Recent Examples of Divergent Catalysis in Organic Reactions: Unexpected Findings or Rational Design?

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Abstract : The term ‘divergent catalysis’ describes different catalytic chemical reactions that occur with the same substrates (reactants) under controllable conditions, especially using different catalysts. Various substrates were found to work with versatile reactivity under different catalytic conditions, resulting in the formation of different products. However, the examples of rationally designed divergent catalysis are still few. This review is focused on the achievements of divergent catalysis with the simplest substrates in the past decades. It includes divergent catalysis of one-component and two-component reactions with the same and simple reagents, ranging from carbon-carbon-forming pinacol coupling, benzoin condensation, Ullmann coupling, C-H homocoupling or activation, ring-closing metathesis, cyclization, Stetter reaction, Baylis-Hillman reaction, Friedel-Crafts reaction, C-H Heck coupling, 1,2-additon reaction and Michael addition, to the carbon-heteroatom bond-forming C-N cross coupling, hydroamination reaction, aza-Michael reaction, C-H oxidative amination, acetalization, and esterification.

Keywords: Divergent catalysis, homogeneous catalysis, organic reaction, carbon-carbon bond, carbon-heteroatom bond.

1. INTRODUCTION

In the past several decades, a wide variety of transition metal-based complexes or organic molecules were identified as efficient catalysts and promoters in many reactions, including enantioselective transformations, however, the true power and elegant application of catalysis to organic reactions has begun to be realized only in the last three decades. With ever increasing demands for the preparation of new compounds in synthetic chemistry, many divergent reactions occured with same substrates under different conditions. Although the synthetic potential of this phenomenon was largely unappreciated for many years, the discovery and development of different catalyst systems in the divergent reactions with the same simple reactants was inspired by a need in organic synthesis. As a known phenomenon, the divergent catalysis has made the organic synthesis more attracted and interesting. The term ‘divergent catalysis’ describes different catalytic chemical reactions that occur with the same substrates (reactants) under controllable conditions, especially using different catalyst. Various substrates were found to work with versatile reactivity under different catalytic conditions, resulting in the formation of different products. The focus of this review will be the brief summary of representative synthetic examples with divergent catalysis of one-component and two-component with the simplest reactants in the past decades.

2. DIVERGENT CATALYSIS OF ONE-COMPONENT REACTIONS

2.1 Aldehydes: Pinacol Coupling and Benzoin Condensation

The pinacol coupling reaction and the benzoin condensation of aldehydes (**1**) are classic organic reactions, and they are one of the most famous divergent transformations each other for the construction of carbon-carbon bond in organic synthesis. The intermolecular pinacolic coupling of aldehydes to produce 1,2-diol (**2**) can be initiated photochemically, electrochemically, or with a range of metal reducing agents [1]. The introduction of low-valent transition metal and lanthanoid based reducing systems, especially those based on titanium, has provided dramatic advances in efficiency and selectivity. It is now possible to select appropriate conditions for efficient coupling of all types of carbonyl compounds, often with high chemo-, regio- and stereo-selectivity [2]. In recent years, various transition metal complexes derived from Ce, Ti, U, Sm, Cr, V, and Nb, have been used to catalyze pinacol coupling reaction with high yield and stereoselectivity [3]. Comparably, the benzoin reaction of aldehydes has been recognized as one of the promising methods for preparing a variety of α-hydroxyl ketones (**3**) since 1903 [4]. Generally, benzoins are generated by the action of sodium cyanide or potassium cyanide on aromatic aldehydes in aqueous ethanol *via* cyanohydrin intermediate. It has shown subsequently that functional thiazolium salts could also catalyze the benzoin reaction of aldehydes in impressive results [5]. The above reaction of the same aldehyde results in different product due to different catalytic procedure. Pinacol coupling is propagated by single-electron reduction of the carbonyl group to form a ketyl radical anion, which either undergoes radical-radical coupling, or is further reduced to the corresponding dianion and then nucleophilically attacks a second carbonyl group, leading to pinacol formation. However, it is different in this catalytic cycle for the benzoin condensation of aldehyde that the key intermediate of benzoin condensation in this reversible reaction is nitrile-stabilized carbanion or the carbene (ylide), which derived from deprotonation of the thiazolium salt or imidazolium salt [6].

Similarly to aromatic aldehyde, the 2-formylthiopene (**4**) was easily transformed to benzoin (**6**) [7] or pinacol (**5**) [8] derivatives in the presence of corresponding catalysts. Interestingly, Mori *et al.* found a novel procedure for the preparation of thiophene derivatives (**7**) *via* the catalytic homo-coupling at C-H bond except the above two compounds took place, when $PdCl_2(PhCN)_2$ was used as catalyst in the presence of AgF or $AgOCOCH_3$ under mild conditions. The AgF played a markedly different role from homocoupling [9].

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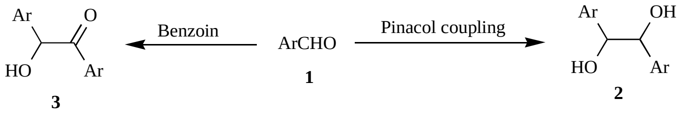
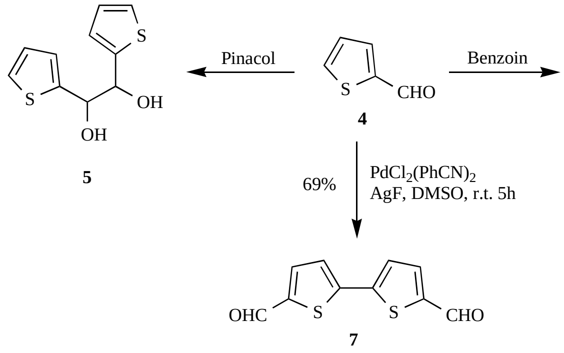


Scheme 1.

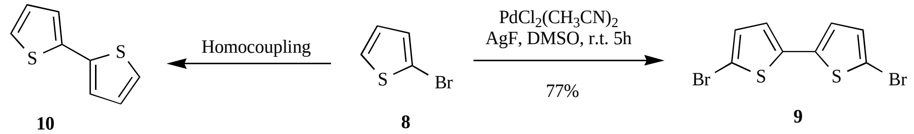


Scheme 2.

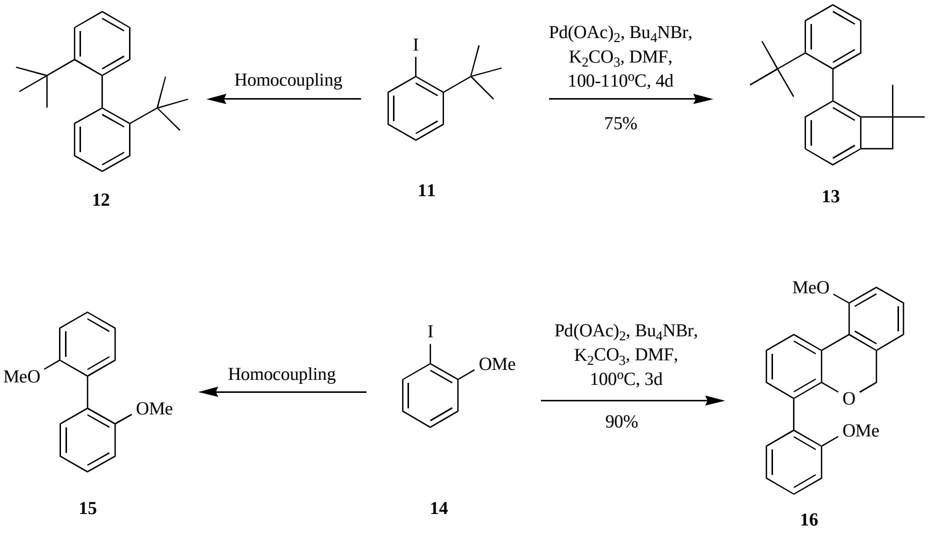
2.2 Aromatic Halides: Homo Coupling and C-H Activation

The aromatic halides belong to an important class of organic intermediates that are used as precursors of organometallic compounds applied in the manufacturing of a number of natural and bio-active substances. The homocoupling of aromatic halides, named as Ullmann reaction, has long been employed by chemists to generate a C-C bond between two aromatic nuclei [10]. Since the first discovery of Kende Which Ni(0) generated in situ was efficient for the homocoupling of aryl bromides, many alternatives and improvements to this nickel-catalyzed coupling reaction have been performed [11]. As shown in Scheme **3**, the bi-thiophene (**10**) can be easily obtained by the been homocoupling 2-bromothiphene (Ullmann reaction) [12], however, it would be more straightforward if the carbon-carbon bond formation is achieved directly by functionalization of a C-H bond of thiophene. Fortunately, Mori and coworkers have developed a method for direct synthesis of bromo-substituted bithiophene (**9**) *via* C-H homocoupling using bimetal catalyst, $PdCl_2(PhCN)_2$/AgF [9]. Under the reported conditions, the reaction took place at room temperature within 5h to give the coupling product at the 5-position in excellent yield, and the bromo group did not react in above conditions.

