REVIEW:

Reductive Functional Group Transformations

1.1. INTRODUCTION

The functional group transformation is one of the most fundamental and useful reactions in organic synthesis. Though the transformation of an isolated functional group can be carried out conveniently with a number of reagents, selective transfer of one functionality in presence of other such groups with minimal or without damage to the sensitive portion of a molecule in substrate is a frequent problem in organic synthesis. Consequently, a significant effort has been undergone in developing new methods and finding new reagents that are chemo-selective or able to transform one functional group in a polyfunctional group molecule, leaving the remaining ones untouched and this area of developing selective, mild and effective reagent systems is still an area of prominent interest.
To perform desired modifications to a functional group in organic synthesis, reduction is considered as one of the significant tools in the hands of chemists. The most widely used general methods of reduction are, i) metal/acid reduction, ii) catalytic hydrogenation, iii) electrolytic reduction, iv) metal hydride reduction.

Generally the methods effecting reduction may or may not lead to hydrogenation. Reduction of organic functional groups can be categorized into (i) addition of hydrogen to unsaturated groups as, for example in the reduction of ketones to alcohols and (ii) addition of hydrogen across single bonds leading to cleavage of functional groups (hydrogenolysis). Of all the methods available for reductions, heterogeneous catalytic transfer reactions have been relatively underutilized. This lack of popularity can be traced to the relatively meager success of much of the earlier research, which suggested that the technique was of only limited scope and could provide only modest yields of products. The early pioneering work of Braude [1] was largely ignored because of poor yields and long reaction times, but the situation has changed considerably following the introduction of greater catalyst loadings and different hydrogen donors [2]. Another reason for the underutilization of transfer reductions has been the very successful exploitation of molecular hydrogen and hydrides for reduction of organic compounds. In view of the above said facts, the following sections of this review on reductive functional group transformations are focused on catalytic transfer hydrogenation (CTH) methods of reductions.

The transfer reductions carried out using hydrogen donors have some real and potential advantages over catalytic reductions, where the molecular hydrogen is being used. The use of hydrogen donors for reductions makes the processes simple and environmental friendly which involves usually just stirring of solutions. Unlike catalytic reductions, it requires no pressure vessels and gas containers, and there by avoid the use of molecular hydrogen of high diffusibility which can be easily ignited and lead to substantial amount of hazards. Potentially, transfer methods could afford enhanced selectivity in reduction. With a catalyst and molecular hydrogen,
changes of catalyst, solvent, and temperature are possible variations in reaction conditions but, with hydrogen donors, a new dimension is opened up because the choice of hydrogen donor can affect the reaction through its competitive adsorption onto the catalyst surface. Thus, rate and specificity of reduction are amenable to control through choice of hydrogen donors. Most transfer hydrogenation mechanisms are poorly understood and there are a few direct comparisons of products of reactions following the use of molecular hydrogen or a hydrogen donor. Research in these areas is needed not only to unravel details of mechanisms, but also to provide a proper appraisal of the advantages or disadvantages of the two methods.

According to Pauling’s definition of electronegativity [3], hydrogen, having a value of 2.1, lies between fluoride (4.0) and many metals, which typically have values of about 0.9-1.5. Therefore, in reactions involving its transfer, hydrogen may appear as a proton, atom, or hydride depending on reagents and conditions. For example, when a gaseous HCl is dissolved in water, hydrogen is transferred as proton to water similarly the reaction of lithium tetrahydroaluminate to a carbonyl group involves the addition of hydride to carbon of the carbonyl and in many catalytic hydrogenations with molecular hydrogen; atomic hydrogen is dispersed in and over the catalyst. But, in many reductions with hydrogen donors, it is difficult to decide how hydrogen is transferred.

1.1.1 HYDROGEN DONORS:

The low oxidation potential of the compound (donor) facilitates the transfer of hydrogen(s) from the donor to the substrate even under mild reaction conditions. Hence, any compound (organic or inorganic) with a low oxidation potential can be served as a useful hydrogen donor. The choice of donor is based on the nature of the reaction, its availability, and solubility in the reaction medium. Alcohols, hydrazine, cyclic olefins, and hydroaromatics have been employed as hydrogen donors for the transfer hydrogenation of various functional groups. Formic acid and its salts occupy a special place as hydrogen donors because, the ease of hydrogen donation
is higher than with the donors listed above. This results from the fact that a stable molecule such as CO₂, which has a very large negative enthalpy of formation (ΔHᵋ, 298 °C = 395.51 kJ/mol), is released from the hydrogen donor during the transfer hydrogenation reaction. Simply stated, the hydrogen donation is irreversible. This is one of the major driving forces for the high reactivity of formates.

The common property of the useful donors is irreversible nature of their dehydrogenated products. For instance, CO₂, N₂ and C₆H₆ are the dehydrogenated products of ammonium formate, hydrazine and cyclohexadiene respectively.

As previously said, the nature of the hydrogen donor influences the selectivity of the reduction. This can be demonstrated with the reduction of aromatic nitro compound containing halogen using palladium in conjunction with a formate salt, where halogen being effectively removed and nitro group reduced to amino group. While, the same catalyst coupled with phosphinic acid as hydrogen donor reduces only nitro group without affecting halogen [4].

Even though one can use common types of compounds as hydrogen donors in both homo- and heterogeneous catalysis, it is more often the case that different types of compounds are favored in the two systems. The more active hydrogen donors for homogeneous catalysis appear to be predominantly alcohols, hydroaromatics, cyclic ethers, and occasionally formic and ascorbic acids whereas, for heterogeneous catalysis, the more widely used donors tend to be hydrazine, formic acid and formates, phosphinic acid and phosphinates, indoline, and cyclohexene. There is no clear division between the two types, but some of the hydrogen donors, which are active for heterogeneous catalysts, are water-soluble inorganic salts and cannot be used with many homogeneous catalysts. Trialkylsilanes and trialkylstannanes have proved to be good hydrogen donors in both homo- and heterogeneous catalysis [5], where tri-n-butylstannane reduced α,β-unsaturated aldehydes in methanol under fairly drastic conditions [6], in
the presence of Pd(PPh₃)₄ and a promoter, the reduction can be achieved in 10 min at room temperature [5].

1.1.2 CATALYSTS:

The transfer hydrogenation reactions can be accomplished using both homogeneous and heterogeneous catalysts.

**Homogeneous Catalysts:** The majority of the homogeneous hydrogenation catalysts are soluble complexes of noble metals and are equally active for transfer hydrogenations also. Literature [7] accounts the applications of RuCl₂(PPh₃)₃, RhCl(PPh₃), PdCl₂(PPh₃)₂ and IrCl(PPh₃)₃. As most of these complexes are insoluble in water, these reactions are carried out in nonaqueous media. Metal complexes having water-soluble ligands (m-sulphophenylbiphenylphosphine, for example) have been designed for reactions that demand an aqueous or a biphasic medium. The homogeneous catalysts are often appended to an insoluble polymer to overcome the product isolation difficulty while retaining the advantages of homogeneous catalysts.

The catalytic activity of the transition-metal salts and complexes is the result of a delicate balance of valence states and strengths of chemical bonds [7]. Too strong a bond between hydrogen donor and the transition metal results in stable compounds showing no catalytic activity. Similarly, there is no catalytic activity if reaction between hydrogen donor and the transition element cannot occur. Not only must the hydrogen source be accommodated by the transition metal, but also the organic substrate must be able to bond if transfer of hydrogen to the substrate is to occur.

