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Urea Activation of Nitrimines: A Mild, Metal-Free Approach to Sterically Hindered Enamines

David M. Nickerson, Veronica V. Angeles, and Anita E. Mattson*

The Ohio State University, Department of Chemistry and Biochemistry, 100 West 18th Avenue, Columbus, Ohio 43210, United States

mattson@chemistry.ohio-state.edu

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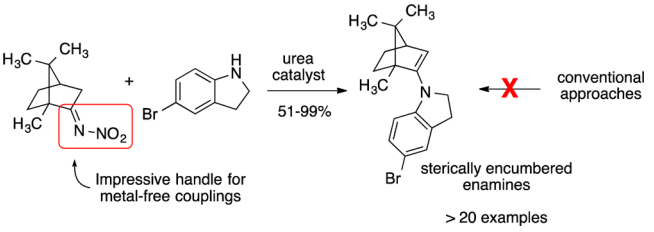
ABSTRACT



Nitrimines have been identified as impressive starting points for the syntheses of otherwise inaccessible, sterically encumbered enamines. The activation of nitrimines with urea catalysts for reaction with a variety of amines enables the formation of highly substituted enamines in high yield. The reactions benefit from mild, metal-free conditions, high functional group tolerance, and straightforward scale up.

Enamines have long been a staple in the organic chemist's toolbox accomplishing a wide variety of synthetic transformations.[1] For example, through asymmetric hydrogenation, enamines provide access to highly substituted, enantioenriched amines, key components in a number of active pharmaceutical ingredients.[2] Many simple enamines are accessible via traditional Lewis or Brønsted acid promoted condensation reactions of amines with carbonyl compounds; however, these methods often suffer from harsh reaction conditions and fail with sterically hindered carbonyls or electronically poor amines (Scheme 1, eq 1).[3]

To address the limits of conventional methods, chemists have recently developed organometallic processes as alternatives for certain enamine preparations (Scheme 1, eq 2).[2b,4] Still, transition metal catalyzed enamine cross-couplings are limited by low functional group tolerance and failure in the presence of hindered substrates.[4a] Mild, reliable, and general conditions to construct highly functionalized, sterically encumbered enamines remain an unmet demand.

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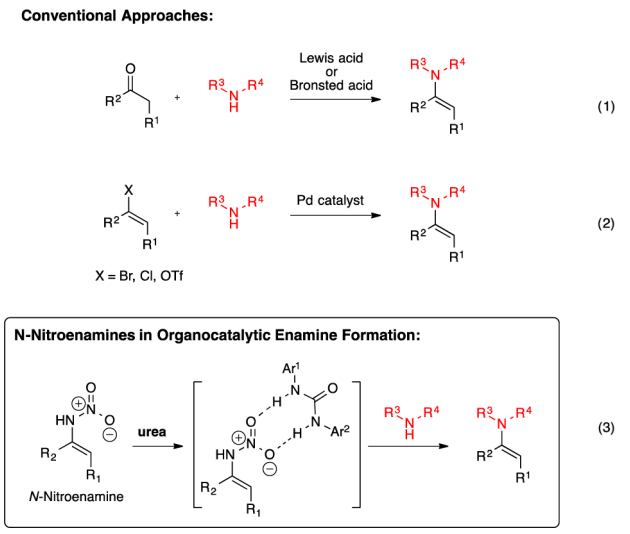
Organocatalytic methods offer mild, metal-free platforms to accomplish synthetic transformations.[5] We are particularly attracted to the potential of urea catalysis[6] and hypothesized that the urea-nitro group interaction[7] may offer a solution for direct and mild access to sterically hindered enamines (Scheme 1, eq 3). Specifically, we envisioned that urea activation of *N*-nitroenamines would enable the direct formation of sterically encumbered enamines that are inaccessible with conventional methods.

