Section VI - Topics in Chemistry

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Chapter 28. Reactions of Interest in Medicinal Chemistry

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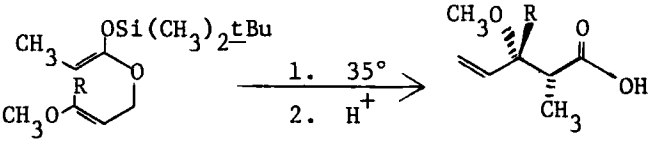
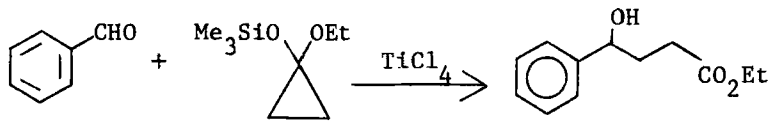
Useful reference books published in 1977 include: Compendium of Organic Synthetic Methods, Volume 3, by L. S. Hegedus and L. G. Wade, Jr; Reagents for Organic Synthesis, Volume 6, by M. Fieser and L. M. Fieser; Synthetic Methods of Organic Chemistry, Volume 31, edited by W. Theilheimer; Organic Synthesis, Volumes 56 and 57, edited by G. H. Büchi and C. R. Johnson, respectively; Organic Reactions, Volume 25, edited by W. G. Dauben; Advances in Heterocyclic Chemistry, Volumes 20, 21, 22, edited by A. R. Katritzky and A. J. Boulton; Annual Reports in Organic Synthesis - 1976, by R. B. Miller and L. G. Wade, Jr.

Reviews - Dimetalated heterosubstituted organic molecules,[1] cyclometalation,[2] Claisen rearrangements,[3] ketene equivalents,[4] phase transfer catalysis,[5] O-silylated enolates,[6] titanium tetrachloride in synthesis,[7] and umpolung through sulfur compounds[8] have been reviewed. A useful table for selective oxidations and reductions has been published.[9]

C-C Bond Formations - Several improvements in the aldol reaction have been noted. Coupling of an α-bromocarbonyl compound with another carbonyl compound via dialkylaluminum chloride-zinc produces the aldol regiospecifically in high yield.[10] Fluoride ion catalyzed reaction of enol silyl ethers and carbonyl compounds prepares aldol products regiospecifically.[11] Aldol-type products are stereoselectively synthesized by Claisen rearrangement of silylketene acetals.[12]

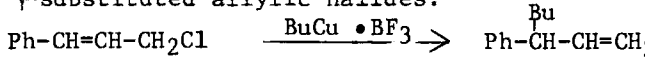


1-Ethoxy-1-trimethylsiloxycyclopropane acts as a homoenolate anion precursor with $TiCl_4$.[13]



Nucleophiles readily add to 2-chloro-1,3-dithiane, a formyl cation equivalent.[14,15]

An alkyl copper-boron trifluoride complex gives complete γ-alkylation of γ-substituted allylic halides.[16]



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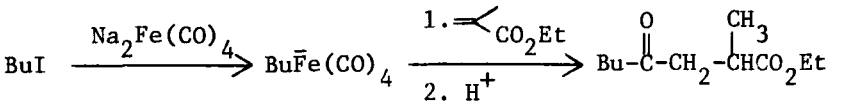
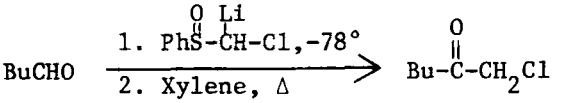
Tosylmethyl isocyanide (TosMIC) can be used to prepare both symmetrical and unsymmetrical α-diketones and ketones.[17,18]

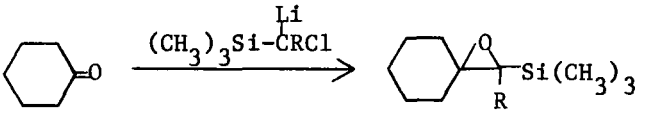
An acyl anion-type Michael addition can be achieved via an organotetracarbonylferrate.[19]



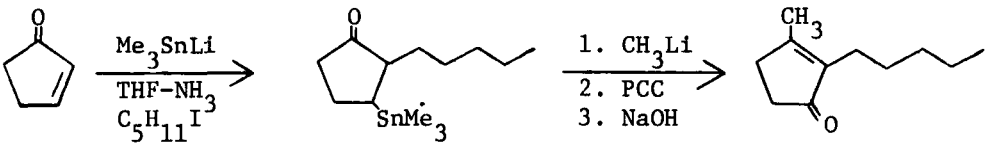
Chloromethyl ketones are prepared by addition of lithio chloromethyl phenyl sulfoxide to aldehydes.[20]



