



REVIEW ARTICLE

Synthesis of ruthenium complexes and their catalytic applications: A review



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Received 7 April 2022; accepted 30 July 2022

Available online 4 August 2022

KEYWORDS

Ruthenium;
Complexes;
Synthesis;
Catalysis;
Bioactivity;
Pincer;
Shiff-base;
NHC

Abstract Ruthenium complexes are an important class that has multiple catalytic and biological applications. Ruthenium has a remarkably broad and diversified chemical spectrum. In the emerging fields of catalysis, such as homogeneous, heterogeneous, and photo catalysis, ruthenium complexes are being studied. Moreover, Ruthenium complexes can be used in the development of efficient chemotherapeutic drugs for cancer, even though some of them are in the final stage of clinical trials. This review covers the synthesis of the pincer, Shiff base, phosphine, *N*-heterocyclic carbenes, cycloruthenated, and half sandwiched ruthenium complexes and their potential catalytic and biological applications reported in the last 15 years.

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Peer review under responsibility of King Saud University.



1. Introduction

Ruthenium metal was discovered by Russian chemist Karl Klaus (1796–1864) in the 18th century (Sahu et al., 2018). Ruthenium serves as a unique catalyst in oxidative reactions due to its variable oxidation state which ranges from +2 to +8 (Ablialimov et al., 2014). Ru exists in two stable oxidation states (II and III), that can be linked with auxiliary ligands of various geometries to form a variety of Ru(II/III) complexes with varied electronic and steric properties (Jabłońska-Wawrzycka et al., 2013; Lee et al., 2020).

Ruthenium metal occupies a significant position in both excited-state chemistry and catalysis due to their well-studied organometallic and coordination chemistries. Various ruthenium compounds have promising applications in catalysis and their low toxicity tends to make them an ideal option for catalytic drug synthesis (Clarke, 2002; Crochet and Cadierno, 2014). These characteristics, together with the fact that ruthenium compounds are less expensive than other platinum-group metal compounds (Pd, Pt, Rh, and Ir), have made them the favored choice for many catalytic reactions. Ruthenium compounds are increasingly being investigated for use as pharmaceuticals because of their better biocompatibility compared to many other metallo-drugs (Lawrence et al., 2018).

It is worth noting that the medicinal properties of ruthenium are now being discovered, and anticancer agents of ruthenium have recently entered clinical trials, with promising results on resistant tumors. Most investigations of organometallic reagents have targeted their anti-tumor activity throughout the last two decades. While cisplatin is considered the “golden standard” in this respect, it is faced with a vast array of drug resistance and adverse effects (Hartinger et al., 2008; Wheate et al., 2010; Biot et al., 2011; Gasser, 2015). Complex compounds having ruthenium ions are the type of metal complex which has been extensively studied for anticancer action; for example, NAMI-A and KP1019 are now in phase 2 clinical trials. Ruthenium complexes have a wide range of biological features, although their anticancer potential is probably the most well-known. The ruthenium complexes (Ru-1 and Ru-2) exhibit excellent activity against cancer (Fig. 1). The (Ru-2) particularly exhibits excellent results in MCF-7 breast cancer cells (Pastuszko et al., 2016; Skoczynska et al., 2017b; Skoczynska et al., 2017a; Namiecińska et al., 2019; Małecka et al., 2021).

The current research proposed by Lu et al. based on the potential dual-targeting Ru(IV) candidate with antimetastatic and anticancer properties of ruthenium complexes which is under in vitro and in vivo investigation via the PARP/ATM route (Lu et al., 2021).

Ruthenium complexes can be used in the development of efficient chemotherapeutic drugs for human lung cancer (Sun et al., 2021). Ruthenium complexes have overall low toxicity and cumulate in cancer cells because these complexes have a range of accessible oxidation states, a fast rate of ligand exchange, and the potential to simulate strong metal interaction with certain biomolecules (Zeng et al., 2022).

The most likely first findings on biological properties triggered by metal N-heterocyclic carbene (NHC) complexes seem between 1996 and 1999 when antifungal and antibacterial activities were described for various rhodium(I) and ruthenium(II) complexes (Çetinkaya et al., 1996; Durmaz et al., 1997; Cetinkaya et al., 1999). Ruthenium compounds have recently been explored as potential antibacterial agents (Namiecińska et al., 2022). Jian et al. reported the antibacterial properties of ruthenium (II) polypyridyl complex [RuCl (MePhtpy)(dpp)]⁺. These complexes show antibacterial properties in the absence of light which is further enhanced by photoirradiation (Jain et al., 2022).

The chemistry of ruthenium is extremely diverse and vast, and new fields in catalysis are continuously emerging (homogeneous, heterogeneous, photo catalysis, etc.). Ruthenium catalysis has now become a significant catalytic tool in synthetic chemistry (Kaur, 2018; Udvardy et al., 2021). In general, ruthenium metal is far less costly than iridium metal (around ten times cheaper) (Siek et al., 2017).

The ruthenium-catalyzed functionalization and C–H bond activation are widely employed in modern synthetic approaches because of significant aspect of catalysis which based on the pioneering work of Kakiuchi, Ackermann, Bruneau Inoue, and Dixneuf groups (Oi et al., 2001; Oi et al., 2002; Kakiuchi et al., 2003; Ackermann et al., 2006; Ueno et al., 2006; Ackermann et al., 2008; Ferrer Flegeau et al., 2011). Murai, Kakiuchi, and Chatani were the first to describe Ru(0)-complex-mediated coupling of olefins with aromatic ketones in 1993 followed by the pioneering work of Lewis in the synthesis of C–C bonds accelerated by Ru-complexes having ortho-metallated triphenyl phosphite ligand (Murai et al., 1993; Özdemir et al., 2008).

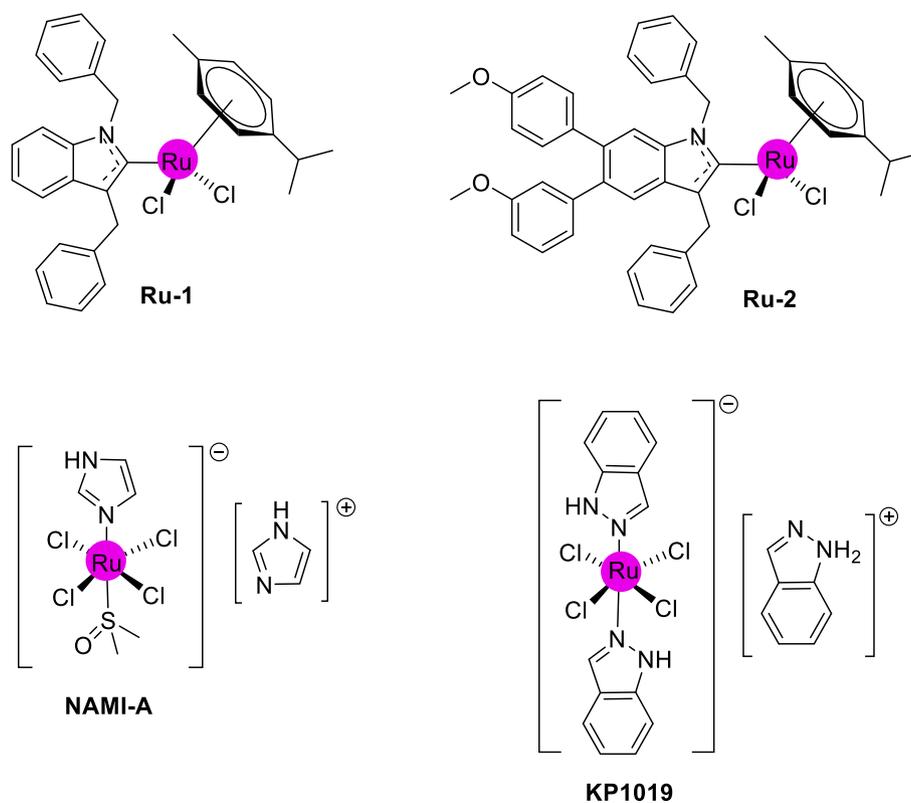


Fig. 1 Some important bioactive complexes.

Ruthenium complexes also capable of catalyzing the oxidative reactions known as “borrowing hydrogen transformations” (Huq et al., 2009; Sahu et al., 2018). The simple synthetic approaches of cyclometallated species through C–H bond breakage, their stability in both water and air, and their stability with currently utilized oxidants are likely reasons for the success of Ru(II) catalysis (Dupont et al., 2005; Boutadla et al., 2009; Djukic et al., 2009). Recently, ruthenium complexes have been utilized as attractive and outstanding catalysts due to good selectivity, versatility, variable oxidation states, high reactivity, and are less expensive than Rh, Pd, Pt, or Ir catalysts (Li et al., 2015; Paterson et al., 2015; Ruiz et al., 2016; Nareddy et al., 2017; Shan et al., 2018).

Ruthenium complexes have been classified based on auxiliary ligands that can coordinate with the ruthenium metal such as Ru-pincer complexes, Ru-phosphine complexes, Ru-Schiff base complexes, Ru-half sandwich arene complexes, Ru-NHC complexes, etc. These ruthenium complexes have promising catalytic potential for a vast range of synthetic applications. Dehydrogenation, oxidation, hydrogenation, amination of alcohols, *N*-alkylation of amines, olefin metathesis reaction, and synthesis of *N*-heterocycles are some promising catalytic applications of ruthenium complexes. One of the most significant catalytic applications of ruthenium complexes is the formation of α -alkylated ketones which are an important area of interest due to their biological activity and are used as intermediate in organic synthesis. Transfer hydrogenation (TH) is an important alternative method for obtaining a wide range of medicinal and industrial compounds. This is a notably green synthetic method due to features which are simple mechanism, high atom-economy, and inexpensive hydrogen donors. Ruthenium complexes containing various auxiliary ligands have been successfully used in this synthetic approach (Çalk et al., 2016; Türkmen and Kavukcu, 2019; Pakyapan et al., 2020). This review gives a brief account of the synthesis of ruthenium complexes and various catalytic applications which can be exploited for applications in the medical field (Fig. 2).

2. Ru-Pincer Complex (RPCs)-Synthesis and applications

Pincer complexes are made up of “tridentate pincer ligands”. These tridentate ligands compel meridional symmetry at the central atom when complexed with metals. Several pincer complexes and their intermediates are become growing more common in chemical synthesis and commercially available because

of their wider application and use in chemical synthesis. These unsaturated and saturated ruthenium pincer complexes having aliphatic and hetero-aromatic frameworks exhibit efficient reactivity and serve as effective catalysts in a variety of synthetic methodologies (Gunanathan and Milstein, 2014). Pincer-based catalytic metal complexes have extraordinary stability to reactivity ratios. RPCs have superior functional group tolerance, selectivity, and efficiency than typical ruthenium catalysts. RPCs have a broad range of uses in catalysis. RPCs possess a significant catalytic capability, which is crucial for turning chemicals into useful products. Dehydrogenative oxidation reactions, hydrogenation reactions, terminal alkynes hydroboration, amination of alcohols, cyclopropanation of olefins, hydrolysis of amines, carbonyl compound olefin metathesis, alkynylation by using terminal alkynes, and racemization of alcohols are few examples of RCPs catalyzed reactions (Younus et al., 2015; Zhang et al., 2020).

2.1. Synthesis of Ru(II)-CNN complexes having pyrazol-indolyl pyridine ligand and their applications

The *N*-heteroarenes and carbonyl compounds are very important in medicinal chemistry and organic transformations. Allen and their coworkers reported (2013) that the metal-catalyzed oxidation of organic compounds using air as an oxidant. Eftekhari-Sis and their coworkers reported (2015) the formation of heterocyclic compounds by using α -oxoesters as starting material. Guo and their colleagues (2015) reported the synthesis of a range of significant structural moieties including *N,O*-heterocycles, *N*-heterocycles, *N,S*-heterocycles, and *O*-heterocycles by using Cu-mediated C–H functionalization. Giustra and their coworkers (2016) reported the homogeneous catalysts for the hydrogenation of heteroarenes and arenes and dehydrogenation of saturated heterocycles, and cycloalkanes respectively (Allen et al., 2013; Eftekhari-Sis and Zirak, 2015; Guo et al., 2015; Giustra et al., 2016). Dehydrogenative catalysis is a cost-effective and green synthetic method (Gunanathan and Milstein, 2013; Peña-López et al., 2015; Daw et al., 2016). This strategy also avoids the use of

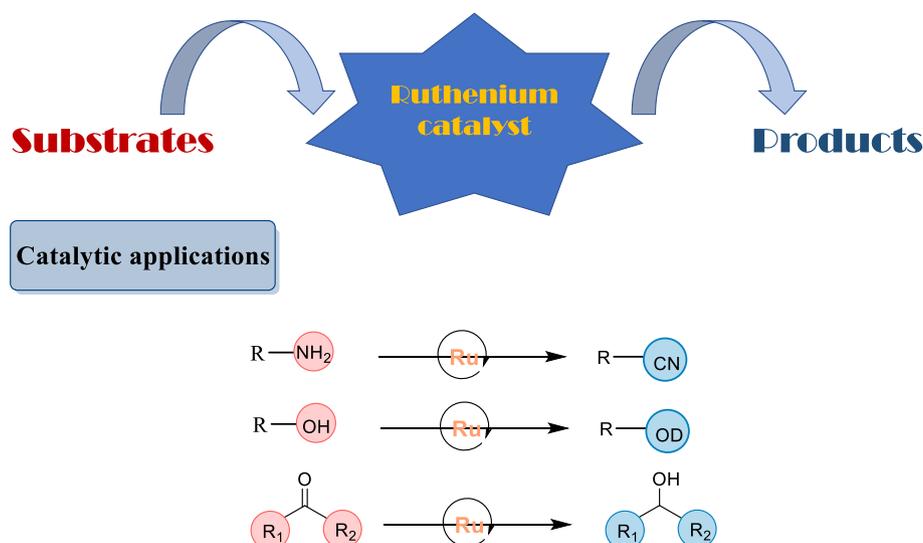


Fig. 2 Generalized scheme of catalytic applications of Ru-complexes.

stoichiometric oxidants and this method is highly desirable in organic synthesis (Suzuki, 2011; Song et al., 2014; Kopylovich et al., 2015; Gülcemal et al., 2016; Crabtree, 2017).

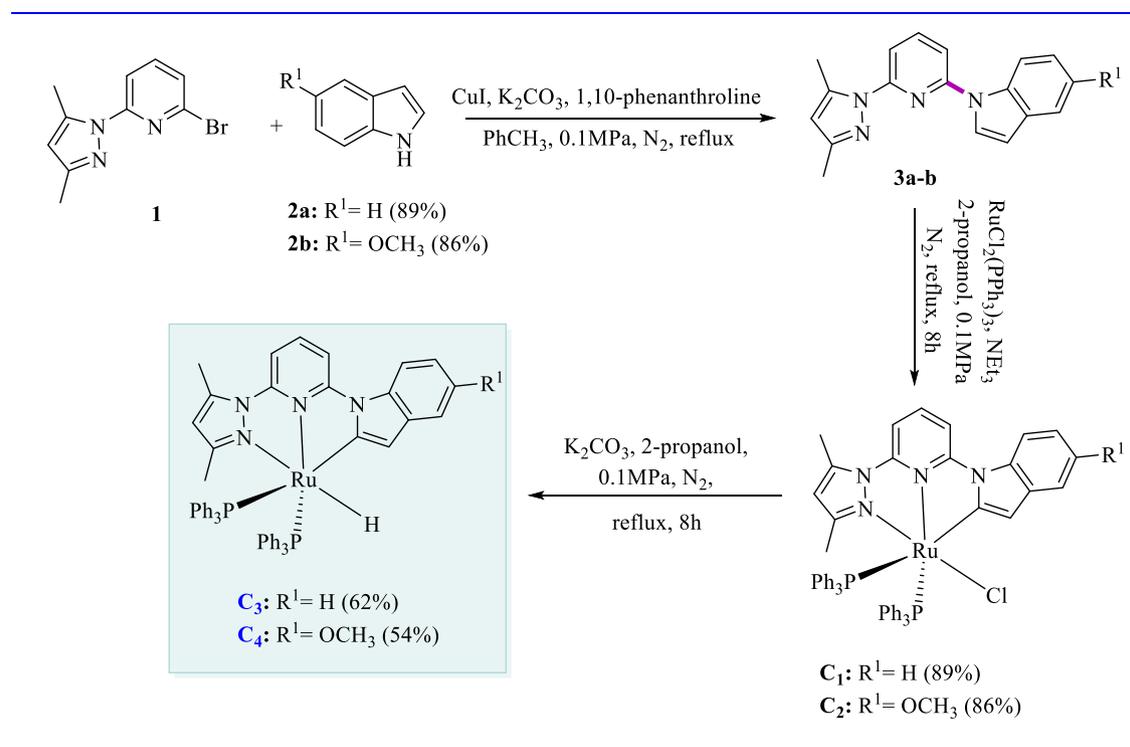
The ruthenium (II) hydride complexes (**C**₃-**C**₄) containing pyrazolyl-(2-indolyl)-pyridine ligand effectively catalyzed the alcohols and *N*-heterocycles dehydrogenation with a wide substrate scope. Ligands (**3a-3b**) were obtained in fair to good yields (68-83%) by the reactions of indole or 5-substituted indoles (**2a-2b**) with pyrazolyl pyridine-based compound (**1**) via *C-N* cross-coupling in the presence of a catalytic amount of copper iodide. The ligands (**3a-3b**) on reaction with RuCl₂(PPh₃)₃ having equimolar concentration with 2-propanol upon refluxing by using NEt₃ as a base afforded the Ruthenium (II) complexes (**C**₁-**C**₂) in 86-89% yields. Ru-hydride complexes **C**₃ and **C**₄ were formed in moderate yields by reacting the mixture of complexes (**C**₁-**C**₂) with K₂CO₃ in 2-propanol upon refluxing (Scheme 1).

It was found that complex (**C**₄) is very efficient in catalyzing the dehydrogenation of alcohols and *N*-heterocycles. The derivatives of *N*-heterocycles tetrahydroquinoline (**4**) with complex (**C**₄) were transformed to derivatives of quinoline (**5**) at 140°C for 48h in the presence of *o*-xylene (Scheme 2). The complex (**C**₄) exhibit highest catalytic activity then Ru (II) complex (**C**₃), producing the quinoline via dehydrogenation product in good yield. Lepidine (**7**) possesses antibacterial properties obtained in a 75% yield via reaction of 4-methyltetrahydroquinoline (**6**) (Scheme 3). The tetrahydroquinolines modified at the 3- or 2-position by a phenyl or methyl group yield the target products (72-89%). The substitution on the substrates having aryl moiety was varied to produce products in good yields (83-93%). The reaction efficiency was lowered when the temperature was decreased up to 120°C. The mild conditions such as reduced the loading

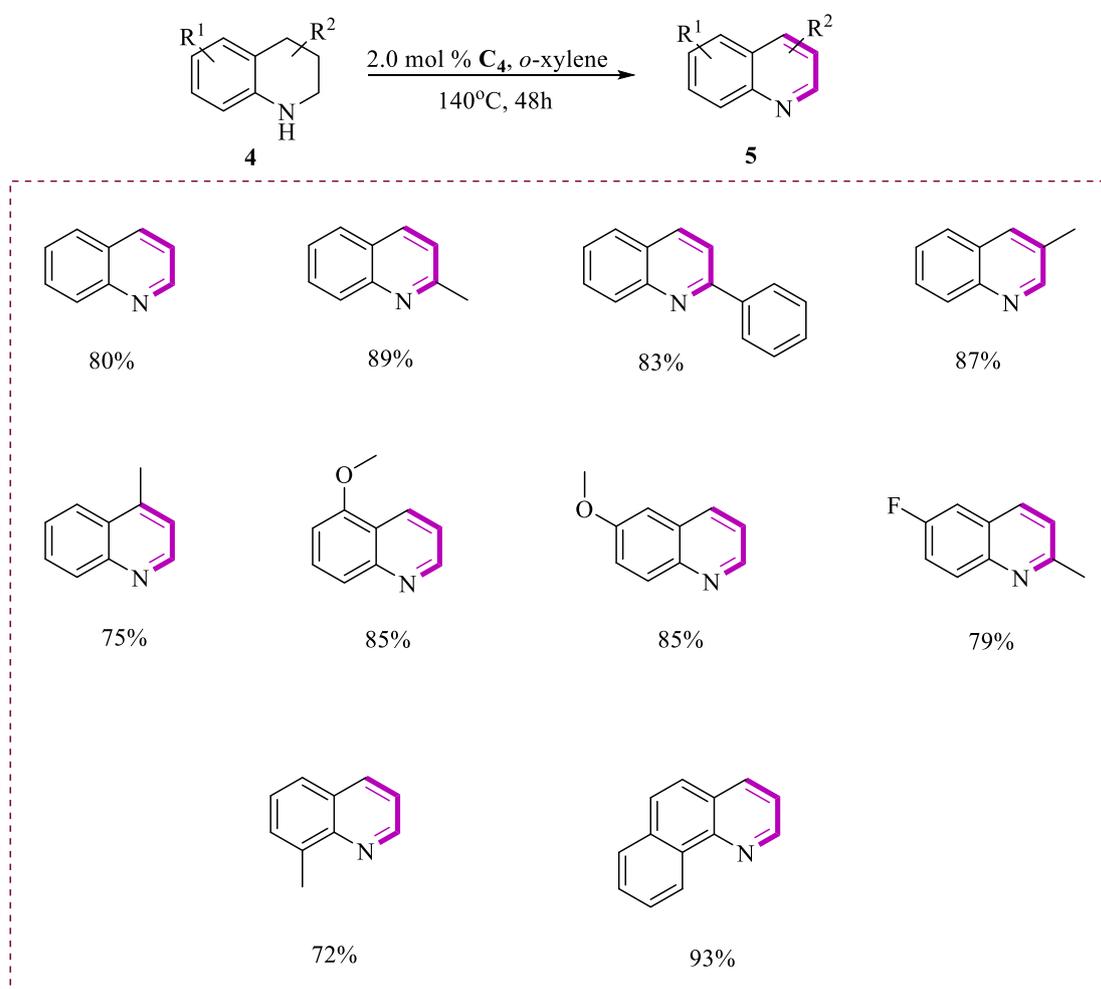
of ruthenium catalyst **C**₄ (2 mol%) at 140°C, higher TONs or TOFs were achieved. These findings show that the current catalysts have excellent catalytic activity and tolerate a wide range of substrates. Under base-free circumstances, the ruthenium (II) hydride complex (**C**₄) could perform the dehydrogenation process more efficiently.

A variety of synthetic methods have been devised to produce derivatives of indoles due to their importance in pharmaceutical and chemical fields. Using the ruthenium complex (**C**₄), derivatives of indoline (**8**) could be effectively dehydrogenated to derivatives of indoles (**9**) in the presence of *o*-xylene at 140°C for 48h (Scheme 4). Indole obtains an 82% yield by a reaction of indoline. Dehydrogenation reactions were also successful on indoline substrates containing 2-Ph, 2-Me, or 3-Me substituent, giving substituted indoles in fair to good yields (78-91%). Indolines with electron-donating substituents dehydrogenated to give (76-88%), and the negative steric effect on the reaction effectiveness is due to the 7-methyl substituent on the substrate. On the phenyl ring of indoline substrates, chloro, fluoro, nitro, and bromo substituents lowered reaction outcomes, yielding remarkably low yields (54-75%). These findings show that the fused benzo moiety, as well as NH-functionality in the *N*-heterocycles, are required for catalytic dehydrogenative reactions to be carried out under the specified conditions.

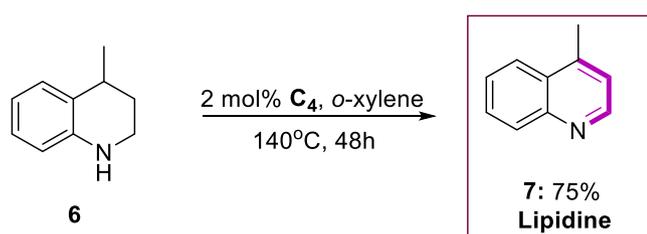
The β-carboline motif has long been known to have a significant role in numerous medications. As a result of the Pictet-Spengler reaction of tryptamine (**A**) and aldehyde (**B**), 1,2,3,4-tetrahydro-carbolines (**10a-10b**) were produced in the presence of TFA under reflux. Compounds (**10a-10b**) underwent comparable dehydrogenative reactions in the presence of complex (**C**₄), yielding the desired β-carboline alkaloids (**11a-11b**) in high yields (75–80%). The current process is a



Scheme 1 Synthesis of pyrazolyl-(2-indolyl)-pyridine-based Ru(II) complexes.



Scheme 2 Dehydrogenation of tetrahydroquinolines.



Scheme 3 Lepidine synthesis.

simple and green synthetic way to obtain derivatives of β -carboline (Scheme 5).

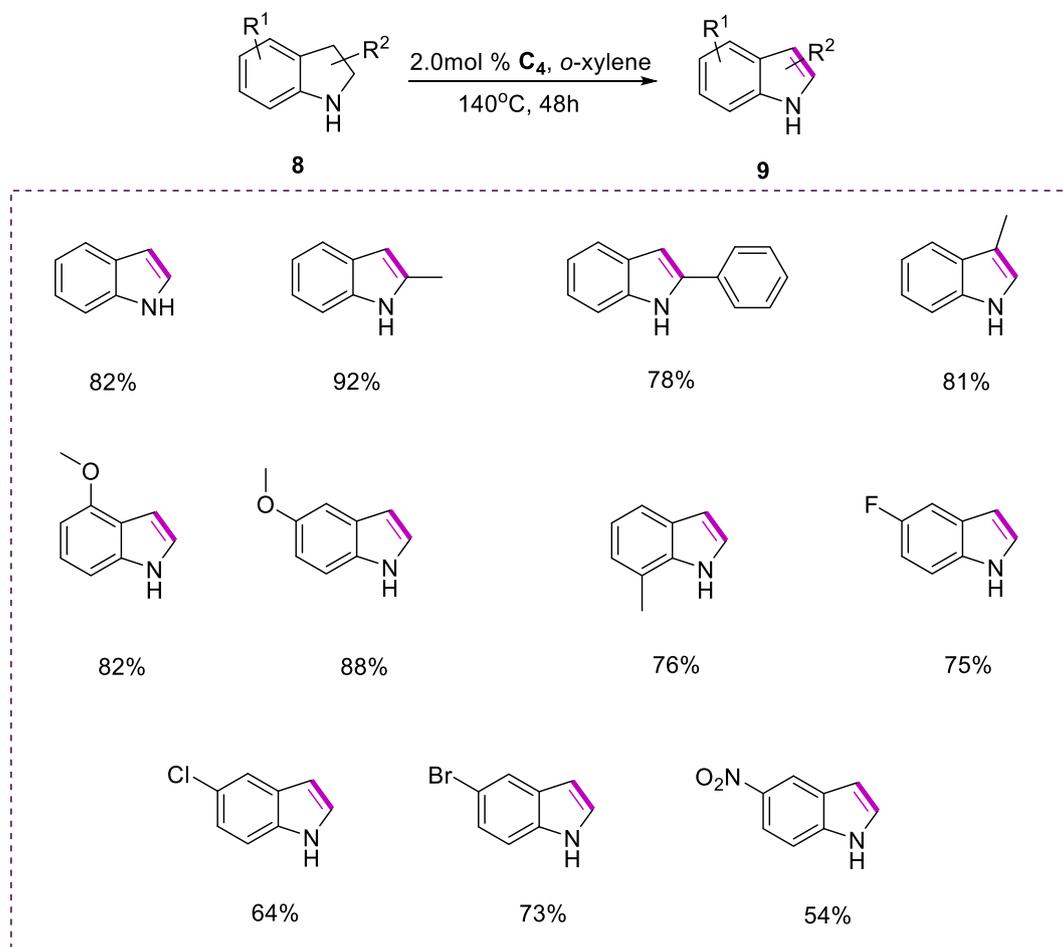
The catalytic dehydrogenation of secondary alcohols (**12**) into corresponding ketones (**13**) was achieved by using toluene as a solvent in the presence of complex (**C₄**) at 110°C. The phenylethanol was converted into acetophenone in excellent yield (92%) in 24h using complex **C₄** (0.5mol%) as the catalyst under reflux in toluene (Scheme 6). The alcohols containing aryl moieties acted as a steric barrier but does not affect the reaction efficacy. Dehydrogenation of 2-methyl-1-phenylethanol, 1-phenylpropanol, and analogs resulted in 94-98% yields of the target ketone products, irrespective of the electron-withdrawing and electron-donating substituents. The

dehydrogenation of diphenylmethanol and naphthalene-2-yl-ethanol resulted in the formation of the respective ketones (98%) and (92%). By increasing the catalyst loading up to 1.0 mol %, ketones were also obtained in excellent yields (87-99 %) as a product of efficient catalytic dehydrogenation of corresponding aliphatic alcohols. Despite comparatively less reactivity of cyclohexanol, a good yield (82%) of cyclohexanone was observed.

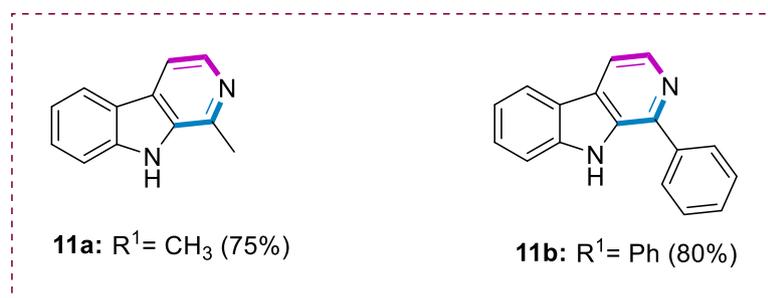
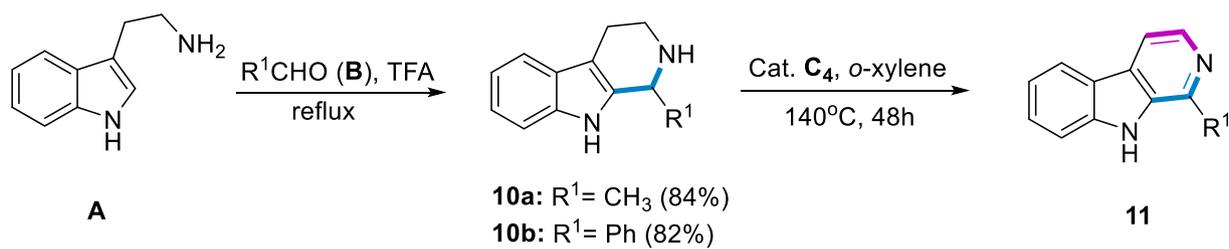
Cholest-5-en-3-ol was also dehydrogenated under the same conditions as α,β -unsaturated ketone cholest-4-en-3-one (**14**) in moderate yield (62%). methyl glycyrrhetinate and 5-Cholestan-3-ol and were also dehydrogenated to the respective ketones (**15** and **16**) in (76%) and (52%) yields indicating that the synthesis procedure might be used in specialized pharmaceutical synthesis (Wang et al., 2018).

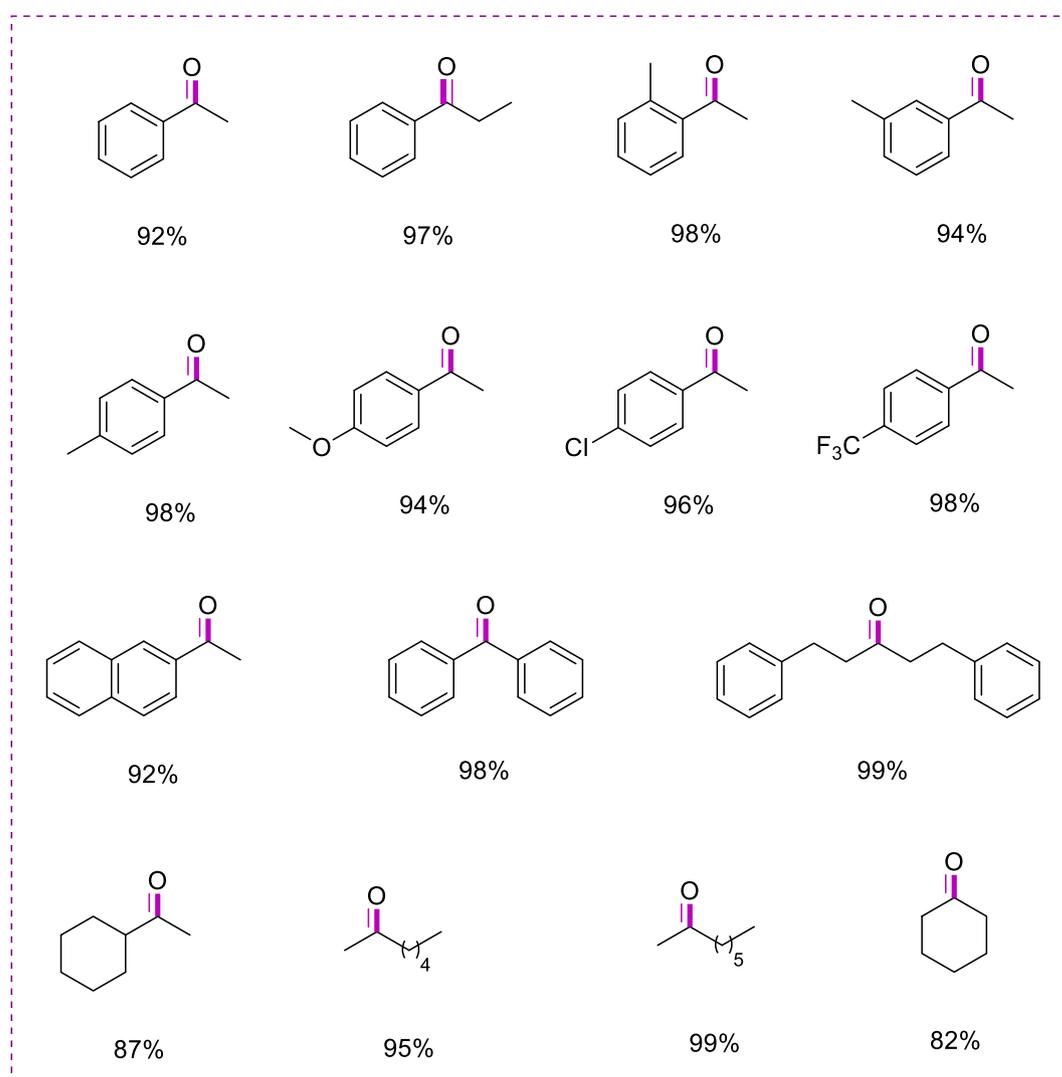
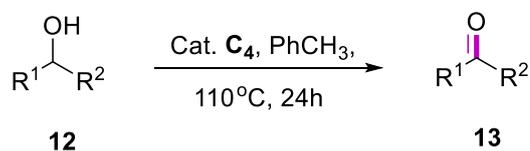
2.2. Synthesis of PNP-type Ru(II) hydrido borohydride complex and its application

The borohydride transition metal complexes have good reactivities towards organic substrates, thus they are served as good building blocks for transition metal borides and hydrides (White et al., 1991; Dick et al., 1993). These complexes are useful in the catalytic dehydrogenation of diols into cyclic esters



Scheme 4 Dehydrogenation of indolines.

Scheme 5 Synthesis of β -Carbolines.



Scheme 6 Dehydrogenation of secondary alcohols.

(Palard et al., 2004). The diols dehydrogenation to cyclic esters is catalyzed by the bulky, electron-rich ^tBu-PNP-Ru-complexes (Zhang et al., 2004). The reaction catalyzed by these complexes does not need the base to accelerate the reaction, proceeds very efficiently in neutral or mild conditions (Zhang et al., 2005a).

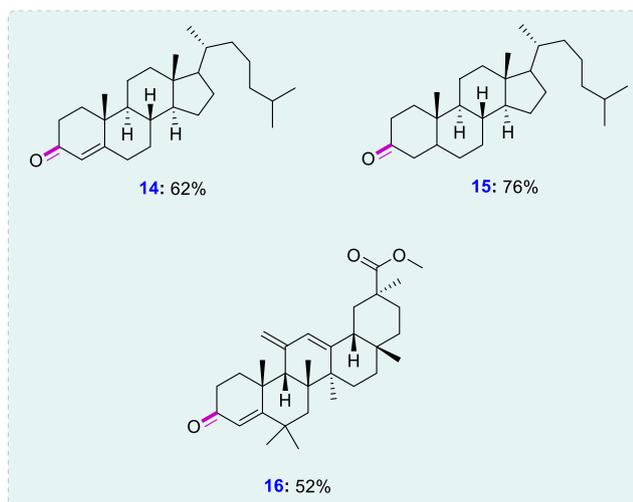
The RuCl₂(PPh₃)₃ complex reacts with the ^tBu-PNN pincer ligand (one eq.) yielding the N₂-linked binuclear Ru(II) complex [(RuCl₂(-PNN))₂(-N₂)] (C₅). The ruthenium(II) hydrido borohydride complex (C₆) was formed in excellent yield by the reaction of complex (C₅) with excess (5 eq.) of reducing agent NaBH₄ in the presence of 2-propanol for 12h (Scheme 7).

The Ru-PNN complex (C₆) is the most efficient in catalyzing the dehydrogenative cyclization of diols (17) into lactones (18) under very mild reaction conditions with hydrogen gas

evolution (Scheme 8). Thus, a toluene solution containing diol (containing both primary and secondary alcohol groups) and a catalytic quantity of complex (C₆) (0.01 mmol) was refluxed for 48h under an argon environment, afforded good yields of lactones (cyclic esters). Several diols were dehydrogenated to the respective lactones in this generic reaction. These dehydrogenative reactions of alcohols are interesting for the storage of hydrogen as well as the synthesis of various organic compounds (Zhang et al., 2011a).

2.3. Synthesis of pincer Ru(II) hydrido olefin complexes and their application

Catalytic dehydrogenation of alkene is a significant synthetic reaction because it transforms saturated hydrocarbon



Scheme 6a Pharmaceutically active compounds having ketone functionality formed via dehydrogenation.

having low value into alkenes that are extremely versatile intermediates in synthesis. Choi and their coworkers (2011) reported the dehydrogenation of alkenes and heteroarenes by using pincer complexes. Zhang and their coworkers (2015) reported the synthesis of homogeneous transition-metal catalysts for the dehydrogenation of alkanes (Choi et al., 2011; Pérez, 2012; Fang and Huang, 2015). Alkenes are generally produced in the industry by dehydrogenating alkanes over heterogeneous catalysts (Burk et al., 1984; Felkin et al., 1985; Burk and Crabtree, 1987). In the dehydrogenation of cyclic and linear alkanes, the hydrido Ru(II) olefin complexes are thermally labile at high temperatures. In the absence of a hydrogen acceptor, they are also capable of dehydrogenating the cyclooctane (COA) (Six et al., 1999). The efficacy of these Ru-pincer complexes is based on their thermal lability at high temperatures. The catalyst could be used to modify natural products in a late-stage process by dehydrogenating the alkyl chain with polar functional groups and heterocycles.

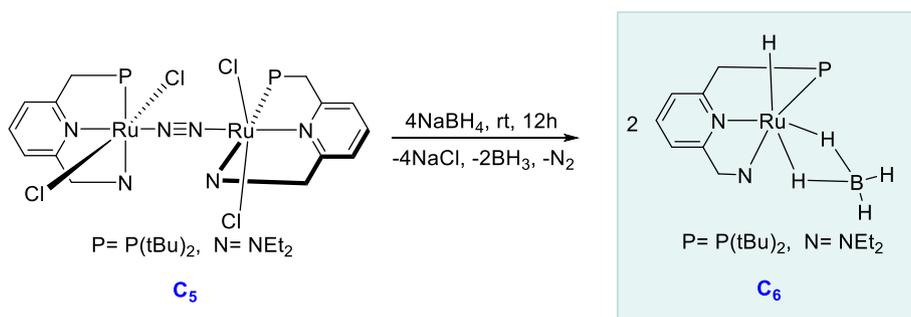
The ligand precursors *i*PrPOCOP-H (a), *i*PrPCP-H (b), *p*-C₆F₅-*i*PrPOCOP-H (c), and *i*PrPSCOP-H (d) reacts with RuCl₂(PPh₃)₃ complex in the presence of THF at 80°C for 8h resulted in the production of novel isopropyl-substituted pincer Ru(II) complexes (*i*PrPOCOP)RuCl(PPh₃) (C₇),

(*i*PrPCP)RuCl(PPh₃) (C₈), (*p*-C₆F₅-*i*PrPOCOP)RuCl(PPh₃) (C₉), and (*i*PrPSCOP)RuCl(PPh₃) (C₁₀). We wanted to replace the coordinated PPh₃ in complexes (C₇-C₁₀) with a more stable olefin ligand since the presence of PPh₃ could hinder the activity of dehydrogenation. The reactions of complexes (C₇-C₁₀) with CuCl (used as a PPh₃ scavenger) (5 eq. each) and norbornadiene (NBD) resulted in the formation of the respective Ru(II) chloro NBD complexes (C₁₁-C₁₄) in moderate yields (58-72%) as orange solid. The hydrido Ru(II) NBD complexes (C₁₅-C₁₈) were obtained in excellent yields by reacting complexes (C₁₁-C₁₄) with excess NaBH₄ (10 eq.) in THF. These complexes are found to be efficient for the catalytic dehydrogenation of alkane and are thermally stable (Scheme 9).

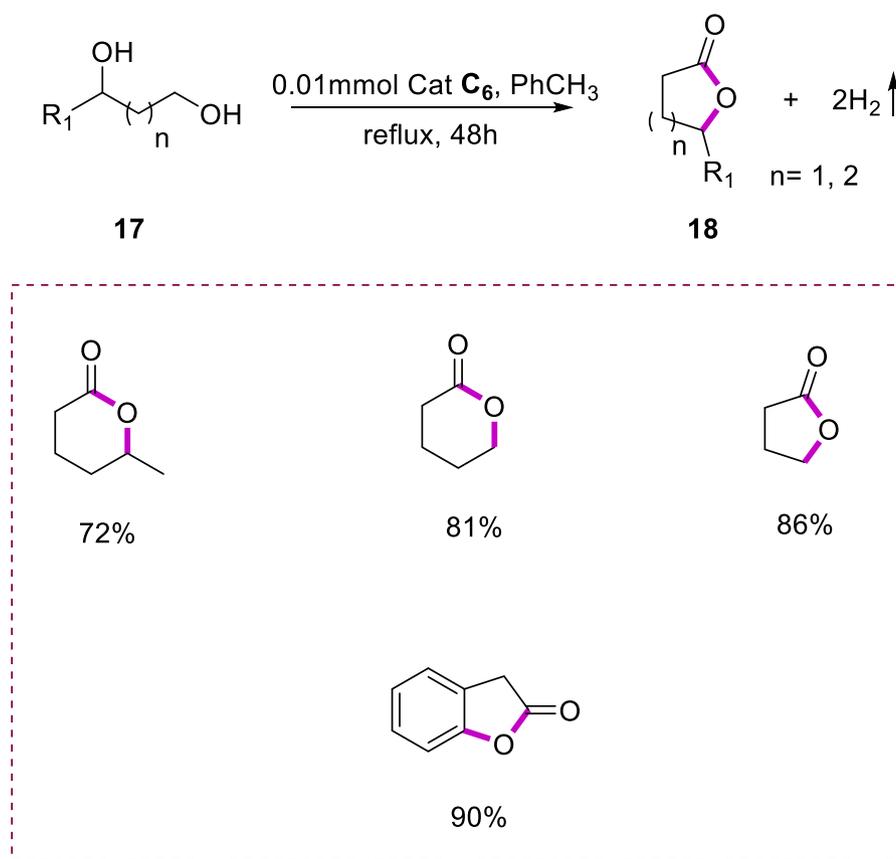
The novel Ru complexes were initially put to the test for cyclooctane **19** (COA) transfer dehydrogenation by using tert-butylethene **20** (TBE) as the H₂ acceptor. The 0.35M TBE was found to be effective to carry out transfer dehydrogenation of COA/TBE with several Ru-complexes (C₁₅-C₁₈). The activity of the POCOP Ru-complexes (C₁₅ and C₁₇) and the PCP complex (C₁₆) is good. The PSCOP analog Ru-complex (C₁₈) was found to be inactive for catalytic dehydrogenation. Despite the moderate beginning rate, complexes (C₁₅ and C₁₇) have the higher productivity for the transfer dehydrogenation of COA/TBE among all Ru-complexes. These dehydrogenation reactions, which tolerate ethers, esters, ketones, water, and other impurities in the starting materials, are a significant step forward in the formation of a practical catalyst for dehydrogenation (Scheme 10) (Zhang et al., 2016c).

2.4. Synthesis of pyridine-based Ru-CNN pincer complexes and their application

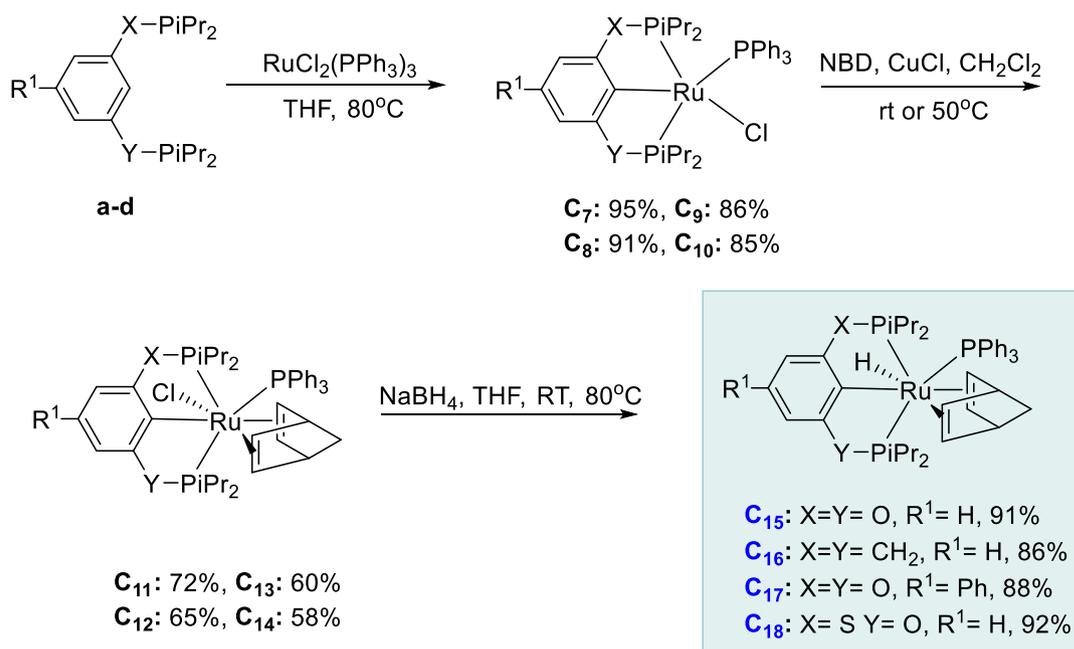
The conversion of esters to alcohols via reduction is a principal step in organic synthesis. Traditional methods that utilize stoichiometric reagents like LiAlH₄ for laboratory-scale ester reduction are reliable and efficient, but they have a low atom economy (Seyden-Penne, 1997). The formation of effective homogeneous catalysts for the ester hydrogenation that perform under mild conditions is of considerable significance for environmental and economic reasons. The homogenous catalysts that are used for the hydrogenation of esters are based primarily on ruthenium (Turek et al., 1994; Rieke et al., 1997; Teunissen, 1998; Pouilloux et al., 2000; Nomura et al., 2001). Various ruthenium pincer ligand-based complexes have been recently introduced as bifunctional catalysts for coupling pri-



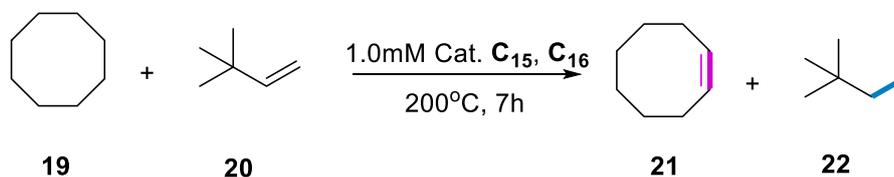
Scheme 7 Synthesis of PNP-type Ru(II) hydrido borohydride complex.



Scheme 8 Dehydrogenation of diols into lactones.



Scheme 9 Synthesis of pincer Ru(II) hydrido olefins complexes.



Scheme 10 Dehydrogenation of alkene.

mary alcohols to esters via dehydrogenation or ester hydrogenation in the reverse reaction (Del Pozo et al., 2011; Fogler et al., 2011; Sun et al., 2011; Filonenko et al., 2015).

Compounds (**25** and **26**) were obtained by reaction of suitable secondary amines (**24**) with pyridine-2-carboxaldehyde (**23**) via reductive amination. The palladium-catalyzed coupling of mesityl bromide (**27**) and 1,2-diaminobenzene (**28**) yielded the known diamine (**29**), which had previously been produced in two steps. The ligand precursors (**30** and **31**) were obtained by coupling compounds (**25** and **26**) with diamine (**29**). Finally, the ligands (**30** and **31**) were cyclized using triethylorthoformate and HCl to produce trihydrochloride salts (**32** and **33**). The ruthenium-pincer complexes (**C₁₉** and **C₂₀**) are formed through transmetalation of the ligands (**32** and **33**) with Ru-complex RuHCl(CO)(PPh₃)₃. These Ru-pincer complexes (**C₁₉** and **C₂₀**) are moderately air-stable in solution and so use air-free column chromatography to separate these complexes (Scheme 11).

The complexes (**C₁₉** and **C₂₀**) were evaluated as catalysts for the ethyl benzoate hydrogenation by using a catalytic amount of NaOtBu under mild conditions (105°C, 6 bar H₂). Remarkably, a subtle change is linked with the improvement of catalytic activity when move from complex **C₁₉** to **C₂₀**. The complex (**C₂₀**) consider as promise catalyst for this transformation and more active than complex (**C₁₉**). In comparison to ruthenium complexes, yields of reactions were more consistent when more equivalents of the base were utilized. The Ru-complex (**C₂₀**) is also much more active than the Ru-complex (**C₁₉**). Catalyst **C₂₀** has been evaluated on a variety of esters (**34**) hydrogenation. The variety of catalyst loadings was investigated for different ester substrates. The lowest catalyst loading resulted in approximately full conversion. This catalyst tolerates a wide range of aliphatic and aromatic esters involving hexyl, ethyl, and benzyl esters. The complete hydrogenation of phthalide required H₂ pressure (30 bar), but only 36% conversion was recorded at 6 bar. While complex **C₂₀** is a very effective catalyst but when it comes to hydrogenating methyl esters then this complex becomes remarkably inactive such as ethyl cyclohexane carboxylate and ethyl benzoate hydrogenate very effectively, while this complex produces very low yields of the respective methyl esters. The main reason for the low reactivity of methyl esters in the current catalytic system is because methanol that is formed as a byproduct is a very potent catalyst toxin, reducing catalyst activity (Scheme 12) (Kim et al., 2016).

