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# Deaminative Olefination of Methyl *N*-Heteroarenes by an Amine Oxidase Inspired Catalyst

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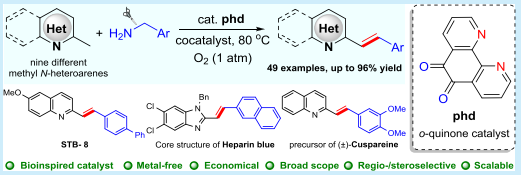
**ABSTRACT:** We explored the bioinspired *o*-quinone cofactor catalyzed aerobic primary amine dehydrogenation for a cascade olefination reaction with nine different methyl *N*-heteroarenes, including pyrimidines, pyrazines, pyridines, quinolines, quinoxolines, benzimidazoles, benzoxazoles, benzthiazoles, and triazines. An *o*-quinone catalyst phd (1,10-phenanthroline-5,6-dione) combined with a Brønsted acid catalyzed the reaction. *N*-Heteroaryl stilbenoids were synthesized in high yields and (*E*)-selectivities under mild conditions using oxygen (1 atm) as the sole oxidant without needing transition-metal salt, ligand, stoichiometric base, or oxidant.




In biological systems, the multielectron catalysis is often maneuvered by the organic cofactor present in the active site of the enzyme.[1] For example, the quinone cofactor exists in copper amine oxidases (CAOs), and several quinoenzymes performs the two-electron *in vivo* metabolism by virtue of the *dione* and *enediol* redox couple (Scheme 1a).[1] The initial studies with *o*-quinones involved the understanding of the mechanism of these enzymes.[2] However, recently, CAO-inspired quinone-based catalytic systems were developed for the aerobic dehydrogenations of primary as well as secondary and tertiary amines.[3] For example, Largeron et al. have reported a class of *o*-iminoquinone catalysts for the dehydrogenation of primary amines.[4] Kobayashi utilized a Pt/Ir nanocluster and 4-*tert*-butyl catechol catalyst system for the oxidation of secondary amines in moderate to good yields.[5] Stahl et al. have reported the oxidations of primary, secondary, and tertiary amines with the aid of 1,10-phenanthroline-5,6-dione (phd) complexed with transition metals such as zinc and ruthenium as the catalyst.[6] Oh and co-workers have developed the *o*-naphthoquinone catalysts for the $\alpha$-branched primary amine oxidations.[7] Similarly, Luo et al. have developed *o*-quinone catalysts for the aerobic oxidations of $\alpha$-branched primary benzylic amines and cyclic secondary and tertiary amines.[8] Murugavel and co-workers have described primary amine oxidation at room temperature using a CAO mimicking catalyst.[9] Kumar et al. have utilized polydopamine to synthesize *N*-heterocycles via aerobic amine oxidation cascade.[10] Recently, we have demonstrated that the CAO inspired *o*-quinone catalyst phd complexed with copper(I) ion can perform one-pot cascade aerobic dehydrogenation of primary and *in situ* formed secondary amines, enabling the synthesis of quinazolin-4(3*H*)-one core.[11] However, an expansion of CAO mimicking catalysis for a cascade C−C bond formation reaction to synthesize value-added products is highly desirable. In this regard, we recently have envisioned that the initially formed oxidized product during the *o*-quinone catalyzed amine dehydrogenation reaction could be condensed with the methyl-substituted *N*-heteroarenes under milder conditions leading to the formation of (*E*)-2-alkenyl heteroarenes.[12] Herein, we pursue this aim and report the first metal-free CAO-inspired *o*-quinone catalyzed olefination of methyl-substituted *N*-heteroarenes by primary amines utilizing ambient air as the sole oxidant (Scheme 1b).

