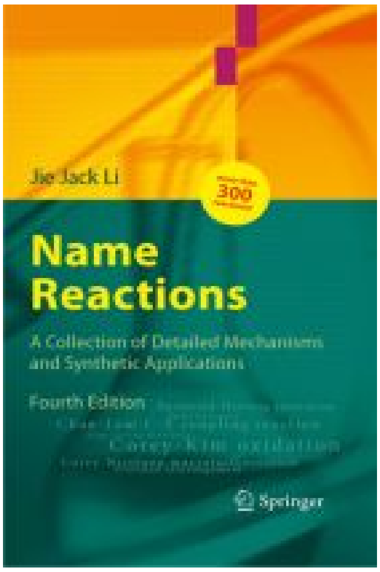
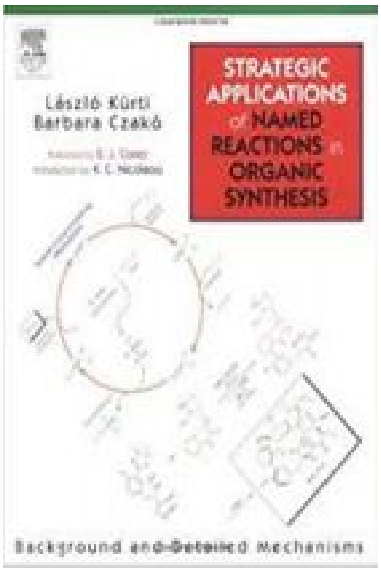
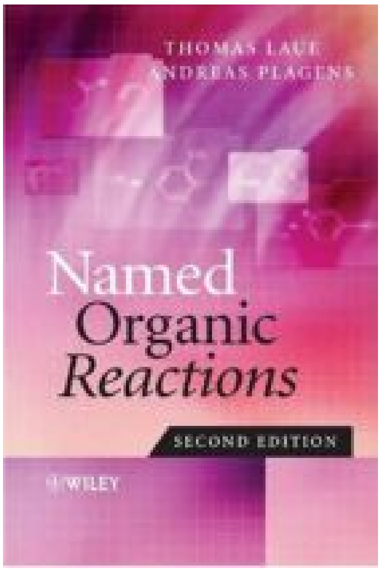
V.Santhanam

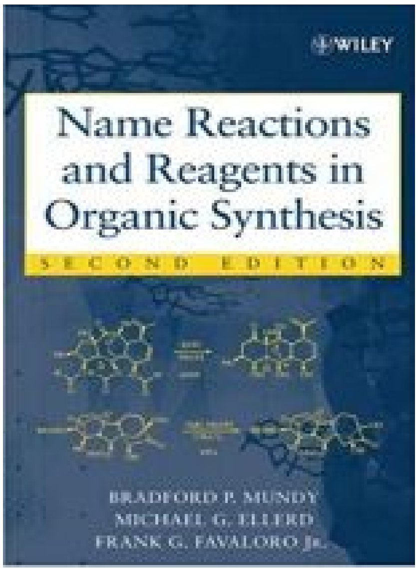
Department of Chemistry

SCSVMV









Unit: 4 - Modern Synthetic Methods

Aim:

To introduce and familiarize the mechanistic information and applications of modern synthetic reactions which are versatile and industrially important.

Objective:

- Understanding the mechanisms of the industrially important synthetic pathways leading to C-C bond formations.
- Steady building the knowledge about the difficulties in industrial organic synthesis by studying reactions of the most simple to highly constrained reacting systems.

Expected Outcome:

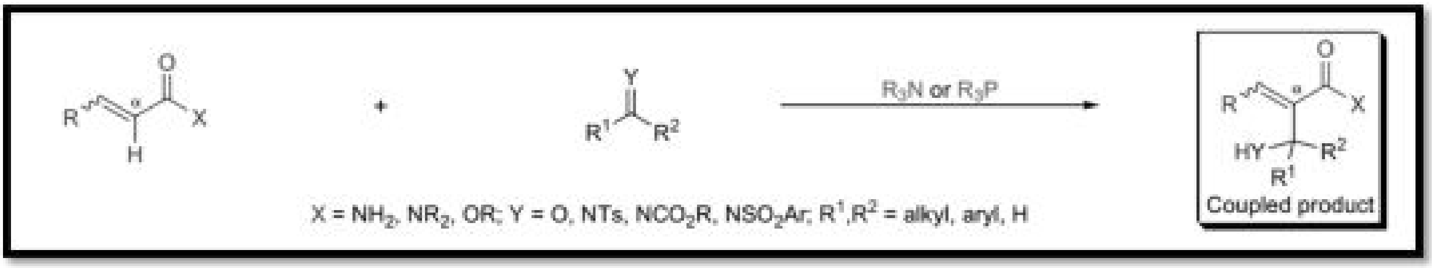
- A sound knowledge on the mechanistic pathways of the synthetic methods.
- How to choose a reacting system to get the desired target by using reliable reactions with atom economy.
- Knowing the constraints of each reaction and being able to choose between the available options.

Prerequisites:

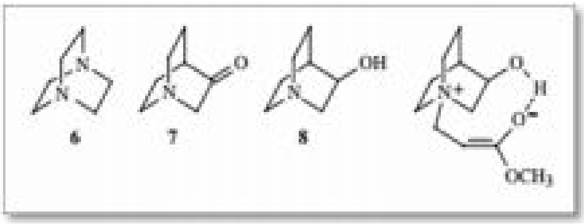
- General organic reaction pathways.
- Concepts of chemo and regioselectivites.
- Coordinately unsaturated systems
- Oxad and Redel reactions.
- General principles of organic synthesis
- Knowledge in reterosynthesis (Preferred but not mandatory).