Mechanistically related to those in the intermolecular coupling of 2-bromothiophene, a number of di- or trimerization reactions of aryl and vinyl halides also have been reported. In the reaction of *o-tert-*butyl- and *o*-methoxyiodobenzenes, the aliphatic C-H bonds in the *ortho*-substituents are intramolecularly activated (C-H activation) to furnish di- and trimerized products (**13** and **16**), respectively, with good yields [13]. For example, with 2-iodoanisole (**14**) as substrate, novel benzofuran derivative (**16**) was obtained in high yield *via* the



Scheme 3.



Scheme 4.

key step of palladium-catalyzed C-H activation at methoxy groups.

2.3 Diene or Enynes: Cyclization and Ring-Closing Metathesis

α,ω-Enynes and α,ω-diene have long been recognized as latent functional groups compatible with a number of traditional methods of C-C bond-forming reactions that use different procedures [14]. In this context, two of the most important attributes relevant to divergent catalysis are: the art for developing catalytic processes and the other is, reaction condition modifications in cyclization and ring-closing metathesis. Above reactions are complicated and depend on reaction variables, such as the nature of the catalyst, additives, solvents, and others as well. For the cyclization of α,ω-enynes, electrophilic transition metal complexes or halides MX_n catalyzed the cyclizations of α,ω-enynes **17** to give 1,3-conjugate dienes (**19** or **21**) and 1,4-dienes (**18**) (Scheme **5**) [15]. Thus, palladium complexes $[Pd(L_2)X_2]$ favored the cycloisomerization pathway to produce conjugate diene **19** [16]. A rearrangement that yields metathesis-type products **21** was first found to be catalyzed by palladacyclopentadienes [15]. Subsequently, several electrophilic Ru(II) and Pt(II) complexes were also found to catalyze the formation of dienes of type **21** from enynes **17** [17]. Cationic Ru(II) complexes such as $[CpRu(MeCN)_3]^+PF_6$-catalyzed the cycloisomerization of enynes containing disubstituted alkenes (**17**) to give selectively 1,4-dienes **18** under mild conditions [18]. Another complementary process can be carried out with cationic Rh(I) complexes and an iridium complex, leading to cycloisomerization of enynes containing *cis*-olefins **18** [19]. The cyclization or cyclorearrangement of α,ω-enynes to give bicyclo[4.1.0]heptene derivatives (**20**) was proceeded easily with catalytic amount of $PtCl_4$ at room temperature [20]. If Y is NTs (see Scheme **5**), $PtCl_2$ was another efficient catalyst with good chemoselectivity for the formation of bicyclo[4.1.0]heptene derivatives (or cyclopropane derivative) [20c].

Cyclization of α,ω-Diene has received less attention due to the lack of reactivity compared to the alkynyl bifunctional molecules. To realize such a diene-cyclization, the most extensively studied systems were the intramolecular reductive alkene couplings promoted by low valent titanium or zirconium reagents [21].

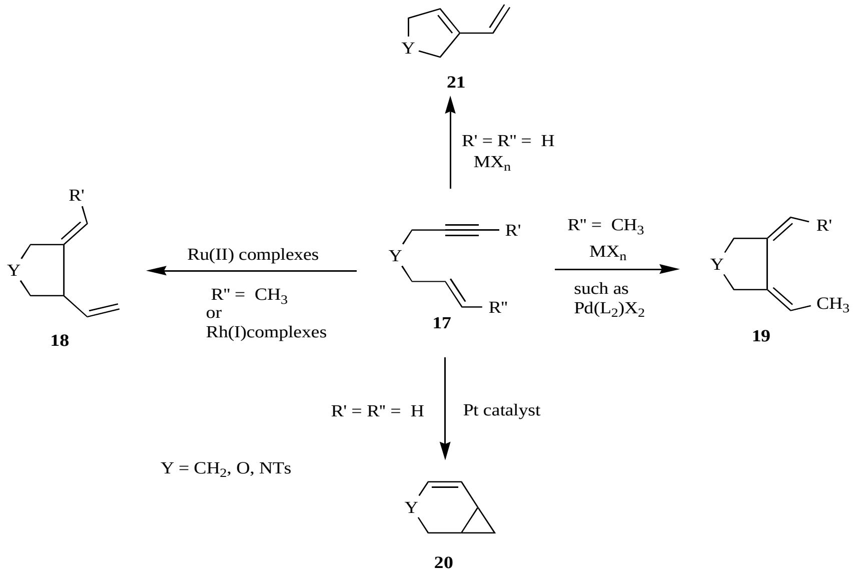
With respect to the goal of cycloisomerization of functional dienes, Widenhoefer *et al.* have shown that cationic palladium phenanthroline complexes catalyzed the selective *exo,exo*-cycloisomerization of 1,6-dienes to form cyclopentenes. And in this transformation of cycloisomerization, a number of highly selective late transition metal-catalyzed diene cycloisomerization protocols have been reported, including the conversion of 1,6-dienes to methylenecyclopentanes (**24**) catalyzed by ruthenium and nickel complexes and the $PdCl_2(CH_3CN)_2$ [22]. Closely related, a combination of a catalytic amount of Ni-phosphine complex and triethylaluminium or chlorodiethylaluminium was able to selectively cyclize a number of 1,7-heptadienes to methylidene(methyl) cyclopentanes (**25**) and cyclopentenes even in cases where the dienes were prone to deallylation [23].

The most useful divergent reaction of α,ω-diene or α,ω-enynes was a famous ring-closing metathesis (RCM), which has been established as a powerful and generally applicable method for construction of carbocycles [24]. Different Grubbs catalysts, such as well-defined ruthenium vinylidene complexes bearing *N*-heterocyclic carbene or phosphane ligands, are highly active in ring-closing metathesis (RCM) of α,ω-diene or α,ω-enynes. Here are given some representative active catalysts in the ring-closing metathesis (RCM) of α,ω-diene in Scheme **7** [25].

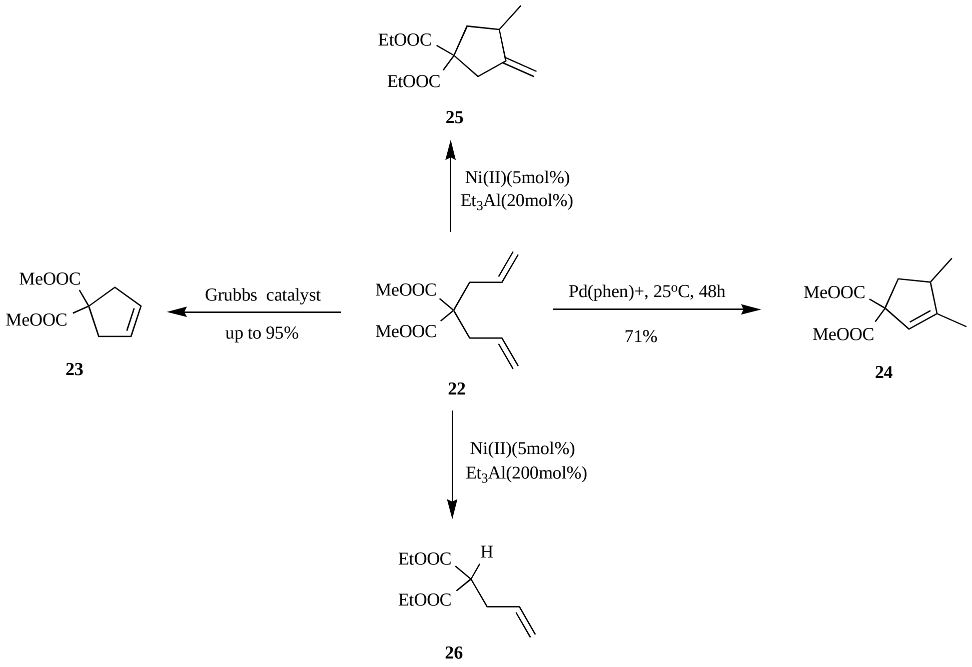
2.4 Other Examples of Intramolecular Divergent Catalysis

