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Letter

Synthesis of Densely Functionalized Pyrimidouracils by Nickel(II)-Catalyzed Isocyanide Insertion

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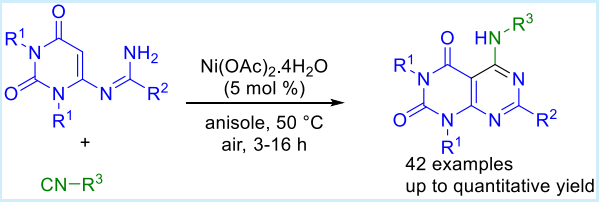
ABSTRACT: A robust nickel-catalyzed oxidative isocyanide insertion/C−H amination by reaction of readily available *N*-uracil-amidines with isocyanides affording polysubstituted pyrimidouracils has been reported. The reaction proceeds in moderate to quantitative yield, under mild conditions (i.e., *green* solvent, air atmosphere, moderate temperature). The broad range of structurally diverse isocyanides and *N*-uracil-amidines that are tolerated make this method an interesting alternative to the currently available procedures toward pyrimidouracils.



Transition-metal-catalyzed isocyanide insertions have been dominated by palladium catalysis,[1] but the last couple of years have seen a surge in row IV base metal catalysis.[2] In addition to their higher natural abundancy and lower cost as advantages, which render these base metals more interesting from an economic and sustainability standpoint, row IV metals can also participate in one-electron transfer processes.[3] This reactivity is not observed in palladium catalysis, and opens up new, mechanistically distinct reaction pathways for the synthesis of heterocyclic scaffolds. For example, fused pyrimidine scaffolds commonly occur in nature, and related heterocycles have been reported to demonstrate a variety of biological activities, like adenosine potentiating (coronary dilatators),[4] antioxidant,[5] antifungal,[6] antiviral,[7] and antibacterial[8] activities. Additionally, similar structures have been reported as phosphoribosyl-1-pyrophosphate synthetase inhibitors[9] and dihydrofolate reductase inhibitors.[10] Although these pyrimidouracils show promise as biologically active scaffolds, the current syntheses have a very narrow scope, utilize highly specific reactants, or require harsh conditions. Recently, we reported the Cu(I)-catalyzed oxidative amination of *N*-uracil-amidines **1** to afford substituted xanthines (Scheme 1).[11] We envisioned that combining this with isocyanide insertion could provide efficient access to pyrimido[4,5-*d*]pyrimidine-2,4-diones (pyrimidouracils) (Scheme 1). The starting materials, the *N*-uracil-amidines **1**, are readily available from 6-chlorouracils.[11] We started our studies to develop an intramolecular imidoylative amination toward functionalized pyrimidouracils with the model reaction of *N*-(1,3-dibenzyluracil)benzamidine **1a** with *t*-BuNC (**2a**). When applying the reaction conditions developed to obtain 1,3-dibenzyl-8-phenylxanthine (Scheme 1) in combination with **2a**, no formation of the desired compound **3a** was observed, irrespective of the oxidant (see Supporting Information (SI)).[11] Optimization of the transition metal catalyst led to $Ni(OAc)_2{\cdot}4H_2O$ as the optimal catalyst (see SI). Nickel catalysis has been extensively investigated in polymerization of isocyanides.[13] Although imidoylative nickel catalysis in small molecule synthesis was first reported in 1993,[14] it has remained underinvestigated, and only a handful of redox-neutral[15] and oxidative[16] examples have been reported since. Satisfyingly, 15 mol % $Ni(OAc)_2{\cdot}4H_2O$ in DMSO at 120 °C under an oxygen atmosphere gave 93% pyrimidouracil **3a** after 5 h (Table 1, entry 1). Subsequently, the influence of the temperature, reaction time, and solvent was studied. The temperature could be lowered to 50 °C without a significant drop in yield of **3a**

Scheme 1. Direct Oxidative and Oxidative Imidoylative Amination of *N*-Uracil-amidines

