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Synthesis of Indole-2-carboxylate Derivatives via Palladium-catalyzed Aerobic Amination of Aryl C–H Bonds

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Abstract

A direct oxidative C–H amination to 1-acetyl indole-carboxylates is achieved starting from 2-acetamido-3-aryl-acrylates. Indole-2-carboxylates can be targeted with a straightforward deacetylation of the initial reaction product. The C–H amination reaction is carried out using a catalytic Pd(II) source with oxygen as the terminal oxidant. The scope and application of this chemistry is demonstrated with good to high yields for numerous electron-rich and electron-poor substrates. Further reaction of select products via Suzuki arylation and deacetylation provides access to highly functionalized indole structures.

Graphical abstract

The construction of C–N bonds is of fundamental importance in the synthesis of biologically active organic molecules. Cross-coupling reactions between aryl halides and nitrogen nucleophiles in the presence of palladium catalysts (Buchwald-Hartwig coupling) provide an effective means for generating aryl C–N bonds.^{1,2} In the interest of streamlining the

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ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization data for all isolated compounds are available free of charge via the Internet at <http://pubs.acs.org>.

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synthesis of complex molecules, significant effort has been placed on the development of palladium-catalyzed methods for the generation of aryl C–N bonds by direct, oxidative functionalization of aryl C–H bonds.^{3,4} A challenge with these reactions is the ability to couple the palladium-mediated oxidative transformation of the substrate with atom-economically attractive molecular oxygen (O₂) as the terminal oxidant.

Prior studies in the development of palladium-catalyzed intramolecular aryl C–H aminations⁵ have uncovered methods for the synthesis of indazoles from aryl hydrazones,⁶ lactams from α -aryl-*N*-methoxyamides,⁷ benzimidazoles from *N*-phenylbenzimidamides,⁸ indolines from β -arylethylamines,^{9,10} indoles from α -aryl oxime acetates,¹¹ carbazoles from 2-aminobiphenyls,^{12,13} and, most recently, indoles from (*Z*)-NTs-dehydroamino acid esters using Oxone as oxidant.¹⁴ Notably, the only examples in which O₂ was used as the terminal oxidant is for carbazole synthesis, and a limited substrate scope was demonstrated under the reported conditions.^{12,13d}

Here, we report the discovery of a palladium-catalyzed aerobic amination of aryl C–H bonds for the synthesis of indole-2-carboxylate derivatives (Scheme 1). We envisioned that indole-2-carboxylates, which are useful building blocks in the synthesis of indole-containing bioactive molecules,¹⁵ could be derived from the intramolecular aryl C–H amination of 2-acetamido-3-aryl-acrylates. These substrates are particularly attractive because they are readily accessible from benzaldehyde derivatives and *N*-acetyl glycine via Erlenmeyer-Plöchl chemistry.¹⁶ This methodology has been used extensively in the synthesis of unnatural amino acids and is amenable to large-scale processes.¹⁷ Previous reports employing 2-acetamido-3-aryl-acrylate substrates under oxidative conditions have yielded oxazoles from alkene functionalization (Scheme 1, upper reaction pathway).^{18,19} In contrast, while 2-toluenesulfonamido-3-aryl-acrylates were shown to form indoles via palladium (II) catalysis with Oxone, the equivalent 2-acetamido substrates failed to do so.¹⁴ Here, we show that aryl C–H amination with the latter substrates proceeds with Pd(II) catalysis, and these are capable of using O₂ as the stoichiometric oxidant.

We initiated our study by testing ethyl 2-acetamido-3-phenyl-acrylate (Substrate **1a**) under the aerobic oxidation conditions reported by Buchwald for carbazole synthesis (Table 1, entry 1).¹² This catalyst system employed dimethyl-sulfoxide as solvent, allowing carbazole synthesis at high temperatures (120 °C) and reasonable yields for most substrates. Under these conditions substrate **1a** reacted to give a mixture of acetylated indole product **2a** and indole product **3a** in 45% total yield. In contrast to Buchwald's findings, lowering the temperature facilitated the C–H amination but not the deacetylation (entry 2). Introduction of toluene as co-solvent improved the yield of indole product **2a** to an extent (entries 3–6). Lowering the loading of palladium catalyst from 10 mol % to 7 mol % was tolerated, but the yield of indole began to drop at 5 mol % (Table 1, entries 8–9). Introduction of diacetoxyiodobenzene, a strong oxidant commonly employed to access Pd(IV) species,²⁰ resulted in complete decomposition of the substrate without formation of the desired indole product (Table 1, entry 11).

