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Additional Information

Catalytic Reductive N-Alkylations using CO₂ and Carboxylic Acid Derivatives: Recent Progress and Developments

Jose R. Cabrero-Antonino,*[a, b] Rosa Adam,[a, b] and Matthias Beller*[a]

Abstract: *N*-Alkylamines are key intermediates in the synthesis of fine chemicals, dyes and natural products, hence being highly valuable building blocks in organic chemistry. Consequently, the development of greener and more efficient protocols for their production continues to attract the interest of both academic and industrial chemists. So far, reductive protocols such as reductive amination or N-alkylation through hydrogen autotransfer employing carbonyl compounds or alcohols as alkylating agents prevail for the synthesis of amines. In addition, in the last years, carboxylic/carbonic acid derivatives and carbon dioxide have been introduced as alternative convenient alkylating sources. The safety, easy accessibility and high stability of these reagents makes the development of new reductive transformations using them as N-alkylating agents a useful alternative to existing protocols. In this minireview, we will summarize all the reported examples up to date dealing with the one-pot reductive N-alkylation methods using carboxylic/carbonic acid derivatives or carbon dioxide as alkylating agents.

1. Introduction

N-Alkylamines play a central role in nature as they are present in essential compounds for life, such as amino acids, nucleotides, and alkaloids.[1] Notably, the majority of the currently marketed drugs and agrochemicals present N-alkyl groups in their structure (Figure 1). Thus, the biological activity of products containing amino groups has been intensively studied. In addition, N-alkylamines -including methylamines- are used as highly valuable intermediates for the synthesis of fine chemicals, dyes and natural products.[1-2] Consequently, the development of novel green and efficient N-alkylation methodologies continues to be of great interest for chemists.

Among the general methods for the direct N-alkylation of amines (Scheme 1, up), the use of strong electrophiles prevailed at g-scale.[3] Traditionally, alkyl halides, diazo or triflates, dimethyl sulfate and trimethyloxonium tetrafluoroborate have been employed as alkylating agents.[1b-d, 2-3] However, the toxicity of these compounds and the inherent waste formation led to their substitution by other milder electrophilic reagents, as trialkyl orthoesters,[4] dialkyl carbonates[5] and dimethyl sulfoxide.[6]

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Instead of using strong electrophiles, reductive methods employing carbonyl compounds (reductive amination)[7] or, much less frequently, phenols/ethers[8] are valuable methodologies. In fact, reductive aminations are commonly used in industry, especially for the synthesis of methyl amines (e. g. Eschweiler-Clarke methodology using formaldehyde as C1 source).[7a, 7b, 7d] In this respect, the tandem olefin hydroformylation/reductive amination, so-called hydroaminomethylation, deserves also to be highlighted being an atom-economical approach to obtain aliphatic amines.[7i, 9]
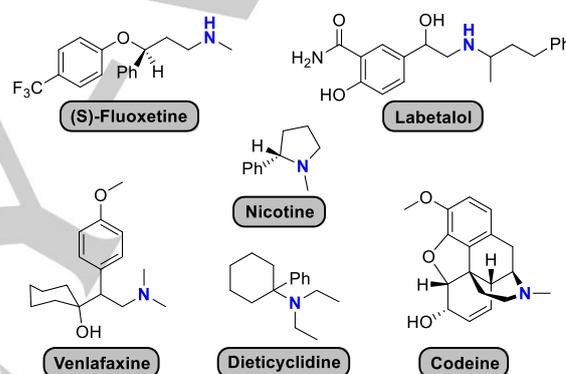

Figure 1. Some examples of N-alkylamines with relevant biological activity.

In addition, most of the available methods for the synthesis of chiral alkylamines are based on the asymmetric hydrogenation of imines.[7f, 7g, 10] Closely related with reductive amination, N-alkylation with alcohols or amines by hydrogen borrowing or autotransfer has emerged as a growing methodology.[11] For example, the N-methylation of amines using methanol in the presence of zeolites is in use in the chemical industry.[11a, 11b]
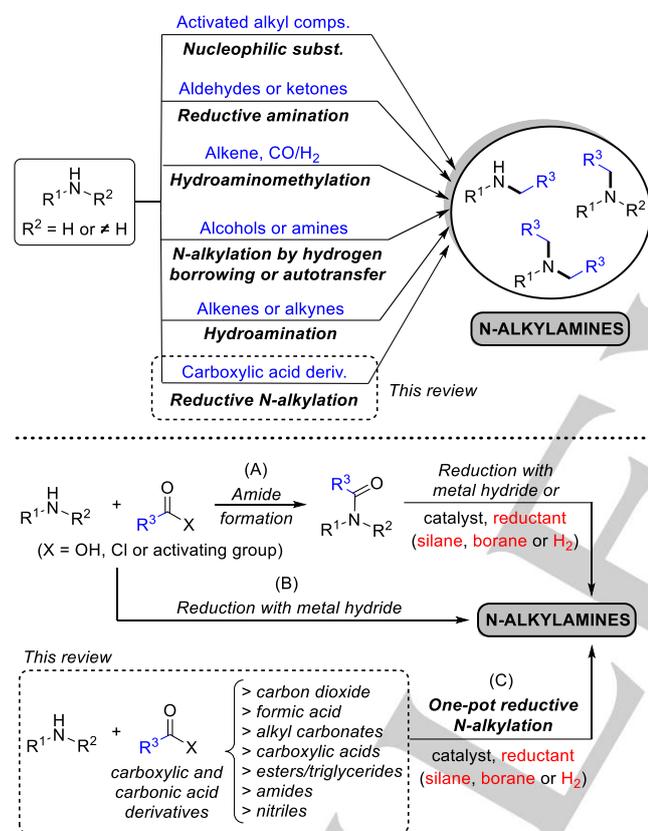
Apart from reductive methods, hydroamination using alkenes or alkynes is another straightforward approach for the synthesis of N-alkylamines.[12] Moreover, although more far from the topic of this review, the Buchwald-Hartwig Pd-catalyzed amination of aromatic halides or triflates is worth mentioning due to its utility.[13]

Tandem or domino processes, such as reductive amination or N-alkylation through hydrogen autotransfer, have been widely employed to avoid multi-step transformations[14] using safe carbonyl compounds or alcohols as alkylating agents. In contrast, the same strategy with the more oxidized carboxylic acid derivatives or carbon dioxide as alkylating agents has been less investigated, due to the lower reactivity of these compounds. However, the employment of these building blocks with a higher oxidation state can entail advantages from the points of view of their high stability and safety, as well as their availability.

Indeed, carbon dioxide, is a non-toxic, cheap and widely available compound, present in the atmosphere –although low concentrations (>400 ppm)- as a greenhouse gas.[15] In recent years, its use for applications in energy storage or for the synthesis of bulk chemicals, e.g. methanol or formic acid found significant attention.[15c, 15h, 16] Apart from that, carbon dioxide constitutes an attractive building block for making fine chemicals. The problem is that owing to its inherent thermodynamic stability and kinetic inertness, CO_2 utilization is challenging.[17] In the past decade, advancements in catalysis and organometallic chemistry provided new practical transformations for the production of valuable synthetic organic molecules using CO_2 as building block.[17] However, the most important process, the formation of urea on >150 million ton-scale from CO_2 and NH_3 by the Bosch-Meiser process, exists already for a long time.[15a]
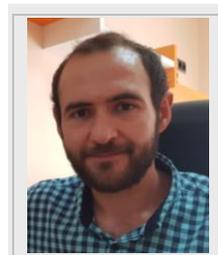

Carboxylic and carbonic acid derivatives (mainly acids, anhydrides, acid chlorides, esters, amides and dialkyl carbonates) are polar organic functionalities with a poorly electrophilic carbonyl group.[19] Because of its high stability, accessibility and safe manipulation, their use as N-alkylation agents is desirable.

In the last two decades, general routes for the synthesis of alkylamines using carboxylic acid derivatives mainly focused in the two-step amide formation[20] followed by C-O reduction (Scheme 1, bottom, A). The amide C-O reduction has been performed either by using a large excess of metal hydrides[21] or by the greener catalytic reduction.[19d, 19f, 21c, 22] On the other hand, the direct N-alkylation of amines using carboxylic acid derivatives has employed over-stoichiometric amounts of metal hydride reagents that produce large amounts of waste-products (Scheme 1, bottom, B).[21b, 23]

More recently, homogeneous and heterogeneous catalysts have been successfully applied to this transformation using different reducing agents (Scheme 1, bottom, C). These protocols constitute underrated strategies to directly alkylate amines using readily available alkyl sources. The stability of CO_2 and carboxylic/carbonic acid derivatives are important advantages of these reactions that normally avoid the formation of secondary products.

In this minireview, we summarize the reported examples employing CO_2 and carboxylic/carbonic acid derivatives as alkyl sources in catalytic reductive N-alkylation processes. Although nitriles are not considered carboxylic acid derivatives, examples where they are used as N-alkyl sources will be also commented due to their close relationship with carboxylic acid derivatives (nitrile hydration affords an amide).

Scheme 1. Up: general methods for the direct N-alkylation of amines. Bottom: (A) two-step amide formation followed by reduction using an excess of metal hydride or catalytic reduction with a mild reductant; (B) direct N-alkylation of amines with carboxylic acid derivatives using stoichiometric amounts of metal hydrides; (C) catalytic reductive one-pot N-alkylation of amines using CO_2 and carboxylic and carbonic acid derivatives, topic discussed in this review.