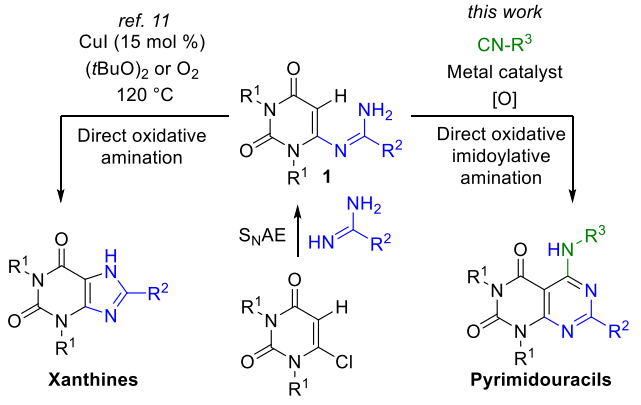


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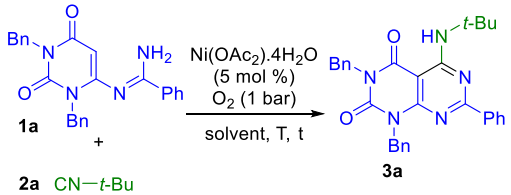
Table 1. Optimization of Conditions for Direct Oxidative Imidoylative Amination towards 3a[a]

