%) and with excellent enantioinduction (up to 99%) (Scheme 1).[7] Mechanistic studies indicate that conversion of the starting aldehyde and L-*tert*-leucine gives an imine intermediate suitable for chelated C–H activation to give an axially stereo-enriched biaryl palladacycle intermediate, which then reacts with an alkyne to form the annulated product; subsequent hydrolysis of the imine unit releases the aldehyde and L-*tert*-leucine. Pd^0 is reoxidized to Pd^{II} by silver(I) to continue the



Scheme 1

catalytic cycle. The chiral aldehyde may be manipulated further to introduce new aromatic functionality. A Ru(II)-catalyzed cross-dehydrogenative Heck-type olefination of arenes with allyl sulfones, assisted by weakly coordinating ketone or amide functions, proceeds by a reversible metalation step, with β-hydride elimination from the benzylic position and without β-sulfonyl elimination.[8] Although a sub-stoichiometric amount of Cu(II) acetate and oxygen is required, experiments exclude an SET or radical pathway.

The synthesis of homoallenyl alcohols (**6**) from the corresponding aldehyde and chloroprene-derived Grignard reagents using bis[2-dimethylaminoethyl]ether (BDMAEE) as an additive at low temperature has been reported (Scheme 2); this allows the almost exclusive formation of the allene product, which is suggested to be favored by chelation of the magnesium in a six-membered transition state.[9]



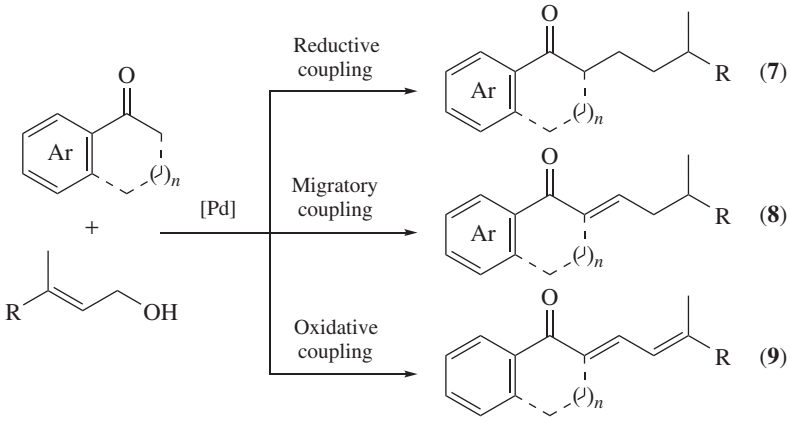
Scheme 2

Aryl aldehydes and ketones may be converted either to alcohols or to pinacol products using CdSe/CdS core/shell quantum dots as photocatalysts by adjusting the amount of 4-methylthiophenol, which is present; the catalyst may be recycled, the reaction shows good functional group tolerance, and an intermediate ketyl radical is proposed.[10] $Fe(PMe_3)_4$-catalyzed coupling using a perdeuterio-labeled aromatic ketone with various alkenes showed linear alkylation products formed by 1,2-insertion of alkene into an Ar—Fe—H bond. Reversible 2,1-insertion is possible but depends on the choice of the alkene, being favored for styrene but not for vinylsilanes and *N*-vinylcarbazoles.[11]

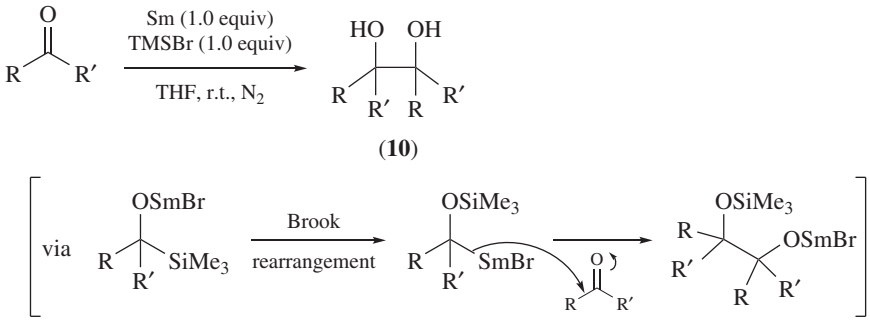
A review covering the organocatalyzed enantioselective α-functionalization of aldehydes, with a focus on catalytic cycles and mechanisms, has appeared; Horner–Wadsworth–Emmons, aldol and organometallic addition reactions are considered explicitly.[12] A review of methodologies to access α-aminoketones of relevance to synthetic and medicinal chemistry, including mechanistic details, has been published.[13] A Pd-catalyzed redox coupling of ketones with terpenols gives α-substituted ketones at various levels of unsaturation, which can be controlled using different additives to give reductive, migratory, or oxidative coupling; using $[\eta^3$-allylPdCl$]_2$, an *N*-heterocyclic carbene ligand (SIPr·HCl) and aniline solvent, in the presence of benzyl alcohol, the reductive coupling is thermodynamically favored and gives the product of alkylation (**7**), while in the presence of LiBr and 4-aminopyridine, α,β-unsaturated ketones (**8**), are formed and by switching the solvent to chlorobenzene in the presence of piperidine and NaOMe, oxidative coupling gives α,β,γ,δ-unsaturated ketones (**9**), with exclusive *E*-stereoselectivity (Scheme 3). An alkoxide-Pd(II) intermediate $XPd(L)OCH_2CH{=}CMe_2$ is a key intermediate common to the formation of all products, and the process can be considered to be complementary to Tsuji–Trost allylation of ketones.[14]

The pinacol coupling reaction of aldehydes or ketones with samarium and TMSBr gives the expected diol products (**10**), proceeding best for aliphatic ketones and less well for aromatic ketones (Scheme 4). Mechanistic studies suggest an anionic Brook rearrangement of a Sm(II) or Sm(III) silyl species rather than a direct radical coupling pathway.[15]

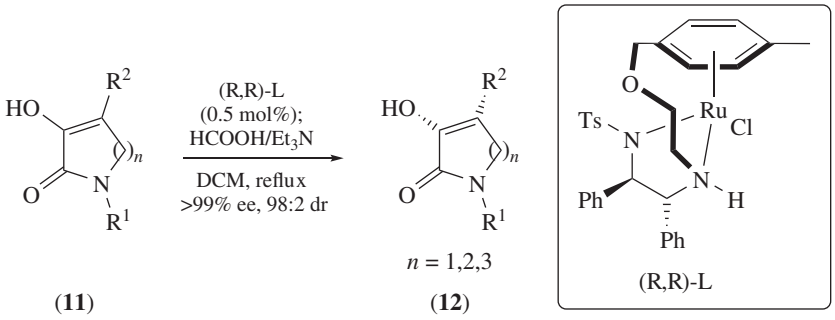
A dynamic kinetic resolution—asymmetric transfer hydrogenation of α-keto/enol-lactams (**11**) leading to a range of disubstituted cis-α-hydroxylactams (**12**) with high enantiopurity (>99%) has been reported; a transition state stabilized by η^6-arene CH—O interaction was proposed (Scheme 5).[16]



