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## Mini review

## Metal Catalyzed Defunctionalization Reactions

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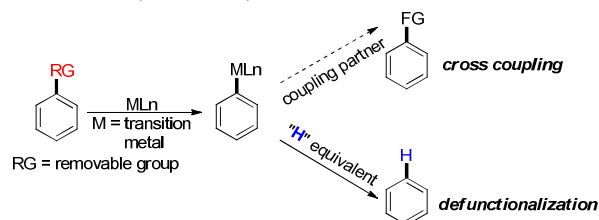
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Defunctionalization has direct impact in the synthesis of value added product (e.g. biomass degradation). In synthetic chemistry it enables the functional group to act as a transient directing group. In this mini review, we have described the chronological development of metal assisted defunctionalization reactions from stoichiometric to catalytic stage with their application in synthetic organic chemistry. The proposed catalytic cycles of the transformations have been described to make this review comprehensible.

## 1. Introduction

Defunctionalization reactions have become an indispensable aspect in the advancement of chemical synthesis despite affording less functionalized entity from a more functionalized organic material. The key challenge of the defunctionalization reaction lies in the high bond dissociation energy of C–X (X= carbon or heteroatom) bond. Metal mediated methods emerged as savior in addressing this issue as metal destabilizes the C–X bond through single or two electron transfer processes. Moreover, the remarkable electrophilicity of the metal allows them to form the metal carbanion complex which is the key intermediate of defunctionalization as well as the cross coupling reactions. In case of defunctionalization reaction the metal carbanion intermediate is intercepted by a hydrogen equivalent to result the required defunctionalized product whereas, in cross coupling reaction other coupling partner comes into the role. Therefore, defunctionalization has an eminent significance in the functionalization reaction in terms of mechanistic point of view (Scheme 1).

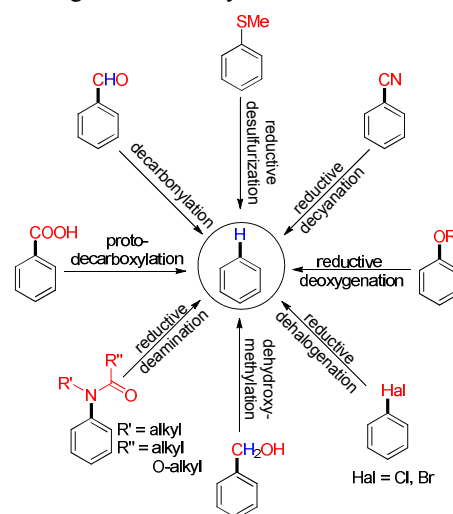


**Scheme 1** Schematic diagram of transition metal mediated defunctionalization

Besides, defunctionalization reactions have also direct impact in synthetic organic chemistry, facilitating functional groups to be utilized temporarily in a particular synthetic transformation.<sup>1, 2</sup> In some diverse aspects, defunctionalized substrates are considered as more useful

than their functionalized form e.g. preparation of useful material through biomass degradation,<sup>3-9</sup> converting environmentally hazardous entities to relatively harmless forms through desulfurization<sup>10, 11</sup> or dechlorination<sup>12-16</sup> etc.

In this mini review, we have highlighted the chronological development of metal assisted defunctionalization reactions from stoichiometric to catalytic stage with their application in synthetic organic chemistry.



**Scheme 2** Scope of defunctionalization

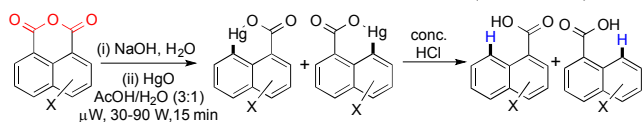
## 2. Decarboxylation

Decarboxylation of aromatic carboxylic acids has great significance in the up-gradation of coal derived substrates, as aromatic carboxylic acids are the major air oxidized products of coal.<sup>17</sup> In synthetic chemistry, carboxylic moiety serves as directing group through metal-chelation assisted C–H activation or electronically assisted aromatic functionalization. Therefore, an efficient decarboxylation of aromatic carboxylic acid can make the carboxylic group as traceless directing group in aromatic C–H functionalization. A number of metal mediated/catalyzed methods are known for effective protodecarboxylation of carboxylic acid which occurred through a metal assisted anionic or radical decarboxylation.

## 2.1 Mercury mediated decarboxylation

Mercury mediated decarboxylation of aromatic carboxylates are known since long ago. In 1901, Pesci first reported the mercury mediated decarboxylation of aromatic anhydride to produce aromatic mono acid.<sup>18</sup> Since then a

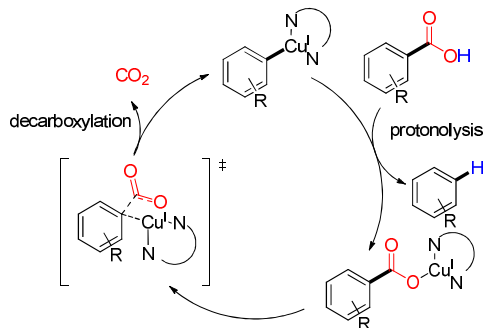
number of groups have worked on mercury as a decarboxylating agent.<sup>19-23</sup> Unfortunately, all of these methods are limited to high reaction temperature, use of large amount of toxic metal or long reaction time. Recently in 2006 Moseley and coworkers have reported mercury mediated decarboxylation of naphthoic anhydride with faster reaction rate in microwave condition (Scheme 3).<sup>24</sup>



**Scheme 3** Mercury mediated decarboxylation of naphthoic anhydride in microwave condition

## 2.2 Copper salt as decarboxylating agent

After mercury, copper was the second metal which was exploited for effective protodecarboxylation. The first copper mediated decarboxylation was performed in 1930 by Shepard and coworkers using stoichiometric copper-quinoline combination.<sup>25</sup> They successfully decarboxylated halogenated furan carboxylic acid at very high temperature. Later, decarboxylation method was further developed by Nilsson<sup>26</sup>, Cohen<sup>27, 28</sup> and Shepard<sup>29</sup> groups for activated aromatic carboxylic acid. According to their study it was observed that N-heterocyclic amine type solvent/ ligand is essential for stabilization of copper-decarboxylate intermediate. In 2007, Goossen and coworkers for the first time reported copper catalyzed decarboxylation of deactivated carboxylic acids with the help of bis-N-chelating ligand at 170 °C.<sup>30</sup> Decarboxylation of deactivated acids was achieved by introducing a sterically hindered ligand like 4, 7-diphenyl-1,10-phenanthroline. A quick version of protodecarboxylation protocol was also developed by Goossen group under microwave condition with the catalytic amount of Cu/phenanthroline.<sup>31</sup> According to the mechanistic study and DFT calculation, it was proposed that, copper directly inserts into the aryl carboxylate bond and then hydrolytic cleavage of the copper-carbon bond results the protodecarboxylated product (Scheme 4).<sup>30</sup>

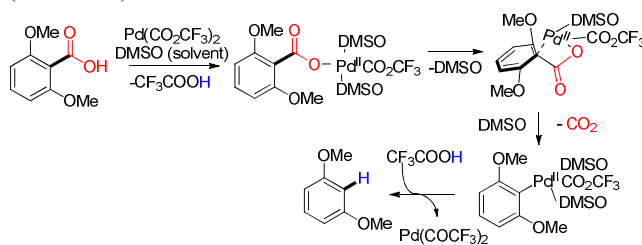


**Scheme 4** Catalytic cycle of the decarboxylation in copper-phenanthroline system

## 2.3 Palladium catalyzed decarboxylation

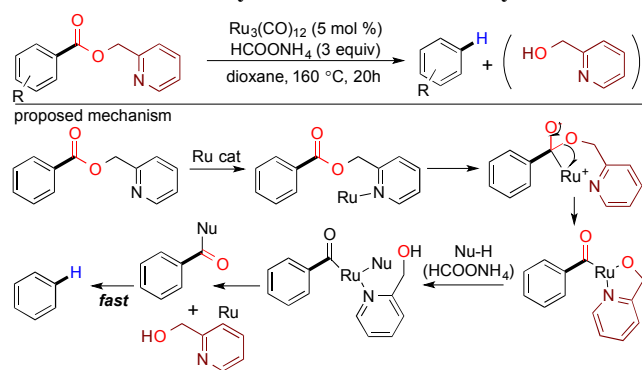
Schleyer successfully achieved decarboxylation in gas phase at very high temperature with nickel (180 °C) and palladium (330 °C) catalyst under hydrogen gas atmosphere.<sup>32</sup> Later in 2004 Matsubara and coworkers

reported a palladium/ charcoal catalyzed hydrothermal condition for decarbonylation and decarboxylation.<sup>33</sup> A high deuterium containing entity was ensued from completely non-deuterated substrate due to H-D exchange under their hydrothermal reaction condition using deuterium oxide as solvent.<sup>33</sup> In 2007 Kozolowski reported a palladium catalyzed method for decarboxylation of electron rich bis-ortho-substituted aromatic carboxylic acid using trifluoroacetic acid as proton source.<sup>34</sup> In the reaction mechanism, a four-membered palladium species was proposed as an intermediate prior to the decarboxylation (Scheme 5).<sup>35</sup>