2.5. Synthesis of novel dearomatized Ru-PNN complex and its applications

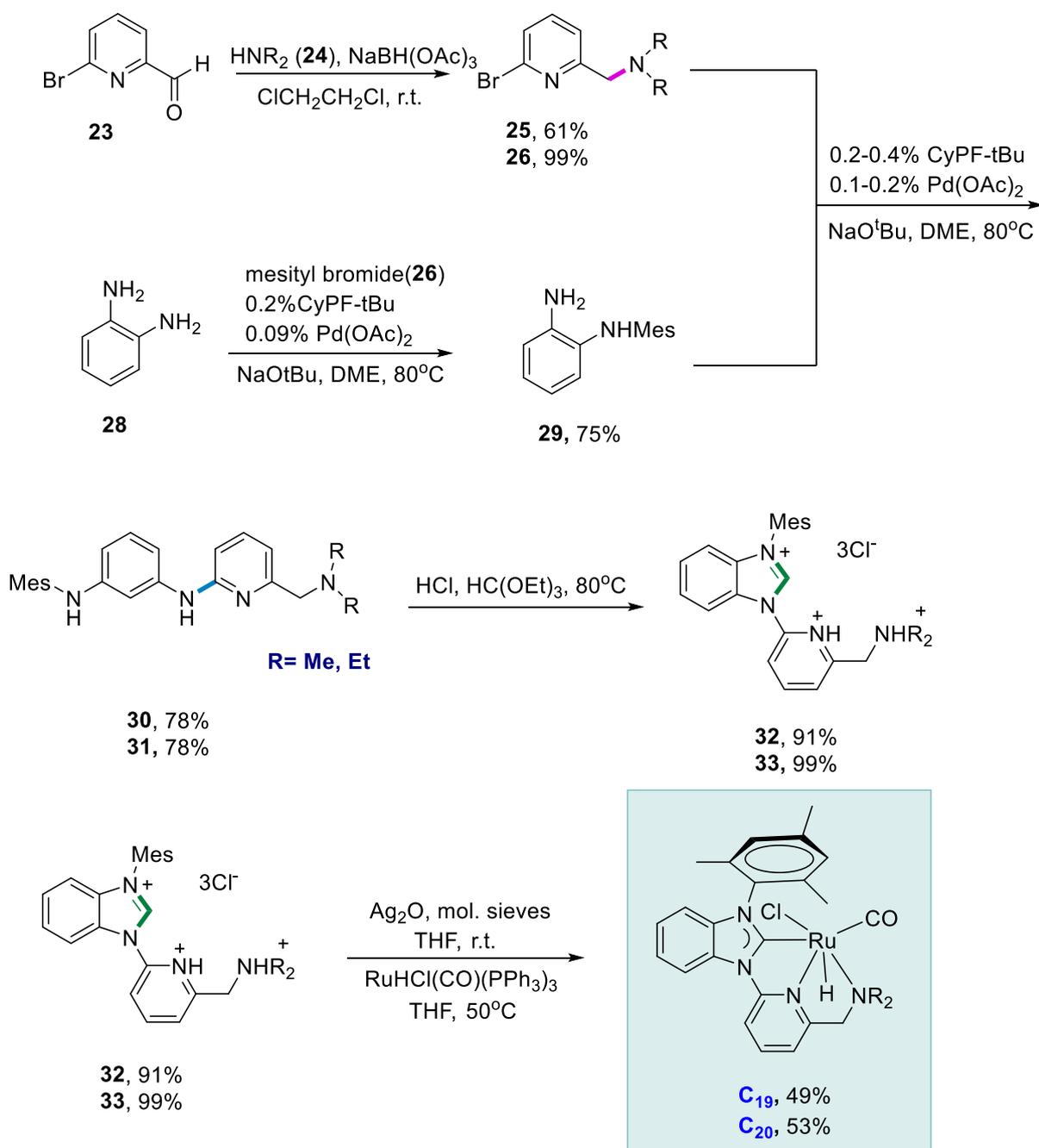
One of the most elementary reactions in organic chemistry is esterification. It has various applications in various fields such as used to make biologically active natural compounds, syn-

thetic intermediate fats and oils esters, polymers, and medicines (Otera and Nishikido, 2009). Among other esterification processes, transesterification is a particularly helpful process for the synthesis of the ester from other alcohols and esters through exchanging alkoxy groups, which avoids the utilization of moisture-sensitive and air-sensitive substrates such as acid halides (Hoydonckx et al., 2004; Otera, 2004; Enders et al., 2007). The Ru-PNN catalyst was used to accelerate the ester transesterification with different secondary alcohols. This reaction is efficient, and non-harmful to the environment. It takes place in neutral conditions without the use of bases or acids, activators, or molecular sieves. The only co-product of this reaction is molecular hydrogen when secondary alcohols and symmetrical ester (such as ethyl acetate) are used as substrate.

The reaction of Ru-complex RuHCl(CO)(PPh₃)₃ with the novel pyridine-based PNN ligand produced Complex (**C₂₁**) in 90% yield. Complex (**C₂₁**) was treated with 1eq. of KO^tBu resulting in the benzylic phosphine “arm,” deprotonation occur rather than hydride ligand affording an 89% yield of Ru-complex (**C₂₂**) at -32°C in the form of brown-red solid. Complex **C₁₄** is an effective acylation catalyst that uses ester as the acylation agent (Scheme 13) (Zhang et al., 2005b).

The secondary alcohols (**37**) acylation by using esters as the acylating reagent (**38**) was effectively accelerated by complex **C₂₂** (0.05 mmol) as a catalyst by refluxing the reaction mixture in toluene under neutral conditions. The symmetrical esters such as ethyl acetate when used in the reaction, both the alkoxy and acyl and portions of the esters as substrate are integrated into the final ester product resulting in hydrogen liberation as a side product. This process of ester to ester conversion is environmentally friendly. Unsymmetrical esters were also used to study these reactions. Unlike the classic transesterification strategy, this method cannot afford alcohol as a byproduct. In this reaction, both the alkoxy and acyl portions of the ester substrate are irreversibly integrated into the final ester (Scheme 14) (Gnanaprakasam et al., 2010a).

The carboxamides are an extremely important functional group in both chemistry and biology. The amide formation from esters is an interesting synthetic approach; however, a catalytic amount of metal mediator or promoters is usually required (Shimizu et al., 1997; Kurosawa et al., 2003; Constable et al., 2007; Ferroud et al., 2008). Complex **C₂₁** and its analogous Ru-PNP complex (**C₂₂**) accelerate the primary alcohols dehydrogenation to produce esters, the formation of alcohols from ester hydrogenation, the secondary alcohol dehydrogenation to ketones, and most recently, the secondary alcohol acylation by using esters (Zhang et al., 2004, 2005b, 2006, 2007; Gnanaprakasam et al., 2010a). The coupling of esters with amines is a new catalytic amide synthesis method. This reaction of amide synthesis is an efficient, broad, and green synthetic method. Neutral conditions are

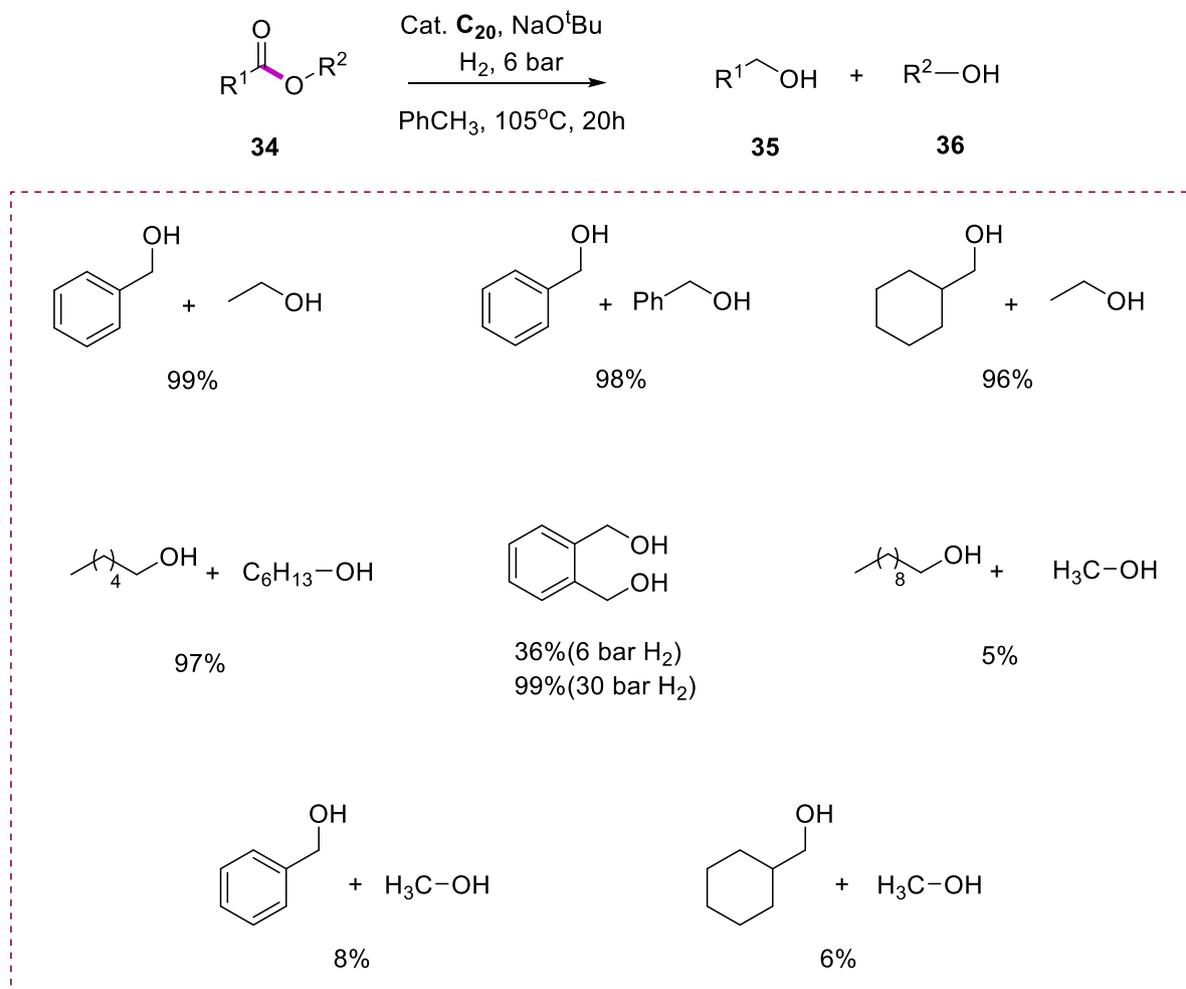


Scheme 11 Synthesis of pyridine-based Ru-CNN pincer complexes.

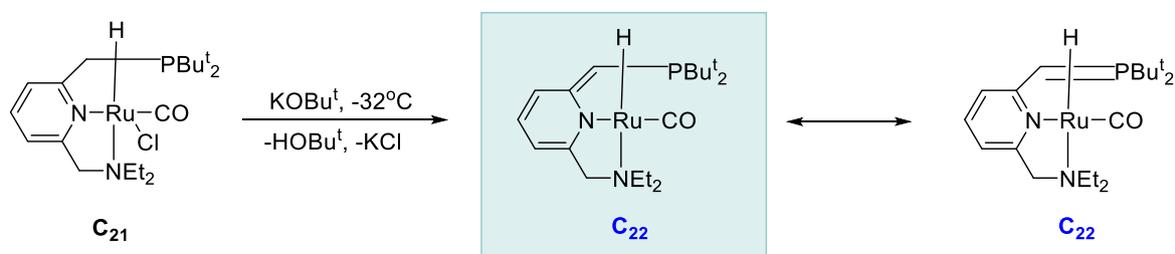
required to proceed with this reaction. The remarkable property of this reaction is that it produces H_2 rather than alcohol as a byproduct.

The synthesis of corresponding amides (**42**) was achieved by refluxing a reaction mixture of esters (**40**) and amines (**41**) with Complex **C₂₂** (0.01 mmol) in the presence of toluene/benzene at 135°C in an oil bath. This reaction can tolerate a broad range of esters and amines. This reaction had also great tolerance toward symmetrical esters. The amines acylation with

esters as the acylating agent is effectively accelerated by the dearomatized Ru-complex (**C₂₂**) under mild reaction conditions with no production of waste in this transformation. When symmetrical esters are used as a substrate both the alkoxy and acyl part of the ester substrate are incorporated into the final amide product resulting in the liberation of hydrogen gas. The high turnover numbers (TON) were attained in this reaction which is greater in magnitude up to two orders. The use of primary and secondary amines in this



Scheme 12 Ester hydrogenation.



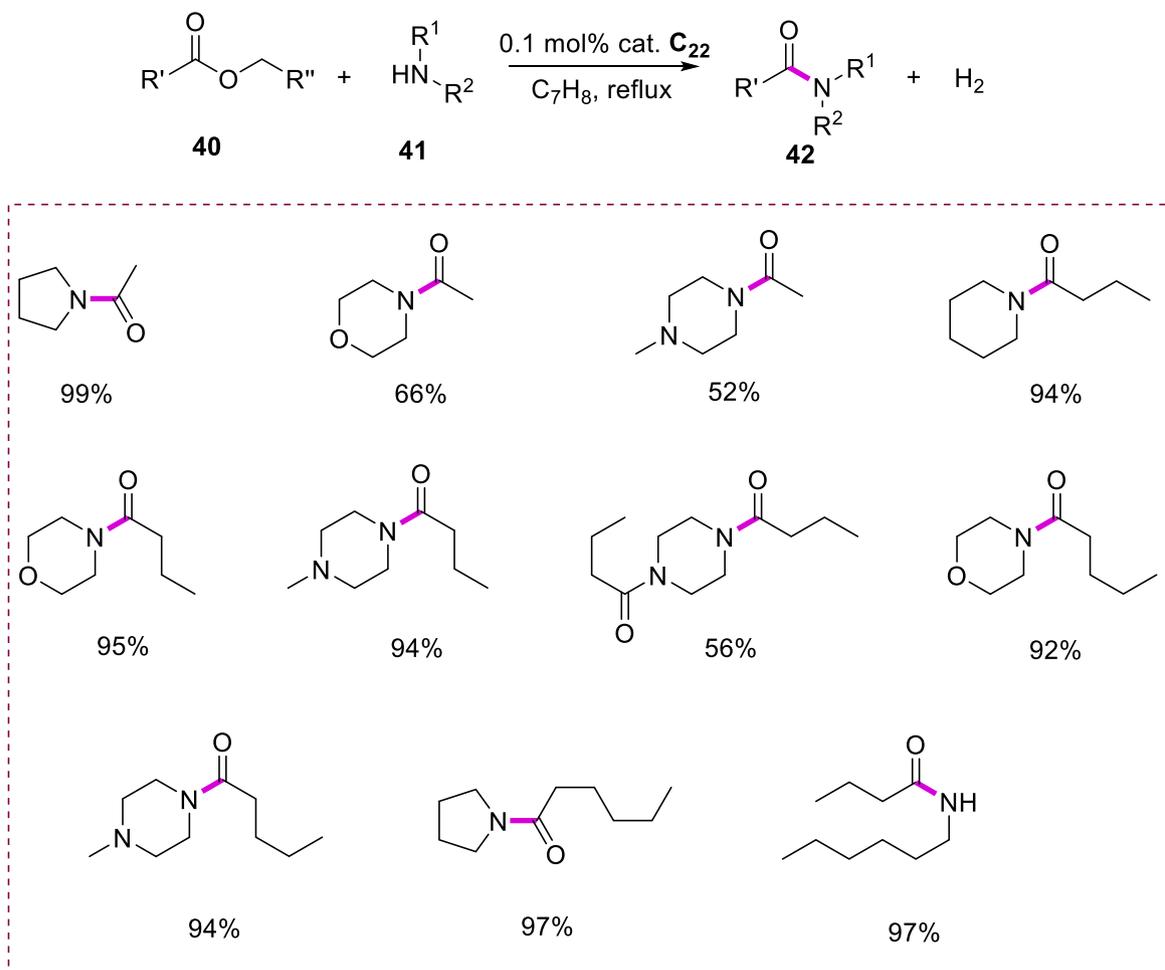
Scheme 13 Synthesis of novel dearomatized Ru-PNN complex.

approach was also tolerated (Scheme 15) (Gnanaprakasam and Milstein, 2011).

Imines are a versatile moiety that is used as a synthetic building block for the formation of organic compounds containing nitrogen atoms indicating their significance in synthetic chemistry. Moreover, these imines serve as functional reagents and building blocks in the formation of pharmaceuticals and natural products (Bloch, 1998; Kobayashi and Ishitani, 1999;

Córdova, 2004). The Ru-pincer complexes have higher reactivities for direct amine coupling to produce an imine via the introduction of imine functionality to the pincer ligand. These complexes provide the simple, direct synthetic route for imine synthesis under a base-free system.

The reaction mixture containing an appropriate amount of Ru-complex **C₂₂** (1.0 mol %) and amine (**43**) in toluene or aniline was heated under an argon environment at the given tem-



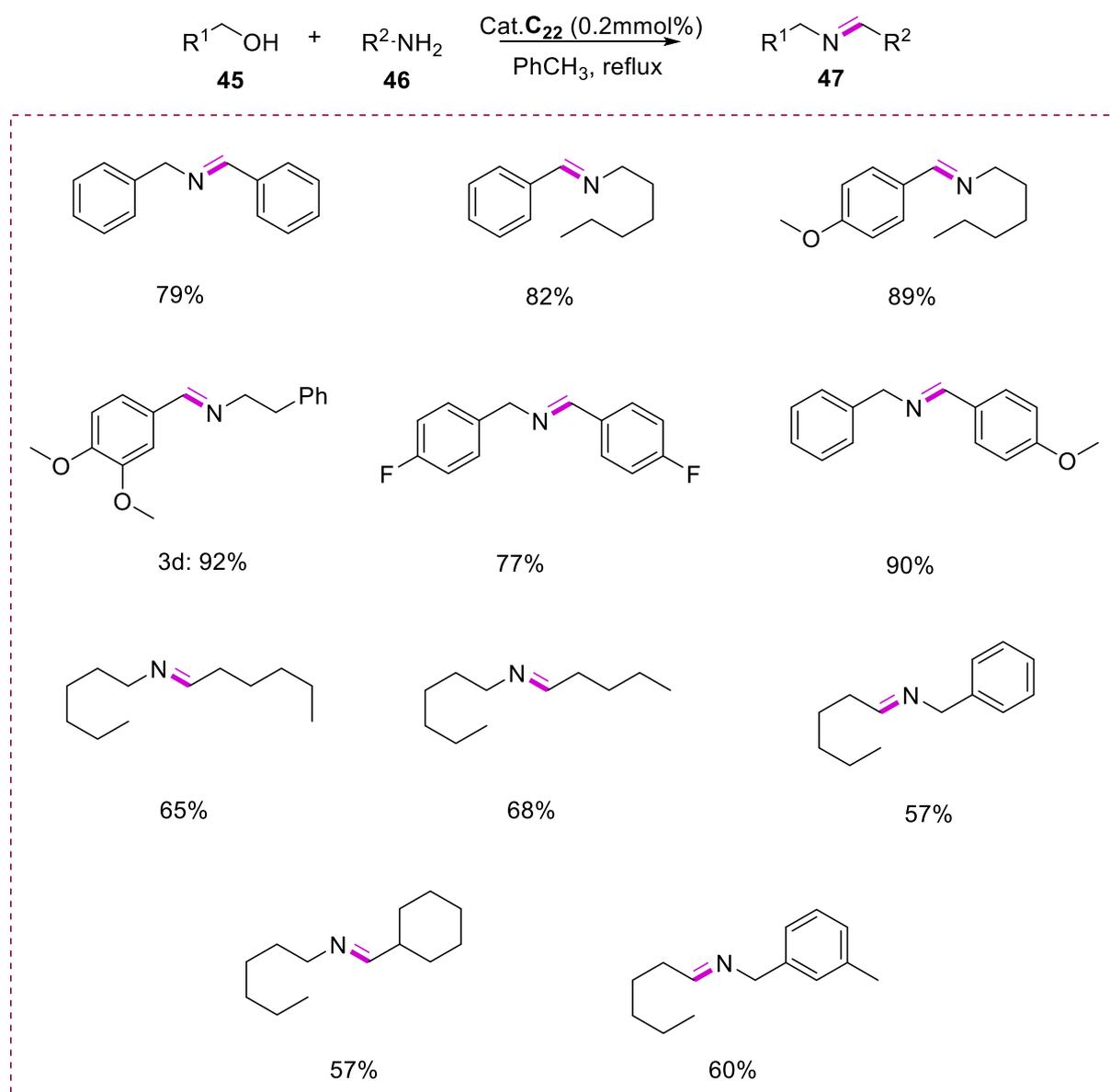
Scheme 15 Synthesis of amides from esters and amines.

other organic transformations (Hudlicky, 1996; Andersson and Munslow, 2008). Traditional amide reduction methods are non-catalytic and rely on stoichiometric concentrations of hydride reducing agents, resulting in the production of stoichiometric waste (Seyden-Penne, 1997). It is desirable in this context to develop an efficient catalytic system for amide hydrogenation. The low electrophilicity of the carbonyl group of amide makes amide hydrogenation more challenging than the hydrogenation of many other carboxylic acid derivatives (Smith and Whyman, 2014; Pritchard et al., 2015; Chardon et al., 2018; Zhou et al., 2019). C-N bond cleavage or C-O bond cleavage can both be used to hydrogenate amides. The formation of amines and alcohols via hydrogenation of amides at room temperature is accelerated by low catalyst loading of Ru-PNNH complexes (0.5 mol%) under low hydrogen pressures (Fogler et al., 2014; Kumar et al., 2017; Kumar et al., 2018a; Kumar et al., 2018b; Kumar et al., 2019).

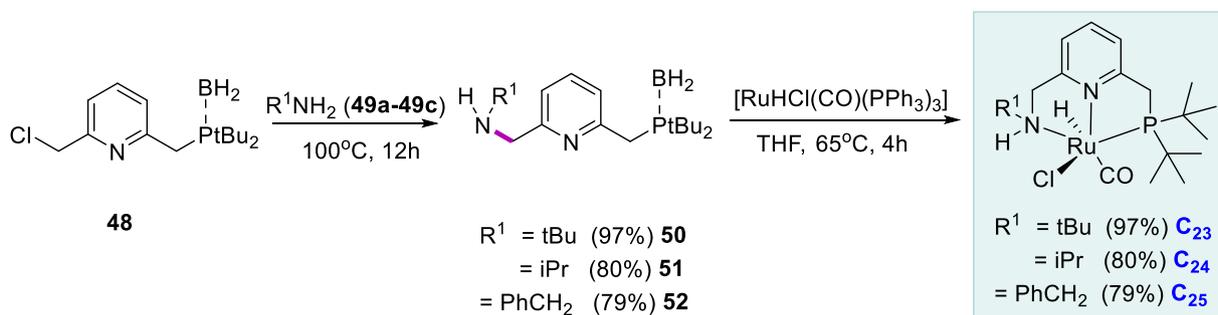
The reaction of compound (48) with respective amines (49a-49c), three PNNH ligands with various substituents [R = tert-butyl (50), isopropyl (51), and benzyl (52)] were produced. In the reaction of ligands (50-52) with [Ru(H)Cl(CO)(PPh₃)₃] complex, the respective Ru-complexes (C₂₃-C₂₅) were produced in excellent yields (85-90%) (Scheme 18). It's worth noting that acidic character of the N-H hydrogen of PNNH ligand helps to reduce the energy demand of rate determining

step, enabling hydrogenation to occur even at room temperature via the amido route. This can also illustrate why Ru-C₂₅ has better catalytic activity than Ru-C₂₃ and Ru-C₂₄ because the benzyl substitution of a donor atom makes the PNNH ligand of Ru-C₂₅ less basic than Ru-1 having ^tBu substitution in the donor atom. Alternatively, the decreased steric hindrance of Bn- group could help to explain the observed higher rate of hydrogenation with Ru-C₂₅ over Ru-C₂₃ and Ru-C₂₄.

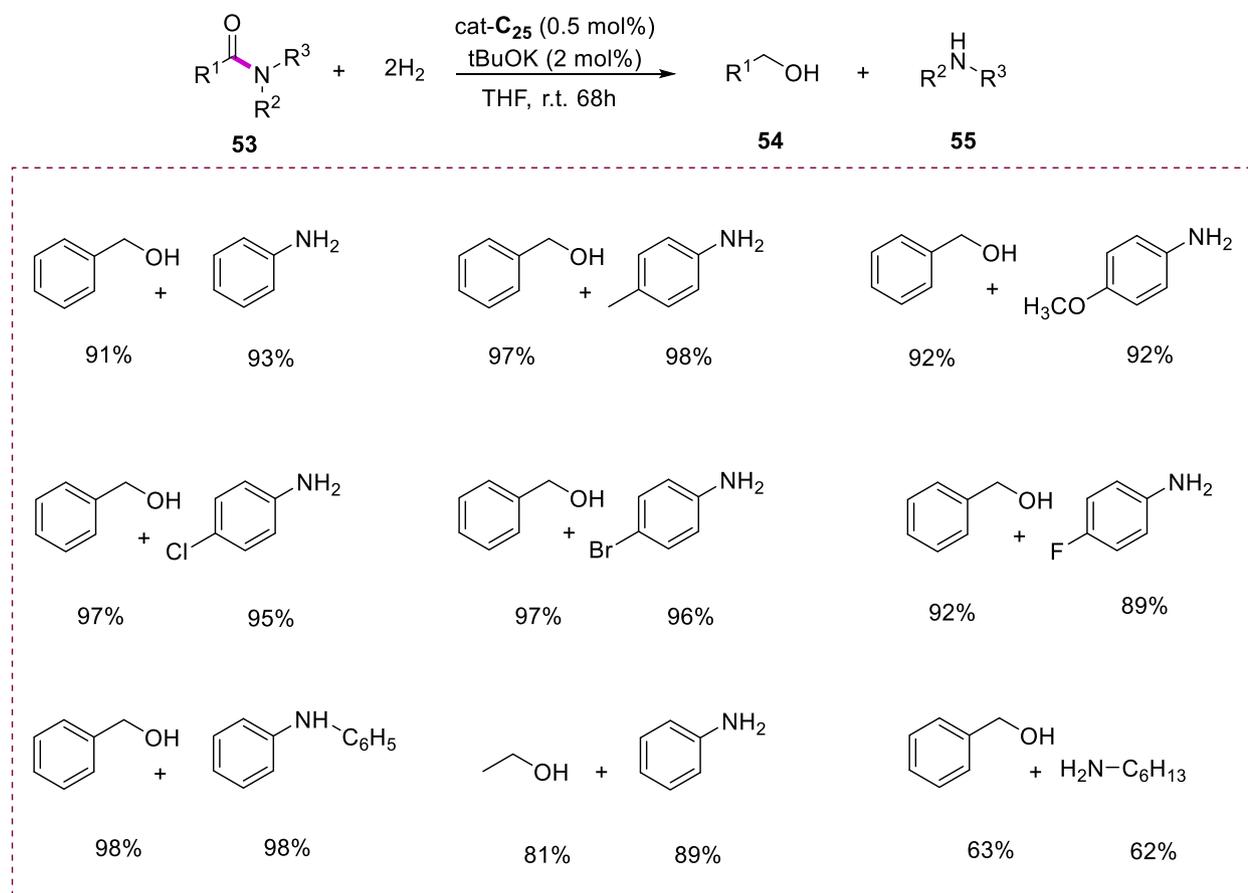
The amide (53) hydrogenation was accelerated by Ru-PNNH complexes with catalyst loading (0.5 mol %) in the presence of ^tBuOK as a base and THF as a solvent at low Hydrogen pressures (5-10 bars) at ambient temperature resulting in the formation of amines (55) and alcohols (54). The hydrogenation of benzanilide at 45°C with Ru-PNN^tBuH complex (Ru-C₂₃; 0.5 mol %) as the catalyst under hydrogen pressure (10 bars) in the presence of ^tBuOK base (2 mol %) results in the formation of moderate amide conversion to aniline and benzyl alcohol after 20h, indicating that cleavage of C-N bond is the desired route under these conditions. The catalytic activity improved when the *N*-substitution of the catalyst was replaced from tert-butyl (^tBu-) to benzyl (Bn-) group (Ru-C₂₅) resulting in the complete transformation of amide to alcohol and amine was observed after 20h. This transformation can undergo completion even at low temperature (35°C) within 20h by using complex (Ru-C₂₅). Furthermore, complete con-



Scheme 17 Imines synthesis from amines and alcohols.



Scheme 18 Synthesis of pyridine-based Ru-PNNH complexes.



Scheme 19 Hydrogenation of amides.

The metal-ligand coordination (MLC) in catalysis involves both the ligand and metal bond breaking and making with different substrates is very significant (Noyori and Ohkuma, 2001; Noyori et al., 2004; Ikariya and Blacker, 2007; Friedrich and Schneider, 2009; Crabtree, 2011a; van der Vlugt, 2012). Based on dearomatization/aromatization methodology, various new green synthetic transformations catalyzed by PNN or PNP Ru-pincer complexes have been investigated. The alcohols coupling to esters via dehydrogenation, coupling of primary amines with alcohols to synthesize amides with H_2 as a sole byproduct, formation of alcohols via hydrogenation of esters, formation of imine by catalytic coupling of amines and nitriles, direct synthesis of imines by coupling of amines and alcohols with H_2 as a byproduct, and a variety of other synthetic transformations are among them (Milstein, 2010; Gunanathan and Milstein, 2011b; Gunanathan and Milstein, 2011a; Gunanathan and Milstein, 2013).

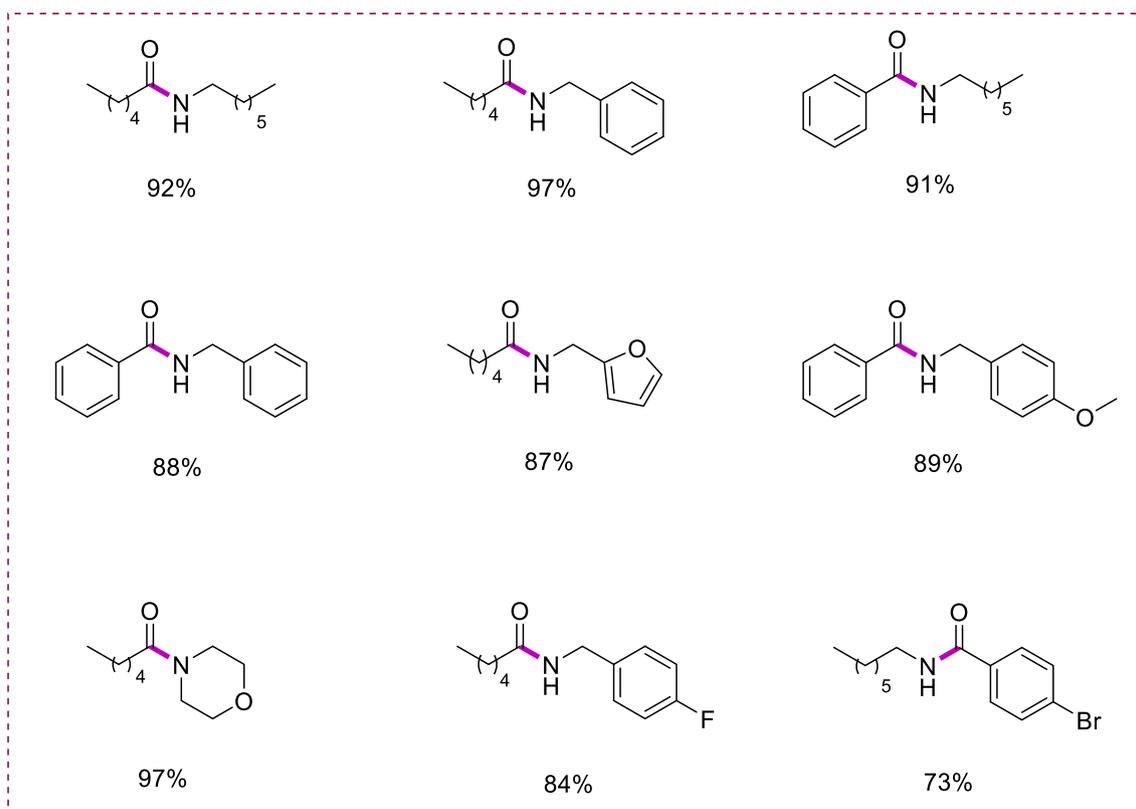
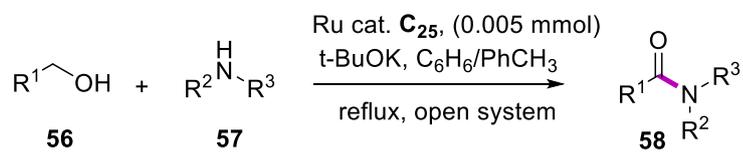
The synthesis of corresponding esters (**61**) results from the primary alcohols (**59** and **60**) coupling through dehydrogenation with complex \mathbf{C}_{25} (0.1 mol %) by using $^t\text{BuOK}$ as a base and diethyl ether as a solvent under reflux at 35°C (Scheme 21). The reactivity order of the pre-catalysts was $\mathbf{C}_{25} > \mathbf{C}_{24} > \mathbf{C}_{23}$. PNNH-type Ru pincer complexes were synthesized, which were capable of metal-ligand cooperation (MLC) via ligand amide-amine as well as dearomatization/aromatization pathways. The alcohols coupling via dehydrogenation catalyzed

by complex \mathbf{C}_{25} by using base (2.2 eq.) (relative to Ru) under extremely mild conditions. This reaction tolerates a wide range of substituted primary alcohol substrates (Scheme 18) (Fogler et al., 2014).

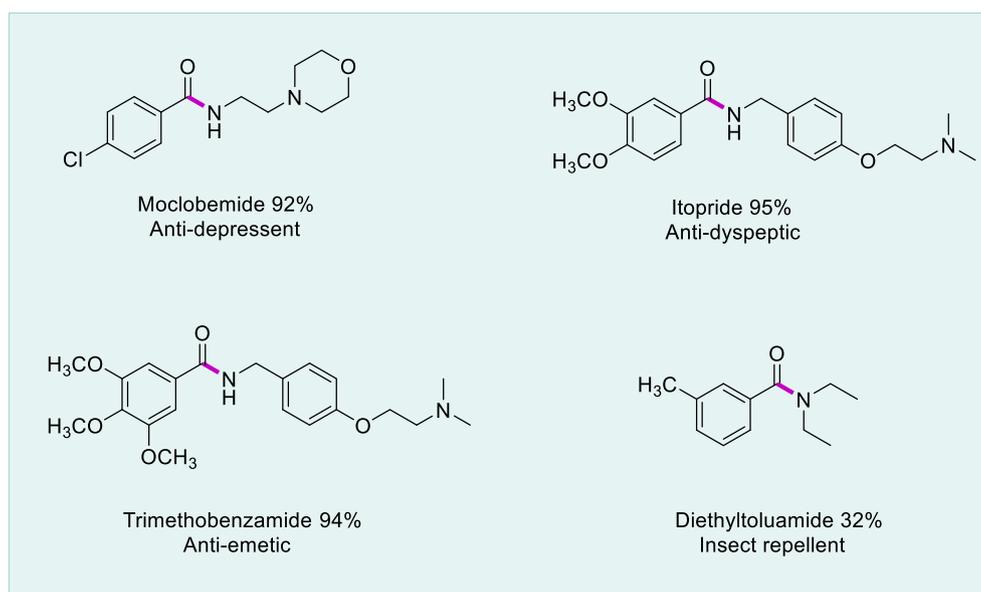
2.7. Synthesis of acridine-based PNP ruthenium pincer complex and its applications

Amines are a very important class of compounds due to their significance in pharmaceuticals, dyestuffs, pigments, agrochemicals, fine chemicals, polymers, emulsifiers, and plasticizing agents (Lawrence, 2004). The primary amines are the most valuable amines but their selective formation is more challenging owing to their high reactivity. Traditional primary amine preparation methods typically use stoichiometric concentrations of hazardous chemicals, resulting in poor atom economy and selectivity (White and Elliger, 1965; Miriyala et al., 2004; Bartoli et al., 2008). The new pyridine-based pincer complex is capable of accelerating the highly desirable reaction of alcohols with ammonia to produce water and primary amines preferentially. This reaction can be carried out at low pressures and temperatures, without the use of any solvents, and in water.

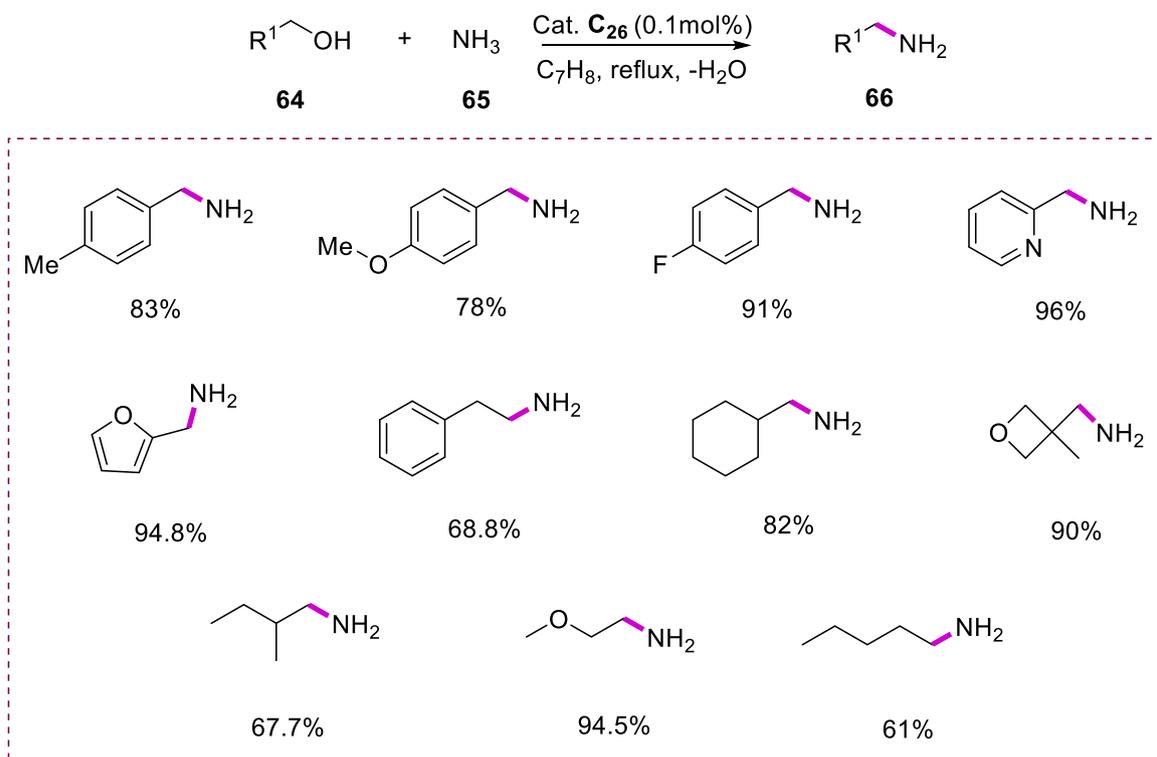
The new tridentate electron-rich PNP pincer ligand (**63**) obtained from compound (**62**) reacts with Ru-complex $[\text{RuHCl}(\text{PPh}_3)_3(\text{CO})]$ in toluene at 65°C for 2h resulting in the formation of novel acridine-based ruthenium pincer com-



Scheme 20 Amides synthesis via dehydrogenation.



Scheme 20a Pharmaceuticals containing amide functionality.



Scheme 23 Primary amines synthesis from alcohols and ammonia.

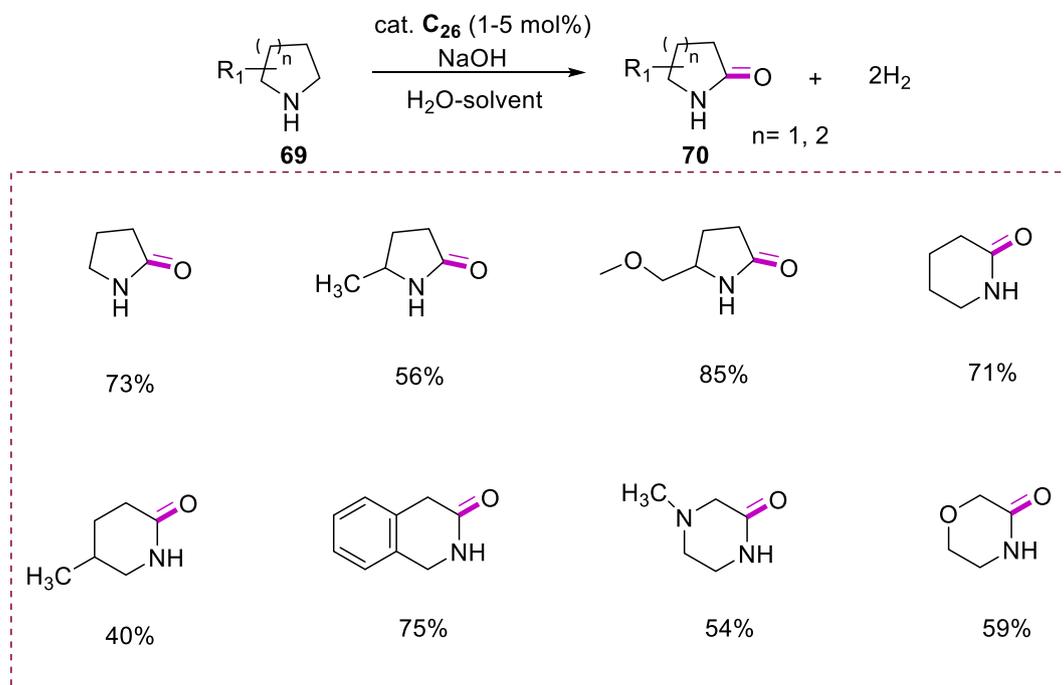
The amine functionality is used as a chemical precursor in different transformations. Chemical reactions including primary amines are extremely important in chemistry and biology. The classical approach for selective deamination includes oxidizing the amines by using HNO_2 to produce diazonium ions (unstable) that can then be treated with a variety of nucleophiles while the reaction is carried out by the removal of N_2 . Such reactions often have limited selectivity due to the formation of carbocation as intermediate and high reactivity of diazonium salts (Baumgarten, 1966; Doyle et al., 1978; Shin et al., 2000; Deechongkit et al., 2004; Cupido et al., 2005). Complex (C_{26}) catalyzes the aliphatic amines deamination into alcohols in the reverse reaction. The synthesis of a hemiaminal intermediate is proposed as a key component that leads to the removal of ammonia as a byproduct in this reaction, which occurs via a reversible dehydrogenation/hydrogenation process. The acridine-based pincer complex (C_{26}) has a distinctive reversible reactivity for deamination of amines and amination of alcohols due to its capacity to facilitate both dehydrogenation of alcohols and amines as well as hydrogenation of both aldehydes and imines within a same complex.

When the solution of amine (**67**) in water or a dioxane/water mixture is heated by using catalytic amounts of complex (C_{26}) results in the synthesis of alcohol (**68**) as the main product. The reaction was carried out in a water/dioxane mixture due to the limited solubility of substrates in water and the catalyst which results in minimal conversion. The controlled experiment showed that no reaction proceeded without the use of a catalyst. Overall, deamination that occurs under a hydrogen environment increases the reaction rate by increasing the yield of the required alcohol product and selectivity, even though H_2 is not required for this strategy. Under this reaction

environment, substituted benzylamines having electron-withdrawing and electron-donating substituents were rigorously tolerated. Substrates such as ethylenediamine, diethylenetriamine, and 2-(aminomethyl)pyridine act as chelating ligands were stable towards deamination due to their strong coordination with the metal center, whereas furfuryl amine goes through non-selective reaction, yielding a mixture of products (Scheme 24) (Khusnutdinova et al., 2013).

Lactams are widely utilized as building blocks for the formation of physiologically active chemicals, medicines, and polymers, and their production is one of the most significant conversions in organic synthesis (Moody, 1995). Acridine-based ruthenium pincer complex $[\text{Ru}(\text{AcrPnP})\text{H}(\text{CO})\text{Cl}]$ by using the catalytic quantity of base catalyzes the cyclic amines dehydrogenation in water to form lactams as a product (Gunanathan and Milstein, 2008; Gunanathan et al., 2009; Gunanathan et al., 2010). Water acts as an oxygen source in the amide functionality, and this transformation is accompanied by the release of H_2 .

Cyclic amines entropically stabilized the cyclic hemiaminal intermediate contrary to deamination. The solution of pyrrolidine (**69**) in a degassed dioxane-water mixture (1:1 v/v) upon heating for 48h under nitrogen in a closed system at 150°C by using complex C_{26} (1mol%) results in the formation of a 24% yield of 2-pyrrolidone (**70**) as well as H_2 gas. The production of pyrrolidone in 59% yield was reported when the solution of pyrrolidine was heated in dioxane/water by using complex C_{26} (1 mol%) in the presence of NaOH (1.5mol%). The significant outcome of the base could be due to the generation of Ru (0) catalyst through deprotonation of complex C_{26} or the hemiaminal intermediate stability against the elimination of amine. The controlled experiment displayed no conversion



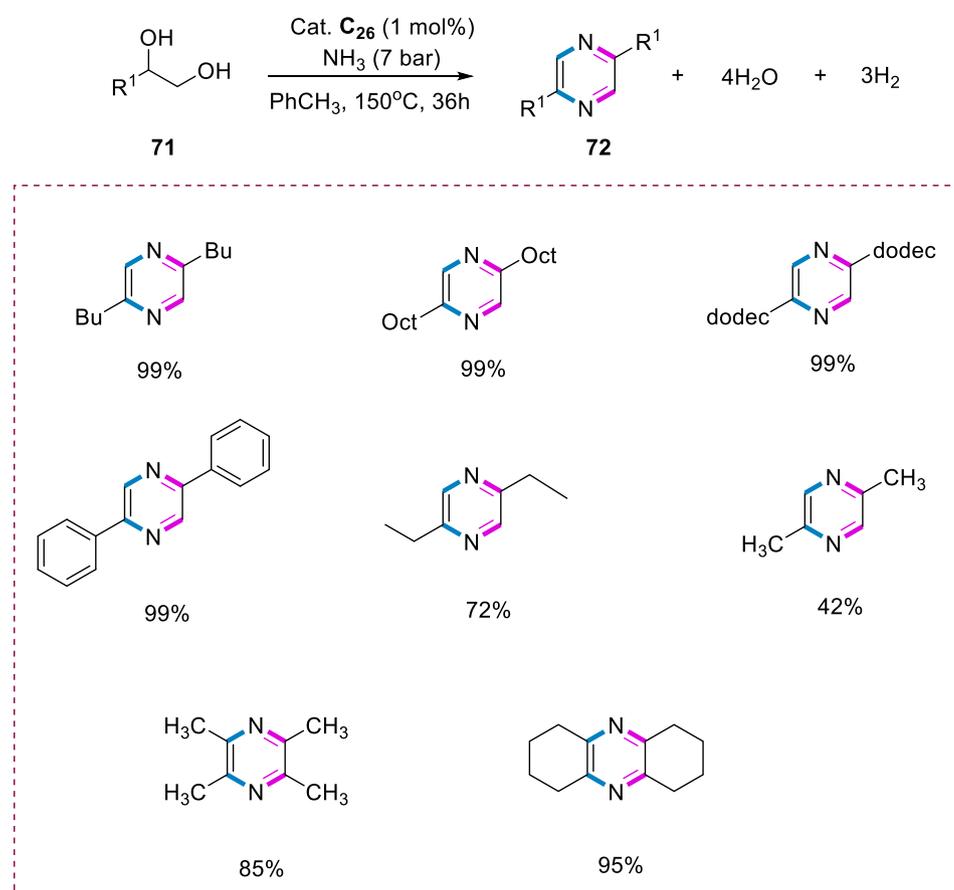
Scheme 25 Lactam synthesis from cyclic amines.

synthesis of *N*-heterocycles, an alternative ecologically friendly reaction involving the coupling of amines and alcohols via dehydrogenation, with water and H_2 as the only byproducts, is catalyzed by Ru-pincer complexes based on acridine and pyridine backbones (Gunanathan et al., 2007; Gnanaprakasam et al., 2011; Srimani et al., 2013b; Khusnutdinova et al., 2014). Acceptorless dehydrogenative coupling routes for the sustainable development of *N*-heteroaromatic molecules using amines and alcohols (Michlik and Kempe, 2013; Zhang et al., 2013; Deibl et al., 2015; Daw et al., 2016; Daw et al., 2018).

The pyrazine derivatives (**72**) were formed by the coupling of gaseous ammonia and 1,2-diols (**71**). The acridine-based ruthenium pincer complex is used as a catalyst and ammonia is used as a nitrogen source that requires no further additions like a base or an oxidant. The amination of alcohols with ammonia by using a catalyst (**C₂₆**) results in the synthesis of pyrazine. Heating a solution of toluene with 1,2-hexanediol (1 mmol) in a Fischer-Porter tube with complex **C₂₆** (1 mol percent) at 150°C (bath temperature) for 36h under 7bar pressures of ammonia results in the quantitative consumption of diols yielding the mixture of 2,5- and 2,6- dibutylpyrazine. In drug development, pyrazine derivatives are important scaffolds in potential bioactive compounds. Long-chain linear alcohols, such as 1,2-tetradecanediol, and 1,2-decanediol resulted in the formation of a 1:1 mixture of both isomers after conversion. The reaction with 1,2-ethanediol-1-phenyl gave quantitative yields of derivatives of diphenylpyrazine with a 68:32 ratio. Reaction with 1,2-butanediol yielded 72% of the desired derivatives of diethylpyrazine, whereas 1,2-propanediol yielded only 42% of the target product, as well as several side products. 2,3-butanediol gave 85% tetramethylpyrazine as the main product, whereas 1,2-cyclohexanediol gave 95% octahydrophenazine with a minor amount of hydrogenated byproducts by using similar conditions (Scheme 26).

Pyrroles are a significant class of compounds because of their anticancer, anti-inflammatory, antibacterial, antioxidant, and antifungal potential in pharmaceuticals (Amishiro et al., 2000; Suckling, 2008; Wang et al., 2008b; Wang et al., 2011). They can also be used in conducting polymers and molecular optics (Gimenez and Alves, 1999; de Lacy Costello et al., 2000; Chou and Yeh, 2001). Pyrroles are formed by the coupling of 1,4-diols with amines via dehydrogenation. The acridine-based pincer complex (**C₂₆**) has a distinctive reversible reactivity for deamination of amines and amination of alcohols due to its capacity to facilitate both dehydrogenation of alcohols and amines as well as hydrogenation of both aldehydes and imines within a same complex.

The synthesis of pyrroles (**75**) was carried out by reacting derivatives of 1,4-butanediol (**73**) with primary alcohols (**74**) and ammonia in the presence of acridine-based pincer complex (**C₂₆**). The multicomponent dehydrogenative coupling reaction occurred when a 2,5-hexanediol was added to primary alcohols, producing *N*-substituted pyrroles as a product. The Paal-Knorr reactions are used in traditional strategies for the formation of *N*-substituted pyrrole as a product. The coupling of secondary alcohols with derivatives of 2-amino alcohol via dehydrogenation also produced derivatives of pyrrole. Treatment of 1-hexanol and 2,5-hexanediol in 0.5 ml toluene with complex **C₂₆** (1mol%) under ammonia (7 bar) at 150°C for 24h yielded 2,5-dimethyl-1-hexylpyrrole as the coupling product of dehydrogenation. Various primary alcohols were tolerated for the dehydrogenative coupling with ammonia to generate pyrroles. 1-octanol, 1-butanol, and 1-pentanol generated 83%, 77%, and 76% of the respective *N*-substituted pyrroles as products respectively, under the optimal reaction conditions. The *N,N*-dimethylamino-1-propanol yielded the appropriate 1,2,5-substituted pyrrole derivative (74%) as the major product, whereas 3-phenyl-1-propanol and 2-phenyl-1-ethanol yielded the required products in 74%



Scheme 26 Synthesis of pyrazines from 1,2-diols and ammonia.

and 76% yields respectively. When using primary alcohols having low boiling point like ethanol, methanol, or 1-propanol, the alcohol (4equiv) were used in comparison to 2,5-hexanediol, producing moderate to good yields of the appropriate 1,2,5-substituted pyrroles respectively. Under the same conditions, replacing straight-chain primary alcohols with benzyl alcohols results in decreased reactivity and a modest yield of 1,2,5-substituted pyrroles were obtained. The corresponding pyrrole derivatives were formed in 48% and 57% by the reaction of 4-methyl benzyl alcohol and benzyl alcohol reactions, respectively, whereas the sterically hindered 3,4-dimethoxybenzyl alcohol yielded the product in just 13% yield. Heteroatom substituted primary alcohols were also well tolerated under the same conditions of the reaction. The corresponding 2,5-dimethyl-*N*-substituted pyrrole was obtained in 69% and 84% yields from nicotiny alcohol and furfuryl alcohol respectively (Scheme 27) (Daw et al., 2018).

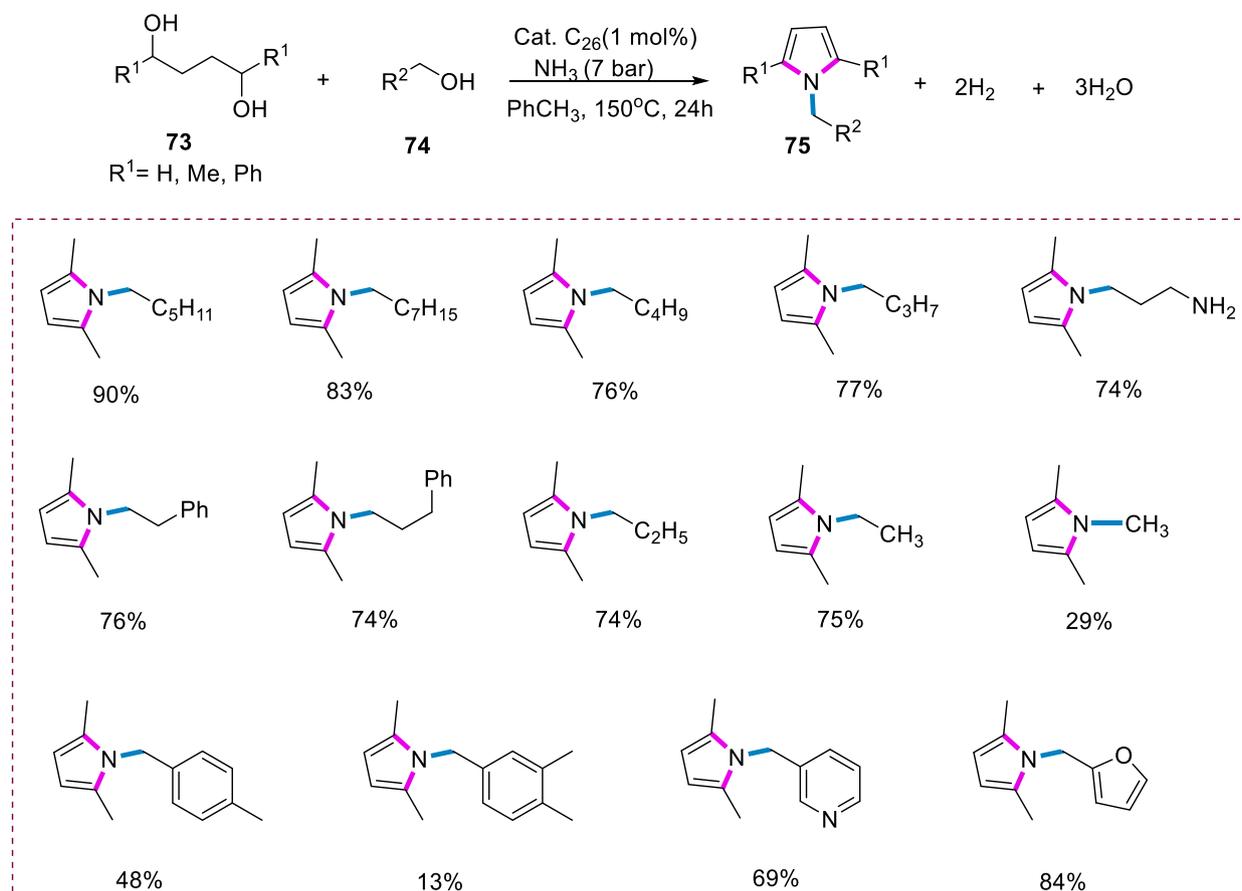
2.8. Synthesis of amide-derived Ru-NNN hydride complex and its application

Nitriles are the well-known category of organic compounds found in a broad range of biologically active agents, industrial processes (for the synthesis of agrochemicals, polymers, and pigments/dyes), and natural products synthesis as well as being utilized as synthons for further synthesis (Fleming, 1999; Pollak et al., 2000; Fleming et al., 2010; Gunanathan et al.,

2011; Srimani et al., 2012a). Conventional nitrile preparation routes are inefficient in terms of atom economy, use of harmful reagents, and low selectivity. The Ru-NNN hydride complex derived from amines (RuH(PPh₃)₂(bmpi); bmpi = 1,3-bis(6-methyl-2-aminopyridinyl)isoindoline) is used as a catalyst to effectively promote the secondary and primary amines dehydrogenation to nitriles and imines respectively. This reaction proceeds without the use of a hydrogen acceptor or exogenous oxidant.

