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A Guide for Mono-Selective N-Methylation, N-Ethylation, and N-n-Propylation of Primary Amines, Amides, and Sulfonamides and Their Applicability in Late-Stage Modification

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This review provides a comprehensive overview of mono-alkylation methodologies targeting crucial nitrogen moieties – amines, amides, and sulfonamides – found in organic building blocks and pharmaceuticals. Emphasizing the intersection of chemical precision with drug discovery, the central challenge addressed is achieving one-pot mono-selective short-chain N-alkylations (methylations, ethylations, and *n*-propylations), preventing undesired overalkylation. Additionally, sustainable, safe, and benign alternatives to traditional alkylating agents, including alcohols, carbon dioxide, carboxylic acids, nitriles, alkyl phosphates, quaternary ammonium salts, and alkyl carbonates, are explored. This review, categorized by the nature of the alkylating agent, aids researchers in selecting suitable methods for mono-selective N-alkylation.

1. Introduction

Nitrogen-containing motifs, encompassing amines, amides, and sulfonamides, serve as crucial structural elements in both simple organic building blocks and complex molecules, particularly bioactive compounds and pharmaceuticals (see Figure 1).[1] These motifs exert significant influence on pharmacological properties, engaging in diverse interactions within biological systems, thereby establishing their indispensability in drug development.[1–2] This review aims to provide a comprehensive exploration of mono-alkylation methodologies tailored for these nitrogen moieties, highlighting the importance of chemical precision and their potential application in drug discovery.[2–3]

The primary challenge addressed here revolves around accomplishing one-pot mono-selective short-chain N-alkylations (specifically methylations, ethylations, and *n*-propylations) of primary amines, amides, and sulfonamides while rigorously excluding undesired overalkylation. This overalkylation is prompted by the increased nucleophilicity of nitrogen with higher substitution levels. Noteworthy is that related reviews often exclusively focus on N-methylations[4] and may not concentrate on mono-selectivity for aliphatic short-chain alkylation of primary nitrogen moieties.[4a–c,e,f,5] Nevertheless, achieving a high degree of mono-selectivity in nitrogen alkylation is paramount for designing and controlling alterations in the pharmacological activity of therapeutic agents.

Additionally, this review offers valuable methods for utilizing sustainable, safe, and generally more benign alternatives (such as alcohols, carbon dioxide, carboxylic acids, nitriles, alkyl phosphates, quaternary ammonium salts, and alkyl carbonates) to traditionally applied alkylating agents like alkyl halides. The comprehensive overview of current strategies, categorized by the nature of the alkylating agent, aims to assist readers in selecting suitable methods for N-alkylation when mono-selectivity is crucial. Furthermore, it covers strategies for mono-selective N-ethylation and N-*n*-propylation, providing a well-rounded understanding of the field .

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2. Amines

Amines are ubiquitous and fundamental motifs in organic chemistry, playing a central role in the synthesis of various bioactive compounds and pharmaceuticals.[3d,6] Their significance lies in their unique reactivity and versatility, making them essential building blocks for constructing complex molecular structures. Within drug design, amines serve as key components, influencing the pharmacological activity of therapeutic agents through diverse interactions within biological systems, impacting molecular recognition and binding.[7]

N-Alkylation stands out as a transformative strategy in amine functionalization.[3d] This modification introduces a new layer of variability to amine-containing compound for precise tuning of their chemical and physical properties. The ability to precisely control the degree of alkylation is crucial in many chemical transformations. Particularly in drug development, where subtle modifications can significantly influence a compound's pharmacokinetic and pharmacodynamic properties, methods ensuring strictly mono-selective N-alkylation become not only desirable but often indispensable.

This chapter aims to provide an overview of methodologies and strategies for achieving mono-selective short-chain alkylation of amines, highlighting their applicability in late-stage modifications of bioactive compounds.

2.1. Alcohols

Alcohols present a very valuable and sustainable alternative to traditional alkylating agents, as they are inexpensive, readily available, and renewable. Giving water as the sole byproduct, their application in alkylation reactions enhances atom-efficiency and thus contributes to making chemical processes more environmentally benign.

When using alcohols as the alkylating agents, the formation of the carbon-nitrogen bond proceeds through a concept known as hydrogen autotransfer or borrowing hydrogen (see Figure 2).[8] In this process, a transition-metal mediates alcohol dehydrogenation, generating a reactive intermediate, such as an aldehyde or ketone. Subsequent condensation with an amine leads to imine formation, with water released as the sole byproduct. The intermediate metal-hydride complex [MH_2], previously formed during dehydrogenation, effectively reduces the imine species, releasing the alkylated amine, and simultaneously regenerating the catalytically active species [M]. The net N-alkylation of amines with alcohols proceeds without external hydrogen gas; instead, hydrogen is formally "bor-

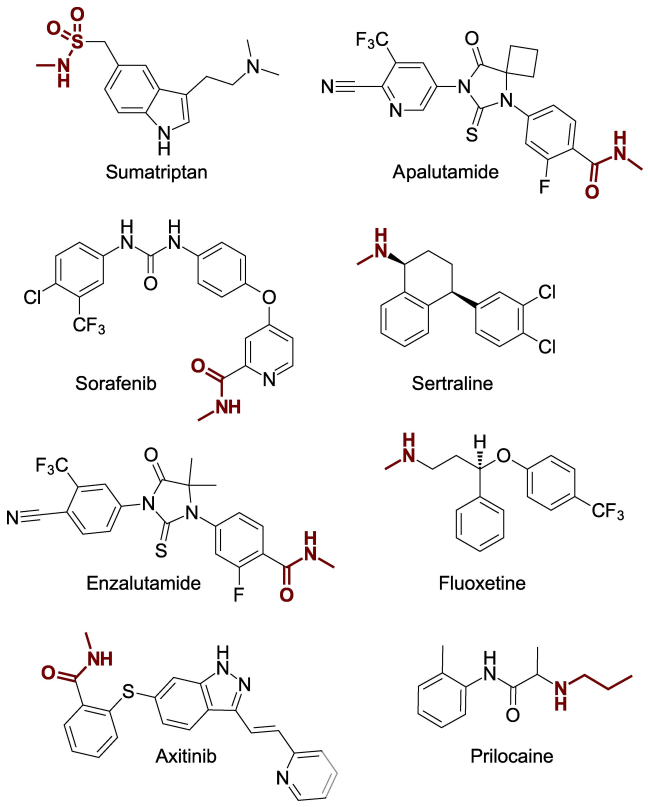

Figure 1. Examples for bioactive molecules bearing N-alkylated motifs.

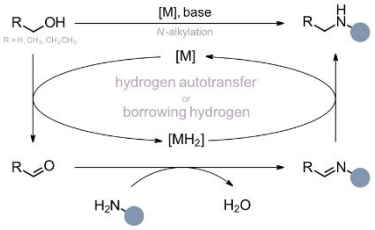

Figure 2. Simplified mechanism for metal catalyzed hydrogen autotransfer or borrowing hydrogen reactions in the alkylation of primary amines using alcohols

rowed" and "returned" by the active catalytic species during the reduction step.

Conventionally, noble transition metals like ruthenium, iridium, and palladium are used in these hydrogen autotransfer-mediated N-alkylations with alcohols. Recent efforts have aimed to replace these costly transition metals with earth-abundant alternatives, such as iron, manganese, nickel, and copper. Nevertheless, a significant challenge that remains is developing catalytic systems that can operate effectively at lower temperatures, as current N-alkylation reactions with alcohols typically require high temperatures exceeding 100 °C and often involve prolonged reaction times, which in turn often requires special high-pressure equipment.

2.1.1. Rhodium catalysis

In 1981, Grigg and co-workers were the first to report mono-selective homogeneous transition-metal catalyzed N-methylation of primary amines with methanol, using $RhH(PPh_3)_4$ as catalyst.[9] While this early publication featured only three examples of mono-N-methylation, it unquestionably laid the foundation for subsequent advances in this field.

2.1.2. Ruthenium catalysis

Fifteen years after Grigg's pioneering work, Watanabe, Mitsudo, and co-workers studied the mono-selective N-ethylation on aminopyridines with ethanol under ruthenium catalysis (Figure 3, I)[10] Employing a Ru(0)(cod)(cot) catalyst, they run the reactions at 150–180 °C for 5 h in the respective alcoholic solvent, achieving outstanding selectivity for the mono-methylated, -ethylated, and -propylated products with up to 92% yield. Only at higher temperatures (200 °C), extended reaction times (20 hours), and using $RuCl_2(PPh_3)_3$ as the catalyst, they could manipulate the degree of substitution and isolate the diethylated product in 70% yield. This marked the first instance of such mono-selectivity in transition-metal-catalyzed N-alkylations, paving the way for numerous succeeding reports.

The Bhattacharjee group reported the use of $[(PPh_3)_2Ru(CH_3CN)_3Cl][BPh_4]$ catalyst for mono-alkylation of various para-substituted anilines under mild basic conditions, maintaining high mono-selectivity, though only achieving moderate yields,

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Prof. Michael Schnürch carried out PhD research in the field of heterocyclic and cross-coupling chemistry under the supervision of Prof. Peter Stanetty. During postdoctoral studies at the Columbia University, NY in the group of Prof. Dalibor Sames as Erwin Schrödinger fellow of the Austrian Science Fund, he investigated decarbonylative coupling reactions. After the start of his independent career, he established a research program on C–H activation chemistry and cross-dehydrogenative coupling reactions, supported by several research grants (financed by FWF, FFG, The City of Vienna, and TU Wien).

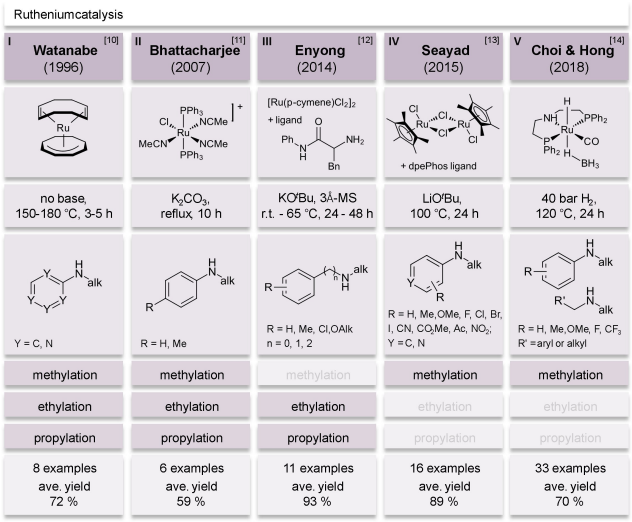


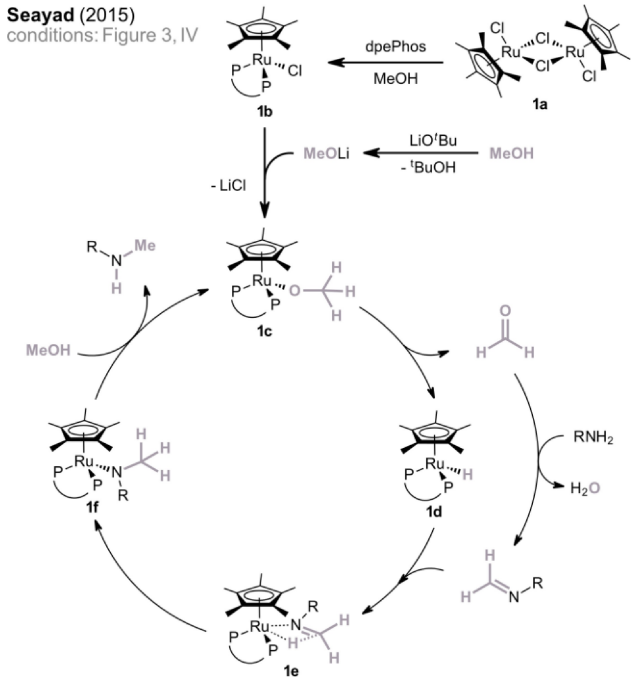
Figure 3. Methods for mono-selective N-alkylation of amines using alcohols as alkylating agents under ruthenium catalysis.

especially with "longer" chain alcohols like ethyl and propyl (Figure 3, II)[11]

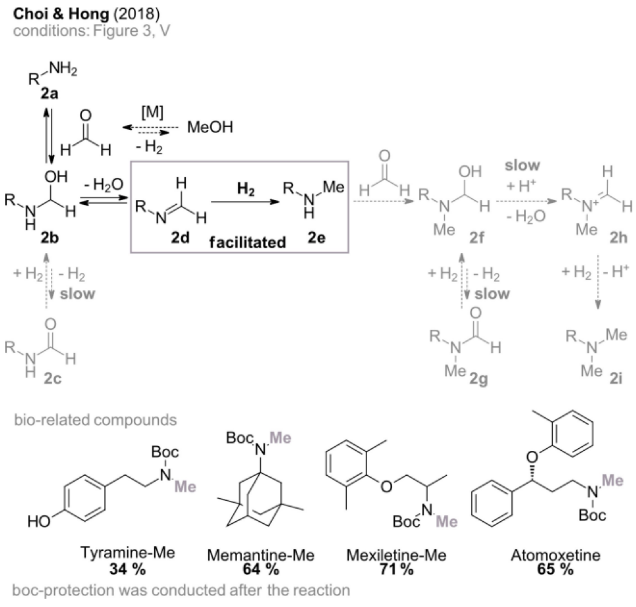
In 2014, Enyong *et al.* established a novel protocol using cheap and commercially available $[Ru(cymene)Cl_2]_2$ catalyst and a readily available amino amide ligand, enabling N-alkylation at temperatures below 70 °C (Figure 3, III).[12] This lower reaction temperature was only feasible when the respective alcohol was used as reaction solvent. In toluene with near-stoichiometric amounts of alcohol, higher temperatures up to 110 °C were required for full conversion. They successfully mono-ethylated and mono-propylated a wide range of substituted anilines and benzylamine with excellent yields of up to 98%. Unfortunately, the absence of an example for mono-methylation left open the question whether methanol could act as an effective N-alkylating agent under these conditions.

The lack of mild and viable protocols for Ru-catalyzed N-methylation using methanol, encouraged the group of Seayad to develop a method for mono-selective N-methylation of substituted primary anilines (Figure 3, IV) and sulfonamides (see Section 4. Sulfonamides).[13] This mono-selectivity was observed for aniline-derived substrates and sulfonamides but not for aliphatic primary amines, where exclusively *N,N*-dimethylated products were obtained. They employed $[RuCp^*Cl_2]_2$ (0.5 mol%) with dpePhos ligand (1.2 mol%) as precatalytic system, which, upon activation with LiO^tBu (5 mol%) generated an active Ru-methoxy complex (Scheme 1). Various substituted aniline derivatives could be mono-methylated with excellent yields ranging from 73% to 96% at 100 °C.

In 2018, Choi and Hong expanded the scope of mono-selective N-methylation under Ru-catalysis, moving beyond primarily anilines to encompass aliphatic primary amines (Figure 3, V).[14] This milestone was achieved through the deployment of pincer ligands, combined with the introduction of an H_2 atmosphere. The intent was to facilitate the formation of mono-methylated products while any further methylation of the secondary amine should be kinetically hindered (Scheme 2).



Scheme 1. Proposed catalytic cycle for the mono-N-alkylation of primary amines *via* ruthenium catalysis by the group of Seayad (ref. [13]).



Scheme 2. Proposed reaction pathway by Choi & Hong for the mono-N-methylation with alcohols using a ruthenium pincer catalyst (top) and the application of their method in a late-stage N-methylation of bio-related compounds (bottom) (ref. [14]).

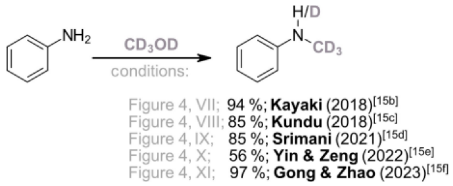
They hypothesized that under these reaction conditions, the intermediate charged iminium species (**2h**) formed from a secondary amine (**2e**) should have a significantly higher activation barrier compared to the lower activation barrier of an uncharged species formed from the primary amine (**2d**).

The optimal results were achieved using the pincer catalyst Ru-MACHO-BH (2 mol%; Figure 3, V) in MeOH as solvent at an

H_2-pressure of 40 bar and a reaction temperature of 120 °C for 24 hours. This method yielded a wide range of mono-methylated secondary amines with yields ranging from 34 % to 99 %. Notably, this method demonstrated its feasibility for the late-stage modification of several biologically relevant compounds.

The following years, reports on using various Ru-pincer complexes for selective mono-methylation of aniline derivatives were disclosed by several groups (Figure 4, VI–XII).[15] Most systems require strong alkoxy bases like NaOMe[15a,c], KOMe[15e], or KO^{t}Bu[15b,d] to form the catalytically active Ru-alkoxy species. Recently, Gong, Zhao and co-workers found Cs_2CO_3 as very mild base in a ruthenium POP-pincer-complex catalyzed mono-selective N-methylation protocol[15f] (Figure 4, XI). Additionally, some of those protocols could be successfully applied for mono-selective trideutero methylation of primary amines using CD_3OD[15b–f] (Scheme 3). In 2023, the group of Paul expanded the scope of Ru-pincer-complex catalyzed N-methylation towards a more general protocol for N-alkylation using C1–C10 aliphatic alcohols to mono-selectively alkylate several aniline derived substrates in up to 85 % yield (Figure 4, XII).[16]

N-Hetrocyclic carbenes (NHCs) represent another prominent class of ligands frequently used in ruthenium-catalyzed N-alkylation reactions employing alcohols as reagents (Figure 5, XIII–XV). Numerous studies have explored these catalytic systems, with notable contributions from the groups of Rit[17] (Figure 5, XIII & XV) and Liu & Ke[18] (Figure 5, XIV). Typically, these protocols necessitate the use of a strong base such as KO^{t}Bu[18] or KOH[17] and operate at elevated temperatures surpassing 100 °C. While primary aryl amines predominantly served as substrates in these protocols, exceptions included the utilization of cyclohexylamine and benzylamine, as reported by Illam and Rit.[17b]



Scheme 3. N-Trideuteromethylations using CD_3OD under ruthenium pincer complex catalysis.

Yang, Li and co-workers have developed a robust bidentate, cyclometalated ruthenium complex, suitable to methylate primary amines and sulfonamides mono-selectively (Section 4 Sulfonamides) using methanol under mildly basic conditions (Cs_2CO_3), while being stable under ambient atmosphere[19] (Figure 5, XVI). The approach, executed at 120 °C for 15 hours, afforded selective mono-methylation of primary aryl amines with methanol, in yields up to 93 %. However, the same degree of mono-selectivity could not be ensured for aliphatic amines. The authors could prove that the bipyridonate ligand within the [(*p*-cymene)Ru(2,2′-bpyO)(H_2O)] system plays a crucial role in the catalytic cycle of the reaction (Scheme 4). The cycle initiates with the loss of water, leading to the formation of a vacant site on the metal center **(3 b)**. Subsequent base-induced activation of methanol triggers the protonation of the ligand and simultaneous coordination of methoxy to the metal center **(3 c)**. The resulting catalytic intermediate then dehydrogenates methanol to formaldehyde, which promptly combines with an amine to the corresponding imine and is hereby converted to a metal hydride species. The hydration of the imine is facilitated by the donation of the hydride coordinated to the metal center **(3 e)** and the hydroxy proton of the ligand, thereby regenerat-

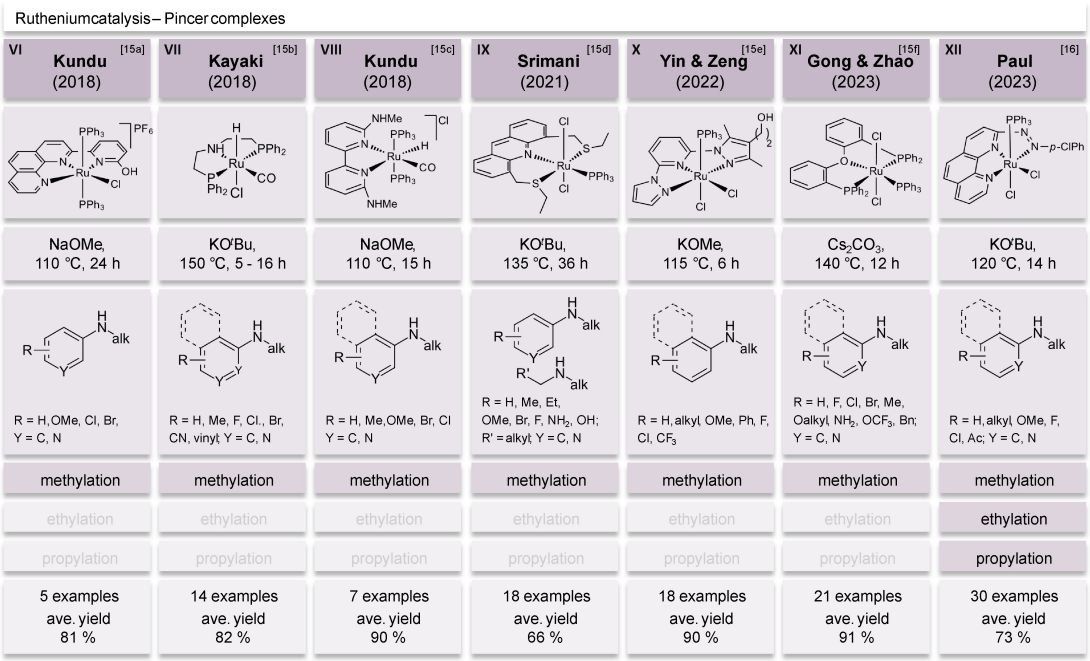


Figure 4. Methods for mono-selective N-alkylation of amines using alcohols as alkylating agents under ruthenium pincer complex catalysis.