Usually the operational temperatures for homogeneous catalytic reactions are rarely low (i.e., 20-80 °C), they require moderate to high temperatures in the range of 100-200 °C. Another problem associated with homogeneous catalysts has been the difficulty of their recovery from reaction products. Unfortunately, many of these catalysts appear to be unstable and lose the complexed metal to the reaction medium (i.e., the
catalyst is dissolved from its support) or the complex salt is reduced to the metallic state.

**Heterogeneous Catalysts:** Most of the heterogeneous hydrogenation catalysts are also of transition metal elements but they are used in their zero oxidation state. Sometimes, the catalyst is used in the bulk form; this is possible when a base metal is used, for example, Raney nickel. But, it is not advisable to use in bulk when a costly metal like platinum is used. To maintain the cost effectiveness, such catalysts are used in supported form which increases the surface area as well the availability of metal atoms for catalysis, thus more efficient the catalyst. Generally, catalyst supports employed are activated carbon, alumina, silica, amorphous silica-alumina, zeolites, BaSO₄, and CaCO₃. The crystalline size and hence dispersion of the supported metal depends on the method of preparation and subsequent treatments. For 10% Pd/C, the Pd crystalline size is estimated to be 3.5 - 5 nm [8].

The most widely used catalyst support for liquid phase hydrogenation reactions is activated carbon. This can be justified by the following reasons: (1) Activated carbon can be synthesized with high purity and possesses large surface area (~1000 m²/g); (2) The metal support interaction is the least among the various common catalyst carriers and thus the electronic properties of the active material are not modified; and (3) Activated carbon, being a good adsorbent for organic compounds, can facilitate the reaction by aiding the migration of the adsorbate to the active sites of the catalyst.

Even though palladium is preferred for most of the common reactions, platinum, ruthenium, and rhodium are also useful complementary candidates when selectivity is crucial. For instance, a ruthenium complex can be used to selectively transfer hydrogenate the carbonyl group to a carbinol in α,β-unsaturated carbonyl compounds [9], while Pd/C is used to selectively reduce the C=C double bond [10]. Similarly, in halo-nitroaromatics, Pt/C can be employed to reduce nitro groups without
eliminating halogen functionality while Pd/C may be utilized to remove halogens with simultaneous reduction of nitro groups to amines [11].

1.1.3 REACTION CONDITIONS:

Influence of Temperature: In homogeneous systems, at equilibrium or under steady-state conditions, normal solution kinetics can be applied and energies of activation and enthalpies have been determined experimentally for several systems [12-18]. In a practical sense, increase in temperature will lead usually to a faster overall rate of reaction, i.e., faster reduction, but for equilibria, the change in position of equilibrium with increasing temperature is not easy to predict. In many reductions, a linear increase in rate of reduction with increase in temperature has been observed [12,13,16,17,19].

Comparatively, homogeneous catalyst requires higher temperature to transfer the hydrogen from a donor to an acceptor than heterogeneous catalyst of the same metal. However, increasing temperature may lead to unwanted reactions like over reduction and isomerization [20,21]. Given the less importance to side-reactions, increase in temperature of reaction can afford higher yields of product for a given time of reaction. Different hydrogen donors may require different optimum temperatures. Similarly, variation in the hydrogen acceptor will afford various optimum temperatures for any one hydrogen donor. As mentioned above, the effect of temperature on equilibria is unpredictable without experimental data.

Influence of Solvent: Choosing a suitable solvent is an important factor for governing the activity of a soluble catalyst in transfer reduction. Most soluble catalysts are either coordinated to ligands or coordinated with solvent. Often, ligands can be displaced from a metal complex by a suitable solvent to form new complexes. These new complexes incorporated in solvent molecules may be more or less active than the original complex, because binding by the solvent alters the electron density around the central metal atom and changes its ability to effect oxidative addition. Some metal catalysts are active in solution only after dissociation of one or
more ligands leaves the central metal atom with less than its maximum coordination number, thereby facilitating oxidative addition. If solvent molecules displace the original ligands and they themselves do not dissociate from the central metal, then all catalytic activity is lost. In additions to these ligand-displacement mechanisms by the solvent, catalyst activity may be reduced or destroyed completely if the solvent coordinates to the catalyst better than the hydrogen donor or hydrogen acceptor. Finally, the solvent should not deactivate the catalyst by destroying it, as may happen with water.

In heterogeneous catalyst systems also, coordination of solvent to the catalyst must be competitive with binding of hydrogen donors and acceptors. If the coordination between solvent and catalyst is stronger than the binding of donor or acceptor, then transfer reduction is inhibited or stopped altogether. Hence in order to optimize the conditions for any attempted transfer reduction, a trial of a range of solvents should be a principal consideration.

The most common solvents for these reactions are alcohols, particularly methyl or ethyl alcohol. Dimethylformamide and dimethylacetamide are useful for reactants that are less soluble in alcoholic solvents. Acetic acid is very effective as a solvent medium when acidic conditions are demanded.

The rate of mixing or stirring of reactants in heterogeneous transfer reductions can also make the difference in reaction rate. Increased mixing improves the contact between the catalyst and the reactants, thus results in a beneficial effect on the reaction rate. In addition to the familiar process parameters such as temperature and pressure, ultrasound is found to promote the Pd-catalyzed reduction of olefins using HCOOH in alcohols [22].

1.1.4 MECHANISM OF TRANSFER HYDROGENATION:

To the date, Pd/C is the most preferred catalyst for transfer reduction reactions and at the same time formate slats as donors. In an attempt to know the mechanism of transfer hydrogenation, the following
postulate is advanced to rationalize the various literature observations that have been made.

The first step in these reactions is the chemisorption of formate salts that may decompose into CO$_2$ and H$^+$ ions on the metal surface. The adsorbed hydrogen can exhibit H$^-$, H, or H$^+$ behavior depending on the environment. There is some evidence that hydrogen exhibits either H$^-$ or H$^+$ character on palladium in the liquid-phase. For example, in the case of dehalogenation, it is most likely that the hydride-like behavior is predominant. In the case of coupling reactions performed in the presence of a strong base such as NaOH, the chemisorbed hydrogen on palladium may exhibit H$^+$ character; the abstraction of this H$^+$ by OH$^-$ would leave two electrons on the surface of the metal cluster. These electrons may be responsible for the radical chemistry witnessed in the coupling reaction of bromobenzene to biphenyls. The H-D exchange reactions also support the H$^+$ nature of PdH$^-$ species. For example, the deuterium of PdD$^-$ can exchange freely with H$_2$O, alcohols, benzylic protons, organic acids, and NH$_4^+$.

1.1.5 REACTIONS INVOLVING VARIOUS FUNCTIONAL GROUPS:

A wide range of functional groups are modified by applying transfer hydrogenation or hydorgenolysis methods. In all cases, the advantages of transfer hydrogenation over conventional hydrogenations are obvious. The most important functional groups reduced by CTH include alkenes, alkynes, arenes, nitroalkanes, nitroarenes, azo compounds, aldehydes and ketones, nitriles, azides, hydrazo compounds and imines [23]. Several important functional groups have received little study, in particular, carboxylic acids, their esters and their amides. All of them are frequently reduced efficiently by hydride reagent, but are usually found not to be reduced under any of the conditions described in this catalytic transfer hydrogenation.