2-Alkenyl heteroarenes are versatile building blocks for constructing diverse molecular scaffolds, including natural products and bioactive molecules,[13] *in vivo* imaging agents,[14] sensors,[15] and light-emitting diodes.[16] In fact, several FDA-approved therapeutics contain *N*-heteroaryl stilbenoids as the core structure (Scheme 1c).[17] They also served as a valuable precursor in polymer[18] and organic synthesis.[19]

Classically, carbonyl olefination reactions[12b] and recently, transition-metal-catalyzed Heck[20] and olefin metathesis[21] reactions were used as the powerful strategy to synthesize alkenes. *N*-Heteroaryl stilbenoids could also be accessed via the condensation *N*-heteroarenes with imines or amines in the presence of strong acids and/or stoichiometric amount oxidants at high temperatures.[22] Recently, Newhouse et al. reported the synthesis of (*N*)-alkenyl heteroarenes via nickel catalyzed benzylic dehydrogenation in the presence of a stoichiometric base, additive, and thiophene oxidant.[23] However, multistep functional group interconversions, precious metals as catalysts, stoichiometric oxidants, base, additive, high temperature, poor selectivity, and copious

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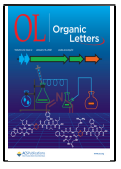







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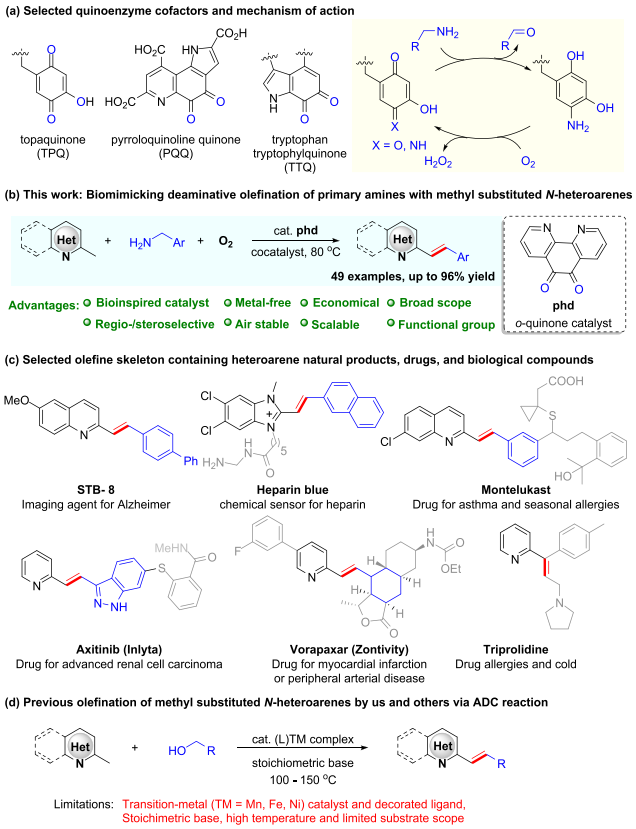
**Scheme 1. (a) Quinoenzymes and Their Mechanism of Action. (b) This Work. (c) Selected (*E*)-2-Alkenyl Heteroarene Containing Bioactive Molecules and FDA-Approved Drugs. (d) Previous Olefination of Methyl *N*-Heteroarenes via Acceptorless-Dehydrogenative-Coupling Reaction**



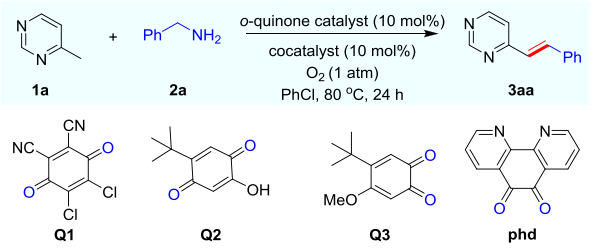

waste production are considered the drawbacks of these methods.[12b,20−23]

Not long ago, we and others have demonstrated that the acceptorless-dehydrogenative-coupling (ADC) of methyl-substituted heteroarenes with alcohols provide an alternative method for synthesizing *N*-heteroaryl stilbenoids (Scheme 1d).[24] However, we have realized severe limitations of those protocols in terms of using a transition metal complex of the decorated ligand as a catalyst, high reaction temperature (mostly 130−140 °C), a stoichiometric amount of strong base, and limited scope of the reaction. Therefore, it is highly desirable to develop a general and efficient method for synthesizing *N*-heteroaryl stilbenoids to widen the scope of these valuable classes of molecules.

