1. Introduction

1.1. Scope and Organization of Review

Heterocycles constitute the largest and most diverse family of organic compounds and have been mostly identified by their profound application in synthetic biology and materials science.\[^{[1]}\] The extent to which they can be utilized in these endeavors depends on the selective and efficient synthetic methods for their synthesis from simple, and abundant starting materials. Hence, the development of an efficient strategy for the construction of heterocycles is a key motivation in contemporary science.

In the past few decades, the transition-metal-catalyzed hydrogen-transfer strategy has attracted much interest from the synthetic and organometallic community.\[^{[2]}\] Transfer of H\(_2\) plays a crucial role in activating the substrate for further transformation through C–X (C, N, and O) bond-forming annulations with the liberation of H\(_2\)O and H\(_2\). The hydrogen-transfer strategy involves utilization of the initially extracted hydrogen gas for the hydrogenation of an intermediate (derived from the reaction of the dehydrogenated precursor with nucleophilic partners) in the final step of the reaction, thus leading to the net release of water as the only by-product.\[^{[2g]}\] Despite reports on several transition-metal-catalyzed (Cu, Ni, Zn, Pd, etc.) hydrogen-transfer reactions,\[^{[3]}\] Ru-, Ir-, and rare examples of Fe-based catalytic systems have shown excellent activity and selectivity in hydrogen-transfer annulations to deliver heterocyclic compounds. In 2010, Yamaguchi et al. reported a review article focusing on the construction of nitrogen-based heterocycles by transition-metal-catalyzed hydrogen-transfer annulations.\[^{[4]}\] In recent years, this field has evolved in terms of catalyst and ligand design, and reaction conditions, thus taking the place of conventional synthetic processes and receiving an overwhelming amount of attention. In this respect, there is need for a review article focused on the potential of catalytic hydrogen-transfer annulation strategies for the formation of heterocyclic scaffolds. Herein we highlight recent advancements in hydrogen-transfer annulations of alcohols with various nucleophilic partners, thus leading to the formation of heterocyclic scaffolds. This review material is organized into four different categories: a) N-alkylation of amines by alcohols, b) dehydrogenative amide formation from amines and alcohols, c) oxidative cyclization of alcohols, and d) annulation of unsaturated systems.

1.2. N-Alkylation of Amines by Alcohols

Catalytic N-alkylation of amines is a promising atom-economical and eco-benign approach for the selective con-
Amines

Dehydrogenative Amide Formation from Alcohols and Amines

The construction of amide/peptide bonds is one of the most important and valuable processes in synthetic organic chemistry since it plays a significant role in organic and biological chemistry. Conventional methods for the construction of an amide bond are mostly based on the activation of acid derivatives or acid/base-catalyzed rearrangement reactions. Although several methods for the construction of an amide bond have been reported, stoichiometric amounts of reagents are usually required and equimolar amounts of by-products are formed as waste. Initially, the transition-metal-catalyzed hydrogen-transfer methodology was developed for the synthesis of amides by the reaction of an alcohol and an amine in the presence of an equimolar amount of a hydrogen acceptor as an additive. Further development of transition-metal catalysts has resulted in acceptorless dehydrogenative amide formation with the liberation of H$_2$ gas as a by-product, thus providing an eco-benign and atom-economical method. The liberation of H$_2$ gas favors the thermodynamic equilibrium towards amide formation. The strategy is illustrated in Figure 2. The initial catalytic oxidation of an alcohol to an aldehyde and subsequent reaction with an amine produces a hemiaminal intermediate which is further oxidized to an amide with the liberation of H$_3$. The hemiaminal oxidation depends on the nature of the catalyst, ligand, and substrate. Intra- and intermolecular annulations of amino alcohol derivatives afford five-, six-, and seven-membered lactams.

1.3. Dehydrogenative Amide Formation from Alcohols and Amines

Figure 1. N-alkylation of amines by alcohols. TM = transition metal.
1.4. Oxidative Cyclization of Alcohols

Transition-metal-catalyzed dehydrogenative coupling of alcohols with various nucleophilic partners has resulted in the formation of C–X (C, N, and O) bonds with the liberation of H₂ and H₂O as by-products (Figure 3). Inter- and intra-molecular hydrogen-transfer annihilations of alcohols with various coupling partners enable the formation of functionalized saturated and aromatic heterocyclic compounds. This methodology has provided direct and rapid access to a variety of heterocyclic frameworks.

1.5. Annulation of Unsaturated Systems (Alkenes and Alkynes)

Unsaturated systems such as alkenes and alkynes are important building blocks in the chemical sciences. Their utility in organic synthesis has increased because of the development of newer synthetic methodologies based on transition-metal catalysts. Transition-metal-catalyzed hydrogen-transfer annihilations of these building blocks provide novel heterocyclic frameworks.