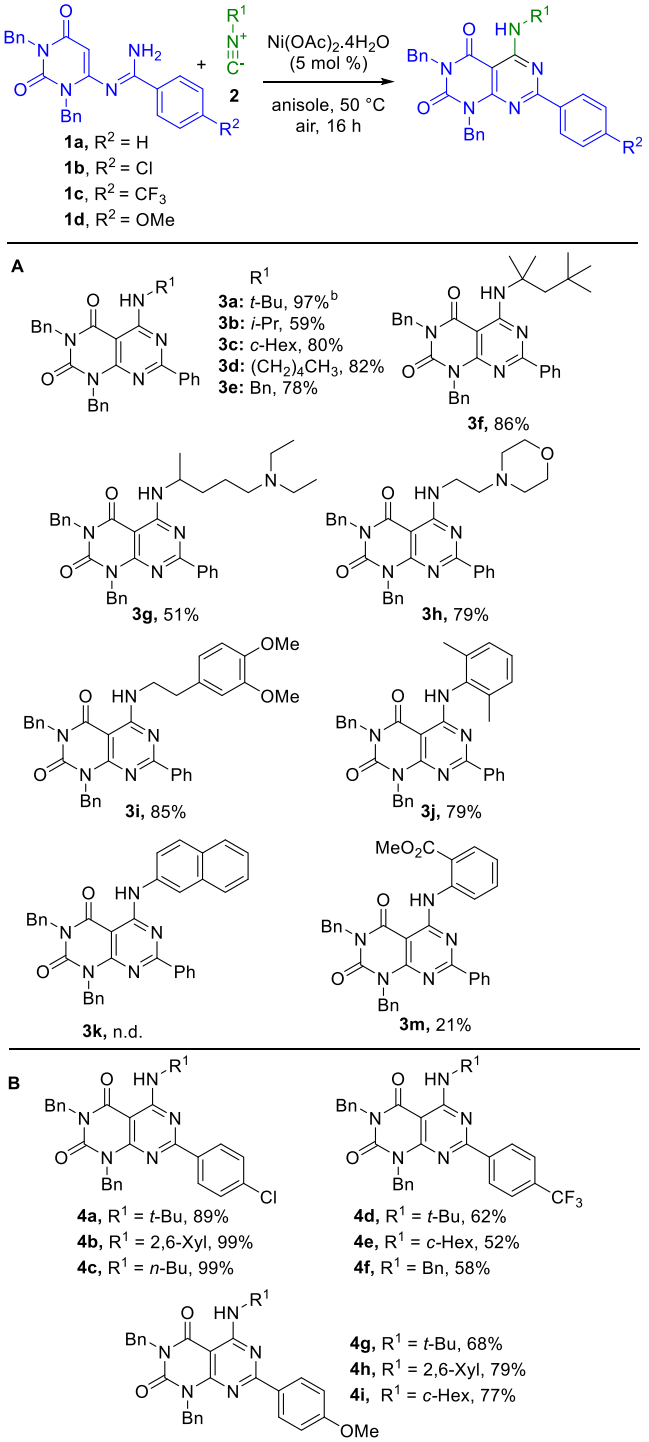


entry	Solvent[b]	T (°C)	t (h)	conversion (%)	yield (%)[c]
1[d]	DMSO	120	5	100	93
2[d]	DMSO	60	5	100	94
3[d]	DMSO	40	18	100	90
4[d]	DMSO	25	18	80	68
5	DMSO	40	18	95	91
6	DMSO	50	18	100	97
7	$CHCl_3$	50	16	67	66
8	EG	50	48	24	-
9	MIBK	50	48	98	95
10	BuOAc	50	48	95	93
11	Anisole	50	16	100	99
12	DMC	50	48	100	94
13	PC	50	48	100	95
14[e]	**Anisole**	**50**	**16**	**100**	**99**
15[e,f]	Anisole	50	16	100	99
16[g]	Anisole	50	16	90	90

[a]Selected examples, full optimization study in the SI. Reaction conditions: *N*-(1,3-dibenzyluracil)benzimidamide (**1a**, 0.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**, 1.5 mmol, 3.0 equiv), and $Ni(OAc)_2 \cdot 4H_2O$ (0.025 mmol, 5 mol %) were stirred at indicated temperature for indicated time. [b]Colored according to Chem21 solvent guide[12] (red = hazardous, yellow = problematic, green = recommended). [c]Yield determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [d]$Ni(OAc)_2.4H_2O$ (15 mol %) and *t*-BuNC (**2a**, 1.0 mmol, 2.0 equiv). [e]Performed under an air atmosphere. [f]$Ni(OAc)_2 \cdot 4H_2O$ (1 mol %). [g]Performed under an Ar atmosphere. EG = ethylene glycol, MIBK = methyl isobutyl ketone, DMC = dimethyl carbonate, PC = propylene carbonate.

(entries 1–6). At this temperature, the reaction is effective in both polar and apolar aprotic solvents. The efficacy of recommended solvents with respect to *green* chemistry[12] was investigated, most of which afforded **3a** in good yield (entries 9–13), although protic ethylene glycol did not lead to product formation (entry 8). Anisole proved to be the optimal solvent in terms of both efficiency and *green* credentials, affording **3a** in 99% yield after 16 h at 50 °C (entry 11). When we performed the reaction under air rather than under an atmosphere of molecular oxygen, no discernible decrease in yield of **3a** (entries 11 and 14) was observed. In the model reaction, combining **1a** and **2a**, the catalyst loading could be lowered to 1% (entry 15). Unfortunately, this low loading was later found to give diminished yields when isocyanides other than *t*-BuNC (**2a**) were employed. Thus, we selected a 5 mol % catalyst as the optimal conditions for this imidoylative amination (entry 14). Curiously, when the reaction was performed under an argon atmosphere under otherwise identical conditions, the corresponding pyrimidouracil **3a** was still formed in high yield (entry 16).[17] With these conditions in hand, we set out to investigate the scope of this transformation. First we investigated the reaction of different isocyanides **2** with benzimidamide **1a**, affording pyrimidouracils **3** (Scheme 2A). Tertiary aliphatic isocyanides smoothly couple with **1a** to afford the corresponding pyrimidouracils **3a** and **3f** under the

Scheme 2. Isocyanide Scope in Combination with Substituted *N*-(1,3-Dibenzyluracil)-benzimidamides 1a–d[a]



[a]Reaction conditions: **1** (0.5 mmol), isocyanide **2** (1.25 mmol), $Ni(OAc)_2 \cdot 4H_2O$ (0.025 mmol) in anisole (2 mL), run under air at 50 °C. [b]Performed on 1 mmol scale.

