Dearomative Selective Reduction of Structurally Diverse *N*-Heteroarenes Enabled by Titanium Catalysis

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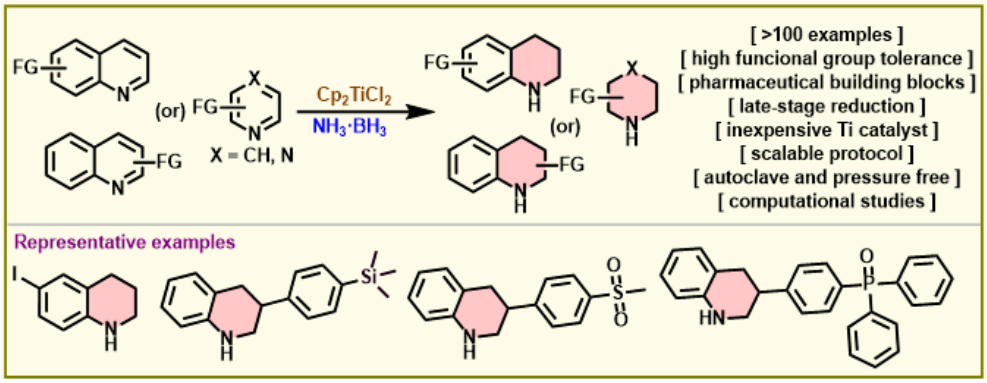


ABSTRACT: The reduction of aromatic compounds is a stalwart transformation in modern organic synthesis since it allows the generation of novel complex three-dimensional (3D) chemical entities from two-dimensional precursors (2D), linking readily available aromatic feedstocks with unobtainable alicyclic structures. However, controlling the high level of selectivity of *N*-heteroarenes (quinolines and pyridines), particularly substituents positioned on the reducible quinoline ring, is both intriguing and challenging, and methods for selective saturation of structurally complex derivatives (multiple aromatic rings) are rarely unaddressed and need some advances. Also, many approaches suffer from scalability problems as well as high cost and low availability of both catalysts and tailor-made ligands. To address this issue, we herein report the first example of commercially available titanocene dichloride (Cp_2TiCl_2)-catalyzed dearomative selective reduction of structurally diverse nitrogen-based heteroarenes with ammonia borane as a reducing agent (>100 examples). The developed protocol features the advantage of chemoselectivity and wide functional group tolerance of quinolines. Meanwhile, the efficient reduction of challenging and unprotected functionalized pyridines as well as pyrazines is also furnished with remarkable functional group preservation and also with an improved F(sp^3) carbon fraction. Additionally, a few selected furans and benzofuran derivatives were also successfully demonstrated under synthetically relevant conditions, and gram-scale synthesis was effectively executed. The methodology can be extended to the saturation of complex *N*-heteroarenes with conserved selectivity. In addition, density functional theory (DFT) calculations were carried out to shed light on the mechanistic insights into the reduction of quinoline.

■ INTRODUCTION

Arenes and heteroarenes are very important structural building blocks and are ubiquitously seen in several life science products and agrochemicals.[1-6] Since a larger pool of inert and planar aromatic compounds is accessible from the processing of coal and petroleum feedstocks, including bio-based resources,[7, 8] they can be readily modified and or functionalized using a variety of well-established synthetic techniques such as nitration,[9] halogenation,[10] cross-coupling,[11] and many more, especially for preparing core drug analogs.

In turn, straightforward access to privileged 3D chemical space using ubiquitous aromatic feedstocks is of prime importance, as their integration into the complex organic framework holds extensive value in drug development **(Figure 1A)** and finds application in a multitude of organic reactions.[12, 13] The dearomative selective reduction of (hetero)arenes[12-19] and reductive deuteration,[20] especially nitrogenous heterocyclic compounds represent the shortest way to leverage the construction of saturated nitrogen-containing heterocycles (cyclic amines),[16, 18, 21, 22] which are advanced chemical building blocks enabling their exploration for targeted therapies.[1-6] For instance, substituted 1,2,3,4-tetrahydroquinolines, piperidines, piperazines, indolines, pyrrolidines, and related ring systems are integral parts of 3D-pharmacophores, orally bioavailable drugs, as well as bio-active natural products **(Figure 1B)**.[23-27] However, generating saturated *N*-heterocyclic analogues can be a substantial synthetic burden and labor-intensive.[16, 18] Therefore, the expansion of robust methodologies is necessary not only to access nitrogen-based 3D-like sp^3-rich fragments for efficient clinical research but also to search for innovative pharmaceutical compounds with enhanced therapeutic efficiency. In addition, the latest accomplishments in the medicinal chemistry community invented "*escaping from flatland" i.e.*, increasing saturation as a tool for improving clinical development success.[25, 26] In this sense, saturated heterocyclic

rings allow improved F(sp^3) carbon fraction, increased substitution, and greater structural diversity, as well as enhanced aqueous solubility that may lead to higher bioavailability, which makes them appealing in the drug discovery setting **(Figure 1C)**.[12, 25, 28-30] In contrast, excessive flat sp^2-rich aromatic cores are associated with some parameters like low specificity (selectivity) and poor solubility in aqueous media.[31, 32] For this reason, saturated carbo- and/or heterocyclic ring motifs are present in a large number of top-selling pharmaceuticals and FDA-approved drugs, signifying that 82% of small-molecule therapeutics contain at least one *N*-heterocycle, with the piperidine, piperazine, and pyrrolidine analogs ring being the most prime ones.[6]

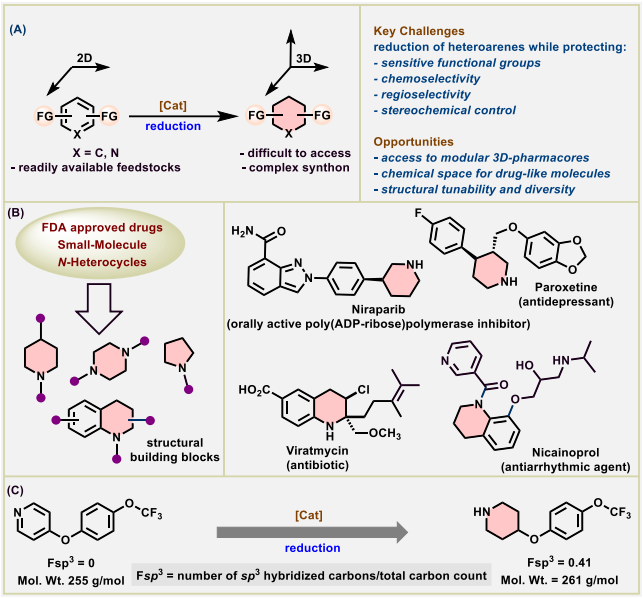


Figure 1. (A) Overview of aromatic rings to the saturated carbocycles; (B) FDA-approved and top pharmaceuticals bearing piperidine unit; (C) Improved F(sp^3) through the saturation of *N*-heterocycle.

