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Pd(II)/Ag(I)-Promoted One-Pot Synthesis of Cyclic Ureas from (Hetero)Aromatic Amines and Isocyanates

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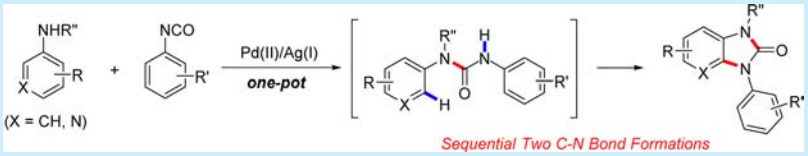
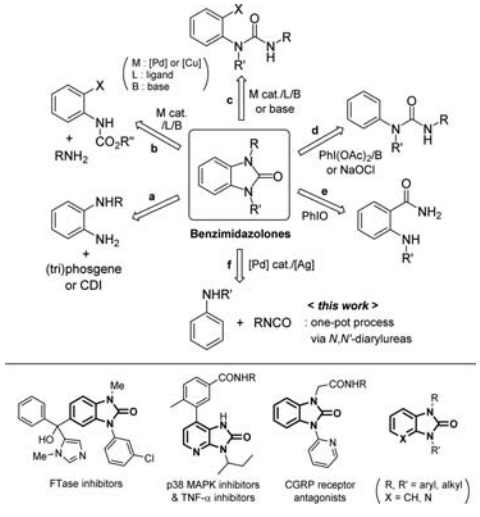
Supporting Information



ABSTRACT: A simple and facile one-pot reaction has been developed to afford a diverse range of *N*,*N*′-disubstituted benzimidazolones and imidazopyridinones containing two differently substituted N atoms. A cooperative Pd(II)/Ag(I) system promotes the sequential addition/intramolecular C−H amidation reaction of (hetero)aromatic amines and isocyanates, leading to the formation of two C−N bonds. A mechanism involving radical intermediates generated by single-electron transfer (SET) in the presence of a Ag_2CO_3 oxidant and $Pd(OAc)_2$ Lewis acid is proposed. This protocol offers an operationally easy, simple, and robust approach with the use of readily available starting materials, good functional group tolerance, and high efficiency.

Benzimidazolones and imidazopyridinones with a benzo- and pyrido-fused cyclic urea framework, respectively, are versatile building blocks and privileged structural motifs found in a wide range of pharmaceuticals[1] and functional molecules[2] (Scheme 1, bottom). In particular, *N*-arylbenzimidazolones are known to exhibit a diverse range of biological activities.[3] Regioselective synthesis of benzimidazolone derivatives bearing two different substituents on each nitrogen atom is highly desirable. Conventional synthesis of such compounds typically requires the use of 1,2-diaminobenzenes and toxic phosgene or its equivalent, inevitably involving protecting group stategies for the regioselective functionalization of each N atom (Scheme 1, path a).[4] Due to its inefficiency, the use of toxic reagents, and limited availability of diversely substituted 1,2-diaminobenzenes, alternative protocols such as transition-metal-catalyzed inter- (path b)[5] or intramolecular (path c)[6] C−N bond formation using *ortho*-haloaniline derivatives have been developed. Obviously, a direct C−H amidation of *N*,*N*′-disubstituted ureas would be a more efficient route toward this scaffold, obviating the need for prehalogenation (path d): A handful of experimental studies under metal-free conditions have been reported.[7]

Scheme 1. Methods for the Synthesis of Unsymmetrical Benzimidazolones (top) and Selected Bioactive Derivatives (bottom)



