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Mild and Regioselective $Pd(OAc)_2$-Catalyzed C−H Arylation of Tryptophans by $[ArN_2]X$, Promoted by Tosic Acid

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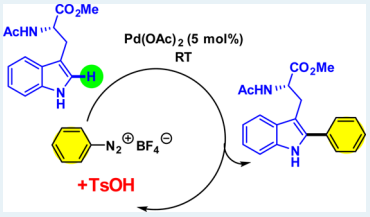
Supporting Information

ABSTRACT: A regioselective Pd-mediated C−H bond arylation methodology for tryptophans, utilizing stable aryldiazonium salts, affords C2-arylated tryptophan derivatives, in several cases quantitatively. The reactions proceed in air, without base, and at room temperature in EtOAc. The synthetic methodology has been evaluated and compared against other tryptophan derivative arylation methods using the CHEM21 green chemistry toolkit. The behavior of the Pd catalyst species has been probed in preliminary mechanistic studies, which indicate that the reaction is operating homogeneously, although Pd nanoparticles are formed during substrate turnover. The effects of these higher order Pd species on catalysis, under the reaction conditions examined, appear to be minimal: e.g., acting as a Pd reservoir in the latter stages of substrate turnover or as a moribund form (derived from catalyst deactivation). We have determined that TsOH shortens the induction period observed when $[ArN_2]BF_4$ salts are employed with $Pd(OAc)_2$. $Pd(OTs)_2(MeCN)_2$ was found to be a superior precatalyst (confirmed by kinetic studies) in comparison to $Pd(OAc)_2$.



KEYWORDS: *regioselectivity, cross-coupling, palladium, heteroarene, chirality, directing group, aryldiazonium salt*

INTRODUCTION

Pd-catalyzed cross-couplings are well-established, versatile methods for the selective modification of natural products,[1] macrocycles,[2] and biomolecules.[3] The intrinsic synthetic methodology limitation is the requirement for substrate prefunctionalization, which adds synthetic complexity to a multistep sequence, in addition to decreasing atom economy and increasing downstream chemical waste. For these reasons, the direct functionalization of C−H bonds has emerged as an alternative to classical approaches,[4,5] where high selectivities can be achieved in complex systems such as pharmaceutical targets[6] and biological probes involving metal catalysis.[7,8]

The C2-selective Pd-mediated arylation of tryptophan derivative **1**, and tryptophan-containing peptides, has attracted interest from several groups within the C−H activation field;[9] a summary of our previous work[10] and the key contributions of Lavilla[9b] and Ackermann[9c] are given in Scheme 1. For all the synthetic methodologies reported to date, one can be critical of the stoichiometric byproducts (e.g., iodoarenes or Ag) generated from these reactions, which complicate product purification and in effect mask their global atom efficiency and utility. For example, Pd-mediated processes using $PhB(OH)_2$/$PhI(OAc)_2$[11] gave the arylated products in moderate yields, in addition to PhI and other byproducts. The conditions require that the aromatic group of the organoboronic acid be matched with that of the I^{III} reagent—an issue for the introduction of substituted aromatics. This problem was in part obviated by eliminating $PhI(OAc)_2$ as reagent/oxidant, using instead $Cu(OAc)_2$ as a cocatalyst along with $PhB(OH)_2$, with air serving a role as a terminal oxidant.[10a] Under such conditions specific tryptophan-containing peptides were susceptible to aromatic oxidation by Cu^{II}. This can be overcome using presynthesized $[Ar^1IAr^2]X$ salts at 25 °C in EtOAc in air (Scheme 1).[10b] However, in that chemistry the arylation selectivity emerged as an issue, where two arylation products, derived from the transferring (Ar^1 = phenyl) phenyl and static (Ar^2 = mesityl) aromatic groups, was found.

In this study aryldiazonium salts, $[ArN_2]BF_4$, have been examined as electrophilic arylating coupling partners with tryptophan derivatives (**1** + **2** → **3**, Scheme 1). $[ArN_2]BF_4$ salts share similarities with $[Ar^1IAr^2]X$, in terms of both their structure and reactivity.[12] As oxidative addition of $[ArN_2]BF_4$ to Pd^0 is rapid,[13,14] we anticipated development of a mild and selective process, in the absence of an exogenous base. In this context, a mild methodology for the arylation of mainly indole derivatives was reported by Noel et al., employing aryldiazonium salts and catalytic $Pd(OAc)_2$.[14d] Noel et al. further suggested a mechanism akin to Heck−Matsuda type coupling reactions.[14d] For several years we have independently been investigating synthetic protocols (Pd catalyst, solvent, temperatures) similar to those of Noel et al. for tryptophan arylations.[14h]

A novel arylation protocol has therefore been developed that provides a clean and mild synthetic method for the preparation of arylated tryptophan derivatives. A significant initial rate enhancement in arylation efficacy was found using catalytic quantities of either TsOH or $Pd(OTs)_2(MeCN)_2$: i.e., in place of $Pd(OAc)_2$.