Jose R. Cabrero-Antonino was born in Torrent (Valencia, Spain) in 1985. From 2003 to 2008, he studied Chemistry at the University of Valencia. In 2013, he obtained his PhD with honors under the supervision of Prof. Avelino Corma and Dr. Antonio Leyva-Pérez at the Instituto de Tecnología Química (ITQ) and the Polytechnic University of Valencia. As recipient of Ramon Areces fellowship, he performed a postdoctoral stay from 2014 to 2017, at the Leibniz Institute Für Katalyse (LIKAT) in Rostock (Germany) under the guidance of Prof. Matthias Beller. In 2017 he came back to the group of Prof. Corma as a Juan de la Cierva fellow. This year he was granted with a prestigious Ramon y Cajal contract. His scientific work has been focused in the design and development of new homogeneous and heterogeneous metal catalyst systems and their application in organic transformations.

More recently, the reduction of CO_2 in the presence of nucleophiles such as amines allowed developing green and one-pot reductive alkylation processes.[18] In this respect, also straightforward valorizations of CO_2 for the direct N-alkylamine production have been disclosed, although the generalization of these protocols still remains a current task.[18]

Rosa Adam was born in Llombai (Valencia, Spain) in 1985. In 2008 she obtained her Bs. C. in Pharmacy by the University of Valencia. In 2013, she received her PhD degree with honors under the supervision of Prof. Belén Abarca and Prof. Rafael Ballesteros at the Organic Chemistry Department of the same university, working in heterocyclic chemistry. From 2014 to 2017 she joined the group of Prof. Matthias Beller at LIKAT (Rostock, Germany) as a Ramon Areces fellow. Her work there was mainly focused in the development of new N- and P-based multidentate ligands and their application in hydrogenation catalysis. In 2017, she joined the group of Prof. Avelino Corma and Dr. Antonio Leyva-Pérez at the Instituto de Tecnología Química (ITQ) at the Polytechnic University of Valencia where she is currently fellow from "La Caixa" Junior Leader Incoming program. Her current research interests are related with the development of new well-defined homogeneous and heterogeneous catalysts for synthetic applications.
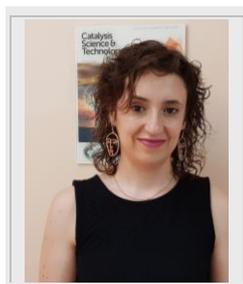
Matthias Beller, born in Gudensberg (Germany) in 1962, obtained his Ph.D. in 1989 under the supervision of Prof. Lutz F. Tietze at the University of Göttingen. After one year of postdoctoral research with Prof. Barry Sharpless at MIT (USA), from 1991 to 1995 he worked at Hoechst AG in Frankfurt. He then started his career at T. U. Munich for inorganic chemistry professor. In 1998, he relocated to Rostock to head the Institute for Organic Catalysis, which became the Leibniz-Institute for Catalysis in 2006. Prof. Beller is head of the German Chemical Society working group "Sustainable Chemistry" and a member of three German Academies of Sciences including the German National Academia "Leopoldina". His research is mainly focused on applying homogeneous and heterogeneous catalysis for the synthesis of fine and bulk chemicals as well as energy technology. He is married to Dr. Anja Fischer-Beller and they have two sons.

2. Catalytic reductive *N*-alkylation of amines using hydrosilanes as reductor

Hydrosilanes have been used extensively as selective and easy-to-use reducing agents in organic chemistry.[16i, 19k, 22f, 24] Their polarized Si-H bonds allow them to act as mild hydride sources, showing increased chemoselectivity for the reduction of carbonyl groups.[24a-c] Hence, they have been also used for the catalytic reductive N-alkylation of amines using CO_2 or carboxylic/carbonic acid derivatives as alkylating sources. In these protocols, amines are selectively functionalized preserving the nature of other reducible moieties.

In Table 1 the reported procedures for the silane-mediated catalytic N-methylation of amines using carbon dioxide as methyl source are summarized. These methodologies allow obtaining secondary and tertiary N-methyl amines with good to excellent yields using CO_2. Original work on this N-methylation using carbon dioxide was described by Cantat et al. in 2013 (Table 1, entry 1).[25] In their work, a wide range of amines were efficiently methylated using as catalyst a novel zinc N-heterocyclic carbene [(IPr)ZnCl$_2$] and PhSiH$_3$.

Shortly after, Beller's group developed an efficient and selective ruthenium-catalyzed protocol in the presence of the suitable phosphine ligand (BuPAd$_2$).[26] More than 20 different amines were subjected to the reaction conditions affording high yields of the desired products (Table 1, entry 2).

After these two initial examples, several protocols appeared showing the importance of this novel catalytic transformation (Table 1, entries 3-17).[27-41] Both metal or metal-free based catalytic systems under different reaction conditions were developed, allowing to prepare in general, the corresponding N-methyl amines in good to excellent yields. Notably, a catalyst-free strategy for the N-methylation of amines with CO_2 and PhSiH$_3$ was reported by the group of Chiang and Lei (Table 1, entry 13).[37]

Table 1. Catalytic N-methylation of amines using CO_2 and silanes
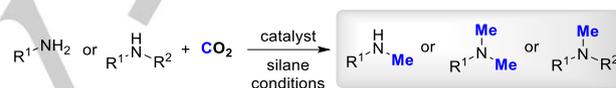
Entry	Catalyst	Reaction conditions	Scope	Ref.
1	[(IPr)ZnCl$_2$] (5 mol%)	PhSiH$_3$ (2-3 eq), CO$_2$ (1-5 bar), THF, 100 °C, 20-72 h	19 exm.	[25]
2	[RuCl$_2$(dmso)$_4$] / n-BuPAd$_2$ (2/4 mol%)	PhSiH$_3$ (4 eq), CO$_2$ (30 bar), toluene, 100 °C, 10-36 h	23 exm.	[26]
3	Free [NHC] (5 mol%)	Ph$_2$SiH$_2$ (3-4 eq), CO$_2$ (1 bar), DMF, 50 °C, 24-48 h	27 exm.	[27]
4	[Fe(acac)$_2$] / PP$_3$ (10/10 mol%)	PhSiH$_3$ (4 eq), CO$_2$ (1 bar), THF, 100 °C, 18 h	4 exm.	[28]
5	[(dippe)Ni(μ-H)]$_2$ or [Ni(COD)$_2$]/dppe (4 or 4/4 mol%)	PhSiH$_3$ (2-4 eq), CO$_2$ (1 bar), toluene, 100 °C, 20 h	7 exm.	[29]
6	[(IMes)CuOt-Bu] (10 mol%)	PhSiH$_3$ (2-4 eq), CO$_2$ (2 bar), PhMe, KOt-Bu (0.1 eq), 100 °C, 20 h	13 exm.	[30]
7	[B(C$_6$F$_5$)$_3$] (5 mol%)	PhSiH$_3$ (2-4 eq), CO$_2$ (5 bar), CH$_3$CN, 140 °C, 24 h	14 exm.	[31]
8	[Thiazolium carb.]	PMHS (4 eq), CO$_2$ (1 bar), DMA, 100 °C,	2	[32]

|		(7.5 mol%)	24 h		exm.	
9	[Cs_2CO_3] (5-10 mol%)	Ph_2SiH_2 (3-6 eq), CO_2 (1 bar), CH_3CN, 80 °C, 24-72 h	21 exm.	[33]
10	[Bis(tzNHC)Rh]OTf (0.5 mol%)	Ph_2SiH_2 (4.5 eq), CO_2 (25 bar), DCM, 25 °C, 24 h	7 exm.	[34]
11	[TBAF] (5 mol%)	PhSiH_3 (3-6 eq), CO_2 (1 bar), CH_3CN, 50 °C, 12 h	15 exm.	[35]
12	[HCO_2Cs] (5 mol%)	Ph_2SiH_2 (4-8 eq), CO_2 (1 bar), CH_3CN, 50 °C, 6-12 h	15 exm.	[36]
13	none	PhSiH_3 (2 eq), CO_2 (1 bar), DMF, 90 °C, 24 h	20 exm.	[37]
14	[Glycine betaine] (3 mol%)	PhSiH_3 (4 eq), CO_2 (3 bar), CH_3CN, 100 °C, 6 h	8 exm.	[38]
15	[NHP]H (20 mol%)	Ph_2SiH_2 (3 eq), CO_2 (45 mg), CD_3CN, 50 °C, 12 h	1 exm.	[39]
16	[K_2WO_4] (7.5 mol%)	PhSiH_3 (3 eq), CO_2 (1 bar), CH_3CN, 70 °C, 12 h	15 exm.	[40]
17	[Lecithin] (5 mol%)	PhSiH_3 (4 eq), CO_2 (3 bar), CH_3CN, 100 °C, 10 h	7 exm.	[41]

IPr = 1,3-bis(2,2-diisopropylphenyl)-imidazolium. THF = tetrahydrofurane. Ad = adamantyl. Acac = acetylacetonate. DMF = N,N-dimethylformamide. DMSO = dimethyl sulfoxide. IMes = 1,3-bis(2,4,6-trimethylphenyl)-imidazolium. PMHS = polymethylhydrosiloxane. NHC = N-heterocyclic carbene. Dippe = 1,2-bis(diisopropylphosphino)ethane. Dppe = 1,3-bis(diphenylphosphino)ethane. DMA = N,N-dimethylacetamide. tz = 1,2,3-triazol-5-ylidene. TBAF = tetra-n-butylammonium fluoride. [NHP]H = 1,3,2-diazaphospholene.