Further, the application of CTH systems for reduction of aromatic nitro compounds to corresponding amines, azoarenes to hydrazoarenes, imines to secondary amines, synthesis of indolones and quinolones via
reductive cyclization, and synthesis of amides of amino acids and peptides are discussed in detail which comprise the present work of this thesis.

1.2 REDUCTION OF AROMATIC NITRO COMPOUNDS

The transfer reduction of nitro compounds dates way back to 1943 by Davison and Hodgson [24], they used copper to catalyze the transfer hydrogenation of nitrobenzene in the presence of HCOOH at 200 °C. More and Furst [25] have used Raney-nickel with hydrazine hydrate to reduce 2,2'-dinitrobiphenyl to 2,2'-diaminobipheyl, wasn’t a mono-reduction. Entwistle and coworkers [2, 4] have used cyclohexene as a hydrogen donor and 10% Pd-C as the catalyst for the mono-reduction of polynitrobenzenes (Table 1.1, Entry 1). They [4] also reduced nitroarenes in 75-90% yields using Pd-C catalyst and one of phosphinic acid, sodium phosphinate, phosphorous acid or sodium phosphite as donor. Selective mono-reduction of dinitroarenes could not be achieved with the donors other than cyclohexene because, with them, the rate of reduction of nitro aniline is greater than its rate of formation from a dinitroarene. Triethylammonium formate and 5% Pd-C at ~90-100 °C was used to reduce the nitroarenes (Table 1.1, Entry 2) [11] and have reported the formation of cyclized products with o-nitrophenylacetic acid and o-nitro cinnamic acid. Similar works with a Pd/AlPO₄/SiO₂ catalyst has been reported [26].

Dehalogenations are common during catalytic transfer reduction and substitution reactions may also be observed. Later on, successful attempts made to gain greater control of these reductions by using less active catalysts and variation of the solvent have been reported [27]. In the presence of a 50% excess of hydrazine hydrate; a number of nitro benzenes were reduced with Fe(III) chloride on active carbon. An indication of how much less active Fe(III) is as a catalyst than Pd is found in the lengthy reduction times (Table 1.1, Entry 3). However, high yields of amines were obtained and reduction of 5-chloro-2,4-dimethoxynitrobenzene to the corresponding aniline was effected without loss of the chloro group.
Other formate salts such as alkali metal formates are also useful but result in the formation of bicarbonate. Water-soluble organic nitro compounds [e.g., disodium salt of 3,6,8,1-(HO₃S)₃C₁₀H₄NO₂] were reduced to the corresponding amines in aqueous HCO₂H or its salts in the presence of Pd-C [28]. Aromatic nitro compounds like nitro phenols and nitro amines were conveniently reduced by catalytic transfer hydrogenation employing HCOOH in the presence of palladium black by Sivanandaiah and coworkers (*Table 1.1, Entry 4*) [29].

Ram and Ehrenkaufer [30] described the transfer hydrogenation of a wide variety of both aliphatic and aromatic nitro compounds using ammonium formate at room temperature with conversions ranging from 31% to 98% (*Table 1.1, Entry 5*). Reductive cyclization of 2-nitro-β-nitrostyrene to indole is achieved using ammonium formate and 10% Pd-C in fair yield (60%) [31].

Lin et al. [32] have reported the system triethylammonium formate with Pd-C catalyst for the transfer hydrogenation of nitrocoumarins to give aminocoumarins in good yields.

Namura [33] has used the ruthenium-carbonyl complexes in presence of small amounts of amines for selective reduction under CO/H₂O conditions to get excellent yields (*Table 1.1, Entry 6*). He has observed that the use of amines enhanced the catalytic activity. Brinkman et al. [34] selectively reduced the nitro groups using rhodium complexes in conjunction with triethylsilane at higher temperatures (*Table 1.1, Entry 7*).

Upadhya et al. [35] described the chemoselective reduction of nitroarenes using nickel stabilized zirconia (Zr₀.₈Ni₀.₂O₂), propan-2-ol and KOH under reflux condition with good yields (*Table 1.1, Entry 8*).

Ultrasonic promoted reactions for the reduction of nitro compounds is reported to be of useful methods. Nagaraja et al. [36] have used alluminium/ammonium chloride system to effect the reduction under ultrasonic bath at 25°C, where as the reaction takes much longer time.
(24 hrs) under conventional reflux conditions with the same system (Table 1.1, Entry 9). Basu et al. [37] also reported the reduction of several aromatic nitro compounds to aromatic amines with high yields using samarium/ammonium chloride mediated reactions.

Benz and Prins [38] reported a kinetic model for the reduction of 4-nitrotoluene to 4-toluidine and 4-nitroaniline to p-phenylenediamine by hydrazine hydrate in the presence of iron oxide as hydrogen-transfer catalyst. Bae et al. [39] described the chemo-selective reduction of nitrobenzenes to corresponding anilines with decaborane (B_{10}H_{14}) in the presence of Pd-C and two drops of acetic acid at reflux temperature under nitrogen atmosphere (Table 1.1, Entry 10).

Use of microwave heating for chemical applications has given a new dimension to organic synthesis. This technique is widely accepted as non conventional energy source for performing organic synthesis. Vass et al. [40] have reported the microwave assisted reductions using iron chloride hexahydrate and hydrazine hydrate to get fairly good yields with time range 7 to 10 minutes (Table 1.1, Entry 11).

Mahapatra and co-workers [41-43] reported the use of various metal incorporated molecular sieves for the CTH of nitroarene. They used cobalt (II) (CoHMA) and trivalent iron (FeHMA) incorporated hexagonal mesoporous aluminophosphate molecular sieves (Table 1.1, Entry 12 and 14). Further, they observed regio- and chemoselective CTH upon using nickel containing mesoporous silicate (NiMCM-41) molecular sieve catalyst (Table 1.1, Entry 13) with propan-2-ol as hydrogen donor. In extension, Selvam et al. [44] reported the use of nickel incorporated hexagonal mesoporous aluminophosphate molecular sieves (NiHMA) (Table 1.1, Entry 15). They also used mesoporous PdMCM-41 catalyst with HCO_{2}NH_{4} in MeOH as solvent for chemoselective reductions of nitroarenes [45] (Table 1.1, Entry 16).

Ionic liquids are being used as reaction medium, which are considered as environmentally benign and are widely used in recent years. In this concern, Khan et al. [46] have reported zinc mediated chemoselective
reduction of nitroarenes to amines using ammonium salts in imidazolium ionic liquids (*Table 1.1, Entry 17*).

Wang et al. [47] have reported the use of nanosized activated metallic iron powder in water at an elevated temperature of 210 °C (near critical water) (*Table 1.1, Entry 18*).

Polymer supported reagents are mostly talked of, when we consider the clean and recyclable reagents. Very recently in our laboratory, Abiraj et al. [48 (*Table 1.1, Entry 19*), 49] utilized polymer supported reagents in various functional group transformation reactions. They used polymer supported formate as hydrogen donor to reduce nitroarenes to corresponding amines in excellent yields. Shi et al. [50] have prepared aromatic amines through chemoselective reduction of the corresponding aromatic nitro compounds by using polymer supported hydrazine hydrate over iron oxide hydroxide catalyst in propan-2-ol at reflux temperature (*Tabel 1.1, Entry 20*).