SOC-Unit-IV: Modern Synthetic Methods: Name Reactions

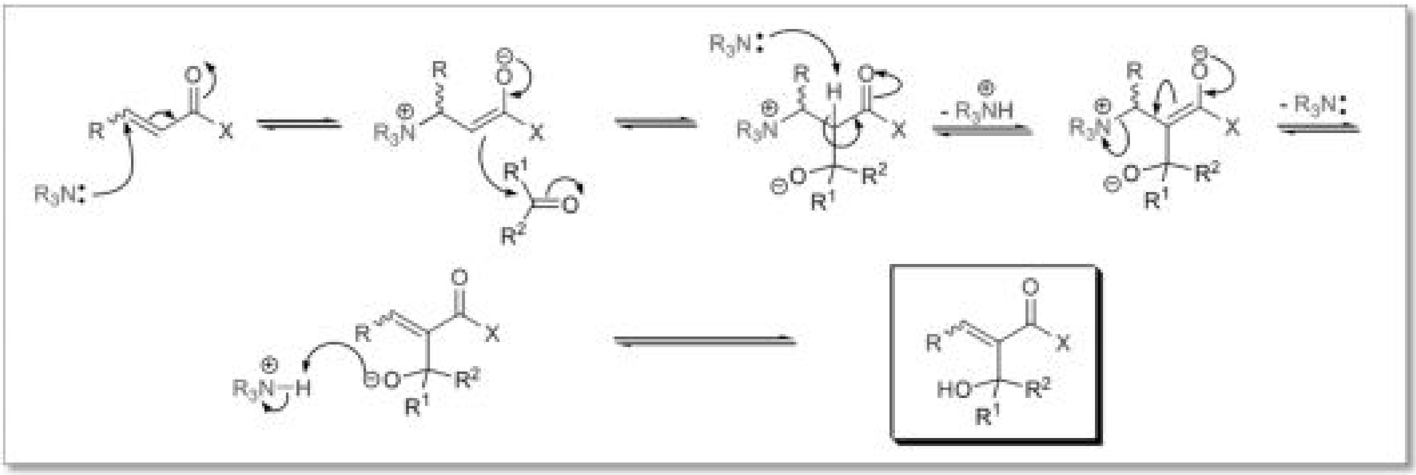
Baylis- Hilman Reaction:



An alkene activated by an electron-withdrawing group(often an acrylic ester is used) can react with an aldehyde or ketone in the presence of catalytic amounts of a tertiary amine, to yield an hydroxyalkylated product. This reaction, known as the Baylis–Hillman reaction, leads to the formation of useful multifunctional products, e.g. ˛-methylene-ˇ hydroxy carbonyl compounds with a chiral carbon center and various options for consecutive reactions.

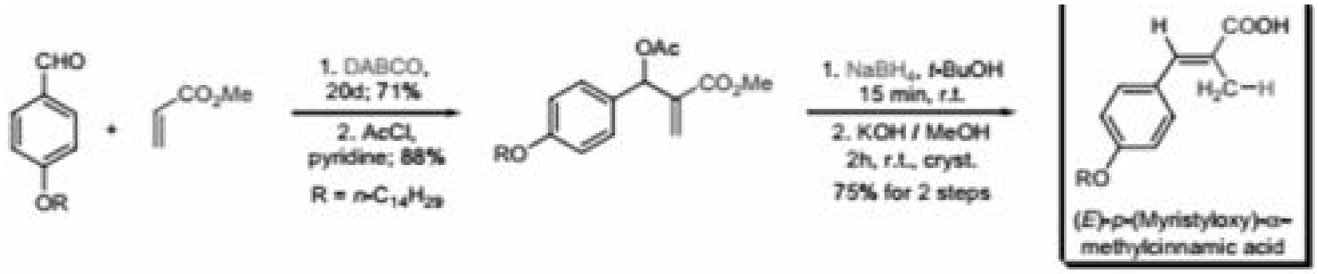


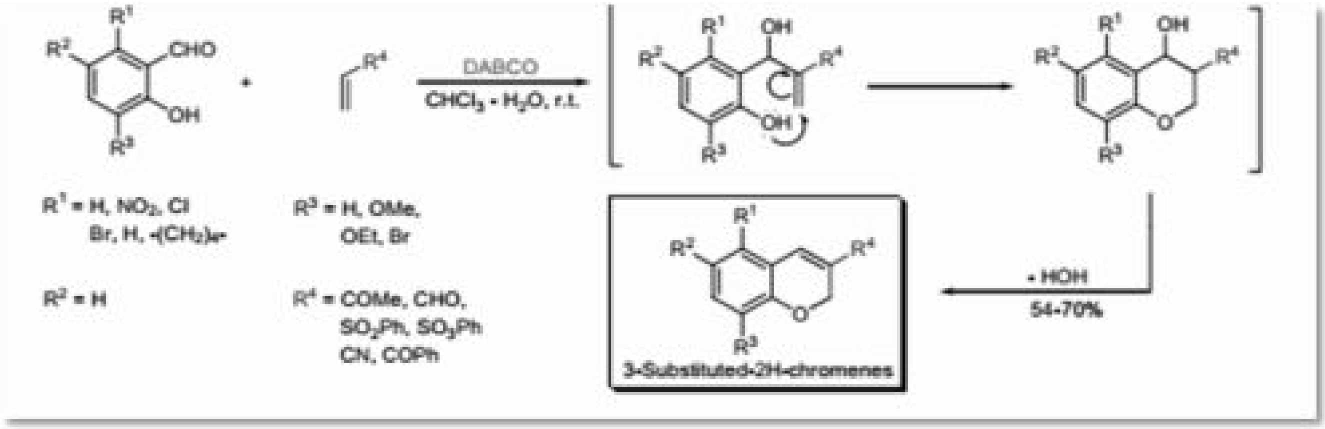
The reaction starts with the nucleophilic addition of a tertiary amine to the alkene bearing an electron-withdrawing group. The zwitterionic intermediate thus formed, has an activated carbon center ˛ to the carbonyl group, as represented by the resonance structure The activated ˛-carbon acts as a nucleophilic center in a reaction with the electrophilic carbonyl carbon of the aldehyde or ketone.

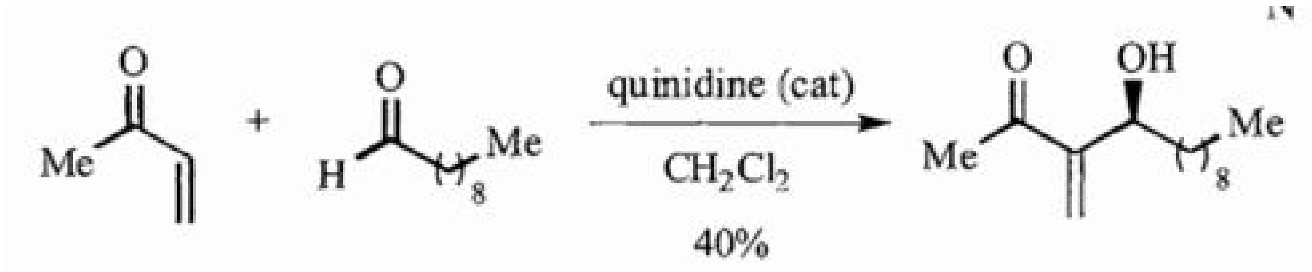


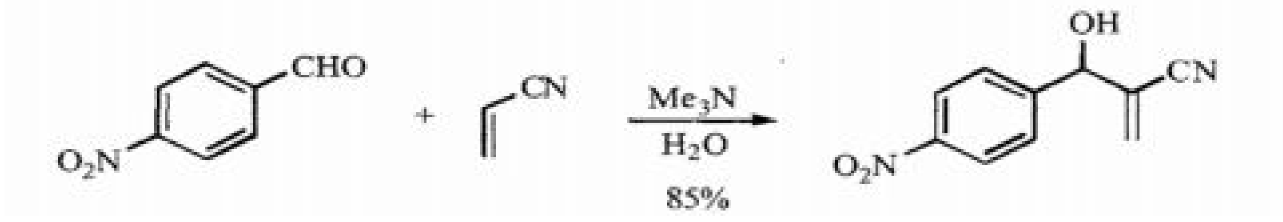
Apart from tertiary amines, the reaction may be catalyzed by phosphines, e.g. tri-n-butylphosphine or by diethylaluminium iodide.When a chiral catalyst, such as quinuclidin-3-ol is used in enantiomerically enriched form, an asymmetric Baylis–Hillman reaction is possible. In the reaction of ethyl vinyl ketone with an aromatic aldehyde in the presence of one enantiomer of a chiral 3-(hydroxybenzyl)-pyrrolizidine as base, the coupling product has been obtained in enantiomeric excess of up to 70%.