In addition to the results summarized in Table 1, other elegant metal-free examples employing carbon dioxide and silanes for formations of C-N bonds were reported (Scheme 2-4). More specifically, Cantat and co-workers described in 2013 NHC-catalyzed reactions for the efficient synthesis of benzimidazoles and 3,4-dihydroquinazolines from carbon dioxide and diamines (Scheme 2).[42] Two years later, the same group performed the one-pot synthesis of symmetrical and unsymmetrical aminals from CO_2 and secondary amines.[43] Here, using TBD (5 mol%) as organocatalyst more than 20 different aminals could be obtained in excellent isolated yields (Scheme 3).
Complementarily, the groups of Song and Han reported the synthesis of two different aminal derivatives by using glycine

betaine as catalyst (see also Table 1, entry 14). Finally, the group of Xia reported this year an attractive tandem C-C and C-N bond formation strategy for the synthesis of spiro-(indole/indoline)pyrrolidines from N-aryl-2-alkyltryptamines and CO_2 (Scheme 4).[44]
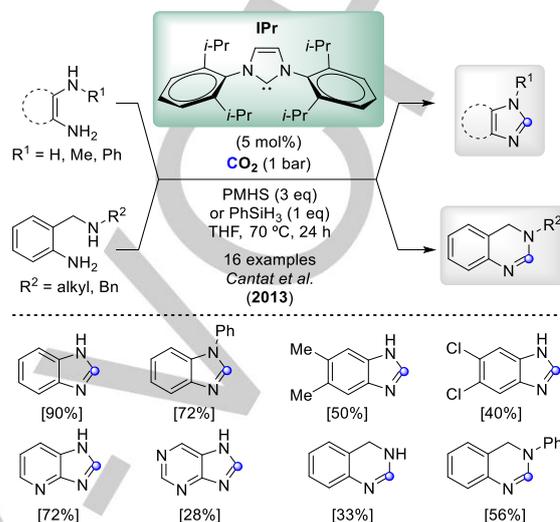
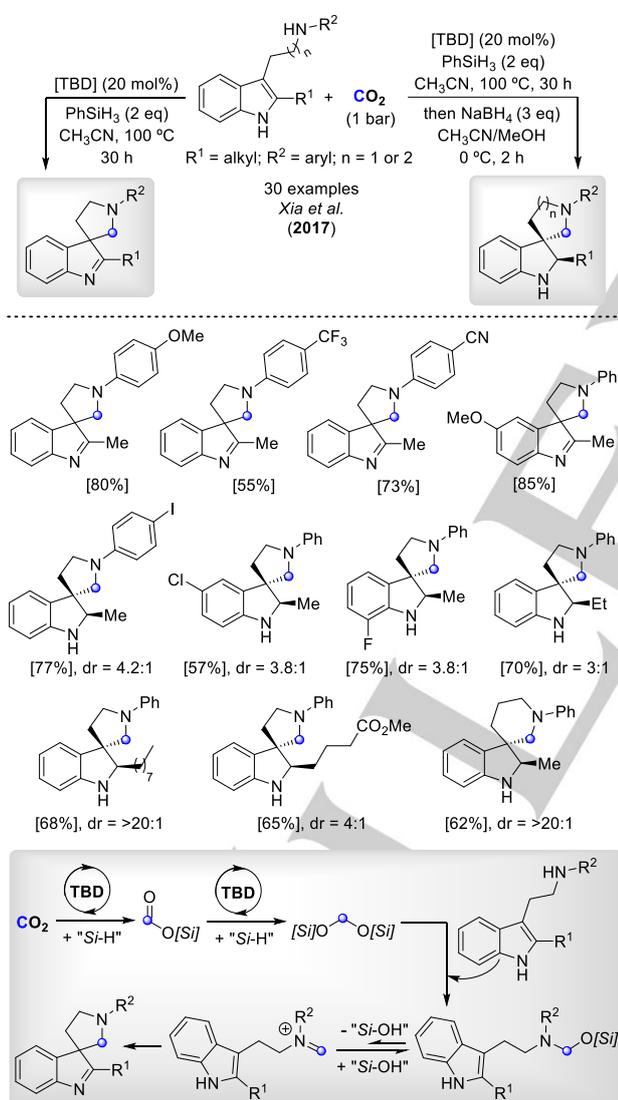**Scheme 2.** Synthesis of benzimidazoles and 3,4-dihydroquinazolines from CO_2 and diamines. Isolated yields are given.
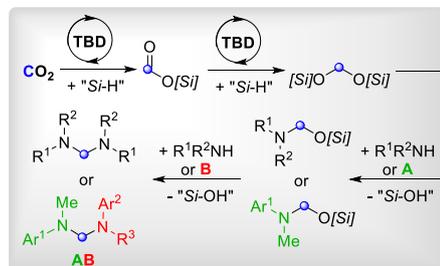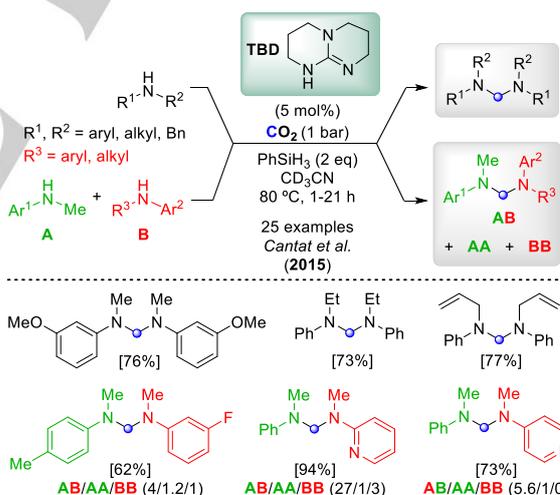
Scheme 3. Organocatalyzed one-pot synthesis of aminals from carbon dioxide and secondary amines by using silanes. TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene. ^{1}H NMR yields are given between brackets. The relative selectivity of the products AB, AA and BB is given between parentheses.

Employing also TBD (20 mol%) as organocatalyst, a wide range of tricyclic organic derivatives were obtained with high yields in a straightforward fashion. In the case of the spiro-indoline based derivatives, good to excellent diastereoselectivities were observed after reduction of the former spiro-indole fragment with NaBH₄.
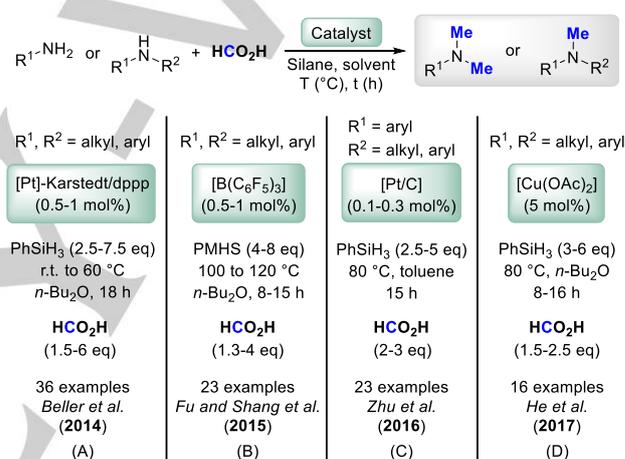
Formic acid is, compared to carbon dioxide, a liquid under ambient conditions, which makes it more convenient to use. This compound is mainly produced through reaction of carbon monoxide and methanol to methyl formate and subsequent hydrolysis, but also can be accessed by CO₂ hydrogenation or via oxidation from biomass.[16a-g, 16i-l, 17b] Formic acid, although known for a long time as mild transfer hydrogenation reagent, recently attracted substantial interest as a potential hydrogen storage material in hydrogen production processes[45] and modern reduction reactions.[46]

Due to its environmentally-benign properties, facile use and storage, formic acid offers stimulating prospective as C1-alkylating source for the N-methylation of amines. In Scheme 5, the reported examples for the synthesis of methylamines using formic acid as C1 feedstock and silanes as hydride source are illustrated.[47] Originally, Beller and co-workers developed in 2014, the first protocol based on the use of formic acid as methylating agent under reductive conditions (Scheme 5, A).[47a] The active platinum catalyst allowed to perform the one-pot synthesis of more than 35 methylamines in high yields.

After this first example, additional homogeneous and heterogeneous systems were chronologically presented as active catalysts for this transformation by the groups of Fu and Shang (Scheme 5, B),[47b, 47c] Zhu (Scheme 5, C)[47d] and He (Scheme 5, D).[47e] In all cases, good to excellent yields of the desired methylamines were obtained under the different reaction conditions noted.

Scheme 4. TBD-catalyzed synthesis of spiro-(indole/indoline)pyrrolidines from N-aryl-2-alkyltryptamines and CO₂ by using silanes in one-pot fashion. Isolated yields are given. Diastereoselectivity (dr) was determined by crude ¹H NMR after in situ reduction.

Scheme 5. N-methylation of amines using formic acid as C1 source in the presence of silanes. Dppp = 1,3-bis(diphenylphosphino)propane.

In the context of the use of greener N-methylation reagents, dialkyl carbonates (carbonic acid derivatives) and, more specifically, dimethyl carbonate (DMC) is a biodegradable and safe compound, which is applied in the chemical industry.[5] The growing worldwide production of DMC (around 1000 barrels/day) is mainly based on the transesterification of cyclic carbonates or the oxidative carbonylation of methanol, albeit emerging protocols using directly CO₂ have been proposed.[5a-d] In this context, the development of N-methylation reactions using DMC offers the possibility to perform eco-friendly processes and constitutes a way towards the indirect valorization of CO₂.

Traditionally, DMC has been used as a green N-methylation agent of primary aromatic amines through a B$_{AL}$2 mechanism.[5] In this reaction a nucleophile attack of the amine to the activated methyl carbon of the methoxy group occurs, requiring harsh reaction conditions. Up to date, only two examples based on the reductive silane-mediated N-methylation of amines by dialkyl carbonates have been reported.[48] In these protocols the C=O moiety is the one used for the methylation, instead of the methyl carbon of the methoxy group (Scheme 6).
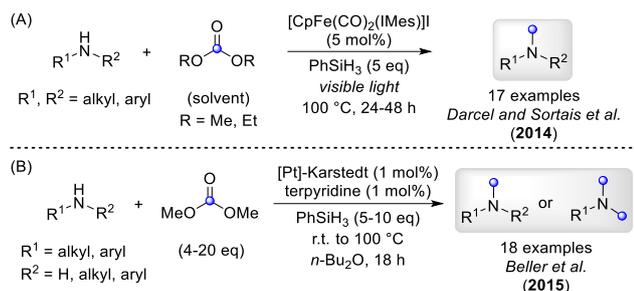
Scheme 6. Silane-mediated reductive N-methylation of amines using dialkyl carbonates catalyzed by: (A) iron complex and (B) platinum system.

