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Regioselective C–H Bond Amination by Aminoiodanes

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Abstract

A new approach for the direct amination of 2-phenylpyridine derivatives using a diphthalimide-iodane and copper triflate has been developed. A series of different 2-phenylpyridine derivatives were aminated with yields up to 88%. Mechanistic investigations indicate that the reaction proceeds via a copper-mediated single electron transfer.

Over the past two decades advances in transition metal catalyzed C–H functionalization have provided efficient strategies for the construction of C–C and C–heteroatom bonds.¹ During this time an extensive amount of effort has been devoted to the development of novel methodologies for the construction of C–N bonds, as they are ubiquitous in pharmaceuticals and other high value molecules. However, synthetic routes for the direct amination of the C–H bonds of arenes are relatively rare.² Recent examples involve the addition of nitrene intermediates into allylic and benzylic C–H bonds,³ though methods involving radical intermediates have also been investigated.^{4,5} Most of the metal-mediated directed aminations involve late transition metal catalysts, such as palladium or ruthenium,⁶ though recently, efforts to discover highly efficient, economical, and environmentally benign methods for C–N bond formation have led to the development of copper-mediated C–H aminations.^{7,8} Notably, Yu reported a C–N bond formation process using stoichiometric copper acetate,^{2b} and Nicholas reported a copper-catalyzed C–N bond formation process; however, this method required harsh conditions.^{9a} Likewise, Li reported the copper-catalyzed dual C–H/N–H cross-coupling of 2-phenylpyridine with acetanilide.^{9b}

Recently, we and both Chang and Antonchick simultaneously developed an I(III)-mediated intermolecular oxidative C–N bond formation processes for synthesizing anilines by a formal tandem C–H/N–H activation. Though these reactions provided high yields of amination products, the radical mechanism produced mixtures of regiomeric products for mono-substituted arene substrates such as toluene (Scheme 1).^{2d,2e,10} Subsequently, Hartwig reported a related palladium-catalyzed amination reaction that enhanced the regioselectivity, though both meta and para aminated products were observed for mono-substituted substrates.¹¹ To remedy the regioselectivity issues associated with our metal-free protocol,

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we proposed to develop an I(III)-mediated reaction that achieved regioselectivity via a metal-mediated C–H activation with a substrate containing a Lewis base directing group.^{2d}

During the course of our previous investigations, we also became interested in the synthesis of new iodane and iodonium reagents containing I–N bonds that could be used as C–H aminating agents. Recently, Muniz reported several novel hypervalent iodine(III) reagents for metal-free intermolecular allylic amination and diamination of alkenes.¹² Furthermore, diaryliodonium salts had been used by the Sanford group to arylate C–H bonds in the presence of catalytic palladium¹³ and by the Gaunt group to arylate C–H bonds in the presence of catalytic copper.¹⁴ Consequently, we synthesized phenyl(diphthalimido)- λ^3 -iodane (**3**) by ligand exchange from iodobenzenebis(trifluoroacetate), PIFA, using a relatively simple ligand exchange reaction.¹⁵ We also successfully synthesized a saccharin-derived iodane (**4**) and the phthalimide-iodonium salt (**5**) by modifying a route for synthesizing diaryliodonium salts from in situ-generated iodosobenzene (Scheme 2).¹⁶

The new iodanes and the iodonium salt were subjected to a variety of reaction conditions mediated by palladium or copper with 2-arylpyridine substrates. We hypothesized that the I(III) species would react as an electrophilic amine, and that regioselective metalation of the ortho C_{aryl}–H would create a nucleophilic carbon. Though this initial hypothesis proved to be incorrect, we discovered a novel method to selectively aminate 2-phenylpyridines using iodanes such as **3**, the results of which are presented herein.