Applications:

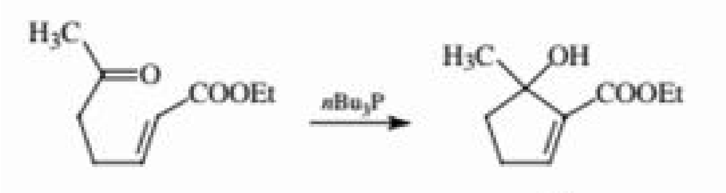

CHO
OR
CO2Me
1. DABCO, 20d; 71%
2. AcCl, pyridine; 88%
R = n-C14H29
OAc
CO2Me
RO
1. NaBH4, t-BuOH 15 min, r.t.
2. KOH / MeOH 2h, r.t., cryst.
75% for 2 steps
H
COOH
H2C—H
RO
(E)-p-(Myristyloxy)-α-methylcinnamic acid


R1
R2
CHO
OH
R3
R4
DABCO
CHCl3 - H2O, r.t.
R1 OH
R2
R4
OH
R3
R1 OH
R2
R4
O
R3
R1 = H, NO2, Cl
Br, H, -(CH2)4-
R3 = H, OMe,
OEt, Br
R2 = H
R4 = COMe, CHO,
SO2Ph, SO3Ph
CN, COPh
- HOH
54-70%
R1
R2
R4
O
R3
3-Substituted-2H-chromenes


O
Me
+
O
H
Me
8
quinidine (cat)
CH2Cl2
40%
O
OH
Me
Me
8


CHO
O2N
+
CN
Me3N
H2O
85%
OH
CN
O2N


CHO
O
O
+
CO2Me
DABCO
ultrasound
OH
CO2Me
O
O



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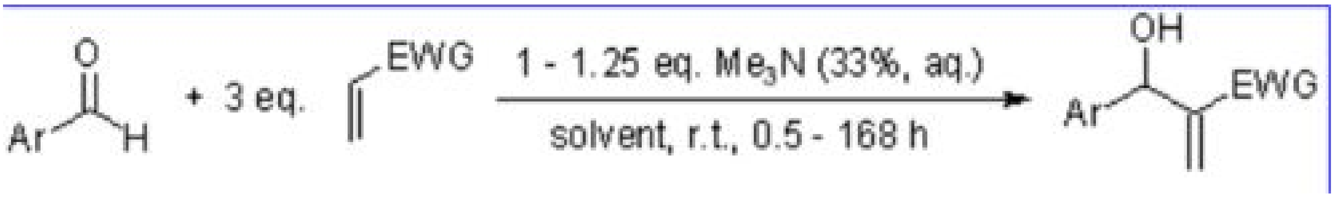

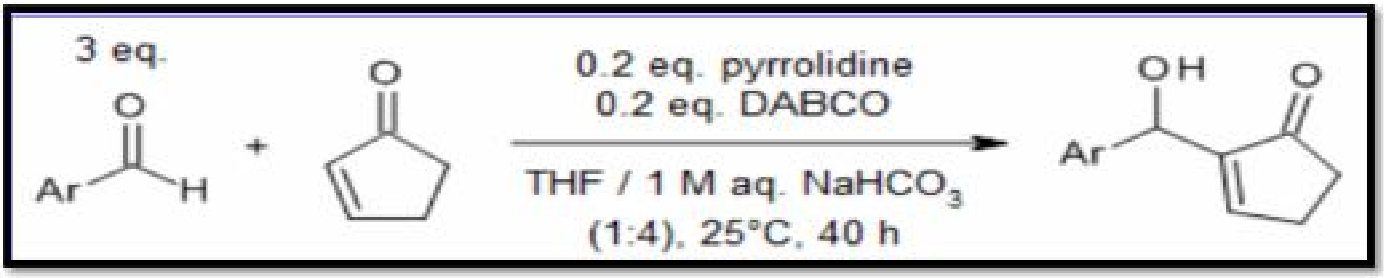

The Baylis–Hillman reaction is usually carried out under mild conditions (0 C or room temperature). The reaction time varies from a few minutes to even days. With the proper catalyst, good yields are possible. In the absence of an aldehyde or ketone as the electrophilic component, a dimerization of the activated alkene can take place under the influence of the catalyst, as also observed as a side reaction under the usual reaction conditions:

Apart from the acrylates discussed above, various other types of acceptor substituted alkenes can serve as substrates. As electron withdrawing substituents, aldehyde, keto or nitrile groups, as well as sulfur- and phosphor-based substituents such as SOPh, SO_2Ph and $PO(OEt)_2$, have found application. As the electrophilic component , some substrates containing appropriately substituted nitrogen instead of the carbonyl oxygen (e.g. DNCOOR, $DNSO_2Ph$ and DNp-Tosyl) have been used successfully. Because of the large variety of possible starting materials and the many possible subsequent reactions, the Baylis–Hillman reaction has become an important method for the construction of carbon–carbon bonds.

Henry Reaction:

In 1895, L. Henry discovered that nitroalkanes were easily combined with aldehydes and ketones to give β-nitro alcohols in the presence of a base.[1,2] Since its discovery, the aldol condensation between nitroalkanes and carbonyl compounds (nitro-aldol reaction) has become a significant tool in the formation of C-C bonds and is referred to as the Henry reaction.

The reaction is completely reversible in al steps. In the first step base abstracts α- H to form an enolate ion which is resonance stabilaized. This enolate attacks the carbonyl carbon of the other reactant to form β-nitro alkoxide. Reprotonation by the BH^+ species produces the β-nitro alcohol.

