Strategic Applications of Named Reactions in Organic Synthesis

Strategic Applications of Named Reactions in Organic Synthesis

Background and Detailed Mechanisms

by

László Kürti and Barbara Czakó

UNIVERSITY OF PENNSYLVANIA

250 Named Reactions

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This book is dedicated to

Professor Madeleine M. Joullié

for her lifelong commitment

to mentoring graduate students

ABOUT THE AUTHORS

Barbara Czakó was born and raised in Hungary. She received her Diploma from Lajos Kossuth University in Debrecen, Hungary (now University of Debrecen). She obtained her Master of Science degree at University of Missouri-Columbia. Currently she is pursuing her Ph.D. degree in synthetic organic chemistry under the supervision of Professor Gary A. Molander at the University of Pennsylvania.

László Kürti was born and raised in Hungary. He received his Diploma from Lajos Kossuth University in Debrecen, Hungary (now University of Debrecen). He obtained his Master of Science degree at University of Missouri-Columbia. Currently he is pursuing his Ph.D. degree in synthetic organic chemistry under the supervision of Professor Amos B. Smith III at the University of Pennsylvania.

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VII. NAMED ORGANIC REACTIONS IN ALPHABETICAL ORDER

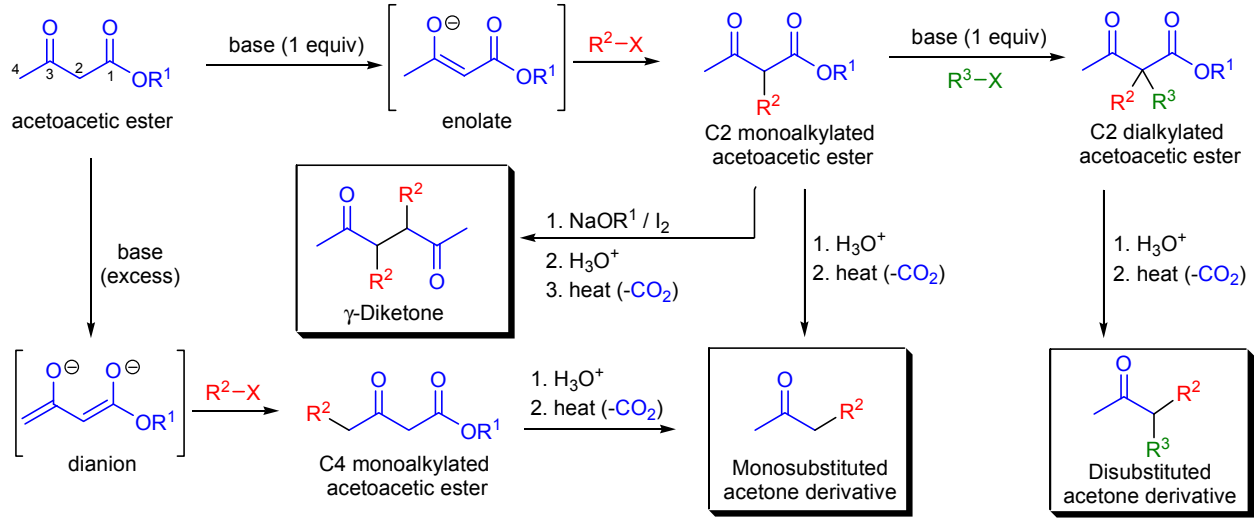
ACETOACETIC ESTER SYNTHESIS

(References are on page 531)

Importance:

[*Seminal Publications*[1-4]; *Reviews*[5-9]; *Modifications & Improvements*[10-19]]

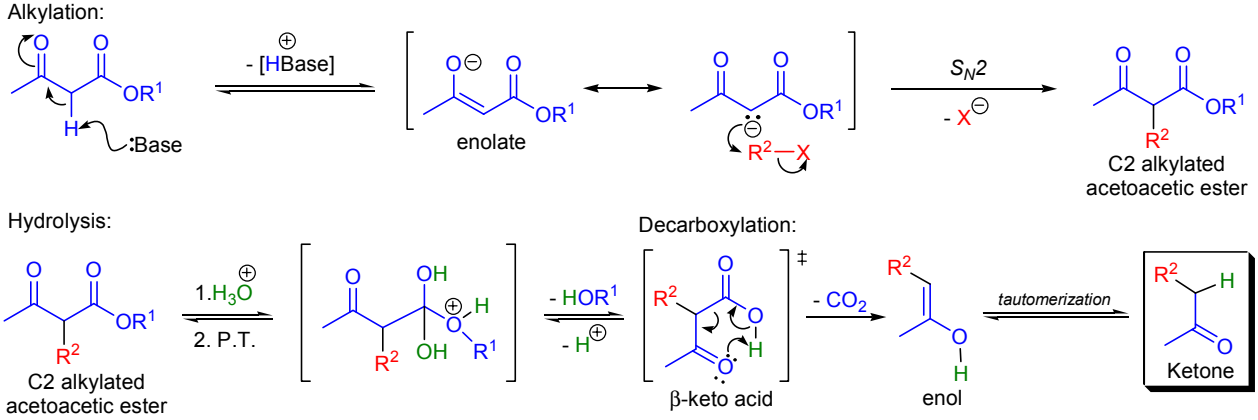
The preparation of ketones *via* the *C*-alkylation of esters of 3-oxobutanoic acid (acetoacetic esters) is called the *acetoacetic ester synthesis*. Acetoacetic esters can be deprotonated at either the C2 or at both the C2 and C4 carbons, depending on the amount of base used. The C-H bonds on the C2 carbon atom are activated by the electron-withdrawing effect of the two neighboring carbonyl groups. These protons are fairly acidic (pK_a ~11 for C2 and pK_a ~24 for C4), so the C2 position is deprotonated first in the presence of one equivalent of base (sodium alkoxide, LDA, NaHMDS or LiHMDS, etc.). The resulting anion can be trapped with various alkylating agents. A second alkylation at C2 is also possible with another equivalent of base and alkylating agent. When an acetoacetic ester is subjected to excess base, the corresponding dianion (extended enolate) is formed.[13-15,18,19] When an electrophile (e.g., alkyl halide) is added to the dianion, alkylation occurs first at the most nucleophilic (reactive) C4 position. The resulting alkylated acetoacetic ester derivatives can be subjected to two types of hydrolytic cleavage, depending on the conditions: 1) dilute acid hydrolyzes the ester group, and the resulting β-keto acid undergoes decarboxylation to give a ketone (mono- or disubstituted acetone derivative); 2) aqueous base induces a *retro-Claisen reaction* to afford acids after protonation. The hydrolysis by dilute acid is most commonly used, since the reaction mixture is not contaminated with by-products derived from ketonic scission. More recently the use of the *Krapcho decarboxylation* allows neutral decarboxylation conditions.[11,12] As with malonic ester, monoalkyl derivatives of acetoacetic ester undergo a base-catalyzed coupling reaction in the presence of iodine. Hydrolysis and decarboxylation of the coupled products produce γ-diketones. The starting acetoacetic esters are most often obtained *via* the *Claisen condensation* of the corresponding esters, but other methods are also available for their preparation.[5,8]



R^1 = 1°, 2° or 3° alkyl, aryl; R^2 = 1° or 2° alkyl, allyl, benzyl; R^3 = 1° or 2° alkyl, allyl, benzyl; base: NaH, $NaOR^1$,LiHMDS, NaHMDS

Mechanism: [3,20]

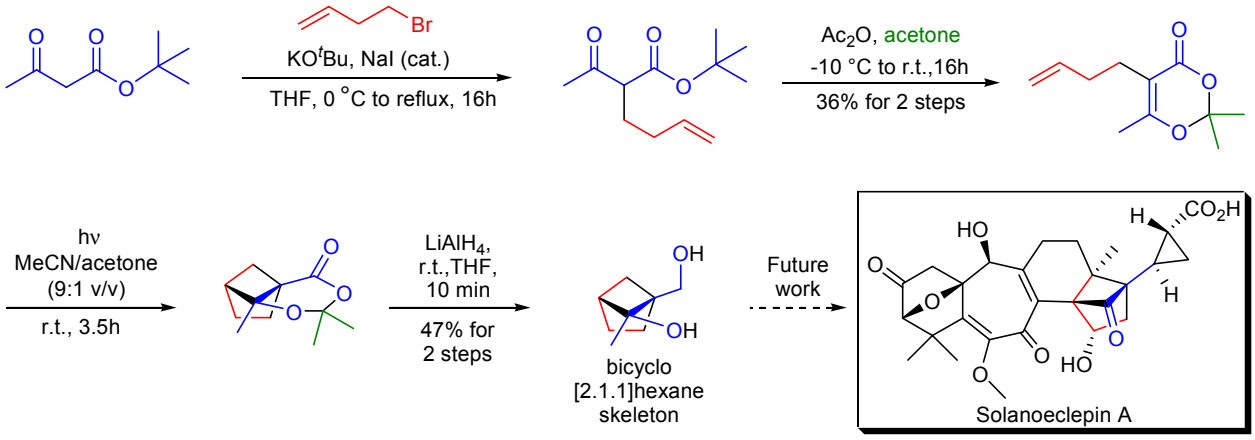
The first step is the deprotonation of acetoacetic ester at the C2 position with one equivalent of base. The resulting enolate is nucleophilic and reacts with the electrophilic alkyl halide in an S_N2 reaction to afford the C2 substituted acetoacetic ester, which can be isolated. The ester is hydrolyzed by treatment with aqueous acid to the corresponding β-keto acid, which is thermally unstable and undergoes decarboxylation *via* a six-membered transition state.



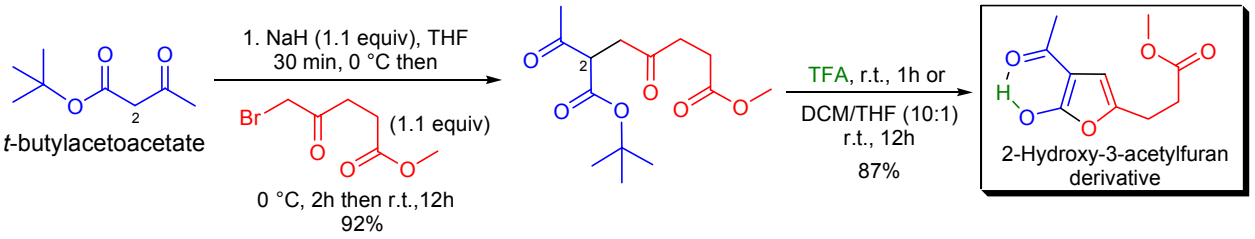
ACETOACETIC ESTER SYNTHESIS

Synthetic Applications:

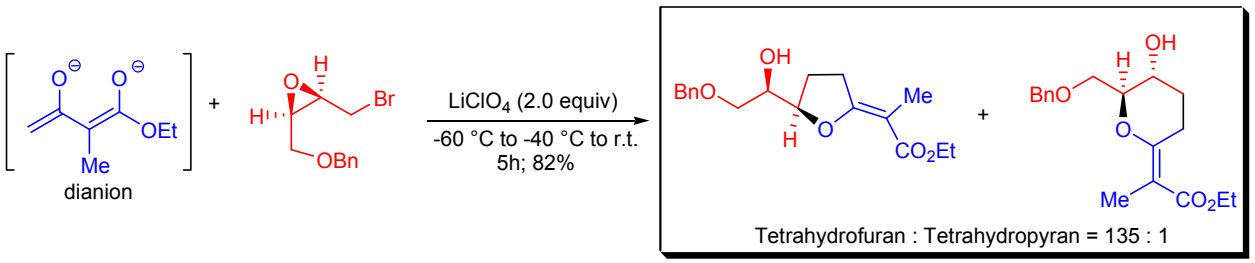
In the laboratory of H. Hiemstra, the synthesis of the bicyclo[2.1.1]hexane substructure of solanoeclepin A was undertaken utilizing the intramolecular photochemical dioxenone-alkene [2+2] cycloaddition reaction.[21] The dioxenone precursor was prepared from the commercially available *tert*-butyl acetoacetate using the *acetoacetic ester synthesis*. When this dioxenone precursor was subjected to irradiation at 300 nm, complete conversion of the starting material was observed after about 4h, and the expected cycloadduct was formed in acceptable yield.



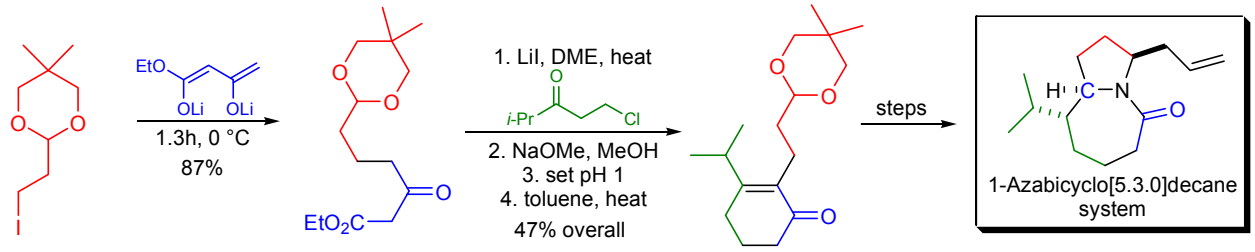
R. Neier et al. synthesized substituted 2-hydroxy-3-acetylfurans by the alkylation of *tert*-butylacetoacetate with an α-haloketone, followed by treatment of the intermediate with trifluoroacetic acid.[22] When furans are prepared from β-ketoesters and α-haloketones, the reaction is known as the *Feist-Bénary reaction*. A second alkylation of the C2 alkylated intermediate with various bromoalkanes yielded 2,2-disubstituted products, which upon treatment with TFA, provided access to trisubstituted furans.



M. Nakada and co-workers developed a novel synthesis of tetrahydrofuran and tetrahydropyran derivatives by reacting dianions of acetoacetic esters with epibromohydrin derivatives.[23] The selective formation of the tetrahydrofuran derivatives was achieved by the use of $LiClO_4$ as an additive.



A synthetic strategy was developed for the typical core structure of the *Stemona* alkaloids in the laboratory of C.H. Heathcock.[24] The precursor for the 1-azabicyclo[5.3.0]decane ring system was prepared *via* the successive double alkylation of the dianion of ethyl acetoacetate.



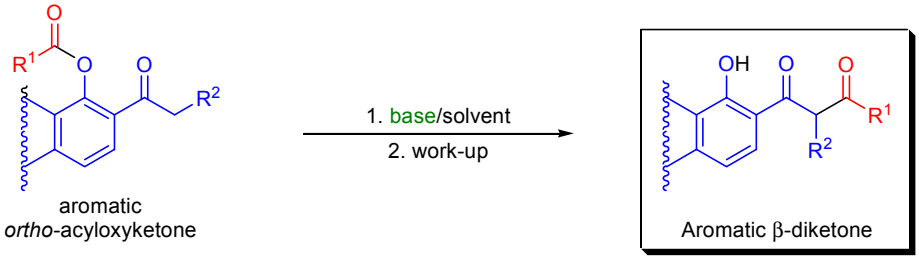
BAKER-VENKATARAMAN REARRANGEMENT

(References are on page 542)

Importance:

[*Seminal Publications*[1-4]; *Reviews*[5-7]; *Modifications & Improvements*[8-17]]

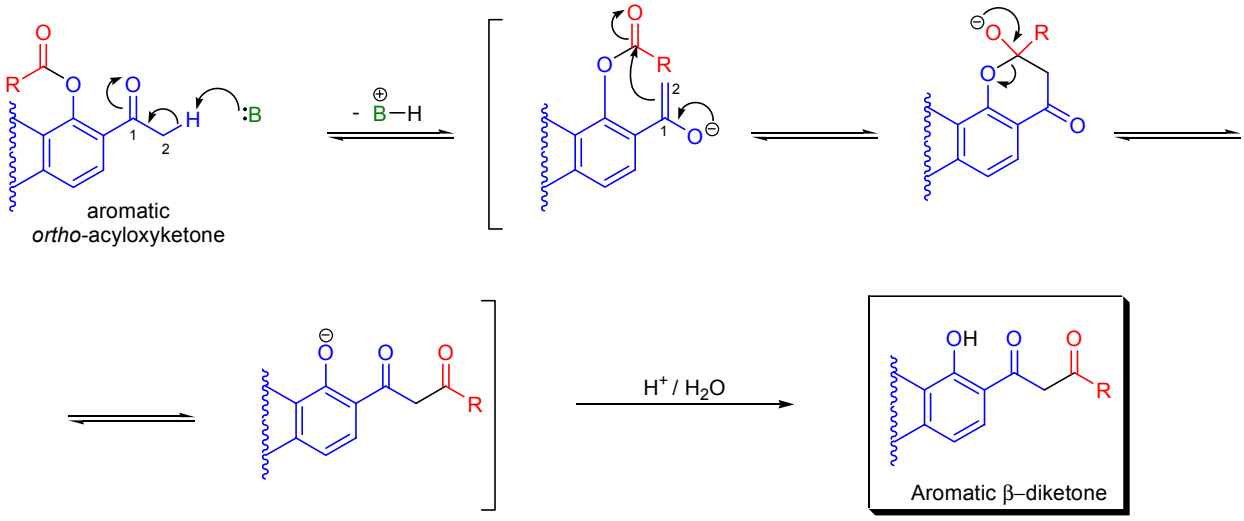
The base-catalyzed rearrangement of aromatic *ortho*-acyloxyketones to the corresponding aromatic β-diketones is known as the *Baker-Venkataraman rearrangement*. β-Diketones are important synthetic intermediates, and they are widely used for the synthesis of chromones, flavones, isoflavones, and coumarins. The most commonly used bases are the following: KOH, potassium *tert*-butoxide in DMSO, Na metal in toluene, sodium or potassium hydride, pyridine, and triphenylmethylsodium.