**Scheme 5** Proposed mechanism for palladium catalyzed decarboxylation of bis-ortho-substituted aromatic carboxylic acid

## 2.4 Ruthenium catalyzed directed decarboxylation



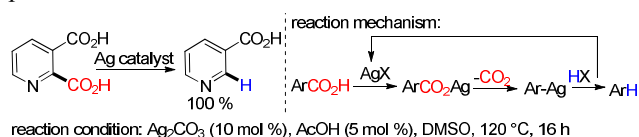
**Scheme 6** Chelation assisted decarboxylation of esters

Murai and coworkers in 2001 demonstrated chelation assisted decarboxylation of esters using  $\text{Ru}_3(\text{CO})_{12}$  catalyst through acyl C–O bond fission (Scheme 6).<sup>36</sup> According to their proposed reaction mechanism, heteroatom containing directing group promotes the metal center for site-selective cleavage of acyl C–O bond through a tetrahedral intermediate followed by a fast decarbonylation yielding the resultant hydrocarbon (Scheme 6).

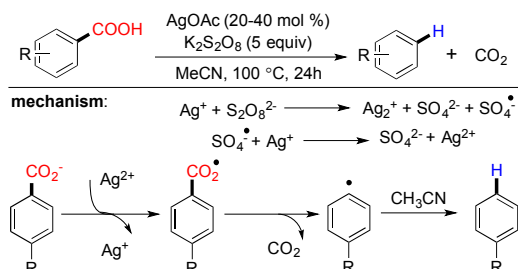
## 2.5 Silver catalyzed decarboxylation

Silver catalyzed protodecarboxylation of heteroaromatic carboxylic acid was explored by Larossa and coworkers in 2009.<sup>37</sup> From their substrate scope study it was observed that  $\alpha$  heteroatom is a prerequisite for decarboxylation (Scheme 7). In 2012 they nicely showed that deuterio-substrate can be prepared through deuterio-decarboxylation of the corresponding carboxylic acid using  $\text{D}_2\text{O}$  as  $\text{D}^+$  source.<sup>38</sup> In the same year, Greaney and coworkers established a new approach of protodecarboxylation under oxidative radical condition using catalytic  $\text{Ag}(\text{I})/\text{K}_2\text{S}_2\text{O}_8$  (Scheme 8).<sup>39</sup> Variety of

benzoic acid derivatives with electron rich and electron donating functional groups were decarboxylated successfully. According to their hypotheses, first Ag(I) is *in situ* oxidized to Ag(II) in presence of  $K_2S_2O_8$ , later carboxylate anion is oxidized to carboxylated radical by *in situ* generated Ag(II). After that, a successful decarboxylation resulted aryl radical from the carboxylate radical. Finally, aryl radical abstracted a hydrogen radical from acetonitrile to deliver the protodecarboxylated product.



**Scheme 7** Silver catalyzed decarboxylation of hetero-aromatic carboxylic acid

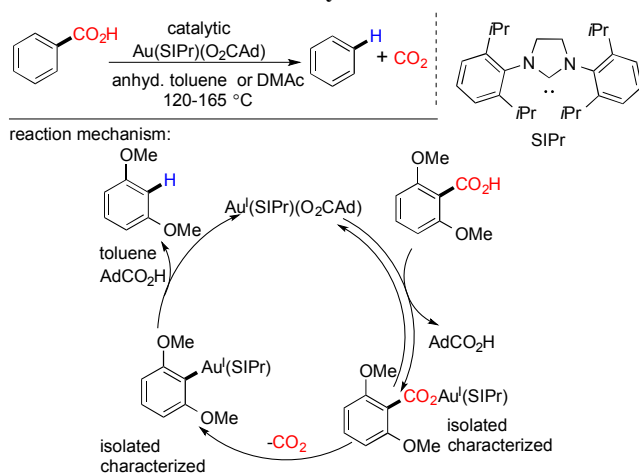


**Scheme 8** Silver catalyzed protodecarboxylation under oxidative radical condition

## 2.6 Rhodium catalyzed decarboxylation

A rhodium catalyzed protodecarboxylation was demonstrated by Zhao and coworkers using  $(cod)Rh(\mu-OH)_2$  as catalyst in 2010.<sup>40</sup> Unfortunately, their substrate scope was limited to *ortho*-substituted arenecarboxylic acid. Non-activated benzoic acid and *ortho*-methoxy benzoic acid remained unreactive under their optimized condition.

## 2.7 Gold mediated decarboxylation



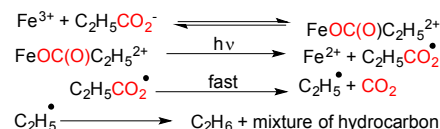
**Scheme 9** Gold catalyzed protodecarboxylation

In 2011, Nolan and coworkers first explored gold mediated decarboxylation of aromatic carboxylic acids with N-heterocyclic carbene-gold(I) complex.<sup>41</sup> After their initial

breakthrough, in 2013 they reported the first gold catalyzed proto-decarboxylation of aromatic carboxylic acids.<sup>42</sup> Both electron-rich and electron-poor benzoic acid derivatives were successfully employed for decarboxylation. According to the reaction mechanism, proto decarboxylation takes place through gold carboxylate and gold aryl intermediate (Scheme 9).

## 2.8 Decarboxylation in photochemical condition

In photochemical condition decarboxylation of aliphatic acid was achieved by Bakac and coworkers.<sup>43</sup> In presence of  $Fe^{3+}$  ion, aqueous solution of propionic acid was converted to a mixture of hydrocarbons and  $CO_2$  in near UV photolysis using anaerobic condition (Scheme 10).



**Scheme 10** Decarboxylation in photochemical condition

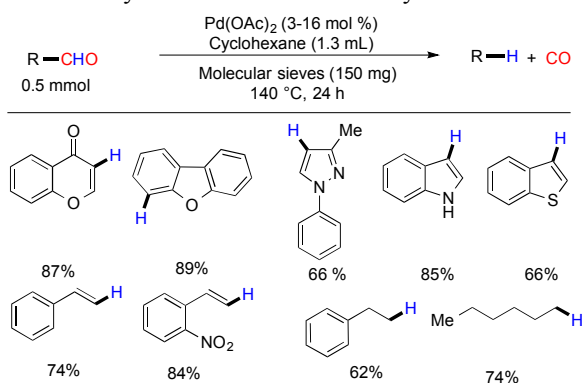
## 3. Decarbonylation

Transition metal catalyzed decarbonylation of aldehyde has a great importance in synthetic as well as biological chemistry. In biological system, cyanobacterial aldehyde decarbonylase enzyme causes decarbonylation of fatty aldehyde resulting the alkane or alkene and formic acid.<sup>44</sup> The synthetic alternative methods of such reaction can solve the energy crisis producing low boiling fuel. In terms of reaction pathway, the decarbonylation of aldehyde in synthetic chemistry differs from the nature as it emits carbon monoxide instead of formic acid. On the other hand, aldehyde group possess worthwhile features like ortho directing ability in aromatic systems, increasing electrophilicity of dienophile for facile addition reaction, in-situ carbon monoxide generator etc. In this regard, decarbonylation of aldehyde has potential significance in organic synthesis to utilize the aldehyde group temporarily in a particular transformation.