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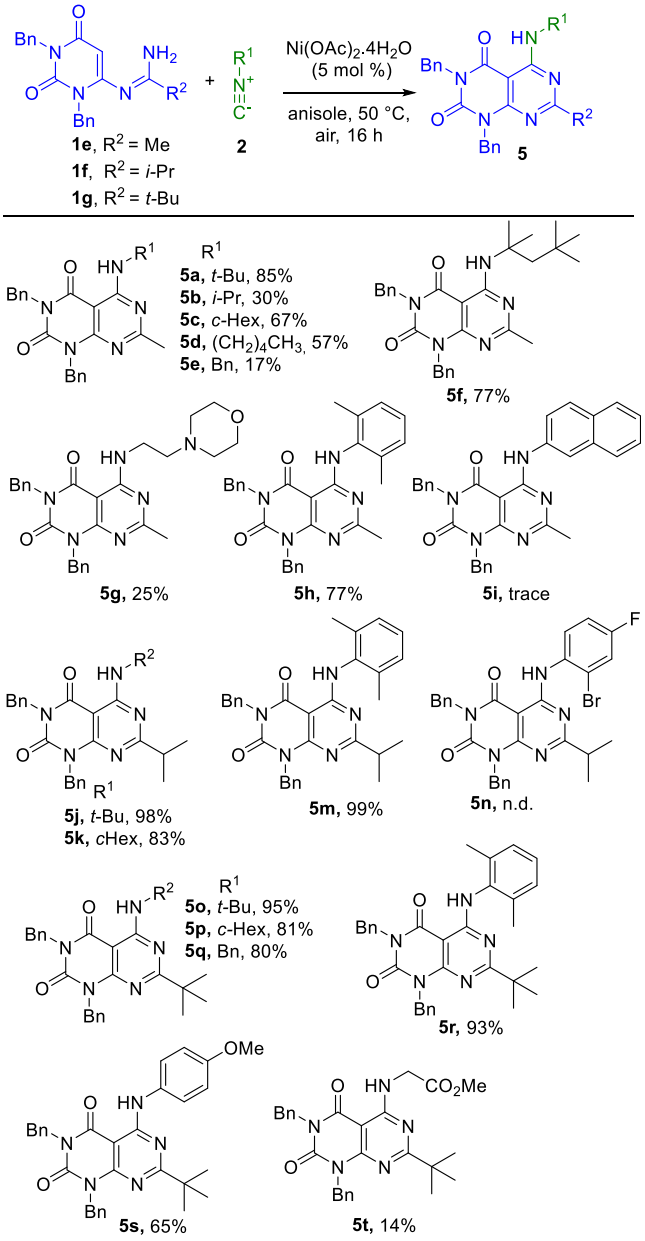
optimized conditions. Utilization of aliphatic secondary isocyanides afforded pyrimidouracils **3b** and **3c**, in good yields, and even the use of functionalized *N,N*-diethyl-4-isocyanopentan-1-amine furnished the product **3g** in acceptable yield. Both cyclic (**3c**) and acyclic (**3b**, **3g**) secondary isocyanides are tolerated. Primary and benzylic isocyanides were also readily inserted, leading to the corresponding pyrimidouracils **3d**, **3e**, **3h**, and **3i** in high yield. Even aromatic isocyanides appear compatible with the optimized conditions. For example pyrimidouracil **3j** was formed in good yield using our methodology. Even the electron-deficient methyl 2-isocyanobenzoate could be converted into pyrimidouracil **3m**, although in diminished yield. Employing the notoriously unstable 2-naphtyl isocyanide did not furnish pyrimidouracil **3k**, but led to immediate and full decomposition. Next, we turned our attention to chart the scope of the *N*-(1,3-dibenzyluracil)amidines **1** in this nickel-catalyzed cross-dehydrogenative imidoylative amination process. First, we studied substitutions on the *N*-(1,3-dibenzyluracil)-benzimidamides (**1b–d**) as input for our reaction (Scheme 2B). The use of *N*-(1,3-dibenzyluracil)-4-chloro-benzimidamide **1b** with differently substituted isocyanides **2** led to the isolation of the corresponding functionalized pyrimidouracils **4a–c** in excellent yields. With a stronger electron-withdrawing trifluoromethyl group on the benzimidamide moiety (**1c**), our protocol generally afforded pyrimidouracils **4d–f** in slightly lower yields. Similar observations were observed with the more electron-rich *N*-(1,3-dibenzyluracil)-4-methoxybenzimid-amide **1d** affording pyrimidouracils **4g–i** (Scheme 2B). These results confirm the above-described finding that our reaction not only is quite generally compatible with tertiary isocyanides but also tolerates primary, secondary aliphatic and aromatic isocyanides. Hereafter, *N*-(1,3-dibenzyluracil)alkimidamides **1e–g** featuring an aliphatic rather than an aromatic R^2-functionality were also investigated (Scheme 3). Gratifyingly, *N*-(1,3-dibenzyluracil) acetimidamide **1e** was readily converted to the corresponding pyrimidouracils **5a–h** under the previously optimized conditions using a range of diversely functionalized isocyanides **2**.