2. Synthesis of N-Heterocycles

Nitrogen-containing heterocycles are omnipresent in nature and biologically active compounds, including nucleobases within RNA, DNA, nucleotides, nucleosides, and haemoglobin. They also have applications in a variety of fields such as agrochemicals and pharmaceuticals, as well as in the preparation of foods, dyes, detergents, and surfactants. Hence, there is a plethora of methods for the preparation of novel nitrogen-based heterocycles for various applications. Transition-metal-catalyzed hydrogen-transfer annihilations have provided a platform to synthesize the basic skeletons for complex nitrogen-containing heterocyclic compounds in a single operation, thus enabling environmentally benign and efficient protocols.

2.1. Annulation by N-Alkylation of Amines by Alcohols

Saturated nitrogen-containing heterocyclic scaffolds are found in many natural products and biologically important compounds. The first example of the N-alkylation of an amine by an alcohol through a hydrogen-transfer annulation was reported by Grigg et al. in 1981. Thus pyrrolidines were formed by the intramolecular reaction of N-substituted 4-aminobutan-1-ols in the presence of 5 mol % [RhH(PPh₃)₄] as the catalyst in boiling 1,4-dioxane. The cascade reaction consists of dehydrogenative oxidation of the alcohol to an aldehyde, imine formation with an amine, and hydrogénative reduction of the imine to afford the N-substituted pyrrolidines 1a and 1b in 56 and 82 % yields, respectively [Eq. (1)]. Similar catalytic conditions were used to synthesize 1b by the amination of butane-1,4-diol with benzylamine in a ratio of 10:1 to yield 1b in 31 % [Eq. (2)].

Direct coupling of a diol with an amine through a borrowing-hydrogen strategy is the most promising protocol for the construction of N-heterocyclic compounds since diol derivatives can be easily accessed. [Ru(p-cymene)Cl₂]₂ combined with the bidendate DPEphos ligand provided access to saturated five-, six-, and seven-membered N-heterocyclic compounds by the N-alkylation of diols with amines [Eq. (3); DPEphos = bis(2-diphenylphosphinophenyl)ether]. Thus, 1,4-butanediol reacted with various anilines and aliphatic amines to provide N-substituted pyrrolidines in the presence of trimethylamine as an additive in refluxing toluene. Other diols such as 1,5-pentanediol and 1,6-hexanediol were also converted into the corresponding N-substituted piperidine and azepane derivatives under similar catalytic conditions. Significantly, Enyong et al. used the simple, inexpensive, and readily accessible (S)-2-hydroxy-N,3-diphenylpropanamide ligand in combination with [[Ru(p-cymene)Cl₂]₂ for the N-alkylation of diols with aliphatic amines under mild conditions.

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Figure 2. Dehydrogenative amide formation from alcohols and amines.

Figure 3. Dehydrogenative coupling of alcohols with nucleophiles.
reaction conditions where the diol acts as both a substrate and reaction medium, thus affording N-alkylated pyrrolidines and piperidines in 99% yields [Eq. (4); M.S. = molecular sieves].

The same ruthenium complex was used along with Xanthphos for the construction of the benzodiazepine core, which has many applications in medicinal chemistry, through consecutive hydrogen-borrowing steps using 2-aminobenzyl-alcohols and 1,2-amino alcohols (Scheme 1). Based on the identification of the intermediates 6 and 7 in the reaction mixture, the tandem reaction starts with the oxidation of the more reactive benzyl alcohol to an aldehyde through a borrowing-hydrogen process. Subsequent imine formation with the more reactive 1,2-amino alcohol leads to the N-alkylation of the benzyl alcohol. Then intramolecular N-alkylation of the alcohol with an aromatic amine affords the benzodiazepine.

Recently, Krišč and co-workers reported a method for the synthesis of C2-substituted pyrrolidines (14) through hydrogen-transfer hydroaminoalkylation of amino alcohols with dienes (Scheme 2). The reaction proceeds with complete branch selectivity and good to excellent levels of anti-diastereoselectivity. Optimization of the reaction conditions and catalyst identified in situ generated catalysts, derived from [HClRu(CO)(PPh₃)₃] and various phosphine ligands, for delivery of 2-substituted pyrrolidines in high yield and with maximum diastereoselectivity. Mechanistically, alcohol dehydrogenation triggers generation of an electrophilic imine, 3,4-dihydro-2H-pyrrole (9), and ruthenium hydride. The latter undergoes hydrometalation with the diene to form the nucleophilically less-stable disubstituted π-allylruthenium complex 10. The complex 10 undergoes reversible isomerization to form the more-stable isomeric monosubstituted π-allylruthenium complex 11 which is involved in imine addition via the (E)-π-allylruthenium haptomer to afford C2-substituted pyrrolidines. The reversibility of the hydrometallation step was studied for the coupling reaction of a deuterated amino alcohol [HOCD₂(CH₂)₃NH₂] with butadiene under standard reaction conditions. Significantly, deuterium incorporation was observed at all vinylic positions, allyl positions, and in the methyl group (R = H) of the product, thus confirming the reversibility of the hydrometallation step. Complete retention of deuterium (>95) at the methine position adjacent to the nitrogen atom confirmed the non-reversibility of alcohol dehydrogenation for imine formation. The intermediate 12 was proposed for the anti-diastereoselectivity of the product.