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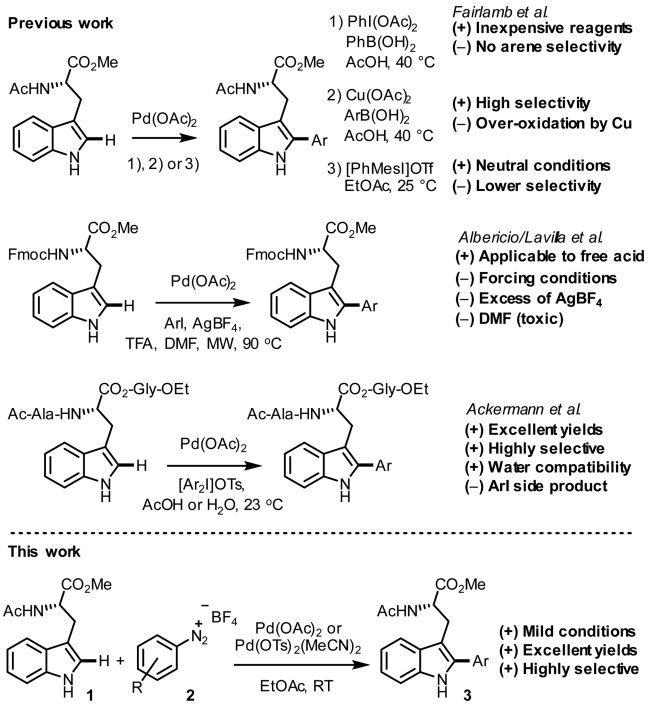
Scheme 1. Development of Conditions for the Direct C2-Arylation of Tryptophan Derivatives and Peptides (Selected Examples)



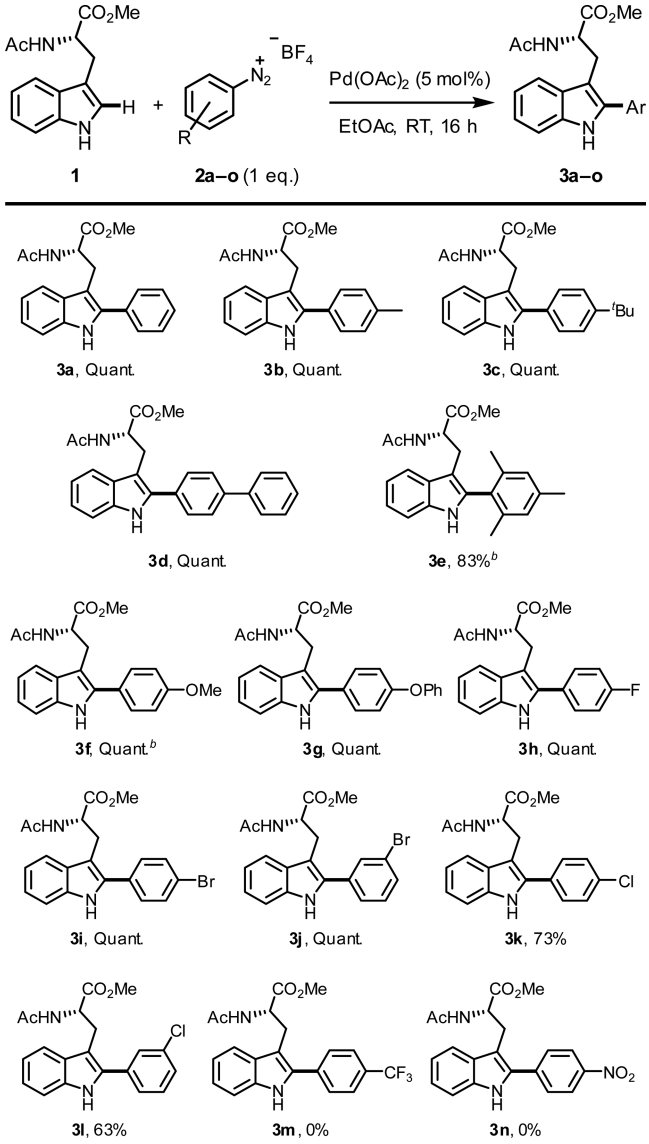
RESULTS AND DISCUSSION

The aryldiazonium salts employed within this study are readily available from the corresponding anilines by an oxidative process to generate the tetrafluoroborate salts in excellent yields (see the Supporting Information).[15] Treatment of protected tryptophan **1** with 1 equiv of $[PhN_2]BF_4$ (**2a**) in the presence of catalytic $Pd(OAc)_2$ in ethyl acetate gave the desired C2-arylation product **3a** in quantitative yield after 16 h at room temperature (ca. 20 °C). This synthetic protocol was then demonstrated on a series of substituted aryldiazonium salts, which are collated in Table 1.

