Methanol Activation: Strategies for Utilization of Methanol as C1 Building Block in Sustainable Organic Synthesis

Hung-Vu Tran,*[a] Tuan Thanh Dang,*[b] Nguyen Hoang Nguyen,[b] Huyen Thu Tran,[c] Dung Tien Nguyen,[d] Dang Van Do,[b] Thanh Son Le,[b] Thuong Hanh Ngo,[d] Yawa K. E. Late,[e] Prince N. Amaniampong,[e] Eugene Fletcher,[f] Tran Quang Hung,[g] Yuran Cheng,[h] Tuan Khoa Nguyen,[h] Tuan Sang Tran,[h] Jun Zhang,[h] Hongjie An,[h] Nam-Trung Nguyen,*[h] Quang Thang Trinh*[h]

[a] Dr. H.-V. Tran
NTT Hi-Tech Institute, Nguyen Tat Thanh University, 298-300A Nguyen Tat Thanh St, District 4, Ho Chi Minh City 7280, Vietnam.
E-mail: hung.tranvu@gmail.com; tranhung@ntt.edu.vn

[b] N.H. Nguyen, Prof. D.V. Do, Prof. T.S. Le, Prof. T.T. Dang
Faculty of Chemistry, VNU University of Science, Vietnam National University, Hanoi, 19 Le Thanh Tong, Hoan Kiem, Hanoi, 11021, Vietnam.
Email: dangthanhtuan@hus.edu.vn

[c] H.T. Tran
Department of Chemistry, Simon Fraser University, Burnaby, BC V5A 0A7, Canada.

[d] Dr. D.T. Nguyen, Dr. T.H. Ngo
Vietnam University of Traditional Medicine, No. 2 Tran Phu St, Ha Dong, Hanoi, 12110, Vietnam

[e] Y.K.E. Late, Dr. P.N. Amaniampong
CNRS, Institut de Chimie des Milieux et Matériaux de Poitiers, Université de Poitiers, 1 rue Marcel Doré, Bat B1 (ENSI-Poitiers), 86073 Poitiers, France

[f] Prof. E. Fletcher
Department of Biology, Carleton University, Ottawa ON K1S 5B6, Canada.

[g] Dr. T.Q. Hung
Institute of Chemistry, Vietnam Academy of Science and Technology, 18 Hoang Quoc Viet, Hanoi, Viet Nam.

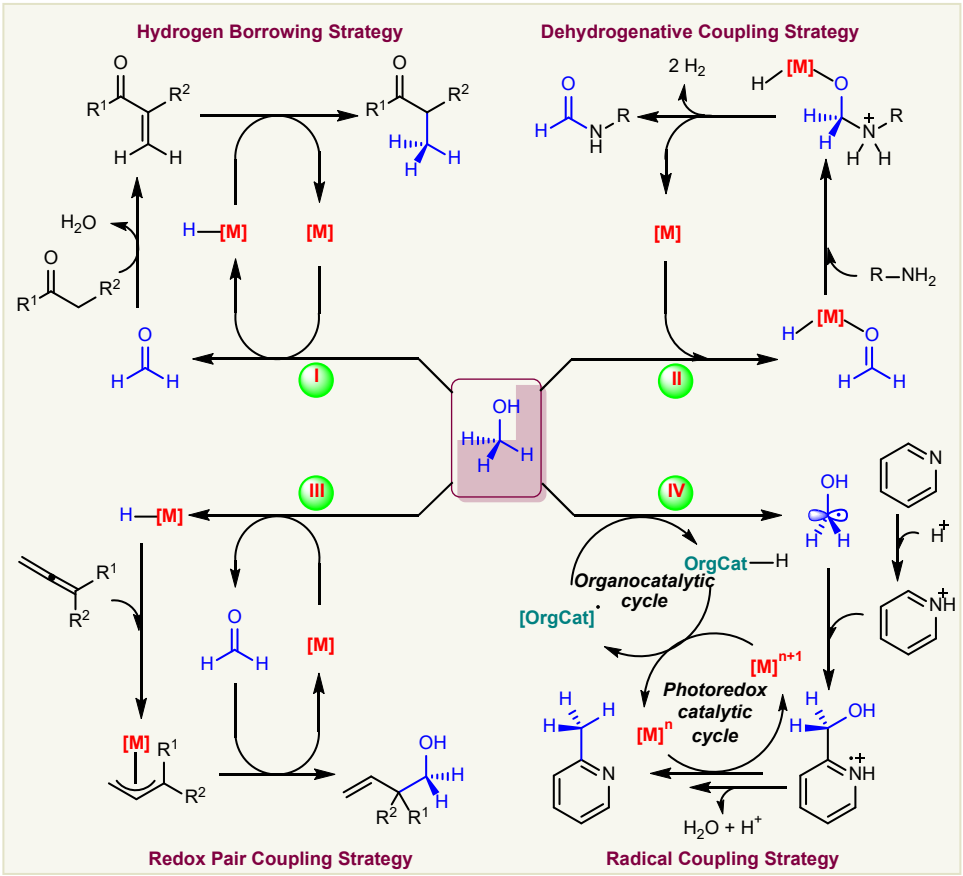
[h] Y. Cheng, Dr. T.K. Nguyen, Dr. T.S. Tran, Dr. J. Zhang, Prof. H. An, Prof. N.-T. Nguyen, Dr. Q.T. Trinh
Queensland Micro and Nanotechnology Centre, Griffith University, Nathan, Queensland, 4111, Australia.
E-mail: nam-trung.nguyen@griffith.edu.au (N-T.N.)
t.thang@griffith.edu.au (Q.T.T.)

Abstract: The development of efficient and sustainable chemical processes which use greener reagents and solvents, currently play an important role in current research. Methanol, a cheap and readily available resource from chemical industry, could be activated by transition metal catalysts. This review provides a systematic summary of strategies for methanol activation and the use in organic chemistry. Based on these strategies, many new synthetic methods have been developed for methanol utilization as the C1 building block in methylation, hydromethylation, aminomethylation, formylation reactions, as well as the syntheses of urea derivatives and heterocycles. The achievements, synthetic applications, limitations, some advanced approaches, and future perspectives of the methanol activation methodologies have been described in this review.

1. Introduction

Methanol, produced from natural gas, coal, carbon dioxide (CO_2), and biomass (about 65 million tons annually),[1] is an enormous, cheap and renewable feedstock with many well-established processes in chemical industry (methanol-to-gasoline, methanol-to-olefins, methanol-to-acetic acid,…).[2] It has even been considered as a future energy carrier and synthetic feedstock in the "methanol economy".[3] Recently, the "*waste to methanol*" appears as a potential technology for efficient chemical recycling of municipals waste and presents an important contribution towards building a circular and sustainable chemical supply chain.[4] In fact, methanol can be activated by transition metal catalyzed transformation to the more reactive formaldehyde, with formation of metal-hydrides or release of hydrogen gas.[5] Based on these formations of formaldehyde and metal-hydrides/hydrogen gas, many new synthetic methods have been developed for methanol utilization as the C1 building block in methylation, hydromethylation, aminomethylation, formylation reactions, as well as the syntheses of urea derivatives and heterocycles.[6] Notably, the by-products of these reactions are only environmentally benign water and, in some case, hydrogen. Therefore, these transformation routes provide an alternative greener[7] and more sustainable approach for conventional methods which generally require the use of reactive and toxic species in harsh conditions, together with the employing of stoichiometric amounts of various additives and co-catalysts. Because of that, copious stoichiometric quantity of wastes, which are often toxic, has been generated at the end of those conventional methods.[7-8] Hence, the direct use of methanol as the C1 source in organic synthesis, *via* transition metal-catalyzed methanol activation, is promising towards developing green and sustainable manufacturing technologies in the near future.

While the activation of higher alcohols has been in a relatively advanced stage, the methanol activation is still a drawback. The activation energy of methanol is significantly higher than that of other higher alcohols, such as ethanol (ΔH = +84 vs. +68 *kJ*.mol^{-1}), making it challenging to activate under mild conditions.[9]That has not been solved until recently with a series of novel transition metal catalysts, based on Ru, Ir, Rh and Mn, for efficient activation of methanol. Hinged on these novel catalysts, several transformations using methanol as C1 building block have already been developed in very recently years.[10] Considering the importance of methanol activation methods in modern organic synthesis, together with enormously potential applications in fine chemical and pharmaceutical industries, we believe that a review with particular emphasis on a systematic classification of the strategies used for methanol activation is useful for broad readers with long-term effects in both academy and industry. In the interest of brevity, we limit this review to the transition metal-catalyzed transformations with the formation of new bond between the carbon atom in methanol and another atom of the coupling partners. Beside highlighting new methods in methanol activation, this review also aims to bring perspectives to the limitations, and possible developments in the field. We also spotlight some applications of these methods in organic synthesis and medicinal chemistry as well as feature some advanced techniques, which have been used to promote the research on methanol activation.



Scheme 1. Main strategies for transition metal-catalyzed methanol activation in organic synthesis.

In general, methanol has been activated via four main transition metal-catalyzed strategies (Scheme 1). The most common approach is hydrogen borrowing (HB) strategy (Scheme 1, path I). The reaction starts with a hydrogen transfer from methanol to a transitional metal catalyst and generates the metal-hydride species together with formaldehyde. Subsequent condensation of the

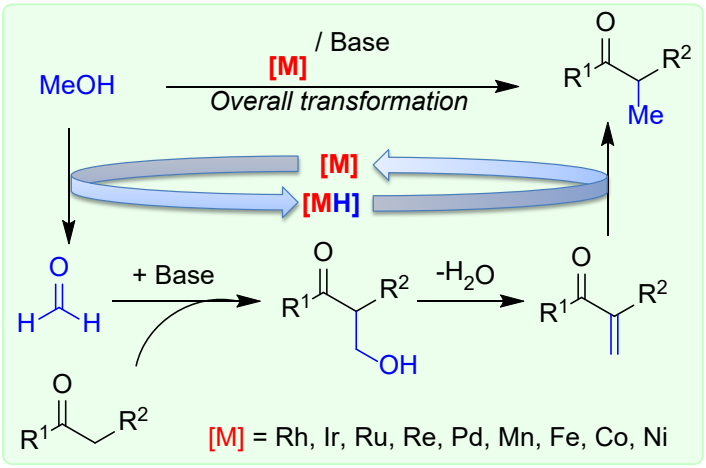
new-formed formaldehyde with a carbonyl compound would lead to the formation of an *α, β*-unsaturated carbonyl intermediate. This intermediate is then transformed into *α*-methylated product *via* hydrogenation with the metal-hydride species. The mechanism for the dehydrogenative coupling strategy (Scheme 1, path II) is still under consideration. However, it is possible that in this case, amine attaches to the transition metal-coordinated formaldehyde then follows by dehydrogenation to produce the formamide. Therefore, there is no free formaldehyde in the solution. Whereas in the case of HB strategy, the formaldehyde dissociates from transition metal catalyst to solution before reacts with amine to form free hemiaminal in the solution. An elegant approach in methanol activation is the redox pair coupling strategy (Scheme 1, path III). In these transformations, metal-hydride intermediate migratory inserts to a *π*-system compound (e.g. allene), following by the reaction with formaldehyde to generate hydrohydroxyl methylation product. Scheme 1, path IV represents a general mechanism for methanol activation *via* radical strategy developed by Jin and MacMillan.[11] This bio-inspired strategy engages organocatalysis with transition metal photoredox catalysis. The reaction starts with the initial formation of hydroxylmethyl radical via an organocatalytic cycle. Hydroxylmethyl radical adds to a protonated pyridine producing a radical cation intermediate, which is transformed to desired methylated product via a photoredox catalytic cycle.

2. Hydrogen Borrowing Strategy in Methylation Reactions using Methanol

Methylation is one of the most essential chemical transformations, playing a crucial role in the synthesis and functionalization of bioactive molecules.[12] In fact, methyl fragment is present in more than 67% of top selling pharmaceuticals and is responsible for adjusting both physical and biological properties of the molecules.[13] Consequently, methods for introduction of methyl group to organic compounds have been important topics of current research in both academia and industry.[14] Classical methylations often use highly toxic methyl halides, diazomethane and dimethyl sulfate as methylating reagents, which have a tendency to produce over-methylated products causing selectivity issues.[15] This not only affects overall product yield but also causes separation challenges, in addition to producing toxic halogenated wastes that require additional downstream processing, increasing production costs. In this context, the utilization of readily available, inexpensive, and less-toxic methanol as a methylating reagent via the recently developed catalytic hydrogen borrowing method gives a green and sustainable alternative for the direct methylation of amines, alcohols, carbonyls, nitriles, and related compounds.[16]

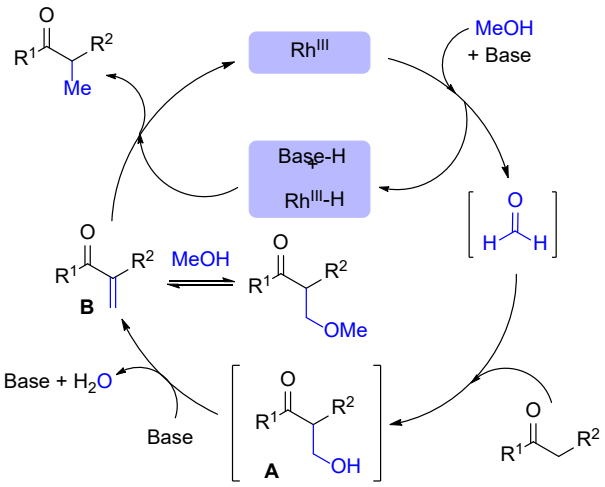
2.1. α-Methylation of carbonyl and related compounds

α-Methyl ketones, esters and related compounds are present in many important and pharmaceuticals[17] and bioactive natural products[18]. Therefore, the development of green and convenient catalytic α-methylation methods of these compounds has been necessary and attracted much attention. Recently, in light of new research based on the hydrogen borrowing methodology, direct transition-metal catalyzed α-methylation of carbonyl compounds using methanol offered an efficient and sustainable approach to α-methylated carbonyl compounds, in which, the only by-product is water.[5b, 5d, 6g, 19] A general mechanism for this kind of reaction is described in Scheme 2. The initial step in this process utilizing a transition metal catalyst is the oxidation of methanol to formaldehyde, which results in the formation of a metal-hydride intermediate as a catalytic active species. Then, the aldol condensation of a carbonyl compound with formaldehyde produces enol A, (Scheme 3) which could be dehydrated to give an α, β-unsaturated carbonyl compound B (detected as an intermediate). The last step is the reduction of intermediate B by metal-hydride, resulting in the formation of the α-methylated product and the regeneration of the transition metal catalyst.



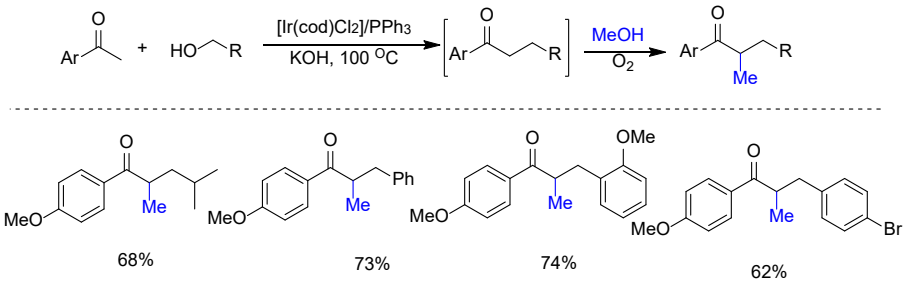
Scheme 2. Pathway for transition metals catalyzed α-methylation of ketones and related compounds.

Transition metal catalysts such as Rh, Ir, and Ru have often been designed using methanol as the methylating reagent to facilitate the α-methylation of ketones. In 2014, the first Rh-catalyzed α-methylation of ketones using methanol was reported by Donohoe's group (Scheme 3).[20] In the same year, Obora *et al*. developed a practical Ir-catalyzed α-methylation of ketones using methanol.[21] Up to 91% yield of α-methylated ketones were achieved in the presence of $[IrCp^*Cl]_2$ (5 mol%) at 120°C. In this study, the choice of bases (50 mol%) may give control over mono- or double-methylated products. The Ir-catalyzed α-methylation of benzyl ethyl ketone with methanol in the presence of a strong base (KOH) resulted in the formation of double-methylated product, while only mono-methylated product was formed when a weak base (Na_2CO_3) was used. Interestingly, three-component one-pot procedure for α-methyl-alkylations of methylketones with methanol and a primary alcohol in the presence of $[IrCp^*Cl_2]_2$ (5 mol%) was successfully achieved in up to 90% isolated yield of the desired products.

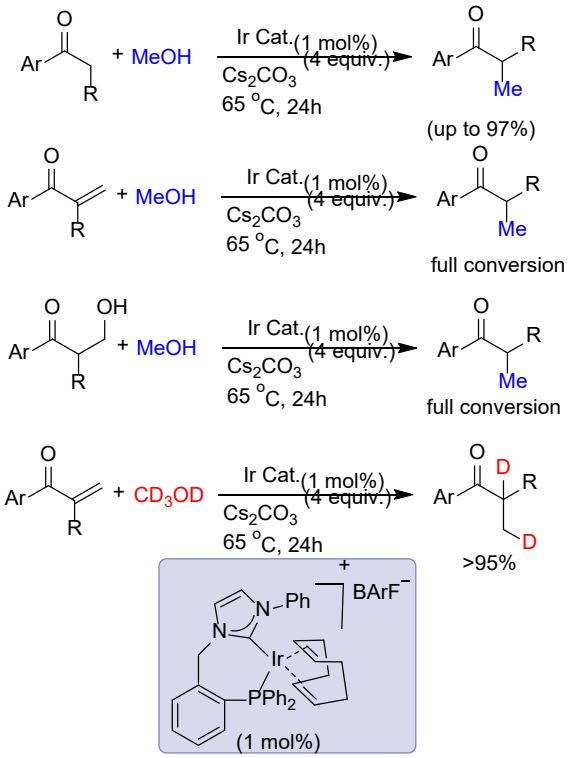


Scheme 3. Plausible mechanism for Rh-catalyzed α-methylation of ketones with methanol by Donohoe's group.

Another Ir-catalyzed α-methylation of ketones using methanol was also disclosed by Donohoe and coworkers.[22] A simple, mild condition (at 65ºC) using $[Ir(COD)Cl_2]_2$ (1 mol%) in the combination of PPh_3 (4 mol%) as a single catalyst under oxygen atmosphere was demonstrated to be convenient for both mono-methylation of *p*-methoxyacetophenone (Scheme 4). This protocol could be used for a double alkylation of *p*-methoxyacetophenone with alcohols at 100ºC. Subsequently, the second Ir-catalyzed α-methylation of the intermediate with methanol was carried out by adding PPh_3, KOH, and a balloon of oxygen to form α-methylated products in high yield. Due to the difficulty in hydrogenation transfer step, the use of oxygen (O_2) is crucial to improve the reactivity of methylation reaction. The presence of O_2 significantly improves the yield and is speculated to regenerate the metal hydride after the oxidation of MeOH to formaldehyde.



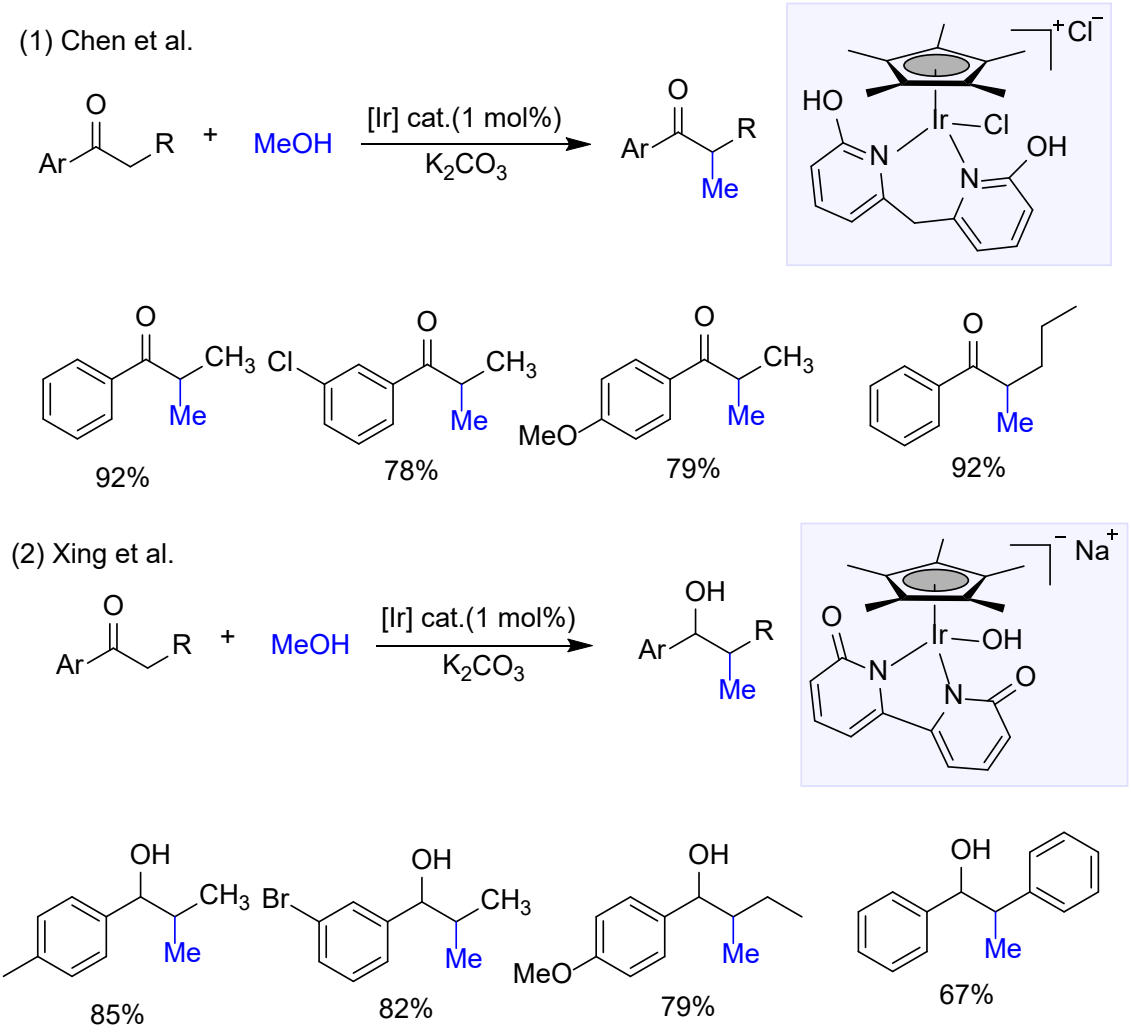
Scheme 4. Ir-catalyzed tandem synthesis of highly functionalized ketones using methanol.



Scheme 5. Mechanistic studies on α-methylation of ketones catalyzed by Ir.

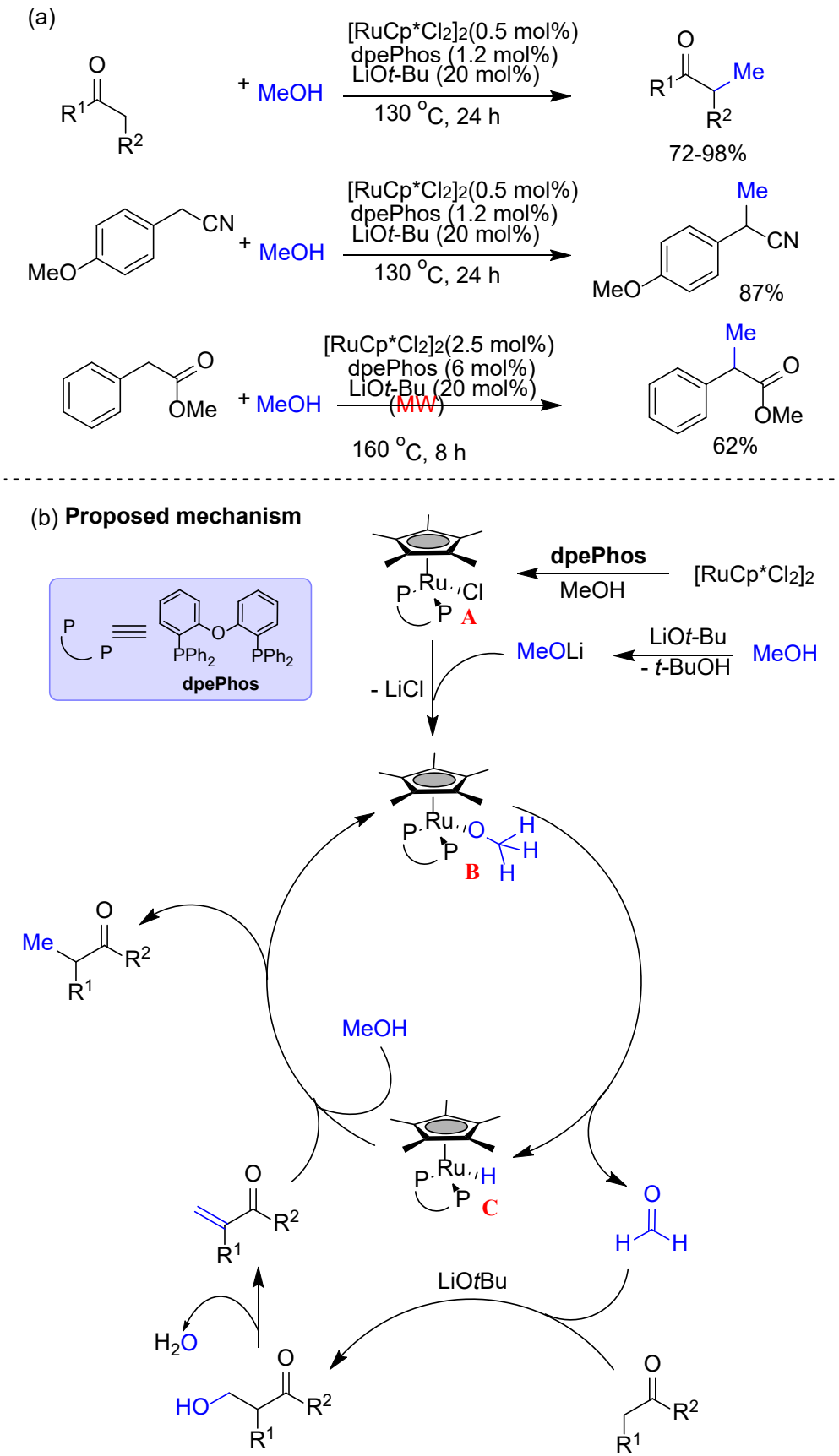
Andersson et al. described a highly efficient NHC-phosphine iridium catalyst system for α-methylation of ketones using methanol under mild condition (65°C).[23] Up to 97% yield of α-methylated products were achieved when using 4 equiv. base (Cs_2CO_3) with low catalyst loading (1 mol%). Some mechanistic studies were performed to understand more about the hydrogen transfer process (Scheme 5). The two possible intermediates were prepared and used under standard conditions. Both reactions are fully converted to desired product. The employment of CD_3OD as solvent gave more than 95% yield of deuterated product. The control experiment in the absence of Ir catalyst was conducted which did not form the desired product. Similar C-methylation transformations were recently reported for Ir catalysis, for examples, [Cp*Ir($HOC_5H_3CH_2C_5H_3OH$)Cl][Cl],[24] [IrCl(cod)]$_2$/dppe,[16e] and [Cp*IrCl$_2$]$_2$. Obora et al. also applied [IrCl(cod)]$_2$/dppe catalytic system for the methylation of more challenging esters using methanol.[16e] In this study, both monodentate and bidentate phosphine could be successfully used for this transformation.

Recently, Xing et al. disclosed a general method for the preparation of β-methylated secondary alcohols via tandem α-methylation/transfer hydrogenation process from non-methylated ketones with methanol in the employment of a Cp*Ir complex containing bipyridine-based functional ligand [Cp*Ir(2,20-bpyO)(OH)]Na (Scheme 6).[25] The possible mechanism involving Ir complex was proposed via two cycles. Especially, H_2 could be produced from dehydrogenation of methanol reacting with Ir catalyst to give Ir-H complexes. Then, these *in-situ* formed Ir-H complexes reduced α-methylated ketone intermediate to afford to β-methylated secondary alcohol product.



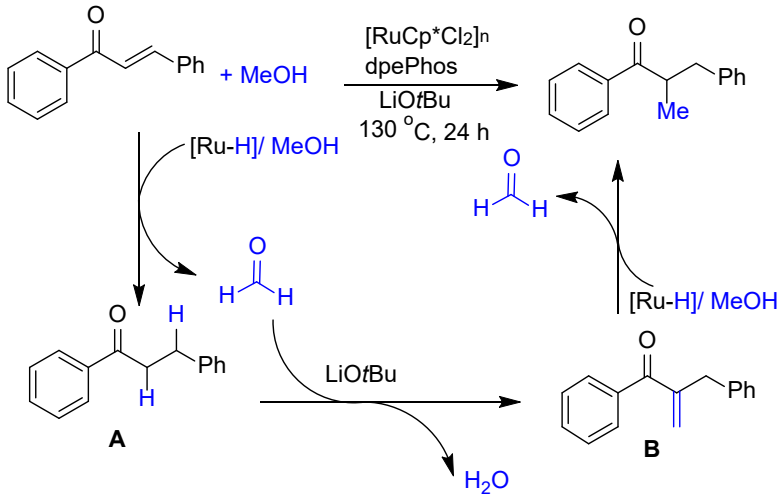
Scheme 6. Presentative Ir-catalyzed α-methylation methods of ketones using methanol.

In 2016, Dang and Seayad reported the first efficient and practical using methanol in Ru-catalyzed α-methylation of esters and ketones via catalytic borrowing hydrogen (BH) method.[26] This procedure required the employment of an *in-situ* generated Ru-Cp*(dpePhos)Cl catalyst and small quantity of Li*O*t*Bu (20 mol%) as the base. Under optimized condition, α-methylation of ketones resulted in up to 98% isolated yield with the tolerance of many sensitive functional groups (Br, I, OH, etc.). A gram-scale reaction of α-methylation of ketone with 0.1 mol% catalyst achieved a TON of 710, demonstrating the viability of scaling up. Several substrates that have two α-carbons on ketones were the subject for selective α-methylation studies. The authors demonstrated that the mono-methylation of ketones could be controlled at lower temperature. At higher temperature (130°C), α,α'-multi-methylation of ketones occurred in very good yields (Scheme 7a). Notably, less active substrates such as nitriles and esters could be methylated under standard condition. 87% yield of methylated nitrile product was obtained at 130°C for 24h reaction. However, with less active esters, the α-methylation reaction needs to be carried out under microwave condition in 8 h at higher temperature (160°C) which only give moderate yields of the target products (Scheme 7a). A plausible mechanism to explain the formation of α-methylated ketones was clearly described in Scheme 7b.



Scheme 7. (a) Ru-catalyzed α-methylation of ketones, nitrile and ester using methanol; (b) Proposed mechanism.

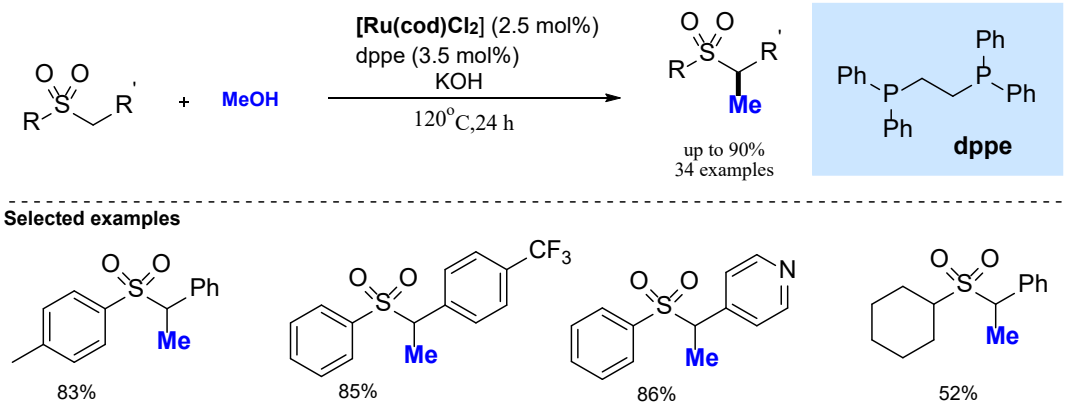
A significant improvement for the three-component one-pot procedure for α-methyl-alkylations of methylketones with methanol has been recently reported by Kundu's group.[27] Only 1 mol % of Ru catalyst need to be used for the success of reaction which gave up to 93% of methylated products. This catalyst system showed very good performance in the selective mono, dimethylation, and tandem three-component coupling of aryl ketone with methanol and primary alcohol, resulting in moderate to excellent yields of desired products. The effectiveness of the bifunctional catalyst in catalyzing the β-alkylation of secondary alcohols with primary alcohols was investigated by kinetic measurements and comprehensive DFT simulations.



Scheme 8. Ru-catalyzed sequential conjugate reduction/α-methylation of chalcone using methanol.

Notably, up to 74% of the isolated yield of saturated α-methylated ketone was produced by methylating α,β-unsaturated ketone in the presence of the current Ru catalyst system(Scheme 8).[24] The methylated ketone product was produced by two consecutive reactions: first, the conjugate reduction of chalcone to form intermediate **A**; next, intermediate **B** was formed by the aldol condensation of **A** with the formaldehyde generated in situ. Finally, **B** was reduced to give the desired product through a hydrogen transfer pathway. The intermediates **A** and **B** along with the product were observed by GC-MS gave some valuable evidence to support for the proposed mechanism (Scheme 7b). In 2022, Kundu et al. reported a similar transformation using α,β-unsaturated ketones to prepare**α**-methylated ketones with methanol as a methylating reagent.[28] A series of phosphine-free bis-N-heterocyclic carbene-Mn complexes were successfully designed and synthesized. The methylation of a broad range of substrates, such as aromatic and aliphatic chains in α,β-unsaturated ketones, was achieved with remarkable efficiency using this Mn catalytic system.

α-methylated sulfones are commonly found in bioactive chemicals, medicines, and natural products. The hydrogen borrowing method for methylating sulfones is problematic due to the high reactivity of Julia-like intermediates, which can result in the creation of olefin or cyclopropane as major products. Zhong and co-workers disclosed the first report on the utilization of methanol as a methylating agent for the α-methylation of sulfones employing the catalytic system based on [Ru(cod)Cl_2] and dppe ligand (Scheme 9).[29] Up to now, several expensive transition metals complexes such as palladacycle-phosphine-based,[30] cyclo-metalated (NNC)Ru(II) complex,[31] $ReCl(CO)_5$/triphos,[32] were found to be successful catalysts for the α-methylation of ketones using methanol.