The amide-derived Ru-NNN pincer complexes with the bmpi ligand (1,3-bis(6-methyl-2-aminopyridinyl)isoindoline) promote the fast dehydrogenative reactivity. The deprotonated Hbmpi ligand (**76**) was added to RuCl₂(PPh₃)₃ in tetrahydrofuran (THF) as solvent resulting in the synthesis of ruthenium complex (**C**₂₇) RuCl(bmpi)(PPh₃) in excellent yield (92%). The complex **C**₂₇ react with NaHET₃B (1.05 eq) and triphenylphosphine (PPh₃) in tetrahydrofuran solution for 2h at ambient temperature, and the Ru-complex RuH(bmpi)(PPh₃)₂ (**C**₂₈) was obtained in 89% yield (Scheme 28) (Tseng et al., 2013b).

Amines (**77**) were dehydrogenated with Ru-pincer complex (**C**₂₈) (1mol %) in the presence of toluene at 110°C for 24h, resulting in moderate yields of corresponding nitriles (**78**). The dehydrogenation of aliphatic amines was often used to obtain the respective nitriles as the sole product. The 1-cyclohexylmethanamine as substrate was dehydrogenated to give cyclohexanecarbonitrile a product in good yield (74%). Moreover, the 2-phenethylamine undergoes dehydrogenate to



Scheme 27 Synthesis of pyrroles from diols.

give 2-phenylacetonitrile in good yield (76%) yield which is a key precursor to several pharmaceuticals. The transformation of the respective phenylacetonitriles was dependent on the electron-withdrawing and electron-donating substituent on the phenyl ring when phenethylamines with para- and ortho-substituent were utilized as substrates. The ortho-substituted chlorophenethylamine yielded 33%, but when the chloro group was replaced with an electron-rich substituent such as the methoxy group increased the yield up to 53%. The ortho- and para-substituted methoxy-phenethylamines produced similar yields, and the proximity of the $-\text{OCH}_3$ group to the CH_2NH_2 group had minimal effect on the efficiency of conversion. Benzylic substrates were also used to explore the dehydrogenative process of activated amines which were effectively transformed to the corresponding benzonitriles. A series of functionalized benzylamines were used to investigate substituent effects. Electron-withdrawing groups reduced the yields while in the case of electron-withdrawing substituent on the aromatic ring enhanced the yield of the reaction. Deactivating the chloro group in the ortho-, meta-, or para-positions, for example, resulted in decreased conversions (Scheme 29) (Tseng et al., 2013a).

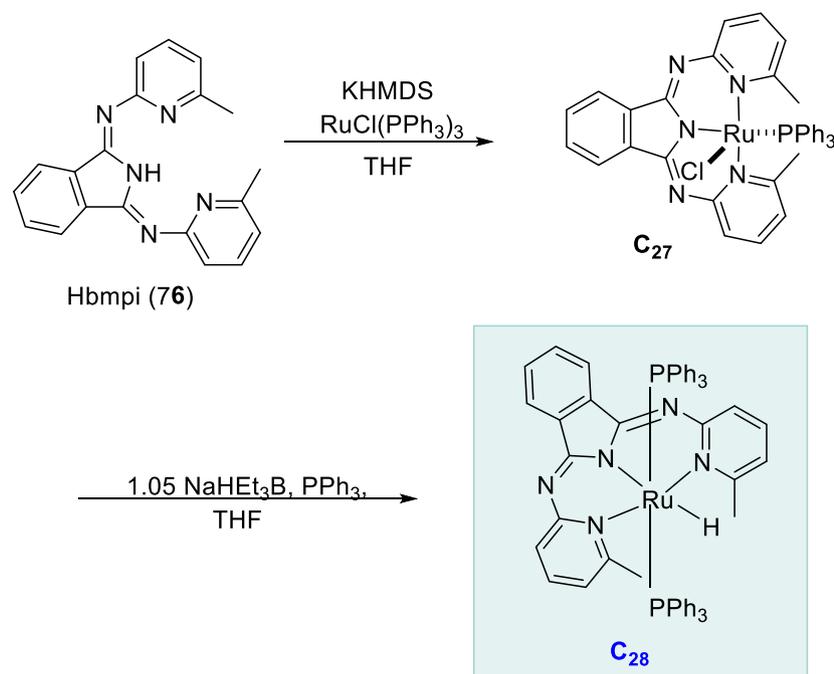
2.9. Synthesis of PNN- and PNP-lutidine-based Ru-complexes and their application

Chemical bond catalysis and activation rely heavily on metal-ligand cooperative bifunctional complexes (Khusnutdinova

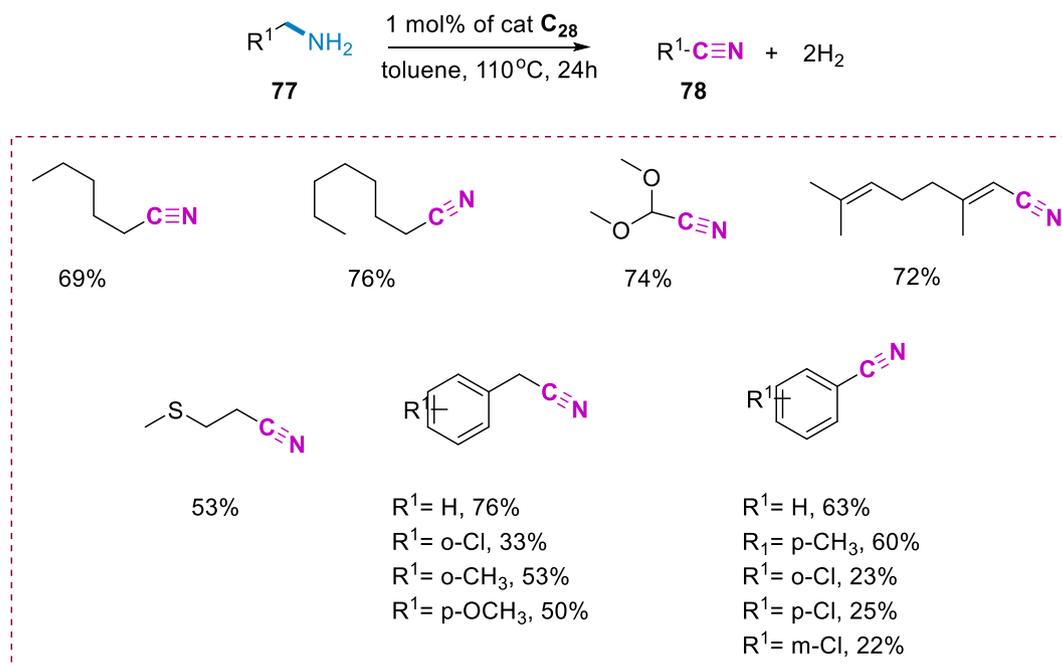
and Milstein, 2015; Younus et al., 2015; Chen et al., 2016; Gorgas et al., 2017). PNN- and PNP-lutidine-based complexes have methylene protons that are slightly acidic and show fascinating ligand metal coordination based on a dearomatization/aromatization process that has been used in a variety of chemical reactions (Gunanathan and Milstein, 2011a; Jia and Huang, 2016; Xie et al., 2016; Espinosa-Jalapa et al., 2017; Hou et al., 2017). These bifunctional catalysts are effective for β -alkylation of a primary alcohol with secondary alcohols.

The ligand (**79**) undergoes a reaction with ruthenium complex $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ in methanol under reflux resulting in the formation of Ru-complex (**C₂₉**). Then ligands (**80**) and (**81**) were reacted with $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ resulting in the synthesis of Ru-complexes (**C₃₀**) and (**C₃₁**) in good yields respectively. These ruthenium complexes demonstrated strong catalytic activity for beta-alkylation of primary alcohols with secondary alcohols, which is considered an ecologically sustainable approach to β -alkylation (Scheme 30).

The coupling of benzyl alcohol (**82**) and 1-phenylethanol (**83**) by using Ru-complexes (**C₂₉**-**C₃₁**) was used as a model transformation. This reaction was proceeded by using Ru-complexes (0.5 mol%) as catalysts and tBuOK (0.5 eq) used as a base in PhCH_3 solvent for 60 minutes under a nitrogen environment at 110°C . Complex (**C₃₁**) exhibits excellent catalytic efficiency resulting in 94% of conversion in 1h. The conversion rate was greatly enhanced by using strong bases like KOH, t-BuOK, and NaOH in comparison to weak bases. Surprisingly, the conversion rate did not decrease when the reac-



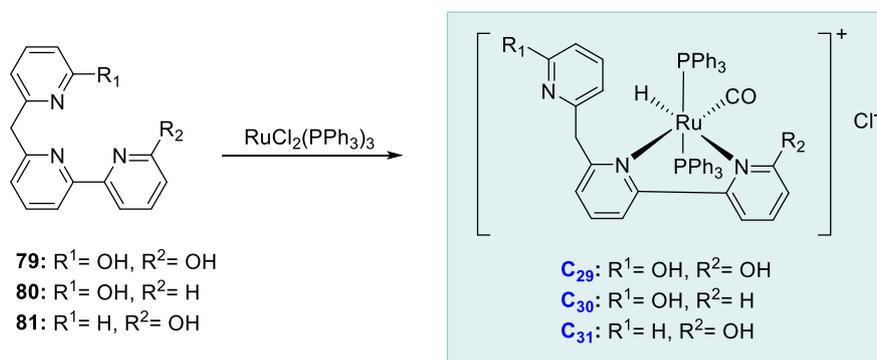
Scheme 28 Synthesis of amide-derived Ru-NNN hydride complex.



Scheme 29 Dehydrogenation of amines to nitriles.

tion proceeded under the air atmosphere. This was optimistic because such reactions usually necessitate the presence of N₂. Derivatives of phenylethanol were β-alkylated with a wide range of primary alcohols. The majority of substrates show high selectivity and conversion. Because of a steric hindrance effect, benzyl alcohols with chloro-substituent in para- and

meta-position with 1-phenylethanol converted into the corresponding secondary alcohols with better selectivity and conversion than those substituted at ortho-position. Furthermore, when an electron-donating or electron-withdrawing substituents were added to the benzyl alcohol at para-position, no noticeable substituents effect was observed.



Scheme 30 Synthesis of PNN- and PNP-lutidine-based Ru-complexes.

The electron-poor substituent on the 1-phenylethanol substrate at the para-position had no discernible effect on the reaction, whereas an electron-rich substituent drastically reduces the selectivity and reactivity (Scheme 31) (Shi et al., 2018).

2.10. Synthesis of bipyridine-based electron-rich Ru(II)-PNN pincer complex and its applications

Hydrogenation of polar organic carbonyl groups has attracted a lot of attention because of its environmentally friendly nature and synthetically useful way to make elementary synthetic intermediates like amines and alcohols (Clapham et al., 2004; Ito and Ikariya, 2007; Wylie et al., 2010). Carbamate hydrogenation is of great importance both theoretically and practically, because carbamates may be easily obtained from CO or CO₂, and their mild hydrogenation would result in the conversion into methanol. Pyridine and acridine-based Ru-pincer complexes accelerate the hydrogenation of organic carbamates into alcohols and amines. This reaction is very selective and proceeds effectively under neutral or mild conditions in the absence of solvent has a high turnover rate, and produces no waste. Furthermore, this novel reaction offers intriguing alternatives for mild CO and CO₂ hydrogenation into methanol.

The tridentate ligand BPy-tBuPNN (**85**) was reacted with [RuHCl(PPh₃)₃(CO)] (**86**) in tetrahydrofuran at 65°C to produce the bipyridine-based electron-rich Ru(II)-PNN pincer complex (C₃₂). Complex (C₃₂) was deprotonated with KOtBu at -32°C, yielding the dearomatized, coordinatively unsaturated complex (C₃₃) (Scheme 32) (Balaraman and Milstein, 2014).

The methyl carbamates (**87**) hydrogenation to corresponding amines (**88**) and methanol (**89**) was effectively catalyzed by Complex (C₃₃). The solution of dihydrogen and methyl *N*-benzyl carbamate was heated in THF for 48h at 110°C with a catalytic quantity of complex C₃₃ (0.01 mmol) afforded the methanol and benzylamine in quantitative yield. The benzyl carbamates were hydrogenated selectively without breakage of the benzyl *O*-bond to give methanol, respective benzyl alcohols, and amines. The benzyl morpholine-4-carboxylate reacts with hydrogen (10atm) at 110°C in dry tetrahydrofuran for 52h with the catalytic quantity of C₃₃ (1mol percent) resulting in the formation of benzyl alcohol (88%), morpholine (87%),

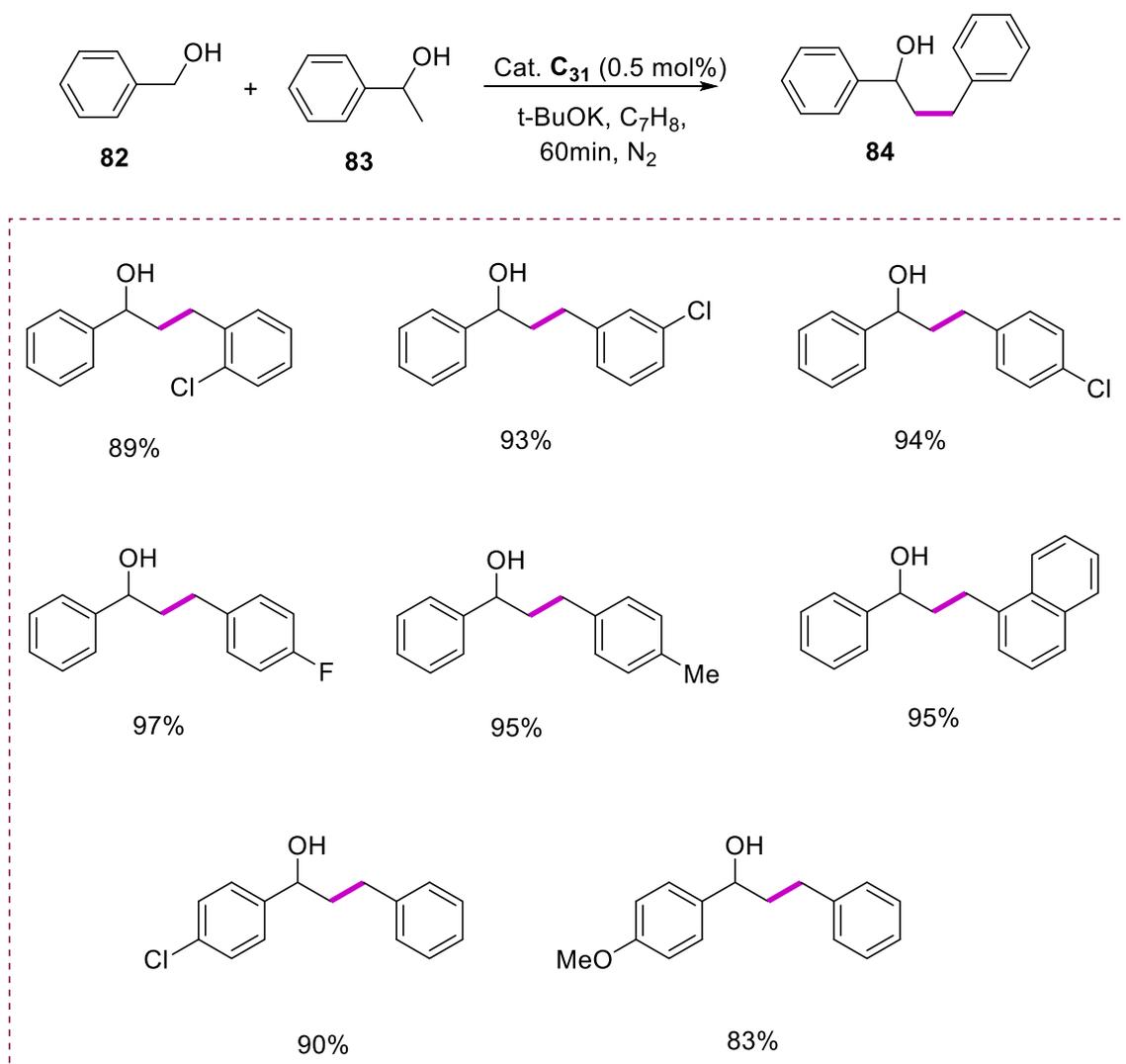
and methanol (81%). It is worth noting that in the hydrogenolysis of benzyl carbamates, the carbamate-*N* functional groups are deprotected (Scheme 33) (Balaraman et al., 2011).

The catalytic hydrogenation of derivatives of carbonyl (C=O) compound using molecular H₂ is a significant transformation in synthetic chemistry. The hydrophilicity of the carbonyl carbon is inversely proportional to its liability to nucleophilic attack through hydride (Carey and Sundberg, 2000). Hydrogenation of derivatives of urea is the most difficult among other carbonyl compounds because of less electrophilicity of the carbonyl group due to the resonance effect. Alkylated urea derivatives have also been employed as solvents in the hydrogenation transformations of other chemicals as well as as “green” solvents in metal-assisted organic reactions (Imperato et al., 2006).

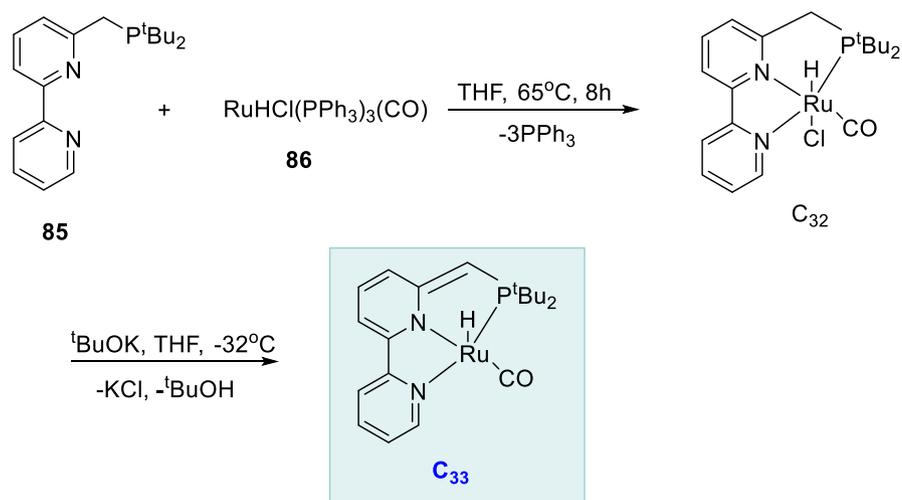
The urea derivatives (**90**) hydrogenation was carried out under milder reaction conditions specifically 110°C and H₂ pressure (13.6atm) in the presence of complex (C₃₃) resulting in the cleavage of strong C–N bonds occurring selectively yielding the corresponding amines (**91**) and methanol (**92**) in high yields. The alkyl- and aryl-urea derivatives may be easily made from amines and CO₂, and their hydrogenation provides a mild, eco-friendly, and efficient method of converting CO₂ to methanol (Scheme 34) (Balaraman and Milstein, 2014).

The selective catalytic alcohol oxidation is a very significant transformation in the formation of industrial building blocks and chemicals (Yamaguchi and Mizuno, 2010; Sheldon, 2012; Simon and Li, 2012). The bipyridine-based ruthenium complex (C₃₃) catalyzed the coupling of different alcohols at basic pH with water, resulting in high yield and large turnovers of the required salts of carboxylic acid and hydrogen gas development. Water might serve as both oxygen donor and reaction medium in a catalytic coupling between alcohols and water without the use of any other oxidant under neutral conditions.

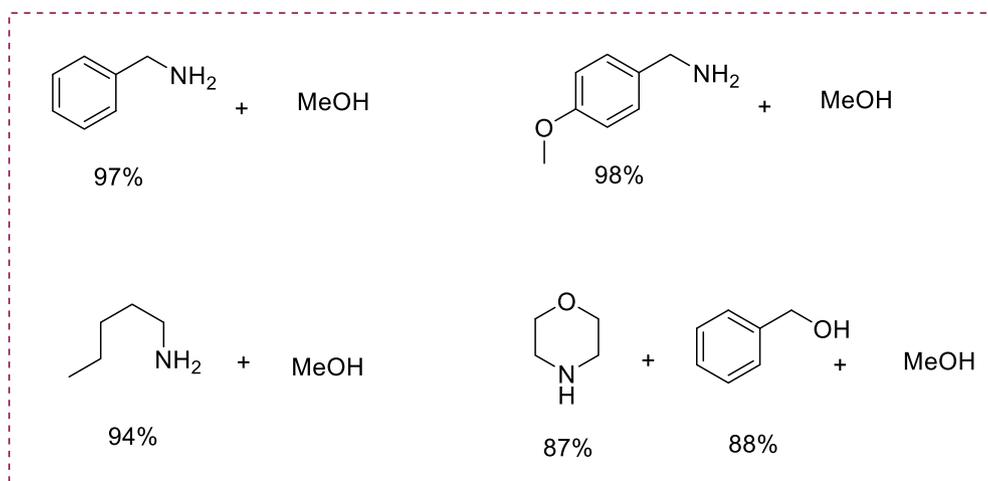
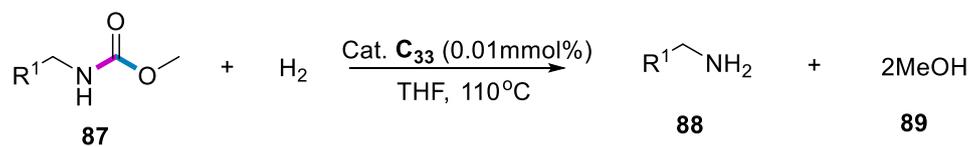
The catalytic transformation was proceeding rapidly by refluxing the mixture of alcohol (**93**), water, and complex C₃₃ (0.2 mol%) under an argon atmosphere. The appropriate salts of carboxylic acid were produced in high yields after 18h of reaction time and converted to corresponding carboxylic acids (**94**) via the treatment of acid. Both aromatic and aliphatic alcohols demonstrate significant turnover and selectivity in this catalytic system (Scheme 35) (Balaraman et al., 2013).



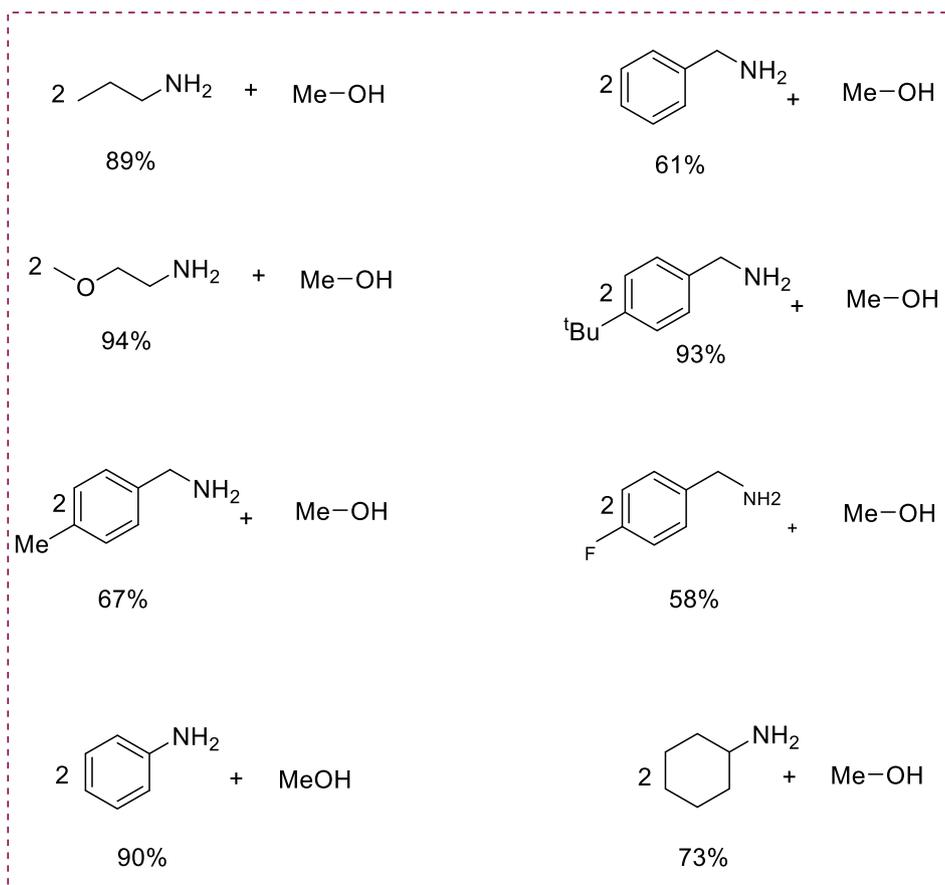
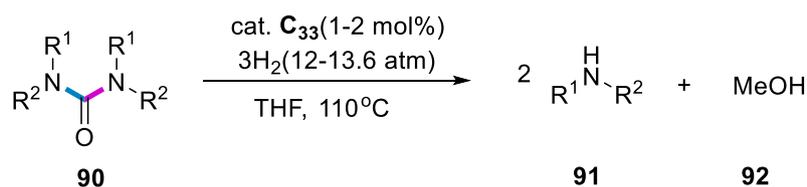
Scheme 31 β -alkylation of alcohols by using alcohols.



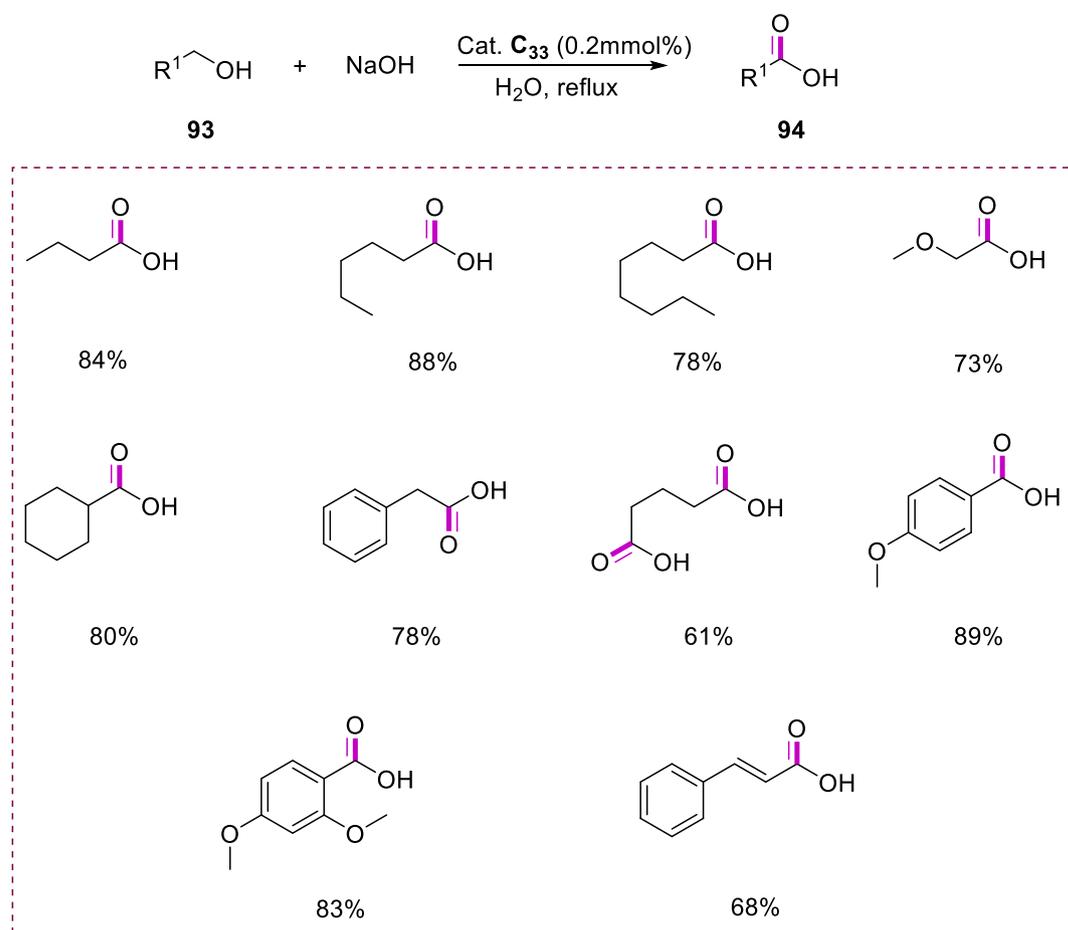
Scheme 32 Synthesis of bipyridine-based electron-rich Ru(II)-PNN pincer complex.



Scheme 33 Hydrogenation of carbamates.



Scheme 34 Hydrogenation of urea derivatives.



Scheme 35 Synthesis of carboxylic acid derivatives.

N-Heterocycles are a significant class of compounds because of their abundance in pharmaceuticals and natural products (Joule et al., 2020). Substituted pyridines are used as important building blocks in bioactive compounds among the *N*-heterocycles, and they are widely applied in medicines, functional materials, and agrochemicals (Henry, 2004; Michael, 2005). The Ru–bipyridine-based pincer complexes catalyze a variety of environmentally friendly reactions. Direct pyrrole synthesis proceeds through the dehydrogenative coupling of secondary alcohols with β -aminoalcohols, as well as efficient, one-step pyridine synthesis via dehydrogenative coupling of secondary alcohols with γ -amino-alcohols was efficiently accelerated by these complexes.

The reaction of 3-aminoalcohol (**95**) with secondary alcohol (**96**) was initially selected as model substrates for the synthesis of pyridines (**97**) via dehydrogenative cross-coupling. Refluxing an equimolar quantity of 1-phenylethanol (2 mmol), 3-aminopropanol, with K₂CO₃ as a base in toluene for 24 h in the presence of 0.5 mol% complex (**C**₃₂) yielded 45% of 2-phenylpyridine. The yield of the product was not improved by increasing the duration of reaction up to 40 h or increasing the loading of catalyst up to 1 mol%. The solvent influence on the reaction rate was also investigated. The 2-phenylpyridine was obtained in higher yields (68%) when the mixture of tetrahydrofuran and toluene was used as a solvent than in THF (25%) or toluene (62%) alone. The reaction of various 3-aminoalcohols with secondary alcohols (cyclic and acyclic)

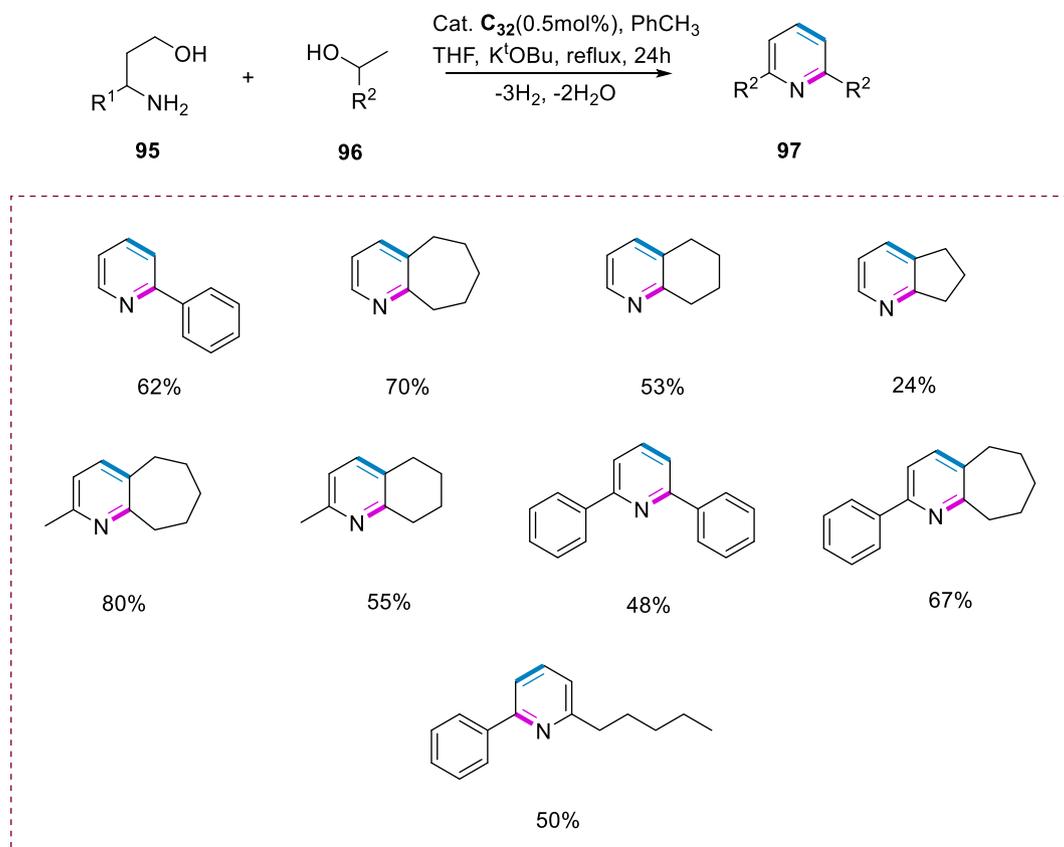
substrates was favored by these reaction conditions and resulted in the synthesis of substituted pyridines in moderate to good yields (Scheme 36).

Many bioactive natural compounds including the quinoline molecule and diverse quinoline derivatives have a wide range of pharmaceutical activities which allow them to employ anti-HIV, anticancer, antihypertensive, anti-Alzheimer, and anti-tuberculosis medicines. Exploring the potential of quinoline synthesis, we investigated the reaction of various secondary alcohols, including cyclohexanol, 1-phenylethanol, cyclododecyl alcohol, and cycloheptanol with 2-aminobenzyl alcohol to obtain tetrahydroacridine, 2-phenylquinoline, decacyclododeca[*b*]quinoline, and tetrahydro-6H-cyclohepta[*b*]quinoline in modest to good yields (Scheme 37) (Srimani et al., 2013a).

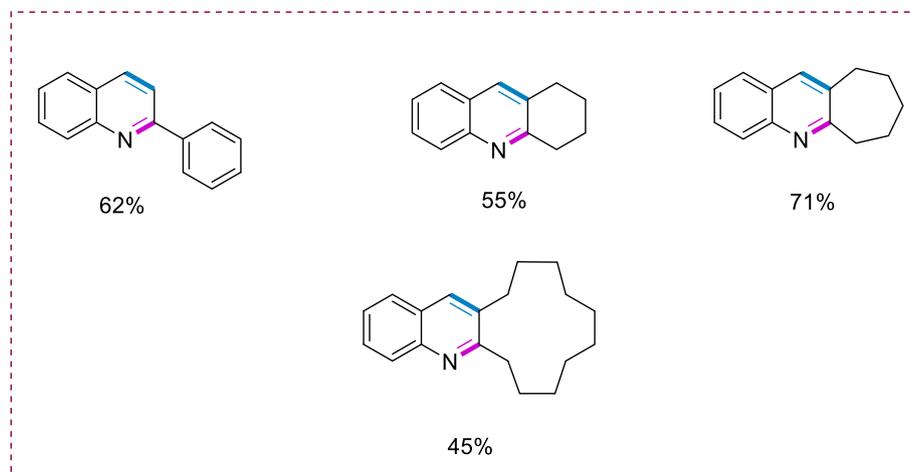
2.11. Synthesis of lutidine-based Ru-CNC complexes and their application

Pincer complexes derived from lutidine have become a popular class of organometallic derivatives (van der Vlugt and Reek, 2009; Gunanathan and Milstein, 2011a). Hydrogenation of C=N bonds of different imines catalyzed by Ru complexes containing dearomatized lutidine-derived pincer ligands (Andersson and Munslow, 2008).

The corresponding 1-substituted 1H-imidazole and 2,6-bis(halomethyl)pyridine were refluxed (1: 2 ratio) in acetonitrile



Scheme 36 Synthesis of substituted pyridines.

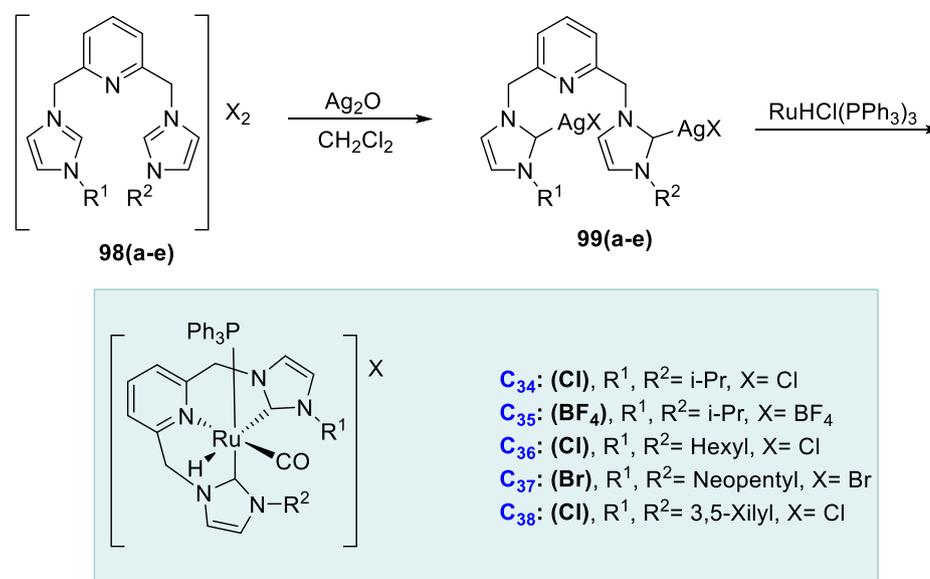


Scheme 37 Synthesis of substituted quinolines.

or THF solutions to synthesize the new bis-imidazolium salts (**98a-98e**). The bis-imidazolium salts were then treated with 1 eq. of Ag_2O at room temperature in CH_2Cl_2 resulting in the synthesis of bimetallic silver reagents (**99a-99e**). Complexes **C₃₄(Cl)** and **C₃₆(Cl)** were easily prepared in THF at 55°C using $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ and a suitable silver reagent. Complexes **C₃₅(BF₄)** and **C₃₇(Br)** were similarly prepared by reacting the corresponding silver reagents with $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ respectively. Finally, the formation of 3,5-xilyl-substituted

C₃₈(Cl) was carried out more efficiently with $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ at room temperature. These complexes are specifically deprotonated by potassium tertiary butoxide at one of the methylene arms in the pincer complex, resulting in catalytically active species in the imines hydrogenation. (**Scheme 38**).

The Ru-complexes (**C₃₄-C₃₈**) exhibit outstanding catalytic activity for the imine (**100**) hydrogenation. Complexes (**C₃₄-C₃₈**) catalyze the *N*-benzylideneaniline hydrogenation in 2-methyltetrahydrofuran under H_2 (5 bar) at 70°C by using



Scheme 38 Synthesis of lutidine-based Ru-CNC complexes.

tBuOK as a base. Complex **C₃₆(Cl)** is the more active catalyst in the series. This reaction tolerated a variety of *N*-alkyl and *N*-aryl aldimines. Substrates having electron-donating substituents enhanced the reactivity, but the substrates having highly electron-poor substituents in both of the aryl groups greatly minimize the reactivity. The *N*-phenyl imine was also hydrogenated very efficiently than the analogous *N*-benzyl aldimine. Complex **C₃₆(Cl)** was also found to be effective in the catalytic hydrogenation of a variety of *N*-arylated ketimines with excellent turnover (**Scheme 39**) (**Hernández-Juárez et al., 2013**).

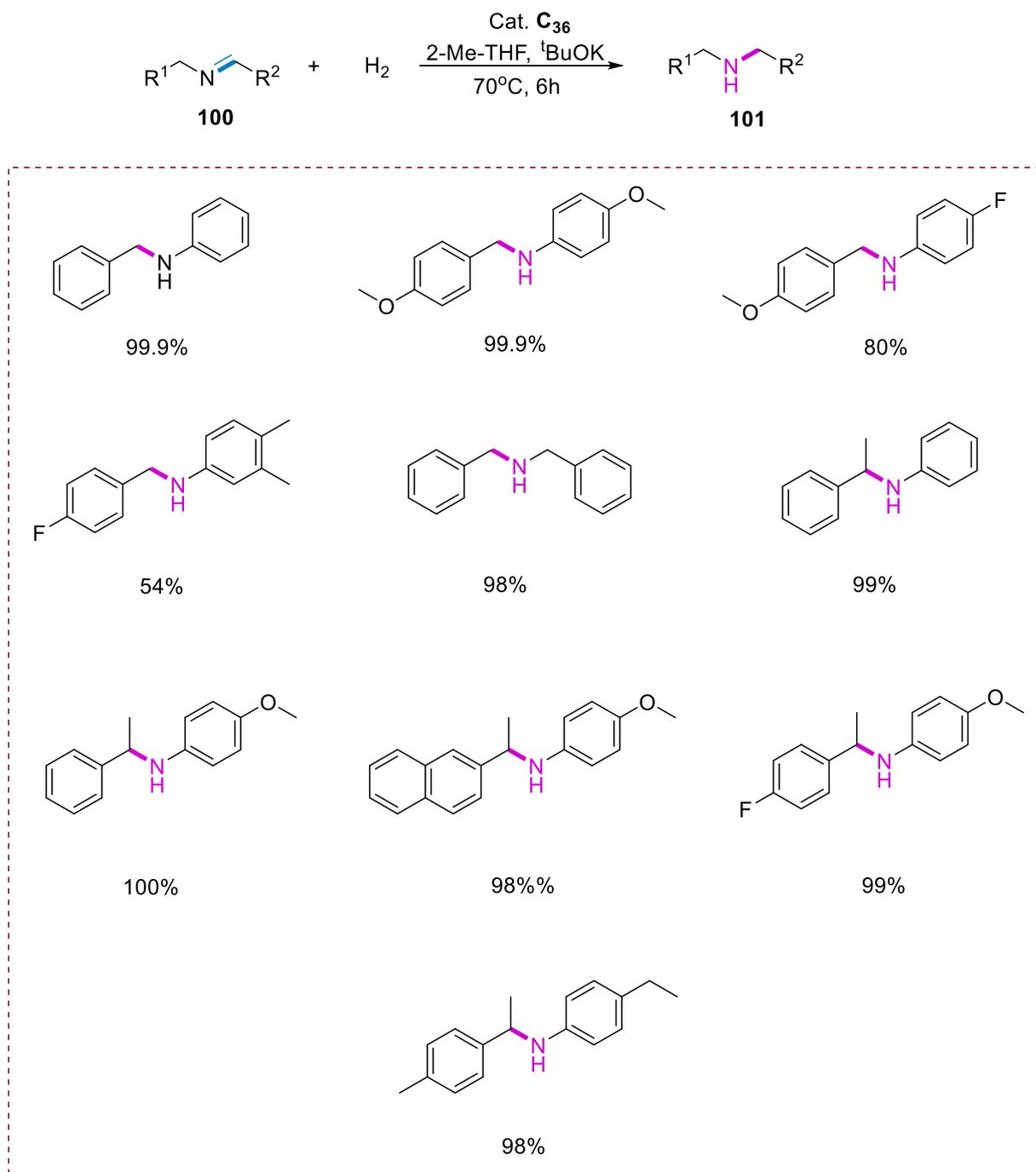
2.12. Synthesis of PNP-Ru(II) and Ru-MACHO-BH Ru(II) complexes and their applications

One of the most significant challenges in modern chemistry is the development of sustainable strategies for converting biomass into valuable compounds (**Caetano and Fernandes, 2018**). The addition of nitrogen to biomass-derived chemicals increases their value and broadens their industrial application (**Dunbabin et al., 2017**). Furfurylamines (amines generated from furfurals) are used to make a variety of medicines in the pharmaceutical industry, including Furtrethonium, Fure-somide, which are used against the hepatitis-B drug, and Barmastine used as antiseptics as well as used in polymers, agrochemicals, synthetic resins, and insecticides (**He et al., 2020**). Various reducing agents and catalysts have been used to study the formation of furfurylamines through reductive amination by using furfurals. This conversion as the synthetic tool is non-toxic, environmentally benign, does not use combustible gases, and uses an easy-to-handle, stable, and low-cost hydrogen supply (**Yao, 2001; Wang et al., 2008a; Wang and Astruc, 2015; Werkmeister et al., 2015; Farrar-Tobar et al., 2020; Piccirilli et al., 2020**). The Ru-MACHO (carbonylhydrido-(tetrahydroborato)[bis(2-diphenylphosphi

noethyl)amino] Ru(II) and RuMACHO-BH complexes are appropriate catalysts for hydrogenation via reductive amination due to their excellent selectivity and activity.

Ru-MACHO-BH ruthenium(II) complex (**C₄₀**) was produced by reducing ruthenium complex (**C₃₉**) with NaBH₄. The PNP-Ru(II) complex (**C₃₉**) was prepared from commercially available bis-(2-diphenylphosphinoethyl)ammonium chloride (**102**) and carbonylchlorohydridotris-(triphenylphosphine)-Ru(II). These complexes are miscible in protic solvents like tetrahydrofuran, ethanol, and methanol as well as in toluene (**Scheme 40**) (**Yao, 2001**).

Ru-MACHO-BH (**C₄₄**) catalyzed the one-pot formation of furfurylamines (**105**) by using anilines (**103**) and furfurals (**104**) in the presence of MgSO₄ and iPrOH at 90°C. Furfurylamines were obtained in modest to excellent yields in most cases. The furfurylamine was obtained in excellent yield (93%) from the parent aniline compound. When anilines with electron-withdrawing or electron-donating substituents were compared, the substrates carrying electron-withdrawing groups afforded excellent yields than others. The substituted anilines such as 4-CF₃-aniline, 4-F-aniline, and 4-aminopyridine have produced the highest yields of different substituted furfurylamines (74 to 95%). The anti-hepatitis-B molecule is analogous to a compound (**106**) which demonstrates the direct utilization of this strategy for the development of pharmacologically active molecules. The furfurylamine was obtained at a low yield (61%) when aniline having an electron-donating group such as 4-CH₃-aniline was used in the reaction. Various halogens containing aniline substrates were also well-tolerated given the yields ranged from modest to excellent. Compounds like 3-Cl-aniline and 2-F-aniline exhibit good tolerance, giving good yields (60% and 56%) respectively. This strategy was also examined with *N*-methylaniline (secondary amine) which resulted in a high yield of the tertiary amine (89%) (**Scheme 41**), (**Scheme 41a**).



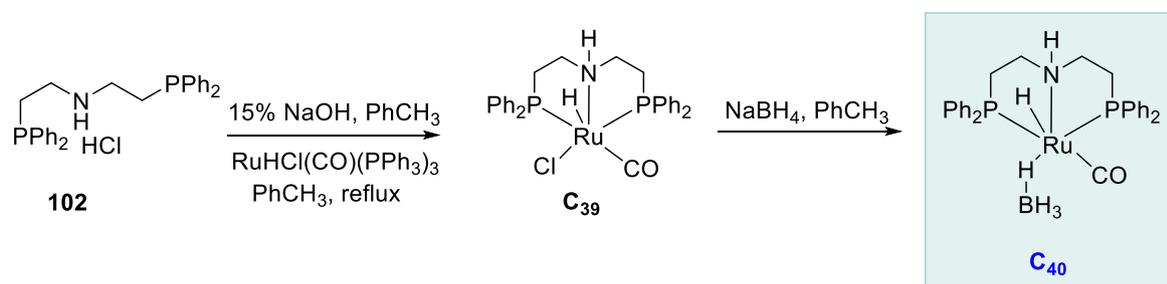
Scheme 39 Hydrogenation of imines.

Several furfurylamines synthesized from this method are used to make biopolymers (polyamides) and pharmaceuticals like Furtrethonium (the drug that is used against hepatitis-B), Barmastine, and Furesomide. The *N*-(5-methylfurfuryl) aniline is a key ingredient in the production of epoxyisoindoles and bioactive molecules such as anticancer, antibacterial, antituberculosis, and anti-inflammatory agents (Pinheiro and Nielsen, 2021).

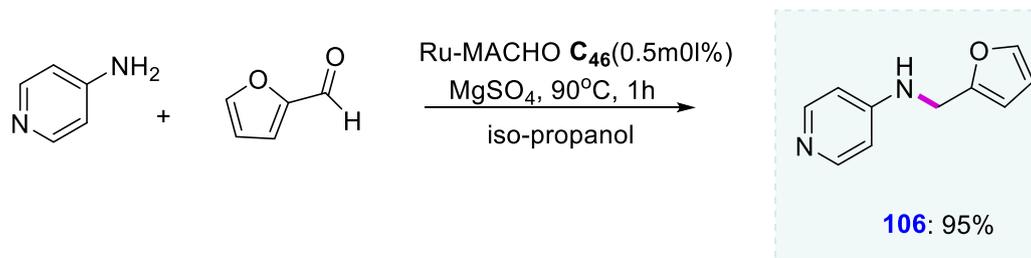
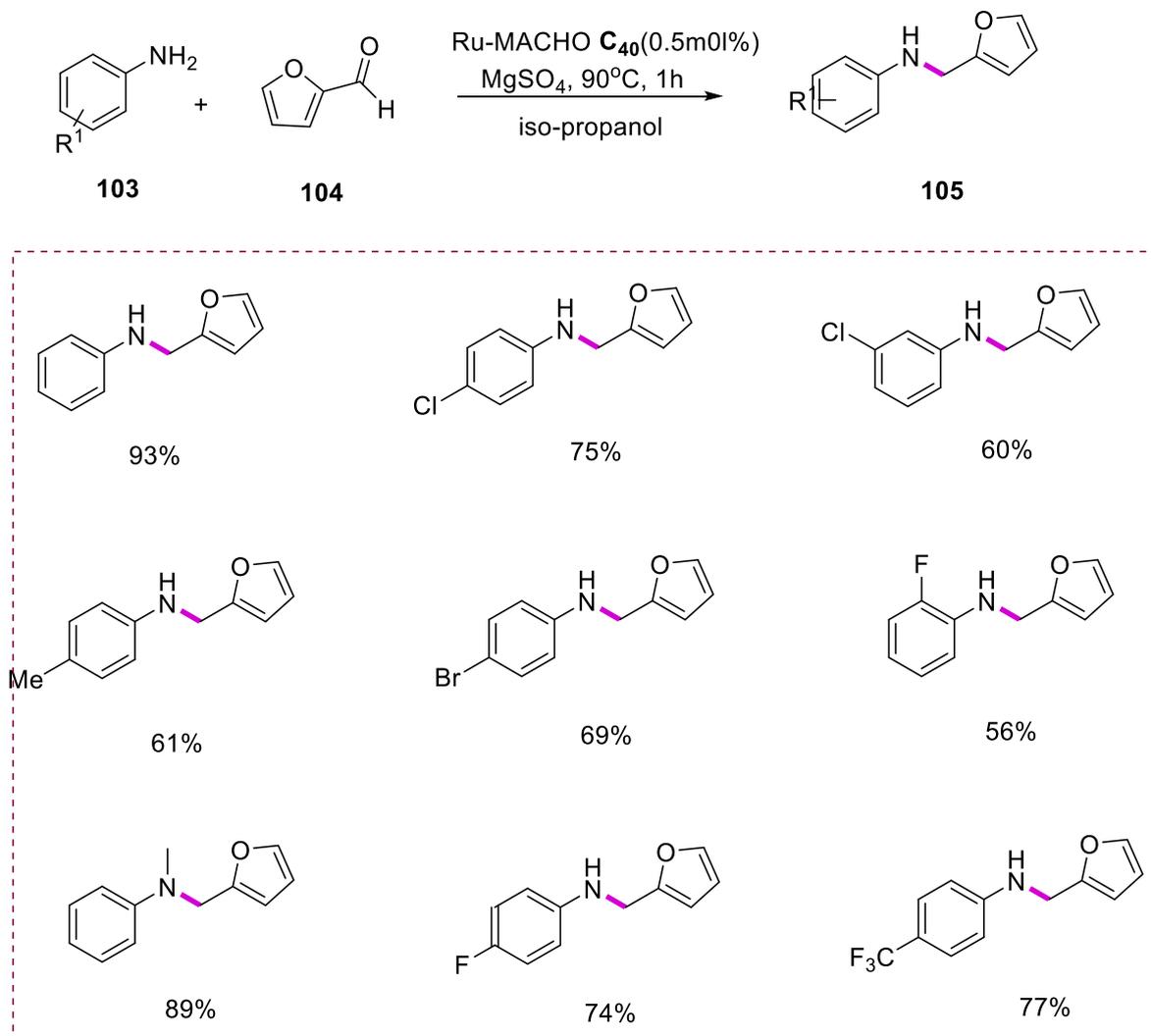
CO₂ is an appealing building block in the formation of organic compounds, carbohydrates, and materials because it is a cost-effective, safe, and renewable carbon resource (Aresta, 2010). Milstein and coworkers introduced an indirect

route for the formation of methanol from CO₂ by homogeneous carbonates hydrogenation under mild conditions employing pincer-type ruthenium (II) catalysts having a common structure [(PNP)Ru-(CO)(H)]. Furthermore, this approach is cost-effective. The utilization of an easily available (PNP)Ru(II) complex for the homogenous cyclic carbonates hydrogenation from readily available epoxides and CO₂ to produce corresponding diols and methanol with high efficiency of the catalyst.