Fujita and co-workers developed the first iridium-catalyzed intramolecular annulation reaction of 3-(2-aminophenyl)propanol to yield 1,2,3,4-tetrahydroisoquinolines in moderate to high yields. The reaction proceeded by an initial catalytic dehydrogenative oxidation of the alcohol by using 2 mol% of [Cp*IrCl₂]₂ as the catalyst. Aromatic substrates having different substituents were converted into the corresponding 1,2,3,4-tetrahydroquinolines in moderate to excellent yields and 2,3,4,5-tetrahydro-1-benzazepine was also synthesized from 4-(2-aminophenyl)butanol using the same iridium catalyst [Eq. (5); Cp* = C₅Me₅]. The success of the Cp*Ir complex was extended to the synthesis of piperazines from 1,2-diamines and 1,2-diols by using an intermolecular borrowing-hydrogen N-alkylation strategy with a weak base, such as NaHCO₃, as an additive, in either water or toluene [Eq. (6)]. Additionally, piperazine (17) formation was also derived from a primary benzyl amine and 1,2-diol through the

\[ R^1\text{NH} + HO\text{R}^2 \rightarrow R^1\text{NHR}^2 \]

\[ \text{[Cp*IrCl₂]}_2 (5 \text{ mol %) \quad K_2CO_3 (10 \text{ mol %) \quad toluene, 111 °C \quad n = 1.2} \]

\[ 15 (54-96 \%) \]

Scheme 2. Synthesis of C2-substituted pyrrolidines by hydroaminoalkylation of amino alcohols with dienes. DMAP = 4-(N,N-dimethylamino)pyridine, dCypp = 1,3-bis(dicyclohexylphosphino)propane, Ts = 4-toluenesulfonyl. 

\[ \text{HCl} \quad \text{RuCl₃}(PPPh₃)₂ \quad (5 \text{ mol %) \quad } \text{NaHCO}_₃ \quad (5 \text{ mol %) \quad toluene or water \quad ∆, 17 h} \]

\[ 16 (54-100 \%) \]
formation of four new C–N bonds resulting from a hydrogen-transfer annulation using neat conditions at 160 °C [Eq. (7)].\textsuperscript{18,19}

\[
\text{2 BnNH}_2 + \text{2 HO}_2 \xrightarrow{\text{160 °C, 6 h}} \text{N}_2 \text{N}^\bullet \text{Bn} \quad (17 \text{ (94 %)})
\]

Impressed by the catalytic performance of the Cp*Ir complex in hydrogen-transfer N-alkylations, new ionic and water-soluble Cp*Ir complexes having an amine ligand were synthesized for the N-alkylation of alcohols in aqueous medium. Notably, the 1,5,9-nonanetriol was successfully transformed into the N-bridged heterocycle quinolizidine 19 using the water-soluble 18 as a catalyst and aqueous ammonia as the nitrogen source [Eq. (8)].\textsuperscript{20} The application of 18 was extended to the annulation reaction of diols with amines in water and open to air. Thus, the reaction of benzyl amine with 1,4-butanediol, 1,5-pentanediol, and 1,6-hexanediol provided the five-, six-, and seven-membered heterocyclic compounds (20), respectively, in good yields [Eq. (9)]. Furthermore, N-benzyl morpholine was also derived successfully with the aid of diethylene glycol as the diol precursor.\textsuperscript{21}

\[
\begin{align*}
\text{R NH}_2 & + \text{HO}_2 \xrightarrow{\text{H}_2\text{O}, \text{reflux, 24 h}} \text{R NH}_2 \text{N}^\bullet \text{Ph} \quad (\text{18 (1–3 mol %)}; \text{140 °C, 24 h} \text{under air}) \\
\text{Ph NH}_2 & + \text{HO}_2 \xrightarrow{\text{H}_2\text{O}, \text{reflux, 24 h}} \text{Ph NH}_2 \text{N}^\bullet \text{Ph} \quad (\text{20 (74–94 %)})
\end{align*}
\]