Alkylated, electron-donating, and halide-containing examples provided good to excellent yields, while the sterically encumbered 2,4,6-trimethylphenyl salts also proved effective, giving **3e**. The quantitative synthesis of the biphenyl-substituted product **3d** provided access to a product exhibiting fluorescence at long-wave UV light (excitation at 365 nm), markedly distinct from that of the single-arene-containing examples or the parent compound **1**.[10] The tolerance of the synthetic protocol toward halogenated arenes provides a useful orthogonality to further functionalization to produce, for example, other biaryl derivatives (from **3h–l**). It is important to note that aryldiazonium salts containing strongly electron withdrawing substituents (**3m,n**) were not tolerated by this arylation protocol, an observation also made by Correia and co-workers,[14b] who described the formation of a diazo side product generated by the nucleophilic attack of a C2-arylated indole on electron-deficient aryldiazonium salts. These electron-deficient aromatic groups can be installed via the reported complementary conditions.[10]

Single-crystal X-ray diffraction structures of **3a,e,k** were obtained (see the Supporting Information); the absolute stereochemistry of **3k** was determined by the crystallographic analysis and the product confirmed as *S* (stereochemistry

Table 1. Scope of Aryldiazonium Tetrafluoroborate Salts for Direct Arylation of 1[a]



[a]All reactions conducted with **1** (0.192 mmol), **2** (0.192 mmol), $Pd(OAc)_2$ (5 mol %), and EtOAc (5 mL) at room temperature (ca. 20 °C). Reactions require $Pd(OAc)_2$ for effective product conversion. [b]Reaction time extended to 24 h.

identical with that of the L-tryptophan starting material **1**, confirming that no racemization takes place at the chiral center). In the examples where complete substrate conversion was recorded (i.e., **3a–d,f–j**), the desired arylation product could be isolated without the need for column chromatography, which provided a distinct practical benefit over the equivalent diaryliodonium salt methodologies, in addition to the selective formation of one arylation product. This advantage is reflected in the green reaction metrics calculated for both this and our previously published protocols (Table 2, conditions A–D),[10] determined by the CHEM21 green metrics toolkit.[16]

In addition to an increase in product yield and decrease in reaction temperature from the initial set of conditions, several key mass-based metrics have been improved upon. Conditions utilizing hypervalent iodine reagents (A and C) have noticeably lower values for atom economy (AE): i.e., the theoretical maximum efficiency for a particular transformation. While

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Table 2. Comparison of Mass-Based Metrics for Several Direct Arylation Conditions[a]

1 3a

	conditions, reagent			
	A, $PhI(OAc)_2/PhB(OH)_2$	B, $PhB(OH)_2$ with Cu^{II}	C, [PhMesI]OTf	D, $[PhN_2]BF_4$
yield/%	56	93	85	100
temp/°C	40	40	25	room temp (ca. 20)
solvent	AcOH	AcOH	EtOAc	EtOAc
AE	48	88	46	74
RME	16	62	24	74
OE	33	70	52	100
MI	6902	4139	4504	602

[a]Calculated using the CHEM21 unified metrics toolkit.[16] Abbreviations: RME, reaction mass efficiency; AE, atom economy; OE, optimum efficiency; MI, (total) mass intensity.