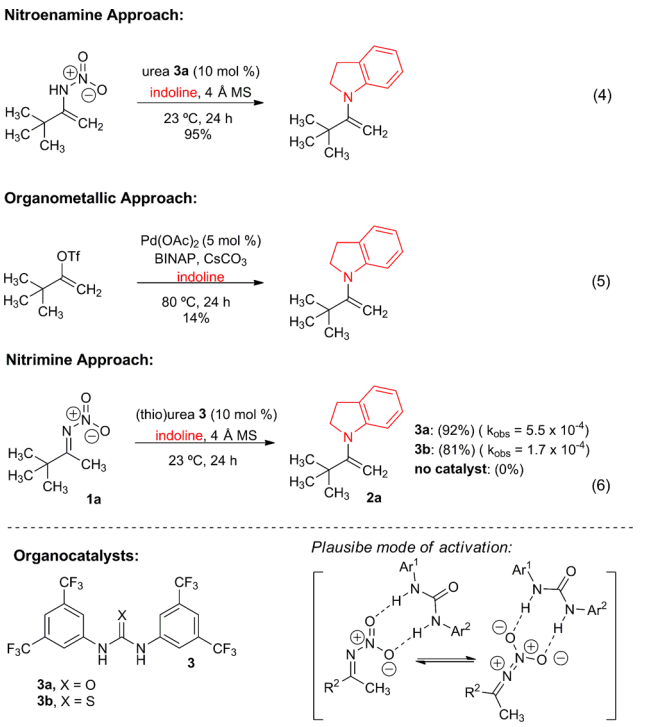
Scheme 1. Approaches toward the Synthesis of Enamines



We were delighted to find initial testing supported our hypothesis: the activation of pinacoline-derived *N*-nitroenamine for reaction with indoline under the influence of 10 mol % of urea **3a** gave rise to the desired enamine product in excellent yield (95%) (Scheme 2, eq 4). Our new method was found to be superior to known Buchwald–Hartwig conditions[4a] for construction of the same enamine (14%) (Scheme 2, eq 5). While the mechanism of action remains uncertain, we propose initial urea coordination to the *N*-nitroenamine yields an activated species capable of undergoing facile reaction with the nucleophile present. The absence of nitramide in the crude product along with the observed formation of gas suggests release of N_2O and H_2O during the reaction.

Since *N*-nitroenamines are known to equilibrate slowly to their more stable nitrimine tautomer,[8] we were curious to try our urea catalyzed coupling conditions with the less reactive nitrimine **1a**.[9] Nitrimines are known to react with highly active secondary aliphatic amines such as pyrrolidine, piperidine, and morpholine;[10] however, to the best of our knowledge, no reports of their coupling with less reactive nucleophiles such as aromatic amines or sterically hindered amines have been reported. We were pleased to find that the coupling of pinacolone derived nitrimine **1a** with indoline in the presence of a urea catalyst was almost identical to that of the nitroenamine.

Scheme 2. Urea-Catalyzed Enamine Synthesis



To benchmark the utility and significance of urea catalysis on *N*-nitrimine to enamine conversion, we performed a rate study comparing urea **3a** and thiourea **3b** catalysts and found that the urea catalyst promoted the reaction three times faster than the thiourea (Scheme 2, eq 6). Importantly, the reaction did not proceed without a hydrogen bond donor catalyst.

After demonstrating the feasibility of mild, urea-catalyzed cross-coupling approaches to sterically hindered enamine formation, our attention turned to comparing our methodology to the more conventional Lewis acid, Brønsted acid, and organometallic approaches to synthesize enamines (Scheme 3). More specifically, we set out to determine if urea catalyst **3a** would enable enamine formation from less reactive amines that were not amenable to