Scheme 3



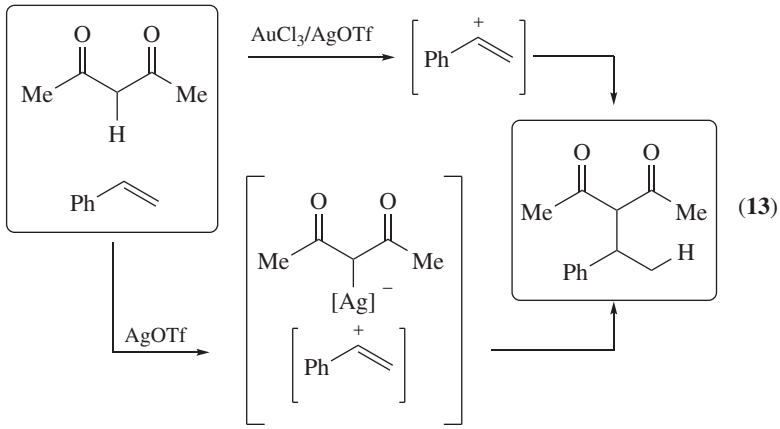
Scheme 4



Scheme 5

The formation of enamines from primary arylamines, leading to α-enaminones by reaction with ketones, proceeds by amine radical cation generation involving O_2 singlet energy transfer. Their use for [3+3] cycloaddition reaction to give dihydropyridines in good yields (58–85%) was established. α-Enaminones displayed a set of reactivities that were different from those of enamines.[17] The *O*-alkylation of extended tricarbonyl-conjugated tetramates could be achieved under Mitsunobu conditions but gave regioisomeric products. Thus, both C-9 and C-6 *O*-alkylation were observed but not C-8 *O*-alkylation for tetramate carboxamides, while C-7 alkylation with allyl and prenyl derivatives arose by the rearrangement of initially

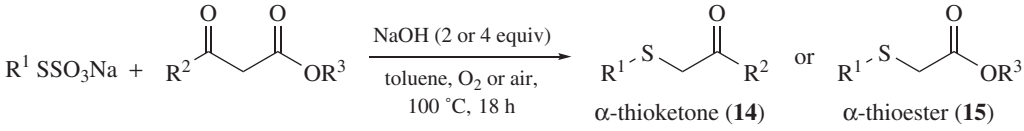
formed *O*-alkyl products. These modifications at C-6/C-9 of tetramates were found to lead to a complete loss of metal-chelating ability, which correlated with the loss of antibacterial activity, demonstrating that the metal-chelating capability of tetramates can be significant.[18] The benzylic alkylation of chiral benzyl esters with malonates as a carbon nucleophile can be catalyzed by $[Cp^*RuCl_2]_2$ and picolinic acid and proceeds with retention of the stereochemistry of the starting material via a double inversion mechanism.[19] The mechanism of hydroalkylation of styrenes with 1,3-diketones to give products (**13**) promoted by either $AuCl_3$/AgOTf or AgOTf catalyst was studied by density functional theory (DFT) analysis. For the former, the reaction is initiated by the generation of highly electrophilic $Au(OTf)_3$, which coordinates with the enol tautomer of the 1,3-diketone substrate; the resulting Bronsted acidic π-complex protonates the styrene giving a benzylic carbocation intermediate that is intercepted by the enolate to give the product. For the AgOTf catalyst, the reaction proceeds via an ion-pair intermediate, which collapses into the product by demetallation (Scheme 6).[20] The process requires the slow addition of styrene; otherwise, polymerization initiated by the benzylic carbocation is observed.



Scheme 6

Four β-keto acids proposed as intermediates in a metal oxide-catalyzed decarboxylative cross-ketonization of acetic and isobutyric acids have been prepared and structurally characterized; these are $MeC(O)CMe_2CO_2H$, $MeC(O)CH_2CO_2H$, $Me_2CHC(O)CH_2CO_2H$, and $Me_2CHC(O)CMe_2CO_2H$. First-order rate constants for their decarboxylation correlate with the increasing length of the C—C bond caused by the presence of alkyl groups at the α- position, and this is important because decarboxylation is shown to be the kinetically important step of the decarboxylative cross-ketonization process. It was also established that β-keto acids leading to symmetrical ketones decompose faster with ZrO_2 catalysts, while decarboxylation leading to unsymmetrical ketones is faster with $KOH–TiO_2$, consistent with earlier observations. It is suggested that this may be due to the increased entropy by α- proton exchange between neighboring carboxylates on the surface, one of which is enolized.[21]

The reaction of β-keto esters with sodium *S*-benzyl sulfurothioate or sodium *S*-alkyl sulfurothioate (Bunte salts) under basic conditions in toluene gave α-organylthio esters (**15**) and α-organylthio ketones (**14**). With 4 equiv of base, substituted α-thio esters were obtained in up to 90% yield, while with 2 equiv of a base, α-thio ketones were formed (Scheme 7). For short reaction times, keto-enol tautomers were formed, consistent with their existence as reaction intermediates.[22]



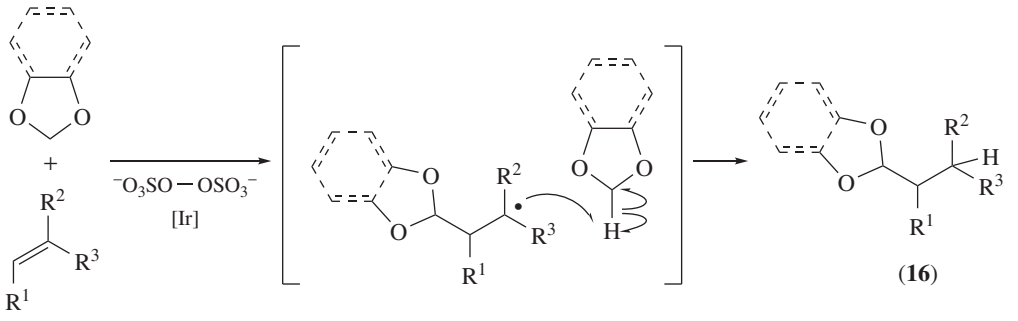
Scheme 7

The synthesis of both spiro-β-lactams (spiroazetidin-2-ones) and spiro-δ-lactams (spiropiperidon-2-ones) since 2015 has been reviewed.[23] The decarbonylative trifluoromethylthiolation of aldehydes using photoexcitation of electron donor–acceptor (EDA) complexes, formed from 1,4-dihydropyridines (donor) with *N*-(trifluoromethylthio)phthalimide (acceptor), proceeds by S_H2 addition of an alkyl radical to the intermediate radical EDA complex, which is highly favorable, and that further S_H2 reaction of alkyl radicals with 1,2-bis(trifluoromethyl)disulfane, generated *in-situ* through the combination of thiyl radicals, is a key step.[24]

Formation and Reactions of Acetals and Related Species

The stereo preference in amino-catalyzed resolution of chiral lactols shows the existence of chiral recognition between the catalyst and intermediates; a stereoelectronic model to account for chiral transmission was proposed.[25] The hydrolytic activity of an artificial enzyme-cofactor complex can be enhanced by locating an acidic group near the acetal oxygen of 2-(4-nitrophenyl)-1,3-dioxolane in the enzyme-substrate complex; acetal hydrolysis activity can be controlled by the size and shape of the active site such that less reactive acetals can be hydrolyzed selectively over those that are more reactive.[26]

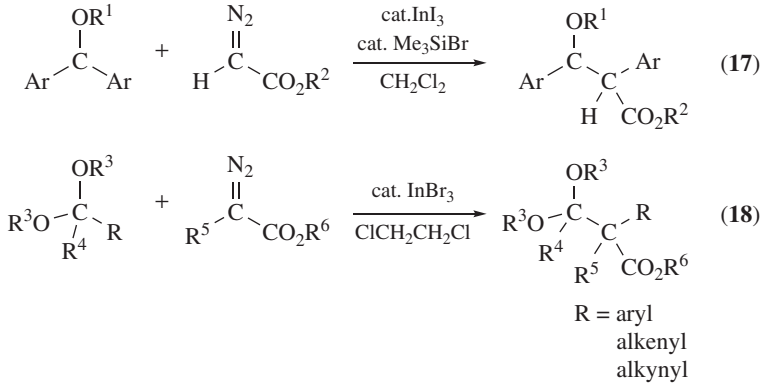
1,3-Dioxolane may be converted into its radical species by persulfate, which, in the presence of an iridium catalyst upon visible-light irradiation, adds across electron-deficient alkenes to give products (**16**); the reaction proceeds by a radical chain mechanism (Scheme 8). That hydrogen atom transfer from 1,3-dioxolane to α-malonyl radicals is possible was confirmed by experimental and DFT studies, and is likely to be the rate-determining step, although might also be reversible, even though the reaction overall is exergonic.[27] Initial homolysis of persulfate to give sulfate radical anions (BDE of O–O = 28.7 kcal mol^{-1}) may proceed directly or heterolytically by SET with Ir(III)*. This abstracts a hydrogen atom from 1,3-dioxolane, which undergoes conjugate addition to alkene, and the resulting α-malonyl radical abstracts a hydrogen atom from starting 1,3-dioxolane to propagate the radical chain leading to a product.