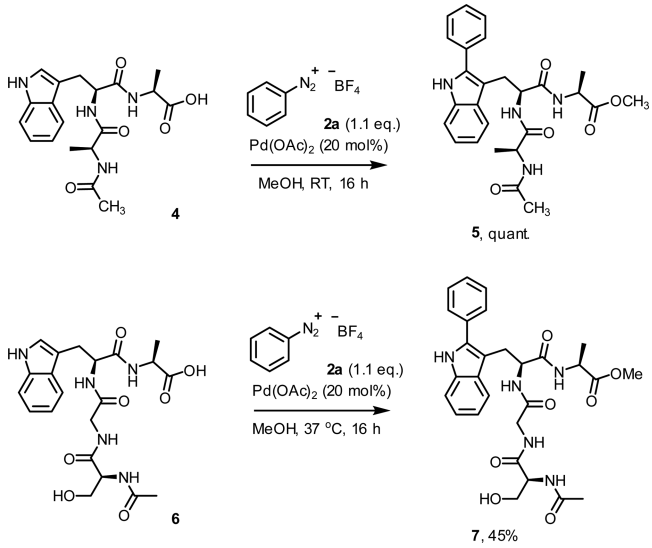
conditions B do not suffer from this, they do require the undesirable addition of a second transition metal (in addition to the drawbacks with certain peptides highlighted above). These trends are also observed for the reaction mass efficiency (RME), which incorporates yield and stoichiometry into the simpler AE calculation, thus giving a measure of the observed reaction efficiency, in comparison to the theoretical value provided by AE. This can be rationalized through use of the optimum efficiency metric, which directly correlates these two factors, highlighting this new process (conditions D) as the most atom and mass efficient overall.

The most striking improvement can be seen in the mass intensity (MI) value, which is an order of magnitude lower for conditions D in comparison to our initial conditions A. The primary reason for this dramatic increase is the removal of purification by column chromatography (silica gel), with other secondary effects including the number of equivalents of arylating agent used for each set of conditions (a full breakdown of the MI values can be found within the Supporting Information). Finally, switching the reaction solvent from neat acetic acid to the more benign ethyl acetate has a demonstrable health impact, as acetic acid has been ranked as a "problematic" reaction solvent by the recently published CHEM21 solvent selection guide[17] (ethyl acetate is ranked as "recommended").

Peptides (**4** and **6**) that had previously demonstrated oxidative sensitivity to Pd^0/Cu^{II}-mediated reaction conditions[10b] were subjected to the new synthetic protocol. The first arylation product **5** was isolated in excellent yield, with no evidence of undesired aromatic hydroxylation, seen when Cu^{II} was used (Scheme 2). A usable yield was recorded for **7** (45%). Note that, for these complicated polar molecules, methanol was used in place of ethyl acetate as the reaction solvent; the catalyst loading was increased, primarily to ensure quantitative conversion (thus, products **5** and **7** were isolated as the methyl esters). The $[\alpha]_D$ values for **5** and **7** were of magnitude similar to those of the peptide starting materials **4** and **6**, respectively, showing that their stereochemical integrity was preserved under the reaction conditions, in keeping with the previous arylations of **1**.

Preliminary mechanistic investigations for the arylation of tryptophan derivatives by aryldiazonium salts were conducted

Scheme 2. C2-Arylation of Two Selected Peptides with Aryldiazonium Salt 2a



to understand the behavior of the catalyst system. The C2-phenyl derivative **3a** possesses a bathochromic shift of 62 nm relative to **1**,[10a] enabling the kinetic profile of the arylation reaction to be examined by ex situ UV−visible spectroscopic analysis. The evolution of **3a** at 304 nm at 37 °C was monitored against time (Figure 1a), reaching completion within ca. 2 h. Product evolution exhibited a sigmoidal-like curve (Figure 1b), in addition to a significant induction period (ca. 1 h). Elimination of either substrate **1** or **2a** for the duration of the induction period produced kinetic profiles mirroring that found in Figure 1b, upon addition of all substrates. Thus, both substrates **1** and **2a** are required for the formation of the active catalyst.

Reported mechanistic work on the arylation of **3a** using conditions A indicated that palladium nanoparticles (PdNPs) were formed in operando,[10a] where stabilized Pd(PVP)NP (ca. 2 nm, PVP = polyvinylpyrrolidinone) was found to be a viable catalyst in this instance. It was postulated initially that the sigmoidal curve observed in the current system could be indicative of a quasi-heterogeneous process and autocatalysis.[18]

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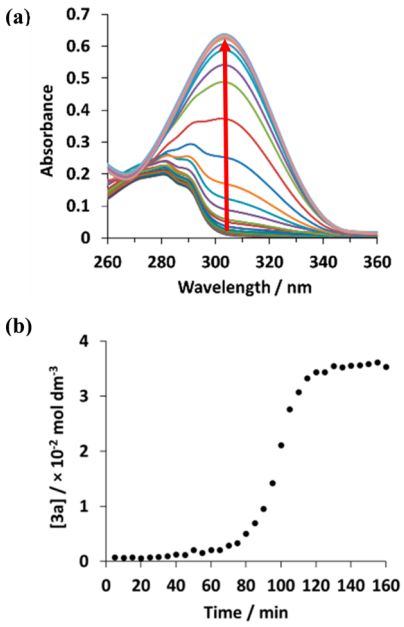