In 2004, Trost *et al.* found that Pd(0)-catalyzed cyclization of compound **27** produced different products under different conditions. The eight-membered ring product (**28**) was obtained using $Pd(OAc)_2$-PPh_3-DBU catalyst system wherein the primary alcohol served as the nucleophile. In contrast, the chemoselectivity was completely switched to form the tetrahydrofuran (**29**) in 99% yield with addition of Et_3B [26].

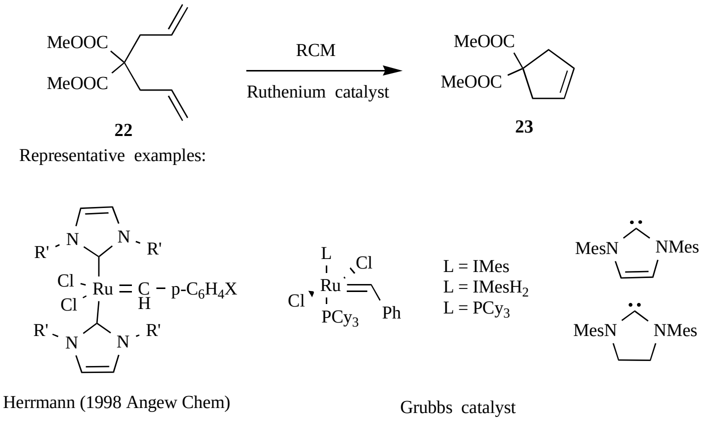
During the course of investigating the development of catalytic reactions involving ruthenium vinylidene intermediates, a novel divergence of reactivity was discovered by Trost *et al.* [27]. A catalytic system composed of $CpRu[(p\text{-}CH_3OC_6H_4)_3P]_2Cl$ and excess



Scheme 5.

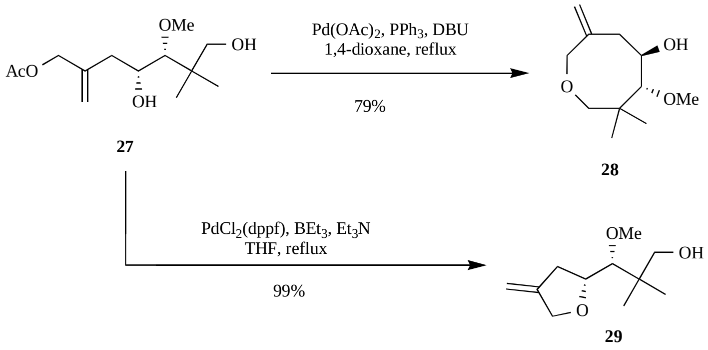


Scheme 6.

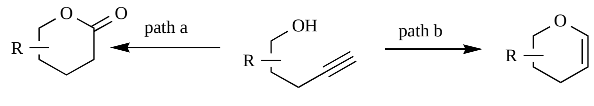


Scheme 7.

(p-CH_3O-$C_6H_4)_3P$ directs the reaction toward the oxidative cyclization to form δ-lactones in good yields (path a) (**32**). Significantly, a simple switch of catalyst to CpRu-[(p-$FC_6H_4)_3P]_2Cl$ redirects the reaction to a cycloisomerization to form dihydropyrans (**31**) in good yields (path b). In the Ru(II)-catalyzed transformation of homopropargylic alcohols, a ligand possessing suitable electronic properties to facilitate formation of the pivotal intermediate **I** is needed. If the electron is rich enough, it can promote protonation at carbon to form the oxacarbene complex **II** leading to lactone. On the other hand, if the electron is less rich, ligand exchange to form an anionic complex **III** may occur and allows simple protonation of the C-bound ligand to liberate the dihydropyran.

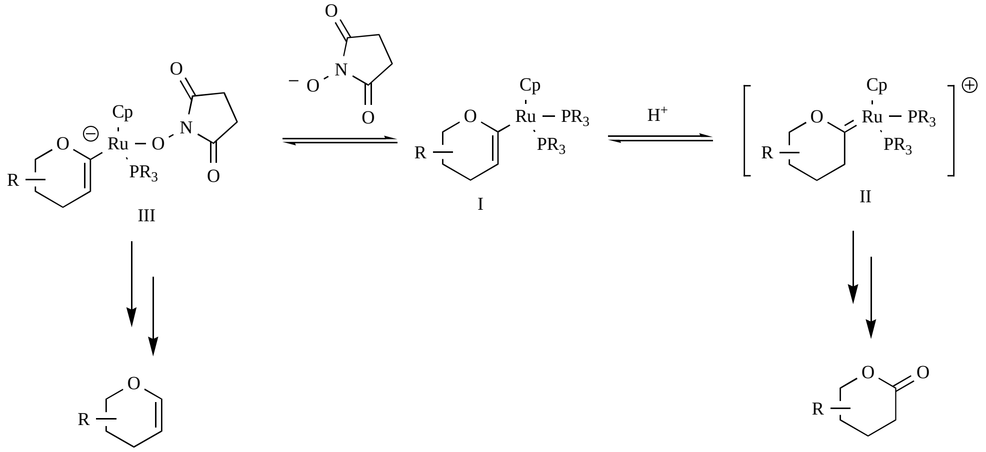


Scheme 8. Divergence on Pd(0)-catalyzed cyclization reaction.



32 **30** **31**

Scheme 9.



Scheme 10. Possible intermediates in the divergent reactions of homopropargylic alcohols.

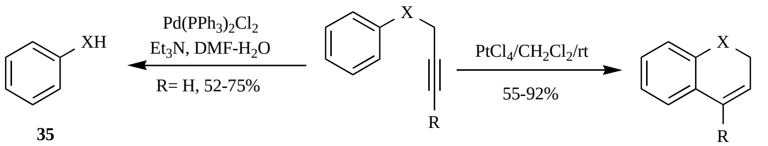
Recently, Sames *et al.* reported that $PtCl_4$ promoted cyclization of similar propargyl ethers or propargyl amines substrates (**33**) to give compound **34** in good yields *via* intramolecular electrophilic hydroarylation. This is in sharp contrast to the result disclosed for another divergent reaction where Pal *et al.* have demonstrated the depropargylation reaction proceeded well in the presence of $(PPh_3)_2PdCl_2$ and $(PPh_3)_4Pd$ [28]. In fact, the authors also found that no desired product **34** was formed using palladium catalyst. It appears that $PtCl_4$ possesses a special blend of reactivity and selectivity, as it selectively activated the triple bond toward one class of nucleophiles. It is precisely the rate differences of these competing processes that ultimately determine the distribution of products that are obtained [29].

3. DIVERGENT CATALYSIS OF TWO-COMPONENT REACTIONS

The classic arylation procedure of phenols with aryl halides (or named C-O cross coupling reactions) usually requires stoichiometric amounts of copper powder or copper salts, and a large amount of the phenols and high temperatures as a results of the poor nucleophilicity of the phenoxide and the low reactivity of aryl halides involved [30]. From the mid of the 90s until now, palladium based approaches set out to conquer these synthetic problems, mainly pushed by numerous contributions of Buchwald and Hartwig. Bulky biaryl phosphine ligands facilitated Pd-catalyzed C-O coupling reactions of aryl halides with phenols (**38** and **42)** [31]. Interestingly, another new synthetic procedure *via* aromatic *ortho* aromatization for preparation of biaryls was also possible, there have been published some findings focused on the aromatic aromatization of phenols with aryl halides to impart novel phenol derivatives. Phenol and other substituted phenols can be arylated with aryl halides around the oxygen to selectively give 2-biphenyl-6-terphenylphenols (**39**, **43**, **46**) in the presence of palladium or rhodium catalyst [32].