Three-component tandem reactions for the construction of C3-functionlized piperidines were developed and employed easily accessible anilines, diols, and aldehydes and phosphanesulfonate-chelated iridium complex 21 (Scheme 3). The key step is the \textit{endo} dehydrogenation leading to C3-functionalization of piperidines (26). The overall reaction involves double N-alkylation of an aniline with a diol and subsequent \textit{endo} dehydrogenation of piperidine, thus enabling a highly regioselective C3-functionalization process. When this three-component reaction is run in the presence of the ruthenium complex 22 the N-alkylated compound 23 is the major product. Other commercially available catalysts such as \{[Ru(p-cymene)Cl\textsubscript{2}]\} and \{[Cp*IrCl\textsubscript{2}]\} were not effective for the above reaction. Based on the overall catalytic cycle, 21 is the sole catalyst for the N- and C-alkylation process which results from two C–N and one C–C bond-forming hydrogen transfer in a single operation. Substituted diols were also successfully converted into the corresponding piperidine derivatives with high regio- and diastereoselective control.\textsuperscript{22}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure3.png}
\caption{Scheme 3. Three-component tandem reaction for C3-functionalized piperidines. CSA = d-(+)-camphor sulfonic acid.}
\end{figure}

\textbf{2.2. Annulation by Dehydrogenative Amide Formation}

Benzo-fused lactams, such as oxindoles, dihydroquinoliones, and tetrahydrobenzazepinones are found in many natural products and drug candidates. Eco-benign and atom-economical methods for the synthesis of such heterocyclic compounds are highly desirable. Fujita and co-workers reported a Cp*-based rhodium complex in acetone as a selective catalyst for the synthesis of benzo-fused five-, six-, and seven-membered lactams (27), through a dehydrogenative amide formation reaction [Eq. (10)]. The change to other solvents, such as toluene, resulted in the formation of 1,2,3,4-tetrahydroisoquinoline (15) from 3-(2-aminophenyl)-1-propanol, thus confirming that acetone plays a key role as a hydrogen acceptor. A five-membered benzo-fused lactam, that is, oxindoles, were synthesized in moderate to excellent yields with lower catalytic loading (3 mol %) in acetone under reflux for 8 hours.\textsuperscript{23}

\[
\begin{align*}
\text{R NH}_2 & + \text{RCO}_2 \xrightarrow{\text{K}_2\text{CO}_3 (10 \text{ mol %); \text{aceton, 100 °C, 20–30 h}} \text{1,2,3}} \text{R-NH}_2 \text{CO}_2 \quad (\text{27 (46–97 %)}) \quad \text{15 (47–88 %)}
\end{align*}
\]

Milstein and co-workers developed well-defined pyridine-based PNN/Ru\textsuperscript{II} pincer complex for the direct synthesis of amides from alcohols and amines with the release of H\textsubscript{2}, thus enabling base-free, additive-free, and acceptorless amide formation.\textsuperscript{20} β-amino alcohols were effectively converted into the cyclic dipeptides 29 in the presence of the dearom-
atized PNN/Ru complex 28 in 1,4-dioxane, under argon, without racemization of the products [Eq. (11)]. Interestingly, large substituents (R ≠ H, Me) at the α-position to the amino group resulted in the formation of the cyclic dipeptide as the sole product, whereas (S)-(+)2-amino-1-propanol under the same catalytic conditions gave 72% of the polypeptide and a minor amount of the cyclic dipeptide. A plausible catalytic cycle involves a new mode of metal–ligand cooperation based on ligand aromatization/dearomatization. It was observed that the hemilability of the N-arm is important and plays a crucial role in the amide bond formation. In contrast, the complementary PNP/Ru complexes gave the aromatized product [see Eq. (16)].

Madsen and co-workers reported the application of a strongly donating N-heterocyclic carbene (NHC) complexed with ruthenium as a catalyst for the selective synthesis of amides from alcohols and amines. Three different NHC/Ru systems (30–32) were designed and analyzed for their activity in amide formation starting from 1,4- and 1,6-amino alcohols [Eq. (12); cod = 1,5-cyclooctadiene]. All three catalytic systems showed similar reactivities and product yields, thus revealing that a common catalytically active species is involved.

An atom-economical strategy for the formation of cyclic imides (39) from diols and nitriles was developed by Hong et al. (Scheme 4). They used a ruthenium complex in combination with the NHC catalyst 34 as the catalyst. Notably, transfer of hydrogen from the diol produces the active electrophile 35 and nucloephile 36 as intermediates through a ruthenium-catalyzed redox-neutral catalytic cycle. Nitrile precursors act as a nitrogen source as well as a hydrogen acceptor in the reaction. The reaction of 35 and 36 affords the hydroxy amide 37 which can be further converted into a cyclic imide by dehydrogenative formation of the hemiaminal 38 as a potential intermediate.