The *o*-quinone catalysis developed in this work is operated at milder metal-free conditions (80 °C, 1 atm oxygen) and displayed broader substrate scope and functional group compatibility than the previously reported protocols.[13−24] Particularly, the reaction accommodates nine different classes of *N*-heteroarenes, including the pyridine derivatives, which performed poorly in the transition-metal catalyzed ADC reactions.[24] The reactions proceed smoothly under the biomimetic catalysis delivering the valuable vinyl *N*-heteroarenes in high yields and selectivities. As an application of this method, we have synthesized the core structure of Montelukast[25] and Heparin blue,[15a15c] STB-8,[14,15] and the Hancock alkaloid (±)-cuspareine.[26]

Our initial optimization using 4-methyl pyrimidine (**1a**) and benzylamine (**2a**) as the model substrates revealed that the *o*-quinone catalyst phd displayed better catalytic activity, 53% yield of **3aa**, than **Q1**-**3** in chlorobenzene at 80 °C under oxygen atmosphere (Table 1, entries 1−4).[6a,b,27] We have

**Table 1. Key Optimization Studies**[a]




| entry | *o*-quinone catalyst (*x* mol %) | cocatalyst (*y* mol %) | yield of **3aa** (%)[b] |
|---|---|---|---|
| 1 | phd (10) | - | 53 |
| 2 | **Q1** (10) | - | 4 |
| 3 | **Q2** (10) | - | 6 |
| 4 | **Q3** (10) | - | 40 |
| 5 | phd (10) | $TsOH·H_2O$ (10) | 88 |
| 6 | phd (10) | TfOH (10) | 94 |
| 7 | phd (10) | BzOH (10) | 90 |
| 8 | phd (5) | TfOH (10) | 92 (**90**)[c] |
| 9 | phd (5) | TfOH (5) | 65 |
| 10 | phd (5) | TfOH (10) | 74[d] |
| 11 | phd (5) | TfOH (10) | <20[e] |
| 12 | - | TfOH (10) | trace |

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), phd (*x* mol %), cocatalyst (*y* mol %) in chlorobenzene (1 M), $O_2$ (1 atm), 80 °C, 24 h. [b]Yields were determined in gas chromatography by using mesitylene as an internal standard. [c]Isolated yield. [d]Air (1 atm). [e]$N_2$ or Ar (1 atm).

reasoned that a Brønsted acid cocatalyst might facilitate the catalysis by providing an increased concentration of the enamine tautomer of **1a** and catalyzing the subsequent C−C bond formation reaction. Pleasingly, the addition of *p*-toluene sulfonic acid (TsOH, 10 mol %) dramatically improves the catalysis, and the best 94% yield of **3aa** was obtained when trifluoromethanesulfonic acid (TfOH) was used (entries 5−7). The *o*-quinone catalyst loading could be lowered to 5 mol % without significantly affecting the yield, and **3aa** was isolated in 90% yield (entry 8). However, lower loading of TfOH had a detrimental effect (entry 9). The reaction could be performed using air as the oxidant at a slight decrease in yield (entry 10). However, under an inert atmosphere, a low irreproducible yield of **3aa** was obtained (entry 11). The control experiment demonstrated that a trace amount of **3aa** was produced in the absence of the *o*-quinone catalyst (entry 12). Please see Tables S1−S9 for further details of the optimization studies.

