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Acceptorless dehydrogenative coupling reactions with alcohols over heterogeneous catalysts

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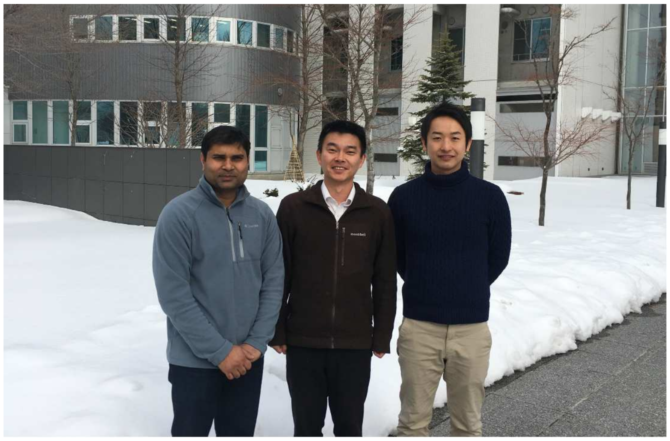

From left to right: S. M. A. Hakim Siddiki, Ken-ichi Shimizu, and Takashi Toyao.

S. M. A. Hakim Siddiki completed his PhD in 2011 at the University of Hyogo (Japan) under the supervision of Prof. Takashi Sugimura. After carrying out postdoctoral research at Kyoto University, he joined Hokkaido University as a specially appointed Assistant Professor in 2016. His research focuses on heterogeneous catalysis for sustainable organic synthesis.

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Abstract

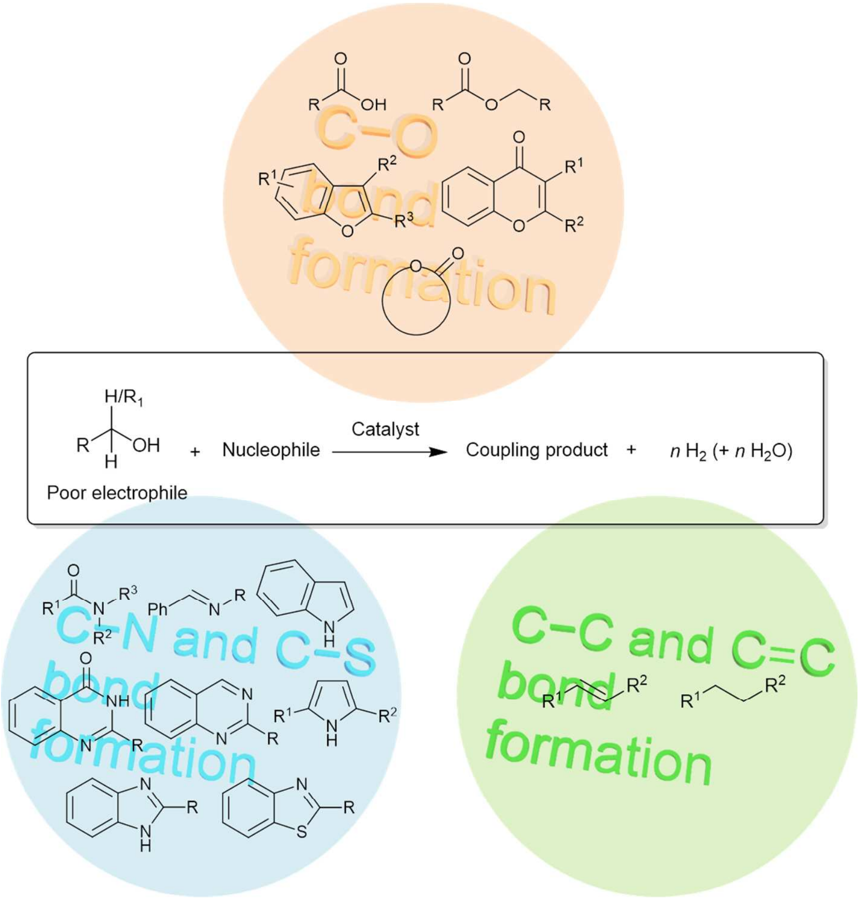
Heterogeneous catalysis for the one-pot synthesis of added-value chemicals is a growing area in green chemistry. Among various types of organic transformations that are accessible by this approach, acceptorless dehydrogenative coupling (ADC) reactions have been established as efficient processes that generate various classes of organic compounds via the formation of C–O, C–N, C–S, C–C, and C=C bonds. In this review, we summarize recent developments on the one-pot synthesis of organic compounds that are driven by the dehydrogenation of alcohols promoted by supported transition-metal catalysts in the absence of hydrogen acceptors. A major feature of the design of such catalysts is the cooperation between the metal sites and the acid and/or base sites on the metal-oxide supports. Recent examples for the organometallic catalysis of ADC reactions of alcohols are presented and their efficiency is put into contrast with that of related reactions carried out using conventional supported transition-metal catalysts. Finally, aspects pertaining to the mechanism and catalyst design of these new ADC reactions are discussed in the context of directions for future developments in this area.

1. Introduction

The dehydrogenation/oxidation of organic compounds represents an important class of processes currently employed in the chemical industry.[1,2] Traditionally, these types of reactions have been performed using stoichiometric amounts of inorganic oxidants, and they often require large amounts of additives and/or promoters.[3] As a consequence, these processes are often uneconomical and lead to the generation of toxic waste.[4] Similarly, catalytic transfer-hydrogenation reactions, in which stoichiometric quantities of sacrificial organic acceptors are used, also generate stoichiometric amounts of organic waste.[5] From a 'green chemistry' perspective, new and economically efficient processes that do not rely on the use or formation of toxic and hazardous materials are critically important. In this sense, green chemistry and 'sustainable technology' approaches have recently attracted substantial attention from academic and industrial chemists.[4,6,7] This has led to a paradigm shift in the reaction design away from the traditional focus on chemical yield to a more contemporary focus on waste elimination and the minimization of the use of toxic and/or hazardous substances. In this regard, ideal synthetic methods are now characterized in terms of catalytic activity, selectivity, as well as atom- and step-efficiency.[8] Although substantial progress toward these goals has been made during the past century, contemporary chemical processes used to manufacture organic compounds still largely depend on the use of stoichiometric reagents and produce large amounts of waste.[9]

Acceptorless dehydrogenation (AD) reactions of organic compounds, which occur together with H_2 evolution, have recently attracted attention as they are both 'green' and 'sustainable'. Given that AD reactions do not require the use of conventional oxidants or sacrificial acceptors, they do not produce stoichiometric amounts of waste. Furthermore, the gaseous H_2 generated in these processes is valuable and can potentially be used as an energy source.[10,11] Recent developments in this area of catalysis have enabled AD reactions to be applied to the synthesis of organic substances.[12] Among the various types of AD reactions, those that use alcohols as substrates have attracted particular interest. This is due to (i) the ready accessibility and usually low cost of alcohols, and (ii) the environmentally benign and atom economical nature of these processes. These reactions serve as straightforward methods for the coupling alcohols with various nucleophiles via the formation of C–O, C–N, C–S, C–C, and C=C bonds. Although homogeneous transition-metal catalysts display high levels of activity and selectivity in promoting industrially important AD reactions,[13] they generally suffer from product-separation issues and the limited potential for catalyst recycling. This is especially problematic with respect to sustainability and large-scale applications. Therefore, recyclable heterogeneous catalysts should be better suited for such AD processes. Another shortcoming of homogeneous catalysts is that they frequently require the use of stoichiometric amounts of additives. In this regard, an important goal in the design and development of environmentally benign atom-efficient AD processes is the development of heterogeneous catalysts that exhibit high activity, stability, and recyclability, and that operate in the absence of hydrogen acceptors.

In this review, we present and discuss recent advances regarding the development of acceptorless dehydrogenative coupling (ADC) reactions of alcohols with nucleophiles that are promoted by heterogeneous catalysts (**Scheme 1**). Borrowing-hydrogen reactions,[14–18] represent another important class of reactions that are based on a similar concept, but these reactions are not covered in this review. We would like to suggest that readers, who are interested in the latter topic consult the review "*Heterogeneous catalysis for the direct synthesis of chemicals by borrowing hydrogen methodology*", which has recently been published in *Catalysis Science and Technology*.[19] The present review also excludes the discussion of AD transformations of alcohols into aldehydes/ketones,[20–22] and of amines into nitriles,[23] dehydrogenative aromatizations,[24–26] and the dehydrogenation of other substrates such as formic acid, which are used as H_2 carriers.[27] However, it should be noted that many ADC reactions of alcohols have initially been conducted under homogeneous catalysis conditions.[28–32] While only selected examples of homogeneously catalyzed ADC reactions are briefly introduced, more detailed reviews of these processes have been published elsewhere.[12,33–41]

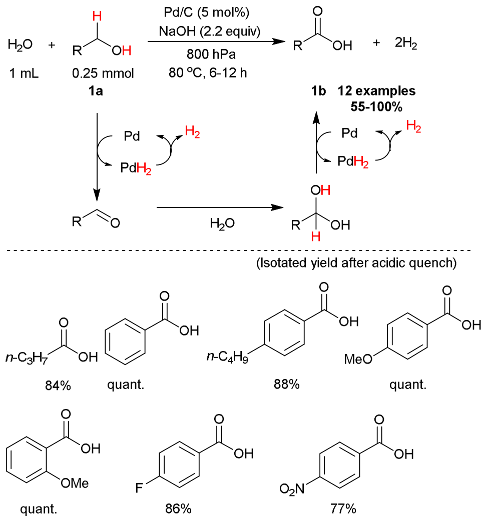


Scheme 1. Products obtained from ADC reactions between alcohols and nucleophiles using heterogeneous catalysts.