As a control, we began by heating a solution of phthalimide, 2-phenylpyridine (**6**), and iodobenzene diacetate (PIDA) in acetonitrile using microwave irradiation and determined that PIDA was not able to directly aminate the pyridine derivative. As a result, the addition of catalytic palladium, along with PIDA or PIFA, was also explored. While modest amination was observed, palladium catalysis did not facilitate amination with acceptable yields. Interestingly, the use of the iodane oxidant (**3**) provided the desired amination product (**7**), while the iodonium oxidant (**5**) exclusively provided the arylated product (**8**). Consequently, we concluded that the iodane structure apparently favoured C–N bond formation, while the iodonium favoured C–C bond formation. The reason for this trend is not readily apparent and will be the subject of future studies.

As a result, we elected to screen copper catalysts and discovered that copper(II) triflate showed higher amounts of amination products when compared to the previously successful experiment with palladium acetate, albeit at a higher catalyst loading (Table 1, entry 2).

The reactions were sluggish, even at 145 °C, so as a compromise, we elected to increase the catalyst loading to 1 equiv. Such a consideration is only possible when dealing with affordable and non-toxic metals such as copper, as opposed to precious metals, like palladium.

Further optimization indicated that Cu(OTf)₂ was the preferred copper salt and that dichloroethane (DCE) was the preferred solvent (See supporting information). Cu(OAc)₂ and CuCl₂ provided low yields of **10** along with acetylated and chlorinated by-products (Table 1, entries 8 and 9). When optimizing the stoichiometry necessary for the iodane, an interesting pattern was observed. Since the I(III) species acted as both the nitrogen source and the

oxidant in reactions containing substoichiometric Cu(OTf)₂, **3** had to be used in excess. However, when reactions containing stoichiometric Cu(OTf)₂ were run with 1 equiv of **3**, lower yields were also observed (entry 6), so the excess iodane reagent was determined to be optimal.

Optimized conditions required heating the iodane (**3**), the 2-arylpyridine substrate (**9**) and 1 equiv of copper triflate in dichloroethane at 80 °C for 48 h (entry 5). Amination was exclusively observed at the ortho position, relative to the pyridine substituent to yield **10**, and no arylated products (*e.g.* **8**) were observed. The presence of the iodane was crucial for the reactivity of the system, as reactions employing both stoichiometric copper and phthalimide produced only trace amounts of **10** (entry 7). It is also noted that freshly prepared iodane (**3**) exhibited higher yields than batches that had been stored under air at room temperature.

A variety of 2-phenylpyridine substrates could be aminated using the optimal reaction conditions (Table 2). First, substrates containing different phenyl-substituted groups were screened. 4-Tolylpyridine (**10**) showed a comparable yield to unsubstituted 2-phenylpyridine (**7**); however, substrates having additional electron density, such as the 4-methoxy derivative (**12**), showed a drop in yield. Additionally, it appears that the central dihedral angle of the biaryl substrate may also play a part in determining the substrate's reactivity, as benzo[h]quinoline, a substrate commonly employed in C–H activation reactions, produced only trace yields of the aminated product (**13**). Substitution on the pyridine ring of the substrate did not appear to dramatically affect the reaction. Fluorination of the pyridine directing group did not dramatically alter the yield of the amination, but fluorination of the phenyl ring caused the yield to drop (compare **7**, **14** and **18**). Additionally, the amination reaction proceeded with the saccharin iodane (**4**), to yield the expected aminated product (**20**). To elucidate the reaction mechanism, competition studies were conducted using an equimolar mixture of two different pyridine substrates in the lead reaction. In each case, amination of the more electron rich arene was favored over the electron poor arene.

The kinetic isotope effect was also studied using an intramolecular competition between a C–H bond and C–D bond in 2-phenylpyridine. The observed KIE of 1.15 indicates that C–H bond cleavage was not involved in the rate-determining step. This rules out the possibility of a metal-mediated C–H activation step via oxidative addition, σ -bond metathesis, or concerted metalation-deprotonation, where significant isotope effects are usually observed. Additionally, the substrate scope (Table 2), and the competition studies (Table 3) indicate that the reaction favors electron rich arenes, which could be easily oxidized. Thus, we propose a pathway mediated by a radical cation (**23**) to explain the data (Scheme 4).^{2b}

