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Review

A Brief Review: Advancement in the Synthesis of Amine through the Leuckart Reaction

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Abstract: This review presents a summary of reactions that take place during the "Leuckart-type reaction". The significance of, as well as recent advancements in, the synthesis of amines through simple and inexpensive methods using readily available raw materials is discussed. This review includes all catalytic and noncatalytic reactions that involve the Leuckart method. Recent studies have shown that at least a quarter of C–N bond-forming reactions in the pharmaceutical industry are occur with the support of reductive amination. Recently, experimental conditions have achieved excellent yields. The "Leuckart-type reaction" is technically associated with Eschweiler–Clarke methylation. Compounds are grouped in accordance with the precept of action. This includes drugs affecting the central nervous system, cardiovascular system and gastrointestinal tract; anticancer drugs, antibiotics, antiviral and antifungal drugs; drugs affecting anxiety; convulsant, biotic, and HIV drugs; and antidiabetic drugs. Therefore, this review supports the development of the Leuckart-type preparation of nitrogenous compounds, as well as their advancement in other areas of human development.

Keywords: Leuckart-type reaction; synthesis of amines; catalytic and noncatalytic reaction; Leuckart method

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1. Introduction

1.1. Background

The Leuckart reaction is a process commonly known for its use in the reductive amination of aldehydes and ketones [1–4]. The Leuckart reaction is a very famous and unique method used for the synthesis of amines and one-pot reductive amination [5–7].

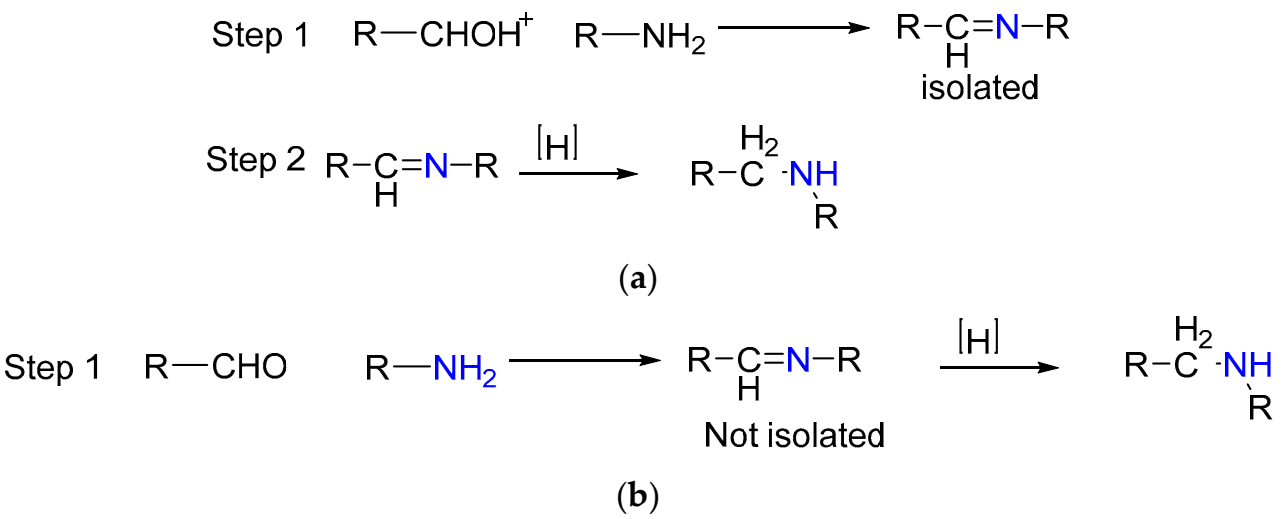
In 1885, Leuckart first discovered this reaction, and as a result of his experimental work, he concluded that heating a mixture of benzaldehyde and formamide results in the production of various kinds of benzalamine, instead of his sought product. Wallach explained the preliminary steps of the reaction [8], and Ingersoll and his colleagues used this reaction in the preparation of a series of substituted α-phenethylamine compounds. As a result, this method has been widely used and become well known. The most famous applications of this method include the preparation of "trimethylamine" from NH_3, "formaldehyde" and "formic acid", and the "Eschweiler–Clarke" method for the methylation of 1° and 2° amine [3]. Recently, this reaction has been used to synthesize a large number of amines and useful drugs [8].

Nitrogen heterocycles exhibit various organic and pharmacological activities due to their similarities to many herbal and artificial molecules with acknowledged biological activity [9]. Thus, they play a key role in the synthesis of "polyamides", "polyureas", and "polyepoxydes", which are all useful in automotive, aerospace, building and health applications [10]. Reductive amination plays an important role in pharmaceutical and medicinal chemistry. According to research performed by Roughley et al. a quarter of C–N bond-forming reactions in pharmaceutical applications are carried out using the reductive amination method [11]. Thus, reductive amination has attracted much attention throughout the 20th century [12]. Reductive amination in the presence of formic acid is called the

"Leuckart Wallach reaction", wherein formic acid serves as a reducing agent by supplying a hydride ion [13]. This reaction is also known as the "Leuckart reaction", sometimes called "Leuckart reductive amination", "Leuckart alkylation", "Leuckart synthesis" or "Leuckart reduction". It requires a carbonyl-containing center and a formamide reagent. It has been reported that using a formamide instead of an ammonium format produces good yields, and ammonium formate is the prime reactant. A "Leuckart-type reaction" is not affected by the presence of water (other than formamide). Similarly, at a lower reaction temperature, a higher yield of 2° amine can be obtained by reacting with a higher concentration of "formic acid". However, the concentration of formic acid at high reaction temperatures is not as effective as that at low temperatures [4]. According to Roughleg's analysis of reactions used in the production of medicines, 25% of C–N bond-forming reactions include "reductive aminations". Common reducing agents that influence "reductive amination" include $NaBH_4$, $NaBH_3CN$", and $NaBH(OAc)_3$, and more precise operations include the "Leuckart" and "Eschweiler–Clarke reactions" [14]. The use of formic acid as a "reducing agent" has already been well explored for its use in mono-catalytic reductive amination, i.e., the Leuckart–Wallach and Eschweilar–Clarke reactions [15].

Very recently, the reductive amination of "carbonyl compounds" has been very effective in synthesis because ketones or aldehydes are convertible into the corresponding alkyl amines in a single reaction step. Compared with previous methods, the LW reaction is easy and clean. It achieves higher productivity and high purity [16]. When ammonium formate or formamide is used as a reducing agent, reductive amination is called the "Leuckart reaction" [17]. This reaction appears to be very suitable for the "stereoselective synthesis" of (amine precursors), i.e., "bicyclic amines", "amino alcohols", and "diamines", all of which have numerous uses in pharmaceuticals and in asymmetric synthesis [18]. The "Leuckart-type reaction" is particularly recognized for the conversion of certain aldehydes and ketones and their derivatives into amines. It is a form of amination reaction that involves the transformation of carbonyl groups to amines through intermediate carbon double-bond nitrogen groups of compounds (imine compounds), sometimes called Schiff bases. It is considered a simple and important method for the synthesis of amines, and most of the pharmaceutical industry uses this method to produce amines. This reaction requires a mixture of carbonyl compounds and formate or amine in the presence of heat [3].

The "Leuckart reaction" has two types [17], including indirect reductive amination, in which the imine is separated from the product of the corresponding carbonyl compound and amine and reduced with a suitable reducing agent to obtain the "corresponding amine" (Scheme 1a), and direct reductive amination (Scheme 1b) or the "one-pot reaction", wherein the intermediate imine is not separated, but a "reducing agent" is added to the same reaction tank to form a carbonyl compound and amine [17]. "Leuckart's reaction" was not widely used as a preparation method until 1936, when Ingersoll and colleagues developed a procedure with high yields derived from various ketones. Novelli showed that under similar experimental procedures, N-alkyl formamide was able to achieve a comparable secondary amine yield on some alternative acetophenones when using the same experimental method [19].



Scheme 1. Mode of reductive amination. (**a**) Indirect reductive amination. (**b**) Direct reductive amination.

1.2. Related Reactions

This reaction correlates to the "Eschweiler–Clarke methylation" reaction [20]. Primary and secondary amines are aminated into tertiary amines. When the ketone is replaced by formaldehyde, the "Eschweiler–Clarke reductive" alkylation of amines takes over [13,21]. Some related reactions are given in (Figure 1).

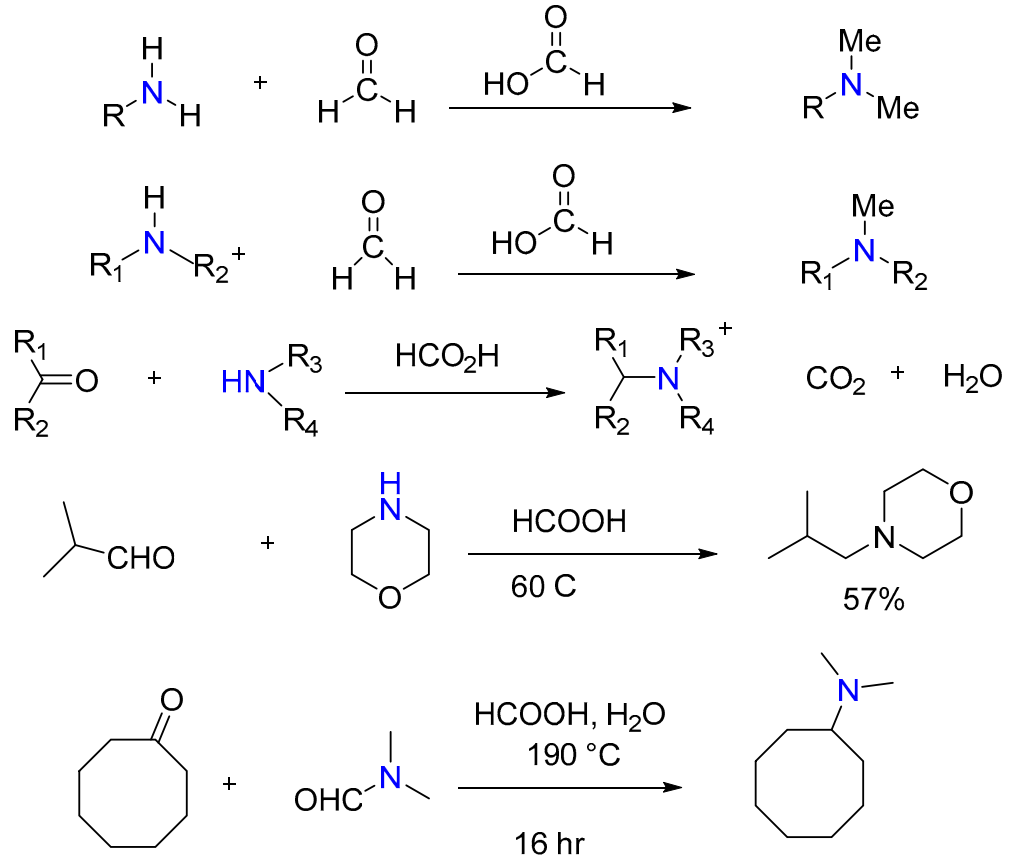


Figure 1. Leuckart's related reactions.

The Eschweiler–Clarke process is the reductive methylation of primary and secondary amines using formaldehyde and formic acid [17].

1.3. Mechanism

The "Leuckart-type reaction" process can be divided into two random steps (Figure 2), namely, the formation of N–C bonds and the reduction of intermediates by formic acid. The maximum rate of reaction was observed at 166–169 °C [22]. Musseron studied the effects of formamide, N-mono and N,N-dialkylformamides on cyclopentanones and cyclohexenes in an attempt to establish an appropriate mechanism [23]. The mechanism for the reaction was proposed by Wallach and reiterated by Crossley and Moore. Doevre, Courtois, Davies and Rogers proposed that in this reaction, the primary step is the attack of formamide on the carbonyl center [24]. The formed base can react with carbonyl compounds to yield additional products. These are then reduced by formic acid to amines and react with more formamide to form salts or amides. These conversions seem to be the only transitions related to the formation of tertiary amines by formats or formyl derivatives of carbonyl compounds and secondary amines [3].

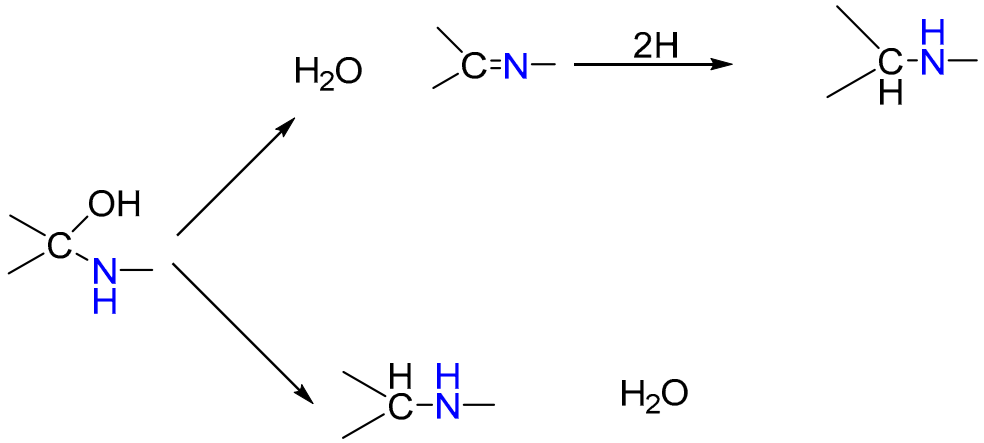
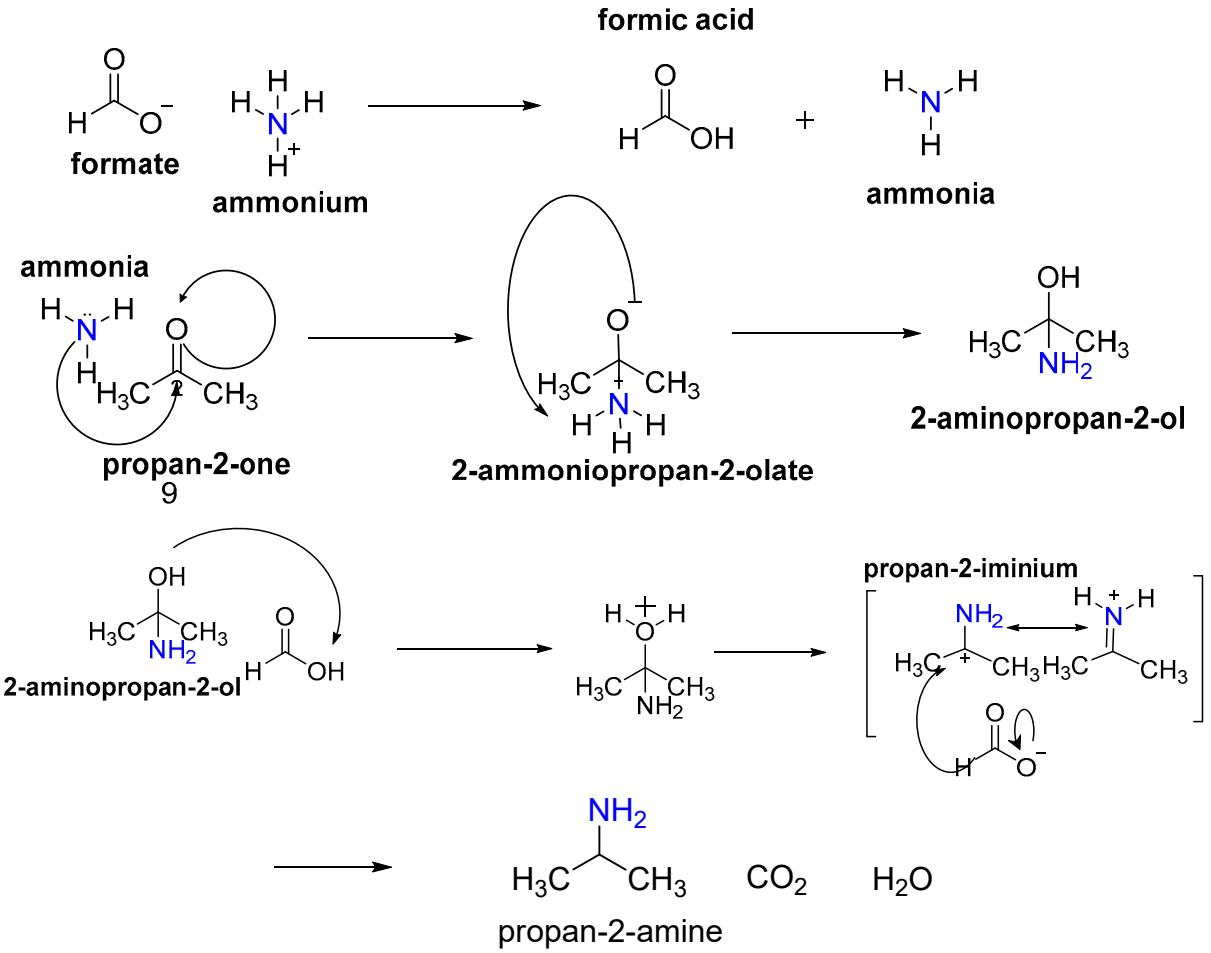


Figure 2. Leuckart's reaction two random steps.