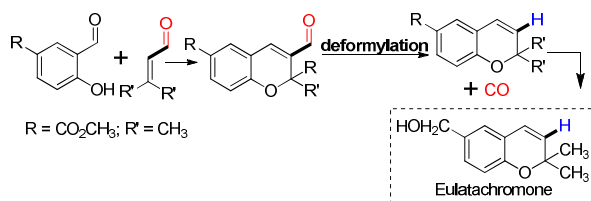
### 3.1 Palladium as decarbonylating agent

The first decarbonylation of aldehyde was done in 1960 by Wilt with heterogeneous Pd/charcoal at high temperature (more than 180 °C).<sup>45</sup> Few years later, in 1965 Tsuji and coworkers reported the palladium catalyzed decarbonylation of acylchloride and aldehyde, but this protocol is limited for high temperature requirement.<sup>46</sup> Recently, Maiti and coworkers demonstrated palladium acetate catalyzed efficient, mild and ligand free protocol for decarbonylation of aldehydes.<sup>47</sup> The reaction exhibited tolerance against a wide range of functional groups such as cyano, ester, keto, nitro and acid. Heterocyclic aldehyde with single heteroatom and two heteroatoms gave good yields of the corresponding decarbonylated products. It was observed that there was no trace of  $\beta$ -H eliminated side product formed against simple alkyl aldehydes (Scheme 11). In the microwave conditions, decarbonylation of the aldehyde was also reported by the same group.<sup>48</sup> A biologically active molecule, eulatacomone was synthesized by utilizing the

deformylation strategy judiciously (Scheme 12).<sup>48</sup> The same strategy also used by Barse group, where they used rhodium catalyzed method for decarbonylation.<sup>49</sup>

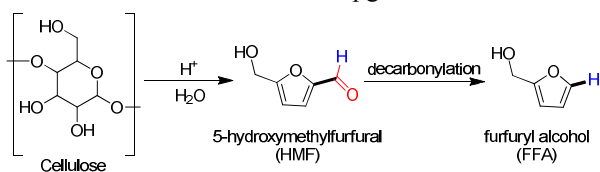


5 **Scheme 11** Palladium acetate catalyzed decarbonylation



**Scheme 12** Synthesis of Eulatachromone

In 2013, Fu and co-workers reported a heterogeneous decarbonylation of biomass derived feedstocks, 5-hydroxymethylfurfural (HMF) to furfuryl alcohol (FFA) with catalytic palladium nanoparticles under mild conditions (Scheme 13). Furfuryl alcohol has great significance in the preparation of furan based light fuels.<sup>4</sup> Later, in 2015 Thomas Rauchfuss and co-workers demonstrated Pd/C catalyzed decarbonylation of furfural derivative with the intention to upgrade cellulosic biomass.<sup>5</sup>

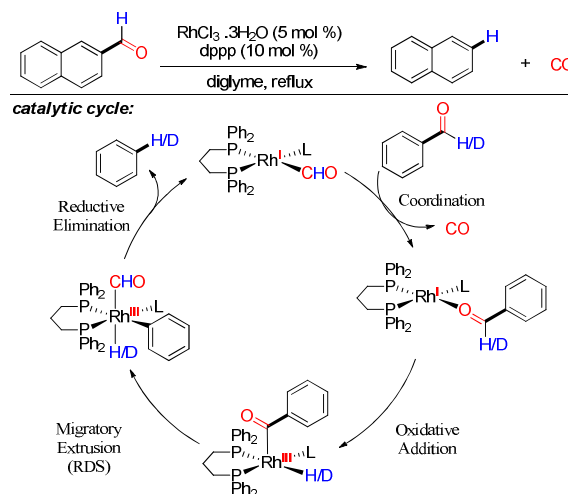


**Scheme 13** Furfuryl alcohol synthesis from cellulose by decarbonylation of aldehyde

### 3.2 Rhodium as decarbonylating agent

Rhodium is most abundantly used in decarbonylation reaction compared to other metals. First report on rhodium as decarbonylating agent was communicated in 1965 by Tsuji and Ohno, using stoichiometric amount of Wilkinson's catalyst.<sup>50</sup> Later, catalytic decarbonylation of aldehyde was reported by Doughty and Pignolet in 1978 with  $\text{Rh}(\text{dpp})\text{Cl}$  as catalyst.<sup>51</sup> In 1992 O'Connor demonstrated a rhodium catalyzed efficient method for decarbonylation of primary aldehyde, where diphenylphosphoryl azide acted as carbon monoxide trap.<sup>52</sup> Crabtree and coworkers in 1999 discovered yet another efficient way of decarbonylation of primary and aryl aldehydes under mild condition using catalytic  $[\text{Rh}(\text{CO})(\text{triphos})][\text{SbF}_6]$  complex.<sup>53</sup> In 2006, Madsen group reported a method for deformylation of aldehyde

with the combination of  $\text{RhCl}_3 \cdot 3\text{H}_2\text{O}$  and phosphine ligand with wide substrate scope.<sup>54</sup>



**Scheme 14** Catalytic cycle for rhodium catalyzed decarbonylation of aldehyde

Following experimental and computational studies they proposed a catalytic cycle for decarbonylation of aldehyde, where the aldehyde first oxidatively adds to the metal center.<sup>55</sup> In the next step, migratory extrusion occurs and then reductive elimination results the defunctionalized product. Subsequently, substrate binds with the metal center by oxygen donor site, replacing the carbon monoxide and repeats the catalytic cycle. Migratory extrusion step is established as the turnover limiting step (Scheme 14). Madsen also applied the decarbonylation strategy to the unprotected aldose using catalytic amount of  $\text{Rh}(\text{dppp})_2\text{Cl}$  and resulted in alditol which is one carbon lesser than the starting material.<sup>6</sup> This one step degradation of aldose through decarbonylation reaction has great significance in glycochemistry. Recently, Kappe and coworkers engineered a continuous-flow protocol for decarbonylation of aldehyde using catalytic amount of  $\text{Rh}(\text{OAc})_2/\text{dppe}$ .<sup>56</sup>

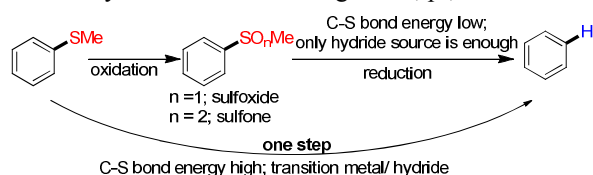
### 3.3 Decarbonylation using other metals

After palladium and rhodium, ruthenium also proved as capable for decarbonylation reaction. In 1980, Dolphin and co-workers discovered a ruthenium-porphyrin based complex for stoichiometric decarbonylation.<sup>57</sup> An iridium catalyzed decarbonylation method was reported by Tsuji and coworkers in 2008, wherein a variety of functional groups were tolerated under their mild reaction condition.<sup>58</sup>

## 4. Desulfurization

Reductive desulfurization is one of the key step in manufacturing nonpolluting fuel from the natural resources. In view of synthetic organic chemistry, the reductive desulfurization has great significance owing to temporary advantages coming from the sulfur moiety on its neighbor atoms.<sup>59</sup> There are two strategies for reductive desulfurization, one is direct desulfurization of thio ether and the other being a two-step process where first thio ether gets oxidized to sulfone or sulfoxide followed by reductive

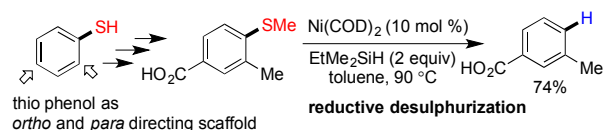
cleavage of sulfur-carbon bond. The former strategy is more challenging owing to higher C–S bond dissociation energy in thio ether compared to that in sulfone. Desulfurization of sulfone moiety has been achieved through simple reduction in presence of hydride source. But, in case of direct desulphurization of thio ether, it requires special condition for activating C–S bond (Scheme 15). A number of transition metal mediated methodologies have been reported for direct desulfurization of thio ether. In this review we mainly focused on the desulfurization of (hetero)aromatic thio ether which is occurring through metal catalyzed reductive cleavage of C(sp<sup>2</sup>)-SR bond.



