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Catalytic α-Hydroarylation of Acrylates and Acrylamides via an Interrupted Hydrodehalogenation Reaction

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ABSTRACT: The palladium-catalyzed, α-selective hydroarylation of acrylates and acrylamides is reported. Under optimized conditions, this method is highly tolerant of a wide range of substrates including those with base sensitive functional groups and/or multiple enolizable carbonyl groups. A detailed mechanistic study was undertaken, and the high selectivity of this transformation was shown to be enabled by the formation of an [Pd^{II}(Ar)(H)] intermediate, which performs selective hydride insertion into the β-position of α,β-unsaturated carbonyl compounds.

INTRODUCTION. α-Arylated carbonyl compounds are ubiquitous substructures in organic synthesis, and the diverse bioactivity of such molecules is exemplified by familiar blockbuster drugs, such as Naproxen and Ibuprofen. Traditionally, this structural motif can be prepared using Pd(0)-catalyzed α-arylation of enolates, as pioneered by Buchwald and Hartwig (Figure 1A).[1,2] In these systems the reactive nucleophile is generated via *in situ* deprotonation of carbonyl compounds with strong base or via pre-formation of the corresponding silyl enol ether. Alternatively, cross-coupling-based methods from the corresponding α-halocarbonyl electrophiles have also been described under nickel or palladium catalysis (Figure 1B).[1,3]

While these methods are highly enabling and can even be performed in an enantioselective fashion through use of an appropriate chiral ligand, they possess inherent limitations. For example, in enolate α-arylation, strong bases such as NaO*t*Bu and LiTMP are required, which can preclude the use of certain functional groups, such as those with racemizable stereocenters, and can introduce site selectivity issues in compounds possessing multiple carbonyl groups. In the case of cross-coupling methodology, the α-halo carbonyl electrophiles must be pre-synthesized and are not always stable. To address these issues, we envisioned an alternative disconnection where the aryl group is installed at the α-position via a palladium-catalyzed hydroarylation reaction of α,β-unsaturated carbonyl compounds.

At the outset we recognized that the envisioned mode of regioselectivity is opposite to what has previously been documented in reductive Heck systems that proceed via a canonical mechanism involving: oxidative addition of [Pd(0)] to the aryl (pseudo)halide to furnish a [Pd^{II}(Ar)(X)] intermediate, coordination of the alkene substrate, 1,2-migratory insertion to deliver the aryl moiety to the partially positively charged β-position, and interception of the [Pd^{II}(enolate)] with a hydride source.[4,5] We imagined that under appropriate conditions, this process could take place in a polarity-inverted fashion via a [Pd^{II}(Ar)(H)] species that would undergo hydride insertion into the β-position to access a [Pd^{II}(Ar)(enolate)] intermediate that is analogous to that of typical enolate α-arylation methodology (Figure 1C).