The β-nitro alcohols are easily converted to other useful synthetic intermediates:

- Upon dehydration, nitroalkenes are formed that may be used as: a) dienes and dienophiles; b) Michael acceptors or c) masked ketones (since the Nef reaction converts them to the corresponding ketones);
- Oxidation of the secondary alcohol functionality affords α-nitro ketones;
- Reduction of the nitro group gives β-amino alcohols;
- Radical denitration

Applications:

General features of the Henry reaction are:

1. Only a catalytic amount of base is necessary.
2. Both ionic and nonionic bases may be used such as alkali metal hydroxides, alkoxides, carbonates, sources of fluoride ion (e.g., TBAF, KF, Al_2O_3-supported KF), solid supported bases, rare earth metal salts, transition metal complexes and nonionic organic nitrogen bases (e.g., amines, TMG, DBU, DBN, PAP).
3. The solvents and bases do not have significant influence on the outcome of the reaction.
4. The steric properties of the reactants play an important role: hindered substrates (usually ketones) react slowly and side reactions often occur; usually the β-nitro alcohols are formed as a mixture of diastereomers (syn and anti) but by modification of the reaction conditions high levels of diastereoselectivity can be achieved.
5. The stereocenter to which the nitro group is attached to is easy to epimerize.

Nef Reaction:

In 1893, M. Konovalov observed that the treatment of the potassium salt of 1-phenylnitroethane with dilute acid

(AcOH, H_2SO_4) led to the formation of 1-phenylnitroethane and acetophenone.1 In 1894, J.U. Nef systematically studied the acidic hydrolysis of several nitroparaffin sodium salts, while he was completely unaware of Konovalov's experiments, and showed that the major product of all these reactions were the corresponding carbonyl compounds Since Nef demonstrated the generality of this transformation, which he discovered independently, the conversion of nitroalkanes into the corresponding carbonyl compounds is known as the Nef reaction.

The general features of the reaction are:

1) The product distribution is strongly influenced by the acid concentration, and for best results the ph need to be smaller than unity

2) When the ph>1, a number of by-products such as oximes and hydroxynitroso compounds can be formed; and 3) Original reaction conditions required the addition of the nitronate salt to the solution of the acid to avoid the formation of undesired products.

- Oxidative methods allow the conversion of primary nitroalkanes into aldehydes or carboxylic acids, while secondary nitroalkanes are converted to ketones

- Reductive methods are available for the direct preparation of nitroalkanes to aldehydes, ketones, or oximes carbonyl compounds and oximes can also be prepared from nitroolefins (nitroalkenes) using various reducing agents.

Mechanism:

The mechanism of the Nef reaction has been extensively studied. Under the original reaction conditions, the nitronate salt is first protonated to give the nitronic acid, which after further protonation is attacked by a molecule of water. The process is strongly dependent on the pH of the reaction medium. Weakly acidic conditions favor the regeneration of the nitro compound and by-product formation (oximes and hydroxynitroso compounds), whereas strongly acidic medium (pH 1) promotes the formation of the carbonyl compound.

The most popular reductive method (McMurray modification involving TiCl3) proceeds via a nitroso compound that tautomerizes to form an oxime and finally upon work-up the desired product is obtained.

Applications:

SOC-Unit-IV: Modern Synthetic Methods: Name Reactions

Kulinkovich Reaction:

In 1989, O.G. Kulinkovich reported that 1-alkylcyclopropanols were formed when an excess of ethylmagnesium bromide was added to simple carboxylic esters in the presence of one equivalent of titanium tetraisopropoxide.1 The reaction could also be carried out with catalytic amounts of Ti(Oi-Pr)4 and only two equivalents of Grignard reagent was necessary. The titanium(II)- mediated one-pot conversion of carboxylic esters and amides to the corresponding 1- alkylcyclopropanols and 1- lkylcyclopropylamines is known as the Kulinkovich reaction.

The general features of the reaction are:

1. The active species is a titanacyclopropane intermediate that acts as a 1,2-dicarbanion equivalent and doubly alkylates the carbonyl group
2. More complex Grignard reagents yield 1,2-cis disubstituted cyclopropanols with good diastereoselectivity; 3. The observed cis-selectivity is lower for the formation of 1,2-disubstituted cyclopropylamines from amides; 4. The reaction is sensitive to the nature of the R1 group (aromatic esters do not react) and steric crowding (α-branched R1 groups and too bulky R2 groups give lower yields)
5. When terminal alkenes are added into the reaction mixture, these are incorporated into the cyclopropane products. There are several important modifications of the procedure, which helped to expand the scope of the reaction.

Mechanism:

If ethylmagnesium bromide is used, the formation of ethane and a trace of ethene can be observed. Two equivalents of the Grignard reagent react with titanium(IV) isopropoxide to give a thermally unstable diethyltitanium compound, which rapidly undergoes β-hydride elimination with the loss of ethane to yield the substituted titanacyclopropane. The titanacyclopropane reacts with the ester as a 1,2-dicarbanion equivalent to produce a cyclopropanol after a 2-fold alkylation.

Titanium(II) is reoxidized to titanium(IV) over the course of this addition process. The last intermediate in the sequence can be recognized as a Ti(OR'')4 species, which can undergo reaction with EtMgBr similar to Ti(OiPr)4. Thus, titanium(IV) isopropoxide can be used in catalytic amounts The production of ethene has been attributed to a side reaction of the titanacyclopropane with additional titanium(IV) isopropoxide to afford 2 equivalents of titanium(III) isopropoxide This non-productive side reaction reaches a maximum as the ratio of titanium(IV) isopropoxide to EtMgBr approaches a stoichiometry of 1:1.

The disproportion aspect of the mechanism means that only one of the two organomagnesium ligands is incorporated into the reaction product, which is a concern when the Grignard reagent used is not a commercial item. Two interesting modifications help to improve the atom economy for more specialized ligands.

One method is to use a terminal alkene that can undergo a ligand exchange. The exchange is fast for styrenes, and allows the use of EtMgBr as the Grignard reagent. For other terminal alkenes, the bulkier cyclohexylmagnesium halides can be be used to retard the participation of the initially formed titanium(II) species in the alkylation reaction and to promote the reaction of the desired ligand with the ester. Sub-stoichiometric amounts of titanium(IV) isopropoxide can still be used in this ligand exchange modification.

In the other modified procedure, described by de Meijere, MeTi(OiPr)3 is formed first, and a stoichiometric amount is used with only 1.1 eq. of a Grignard Reagent. Here, the disproportionation produces methane as a gaseous side product and allows the Grignard reagent to be fully utilized.

Applications:

Ritter Reaction:

Treatment of nitriles with alkenes or tertiary alcohols under acidic conditions resulted in the formation of N-tert-alkylamides. When hydrogen cyanide was used as the nitrile component, N-tert-alkyl formamides were obtained, which could be easily hydrolyzed with base to give the corresponding tert-alkylamines. The formation of N-alkyl carboxamides from aliphatic- or aromatic nitriles and carbocations is known as the Ritter reaction.