Vogt et al. reported ruthenium catalyst systems, comprising [Ru(CO)3] and CataCXiumPCy (40), for intramolecular cyclization of α,ω-amino alcohols to afford the cyclic amines 41 as well as the cyclic amides 42 [Eq. (13)]. The ratio of 41 to 42 depends on the ring size of the product formed. The addition of water or phenol as an additive resulted in a complete shift of equilibrium towards the amine formation. This result might be due to water or phenol serving as a weak acid, which might facilitate the dehydration of a cyclic hemiaminal to an imine. Complete selectivity for amide formation was achieved using propiophenone as a sacrificial hydrogen acceptor.

### 2.3. Annulation by Oxidative Cyclization of Alcohols

Oxidative cyclization of diols with amines provide an alternative protocol for the construction of five- and six-membered heteroaromatic compounds by consecutive hydrogen-transfer C–C and C–N bond formation. A straightforward, one-pot synthesis of the quinolines 46 from anilines and 1,3-diols was reported to proceed in the presence of a catalytic amount of [RuCl3·xH2O], PBu3, and MgBr2·OEt2 in mesitylene (Scheme 5). The addition of magnesium salt is believed to improve the electrophilic cyclization of 45 to 46 through a C–C bond-forming process. Substituents on the aniline and diol both played significant roles in the heterocyclization reactions. Interestingly, the regioselectivity of product formation reveals that the reaction proceeds with the formation of the α,β-unsaturated aldehyde 44 from the diol by ruthenium-catalyzed dehydrogenation and subsequent elimination of water. Aniline then undergoes Michael addition with 44 followed by electrophilic cyclization to afford either the 2- or 3-substituted quinolines in moderate to good yields which is similar those of the Doebner–von Miller quinoline synthesis.
An atom-economical practical method for the synthesis of highly substituted-functionalized pyrroles (47) was achieved by a ruthenium-catalyzed three-component annulation of ketones, amines, and vicinal diols [Eq. (14)]. To derive better catalytic systems, various ruthenium catalysts, ligands, and bases were analyzed for the three-component annulation reaction. Better activity resulted from employing 1 mol% \([\text{Ru(p-cymene)}\text{Cl}_2]_2\), 2 mol% Xantphos, and 20 mol% tBuOK in tert-amy1 alcohol at 130°C. Significantly, less-reactive ketones and \(\alpha\)-functionalized ketones under the same catalytic conditions yielded the corresponding pyrrole derivatives. Aliphatic and aromatic amines and ammonia effected pyrrole synthesis and the latter provided the NH-pyrroles.

Biomass-derived 1,2-diol derivatives were effectively utilized for the construction of quinoxalines using 2-nitroanilines in a ruthenium-catalyzed hydrogen-transfer reaction wherein the diol and nitroaniline serve as hydrogen donor and acceptor, respectively [Eq. (15)]. Optimization studies reveal that \([\text{Ru}_3(\text{CO})_{12}]\) in combination with dppf served as an active catalyst in the presence of 50 mol% CsOH-H_2O in tert-amy1 alcohol at 150°C. Both symmetrical and unsymmetrical diol derivatives were converted into the corresponding 2,3-substituted quinoxaline derivatives (48) and electron-donating and electron-withdrawing substituents on anilines significantly influenced the product yield.

Milstein and co-workers reported the Ru\(^{II}\)/PNP complex 49 to catalyze the synthesis of the pyrazines 50 from \(\beta\)-amino alcohols in the presence of a base [Eq. (16)]. The toluene solution of a \(\beta\)-amino alcohol was heated to reflux vigorously under argon atmosphere for 24 hours to give corresponding pyrazines, presumably via an intermediate 1,4-dihydropyrazine. The same group explored a bipyridine-based Ru/pincer complex (51) for the synthesis of substituted pyridines (52) through acceptorless hydrogen-transfer annulation of \(\gamma\)-amino alcohols with secondary alcohols [Eq. (17)]. The complex 51 in the presence of tBuOK in 4:1 mixture of toluene and THF was found to be optimal for the secondary alcohol initiated annulation process. Cyclic and acyclic secondary alcohols were successfully incorporated into the pyridine core of the products by consecutive C–N and C–C bond-forming hydrogen-transfer steps.

Beller et al. reported a general route to indoles (56) from easily accessible anilines and epoxides by a ruthenium-catalyzed oxidative annulation process (Scheme 6). After screening several catalyst systems, the commercially available \([\text{Ru}_3(\text{CO})_{12}]\) complex and the dppf ligand were found to be the optimal catalyst system for the efficient synthesis of indoles (Scheme 6; 56). Notably, no reaction was observed in the absence of para-toluenesulfonic acid (\(p\)-TsOH), which is necessary both for the epoxide ring opening (53) and the electrophilic cyclization reaction (55 – 56). Various substituents on aniline underwent cyclization to provide the corresponding indoles in good yields. Initially, the ring opening of the epoxide with aniline provides 1,2-amino alcohol derivatives (53) which additionally undergo oxidative cyclization to form indole derivatives.