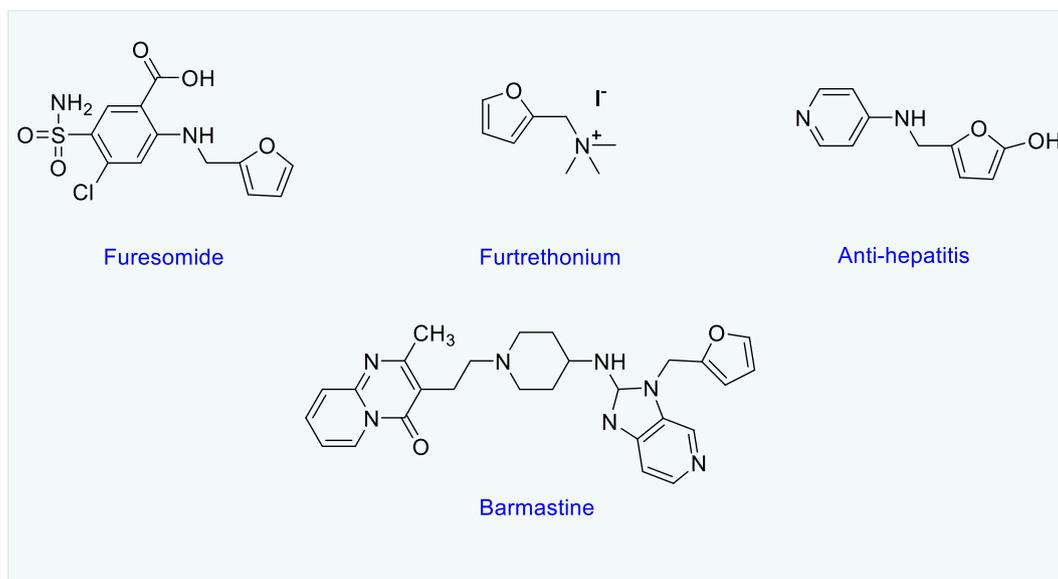
The pincer-type ruthenium (II) complex is used as a catalyst to accelerate the hydrogenation of cyclic carbonates (107) effectively. The reaction was carried out in THF at 140°C in



Scheme 40 Synthesis of PNP-Ru(II) and Ru-MACHO-BH Ru(II) complexes.



Scheme 41 Synthesis of furfurylamines.



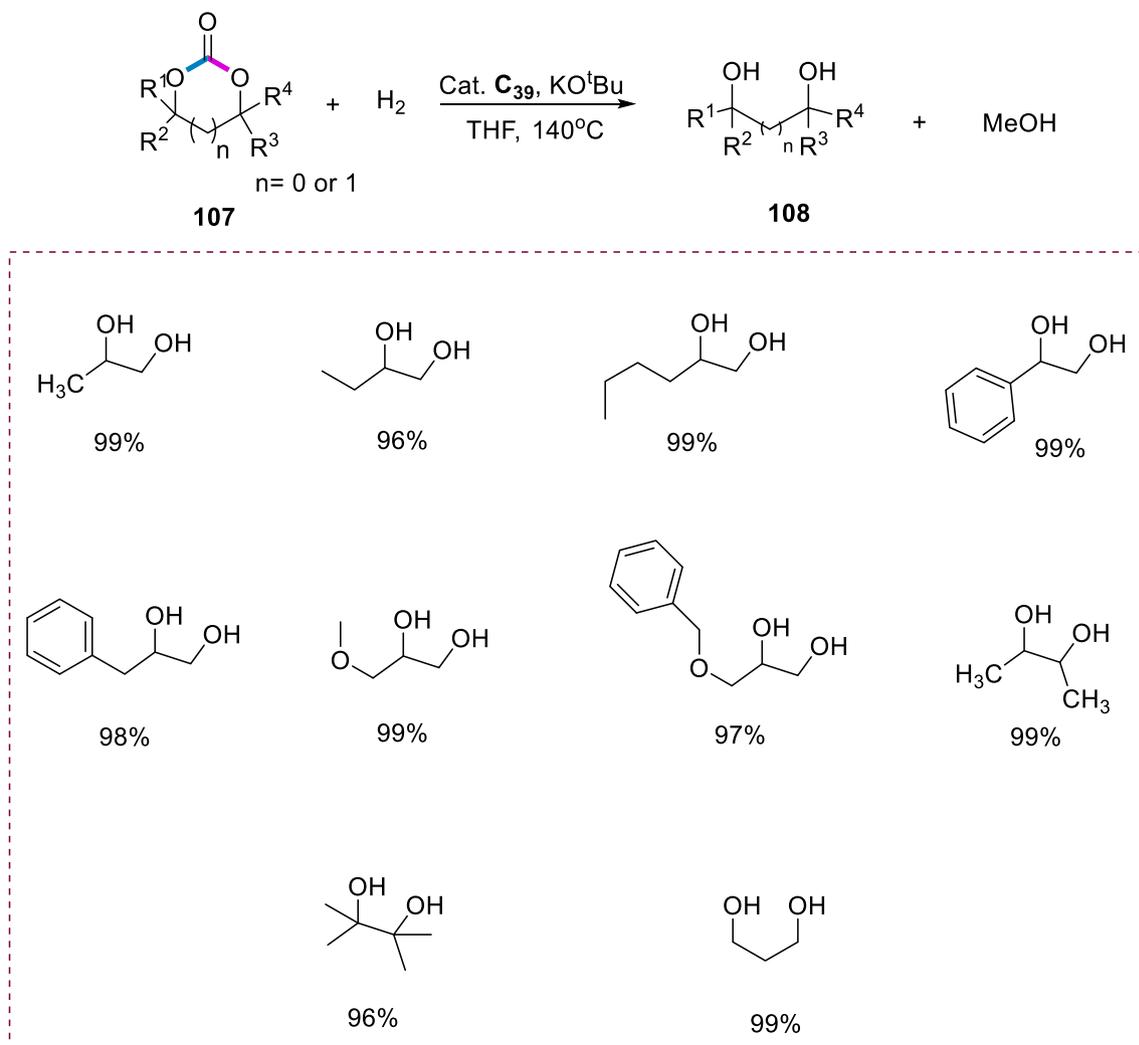
Scheme 41a Pharmaceutically active compounds derived from furfurylamines.

the presence of the catalytic Ru(II) complex (**C₃₉**) and the base tBuOK under a pressure of 50 atm of H₂. Ru(II) complex was shown to be active for hydrogenation at a catalyst loading of 0.1 mol %, yielding methanol and ethylene glycol **108** (EG) at varied yields. When the loading of catalyst was reduced to 0.01 mol%, the process could be accomplished in 48h, producing >99% methanol and EG. The reaction was carried out smoothly under an H₂ environment (60atm) with an 89% transformation of ethylene carbonate within 72h, affording the ethylene glycol (87%) and methanol (84%) yields respectively by reducing a load of catalyst up to 0.001 mol%. This result indicates the good stability and excellent efficiency of the catalyst. Various cyclic carbonates such as 5-membered as well as six-membered 1,3-dioxolan-2-ones having one, two, or even four substituents can be hydrogenated selectively and efficiently into their corresponding diols and methanol under similar conditions. The sterically hindered substituents on the substrates of cyclic carbonates have a major impact on the activity of reactions, as it requires a greater loading of catalyst and more reaction time to complete the transformation of more sterically demanding substrates (Scheme 42) (Han et al., 2012).

The chemical synthesis relies heavily on the synthesis of the C=C bond (Maryanoff and Reitz, 1989). Only ruthenium-catalyzed alkene metathesis is available as a catalytic technique for intermolecular olefin synthesis (Hoveyda and Zhugralin, 2007; Vougioukalakis and Grubbs, 2010). Vinyl nitriles are common in pharmaceuticals, and natural products and are essential intermediates in organic transformations. They are important intermediate and building blocks in a variety of chemical reactions. In traditional vinyl-nitrile synthesis, a stoichiometric quantity of base is used to mediate the reaction between nitriles and carbonyl compounds (Knoevenagel condensation) (Guillot et al., 2005). Base-promoted condensation transformations with cross-reactions like the aldol condensation, self-condensation of nitriles, and the Cannizzaro reactions are limited to base-sensitive substrates (Arseniyadis et al.,

1984). The Ru-catalyzed α -alkylation of aryl methyl nitriles with alcohols as an alkylating agent was recently reported (Thiyagarajan and Gunanathan, 2017). This environmentally friendly and effective alkylation reaction was facilitated by ligand-metal coordination in ruthenium-pincer complex, and the reactions were carried out by borrowing hydrogen pathway. Remarkably, water and liberated H₂ are the byproducts obtained from this green synthetic method.

The dehydrogenative coupling of nitriles (**109**) and alcohols (**110**) takes place through amide-amine ligand-metal coordination in the activated complex (**C₃₉**). The phenyl acetonitrile and cyclohexanol were reacted in the presence of Ru-pincer complex (mol%, Ru-MACHO) in toluene resulting in the synthesis of the desired olefin in moderate yield. Although full nitrile conversion was observed in 16h. However, no alkylated product was obtained by using the primary alcohol as a substrate. Additionally, reducing the catalyst loading (1 to 0.5mol%) and decreasing the temperature from 135 to 120°C increase the yield of the reaction. The olefination reaction requires a catalyst and base to proceed with the transformation. The range of substrates including various nitriles was tolerated concerning cyclohexanol in catalytic olefination reaction. The reaction of cyclohexanol with 4-methyl phenyl-acetonitrile afforded the respective olefin product in good yield (78%). When 2-methoxy phenyl-acetonitrile was used in the reaction under controlled conditions result in a lower yield (72%), showing that the olefination reaction is sensitive to steric hindrance in the substrates in proximity. However, excellent conversions were achieved with meta- and para-methoxyphenylacetonitrile and the resultant products were extracted in excellent yields. This catalytic transformation was particularly effective on heteroarylmethyl nitriles, aryl methyl nitriles, and aliphatic nitriles. In this reaction, unsymmetrical and symmetrical secondary alcohols, as well as acyclic and cyclic secondary alcohols, were also used resulting in a variety of α -vinyl nitrile derivatives. The electron-poor substituent on the substrates was also permitted (Scheme 43) (Thiyagarajan and Gunanathan, 2018).



Scheme 42 Hydrogenation of cyclic carbonates.

Deuteration of alcohols is selectively important due to a variety of applications, including the production of deuterated medicines and other biologically active molecules (Pleiss and Voges, 2001). Although the interaction of simple hydrocarbons with D_2O is a well-known catalytic deuteration reaction. The direct and selective catalytic deuteration of alcohols is less common.

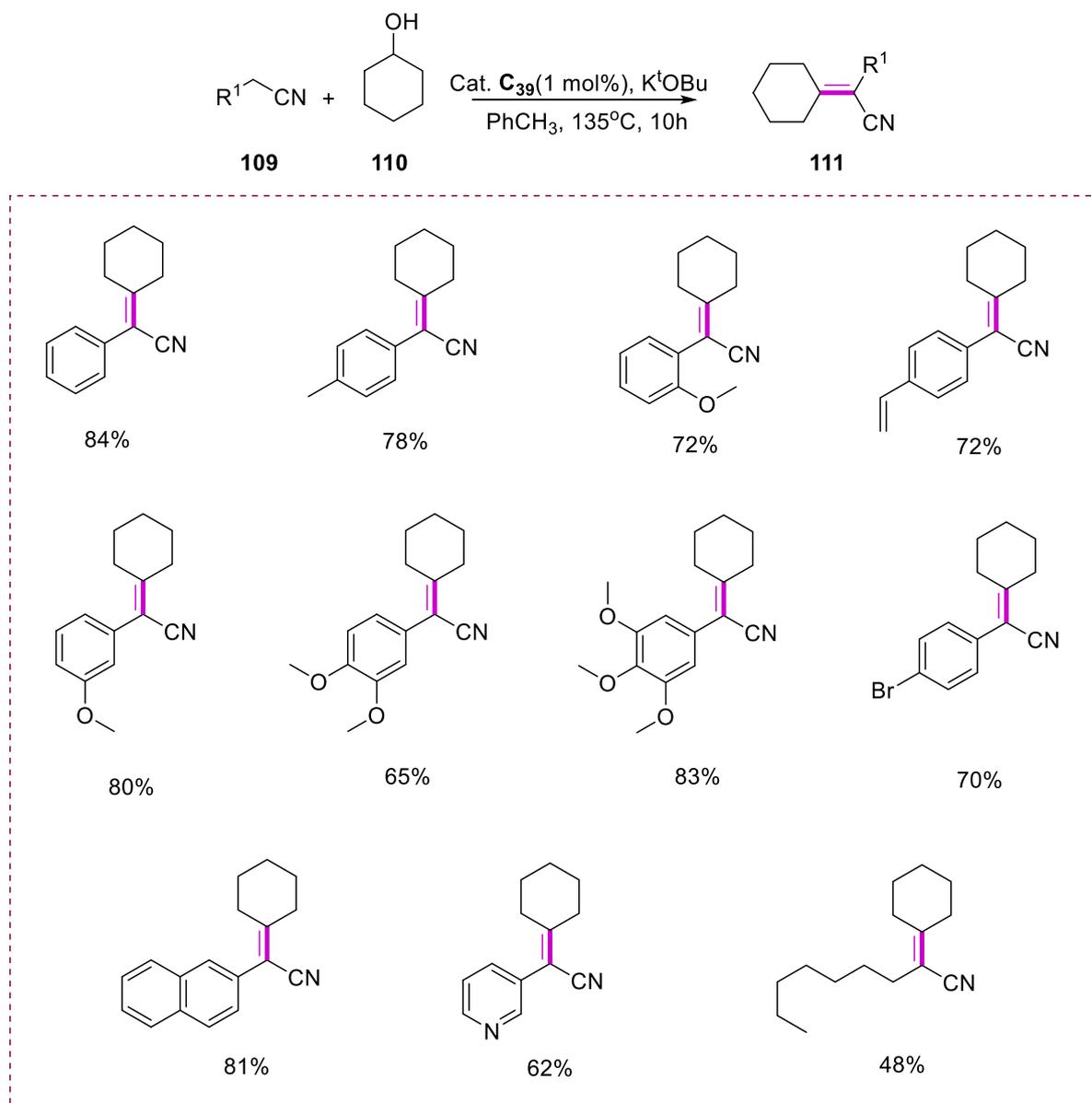
The efficient selective alpha-deuteration was observed when benzyl alcohol was subjected to selective deuteration in the presence of ruthenium complex **Ru-C₃₉** (0.2mol%) catalyst and $KOtBu$ in D_2O (0.4 mL) at $60^\circ C$. The deuteration occurred at the alpha-position within only 3h to provide benzyl alcohol- d_3 as a product in 96% yield, while there was no detectable H/D interchange with aromatic protons. The catalytic deuteration of a variety of heteroaryl methanols and aryl methanol were observed using similar catalytic conditions. This methodology was also used to selectively deuterate linear aliphatic alcohols. The variety of aliphatic alcohols involving heteroaryl-appended straight chain aliphatic alcohols demonstrated strong deuterium integration selectively at the alpha position when they are exposed to the catalytic deuterated condition. However, several of these linear alcohols have a

minor amount of beta-deuteration (9-20%) (Scheme 44) (Chatterjee and Chidambaram, 2018).

2.13. Synthesis of lutidine-based Ru-CNN(H) complexes and their applications

Metal complexes derived from lutidine have gotten a lot of attention because they can be easily deprotonated at the methylene arms in the pincer complex. Pincer complexes containing lutidine and N-H have proven to be highly selective and active catalysts for a wide range of dehydrogenation and hydrogenation transformations. The reduction of cyclic *N*-heteroaromatic to their respective saturated derivatives and the saturated *N*-heterocycles to their parent *N*-heteroaromatic compounds via oxidation, respectively, were green synthetic approaches involving hydrogenation and dehydrogenation (Milstein, 2015).

The imidazolium salts (**114a-114c**) were mixed with Ag_2O in CH_2Cl_2 and the silver complexes (**115a-115c**) were formed. The Ru-CNN(H) complexes (**C₄₁-C₄₃**) were isolated in good to moderate yields (33-85%) by subsequent reactions of compound (**115a-115c**) with Ru-complex $[RuHCl(CO)(PPh_3)_3]$ in

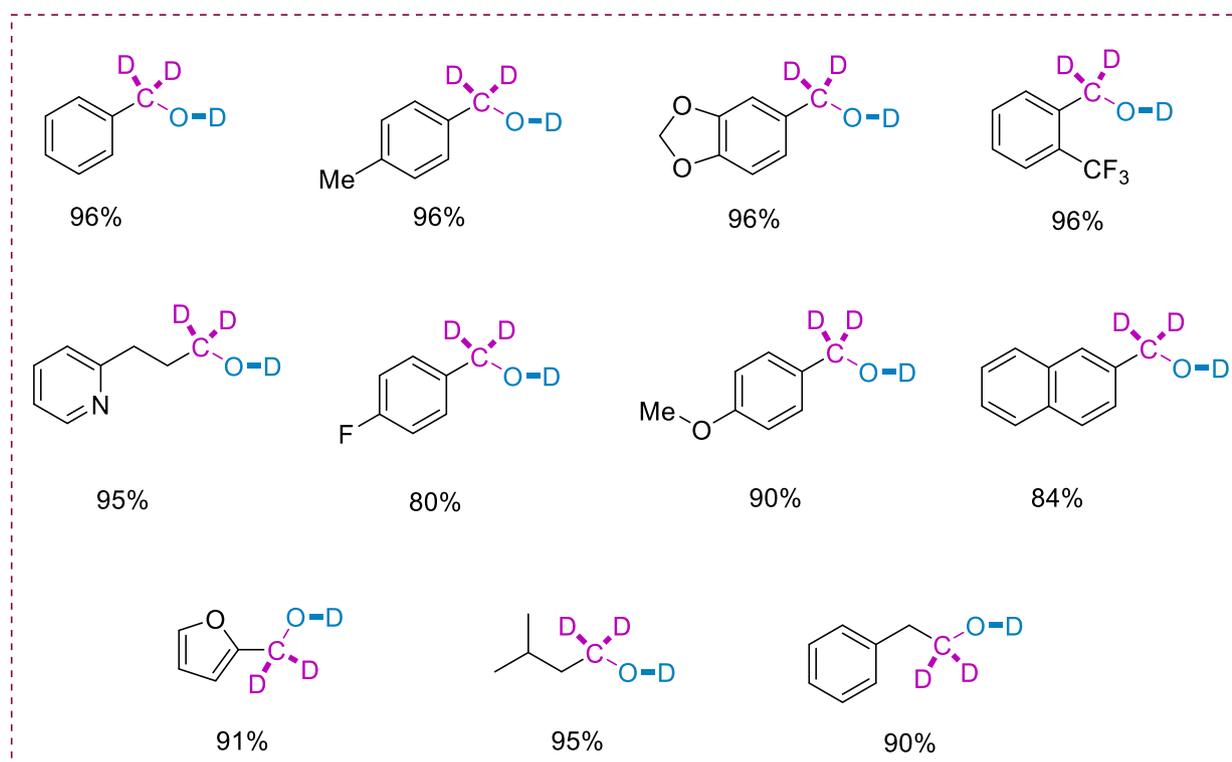
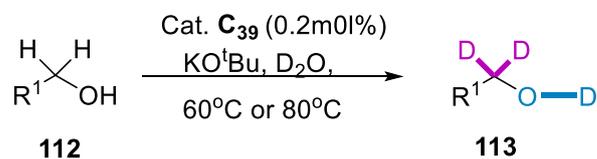


tetrahydrofuran, followed by reaction with NaBF_4 and PPh_3 in CH_3CN . Ru complexes based on lutidine-based ruthenium pincer complexes (\mathbf{C}_{41} - \mathbf{C}_{43}) having $\text{CNN}(\text{H})$ ligands with side donor of secondary amine are used as precatalysts for the dehydrogenation and hydrogenation of *N*-heterocycle. The Ru- $\text{CNN}(\text{H})$ complex reacts with an excess of base leads to ruthenium (0) complex observed under catalytic conditions. The Ru- $\text{CNN}(\text{H})$ complex (\mathbf{C}_{41}) was found to be more effective among other complexes to catalyze both the dehydrogenation and hydrogenation of a series of *N*-heterocyclic compounds (Scheme 45).

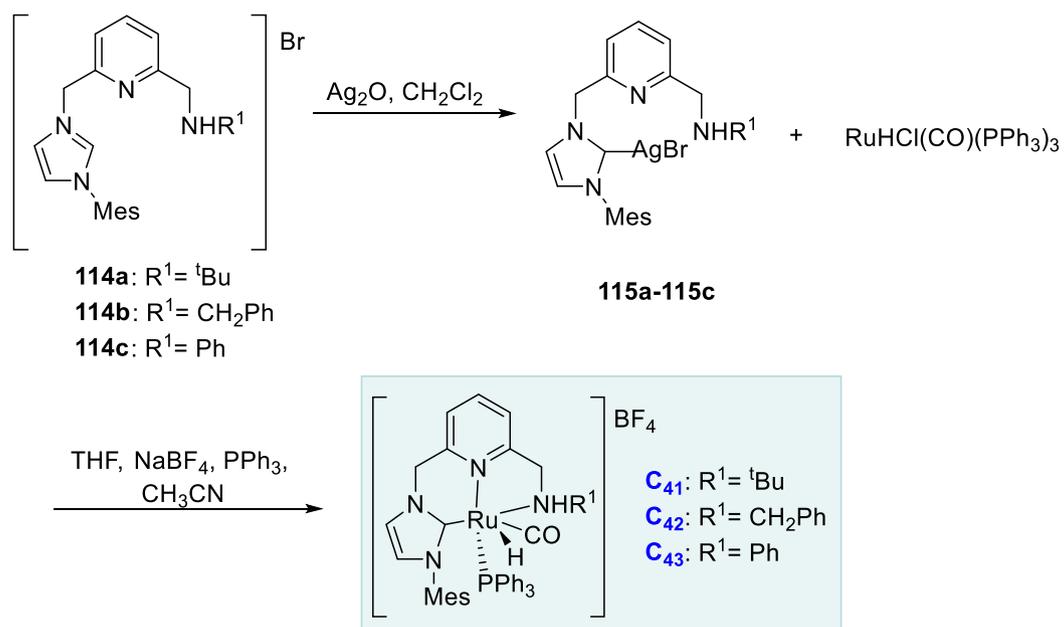
The catalytic reactivity of complex (\mathbf{C}_{41} - \mathbf{C}_{43}) was studied in the *N*-heterocycles hydrogenation. Complex \mathbf{C}_{41} (0.5 mol%) catalyzed the *N*-heterocycles ($\mathbf{116}$) hydrogenation under H_2 (4 bar) at 80°C in the presence of K^tOBu , resulting in complete conversion in 6h. Complexes (\mathbf{C}_{42} and \mathbf{C}_{43}) were shown to be less active than complex (\mathbf{C}_{41}) under the same conditions. The 2-methylquinoxaline was reduced with excellent

conversions in 24h under similar conditions. Similarly, phenanthridine and acridine were hydrogenated with good conversions in 19h using complex \mathbf{C}_{41} (0.5 mol%). However, to achieve greater than 95% conversion, the hydrogenation of quinoline and quinaldine need harsh reaction conditions (1.0mol% \mathbf{C}_{41} , 48h, 95°C). (Scheme 46)

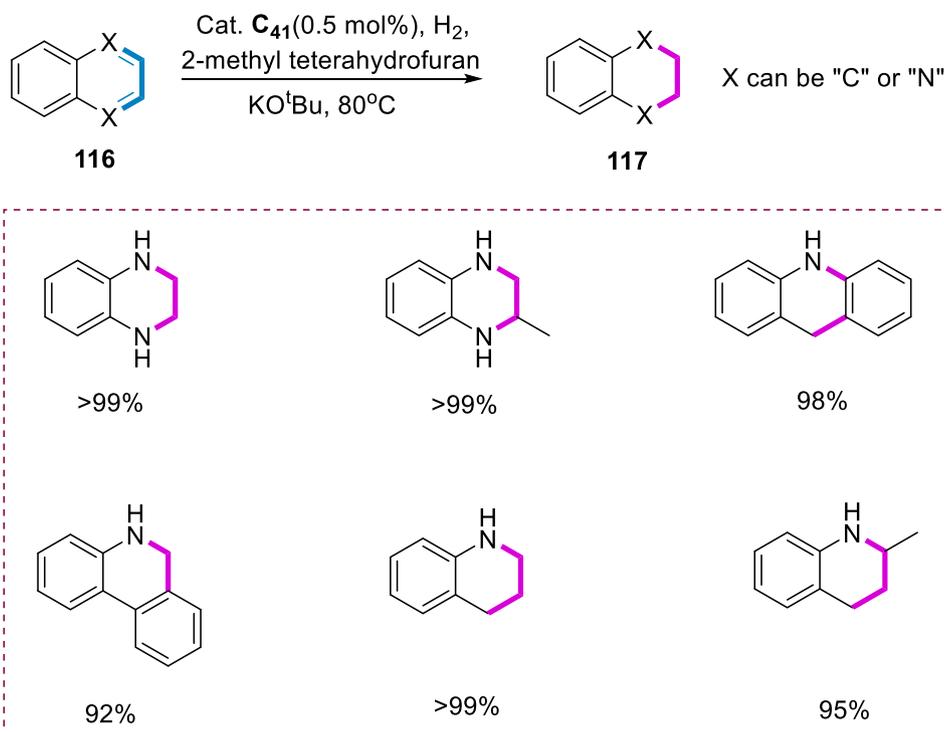
It was observed that complex (\mathbf{C}_{41}) is also efficient for catalytic *N*-heterocycles ($\mathbf{118}$) dehydrogenation. Initially, 1,2,3,4-tetrahydroquinoxaline dehydrogenation was investigated in 2-methyltetrahydrofuran at 85°C with complex \mathbf{C}_{41} (4.0mol%) and K^tOBu , yielding complete production of quinoxaline after 24h. However, the reaction of 2-methylquinoxaline (160°C , *o*-xylene) required a greater temperature. Other *N*-heterocyclic substrates were also investigated for dehydrogenation. With moderate catalytic activity, 9,10-dihydroacridine was also dehydrogenated under reflux in *o*-xylene. A variety of *N*-heterocyclic substrates were tolerated for this transformation. The quinoline and 2-methylquinoline were formed via



Scheme 44 Selective alpha-deuteration of alcohols.



Scheme 45 Synthesis of lutidine-based Ru-CNN(H) complexes.



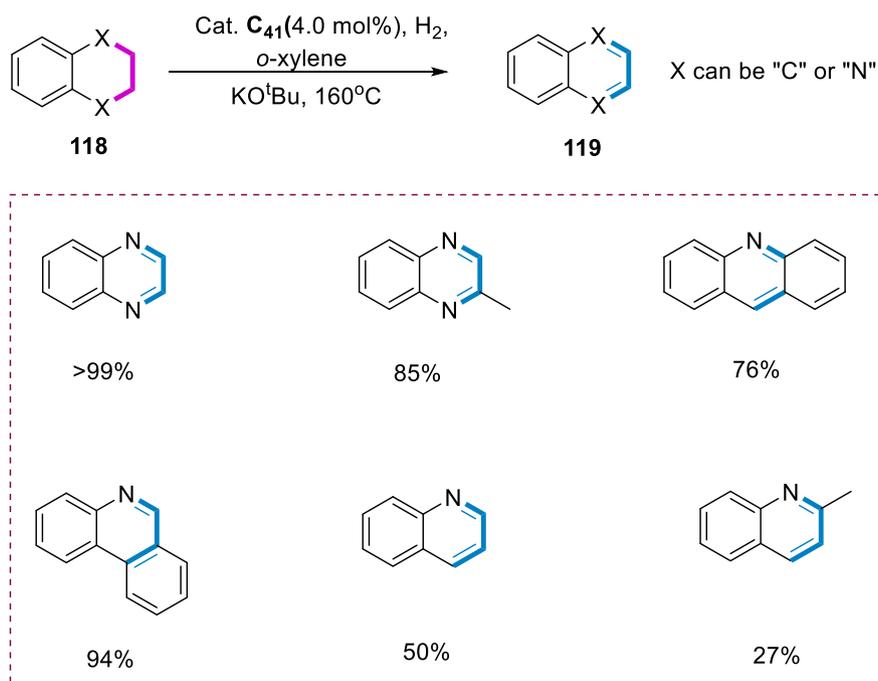
Scheme 46 Hydrogenation of *N*-heterocycles.

dehydrogenation after 48h with relatively low yields (Scheme 47) (Sánchez et al., 2020).

3. Cycloruthenated complexes-synthesis and applications

The cyclometallated compounds are used as mesogenic, photoluminescent chemicals and as chiral auxiliaries as well as their

potential use as biologically active molecules against cancer (Dupont and Pfeffer, 2008). The use of cycloruthenated compounds as catalysts demonstrates that they are particularly effective for hydrogenation transformation, either by hydride transfer or H₂, C-C bond formation, and ortho-deuteration (Djukic et al., 2009). The cycloruthenated compounds are also used in dye-sensitized solar cells as molecular sensitizers (Wadman et al., 2007).



Scheme 47 Dehydrogenation of *N*-heterocycles.

3.1. Synthesis of mono-nuclear ortho-metallated cyclic ruthenium complexes and their applications

The C-H bonds at the ortho-position of phenyl are the active sites of ligand for deuteration catalyzed by cycloruthenated triphenyl phosphite and -phosphine complexes.

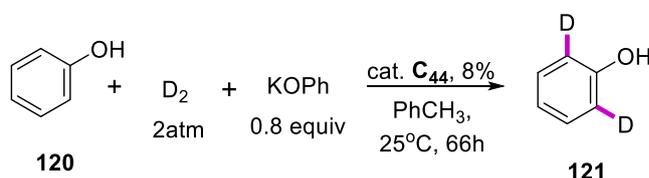
The ortho-bonded complex (**C₄₄**) is formed when triphenyl phosphite reacts with chlorohydridotris(triphenylphosphine)-ruthenium. When complex (**C₄₄**) reacts with hydrogen, it forms ruthenium-(chlorohydrido tetrakis-triphenyl phosphite), which rapidly returns to complex (**C₄₄**) when heated. The reversibility of triaryl phosphites is a distinguishing property of this reaction. Lewis developed this catalytic system that allowed for effective ortho-deuteration (Scheme 48) (Parshall et al., 1969).

The ortho-deuteration of phenol (**120**) by using deuterium (D_2), in the presence of cycloruthenated complex (**C₄₄**) as a catalyst and potassium phenoxide (KOPh) as co-catalyst, and toluene as a solvent at 25°C for 66h results in the synthesis of 2,6-dideutrophenol (**121**). Only the addition of a transesterification co-catalyst dramatically enhanced the catalytic deuteration of phenol. Complex (**C₄₄**) is a selective catalyst for the H-D exchange at the ortho-position of phenols by Lewis and coworkers. This was the first example of catalysis carried out by an ortho-metallated complex by the use of a complexing atom (e.g., phosphorus) to improve catalytic activity (Scheme 49) (Lewis, 1985).

The $Ru(CO)_2Cl$ core part in (N,C)-chelates promotes C-C coupling processes. Metal-mediated "dimerization" of terminal alkynes via C-C bond formation produces conjugated enynes, which have antimicrobial activity (Yamaguchi et al., 1995; Liu et al., 2006; Ogata and Toyota, 2007; Ciclosi et al., 2008).

The complex $[Ru(CO)_2Cl_2]_n$ reacts with 2-[tricarbonyl(6-phenyl)chromium]pyridine (**122**) in the presence of degassed and dry 1,2-dimethoxyethane, Na_2CO_3 , and the subsequent suspension is refluxed for 15h, complex (**C₄₅**) formed as dense yellow and deep red precipitate in 83% yields (Hijazi et al., 2006). The reaction of ruthenium complex $[Ru(CO)_2Cl_2]_n$ with 2-phenyl-4,5-pinenopyridine (**123**) in the presence of 2-methoxyethanol and the resultant solution was refluxed overnight producing complex (**C₄₆**) in 80% yield. Complex (**C₄₅**), which is only moderately soluble in dimethylformamide and slightly soluble in warm tetrahydrofuran while complex (**C₄₆**) shows greater solubility in most polar protic and aprotic solvents (Scheme 50).

Homo-coupling of aryethynes (**124**) with catalytic quantities of dimeric ruthenacycles (**C₄₅** and **C₄₆**) having the chloro-(dicarbonyl)-ruthenium motif $[Ru(CO)_2Cl]$ selectively



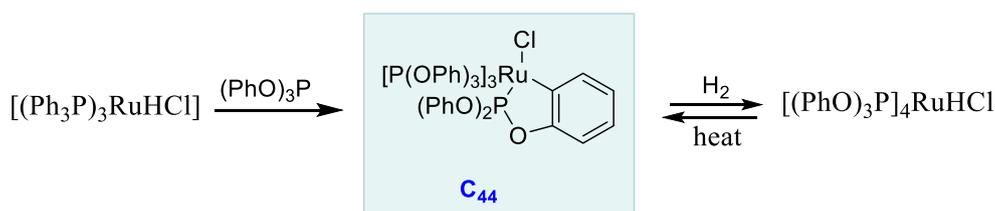
Scheme 49 Ortho-deuteration of the substrate.

and efficiently produces (E)-1,4-diaryl-but-1-en-3-yne (**125**) in excellent yields. This reaction proceeds in the presence of sodium carbonate (Na_2CO_3) (excess), i-PrOH/THF (2:1) at 80°C for 15–18h (reflux) resulting in the synthesis of conjugated 1,3-enynes in excellent to good yield (54–100%) (Scheme 51) (Hijazi et al., 2008).

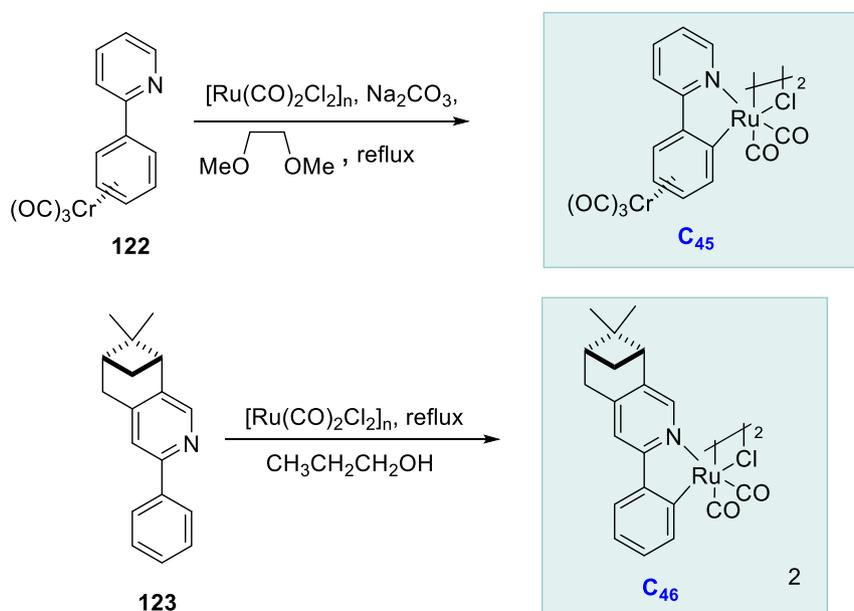
Transfer hydrogenation is a chemical reaction in which addition of hydrogen into organic molecules from the source poorer than gaseous hydrogen. Noyori pioneered transfer hydrogenation and awarded with noble prize (Hashiguchi et al., 1995; Ohkuma et al., 1995; Fujii et al., 1996; Gao et al., 1996; Haack et al., 1997; Matsumura et al., 1997; Noyori and Hashiguchi, 1997; Yamakawa et al., 2000; Noyori and Ohkuma, 2001; Noyori, 2002; Sandoval et al., 2003; Ikariya et al., 2006). The catalytic systems which are Ru-based are successful in the reduction of ketones by transfer hydrogenation (HT) among the many metal-catalyzed reactions (Naota et al., 1998). In the presence of isopropanol, the ruthenacyclic complex $[RuBr(AsPh_3)_2(azo-OMe)]$ in the presence of isopropanol was found to be a good catalyst for ketone reduction with excellent yields.

The ruthenium (III) complex $[RuBr_3(AsPh_3)_3]$ (**C₄₇**) as a catalyst was reacted with 2-(aryloxy)-phenol (**126**) under reflux in the presence of dry benzene to produce a series of mono-nuclear ortho-metallated Ru-complexes (**C₄₈[a-e]**) $[RuX(AsPh_3)_2(L)]$ (X = Br or Cl; L = CNO donor of the ligands). Because of their versatility as ligands, these compounds have biological and catalytic significance. Among other complexes, the complex $[RuBr(AsPh_3)_2(azo-OMe)]$ was found to be effective catalyst for the ketones hydrogenation with excellent yields under suitable reaction conditions (Scheme 52).

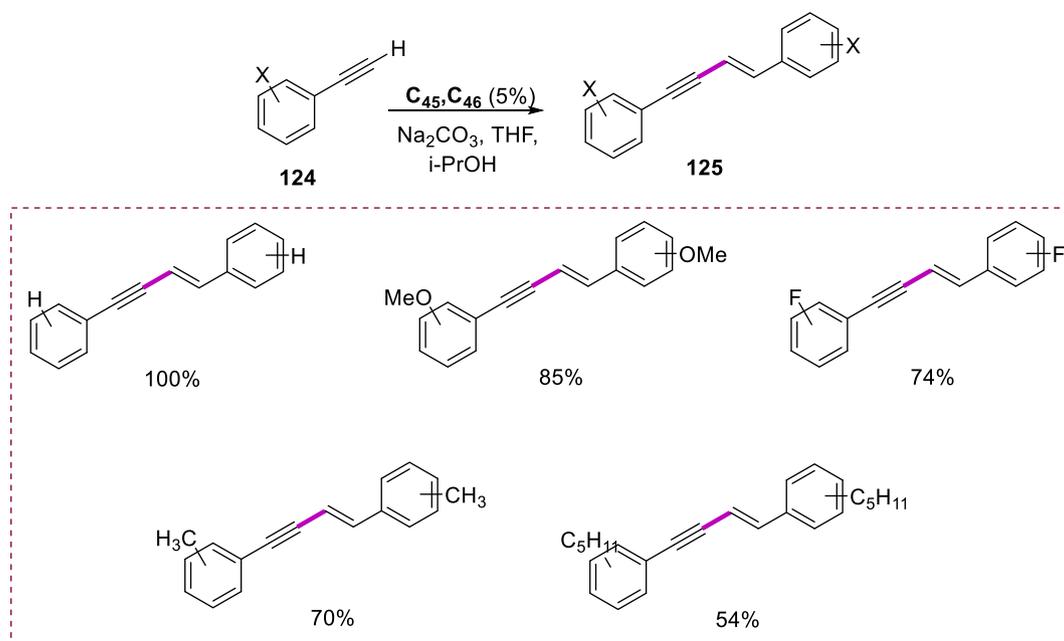
Ru complex $[RuBr(AsPh_3)_2(azo-OMe)]$ **C₄₈(c)** was used for catalytic hydrogenation of a variety of aromatic and aliphatic ketones (**127**). When the ketone, ruthenium catalyst **C₄₈(c)**, and KOH were heated under reflux in i-PrOH at 80°C for a suitable period in an inert environment resulted in the formation of alcohols (**128**) in good yield. There is no hydrogenation of ketones without the use of the base. The base promotes the catalytic hydrogenation of ketones. The catalyst



Scheme 48 Synthesis of ortho-bonded ruthenium complex.



Scheme 50 Synthesis of cyclo ruthenium complexes.

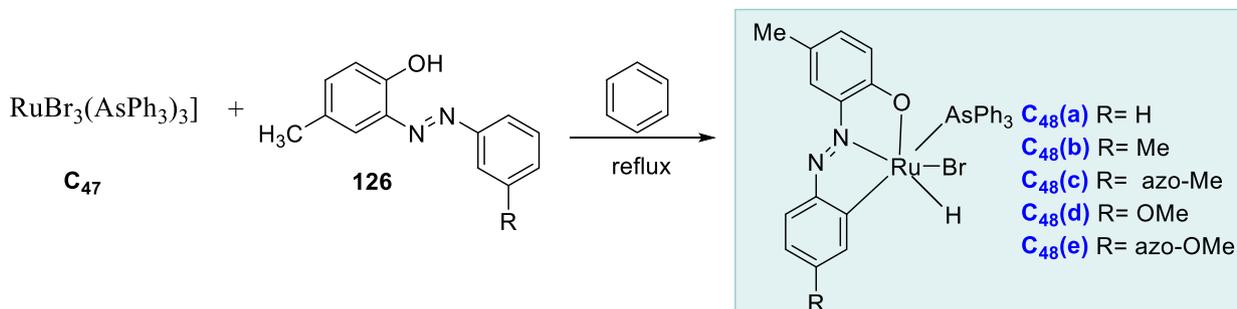


Scheme 51 Synthesis conjugated 1,3-enynes.

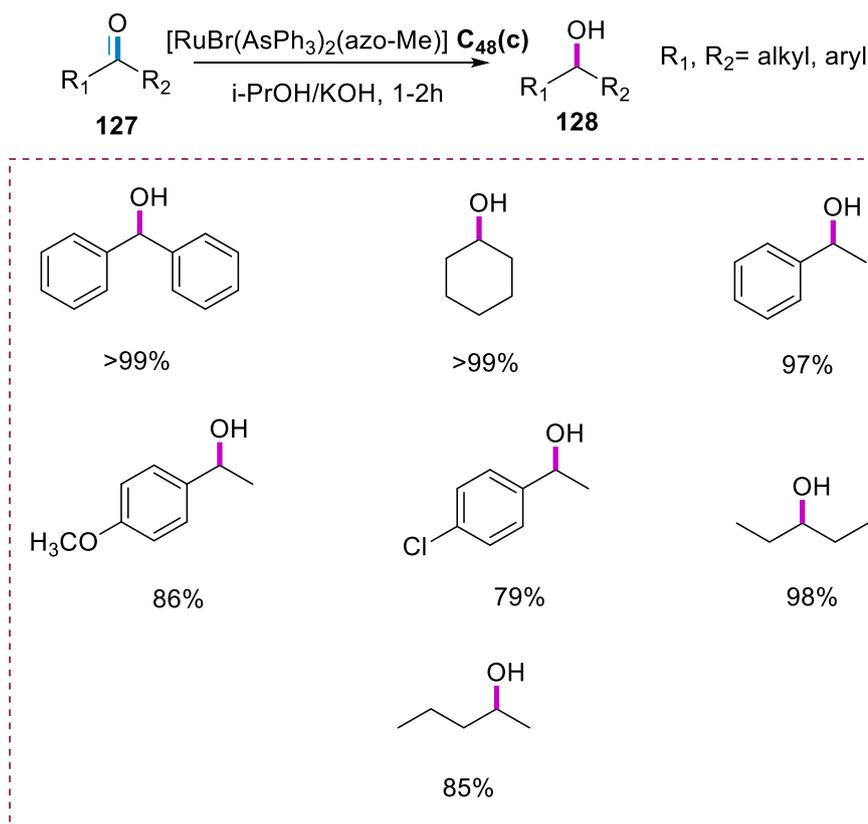
works well for both aliphatic and aromatic ketones with excellent yields and turnover. The reduction of *p*-chloro and *p*-methoxyacetophenone was and had lower reaction yields as compared to the reduction of phenylethanone. It was noticed that hydrogenation of aliphatic ketones is challenging and takes a long reaction time to achieve higher conversion (Scheme 53) (Venkatachalam and Ramesh, 2005).

3.2. Synthesis of amino-pyridine based cycloruthenated complexes and their applications

The secondary alcohols are useful chiral auxiliaries and intermediate in the fine chemical industry (Sheldon, 1993). Hydrolytic enzymes such as esterases and lipases are commonly used to attain a variety of enantioenriched alcohols from racemic



Scheme 52 Synthesis of mono-nuclear ortho-metallated Ru-complexes.



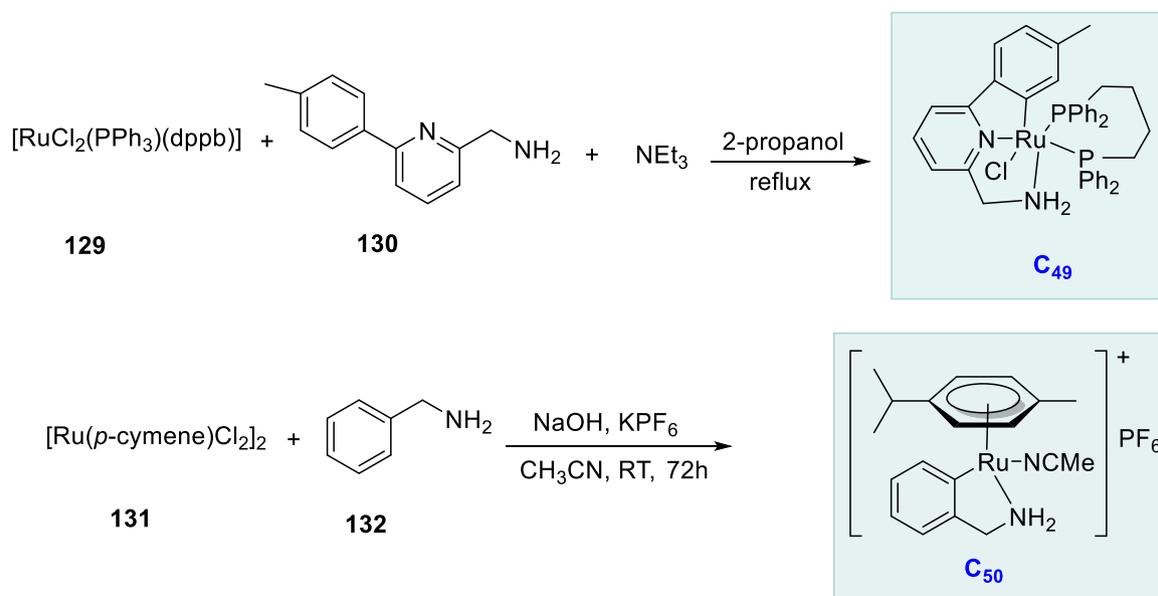
Scheme 53 Reduction of ketones.

sec. alcohol by kinetic resolution (KR) (Bakker et al., 2000). The ruthenium-amino structural core in the ruthenacycles and amino-pyridine Ru-complexes is very effective and is also used in the kinetic resolution of sec. alcohols via hydrogen transfer.

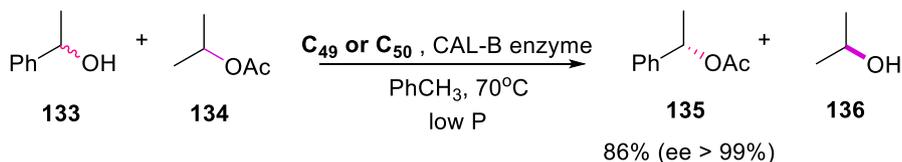
The thermally stable ortho-metallated Ru(II) complex (**C₄₉**) is obtained in high yield by treating [RuCl₂(PPh₃)(dppb)] (**129**) an equimolar quantity of 6-(4-methylphenyl)-2-pyridylmethylamine (**130**) in the presence of 2-propanol under reflux by using NEt₃ (Baratta et al., 2005). Ruthenacycles (**C₅₀**) were produced by cyclo-metallating an enantiopure aromatic primary amine (**131**) with [(*p*-cymene)RuCl₂]₂ (**132**) by using

NaOH, KPF₆ for 72h at room temperature (Scheme 54) (Sortais et al., 2005).

Amino-ruthenium complexes (**C₄₉**) and (**C₅₀**) were subjected to dynamic kinetic resolution in toluene (PhCH₃) at 70°C by using potassium tert-butoxide and CAL-B enzyme. The isopropyl is used as an acyl donor. The racemization of (S)-1-phenylethanol is catalyzed very efficiently by complexes (**C₄₉**) and (**C₅₀**). These ruthenacycles resolve rac-1-phenylethanol (**133**) into enantiopure (R)-1-phenyl ethylacetate (**135**) in excellent yields and enantioselectivity (86% and 99% ee) after 48 hours at 70°C by using isopropyl acetate (**134**) as an acyl donor and *Candida Antarctica* lipase B as an



Scheme 54 Synthesis of amino-pyridine based cycloruthenated complexes.



Scheme 55 Dynamic kinetic resolution of the secondary alcohols.

enzyme. In comparison to complex **C₄₉**, the ruthenacycle **C₅₀** gives good results (Scheme 55) (Eckert et al., 2007).

The synthesis of a broad range of alcohols relies heavily on transition metal-catalyzed catalytic hydrogenation of carbonyl compounds (Gladiali and Alberico, 2006; Samec et al., 2006). The tridentate $\text{RuCl}(\text{CNN})(\text{dppb})$ catalyst quantitatively and chemo-selectively converted the aromatic, aliphatic, and, α,β -unsaturated aldehydes into primary alcohols in the presence of 2-propanol as hydrogen donor. The Ru-complex $[\text{RuX}(\text{CNN})(\text{dppb})]$ ($\text{dppb} = \text{Ph}_2\text{P}(\text{CH}_2)_4\text{PPh}_2$; $\text{X} = \text{Cl}, \text{H}$), which is a very active catalyst for transfer hydrogenation (Yang et al., 1997; Braunstein et al., 1999; Clark et al., 1999; Toner et al., 2000).

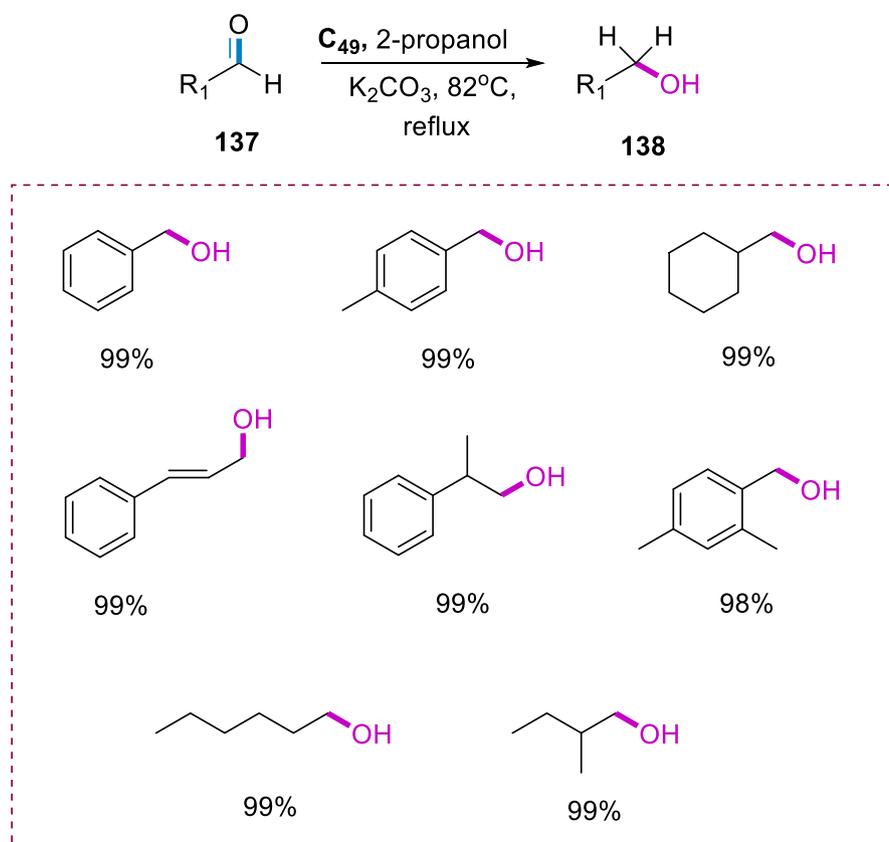
The aldehydes (**137**) solution was refluxed in isopropanol with complex (**C₄₉**) and K_2CO_3 at 82°C , quantitative formation of alcohols (**138**) occurs in 1-5 minutes with excellent yields. The reaction takes 30 and 20 seconds to complete when the base concentration is increased to 5 and 10mol percent. The effectiveness of applying complex (**C₄₉**) in synthesis is due to the reaction taking place at a lower complex (**C₄₉**) loading. Because of the excellent catalytic activity of this complex, the wide range of aldehyde substrates was reduced. The short reaction time (minutes) necessary for full reduction and minimum chances of side reactions making this approach a highly chemoselective for hydrogenation of aldehydes (Scheme 56) (Baratta et al., 2007b).