Figure 1. (a) UV−visible spectra showing formation of **3a** (ε = 17626 dm^3 mol^{-1} cm^{-1}) at 304 nm (between 5 min intervals) from reaction of **1** with **2a** at 37 °C. (b) Kinetic plot showing the evolution of **3a** over time (samples filtered through Celite; dilution ×10^4 in EtOAc for direct analysis by UV−vis). General procedure: **1** (1.92 × 10^{-4} mol, 1 equiv), $[PhN_2]BF_4$ (**2a**; 1.92 × 10^{-4} mol, 1 equiv), $Pd(OAc)_2$ (9.6 × 10^{-6} mol, 5 mol %) in EtOAc (5 mL); overall concentration in [**1**] = 0.0384 mol dm^{-3} and [Pd] = 0.00192 mol dm^{-3}. The water content in the EtOAc solvent was found to be ∼430 ppm (Karl Fischer titration).

Established tests[5] were therefore used to probe the catalytic behavior in our system (Figure 2a). Excess Hg (200 equiv) was added to the reaction mixture at 90 min (a well-known and widely applied heterogeneous catalyst poison), which had no effect on substrate turnover.[19,20] The outcome suggests that aggregated Pd nanoparticulate species are not required for substrate turnover to occur. Addition of polyvinylpyridine (PVPy, 200 equiv), thought to bind solubilized Pd^{II} ions,[21] to the reaction mixture during substrate turnover (at 90 min) caused cessation of substrate conversion (**1**). The result of this experiment gave the first indication that the reaction was likely operating in a homogeneous manner. Filtration of the reaction mixture through a preheated Celite pad ("hot filtration test" to remove insoluble Pd black), again applied during substrate turnover, similarly had no effect on substrate conversion (see the Supporting Information). Finally, ex situ TEM images (Figure 2b) of an aliquot taken from the reaction mixture during substrate turnover showed the presence of a few nanoparticles to the limit of detection (ca. 1 nm), which were not commensurate with PdNPs observed in other C−H functionalization reactions.[5,10a,19c] These findings, taken together, led us to question whether heterogeneous Pd species were playing a significant role in these tryptophan arylation reactions at all: that is, beyond the aggregated Pd contributing via an off-cycle catalyst reservoir or by a typical catalyst deactivation process.

The induction period observed in the reaction of **1** + **2a** → **3a** mediated by $Pd(OAc)_2$ suggested that other additives could influence this process. Following a screen of different acids, TsOH exhibited a profound positive effect, drastically reduced the previously observed induction period seen with $Pd(OAc)_2$ alone, and thus accelerated product conversion over time. This

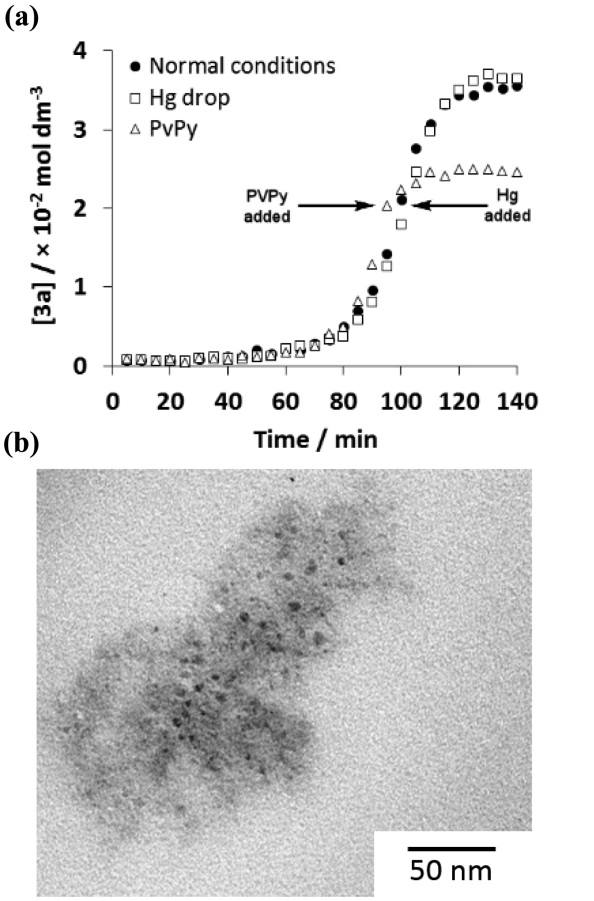

Figure 2. (a) Reaction profiles monitored by UV−vis spectroscopic analysis, where addition of catalyst poison/filtration occurred at 90 min. (b) Transmission electron microscopy (TEM) image of particles obtained from an aliquot of the reaction mixture at 90 min.

observation can be explained by formation of catalytically active "Pd−OTs" complexes in the reactions; indeed cyclopalladated tosylate Pd catalyst systems have been reported by both Brown[22] and Bedford.[23] Therefore, $Pd(OTs)_2(MeCN)_2$ was prepared and tested.[24] $Pd(OTs)_2(MeCN)_2$ (5 mol %) displayed the same accelerated reaction kinetic profile as that determined when $Pd(OAc)_2$ (5 mol %)/TsOH (5 mol %) was used (Figure 3).