2. Reactions that form C–O bonds

2.1. Carboxylic acids from alcohols and water

The selective oxidation of primary alcohols to generate carboxylic acids is an industrially important process used for the production of bulk and fine chemicals.[42–46] Current methods used for this process generally depend on stoichiometric amounts of toxic oxidizing agents or a catalytic protocol using O_2 under high pressure.[47,48] Milstein *et al.* have discovered a new procedure for carrying out the dehydrogenative coupling of primary alcohols in aqueous NaOH under Ar, which uses a homogenous Ru-PNN pincer catalyst.[49] The process, in which water serves as the oxygen donor, produces the desired carboxylates in high yield under concomitant emission of H_2. Subsequently, Sajiki *et al.* have described the first heterogeneous catalyst system for this reaction.[50] Initially, it was observed that Rh supported on carbon (Rh/C) promotes the dehydrogenation of 6-phenyl-1-hexanol in aqueous NaOH solution in a closed tube under Ar to generate the corresponding carboxylic acid in low yield. A thorough investigation revealed that when the reaction is carried out using a Pd/C catalyst at moderate pressure (800 hPa) using a vacuum controller on a rotary evaporator, the generated hydrogen can be removed effectively, which minimizes the reduction (reverse reaction) of aldehyde intermediates and other undesirable side reactions. Under the optimized pressure-controlled conditions, using commercially available palladium on carbon (Pd/C) and 2.2 equiv of NaOH in water at 80 °C, various primary alcohols, including aliphatic and benzylic alcohols, are selectively transformed into the corresponding carboxylic acids in good to excellent yield (**Scheme 2**). The method tolerates fluoride- and nitro-containing benzyl alcohols, even in the presence of the generated H_2 during the dehydrogenation process, which may cause the Pd/C-catalyzed hydrogenation of co-existing reducible functional groups. It should also be noted that this catalytic system does not tolerate chloride-substituted benzyl alcohols, which engage in reductive dichlorination and generate benzoic acid. The aforementioned Pd/C catalyst can be reused at least 5 times. The results of mechanistic studies, including a reaction in $H_2{}^{18}O$, showed that the process proceeds via a pathway (**Scheme 2**) that involves the production of H_2 and an aldehyde, which subsequently forms a hydrate that undergoes a Pd-catalyzed dehydrogenation to afford the carboxylic acid and H_2.[51]



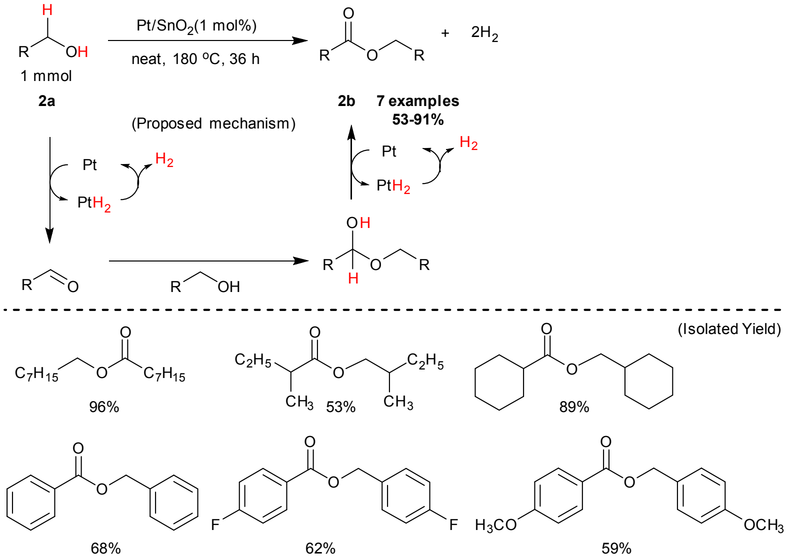
Scheme 2. Synthesis of carboxylic acids from primary alcohols and water using a Pd/C catalyst.

2.2. Esters from the self-coupling of alcohols

Esterification is recognized as one of the most fundamental and important reactions in organic synthesis.[52] The conventional esterification of carboxylic acids or activated carboxylic acid derivatives such as acid chlorides or anhydrides using an excess of alcohol produces significant amounts of waste.[53] The direct aerobic oxidation of alcohols by heterogeneous catalysts represents a greener method to generate these substances.[54–56] Even more preferable methods to prepare esters are based on one-step dehydrogenative reactions of alcohols in the absence of either oxygen donors or hydrogen acceptors. Homogeneous Ru[57–61] and Ir[62–64] catalysts effectively promote this reaction. For example, Murahashi and co-workers showed in 1981 that $[RuH_2(PPh_3)_4]$ catalyzes the transformation of primary alcohols into esters under AD reaction conditions. While this was the first example for using a homogeneous catalyst to induce this synthetically valuable process, many heterogeneous catalysts have been reported to form esters via AD reactions. For example, heterogeneous Cu catalysts effectively promote gas-phase dehydrogenation reactions of ethanol to form ethyl acetate.[65–69] The synthesis of methyl formate from methanol via AD has also been well documented. Cu-based complexes such as Raney copper[70–75] and Pd/ZnO have also been used in the catalytic synthesis of methyl formate.[76] Moreover, the photocatalytic (λ_{irr} = 400 nm) conversion of methanol into methyl formate in the presence of $TiO_2(110)$ has been reported.[77]

Although these seminal investigations have resulted in significant advances with respect to the use of self-coupling reactions of alcohols to produce esters, the required harsh conditions often limit the applications of these catalytic systems. A milder (typically < 200 ºC) and more efficient catalytic system has been reported by Sánchez, who observed that a silica-immobilized pincer-type Ru complex can serve as a reusable catalyst for the dehydrogenation of 1-hexanol to form a hexyl hexanoate.[78] Even though this process proceeds at 110 ºC, it still requires the use of the basic additive KOH and the substrate scope is limited to simple alcohols such as hexanol. In contrast, SnO_2-supported Pt (Pt/SnO_2) represents a reusable heterogeneous catalyst for the ADC of various primary alcohols to form esters under additive- and solvent-free conditions.[79] An examination of the substrate scope of this Pt/SnO_2-catalyzed esterification (**Scheme 3**) revealed that linear and cyclic aliphatic primary alcohols as well as benzyl alcohols are converted into the corresponding esters in good to moderate yield. Pt/SnO_2 displays a higher activity than various other SnO_2-supported transition metals such as Ir, Re, Ru, Rh, Pd, Ag, Co, Ni and Cu. The catalytic activity of Pt thereby depends on the nature of the support, whereby SnO_2 exhibits a superior performance relative to ZrO_2, CeO_2, Nb_2O_5, TiO_2, carbon, Al_2O_3, SiO_2, H-beta zeolite, and MgO. The results suggest a mechanism for the esterification reaction that involves interactions between Pt and SnO_2. Accordingly, the reaction pathway was proposed to start with the dehydrogenation of the alcohol to form an aldehyde that is adsorbed on the SnO_2 surface, which reacts with the alcohol to produce a hemiacetal. Finally, the dehydrogenation of this acetal leads to the formation of the ester as shown in the proposed mechanism (**Scheme 3**). The interactions between the Sn cation in SnO_2 and the carbonyl oxygen of the aldehyde at -50 ºC were examined by IR spectroscopy using benzaldehyde as the model aldehyde (**Figure 1**). The C=O stretching bands of benzaldehyde adsorbed on SnO_2 occur at lower wavenumbers (1680, 1686 cm^{-1}) relative to those of the aldehyde absorbed on the conventional Lewis-acidic metal oxide Al_2O_3 (1689 cm^{-1}) and non-Lewis-acidic oxide SiO_2 (1694 cm^{-1}). These observations indicate that Lewis acid-base interactions occur between the Lewis-basic carbonyl oxygen atom of benzaldehyde and that these interactions are higher than those on metal ion sites in Al_2O_3 and SiO_2. This Lewis acid/base interactions enhance the electrophilicity of the aldehyde and promote the nucleophilic addition of the alcohols. Shishido and co-workers have demonstrated that the ZrO_2-supported Cu catalyzes the ADC of primary alcohols into esters (**Scheme 4**). Different esters were synthesized from primary alcohols and diols in moderate to high yield, whereas the use of benzyl alcohol resulted in the formation of benzyl benzoate in merely 35% yield. It has been suggested that the low selectivity toward benzyl benzoate is due to the fast conversion of benzyl alcohol to benzaldehyde, which reduces the concentration of the alcohol as a coupling partner in the formation of the hemiacetal. It has been demonstrated that the acid/base pair sites and the metallic Cu species on the Cu/ZrO_2 catalyst cooperate as an efficient catalyst for the selective esterification of primary alcohols. When the dehydrogenation of the alcohol into the aldehyde is enhanced by the metallic nanoclusters and base sites on the support, and the formation of the hemiacetal via the condensation of the aldehyde and the alcohol is promoted by the Lewis-acidic Zr center, the hemiacetal is dehydrogenated by the surface base and the metallic Cu affords the ester.[80] Employing a MoS_2 catalyst, the group of Notestein achieved the ADC of ethanol into ethyl acetate in 43% yield with 90% selectivity under equilibrium conditions.[81] Using this catalytic system, the reaction of 1-butanol afforded butyl butanoate in only 18% yield and the cross esterification of 1-butanol and ethanol furnished a mixture of four different esters (**Scheme 5**). This catalytic system thus favors the dehydration relative to the dehydrogenation of alcohols with longer alkyl chains.

In order to compare the catalytic properties of several heterogeneous catalysts, the reaction conditions and catalytic efficiencies (yield, TON, and reusability) for the synthesis of esters from the self-coupling of 1-hexanol are summarized in **Table 1**. The reported heterogeneous catalysts (entries 1-3) show comparable yield and TON values. Even though the TON values of the heterogeneous catalyst systems are lower than that of the most effective homogeneous Ru catalyst reported by Leitner *et al.*,[61] other properties such as the facile recyclability may render heterogeneous catalysts such as Pt/SnO_2 advantageous.



Scheme 3. Synthesis of esters from primary alcohols using a Pt/SnO_2 catalyst.

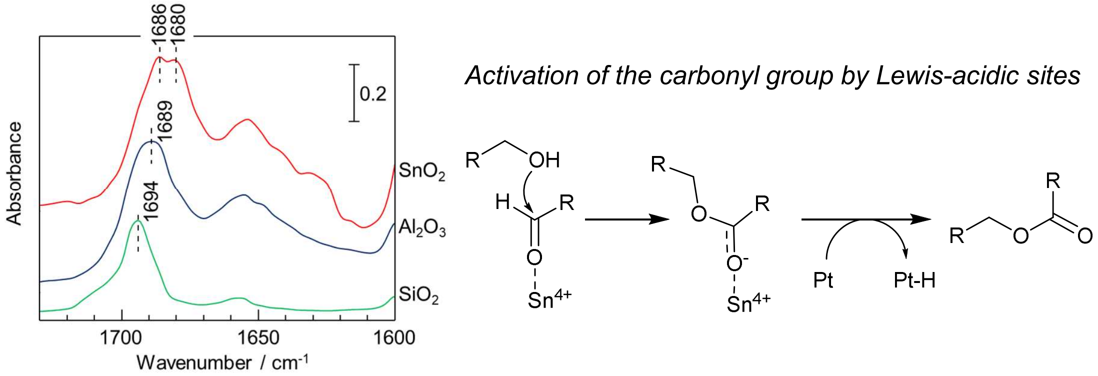
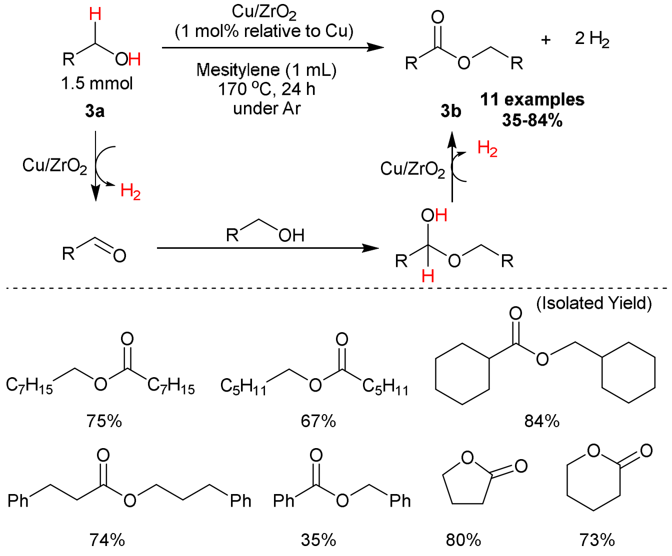
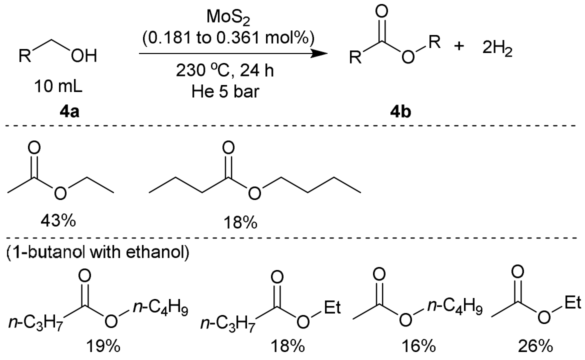


Figure 1. Role of the Sn^{4+} Lewis-acidic site in SnO_2 in the esterification of primary alcohols promoted by Pt/SnO_2.