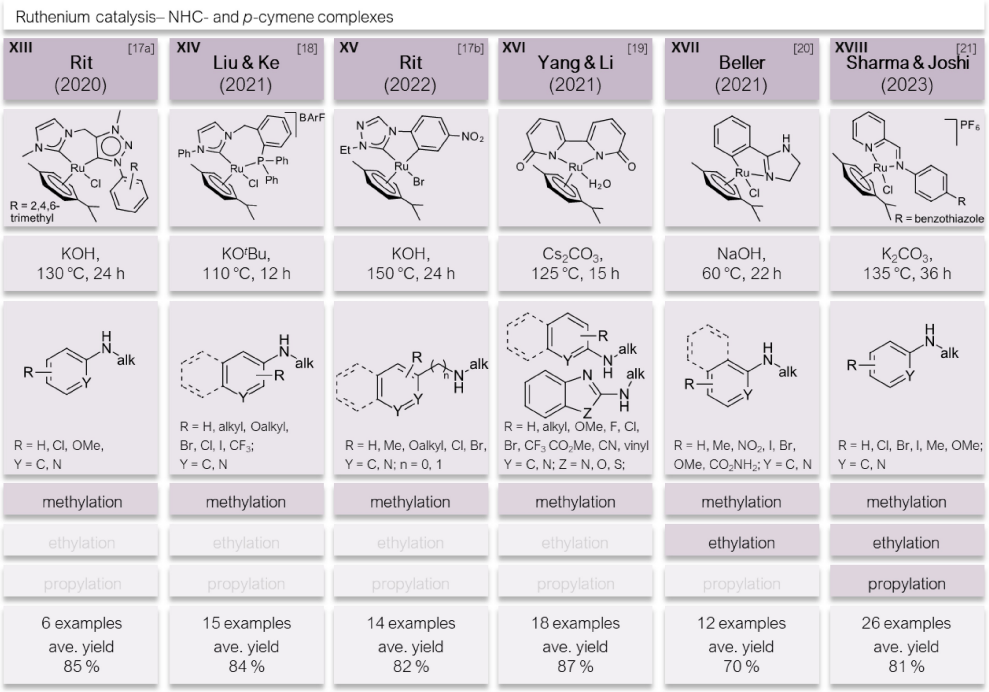
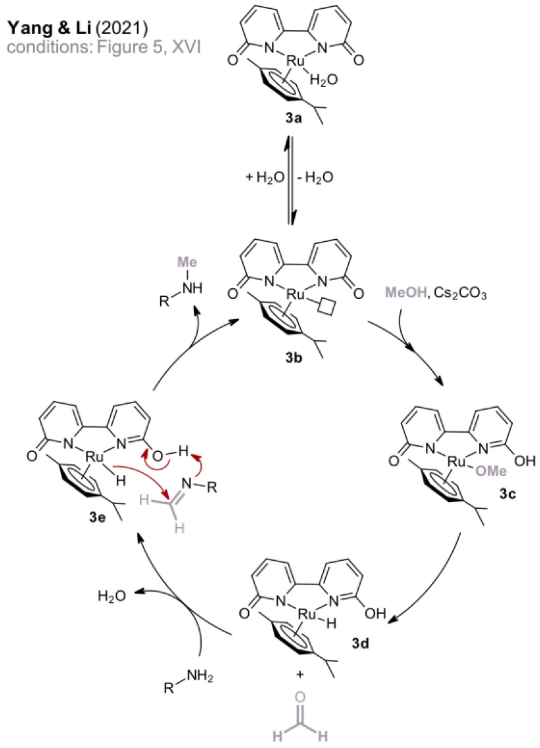


Figure 5. Methods for mono-selective N-alkylation of amines using alcohols as alkylating agents under ruthenium NHC- and *p*-cymene complex catalysis.



Scheme 4. Proposed catalytic cycle for the mono-N-alkylation of primary amines *via* ruthenium catalysis by Yang & Li indicating the crucial role of the bipyridonate ligand (ref. [19]).

ing the catalytic active species (**3 b**), and liberating the desired methyl amines. In this final step, the crucial role of the oxygen species within the ligand becomes evident.

In 2021, an exceptionally mild protocol in terms of reaction temperature was devised by the group of Beller[20] (Figure 5, XVII). They used a cyclometalated Ru-complex as well which is activated by NaOH (10 mol %). This approach smoothly gave the desired mono-alkylated amines at 60 °C after 22 hours in yields up to 99 %.

Recent work of Sharma, Joshi and co-workers introduced the use of a bidentate Ru-complex for mono-selective alkylation of primary anilines and aminopyridines with C1–C3 alcohols, carried out at 135 °C for 36 hours, employing K_2CO_3 as a mild base[21] (Figure 5, XVIII).[21] High yields up to 95 % could be obtained for the targeted *N*-ethylated, and *N*-propylated products. Notably, N-methylation, could only be achieved with moderate maximum yields of 54 %.

2.1.3. Iridium catalysis

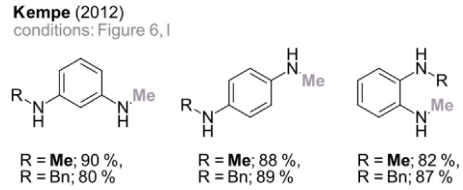
In addition to ruthenium, iridium complexes have emerged as versatile and highly efficient catalysts in hydrogen autotransfer mono-selective N-alkylations, using alcohols as the alkylating agent. The first report of an iridium catalyzed N-alkylation with short-chain alcohols was disclosed by the group of Kempe in 2009.[22] They reported the use of a P,N-ligand-stabilized iridium catalyst to achieve mono-selective N-alkylation of various aromatic diamines.

This early report featured a single example of short-chain alkylation employing methanol, yielding 88 % of the doubly mono-methylated 2,6-diaminopyridine, facilitated by KO'Bu as the base at 70 °C for 48 hours.

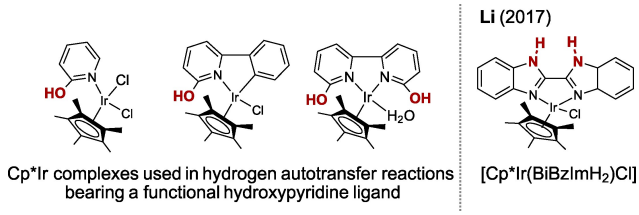
Just three years later, the same group expanded their investigations to present a closely related protocol for the symmetric and asymmetric alkylation of diamines[23] (Figure 6, I). This innovation led to the successful synthesis of symmetric mono-N-methylated *ortho*-, *meta*-, and *para*-benzenediamines using methanol, in yields ranging from 82% to 90%, as well as unsymmetrical N-methylation of *N*-benzyl benzenediamines, in 80% to 89% yield (Scheme 5).

Inspired by the work of Fujita involving Cp*Ir complex catalyzed N-alkylations[24], the group of Williams reported the use of $[Cp^*IrI_2]_2$ (SCRAM™) as catalyst for mono-selective N-alkylations of various aliphatic and aromatic primary amines employing *n*-propanol and higher carbon alcohols[25] (Figure 6, II). Notably, the reactions were carried out in water at 115 °C, yielding a range of mono-*N*-propylated amines in yields up to 94%.

In 2012, Feng Li and co-workers reported the use of a $[Cp^*IrCl_2]_2$/NaOH system for mono-N-methylation of primary arylamines (Figure 6, III) and sulfonamides (Section 4 Sulfonamides).[26] With only 0.1 mol% catalyst loading and under solvent-free conditions at 150 °C, they could successfully mono-methylate arylamines substituted at different positions on the aromatic ring in excellent yields up to 96%. Remarkably, this protocol extended its applicability to various substituted amino-azole compounds, yielding the desired mono-*N*-methylated products with remarkable efficiency, reaching yields up to 95%. The group continued their work with Cp*Ir complexes for mono-selective N-alkylations with alcohols and, in 2017, published a new protocol featuring an *N,N*-bidentate Cp*Ir complex ($[Cp^*Ir(BiBzImH_2)Cl][Cl]$)[27] (Figure 6, IV). These 2,2′-bibenzimidazole ligands, containing protic hydrogen, exhibit structural tautomerism reminiscent of hydroxy pyridine ligands (Scheme 6).



Scheme 5. Mono-N-methylation of *ortho*-, *meta*-, and *para*-benzenediamines using methanol under iridium catalysis by Kempe and co-workers (ref. [23]).



Scheme 6. Structural similarity of a 2,2′-bibenzimidazole ligand by Li and co-workers (right) to previously reported hydroxypyridine ligands (left) (ref. [27]).

The reaction is characterized by low catalyst loadings of 1 mol%, the use of mild base (Cs_2CO_3, 30 mol%) and a robust catalytic system that demonstrated stability in the presence of air. Under these conditions, a range of substituted primary aryl amines was selectively mono-methylated in generally high yields between 78–95% at 120 °C within 12 hours reaction time. Notably, mono-selectivity was exclusively observed for primary aryl amines, with aliphatic amines inevitably undergoing full bis-methylation.

In 2018, Chen's group designed a novel, air-stable Cp*Ir catalyst with a bidentate α-hydroxybipyridine derived ligand

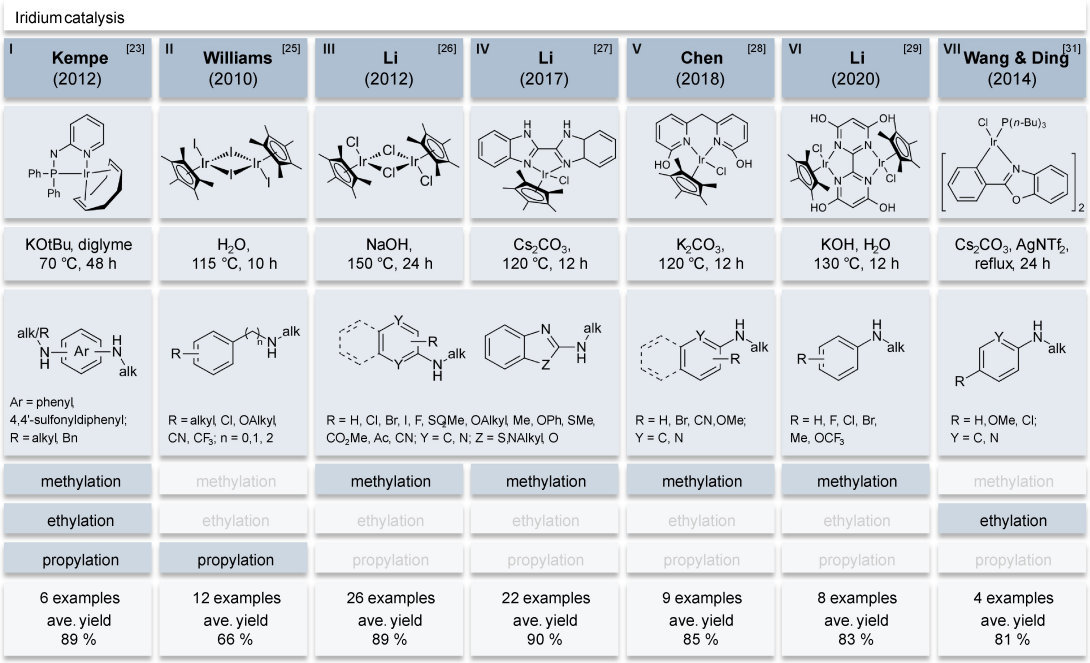


Figure 6. Methods for mono-selective N-alkylation of amines using alcohols as alkylating agents under iridium catalysis.

designed for N-methylation of primary aryl amines[28] (Figure 6, V). 30 mol% of K_2CO_3 were used as mild base for catalyst activation, forming an unsaturated intermediate with a free coordination site **(4b)**, which in turn can coordinate methanol **(4c)**, and further participate in the catalytic cycle (Scheme 7). The method showed high mono-selectivity for aryl amines giving the desired products in up to 94% yield. However, akin to previous reports on Cp*Ir catalysts, this protocol did not exhibit mono-selectivity in the N-methylation of aliphatic amines, resulting exclusively in bis-methylated products.

The group of Feng Li reported two additional protocols using Cp*Ir catalysts. In 2020, they designed a water-soluble bifunctional dinuclear iridium catalyst, enabling mono-N-methylation of aryl amines and sulfonamides (Section 4 Sulfonamides), with similar substrate scope and yields (79–88%) to their prior reports[26–27], under basic conditions (KOH, 1 equiv.) at 120 °C with a 12 hour reaction time[29] (Figure 6, VI). Again, mono-selectivity remained elusive for primary aliphatic amines.

Two years later, they introduced an air and moisture stable Ir-catalyst bearing a bipyridonate ligand for N-trideuteromethylation of aromatic amines with CD_3OD at 125 °C using 30 mol% KOH as base.[30] The scope for mono-N-methylation exhibited similarities to their earlier reports.[26–27,29]

In 2014, Wang and Ding's research group investigated a different class of bidentate iridium species, specifically the benzothienyl iridium(III) complexes featuring phosphine substituents, as catalysts for the mono-N-alkylation of primary aryl amines[31] (Figure 6, VII). Interestingly, their investigation revealed a remarkable enhancement in catalytic activity when non-coordinating anions were introduced, in form of corresponding silver salts such as $AgBF_4$, $AgSbF_6$, $AgPF_6$, or $AgNTf_2$. Among these, $AgNTf_2$ exhibited the most substantial increase in reaction yield (details see Section 2.11 Trialkylamines). While their study encompassed just four examples for mono-N-ethylation of primary aromatic amines with ethanol, the scope is limited in terms of the variety of alcohols employed as alkylating agents. In this reaction Cs_2CO_3 served as the base with a catalyst loading as low as 1 mol% in conjunction with 2 mol% of $AgNTf_2$, proved to be sufficient to achieve high yields up to 86%. The authors could show, however, that their catalytic system enabled mono-N-ethylation using triethylamine, an aspect discussed in greater detail in a subsequent section of this review (Section 2.11 Trialkylamines).

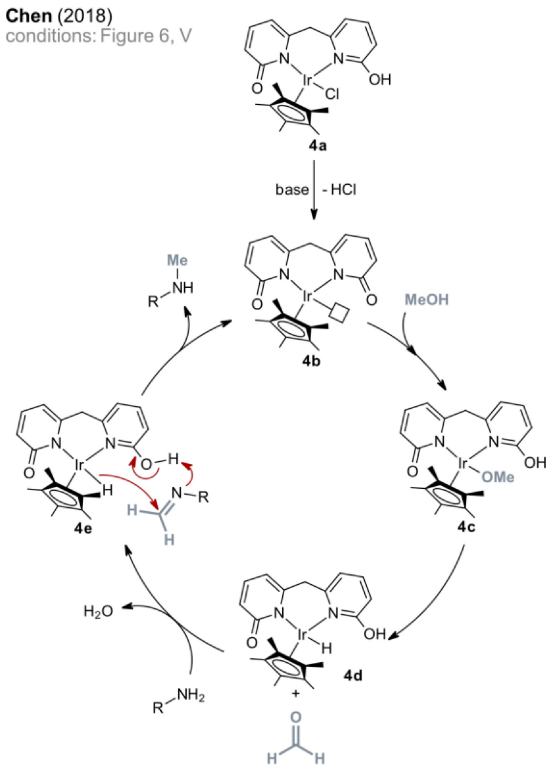
Similar to ruthenium catalysts, NHC type ligands also find applications in iridium catalyzed mono-N-alkylations using alcohols. In 2013, Li and Andersson introduced a bidentate iridium NHC-phosphine complex for the N-alkylation of primary aryl amines with alcohols.[32] However, it is important to note that this study had a primary focus on aromatic alcohols, and the sole instance involving a short, unbranched alcohol was the N-ethylation of aniline, giving the product in 94% yield. While the scope was somewhat limited, this research marked the initial step toward further advancements in employing NHC ligands in Ir-catalyzed hydrogen autotransfer protocols.

An alternative protocol utilizing iridium NHC-ligand complexes, coupled with microwave irradiation, was developed by the Crabtree research group in 2015[33] (Figure 7, VIII). Their catalytic system comprised two NHC-ligands and two CO ligands coordinated to iridium, administered in form of its BF_4 salt. Although the substrate scope was modest, comprising eight different aniline-derived substrates, mono-selective N-methylation was accomplished with yields ranging from 14 to 95% using methanol and KOH at 120 °C under microwave irradiation for 5 h.

Fujita and co-workers screened various Cp*Ir NHC-ligand complexes for the catalytic methylation of primary aromatic amines.[34] They achieved mono-selective N-methylation using a $[Cp^*Ir(NH_3)_2][I_2]$-derived catalyst with a bis-isopropyl imidazole NHC-ligand at a loading of 0.5 mol%. K_2CO_3 (5 mol%) was employed as base (Figure 7, IX). The reaction yielded several secondary aromatic amines in high yields up to 98%.

In 2019 and 2020, Hou and collaborators reported the synthesis and application of novel Ir $^{ABO}N,C_{(carbene)}$ complexes featuring rigid and tunable benzoxazole backbones[35] (Figure 7, X & XI).

A range of *ortho*-, *meta*-, and *para*-substituted anilines, as well as aminoquinolines, benzothiazole and sulfonamides, could be selectively N-methylated at 130 °C within reaction times of 4 or 12 hours, using KO^{t}Bu or Cs_2CO_3 as the base. Intriguingly, control experiments revealed that *para*-substituted anilines exhibited higher reactivity in this catalytic system compared to their *ortho*-substituted counterparts (Scheme 8). Assumingly, the less sterically hindered *para*-substituted imines could more readily approach the intermediate Ir-hydride complex, leading to faster hydration than *ortho*-substituted imines.



Scheme 7. Proposed catalytic cycle for the N-methylation of amines under iridium-catalysis by Chen and co-workers (ref. [28]).

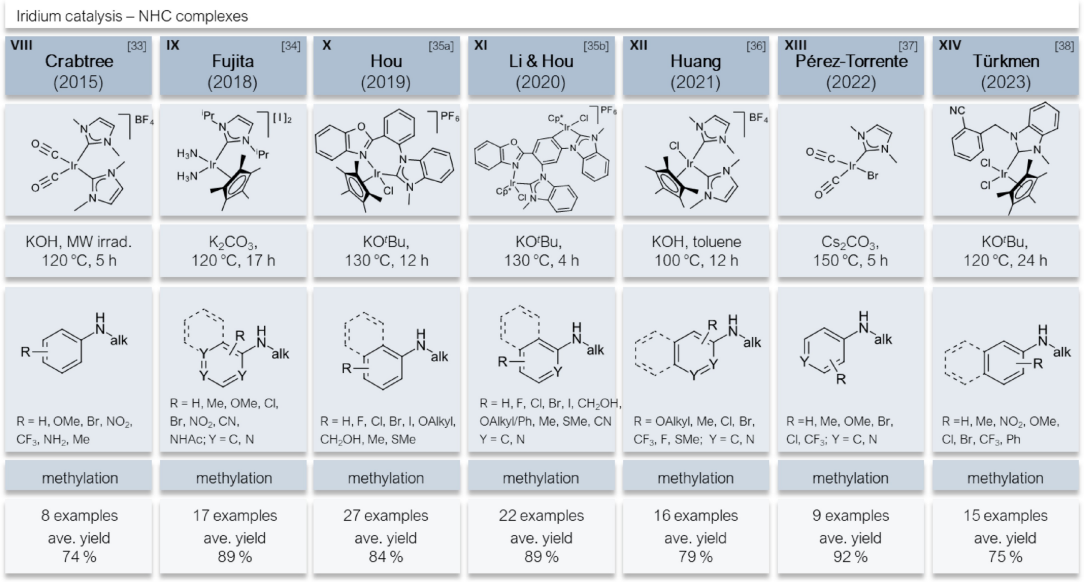
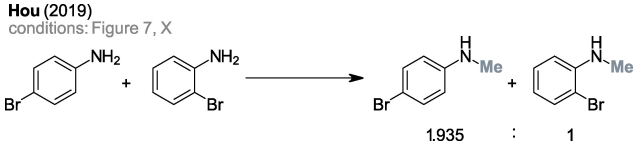


Figure 7. Methods for mono-selective N-alkylation of amines using alcohols as alkylating agents under iridium NHC-catalysis.



Scheme 8. Selectivity in the iridium NHC-complex catalyzed N-methylation of *ortho*- and *para*-bromo aniline by Hou and co-workers (ref. [35a]).

Additional iridium NHC-catalysts have been developed by the group of Huang (2021; Figure 7, XII),[36] Perez-Torrente (2022; Figure 7, XIII),[37] and Türkmen (2023; Figure 7, XIV)[38] all suitable for mono-N-methylation of primary aromatic amines with methanol under basic conditions.

Iridium catalysts undoubtedly represent a valuable and widely employed system for borrowing hydrogen reactions, enabling the N-alkylation of primary aromatic amines in a mono-selective manner, often characterized by high functional group tolerance, high conversion rates, and impressive turnover numbers. Nevertheless, it's worth noting that all the described protocols exhibit limitations when primary aliphatic amines are utilized as substrates, as mono-selectivity is not guaranteed in such cases.

2.1.4. Miscellaneous noble metal catalysis

In addition to ruthenium and iridium catalysts, which are the most commonly utilized metals for hydrogen autotransfer reactions, precious metals like palladium and rhenium have also proven efficient catalysts in the mono-selective N-alkylation of amines with alcohols.

In 2018, the group of Sortais designed a series of cationic tricarbonyl Re(I) PNP-ligand complexes for the mono-N-methylation of aromatic amines with methanol[39] (Figure 8, I). The

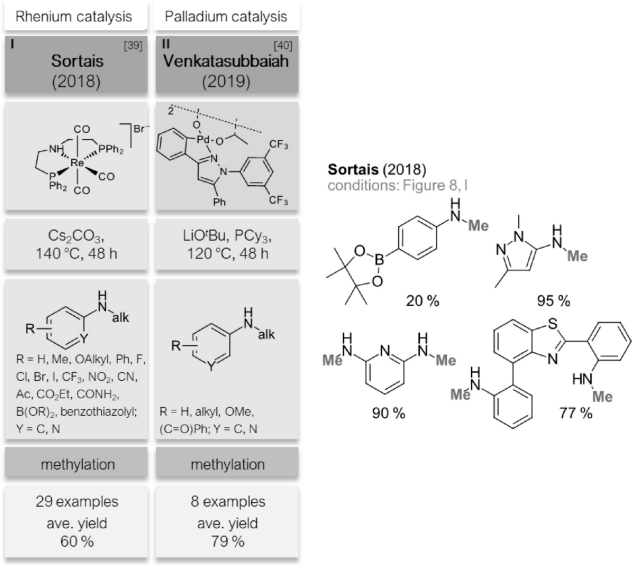


Figure 8. Methods for mono-selective N-alkylation of amines using alcohols as alkylating agents under rhenium and palladium catalysis.

most effective catalytic system relied on an $NH(CH_2CH_2PPh_2)_2$ ligand and was activated by Cs_2CO_3 (5–10 mol%) as the base. This reaction took place in methanol as the solvent at 140 °C for 48 hours under an argon atmosphere, yielding a variety of N-methylated aromatic amines, including complex boronic esters, pyridinyl- and pyrazolyl-amines, and benzothiazolyl derivatives (Figure 8, right).

Palladium based catalysts are primarily employed in their heterogenous Pd/C form for hydrogen borrowing reactions. The use of a homogeneous palladium complex for N-methylation was only reported once in 2019 by Venkatasubbaiah's group[40] (Figure 8, II). They synthesized a palladacycle-phosphine complex, which, upon activation with 30 mol% LiO^{t}Bu, gave access

to eight different mono-N-methylated aromatic amines in moderate to good yields.

Over the last few decades, there has been a growing trend toward the utilization of more sustainable, earth-abundant, and cost-effective non-precious metal catalysts. Multiple research groups have invested significant efforts in developing new catalytic systems containing manganese, nickel, iron, copper, and cobalt for mono-selective N-alkylation reactions with alcohols, which will be discussed further below.

