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Broad Survey of Selectivity in the Heterogeneous Hydrogenation of Heterocycles

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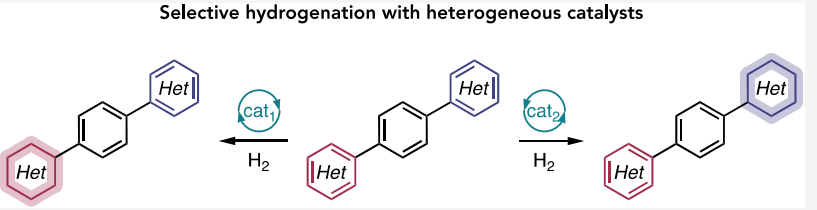

ABSTRACT: A broad survey of heterogeneous hydrogenation catalysts has been conducted for the reduction of heterocycles commonly found in pharmaceuticals. The comparative reactivity of these substrates is reported as a function of catalyst, temperature, and hydrogen pressure. This analysis provided several catalysts with complementary reactivity between substrates. We then explored a series of bisheterocyclic substrates that provided an intramolecular competition of heterocycle hydrogenation reactivity. In several cases, complete selectivity could be achieved for reduction of one heterocycle and isolated yields are reported. A general trend in reactivity is inferred in which quinoline is the most reactive, followed by pyrazine, then pyrrole and with pyridine being the least reactive.

INTRODUCTION

Among bioactive cyclic structures, N-heterocycles represent one of the most important motifs in drug design, with at least one ring present in most FDA-approved drugs.[1] The addition of saturated cores to drug molecules has several demonstrated advantages. Chief among them is that increased three-dimensionality of a drug candidate has been correlated with greater clinical success.[2] An increase in the fraction of sp^3 carbons (F_{sp^3}) has been shown to improve physical properties such as solubility[3−5] as well as reduce promiscuity toward off target interactions, which can lead to toxicity and clinical candidate failure.[6] Additionally, increased F_{sp^3} provides greater complexity (often via stereocenters) enabling access to diverse chemical space. Despite recent developments in sp^2-sp^3 coupling methods,[7−15] there are limited general strategies for incorporating saturated heterocycles into drug molecules. By contrast, there are many robust strategies for the construction of sp^2-sp^2 carbon−carbon bonds.[16−18] Given this, a desirable approach to constructing high F_{sp^3} target molecules for drug discovery would involve constructing biheteroaryl cores via known cross-coupling methods, then selectively reducing the desired heterocycle (Scheme 1).

The hydrogenation of simple *N*-heteroarenes can be achieved through a variety of homogeneous or heterogeneous catalysts.[19−21] However, in more complex drug-like molecules with multiple aromatic moieties, chemoselectivity can be elusive and difficult to predict, often requiring extensive screening of catalysts and conditions. To date, little has been reported about chemoselectivity in multiaromatic substrates despite the synthetic potential of such a strategy and the availability of hundreds of hydrogenation catalysts.[22−24] A better understanding of hydrogenation selectivity in substrates with multiple heteroarenes would provide a guide allowing for rapid access to saturated heterocycles with greater complexity. For example, the synthesis of triaryl intermediate **I** (accessed via standard sp^2-sp^2 coupling) would allow access to multiple reduced analogues via a hydrogenative diversification approach (Scheme 1), furnishing multiple compounds from a common core. Such a strategy could be a highly advantageous approach to rapidly synthesize saturated drug motifs.

Research in chemoselective hydrogenation has largely focused on the reduction of fused bicyclic heterocycles using homogeneous transition metal complexes. Substrates such as quinolines, isoquinolines, and acridines possess a smaller energetic penalty for dearomatization by comparison to their monocyclic counterparts, resulting in milder reduction conditions. Remarkable selectivity can be achieved in these systems with the use of homogeneous catalysts, and recent developments