Scheme 4. Synthesis of esters from primary alcohols using a Cu/ZrO$_2$ catalyst.



Scheme 5. Synthesis of esters from primary alcohols using MoS$_2$ catalyst as a catalyst.

Table 1. Catalysts for the synthesis of esters by self-coupling of 1-hexanol under concomitant liberation of H$_2$.

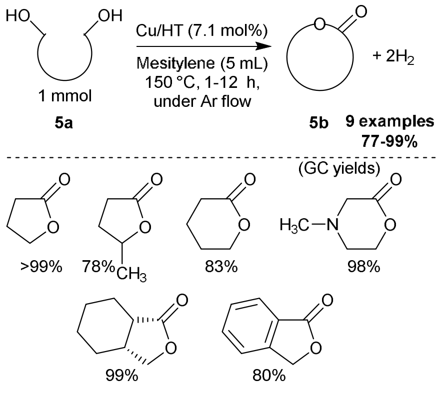
entry	catalyst	catalyst amount / mol%	additive	*T* / °C	*t* / h	yield / %	TON [a]	catalyst reuse	ref.
1	Ru complex immobilized on SiO$_2$	1	KOH	110	8	88	88	-	78
2	Pt/SnO$_2$	1	-	180	36	84	84	4 cycles	79
3	Cu/ZrO$_2$	1	-	170	24	67	67	deactivated	80
4	Ru complex (homogeneous catalyst)	0.02	-	120	20	85	4250	-	61

[a] TON relative to all the active metals used in the catalyst

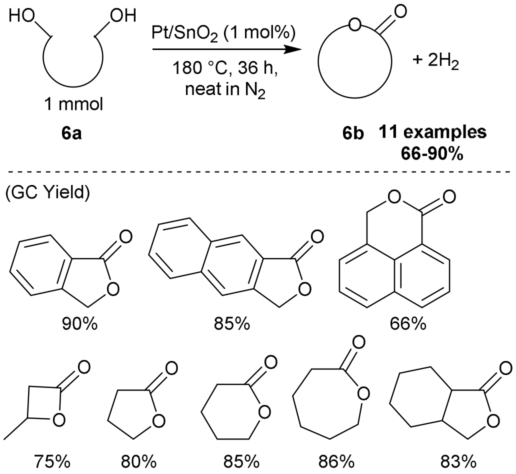
2.3. Lactones from diols

Lactones represent important chemical intermediates and solvents in organic reactions.[82–84] The conventional protocol for the preparation of lactones involves Brønsted-acid-catalyzed intramolecular dehydrative esterifications of hydroxyl-substituted carboxylic acids.[85] Recent efforts have led to the development of various methods to generate lactones via reactions of epoxides or aliphatic alcohols with carbon monoxide,[86] and of allenols or butadienes with carbon dioxide.[87,88] Lin *et al.*, Murahashi *et al.*, and Hartwig *et al.* have reported homogeneous Ru-catalyzed methods for the lactonization of 1,4-butanediol into γ-butyrolactone in the absence of hydrogen acceptors.[80,87-88]

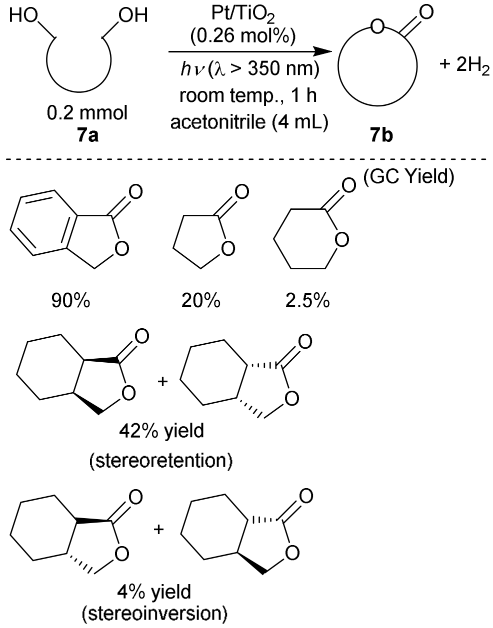
Kaneda *et al*. have reported the heterogeneous lactonization of diols using a hydrotalcite-supported Cu catalyst for the acceptorless dehydrogenative lactonization of diols (**Scheme 6**).[89] This method effectively affords a wide range of diols, including linear, cyclic and aromatic diols. It has also been demonstrated that Pt/SnO_2 catalyzes the dehydrogenative lactonization of diols as well as the esterification of primary alcohols (**Scheme 7**).[90] The results show that benzylic, linear, and branched aliphatic diols are converted into the corresponding lactones in 66-90% yield. From a biorefinery perspective, the Pt/SnO_2-promoted lactonization of 1,6-hexanediol into ε-caprolactone in 86% yield is of particular importance, as the substrate can be produced by a multistep hydrogenation of lignocellulosic biomass substances such as 5-hydroxymethyl-2-furfural and furfural, and the product ε-caprolactone can be converted into ε-caprolactam. A method for carrying out this dehydrogenative lactonization at room temperature using a Pt/TiO_2 photocatalyst has been developed by Yoshida and co-workers (**Scheme 8**),[91] who discovered that Pt-loaded rutile TiO_2 exhibited a higher photocatalytic activity and selectivity relative to anatase, and that heterogeneous acid catalysts such as Al_2O_3 accelerate this photocatalytic lactonization. The lactonization of 1,2-benzenedimethanol afforded the targeted stereoretentive product in 90% yield, whereas *cis*-1,2-benzenedimethanol produced the targeted stereoretentive product in 42% yield together with stereoinversion products in 4% yield. Moreover, the reactions of 1,4-butanediol and 1,5-pentanediol hardly proceeded using this system.



Scheme 6. Lactonization of diols catalyzed by a Cu/HT catalyst.



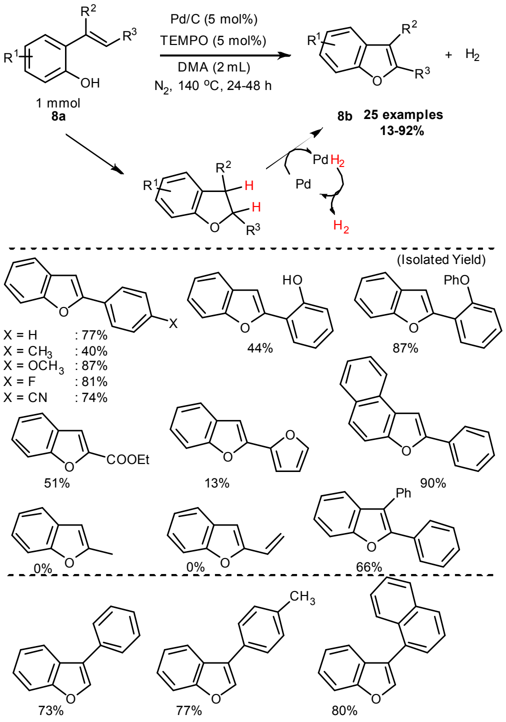
Scheme 7. Lactonization of diols catalyzed using Pt/SnO_2.



Scheme 8. Lactonization of diols using a Pt-loaded TiO_2 photocatalyst.

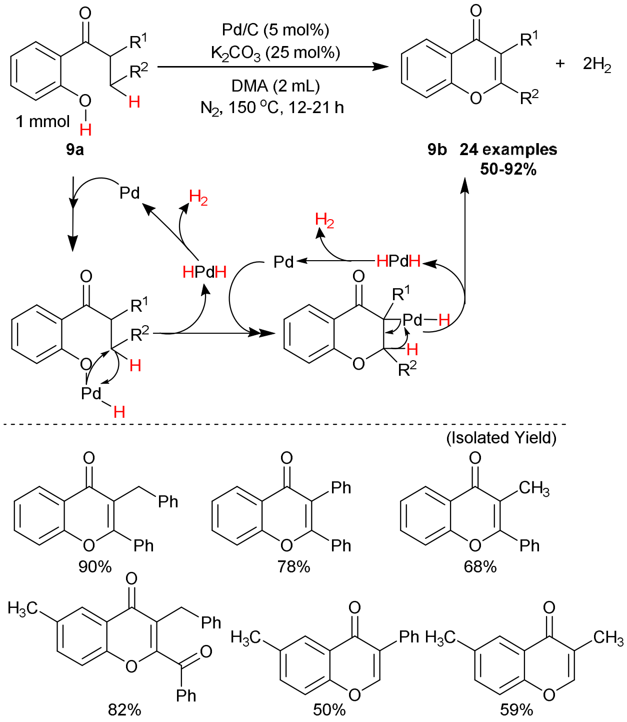
2.4. Benzofurans and Chromones from *ortho*-substituted phenols

The benzofuran ring is a valuable structural motif in numerous natural and pharmaceutically active compounds.[92,93] A straightforward procedure for the preparation of benzofurans involves the intramolecular C–O bond formation from a coupling of phenolic hydroxy groups with the vinyl carbons in *ortho*-substituted alkenyl moieties. Previous methods developed for this process, which use sacrificial hydrogen acceptors such as 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ), often result in the competitive formation of byproducts and undesired waste.[94] Recently, highly efficient homogeneous Pd catalysts have been used for the synthesis of benzofurans from phenols in the presence of air as the oxidant.[92,93] Following these studies, Liu and co-workers have demonstrated that substituted benzofurans can be produced from Pd/C-catalyzed dehydrogenative intramolecular C–O bond formations of *ortho*-alkenylphenols in the absence of oxidants or sacrificial hydrogen acceptors.[95] As can be seen in **Scheme 9**, electron-rich and -poor aromatic nuclei containing phenols with a wide range of functional groups undergo intramolecular dehydrogenative couplings to generate the corresponding furans. Conversely, a furan-containing substrate afforded **8b** in poor yield. This is most likely due to the fact that substrates with electron-rich phenol hydroxy groups couple with electron-poor coupling partners. Electron-rich moieties as coupling partners such as phenol hydroxy substrates were also applicable for the intramolecular dehydrogenative cyclization (-OCH_3, -OEt, -OPh). Using this catalytic system, the reactions of 1-alkyl-2-arylalkenes as substrates hardly proceeded to give the intramolecular ADC products.



Scheme 9. Dehydrogenative coupling of *ortho*-alkenylphenols to form benzofurans using a Pd/C catalyst.