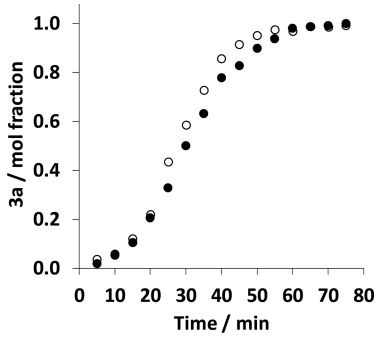

Figure 3. Formation of **3a** from reaction of **1** with **2a** mediated by either 5 mol % of $Pd(OAc)_2$ with 5 mol % of TsOH (open circles) or $Pd(OTs)_2(MeCN)_2$ (closed circles) at 37 °C. All data were obtained by ex situ UV−vis spectroscopic analysis.

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Equivalent yields of the substrates previously tested (Table 1) were found when 5 mol % of $Pd(OTs)_2(MeCN)_2$ was used in place of $Pd(OAc)_2$ (see the Supporting Information). Additionally, the catalyst loading of $Pd(OTs)_2(MeCN)_2$ could be decreased to 1 mol %, providing the C2-phenyl arylation product **3a** in quantitative yield after 16 h at ambient temperature (cf. 5 mol % when using $Pd(OAc)_2$, Table 1). We tentatively attribute the TsOH effect to more reactive Pd catalyst species, while acknowledging that tosylate anion can influence the reactivity and stability of the ArN_2^+ species.[25]

Finally, in our early screening studies we determined that the N-protecting group in **1** exerts a profound influence on arylation yield. For example, **1**, possessing a NHBoc group, gave arylated product with 53% conversion (by ^1H NMR), significantly lower than that when a NHAc group was employed (resulting in quantitative yield). In addition, employment of a NHTFA group in **1** appears to either deactivate or inhibit arylation completely, resulting in no arylation.

CONCLUSION

A high-yielding, mild, base-free, and regioselective Pd-mediated protocol for generation of 2-aryltryptophan derivatives, utilizing aryldiazonium salts, has been developed. This process offers a significant improvement over previously reported methods in terms of optimum efficiency, mass intensity, synthetic utility, and selectivity. The applicability of this procedure in the modification of two peptides, known to be susceptible to aromatic oxidation using Pd/Cu cocatalysis, has been demonstrated.

Preliminary mechanistic studies show that this reaction network is likely a complex, multistep reaction pathway. Tests for homogeneous/heterogeneous behavior, taken together, lead us to conclude that the reaction is most likely mediated by homogeneous Pd species. Aggregated PdNPs are formed under the reaction conditions, but during the latter stages of substrate turnover (confirmed by TEM measurements), most likely due to catalyst deactivation. Addition of TsOH considerably reduced the observed induction period. A lower catalyst loading could be used when the $Pd(OTs)_2(MeCN)_2$ catalyst was employed. Our research group is currently engaged in elucidating the mechanistic behavior of this and similar[14b,d] systems, in addition to expanding the methodology to peptide arylations (containing tryptophan).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b03121.

Experimental procedures, characterization data of all new compounds, and representative spectral data (PDF)

X-ray data for compound **3a** (CCDC no. 1053549), compound **3e** (CCDC no. 1053551), and compound **3k** (CCDC no. 1053550) (CIF)

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442−4489.

(2) Ronson, T. O.; Taylor, R. J. K.; Fairlamb, I. J. S. *Tetrahedron* **2015**, *71*, 989−1009.

(3) De Ornellas, S.; Williams, T. J.; Baumann, C. G.; Fairlamb, I. J. S. In *C−H and C−X Bond Functionalization: Transition Metal Mediation*; Ribas, X., Ed.; RSC Publishing: Cambridge, U.K., 2013; pp 409−407.

(4) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792−9826.

(5) Reay, A. J.; Fairlamb, I. J. S. *Chem. Commun.* **2015**, *51*, 16289−16307.

(6) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960−9009.