2.1.5. Manganese catalysis

A pioneering work in the field of manganese catalyzed N-alkylation of amines was published by Beller's group in 2016[41] (Figure 9, I). They were the first to use a defined manganese-based PNP-pincer complex to mono-selectively N-alkylate various primary amines with complex alcohols. Their protocol applied 3 mol% of the catalyst, which was activated by KO^{t}Bu to effectively partake in this hydrogen autotransfer reaction. In addition to a wide array of aromatic alcohols, short-chain, unbranched aliphatic alcohols (C1–C7) were successfully harnessed as alkylating agents. Notably, 2-aminopyridine could be ethylated and butylated in a mono-selective fashion at 80 °C in up to quantitative yields. To explore the generality of this approach using methanol as the alkylating agent, diverse primary aromatic amines were examined and could be readily N-methylated with exceptionally high yields of up to 94% at 100 °C within 24-hours reaction time.

Sortais and his colleagues continued this research, revealing in 2017 a protocol for the mono-selective N-methylation of anilines using a cationic manganese PN^{3}P-pincer complex[42]

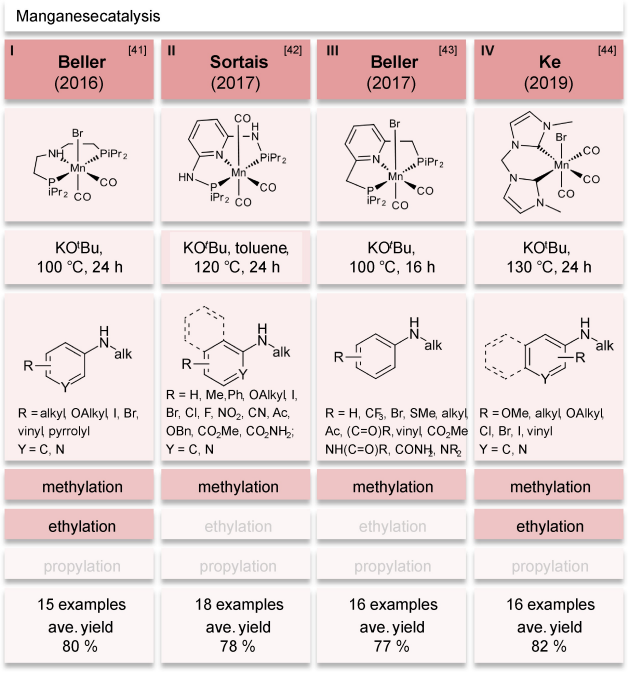


Figure 9. Methods for mono-selective N-alkylation of amines using alcohols as alkylating agents under manganese catalysis.

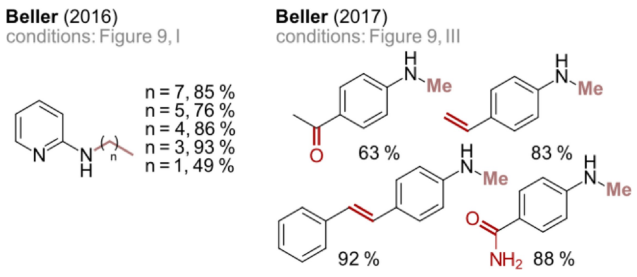
(Figure 9, II). Small quantities of KO^{t}Bu (20 mol%) were essential to activate the catalytic system through N–H deprotonation. This process led to dearomatization, facilitating the decoordination of a CO ligand to generate the active catalyst. The catalyst in its active state can then dehydrogenate methanol, leading to the formation of formaldehyde. This transformation further proceeds with the creation of a metal-hydride complex, which subsequently participates in the catalytic cycle for hydrogen autotransfer reactions as previously described. Primary aromatic amines as well as sulfonamides could be readily methylated at 120 °C giving the desired products in isolated yields between 42–98%. Interestingly, an acidic phenol substituent completely inhibited the reaction.

In the same year, the group of Beller published a second-generation pyridine-based manganese PNP-pincer complex with enhanced reactivity, even under milder conditions (100 °C instead of 120 °C) and shorter reaction times[43] (Figure 9, III). This remarkable catalytic system successfully N-methylated a diverse range of primary aromatic amines with complete mono-selectivity, giving the desired products in up to 93% yield. Notably, anilines containing a stilbene or vinyl group could be readily methylated without affecting the double bond. Furthermore, amide and ketone functional groups remained unaltered (Scheme 9). However, nitrile substituents hampered the reaction giving only 3% of the desired product. Interestingly, when benzyl or hexylamine were used as the substrates, the imine was the predominant product.

In 2019, Ke's group developed a manganese phosphine-free catalytic system with NHC-ligands, to enable the N-alkylation of anilines with alcohols[44] (Figure 9, IV). Remarkably, this catalytic system operated at room temperature, after activation by KO^{t}Bu, when long-chain aromatic and aliphatic alcohols were employed as alkylating agents (RCH_2OH with $R \neq H$). Notably, N-ethylation of aniline could be achieved at room temperature giving the product in 70% yield. However, for N-methylation higher temperatures (100 °C) were still required to yield the desired mono-methylated products in 53–94% yield.

2.1.6. Iron catalysis

Iron, the most abundant transition metal in the Earth's crust, holds great promise for sustainable, non-precious metal catalysis. Recognizing the environmental benefits of iron-based



Scheme 9. Short-chain N-alkylations (left) under manganese catalysis and the presence of reducible groups unaltered under the given reaction conditions by the group of Beller (ref. [41, 43]).

catalysis, Poater, Renaud and colleagues investigated the use of iron-containing catalytic system for N-alkylation of amines with alcohols[45] (Figure 10, I). Their investigation unveiled the efficacy of an iron(0) tricarbonyl complex equipped with a cyclopentadienone ligand as catalyst in hydrogen autotransfer reactions, facilitating the N-methylation and N-ethylation of primary amines. In-depth mechanistic insights, derived from a combination of DFT calculations and experimental observations (Scheme 10), highlight the pivotal role of CsOH (10 mol%) as base in facilitating the release of a CO ligand. Additionally, the significance of H_2 pressure is emphasized, driving the equilibrium toward a catalytic intermediate responsible for the reduction of the imine to the desired alkylated amine. This phenomenon becomes apparent when considering that intermediate **5d** can follow two pathways: direct hydrogen release to intermediate **5g** or methanol-assisted indirect hydrogen cleavage toward intermediate **5e**. DFT calculations revealed that the second pathway is 9.6 kcal/mol more energy-demanding. Consequently, external hydrogen pressure could shift this equilibrium **(5d–5g)** *via* the second pathway to intermediate **5e**, leading to the desired reduction of the imines. As observed in analogous transition-metal catalyzed N-alkylations using hydrogen borrowing strategies, mono-selective alkylation is attainable for primary aromatic amines, while overalkylation remains an issue for primary aliphatic amines. Nonetheless, the authors successfully demonstrated the adaptability of their protocol for achieving mono-N-methylation and -ethylation using alcohols at 110 °C across a range of substrates derived from anilines and aminopyridines, giving the desired products with impressive yields of up to 99% for both the methylated and ethylated species.

Concurrently, the Morrill group introduced a protocol employing a Knölker-type (cyclopentadienone)iron carbonyl pre-catalytic system, activated by trimethylamine *N*-oxide (4 mol%)[46] (Figure 10, II). K_2CO_3 served as the base and the reaction was performed in MeOH at a remarkably low temperature of 80 °C for 24 hours. However, it became apparent that employing a mixture of MeOH and toluene (1:1) led to a substantial reduction in reaction yield, emphasizing the critical role of utilizing the alcohol itself as the reaction medium. While the authors concentrated primarily on the methylation of

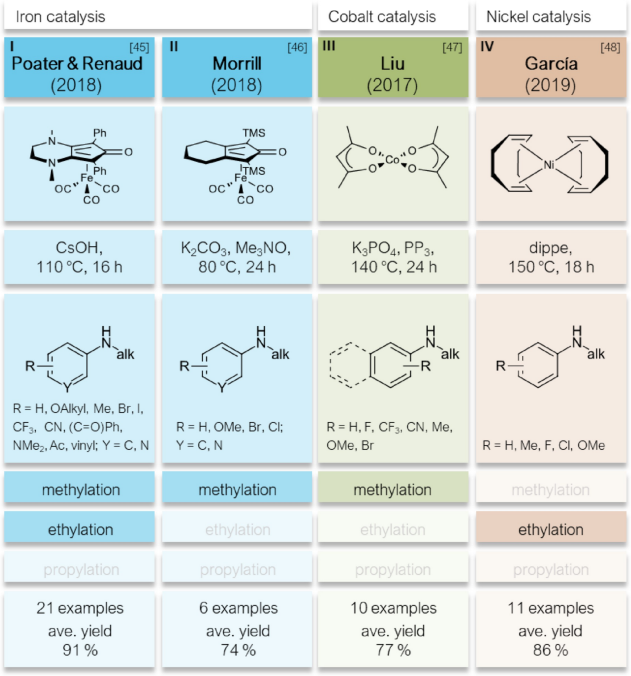
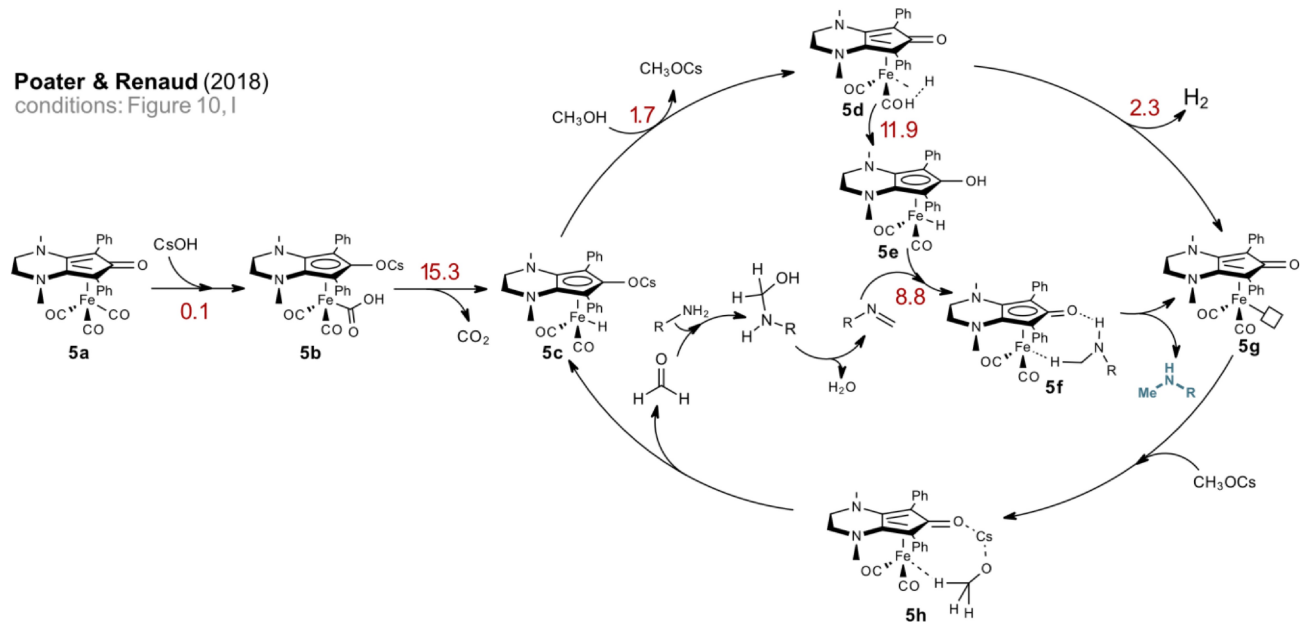


Figure 10. Methods for mono-selective N-alkylation of amines using alcohols as alkylating agents under iron-, cobalt-, and nickel-catalysis.



Scheme 10. Proposed catalytic pathway for the iron-catalyzed N-alkylation of amines using alcohols by Poater & Renaud (the red numbers display the relative energy for transition states in kcal/mol) (ref. [45]).

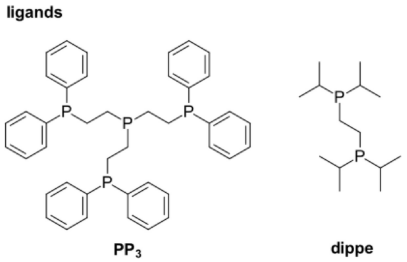
indoles and ketones, they presented only a handful of instances showcasing selective mono-methylation of primary aryl amines, resulting in yields ranging from 54 to 87%.

2.1.7. Cobalt-catalysis

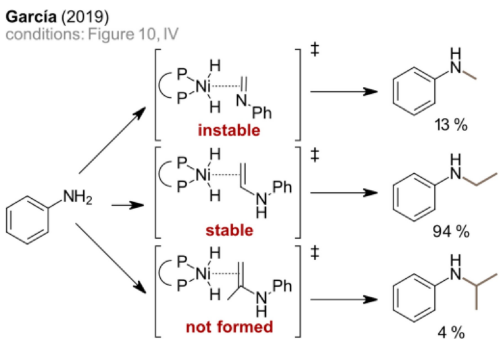
In 2017, Zhenghui Liu *et al.* reported the successful application of a cobalt-catalyzed N-methylation of amines using methanol[47] (Figure 10, III). Their catalytic system was generated *in situ*, combining readily available $Co(acac)_2$ with the tetradentate ligand $P(CH_2CH_2PPh_2)_3$ (PP_3) (Scheme 11, left), which was then activated with K_3PO_4. The mono-methylation of aniline-derived substrates was successfully carried out at 140 °C, withyields ranging from 82% to 95%. Primary and secondary aliphatic amines, however, were found to undergo complete bis-methylation under this protocol.

2.1.8. Nickel catalysis

In 2019, Medina and García described the use of a homogenous nickel catalyst for the N-alkylation of aniline derivatives using alcohols[48] (Figure 10, IV). Their catalytic system comprised a $[Ni(cod)_2]$ pre-catalyst and the dippe ligand (Scheme 11, right), forming the catalytic active species [Ni(cod)(dippe)] *in situ*, eliminating the need for an external base. Notably, their system exhibited good conversions when employing ethanol as the alkylating agent, while methanol or propanol resulted in maximum conversions of only 13%. They proposed a hypothesis that the imine, which forms after the dehydrogenation of methanol, might be inherently unstable, resulting in a lower selectivity towards the N-alkylated product (Scheme 12). In contrast, with 2-propanol, it appeared that the generated ketone did not lead to the formation of the corresponding iminium intermediate at all. They successfully ethylated 11 differently substituted anilines at 150 °C over an 18-hour reaction period, achieving high mono-selectivity and conversion rates ranging from 30% to quantitative yields.



Scheme 11. Ligands applied in cobalt- (left) and nickel-catalyzed (right) N-alkylation of primary amines by Liu (ref. [47]) and García (ref. [48]).



Scheme 12. Stability of potentially formed imine species in the catalytic N-alkylations of amines under nickel-catalysis by Medina & García (ref. [48]).

Remarkable progress in Ni-catalyzed N-alkylations using short-chain aliphatic alcohols has also been achieved through heterogeneous catalytic systems such as Raney-Nickel or Ni-nanoparticles, which will be discussed in more detail below.

2.1.9. Heterogenous catalytic systems

Amidst the growing demand for more sustainable and eco-friendly processes, the reusability and recyclability of catalysts have become increasingly important. Unlike homogeneous catalytic systems, heterogeneous catalysts are often easier to separate and reuse, and can even be employed in fixed bed flow reactors. Over the past 15 years, numerous heterogeneous catalytic systems have been developed for efficient and selective N-alkylations using aliphatic alcohols. The catalytically active species can be immobilized on inorganic carrier materials,[49] charcoal,[50] used directly as metal nanoparticles,[51] or coordinated with organic frameworks.[52]

Immobilized metals on charcoal, such as Pd/C, are widely recognized as versatile catalysts for various hydrogenation reactions, including reductive amination, carbonyl reduction, and imine reduction, among others. It is logical to consider their potential application in N-alkylation using alcohols.

In 2019, the Natte research group introduced a protocol for mono-selective N-methylation, employing 10 mol% Pd/C and KO^tBu in methanol at 130 °C[50a] (Figure 11, I). Their primary focus was on the N-methylation of nitroarenes using methanol as both C1 and H_2 source. Regarding the direct and mono-selective methylation of primary amines with methanol, only 4 examples were provided in yields between 91% and 98%.

However, in the same year, Guo, Hou, and co-workers expanded this limited scope to encompass a broader range of substrates[50c] (Figure 11, II). They utilized 2 mol% of Pd/C and 2 equiv. of NaO^tBu at 150 °C to N-methylate 17 different aniline derivatives, achieving yields of up to 92% with 4 reactions performed on a gram scale. Again, no mono-selectivity is achieved for primary aliphatic amines.

A similar catalytic system employing Pt/C, NaOH, and methanol at 150 °C for N-methylation of primary amines was reported by Siddiki, Shimizu and colleagues[50b] (Figure 11, III). In addition to achieving mono-N-methylation of primary aromatic amines (8 examples, 81–98%), they successfully attained high mono-selectivity for primary aliphatic amines by applying an additional H_2 pressure of 40 bar (4 examples, 74–86%).

Recently, the Cui research group introduced a series of heterogeneous Pd/Zn(Al)O catalysts, characterized by a Zn/Al ratio of 10:1[49h] (Figure 11, IV). These catalysts enabled the

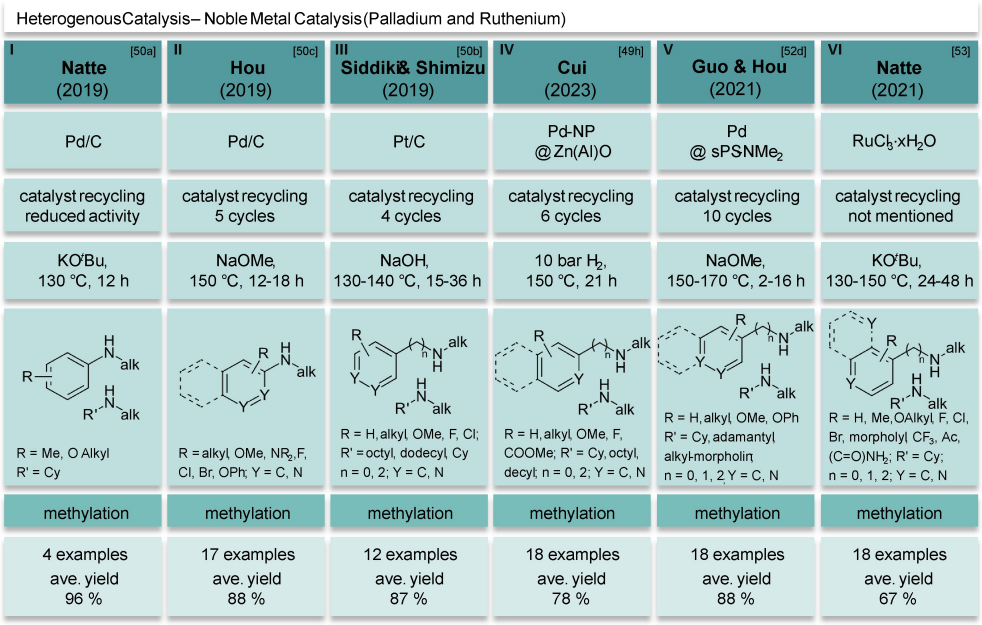


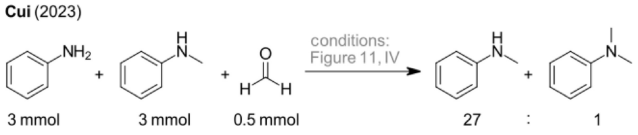
Figure 11. Methods for mono-selective N-alkylation of amines using alcohols as alkylating agents under heterogenous noble metal catalysis.

mono-selective N-methylation of primary aromatic and aliphatic amines using methanol. Importantly, this method required no additional base, as the inherent basic properties of the catalyst were sufficient to facilitate the formation of the desired amines. The authors also demonstrated the remarkable durability of their system by recycling the catalyst six times without any significant decrease in efficiency. Under an external H_2 pressure of 10 bar and a reaction temperature of 150 °C, they achieved the synthesis of several N-methylated aromatic and aliphatic secondary amines with yields ranging from 44% to 94%. The remarkable mono-selectivity of this system was demonstrated by a competitive reaction of a 1:1 mixture of aniline and N-methylaniline with formaldehyde yielding the mono- vs. bis-methylated product in a 27:1 ratio (Scheme 13).

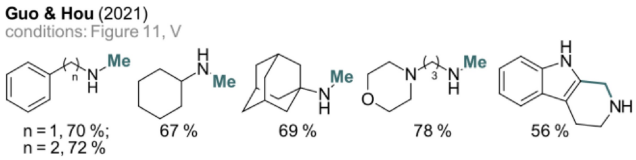
In 2021, the Guo and Hou research group reported an outstanding mono-selectivity in heterogeneous Pd-catalyzed N-methylation of both aliphatic and aromatic amines, without the need for external hydrogen pressure[52d] (Figure 11, V). Their catalytic system involved Pd nanoparticles supported by syndiotactic polyaminostyrene (Pd@sPS-NMe_2), known for its high amine-adsorbing capacities. Additionally, the catalyst could be easily recovered by filtration and reused more than ten times without any loss of reactivity. They employed 2 equiv. of $NaOCH_3$ as the base and conducted the reaction at 150 °C for aromatic amines, yielding products with average yields exceeding 90%. For aliphatic amines, the reaction was carried out at 170 °C, achieving average yields greater than 70% (Scheme 14).

In 2021, the Natte research group introduced an elegantly simple yet highly effective catalytic system for mono-N-methylation[53] (Figure 11, VI). They utilized relatively cheap and readily available $RuCl_3 \cdot xH_2O$ as a ligand-free catalyst in the mono-selective N-methylation of primary amines. The reactions were carried out at 130–150 °C for 24–48 hours, employing KO^{t}Bu as the base in a sealed tube under ambient air conditions. This straightforward approach demonstrated its versatility, with a variety of aniline-derived substrates being successfully mono-methylated, yielding products with up to 94%, and aliphatic primary amines achieving up to 77% yield. Upon completion of the reaction, the catalyst could be effortlessly removed *via* simple filtration.

As previously mentioned, iridium stands out as a highly favored noble metal for catalytic hydrogen autotransfer reactions leading to N–C bond formation with alcohols. This trend is further reflected in the prominent presence of iridium in heterogenous catalysts for these reactions. A pioneering work in this field was made by the group of Tu in 2017[52a] (Figure 12, VII). They incorporated the active iridium metal into NHC coordination assemblies, obtaining a solid and easily prepared



Scheme 13. Mono-selectivity in the heterogenous Pd-catalyzed reaction of aniline by Cui applying a 1:1 mixture of mono- and bis-methylated aniline yielding primarily the mono-methylated species (ref. [49 h]).



Scheme 14. Scope of aliphatic primary amines in the N-methylation using a heterogenous Pd-nanoparticle catalyst by Guo & Hou (ref. [52d]).