The first protocol, catalyzed by a photoactive half-sandwich iron complex, was described by the group of Darcel and Sortais in 2014 (Scheme 6, A).[48a] Different secondary aromatic and aliphatic amines could be efficiently converted into the corresponding N-methyl derivatives. One year later, our group developed an efficient [Pt]-catalyzed methodology for the same transformation achieving the desired methylamines in very good yields (Scheme 6, B).[48b] In both cases, mild reaction conditions were used but the substrate scope was limited to the methylation of secondary amines, with the only exception of aniline, which could be moderately converted with the Pt system.
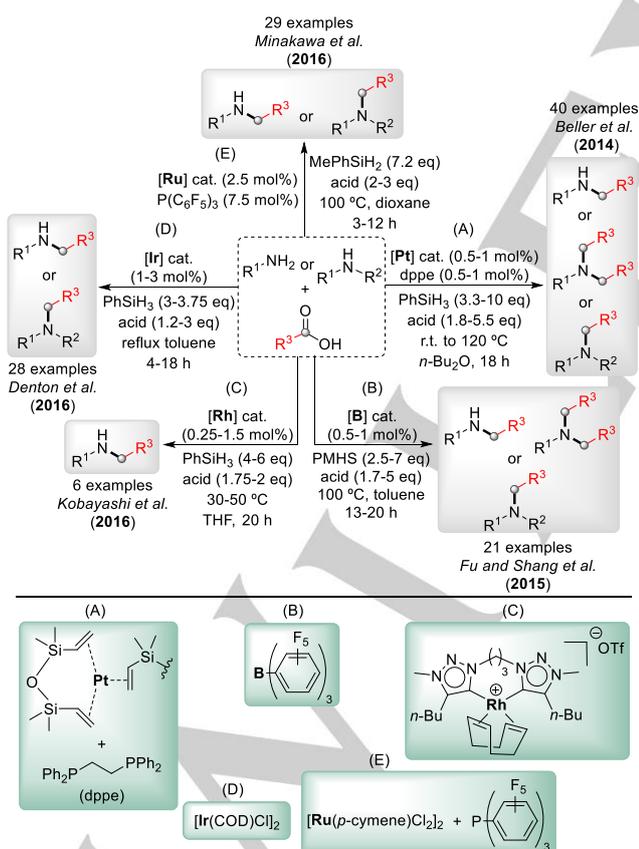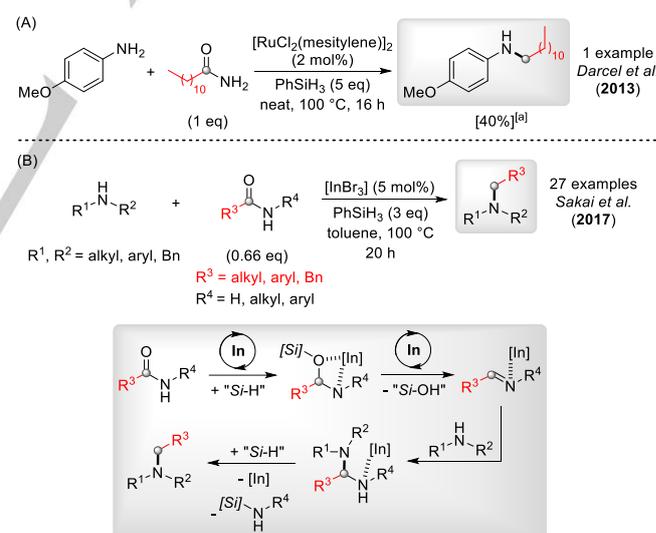
Besides from the N-methylation of amines using C1 sources and with the aim to further functionalize the amine group, carboxylic acids have emerged recently as novel N-alkylating agents of amines. Carboxylic acids are promising alkyl sources due to their wide (bio)availability, stability and large structural diversity.[19d, 19g, 19i, 19k]

In Scheme 6 the methodologies for the N-alkylation of amines with carboxylic acids in the presence of silanes are summarized.[34, 47b, 47c, 49] Pioneering work was reported by Beller's group in 2014, where a [platinum/dppe] system was found as an effective catalyst for the N-alkylation of a wide scope of amines under comparably mild reaction conditions (Scheme 7, A).[49a] In 2015 the group of Fu and Shang published an elegant methodology using a boron-based Lewis acid system where more than twenty N-alkylamines were obtained in excellent yields after reaction with different carboxylic acids (Scheme 7, B).[47b, 47c] Complementarily to these two early described procedures, novel homogeneous systems were found by the groups of Kobayashi,[34] Denton,[49b] and Minakawa[49c] as powerful catalysts for the same transformation (Scheme 7, C-E, respectively).

Remarkably, last year a new practical and catalyst-free approach for the trifluoroethylation of amines with trifluoroacetic acid and phenylsilane was presented by the group of Denton.[50] In this work the authors showed that the trifluoroethylation of a wide range of amines, in the absence of any catalyst, proceeds with excellent yields under mild reaction conditions and avoiding product degradation.

Scheme 7. Hydrosilane-mediated catalytic *N*-alkylation of amines using carboxylic acids and catalyzed by: (A) platinum, (B) boron, (C) rhodium, (D) iridium and (E) ruthenium.

Scheme 8. Amides as N-alkylating sources of amines catalyzed by (A) ruthenium complex and (B) indium salt. [a] Isolated yield.

Apart from carboxylic acids, amides[19d-g] can also be employed as stable and safe alkyl sources for the N-alkylation of the amino group under reductive conditions. So far, only two reported catalytic procedures are known for this transformation (Scheme 8).[51] Considering the work with other carboxylic acid derivatives, it is clear that additional catalytic protocols are feasible and will

be developed in the future. For the first time, in 2013, Darcel et al. described an example of a ruthenium-catalyzed N-alkylation of *p*-anisidine with dodecanamide in the presence of silanes (Scheme 8, A).[51a]

The authors proposed a reaction mechanism in which the catalyst and the silane promoted the dehydration of the amide to a nitrile, which is reduced to an imine that reacted with the *p*-anisidine to afford a secondary imine, that finally is reduced to give the desired alkylated product. Later, the group of Sakai described a general and effective indium tribromide-catalyzed methodology, where more than 25 alkylamines were obtained in high yields by using different amides as N-alkylating sources (Scheme 8, B).[51b] In the same year, the groups of Liu and Sun reported an elegant catalyst-free methodology for the synthesis of benzimidazoles by the N-methylation of *o*-phenylenediamines with DMF derivatives and PhSiH₃.[52] More than 15 different compounds were obtained in good to excellent yields.

Additionally, α-ketoesters have also been used as alkyl sources in the presence of silanes (Scheme 9). This year, Xu, Fan and Xiao et *al.* reported an interesting boron-catalyzed methodology for the synthesis of tetrahydroquinoxalines and their 2(*1H*)-one analogues from 1,2-diaminobenzenes and α-ketoesters.[53] In this metal-free strategy, a fine-tuning of the reaction conditions allowed to selectively obtain several class of derivatives in excellent isolated yields (more than 65 compounds were synthetized). Using a chiral ligand, the asymmetric version of the present protocol was performed, albeit moderate enantiomeric purities were achieved.

The N-alkylation of amine related compounds such as amides,[42, 51a] imines,[47d] nitro compounds[54] and tosylamides[55] has also been reported in the literature. These one-pot reductive procedures employ different starting materials to afford the desired N-alkyl amines under the suitable reaction conditions. As an example already in 2013, the group of Cantat presented a metal-free example that used carbon dioxide and silanes to form new C-N bonds in the reductive N-alkylation of anthranilamide derivatives, to give 4-quinazolinones as main products (Scheme 10).[42] At the same time, a ruthenium-catalyzed procedure for the reductive self N-alkylation of amides to form secondary amines was described by Darcel and co-workers (Scheme 11).[51a] The reaction mechanism, depicted in Scheme 10, also proceeds via the nitrile, as it as the case of the example of the same authors in Scheme 8A.
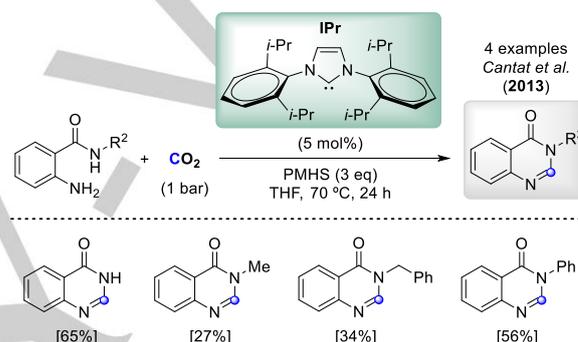
Scheme 10. One-pot synthesis of 4-quinazolinones from carbon dioxide and anthranilamide derivatives. Isolated yields are given.
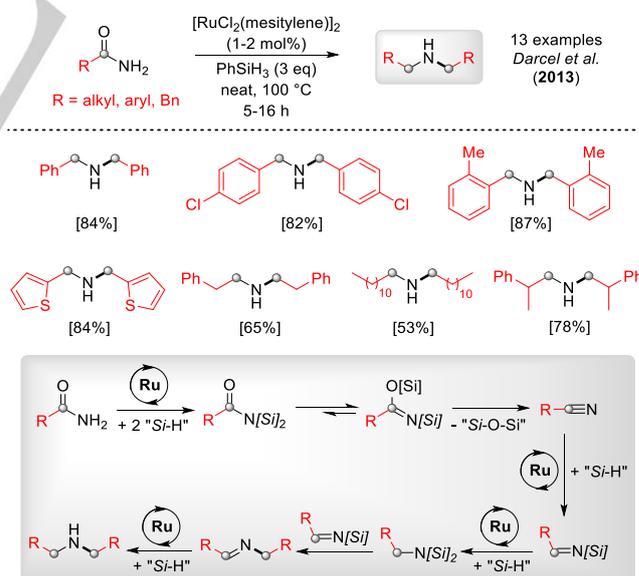
Scheme 11. Ru-catalyzed synthesis of secondary amines from primary amides in the presence of hydrosilanes. Isolated yields are given.

