

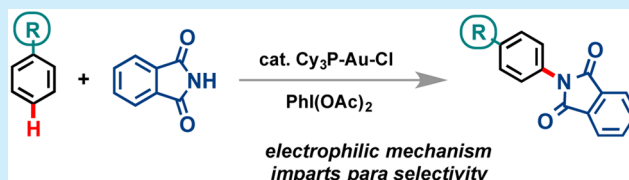
# Regioselective Gold-Catalyzed Oxidative C–N Bond Formation

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**S** Supporting Information

**ABSTRACT:** A novel protocol for the regioselective intermolecular amination of various arenes has been developed. By using an I(III) oxidant in the presence of a Au(I) catalyst, a direct and novel route for regioselectively accessing a variety of substituted aniline moieties has been achieved with yields as high as 90%. Mechanistic insight suggests that regioselectivity can be predicted based on electrophilic aromatic metalation patterns.



The synthesis of carbon–nitrogen (C–N) bonds through the oxidative cross-coupling of carbon–hydrogen (C–H) and nitrogen–hydrogen (N–H) bonds is an area that has generated significant interest due to the ubiquity of C–N bonds in a variety of pharmaceuticals and natural products. The utility of late-stage transition metals, more specifically Pd, Rh, Ru, and Cu, for C–H bond activation has been extensively studied, and the research field has been reviewed several times.<sup>1</sup> Over the course of the past two decades, gold-catalyzed reactions have played a significant role in carbon–carbon (C–C), carbon–oxygen (C–O), and C–N bond forming methodologies, despite the long-held assumption that gold was an unreactive noble metal.<sup>2</sup>

Recently, the use of gold catalysis has been explored for the purposes of C–H activation; however, few precedents exist.<sup>3</sup> The majority of the work in gold-catalyzed C–N bond formation involves hydroamination processes,<sup>4</sup> though one example of arene amination via nitrenes has also been reported.<sup>3b</sup> Herein, we report a novel gold-catalyzed reaction that regioselectively synthesizes the C–N bond of phthalimide-protected aniline moieties by oxidatively cleaving C–H and N–H bonds.

We, along with Chang and Antonchick, recently reported the metal-free synthesis of phthalimide-protected aniline derivatives utilizing phenyliodine(III) diacetate (PIDA), phthalimide, and various simple arene substrates.<sup>5</sup> While this reaction was high yielding, it was plagued with poor regioselectivity. In a subsequent communication, Hartwig disclosed that introducing catalytic amounts of Pd(OAc)<sub>2</sub> into the reaction greatly enhanced the regioselectivity.<sup>6</sup> The use of the palladium(II) catalyst also resulted in a lowering of the reaction temperature, but it required additional equivalents of the oxidant, relative to the metal-free conditions. While Hartwig was able to enhance regioselectivity, product formation was almost exclusively governed by sterics, and owing to the fact that the palladium-catalyzed reaction proceeded via a concerted metalation deprotonation (CMD) pathway, regioselectivity between meta- and para-substituted regiomers was generally not observed (Scheme 1).

**Scheme 1. Regioselectivity of Oxidative Amination As a Function of Catalyst**

	catalyst	major isomer(s)	ref
	none	o/m/p mixture	5
	Pd(OAc) <sub>2</sub>	m/p mixture	6
	Cy <sub>3</sub> PAuCl	para	this work

We hypothesized that transition metal catalysts that do not metalate arenes by the CMD mechanism would further enhance the regioselectivity of our original findings, and we quickly discovered that heating a solution of chloro(triphenylphosphine)gold(I), phthalimide (1), and PIDA in *o*-xylene resulted in a 56% conversion of 1 to the desired phthalimide-protected aniline derivatives, 2a and 2b, in a 7:93 ratio, as determined by gas chromatography. Excited by this new lead, we began the optimization process by probing the role of PIDA in the reaction. By conducting control reactions and varying the loading of PIDA, several important trends were observed (Table 1).