There are a couple of examples of the domino process involving a reaction between isocyanates[8] and amines to form ureas and ultimately benzimidazolones. Hu et al. reported a PhIO-induced Hofmann rearrangement of amides for the *in situ* generation of an isocyanate moiety which undergoes intramolecular nucleophilic attack by an *ortho* amine substituent, leading to benzimidazolones (path e).[9] Very recently, it has been described that a one-pot reaction of *N*-aryl-2-nitrosoanilines using CO_2 and phosphite for the synthesis of 1-arylbenzimidazolones involves the intramolecular cyclization of an intermediate isocyanate group with an *ortho* arylamino group.[10] Alper and Beauchemin demonstrated a cascade reaction consisting of the reaction of *in situ* generated *N*-isocyanates and 2-iodoanilines followed by Cu(I)-catalyzed intramolecular coupling (via path c).[6d]

Inspired by these literature reports, we reasoned that new, carefully chosen oxidative conditions would promote a direct C−H amidation of *in situ* generated *N*,*N*′-disubstituted ureas from anilines and isocyanates, leading to *N*,*N*′-disubstituted benzimidazolones. Given the diversity of commercially available anilines

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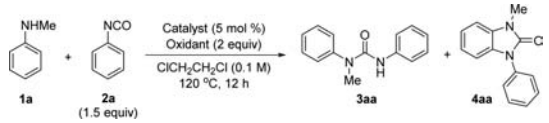
and isocyanates, the realization of this proposal would provide another facile route to such compounds and overcome some drawbacks of the precedents such as the need for often not readily available starting materials, use of hazardous chemicals, and requirement of multistep manipulations for the substrate preparation. As part of our continued interest in the oxidative cyclization reaction,[11] herein we report a Pd(II)/Ag(I)-promoted one-pot synthesis of benzimidazolones and imidazopyridinones containing two differently substituted N atoms from (hetero)-aromatic amines and isocyanates (path f).

In light of our recent success in Ag(I)-mediated C−H amidation[11f] and considering the beneficial effect of Lewis acids for the activation of the carbonyl substrate in the Ag-mediated oxidative cyclization,[11c] we began our studies on the proposed reaction using **1a** and **2a** as the test substrates in the presence of Ag_2CO_3 and $Pd(OAc)_2$ as an oxidant and Lewis acid, respectively. Much to our delight, the desired benzimidazolone **4aa** was obtained in good yield along with a small amount of uncyclized urea intermediate **3aa** (Table 1, entry 1). A variety of other Ag

Table 1. Optimization Studies



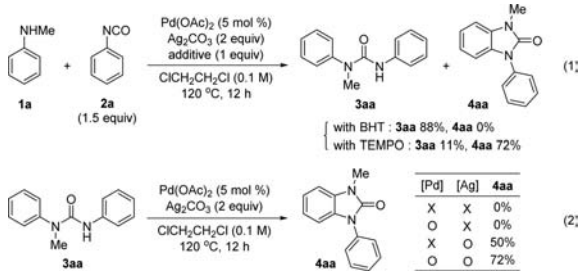
entry	catalyst	oxidant	**3aa** (%)[a]	**4aa** (%)[a]
1	$Pd(OAc)_2$	Ag_2CO_3	(15)	(82)
2	$Pd(OAc)_2$	AgOAc	84	16
3	$Pd(OAc)_2$	Ag_2O	56	–
4	$Pd(OAc)_2$	$AgNO_3$	100	–
5	$Pd(OAc)_2$	$Cu(OAc)_2$	50	–
6	$Pd(OAc)_2$	$FeCl_3$	(25)	–
7[b]	$Pd(OAc)_2$	$PhI(OAc)_2$	–	–
8	$In(OTf)_3$	Ag_2CO_3	trace	trace
9	$ZnCl_2$	Ag_2CO_3	–	68
10	$AlCl_3$	Ag_2CO_3	18	66
11	CF_3CO_2H	Ag_2CO_3	35	49
12	–	Ag_2CO_3	(22)	(54)
13[c]	$Pd(OAc)_2$	Ag_2CO_3	(24)	(68)
14[d]	$Pd(OAc)_2$	Ag_2CO_3	(26)	(67)
15[e]	$Pd(OAc)_2$	Ag_2CO_3	(10)	(75)
16[e,f]	$Pd(OAc)_2$	Ag_2CO_3	(14)	(64)