Scheme 8

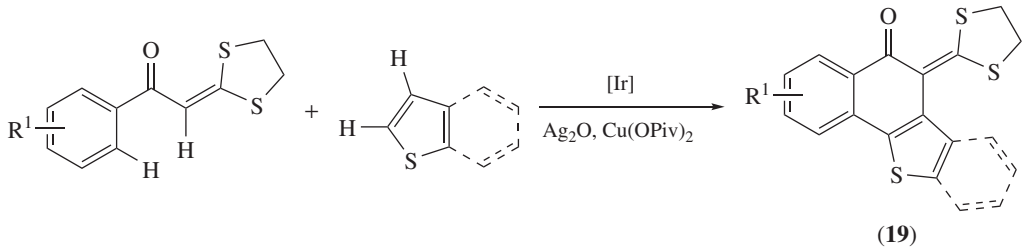
The homologation of alkyl acetates, alkyl ethers, acetals, and ketals by the formal insertion of diazo esters into carbon–carbon sigma-bonds by either InI_3 or $InBr_3$ with Me_3SiBr catalysis to

give products (**17**) or (**18**) has been reported (Scheme 9).[28] The reaction proceeds by abstraction of a leaving group by the indium-derived Lewis acid, electrophilic addition of carbocation or oxonium intermediates to diazo esters, and rearrangement to give the corresponding cation intermediates. The return of the leaving group from the Lewis acid then gives the homologated products. The appropriate level of Lewis acidity of the indium system is crucial to allowing both the abstraction and the release of leaving groups.



Scheme 9

The Ir(III)-catalyzed and Ag_2O-promoted coupling and cyclization of ketene dithioacetals with benzothiophenes gives products (**19**) containing sulfur, after intramolecular cyclization (Scheme 10); C–H activation by an iridium cyclometallation leads to the introduction of the benzothiophene by aryl-heteroaryl coupling, which then ring closes to the product by a radical process possibly assisted by hexafluoroisopropanol solvent. It proceeds with a range of substrates and good functional group tolerance.[29]



Scheme 10

Reactions of Glucosides

Both inverting α-glucosidase (BtGH97a) and retaining α-galactosidase (BtGH97b) *τιο* enzymes from glycoside hydrolase (GH) family 97 have been examined for hydrolyses of cyclohexenyl-based carbasugars that mimic either α-D-glucose or α-D-galactose; both enzymes catalyze nucleophilic substitutions at the pseudo-anomeric center of the carbasugar substrates, although with very different rate constant, as a function of the leaving group ability. For the inverting α-glucosidase, the reaction proceeds by a mechanism with little nucleophilic participation by a bound water molecule at the reaction transition state but that for retaining α-galactosidase is very different, involving a rate-limiting nonchemical step, likely

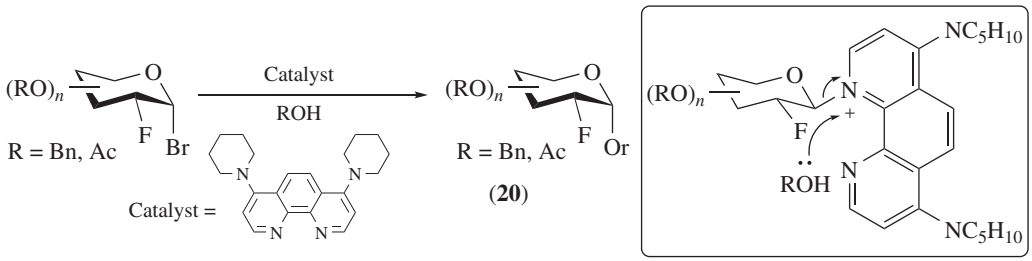
to be a conformational interchange, followed by rapid substitution involving a nucleophilic amino acid residue to give a covalently bound intermediate.[30] The GH family has evolved such that their substrates are distorted from their ground state conformation so that multiple C—O bonds are in pseudoaxial positions, leading to increased reactivity in glycosylation by stabilization of oxocarbenium-like transition states; they thus create super-armed glycosyl donors. GHs 6 and 47 achieve this by sterically interacting with aromatic residue, while GHs 45, 81, and 134 achieve this through hydrogen bonding rather than steric interactions. The recognition of substrate super-arming by select GH families provides a further parallel with synthetic carbohydrate chemistry and nature and opens further avenues for the design of improved glycosidase inhibitors.[31] Carbohydrate side chain conformation is an important factor in the control of reactivity at the anomeric center of glycosides. It has been reported that most enzymes that catalyze glycoside synthesis, such as glycosyltransferases (GTs), glycoside phosphorylases, or *trans*-glycosidases, restrict their substrate side chains to the most reactive gauche, gauche (gg) conformation in order to achieve maximum stabilization of the oxocarbenium ion-like transition state for glycosyl transfer. However, *a*-galactosyltransferases preferentially restrict their substrates to the second-most reactive gauche,trans (gt) conformation, and α-galactosyltransferases favor the least reactive trans,gauche (tg) conformation. It is suggested that the application of this observation will help in the design of better GT inhibitors.[32] A study of the mechanism of hydrolysis of 4-nitrophenyl β-D-glucoside at different pH values shows an inverse kinetic isotope effect of $k(H_3O^+)/k(D_3O^+) = 0.65$ in the acidic region, indicating that formation of the conjugate acid of the substrate is required for the reaction to proceed by heterolytic cleavage of the glycosidic C—O bond. Reactions in the pH-independent region exhibit general catalysis with a single proton, consistent with water attack through a dissociative mechanism. In the basic region, bimolecular hydrolysis and neighboring group participation, with a minor contribution of nucleophilic aromatic substitution, occur. At high pH, the formation of a 1,2-anhydrosugar is the rate-determining step.[33] A study of the effect of configuration at the 4- and 6-positions on the conformation, anomeric reactivity, and selectivity of 7-deoxyheptopyranosyl donors has shown that for D- and L-glycero-D-galacto glycosyl donors, the D-glycero-D-galacto isomer with the more electron-withdrawing tg conformation of its side chain was the more equatorially selective isomer. In the D- and L-glycero-D-gluco glycosyl donors, the L-glycero-D-gluco isomer with the least disarming gg side-chain conformation was the most equatorially selective donor. On this basis, it is suggested that the equatorial selectivity of the L-glycero-D-gluco isomer arises from H-bonding between the glycosyl acceptor and O6 of the donor, which delivers the acceptor antiperiplanar to the glycosyl triflate with a high degree of S_N2 character in the reaction.[34]

Phosphorylase activity in GH3 GHs from *Pseudomonas aeruginosa* and *Bacillus subtilis* has been demonstrated and optimized by single-site amino acid substitutions allowing the production of glycosyl phosphates; this work provides insights into phosphorylase activity in natural GH3 phosphorylases.[35]