First, copper triflate reacts with the iodane (**3**) to generate a copper-phthalimide species (**21**) and the iodonium (**5**). We have detected the formation of **5** via mass spectrometry of crude reaction mixtures, and we have independently synthesized and characterized it (Scheme 2). Thus, we propose that **21** reacts with 2-phenylpyridine (**6**) to generate a complex having Cu(II) coordinated to the pyridine substrate (**22**). A single electron transfer (SET) from the aryl ring to the coordinated Cu(II) generates the radical cation intermediate (**23**). Homolytic

cleavage of the Cu–N bond and subsequent intramolecular anion transfer from the Cu(I) intermediate generates the ortho-aminated product (**7**). Competition studies show that the reaction is favored when an electron donating group is present on the aryl ring, and the SET from an aryl ring containing an electron-donating group should be faster than that from an aryl ring containing an electron withdrawing group. We propose that SET is the rate-limiting step in this reaction.

In conclusion, we have developed a novel, useful and economical process for the direct amination of 2-phenylpyridine derivatives. This process requires cheap and commercially available copper triflate and works for a variety of different 2-phenylpyridine derivatives. Additionally, the process also works with a bis-saccharin iodane. Future endeavors aim to synthesize additional novel iodanes that contain I–N bonds in order to further develop this and other amination processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