**Scheme 15** Schematic diagram of reductive desulfurization of phenyl methyl thioether

#### 4.1 Nickel as desulfurizing agent.

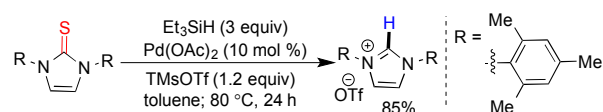
In 1940 Mozimbo and coworkers first reported the desulfurization of thio ether and S-containing amino acids using Raney nickel.<sup>60</sup> After that, several reports have been published on desulfurization using nickel containing reagents like Raney nickel, nickel/borohydride,<sup>61, 62</sup> nickel-containing complex reducing agent (NiCRA).<sup>10</sup> But, all these methods require a high metal/substrate ratio and also render poor chemoselectivity. In 2012, Martin and coworkers demonstrated a general and convenient protocol for cleaving carbon-sulphur bond of aryl methyl thioether with catalytic amount of Ni(COD)<sub>2</sub>.<sup>63</sup> They have also nicely depicted the synthetic applicability of desulfurization reaction where aryl sulfide was used as temporary directing group (Scheme 16).



**Scheme 16** Application of reductive desulfurization

#### 4.2 Palladium as desulfurizing agent

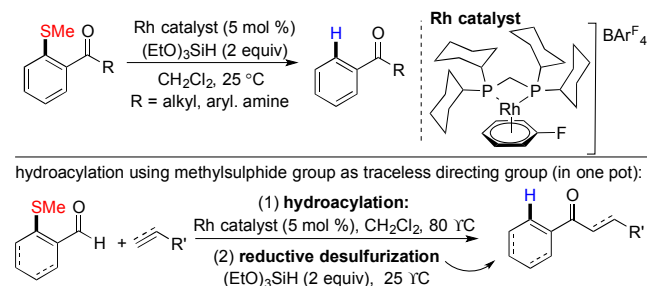
The combination of catalytic palladium/charchol and a hydride source is capable of reductive desulfurization in heterogeneous condition. In 1994, hydrazine-Pd/C was used for catalytic desulfurization of methylthioether of pyridimine derivatives.<sup>64</sup> Later Graham<sup>65</sup> and Nakada<sup>66</sup> independently developed the palladium catalyzed reductive desulfurization of alkyl aryl/heterocyclic thio-ethers using triethyl silane as reducing agent. After their initial report, Nakada and coworkers developed an efficient method for the synthesis of imidazolium salts by the Pd-catalyzed reduction of their corresponding thioureas with triethylsilane and trialkylsilyl triflate (Scheme 17).<sup>67</sup>



**Scheme 17** Imidazolium salts preparation through reductive desulfurization

#### 4.3 Rhodium as desulfurizing agent

Recently in 2013, Willis and co-workers reported a rhodium catalyzed reductive desulfurization of *ortho*-keto aryl methyl sulfide under mild condition. The excellent tolerance of the keto group enabled them to use the methyl sulfide moiety as traceless directing scaffold for hydroacylation of alkanes and alkynes (Scheme 18).<sup>68</sup>



**Scheme 18** Rhodium catalyzed reductive desulfurization of methyl phenyl thio ether

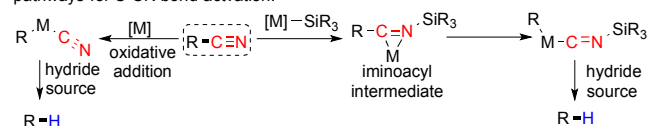
#### 4.3 Other metal mediated desulfurization

Except palladium and nickel mediated reductive desulfurization protocols, Raney copper<sup>69</sup>, zinc/HCl<sup>70</sup>, Red-Al<sup>71, 72</sup>, Al/HgCl<sub>2</sub><sup>73</sup>, Zn/AcOH/Ac<sub>2</sub>O<sup>74</sup> are known. But, all these protocols are inadequate for broader use due to poor chemoselectivity, limited substrate scope, harsh reaction condition, excess metal waste etc.

#### 5. Decyanation:

An efficient methodology for removal of cyano group permits to explore the expedient feature of cyano moiety temporarily in synthesis of complex molecules. Cyano group has been widely used in chelation assisted C–H activation through end on and side on directing fashion.<sup>75-79</sup> Due to its high electron withdrawing ability, it can enhance the α-acidity for desired organic transformation.<sup>80, 81</sup> Despite of the high C–CN bond dissociation energy,<sup>82</sup> decyanation has been achieved with the help of metal mediated reduction. Reductive decyanation with alkali metal is well known but, these processes are limited for harsh reaction conditions. In contrary, transition metal complex/hydride source combination is accepted as celebrated class for their milder and easily accessible reaction condition. From mechanistic point of view, there are two categories of reaction pathway known for transition metal catalyzed C–CN bond cleavage.<sup>83</sup> One of them is the direct insertion of low valent metal in C–CN bond through oxidative addition and the other being silylmetal-assisted carbon cyano bond cleavage through an iminoacyl intermediate (Scheme 19).

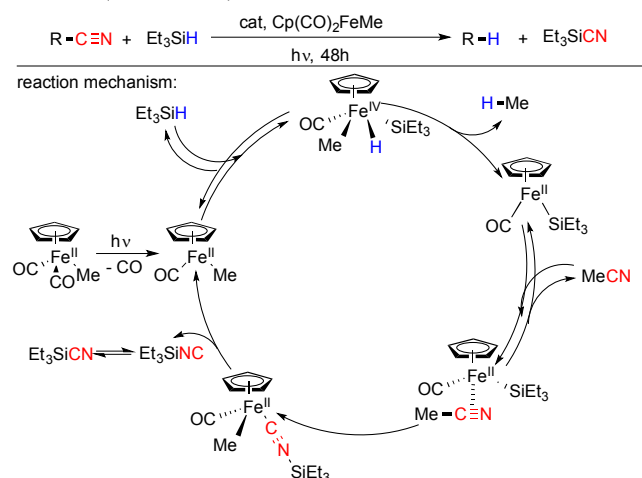
pathways for C–CN bond activation:



**Scheme 19** Decyanation pathways

### 5.1 Iron catalyzed reductive decyanation

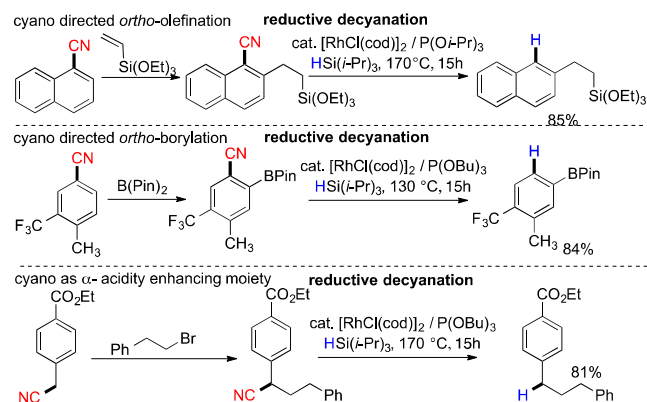
In 2005, Nakazawa and co-workers developed an iron catalyzed C–CN bond cleavage in presence of  $\text{Et}_3\text{SiH}$  promoted by a photochemical pathway.<sup>84</sup> Aliphatic and aromatic nitriles are successfully decyanated in their protocol. According to their proposed mechanistic pathway,  $\text{Cp}(\text{CO})\text{FeMe}$  is generated by photolysis of  $\text{Cp}(\text{CO})_2\text{FeMe}$ , then  $\text{Cp}(\text{CO})\text{FeMe}$  reacts with  $\text{Et}_3\text{SiH}$  resulting in  $\text{Cp}(\text{CO})\text{FeMe}(\text{H})(\text{SiEt}_3)$ . Decyanated species was formed after a successive reductive elimination and yielded active species  $\text{Cp}(\text{CO})\text{Fe}(\text{SiEt}_3)$  which carried the catalytic cycle forward (Scheme 20).<sup>85</sup>