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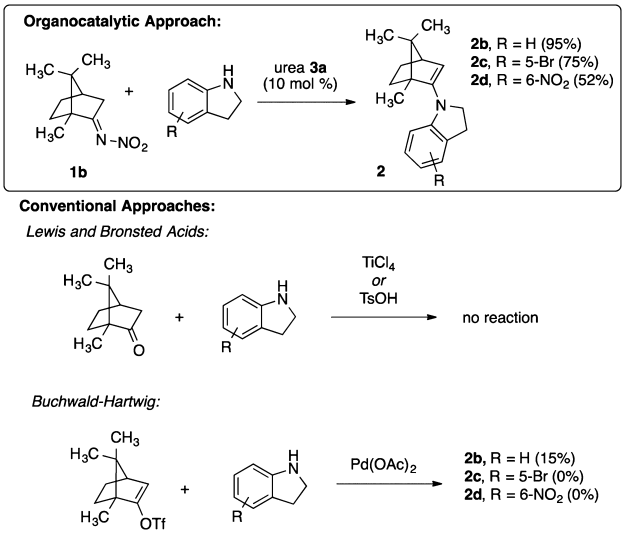
traditional conditions. Focusing on the syntheses of sterically encumbered enamines **2b**, **2c**, and **2d**, we were pleased to find camphor-derived nitrimine **1b** coupled in excellent yield with indoline under the influence of 10 mol % of **3a** to yield 95% of **2b**. Less electron-rich indolines also coupled well in the process: the incorporation of 5-bromo indoline afforded product **2c** in high yield (75%) while 6-nitroindoline gave rise to **2d** in 52% yield. Importantly, all of our attempts to isolate the same sterically encumbered enamines **2b**–**2d** were unsuccessful under traditional Lewis or Brønsted acid catalyzed conditions. Only product **2b**, albiet in low yield (15%), could be prepared under conventional, previously optimized Buchwald–Hartwig type reaction conditions.[4a] No products were observed under identical palladium-catalyzed conditions with the 5-bromo or 6-nitro indoline derivatives.

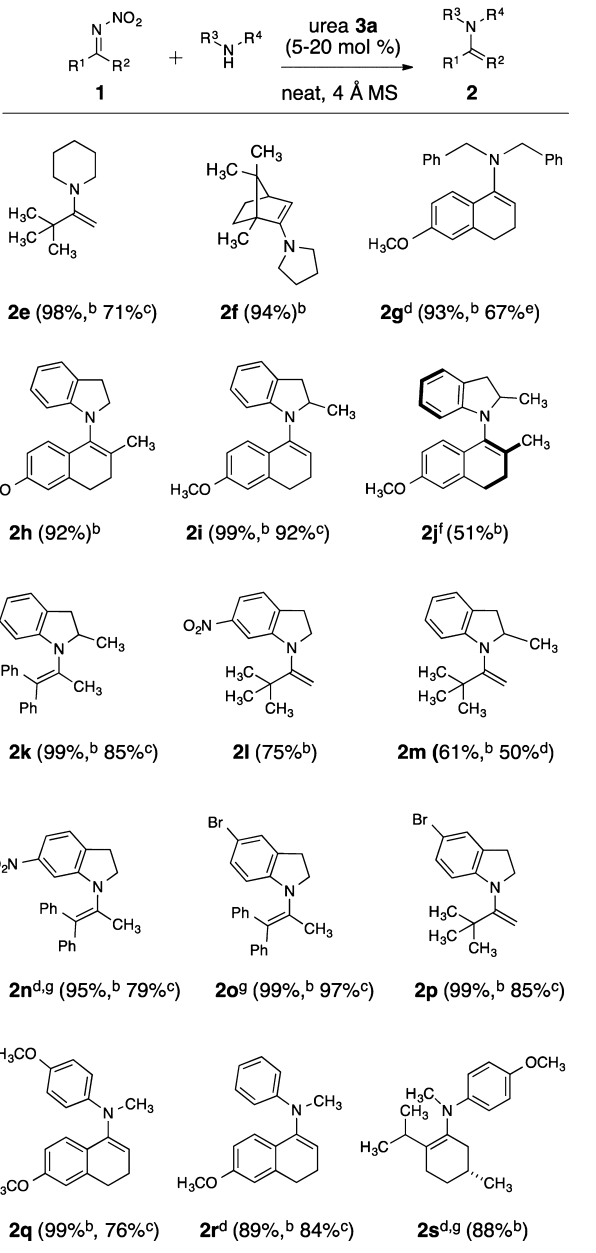
Scheme 3. Urea-Catalyzed Sterically Hindered Enamine Formation Compared to Conventional Approaches



To further probe the limits of the reaction, a variety of hindered nitrimines and amines were explored (Scheme 4). As expected, the reaction was rapid and nearly quantitative with unhindered aliphatic secondary amines **2e** and **2f** (98% and 94% yield respectively). Impressively, even dibenzylamine was successful with our method and afforded a 93% yield of **2g**; this excellent yield is in stark contrast to the reported $< 5\%$ yield using an optimized Buchwald–Hartwig approach with a similarly substituted substrate.[4a]

