# Nickel-Catalyzed Dehydrogenation of N-Heterocycles Using Molecular Oxygen

Sourajit Bera, Atanu Bera, and Debasis Banerjee*

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**ABSTRACT:** Herein, an efficient and selective nickel-catalyzed dehydrogenation of five- and six-membered N-heterocycles is presented. The transformation occurs in the presence of alkyl, alkoxy, chloro, free hydroxyl and primary amine, internal and terminal olefin, trifluoromethyl, and ester functional groups. Synthesis of an important ligand and the antimalarial drug quinine is demonstrated. Mechanistic studies revealed that the cyclic imine serves as the key intermediate for this stepwise transformation.
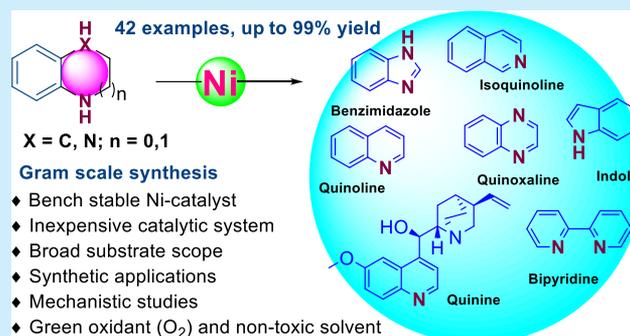
Bioactive molecules having an aromatic N-heteroarene core represent an elegant toolbox as life-saving drugs and are widely used to target numerous medicinal issues.[1] Such aromatic N-heteroarenes have potential applications for antimalarial, anticancer, and anti-HIV treatments.[1,2] Therefore, development of novel and innovative methods for the synthesis of aromatic N-heteroarenes is highly desirable and will provide access to a broad collection of such privileged scaffolds.

Classical approaches for N-heteroarenes involve stoichiometric oxidants (DDQ and sulfur) or harsh reaction conditions and are associated with poor selectivity and functional group tolerance.[3] Therefore, providing a more sustainable and atom-economic technology that avoids such toxic and harmful chemicals is highly desirable.

Notably, dehydrogenation of partially saturated aromatic N-heterocycles has attracted significant attention due to its sustainability and flexibility to the introduction of substitutions at the desired position, which is sometimes difficult to achieve by cross-coupling reactions.[4] Therefore, a number of heterogeneous catalysts based on noble metals, Co-based metal oxide, Fe-based metal oxide, etc., have been demonstrated for dehydrogenation reactions.[5] However, most of them rely on a high reaction temperature (>130−150 °C) and showed poor functional group tolerance. Again, the use of electrocatalysis[6] and photocatalysis has also been developed for dehydrogenation reactions.[7]

Surprisingly, only a handful of examples of homogeneous catalysts have been identified for such reactions (Scheme 1A). Pioneering reports by Yamagushi and Fujita on Ir catalysts at the refluxing temperature of p-xylene or toluene are noteworthy.[8,9] Similar reactions using Ir-based catalysts have been reported by Crabtree,[10] Albrecht,[11] Fischmeister,[12] and

others.[13] Moreover, their low natural abundance and high cost restrict their application for large scale industrial uses.[14] Therefore, in terms of sustainability, replacement of such precious metals using a more abundant and inexpensive base—metal catalyst has attracted significant attention.[15] In this direction, Jones and co-workers established a remarkable and highly selective dehydrogenation process using iron-based[16] and cobalt-based[17] molecular pincer complexes. Nevertheless, these PNP pincer ligands require multistep synthesis and are highly expensive.