4. Half-sandwich arene Ru-complexes-synthesis and application:

Half-sandwich arene Ru-complexes have a broad range of applications in synthetic chemistry, including hydrogenation, cycloaddition, esterification, Diels–Alder cycloadditions, olefin-metathesis, and 1,3-dipolar (Moriarty et al., 1988; Le Bozec et al., 1989; Noyori et al., 1997). These complexes have proven to be effective precursors in organometallic chemistry due to the mild reaction conditions mandatory for synthesis, good yields, and a vast range of solubility and stability under an aqueous environment (Canivet and Süß-Fink, 2007; Singh et al., 2007). The chemical and biological activity of these complexes is substantially influenced by the type of the arenes, chelating ligands, and leaving group, which display structure-activity relationships (Habtemariam et al., 2006). Furthermore, these complexes are biologically active compounds that could be used to treat cancer (Kurzwernhart, 2013).

4.1. Synthesis of unsaturated cationic arene β -diketiminato ruthenium complexes and their application

The Diels–Alder (DA) reactions due to their high efficiency and selectivity catalyzed by optically active Lewis acids are one of the most valuable tools in the formation of complex compounds. The enantioselective Diels–Alder reactions



Scheme 56 Reduction of aldehydes.

between dienes and α,β -unsaturated aldehydes catalyzed by half-sandwich cationic complexes having chiral [(arene)-M (L1L2)] motif with only one vacant site (Carmona et al., 1997; Davies et al., 1997; Faller et al., 2001).

The coordinatively unsaturated cationic complexes (C_{52}) and (C_{53}) are formed by the abstraction of chloride from complex (C_{51}) using the weakly coordinating anion sodium tetrakis (3,5-bis(trifluoromethyl)phenyl)borate ([Na]BARF), (BARF = B(3,5-(CF₃)₂C₆H₃)₄) results in the formation of arene Ru(II) complexes having fluorinated β -diketiminato ligands. In comparison to complex (C_{53}), the complex (C_{52}) has a higher endo selectivity in cyclopentadiene and acrolein synthesis. The β -diketiminato ligand in complex (C_{52}) improves the Diels–Alder processes' selectivity. The respective unsaturated cationic complexes (C_{52}) and (C_{53}) are attained by abstraction of chlorine atom in the presence of poorly coordinated anion BARF. Remarkably, these ruthenium complexes were discovered to be strong Lewis acid catalysts for Diels–Alder reaction of dienes (2,3-dimethyl-1,3-butadiene, cyclopentadiene) and α,β -unsaturated aldehydes (acrolein, methacrolein). The structurally robust ligand (β -diketiminato ligand) not only gives the sufficient Lewis acidity at the central metal center but also improves the selectivity of the Diels–Alder reactions. Significantly, complexes (C_{52}) and (C_{53}) allow the use of mild condition of reaction, lowering the possibility of side products (Scheme 57).

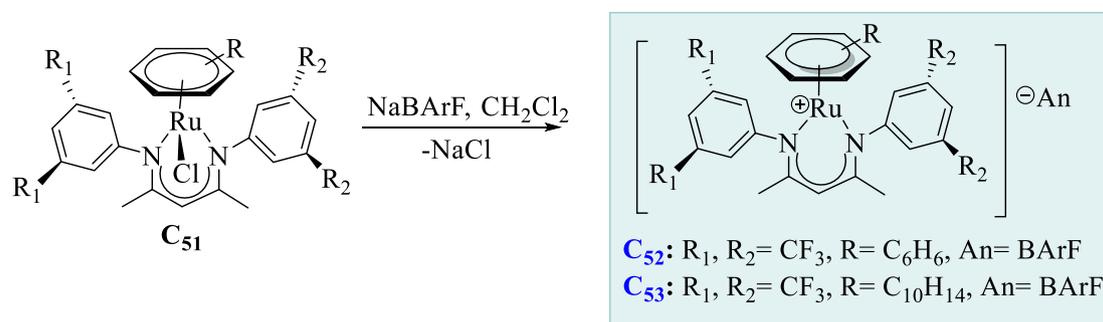
The bicyclic endo- or exo-2-methyl-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (**141a** or **141b**) and endo- or exo-bicyclo[2.2.1]hept-5-ene-2-carboxaldehyde (**142a** or **142b**) are

efficiently formed in excellent yields by Diels–Alder cycloaddition between acrolein or methacrolein (**139**) and cyclopentadiene (**140**) catalyzed by either complex (C_{52}) or (C_{53}) in the presence of dichloromethane at 20°C. Complexes (C_{52}) and (C_{53}) facilitate the use of milder reaction conditions, which reduces the chances of side products in the reaction (Scheme 58) (Schreiber et al., 2011).

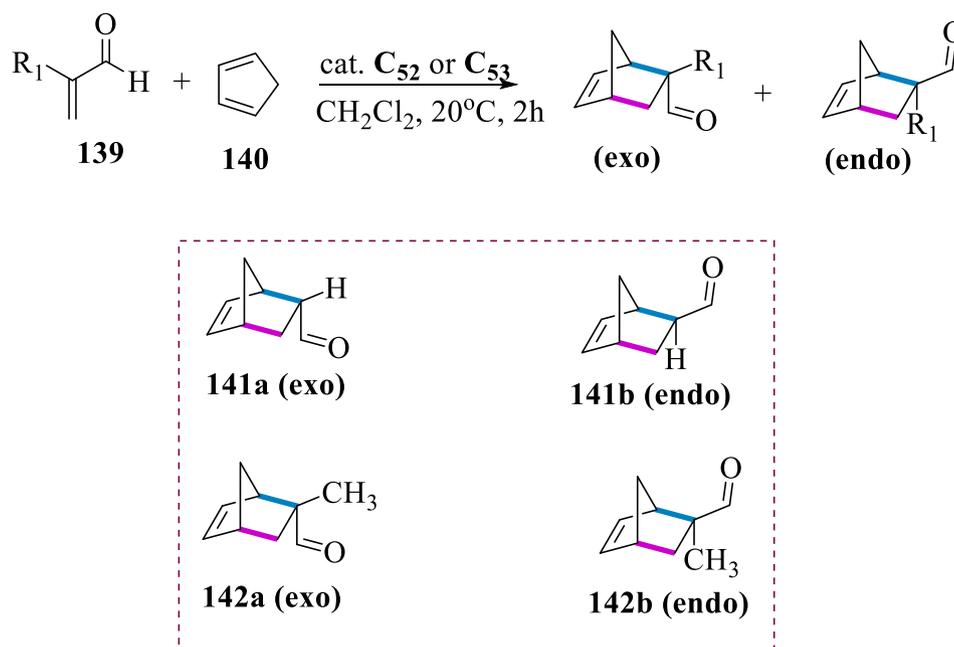
4.2. Synthesis of cationic cyclopentadienyl Ru-complex and its application

Isoxazolines are enantiopure which are used as precursors for the formation of chiral 1,3-amino alcohols that are useful synthons for building physiologically active compounds (Frederickson, 1997). The 1,3-dipolar cycloaddition process between alkenes and nitrones mediated by chiral Lewis acids is the versatile and direct method for these molecules (Gothelf and Jørgensen, 1998; Gothelf and Jørgensen, 2000). The transition metal Lewis acid catalyst [Ru (acetone)-(R,R)-BIPHOP-F]Cp][SbF₆] catalyzes the 1,3-dipolar cycloaddition reaction between α,β -unsaturated aldehydes, and aryl nitrile oxides.

The reaction of hydrobenzoin (**143**) with NEt₃ and BrP (C₆F₅)₂ in the presence of THF at room temperature for 24 hours yields the chiral ligand [(R,R)-BIPHOP-F] (**144**), which is then further reacted with Ru₃(CO)₁₂, CpH, and CHI₃ to form complex (C_{54}). Then complex (C_{54}) reacts with AgSbF₆ and acetone at room temperature, and a cationic cyclopentadienyl Ru-complex (C_{55}) [Ru (acetone)(R,R)-BIPHOP-F]Cp]



Scheme 57 Synthesis of coordinatively unsaturated cationic ruthenium complexes.



Scheme 58 Diels-Alder reaction.

[SbF₆] is formed after 1.5 hours. The enantioselective 1,3-dipolar cycloaddition of methacrolein with nitrones was efficiently mediated by Ru complex (**C₅₅**) as catalyst (**Scheme 59**) (**Brinkmann et al., 2007**).

The 1,3-dipolar cycloaddition reaction of methacrolein (**145**) and C,N-diaryl nitrones (**146**) gave endo and exo-isoxazolidines (**147a** and **147b**) by using complex (**C₅₅**). Through coordination, the catalyst activates the substrate aldehyde, making it more susceptible to nitron attack. Catalytically active cationic complex (**C₅₅**) were found to be active in catalyzing the 1,3-dipolar cycloaddition reaction of a broad range of substrates with good to excellent yields (79% to 92%) and moderate to excellent enantiomeric excess (66% to 94%) (**Scheme 60**) (**Viton et al., 2002**).

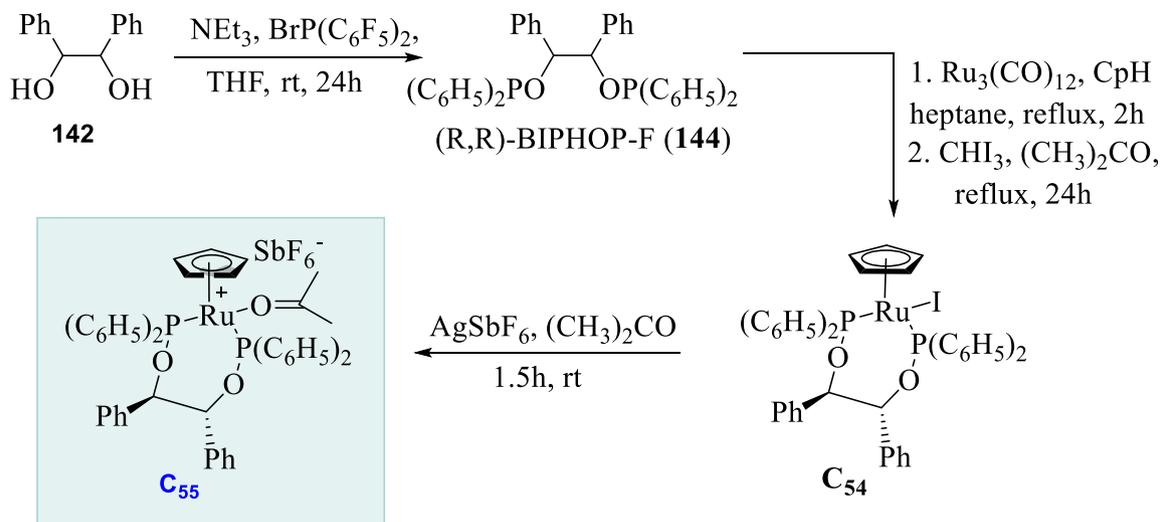
4.3. Synthesis of Dichloro(*p*-cymene)[(R)-(isopropyl)(1-naphthyl)phenylphosphine] Ru(II) complex and its application

One of the most effective approaches for the selective production of optically active cyclopropane chemicals is catalytic asym-

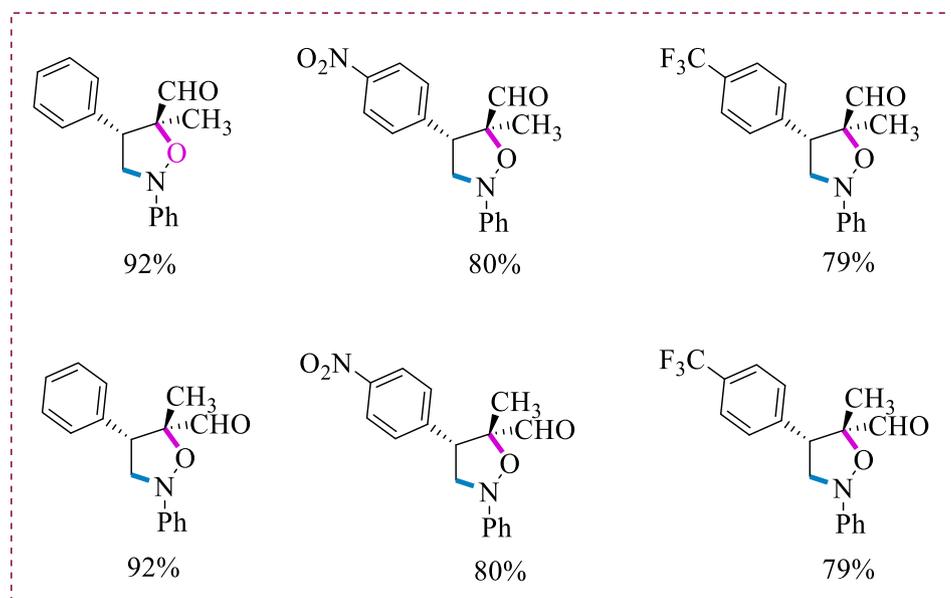
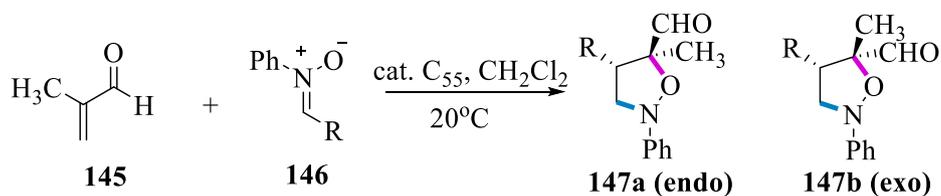
metric cyclopropanation of alkenes (**Lebel et al., 2003**). Ru-complexes having mono-dentate phosphorus ligands are efficient for cyclopropanation-competent systems (**Lasa et al., 2005**).

The synthesis of Dichloro(*p*-cymene)[(R)-(isopropyl)(1-naphthyl)phenylphosphine] Ru(II) complex (**C₅₆**) results from the reaction of ruthenium *p*-cymene dimer (**148**) with phosphine ligand (**149**) by using dichloromethane at ambient temperature. Ruthenium complex (**C₅₆**) was utilized as an efficient catalyst in the asymmetric cyclopropanation reaction between ethyl diazoacetate and styrene with high diastereoselectivity and enantioselectivity (up to 74%) (**Scheme 61**).

The formation of chiral cyclopropanic compounds (**152a** and **152b**) is achieved via cyclopropanation of styrene (**150**) through ethyl diazoacetate (**151**) with complex (**C₅₆**) by using dichloromethane for 6h. The more electron-rich nature of α -methylstyrene gives better results via cyclopropanation than unsubstituted styrene. The presence of a bulky alkyl group along with complex (**C₅₆**) containing phosphines with an isopropyl group gives the best results in the cyclopropanation reaction (**Scheme 62**) (**Grabulosa et al., 2012**).



Scheme 59 Synthesis of cationic cyclopentadienyl Ru-complex.



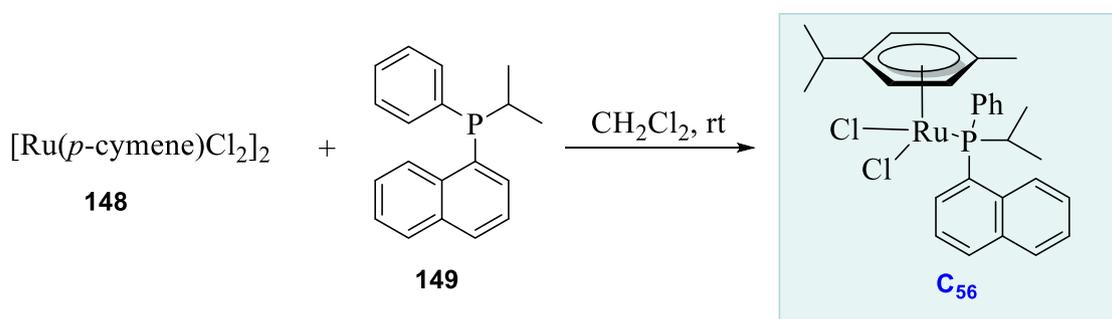
Scheme 60 1,3-dipolar cycloaddition reaction.

4.4. Synthesis of dinuclear Shvo type Ru-complex and its application

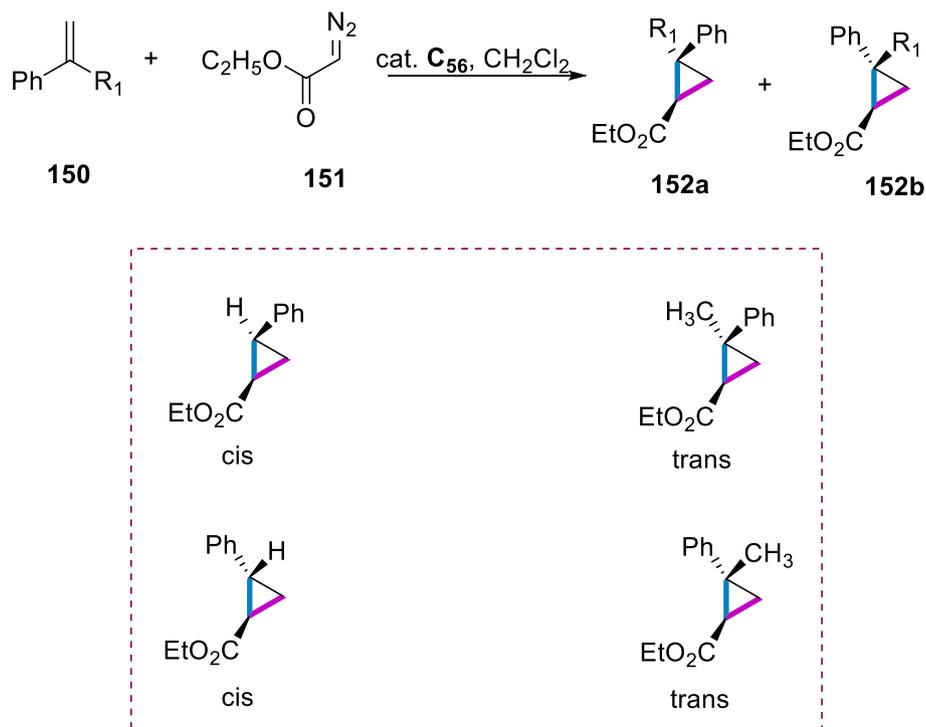
The 1,3-cycloalkanediols are used as building blocks in many pharmaceuticals. They can be synthesized from corresponding

diones via reduction (Fransson et al., 2006). The Shvo complex serves as an effective catalyst for the transfer of hydrogenation of ketones in the presence of 2-propanol (Blum et al., 1985).

The ligand tetraarylcyclopentadienone (**155**) was prepared by the reaction of diaryl- α -diketones (**153**) with diphenylace-



Scheme 61 Synthesis of Dichloro(*p*-cymene)[(R)-(isopropyl)(1-naphthyl)phenylphosphine] Ru(II) complex.



Scheme 62 Cyclopropanation reaction.

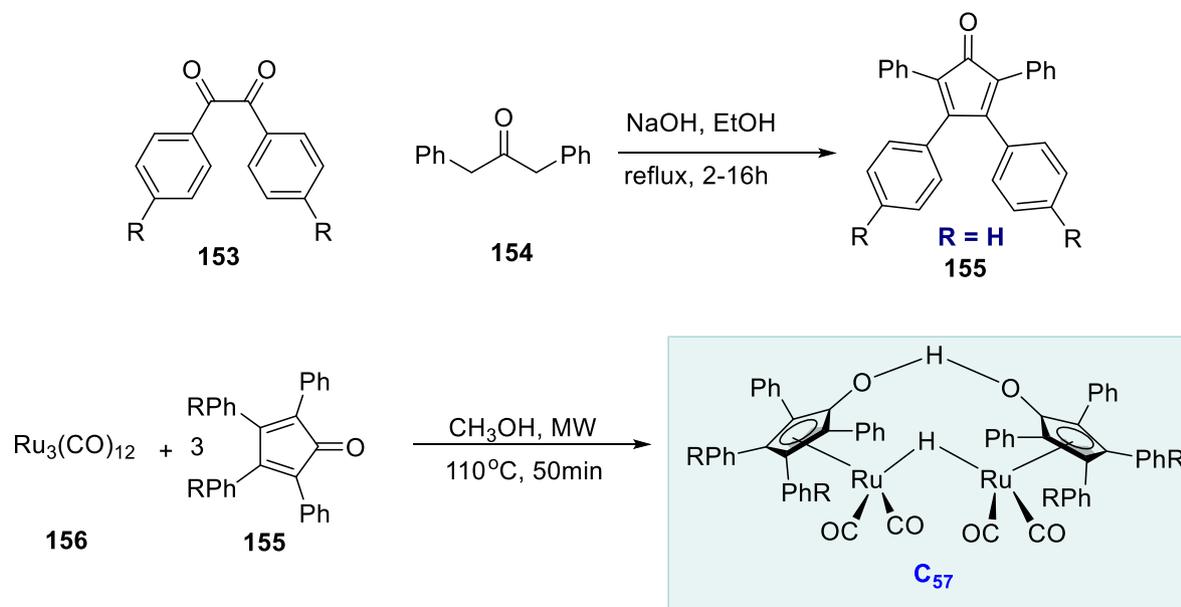
tone (**154**) in the presence of NaOH under reflux in EtOH for 2 to 16 hours. The dinuclear Ru-complex (**C₅₇**) was obtained by reacting tetraphenylcyclopentadienone (**155**) with Ru₃(CO)₁₂ (**156**) in methanol under microwave irradiation. It was discovered to be one of the most active catalysts for the transfer hydrogenation of carbonyl compounds and related reactions (**Scheme 63**) (Cesari et al., 2014).

The 1,3-cycloalkanediones (**157**) react in the presence of ruthenium catalyst (**C₅₇**) and 2-propanol by using toluene as solvent at 120°C resulting in the effective synthesis of corresponding diols (**158**) through the reduction in good yield. The loading of the catalyst could be reduced by increasing the amount of 2-propanol, and the reaction was completed within 60 minutes. Six-membered cyclic 1,3-diones undergo transfer hydrogenation by using ruthenium catalyst (**C₅₇**) in the presence of isopropanol as an H₂ donor under microwave

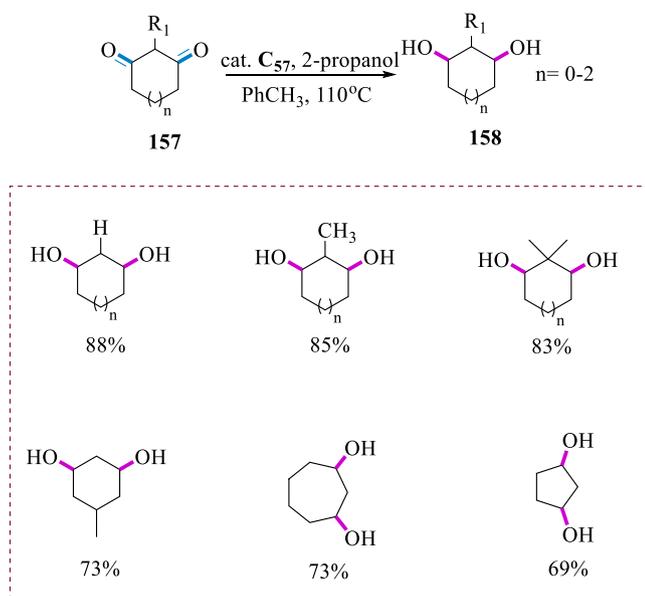
heating resulting in the formation of corresponding 1,3-diols. The diols were obtained with a yield of up to 93 percent. The reduction of seven-membered and five-membered cyclic 1,3-diones to the respective diols was also feasible, but a longer reaction duration and hydrogen gas were required. In dynamic kinetic asymmetric transformations, diols are significant building blocks (**Scheme 64**) (Leijondahl et al., 2006).

4.5. Synthesis of arene Ru(II) complexes carrying pyridine-2-thiocarboxamide ligands and their application

The oxidation of secondary and primary alcohols into their corresponding ketones and aldehydes without further oxidation into carboxylic acids by using *N*-methylmorpholine *N*-oxide (NMO) oxidant is a significant transformation in synthetic chemistry.



Scheme 63 Synthesis of dinuclear Shvo type Ru-complex.



Scheme 64 Transfer of hydrogenation of ketones.

The substituted pyridine-2-thiocarboxamide (**162a-f**) ligands were formed by reacting an aromatic amine (**161**) with sulfur (**160**) and 2-methylpyridine (**159**) for 48 hours at 150°C. The reaction of bidentate thiocarboxamide ligands (**162a-f**) with ruthenium complex $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (**163**) and AsPh_3 in methanol yielded arene Ru(II) complexes $\text{C}_{58}(\text{a-f})$ carrying pyridine-2-thiocarboxamide ligands of the type $[\text{Ru}(p\text{-cymene})(\text{AsPh}_3)(\text{L})]$. These Ru(II) complexes are colored, light and air-stable, and soluble in dichloromethane, chloroform, DMSO, and DMF. These complexes are diamagnetic in nature. The complex (**C_{58a}**) found to be more effective among other complexes for this transformation (**Scheme 65**).

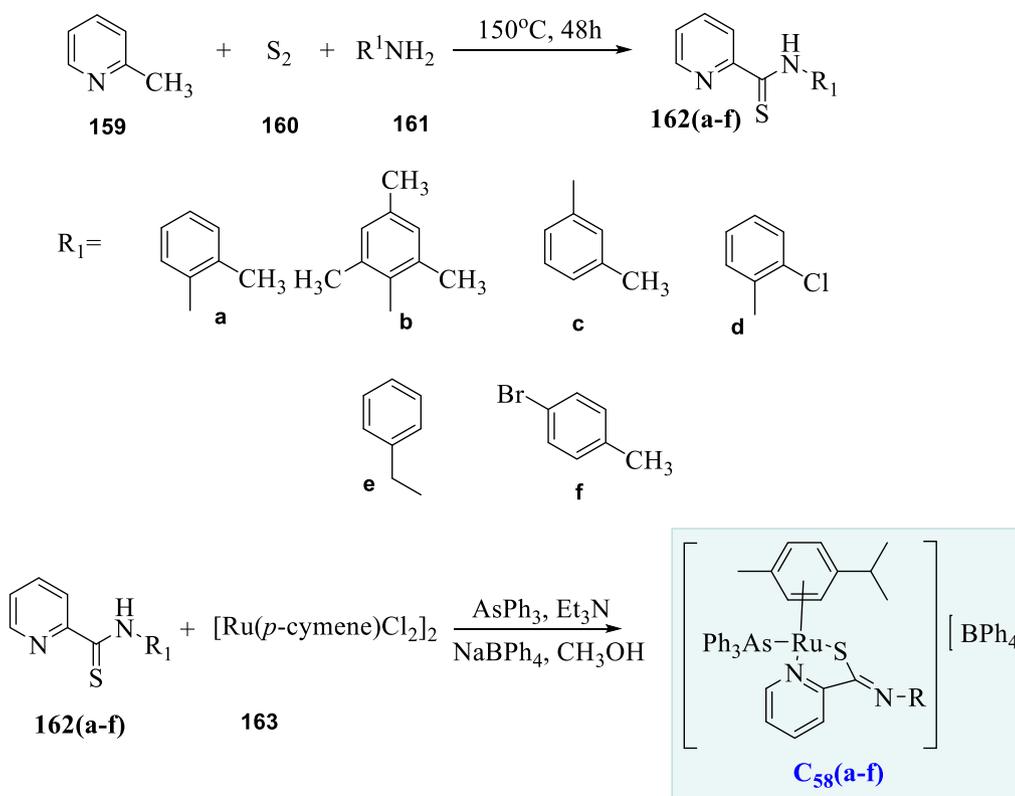
Ruthenium (II) complexes $\text{C}_{58}(\text{a-f})$ catalyze the oxidation of secondary or primary alcohols (**164**) to the corresponding ketones or aldehydes (**165**) in the presence of NMO as a co-oxidant. The corresponding ketones and aldehydes were obtained in good yield by using the complex (**C_{58a}**) as a catalyst and secondary or primary alcohols as substrates in the presence of NMO (*N*-methylmorpholine *N*-oxide) as oxidant and dichloromethane by refluxing for three hours (**Scheme 66**) (**Raja and Ramesh, 2012**).

4.6. Synthesis of arene/*N*-tosylethylenediamine ruthenium (II) complex and its application

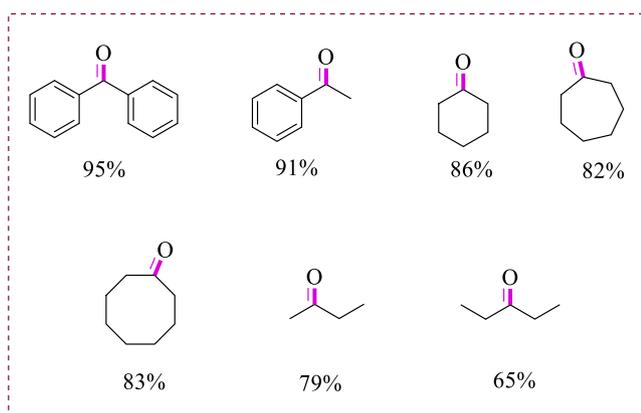
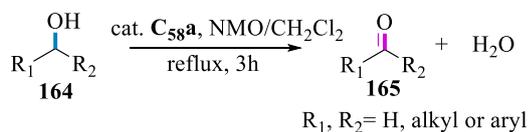
The asymmetric hydrogenation of C=N double bonds effectively proceeds by half-sandwich Ru-complexes due to their potential applicability. Chiral amines are essential synthetic intermediate in the pharmaceutical, chemical industry, and agriculture (**Kumar et al., 2014**). Catalytic systems for the heterocycles hydrogenation such as quinolines, indoles, and pyrroles based on the combination of Ru-complexes. Ruthenium complexes with diamines as a chiral ligand are very effective catalysts for the quinolines asymmetric hydrogenation in ionic liquids. This transformation under extremely concentrated and solvent-free conditions produced excellent outcomes (**Kuwano and Kashiwabara, 2006; Zhou et al., 2008a**).

Noyori and Ikariya's sulfonyl/arene diamine ruthenium (II) complex (**C₅₉**) has been demonstrated to have outstanding catalytic activity in the vast range of asymmetric hydrogenations of imines, including quinolone hydrogenation. The synthesis of the arene/sulfonyldiamine-Ru(II) complex (**C₅₉**) arises from the complexation of the (*R,R*)-TsDPEN ligand (**166**) with ruthenium complex $[\text{RuCl}_2(p\text{-cymene})]_2$ (**167**) by using Et_3N , 2-propanol at 80°C for 1h (**Scheme 67**) (**Touge and Arai, 2016**).

Hydrogenation of quinoline substrates (**168**) yielded 1,2,3,4-tetrahydroquinolines (**169**) with good enantioselectivity



Scheme 65 Synthesis of arene Ru(II) complexes carrying pyridine-2-thiocarboxamide ligands.



Scheme 66 Oxidation of alcohol.

(up to 99% ee). Complex (C_{59}) catalyzes the asymmetric hydrogenation of quinoline derivatives in [BMIM]PF₆ in the presence of hydrogen at 25°C for 15-24h, yielding 1,2,3,4-tetrahydroquinolines with good enantioselectivities (up to 99% ee). All 2-alkyl-substituted quinolines were hydrogenated with high yields and enantioselectivities in general (up to 99 percent ee). In an ionic liquid, hydrogenation with complex 1

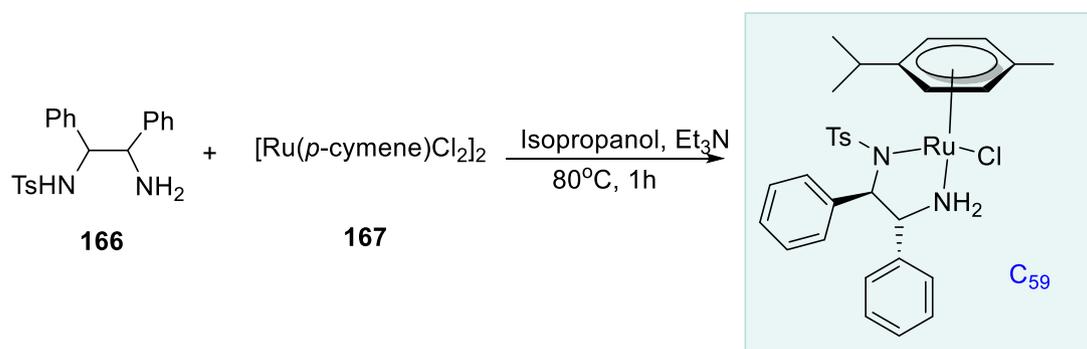
was selective for C=N bond (quinoline) over C=O bonds (Scheme 68) (Zhou et al., 2008a).

5. Ruthenium phosphine complexes

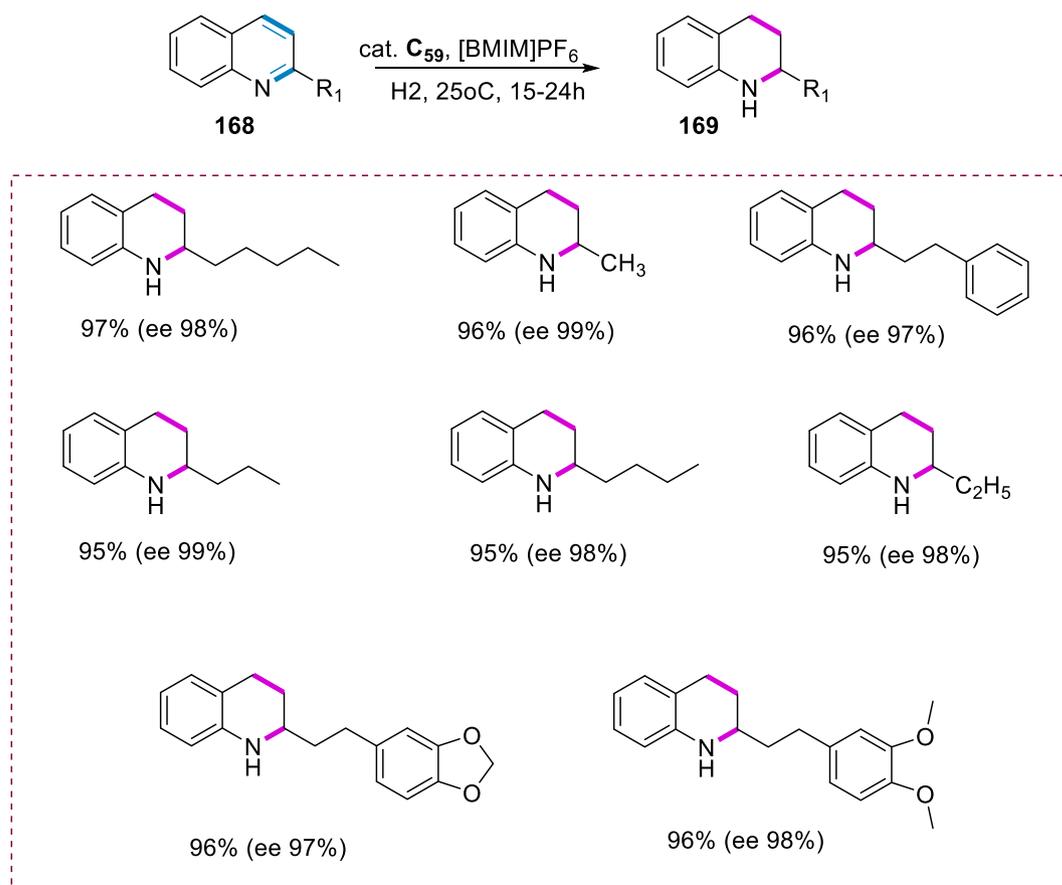
5.1. Synthesis of Ru-phosphine complexes having 2-aminopiperidine ligand and its application

Baratta and colleagues examined the excellent ability of ruthenium (II) complexes having the 2-aminomethylpiperidine (ampi) ligand to catalyze the reduction of ketones (Baratta et al., 2007a; Del Zotto et al., 2007; Baratta et al., 2010). The transfer hydrogenation (TH) of polar substrates like ketones from hydrogen donors such as formic acid and isopropanol is rapidly catalyzed by the ruthenium (II) phosphine complex. However, they are shown to be active in the presence of hydrogen donors (Gladiali et al., 2004; Ikariya and Blacker, 2007; Soltani et al., 2010).

Ru(II) complexes containing 2-aminomethylpiperidine ligand and different phosphine moieties were found to be effective in TH. The complexes C_{60} (a-d) were formed by reacting RuCl₂(PPh₃)₃ (171) with 2-aminomethylpyridine (ampi) 170 and the diphosphine ligands in dichloromethane at room temperature. The diphosphine ligands (PP) are well-known due to their excellent chelating properties with transition metals, enabling them to adjust the reactivity, stability, and catalytic performance of their complexes. The ampi is a suitable neutral bidentate ligand of Ru(II) complexes for transfer hydrogenation catalysis. The electron-rich NH and NH₂ groups stimulate



Scheme 67 Synthesis of arene/*N*-tosylethylenediamine ruthenium (II) complex.

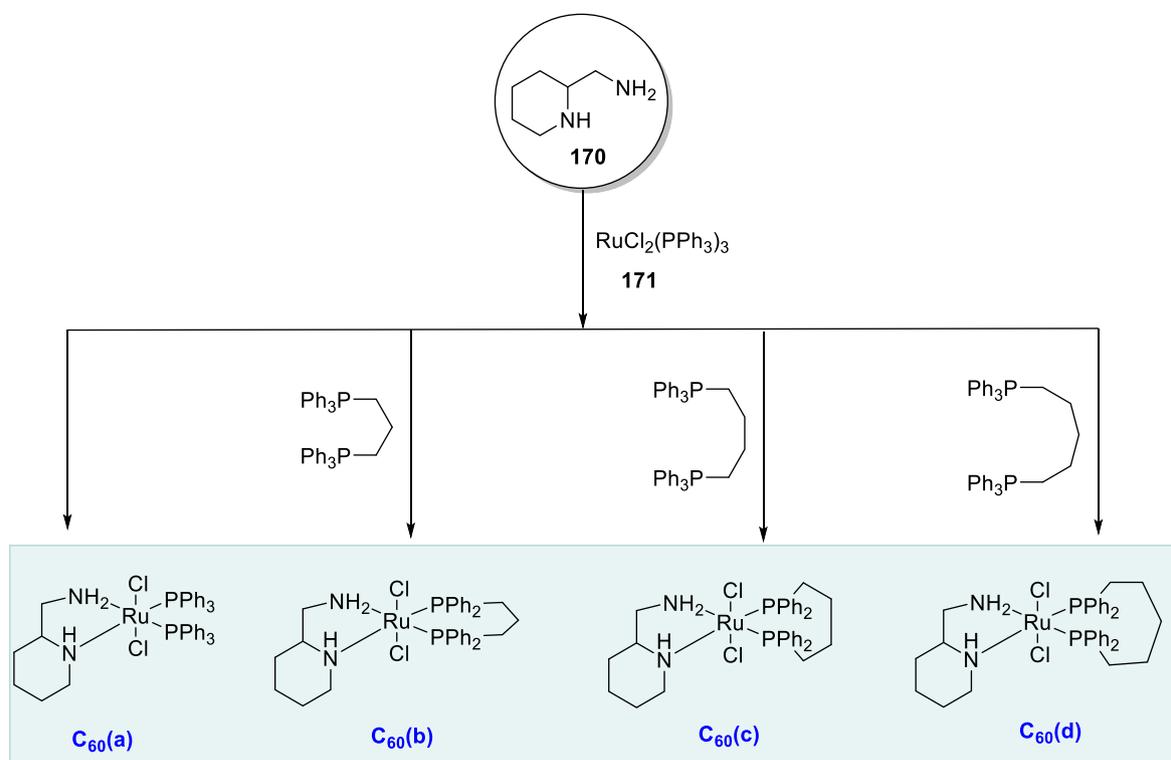


Scheme 68 Hydrogenation of imines.

the TH activity. This ligand provides more hydrogen bonds at the metal atom. The remarkable catalytic activity of these [RuCl₂(phosphine)(ampi)] complexes can be attributed to the Ru-NH₂ linkage and flexible ampi system, which are both involved in the H-bonding interaction with the alcohol and ketone and are important for substrate access to the ruthenium core. (Scheme 69).

Transfer hydrogenation (TH) of acetophenone (**172**) by using 2-propanol at 80°C in the presence of complex **5** and using KOH as a base to yield phenylethanol (**173**). Complexes

C₆₀(b-d), which include the diphosphine ligand [(PPh₂(CH₂)_nPPh₂, n = 3, 4, and 5)] have much more activity than complex **C₆₀(a)**, which has two PPh₃ ligands. Complex **C₆₀(d)** with the diphosphine ligand [PPh₂(CH₂)₅PPh₂] and ampi exhibits the maximum catalytic activity, resulting in 99 percent ketone conversion in 5 minutes. Potassium hydroxide was found to be the most efficient than other bases such as NaOH, K₃PO₄, Et₃N, K₂CO₃, and pyridine being slightly less effective and requiring longer reaction times. Ampii ligand, which is commercially available and has a particularly strong acceleration effect on



Scheme 69 Synthesis of Ru-phosphine complexes having 2-aminopiperidine ligand.

transfer hydrogenation catalyzed by ruthenium (II) complexes in the presence of 2-propanol (Scheme 70) (Türkmen, 2012).

5.2. Synthesis of ruthenium (II) complexes carrying the 2-(2-(diphenylphosphino) benzylidene)-N-ethylthiosemicarbazone ligand and its application

N-alkylation of amides/amines by using alcohols could be a relatively eco-friendly and green synthetic alternative due to the formation of water being the only byproduct. Furthermore, alcohols are generally available, less toxic, very stable, easily handled and stored, cost-effective, and relatively high in atom efficiency enabling them to use as an alkylating agent which is very simple and easy (Chang et al., 2009; Dobereiner and Crabtree, 2010; Bähn et al., 2011; Crabtree, 2011b; Zhang et al., 2011b). The electronic effects (basicity) of ligand and the steric (bulkiness) enable the complexes having phosphine coordinating arms usually to show excellent catalytic activity (Prakash et al., 2014; Prakash and Viswanathamurthi, 2014; Ramachandran et al., 2014).

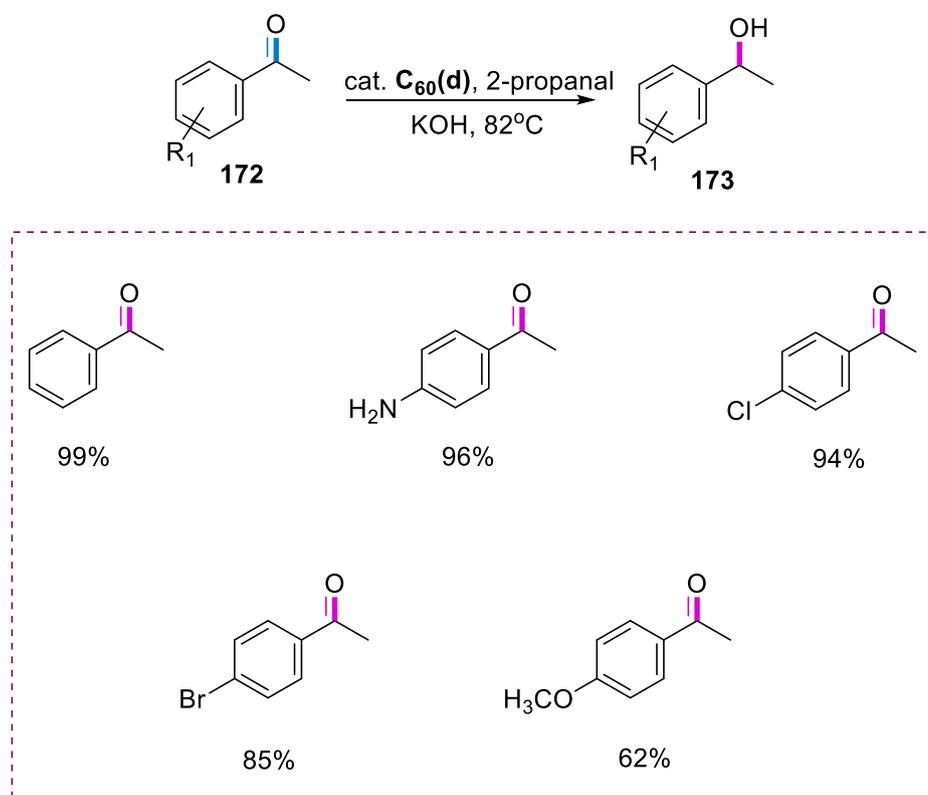
The 4-ethyl-3-thiosemicarbazide (174) reacts with the 2-(di phenylphosphino)-benzaldehyde (175) in the presence of acetic acid resulting in the synthesis of PNS-Et (176) in 96 percent yield. The complexes (C₆₁-C₆₃) were formed by reacting isolated PNS-Et (176) with an equimolar quantity of [RuH₂(CO)(PPh₃)₃], [RuHCl(CO)(PPh₃)₃], and [RuCl₂(PPh₃)₃]. These new complexes were miscible in common organic solvents like chloroform, benzene, dichloromethane, acetonitrile, dimethylsulfoxide, ethanol, methanol, and dimethylformamide. The complexes (C₆₁-C₆₃) have been shown to be effective catalysts

for the *N*-alkylation reaction under moderate conditions. Additionally, these complexes have demonstrated significant tolerance for the functional groups found in hetero(aromatic) amine and benzyl alcohol moieties. Furthermore, these complexes exhibit excellent selectivity for the mono-alkylation of hetero(aromatic) amines. (Scheme 71).

The hydrogen auto-transfer reaction with KOH as the promoter and in the presence of solvent catalyzed the heteroaromatic amines (177) *N*-alkylation by using substituted benzyl alcohols (178) into the respective *N*-alkylated products (179) by the ruthenium (II) complexes (C₆₁-C₆₃). The 2-aminobenzothiazole is *N*-alkylated with 4-methoxybenzyl alcohol by using different bases. The results demonstrate that bases were screened as catalytic reaction initiators. The use of toluene as a solvent and a strong base KOH resulted in excellent yields of the desired product. Catalysts (C₆₁-C₆₃) were found to be the most effective complexes for the 2-aminobenzothiazole *N*-alkylation in terms of selectivity and yield. The catalyst loading of 0.5 mol% was chosen due to the good yields and short reaction durations required. These reactions have a lot of appealing features such as cost-effectiveness, water as a by-product, use of less toxic organic materials, and excellent selectivity to respective products (Scheme 72) (Ramachandran et al., 2015).

5.3. Synthesis of tris-(*N*-pyrrolylphosphine) ruthenium complex and its application

The new ruthenium phosphine complex is catalytically active for the propargylic alcohol etherification and the synthesis of



Scheme 70 Hydrogenation of arylated ketones.

new and known xanthenes through propargylic alcohols. The P(pyr)₃ ligand is easily assessable and exhibits improved p-acidity and electronic properties similar to CO in the [RuCl(ind)(PPh₃)P(pyr)₃] complex (Moloy and Petersen, 1995; Angurell, 2004; Menye-Biyogo et al., 2007). In the production and application of ruthenium complexes, phosphonates are the most extensively used ligand class (Mezzetti, 2010; Delaude and Demonceau, 2012).

The ruthenium complex [RuCl(ind)(PPh₃)₂] has been utilized as a precursor for ligand-substitution reactions to synthesize ruthenium complexes. The mono(pyrrylphosphine) ruthenium complex [RuCl(ind)(PPh₃)-P(pyr)₃] **C**₆₄ was isolated in moderate yield (73%) as a red solid after chromatographic workup when [RuCl(ind)(PPh₃)₂] (**180**) was treated with P(pyr)₃ (**181**) ligand upon heating in THF under reflux for 4h. The synthesis of P(pyr)₃ analogs [RuCl(ind)(PPh₃)₂] to attain Ru-complexes with higher Lewis acidity to enhance the catalytic activity for the transformation of propargylic alcohol (Scheme 73).

The activated ruthenium complex [RuCl(ind)(PPh₃)P(pyr)₃] (**C**₆₄) catalyzed the etherification of various propargylic alcohols (**182**) into respective propargyl ethers (**183**) in isolated yields of 42% to 27% in the presence toluene at 70 to 95°C for 16–72h. In the etherification of propargylic alcohols, these new complexes are catalytically active (Scheme 74) (Stark et al., 2016).

5.4. Synthesis of phosphino-oxime containing Ru(II) complex and its applications

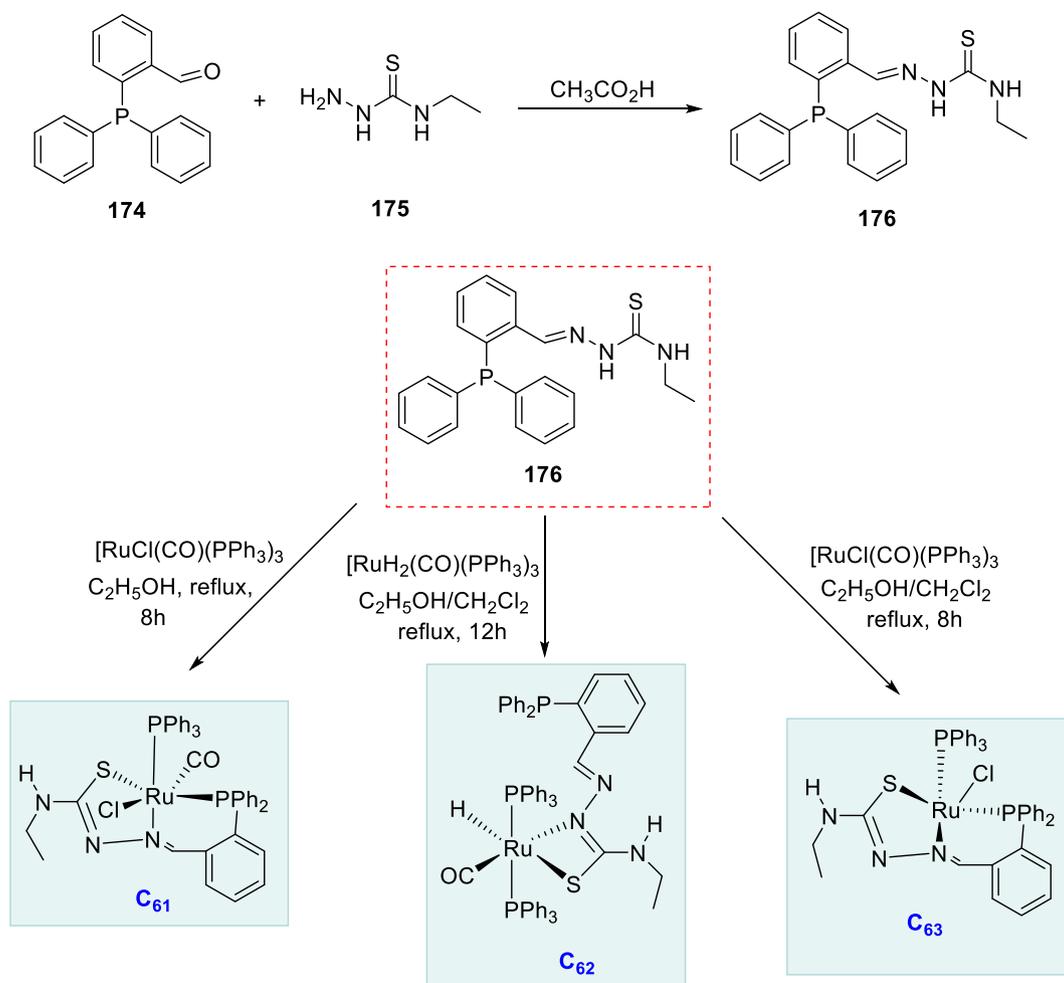
The hybrid ligands with soft phosphorus donor sites and hard nitrogen are extremely useful in coordination chemistry and

homogeneous catalysis (Kostas, 2008; Zhang et al., 2011c; Noël and Van der Eycken, 2013; García-Alvarez et al., 2014). The phosphino-oxime 2-Ph₂PC₆H₄CH=NOH containing ruthenium complexes have enormous synthetic potential and are the efficient catalyst in the aldoximes rearrangement into amides (Crochet and Cadierno, 2015).