The mechanistic pathways for the transformation of substituted glycals to chiral fused acenes by Diels–Alder (DA) reaction with arynes have been studied computationally using the SMDACN-M06-2X/6-31G(d) level of theory. The DA reactions of E and Z forms of a C-2 alkenyl glycal with an aryl glycal as a diene were examined with a benzyne intermediate generated as a dienophile. The computational results reveal that these can only be transformed into the fused aromatic cores by the base-catalyzed reaction because a [1,5] sigmatropic hydrogen shift is not feasible. The activation-free energy barrier for the base-catalyzed proton abstraction process is 4.2 kcal mol^{-1} and there is almost no barrier for stereoisomeric DA-complexes. Structural analysis reveals the formation of the preferred S-stereoisomer over the R-stereoisomer with the respective dienes.[36]

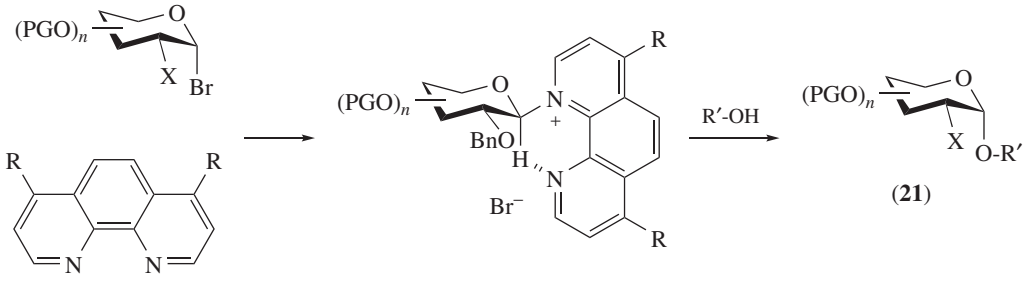
A theoretical study at the CBS-QB3 level of theory of the thermal decomposition of β-1,4-xylan, as a model of hemicelluloses, by a consideration of elementary reactions, including dehydration, retro-aldol, retro-DA, retro-ene, glycosidic bond fissions, and isomerizations. It was shown that dehydrations require high activation energy and cannot compete with other reactions.[37]

Efficient and selective glycosylation processes continue to be a focus. A review of computational approaches developed over the last ten years to understand the role of S_N1-type and S_N2-type mechanisms, along with the intermediacy of glycosyl cations (oxocarbenium ion) and related ion pairs, in glycosylation reactions, has appeared.[38] An efficient and stereoselective catalyst derived from phenanthroline for the formation of α-1,2-*cis*-fluorinated glycosides (**20**) from 2-deoxy-2-fluoroglycosyl halides proceeds with high α-selectivity and moderate to high yields; it is suitable for several glycosyl halide electrophiles and a range of glycosyl nucleophilic acceptors (Scheme 11). A mechanism, established by DFT calculations, involving double S_N2 displacement by initial phenanthroline displacement on the starting bromide, followed by a second displacement by alcohol, is proposed.[39] (*de*)



Scheme 11

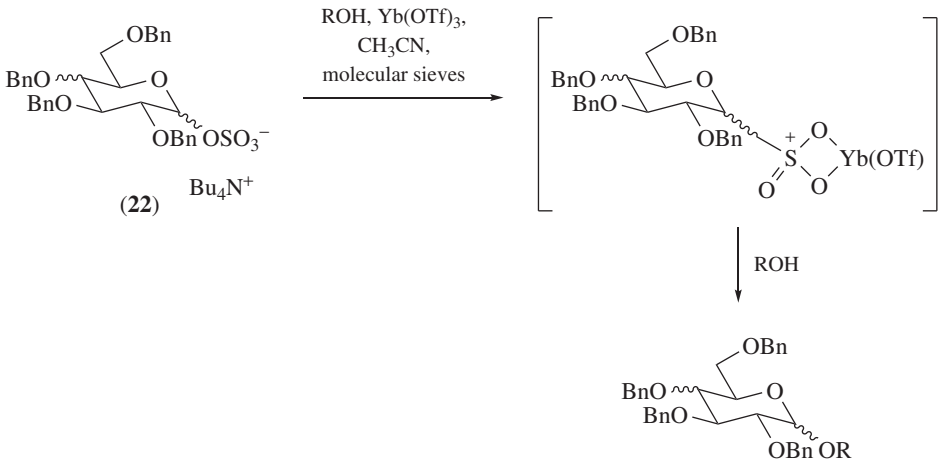
The coupling of hydroxyl acceptors with α-glycosyl bromide donors using phenanthroline as a nucleophilic catalyst gives α-1,2-*cis*-glycosides (**21**) in a high-yielding and diastereoselective process, proceeding via the intermediacy of two glycosyl phenanthrolinium ions, a C-4(1) chair-linked β-conformer and a B-2, B-5 boat-like α-conformer, detected using variable temperature nuclear magnetic resonance (NMR) experiments, and a hydrogen bond formed between the second nitrogen atom of phenanthroline and the C1-anomeric hydrogen of sugar moiety stabilizes them (Scheme 12). It is proposed that the high α-1,2-*cis*-stereoselectivity arises by interconversion of the C-4(1) chair-like β-conformer and B-2,B-5 boat-like α-conformer, which is more rapid than nucleophilic addition, and hydroxyl attack from the α-face of the more reactive C-4(1) β-phenanthrolinium intermediate gives the α-anomeric product. The use of phenanthroline catalysis enables the use of sterically hindered hydroxyl nucleophiles and chemoselective coupling of an alkyl hydroxyl group in the presence of a free C1-hemiacetal.[40] (*de*)



Scheme 12

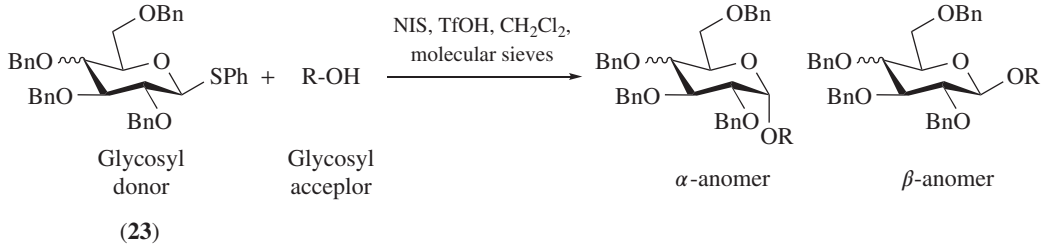
The catalytic glycosylation of disarmed glycosyl fluorides is largely undeveloped. Using $(C_6F_5)_3B{\cdot}(H_2O)_n^-$, a variety of O- and C-nucleophiles react under mild reaction conditions to give the desired glycosides in good to excellent yields, with broad substrate scope functional group tolerance. It is suggested that $(C_6F_5)_3B{\cdot}(HF)_n$ is the actual catalyst, formed from HF generated during the reaction, giving a Lewis acid-assisted Bronsted acid with enough acidity to effect catalytic glycosylation of the disarmed glycosyl fluoride starting material.[41] Using liquid SO_2 as a solvent, both armed and disarmed glucose and mannose-derived glycosyl fluorides can be glycosylated to give pivaloyl-protected O- and S-mannosides or a C-mannoside in moderate to excellent yields without any external additives. Mechanistically, a fluorosulfite species forms, and sulfur dioxide-assisted glycosylation via solvent-separated ion pairs is proposed; the observed α,β-selectivity is substrate-controlled and depends on a thermodynamic equilibrium.[42]

The use of anomeric tetrabutylammonium sulfates of glucose and galactoses (**22**) as donors in glycosylations proceeds best with metal triflates, and especially ytterbium triflate in stoichiometric amounts, which activate sulfate as the leaving group; high reaction rates and excellent glycosylation yields were obtained under mild reaction conditions (Scheme 13). Alternatively, barium oxide and trimethylsilyl trifluoromethanesulfonate (TMSOTf) were effective as activators. Benzylated sulfates were much more reactive than benzoylated donors when activated by both of these systems. Different acceptors, such as isopropanol, cholesterol, and other common sugar derivatives, are suitable coupling agents. The α,β-anomeric ratio suggests a predominant S_N2-like reaction mechanism.[43]