It is widely used for the preparation of acyclic amides as well as heterocycles (e.g., lactams, oxazolines, dihydroisoquinolines, etc.).

The general features of this transformation are:

1. The carbocation can be generated in a variety of ways from tertiary-, secondary, or benzylic alcohols, alkenes or alkyl halides; 2. The classical reaction conditions involve the dissolution of the nitrile substrate in the mixture of acetic acid and concentrated sulfuric acid followed by the addition of the alcohol or alkene at slightly elevated temperatures (50-100 °c). 3. Alcohols that are easily ionized (e.g., 2° and 3° alcohols, benzylic alcohols) give the best results.

4. 1,1-disubstituted alkenes give rise to regioisomerically pure products, but with 1,2-disubstituted alkenes a mixture of regioisomers may be formed.

5. The initially formed carbocation (which can be obtained from a large number of different functionalities)5,8 may undergo a wagner-meerwein rearrangement to give rise to the most stable carbocation before reacting with the nitrile. 6. Besides protic acids, lewis acids (e.g., sncl4, bf3·oet2, alcl3, etc.) Have been successfully employed in the ritter reaction to generate the required carbocations.

7. The structure of the nitrile component can be varied widely and most substrates containing a cyano group will undergo the reaction, so, for example, besides aliphatic and aromatic nitriles, compounds like cyanogen and cyanamide will also react. 8. The nitrile substrate may not contain acid sensitive functional groups that would be destroyed under the strongly acidic reaction conditions, but modifications (ritter-type reactions) that proceed under neutral conditions expanded the scope of the substrates.

Mechanism:

The mechanism of the Ritter reaction has been intensely studied. When alcohols are used to generate the carbocation, the hydroxyl group is protonated then under the reaction conditions the C-O bond is heterolytically cleaved to generate a carbocation. This cation is then attacked by the nitrogen atom of the nitrile to form a nitrilium ion, which upon reacting with the conjugate base of the acid (hydrogen sulfate anion in the scheme) gives rise to an imidate. Finally, hydrolysis produces the desired N-alkyl carboxamide.

Applications:

Sakurai Reaction / Hosomi-Sakurai Reaction / Sakurai Allylation

In 1976, H. Sakurai reported that allylsilanes react with a wide variety of aldehydes and ketones in the presence of stoichiometric quantities of TiCl4 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 $AlCl_3$, $BF_3 \cdot OEt_2$, $SnCl_4$, $EtAlCl_2$. 3. Most commonly trimethylallylsilanes and phenyldimethylallylsilanes are utilized as the allylsilane reactant 4. The reaction is highly regioselective, the electrophile attacking at the C3 terminus of the allylsilane 5. C1 substituted allylsilanes give the (E)-alkene product

6. Allenyl-, propargyl-, vinyl-, and ethynylsilanes also undergo the reaction in the presence of Lewis acids; 7. The most commonly used electrophiles are aldehydes and ketones, but acetals and ketals are also often utilized; 8. Dithioacetals, monothioacetals, alkoxymethyl-, and phenylthiomethyl chlorides undergo the allylation reaction; 9. α,β-unsaturated aldehydes react at the carbonyl group, while α,β-unsaturated ketones undergo conjugate addition 10. Intramolecular reactions are also feasible

11. C3 monosubstituted allysilanes give the syn-diastereomer as the major product.

12. 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.

Mechanism:

When a Lewis acid, e.g. titanium tetrachloride, coordinates to the carbonyl oxygen of an α,β-unsaturated carbonyl compound, the ˇβγ-carbon center becomes more positively polarized. The allylsilane adds as a nucleophile with its γ -carbon to the β carbon of the α,β-unsaturated carbonyl substrate. This carbon–carbon single-bond forming step is the rate determining step. Cleavage of the trimethylsilyl group from the intermediate carbenium ion leads to formation of a new carbon–carbon double bond. After hydrolytic workup the υ,ε-unsaturated ketone is obtained and (E)-allylsilanes give higher diastereoselectivities than (Z)- allylsilanes. The reaction presumably goes through an open transition state. The possible transition states leading to the syn diastereomer are depicted below.

Applications:

Tishchenko Reaction:

W.E. Tishchenko found that both enolizable and non-enolizable aldehydes can be converted to the corresponding esters in the presence of magnesium- or aluminum alkoxides. The reaction involves a hydride shift from one aldehyde to another that leads to the formation of the ester product. This transformation is known today as the Tishchenko reaction.

Mechanism:

The mechanism of the Tishchenko reaction was extensively studied and there were three different mechanisms proposed. The most commonly accepted mechanism is depicted below. According to this proposal, first the aluminum alkoxide coordinates to the aldehyde. This is followed by the attack of a second molecule of aldehyde. Subsequent hydride shift leads to the regeneration of the catalyst and formation of the product.

The general features of the reaction are:

- In the traditional transformation, the reaction takes place between the same aldehydes.
- In the crossed Tishchenko reaction, two different aldehydes are reacted to form the ester product.
- The reaction can take place in an intramolecular fashion, yielding the corresponding lactone
- Common side reactions are the aldol reaction, Cannizzaro reaction, Merwein-Ponndorf-Verley reduction, and Oppenauer oxidation.
- The most general catalysts in the traditional Tishchenko reaction are aluminum alkoxides, but a wide-variety of catalysts can be usedAlkali and alkali earth metal oxides and alkoxides.Transition metal-based catalysts such as ruthenium complexes

($RuH_2(PPh_3)_4$,certain rhodium- iridium- and iron complexes, and metallocenes of group IV metals (Cp_2MH_2 M = Hf, Zr). Lanthanide based catalyst such as lanthanide amides ($Ln[NSiMe_2)_3]$, Ln = La, Sm, Y),organolanthanoid halides (EtLnX, Ln = Pr, Nd, Sm, X = I) and SmI_2

- A modification of the Tishchenko reaction is the aldol-Tishchenko reaction where the aldehyde first undergoes an aldol reaction followed by the Tishchenko reaction to form monoesters of 1,3-diols. In the homo aldol-Tishchenko reaction, the same aldehyde molecules react. In the hetero aldol-Tishchenko reaction, a ketone or aldehyde reacts with two equivalents of a different aldehyde over the catalyst.
- The most widely used modification of the Tishchenko reaction is the EvansTishchenko reaction.20 In this transformation, a chiral β-hydroxy ketone reacts with an aldehyde in the presence of catalytic SmI2 to provide the anti 1,3-diol monoester product with excellent diastereoselectivity .