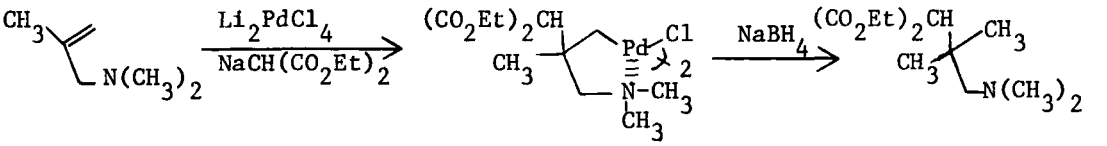
Addition of α-chloro-α-trimethylsilyl carbanion to carbonyl compounds, however, generates α,β-epoxysilanes which are convertible to the homologated carbonyl or alkene compounds.[21,22]



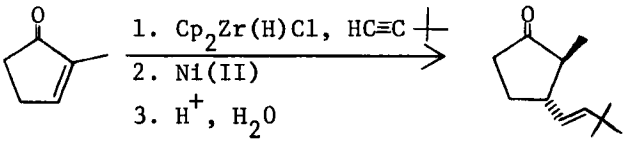
Organotin compounds offer an attractive route to dialkylative enone transposition.[23] Trialkylstannyllithium adds exclusively 1,4. Alkylation of the resultant enolate, methyllithium addition and oxidation afford the transposed enone.



Stabilized carbanions add to simple olefins and allyl amines and sulfides through the intermediacy of palladium complexes.[24,25] Addition occurs predominately at the more substituted position. The resulting palladocycle may be reduced to the hydrocarbon or transformed further by an oxidative addition-reductive elimination sequence.[42]

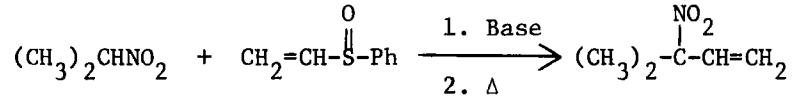


Zirconium alkenyls, available by hydrozirconation of acetylenes, add to α,β-unsaturated ketones with catalytic nickel (II).[26] Zirconium alkenyls also couple with arylhalides under nickel catalysis.[27] More difficultly prepared aluminum alkenyls and copper (I) alkenyls are available by transmetalation of zirconium compounds.[28,29]

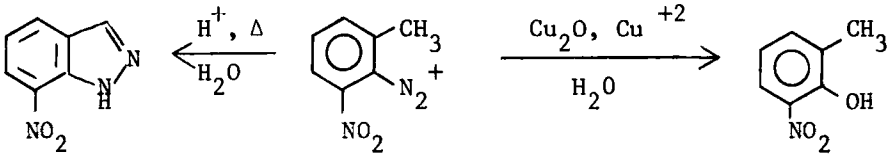


Mannich bases can be prepared regiospecifically by employing dimethyl (methylene)ammonium trifluoroacetate and anions derived from ketones, esters and carboxylic acids.[30,31,32]

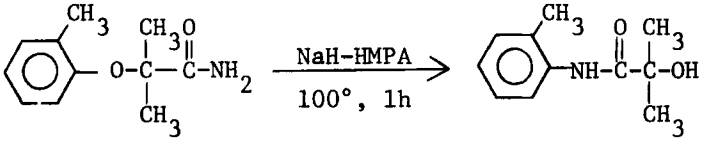
Interesting olefins can be prepared by Michael addition to aryl vinyl sulfoxides followed by sulfoxide elimination.[33]



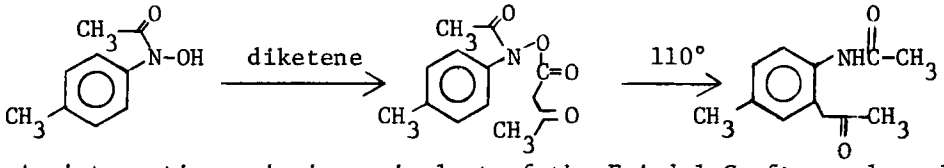
Aromatic Substitution - Arylamines are directly converted to aromatic hydrocarbons by alkyl nitrites in DMF.[34] Alternatively an aryl halide is produced when cupric halides are added in acetonitrile.[35] The alkyl-nitrite deamination method also provides a convenient variant of the Meerwein arylation reaction.[36] In a related method diazonium ions are converted to phenols with cuprous oxide-cupric nitrate.[37] This radical process avoids the problems of the strongly acidic classical transformation.



