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Catalytic α -Hydroarylation of Acrylates and Acrylamides via an Interrupted Hydro-Dehalogenation 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 $[\text{Pd}^{\text{II}}(\text{Ar})(\text{H})]$ 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 base is required which can preclude the use of certain functional groups and 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 selectively at the α -position via a palladium-catalyzed hydroarylation reaction of α,β -unsaturated carbonyl compounds.

At the outset we realized 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 $[\text{Pd}(0)]$ to the aryl (pseudo)halide to furnish a $[\text{Pd}^{\text{II}}(\text{Ar})(\text{X})]$ 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 $[\text{Pd}^{\text{II}}(\text{enolate})]$ with a hydride source.^{4,5} We imagined that under appropriate conditions, this process could take place in a polarity-inverted fashion via a $[\text{Pd}^{\text{II}}(\text{Ar})(\text{H})]$ species that would undergo hydride insertion into the β -position to access a $[\text{Pd}^{\text{II}}(\text{Ar})(\text{enolate})]$ intermediate

that is analogous to that of typical enolate α -arylation methodology (Figure 1C).

A. palladium(0)-catalyzed α -arylation of carbonyl compounds

B. metal-catalyzed cross-coupling of α -halo-carbonyl compounds

C. *this work*

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

$[\text{Pd}^{\text{II}}(\text{Ar})(\text{H})]$ species and progenitor complexes, such as $[\text{Pd}^{\text{II}}(\text{Ar})(\text{formate})]$, 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 $[\text{M}(\text{R})(\text{H})]$ (R = alkyl or aryl), accessed via C-H oxidative, or less commonly O-

Figure 2. Aryl iodide scope. Conditions: **1a** (0.20 mmol), **2** (0.24 mmol), Pd₂(dba)₃ (0.005 mmol), P(4-F-C₆H₅)₃ (0.040 mmol), tripotassium phosphate (0.40 mmol), 30% aq. TMA•HCO₂ (0.30 mmol, 0.100 mL), and dioxane (0.133 mL), 80 °C, 4–12 h. Ratios of $\alpha:\beta$ were determined via ¹H NMR (600 MHz) of the crude reaction mixture. Percentages represent isolated yields of the α -arylated product.

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 cost-efficient strategy to form α -arylated products not only under ambient atmosphere but with water as a co-solvent.

OPTIMIZATION AND SCOPE. The study began by attempting to optimize the reaction conditions with **1a** and **2a** as pilot substrates (see Table S1). To summarize key observations, we found that optimal conditions for hydroarylation are 2.5% Pd₂(dba)₃, 20% tris(4-fluorophenyl)phosphane ligand, and 30% aqueous tetramethylammonium formate (TMA•HCO₂) premixed in dioxane. Triarylphosphine ligands containing an electron-withdrawing group in the 3 or 4 position give consistently higher selectivity than triphenylphosphine. An excess of ligand is necessary for high selectivity as ligand to palladium ratios of less than 2:1 give high amounts of β -arylated products. The solubility of the formate salt is critical to the selectivity of the reaction, and low solubility is observed with inorganic counterions. Under optimal conditions, the major byproduct of this chemistry is the fully reduced alkene.

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 reac-

tion 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 bromide and iodide (**3d**).

Next, the reaction was evaluated with different acrylamides and acrylates (Figure 3). The amount of base is critical to the success of these substrates and the reaction was performed with 1% Pd₂(dba)₃, 5% ligand, and 1 equivalent K₃PO₄. 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-amioquinoline (see Figure S3). 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 diastereometric, opposite diastereoselectivity would be observed for *E* and *Z* alkene isomers.

Figure 3: Acrylamide and Acrylate Scope. ^a Conditions: **4a-l** (0.20 mmol), **2a** or **2d** (0.24 mmol), Pd₂(dba)₃ (0.002 mmol), tris(4-fluorophenyl)phosphane (0.010 mmol), tripotassium phosphate (0.20 mmol), 30% aq. TMA•HCO₂ (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), Pd₂(dba)₃ (0.005 mmol), tris(4-fluorophenyl)phosphane (0.050 mmol), tripotassium phosphate (0.40 mmol), TMA•HCO₂ (0.30 mmol, 0.100 mL), and 1,4-dioxane (0.133 mL), 100 °C, 24 h. Ratios of $\alpha:\beta$ were determined via ¹H NMR (600 MHz) of the crude reaction mixture. Percentages represent isolated yields of the α -arylated product.

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 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 millimolecular peptides or bifunctional molecules.

Figure 4: Examples demonstrating chemoselectivity and functional group compatibility.

MECHANISTIC STUDIES. The unusual selectivity of this transformation prompted us to examine the underlying reaction mechanism. We considered four potential pathways (Scheme 1). In Pathway A, the alkene is first reduced to the corresponding aliphatic amide (step i) 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 ii), and subsequent reductive elimination (step iii).

The second possibility (Pathway B) involves aryl insertion into the α -position of the alkene (step iv), the resulting [Pd^{II}(1°-alkyl)(I)] complex β -hydride eliminate (step v) in a classical Mizoroki–Heck mechanism. The resulting alkene can be reduced to generate the α -arylated product (step vi). Alternatively, in a reductive Heck (Pathway C), 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 vii). This can perform reductive elimination to provide the α -arylated product (step viii).

At the outset, Pathways A and B 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.¹⁰ This suggests formate may be involved in selectivity determination for α - versus β -hydroarylation and could be consistent with Pathway D but not B or C. Although α -selectivity has been observed in intramolecular cyclizations, this has not been previously documented in intermolecular systems.¹¹

Fourth, we considered a general hydroarylation reaction paradigm (Pathway D). In this “formate-first” pathway, the [Pd^{II}(Ar)(I)] complex can exchange iodide for formate and undergo decarboxylation to furnish a [Pd^{II}(Ar)(H)] complex (step ix). This can insert hydride into the β -position of the alkene (step x). The resulting [Pd^{II}(Ar)(enolate)] can undergo reductive elimination to provide the α -arylated product (step xi).

