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A Perspective on Aldoximes as Platform Chemicals: Rethinking C–N Bond Formation

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Primary amines and nitriles play a central role in almost every branch of the chemical industry, and many synthetic strategies exist to obtain them. The major drawbacks of these existing approaches are low selectivities and highly toxic reagents like hydrogen cyanide. This article presents alternative catalytic routes based on aldoximes to address those challenges and outlines what needs to be done to implement aldoximes into a greener amine and nitrile production.

Introduction

The annual production of alkyl amines is estimated to be two million tons, with a projected increase of another million tons by 2030. A select number of established processes are essential to produce these amines and other nitrogen compounds, such as nitriles, which have a similar industrial relevance to amines.[1] To date, all of the major processes remain susceptible to deficiencies that present opportunities for enhancement. Often, the introduction of nitrogen into the compound represents the most challenging aspect.[1–5]

As an alternative starting point, where nitrogen is already introduced into the carbon scaffold, oximes offer a significant potential benefit over existing methods. This is particularly evident in relation to their role in the development of an alternative and potentially more sustainable approach in the formation of C–N bonds, such as amines or nitriles. By gaining a deeper understanding of the distinctive properties of oximes and comparing them to those of existing methods, we can drive innovation and ensure the sustainability of essential industrial products.

The following provides a comprehensive overview of different state-of-the-art processes for synthesizing relevant N-compounds.

Firstly, nitriles are crucial intermediates that often undergo further functionalization. Examples include *n*–hexanenitrile and *n*–nonanenitrile, which are utilized as solvents or intermediates for surfactant amines.[6] Adiponitrile is of particular importance due to its role in the production of hexamethylenediamine, one of the two monomers for nylon 6,6.[7] Additional relevant nitriles are acrylonitrile, which serves as a precursor for ABS, and acetonitrile, which is found to be extensively used as a solvent.[8] In the production of adiponitrile via the Ni-catalyzed hydrocyanation of 1,3-butadiene is the most significant approach, whereby 1-alkenes are employed as the starting material and hydrogen cyanide (HCN) is utilized as the reagent.[7] However, its industrial utilization is unfavored by the use of highly toxic hydrogen cyanide, prompting ongoing research to identify safer alternatives. Furthermore, there are significant regioselectivity issues, which lie in the favored formation of the Markovnikov product. This process yields branched nitriles, which are unwanted by-products. In the absence of viable alternatives, this process remains the preferred option despite its inherent disadvantages.[7,9]

A further but less commonly used approach for nitrile production is the ammoxidation of alkenes with ammonia and oxygen, which is particularly useful in functionalizing the allylic position of unsaturated hydrocarbons.[10] This is a commercially utilized method in propene ammoxidation. This gas-phase reaction with heterogeneous catalysts is more favorable for substrates with fewer functional groups due to the potential for side reactions and higher volatility.[11] Therefore, short-chained alkenes are preferable. The Sohio (Standard Oil of Ohio) Process[12] employs this method in the production of acrylonitrile from propene, which is used for ABS, yielding acetonitrile as a byproduct, which is broadly applied as a solvent.[13]

Amides represent another essential structural motif found in amino acids[14] and polyamides.[15] As solvents, dimethylformamide and dimethylacetamide are prominent examples of amides.[3] The latter is produced by the reaction of dimethylamine with the corresponding methyl formate or acetic acid. Other amides can be produced by the reaction of an amine with a carboxylic acid, as exemplified by the synthesis of polyamide and proteins.