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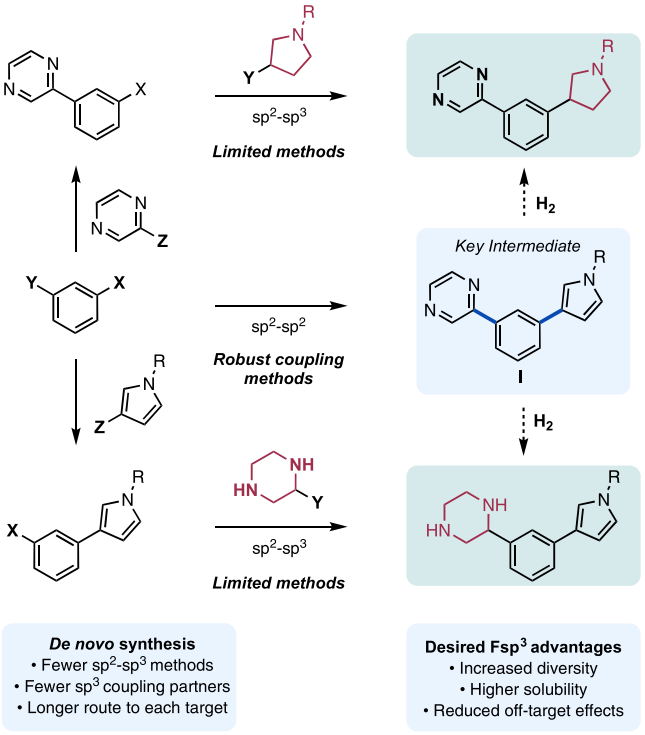
Scheme 1. Chemoselective Reduction for Complex Molecules



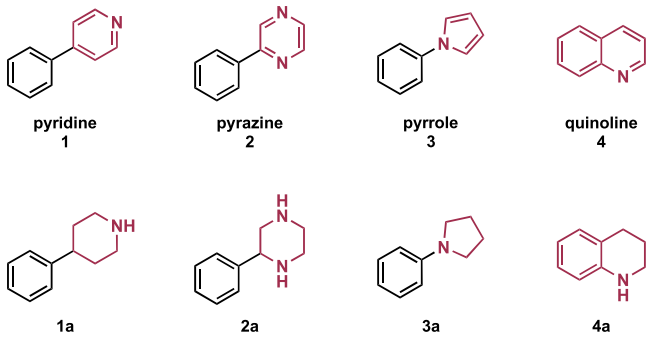
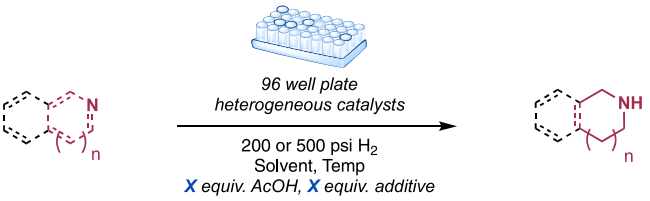


Figure 1. Model substrates and expected products.

different manufacturers, representing the diversity of carbon sources and microstructures.[44] Additionally, we explored temperature (30 or 60 °C), pressure (200 or 500 psi), and the effect of acetic acid as an additive (Scheme 2).

Scheme 2. Survey of Hydrogenation Conditions



in asymmetric hydrogenation[21,25] and catalyst controlled regioselectivity[26−31] are noteworthy. However, these approaches are limited to substrates for which reduction is more facile. Homogeneous catalysts are largely unsuitable for the hydrogenation of more challenging classes of arenes such as pyrroles,[31,32] pyridines,[33,34] and benzene derivatives,[31,35−39] which have higher aromatic stability.[40−43] To ensure these important motifs could be included in our efforts, we chose to focus our work on heterogeneous hydrogenation catalysts.

RESULTS AND DISCUSSION

To explore whether selectivity was possible in heterocyclic systems and establish any empirical trends, we undertook a systematic survey of the heterogeneous hydrogenation catalysts employing high-throughput experimentation techniques. Herein, we describe our initial broad catalyst screening approach with a series of simple substrates and subsequent efforts to reduce our initial catalyst list. The resulting set of catalysts was then applied to more elaborate biaryl compounds for a series of intramolecular competition experiments. The resulting data reveals important hydrogenation reactivity trends among the most common pharmacophores. At the outset, we hypothesized that a screening effort of heterogeneous catalysts might uncover complementary selectivity. We began our efforts by focusing on the most prevalent heterocycles in pharmaceuticals; pyridine (**1**), pyrazine (**2**), pyrrole (**3**), and quinoline (**4**) (Figure 1).[1] To enable analytical detection we chose substrates with a phenyl ring appended, ensuring a UV chromophore for LCMS measurement.

We conducted an initial screening campaign using 96 well plates in high-throughput format. The screen was composed of 93 different catalysts including Pd, Pt, Rh, Ru, Ir, and Ni compounds compiled from commercial sources. Within this catalyst library was a large selection of Pd/C catalysts from

Each reaction was evaluated using calibrated yields against an internal standard with authentic products. Washing the catalyst with excess acetonitrile ensured little product was bound to the leftover catalyst.[45] The data from our initial screen at 200 psi and 30 °C can be seen in Figure 2. Satisfyingly, numerous catalysts demonstrate complementary reactivity as a function of the heterocycle. For example, quinoline (**4**) is reduced by almost all the catalysts in the screen. In contrast, only a small number of catalysts can reduce pyridine (**1**) under these conditions. The data from all screens can be found compiled in the Supporting Information.