Pyrimidouracil **5b** was isolated in moderate yield (30%), presumably due to the volatility of isopropyl isocyanide. Compared to the 2- arylated pyrimidouracils **4**, the 2-methylpyrimidouracils **5** are generally produced in somewhat lower yields. The relatively low yield of **5g** can be explained by the promiscuous reactivity of *N*-(2-isocyanoethyl)morpholine. These *β*-amino isocyanides are known to intramolecularly form internal imidoyl species as a side reaction.[18] Aromatic isocyanides such as 2,6-dimethylphenylisocyanide are compatible with the developed conditions (**5h**), although naphthyl isocyanide again did not furnish isolable quantities of **5i**. Increasing the size of the amidine substituent (R^2) leads to a significant and consistent increase in the yield of pyrimidouracils **5**. Thus, when isopropyl-substituted amidine **1f** was reacted with *tert*-butyl-, cyclohexyl-, and 2,6-dimethylphenyl isocyanide, the corresponding pyrimidouracils **5j–m** could be isolated in good to quantitative yield. Unfortunately, immediate polymerization was observed in the synthesis of **5n**, as the reaction mixture turned black and turbid upon adding 2-bromo-4-fluorophenyl isocyanide. Pyrimidouracil **5n** was not observed. Satisfyingly, our catalytic system has a high tolerance for the amidine substrate, as illustrated by the use of *N*-(1,3-dibenzyluracil)pivalimidamide **1g** (Scheme 3). The corresponding 7-*tert*-butyl pyrimidouracils **5o–s** could be

Scheme 3. Isocyanide Scope in Combination with *N*-(1,3-dibenzyluracil)alkanimidamides 1e–g



[a]Reaction conditions: **1** (0.5 mmol), isocyanide **2** (1.25 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (0.025 mmol) in anisole (2 mL), run under air at 50 °C.

obtained in good to excellent yields under the optimized conditions. The substrate **1g** showed excellent compatibility with secondary and tertiary aliphatic isocyanides to afford **5o** and **5p**, but also with benzyl isocyanide, allowing for the formation of **5q**. Our system proves to be compatible with commercially available aromatic isocyanides as well, as evidenced by the isolation of **5r** and **5s** in good yields. Even the use of the *α*-acidic methyl isocyanoacetate led to the formation of **5t**, albeit in low yield (14%). To directly access pyrimidouracils of type **6**, featuring *N*-methyl substituents, we also performed several reactions with *N*-(1,3-dimethyluracil)-benzimidamide **1h** (Scheme 4). The combination of **1h** with primary, secondary, and tertiary aliphatic isocyanides gave the corresponding dimethylated pyrimidouracils **6a–c** in good to