Scheme 1. Possible mechanistic pathways

To probe mechanistic Pathways A and B, the putative Mizoroki–Heck (**6**) and reduced (**7**) intermediates were subjected to the reaction conditions and no reaction took place, showing “aryl-first” Mizoroki–Heck pathways and Buchwald–Hartwig-

type palladium-enolate generation are not viable intermediates in this catalytic system (Scheme 2A). Having quickly ruled out two mechanistic pathways, we set our attention to differentiating between the reductive Heck and interrupted hydrodehalogenation pathways.

In an effort to disambiguate between Pathways C and D 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 -Heck product **10** (Scheme 2B). The reaction proceeds in the presence of mercury, albeit in lower conversion, ruling out the possibility of palladium nanoparticle catalysis. When independently prepared *trans*-Pd(Ar)(I)(PAr₃)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(Ar)(I) promote traditional Mizoroki–Heck pathways. In addition, a competition kinetic isotope experiment was performed using equal parts sodium formate and *d*₁-sodium formate yielding a kinetic isotope effect of 1.5, suggesting formate is involved in the product-determining step (Scheme 2D).¹² These results are consistent with a general “hydride-first” pathway.

Scheme 2. Control experiments

Having established that the general reactivity paradigm of Pathway D is operative, we next sought to gain insight into the details of the catalytic process through reaction progress kinetic analysis (RPKA).¹³ 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).

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 by-product **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 S8), 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 experiments 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).

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.¹⁴ 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.

To test this hypothesis, the catalyst resting state was determined using *in situ* ³¹P NMR spectroscopy. Monitoring was performed at 162 MHz, in DMF-d₇, at 70 °C, using triphenylphosphine sulfide (42.59 ppm) as reference with scans taken every 2 min for 10 min. Triphenylphosphine was used as ligand so that the spectra could be compared to known complexes reported in the literature.^{6,15} By ³¹P NMR, major resonances were observed at 27.55 ppm (triphenylphosphine oxide), 22.58 ppm (*trans*-Pd(Ar)(formate)(PPh₃)₂), 5.87 (phosphate tribasic), and -4.42 (triphenylphosphine) (Figure 6). The only observable palladium species is the [Pd^{II}(aryl)(formate)] complex, suggesting this is the catalyst resting state and providing support for formate decarboxylation being rate limiting.

Numerous studies have been performed to study the behavior of palladium complexes in the presence of acetate and have shown that oxidative addition into aryl-halide bonds in the presence of acetate leads exclusively to $[\text{Pd}^{\text{II}}(\text{Ar})(\text{OAc})]$ complexes.^{15,16} This reactivity trend can be extended to formate suggesting that ligand exchange of iodide for formate is also very fast, driving the selectivity for 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 $\text{Pd}^{\text{II}}(\text{Ph})(\text{I})(\text{PAr}_3)_2$ 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 $[\text{Pd}^{\text{II}}(\text{Ar})(\text{formate})]$ complex **[a3]**. The formate-complex undergoes irreversible decarboxylation in the turnover limiting step to generate CO_2 and $[\text{Pd}^{\text{II}}(\text{Ar})(\text{H})]$ 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 $[\text{Pd}^{\text{II}}(\text{Ar})(\text{enolate})]$ **[a6]**. This can undergo reductive elimination to furnish the α -arylated product **3a**.

Figure 6. ^{31}P NMR spectrum

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 S9).

Scheme 3. Proposed Catalytic Cycle

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 Michael acceptors 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 $[\text{Pd}^{\text{II}}(\text{Ar})(\text{formate})]$ complex.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest.

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

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GENERAL INFORMATION

Unless otherwise noted, all materials were used as received from commercial sources without further purification. All chemicals were purchased from Aldrich, Alfa Aesar, Oakwood, and Combi-Blocks. ^1H and ^{13}C spectra were recorded on Bruker DRX-500 and AV-600 instruments. Spectra were internally referenced to SiMe_4 or solvent signals. The following abbreviations (or combinations thereof) were used to explain multiplicities: b = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet. High-resolution mass spectra (HRMS) for new compounds were recorded on an Agilent LC/MSD TOF mass spectrometer.

SYNTHETIC PROCEDURES

Reaction Optimization

Table S1. Optimization of reaction conditions.

Entry	Deviation from Written Conditions	A	B	C	D	E	A:B
1	None	89%	4%	6%	0%	2%	22:1
2	0.5 % $\text{Pd}_2(\text{dba})_3$ / 5% $\text{P}(4\text{-F-C}_6\text{H}_4)_3$	38%	2%	3%	13%	18%	14:1
3	1.0 % $\text{Pd}_2(\text{dba})_3$ / 5% $\text{P}(4\text{-F-Ph})_3$	11%	1%	1%	11%	55%	11:1
4	2.5 % $\text{Pd}_2(\text{dba})_3$ / 5% $\text{P}(4\text{-F-Ph})_3$	20%	0%	2%	11%	28%	>20:1
5	2.5 % $\text{Pd}_2(\text{dba})_3$ / 10% $\text{P}(4\text{-F-Ph})_3$	59%	3%	5%	3%	0%	20:1
6	No ligand	0%	0%	0%	64%	18%	-
7	PPh_3 instead of $\text{P}(4\text{-F-Ph})_3$	62%	5%	6%	0%	2%	12:1
8	$\text{P}(4\text{-OMe-Ph})_3$ instead of $\text{P}(4\text{-F-Ph})_3$	42%	5%	22%	6%	0%	8:1
9	$\text{P}(4\text{-CF}_3\text{-Ph})_3$ instead of $\text{P}(4\text{-F-Ph})_3$	36%	2%	1%	25%	5%	18:1
10	$\text{KHCO}_2 + \text{TBABF}_4$ (20%) + H_2O (30 equiv.) instead of $\text{TMA}\cdot\text{HCO}_2$	31%	3%	4%	41%	4%	10:1
11	$\text{NaHCO}_2 + \text{TBABF}_4$ (20%) + H_2O (30 equiv.) instead of $\text{TMA}\cdot\text{HCO}_2$	29%	2%	6%	45%	5%	15:1
12	$\text{NH}_4\text{HCO}_2 + \text{TBABF}_4$ (20%) + H_2O (30 equiv.) instead of $\text{TMA}\cdot\text{HCO}_2$	59%	3%	4%	9%	0%	20:1
13	KOH instead of K_3PO_4	14%	24%	4%	0%	0%	1:2
14	K_2CO_3 instead of K_3PO_4	67%	4%	8%	0%	4%	17:1
15	DCM instead of 1,4-dioxane	38%	10%	8%	32%	5%	4:1
16	DMF instead of 1,4-dioxane	63%	3%	11%	4%	6%	21:1
17	No $\text{Pd}_2(\text{dba})_3$	0%	0%	0%	80%	0%	-
18	No $\text{TMA}\cdot\text{HCO}_2$	0%	0%	0%	90%	4%	-
19	No TMAHCO_2 , 30 equiv. H_2O	0	0	8%	0%	76%	-