Speaking of amines, linear primary alkylamines play a pivotal role in applications such as crop protection in agriculture, which is a rapidly expanding market.[5] Furthermore, they are also integral to surfactant formulations. A number of industrial synthesis approaches using either heterogeneous, homogeneous, or biocatalysis exist for introducing nitrogen to form non-activated amines, meaning no electron-withdrawing groups, aromatics, or other functional groups (Figure 1). However, these methods are notably challenging due to their low reactivity.[16]

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Using aldehydes instead of non-activated alkenes, catalyzed reactions such as the reductive amination come into play. In reductive amination, aldehydes are converted into primary amines using ammonia, but this method suffers from poor chemoselectivity.[17,18] Achieving selective production of primary aliphatic linear amines remains a significant challenge, primarily due to issues related to the formation of secondary and tertiary products during the production process.[16,18] This is due to the higher nucleophilicity of primary amines compared to ammonia, which is used as a substrate, resulting in consecutive reactions producing secondary and tertiary amines.[16] High ammonia pressures are therefore required to mitigate these selectivity issues.[19]

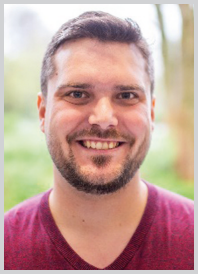
Another method, alcohol amination, employs alcohols and ammonia to produce primary amines, but it is hindered by low productivity.[4,20] This catalytic process involves a borrowing hydrogen mechanism, resulting in slow and selective formation of catalytic amounts of reactive aldehyde/ketone. In order to achieve decent productivities, it is necessary to employ a high excess of ammonia. However, the aforementioned processes are rendered less sustainable as a consequence of the considerable energy consumption involved in the production of ammonia.[21]

Diamines constitute an important substrate class for polymers, notably in polyamides such as nylon and as precursors for isocyanates used in polyurethanes. Notable compounds such as hexamethylenediamine have been previously discussed.

In the context of nitrogen introduction, oximes present an alternative to traditional methods involving ammonia, hydrogen cyanide, or the use of nitric acid. Oximes are often found in organic chemistry synthesis and are usually derived from carbonyl compounds and hydroxylamine.[22] They are categorized into ketoximes, which originate from ketones, and aldoximes, which are derived from aldehydes. The synthesis of oximes involves condensation (Figure 2) or a reduction process of nitrites. The reduction of oximes typically necessitates the use of catalysts or additives, although this process can yield various side products such as amines, substituted hydroxylamines, or imines.[23]

The oximation reaction via condensation is occasionally employed to identify aldehydes or ketones in a solution due to the precipitation or phase separation of the formed oxime from an aqueous phase. Additionally, this shifts the equilibrium of the reaction towards the oxime, thereby achieving a quantitative conversion. The poor water solubility of the oxime allows for its straightforward isolation. This can be achieved through the filtration of the formed crystals or through phase separation. Consequently, no extensive work-up is necessary for isolation, and high purities can be readily achieved. This condensation reaction is selective and does not require a significant excess compared to ammonia-based reactions. These factors make this an efficient means of introducing nitrogen functionality into molecules without the need for high pressures or noble metal catalysts.

When hydroxylamine is used in the form of its hydrochloride salt ($H_2NOH{\cdot}HCl$), stoichiometric quantities of waste are generated.[24] Conversely, employing hydroxylamine as an aqueous solution results only in water as a by-product, rendering the process environmentally benign. Oximes thus represent a versatile substrate class conducive to further functionalization and exploration in chemical synthesis.[25]