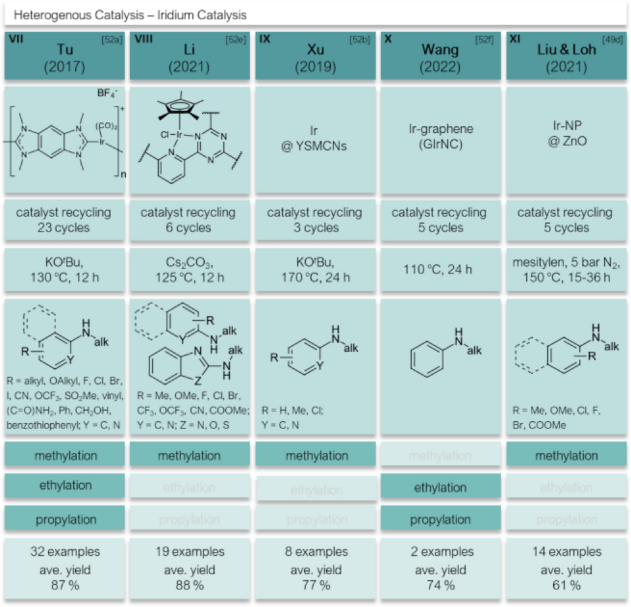
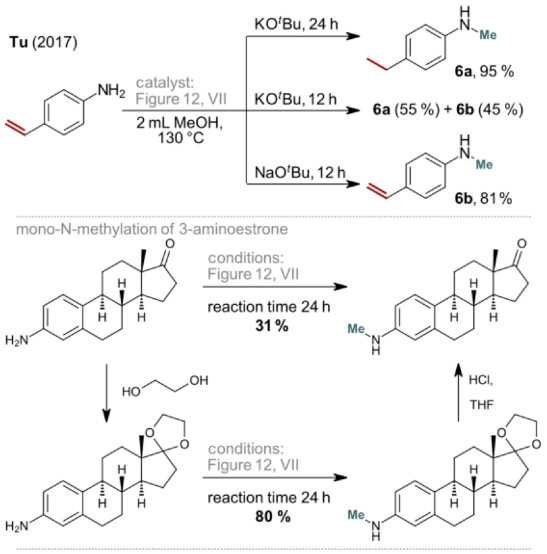


Figure 12. Methods for mono-selective N-alkylation of amines using alcohols as alkylating agents under heterogenous iridium-catalysis.



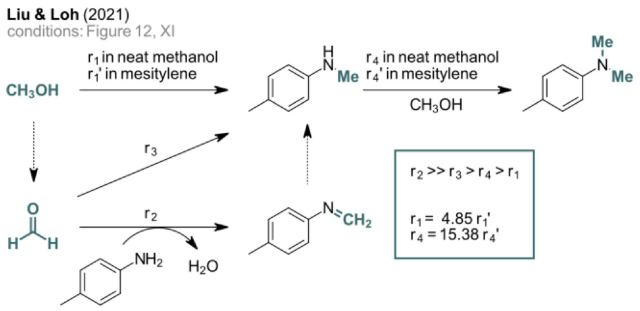
Scheme 15. Base and reaction time dependent selectivity in the *N*-methylation and vinyl reduction under heterogenous iridium-catalysis (top) and late-stage *N*-methylation by the group of Tu (ref. [52a]).

molecular catalyst. Impressively, this catalyst demonstrated recyclability and could be reused up to 20 times without a significant loss in reactivity. Operating with 0.5 mol% of the catalyst and 1 equiv. of KO^{t}Bu, they successfully achieved the mono-selective N-methylation of 29 different substrates derived from aniline at 130 °C within 12 hours. Interestingly, they observed that besides N-methylation, the double bond in 4-aminostyrene was reduced when using KO^{t}Bu as the base over a 24-hour reaction period. However, when they switched to NaO^{t}Bu as the base and reduced the reaction time to 12 hours, solely N-methylation occurred with the vinylic double bond being unreacted (Scheme 15, top). A remarkable demonstration of the method's applicability for late-stage modification of biologically active compounds, was the methylation of 3-aminoestrone in 31% yield when the ketone moiety was present as a free ketone and an 80% yield when the ketone moiety was protected as an acetal (Scheme 15, bottom). Although N-ethylation and N-propylation were feasible, the yields were significantly lower, standing at 59% and 29%, respectively.

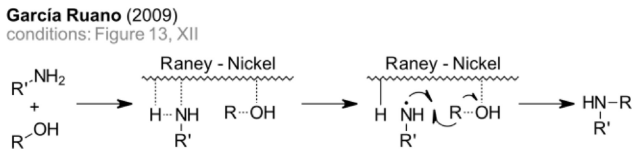
In 2021, Feng Li's group achieved the coordinative immobilization of catalytically active $[Cp^*IrCl_2]_2$ within a functionalized covalent triazine framework (CTF)[52e] (Figure 12, VIII). This catalyst proved to be highly efficient in the N-methylation of aromatic amines with methanol using a very mild Cs_2CO_3 base. Remarkably, the catalyst maintained its reactivity even after six consecutive recycles. Primary aromatic amines were readily methylated using only 0.5 mol% of the iridium-containing catalyst at 125 °C within a 12-hour reaction time, exclusively yielding *N*-mono-methylated products exceeding 80% yield. However, the same mono-selectivity was not observed for aliphatic amines, which resulted in the exclusive formation of di-methylated products.

The group of Xu in 2019 achieved further mono-N-alkylations of aromatic primary amines using an encapsulated Ir-nanocatalyst (Ir@YSMCNs) under basic conditions at 170 °C[52b] (Figure 12, IX). In contrast, Wang's team in 2022 utilized an iridium/graphene nanostructured catalyst under base-free conditions at 110 °C, focusing on N-alkylations with higher carbon aldehydes (RCH_2CHO, $R \neq H$)[52f] (Figure 12, X). While the former group primarily concentrated on N-methylation, the latter group expanded the substrate scope, demonstrating successful N-ethylation and N-propylation with good yields.

In 2021, Liu, Loh and co-workers developed a catalytic system featuring zinc oxide-supported iridium nanoparticles (Ir/ZnO)[49d] (Figure 12, XI). They fine-tuned the catalyst loading and reaction solvent to control the selectivity between mono- and bis-methylation of primary aromatic amines. Notably, higher catalyst loadings (2 mol% Ir) in neat methanol yielded *N,N*-dimethylated products, whereas using only 0.3 wt% Ir/ZnO (0.5 mol%) in mesitylene/methanol mixtures provided mono-N-methylated amines with moderate to good yields (48–83%) at 150 °C and 5 bar N_2 pressure. Kinetic experiments were conducted to elucidate the solvent-dependent mono- vs. bis-methylation, and reaction rates for the individual steps were calculated (Scheme 16). The condensation between the *p*-toluidine and formaldehyde occurred rapidly, indicating a significantly higher rate compared to other involved steps in the reaction. Examining the initial reaction rates for each step revealed a decreasing order of $r_2 \gg r_3 > r_4 > r_1$, with the activation of methanol (r_1) identified as the rate-determining step. Comparison of the initial reaction rates in neat methanol (r_1 and r_4) with those in mesitylene as the solvent (r_1' and r_4') suggested a significant reduction in the overall reactivity in the latter solvent system. Interestingly, the effective suppression of over-methylation of monomethyl amine hinted at mesitylene potentially interfering with the active sites on the catalyst,



Scheme 16. Kinetic studies for the mono- vs. bis-methylation of *p*-toluidine under heterogenous iridium-catalysis by Liu & Loh (ref. [49d]).



Scheme 17. Proposed radical pathway in the N-alkylation of primary amines catalyzed with Raney-Nickel by García Ruano and co-workers (ref. [51a]).

thereby altering absorption and diffusion kinetics in this methylation reaction.

The ability to easily recover and reuse heterogeneous catalysts is a key factor in enhancing the sustainability of chemical processes. Furthermore, the substitution of precious metals with more readily available and cost-effective earth-abundant metals, like nickel, copper, or cobalt is a compelling goal.

García Ruano and colleagues introduced a well-established heterogeneous catalyst, Raney-nickel, for the purpose of mono-selective N-alkylations using alcohols, in 2009[51a] (Figure 13, XII). Their study demonstrated the successful ethylation, *n*-butylation, and *iso*-propylation of various aliphatic and aromatic primary amines, with yields reaching up to 86%. Remarkably, when methanol was used as the alkylating agent, no N-methylated products were observed. In-depth mechanistic investigations excluded a pathway involving hydrogen auto-transfer and the formation of aldehyde intermediates. Instead, the authors proposed a pathway that entails radical intermediates, substantiated by the observation that the reaction was completely inhibited when TEMPO, a radical scavenger, was introduced (Scheme 17).

In 2018, the Barta research group introduced a novel method utilizing *in situ* generated nickel nanoparticles (NiNP) from $Ni(cod)_2$ and KOH at 140 °C in cyclopentyl methyl ether (CPME)[51b] (Figure 13, XIII). The formation of NiNP as the catalytically active species was firmly substantiated through various control experiments and transmission electron microscopy (TEM). Mono-N-alkylation of aniline was successfully achieved with a range of aliphatic alcohols, yielding moderate results for N-methylation (38%) and more favourable results for N-ethylation (69%). The versatility of this method was exemplified through the N-butylation of 18 different primary amines, yielding products in the range of 25–86%. While the catalyst could be recycled, a gradual reduction in substrate conversion was observed over time.

Furthermore, an innovative approach for N-methylation with methanol, employing ZnAlOx-600 supported NiNP, was recently developed by Liu, Zhang and co-worker[49g] (Figure 13,

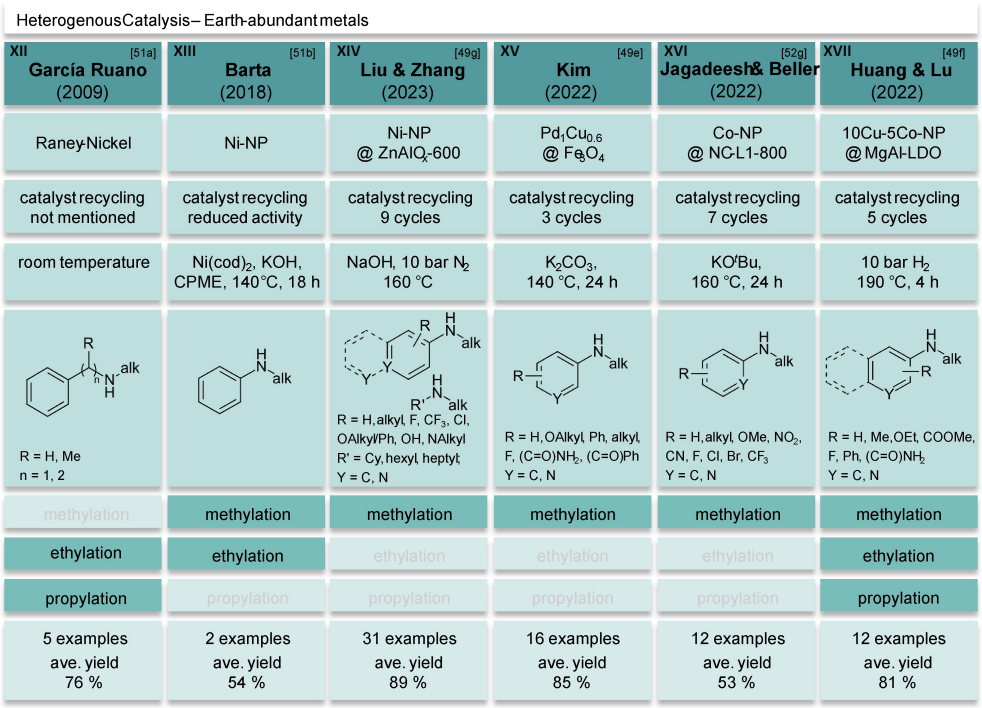


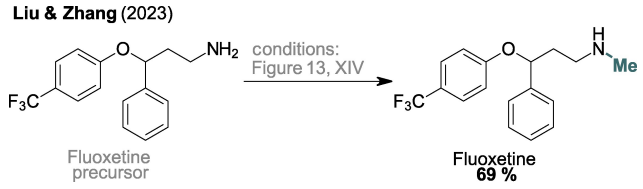
Figure 13. Methods for mono-selective N-alkylation of amines using alcohols as alkylating agents under heterogenous earth-abundant metal-catalysis.

XIV). Notably, this method marked a significant advancement in Ni-catalyzed hydrogen autotransfer reactions. It not only enabled the mono-selective methylation of primary aromatic amines but also showed no undesired overalkylation with primary aliphatic amines. The reactions were conducted at 160 °C in methanol, with the addition of 25 mol% NaOH at a nitrogen pressure of 10 bar. The approach delivered an exceptionally high average isolated yield of 87% for 31 different primary amines. This methodology's remarkable effectiveness was exemplified in the final step of the synthesis of fluoxetine, a drug produced with 69% isolated yield (Scheme 18).

The Kim research group introduced a protocol for the selective N-methylation of aromatic amines using MeOH. They employed a PdCu alloy (1:0.6 ratio) supported on Fe_3O_4, which exhibited superior catalytic activity compared to monometallic Pd and Cu catalysts[49e] (Figure 13, XV). This innovative catalyst enabled the mono-selective N-methylation of various primary aromatic amines at an average yield of 85% when using K_2CO_3 as a very mild base. A remarkable feature of this catalyst is its solid support with ferromagnetic properties, facilitating easy catalyst separation and recycling.

In 2022, Jagadeesh, Beller and co-workers established a method for the mono-N-alkylation of amines and ammonia with alcohols, catalyzed by reusable Co-nanoparticles supported on *N*-doped carbon (Co@NC–L1-800)[52g] (Figure 13, XVI). The versatility of their new catalytic system was confirmed by N-alkylating over 100 substrates using different aromatic and aliphatic alcohols. Concerning short-chain, unbranched alcohols, they were able to selectively mono-methylate 11 different aromatic amines at 160 °C in methanol, albeit with moderate yields ranging from 24% to 67%.

In the same year, Huang, Lu, and their team developed a bimetallic catalytic system employing CuCo nanoparticles for mono-N-methylations[49f] (Figure 13, XVII). This innovative approach uses the support-dependent regulation of the degree of substitution by rationally integrating acid-base and metal sites. They obtained *N,N*-dimethylated products using Cu–Co on an Al_2O_3 support, while mono-*N*-methylated products were produced using Cu–Co on a Mg–Al layered double hydroxide (MgAl-LDO) support. Notably, no additional base was required for either system. They selectively mono-methylated a range of primary aromatic amines in MeOH at 190 °C and 10 bar H_2 pressure using 10Cu-5Co/MgAl-LDO, achieving yields of up to 95%. Remarkably, N-ethylation, N-propylation, and N-butylation were also feasible for aniline, yielding mono-alkylated products with 84–85% yields.



Scheme 18. Mono-selective N-methylation of a precursor in the final step of the synthesis of Fluoxetine under heterogenous nickel-nanoparticle catalysis by Liu, Zhang and co-workers (ref. [49 g]).

Heterogeneous metal-catalyzed N-alkylations with alcohols *via* hydrogen borrowing strategy usually necessitate high reaction temperatures, leading to high internal pressures. This often requires the use of specialized pressure equipment, such as autoclaves, which many small to medium-sized chemical labs lack. Therefore, finding new catalytic systems with comparable activity and performance at even lower temperatures and pressures is highly desirable. One alternative approach to provide the energy required for these reactions, even at room temperature, is the use of light irradiation. Remarkable efforts in photocatalytic mono-N-alkylations of amines with alcohols were made by Shiraishi *et al.* in 2013[49a] (Figure 14, XVIII). They employed a catalytic system that featured Pd nanoparticles immobilized on a photoactive TiO_2 surface in a defined ratio ($Pd_{0.3}/TiO_2$).

Mechanistic investigations unveiled a tandem photocatalytic/catalytic process comprising three consecutive stages (Scheme 19). First, the alcohol is oxidized on the photoactivated

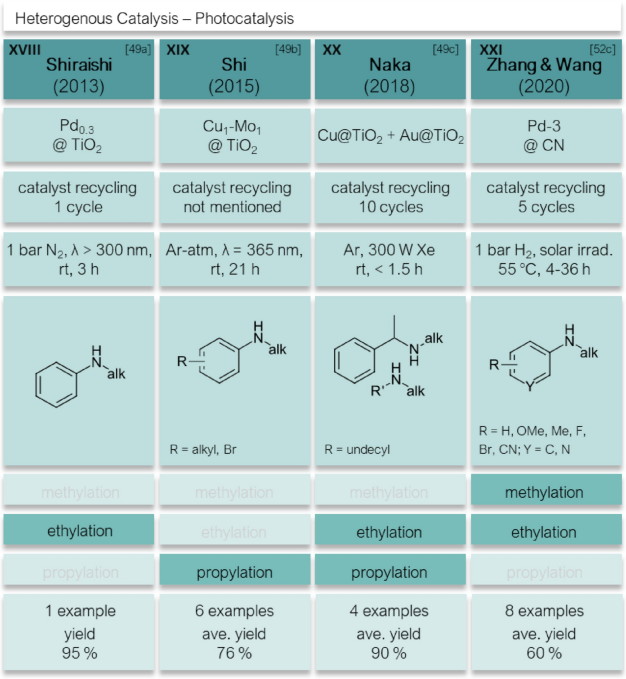
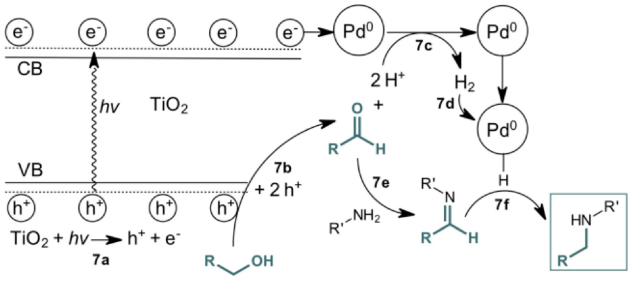


Figure 14. Methods for mono-selective N-alkylation of amines using alcohols as alkylating agents under heterogenous earth-abundant metal-catalysis.



Scheme 19. Mechanism for the photocatalytic N-methylation of amines using a heterogenous TiO_2/Pd catalytic system by Shirashi *et al.* (VB = valence band; CB = conduction band) (ref. [49a]).

TiO_2-surface (**7b**). Subsequently, the resulting aldehyde readily undergoes a condensation reaction with the amine (**7e**). Finally, the formed imine is reduced by surface hydrogen atoms on the Pd-surface (**7f**). These reactions were conducted at room temperature in the respective alcoholic solvent at 1 bar N_2 pressure under base-free conditions with $\lambda > 300$ nm. While the work presented only two examples of N-alkylation with short-chain alcohols, specifically N-ethylation (95% yield) and N-butylation (91% yield) of aniline, it highlighted the potential of photocatalysis in these catalytic systems. Similar approaches were used by the Shi research group in 2015[49b] (Figure 14, XIX), employing a Cu–Mo/TiO_2 catalyst, and the Naka research group in 2018[49c] (Figure 14, XX) using Cu/TiO_2 and Au/TiO_2 mixed systems. In both protocols, mono-selectivity in N-alkylation of primary amines was only observed for some higher alcohols (RCH_2OH, $R \neq H, CH_3$). Remarkably, the latter protocol by Naka's group allowed for a solvent-controlled selectivity of the mono- vs. bis-alkylated products. For α-methyl benzylamine and undecylamine, mono-selective N-ethylation and N-propylation could be achieved when hexane was used as solvent for the reaction. In contrast, when the reactions were performed in alcoholic solvent, the *N,N*-bis-alkylated products were obtained exclusively.

A more general photocatalytic approach for the mono-selective N-methylation of primary anilines was established by Zhang, Wang, and Gao in 2020[52c] (Figure 14, XXI). They used a Pd loaded mesoporous carbonitride (mpCN) based Mott-Schottky catalyst with a palladium to CN ratio of 3:1 (Pd-3@CN). The authors demonstrated that the primary oxidation zones of the catalyst were located at the CN, promoting aldehyde formation, while Pd nanoparticles were the primary reduction sites. Under 1 bar H_2 pressure and visible light irradiation (300 W Xenon lamp), several primary aromatic amines could be methylated with methanol in yields up to 99%. Mono-selectivity, however, could not be guaranteed for every substrate used within the protocol, as some para-substituted ones predominantly formed *N,N*-dimethylated products. Notably, aniline could be mono-selectively ethylated and butylated under the given reaction conditions with ethanol or *n*-butanol as the solvent.

Considering the recent progress in photocatalytic systems for N-alkylation reactions with alcohols, there is still room for improvement, especially regarding mono-selectivity when using primary aromatic and aliphatic amines. Nevertheless, these novel photocatalytic approaches offer remarkable user-friendliness and align with evolving environmental standards.

2.2. Aldehydes

The Eschweiler-Clarke reaction, a method for alkylating amines with aldehydes, has a long history in organic synthesis. However, recent developments have introduced advanced methods using aldehydes as efficient alkylating agents. These modern approaches place a strong emphasis on achieving high mono-selectivity in the alkylation of primary amines.

In 2007, the group of Rhee disclosed an innovative protocol for the reductive mono-N-alkylation of anilines using aldehydes[54] (Figure 15, I). Their method relied on a Pd/C catalyst and ammonium formate as the hydrogen source in aqueous alcoholic media (*i*-PrOH/H_2O 10:1) at room temperature (Scheme 20). While the use of formaldehyde yielded mono-N-methylated products in moderate yields (≤50%), the aldehydes ethanal and propanal exhibited exceptional reactivity, resulting in excellent yields exceeding 90%. Notably, the catalyst demonstrated impressive recyclability, maintaining its activity for up to 10 cycles without a significant decrease in performance.

In 2016, Métay, Lemaire and colleagues established a protocol which expanded the so far narrow scope for mono-N-methylation using aldehydes and, besides aryl amines, also including primary aliphatic amines[55] (Figure 15, II). In this protocol CaH_2 served as the hydrogen source, giving access to a variety of methylated amines in moderate yields (11–80%).