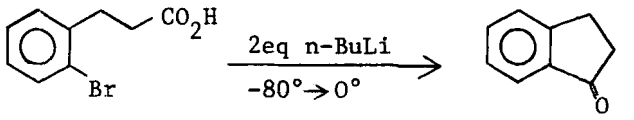
Phenols may also be converted to anilines via a Smiles rearrangement that is greatly accelerated by HMPA solvent.[38]



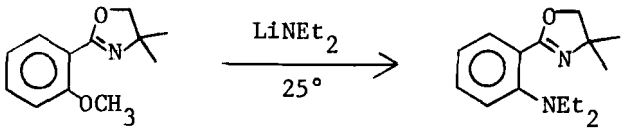
N-Acyl-N-arylhydroxylamines are converted into the ortho-alkylated benzamides via a two step procedure.[39] Variations generate ketone, ester or amide functionalized ortho-alkyl substitutions.



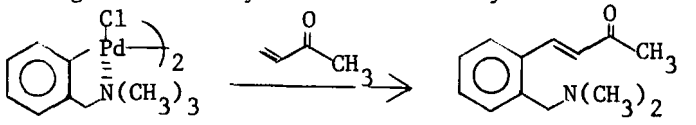
An interesting anionic equivalent of the Friedel-Crafts cycloacylation has been demonstrated.[40]



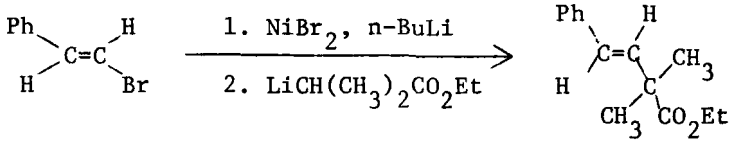
o-(Aminoaryl)oxazolines are prepared by a facile methoxy displacement with lithium amides.[41]



Transition metal catalyzed aromatic substitution continues to be a fruitful area. Aromatic palladium complexes of benzylamines and benzoic acids add enones to generate vinyl substituted aryl derivatives.[42,43,44]

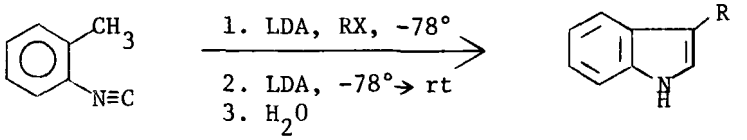


Direct arylation and vinylation of lithium ester enolates is catalyzed by nickel.[45]

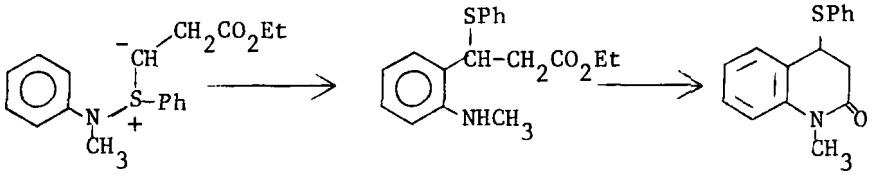


Heterocycles - Two new direct preparations of cyanated indoles and pyrroles utilize either triphenylphosphine-thiocyanogen or anodic electrochemical substitution with methanolic cyanide solution.[46,47]

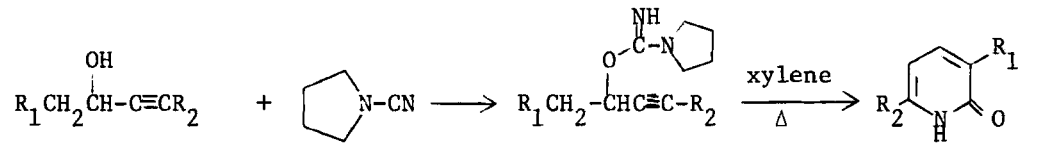
Indoles are efficiently prepared from o-tolyl isocyanide.[48]



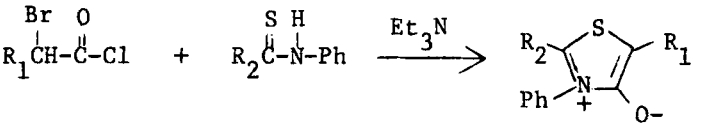
Gassman and coworkers have extended their [2,3] sigmatropic rearrangement of N-aryl-azasulphonium ylides to the synthesis of isatins,[49] and N-methyl-2-quinolones.[50]



Substituted 2-pyridones are formed by base catalyzed condensation of secondary propargylic alcohols and 1-cyanopyrrolidine.[51]



A general route to five-membered mesoionic compounds uses α-bromoacyl chlorides and monoprotonic 1,3-binucleophiles such as N-monosubstituted thioamides.[52] The 1,3-dithiolium and 1,3-oxathiolium systems were also prepared.