^a Reactions were performed on 0.05 mmol scale following general procedure A. For entries 2–9, 14, 15, palladium and ligand were premixed with base before adding iodobenzene, amide, and formate. For entries

10 and 11, formate, base, TBABF₄, water, iodobenzene, and alkene were mixed before addition of palladium/ligand stock solution.

Starting Material Synthesis

Substrates **4d**,¹ **4e**,¹ **4h**,² **4i**,² **4j**,³ **4m**,⁴ **4n**,⁵ **4o**,⁵ **4p**,⁶ and **4q**,⁷ **4r**,¹⁰ **4s**,¹¹ **9**¹² were prepared according to literature procedures. Substrates **1a**, **4a**, **4b**, **4c**, **4f**, **4k**, **4l**, and **2a–q** were purchased from MilliporeSigma.

Scheme 1: Synthesis of **4g**

To a stirred solution of cyclobutylamine (213 mg, 3.00 mmol) in DCM (10 mL) was added triethylamine (911 mg, 1.2 mL) and acryloyl chloride (272 mg, 3.00 mmol) dropwise. The solution was allowed to warm to room temperature overnight. Sodium bicarbonate was added, and the aqueous solution was extracted with Et₂O (10 mL × 3). The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified by flash column chromatography to yield **4g** as a white solid (330 mg, 89%). ¹H NMR (600 MHz, CDCl₃) δ 6.29 (dd, *J* = 17.0, 1.4 Hz, 1H), 6.11 – 6.03 (m, 1H), 5.72 (broad s, 1H), 5.65 (dd, *J* = 10.3, 1.4 Hz, 1H), 4.55 – 4.47 (m, 1H), 2.40 (tddd, *J* = 8.7, 3.9, 3.2, 2.1 Hz, 2H), 1.96 – 1.86 (m, 2H), 1.80 – 1.70 (m, 2H). ¹³C NMR (150 MHz, CDCl₃) δ 164.00, 130.39, 125.98, 44.26, 30.82, 14.69.

General Procedure for α-Arylation

Preparation of Pd-Ligand Stock Solution:

Figure S1. Pd-ligand stock solution

To a one-dram vial containing a stir bar were added Pd₂(dba)₃ (45.8 mg, 50 μmol for A; 18.3 mg, 20 μmol for B), tris(4-fluorophenyl)phosphine (127 mg, 0.400 mmol for A; 31.6 mg, 0.100 mmol for B), and dioxane (1.33 mL). The suspension was capped and allowed to stir until all solids had dissolved (around 5 min). An aliquot (133 μL) was then transferred into the reaction vial.

Notes:

- It is recommended that stock solution be freshly made and used immediately for each experiment.
- When solvent is initially added, the solution will appear dark red in color and will become brown/dark orange in color after stirring for a few minutes, at which point it should be used.
- If the solution changes color and becomes red again, it is no longer suitable for use.
- For a recommended workflow, we suggest first preparing the stock solution, and allowing it to mix while measuring the other liquid reaction components (aryl iodide, acrylamide formate). Upon completion of these operations, the stock solution is typically ready for use.

General Procedure A:

Scheme S2. Gernal Procedure A

To a one-dram vial containing a stir bar was added K_3PO_4 (85 mg, 0.40 mmol). Using a micropipette, aryl iodide (0.240 mmol), 4-acryloylmorpholine (28.2 mg, 25.2 μL , 0.200 mmol), tetramethylammonium formate (30 wt%, 100 μL , 0.290 mmol), and Pd/Ligand stock solution (133 μL) were added sequentially to the vial. The vial was sealed and placed in a pre-heated heating block at 80 °C for 4 h. After 4 h, the vial was cooled to room temperature. A small aliquot was removed and dissolved in CDCl_3 for ^1H NMR analysis (600 MHz). Regioisomeric ratios ($\alpha:\beta$) were determined by comparing the average integration of the β - CH_2 triplets (~2.5-3 ppm) to the integration of methyl CH_3 doublet (~1.5 ppm). Percentage yields represent the isolated yields of pure α -arylated product unless otherwise specified.

General Procedure B:

Scheme S3. General Procedure B

To a one-dram vial containing a stir bar was added K_3PO_4 (43 mg, 0.2 mmol). Using a micropipette, PhI (49.0 mg, 26.9 μL , 0.240 mmol), acrylate/acrylamide (0.200 mmol), tetramethylammonium formate (30 wt%, 100 μL , 0.290 mmol), and Pd/Ligand stock solution (133 μL) were added sequentially to the vial. The vial was sealed and placed in a pre-heated heating block at 80 °C for 4 h. After 4 h the vial was cooled to room temperature. A small aliquot was removed and dissolved in CDCl_3 for ^1H NMR analysis (600 MHz). Regioisomeric ratios ($\alpha:\beta$) were determined by comparing the average integration of the β - CH_2 triplets (~2.5-3 ppm) to the integration of methyl CH_3 doublet (~1.5 ppm). The NMR sample was recombined with the reaction mixture, and the solution was loaded directly onto a preparative TLC plate (40% EtOAc/Hexanes). Percentage yields represent the isolated yields of pure α -arylated product unless otherwise specified.