In Figure 3, the data are color coded according to the type of metal used. Pd and Pt are the most active in the screen, as reflected by the large number of red and purple data points. The mixed catalysts (orange) represent mixed metal hydrogenation catalysts (see SI for more info). In this subset, the Pd doped species led to higher conversion across the substrates screened.

To boost the conversion of phenylpyridine, the poorest performing substrate above, we evaluated several common variables across this catalyst set: pressure, temperature, and acetic acid. Acidic solvents—and acetic acid in particular—are common promotors for arene hydrogenation.[46−48]

Screening conditions with higher pressure (500 psi) and temperature (60 °C) had minimal effect on the yield of phenylpyridine hydrogenation. Acetic acid was the most effective, providing a dramatic boost at 200 psi (Figure 3). Using acetic acid as a solvent in this screen was also effective but provided little advantage over 10 equiv of acetic acid in methanol (see SI for more information).

With an initial survey of our model substrates and catalyst collection complete, we sought to simplify the screening procedure for future studies by reducing the number of catalysts. Our initial list was composed of 93 different catalysts. Achieving a similar diversity of reactivity with fewer catalysts would

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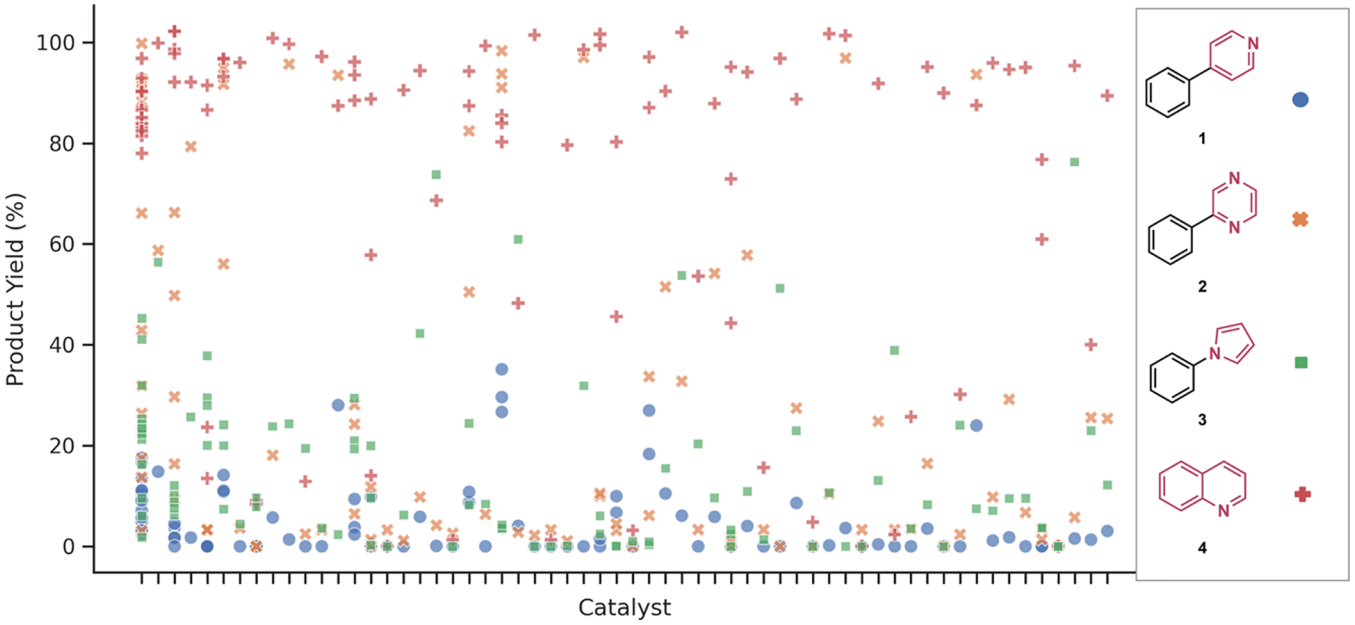

Figure 2. Hydrogenation Screen at 200 psi, 30 °C. [a]Reactions run with 0.1 mmol substrate, 2 (dry) or 4 (wet −50% H_2O) mg catalyst per 0.1 mmol substrate in 5 mL MeOH.