Scheme 13

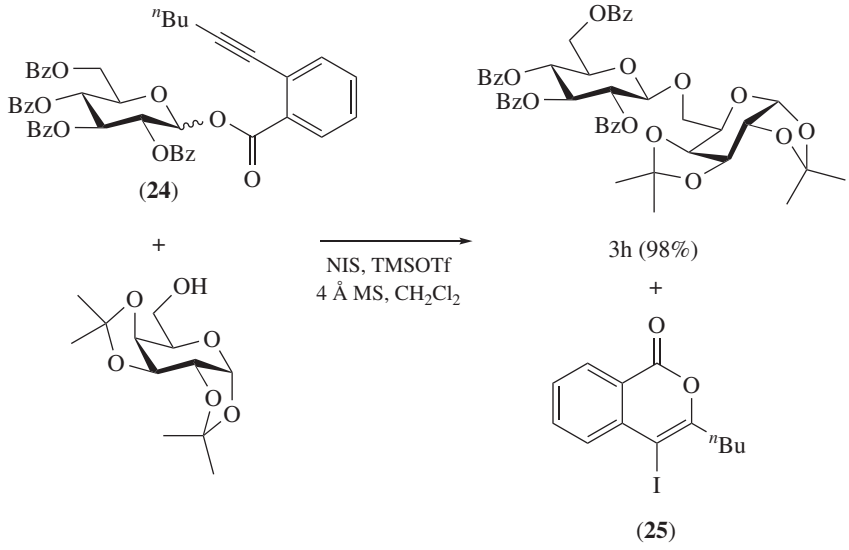
A statistical analysis using relative reactivity value (RRV) of the stereoselectivity of sialylation reactions of *p*-tolyl thiosialosides using a NIS/TfOH mixture showed the intermediacy of glycosyl bromide and glycosyl chloride intermediates from halide- and triflate-containing promotors in the absence of an acceptor. The α/β-anomeric selectivity and yields were associated with donor reactivity.[44] The α/β-anomeric selectivity in the reaction of glycosyl donor phenyl 2,3,4,6-*tetra*-*O*-benzyl-1-thio-*β*-D-glucopyranoside (**23**) with NIS/TfOH(cat.) with L-menthol as glycosyl acceptor has been studied in detail (Scheme 14); it was found that the amount of NIS activator did not change the α/β-ratio but increasing concentration and the amount of triflic acid catalyst did increase β-selectivity, and temperature showed strong effect on the glycosylation outcome.[45]



(**23**)

Scheme 14

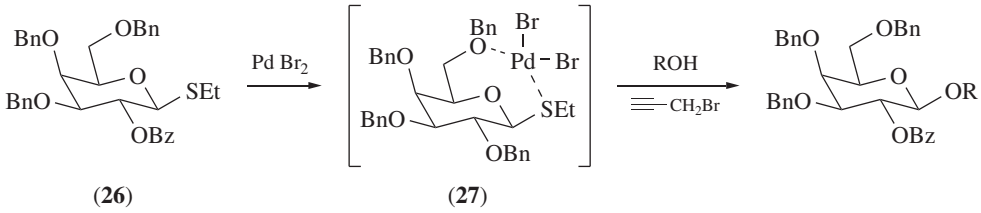
The *N*-iodosuccinimide/trimethylsilyl triflate (NIS/TMSOTf)-promoted glycosidation using glycosyl *ortho*-hexynylbenzoates (**24**) as donors provides access to *O*-glycosides and nucleosides under mild conditions with wide substrate scope and good to excellent yields (Scheme 15). A proposed mechanism involves activation of the C≡C triple bond of glycosyl *ortho*-hexynylbenzoate by I^+ generated from NIS and TMSOTf to give an intermediate iodovinyl cation. Expulsion of this leaving group leads to the formation of an oxocarbenium ion along with a 4-iodoisocoumarin derivative (**25**). The former is then captured by alcoholic or nucleobase nucleophiles, giving *O*-glycosides or nucleoside products, respectively.[46]



Scheme 15

The synthesis of mono-, di-, and trifluorinated *N*-acetyl-D-glucosamine and D-galactosamines from their corresponding fluoroglucosazide and galactosazide thioglycosides has been reported. The latter were prepared from deoxyfluorinated 1,6-anhydro-2-azido-*β*-D-hexopyranose precursors by ring-opening with phenyl trimethylsilyl sulfide, followed by nucleophilic deoxyfluorination at C4 and C6 using DAST, thioglycoside hydrolysis, and azide/acetamide formation.[47] The palladium(II) bromide-assisted glycosidation of thioglycosides (**26**) gives higher yields and cleaner reactions in the presence of propargyl bromide; it is suggested that the latter creates an ionizing complex, accelerating the departure of the leaving group. Selective and chemoselective activation of thioglycosides over other leaving groups was achieved (Scheme 16).[48] It is proposed that complex (**27**), formed in the presence of propargyl bromide, undergoes oxidative addition to form an allenyl complex, which collapses with the

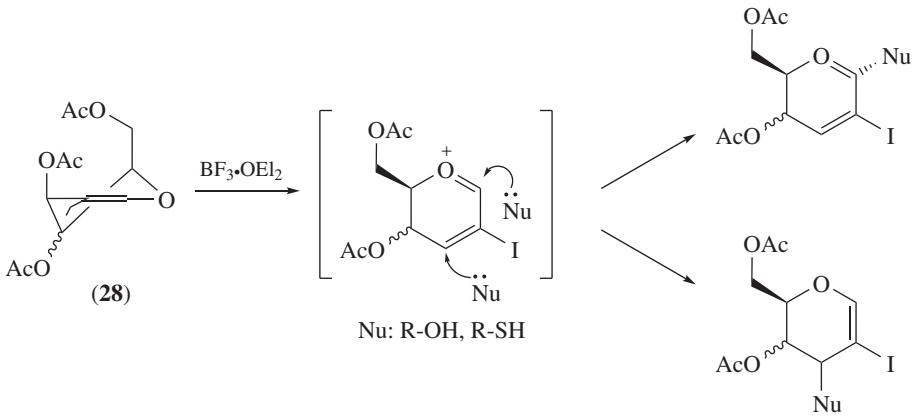
formation of an oxacarbenium, which is intercepted by the alcohol, ultimately leading to the glycoside product.



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

Scheme 16

α-2-Iodo-2,3-unsaturated O- and S-glycosides are available from 2-halo-glycals (**28**) react with S-nucleophiles to give products either of C-1 or C-3 substitution by Ferrier rearrangement in good yields and with high α-anomeric selectivity (Scheme 17).[49] (de)



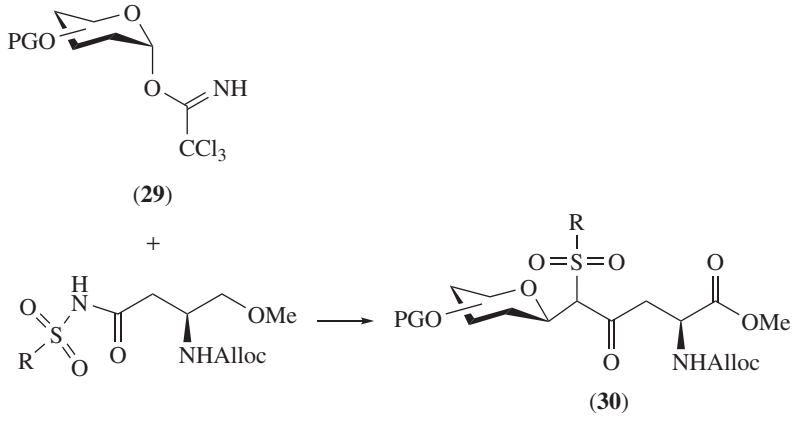
(**28**)