A hydrogen-transfer strategy enabled the use of 1,3-diols, instead of potentially unstable carbonyl compounds, for the preparation of 1,4-disubstituted pyrazoles [Eq. (18)]. An in situ generated catalyst derived from 3 mol%...
[RuH₂(PPh₃)₃CO] and 3 mol % Xantphos was used for the synthesis of pyrazoles (57) from 1,3-diols and alkyl and aryl hydrazines in the presence of crotonitrile as a hydrogen acceptor and 15 mol % AcOH as cocatalyst at 110°C in toluene. It could be observed that the hydrogen acceptor (crotonitrile) increased the rate of dehydrogenation of the diol, and that the co-catalyst (AcOH) enhanced the condensation reaction of the aldehyde with hydrazine. Thus the reaction yield drastically decreased in the absence of either a hydrogen acceptor or co-catalyst.⁴²

A one-pot reaction for the preparation of indoles and subsequent C₃-alkylation was reported to proceed through a C–N and C–C bond-forming-hydrogen-transfer process (Scheme 7). Cp*Ir was efficiently utilized for both intramolecular oxidative cyclization of 2-aminophenyl ethyl alcohol and consecutive intermolecular hydrogen borrowing C₃-alkylation of the indole by excess of benzyl alcohol in the presence of KOH under solvent-free conditions at 110°C for 24 hours. The amount of base plays an important role in C₃-versus N-alkylation of indole. The analogue of commercially available anti-migraine drugs, such as N,N-dimethyltryptamine (60), was also synthesized by using above methodology. The 2,3-disubstituted indole 61 was synthesized by oxidative cyclization of the corresponding secondary alcohol derivative. The efficiency of the iridium catalyst was once again proven by the reaction of 2-nitrophenyl ethyl alcohol to give the C₃-alkylated indole 62 in the presence of excess of benzyl alcohol, thereby employing multiple oxidations and reductions in a single catalytic cycle [Eq. (19)].³³

A sustainable approach for the synthesis of pyroles was developed from the condensation of renewable secondary alcohols with 1,2-aminocarboxylic acids and moisture- and air-stable crystalline tridendate ligands with iridium (63; Scheme 8). Acceptorless dehydrogenation initially starts with secondary alcohol derivatives followed by base-promoted condensation to afford the imine intermediate 65, which undergoes dehydrogenative electrophilic cyclization to lead to formation of pyrrole derivatives (67), with a diversity of substituents, under mild reaction conditions and in good yields. Interestingly, 63 was also successfully utilized for N-alkylation of the aniline derivatives 68 through a borrowing hydrogen reaction and subsequent hydrogen-transfer condensation with 1,2-amino alcohols to form 3-amino-substituted pyrroles (69) in very good yields [Eq. (20)].³⁴

In situ generation of a carbonyl precursor from an alcohol by catalytic dehydrogenation presents many opportunities to modify conventional synthetic protocols, wherein the presence of a carbonyl functionality would decrease the efficiency of synthetic transformations because of the unusual condensation with the nucleophilic partner and self-aldol-type condensation process. Oxidative cyclization of primary alcohols with o-aminobenzamides provided a new methodology for the construction of quinazolinones (70), thus enabling a base-free, acceptorless hydrogen-transfer annulation process [Eq. (21)].³⁵
2.4. Annulation of Alcohols with Unsaturated Systems

Organic building blocks such as alkenes and alkynes have been utilized in combination with alcohols, as precursors for carbonyls, to construct heterocyclic compounds by a catalytic hydrogen-transfer annulation process. Ruthenium-catalyzed redox isomerization of propargyl alcohols resulted in the sensitive α,β-unsaturated carbonyl compounds 71, which undergo an intramolecular acid-catalyzed Michael addition, for the construction of five- and six-membered N-heterocycles (72) in one pot (Scheme 9).[36]

Ruthenium-catalyzed redox isomerization of propargyl alcohols resulted in the sensitive α,β-unsaturated carbonyl compounds 71, which undergo an intramolecular acid-catalyzed Michael addition, for the construction of five- and six-membered N-heterocycles (72) in one pot (Scheme 9).

Selective intermolecular coupling of terminal propargylic amines with allylic alcohols was reported to occur at the cationic ruthenium center for the preparation of piperidine derivatives (75), having an exocyclic olefin, with the elimination of water as the only side product (Scheme 10).


Scheme 10. Synthesis of functionalized piperidines from unsaturated systems.