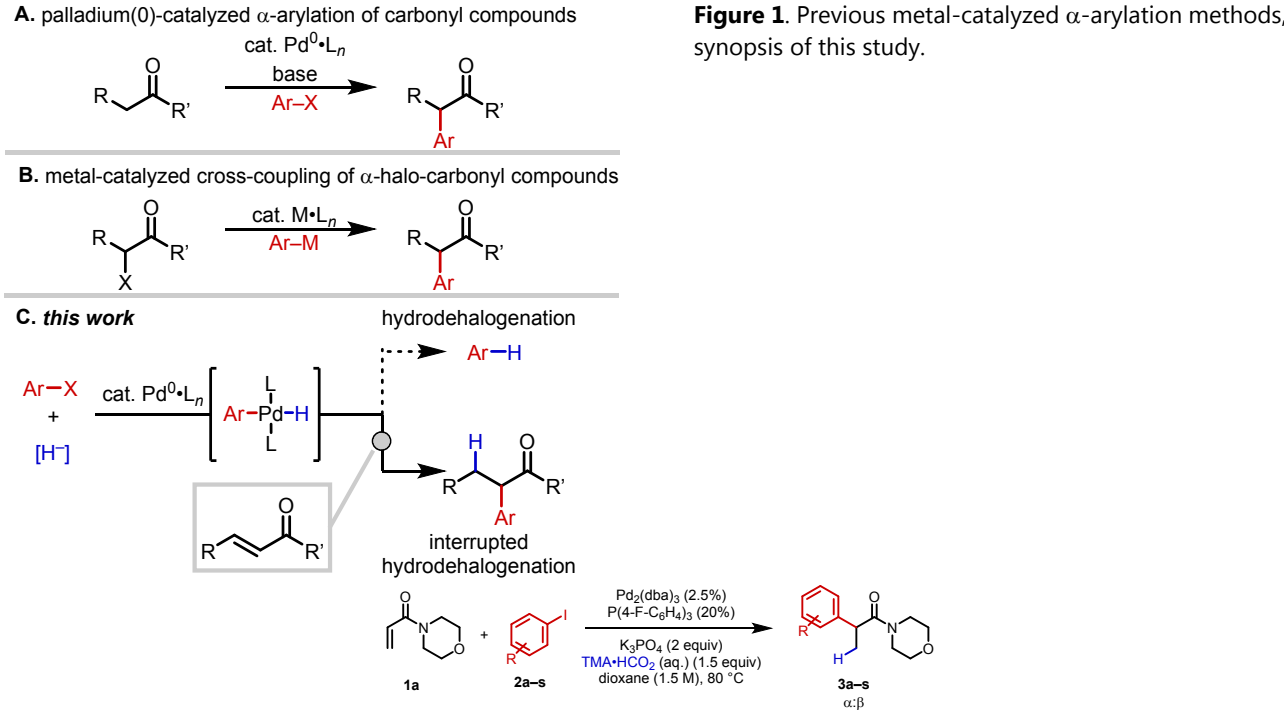


Figure 1. Previous metal-catalyzed α-arylation methods, and synopsis of this study.

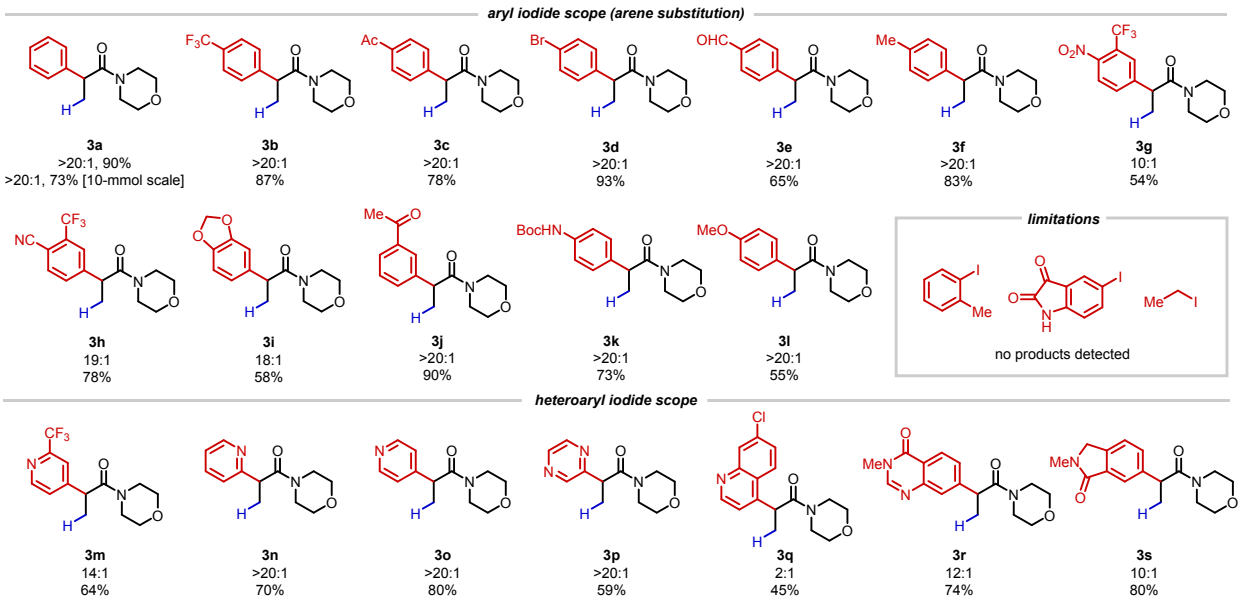


Figure 2. Aryl iodide scope. Conditions: **1a** (0.20 mmol), **2** (0.24 mmol), $Pd_2(dba)_3$ (0.005 mmol), $P(4\text{-F-}C_6H_5)_3$ (0.040 mmol), tripotassium phosphate (0.40 mmol), 30% aq. TMA•HCO_2 (0.30 mmol, 0.100 mL), and dioxane (0.133 mL), 80 °C, 4–12 h. Ratios of α:β were determined via ^{1}H NMR (600 MHz) of the crude reaction mixture. Percentages represent isolated yields of the α-arylated product.

[Pd^{II}(Ar)(H)] species and progenitor complexes, such as [Pd^{II}(Ar)(formate)], have been synthesized and studied in pioneering work by Alper and have been widely invoked as intermediates in palladium-catalyzed hydrodehalogenation chemistry.[6,7] Though at first glance it would seem that these intermediates would be prone to immediate Ar–H reductive elimination, a growing body of literature has invoked [M(R)(H)] (R = alkyl or aryl), accessed via C–H oxidative, or less commonly O–H oxidative addition, followed by transmetalation, as key intermediates in alkene addition processes (Figure **1c**).[8,9]

Herein, we describe the successful realization of the blueprint described above, wherein [Pd^{II}(Ar)(H)] intermediates are leveraged for alkene additions. This hydroarylation chemistry represents a mild and operationally convenient strategy to form α-arylated products under ambient atmosphere, with water as a co-solvent, using common and commercially available starting materials.