General Procedure C:

Scheme S4. Gernal Procedure C

To a one-dram vial containing a stir bar was added K_3PO_4 (85 mg, 0.40 mmol). Using a micropipette, aryl iodide (0.240 mmol), acrylamide (0.200 mmol), tetramethylammonium formate (30 wt%, 100 μ L, 0.290 mmol), and Pd/Ligand stock solution (133 μ L) were added sequentially to the vial. The vial was sealed and placed in a pre-heated heating block at 100 $^{\circ}C$ for 16 h. After 16 h the vial was cooled to room temperature. A small aliquot was removed and dissolved in $CDCl_3$ for 1H NMR analysis (600 MHz). The NMR sample was recombined with the reaction mixture, and the sample was purified by prep LCMS. Percentage yields represent the isolated yields of pure α -arylated product unless otherwise specified.

Representative 1H NMR Spectrum of Crude Reaction Mixture:

Figure S2. Representative NMR spectra.

Characterization Data for α -Arylated Products:

1-morpholino-2-phenylpropan-1-one (3a): The title compound was prepared on a 0.200 mmol scale according to General Procedure A. The crude residue was purified by preparative TLC (40% EtOAc/hexanes). Purification afforded **3a** as an off-white solid (39.6 mg, 90%). 1H NMR (600 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 2H), 7.28 – 7.23 (m, 3H), 3.89 – 3.78 (m, 2H), 3.69 (ddd, $J = 13.6, 9.4, 5.2$ Hz, 1H), 3.59 – 3.53 (m, 2H), 3.53 – 3.47 (m, 2H), 3.45 – 3.38 (m, 1H), 3.36 – 3.29 (m, 1H), 3.13 (ddd, $J = 11.1, 7.4, 3.0$ Hz, 1H), 1.48 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.71, 141.39, 128.55, 126.69,

126.44, 66.33, 65.83, 45.54, 42.81, 41.92, 20.17. **HRMS** calcd. for $C_{13}H_{17}NO_2^+$ $[M+H]^+$: 220.1338, Found: 220.1337.

1-morpholino-2-(4-(trifluoromethyl)phenyl)propan-1-one (3b): The title compound was prepared on a 0.200 mmol scale according to General Procedure A. The crude residue was purified by preparative TLC (40% EtOAc/hexanes). Purification afforded **3b** as an off-white solid (49.7 mg, 87%). **¹H NMR** (600 MHz, $CDCl_3$) δ 7.61 (d, J = 8.1 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 3.95 (q, J = 6.9 Hz, 1H), 3.80–3.63 (m, 2H), 3.58 (h, J = 8.0 Hz, 3H), 3.50–3.36 (m, 1H), 3.37–3.17 (m, 2H), 1.49 (d, J = 6.9 Hz, 3H). **¹³C NMR** (150 MHz, $CDCl_3$) δ 171.42, 145.74, 129.37 (q, J_{C-F} = 35 Hz), 127.61, 125.99 (q, J_{C-F} = 2.8 Hz), 123.96 (q, J_{C-F} = 274 Hz), 66.32, 65.85, 45.73, 42.40, 41.97, 20.01. **¹⁹F NMR** (376 MHz, $CDCl_3$) δ -62.8 **HRMS** calcd. for $C_{14}H_{16}F_3NO_2^+$ $[M+H]^+$: 288.1211, Found: 288.1208.

2-(4-acetylphenyl)-1-morpholinopropan-1-one (3c): The title compound was prepared on a 0.200 mmol scale according to General Procedure A. The crude residue was purified by preparative TLC (40% EtOAc/hexanes). Purification afforded **3c** as an off-white solid (40.8 mg, 78%). **¹H NMR** (600 MHz, $CDCl_3$) δ 7.98–7.93 (m, 2H), 7.40–7.34 (m, 2H), 3.94 (q, J = 6.9 Hz, 1H), 3.82–3.76 (m, 1H), 3.70 (t, J = 7.5 Hz, 1H), 3.55 (p, J = 9.0, 8.3 Hz, 3H), 3.43 (dd, J = 13.4, 7.6 Hz, 1H), 3.29 (d, J = 13.4 Hz, 1H), 3.18 (t, J = 10.1 Hz, 1H), 2.62 (s, 3H), 1.50 (d, J = 6.9 Hz, 3H). **¹³C NMR** (150 MHz, $CDCl_3$) δ 197.08, 170.98, 146.72, 135.49, 128.69, 127.01, 66.31, 65.84, 45.54, 42.67, 41.99, 26.14, 19.92. **HRMS** calcd. for $C_{15}H_{19}NO_3^+$ $[M+H]^+$: 262.1443, Found: 262.1448.

2-(4-bromophenyl)-1-morpholinopropan-1-one (3d): The title compound was prepared on a 0.200 mmol scale according to General Procedure A. The crude residue was purified by preparative TLC (40% EtOAc/hexanes). Purification afforded **3d** as an off-white solid (55.6 mg, 93%). **¹H NMR** (600 MHz, $CDCl_3$) δ 7.44–7.39 (m, 2H), 7.24–7.18 (m, 2H), 3.84 (q, J = 6.8 Hz, 1H), 3.80–3.75 (m, 1H), 3.74–3.66 (m, 1H), 3.57 (h, J = 8.3, 7.6 Hz, 3H), 3.47–3.40 (m, 1H), 3.24 (ddd, J = 10.6, 7.1, 2.9 Hz, 1H), 1.47 (d, J = 6.8 Hz, 3H). **¹³C NMR** (150 MHz, $CDCl_3$) δ 171.50, 144.02, 130.58, 130.32, 130.16, 125.80, 122.96, 66.33, 46.02, 42.75, 42.43, 20.53. **HRMS** calcd. for $C_{13}H_{16}BrNO_2^+$ $[M+H]^+$: 298.0443, Found: 298.0439.