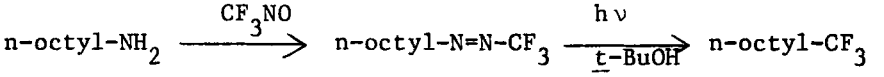


The Darzens condensation has been extended to the synthesis of 1,3-diphenylaziridines.[53]

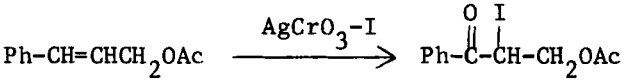
Halogenations - Primary, secondary and tertiary alcohols can be converted to the iodides with trimethylsilyl iodide.[54]

Primary amines can be converted into iodides with 2,4,6-triphenylpyrylium iodide.[55]

Aliphatic trifluoromethyl groups are prepared by reaction of amines with commercially available trifluoronitroso methane followed by photolysis.[56]



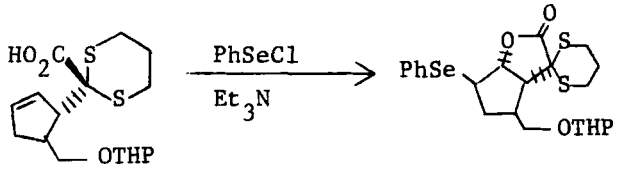
α-Iodoketones are conveniently synthesized with silver chromate-iodine.[57]



Carboxylic Acids and Derivatives - Esters are mildly converted to amides or t-butylthioesters by trimethyl aluminum and the primary or secondary amine or t-butyl thiol.[58,59]

Thiol and selenol esters are prepared from the corresponding thiol or selenol and the carboxylic acid-imidazolides.[60]

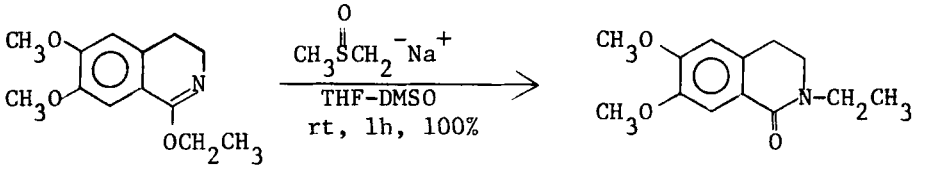
Procedures for phenylseleno and phenylsulphenyllactonization have appeared.[61,62,63] The methods are mild and introduce, for instance, the useful phenylselenyl moiety into the molecule. Similarly cyclic ethers can be prepared from an appropriately positioned alcohol and alkene.[64]



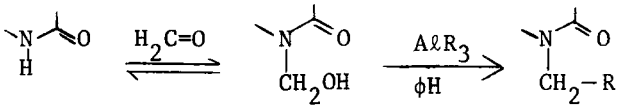
Lactones are cleaved by sodium phenyl selenolate to the ω-phenylselenyl carboxylic acids. Esterification, oxidation and elimination generates ω-olefinic esters. [65,66]

Nitriles can be prepared directly from primary nitro compounds using phosphorus trichloride.[67] β-Acetoxy nitromethanes yield cyanohydrin acetates.

Catalytic dimsylsodium induces a very mild O-alkylimidate to N-alkyllactam conversion.[68] The reaction appears to be both mild and gentle.



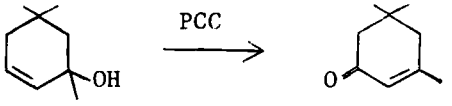
N-Alkylamides are formed by alkylaluminum reduction of the methylol.[69]



Oxidations - The use of oxidants absorbed on alumina or silica has blossomed. These reagents are generally milder and more selective and provide for convenient reaction workup. Oxidations of cyclobutanol to cyclobutanone and β-hydroxysulfides and selenides to the β-keto compounds are accomplished by trichloroacetaldehyde on alumina.[70,71] Basic dry silica gel converts nitro groups into carbonyls[72] and chromyl chloride on silica-alumina oxidizes alcohols.[73]

Pyridinium chlorochromate (PCC) will directly oxidize cyclic and acyclic enol ethers to lactones and esters.[74]

PCC oxidizes tertiary allylic alcohols to the transposed 3-alkyl α,β-unsaturated ketones.[75]