Moreover, dehydrogenation of N-heterocycles using an oxidant represents an exciting alternative route to the established methods and could be successfully performed under relatively milder conditions.[18−20] Notably, the true potential of homogeneous base—metal catalysts for dehydrogenation of N-heterocycles using an oxidant is still rather unexplored in comparison to that of metal-catalyzed accept-orless dehydrogenation.[21] More importantly, application of a nickel-based catalyst in combination with molecular oxygen for dehydrogenation of N-heterocycles remains unknown (Scheme 1B).[22]

Herein, for the first time, we report that an inexpensive nickel catalyst supported by a bidentate nitrogen-based ligand in combination with molecular oxygen as an oxidant is capable of affecting sequential dehydrogenation of various partially

**Scheme 1. (A) Previous Reports, (B) Ni-Catalyzed Dehydrogenation Using Molecular Oxygen, and (C) Key Challenges for Dehydrogenation of N-Heterocycles**



**Table 1. Optimization of the Reaction Conditions**[a]



| entry | Ni salt (mol %) | L (mol %) | solvent | 3a (%) |
|---|---|---|---|---|
| 1 | NiBr₂ (10) | – | toluene | 22 |
| 2 | NiCl₂ (10) | – | toluene | 3 |
| 3 | Ni(acac)₂ (10) | – | toluene | 5 |
| 4 | NiCl₂(dme) (10) | – | toluene | 10 |
| 5[b] | NiBr₂ (10) | L1 (12) | toluene | 70 (68)[b] |
| 6 | NiBr₂ (10) | L2 (12) | toluene | 25 |
| 7 | NiBr₂ (10) | L5 (12) | toluene | 30 |
| 8[c] | NiBr₂ (10) | L1 (12) | toluene | 92 (90)[b] |
| 9[c] | NiBr₂ (10) | L1 (12) | p-xylene | 56 |
| 10[c] | NiBr₂ (10) | L1 (12) | 1,4-dioxane | 14 |
| 11[c] | NiBr₂ (10) | L1 (12) | t-amyl-OH | 100 (99)[b] |
| 12[c,d] | NiBr₂ (5) | L1 (6) | t-amyl-OH | 100 (99)[b] |
| 13[c] | NiBr₂ (5) | L1 (6) | t-amyl-OH | 70 |
| 14[c,e] | NiBr₂ (10) | L1 (12) | t-amyl-OH | 20 |
| 15[c,f] | NiBr₂ (10) | L1 (12) | t-amyl-OH | 42 |
| 16[c,g] | NiBr₂ (10) | L1 (12) | t-amyl-OH | 8 |
| 17[c,h] | – | – | t-amyl-OH | – |
| 18[c,h] | – | L1 (12) | t-amyl-OH | 3 |

[a]Reaction conditions: **1a** (0.25 mmol), NiBr₂ (*x* mol %), phen (*y* mol %), TEMPO (10 mol %), t-BuOK (1.0 equiv), and solvent (1.0 mL) in a glass vial using an O₂ balloon at 80 °C in a preheated oil bath for 24 h. GC conversion using mesitylene as the internal standard. [b]Isolated yield (average of two runs). [c]Oil bath temperature of 95 °C. [d]t-BuOK (1.5 equiv) was used. [e]Reaction carried out without an O₂ balloon. [f]Reaction carried out without TEMPO. [g]No base was used. [h]t-BuOK (1.0 equiv) was used.

saturated N-heterocycles to nitrogen-containing heteroarenes in good to excellent yields (Scheme 1B,C).

Recently, we have successfully explored a series of Ni- and Fe-catalyzed (de)hydrogenation reactions using alcohols.[23] Therefore, to study the successive dehydrogenation presented here, 1,2,3,4-tetrahydroquinoline (THQ) **1a** was chosen as a model substrate with four different nickel precatalysts. Only 22% quinoline **3a** was obtained when the reaction was performed with an O₂ balloon in combination with TEMPO (10 mol %) and t-BuOK (1.0 equiv) in toluene at 80 °C for 24 h (Table 1, entries 1–4).