Scheme 9. Synthesis of tetrahydroquinoxaline derivatives and their 2(*1H*)-one analogues (including chiral derivatives) through the boron-catalyzed N-methylation of 1,2-diaminobenzenes using α-ketoesters.

2.1. Catalytic reductive *N*-alkylation of amides, nitro compounds, imines and tosylamides using hydrosilanes as reductant

On the other hand, the use of formic acid as alkyl source in the N-methylation of imines and nitro derivatives has been studied.

In 2016, Zhu and collaborators described the [Pt/C]-catalyzed one-pot N-methylation of aromatic imines to the corresponding methylamines using silanes (Scheme 12).[47d] Several methylated amines were synthetized from the former imines and formic acid in straightforward manner.

One year later, in a joint effort the groups of Sorribes, Llusar, and Beller reported a general methodology using a specific well-defined cubane-type [Mo₃Pt(PPh₃)S₄Cl₃(dmen)₃]BF₄ cluster, formed *in situ* from a mixture of [Mo₃S₄Cl₃(dmen)₃]BF₄ and [Pt(PPh₃)₄] complexes in a (3:1) molar ratio, as unusual catalyst for the dimethylation of nitro compounds to N,N-dimethylamines (Scheme 13).[54] Apart from nitrobenzenes, benzylic and aliphatic nitro derivatives could be directly methylated with formic acid under mild conditions employing this domino transformation.
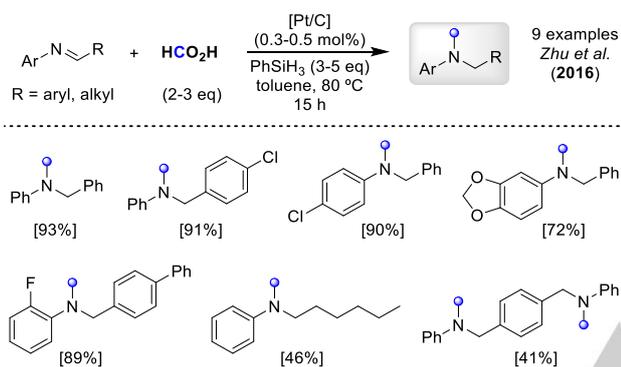
Scheme 12. Synthesis of tertiary amines by N-methylation of aromatic imines using formic acid and silanes. Isolated yields are given.
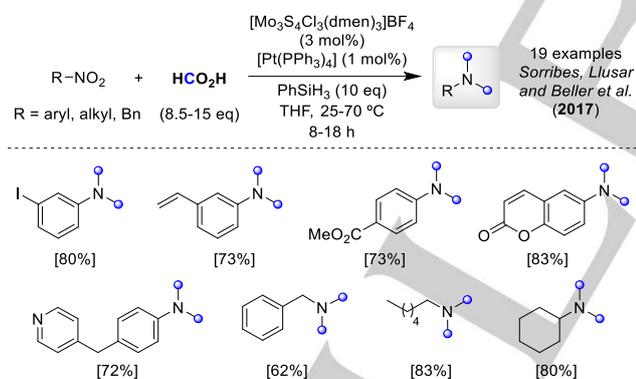
Scheme 13. Direct N-dimethylation of nitro compounds catalyzed by an *in situ* formed well-defined [Mo₃Pt(PPh₃)S₄Cl₃(dmen)₃]BF₄ cubane-type complex catalyst. Dmen: *N,N'*-dimethylethylenediamine. Isolated yields are given.

Moreover, the alkylation of tosylamides with carboxylic acid derivatives was described already in 2012 by the group of Nagashima using a ruthenium-based protocol (Scheme 14).[55] In this work, the authors made use of simple esters as N-alkylating agents for the first time. With this novel methodology in hand, both inter- and intramolecular alkylations of the amino group were performed with very high yields in the presence of silanes. Furthermore, the synthesis of azacycloalkanes and

azaspirocycles could also be achieved with this elegant procedure.
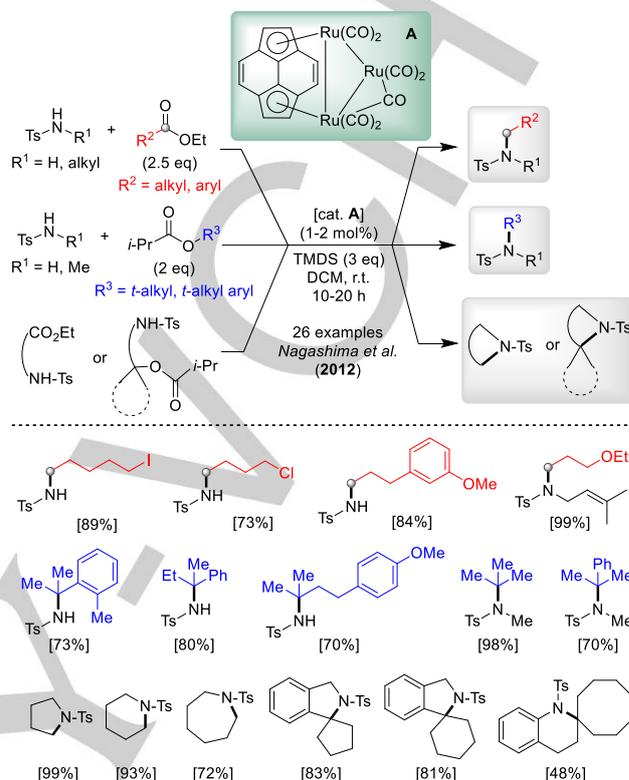
Scheme 14. Ru-catalyzed inter- and intramolecular N-alkylation of sulfonamides with esters in the presence of silanes. Ts = 4-toluenesulfonyl. Isolated yields are given.

3. Catalytic reductive *N*-alkylation of amines using hydroboranes

Boranes are classic strong organic reductants with polarized B-H bonds which have been used in numerous reductive catalytic transformations,[24c, 24e, 56] likewise Si-H bond in silanes. Not surprisingly, few protocols for the N-methylation of amines with carbon dioxide using hydroboranes as reducing agents have been developed recently.[57]

As a first example, the group of Cantat described a novel methodology to produce N-methylamines under metal-free conditions (Scheme 15, A).[57a] In this work, proazaphosphatrane superbases were presented as highly active catalysts for the borane-mediated N-methylation of a wide range of amines under mild conditions. In 2015, Ong and co-workers described another metal-free method of boron activation for the reductive N-methylation of amines with CO₂ catalyzed by carbodicarbenes (CDCs) (Scheme 15, B).[57b] Finally, the groups of Sabo-Etienne and Bontemps reported an iron-catalyzed reduction of CO₂ into methylene followed by C-N bond formation to afford N-alkyl functionalities (Scheme 16).[57c]
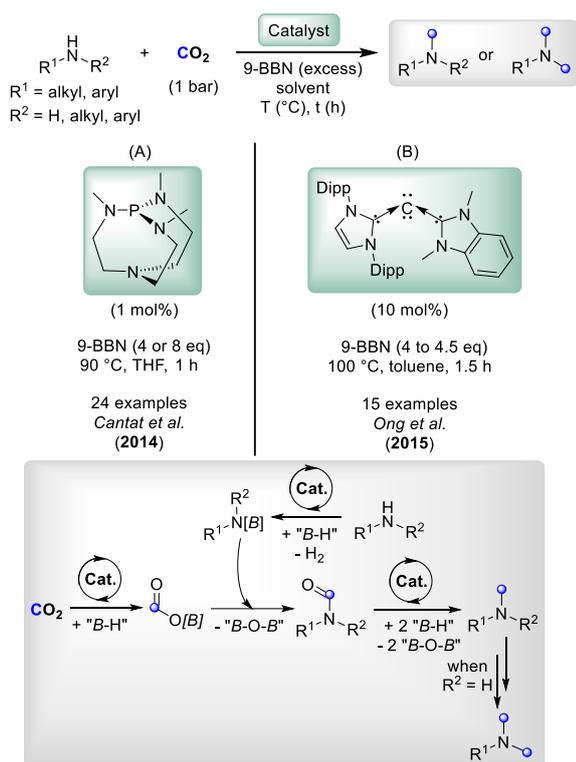
Scheme 15. N-methylation of primary and secondary amines using CO_2 as C1 source and 9-borabicyclo[3.3.1]nonane (9-BBN) as reductor. Dipp = 2,6-diisopropylphenyl.
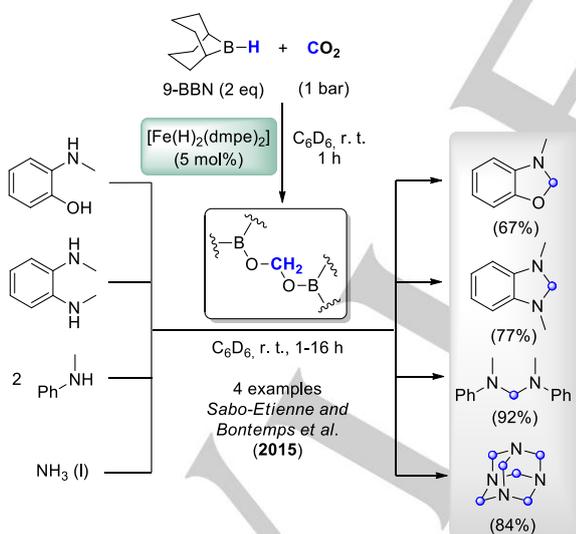
Scheme 16. Iron-catalyzed C-N bond formation using carbon dioxide as C1 source and 9-BBN as reductor. Dmpe = 1,2-Bis(dimethylphosphino)ethane.

