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# Enantioselective Transformation of Hydrazones via Remote NHC Catalysis: Activation Across C═N and N−N Bonds

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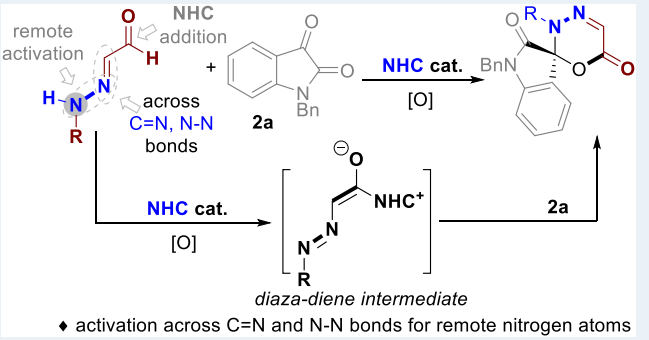
**ABSTRACT:** The catalytic asymmetric transformation of nitrogen atoms to prepare heterocyclic molecules is of significant value in organic synthesis and biological applications. Here, we disclose the activation of the nitrogen atom in hydrazine-derived hydrazone via an *N*-heterocyclic carbene (NHC) organic catalyst for highly enantioselective formal cycloaddition reactions. The range of NHC catalysis extends across several (carbon and hetero) atoms and diverse chemical bonds (C═N and N−N bonds) to activate nitrogen atoms at remote sites with excellent reactivity and (stereo)selectivity control. Our strategy for nitrogen atom activation, along with the NHC-bound diaza-diene intermediate generated during the catalytic process, offers alternative solutions for organic synthesis.




**KEYWORDS:** *enantioselective transformation, hydrazones, N-heterocyclic carbene, nitrogen atom activation, chiral heterocyclic molecule*



## INTRODUCTION

Nitrogen atoms are undeniably essential components in both natural and synthetic molecules.[1] Nitrogen−nitrogen bonds are found in a considerable number of molecules with important applications, particularly in the biomedical field and natural products (Figure 1A).[2] For example, FR-900137, a molecule containing an N−N bond derived from a strain of Streptomyces, demonstrates antibacterial activity against both Gram-positive and Gram-negative bacteria.[3] Additionally, Kutzneride 1, a cyclic hexadepsipeptide isolated from the soil actinomycete Kutzneria sp. 744, exhibits antifungal and antimicrobial properties.[4] Transforming the intrinsic N−N bonds in molecules through chemical modification offers a dependable and efficient approach for acquiring a variety of nitrogen-containing compounds.[5] In contemporary organic synthesis, the incorporation of N−N bond motifs into molecules is typically achieved by manipulating hydrazine as a nucleophilic reagent.[6] As an illustration, our group[7] and other groups[8] have implemented a carbene organocatalysis strategy to achieve the asymmetric transformation of hydrazine substrates as nucleophilic reagents, facilitating the construction of valuable chiral nitrogen heterocycles and N−N axis chiral compounds. Notably, the chiral induction in these reactions is attributed to the covalent attachment of the catalyst to the electrophilic partners. In the arena of N-heterocyclic carbene (NHC) catalysis, most of the current achievements are based on the activation of carbon atoms at varying distances from the carbonyl group.[9] Replacing carbon atoms in these substrates' carbon chains with heteroatoms would yield new reaction intermediates, thereby expanding the applicability of NHC organocatalysis methodologies and leading to unexplored heterocyclic structures. However, despite the value and allure of these efforts, they appear to present significant challenges, with successful transformations being quite limited. (Figure 1B).[10] These examples reported by us and others predominantly involve the catalytic generation of azadienolate intermediates, in which the heteroatom is activated across two or more conjugated carbon atoms, facilitating its reaction with electrophilic acceptors to produce heteroatom-enriched chiral cyclic compounds.