However, the first objection to these proposed mechanisms is to the acceptance of formamide as a nucleophile for the carbonyl group of the substrate, and the claim of the reduced nucleophilic toxicity achieved with amines. The second objection is to the suggestion of transferring the hydride from the nitric acid formed in the reaction [25].

First, formic acid and ammonia are formed by the dissociation of ammonium formate (hygroscopic crystalline solid). Due to the existence of a lone pair, ammonia (an electron-rich species) acts as a nucleophilic attacker on carbonyl carbon, and the hydroxyl form, such as oxygen, deprotonates hydrogen from nitrogen. Since hydrogen ions are a good leaving group (OH_2), this hydroxyl group allows water molecules to be used by the protonated hydrogen from formic acid. Resonance-stable carbon-positive ionization (RRNH2C+) forms, which provide more space for unoccupied electrons, reduce the energy of the molecule and form a more stable molecule in addition to having high energy. Carbon dioxide and amines are formed by the attack of formic acid [8]. As formic acid is added to formamide, the yield can be improved over that obtained with ammonia and formic acid reagents shown in (Scheme 2) [5].



Scheme 2. Mechanism of the "Leuckart-type reaction".

1.4. Kinetic Study of the Leuckart–Wallach Reaction

Ostovari and Zahedi in 2018 successfully identified all stationary points of a five-step mechanism, which included

(i) Dissociation of ammonium formate into HCOOH and NH_3;
(ii) Nucleophilic attack of ammonia on the carbonyl carbon;
(iii) Dehydration;
(iv) Trans to cis isomerization of the formic acid;
(v) Formation of amphetamine by the reduction of the produced 1-phenyl propane-2-imine. The reaction is spontaneous, and the reaction kinetics are of the first order [26].

2. Significance of the Leuckart-Type Reaction

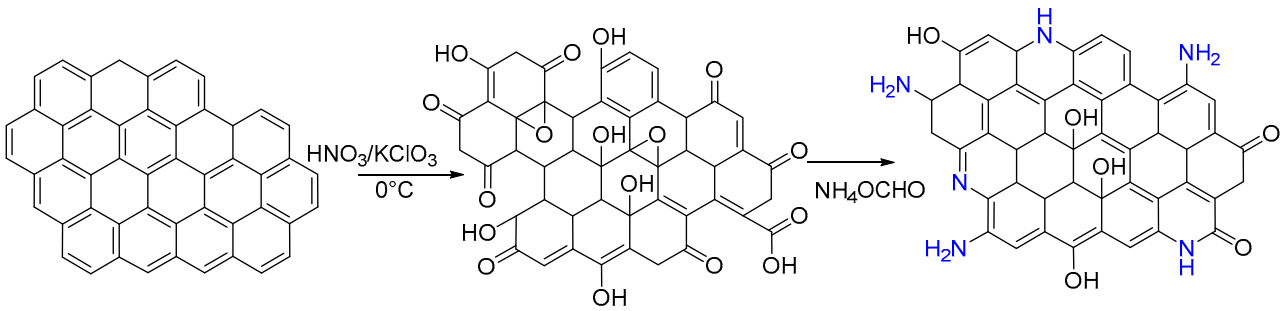
Since the beginning of medical science, scientists and chemists have tried to synthesize or extract pharmaceutically active compounds to benefit mankind and protect the natural environment, ultimately promoting a safe and healthy human life and reducing the chance of disease. In modern medicinal chemistry, "amines" are the most essential building blocks. In both pure and applied chemistry, the synthesis of 2° and 3° amines is becoming increasingly significant. Synthetic chemists have paid close attention in recent years to the functional procedures used for the production of tertiary amines, owing to their wide range of uses in catalysis [17]. The "Leuckart-type reaction" is a characteristic one-pot reaction method that has been widely used for the production of a variety of products, including medicinally useful compounds such as 1°, 2°, and 3° amines. For example, the "Leuckart-type reaction" is used to produce "abemaciclib", "cyclin-dependent kinase inhibitor", "bromantane analogues", "1H-pyrrolo", and "quinoline derivatives". These have

antibiotic activities and anti-inflammatory effects and can also be used to treat pain failure and reduce fever [8]. Additionally, this method appears to be suitable for the production of aromatic aldehydes and water-insoluble ketones. For this reaction, ammonium formate or formamide is not limited, and methyl formate has been used with some primary amines. Substituted ammonium formate, such as monomethyl ammonium or dimethyl ammonium formate, will react satisfactorily and lead to the formation of mixed secondary and tertiary amines that cannot be easily obtained by other methods [3]. The isocyanide-based multicomponent reaction (IMCR) is one of the most commonly used chemical reactions for increasing molecular diversity. Isocyanates are usually made in two stages, beginning with primary amines. The Leuckart–Wallach reaction produces isocyanide with greater variability [27]. Chiral, enantiomerically pure vicinal diamines and their derivatives have been increasingly used in asymmetric catalysis reactions. One of the classic methods used for the synthesis of amine derivatives is the "Leuckart–Wallach reaction", which is based on the reductive amination of carbonyl compounds with a mixture of formamide, formic acid, or ammonium formate. In all cases, the final product is a formamide derivative, which can then be reduced or hydrolyzed in an alkaline or acidic medium to obtain the desired free amine [28]. The Leuckart–Wallach reaction, which yielded almost exclusively anomers with Z-configurations, and then isocyanide. These represent a fascinating class of sugar and organic moiety chimeric compounds with important applications in medicine and with great potential for drug discovery. In the case of D-glucose, the method's stereoselectivity is notable, as enantiomeric D-glucose is commonly used [29]. For many years, the "Leuckart-type reaction" has been the most popular method used for the synthesis of illicit amphetamines in the United States, the United Kingdom, and the Netherlands. The reductive amination of benzyl methyl ketone is very important, and in Sweden and the United States, the nitro propene route is used, similar to the phenyl oxime route used in the United States. The Leuckart route was also used for the synthesis of amphetamine [30]. Many studies have shown that amines contain most of the MDMA-HCl contaminants. As a result, extraction appears to be more effective in alkaline environments [31–33].

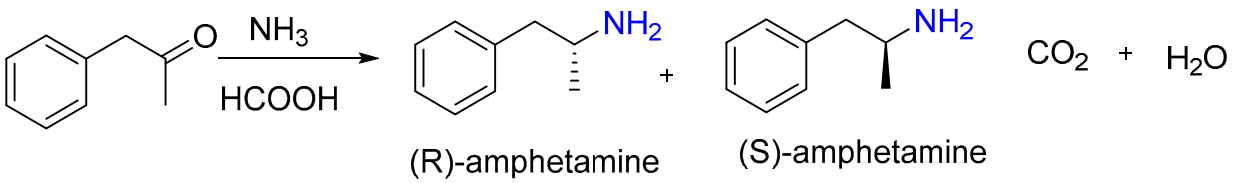
The Leuckart reaction is the most common route used to produce the amphetamine-type stimulant ATS [34–36] and to synthesize thiophenols [37], as well as N-alkylaminomethylanthracenes [38]. Amines are universal and valuable compounds in synthetic chemistry, with a wide range of applications in organic catalysis, organometallic complexes [39], organocatalysis in organic synthesis [40], biological processes, and the pharmaceutical chemistry [41]. The reductive amination of carbonyls is one of the most popular processes used for making amines [42,43]. Numerous legal methods for the synthesis of amphetamine have been reported, including Hofmann, Curtius, and Schmidt rearrangements, heterogeneous reduction, Friedel–Crafts alkylation, the Henry reaction, Knoevenagel condensation, the Ritter reaction, and the Leuckart–Wallach reductive amination reaction. However, due to the simplicity, speed and safety of the procedure, characterized high efficiency, the Leuckart–Wallach is more useful [26,30]. A prominent example of the Leuckart reaction is its use in the synthesis of tetrahydro-1,4 benzodiazepin-5-one, a molecule that is part of benzodiazepine [6]. Many compounds in this family are central nervous system suppressants and are associated with therapeutic uses and a variety of medications, such as antibiotics, antiulcer, and anti-HIV agents. Researchers have synthesized tetrahydro-1,4-benzodiazepin-5-ones with excellent yields and high purity by utilizing the Leuckart reaction, and they have performed the reaction via solid-phase synthesis using formic acid as the reducing agent [6]. The "Leuckart-type reaction" provides a useful way to prepare numerous formamides, amines, and bulky compounds that are pharmaceutically useful. In 2018, Skachilova et al. first synthesized 5-(N-piperidine)-1-arylpentan-1-ones, and then, using a modified Leuckart method, synthesized 5-(N-piperidine)-1-aryl-1-aminopentanes [22]. In 2017, Frederick et al. successfully synthesized abemaciclib via the Leuckart reaction [44,45]. The synthesis process of some important drugs through the Leuckart reductive method is summarized and given below.

2.1. Synthesis of Animated Graphene and Amphetamine

The "Leuckart-type reaction" was used to reduce graphite oxide (Scheme 3). This work reported the first use of the "Leuckart-type reaction" to reduce GO and obtain animated graphene [46]. Barba, Recio, and Batanero (2013) reported that, when formamide is used in the reaction, N-formyl derivatives of amines can be obtained instead of free amines [25]. The most popular synthetic drug type in Europe is amphetamine-type substances, a category which includes amphetamine (shown in Scheme 4), methamphetamine, and 3,4-methylenedioxymethamphetamine (MDMA). Hauser et al. (2020) used the "Leuckart-type reaction" pathway, the most commonly used method for synthesizing amphetamine [47].



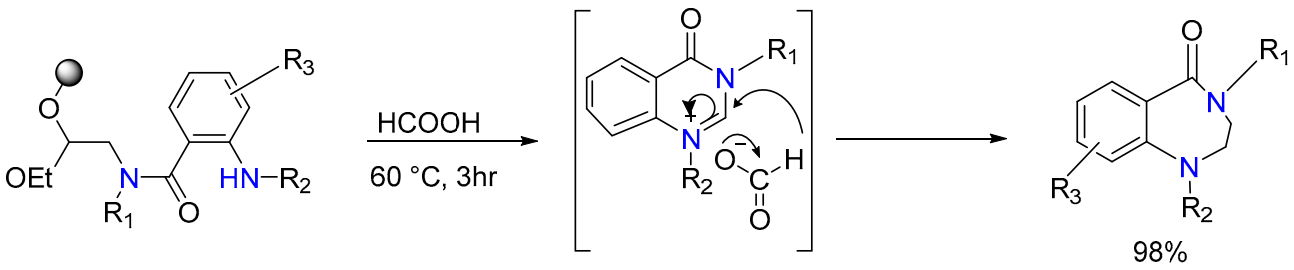
Scheme 3. Possible structures of GO and rGO-Am.



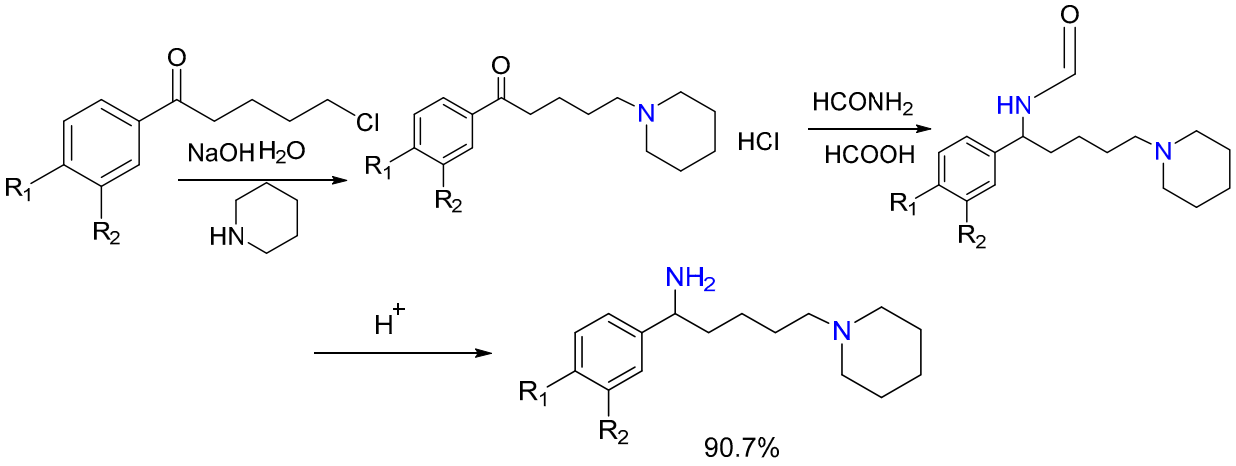
Scheme 4. Synthesis of amphetamine through the LW method.

2.2. Synthesis of Tetrahydro-1,4-benzodiazepine-5-one and Arylamine

In 2006, Lee and Park synthesized tetrahydro-1,4-benzodiazepine-5-one (Scheme 5) (a member of the benzodiazepine family) through a "Leuckart-type reaction" using a single step instead of the multiple steps previously reported [48,49]. It can be used as an antibiotic, anti-ulcer, and anti-HIV agent. Sung Chen li et al. introduced bromoacetal resin as a solid support for the in situ generation of iminium intermediates during the acidolytic cleavage step, which increased the product and scope of the LW reaction [46]. The "Leuckart-type reaction" offers a fast and convenient method for synthesizing various formamides (an important class of compounds in synthesis) [50], amines, and large numbers of biologically active compounds and pharmaceuticals. New 5-(N-piperidine)-1-arylpentan-1-one and 5-(N-piperidine)-1-aryl-1-amino pentane (Scheme 6) were synthesized [22].