Application of bidentate nitrogen-based ligand 1,10-phenanthroline (**L1**) significantly improved the yield of **3a** [68% (Table 1, entry 5)]. However, the use of other ligands, **L2–L5**, led to low conversion to **3a** (Table 1, entries 6 and 7, and Table S2). Under identical conditions, the use of different inorganic bases (t-BuONa, Na₂CO₃, K₂CO₃, Cs₂CO₃, K₃PO₄, and NaOH) as well as organic bases (N,N-diisopropylethylamine and pyridine) resulted in only 3–35% conversion to **3a** (Table S3). The catalytic dehydrogenation could be performed at a lower reaction temperature; however, the maximum yield to **3a** was obtained at 95 °C [90% (Table 1, entry 8, and Table S4)]. Next, p-xylene, 1,4-dioxane, and N,N-dimethylformamide (DMF) were tested as solvents in place of toluene and proved to be less efficient (entries 9 and 10 and Table S5). Nevertheless, t-amyl alcohol as a solvent catalyzed the successive dehydrogenation of **1a** into **3a** in quantitative yield with excellent selectivity (>99%, entry 11). Dehydrogenation could be performed at a lower catalyst loading (5 mol

%); however, the base plays a crucial role in complete transformations (entries 11–13).

Control experiments in the absence of O₂, TEMPO, base, catalyst, and ligand revealed the potential role of the individual component for the dehydrogenation process (Table 1, entries 14–18, and Table S6). Notably, a significantly smaller amount of **3a** was obtained in the absence of TEMPO (10 mol %), evidence that TEMPO plays a crucial role in improving product selectivity (Table 1, entry 15 vs entry 11). However, we anticipated that the base plays a key role in the activation of nickel precatalysts. Base-mediated initial dehalogenation followed by substitution with a secondary amine (THQ **1a**) resulted a nickel–amine species.[23] Thereafter, such a preformed nickel–amine species undergoes β-hydride elimination in the presence of a base, which results in the formation of **1a′**, which successively completes the stepwise dehydrogenation to **3a** (Scheme 1C).[23]

The scope of the oxidative dehydrogenation was tested using the optimized conditions of Table 1. 1,2,3,4-Tetrahydroisoquinoline **1b** and 1,2,3,4-tetrahydrolepidine **1c** smoothly participated in the reaction, and **3a–3c** were obtained in excellent yields (86–99%) (Scheme 2).[21b–d] However, sterically hindered 1-methyl-1,2,3,4-tetrahydroisoquinoline **1d** and 2-methyl-1,2,3,4-tetrahydroquinoline **1e** needed slightly longer reaction times to give 95% **3d** and 96% **3e** (Scheme 2). Next, 2,8-disubstituted N-heterocycles were employed and did not influence the dehydrogenation reactivity [**3g–3i**, ≤98% yields (Scheme 2)]. N-Heterocycles having -NO₂, -Cl, and free

## Scheme 2. Dehydrogenation of Substituted Quinolines[a]



79–99% yields (Scheme 3). Hantzsch dihydropyridine **2d** having reducible ester functionalities smoothly transformed