[a]Yields were determined by ^1H NMR using trichloroethylene as an internal standard. Values in parentheses indicate isolated yields. [b]Acetanilide was obtained in 88% yield. [c]Using 1.5 equiv of Ag_2CO_3. [d]At 100 °C. [e]Using 2 mol % $Pd(OAc)_2$. [f]Using 2.5 equiv of Ag_2CO_3.

salts and oxidants were examined (for complete data, see Supporting Information), and with the exception of AgOAc, all were not effective for the formation of **4aa**, giving only **3aa** (entries 2−7). Very interestingly, in sharp contrast to the previous report,[7a,b] the reaction with $PhI(OAc)_2$ afforded neither **3aa** nor **4aa**; acetanilide was instead obtained presumably as a consequence of the reaction of **2a** with an acetate anion from $PhI(OAc)_2$ followed by a rearrangement and the concomitant release of CO_2 (entry 7).[12]

Next, a variety of Lewis and Brønsted acids were examined (entries 8−11). $Pd(OAc)_2$ proved to be the most effective while other common Lewis and Brønsted acids could also promote this reaction to some extent. Decreasing the reaction temperature and the amount of $Pd(OAc)_2$ or Ag_2CO_3 significantly reduced the yield of **4aa** (entries 13−16). In addition, a control experiment employing only Ag_2CO_3 led to the formation of **4aa**, albeit in a much lower yield (entry 12). Thus, although a mechanism remains elusive at this juncture, in line with our recent work,[11c] we speculated that this oxidative cyclization might proceed through a radical mechanism[13] facilitated by $Pd(OAc)_2$ as a Lewis acid[14] for the activation of **2a**.

To gain further mechanistic insight, this reaction was performed in the presence of radical scavengers under the standard reaction conditions. Inclusion of BHT as an additive had a deleterious effect on the reaction to afford only **3aa**, whereas the addition of TEMPO had only a marginal effect to give **4aa** in 72% yield (eq 1). It cannot be completely ruled out that Ag_2CO_3 was



consumed by its direct reaction with BHT, leading to its depletion and thus shutting down this reaction. However, a similar observation, no effect with TEMPO but decreased yield of product with BHT, in radical processes is precedented in the literature.[15] Therefore, these results may suggest a mechanism involving a radical intermediate during the reaction, although the corresponding trapping products were not observed in both cases.

Subjecting the uncyclized urea intermediate **3aa** to the standard reaction conditions resulted in the formation of **4aa** in 72% yield (eq 2). Control experiments employing only either $Pd(OAc)_2$ or Ag_2CO_3 gave no or much lower conversion, respectively. These outcomes suggest that Ag_2CO_3 is crucial for this transformation and the presence of $Pd(OAc)_2$ is also required to result in high reactivity and chemical yields. In addition, the one-pot reaction proved to be superior to the stepwise reaction with regard to product yield and efficiency, avoiding the tedious and time-consuming step by step isolations and purifications of urea intermediates and reducing the amount of waste.

Subsequently, we set out to explore the scope of this one-pot domino process. First, we examined the reaction of various *N*-methylanilines (**1**) with phenylisocyanate (**2a**) (Scheme 2a). Electron-neutral, moderately electron-rich and -deficient aryl groups were well tolerated to afford the corresponding benzimidazolones in good yields. In contrast, strongly electron-donating and -withdrawing aryl substituents, such as MeO and NO_2, respectively, resulted in moderate yields of the desired product (e.g., **4ba**, **4ea**). The steric effect of *N*-substituted anilines seems to play an important role in this oxidative cyclization: Transformation of uncyclized urea intermediates to benzimidazolones was drastically impeded by the *ortho* substituents, resulting in very low conversion (ca. 20%). In the case of *meta*-substituted anilines, oxidative cyclization took place preferentially at the sterically less encumbered aryl C−H bond (**4fa** 46% vs **4fa′** 29%). *N*-Methyl-3-aminopyridine proved to be a suitable substrate for the formation of the corresponding imidazopyridinones (e.g., **4ha**, **4hd**, **4hf**), while this reaction failed with 2- and 4-aminopyridines.