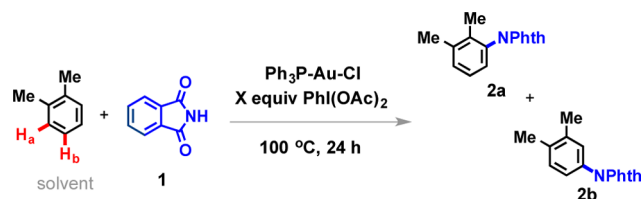
First, the necessity for hypervalent iodine in the reaction was illustrated when PIDA was completely omitted from the reaction (entry 1). Additionally, we observed a steady increase in the conversion of 1 to the desired phthalimide-protected aniline derivative (2) until the reaction plateaued at 4 equiv of PIDA (entries 2–7).

One key facet of the data that could not be ignored was the ability for the amination to proceed in the absence of a gold catalyst, albeit with a low conversion (entry 8). It appears that the radical-mediated pathway reported in our original communication could not be completely inhibited. However, the presence of gold dramatically impacted regioselectivity (compare entries 7 and 8). As a result, we hypothesized that two competing reaction pathways were taking place in these

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Table 1. Control and Optimization Results



entry <sup>a</sup>	PIDA (equiv)	[Au] (equiv)	% yield (2a + 2b) <sup>b</sup>	2a:2b <sup>b</sup>
1	0	0.10	2%	100:0
2	1	0.10	24%	9:91
3	2	0.10	56%	7:93
4	3	0.10	69%	7:93
5	5	0.10	73%	8:92
6	4	0.10	77%	7:93
7 <sup>c</sup>	4	0.10	93%	6:94
8	4	0	12%	2:1

<sup>a</sup>General reaction conditions: **1** (0.10 mmol), PIDA (0–5 equiv), 3.0 mL of reagent grade *o*-xylene (solvent), aluminum well-plate heating at 100 °C for 24 h. <sup>b</sup>Yield and product ratio obtained via GC; see Supporting Information for details. <sup>c</sup>Assembled in a nitrogen-containing glovebox, anhydrous *o*-xylene.

reactions, with metalation of the arene by the gold catalyst being favored over the noncatalyzed amination that we previously described. Other hypervalent iodine sources such as phenyliodine(III) bis(trifluoroacetate) (PIFA), and 2-iodoxybenzoic acid (IBX) were not amenable to this amination; nor were other metal-based oxidants, such as silver acetate.

Attempting to further enhance starting material conversion, we sought to determine if the reaction was stalling as a result of catalyst decomposition or oxidant consumption. A phosphorus NMR of the crude reaction mixture showed that the original gold catalyst still remained in solution. Drawing inspiration from Hartwig's Pd-catalyzed amination, we began adding additional equivalents of oxidant throughout the course of the reaction.<sup>6</sup> It was ultimately determined that, by adding an additional 4 equiv of PIDA to the reaction after 12 h, a moderate increase in yield could be obtained without impacting regioselectivity. Both the gold-catalyzed reactions that are described herein and the previously described palladium catalyzed and metal-free aminations also form biaryl side products, thus at least partially accounting for the need for additional equivalents of the oxidant.

Upon the completion of the oxidant screen, we sought to further enhance the conversion of starting material and the regioselectivity by probing the effects of different phosphine ligands (Table 2). Various gold–phosphine complexes were synthesized according to known precedures<sup>7</sup> and then subjected to the optimized reaction conditions. Bulky biaryl-containing ligands exhibited a drop-off in conversion, while trialkylphosphine ligands provided enhanced conversion of the starting material and simultaneously preserved the lead reaction's regioselectivity. It was ultimately decided to continue the investigation with tricyclohexylphosphine due to its ease of handling. It is also worth mentioning that decreasing the catalyst loading severely reduced the reaction rate, while an increase in catalyst loading only modestly impacted regioselectivity.