OPTIMIZATION AND SCOPE. The study began by attempting to optimize the reaction conditions with **1a** and **2a** as pilot substrates to provide **3a** as the product (see Table S1). We found that optimal conditions for hydroarylation were as follows: 2.5% $Pd_2(dba)_3$, 20% tris(4-fluorophenyl)phosphane ligand, 2 equiv K_3PO_4, and 1.5 equiv 30% aqueous tetramethylammonium formate (TMA•HCO_2), in dioxane at 80 °C. Under these conditions, >20:1 α:β selectivity was observed, and **3a** could be prepared in 90% yield on 0.2 mmol scale and 73% on 10 mmol scale. To summarize key observations, the solubility of the formate salt is critical for maintaining high selectivity for the desired α-hydroarylated product. Formate sources with metallic counterions were inferior to tetramethylammonium, even when used with a phase transfer catalyst, likely due to reduced solubility. Under optimal conditions, the major byproduct arises from reduction of the alkene.

An excess of ligand is necessary for high selectivity observed; with ligand-to-palladium ratios of <2:1, high amounts of β-arylated products were observed (see Figure S11). The origin of this phenomenon could be premature coordination of the alkene to the *trans*-L_n•Pd^{II}(Ar)(I) intermediate, leading to classical polarity Heck-type products. Chelating bidentate phosphine ligands, which could potentially function in their native form or as the monophosphine/monophosphine-oxide,[10] are low yielding due to being both *cis*-coordinating and sterically demanding (see Table S1). We believe that the ligand needs to be of sufficient coordination strength to prevent premature alkene coordination but also labile enough to dissociate in downstream steps. The 4-fluoro-substituent on the triarylphosphine serves to tune the electronic properties of phosphorous to provide this balance in coordination strength, while also being sterically unobtrusive to allow formate to adopt an η^3 configuration in the 5-coordinate decarboxylation transition state.[6]

We next tested the scope and functional group tolerance. Electron-donating and -withdrawing substituents on the aryl iodide were tolerated in the reaction, with electron-withdrawing groups giving consistently higher yields (Figure 2). The reaction is sensitive to steric hindrance, with 2-substituted aryl iodides giving little to no conversion. The reaction is tolerant of heterocycles (**3m-s**), protected amines (**3k**), and alcohols (**3i**, **3l**). Moreover, potentially reductively labile groups, including an unprotected aldehyde (**3e**), a nitro group (**3g**) a nitrile (**3h**), and an unprotected ketone (**3j**), remained intact. Complete selectivity was observed in coupling partners bearing both a br mide and iodide (**3d**). Next, the reaction was evaluated with different acrylamides and acrylates (Figure 3). The amount of