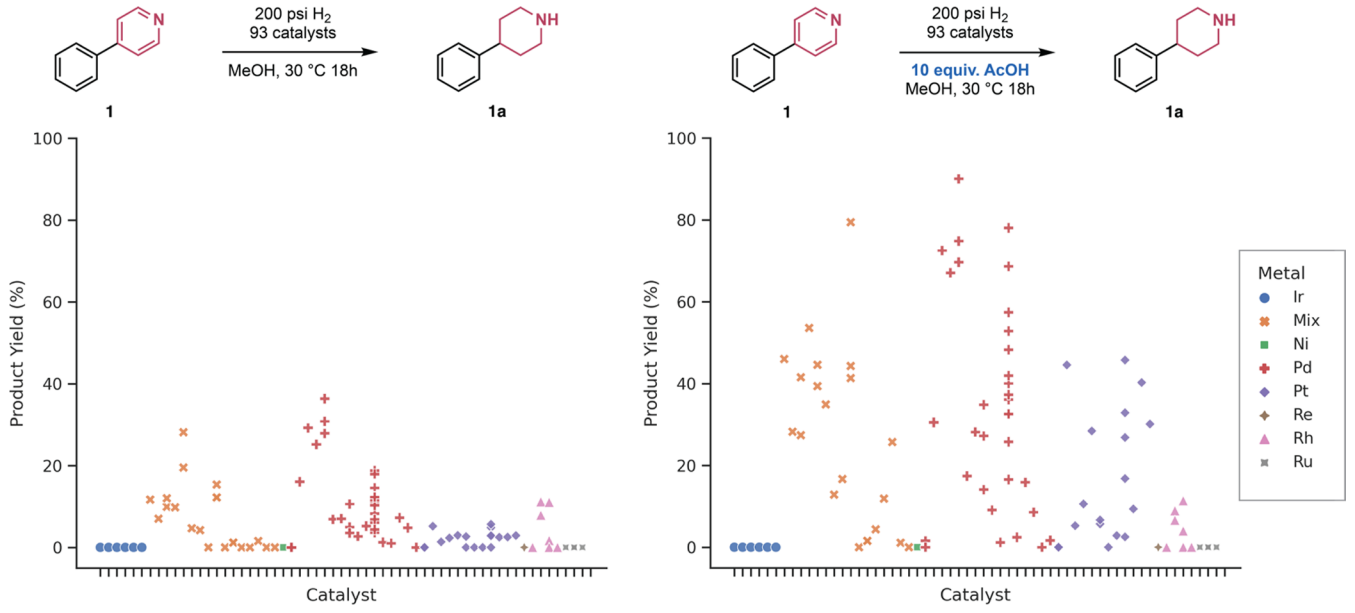

Figure 3. Hydrogenation of phenylpyridine **1** with and without AcOH at 200 psi, 30 °C.

dramatically increase the screening efficiency and reduce future substrate demands.

To begin this process of catalyst prioritization, we eliminated catalysts that were inactive across our substrates. Approximately 50% of ∼1200 initial reactions screened represent failed reactions (0−10% yield). We then prioritized catalysts that showed a range of reactivity across our substrates and gave a broad distribution of yields. Ultimately, we chose 23 catalysts to represent the diversity of reactivity observed in our initial screening experiments. Logistically, a 23 catalyst set enabled us to perform four screens in one 96 well plate (23 catalysts + control) and reduced the material burden as other variables were explored.

Intramolecular Competitions. With a smaller catalyst set in hand, we sought to apply these findings to more complicated substrates. To enable these efforts, we synthesized the bisheterocyclic substrates (**5**−**10**) shown in Figure 4. These substrates utilize the common heterocycles chosen above (Figure 1) tethered together with a benzene ring and provide a unique opportunity to probe intramolecular chemoselectivity. The benzene linker was chosen for its ease of synthesis and resistance to hydrogenation under these conditions, allowing a chromophore to be retained after the reaction.

Substrates (**5**−**10**) were screened using analogous conditions to those used above (Figure 1), however reduced solubility in methanol led us to use different solvents. Thus, we conducted hydrogenation screens in dioxane, trifluoroethanol, and dimethoxyethane at either 200 or 500 psi H_2, and either 30 or 60 °C over 18 h.

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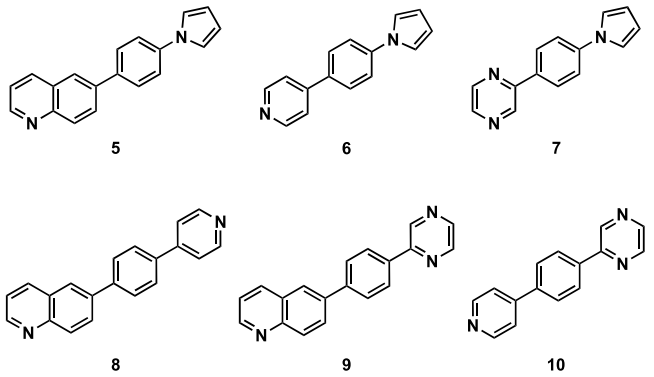

Figure 4. Bisheterocycles for hydrogenation screen.