3.1. Catalytic reductive *N*-alkylation of nitrobenzenes using boranes

Interestingly, boranes have also been employed as mild reducing agents in the direct methylation of nitrobenzenes. Cantat et al., reported in 2014, the only example describing the one-pot reductive N-methylation of nitrobenzenes with CO_2 as methylating agent and boranes as hydride source (Scheme 17).[57a] Using a superbase as catalyst (see also Scheme 15, A), different nitro derivatives could be converted into the desired methylamines in good to excellent yields.
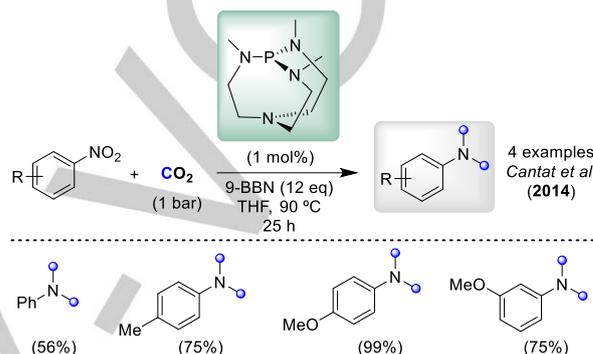
Scheme 17. Metal-free direct N-methylation of nitrobenzenes to dimethylanilines with CO_2 and boranes. GC yields are shown.

4. Catalytic reductive *N*-alkylation of amines using molecular hydrogen

The general advantages of reductive N-alkylation methodologies using hydrosilanes and hydroboranes are the mild conditions, which are applied in these protocols. However, as a downside these methods suffer from low atom-efficiency and tedious work-up procedures. In addition, due to the price of the stoichiometric reductant, such methods are mainly limited to g-scale synthesis. In this respect, the use of molecular hydrogen as a greener and more practical reducing agent offers possibilities for large scale applications.[19d, 19f, 19g, 24c, 24e, 58] Specifically, the industrial synthesis of methylamines is interesting. In this part of the review the methodologies for the reductive N-alkylation of amines (including ammonia) and related compounds using CO_2 and carboxylic acid derivatives in the presence of hydrogen will be summarized.

Scheme 18. Synthesis of monomethylamine (MMA), dimethylamine (DMA) and trimethylamine (TMA) by catalytic N-methylation of ammonia and its surrogates using (CO_2/H_2). LDH = lamellar double hydroxides.

Concerning the methylation of ammonia,[59] more than twenty years ago, Baiker et al. reported the first example of the synthesis of methylamines (MMA, DMA and TMA) using a mixture of NH_3, H_2 and CO_2 (Scheme 18, A).[59a, 59b] The reaction was catalyzed by a heterogeneous [Cu/Al_2O_3] system under harsh reaction conditions. Based on this original work, the same group developed other related heterogeneous catalysts for this reaction (Scheme 18, B-D).[59c-e] Thus, [metal/Al_2O_3],[59c] [Cu/metal oxide][59d] and [Cu-Mg-Al] lamellar double hydroxides (LDH)[59e] (Scheme 18, B, C and D, respectively) were studied as novel catalysts for the selective methylation of ammonia using carbon dioxide and molecular hydrogen.

After the seminal work of Baiker et al., two examples synthesizing trimethylamine (TMA) from ammonia, or its surrogates, and CO_2 have been recently described.[59f, 59g] On the one hand, the groups of Leitner and Klankermayer found a homogeneous [Ru/Triphos/Al] system able to perform the

selective methylation of ammonia or ammonium chloride with CO_2 and H_2, under milder conditions than the previously described heterogeneous systems (Scheme 18, E).[59f] On the other hand, Shimizu and Toyao groups showed that the heterogeneous catalyst [Pt-MoOx/TiO_2] can promote the synthesis of TMA starting from ammonia or different surrogates (Scheme 18, F).[59g]

Closely related with the methylation of ammonia, several homogeneous and heterogeneous systems have been described as active catalysts for the reductive methylation of amines with CO_2 and H_2 (Scheme 19).[60] In 2013, the groups of Klankermayer and Beller simultaneously described the first homogeneous catalyst systems able to directly synthesize methylamines from CO_2 and H_2 (Scheme 19, A and B, respectively).[60a, 60b] Both examples used a [Ru/Triphos] complex in combination with the suitable acid additive ($HNTf_2$, CH_3SO_3H or LiCl) as co-catalyst, under similar temperatures and pressures. While the example reported by Klankermayer focused on the methylation of aromatic amines to give N,N-dimethylanilines,[60a] Beller's protocol could be applied for both aromatic and aliphatic amines by changing the acid co-catalyst (MSA for aromatic amines and LiCl for the aliphatic ones).[60b] Moreover, the selective monomethylation of a few primary anilines was carried out under the suitable reaction conditions. In addition, the selective monomethylation of aromatic diamines with different electronic character was showcased. Despite the reductive conditions of these methylation processes, both methodologies showed good tolerance for different sensitive groups such as halogens, ester, and hydroxyl groups. In one example also the more challenging alkene moiety was preserved, although a high degree of substitution was required. From a mechanistic point of view, both groups proposed a sequential formylation of the amine followed by the formamide reduction as the main pathway of the process.

Next, Shi and collaborators described the heterogeneous systems [CuAlOx] (Scheme 19, C)[60c] and [Pd/CuZrOx] (Scheme 19, D)[60d] as active catalysts for the N-methylation of a broad scope of amines with CO_2/H_2 mixtures. In the case of the Pd-based system, milder reaction conditions were required in comparison with the copper-aluminum oxide catalyst.

Complementary to these works, other heterogeneous materials such as [Pt-MoOx/TiO_2],[60e] [Au/Al_2O_3-VS],[60f, 60g] [PdGa/TiO_2][60h] and [Re/TiO_2][60i] were reported by the groups of Shimizu, Toyao, Wang and Su, and Lin, Yu and Zhao (Scheme 19, E-H) as efficient catalysts for the same transformation. Notably, the [Au/Al_2O_3-VS][60f, 60g] catalyst described by the groups of Wang and Su was also able to produce unsymmetrical N-tertiary alkylamines from primary amines, aldehydes and CO_2 in one-pot.

In 2013, Liu and co-workers described a synthetic application of this methodology for obtaining benzimidazoles in high yields from o-phenylenediamines using a CO_2/H_2 mixture in the presence of a ruthenium complex (Scheme 20).[61] This work complements the protocol reported by Cantat in the same year but employing silanes (see Scheme 2 of this review).[42]

Scheme 19. Synthesis of N-methyl and N,N-dimethylamines by catalytic N-methylation of amines using CO_2 and H_2. MSA = methanesulfonic acid.

Amine substrates	Catalyst	Reaction conditions	
(A) R^1 = aryl R^2 = H, aryl, alkyl	[Ru(Triphos)(tmm)] (2.5 mol%) HNTf$_2$ (5 mol%)	CO_2 (20 bar) H_2 (60 bar) THF, 150 ºC 10-48 h	14 examples *Klankermayer et al.* (**2013**)
(B) R^1 = aryl, alkyl, Bn R^2 = H, aryl, alkyl, Bn	[Ru(acac)$_3$] (1-5 mol%) Triphos (2-10 mol%) MSA or LiCl (1.5-7.5 mol%)	CO_2 (20 bar) H_2 (60 bar) THF, 140 ºC 5-36 h	33 examples *Beller et al.* (**2013**)
(C) R^1 = aryl, alkyl, Bn R^2 = H, aryl, alkyl, Bn	[CuAlO$_x$] (50 mg/mmol s.m.)	CO_2 (30 bar) H_2 (60-70 bar) Hexane, 160 ºC 24-48 h	27 examples *Shi et al.* (**2014**)
(D) R^1 = aryl, alkyl, Bn R^2 = H, alkyl	[Pd/CuZrO$_x$] (2 wt% Pd) (0.75 mol% Pd)	CO_2 (10 bar) H_2 (25 bar) Octane, 150 ºC 30-48 h	27 examples *Shi et al.* (**2014**)
(E) R^1 = aryl, alkyl, Bn R^2 = alkyl	[Pt-MoO$_x$/TiO$_2$] (0.1-3 mol% Pt)	CO_2 (5 bar) H_2 (40-50 bar) neat, 170-230 ºC 24 h	10 examples *Shimizu et al.* (**2014**)
(F) R^1 = aryl, alkyl, Bn R^2 = H, aryl, alkyl, Bn	[Au/Al$_2$O$_3$-VS] (0.5 mol% Au)	CO_2 (20 bar) H_2 (60 bar) Hexane 140-170 ºC, 7 h	23 examples *Wang and Su et al.* (**2015**)
(G) R^1 = Ph R^2 = Me	[PdGa/TiO$_2$] (0.3 mol% Pd)	CO_2 (50 bar) H_2 (50 bar) Octane 180 ºC, 8 h	1 example *Lin, Yu and Zhao et al.* (**2016**)
(H) R^1 = aryl, alkyl, Bn R^2 = alkyl	[Re/TiO$_2$] (2 mol% Re)	CO_2 (10 bar) H_2 (50 bar) Octane 180-200 ºC 24-36 h	10 examples *Toyao and Shimizu et al.* (**2017**)