In recent years, various research groups have achieved significant advances in the reduction of *N*-heteroarenes, namely, quinolines, pyridines, and related heterocycles.[12-18, 33-52] Despite remarkable progress, there is still a notable gap in the substrate scope. The substrate scope of quinoline derivatives is divided into two types **(Figure 2A)**: 1) substituents present on the phenyl ring and 2) substituents present on the *N*-heteroarene ring. Although the first one is well-established,[12-18, 33-40] there are still drawbacks with some functional group compatibility. For example, during the ring saturation process, the persistence of the iodine (I) moiety situated on the benzene core of quinoline is subpar.[39, 42, 47] Further, methods that tolerate sulfur groups are inadequate,[53, 54] and phosphorus, as well as silanes[55, 56] and many more are barely known. On the other hand, the second type, *i.e.*, the tolerance of the substituents on the reducible nitrogen ring, remains conspicuously incipient. Additionally, the catalytic reduction of functionalized pyridines offers a gateway to piperidine analogs that are found in a vast array of FDA-approved drugs [13, 33, 35, 40, 41], which is due to the increased fraction of sp^3 carbon atoms (Fsp^3) that manifest improved drug-like properties.[12, 25, 28-30] Alternatively, piperidines can be prepared by multiple synthetic techniques, such as cycloadditions, ring expansions, radical cyclizations, nucleophilic substitutions, etc.[19] Among all of these, the reduction of pyridines is an ideal route to access diverse piperidines on a large scale owing to the availability of bulk pyridine derivatives and step-economy. One of the key problems in this chemistry is the binding of coordinating nitrogen atoms to the metal center or the presence of weak C-H bonds close to nitrogen atoms that assist unwanted side reactions.[57, 58] Due to this reason, the aromatic reduction of unprotected functionalized pyridines is less known.[13, 33, 35, 40, 41] Thus, it is not able to expand the wider piperidine-based 3D chemical space in the small molecule drug discovery process.

Just recently, Glorious and co-workers discovered an unprecedented conversion of complex aromatic building blocks into saturated pharmaceuticals by using an Rh-based catalyst and a boron-based H_2 source.[59] Subsequently, the same group also reported PtO_2-catalyzed controllable and chemoselective hydrogenation of benzene and pyridine rings that exist in pharmaceutically relevant complex molecules.[60] These two reports proved useful in terms of chemo- and diastereoselectivity and overcame intractable limitations in the hydrogenation of (hetero)arene chemistry and opened up new frontiers in medicinal and synthetic chemistry.[59, 60] Despite these potential transformative innovations, the high cost of precious metal-based catalysts, the functional group existence on the reducible nitrogen ring of quinoline, as well as the reduction of pyridines bearing sensitive functional groups remain a significant challenge. Indeed, such skeletons are of great importance owing to their wide range of applications in the synthesis of several drugs and natural products.[23-25] Therefore, the development of the selective and sustainable synthesis of diverse saturated *N*-heterocycles (e.g., 2-, 3-, or 4-substituted 1,2,3,4-tetrahydroquinolines, and functionalized phenylpiperidine analogs), is highly coveted.

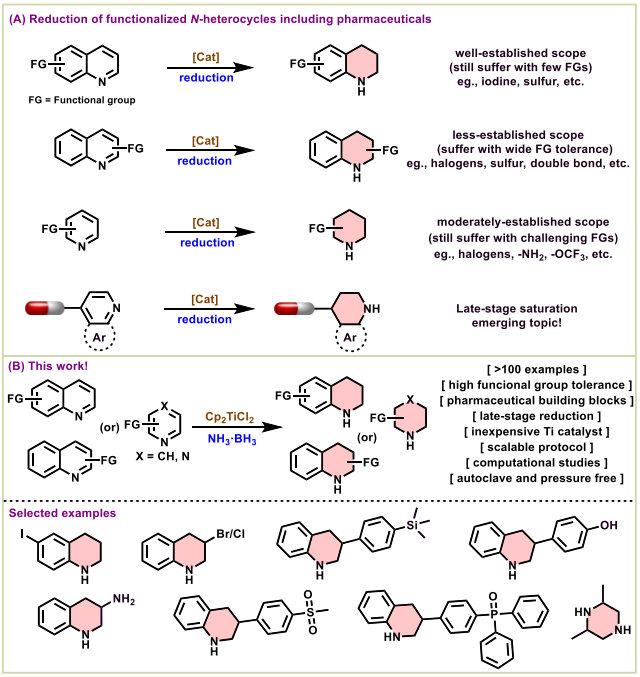


Figure 2. (A) Reduction of functionalized *N*-heteroarenes; (B) Ti-catalyzed reduction of structurally diverse *N*-heteroarenes using AB.

Over the last two decades, transfer hydrogenation reactions have emerged as an attractive alternative to the conventional hydrogenation approach.[61, 62] A few benefits of the transfer hydrogenation process are (a) the avoidance of special equipment and gaseous H_2 cylinder and (b) the large availability of relatively inexpensive hydrogen donors. Among available hydrogen donors,[61, 62] Ammonia borane ($NH_3{\cdot}BH_3$, AB) is one of the potential solid-state hydrogen-rich material (19.6 wt.%) and is comparatively stable in air and moisture.[63-66] Further, AB is non-explosive, non-toxic, and moderately inexpensive, and it can be successfully recyclable.[63-66] For these reasons, AB is applied as an efficient H_2 source in various chemical transformations. [63-65] In this context, our group also recently utilized AB for the reduction of nitroarenes, heteroarenes, and carboxylic esters.[67-69]

Material insufficiency is a particularly crucial problem to be addressed in modern catalysis research.[70, 71] Noble metals are often applied not only in the hydrogenation of (hetero)arenes[1-6] but also in other related reactions,[21, 72] and several industrial processes rely on them. As such, there is an increasing demand to substitute expensive and endangered metals (e.g., Rh, Ir, Pd, Pt, and Ru) with considerably cheaper, sustainable, and abundant 3d metals.[73-75] However, this is a challenging task, as the reactivity of non-precious metals is typically different from that of precious metals. Over the last decade, earth-abundant metal catalysts