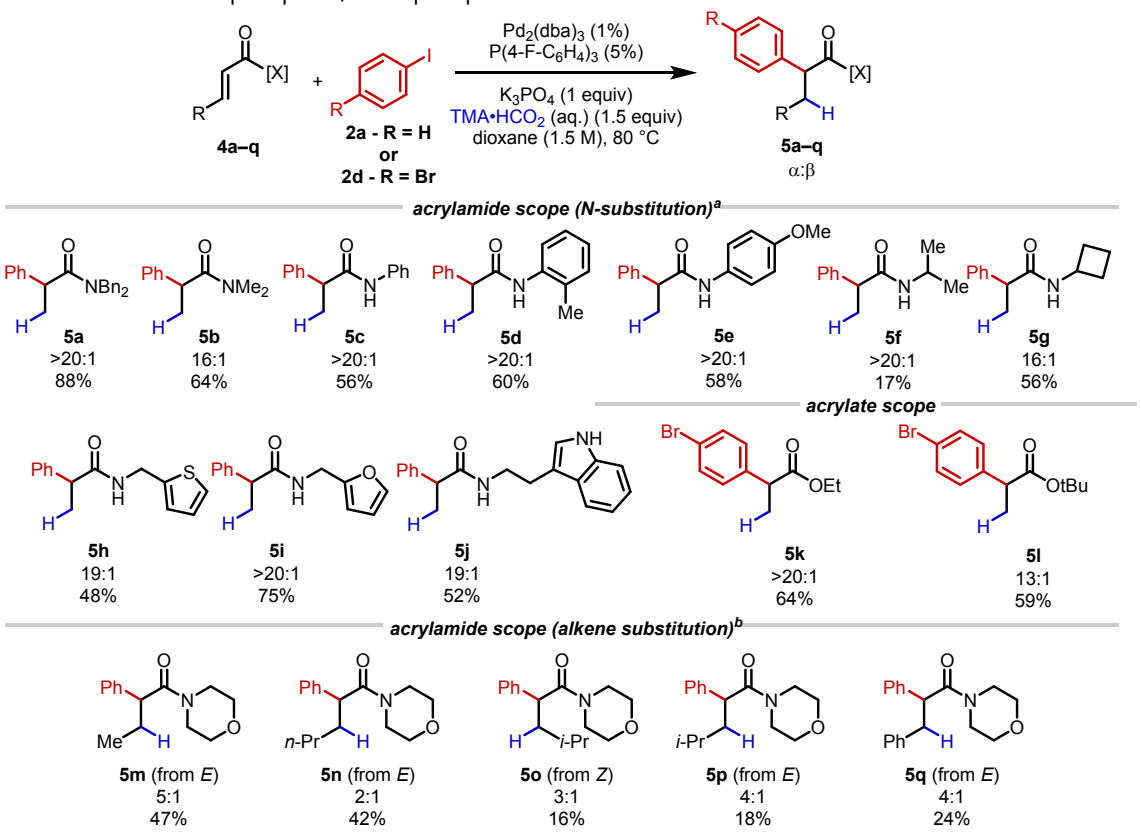


Figure 3. Acrylamide and Acrylate Scope. [a] Conditions: **4a-l** (0.20 mmol), **2a or 2d** (0.24 mmol), $Pd_2(dba)_3$ (0.002 mmol), tris(4-fluorophenyl)phosphane (0.010 mmol), tripotassium phosphate (0.20 mmol), 30% aq. TMA•HCO_2 (0.30 mmol, 0.100 mL), 1,4-dioxane (0.133 mL), 80 °C, 4-12 h. [b] Conditions: **4n-q** (0.20 mmol), **2a** (0.24 mmol), $Pd_2(dba)_3$ (0.005 mmol), tris(4-fluorophenyl)phosphane (0.050 mmol), tripotassium phosphate (0.40 mmol), TMA•HCO_2 (0.30 mmol, 0.100 mL), and 1,4-dioxane

(0.133 mL), 100 °C, 24 h. Ratios of α:β were determined via ^{1}H NMR (600 MHz) of the crude reaction mixture. Percentages represent isolated yields of the α-arylated product.

base is critical to the success of these substrates and the reaction was performed with 1% $Pd_2(dba)_3$, 5% ligand, and 1 equivalent K_3PO_4. The reaction performs well with secondary and tertiary amides, tolerating a wide range of heterocycles. The reaction is limited to either monodentate or weakly bidentate amides as no reaction is seen with strongly chelating groups such as 8-aminoquinoline (see Figure S3 for additional limitations). The reaction is also highly compatible with acrylates (**5k**–**5l**), presumably because the pK_a of the putative enolate is in a similar range to that of the acrylamide substrates.

The reaction is not limited to terminal olefin substrates and works with a range of 1,2-disubstituted olefins, albeit with lower conversion. The reaction is compatible with both *Z*- and *E*-α,β-unsaturated amides, furnishing the corresponding products in moderate yields and selectivity (**5m-q**). We believe that mechanistically, hydride and aryl are inserted-*syn* to one another. Therefore, if the product formed was diastereomeric, opposite diastereoselectivity would be observed for *E* and *Z* alkene isomers.

To highlight the mild and chemoselective nature of this method, a racemization experiment was performed with amino acid **9.** When subjected to the reaction conditions, no loss of enantiomeric excess (*ee*) was detected (Figure **4**). In addition, substrates **4r** and **4s** were subjected to the reaction conditions and only the hydroarylated products **5r**/**5s** were formed. The potential Buchwald–Hartwig α-arylated byproduct was not

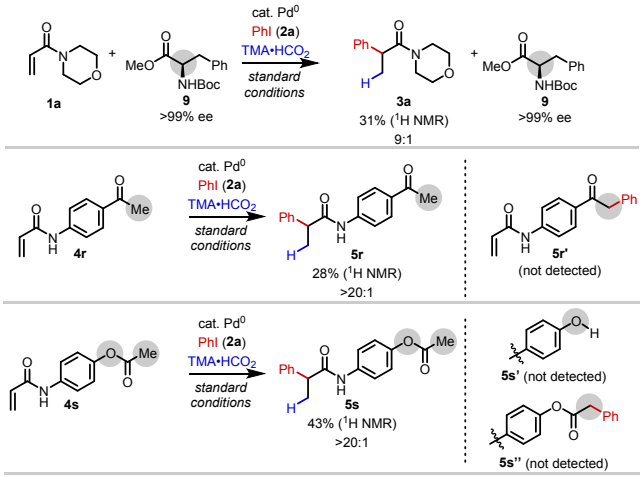


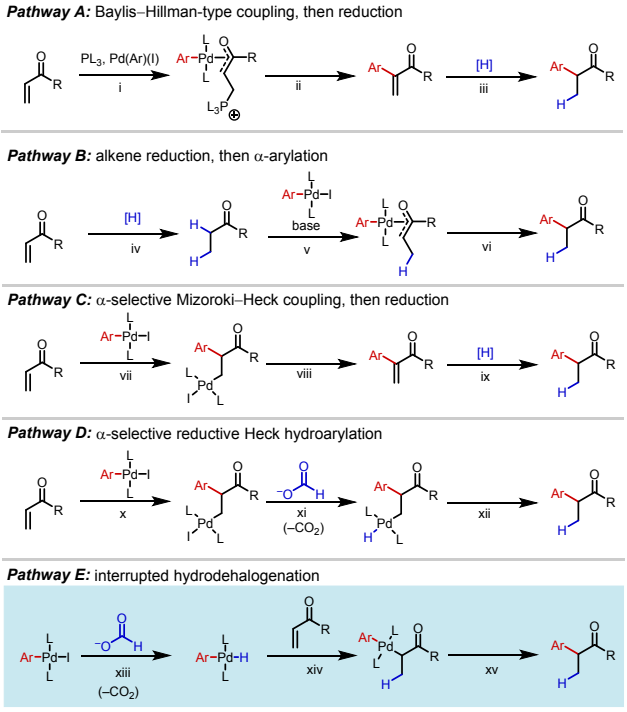
Figure 4. Examples demonstrating chemoselectivity and functional group compatibility.

