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Palladium(II)-Catalyzed Cycloamidination *via* C(sp^2)–H Activation and Isocyanide Insertion

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Abstract: An efficient method for the synthesis of nitrogen heterocycles containing a cyclic amidine moiety has been developed. The process involves palladium-catalyzed C(sp^2)–H activation and isocyanide insertion starting with readily accessible *ortho*-heteroarene-substituted aniline derivatives under mild conditions.

Keywords: C–H activation; cycloamidination; heteroaromatic compounds; isocyanides; palladium

The cyclic amidine moiety is a very common subunit in many nitrogen-containing heteroaromatic compounds exhibiting a wide range of bioactivities. For example, gefitinib and erlotinib, bearing the general structure of 4-anilinoquinazoline, are clinically approved anticancer drugs targeting EGFR tyrosine kinase.[1] CX-4945, containing a substructure of 5-anilinobenzo[*c*][2,6]naphthyridine, is a first-in-class, orally bioavailable ATP-competitive inhibitor of protein kinase CK2 in clinical trials for cancer.[2] 6-Aminoindolo[3,2-*c*]quinolines exhibit promising inhibitory activities against telomerase or DNA topoisomerase,[3] and 4-amino-pyrrolo[1,2-*a*]quinoxalines act as antimalarial agents,[4] and agonists of 5-HT_3 receptors (Figure 1).[5]

The most widely used method to prepare this class of molecules is nucleophilic substitution of the corresponding chlorides with various amine nucleophiles (path a, Scheme 1).[1–5] However, chlorination of lactams needs acidic and hazardous phosphorus oxychloride ($POCl_3$) at reflux temperature.[6] In 2007, Wan et al. reported a direct one-pot S_NAr reaction of heterocyclic amides and ureas with nucleophiles mediated by stiochoimetric amounts of a phosphonium reagent, such as BOP.[7] An alternative uncommon approach was electrocylization of carbodiimides, derived from aza-Wittig reactions of corresponding iminophosphorane and isocyanates (path b Scheme 1).[8] These methods suffer from lengthy synthetic steps, harsh reaction conditions, and/or limited substrate scope. As a result, an efficient and general method to synthesize this important class of molecules starting from readily available substrates is highly desirable.

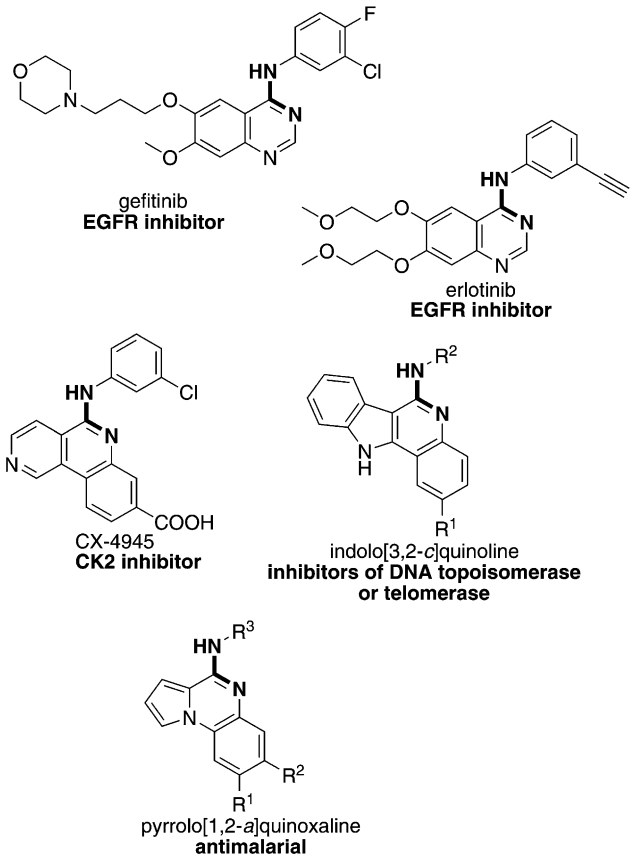
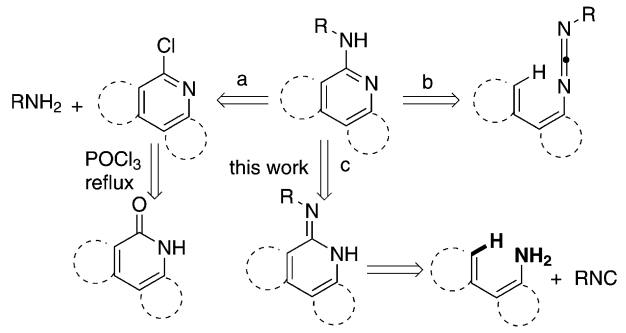