(7) Noisier, A. F. M.; Brimble, M. A. *Chem. Rev.* **2014**, *114*, 8775−8806.

(8) (a) Storr, T. E.; Firth, A. G.; Wilson, K.; Darley, K.; Baumann, C. G.; Fairlamb, I. J. S. *Tetrahedron* **2008**, *64*, 6125−6137. (b) Storr, T. E.; Baumann, C. G.; Thatcher, R. J.; De Ornellas, S.; Whitwood, A. C.; Fairlamb, I. J. S. *J. Org. Chem.* **2009**, *74*, 5810−5821. (c) Storr, T. E.; Strohmeier, J. A.; Baumann, C. G.; Fairlamb, I. J. S. *Chem. Commun.* **2010**, *46*, 6470−6472.

(9) (a) Ruiz-Rodríguez, J.; Albericio, F.; Lavilla, R. *Chem. - Eur. J.* **2010**, *16*, 1124−1127. (b) Preciado, S.; Mendive-Tapia, L.; Albericio, F.; Lavilla, R. *J. Org. Chem.* **2013**, *78*, 8129−8135. (c) Zhu, Y.; Bauer, M.; Ackermann, L. *Chem. - Eur. J.* **2015**, *21*, 9980−9983. For the postsynthetic direct C2-arylation of a tryptophan-containing natural product, see: (d) Preciado, S.; Mendive-Tapia, L.; Torres-García, C.; Zamudio-Vázquez, R.; Soto-Cerrato, V.; Pérez-Tomás, R.; Albericio, F.; Nicolás, E.; Lavilla, R. *MedChemComm* **2013**, *4*, 1171−1174. For a sophisticated Pd-mediated peptidic macrocyclization via an intramolecular C2-arylation of a tryptophan residue, see: (e) Dong, H.; Limberakis, C.; Liras, S.; Price, D.; James, K. *Chem. Commun.* **2012**, *48*, 11644−11646. An elegant preparation of stapled tryptophan−phenylalanine/tyrosine peptides via direct C2-functionalization can be found in: (f) Mendive-Tapia, L.; Preciado, S.; Garcia, J.; Ramon, R.; Kielland, N.; Albericio, F.; Lavilla, R. *Nat. Commun.* **2015**, *6*, 7160. For the direct C2-arylation of a protected tryptophan derivative using Ru, see: (g) Ackermann, L.; Lygin, A. V. *Org. Lett.* **2011**, *13*, 3332−3335. For the metal-free C2-arylation of C3-substituted indole derivatives on non-natural peptidic scaffolds using $[Ph_2I]^+$ salts, see: (h) Zhu, Y.; Bauer, M.; Ploog, J.; Ackermann, L. *Chem. - Eur. J.* **2014**, *20*, 13099−13102.

(10) (a) Williams, T. J.; Reay, A. J.; Whitwood, A. C.; Fairlamb, I. J. S. *Chem. Commun.* **2014**, *50*, 3052−3054. (b) Reay, A. J.; Williams, T. J.; Fairlamb, I. J. S. *Org. Biomol. Chem.* **2015**, *13*, 8298−8309.

(11) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972−4973.

(12) Bonin, H.; Fouquet, E.; Felpin, F.-X. *Adv. Synth. Catal.* **2011**, *353*, 3063−3084.

(13) For reviews, see: (a) Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. *Chem. Rev.* **2006**, *106*, 4622−4643. (b) Taylor, J. G.; Moro,

DOI: 10.1021/acscatal.6b03121
ACS Catal. 2017, 7, 5174−5179

A. V.; Correia, C. R. D. *Eur. J. Org. Chem.* **2011**, *2011*, 1403−1428. (c) Mo, F.; Dong, G.; Zhang, Y.; Wang, J. *Org. Biomol. Chem.* **2013**, *11*, 1582−1593. Cross-couplings of $[ArN_2]BF_4$ salts catalyzed by Pd nanoparticles have been reported. For Suzuki−Miyaura reactions, see: (d) Li, X.; Yan, X.-Y.; Chang, H.-H.; Wang, L.-C.; Zhang, Y.; Chen, W.-W.; Li, Y.-W.; Wei, W.-L. *Org. Biomol. Chem.* **2012**, *10*, 495−497. For Heck−Matsuda reactions, see: (e) Li, X.; Wang, L.-C.; Chang, H.-H.; Zhang, C.-X.; Wei, W.-L. *Appl. Catal., A* **2013**, *462*−*463*, 15−22. For Stille reactions, see: (f) Li, X.; Zhu, T.; Shao, Z.; Li, Y.; Chang, H.; Gao, W.; Zhang, Y.; Wei, W. *Tetrahedron* **2016**, *72*, 69−75.