Applications:

Ugi Reaction:

In 1959, I. Ugi reported that isocyanides undergo a four-component reaction (4-CR) in the presence of an amine, aldehyde or ketone and a nucleophile to provide a single condensation product.1-3 The most commonly used nucleophiles are carboxylic acids, but hydrazoic acid, cyanates, thiocyanates, carbonic acid monoesters, salts of secondary amines, water, hydrogen sulfide, and hydrogen selenide can also be used.1-3 Today, this transformation is referred to as the Ugi four-component reaction (U-4CR)

The general features of the reaction are:

- It is very easy to carry out, usually, the isocyanide is added to a stirring and well cooled solution of the other three components;
- In case of less reactive aldehydes and ketones, it is advisable to precondense the carbonyl compounds and the amine to form the imine;
- As the reaction is very exothermic, adequate cooling is necessary. The reaction typically is carried out between -80 °c to 80 °c and it may take from a few minutes to a week to go to completion.
- Methanol is generally a suitable solvent, although many other solvents can be used;
- The amine component can be any compound with a sufficiently nucleophilic nh group such as ammonia, primary and secondary amines, hydrazine and derivatives, diaziridines as well as hydroxylamine
- Diarylamines are usually not nucleophilic enough to undergo the reaction;
- With the exception of diarylketones, almost all aldehydes and ketones are suitable for the U- 4CR
- A wide range of C-isocyanides undergo the transformation; and
- When nonpolar solvents are used, or the reacting components are bulky, the Passerini Reaction may occur as a side reaction leading to the formation of α- acyloxycarboxamides.

Mechanism:

Applications:

Brook Rearrangement:

Rearrangement of α-silyl oxyanions to α-silyloxy carbanions via a reversible process involving a pentacoordinate silicon intermediate is known as the [1,2]-Brook rearrangement, or [1,2]-silyl migration. In the late 1950s, A.G. Brook observed the intramolecular anionic migration of silyl groups from a carbon to an oxygen atom. This migratory aptitude of the silyl group was later found to be more general. Therefore, all the

[1,n]- carbon to oxygen silyl migrations are referred to as Brook rearrangements. The reaction is based on the great susceptibility of silicon toward a nucleophilic attack and the formation of a strong silicon-oxygen bond (Si-O) from the relatively weak silicon-carbon bond. The reverse process is called the retro-Brook rearrangement and was first reported by J.L. Speier.

Applications:

K.Takeda's Stereo selective construction of eight membered carbocycle by Brook rearrangement followed by [3+4] annulation.

Tebbe Olefination / Petasis-Tebbe Olefination:

In 1978, F.N. Tebbe et al. reported that titanocene dichloride reacted with two equivalents of $AlMe_3$ to produce a methylene-bridged titanium-aluminum complex (Tebbe reagent), which transferred a methylene group (CH_2)

efficiently to various carbonyl compounds to afford olefins. It was shown early on that the Tebbe reagent converted carboxylic esters, lactones, and amides to the corresponding enol ethers and enamines in high yield. The one-carbon homologation (methylenation) of carbonyl compounds using the Tebbe reagent is known as the Tebbe olefination.

The Tebbe reaction has the following general features:

- The active species (titanocene methylidene) is more nucleophilic and much less basic than the corresponding Wittig reagents. Consequently, less reactive (bulkier) and enolizable carbonyl compounds can be readily olefinated;
- The Tebbe reagent is stable in solution and reacts at low temperature with the various carbonyl groups in the following order: aldehydes>ketones>esters>amides;
- Acid halides and anhydrides do not undergo methenylation. Instead, the corresponding titanium enolates are formed, which can be used in subsequent aldol reactions
- Only methenylations can be performed; higher alkenyl groups cannot be introduced with this method;
- A wide range of functional groups are tolerated. However, the presence of the Lewis acidic aluminum may cause complications with certain substrates.

Mechanism:

1. The active species in the Tebbe olefination is believed to be the nucleophilic (Schrock-type) titanocene methylidene,which is formed from the Tebbe reagent upon coordination of the aluminum with a Lewis base (e.g., pyridine).
2. This methylidene in its uncomplexed form, however, has never been isolated or observed spectroscopically owing to its extreme reactivity. The same intermediate can also be generated by other means.
3. The titanocene methylidene reacts with the carbonyl group to form an oxatitanacyclobutane intermediate that breaks down to titanocene oxide and the desired methenylated compound (alkene).
4. The driving force is the formation of the very strong titanium-oxygen bond.

Applications:

Heck Reaction:

In the early 1970s, T. Mizoroki and R.F. Heck independently discovered that aryl, benzyl and styryl halides react with olefinic compounds at elevated temperatures in the presence of a hindered amine base and catalytic amount of Pd(0) to form aryl-, benzyl-, and styryl-substituted olefins Today, the palladium-catalyzed arylation or alkenylation of olefins is referred to as the Heck reaction.

The General Features of the Heck reaction are:

1. It is best applied for the preparation of disubstituted olefins from monosubstituted ones;

2. The electronic nature of the substituents on the olefin only has limited influence on the outcome of the reaction; it can be either electron-donating or electron-withdrawing but usually the electron poor olefins give higher yields; 3. The reaction conditions tolerate a wide range of functional groups on the olefin component: esters, ethers, carboxylic acids, nitriles, phenols, dienes, etc., are all well-suited for the coupling, but allylic alcohols tend to rearrange;

4. The reaction rate is strongly influenced by the degree of substitution of the olefin and usually the more substituted olefin undergoes a slower Heck reaction;

5. Unsymmetrical olefins (e.g., terminal alkenes) predominantly undergo substitution at the least substituted olefinic carbon; 6. The nature of the X group on the aryl or vinyl component is very important and the reaction rates change in the following order: I > Br ~ OTf >> Cl;

7. The R1 group in most cases is aryl, heteroaryl, alkenyl, benzyl,and rarely alkyl (provided that the alkyl group possesses no hydrogen atoms in the β-position), and these groups can be either electron-donating or electron-withdrawing; 8. The active palladium catalyst is generated in situ from suitable precatalysts (e.g., $Pd(OAc)_2$, $Pd(PPh_3)_4$) and the reaction is usually conducted in the presence of monodentate or bidentate phosphine ligands and a base;

9. The reaction is not sensitive to water, and the solvents need not be thoroughly deoxygenated

10. The Heck reaction is stereospecific as the migratory insertion of the palladium complex into the olefin and the β-hydride elimination both proceed with syn stereochemistry.

Drawbacks of the Heck reaction:

1. The substrates cannot have hydrogen atoms on their β-carbons, because their corresponding organopalladium derivatives tend to undergo rapid β-hydride elimination to give olefins.
2. Aryl chlorides are not always good substrates because they react very slowly.