Figure 1. Examples of biologically active molecules containing a cyclic amidine subunit.

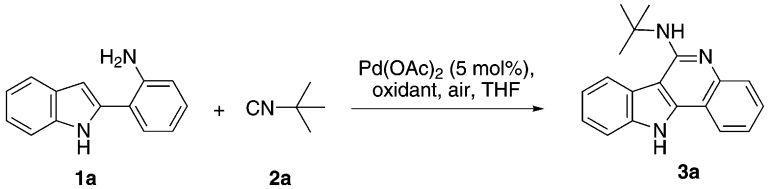


Scheme 1. Approaches towards the cyclic amidine structure.

Isocyanides, acting as isoelectronic species of carbon monoxide, have been successfully used in Pd(0)-catalyzed amidination[9] and amidation reactions.[10] Meanwhile, the transition metal-catalyzed oxidative carbonylation of C–H bonds using CO as C_1 source[11] is now recognized as an environmentally benign and atom economic alternative to traditional carbonylation reactions employing (pseudo)halogen-containing substrates. However, a similar process involving isocyanide insertion instead of CO is relatively undervalued.[12] Recently, we reported a Pd-catalyzed oxidative amidination reaction of *N*-arylamidines *via* C–H activation followed by isocyanide insertion[12c], in which one of the NH groups in the amidine moiety acted as a directing group. We anticipated that when an analogous intramolecular amino group is present, a cycloamidination product will be formed following isocyanide insertion and tautomerization (path c, Scheme 1). Herein, we wish to report an efficient synthesis of 6-aminoindolo[3,2-*c*]quinolines and 4-aminopyrrolo[1,2-*a*]quinoxalines from readily available 2-(2-aminoaryl)indoles and 1-(2-aminoaryl) pyrroles *via* Pd(II)-catalyzed sequential C–H activation and isocyanide insertion employing Cu(II) as the stoichiometric oxidant. This method allows the reaction to occur under mild conditions (50 °C), and a broad range of isocyanides and functional groups are tolerated.

We initiated the investigation by using 2-(2-aminophenyl)indole **1a** and *tert*-butyl isocyanide **2a** as the model substrates. Under our previously reported conditions [$Pd(OAc)_2$ (5 mol%) as catalyst, Cs_2CO_3 (1.5 equiv.) as base, in refluxing toluene under an oxygen atmosphere],[12c] no trtace of the desired product *N-tert*-butyl-6-aminoindolo[3,2-*c*]quinoline **3a** was obtained (entry 1, Table 1). Some Cu(II) salts were screened as the oxidant of $Pd(OAc)_2$ instead of O_2 in the absence of base in THF (entries 2–5). It was intri-

Table 1. Optimization of the reaction conditions.[a]