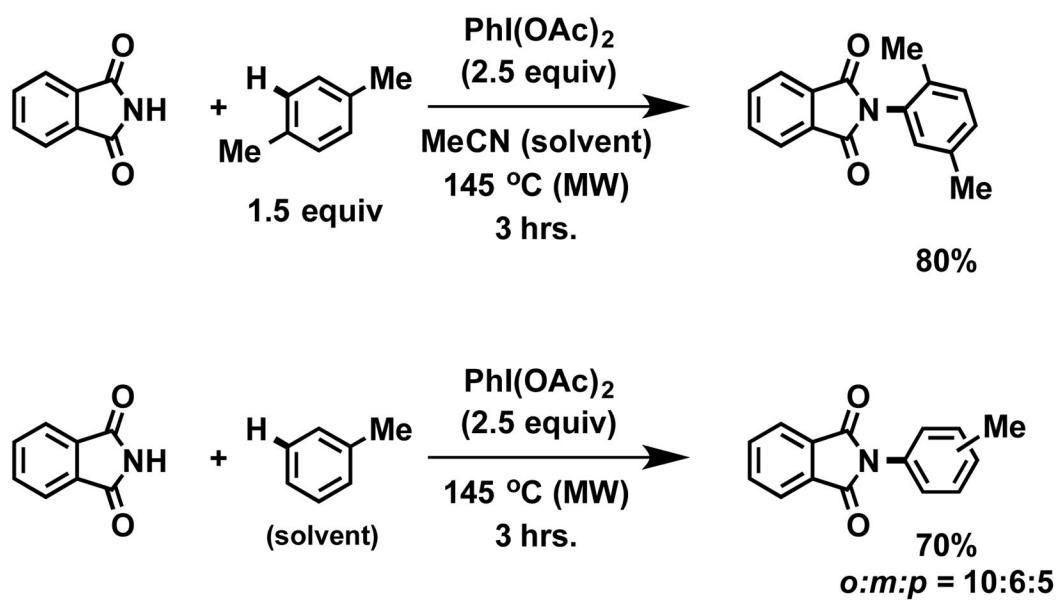
Acknowledgments

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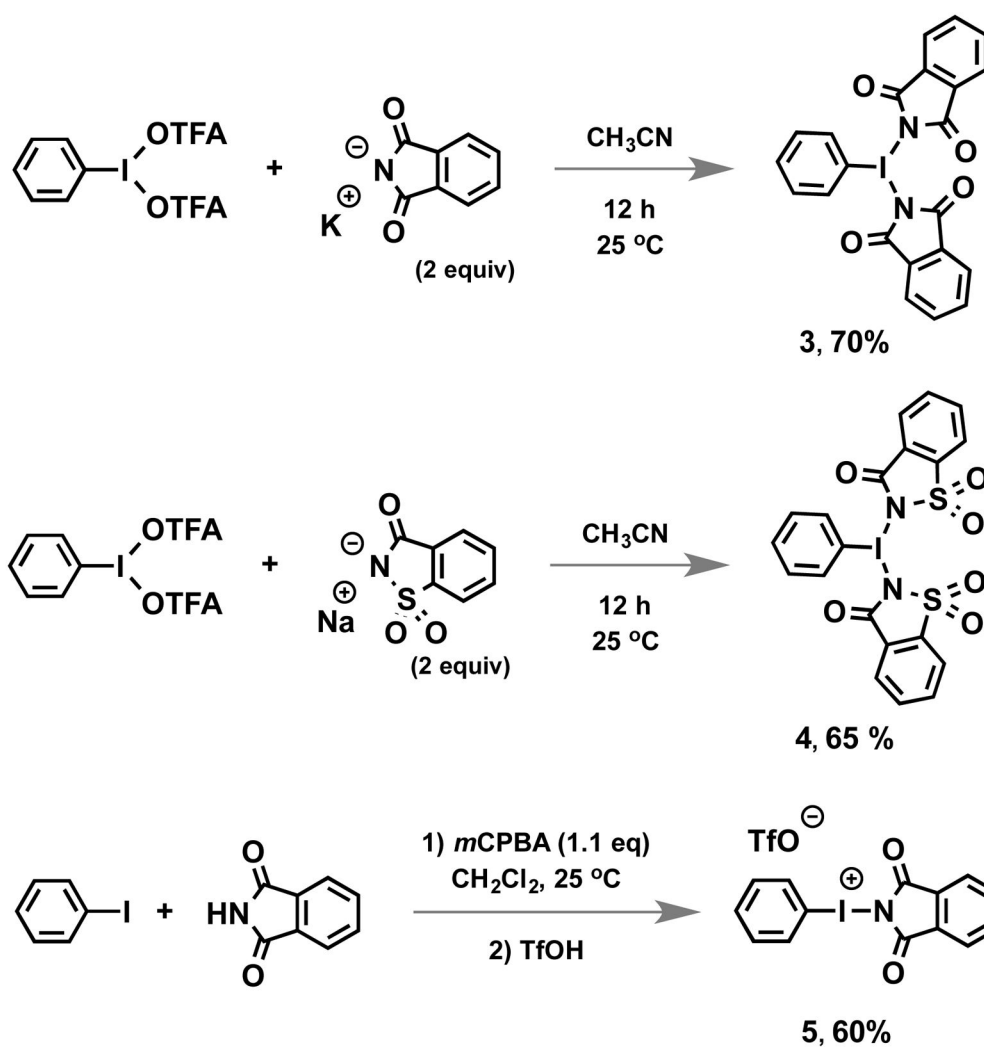
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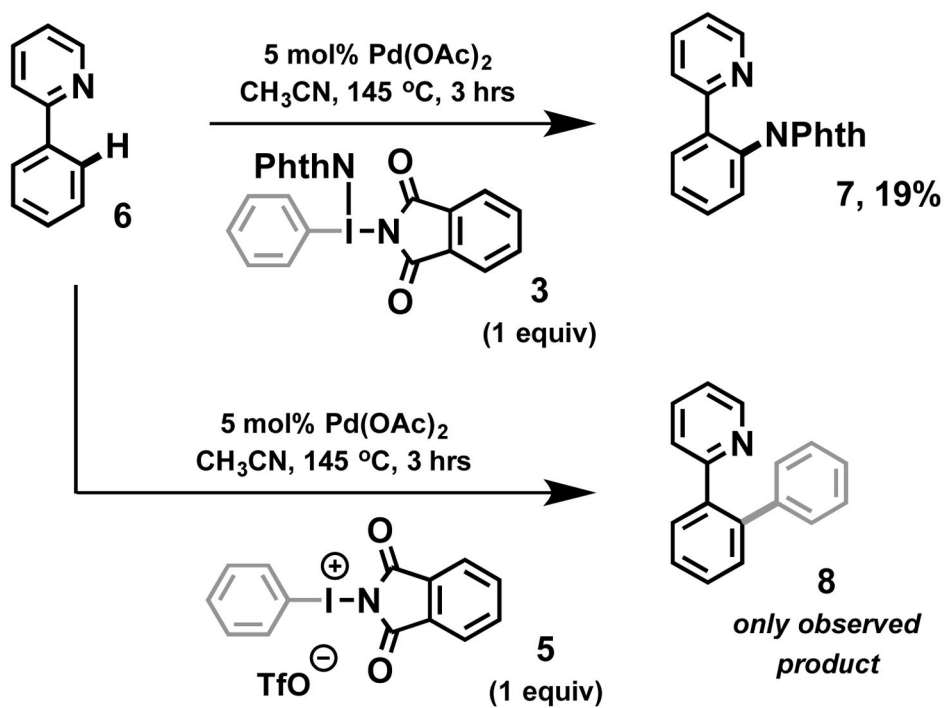
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**Scheme 1.**