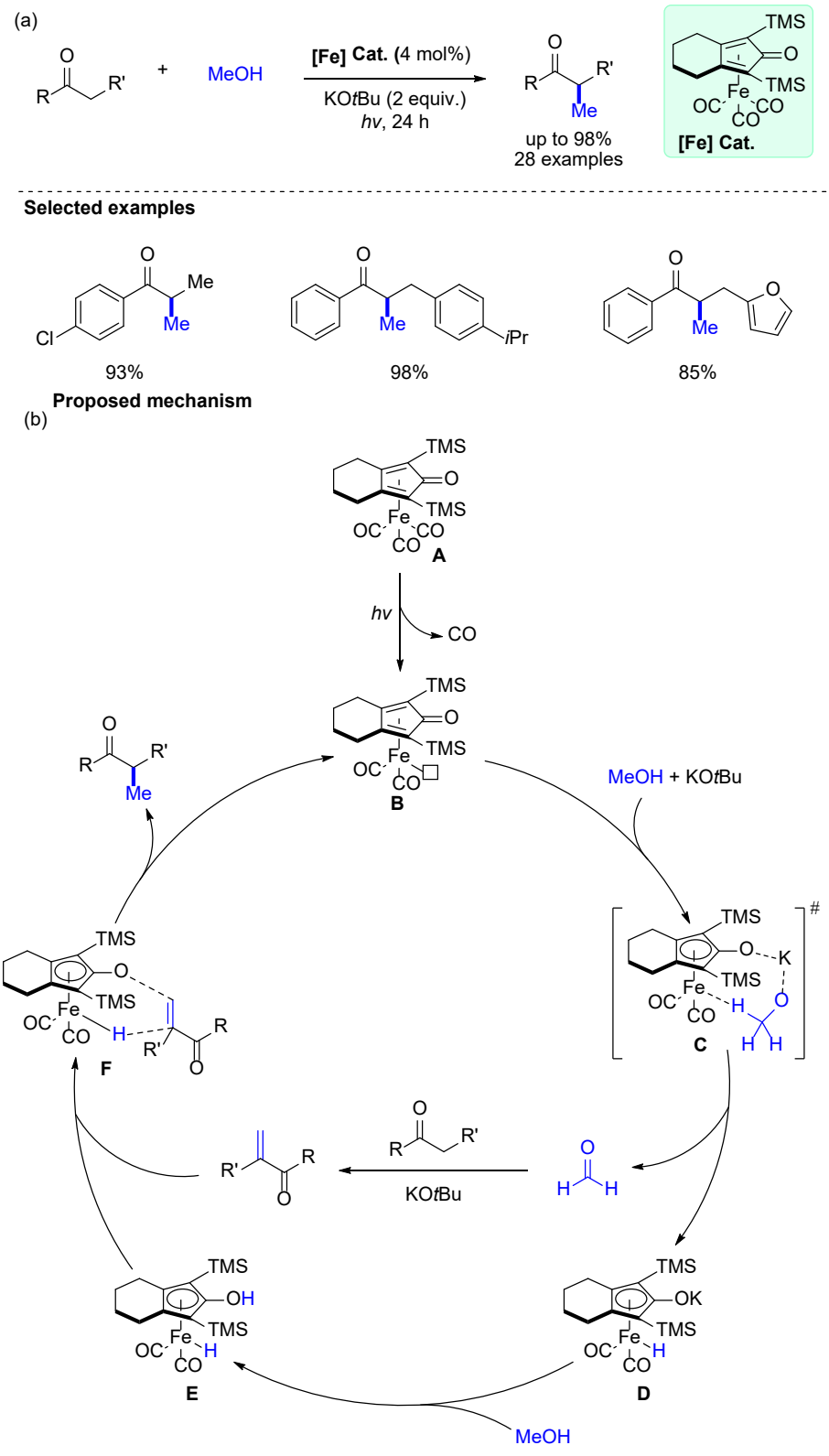


Scheme 9. Ru-catalyzed α-methylation of sulfones using methanol.

In 2017, in an attempt to find a cheap and less toxic catalyst to facilitate the α-methylation of ketones, Liu and coworkers demonstrated the first efficient Co catalyst using $Co(BF_4)_2.6H_2O$ in the combination with $P(CH_2CH_2PPh_2)_3$ ligand which was found to be the convenient catalytic system for this reaction.[33] In 2019, Sortais et al. used a Mn-PN^3P complex as a precatalyst to directly α-methylate several ketones, including cyclic, acyclic, and heterocyclic, using methanol.[30a] Additionally, they also found that α-methylation could be tolerated well with dihydrochalcones. The catalytic α-methylation of esters on this Mn-complex gave moderate reaction yields of desired products. Then, Rueping et al. reported an air and moisture-stable Mn-pincer catalyst for α-methylation and α-trideuteromethylation of ketones and esters.[30b] The use of isotope-labeled methanol (CD_3OD, CD_3OH, $^{13}CH_3OH$) indicated that this process occurred via a hydrogen borrowing pathway. Very recently, de Ruiter's group reported that a novel Mn-$PC_{NHC}P$ pincer complex was successfully employed for this transformation giving high yields of methylated ketones.[34] In 2022, Ganguli et al. reported a tandem reaction of α,β-unsaturated ketones to α-methylated ketones using methanol as both the hydrogen and methylating reagent in the employment of a bis(NHC)Mn(I) complex as the catalyst.[28] Interestingly, the authors demonstrated that pharmaceutically important drugs such as eperisone and lanperisone were successfully synthesized using this reaction.

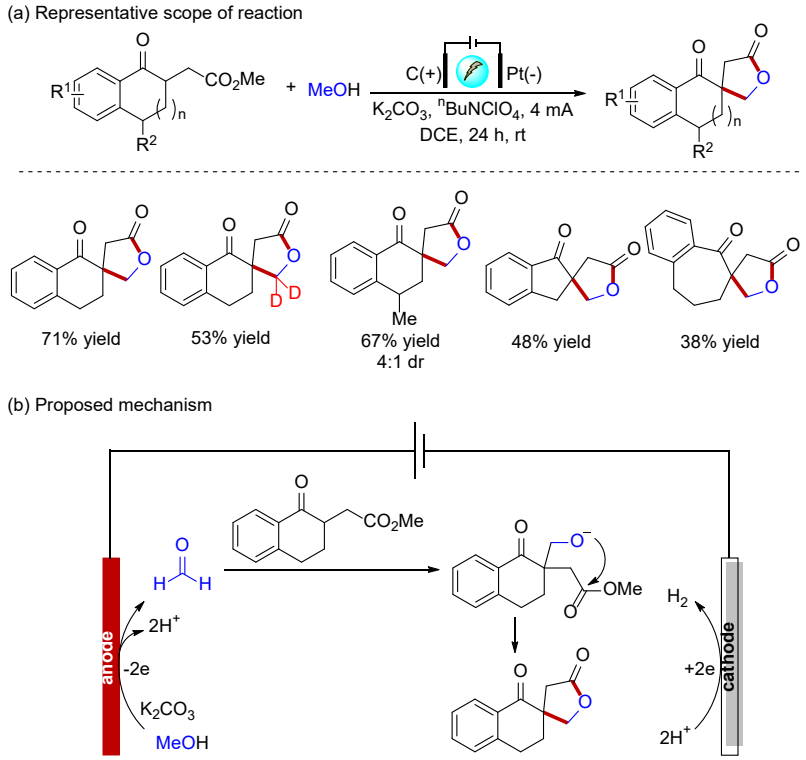
Another new study in cheap catalyst system was made in 2018 as Polinado *et. al.* described cyclopentadienone iron carbonyl complex as an efficient catalyst in mono-methylating ketones.[16g] This catalyst system is quite versatile and could methylate other nucleophiles other than ketones (amines, sulfonamides and indoles, oxindoles) which will be discussed in their respective sections.

The catalyst requires a catalytic amount of Me_3NO as an activator, but the reaction requires a stochiometric amount (2 eq.) of K_2CO_3 as the base. Dimethylation can occur when the α-carbon is not substituted. This reaction has a good scope: CF_3, halide and OMe substitution are well tolerated in the aryl unit; heteroaryl systems in the ketones are also efficiently methylated. The proposed mechanism for this catalytic cycle is firstly the de-coordination of CO facilitated by Me_3NO, then the catalyst can abstract H_2 from MeOH to form formaldehyde, which can then go through an aldol reaction with our nucleophile (an enone in this case). Finally, the product was achieved by the reduction of the unsaturated ketones by the iron hydride complex and return the iron catalyst into the catalytic cycle. When conducting the reaction in CD_3OD the product was yielded 95% in the deuterated form, confirming that methanol is the methylating agent. Also, when adding the unsaturated ketone, it is converted into a deuterated ketone, which strongly suggests the iron hydride complex as an intermediate. Similar research related to the utilization of well-defined bifunctional Fe-complexes for this transformation was also reported by Renaud's and Sundararaju's groups (Scheme 10).[35] Banerjee et al. used 1,10-phenanthroline as a ligand for the commercially available $NiBr_2$ salt to catalyze the α-methylation of ketones.[36] However, methylated ketones were only formed with moderate yields.



Scheme 10. Fe-catalyzed α-methylation of ketones using methanol and proposed mechanism.

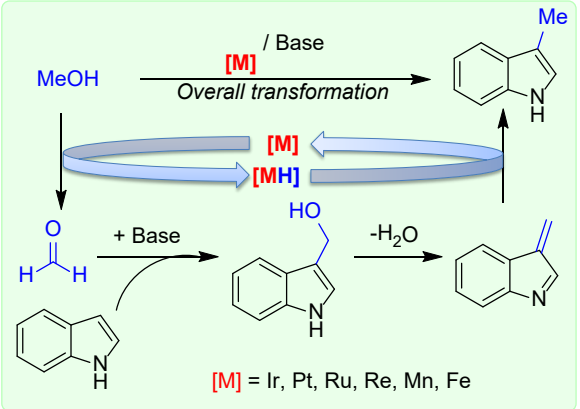
Heterogeneous catalysts serve a critical role in industrial chemical synthesis. They are preferred because of their robustness and lower operational costs, particularly due to simpler recovery/separation from the products, which allows chemical processes to be optimized. In fact, many processes using transition metals/metal oxides as efficient heterogeneous catalysts for methylation of carbonyl compounds via hydrogen borrowing strategy, for example, Pt/C catalyst.[16d] Das' and Hou's groups developed heterogeneous catalysts based on polymer-stabilized Pd nanoparticles to utilize methanol in α-methylation of ketones.[37] Like many other organic reactions, transition metal-catalyzed α-methylation of carbonyl compounds using methanol has been successfully adapted to electrochemical transformation. In 2024, Xiao and coworkers described an electrochemical method for the synthesis of spirolactones from α-tetralone derivatives, using methanol as a C1 source.[16k] This method is compatible with a wide range of functional groups including methyl, methoxy, fluoro, chloro, bromo, trifuoromethyl, and ester, yielding the desired spirolactone products in 31% to 84% yields (Scheme 11a). The proposed mechanism, illustrated in Scheme 11b, begins with the oxidation of methanol to formaldehyde at the anode in the presence of K_2CO_3. This is followed by an aldol reaction between the α-tetralone derivatives and formaldehyde, leading to an intramolecular lactonization that forms the final spirolactones. Thus, hydrogen borrowing-based α-methylation of carbonyl and related derivatives using methanol offers promising routes for synthesizing various valuable organic substrates.



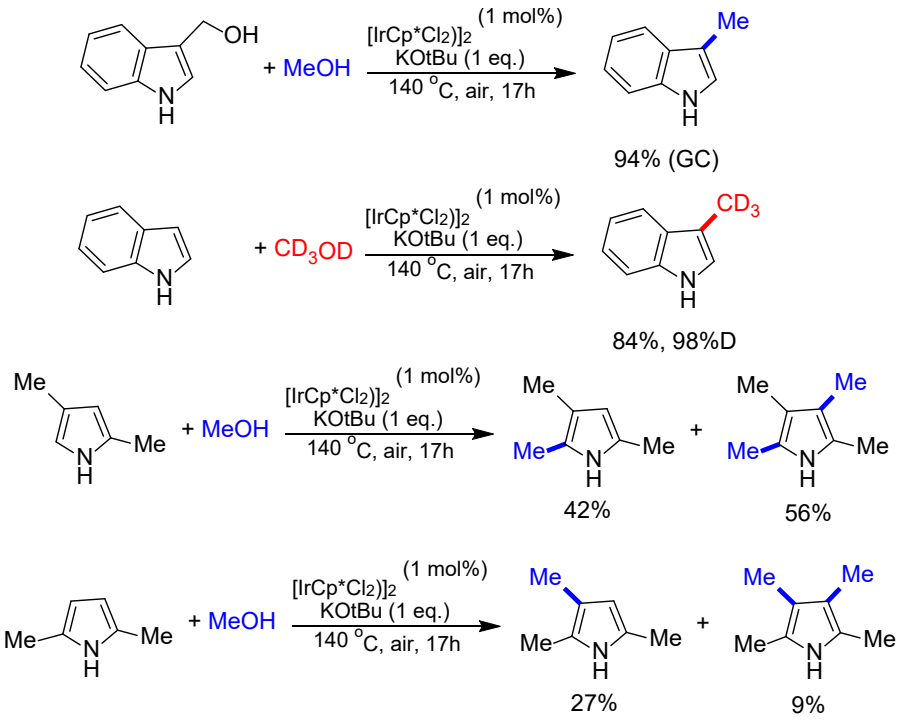
Scheme 11. Electrochemical synthesis of spirolactones from α-tetralone derivatives with methanol: (a) Representative scope of reaction, (b) proposed reaction mechanism.

2.2. Methylation of phenols, indoles, oxindoles and pyrroles

The general methylation of indole with methanol using different catalysts is presented in Scheme 12. In 2015, Cai *et al*.[38] disclosed Ir-catalyzed methylation of indoles using methanol under air atmosphere at 140°C which resulted in the formation of 3-methyl indoles in up to 91% yield. In order to understand this reaction pathway, several mechanistic studies were carried out. Under optimized condition, (1H-indol-3-yl) methanol was converted to the product in 94% yield, which was considered as strong evidence to verify the proposed mechanism (Scheme 13). In addition, the Ir-catalyzed methylation of indoles using CD_3OD also gave the deuterium isotope methylated product.



Scheme 12. General transition metals-catalyzed methylation of indole with methanol.

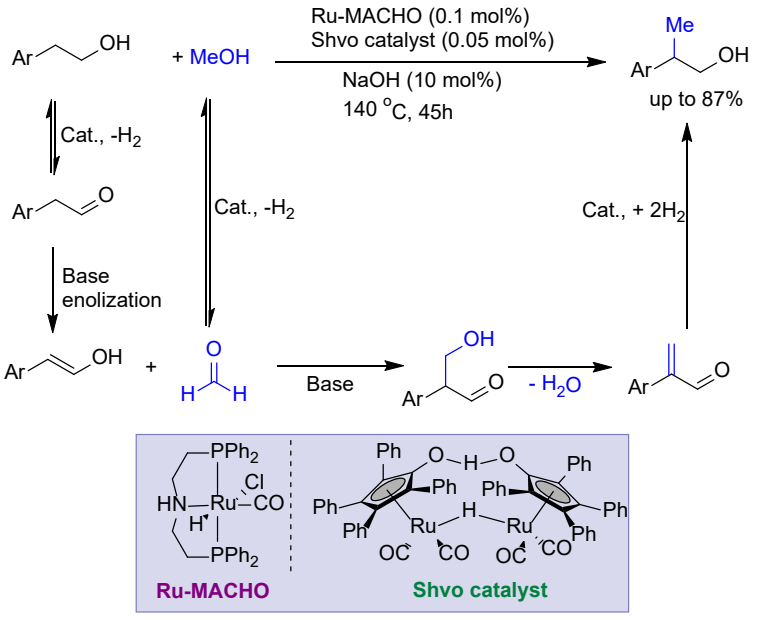


Scheme 13. Ir-catalysed α-methylation of pyrroles with methanol.

However, the methylation of pyrroles under this condition gave an unseparated mixture of mono- and multi-methylated pyrroles (Scheme 13).[38] A cheaper Fe-based catalyst system was reported by Polinado and coworkers for the efficient methylation of indoles and oxindoles.[16g] The reaction conditions were similar to that reported for ketones, with catalytic Me_3NO activator and K_2CO_3 as the base. Recently, Kim and Hong reported an interesting Ru-catalyzed methylation of 2-naphthol derivatives using methanol which afforded to 1-methyl-2-naphthol derivatives in up to 87%.[39] A possible pathway via the formation of key intermediates 1-(hydroxymethyl)naphthalen-2-ol and 1-methylenenaphthalen-2(1H)-one were proposed. Moreover, Pt/C-catalyzed C3-methylation of indoles was also reported by Shimizu and co-workers.[16d] In 2020, Srimani's group disclosed a Ru-catalyzed C3-methylation of indoles with methanol.[40] Their control experiments suggested that formaldehyde was gradually formed from methanol. Subsequently, the in situ formed aldehyde would coordinate to the pincer complex and led to the generation of C3-methyl indole as product in up to 95 % yield. Most recently, catalytic systems including Os(II)PC(sp^3)P pincer complex,[41] $ReCl(CO)_5$/triphos,[32] and Mn(I)$PC_{NHC}P$ prince complex[34] were reported for this type of reaction.

2.3. β-Methylation of alcohols

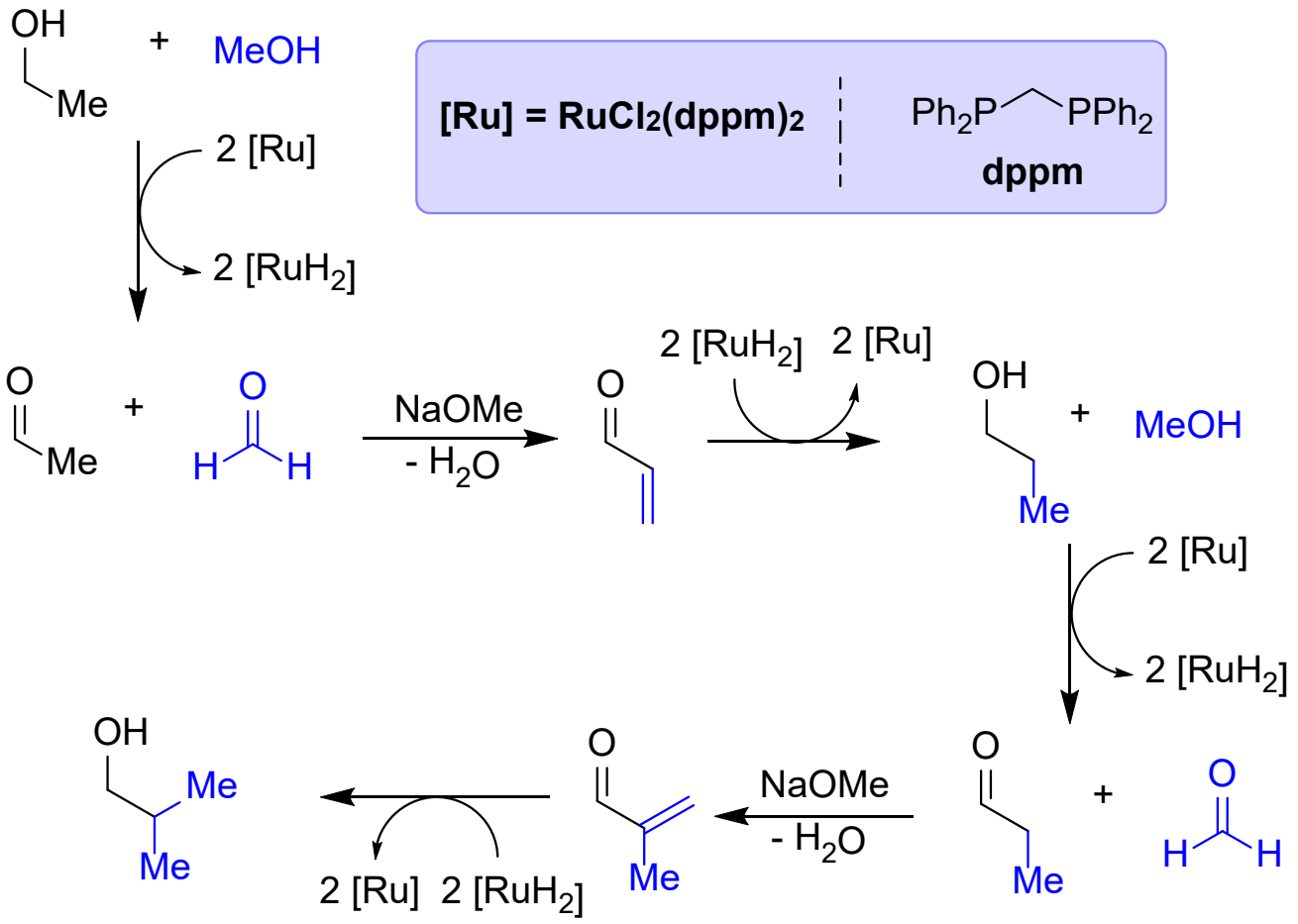
In 2014, Beller and coworkers described an interesting direct Ru-catalyzed methylation of alcohols with methanol to form 2-arylethanols at 140°C in the presence of NaOMe (Scheme 14).[42] A mixture catalysts of Ru-MACHO and Shvo's Ru complex was required for the success of reaction. The addition of second catalyst (Shvo's Ru-catalyst) played a crucial role in the dehydrogenation of 2-arylethanol step. Up to 87% yield of 2-arylethanols was achieved under optimized conditions.



Scheme 14. Ru-catalyzed β-methylation of alcohols with methanol.

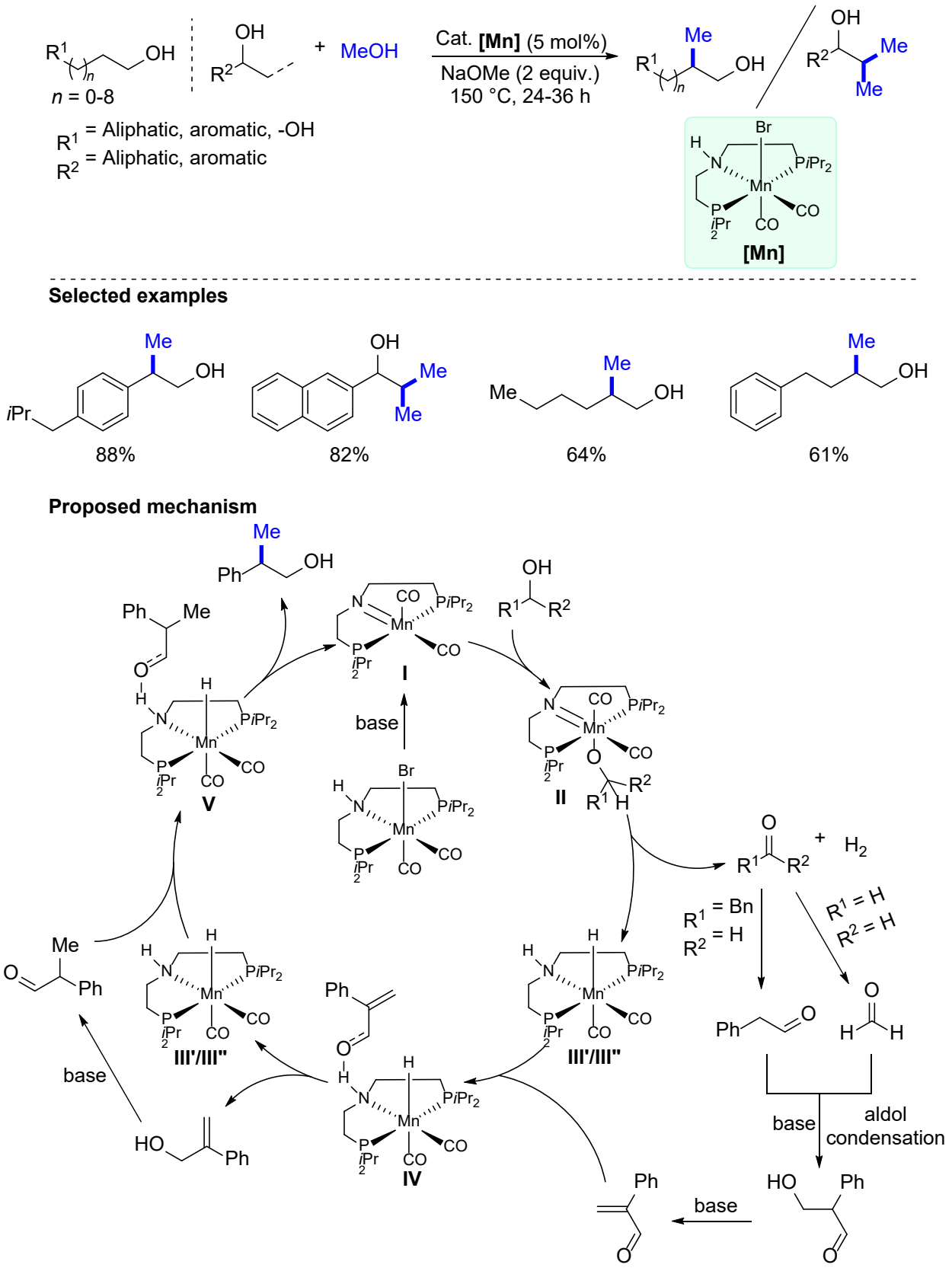
Lu et al. demonstrated bis-*N*-heterocyclic carbene iridium (bis-NHC-Ir) complexes as efficient catalysts giving good selectivity and turnover number (TON) for β-methylation of primary and secondary alcohols on a variety of substrates.[43] Crystallographic and DFT studies revealed that the ligand played an important role in improving catalytic efficiency and permitting the challenging Guerbet reaction. In 2017, Obora *et al.* also reported a similar β-methylation of alcohols with methanol catalyzed by DMF-stabilized Ir-nanoclusters.[44] Ir nanocatalyst (1-1.5 nm) played dual roles in the oxidative dehydrogenation of methanol and other alcohols to formaldehyde and corresponding ketone or aldehyde. Then, the aldol condensation reaction of formaldehyde and ketone in the presence of a base (Cs_2CO_3) gave α,β-unsaturated ketone or aldehyde, which was subsequently reduced by Ir nanoclusters-hydride via hydrogen borrowing mechanism. Ir nanocatalyst was demonstrated to show higher catalytic performance (TON~48000) than several common Ir complexes. Most recently, another Ir complex catalyst system for this transformation was demonstrated by Li and co-workers.[45]

In 2016, Wass and co-workers described an interesting Ru-catalyzed transformation of a mixture of methylation of ethanol which resulted in the formation of biodiesel isobutanol in 75% conversion (>99% selectivity) via Guerbet-type reaction (Scheme 15).[46] Only 0.1 mol% of $RuCl_2(dppm)_2$ was required for the success of reaction in the presence of NaOMe (2 equiv.) base at 180°C in 20 h. Interestingly, the catalyst could be recycled up to 3 times. The proposed mechanism is supported by the formation of n-propanol intermediate which could be detected during the course of reaction. A labelling study using $^{13}CH_3OH$ under optimized conditions with unlabeled EtOH was carried out. NMR results showed that ^{13}C label was introduced into two methyl groups in isobutanol product.



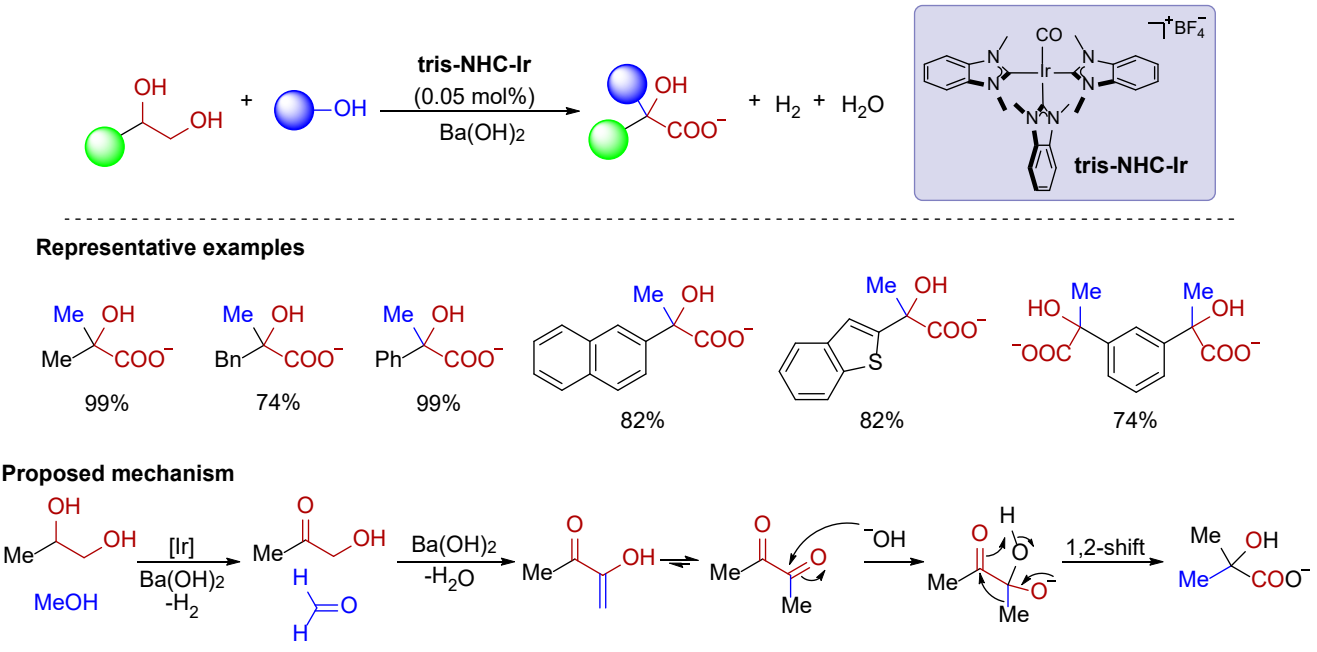
Scheme 15. Ru-catalyzed β-methylation of ethanol with methanol.

Srimani et al. used an acridine-based SNS-Ru pincer complex as convenient catalyst for β-methylation of 2-arylethanols using methanol. Arylethanols easily underwent methylation due to their electron-rich and deficient, yielding up to 95% of the product.[47] Polidano *et. al.* succeeded in using common earth metal for their catalyst system using cyclopentadienone iron carbonyl complex as the catalyst to methylate the β-position of a β-aryl alcohol.[48] The yields are high (60 - 85%) and the reaction accommodates heteroaryl systems at the β-position as well as electron donating substituents (except for 4-OH) on the aromatic system. Using deuterated methanol showed significant incorporation of deuterium at both the α- and β- position; the β-methyl group was 83% in its deuterated form, confirming methanol as the methylating reagent and support the iron hydride species as an intermediate.[48] A similar research for β-methylation of alcohols using methanol on diaminocyclopentadienone iron tricarbonyl complex catalyst was also reported by Renaud and coworkers. Mechanistic studies using deuterium-labeling reactions were conducted to confirm hydrogen borrowing process.[49] Shimizu and colleagues reported one of the rare examples of C-methylation of alcohols using methanol with heterogeneous catalysts.[16d] The reactions employed Pt nanoparticles supported on carbon (Pt/C) in the presence of NaOH, yielding β-methylated alcohol products with isolated yields ranging from 73% to 95%. The Pt/C catalyst demonstrated a high turnover number (TON) of 3280 and retained its activity well after five cycles of reuse. In 2024, Biswas and Gelman reported that structurally well-defined Os(II)PC(sp^3)P pincer complexes can effectively catalyze the methylation of alcohols using methanol as a C1 source.[41]



Scheme 16. Mn-catalyzed β-methylation of alcohols with methanol and proposed mechanism

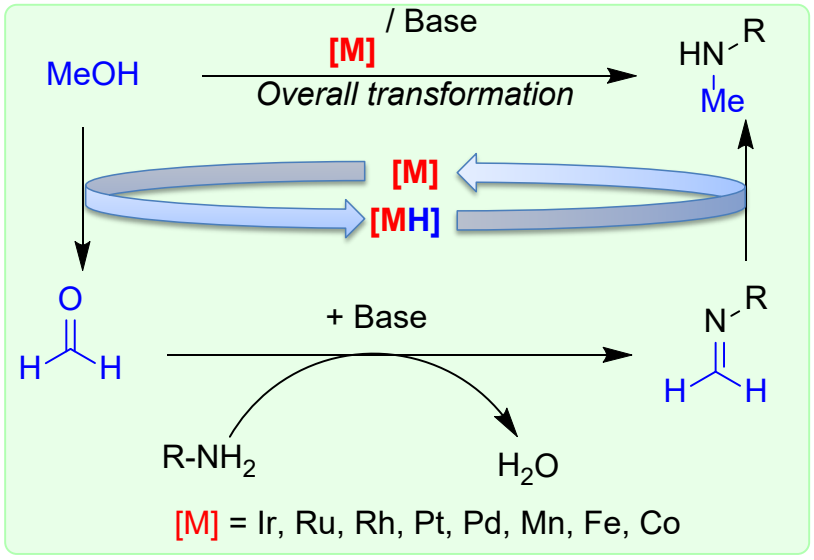
In 2020, two manganese catalyst systems for the β-methylation of alcohols were independently developed by Kaithal et al.[50] (Scheme 16) and Schlagbauer et al.[51] Both groups used methanol as a methylation reagent, Mn-pincer complexes as the catalyst and a stoichiometry amount of base. In both cases, excellent yield and selectivity of methylated alcohols were achieved. Detailed mechanistic studies were performed, and results supported a borrowing hydrogen pathway for both reactions. These two protocols offered simple, inexpensive, and environmentally friendly methods for selective C−C bond formation. Very recently, Tu and colleagues reported a selective and convenient method for synthesizing quaternary α-hydroxyl acetates via dehydrogenative cross-coupling of 1,2-diols and methanol or other primary alcohols, using a tris-NHC-Ir catalyst (Scheme 17).[52] The reaction achieved good to excellent yields and high selectivity, with water and hydrogen gas as the only clean byproducts. The authors also demonstrated that other possible side products generated from Guerbet reaction were well suppressed under the established reaction conditions.[52]



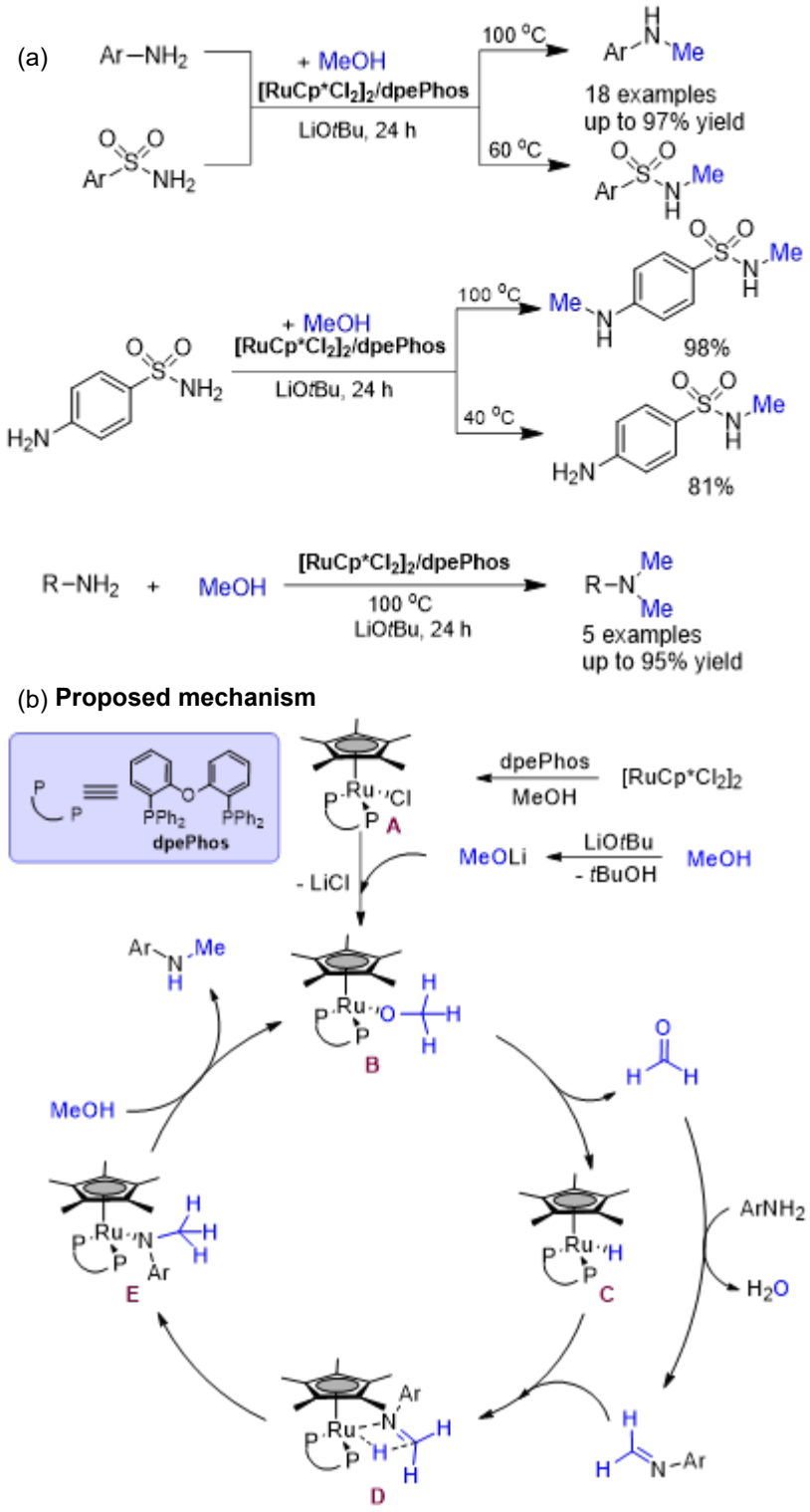
Scheme 17. Ir-catalyzed cross-coupling of 1,2-diols and methanol for synthesis of quaternary α-hydroxyl acetates.