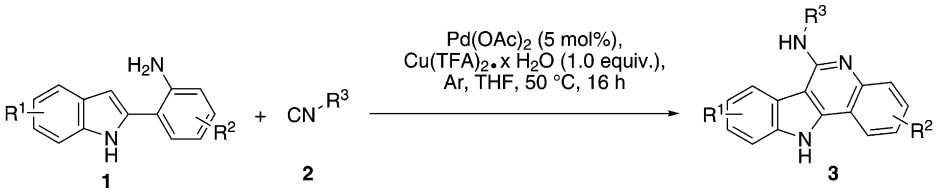


1a **2a** **3a**

Entry	Oxidant (equiv.)	Temperature [°C]	Time [h]	Yield [%][b]
1[c]	O_2	120	8	0
2	$Cu(OAc)_2$ (1.0)	70	2	0
3	$Cu(OAc)_2 \cdot H_2O$(1.0)	70	2	0
4	$Cu(OTf)_2$ (1.0)	70	8	0
5	$Cu(TFA)_2 \cdot x\,H_2O$ (1.0)	70	2	65
6	$Cu(TFA)_2 \cdot x\,H_2O$ (1.0)	50	3	69
7	$Cu(TFA)_2 \cdot x\,H_2O$ (1.0)	25	6	51
8[d]	$Cu(TFA)_2 \cdot x\,H_2O$ (1.0)	50	2	40
9[d]	$Cu(TFA)_2 \cdot x\,H_2O$ (0.2)	50	2	31
10[e]	**$Cu(TFA)_2 \cdot x\,H_2O$ (1.0)**	**50**	**16**	**79**
11[f]	$Cu(TFA)_2 \cdot x\,H_2O$ (1.0)	50	16	0
12	$Cu(OAc)_2$ (1.0)/TFA (2.0)	50	16	50
13[g]	O_2	50	16	0

[a] *Reaction conditions:* **1a** (0.2 mmol), *tert*-butyl isocyanide **2a** (0.3 mmol), $Pd(OAc)_2$ (5 mol%), THF (1 mL), under an air atmosphere.
[b] Isolated yield of **3a**.[c] The reaction was performed in toluene in the presence of Cs_2CO_3 (1.5 equiv.).
[d] The reaction was carried out under an oxygen atmosphere.
[e] The reaction was carried out under an argon atmosphere.
[f] In the absence of $Pd(OAc)_2$.
[g] TFA (2.0 equiv.) was added. Trifluoroacetylation of the aniline occurred and 2-(2-trifluoroacetamidophenyl)indole was obtained in 34% yield.

Table 2. Synthesis of 6-aminoindolo[3,2-*c*]quinolines.[a]



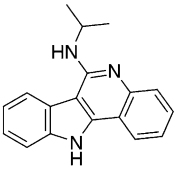
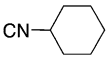
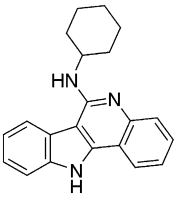
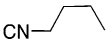
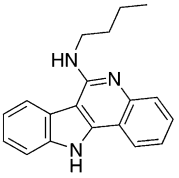
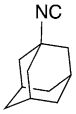
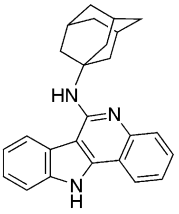
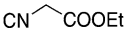
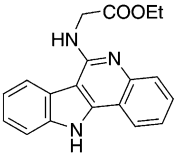
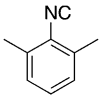
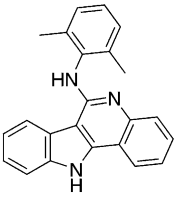
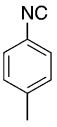
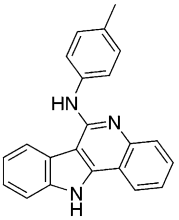
Entry	Substrate **1**	Substrate **2**		Product **3**	Yield [%]
1	**1a**	**2b**		**3b**	 79
2	**1a**	**2c**		**3c**	 72
3	**1a**	**2d**		**3d**	 90
4	**1a**	**2e**		**3e**	 85
5	**1a**	**2f**		**3f**	 50[b]
6	**1a**	**2g**		**3g**	 81
7	**1a**	**2h**		**3h**	 41

Table 2. (Continued)