4-(1-morpholino-1-oxopropan-2-yl)benzaldehyde (3e): The title compound was prepared on a 0.200 mmol scale according to General Procedure A. The crude residue was purified by preparative TLC (40% EtOAc/hexanes). Purification afforded **3e** as an off-white solid (32.2 mg, 65%). **¹H NMR** (600 MHz, $CDCl_3$) δ 10.01 (s, 1H), 7.90–7.85 (m, 2H), 7.46–7.42 (m, 2H), 3.96 (q, J = 6.8 Hz, 1H), 3.77 (dt, J = 12.8, 7.0 Hz, 1H), 3.69 (dd, J = 9.0, 6.1 Hz, 1H), 3.55 (t, J = 8.6 Hz, 3H), 3.43 (ddd, J = 13.1, 7.1, 3.0 Hz, 1H), 3.29 (ddd, J = 13.4, 5.8, 2.9 Hz, 1H), 3.19 (ddd, J = 10.8, 7.2, 2.9 Hz, 1H), 1.50 (d, J = 6.9 Hz, 3H). **¹³C NMR** (150 MHz, $CDCl_3$) δ 191.18, 170.81, 148.22, 134.82, 130.03, 127.49, 66.30, 65.82, 45.55, 42.78, 42.00, 19.89. **HRMS** calcd. for $C_{14}H_{17}NO_3^+$ $[M+H]^+$: 248.1287, Found: 248.1287.

1-morpholino-2-(p-tolyl)propan-1-one (3f): The title compound was prepared on a 0.200 mmol scale according to General Procedure A. The crude residue was purified by preparative TLC (40% EtOAc/hexanes). Purification afforded **3f** as an off white solid. (38.8 mg, 83%). **¹H NMR** (600 MHz, $CDCl_3$) δ 7.17 – 7.11 (m, 4H), 3.81 (dq, J = 12.7, 6.8 Hz, 2H), 3.71 – 3.66 (m, 1H), 3.59 – 3.47 (m, 3H), 3.41 (ddd, J = 13.3, 7.4, 3.0 Hz, 1H), 3.36 – 3.29 (m, 1H), 3.15 (ddd, J = 11.2, 7.4, 3.2 Hz, 1H), 2.34 (s, 3H), 1.45 (d, J = 6.8 Hz, 3H). **¹³C NMR** (150 MHz, $CDCl_3$) δ 171.91, 138.35, 136.03, 129.21, 126.55, 66.34, 65.87, 45.53, 42.37, 41.90, 20.56, 20.22. **HRMS** calcd. for $C_{14}H_{19}NO_2^+$ $[M+H]^+$: 234.1494, Found: 234.1491.

1-morpholino-2-(4-nitro-3-(trifluoromethyl)phenyl)propan-1-one (3g): The title compound was prepared on an 0.200 mmol scale according to General Procedure A. The crude residue was purified by preparative TLC (40% EtOAc/hexanes). Purification afforded **3g** (containing 5% tris(4-fluorophenyl)phosphine oxide) as an off white solid. (35.7 mg, 54%). ¹H NMR (600 MHz, CDCl₃) δ 7.90 (d, *J* = 8.3 Hz, 1H), 7.74 (d, *J* = 2.0 Hz, 1H), 7.68 (dd, *J* = 8.3, 2.0 Hz, 1H), 4.08 (q, *J* = 6.9 Hz, 1H), 3.68 (tdd, *J* = 22.0, 9.2, 4.5 Hz, 5H), 3.53 (ddd, *J* = 12.9, 6.6, 2.8 Hz, 1H), 3.44 (ddd, *J* = 11.0, 6.7, 3.0 Hz, 1H), 3.36 (ddd, *J* = 13.2, 6.4, 2.8 Hz, 1H), 1.54 (d, *J* = 6.9 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 170.45, 147.20, 146.88, 132.00, 127.11 (q, *J*_{C-F} = 5.17 Hz), 125.76, 124.29 (q, *J*_{C-F} = 33.93 Hz), 121.79 (q, *J*_{C-F} = 275 Hz), 66.77, 45.81, 42.57, 42.09, 20.26. ¹⁹F NMR (564 MHz, CDCl₃) δ -60.1193. HRMS calcd. for C₁₄H₁₅F₃N₂O₄⁺ [M+H]⁺: 333.1062, Found: 333.1066.

4-(1-morpholino-1-oxopropan-2-yl)-2-(trifluoromethyl)benzonitrile (3h): The title compound was prepared on a 0.200 mmol scale according to General Procedure A. The crude residue was purified by preparative TLC (40% EtOAc/hexanes). Purification afforded **3h** as an off white solid. (35.9 mg, 54%). ¹H NMR (600 MHz, CDCl₃) δ 7.84 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 1.8 Hz, 1H), 7.65 (dd, *J* = 8.0, 1.8 Hz, 1H), 4.06 (q, *J* = 6.9 Hz, 1H), 3.74–3.61 (m, 5H), 3.55–3.49 (m, 1H), 3.45–3.38 (m, 1H), 3.38–3.31 (m, 1H), 1.54 (d, *J* = 6.9 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 170.14, 146.96, 134.79, 132.94 (q, *J* = 32.6 Hz), 130.85, 125.51 (q, *J* = 4.5 Hz), 121.75 (d, *J* = 274.0 Hz), 114.77, 108.36, 66.31, 65.90, 45.73, 42.21, 42.01, 19.68. ¹⁹F NMR (564 MHz, CDCl₃) δ -62.08. HRMS calcd. for C₁₅H₁₅F₃N₂O₂⁺ [M+H]⁺: 313.1164, Found: 313.1165.