R^1 = alkyl, aryl, NH_2; R^2 = alkyl, aryl; base: KOH, KO*t*-Bu, NaH, Na metal, KH, C_5H_5N

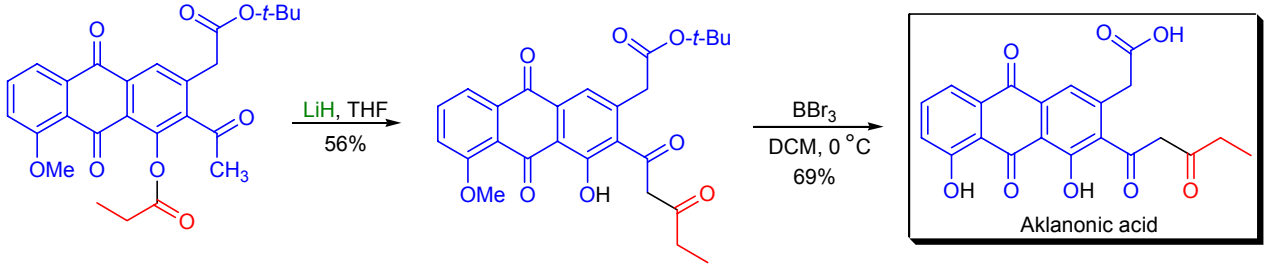
Mechanism: [18-22]

In the first step of the mechanism, the aromatic ketone is deprotonated at the α-carbon and an enolate is formed. This nucleophile attacks the carbonyl group of the acyloxy moiety intramolecularly to form a tetrahedral intermediate that subsequently breaks down to form the aromatic β-diketone.



Synthetic Applications:

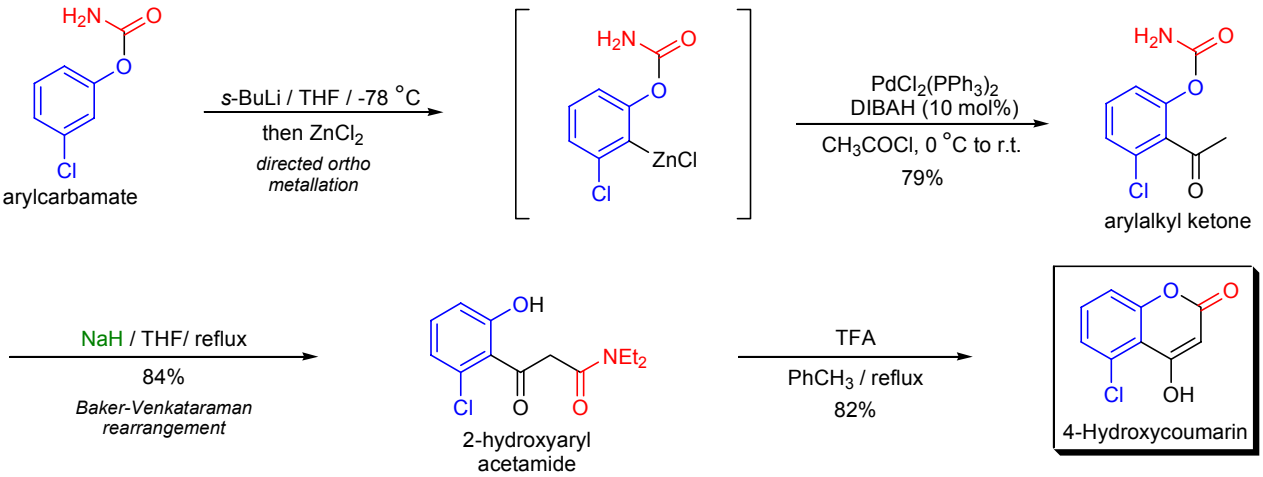
In the laboratory of K. Krohn, the total synthesis of aklanonic acid and its derivatives was undertaken, utilizing the *Baker-Venkataraman rearrangement* of *ortho*-acetyl anthraquinone esters in the presence of lithium hydride.[23] Using this method, it was possible to introduce ketide side-chains on anthraquinones in a facile manner.



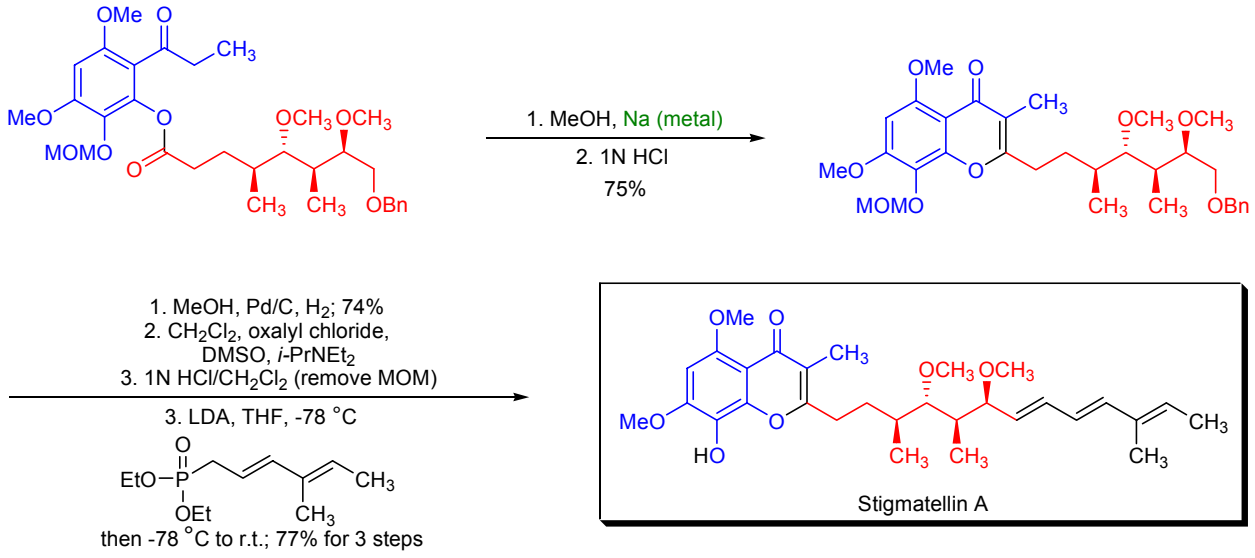
BAKER-VENKATARAMAN REARRANGEMENT

Synthetic Applications:

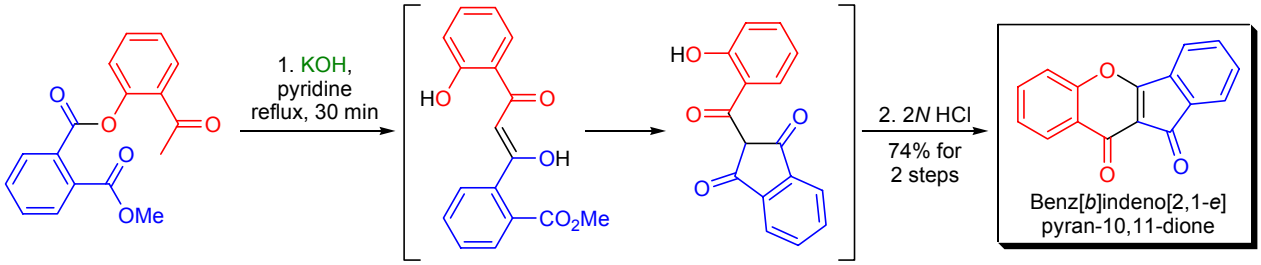
V. Snieckus and co-workers developed a new *carbamoyl Baker-Venkataraman rearrangement,* which allowed a general synthesis of substituted 4-hydroxycoumarins in moderate to good overall yields.[16] The intermediate arylketones were efficiently prepared from arylcarbamates *via directed ortho metallation* and *Negishi cross coupling*. The overall sequence provided a regiospecific anionic *Friedel-Crafts* complement for the construction of *ortho*-acyl phenols and coumarins.



Stigmatellin A is a powerful inhibitor of electron transport in mitochondria and chloroplasts. During the diastereo- and enantioselective total synthesis of this important natural product, D. Enders et al. utilized the *Baker-Venkataraman rearrangement* for the construction of the chromone system in good yield.[24]



A highly efficient and operationally simple domino reaction was developed in the laboratory of S. Ruchiwarat for the synthesis of benz[*b*]indeno[2,1-*e*]pyran-10,11-diones.[25] The initial aroyl-transfer was achieved by the *Baker-Venkataraman rearrangement* by subjecting the starting material to KOH in pyridine under reflux for 30 minutes.



BALDWIN'S RULES / GUIDELINES FOR RING-CLOSING REACTIONS

(References are on page 542)

Importance:

[*Seminal Publication*[1]*; Reviews*[2,3]*; Related Publications*[4-14]]

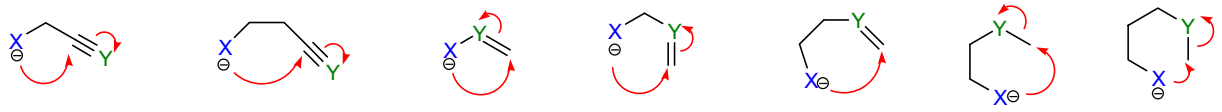
In 1976, J.E. Baldwin formulated a set of rules/guidelines governing the ease of intramolecular ring-closing reactions, the so-called *Baldwin's rules* or *Baldwin's guidelines*.[1] Baldwin used these rules/guidelines to gain valuable insight into the role of stereoelectronic effects in organic reactions and predict the feasibility of these reactions in synthetic sequences. A few years later in 1983, J.D. Dunitz and co-workers demonstrated that there are favored trajectories for the approach of one reactant molecule toward another.[15] We must note, however, that there is substantial limitation on these rules/guidelines; a large number of examples are known for which they do not apply.

Summary of most important ring closures:

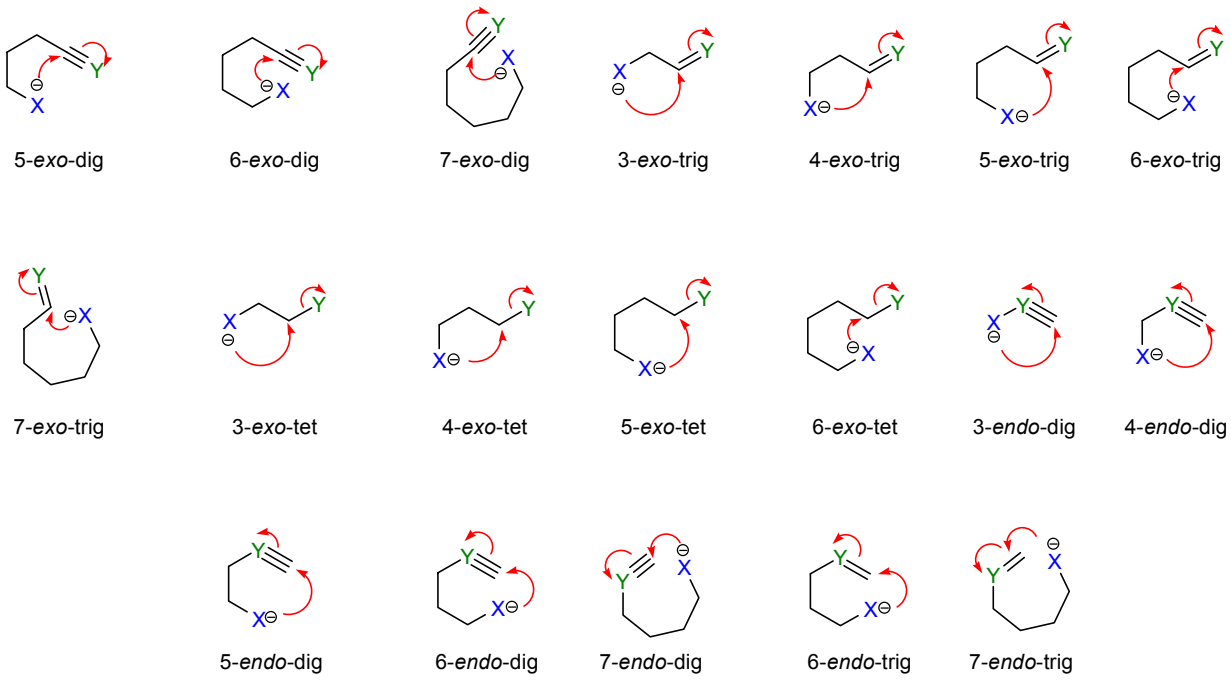
(**F**=favored, **D**=disfavored)

Ring size	Exo-dig	Exo-trig	Exo-tet	Endo-dig	Endo-trig	Endo-tet
3	**D**	**F**	**F**	**F**	**D**	-
4	**D**	**F**	**F**	**F**	**D**	-
5	**F**	**F**	**F**	**F**	**D**	**D**
6	**F**	**F**	**F**	**F**	**F**	**D**
7	**F**	**F**	**F**	**F**	**F**	-

Disfavored Processes



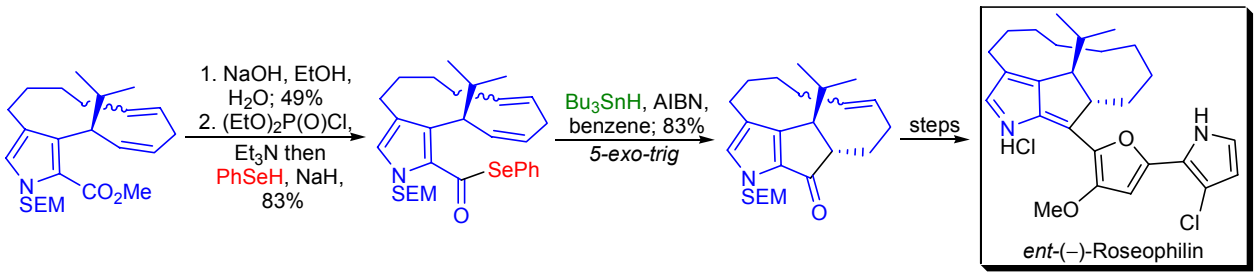
Favored Processes



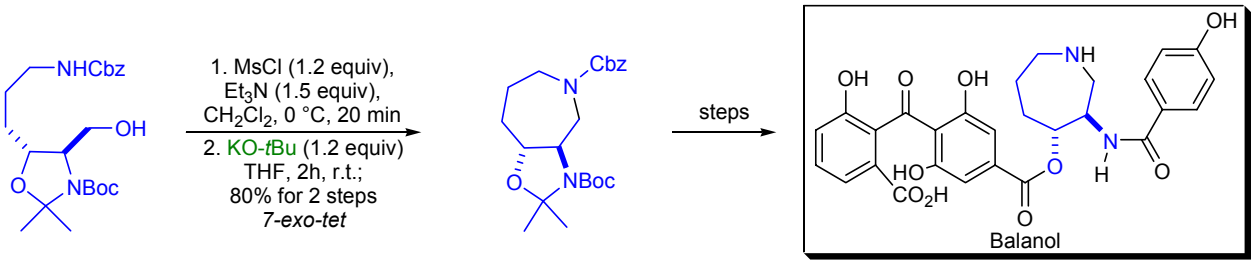
BALDWIN'S RULES / GUIDELINES FOR RING-CLOSING REACTIONS

Synthetic Applications:

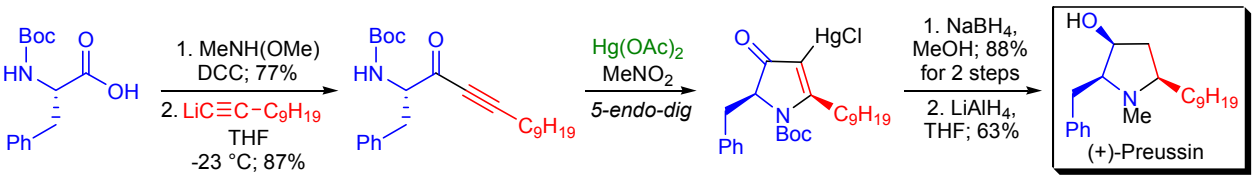
D.L Boger and co-workers reported an asymmetric total synthesis of *ent*-(–)-roseophilin, the unnatural enantiomer of a naturally occurring antitumor antibiotic.[16] Their approach featured a *5-exo-trig* acyl radical-alkene cyclization to construct the fused cyclopentanone unit. To this end, the hindered methyl ester functionality was hydrolyzed and the resulting acid was transformed to the corresponding phenyl selenoester *via* a two-step sequence. The *5-exo-trig* acyl radical-alkene cyclization was achieved by using AIBN and Bu_3SnH to provide the tricyclic *ansa*-bridged azafulvene core.



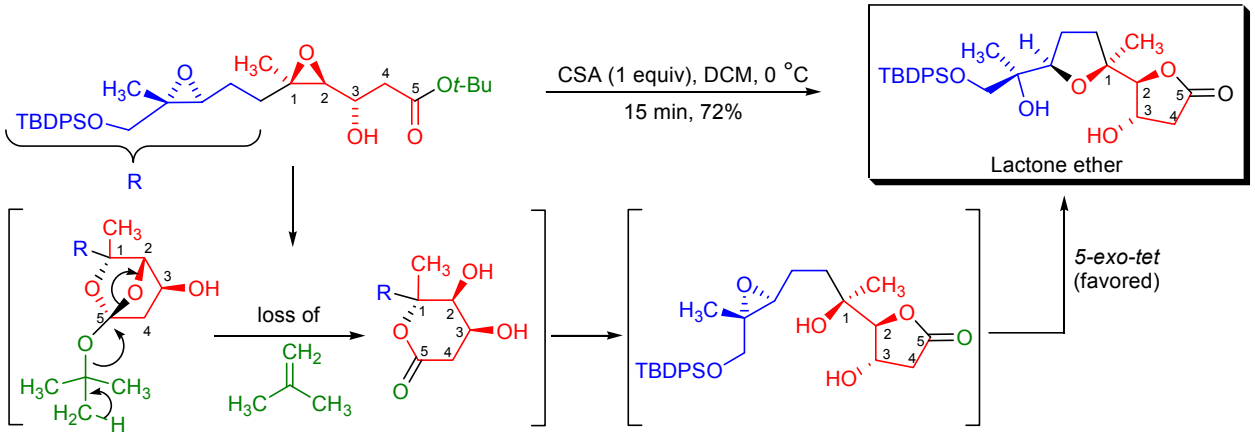
The total synthesis of balanol, a fungal metabolite was accomplished by K.C. Nicolaou *et al.*[17] For the construction of the central hexahydroazepine ring, they have utilized a *7-exo-tet* cyclization. The substitution reaction between the mesylate of the primary alcohol and the Cbz-protected amine was effected by a slight excess of base to produce the desired 7-membered ring in high yield.