Alternatively to the use of CO_2/H_2 mixtures for the direct synthesis of N-methylamines, Cantat et al. developed in 2014 an appealing strategy where formic acid acts as the unique source of carbon and hydrogen (Scheme 21, A).[62] This methodology was the first example where no sacrificial external reductant is required to perform the reductive N-methylation of an amine. The catalyst is based on the previously studied [Ru/Triphos] complex in combination with acid additives. One year later, Kim and co-workers developed a new heterogeneous PdAg nano-alloy supported on magnetite/graphene oxide [Pd$_{47}$Ag$_{53}$/Fe$_3$O$_4$/N-rGO], able to perform the same transformation without additives but using a large excess of formic acid (Scheme 21, B).[63]
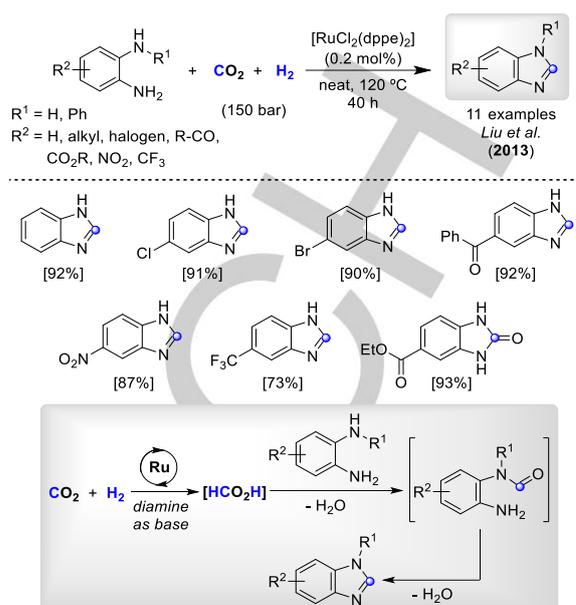
Scheme 20. Ruthenium-catalyzed direct synthesis of benzimidazoles using CO_2/H_2 and *o*-phenylenediamines. Isolated yields are given.
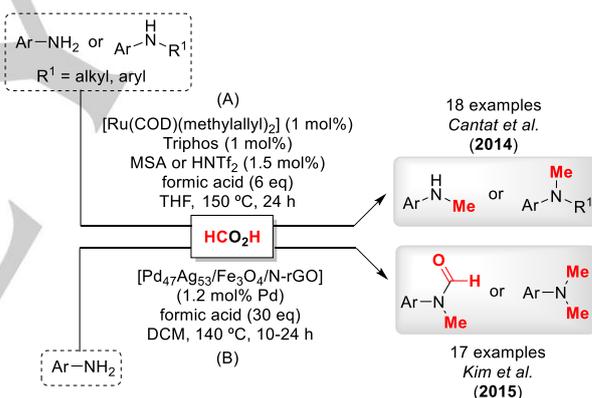
Scheme 21. N-methylation of aromatic amines using formic acid as the unique carbon and hydrogen source, catalyzed by: (A) [Ru/Triphos/acid] system and (B) heterogeneous PdAg nano-alloy catalyst.

Dimethyl carbonate (DMC) *vide supra* is an attractive C1 source for synthetic and industrial chemists due to its safety and availability.[5] In 2016, Beller et al. reported the only example in which DMC has been used as methylating agent in the presence of H_2 as reductor (Scheme 22).[64] In this work, again a [Ru/Triphos/additive] catalyst combination was able to carry out the methylation of aromatic and aliphatic primary and secondary amines (more than 40 examples) using the carbonyl function of DMC as methyl source.
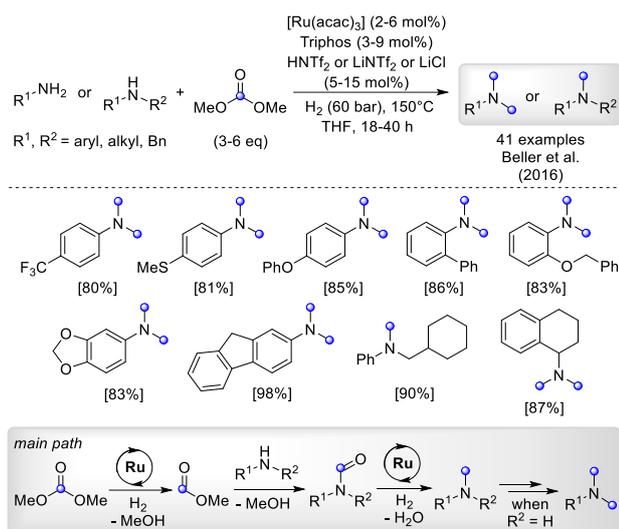
Scheme 22. Ruthenium-catalyzed synthesis of methylamines by using dimethyl carbonate and molecular hydrogen. Isolated yields are given.

This process represents an improvement when compared with the earlier described protocols for the same reaction but using silanes (see Scheme 5).[48]

As we previously commented, the use of carboxylic acids/esters as alkyl sources in N-alkylation is attractive to produce a variety of functionalized alkylamines. In addition, the employment of H_2 as reductant in combination with these alkyl sources is highly desired. In 2007, following this general idea Cole-Hamilton and co-workers reported a [Ru/Triphos]-catalyzed hydrogenation of nonanoic acid in the presence of ammonia, affording a mixture of nonylamine and dinonylamine, albeit in relatively low yields and selectivities.[65]

Based on this pioneering work, Beller's group developed during the last three years several methodologies[66] for the reductive N-alkylation of amines using carboxylic acids (also in combination with CO_2),[66a] natural occurring triglycerides from biomass and esters[66b, 67] (Scheme 23, A-B, C and D, respectively). An in situ [Ru(acac)$_3$/Triphos/HNTf$_2$] system was the active catalyst in all these transformations, affording excellent yields of a wide range of N-alkylated products. Remarkably, multicomponent selective couplings between aniline, CO_2 and a carboxylic acid were efficiently performed to produce tertiary N-alkylamines in a one-pot strategy (Scheme 23, B).[66a] Moreover, sunflower oil[67b, 67c] was directly used as a highly effective N-alkylating source (Scheme 23, C).[66b] From a mechanistic standpoint, an amide formation and its subsequent hydrogenation was postulated as a major pathway of the overall process. Very recently, a related tailor-made homogeneous cobalt catalyst formed in situ from [Co(BF$_4$)$_2$·6H$_2$O] and the (p-anisole)-Triphos ligand, was also developed by our group for the additive-free N-alkylation of amines with carboxylic acids.[68]
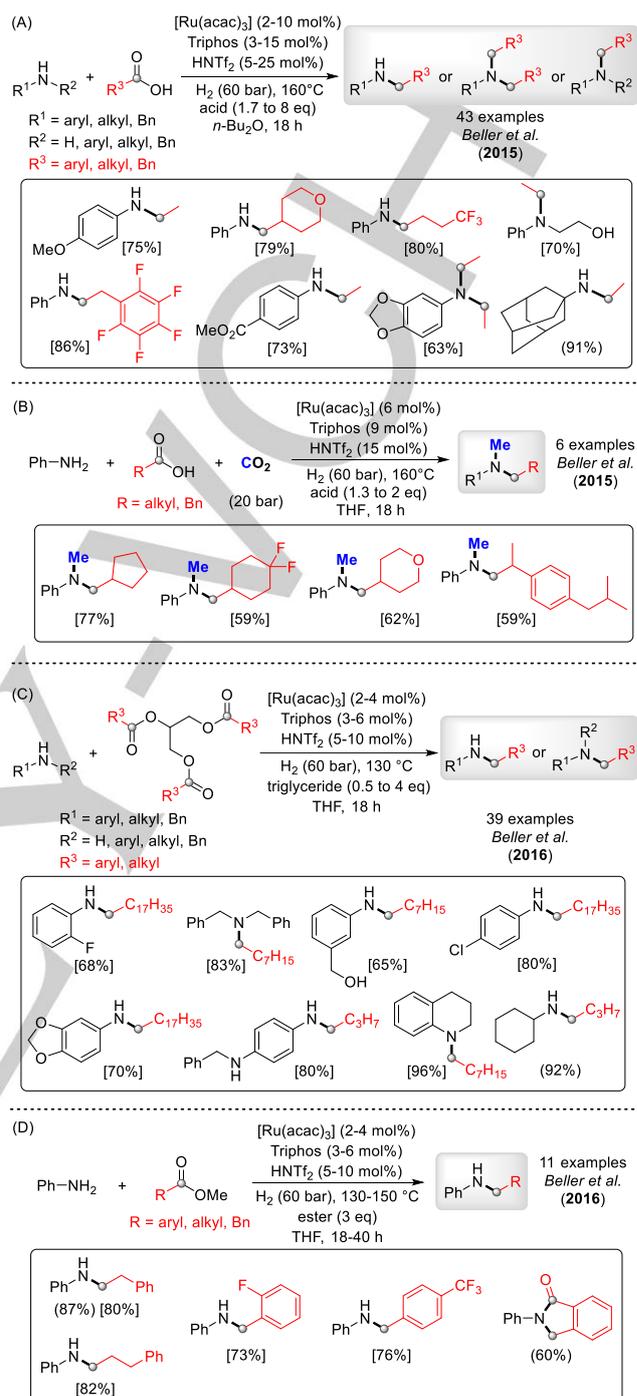
Scheme 23. Reductive catalytic one-pot synthesis of N-alkylated amines using H_2 and: (A) carboxylic acids, (B) carboxylic acids and CO_2, (C) triglycerides and (D) methyl esters as alkylating agents. Between parentheses are shown GC yields. Isolated yields are given between brackets.