In the recent past, our laboratory has produced a number of reagent systems for the reduction of aromatic nitro compounds containing other reducible moieties such as carbonyl, ethene, ethyne, nitrile, acid, phenol, etc., in good yields. Some of the systems are Zn/NH₂NH₂ [51], HCOONH₄ or HCOOH [52], Raney-Ni/NH₂NH₂.HCOOH [53] or HCOONH₄ or HCOOH [54], Pd-C/HCOONH₄ or HCOOH [55] and Pt-C/HCOONH₄ or HCOOH [56].
### Table 1.1. Reduction of nitroarenes to arylamines.

![Chemical structure of nitroarene and arylamine](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>R (Yield %)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10% Pd/C, Cyclohexene, 10-120 min</td>
<td>2-NO₂, 3,6-OMe (85%), 4-NO₂, 3,6-OMe (85%), 3-NO₂, 2,5-OMe (70%), 2-NH₂, 6-NO₂ (95%), 2-NHCH₃, 6-NO₂ (85%), 2-NH₂, 3,6-OMe (70%), 2-NHCH₃, 3,6-OMe (70%), 2-NH(CH)CH₂CONHCH₃, 3-NO₂ (30%), 2-NO₂ (&gt;90%)a, 3-NO₂ (&gt;90%)a, 4-NO₂ (&gt;90%)a</td>
<td>[2]</td>
</tr>
<tr>
<td>2</td>
<td>5% Pd/C, Et₃N, HCO₂H, ~90-100 °C, 1.3-4.5 h</td>
<td>H (100%), 4-CO₂CH₃ (97%), 2-OCH₃ (94%), 4-OCH₃ (89%), 4-NHCOCH₃ (85%), 2-Br (94%), 3-CH=CHCO₂CH₃ + 3-(CH₂)₂CO₂CH₃ (75%)</td>
<td>[11]</td>
</tr>
<tr>
<td>3</td>
<td>Fe(III)/C, NH₂NH₂.H₂O, reflux, 5-28 h</td>
<td>3-CH₃ (99%), 4-OCH₃ (98%), 2-OMe (98%), 3,4-Me(99%), 4-NHCOCH₃ (92%), 4-OC₆H₅ (98%), 4-OC₆H₄(4'-NH₂) (98%), 2,H₅, 5-Cl (97%), 2-Ome, 5-NHCOC₂H₈ (94%), 4-NHC₂H₄ (4'-OMe) (91%)</td>
<td>[27]</td>
</tr>
<tr>
<td>4</td>
<td>Pd Black/HCO₂H, rt, 1-12 h and Pd Black/HCO₂Na, rt, 15 min-6 h</td>
<td>4-CH₃ (92%), 2-OH (91%), 4-OH (90%), 2-NH₂ (82%), 4-NH₂ (81%), 3-NH₂ (79%), 4-CO₂H (81%), 3-OH (92%), 4-CH₂CO₂H (81%)</td>
<td>[29]</td>
</tr>
<tr>
<td>5</td>
<td>10% Pd-C/HCO₂NH₄, MeOH, rt, 5-60 min</td>
<td>4-CO₂H (52%), 2-Ome, 5-CO₂H (75%), 4-CH₂CO₂H (86%), 4-CO₂CH₂ (89%), H (76%), 2-F (70%), 4-OMe (93%), 2-NH₂, 4-CH₂ (79%), 4-CH₂C≡N (85%), 3-COC₂H₅, 4-NH₂ (91%), 3-CH₂NHCH(=NH)NH₂ (70%)</td>
<td>[30]</td>
</tr>
<tr>
<td>6</td>
<td>Ru₃(CO)₁₁, Et₃N or Pr₂NH, Diglyme, CO (20atm), H₂O, 150 °C, 2 h</td>
<td>2-Cl (&gt;99%), 4-Cl (&gt;99%), 2-Br (&gt;99%), 4-CN (&gt;99%), 4-COC₂H₅ (&gt;99%)</td>
<td>[33]</td>
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<tr>
<td>Reaction</td>
<td>Conditions</td>
<td>Products</td>
<td>References</td>
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<td>7</td>
<td>RhCl((\text{Ph}_3)_3), Et$_3$SiH, PhMe, 110 °C, 2-6 h</td>
<td>4-OMe (86%), 4-Cl (71%), 3-COMe (71%), 4-CO$_2$Me (49%)</td>
<td>[34]</td>
</tr>
<tr>
<td>8</td>
<td>Zr$<em>{0.8}$Ni$</em>{0.2}$O$_2$, KOH, Pr'OH, reflux, 3-6 h</td>
<td>H (96%), 4-Cl (85%), 4-COMe, (88%), 2-OMe (86%), 4-COC$_6$H$_5$ (90%)</td>
<td>[35]</td>
</tr>
<tr>
<td>9</td>
<td>Al, NH$_4$Cl, MeOH, )))), 25 °C, 1-3 h</td>
<td>H (75%), 4-Cl (80%), 2-Cl (70%), 3,4-Cl (75%), 2-NH$_2$ (85%), 3-NH$_2$ (70%), 2-Me (72%), 2-OH (90%), 3-CO$_2$H (70%),</td>
<td>[36]</td>
</tr>
<tr>
<td>10</td>
<td>Pd/C, B$<em>{10}$H$</em>{14}$, 2 drops of AcOH in MeOH, reflux, 0.5-3 h</td>
<td>4-CO$_2$H (97%), 4-CO$_2$Me (96%), 4-CO$_2$CH$_2$C$_6$H$_5$ (91%), 4-NHCOMe (96%), H (90%), 3-Me, 4-Br (81%), 4-Me (91%), 4-CH$_2$CN (95%), 3-CH$_2$OH (94%)</td>
<td>[39]</td>
</tr>
<tr>
<td>11</td>
<td>FeCl$_3$·6H$_2$O, NH$_2$NH$_2$·H$_2$O, µW, 30-70 W, 7-10 min</td>
<td>4-OMe (96%), 4-CH$_3$ (89%), 4-Cl (96%), 4-I (91%), 3-OH (92%), 2-OH (81%)</td>
<td>[40]</td>
</tr>
<tr>
<td>12</td>
<td>CoHMA, KOH, Pr'OH, 356 K, 1.5-5 h</td>
<td>H (91%), 2-Cl (83%), 3-Cl (88%), 4-Br (90%), 4-F (84%), 2-Me (67%), 4-OMe (88%), 2-NH$_2$ (92%), 3-NH$_2$ (86%)</td>
<td>[41]</td>
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<tr>
<td>13</td>
<td>NiMCM-41, KOH, Pr'OH, 356 K, 3.5-5 h</td>
<td>H (93%), 2-Cl (85%), 4-Br (91 %), 4-OMe (90%), 2-NH$_2$ (85%), 4-COMe (83%)$^b$, 2-CHO (84%)$^b$, 3-NO$_2$, 4-Me (82%)$^c$, 3-NO$_2$, 4-Cl (84%)$^c$</td>
<td>[42]</td>
</tr>
<tr>
<td>14</td>
<td>FeHMA, KOH, Pr'OH, 356 K, 2.5-3 h</td>
<td>H (92%), 2-Cl (79%), 4-Cl (89%), 4-F (82%), 4-Br (85 %), 4-OMe (88%), 2-NH$_2$ (73%), 3-NH$_2$ (80%), 2-Me (70%), 3-Me (85%)</td>
<td>[43]</td>
</tr>
<tr>
<td>15</td>
<td>NiHMA, KOH, Pr'OH, 356 K, 1.5-4 h</td>
<td>H (97%), 2-Cl (86%), 3-Cl (90%), 4-Br (93 %), 4-F (91%), 4-OMe (93%), 2-NH$_2$ (89%), 4-Me (89%), 4-OMe (89%) 4-COMe (92%)$^b$, 2-CHO (84%)$^b$, 3-NO$_2$, 4-Me (87%)$^c$, 3-NO$_2$, 4-Cl (88%)$^c$</td>
<td>[44]</td>
</tr>
<tr>
<td>16</td>
<td>PdMCM-41, HCO$_2$NH$_4$, MeOH, 356 K, 30-60 min</td>
<td>H (99%), 2-Me (92%), 3-Me (90%), 3-CO$_2$H (85%), 4-COMe (80%), 3-CHO (82%), 4-OMe (88%), 2-OH (86%), 2-NH$_2$ (87%), 4-CH$_2$CN (83%)</td>
<td>[45]</td>
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</tbody>
</table>
17 Zn, NH₄Cl, [bmim][PF₆]:H₂O (10:1), rt, 7-18 h  
H (93%), 4-Me (94%), 2-Me (85%), 4-O Me (85%), 2-O Me (83%), 4-Cl (89%), 4-I (81%), 3-COMe (91%), 3-F, 4-Me (93%), 2, 3-Cl (90%), 4-OH (77%), 4-NH₂ (79%)  