The total synthesis of pyrrolidinol alkaloid, (+)-preussin was achieved in five efficient transformations from commercially available *tert*-Boc-(*S*)-phenylalanine in the laboratory of S.M. Hecht.[18] The key step involved the $Hg^{(II)}$-mediated *5-endo-dig* cyclization of ynone substrate affording the desired pyrrolidinone which, in two more steps, was converted into the natural product.



In the laboratory of K. Nacro, a cyclization process leading stereoselectively to *six- and/or five-membered ring lactones* and *lactone ethers* from optically active epoxy- or diepoxy β-hydroxyesters or diastereomeric epoxy lactones was developed.[19] The diastereomeric lactones were prepared from nerol and geraniol. The acid catalyzed cyclization of epoxyalcohols is one of the most effective methods for constructing cyclic ethers. The cyclization proceeds in the *exo* mode giving cyclic ethers with a hydroxyl group in the side chain. The regioselectivity of the cyclization is predicted by the *Baldwin's rules*; in the case shown below the ether formation takes place *via* a *5-exo-tet* cyclization.



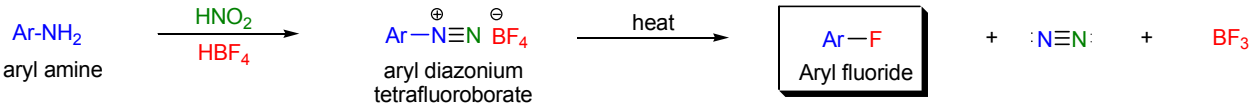
BALZ-SCHIEMANN REACTION
(SCHIEMANN REACTION)

(References are on page 543)

Importance:

[*Seminal Publication*[1]; *Reviews*[2-6]; *Modifications & Improvements*[7-14]]

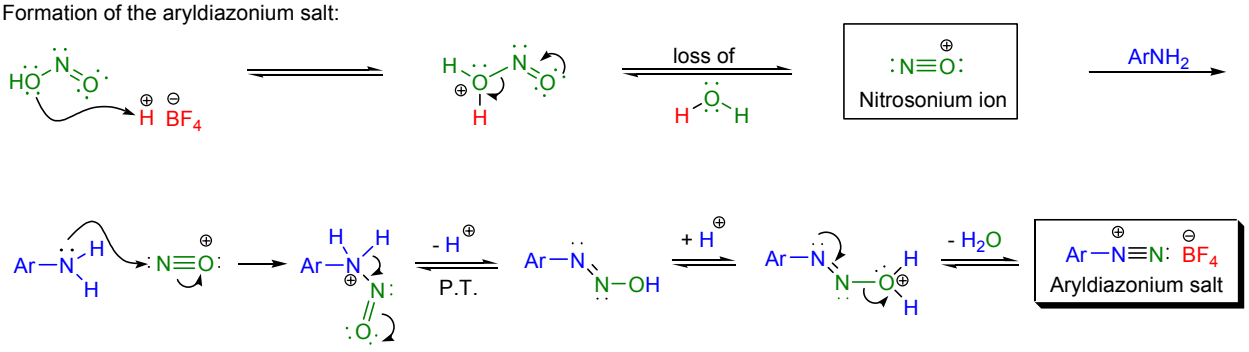
The thermal decomposition of aromatic diazonium tetrafluoroborates ($ArN_2^+BF_4^-$) to give aromatic fluorides is called the *Balz-Schiemann reaction*. Normally diazonium salts are unstable but diazonium tetrafluoroborates are fairly stable and may be obtained in high yields. Aromatic heterocyclic diazonium tetrafluoroborates may also be used. The diazonium salts are obtained from the diazotization of aromatic amines in the presence of hydrogen tetrafluoroborate (HBF_4). Improved yields of aryl fluorides may be achieved when instead of tetrafluoroborates, hexafluorophosphates (PF_6^-) or hexafluoroantimonates (SbF_6^-) are used as counterions.[7,8] One drawback of the reaction is the potential danger of explosion when large-scale thermal decomposition of the aromatic diazonium tetrafluoroborates is attempted. However, when the decomposition is carried out, either thermally or photolytically, in pyridine·HF solution, the reaction proceeds smoothly even on a larger scale. This approach is especially useful for the preparation of aryl fluorides having polar substituents (OH, OMe, CF_3, etc.).[15]



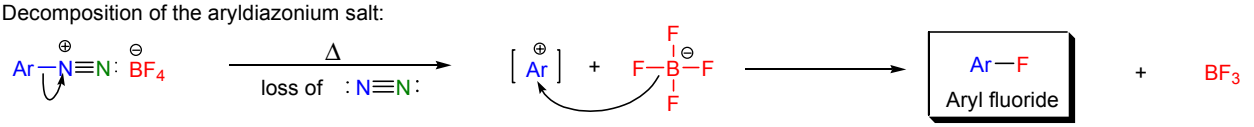
Mechanism: [16-24]

The mechanism involves a positively charged intermediate,[21] which is attacked by BF_4^- rather than the fluoride ion.[20] Both the thermal and photochemical decomposition of diazonium tetrafluoroborates afford the same product ratio, which suggests the intermediacy of the aryl cation. The decomposition follows a first-order rate law, so it is probably of S_N1 type.

Formation of the aryldiazonium salt:

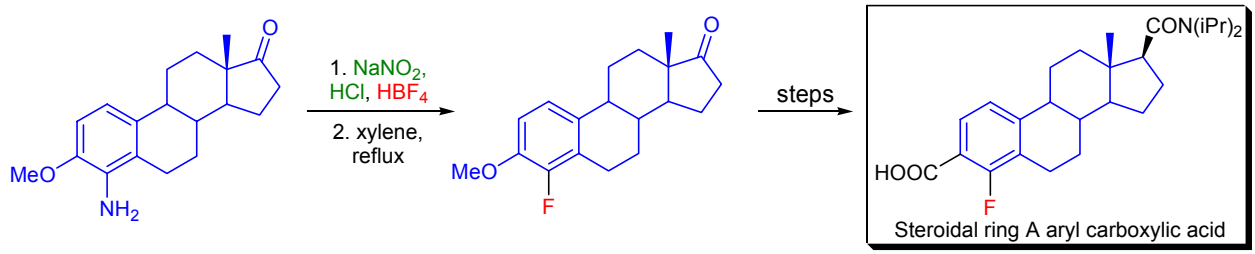


Decomposition of the aryldiazonium salt:



Synthetic Applications:

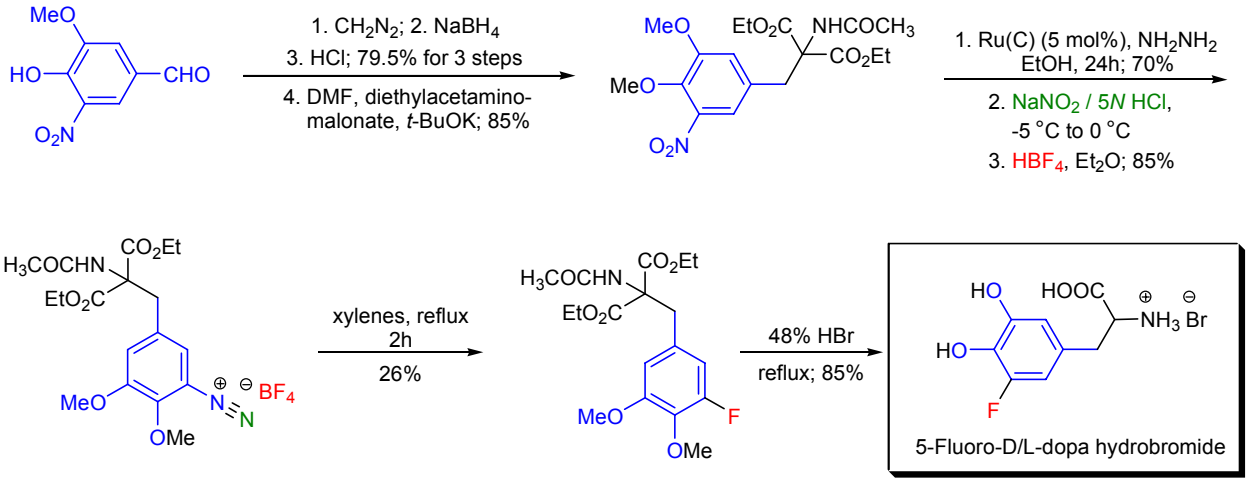
In the laboratory of D.A. Holt, the synthesis of a new class of steroid 5α-reductase inhibitors was undertaken.[25] They found that unlike the steroidal acrylates, steroidal A ring aryl carboxylic acids exhibit greatly reduced affinity for rat liver steroid 5α-reductase. The tested steroidal A ring carboxylic acids were synthesized from estrone; in one example, fluorine was incorporated into the 4-position of estrone *via* the *Balz-Schiemann reaction*.



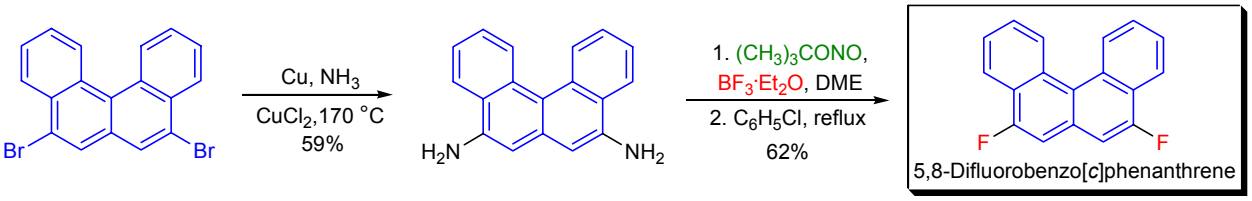
BALZ-SCHIEMANN REACTION
(SCHIEMANN REACTION)

Synthetic Applications:

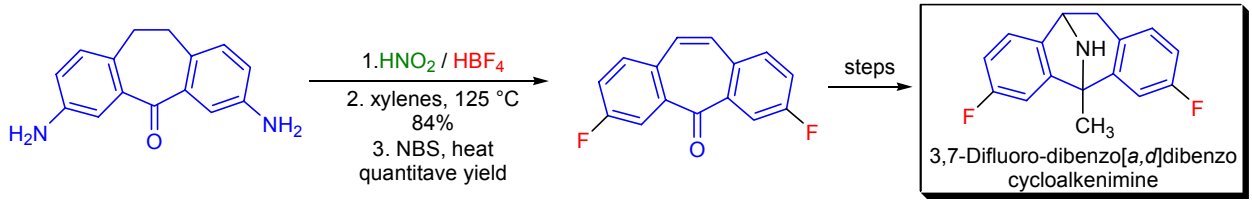
C. Wiese and co-workers have synthesized 5-fluoro-D/L-dopa and the corresponding [^{18}F]5-Fluoro-L-dopa starting from 5-nitrovanillin *via malonic ester synthesis*, the *Balz-Schiemann reaction*, and the separation of the racemic mixture [^{18}F]5-fluoro-D/L-dopa utilizing a chiral HPLC system.[26] The inactive 5-fluoro-D/L-dopa was obtained in an eight-step synthesis with an overall yield of 10%.



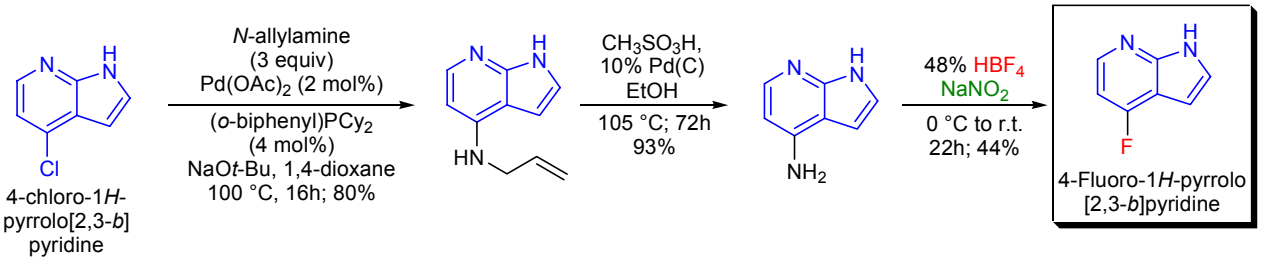
D.R. Thakker synthesized K-region monofluoro- and difluorobenzo[c]phenanthrenes using the *Balz-Schiemann reaction* in order to elucidate the metabolic activation and detoxification of polycyclic aromatic compounds.[27]



Dibenzo[*a,d*]cycloalkenimines were synthesized and pharmacologically evaluated as *N*-methyl-D-aspartate antagonists by P.S. Anderson et al.[28] A symmetrical 3,7-difluoro derivative was accessed by applying the *Balz-Schiemann reaction* on the corresponding 3,7-diamino analog.



The synthesis of 7-azaindoles is a challenging task and there are few efficient routes to substituted derivatives. In the laboratory of C. Thibault, the concise and efficient synthesis of 4-fluoro-1*H*-pyrrolo[2,3-*b*]pyridine was achieved.[29] The fluorination was carried out using the *Balz-Schiemann reaction*. The aromatic amine precursor was prepared *via* the *Buchwald-Hartwig coupling* of the aryl chloride with *N*-allylamine followed by deallylation. The diazonium tetrafluoroborate intermediate was generated at 0 °C and it decomposed spontaneously in 48% HBF_4 solution to afford the desired aromatic fluoride.



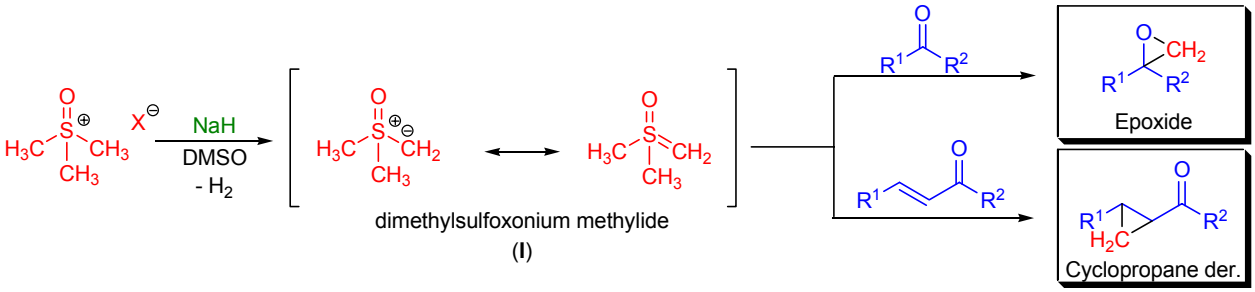
COREY-CHAYKOVSKY EPOXIDATION AND CYCLOPROPANATION

(References are on page 565)

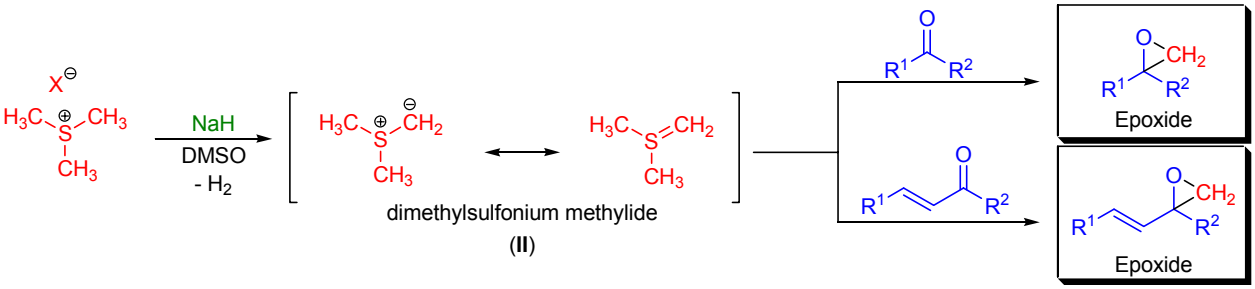
Importance:

[*Seminal Publications*[1,2]*; Reviews*[3-11]*; Modifications & Improvements*[12-14]*; Theoretical Studies*[15-17]]