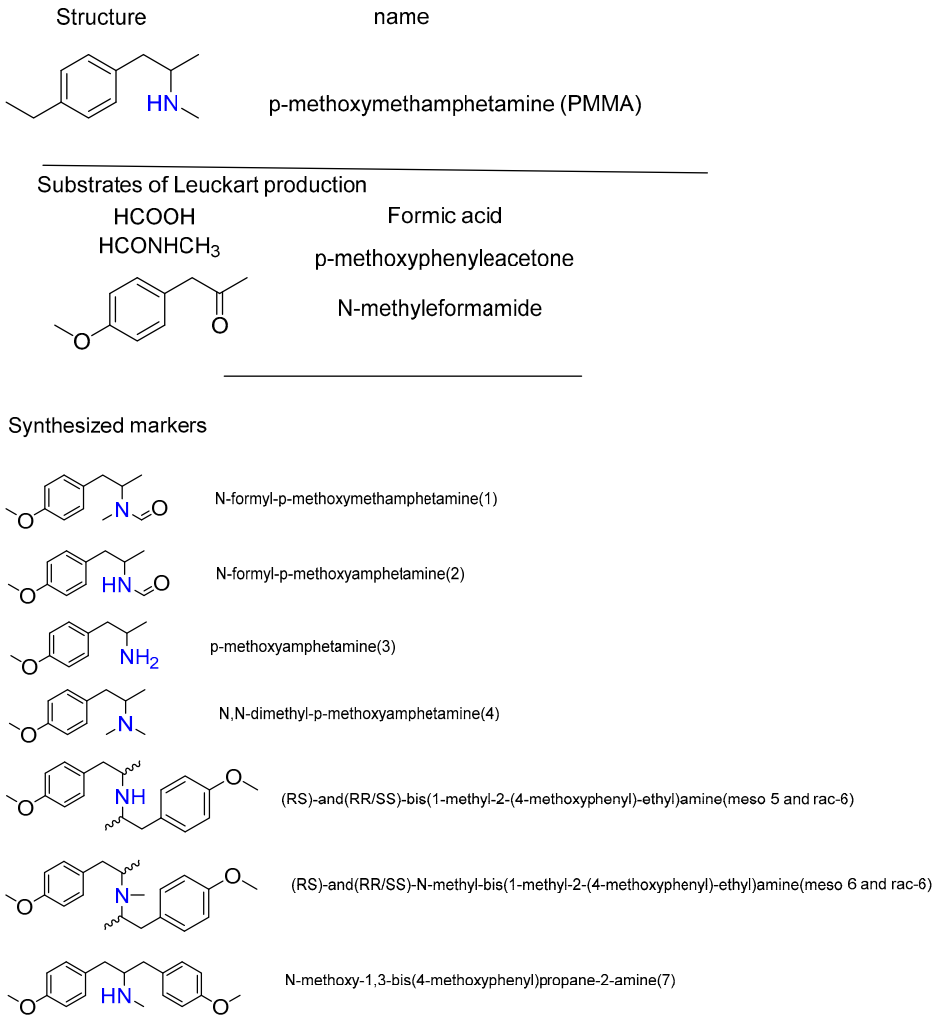
Scheme 5. Synthetic route of tetrahydro-1,4 benzodiazepin-5-one.



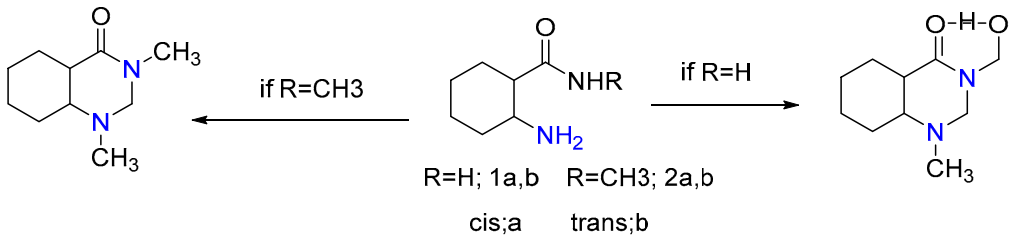
Scheme 6. Synthesis of 5-(N-piperidino)-1-phenyl-1-aminopentanones.

2.3. Synthesis of 4-methylthioamphetamine (4-MTM), (PMMA) and Heterocycles

Dariusz Bachut et al. (2012) experimentally proved that 4-methylthioamphetamine can be obtained via the Leuckart method [51]. J. Kochana et al. (2003) explained the synthesis of PMMA obtained by the Leuckart method (Scheme 7). They can be divided into two groups (Scheme 8) [52].



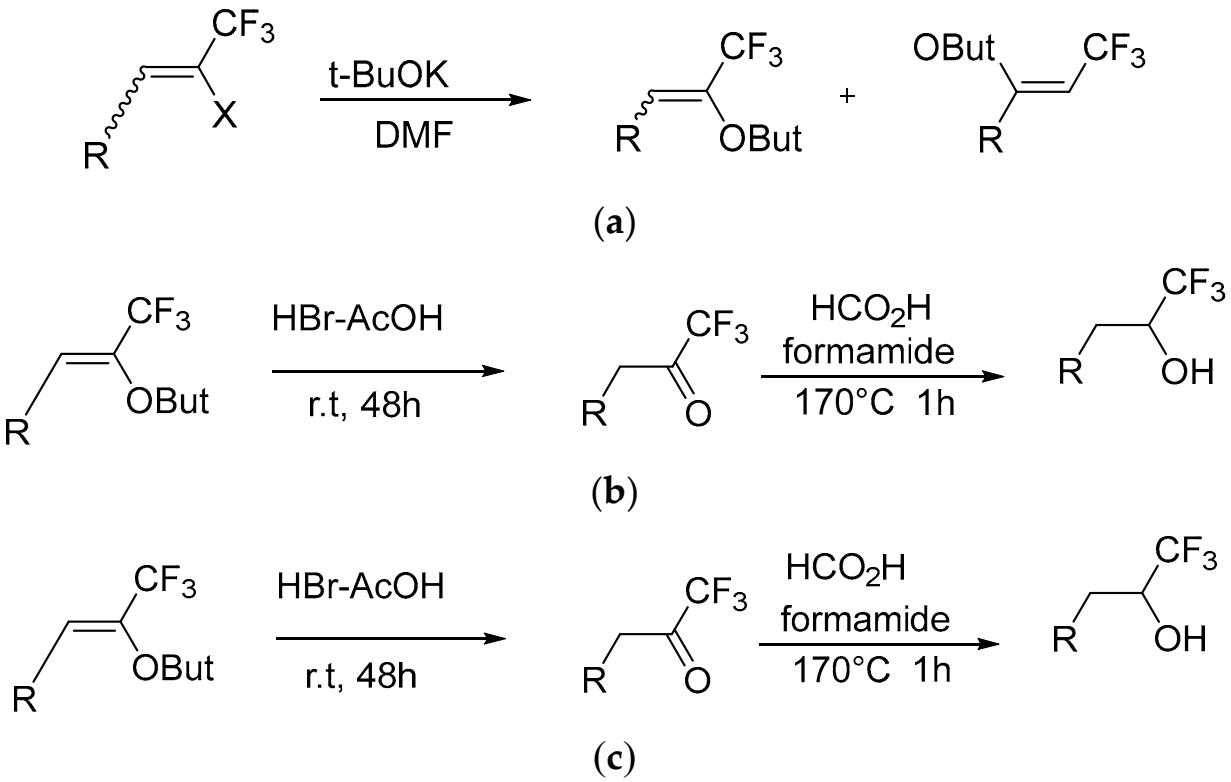
Scheme 7. Chemical structures of PMMA, substrates of Leuckart synthesis, and synthesized markers.



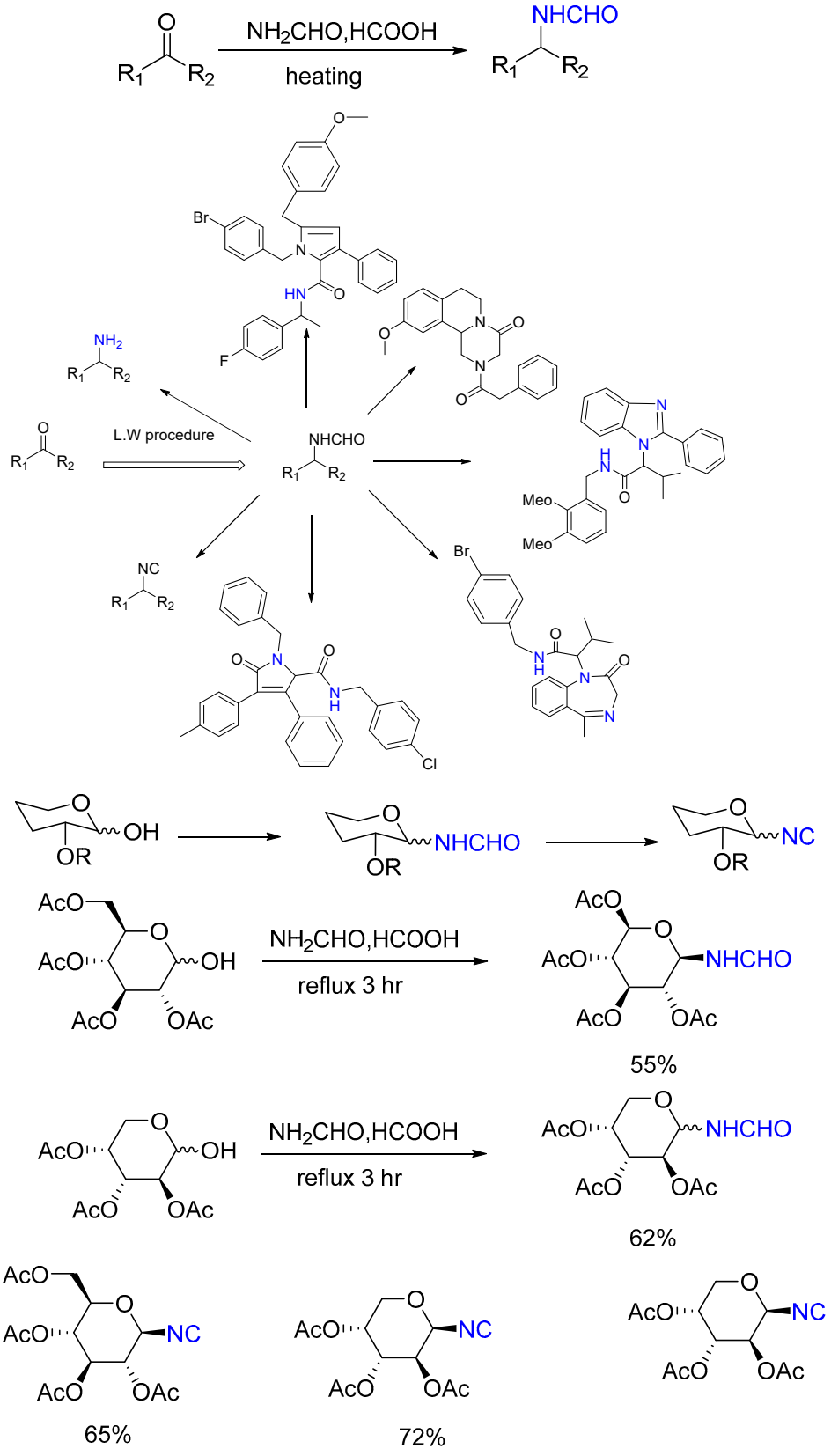
Scheme 8. Synthesis of l-methyl and/or 3-hydroalkylmethyl-1,3-heterocycles.

2.4. Synthesis of Trifluoromethyl Alcohol and Isocyanides

Vasiliy M. Muzalevskiy et al. (2008) studied a new experimental method for preparing trifluoromethanol from tert-butoxy-b-(trifluoromethyl) styrene and trifluoromethylbenzyl ketone under Leuckart–Wallach reaction conditions (Scheme 9). However, they did not find any amines in the product [53–56]. Neochoritis et al. (2015) proposed that through the reductive amination reaction of formamide and formic acid, a variety of oxygenated isocyanates (Scheme 10) can be synthesized [56]. Neochoritis, Zhang, et al. (2015) introduced a short and convenient method for the synthesis of glycosyl and arabinosyl isocyanides, directly from sugar, via a two-step modified Leuckart–Wallach procedure [29].



Scheme 9. (**a**) Synthesis of tert-butoxy-b-(Trifluoromethyl) styrene. (**b**) Synthesis of trifluoromethyl alcohols. (**c**) Preparation of trifluoromethyl alcohols via trifluoromethyl ketones.

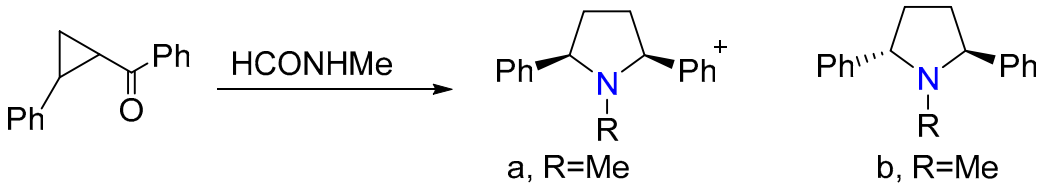


Scheme 10. Synthesis of isocyanides directly from the sugar via the Leuckart–Wallach reaction.

2.5. Synthesis of cis- and trans-l-Methyl-2,5-diphenylpyrrolidines

In 1972, Brkukr and Melumad synthesized a mixture of *cis*- and *trans*-l-benzoyl-2-phenylcyclopropane (Scheme 11) from the reaction of two compounds, benzylacetophenone

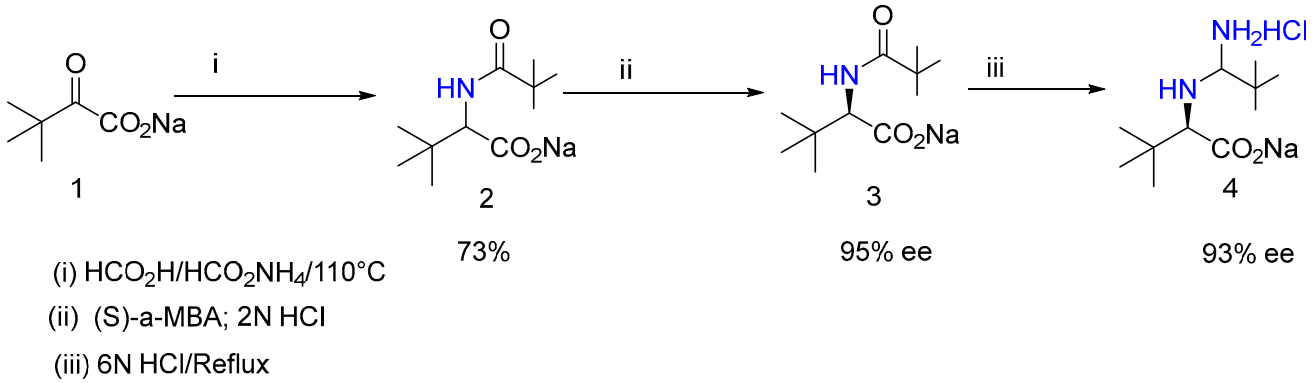
and dimethylsulfoxonium methylidene, in the presence of catalytic quantities of magnesium chloride for 25 h. Two products were obtained with 50% yield [57].



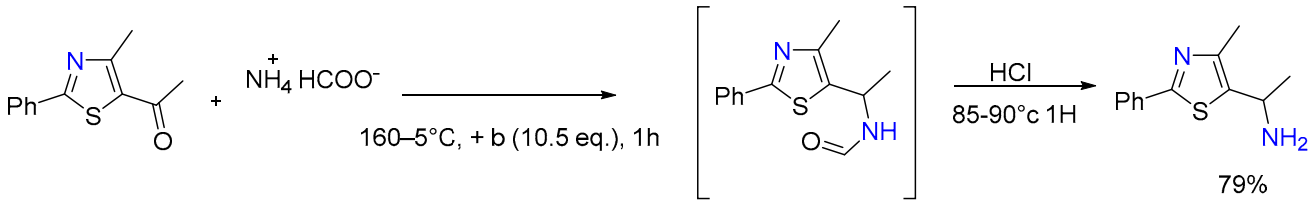
Scheme 11. Synthesis of *cis*- and *trans*-l-methyl-2,5-diphenylpyrrolidines using the Leuckart method.

2.6. Synthesis of Racemic Tert-Leucine and Polyether Amines and PPGs

Brian M. Adger et al. (1997) used the Leuckart reaction method of reduction for the synthesis of tert-leucine (Scheme 12). This method is more favorable compared to previous methods due to the need for high-pressure hydrogenation or the use of environmentally unfriendly reagents [58]. Kulyk et al. (2020) used the Leuckart reaction (with CO_2 and H_2O as the only byproducts), which appeared to be more environmentally friendly than other routes for the amination of polypropylene glycols (PPGs) (Scheme 13) [59].