Next, the tolerance of the reaction with respect to steric hindrance was explored with a series of substituted tetralone nitrimines and indolines. 6-Methoxy-2-methyltetralone-derived nitrimine easily reacted with indoline to afford **2h** in excellent yield. The reaction was also easily able to accommodate substituents on the indoline as 2-methylindoline gave rise to **2i** in quantitative yield. Even the nitrimine derived from 6-methoxy-2-methyltetralone coupled with 2-methylindoline to afford **2j** in moderate yield (51%) as a mixture of two atropisomers. This emphasizes the point that this methodology can be used to form extremely hindered enamines, even to the point of restricted N–C bond rotation.

Scheme 4. Substrate Scope for the Formation of Hindered Enamines Using Organocatalytic Coupling[a]

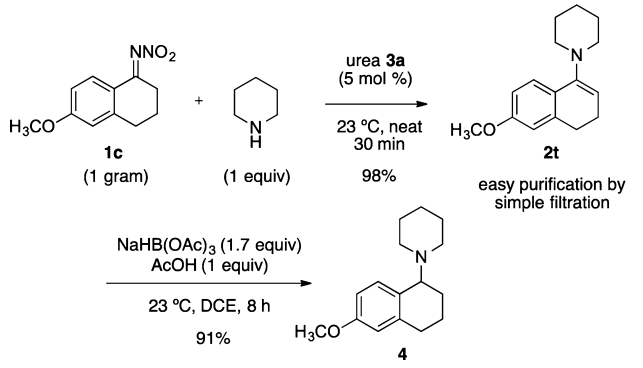


[a] See Supporting Information for detailed experimental information and also for additional enamines not shown. [b] Yield determined by ^{1}H NMR spectroscopy based on an internal standard. [c] Isolated yield. [d] Pyridine (1 equiv) added to promote solubility. [e] Yield based on $NaBH(OAc)_3$ reduction and subsequent isolation of the amine. [f] Mixture of two atropisomers. [g] Only the thermodynamic enamine was observed.

Bromo-substituted substrates, which are incompatible with palladium cross-coupling technologies, were also well tolerated in the reaction. For example, 5-bromoindoline readily coupled with the nitrimines derived from 1,1-diphenylacetone and pinacolone to afford the corresponding enamines **2o** and **2p** in 97% and 85% isolated yields, respectively.

N-Methyl anilines also proved to be valuable substrates in the organocatalytic cross-coupling reaction. For example 4-methoxy-*N*-methylaniline gave rise to **2q** and **2s** in high yields. An 84% yield of **2r** was isolated with the coupling of *N*-methyl aniline and 6-methoxytetralone-derived nitrimine.

Scheme 5. Scale-up and Reduction



As demonstrated in the formation of enamines **2e**, **2f**, and **2g**, the urea-catalyzed cross-coupling of aliphatic amines and nitrimines is highly efficient, producing high yields with few byproducts in solvent-free conditions. We found the reaction to be suitable for the preparation of enamines on a large scale without the need for significant purification (Scheme 5). For example, on a gram scale, the coupling of nitrimine **1c** and 1 equiv of piperidine gave rise to enamine **2t** in 98% yield in solvent-free conditions requiring only a filtration to access the pure enamine product. Subsequent reduction gave the amine **4** in excellent yield. The efficiency of the organocatalytic methodology is in contrast to the traditional Brønsted acid, Lewis acid, and cross-coupling enamine procedures which typically require excess amine thereby necessitating further purification steps.

In summary, sterically encumbered enamines are readily accessible via the coupling of a wide array of amines and nitrimines under the influence of urea catalysis. This mild, metal-free approach to enamines is tolerant of a wide range of functional groups and easy to scale up. Ongoing efforts in our laboratory are dedicated toward uncovering the potential of nitrimines as handles for organocatalytic cross-coupling reactions.

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Supporting Information Available. Experimental procedures and spectral data (PDF) and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.