In 1962, E.J. Corey and M. Chaykovsky deprotonated trimethylsulfoxonium halides using powdered sodium hydride under nitrogen at room temperature to form a reactive compound, dimethylsulfoxonium methylide (**I**).[1] When simple aldehydes and ketones were mixed with **I**, the formation of epoxides was observed. Likewise, the reaction of dimethylsulfonium methylide (**II**) with aldehydes and ketones also resulted in epoxide formation.[2] Compounds **I** and **II** are both sulfur ylides and are prepared by the deprotonation of the corresponding sulfonium salts. The preparation of epoxides (oxiranes) from aldehydes and ketones using sulfur ylides is known as the *Corey-Chaykovsky epoxidation*. When **I** is reacted with α,β-unsaturated carbonyl compounds, a conjugate addition takes place to produce a cyclopropane as the major product. This reaction is known as the *Corey-Chaykovsky cyclopropanation*.[1] Sulfur ylide **II** is more reactive and less stable than **I**, so it is generated and used at low temperature. The reaction of substituted sulfur ylides with aldehydes is stereoselective, leading predominantly to *trans* epoxides. Asymmetric epoxidations are also possible using chiral sulfides.[12,6] The use of various substituted sulfur ylides allows the transfer of substituted methylene units to carbonyl compounds (isopropylidene or cyclopropylidene fragments) to prepare highly substituted epoxides. Since the S-alkylation of sulfoxides is not a general reaction, it is not practical to obtain the precursor salts in the trialkylsulfoxonium series. This shortcoming limits the corresponding sulfur ylides to the unsubstituted methylide. However, sulfur ylide reagents derived from sulfoximines offer a versatile way to transfer substituted methylene units to carbonyl compounds to prepare oxiranes and cyclopropanes.[12]

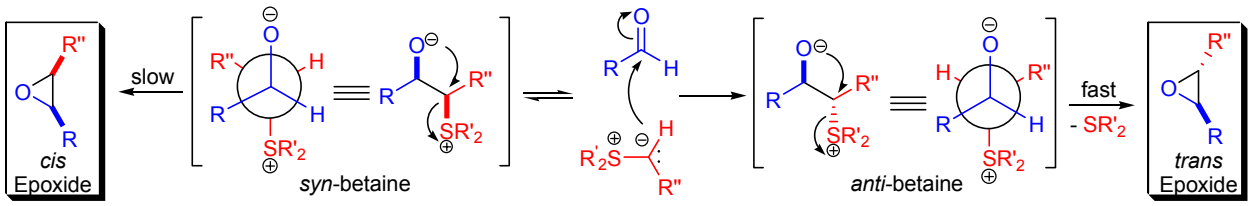


X = Cl, Br, I

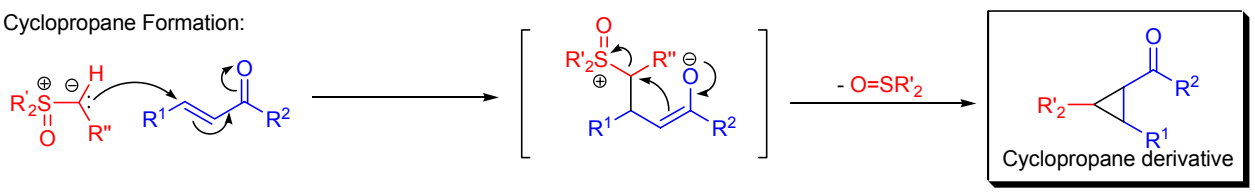


Mechanism:[18-25]

Epoxide Formation:



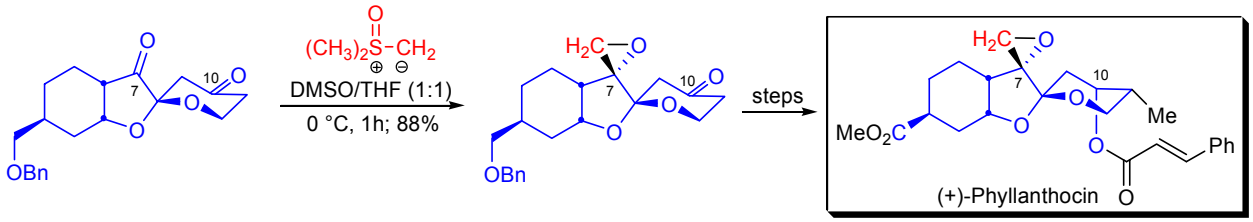
Cyclopropane Formation:



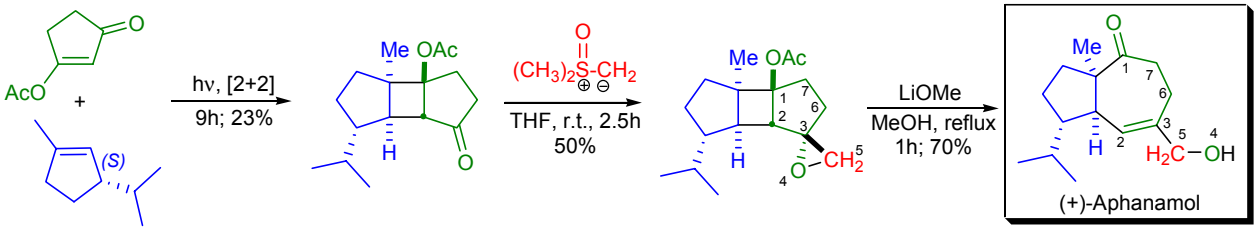
COREY-CHAYKOVSKY EPOXIDATION AND CYCLOPROPANATION

Synthetic Applications:

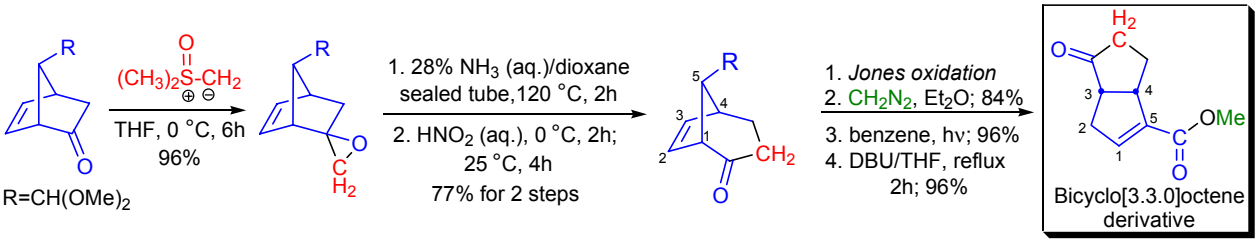
During the total synthesis of (+)-phyllanthocin, A.B. Smith and co-workers installed the epoxide functionality *chemo-* and *stereoselectively* at the C7 carbonyl group of the intermediate diketone by using dimethylsulfoxonium-methylide in a 1:1 solvent mixture of DMSO-THF at 0 °C.[26] The success of this chemoselective methylenation was attributed to the two α-alkoxy substituents, which render the C7 carbonyl group much more electrophilic than C10.



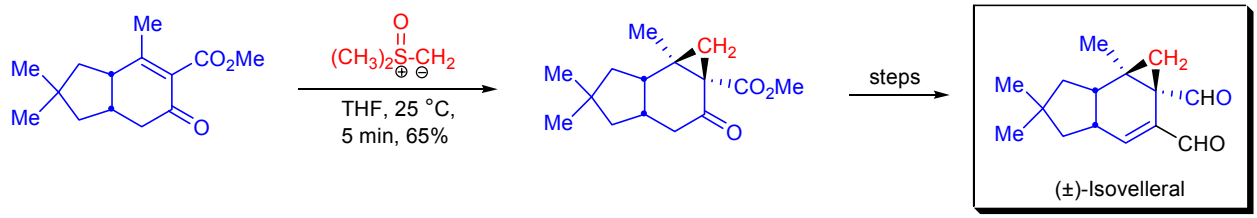
A short enantiospecific total synthesis of (+)-aphanamol I and II from limonene was achieved and the absolute stereochemistry of I and II established in the laboratory of B. Wickberg.[27] The key steps were a *de Mayo photocycloaddition*, a *Corey-Chaykovsky epoxidation* and finally a *base-catalyzed fragmentation* of the γ,δ-epoxyalcohol intermediate. Upon treating the photocycloadduct with dimethylsulfoxonium methylide, only the *endo* epoxide diastereomer was formed due to the steric hindrance provided by the methyl and isopropyl groups.



The conversion of a bicyclo[2.2.1]octenone derivative to the corresponding bicyclo[3.3.0]octenone, a common intermediate in the total synthesis of several iridoid monoterpenes, was achieved by N.C. Chang et al. The target was obtained by sequential application of the *Corey-Chaykovsky epoxidation*, *Demjanov rearrangement* and a *photochemical [1,3]-acyl shift*. [28]



One of the steps in the highly stereoselective total synthesis of (±)-isovelleral involved the cyclopropanation of an α,β-unsaturated ketone using dimethylsulfoxonium methylide.[29] C.H. Heathcock and co-workers studied this transformation under various conditions and they found that THF at ambient temperature gave superior results to DMSO, which is the most common solvent for the *Corey-Chaykovsky cyclopropanation*.



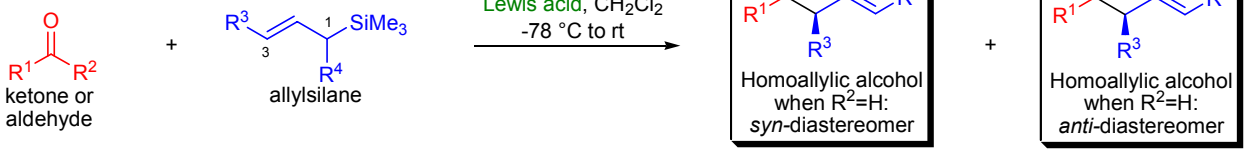
SAKURAI ALLYLATION

(References are on page 668)

Importance:

[*Seminal Publications*[1,2]; *Reviews*[3-9]; *Modifications & Improvements*[10-23]; *Theoretical Studies*[24,25]]

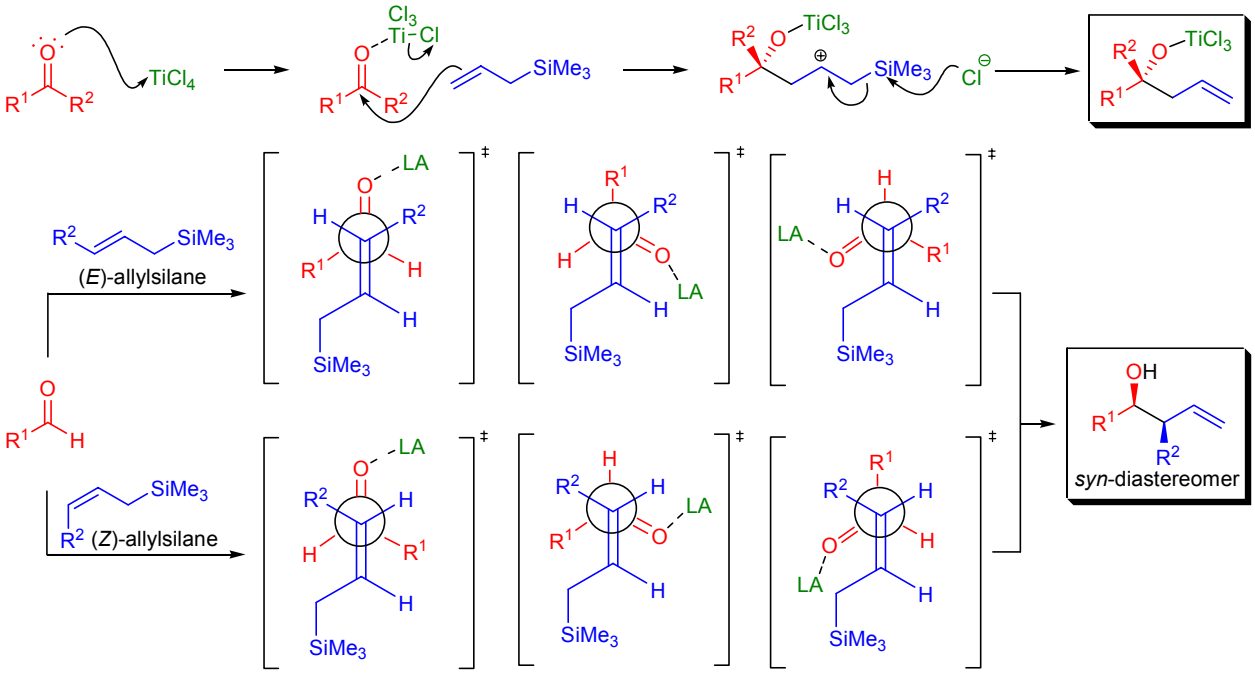
In 1976, H. Sakurai reported that allylsilanes react with a wide variety of aldehydes and ketones in the presence of stoichiometric quantities of $TiCl_4$ to form the corresponding homoallylic alcohols. Today, this transformation is referred to as the *Sakurai allylation*, and it is one of the most important carbon-carbon bond forming reactions. The general features of the reaction are: 1) typically, it is carried out in dichloromethane under nitrogen atmosphere at a temperature range between -78 °C and 25 °C; 2) in addition to $TiCl_4$, several other Lewis acids can be used such as $AlCl_3$, $BF_3{\cdot}OEt_2$, $SnCl_4$, $EtAlCl_2$;[1,2] 3) most commonly trimethylallylsilanes and phenyldimethylallylsilanes are utilized as the allylsilane reactant;[4,6] 4) the reaction is highly regioselective, the electrophile attacking at the C3 terminus of the allylsilane;[1,2,4] 5) C1 substituted allylsilanes give the (*E*)-alkene product;[26] 6) allenyl-,[27] propargyl-,[28] vinyl-,[29] and ethynylsilanes[29] also undergo the reaction in the presence of Lewis acids; 7) the most commonly used electrophiles are aldehydes and ketones, but acetals and ketals[30] are also often utilized; 8) dithioacetals,[31] monothioacetals,[32] alkoxymethyl-,[33] and phenylthiomethyl chlorides[34] undergo the allylation reaction; 9) α,β-unsaturated aldehydes react at the carbonyl group, while α,β-unsaturated ketones undergo conjugate addition;[35,36] 10) intramolecular reactions are also feasible;[37] and 11) C3 monosubstituted allysilanes give the *syn*-diastereomer as the major product.[38] Common side reactions in the *Sakurai allylation* are the following: 1) protodesilylation;[39] 2) allylic alcohol products, especially tertiary allylic alcohols can undergo ionization;[40] and 3) in the case of 1,1-disubstituted allylsilanes, the trisubstituted alkene product may react further.[41] Side reactions usually can be avoided by carefully controlled conditions or utilizing acetal or ketal substrates. Catalytic versions of the *Sakurai allylation* are known as well, utilizing TMSOTf,[10] TMSI,[11] Ph_3CClO_4,[12] $Cp_2Ti(CF_3SO_3)_2$,[14] TMSOMs,[19] and $InCl_3$/TMSCl[20] as catalysts. Recently, catalytic asymmetric versions were developed.[15,22,23]



R^1 = alkyl, aryl; R^2 = H, alkyl, aryl; R^3 and R^4 = H, alkyl, aryl; Lewis acid = $TiCl_4$, $BF_3{\cdot}OEt_2$, $SnCl_4$, $EtAlCl_2$

Mechanism:[42,43,38,44-46]

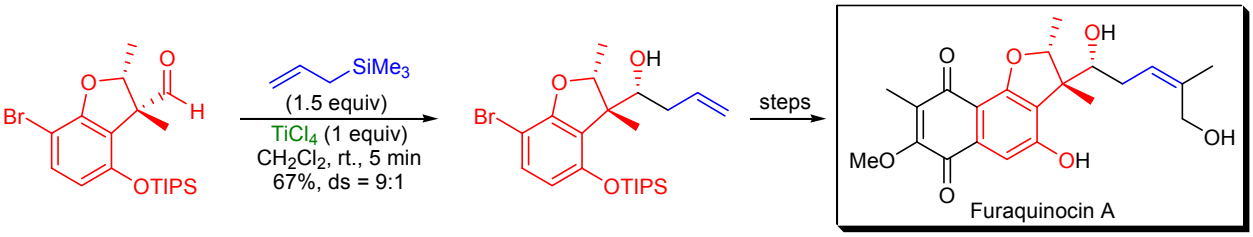
The reaction starts with the activation of the carbonyl group by the Lewis acid. Subsequent carbon-carbon bond formation leads to a silyl-stabilized carbocation,[45] which after loss of the trimethylsilyl group, gives the double bond. From studies conducted on chiral allylsilanes, it was concluded that the incoming electrophile attacks the double bond on the surface opposite to the silyl group.[42] The reaction of aldehydes with C3 substituted allylsilanes leads to the *syn*-diastereomer as the major product, and (*E*)-allylsilanes give higher diastereoselectivities than (*Z*)-allylsilanes. The reaction presumably goes through an open transition state.[38] The possible transition states leading to the *syn*-diastereomer are depicted below.[43,44]



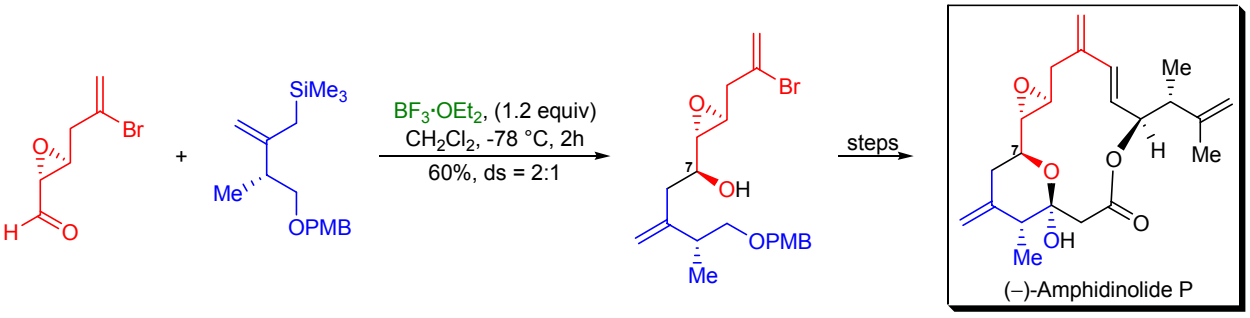
SAKURAI ALLYLATION

Synthetic Applications:

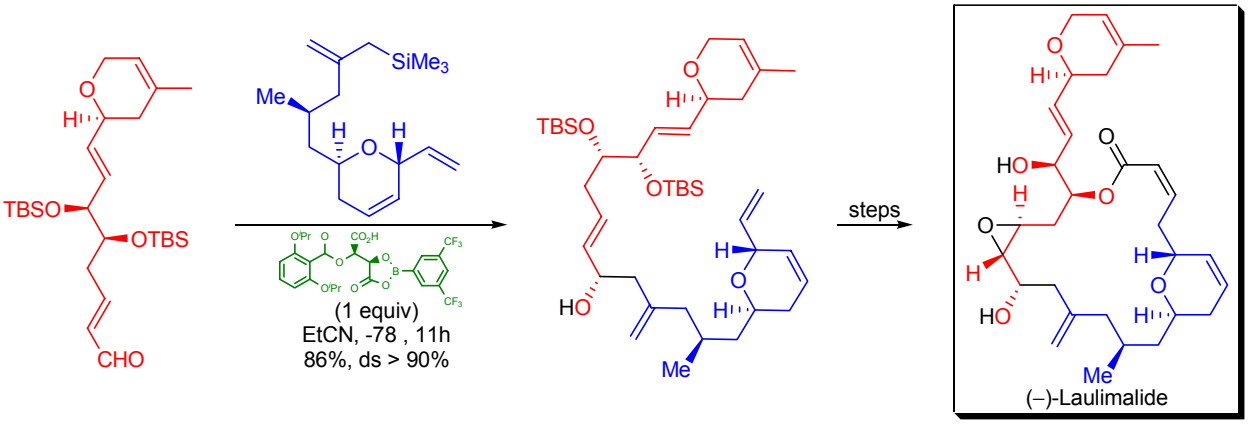
In the laboratory of B.M. Trost, a modular approach toward the total syntheses of furaquinocins was developed.[47] To introduce the homoallylic side chain in a diastereoselective fashion, they utilized the *Sakurai allylation reaction*. During their studies they found that the highest diastereoselectivity can be achieved using 1 equivalent of $TiCl_4$ at room temperature. Application of other Lewis acids such as $BF_3{\cdot}OEt_2$ gave the product with lower selectivity. Attempts to perform the allylation using catalytic amounts of Lewis acids such as $FeCl_3$ or $Sc(OTf)_3$ led to no conversion. The resulting homoallylic alcohol served as a common intermediate toward the syntheses of both furaquinocin A and B.