## Scheme 3. Scope of Five- and Six-Membered N-Heteroarenes[a]
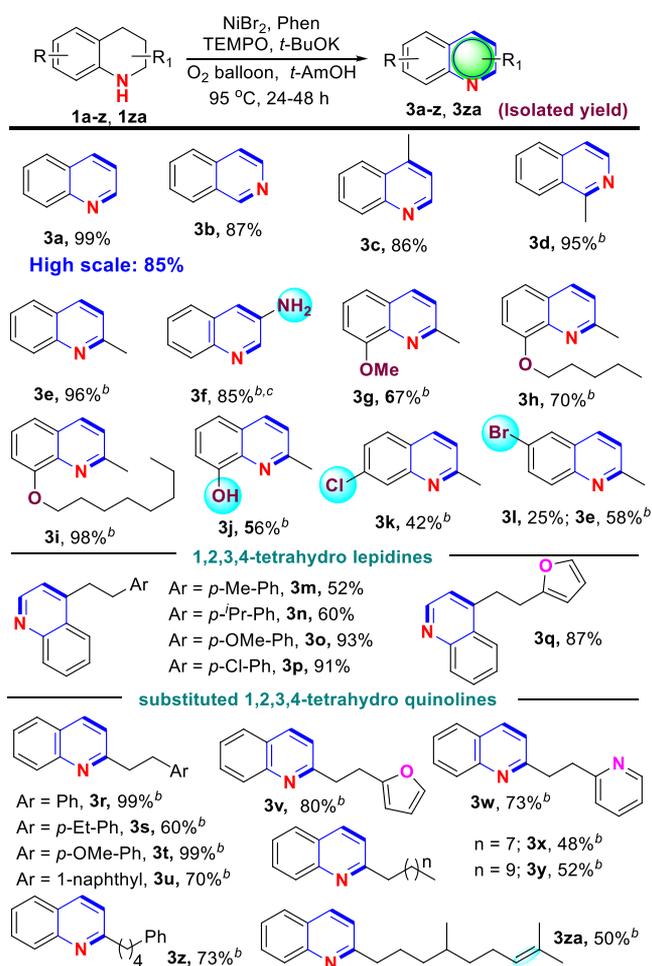


[a]See Table 1 for the reaction conditions. [b]TEMPO (20 mol %), 48 h. [c]From 3-nitroquinoline.

[a]See Table 1 for the reaction conditions. [b]TEMPO (20 mol %), 48 h. [c]From 5-nitroindoline.

-OH groups were well tolerated, affording 42–85% yields of **3f**, **3j**, and **3k**. Notably, the sensitive -NO$_2$ group was reduced by the *in situ*-generated molecular hydrogen in the presence of a nickel catalyst to give **3f** (Scheme S1). Bromo-substituted 1,2,3,4-tetrahydroquinoline **1l** resulted in only 25% **3l**, and we observed 58% dehalogenated product **3e** (Scheme 2). However, in the case of **3j** and **3k**, we recovered the unreacted starting materials and did not observe any dehalogenated product **3e**.

Next, 1,2,3,4-tetrahydrolepidine and 1,2,3,4-tetrahydroquinolines were tested (Scheme 2). Lepidines substituted with *p*-methyl, *p*-isopropyl, *p*-methoxy, and *p*-chloro functionalities on the aryl ring furnished moderate to quantitative yields of **3m**–**3p**, respectively (≤93%). 2-Furyl-substituted lepidine was also obtained in 87% yield (**3q**). Pharmaceutically important 2-arylethylquinolines, comprising 1-naphthyl, 2-furyl, and 2-pyridine groups, were isolated in quantitative yield (60–99%, **3r**–**3w**). Similarly, this strategy provides an exciting route to alkyl-substituted quinolines, such as 2-nonylquinoline **3x**, 2-undecylquinoline **3y**, and 2-(4-phenylbutyl)quinolone **3z** in 48–73% yields. Next, 2-(4,8-dimethylnon-7-en-1-yl)quinoline **3za** was obtained in moderate yield without affecting the internal double bond (Scheme 2).

Similarly, the parent indoline and methoxy- and nitro-substituted indolines afforded indoles **4a–4c**, respectively, in

into the tetrasubstituted pyridine **4d**. 2,3-Dihydrobenzimidazoles having a free NH group or N-benzylated substituent gave **4e** or **4h**, respectively, in quantitative yield [87–99% (Scheme 3)]. 2,3-Dihydrobenzimidazoles bearing 2-aryl substituents only weakly influence the dehydrogenation activities and gave 78–85% yields of **4f** and **4g**. In addition, 1,2,3,4-tetrahydroquinoxalines (**2i**–**2k**) were transformed into quinoxalines **4i**–**4k**, respectively, in quantitative yields (Scheme 3). However, medicinally important quinoxanaline **4l** was obtained in 45% yield, due to the influence of the electron poor trifluoromethyl functionality (Scheme 3). Nevertheless, we did not observe any product **4m** in the presence of a nitrile functionality. Again, piperidine substituted with methoxy and trifluoromethyl functionalities did not result in any desired product [**4n** and **4o** (Scheme 3)].