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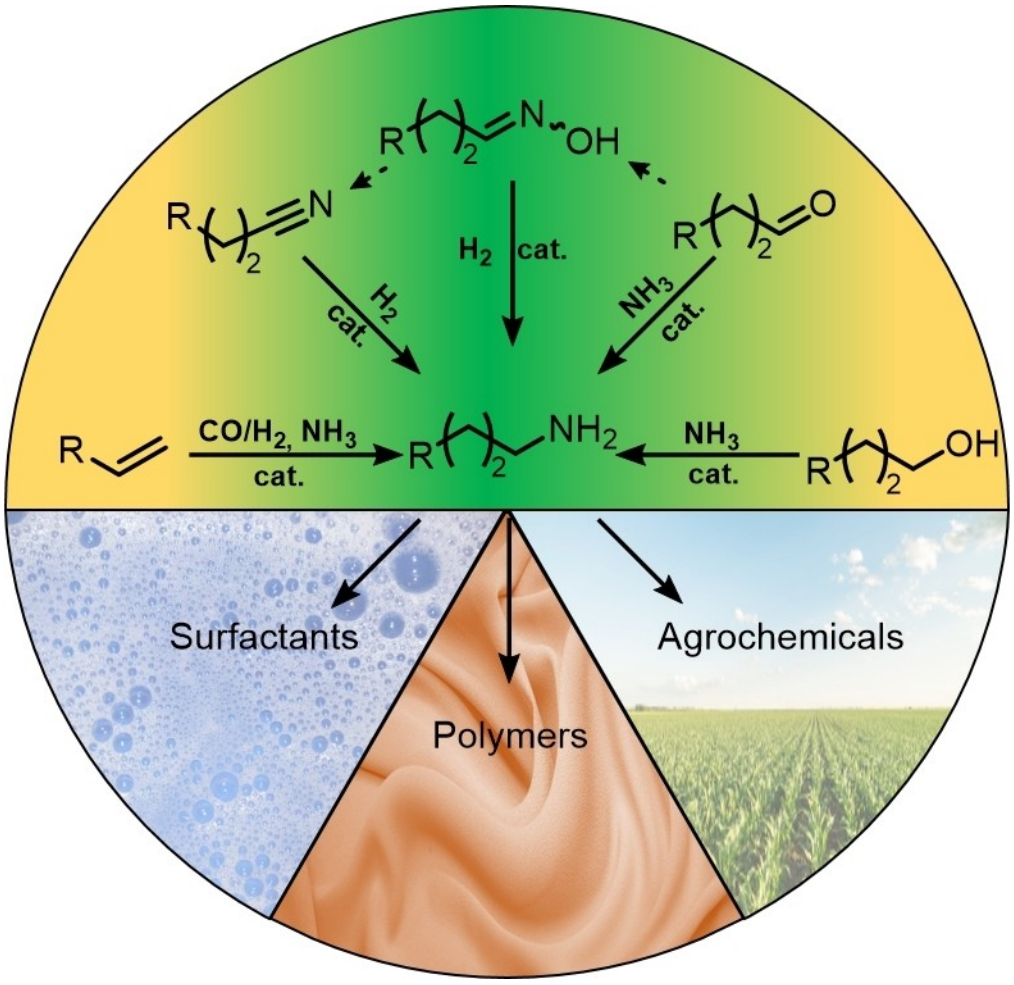

Figure 1. Different catalyzed amination reactions and downstream products.

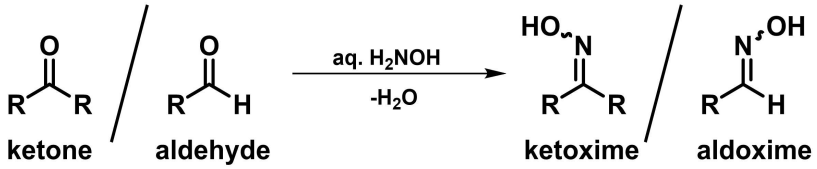

Figure 2. Condensation of carbonyl compounds with aqueous hydroxylamine.

Sustainability Challenges in Hydroxylamine Production

Recent developments in oxime research have demonstrated the potential and significance of oximes. To gain a comprehensive understanding, it is also crucial to examine the production processes and the reagents utilized. In examining the deficiencies of current methodologies, such as the utilization of HCN or the imposition of excessive ammonia pressure, it is imperative to also consider the associated issues with hydroxylamine.

Hydroxylamine, an essential chemical in oximation processes, faces challenges in terms of sustainability and production.[24] Global production totals approximately 800,000 tonnes annually.[26] Current methods include hydrogenation of nitrates/nitric acid or the Raschig process. The Raschig process generates significant quantities of $(NH_4)_2SO_4$ salt as a by-product and involves the use of corrosive and polluting SO_2, producing four tons of waste per ton of product. Reduction methods often necessitate the use of expensive noble metals and harsh conditions, such as temperatures exceeding 800 °C.[27] In all cases, ammonia is the initial component, which is an energy-intensive process involving the Haber-Bosch process.