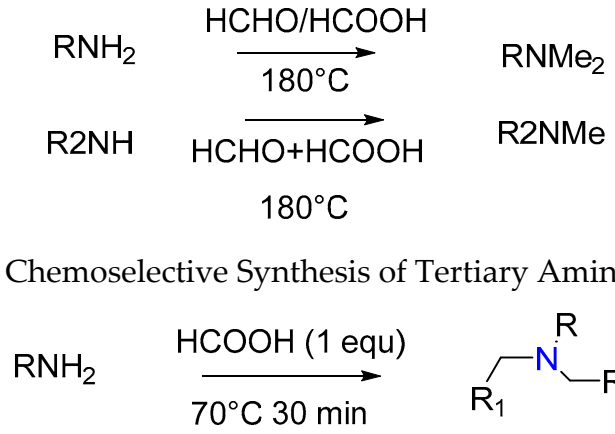
Scheme 12. Synthesis of racemic tert-leucine from trimethylpyruvic.



Scheme 13. Optimization of the Leuckart–Wallach reductive amination reaction.

2.7. Synthesis of Tertiary Amines

The Eschweiler–Clarke process is based on the reductive methylation of primary and secondary amines using formaldehyde and formic acid. Araminta De et al. established in 2018 that, by modifying both amines and aldehydes, it is feasible to make a range of tertiary amines (Scheme 14) [17]. Smith and John McDonnell (1950) investigated the preparation of triamide, and Bonnet and Max also reported this work with slight modifications. They did not use excessive amounts of formic acid or other catalysts, such as magnesium chloride, and achieved good results [60]. Abbruscato and Trippier (2018) found that amphetamine, synthesized through the Leuckart method, is a better stimulant [35].

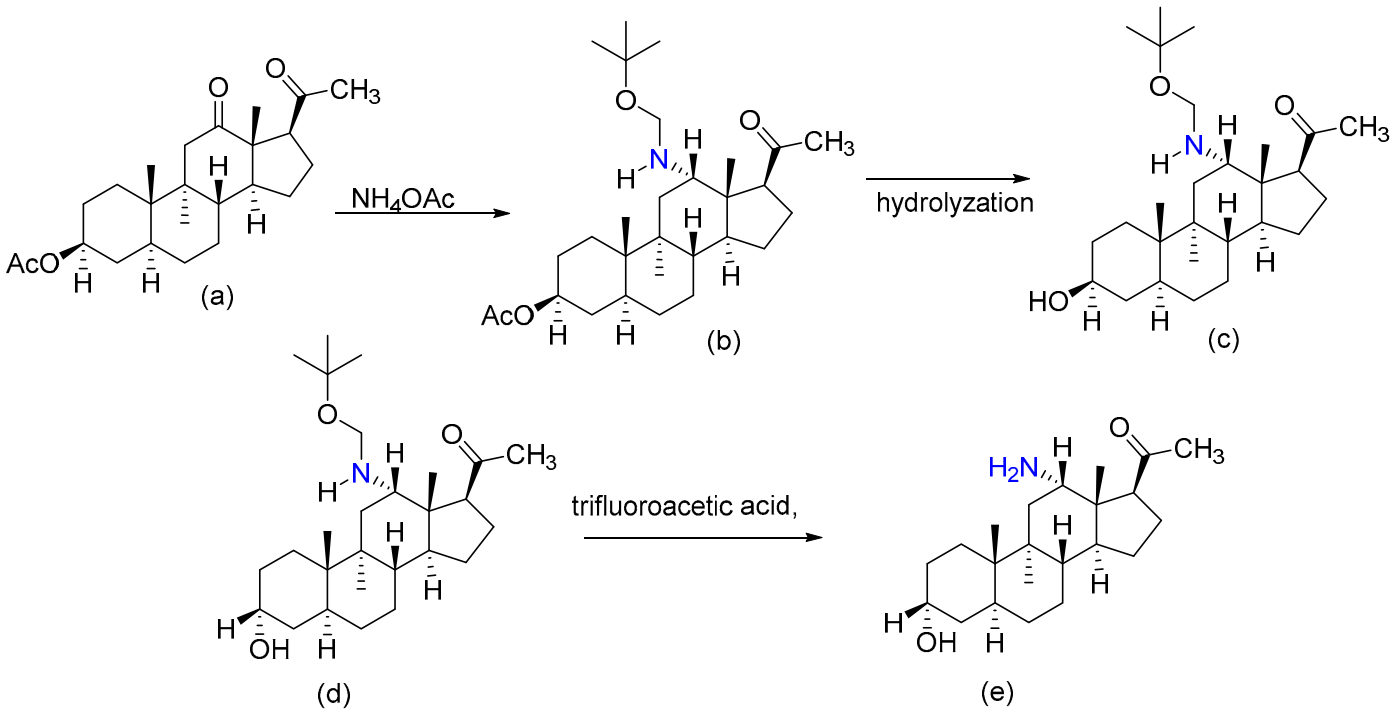


Scheme 14. Synthesis of tertiary amines.

The formation of mono-methylated (R2NMe) or dimethylated amines (RNMe2):

2.8. Synthesizing a 12β-Amino Derivative of Allopregnanolone

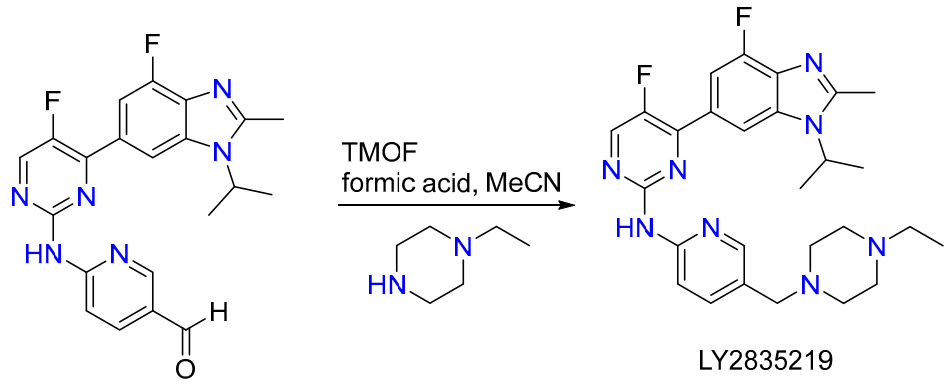
Slavikova et al. (2013) reported Leuckart–Wallach's reductive amination for the production of a 12β-amino derivative of allopregnanolone (Scheme 15) [61].



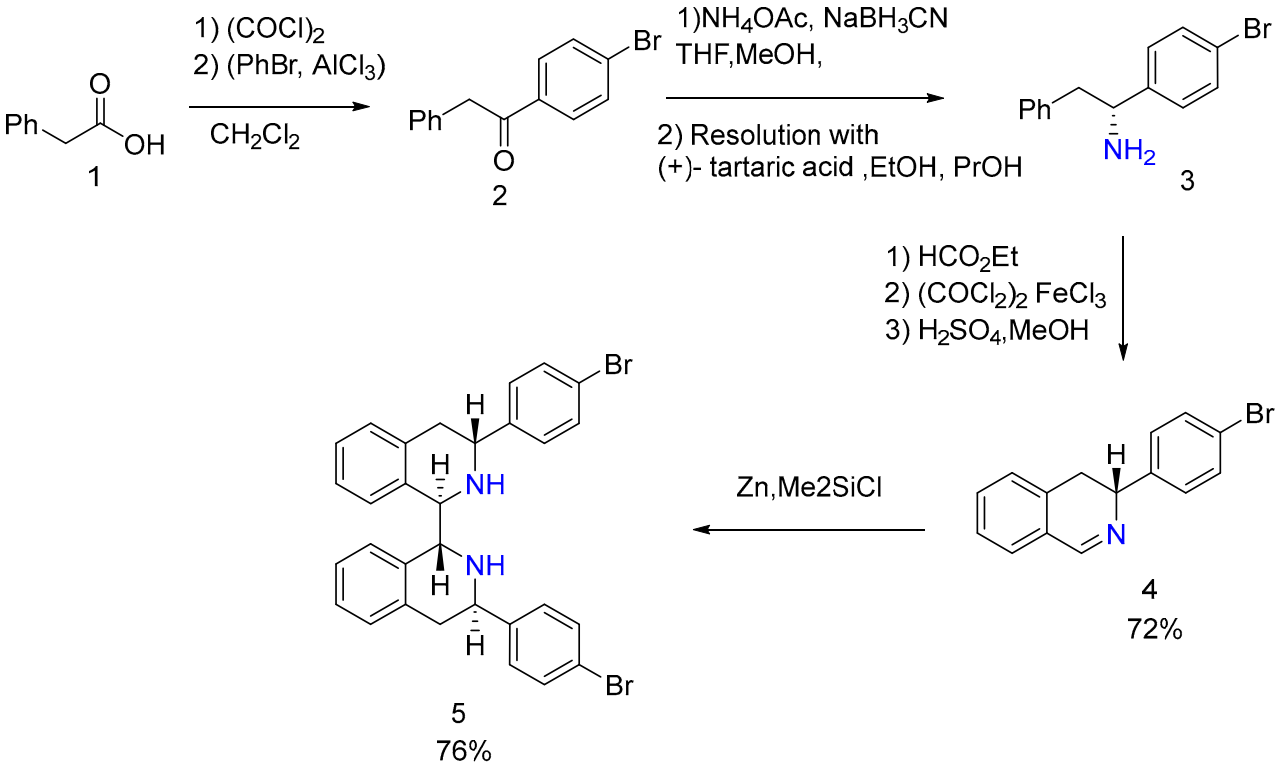
Scheme 15. Synthesis of 12β-amino derivative of allopregnanolone.

2.9. Synthesis of Abemaciclib, Chiral Bis and Racemic Methamphetamine

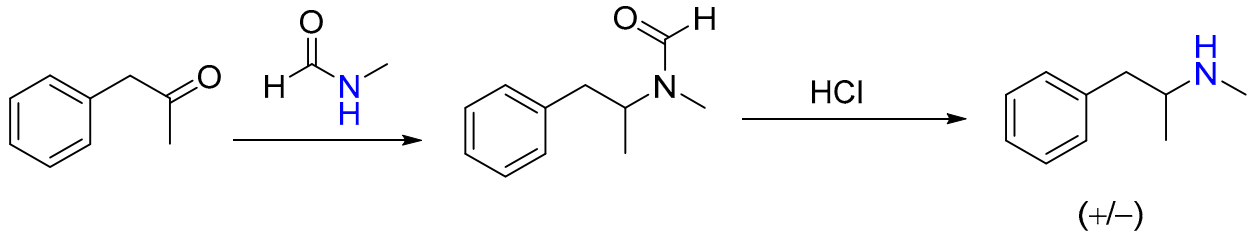
Reizman et al. (2019) reported that the Leuckart–Wallach reaction of aldehyde and ethyl piperazine leads to the synthesis of abemaciclib (LY2835219) (Scheme 16) [62]. In 2011, Wilckens, Lentz, and Czekelius successfully applied the LW reaction method to synthesize chiral Bis (Scheme 17) [63]. In 2018, Abbruscato and Trippier reported the synthesis of racemic methamphetamine (Scheme 18) from a phenyl-2-propanone precursor using the Leuckart method [35].



Scheme 16. Synthesis of chiral bis (tetrahydroisoquinoline).



Scheme 17. Synthesis of chiral bis tetra-hydro isoquinoline.

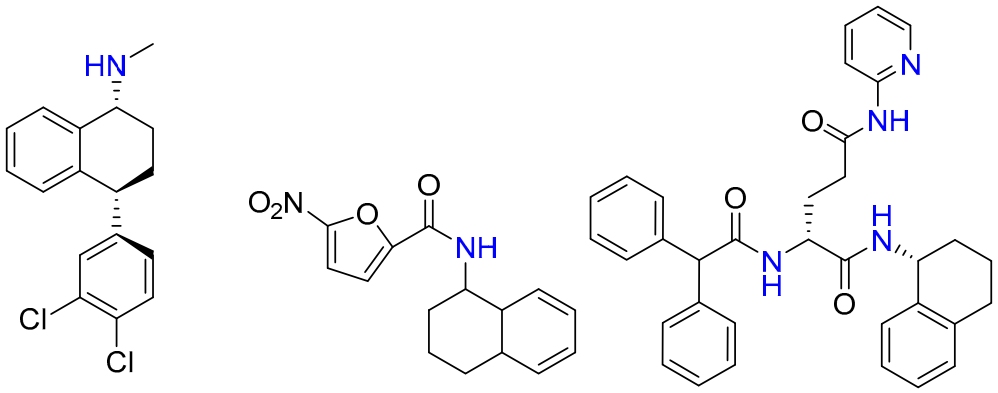


Scheme 18. Synthesis of racemic methamphetamine.

2.10. Synthesis of Hydro naphthylamines

Hydronaphthylamines (Scheme 19) are ubiquitous structural motifs that widely exist in natural products, pharmaceuticals, and biologically active molecules, and the LW reaction suffers from its harsh reaction conditions, multiple steps, and narrow substrate scope when synthesizing such compounds [64]. The monoterpene amine bornylamine was first

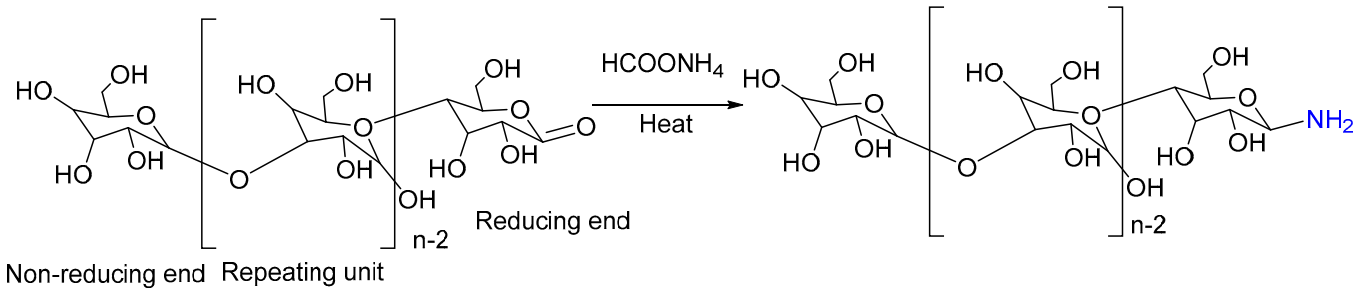
synthesized by Leuckart in 1887 through the reaction of camphor and formamide, and then, by the reduction of camphor oxime by Forster in 1898. However, with the recent preparation of terpene amines by reducing oximes, the "Leuckart-type reaction" and the reductive amination reaction of carbonyl-containing terpene compounds have shown good potential [65].



Scheme 19. Synthesis of hydronaphthylamines.