Zn, HCO₂NH₄, [bmim][BF₄]:H₂O (10:1) rt, 10-12 h  
H (87%), 4-Me (92%), 4-O Me (89%), 2-O Me (81%), 4-I (89%), 3-COMe (90%), 3-F, 4-Me (87%), 2, 3-Cl (89%), 4-NH₂ (76%)  

18 Fe powder (nm), H₂O, 210 ºC, 2 h  
H (95%), 4-Me (96%), 3-O Me (91%), 3-Me (94%), 4-COMe (92%), 4-CO₂Et (94%), 4-F (95%), 4-Cl (95%), 4-Br (90%), 2-Cl (89%)  

19 Mg, NH₃HCOO + MeOH, rt, 1-3 h  
4-I (95%), 3-Cl (94%), 2-Br (96%), 2-O Me (92%), 4-Me (97%), 4-CH=CH₂ (95%), 4-CH₂CN (93%), 4-CHO (91%), 4-COCH₃ (96%), 2-CO₂H, 4-Br (94%), 4-CO₂H (96%), 4-NHCOCH₃ (95%)  

20 Iron oxide hydroxide, HCOO⁻NH₃ NH₂, Pr³OH, reflux, 30-50 min  
H (98%), 2-Me (97%), 3-Me (98%), 2-Cl (93%), 3, 4-Cl (98%), 2-OH (96%), 2-NH₂ (95%), 4-O Me (99%), 4-CO₂Et (95%)  

a Personal communication (I. D. Entwistle), b chemoselective, c regioselective

1.3 REDUCTION OF AZOARENES TO HYDRAZOARENES

The reduction of azo compounds is considered as one of the best way to synthesize hydrazo compounds. In 1930, Ritter and Ritter [57] reported the reduction of azo compounds to hydrazo compounds, in their effort to synthesize mono-acetyl derivatives of the unsymmetrical hydrazobenzenes. They used zinc dust and glacial acetic acid in boiling alcohol for reduction. Here they claim that, their method of reduction is more convenient than that of Jacobson and Lischke [58] in which reduction was accomplished with zinc dust and sodium hydroxide.

Hayashi et al. [59] demonstrated the catalytic reduction of 4,4'-azopyridine 1,1'-dioxide (I) and 4,4'-azoxyppyridine 1,1'-dioxide (II) in
methanol using Raney nickel as catalyst at atmospheric temperature and pressure (Scheme 1.1 and Scheme 1.2). Here, they observed that the formation of the corresponding hydrazo compound was a result of absorption of 3 moles of hydrogen. The same reduction with palladium-carbon as a catalyst afforded the 4,4’-hydrazopyridine 1,1’-dioxide(VI).

Cousino [60] has reported his invention of reduction of certain 2,2’-disubstituted azoxybenzenes and azobenzene to corresponding hydrazobenzenes. According to his invention certain 2,2’- disubstituted hydrazobenzenes, namely 2,2’- dichlorohydrazobenzene 2,2’-dimethylhydrazobenzene and 2,2’-dimethoxyhydrazobenzene were produced from the corresponding 2,2’-disubstituted azoxybenzene or azobenzene. Here, he used iron filings or powdered iron, lead acetate and dilute acid (5% HCl) for reduction at the temperatures of about 55° to 65 °C. The solvents used are benzene and methanol.

Casewit et al. [61] used Molybdenum(IV) complexes of composition [MeCpMo(µ-S)]$_2$S$_2$CH$_2$(I) and [MeCpMO(µ-S)(µ-SH)]$_2$(II), where
MeCp = CH$_3$C$_5$H$_4$, as homogeneous catalysts for the reduction of a azoarenes under 2-3 atm of hydrogen at mild temperatures (25 ºC) (*Scheme 1.3*).

\[
\text{PhN=NPh + H}_2 \xrightarrow{\text{(MeCpMoSSH)}_2 \text{ or (MeCpMoS)}_2 \text{S}_2 \text{CH}_2} \text{PhHN-NPh}
\]

Organic solvent, 25 ºC

*Scheme 1.3*

Alberti et al [62] reported the reaction of a series of substituted azoarenes with tributyltin hydride to afford hydrazo compounds with high chemoselectivity and good to high yields (*Scheme 1.4*). But, they observed the formation of mixtures of hydrazo derivatives and N-heterocycles or cyclic products when, *ortho*-substituted azoarenes were used i.e., azoarene bearing substituents such as CN, COOR or CH$_2$OH at ortho to azo function.

\[
\text{ArN=NAr'} \xrightarrow{\text{Bu}_3\text{SnH}} \text{ArHN-NAr'}
\]

benzene, reflux (3-5 h)

Ar = Ph, 3,5-(MeO)$_2$C$_6$H$_3$

Ar' = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-IC$_6$H$_4$, 4-NCC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-CH$_2$OH, 4-MeC(O)C$_6$H$_4$, 4-pyridyl

*Scheme 1.4*

Park and Han [63] reported the reduction of various azoarenes and azoxyarene almost quantitatively to the corresponding hydrazoarenes by sodium dithionite under mild conditions without the formation of aniline derivatives, using dioctyl viologen as an electron-transfer catalyst in acetonitrile-water (*Scheme 1.5*).