In summary, these production methods are not environmentally sustainable. However, promising new approaches have been developed with the aim of eliminating waste formation and reducing dependence on ammonia. In a recent publication by Geng & Zeng and coworkers, innovative methods for the sustainable production of hydroxylamine are

proposed, which could potentially revolutionize its industrial applications.[24]

The intrinsic limitations of the existing approaches for nitrogen introduction are inherent to these methods due to the nature of the reaction. However, the drawback of the oxime method could be readily addressed through the implementation of more sustainable production processes. It could be postulated that breakthroughs in ammonia synthesis would negate the ills of using high excesses, yet the handling of an aqueous solution in stochiometric amounts like hydroxylamine might still be favored over high pressures of toxic gases (Table 1).

The before-mentioned approach by Geng & Zeng and coworkers utilizes ambient air as a nitrogen source and water in a plasma electrochemical cascade. This pioneering approach commences with the plasma synthesis of HNO_3 from air and water, followed by electrolysis to convert it into hydroxylamine. This process operates under mild conditions, devoid of ammonia usage, and employs inexpensive catalysts. The method exhibits high selectivity and generates no waste, thereby offering significant advantages over conventional methods.[24]

While the technology displays considerable promise, it is not yet suitable for large-scale production. Each of the two process steps presents its own challenges, which must be addressed for the technology to become a viable alternative. In the initial step, the HNO_3 plasma synthesis, even at the laboratory scale, this step is characterized by high energy consumption and a low conversion of the utilized air. It is therefore imperative that intensive research be conducted to identify the optimal plasma discharge device, with the aim of enhancing efficiency, even at the small-scale level. Moreover, for a sustainable scale-up to be feasible, it is not sufficient to address the issues inherent to the laboratory scale; rather, the energy supply of a plant must also be considered. Given the inherently energy-intensive nature of this process, the availability of a sustainable energy source, such as wind parks, solar farms, or tidal energy, is essential for its long-term viability. The second process step is characterized by low levels of activity, which in turn affects the efficiency and durability of the catalyst.

A techno-economic analysis of the authors' process revealed that profitability is contingent upon energy costs below 2.7 cents per kWh. However, the prevailing cost in the US (as of November 2023) was 7.9 cents per kWh, indicating a significant discrepancy.[28] This highlights the imperative for further enhancements in energy efficiency to render the process economically viable. Nevertheless, it may serve as a foundation for subsequent research and improvements.

This advancement may potentially serve as an alternative to the routes that originate from the Haber-Bosch process, thereby addressing concerns pertaining to high energy consumption and the necessity for N-containing substrates associated with conventional nitrogen introduction methodologies.[29] The process presents a sustainable, environmentally friendly pathway for integrating nitrogen functionalities into platform chemicals, thereby illustrating a shift towards environmentally friendly industrial practices.

Oximes as Starting Compounds

In organic synthesis, oximes are commonly used as precursors for various functional groups. They can undergo reduction to form amines or dehydration to yield nitriles.

In industrial applications, cyclohexanone oxime stands out, consuming 95% of the annual 800,000 tons of hydroxylamine production.[26]

It serves as a precursor in the Beckmann rearrangement, which is a crucial step in the synthesis of nylon-6 (Figure 3).

In addition to ketones, aliphatic aldehydes, which are readily available from 1-alkenes via hydroformylation, are of interest for

Table 1. Comparison of different reagents for the introduction of nitrogen moieties.