A convergent total synthesis of 15-membered macrolactone, (–)-amphidinolide P was reported by D.R. Williams and coworkers.[48] In their approach, they utilized the *Sakurai allylation* to introduce the C7 hydroxyl group and the homoallylic side chain. The transformation was effected by $BF_3{\cdot}OEt_2$ at -78 °C to provide the homoallylic alcohol as a 2:1 mixture of diastereomers. The desired alcohol proved to be the major diastereomer, as it resulted from the Felkin-Ahn controlled addition of the allylsilane to the aldehyde. The minor diastereomer was converted into the desired stereoisomer *via* a *Mitsunobu reaction*.



A highly convergent, enantioselective total synthesis of structurally novel, cancer therapeutic lead, (–)-laulimalide was achieved by P.A. Wender and co-workers.[49] During the synthesis, they performed an unprecedented complex asymmetric *Sakurai allylation reaction* as a key step to form the C14-C15 carbon-carbon bond. In this transformation, they utilized a chiral, nonracemic (acyloxy)borane Lewis acid that was developed by H. Yamamoto.[15] According to Yamamoto's original procedure, only a catalytic amount (10-20 mol%) of the Lewis acid was needed to bring about the desired transformation with high yield and enantioselectivity. However, in this case, one equivalent of the Lewis acid was necessary to effect the allylation. The reaction was carried out in propionitrile at -78 °C, and the product was obtained in high yield and as the only detectable diastereomer by spectroscopic methods.



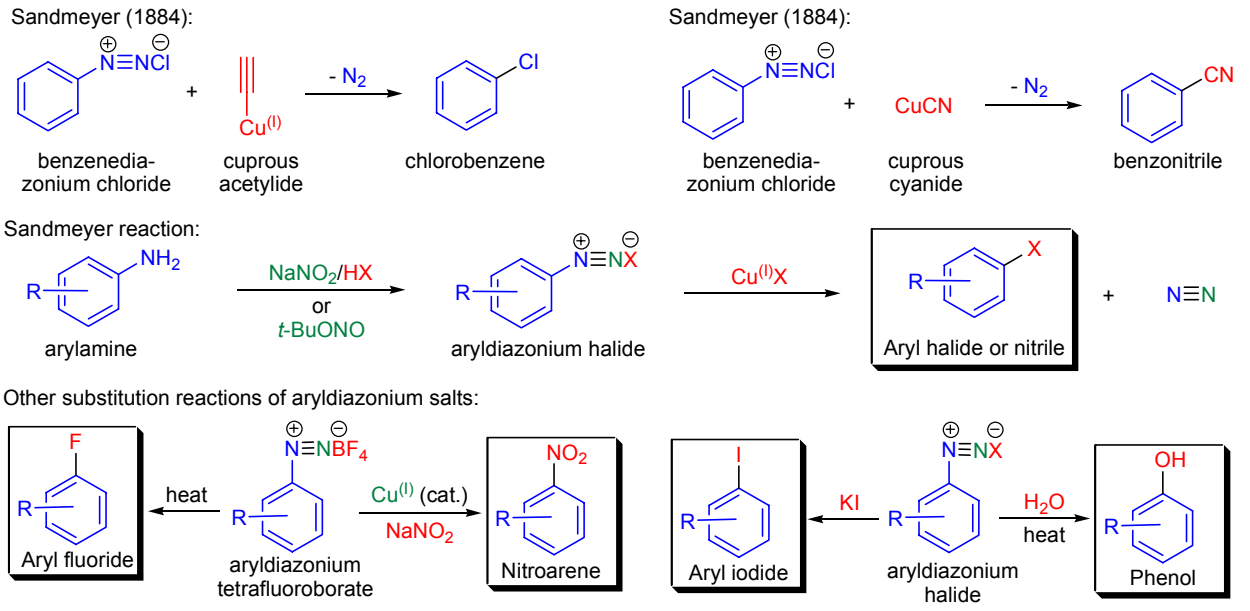
SANDMEYER REACTION

(References are on page 669)

Importance:

[*Seminal Publications*[1-4]*; Reviews*[5-11]*; Modifications & Improvements*[12-19]]

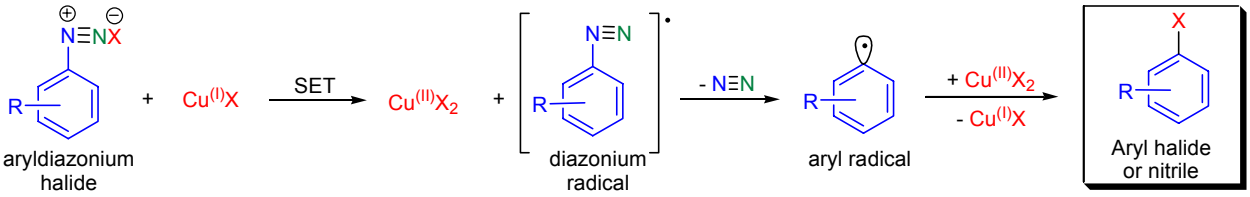
In 1884, T. Sandmeyer intended to prepare phenylacetylene by reacting benzenediazonium chloride with copper(I) acetylide, but the major product of the reaction was chlorobenzene, and no trace of the desired product was detected.[3] Careful examination of the reaction conditions revealed that copper(I) chloride was formed *in situ* and it catalyzed the replacement of the diazonium group with a chlorine atom.[4] Sandmeyer also showed that bromobenzene was formed by using copper(I) bromide, and copper(I) cyanide led to benzonitrile. The substitution of aryldiazonium salts with halides or pesudohalides is known as the *Sandmeyer reaction*. The general features of this transformation are: 1) the required aryldiazonium halides are usually prepared from arylamines *via* diazotization using either $NaNO_2$/hydrohalic acid in water or alkyl nitrites (e.g., *tert*-butyl nitrite) under anhydrous conditions; 2) the aryldiazonium halides are not isolated but reacted in the same pot with copper(I) chloride, bromide or cyanide to obtain the corresponding aryl chloride, aryl bromide, and aryl nitrile, respectively; 3) the counterion of the copper(I) salt has to match the conjugate base of the hydrohalic acid otherwise product mixtures are formed; 4) the preparation of aryl iodides does not require the use of a copper(I) salts; simply adding potassium iodide brings about the substitution accompanied by the loss of dinitrogen; and 5) the substitution pattern on the aromatic amine can be widely varied, both electron-donating and electron-withdrawing groups are tolerated. There are other useful substitution reactions of aryldiazonium salts, but these are referred to with different names (or with no specific name):[8] 1) when the aryldiazonium halides are treated with hydrogen chloride or hydrogen bromide in the presence of copper metal to afford aryl chlorides and bromides, the process is called the *Gattermann reaction*; 2) the thermal decomposition of aryldiazonium tetrafluoroborates to give aryl fluorides is known as the *Balz-Schiemann reaction*; 3) aryldiazonium tetrafluoroborates react with sodium nitrite in the presence of catalytic amounts of copper(I) salt to give nitroarenes;[20,21] and 4) aryldiazonium salts can also be converted to phenols by heating with trifluoroacetic acid, aqueous sulfuric acid, or with aqueous solution of copper salts (occasionally called the *Sandmeyer hydroxylation*).[22-24]



R = H, alkyl, aryl, electron-withdrawing groups (EWG) or electron-donating groups (EDG); HX: HCl, HBr; X = Cl, Br, CN

Mechanism:[25-32,9,33,34,16,35,36,19,24]

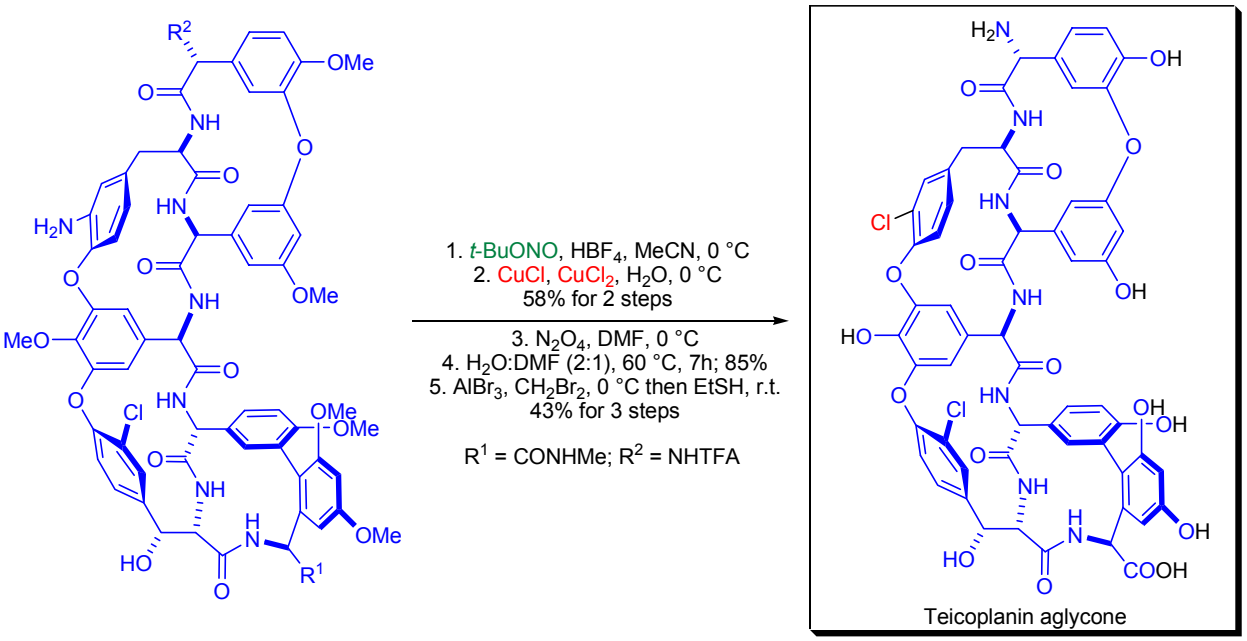
The mechanism of the *Sandmeyer reaction* is not completely understood. For a long time it was believed to proceed *via* aryl cations, but later W.A. Waters and then later J.K. Kochi proposed a radical mechanism which was catalytic for the copper(I) salt.[25,26] In a single electron-transfer event the diazonium halide is reduced to a diazonium radical which quickly loses dinitrogen to afford an aryl radical. A final ligand transfer from the copper(II) salt completes the catalytic cycle and regenerates the copper(I) species.



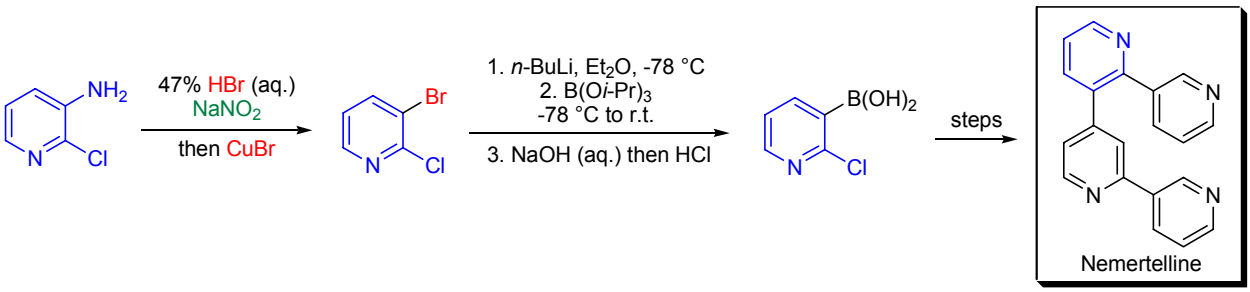
SANDMEYER REACTION

Synthetic Applications:

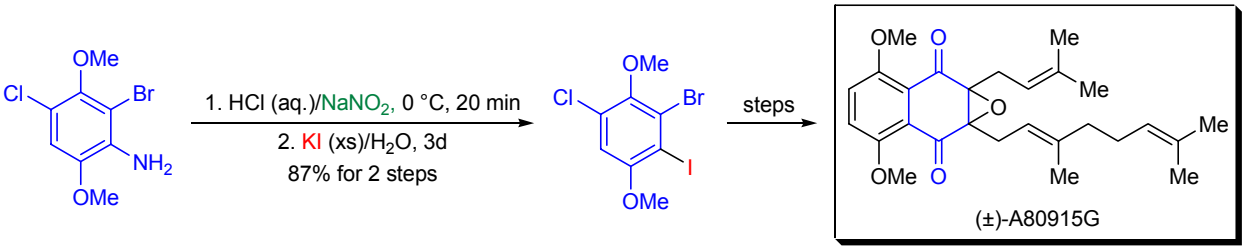
In the laboratory of D.A. Evans the total synthesis of the teicoplanin aglycon was accomplished.[37] In the endgame of the synthetic effort the introduction of the required chloro substituent on ring-2 under mild conditions was necessary. The authors chose the *Sandmeyer reaction* to bring about the desired transformation of the aromatic amine moiety. First the substrate was diazotized with *t*-butyl nitrite and HBF_4 in acetonitrile and then in the same pot a mixture of copper(I) chloride and copper(II) chloride in large excess was added at low temperature. The desired aryl chloride was isolated in moderate yield. To complete the synthesis, the following steps had to be carried out: 1) deprotection of the carboxy-terminal *N*-methylamide with N_2O_4 followed by a pH neutral hydrolysis; and 2) global demethylation at room temperature using $AlBr_3$/EtSH with concomitant *N*-terminal trifluoroacetamide hydrolysis.



The neurotoxic quaterpyridine natural product nemertelline was successfully synthesized by S. Rault et al. using a *Suzuki cross-coupling* as the key step. The boronic acid coupling partner, required for the *Suzuki reaction*, was prepared by first subjecting 3-amino-2-chloropyridine to the conditions of the *Sandmeyer reaction* followed by a lithium-halogen exchange and trapping the lithiopyridine derivative with triisopropylborate.



M. Nakata and co-workers completed the concise total synthesis of (±)-A80915G, which belongs to the napyradiomycin family of antibiotics.[38] There were two key carbon-carbon bond forming reactions in the synthetic sequence: a *Stille cross-coupling* between an aromatic trihalide and geranyl tributyltin and a *Diels-Alder cycloaddition* employing the Danishefsky-Brassard diene. A *Sandmeyer reaction* was used to introduce the iodine substituent to the 2-bromo-4-chloro-3,6-dimethoxy-aniline substrate in order to obtain the required trihalogenated 1,4-dimethoxy-benzene precursor.