Complementarily, Cole-Hamilton and co-workers described an interesting methodology for the direct synthesis of aliphatic N-phenyl heterocycles from diesters and aniline.[69] The desired heterocycles were efficiently produced through the double N-

alkylation of the amine. The authors postulate a main pathway in which one of the ester groups is partially hydrogenated to aldehyde and then affords the monoalkylated amine through the reductive amination at low hydrogen pressure (10 bar). Next, the hydrogenation of the second ester group gives an aldehyde which intramolecularly reacts with the secondary amine producing the final desired N-phenyl heterocycle. However, hydrogen borrowing reactions between the diol (formed from the total hydrogenation of both ester groups) or methanol and the amine are also postulated as a minor pathway and explain some of the by-products. The *in situ* [Ru/Triphos/MSA] combination is used as catalyst and high temperatures (220 ºC) are required.

Closely related with this protocol, the same authors described the synthesis of α,ω-diamines using dicarboxylic acids and their esters with the same catalytic system in similar conditions.[70] Interestingly, primary diamines could also be obtained from aqueous ammonia and diacids or diesters, although by a sequential one pot reaction involving a first hydrogenation of the diacid or diester to diol followed by addition of ammonia.

Finally, Shimizu and co-workers reported in 2017 the first heterogeneous catalyst [Re/TiO$_2$] able to perform the N-alkylation of amines with carboxylic acids or esters.[60i] Specifically, the authors performed the N-alkylation of dimethylamine with 3-phenylpropionic acid and the methyl ester in good yields at 200 ºC.

4.1. Catalytic reductive *N*-alkylation of amides, nitrobenzenes, nitriles, imines and quinoline derivatives using hydrogen

The one pot reductive N-alkylation of amine related compounds such as amides,[60a] nitro,[60c, 60d] nitriles,[60c] imines,[71] and quinoline[72] derivatives using hydrogen and the corresponding alkylating agent was also developed in the last years. In fact, several homogeneous and heterogeneous catalysts with good activity for the N-alkylation of amines are able to perform such related one-pot reductive methylations using CO$_2$ (Scheme 24). Smart examples have been reported by the groups of Klankermayer (Scheme 24, A and E),[60a, 71] Shi (Scheme 24, B-D),[60c, 60d] and Liu and Han (Scheme 24, F)[72] since 2013. Generally, good to excellent yields of the corresponding N-methylated products could be obtained in one-pot fashion.

Moreover, Cao *et al.* employed formic acid as alkylating source for the one-pot N,N-dimethylation of nitrobenzenes in the presence of H$_2$ and using [Au/rutile] as heterogeneous catalyst (Scheme 24, A).[73] Interestingly, the same system catalyzed the direct formation of benzimidazoles from *o*-dinitrobenzenes without requiring hydrogen (Scheme 24, B). Both, dimethylanilines and N-heterocycles were synthetized in very high yields using gold catalysis.

	Catalyst	Reaction conditions	
(A)	[Ru(Triphos)(tmm)] (2.5 mol%) HNTf$_2$ (5 mol%)	CO$_2$ (20 bar) H$_2$ (60 bar) THF, 150 ºC 15 h	1 example *Klankermayer et al.* (**2013**)
(B)	[CuAlO$_x$] (50 mg/mmol s.m.)	CO$_2$ (30 bar) H$_2$ (70 bar) Hexane, 170 ºC 48 h	4 examples *Shi et al.* (**2014**)
(C)	[Pd/CuZrO$_x$] (2 wt% Pd) (0.75 mol% Pd)	CO$_2$ (10 bar) H$_2$ (25 bar) Octane, 150 ºC 30 h	4 examples *Shi et al.* (**2014**)
(D)	[CuAlO$_x$] (50 mg/mmol s.m.)	CO$_2$ (30 bar) H$_2$ (70 bar) Hexane, 170 ºC 48 h	3 examples *Shi et al.* (**2014**)
(E)	[Ru(Triphos)(tmm)] (5 mol%) HNTf$_2$ (10 mol%)	CO$_2$ (20 bar) H$_2$ (60 bar) THF, 100-160 ºC 20-24 h	23 examples *Klankermayer et al.* (**2014**)
(F)	[Ru(acac)$_3$] (0.5-1.5 mol%) Triphos (1-3 mol%) MSA (10 mol%)	CO$_2$ (20 bar) H$_2$ (80 bar) THF, 160 ºC 16-36 h	7 examples *Liu and Han et al.* (**2017**)

Scheme 24. Synthesis of N-methylamine derivatives by reductive methylation of: (A) amides, (B) nitrobenzenes, (C) nitriles, (D) imines and (E) quinoline compounds using (CO$_2$/H$_2$).

Scheme 25. [Au/rutile]-catalyzed (A) one-pot N-methylation of nitrobenzenes to dimethylanilines and (B) direct synthesis of benzimidazoles from *o*-dinitroarenes by using formic acid with or without hydrogen.

5. Catalytic reductive *N*-alkylation of amines using nitriles as alkylating sources

Nitriles are important building blocks for polymers, agrochemicals, molecular electronics, and high-performance materials.[74] In organic synthesis, they serve as key intermediates for obtaining heterocycles as well as precursors for different valuable fine chemicals.[74-75] In the last years, only two examples of reductive procedures using nitriles as N-alkylating sources have been reported.[76]

In this respect, original work was published by the group of Sajiki in 2012 (Scheme 26, A and B).[76a] In this contribution, more than 45 different alkylated amines were efficiently produced using [Pd/C] in the presence or H$_2$ under mild reaction conditions (Scheme 26, A). In addition, selective N-monoalkylation reactions of primary aliphatic amines were performed with [Rh/C] as catalyst enhancing the possibilities of this methodology (Scheme 26, B).

Very recently, a general and selective non noble metal-catalyzed N-alkylation of amines with nitriles in the presence of ammonia borane as hydride source, was described by Zhou, Liu and co-workers (Scheme 26, C).[76b] In this work, a novel well-defined cobalt NNP pincer complex was shown to be highly active for the synthesis of a wide range of N-alkylated amines from nitriles and amines.

Closely connected with this approach are several examples reported[77] by the groups of García,[77a] Milstein,[77b, 77e] Berke,[77c] and Prechtl[77d] that imply nitrile self-coupling or cross-coupling with an amine to afford imines.

5.1. Catalytic reductive *N*-alkylation of nitrobenzenes and nitriles using nitrile derivatives as alkylating sources

Nitriles can also participate as N-alkylating sources of amine related compounds in a one pot procedure. In this regard in 2012, the group of Sajiki reported a protocol in which nitrobenzenes are reduced and alkylated with nitriles using [Pd/C] as catalyst (Scheme 27) in the presence of hydrogen.[76a]

Scheme 27. [Pd/C]-catalyzed preparation of aromatic secondary amines from nitrobenzenes, using nitriles as N-alkylating source and H$_2$ as redactor. [a] NH$_4$OAc (1 eq) was added. Isolated yields are given.

Scheme 28. Cobalt-catalyzed synthesis of secondary amines from nitriles and ammonia borane. Isolated yields are given.

Scheme 26. (A) [Pd/C]-catalyzed N-alkylation of primary and secondary amines with nitriles as alkyl source and H$_2$ as reductant. N-monoalkyl products are formed exclusively when (R^1 = aryl) and N,N-dialkyl products when (R^1 = alkyl). (B) [Rh/C]-catalyzed selective N-monoalkylation of primary alkylamines using nitriles. (C) Synthesis of N-alkylated amines with a cobalt pincer catalyst using nitriles and ammonia borane. HFIP = hexafluoroisopropanol.

Finally, Zhou and Liu et al. developed in 2016, the only up to date described methodology able to afford secondary amines from the self-coupling of a nitrile (Scheme 28).[76b] The authors employed ammonia borane as reducing agent and a cobalt complex as catalyst to synthetize several secondary amines in one-pot fashion. Contrary to previously reported systems,[77] the active catalyst was able to hydrogenate the secondary imine intermediate using low catalyst loadings.

6. Summary and Outlook

The development of new synthetic tools for the N-alkylation of amines is an important topic for organic synthesis and catalysis due to the large number of applications of these compounds. In the last 5 years, a number of interesting catalytic reductive N-alkylation procedures using compounds with a high oxidation state as alkyl sources have been described. CO_2 and carboxylic acid derivatives are now feasible N-alkylating agents, at least at the laboratory scale. The wide availability of CO_2, the great structural diversity of carboxylic acid derivatives and the stability and non-toxicity of these compounds make them ideal alkyl sources. This impressive development probably responds to our higher capacity for better designing more powerful catalysts with better selectivities. In this review we tried to show an updated picture of the currently available methods to perform the reductive N-alkylation of amines using CO_2 or carboxylic acid derivatives in a one pot fashion.

It is important to consider the growing interest in greener alkylation protocols that avoid the generation of large amounts of waste and use safer reagents, especially for industrially relevant processes. In this context, the existing methodologies that use silanes or boranes as reducing agents have the advantage of employing very mild conditions, but are less desirable from the point of view of the waste generation. Due to these reasons, the future development in this field will be probably more concentrated in the design of new catalysts, either homogenous or heterogeneous, able to perform the N-alkylation of amines using H_2 as reducing agent. Obviously, this topic will evolve parallel to the development of more efficient hydrogenation catalysts, able to work at lower concentrations and milder conditions. On the homogeneous side is interesting to pay attention to the design of new ligands and to metal ligand cooperation catalysts, frequently enabling the employment of less expensive base metals. On the heterogeneous area, the design of new materials with improved metal-support interactions and fine-tuned structures is currently experiencing a growing development that will probably find practical applications in hydrogenation chemistry.

We hope that this minireview inspire to homogeneous and heterogeneous catalytic chemists to explore the potential of their new materials in this class of N-alkylation reactions. Moreover, these methodologies already show interesting synthetic applications (e. g. synthesis of heterocycles or diamines) that will certainly undergo a further development in the near future.

Acknowledgements

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