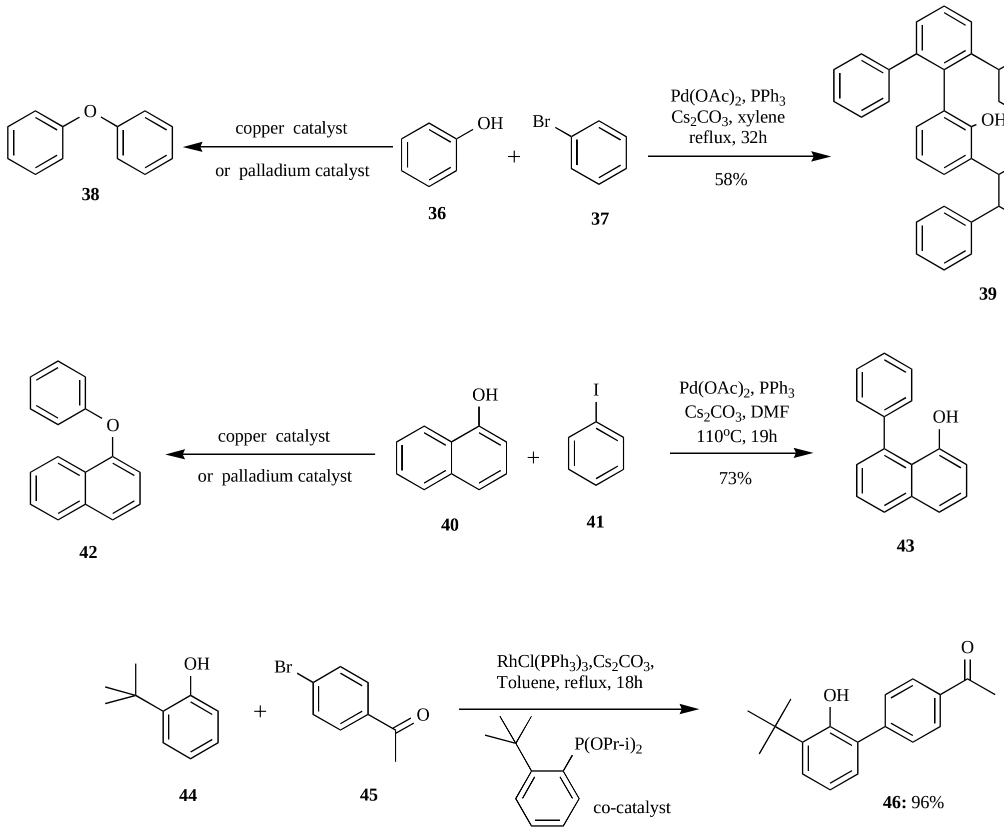
In the Suzuki-type cross coupling reactions, if the substrates have several functional groups, divergent reactions might occurred. Rault observed that palladium catalyzed Suzuki reaction of 2-furyl boronic acids with 3-iodoindazole gave a C-C coupling product (**48**) in 65% yield after 6h in refluxing DME [33]. With similar substrate, the different C-N coupling reaction occurred in the presence of copper catalyst. The general conditions for this C-N coupling reaction involved the addition of 2.0 equivalents of base (pyridine) and 1.5 equivalent of cupric acetate and 4Å molecular sieves [34].

Kanemasa *et al.* found the conjugate addition of aldoximes to α,β-unsaturated carbonyl compounds (aza-Michael addition) resulted in the formation of a new nitrone (**51**) in the presence of Lewis acid catalyst, such as ZnI_2/BF_3-OEt, $TiCl_2(i\text{-}OPr)_2$, $Zn(ClO_4)_2$, etc. [35]. However, when Lewis base was used as a catalyst, the oxygen of oximes becomes a nucleophilic center in this Michael reaction. For example, Bhuniya reported that phosphine was an efficient catalyst for the Michael addition of aldoximes with α,β-unsaturated carbonyl compounds [36].

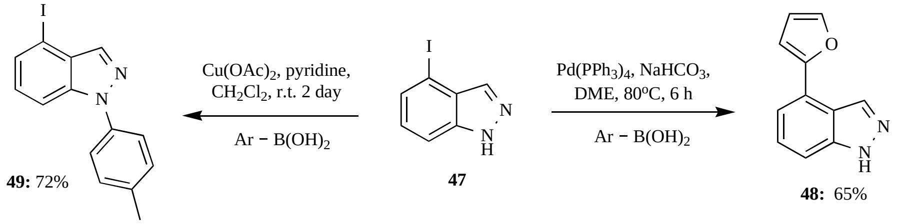


35 **33,** X = NH, O **34**

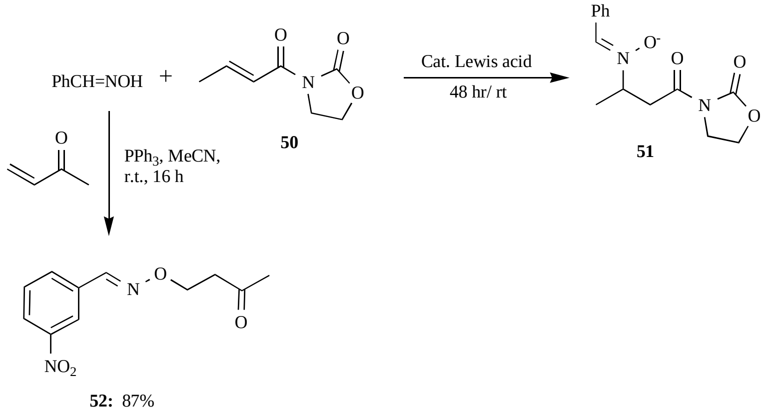
Scheme 11.



Scheme 12.

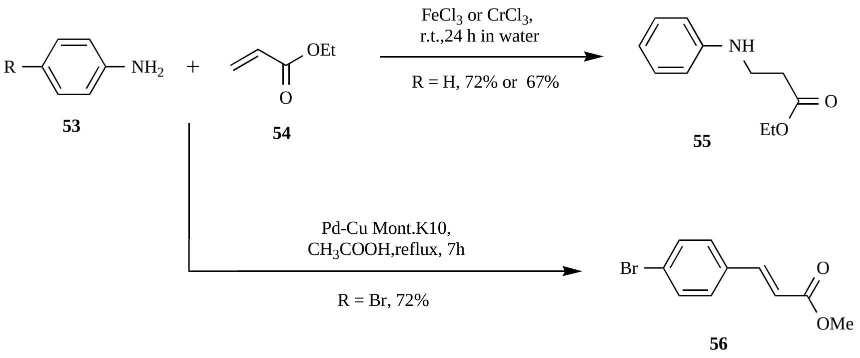


Scheme 13.

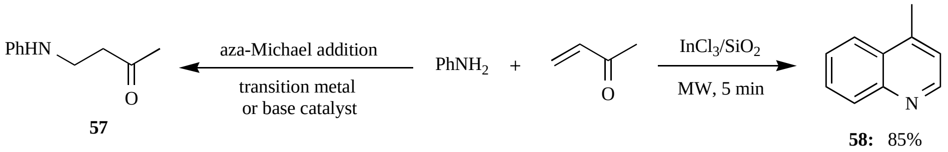


Scheme 14.

Anilines (aromatic amines) as a nitrogen nucleophile in the aza-Michael reaction were known in the literature [37]. For example, we have reported that aza-Michael reaction of aniline activated olefin to produce alkylated amine derivatives (**55**), facilitated by transition-metal based Lewis acid catalyst in water [38]. Marked differently, Rigo *et al.* developed the direct use of anilines in Heck reaction for the preparation of methyl cinnamates. By using the modified Pd-Cu exchanged montmorillonite K10 clay as catalyst, good yields in methyl cinnamates (**56**) were obtained from aromatic amines without the formation of by-products (63-76%) [38].