Motivated by the achievements of Métay and Lemaire in the field of atom-efficient catalysis, Shi's research group endeavored to create a cost-effective and highly efficient catalytic system,

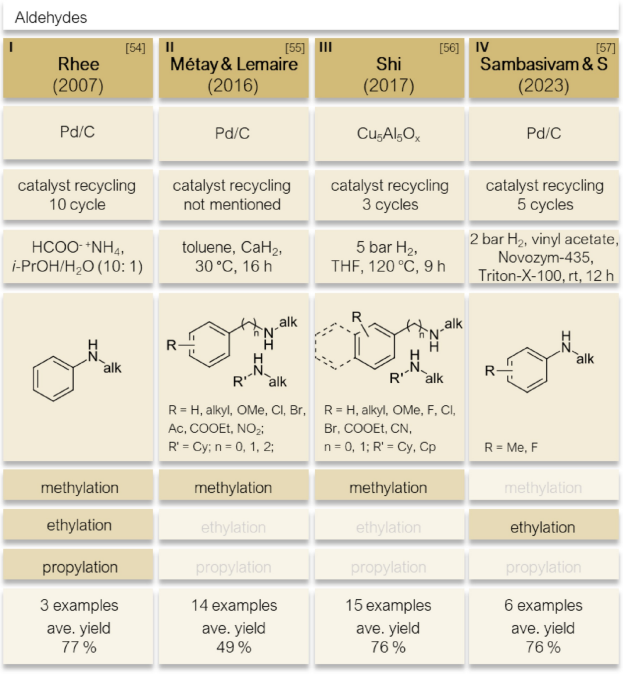
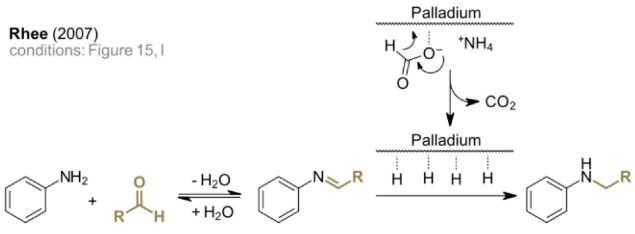


Figure 15. Methods for mono-selective N-alkylation of amines using aldehydes as alkylating agents.



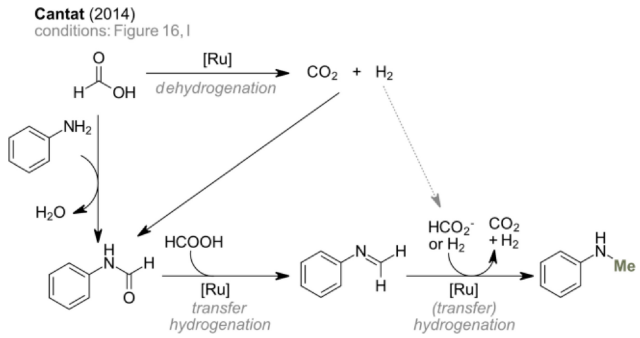
Scheme 20. Proposed mechanistic pathway for the mono-N-alkylation of amines with aldehydes under Pd-catalysis by Rhee and co-workers (ref. [54]).

with a particular focus on its potential for industrial applications[56] (Figure 15, III). Their groundbreaking protocol, developed in 2017, harnessed the atom-economical reductant H_2 under a moderate pressure of 5 bars, in conjunction with $CuAlO_x$ as a remarkably active catalyst. These reactions took place in THF at 120 °C, performing mono-selective methylation of various aromatic and aliphatic amines with good to excellent yield, using paraformaldehyde as C1 source. Notably, the authors speculated that the active species in this catalytic system might even be pure metallic copper.

In the realm of chemoenzymatic processes, an unconventional yet promising strategy for aldehyde formation and subsequent selective N-alkylation of primary amines was recently published by Ganesh, Sambasivam, and S[57] (Figure 15, IV). In this process, acetaldehyde is formed in situ from vinyl acetate, facilitated by Candida antartica Lipase-B (CALB)/ Novozyme-435. Subsequently, this acetaldehyde undergoes reductive amination. Notably, this method is distinguished by its exceptionally mild reaction conditions, conducted at only 2 bars of H_2 pressure and at room temperature. The reduction of the imine is catalyzed by Pd/C. This methodology has been demonstrated to achieve mono-N-ethylation for six different aniline derivatives in up to 85% yield, and while isopropylation is also feasible, it falls beyond the scope of this review.

2.3. Carboxylic Acids

Carboxylic acids, due to their industrial-scale production and non-toxic nature, have the potential to serve as valuable alternatives in alkylation reactions. However, applying them in amine alkylation typically demands high temperature and pressure conditions, making them more suitable for large-scale industrial applications than small-scale laboratory setups.



Scheme 21. Proposed catalytic pathway for the mono-N-methylation of primary amines using formic acid as alkylating agent under ruthenium catalysis by the group of Cantat (ref. [58]).

In 2014, Cantat's group introduced a groundbreaking method for the direct methylation of amines using formic acid, which not only served as the carbon source but also as the hydrogen source[58] (Figure 16, I and Scheme 21 for catalytic pathway). Their catalytic system featured Ru(cod)(methylallyl)$_2$ (1 mol%) and triphos (1 mol%) in THF at 150 °C within a sealed autoclave. Importantly, distinct additives enabled control over the selectivity between mono- and bis-methylation of aniline. When adding 1.5 mol% methane sulfonic acid (MSA) a variety of mono-methylated aniline derivatives were obtained with up to 71% yield. For the synthesis of tertiary amines $HNTf_2$ was employed as the additive.

In the same year, the group of Beller disclosed a different protocol, using higher carboxylic acids in the N-alkylation of primary amines[59] (Figure 16, II). Through systematic optimization, they identified optimal conditions for mono-selective alkylation, using commercially available Karstedt's catalyst ([Pt-(CH_2=$CHSiMe_2$)$_2$O]) with dppe as the ligand in a 1:1 ratio. Astonishingly, this reaction could be performed at 60 °C or even

Carboxylic Acids

I Cantat [58] (2014)	II Beller [59] (2014)	III Beller [60] (2015)	IV Beller [61] (2018)	V Sudararaju [62] (2019)	VI Shang & Fu [63] (2015)	VII Song [64] (2018)	VIII Lin [65] (2020)
Ru(cod)(methylallyl)$_2$ + triphos, MSA	Karstedt's catalyst + dppe	$Ru(acac)_3$ + triphos, $HNTf_2$	$Co(BF_4)_2{\cdot}6H_2O$ + triphos$^{(p\text{-anisole})}$	$[Co(H_2O)_6]^{2+}(BF_4^-)_2$ + triphos	$B(C_6F_5)_3$	catalyst-free	K_3PO_4, 18-crown-6
reductant HCOOH	reductant $PhSiH_3$	reductant H_2	reductant H_2	reductant H_2	reductant PMHS	reductant $H_3B{\cdot}NH_3$	reductant $PhSiH_3$
THF, 150 °C, 17 h	nBu_2O, rt or 60 °C, 18 h	60 bar H_2, THF, 160 °C, 18 h	40 bar H_2, 1,4-dioxane, 100 °C, 24 h	60 bar H_2, nBu_2O, 120 °C, 24 h	toluene, 100 °C, 13 h	MSA, CH_3CN, 60 °C, 5 h	4 Å MS, THF, 80 °C, 12 h
R = H,alkyl, F, Cl,OMe, COOBu, NO_2	R = H, Me, Cl,OMe, F	R = H, Me, Cl, F,OMe, OPh; R' = adamantly	R = H,alkyl, O Me, OPh, SMe, F, Ph, Cl, CH_2OH, $NH(C{=}O)Ph$, $(C{=}O)NH_2$, COOMe, CHCHPh	R = H, Me,OMe		R = H,alkyl methylation of fluoxetine	R = H, Cl, Br, OCF_3, CN, NO_2, CF_3, OMe, SMe,
methylation	methylation	methylation	methylation	methylation	methylation	methylation	methylation
ethylation	ethylation	ethylation	ethylation	ethylation	ethylation	ethylation	ethylation
propylation	propylation	propylation	propylation	propylation	propylation	propylation	propylation
11 examples ave. yield 50 %	6 examples ave. yield 91 %	10 examples ave. yield 77 %	22 examples ave. yield 76 %	7 examples yield 67 %	3 examples ave. yield 73 %	5 examples ave. yield 74 %	10 examples ave. yield 64 %

Figure 16. Methods for mono-selective N-alkylation of amines using carboxylic acids as alkylating agents.

at room temperature, yielding a variety of mono-alkylated aniline derivatives with up to 97% yield and exceptional mono-selectivity. However, a major drawback was the use of over-stoichiometric amounts of $PhSiH_3$ as the reducing agent.

To address this limitation, the same group reported a more sustainable approach using H_2 as the reducing agent for amine alkylation with carboxylic acids. (RCOOH with $R \neq H$)[60] (Figure 16, III). $Ru(acac)_3$ (2 mol%) and triphos (3 mol%) were identified as an efficient catalytic system for the reaction. The degree of alkylation (mono- vs. di-alkylation) was dependent on the amount of the additive $HNTf_2$ used. When 7.5 mol% of the additive was used, the di-alkylated product was obtained almost exclusively, while using only 2 mol% allowed for the mono-selective alkylation of various primary amines with excellent yields. However, the high temperature (160 °C) and pressure (60 bar H_2) required for this reaction necessitate a specialized setup.

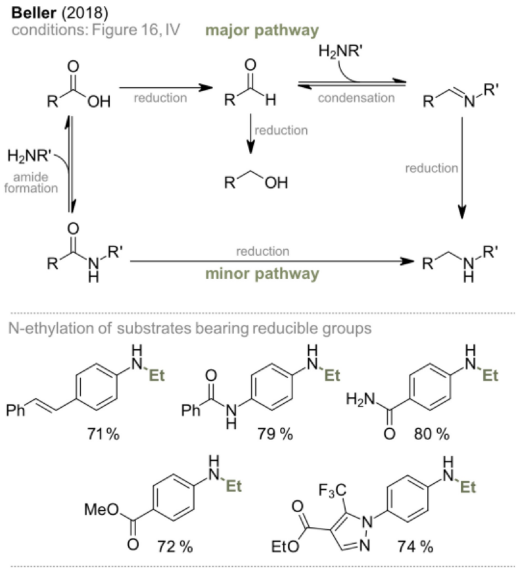
Subsequent refinements by the Beller group introduced a protocol for alkylation of anilines under milder conditions, employing a tailored Co-catalyst, thus eliminating the need for expensive noble metals[61] (Figure 16, IV and Scheme 22 (top) for catalytic pathway). This method also eliminated the use of air-sensitive additives such as $HNTf_2$. A wide range of anilines could be selectively mono-N-ethylated using $Co(BF_4)_2 \cdot 6H_2O$ (3 mol%) as catalyst and triphos(*p*-anisole) as ligand (6 mol%) in dioxane at 40 bar H_2 pressure and 100 °C. However, the method may not ensure mono-selectivity when using formic acid for methylation, as only secondary amines were used in this reaction. However, it is noteworthy that mono-N-ethylation and -propylation were successfully accomplished for a variety of primary aryl amines. Remarkably, substrates containing reducible groups, including amides, esters, or vinylic double bonds, could be selectively ethylated while preserving the integrity of these functional groups (Scheme 22, bottom).

A very similar protocol, using a $Co(BF_4)_2 \cdot 6H_2O$/triphos catalytic system at 60 bar H_2 and 120 °C, was reported by the group of Sundararaju in 2019[62] (Figure 16, V). The scope for mono-ethylation encompasses seven aniline derived substrates with moderate yields.

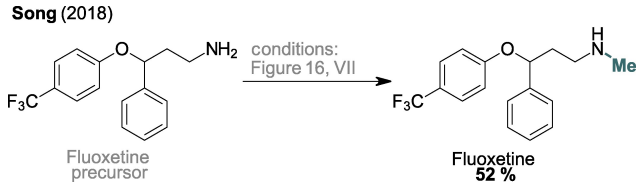
The first mono-selective transition-metal free N-alkylation using carboxylic acids as the alkylating agent was published in 2015 by Shang, Fu, and colleagues employing air-sensitive Lewis-acid $B(C_6F_5)_3$ as the catalyst and an excess of polymethylhydrosiloxane (PMHS) as reducing agent at 100 °C in *n*-Bu_2O[63] (Figure 16, VI). Mono-*N*-methylated aniline was obtained in a moderate yield of 62%, while the ethylation, trifluoroethylation, and propylation of primary anilines proceeded smoothly, yielding up to 81%.

In 2018, Song's group introduced a transition-metal-free approach using stoichiometric ammonia borane ($BH_3 \cdot NH_3$) as the reductant and methane sulfonic acid (MSA) for the alkylation of various aniline derivatives[64] (Figure 16, VII). Under these conditions, aniline underwent mono-methylation with a yield of 81%. Furthermore, mono-ethylation of aniline and two of its derivatives was achieved with remarkable success, affording the product in 84% yield, all at a significantly lower reaction temperature of 60 °C compared to previously reported methods. A noteworthy accomplishment was the successful mono-methylation of the bioactive compound Fluoxetine, with an isolated yield of 52% (Scheme 23).

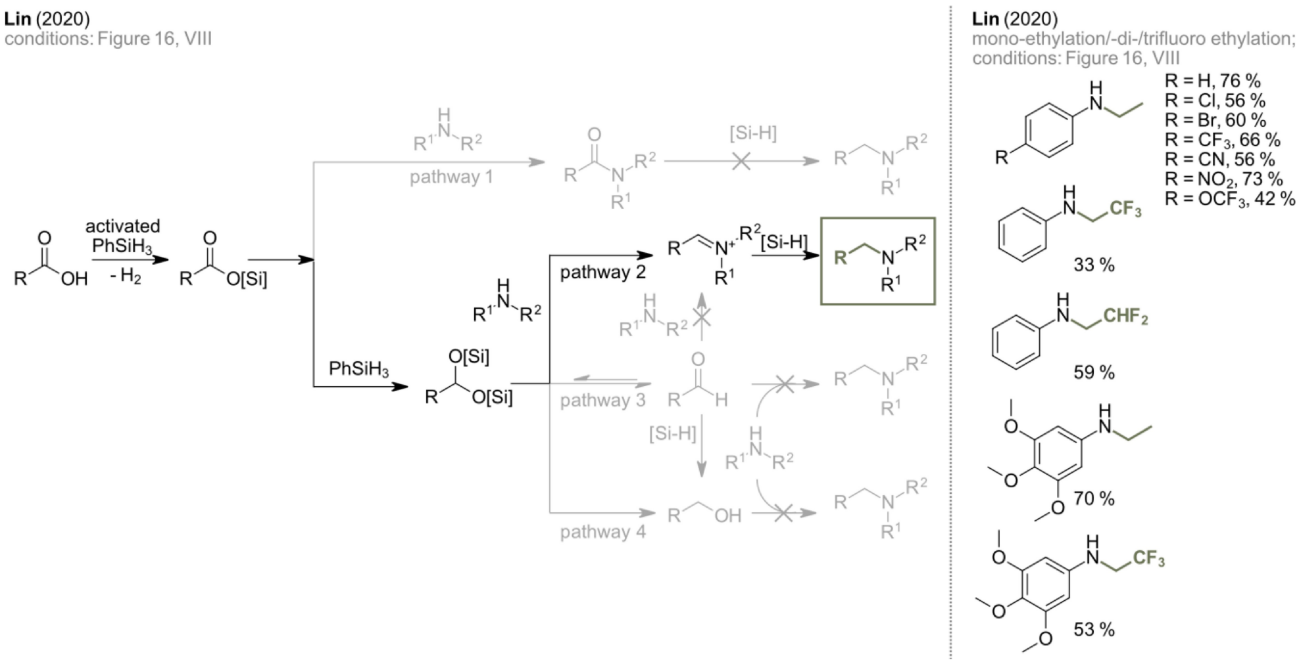
A groundbreaking protocol for the reductive alkylation of primary amines using carboxylic acids was introduced by the group of Lin in 2020[65] (Figure 16, VIII). Their outstanding protocol features an air-tolerant and easy-to-handle transition-metal-free catalytic system. Phenylsilane was applied as super-stoichiometric reductant and K_3PO_4 (10 mol%) in combination with 18-crown-6 (20 mol%) was identified as an efficient catalytic system in THF at 80 °C with small amounts of molecular sieves added. This protocol achieved mono-N-ethylation, -di-, and -trifluoroethylation in moderate to good yields, up to 76%, for various aromatic primary amines (Scheme 24, right). The authors could prove that the reaction pathway diverged from common catalytic pathways, which directly alkylate amines using carboxylic acids and proceed *via* the reduction of a previously formed amide. They identified a distinct pathway *via* the formation of a silyl acetal/hemiacetal, subsequent formation of an iminium intermediate and the reduction thereof (Scheme 24, left).



Scheme 22. Proposed catalytic pathway for the mono-N-methylation of primary amines using carboxylic acids as alkylating agent under cobalt catalysis (top) and the mono-selective N-ethylation of primary amines bearing reducible functional groups (bottom) by the group of Beller (ref. [61]).



Scheme 23. Mono-selective N-methylation of a precursor in the final step of the synthesis of Fluoxetine using formic acid as methylating agent under catalyst-free conditions by Song and co-workers (ref. [64]).



Scheme 24. Proposed reaction pathway in the mono-selective N-alkylation of amines using carboxylic acids as alkylating agents and phenyl silane as reducing agent *via* the formation of a silyl acetal/hemiacetal, subsequent formation of an iminium intermediate and the reduction thereof (left) and mono-N-ethylation, -di-, and -trifluoro ethylation of aniline derivatives (right) by Lin and co-workers (ref. [65]).

2.4. Carbon Dioxide

The utilization of carbon dioxide (CO_2) as an abundant and cost-effective source of C1 for the synthesis of fine chemicals has gained significant attention over recent decades. Particularly in the face of growing concerns about greenhouse gas emissions, the ability to capture and employ CO_2 in the production of high-value chemicals has become increasingly desirable. However, catalytic activation of CO_2 for a defined incorporation into molecules can be a very challenging task, driving ongoing research efforts.

In 2013, Cantat's group achieved a significant breakthrough by pioneering the use of CO_2 as a C1 source in a mono-selective N-methylation reaction[66] (Figure 17, I). They employed $IPrZnCl_2$ as the catalyst and $PhSiH_3$ as the reducing agent. This innovative approach enabled the N-methylation of several primary aryl amines at 100 °C and 1 bar CO_2 pressure within 20 hours in moderate yields. Intriguingly, with an extended

Carbon Dioxide

I [66] Cantat (2013)	II [67] Beller (2013)	III [68] Shi (2014)	IV [69] Shi (2014)	V [70] García (2015)	VI [71] Cortes, Zhu & Liu (2023)	VII [72] Gao (2023)
$IPrZnCl_2$	$Ru(acac)_3$ + triphos, + MSA	$CuAlO_x$	$Pd/CuZrO_x$	$[(dippe)Ni(\mu\text{-}H)]_2$ or $[Ni(cod)_2]$/dcype	Ag/Al_2O_3	DIC
reductant $PhSiH_3$	reductant H_2	reductant H_2	reductant H_2	reductant $PhSiH_3$	reductant H_2	reductant $BH_3{\cdot}SMe_2$
1 bar CO_2, THF 100 °C, 20 h	20 bar CO_2, 60 bar H_2, THF, 140 °C, 5 - 24 h	30 bar CO_2, 60 bar H_2, hexane, 160 °C, 24 h	10 bar CO_2, 25 bar H_2, octane, 150 °C, 30 h	1 bar CO_2, toluene, 100 °C, 20 h	30 bar CO_2, 30 bar H_2, cyclohexane, 230 °C, 24 h	1 bar CO_2, piperazine, toluene, 95 °C, 10 h
R = H, alkyl, OMe, F, Cl	R = H, F, Cl, Br, CF_3, NH_2, OBn, OAlkyl, COOMe	R = H, Me, OMe, Cl, Ph; R' = dodecyl	R = H, Me, OMe, Cl, Ph;	R = H, F; Y = C, N; n = 0, 1; R' = butyl, Cy	R =H, alkyl, NMe_2, Cl, F;	R = H, alkyl, OMe, SMe, NMe_2, F, Cl, Br, I CF_3, Ph, BPin, pyrrolyl
methylation	methylation	methylation	methylation	methylation	methylation	methylation
7 examples ave. yield 45 %	13 examples ave. yield 55 %	7 examples ave. yield 72 %	8 examples ave. yield 69 %	7 examples yield 57 %	21 examples ave. yield 73 %	21 examples ave. yield 60 %

Figure 17. Methods for mono-selective N-alkylation of amines using carbon dioxide as alkylating agent.

reaction time of 72 hours, aniline could be selectively *N,N*-dimethylated with a yield of 79%.

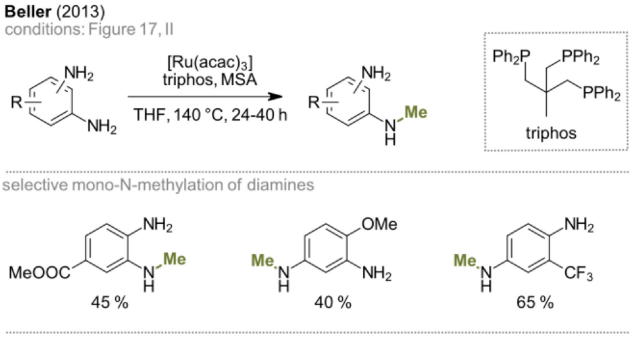
The same year, the group of Beller reported the utilization of ruthenium(III) acetylacetonate [$Ru(acac)_3$], in combination with the triphos ligand and methanesulfonic acid (MSA) as an additive, for the successful methylation of various aryl amines[67] (Figure 17, II). This method encompassed a broad scope for the methylation of secondary aryl amines and remarkably achieved mono-N-methylation for seven *para*-substituted anilines (13–90% yield), three aryl diamines (40–65% yield, Scheme 25) and two *ortho*-substituted anilines (70 and 85% yield) at 140 °C in THF, under 60 bars of H_2 pressure and 20 bars of CO_2 pressure.

Just a year later, in 2014, Shi and co-workers introduced two analogous strategies for achieving mono-selective N-methylation using heterogeneous catalysts in combination with molecular hydrogen and CO_2. Their first protocol featured a $CuAlO_x$ catalyst, allowing control over the degree of methylation in primary amines through variations in reaction time and H_2 pressure. Notably, a reaction time of 48 h at 70 bar H_2 pressure led to bis-methylated amines, while a shorter reaction time of 24 h at 60 bars H_2 exclusively furnished the mono-*N*-methylated products[68] (Figure 17, III). Their subsequent method employed a $Pd/ZrCuO_x$ catalyst, demonstrating mono-selectivity for a divers variety of aryl amines at lower CO_2 and H_2 pressures of 10 bar and 25 bar, respectively[69] (Figure 17, IV).