STORK ENAMINE SYNTHESIS

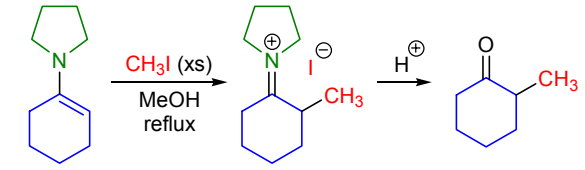
(References are on page 689)

Importance:

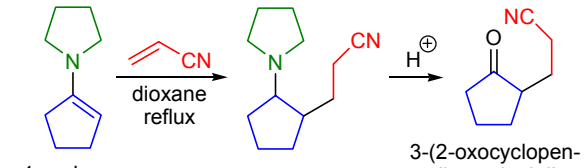
[*Seminal Publications*[1-4]; *Reviews*[5-11]; *Modifications & Improvements*[12-21]; *Theoretical Studies*[22]]

In 1936, C. Mannich and H. Davidson reported that in the presence of a dehydrating agent (K_2CO_3 or CaO), secondary amines underwent facile condensation with aldehydes or ketones to afford enamines (non-charged enolate equivalents).[23] At that time the reaction of enamines with electrophiles was not investigated, but it was established that enamines were relatively labile compounds that underwent facile hydrolysis upon exposure to dilute aqueous acid. Two decades later, in 1954, G. Stork and co-workers discovered that the reaction enamines with alkyl- or acyl halides followed by acidic hydrolysis constituted a novel way for the α-alkylation or α-acylation of carbonyl compounds.[3,4] The synthesis of α-alkyl- or acyl carbonyl compounds *via* the alkylation or acylation of the corresponding enamines is known as the *Stork enamine synthesis*. The general features of this method are: 1) the enamines are prepared by reacting the aldehyde or ketone with one equivalent of secondary amine (e.g., piperidine, morpholine or pyrrolidine) in the presence of a catalyst (or dehydrating agent); 2) with unsymmetrical ketones the formation of enamine regioisomers is expected but usually the less substituted regioisomer is favored; 3) the preparation of aldehyde enamines is often accompanied by the formation of aminals, which can be converted to the desired enamines by destructive distillation;[9] 4) activated alkyl and acyl halides are the best reaction partners (e.g., allyl-, benzyl-, propargylic-, or activated aryl halides); 5) tertiary alkyl halides do not alkylate the enamines but rather undergo elimination; 6) other electrophiles such as Michael acceptors and epoxides can also be used; and 7) the bulkier the ketone and the amine components, the better the yields of the monolakylated product, but the reaction rates tend to drop. Advantages of the *Stork enamine synthesis* are: 1) the alkylation of the enamine takes place under neutral conditions, which is important when the substrate is base or acid sensitive; 2) polyalkylated products are seldom observed; 3) the alkylation takes place on the less substituted side of the ketone; and 4) an asymmetric version utilizing chiral enamines is also available.

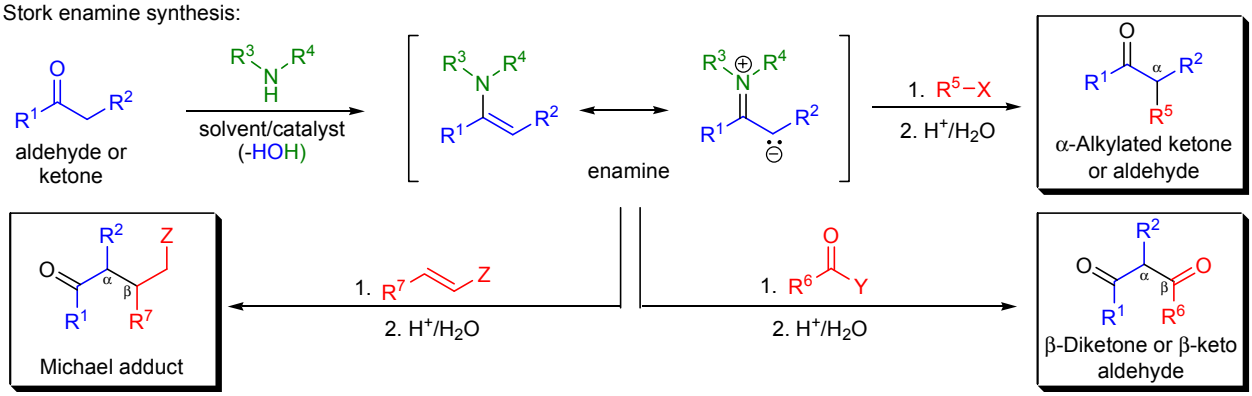
Stork, Terrell & Szmuszkovicz (1954):



Stork & Landesman (1956):



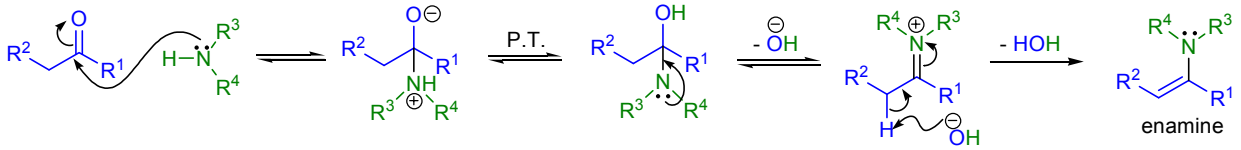
Stork enamine synthesis:



R^1 = H, alkyl, substituted alkyl; R^2 = H, alkyl, aryl; R^{3-4} = alkyl, aryl; R^5 = 1° or 2° alkyl, allylic, benzyl, CH_2CO_2R, CH_2CN, propargylic; R^6 = alkyl, aryl, OR, H; R^7 = H, alkyl, aryl; X = Cl, Br, I, OTs; Y =OCOR, CN, Cl, Br, I; Z = CN, COR, CO_2R, NO_2

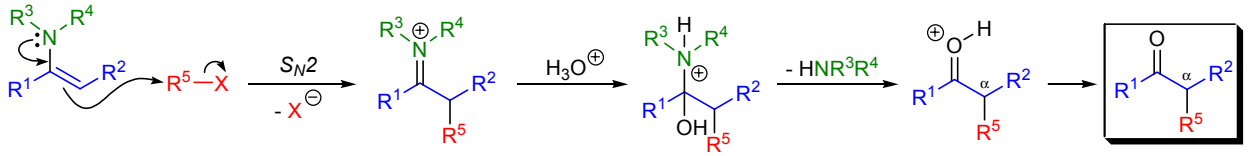
Mechanism:[24,25]

Formation of the enamine:



Alkylation of the enamine:

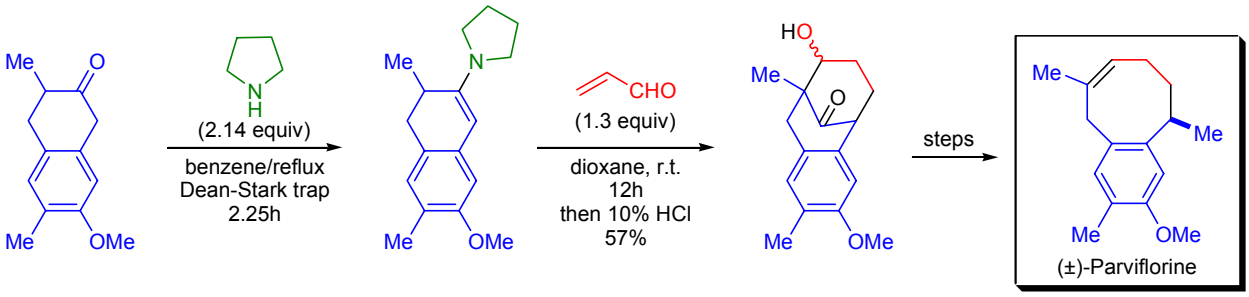
Hydrolysis with dilute acid:



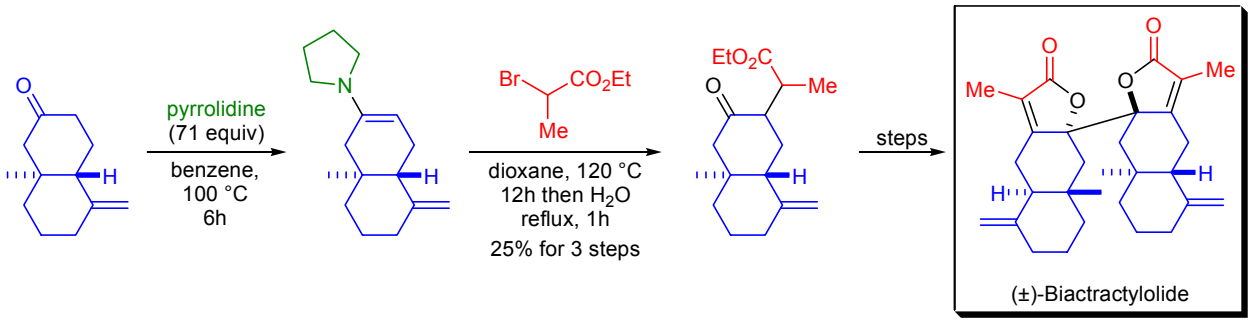
STORK ENAMINE SYNTHESIS

Synthetic Applications:

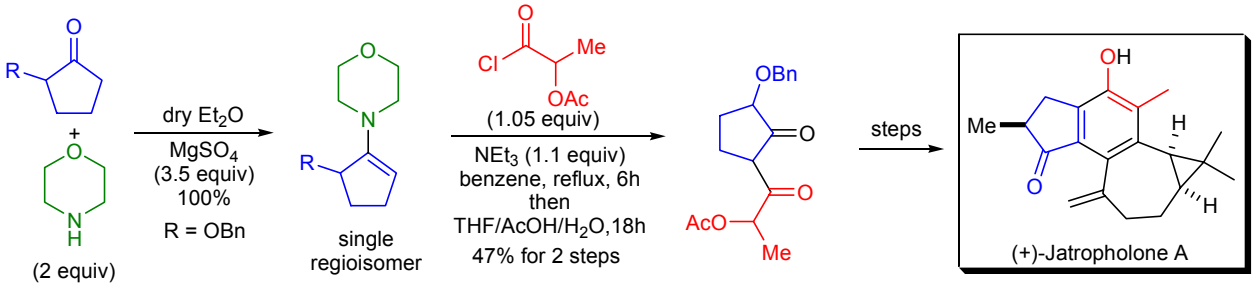
The total synthesis of the phenolic sesquiterpene (±)-parviflorine was accomplished by L.A. Maldonado and co-workers.[26] The key step in the synthetic sequence was the reaction of an enamine with acrolein to form a bicyclic intermediate, which was subjected to a *Grob fragmentation* to afford the eight-membered ring of the natural product. The bicyclic ketone substrate was refluxed in benzene using a Dean-Stark trap and the resulting enamine was taken to the next step as crude material.



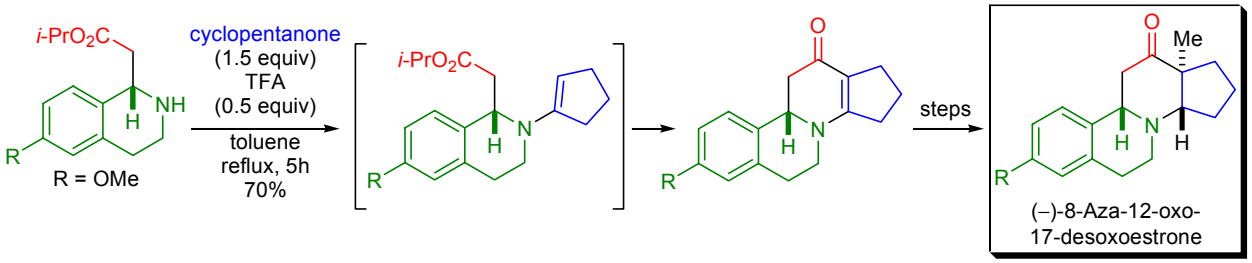
The biomimetic synthesis of the structurally novel bisesquiterpenoid (±)-biatractylolide was reported by J.E. Baldwin et al.[27] The cornerstone of the synthetic strategy was the radical dimerization of two atractylolide units. The atractylolide precursor was prepared from a bicyclic ketone using the *Stork enamine synthesis*. The pyrrolidine enamine was generated using large excess of pyrrolidine in refluxing benzene (the excess pyrrolidine was removed under reduced pressure). The alkylation of the crude enamine with ethyl α-bromopropionate took place in refluxing dioxane and afforded a mixture of ethyl ester diastereomers.



In the laboratory of A.B. Smith, the synthesis of (+)-jatropholone A and B was achieved using a *high-pressure Diels-Alder cycloaddition* between a tetrasubstituted furan and a homochiral enone. During the preparation of the furan component, the *Stork enamine synthesis* was used. The α-benzyloxy cyclopentanone was converted to the corresponding morpholine enamine in quantitative yield. The enamine was isolated as a single regioisomer. In contrast, the corresponding piperidine or pyrrolidine enamines were obtained always as a mixture of regioisomers. The acylation of the enamine with *O*-acetoxyacetyl chloride yielded a 1,3-diketone, which was converted to the desired tetrasubstituted furan component.



An intramolecular variant of the *Stork enamine synthesis* was utilized during the asymmetric total synthesis of (–)-8-aza-12-oxo-17-desoxoestrone by A.I. Meyers et al.[28]



VILSMEIER-HAACK FORMYLATION

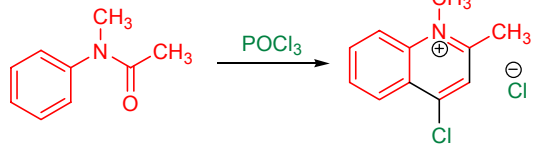
(References are on page 699)

Importance:

[*Seminal Publications*[1,2]*; Reviews*[3-16]*; Modifications & Improvements*[17-30]*; Theoretical Studies*[31-33]]

In 1925, A. Vilsmeier and co-workers reported that upon treatment with phosphoryl chloride ($POCl_3$), *N*-methylacetanilide gave rise to a mixture of products among which 4-chloro-1,2-dimethylquinolinium chloride was one of the major products.[1] Further investigation revealed that the reaction between *N*-methylformanilide and $POCl_3$ gave rise to a chloromethyliminium salt (Vilsmeier reagent), which readily reacts with electron-rich aromatic compounds to yield substituted benzaldehydes.[2] The introduction of a formyl group into electron-rich aromatic compounds using a Vilsmeier reagent is known as the *Vilsmeier-Haack formylation* (*Vilsmeier reaction*). The general features of this transformation are:[8,11] 1) the Vilsmeier reagent is prepared from any *N,N*-disubstituted formamide by reacting it with an acid chloride (e.g., $POCl_3$, $SOCl_2$, oxalyl chloride); 2) most often the combination of DMF and $POCl_3$ is used and the resulting Vilsmeier reagent is usually isolated before use; 3) mostly electron-rich aromatic or heteroaromatic compounds[8] as well as electron-rich alkenes and 1,3-dienes[11] are substrates for the transformation, since the Vilsmeier reagent is a weak electrophile; 4) the relative reactivity of five-membered heterocycles is pyrrole > furan > thiophene; 5) the solvent is usually a halogenated hydrocarbon, DMF or $POCl_3$ and the nature of the solvent has a profound effect on the electrophilicity of the reagent, so it should be carefully chosen; 6) the required reaction temperature varies widely depending on the reactivity of the substrate and it ranges from below 0 °C up to 80 °C; 7) the initial product is an iminium salt, which can be hydrolyzed with water to the corresponding aldehyde, treated with H_2S to afford thioaldehydes, reacted with hydroxylamine to afford nitriles, or reduced to give amines; 8) the transformation is regioselective favoring the less sterically hindered position (this means the *para* position on a substituted benzene ring); but electronic effects can also influence the product distribution; and 9) vinylogous chloromethyliminium salts undergo similar reaction to afford the corresponding α,β-unsaturated carbonyl compounds upon hydrolysis.