Several modifications were introduced during the past decade:

- Asymmetric versions
- Generation of quaternary stereocenters in the intramolecular heck reaction

- Using water as the solvent with water-soluble catalysts
- Heterogeneous palladium on carbon catalysis

Mechanism:

The catalytic cycle of the Heck reaction can be formulated with four steps as follows:

1. Formation of an arylpalladium complex 4 from the palladium(0) complex 3 and the aryl derivative 5 by oxidative addition.
2. Addition of complex 4 to the alkene (olefin insertion).
3. A β-elimination reaction from complex 6, releasing the substituted alkene 7.
4. Regeneration of the palladium(0) complex 3 by reaction with a base, e.g. triethylamine.
5. The regioselectivity of the addition of complex 4 to a substituted alkene is mainly influenced by steric factors. The substitution of hydrogen occurs preferentially at the carbon center which has more number of hydrogens

The coupling of bromo- or iodobenzene to styrene yields regioselectively a mixture of E- and Z-stilbenes 12 and 13. An electron-withdrawing substituent at the olefinic double bond often improves the regioselectivity, while an electrondonor substituted alkene gives rise to the formation of regioisomers.

With respect to the olefinic substrate, various functional groups are tolerated, e.g. ester, ether, carboxy or cyano groups. Primary and secondary allylic alcohols, e.g. 14, react with concomitant migration of the double bond, to give an enol derivative, which then tautomerizes to the corresponding aldehyde (e.g. 15) or ketone.

Another instructive example of the potential of this reaction for the construction of ring systems has been reported by de Meijere and coworkers taking advantage of a sequence of four consecutive intramolecular Heck reactions. The bromodiene-yne 18 reacts in a sequence of domino reactions within 3 d at 80 °C under Heck conditions to give the tetracyclic product 19 in 74% yield:

Heck Reaction 36

Stille Cross-Coupling
(Migita-Kosugi-Stille Coupling)

The Pd(0)-catalyzed coupling reaction between an organostannane and an organic electrophile to form a new C-C sigma bond is known as the Stille cross coupling.

Together with reactions named after Heck and Suzuki, the Stille reaction belongs to a class of modern, palladium-catalyzed carbon– carbon bond forming reactions. The palladium-catalyzed reaction of an organotin compound 2 with a carbon electrophile 1 is called Stille coupling. As in case of other palladium-catalyzed reactions, the general mechanism of the Stille reaction is best described by a catalytic cycle.

Mechanism

The catalytic cycle for the Stille coupling reaction was first proposed for the reaction with benzylic and aryl halides in 1979, although the detailed mechanism is still a matter of some debate. The catalytic cycle has three steps:

1) Oxidative addition
2) Transmetallation
3) Reductive elimination.

🌍 The active catalyst is believed to be a 14-electron Pd(0)-complex which can be generated in situ.

🌍 Palladium(0)-catalysts such as $Pd(PPh_3)_4$ and $Pd(dba)_2$, with or without an added ligand, are often used. 🌍 Alternatively, Pd(II)-complexes such as $Pd(OAc)_2$, $PdCl_2(MeCN)_2$, $(PdCl_2(PPh_3)_2$,$BnPdCl(PPh_3)_2$, etc. are also used as precursors for the catalytically active Pd(0) species, as these compounds are reduced by the organostannane or by an added phosphine ligand prior to the main catalytic process.

- The transmetallation step is the rate-determining step in the catalytic cycle.
- Different groups on the tin coupling partner transmetallate to the Pd(II) intermediate at different rates and the order of migration is: alkynyl > vinyl > aryl > allyl ~ benzyl »» alkyl.
- The very slow migration rate of the alkyl substituents allows the transfer of aryl or vinyl groups when mixed organostannanes containing three methyl or butyl groups are used.

- The transfer of simple alkyl groups (R3 in the table—mostly n-Bu or Me), from tin to palladium complex 6 is a very slow process, and the substituent R2 (see table) is transferred selectively. The leaving group X on the coupling component can be halide or sulfonate—in many cases triflate is used. Iodide is a better leaving group than bromide; this can be used for a regioselective coupling reaction. In the coupling with vinyl groups, the olefin geometry is usually retained; E/Z isomerization is only rarely observed.

Applications:

A closely related aryal coupling reaction catalyzed by organostannanes also exists. The Pd-catalyzed intramolecular biaryl coupling of aryl halides or aryl triflates in the presence of distannanes is known as the Stille-Kelly coupling.

The Stille-Kelly coupling consists of two connected catalytic cycles and the following steps:

1. The oxidative addition of the Pd(0) complex into one of the C-X bond of the aryl halide

2. Transmetallation with the distannane followed by reductive elimination to afford the

organostannane 3. Oxidative addition of the Pd(0) complex into the C-X bond of the organostannane

4. Intramolecular transmetallation

5. Reductive elimination to give the coupled product.

Applications:

Suzuki Coupling:

In 1979, A. Suzuki and N. Miyaura reported the stereoselective synthesis of arylated (E)-alkenes by the reaction of 1- alkenylboranes with aryl halides in the presence of a palladium catalyst The palladium-catalyzed cross-coupling reaction between organoboron compounds and organic halides or triflates provides a powerful and general method for the formation of carbon-carbon bonds known as the Suzuki cross-coupling.

Mechanism:
The mechanism of the Suzuki reaction is closely related to that of the Stille coupling reaction, and is also best described by a catalytic cycle

1. . Oxidative addition— Reaction of the halide component with a palladium-(0) complex 5 to give a palladium-(II) species 6. 2. Transmetallation—Transfer of substituent R0 from boron to the palladium center, thus generating a palladium-(II) species that contains both the substituent R and R0 that are to be coupled.

3. Reductive elimination—to yield the coupling product 3 and the regenerated catalytically active palladium-(0) complex 5. 4. The boronic acid 2 is first converted to an activated species 8 containing a tetravalent boron center by reaction with a base. Halides or triflates (OTf trifluoromethanesulfonate) are used as coupling partners RX for the boronic acids. 5. In many cases the rate-limiting step is the oxidative addition.

6. With respect to the leaving group X, the rate decreases in the orderI > OTf > Br × Cl

For the synthesis of a suitable arylboron compound, usually an aryl halide is converted to an aryllithium or aryl Grignard derivative, and then reacted with a trialkoxyborane to yield an arylboronic ester, e.g. the phenylboronic acid diisopropyl ester from bromobenzene .

Of particular synthetic importance is the coupling of aryl- and hetarylboronic acids to aryl- and hetaryl halides (or triflates), allowing for a convenient synthesis of biphenyls, even sterically demanding derivatives, hetaryl phenyls and bis-hetaryls. With appropriately disubstituted aromatic substrates, the Suzuki coupling reaction can be applied in the synthesis of polyphenylene materials. The coupling of alkenylboronic acids with alkenyl halides is a good method for the E/Z-selective synthesis of conjugated dienes. An example is the Suzuki coupling step from a synthesis of retinol (vitamin A) ; this coupling occurs with retention of configuration at the sp^2-carbon centers, so leading to the E,E configurated product only.