Nu: R-OH, R-SH

Scheme 17

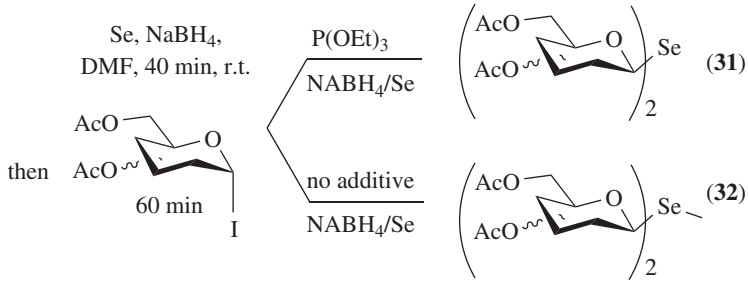
Synthetic methods to access aryl or heteroaryl C-nucleosides have been reviewed, including coupling of sugar donor precursors (e.g. hemiacetal riboses, ribonolactones, ribofuranosyl halides, and glycals) with organometallic reagents, transition metal-catalyzed coupling of ribose derivatives with organometallic reagents, and acid-catalyzed Friedel–Crafts reaction of ribose derivatives; mechanistic explanations of α/β product formation are included.[50] (de) The nickel-catalyzed cross-coupling of bench-stable glycosyl chlorides with aryl bromides under visible-light irradiation gives C-aryl glycosides stereoselectively.[51] (de) β-configured 2-indolyl-C-deoxyglycosides are available by an Ir(I)-catalyzed, pyridine-group-directed C–H functionalization in a regioselective, stereoselective process.[52] Glycosyl bromides derived from monosaccharides (D-lyxose, D-ribose, L-arabinose, D-glucose, D-mannose, D-glucuronide, and D-fucose), disaccharides (lactose, melibiose, and maltose), and polysaccharide (maltriose) can couple with a series of non-functionalized heteroarenes (purine, benzothiazole, thiazolopyridine, benzoxazole, benzimidazole, imidazopyridine, and phenanthridine) catalyzed under photoredox conditions, to give C-nucleoside analogs under mild conditions, with good functional group tolerance, and stereoselectivities (α-configuration); it proceeds by a radical mechanism. It has been applied for late-stage modification of systems such as theophylline, famciclovir, ribufuranoside, and adenine, and reaction selectivity has been rationalized using DFT calculations.[53]

Trichloroacetimidate glycosyl donors (**29**) react directly, without catalysts or other additives, with sulfonylated asparagines, to give β-*N*-Glycosyl *N*-sulfonyl amides (**30**) in high yields (Scheme 18); at lower temperatures, a mixture of N- and O-glycosides was obtained, which could be converted to the β-*N*-glycosides at elevated temperatures.[54]



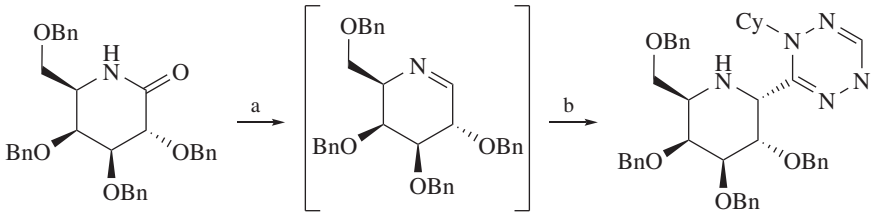
Scheme 18

Symmetrical and unsymmetrical diglycosyl-selenides (**31**) or diselenides (**32**) can be readily prepared from glycosyl halides as glycosyl donors with high chemoselectivity and a selenating agent (selenium reduced *in situ* by sodium borohydride) (Scheme 19); the chemoselectivity depends on the presence or absence of triethyl phosphite and the sodium borohydride-to-selenium stoichiometric ratio. Some of these compounds showed antiproliferative effects against some tumor cell lines.[55]



Scheme 19

The asymmetric synthesis of tetrazole-functionalized 1-deoxynojirimycin derivatives (**33**) from sugars via a reductive amide functionalization mediated by Schwartz's reagent ($Cp_2Zr(H)Cl$) followed by an Ugi–azide multicomponent reaction (CyNC and $TMSN_3$) has been reported (Scheme 20). Surprisingly, Ugi–azide products were observed in the absence of a proton donor, and this led to the proposal of a mechanism involving the reduction of amide by Schwartz's reagent to give a hemiaminal zinc complex that undergoes slow, spontaneous decomposition to an imine. This then reacts with $TMSN_3$, to give an activated imine along with an azide anion, which then undergoes the addition of isocyanide, followed by an azide anion addition cyclization, producing the silyl tetrazole, which, upon hydrolysis, gives the observed product.[56]

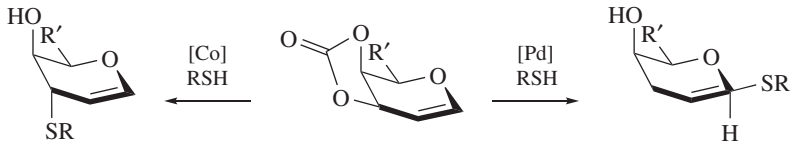


(**33**)

Scheme 20

The synthesis of a hyper-branched core tetrasaccharide motif from chloroviruses, in which there are four different sugar residues in which L-fucose is connected to D-xylose and L-rhamnose via a 1,2-*trans*-glycosidic bond, while D-galactose is connected through a 1,2-*cis*-glycosidic bond, has been reported in 14 steps; the 1,2-*cis*-galactopyranosidic linkage was introduced stereoselectively using [Au]/[Ag]-catalyzed glycosidation.[57] (*de*)

The regioselective synthesis of 1- and 3-thiosugars using either palladium or cobalt catalysis, respectively, has been achieved (Scheme 21). For the former, 3,4-*O*-carbonate-glycals and various thiols using $Pd_2(dba)_3$ give β-1-thiosugars (**34**) in good yields with full stereoselectivity and chemoselectivity, while for the latter, $Co(BF_4)_2$ gave only (3*S*)-3-thiosugars (**35**). A mechanism, supported by experiment and DFT calculations, indicated that the formation of a hydrogen bond of the thiol with the top-face C4-oxygen under Pd conditions facilitated nucleophile delivery from that face, but coordination of the nucleophile with the bottom-face chelated Co ensured nucleophile delivery from that face. Differences between Pd/Co–C1 and Pd/Co–C3 bond lengths appear to be important for 1,3-regioselectivity.[58] (*de*)

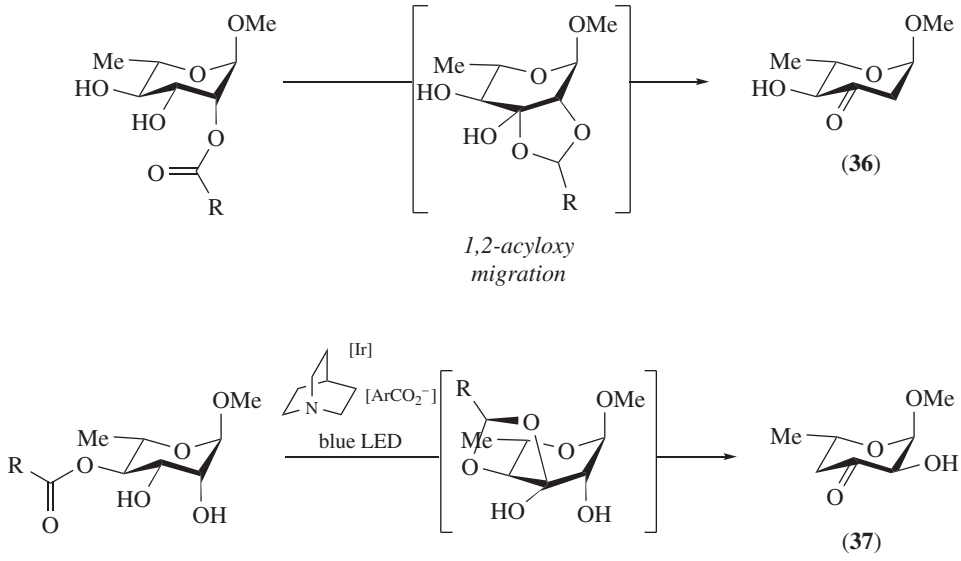


3-thiosugars (**35**) carbonate glycals 1-thiosugars (**34**)