A detailed example of one screen with **7** can be seen in Figure 5. Here, the ratio of pyrazine to pyrrole reduction (**7a**/**7b**) is plotted as a function of catalyst and conversion. The plot is shaped according to solvent; dioxane (cross), trifluoroethanol (circle), and dimethoxyethane (square) and each point represents a unique catalyst/solvent combination. Upon analysis, it was observed that selectivity was strongly influenced by both catalyst and solvent. Most catalysts showed a strong preference (>100:1) for pyrazine reduction in dioxane and dimethoxyethane. Interestingly, the selectivity appears to erode in trifluoroethanol, with a mixture of **7a**, **7b**, and **7c** observed. For example, one of the $Pd(OH)_2/C$ catalysts provides 78% conversion with a >100:1 selectivity of pyrazine reduction in dimethoxyethane, but a mixture of all three products is formed in trifluoroethanol, albeit with 100% conversion.

A second example is shown in Figure 6, using substrate **9**, which subjects pyrazine and quinoline to an intramolecular hydrogenation competition. Again, plotting data from all three solvents together illustrates the stark variation in reactivity. Both dioxane and dimethoxyethane promoted high levels of selectivity for quinoline reduction (**9b**). Dimethoxyethane in particular showed high levels of selectivity and conversion. Trifluoroethanol provided high levels of conversion across several catalysts screened. However, in trifluoroethanol, nearly all the catalysts led to reduced selectivity for quinoline reduction. In dimethoxyethane, a $Pd(OH)_2/C$ catalyst led to 100% conversion with ~100:1 selectivity for quinoline reduction. In contrast, changing solvents to TFE with the same catalyst led to an erosion of selectivity and a greater amount of bisreduction, **9c**.

A summary of these screens is shown in eqs 1−6 with the optimal catalyst and conditions listed for each substrate. While complete selectivity could not be achieved for all substrates, synthetically useful selectivity was observed for many. Quinoline could be selectively reduced in the presence of pyrrole (eq 1), pyridine (eq 2), and pyrazine (eq 3) with high chemoselectivity. A mixture of tetrahydroquinoline and decahydroquinoline was observed in most reactions. Complete reduction to the decahydroquinoline product could be achieved with longer reaction times. PtO_2 provided the best conversion and selectivity for each of these reactions, but several other catalysts performed