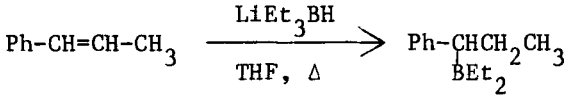


α-Keto sulfides, prepared by sulfenylation of enolates with diphenyl disulfide, are acetoxylated by lead tetraacetate to afford mono-protected 1,2-dicarbonyl compounds.[76]

Reductions - The experimental details and scope of alumina as a medium for carbonyl reductions have been published.[77]

Aldehydes are selectively reduced in the presence of ketones and other functional groups by either 9-borabicyclo [3.3.1] nonane-pyridine or sodium borohydride modified by thiols.[78,79]

Lithium triethylborohydride causes a number of useful reductions. Tertiary amides are cleaved by carbon-nitrogen fission to alcohols[80] and alkyl methanesulfonate esters are reduced to hydrocarbons.[81] Additionally, $LiEt_3BH$ adds to substituted styrenes in a Markownikoff manner.[82]



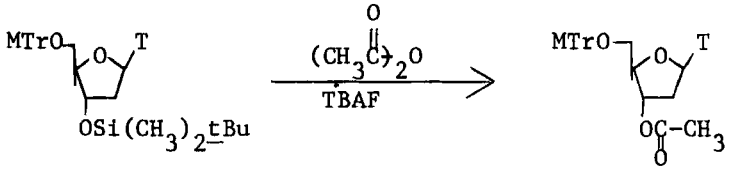
Protecting Groups - Acetals are formed rapidly in high yields at room temperature using trimethylorthoformate absorbed on commercially available montmorillonite clay K-10.[83]

Thiosilanes react with aldehydes and ketones under Lewis acid, anion or thermal catalysis to generate O-silylhemithioketals.[84] An additional equivalent of thiosilane produces thioketals. Exclusive 1,4-addition to α,β-unsaturated carbonyl compounds occurs.

Ketals (except ethylene) can be converted to ketones under non-aqueous conditions with trimethylsilyl iodide.[85]

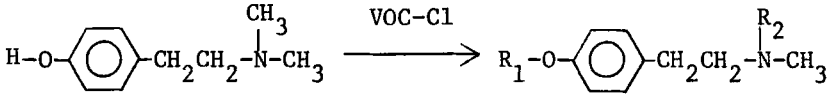
Ketones are regenerated from hydrazones, oximes, semicarbazones and thioketals by benzeneseleninic anhydride.[86,87]

Acylation of sterically hindered hydroxyl groups is facile with an anhydride and fluoride ion.[88] Additionally a silyl group may be directly replaced by an acyl group using the anhydride and tetrabutylammonium fluoride. This transformation permits the in situ exchange of an alkali resistant for an alkali sensitive protecting group.



Crotonyl esters are useful alcohol protecting groups removable with dilute hydrazine in methanol-pyridine.[89]

The vinyloxy carbonyl group (VOC) appears to be very useful for alcohol and amine protection and an extremely mild reagent for amine dealkylation.[90,91,92] For example, one equivalent of vinyl chloroformate produces the VOC ester (R_1=VOC, R_2=CH_3). An additional equivalent of VOC-Cl in methylene chloride at 25° produces the N-demethylated compound (R_1=R_2=VOC). The ester can be cleaved in the presence of the urethane with dilute base while the urethane can be cleaved in the presence of the ester by one equivalent of HBr in methanol. Refluxing 5% methanolic-HCl cleaves both protecting groups.



Esters and ethers can be cleaved with trimethylsilyl iodide.[93,94]

Miscellaneous - Azides are converted to amines in a non-reductive aza transfer reaction to acetylacetone.[95]

Thioethers are formed when an alcohol, sulfenamide and tri-n-butylphosphine react.[96]

Nitrile oxides are converted into isocyanates by catalytic sulfur dioxide in refluxing benzene.[97]

Primary amines are transformed into acetates or benzoates via a two step procedure by reaction with triphenylpyrylium tetrafluoroborate and subsequent pyrolysis of the pyridinium salt in the presence of acetate or benzoate.[98]

Alumina and silica have been used as catalysts for opening arene oxides and vinyl epoxides using weak oxygen and amine nucleophiles[99] and dry ozonization of amines to nitro compounds.[100]

Triphase catalysis allows conversion of alkyl halides to nitriles and alkyl bromides to chlorides.[101]

Vinyl bromides, enol acetates, enol ethers and enamides can be prepared stereospecifically from α,β-epoxysilanes.[102]

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