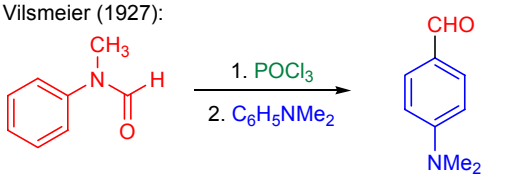
Vilsmeier (1925):



N-methyl-*N*-phenyl-acetamide

4-chloro-1,2-dimethyl-quinolinium chloride

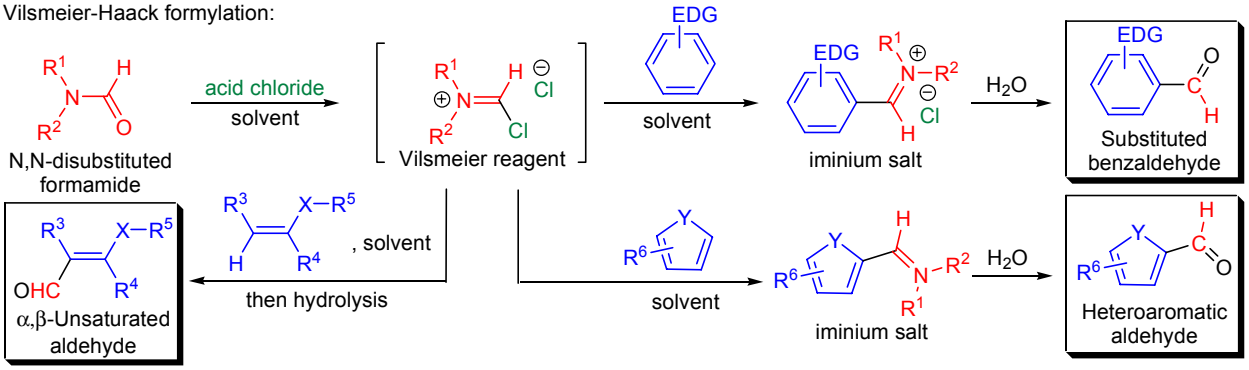
Vilsmeier (1927):



N-methyl-*N*-phenyl-formamide

4-dimethylamino benzaldehyde

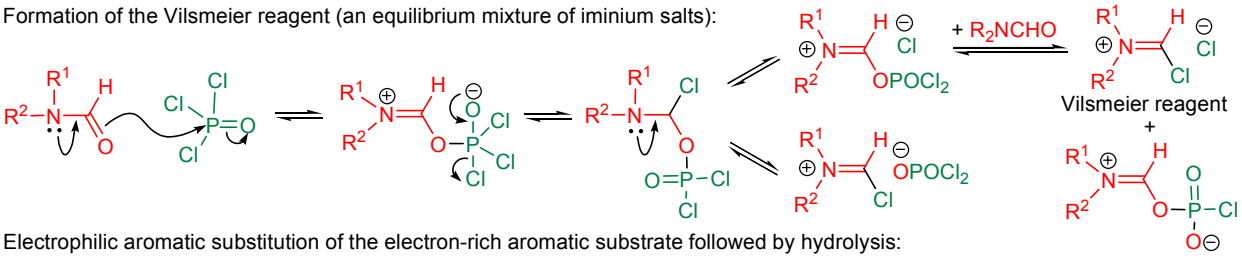
Vilsmeier-Haack formylation:



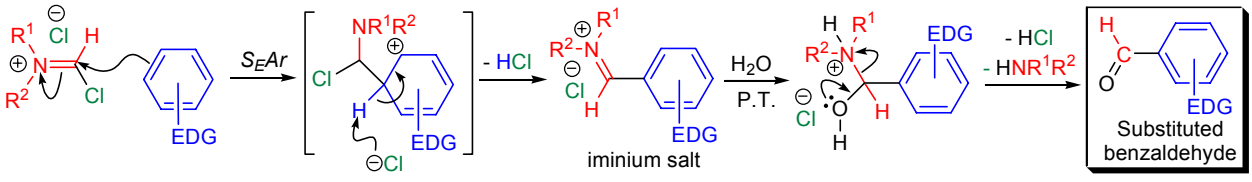
R^{1-2} = alkyl, aryl; acid chloride: $POCl_3$, $SOCl_2$,$COCl_2$, $(COCl)_2$, Ph_3PBr_2, 2,4,6-trichloro-1,3,5-triazine; solvent: DCM, DMF, $POCl_3$; EDG = OH, *O*-alkyl, *O*-aryl, NR_2; R^{3-4} = H, alkyl, aryl; R^5 = alkyl, aryl; X = O, NR, CH_2, CR_2; Y = O, S, NR, NH; R^6 = H, alkyl, aryl

Mechanism:[34-41,8,42,11]

Formation of the Vilsmeier reagent (an equilibrium mixture of iminium salts):



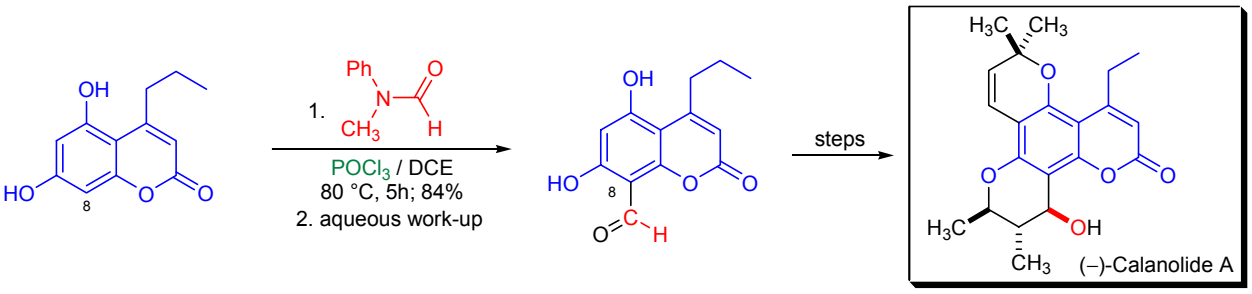
Electrophilic aromatic substitution of the electron-rich aromatic substrate followed by hydrolysis:



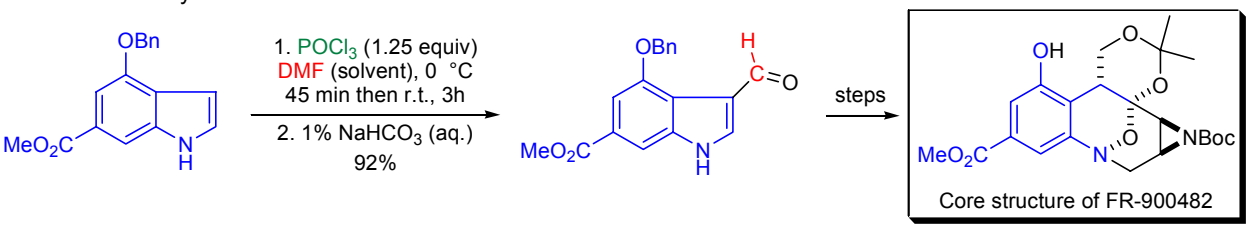
VILSMEIER-HAACK FORMYLATION

Synthetic Applications:

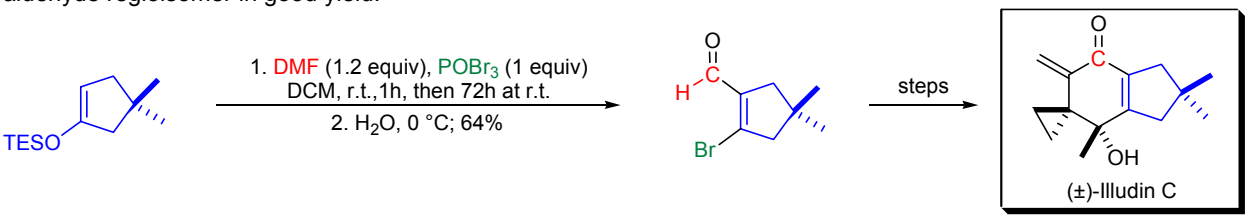
The total synthesis of the calophylium coumarin (–)-calanolide A was accomplished by D.C. Baker and co-workers.[43] This compound attracted considerable attention because it is a potent inhibitor of HIV-1 reverse transcriptase. In order to introduce a formyl group at C8, a regioselective *Vilsmeier reaction* was employed on a coumarin lactone substrate.



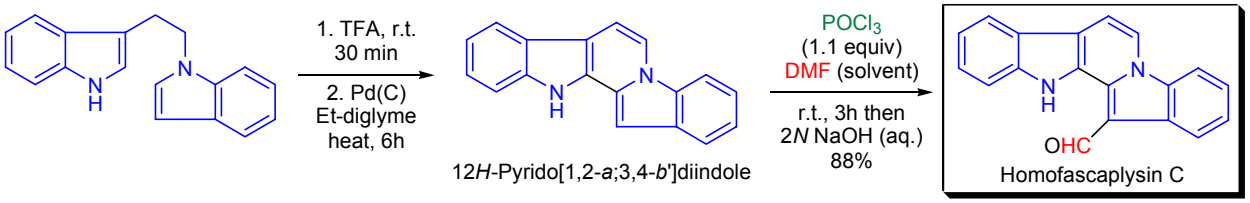
In the laboratory of F.E. Ziegler, the cyclization of a chiral aziridinyl radical into an indole nucleus was utilized to prepare the core nucleus of the potent antitumor agent FR-900482.[44] In the early stages of the synthetic effort, the *Vilsmeier-Haack formylation* was chosen to install an aldehyde functionality at the C3 position of a substituted indole substrate. The initial iminium salt was hydrolyzed under very mildly basic conditions to minimize the hydrolysis of the methyl ester moiety. Eventually the formyl group was removed from the molecule *via decarbonylation* using Wilkinson's catalyst.



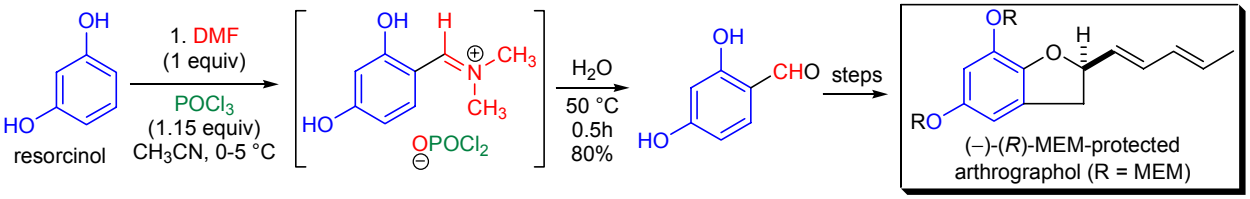
Since the *Vilsmeier-Haack formylation* is feasible on electron-rich alkenes such as enol ethers, it was a method of choice to prepare an α,β-unsaturated aldehyde during the total synthesis of (±)-illudin C by R.L. Funk et al.[45] The TES enol ether was treated with several reagent combinations (e.g., PBr_3/DMF/DCM), but unfortunately only regioisomeric product mixtures were obtained. However, the use of $POBr_3$/DMF/DCM allowed the clean preparation of the desired aldehyde regioisomer in good yield.



The marine sponge pigment homofascaplysin C was synthesized by the research team of G.W. Gribble.[46] The natural product had a novel 12*H*-pyrido[1,2-a:3,4-b']diindole ring system and a formyl group at the C13 position. The *Vilsmeier reaction* allowed the introduction of this substituent in excellent yield.



The total synthesis of (–)-(*R*)-MEM-protected arthrographol was accomplished by G.L.D. Krupadanam et al.[47] The authors used sequential *Vilsmeier reaction*/*Dakin oxidation* to prepare a 1,2,4-trihydroxybenzene derivative.



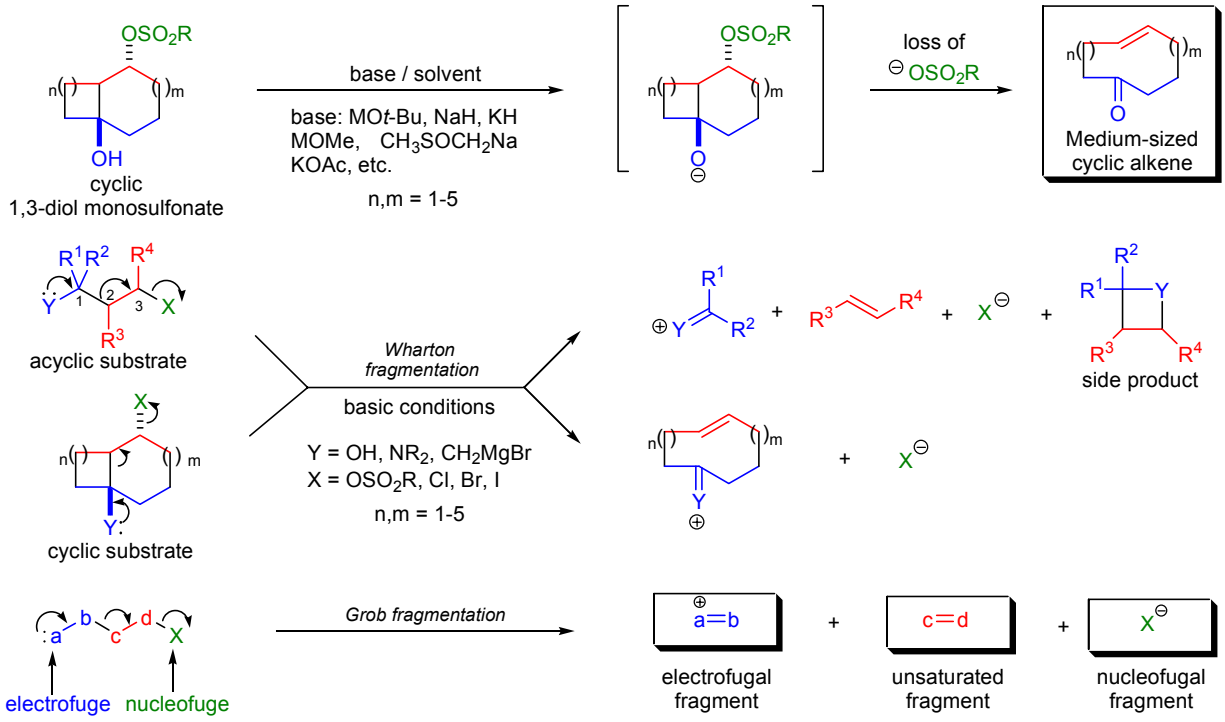
WHARTON FRAGMENTATION

(References are on page 705)

Importance:

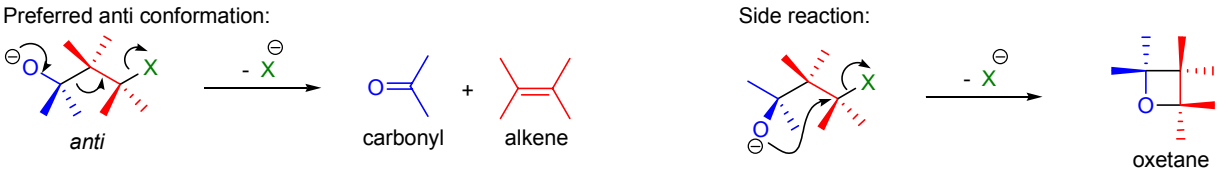
[*Seminal Publications*[1-5]; *Reviews*;[6-11] *Modifications & Improvements*[12-17]]

In 1961, P.S. Wharton investigated the potassium-*tert*-butoxide-induced heterolytic fragmentation of a bicyclic 1,3-diol monomesylate ester (functionalized decalin system), to form a 10-membered cyclic alkene stereospecifically.[2] The base-induced stereospecific fragmentation of cyclic 1,3-diol monosulfonate esters (X=OSO_2R; Y=OH) to form medium-sized cyclic alkenes is known as the *Wharton fragmentation*. Wharton and co-workers contributed to this area extensively by uncovering the stereoelectronic requirements for the reaction as well as demonstrating its synthetic utility. This fragmentation, however, falls into the category of *Grob-type fragmentations* in which carbon chains with a variety of combinations of nucleophilic atoms (heteroatoms) and leaving groups give rise to three fragments.[18] The general features of the *Wharton fragmentation* are the following: 1) synthetically, cyclic 1,3-diol derivatives are the most useful substrates, since acyclic precursors often give rise to side-products (e.g., oxetanes, Y=O) resulting from an intramolecular displacement; 2) cyclic 1,3-hydroxy monotosylates and monomesylates are the most widely used substrates, and they are prepared by treating the unsymmetrical 1,3-diol with one equivalent of MsCl or TsCl; 3) the rate of the fragmentation depends on the concentration of the anion derived from the 1,3-diol derivative; 3) strong and less nucleophilic bases favor the fragmentation, whereas more nucleophilic bases favor intramolecular substitution and elimination of the leaving group; 4) KO*t*-Bu/*t*-BuOH and dimsylsodium/DMSO are the most often used base/solvent combination; 5) if the substrate has considerable ring strain (e.g., n=1), even weaker bases (e.g., NEt_3) will initiate successful fragmentation; 6) when the fragmentation product is labile (e.g., aldehyde), $LiAlH_4$ can serve as both a basic initiator and a reducing agent, since it instantly traps (reduces) the initial product avoiding undesired side reactions (e.g., *aldol condensation*); 7) alkenes are generated stereospecifically from cyclic substrates in high yield; 8) fragmentations leading to ketones occur more readily than those that give aldehydes; 9) more highly substituted alkenes are formed faster than less substituted ones; and 10) substrates with more ring strain generally fragment faster.



Mechanism:[4,19,10]

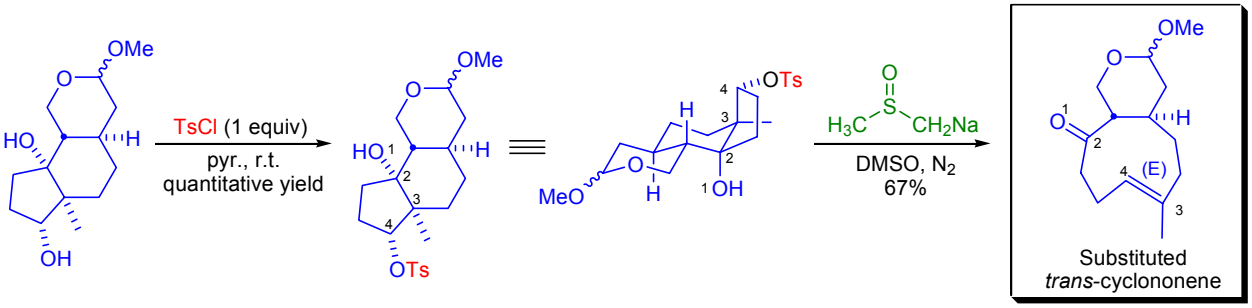
The *Wharton fragmentation* is a concerted reaction and the stereoelectronic requirement is that the bonds that are undergoing the cleavage must be *anti* to each other. This requirement is easily met in cyclic systems; however, acyclic systems have much larger conformational freedom, so side reactions may arise when the conformation of the bonds undergoing cleavage is *gauche*. In cyclic systems the fragmentation becomes slow and complex product mixtures are formed when the conformation of the bonds undergoing cleavage is *gauche*.