[Cp*Ru]-catalyzed oxidative C–C coupling of propargylic amines and allylic alcohol gives amino aldehyde intermediate 74 in THF. In situ enamine formation of 74 provides a new method for constructing functionalized piperidines (75).[11a]

Messerle et al. reported new pyrazolyl-1,2,3-triazolyl N,N′bidentate donor ligands for coordination to ruthenium and iridium for C–C and C–N bond-forming annulations [Eq. (22)]. The complex 76, containing electron-withdrawing substituents on the phenyl ring, was efficient for the preparation of the tricyclic indole 77 from 2-(hydroxyalk-1-y)anilines through a C–N bond formation/hydrogen-transfer C–C bond formation sequence in one pot.[11b]


Oxygen- and sulfur-containing heterocycles are frequently used in materials and biological chemistry.[37] Cyclic carboxylates are present in large number of natural products and biologically important compounds, and it is a useful building block in organic synthesis and polymer synthesis.[38] Over the past decades, there has been considerable attention focused on the asymmetric synthesis of chiral lactones. Transition-metal-catalyzed hydrogen transfer provides access to lactones in an environmentally friendly approach.

3.1. Annulation by Oxidative Cyclization of Alcohols

Dehydrogenative annihilation of diols into lactones is one of the most promising protocols for the construction of cyclic esters from easily accessible starting materials, with extrusion of H₂ as the by-product. Milstein and co-workers developed a new catalytic system, the PNN ruthenium dihydrido borohydride pincer complex 78, to achieve the base-free and acceptorless dehydrogenative coupling reaction of alcohols into esters [Eq. (23)].[9c] Various 1,4- and 1,5-diols were transformed into five- and six-membered lactones (79) in refluxing toluene, thus enabling an acceptorless strategy with the liberation of H₂ as a by-product.

Chemo- and enantioselective formation of five- and six-membered lactones (84) were achieved from 1,4-keto alcohols using Noyori’s transfer-hydration catalyst (Scheme 11). 1,4-keto alcohols are precursors for 1,4-keto aldehydes, which are sensitive to decomposition through an aldol-type pathway. The mechanism consists of Noyori’s transfer hydrogenation of the ketone followed by oxidation of the primary alcohol, thus leading to formation of a lactone via the hemiacetal intermediate 83.[39]
Intramolecular hydrogen-transfer Knoevenagel-type condensation was also developed using alcohols which act as carbonyl precursors and active methylene groups, thus leading to cyclic compounds through a C–C bond formation process. Cossey et al. reported the synthesis of chromanes and thiochromane (85) by an iridium-catalyzed borrowing-hydrogen reaction [Eq. (24)]. Iridium catalytic systems such as [{Cp*IrCl₂}₂] and [{Ir(cod)Cl}₂]/PPh₃ were highly efficient catalysts under microwave conditions. Both catalytic systems showed similar reactivities and cis/trans selectivities for the construction of chromanes, whereas [{Ir(cod)Cl}₂]/PPh₃ showed better yields for the synthesis of thiochromane-4-carbonitrile. The reaction path consists of initial catalytic dehydrogenation of an alcohol to form a carbonyl compound and subsequent intramolecular condensation of the carbonyl with an active methylene group to provide olefin functionalities. Finally hydrogenation of the condensed product utilizing the borrowed hydrogen affords the corresponding O- and S-containing heterocyclic compounds 85.

![Scheme 11. Enantioselective synthesis of lactones.](image)

Hydrogen-transfer condensation of alcohols with active methylene groups in the presence of a hydrogen acceptor, which suppresses the final hydrogenation step, provides a strategy to construct heterocyclic compounds. The diversity of the substituted benzofurans and benzothiophenes 86 was achieved by iridium-catalyzed intramolecular dehydrogenative condensation of alcohols with active methylene groups using p-benzoquinone as the hydrogen acceptor [Eq. (25)].

![Scheme 12. Synthesis of 2,5-disubstituted furans.](image)

3.2. Annulation of Alcohols with Unsaturated Systems

Williams and co-workers reported the synthesis of 2,5-substituted furans from readily available 1,4-alkynediols by ruthenium-catalyzed hydrogen-transfer isomerization. [Ru(PPh₃)₃(CO)H₂] in association with Xantphos was utilized for isomerization of 1,4-alkynediols into 1,4-diketones (87) which then undergo acid-catalyzed dehydration, thus providing a range of 2,5-disubstituted furans (88; Scheme 12).

![Scheme 13.](image)

Krische et al. reported the enantioselective synthesis of α-exo-methylene γ-butyrolactones (90) through a C–C bond-forming reaction of acrylic esters and alcohols by using a cyclometallated chiral iridium complex (89) under mild reaction conditions for a carbonyl 2-(alkoxycarbonyl)allylation [Eq. (26)]. The above reaction in THF provides the maximum yield with moderate ee values, whereas MeCN provides a moderate yield with high ee values. To balance this reaction in terms of yield and ee value, the reactions were conducted in a 1:1 mixture of THF/MeCN.