2.11. Synthesis of N-Alkylated-l, 2-Phenylethylamine and Some High-MW Compounds

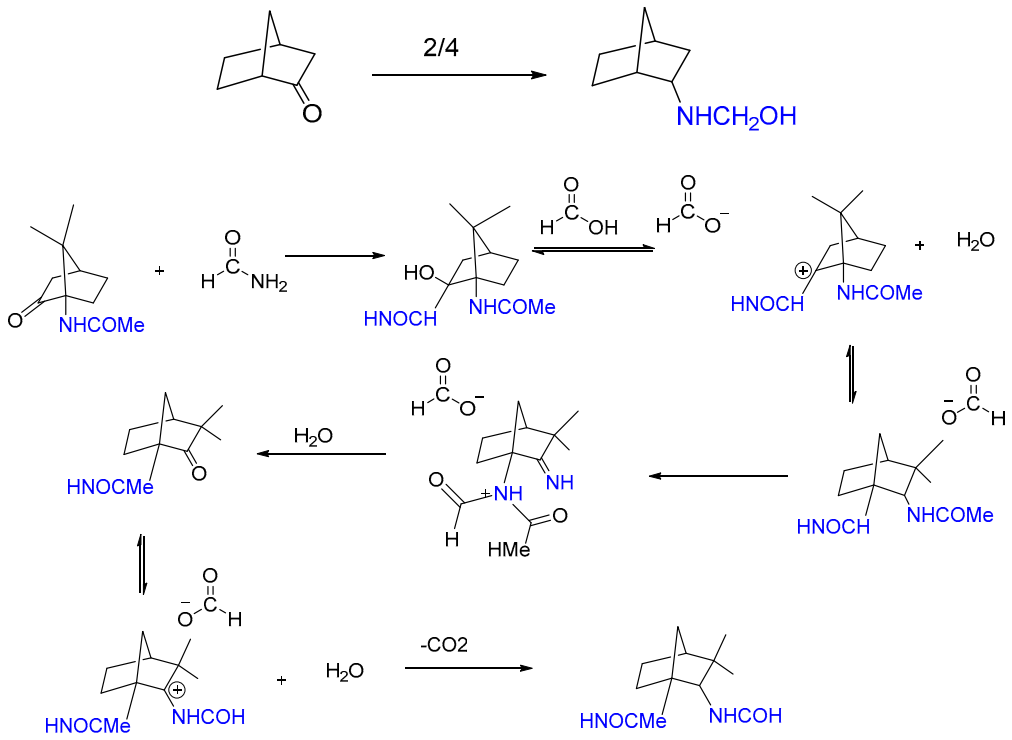
Goodson, Wiegand, and Splitter (1946) synthesized 12 novel substituted 1,2-phenylethylamine compounds that were all produced using the "Leuckart-type reaction" [66]. The "Leuckart-type reaction" has been fruitfully applied to some ketones of high molecular weight to give the corresponding amines [67]. Ingersoll and coworkers successively studied the behavior of 1,5-diketones when used to synthesize 1,5-diamines in relation to the ammonium formate–formamide reagent [68]. Afanasyev et al. (2019) used drug-type molecule diversity-oriented synthesis (DOS), which can improve the synthesis of useful drug-like compounds with a high degree of molecular diversity. Leuckart-type reactions were successfully applied here to synthesize polyheterocyclic scaffolds in high yields with excellent stereo- and regioselectivity [11]. Jaekel and Antonietti (2021) used the Leuckart reagent to achieve reactivity towards the reductive amination of carbonyl groups in cellulose chains during a one-step method for the preparation of cationic nanocellulose seen in (Scheme 20) [54].



Scheme 20. Reduction of cellulosic carbonyl.

2.12. Enantiospecific Synthesis

Garcia Martinez et al. (1999) reported experiments on the formation of rearranged (1S,2S)-N-(3,3-dimethyl-2-carboxamideamino-1-norbornyl) acetamide, and according to Garcia Martinez et al. (1999), no alcohol is created during the reduction process (Scheme 21) [69].



Scheme 21. Enantiospecific synthesis.

3. Recent Advancement

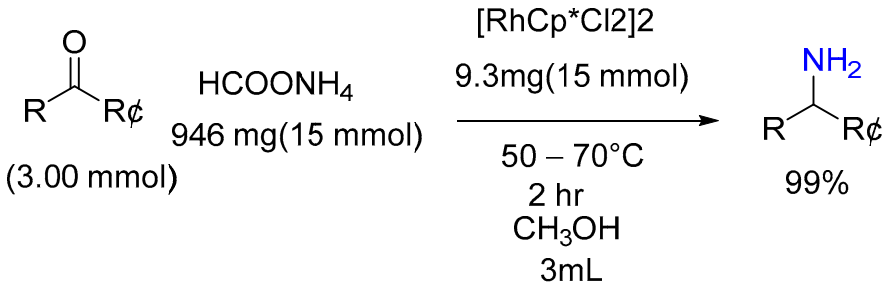
The "Leuckart-type reaction" has been fruitfully applied to some ketones of high molecular weight, producing the corresponding amines that are desired for pharmacodynamics and chemotherapeutic studies [67]. It has also been suggested that an alternative approach to "primary" and "secondary" alkyl ammonium formats may involve reducing imines formed from the loss of water in carbonyl ammonia [70]. As formic acid is added to formamide, the yield can be improved over that obtained with ammonia and formic acid reagents [5]. The yield is affected by the temperature at which condensation is carried out, and the yield was twice that achieved at 160–170 °C and twice that at 190–200 °C [5]. The higher alkyl-substituted ammonium format is more difficult to condense with ketones, and it may be desirable to use higher temperatures in these reactions [5]. However, using a 6.6% NaOH solution or concentrated HCl also significantly affected the yield [5].

3.1. Catalytic Advancement

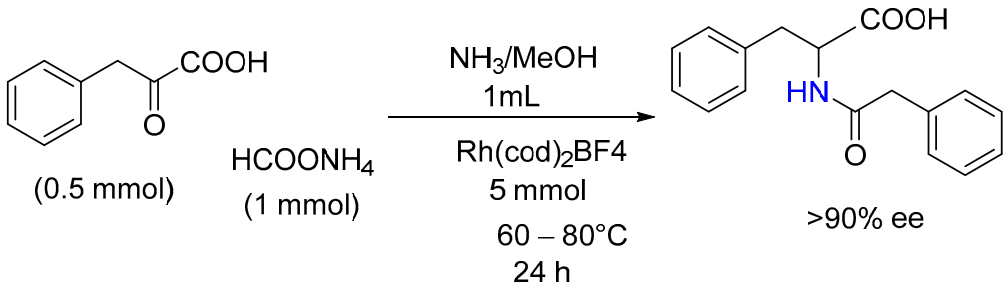
3.1.1. Rh(III) Complex Catalysis

In recent years, many catalytic systems used for the reductive amination of carbonyls to synthesize C–N bonds have been reported [71–75]. However, only a few precious metal (e.g., Rh, Ru, and Ir) catalytic systems have been reported for the Leuckart-type reductive amination of carbonyl compounds that have usually using ammonium formate or formamide as a nitrogen source [76–78]. Additionally, noble metal catalysts have achieved acceptable results in "Leuckart-type reactions", and it is desirable to replace them with non-noble metals (e.g., Cu, Ni, Co, Fe, and Mn) to reduce the overall production costs. However, it is a major challenge to eliminate the defects of non-noble metals in organic synthesis, such as inferior catalytic activity, poor selectivity, thermal instability, metal agglomeration, and easily reaction with acid [79–81]. Kitamura et al. (2002) applied the Cp*Rh(III) complex to catalyze the reductive amination of ketones, using the ammonium format at 50–70 °C to give the relevant 1° amines in a 99% yield (Scheme 22) [16]. Senthamarai et al. (2018) reported the synthesis of a class of amines by Ru-catalyzed reductive amination with H_2, starting with carbonyls and NH_3 [82]. In 2003, Kadyrov and Riermeier successfully investigated rhodium-catalyzed asymmetric reductive amination with hydrogen as the

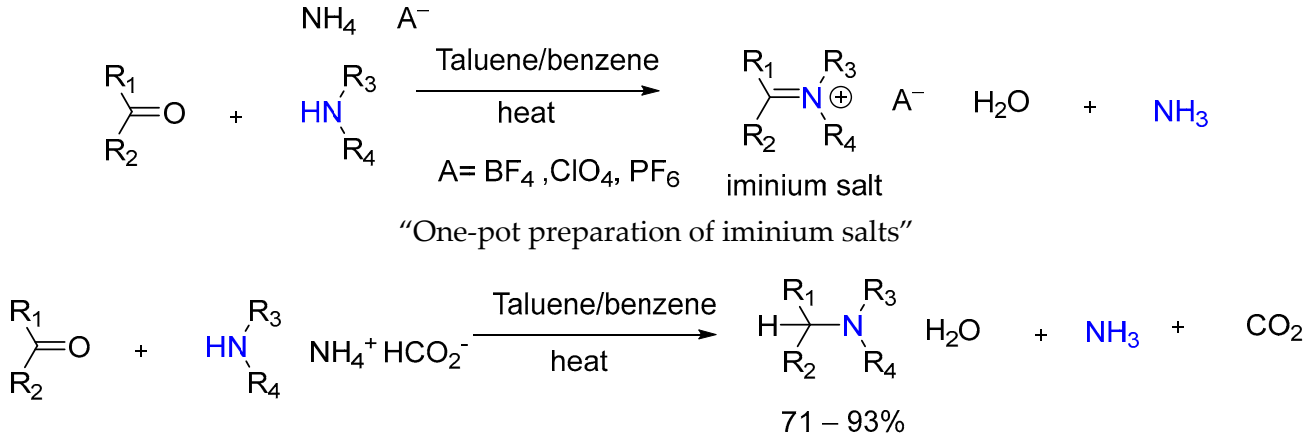
reducing agent, and a highly active and enantioselective catalytic system was constructed (Scheme 23) [83]. Santos et al. (2013) identified the direct combination of an aldehyde or ketone with a 2° amine-free base in the presence of "ammonium tetra fluoroborate", "ammonium perchlorate", or "ammonium hexa fluoro phosphate" as a high-yielding "one-pot procedure" for the preparation of a wide range of iminium salts (Scheme 24) [84]. To manage the chemoselectivity via reductive amination, Tanaka et al. (2019) used formic acid and formate salts as potential hydrogen replacements. Kitamura and coworkers reported that using ammonium formate instead of ammonia in the transfer of hydrogenative DRA is a highly selective method for the preparation of primary amines in the presence of catalytic amounts of [Cp*RhCl$_2$]2 [85].



Scheme 22. Reductive amination of acetophenone using a Cp*Rh(III) catalyst.



Scheme 23. Asymmetric reductive amination with hydrogen using a rhodium catalyst.

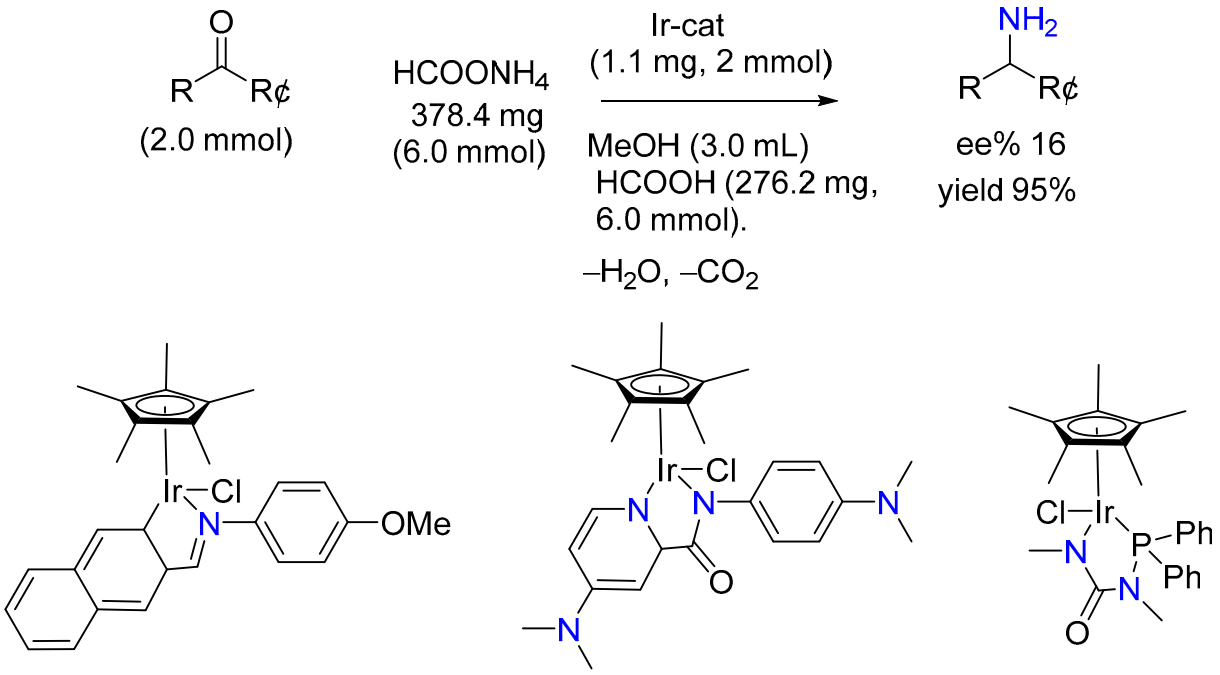


Scheme 24. One-pot Leuckart-type preparation of amines.

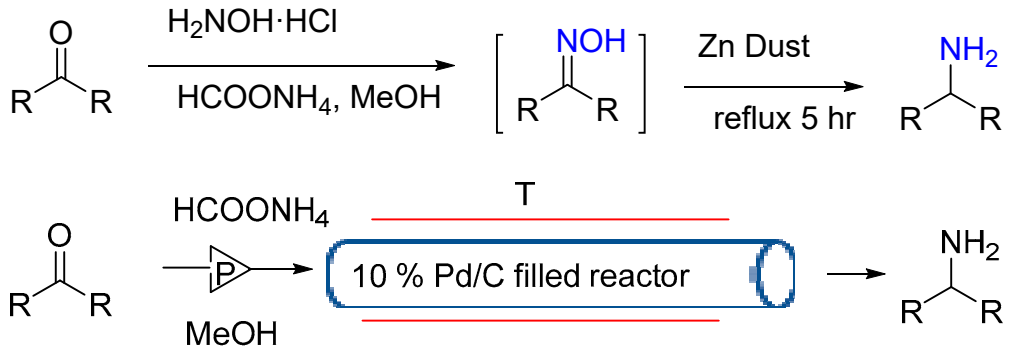
3.1.2. Ir(III) Complex Catalysis (Half-Sandwich Iridium Complexes)

Dai et al. (2021) identified a series of Ir(III) complexes bearing an amidato bidentate ligand capable of catalyzing the "Leuckart–Wallach reaction" with high efficiency, and attempted asymmetric transformations with several chiral Ir(III) complexes (Scheme 25) [86]. Falus et al. (2011) explored a useful method for the reductive amination of ketones. The

methods use ammonium formate as the hydrogen source, but the application of Zn dust or a 10% Pd/C-catalyst (Scheme 26) in methanol makes the Leuckart method smoother and generally more favorable [87].

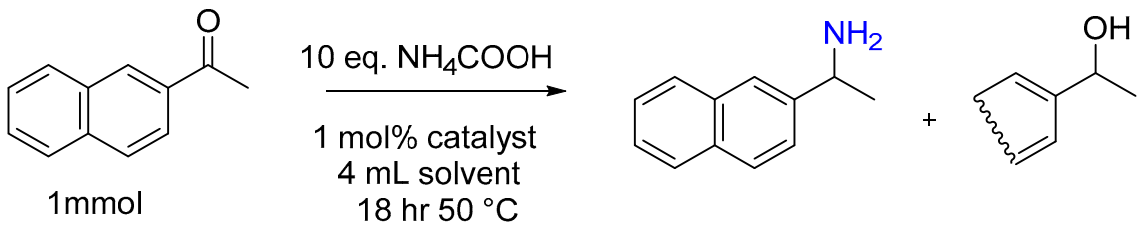


Scheme 25. Asymmetric reductive amination with Ir(III) complexes.



Scheme 26. Reductive amination of ketones in a packed-bed continuous-flow reactor at 40 °C and a 0.2 mL/min flow rate.