Many types of functional groups are tolerated in a Suzuki reaction, and the yields are often good to very good. The presence of a base, e.g. sodium hydroxide or sodium/potassium carbonate, is essential for this reaction. The base is likely to be involved in more than one step of the catalytic cycle, at least in the transmetallation step. Proper choice of the base is important in order to obtain good results. In contrast to the Heck reaction and the Stille reaction, the Suzuki reaction does not work under neutral conditions.

Applications:

Negishi Cross Coupling:

In 1976, E. Negishi and co-workers reported the first stereospecific Ni-catalyzed alkenyl-alkenyl and alkenyl-aryl cross coupling of alkenylalanes (organoaluminums) with alkenyl- or aryl halides. Extensive research by Negishi showed that the best results (reaction rate, yield, and stereoselectivity) are obtained when organozincs are coupled in the presence of Pd(0)-catalysts.The Pd- or Ni- catalyzed stereoselective cross-coupling of organozincs and aryl-, alkenyl-, or alkynyl halides is known as the Negishi cross coupling.

The general features of the reaction are:

1. Both Ni- and Pdphosphine complexes work well as catalysts. However, the Pd-catalysts tend to give somewhat higher yields and better stereoselectivity, and their functional group tolerance is better.
2. The active catalysts are relatively unstable Ni(0)- and Pd(0)-complexes but these can be generated in situ from more stable Ni(II)- and Pd(II) -complexes with a reducing agent (e.g., 2 equivalents of DIBAL-H or n-BuLi).
3. In the absence of the transition metal catalyst, the organozinc reagents do not react with the alkenyl halides to any appreciable extent.

4. The most widely used ligand is PPh_3, but other achiral and chiral phosphine ligands have been successfully used 5. The various organozinc reagents can be prepared by either direct reaction of the organic halide with zinc metal or activated zinc metal or by transmetallation of the corresponding organolithium or Grignard reagent with a zinc halide (ZnX_2). 6. The use of organozinc reagents allows for a much greater functional group tolerance in both coupling partners than in the Kumada cross-coupling where organolithiums and Grignard reagents are utilized as coupling partners

7. Other advantages of the use of organozincs include: high reactivity, high regio-, and stereoselectivity, wide scope and applicability, few side reactions and almost no toxicity
8. The reaction is mostly used for the coupling of two C(sp^2) carbons but C(sp^2)-C(sp) as well as C(sp^2)-C(sp^3) couplings are well-known
9. Besides organozincs, compounds of Al and Zr can also be utilized.
10. If the organoaluminum and organozirconium derivatives are not sufficiently reactive, they can be transmetallated by the addition of zinc salts, and this protocol is referred to as the double metal catalysis.
11. Of all the various organometals (Al, Zr, B, Sn, Cu, Zn), organozincs are usually the most reactive in Pd-catalyzed cross coupling reactions and do not require the use of additives (e.g., bases as in Suzuki crosscouplings) to boost the reactivity.

Mechanism:

Limitations of Negishi reaction:

Some of the limitations of the Negishi cross-coupling are:

- Propargylzincs do not couple well but homopropargylzincs do.
- Secondary and tertiary alkylzincs may undergo isomerization, but crosscouplings of primary alkyl- and benzylzincs give satisfactory results.
- Due to the high reactivity or organozincs, CO insertion usually does not happen unlike in the case of less reactive organotins. Applications:

Negishi Reaction 47

Negishi Reaction 48

Sonogashira Reaction:

In 1975, K. Sonogashira and co-workers reported that symmetrically substituted alkynes could be prepared under mild conditions by reacting acetylene gas with aryl iodides or vinyl bromides in the presence of catalytic amounts of Pd(PPh$_3$)Cl$_2$ and cuprous iodide (CuI). During the same year the research groups of both R.F. Heck and L. Cassar independently disclosed similar Pd-catalyzed processes, but these were not using copper co-catalysis, and the reaction conditions were harsh. The copper-palladium catalyzed coupling of terminal alkynes with aryl and vinyl halides to give enynes is known as the Sonogashira cross-coupling and can be considered as the catalytic version of the Castro-Stephens coupling.

Mechanism:

The mechanism of the Sonogashira cross-coupling follows the expected oxidative addition-reductive elimination pathway. However, the structure of the catalytically active species and the precise role of the CuI catalyst is unknown. The reaction commences with the generation of a coordinatively unsaturated Pd(0) species from a Pd(II) complex by reduction with the alkyne substrate or with an added phosphine ligand. The Pd(0) then undergoes oxidative addition with the aryl or vinyl halide followed by transmetallation by the copper(I)-acetylide. Reductive elimination affords the coupled product and the regeneration of the catalyst completes the catalytic cycle.

The general features of the reaction are:

1. The coupling can usually be conducted at or slightly above room temperature, and this is a major advantage

over the forcing conditions required for the alternative Castro-Stephens coupling.

2. The handling of the shock-sensitive/explosive copper acetylides is avoided by the use of a catalytic amounts of copper(I) salt. 3. The copper(I) salt can be the commercially available CuI or CuBr and are usually applied in 0.5-5 mol% with respect to the halide or alkyne.

4. The best palladium catalysts are $Pd(PPh_3)_2Cl_2$ or $Pd(PPh_3)_4$.

5. The solvents and the reagents do not need to be rigorously dried. However, a thorough deoxygenation is essential to maintain the activity of the Pd-catalyst.

6. Often the base serves as the solvent but occasionally a co-solvent is used.

7. The reaction works well on both very small and large scale (>100g).

8. The coupling is stereospecific; the stereochemical information of the substrates is preserved in the products. 9. The order of reactivity for the aryl and vinyl halides is I ≈ OTf > Br >> Cl.

10. The difference between the reaction rates of iodides and bromides allows selective coupling with the iodides in the presence of bromides.

11. Almost all functional groups are tolerated on the aromatic and vinyl halide substrates. However, alkynes with conjugated electron-withdrawing groups (R_2=CO_2Me) give Michael addition products and propargylic substrates with electron-withdrawing groups (R_2= CH_2CO_2Me or NH_2) tend to rearrange to allenes under the reaction conditions.

12. The exceptional functional group tolerance of the process makes it feasible to use this coupling for complex substrates in the late stages of a total synthesis.

Limitations:

The coupling of sp^2-C halides with sp-C metal derivatives is also possible by using other reactions such as the Negishi-, Stille-, Suzuki-, and Kumada cross-couplings. In terms of functional group tolerance, the Negishi cross-coupling is the best alternative to the Sonogashira reaction.

There are certain limitations on the Sonogashira coupling:

- Aryl halides and bulky substrates that are not very reactive require higher reaction temperature; and
- At high temperatures terminal akynes undergo side reactions

Applications:

Sonogashira Reaction 51

SOC-Unit-IV: Modern Synthetic Methods: Name Reactions

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