Scheme 15.



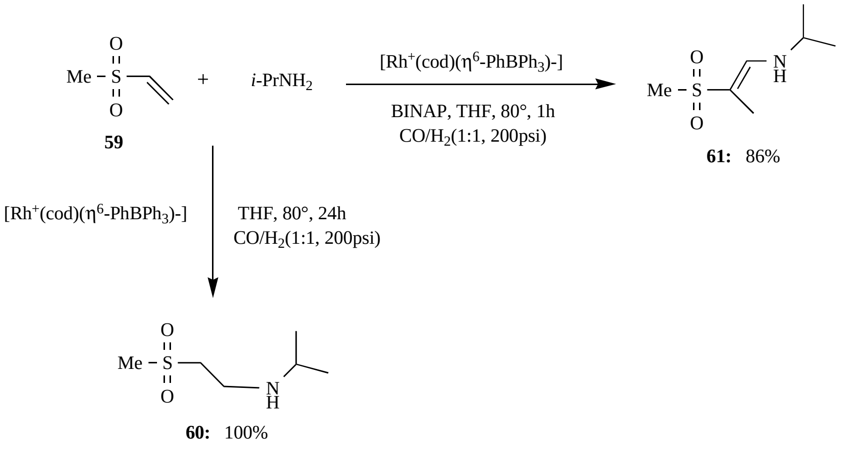
Scheme 16.

It should be noted that Heck reaction of substituted aromatics is one of the most frequently studied reactions in organic synthesis, whcih is generally performed with aryl halides using palladium catalyst.

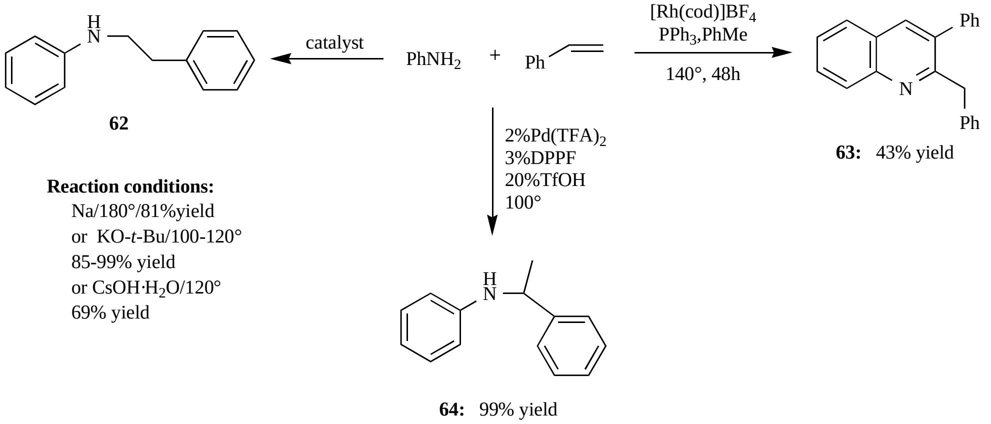
Closely related to the general transition metal salt catalyzed aza-Michael reactions of enones with aromatic amines, silica gel impregnated with $InCl_3$ was found to be an efficient catalyst for the one-pot coupling reaction of anilines with alkyl enones to give quinolines **58**. Presumably, this divergent process involves aza-Michael addition of the aniline to enone followed by subsequent cyclization and aromatization under the catalysis of $InCl_3/SiO_2$ [39].

Another novel divergent procedure for amines and activated olefin is hydroaminovinylation, which was developed by Alper *et al.* [40]. The novel one-pot hydroaminovinylation reaction was achieved from the synthesis of sulfonated and phosphonated enamines, using the zwitterionic rhodium complex ($[Rh^+(cod)(\eta^6\text{-}PhBPh_3)^-]$ together with a chelating phosphine ligands (BINAP) as the catalyst. Other chelating phosphine ligands, such as 1,4-bis(diphenylphosphine) butane (dppb) and 1,2-bis(diphenylphosphino)ethane (dppe) also afforded sulfonated enamine (**61**) in good yields. In contrast, aza-Michael type addition product was the principal product using bis (diphenylphosphino) methane (dppm) as the ligand. The reason for this change in behavior is not clear. And in the absence of phosphine ligand, aza-Michael adduct (**60**) was formed exclusively (100% yield).

Hydroamination is the formal direct addition of an N-H bond to C-C multiple bonds. In general, the direct addition of amines to olefins can lead to two regioisomeric amines, the Marknovnikov and the *anti*-Marknovnikov products. The Marknovnikov product is usually favored in the presence of Brønsted or Lewis acid catalyst in the case of aliphatic as well as most of the aromatic olefins because of the higher stability of the intermediate carbocation [41]. For example, *ortho*-alkylation of anilines (hydroamination reaction of Styrene and anilines) occurred using catalytic amounts of $[Rh(cod)_2]BF_4/4PPh_3$ and HBF_4 [42]. One highly promising approach to the hydroamination of olefins, reported by Hartwig and coworkers, is the addition of anilines to aryl olefin catalyzed by a combination of $Pd(TFA)_2$, a chelating bisphosphine such as DPPF, and a triflate ion source such as TfOH. This system exhibited high Markovnikov selectivity and high yields [43]. The direct *anti*-Markovnikov transformation of unfunctionalized olefins to amines is difficult in the absence of catalyst, particularly to industrially important linear *anti*-



Scheme 17.

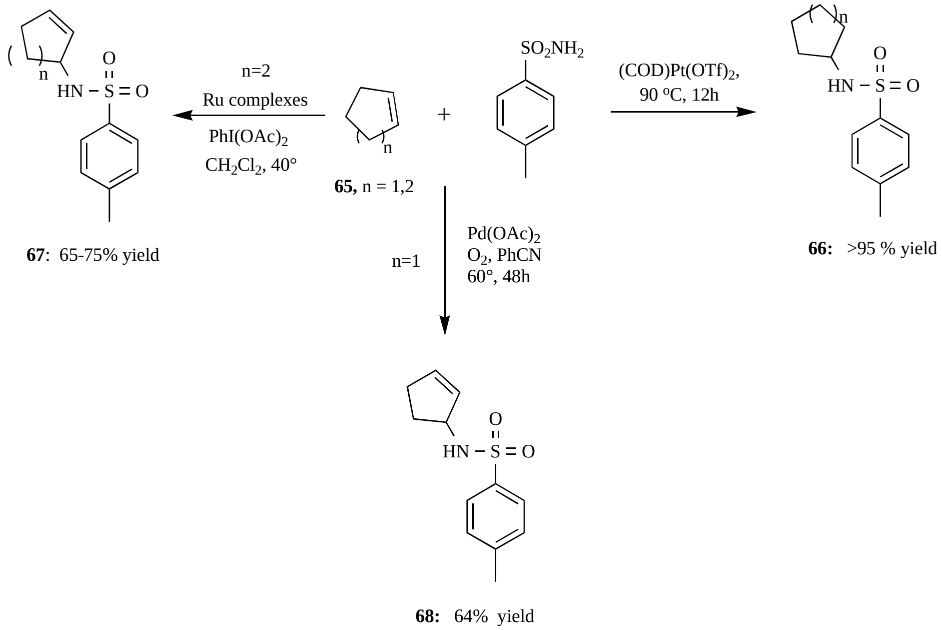


Scheme 18.