*Scheme 1.5*
Patil et al. [64] also investigated the same approach and observed that hydrated zirconia has been found to be an efficient and reusable catalyst for the selective reductions of azoarenes (Scheme 1.6). The product, hydrazo compounds were achieved in 5-10 hrs at reflux temperature in high yields. Azo compounds containing other reducible substituents such as -CH₃, -Cl, -CO₂H, -NH₂, etc, were rapidly reduced to corresponding hydrazo compounds.

\[
\text{Ar} = \text{Ph}, 4\text{-MeC}_6\text{H}_4, 2\text{-MeC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4
\]

Scheme 1.6

Khan et al.[46] reported a chemo-selective reduction of azo compounds in ionic liquids using zinc and ammonium salts (Scheme 1.7). They found that, azobenzenes were smoothly reduced to hydrazobenzenes with Zn/HCO₂NH₄ (aq.) in recyclable [bmim][BF₄] without any over reduction to the corresponding anilines. Recently, Prasad et al. [65,66] reported the synthesis of hydrazo compounds from azo compounds using Raney-Ni/H₂NNH₂·HCO₂H and Zn/H₂NNH₂·HCO₂H in methanol at room temperature.

\[
\text{Ar} = \text{Ph}, 4\text{-MeC}_6\text{H}_4, 2\text{-MeC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4
\]

Scheme 1.7

Recently, Yin et al. [67] reported the reduction of azo compounds to hydrazo compounds in their synthesis of sulfonated diamine isomers, 2,2’-bis(3-sulfopropoxy)benzidine (2,2’-BSPB) and 3,3’-bis(3-sulfopropoxy)benzidine (3,3’-BSPB) (Scheme 1.8). They used zinc powder in presence of weak acid to achieve reduction and further, the diamines were obtained by rearrangement reactions of hydrazo compounds in hydrochloric acid.

Scheme 1.8
1.4 REDUCTION OF IMINES TO SECONDARY AMINES

The reduction of imines is a very convenient and explicit route to the synthesis of substituted amines [68]. Here in this section, the reduction of imines to secondary amines is discussed.

The Fig 1.1 illustrates a brief classification of the major traditional methods for the synthesis of secondary amines. Very recently, Salvatore et al. [69] have given detailed report of secondary amine synthesis. Among all the methods, complete reduction of certain functionalities using a variety of reducing agents is considered as one of the most convenient method.

![Diagram of methods for synthesis of secondary amines](image)

*Fig 1.1: Some of the methods for synthesis of secondary amines [68]*

Botte et al. [70] reported the reduction of several N-alkyl and N-aryl ketimines to the corresponding secondary amines using isopropyl alcohol and aluminum isopropoxide in the presence of Raney-Ni (*Scheme 1.9*). Hoye et al. [71], in their total synthesis of (ent)-korupensamine D, cyclic imine was reduced using H₂ and 10% Pd/C, which gave rise to *cis*-configured secondary amine in 93% yield (*Scheme 1.10*).
Fu and Lopez [72] have reduced a wide variety of imines to the corresponding amines using polymethylhydrosiloxane (PMHS) in ethanol at room temperature in the presence of n-butyltin tris(2-ethylhexanoate) as the catalyst. Alkene, alkynes, alkyl bromides, epoxides, esters and nitriles are stable under the reaction conditions. For example, N-benzylideneaniline cleanly gives N-phenylbenzylamine in 82% yields after 7 h at room temperature (Scheme 1.11). Similarly, titanium based catalysts in conjunction with PMHS have been used to reduce imines to secondary amines (Scheme 1.12) [73]. Here, the titanium species is first reacted with phenylsilane to generate a titanium catalyst. The slow addition of sec-butylamine results in exchange of amine ligands of the titanium complex to release the amine product. The same protocol has been used in highly efficient synthesis of the amine NPS R-568 (Scheme 1.13), a potentially active compound for the treatment of hyperparathyroidism via reduction of the imine [74].
Mao and Baker [75] reported the asymmetric transfer hydrogenation of several heterocyclic imines using a chiral rhodium complex, (R)-Cp*RhCl[(1S,2S)-N-p-toluenesulfonyl-1,2-diphenylethylenediamine] [(R)-Cp*RhClTsDPEN], generated from [Cp*RhCl₂]₂ and (1S,2S)-N-p-toluenesulfonyl-1,2-diphenylethylenediamine [(S,S)-TsDPEN], in combination with HCO₂H-Et₃N as the hydrogen source and have been achieved in up to 99% ee (Scheme 1.14).

Barmore et al. [76], in their one-pot reductive amination of nitriles with DIBAL-H involved trans-imidation by the addition of primary amine and further reduced to the secondary amine using NaBH₄ (Scheme 1.15). Reduction of imines to secondary amines was achieved using Zn(BH₄)₂ supported on silica gel in good yields [77].
Blackwell et al. [78] reduced a wide range of benzaldimines and ketimines via silyliminium intermediate to the corresponding secondary amines. In this legend, B(C₆F₅)₃ was employed as a catalyst (5-10 mol%) in conjunction with PhMe₂SiH (**Scheme 1.16**).

**Scheme 1.16**

Addition of HMPA to SmBr₂ in THF enables ketimines to be reduced to the corresponding amines at 20 ºC [79] (**Scheme 1.17**). Secondary amines free from the common side products of over alkylation and carbonyl starting materials have been prepared by transimination of a resin-bound aldehyde with a solution-phase primary amine to give a solution-phase imine that undergoes reduction with resin-bound borohydride to furnish the secondary amine in solution [80] (**Scheme 1.18**).

**Scheme 1.17**

**Scheme 1.18**

Basu et al. [81] reported a polymer supported reaction procedure for the reduction of imines. The reduction was accomplished within
10-16 hrs with good yields using 10% Pd-C and polymer supported formate at 70-75 °C (Scheme 1.19).

\[
\begin{align*}
\text{R}^1 = \text{R}^2 &= \text{Ph}, \text{Ar}, \text{H} \\
\text{X} &= \text{C}, \text{N} \\
\text{R}^3 = \text{R}^4 &= \text{CN}, \text{COOEt}, \text{COOMe}, \text{NHBoc}, \text{H}, \text{Ph}
\end{align*}
\]

Scheme 1.19

Malkov et al. [82] reported asymmetric reduction of ketimines with trichlorosilane catalyzed by a new N-methyl L-valine derived Lewis basic organocatalyst (Scheme 1.20).

\[
\begin{align*}
\text{Ar} &\text{N} \\
\text{Cl}_3\text{SiH} &\text{Cat.}^* \\
\text{Toluene, r.t} &\text{HN} \text{Ph} \\
(92\% \text{ e.e.}) &\text{Cat.}^*
\end{align*}
\]

Scheme 1.20

Recently, Nolin et al. [83] described the development of a novel Re(V)-oxo complex for the catalytic enantioselective reduction of imines to the corresponding secondary amines. Here, they reports that the catalyst system operates well with either dimethylphenylsilane (DMPS-H) or diphenylmethylsilane (DPMS-H) as hydride source (Scheme 1.21).

\[
\begin{align*}
\text{R} &\text{N} \text{P(O)Ph}_2 \\
\text{3 mol% Cat.} &\text{DMPS-H, CH}_2\text{Cl}_2, \text{r.t} \\
\text{HN} \text{P(O)Ph}_2 &\text{R} \text{N} \text{P(O)Ph}_2
\end{align*}
\]

Scheme 1.21
It has been the central focus in modern organic synthesis to develop highly efficient catalytic processes for the syntheses of natural and unnatural compounds of medicinal interest or intermediates useful for functional materials. One of the most attractive approaches to such aims is to apply transition metal-catalyzed reductive cyclization reactions for the transformations of simple starting materials into monocyclic, bicyclic, and polycyclic scaffolds that can be further elaborated into specific targets. In this account, we brief the synthesis of indolones (oxindoles) and quinolones (quinolinones) in the following section.