	Hydrogen Cyanide	Ammonia	HydroxylAmine
Reactions	Hydro cyanation	Hydroamination, reductive amination, alcohol amination, hydroaminomethylation	Oximation
Substrates	Alkenes	Alkenes, aldehydes, ketones, alcohols	Aldehydes, ketones
Products	Nitriles	Amines	Oximes
GHS			
Major drawbacks	Highly toxic, regioselectivity	High excess necessary Energy intensive production Low selectivity/productivity	Sustainability depends on ammonia production

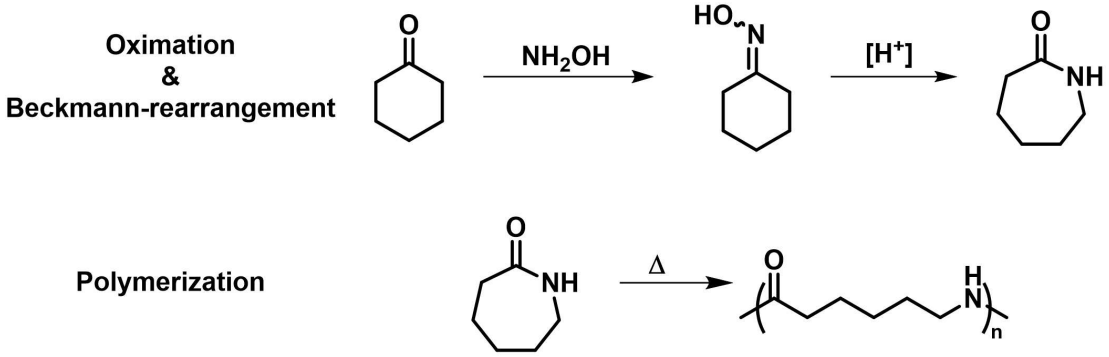

Figure 3. Syntheses of Nylon 6 from Cyclohexanone via ketoxime and caprolactam.

oximation and subsequent modification.[30] The previously mentioned N-functionalities can be all derived from oximes via a variety of approaches, including the shown Beckmann rearrangement, reduction to amines or dehydration to form nitriles.

Starting from 1-Alkenes All the Way to the Oxime

Recent advances in chemical synthesis have explored alternative routes to produce aliphatic nitriles from 1-alkenes, with the aim of circumventing the use of toxic and environmentally hazardous substances such as cyanides. Gröger, Vorholt, and colleagues pioneered a cyanide-free approach for the synthesis of aliphatic nitriles from 1-alkenes, demonstrating a promising pathway toward sustainable chemical manufacturing.[31]

The central concept is based on a novel combination of homogeneous catalysis and biocatalysis techniques. This innovative approach focuses on the selective production of aliphatic nitriles, including compounds such as hexanenitrile and higher homologs, through the condensation of aldehydes with hydroxylamine (Figure 4). This method is notable for its mild reaction conditions and high selectivity, in contrast to traditional processes such as ammoxidation, which utilize harsh conditions and involve the use of toxic cyanides.

The process commences with the hydroformylation of 1-octene using a bi-phasic rhodium Rh/TPPTS (3,3′,3′′-Phosphanetriyltris(benzenesulfonic acid) trisodium salt) catalyst system, resulting in a conversion rate of 74% with a ratio of normal to iso aldehyde of 2.2:1. Subsequently, the organic phase undergoes phase separation and subsequent condensation with hydroxylamine. It is of note that this step is conducted under equimolar conditions, obviating the necessity for excess hydroxylamine, thereby optimizing efficiency and reducing waste.

Further enhancement of the process involves biocatalytic dehydration facilitated by aldoxime dehydratase, also known as the OxdRE whole-cell catalyst. This enzymatic step is highly efficient, converting approximately 90% of aldoxime intermediates into a mixture of nitriles. The overall conversion rate achieved in a streamlined three-step, one-pot reaction sequence is 67%.

This research demonstrates the feasibility and applicability of utilizing aldoximes derived from 1-alkenes as precursors for N-functionalized compounds such as aliphatic nitriles. By circumventing the use of highly toxic substrates, elevated temperatures, and high-pressure conditions that are typically associated with conventional methods, this approach represents a significant advancement towards greener and more sustainable chemical synthesis practices.

Seidensticker's and Vorholt's subsequent work[32] build upon the pioneering efforts of Gröger and coworkers[31] by integrating hydroformylation and condensation steps into a unified one-pot reaction scheme (Figure 5). This innovative approach involves a two-phase hydroformylation reaction in the presence of aqueous hydroxylamine, followed by a consecutive enzymatic dehydration process after the isolation of the post-product. By changing the ligand to sulfoxantphos it was possible to further increase the yield of the hydroformylation compared to the use of TPPTS.