In a screen of various palladium (II) sources, Pd(OAc)₂ was revealed to be superior (see Supporting Information). In the absence of any palladium, no detectable product was

observed in the reaction mixture. Ligand additives that have been employed previously for C–H activation²¹ inhibited the conversion, while protic additives AcOH, PivOH or water, had little impact. With the optimized conditions for the unsubstituted arene, we analyzed the reaction conversion over the course of 24 h and identified the minimum reaction time to be 20 h.

With robust conditions for the aerobic intramolecular aryl C–H amination of substrate **1a** in hand (10 mol % Pd(OAc)₂, 24 h reaction time), we explored the scope of the reaction. In the absence of a nitrogen protecting group, 2-amino-3-phenylacrylate failed to undergo the C–H amination.²² *N*-Benzoyl and *N*-tosyl blocking groups were also tested. The *N*-benzoyl substituted system gave no desired product whereas the *N*-tosyl substrate resulted in decent conversion to the indole.²³ As we believed the *N*-acetyl group to be superior to *N*-tosyl in terms of ease of substrate preparation, yield, and cleavability, we decided to proceed with the former and vary the substitution on the arene.

We applied the conditions to a range of substrates as illustrated in Table 2. Initially, we observed that only methyl- and phenyl-substituted arenes gave reasonable conversions (entries 2–4 and 6–8) while both electron-withdrawing and donating groups were poorly tolerated. Resubjecting the challenging substrates to higher temperatures, however, led to a marked increase in yield (entries 5, 10, 11, and 15). The reason for this improvement is not presently understood though it may be attributed to a higher energy barrier for palladium-mediated C–H activation. Most meta-substituted substrates led to the corresponding 5-substituted indole products based on steric control (entries 3, 7, 12, and 15), while 2-naphthyl- and *m*-fluoro-substituted substrates led to mixtures of isomers, as indicated in entries 5 and 10.

We then tested the reaction tolerance further by exploring more complex substrates, including ones with a distal heterocycle and a halogen substituent. While the initial result for the 5-pyrimidyl substrate was low (18% NMR yield), running the reaction at higher temperature gave an improved yield (Table 2, entry 16). This successful result indicated that certain heterocycles should be tolerated in the C–H amination to support convergent approaches to indoles via this methodology. With ethyl 2-acetamido-3-(4-chlorophenyl)-acrylate, the original temperature (80 °C) balanced C–H amination with subsequent deacetylation (entry 17). Interestingly, no dechlorination was observed in the reaction, enabling subsequent functionalization to access diverse indole structures from a common intermediate.

With the 1-acetyl-6-chloro-indole-2-carboxylate **2q** in hand, we then tested the compatibility of the compound in various C–C cross-coupling reactions, as conditions that utilize indoles as the electrophilic coupling partner are uncommon.²⁴ The strongly basic conditions of Negishi and Kumada-type reactions cleaved the *N*-acetyl and afforded none of the desired product above trace quantities (data not shown). In contrast, certain Suzuki cross-coupling conditions were effective and delivered the desired ethyl 6-phenyl-1H-indole-2-carboxylate **3f** from cross-coupling and deacetylation in a single pot (Table 3, entry 1).²⁵ We tested three more boronic acid coupling partners **4r** – **t** to challenge what the acetyl protecting group could tolerate (entries 2–4). A phenolic partner **4r** was completely incompatible, and a 5-

aminopyrimidyl reagent **4s** gave low yield of the desired product **3s**. On the other hand, the fluoropyridyl boronic acid **4t** was more effective in the one-pot Suzuki / deacetylation, giving access to important structures related to those under investigation for metabolic disorders.²⁶

Previous studies^{12,13} provide the basis for a plausible mechanism for the Pd-catalyzed oxidative cyclization reaction to indoles (Scheme 2). The substrate acetamide can undergo metathesis with an acetate ligand to afford a Pd(II)–amidate species that can metalate the arene to afford the chelated Pd(II)–(aryl)(amidate) species. Subsequent C–N reductive elimination can afford the indole product and a ligated Pd(0) species capable of undergoing oxidation by O₂ to regenerate catalytic Pd(OAc)₂. Previous studies of Pd-catalyzed aerobic oxidation reactions in DMSO provided evidence for the involvement of both molecular and nanoparticle catalysis.²⁷ Presently available data cannot distinguish between these two possibilities, but this issue warrants attention in future studies.