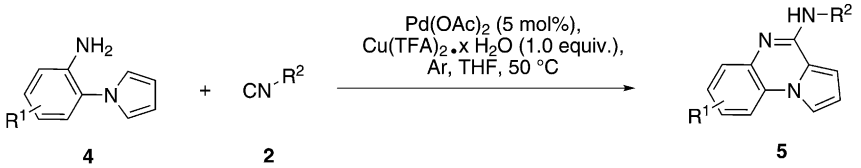
Entry	Substrate **1**	Substrate **2**	Product **3**	Yield [%]
8	**1a**	**2i**	**3i**	68
9	**1b**: R = Me	**2a**	**3j**: R = Me	77
10	**1c**: R = F	**2a**	**3k**: R = F	69
11	**1d**: R = Cl	**2a**	**3l**: R = Cl	67
12	**1e**: R = Br	**2a**	**3m**: R = Br	74
13	**1f**: R = CF_3	**2a**	**3n**: R = CF_3	51[c]
14	**1g**	**2a**	**3o**	75
15	**1h**: R = Me	**2a**	**3p**: R = Me	75
16	**1i**: R = Cl	**2a**	**3q**: R = Cl	81
17	**1j**: R = CF_3	**2a**	**3r**: R = CF_3	80

[a] *Reaction conditions:* **1** (0.2 mmol), isocyanide **2** (0.3 mmol), $Pd(OAc)_2$ (5 mol%), $Cu(TFA)_2{\cdot}xH_2O$ (1.0 equiv.), THF (1 mL), under balloon pressure of argon, at 50 °C for 16 h, yield of isolated **3**.
[b] The reaction time was 20 h.
[c] The reaction time was 24 h.

guing that only copper trifluoroacetate hydrate (1.0 equiv.) can act as an efficient oxidant at 70 °C, producing the desired product **3a** in 65% yield. The isolated yield of **3a** was improved slightly to 69% by lowering the reaction temperature to 50 °C. The product was formed even at room temperature, but with less efficiency (51%, entry 7). Changing the reaction atmosphere from air to oxygen deteriorated the cyclization. However, we were delighted to find that the yield of **3a** was increased to 79% when the reaction was performed under argon, albeit in an extended reaction time (entry 10). A control experiment in the absence of $Pd(OAc)_2$ confirmed that palladium rather than copper was the catalyst of the process. A combination of $Cu(OAc)_2$ (1.0 equiv.) and TFA (2.0 equiv.) also worked, but only a 50% yield of **3a** was obtained (entry 12). However, removal of $Cu(OAc)_2$ hampered the reaction completely, indicating that both copper salt and the counterion were crucial to the reaction (entry 13).

With the optimized reaction conditions established, we next examined the generality of this cycloamidination reaction (Table 2). The scope of isocyanide was evaluated first. Alkyl isocyanides, such as isopropyl, cyclohexyl, *n*-butyl, 1-admantyl isocyanides reacted with **1a** smoothly to form the corresponding products in good yields (**3b**–**3e**). Ethyl isocyanoacetate was also a suitable substrate for the reaction, providing the product **3f** in moderate yield. It is noteworthy that the scope of alkyl isocyanide is normally narrow in transition etal-catalyzed C–H bond activation followed by isocyanide insertion.[9,10,12] Aryl isocyanides were also tested. 2,6-Dimethylphenyl isocyanide reacted with **1a** to give **3g** in good yield (81%), while less sterically hindered *p*-methylphenyl isocyanide furnished the product **3h** in a much lower yield (41%). Importantly, benzyl isocyanide bearing a stereogenic center tolerated the reaction without any loss of enantiomeric purity of the product **3i**, owing to the neutral

Table 3. Synthesis of 4-aminopyrrolo[1,2-*a*]quinoxalines.[a]



4 **2** **5**

Entry	Substrate **4**	Substrate **2**	Product **5**	Yield [%]
1	**4a**: R = H	**2a**	**5a**: R = H	40
2	**4b**: R = Me	**2a**	**5b**: R = Me	44
3	**4c**: R = Cl	**2a**	**5c**: R = Cl	53
4	**4d**: R = F	**2a**	**5d**: R = F	49
5	**4e**	**2a**	**5e**	53
6	**4a**	**2g**	**5f**	52

[a] *Reaction conditions:* **4** (0.2 mmol), isocyanide **2** (0.3 mmol), $Pd(OAc)_2$ (5 mol%), $Cu(TFA)_2{\cdot}xH_2O$ (1.0 equiv.), THF (1 mL), in argon, at 50 °C for 24 h, yield of isolated **5**.

and mild reaction conditions (see the Supporting Information for details).