The concept achieves an impressive overall conversion rate of 85% from 1-octene to nonane nitrile. Furthermore, the work explores the applicability of renewable substrates such as methyl 10-undecenoate, demonstrating a proof of concept but achieving lower conversion rates that require further optimization.

Consequently, the recent advancements in oxime synthesis from basic chemicals have demonstrated a viable pathway for the conversion of alkenes into valuable nitrile derivatives. This

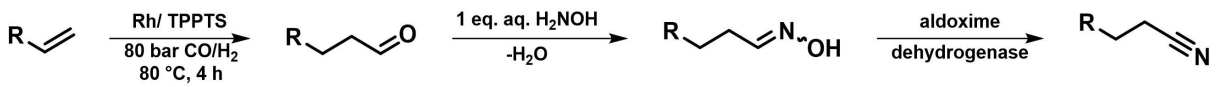

Figure 4. Reaction scheme for the synthesis of aliphatic nitriles starting from 1-alkenes.

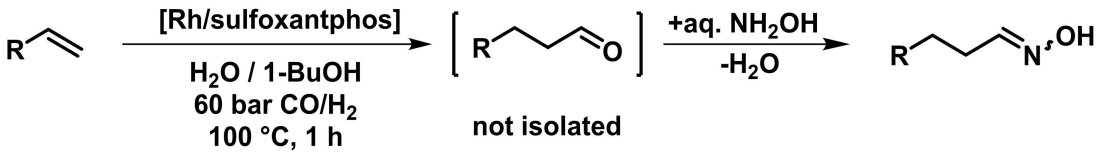

Figure 5. One-pot approach for the synthesis of aldoximes from alkenes.[32]

protocol not only facilitates straightforward access to N-functionalized compounds from readily available starting materials but also capitalizes on the well-established industrial practice of hydroformylation.[30] While current applications have primarily focused on the coupling of oximes with nitrile formation, oximes present a versatile platform for subsequent chemical transformations.

Hydrogenation

Like the reduction of nitro compounds, oximes offer a straightforward pathway for introducing N-functionalization into molecules that can be subsequently hydrogenated to yield the corresponding amines. This process is particularly valuable for synthesizing primary amines from oximes via reduction (Figure 6).

In organic chemistry, reduction attempts have employed hydrides such as $NaBH_4$,[33] which are known for their effectiveness but are associated with significant waste production. As a result, they are more suitable for laboratory-scale applications. In contrast, hydrogen gas (H_2) itself stands out as the cleanest reducing agent, setting the stage for catalytic hydrogenation processes.

The majority of presented catalytic systems for hydrogenating ketoximes and aldoximes are heterogeneous. 1956, Reeve and Christian significantly contributed to this field by developing a RANEY® Cobalt catalyst.[34] Nevertheless, the occurrence of concurrent side reactions posed a challenge to selectivity.

Further studies, including investigations by Müller et al., explored heterogeneous mechanisms using metals such as Ni and Co.[35] These metals, while less active, demonstrated a higher selectivity towards primary amines compared to noble metals such as palladium and rhodium, which are more active but tend towards secondary amine formation. It has been observed that the chemical structure of the substrate significantly influences the outcome, with branched and sterically hindered oximes favoring the production of primary amines. In contrast, linear aliphatic oximes present a challenge in achieving primary amine selectivity.

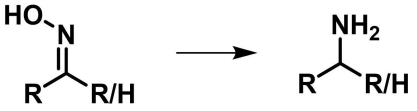

Figure 6. Reduction of Ald-/Ketoximes to primary amines.