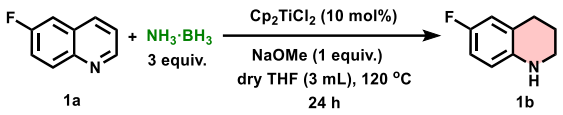
for hydrogenation of (hetero)arenes with high selectivities have attracted much attention due to their analogous properties with those of precious metal-based catalysts in both homogeneous and heterogeneous catalysis.[12-18, 33-41] However, there are some limitations in the substrate scope and late-stage saturation of structurally complex molecules.[59, 60] Another crucial limitation is the lack of "general" catalysts for the selective reduction of *N*-heteroarenes bearing wide reactive functional groups that permit the introduction of greater 3D chemical space and precise structural building blocks into the target molecules. For example,[35, 40, 54] there are exceptionally few reports where a single type of catalyst reduces aromatic rings within heteroarene while preserving different sets of functional groups. Similarly, the same type of catalyst hardly reduces the heteroarene ring in both substituted quinolines and pyridines.[12-18, 33-47] To overcome these problems, new catalytic systems are required, which can lower the activation barrier for the reduction of structurally diverse heteroarenes and features tolerance toward reactive functional groups. Such catalytic systems would bring more incentives to pharmaceutical R&D and manufacturing sectors.

Notably, Titanium is the second most earth-abundant transition metal as well as non-toxic and plays a crucial role in the field of inexpensive metal catalysis in comparison to other 3d-based metal catalysis.[76-78] Also, titanium complexes frequently display strongly Lewis acidic metal centers. Therefore, titanium-based catalysts are well applied in synthetically useful organic transformations,[76-78] particularly titanocene dichloride (Cp_2TiCl_2), showing new vistas in the exhaustive reduction and hydrodehalogenation as well as hydrodeoxygenation reactions is appealing.[79-81] To the best of our knowledge, so far, there is only one report on Ti-mediated catalytic hydrogenation of simple arenes such as benzene, toluene, naphthalene, and anthracene.[78] Ti-catalyzed chemoselective reduction of *N*-heterocycles holding challenging functional groups is, therefore, elusive in the literature. Inspired by the above-mentioned breakthrough reports as well as our continuous interest in the reduction of (hetero)arenes,[68, 82, 83] here, we report that a simple titanocene dichloride allows for chemoselective reduction of *N*-heterocycles, especially functionalized quinolines and pyridines including few benzofurans using AB as an H_2 source, and without the requirement of external sophisticated ligands **(Figure 2B)**.

■ RESULTS AND DISCUSSION

We initiated our investigations by evaluating the reduction of 6-Fluoroquinoline **(1a)** as a model substrate (0.5 mmol) with 3 equivalents of AB as the hydrogen source in the presence of Cp_2TiCl_2 (10 mol%) and NaOMe (1 equiv.) in dry THF (3 mL) at 120°C for 24 h; 93% (isolated yield) of the desired product 6-fluoro-1,2,3,4-tetrahydroquinoline **(1b)** was obtained **(Table 1, entry 1)** and no byproduct (defluorination) is detected. Lowering the amount of AB (from 2 to 1 equiv.) resulted in a decay of 1b yield, and no product **(1b)** formation took place in the absence of AB (**entries 2-4**). Further, other reducing reagents ((^{t}Bu)NH_2·BH_3, $NHMe_2$·BH_3, 9-BBN, HBpin, Ph_3SiH, Et_3SiH, Ph_2SiH_2, Et_2SiH_2) were tested instead of AB were executed, and AB was found to be the best among others (**see supporting information, Table S1**). A number of bases were screened NaOMe, NaOH, KOH, KO*t*Bu, NaO*t*Bu, KOMe, NaOEt, TEA, and DiPEA **(see supporting information Table S2)**. Interestingly, NaOMe was found to be the optimal one among others **(entry 1)**. However, NaOMe with 0.5 equiv. gave only 68% of **1b (entry 5),** and without base, a drastic decrease in the yield of **1b** was observed **(entry 6)**. These results clearly showed the critical role of the base in the reaction. Other Ti catalysts ($Cp_2Ti(OTf)_2$, Cp*$TiCl_3$, and TiO_2) were all found to be less active than Cp_2TiCl_2 (**see supporting information, Table S3).** Next, a few solvents were examined and found that only dry THF afforded **1b** in excellent yield **(entry 1)**, while acetonitrile (ACN), dimethylformamide (DMF), toluene, tertiary butanol (*t*BuOH), 1,4-dioxane, and methyl tertiary butyl ether (MTBE) provided moderate to a good yield of **1b (entries 7-12)**. Lowering the temperature (100 to 60 °C) and shorter reaction times (18-12 h) gave the product **1b** in low to satisfactory yields **(entries 13-18)**. Only a trace of **1b** was observed without adding Cp_2TiCl_2 **(entry 19)**.

Table 1. Optimization of Arene Hydrogenation of 6-Fluoroquinoline[a]