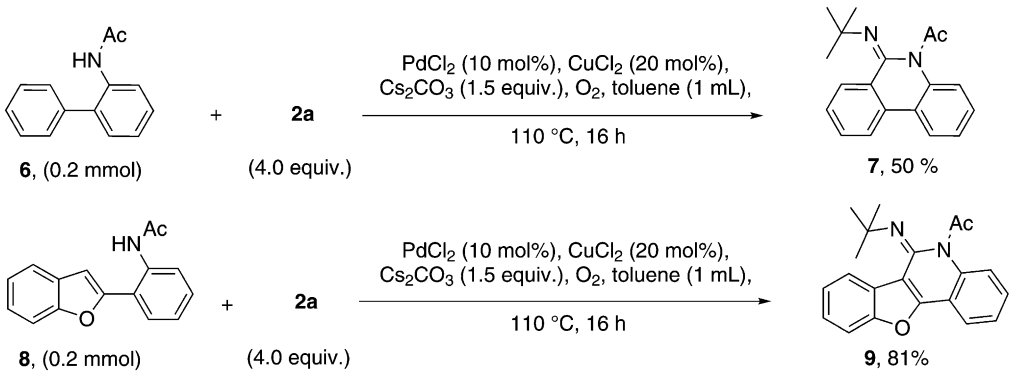
We next focused on exploring the scope of substituted 2-(2-aminophenyl)indoles. A range of substituents including methyl, fluoro, chloro, and bromo on the *para* position of the aniline ring were tolerated, affording the corresponding products in good yields (**3j**–**3m**). Nevertheless, the cycloamidination product **3n** was achieved in only 51% yield when a strong electron-withdrawing CF_3 was present at the same place. This result indicates that the electron density on the aniline nitrogen is crucial in the catalytic cycle. On the other hand, the electronic nature of substituents on C-5 of indole **1** has little influence on the yield of the cyclization (**3p**–**3r**).

The generality of the current cycloamidination reaction was further explored by employing 1-(2-aminophenyl)pyrrole as one of the reactants, and the results are summarized in Table 3. Substituted 1-arylpyrroles **4** with both electron-donating Me and electron-withdrawing Cl, and F on the aniline ring were applicable to the reaction, giving the corresponding 4-aminopyrrolo[1,2-*a*]quinoxaline derivatives in lower yields when compared with their indole counterparts.

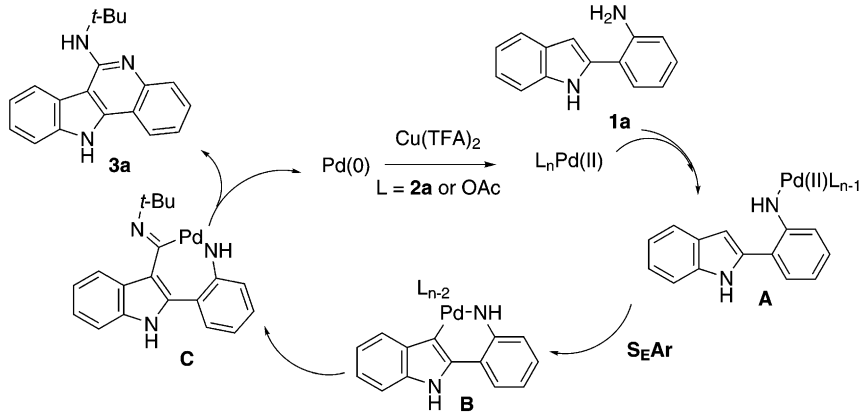
The attempts to expand the cycloamidination reaction to more general aryl substrates under the optimal reaction conditions were unsuccessful. For example, when 2-phenylaniline or 2-(2-aminophenyl)benzofuran was applied, no desired cyclization products were formed. When acetyl-protected **6** and **8** were used as substrates under more forcing conditions involving $PdCl_2$ (10 mol%), $CuCl_2$ (20 mol%), Cs_2CO_3 (1.5 equiv.), in toluene at 110 °C in O_2, the corresponding cyclization products **7** and **9** were isolated in 50% and 81% yield, respectively (Scheme 2).