In comparison, ketoximes tend to exhibit greater selectivity than aldoximes, a result of their distinctive structural properties.[35] Notable recent advancements include Bai-Cheng's successful conversion of heterocyclic aldoximes to primary amines on a 60-gram scale with an over 90% yield, although this process requires the use of excess ammonia and non-linear substrates.[36]

Wang and colleagues achieved notable success using palladium nanoparticles with nitrogen-containing ligands, achieving a 99% yield with benzylaldoxime under atmospheric hydrogen pressure and ambient temperature conditions.[37] However, the yields were significantly reduced when using linear aliphatic aldoximes. For example, the yield of octylamine was only 83%, and that of butylamine was 71%. These advancements, though promising, face challenges such as high dilution and small-scale experimental setups (e.g., 0.05 mmol in 10 ml of H_2O).

The majority of research in this field has been concentrated on heterogeneous catalysis, with a particular focus on ketoximes. There are a few examples of homogeneous hydrogenation of ketoximes in the literature, with the objective of forming secondary amines[38] or hydroxylamines.[39] The primary focus of these works is on the synthesis of more complex organic molecules, using Iridium and Ruthenium catalyst yielding the desired products. The system in question places a significant emphasis on the utilisation of applications pertaining to active pharmaceutical ingredients and fine chemicals, with a comparatively lesser focus on the utilisation of basic platform chemicals.

The investigation of aldoximes remains relatively limited, with fewer studies demonstrating significant success, particularly with linear aliphatic substrates.

Prior to this year, no homogeneous catalyst system had been developed for the reduction of aldoximes. Nevertheless, the recent achievements in homogeneous catalysts for aldoxime hydrogenation by our group represent a significant breakthrough in the field.

Homogeneous Catalyzed Hydrogenation of Aldoximes to Primary Amines

We sought to develop a homogeneous catalyst system for hydrogenation, with the objective of yielding primary aliphatic amines.[40] Hexanal oxime was employed as a model substrate. The final catalyst system involved ruthenium/triphos with DBU as a basic additive, as depicted in Figure 7. A comprehensive screening of ligands, precursors, and bases was conducted to

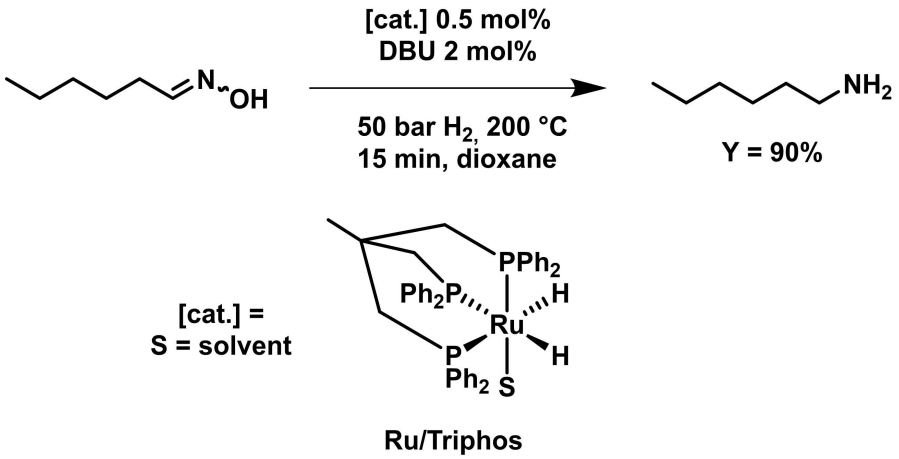

Figure 7. Reduction of hexanaloxime and the corresponding catalyst system (S = solvent).

optimize the system. This resulted in achieving high yields of 90% with full conversion and impressive productivities (TOF_{20} > 7500 h^{-1}).

The investigation also examined the reaction pathways involved in aldoxime hydrogenation. In light of the application of aldoximes, two primary reaction pathways were identified. The initial hydrogenation of the aldoxime to an alkylhydroxylamine is followed by a second hydrogenation step, during which the liberated H_2O forms the primary amine. An alternative pathway begins with the liberation of H_2O to form the nitrile, which is then subjected to two subsequent hydrogenation steps via the imine to the amine. The screening of basic additives demonstrated that the choice of base has a significant impact on the reaction pathways. The pathway leading to the formation of alkylhydroxylamine was found to be more selective, potentially due to the absence of imine, which readily reacts to form secondary and tertiary amines.