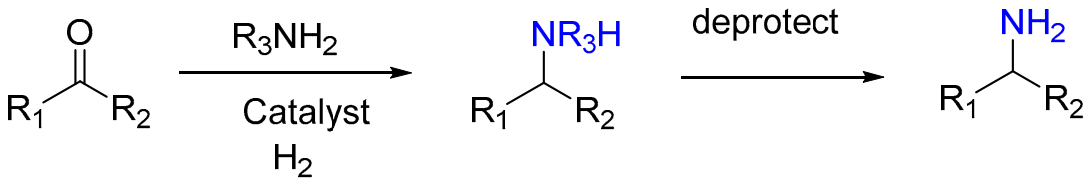
Polishchuk et al. (2021) catalyzed Leuckart–Wallach (NH_4COOH) using half-sandwich iridium complexes bearing bidentate urea–phosphorus ligands in order to catalyze the direct reductive amination of aromatic and aliphatic ketones under mild conditions at 0.5 mol% loading, with high selectivity towards primary amines (Scheme 27) [78].

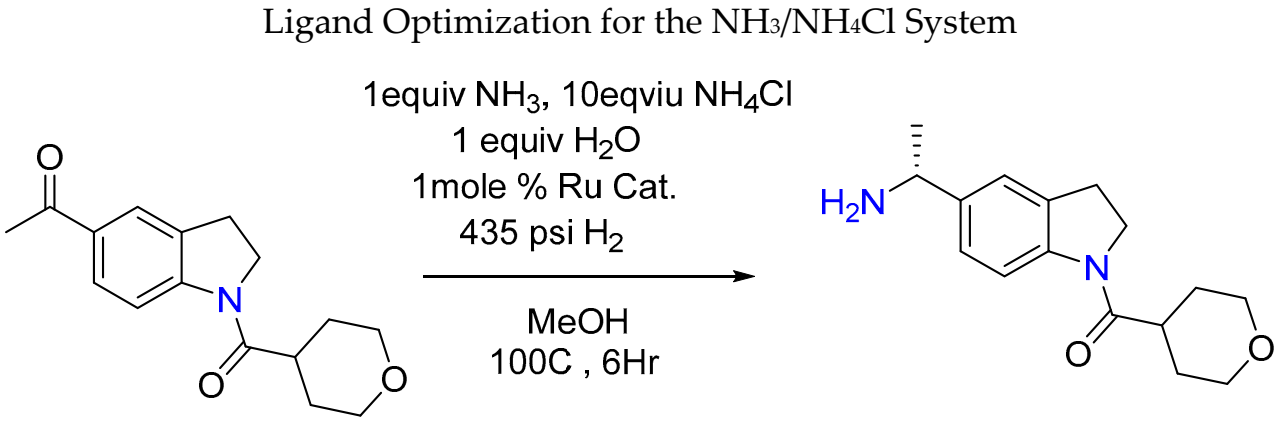


Scheme 27. Reductive amination using half-sandwich iridium complexes.

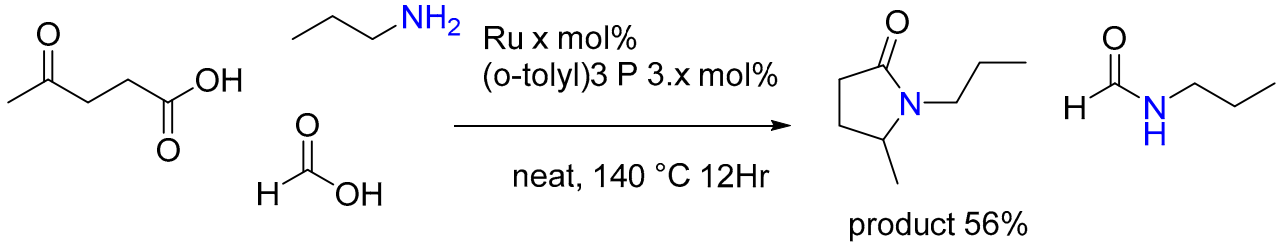
3.1.3. Synthesis of Chiral Amine under Ru and H_2 Catalysis

Ba and Ku (2003) showed the reaction of ketones with NH_4OAc as the ammonia source, and the use of the ligand (R, R)-iPr-DUPHOS resulted in the high chiral purity of the product, with a 1 mole% Ru catalyst (Scheme 28). Changing the ammonia source to NH_3/NH_4Cl leads to a dramatic increase in chiral [88]. In the absence of a solvent and under argon at normal pressure, the researchers found that dramatically reducing the catalyst loading had no significant effect on a reaction outcome. Despite the presence of a 0.05 mol% Ru catalyst, the product was still formed in appropriate amounts (Scheme 29) [89].





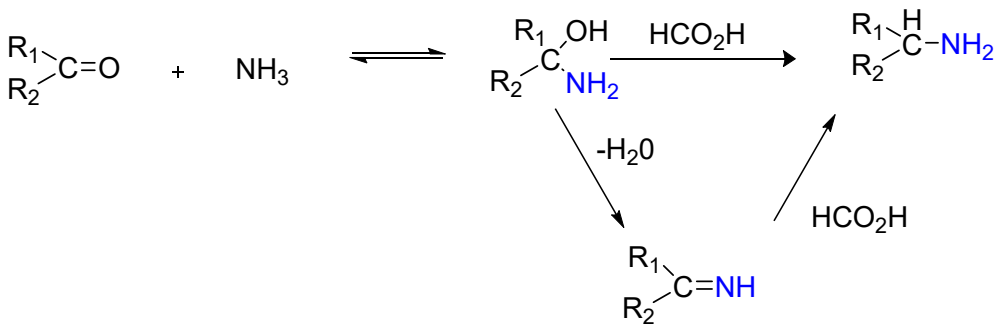
Scheme 28. Synthesis of chiral amines.



Scheme 29. Effect of the catalyst loading.

3.1.4. "Leuckart-Type Reaction" under CHT

Hanson (1997) reported that nitro groups are not reduced and aryl halides are not cleaved under Leuckart conditions, as they are under catalytic transfer hydrogen (CTH) conditions (Scheme 30). Similarly, while aryl amines or their N-formyl derivatives are stable under Leuckart conditions, they appear to hydrogenize under CTH conditions. Moore's analysis of the "Leuckart-type reaction" suggests that ammonium formate dissociates at high temperatures (Figure 3) [90].



Scheme 30. "Leuckart-type reaction" under catalytic hydrogen transfer.

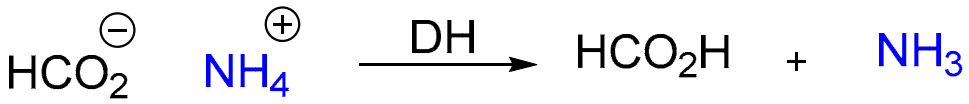
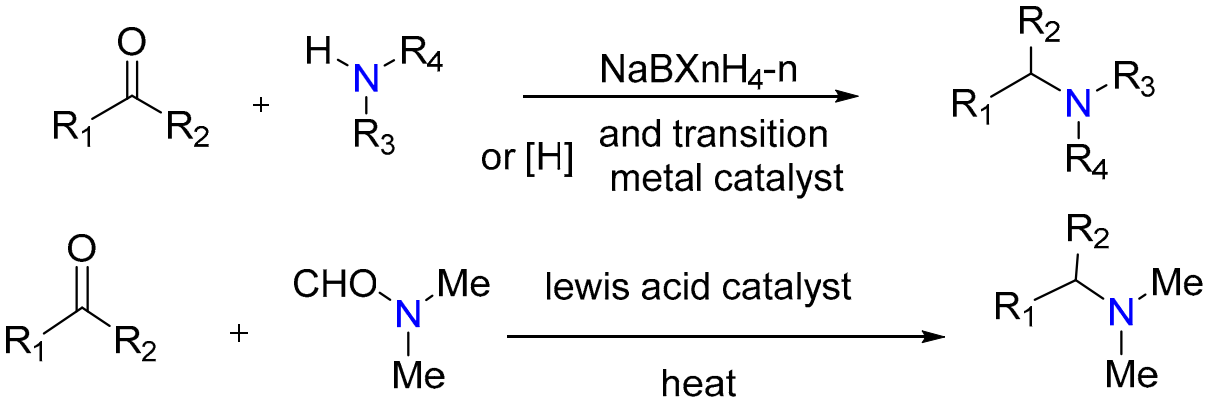


Figure 3. Ammonium formate dissociates at high temperatures.

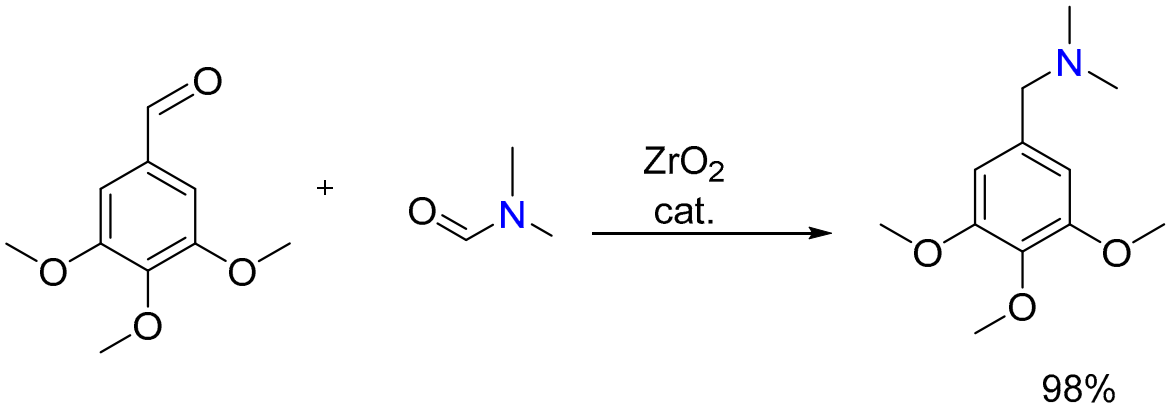
The resulting ammonia reacts with the carbonyl compound to form a hydroxylamine, which can be reduced directly by formic acid or indirectly through an imine.

3.1.5. Synthesis of Tertiary Amines by Bronsted Acid and Lewis Acid Catalysts

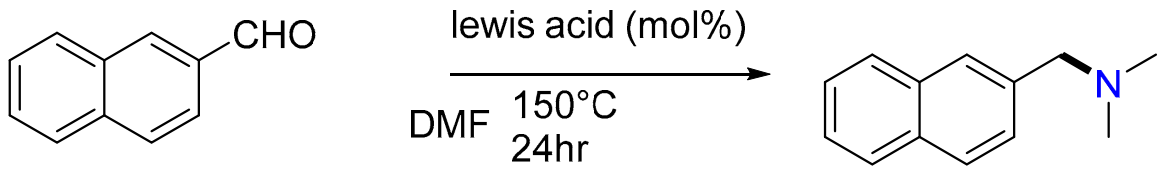
Mohanad A. Hussein et al. (2020) demonstrated a new experimental method to prepare tertiary amines through Lewis acid catalysis (Scheme 31) [41]. Webers and Bruce (1948) showed that the addition of ammonium salts of sulfuric acid, formic acid and anhydrous magnesium chloride (acid in the Lewis sense) can significantly increase the conversion rate to 95.5% yield [24]. Zhang et al. (2018) developed a ZrO $(OH)_2$ catalyst to synthesize an aromatic "tertiary amine", with 98% yield and 100% selectivity of the product (Scheme 32) [91]. Yang et al. (2018) reported the zinc acetate dihydrate-catalyzed reductive amination of various carbonyl compounds with DMF and dimethylamino (Me2N) source reductant and solvent. With $Zn(OAc)_2$ or $ZrO(OH)_2$ as Lewis acid catalysts, carbonyl compounds can efficiently react with DMF at 150–160 °C to produce dimethyl tertiary amine (Scheme 33) [92]. The previous reductive animation method:



Scheme 31. Synthesis of tertiary amine through Lewis acid catalysis.



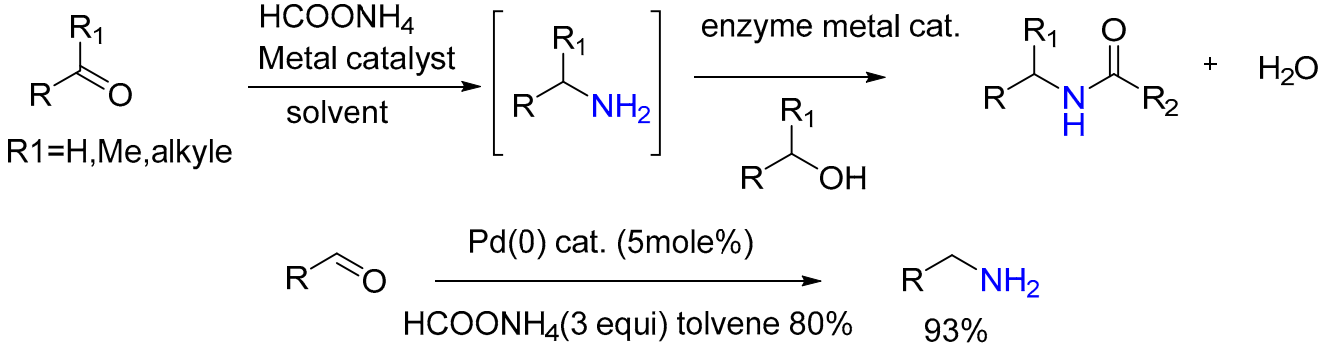
Scheme 32. Synthesis of aromatic tertiary amine.



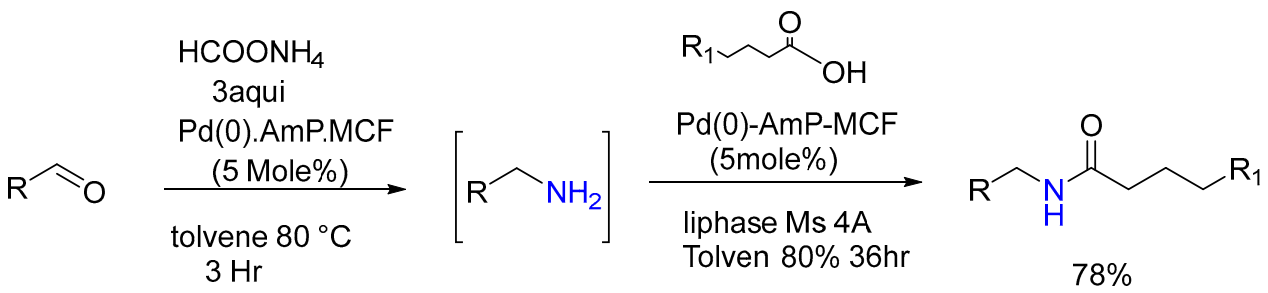
Scheme 33. Synthesis of tertiary amine using DMF and Lewis acid catalyst.

3.1.6. Multiple Relay Catalysis for the Asymmetric Synthesis of Amines

According to Palo-Nieto et al. (2016), reagents, catalysts, and diverse conditions can be introduced via the one-pot technique, including multistep catalytic operations, and then used to synthesize different amines with good yields shown in (Scheme 34) and (Scheme 35) [78].



Scheme 34. One-pot reductive amination/direct amination relay sequence.