**Scheme 20** Proposed mechanism for  $\text{Cp}(\text{CO})_2\text{FeMe}$  catalyzed reductive decyanation

### 5.2 Rhodium catalyzed reductive decyanation

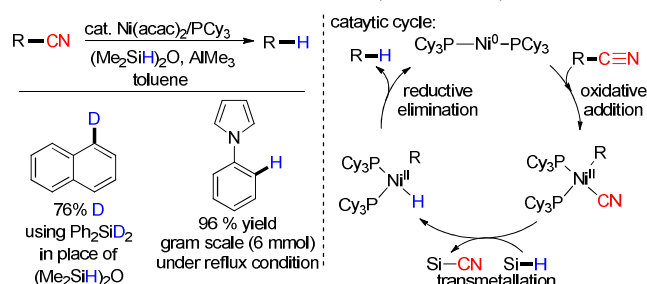
In 2009, Chatani and coworkers reported Rh-catalyzed reductive decyanation of nitriles using hydrosilane as the reducing agent.<sup>86</sup> Utilization of hydrosilane as a mild reducing agent allowed a large functional group tolerance towards ethers, amines, amides and esters. In case of primary alkyl cyanides, the complete suppression of  $\beta$ -hydrogen elimination was achieved using their catalytic system. They also demonstrated the cyano moiety as a transient steering group in regioselective functionalization (Scheme 21). An iminoacyl moiety was proposed as key intermediate prior to C–CN bond cleavage.<sup>87</sup>



**Scheme 21** Application of reductive decyanation as traceless steering group

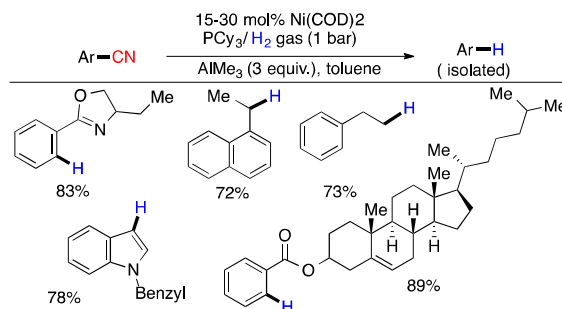
### 5.3 Nickel catalyzed decyanation

Recently in 2013, Maiti and co-workers studied Ni-catalyzed decyanation of inert carbon-cyano bonds with  $(\text{Me}_2\text{SiH})_2\text{O}$  as the hydride source (Scheme 22).<sup>88</sup> It was found that alkyl, aryl and heteroaryl nitriles had been decyanated successfully. Direct insertion of the metal between the C–CN bond through oxidative addition was proposed. The resultant species was trans-metalated with  $(\text{Me}_2\text{SiH})_2\text{O}$  and finally reductive elimination yielded the decyanated compound.  $\text{AlMe}_3$  was used as Lewis acid which formed an adduct with nitrile moiety facilitating the oxidative addition of C–CN bond (Scheme 22).



**Scheme 22**  $\text{Ni}(\text{acac})_2$  catalyzed reductive decyanation

In the same year, Maiti and coworkers reported Ni-catalyzed hydrogenolysis of unactivated carbon-cyano bonds using catalytic  $\text{Ni}(\text{cod})_2/\text{PCy}_3$  and  $\text{AlMe}_3$  (3 equiv) under 1 bar pressure of  $\text{H}_2$  gas.<sup>89</sup> The role of  $\text{AlMe}_3$  was not only to activate inert C–CN bond for facile oxidative addition of  $\text{Ni}(\text{cod})_2$  but also helped the removal of  $\text{HCN}$  produced under the reaction conditions (Scheme 23).



**Scheme 23** Nickel catalyzed hydrogenolysis of unactivated carbon-cyano bond

Thereafter, Enthaler and coworkers have developed a nickel-phosphine precatalyst, which was capable of catalytic hydrodecyanation in presence of tert-butylmagnesium chloride as hydride source.<sup>90</sup> Later the same group, improved their catalytic system, replacing hydride source with  $\text{LiBH}_4$ .<sup>91</sup>

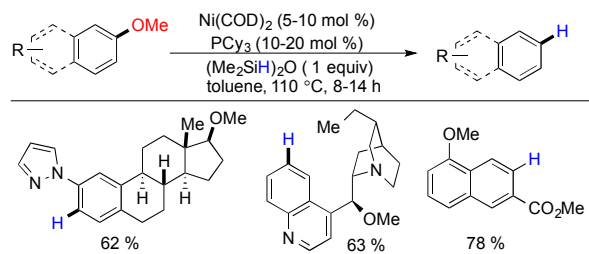
## 6. Deoxygenation of phenol:

Deoxygenation of phenol derivatives through transition metal catalyzed hydrogenolysis of aromatic carbon-oxygen bond has great significance in synthetic chemistry. The electron donating property of phenol or ether linkage favors the ortho/para functionalization in aromatic moiety.<sup>92</sup> On the other hand, ether moiety can also act as directing

scaffold through chelation assisted carbometallation.<sup>93, 94</sup> Thus, deoxygenation can be an interesting strategy for utilizing the beneficial characteristics of the phenol or ether moiety. On the other hand, an efficient deoxygenation protocol can provide a number of deoxygenated analog of biologically active molecules as phenol moiety is ubiquitous in natural products. The direct deoxygenation of phenol is quite difficult due to high C–O bond strength of phenol. So, the well-known pathway to remove the phenol group is, to transform the phenol moiety to electronically poor ester groups like triflates, sulphonates, carbamates etc.<sup>95-97</sup> Then, the metal mediated reductive cleavage of C–O bond results the deoxygenated product. In the other words, the reductive cleavage of C–O bond in ether moiety is quite challenging. An efficient method for reductive dealkoxylation or aryloxylation has immense significance in biomass derived fuel production, as ether linkages are quite common in biomass *e.g.* lignin.

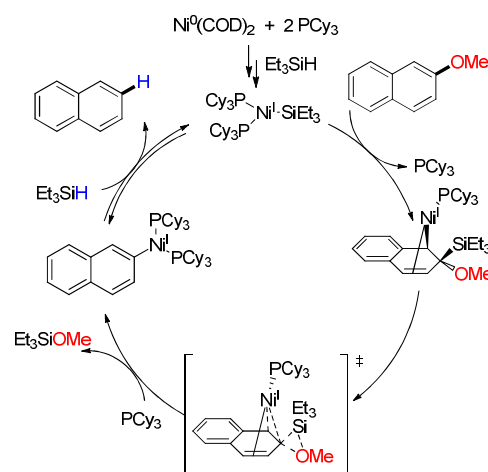
### 6.1 Reductive dealkoxylation and dearyloxylation:

Nickel has proved itself as most appropriate metal for reductive deoxygenation of ether since long ago. In 1935, Duzee and Adkins discovered the deoxygenation/hydrogenolysis of alkyl and aryl ethers in the presence of Raney nickel in H<sub>2</sub> atmosphere (150-250 atm.).<sup>98</sup> But, the disadvantages of this method lie on the uncontrolled hydrogenation of the aromatic ring before and after the hydrogenolysis of ether. In 2010, Martin and coworkers reported the first metal catalyzed protocol for reductive scission of inert C–O bonds of aryl methyl ethers.<sup>99</sup> This methodology showed a broad range of functional group tolerance like silyl, esters, amides, acetals, amine, nitrogen containing heterocycles etc. They also showed that regioselective demethoxylation can be achieved for a particular methoxy group, in presence of more than one methoxy groups in the substrate (Scheme 24).

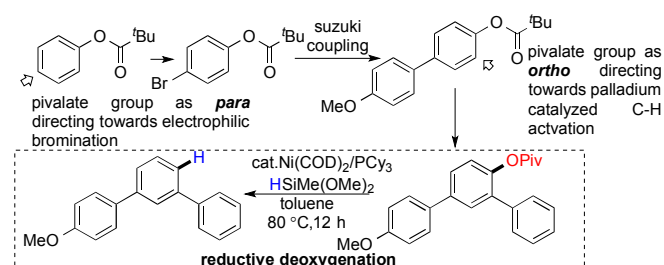


**Scheme 24** Ni(COD)<sub>2</sub> catalyzed demethoxylation of arylmethyl ethers

Based on experimental observation and theoretical calculations, they proposed reaction mechanism for nickel catalyzed reductive demethoxylation, where at first Ni(COD)<sub>2</sub> comproportionates to the key catalytic species Ni(I)–SiEt<sub>3</sub> in presence of PCy<sub>3</sub>, and Et<sub>3</sub>SiH. After that Ni(I)–SiEt<sub>3</sub> coordinates with the 2-methoxy naphthalene in an η<sup>2</sup>-fashion and following a migratory insertion results the benzyl nickel species.<sup>100</sup> Subsequently, a successive migration of the Ni center releases MeOSiR<sub>3</sub>. Finally a reversible σ-bond metathesis delivers the demethoxylated product and regenerate the catalytic cycle (Scheme 25).