Further substrate screening demonstrated high yields (> 77%) for linear aliphatic amines (such as C_6 and C_9), thereby corroborating the robustness of the catalyst system. This idea builds on the concept developed by Gröger and Seidensticker for the one-pot formation of aldoximes from 1-alkenes and extends to the synthesis of linear aliphatic primary amines in a three-step reaction cascade starting from linear alkenes, as illustrated in Figure 8.[31]

For example, when starting from 1-pentene and 1-octene, the cumulative yields of primary amine reached 60% and 57%, respectively. Even renewable substrates, such as methyl 10-undecenoate, were converted with a cumulative yield of nearly 70% for primary amine production, a critical monomer for nylon-12, as illustrated in Figure 9.

In conclusion, our workgroup developed the first homogeneously catalyzed system for aldoxime hydrogenation and demonstrated its advantages over known systems in terms of reaction speed and selectivity. This protocol enables the synthesis of primary amines from alkenes with good cumulative yields over three reaction steps, producing only water as a byproduct and avoiding the use of excess ammonia or highly toxic reagents. The utilization of readily available platform chemicals like 1-alkenes or aldehydes enables the selective conversion of linear aldoximes to primary amines, paving the way for sustainable and efficient nitrogen functionalization in an industrial synthesis approach.

Summary and Outlook

Oximes represent a versatile class of compounds with a wide range of applications in organic synthesis. They are relatively simple to synthesize via the condensation of hydroxylamine with an aldehyde/ketone. Further research could provide new avenues for the sustainable production of hydroxylamine, which is essential for the development of environmentally friendly processes for N-functionalized molecules via oximes.

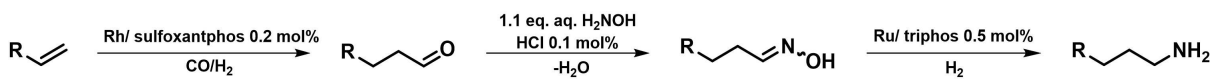

Figure 8. Reaction cascade starting from alkene to primary amines.[40]

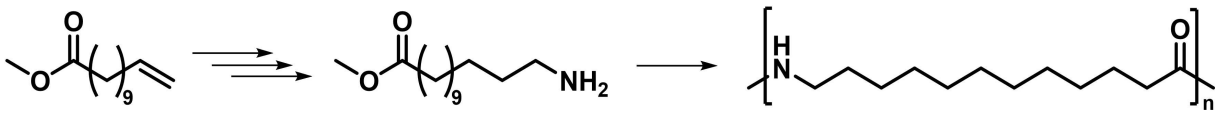

Figure 9. Simplified reaction scheme for the conversion of methyl 10-undecenoate to 12-aminododecanoate.

Recent advances have demonstrated the potential of oximes in industrial contexts. These include protocols that eliminate the use of ammonia or hydrogen cyanide for the introduction of nitrogen into molecules. Methods have been developed for the synthesis of primary amines and nitriles, demonstrating high efficiency even with renewable substrates of industrial interest.

Future research should focus on the hydrogenation of dioximes to produce the highly demanded diamines, such as hexamethylenediamine, while circumventing the use of hydrogen cyanide. The major challenge that needs to be addressed will be the poor solubility of adipaldoxime. Furthermore, the upcoming research should already include concepts of catalyst separation/recycling to ease the step from academic research into industrial application.

With this article, we aim to inspire further exploration of oximes as an additional substance class for a drop-in strategy in existing industrial processes. The development of sustainable processes for hydroxylamine production and research into additional catalyst systems suggest that oximes may offer a promising avenue for more sustainable industrial applications. They can serve as a starting material for a range of substrates and may offer a viable alternative to several existing processes.

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Conflict of Interests

The authors declare no conflict of interest.

Keywords: Oximes · Hydrogenation · Amination · Primary amines · Homogeneous catalysis

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