Scheme 21

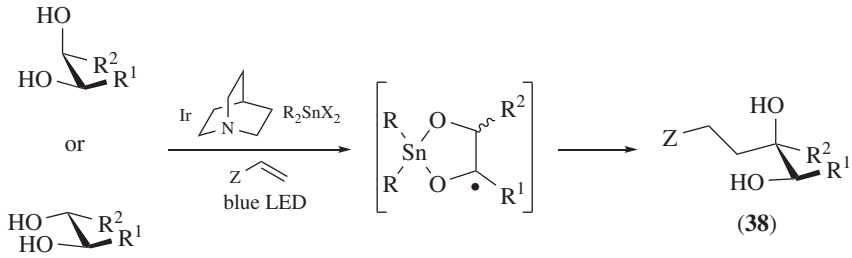
A photoredox catalyst, a hydrogen atom transfer mediator (HAT, quinuclidine), and a boronic acid-derived hydrogen bond acceptor in combination allow the transformation of pyranoside esters into ketodeoxysugars (Scheme 22). The position of the acyl group dictates the site of deoxygenation, enabling the preparation of 2-deoxy- and 4-deoxyketosugar derivatives (**36**) and (**37**), respectively. The products are useful precursors to rare sugar components of bioactive secondary metabolites. Computational studies are consistent with a radical lyase-like mechanism, which commences with oxidation by the excited-state Ir complex and generates a quinuclidinium radical cation, which abstracts a hydrogen atom from the carbohydrate substrate at the 3-position. 1,2-Acyloxy migration, followed by collapse of the resulting *O*-acylated ketone hydrate, generates an α-keto radical, leading to the ketodeoxysugar products (**36**) and (**37**).[59]

Diorganotin dihalides, an Ir(III) photoredox catalyst, and quinuclidine act to mediate site-selective and stereoselective couplings of diol-containing carbohydrates with electron-deficient alkenes (Scheme 23); a mechanism involving the formation of a cyclic



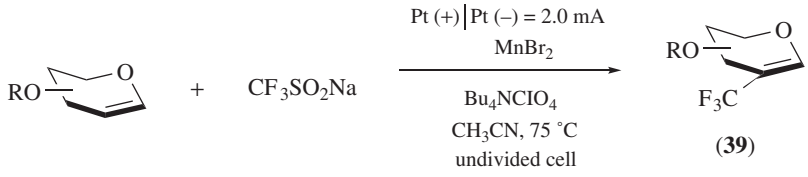
Scheme 22

stannylene acetal intermediate facilitates hydrogen atom abstraction by an intermediate quinuclidinium radical cation, generating a carbon-centered radical that adds to the alkene to give the product (**38**).[60]



Scheme 23

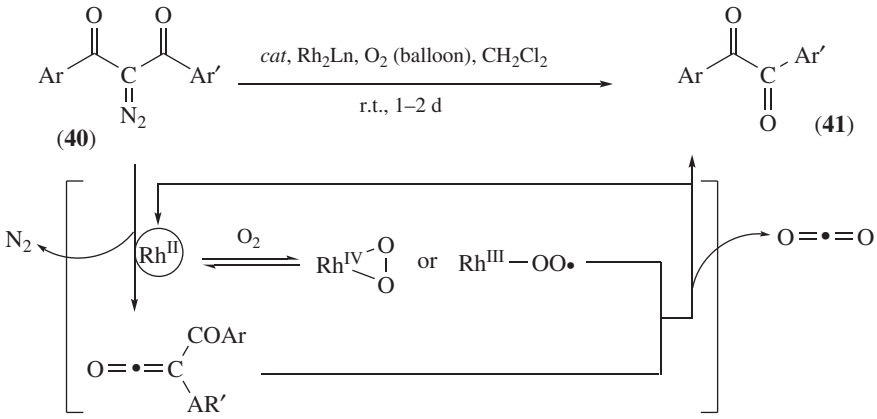
The electrochemical trifluoromethylation of glycals using CF_3SO_2Na as the trifluoromethyl source and $MnBr_2$ as the redox mediator gives trifluoromethylated glycals (**39**) in 60–90% yields with high regioselectivity; a mechanism involving CF_3 radical formation and addition to the alkene moiety was proposed (Scheme 24). Oxidation of the glycosyl oxocarbenium ion on the surface of the anode, followed by deprotonation, gives the product.[61]



Scheme 24

Reactions of Ketenes and Related Cumulenes

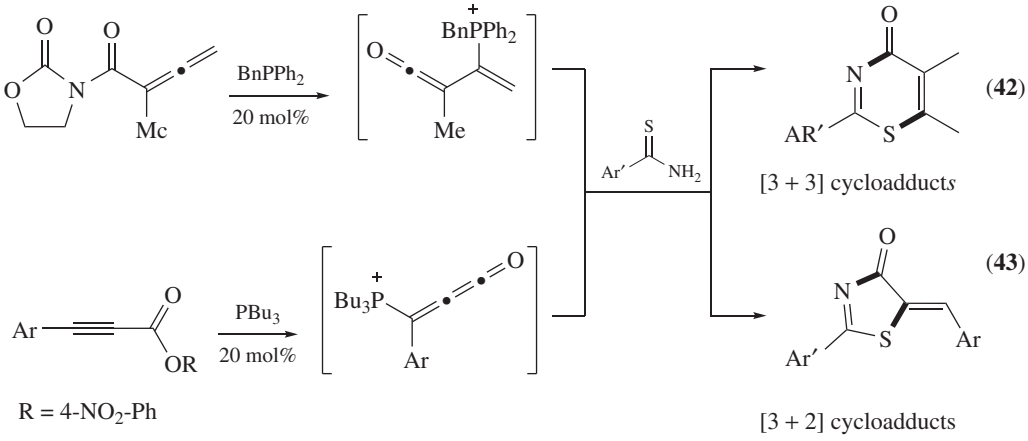
Reduced $ZnCr_2O_4$ spinel surfaces are suitable for syngas conversion to ketene ($H_2C{=}C{=}O$), proceeding by the coupling between CH_2 and CO.[62] Theoretical investigations on mechanisms and kinetics of the reaction of methylketene with H indicate that H association is more energetically beneficial than its abstraction, and the dominant pathway is the formation of ($CH_3CH_2 + CO$).[63] A 3-component Staudinger reaction, by mixing aldehydes, amines, and diazoketones in the dark, followed by photoirradiation after imine formation, gives β-lactams from imines and ketenes formed *in situ*.[64] The rhodium(II)-catalyzed conversion of 1,3-diaryl-2-diazo-1,3-diketones (**40**) to 1,2-diaryl-1,2-diketones (benzils) (**41**) under an oxygen atmosphere proceeds with the incorporation of an oxygen atom and extrusion of a carbonyl unit (Scheme 25). A mechanism is proposed involving the reaction of a ketene arising from Wolff rearrangement of the carbenoid, with a rhodium peroxide or peroxy radical species formed from molecular oxygen. Although benzil derivatives and 9,10-phenanthrenequinone were successfully synthesized, the reaction with 2-diazo-1,3-indandione failed at the initial rearrangement.[65]