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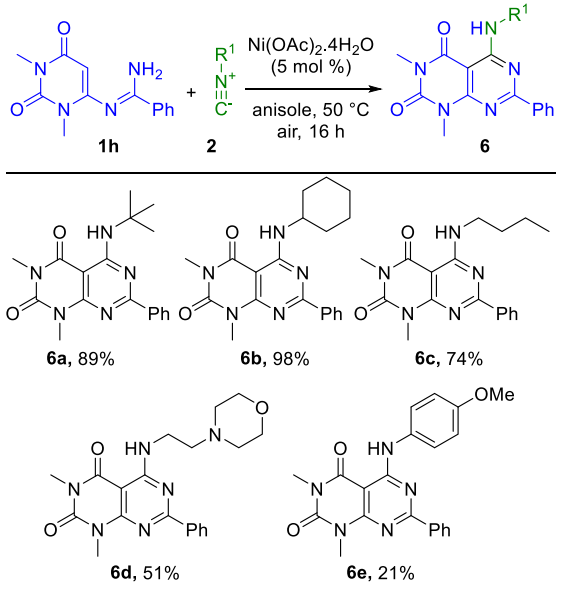
Scheme 4. Isocyanide Scope in Combination with *N*-(1,3-Dimethyluracil)benzimidamide 1h

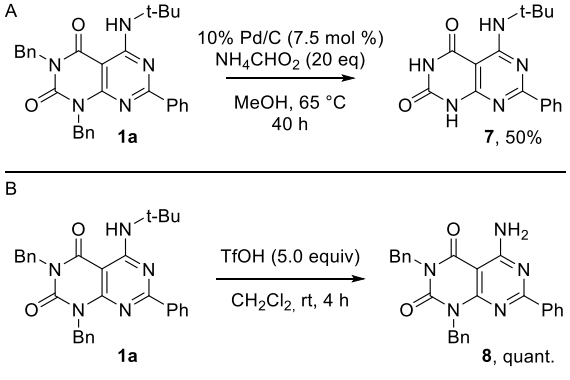


[a]Reaction conditions: **1h** (0.5 mmol), isocyanide **2** (1.25 mmol), $Ni(OAc)_2{\cdot}4H_2O$ (0.025 mmol) in anisole (2 mL), run under air at 50 °C.

excellent yields. Pyrimidouracils **6** are more prone to tailing, rendering column chromatography more cumbersome. Still, functionalized isocyanides perform rather well in combination with **1h**. For example, the *N*5-functionalized pyrimidouracil **6d** was isolated in a respectable 51% yield while 49% of the substrate **1h** could be recovered. Apparently this reaction proceeds less readily, similar to the formation of **5g** (Scheme 3). Satisfyingly, the reaction with aromatic 4-methoxyphenyl isocyanide afforded the corresponding 1,3-dimethylated-5-(4-methoxy-phenyl)-pyrimidouracil **6e**, albeit in only 21% yield.

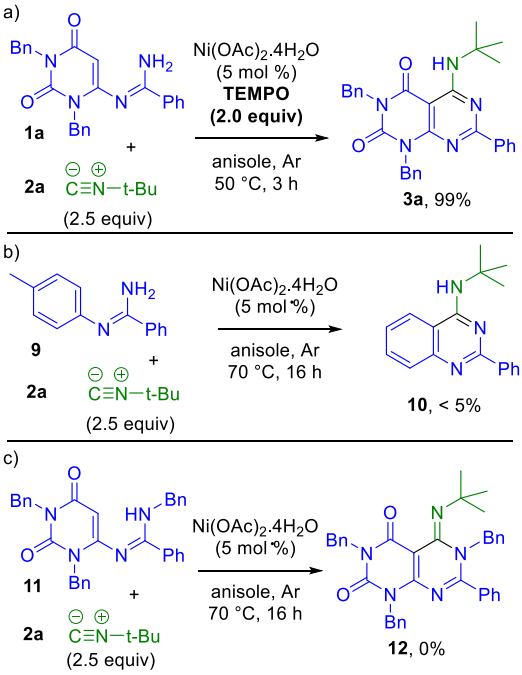
It is noteworthy that our methodology can be used in combination with a deprotection step to liberate 1,3-unsubstituted pyrimidouracils **7** or 5-aminopyrimidouracils **8** allowing postfunctionalization (Scheme 5A). Palladium-catalyzed hydrogenolysis afforded the 1,3-debenzylated pyrimidouracil **7** with excellent conversion. However, purification proved challenging, providing the target compound **7** in only 50% isolated yield. Similarly, when pyrimidouracil **1a** was treated with triflic acid the amine **8** was obtained quantitatively without further purification (Scheme 5B).