In summary, we have identified an aerobic palladium-catalyzed aryl C–H amination strategy for the synthesis of indole-2-carboxylates from 2-acetamido-3-aryl-acrylates with application to a diverse set of substrates. Notably, the mild and selective conditions tolerated electron-rich and electron-poor substrates, chlorinated arenes, and a heteroaromatic-substituted example. The chlorinated arenes also allow for direct Suzuki cross-coupling following indole formation, allowing one to side-step the N–H deprotection step prior to the coupling reaction. Moreover, the halogen substitution also holds promise as a handle for introduction of boronic acid and boronate ester equivalents, and rapid access to these types of indole building blocks. Our methodology complements existing approaches to indoles and should allow for expedited installation of the heterocycle onto bioactive molecules.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

Selective oxidative intramolecular C-H functionalization reactions with 2-acetamido-3-arylacrylates.

Scheme 2.

Simplified catalytic mechanism for Pd-catalyzed oxidative cyclization of 2-acetamido-3-aryl-acrylates.

Table 1

Initial investigation of intramolecular aerobic C–H amination of ethyl 2-acetamido-3-phenyl-acrylate.

X mol % Pd(OAc) ₂ 86 wt % 3 Å MS 1 atm O ₂				DMSO-d ₆ / toluene-d ₈ 0.1 M, temp (°C), 24 h			
1a (0.1 mmol)				¹H NMR yield,^a			
mol % Pd(OAc) ₂				%			
entry	DMSO:Tol		temp (°C)	%1a	%2a	%3a	
1	10	1:0	120	45	23	22	
2	10	1:0	80	16	61	23	
3	10	3:1	80	10	69	21	
4	10	1:1	80	2	77	15	
5	10	1:3	80	2	80	12	
6	10	1:9	80	31	50	13	
7	10	0:1	80	80	1	0	
8	7	1:1	80	5	85	10	
9	5	1:1	80	35	60	5	
10 ^b	7	1:1	80	49	36	12	
11 ^c	7	1:1	80	0	0	0	

^a¹H NMR yields relative to PhTMS added at the end of the reaction.

^b without 3 Å MS.

^c with 2 equiv PhI(OAc)₂.

Table 2

Evaluation of substrate scope in intramolecular C–H amination of ethyl 2-acetamido-3-aryl-acrylates.

		1. 10 mol % Pd(OAc) ₂ 86 wt % 3 Å MS, 1 atm O ₂ DMSO-d ₆ / toluene-d ₈ 80 - 120 °C, 24 h optional step to compounds C: 2. 2 equiv K ₂ CO ₃ 8 equiv water 90 °C, 16 h

entry	substrate (R)	temp (°C)	%1	%2	^a ¹ H NMR yield, %		isol. yield		
1	1a (H)	80	0	100			95		
2	1b (p-Me)	80	0	94			67 ^b		
3	1c (m-Me)	100	0	89			77		
4	1d (o-Me)	80	0	92			85		
5 ^c	1e (2-Naph)	100	25	77 (2:1)			62 (5:3)		
6	1f (p-Ph)	80	11	83			86		
7	1g (m-Ph)	80	0	88			80 ^b		
8	1h (o-Ph)	80	0	90			87		
9	1i (p-F)	80	31	65			56		
10 ^{c,d}	1j (m-F)	120	7	80 (3:2)			83 (4:3) ^b		
11	1k (p-CF ₃)	100	39	45			45 ^b		
12	1l (m-CF ₃)	80	48	38			36 ^b		
13	1m (p-NMe ₂)	80	29	57			50		
14	1n (p-OMe)	80	14	72			59 ^b		
15	1o (m-OMe)	100	0	89			66 ^b		
16	1p (p-5-Pyr) ^e	100	29	69			59		
17	1q (p-Cl)	80	30	69			63 ^b		

^a¹H NMR yields relative to PhTMS added at the end of the reaction time. Unless otherwise indicated, only 5-substituted indole products were observed from meta-substituted substrates.

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^b Products isolated as N-H indoles following optional deacetylation as indicated in graphic.

^c Ratio refers to regioisomeric mixture of products, with least sterically-demanding product predominating in each case.

^d Reaction run in 1:1 DMSO-d₆ / p-xylene-d₁₀.

^e p-5-Pyr refers to 5-pyrimidyl substituted in the para position of the substrate.

Table 3

Evaluation of Suzuki coupling with ethyl 1-acetyl-6-chloro-indole-2-carboxylate.

entry	boronic acid	solvent	HPLC A%		
			2q	3q	3 X
1	4f	5:1 dioxane/H ₂ O	2	0	76
2	4r	1:2 dioxane/H ₂ O	1	77	0
3	4s	1:2 dioxane/H ₂ O	0	73	17
4 ^a	4t	1:4 dioxane/H ₂ O	0	0	86 ^b

^a Reaction run with 4.2 equiv K₃PO₄·H₂O.^b Isolated yield of **3t** of 80% following chromatography.