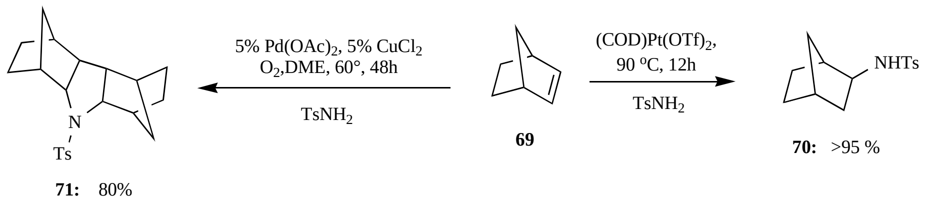
Markovnikov amines. Catalysis is obligatory for this conversion and hence the functionalization of olefin with regioselectivity is viewed as one of the major challenges of catalysis [44]. The aryl olefins reacted readily with sufficient nucleophilic amines in the presence of alkali metal catalysts forming *anti*-Markovnikov 1-amino-2-arylethanes. The pre-catalysts include metallic sodium, and CsOH, which can be formed *in situ* from BuLi, Na$_2$Np, or KO-*t*-Bu [45]. Recently, thenew concept of immobilizing organometallic complexes in a thin film of supported ionic liquids was utilized to synthesis novel bi-functional catalysts combining soft Lewis acidic and strong Brønsted acidic functions, which showed exceptional catalytic activity for the addition of aniline to styrene, providing the Markovnikov product under kinetically controlled conditions and mainly the anti-Markovnikov product in the thermodynamic regime [46].

As shown in Scheme **18**, different from the product of hydroamination, the substituted quinolines derivatives (**63**) were obtained in the presence of cationic rhodium complexes, such as [Rh(cod)$_2$]BF$_4$ and PPh$_3$. Mechanistic investigations strongly supported a new Domino reaction, which is considered as the key reaction step of the regioselective oxidative amination of styrene [47].

During the past decades, the hydroamination reaction has seen exponential growth in terms of all the three essential components, that is, olefin, amines, and catalyst. A variety of NH-containing amines, such as sulfonamides and weakly basic amines, couple with a number of olefins have been used to provide a wide range of amino-molecules. Recently, Bell and Tilly developed a Platinum-based catalyst for the hydroamination of olefins with sulfonamides and weakly basic anilines. With *p*-toluenesulfonamide as a test substrate and (cod)Pt(OTf)$_2$ as catalyst, it was found that cyclopentene was hydroaminated in yields in excess of 95% under experimental conditions [48] given in Scheme **19** (**66**). Comparable divergent procedure of the same substrate, *p*-toluenesulfonamide with olefin, is the amidation reaction which was catalyzed by ruthenium cyclic amines or bipyridine complexes, such as [Ru(Me$_3$tacn) (CF$_3$CO$_2$)·H$_2$O] (Me$_3$tacn = *N,N'N''*-trimethyl-1,4,7-triazacyclononane), and was developed by Che and coworkers in 2000. Recently, the Ruthenium- and Manganese-5,10,15,tris(tolyl)-20-(4-hydroxyphenyl)porphyrins was covalently attached to Merrifield' resin by Wu and Yu *et al.*, the polymer-supported metalloporphyrins efficiently catalyzed the amidation of cyclic olefins in moderate to good yields under mild conditions [49]. A remarkably general method for aerobic oxidative amination of cyclopentene was achieved by Stahl *et al.* in



Scheme 19.



Scheme 20.

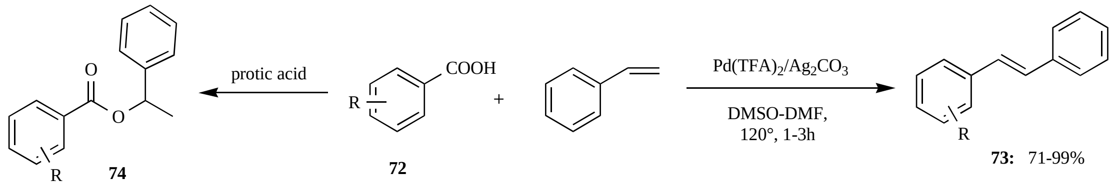
2005 [50]. They found the oxidative amination of cyclic olefins, cyclooctene, and cyclopentene, yield allylic amine products (**67-68**) rather than the corresponding amide or enamine (imine) derivatives with $Pd(OAc)_2$ as the catalyst. Another $Pd(OAc)_2$-$CuCl_2$ cocatalyzed amidation of norbornene with $TsNH_2$ was divergently compared with the known hydroamination reaction, to form the C2-symmetric pyrrolidine (**71**) in good yield (Scheme **20**).

Similarly, the addition of carboxylic acids to olefins (esterification of olefin with carboxylic acids) is known to be catalyzed quite well by strong protic acid, strong acidic ion-exchange resins, and solid acids [51]. Recently, the cationic ruthenium catalyst $(Cp^*RuCl_2)_2$/AgOTf/phosphine catalyzed addition of carboxylic acid to olefins was also developed. The reaction gave the corresponding esters (**74**) in good to excellent yields [52]. Unexpectedly, the Myers and coworkers have developed a novel reaction between carboxylic acids and olefins in accordance to the development of novel palladium catalyst systems. The process can be viewed as proceeding by an initial Ar-S_E reaction, involving ipso attack of an electrophilic Pd(II) intermediate on an arene carboxylate to form an arylpalladium(II) species with loss of carbondioxide. This intermediate was then proposed to react with an olefinic substrate by steps common to the Heck coupling process (**73**) [53]. Two critical reaction parameters were identified by Myers *et al.,* whose modification led to a more general and efficient method. First, the use of the additive silver carbonate, in lieu of K_2CO_3 and $Cu(TFA)_2$, was found to dramatically improve the efficiency of decarboxylation reaction. The second critical parameter proved to be the reaction solvent. The optimum reaction medium was found to have 5% DMSO in DMF.

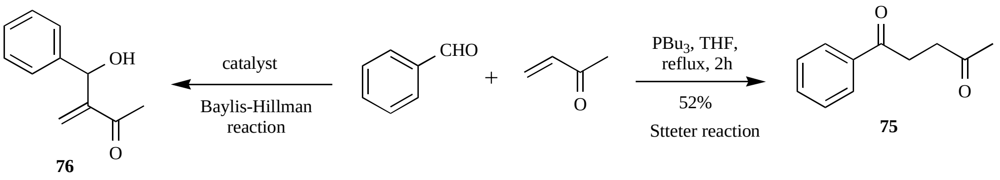
The divergent reactions between aldehydes and α,β-unsaturated carbonyl compounds are Stetter reaction and the Baylis-Hillman reaction. Both are important key reactions in synthetic organic chemistry for the formation of new C-C bonds [54]. For example, in Scheme **22**, different catalysts used in the reactions of benzaldehyde and methyl vinyl ketone resulted in different products *via* divergent procedure [55]. Weak and nucleophilic base, such as thiazolium and thiazolium salts (nucleophilic carbenes) were effective catalysts in Stetter reaction, and tributylphosphine was also reported to be a good catalyst in this reaction [54b].

Baylis-Hillman reaction, now has become one of the most useful and popular carbon-carbon bond-forming procedure with enormous synthetic utility, promise, and potential. During the past decades, various catalysts were developed in the Baylis-Hillman, especially strong organic base, such as DABCO, DMAP, or DBU, which have been proven to be better catalysts in Baylis-Hillman reactions [54d].