Scheme 5. Post-functionalization of Pyrimidouracils



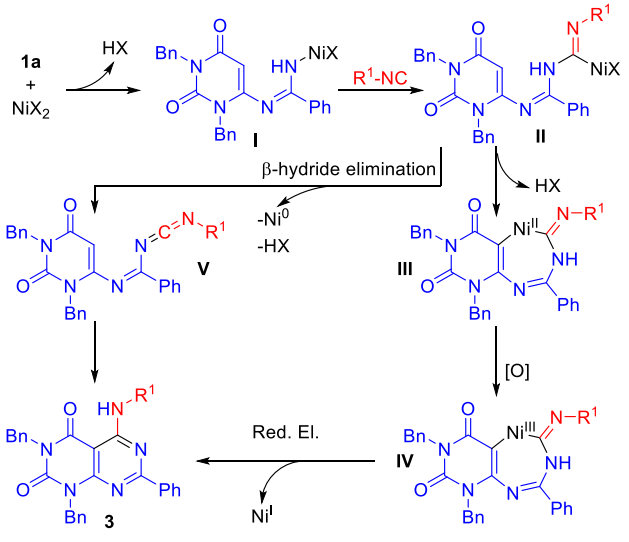
In order to elucidate the mechanism, several control experiments were performed (Scheme 6). A radical mecha-

Scheme 6. Control Experiments



nism[19] involving homolytic aromatic substitution is not deemed likely, as addition of TEMPO (2.0 equiv) does not hamper the formation of pyrimidouracil **3a** under standard reaction conditions (Scheme 6a).[19a,20] Such a mechanism would imply a heterolytic aromatic substitution, which is also deemed unlikely due to the fact this reactivity is not observed in the less electron-rich benzamidine analogue **9**, even under elevated temperatures. Additionally, we investigated the possibility of *β*-hydride elimination of proposed intermediate **II** (Scheme 7). Replacing the amidine proton with a benzyl functionality (**11**) completely inhibits the conversion to 5-(*tert*-butylimino)-5,6-dihydropyrimido[4,5-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione **12**. While this lends some credibility to a

Scheme 7. Proposed Mechanism



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mechanism including a β-hydride elimination mediated formation of the corresponding carbodiimide **V**, it does not fully exclude the Ni(II)/Ni(III) catalyzed mechanism (Scheme 7).[16a,b,21] The reaction is initiated by the formation of *N*-amidinonickel intermediate **I**. Subsequent insertion of the isocyanide affords *C*-amidinonickel intermediate **II**. This intermediate undergoes C−H functionalization to give nickelacycle intermediate **III**. After one-electron oxidation to cyclic Ni(III) intermediate **IV**, reductive elimination furnishes the observed pyrimidouracils and a Ni(I) species, which undergoes a second one-electron oxidation to regenerate the Ni(II) catalyst. Alternatively, β-hydride elimination from the likely intermediate **II** affords the carbodiimide **V**, which may cyclize to the product **3**.

In conclusion, we have developed a highly effective and robust nickel-catalyzed cross-dehydrogenative imidoylative amination of *N*-uracil-amidines (**1**) with isocyanides affording underexplored fused pyrimidouracils. The transformation proceeds with high efficiency, regardless of the steric and electronic nature of the *N*-uracil-amidine substrate. Additionally, this imidoylative C−H functionalization is compatible with a broad range of isocyanides, including primary, secondary, and tertiary aliphatic, benzylic, and aromatic isocyanides. Finally, we were able to liberate the corresponding deprotected products **7** and **8** using standard procedures. Current efforts in our laboratories are directed toward a better understanding of the mechanism of this type of transformation as well as further scaffold variations to access a broader range of nitrogen heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04387.

Experimental details and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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