Next, we proceeded to investigate the scope of isocyanates (**2**) for this reaction (Scheme 2b). A wide range of arylisocyanates underwent a one-pot reaction smoothly to form the correspond-

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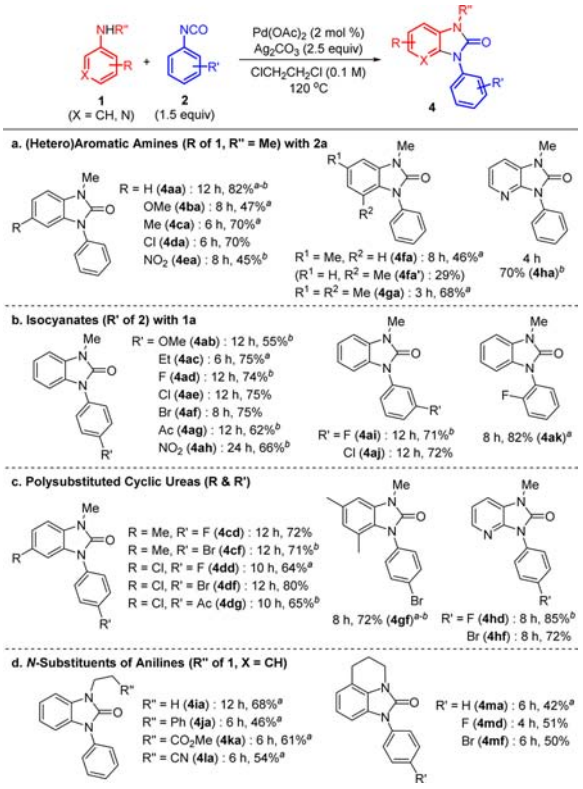
Scheme 2. Substrate Scope with Isolated Yields



[a]5 mol % $Pd(OAc)_2$. [b]2 equiv of Ag_2CO_3.

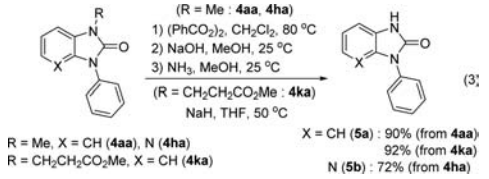
ing benzimidazolones in good yields regardless of electronic property and the position of their substituents. Unfortunately, however, despite extensive experimentations, the reaction with alkylisocyanates failed to afford the desired benzimidazolones, leading to only the corresponding *N*-alkyl-*N*′-aryl-substituted urea intermediates.

Benzimidazolones with substitution on both aromatics rings could be successfully assembled by using diversely substituted *N*-methylanilines and arylisocyanates (Scheme 2c). Noteworthy is the fact that this process can tolerate various functional groups such as methoxy, halogen, nitro, and ketone groups. This functional group tolerance should permit further elaboration and enable greater structural diversity of benzimidazolones and imidazopyridinones.

Last, we explored the effect of substituents (R″) on the N atom (Scheme 2d). The reactions with *N*-alkylanilines and teterahydroquinoline uneventfully proceeded to give the corresponding benzimidazolones; in particular, the latter afforded an interesting fused tricycle, imidazoquinolinones. Both steric and electronic properties of R″ exerted a great influence on the reaction: Only linear alkyl groups were tolerated, while anilines bearing sterically bulky alkyl, aryl, and electron-withdrawing groups directly substituted at a N atom as well as free aniline did not undergo this one-pot oxidative annulation reaction. In addition, when R″ = Bn, the desired product was obtained in very low yields, probably resulting from the facile oxidation of the benzylic position. Much to our delight, however, functional groups (e.g., Ph, CO_2Me, CN) two methylene carbons away from the N atom were well tolerated (**4ja**−**4la**).