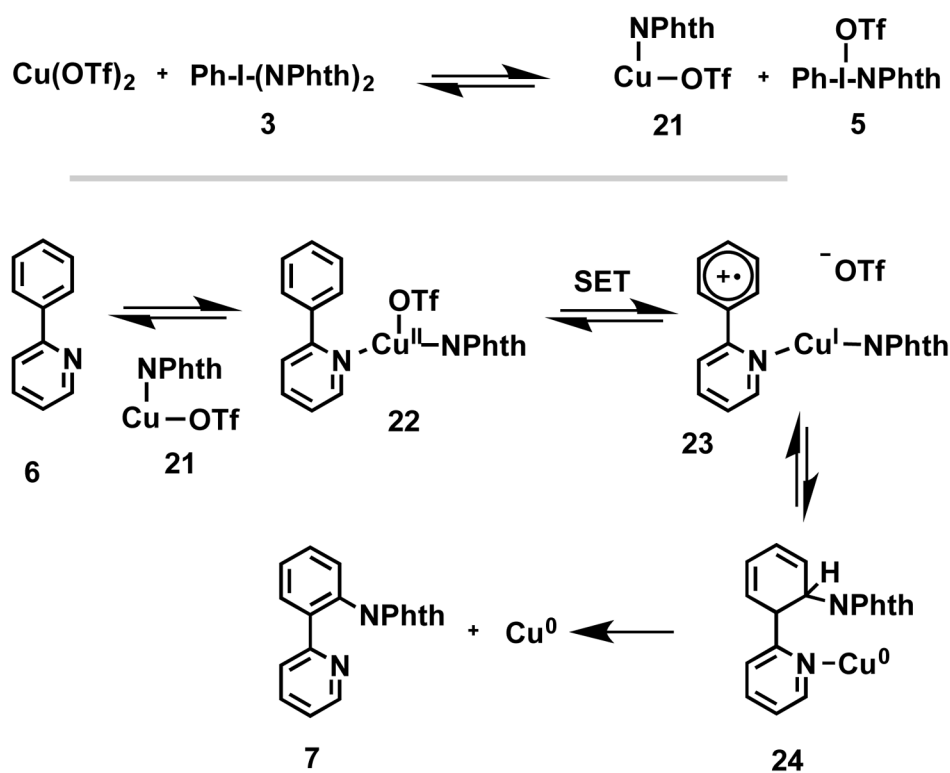
Amination of arenes in the absence of a transition metal catalyst