Subsequently, a variety of simple arenes with various functionalities were subjected to the optimized reaction conditions. These experiments indicated that our protocol

Table 2. Phosphine Ligand Screen

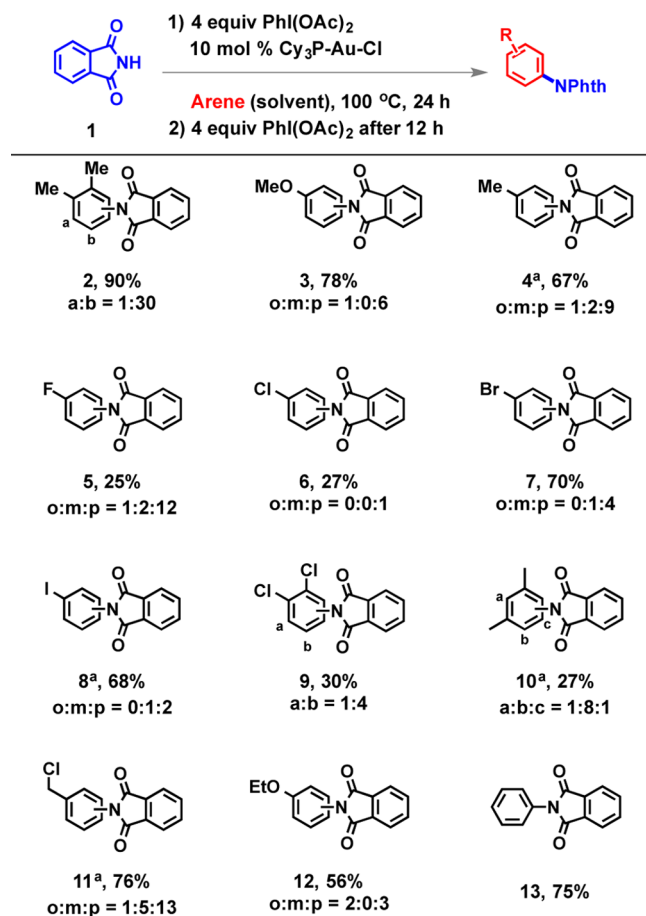


entry <sup>a</sup>	ligand	% yield (2a + 2b) <sup>b</sup>	2a:2b <sup>b</sup>
1	PPh <sub>3</sub>	93%	6:94
2	tetrahydrothiophene	54%	6:94
3	triethyl phosphite	73%	6:94
4	MePhos	20%	15:85
5	DavePhos	13%	46:56
6	TrixiePhos	92%	10:90
7	Cy <sub>3</sub> P	98%	6:94
8	( <i>i</i> -Pr) <sub>3</sub> P	97%	4:96

<sup>a</sup>See Table 1 for reaction conditions. Reactions assembled in a nitrogen-containing glovebox. <sup>b</sup>Yield and product ratio obtained via GC; see Supporting Information for details.

appeared to be most amenable to electron-rich systems. As a result, our substrate scope illustrates the effects of the gold-catalyzed reaction on various halogenated arenes and arenes possessing electron-donating groups (EDG) (Table 3). The benefit of the gold catalyzed reaction lies in its significantly enhanced regioselectivity. While conducting a similar reaction

Table 3. Arene Substrate Scope



<sup>a</sup>Regioselectivities determined via GC/MS against standards.

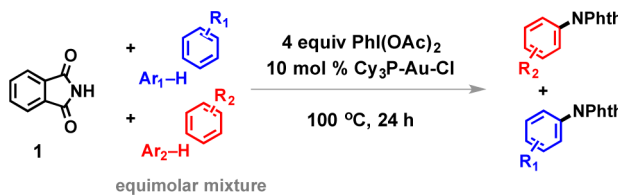
with other transition metals, such as palladium, may allow for amination of more electron-deficient systems,<sup>6</sup> the gold-catalyzed reaction provides significantly enhanced regioselectivities favoring para-substituted isomers. We hypothesize that this is the result of an alternate mechanism that differs from our previously reported metal-free radical initiated pathway and Hartwig's palladium-catalyzed CMD pathway.<sup>5,6</sup> The substitution patterns observed in the gold-catalyzed reaction appear to be governed by the same set of constraints observed in electrophilic aromatic substitution. Moreover, the predominant para-selectivity can be attributed to the large gold atom's preference to avoid positioning itself ortho to substituents.