2.4. N-methylation of amines, amides, nitriles, nitroarenes and related compounds via hydrogen borrowing using methanol

The N-methylation of amines played an important role in the synthesis of fine chemicals, drugs and natural products.[53] The classical N-methylation methods using explosive and toxic methyl halide as methylating reagents possess serious selectivity issues, and normally generate over-alkylated products. That reduces the overall yield of the desired product.[54] The production of methylated amines at industrial scale still bases on the reductive amination using formaldehyde in the employment of toxic reductive reagents (Eschweiler–Clarke methylation).[55] Therefore, the development of efficient methylation procedures using safer and more sustainable methylating agents is necessary and is of obvious importance. N-methylarenes could be synthesized by Buchwald-Hartwig reaction of methyl amines with aryl halides in the presence of palladium[56] or nickel[57] catalysts, often in the use of over-stoichiometric amounts of base. *N*-methyl amines appear in many important pharmaceuticals and biological active alkaloids.[12a, 58] In general, the synthesis of selective *N*-mono-methylated aryl amine intermediates is not only challenging but also requires many synthetic steps.[59] A direct and selective approach to prepare *N*-mono-methylated aromatic amines using methanol could offer an alternative and efficient solution in a sustainable way. On the other hand, selective *N,N*-dimethylation of aliphatic amines with methanol would also be a highly important method to access a series of important drugs, for example, Lexapro, Pheniramine, Piritone, Venlafaxine, etc.[17] Until now, several research on direct transition metal-catalyzed *N*-methylation of amines with methanol via hydrogen borrowing pathway (Scheme 18) have been disclosed.[60] Watanabe *et al.* described the first Ru-catalyzed *N*-methylation of anilines using methanol at 180°C.[60e] A high catalyst loading (20 mol% of Ru) was required to give acceptable yield (30-80%) of the *N*-methylated amines. Naskar and Bhattacharjee reported a Ru-PPh_3 catalyzed *N*-methylation of aminoarenes to afford the *N*-methyl arylamine products in moderate yields (30-76%) with the limitation in substrates scope.[60a] In 2004, a cyclopentadienyl-Ru-PPh_3 complex-catalyzed double *N,N*-di-methylation of aliphatic amines at 100 °C was demonstrated by Zotto's group. However, this catalyst was inactive for the methylation of aniline derivatives.[60b]

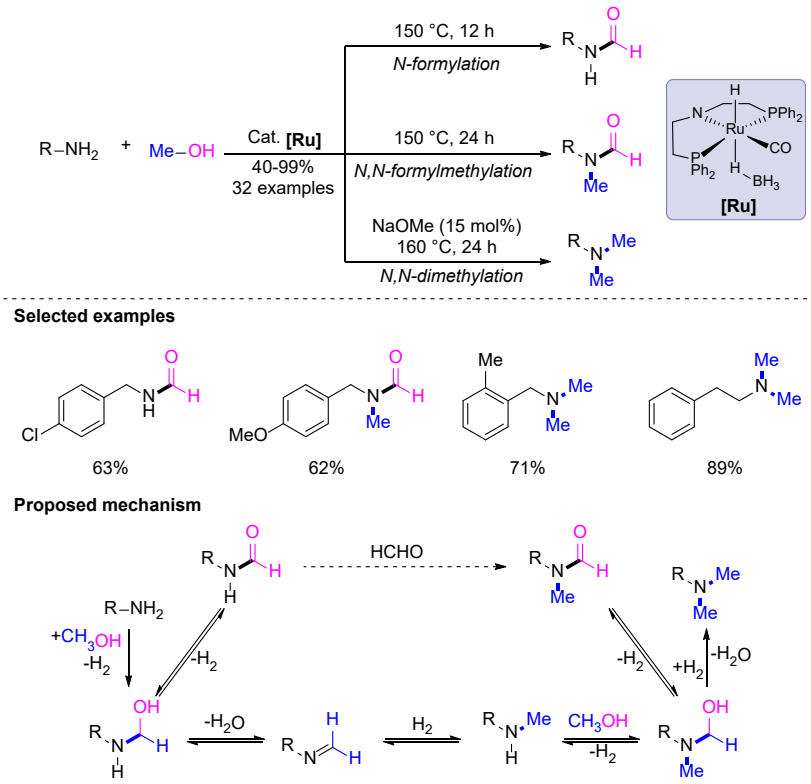


Scheme 18. General pathway for transition metals-catalyzed N-methylation of amines using methanol.



Scheme 19. a) Ru-catalyzed N-methylation of amines with methanol, and b) proposed mechanism.

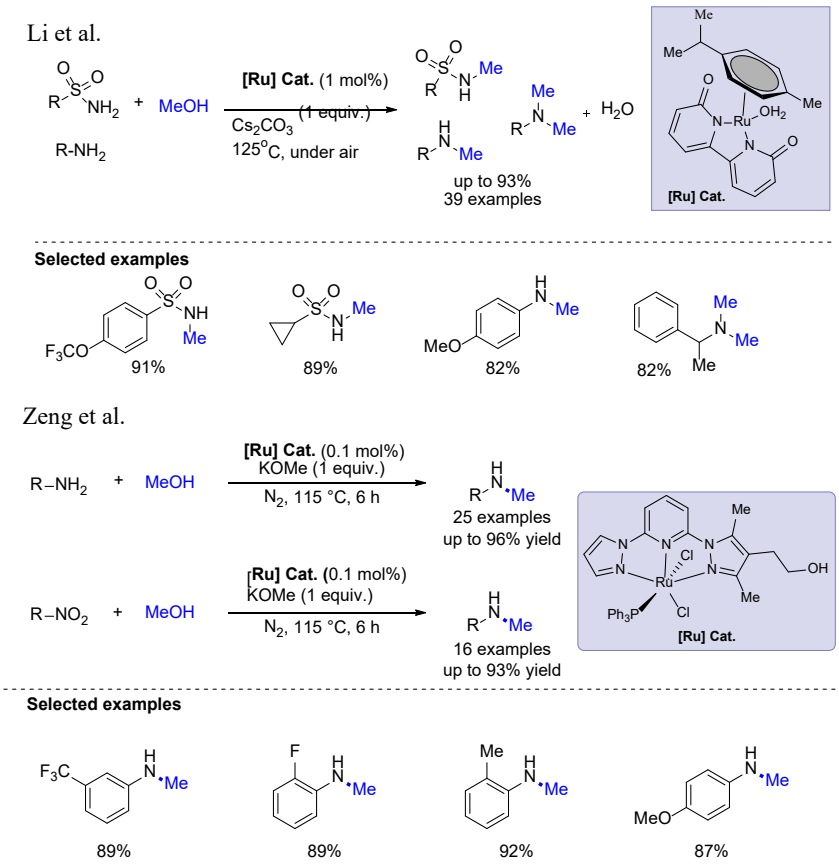
In 2015, Dang and Seayad described an efficient methylation of amines and sulfonamides on Ru-based catalyts in the presence of only catalytic amount of LiO*t*Bu as a base (Scheme 19).[61] N-monomethylated aromatic amines and sulfonamides were prepared in up to 98% yield at 100ºC and 60ºC, respectively. Interestingly, Ru-catalyzed methylation of aliphatic amines afforded the N,N-dimethylated aliphatic amines under standard condition. Based on results obtained from some mechanistic studies, a possible mechanism for N-methylation of amines with methanol in the employment of Ru catalyst was proposed (Scheme 19b).[61] The catalytic cycle begins with the formation of a catalytic active species (Ru-methoxy complex **B**) from in situ produced Ru-phosphine complex A and lithium methoxide. Then, the β-hydride abstraction of Ru-methoxy complex (**B**) occurs to form a new Ru-H species (**C**) and release formaldehyde. The formation of [Cp*Ru(dpePhos)H] (**C**) was identified by NMR spectroscopy and HRMS methods. The imine intermediate which was formed by condensation of the amine substrate with formaldehyde undergoes a transfer hydrogenation releasing the N-methylated product and regenerating the active catalyst (**B**) through the intermediates **D** and **E**. In order to understand the proposed pathway, the catalytic activity of Ru-H (III) was examined in the absence of LiO*t*Bu under described reaction conditions. Catalytic amount (2 mol%) of imine (1-diphenylmethanimine) was used to initiate the catalytic cycle by generating the intermediate **D**. Gratifyingly, the imine promotes the catalytic cycle of the methylation of aniline to form the corresponding product in 65% yield in 18h at 100ºC.



Scheme 20. Selective Ru-catalyzed N-methylation and N-formylation of amines using methanol and proposed mechanism.

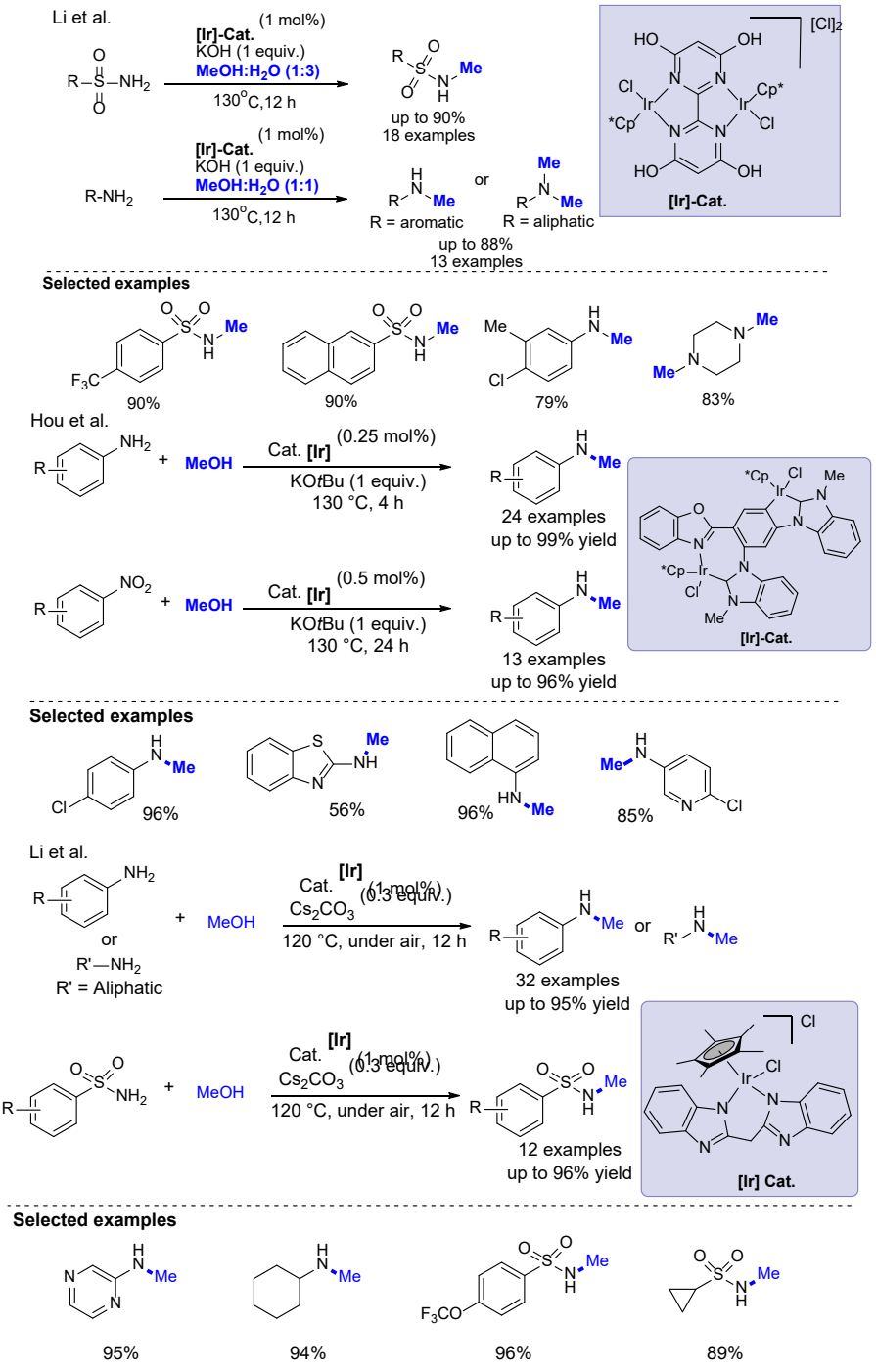
Kundu et al. used a ruthenium(II) NNN-pincer-complex to selectively synthesize monomethylated aniline derivatives.[62] The reaction occurs via an outer sphere mechanism, enhanced by the hydroxy group in the ligand. Another Ru-pincer catalyst (Ru-MACHO-BH) was developed by Choi and Hong which selectively yield monomethylated amines of wide variety: aliphatic, benzylamide derivatives, and notably amines containing coordinating groups like pyridine and thiophene (Scheme 20).[16i]

A similar version using PN^{H}P-pincer Ru catalysts for selective N-monomethylation of primary aromatic amines with MeOH was reported by Kayaki and co-workers in 2018.[16f] Up to now, several well-designed Ru-complexes have been developed as useful catalysts for methylation of amines (Scheme 21).[63]



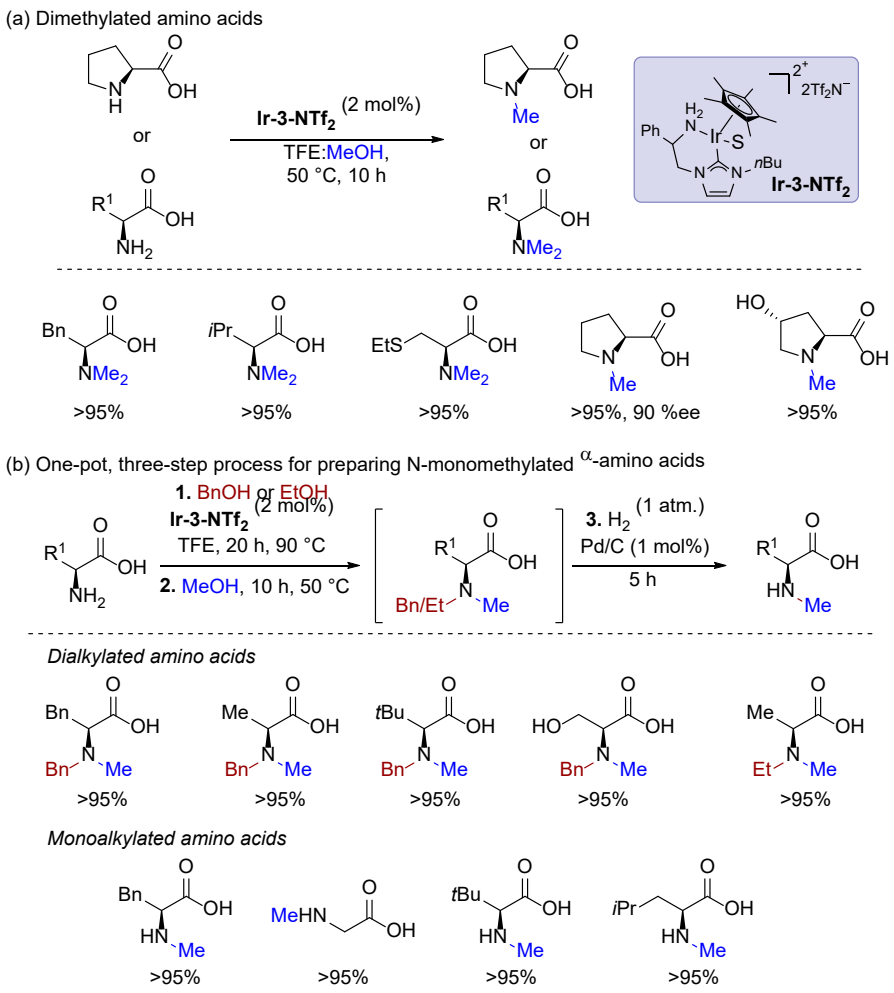
Scheme 21. Ru-catalyzed N-methylation methods of aniline derivatives, sulfoamides and nitroarenes using methanol.

Chen and co-workers developed the first Cp*$IrCl_2$-catalyzed methylation of aryl sulfoamides giving *N*-mono-methylated products.[60c] However, the reaction need to be conducted under high temperature (150 °C) and stoichiometric amounts of a strong base were required for the success of this reaction. Then, Crabtree *et al.* reported a practical Ir-NHC catalyzed N-mono-methylation of aniline derivatives under microwave irradiation conditions at 120°C in the employment of 1–5 equivalents of KOH to give up to 95% yield.[60d] Iridium complexes in the combination with Cp* and/or NHCs seem to be very suitable catalysts for the methylation of amines using methanol. Recent studies related to the development of novel Ir-complexes as convenient catalysts for methylation of amines using methanol were well demonstrated (Scheme 22).[64]



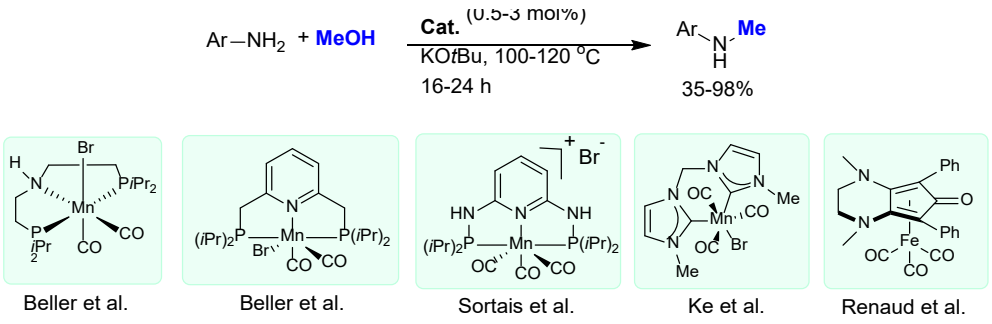
Scheme 22. Ir-catalyzed N-methylation methods of aniline derivatives, sulfoamides and nitroarenes using methanol.

In 2022, Martin-Matute and co-workers developed a method for N-methylation of unprotected α-amino acids using a recyclable homogeneous Ir(III)-NHC catalyst.[16b] The reaction exhibited excellent selectivity for N-monoalkylated α-amino acid products when higher alcohols were used. Interestingly, when methanol was employed as the methylating reagent, the reaction produced N,N-dimethylated products in excellent yields, while maintaining a high degree of stereochemical integrity (Scheme 23a). The reaction can also be employed in a one-pot, two-step synthesis of N-alkyl N-methyl α-amino acids by using two different alcohols, with methanol as the second methylating agent (Scheme 23a. Furthermore, when benzyl alcohol is used for the first alkylation, the resulting N-benzyl N-methyl α-amino acids can undergo hydrogenolysis with H_2 in the presence of a Pd/C catalyst, producing N-monomethylated α-amino acids in a one-pot, three-step process (Scheme 23b). Additionally, this method was successfully applied to the preparation of several amino-acid-based surfactants.



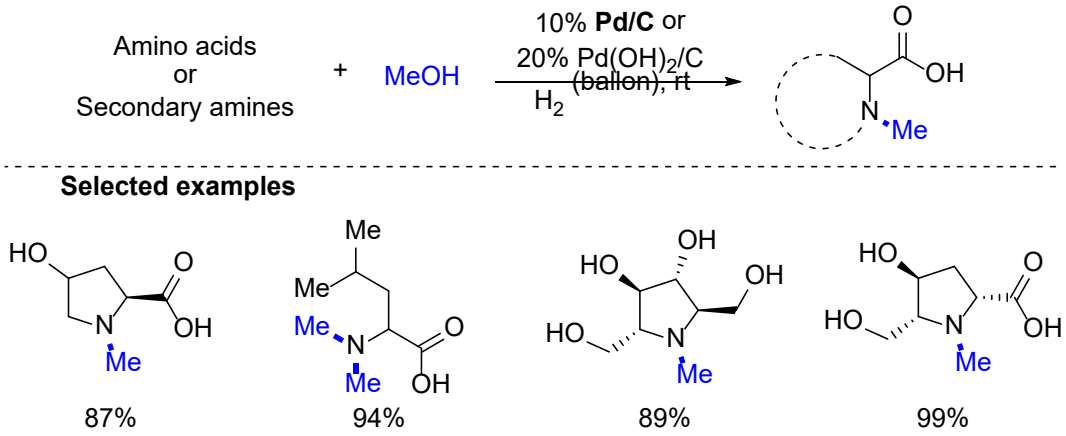
Scheme 23. Ir-catalyzed N-methylation of α-amino acids with methanol

Several research using very expensive metals related to this transformation was reported. In 1981, Grigg et al. reported the first $RhH(PPh_3)_4$ catalyst for direct methylation of amines using methanol.[65] In 2018, Sortai *et al.* successfully developed the mono-N-methylation of aromatic amines with a rhenium PNP pincer complex as a precatalyst with a low catalyst loading (0.5-1 mol%).[66] The reaction only required catalytic amount of Cs_2CO_3 (5-10 mol%) as a base. This procedure tolerated a wide range scope of aromatic amines at 140 °C. For mechanistic studies, DFT calculations were performed, highlighting the importance of the *in situ* formed imine intermediate. In 2024, the Gelman group reported an effective N-methylation of amines and sulfonamides using methanol, catalyzed by an Os(II)PC(sp^3)P pincer complex.[41] In fact, these reported protocols often require either hard reaction conditions and/or the use of stoichiometric amounts of base to obtain high yields of desired products. Therefore, the development of more efficient methods using inexpensive catalysts for sulfonamide, aromatic and aliphatic amine substrates under mild conditions is necessary. In 2016, Beller et al. disclosed the first efficient Mn-catalyzed N-momomethylation of aniline derivatives using methanol.[67] The extension of this catalytic method was efficiently applicable for N-alkylation of amines with higher alcohols. Sortais' group also described another practical Mn-catalyzed N-momomethylation of aniline derivatives using methanol in the employment of only 20 mol% of KO*t*Bu as a base.[68] Recently, several Mn-pincer complexes were also developed as efficient catalysts for this transformation (Scheme 24).[69] Most recently, Tao and co-workers reported a selective process for mono-N-methylation of aliphatic amines employing a pincer manganese complex as a catalyst.[70] This newly developed protocol overcame the requirement for external high pressure hydrogen gas in preparing mono-N-methylated primary aliphatic amines from methanol. The reaction also is tolerated a broad substrate scope, with up to 98 % yield. Control experiments and DFT calculation suggested that the weak base-catalyzed alcoholysis of formamide intermediates helped prevent the secondary N-methylation of mono-N-methylated amines.



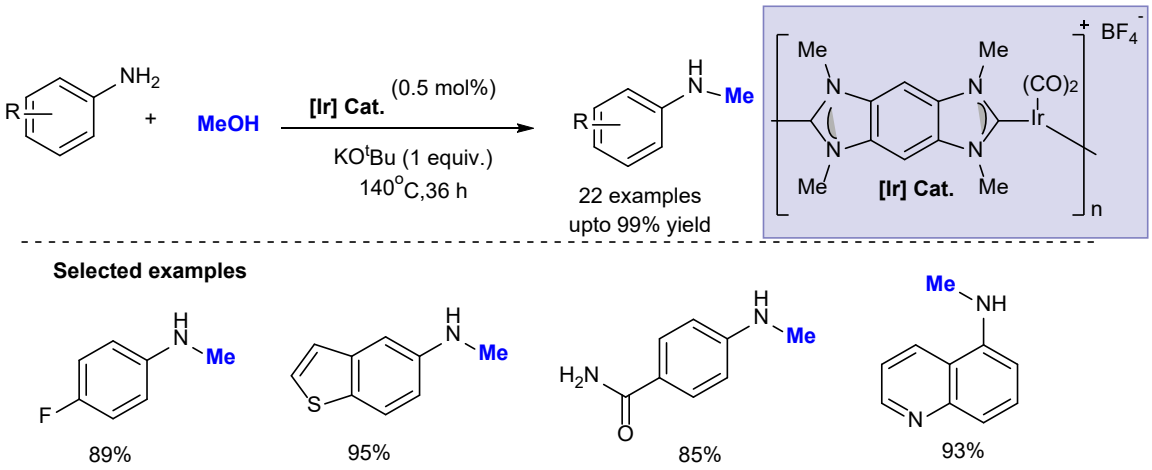
Scheme 24. Mn(Fe)-catalyzed N-methylation of aniline derivatives using methanol.

The first Fe-based methylating catalyst system was reported by Polidano *et. al.* for sulfonamides, aniline derivatives, and secondary amines (both acylic and cyclic).[16g] Methylating sulfonamides requires electron rich pre-catalyst and electron rich aromatic rings on the sulfonamides as well. In the same year, very similar Fe-complex catalyst was also reported for this transformation by Renaud's group.[71] In 2017, Liu et al. described a cobalt-catalyzed methylation of amines process.[16h] In this work, a commercially available $Co(acac)_2$ combined with a tetradentate phosphine ligand $P(CH_2CH_2PPh_2)_3$ provided an excellent catalyst system in the presence of K_3PO_4 base.



Scheme 25. Light-promoted N-methylation of secondary amines and amino acids on Pd/C ($Pd(OH)_2/C$)-catalyst using methanol.

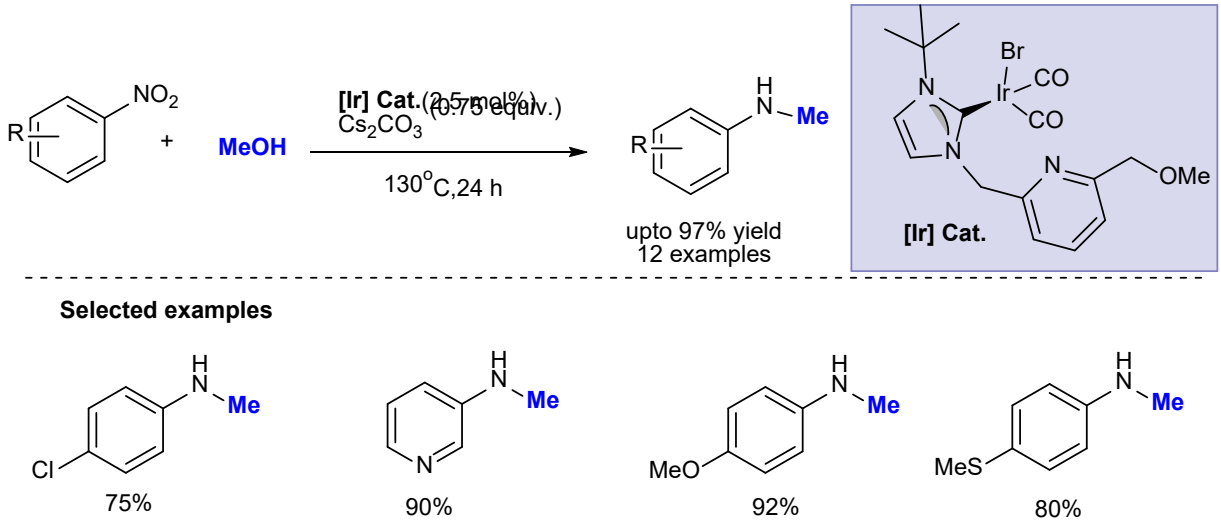
Many research groups attempted to replace homogeneous catalysts with supported transition metal heterogeneous catalysts to discover practical and industrial applications. In 2010, Huang's group reported the employment of Pd/C as an efficient catalyst for methylation of amines/amino acids utilizing methanol with H_2 gas (1 atm) as a methylating reagent under room temperature condition (Scheme 25). This process can be used to prepare N-methylated naturally occurring amino acids, pyrrolidine derivatives, and N,O-dibenzylbulgecinine.[72] In 2021, Jiang and coworkers described the employment of highly stable palladium nanocatalyst supported on syndiotactic polystyrene funtionalized with dimethylamino ($Pd@sPSNMe_2$) for N-methylation of anilines with methanol to prepare monomethylated amines in high yields under air. This robust catalyst could be recycled more than ten times.[73] Recently, Kim's group reported a bimetallic Pd/Cu–Fe_3O_4 catalyst for N-methylation of aniline derivatives with methanol. Different combinations of Pd_xCu_y-Fe_3O_4 nanoparticles were prepared and among these catalysts, $Pd_1Cu_{0.6}$-Fe_3O_4 nanocatalyst showed the best catalytic performance in the comparison with other monometallic Pd-Fe_3O_4 and Cu-Fe_3O_4 catalysts.[74]



Scheme 26. Direct Ir-catalyzed N-methylation of aniline derivatives using methanol.

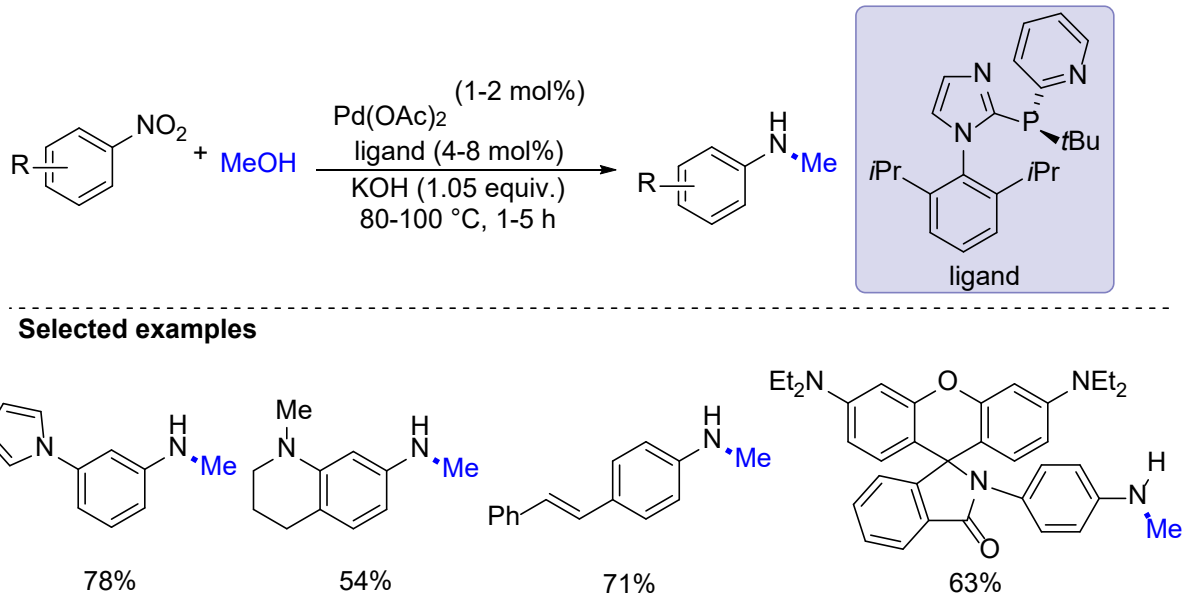
Shimizu et al. carried out the selective N-methylation of amines and nitroarenes on carbon-supported Pt nanoparticles (Pt/C) as a heterogeneous catalyst and achieved the TONs of over 3500. However, the reaction conditions are quite hard and some reactions require to be performed under H_2 gas pressure.[75] In 2024, Liu and co-workers investigated various SnO_x-decorated Pt heterogeneous catalysts for the reductive N-methylation of quinolines with methanol.[76] The study revealed that the most effective catalyst for this transformation is SnO_x-decorated Pt/Al_2O_3 (Pt-SnO_x/Al_2O_3), which successfully catalyzed the conversion of quinolines to N-methyl-1,2,3,4-tetrahydroquinolines in 85-97% yields with conversions of 89-99% at 130 °C, using methanol as the sole source of both hydrogen (H) and methyl (CH_3). Notably, the reaction proceeds without the need for additional bases or additives. Furthermore, the authors assessed the green chemistry metrics, underscoring the environmental sustainability and "green" nature of the process.[7] Several studies on the use of heterogeneous Ir nanoparticles (Ir@YSMCNs, Ir/ZnO) for this transformation were also reported recently.[77] However, these catalytic reactions need to be conducted under high temperature (150-170 °C) and long reaction time. In 2017, Tu's group disclosed a remarkable breakthrough in the synthesis of a new Ir-NHC coordination polymer as a highly active heterogeneous catalyst for the methylation of amines, ketones, and nitriles using methanol (Scheme 26). This Ir-NHC catalyst displayed an outstanding TONs (~2.0×10^4) and could be recycled up to 23 times.[78] In 2021, Beller and Jagadeesh reported that

supported Co nanoparticles catalysts could be employed for N-methylation of amines using methanol.[79] Reusable Co@NC-800-phen catalyst was found to be the most suitable catalyst for this transformation in moderate to good yields. One year later, Huang, Lu and coworkers disclosed a selective N-mono- and di-methylation of amines using heterogeneous CuCo nanoparticle catalysts with adjustable supports and methanol. Cu-Co/MgAl-LDO created N-methylamines in a hydrogen environment, while Cu-Co/Al_2O_3 produced N,N-dimethylamines in a nitrogen atmosphere.[80]



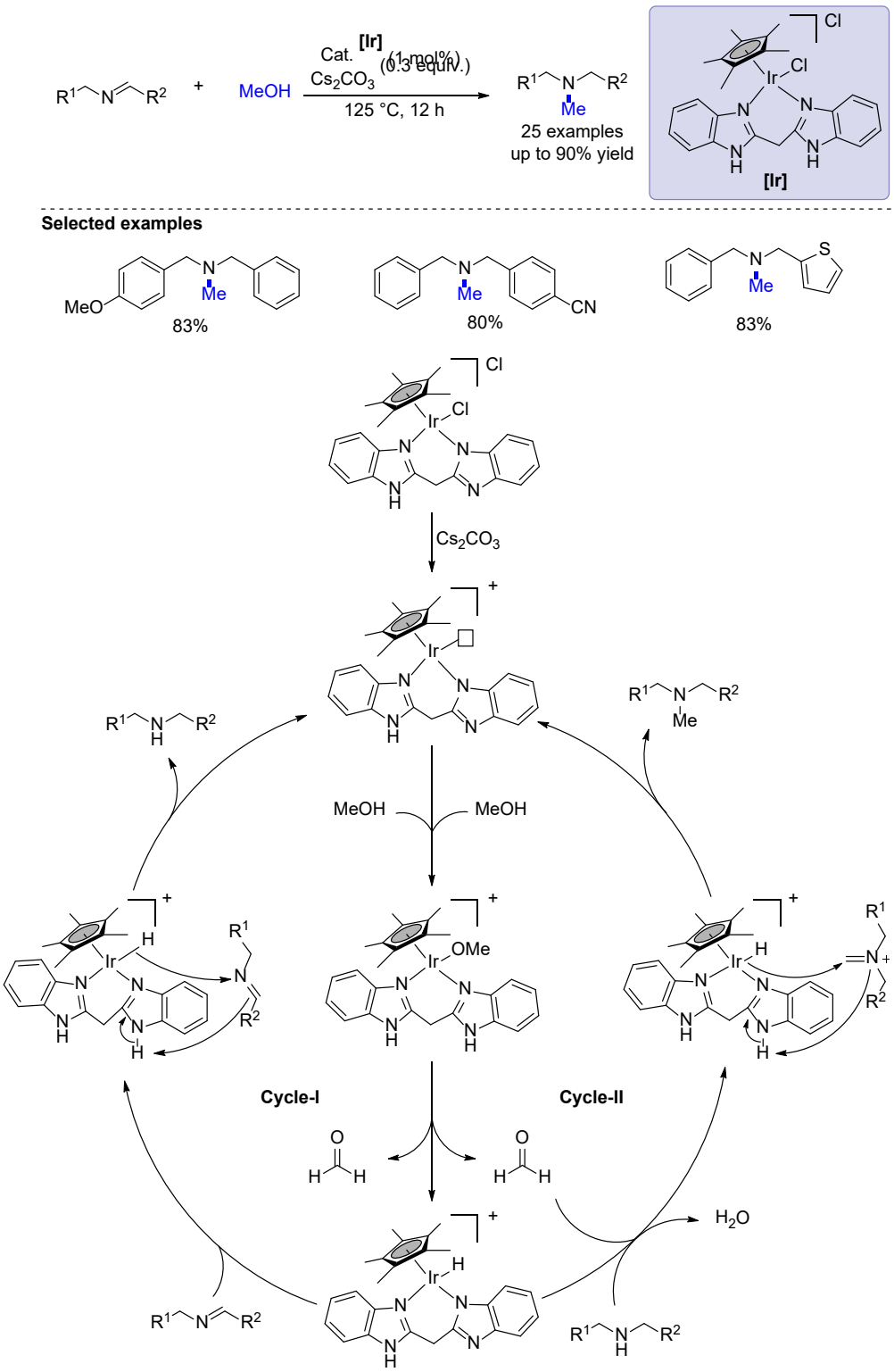
Scheme 27. Direct Ir-catalyzed N-methylation of nitroarenes utilizing methanol.