Scheme 2.
Synthesis of imide-substituted iodanes and an iodonium salt

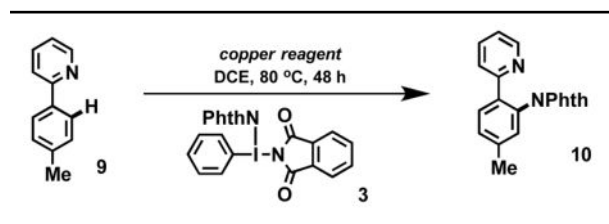


Scheme 3.
Palladium catalyzed reactions of **3** and **5**



Scheme 4.
Proposed mechanism for the regioselective amination

Table 1

Discovery of the regioselective amination of 2-arylpyridine derivatives^a

Entry	Cu reagent (loading)	Iodane (3) loading	Yield (%) ^[b]
1	None	2.5 equiv	0
2	Cu(OTf) ₂ (25 mol%)	2.5 equiv	63 ^[c]
3	Cu(OTf) ₂ (25 mol%)	1 equiv	47 ^[c]
4	Cu(OTf) ₂ (0.5 equiv)	2.5 equiv	71 ^[c]
5	Cu(OTf)₂ (1.0 equiv)	2.5 equiv	88^[c]
6	Cu(OTf) ₂ (1.0 equiv)	1 equiv	80 ^[c]
7	Cu(OTf) ₂ (1.0 equiv)	None ^[d]	2
8	Cu(OAc) ₂ (1.0 equiv)	2.5 equiv	12
9	CuCl ₂ (1.0 equiv)	2.5 equiv	5

^[a] General reaction conditions: **9** (0.146 mmol), **3** (0.365 mmol), catalyst (0.25–1 equiv) and DCE (4 mL), heated in a vial in an oil bath for 48 h.

^[b] GC yield.

^[c] Yield of isolated products after column chromatography.

^[d] This reaction contained 1 equiv phthalimide.

Table 2

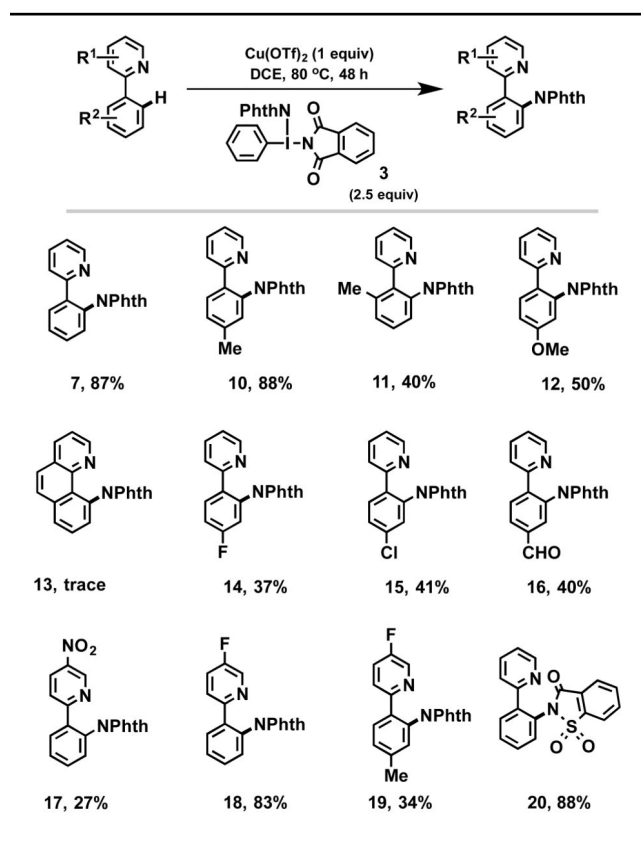
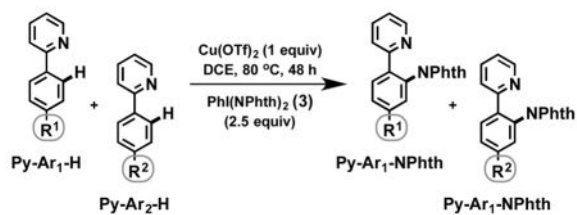
Substrate Scope^a^a Isolated yields following flash chromatography.

Table 3

Competition Reactions^a

Entry	R ¹ (Py-Ar ¹ -H)	R ² (Py-Ar ² -H)	XPy-Ar ¹ -NPhth	XPy-Ar ² -NPhth
1	H	Me	42	58
2	H	F	92	8
3	Me	F	94	6

^aMole fractions determined by GC