We have then explored the generality of the biomimicking olefination protocol (Scheme 2). Pleasingly, the optimized condition for the model reaction in Table 1, entry 8, could be applied for the olefination of nine different classes of *N*-heteroaromatic compounds **1a**−**u** with **2a**, and in all cases, the (*E*)-stilbenoid derivatives were obtained in high yields and excellent selectivities. The olefination of 4-methyl pyrimidine derivatives **1a**−**c** and 2-methyl pyrazine **1d** took place smoothly, and the desired products were obtained in 82−90% yields. Because of lower acidities, 2- and 4-picolines were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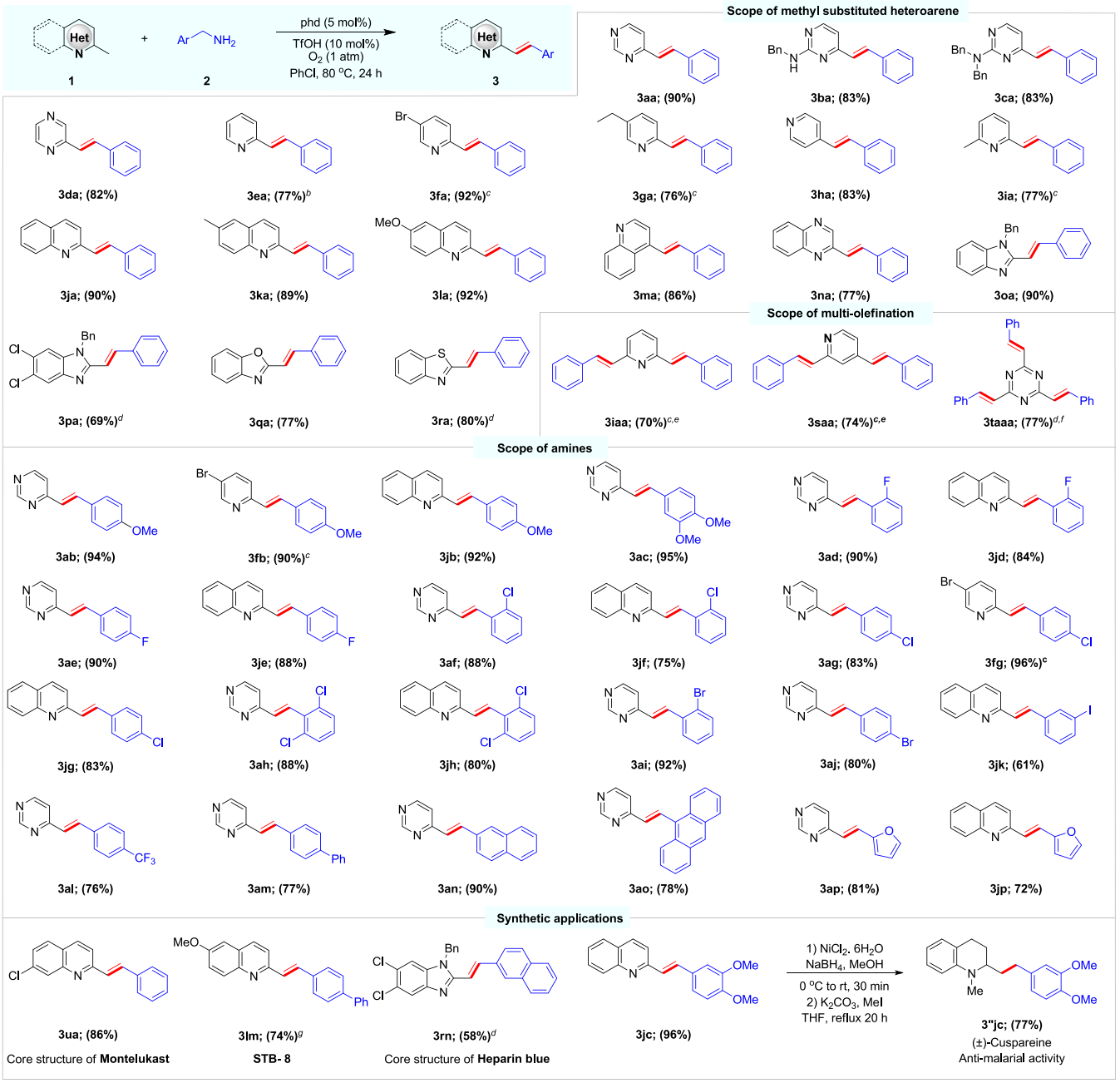
**Scheme 2. Scope of the Biomimicking Deaminative Olefination of Methyl Substituted *N*-Heteroarenes**[a]




[a]Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), phd (5 mol %), TfOH (10 mol %) in chlorobenzene (1 M), $O_2$ (1 atm), 80 °C, 24 h. Isolated yield. [b]48 h. [c]120 °C. [d]140 °C. [e]**2** (0.3 mmol). [f]**2** (0.45 mmol), TfOH (30 mol %). [g]100 °C.

challenging substrates, and previous studies delivered a poor yield of the desired products.[24] In fact, specific transition metal catalysts were needed for the C($sp^3$)−H functionalization of the 2-picolines.[28] Amazingly, the reaction of 2-picoline **1e** with **2a** delivered the desired olefin **3ea** in 77% yield after 48 h. Similarly, the 2-picoline derivatives **1f**, **g** and 4-picoline **1h** yielded the products in 76−92% yields. Selective mono-olefination of the 2,6-lutidine **1i** could also be achieved in 77% yield. The reaction also compatible with quinaldine (**1j**) and its derivatives (**1k**, **l**), lepidine (**1m**), and 2-methylquinoxaline (**1n**), and 2-methyl benzazoles (**1o**−**r**), and in all cases, the desired products were obtained in high yields, maintaining exclusive (*E*)-selectivities.