The cis-[RuCl₂(DMSO)₄] (**184**) was treated with phosphino-oxime ligand (**186**) under reflux in THF, to produce the octahedral Ru(II) derivative [RuCl₂((P,N)-2-Ph₂PC₆H₄CH=NOH)₂] (**C**₆₅) in 87% yield. The reaction of [RuCl₂(*p*-cymene)₂] (**185**) with phosphino-oxime ligand (**186**) in the presence of toluene was heated under reflux overnight as an alternative approach for preparing Ru complex (**C**₆₅). The resulting complex (**C**₆₅) was isolated with a 75% yield. Other aromatic, heteroaromatic, aliphatic, and, unsaturated aldoximes were used to test the flexibility of the most active catalyst (**C**₆₅). The Ru complex (**C**₆₅) is found to be very effective in catalyzing the conversion of aldoximes to amides in high yields (Scheme 75).

The aldoxime (**187**) and water mixture were added to a Teflon-capped sealed tube containing complex (**C**₆₅), and the reaction mixture was stirred at 100°C for 5-10 minutes, producing excellent yields of corresponding amides (**188**). The electronic properties of the phenyl rings were shown to influence the activity of complex in the family of substituted benzaldoximes, with those having electron-withdrawing groups reacting faster. Ortho-substituted substrates showed lower reactivity than their para- and meta-substituted substrates due to steric grounds (Scheme 76) (Francos et al., 2016).

The Ru complex with the phosphino-oxime 2-Ph₂PC₆H₄CH=NOH (**C**₆₅) ligand catalyzes the reduction/ α -alkylation of acetophenones in the presence of primary



Scheme 71 Synthesis of ruthenium (II) complexes carrying the 2-((diphenylphosphino) benzylidene)-*N*-ethylthiosemicarbazone ligand.

alcohols very efficiently (Lundberg and Adolffson, 2016). Alcohols have been used as alkylating agents in the alpha-alkylation of methyl ketones, and both homogeneous and heterogeneous catalysts have been used (Guillena et al., 2007; Td, 2009; Obora and Ishii, 2011; Obora and Catal, 2016).

The acetophenones (189) undergo reaction with alcohols (190) in the presence of KOH, complex (C₆₅) as a catalyst, and toluene as a solvent at 120°C for 3h resulting in the synthesis of secondary aryl-carbinols (191) in 77-91 percent yields. The variety of substituted ketones and alcohols was well tolerated by this reaction (Scheme 77) (Francos et al., 2016).

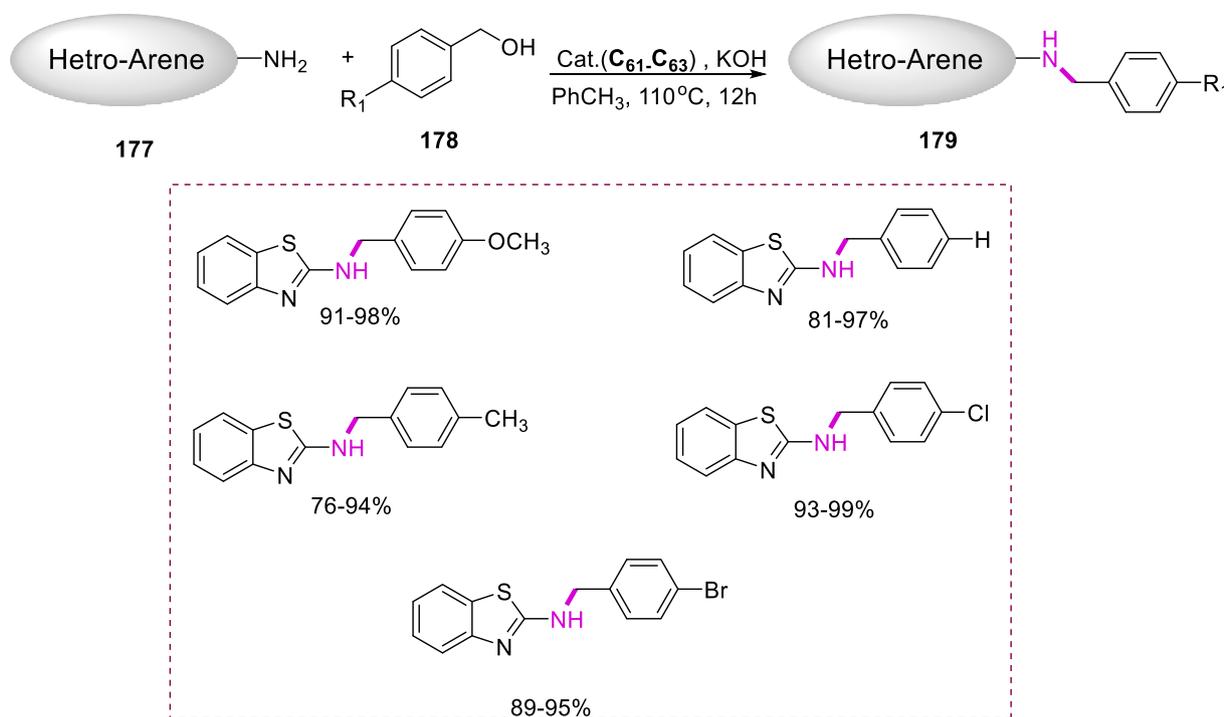
6. Schiff Base-Ruthenium Complexes

In the targeted chemical transformations, the Schiff base ruthenium complexes have attractive catalytic properties, including enhanced activity and selectivity (Dragutan et al., 2000; Dragutan et al., 2001; Katayama and Ozawa, 2004; Rigaut et al., 2004; Winter and Zális, 2004). The use of Schiff bases ligands to develop new selective and active sites in ruthenium catalytic species has proven to be very attractive (De Clercq and Verpoort, 2001; Vigato and Tamburini, 2004).

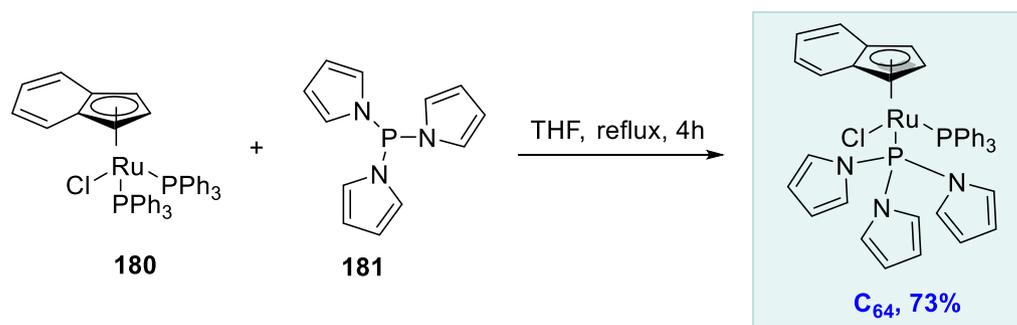
Since they are excellent catalysts in heterogeneous and homogeneous catalysis activity (Deshmukh et al., 2017). A large number of Schiff bases and their ruthenium (II) complexes have been broadly investigated. Schiff bases are the most extensively used as ligands in inorganic chemistry due to their excellent sigma-donor and pi-acceptor properties. The electron acceptor and electron donor features of the ligand affect the coordination compounds' reactivity and have a significant influence on this activity owing to the relationship between reactivity and structure (Tümer, 2011; Çalik et al., 2016; Jia et al., 2017). These novel ruthenium complexes can be easily prepared from very stable and readily available Ru-compounds, have high chemoselectivity and activity in chemical transformations, and have excellent tolerance to organic functionalities, air, and moisture (Nguyen et al., 1992; Schwab et al., 1996).

6.1. Synthesis of Schiff-base substituted ruthenium benzylidene complexes and their applications

Metathesis reaction is a chemical reaction in which two hydrocarbons such as alkane, alkynes, alkenes are transformed into new hydrocarbons by the exchange of C-C bond. It is widely



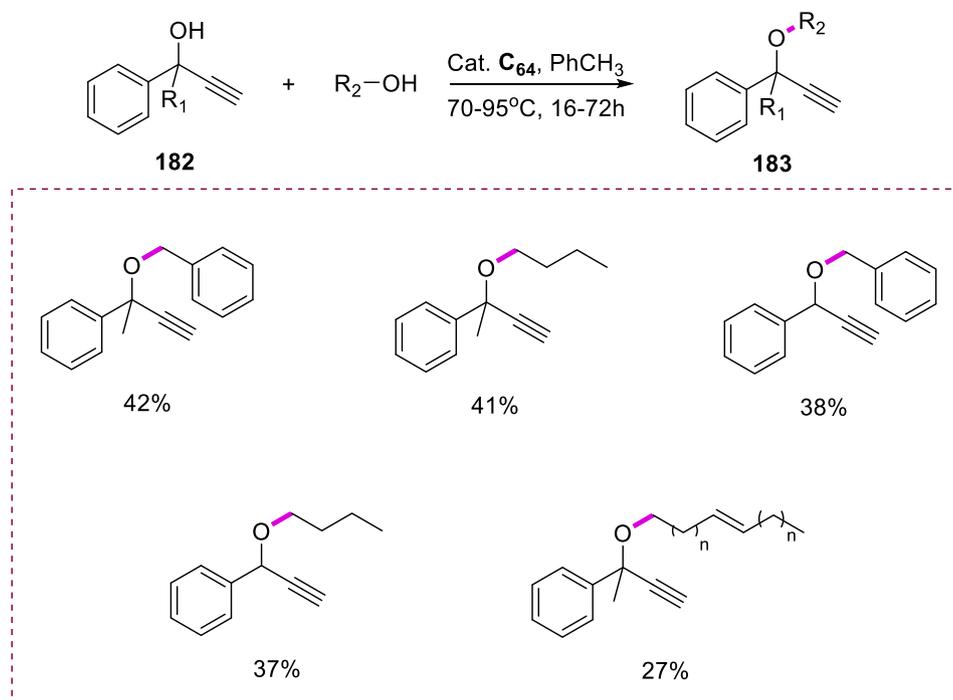
Scheme 72 N-alkylation of amines.

Scheme 73 Synthesis of tris-(*N*-pyrrolylphosphine) ruthenium complex.

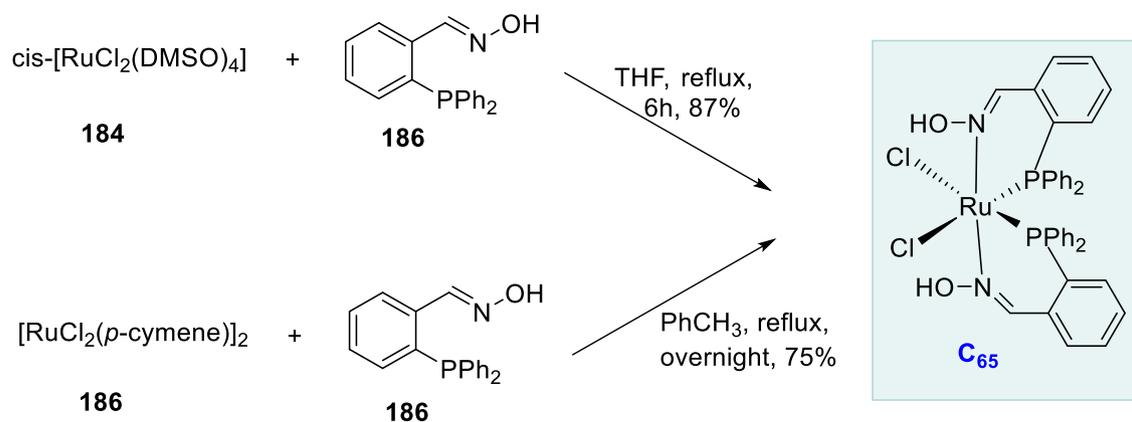
explored by Grubbs (Nguyen et al., 1992; Fu et al., 1993; Scholl et al., 1999b; Scholl et al., 1999a; Louie et al., 2001; Sanford et al., 2001; Trnka and Grubbs, 2001; Love et al., 2002; Michrowska et al., 2004; Lippstreu and Straub, 2005; Colacino et al., 2007; Hong et al., 2007; Alcaide et al., 2009; Vorfalt et al., 2010). The ring-closing metathesis (RCM) reaction has broad scope and reliability and effectively simplified the total synthesis of a broad range of structurally complicated artificial and natural products (Fürstner and Langemann, 1996; Scholl and Grubbs, 1999; Dixon et al., 2000; Paquette et al., 2000). Schiff base ligands containing Ru complexes have very high excellent stability with activity. Furthermore, the electronic and steric environment of the Schiff base has a significant impact on the catalytic activity of these catalysts.

The well-established two-step synthesis of arene Ru-complexes (C₆₆-C₆₈) having the bidentate Schiff base N,O bonding system and linked with the *p*-cymene motif was

successful. The Schiff bases were produced in the first stage by condensation of aliphatic amines (193) with salicylaldehydes (192) in THF under reflux for 2h. The crude yellow, viscous oily product was separated by column chromatography resulting in good yields of salicylaldimines 194 (Schiff bases) (90-99%). Then these Schiff bases (194) were transformed into the respective thallium salts (195) by treating them with thallium ethoxide in the presence of THF at room temperature for 2h under nitrogen to make the arene Ru-complexes (C₆₆-C₆₈). The salts were then employed in the second reaction step, which was carried out at room temperature for 6h with [RuCl₂(*p*-cymene)]₂ (196) in the presence of THF resulting in the synthesis of Schiff base ruthenium arene complexes (C₆₆-C₆₈). The complexes are highly multifunctional catalysts to promote ring-closing metathesis reaction and Kharasch addition. (Scheme 78) (Drozdak et al., 2005c).



Scheme 74 Etherification of propargylic alcohols.



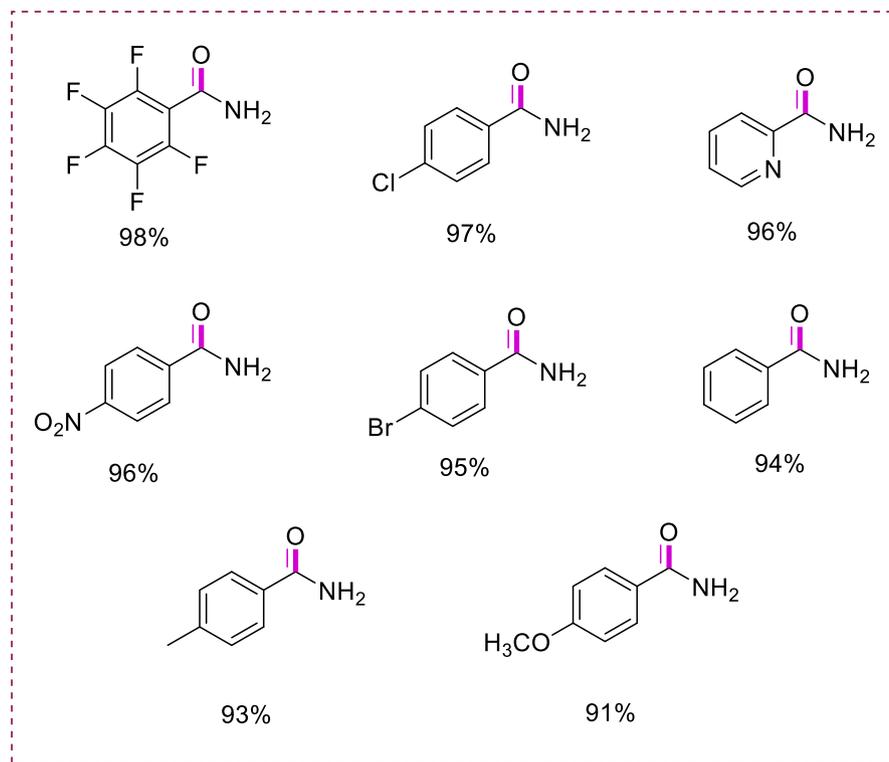
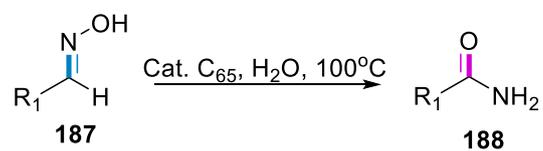
Scheme 75 Synthesis of phosphino-oxime containing Ru(II) complex.

The tri- and tetrasubstituted cycloalkenes (**198**) are synthesized from the respective dienes (**197**) using a 5 mol% catalyst (C_{66} - C_{68}) in toluene and trimethylsilyldiazomethane (added to generate the metal-carbene) at $70^\circ C$. The activity of these complexes is sufficiently high at $70^\circ C$. The three catalysts were formed in moderate to good yields even under more harsh conditions. The strongest, non-transferable chelated Schiff base ligand is present along with the coordinatively stable *p*-cymene group in complexes (C_{66} - C_{68}) which is favorable for their catalytic activity. The capacity of catalysts in RCM is clearly influenced by substituents linked to the *N*-atom in the Schiff base complex (C_{66} - C_{68}) (Scheme 79) (De Clercq and Verpoort, 2001).

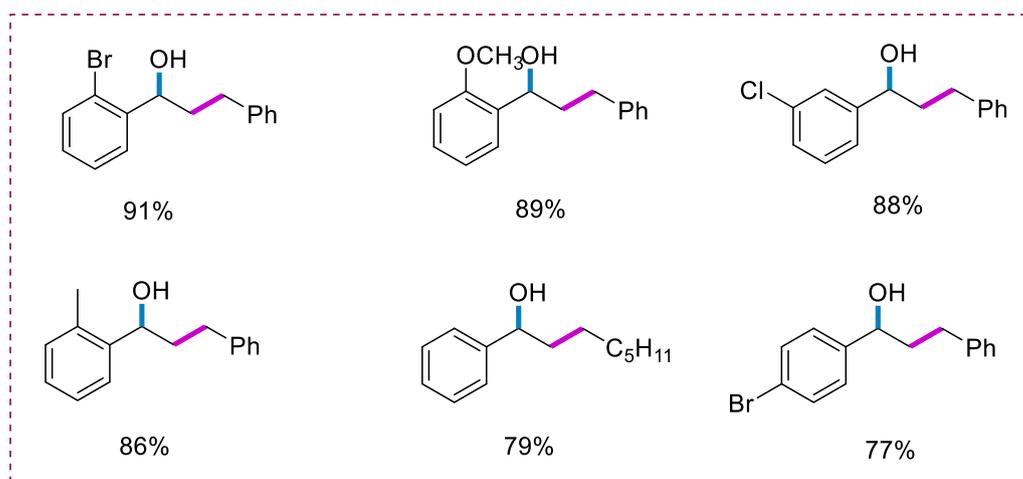
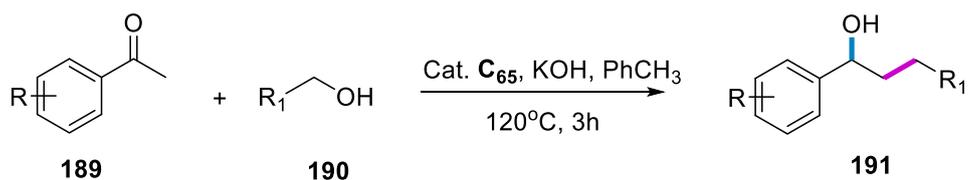
There are several Schiff base-ruthenium that are used as pre-catalysts to perform the Kharasch addition reaction and

also known as atom-transfer radical addition (ATRA) of carbon tetrachloride to a variety of olefinic substrates (De Clercq and Verpoort, 2002c; De Clercq and Verpoort, 2002d). The Kharasch reaction of CCl_4 across olefins was mediated by Ru-Schiff base complexes (C_{66} - C_{68}) with high yields that were very dependent on the catalyst and substrate utilized (De Clercq and Verpoort, 2002c). Standard conditions were used for the Kharasch addition reactions. The catalytic system and the olefin used appeared to have a significant effect on the reaction's outcome.

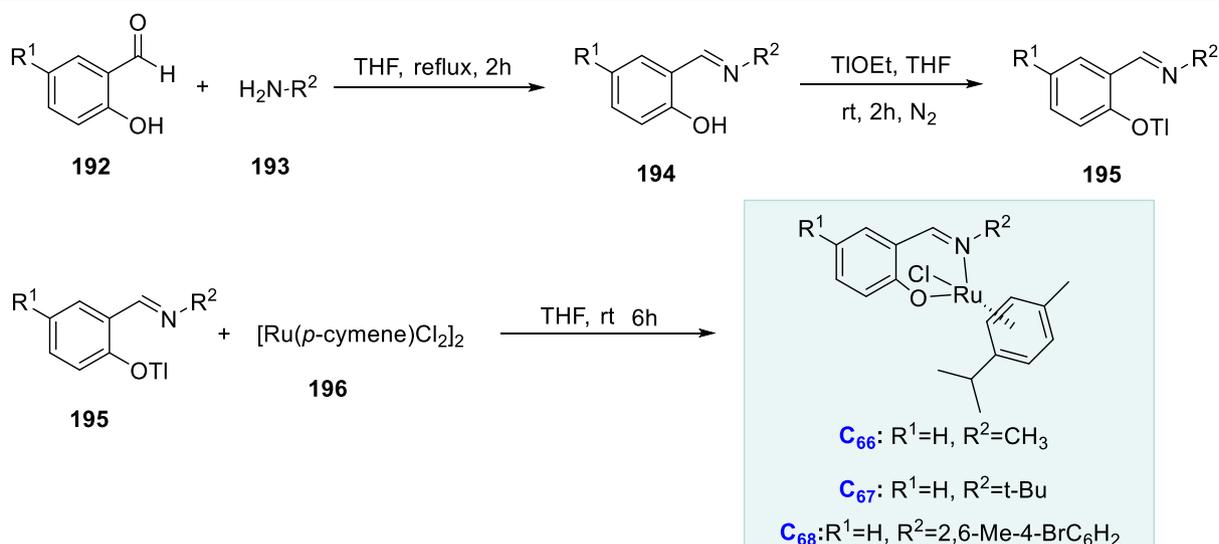
Complexes (C_{66} - C_{68}) have been shown to successfully catalyze the Kharasch addition of haloalkanes (**200**) into olefins (**199**) resulting in the formation of polyhalogenated alkanes (**201**). The styrene and methylmethacrylate undergo clean mono-addition of carbon tetrachloride by using the best



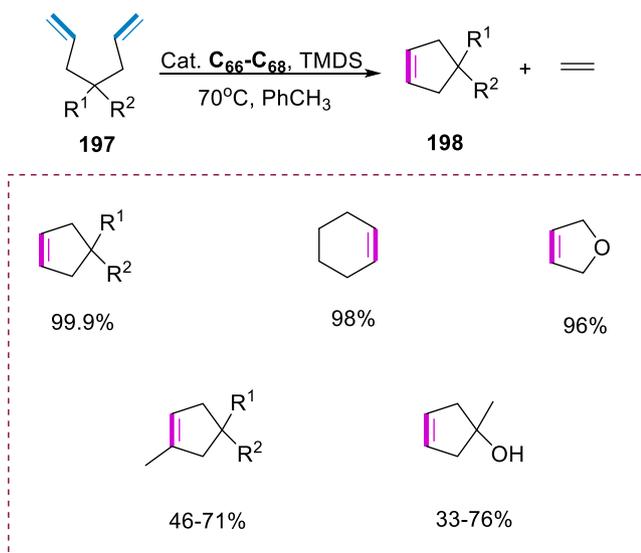
Scheme 76 Aldoximes rearrangement into primary amides.



Scheme 77 Reduction of acetophenone.



Scheme 78 Synthesis of Schiff-base substituted ruthenium benzylidene complexes.



Scheme 79 Ring-closing metathesis.

catalytic complex (**C₆₈**) for 17h at 65°C affording up to 88 and 73 percent product respectively. When the reactions were carried out with diethylallylmalonate, the various catalytic complexes were distinguished. Methacrylates convert more smoothly than acrylates with all three catalytic systems. This reaction was also proceeded at 85°C instead of 65°C to achieve better results in the presence of the best catalytic system (**C₆₈**) for 17 h. In this instance, all substrates were transformed at a higher rate. The best substrate for these catalysts is styrene, which was almost quantitatively transformed, while methyl-methacrylate was also converted to an extent of up to 84 percent. The complexes (**C₆₆**-**C₆₈**) are multifunctional catalysts that promote Kharasch addition reactions with great efficiency. It is worth noting that complexes (**C₆₆**-**C₆₈**) can easily catalyze the Kharasch addition (ATRA) reaction without the use of a co-catalyst (**Scheme 80**) (**De Clercq and Verpoort, 2002a; Drozdak et al., 2005b**).

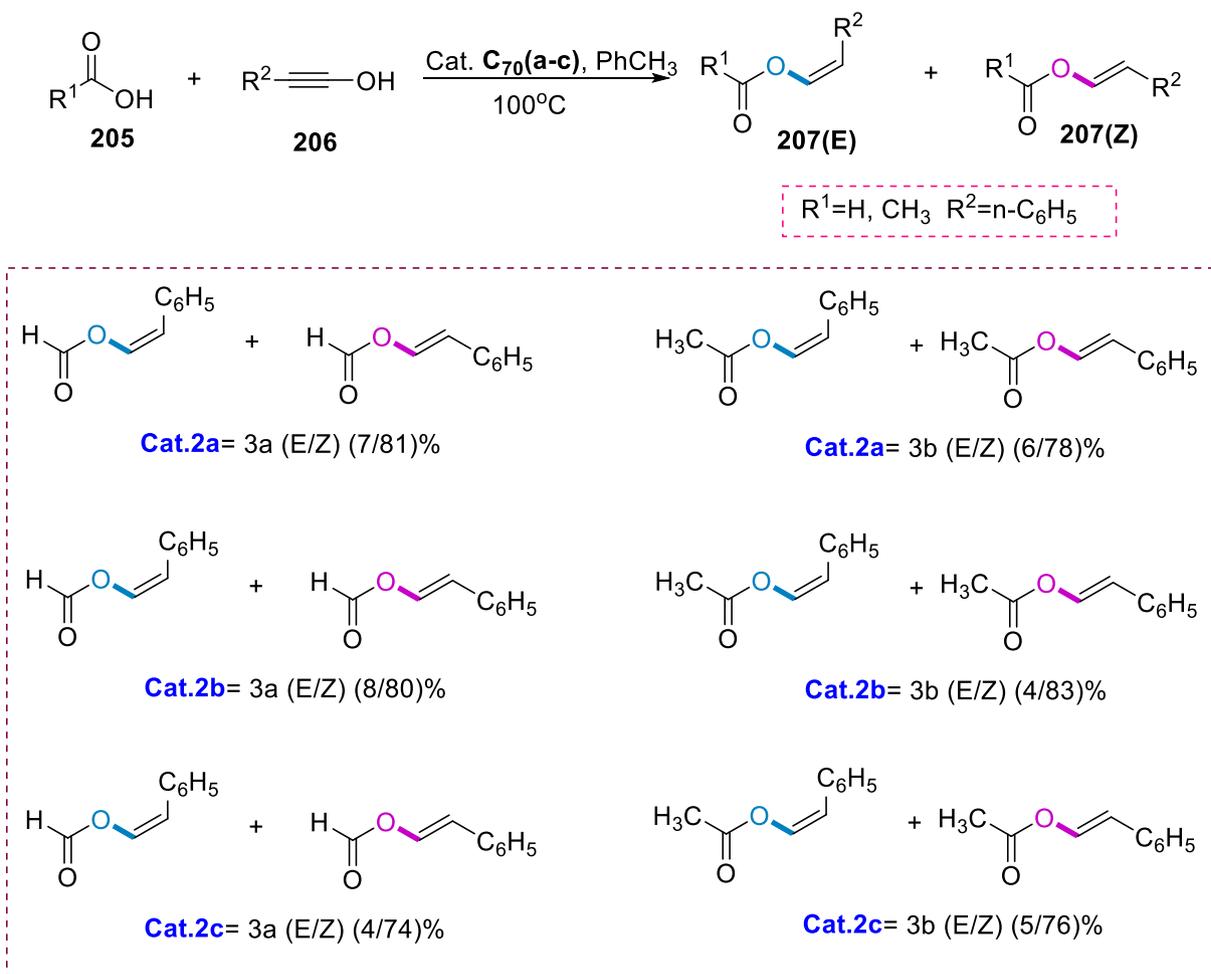
6.2. Synthesis of ruthenium complexes containing Schiff base and *N*-heterocyclic carbene (NHC) ligand and its applications

The Ru-complexes containing Schiff base and *N*-heterocyclic carbene (NHC) ligand is effective in catalyzing enol ester synthesis reactions that were highly dependent on the catalyst and substrate used (**Opstal and Verpoort, 2002**).

The synthesis of complexes **C₇₀(a-c)** was accomplished by replacing the phosphane in the known complexes **C₆₉(a-c)** with a bulky 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene group (**203**) which resulted in excellent yields of compounds **C₇₀(a-c)** as brown solids. The number of imidazolylidene compounds is stable as their free carbene. The free imidazolylidene carbene was formed in situ using the tetrafluoroborate salt and KOTBu as a base. The suspension of tetrafluoroborate salt (**202**) reacts with potassium tert-butoxide in the presence of THF at room temperature to produce an intermediate (**203**). A syringe was used to add one equivalent solution of complexes **C₆₉(a-c)** in dry PhCH₃ after 5 minutes. Complexes **C₇₀(a-c)** were obtained as brown microcrystalline solids in good yields upon heating the mixture to 70-80°C for 1 hour (**Scheme 81**) (**De Clercq and Verpoort, 2003**).

The regioselective addition of carboxylates (**205**) into terminal alkynes (**206**) by using toluene at 100°C provides direct access to enol esters (**207**) of anti-Markovnikov and Markovnikov types respectively. When octadiyn was utilized as a substrate then the addition of carboxylic acids results in the selective synthesis of (E)-alk-1-en-yl esters respective to a stereo- and regioselective anti-Markovnikov type addition of the acid along with the triple bond. The (E)-alk-1-en-yl ester was obtained in good yield varied between 74 and 83 percent for both acids and all six catalytic systems. The total yield is highly reliant on the acid and catalyst utilized. A small amount of the (Z)-alk-1-en-yl ester is formed in addition to the (E)-alk-1-en-yl ester (**Scheme 82**) (**De Clercq and Verpoort, 2003**).

Ring-opening metathesis polymerization (ROMP) has paved the way for novel synthetic methods for a wide range



Scheme 82 Enol-ester synthesis.

undergo systematically lower conversions due to the influence of the electronic environment of Schiff bases in complexes **C**₇₀(**a** and **c**). Furthermore, the steric hindrance of the Schiff base has a greater influence on ROMP catalytic activity than the influence of Schiff base substituents electronic environment (Scheme 83) (De Clercq and Verpoort, 2002b).

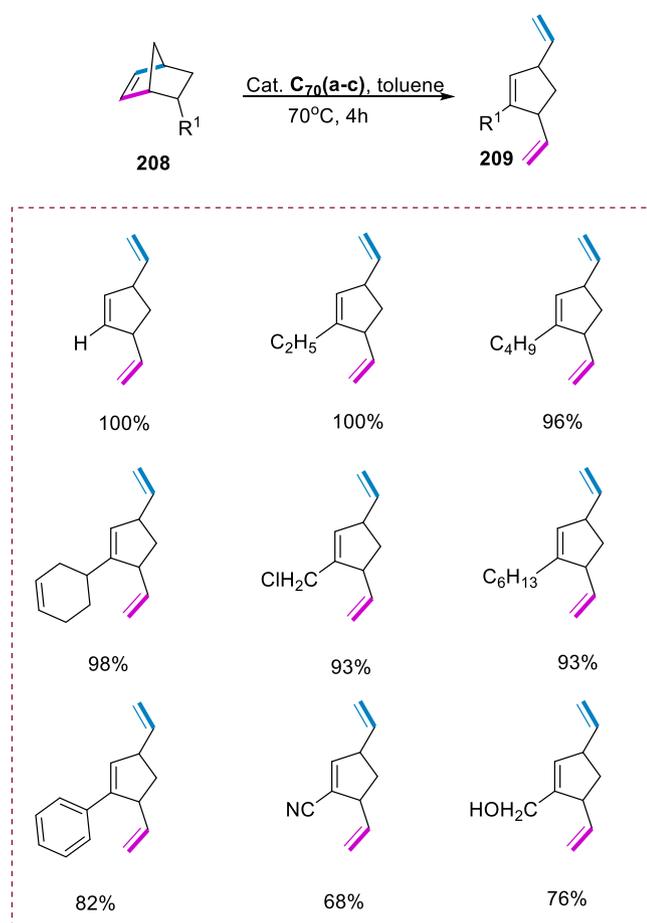
6.3. Synthesis of Ru(II) Schiff-base complexes containing pyridine ligand and its application

The ruthenium (II) complexes were used as catalysts for the hydrogenation of a variety of ketones in a 2-propanol solution. The catalytic reactions showed that Ru(II) complexes comprising Schiff base ligands containing pyridine were effective for transfer hydrogenation as catalysts in the presence of various bases (Gichumbi et al., 2016; Ramos et al., 2019).

Condensation of 6-tertbutyl 3-ethyl 2-amino-4,5-dihydro thieno[2,3-c]pyridine-3,6(7H)-dicarboxylate with various substituted benzaldehydes yielded Schiff base ligands (**210**). Ruthenium (II) complexes **C**₇₁(**a-d**) were formed by reacting the Schiff base (**210**) with the metal salt [RuCl₂(*p*-cymene)]₂ (**211**) in methanol at 70°C for 4-5 hours. The transfer hydrogenations of acetophenone derivatives were catalyzed by a

series of new Ru(II) complexes containing pyridine group-based Schiff bases. These complexes having both electron poor and electron rich groups coordinating to the aryl ring displayed extremely high catalytic activity. Instead of the electrical effect of groups contained in the structure of these Ru(II) complexes employed, this is likely depending on the structure of the ketone that was used as the substrate. (Scheme 84).

Catalytic transfer hydrogenation of various ketones (**212**) (*m*-methoxyacetophenone, acetophenone, *p*-bromoacetophenone, benzophenone, and *p*-methoxyacetophenone) using ruthenium (II) Schiff base complexes **C**₇₁(**a-d**) as a catalyst by using KOH base and isopropanol as H₂ donor by refluxing at 80°C for 8h results in the synthesis of respective secondary alcohols (**213**). The base is used as a promoter to proceed with this transformation. The transfer hydrogenation reactions, on the other hand, required only 8h with an additional base. The strong inorganic bases (such as KOH and NaOH) give better conversion results in the corresponding alcohol products in excellent yields. The weak inorganic bases (such as Cs₂CO₃, Na₂CO₃, KOBut, and K₂CO₃), on the other hand, were shown to be less effective than strong bases. KOH is thought to be a better base. The electronic effects of the groups in the ligand structure and



Scheme 83 Ring-opening metathesis polymerization reaction.

the structures of the ketones used are the factors responsible for the high conversion (**Scheme 85**) (**Buldurun and Özdemir, 2020**).

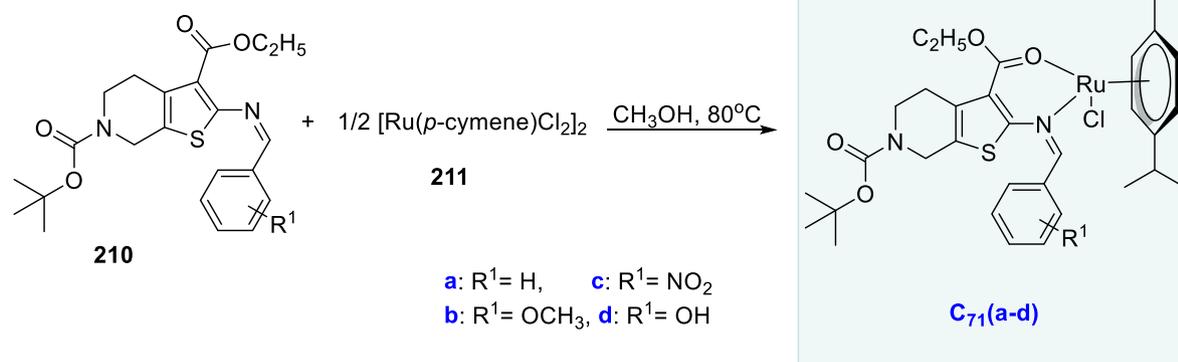
6.4. Synthesis of bidentate Schiff-base ruthenium complexes and their applications

The effective oxidation of alcohols into corresponding ketones or aldehydes is significant in synthetic chemistry (**Yamaguchi**

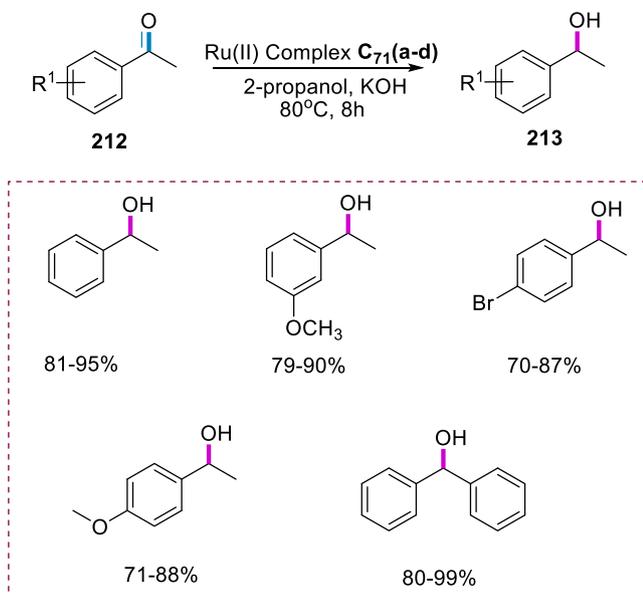
and Mizuno, 2010; Parmeggiani and Cardona, 2012; Steves and Stahl, 2013; Ballester et al., 2014; Cardona and Parmeggiani, 2014). Carbonyl compounds and their derivatives are important and versatile building blocks in the formation of a variety of medicinal and fine chemicals (**Spasyuk and Gusev, 2012; Koh et al., 2015; Hu et al., 2016b**). Acceptorless alcohol dehydrogenation (AAD) reactions are important in the synthesis of carbonyl compounds without the use of oxidants (**Gunanathan and Milstein, 2013; Chelucci, 2017; Crabtree, 2017; Li et al., 2019**).

The Schiff base bidentate ligands RN=CH-(2,4-(tBu)₂C₆H₂OH (R = C₆H₅, **L1**; R = 4-MeC₆H₄, **L2**; R = 4-ClC₆H₄, **L3**; R = 4-BrC₆H₄, **L4**) were produced via condensation reactions of 3,5-di-tert-butyl-2-hydroxybenzaldehyde with the respective primary amine. The RuHClCO(PPh₃)₃ (**214**) reacts with Schiff bases (**L1-L4**) under reflux in THF in the presence of a base (trimethylamine) giving the Ru(II) complexes **C₇₂(a-d)** in isolated yields ranging from 42 to 57 percent. The complex **C₇₂(b)** was then prepared by reaction of Schiff base bidentate ligand with ruthenium complex in which one PPh₃ was replaced with one Cl in the initial ruthenium compound. These complexes were shown to be air and moisture stable. These complexes were shown to be efficient catalytic activity in the acceptorless dehydrogenation of secondary alcohols and good compatibility of functional groups yielding the respective ketones in 82-94 percent yields. This type of catalytic system can work in mild reaction conditions and tolerates a broad variety of functional groups. It offers an environmentally friendly approach to synthesizing ketones (**Scheme 86**).

Secondary alcohols (**215**) are reacted with Ru Schiff base catalysts **C₇₂(a-d)** utilizing t-BuOK as a base in the presence of toluene as a solvent at 110°C for 12 hours under an N₂ environment to produce excellent yields of respective ketones (**216**). The variety of substituted 1-phenylethanols with electron-donating and electron-withdrawing groups on the aryl ring, such as 1-(naphthalen-2-yl)ethan-1-ol can be transformed into corresponding ketones. It is worth mentioning that this catalytic system also dehydrogenated aliphatic alcohols very well providing the aliphatic ketones in good yields (>80%). The complexes **C₇₂(c and d)** having electron-poor substituents on the aromatic ring of the Schiff base ligand are slightly more effective than complexes **C₇₂(a and b)** with electron-donating



Scheme 84 Synthesis of Ru(II) Schiff-base complexes containing pyridine ligand.



Scheme 85 Hydrogenation of ketones.

substituents. The yield increased dramatically when organic bases (such as DBU, *t*-BuOK, and DABCO) were used, and *t*-BuOK was shown to be far more efficient than the other organic bases. The limited solubility of inorganic bases in toluene affects their performance less than that of organic bases. The PhCH₃ was found to be very effective for this transformation. Xylene even at a higher temperature under reflux gives very low yields in other solvents such as THF, CH₂Cl₂, 1,4-dioxane, or acetone as compared to toluene (Scheme 87) (Hao et al., 2021).

Ruthenium complexes are very effective at catalyzing the nitroarenes hydrogenation into aromatic anilines by using a reducing agent such as sodium borohydride in an ethanol solvent (Indra et al., 2011; Tomkins et al., 2015). Aromatic anilines are used in the synthesis of medicines, pigments, agrochemicals, and dyes as intermediates and precursors (Tafesh and Weiguny, 1996; Vaidya et al., 2003). Complex C₇₂(c), in particular, was found to be a very effective catalyst for the hydrogenation of nitroarene compounds with a broad substrate scope functional group compatibility.

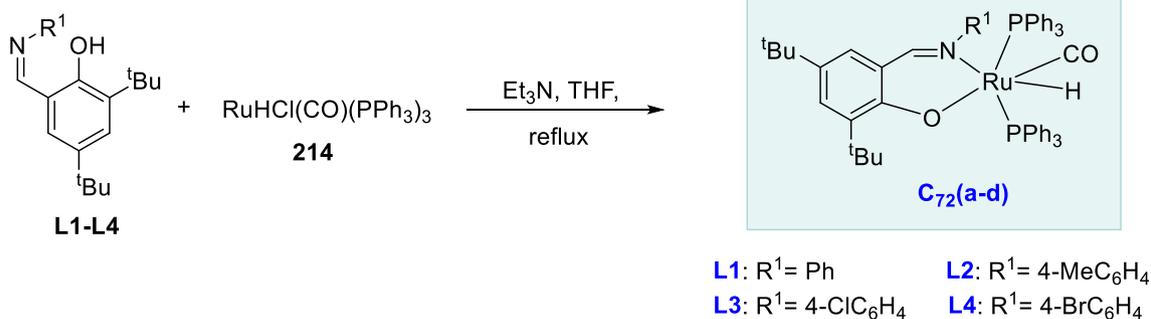
The reduction of 4-nitroanisole by using a reducing agent (NaBH₄) under homogenous conditions proceeds in the presence of Schiff-based Ru-complexes. The Ru-complex C₇₂(c) was discovered to be extremely effective for reducing nitro compounds. The nitroarene (217) underwent reaction with 0.5mol% of complex C₇₂(c) at 30°C in the presence of four eq. of NaBH₄ in ethanol as solvent resulting in the formation of respective amine (218) in good yield. A vast range of aryl functional groups involving electron-withdrawing and electron-donating groups were well tolerated by the reaction. The steric bulkiness of the methyl group on nitroarene appeared to have no impact on the catalytic efficiency of the nitroarene to toluidine conversion. The very sterically crowded 2,6-dimethyl nitrobenzene may be reduced by 95% yield under optimal conditions. The reaction offers broad substrate scope, vast compatibility of functional group, and provides arylated anilines in good to excellent yields (Scheme 88) (Jia et al., 2016).

6.5. Synthesis of Ru(III) Schiff base bis-bidentate complexes and their application

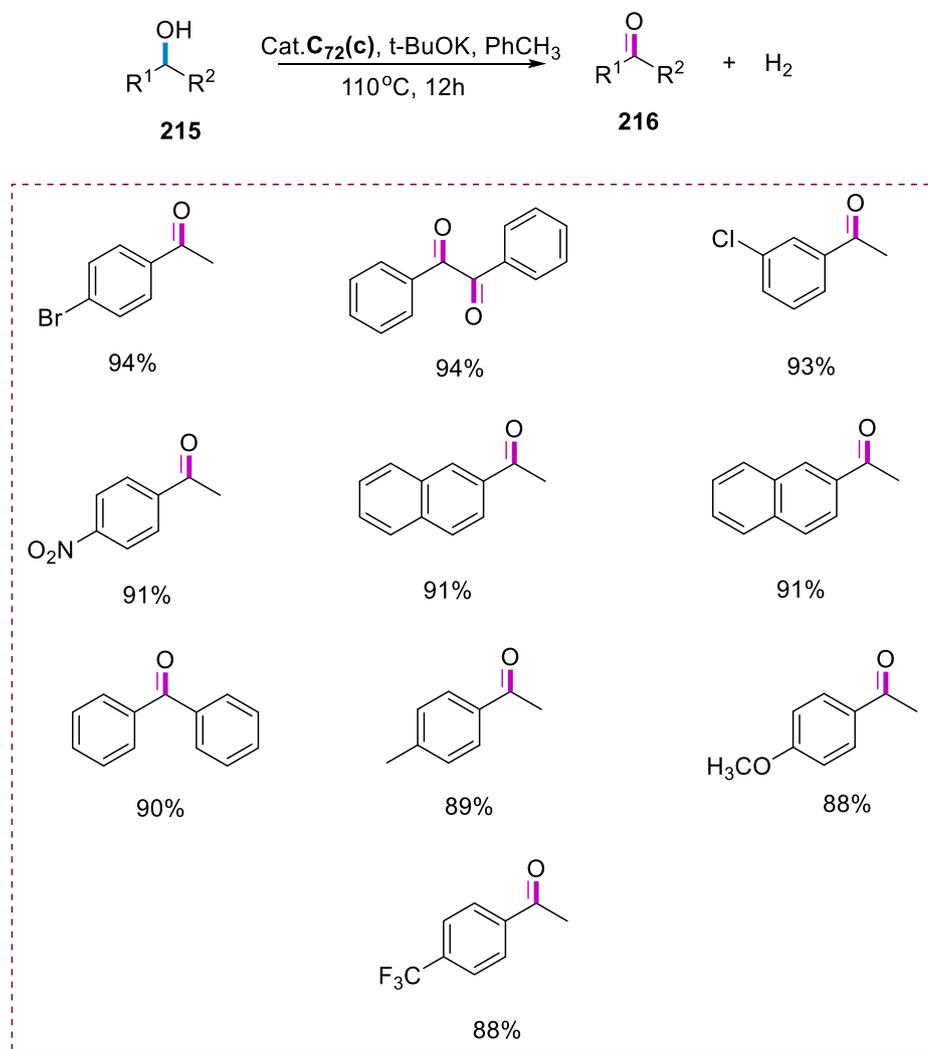
The Schiff base bidentate ligands of the O, N bonding system were used to make a series of new stable Ru(III) complexes [RuCl(PPh₃)(L)₂] (where L = O, N donor of Schiff bases) that are excellent catalysts in the imine hydrogenation to amines with high to moderate conversions. In terms of selectivity and reactivity, ruthenium Schiff base complexes outperform catalysts with amine/diamine or oxazoline ligands in transfer hydrogenation reactions (Gao et al., 2000; Lindner et al., 2003; Hannedouche et al., 2004).

These Ru complexes C₇₃(a-d) were formed in benzene by reacting Schiff base bidentate ligands (L5-L8) with Ru(III) precursors [RuCl₃(PPh₃)₃] (219) in a 2:1 molar ratio under reflux for 5 hours. The complexes were then purified using CH₂Cl₂ (60–80°C) to yield a new class of Ru(III) Schiff base bis-bidentate complexes [RuCl(PPh₃)(L)₂] (L = bidentate Schiff base ligands). These compounds are extremely effective at catalyzing imine transfer hydrogenation (Scheme 89).

The synthesis of corresponding amines (220) arises from the catalytic imine (221) hydrogenation by Ru(III) Schiff-based bis-bidentate complexes [RuCl(PPh₃)(L)₂] C₇₃(a-d) by using KOH which is catalyzed by heating to reflux for 3h in 2-PrOH under inert atmosphere. Both aldimines and ketimines



Scheme 86 Synthesis of bidentate Schiff base ruthenium complexes.



Scheme 87 Dehydrogenation by secondary alcohol.

were converted to respective amines with high conversion by using these complexes. The arylated aldimine having a *p*-methoxy group was converted into the corresponding amine after 3h in 78.5% yield and after 10h, it was 92.6 percent. Ketimines are more difficult to convert to amines than aldimines. When aromatic ketamine with electron-donating groups is reduced, better yields are obtained than when aromatic ketamine with electron-withdrawing groups is reduced. The transfer hydrogenation of imines requires the presence of a catalytic quantity of a base (Scheme 90) (Venkatachalam and Ramesh, 2006).

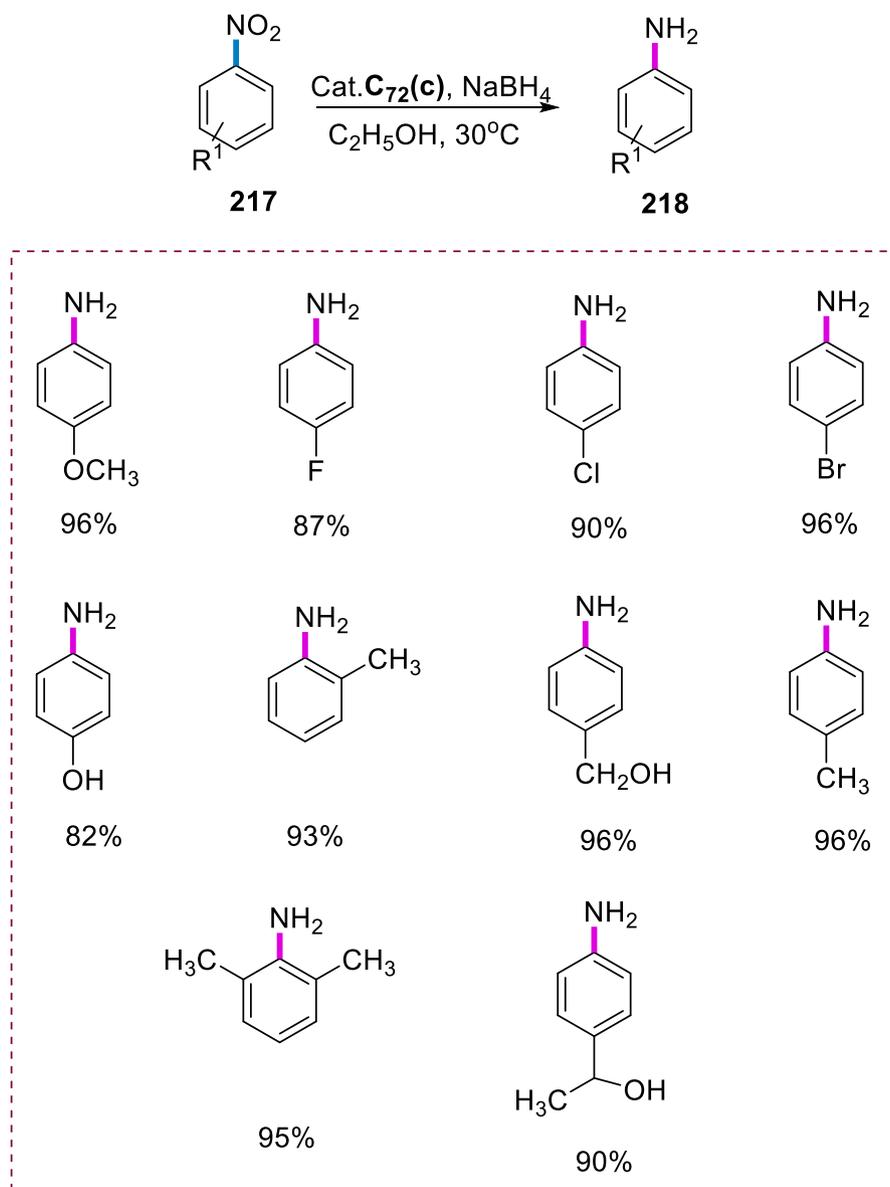
6.6. Synthesis of Schiff base Ru-complexes having *p*-cymene ligand and its application

The Ru(II) Schiff base complexes showed efficient catalytic activity for the one-pot conversion of aldehydes to amides in the presence of $\text{NH}_2\text{OH}\cdot\text{HCl}/\text{NaHCO}_3$. Amides are a significant class of organic compounds that have long been used as chemical building blocks in organic synthesis and as functional groups, as well as biologically active compounds and pharmaceuticals (Drozdak et al., 2005a). Ruthenium complexes have

been widely used because of their catalytic importance in a range of organic conversions, such as the imine synthesis from alcohols and amines.

The dimeric $[(p\text{-cymene})\text{RuCl}_2]_2$ complex (**223**) reacts with the suitable Schiff base ligands **222(a-d)** in CH_2Cl_2 at room temperature, and the Ru(II) Schiff base complexes **C₇₄(a-d)** were readily produced in good yields. The complexes **C₇₄(a-d)** are solid and were stable in air. They are highly miscible in polar solvents but insoluble in non-polar solvents. These Schiff base complexes of ruthenium (II) were produced as reddish-brown solids in excellent yields of up to 90% (Scheme 91).