Building on our interest and earlier success in exploring NHC catalysis for the asymmetric transformation of heteroatoms, we demonstrate here that the versatility of NHC catalysis can span several (carbon and hetero) atoms and diverse chemical bonds to activate nitrogen atoms for enantioselective reactions (Figure 1C). In our new designs, a hydrazone derived from hydrazine and glyoxal, the smallest possible dialdehyde, can be activated via the addition of an NHC catalyst to the aldehyde moiety. Under oxidative

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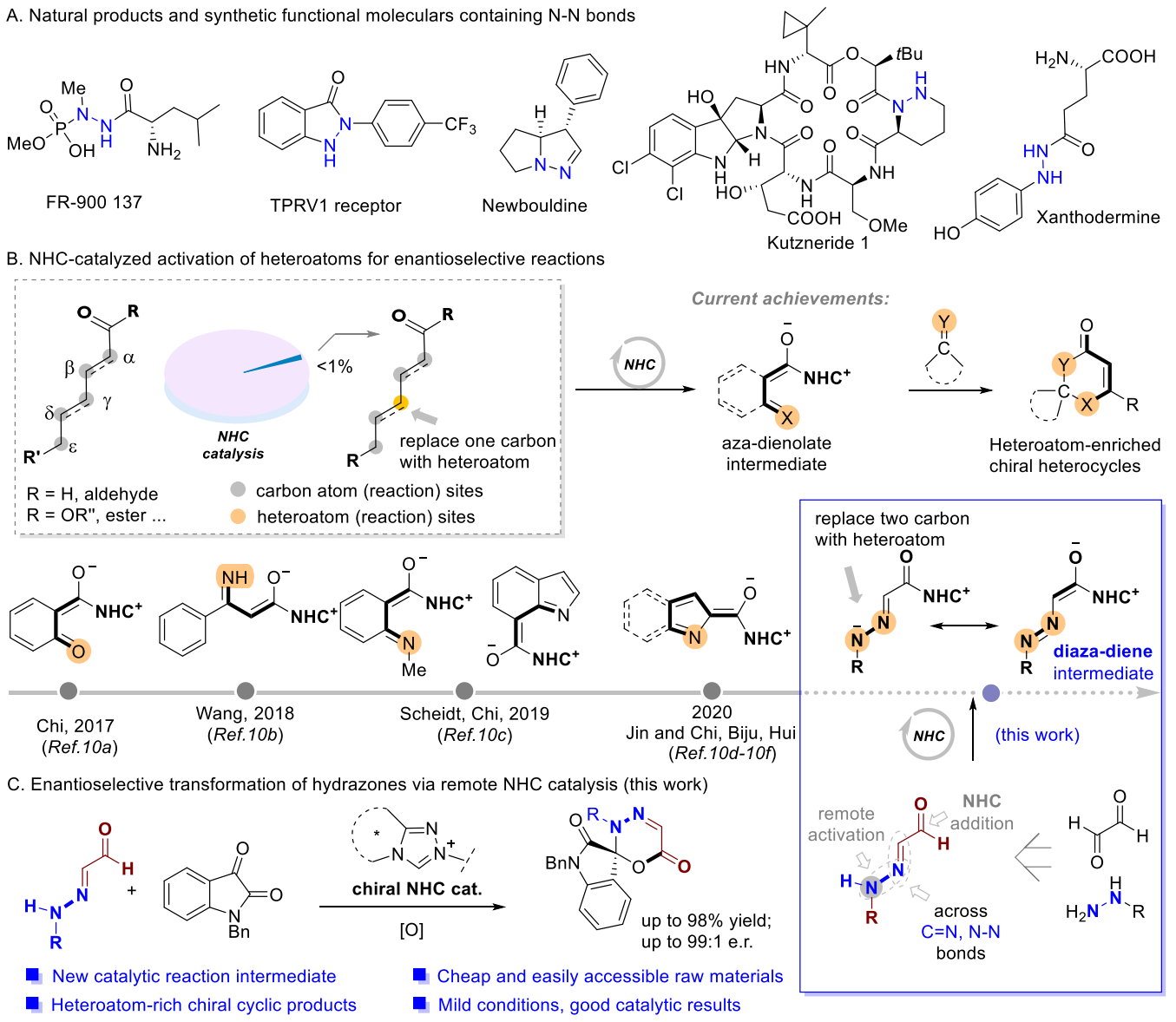


**Figure 1.** Reaction development.

conditions, the most remote nitrogen atom can be activated for enantioselective addition to a ketone substrate, forming the corresponding N and O-acetals with good to excellent stereoselectivity values. Our study demonstrates the first success in extending the potential of NHC catalysis across N=C and N−N bonds to remote atom activations and enantioselective reactions. This approach offers a new strategy for the enantioselective incorporation of N−N bonds in organic synthesis. The new NHC-bound catalytic intermediates, such as diaza-diene intermediate,[11] generated in this study may also find other applications in reaction designs and synthesis.