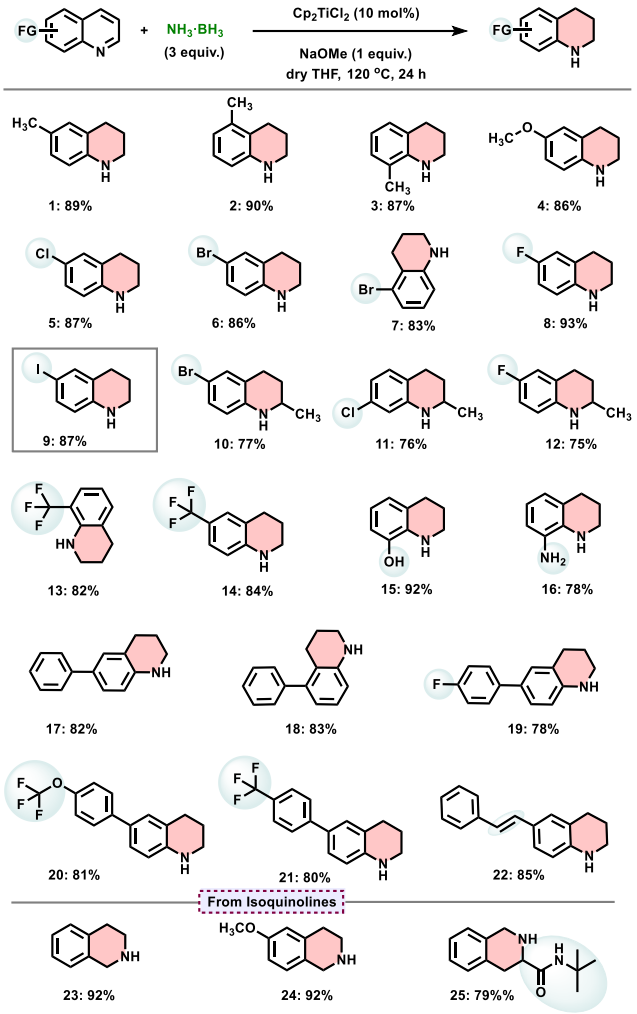


1a 1b

Entry	Deviation from the above	Yield 1b [%]
1	none	97(93[b])
2	NH_3·BH_3 (2 equiv.)	67
3	NH_3·BH_3 (1 equiv.)	29
4	without NH_3·BH_3	n.d.
5	0.5 equiv. NaOMe	68(59[b])
6	without NaOMe	26
7	ACN	17
8	DMF	24
9	Toluene	48
10	^{t}BuOH	56
11	1,4-dioxane	48
12	MTBE	43
13	100 °C	78
14	80 °C	51
15	60 °C	16
16	18 h	76
17	12 h	44
18	6h	13
19	without Cp_2TiCl_2	trace

[a]Reaction conditions: 0.5 mmol **1a**, 3 equiv. NH_3·BH_3, 10 mol% Cp_2TiCl_2, 1.0 equiv of base, 2 mL of solvent in 21 mL sealed tube and stirred at 120 °C for 24 h; Yields were determined by ^{19}F using trifluorotoluene as an internal standard. [b]Isolated yield.

Having identified optimized reaction conditions (10 mol% Cp_2TiCl_2, 1 equiv. NaOMe, 3 equiv. AB, 120 °C, 24 h), we thoroughly investigated the scope and compatibility of the reduction of various quinolines. As shown in **Scheme 1**, methyl substituents at the 6-, 5-, and 8- positions on the phenyl ring of quinoline, including methoxy substituent at the 6-position, were well-tolerated and gave the corresponding 1,2,3,4-tetrahydroquinolines products in very good yields **(entries 1-4)**. The high functional group tolerance of C-X bonds of quinolines is a valuable asset in numerous applications, from drugs to material science.[84] In this context, the reduction of quinolines-bearing sensitive halides despite their substituent position proved possible, as chloro **(5: 87%)**, bromo at 6- and 5-position **(6: 86%**; **7: 83%)**, fluoro at 6-position **(8: 93%)**, iodo at 6-position **(9: 87%)**, and a combination of bromo and methyl unit **(10: 77%)**, chloro and methyl unit **(11: 76%)**, as well as fluoro and methyl unit **(12: 75%)**, were all readily accommodated in this reaction. Remarkably, no reductive dehalogenation of the C-X bond or byproduct took place. It is also worth noting that the preservation of the iodo group in 6-Iodoquinoline **(9)** is extremely challenging, and is rarely reported in the literature with low yields.[39, 42] Quinolines with electron-withdrawing and electron-donating groups were also found to be suitable substrates for this transformation. Thus, CF_3-, free OH and NH_2-containing 1,2,3,4-tetrahydroquinolines **(13: 82%; 14: 84%; 15: 92%; 16: 75%)** were formed from their respective quinolines in high yields. Quinoline substrates featuring 6-phenyl, 5-phenyl, 4-fluoro-, 4-trifluoromethoxylphenyl, and 4-trifluoromethylphenyl in the 6-position were also undergone selective quinoline reduction **(17: 82%; 18: 83%; 17: 83%; 19: 78%; 20: 81%; 21: 80%)**. Notably, 6-styrylquinoline provided exceptional chemoselectivity, and exclusively the quinoline ring was reduced without harming the double bond (**22: 85%**). 1,2,3,4-tetrahydroisoquinolines are unique scaffolds in natural products and medicinal chemistry;[27] a few selected examples are demonstrated here with our optimized conditions and achieved the targeted products in excellent yields **(23-25: 79-92% yields)**. Unfortunately, 7-nitroquinoline and quinoline-6-pinacol were found to be unsuitable and gave undesired products under the standard reaction conditions **(See supporting information, Scheme S2)**.



Scheme 1. Substrate scope for the reduction of quinolines bearing functional groups on phenyl ring under optimized conditions.[a] [a]Reaction conditions: 0.5 mmol of quinoline, 3 equiv. $NH_3{\cdot}BH_3$, 10 mol % Cp_2TiCl_2, 1.0 equiv of NaOMe, 3 mL of dry THF in 21 mL sealed tube and stirred at 120 °C for 24 h, isolated yields.