Perhaps the most significant argument that can be made regarding whether or not the reaction is more heavily influenced by electronics or sterics is best illustrated by **10**. In the amination of *m*-xylene, a clear preference for amination to occur para with respect to either of the methyl groups is observed, rather than aminating at the less sterically encumbered position.

Minor meta-substituted products were also observed in reactions producing **4–8**, **10**, and **11**, all of which are derived from less electron-rich arene substrates. The exception to this rule is the amination of chlorobenzene (**6**), which surprisingly provided exclusive para-amination. We hypothesize that the meta-substituted products originate from a competing mechanism, the metal-free, radical-mediated reaction pathway. The meta-isomers are more often observed in less electron-rich systems, where electrophilic aromatic metalation (EAM) should be much slower. The inverse of this phenomenon is also illustrated in the reaction of the more electron-rich anisole substrate (**3**), which exhibits no meta-substitution, presumably because EAM is the dominant reaction pathway.

Having successfully established the substrate scope, we sought to further elucidate the reaction mechanism. To do this we first probed the kinetic isotope effect by performing a competition reaction using an equimolar solution of benzene/benzene-*d*<sub>6</sub>. A KIE value of 1.04 was obtained, which rules out the possibility of a gold-mediated C–H activation contributing to the rate-determining step and demonstrates that a CMD pathway is unlikely. In order to substantiate our claim that this reaction proceeds via EAM, additional internal competition reactions were performed (Table 4). By carrying out the amination procedure in an equimolar mixture of an electron-rich arene with a comparatively electron-deficient arene we observed that amination of the more electron-rich system was dramatically favored in both instances. These findings support the hypothesis that the observed regioselectivity patterns were

Table 4. Competition Reactions

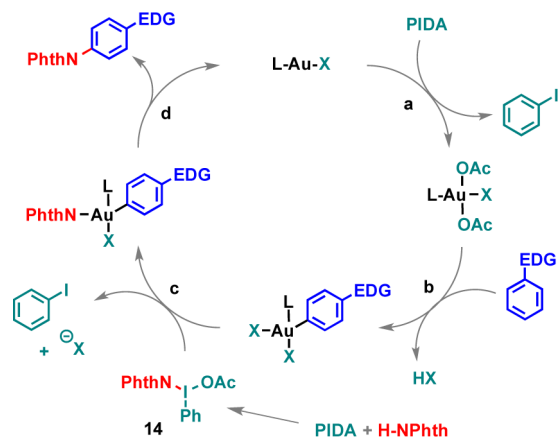


Ar <sub>1</sub> -H	Ar <sub>2</sub> -H	χ <sup>a</sup> PhthN-Ar <sub>1</sub>	χ <sup>a</sup> PhthN-Ar <sub>2</sub>
Anisole	Benzene	87	13
Fluorobenzene	Benzene	20	80

<sup>a</sup>Mole fractions determined by GC/MS.

likely the result of EAM and lead to the proposed mechanism detailed in Scheme 2.

Scheme 2. Proposed Reaction Mechanism<sup>a</sup>

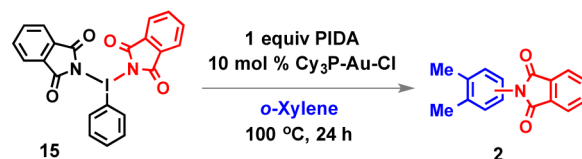


<sup>a</sup>(a) Oxidation, (b) EAM, (c) Transmetalation, (d) Reductive elimination. EDG = electron donating group, X = OAc or Cl, L = Cy<sub>3</sub>P.

The proposed Au(I)/Au(III) pathway is initiated by the oxidation of the Au(I) species to form Au(III) as the active catalyst. The para selectivity of this process is consistent with other Au-catalyzed halogenation, oxygenation, and arylation reactions that have been previously reported.<sup>3c–e</sup> The Au(III) catalyst could then metalate either the ortho- or para-positions, with the para-position being presumably more favored. The metalated arene then proceeds to interact with an in situ generated iodane species (**14**) via transmetalation. Once the imide reagent has been incorporated onto the gold species, the complex undergoes reductive elimination to afford the desired N-coupled product while regenerating the gold(I) catalyst.