Scheme 25

A review of the computational modeling of alkene and alkyne alkoxycarbonylation with palladium catalysts has appeared. For the former with bidentate diphosphine ligands, a hydride pathway operates with an intermolecular alcoholysis step, while for the latter with P, N-chelating ligands, ketene-type intermediates are involved.[66] Allenyl imide and alkynoates with good leaving groups have been used for tandem conjugate addition–elimination reaction (S_N2') promoted by nucleophilic phosphine catalysts ($BnPPh_2$). With thioamides as 1*S*,3*N*-bis-nucleophiles, [3+3] and [3+2] annulations give 1,3-thiazin-4-ones and 5-alkenyl thiazolones in high yields. A mechanism involving the initial formation of vinylphosphonium ketene intermediate, the starting allene, and $BnPPh_2$; interception with the thioamide gives either of the two possible products (**42**) or (**43**) (Scheme 26).[67]

Monomers of carvacrol (5-isopropyl-2-methylphenol), a natural monoterpene exhibiting a wide range of bioactivity, trapped in a cryogenic argon matrix, when irradiated with broad-band UV light (lambda > 200 nm), resulted in the cleavage of the OH group. Recombination of the released H atom at the ortho- or para-position of the ring resulted in the formation of alkyl-substituted cyclohexadienones, which in turn underwent valence and open-ring isomerizations, leading, respectively, to the formation of a Dewar isomer and open-chain conjugated ketenes. Decarbonylation of the photoproducts was observed at longer irradiation times.[68]

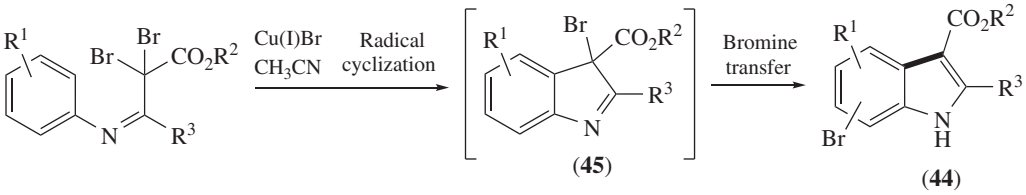


Scheme 26

Imines: Synthesis, and General and Iminium Chemistry

The enantioselective asymmetric alkynylation of aldimines and ketoimines has been reviewed.[69] Incorporation of para-aminophenylalanine (pAF) into the nonenzymatic protein scaffold LmrR creates an artificial enzyme (LmrR_pAF) for the vinylogous Friedel–Crafts alkylation of α,β-unsaturated aldehydes and indoles; it functions by activating enal substrates as intermediate iminium ions, which are receptive to conjugate addition while the protein scaffold exerts stereocontrol. Directed evolution gave a triple mutant that provided higher yields and enantioselectivities for a range of aliphatic enal and substituted indole substrates.[70] (*ee*) (*ee*) (*ee*)

Amines, available from nitro compounds, upon Ugi four-component reaction give access to six- and seven-membered nitrogen-heterocycles; a mechanism for the reaction is proposed.[71] The copper(I)-bromide-mediated radical cyclization reactions of α,α-dibromo-β-iminoesters provide access to 5- or 6-brominated 2-aryl-1*H*-indole-3-carboxylates (**44**) in moderate to good yields. Mechanistically, the bromine atom in the product originates from the substrate through a sequence of radical cyclization to give intermediate (**45**) and electrophilic bromine atom transfer (Scheme 27).[72]



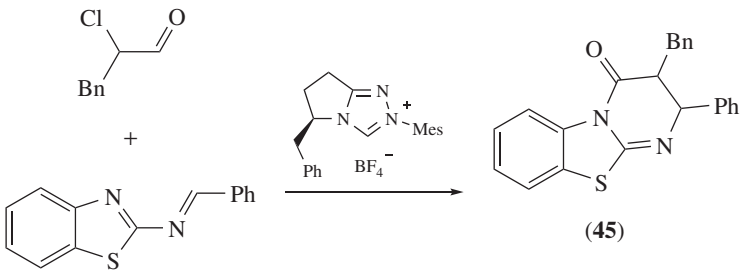
Scheme 27

DFT analysis of the mechanism and origins of stereoselectivity in McGlacken's aldol-Tishchenko reaction for the diastereoselective synthesis of 1,3-amino alcohols using Ellman's t-butylsulfinimines as chiral auxiliaries has shown that an intramolecular hydride transfer step is rate- and stereochemistry-determining, and all prior steps are reversible.[73] Umpolung alkylation of imines catalyzed by cobalt proceeds with broad substrate scope by a radical pathway.[74] The asymmetric α-allylic alkylation of aza-aryl methylamines and π-allylmetal electrophiles in the presence of a chiral aldehyde, a transition metal, and a Lewis acid gives chiral amines and aza-heterocycles in moderate to good yields with good to excellent (*de*)

enantioselectivities; a mechanism involving an attack by an enolate intermediate at the π-allyl Pd(II) complex at the *Si* face gives the corresponding Schiff base, which generates the corresponding product by hydrolysis or amine exchange.[75] DFT calculations have been used to understand the mechanism of the formation of tetrahydro-γ-carbolines under chiral Cu/Ir catalysis, leading to the formation of three stereogenic centers; intramolecular C–C formation of indole C3 to the Si-face of a protonated imine is a key stereo-determining step.[76] (ee)

Mannich and Mannich-type Reactions

DFT calculations (M06-2X) have been used to explore the mechanisms of the *N*-heterocyclic carbene-catalyzed Mannich/lactamization domino reaction of 2-benzothiazolimines and α-chloroaldehydes. The reaction begins with a nucleophilic attack of the NHC on the α-chloroaldehyde, followed by 1,2-proton transfer assisted by the Bronsted acid DABCO·H^+ to generate a Breslow intermediate. Cleavage of the C—Cl bond and deprotonation form an enolate, which reacts with 2-benzothiazolimine, giving a new C—C bond; this step determines the stereochemistry, giving benzothiazolopyrimidinone with SS configuration. Cyclization, the regioselectivity-determining step in which [4+2] annulation pathway is preferred over [2+2], gives the formation of a new C—N bond, followed by catalyst regeneration and final product formation. The basis of the regio- and stereoselectivities have been understood from distortion/interaction, natural bond orbital (NBO), and non-covalent interaction (NCI) calculations.[77] DFT calculations have been used to develop a novel mechanism for Akiyama–Terada chiral phosphoric acid -catalyzed Mannich-type reactions of an aldehyde and an enecarbamate; this involves hydrogen bond formation between both the catalyst hydroxyl group and the aldehyde oxygen and the catalyst P=O and the NH group of the enecarbamate, and this accounts for both the stereoselectivity and the observation that more sterically demanding catalysts give lower levels of enantioselectivity.[78] Three- and four-component variants of the Castagnoli–Cushman reaction proceed by a mechanism in which amide acids derived from maleic anhydride reversibly form free amine and cyclic anhydride. Although this equilibrium is unfavorable, the aldehyde present traps the primary amine through imine formation and reacts with the enol form of the anhydride through a Mannich-like reaction to give the product. This has allowed the development of new conditions using homophthalic anhydride, amines, and aldehydes to give dihydroisoquinolones (**45**) in good yields and excellent diastereoselectivity (Scheme 28).[79] (ee) (de)



Scheme 28

Oximes, Oxime Ethers, and Oxime Esters

Conditions for the synthesis of amides via Beckmann rearrangement of diphenylmethanone oxime using cyanuric chloride (TCT)/DMSO have been studied in detail and applied to