A plausible reaction mechanism for this cycloamidination process is illustrated in Scheme 3, using 2-(2-aminophenyl)indole **1a** and *tert*-butyl isocyanide **2a** as an example. The reaction is initiated by coordination of the aniline nitrogen with isocyanide ligated Pd(II), affording complex **A**. Subsequent electrophilic palladation[13] of the indole ring furnishes Pd(II) intermediate **B**, followed by migratory insertion of an isocyanide. The resulting cyclic imidoyl palladium intermediate **C** undergoes reductive elimination and tautomerization to generate the product **3a** with simultaneous formation of a Pd(0) species, which is reoxidized to Pd(II) by Cu(II).

In conclusion, we have developed an efficient approach for the synthesis of 6-aminoindolo[3,2-*c*]quinoline and 4-aminopyrrolo[1,2-*a*]quinoxaline derivatives *via* palladium(II)-catalyzed C–H activation followed by isocyanide insertion starting with readily available 2-(2-aminophenyl)indoles and 1-(2-aminophenyl)pyr-



Scheme 2. Cyclization with acetyl-protected substrates.



Scheme 3. A plausible reaction mechanism.

roles, respectively. Due to the neutral and mild reaction conditions, a broad range of indole and pyrrole substrates and isocyanides are tolerated. In addition, no racemization occurs at the benzylic position when chiral 1-phenylethyl isocyanide is used. The current strategy should provide a general approach to nitrogen heterocycles containing a cyclic amidine subunit.

Experimental Section

General Procedure for the Synthesis of 3

A mixture of 2-(2-aminoaryl)-1*H*-indole **1** (0.2 mmol), $Pd(OAc)_2$ (2.2 mg, 5 mol%), $Cu(TFA)_2{\cdot}xH_2O$ (59 mg, 0.2 mmol, 1.0 equiv.) and isocyanide **2** (0.3 mmol, 1.5 equiv.) in THF (1.0 mL) was stirred at reflux temperature under balloon pressure of argon for 16 h. EtOAc (20 mL) and ammonium hydroxide (15 mL) were added to the reaction mixture. The organic phase was separated, and the aqueous phase was further extracted with EtOAc (2×10 mL). The combined organic phase was washed with brine and dried over Na_2SO_4. The concentrated residue was purified by column chromatography over silica gel using petroleum ether/ethyl acetate (16:1–8:1) as eluent to give the desired product **3**.

3a: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.82$ (br, 1H), 7.92 (d, $J = 8.4$ Hz, 1H), 7.88 (d, $J = 7.6$ Hz, 1H), 7.82 (d, $J = 8.0$ Hz, 1H), 7.55 (m, 2H), 7.43 (t, $J = 7.6$ Hz, 1H), 7.38 (t, $J = 7.6$ Hz, 1H), 7.24 (m, 1H), 5.19 (br, 1H), 1.77 (s, 9H); ^{13}C NMR (125 Hz, $CDCl_3$): $\delta = 153.02$, 146.37, 140.50, 137.74, 128.22, 127.46, 124.09, 122.18, 121.20, 120.87, 119.95, 119.39, 113.51, 111.39, 104.11, 52.13, 29.72; HR-MS (ESI): $m/z = 290.1654$, calcd. for $C_{19}H_{20}N_3$ $[M+H]^+$: 290.1652.

Acknowledgements

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