The catalytic conversion of aldehydes (**224**) into amides (**225**) is catalyzed by Ru(II) Schiff base complexes **C₇₄(a-d)** in toluene in the presence of $\text{NaHCO}_3/\text{NH}_2\text{OHHCl}$. These complexes are very effective for all Aromatic, heterocyclic aromatic, and conjugated aldehydes. These Schiff-based complexes of Ru(II) effectively catalyze the transformation of aldehydes to their respective amides in a one-pot reaction. In the absence of a catalyst or base, no considerable reaction was seen. Toluene as a solvent and NaHCO_3 as a base was found to be the most effective for the catalytic transformation



Scheme 88 Hydrogenation of nitroarenes.

of aldehydes to amines with good yields. The presence of electron-donating groups in the substrates, such as $-\text{OH}$ and $-\text{OCH}_3$ varies the reactions and the appropriate amides were produced in good yield (87-79%). When compared to substrates having electron-withdrawing groups and electron-donating groups such as the $-\text{NO}_2$ and $-\text{Cl}$ substituents offer higher yields (98-82%). Among all the complexes, catalyst **C₇₄(a)** is thought to be particularly effective of transforming aldehydes to amides in high yields (Scheme 92) (Premkumar et al., 2019).

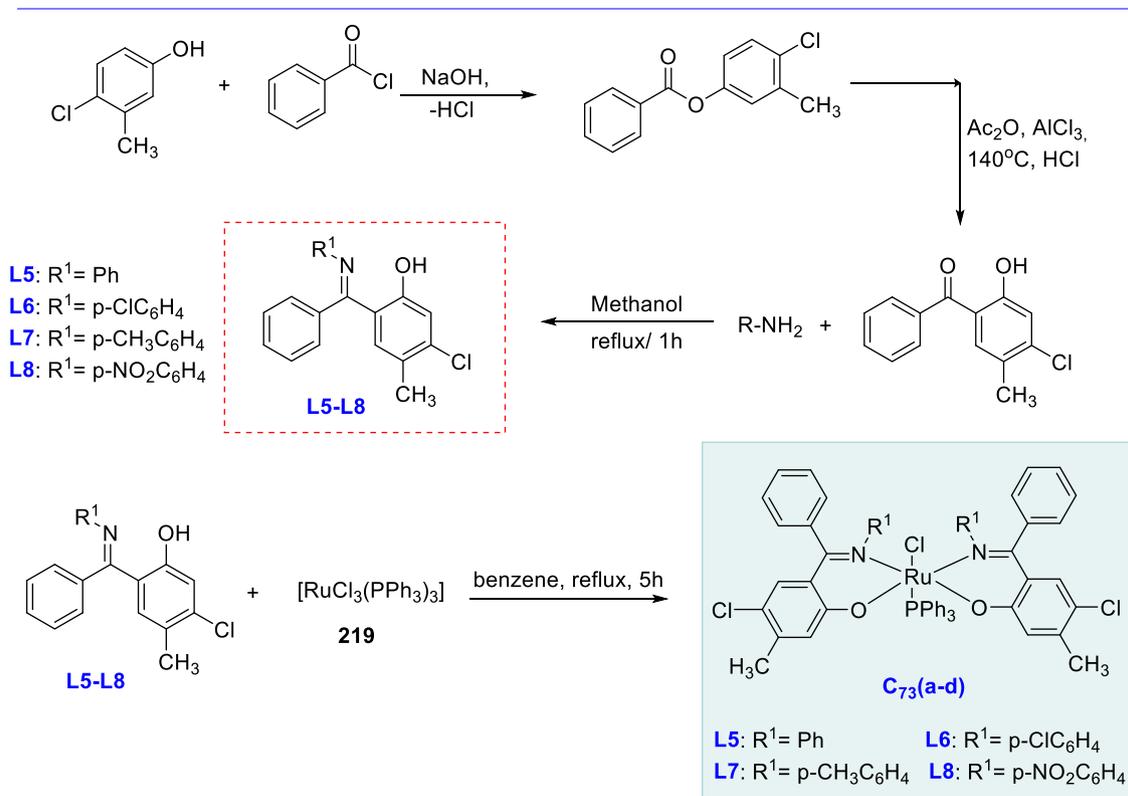
7. NHC–Ru complexes-Synthesis and applications

Organometallic and inorganic coordination chemistry, *N*-heterocyclic carbenes are frequently used. They can act as auxiliary ligands in the growing number of transition-metal catalysts, or even as a catalyst and nucleophilic reagents in a

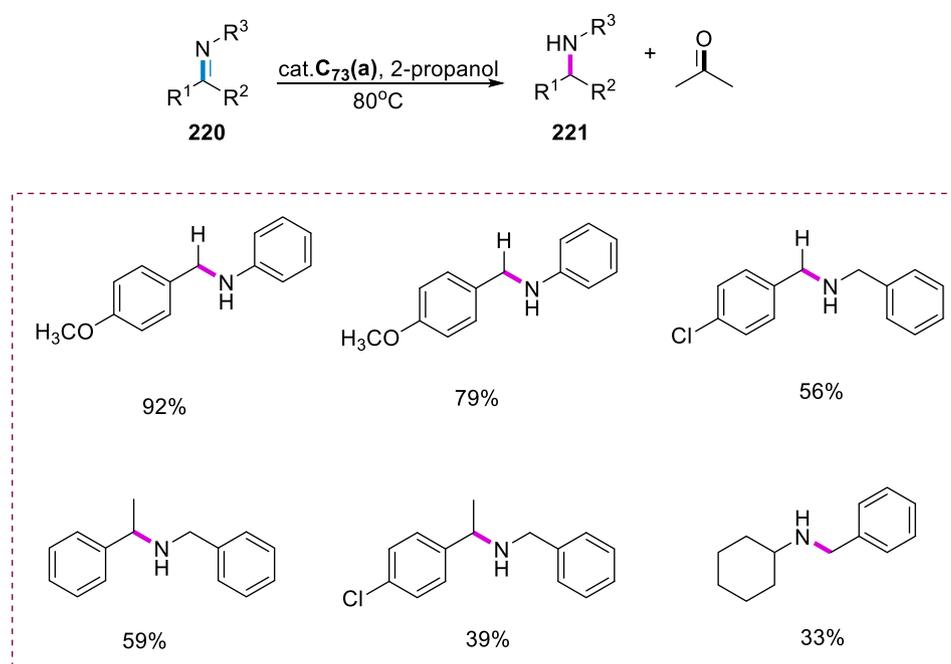
variety of organic syntheses have gotten a lot of attention (Crabtree, 2005; Díez-González and Nolan, 2005; Lai et al., 2005; Singh and Nolan, 2005; Crabtree, 2006). The NHC complexes have exhibited extraordinary stability toward moisture, air, and heat because of their great sigma-donating ability (Egbert et al., 2011; Fortman and Nolan, 2011). NHC ligands were produced and demonstrated excellent catalytic activity in C-C bond coupling, hydrosilylation, and hydrogenation reactions.

7.1. Synthesis of pyridazine-based *N*-heterocyclic carbene diruthenium complex and its application

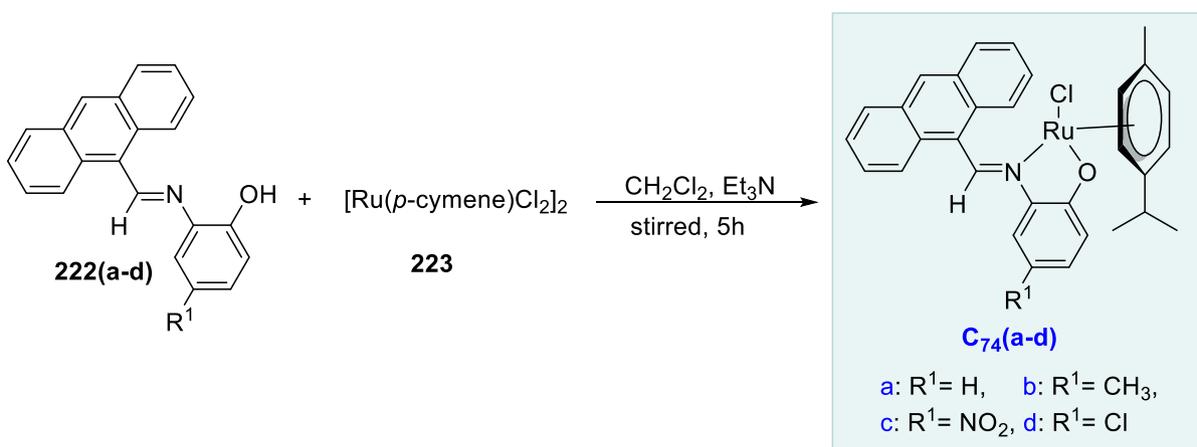
The bimetallic *N*-heterocyclic carbene (NHC) complexes have a high catalytic activity for alkene oxidation processes (Zhou et al., 2008b; Liu et al., 2010). The Ru...Ru cooperative effect is considered to be liable for the strong activity of the



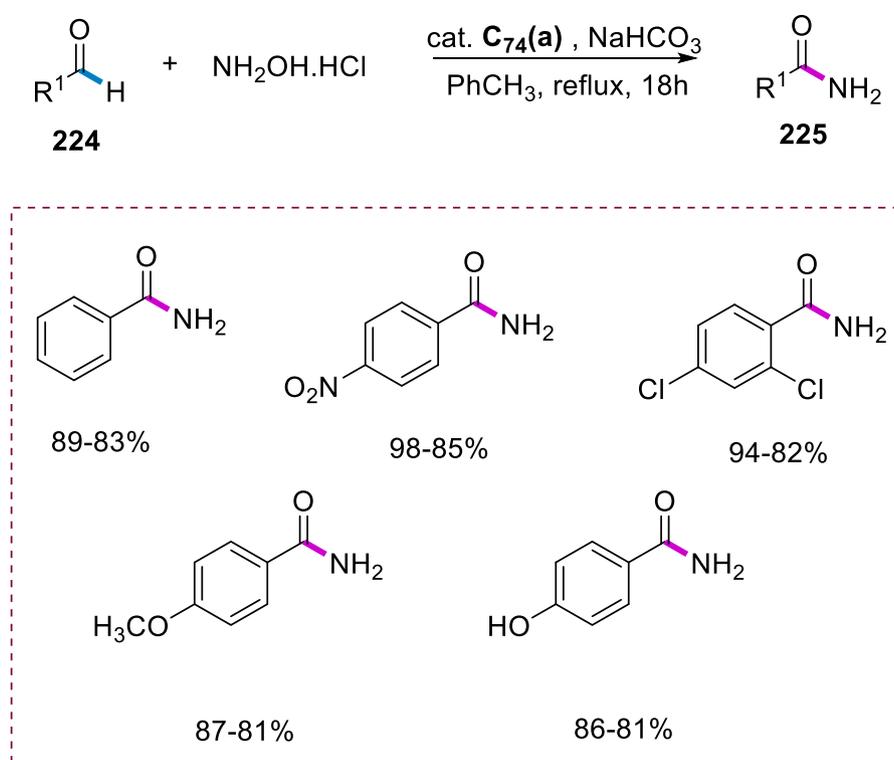
Scheme 89 Synthesis of Ru(III) Schiff base bis-bidentate complexes.



Scheme 90 Hydrogenation of imines.



Scheme 91 Synthesis of Schiff base Ru-complexes having a *p*-cymene ligand.



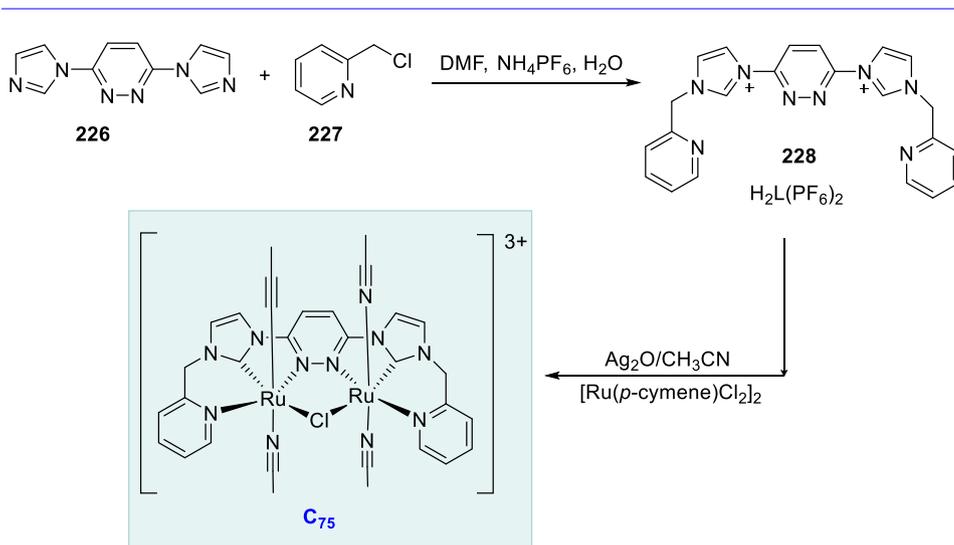
Scheme 92 Synthesis of amides.

di-ruthenium complex (**C₇₅**) towards alkene oxidation. The pyridazine moiety can binucleate, the high donating ability of carbene, and hexadentate characteristic of structure all lead to ensuring the oxidation state stability of complex (**C₇₅**) which could potentially increase its catalytic efficiency in oxidation transformations.

The imidazolium salt of the functionalized pyridazine bis (NHC) ligand precursor ($\text{H}_2\text{L}(\text{PF}_6)_2$) **228** was produced by reacting the 2-(chloromethyl)pyridine (**227**) and 3,6-di(1H-imidazol-1-yl)pyridazine (**226**) in DMF under heat followed by the exchange of anion in water. The salt of imidazolium (**228**) was obtained in the form of a white solid with a moderate yield

(64%). The colorless solution of $[\text{Ag}_6(\text{L})_4](\text{PF}_6)$ was obtained by reacting the imidazolium salt $\text{H}_2\text{L}(\text{PF}_6)_2$ ($\text{L} = 3,6\text{-bis-(N-pyridylmethyl)imidazolylidene}(\text{pyridazine})$) with Ag_2O in the presence of CH_3CN at 50°C . The diruthenium complex $[\text{Ru}_2\text{-Cl}(\text{L})(\text{CH}_3\text{CN})_4](\text{PF}_6)_3$ (**C₇₅**) was obtained by adding $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ complex to solution. The dinuclear ruthenium (II) complex has efficient catalytic activity for the oxidation of the alkene into diketones (Scheme 93).

The reaction mixture containing alkene (**229**), complex (**C₇₅**), and NaI was stirred in 3.0 mL of CH_3CN . Then add the TBHP as an oxidant to this solution with the help of a syringe at r.t. The reactions required only 10 minutes to complete



Scheme 93 Synthesis of pyridazine-based *N*-heterocyclic carbene diruthenium complex.

at room temperature. The alkenes were transformed into their diketone (**230**) counterparts. Acetonitrile was found to be a better solvent than toluene for obtaining good yields, and TBHP was utilized as an oxidant. Alkenes with electron-rich groups yielded better yields than those with electron-poor groups. It is worth noting that *N*-substituted indoles were often used successfully resulting in high yields. Furthermore, heterocyclic alkenes like those containing carbazole and thiophene can be used to give the target product in moderate yields (Scheme 94) (Liu and Chen, 2012).

7.2. Synthesis of benzimidazole-based ruthenium(II)-NHC complexes and their applications

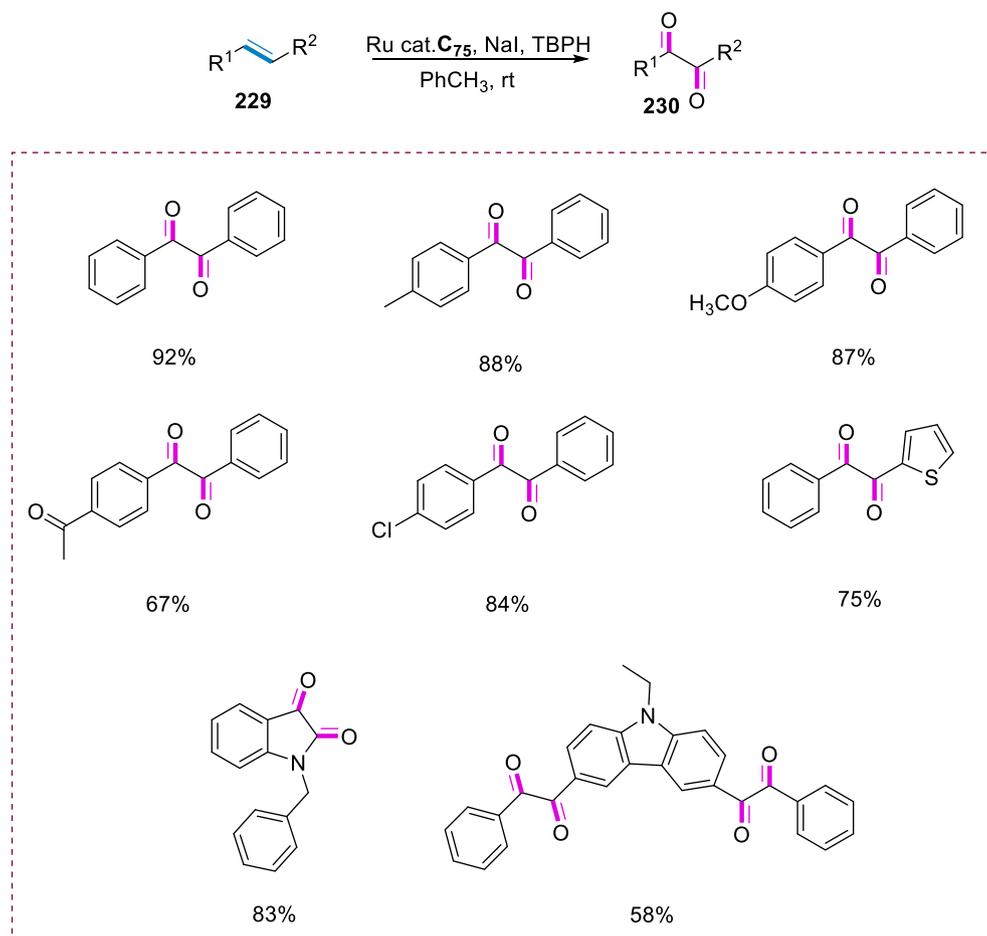
The borrowing hydrogen method was found to be efficient with Ru-complexes that have strong sigma-donor ligands, such as *N*-heterocyclic carbenes (NHC) (Hamid et al., 2007; Td, 2009; Kerdphon et al., 2015; Corma et al., 2018). Borrowing hydrogen (BH) for the alkylation of ketone enolates with a ruthenium(II)-NHC catalyst has emerged as a potent and environmentally friendly method for forming C-C bonds (Gunanathan and Milstein, 2013; Ketcham et al., 2014; Huang et al., 2016). Primary alcohols were employed as alkylating agents and could be used in a one-to-one ratio with the ketones (Srimani et al., 2012b; Xu et al., 2014; Elangovan et al., 2015). Compared to previous methods, the Ru-NHC complexes catalyzed by the borrowing hydrogen strategy offer several advantages including low cost, high atom efficiency, and H₂O as a byproduct (Yan et al., 2014). The pharmaceutically active intermediate core moiety was produced in stages using the hydrogen auto-transfer process.

The reaction of anhydrous K₂CO₃ with 5,6-dimethylbenzimidazole (**231**) in the presence of acetonitrile proceeds by the addition of alkyl halide in stoichiometric quantity under reflux for 16h producing the appropriate benzimidazolium salt **232(a-f)** in good yield (70–90%). The Ru(II)NHC complexes **C₇₆(a-f)** were made using a silver-NHC intermediate **233(a-f)** formed by reacting the silver(I)oxide with ligand precursor to produce

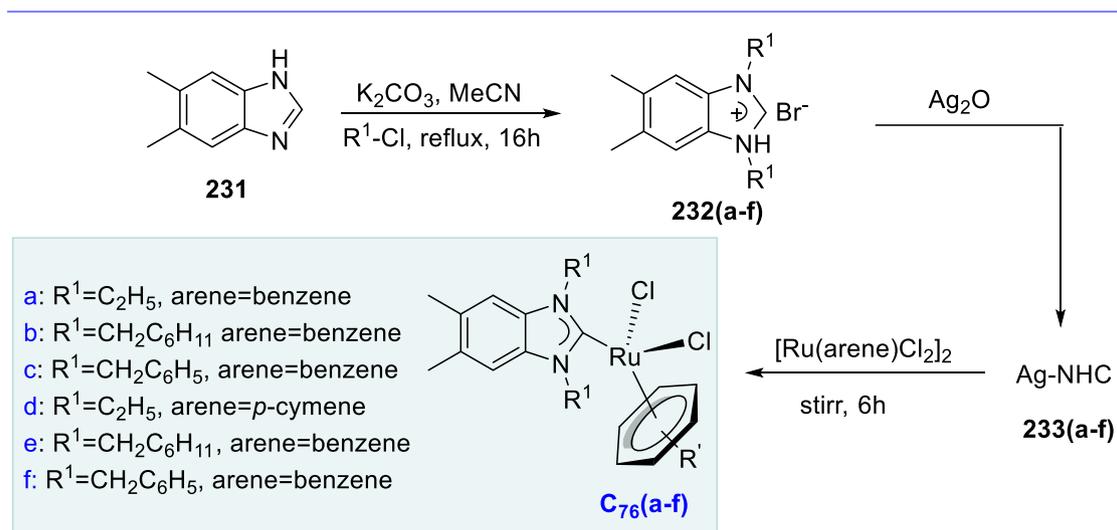
Ag-NHC. The Ag-NHC **233(a-f)** was then treated with ruthenium(II) arene precursors and stirred at r.t. for 6h. Then, by adding pet-ether into the filtrate, brown ruthenium(II)-NHC complexes **C₇₆(a-f)** are precipitated in high yield. The complex **C₇₆(a)** demonstrated excellent catalytic efficiency with 92 percent yield of alkylated product. These complexes have smaller wingtip as compared to other complexes **C₇₆(a-f)** having bulky wingtips along with arene lability probably effect on hydrogen borrowing reaction in α -alkylation. Based on findings, it can be seen that the yield of acetophenone's alkylation was slightly reduced when compared to catalysts **C₇₆(a-f)** with various arene moieties and wingtip, in the following sequence: benzene moiety-ethyl wingtip **C₇₆(a)** > *p*-cymene moiety-ethyl wingtip **C₇₆(d)** > benzene moiety-cyclohexylmethyl wingtip **C₇₆(b)** > *p*-cymene moiety-cyclohexylmethyl wingtip **C₇₆(e)** > benzene moiety-benzyl wingtip **C₇₆(c)** > *p*-cymene moiety-benzyl wingtip **C₇₆(f)** (Scheme 95).

Ketones (**234**) react with alcohols (**235**) in the presence of complex **C₇₆(a)**, NaOH, and toluene at 105°C for 8 hours, resulting in high yields of alkylated ketones (**236**). Compound **C₇₆(a)** demonstrated remarkable catalytic activity. The optimal reaction conditions for alpha-methylation of ketones were NaOH/toluene at 105°C. The yield of the product was dramatically reduced when the reaction proceeded at low temperatures. When compared with other bases used in this reaction, the catalyst reactivity was determined to be efficient by using NaOH. The substrate with electron-donating substituents improves the alkylation reaction with benzyl alcohol which results in excellent yields of respective products (86-92%). In the case of the substrate having electron-withdrawing substituents reduce the yields of alkylated products by 79-86% (Scheme 96) (Ortega et al., 2013).

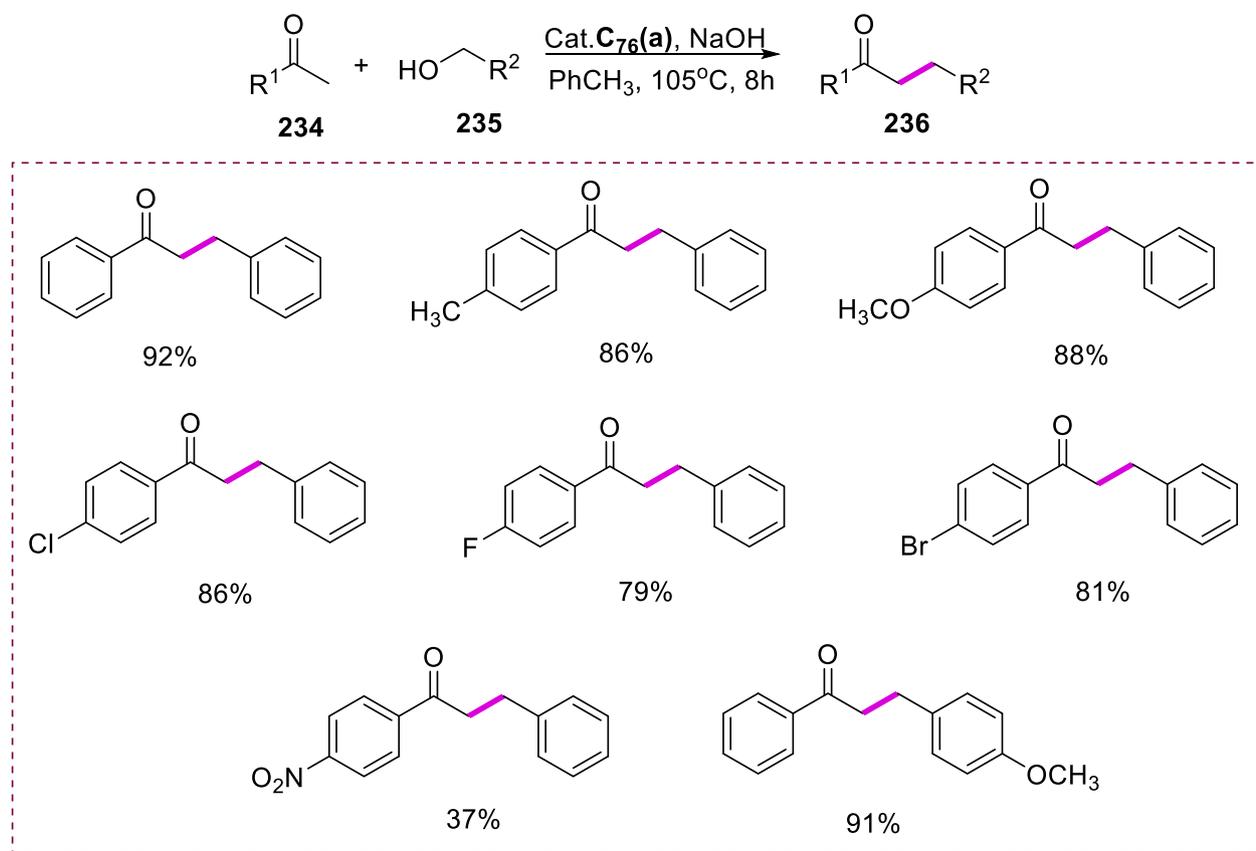
The pharmaceutically active intermediate core moiety was synthesized successfully using the hydrogen auto-transfer technique (Leonard et al., 2015). The arene ruthenium(II)-NHC complexes were used as efficient catalysts in the acceptorless dehydrogenative coupling of 2-aminobenzyl alcohol and ketone to produce quinoline derivatives (Sindhuja et al., 2012;



Scheme 94 Alkene oxidation.



Scheme 95 Synthesis of benzimidazole-based ruthenium(II)-NHC complexes.



Scheme 96 α -Alkylation of methylene ketones.

Sindhuja et al., 2014; Manikandan et al., 2016; Manikandan et al., 2018). Quinoline derivatives are generally found to be excellent candidates for heterocyclic compounds. These scaffolds have significant applications in pharmacology (antitubercular, anticancer, antipsychotic, antibacterial, antiviral, and neurodegenerative disease treatment), material chemistry (OLED complexes and chemo sensors), and catalysis (asymmetric synthesis) (Kim et al., 2005; Jin et al., 2011; Solomon and Lee, 2011; Keri and Patil, 2014; Vlahopoulos et al., 2014; He et al., 2015).

Ketones (**237**) react with 2-aminobenzyl alcohols (**238**) in the presence of catalyst **C₇₆(a)**, NaOH, and toluene at 105°C for 8h, yielding quinolines and their derivatives (**239**) in good yields. The optimal reaction conditions for quinolines derivatives synthesis were NaOH/toluene at 105°C. The yield of the product was dramatically reduced when the reaction proceeded at low temperatures. Under ideal reaction conditions, a vast range of aliphatic, aromatic ketones, and their derivatives offer good yields. The cyclization of 2-aminobenzyl alcohol with ketones includes an electron-rich substituent at the para-position affording an excellent yield (90–92%). The ketones with an electron-poor substituent at the para-position afford the appropriate products in 88% yields (Scheme 97) (Balamurugan et al., 2019).

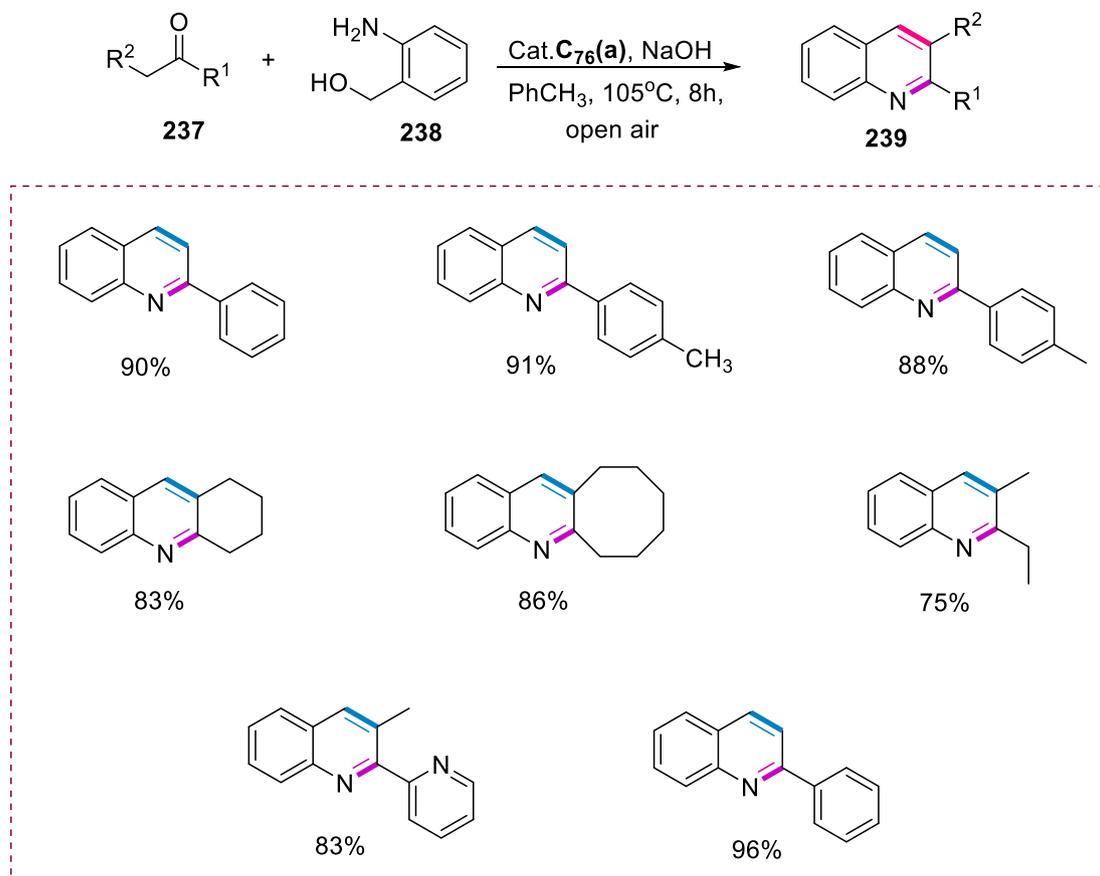
7.3. Synthesis of Ru(II) NHC carbonyl complex and its application

The amide bonds are important functionality in both natural and synthetic systems. Amido linkages can be found in

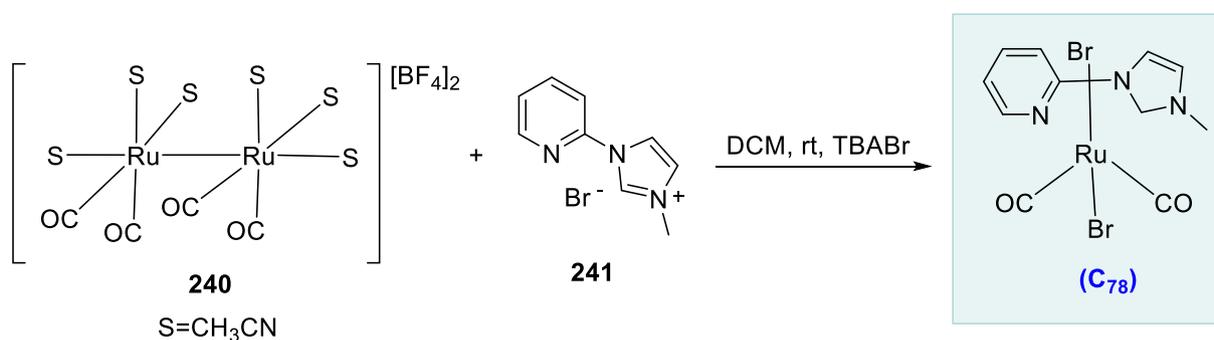
biopolymer proteins and a variety of synthetic polymers (Lectka, 2001; Peptides, 2002; Pattabiraman and Bode, 2011). Madsen introduced the ruthenium *N*-heterocyclic carbene (NHC) complex for amidation reactions (Nordström et al., 2008; Dam et al., 2010; Makarov et al., 2012).

The Ru(II) NHC carbonyl complex [Ru(py-NHC)(CO)₂Br₂] (**C₇₈**) was obtained by treating 3-methyl-1-(pyridine-2-yl)-imidazolium bromide (**240**) with [Ru₂(CO)₄(CH₃CN)₆](BF₄)₂ complex (**241**) by using tetrabutylammonium bromide (TBABr) in dichloromethane at r.t. Catalyst (**C₇₈**) shows a wide substrate range for phosphine-free coupling of amines and alcohols into amides at moderate catalyst loading (Scheme 98).

The catalytic activity of complex (**C₇₈**) for coupling of amines (**242**) and alcohol (**243**) via dehydrogenation was studied. The reaction of amine and alcohol in toluene solvent for 24 hours at 110°C by using a catalyst (**C₇₈**) and NaH gave an amide (**244**) as the only product in excellent yields. The base is required as a promoter for this transformation although strong bases such as KOH, KOtBu, and NaH were found to be effective. The scope of the substrate was investigated under optimal conditions (1mol% catalyst (**C₇₈**), alcohol, amine, 5mol% NaH at 110°C in PhCH₃ for 24h). The electron-donating *p*-methoxybenzyl alcohol with benzylamine, *p*-methylbenzylamine, cyclohexylamine, and hexylamine generated good conversions of the respective amides (90-92%). A variety of amines were tolerated along with the benzyl alcohol and *p*-methylbenzyl alcohol resulting in moderate to excellent yields of respective amides (69-90%). The yields of electron-withdrawing *p*-fluorobenzyl alcohol and *p*-nitrobenzyl alcohol



Scheme 97 Synthesis of quinolines.



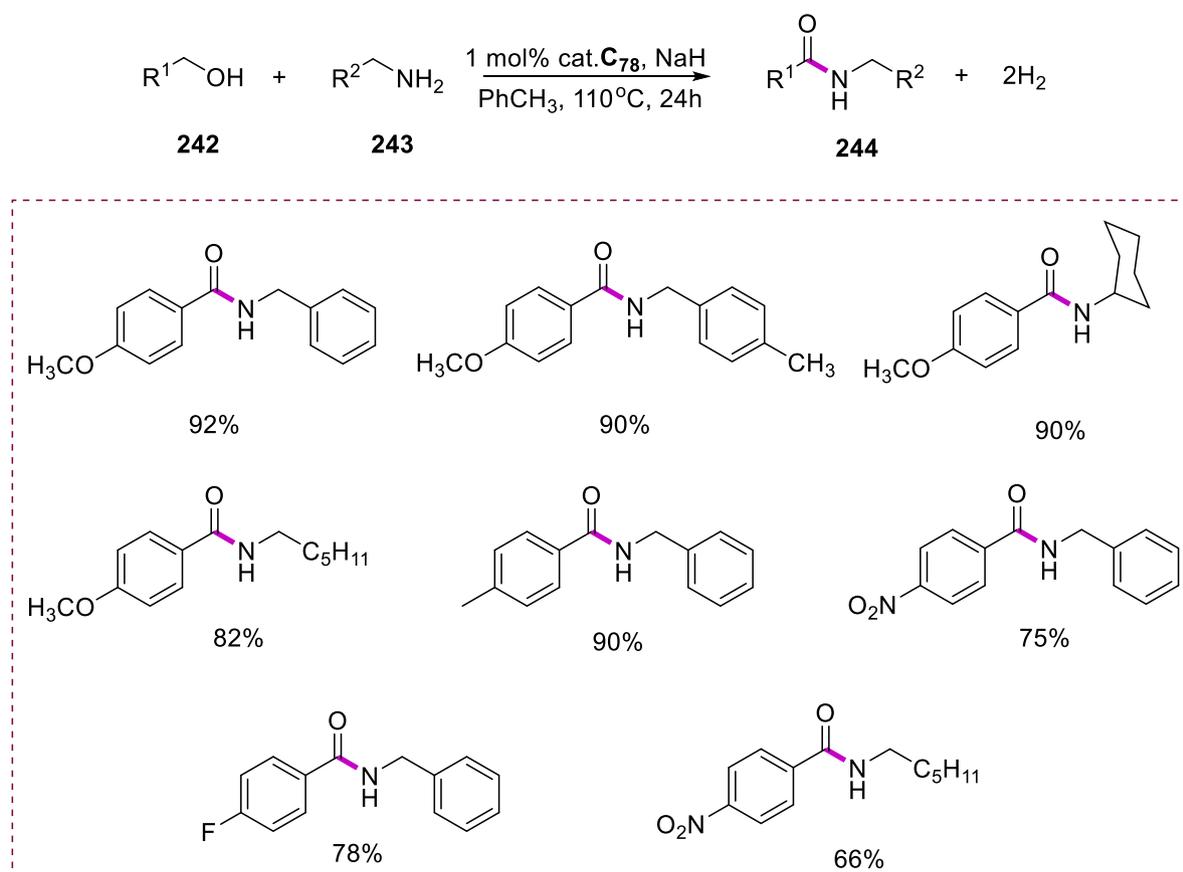
Scheme 98 Synthesis of Ru(II) NHC carbonyl complex.

were lower than those of electron-donating alcohols. The straight-chain alcohols such as hexanol and octanol when treated with hexylamine and benzylamine afforded fewer yields than benzyl alcohol (Scheme 99) (Saha et al., 2014).

7.4. Synthesis of ruthenium complexes [RuCl(*p*-cymene)(*i*Pr-bimy)(PPh₃)]PF₆ and [RuCl(*p*-cymene)(*Bn*-bimy)(PPh₃)]PF₆ and its application

The dehydrogenation of alcohols catalyzed by transition metals is used to make amides and amines, which are significant in

organic chemistry, medicinal chemistry, and biochemistry (Ricci, 2008b; Valeur and Bradley, 2009). Complexes with NHC (*N*-heterocyclic carbene) ligands are particularly effective in this reaction (Nordstrøm et al., 2008; Ghosh et al., 2009; Zhang et al., 2010; Makarov et al., 2012; Kim et al., 2015). Alcohols are less effective for amines as alkylating agents due to their low electrophilicity. However, utilizing transition metal complexes through borrowing hydrogen strategy makes the *N*-alkylation with alcohols potentially atom-efficient and safer process (Guillena et al., 2010; Fogler et al., 2011; Fernandez et al., 2012).



Scheme 99 Synthesis of amides.

The neutral $[\text{RuCl}_2(p\text{-cymene})(\text{bimy})]$ complexes (C_{79} and C_{80}) were treated with triphenyl phosphine and KPF_6 in acetone to produce ruthenium complexes $[\text{RuCl}(p\text{-cymene})(\text{iPr-bimy})(\text{PPh}_3)]\text{PF}_6$ (C_{81}) and $[\text{RuCl}(p\text{-cymene})(\text{Bn-bimy})(\text{PPh}_3)]\text{PF}_6$ (C_{82}). The required complexes (C_{81} and C_{82}) were obtained in good yields as yellow solids by chlorido displacement (97% for complex C_{81} and 94% for complex C_{82}). These complexes are soluble in polar aprotic solvents like DMF and DMSO, as well as MeOH, CH_3CN , and acetone, but in non-polar solvents like hexane, diethyl ether, and toluene, they are almost insoluble. Complexes C_{81} and C_{82} with the 1,3-dibenzyl benzimidazolin-2-ylidene ligand can catalyze both mono- and di-amination (*N*-alkylation) via dehydrogenation in the presence of simple amines with alcohols, resulting in a variety of secondary amines. The complex C_{81} has been shown to be effective and versatile catalyst in the *N*-alkylation reaction under mild conditions. Additionally, this complex has demonstrated a high level of tolerance for functional groups found in alcohol and amine moieties. (Scheme 100).

The production of *n*-alkylated secondary amines ($\mathbf{247}$) arises from the interaction of alcohols ($\mathbf{245}$) with amines ($\mathbf{246}$) by using a catalyst (C_{81}) and NaHCO_3 as a base. The required amines were produced in a modest yield after 24h without the use of an additional base at 120°C . The production of amines increased in the presence of NaHCO_3 and Na_2CO_3 , respectively. The catalytic performance was also improved by increasing the temperature in steps. Complex (C_{81}) can activate benzylic, and aliphatic alcohols in the

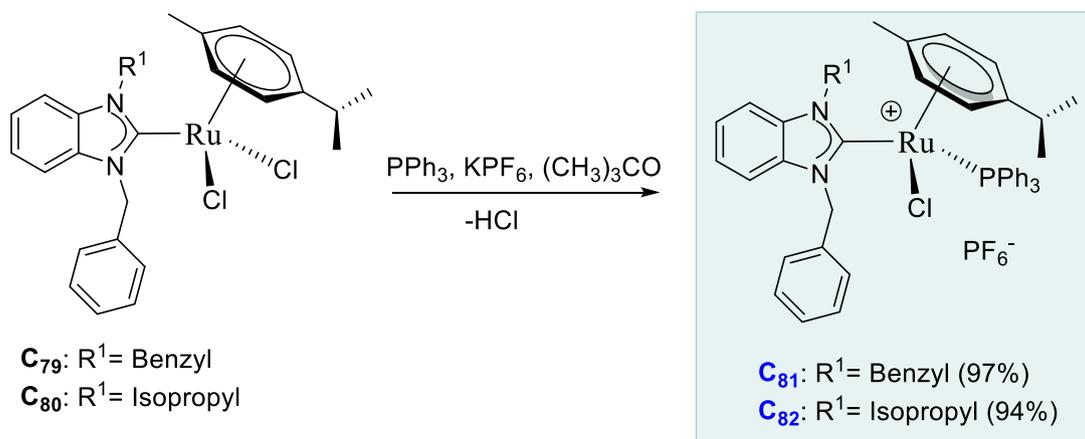
presence of NaHCO_3 and then couple with benzylamine to produce sec. amines in moderate to good yields. The alkylation of aniline derivatives with a variety of alcohols produced the appropriate amines in reasonable yields. In a polar system, a weaker base is responsible for proton transfer to start the amination pathway (Scheme 101) (Xie and Huynh, 2015).

7.5. Synthesis of ortho-metallated imidazolylidene-based Ru (II)-NHC complex and its application

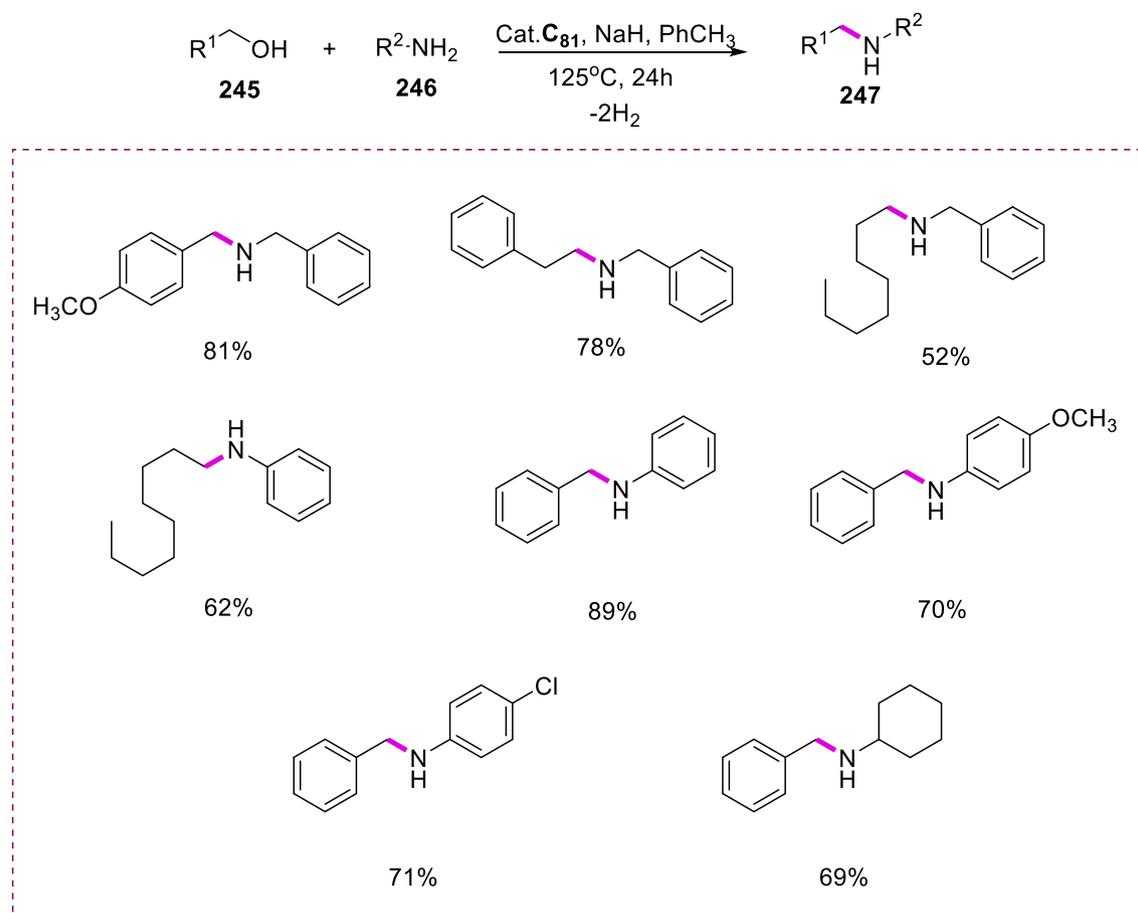
Transfer hydrogenation of carbonyl compounds is usually a less hazardous and more convenient process than direct hydrogenation through hydrogen gas and it can reduce a vast range of substrates (such as imines, nitriles, carbonyl groups, $\text{C}=\text{C}$ bonds, and so on), making it one of the most studied hydrogenation reactions (Nieto et al., 2011; Wang and Astruc, 2015). Ru(II)-NHC complexes are effective catalysts in a variety of important chemical reactions, including the transfer hydrogenation reaction (Daw et al., 2014).

The ortho-metallated Ru(II)-NHC complex (C_{83}) was produced in moderate yield (60.8%) by reacting imidazolium salt ($\mathbf{248}$) with $[(p\text{-cymene})\text{RuCl}_2]_2$ ($\mathbf{249}$) in the presence of Cs_2CO_3 as the base. This complex is found to be particularly efficient in the transfer hydrogenation of ketones even at minimal catalyst loading (Scheme 102).

The synthesis of corresponding alcohols ($\mathbf{249}$) arises from the catalytic hydrogenation of ketones ($\mathbf{250}$) and proceeds



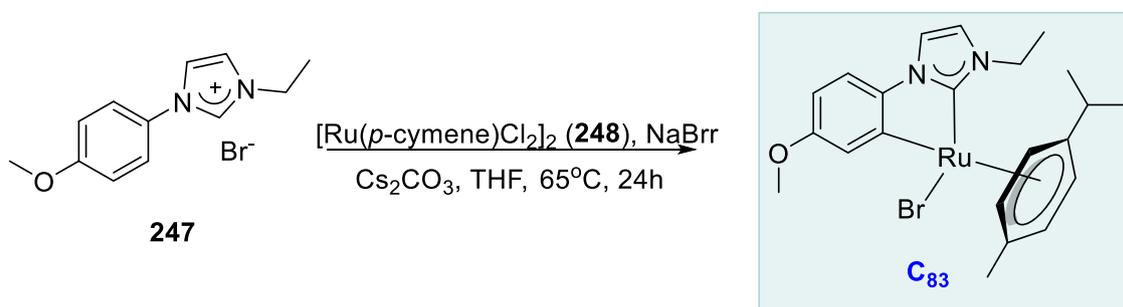
Scheme 100 Synthesis of ruthenium complexes [RuCl(*p*-cymene)(iPr-bimy)(PPh₃)]PF₆ and [RuCl(*p*-cymene)(Bn-bimy)(PPh₃)]PF₆.



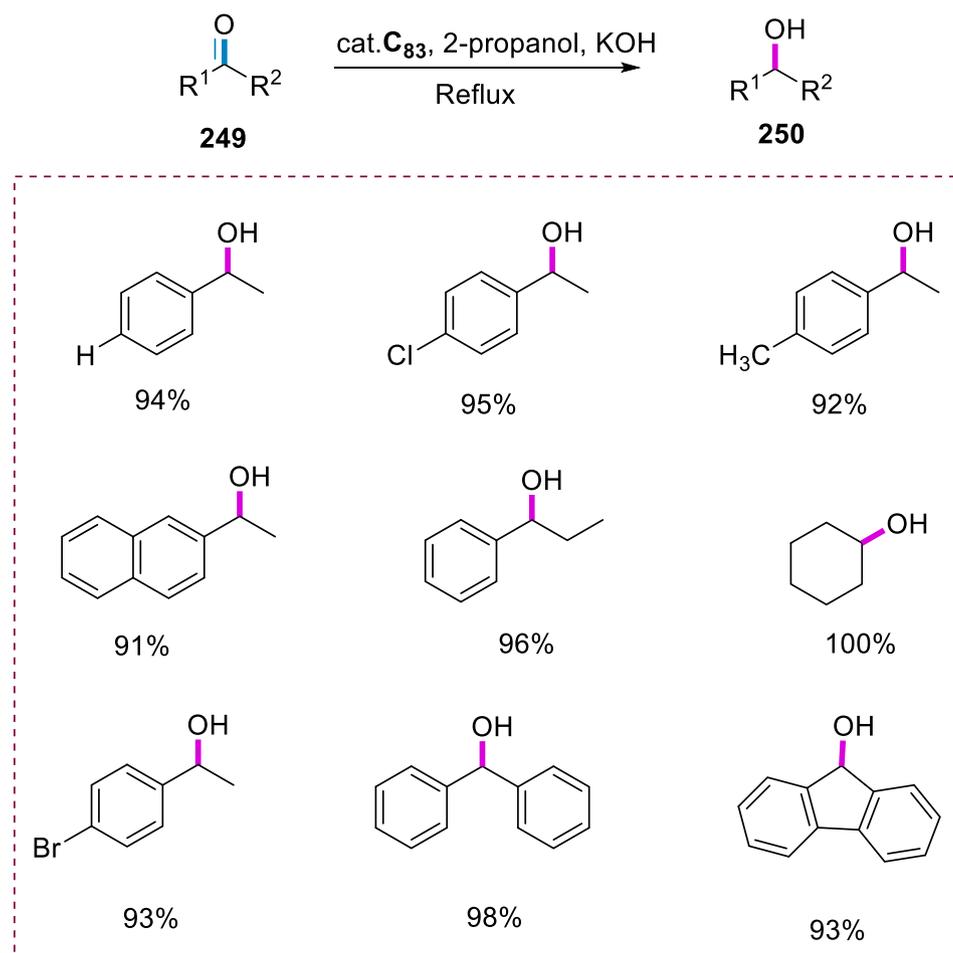
Scheme 101 *N*-alkylation of amines.

via Ru-complex (**C₈₃**) in the presence of KOH as a base and isopropanol as a hydrogen donor. When a para-methoxy substituent is present on the *N*-heterocyclic carbene ligand backbone, the catalytic activity of complex (**C₈₃**) is significantly increased while other parameters remain unchanged. This

reaction tolerates a variety of substrates including aliphatic (cyclic and acyclic) ketones, aromatic, and hetero-aromatic ketones, and secondary alcohols were obtained in excellent yields (89-98%). Although electron-donating carbonyl substrates provide a lower yield of corresponding products than



Scheme 102 Synthesis of ortho-metallated imidazolylidene-based Ru(II)-NHC complex.