Gratifyingly, double olefination of 2,6- and 2,4-lutidines **1i**, **s** could be performed using a double amount of **2a**, and at a slightly higher temperature, and the products **3iaa** and **3saa** were isolated in 70 and 74% yields, respectively. The tris olefination product **3taaa** could also be isolated in moderate yield by using 2,4,6-trimethyl-1,3,5-triazine **1t**, a triple amount of **2a**, and slightly higher loading of TfOH.

Subjecting a range of primary amines to our reaction condition allowed the synthesis of *E*-configured heteroaryl stilbenoids derivatives. Again, the thermodynamically more stable *E*-product was formed exclusively. Nine products out of 24 examples were isolated in more than 90% yields. Benzylic amines with both electron-rich and electron-deficient sub-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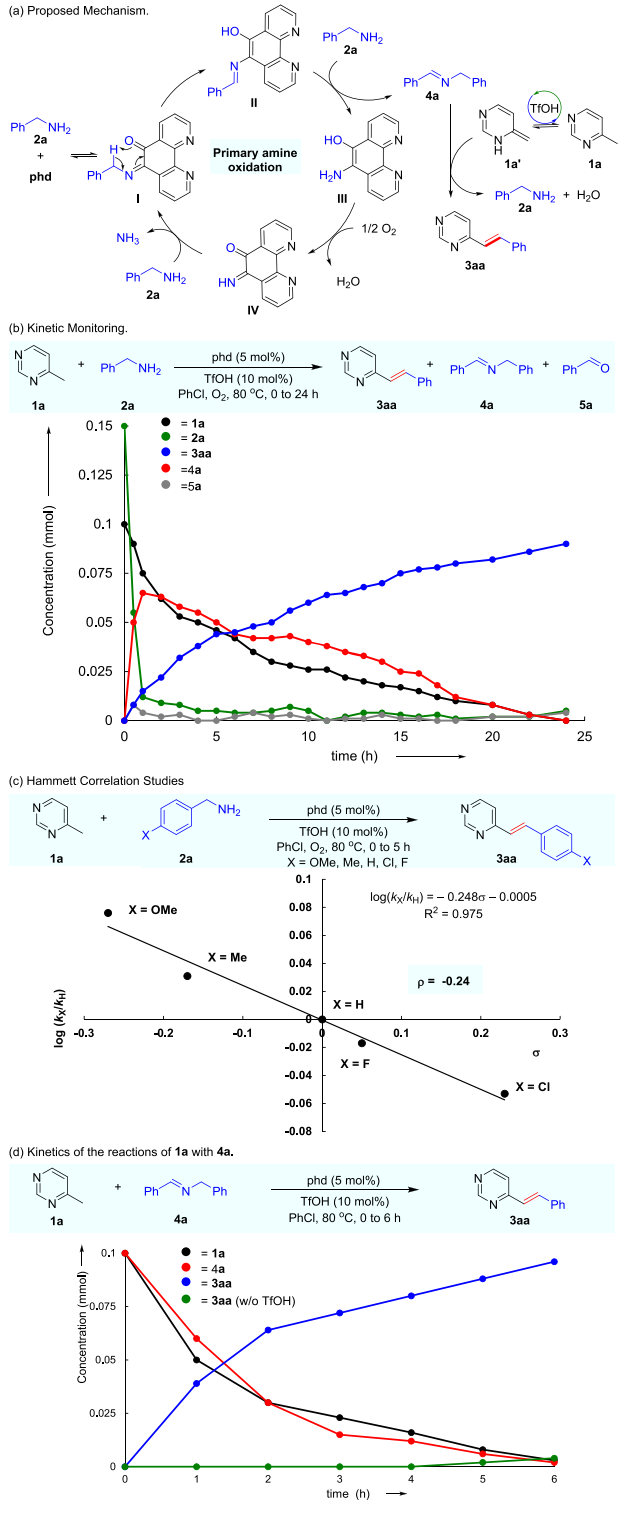
stituents at *o*-, *m*-, or *p*-position of the aryl ring **2b**−**l** were compatible with the mild reaction conditions and delivered the products in 61−95% yields. Similarly, biphenyl-, 2-naphthyl-, 9-anthracenyl, and 2-furanyl methanamines (**2m**−**p**) also reacted smoothly, and the desired *E*-disubstituted olefins were isolated in 72−90% yields.