1.5 SYNTHESIS OF INDOLONES AND QUINOLONES

In 1945, Sumpter reported a detailed survey on indolone (oxindole) synthesis [84]. According him, the first reports of synthesis of oxindole was by Baeyer in the year 1866 and 1868. Baeyer and Knop [85] synthesized indolone by the reduction of isatin. They obtained 3-hydroxyindolin-2-one (dioxindole) upon reducing isatin with sodium amalgam in alkaline medium. Further reduction of dioxindole with tin and mineral acids or sodium amalgam in acid medium gave oxindole. Later, there are several reports on reduction of isatin to oxindole using various reagent systems. But, the first synthesis of oxindole, other than by the reduction of isatin was again by Baeyer [86] through the reduction of 2-nitrophenylacetic acid with tin and hydrochloric acid (Scheme 1.22).

![Scheme 1.22](image)

Di Carlo [87] found that catalytic reduction of o-nitrophenylacetic acid with Adams catalyst gave oxindole in good yield. Under certain conditions some 1-hydroxyoxindole was obtained as a by-product. Later on
Walker [88] utilized a similar protocol for the synthesis of 5,6-dimethoxyoxindoles. The process was a low-pressure hydrogenation of 4,5-dimethoxy-2-nitrophenylacetic acid or ester in presence of palladium-charcoal. He obtained amino ester upon hydrogenation of nitro-ester in ethyl acetate at room temperature in presence of palladium-charcoal, but on using acetic acid as solvent at an elevated temperature, 80 °C, he found the ring closure to the oxindole (Scheme 1.23).

\[ \text{NO}_2 \quad \text{COOEt} \]
\[ \text{H}_3\text{CO} \quad \text{H}_3\text{CO} \]
\[ 3\text{H}_2 \quad (\text{H}^+) \]
\[ \text{Pd-C, Ethyl acetate} \]
\[ \text{Pd-C, Acetic acid, 80°C} \]

Scheme 1.23

Wright, Jr., and Collins [89] prepared a series of oxindoles and 1-hydroxyindoles by the zinc and sulfuric acid reduction of the appropriate o-nitrophenylacetic acids. Here, they obtained 1-hydroxyindolone as the major product and oxindole as a by-product (Scheme 1.24). In an attempt to improve the yields of 1-hydroxyoxindole, they have tried the reduction with (a) zinc and calcium chloride (b) calcium sulfhydrate. But, yield was 15% in the first case where as in second case no product. In continuation, they synthesized 5-bromooxindole through 1-hydroxyoxindole (Scheme 1.25).

\[ \text{CH}_3 \quad \text{NO}_2 \quad \text{R} \quad \text{diethyl oxalate} \]
\[ \text{sodium methylate} \]
\[ \text{HCl} \quad \text{H}_2\text{O} \]
\[ \text{H}_2\text{O}_2 \]
\[ \text{Zn} \quad \text{H}_2\text{SO}_4 \]

Scheme 1.24
Simet [90] utilized Baeyer method of oxindole synthesis \textit{i.e.}, acid reduction of the appropriately substituted 2-nitrophenylacetic acid, in the preparation of 6-trifluoromethylisatin from the corresponding oxindole (\textit{Scheme 1.26}).

Beckett et al. [91] have prepared a series of oxindole derivatives substituted in the aromatic ring and their N-Me homologues. They synthesized appropriate \textit{o}-nitrophenylacetic acid and performed catalytic reduction using Pd/C to get the corresponding cyclized product.

Gassman and van Bergen [92] reported a new method of oxindole synthesis as shown below. (\textit{Scheme 1.27, Table 1.2}). Later on Wright et al. [93] modified the Gassman oxindole synthesis. They described the procedure that proceeds through anilines and ethyl(methylsulfinyl)acetate, using oxalyl chloride to activate the sulfoxide to facilitate the formation of the key \textit{N-S} bonded intermediate (\textit{Scheme 1.28}).
Table 1.2: Yields obtained in conversion of anilines (I) to oxindoles (IV) with ethyl methylthioacetate.

<table>
<thead>
<tr>
<th>Aniline</th>
<th>X</th>
<th>R</th>
<th>Methylthio-oxindole</th>
<th>Yield of (III) (%)</th>
<th>Oxindole</th>
<th>Yield of (IV) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Ia)</td>
<td>H</td>
<td>H</td>
<td>(IIla)</td>
<td>84</td>
<td>(IVa)</td>
<td>76</td>
</tr>
<tr>
<td>(Ib)</td>
<td>p-CH₃</td>
<td>H</td>
<td>(IIlb)</td>
<td>34</td>
<td>(IVb)</td>
<td>55</td>
</tr>
<tr>
<td>(Ic)</td>
<td>o-CH₃</td>
<td>H</td>
<td>(IIlc)</td>
<td>67</td>
<td>(IVc)</td>
<td>72</td>
</tr>
<tr>
<td>(Id)</td>
<td>H</td>
<td>CH₃</td>
<td>(IIId)</td>
<td>46</td>
<td>(IVd)</td>
<td>77</td>
</tr>
<tr>
<td>(Ie)</td>
<td>p-CO₂C₂H₅, o-CH₃</td>
<td>H</td>
<td>(IIle)</td>
<td>66</td>
<td>(IVe)</td>
<td>67</td>
</tr>
<tr>
<td>(If)</td>
<td>p-NO₂</td>
<td>H</td>
<td>(IIIf)</td>
<td>51 a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a No attempt was made to carry out a Raney-nickel desulfurization of (IVf)

Scheme 1.28

Cortese and Hack [11] reported the formation of saturated lactams *i.e.*, oxindole and quinolinone on reduction of *o*-nitrophenylacetic acid and *o*-nitrocinnamic acid respectively. They used triethylammonium formate with palladium on charcoal as catalyst for reduction at boiling temperature of the reaction mixture (~90-100 °C) (Scheme 1.29). The product,
quinolinone obtained was in 72% yield where as the other one was a 1:1 mixture of oxindole and o-aminophenylacetic acid. Sublimation of the product mixture produced the oxindole in 75% yield.

RanjanBabu et al. [94] synthesized various 2-indolinones (oxindoles) by reductive cyclization of α-(2-nitroaryl)acetic acid derivatives in 20% ethyl acetate in ethanol at 40-59 psi of hydrogen. Depending on the catalyst used, they observed the dechlorination with certain chlorinated substrates. Hence, they have used sulfided platinum and palladium carbon as catalysts and obtained moderate to good yields (Table 1.3). They also reported the catalytic reduction of the γ-butyrolactone adducts to obtain 3-(2-hydroxyethyl)-2-indolinones (Table 1.4).

Table 1.3: Synthesis of oxindoles by RanjanBabu et al [94].