## RESULTS AND DISCUSSION

We initiated our study with phenyl-substituted hydrazone (**1a**) and isatin (**2a**) as model substrates. Regrettably, despite testing many reaction conditions, including the use of several triazolium-based NHC catalysts (**A**−**D**), the proposed spirooxindole[12] product was not observed (entry 1). It is widely known that replacing all-carbon aryl rings with heteroatom-containing aryls can lead to drastic reactivity changes. Such changes are observed in NHC-catalyzed reactions as well, with examples from our own laboratory.[13] We therefore prepared 2-pyridyl-substituted hydrazone (**1b**) as the model N−N bond-containing aldehyde substrate. To our delight, the use of **1b** to react with **2a** gave the proposed product **3a** with encouraging yields and er values when amino indanol-derived triazolium-based NHC precatalysts (**A**−**D**) were present (entries 2−5).

Specifically, when amino indanol-derived triazolium **A** with an N-mesityl substituent was used as the NHC precatalyst in the presence of $Et_3N$ as the base and DQ (3,3′,5,5′-tetra-*tert*-butyldiphenoquinone) as the oxidant, the reaction in DCM as the solvent gave **3a** in 30% yield with an excellent 96:4 er value (entry 2). Using precatalyst **B** with an *N*-phenyl substituent significantly improved the reaction yield to 92% with 97:3 er (entry 3). Catalysts **C** and **D** with different N-aryl substituents did not perform as well as catalyst **B** (entries 4 and 5). We then chose NHC precatalyst **B** for further optimizations. With DCM as the solvent, common organic and inorganic bases


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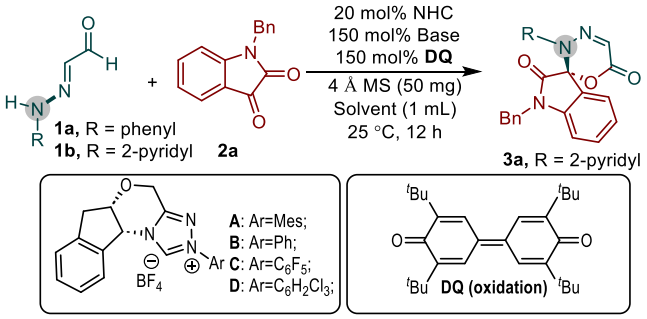
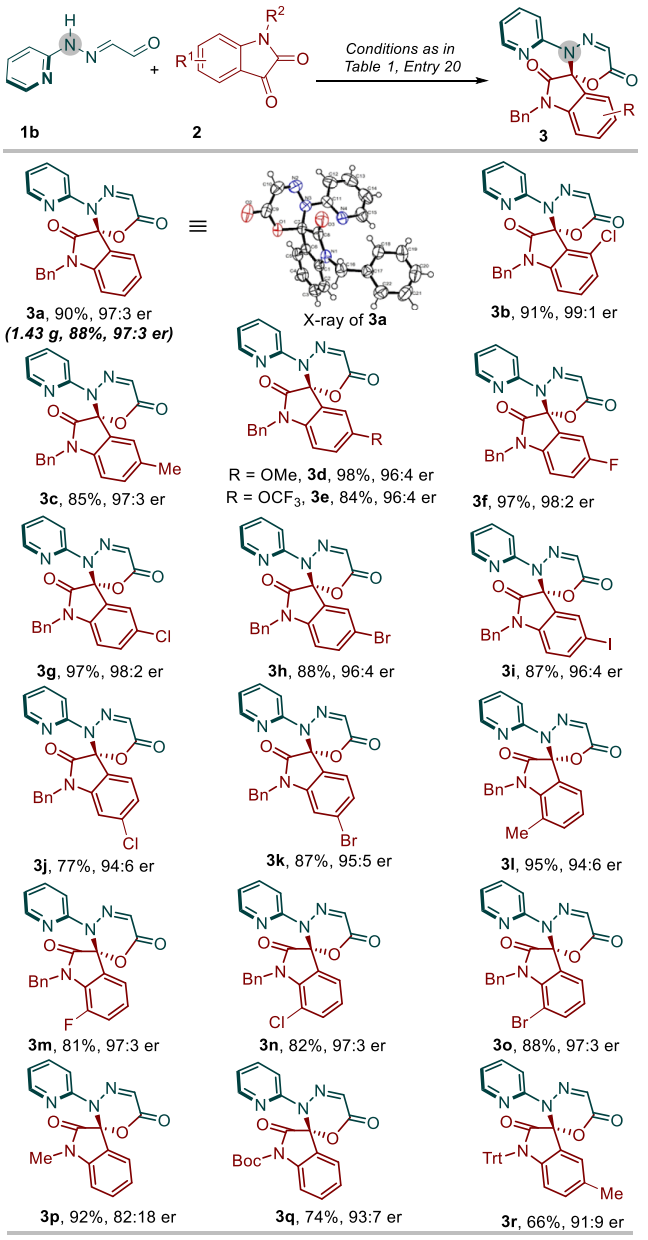
**Table 1. Optimization of the Reaction Conditions**[a]