To explore the synthetic utility, the stepwise dehydrogenation of 2-(piperidin-2-yl)pyridine **5** resulted in bipyridine ligand **8** in 76% yield. Also, the antimalarial drug quinine **9** was isolated in moderate yield (35%) from **6** (Scheme 4). The catalytic transformation is not impacted by free hydroxyl and terminal olefin functionalities. Notably, dehydrogenation of N-substituted indoline **7**, a tertiary amine derivative, into **10** can be performed in 57% yield en-route to the synthesis of a protein kinase inhibitor C (Scheme 4).[21b–d] Additionally, for a

**Scheme 4. Synthetic Applications**



**Ligand synthesis**

2-(piperidin-2-yl)pyridine **5** → NiBr₂, Phen, TEMPO, t-BuOK, O₂ balloon, t-AmOH, 95 °C, 48 h → 76% yield, **8** **Bi-pyridine**

**Synthesis of Antimalarial drug**

**6** → NiBr₂, Phen, TEMPO, t-BuOK, O₂ balloon, t-AmOH, 95 °C, 24 h → 35% yield, **9**, **Quinine**

**Synthesis of drug intermediate using N-substituted indolines**

**7** **Tertiary-amine** → NiBr₂, Phen, TEMPO, t-BuOK, O₂ balloon, t-AmOH, 95 °C, 48 h → 57% yield, **10**

**Intermediate of protein kinase C inhibitor LY317615**

**Scheme 5. Mechanistic Studies**



**A. Control experiments:**

a) **11** → standard conditions of Table 1 → **12** no conversion

b) **13** → standard conditions of Table 1 → **14** no conversion

**B. Radical inhibiting experiments:**

c) **1a** → standard conditions of Table 1 BHT 1 equiv → **3a**, 10% yield

d) **1a** → standard conditions of Table 1 p-benzoquinone 1 equiv → **3a**, 12% yield

**C. Detection of intermediates:**

e) **1e** → standard conditions of Table 1, 24 h → **1e'**, 15% yield + **3e**, 40% yield

Detected using GC-MS

standard conditions of Table 1, 48 h → **1e'**, nd + **3e**, 98% yield

practical application, a high-scale reaction was conducted and yielded 85% product **3a** (Scheme S2).[24]

Notably, the catalytic reactions could be performed in the presence of chloro, free hydroxyl and primary amine, internal and terminal olefin, trifluoromethyl, and ester functionalities, including pyridine and furyl motifs. Nevertheless, sterically hindered 2-methylisoquinoline as well as N-substituted indoline **7**, a tertiary amine derivative, enables the transformations in good yields.[21b−d]

Further, to gain more insight into the reaction mechanism and to prove our hypotheses (Scheme 1C), dehydrogenation of N-acetyl-1,2,3,4-tetrahydroquinoline **11** was performed. However, in agreement with our proposal, we did not detect any desired product (Scheme 5Aa). Moreover, no dehydrogenation product was observed when N-methyl-2,4,4,7-tetramethyl-1,2,3,4-tetrahydroquinoline **13** was used as the substrate, indicating that the direct transformation of a C=C bond is difficult. These experimental observations strongly support our hypothesis that the reaction proceeds by stepwise dehydrogenation reactions as demonstrated by Jones and co-workers (Scheme 5A).[16]