2-(benzo[d][1,3]dioxol-5-yl)-1-morpholinopropan-1-one (3i): The title compound was prepared on a 0.200 mmol scale according to General Procedure A. The crude residue was purified by preparative TLC (60% EtOAc/hexanes). Purification afforded **3i** as an off-white solid (30.3 mg, 58%). ¹H NMR (600 MHz, CDCl₃) δ 6.79–6.74 (m, 2H), 6.68 (dd, *J* = 8.0, 1.8 Hz, 1H), 5.96 (s, 2H), 3.78 (q, *J* = 6.7 Hz, 2H), 3.72–3.66 (m, 1H), 3.55 (dtdd, *J* = 14.2, 10.7, 7.2, 2.7 Hz, 3H), 3.43 (ddd, *J* = 13.2, 7.0, 2.8 Hz, 1H), 3.39–3.33 (m, 1H), 3.24 (ddd, *J* = 10.8, 7.3, 3.0 Hz, 1H), 1.43 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 171.73, 147.63, 145.97, 135.19, 119.80, 108.10, 107.10, 100.62, 66.35, 65.94, 45.55, 42.31, 20.28. HRMS calcd. for C₁₄H₁₇NO₄⁺ [M+H]⁺: 264.1236, Found: 264.1232.

2-(3-acetylphenyl)-1-morpholinopropan-1-one (3j): The title compound was prepared on a 0.200 mmol scale according to General Procedure A. The crude residue was purified by preparative TLC (40% EtOAc/hexanes). Purification afforded **3j** as an off-white solid. (47.2 mg, 90%). ¹H NMR (600 MHz, CDCl₃) δ 7.85 (dt, *J* = 6.1, 1.6 Hz, 2H), 7.51 (dt, *J* = 7.7, 1.5 Hz, 1H), 7.49–7.43 (m, 1H), 3.96 (q, *J* = 6.9 Hz, 1H), 3.76 (t, *J* = 8.5 Hz, 1H), 3.69 (t, *J* = 7.3 Hz, 1H), 3.61–3.51 (m, 2H), 3.49–3.42 (m, 1H), 3.32 (s, 1H), 3.21 (dd, *J* = 11.4, 7.5 Hz, 1H), 2.63 (s, 3H), 1.50 (d, *J* = 6.9 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 197.44, 171.27, 141.97, 137.29, 131.34, 128.87, 126.76, 126.57, 66.36, 65.88, 45.58, 42.39, 41.96, 26.26, 20.04. HRMS calcd. for C₁₅H₁₉NO₃⁺ [M+H]⁺: 262.1443, Found: 262.1440.

tert-butyl (4-(1-morpholino-1-oxopropan-2-yl)phenyl)carbamate (3k): The title compound was prepared on a 0.200 mmol scale according to General Procedure A. The crude residue was purified by preparative TLC (80% EtOAc/hexanes). Purification afforded **3k** as an off-white solid. (48.9 mg, 73%). ¹H NMR (600 MHz, CDCl₃) δ 7.34 (d, *J* = 8.1 Hz, 2H), 7.20–7.15 (m, 2H), 6.47 (s, 1H), 3.80 (dq, *J* = 9.3, 6.8 Hz, 2H), 3.72–3.66 (m, 1H), 3.58–3.48 (m, 3H), 3.41 (dd, *J* = 12.7, 8.1 Hz, 1H),

3.32 (d, $J = 13.0$ Hz, 1H), 3.20 – 3.14 (m, 1H), 1.54 (s, 9H), 1.44 (d, $J = 6.8$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 172.28, 152.85, 137.30, 136.24, 127.66, 119.06, 66.75, 66.33, 60.39, 45.97, 42.53, 28.33, 21.04, 14.18. HRMS calcd. for $\text{C}_{18}\text{H}_{26}\text{N}_2\text{O}_4^+$ $[\text{M}+\text{H}]^+$: 335.1971, Found: 335.1978.

2-(4-methoxyphenyl)-1-morpholinopropan-1-one (3l): The title compound was prepared on a 0.200 mmol scale according to General Procedure A. The crude residue was purified by preparative TLC (60% EtOAc/hexanes). Purification afforded **3l** as an off-white solid. (27.6 mg, 55%). ^1H NMR (600 MHz, CDCl_3) δ 7.23 – 7.14 (m, 2H), 6.90 – 6.85 (m, 2H), 3.85 – 3.78 (m, 5H), 3.73 – 3.64 (m, 1H), 3.58 – 3.49 (m, 3H), 3.45 – 3.38 (m, 1H), 3.34 (dd, $J = 10.8, 6.2$ Hz, 1H), 3.16 (td, $J = 8.4, 7.6, 3.9$ Hz, 1H), 1.44 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 172.01, 157.97, 133.44, 127.72, 113.89, 66.36, 65.91, 54.80, 45.55, 41.89, 41.85, 20.25. HRMS calcd. for $\text{C}_{14}\text{H}_{19}\text{NO}_3^+$ $[\text{M}+\text{H}]^+$: 250.1443, Found: 250.1443.

1-morpholino-2-(2-(trifluoromethyl)pyridin-4-yl)propan-1-one (3m): The title compound was prepared on a 0.200 mmol scale according to General Procedure A. The crude residue was purified by preparative TLC (40% EtOAc/hexanes). Purification afforded **3m** as an off-white solid. (38.9 mg, 64%). ^1H NMR (600 MHz, CDCl_3) δ 8.70 (d, $J = 5.0$ Hz, 1H), 7.64–7.59 (m, 1H), 7.44 (dd, $J = 5.1, 1.7$ Hz, 1H), 4.00 (q, $J = 6.9$ Hz, 1H), 3.75–3.58 (m, 5H), 3.54–3.44 (m, 1H), 3.43–3.30 (m, 2H), 1.53 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 169.75, 150.93, 150.09, 148.48 (q, $J = 34.5$ Hz), 124.79, 120.03, 119.00 (q, $J = 2.7$ Hz), 66.30, 65.87, 45.65, 42.09, 41.61, 19.41. ^{19}F NMR (564 MHz, CDCl_3) δ -68.1845. HRMS calcd. for $\text{C}_{13}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_2^+$ $[\text{M}+\text{H}]^+$: 289.1164, Found: 289.1165.