| entry | NHC | base | solvent | yield (%)[c] | er[d] |
|---|---|---|---|---|---|
| | | **1a** as the Substrate, Entry 1 | | | |
| 1[b] | **A**–**D** | $Et_3N$ | DCM | | |
| | | **1b** as the Substrate, Entries 2–20 | | | |
| 2 | **A** | $Et_3N$ | DCM | 30 | 96:4 |
| 3 | **B** | $Et_3N$ | DCM | 92 | 97:3 |
| 4 | **C** | $Et_3N$ | DCM | 85 | 88:12 |
| 5 | **D** | $Et_3N$ | DCM | 52 | 88:12 |
| 6 | **B** | $Cs_2CO_3$ | DCM | 20 | 82:18 |
| 7 | **B** | DBU | DCM | 15 | 94:6 |
| 8 | **B** | NaOAc | DCM | 72 | 97:3 |
| 9 | **B** | $K_2CO_3$ | DCM | 84 | 96:4 |
| 10 | **B** | DIEA | DCM | 80 | 97:3 |
| 11 | **B** | DABCO | DCM | 82 | 96:4 |
| 12 | **B** | $Et_3N$ | DCE | 87 | 96:4 |
| 13 | **B** | $Et_3N$ | $CHCl_3$ | 84 | 97:3 |
| 14 | **B** | $Et_3N$ | THF | 80 | 97:3 |
| 15 | **B** | $Et_3N$ | ACN | 86 | 95:5 |
| 16 | **B** | $Et_3N$ | toluene | 72 | 97:3 |
| 17 | **B** | $Et_3N$ | EA | 84 | 97:3 |
| 18 | **B** | $Et_3N$ | acetone | 88 | 97:3 |
| 19 | **B** | $Et_3N$ | $Et_2O$ | 56 | 95:5 |
| **20**[e] | **B** | **$Et_3N$** | **DCM** | **90** | 97:3 |

[a]The reactions were carried out using **1a** (0.15 mmol), **2a** (0.10 mmol), NHC (0.02 mmol), base (0.15 mmol), DQ (0.15 mmol), 4 Å MS (50 mg), and solvent (1.0 mL) at 25 °C for 12 h. [b]**1b** (0.15 mmol) was used as the substrate. [c]Isolated yield of **3a**. [d]er value was determined via HPLC on the chiral phase. [e]The reactions were carried out using NHC-**B** (0.01 mmol), $Et_3N$ (0.10 mmol), and DQ (0.12 mmol).

**Scheme 1. Scope of Isatin 2**[a]




[a]Reaction conditions as stated in Table 1, entry 20. Yields are isolated yields after purification by column chromatography. er values were determined via HPLC on the chiral stationary phase.

could all mediate this transformation to give **3a** in various yields (15–84%) and excellent er values (82:18 to 97:3) (entries 6–11). Triethylamine ($Et_3N$) remained the best-performing base (entry 3 vs entries 6–12). We then evaluated the effects of solvents with the use of $Et_3N$ as the base (entries 13–19). All of the common organic solvents evaluated in our study worked effectively to give **3a** with mostly excellent yields and er values. Lastly, we found that the NHC catalyst loading could be reduced from 20 mol % (entry 3) to 10 mol % (entry 20), affording **3a** with similar yields and er values. As a technical note, further reduction of the NHC catalyst loading is possible for practical applications.