Pd/C is an effective catalyst for the dehydrogenative conversion of *ortho*-acyl phenols into chromone derivatives without the need for oxidants and hydrogen acceptors (**Scheme 10**).[96] In this process, a *β*-hydrogen atom in the *ortho*-acyl side chain undergoes substitution by a phenolic hydroxyl oxygen atom to form a six-membered oxygen heterocycle that produces a flavonoid product upon dehydrogenation. While substituents at the *α*-position in the acyl side chain have little effect on the outcome of this reaction, substrates containing *β*-aryl and -benzyl groups generate chromones in higher yield. In addition, substrates that lack *β*-substituents produce the corresponding chromones in low yield (50-59%) owing to their high *β*-C−H bond dissociation energies.



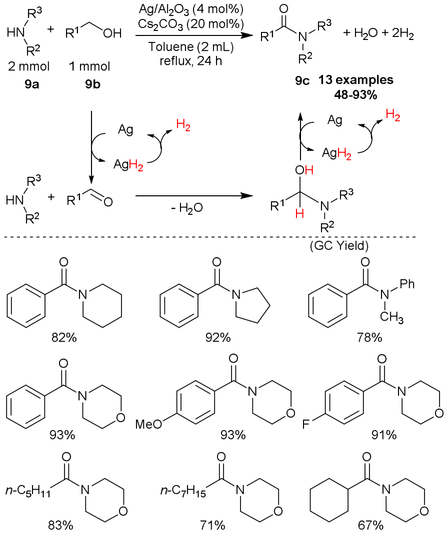
Scheme 10. Dehydrogenative conversion of *ortho*-acyl phenols into chromones using a Pd/C catalyst.

3. Reactions that form C-N and C-S bonds

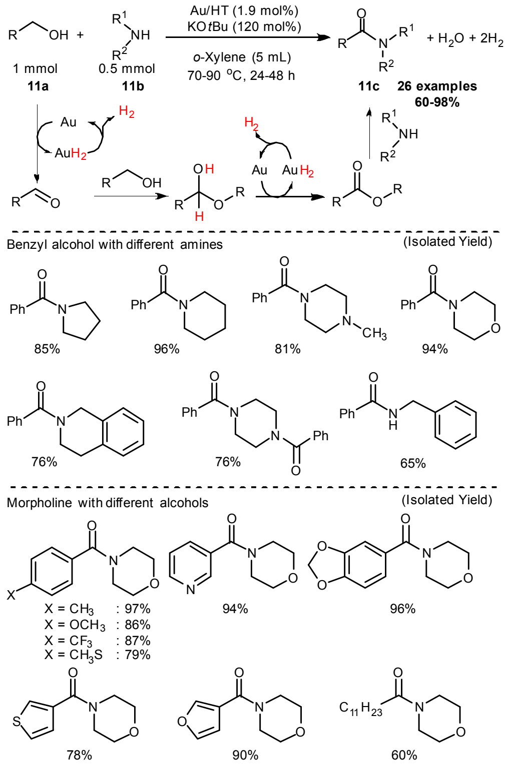
3.1. Amides from alcohols and amines

The importance of the amide functional group in biological and bioactive systems can hardly be overstated. This is exemplified by the wide presence of amide groups in agrochemicals, insecticides, polymers, pharmaceutical agents, and a vast number of naturally occurring, biologically active organic compounds. As a consequence, methods for the formation of amide bonds are very important in the context of organic synthesis. Traditional protocols for the synthesis of amides involve reactions of amines with activated carboxylic acid derivatives such as acyl chlorides or anhydrides, as well as the reactions of carboxylic acids in the presence of stoichiometric amounts of coupling reagents such as DCC (dicyclohexylcarbodiimide).[97,98] These processes are not only expensive, as they require the pre-activation of the carboxylic acids, but they also include significant drawbacks such as long reaction times, harsh reaction conditions, and low to moderate yields, especially in cases when hindered or less reactive substrates are employed. Furthermore, all of the hitherto developed processes produce large amounts of byproducts, commensurate with poor atom-economy and the need for difficult purification procedures. As a result, new catalytic strategies have been developed in recent years to devise efficient, economical, and environmentally friendly methods for the synthesis of amides. These approaches have been summarized in a recent comprehensive review.[99]

ADC reactions of alcohols with secondary amines, uncovered by Milstein *et al.*, are among the most atom-economical routes toward the preparation of amides.[100] Various homogeneous catalytic systems, mainly those that employ Ru complexes, promote this type of AD reaction.[101–104] Recently, a reusable heterogeneous catalytic system based on an alumina-supported Ag cluster has been reported.[105] The reaction, carried out in refluxing toluene or xylene in the presence of the weak base Cs_2CO_3 (**Scheme 11**), transforms benzyl and primary aliphatic alcohols and secondary amines into the corresponding carboxamides in 67%-93% yield. It has been suggested that the mechanistic pathway for the amide formation does not involve the intermediacy of free aldehydes, but that the reaction occurs via a catalyst-adsorbed aldehyde species, which then reacts with the amines to afford the hemiaminals. The Ag clusters induce the dehydrogenation of the hemiaminal that subsequently generates the amide products. Shi and co-workers have reported that the same reaction occurs at lower temperatures (70-90 ºC) when a hydrotalcite-supported Au nanoparticles catalyst is used (**Scheme 12**).[106] This system promotes the amidation of benzyl alcohol with different cyclic secondary amines and affords the products in good to high isolated yield. Although benzylamine was converted into the corresponding amide in 65% yield, reactions of most primary amines and non-cyclic secondary amines tested resulted in the formation of imines as the major product. The same catalytic system was also used for the a effective amidation of morpholine with different benzylic, heteroatom-containing, and aliphatic alcohols. Given that a control reaction between benzyl benzoate and morpholine afforded the corresponding amide in high yield, it was suggested that the reaction between benzyl alcohol and amines could proceed via a pathway involving the initial formation of an ester that subsequently generates the amide.



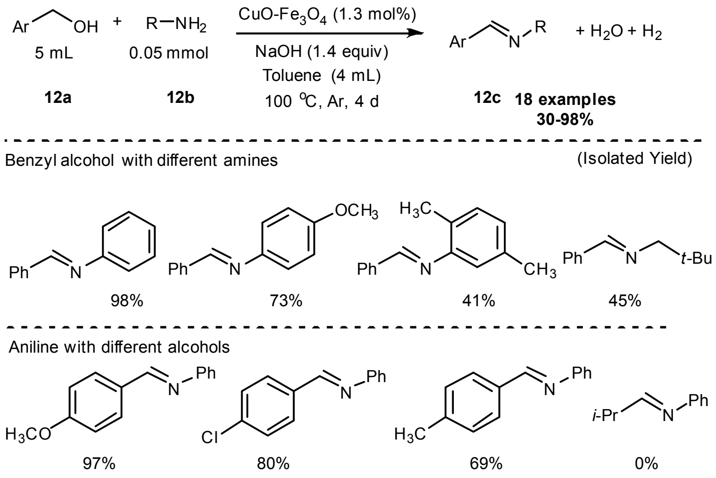
Scheme 11. Synthesis of amides from primary alcohols and secondary amines using an Ag/Al$_2$O$_3$ catalyst.



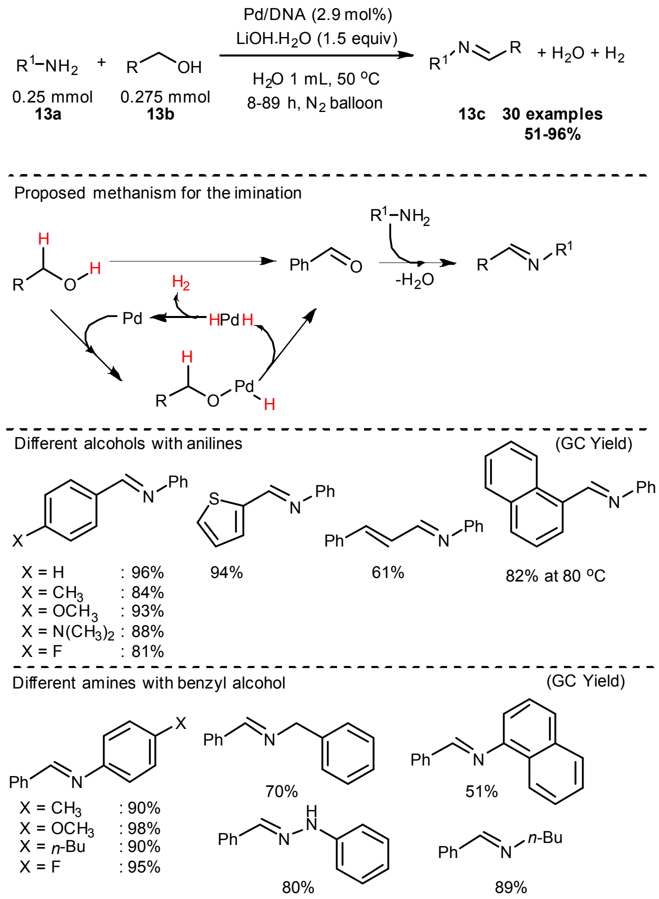
Scheme 12. Synthesis of amides from primary alcohols and secondary amines using an Au/HT catalyst.

3.2. Imines from alcohols and amines

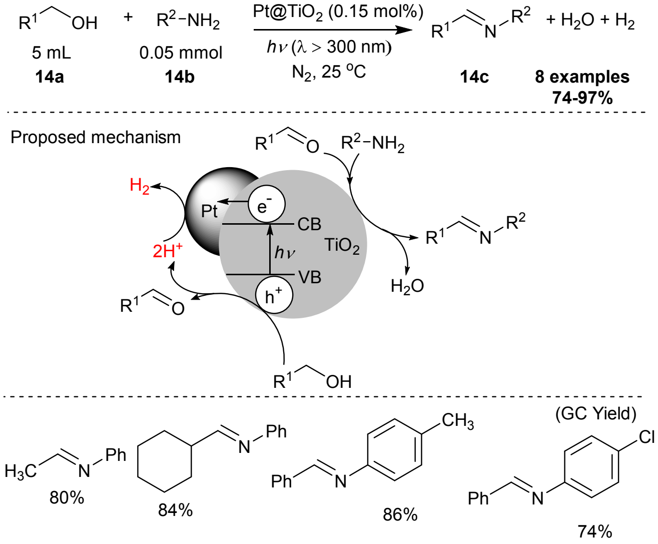
Due to their widespread use as electrophilic reagents in many transformations, such as reductions, condensations, additions, and cyclizations, imines are an important class of nitrogen-containing compounds. Traditionally, imines are synthesized by reactions between ketones or aldehydes and primary amines in the presence of acid catalysts.[107,108] In addition, self-condensation reactions of amines that occur upon oxidation and oxidations of secondary amines have been used to prepare imines.[109,110] The AD reaction, which produces imines from alcohols and primary amines, proceeds smoothly as the hemiaminal intermediates readily dehydrate under the applied reaction conditions. The same pathway is followed in reactions between benzylalcohols and anilines, which selectively produce stable *N*-arylimines. Several heterogeneous catalysts promote this process under acceptor-free conditions.[111–114] For example, the reaction between aniline and benzyl alcohol is catalyzed by Ag/Al_2O_3 in the absence of additives and generates the corresponding imine in 63% yield.[112] When this process is conducted in the presence of a Lewis-acidic co-catalyst such as $FeCl_3 \cdot 6H_2O$, hydrogen atoms that are transferred to the Ag catalyst in the first step participate in the reduction of the imine to afford *N*-benzylaniline.[112] Ramón *et al*. have developed a straightforward method for the synthesis of aromatic imines from benzylalcohols and anilines using $CuO\text{-}Fe_3O_4$ as a catalyst in the presence of NaOH (**Scheme 13**).[113] This catalytic system can be applied to a variety of primary alcohols and primary amines. Reactions of benzyl alcohol with different benzyl amines furnished the corresponding imines in moderate to high yield regardless of the presence of electron-withdrawing and -donating groups. Aliphatic amines also undergo this reaction. In addition, reactions between aniline and different benzyl alcohols generate the corresponding imines. In contrast, the corresponding reactions between aliphatic alcohols and aniline did not take place. Organosilicon-supported TiO_2 is able to promote this reaction, which occurs under solvent-free conditions in the presence of K_2CO_3 at 160 °C.[114] Wang *et al.* have reported that Pd nanoparticles stabilized by DNA (Pd/DNA) can serve as a reusable catalyst for the synthesis of imines from alcohols and primary amines under mild conditions, *i.e.*, at 50 °C in water containing LiOH under 1 atm N_2 (**Scheme 14**).[111] This method is generally applicable to reactions of a variety of alcohols and secondary amines. By virtue of its differential solubility in water and ethanol, Pd/DNA can be simply recovered from the reaction mixture and reused. Shiraishi and co-workers have developed a photocatalytic system that consists of TiO_2-loaded Pt nanoparticles ($Pt@TiO_2$), which promotes the one-pot synthesis of imines from alcohols and primary amines under UV irradiation at room temperature (**Scheme 15**).[115] This process occurs via the Pt-assisted photocatalytic oxidation of alcohols under concomitant formation of H_2 gas followed by condensation of the formed aldehydes with amines catalyzed by TiO_2. An advantage of this reaction is that it proceeds at room temperature, provides no harmful byproducts, and generates H_2 gas, which can be used as a clean energy source.