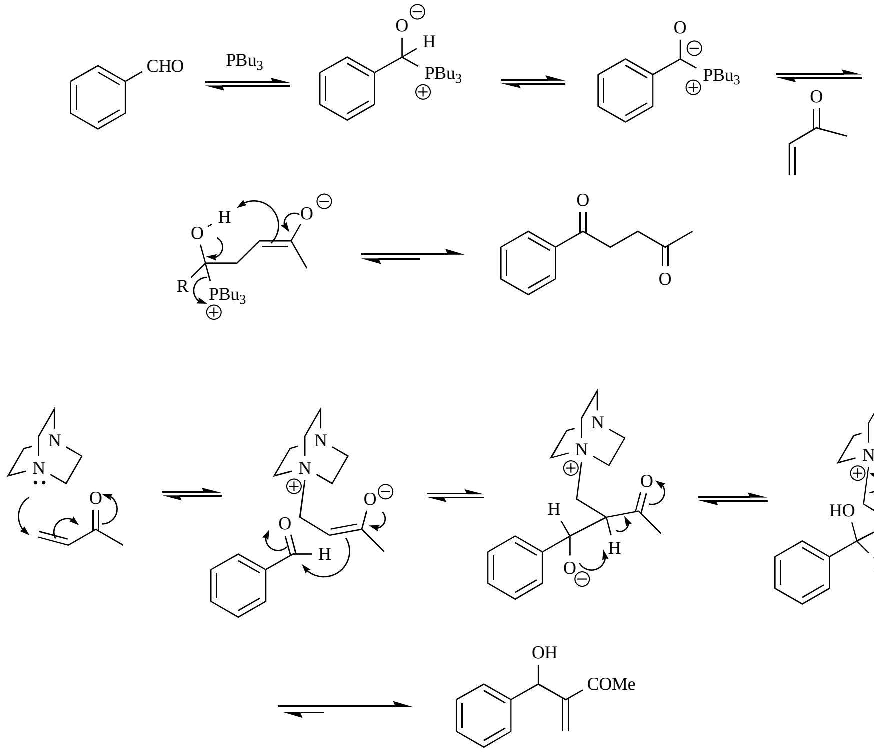
The mechanism of Stetter reaction was shown in Scheme **23** using tributylphosphine-catalyzed reaction of benzaldehyde and methyl vinyl ketone as a model. The first step, tributylphosphine attacked benzaldehyde to generate the tautomeric betaine-ylide species, which was added to methyl vinyl ketone in a 1,4-fashion to give the product after elimination of PBu_3 [56]. Different from the action of catalyst in Stetter reaction, the mechanism of Baylis-Hillman reaction was believed to proceed through the Michael-initial addition-elimination sequence. The first step in this catalytic cycle involves the Michael-type nucleophilic addition of the tertiary amine to the activated olefin (methyl vinyl ketone) to produce a zwitterionic enolate, which makes a nucleophilic attack onto the aldehyde in an aldol fashion to generate zwitterions intermediate. Subsequent proton migration and release of the catalyst provide the desired multifunctional molecules. Based on different mechanisms of Stetter reaction and Baylis-Hillman reaction, chemists can design suitable catalysts or reaction conditions rationally. The recent examples of phosphine and imidazole-catalyzed Baylis-Hillman reactions are representative in this topic [57]. Although phosphine or imidazole is a weak Lewis base and not suitable for promoting the Baylis-Hillman reaction, the presence of Lewis acid (such as BINOL) could restrain the interaction with aldehyde and promote the Baylis-Hillman reaction successfully [57].



Scheme 21.



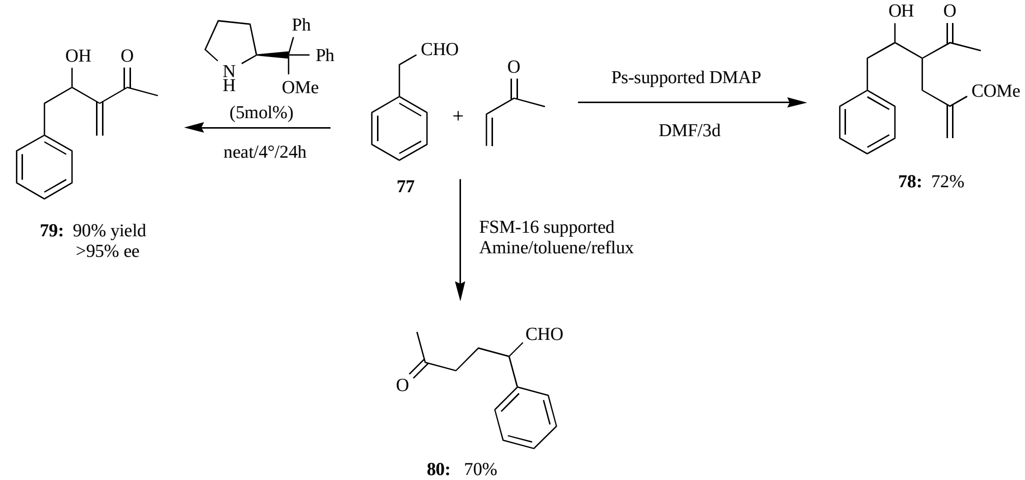
Scheme 22.



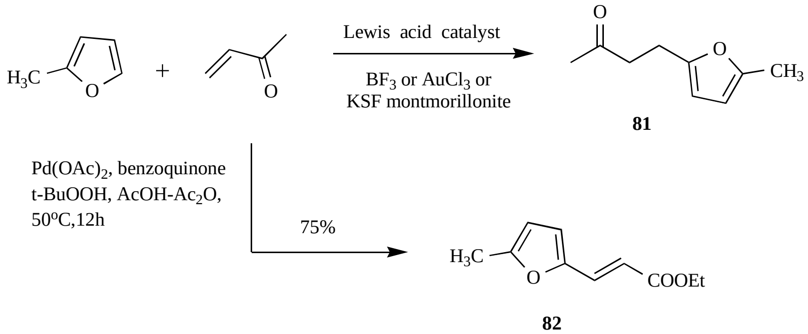
Scheme 23.

Except for Baylis-Hillman reaction and Stetter reaction, there are two different possible transformations for α-CH_2-containing aldehydes and enones [58]. As shown in Scheme **24**, direct 1,4-conjugate addition of naked aldehydes (**77**) to vinylketones was catalyzed effectively by *N*-methyl-3-aminopropylated FSM-16 mesoporous silica, which was regarded as a novel divergent catalysis for an another practical C-C bond formation [59]. When Corma and coworkers studied the heterogeneous Baylis-Hillman reaction of α-CH_2-containing aldehydes and MVK using a polystyrene-bound 4-(*N*-benzyl-*N*-methylamino)pyridine as reusable catalyst, they found a new product (**78**) was obtained, which was produced by the domino Baylis-Hillman-Michael addition reaction [60].

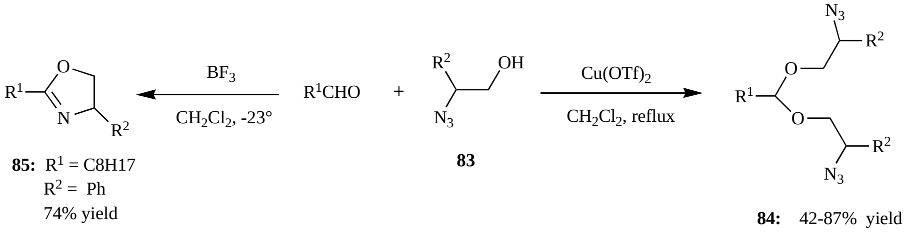
The addition of aromatic substrates to electron-deficient alkenes, such as enones, which in many respects may be considered as a Friedel-Crafts type alkylation or Michael-type Friedel-Crafts reaction, is a key reaction in synthetic organic chemistry for the formation of new single C-C bonds [61]. The Michael-type Friedel-Crafts reaction of furan is a widely investigated process because it is involved in the synthesis of a class of bioactive furan derivatives (**81**). During past years a variety of Lewis acid catalysts, such as BF_3, $AuCl_3$, KSF montmorillonite, have been applied in this reaction. Surprisingly, the oxidative coupling of furan with α,β-unsaturated carbonyl compounds resulted in novel aromatic α,β-unsaturated carbonyl compounds (**82**). Fujiwara *et al.* reported a new catalyst system, catalytic amounts of palladium acetate and benzoquinone (BQ) with *tert*-butyl hydroperoxide as the oxidant. It was especially effective for the coupling of furan with α,β-unsaturated carbonyl compounds [62].



Scheme 24.



Scheme 25.

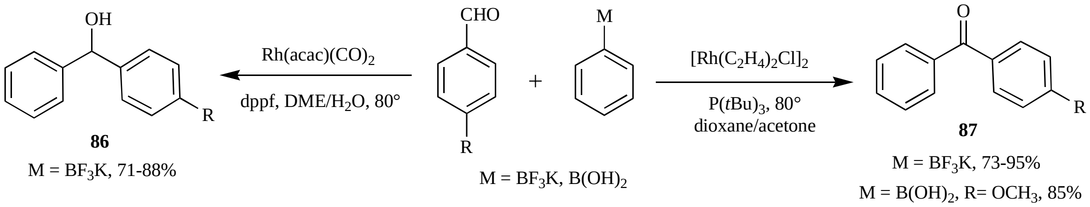


Scheme 26.