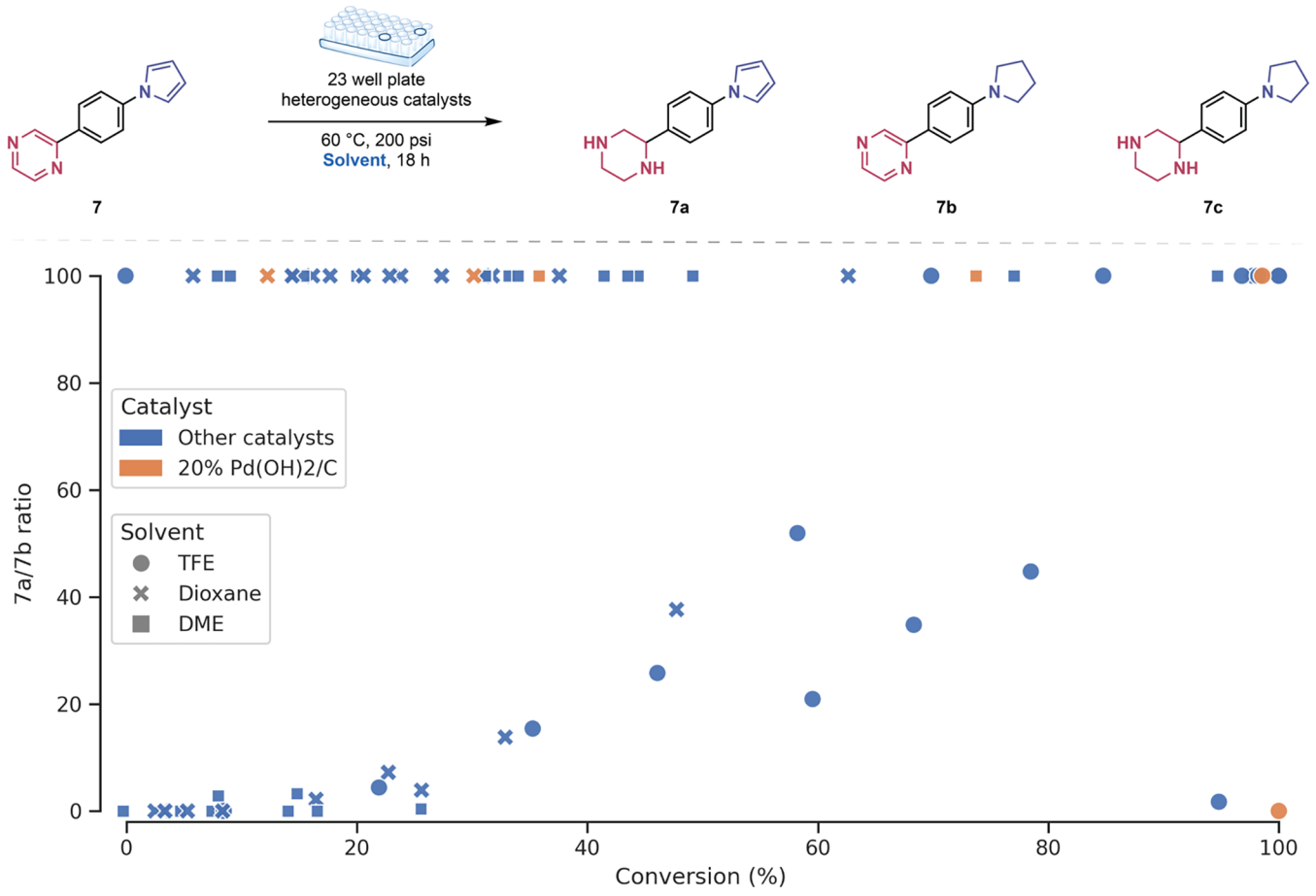

Figure 5. Hydrogenation screen of **7**.