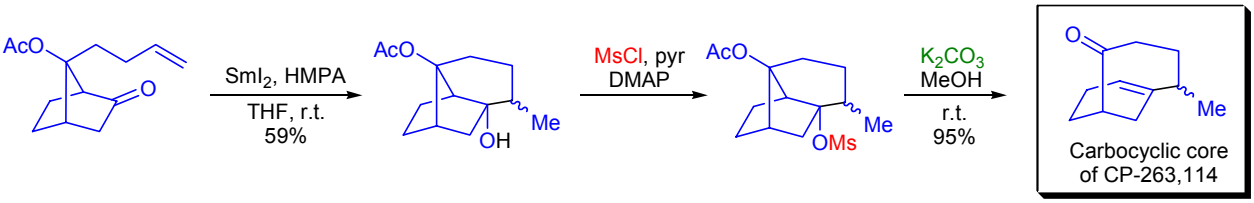
WHARTON FRAGMENTATION

Synthetic Applications:

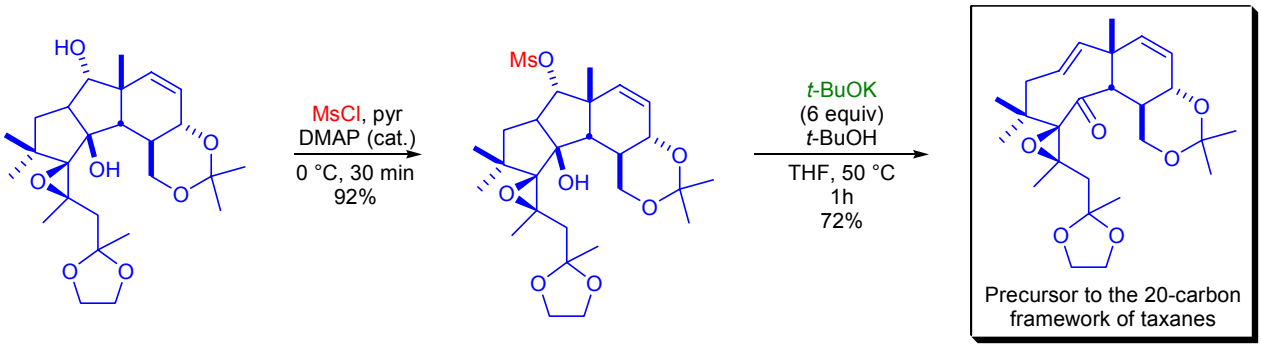
The *Wharton fragmentation* was used as a key step in an approach toward the total synthesis of xenicanes by H. Pfander et al.[20] Two optically active substituted *trans*-cyclononenes were synthesized starting from (-)-Hajos-Parrish ketone. First, the bicyclic 1,3-diol was protected regioselectively on the less sterically hindered hydroxyl group with *p*-toluenesulfonyl chloride in quantitative yield. Next, the monosulfonate ester was exposed to dimsylsodium in DMSO, which is a strong base, to initiate the desired heterolytic fragmentation.



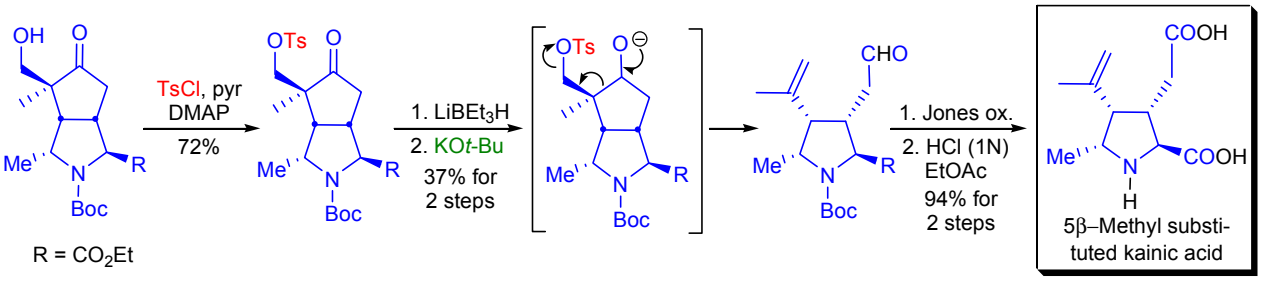
A novel synthetic approach was developed for the norbornane-based carbocyclic core of CP-263,114 in the laboratory of J.L. Wood.[21] Initial attempts to prepare the core using the *oxy-Cope rearrangement* failed even under forcing conditions, so an alternative approach utilizing the *Wharton fragmentation* was chosen. The tricyclic 1,3-diol substrate was prepared by the SmI_2-mediated 5-exo-trig *ketyl radical cyclization*. The resulting tertiary alcohol was mesylated and subjected to methanolysis, which afforded the *Wharton fragmentation* product in an almost quantitative yield.



Research by S. Arseniyadis and co-workers showed that the *aldol-annelation-fragmentation* strategy could be used for the synthesis of complex structures, which are precursors of a variety of taxoid natural products.[22] This strategy allows the preparation of the twenty-carbon framework of taxanes from inexpensive and simple starting materials.



The stereocontrolled synthesis of 5β-substituted kainic acids was achieved by A. Rubio et al.[23] The C3 and C4 substituents were introduced by the *Wharton fragmentation* of a bicyclic monotosylated 1,3-diol. When this secondary alcohol was exposed to KO*t*-Bu, the corresponding fragmentation product was obtained in moderate yield. *Jones oxidation* of the aldehyde to the carboxylic acid followed by hydrolysis of the ester and removal of the Boc group resulted in the desired substituted kainic acid.



VIII. APPENDIX

8.1 Brief explanation of the organization of this section

The primary function of this section is to help advanced undergraduate students and first year graduate students in organizing the large amount of information available on various chemical transformations. It is important to note that the categorization of named reactions is a subjective one and has been addressed differently in other textbooks.

The categorization of named reactions is mainly based on the mechanism of the various processes. To make studying more friendly, we included a brief description of each named reaction and the page number for that particular transformation.

Because a large number of functional group transformations are affected by the reactions covered in the book, we felt that tables showing the interconversion of functional groups should be included.

Various functional groups are listed in alphabetical order in the first column and the functionalities that can be created from them are shown in the second column. The names of all reactions that can bring about these transformations are listed in the third column.

In the second table we listed the target functional groups in alphabetical order in the first column and showed the substrate functionalities in the second column. In the third column the names of these transformations are listed.

A note of caution: none of these tables were created with the intent to be comprehensive, since that would be beyond the scope of this book. The reader should always check the details for each reaction to find out the true scope and limitations of a given transformation. We welcome any suggestions on how to make this section more effective in future editions.

8.2 LIST OF NAMED REACTIONS IN CHRONOLOGICAL ORDER OF THEIR DISCOVERY

8.3 REACTION CATEGORIES

REACTION CATEGORY	NAME OF REACTIONS	BRIEF DESCRIPTION OF SYNTHETIC USE	Page#
CARBOCYCLE FORMATION			
	Acyloin condensation	Formation of cyclic α-hydroxy ketones from diesters.	**4**
	Alkene metathesis	Formation of cyclic alkenes from dienes.	**10**
	Alkyne metathesis	Formation of cyclic alkynes from diynes.	**12**
	Danheiser cyclopentene annulation	Formation of cyclopentenes from enones and allenes.	**124**
	Danishefsky's diene cycloaddition	Formation of six-membered carbocycles using 1-methoxy-3-trimethylsilyloxy-1,3-butadiene.	**126**
	Dieckmann condensation	Formation of cyclic β-keto esters from diesters.	**138**
	Diels-Alder cycloaddition	The [4+2] cycloaddition of alkenes and dienes to afford substituted cyclohexenes.	**140**
	Hajos-Parrish reaction	Enantio-enriched bicyclic enones from 1,5-diketones.	**192**
	Nazarov cyclization	Cyclopentenones and cyclopentanones from divinyl ketones.	**304**
	Pauson-Khand reaction	Formation of cyclopentenones from alkenes, alkynes and CO.	**334**
	Robinson annulation	Formation of bicyclic enones from 1,5-diketones.	**384**
CYCLO-AROMATIZATION			
	Bergman cycloaromatization reaction	Thermal or photochemical cycloaromatization of enediynes to form substituted benzene rings.	**56**
	Danheiser benzannulation	Reaction of cyclobutenones with alkynes to give highly substituted benzene rings.	**122**
	Dötz benzannulation	Reaction of Fischer chromium carbenes with alkynes to give substituted hydroquinone derivatives.	**148**
DEGRADATION			
	Hofmann rearrangement	Conversion of primary carboxamides to one-carbon shorter primary amines.	**210**
	Hunsdiecker reaction	Conversion of carboxylic acids to one-carbon shorter alkyl, alkenyl or aryl halides.	**218**
	Lieben haloform reaction	Conversion of methyl ketones to one-carbon shorter carboxylic acids.	**262**
ELECTROPHILIC ADDITION TO C-C MULTIPLE BONDS			
Addition to alkenes			
cyclopropanation	Simmons-Smith cyclopropanation	Formation of cyclopropanes from alkenes.	**412**
epoxidation	Davis' oxaziridine oxidation	Formation of epoxides from alkenes using oxaziridines.	**130**
epoxidation	Jacobsen-Katsuki epoxidation	Formation of epoxides from alkenes using metal salen complexes.	**222**
epoxidation	Prilezhaev reaction	Formation of epoxides from alkenes using peracids.	**362**
epoxidation	Sharpless asymmetric epoxidation	Formation of epoxy alcohols from allylic alcohols.	**408**
epoxidation	Shi asymmetric epoxidation	Formation of epoxides from alkenes.	**410**
hydrogenation	Noyori asymmetric hydrogenation	Formation of enantio-enriched carboxylic acids, alcohols and amino acids from unsaturated carboxylic acids, allylic alcohols and enamides, respectively.	**316**
hydrometalation	Brown hydroboration reaction	Formation of alkylboranes from alkenes.	**66**
hydrometalation	Schwartz hydrozirconation	Formation of alkylzirconium compounds from alkenes.	**400**
Addition to alkynes			
hydrometalation	Brown hydroboration reaction	Formation of alkenylboranes from alkynes.	**66**
hydrometalation	Schwartz hydrozirconation	Formation of alkenylzirconium compounds from alkynes.	**400**
ELECTROPHILIC AROMATIC SUBSTITUTION			
	Bischler-Napieralski isoquinoline synthesis	Preparation of isoquinolines from acylated phenylethylamines.	**62**
	Combes Quinoline synthesis	Preparation of quinolines from aryl amines and 1,3-diketones.	**94**
	Friedel-Crafts acylation	Synthesis of aromatic ketones using acyl halides or anhydrides.	**176**
	Friedel-Crafts alkylation	Synthesis of alkylbenzenes using alkyl halides.	**178**
	Fries rearrangement	Synthesis of acylated phenols from *O*-acyl phenols.	**180**

8.4 AFFECTED FUNCTIONAL GROUPS

AFFECTED FUNCTIONAL GROUP	NEWLY FORMED FUNCTIONAL GROUP	NAME OF TRANSFORMATION
ACETAL		
	γ,δ-unsaturated amide	Eschenmoser-Claisen rearrangement
ALCOHOL		
1° alcohol	γ-hydroxy oxime	Barton nitrite ester reaction
1° alcohol	aldehyde	Corey-Kim oxidation, Dess-Martin oxidation, Ley oxidation, Oppenauer oxidation, Pfitzner-Moffatt oxidation, Swern oxidation
1° alcohol	alkane	Barton-McCombie radical deoxygenation
1° alcohol	alkene	Chugaev elimination
1° alcohol	amine	Mitsunobu reaction
1° alcohol	azide	Mitsunobu reaction
1° alcohol	carboxylic acid	Jones oxidation
1° alcohol	ester	Mitsunobu reaction
1° alcohol	ether	Mitsunobu reaction, Williamson ether synthesis
1° alcohol	lactone	Corey-Nicolaou macrolactonization, Keck macrolactonization, Yamaguchi macrolactonization
1° alcohol	nitrile	Mitsunobu reaction
1° alcohol	sulfide	Mitsunobu reaction
2° alcohol	γ-hydroxy oxime	Barton nitrite ester reaction
2° alcohol	alkane	Barton-McCombie radical deoxygenation
2° alcohol	alkene	Burgess dehydration, Chugaev elimination
2° alcohol	amine	Mitsounobu reaction
2° alcohol	azide	Mitsunobu reaction
2° alcohol	ester	Mitsunobu reaction, Schotten-Baumann reaction
2° alcohol	ether	Mitsunobu reaction, Williamson ether synthesis
2° alcohol	ketone	Corey-Kim oxidation, Dess-Martin oxidation, Jones oxidation, Ley oxidation, Oppenauer oxidation, Pfitzner-Moffatt oxidation, Swern oxidation
2° alcohol	lactone	Corey-Nicolaou macrolactonization, Keck macrolactonization, Yamaguchi macrolactonization
2° alcohol	nitrile	Mitsunobu reaction
2° alcohol	sulfide	Mitsunobu reaction
3° alcohol	γ-hydroxy oxime	Barton nitrite ester reaction
3° alcohol	alkane	Barton-McCombie radical deoxygenation
3° alcohol	alkene	Burgess dehydration, Chugaev elimination, Grob fragmentation
3° alcohol	amide	Ritter reaction
3° alcohol	ester	Schotten-Baumann reaction
3° alcohol	ether	Williamson ether synthesis
3° alcohol	lactone	Corey-Nicolaou macrolactonization, Keck macrolactonization, Yamaguchi macrolactonization
allylic alcohol	γ,δ-unsaturated amide	Eschenmoser-Claisen rearrangement
allylic alcohol	γ,δ-unsaturated ester	Johnson-Claisen rearrangement
allylic alcohol	allylic amide	Overman rearrangement
allylic alcohol	epoxy alcohol	Sharpless asymmetric epoxidation
allylic alcohol	saturated enantio-enriched alcohol	Noyori asymmetric hydrogenation
propargylic alcohol	α,β-unsaturated ketone	Meyer-Schuster and Rupe rearrangement
propargylic alcohol	propargyl-substituted compound	Nicholas reaction
ALDEHYDE		
	α,β-epoxy ester	Darzens glycidic ester condensation
	α,β-unsaturated carboxylic acid	Perkin reaction
	α-amino nitrile	Strecker reaction
	β-nitro alcohol	Henry reaction
	γ-oxo ester	Stetter reaction
	γ-oxo nitrile	Stetter reaction
	1,3-diol	Prins reaction
	1,4,7-triketone	Stetter reaction
	1,4-diketone	Stetter reaction
	alkane	Tsuji-Wilkinson decarbonylation

8.5 PREPARATION OF FUNCTIONAL GROUPS

TARGET FUNCTIONAL GROUP	SUBSTRATE FUNCTIONAL GROUP	NAME OF TRANSFORMATION
ALCOHOL		
	α,β-epoxy alcohol	Payne rearrangement
	aldehyde	Grignard reaction, Barbier coupling reaction, Nozaki-Hiyama-Kishi reaction, Baylis-Hillman reaction, Cannizzaro reaction, Henry reaction, Keck asymmetric allylation, MPV reduction, Prins reaction, Roush asymmetric allylation, Sakurai allylation, Kagan-Molander coupling
	alkene	Sharpless asymmetric aminohydroxylation
	alkenyl halide or triflate	Nozaki-Hiyama-Kishi coupling
	aryl alkyl ether	Wittig-[1,2]-rearrangement
	enol ether and silyl enol ether	Davis' oxaziridine oxidation
	ketone	Grignard reaction, Barbier coupling reaction, Nozaki-Hiyama-Kishi reaction, Baylis-Hillman reaction, Henry reaction, Keck asymmetric allylation, MPV reduction, Prins reaction, Roush asymmetric allylation, Sakurai allylation, CBS reduction, Luche reduction, Midland Alpine borane reduction, Molander-Kagan coupling, Noyori asymmetric hydrogenation
	nitroalkane	Henry reaction
	organomagnesium species	Grignard reaction
	2° alcohol	Mitsunobu reaction
	silane	Fleming-Tamao oxidation
allylic alcohol	aldehyde	Baylis-Hillman reaction, Grignard reaction, Prins reaction, Nozaki-Hiyama-Kishi coupling
allylic alcohol	alkene	Prins reaction, Riley selenium dioxide oxidation
allylic alcohol	allylic sulfoxide	Mislow-Evans rearrangement
allylic alcohol	enone	Luche reduction, Baylis-Hillmann reaction
allylic alcohol	epoxyhydrazone	Wharton olefin synthesis
allylic alcohol	epoxyketone	Wharton olefin synthesis
allylic alcohol	ketone	Baylis-Hillman reaction, Grignard reaction, Nozaki-Hiyama-Kishi coupling, Wharton olefin synthesis
homoallylic alcohol	aldehyde	Grignard reaction, Barbier coupling reaction, Keck asymmetric allylation, Roush asymmetric allylation, Sakurai allylation
homoallylic alcohol	alkyl allyl ether	Wittig-[2,3]-rearrangement
homoallylic alcohol	ketone	Grignard reaction, Barbier coupling reaction, Keck asymmetric allylation, Roush asymmetric allylation, Sakurai allylation
propargylic alcohol	aldehyde	Barbier reaction, Grignard reaction
propargylic alcohol	ketone	Barbier reaction, Grignard reaction
ALDEHYDE		
aliphatic	aliphatic nitro compound	Nef reaction
aliphatic	cyclic epoxy hydrazone	Eschenmoser-Tanabe fragmentation
aliphatic	cyclic epoxy ketone	Eschenmoser-Tanabe fragmentation
aliphatic	3° amine *N*-oxide	Polonovski reaction
aliphatic/aromatic	1° or 2° alkyl halide	Kornblum oxidation
aliphatic/aromatic	1,2-diol	Criegee oxidation
aliphatic/aromatic	nitrile	Stephen aldehyde synthesis
aliphatic/aromatic	1° alcohol	Corey-Kim oxidation, Dess-Martin oxidation, Ley oxidation, Swern oxidation, Oppenauer oxidation, Pfitzner-Moffatt oxidation
aromatic	activated benzyl halide	Kornblum oxidation
aromatic	electron-rich heteroaromatic ring	Vilsmeier-Haack formylation
aromatic	electron-rich substituted benzene	Vilsmeier-Haack formylation, Reimer-Tiemann reation
aromatic	*N,N*-disubstituted formamide	Vilsmeier-Haack formylation
aromatic	substituted benzene	Gatterman formylation and Gatterman-Koch formylation
ALKENE		
	α-halo sulfone	Ramberg-Bäcklund rearrangement
	1,2-diol	Corey-Winter olefination
	1,3-diol monosulfonate ester	Wharton fragmentation, Grob fragmentation
	1,5-diene	Cope rearrangement
	2° or 3° alcohol	Burgess dehydration, Chugaev elimination

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