detected, showing that it is possible to selectively functionalize one α-carbon over another. In addition, the acetate protecting group, which is labile under basic conditions, was not removed showing this method to have high functional group tolerance. The observed functional group tolerance suggests that this method could be employed in the synthesis of increasingly complex targets, such as millamolecular peptides or bifunctional molecules.

MECHANISTIC STUDIES. The unusual selectivity of this transformation prompted us to examine the underlying reaction mechanism. We considered four potential pathways (Scheme **1**). Pathway A involves a Baylis–Hillman-type mechanism where excess phosphine in solution performs 1,4-addition to access a zwitterion that binds the oxidative addition complex [Pd^{II}(Ar)(I)] (step i). Reductive elimination followed by β-phosphine elimination then delivers an α-arylated α,β-unsaturated intermediate (step ii). Reduction of this alkene intermediate furnishes the α-arylated product (step iii). In Pathway B, the alkene is first reduced to the corresponding aliphatic amide (step iv) and then undergoes Buchwald–Hartwig α-arylation to forge the key C(α)–Ar bond via a mechanism of enolate formation, complexation with [Pd^{II}(Ar)(I)] (step v), and subsequent reductive elimination (step vi).

The third possibility (Pathway C) involves aryl insertion into the α-position of the alkene (step vii), the resulting [Pd^{II}(1°-alkyl)(I)] complex β-hydride eliminate (step viii) in a classical Mizoroki–Heck mechanism. The resulting alkene can be reduced to generate the α-arylated product (step ix). Alternatively, in a reductive Heck mechanism (Pathway D), the resulting [Pd^{II}(1°-alkyl)(I)] can ligand exchange iodide for formate which can undergo decarboxylation to provide a [Pd^{II}(1°-alkyl)(H)] complex (step xi). This can perform reductive elimination to provide the α-arylated product (step xii).

Scheme 1. Possible mechanistic pathways



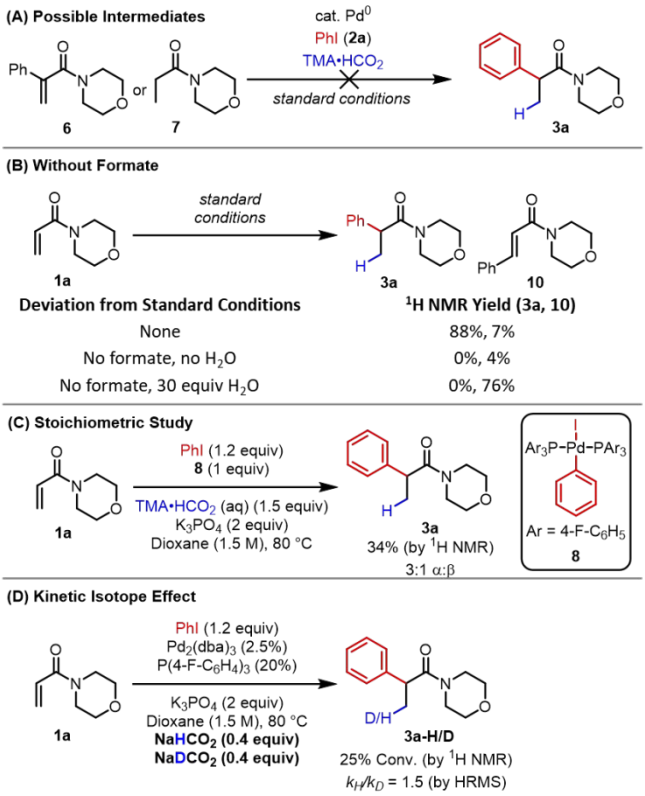
At the outset, Pathways C and D seemed unlikely given that it would involve the opposite regioselectivity in the migratory insertion step than what has been previously reported on

Heck-coupling of α,β-unsaturated amides, esters, and ketones. In fact, during Minnaard, de Vries, and Reek's study of reductive Heck hydroarylation of enones, which uses Hünig's base as the source of hydride and NHC as choice of ligand, only β-arylated products were observed.[11] This suggests formate may be involved in selectivity determination for α- versus β-hydroarylation and could be consistent with Pathway E, but not with C or D. Although α-selectivity has been observed in intramolecular cyclizations, this has not been previously documented in intermolecular systems.[12]

Next, we considered an interrupted hydrodehalogenation paradigm (Pathway E). In this pathway, the [Pd^{II}(Ar)(I)] complex exchanges iodide for formate and undergo decarboxylation to furnish a [Pd^{II}(Ar)(H)] complex (step xiii). This high reactive species can insert hydride into the β-position of the alkene (step xiv). The resulting [Pd^{II}(Ar)(enolate)] can undergo reductive elimination to provide the α-arylated product (step xv).