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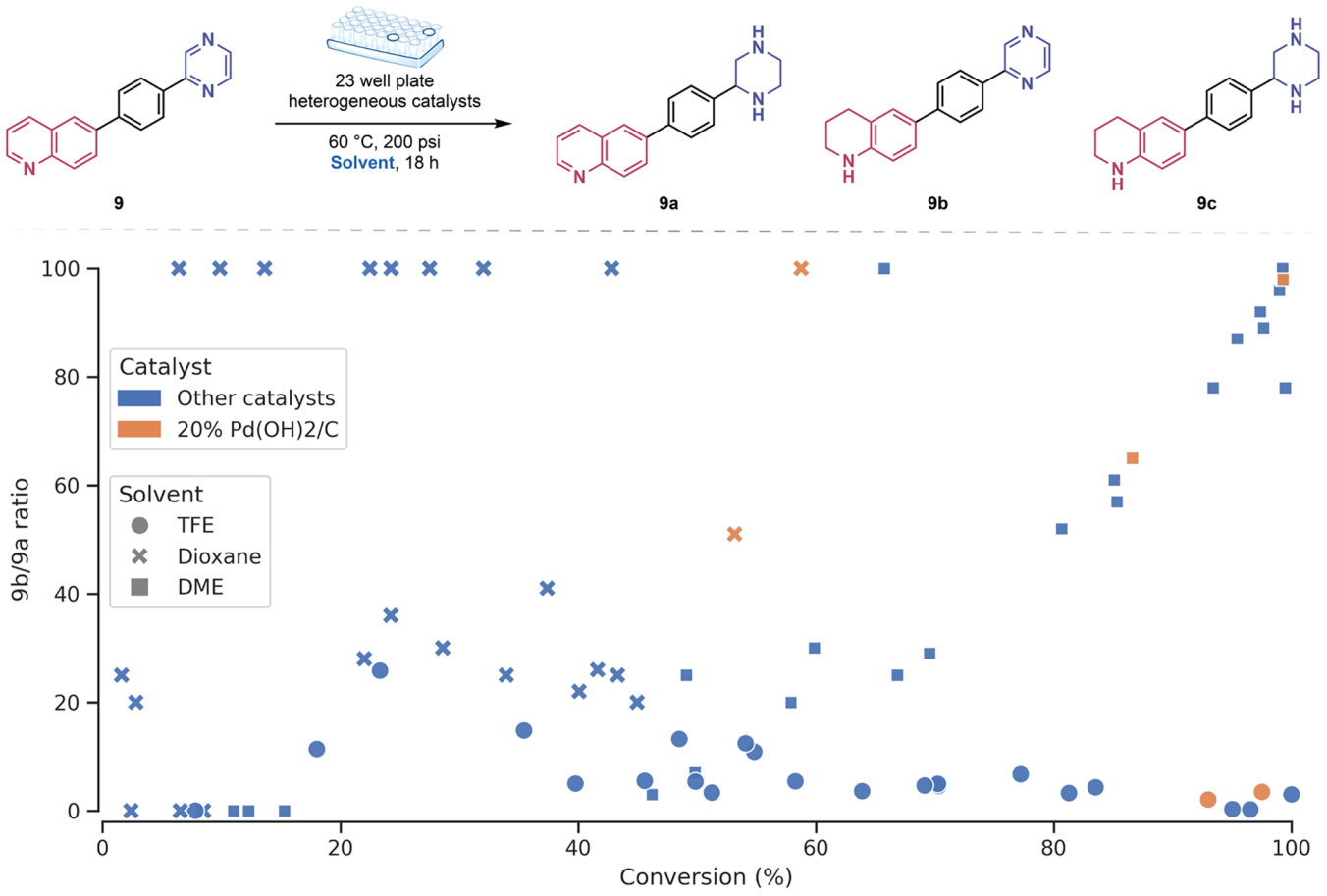
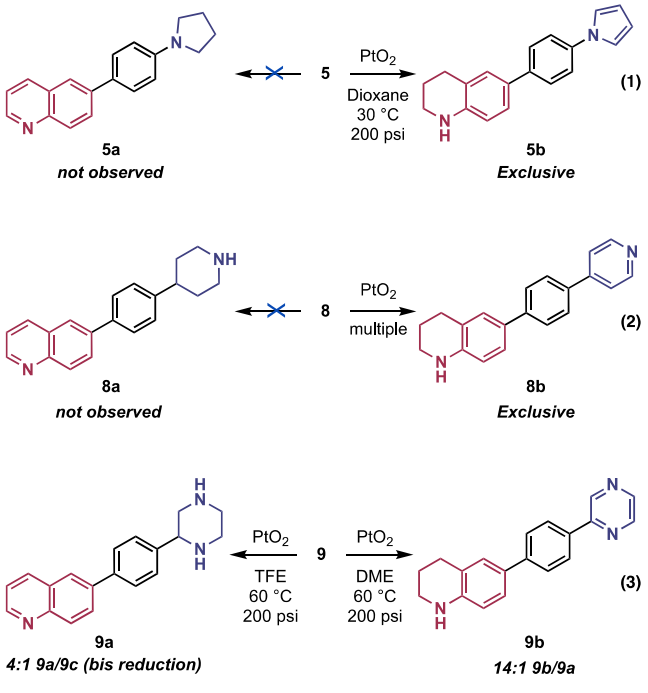
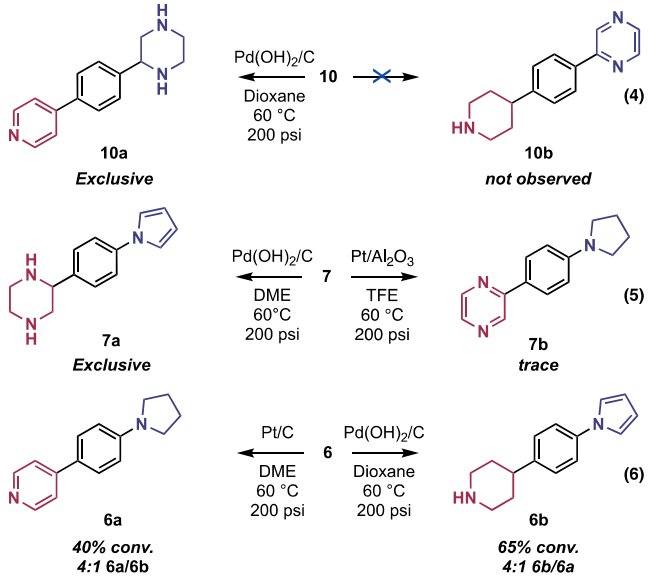


Figure 6. Hydrogenation screen of **9**.

similarly (SI). As shown previously with **9**, (Figure 6) using trifluoroethanol as a solvent led to high conversions, but reduced selectivity for quinoline reduction.





Multiple catalysts were sufficient to reduce pyrazine in the presence of pyridine (eq 4), but we highlight optimal conditions in dioxane. The selective reduction of pyridine in the presence of pyrazine was not observed. $Pd(OH)_2/C$ was also optimal for the reduction of pyrazine in the presence of pyrrole, however only small amounts of the desired pyrrole reduction could be observed using Pt/Al_2O_3 in TFE (eq 5). Achieving selectivity in the pyridine/pyrrole system was more challenging. Only slightly biased product ratios could be obtained as a result of catalyst and solvent choice (eq 6). Despite the lack of selectivity, such