To highlight the synthetic potential of the metal-free olefination method, we have synthesized the olefin **3ua** in 86% yield. **3ua** is the core structure of the drug Montelukast[25] and UCF-501,[29] which are used to treat asthma/seasonal allergies and malaria, respectively. The compound **3lm**, named STB-8 and a specific *in vivo* imaging agent for *β*-amyloid plaques in Alzheimer's disease,[14,15] and the core structure of 2E10, another green imaging agent of amyloid deposits,[15a] have also been synthesized in 74% isolated yield. Similarly, the olefin **3rn**, which is the core structure of heparin blue, could be isolated in moderate yield.[15a,c] Additionally, we have synthesized the molecule **3jc**, which is the precursor of the Hancock alkaloid (±)-cuspareine **3′′jc**, in excellent 96% yield under the optimized reaction conditions.[26] From **3jc**, (±)-cuspareine was isolated in 77% overall yield in two steps.

Regarding the mechanism, we hypothesized that the biomimicking synthesis of the olefins **3** proceeded through the phd-catalyzed primary amine dehydrogenation and nucleophilic C−C bond formation cascade reaction (Scheme 3a).[3,11] The kinetic analysis suggests that the amine substrate consumed within the first hour of the reaction and concurrently formed the imine **4** (Scheme 3b).[4] On the basis of the previous reports, we have hypothesized a "transamination" pathway for the dehydrogenation of the native primary amine substrate.[3,11] We were able to detect the intermediate **I**/**II** via high-resolution mass spectrometry at *m*/*z* = 330.1244 (calculated for $C_{20}H_{16}N_3O_2^+$ = 330.1237). It was further supported by observing very small electronic influence ($\rho$ = 0.24) on reaction rate on a Hammett correlation study (Scheme 3c). The produced intermediate **4a** then underwent a Brønsted acid-mediated coupling reaction with **1a** to produce the desired product with the expulsion of water and **2a**. The latter is then utilized in the next catalytic cycle. The beneficial effect of the cocatalyst is evident from the optimization studies (Table 1), which might mediate the transamination, imine formation, and C−C bond formation steps. We have also observed its first-order dependency on the overall reaction rate (see the SI). It was further corroborated via a kinetic analysis of the reaction of **4a** with **1a** (Scheme 3d). The TfOH catalyzed formation of the product **3aa** was found about 2 orders of magnitude faster than the uncatalyzed one. Finally, the *o*-quinone catalyst was regenerated via the aerial oxidation of the intermediate **III** followed the transamination with **2a**, as previously described.[6a,b,11]

In conclusion, we have demonstrated that a biomimetic *o*-quinone cofactor catalyzed the deaminative olefination of benzylic amines with nine different classes of methyl-substituted *N*-heteroaromatic compounds. The reaction operates at a milder condition under atmospheric pressure oxygen and produces water and ammonia as the byproducts. It not only avoids the use of transition-metal salt or expensive ligand system as a catalyst but also avoids the use of stoichiometric amounts of base or oxidant as an additive. A large number of (*E*)-disubstituted olefins, including the core structure of Montelukast and Heparin blue, STB-8, and the precursor of the Hancock alkaloid (±)-cuspareine, as well as challenging vinylpyridine derivatives, were synthesized in high yields and selectivities. The operation simplicity, inexpensiveness, and broad scope of the developed protocol would render an alternative synthetic route to *E*-selective 2-alkenyl heteroarenes and might trigger further opportunities in bioinspired oxidative cascade reactions in organic synthesis.

**Scheme 3. Proposed Catalytic Cycle and Mechanistic Investigations**



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## ■ ASSOCIATED CONTENT

### Supporting Information

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Experimental procedures, analytical data, NMR spectra (PDF)

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### Author Contributions

All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

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