In order to determine if **14** was a plausible intermediate for this reaction, we synthesized the *N,N*-diphthalimidoiodane, **15**.<sup>8</sup> When this iodane was subjected to the reaction (instead of phthalimide), an isolated yield of 38% was observed with a regioselectivity comparable to that of the parent reaction (Scheme 3).

Scheme 3. Iodane-Mediated Amination



The success of this reaction indicates that transmetalation from a phthalimide-containing iodane intermediate is a viable reaction pathway. Our hypothesis for the formation of **14** is also supported by our observation of a moderate amount of the acetoxyated arene as a minor reaction product. We hypothesize that **15** allows for transfer of either the N- or O-ligand via transmetalation. Alternatively, a nucleophilic Au–arene species could directly attack the electrophilic nitrogen in **14** (not shown). Future studies will be directed toward isolating N,O-iodanes, such as **14**, and studying their reactivities.

In conclusion, a regioselective gold-catalyzed protocol for the amination of arenes has been developed. As phthalimides can

be easily converted into free amines, a direct route for regioselectively synthesizing aniline derivatives has been achieved. Future work will focus on mechanistic studies, the lowering of the arene concentration, and the further enhancement of the regioselectivity by shutting off the uncatalyzed background reactions. The accomplishment of these aims will allow for the application of this reaction to the synthesis of a variety of high-value amine-containing compounds.

## ■ ASSOCIATED CONTENT

### ■ Supporting Information

Experimental procedures as well as NMR and mass spectroscopy data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

- (1) For recent reviews and books describing oxidative C–H bond activation, see: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (b) Du Bois, J. *Org. Process Res. Dev.* **2011**, *15*, 758. (c) *From C–H to C–C Bonds: Cross-Dehydrogenative Coupling*; Li, C.-J., Ed. RSC Green Chemistry: London, 2014.
- (2) For recent reviews of gold-catalyzed reactions, see: (a) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (b) Corma, A.; Leyva-Pérez, A.; Sabater, M. J. *Chem. Rev.* **2011**, *111*, 1657.
- (3) For examples, see: (a) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917 and references therein. (b) Li, Z.; Capretto, D. A.; Rahaman, R. O.; He, C. *J. Am. Chem. Soc.* **2007**, *129*, 12058. (c) Mo, F.; Yan, J. M.; Qui, D.; Li, F.; Zhang, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 2028. (d) Pradal, A.; Toullec, P. Y.; Michelet, V. *Org. Lett.* **2011**, *13*, 6086. (e) Ball, L. T.; Lloyd-Jones, G. C.; Russell, C. A. *Science* **2012**, *337*, 1644. (f) Kar, A.; Mangu, N.; Kaiser, H. M.; Tse, M. K. *J. Organomet. Chem.* **2009**, *694*, 524. (g) Kar, A.; Mangu, N.; Kaiser, H. M.; Beller, M.; Tse, M. K. *Chem. Commun.* **2008**, 386.
- (4) For selected examples, see: (a) Mukherjee, P.; Widenhoefer, R. A. *Org. Lett.* **2010**, *12*, 1184. (b) Zhang, G.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 1474. (c) Brouwer, C.; He, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1744.
- (5) The following papers simultaneously reported metal-free C–N bond formation: (a) Kantak, A.; Potavathri, S.; Barham, R. A.; Romano, K.; DeBoef, B. *J. Am. Chem. Soc.* **2011**, *133*, 19960. (b) Antonchick, A. P.; Samanta, R.; Kulikov, K.; Lategahn, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 8605. (c) Kim, H. J.; Kim, J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 16382.
- (6) Shrestha, R.; Mukherjee, P.; Tan, Y.; Litman, Z. C.; Hartwig, J. J. *Am. Chem. Soc.* **2013**, *135*, 8480.
- (7) Wang, M.-Z.; Wong, M.-K.; Che, C.-M. *Chem.—Eur. J.* **2008**, *14*, 8353.
- (8) Hadjiarapoglou, L.; Spyroudis, S.; Varvoglis, A. *Synthesis* **1983**, *3*, 207.