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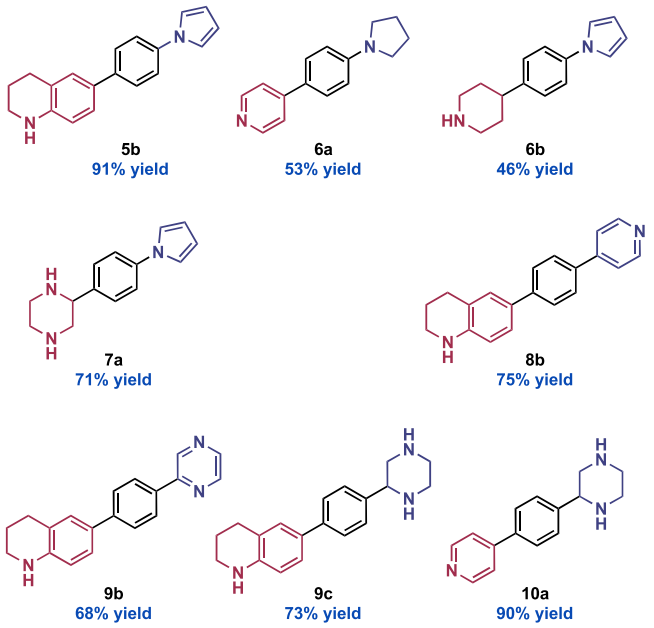
mixtures may be quite useful in a medicinal chemistry context, where both **6a** and **6b** can be isolated from one reaction.

Scale-up reaction yields based on the optimized conditions of eqs 1−6 can be found in Table 1. The Trifluoroacetic acid or

Table 1. Isolated Yields of Hydrogenation Reactions



hydrochloric acid salts of these compounds were isolated in good yields. In all substrates, quinoline reduction was observed in preference to pyrazine, pyrrole, or pyridine (Table 1, **9b**, **6b**, **8b**). A small amount of the tetrahydroquinoline (THQ) product was observed in each case but could easily be separated by chromatography. Consistent with the screens above, we observed good yields of pyrazine reduction in the presence of pyrrole (**7a**) as well as in the presence of pyridine (**10a**). Finally, despite initial screens suggesting pyrrole to be more reactive than pyridine (Figures 2 above), we obtained mixtures of these reduction products **6a**/**6b** using substrate **6.**

These results suggest a general trend for the hydrogenation of nitrogen heterocycles is as follows: quinoline, pyrazine, pyrrole, then pyridine as the least reactive (Figure 7). Our initial

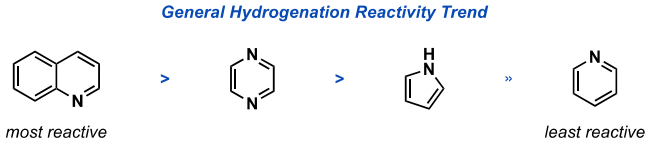


Figure 7. Observed hydrogenation reactivity.

experiments show that acetic acid is an effective promoter of substrates that are sluggish toward reduction. We note that pyridine and pyrrole appear to have similar reactivity in the intramolecular competition experiment. Surprisingly, both catalyst and solvent have a dramatic impact on chemoselectivity in the substrates screened. Density functional theory calculations were employed to determine if thermodynamics were responsible for the selectivity observed. However, after calculating and comparing the energies of the respective starting materials and products in eqs 1−6, no correlation with thermodynamic preference was found. The source of selectivity is most likely governed by the kinetics of each reaction as well as the specific binding interactions with the surface bound metal, which is beyond the scope of this work. Mechanistic investigations of these and related hydrogenations remains an important area of study, with future implications for selectivity.

In summary, we compiled and surveyed a large collection of heterogeneous catalysts in order to uncover general trends in reactivity among the most common heterocycles in pharmaceuticals. To our satisfaction, we observed several catalysts and conditions that could provide complementary reactivity between the simple heterocycles employed (Figures 1 and 2). Within this broad collection of catalysts, we explored the effect of temperature, pressure, and acetic acid as variables to increase the reactivity of a substrate. Additionally, we screened a series of bisheterocyclic substrates and provided a systematic competition for heterocycle reactivity toward hydrogenation. In several cases, complete selectivity could be achieved and the isolated yields of these reactions are summarized in Table 1. While the nature of this chemoselectivity is not fully understood, these results can serve as a guide for chemists looking to achieve chemoselectivity in related and more complex systems. Future work involves expanding these intramolecular experiments to other classes of heterocycles as well as exploring predictive modeling techniques to help assess chemoselectivity *a priori*.

■ ASSOCIATED CONTENT

Data Availability Statement

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 at https://pubs.acs.org/doi/10.1021/acs.joc.3c02028.

Synthetic procedures, spectral data, compound characterization (PDF)

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Author Contributions

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

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

UV, ultraviolet; LCMS, liquid chromatography mass spectroscopy

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