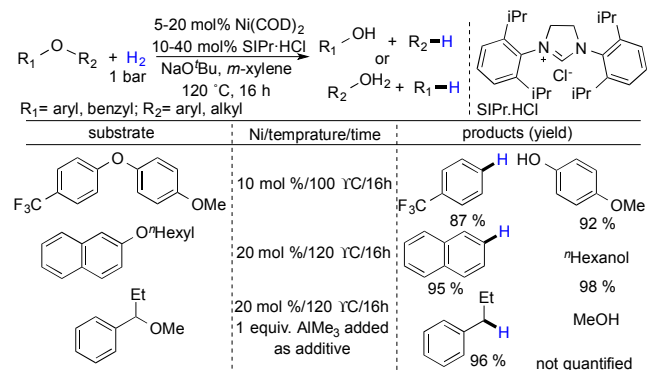


**Scheme 25** Proposed mechanism for Ni(COD)<sub>2</sub> catalyzed demethoxylation of arylmethyl ethers



**Scheme 26** Synthetic application of reductive deoxygenation

Chatani's group reported reductive cleavage of aryl-oxygen bonds in alkoxy and pivaloxy arenes using catalytic Ni(COD)<sub>2</sub>/PCy<sub>3</sub> combination and HSiMe(OMe)<sub>2</sub> as a mild reducing agent.<sup>101</sup> In the reaction condition, ethoxy and isopropoxy group had been cleaved, but bulky alkoxy substituent showed lesser reactivity. They also judiciously presented the importance of reductive deoxygenation of aryl pivalate, by using pivalate moiety as transient directing group in regioselective aromatic functionalization (Scheme 26).



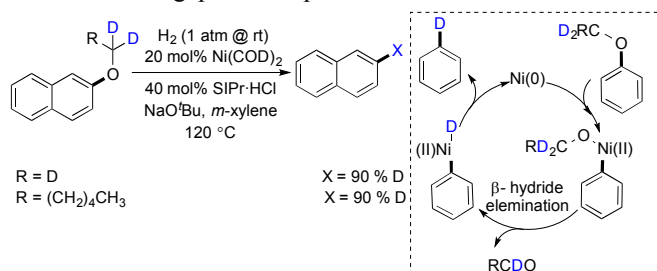
**Scheme 27** Hydrogenolysis of aryl ethers with catalytic Ni(COD)<sub>2</sub> and SIPr–HCl as ligand

Hartwig and Sergeev in 2011 discovered the first hydrogenolysis of aryl ethers with catalytic Ni(COD)<sub>2</sub> and SIPr–HCl as ligand.<sup>7</sup> A strong base, NaO<sup>t</sup>Bu was used for this transformation, which was thought to help in the C–O bond cleavage or dihydrogen activation forming anionic



nickel complexes. The preferential scission of the C–O bond adjacent to the more electron-deficient aryl ring in unsymmetrical diaryl ethers had been attained in their hydrogenolysis condition. Hydrogenolysis of aryl *n*-hexyl ethers and alkyl benzyl ethers were achieved successfully (Scheme 27).

A year later, the same group reported a ligand free hydrogenolysis of C–O bond using Ni(CH<sub>2</sub>TMS)<sub>2</sub>(TMEDA) as catalyst which was proved to be more active than their previously reported catalytic condition.<sup>102</sup> Agapei and coworkers studied the mechanism of the hydrogenolysis reaction of alkyl aryl ether to gain the knowledge about the source of hydrogen.<sup>103</sup> The isotope labeling study showed that, the  $\alpha$ -hydrogen of the alkyl aryl ether was the hydrogen source for reduction in Ni(COD)<sub>2</sub>-NHC catalytic system (Scheme 28). Recently, Chatani and coworkers developed an external reductant free nickel catalyzed reaction condition for reductive deoxygenation of alkyl aryl ether.<sup>104</sup> Their proposed reaction mechanism is similar to the Agapei's<sup>103</sup> reported one.



**Scheme 28** Proposed mechanism for hydrogenation of aryl alkyl ether

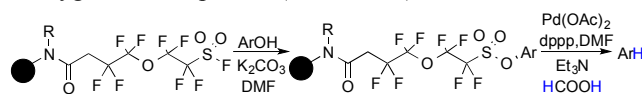
In 2013 Kawanami and coworkers reported a Rh/C catalyzed hydrogenolysis of diphenyl ether derivatives in presence of H<sub>2</sub> gas (0.5 MPa) in super critical CO<sub>2</sub>- water medium.<sup>105</sup> Wang obtained the selective reductive cleavage of inert aryl C–O bonds by using catalytic amount of Fe(acac)<sub>3</sub> with LiAlH<sub>4</sub> as reducing agent and NaOtBu as base.<sup>106</sup> The experimental studies established that the catalytic reaction was occurring through an active heterogeneous species. The same group shown that Co(acac)<sub>2</sub> was also capable for the reductive cleavage of inert aryl C–O bonds in similar reaction condition as in the iron catalyzed reaction.<sup>107</sup> Recently, Stephenson and coworkers reported the depolymerization of Lignin in photolytic condition using [Ir(ppy)<sub>2</sub>(dtbbpy)]PF<sub>6</sub> as photocatalyst.<sup>108</sup>

## 6.2 Reductive deoxygenation of sulfonate ester of phenol:

Palladium is the most acknowledged transition metal for reductive deoxygenation of aryl sulfonate esters in presence of a hydrogen source. Catalytic palladium on charcoal in hydrogen atmosphere is one of the well-known reagent combination for hydrogenation of aryl nonaflate.<sup>109</sup> Afterwards, reductive deoxygenation of aryl triflates was reported by Orter,<sup>110</sup> Wulff,<sup>111</sup> Chen<sup>112</sup> groups independently using trialkylammonium formate as hydrogen donor in presence of catalytic amount of

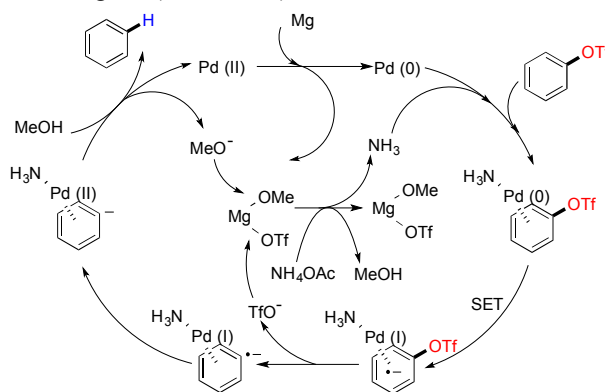
palladium salt/ phosphine ligand.<sup>113</sup> Later, in 1989, Saa and his group showed that naphthyl triflate can be deoxygenated in presence of catalytic amount of (Ph<sub>3</sub>P)<sub>2</sub>PdCl<sub>2</sub>/dppp in DMF solvent, with Bu<sub>3</sub>N as hydride donor.<sup>114</sup> Using, triethyl silane as hydride source, Kotsuki reported the reductive deoxygenation of aryl and enol triflates in presence of catalytic amount of palladium (II) salt and bi-dentate phosphine ligand combination.<sup>115</sup> Later Neumeyer successfully employed Katsuki's method in synthesizing pharmacologically important molecules from opioid derivatives.<sup>116</sup> Afterwards, Lipshutz found a Pd(0) catalyzed simple, mild deoxygenation protocol for aryl perfluorosulphonates with Me<sub>2</sub>NH·BH<sub>3</sub> as hydrogenating source.<sup>117</sup>

Holmes and Pan in 2001, reported a novel method for deoxygenation of phenol with the help of a solid supported perfluoroalkylsulphonyl (PFS) fluoride linker.<sup>118</sup> The PFS linker was attached with the phenol, resulting an aryl sulphonate, and a palladium catalyzed cleavage of Aryl C–O bond followed. Using the same strategy, Revell and Ganesan in 2004, developed a tetrafluoroarylsulphonate linker as traceless functionality for solid-phase deoxygenation of phenol (Scheme 29).<sup>119</sup>



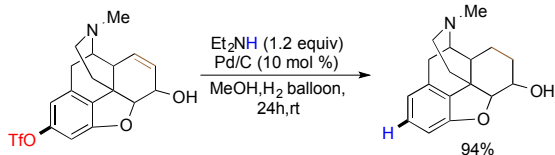
**Scheme 29** Solid supported deoxygenation of phenol

Sajiki and co-workers published a Pd/C catalyzed deoxygenation protocol of aryl triflates and mesylates with Mg metal-MeOH combination as hydrogen source.<sup>120</sup> A stoichiometric amount of NH<sub>4</sub>OAc was used for better conversion. According to their mechanistic study it was hypothesized that, two consecutive single electron transfer (SET) from Pd(0) to aryl sulfonate resulted Pd(II) and aryl anion.<sup>121</sup> After a protonation by methanol, aryl anion formed the deoxygenated arene. Palladium (II) transformed to Pd(0) after a successive reduction with magnesium. The role of NH<sub>4</sub>OAc was speculated to possess a dual activating effect caused by acetic acid and ammonia. Acetic acid helped the magnesium species for better solubility in methanol and ammonia coordinated to Pd/C as ligand (Scheme 30).