Amides, sulfoamides, hydrazines, nitroarenes, imines and nitriles have been regarded as more difficult substrates than amines in N-methylation processes with methanol. In fact, they are significantly less expensive starting materials than amines. Therefore, the catalytic transformations using methanol of such substrates to N-methylated products may give potential applications in the development of pharmaceutical, agrochemical and fine chemical industries. In 2020, Hou et al. reported that the bimetallic bis-NHC Ir catalyst could be successfully employed for the preparation of N-methylated aniline derivatives from both amines and nitroarenes and methanol.[64e] However, they had to use double amount of Ir catalyst (0.5 mol%) and extended reaction time from 4 hours to 24 hours when this catalyst was applied for the N-methylation of nitroarenes (Scheme 27). Recently, Torrente's group also disclosed another efficient Ir-NHC catalyst for this transformation.[81]



Scheme 28. Direct Pd-catalyzed N-methylation of nitroarenes using methanol.

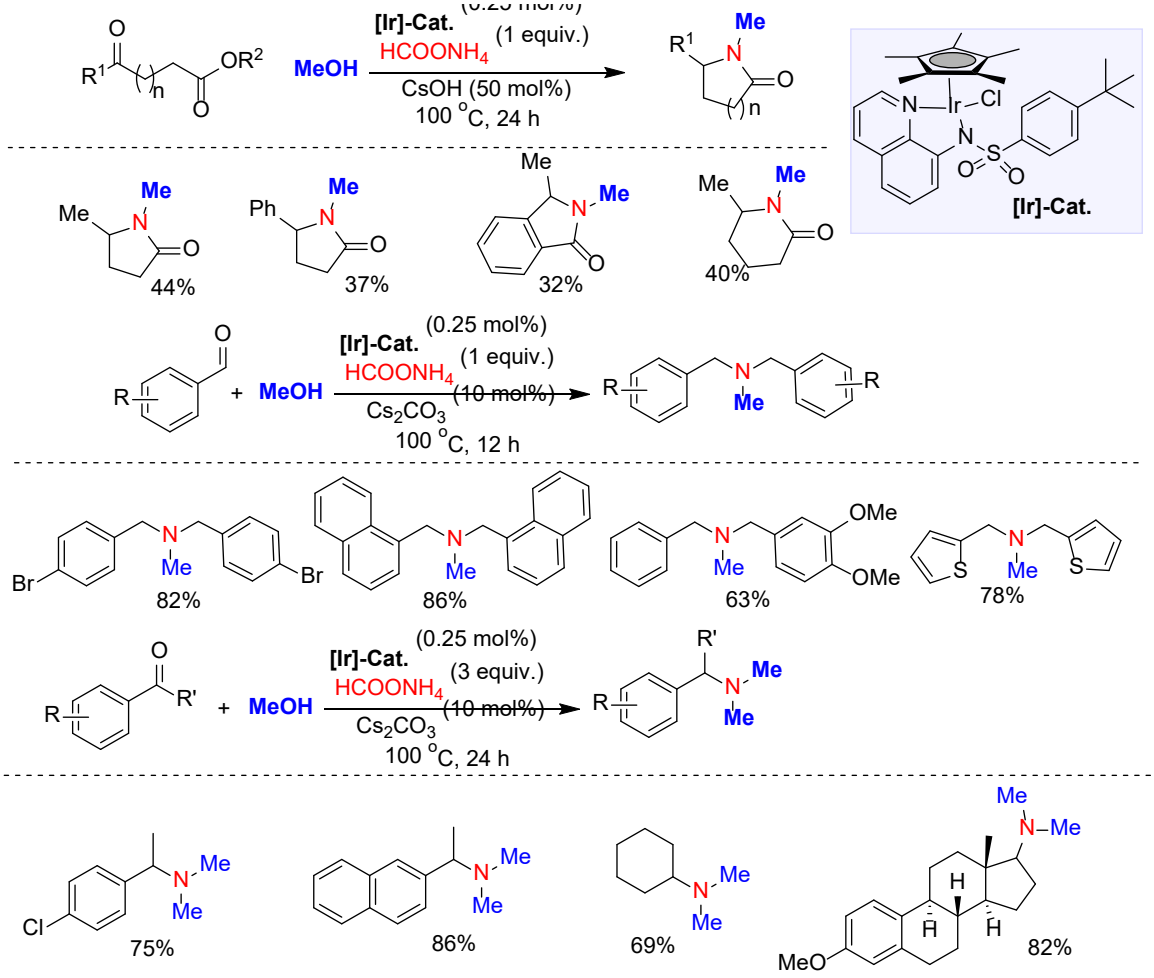
In 2021, Natte et al. reported a simple, ligand-free $RuCl_3$ N-methylation of amines and nitroarenes using methanol. However, high catalyst loading (up to 25 mol%) and long reaction time (60 h) were necessary for the transformation of nitroarenes.[82] Significant improvement in N-methylation of nitroarenes using pincer Ru complexes were demonstrated by Balaraman's and Yang's groups.[83]. Beller et al. developed a novel approach for the N-methylation of nitro compounds utilizing palladium acetate and a well-designed ligand, using methanol as the methylating agent (Scheme 28).[84] The researchers discovered that a ligand with a pyridyl group (L) is optimal for N-methylation of nitroarenes after experimenting with several substituents. The authors evaluated the proceduce's scope and limitations by using several substituted nitroarenes. Especially, the advantage of this approach was that it used minimal catalyst loading (1-2 mol%) and had a short reaction time (1-5 h).[84]



Scheme 29. Ir-catalyzed synthesis of N-methyl tertiary amines from imines using methanol.

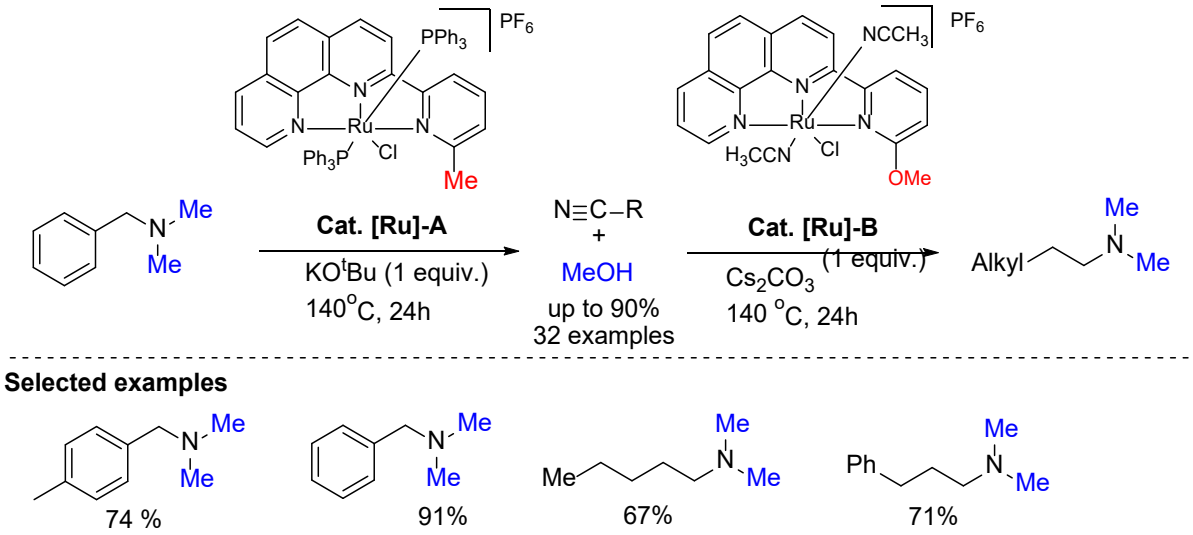
In the development of more sustainable methods for N-methylation of nitroarenes using methanol and deuterated methanol ($CDCl_3$), Morrill's and Balaraman's groups demonstrated that Mn-pincer complexes could be efficiently employed as catalysts in short reaction time (4 hours).[85] Several recyclable heterogeneous catalysts (Pd/C, Pt/C, Ir@YSMCNs, Cu/Al_2O_3) could be utilized for this transformation. However, hard conditions (high temperatures and long reaction time) were required to obtain high conversion. In 2020, by expanding the p-ring within the solid Ir catalyst, Xu, Tu, and their team developed a highly active and robust N-heterocyclic carbene-iridium (NHC-Ir) coordination solid assemblies for N-methylation of nitroarenes using methanol.[86] This Ir-solid material was highly stable in air and moisture condition and remained catalytically active and selective after up to 10 runs.

Li et al. (2020) successfully synthesized N-methyl tertiary amines from imines by a tandem process including transfer hydrogenation and N-methylation (Scheme 29).[86] They used a Cp*Ir complex catalyst with 2,2′-methylene-bibenzimidazole ligand and methanol as the C1 source. In order to understand of reaction mechanism insights, a kinetic study was carried out. Under typical reaction circumstances, imine underwent two simultaneous N-methylation reactions with CH_3OH and CD_3OD, resulting in a significant kinetic isotope effect (KIE) (k_H/k_D = 3.11). In addition, the presence of Ir-H signals in the ^1H NMR spectra support the proposed reaction mechanism.



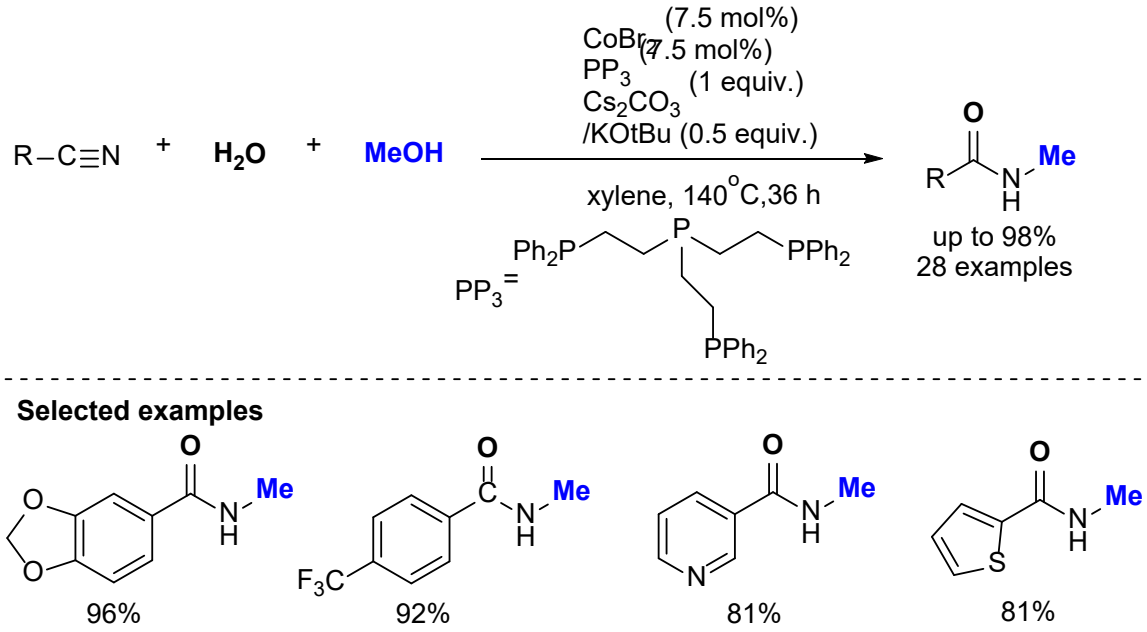
Scheme 30. Ir-catalyzed dual reductive amination followed by N-methylation of aldehydes and ketones.

Very recently, Kundu et al. demonstrated an Ir(III)-catalyzed dual reductive amination followed by N-methylation of aldehydes and ketones, enabling the synthesis of N,N-dimethyl and N-methyl tertiary amines, respectively (Scheme 30).[87] The reaction utilizes ammonium formate and methanol as the N1 and C1 sources. Moreover, the authors applied this approach to synthesize N-methyl lactams through a tandem reductive amination/N-methylation/cyclization of keto acids/esters. The ability to synthesize bioactive compounds on a diverse range of substrates was established. Control experiments, kinetic studies, and DFT calculations were used to provide a viable mechanism. Later, Kundu's group investigated N,N-dimethylation of amines from nitriles using methanol and similar ruthenium complexes as catalysts (Scheme 31).[88] However, the discussion does not cover the catalyst's reactivity in methylating benzonitriles and alkyl nitriles with other ligand systems, such as Py-Me and Py-OMe. A variety of aromatic and aliphatic nitriles produced N,N-dimethylated amines under slightly modified reaction conditions. The authors demonstrated a possible application of this method by the synthesis of the antiallergic drug "avil". DFT calculations and kinetic investigations were conducted to confirm the borrowing/auto hydrogen method used in the reaction.



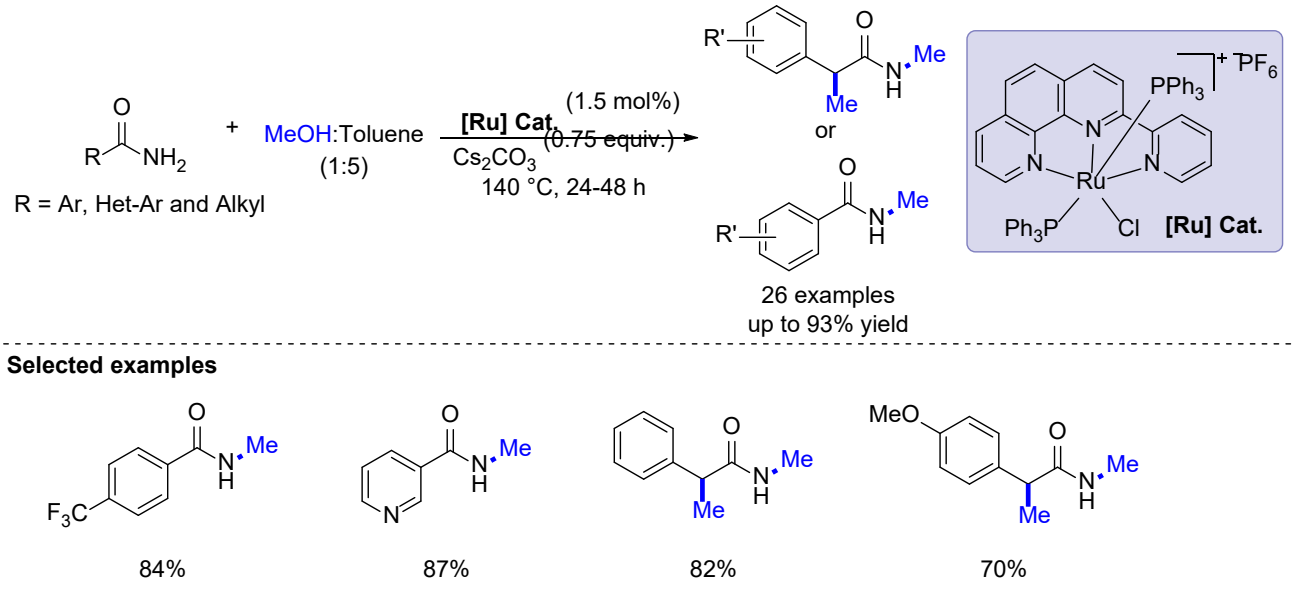
Scheme 31. Ru -catalyzed N,N-dimethylation of nitriles using methanol.

In another approach, Kundu et al. used a mixture of methanol and water with $CoBr_2/PP_3$ ($P(CH_2CH_2PPh_2)_3$) catalyst to convert nitriles to N-methylated amides (Scheme 32).[89] Cs_2CO_3 and KOtBu were employed as the bases. To selectively monomethylate amides, the rate of nitrile hydration must exceed that of nitrile hydrogenation. The ideal amount of water for this process was determined to be 10 equiv. Hydrogenation of N-methylene amides may help distinguish between mono- and di-N-methylation. Various functional group substituted nitriles can be easily transformed to N-methylated amides.

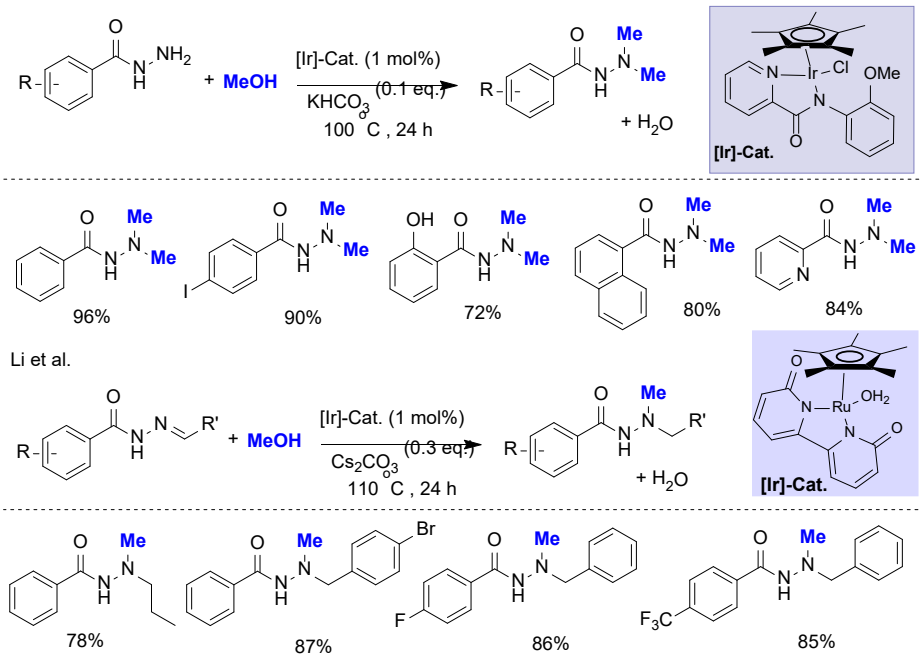


Scheme 32. Co-catalyzed synthesis of N-methyl amides from nitriles using methanol.

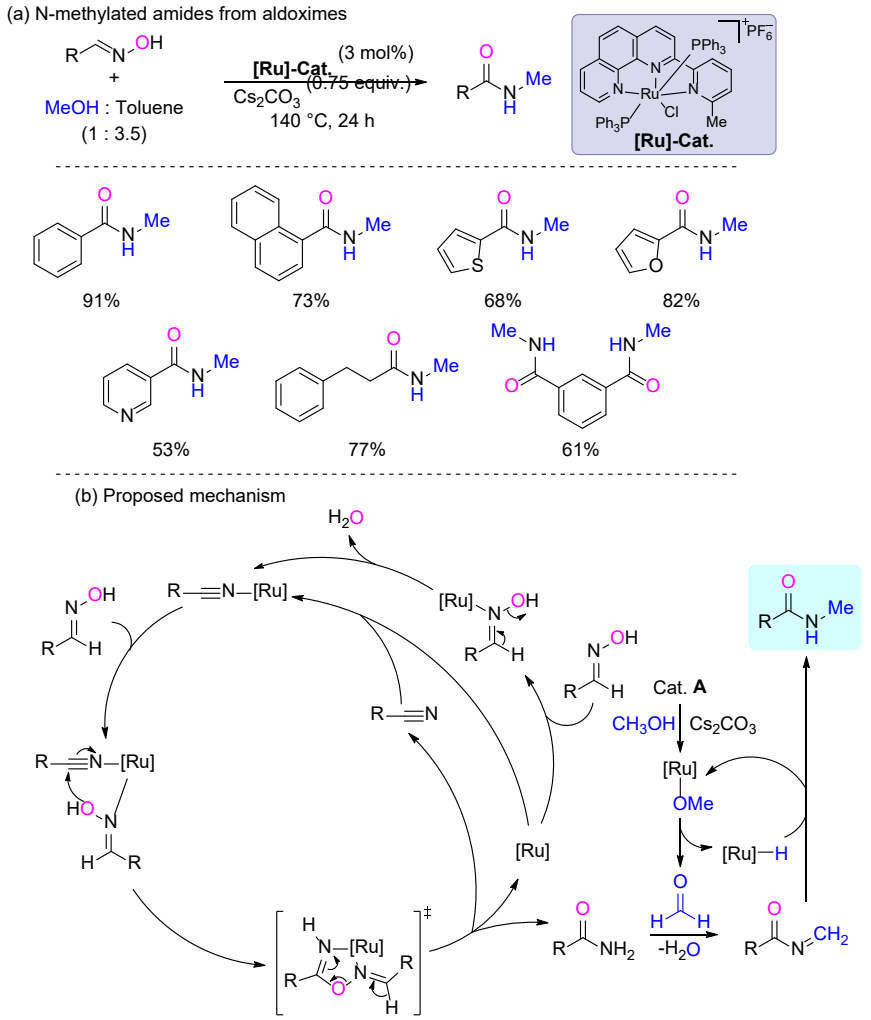
Direct N-methylation of amides with methanol has been considered to be more challenging due to low nucleophilic activity of amides (Scheme 33). Again, Kundu et al. successfully employed the Ru(II) complex catalyst for N-methylation of both aliphatic and aromatic amides. A tandem C-methylation and N-methylation process happen with aliphatic amides in the presence of Ru catalyst.[89] Very recently, Wang, Bao and coworkers described the process of direct N,N-methylation of acyl hydrazide which is catalyzed by a series of amidato iridium complexes bearing an electron-donating group in the ligand and methanol as the methylating reagent.[90] Excellent yields are obtained by converting a variety of acyl hydrazide derivatives to the corresponding N,N-dimethylated products (Scheme 34). Experiments show that ortho electron-donating groups on the phenyl moiety of the picolinamide ligand are critical for catalytic activity. In 2022, Li et al. described a novel method for synthesizing N′,N′-methylaliphatic acylhydrazides from acylhydrazones using methanol as both a hydrogen source and methylating reagent.[91] The employment of [Cp*Ir(2,2′-bpyO)(H_2O)] (1 mol%) catalyst and Cs_2CO_3 (0.3 equiv) base resulted in excellent yields of desired compounds (Scheme 34). Functional units of the catalyst's bpy ligand play a significant role in catalytic activity of iridium complexes. The mechanistic investigation and practical application of the current catalytic system were also demonstrated.



Scheme 33. Direct Ru-catalyzed N-methylation of amides using methanol.



Scheme 34. Direct Ir-catalyzed N,N-dimethylation of acyl hydrazide and hydrazone derivatives using methanol.

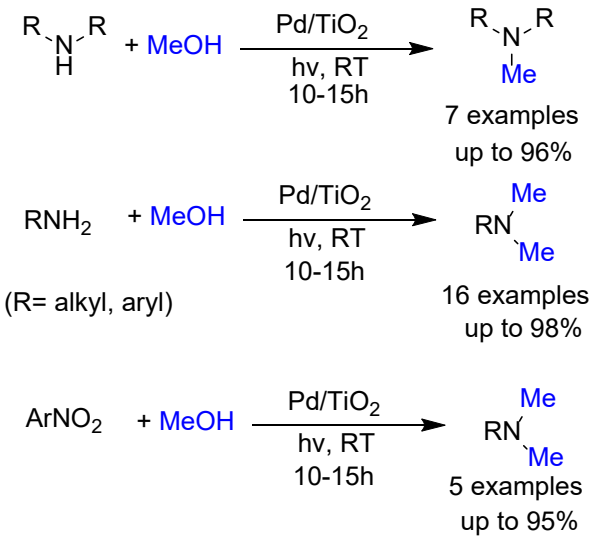


Scheme 35. Ru-catalyzed tandem transformation of aldoximes into N-methylated amides using methanol.

In 2019, Kundu and colleagues reported a Ru(II)-catalyzed tandem transformation of aldoximes into N-methylated amides using methanol as the alkylation agent, employing a hydrogen borrowing approach (Scheme 35a).[16j] Mechanistic studies revealed that the reaction begins with Ru(II)-catalyzed rearrangement of the aldoxime starting substrate into an amide. The amide then undergoes condensation with formaldehyde, generated in situ from methanol), forming an imine mediate, which is subsequently converted into the final N-monomethyl amide final product (Scheme 35b). This transformation, along with previously discussed methods, highlights the practicality and utility of “greener” N-methylation of amines and related compounds via hydrogen borrowing using methanol.

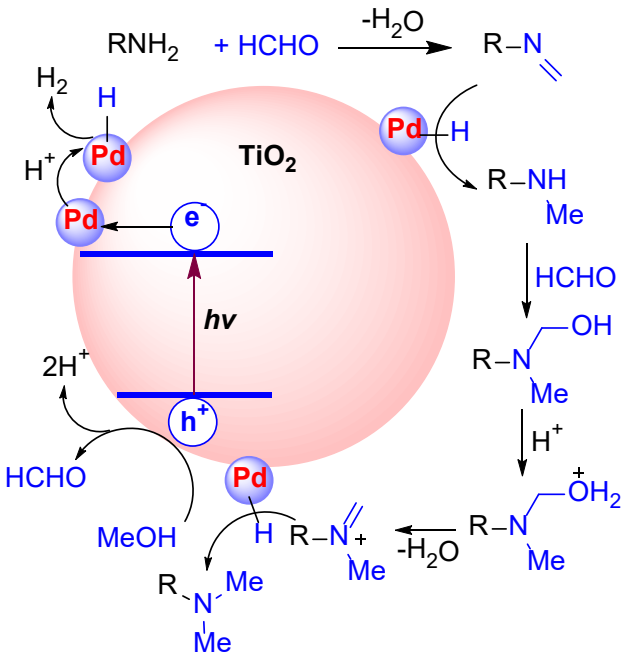
2.5. Light-promoted N,N-dimethylation of amines and nitro compounds using methanol

Heterogeneous photocatalysis using semiconductors (TiO_2, SiO_2) as catalysts have been applied in the environmental treatment and water splitting research.[92] In 1986, Kagiya's group described the first report on Pt/TiO_2-catalyzed N-methylation of primary amines under UV irradiation.[93] However, this photocatalyst showed poor activity in the methylation of aniline and a miture of mono-and demethylated amines was obtained. In 2015, Shi *et. al*. reported an efficient Pd/TiO_2-catalyzed N,N-dimethylation of amines and nitrobenzenes with methanol under photoirradiation of a LED light (λ=365 nm).[94] Especially, in the presence of photocatalyst (Pd/TiO_2), the preparation of N,N-dimethylamines could be carried out at room temperature and did not require the presence of any bases. Notably, a large range of amines and nitrobenzenes was efficiently converted to N,N-dimethylamines in up to 98% yield (Scheme 36).



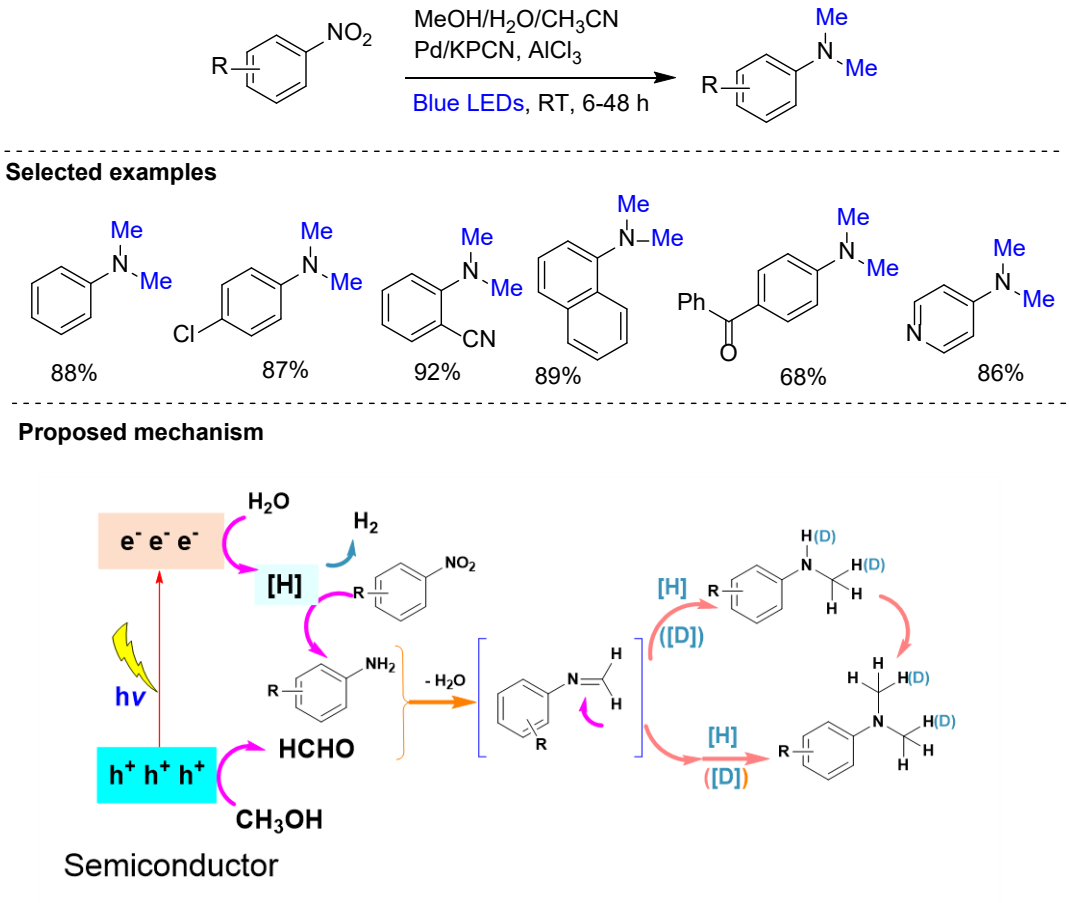
Scheme 36. Light-promoted Pd/TiO_2-catalyzed N,N-dimethylation of amines and nitroarenes using methanol.

To understand the mechanism, methylation of aniline with methanol was chosen as the model reaction. GC-MS analysis of *in situ*-formed intermediates was carried out during the reaction. Based on the observation of the formed intermediates, a plausible mechanism for the formation of N,N-dimethylamines was proposed (Scheme 37).[94] The reaction is believed to be initiated by the photoexcitation of TiO_2 to generate a pairs of electron (e^-) and positive hole (h^+). Then the h^+ oxidizes methanol to form formaldehyde and H^+. The reduction of H^+ occurred on the surface of Pd nanoparticles by the e^- transferred from the TiO_2 conduction band to form a Pd–H species. The condensation of amine with *in-situ* formed formaldehyde generates an imine, which was reduced to N-methylamine by Pd–H species on the surface of TiO_2. Next, the second condensation of N-methylamine with another formaldehyde formed an iminium, which was also reduced by Pd–H species to the N,N-dimethylamine product. Similar research using Pd/TiO_2 and Pd@CN photocatalysts under UV irradiation was carried out by Naka's and Zhang's groups.[95] Later, the Naka et al. subsequently developed a mixed Cu-Au photocatalytic system for N-methylation of pharmaceutically relevant amines.[96] The selectivity of N-mono- and N-dimethylation of primary amines was solvent-controlled. Several drugs were successfully synthesized using this catalyst, such as Alverine, Venlafaxine-d_6, and Imipramine-d_3 with the current method.[96]



Scheme 37. Possible mechanism for light-promoted Pd/TiO_2-catalyzed N,N-dimethylation of amines with methanol.

Earlier in 2015, Saito *et al*. published a research on N-methylation of amines with methanol in the presence of Ag/TiO_2 photocatalyst under UV irradiation at room temperature.[97] Up to 97% of N-methylated products were achieved with the tolerance of various functional groups. Interestingly, Ag/TiO_2 catalyzed N-methylation of amonia using methanol gave 80% yield of trimethylamine salt. In 2018, Naka and co-workers demonstrated the N-methylation of complex pharmaceutically relevant amines using methanol via a photocatalytic process under mild conditions.[96] Initially, with Cu/TiO_2 as the photocatalyst, the reaction yielded the desired N,N-dimethylated amine in 89% yield after 7 hours of light irradiation. Further optimization showed that adding Au/TiO_2 as a co-catalyst reduced the reaction time to 2 hours and slightly increased the yield to 91%. Additionally, the selective mono- or dialkylation of primary amines could be achieved by varying the solvent. Control experiments indicated that formaldehyde generation from methanol was primarily driven by Au/TiO_2, while the hydrogenation of the imine intermediate was catalyzed by Cu/TiO_2. This method was successfully applied to the synthesis of several drugs,[96] including Alverine, Venlafaxine-d_6, and Imipramine-d_3. More recently, by replacing TiO_2 with inexpensive but stable carbon nitride (CN), Wang's group successfully developed a Pd-CN heterogeneous photocatalytic system for the N-methylation of amines.[95b] The reaction was performed under light irradiation and 1 bar H_2. The corresponding N-methylated compounds were produced in good to excellent yield. This Pd-CN photocatalytic system was well-tolerated with several functional groups, and showed exceptional reusability, which indicated high potential for practical applications.