In an initial control experiment, we found that reaction proceeds in the presence of elemental mercury, albeit in lower conversion, ruling out the possibility of palladium nanoparticle catalysis, supporting a homogenous process as in Pathways A–E. To probe the feasibility of Pathways A, B, and C, the putative α-arylated acrylamide (**6**) and reduced amide (**7**) intermediates were subjected to the reaction conditions, and no reaction took place in either case, establishing that pathways involving Baylis–Hillman-type coupling or Mizoroki–Heck arylation followed by reduction, and reduction followed by Buchwald–Hartwig-type α-arylation are not viable mechanisms in this catalytic system (Scheme **2A**). Having quickly ruled out these mechanistic pathways, we set our attention to differentiating between the reductive Heck and interrupted hydrodehalogenation pathways (Pathways D and E).

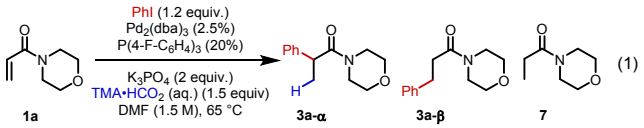
Scheme 2. Control experiments



In an effort to disambiguate between Pathways D and E experimentally, we performed the reaction under standard conditions without formate. We found that without the addition of formate, the only observable product is the classical β-Mizoroki–Heck product **10** (Scheme **2B**). When independently prepared *trans*-Pd^{II}(Ar)(I)(PAr_3)$_2$ complex **8** was subjected to the standard reaction conditions, a 3:1 (α:β) mixture was observed, along with 24% Mizoroki–Heck byproduct, which is typically not detectable under catalytic conditions (Scheme **2C**). This result suggests that high concentrations of Pd^{II}(Ar)(I) promote traditional Mizoroki–Heck pathways. The data from a competition kinetic isotope effect experiment using equal parts sodium formate and d_1-sodium formate (k_H/k_D = 1.5), is consistent with formate being involved in the product-determining step (Scheme **2D**).[13] In addition, in the examples shown in Figures 2 and 3, hydrodehalogenated byproducts (Ar–H) are commonly observed in the ^{1}H NMR spectra of crude reaction mixtures. The products likely arise from reductive elimination from a [Pd^{II}(Ar)(H)] species, suggesting that this intermediate is generated under the reaction conditions (see Figure **S7** for crude NMR of **3q**). Collectively, these results are inconsistent with Pathway D.

Having established that the general reactivity paradigm of Pathway E is operative, we next sought to gain insight into the details of the catalytic process through reaction progress kinetic analysis (RPKA).[14] Due to the biphasic, heterogeneous reaction system with dioxane as solvent, reaction kinetics were performed in DMF, which gives a homogenous mixture and leads to similar yields and selectivity (see SI). In DMF at 80 °C, the reaction proceeds to completion in four minutes,

so the kinetics were performed at 65 °C to extend the reaction time for ease of sampling (Eq. 1).

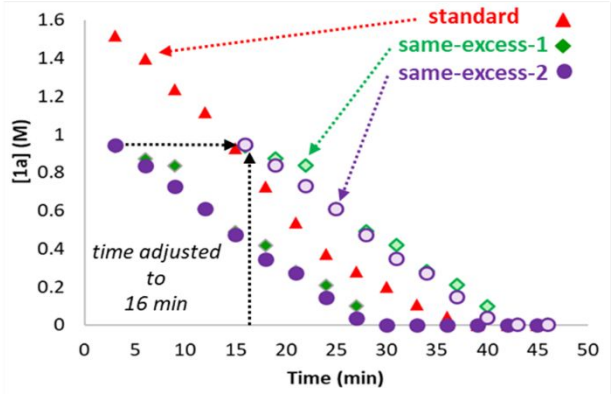


(1)

In terms of general features, the reaction exhibits a short induction period (~2 min). A same-excess experiment showed that the rate of starting material consumption accelerates over time; addition of product did not influence this rate. Though at first glance, this would appear to signal catalyst activation (Figure **5a**), when one tracks formation of **3a-α** and byproducts over the course of the reaction, it is evident that reduced byproduct **7** does not start forming until approximately 40% conversion. Since the rate of **3a-α** formation does not change over the course of the reaction, the increased production of **7** accounts for the change in rate of starting material consumption (See Figure S10), suggesting that it is a secondary process not directly related to the main catalytic cycle. With this in mind, we focused the remainder of the analysis on the early portion of the reaction, before secondary processes predominate since they are more likely to reflect the intrinsic kinetics.