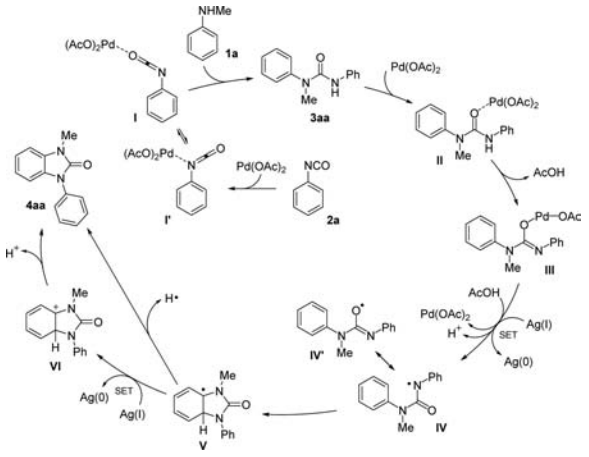
From a practical perspective, this newly developed method offers a user-friendly access to a variety of benzimidazolones and imidazopyridinones from the readily available, simple starting materials under air without the need for an inert atmosphere: Very similar product yields could be obtained under both an ambient and inert atmosphere, thereby obviating any precautionary measures to rigorously exclude air and moisture from the reaction mixture.

To improve the utility of the products synthesized by this protocol, removal of *N*-substituents was performed. Deprotection of both Me and $CH_2CH_2CO_2Me$ groups was readily accomplished to provide **5a** and **5b** in good to high yields (eq 3).



Scheme 3 outlines a plausible mechanistic proposal for this reaction. In sharp contrast to the related Pd-catalyzed reactions of

Scheme 3. Proposed Mechanism



aniline derivatives involving a Pd^{II}/Pd^0 catalytic cycle and *ortho* palladation of the anilines,[16] our experimental findings suggest that $Pd(OAc)_2$ acts as a Lewis acid[14] and this oxidative cyclization might proceed through a radical mechanism.[11c,f,13] Coordination of the NCO moiety by $Pd(OAc)_2$ (**I**/**I**′) activates phenylisocyanate **2a** toward intermolecular nucleophilic attack by the N atom of *N*-methylaniline **1a**, leading to the uncyclized urea intermediate **3aa**. Activation of urea **3aa** by coordination to $Pd(OAc)_2$ followed by tautomerization of the resulting **II** facilitates SET from the so-obtained intermediate **III** to Ag(I) to produce **IV**′ and its resonance structure **IV**. Subsequently, further oxidation of radical intermediate **V**, resulted from the cyclization of **IV**, to cationic intermediate **VI** followed by the deprotonation forms the desired benzimidazolone product **4aa**. Alternatively, hydrogen abstraction of **V** to directly give benzimidazolone **4aa** could also be invoked.

In summary, we developed a new and straightforward one-pot reaction for the synthesis of benzo- and pyrido-fused cyclic ureas containing two differently substituted N atoms. This new protocol represents an attractive route for an expedient access to a diverse range of *N*,*N*′-disubstituted benzimidazolones and imidazopyridinones, privileged motifs found in numerous pharmaceuticals and functional molecules. For example, **4aj** is the key precursor for the synthesis of benzimidazolone-based FTase inhibitors which show high potency and selectivity

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(Scheme 1, bottom).[1e] A cooperative Pd(II)/Ag(I) system enables two C−N bond formations through the sequential addition/intramolecular C−H amidation reaction of two types of readily available, simple starting materials, namely, (hetero)-aromatic amines and isocyanates. Our experimental findings suggest that Ag_2CO_3 and $Pd(OAc)_2$ serve as a one-electron oxidant and a Lewis acid, respectively, and this one-pot reaction implicates radical intermediates generated by SET. This operationally easy and simple one-pot protocol with good functional group tolerance and high efficiency could be an effective alternative to the known methods for related transformations.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03151.

Crystallographic data (CIF)
Full experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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