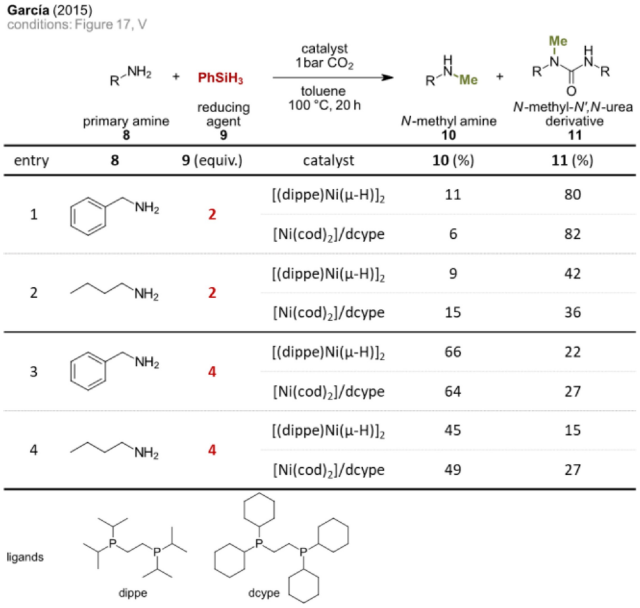
A methylation protocol working at a remarkably low CO_2 pressure (1 atm) was disclosed by the group of Garcia in 2015[70] (Figure 17, V). The reaction was catalyzed by either [(dippe)Ni(μ-H)]$_2$ or [Ni(cod)$_2$]/dcype (Scheme 26, bottom), which exhibited comparable performance, while $PhSiH_3$ served as the reductant. This innovative method enabled the mono-methylation of various primary aromatic and aliphatic amines in toluene at 100 °C, giving moderate product yields and selectivity. The use of four equivalents of the reducing agent was pivotal for obtaining the desired *N*-methylated products, as fewer equivalents resulted almost exclusively in *N*-methyl-*N*′,*N*-urea derivatives (Scheme 26, top).

Recently, Cortes, Zhu, Liu, and co-workers introduced a highly selective protocol for the mono-N-methylation of aniline derivatives using CO_2/H_2 as a C1 source, employing a supported Ag/Al_2O_3 catalyst[71] (Figure 17, VI). The remarkable mono-selectivity was achieved through the reversible binding of the protonated hydrogen, formed upon heterolytic dissociation of H_2 on the Ag surface, to the mono-*N*-methylated amine, thereby reducing its reactivity. A range of primary aryl amines could be methylated at 30 bars CO_2 and H_2 pressure each at 230 °C in yields up to 98%.

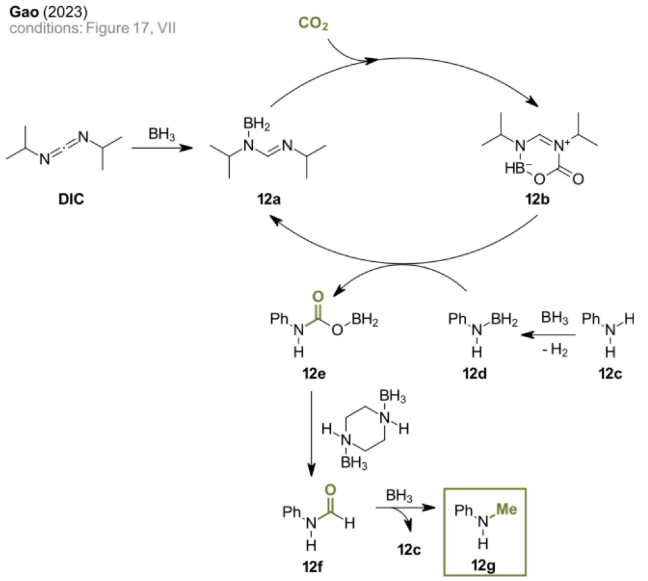
Gao's group recently reported a metal-free protocol for N-methylation at a remarkably low CO_2 pressure of just 1 atm.[72] The reaction was catalyzed by *N,N*′-diisopropylcarbodiimide (DIC), with borane-trimethylamine and borane-piperazine complexes serving as the reducing agents to obtain either *N,N*-dimethylated or *N*-monomethylated products, respectively. Mechanistic insights propose the following sequence (Scheme 27): Initially, DIC undergoes hydroboration, generating an active species **12a** capable of forming a cyclic, zwitterionic intermediate through the intermolecular frustrated Lewis pair capture of CO_2 (**12b**). A previously formed amino borane species **12d** subsequently reacts with **12b** to yield the carbamoyl borate **12e**, concurrently releasing the catalytic frustrated Lewis pair species **12a**. This species undergoes reduction by a borane-piperazine complex to form anilide **12f**, believed to be the rate-determining step. Subsequent reduction leads to the formation of the desired mono-N-methylated product **12g** and aniline **12c**. Presumably, the sterically congested interaction between the borane-piperazine complex and *N*-methyl aniline impedes a second reaction of the mono-methylated product with CO_2. Various primary aryl amines were mono-methylated in toluene at 95 °C in moderate yields ranging from 31–71%.



Scheme 25. Selective mono-N-methylation of various substituted diamines using carbon dioxide as the alkylating agent under ruthenium catalysis by Beller and co-workers (ref. [67]).



Scheme 26. Methylation of primary amines using carbon dioxide as alkylating agent under nickel-catalysis and the crucial role of the reducing agent for controlling the degree of substitution by García and co-workers (ref. [70]).



Scheme 27. Proposed catalytic pathway for the mono-selective methylation of primary amines using carbon dioxide as alkylating agent catalyzed by *N,N'*-diisopropylcarbodiimine (DIC) with a borane-piperazine complex serving as the reducing agent by Gao an co-workers (ref. [72]).

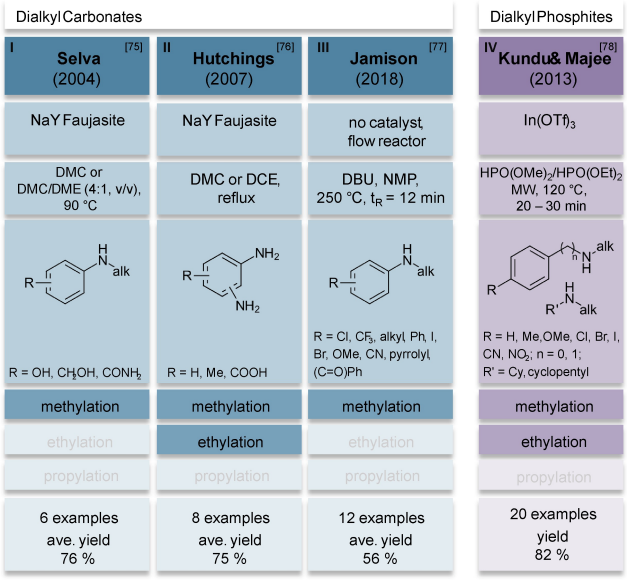
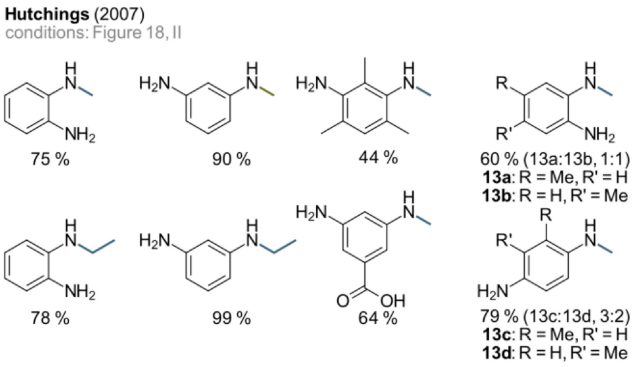


Figure 18. Methods for mono-selective N-alkylation of amines using dialkyl carbonates (I–III) and dialkyl phosphites (IV) as alkylating agent



Scheme 28. Mono-selective alkylation of symmetrical and asymmetrical aryl diamines using dialkyl carbonates as alkylating agent under NaY Faujasite catalysis by Hutchings and co-workers (ref. [76]).

2.5. Dialkyl Carbonates

Alkylations using dialkyl carbonates are considered as environmentally benign processes, releasing alcohol and CO_2 as the sole byproducts. These reagents offer affordability, wide availability, biodegradability, and nontoxicity. However, given their relatively lower reactivity compared to alkyl halides, catalytic activation becomes a necessity.

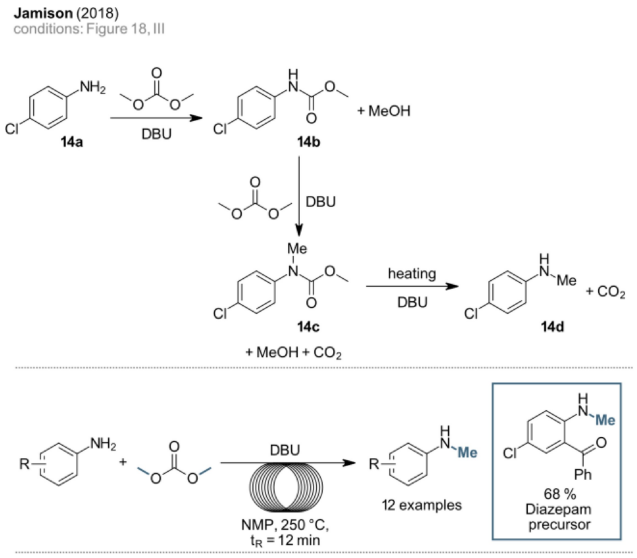
Pioneering works by Fu and Ono[73], Tundo[74], later extended by Selva *et al.*[75], employed zeolite-type catalysts (NaY faujasite). These reports by Selva and colleagues enabled the mono-selective methylation of various primary aromatic amines at 90 °C, using dimethyl carbonate both as the solvent and C1 source, giving quantitative yields with complete mono-selectivity (Figure 18, I). Notably, several aniline-derived substrates bearing free hydroxy, amide, or carboxylic acid groups were selectively N-methylated at the amine moiety while leaving the other functional groups unaltered.

A similar approach using NaY zeolites and dialkyl carbonates as alkylating agents was presented in 2007 by Hutchings and co-workers, expanding the scope of previous research to arylenediamines[76] (Figure 18, II). Remarkably, under reflux conditions with the respective dialkyl carbonate as a solvent, outstanding selectivity was achieved for symmetrically substituted starting materials, yielding up to quantitative yields. For non-symmetric aryldiamines, mixtures of isomers were obtained, yet with a high degree of mono-selectivity for N-alkylation (Scheme 28).

In 2018, Jamison's group introduced a modern approach to mono-N-methylation using a continuous flow setup that enabled safe reactions in superheated solvents (250 °C) under high pressure (7 bars), regulated through a backpressure control unit employing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base[77] (Figure 18, III). The exceptional mono-selectivity observed in this methylation reaction is attributed to an *in situ* protection/deprotection sequence outlined in Scheme 29. Initially, the DMC forms a carbamate with the amine moiety (**14b**), facilitating a single methylation (**14c**). Subsequently, the carbamate undergoes thermal decarboxylation, ultimately yielding the desired mono-N-methylated product (**14d**). This innovative technique successfully transformed various primary aryl amides into their *N*-methyl derivatives with yields reaching up to 96 %. Remarkably, this protocol enabled the synthesis of a key precursor for diazepam, specifically 5-chloro-2-(methylamino)benzophenone, in 68 % yield.

2.6. Dialkyl Phosphites

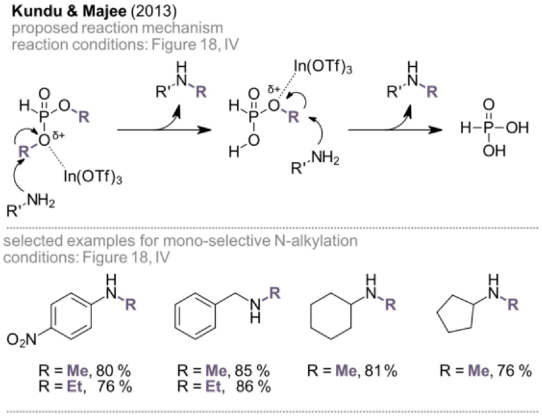
In 2013, Kundu, Mitra, and Majee introduced a groundbreaking method employing dialkylphosphites as alternative alkylating



Scheme 29. Mono-N-methylations in a flow reactor setup (bottom) *via* an *in situ* protection/deprotection approach using dimethyl carbonate as methylating agent (top) and the application in the methylation of a Diazepam precursor (bottom right) by the group of Jamison (ref. [77]).

agents for achieving mono-selective N-alkylation reactions of primary amines, catalyzed by indium triflate ($In(OTf)_3$).[78] The real innovation emerged when microwave irradiation was utilized to facilitate heating under neat conditions for just 30 minutes at 120 °C, significantly enhancing mono-selectivity.

This approach demonstrated exceptional atom efficiency in alkyl transfer from the dialkyl phosphite to the amine, requiring a mere 0.6 equivalents of the alkylating agent (Scheme 30, top). This allowed for the mono-selective N-methylation and N-ethylation of a wide range of para-substituted anilines, benzylamine, and even primary aliphatic amines, such as cyclopentyl- and cyclohexylamine (Scheme 30, bottom). Impressively, this method gave high product yields, ranging from 65 % to 91 %.



Scheme 30. Proposed reaction mechanism for the mono-selective N-alkylation of primary amines using dialkyl phosphites under $In(OTf)_3$ catalysis (top) and selected examples (bottom) by Kundu and Majee (ref. [78]).

2.7. MeX

For decades, alkyl halides, particularly methyl iodide, have served as versatile alkylating agents for a wide array of *O-*, *C-*, and *N*-nucleophiles. However, controlling the degree of alkylation when using MeX with primary amines has been exceedingly challenging.

A strategy exploited by Bar-Haim and Kol in 2004, was harnessing the formation of a stable chelate complex between an γ-amino alcohol and 9-BBN[79] (Figure 19, I). The oxygen is herein covalently bound to the boron, the nitrogen in turn coordinates to the boron (Scheme 31, top). This coordination prevents an overalkylation of the nitrogen, giving solely the mono-*N*-alkylated products with the respective alkyl halides after acidic workup in over 90 % which was demonstrated for 3 different amino alcohols (Scheme 31, bottom).

In 2009, Yebeutchou and Dalcanale presented a distinct approach to "block" the nitrogen from undergoing further alkylation[80] (Figure 19, II). They employed a tetrabridged phosphorylated cavitand in its **iiii** configuration (**Tiiii**), known for its exceptionally high affinity for *N*-methyl ammonium salts

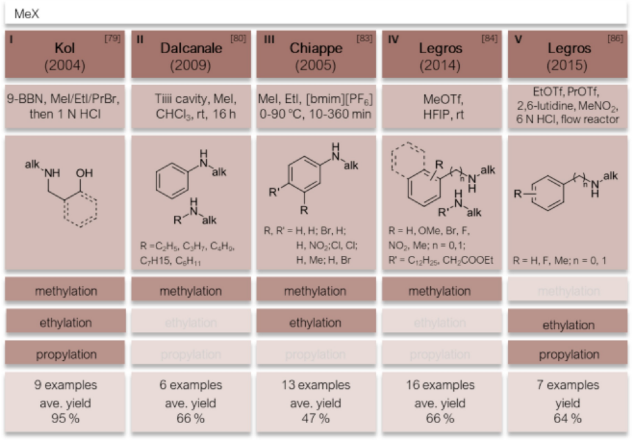
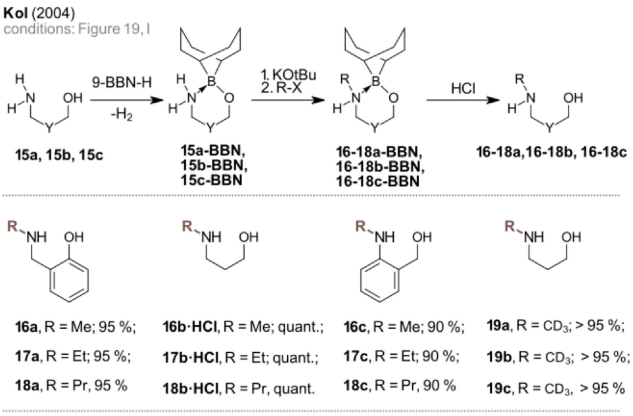


Figure 19. Methods for mono-selective N-alkylation of amines using alkyl halides or alkyl triflates as alkylating agents.



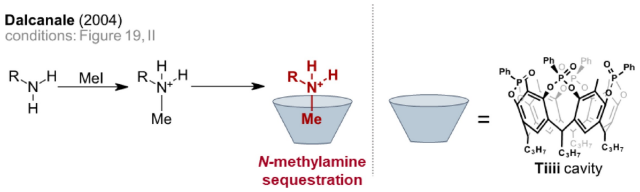
Scheme 31. Mono-selective N-alkylation *via* the formation of a stable borane complex intermediate (top) and scope of thereof by Kol and Bar-Harim (ref. [79]).

(Scheme 32, right).[81] By an efficient sequestration of the mono-methylated intermediate further bis-methylation is hampered, leading to highly mono-selective methylation of five different aliphatic amines and aniline (Scheme 32, left). Excellent isolated yields of up to 87% were achieved using methyl iodide as the alkylating agent. However, it's worth noting that this approach may not be suitable for achieving mono-selectivity with longer alkyl groups.

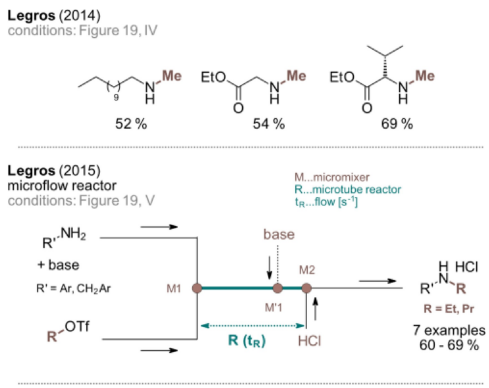
Building on earlier research that explored the manipulation of solute nucleophilicity with room temperature ionic liquids (IL),[82] Chiappe *et al.* introduced a protocol for the synthesis of various mono-*N*-alkylated anilines using the ionic liquid [bmim][PF_6][83] (Figure 19, III). This method yielded mono-*N*-methylated products with moderate yields of up to 60% and mono-*N*-ethylated products with yields up to 77%.

In 2014, the Legros group made a significant discovery, finding exceptional mono-selectivity for N-methylation using MeOTf when hexafluoroisopropenol (HFIP) was employed as the reaction solvent[84] (Figure 19, IV). Their reasoning was based on previous observations that HFIP deactivated secondary and tertiary amines but not primary amines.[85] This conclusion led them to predict that alkylation would occur in a mono-selective manner. Subsequently, they demonstrated the mono-methylation and mono-ethylation of a wide range of primary amines, achieving yields of up to 96% with the respective alkyl triflate, all at room temperature (Scheme 33, top).

Furthermore, in a follow-up report, the same group optimized the reaction conditions for a flow microreactor system, expanding the scope to include mono-N-ethylations and mono-N-propylations[86] (Figure 19, V and Scheme 33, bottom).



Scheme 32. Sequestration of mono-N-methylated amines (left) by a tetra-bridged phosphorylated cavitand in its **iiii** configuration **(Tiiii)** (right) by Dalcanale (ref. [80]).



Scheme 33. Selected examples for the mono-selective N-alkylation of primary amines using alkyl triflates as alkylating agents and HFIP as reaction solvent (top) and the application of this methodology in a microflow reactor setup (bottom) by the group of Legros (ref. [84, 86]).

2.8. N,N-Dialkyl Formamides

N,N-Dimethyl formamide (DMF) is an abundant, cheap and easy-to-handle chemical, which to date found ample utilization in various areas of organic syntheses. It is frequently used as solvent in chemical transformations, however, its application in organic synthesis additionally comprises its utilization as catalyst, stabilizer, and reagent.[87]

In 2020, the group of Wang and Zhang disclosed a protocol for a catalyst-free mono-selective methylation, and deutero-methylation using a Me_3N-BH_3/DMF system or respective deuterated analogue[88] (Figure 20, I). Their mechanistic findings could proof that the newly attached methyl group is formed by the donation of a carbon and one hydrogen atom from the formyl group of DMF, and two hydrogen atoms from the amino borane (R_3N-BH_3) (Scheme 34, top). The reaction was performed in DMF as both reagent and solvent and using NaH as the base at 80 °C. A very broad range of substrates were amenable to this approach giving the desired mono-N-methylated products in yields up to 91%. The authors could show on one example that this approach might be also suitable for ethylation using the respective *N,N*-dimethylacetamide, however with a moderate yield of 34% (Scheme 34, bottom). Remarkably, this approach can give access to the controlled formation of N-CH_2D, N-CHD_2, and N-CD_3 anilines by using Me_3N-BH_3/d_7-DMF, Me_3N-BD_3/DMF, and Me_3N-BD_3/d_7-DMF systems with an outstandingly efficient deuterium incorporation (>95%) (Scheme 34, middle).

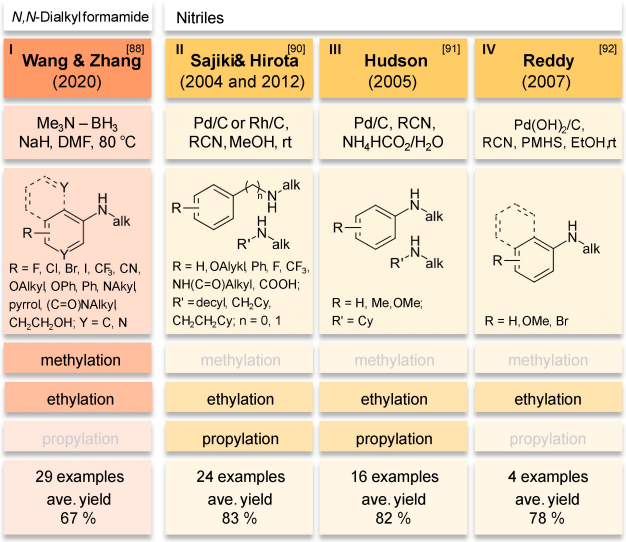
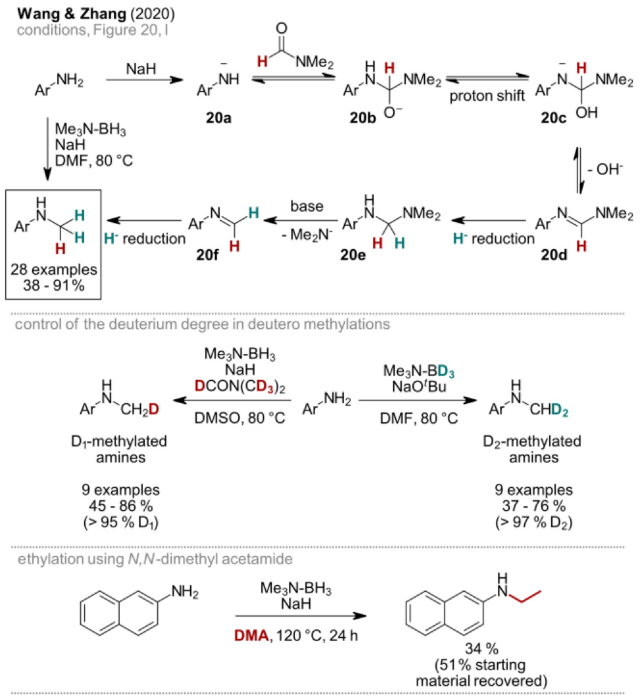
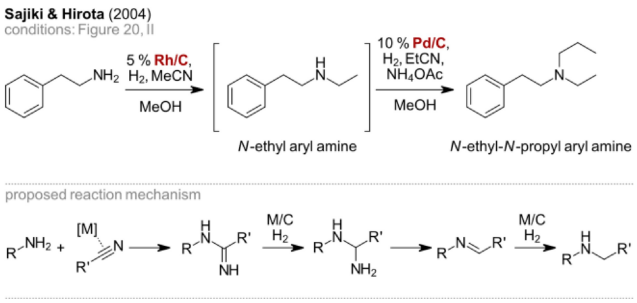


Figure 20. Methods for mono-selective N-alkylation of amines using *N,N*-dialkyl formamides (I) or nitriles (II–IV) as alkylating agents.