A series of different-excess experiment were next performed. The order in palladium was determined by measuring initial rates with varying palladium concentrations. A linear fit when plotting the rate of product formation vs palladium concentration showed first order dependence in catalyst. The reaction was also shown to have apparent overall zero-order kinetics although the rate is influenced positively by the concentration of formate and negatively by the concentration of alkene (Figure **5B**).

A	[1a]	[2a]	[TMAHCO$_2$]	[3a]
standard	1.50 M	1.81 M	2.88 M	0 M
same-excess 1	0.98 M	1.35 M	2.13 M	0 M
same-excess 2	0.98 M	1.35 M	2.13 M	0.52 M



B	[1a]	[2a]	[TMAHCO$_2$]	[3a]
standard	1.30 M	1.56 M	2.88 M	0 M
diff.-excess 1	1.30 M	1.56 M	**1.44 M**	0 M
diff.-excess 2	**2.60 M**	1.56 M	2.88 M	0 M
diff.-excess 3	1.30 M	**3.12 M**	2.88 M	0 M

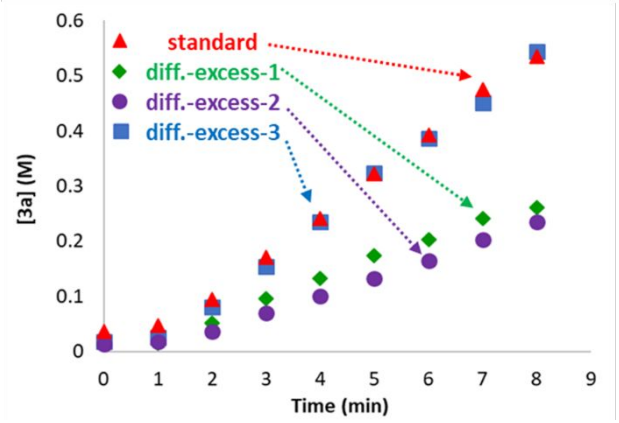
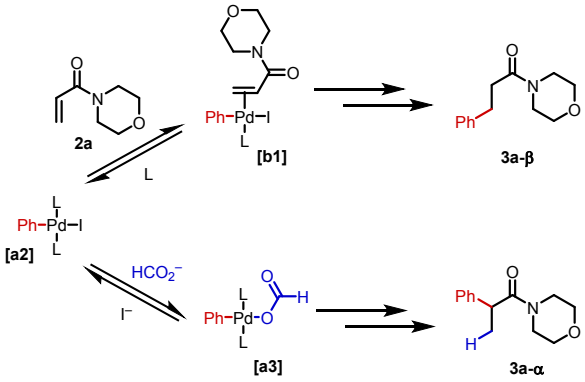


Figure 5. (A) Same excess experiment for reaction shown in eq. 1. (B) Different excess experiments of the reaction shown in eq. 1

This could be explained by the situation represented in eq. 2, where high concentrations of formate drive the equilibrium to favor formation of the on-cycle palladium-formate complex **[a3]** and high concentrations of acrylamide favor the formation of the off-cycle palladium-iodo complex **[b1]**, where ligand exchange to generate neither **[a3]** or **[b1]** is turnover limiting.[15] In addition, zero-order kinetics suggest nothing is coming on to the catalytic cycle during the turnover limiting step which, combined with the KIE data, is evidence for formate decarboxylation being turnover limiting.



(2)

To test this hypothesis, we sought to observe the catalyst resting state using *in situ* ^{31}P NMR spectroscopy. Monitoring was performed at 162 MHz, in DMF-d_7, at 70 °C, using triphenylphosphine sulfide (42.59 ppm) as reference with scans taken every 2 min for 10 min. In order to be able to compare the NMR data with known structures reported in the literature and to avoid issues with aryl group exchange with the oxidative addition complex, we elected to use triphenylphosphine as ligand for this experiment.[6,16]

Initial optimization showed that when using triphenylphosphine as ligand under otherwise standard conditions, the reaction provided 62% ^{1}H NMR yield of **3a** with 12:1 α:β selectivity, suggesting that the key features of the reactions with PPh_3 and P(4-F-C_6H_4)$_3$ are qualitatively similar (Table S1). Additionally, a separate *in situ* ^{19}F NMR monitoring experiment with P(4-F-C_6H_4)$_3$ showed analogous speciation to triphenylphosphine (Figure S13).