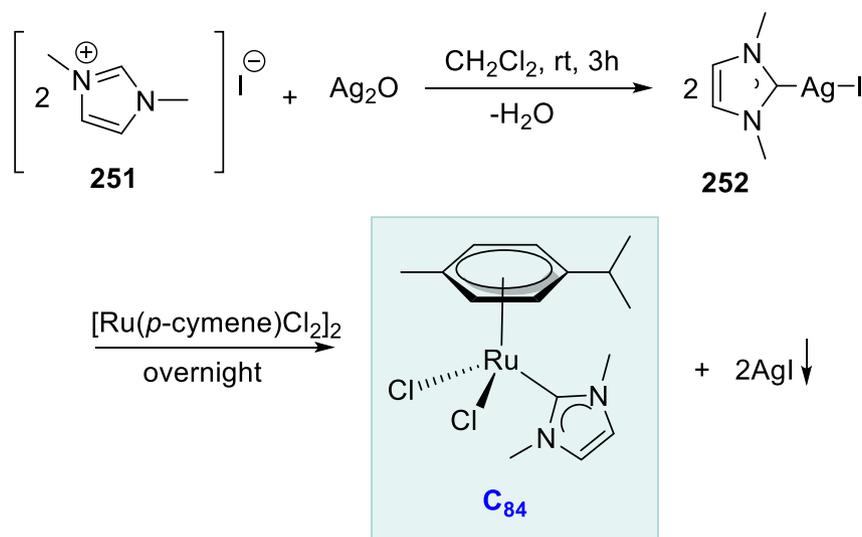


Scheme 103 Hydrogenation of ketones.

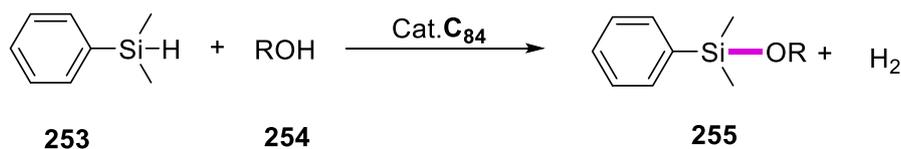
electron-withdrawing carbonyl substrates. This catalytic system performs well for both electron-withdrawing and electron-donating substituents. This may be related to the electrophilicity of carbonyl groups which is affected by the electron-withdrawing and electron-donating character of substituents (Scheme 103) (Hey et al., 2018).

7.6. Synthesis of ruthenium Schiff-base complexes of the type $[\text{Ru}(p\text{-cym})(\text{NHC})\text{Cl}_2]$ and its application

The catalytic reaction of alcohols with hydrosilanes is a simple way of producing pure molecular hydrogen. Complexes of the type $[\text{Ru}(p\text{-cym})(\text{NHC})\text{Cl}_2]$ are based on a less expensive metal



Scheme 104 Synthesis of Ru-complexes of the type [Ru(p-cym)(NHC)Cl₂].



Scheme 105 Dehydrogenative coupling of alcohols and silanes.

like ruthenium that can effectively catalyze the alcohol-silane coupling reaction at even lower temperatures and catalyst loading (Ventura-Espinosa et al., 2017; Ventura Espinosa et al., 2017).

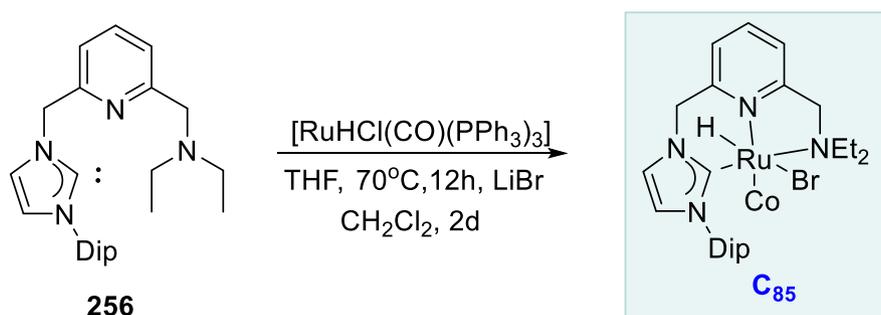
The silver carbene intermediate (252) is obtained by reacting the imidazolium salt (251) with silver oxide in dichloromethane. This intermediate was not separated and further reacts with the ruthenium dimer in situ to form the catalyst (C₈₄). The reaction should take 4h to complete and overnight stirring gives a higher yield of catalyst (C₈₄) (Scheme 104).

When Ru-NHC complex (C₈₄) is used as a catalyst, catalytic dehydrogenative coupling between alcohols (254) and hydrosilanes (253) produces silyl ethers (255) as a major product and hydrogen gas as a by-product at high rates. Model

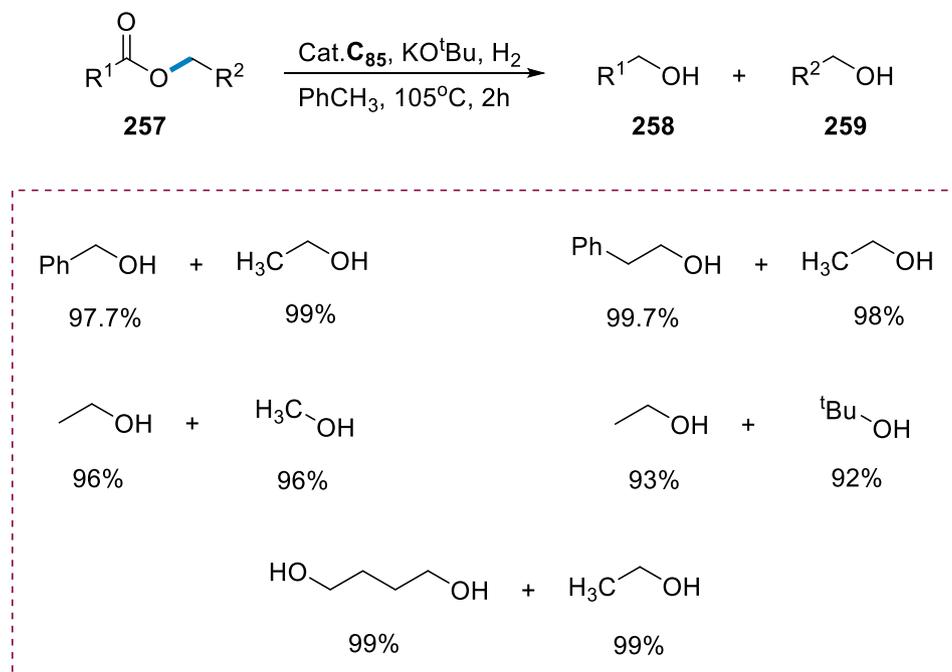
substrates include dimethylphenyl silane and methanol. The selective coupling of alcohols and hydrosilanes via dehydrogenation is mediated by Complex (C₈₄). The catalytic alcohol/silane coupling is versatile, allowing different hydrosilanes and alcohols to be used (Scheme 105) (Mollar-Cuni et al., 2021).

7.7. Synthesis of Ru-CNN hydride NHC complex and its application

The hydrogenation of esters to respective alcohols is one of the most important transformations in organic chemistry because it is used in the synthesis of valuable compounds. The process of catalytic hydrogenation is environmentally friendly



Scheme 106 Synthesis of ruthenium hydride NHC complex.



Scheme 107 Hydrogenation of esters.

(Gribble, 1998; Clarke, 2012). The ester hydrogenation reactions have mostly utilized Ru (II) complexes of NHCs (Sun et al., 2011; Morris, 2013; Filonenko et al., 2014; Le et al., 2018; Le et al., 2019). Because of their high sigma-donor and comparatively weak pi-acceptor properties, these complexes have a significant increase in catalytic activity.

The CNN-NHC ligand with electron-donating diethylamino and imidazolyl NHC groups as side-arms was synthesized in good yields by nucleophilic replacements using suitable imidazole, 2,6-bis-(bromomethyl)pyridine, and diethylamine. Then this ligand (**256**) on treatment with [RuHCl(CO)(PPh₃)₃] complex in the presence of lithium bromide yielded ruthenium hydride complex (**C₈₅**) (Scheme 106).

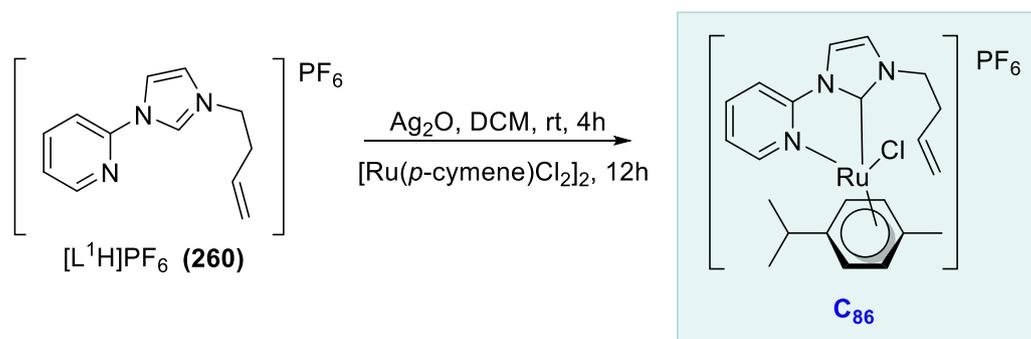
The Ru-CNN NHC complex (**C₈₅**) catalyzes the hydrogenation of inactivated esters (**257**) by using base (KHMDS or KOtBu) under mild conditions (5.3 bar H₂ and 105°C). The Ru(II) complex (**C₈₅**) displays excellent activity and high

TONs for various aliphatic and aromatic esters hydrogenation (yields up to 92%)(Scheme 107) (Pandey and Choudhury, 2020).

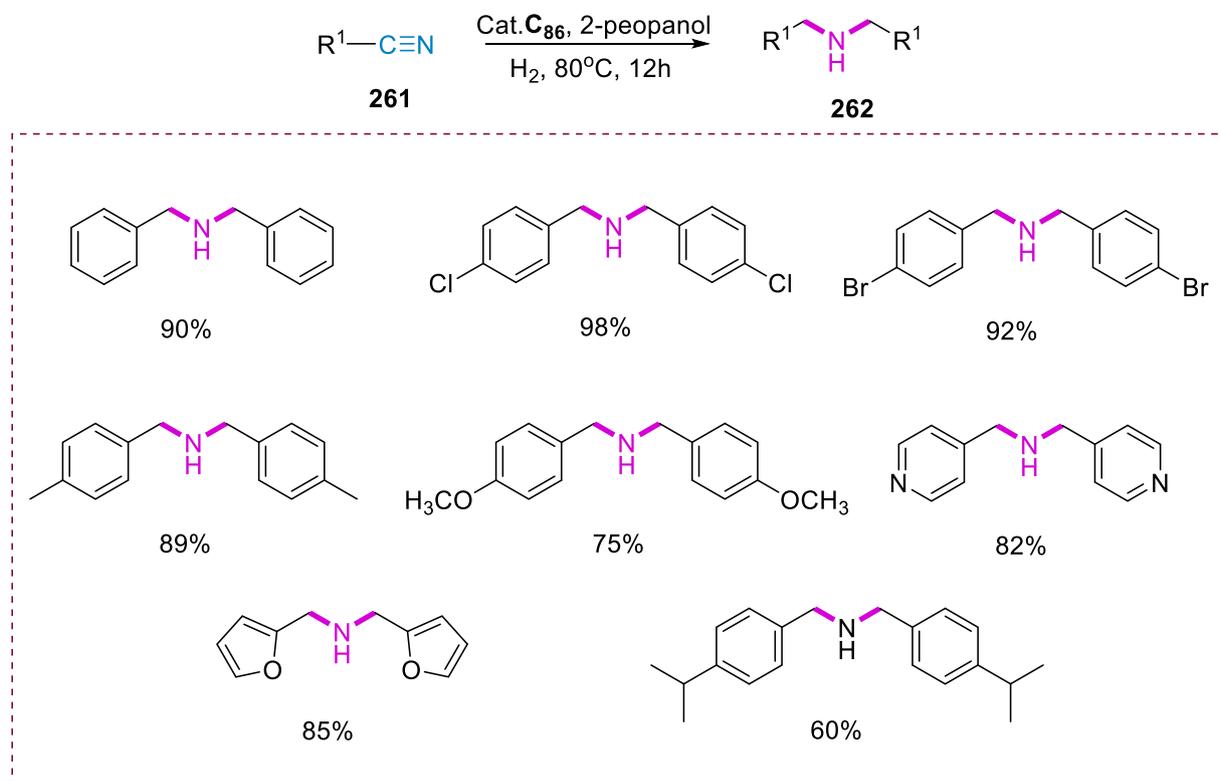
7.8. Synthesis of pyridyl-functionalized and alkenyl-tethered NHC Ru(II) complex and its application

Amines are one of the most significant class of compounds found in a vast range of natural products, medicines, polymers, and pigments, as well as agricultural chemicals (Lawrence, 2004). Metal *N*-heterocyclic carbene (NHC) complexes which are effective for hydrogenation processes, particularly for nitrile hydrogenation are being developed (Baskakov et al., 2007; Camm et al., 2007; Chen et al., 2007; Addis et al., 2009).

The [L1H]PF₆ (**260**) solution in dichloromethane (DCM) was treated with silver oxide and the resulting suspension



Scheme 108 Synthesis of pyridyl-functionalized and alkenyl-tethered NHC Ru(II) complex.



Scheme 109 Hydrogenation of nitriles.

was stirred for 4h at room temperature under an N_2 atmosphere. The $[\text{RuCl}_2(p\text{-cymene})_2]$ was then added to the solution after 4h, which was then stirred at room temperature for 12h resulting in the formation of $[\text{RuL}1(p\text{-cymene})\text{Cl}]\text{PF}_6$ (C_{86}) in high yield (85%). Complex (C_{86}) was found to be effective for the hydrogenation of nitriles (Scheme 108).

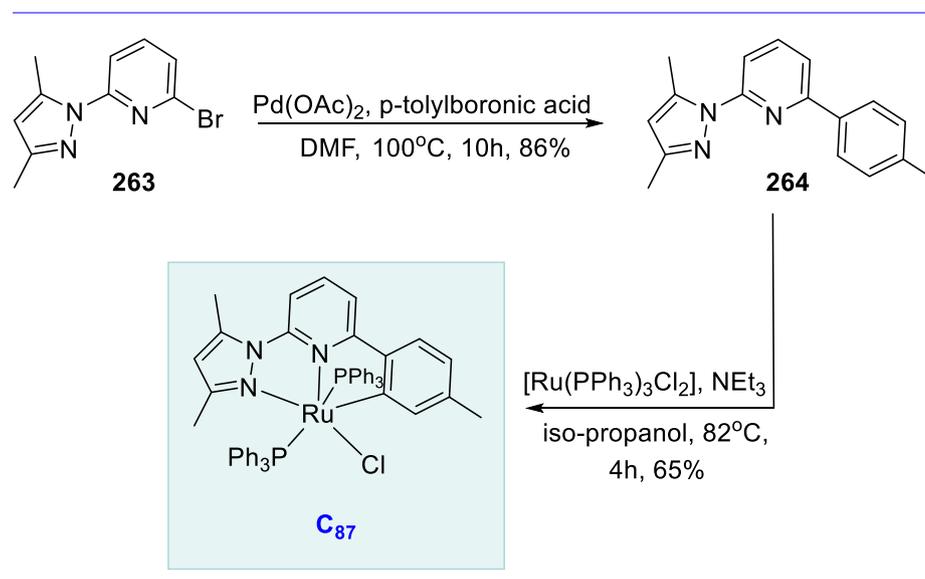
Catalyst (C_{86}) was found to be effective for the hydrogenation of nitriles (**261**) into secondary amines (**262**) in 90 percent conversion when used with hydrogen (60 bar) at 80°C in dry 2-propanol for 12h. The yield of the product was reduced at low temperature, H_2 pressure, and reaction time, as well as altering the solvent from 2-propanol to 1,4-dioxane, toluene, and THF. The Ru(II) complex (C_{86}) is an effective homogeneous catalyst for the coupling of nitriles via hydrogenation to produce symmetrical amines with high yields and selectivity. Aromatic nitriles having electron-deficient groups afforded higher yields than aromatic nitriles having electron-rich groups under optimal reaction conditions resulting in the formation of symmetrical secondary amines (Scheme 109) (Saha et al., 2016).

7.9. Synthesis of pyridyl-based pyrazolyl-NHC ruthenium complex and its application

The Oppenauer-type oxidation of alcohols in the absence of catalytic amounts of oxidants has been frequently used to synthesize carbonyl compounds. Beyond traditional reduction and oxidation reactions, Oppenauer-type dehydrogenative oxidation has proven to be a reliable synthetic protocol (Addis et al., 2009; Coleman et al., 2010; Moyer and Funk, 2010; Baratta et al., 2011).

The Pd-catalyzed Suzuki reaction of compound (**263**) with para-tolylboronic acid produced compound (**264**) in 86 percent yield. Ru(II) complex (C_{87}) was produced in 65 percent yield by the reaction of compound (**264**) and equimolar quantity of $[\text{Ru}(\text{PPh}_3)_3\text{Cl}_2]$ complex heated under reflux in isopropanol in the presence of trimethylamine. Air-stable red-brown crystals were obtained by recrystallizing complex (C_{87}) from toluene/n-hexane. The unsymmetrical environment around the metal center is thought to be capable of the increase in the catalytic activity of complex (C_{87}), implying that the combined steric and electronic effects due to two different coordinating donor arms at the 2,6 positions of the backbone of the pyridinyl group are essential for the high catalytic efficiency of complexes (Scheme 110).

Complex (C_{87}) was used as the catalyst in the presence of tBuOK as a base for the dehydrogenative oxidation of secondary alcohols (**265**) into ketones (**266**) in acetone under reflux. Secondary alcohols were selectively oxidized to their respective ketones within 1min to 3h. Most of the alcohol substrates give more than 97% conversion within 1–20 minutes which makes these complexes the best catalytic systems for this sort of reaction. The Ru-complex having an unsymmetrical NNC ligand exhibit excellent activity for the Oppenauer-type oxidation of alcohols. Using a greater catalyst loading and longer reaction duration, aliphatic alcohols were also oxidized to the appropriate ketones. The ortho substituents on the aromatic ring of substrates had a negative influence on the yield of reaction because of the increased steric hindrance (Scheme 111) (Du et al., 2012).



Scheme 110 Synthesis of pyridyl-based pyrazolyl-NHC ruthenium complex.

7.10. Synthesis of tri-nuclear Ru-NHC complex and its application

The potential of Ru mono, bi, tri, and multi-dentate NHC complexes in a variety of C-C coupling processes in synthetic chemistry has been studied (Colacino et al., 2007). Besides their industrial significance, group (XI) metal NHC chemistry is primarily concerned with the development of novel anti-cancer and antibiotics drugs (Patil et al., 2015).

The reaction of $[\text{Ru}_3(\text{CO})_{12}]$ (**267**) with methyl/1,3-Diisopropyl substituted six-membered NHC free NHC ligand (**268**) in the presence of THF under a nitrogen environment at ambient temperature results in the formation of corresponding trinuclear Ru complex (**C₈₈**) in good yields. The catalytic acylation of pyridine by Complex (**C₈₈**) was investigated (Scheme 112) (Ellul et al., 2018).

Complex (**C₈₈**) catalyzed the insertion of terminal alkene (**270**) and CO into the ortho C-H bond of pyridine (**269**) at high pressure (10 atm CO) for 16h at 150°C affording the primarily linear acylation products (**271** and **272**) in low yield. The activity of Complex (**C₈₈**) was lower than that of the beginning precursor $[\text{Ru}_3(\text{CO})_{12}]$ (Scheme 113) (Narayana et al., 2021).

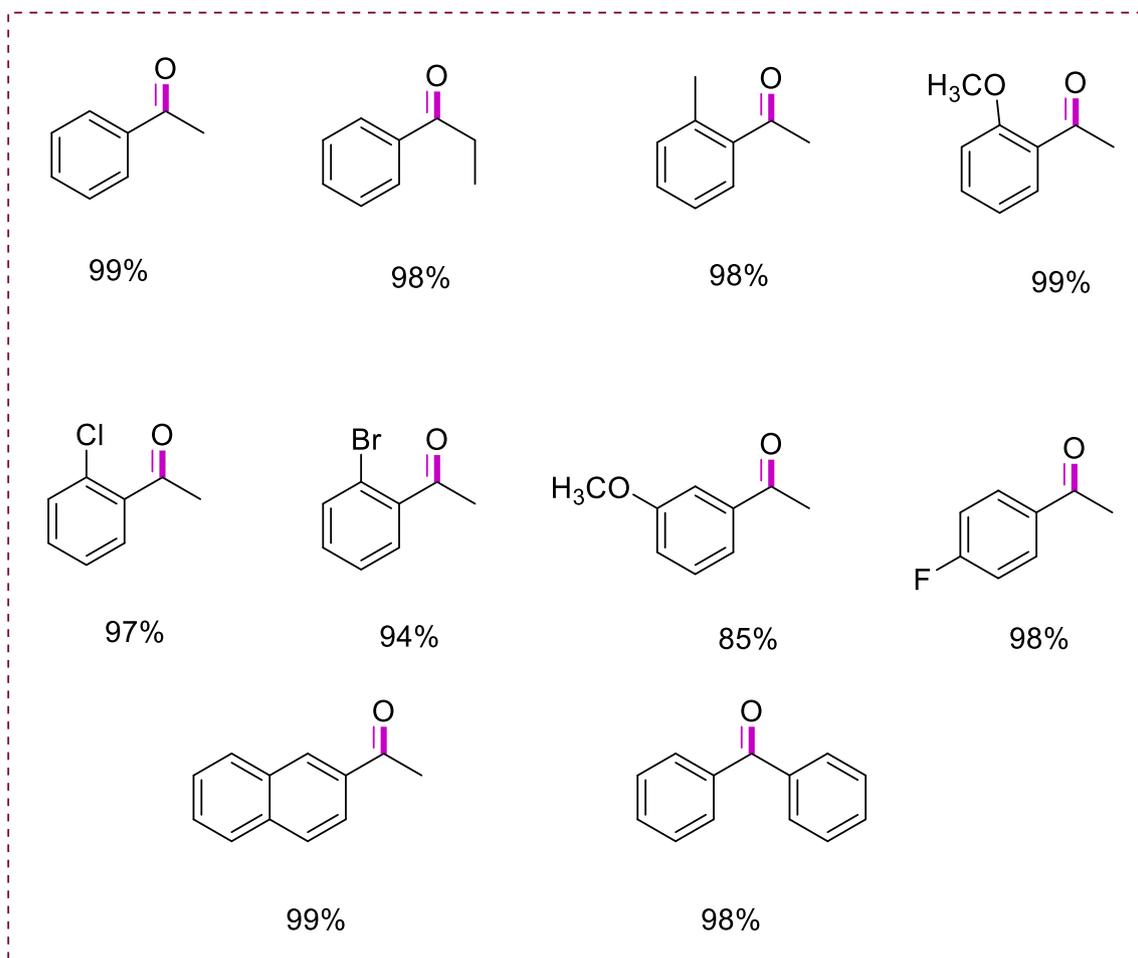
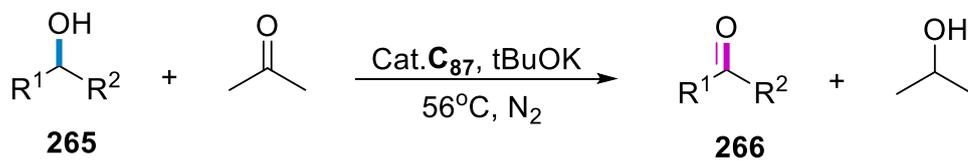
7.11. Synthesis of benzimidazole-based Ru-NHC complex and its application

Oxindole is a nitrogen-based heterocycle that can be found in a wide range of pharmaceuticals and naturally occurring compounds. The arylidene-oxindoles, in particular, are oxindole analogs and a preferred scaffold in medicinal chemistry due to their widespread use in a variety of physiologically active compounds as anti-cancer and anti-malarial drugs (Huber et al., 2010; Eissenstat et al., 2012; Lv et al., 2013; Ribeiro et al., 2014; Kaur et al., 2016). Chen et al. reported the direct amidation from amines and alcohols by using bidentate NHC-based Ru-complex and carbonate containing Ru-NHC

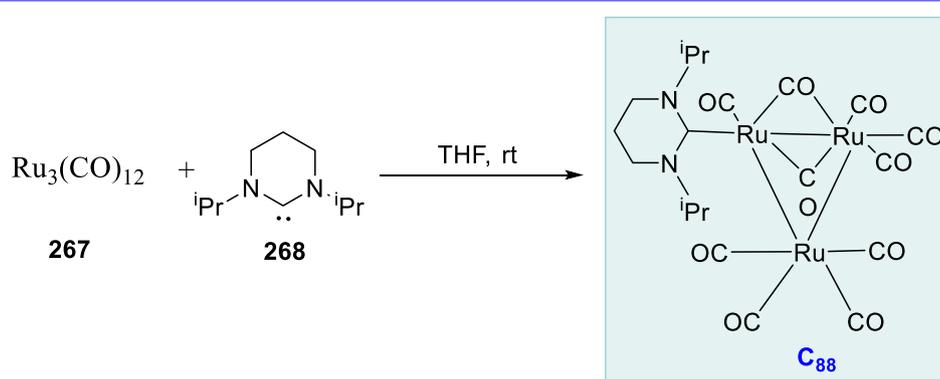
complex (Wu et al., 2019; Wang et al., 2020). The air-stable Ru *N*-heterocyclic carbene (Ru-NHC) was used as the catalyst for alpha-olefination of 2-oxindole (amide) by coupling of diaryl methanols via dehydrogenation. As a result, the formation of a C=C bond that yields derivatives of alpha-vinyl 2-oxindole is extremely useful in the synthesis of organic compounds (Dalpozzo et al., 2012; Gicquel et al., 2013; Zhang et al., 2016a, 2016b).

The Ru(II) complexes containing NHC ligands of the general type (arene)(NHC)Ru(II)X₂ (where X = halide) were investigated as antibacterial and anticancer agents. The two-step process was used to make the (*p*-cymene)(NHC)Ru(II)Cl₂ complex. The benzimidazole (**273**) was alkylated by using benzyl bromide in the first stage, yielding benzimidazolium bromide (**274**). The target compound (**C₈₉**) was produced in the second stage in a one-pot reaction of compound (**274**) with silver oxide and then transmetalation with $[(p\text{-cym})\text{RuCl}_2]_2$. Complex (**C₈₉**) is often employed for the α -olefination of 2-oxindole because of its high catalytic activity (Scheme 114) (Burmeister et al., 2021).

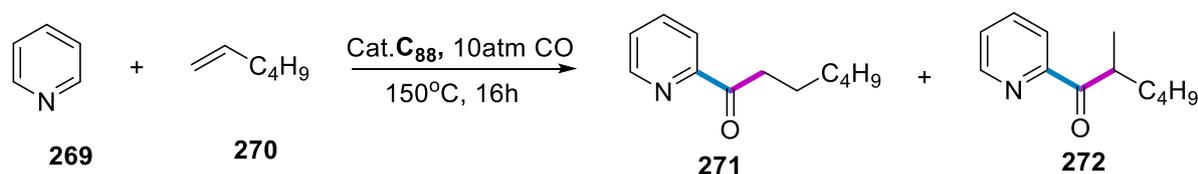
The Ru-NHC catalyst (**C₈₉**) is often utilized in the borrowing hydrogen method to synthesize bis-arylidene oxindole by alpha-olefination of 2-oxindole. Ru-NHC complex (**C₈₉**) is air-stable and used as a catalyst in the formation of oxindoles (amide) by dehydrogenative coupling of diaryl methanols (**276**) and 2-oxindole (**275**) generates various substituted derivatives of 3-(diphenylmethylene)indolin-2-one (**277**) in good yield and produces eco-friendly by-products like H₂ and H₂O. Furthermore, a controlled experiment was carried out with toluene and KOtBu, under heat at 140°C for 48 hours. This transformation was tolerate the number of functional groups involving the -CF₃ group, which resulted in the synthesis of 3-(phenyl(3-(trifluoromethyl)phenyl)indolin-2-one in 38 percent yield. Unfortunately, bis(4-fluorophenyl)methanol, bis(4-methoxyphenyl)methanol, and di-substituted diphenyl methanol derivatives were failed to give the expected products. This might be due to the strong nucleophilicity of the base, which



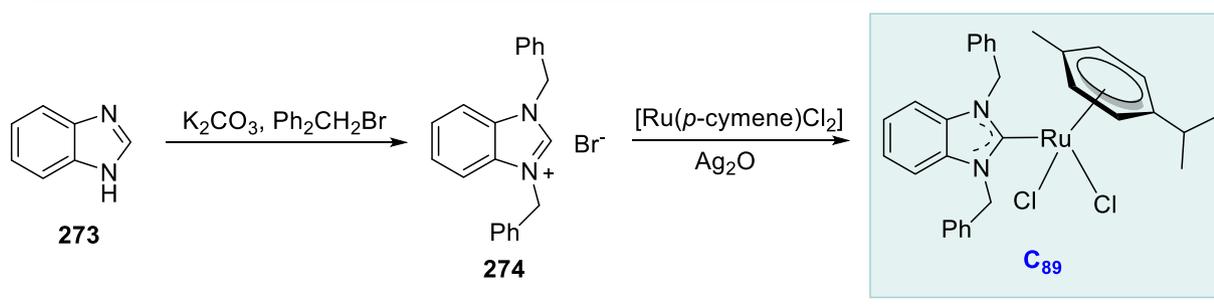
Scheme 111 Oxidation of alcohols.



Scheme 112 Synthesis of trinuclear Ru-NHC complex.



Scheme 113 Acylation of pyridine.



Scheme 114 Synthesis of benzimidazole-based Ru-NHC complex.

causes them to substitute the fluorine in the aryl ring. Intriguingly, the addition of Cs_2CO_3 (mild base) resulted in the formation of respective products in low yields respectively. In addition, 7-chloro-2-oxindole was reacted with a variety of diaryl methanols to give the corresponding compounds in a reasonable yield (Scheme 115) (Bisht et al., 2018).

7.12. Synthesis of imidazole-based Ru-NHC complex and its applications

One of the most fundamental transformations in synthetic chemistry is the formation of carboxylic acid from primary alcohol (Tojo and Fernández, 2007; Gunanathan and Milstein, 2013). Several ruthenium complexes are used as a catalyst to dehydrogenate the primary alcohol into the appropriate aldehyde. Chen et al. reported the bidentate Ru-NHC complexes for the coupling of alcohols via dehydrogenation into carboxylic acids (Wang et al., 2019; Wu et al., 2022). The dehydrogenation of primary alcohol can result in the formation of a carboxylic acid in the presence of water as a nucleophile (Gianetti et al., 2016).

The imidazole-based complexes have traditionally been made by transferring the free *N*-heterocyclic carbene ligand into $[\text{RuCl}_2(p\text{-cymene})]_2$. Carbene transfer has recently been made achievable through the reaction of 1,3-dialkylimidazolium chlorides (277) with Ag_2O in the presence of dichloromethane (DCM). The respective silver carbene is produced by this approach and then transmetallated in situ with $[\text{RuCl}_2(p\text{-cymene})]_2$ complex. Complex (C₉₀) was produced in a high-yields by this method (Scheme 116) (Dam et al., 2010).

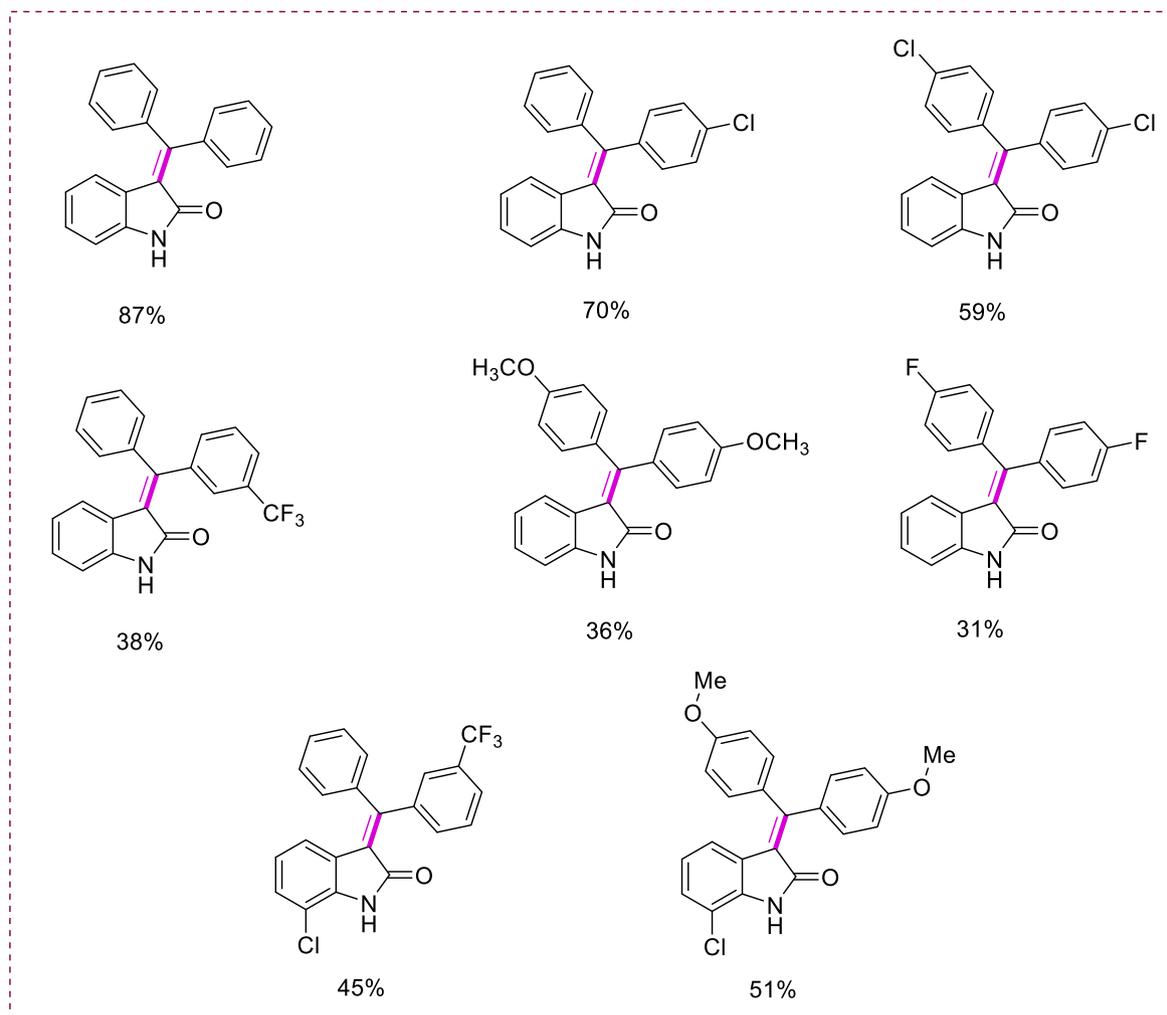
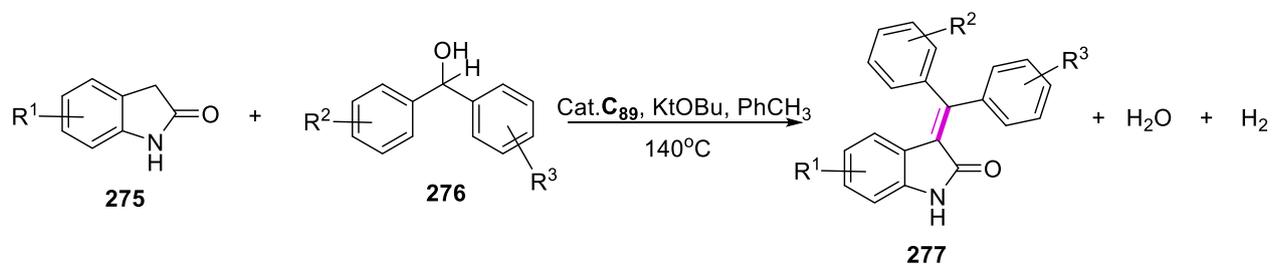
The corresponding carboxylic acid (279) was produced from alcohols (278) under optimal conditions, which required the complex (C₉₀), PCy_3 , in the presence of a stoichiometric quantity of KOH upon refluxing in toluene under an argon

flow. However, when using a higher quantity of KOH or lower catalyst loading, the yield of the reaction was reduced. The carboxylic acids are isolated easily using an organic solvent after being precipitated as salts of potassium and then transformed into corresponding acids with HCl. The number of para-substituted benzyl alcohols was transformed into benzoic acids. The oxidation of *p*-chloro and *p*-methylbenzyl alcohol went smoothly, producing high yields of carboxylic acids. The same reaction with *p*-iodo and *p*-bromobenzyl alcohol yielded slightly lower yields due to the competitive dehalogenation reaction of benzoic acid. The carboxylic acids were also obtained from *p*-trifluoromethyl and *p*-phenylbenzyl alcohol, though in a lower yield than the former (Scheme 117) (Santilli et al., 2016).

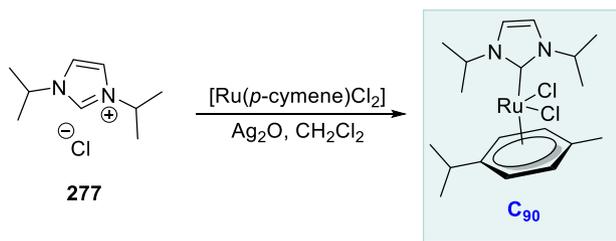
The number of aliphatic primary alcohols (280) was also transformed into their corresponding carboxylic acids (281) by using the Ru-complex (C₉₀), and because these aliphatic alcohols are more stable than benzylic substrates, an 18h reaction period was required to ensure complete conversion. Linear alcohols produced excellent yields, as were substituents at the third position. The yields of alcohols with substituents in the 2-position were slightly lower (Scheme 118).

7.13. Synthesis of imidazolyliidene-based untethered Ru-NHC complex and its applications

Amines are undeniably one of the most main classes of organic compounds, particularly because many of them are biologically active. A wide range of natural goods, agrochemicals, medicines, dyes, and pigments contain them (Larock, 1999; Lawrence, 2004; Ricci, 2008a; Ricci, 2008b). For reduction chemistry, Ru-based catalysts have been widely explored, particularly in asymmetric hydrogenation or transfer hydrogenation of imines. [206] Many ruthenium NHC complexes are catalytically active in the reduction of ketimines and aldimines.



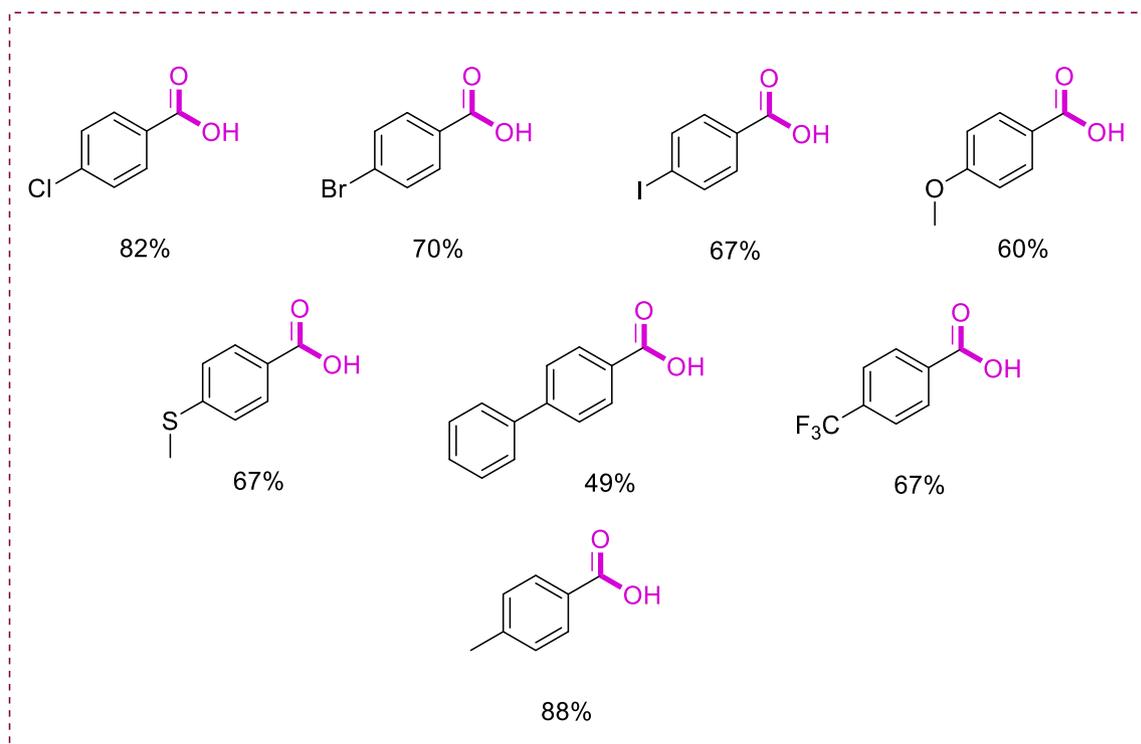
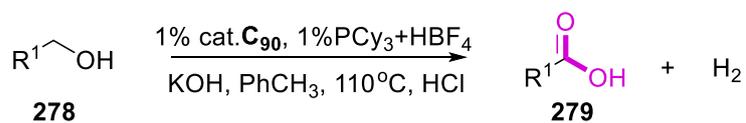
Scheme 115 Synthesis of arylidene oxindoles.



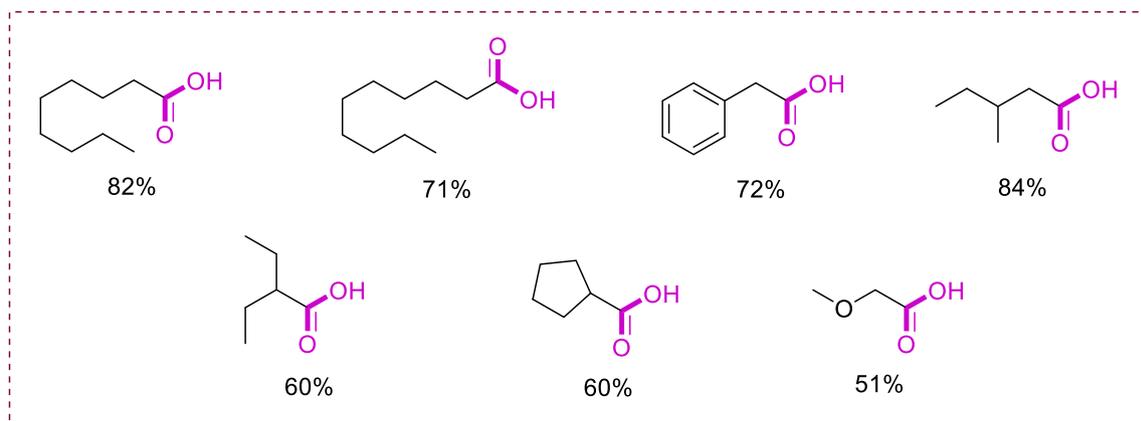
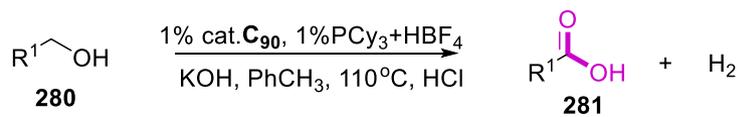
Scheme 116 Synthesis of imidazole-based Ru-NHC complex.

In the hydrogenation of imines, hydrosilanes are used as a reducing agent along with the Ru-NHC complexes. Aldimines might be converted to the appropriate secondary amine much faster than ketimines due to the steric crowd between the aryl or alkyl group on the ketimine, rather than the hydrogen on the aldimine substrate.

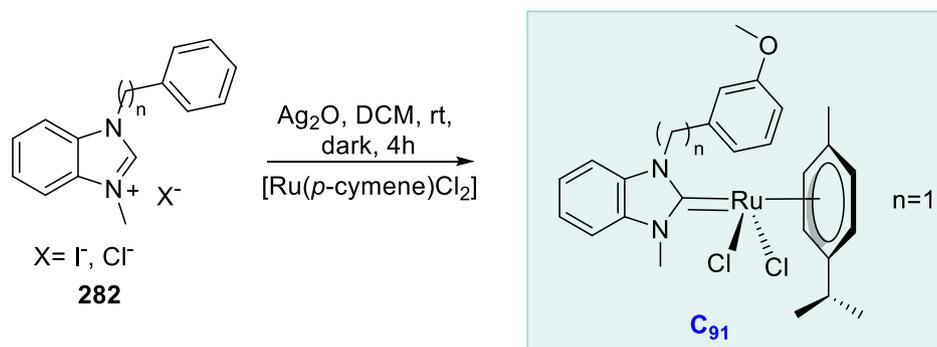
The Ru-NHC complex (C_{91}) was made by transferring the NHC ligand (282) from Ag-NHC produced in situ in the dark from the NHC ligand and silver oxide to Ru in the dimer of dichloro(*p*-cymene)ruthenium (II). The orange to red-colored crystalline solid of the Ru-NHC complex (C_{91}) was separated in good to excellent yield and these complexes are air-stable (Scheme 119) (Kathuria et al., 2020).



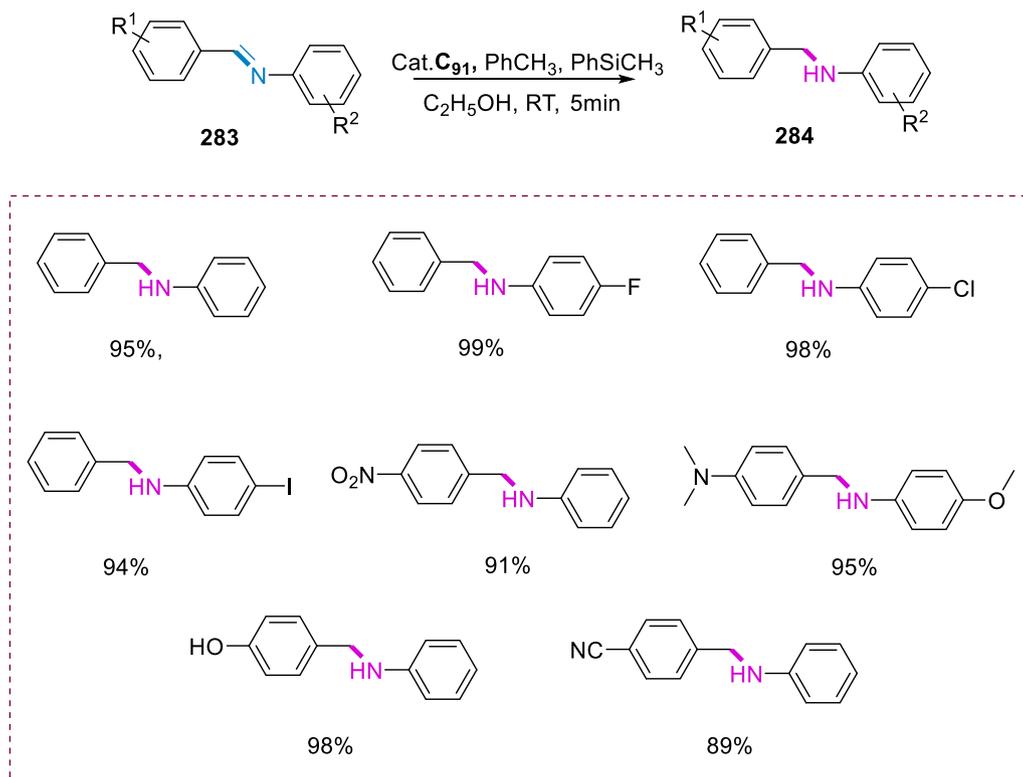
Scheme 117 Synthesis of carboxylic acid from aromatic alcohols.



Scheme 118 Synthesis of carboxylic acid from aliphatic alcohols.



Scheme 119 Synthesis of imidazolylidene-based untethered Ru-NHC complex.

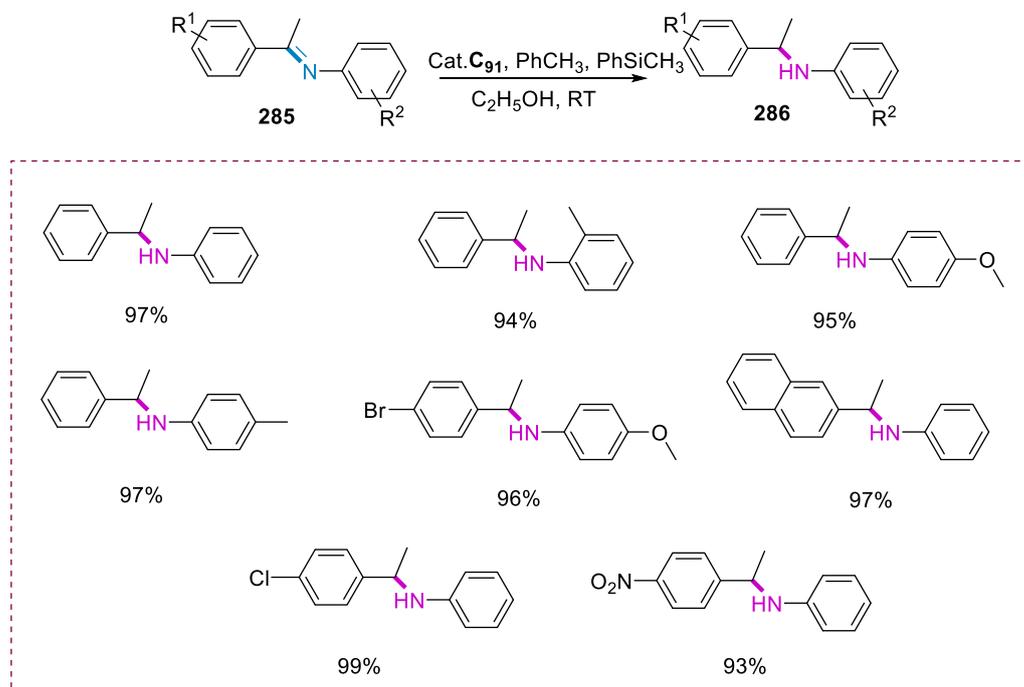


Scheme 120 Reduction of aldimines.

Aldimine (**283**) with PhSiH_3 in the presence of Ru-NHC catalyst (**C₉₁**) and ethanol at room temperature provides the secondary amines (**284**) in good yields. The complex *N*-methoxy was tested for the hydrogenation of a variety of aldimines with diverse electronic and steric properties. This transformation tolerates the presence of different functional groups on the substrate, such as halogens, $-\text{NO}_2$, $-\text{CN}$, $-\text{OH}$, $-\text{NMe}_2$, $-\text{CONH}_2$, and $-\text{COOMe}$. So, the vast range of aldimines may be efficiently reduced. These functionalities remained unaffected in the reaction, and the catalyst was not poisoned. Surprisingly, in addition to functional group tolerance, electron-deficient groups such as halide and nitro groups had

no adverse effect on reaction rate. The reaction rate was unchanged even by ortho substitution with CH_3 on the *N*-aryl group. The substrate with various electron-rich groups could also be hydrogenated even in a short reaction time. In an ester-containing imine substrate, a complete reduction of imine could be accomplished in 5 minutes without affecting the ester functionality. When the loading of catalyst was increased to 5mol%, full conversion was seen in 2h (**Scheme 120**).

Ketimines were reduced by using Ru-NHC complex (**C₉₁**) (*N*-mOMe). The reduction of the range of ketimines with various steric and electronic factors was investigated. Ketimines



(**285**) generate high yields of secondary amines (**286**) when reacting with PhSiH_3 in the presence of a Ru-NHC catalyst and ethanol at room temperature. The catalyst was able to efficiently reduce all of the ketimines tested, giving nearly quantitative yields. Unlike aldimines, ketimines acquired a longer reaction time due to steric and electronic effects. The reaction of *N*-1-diphenylethanamine with an ortho-substituent, for example, took 120 minutes to complete. It was also difficult to reduce a ketimine produced from a cyclic amine. The reaction occurred at a slower rate when a nitro substituent was present on the aryl ring of the imine, and full conversion was detected after 120 minutes. The desirable selectivity was not lost despite the lower reactivity, and the nitro group was unaffected (Scheme 121) (Kathuria and Samuelson, 2020).

8. Future perspective and conclusion

In the case of ruthenium, researchers can still find lots of opportunities in the field of Carbon-heteroatom coupling reactions, which appear to be in their infancy. Many advances in Carbon-Carbon couplings are still feasible, particularly in the less known activation of $\text{Csp}_3\text{-H}$ bonds and couplings with unsaturated small molecules, allenes, or allyl groups. Furthermore, the methods by which these reactions occur are poorly understood: astonishingly, very identical reactions can occur via diverse mechanisms, as demonstrated in cases where intermediates could be identified.

Similarly, molecular modeling of processes has largely been neglected. The diverse photocatalytic activity of ruthenium is not covered here, although it is unquestionably an intriguing field. As a result, this is an exciting field with lots of fresh discoveries and discoveries to come. Ruthenium quickly forms coordination complexes, which have uses in medicine, catalysis, biology, nanoscience, redox, and photoactive materials, among other domains. Ru is utilized in biomedical disciplines for diagnosis and treatment. In comparison to current Pt-based anticancer medications, a variety of Ru complexes have demonstrated enhanced anticancer characteristics, including increased

selectivity for cancer cells and reduced toxicity against normal cells. The synthesis of ruthenium complexes, as well as their catalytic and biological uses, are briefly discussed in this article. Further study is likely to lead to even more practical applications of this miracle element in the future years.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

We strongly acknowledge the synthetic organic chemistry laboratory, Department of Chemistry, Government College University Faisalabad, Punjab, Pakistan for their continuous support.

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