**Reaction Scope.** With acceptable conditions in hand (Table 1, entry 20), we then evaluated the scope of the cycloaddition reaction for isatin substrates by using pyridine hydrazone **1b** as a model substrate. Isatins (**2**) with both electron-donating groups (such as methyl and methoxy) and electron-withdrawing groups (such as halogens and $CF_3$) at the 4- or 5-position of the phenyl ring were well tolerated, giving the corresponding products in excellent yields and enantioselectivities (**3b**–**3i**). Introducing a chlorine or bromine atom at the 6-position of isatin produced the desired products with excellent optical purities (**3j** and **3k**). However, the yield of product **3j** was lower than that of product **3k**. When methyl and halogen groups were introduced at the 7-position of isatin, the corresponding N,O-acetal products were obtained with significant yields and enantioselectivities (**3l**–**3o**). Additionally, when the benzyl protecting group was replaced with a methyl group, the reaction proceeded to generate the product in high yield but with a slight decrease in the er value (**3p**). Replacing the Bn group with Boc or trityl groups resulted in decreases in yields while maintaining good optical purities (**3q** and **3r**).



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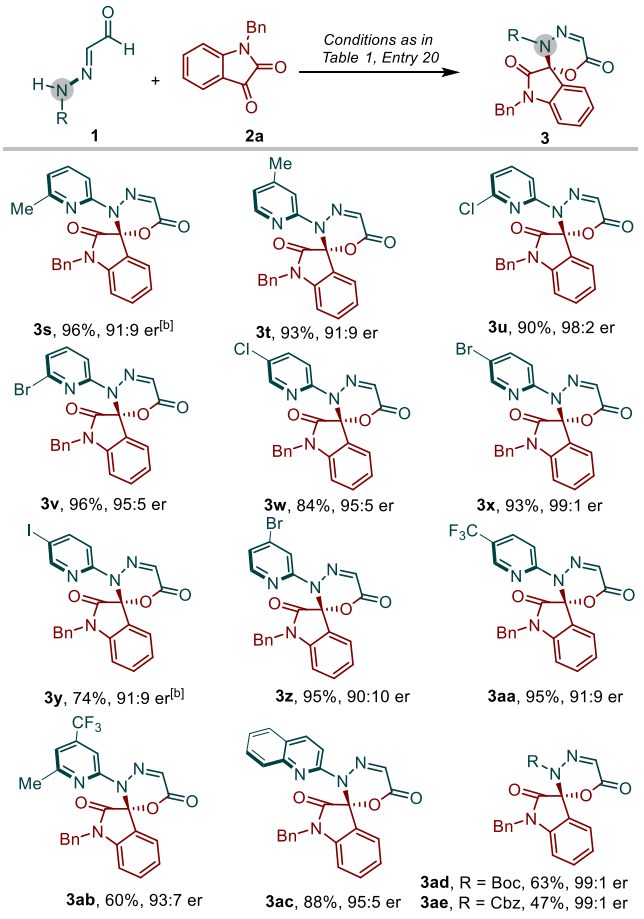
**Scheme 2. Scope of Hydrazone 1**[a]




[a]Reaction conditions as stated in Table 1, entry 20. Yields are isolated yields after purification by column chromatography. er values were determined via HPLC on the chiral stationary phase. [b]NaOAc (0.10 mmol) was used as the base.

Next, we explored the compatibility of hydrazone substrates containing various pyridine substituents with the optimal reaction conditions. Specifically, introducing a methyl group at the ortho-position of the pyridine ring yielded the desired product with an excellent yield and acceptable enantioselectivity (**3s**). As a contrast, changing the methyl group to the para position of the nitrogen atom had no effect on the results (**3t**). The introduction of halogen atoms (Cl, Br, and I) at the different positions of pyridine (*ortho*, *meta*, and *para*) does not affect the efficiency of the reaction, allowing the target enantioenriched N,O-acetals product to be obtained with good to excellent yields and enantioselectivities (**3u**−**3z**). It is foreseeable that the success of these examples can bring diverse synthetic transformations to these products. Placing trifluoromethyl groups at the meta-position of the pyridine also gives a good result with 95% yield and 91:9 er value (**3aa**). Hydrazone with 2-methyl-4-trifluoromethylpyridine delivered the desired product with acceptable chiral control but decreased yield (**3ab**). Additionally, quinoline was also found to be a suitable heterocycle to facilitate the smooth reaction (**3ac**). Significantly, the hydrazone synthesized from Boc and Cbz protected hydrazine and glyoxal was compatible well with our reaction, resulting in the formation of **3ad** and **3ae** with moderate yields but excellent er value. We evaluated the antimicrobial activities of the obtained (chiral) heterocyclic