Scheme 34. Proposed reaction mechanism for the mono-selective N-methylation of primary amines using *N,N*-dimethyl formamide (DMF) as alkylating agent (top) and control of the degree of deuterium incorporation using deuterated borane and deuterated DMF (middle) and the N-ethylation using *N,N*-dimethyl acetamide by Wang and Zhang (bottom) (ref. [88]).



Scheme 35. Strategy for the controlled N,N-dialkylation by sequential mono-alkylation of a primary amine using Rh/C catalysis and subsequent alkylation of the secondary amine by Pd/C catalysis (top) and proposed reaction mechanism for the mono-selective N-alkylation under metal catalysis using nitriles as alkylating agents (bottom) by Sajiki and Hirota (ref. [90]).

2.9. Nitriles

Nitriles, known for their versatility and cost-effectiveness, have emerged as sustainable alkylating agents with the added environmental benefit of forming ammonia as the sole by-product. This unique attribute positions nitriles as intriguing candidates for achieving mono-selective N-alkylation of primary amines.

To date, established strategies for mono-selective N-alkylations predominantly rely on noble metal catalysts like Pd or Rh under reducing conditions. In these reactions short and linear nitriles (RCN, R = alkyl) can be successfully applied as alkylating agents for ethylation, propylation, and butylation, respectively. However, none of these protocols allowed for methylation, presumably due to the strong coordination of $^{-}$CN to the catalyst, leading to blockage.[89] Additionally, the consistent observation of lower yields in alkylations with non-distilled nitriles underscores the evident necessity for prior reagent purification.

In 2004, Sajiki, Ikawa, and Hirota published a pioneering work on the mono-N-alkylation of primary aromatic and aliphatic amines with nitriles using Pd/C or Rh/C with H_2 as the reducing agent in methanol at room temperature[90] (Figure 20, II and Scheme 35, bottom for proposed reaction mechanism). Notably, the Pd/C catalyst exhibited remarkable mono-selectivity in the alkylation of anilines, yet it converted aliphatic amines quantitatively into dialkylated tertiary amines. In contrast, a transition to Rh/C exclusively furnished the desired mono-alkylated products. The combination of these two approaches offers a pathway to bis-alkylated amines, incorporating two alkyl groups with different chain lengths (Scheme 35, top). The protocol demonstrated successful ethylation, propylation, and butylation of a variety of aromatic amines and undecylamine with high yields and outstanding mono-selectivity. In 2012, the same group further advanced their work, employing Pd/C or Rh/C catalysts in the reductive alkylation of primary amines with nitriles, significantly expanding the scope, particularly for aliphatic amines[89] (Figure 20, II).

Hudson's group presented a similar protocol in 2005, using Pd/C and ammonium formate as the hydrogen source in aqueous methanol at room temperature for the alkylation of primary aromatic amines[91] (Figure 20, III). While achieving high mono-selectivity in the ethylation, propylation, and butylation of primary aromatic amines, the range of functional group substituents was somewhat limited to aniline, toluidines, anisidines, and cyclohexylamine.

In 2007, Reddy et al. discovered the efficiency of polymethylhydrosiloxane (PMHS) as a reducing agent in $Pd(OH)_2$/C-catalyzed reductive N-alkylation of primary aryl amines using acetonitrile[92] (Figure 20, IV). However, with only four examples for mono-N-ethylation the scope was little investigated in terms of short-chain aliphatic alkylation.

The exclusive use of noble metal catalysts in mono-selective N-alkylation using nitriles underscores the potential for further investigations to identify sustainable catalytic systems featuring earth-abundant metals.

2.10. Peroxides

The utilization of alkylsilyl peroxides as mono-selective N-alkylating agents will be further explored in the amide alkylation section, as their application in this transformation is more prevalent (Section 3 Amides).

However, in 2017, the Maruoka's group included primary aryl amines in the scope of their protocol for the mono-selective N-alkylation of primary amines and arylamides[93] (Figure 21, I). Employing CuI as an affordable and readily available catalyst, along with 1,10-phenanthroline or its derivatives as ligands,

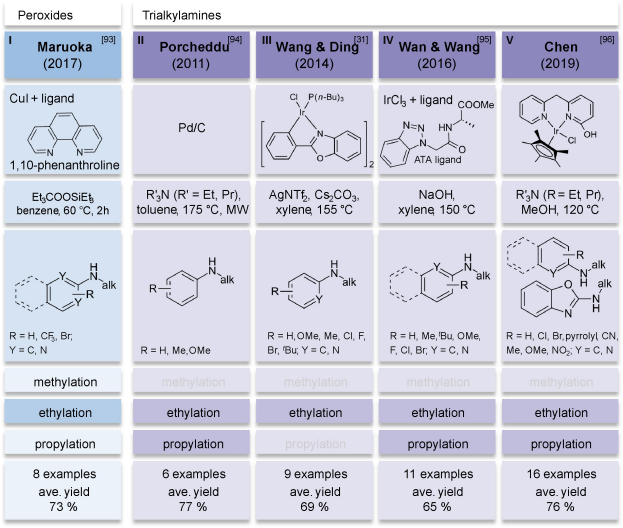


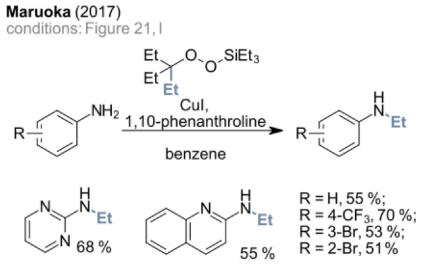
Figure 21. Methods for mono-selective N-alkylation of amines using peroxides (I) or trialkyl amines (II–V) as alkylating agents.

they efficiently generated alkyl radicals from alkylsilyl peroxides. This method allowed for the selective mono-ethylation of a limited selection of primary aryl amines in benzene at 50–80 °C, yielding the desired secondary amines with moderate maximum yields of 70 % (Scheme 36).

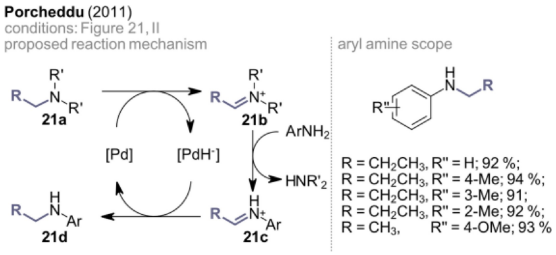
2.11. Trialkylamines

Similar to alcohols, alkylamines can engage in metal-catalyzed borrowing hydrogen reactions, generating an intermediate imine species susceptible to attack by a second amine (Scheme 37, left). However, hydrogen autotransfer reactions of amines remain less explored compared to their alcohol counterparts. Nonetheless, these net transalkylation reactions offer a valuable alternative pathway for synthesizing secondary and tertiary amines.

In a pioneering study in 2011, Porcheddu's group introduced the alkylation of primary aryl amines using heterogeneous Pd/C as a catalyst and tertiary amines ($(RCH_2)_3N$ with $R \neq H$)) in toluene under microwave irradiation[94] (Figure 21, II). The method allowed for mono-selective ethylation and propylation



Scheme 36. Selected examples for the mono-selective N-ethylation using peroxides as alkylating agents by Maruoka and co-workers (ref. [93]).

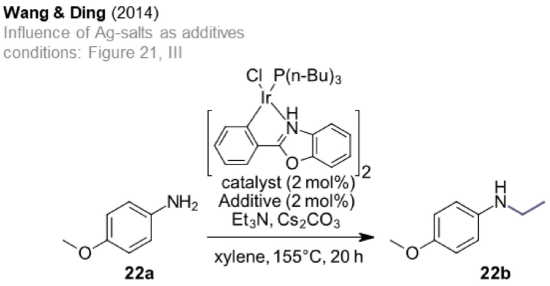


Scheme 37. Proposed reaction mechanism for the mono-selective N-alkylation of primary amines using trialkyl amines as the alkylating agent under palladium catalysis (left) and selected examples for N-alkylation by Porcheddu and co-workers (ref. [94]).

of various primary aryl amines, yielding desired products in up to 96 % (Scheme 37, right).

Wang, Ding and co-workers developed a versatile bisbenzoxazoyl iridium(III) complex designed for catalyzing hydrogen autotransfer reactions with both alcohols and tertiary amines[31] (Figure 21, III). They observed a substantial increase in yield when applying phosphine ligands and adding silver salts (e.g., $AgNTf_2$) to form an ionic complex *in situ* with increased activity (Scheme 38). Under mildly basic conditions (Cs_2CO_3) in xylene at 155 °C, several aryl amines underwent mono-selective ethylation using triethylamine, with yields ranging from 57 % to 85 %. In a subsequent study in 2016, the same group reported an Ir-based catalytic system with improved stability for the N-ethylation of primary aryl amines with triethylamine[95] (Figure 21, IV). This protocol featured $IrCl_3$ and a novel alanine triazole (ATA) ligand, employing NaOH as the base in xylene at 150 °C, resulting in mono-ethylated products with a maximum yield of 79 %.

In 2019, Chen's group explored various bidentate iridium catalysts for the selective mono-N-alkylation of primary amines



entry	additive	Yield **22b** [%]
1	-	36
2	AgOTf	69
3	$AgBF_4$	61
4	$AgSbF_6$	73
5	$AgPF_6$	75
6	$AgNTf_2$	81

Scheme 38. Influence of silver salts as additives in iridium-catalyzed mono-selective N-ethylation of primary aryl amines using trialkyl amines as alkylating agents by Wang and Ding (ref. [31]).

with trialkyl amines[96] (Figure 21, V). The exceptionally stable catalyst, active even under ambient conditions, facilitated alkylations in the presence of air. The reaction proceeded without the need for an additional base, and the use of the hydrochloric salt of the alkylating amine further enhanced the process. Despite employing methanol as the reaction solvent, hydrogen autotransfer occurred exclusively with tertiary amines, and no N-methylation by methanol was observed under the specified reaction conditions. A great range of substituted aryl amines could be mono-ethylated and -propylated in high average yields at 120 °C within 12 h reaction time.

3. Amides

Amides display a fundamental structural motif in pharmaceuticals and various biologically relevant compounds. The distinctive structure of the amide group imparts crucial characteristics influencing molecular stability and interactions within biological systems.[97]

A frequently used approach for manipulating amides is through strategic N-alkylation, involving the introduction of short alkyl chains such as methyl, ethyl, or propyl.[3d] This tailored modification enhances the chemical diversity of amide-containing compounds, offering a nuanced approach to modulate their biological properties.[98] The consequences of N-alkylation can be far-reaching, influencing essential factors like solubility, lipophilicity, and overall bioavailability. As a result, the exploration of methods for amide N-alkylation emerges as a pivotal strategy for fine-tuning the properties of bioactive compounds like proteins, opening new possibilities for therapeutic applications in drug discovery and design.[99]

3.1. Alcohols

The use of alcohols as mono-selective N-alkylating agents for amines *via* a metal-catalyzed borrowing hydrogen approach is well studied (Section 2 Amines, alcohols). In contrast, only a few protocols report the use of short-chain aliphatic alcohols for the selective N-alkylation of primary amides.

In 2019, the group of Kundu disclosed a pioneering protocol using methanol as the C1-soure in a ruthenium (II)-catalyzed N-methylation of amides[100] (Figure 22, I). Their catalytic system featured a ruthenium-pincer complex and substoichiometric amounts of Cs_2CO_3 as the base at 140 °C in a mixed solvent system (methanol/toluene, 1:5). Remarkably, aromatic as well as aliphatic primary amides could be selectively mono-methylated in yields up to 93%. When using phenylacetamide derivatives, however, the benzylic position was readily methylated as well, with still obtaining mono-selectivity for the nitrogen. Furthermore, NH_2 substituents on the aryl moiety underwent swift mono-methylation, and with prolonged reaction times, mono-methylation extended to the amide nitrogen. (Scheme 39, right). Extensive DFT calculations strongly suggested a pathway operating according to known hydrogen autotransfer systems (Scheme 39, left) with three main steps

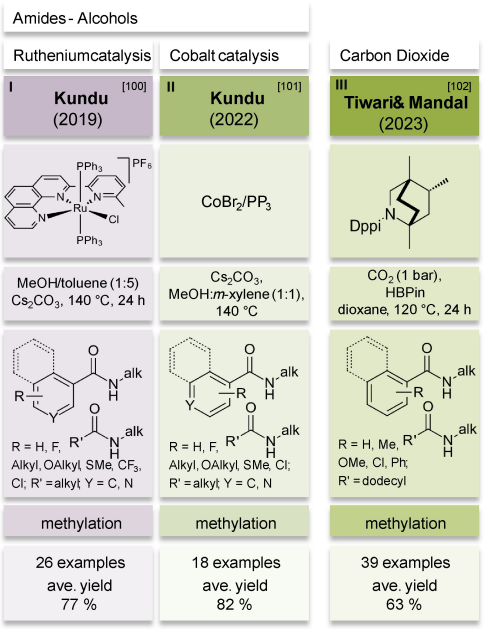


Figure 22. Methods for mono-selective N-alkylation of amides using alcohols (I–II) or carbon dioxide (III) as alkylating agents.

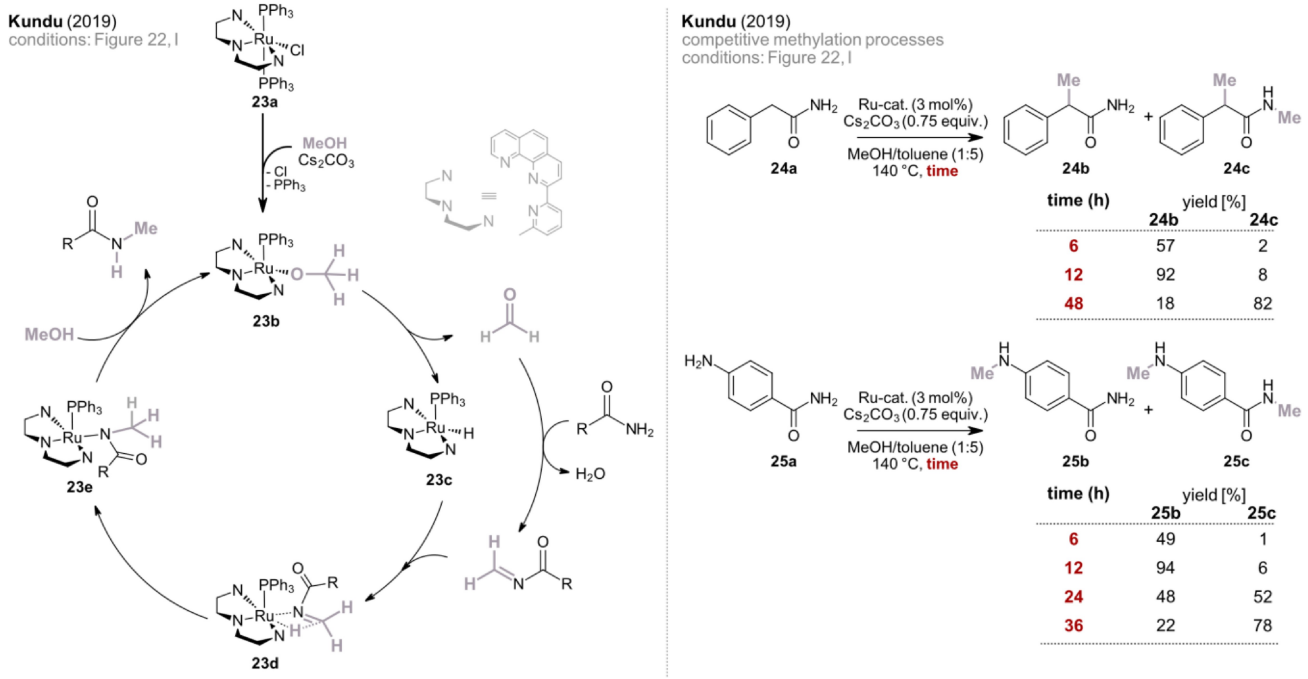
being dehydration of methanol (**23 b**→**23 c**), N-methyleneamide insertion in the metal hydride complex **(23 d)**, and finally, alcoholysis to release the final product (**23 e**→**23 b**).

Three years later the same group reported an additional protocol for mono-selective N-methylation of amides with methanol and a distinct catalytic system[101] (Figure 22, II). *In situ* generation of an active cobalt complex obtained by combination of $CoBr_2$ and PP_3 (Scheme 10) facilitated N-methylation under basic conditions (Cs_2CO_3) at 140 °C in a 1:1 solvent mixture of MeOH/*m*-xylene. Interestingly, control experiments identified active cobalt(I) hydride [Co^I-H] as an active species, strongly suggesting its involvement in this catalytic hydrogen autotransfer process. Primary aromatic as well as aliphatic amides were readily methylated with high yields with three examples performed on a gram scale.

3.2. Carbon Dioxide

Very recently, Tiwari, Mandal and co-workers were the first to report a protocol for the catalytic methylation of primary amides using CO_2[102] (Figure 22, III). Both reactants are activated by a bicyclic (alkyl)(amino)carbene (BICAAC) having high σ-donating and π-accepting properties. The reaction was performed in dioxane at 140 °C with an atmospheric pressure of CO_2 and 4 equivalents of pinacolborane (HBpin) as reducing agent.

Several control experiments and DFT calculations strongly suggest a catalytic pathway operating by dual activation of the amide as well as CO_2 (Scheme 40, top). The amide activation commences *via* the activation of the pinacole borane by BICAAC **26 a**. A BICAAC·B–H intermediate **26 e** is formed, which subsequently activates the amide *via* N–H bond borylation



Scheme 39. Proposed catalytic circle for the mono-selective N-methylation of primary aryl amides under ruthenium catalysis using alcohols as the alkylating agent (left) and time-dependent benzylic and amine methylation vs. amide methylation by Kundu and co-workers (ref. [100]).

(26 f) upon hydride formation and regeneration of the catalyst **26 a**. On the other hand, CO_2 is activated by forming a zwitterionic adduct (BICAAC–CO_2, **26 b**) which in the following reacts with the pinacolborane and undergoes a hydride transfer **(26 c)** to finally liberate boron formate **26 g** and regenerate the catalytic species **26 a**. In the end, both activated species, the *N*-borylated amide **26 f** and the boron formate **26 g**, undergo formyl transfer, forming $(Bpin)_2O$ as the byproduct and an *N*-formylated product **26 h**. The latter species is eventually undergoing hydroboration at the carbonyl center, generating the *N*-methylated amide **26 i**. Considering this mechanistic pathway, it is clear that 4 equivalents of the pinacolborane as reducing agent are crucial.

A variety of primary aromatic, heterocyclic, and aliphatic amides readily underwent mono-N-methylation, giving the desired products in yields between 37 and 77 %. The potential applicability of this protocol in the late-stage functionalization of biologically active compounds was demonstrated in the diversification of bioactive molecules and selected drugs. Borneol, menthol, and estrone could be selectively N-methylated in up to 71 % yield. Examples for late-stage modification of drug molecules include the N-methylation of Probenecid, Adapalene, and Tocopherol. Remarkably, ^{13}C isotope labelling of these biologically important molecules could be realized using $^{13}CO_2$ (Scheme 40, bottom).

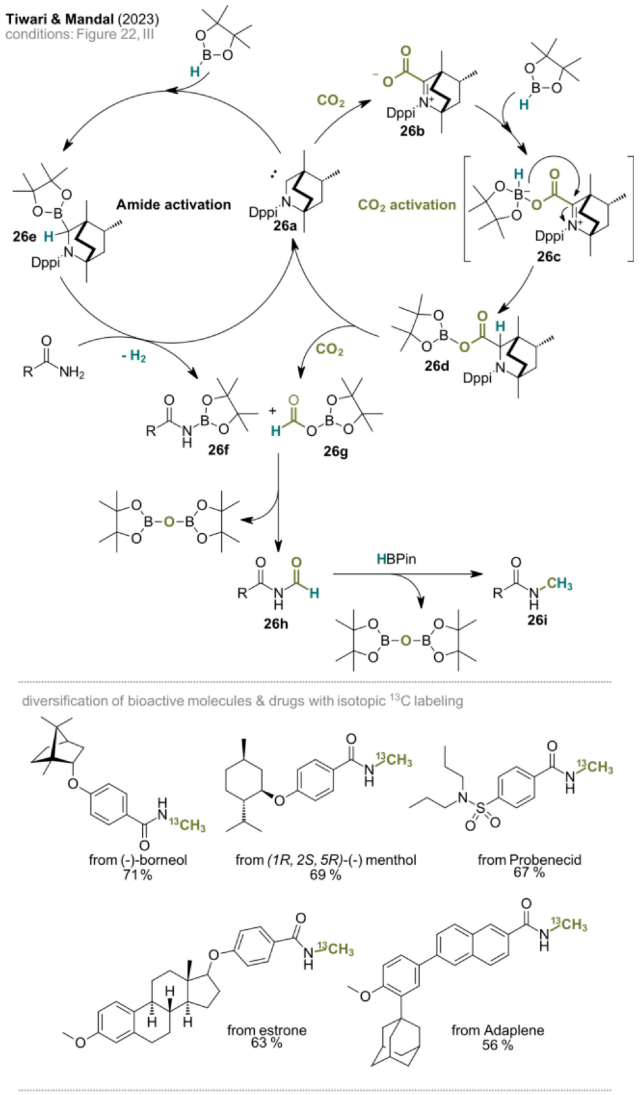
3.3. Peroxides

In the last decade, several protocols for N-methylation using different peroxides have been reported. The reaction usually proceeds *via* metal catalyzed alkyl radical formation (Scheme 41): Initially, an alkoxy radical is formed, which upon β-scission eventually forms an alkyl radical and the corresponding ketone from the tertiary alkoxide.[103] The amide coordinates after ligand exchange to the metal center and subsequently the alkyl radical is inducing reductive elimination of the desired N-methylated amides or sulfonamides (Section 4.2).

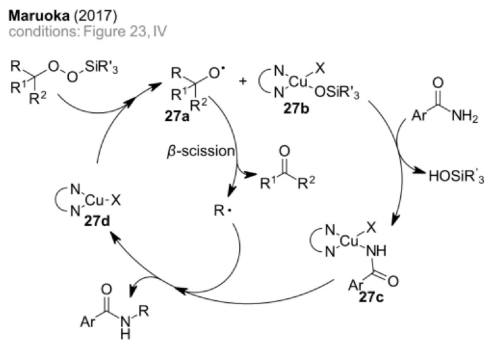
In 2013, Chen's group was the first to report the use of peroxides as mono-selective N-methylating agents for amides[104] (Figure 23, I). They used dicumyl peroxide (DCP) (Scheme 42, top) as methyl radical precursor under CuCl catalysis in chlorobenzene as solvent. Elevated temperatures of 110-130 °C were crucial for efficient radical formation as no product formation could be detected at 80 °C. A variety of primary aromatic, heteroaromatic, and allylic amides could be successfully methylated in 66-90 % yield.