Thereafter, we independently conducted the dehydrogenation studies using 1 equiv of BHT (2,2,6,6-butylated hydroxytoluene) and 1 equiv of p-benzoquinone (Scheme 5B). The yield of **3a** was significantly decreased, indicating that a radical mechanism might be operating, and the reaction proceeds via a superoxide radical anion (•O₂⁻).[19a] It is assumed that, under standard catalytic conditions, O₂ is reduced to •O₂⁻. Additionally, the radical process also indicated the involvement of the imine species during the dehydrogenation process.[6a] Nevertheless, to probe the intermediate imine species, the dehydrogenation reaction of **1e** was monitored using GC-MS, and a mixture of **1e'** and **3e** was detected after 24 h. Notably, **3e** was obtained in quantitative yield after 48 h (Scheme 5C). These control studies also support our hypothesis of the involvement of an
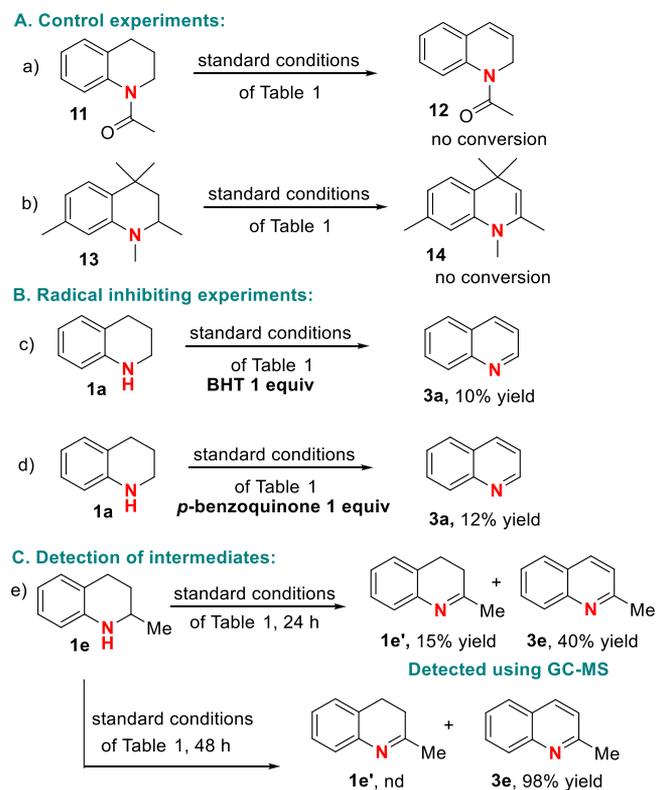
imine intermediate during such stepwise transformations (Scheme 5). Interestingly, to trap the in situ-generated molecular hydrogen, the model reaction was performed in an experiment setup presented in Scheme S1, where application of Pd/C reduced styrene to ethylbenzene in ≤20% yield. These experiments are consistent with the generation of hydrogen gas during the dehydrogenation process.

On the basis of the observations described above and previous studies,[25−27] we believe that an in situ-generated Ni precatalyst, **1a**, and TEMPO produced imine **1a'** following β-hydride elimination.[26] Next, stepwise isomerization of the double bond results in the desired quinoline **3a**. However, more detailed mechanistic investigations are ongoing in our laboratory and will be reported in due course.[19a]

In summary, we have demonstrated a simple and inexpensive Ni-catalyzed system for dehydrogenation of various N-heterocycles. Application of molecular oxygen as an oxidant facilitates the synthesis of a series of medicinally important quinolines, quinoxalines, indoles, and benzimidazoles (>42 examples) in ≤99% yields. The catalytic protocol enables the transformations in the presence of alkyl, alkoxy, chloro, free hydroxyl and primary amine, internal and terminal olefin, trifluoromethyl, and ester functionalities, including pyridine and furyl motifs. We have also demonstrated the synthesis of an important bipyridine ligand and antimalarial drug quinine. Mechanistic studies indicated that dehydrogenation is a stepwise process that starts by enamine−imine tautomerization followed by C=C bond isomerization to achieve the desired products.

## ■ ASSOCIATED CONTENT

**ⓈⒾ Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02271.

Detailed experimental procedures, spectral data, and $^1$H and $^{13}$C NMR spectra for all new compounds (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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