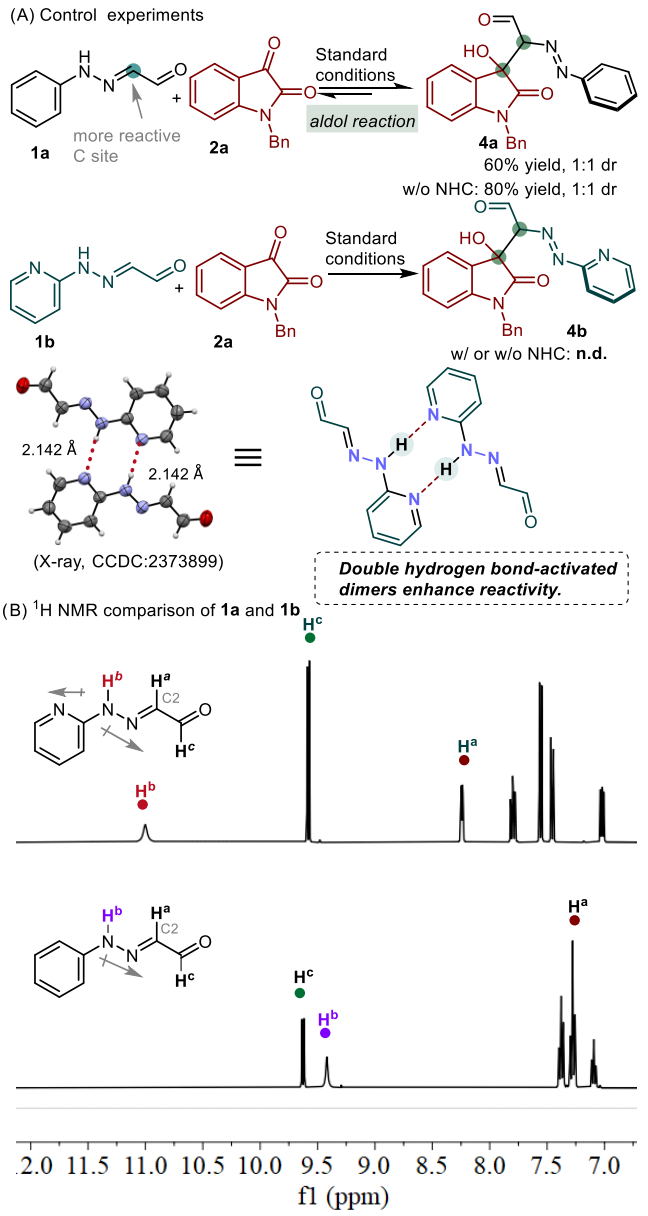



**Figure 2.** Control experiments.

compounds against *Xanthomonas oryzae pv oryzicola* (Xoc), which infects rice plants; these results can be found in the Supporting Information.

**Mechanistic Study.** The pyridine moiety in the hydrazone substrates plays an essential role in displaying the observed reactivities (Table 1 and Schemes 1 and 2). We therefore conducted several studies to elucidate the possible origins of the effects of the pyridine unit (Figure 2A). Our attempts to employ *N*-phenyl-substituted hydrazone **1a** to react with **2a** under NHC catalysis to give the desired product were unsuccessful (Table 1, entry 1). Instead, an aldol reaction adduct (**4a**) was observed in around 60% yield, as estimated via $^1$H NMR analysis of the crude reaction mixture (Figure 2A). A comparison reaction without the addition of the NHC catalyst gave similar results, with the formation of **4a** in around 80% yield, indicating that the formation of **4a** proceeds via a base-promoted aldol reaction pathway. Interestingly, when pyridine-containing hydrazone **1b** was used as the substrate under otherwise similar conditions, the corresponding aldol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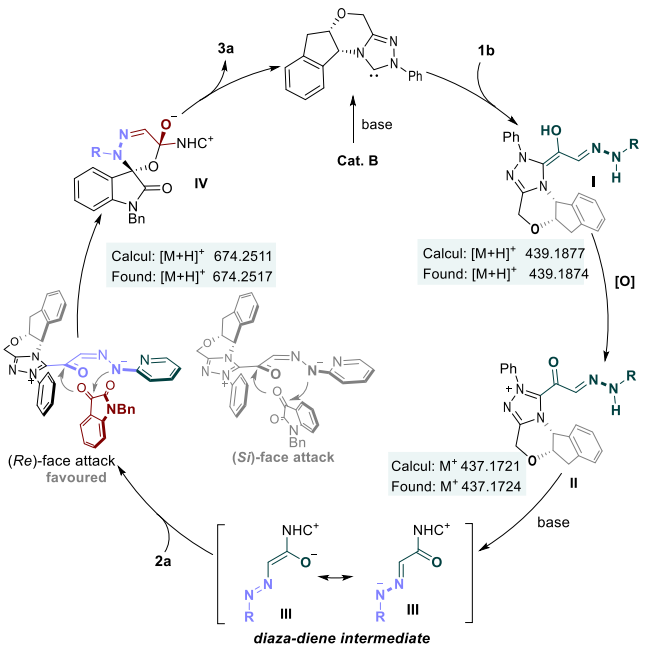