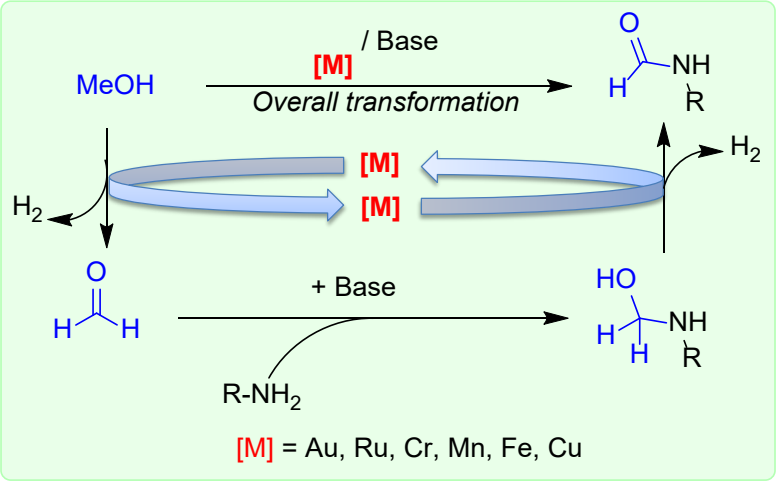
Scheme 38. Integrated selective N-methylation of nitroarenes over Pd/KPCN catalyst

In 2021, Su and coworkers reported the full use of the holes and liquid H-source during water splitting for the photo-reductive N-methylation of nitroarenes.[98] In this integrated catalyst system, methanol was oxidized by holes to produce cascade methylating of anilines as well as the generated secondary amines, while H-species in-situ formed via water splitting were designed for nitroarenes reduction to produce N,N-dimethylated amines (Scheme 38). Through the synergistic exploitation of the photogenerated redox centers over Pd/KPCN catalyst, semiconductor photoredox catalytic N-methylation of nitroarenes with water and methanol was successfully accomplished. Methanol could act as green precursor to formaldehyde generated by photoexcited holes-induced oxidation, while water could act as the green "liquid hydrogen source" in this system by photoexcited electron-induced reduction.

3. Dehydrogenative Coupling Strategy in Incorporation of Methanol as C1 Building Block

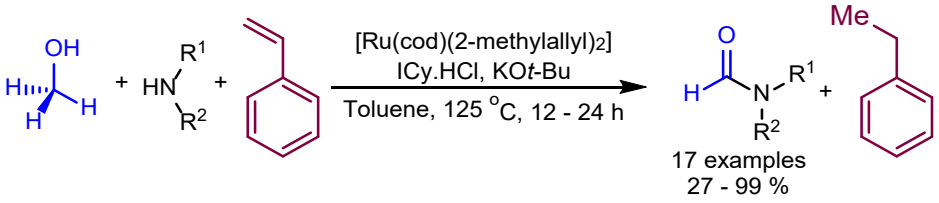
3.1. N-formylation of amines and nitriles

Formamides are vital intermediates for syntheses of many important organic substrates such as formamidines, isocyanates, nitriles, drugs, and fungicides, as well as for biosynthesis of proteins.[99] Formamides have also been used as a protecting group in organic sythesis and useful reagents in Vilsmeier formylation, allylation, and hydrosilation reactions.[100] Traditional N-formylation of amines require the use of excess amounts of moisture sensitive, toxic, expensive formylating reagents. Hence, using methanol as a cheap and "green" formylating reagent is highly beneficial. A general mechanism for transition metals-catalyzed N-formylation of amines with methanol via dehydrogenative pathway is depicted in Scheme 39.



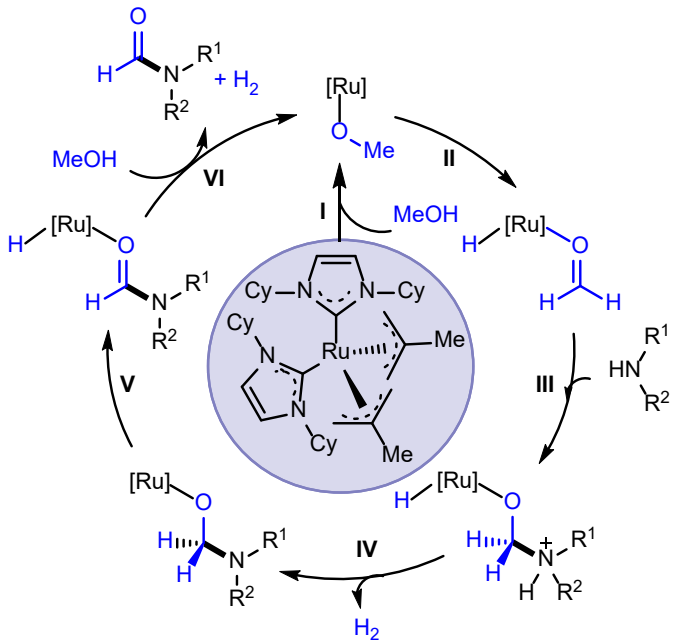
Scheme 39. Transition metals-catalyzed N-formylation of amines using methanol.

The first homogeneous catalyzed dehydrogenative N-formylation of amines with methanol was reported by Glorius and co-workers.[6i] Formamides can be synthesized via dehydrogenative cross-coupling of methanol with either primary or secondary amines in the presence of a ruthenium/N-heterocyclic carbene (NHC) complex catalyst (Scheme 40). However, sterically hindered tertiary amines gave only low yields. Aromatic amines and aliphatic amines with good coordinating groups such as pyridines or carboxylic acids are not reactive in this reaction condition. However, the main limitation of this transformation is the use of 3 equivalents (eq.) of styrene as the sacrificial hydrogen acceptor.

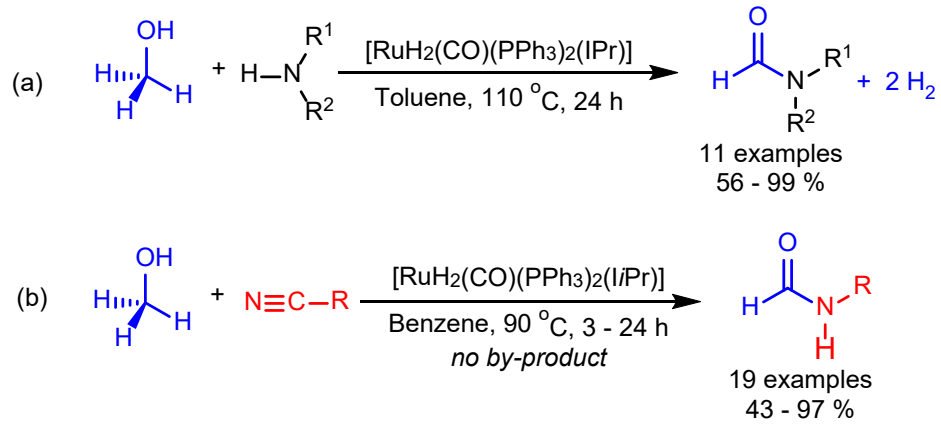


Scheme 40. Ruthenium-catalyzed dehydrogenative N-formylation of amines with methanol.

Scheme 41 presents the reaction mechanism.[6i] The reaction of NHC ruthenium catalyst with methanol generates a methoxide ruthenium species (step I). That follows a *β*-elimination to form the coordinated formaldehyde ruthenium hydride complex (step II), which is subsequently attached by amine (step III). The formamide coordinated ruthenium hydride intermediate is formed after the liberation of one hydrogen molecule and second *β*-elimination (steps IV and V). For closing of the catalytic cycle, methanol reacts with the formamide coordinated ruthenium hydride intermediate to regenerate the methoxide ruthenium species together with the release of second hydrogen molecule (step VI). Interestingly, only trace formamide products were detected when methanol was replaced by paraformaldehyde. Hence, free formaldehyde is either not present or present only at very low concentration during the reaction.

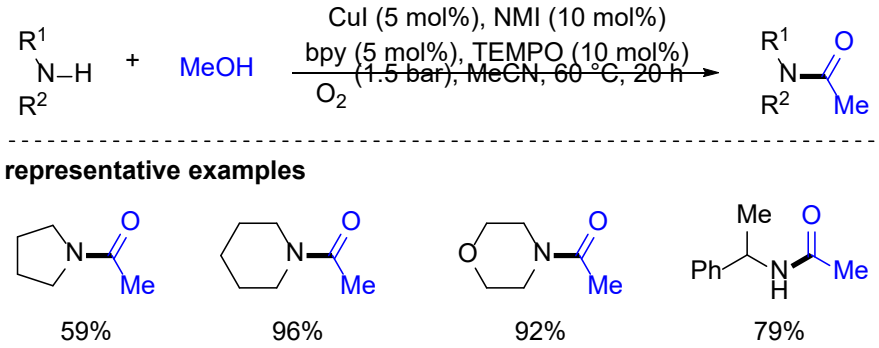


Scheme 41. Proposed mechanism for ruthenium-catalyzed dehydrogenative N-formylation of amines with methanol.



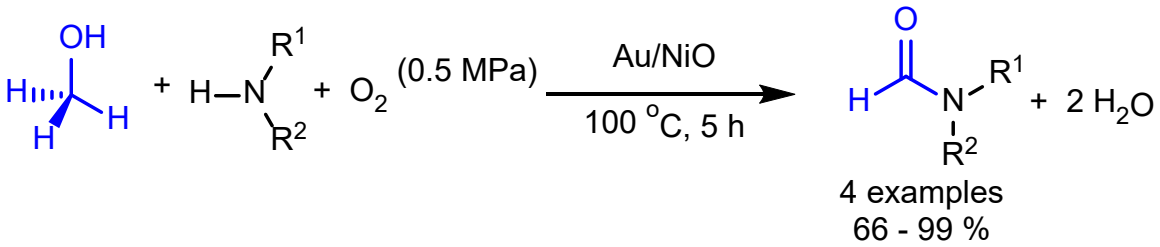
Scheme 42. Ruthenium-catalyzed dehydrogenative N-formylation of (a) amines and (b) nitriles with methanol.

In 2015, Kang and Hong reported the first hydrogen acceptorless dehydrogenative N-formylation of amines with methanol.[100] By using a different ruthenium NHC complex catalyst, primary and secondary amines react with methanol to form primary and secondary formamides, respectively. The reaction does not require any external bases, hydrogen acceptors, or oxidants and releases two equiv. of hydrogen gas (H_2). Similar to Glorius' method,[6i] no erosion of enantiomeric purity was found in the N-formylation of enantiomerically pure phenylethylamine. Moreover, the reaction works well for the heterocyclic amines (Scheme 42a). Interestingly, this method has been extended for the N-formylation of nitriles. In this case, the transformation is very atom and step economical with no by-product formation (Scheme 42b). In 2017, Prakash and co-workers pointed out that the ruthenium-catalyzed dehydrogenative N-formylation 1,2-diamines with methanol is reversible.[101] Based on that, a novel reversible hydrogen storage system has been developed. In this system, an overall carbon neutral cycle is established with N-formamide which is the carbon trapping form.



Scheme 43. Copper catalyzed N-formylation of amines with methanol.

Instead of using ruthenium catalysts, first raw transition metal catalysts also can be used for the reaction. The Cu-catalyzed N-formylation of amines with methanol in the presence of hydrogen peroxide has been established.[102] Remarkably, Milstein and co-workers revealed the use of manganese catalyst for this transformation.[102a] The acceptorless dehydrogenative couplings of amines and methanol to form formamides have been catalyzed by a novel pincer manganese complex under mild conditions. The proposed reaction mechanism includes the metal-ligand cooperation in methanol O–H bond cleavage step. In 2017, Bernskoetter et al. demonstrated an iron-pincer complex catalyzed the intermolecular dehydrogenative coupling between secondary amines and alcohols.[103] The amide coupling product was yielded smoothly even with very low catalyst loading (as low as 0.1 mol%). However, this protocol was not compatible for sterically demanding amines. More recently, Prechtl et al. reported the N-formylation of amines with methanol in the employment of copper catalyst (Scheme 43).[104] The reaction employed the combination of (bpy)CuI(NMI)/TEMPO under oxygen atmosphere. Several amines were compatible with this protocol, delivering products in good to excellent yield.



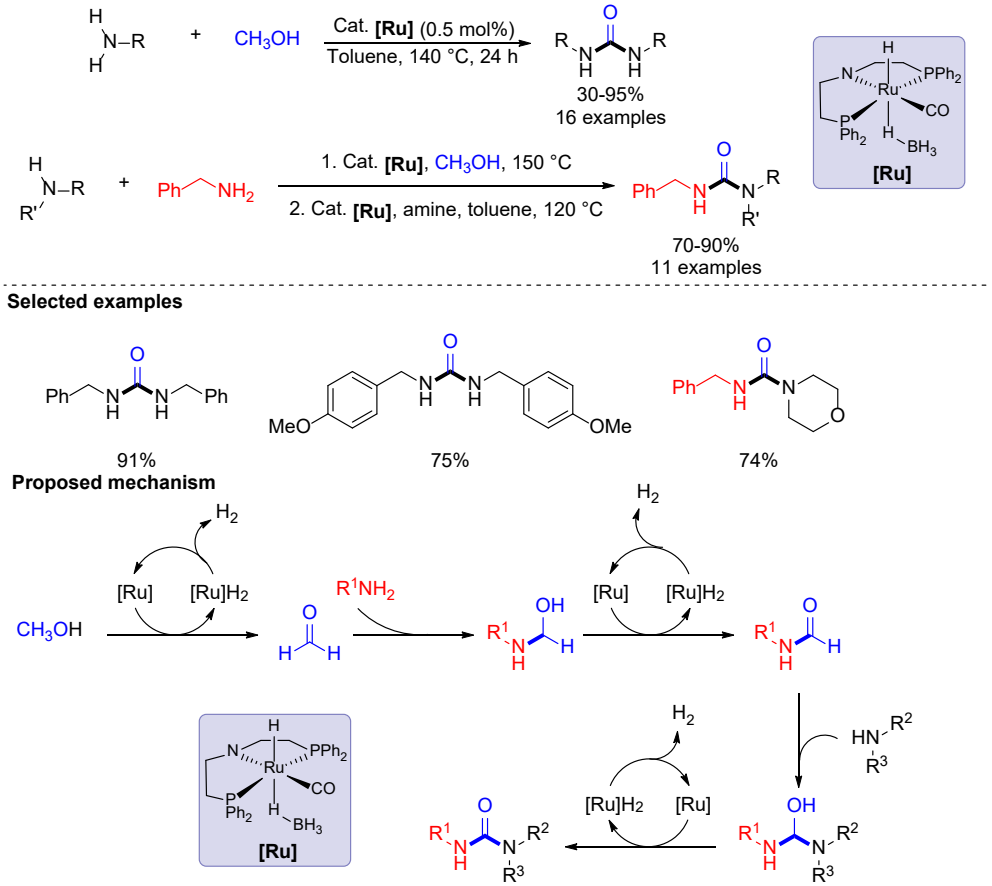
Scheme 44. Heterogeneous gold-catalyzed aerobic oxidative N-formylation of amines with methanol.

One of the first examples for N-formylation of amines with methanol using heterogeneous catalysts was published in 2009 by Ishida and Haruta.[52] The reaction is conducted under an oxygen atmosphere with the use of supported gold nanoparticle catalysts. Notably, the reaction works well for aniline, a less nucleophilic amine, which is inactive in the homogeneous catalysis methods

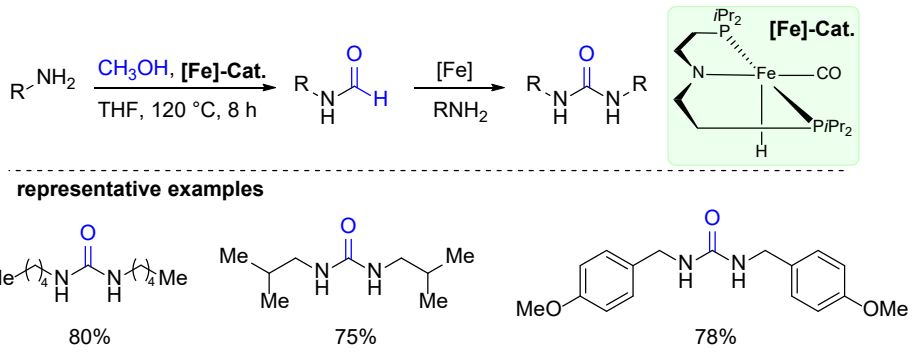
(Scheme 44). Later, Sakurai and Asao shown that the reaction also proceeds well with the use of gold-nanoclusters stabilized by poly(N-vinyl-2-pyrrolidone) (Au:PVP) and nanoporous gold (AuNPore) catalysts.[105] Kim et al. reported a bimetallic catalyst basing on Au and Pd (AuPd-Fe_3O_4 that can carry out N-formylation of secondary amines at ambient temperature with good yields. O_2 gas (1 atm) was required as an external oxidant. Especially, a synergistic effect between Au and Pd metals made this process happen smoother under mild condition.[106] In 2019, Wei's group successfully employed a cheaper inorganic ligand-supported chromium(III) ($(NH_4)_3[CrMo_6O_{18}(OH)_6]$ as a catalyst for the formylation of primary and secondary amines using methanol.[107] The N-formulation was performed smoothly with 0.1 mol% catalyst loading in the presence of H_2O_2 and Na_2SO_3, giving the coupling products in high yield.

3.2. Synthesis of urea derivatives

In 2016, Kim and Hong developed a practical method for preparation of both symmetrical and unsymmetrical urea derivatives based on dehydrogenative coupling of 2 equivalents of amines with methanol (Scheme 45).[108] Thus, methanol has been used as the CO moiety in this transformation. Moreover, the reaction proceeds without the use of oxidant, hydrogen acceptor, base, or additive. In the reaction mechanism, methanol couples with the first amine to generate formamide, which subsequently reacts with the second amine to form the urea derivative product.



Scheme 45. Ruthenium-catalyzed synthesis of symmetrical (A) and unsymmetrical (B) urea derivatives from amines and methanol.

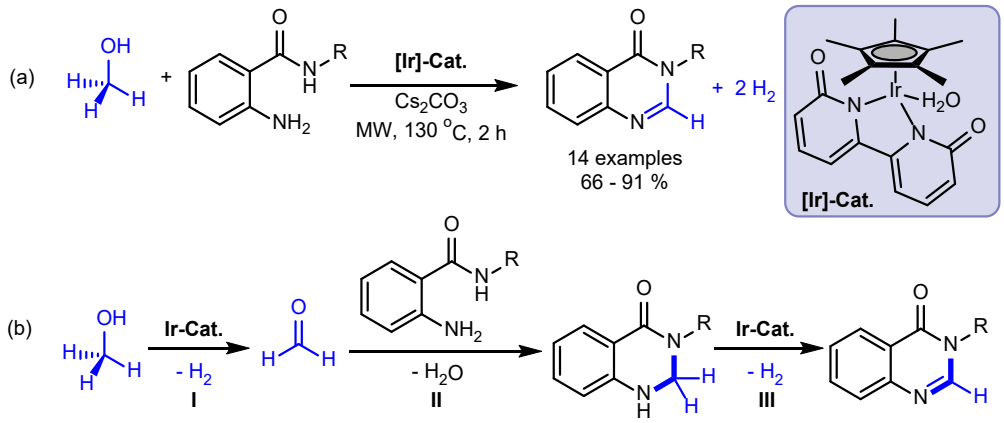


Scheme 46. Fe-catalyzed synthesis of urea derivatives from amines and methanol.

Bernskoetter et al. disclosed the first non-noble metal-catalyzed synthesis of urea derivatives using methanol as CO surrogate.[109] The reaction was performed in the employment of an Fe-pincer catalyst at 120 °C, giving various symmetrical ureas in moderate to good yield (Scheme 46). The authors proposed that the process underwent the formation of isocyanate intermediate from primary amine and methanol, which then reacted with other molecules of amine to furnish ureas.

3.3. Synthesis of N-heterocycles

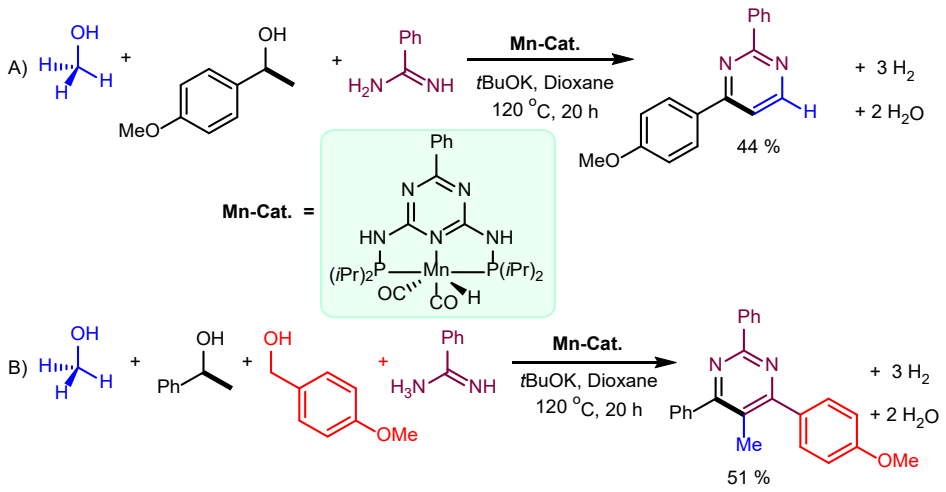
Nitrogen-containing heterocycles are essential unit structures with important applications in many fields including pharmaceuticals, agrochemicals, food industry, dyes, and advanced materials.[110] They also can be found in variety of biologically active compounds such as DNA, RNA, nucleosides, nucleotides, and hemoglobin.[111] Therefore, the utilization of methanol for the synthesis of N-heterocycles is a subject of interest. Liu and co-workers developed a convenient method for construction of quinazolinones via acceptorless dehydrogenative coupling of *o*-aminobenzamines with methanol in the employment of an iridium complex catalyst.[112] The reaction requires the use of catalytic amount of base and was performed at 130°C in a single-mode microwave (MW) synthesizer. Fourteen quinazolinones containing alkyl, ether, fluoride, chloride, and bromide functional groups have been prepared in high yields (Scheme 47a). For mechanism, the reaction starts with the dehydrogenation of methanol with the assistance of iridium catalyst to generate formaldehyde. That subsequently reacts with *o*-aminobenzamides to form 2,3-dihydroquinazolinones though a condensation step. Then iridium-catalyzed dehydrogenation of 2,3-dihydroquinazolinones to afford the quinazolinones as the final products (Scheme 47b).



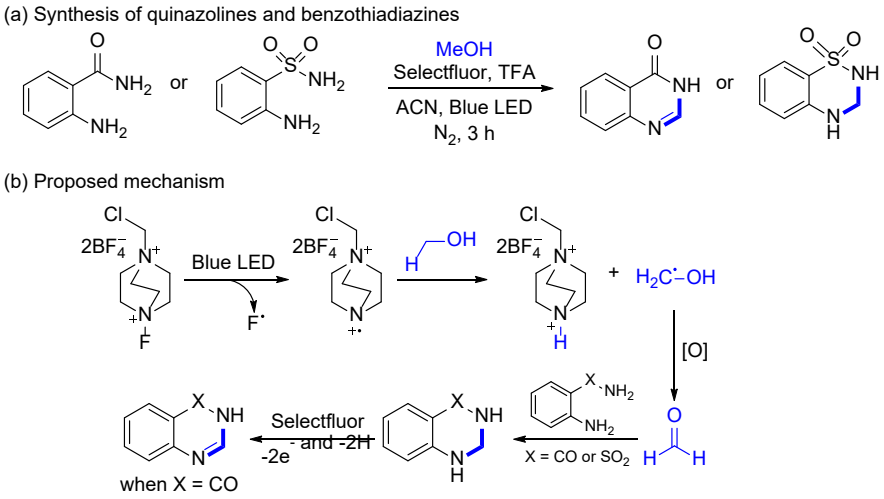
Scheme 47. a) Iridium-catalyzed acceptorless dehydrogenative coupling of *o*-aminobenzamides with methanol for synthesis of quinazolinones; b) proposed reaction mechanism.

In 2020, Meepowpan et al. developed a Cu-catalyzed synthesis of quinazolinones using aminobenzamides and methanol as starting materialsto achieve environmentally friendly and cost-effective heterocyclic synthesis.[113] The process used methanol as both a building block and solvent in an oxygen atmosphere, yielding a variety of quinazolinone derivatives with Cs_2CO_3 as the base. Appealingly, first-row transition-metal catalysts are also reactive for the synthesis of N-heterocyles from methanol.[114] The construction of benzimidazoles from 1,2-diaminobenzenes or 2-nitroanilines and methanol in the employment of Cu-doped porous metal oxide (Cu-PMO) catalyst was reported by Barta et al.[112] The reactions of 1,2-diaminobenzenes gave a mixture of N-methylated analogues and benzimidazoles. Interestingly, high selectivity for benzimidazoles has been achieved when more challenging 2-nitroanilines were used as the starting materials. Unfortunately, this method proceeds in very harsh conditions thus limits its application.

In 2017, Deibl and Kempe reported a Mn-catalyzed multicomponent synthesis of pyrimidines from amidines and methanol.[114a] In the course of reaction, multiple C–N and C–C bonds have been constructed via dehydrogenation and condensation steps from an amidine and two or three alcohols (Scheme 48). The authors emphasized that manganese is comparable to more expensive iridium catalysts, leading to a great potential application. In 2022, Song et al. reported the Cu- catalyzed synthesis of highly functionalized pyrimidines prepared by an aerobic cyclo-condensation reaction of α-acyl ketene dithioacetals using ammonium acetate and methanol. $CuCl_2$ catalyst played dual functions as Lewis acid and dehydrogenation which were necessary for this domino process. Single C-S ammonolysis driven by an in situ formed imine was the first step, and it was followed by cyclocondensation with aldehyde generated from alcohol and concurrent oxidative dehydrogenation in an oxygenated environment.[115]

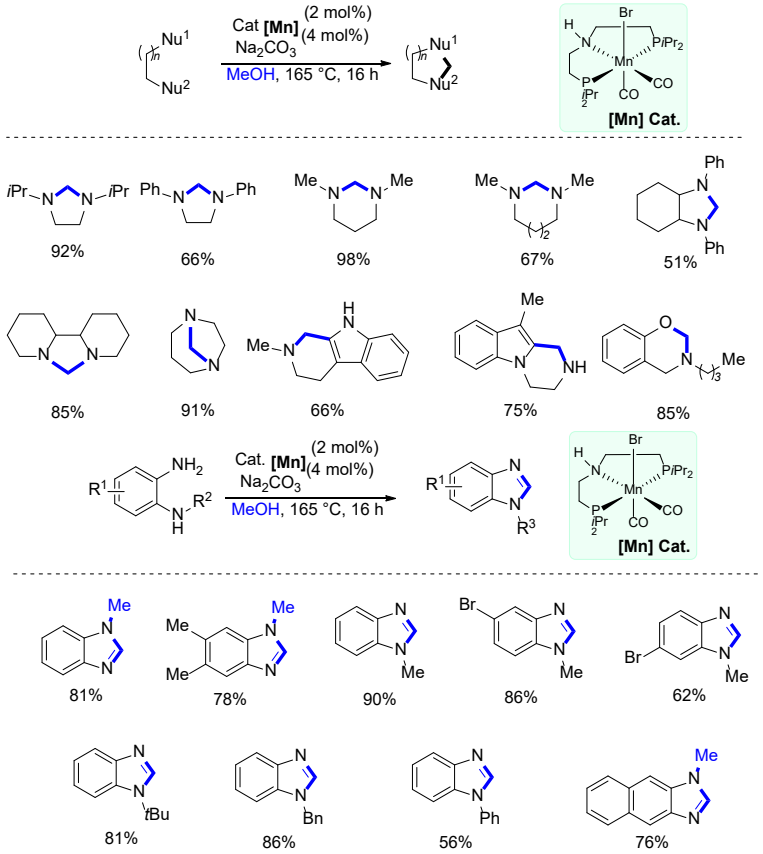


Scheme 48. Mn-catalyzed multicomponent synthesis of pyrimidines from methanol.



Scheme 49. Synthesis of quinazolinones and benzothiadiazines catalysed by a selectfluor photocatalyst.

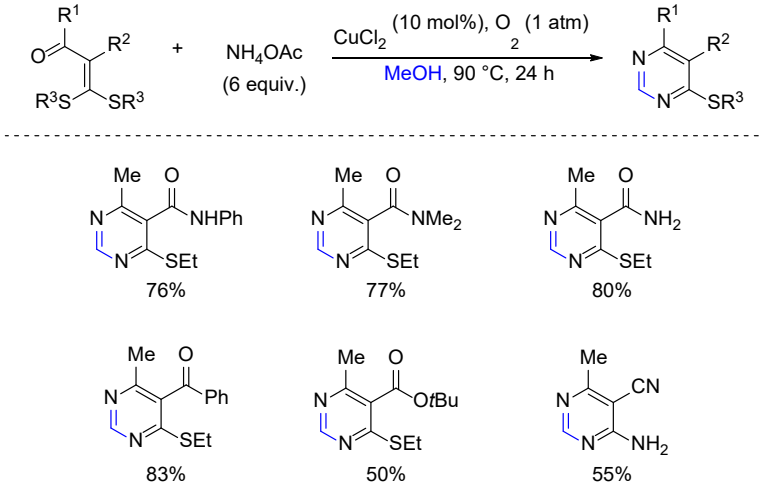
In 2020, Anandhan *et al.* addressed the copper-catalyzed oxidative cyclization of *o*-aminobenzamide and methanol under light irradiation for the synthesis of quinazolinones.[116] By employing Cs_2CO_3 as a base and methanol as solvent, the protocol performed well with various *o*-phenylformamide derivatives, furnishing the corresponding quinazolinones. This protocol could also be applied to ethanol, but the reactivity was slightly poorer. In 2022, the same group disclosed the synthesis of quinazolinones or benzothiadiazines from primary alcohols and *o*-aminobenzamide or *o*-aminobenzenesulfonamides, respectively (Scheme 49a).[117] In this reaction, under light irradiation, selectflour oxidized alcohol to aldehyde, which then underwent condensation and cyclisation to form the N-heteroarenes in moderate to good yields (Scheme 49b). A broad substrate scope of *o*-aminobenzamides, *o*-aminobenzene-sulfonamides, and alcohols were demonstrated under these photochemical conditions. regardless of the electronic nature of the substituents on the anthranilamide starting materials.



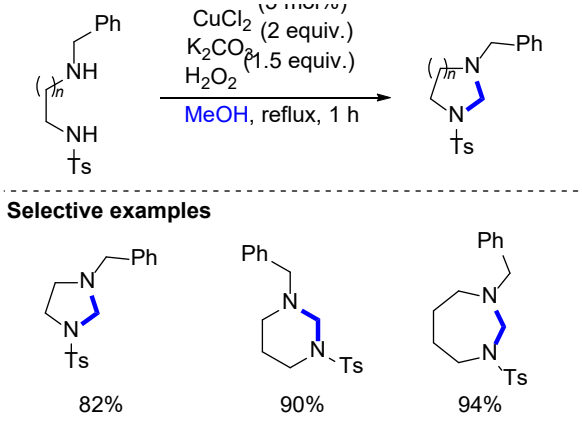
Scheme 50. Mn-catalyzed synthesis of N-heterocycles using methanol.

In 2022, Wei et al. described the synthesis of 2,3-dihyroquinazolin-4(1H)-one employing an electrochemical strategy with methanol as the C1 source.[118] The protocol delivered the dihydroquinazolinone products in high yield, In the same year, An and co-workers presented an ecofriendly protocol for synthesizing benzimidazoles from commercially available 2-nitroaniline derivatives with methanol as C1 source.[119] The redox coupling was catalyzed by first-row-transition metal (Fe) at milder temperature, delivering benzimidazoles in excellent yield. The generality and regioselectivity of this protocol were significantly improved compared to conventional approaches. Control experiments suggested that the reaction follows a hydrogen borrowing pathway catalyzed by iron metal. A general protocol for the synthesis of N-Heterocycles via Mn-catalyzed dehydrogenative cyclization was disclosed by Liu and

coworkers (Scheme 50).[120] Various types of N-heterocycles were prepared by employing methanol as a formaldehyde surrogate, which underwent condensation with a variety of dinucleophiles. This protocol showcased a wide range of substrate scope and tolerated well with various functional groups. Furthermore, ^{13}C-labeled N-heterocycles could be easily generated from $^{13}CH_3OH$.

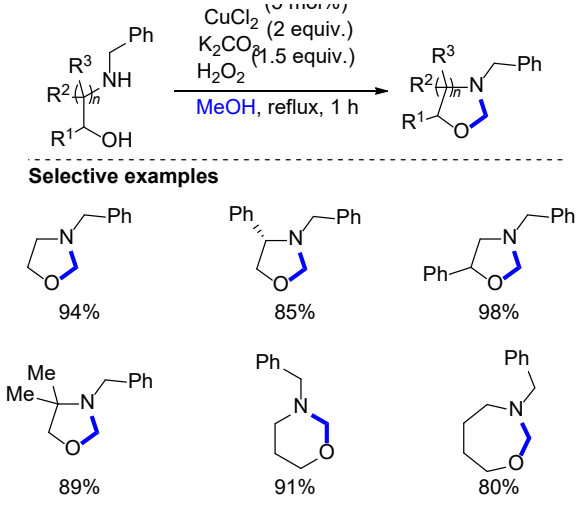


Scheme 51. Cu-catalyzed synthesis of pyrimidine derivatives.



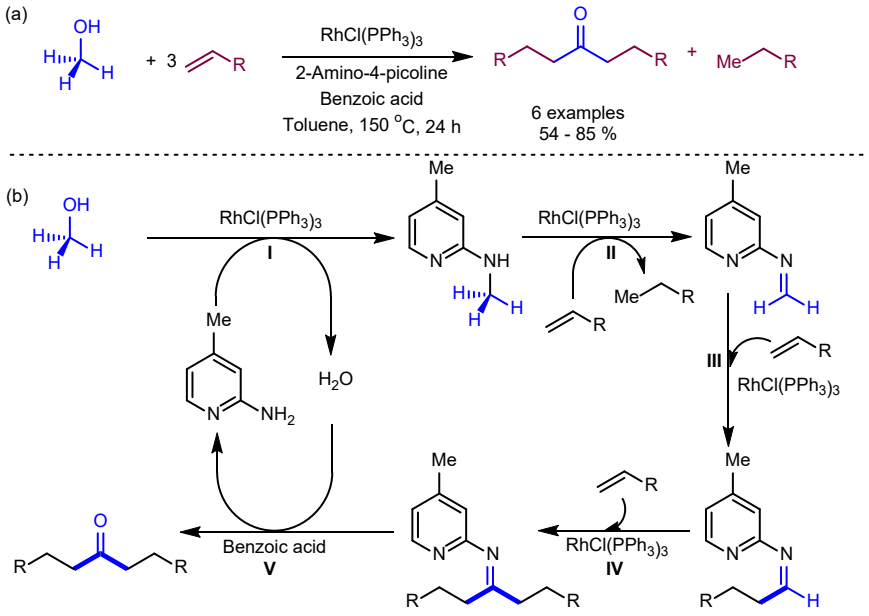
Scheme 52. Cu-catalyzed synthesis of N-heterocycles.