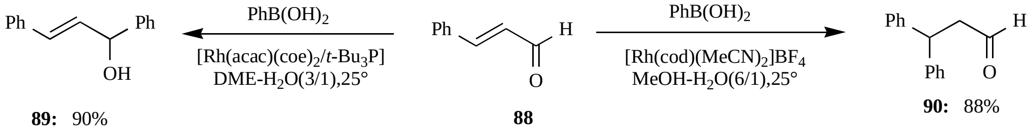
Although most of the Lewis acids catalyzed the reaction of 2-azidoethanols and aliphatic aldehydes to afford the reported 2-oxazolin products (Boyer reaction), Zhao and coworkers found that $Cu(OTf)_2$ behaved quite differently. Instead of the normal 2-oxazoline, this reaction gave acetal as the product (**84**) [63]. As shown in Scheme **26**, when 5mol% of $Cu(OTf)_2$ was used as the catalyst, an acetal was formed in moderate to good yield, whereas, when 2-aryl-2-azidoethanol was used with BF_3 as the catalyst, formation of 3-oxazoline (**85**) was observed.

For developing a novel approach to access ketones from aldehydes, Darses and Genet have found the first catalytic cross-coupling reaction of organoboronic acids with arylaldehydes to afford diaryl ketones (**87**) *via* a Heck-type mechanism [64]. This result was very surprising compared with the known 1,2-addition of organometallic reagents to aldehydes, affording diarylcarbinols (**86**) [65]. In fact, it appeared that the presence of acetone as co-solvent was crucial for the process, diarylcarbinols being obtained in quantitative yields in its absence. Previous results [66] also indicated the 1,2-additon reaction was accelerated by the bidentate phosphine (dppf) or bulky and electron-donating trialkylphosphines (t-Bu_3P). Interestingly, the t-Bu_3P complex of rhodium yields 1,2-addition product in the preference to the conjugate 1,4-addtion (**90**), which was demonstrated in the addition of phenylboronic acid to cinnamaldehyde. The t-Bu_3P complex, did not catalyze the conjugate 1,4-addition but produced a 1,2-addition product (**89**) in excellent yield (90%) with good chemoselectivity [67].

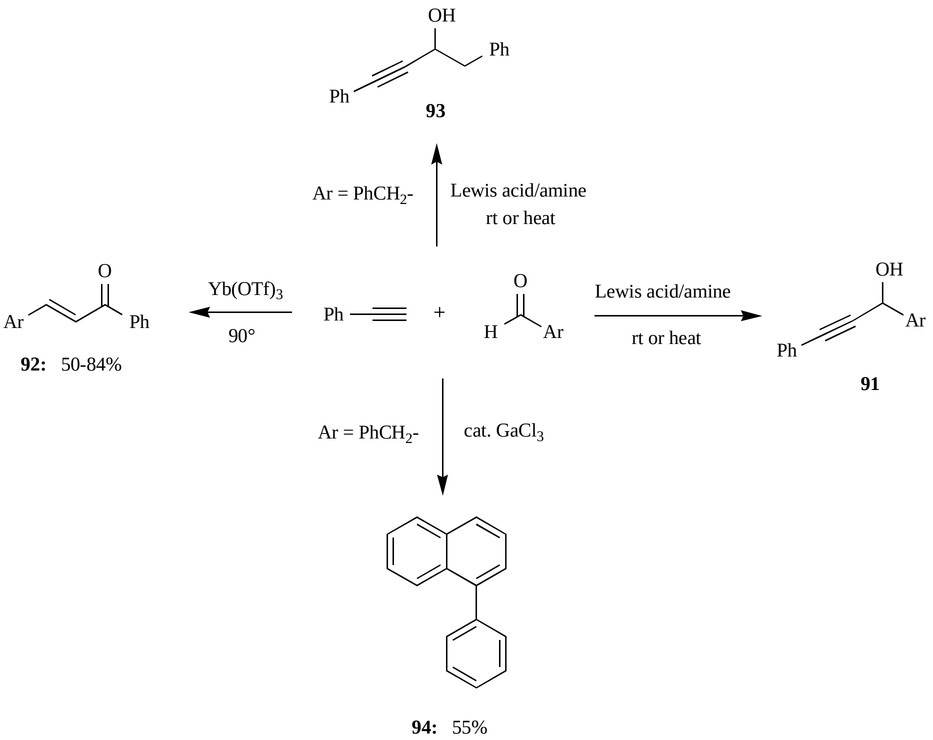
The addition of terminal acetylenes to aldehydes affords direct access propargyl alcohols (for example, **91** and **93**) which are of great importance in synthetic chemistry, as they generate versatile building blocks that enjoy wide application in chemical synthesis. The existing catalytic methods for carrying out these coupling reactions (or alkynylation of aldehydes) required the use of stoichiometric quantities of metallated acetylenes, which have taken the formation of boryl acetylides or in situ generated Zn-alkynilides [68]. In the past decades, the addition of alkynes to aldehydes resulting in the formation of propargyl alcohols had been extensively studied. Considerable progress has been made in the alkynylation of aldehydes using a Lewis acid in combination with a base. For example, $SnCl_4$, GaI_3, $Sn(OTf)_2$, $Zn(OTf)_2$, and $InBr_3$ [69]. However, the novel reaction with divergent catalysis between alkynes and aldehydes to give conjugated enones or other products has received less attention. The most effective catalyst in this transformation was shown to be $Ni(COD)_2/P(n\text{-}C_8H_{17})_3$, SbF_5, $In(OTf)_3$, $GaCl_3$,



Scheme 27.



Scheme 28.



Scheme 29.

Yb(OTf)$_3$, and FeX$_3$, give α,β-unsaturated enones (**92**) in moderate to excellent yields [70]. We also reported a novel method for the coupling reaction of arylalkynes and aldehydes leading to the synthesis enones using acidic ionic liquids catalyst system [71]. In accordance with previous results, the addition of Lewis acid or Brönsted acid to acetylene is the crucial step to form different products compare to the propargyl alcohols of C-H addition products. It should be pointed that in the investigation of GaCl$_3$-catalyzed coupling reaction between 1-phenyl-1-propyne and phenylacetaldehyde in CH$_2$Cl$_2$, surprisingly, neither expected enone product (**92**) or propargyl alcohol (**93**) was obtained. Instead, a new product (**94**) was obtained. The unique cyclization reactions of aromatic alkynes and phenyl acetaldehydes catalyzed by gallium trichloride produce naphthalene derivatives (**94**) in moderate yields [72]. Mechanistic investigations supported gallium trichloride hydrolyzes in air to generate the active catalyst gallium hydroxide dichloride, which catalyzes the electrophilic addition of aldehydes-Lewis acid complex to C2 of the 1-phenylalkyne. Intramolecular electrophilic attack of the formed alkynyl cation to aromatic system followed by elimination of a proton generates the unique cyclization products (**94**).

4. CONCLUSIONS

It is remarkable that despite the diversity of reactions with the simplest substrates discussed in this review, ranging from carbon-carbon-forming pinacol coupling, benzoin condensation, Ullmann coupling, C-H homocoupling or activation, ring-closing metathesis, cyclization, Stetter reaction, Baylis-Hillman reaction, Friedel-Crafts reaction, C-H Heck coupling, 1,2-additon reaction, and Michael addition, etc. to the carbon-heteroatom bond-forming C-N cross coupling, hydroamination reaction, aza-Michael reaction, C-H oxidative amination, acetalization, and esterification, we are only beginning to understand the basic factor that control the procedure of divergent reaction with the same substrates, and the rational design of catalyst systems or reaction conditions remain in most cases a dream. Development and implementation of catalyst screening techniques, and the mechanism or mechanistic study of organic reaction will allow for exciting advancement into a larger realm of diversity space, allowing for the discovery of unpredicted and unexpected divergent catalysis. While there is much to be done to understand and explain the mechanistic approach of divergent catalysis so that it would ultimately leads to the construction of more complex molecules under the controlling of chemical reactivity of the simple and same substrates freely, it is very reasonable to expect more and more examples of divergent catalysis to be disclosed in the near future.

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