**Scheme 30** Proposed mechanism for palladium catalyzed reductive cleavage of aryl sulfonate

After their initial contribution, Sajiki reported catalytic Pd/C-diethylamine mediated hydrodeoxygenation of aryl triflate (Scheme 31).<sup>122</sup> Unfortunately, their protocol was limited due to poor tolerance towards the functional groups like olefins, benzyl esters, and nitro/aromatic ketones.



**Scheme 31** Reductive deoxygenation with catalytic Pd/C-diethylamine combination

Recently, Kwong and coworkers developed a palladium catalyzed facile deoxygenation of aryl tosylate using isopropanol as mild reducing agent.<sup>123</sup>

In reductive deoxygenation reactions, nickel has also been greeted as celebrated class. In 1975 Kartzl reported a Raney nickel assisted deoxygenation of aryl sulphonate.<sup>124</sup> Later Sasaki developed the nickel catalyzed deoxygenation of aryl sulphonate.<sup>125</sup> They reported NiBr<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>/bidentate phosphine ligand catalyzed method for deoxygenation with stoichiometric amount of Zn/KI in methanol solvent.<sup>126</sup> Recently Lipshutz and coworkers explored nickel/graphite as catalyst for reductive deoxygenation of aryl sulphonates using Me<sub>2</sub>NH.BH<sub>3</sub> as hydride source.<sup>127</sup> They have also tuned the reaction in microwave condition with shorter reaction time.<sup>128</sup>

## 7. Reductive dehalogenation:

The reductive removal of halo moiety is treated as one of the tempting research area since long ago. Halo-moieties are used as blocking group in a particular organic transformation.<sup>129-131</sup> Hence, an easy selective removal of this halo moiety allows the synthetic chemist to utilize the halo group as a fertile blocker. On the other hand, reductive dehalogenation has great significance for environmental cause. Some halogenated, mainly chlorinated arenes are toxic and considered as persistent organic pollutants, but their dehalogenated outcome are not.<sup>12-16</sup> These halogenated arenes are resistant to biodegradation also. So an efficient artificial degradation through the reductive dehalogenation is considered as savior from these toxic halogenated materials. Transition metal is well known for the activation of C-halo bond. Therefore, a number of reductive dehalogenation methods are known with a transitional metal and a hydride source combination.

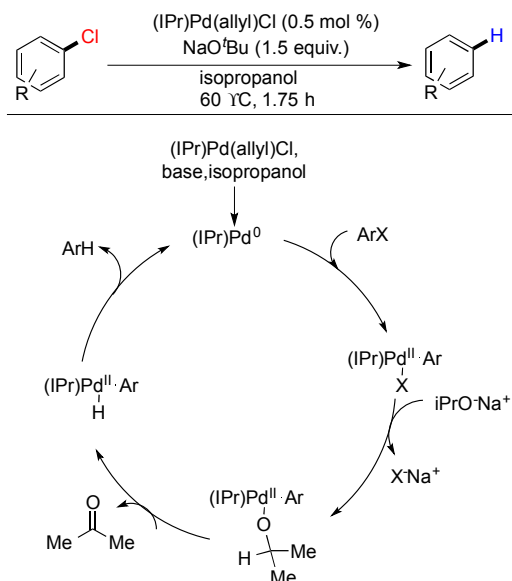
### 7.1 First row transition metal complexes for reductive dehalogenation.

During early stages, reductive dehalogenation was performed by Masamune using lithium-copper hydride complex.<sup>132, 133</sup> Afterwards, a copper-hydride species, (KCuH<sub>2</sub>)<sub>n</sub> was prepared by Negishi, which shown the reductive dehalogenation of aryl halide.<sup>134</sup> Later, Tashiro and coworkers reported reductive dehalogenation with the help of Ni-Al alloy in alkaline aqueous solution.<sup>131, 135</sup> In 1975, Tyrlic<sup>136</sup> and Tufarieilo<sup>137</sup> independently showed Mg-Ti complex as dehalogenating reagent, where solvent

molecules (THF and H<sub>2</sub>O, respectively) were speculated as hydrogen source. The admixture of LiAlH<sub>4</sub> with catalytic/stoichiometric amount of first transition metal chloride salt was used for reductive dehalogenation by Ashby.<sup>138</sup> Roth and coworkers reported a Ni(0) catalyzed mild and simple protocol for reductive debromination using NaBH<sub>4</sub> as hydride source.<sup>139</sup> In another approach, Ni(0) catalyzed reductive dehalogenation in presence of Zn and H<sub>2</sub>O was developed by Colon.<sup>140</sup> Using MgH<sub>2</sub> as reducing agent, Ni(II) catalyzed reductive dehalogenation was reported by Carfagna and coworkers.<sup>141</sup> In 2001, Lipshutz and coworkers examined the Ni/C catalyzed reductions of aryl chlorides in presence of Me<sub>2</sub>NH.BH<sub>3</sub> and K<sub>2</sub>CO<sub>3</sub>.<sup>142</sup> Aryl chloride containing electron rich and electron donating functional groups and a heterocyclic chloride was successfully dehalogenated in their reaction condition. They have efficiently converted trichlorobiphenyl to biphenyl through this protocol.

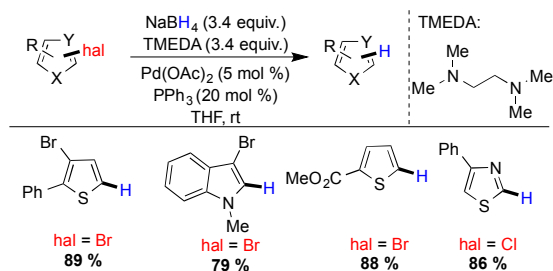
### 7.2 Palladium as reductive dehalogenating agent.

Palladium emerged as one of the efficient metal for reductive dehalogenation for its renowned reactivity towards the C-halo bond through oxidative addition. Heck exploited Pd/C as useful catalyst for reductive dehalogenation in presence of diethyl ammonium formate.<sup>143</sup> Palladium catalyzed reductive dehalogenation was further developed by Helquest<sup>144, 145</sup> and Blum<sup>146</sup> independently. They discovered Pd(PPh<sub>3</sub>)<sub>4</sub> catalyzed reductive dehalogenation of organic halides using sodium methoxide<sup>145</sup> or sodium formate<sup>144</sup> or benzyl alcohol<sup>146</sup> as hydride source. Reductive dehalogenation using palladium carbene complex (IPr)Pd(allyl)Cl was explored by Nolan and coworkers in both conventional heating and microwave condition using isopropanol as hydrogen equivalent.<sup>147</sup> According to their proposed catalytic cycle, Pd(0) was formed in presence of base, then oxidative addition of aryl halide occurred. The Ar-[Pd]-H complex was formed in presence of isopropanol releasing acetone. Finally, reductive elimination produced the dehalogenated product (Scheme 32).



**Scheme 32** Proposed mechanism for palladium catalyzed reductive dehalogenation

In 2010, Jimenez and coworkers presented Pd/C catalyzed hydrogenation of aryl chloride and bromide.<sup>130</sup> A broad range of functional groups including phenol, ketone, carboxylic acid, amide, nitro cyano moieties were tolerated in their reaction conditions. Recently, Chelucci and coworkers reported a palladium catalyzed mild reaction condition for dehalogenation of heterocyclic chloride and bromide using NaBH<sub>4</sub>-TMEDA as the hydride source.<sup>148</sup> Regioselective hydrodebromination was also achieved in presence of more than one bromide group in the (Scheme 33).