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>R</th>
<th>Method*</th>
<th>Yield % (2-indolinone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>H</td>
<td>A</td>
<td>76</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>Cl</td>
<td>H</td>
<td>H</td>
<td>A</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>Cl</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>A</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>B</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>Cl</td>
<td>H</td>
<td>Me</td>
<td>B</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>Cl</td>
<td>Cl</td>
<td>H</td>
<td>Me</td>
<td>B</td>
<td>54</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>B</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>OMe</td>
<td>H</td>
<td>Me</td>
<td>B</td>
<td>68</td>
</tr>
</tbody>
</table>

*Method A. Pt/S/C/H₂  B. Pd/C/H₂
Table 1.4: Synthesis of 3-(2-Hydroxyethyl)-2-indolinones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting material</th>
<th>Method</th>
<th>Indolinone</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Pd/C/H₂</td>
<td>H</td>
<td>52</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>Pd/C/H₂</td>
<td>H</td>
<td>45</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>Pd/C/H₂</td>
<td>H</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>Cl</td>
<td>Pd/C/H₂</td>
<td>OH</td>
<td>63</td>
</tr>
<tr>
<td>5</td>
<td>Cl</td>
<td>Fe/AcOH</td>
<td>H</td>
<td>28</td>
</tr>
</tbody>
</table>

Quallich and Morrissey [95] reported a general three-step synthesis of oxindoles which is formulated on employing a malonate addition to a substituted \( \alpha \)-halo nitrobenzene to control regiochemistry (Scheme 1.30)

Scheme 1.30

Boix et al. [96] have prepared indole and quinoline derivatives by reduction of suitably functionalised \( \alpha \)-nitroarenes with zinc in near-critical water at 250 °C. In the process they observed the formation of hydroquinoline or hydroquinolinone depending upon the substrate used. They found that the dihydroquinolinone was the major product upon using \( \alpha \)-nitrocinnamic acid. Hennessy and Buchwald [97] have developed a novel variant of the Friedel-Crafts procedure using palladium-catalyzed C-H functionalization. They used the combination of catalytic amounts of palladium acetate, 2-(di-\( \text{di-} \)-tert-butylphosphino)biphenyl as a ligand and...
triethylamine as base to convert α-chloroacetanilides to oxindoles in high yields (Scheme 1.31).

Recently, Poondra and Turner [98] reported the microwave-assisted synthesis of N-substituted oxindoles. The method is a two-step process which involves initial microwave-assisted amide bond formation between 2-halo-arylacetic acids and various alkylamines and anilines, followed by a palladium catalyzed intramolecular amidation under aqueous conditions. The procedure can be carried out as one-pot process without isolation of the intermediate amide, while using alkylamines (Scheme 1.32). In optimizing the reaction conditions for palladium catalyzed intramolecular amidation they have screened various phosphine ligands in combination of palladium source/solvent/base (NaOH) and found that the ligand shown bellow is suitable one.
1.6 SYNTHESIS OF AMIDES OF AMINO ACIDS AND PEPTIDES

The abundance of the amide function in both natural products and man-made compounds shows the significance of the amide functional group and their synthesis. Although many methods are available to synthesize amide functional group, there remains the opportunity to develop new techniques that may be more efficient.

One of the most adopted methods to synthesize amides is solid phase synthesis through cleavable linkers. James [99] has published a detailed report on linkers that are commonly used for solid phase organic synthesis. Marzinzik and Felder [100] reported a procedure that, the nitrogen of the linker is acylated by a carboxylic acid using a range of acylating reagents such as DIC/DMAP or HOBt/BOP, although more forcing conditions may be required to prepare bulky amides. Cleavage is typically achieved with 50% TFA/DCM, although lower concentrations of TFA may be used, e.g. 20% TFA/DCM (Scheme 1.33).

\[
\text{NH}_2 \xrightarrow{\text{acylation}} \text{OH}_2 \xrightarrow{20-50\% \text{TFA/DCM}} \text{R}
\]

Scheme 1.33

Sieber: the amine of the Sieber linker can be easily acylated [101] and the amide is very acid labile, cleaved in 1% TFA/DCM [102] (Scheme 1.34).

\[
\text{O} \xrightarrow{\text{acylation}} \text{O} \xrightarrow{1\% \text{TFA/DCM}} \text{H}_2\text{N} \text{R}
\]

Scheme 1.34

PAL: The PAL linker [103,104] can be used to generate primary amide by cleaving with 70% TFA/DCM (Scheme 1.35).

Benzhydryl: The benzhydryl amine and related \( p \)-methylbenzhydryl amine linkers are also used for the preparation of primary amides. Here, due to its electron richness, the strong acid HF is used for cleavage (Scheme 1.36) [105,106].
Ester Linker: The benzylic ester linker can be treated with an unhindered amine to cleave the product as an amide incorporating the amine used for the cleavage (Scheme 1.37). Primary amides are obtained by the aminolysis of the HMB [107] and glycolamido [108,109] linkers.

Kaiser Linker: Kaiser’s oxime linker has been used to couple carboxylic acids, which then may be cleaved with ammonia to obtain primary amide (Scheme 1.38) [110,111].

Photolabile: 2-Nitrobenzyl amine linkers have been used as photolabile amide linkers (Scheme 1.38) [112]. 2-Nitrobenzhydryl amine linker is used as improvised methods to obtain primary amides (Scheme 1.39) [113].
Peptides prepared on Pepsyn KB resin (polydimethylacrylamide Kieselguhr resin) were cleaved with ammonia/tetrahydrofuran vapour to get the peptide amide (Scheme 1.40) [114].

Pozdnev [115] reported the application di-tert-butyl pyrocarbonate as condensing reagent in the presence of pyridine and ammonium hydrogen carbonate for the preparation of amides of protected amino acids and peptides (Scheme 1.41).

Scott et al. [116] synthesized amino amides and peptide amides with unnatural side chains using solid-phase chemistry, from glycine attached directly (or through an intervening peptide sequence) to a Rink resin. The glycine is converted to an activated benzophenone imine derivative,
followed by C-alkylation and hydrolysis. Cleavage with trifluoroacetic acid produced the final amide products (Scheme 1.42).

Scheme 1.42

Cros et al. [117] described new strategy for solid-phase synthesis of C-terminal peptide amides based on the use of N-tetrachlorophthaloyl protected amino acids with acid-labile side-chain protection (Scheme 1.43).

Recently, Chinchilla et al. [118] prepared new ammonium and alkylammonium salts derived from a polymeric N-hydroxysuccinimide (P-HOSu) and used for amidation of carboxylic acids and amino acids mediated by 1-ethyl-3-(3’-dimethylamino-propyl)carbodiimide hydrochloride (EDC) (Scheme 1.44).

Scheme 1.43
Scheme 1.44
1.7 REFERENCES

45. Selvam, P.; Sonavane, S. U.; Mohapatra S. K.; Jayaram, R. V. 
   13, 7783 (2003).
47. Wang, L.; Li, P.; Wu, Z.; Yan, J.; Wang, M.; Ding, Y. *Synthesis.* 2001
   (2003)
   (2005).
   (2005).
   Japan.* 8, 649 (1960).
61. Casewit, C. J.; Casewit, D. E.; Wright, L. L.; Miller, W. K.; Rakowski
86. Baeyer, A. Ber. 11, 582, 1228 (1878).