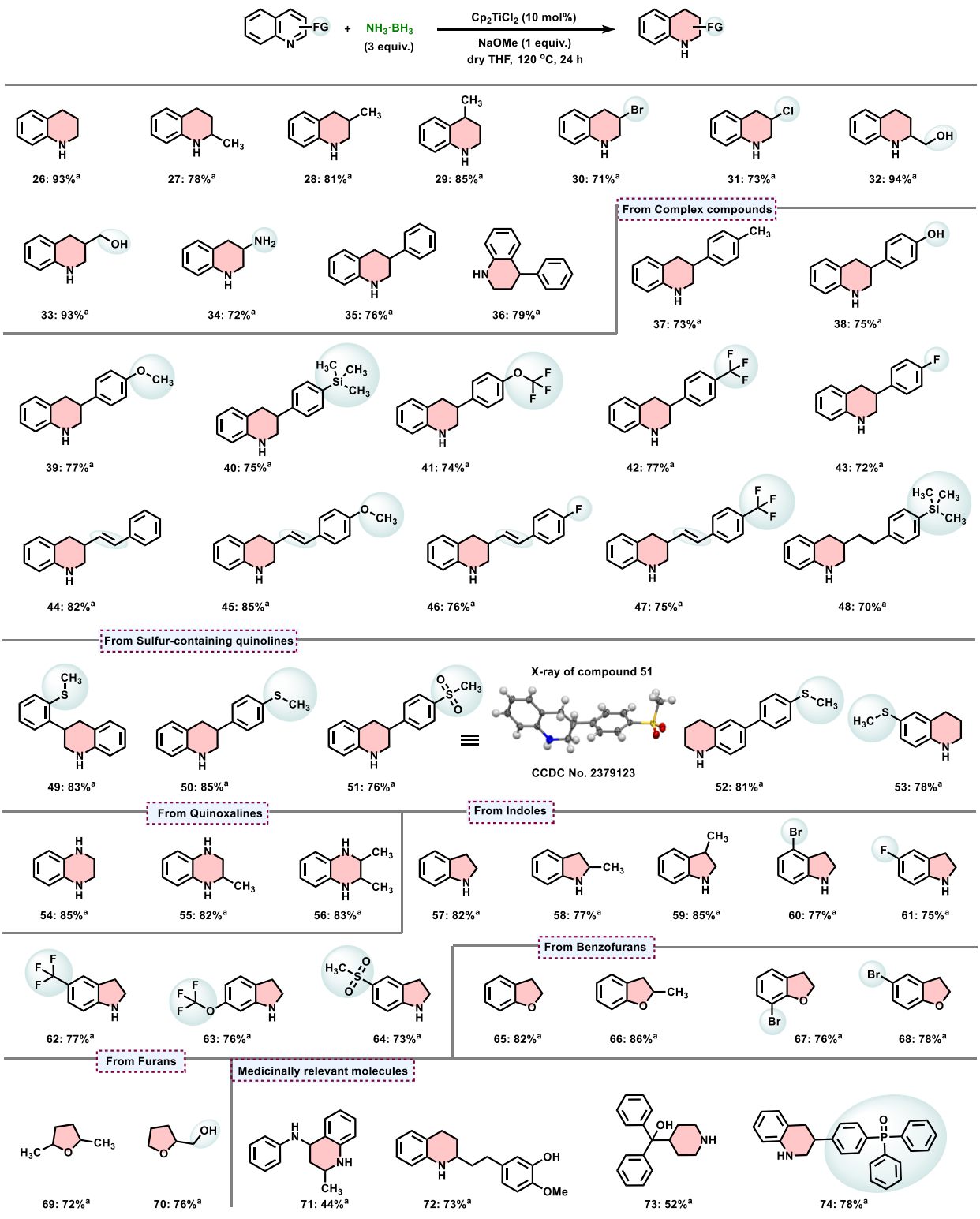
Next, we explored the structural diversity of quinolines-bearing substituents directly on the reducible ring **(Scheme 2)**. Simple and methyl substituents at the 2-,3-, and 4-position of quinoline gave products **26, 27, 28**, and **29** in good to high yields, respectively. Interestingly, bromo and chloro substitution on the 3-position of quinoline ring were tolerated under standard procedure, providing the corresponding products in high yields **(30 and 31)**, which can be used for further cross-coupling reactions involving oxidative addition of an aryl-X (X=Cl, Br). Sensitive functional groups such as bromo and chloro (**30 and 31**) were untouched under our optimized conditions, showing notable significance in organic synthesis, and such compounds have scarcely been documented. Alcohol derivatives such as 2-quinolinylmethanol and 3-quinolinylmethanol were amenable to this transformation and afforded the quinoline-reduced product **32 and 33** in good yields. It is noteworthy that no hydrodeoxygenation products were observed, underscoring the high selectivity. Even free NH_2-group on quinoline ring is tolerated and gave 1,2,3,4-tetrahydroquinolin-3-amine **(34)** in high yield without any observed byproduct. Encouragingly, quinolines featuring 3-phenyl, and 4-phenyl groups turned out to be effective substrates, being transformed into the targeted tetrahydroquinoline products in good to high yields **(35-36)**. Selective saturation of the *N*-heteroarene ring in complex molecules can quickly influence the structural and functional diversities.[12, 13, 59, 60] In this respect, several nitrogen-based complex molecules were demonstrated under standard conditions. For instance, 3-(*p*-tolyl)quinoline, 4-(quinolin-3-yl)phenol, and 3-(4-methoxyphenyl)quinoline were cleanly reduced into the corresponding *N*-saturated products in good yields with titanium catalysis **(37-39)** while retaining the aromaticity of other phenyl ring systems. Although organosilicon compounds constitute useful synthetic precursors in Hiyama couplings and Brook rearrangement reactions,[85, 86] the reduction of silyl-substituted substrates tends to be more challenging due to competing desilylation reactions. Our optimal conditions enable selective quinoline reduction of 3-(4-(trimethylsilyl)phenyl)quinoline smoothly and provide a yield of 75% **(40)**. In this substrate, no desilylation occurred. The incorporation of 4-trifluoromethylphenyl and 4-fluorophenyl substituents into the 3-position of quinoline has no influence on the reduction of *N*-heterocycle ring; 3-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoline and 3-(4-fluorophenyl)-1,2,3,4-tetrahydroquinoline congeners **(43 and 44)** were obtained in excellent yields, which are useful compounds in drug discovery. The chemoselective reduction of *N*-heterocycles in the presence of a carbon-carbon double bond constitutes an additional challenge in organic synthesis. Thus, we explored the selective reduction of quinolines comprising double bonds. A series of styryl-*N*-heteroarenes bearing methyl, methoxy, fluoro, and -CF_3 were subjected to this procedure, and exclusively the corresponding quinoline-reduced products **45-47** were obtained and isolated in high yields (75-82%) without further double bond reduction, which revealed that a variety of styryl-*N*-heteroarenes could operate as substrates for our chemoselective *N*-heteroarene reduction reaction. Despite varying the reaction conditions, when using 3-(4-(trimethylsilyl)phenethyl)quinoline, both double bond and quinoline ring were synchronously reduced and afforded the quinoline-reduced product **48** in good yield. We believe the reduction approach of complex molecules, as well as access to such types of functionalized tetrahydroquinoline-based products, will provide an excellent platform for generating structural analogs to meet the demand for optimizing drug activities.

Although there are several catalysts available for the hydrogenation of *N*-heterocycles,[12-18, 33-42] sulfur-containing quinolines are still a formidable challenge because sulfur atoms are capable of binding to metal complexes and may poison catalysts. Very recently, glorius and coworkers made a significant contribution in this area and reported a Ru-based heterogeneous catalyst for the hydrogenation of sulfur-containing quinolines with molecular hydrogen as a reductant.[53] However, still, a few molecules with sulfur substituents were not undertaken. In this respect, we subjected five challenging sulfur-containing quinolines with Ti catalyst under the standard reaction conditions that are scarcely reported in the literature. To our delight, the incorporation of 2-methylthiophenyl, 4-methylthiophenyl, and 4-methylsulfonylphenyl substituents on the 3-position of quinoline did not diminish the reaction yield and furnished the corresponding sulfur-containing 1,2,3,4-tetrahydroquinoline in high yields **(49-51)**. It is worth noting that compound **51** is used for the medical treatment of ferroptosis inhibitory. Similar results were obtained with 4-methylthiophenyl and thiomethyl substituents on the 6-position of quinoline to deliver the targeted products **52** and **53** in high yields, and the success of these examples highlights the Ti catalyst's remarkable sulfur resistance in organic synthesis.