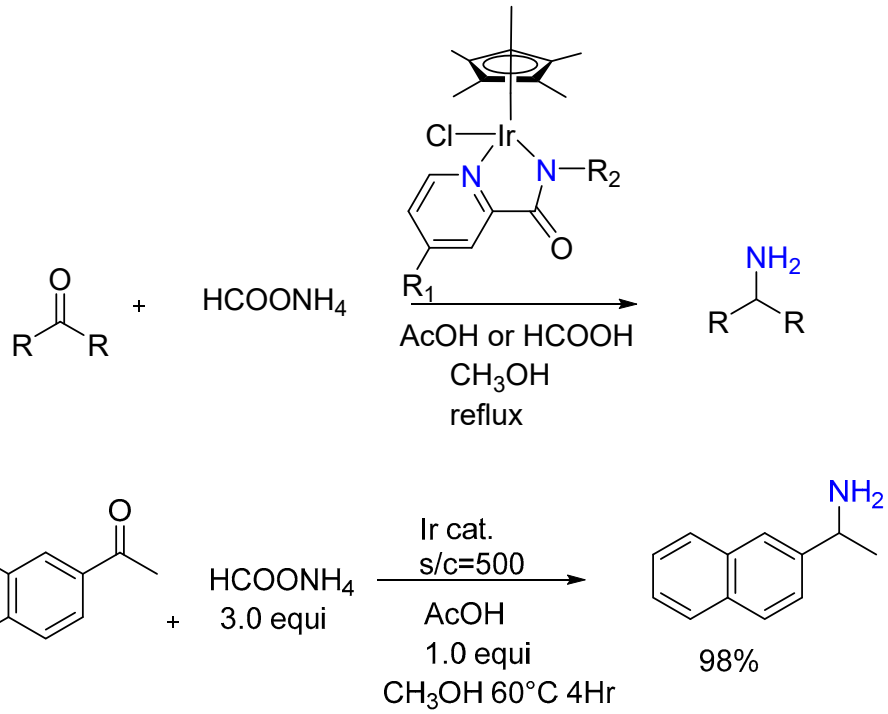


Scheme 35. Reductive amination/amination catalytic relay.

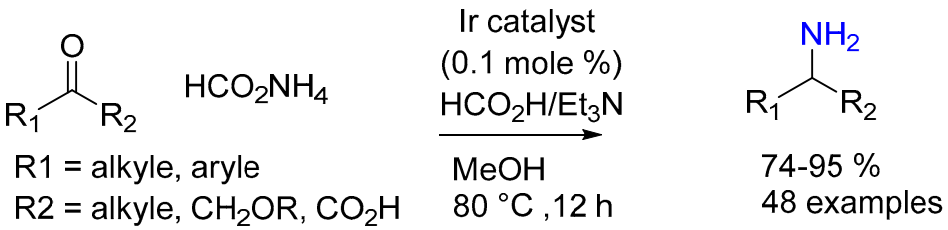
3.1.7. Synthesis of Amines by Catalysis with Cp*Ir(III) Complexes

Tanaka et al. (2019) explained that Cp*Ir complexes with a 2-picolinamide moiety work well as catalysts in the direct reductive amination of ketonic compounds to produce primary amines (Scheme 36) [84]. Morisaki, Morimoto, and Ohshima (2020) presented an Ir-catalyzed "Leuckart Wallach" reaction of many ketones, which synthesized different primary amines with excellent chemoselectivity (Scheme 37) [93]. Afanasyev et al. (2019) reported that stoichiometric amounts of chemicals such as $TiCl_4$ can promote the reaction [11]. Kulyk et al. (2020) explored the preparation of primary amines and the optimization of the reaction conditions for the Leuckart–Wallach reductive amination of ketones using ammonium formate [59].

Chuanhui Li et al. (2021) reported inexpensive and easily recoverable heterogeneous Co/NC-*T* catalysts via the one-step pyrolysis of ZIF-67 precursors in an N2 atmosphere. It was reported to have a great influence on the catalyst performance in the Leuckart-type reductive amination of biomass-derived FUR to NFMF. Among them, Co/NC-800 exhibited the best catalytic activity, with an FUR conversion of 99% and an NFMF yield of 86% (Scheme 38) [94].

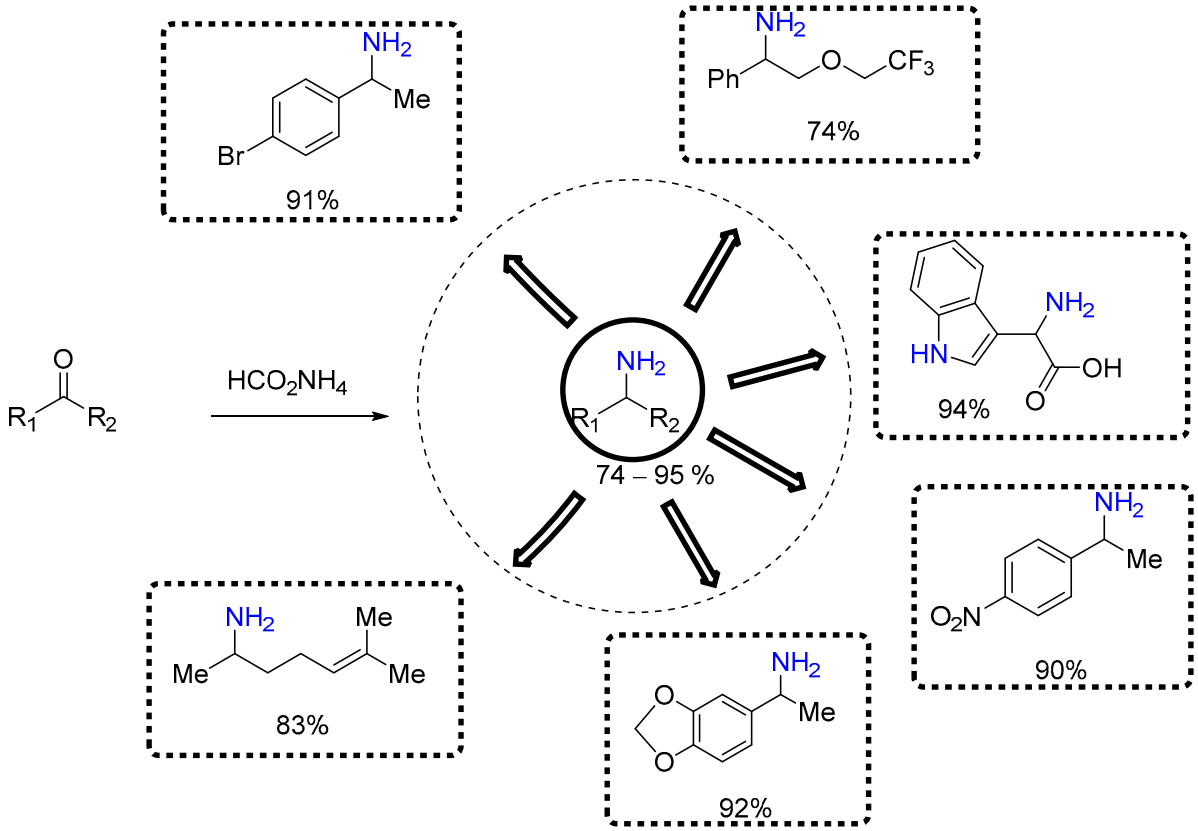


Scheme 36. "Reductive amination" catalyzed by Cp*Ir (III) complexes.

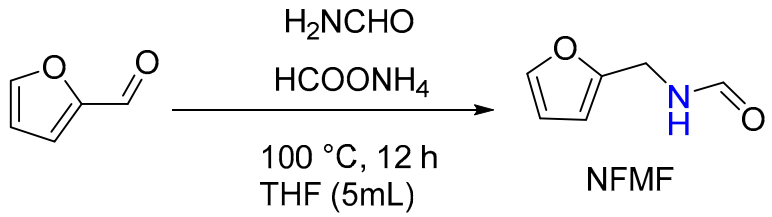


Typical examples of the products.

Scheme 37. *Cont*.



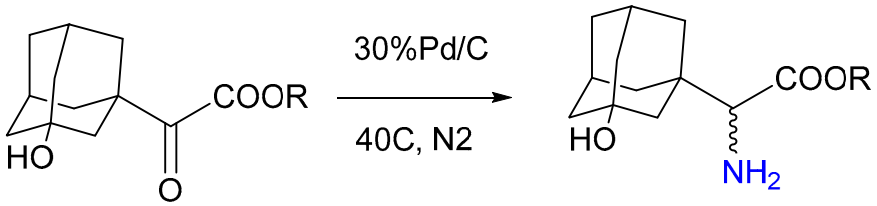
Scheme 37. Typical examples of the products of "reductive amination".



Scheme 38. "Reductive amination" by ZIF-67-derived Co/NC-*T*.

3.1.8. Pd/C Catalysis LW Reaction

Pan et al. (2015) reported a Pd-based catalytic system, with 30% Pd/C loading at 40 °C and 6 atm N2 atmosphere, and racemic 3-hydroxyadamantylglycine ester was obtained with an 85% yield (Scheme 39) [95].



Scheme 39. Reductive amination using Pd/C catalyst.

3.2. Noncatalytic Advancement

3.2.1. MW-Assisted Synthesis of Formylated Secondary Amines and Isocyanide

In recent years, MW technology has improved organic synthesis shown in (Figure 4) and (Table 1) [95]. Barba, Recio, and Batanero (2013) performed the reductive amina-

tion of several carbonyl compounds using N-methylformamide at 250 °C under stirring by microwave radiation for 10 min (Scheme 40) [25]. Rao, Poonguzhali, and Muthukumaran (2021) developed the facile MW-mediated synthesis (Scheme 41) of N-aryl-*cis*-2,6-diphenylpiperidines using arylamine, formic acid, and 1,5-diphenylpentane-1,5-dione through the novel application of microwaves to the classical Leuckart reaction [96]. D. G. Hey et al. (1983) reported experimental work using 4-tert-butylcyclohexanone to develop a convenient procedure for the preparation of secondary "amines" via a "Leuckart-type reaction", examining the stereochemical characteristics after changing the size of the primary amine used as the starting material [97]. Neochoritis and Dömling (2014) used the Leuckart reaction (Scheme 42) for the reduction step during the synthesis of isocyanides. Typical dehydrating conditions with $POCl_3$ and Et_3N afforded the novel 1H-indole-methyl-isocyanide [55].

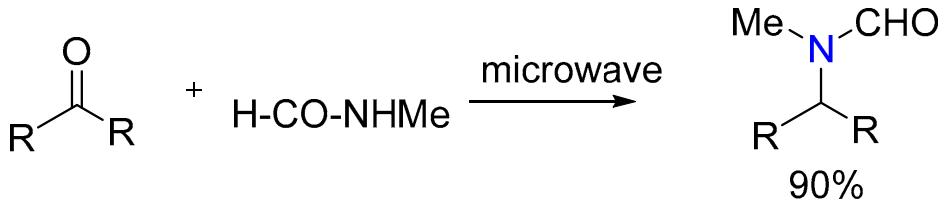
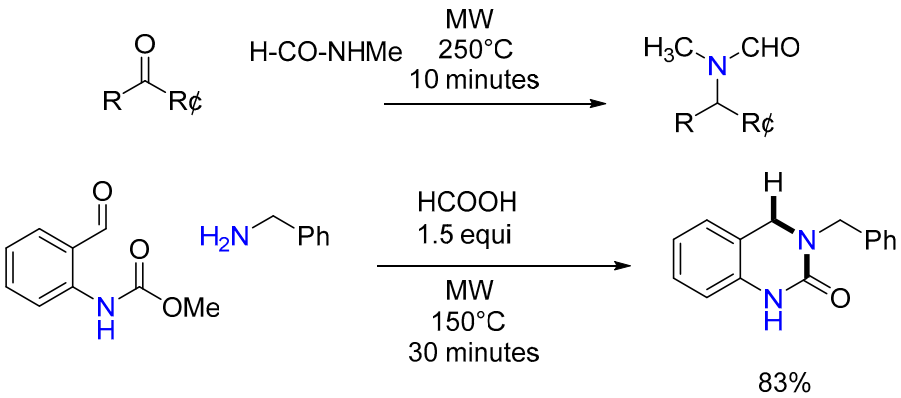


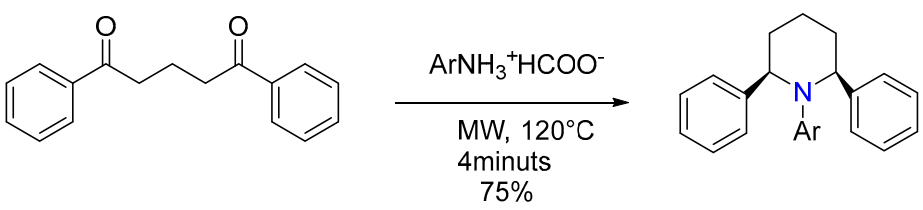
Figure 4. Microwave-assisted Leuckart reaction in N-methylformamide.

Table 1. Obtained yields by MW radiation in methyl formamide.

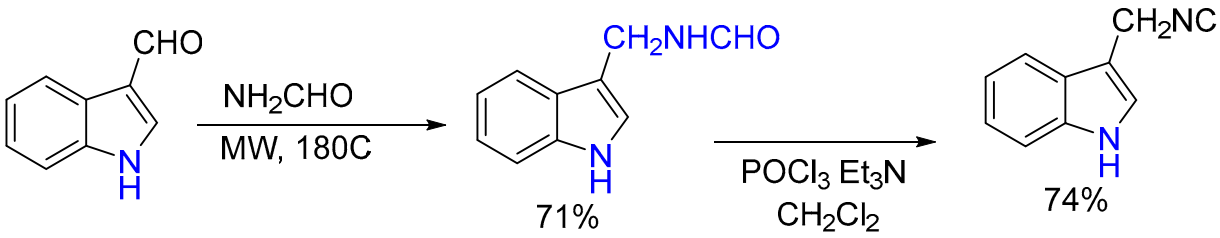
1	Yield of 2%
a; cyclohexane	90%
b; acetophenone	85%
c; propophenone	88%
d; 2-Acetylepyradine	85%
e; thiophene—carbaldehyde	92%
f; benzaldehyde	90%



Scheme 40. Microwave-assisted Leuckart reaction in N-methylformamide.

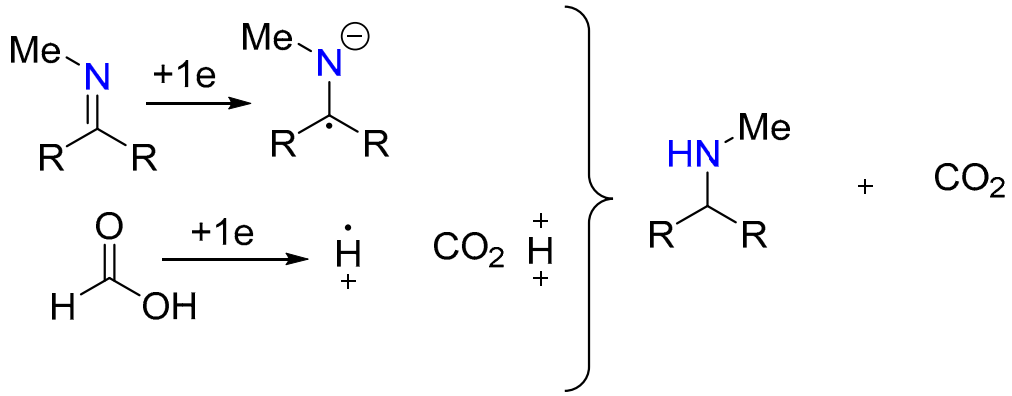


Scheme 41. MW synthesis of 1,2,6-triarylpiperidinesopen.



Scheme 42. The Leuckart–Wallach reaction and preparation of isocyanide.

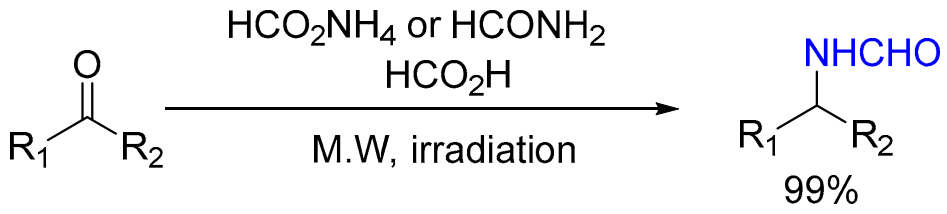
Barba, Recio, and Batanero (2013b) obtained several secondary amines by reducing certain carbonyl imines via a microwave method using N-methyl formamide as a solvent, and obtained the excellent yields (Scheme 43) [25].