Scheme 13. Synthesis of imines from alcohols and amines using a $CuO\text{-}Fe_3O_4$ catalyst.



Scheme 14. Synthesis of imines from alcohols and amines using a Pd/DNA catalyst.

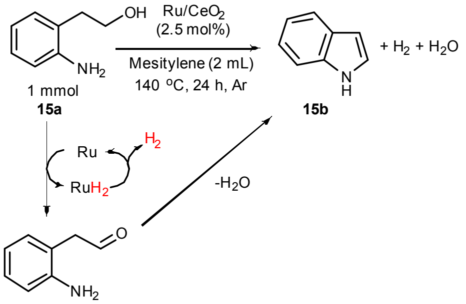


Scheme 15. Synthesis of imines from alcohols and amines using a Pt@TiO$_2$ photocatalyst under UV irradiation.

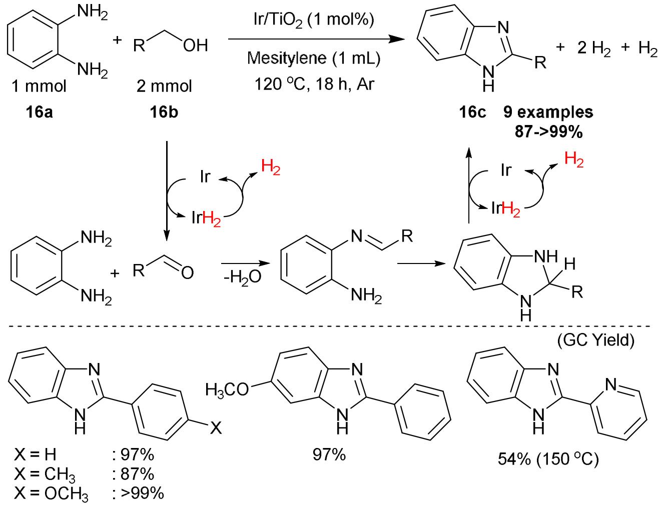
3.3. Indoles, Benzimidazoles, Quinazolinones, and Pyrroles

Indole is a common heterocyclic skeleton found in fine chemicals, natural products, pharmaceuticals agents, functional materials, and agrochemicals. Among the variety of reported methods for the synthesis of indole, the oxidative or dehydrogenative *N*-heterocyclization of 2-(2-aminophenyl)ethanol is particularly promising.[116,117] Wada and co-workers have devised an additive-free heterogeneous catalytic system for the promotion of the AD synthesis of indole from 2-(2-aminophenyl)ethanol (**Scheme 16**).[118] The catalytic cycle is initiated by the Ru-catalyzed dehydrogenation of the alcohol moiety in the substrate, followed by the formation of an intramolecular enamine from the generated aldehyde and the amine groups. Among the Ru-loaded metal oxides tested, Ru/CeO_2 and Ru/ZrO_2 showed high activity, while catalysts supported on SiO_2, Al_2O_3, TiO_2, and MgO were less effective. Ru/CeO_2 calcined at 200 °C exhibited the highest activity in a process that produces indole in >99% yield at 140 °C. Moreover, the catalyst can be recycled without significant loss of activity. It was proposed that a Ru^{IV}=O species interacting with CeO_2 or ZrO_2 represents the precursor for the catalytically active, reduced Ru species on the catalyst surface. Pt nanoparticles supported on acidic supports such as Nb_2O_5 and H-beta zeolite are also able to catalyze this reaction. For example, the reaction of 2-(2-aminophenyl)ethanol in the presence of 0.2 mol% of Pt/Nb_2O_5 or Pt/H-beta generated indole in 76% and 90% yield, respectively. Importantly, the reusability of Pt/Nb_2O_5 is better than that of Pt/H-beta.[119]

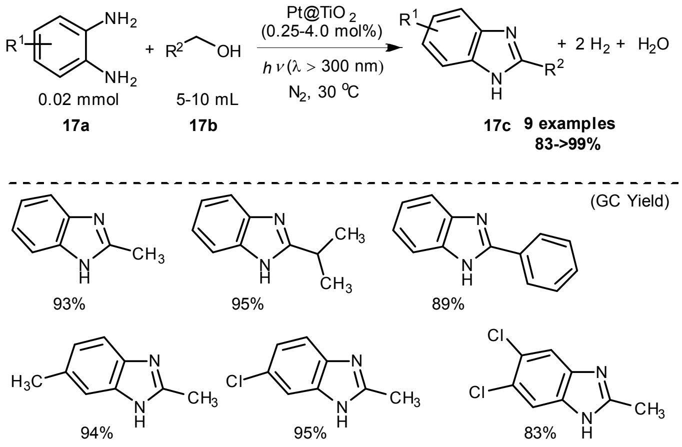
Five-membered heterocycles in the benzazole family include benzoxazoles, benzothiazoles, and benzimidazoles. These ring systems are present in natural products, pharmaceuticals, and agrochemicals. One promising method for the preparation of 2-substituted benzazoles involves the condensation of aldehydes with 2-aminothiophenols, 2-aminophenols, or 1,2-phenelynediamines, followed by oxidation with a strong oxidizing agent. ADC reactions using alcohols as reagents represent greener synthetic routes to these heterocycles.[120–124] Wada and co-workers have developed an additive-free heterogeneous catalyst for the AD synthesis of benzimidazoles from 1,2-phenelynediamines and primary alcohols (**Scheme 17**).[125] TiO_2-supported Ir metal clusters (Ir/TiO_2) catalyze these reactions, which form benzimidazole derivatives from phenylenediamines and various primary alcohols at 120 °C. It should be noted that reactions with pyridine-2-ylmethanol afforded the corresponding products in only 54% yield at 150 °C, while those with 4-flourobenzyl alcohol did not afford the corresponding product. A turnover number (TON) of more than 800 can be obtained when the reaction is carried out using a high substrate-to-catalyst ratio. Furthermore, the catalyst can be recycled without significant loss of activity, and negligible leaching of iridium species occurs during the process. Shiraishi *et al.* have described a photo-assisted, dehydrogenative method for the synthesis of benzimidazoles that uses Pt/TiO_2 as the catalyst (**Scheme 18**).[126] This reaction proceeds at room temperature under photoirradiation (λ > 300 nm). This method affords benzimidazoles in high yields from 1,2-diaminobenzene and various primary aliphatic and benzyl alcohols. The acceptorless coupling of 2-aminothiophenols with 1-octanol, promoted by Pt/Al_2O_3 in refluxing mesitylene, furnishes 2-substituted benzothiazoles in good to high yield (**Scheme 19**).[127]



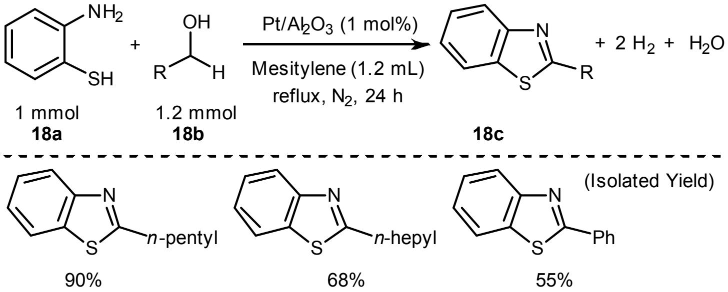
Scheme 16. Synthesis of indole from 2-(2-aminophenyl)ethanol using a Ru/CeO_2 catalyst.



Scheme 17. Synthesis of 2-substituted benzimidazoles from 1,2-phenylenediamine and primary alcohols using an Ir/TiO_2 catalyst.



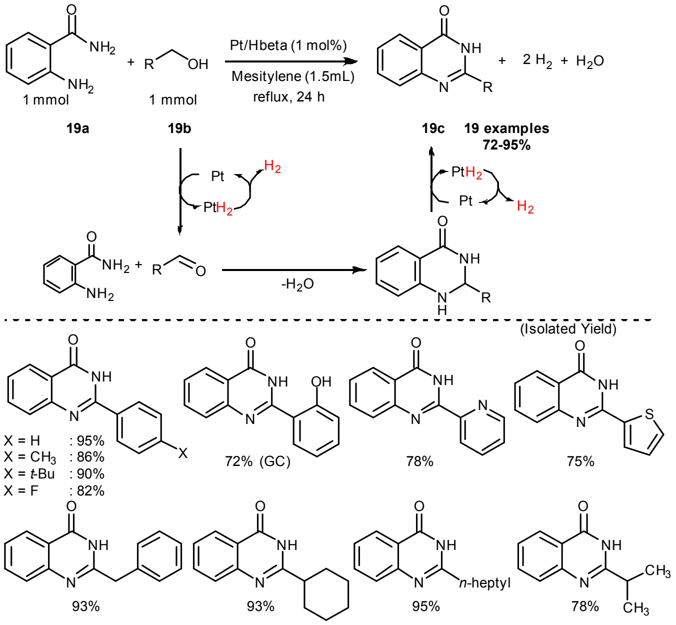
Scheme 18. Synthesis of 2-substituted benzimidazoles from 1,2-phenylenediamine and primary alcohols using a $Pt@TiO_2$ nanoparticle catalyst.