![Scheme 14.](image)

Hydrogen-transfer C–C bond-forming reactions of vicinal diols with methyl acrylate, using the ruthenium(0) complex [Ru₃(CO)₁₂] and dppt, were reported for the construction of lactones and spirolactones from acyclic and cyclic diols, respectively. Diversely substituted cyclic diols were converted into spirolactones in good to excellent yields [Eq. (27)]. The mechanistic pathway for the formation of the lactone through C–C coupling and subsequent lactonization is shown in Scheme 13.

![Scheme 15.](image)

Redox-triggered C–C coupling of diols with alkynes to give β,γ-unsaturated ketones (94) was reported to proceed by using an in situ generated ruthenium complex [Eq. (28)]. The reaction involved hydrohydroxyalkylation with complete regioselectivity. The above coupling reaction was effected with a catalytic amount of [Ru₃(CO)₁₂], PCy₃, and 1-adamantanecarboxylic acid in m-xylene at 130°C. Treatment
of the β,γ-unsaturated ketones with substoichiometric quantities of p-toluenesulfonic acid afforded the tetrasubstituted furans 95 by cyclodehydration.


Benzoxazoles and benzothiazoles are commonly encountered groups in natural products, pharmaceuticals, and agrochemicals. Transition-metal-catalyzed hydrogen-transfer coupling of alcohols with 2-aminophenols and thiophenols resulted in the sustainable synthesis of benzoxazoles and benzothiazoles, respectively, and displaces the conventional use of stoichiometric oxidants to effect the aromatizing condensation of alcohols or aldehydes with 2-aminophenols. Iron-catalyzed formation of benzoxazoles by the reaction of 2-nitrophenol and primary alcohols was reported to proceed through a hydrogen-transfer reaction. Borrowing hydrogen from alcohols was used to reduce the nitro functional group, which upon reduction undergoes condensation and oxidation to provide benzoxazoles [Eq. (29)]. Inexpensive and efficient catalytic methods for the preparation of benzoxazoles and benzothiazoles from alcohols and 2-aminophenols and thiophenols, respectively, were developed using iron(II) phthalocyanine (FePc) as the catalyst [Eq. (30)].

5. Synthesis of Carbocyclic Compounds by Annulation of Alcohols with Unsaturated Systems

Furthermore, the application of hydrogen-transfer annihilations has been extended to the construction of carbocyclic compounds from vicinal diols and dienes. A ruthenium(0) complex generated from [Ru3(CO)12] and BIPHEP was used to synthesize carbocyclic compounds from diols and dienes through a [4+2] cycloaddition [Eq. (31)]. This novel strategy follows oxidative coupling of an in situ generated diene and diene to form the oxametallacycle 98 (Scheme 14), thus leading to the allylruthenium complex 99 by protonolytic cleavage by the diol. Intramolecular allylruthenation of 99 gives the ruthenium(II) alkoxide 100, which undergoes β-hydride elimination to form the ruthenium hydride 101. Reductive elimination of 101 affords the carbocyclic compounds 102 and regenerates the ruthenium(0) complex.

Polycyclic aromatic compounds were efficiently prepared through ruthenium(0)-catalyzed [4+2] cycloaddition of cyclic diols with dienes followed by acid-catalyzed aromatization. This methodology was utilized for the construction of various polycyclic compounds such as substituted fluoranthenes (104), naphthalenes (105), indeno[1,2,3-cd]-fluoranthene (106), and...
6. Summary and Outlook

This review article provides a detailed outline to understanding how simple alcohols in association with a hydrogen-transfer transition-metal catalyst can be converted into versatile starting materials for the construction of diverse heterocyclic scaffolds. This chemistry starts with the initial removal of H$_2$ from an alcohol to afford an electrophilic carbonyl precursor, which subsequently undergoes either condensation, addition, or coupling reactions with various nucleophilic partners such as amines, alcohols, and unsaturated systems, thus providing a wide variety of compounds. H$_2$O and/or H$_2$ are the only by-products. The release of benign low-molecular-weight by-products makes this protocol highly atom-efficient and eco-benign. Most interestingly, the selective functional-group transformation of particular metal catalysts can be altered with the aid of additives and ligands. Based on these facts, remarkable achievements have been made in this field of hydrogen-transfer annihilations for the construction of heterocycles in the past few decades. The notable developments in the catalytic systems have led to catalysts which are described as acceptorless, base-free, bifunctional, water-soluble, and recyclable, and makes this synthetic strategy an alternative for conventional synthetic transformations in academic and industrial settings. Despite several achievements in this area, there is still a need for the development of efficient catalysts based on iron. Recently, a few reports$^{[44,45]}$ were made on using iron as an efficient hydrogen-transfer catalyst, but it is still in its infancy. Indeed, this review describes what the current state-of-the-art is with regard to the hydrogen-transfer annihilations. There are still opportunities to design efficient, environmentally benign, and sustainable catalytic systems for the selective, atom-economic construction of complex heterocyclic frameworks.

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