At the same time, Song et al. disclosed the synthesis of pyrimidine derivatives via a Cu-catalyzed aerobic cyclocondensation of α-acyl ketene dithioacetals with methanol and ammonium acetate under oxygen atmosphere (Scheme 51.[115] The reaction was well tolerated with several different functional groups, indicating the promise of this method in the construction of highly functionalized pyrimidines. In this tandem reaction, copper acted as both Lewis acid catalyst and dehydrogenation catalyst. In 2023, Loro's group disclosed a general method for the synthesis of 1,3-polyheterocyclic systems catalyzed by $CuCl_2$.[121] This method could be applied to aminoalcohols or diaminoalkanes in the presence of H_2O_2 as an external oxidant and K_2CO_3 as a base, furnishing the heterocyclic compounds in excellent yields (Scheme 52, 53). A Cu(II)- catalyzed the oxidation of methanol to formaldehyde was proposed. After the oxidation, copper(I) would be oxidized again to copper (II) by H_2O_2, regenerating the Cu(II) catalyst.



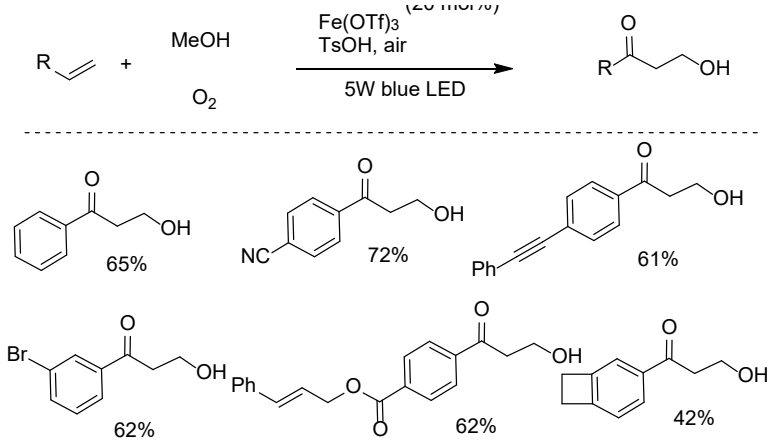
Scheme 53. Cu-catalyzed synthesis of N-heterocycles using methanol.

3.4. Synthesis of ketones from alkenes

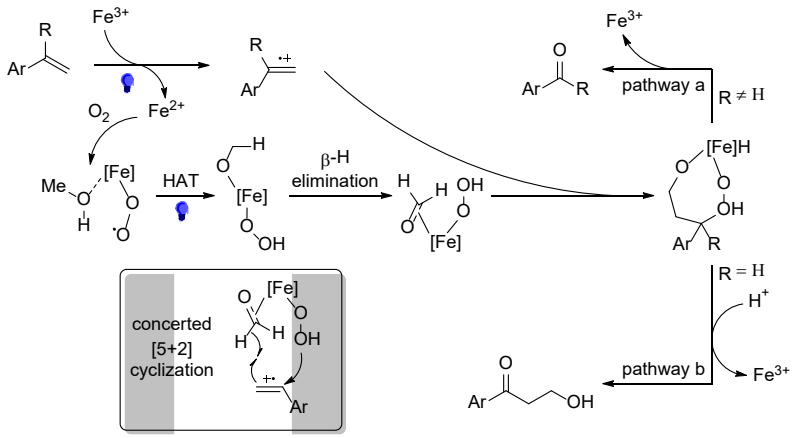


Scheme 54. a) Rh-catalyzed synthesis of dialkyl ketones from alkenes and methanol; b) proposed reaction mechanism.

Jun and co-workers disclosed the Rh-catalyzed synthesis of dialkylketones from alkenes and methanol (Scheme 54)I.[114b] Together with the rhodium(I) complex, 2-amino-4-picoline and benzoic acid were used as the co-catalysts. In these reactions, alkenes serve as both hydroacylation partners and hydrogen acceptors. Therefore, an excess amount of alkenes needs to be used for efficient performance (Scheme 54a). The reaction mechanism has been proposed in Scheme 54b.



Scheme 55. Fe-catalyzed regioselective synthesis of β-hydroxyketones from alkenes.



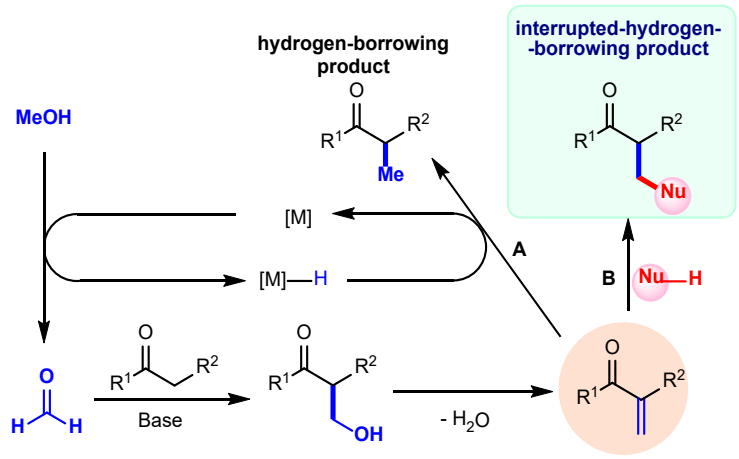
Scheme 56. Iridium-catalyzed regioselective hydroxylmethylation of allenes with methanol via redox pair coupling strategy.

In 2023, Qiu and coworkers reported on the photo-irradiation-induced divergent oxidation of styrene into β-hydroxyl-methylketone and ketone, which is catalyzed by iron (Scheme 55).[122] The usage of different substituents for styrene is the cause of this discrepancy.

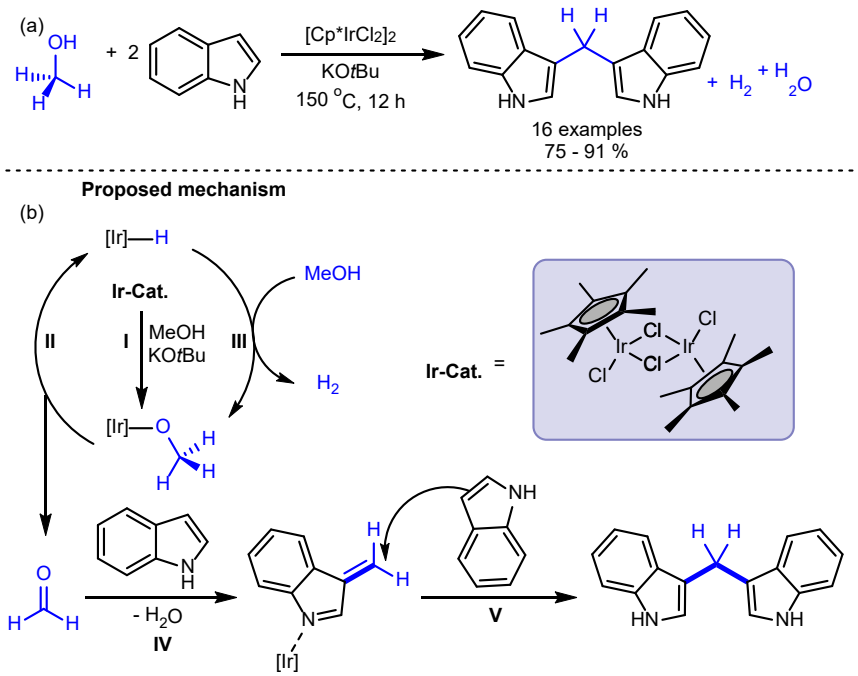
More significantly, methanol functions as a C1 synthon in the reaction by being oxidized into formaldehyde. According to mechanism studies, oxidative SET initiates the process by transferring styrene into the cation radical. In addition to a coordinated cyclization, the reaction pathway experiences HAT and β-hydride elimination (Scheme 56). In particular, a number of drug-like compounds are produced, including analogues of melperone, lenperone, and haloperidol.[122]

3.5. Interrupted hydrogen-borrowing reactions

One major challenge for the utilization of methanol as C1 building block in organic synthesis is the diversification of product structures, especially for the formation of hindered branched products. For solving this problem, one novel strategy naming interrupted hydrogen-borrowing (IHB) (Scheme 57, path B) was developed.[22] In the course of a hydrogen-borrowing (HB) reaction (Scheme 57, path A), the hydrogen returning step (the reduction of double-bond-containing intermediates) is inhibited. That enables the subsequent conjugate addition of a nucleophile to these double-bond-containing species. Hence, a wide range of complex products could be formed. Scheme 57 briefly presents the concept of this strategy.

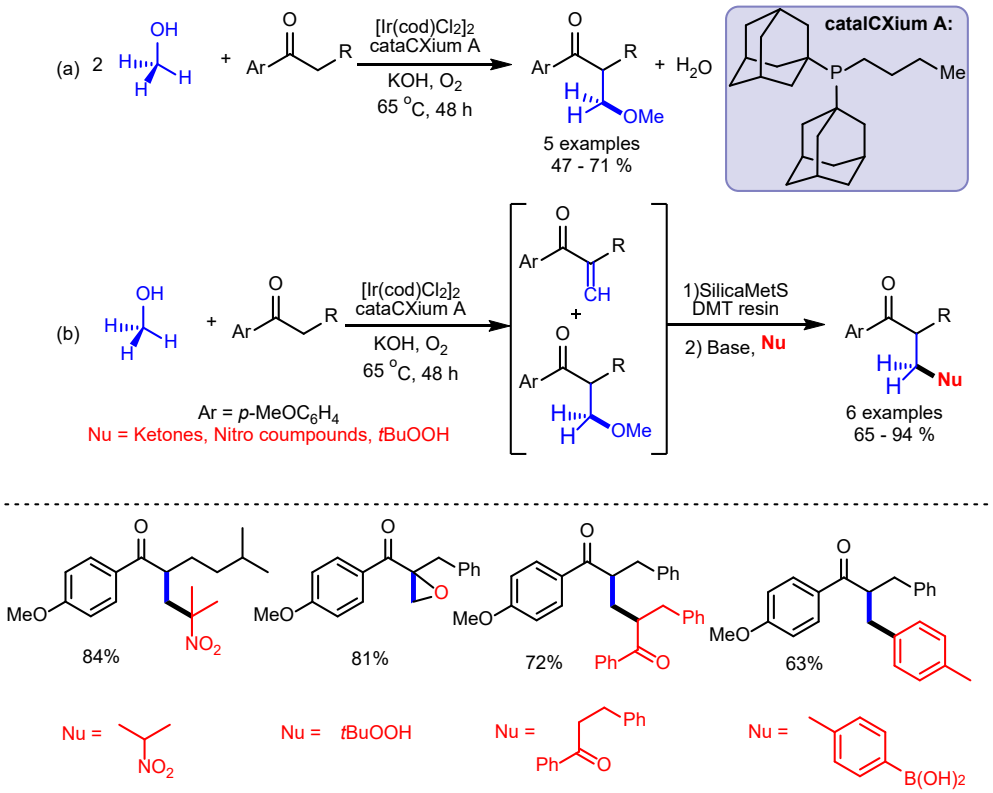


Scheme 57. Concept of interrupted-hydrogen-borrowing (IHB) strategy.



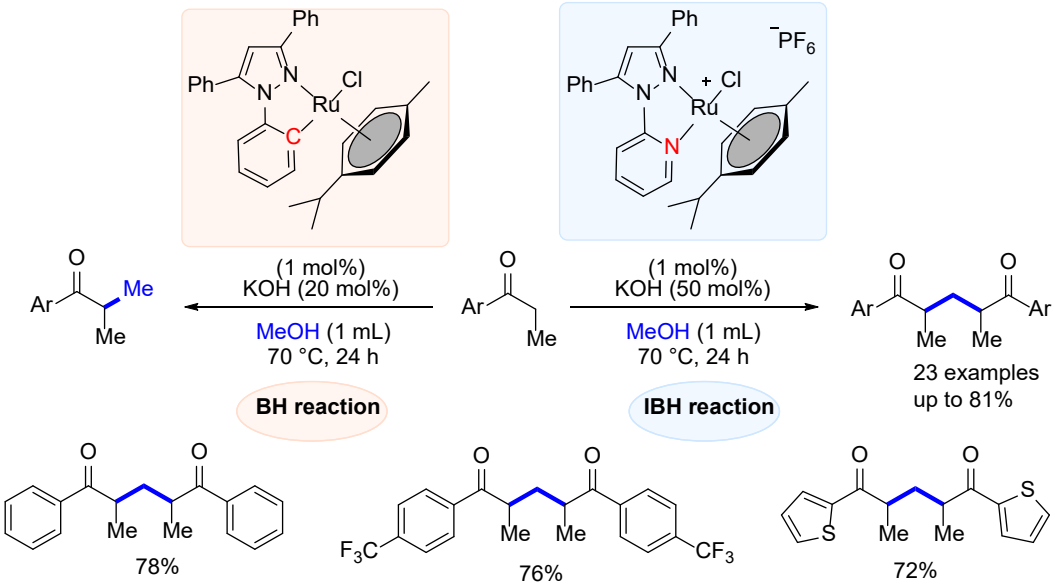
Scheme 58. a) Ir-catalyzed interrupted-hydrogen-borrowing reaction of indoles and methanol; b) proposed reaction mechanism.

The first example of interrupted-hydrogen-borrowing (IHB) strategy with methanol was discovered by Li and co-workers in 2013.[123] A method allowing the direct use of methanol to react with indoles for synthesis of 3,3'-bisindolylmethanes (3,3'-BIMs) was developed. This method worked well for variety of indoles possessing many function groups including alkyl, ether, fluoride, chloride, bromide, and nitro. 7-Azaindole, a pyridine containing indole, is also reactive and affords the desired product with excellent yield (Scheme 58a). The proposed reaction mechanism is presented in Scheme 58b. The iridium complex $[Cp^*IrCl_2]_2$ reacts with methanol and potassium *tert*-butoxide to afford methoxo iridium intermediate (step I). That subsequently forms iridium hydride species and formaldehyde via a β-elimination (step II). Then, the reaction of formaldehyde with the first indole molecule gives enamine species (step IV). With the assistance of iridium complex as a Lewis acid, the Michael addition of the enamine species with the second indole generates the final product (step V). At the end, the methoxo iridium intermediate is regenerated together with the release of hydrogen gas *via* the reaction of the iridium hydride species with methanol (step III).



Scheme 59. Ir-catalyzed one-pot methylenation/conjugate addition of aryl ketones with methanol and a nuclephile.

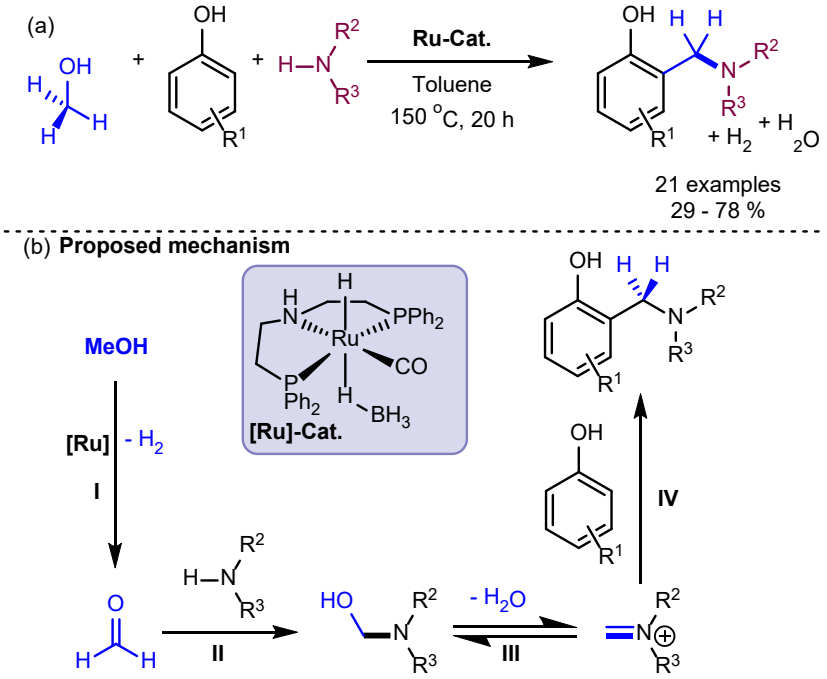
Remarkably, Donohoe's group has established a novel interrupted-hydrogen-borrowing method for targeting a broad range of complex structures.[22] The use of an iridium catalyst in the presence of catalCXium A, a bulky monodentate phosphine ligand, combined with an oxygen atmosphere interrupts the hydrogen-borrowing catalytic cycle by inhibiting the hydrogen returning step. That allows the conjugate addition of second methanol molecule to afford methoxymethylation of ketones (Scheme 59a). Beside this main product, the enone side product is observed. Interestingly, both these products can be used for next step in the one-pot methylation/conjugate addition sequence without the need of isolation (Scheme 59b). The subsequent added nuclephiles include ketones, and nitro compounds. Notably, *t*-butyl hydroperoxide also can be used in this step to generate epoxide products. Moreover, these products could be converted to esters or pyridine derivatives via Baeyer-Villiger and oxidative aromatizing reactions, respectively.



Scheme 60. Ru-catalyzed ligand-controlled reactions of α-methylation of ketones.

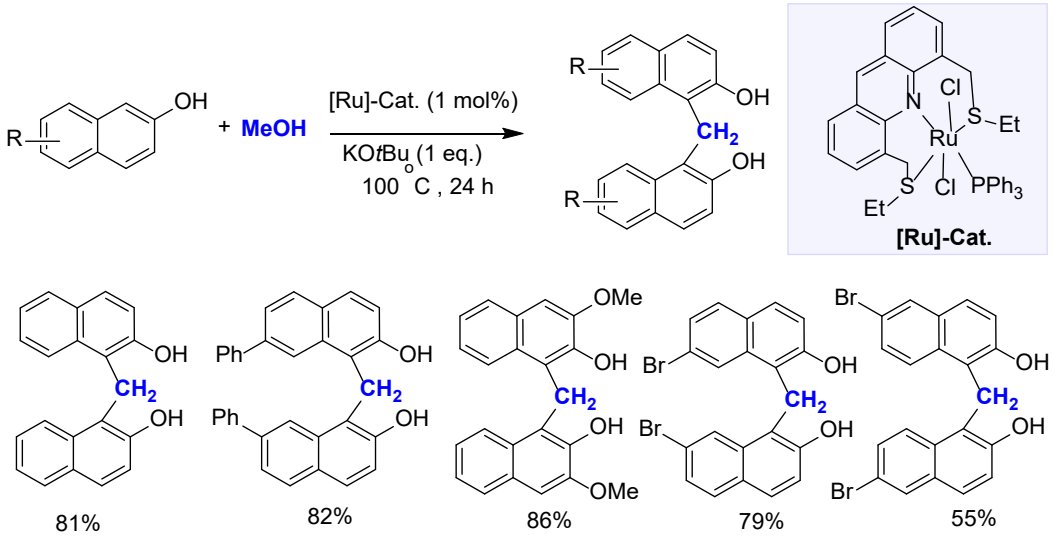
1,5-diketones are used as building blocks to create diverse chemical molecules, including heterocyclic and polyfunctional compounds. Biswal et al. recently described a ligand-controlled Ru-catalyzed IBH functionalization of ketones to form C-C bonds using methanol as the C1 source. By modifying the ligand system, the authors can control the formation of both BH and IBH products, as described in Scheme 60. Optimization experiments show that Ru-N,C catalyst produces α-methyl propiophenone, while Ru-N,N catalyst produces 1,5-diketones.[124] Venkatasubbaiah's group reported employing cobalt (II) porphyrin-mediated interrupted borrowing hydrogen to synthesize 1,5-diketones from various ketones using methanol as a C1 feedstock.[124] Mechanistic investigations and deuterium labeling experiments show that the reaction follows the IBH mechanism, with a protonated Co(II)porphyrin methoxide acting as an intermediate, followed by Michael addition reaction of enolate and α-methylenated ketone).[124]

In 2017, Kim and Hong established the Ru-catalyzed *ortho*-aminomethylation of phenols utilizing methanol as C1 source.[39] In the presence of a Ru catalyst, methanol is dehydrogenated to form formaldehyde (Scheme 61a, step I), which reacts with amine to generate a hemiaminal species (step II). Subsequent dehydration of hemiamial species generates an iminium cation (step III), which combines with phenol to afford the final product (step IV). The reaction can tolerate a variety of functional groups including alkyl, aryl, ether, halides, and protected amine (Scheme 61b). Curiously, when substituting phenols with naphthols, only methylated products were formed. That can be explained based on the stronger basicity and lower aromaticity of naphthols in the comparison to phenols.[39] In 2024, a similar reaction catalyzed by an Os(II)PC(sp^3)P pincer complex was reported by Biswas and Gelman.[41]

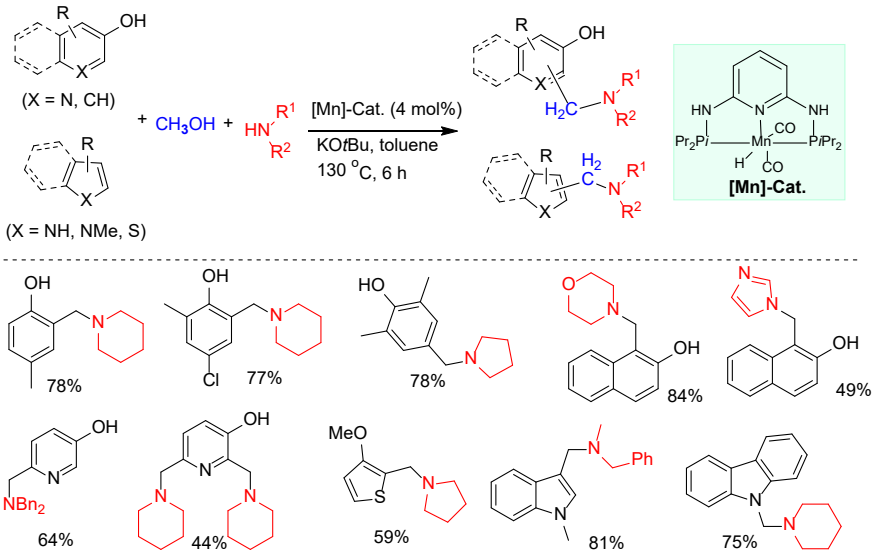


Scheme 61. a) Plausible mechanism for ruthenium-catalyzed *o*-aminomethylation of phenols via interrupted-hydrogen-borrowing reactions; b) reaction scope.

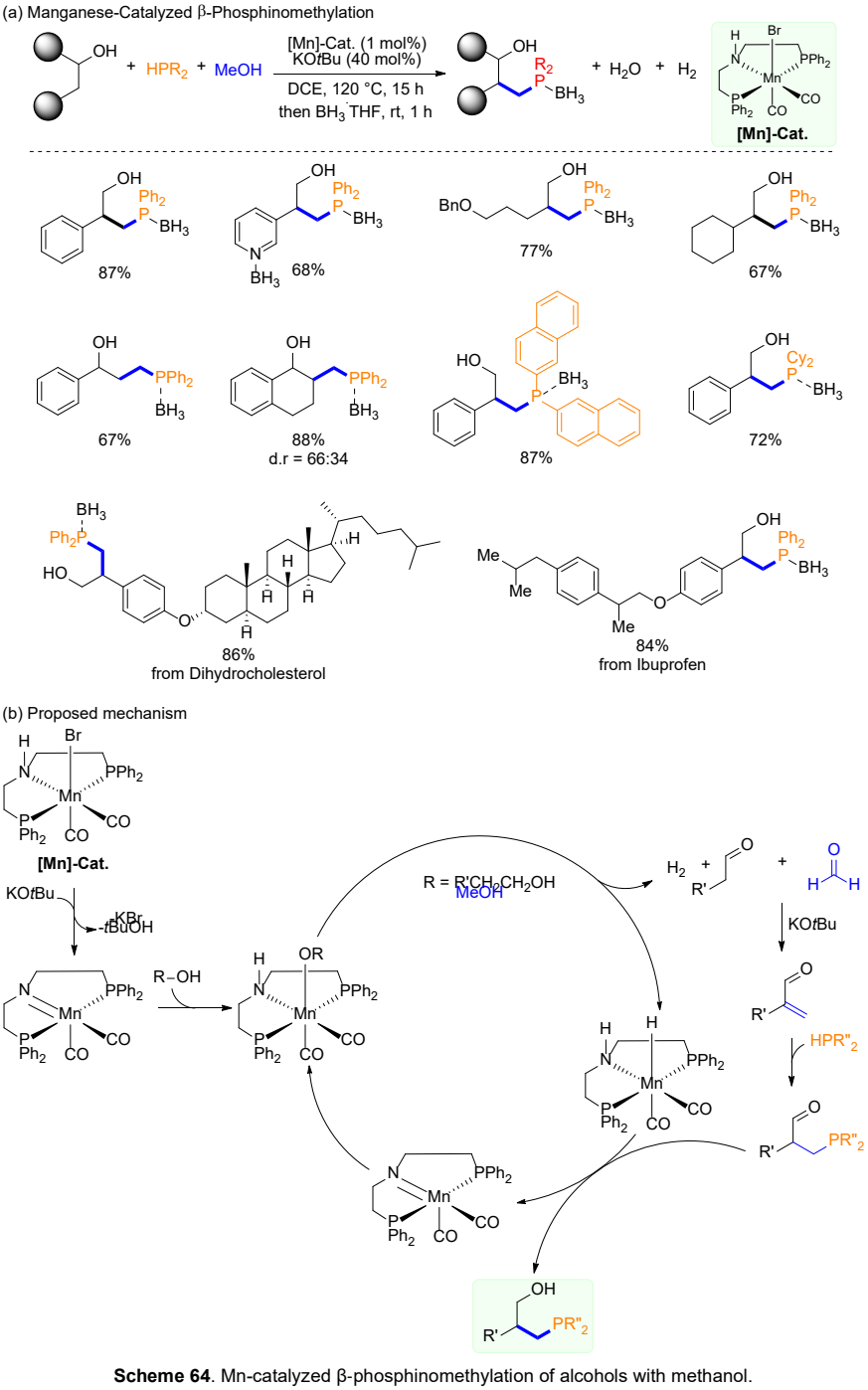
In 2021, Biswas and Srimani disclosed the ability of the acridine-derived SNS-Ru pincer catalyst to activate methanol and use it as a C1 building block (Scheme 62). This work describes dimerization of 2-naphthol via methylene linkage, which can be applied to a variety of substrates with high yields.[47] In 2021, the group of Chandrasekhar and Venkatasubbaiah demonstrated the synthesis of 1,5-diketones from ketones employing methanol as C1 source in the presence of cobalt catalyst.[125] Mechanistic investigation suggested that the reaction followed an interrupted hydrogen borrowing (IBH) pathway. The reaction was initiated with the generation of formaldehyde, which went through aldol condensation to form an α-methylenated ketone intermediate. The *in-situ* generated α-methylenated ketone then followed Michael-addition with enolate ion to furnish the desired 1,5-diketone product. In 2023, the same group disclosed the use of ruthenium as a catalyst for the methylation of ketones using methanol as a C1 source.[124] Interestingly, the choice of ligand controlled how the reaction proceeded. While a N,C−Ru catalyst yielded the borrowing hydrogen product, the N,N−Ru catalyst led to the reaction follow an interrupted hydrogen borrowing mechanism. In 2017, Kirchner et al. reported the first three-component aminomethylation of aromatic compounds with phenols, indoles, thiophenes, pyridines and carbazoles using Mn catalyst, amines, and MeOH as the C1 source (Scheme 63). The process is ecologically friendly and feasible. The high atom efficiency of these reactions is achieved through a series of dehydrogenation and condensation steps, resulting in selective C-C and C-N bond forms and the release of hydrogen and water.



Scheme 62. Ru-catalyzed methylation of 2-naphthol derivatives using methanol.



Scheme 63. Mn-catalyzed regioselective functionalization of phenol derivatives and heterocycles.



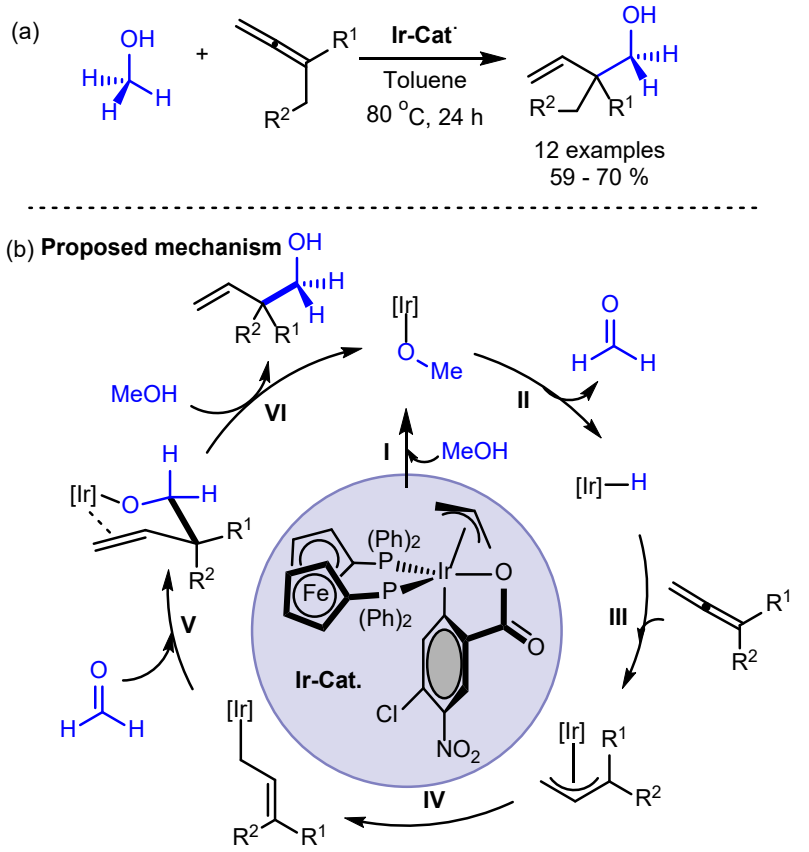
Scheme 64. Mn-catalyzed β-phosphinomethylation of alcohols with methanol.

In 2023, a pincer manganese complex-catalyzed borrowing hydrogen β-phosphinomethylation of secondary alcohols using methanol was established by Liu and co-workers.[16c] This three-component coupling method efficiently enabled the dehydrogenative cross-coupling of a variety of aromatic and aliphatic alcohols with various phosphines, yielding the corresponding β-phosphinomethylated alcohols in good yields (61-91%, Scheme 64). Notably, the reaction performed well with alcohols derived from bioactive molecules such as dihydrocholesterol, lithocholic acid, (S)-naproxen, and ibuprofen, highlighting its potential broad applicability.

4. Redox Pair Coupling Strategy in Reactions of Methanol and *π*-System Compounds

4.1. Hydromethylation of allenes

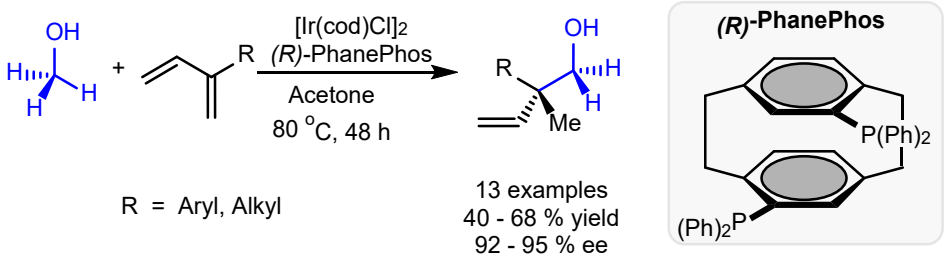
Krische and co-workers identified the conditions for Ir-catalyzed hydromethylation of 1,1-disubstituted allenes with methanol through redox pair coupling strategy.[126] Various homoallylic *neo*-pentyl alcohols were regioselectively synthesized from corresponding 1,1-disubstituted allenes and methanol in moderate to good yields. The reactions were performed at 80°C in toluene solvent with the use of an Ir (III) complex catalyst (Scheme 65a).



Scheme 65. (a) Iridium-catalyzed regioselective hydroxylmethylation of allenes with methanol via redox pair coupling strategy and (b) Proposed mechanism

In the proposed mechanism, the reaction begins with the formation of methoxyl iridium(III) intermediate from methanol and the iridium precatalyst (Scheme 65, step I). Subsequent *β*-elimination to release formaldehyde and a transient iridium(III) hydride (Scheme 65, step II), which inserts to the allene to form an allyl iridium species (Scheme 65, step III). Rearrangement of this allyl iridium species, followed by regioselective insertion to formaldehyde, gives the homoallylic neo-pentoxide iridium intermediate (Scheme 65, steps IV and V). That reacts with methanol to furnish the final homoallylic neo-pentyl alcohol product together with the regeneration of the methoxyl iridium (III) intermediate (Scheme 65, step VI).

4.2. Enantioselective hydromethylation of dienes



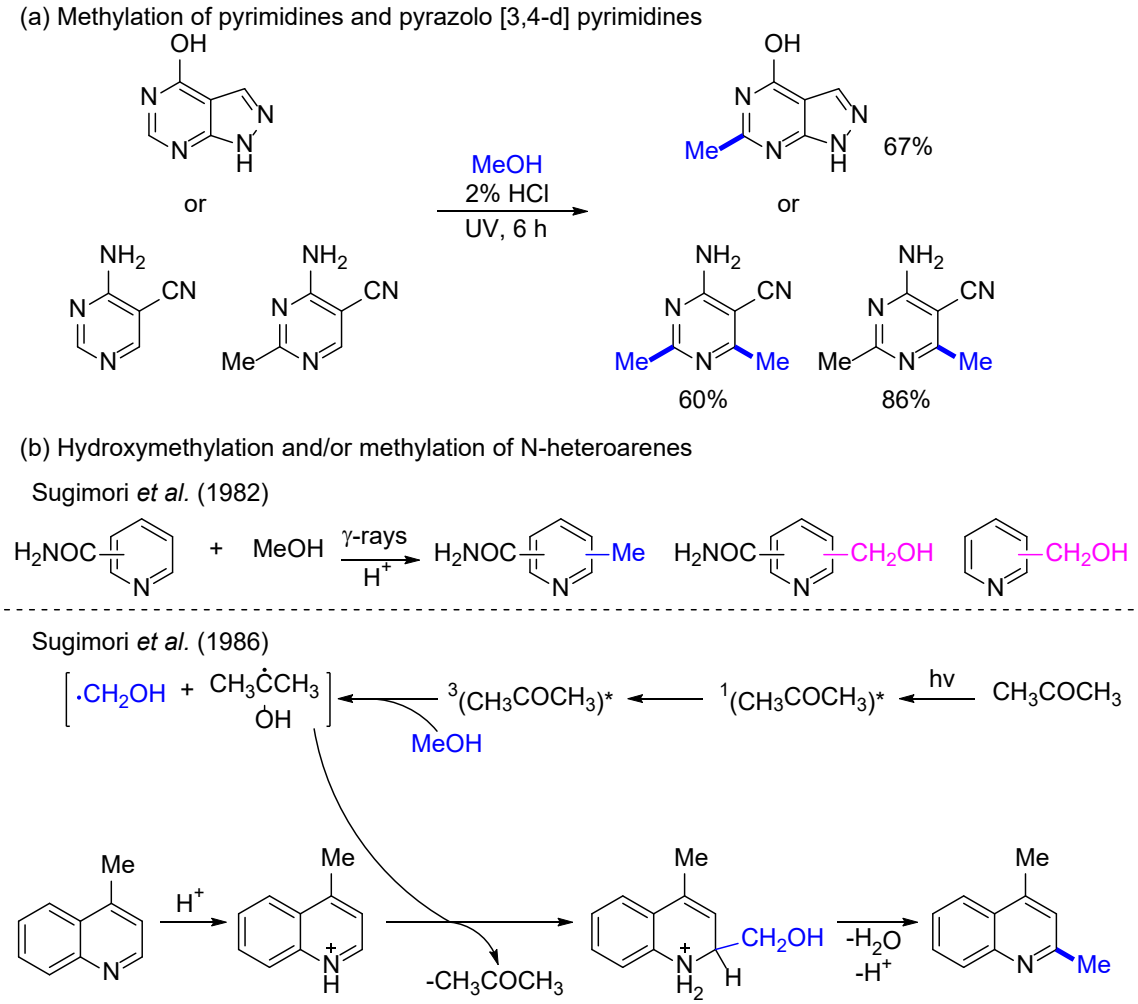
Scheme 66. Iridium-catalyzed enantioselective hydroxylmethylation of dienes with methanol via redox pair coupling strategy.