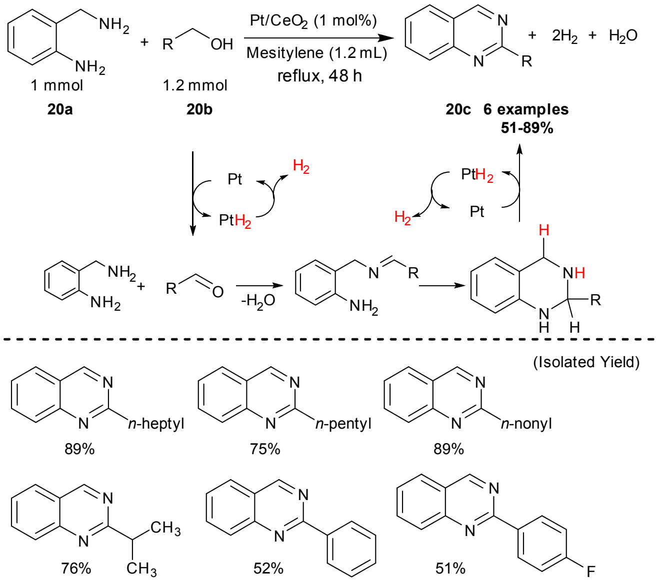
Scheme 19. Synthesis of 2-substituted benzothiazoles from 2-aminothiophenol with alcohols or aldehydes using a Pt/Al_2O_3 catalyst.

The quinazolinone system is an important structural framework in drugs, biological substances, and pharmaceuticals. Generally, quinazolinones are synthesized via the condensation of aldehydes with *o*-aminobenzamides to afford aminal intermediates, which are usually oxidized to quinazolinones using stoichiometric amounts of often hazardous oxidants. Homogeneous catalysts such as $[Cp^*IrCl_2]_2$ promote the oxidant-free direct conversion of primary alcohols and *o*-aminobenzamides to quinazolinones.[128,129] In this process, only H_2 gas and H_2O are generated as chemical waste. Pt-loaded H-beta zeolite was developed in our group as a heterogeneous catalytic system to promote the dehydrogenative cyclization of primary alcohols with *o*-aminobenzamide (**Scheme 20**).[130] Among various Pt supports (TiO_2, MgO, Y_2O_3, CeO_2, ZrO_2, Al_2O_3, SnO_2, SiO_2, C, Nb_2O_5, SiO_2-Al_2O_3, H-ZSM-5, and H-beta), H-beta showed the highest activity in this reaction. The scope of this reaction covers a wide range of alcohols and affords the corresponding quinazolinones in good to high yield. Benzyl alcohols with electron-rich or -poor substituents at the 4-position furnished the quinazolinones in high yield, similar to ethyl benzene, cyclohexyl methanol, and linear aliphatic alcohols, which also efficiently generate the quinazolinones. On the contrary, reactions of heterocyclic primary alcohols and α-substituted primary alcohols afforded the corresponding products in relatively low yield. The TON of this catalytic system is more than 25 times higher than those of the homogeneous catalytic systems. Mechanistic studies suggested that the reaction starts with a dehydrogenation, followed by a dehydrogenative condensation of the thus generated aldehyde with *o*-aminobenzamide to produce quinazolinones under concomitant elimination of water and liberation of H_2.

2-Quinazolines and 2-benzimidazoles are important biologically active substances. Recently developed methods for the preparation of 2-quinazolines and 2-benzimidazoles suffer from a limited scope and the need for basic additives and hydrogen-acceptors.[131] Therefore, an additive- and acceptor-free heterogeneous catalytic system has been developed for the synthesis of 2-quinazolines and 2-benzimidazoles from diamines and alcohols.[132] These efforts revealed that Pt/CeO_2 is an excellent catalyst for the 2-quinazoline-forming reactions between primary alcohols and 2-aminomethyl-phenylamine (**Scheme 21**). Moreover, it was discovered that aliphatic primary alcohols form the corresponding quinazolines more efficiently than benzyl alcohols. The results of mechanistic studies showed that these AD reactions initially generate aldehydes, which undergo a dehydrogenative condensation with 2-aminomethyl-phenylamine to form 2-quinazolines under concomitant elimination of H_2O and H_2. Examining different metal-oxide supports revealed a correlation between the O_{1s} binding energy of the supporting material measured by XPS and the product yield (**Figure 2**). The O_{1s} binding energy decreases with increasing electron density at the oxygen atom in the metal oxide or, in other words, the basicity of the metal-oxide surface. These findings suggest that basic oxides with a low O_{1s} binding energy should be the preferred catalyst supports for these reactions.[133,134] These results should serve as future guidelines for the design of catalyst supports, which have significant impact on the catalytic activity.[135]



Scheme 20. Synthesis of quinazolinones from *o*-aminobenzamide and primary alcohols using a Pt/H-beta catalyst.



Scheme 21. Synthesis of 2-substituted quinazolines from 2-aminobenzylamine and primary alcohols using a Pt/CeO_2 catalyst.

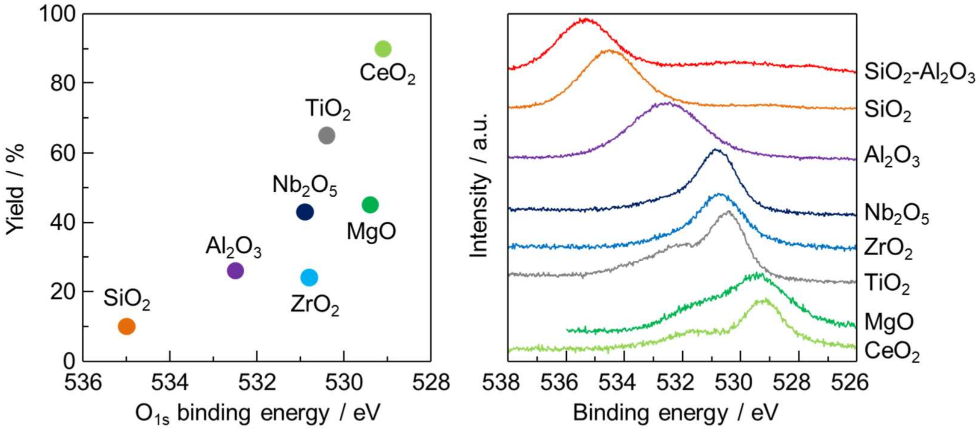
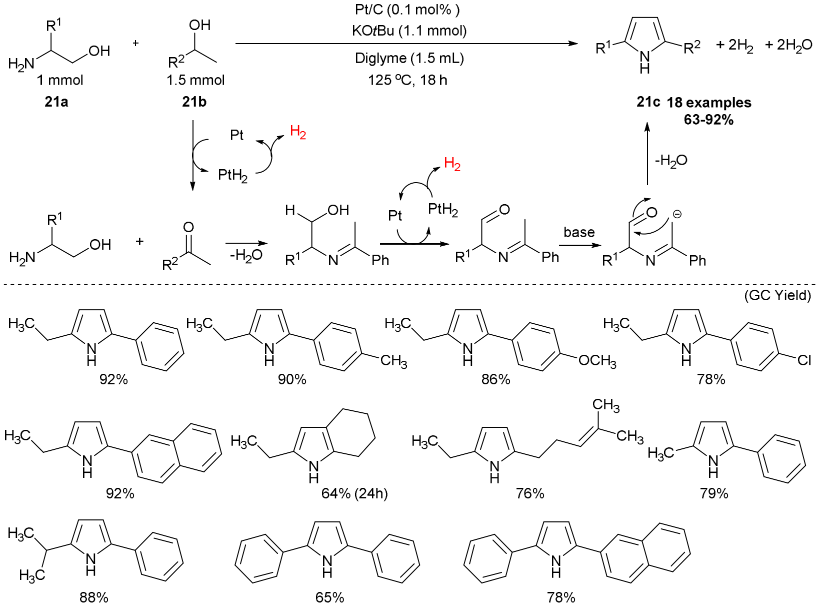


Figure 2. The yield of 2-heptylquinazoline, obtained from the reaction between 2-aminobenzylamine and *n*-octanol using Pt-loaded metal oxides, as a function of the O_{1s} binding energy of the supporting oxides.

The pyrrole ring system is a key structural motif in pharmaceuticals and other important chemicals. Recently, the groups of Kempe,[136] Saito,[137] and Milstein[138] have independently discovered new methods for the direct synthesis of pyrroles via the dehydrogenative condensation of 1,2-aminoalcohols with secondary alcohols (or ketones) promoted by homogeneous Ir or Ru catalysts in the presence of the basic additive KO*t*Bu. The Kempe group was the first to report that Ir@SiCN can serve as a heterogeneous catalyst for the acceptorless dehydrogenative synthesis of pyrroles from 1,2-aminoalcohols and secondary alcohols with KO*t*Bu.[139] Pt-nanoparticle-loaded carbon (Pt/C) also effectively promotes this reaction in the presence of KO*t*Bu and affords a wide range of pyrroles (**Scheme 22**).[140] The method has the advantage that the catalyst, which displays a high TON, can be prepared by a simple impregnation method and that it can be reused without significant loss of activity. This method generates pyrroles from 2-amino-1-butanol and various secondary alcohols such as 1-phenylethanols, as well as cyclic and acyclic aliphatic alcohols. Other aminoalcohols such as 2-amino-3-methyl-1-butanol, (*R*)-(-)-2-aminomethyl-1-butanol, and (*S*)-(+)-2-amino-2-phenylethanol with different secondary alcohols produced the corresponding pyrroles in moderate to high yield. The proposed mechanism for the reaction, outlined in **Scheme 22**, begins with a Pt-catalyzed dehydrogenation of the secondary alcohol to form a ketone, which subsequently undergoes the imine-forming condensation with the 1,2-aminoalcohol. The terminal alcohol group in the imine intermediate then undergoes Pt-catalyzed dehydrogenation, followed by a base-catalyzed condensation to give the 2,5-disubstituted pyrrole. The basic co-catalyst, KO*t*Bu, most likely promotes the dehydrogenation by assisting the deprotonation of the OH group.

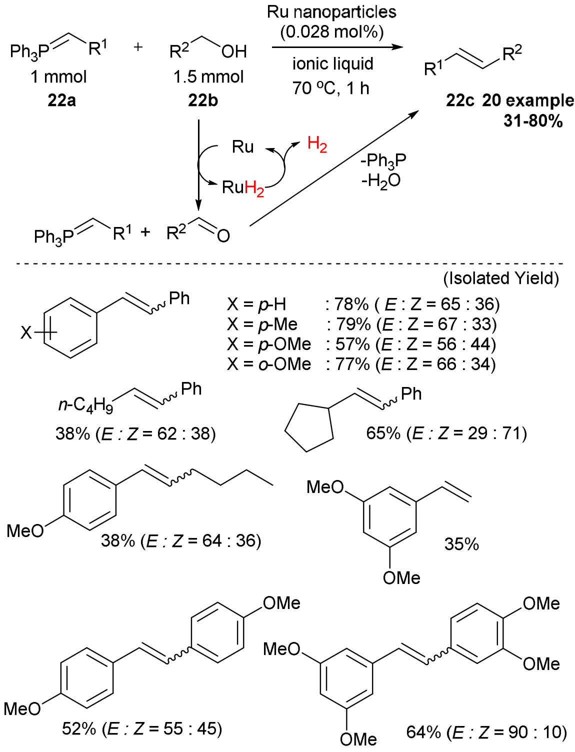


Scheme 22. Synthesis of 2,5-disubstituted pyrroles from 1,2-aminoalcohols and secondary alcohols using a Pt/C catalyst.