Scheme 43. Microwave-assisted Leuckart-type synthesis of secondary amines.

3.2.2. LW Reaction under MW in Solvent-Free Conditions

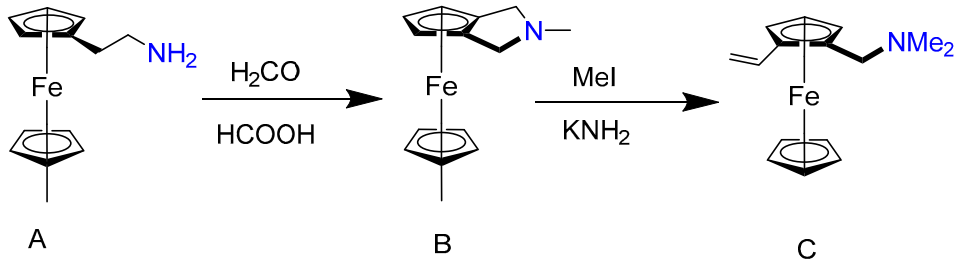
Microwave irradiation can boost the Leuckart reductive amination yield by up to 95% shown in (Scheme 44) [98].



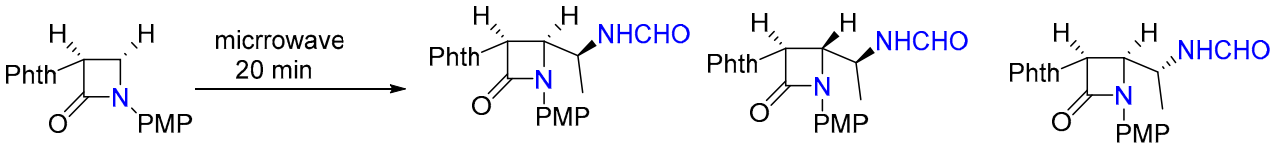
Scheme 44. Leuckart-type reaction using MW in solvent-free conditions.

3.2.3. Synthesis of Dimethylated Tertiary Amine and Ethyl Azetidin-2-ones under MW

Schaarschmidt and Lang (2013) reported that, using the parameters of the Eschweiler–Clark-modified Leuckart–Wallach reaction, 2-ferrocenylethylamine was transformed into the appropriate dimethylated tertiary amine (Scheme 45) [99]. Re et al. (1998) produced 4-[1-(N-formylamino) (in a 55:20:25 molar ratio) within 20 min using a mixture of 15 equivalents of formamide and 10 equivalents of formic acid as the amino formylating agent, with good yields of 73% (Scheme 46) [100].



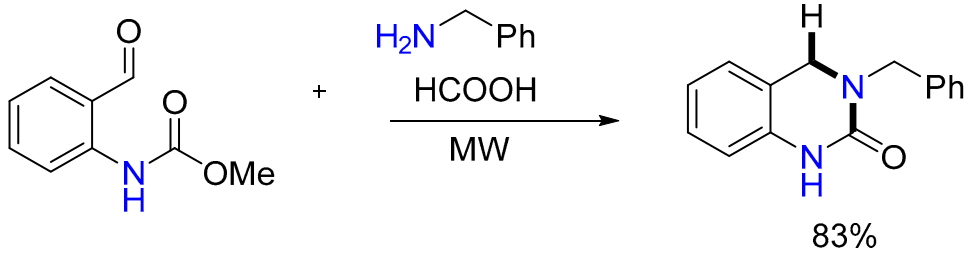
Scheme 45. Synthesis of dimethylated tertiary amine.



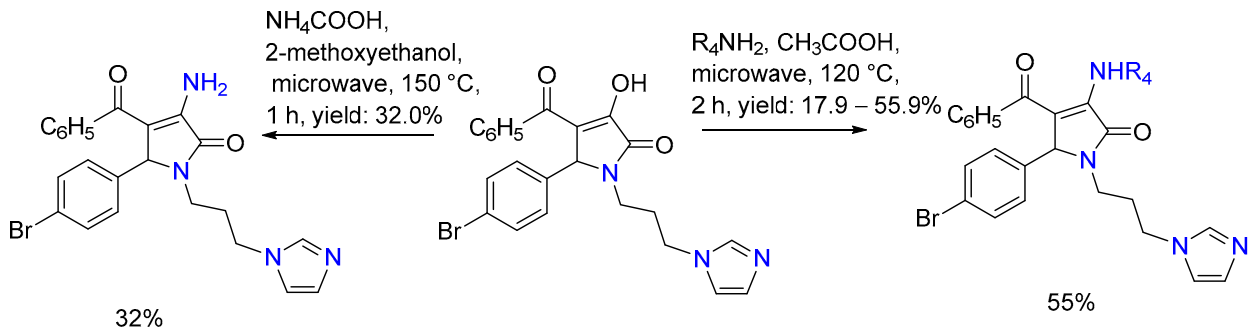
Scheme 46. 4-[1-(N-formylamino) ethyl] azetidin-2-one synthesis.

3.2.4. Metal-Free LW Synthesis of DHQs and Amino-Substituted Pyrrolidines

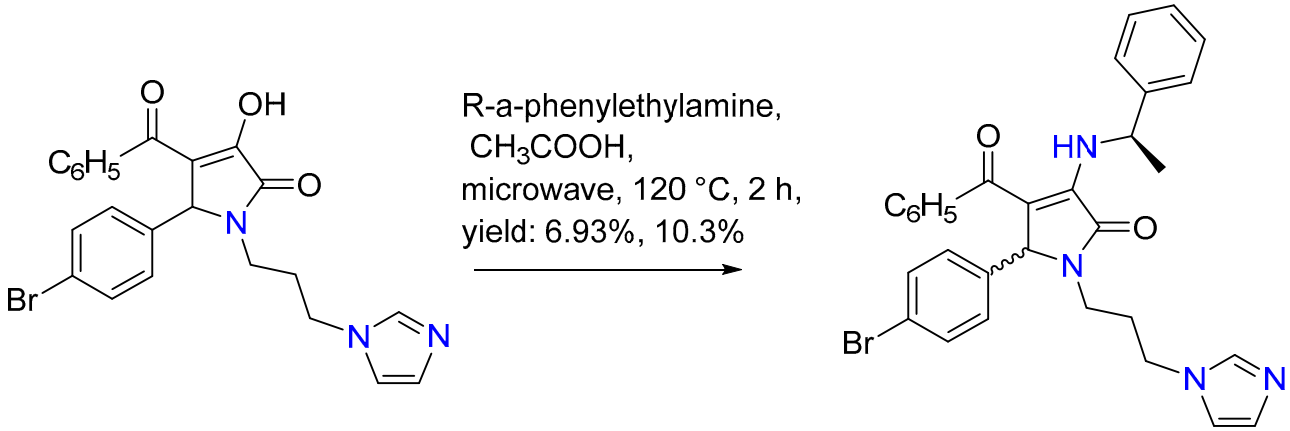
In medicinal chemistry, the 3,4-dihydroquinazolinone (DHQ) (Scheme 47) moiety has been a favored scaffold and has biological activity against a broad variety of therapeutic targets. Bokale-Shivale et al. (2021) used the LW method and synthesized DHQ at an 83% yield [101]. Bokale-Shivale et al. (2020) reported the synthesis of 3,4-dihydroquinazolinone (DHQ, a good anticancer product) [102] under metal-free conditions [103]. Wei et al. (2014) reported the catalyst-free transformation of levulinic acid into pyrrolidinones with formic acid, and showed the effects of different solvents [104]. Zhuang et al. (2012) synthesized amino-substituted pyrrolidine derivatives (Schemes 48 and 49) with good yields (56%) via the Leuckart–Wallach reaction under microwave irradiation and using NH_4COOH and R_4NH_2 at 120 °C [105].



Scheme 47. Metal-free Leuckart–Wallach-style reductive cyclization.



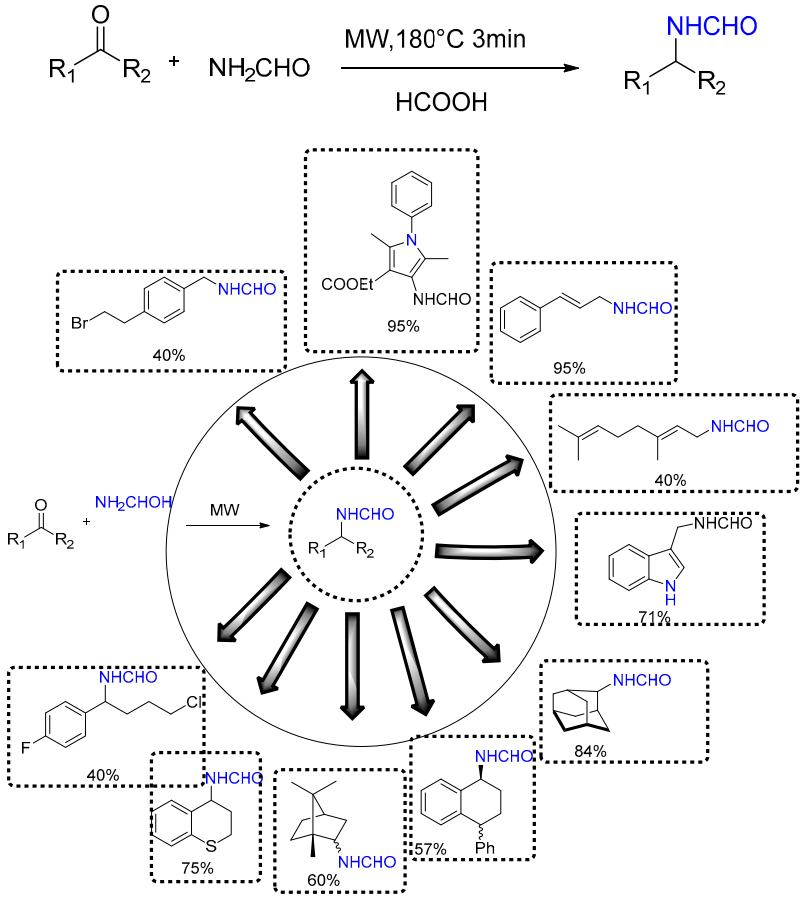
Scheme 48. Synthesis of amino-substituted pyrrolidine derivatives.



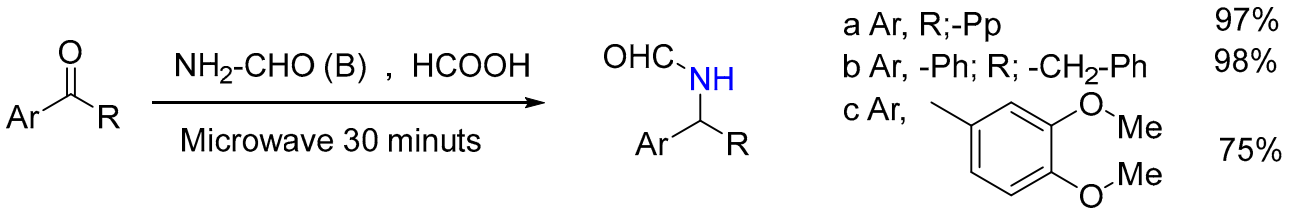
Scheme 49. Synthesis of amino-substituted pyrrolidine derivatives under microwave irradiation and using NH_4COOH.

3.2.5. Modified Leuckart–Wallach Formamide Procedure

Neochoritis, Stotani et al. (2015) used Leuckart–Wallach-produced formamides to develop an in situ isocyanide multicomponent reaction (IMCR) under MW in 3 min at 180 °C without the tedious synthesis and isolation of foul-smelling and toxic isocyanides (Scheme 50) [105]. The desired amines in (Scheme 51) were obtained in excellent yields of 97% in a short reaction time, using microwave technology within 30 min aslong with HCOOH and NH_2-CHO. The best voltage was found to be 60 W [106].

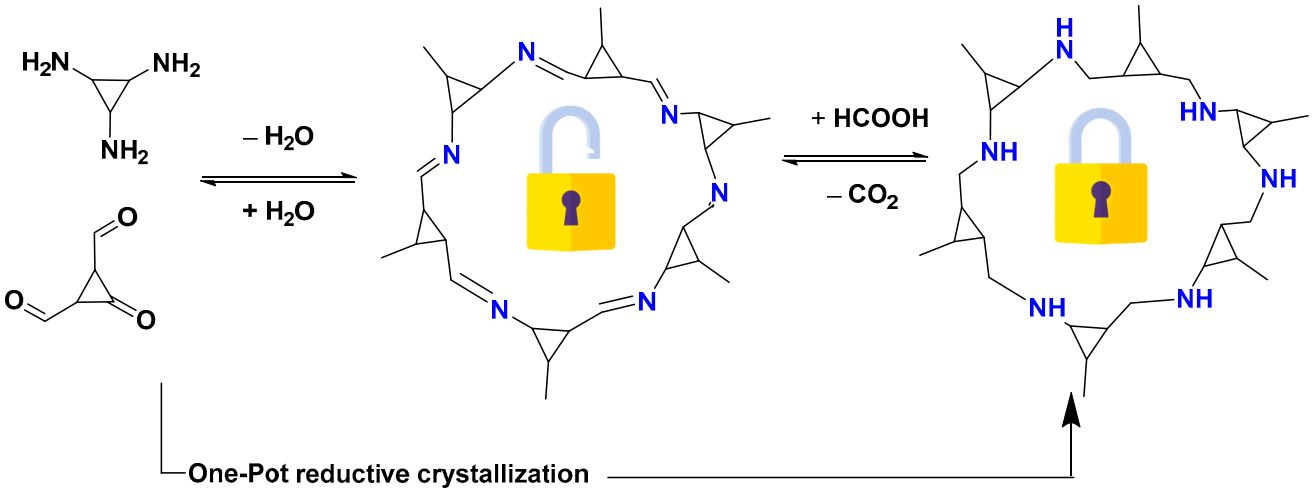


Scheme 50. Modified Leuckart–Wallach formamide procedure and representative examples with yields.



Scheme 51. Study of Leuckart's reductive amination under the microwave condition.

Grunenberg et al. (2021) introduced amine-linked covalent organic frameworks. These serve as scaffolds, enabling pore–wall modification and linkage interconversion via new synthetic methods based on Leuckart–Wallach reduction with formic acid and ammonium formate (Scheme 52) [107].



Scheme 52. Amine-linked covalent organic frameworks formed through the "Leuckart reaction".

4. Outlook and Conclusions

In this study, the classical Leuckart–Wallach (LW) reaction is described. This reaction is well-known worldwide for the synthesis of a large number of amines. This method is unique and environmentally friendly because it produces only CO_2 and NH_3 byproducts. The Leuckart reaction is inexpensive, clean and productive. In this article, we collected all well-known reactions that involve the "Leuckart reaction", as well as all synthesized drugs that have already been synthesized using this unique method. To date, researchers have developed this method and successfully synthesized different products with excellent yields and high enantioselectivity. All these methods have been described in this article. We collected all recent research advancements in using the "Leuckart-type reaction" for the synthesis of amines and bioactive drugs, including: drugs affecting the central nervous system, cardiovascular system and gastrointestinal tract; anticancer drugs, antibiotics, antiviral and antifungal drugs; drugs affecting anxiety; convulsant, biotic, and HIV drugs, and antidiabetic drugs. We hope this review will support the development of the Leuckart-type preparation of nitrogenous compounds, as well their advancement into other areas of human development.

Finally, the "Leuckart reaction" provides a convenient pathway towards the goal of the green/easy synthesis of amines, and is strongly recommended for use in organic preparations. The examples cited above are impressive and provide good insight into the synthesis of amines through the LW method. The benefits of Leuckart organic synthesis have increasingly attracted the attention of researchers worldwide. To achieve further development in this field, novel instruments that offer reproducible performance in synthesis should be used instead of domestic operations.

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