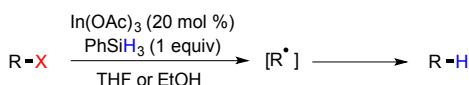


**Scheme 33** Palladium catalyzed reductive dehalogenation of heterocyclic chloride

In 2012, Sajiki and coworkers published Pd/C catalyzed dechlorination of polychlorinated biphenyls in presence of Mg metal/MeOH at room temperature.<sup>149</sup> A broad range of aryl chloride with a variety of functional groups was tolerated in their reaction protocol. Authors proposed a reaction pathway which was similar to their previously reported reductive deoxygenation of aryl triflate.<sup>121</sup>

### 7.3 Other metals in reductive dehalogenation reaction.

In 1999, Esteruelas *et al* reported rhodium catalyzed reductive dechlorination of aryl chloride, using triethylsilane as hydride source.<sup>150</sup> Though a great effort has been concentrated on reductive dechlorination of polychloroarenes, but their substrate scope rarely addressed the functional group compatibility. Miura and coworkers demonstrated an In(OAc)<sub>3</sub>-catalyzed reduction of organic bromide and iodide with PhSiH<sub>3</sub> in ethanol.<sup>151</sup> A radical mechanism was proposed for reductive dehalogenation (Scheme 34).



**Scheme 34** Reductive dehalogenation in radical condition

Corey Stephenson achieved reductive dehalogenation in photochemical condition in 2009 by using Ru(bpy)<sub>3</sub>Cl<sub>2</sub> as electron-transfer photoredox catalyst. Benzyl halide and  $\alpha$ -halo carbonyl compounds were selectively dehalogenated without affecting any other functional group present in the molecule.<sup>152</sup> According to the proposed mechanism, reaction proceeds through a single-electron transfer from the ammonium formate complex to the excited Ru(II)\* yielding Ru(I) and the radical cation of the complex. Subsequently, the electron rich Ru(I) complex reduces the

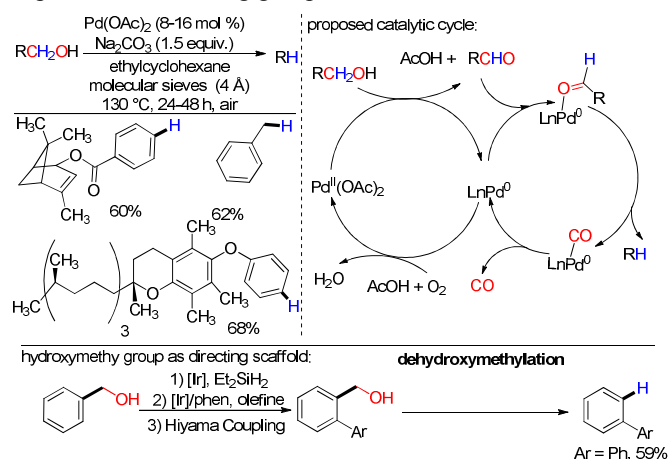
alkyl halide to alkyl radical. In the final step alkyl radical abstracts hydrogen radical from either amine or the formate of ammonium formate radical cation.

## 8. Dehydroxymethylation:

Dehydroxymethylation is the one pot transformation of primary alcohol to one carbon less defunctionalized moiety *i.e.* removal of CH<sub>2</sub>OH group. Dehydroxymethylation permits the synthetic chemist to remove the hydroxymethylene group directly, where alcohol is oxidized to aldehyde first followed by decarbonylation of aldehyde. The successful implementation of one reaction system which can deliver these two processes sequentially is desirable for the development of this strategy. In biological system also, dehydroxymethylation is a key process in DNA demethylase Activity.<sup>153</sup>

In 2006 Madsen reported the dehydroxymethylation reaction employing two separate catalysts for oxidation and decarbonylation.<sup>54</sup> Later, they reported the Ir-catalyzed dehydrogenative decarbonylation of primary alcohols with the liberation of syngas.<sup>154</sup> This is achieved with a catalyst generated in situ from [Ir(coe)<sub>2</sub>Cl]<sub>2</sub> and racemic BINAP in a mesitylene solution saturated with water. Lewis acid such as LiCl was found to enhance the rate of transformation.

In 2013, Maiti and co-workers generalized the dehydroxymethylation reaction using one catalyst for the successful transformation where, catalytic Pd(OAc)<sub>2</sub> was used as both oxidant and decarbonylating agent.<sup>155</sup> A broad range of functional group tolerance proved the utility of this method. Selective dehydroxymethylation was done successfully with the natural product derived substrate, bearing hydroxymethyl group. They have also demonstrated the importance of the dehydroxymethylation, by taking advantage of the CH<sub>2</sub>OH group as an impermanent directing group.<sup>155, 156</sup>

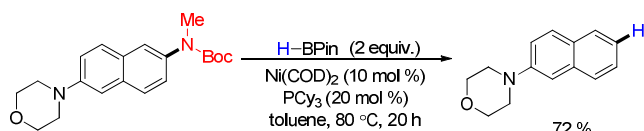


**Scheme 35** Palladium catalyzed dehydroxymethylation

## 9. Deamination:

The transition metal catalyzed reductive deamination was achieved through C–N bond cleavage. An electron withdrawing moiety with the nitrogen center was essential for the successful implementation. In 2014, Chatani and

coworkers have described the Ni-catalyzed reductive aromatic C–N bonds in N-aryl amides and carbamates. A catalytic amount of Ni(cod)<sub>2</sub>/PCy<sub>3</sub> with HB(pin) was required (Scheme 36). Sterically demanding substrates bearing a C–N bond at 1-position of the naphthalene, as well as those containing an ortho substituent underwent the reductive cleavage reaction to give the desired products. Several other fused aromatic systems, also proceeded smoothly under the optimized condition, whereas benzene derivatives were found to be much less reactive.<sup>157</sup>



**Scheme 36** Nickel catalyzed reductive deamination

## 10. Conclusion:

Development of novel strategies for carbon-carbon/heteroatom bond cleavage can lead to exploration of diverse catalytic systems. Development of inexpensive transition-metal catalysts, mild conditions, green and sustainable oxidants, and a wide substrate scope remained major focus of these studies. Efficient defunctionalization strategies are emerging which will play a vital role in the production of energy *viz*: bio-fuels are being made from organic sources like biomass. Defunctionalization is also important in the synthesis of drugs and biomimetics, as they form the core in wide range of pharmaceuticals.

## 11. Acknowledgements

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## 12. Notes and References:

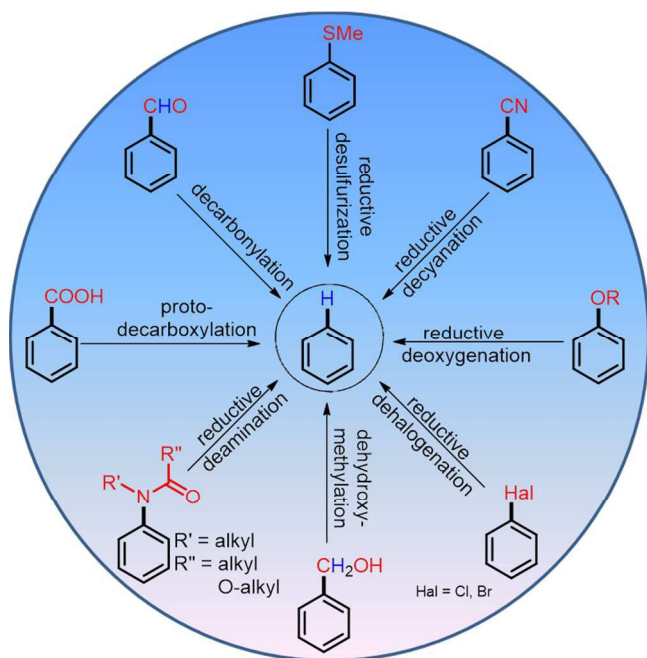
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## Table of Contents:



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The chronological development of metal assisted defunctionalization reactions were discussed from the stoichiometric to catalytic stage with their application in synthetic organic chemistry.

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