4. Reactions that form C=C and C–C bonds

4.1. Wittig-type olefination of alcohols with ylides

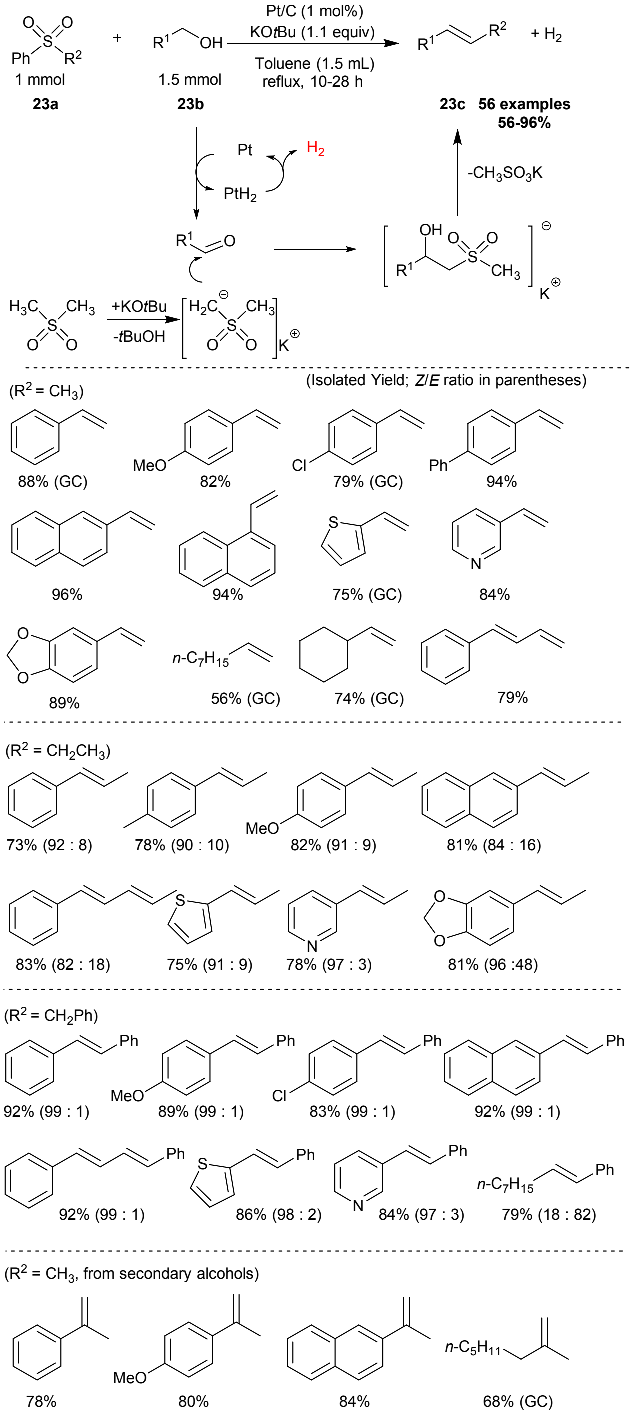
The Wittig olefination is one of the most important C=C-bond-forming reactions in organic chemistry.[141] Conventionally, this process involves the reaction of a phosphorus ylide with a ketone or aldehyde to generate the corresponding alkene and phosphine oxide.[141] Considering that alcohols are generally commercially available, more stable, and less expensive than the corresponding aldehydes or ketones, it would be advantageous to develop a protocol, in which the oxidation of alcohols to the corresponding carbonyl compounds and their subsequent Wittig reaction could be performed in a one-pot fashion. Several heterogeneous catalysts effectively promote this desirable one-pot olefination reaction of alcohols with Wittig reagents, albeit that they require the presence of O_2.[142,143] As Wittig reagents can react with oxidants, Milstein *et al*. have developed an acceptorless catalytic olefination of alcohols with Wittig reagents to form olefins and H_2 based on a homogeneous Ru catalyst.[144] Yus *et al.* have described a one-pot synthesis of stilbenes from benzyl alcohols using a Wittig-type olefination catalyzed by Ni nanoparticles.[145] However, this method is limited as it requires a stoichiometric amount of Ni. Recently, a pseudo heterogeneous catalytic system based on Ru nanoparticles in ionic liquids has been devised for the acceptorless Wittig-type olefination of alcohols.[146] This protocol delivers substituted stilbenes in high yield under mild conditions, albeit with merely low to moderate degrees of stereoselectivity (**Scheme 23**). Two other interesting features of the process include the simplicity of the work-up procedure, which involves removal of volatile organics from the reaction mixture followed by extraction of the ionic-liquid phase with diethyl ether, and the fact that the Ru-nanoparticle catalyst dispersed in the ionic-liquid phase can be easily reduced (H_2, 50 °C) and reused without significant loss of activity.



Scheme 23. Wittig-type synthesis of olefins from alcohols and ylides using a Ru-nanoparticle catalyst in an ionic liquid.

4.2. Olefination of alcohols with sulfones

The familiar Julia process,[147] like other olefination methods, uses carbonyl compounds as substrates. Milstein *et al.* have developed the first dehydrogenative protocol to perform the Julia-type olefination of benzylalcohols with sulfones using a homogeneous Ru catalyst and KO*t*Bu. Unfortunately, this method suffers from a limited scope and low TON.[148] Pt/C in the presence of KO*t*Bu effectively promotes dehydrogenative Julia-type olefination reactions of alcohols with sulfones.[149] Surveying various Pt-loaded catalysts revealed that Pt/C leads to the highest yield of stilbenes from benzylalcohol and dimethyl sulfone in the presence of KO*t*Bu under N_2. The reaction of benzylalcohol with dimethyl sulfone promoted by 0.02 mol% of Pt/C produces styrene in 79% yield with a TON of 3950, which is higher than that observed for the Ru-catalyzed reaction (TON = 25). An exploration of the substrate scope of this reaction with dimethyl sulfone (**Scheme 24**) showed that aryl, aliphatic, allyl, and heterocyclic primary alcohols form the corresponding terminal olefins in high yields. Further studies of the process showed that primary alcohols undergo Pt/C-induced reactions with phenyl ethyl sulfone to form the corresponding propenyl-benzene derivatives in high yield with high *E* selectivity. Moreover, reactions of primary alcohols with benzyl phenyl sulfone afford the stilbene derivatives in a highly *E*-selective fashion. Secondary alcohols also undergo the olefination with dimethyl sulfone under these conditions and generate the corresponding 2,2-disubstituted alkenes in moderate to high yield. Kinetic studies showed that the reaction orders with respect to benzylalcohol, dimethyl sulfone, and KO*t*Bu are 1.2, -0.6, and 1.5, respectively. This suggests that the alcohol and KO*t*Bu are in contrast to dimethyl sulfone involved in the rate-determining steps. The kinetic isotopic effect (KIE) on the process was determined via a reaction of dimethyl sulfone with a mixture of benzylalcohol and α,α-d_2-benzylalcohol. The results revealed a k_H/k_D value of 2.2 for this process, which indicates that the cleavage of the *α*-C–H bond of benzylalcohol, *i.e.*, the dehydrogenation of the alcohol, is a kinetically important step. Examining the effect of various additives showed that the styrene yield from the reaction of benzylalcohol with dimethyl sulfone increases with increasing basicity of the additives. Combined with the observed reaction order for KO*t*Bu (+1.5), this result indicates that the base-promoted step is also rate limiting. Thus, in the a proposed mechanistic pathway for the process (**Scheme 24**), Pt/C promotes the dehydrogenation of the alcohol to form an aldehyde or ketone, while KO*t*Bu deprotonates the sulfone to give the corresponding anion, which reacts with the carbonyl compound to yield a *β*-hydroxy sulfone intermediate that is subsequently converted into the olefin.



Scheme 24. Synthesis of olefins from alcohols and sulfones using a Pt/C catalyst.

5. Computational and mechanistic studies

5.1. Elementary steps in the dehydrogenation of the alcohols

Results from experimental observations show that the first step of the catalyzed dehydrogenative coupling reactions of alcohols involves the formation of the corresponding aldehydes and ketones. This step is followed by the ADC reaction of the carbonyl compounds with nucleophiles. Although the first step in these processes has been well studied,[150–160] it remains difficult to determine the elementary steps in both homogeneously and heterogeneously catalyzed reactions. Especially understanding the physical and chemical details of this reaction, which is induced by heterogeneous catalysts, represents a long-term goal in surface science.[161,162] Unfortunately, full catalytic cycles for the dehydrogenative coupling reactions of alcohols have rarely been obtained so far. Nevertheless, recent efforts using density functional theory (DFT) calculations and surface-science approaches have provided some important insights into the mechanistic aspects of ADC reactions of alcohols promoted by heterogeneous catalysts.[171–194] Great attention has thereby been given to the dehydrogenation reactions of methanol, owing predominantly to its structural simplicity and its potential applications in fuel cells (DMFCs) and as a hydrogen carrier. The obtained information also has important implications for synthetic chemistry.

A major question regarding the alcohol dehydrogenation process is whether the initial step involves the dissociation of the hydroxyl $\underline{H}$-O (eq. 1) of the primary alcohol or the hydrogen atom of the methylene $\underline{H}$-CHOH group (eq. 2):

O−H bond scission:

$$RCH_2OH \rightarrow RCH_2O^* + H^* \qquad (1)$$

C−H bond scission:

$$RCH_2OH \rightarrow RCHOH^* + H^* \qquad (2)$$

The first pathway includes an adsorbed RCH_2O intermediate, whereas the second involves an RCHOH intermediate. In the case of the dehydrogenation of methanol, the cleavage of O−H or C−H bonds in the respective CH_3O and CH_2OH intermediates sequentially forms CH_2O, CHOH, CHO, COH, and finally CO. Observations arising from early experimental studies on the dehydrogenation of methanol show that most of the late transition metals cause methanol to dissociate into CO and H_2 at temperatures of ~200-300 K under ultrahigh-vacuum (UHV) conditions.[168] The reaction involving methanol proceeds via an initial O−H bond scission (eq. 1) to form atomic hydrogen and a surface methoxide (CH_3O) species that subsequently undergoes successive C−H bond cleavage reactions to ultimately form CO on the metal surface. A stable methoxy species exists on Cu and Ag surfaces, where it decomposes into gaseous formaldehyde and H_2 at higher temperatures.[169,170] In addition, in a study examining the decomposition of methanol over Pt(110) under UHV conditions using isotope substitution, Masel *et al.*[171] have shown that the methanol degradation reaction proceeds via an initial scission of an O−H bond, which yields a methoxy intermediate. Similar results were obtained when supported Pt particles were employed to promote the process.[172] While most of the results of experimental studies suggest that the dehydrogenation of methanol involves an initial scission of the O−H bond, followed by a subsequent scission of the C−H bond,[173] computational studies on this process suggest that the nature of the metal and its surface structure determine whether the scission of the O−H bond or the C−H bond occurs first.[171,172,197] Another contradiction between experimental and theoretical results[178] appears to have been resolved in a recent DFT study by López and co-workers, who reported that coverage effects might cause the first step on some metals such as Pt and Ru to change from C−H to O−H bond cleavage, and thus be responsible for the discrepancy between experimental and theoretical results. López has also suggested that solvation effects need to be considered, given that they can influence the energetics of the steps involved in the dehydrogenation pathway.[179]