(14) (a) Kalyani, D.; McMurtrey, K. B.; Neufeldt, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 18566−18569. (b) Biajoli, A. F. P.; da Penha, E. T.; Correia, C. R. D. *RSC Adv.* **2012**, *2*, 11930−11935. (c) Saini, V.; Liao, L.; Wang, Q.; Jana, R.; Sigman, M. S. *Org. Lett.* **2013**, *15*, 5008−5011. (d) Gemoets, H.; Kalvet, I.; Nyuchev, A.; Erdmann, N.; Hessel, V.; Schoenebeck, F.; Noel, T. *Chem. Sci.* **2017**, *8*, 1046−1055. For other key references on aryldiazonium salts, see: (e) Colas, C.; Goeldner, M. *Eur. J. Org. Chem.* **1999**, *1999*, 1357−1366. (f) Hopkinson, M. N.; Sahoo, B.; Li, J. L.; Glorius, F. *Chem. - Eur. J.* **2014**, *20*, 3874−3886. (g) Felpin, F. X.; Nassar-Hardy, L.; Le Callonnec, F.; Fouquet, E. *Tetrahedron* **2011**, *67*, 2815−2831. Most of our developmental work employing aryldiazonium salts as coupling partners for tryptophan derivatives is detailed in a Ph.D. thesis; see: (h) Reay, A. J. Ph.D. thesis, *Development of Pd-Catalysed C-H Bond Functionalisation Methodologies for the Accession of Molecular Complexity*; University of York (U.K.), May 2016. For a general book dedicated to metal-mediated reactions of aryldiazonium salts, see: (i) DeTar, D. F. *Organic Reactions* **2011**, *9*, 409−462.

(15) Matheis, C.; Jouvin, K.; Goossen, L. J. *Org. Lett.* **2014**, *16*, 5984−5987.

(16) McElroy, C. R.; Constantinou, A.; Jones, L. C.; Summerton, L.; Clark, J. H. *Green Chem.* **2015**, *17*, 3111−3121.

(17) Prat, D.; Wells, A.; Hayler, J.; Sneddon, H.; McElroy, C. R.; Abou-Shehada, S.; Dunn, P. J. *Green Chem.* **2016**, *18*, 288−296.

(18) (a) Crabtree, R. H. *Chem. Rev.* **2012**, *112*, 1536−1554. (b) Crabtree, R. H. *Chem. Rev.* **2015**, *115*, 127−150. (c) Mower, M. P.; Blackmond, D. G. *J. Am. Chem. Soc.* **2015**, *137*, 2386−2391.

(19) (a) Ellis, P. J.; Fairlamb, I. J. S.; Hackett, S. F. J.; Wilson, K.; Lee, A. F. *Angew. Chem., Int. Ed.* **2010**, *49*, 1820−1824. (b) Lee, A. F.; Ellis, P. J.; Fairlamb, I. J. S.; Wilson, K. *Dalton Trans.* **2010**, *39*, 10473−10482. For examples involving in situ generated PdNPs in C−H bond functionalization catalysis, see: (c) Baumann, C. G.; De Ornellas, S.; Reeds, J. P.; Storr, T. E.; Williams, T. J.; Fairlamb, I. J. S. *Tetrahedron* **2014**, *70*, 6174−6187. (d) Reay, A. J.; Neumann, L. K.; Fairlamb, I. J. S. *Synlett* **2016**, *27*, 1211−1216.

(20) Widegren, J. A.; Bennett, M. A.; Finke, R. G. *J. Am. Chem. Soc.* **2003**, *125*, 10301−10310.

(21) Yu, K.; Sommer, W.; Richardson, J. M.; Weck, M.; Jones, C. W. *Adv. Synth. Catal.* **2005**, *347*, 161−171.

(22) Rauf, W.; Thompson, A. L.; Brown, J. M. *Dalton Trans.* **2010**, *39*, 10414−10421.

(23) Bedford, R. B.; Haddow, M. F.; Mitchell, C. J.; Webster, R. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 5524−5527.

(24) Drent, E.; Van Broekhoven, J. A. M.; Doyle, M. J. *J. Organomet. Chem.* **1991**, *417*, 235−251. It is acknowledged that tosic acid and water could be working synergistically together; reactions mediated by $Pd(OAc)_2$ (i.e. $Pd_3(OAc)_6$) appear to be more sensitive to water concentration.

(25) Qiu, D.; Meng, H.; Jin, L.; Wang, S.; Tang, S.; Wang, X.; Mo, F.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 11581−11584.

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