Tetrahydroquinoxaline skeletons are present in the structures of various biologically relevant compounds.[23] Utilizing our catalytic protocol, three quinoxaline substrates were reduced with full conversion and yielded the desired products **54**, **55**, and **56** in very good yields. In addition, unprotected simple indole and its derivatives bearing methyl, bromo, fluoro, trifluoromethyl, trifluoromethoxy, and methylsulfonyl functional groups were selectively transformed to the corresponding indolines in excellent yields under standard reaction conditions **(57-64)**. This provides a substantial impact on reduction chemistry, as indolines are widely used in both organic synthesis and drug discovery.[22] The selective reduction of functionalized benzofurans to the corresponding dihydrobenzofuran derivatives is very attractive and remains a challenge.[87-89] Under the standard conditions, benzofuran derivatives, including 2,5-methylfuran and 2-furanmethanol, were also able to reduce very selectively and give access to the corresponding dihydrobenzofurans products in good to high yields **(65-70)**.

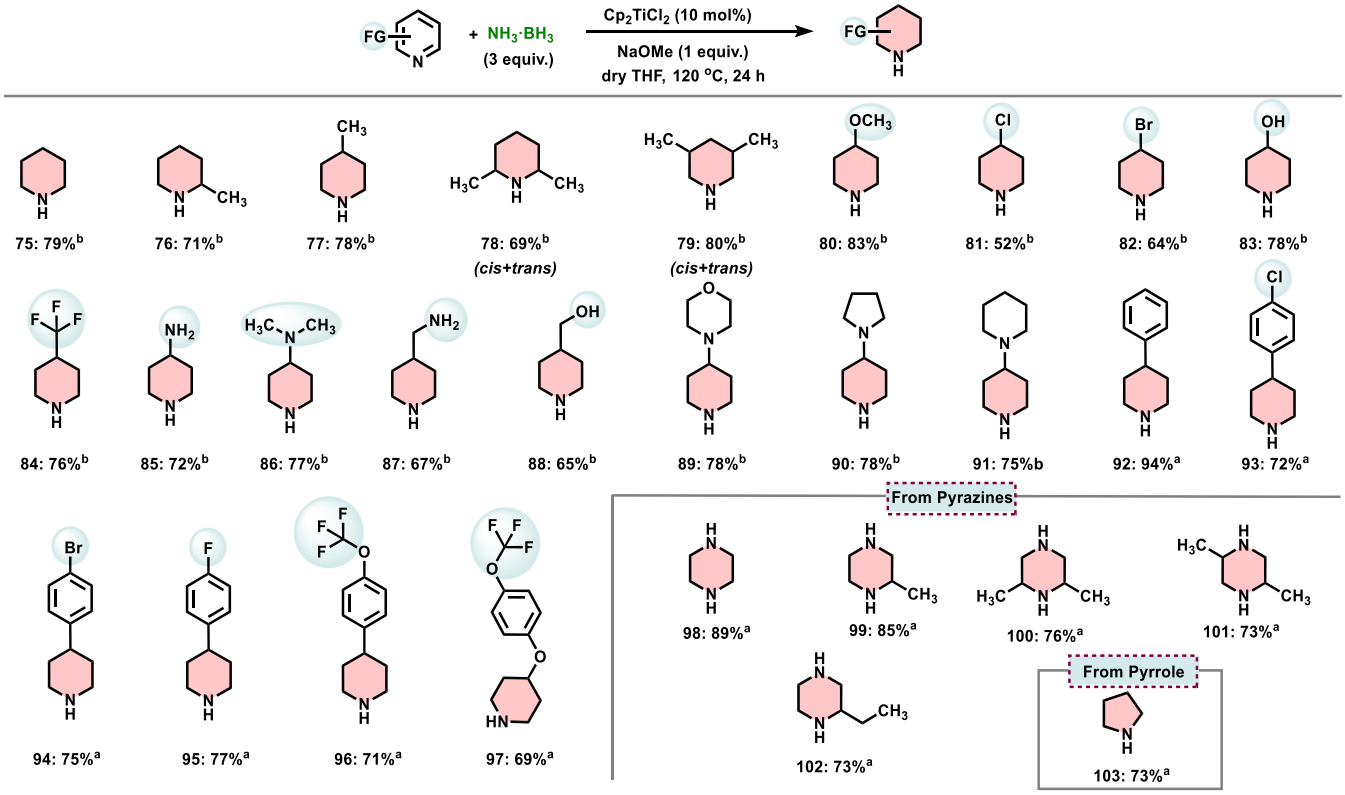
Late-stage saturation of medicinally relevant compounds without disturbing the core structure is a powerful method to quickly generate new analogues.[12, 13, 59, 60] In this regard, we applied our titanium catalyst for the quinoline reduction of some selected bioactive molecules (**Scheme**

2) Firstly, we have synthesized 2-methyl-N-phenyl-1,2,3,4-tetrahydroquinolin-4-amine **(71)** in 44% isolated yield from 2-methyl-N-phenylquinolin-4-amine as a starting material. Interestingly, compound 71 has significant applications in medicinal chemistry. Similarly, an intermediate of galipeine **(72)** was also proved successful, leading to their corresponding reduced derivative with good yield. Remarkably, we also prepared α-(4-piperidyl)benzhydrol in 53% isolated yield, which serves as a crucial building block for the manufacture of terfenadine **(73)**. N-heteroarenes, such as hybrid tetrahydroquinoline derivatives with phosphorated functionality, possess antileishmanial activity, and a multi-component approach is essential to prepare such compounds.[90] By keeping this aspect in mind, we attempted diphenyl(4-(quinolin-3-yl)phenyl)phosphine oxide for this transformation, and selectively quinoline ring was reduced in order to generate the corresponding product **(74)** in high yields while preserving the aromaticity of other phenyl ring systems. These results clearly indicated the wide generality of our Ti catalytic system to afford structurally diverse saturated *N*-heterocycles, thereby making important contributions to the field of medicinal chemistry and drug discovery