With PPh_3, major ^{31}P NMR resonances were observed at 27.55 ppm (triphenylphosphine oxide), 22.58 ppm (*trans*-Pd(Ar)(formate)(PPh_3)$_2$), 5.87 (phosphate tribasic), and -4.42 (triphenylphosphine) (Figure **6**). The only observable PPh_3-bound palladium species was the *trans*-Pd(Ar)(formate)(PPh_3)$_2$ complex. This result suggests this is the predominant catalyst resting state, and based on Alper's detailed study into the behavior of these complexes, provides support for formate decarboxylation being rate-limiting.[6,17]

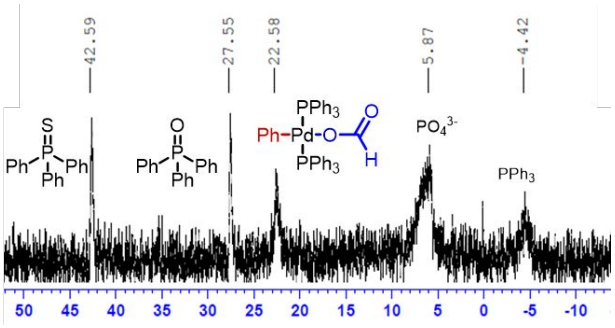
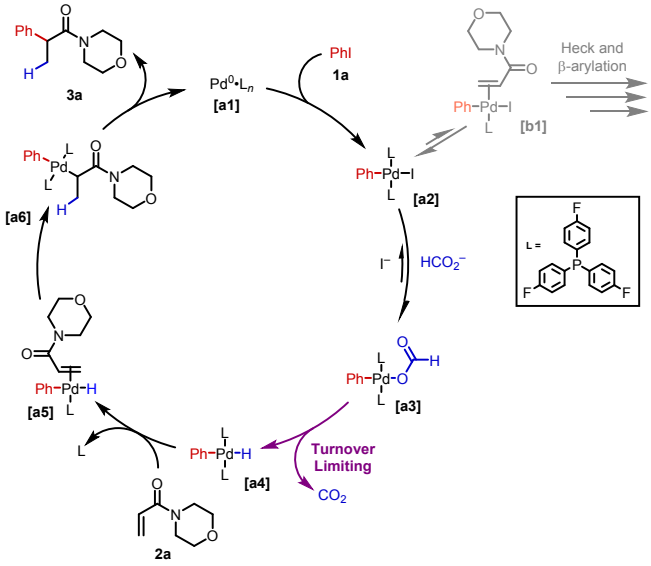


Figure 6. ^{31}P NMR spectrum of reaction in eq 1 after 4 min.

Previous studies have been performed on the behavior of palladium oxidative addition complexes in the presence of acetate. These studies have shown that oxidative addition into aryl-iodide bonds in the presence of acetate favors the [Pd^{II}(Ar)(OAc)] complexes.[16,18] This reactivity trend can be extended to formate, and we propose that ligand exchange of iodide to formate is also fast. This process is reversible with the equilibrium favoring formation of the [Pd^{II}(Ar)(formate)] complex. We believe this equilibrium to be a major driver for the selectivity of this process.

Based on the kinetic data and *in situ* NMR studies, a mechanism is proposed (Scheme **3**). Palladium(0) undergoes oxidative addition into iodobenzene to form a [Pd^{II}(Ph)(I)(PAr_3)$_2$] complex **[a2]**. This complex can progress off-cycle by undergoing exchange of a phosphine ligand for an alkene molecule, which leads to Heck and β-arylated byproducts **[b1]**, explaining the decrease in rate at high alkene and low ligand concentrations. Alternatively, complex **[a2]** can progress on-cycle by undergoing ligand exchange with formate to generate the [Pd^{II}(Ar)(formate)] complex **[a3]**. The formate-complex undergoes irreversible decarboxylation in the turnover limiting step to generate CO_2 and [Pd^{II}(Ar)(H)] complex **[a4]**. This complex coordinates alkene to generate **[a5]** and undergoes migratory insertion into the electronically activated β-position of the alkene to generate an [Pd^{II}(Ar)(enolate)] **[a6]**. This can undergo reductive elimination to furnish the α-arylated product **3a**.

Scheme 3. Proposed catalytic cycle



We believe it is the high ligand loading and rapid exchange of iodide for formate that drives the selectivity for this catalytic cycle. Without the addition of base or water, the reaction suffers from poor selectivity and high amounts of Heck-type products. This is also the case for ligand:Pd ratios of less than 2:1 (see Figure S11).

CONCLUSION. A novel method for the α-arylation of amides and esters using a mild, palladium-catalyzed hydroarylation has been developed. This chemistry is tolerant of a wide range of substrates including heterocycles and internal α,β-unsaturated acrylamides in high yield and selectivity. The mechanism of this reaction has been evaluated using reaction progress kinetic analysis and *in situ* reaction monitoring to suggest an unprecedented hydride first pathway made possible by the rapid formation and decomposition of a [Pd^{II}(Ar)(formate)] complex.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest.

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(18) Based on **Eq. 2**, the resting state is likely partitioned between **a3**, **a2**, and **b1**. Given that only **a3** is identifiable by ^{31}P NMR and that **3a-β** is formed in trace amounts, **a2** and **b1** appear to be minor components.

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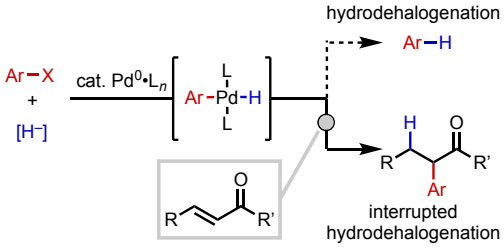
TOC Image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