Nguyen *et. al.* developed the first catalytic enantioselective hydromethylation of dienes with methanol (Scheme 66).[127] This redox pair coupling reaction allows the high regioselective insertion of 2-substituted-1,3-dienes into methanol C–H bond to form homoallylic neo-pentyl alcohols with excellent enantioselectivity. The reaction enantioselectivity is induced by a combination of $[Ir(cod)Cl]_2$ complex and PhanePhos, a chiral bidentate phosphine ligand. Under the mild reaction conditions, a broad range of functional groups bearing dienes can be tolerated in this transformation. The synthetic utility of the homoallylic alcohol products can be facilitated further by converting to corresponding azide and ester compounds, which can serve as building blocks in organic synthesis.

5. Radical Coupling Strategy in Methylation of Heteroarene C–H bonds via Photocatalysis

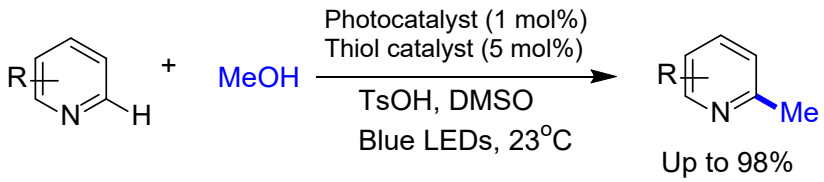
5.1. C-methylation

In the early days, photoreactions were carried out without the presence photocatalysts. In 1967, Ochiai and Morita reported the methylation of pyrimidine and pyrazolo [3,4-*d*] pyrimidine derivatives under light irradiation (Scheme 67a).[128] The protocol utilized methanol as the C1 source in an acidic environment, where the N-heteroarene ring was activated under UV light. Various pyrimidines and pyrazolo[3,4-*d*]pyrimidines were obtained in moderate to good yields. In 1982 and 1986, Sugimori *et al.* disclosed the methylation and hydroxymethylation of pyridines and quinoline derivatives using methanol as the C1 source (Scheme 67b).[129] The reaction was initiated by *γ*-rays in a highly acidic environment. Methanol was proposed to be excited by the high-energy *γ*-rays, generating $\cdot CH_2OH$ radicals. Products with hydroxymethylation and/or methylation at the 2- or 4-position of the N-heteroaroarenes were obtained via radical substitution and dehydration.

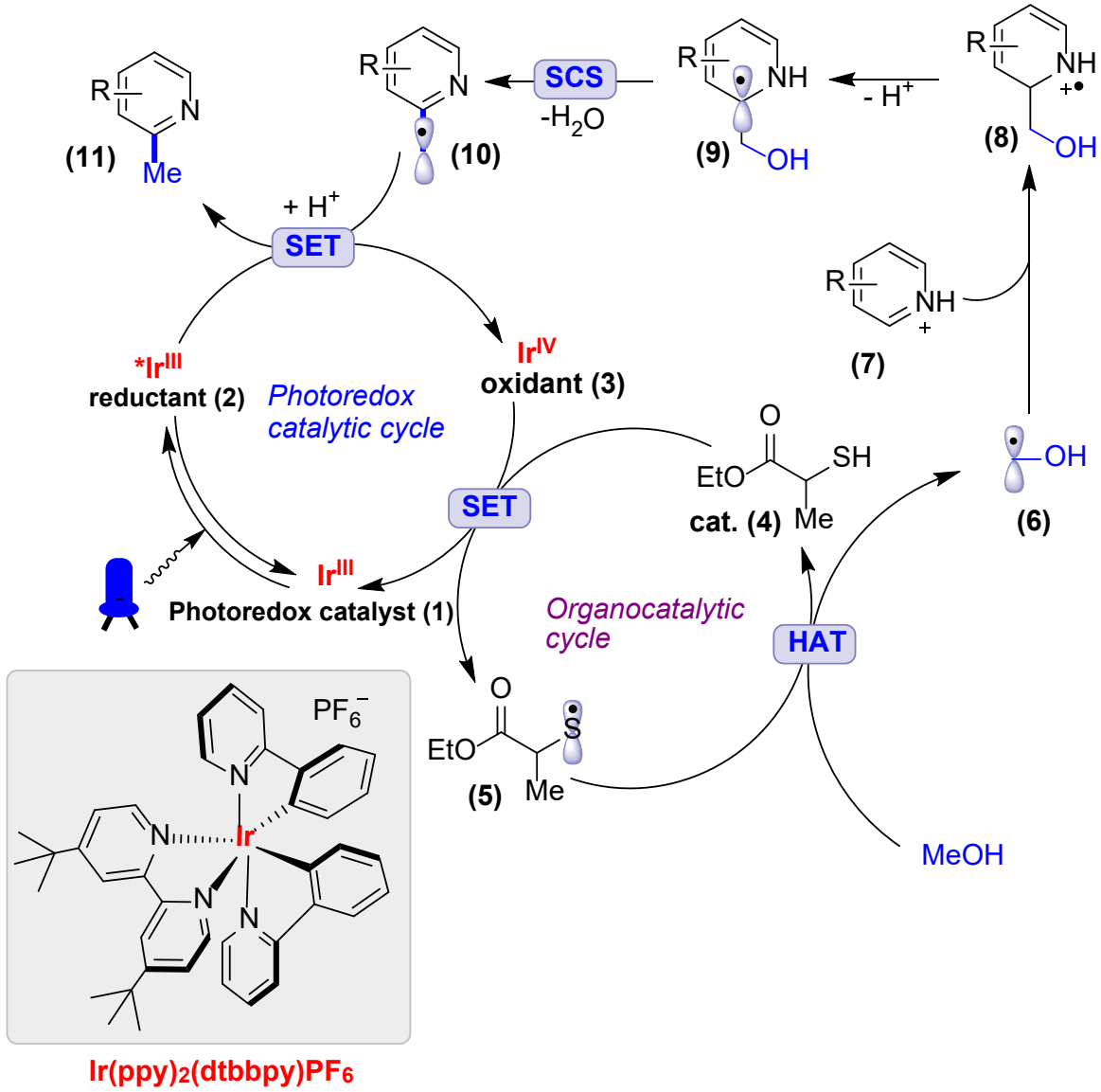


Scheme 67. Radiation-induced methylation of aromatic compounds with methanol.

In the light of recent research on photoredox catalysis, the development of more efficient alkylation methods under mild condition attracted many attentions.[130] In 2015, Jin and MacMillan reported the first direct C-H methylation of N-heterocycles using methanol (Scheme 68, 69).[11] In fact, methanol molecule could also be activated *via* a tandem process merging of photoredox ($Ir(ppy)_2(dtbbpy)PF_6$) and hydrogen transfer (ethyl 2-mercaptopropionate) catalysis. Several N-heterocycles such as pyridines, quinolones, isoquinolines, phenanthridines and phthalazines were successfully methylated in very good yields under mild conditions. Together with the traditional methanol activation methods, this strategy opened up a new avenue in the use of methanol as a “green” methylating reagent. The extension of this method also found to be applicable for the direct C–Halkylation of N-heterocycles using higher alcohols via the same photocatalytic process.



Scheme 68. Radiation-induced methylation

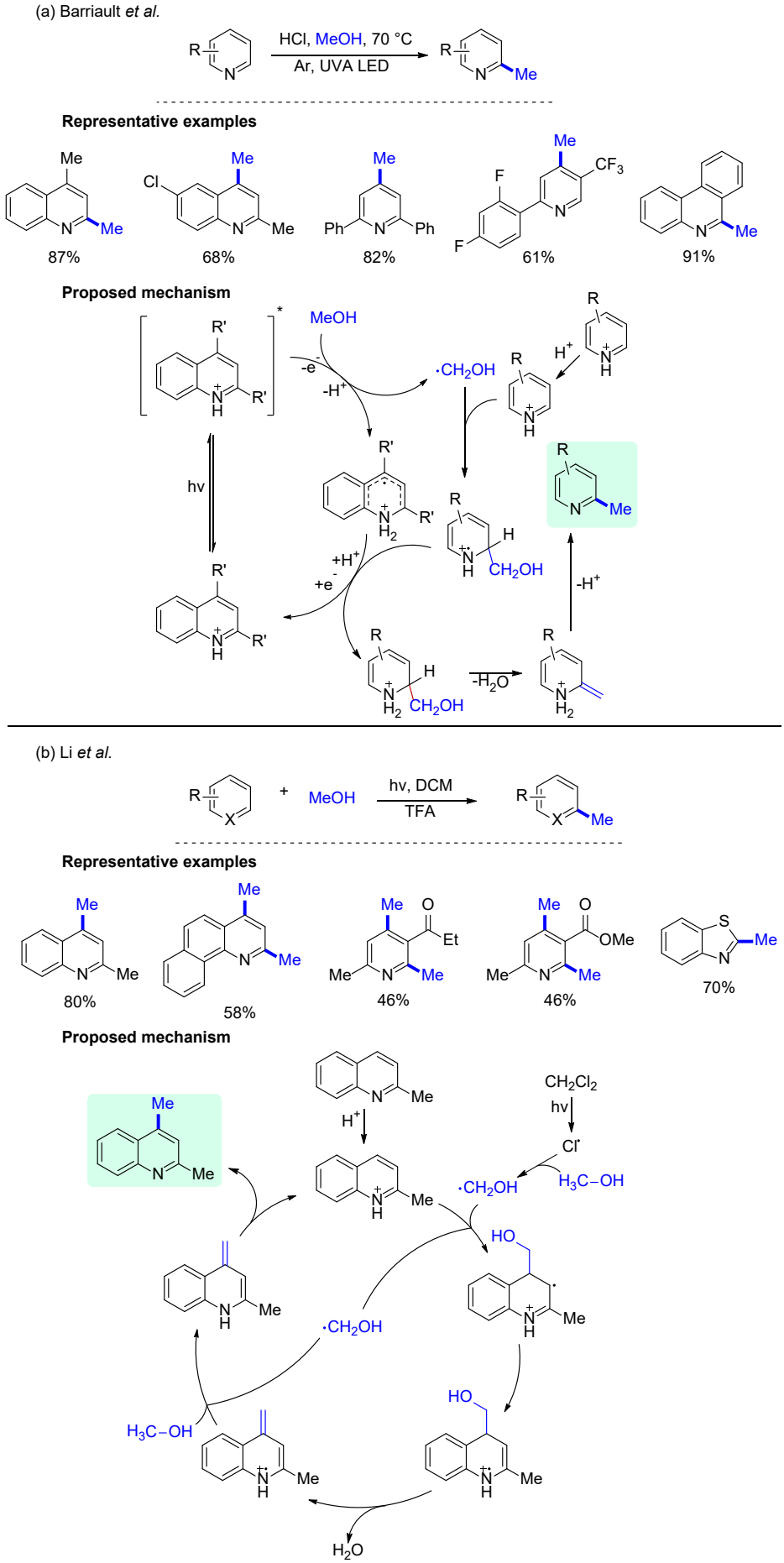


Scheme 69. Possible mechanism for methylation of heteroaromatic C–H bonds via photoredox organocatalysis.

A possible mechanism of this photocatalytic process was proposed (Scheme 69. Under irradiation, the $Ir(ppy)_2(dtbbpy)^+$ catalyst **(1)** was activated to generate the long lived $^*Ir(ppy)_2(dtbbpy)^+$ **(2)** excited state. Activated Ir complex **(2)** could undergo a single-electron transfer (SET) to initiate the photoredox catalytic cycle to give the oxidizing Ir^{IV}-complex **(3).** Then, the second SET catalytic cycle from the thiol organocatalyst **(4)** to Ir^{IV}-complex **(3)** occurred, after deprotonation, giving the thiyl radical **(5)** and regenerating $Ir(ppy)_2(dtbbpy)^+$ catalyst **(1)** for the next catalytic cycle. The authors presumed that the hydrogen atom transfer (HAT) process of the thiyl radical **(5)** and methanol would occur to provide an α-oxy radical **(6)** and regenerate the thiol catalyst **(4).** Then, the nucleophilic attack of α-oxy radical **(6)** to the protonated-heteroarene **(7)** to give the aminyl radical **(8)** cation, which was subsequently deprotonated to form the α-amino radical **(9).** At this state, a spin-centre shift (SCS) of this α-amino radical **(9)** occurred to generate benzylic radical **(10)** and water. In the end, the protonation of benzylic radical **(10),** followed by a second SET process with the excited $^*Ir(ppy)_2(dtbbpy)^+$ **(2)** to form the desired methylated product **(11)** and regenerate the active oxidizing Ir^{IV}-complex **(3)**.

More recent examples of photocatalyst-free, light-induced methylation of heteroaromatic C–H bonds using methanol as C1 source were independently reported by Barriault *et al.* (Scheme 70a),[131] and Li *et al.* (Scheme 70b).[132] The authors successfully performed the photochemical methylation of quinoline, pyridine, and phenanthrene in the presence of an acid as an additive. Barriault's mechanistic studies suggested that heteroarenes acted as photosensitizers, absorbing UV light and forming an excited singlet state. This excited state is then quenched by methanol, generating a protonated radical intermediate and a hydroxymethyl radical, which drive subsequent methylation reactions. Li's group also arrived at similar conclusions, but a poor yield of methylated product was

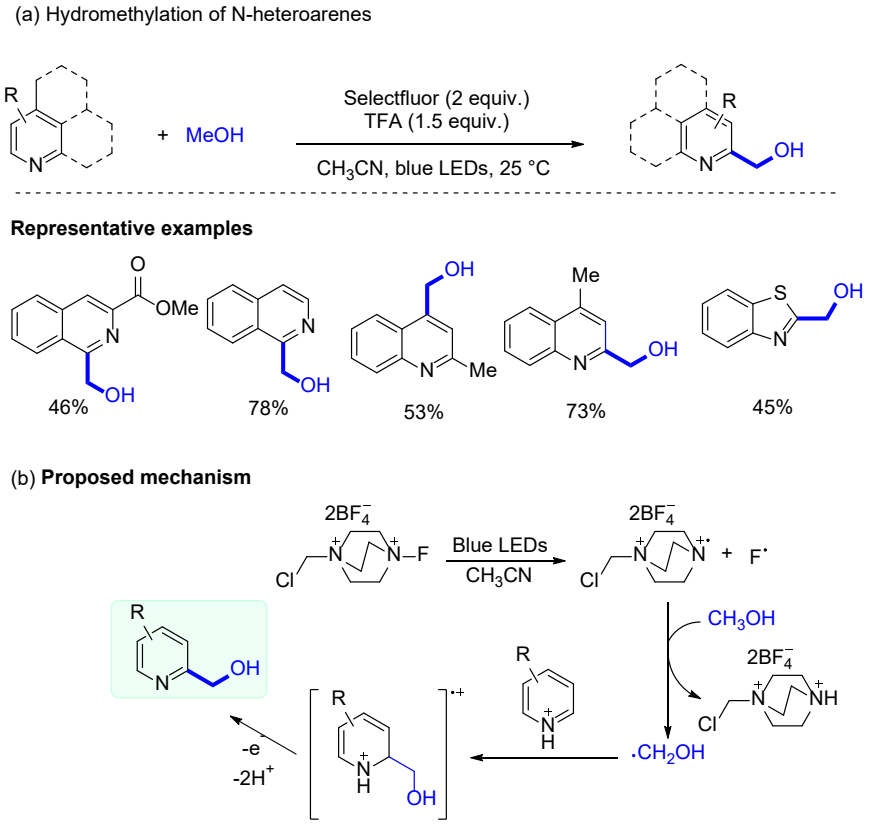
obtained without using a photosensitizer. However, the use of dichloromethane as a co-solvent could significantly improve the reactivity, presumably due to a chlorine radical from dichloromethane would help the formation of a hydroxymethyl radical.



Scheme 70. Photocatalyst-free, light-induced methylation of heteroaromatic C–H bonds with methanol.

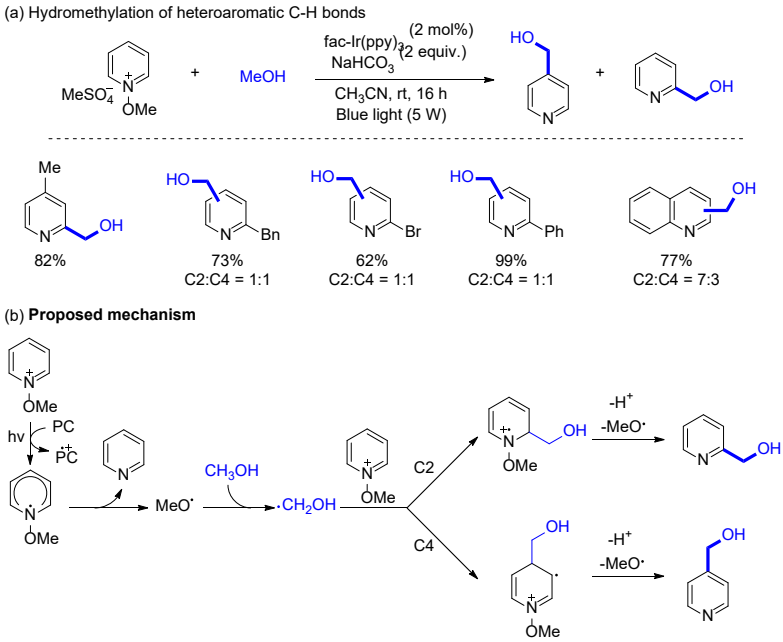
5.2. C-hydromethylation

In addition to methylation, light-induced direct C-H hydromethylation of N-heterocycles using methanol has been developed. In 2019, Lei and co-workers reported that under visible light irradiation, Selectfluor effectively promotes the hydromethylation of heterocycles with methanol.[133] Under the reported conditions, quinoline derivatives, isoquinoline, and benzothiazole exhibited good reactivity, yielding 45-78% (Scheme 71a), while pyridine and pyrazine were less reactive. The proposed mechanism of the reaction is shown in Scheme 71b. Moreover, several research groups independently reported alternative versions of this reaction.[134]



Scheme 71. Light-induced hydromethylation of aromatic compounds with methanol.

Lakhdar and co-workers demonstrated a photochemical hydromethylation of N-methoxypyridinium ion substrates with methanol, using a $Ir(ppy)_3$ complex photocatalyst and $NaHCO_3$ base under blue light irradiation (Scheme 72a).[135] Several techniques, including electron paramagnetic resonance spectroscopy, quantum yield measurements, and density-functional theory calculations, were employed to study the reaction mechanism (Scheme 72b). Due to its simplicity and mild reaction conditions, this method has potential practical applications in pharmaceutical chemistry and materials science.

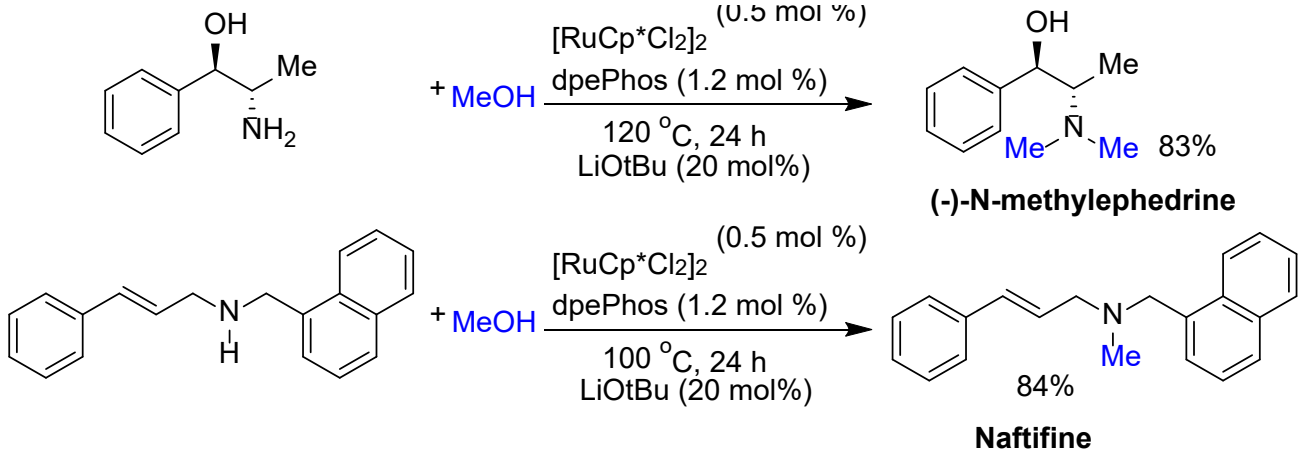


Scheme 72. a) Hydromethylation of heteroaromatic C–H bonds via photoredox organocatalysis; b) proposed reaction mechanism.

6. Application of Methanol Activation in Synthesis of Drugs and Bioactive Compounds

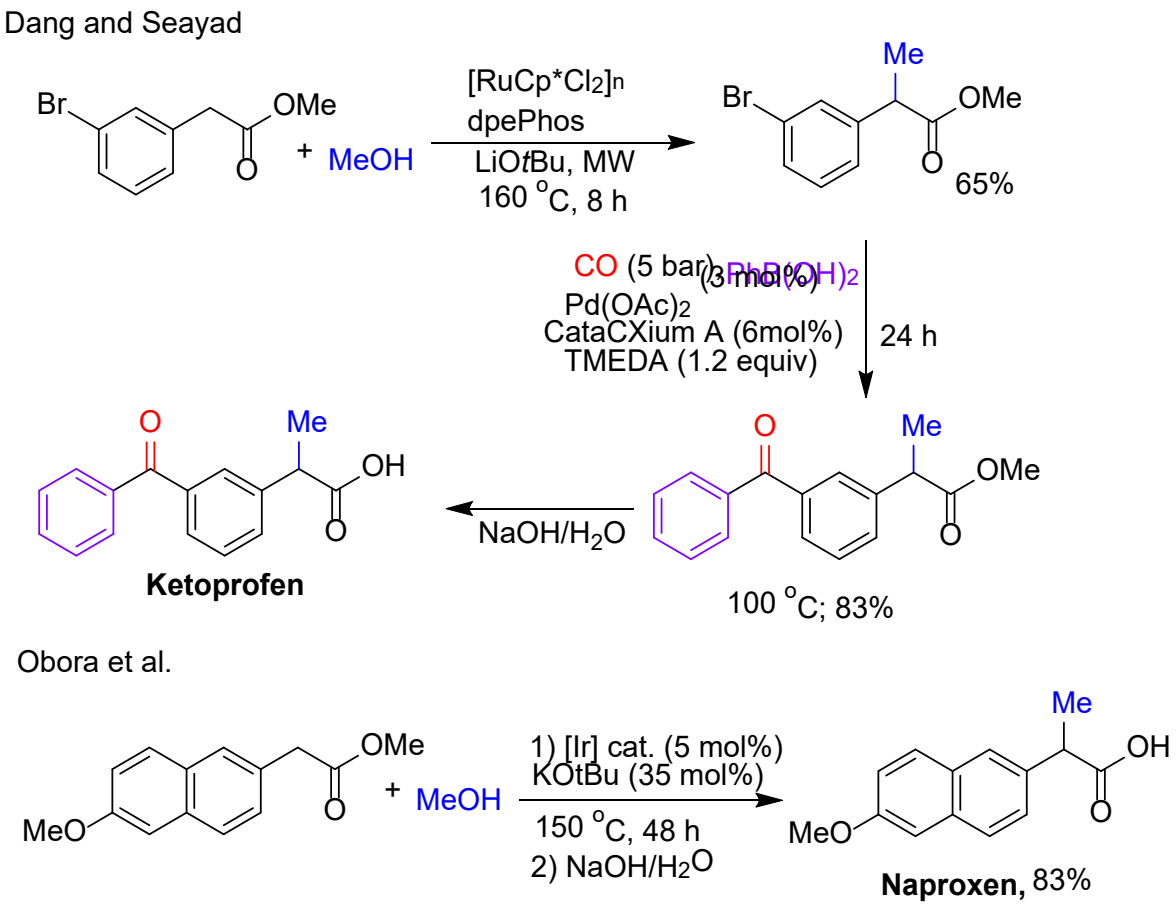
6.1. Hydrogen borrowing methodology

In 2015, in the effort to find applications for Ru-catalysed N-methylation of amines with methanol, Dang and Seayad applied successfully their catalyst system for one-pot synthesis of (-)-N-methylephedrine (a natural product isolated from *Ephedra distachya)* and Naftifine drug (an antifungal agent) in 83% and 84% yields, respectively, from available and easy-synthesized starting materials (Scheme 73).[61] Later, Dang and Seayad also demonstrated the first Ru-catalyzed α-methylation of ester using methanol under microwave condition (Scheme 74).[26] They showed a potential application of this method as the key step in the synthesis of Ketoprofen drug (a nonsteroidal anti-inflammatory agent). In 2019, Obora et al. reported the synthesis of Naproxen, another anti-inflammatory drug by Ir-catalyzed α-methylation of corresponding ester (Scheme 74).[16e]

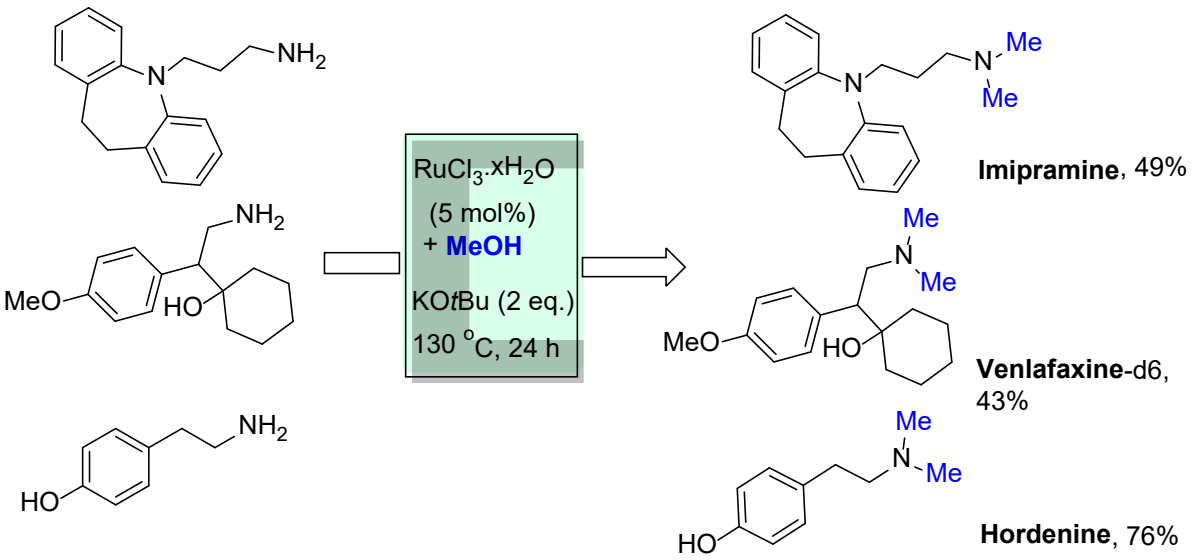


Scheme 73. Synthesis of (-)-N-methylephedrine natural product and Naftifine drug.

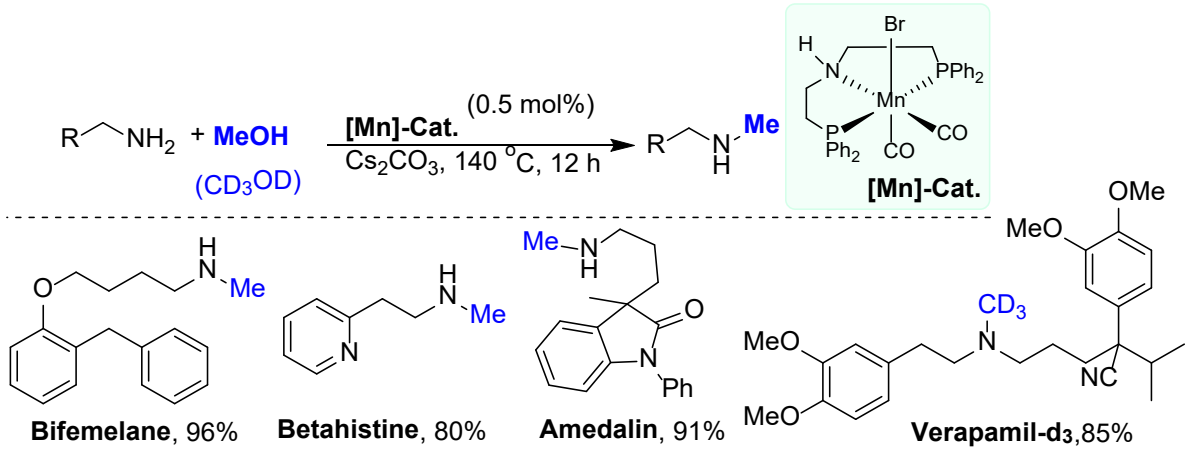
In the effort to find practical applications for the synthesis of N-methylated amines, Natte et al. presented a low-cost, high-efficiency approach for selective N-methylation of amines using methanol as methylating reagent and inexpensive $RuCl_3.xH_2O$ as a ligand-free catalyst (Scheme 75). This widely accessible catalyst can withstand a wide range of amines, including those with electron-donating and electron-deficient groups. Several drugs such as Imipramine, Venlafaxine, Hordenine were synthesized in moderate yields.[82]



Scheme 74. Concise synthesis of Ketoprofen and Naproxen drugs.

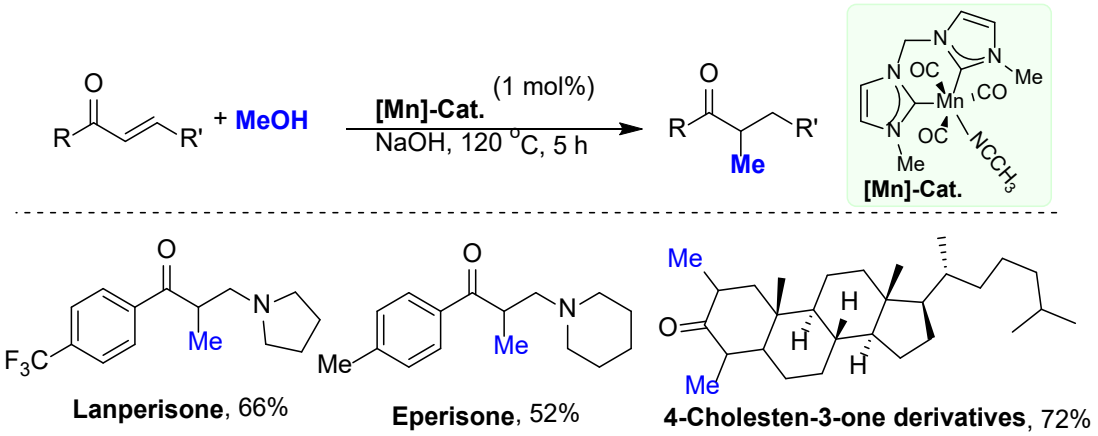


Scheme 75. Ru-catalyzed synthesis of essential drugs

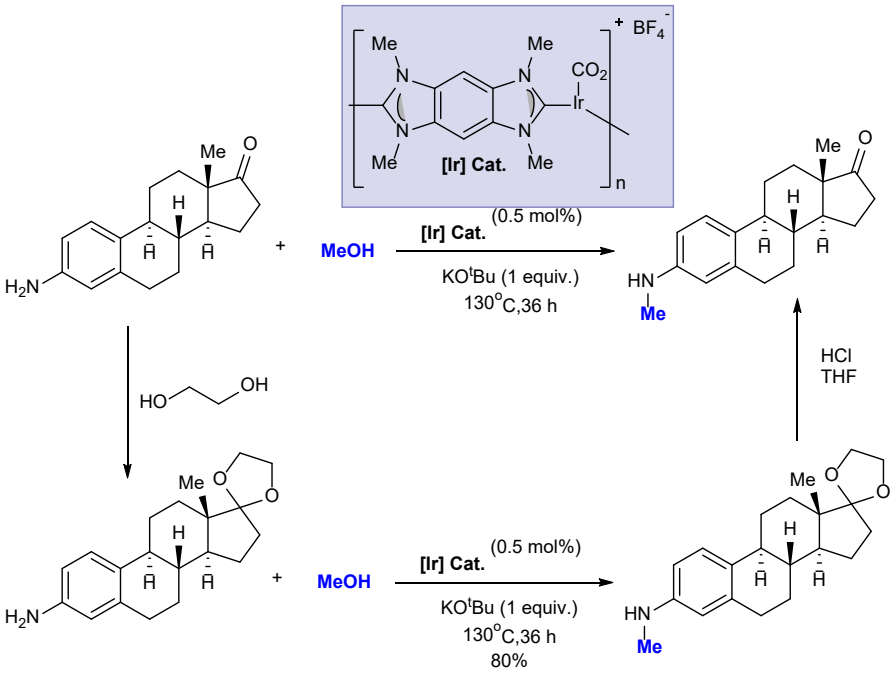


Scheme 76. Mn-catalyzed synthesis of drugs and bioactive molecules.

In 2024, Tu and coworkers developed a practical method for selectively coupling methanol and aliphatic primary amines using a manganese catalyst.[70] In this research, a series of essential drugs and bioactive molecules were successfully synthesized using low catalyst loading of Mn-pincer complex catalyst (Scheme 76). This method showed potential applications in the development of sustainable pharmaceutical processes. Recently, Kundu et al. demonstrated a convenient and sustainable method for tandem coupling reaction of α,β-unsaturated ketones using methanol to prepare α-methylated ketones in the employment of a bis-N-heterocyclic carbene-Mn catalyst (Scheme 77). This study used the minimal catalyst loading of the Mn-pincer complex catalyst to successfully prepare a number of drugs and bioactive compounds. This approach may find possible applications in the development of environmentally friendly pharmaceutical processes.

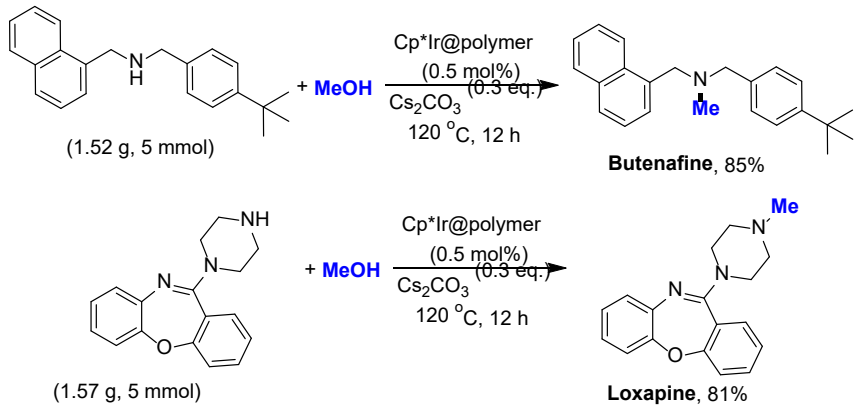


Scheme 77. Mn-catalyzed synthesis of pharmaceuticals.