**Figure 3.** Postulated reaction pathway.

adduct (**4b**) was not observed (Figure 2A). These results indicate that hydrazone **1a** possesses a more reactive nucleophilic $\alpha$-carbon (for the aldol reaction), whereas the reactivity at the $\alpha$-carbon in **1b** is significantly reduced. A comparison of the $^1$H NMR spectra of **1a** and **1b** revealed that **1b** possesses more acidic protons due to the electron-withdrawing ability of the pyridine unit. The pyridine unit (of **1b**) lowers the nucleophilicity of the hydrazone $\alpha$-carbon (and thus avoids the aldol reaction) and facilitates the remote N−H deprotonation process (which favors the observed NHC-mediated formal cycloaddition reaction). The solid-state X-ray structure of **1b** suggests that hydrogen-bonding interactions of **1b** may also contribute to its observed reactivities under NHC catalysis, as such hydrogen bonding can lead to the activation of the hydrazone nitrogen atoms toward deprotonation (Figure 2B). A postulated catalytic reaction pathway is illustrated in Figure 3. Multiple key catalytic reaction intermediates were observed via HRMS analysis (see the Supporting Information for details). The reaction steps include the formation of a Breslow intermediate **I** between the NHC catalyst and **1b**. Oxidation of **I** gives azolium ester intermediate **II** that, upon deprotonation on the remote nitrogen atom, gives azolium diaza-diene intermediate **III**. Addition of the nitrogen atom at the $\gamma$-site of **III** to the ketone moiety of isatin (**2a**) eventually affords product **3a** with the regeneration of the NHC catalyst (Figure 3).

## CONCLUSIONS

In summary, we have developed a new strategy using NHC organic catalysis for the activation and asymmetric transformation of nitrogen atoms. The addition of the NHC catalyst to the aldehyde moiety of a hydrazone derived from hydrazine and glyoxal ultimately leads to the activation of the remote nitrogen atom for an enantioselective reaction with isatins. Unlike previous reports that focus on carbon-based skeletons, our present study shows that the enabling potential of NHC catalysts can extend across several (carbon and hetero) atoms and diverse chemical bonds (C═N and N−N bonds). Mechanistic studies suggest that substituents at the nitrogen atom and possibly noncovalent interactions can influence the formation and reactivity of the key NHC-bound diaza-diene intermediate generated during the catalytic process. Further exploration of our strategy and this class of intermediates will likely offer valuable solutions in the asymmetric transformation of nitrogen and other heteroatoms.

## METHODS

**General Procedure for the Enantioselective Synthesis of 3.** To a 4.0 mL vial equipped with a magnetic stir bar were added chiral NHC-**B** (0.01 mmol), 4 Å MS (50 mg), DQ (0.15 mmol), and substrates **1** (0.15 mmol) and **2** (0.10 mmol). Then, dried DCM (1.0 mL) and $Et_3N$ (0.15 mmol) were added via a syringe. Then, the reaction mixture was stirred for 12 h at 25 °C and then subjected to column chromatography on silica gel (10:1 to 5:1 petroleum ether/EtOAc) directly to give the desired pure products **3** in 47−98% isolated yields.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.4c06029.

Experimental procedures and spectral data for all new compounds (PDF)

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[§]J.J. and Y.L. contributed equally to this work.

### Notes

The authors declare no competing financial interest.

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