Several years later, in 2017, Li and Cai reported two protocols using di-*tert*-butyl peroxides or *tert*-butyl perbenzoate (TBPB) as methyl radical precursor[105] (Figure 23, II and III, and Scheme 42, top for peroxides). Their first method relied on $Ni(OTf)_2$ in a HOAc/water mixture[105a] whereas the following protocol featured $Fe(acac)_2$ as metal catalyst and potassium persulfate ($K_2S_2O_8$) as an additive in chlorobenzene as solvent.[105b] Both reactions operated at 120 °C. A selection of primary aryl amides and for the Ni-catalyzed protocol even primary aliphatic amides, were N-methylated mono-selectively in synthetically useful yields up to 70 %. These two methods were also applicable for the N-methylation of sulfonamides and are described as such below (Section 4.2).

From 2017 to 2019, the group of Maruoka disclosed several different protocols for efficient N-alkylation of various primary



Scheme 40. Proposed reaction mechanism for the mono-selective N-methylation of primary amides using carbon dioxide as the methylating agent and the dual activation of carbon dioxide and the amide by bicyclic(alkyl)(amino)carbene (BICAAC, **26a**) (top) and the application of the method for the diversification of bioactive molecules and drugs by ^{13}C-methylations (bottom) by Tiwari and co-workers (ref. [102]).



Scheme 41. Proposed radical reaction mechanism for the mono-selective N-alkylation of primary amides using peroxides as the alkylating agents by Marouka and co-workers (ref. [103]).

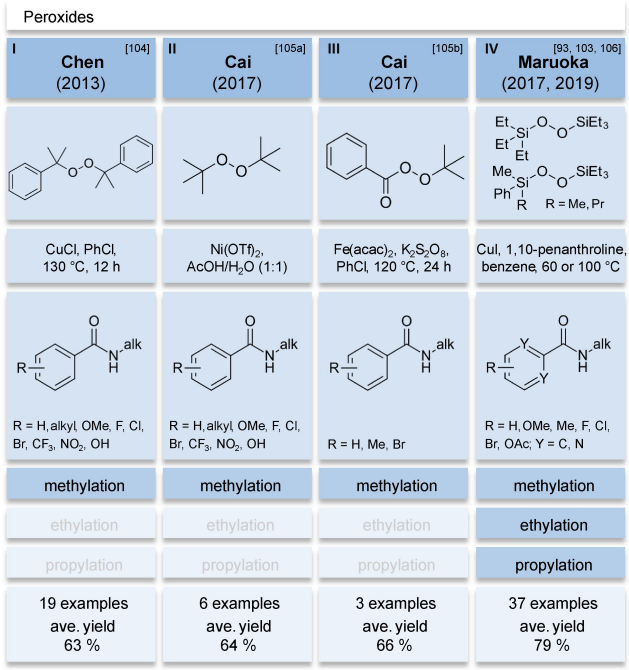
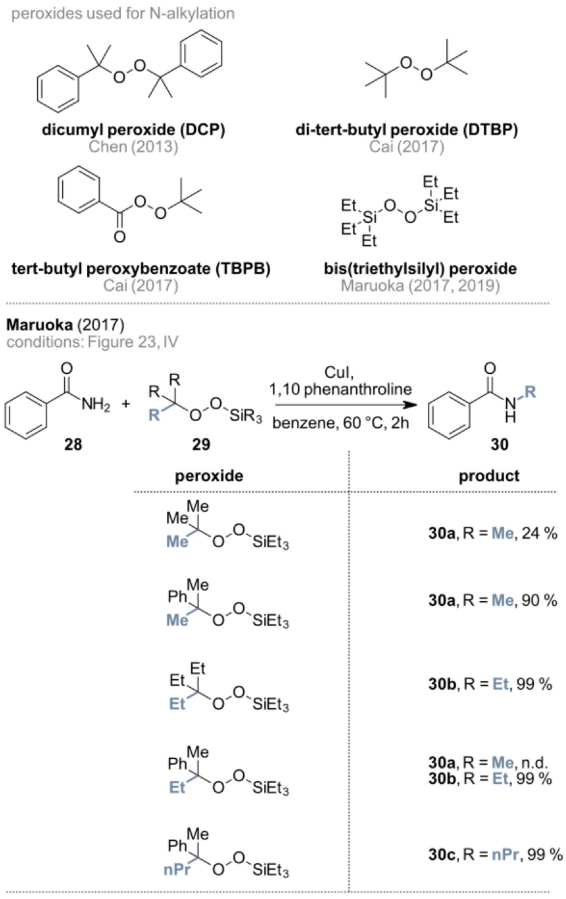


Figure 23. Methods for mono-selective N-alkylation of amides using peroxides as alkylating agents.

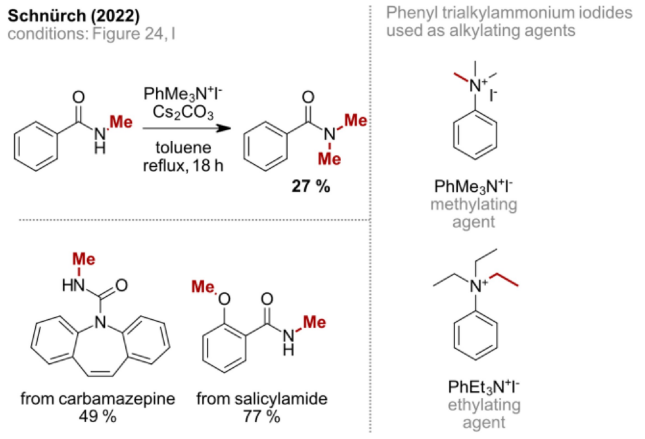


Scheme 42. Peroxides used in the mono-selective N-alkylation of primary amides (top) and the peroxide dependent alkyl transfer enabling controlled N-methylation, N-ethylation, or N-propylation by Marouka (ref. [103]).

amides and thus broadened the scope that was so far limited to methylation[93,103,106] (Figure 23, IV). Ethylation could be realized using either bis(triethylsilyl) peroxide (Scheme 42, top) or related peroxides, which formed the respective alkyl radicals with the catalytic system featuring CuI and 1,10-phenanthroline in benzene as solvent. Several primary aromatic, heteroaromatic and aliphatic amides readily underwent N-ethylation in moderate to quantitative yields. Notably, N-methylation or N-propylation were feasible using dimethyl phenyl or methyl *n*-propyl phenyl peroxides (Scheme 42, bottom).

3.4. Quaternary Ammonium Salts

Using quaternary ammonium salts as alkylating agent displays a distinct advantage, especially in comparison to traditionally applied short-chain alkylating agents like alkyl halides or dialkylsulfates: the nontoxic and solid nature of these salts makes them easy-to-handle and their application entirely safe[107] (Figure 24, I). Recently, our group investigated the use of trialkyl ammonium salts as highly mono-selective methylating and ethylating agents, respectively, in a catalyst-free protocol.[108] Trimethyl and triethyl ammonium iodides (Scheme 43, right) exhibited superior performance as alkylating agents under mildly basic conditions (Cs_2CO_3) in toluene under reflux. Several primary aromatic and aliphatic amides were N-methylated and N-ethylated in yields ranging from 59 to 92%. Interestingly, the method could be applied in a late-stage methylation of two primary amides containing bioactive compounds, namely, carbamazepine and salicylamide, whereas the latter one was additionally *O*-methylated at the phenolic position (Scheme 43, left bottom). The outstanding mono-selectivity of this protocol was proven by reacting *N*-methyl aryl amides under the respective reaction conditions. A maximum yield of 35% of the bis-methylated products were obtained and mainly starting material was recovered (Scheme 43, left top). These results show that even forcing a second methylation, the reaction is significantly hampered most likely by the steric congestion of the methylating agent itself.



Scheme 43. Hampered reaction for the N-methylation of secondary amides (left, top) proving the high mono-selectivity of the N-alkylation of primary amides using quaternary ammonium salts as the alkylating agents (right) and the application of the method for the late-stage methylation of bioactive compounds (left, bottom) by Schnürch and co-workers (ref. [108]).

3.5. Trialkyl Phosphates

Trialkyl phosphates are to date rather underrated alkylating agents. However, they offer the great advantage of being nontoxic, relatively stable, and readily available. Besides being used as alkylating agents for alcohols or dimethylamines, Sajiki's group was the first to report their use as selective N-alkylating agents for primary amides[109] (Figure 24, II). Their catalyst-free protocol used either NaOH or *n*-BuLi as a base in cyclopentyl methyl ether (CPME) as the reaction solvent. The authors, however, did not comment on the rational for the mono-selectivity of these alkylating agents. Eventually, they could methylate several primary aryl amides and one aliphatic amide with a maximum yield of 87%. For aniline they also proved that ethylation and butylation was feasible, but the product yield was only moderate with 54 and 61%, respectively.

4. Sulfonamides

Sulfonamides, recognized for their pivotal role in medicinal chemistry, have become indispensable components in the development of pharmaceutically active compounds and drugs. Their prominence extends to various therapeutic applications, notably in antibacterial agents, where they exert their influence by disrupting bacterial folate synthesis through inhibition of the folic acid pathway.[110]

Concerning antibacterial activity, sulfonamides function as potent inhibitors, targeting dihydropteroate synthase, a key enzyme in the folic acid pathway. By obstructing this essential

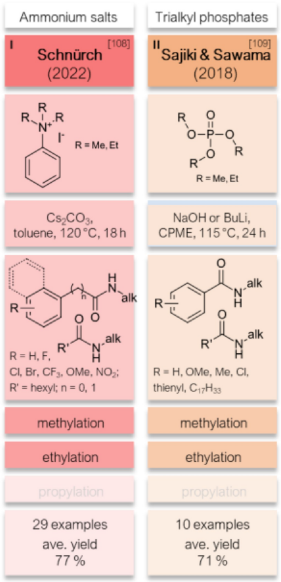


Figure 24. Methods for mono-selective N-alkylation of amides using quaternary ammonium salts (I) or trialkyl phosphates (II) as alkylating agents.

pathway, sulfonamides impede the production of folate, a vital precursor for bacterial DNA synthesis. This distinctive mode of action makes sulfonamides a cornerstone in the arsenal against bacterial infections, showcasing their importance in the field of chemotherapy.[111]

Beyond their role in antibacterial agents, sulfonamides find application in chemotherapeutic agents. Their ability to selectively target specific biological pathways makes them valuable tools in the design of drugs, where their inhibitory effects play a crucial role in modulating cellular functions.[111c,112]

N-Alkylation of sulfonamide-containing drugs offers a versatile approach to fine-tune their properties, impacting factors such as solubility, binding affinity, and metabolic stability. This strategic modification provides chemists with a means to tailor the drug's profile for enhanced therapeutic effectiveness in specific biomedical applications.

4.1. Alcohols

Like amines and amides, sulfonamides can be readily and mono-selectively alkylated using alcohols by metal catalyzed hydrogen autotransfer with a mechanism according to the one in amide alkylation.

The protocols presented below primarily focused on the mono-selective N-alkylation of primary amines and herein further expanded their scope towards primary sulfonamides.[13,28,35a,42,46] Thus, the protocols are described in greater details within the section of amine alkylation. Reports that comprise only very few sulfonamide-containing compounds within their scope are not described in detail within this section. Only publications with a broader scope regarding selective N-alkylation of sulfonamides will be emphasized below.

In the years between 2012 to 2021, the group of Li dominated the field of mono-selective N-methylation of sulfonamides, reporting one ruthenium- and four iridium-catalyzed systems[19,26–27,29,52e] (Figure 25, I–V). Their presented protocols were as well applicable for amine methylation, additionally, they encompass a variety of distinct sulfonamides within their scope.

In a publication on the mono-selective methylation of primary amines with methanol in 2012, Li *et al.* could prove that their herein described method can be also applied to sulfonamides[26] (Figure 25, I). They utilized $[Cp^*IrCl_2]_2$ as catalyst operating under basic conditions (NaOH) at 150 °C to mono-selectively methylate a variety of primary aryl sulfonamides in excellent yields between 87 and 97 %.

Subsequently, the group designed several modified Ir-catalyzed systems with increased reactivity and stability. In 2017, they introduced a bidentate 2,2′-bis-benzimidazole ligand enabling the catalytic system to operate under air with sub-stoichiometric amounts of Cs_2CO_3 as a very mild base[27] (Figure 25, II). A range of aromatic as well as aliphatic primary sulfonamides could be mono-N-methylated in outstanding yields between 89 to 96 % using methanol.

Three years later, they synthesized a novel water-soluble dinuclear iridium catalyst, allowing for N-methylation of amines and sulfonamides in water with methanol as C1-source[29] (Figure 25, III). Using KOH as the base at 130 °C several *N*-methyl sulfonamides were accessible in yields up to 93 % including non-aromatic methylsulfonamide. A few years later, they introduced an easily removable and recyclable iridium-based heterogenous catalytic system[52e] (Figure 25, IV).

By coordinative immobilization, $[Cp^*IrCl_2]_2$ was successfully immobilized on a covalent triazine framework (CTF). The system operates in methanol as both solvent and methylating agent at 125 °C using Cs_2CO_3 as mild base. With regard to sulfonamides,

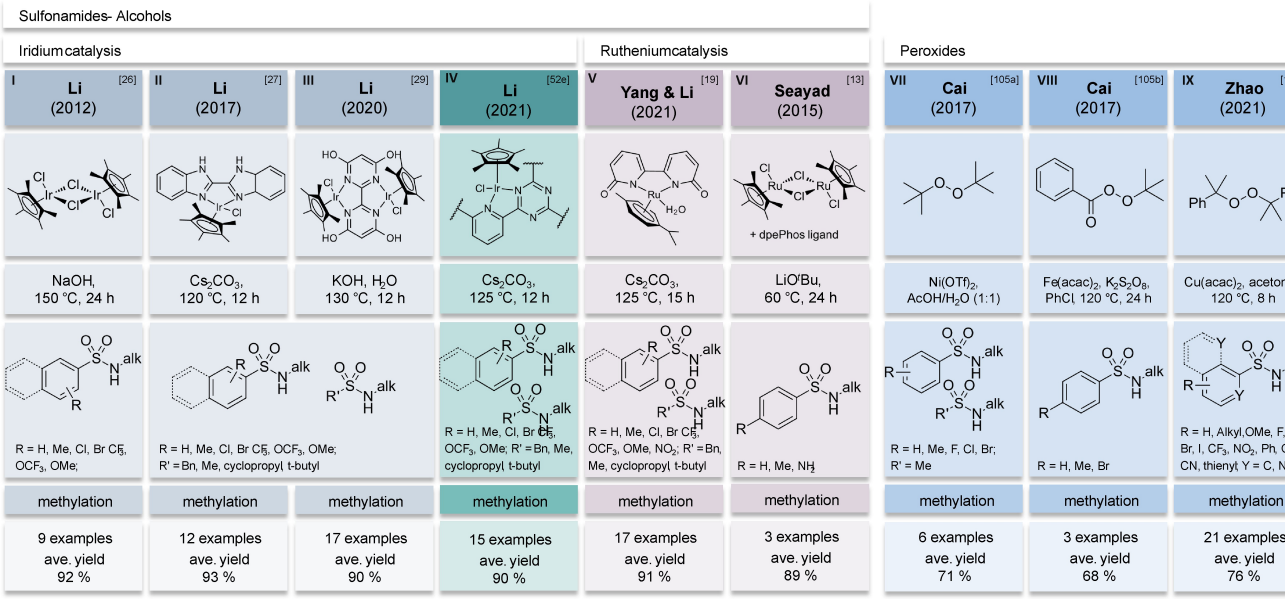


Figure 25. Methods for mono-selective N-alkylation of primary sulfonamides using alcohols (I–VI) or peroxides (VII–IX) as alkylating agents.

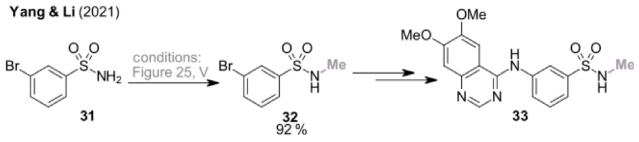
their scope was similar to previous reports with yields of the N-methylated products up to 93%.

In 2021, the group reported another distinct air-stable catalytic system suitable for mono-selective N-methylation which is based on ruthenium[19] (Figure 25, V). The crucial role of the bis-pyridonate ligand within the catalytic [(*p*-cymene)Ru-(2,2′-bpyO)(H_2O)] complex is described in detail in the section of ruthenium catalyzed N-alkylation of amines with alcohols (Section 2.1). The protocol gave access to a variety of mono-N-methylated primary aromatic and aliphatic sulfonamides in up to 94% yield. Notably, the authors applied their novel methylation protocol in the first step of a synthesis of a known kinase inhibiting compound (**33**, Scheme 44).[113]

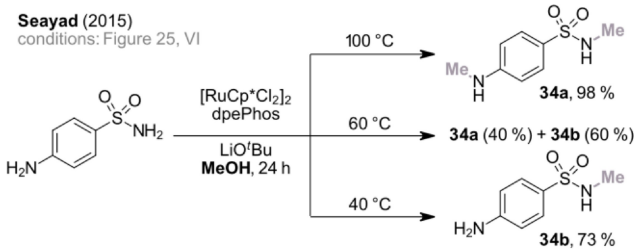
Even though presenting only three examples for the mono-selective N-methylation of sulfonamides, the group of Seayad made a noteworthy discovery: when using sulfanilamide and methanol under their reported [$RuCp^*Cl_2]_2$/dpePhos catalyzed conditions, the chemoselectivity for N-methylation was found to be temperature-dependent[13] (Figure 25, VI and Scheme 45). At 100 °C both the nitrogen of the amine and the sulfonamide were mono-selectively methylated in 90% yield. However, when the reaction was conducted at 40 °C N-methylation occurred exclusively at the sulfonamide moiety yielding 73% of the desired product.

4.2. Peroxides

As already mentioned previously (Section 3.3), peroxides display valuable alkylating agents for the mono-selective introduction of short-unbranched alkyl moieties on the nitrogen atom of amides and sulfonamides. The reaction pathway *via* radical formation is described more detailed above.



Scheme 44. Application of the method for mono-selective N-methylation of primary sulfomamides using methanol as methylating agent under ruthenium catalysis in the first step of a known kinase inhibiting compound **c** by Yang, Li, and co-workers (ref. [19]).



Scheme 45. Temperature dependent chemoselectivity in the mono-selective N-methylation of primary sulfonamides using methanol as methylating agent under ruthenium catalysis by Seayad and co-workers (ref. [13]).

In 2017, Li and Cai disclosed two closely related protocols for the mono-selective N-methylation of amides and sulfonamides using either $Ni(OTf)_2$ with di-tert-butyl peroxide (DTBP)[105a] (Figure 25, VII) or $Fe(acac)_2$ with tert-butyl peroxybenzoate (TBPB) and $K_2S_2O_8$[105b] (Figure 25, VIII). The first protocol encompassed six distinct sulfonamides which could be methylated in good yields up to 74%, whereas the latter protocol featured only three examples thereof with a maximum yield of 70%.

Recently, Zhao, Luo, and Lian disclosed a protocol focusing exclusively on the N-methylation of sulfonamides using dicumyl peroxide[114] (Figure 25, IX). The reaction was catalyzed by simple and readily available $Cu(acac)_2$ in acetone at 80 °C under air. A great variety of aromatic-, heteroaromatic- and benzylsulfonamides could be mono-selectively methylated in up to 90% yield. Subjecting a mono-N-methylated sulfonamide again to the optimized reaction conditions, only 50% of the bis-methylated product could be obtained, suggesting that the rate of a second methylation is slightly reduced.

Considering, that to date described protocols for the mono-selective short-chain N-alkylation of sulfonamides are exclusively focusing on methylation, it becomes obvious that there is a demand for novel protocols for mono-N-ethylation and N-propylation of these frequently occurring and important motifs in biologically active compounds.

5. Outlook

The mono-selective N-alkylation of primary amines, amides, and sulfonamides is a fundamental reaction in both small organic molecules and complex compounds, such as pharmaceuticals. Tailored methods that allow full control over the degree of alkylation, especially to prevent overalkylation, are often crucial. This precision is not only significant for the controlled modification of defined properties but also for waste prevention by eliminating undesired byproducts.

This comprehensive review presents several methods that can be applied to meet individual requirements. However, despite the strengths of each method, certain strategies have significant drawbacks that should prompt researchers in this field to overcome these limitations. Specifically, strategies involving the use of alcohols or gaseous reagents (e.g., CO_2) as alkylating agents under metal catalysis often require high temperatures and pressures, necessitating specialized equipment like autoclaves, which might not be readily available in every laboratory. Furthermore, these harsh conditions often limit the tolerance of functional groups in general or, considering the reductive conditions for hydrogen autotransfer reactions, alter reducible groups within a molecule (ketones, vinyl, amides, alkenes, etc.). Thus, there is a substantial demand for the development of more active catalytic systems that can operate at lower temperatures and pressures while still guaranteeing high mono-selectivity.

Concerning metal catalyzed N-alkylations, the use of catalytic systems featuring earth-abundant metals like iron, manganese, cobalt, and nickel is still underexplored. Ideally, the

use of these abundant metals in a heterogeneous and easily reusable catalyst is highly desirable, especially in times of increasing demand for more environmentally friendly processes. Considering environmental concerns, the use of atom-economic and benign reagents (carboxylic acids, aldehydes, nitriles, and alcohols), or even the fixation of carbon dioxide, is highly desirable.

A second challenge in designing new methodologies for mono-selective N-alkylation is achieving precise control over chemoselectivity when different nitrogen-containing moieties are present in a single molecule. Often, primary amines are more readily alkylated compared to amides or sulfonamides. However, considering the structural complexity of the majority of bioactive compounds and pharmaceuticals, the need for highly chemo- and regioselective methods becomes apparent.

Lastly, especially concerning amine alkylation, the majority of methods only achieve mono-selectivity for aryl amines, lacking complete mono-selectivity for aliphatic amines, which are fully bis-methylated. Given the frequent occurrence of aliphatic motifs in bioactive compounds (e.g., proteins) and pharmaceuticals, the need for refinement of existing or discovery of new methodologies for mono-selective N-alkylation of aliphatic amines is evident.

We genuinely hope that this review aids researchers in choosing suitable methods for a given demand and further inspires and encourages them to find new strategies to overcome present limitations and challenges.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Keywords: mono-methylation · mono-ethylation · mono-propylation · chemical precision · drug discovery

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