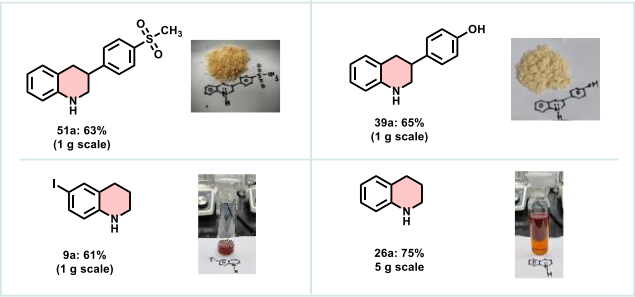
Scheme 2. Substrate scope for the reduction of functionalized quinolines under optimized conditions.[a] [a]Reaction conditions: 0.5 mmol of quinoline, 3 equiv. $NH_3{\cdot}BH_3$, 10 mol % Cp_2TiCl_2, 1.0 equiv of NaOMe, 3 mL of dry THF in 21 mL sealed tube and stirred at 120 °C for 24 h, isolated yields.

Based on these promising results, we extended our catalytic protocol for the reduction of unprotected functionalized pyridines **(Scheme 3)**. The resulting piperidines are key saturated heterocyclic scaffolds often encountered in the synthesis of top-selling drugs.[23-25] Simple and methyl-substituted pyridines, including 4-methoxypyridine, were well tolerated and efficiently reduced, thus providing the piperidines **75-80** in high yields. Halide-containing pyridines are extremely challenging molecules for this type of transformation due to competing hydrodehalogenation pathways. Applying our optimal reaction conditions, 4-chloro and 4-bromopyridine rings were selectively reduced and gave access to the corresponding piperidines **81 and 82** in moderate yields. The reaction was also amenable with pyridines bearing -OH, -CF_3, -NH_2, -NMe_2, -CH_2NH_2, and -CH_2OH at 4-position, thus giving the corresponding piperidines **83-88** in satisfactory to good yields upon isolation. Gratifyingly, 4-substituted pyridines with morpholine, pyrrolidine, and piperidine were capable of chemoselectively reducing the pyridine core, affording the desired products in high yields **(89-91)**, which implies great promise for this approach in applications in clinical studies. Interestingly, *para*-substituted pyridines comprising potential functional groups (-Ph, -PhCl, -PhBr, -PhF, -$PhCF_3$, - $OArOCF_3$) under standard conditions were selectively transformed to the respective functionalized tetrahydropyridines in excellent yields **(92-97)** that are hitherto difficult to access therefore opening up new possibilities for synthetic and medicinal applications, thus highlighting the sustainability of our current catalysis. Notably, compound **97** is a vital intermediate for the production of delamanid, which is an antibiotic medicine used to treat multidrug-resistant tuberculosis in adults. The aromatic reduction of pyrazine-to-piperazine is seldom reported in the literature despite the potential applications of piperazine motifs in medicinal chemistry.[6] To our delight, our Ti-catalyzed protocol could be further extended to simple and alkyl-substituted pyrazines, affording the corresponding piperazines in high yields **(98-102)**, which are hard to prepare by other methods. Pyrrole also proved to be compatible with this reaction, furnishing the corresponding pyrrolidine in a 73% isolated yield **(103)**. It is worth mentioning that the F(sp^3) carbon fraction has been improved along with the functional group persistence in all the products as shown in **Scheme 3**.



Scheme 3. Substrate scope for the reduction of functionalized pyridines under optimized conditions. [a]Reaction conditions: 0.5 mmol of quinoline, 3 equiv. $NH_3{\cdot}BH_3$, 10 mol % Cp_2TiCl_2, 1.0 equiv of NaOMe, 3 mL of dry THF in 21 mL sealed tube and stirred at 120 °C for 24 h, isolated yields. [b]Reaction conditions: 0.5 mmol of quinoline, 5 equiv. $NH_3{\cdot}BH_3$, 10 mol % Cp_2TiCl_2, 1.0 equiv of NaOMe, 3 mL of dry THF in 21 mL sealed tube and stirred at 120 °C for 24 h, isolated yields.

We also applied our titanium catalytic system for the large-scale synthesis of tetrahydroquinoline-based crucial building blocks in an operationally simple manner. We predominantly conducted a range of 1–5 gram scale reactions with some selected quinolines and furnished the products 51a, 39a, 9a, and 26a in good yields, thereby enhancing the practicality of our method **(Scheme 4)**.



Scheme 4. Gram-scale reaction: See supporting information for the reaction procedure.

Based on experimental observations **(See supporting information, Figure S8-S10)**, computational analyses, and insights from prior literature,[73] we proposed a plausible reaction pathway **(Figure 3)**. Initially, Cp_2TiCl_2 undergoes a reaction with sodium methoxide, resulting in the *in-situ* formation of a dimethoxy derivative of the titanocene catalyst. Subsequently, this dimethoxy derivative reacts with ammonia borane, generating an active titanium hydride species and releasing $B(OMe)_3$ **(Figure 3)**.[73] The presence of $B(OMe)_3$ in the reaction mixture was confirmed by ^{11}B NMR, exhibiting a peak at 20.19 ppm **(Figure S10)**, and further validated by gas chromatography, showing a retention time of 1.692 **(Figure S236)**. Additionally, the observed color change from orange to dark blue after stirring a mixture of Cp_2TiCl_2, NaOMe, and $NH_3{\cdot}BH_3$ in dry THF at 120 °C for 30 minutes suggests a possible shift in the oxidation state of the metal, indicating the formation of Ti(III) species **(Figure S8)**. Supporting this observation, an electron paramagnetic resonance (EPR) signal was detected at 298 K, showing a value of g = 1.974, which is consistent with the characteristic EPR signal for Ti(III) species **(Figure S9).**