1-morpholino-2-(pyridin-2-yl)propan-1-one (3n): The title compound was prepared on a 0.200 mmol scale according to General Procedure A. The crude residue was purified by preparative TLC (40% EtOAc/hexanes). Purification afforded **3n** as an off-white solid. (30.8 mg, 70%). ^1H NMR (600 MHz, CDCl_3) δ 8.53 (ddd, $J = 4.9, 1.9, 0.9$ Hz, 1H), 7.69 (td, $J = 7.7, 1.9$ Hz, 1H), 7.34 (dt, $J = 7.9, 1.1$ Hz, 1H), 7.19 (ddd, $J = 7.4, 4.9, 1.1$ Hz, 1H), 4.15 (q, $J = 7.0$ Hz, 1H), 3.83–3.76 (m, 1H), 3.74–3.65 (m, 1H), 3.60–3.45 (m, 5H), 3.21–3.14 (m, 1H), 1.54 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 171.50, 161.40, 149.23, 137.17, 122.00, 121.32, 66.79, 66.52, 46.08, 45.79, 42.49, 18.62. HRMS calcd. for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2^+$ $[\text{M}+\text{H}]^+$: 221.1290, Found: 221.1286.

1-morpholino-2-(pyridin-4-yl)propan-1-one (3o): The title compound was prepared on a 0.200 mmol scale according to General Procedure A. The crude residue was purified by preparative TLC (40% EtOAc/hexanes). Purification afforded **3o** as an off-white solid (34.8 mg, 80%). ^1H NMR (600 MHz, CDCl_3) δ 8.61–8.57 (m, 2H), 7.23–7.19 (m, 2H), 3.87 (q, $J = 6.9$ Hz, 1H), 3.76 (dd, $J = 10.5, 6.1$ Hz, 1H), 3.70 (dd, $J = 8.8, 6.3$ Hz, 1H), 3.62–3.54 (m, 3H), 3.47–3.40 (m, 1H), 3.28 (qd, $J = 10.7, 10.0, 2.9$ Hz, 2H), 1.49 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 170.33, 150.03, 150.00, 122.00, 66.30, 65.83, 45.55, 41.98 (d, $J = 6.4$ Hz), 19.49. HRMS calcd. for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2^+$ $[\text{M}+\text{H}]^+$: 221.1290, Found: 221.1285.

1-morpholino-2-(pyrazin-2-yl)propan-1-one (3p): The title compound was prepared on a 0.200 mmol scale according to General Procedure A. The crude residue was purified by preparative TLC (60% EtOAc/hexanes). Purification afforded **3p** as an off-white solid (26.0 mg, 59%). ^1H NMR (600 MHz, CDCl_3) δ 8.67 (s, 1H), 8.50 (s, 2H), 4.21 (q, $J = 7.0$ Hz, 1H), 3.81–3.67 (m, 2H), 3.60 (t, $J = 8.3$ Hz, 3H), 3.53 (dq, $J = 9.7, 4.8, 3.8$ Hz, 2H), 3.38–3.31 (m, 1H), 1.61 (d, $J = 7.0$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 170.15, 156.19, 143.45,

143.29, 142.62, 66.34, 66.08, 45.72, 42.92, 42.10, 17.63. **HRMS** calcd. for $C_{11}H_{15}N_3O_2^+$ $[M+H]^+$: 222.1243, Found: 222.1242.

2-(7-chloroquinolin-4-yl)-1-morpholinopropan-1-one (3q): The title compound was prepared on an 0.200 mmol scale according to General Procedure A. The crude residue was purified by preparative TLC (60% EtOAc/hexanes). Purification afforded **3q** as an off-white solid (27.2 mg, 45%). **¹H NMR** (600 MHz, $CDCl_3$) δ 8.89 (d, J = 4.6 Hz, 1H), 8.19 (d, J = 2.1 Hz, 1H), 8.04 (d, J = 9.0 Hz, 1H), 7.61 (dd, J = 9.0, 2.2 Hz, 1H), 7.31 (d, J = 4.6 Hz, 1H), 4.53 (q, J = 6.9 Hz, 1H), 3.84–3.76 (m, 1H), 3.74–3.68 (m, 1H), 3.67–3.58 (m, 2H), 3.44 (ddd, J = 11.4, 6.0, 3.0 Hz, 1H), 3.28 (ddd, J = 13.2, 7.1, 2.9 Hz, 1H), 3.12 (ddd, J = 11.1, 6.9, 2.9 Hz, 1H), 3.05–2.99 (m, 1H), 1.60 (d, J = 6.9 Hz, 3H). **¹³C NMR** (150 MHz, $CDCl_3$) δ 170.60, 150.14, 148.76, 147.11, 135.06, 129.38, 127.85, 123.68, 123.02, 118.77, 66.27, 65.67, 45.40, 42.07, 38.40, 18.71. **HRMS** calcd. for $C_{16}H_{17}ClN_2O_2^+$ $[M+H]^+$: 305.1057, Found: 305.1056.

3-methyl-7-(1-morpholino-1-oxopropan-2-yl)quinazolin-4(3H)-one (3r): The title compound was prepared on a 0.200 mmol scale according to General Procedure A. The crude residue was purified by preparative TLC (10% MeOH/DCM). Purification afforded **3r** as an off-white solid (44.7 mg, 74%). **¹H NMR** (600 MHz, $CDCl_3$) δ 8.31 (d, J = 8.3 Hz, 1H), 8.07 (s, 1H), 7.59 (d, J = 1.7 Hz, 1H), 7.45 (dd, J = 8.3, 1.7 Hz, 1H), 4.03 (q, J = 6.9 Hz, 1H), 3.79 (dt, J = 12.3, 7.0 Hz, 1H), 3.69 (q, J = 9.8, 8.6 Hz, 1H), 3.62 (s, 3H), 3.61–3.48 (m, 3H), 3.49–3.38 (m, 1H), 3.32 (d, J = 13.5 Hz, 1H), 3.17 (q, J = 8.0 Hz, 1H), 1.55 (s, 3H). **¹³C NMR** (150 MHz, $CDCl_3$) δ 171.18, 161.21, 148.76, 148.50, 147.29, 127.48, 126.38, 125.87, 120.74, 66.75, 66.29, 46.01, 43.18, 42.44, 34.05, 20.29. **HRMS** calcd. for $C_{16}H_{20}N_3O_3^+$ $[M+H]^+$: 302.1505, Found: 302.1505.