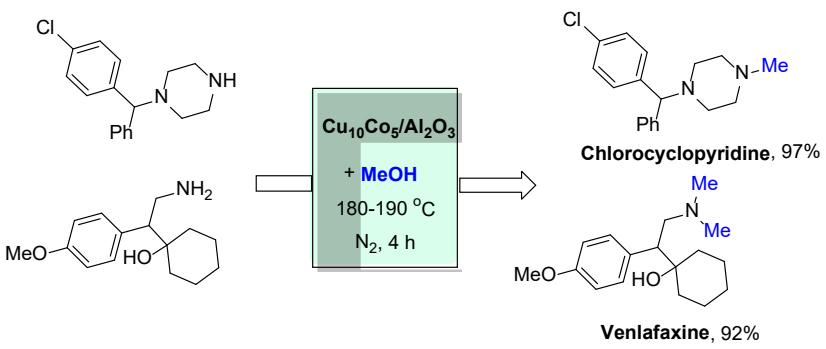


Scheme 78. General pathway for the synthesis of N-methyl-3-aminoestrone.

Recently, the design and synthesis of new robust and recyclable heterogeneous catalysts is one of the most important topics for the development of sustainable processes in pharmaceutical and fine chemical industries. Tu et al. successfully applied his solid Ir-catalyst in the N-methylation of 3-aminoestrone using methanol (Scheme 78).[77] N-methyl-3-aminoestrone is a highly bioactive compound which was used in the treatment of hormone-sensitive diseases (breast and prostate cancers). In 2024, Li and coworkers designed and prepared a stable and recyclable polymer-supported iridium complex catalyst Cp*Ir@Poly(2,2′ -BiBzIm) by the coordinative immobilization of $[Cp^*IrCl_2]_2$ on 2,2′ -bibenzimidazoles.[136] Notably, Butenafine and Ioxapine drugs were successfully synthesized in gram scale with high yields (85% and 81%, respectively) (Scheme 79).



Scheme 79. Synthesis of Butenafine and Loxapine drugs.

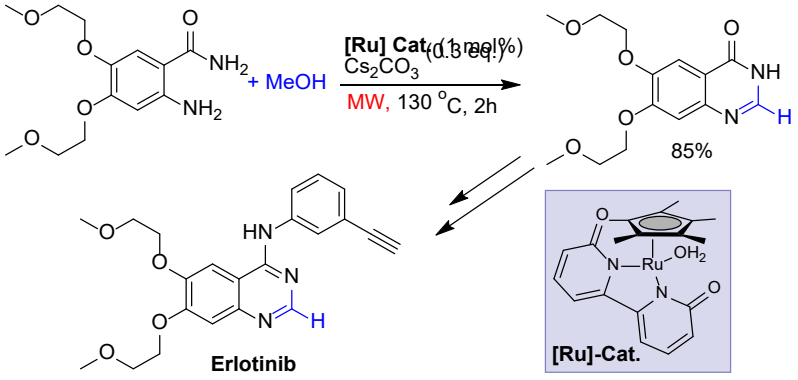


Scheme 80. Synthesis of Chlorocyclopyridine and Venlafaxine drugs

In the development of cheaper and more sustainable heterogeneous catalysts, Huang, Lu and coworkers successfully applied the selective N-methylation and N,N-dimethylation strategy for the gram-scale synthesis of Chlorocyclopyridine and Venlafaxine drugs in the employment of Cu-Co/Al_2O_3 catalyst (Scheme 80).[79] Excellent yields of drug products were achieved, however, these reactions need to be carried out at high temperature 180-190ºC).

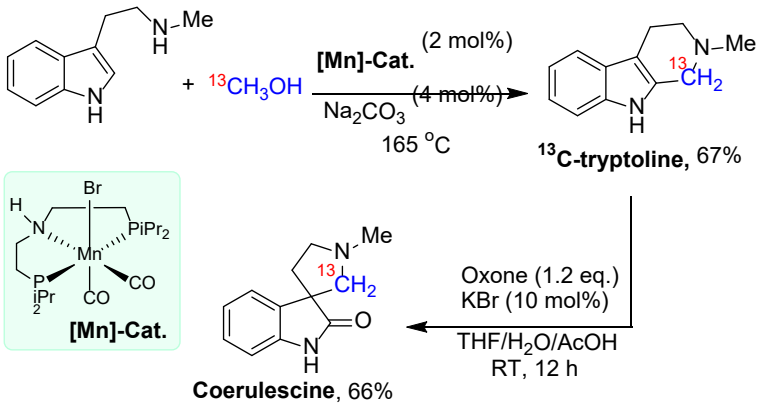
6.2. Dehydrogenative coupling methodology

In 2016, Li et al. reported an interesting application of dehydrogenative coupling method in the Ir-catalyzed synthesis of quinazolinone heterocycle (Scheme 81) which was a key intermediate in the synthesis of Erlotinib, important anticancer drug (a tyrosine kinase inhibitor).[111] However, this reaction condition is hard which required the microwave irradiation at 130°C in 2 hours.



Scheme 81. Synthesis of Erlotinib intermediate.

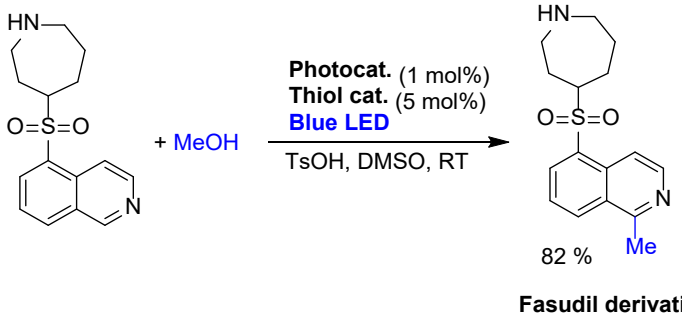
Recently, Liu et al. disclosed an interesting method to prepare ^{13}C-tryptoline by dehydrogenative coupling strategy (Scheme 82).[118] Spirooxindole derivatives are promising candidates for drug discovery and medicinal chemistry research.[137] A ^{13}C-labeled spirooxindole natural product, (±)-coerulescine, was successfully synthesized using commercially available N-methyltryptamine. [Mn]-I catalyzed dehydrogenative transformation using $^{13}CH_3OH$, resulting in 67% yield of ^{13}C-tryptoline. This intermediate can be further converted to ^{13}C-labeled (±)-coerulescine in a single step using halide-catalyzed oxidative rearrangement of ^{13}C-tryptoline.



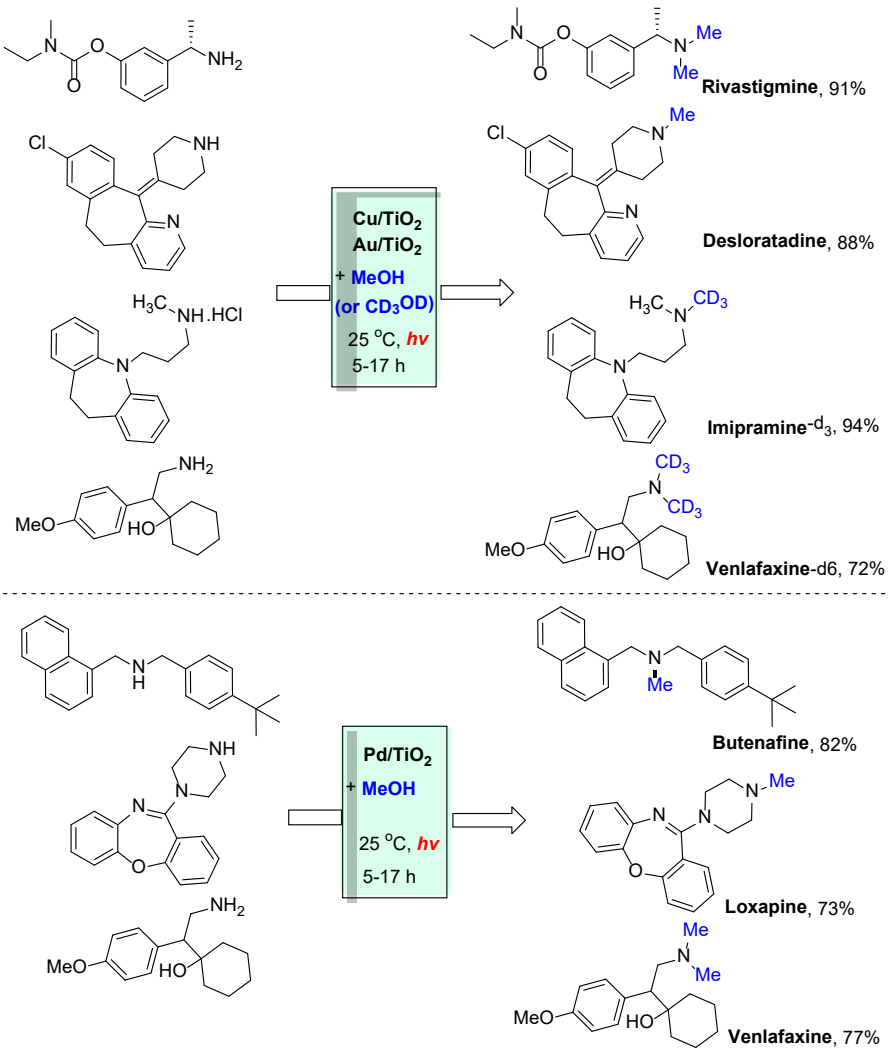
Scheme 82. Synthesis of ^{13}C-labeled (±)-Coerulescine

6.3. Radical coupling and light-promoted methods

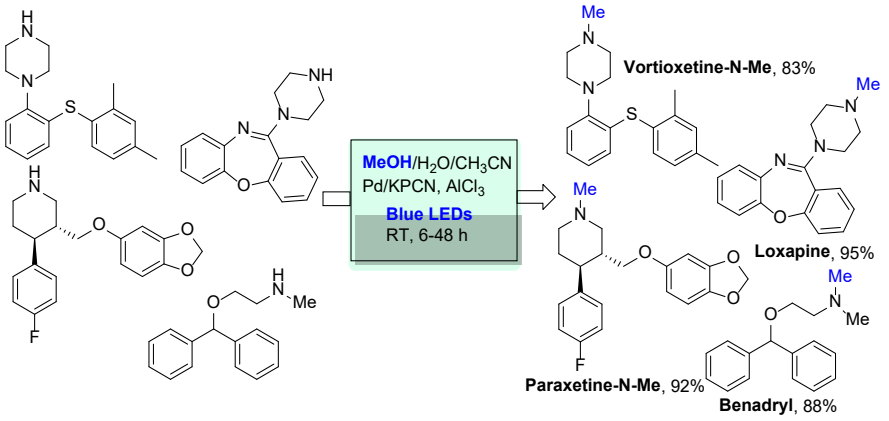
In 2015, Jin and MacMillan showed a potential application of the direct methylation of isoquinoline C–H bond via photoredox organocatalysis. Fasudil derivative (a potent kinase inhibitor) was successfully prepared in 82% yield under very mild condition (Scheme 83).[11] In 2018, A combined Cu–Au photocatalytic system has been developed by Naka's group to quickly provide N-methylated amines that are important to the pharmaceutical industry (Scheme 84).[95] The combined photocatalytic system has demonstrated the synthesis and functionalization of pharmaceuticals, the non-symmetrical dimethylation of primary amines to hetero-substituted tertiary amines, and the controlled mono- and dimethylation of primary amines. Later, Naka et al. reported another photocatalytic system (Pd/TiO_2) for N-methylation of amines and found an interesting application in the synthesis of deuterated drugs, for example, Venlafaxine-d_3 and Butenafine-d_3.[94a]



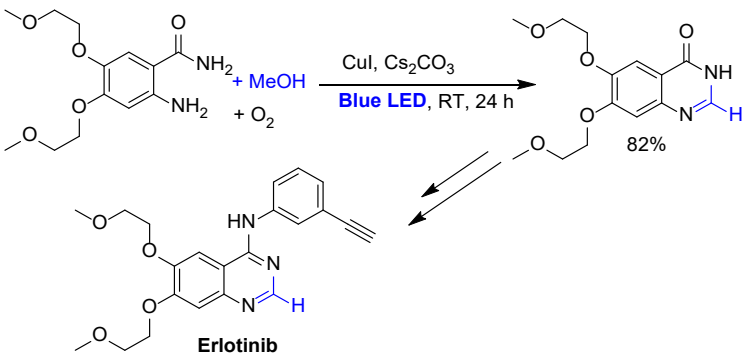
Scheme 83. Synthesis of Fasudil derivative.



Scheme 84. Synthesis of pharmaceuticals by Naka and coworkers.



Scheme 85. Synthesis of drugs by Naka and coworkers.



Scheme 86. Synthesis of Erlotinib intermediate.

In 2021, Su and coworkers demonstrated a surprising application of semiconductor photoredox catalyst for N-methylation of nitroarenes and amines with water and methanol, which was successfully realized under synergistic exploitation of the photogenerated redox centers over Pd/KPCN.[98] A series of highly important drugs were successfully prepared in excellent yields under mild conditions (Scheme 85). Recently, Anandhan et al. disclosed a highly efficient method for the synthesis of the key intermediate in the structure of Erlotinib drug using CuI catalyst under blue LED irradiation at room temperature (Scheme 86). This key intermediate was prepared in 82% isolated yield.[114]

7. Some advanced techniques to promote the research on methanol activation

7.1. Computational chemistry aided design of catalysts for methanol activation.

To facilitate the discoveries of new catalytic methods for methanol activation, the conventional "trial and error" approach was shown to be inefficient. The scale to study the new catalytic reaction is at molecular scale, which is very challenging to be accessed by experiment.[138] With the application of "state-of-the"-art" molecular modelling via Density Functional Theory (DFT) calculations, the factors governing the activity of the catalyst could be determined.[139] Those insightful understanding into the catalytic reaction at the molecular scale could be transferred to the design of novel catalysts and optimizing reaction conditions, offering a faster and more-cost effective approach for the catalyst discovery.[140] Some recent works on the design of high efficient oxygen reduction reaction catalyst,[141] the adsorption and reaction of aldoses sugars on transition metals surface,[142] the promotional effect of B to Ni, Cu and Co in C-H activation[143] or the insights into the selective oxidation of glucose[144] and amines[145] on CuO could illustrate how first principles based modelling is able to shed light into the mechanism and guide the design of heterogeneous catalysts with improved activity, selectivity and stability.

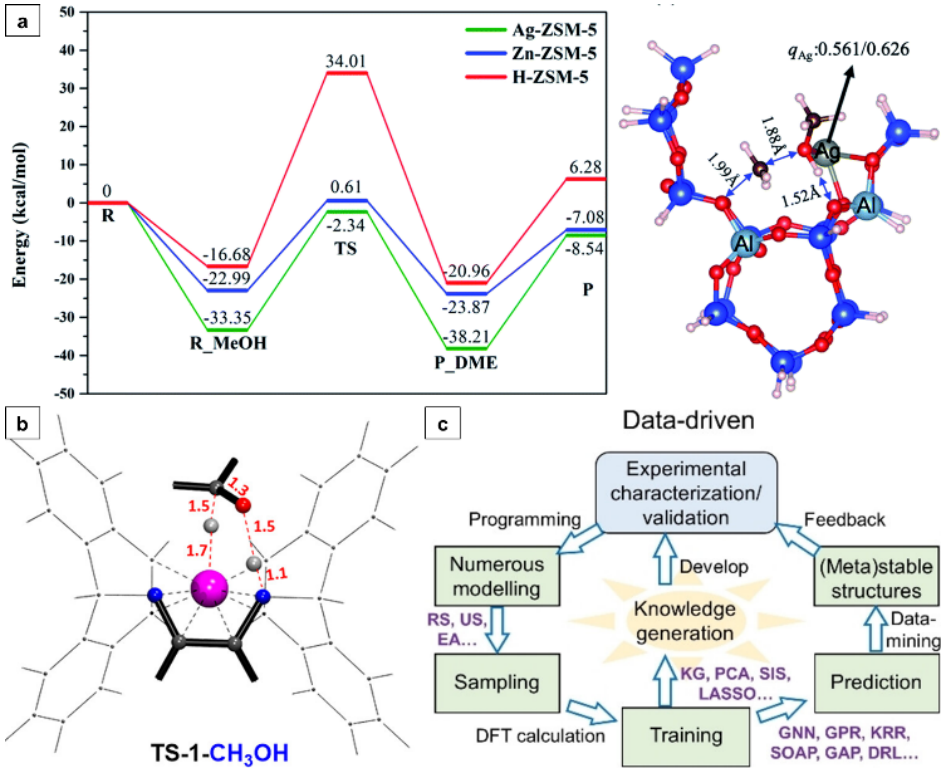


Figure 1. (a) DFT energy profile for methanol activation in modified ZSM-5 catalyst, reproduced under the terms of the CC-BY-NC license.[146] (b) Transition state of methanol activation on [Ru(trop$_2$dad)] catalyst, reproduced under the terms of the CC-BY-NC-ND license.[147] (c) Workflow for modern data-driven method to design heterogeneous catalyst, reproduced from CC-BY open access publication.[148]

In the field of methanol activation, deep understanding into how methanol could be activated on the catalyst has been revealed recently by DFT calculations. Lin et al.[146] observed that by anchoring some transition metal ions (Ag and Zn) into the specified position of the H-ZSM-5 zeolite frame-structure, the Lewis acid acidity of the catalyst was altered, resulting in the significant enhancement of the catalytic activity in methanol activation and conversion (Figure 1a). The integration between DFT calculations and experimental validation was also extensively carried out at the Dalian Institute of Chemical Physics, which led to the construction and operation of the world's first "methanol to olefin" unit in Baotou, China.[149] However, the stability of the catalyst against coking remained a great challenge and hindered the scale up of this process. Recent discoveries by Zhou et al.[150] on the combination of ZSM-5 zeolite with low-melting-point metals (Ga) and by Liu's group on the directly transforming coke to naphthalenic species in SAPO-34 zeolites[151] reported the significant lifetime increment of zeolite-based catalysts in the Methanol-to-Hydrocarbon reaction. Those studies all guided by DFT investigations and confirmed by experiments, marked a new milestone in improving the stability of catalyst and significantly boosted the economics and sustainability of methanol conversion processes. Furthermore, Sinha et al.[147] investigated the detail mechanism of methanol activation on [Ru(trop$_2$dad)] catalyst (wherein trop$_2$dad = 1,4-bis(5*H*-dibenzo-[*a*,*d*]cyclohepten-5-yl)-1,4-diazabuta-1,3-diene) to reveal the crucial role of the dad ligand moiety in changing the Bronsted basicity of Nitrogen center and Lewis acidity of Ru center, cooperatively with the metal active site catalyzing the methanol activation (Fig. 1b). This study therefore explained the excellent activity of [Ru(trop$_2$dad)] catalyst, which is the only catalyst that could activate methanol in aqueous phase without the need of other additives and paved the way for designing higher active catalysts. Su et al.[152] also performed extensive DFT calculations

on metals, MXenes, oxides and Metal/Oxide interfaces to establish the key factors that control the efficiency of methanol activation. This study proposed that good catalyst for methanol activation would be able to maintain the constant charge of H once it was activated from methanol and facilitate the rotation of methanol O−H bond.

The mechanistic knowledge into the methanol activation is very helpful to design better catalyst in this field. With the evolution of data-driven modelling in modern catalyst discovery,[153] the insight from DFT simulations could be transferred to machine learning model, called catalyst informatics, to accelerate the discovery of higher active catalyst in methanol activation (Fig. 1c).[148, 154] Furthermore, the key factors governing the activation of methanol could be used as the descriptors in high-throughput computation, allowing for the automation and highly efficient search for novel catalysts beyond the current catalysts in literature.[148, 155]

7.2. Sono-chemical activation of methanol

The application of ultrasound has been long considered a green method in organic synthesis.[156] Recently the use of ultrasound as an effective activation method is receiving great interest due to its capabilities in boosting and controlling the activity and selectivity of chemical reactions.[157] Acoustic cavitation is a phenomenon that occurs when ultrasound waves of significant intensity pass through a liquid, leading to the oscillation, growth, and forceful collapse of tiny gas bubbles. This collapsing process generates localized extreme conditions within the cavities, including exceptionally high temperatures and pressures. These cavitation bubbles can therefore be viewed as a micro-reactor for activation chemical bonds with high bond dissociation energies.[158]

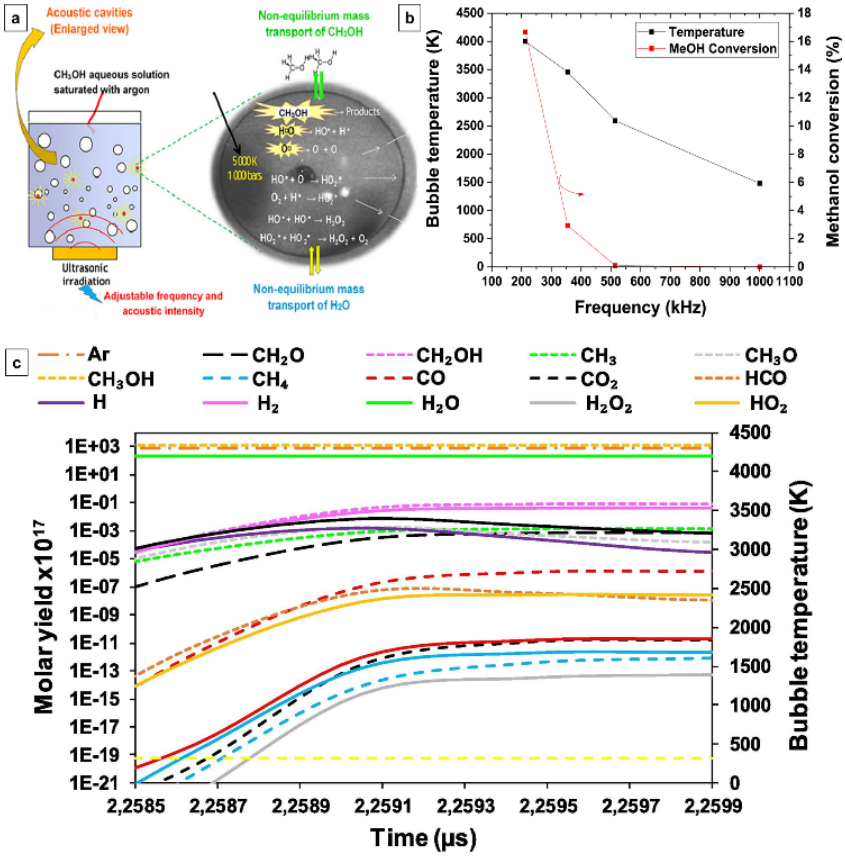


Figure 2. (a) Sonochemical activastion of methanol, reproduced with permission.[159] Copyright 2022, Elsevier. (b) Effect of ultrasound frequency on methanol conversion and bubble temperature, reproduced with permission.[159] Copyright 2022, Elsevier. (c) Time evolution of the products from methanol sonochemical activation, reproduced with permission.[160] Copyright 2022, Elsevier.

During the sonolysis of methanol solution, gaseous molecules of methanol escapes into the cavitation bubbles and undergo localized high temperature sono-pyrolysis (Figure 2a).[159] Buettner and co-workers demonstrated that the sonolysis of methanol under argon atmosphere leads to the generation of typical pyrolysis and combustion products.[161] For instance, H_2, CH_2O, CO, CH_4 and traces amounts of C_2H_4 and C_2H_6 were obtained using a 1 MHz ultrasound frequency of 2 W/cm^2. Rassokhin managed to convert methanol (10 % v/v) to formaldehyde, ethylene glycol, acetylene and ethylene using a 724 kHz high frequency ultrasound reactor and an ultrasound intensity of 10 W/cm^2 under argon atmosphere.[162] Krishna et al. detected the formation of CH_3• (in a relatively important quantity) and CH_2OH• radicals from methanol sono-activation,[163] and the methyl radicals generation was explained by the pyrolysis of methanol in the localized hot spot in the cavity interior of the cavitation bubble. Nonetheless, the formation of CH_2OH• radicals was attributed to either pyrolysis of methanol or to the H abstraction through the reaction of methanol with H•, HO• and CH_3• radicals generated in-situ via the sonolysis of methanol-water mixtures.

In recent 5 years, significant progresses have been made in the field of methanol sono-activation.[159] Dehane et al. investigated the influence of operation parameters on the methanol sono-conversion and observed that frequency range of ultrasound irradiation from 213 to 355 kHz would result in the higher conversion of methanol.[159] This observation was also confirmed in the experimental work by Choi et al. for the sonochemical activation of methanol in a 300 kHz sonoreactor with Ar gas bubbling.[164] Indeed, the gas component was stated as an important factor in the methanol sono-activation, and the configuration of 40% Ar in the Ar-O2 gas mixture was predicted to deliver the best performance.[165] With this setup, the sonochemical-activation of methanol produced a wide

range of active intermediates (CH_2OH, CH_2O, CH_3, CH_3O…,) as was illustrated in Fig. 2c.[160] If the selectivity towards the specified intermediates could be controlled, it could be used to facilitate the conversion of methanol to desired high value add-chemicals. Although this approach is still facing a grand challenge at this moment, recent advances in using nano-structured materials in sonocatalysis serving dual functions as a cavitation agent and a heterogeneous catalyst opened an efficient way to achieve this task.[139a, 144a] With the help of a heterogeneously catalyzed sonochemical reactions, Au/TiO_2 has been demonstrated to work in synergy with cavitation bubbles generated during the sonolysis of methanol solutions to activate methanol towards H_2 production.[166] In this work, Wang et al. showed that the sonocatalytic activation of methanol under argon atmosphere led to the formation of H_2, CO, HCHO and CH_4.[166] Mechanistically, CH_2O was formed by H-abstraction of methanol by HO• and H• radicals during methanol sonolysis. While CH_4 was formed by the reaction/combination of methyl radicals with H• formed via the thermal cleavage of methanol in the localized hot spot in the cavity interior. These approaches demonstrate the feasibility of methanol activation via unconventional ultrasound techniques at relatively near room-temperatures. However, ultrasound activation of methanol towards the formation of high value-added platform chemicals are still fledging and requires deeper optimizations and mechanistic understanding, but recent successes in the selective oxidation of biomass using sonocatalysis have been demonstrated the great potential of sonochemical methanol activation in this field.[139a, 144a, 167]

7.3. Biotechnology approach for methanol activation

For biological systems, methanol is used as a substrate or carbon source which can be catalyzed by series of enzymes in a pathway leading to the formation of metabolites required for cell growth and/or the biosynthesis of valuable compounds like biofuels and drug precursors. Either way, methanol utilization helps to remove C1 carbons from the environment. There are microorganisms commonly referred to as methylotrophs that have a natural ability to convert methanol to useful compounds since they have specific enzymes that catalyze these reactions. Methylotrophs produce biochemicals from methanol conversion at low rates. However, it has been challenging to improve these microorganisms to increase the efficiency of methanol conversion due to limited molecular and genetic tools. Methanol utilization in methylotrophs begins with the oxidation of methanol to formaldehyde which is catalyzed by different enzymes such as methanol dehydrogenase that require specific electron acceptors.[168] Formaldehyde can then be converted to other intermediates required for cell growth or for the bioproduction of valuable chemicals using three main pathways – Ribulose monophosphate (RuMP) pathway, Xylulose monophosphate (XuMP) pathway or the serine pathway. The RuMP pathway occurs in methylotrophic bacteria and has a relatively high energetic efficiency of 40-50%.[169] In this pathway, formaldehyde reacts with ribulose-5-phosphate to yield hexulose-6-phosphate which is converted to fructose-6-phosphate and eventually to pyruvate for cell growth. Pyruvate is also a key precursor molecule that can be converted to a range of biochemicals including biofuels, organic acids.[170] For the XuMP pathway found in methylotrophic yeast, formaldehyde undergoes a condensation reaction with xylulose-5-phosphate to form glyceraldehyde-3-phosphate catalyzed by the Das (dihydroxyacetone synthase) enzyme. Next, glyceraldehyde-3-phosphate gets converted to dihydroxyacetone, followed by its transformation to dihydroxyacetone phosphate which eventually yields building blocks required for cell growth. Even though these biochemical reactions occur in nature, the underlying pathways are not efficient due to carbon and energy loss.

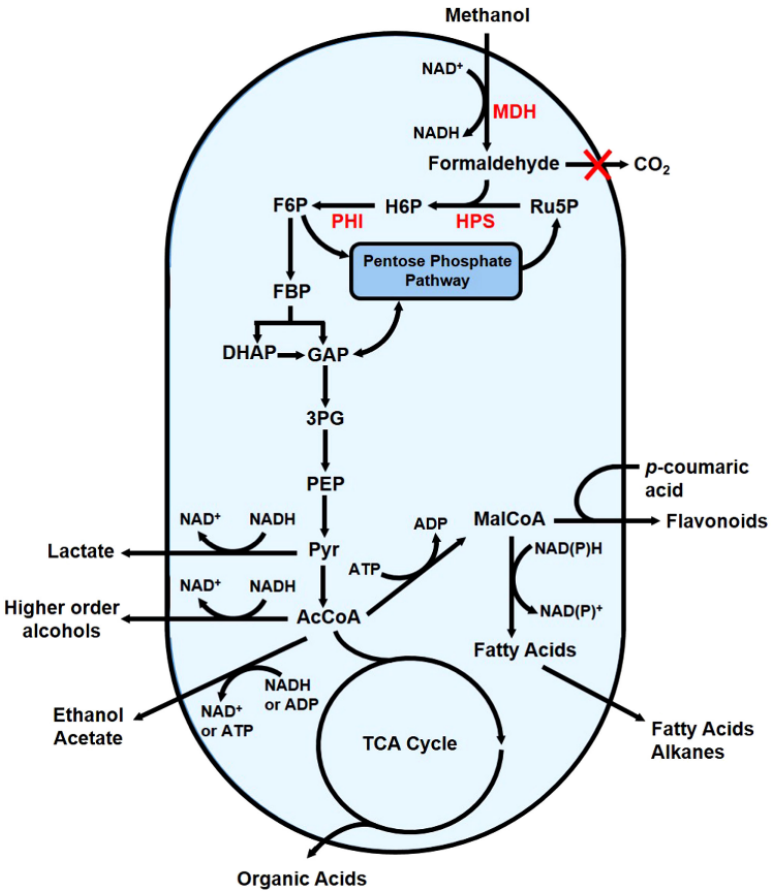


Figure 3. Methanol activation and utilization in *Escherichia coli.* Reproduced with permission.[171] Copyright 2017, Elsevier.

To get around the challenge of using native methylotrophs to activate methanol, synthetic methanol conversion pathways are being engineered in tractable organisms like *Escherichia coli*, *Clostridium glutamicum* and *Saccharomyces cerevisiae*. Whitaker et al. reported the conversion of methanol to high-value specialty chemicals on an engineered *E. coli* strain (Figure 3).[171] While the yield was low, they were able to increase the methanol utilization rate by supplementing the nutritional need of yeast strain.[172] So far, the best demonstration of engineering methanol metabolism in yeast was shown by Zhan et al.,[173] where they screened a combination of different methanol oxidation enzymes, as well as a combination of formaldehyde bioconversion enzymes. The authors obtained the best enzyme combinations and coupled the pathway to the production of flaviolin, a high-value compound.[173] While biological conversion of methanol is looking promising, it is still challenged by the toxicity of methanol and formaldehyde to microorganisms. Additionally, the low efficiency of the methanol conversion rate by the methanol dehydrogenase enzyme hinders industrial application of this process and requires improvement.[174] However, using very active methanol dehydrogenases will result in a rapid accumulation of formaldehyde which comes with its own challenges since formaldehyde is toxic to microbial cells. Therefore, other approaches such as using cell-free systems to catalyze methanol conversion *in vitro* in the presence of a cocktail of enzymes could be an alternative approach to get around the problem of toxicity of methanol and its intermediate, formaldehyde. Taken together, although biological approaches to converting methanol to other compounds is still nascent and being developed, it is evident that this biotechnological strategy will complement chemical approaches being developed to activate methanol.

8. Conclusion and Perspectives

In recent years, the use of methanol in lab and industrial scales gains an increased interest due to the low price and readily availability of methanol in large amount from bio-, chemical processes. In fact, the conversion of methanol to highly value-added compounds is considered to be atom-economical and sustainable for the development of chemical industry in the near future. Beyond well-established applications of methanol in chemical industry and energy production, methanol can be extensively used as C1 source in organic synthesis. Recent reviews on the topic of catalytic transformations using methanol via hydrogen borrowing, dehydrogenation methods have been documented.[10a, 10c, 175] However, other aspects related to methanol activation such as redox pair coupling, radical coupling, light-promoted methods, sono-chemical activation have not been mentioned. This review highlighted recent research and trends in the field of “methanol activation” in organic synthesis. Based on the nature of activation modes to activate methanol, we divided it into four main strategies: *i)* hydrogen borrowing, *ii)* dehydrogenative coupling, *iii)* redox pair coupling, and *iv)* radical coupling. Up to now, many new synthetic methods have been developed using methanol as C1 building block in methylation, hydromethylation, aminomethylation, formylation reactions, as well as the synthesis of urea derivatives, heterocycles and value-added compounds relying on these four main strategies. In addition, the employment of computational chemistry and machine learning to provide valuable information in designing novel efficient and robust catalysts for methanol activation has been mentioned in this review. So far, methanol activation methods have found many practical applications in the efficient synthesis of important heterocycles, drugs and bioactive compounds. Therefore, we also emphasized this issue in our review. We hope this review will inspire and encourage researchers to develop new synthetic methods using methanol as C1 building block.

Although methanol activation field showed many successful applications in making value-added compounds, there remains some obstacles as well as challenges to be solved. Particularly, most of procedures need to be performed at high temperature, required long reaction time, as well as high catalyst loading and the use of excess amount of methanol. Therefore, the design of novel catalyst systems in conjunction with computational chemistry and machine learning to give robust catalysts that work under milder conditions (low temperature, use of less methanol, and low catalyst loading) would be an important goal for current research. Until now, the majority of studies has focused on the use of numerous precious and expensive transition metals (Rh, Ir, and Ru) as catalysts, with fewer papers published on the use of less toxic and earth-abundant base metals such as Fe, Mn, Co, and Cu catalysts. Therefore, the design and synthesis of highly active, robust, cost-effective, and less toxic catalysts (based on Mn, Cu, Co, and Fe metals) are crucial to the development of more sustainable chemical and pharmaceutical processes. It would be extremely advantageous to explore asymmetric C-methylation reactions using chiral transition metal complex catalysts in order to further medicinal chemistry research. In addition, the improvement of TON and TOF of new catalysts via developing of recyclable solid catalysts (supported nanometal particles or anchored transition metal complexes on solid supports) needs to be considered. Besides, cutting-edge technologies can be applied to improve chemical synthesis by effectively using methanol through the employment of photo-induced catalysis, flow chemistry, electrochemical and sono-chemical activation methods.

An important goal of this review is to demonstrate that a series of essential drugs which were successfully synthesized via methanol activation method. Consequently, a major challenge that needs to be addressed is to industrialize these processes and produce important drugs as well as value-added compounds on a large-scale and then industrial scale. So far, biotechnological methods using enzymes to activate methanol have not been employed in organic synthesis. This research field would be fascinating and beneficial for developing new metal-free organic transformations in terms of green chemistry. This review aims to stimulate innovation using methanol in the field of organic synthesis, medicinal chemistry, and industrial chemistry. We anticipate that it will be of interest to a wide range of readers.

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Keywords: methanol activation • transition metals catalysis • hydrogen borrowing • dehydrogenation • sustainable synthesis

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