Dehydrogenation reactions of other alcohols over heterogeneous catalysts have also been investigated by DFT calculations. In a study on the dehydrogenation of propanol over Cu(111), Neurock and co-workers have determined that the activation energy for the cleavage of the O–H or C–H bond in absorbed propanol are 115 and 143 kJ mol^{-1}, respectively. In addition, they have reported that the activation energy for the cleavage of the O–H bond in propanol decreases to 70 kJ mol^{-1} with increasing surface coverage of propanol, as high coverage results in the formation of hydrogen-bonding networks, which stabilize the transition state for the O–H bond cleavage. While hydrogen-bonding interactions at high levels of propanol coverage would also help to promote the formation of alkoxy intermediates on the catalyst surface, the high activation barrier for the cleavage of the C–H bond (115 kJ mol^{-1}) should most likely not be affected by higher levels of coverage and thus remain prohibitive. Cramer *et al.* have reported the results of a computational investigation on AAD carried out over metal–organic frameworks (also known as porous coordination polymers).[180] The findings show that among the transition metals of the first row (*e.g.* Fe, Co, Ni, Cu, and Zn) supported on NU-1000, which consists of $[Zr_6(\mu_3\text{-}O)_4(\mu_3\text{-}OH)_4(OH)_4(OH_2)_4]^{8+}$ nodes and tetratopic 1,3,6,8-tetrakis(*p*-benzoate) pyrene linkers,[181] the Co and Ni derivatives exhibited turnover-limiting free energies of activation of 28.5 and 26.5 kcal mol^{-1}, respectively, and thus the most promising potential as catalysts. Hence, these studies suggest that a variety of materials should be capable of promoting AD reactions.

5.2. Effects of the support material and the importance of the metal/support interface

In many supported metal-catalyst systems, the catalytically active sites are considered to be located at the interface between the metal and the support.[182–185] Despite their potential importance, these interfaces and the chemistry occurring there have so far not been examined systematically, mostly due to the complexity of such surfaces and the processes involved. Lyalin *et al.* have described a theoretical investigation on the elimination of H_2 from isopropanol catalyzed by free and θ-Al_2O_3(010)-supported Ni_{13} clusters.[186] The θ-Al_2O_3(010) surface was selected for this investigation as experimental work has shown that Ni/θ-Al_2O_3 exhibits high catalytic activity for the dehydrogenation of secondary alcohols.[187] It has also been reported that the acid/base properties, such as the electronegativity, of the support material plays a significant role in such dehydrogenation reactions, suggesting that the co-existence of acidic and basic sites on the surface of the oxide support is of critical importance for the success of the Ni-catalyzed dehydrogenation of alcohols (**Figure 3**). It should also be noted that the electronegativity of these supports was obtained according to a model reported by Sanderson.[188] Computational investigations have shown that the dehydrogenation of isopropyl alcohol on free Ni_{13} clusters occurs via a two-step pathway that involves an initial elimination of H_2 from the alcohol hydroxyl group, followed by cleavage of the C−H bond. The results show that the O−H hydrogen transfer to the Ni_{13} cluster represents the rate-determining step with a barrier of 0.95 eV, while the cleavage of the C−H bond from the surface alkoxy species has a barrier of 0.41 eV. When the isopropyl alcohol is adsorbed on the Al surface in close vicinity to the Ni_{13} clusters supported on θ-Al_2O_3(010), the energy barrier for the cleavage of the O-H bond is considerably decreased due to the formation of complementary adsorption sites at the metal/support interface. Thus, the calculated barrier for the hydrogen transfer from the OH group of the isopropyl alcohol becomes negligible (~0.05 eV), while that for C−H bond cleavage (0.38 eV) is similar to that in the free Ni_{13} clusters. These results demonstrate that the intermediate formation of C−Ni bonds in the transition state promotes the cleavage of the C−H bond. These studies thus provide fundamental insights into the mechanistic details of the oxidant-free catalytic dehydrogenation of alcohols on supported nickel clusters. In addition, the studies demonstrate the importance of the metal/support interface, which represents a potential strategy for the rational design of novel types of multifunctional catalysts based on inexpensive and abundant noble-metal-free materials.[189]

Rahman *et al.* have investigated the impact of this interface on the dehydrogenation of methanol.[190] The results of their DFT studies revealed that the increased activity of Au_{13}/TiO_2(110) at interfacial sites originates from charge-transfer-induced coulombic interactions between gold, the reactant, and the reducible TiO_2 support that results from the formation of an ionic O−Au bond between gold and a methoxy group, which renders the participating gold atom cationic. A direct result of the charge-transfer-induced repulsive interaction between cationic gold and the positively charged carbon moiety of the methoxy group is the activation of the latter. This change manifests in a pronounced C−O bond elongation and a tilting of the methoxy axis, which facilitates the C−H bond scission.

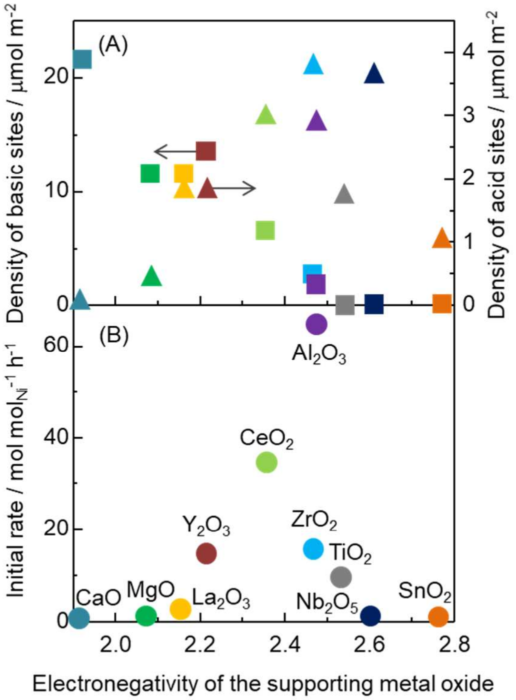


Figure 3 (A) Surface density of basic and acidic sites and (B) reaction rates per total mole of Ni for the dehydrogenation of 2-octanol as a function of the electronegativity of the supporting metal oxide.

5.3. Electronic effects

Rationalizing the properties and behavior of (heterogeneous) catalysts are challenging but inevitable tasks in order to understand the underlying phenomena and ultimately develop rational guidelines for the design of improved catalysts. As the catalytic properties of catalysts should in principle be governed by their electronic structure, electronic factors need to be taken into account in order to gain a more holistic understanding of the catalyst properties. Although a sufficiently accurate theoretical model is not yet available for heterogeneous catalysts, the d-band center represents a versatile descriptor that has already been used for various catalytic reactions. A study on the dehydrogenation of 2-octanol has demonstrated that the d-band-center model can be employed to rationalize the catalytic activity of different metals in AD reactions (**Figure 4**).[191] Especially, platinum, which was the most active metal tested, displays a moderate d-band-center value and a volcano-type correlation for the reaction. It should be noted that the d-band-center model of the metals in Al_2O_3-supported Ag, Cu, Pt, Ir, Pd, Rh, Ru, Ni, and Co generally serves as a good descriptor of the catalytic activity in AD processes. In addition, recent results obtained from DFT calculations in a related area have shown that the adsorption energy of hydrogen atoms on the metal surfaces can also be used as a simple descriptor in order to rationalize the activity of *C*-methylation reactions.[192] This concept is based on the fact that adsorption is a fundamental step in surface-catalyzed reactions that follows the Brønsted−Evans−Polanyi (BEP) relation as well as a Sabatier-type trade-off, which exists between the adsorption of reactants and the desorption of products, so that catalysts that exhibit optimal adsorption energies afford maximal catalytic activity.[193,194] Although the aforementioned *C*-methylation example proceeds via a hydrogen-borrowing reaction mechanism, this rationalization could potentially be applied to ADC reactions. These findings should thus afford additional insights into the catalytic activity of metals in AD reactions, which could be used for the future design of catalysts without the need for extensive trial-and-error experimental testing.

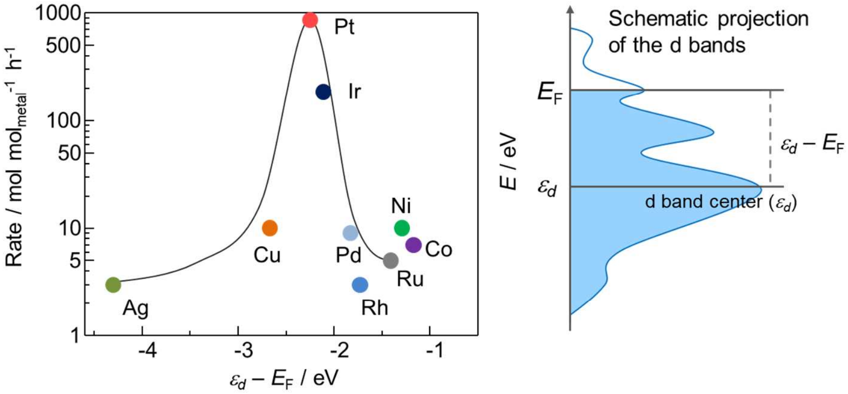


Figure 4 Left: Plot of the initial rate for the dehydrogenation of 2-octanol using various metals loaded onto Al_2O_3 as a function of the d-band center of the metals (ε_d) relative to the Fermi energy (E_F).

Right: schematic illustration of the relationship between the Fermi energy and the d-band center.

6. Summary and outlook

In this review, we have summarized recent results of studies on acceptorless dehydrogenative coupling (ADC) reactions of alcohols promoted by heterogeneous catalysts, a process that can be used for the construction of C–O, C–N, C–S, C–C, and C=C bonds. A major advantage of this method is that these reactions can usually be carried out in a one-pot fashion, and that the generated H_2 can be used as an energy source. It is important to note that analogous reactions promoted by homogeneous organometallic catalyst systems generally require (stoichiometric) amounts of additives (e.g. ligands, acids, or bases), which decreases the atom economy and increases the costs. In contrast, most state-of-the-art heterogeneous catalyst systems operate under additive-free conditions. A key feature of metal-loaded acidic and/or basic metal oxides used to catalyze some of these processes is their multifunctional nature. To date, catalysts for ADC reactions have mostly been designed empirically, and appropriate combinations of metals (with suitable oxidation state and size) and support materials have been determined using screening studies. This less-than-ideal approach is a consequence of the lack of fundamental knowledge on the multifunctional catalysis that occurs at the interface between the metals and the support material. Mechanistic details that will be revealed in future theoretical studies, as well as the development of novel methods for the preparation of structurally well-defined multifunctional catalysts should accelerate the rational design of new heterogeneous catalysts for ADC reactions. Another challenge in the development of AD reactions is the transformation of relatively unreactive substrates such as alkanes, which is currently regarded as a formidable task, even for homogeneous transition-metal catalysts.[195–199]

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TOC

(5.7 cm x 4 cm)

Recent examples for the acceptorless dehydrogenative coupling reactions of alcohols over heterogeneous catalysts for the one-pot synthesis of value-enhanced chemicals are reviewed.