To gain further insights into the reaction mechanism, computational studies were conducted,[91,92,93,94] which indicates that the reaction progresses through the coordination of 3-bromoquinoline **[I], (Figure 3 and 4)** with the coordinatively unsaturated $Cp_2Ti(III)$-H species (A), forms an intermediate **B**, which is ~1.74 kcal/mol more stabilized than **A**. In the next step, the metal hydride transfers from the Ti(III) center to the 2-position C atom of the quinoline ring via **TS1** to yield an intermediate **C**. The formation of species **C** from **B** is an endergonic process (1.47 kcal/mol). The Ti-H/C-H bond distances are 1.712Å/2.696Å (1.746Å/1.821Å) in **B**(**TS1**), indicating a simultaneous breaking of the Ti-H bond and the formation of the C-H bonds towards species **C**. Laplacian electron density [95] for the **TS1** shows the bond critical points between the Ti-H-C confirms hydride transfer pathway **(Figure S7(a))**. The computed IRC pathway further verifies the correctness of the **TS1**. **(Figure S5)** The **TS1** requires a free energy barrier of ~7.8 kcal/mol ($\Delta H_{393.15}$ = 6.75 kcal/mol). In the next step, $NH_3{\cdot}BH_3$ is introduced in the cycle, forming a reaction complex (**D**). The titanium-amido complex **D** is ~8.46 kcal/mol higher in energy than species **C**. Electrostatic potential maps and NPA charge analysis of $NH_3{\cdot}BH_3$ suggest that the BH_3 group is electron-rich while the NH_3 group is electron-deficient in nature **(Figure 4(a))**. The formation of a titanium-amido complex in species **D** can facilitate the activation of the $NH_3{\cdot}BH_3$ by generating hydride-proton species. The next step involves a concerted H^+/H^- mechanism where H^- from the electron-rich BH_3 unit is delivered to the positively charged Ti atom while the H^+ from the electron-deficient NH_3 unit is transferred to the quinoline nitrogen. The computed free energy barrier for **TS2** is ~10.7 kcal/mol and is the rate-determining step. Laplacian electron density of the **TS2** reveals the presence of BCP

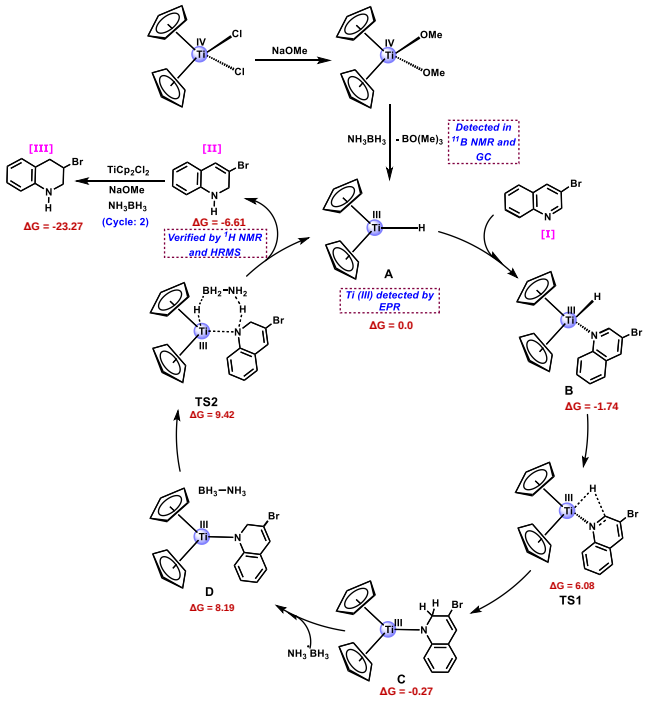


Figure 3: Proposed catalytic cycle for the hydrogenation of 3-bromo-quinoline with DFT optimized Gibbes free energy value in kcal/mol

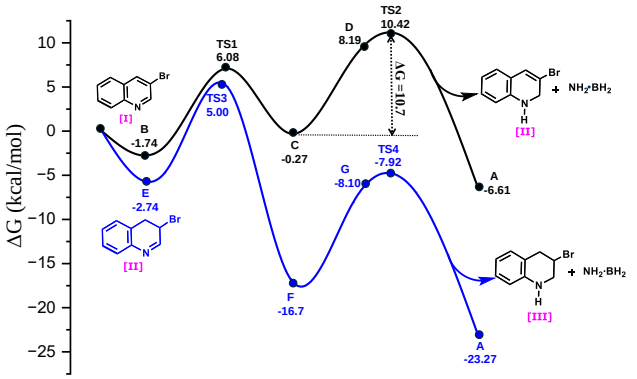


Figure 4: DFT computed free energy profile for the reduction of 3-Bromoquinoline at B3LYP/LANL2DZ (Ti and Br)/6-31G** level of theory.

between the N-H-C and B-H-Ti centers, further confirming the concerted H^+/H^- pathway. The **TS2** yields the formation of 3-bromo-1,2-dihydroquinoline **[II] (Figures 3 and 4)** (characterized by ^1H NMR and HRMS **(Figure S234, S235)),** $NH_2{\cdot}BH_2$, and regenerates the $Cp_2Ti(III)$-H catalyst for the subsequent complete reduction cycle to form 3-bromo-1,2,3,4-tetrahydroquinoline **(III)** (for the complete reduction cycle, **(see Scheme S1**).

■ CONCLUSION

In conclusion, we have developed the first versatile and useful approach for the selective reduction of structurally diverse nitrogen-based heteroarenes with ammonia borane as a reducing agent in the presence of a homogeneous Cp_2TiCl_2 catalyst. The reaction enables a broad functional group tolerance of quinolines under synthetically relevant conditions, which proved useful for complex and medicinally relevant compounds. Particularly, for the first time, we have shown the chemoselective reduction of quinolines-bearing substituents directly on the reducible ring (e.g., Br, Cl, Ph-CF_3, $PhOCF_3$, Ph-F, Ph-SO_2Me, and styryl

derivatives) and many of the isolated corresponding Csp^3-rich *N*-heterocycles are elusive in literature. Further, unprotected functionalized pyridines (e.g., Cl, Br, OH, CF_3, NH_2, CH_2-NH_2, CH_2-OH, Ph-Br, Ph-Cl, Ph-CF_3, $PhOCF_3$), indoles, pyrazines, and some selected benzofuran derivatives were also successfully demonstrated, and gram-scale synthesis was also effectively executed. The Ti-catalyst is also viable for the partial reduction of 3-bromoquinoline illustrating a very nice regioselectivity of this approach. DFT calculations support $Cp_2Ti(III)$-H formation as an active species and predict a concerted H^+/H^- mechanism for the hydrogenation of quinoline. We believe the isolated saturated nitrogenous-based products using ammonia borane and titanium as green catalysts will enhance drug discovery space. The extension of this work to arene systems is in progress and in-depth mechanistic investigations are underway.

ASSOCIATED CONTENT

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge: Experimental details, Characterization data, and Crystallographic data for compound number 51 and (^1H, ^{13}C, and ^{19}F). NMR spectra.

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The manuscript was written through the contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

Any additional relevant notes should be placed here.

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