2-methyl-6-(1-morpholino-1-oxopropan-2-yl)isoindolin-1-one (3s): The title compound was prepared on a 0.200 mmol scale according to General Procedure A. The crude residue was purified by preparative TLC (10% MeOH/DCM). Purification afforded **3s** as an off-white solid (46.1 mg, 80%). **¹H NMR** (600 MHz, $CDCl_3$) δ 7.69 (d, J = 1.7 Hz, 1H), 7.45 (dd, J = 7.9, 1.7 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 4.36 (s, 2H), 3.96 (q, J = 6.9 Hz, 1H), 3.76–3.68 (m, 1H), 3.68–3.58 (m, 2H), 3.58–3.45 (m, 3H), 3.42 (dtd, J = 13.7, 6.7, 6.3, 4.1 Hz, 1H), 3.28 (ddd, J = 13.2, 6.1, 2.9 Hz, 1H), 3.19 (s, 3H), 3.14 (ddt, J = 10.8, 7.3, 3.8 Hz, 1H), 1.46 (d, J = 6.9 Hz, 3H). **¹³C NMR** (150 MHz, $CDCl_3$) δ 171.78, 168.31, 142.12, 139.70, 133.60, 129.87, 123.36, 122.56, 66.76, 66.32, 51.85, 45.99, 42.92, 42.38, 29.50, 20.67. **HRMS** calcd. for $C_{16}H_{21}N_2O_3^+$ $[M+H]^+$: 289.1552, Found: 289.1556.

***N,N*-dibenzyl-2-phenylpropanamide (5a):** The title compound was prepared on a 0.200 mmol scale according to General Procedure B. The crude residue was purified by preparative TLC (40% EtOAc/hexanes). Purification afforded **5a** as an off-white solid (58.0 mg, 88%). **¹H NMR** (600 MHz, $CDCl_3$) δ 7.39–7.22 (m, 11H), 7.17–7.13 (m, 2H), 7.10–7.05 (m, 2H), 5.14 (d, J = 14.8 Hz, 1H), 4.58 (d, J = 17.1 Hz, 1H), 4.16 (dd, J = 26.0, 16.0 Hz, 2H), 3.91 (q, J = 6.8 Hz, 1H), 1.52 (d, J = 6.8 Hz, 3H). **¹³C NMR** (150 MHz, $CDCl_3$) δ 174.36, 141.81, 137.46, 136.70, 128.94, 128.93, 128.75, 128.51, 128.12, 127.56, 127.36, 127.28, 126.97, 126.32, 49.61, 48.41, 43.38, 21.08. **HRMS** calcd. for $C_{23}H_{24}NO^+$ $[M+H]^+$: 330.1858, Found: 330.1862.

***N,N*-dimethyl-2-phenylpropanamide (5b):** The title compound was prepared on a 0.200 mmol scale according to General Procedure B. The crude residue was purified by preparative TLC (40% EtOAc/hexanes). Purification afforded **5b** as an off-white solid (22.7 mg, 64%). **¹H NMR** (600 MHz, $CDCl_3$) δ 7.33 (t, J = 7.5 Hz, 2H), 7.29 (d, J = 1.6 Hz, 1H), 7.28 (d, J = 1.3 Hz,

1H), 7.27–7.20 (m, 1H), 3.90 (q, $J = 6.8$ Hz, 1H), 2.98 (s, 3H), 2.91 (s, 3H), 1.46 (d, $J = 6.9$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 173.67, 141.93, 128.83, 127.33, 126.72, 43.29, 37.15, 35.93, 20.75. HRMS calcd. for $\text{C}_{11}\text{H}_{16}\text{NO}^+$ $[\text{M}+\text{H}]^+$: 178.1232, Found: 178.1234.

N,2-diphenylpropanamide (5c): The title compound was prepared on a 0.200 mmol scale according to General Procedure B. The crude residue was purified by preparative TLC (60% EtOAc/hexanes). Purification afforded **5c** as an off-white solid (25.0 mg, 56%). ^1H NMR (600 MHz, CDCl_3) δ 7.48–7.38 (m, 6H), 7.38–7.27 (m, 3H), 7.12–7.05 (m, 2H), 3.74 (q, $J = 7.1$ Hz, 1H), 1.63 (d, $J = 7.3$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 171.78, 140.46, 137.38, 128.73, 128.46, 127.27, 127.15, 123.79, 119.21, 47.71, 18.10. HRMS calcd. For $\text{C}_{15}\text{H}_{15}\text{NO}$ $[\text{M}+\text{H}]^+$: 226.1232, Found: 226.1232.

2-phenyl-N-(o-tolyl)propanamide (5d): The title compound was prepared on a 0.200 mmol scale according to General Procedure B. The crude residue was purified by preparative TLC (60% EtOAc/hexanes). Purification afforded **5d** as an off-white solid. (28.5 mg, 60%) ^1H NMR (600 MHz, CDCl_3) δ 7.90 (d, $J = 8.1$ Hz, 1H), 7.43 (d, $J = 6.3$ Hz, 4H), 7.40–7.30 (m, 2H), 7.20 (td, $J = 7.8, 1.6$ Hz, 1H), 7.10 (d, $J = 7.4$ Hz, 1H), 7.06–7.01 (m, 1H), 6.90 (s, 1H), 3.82 (q, $J = 7.2$ Hz, 1H), 1.91 (s, 3H), 1.68 (d, $J = 7.3$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 171.83, 140.53, 135.27, 129.84, 128.80, 127.66, 127.43, 127.30, 126.31, 124.33, 121.63, 47.64, 17.56, 16.66. HRMS calcd. for $\text{C}_{15}\text{H}_{15}\text{NO}^+$ $[\text{M}+\text{H}]^+$: 240.1388, Found: 240.1387.

N-(4-methoxyphenyl)-2-phenylpropanamide (5e): The title compound was prepared on a 0.200 mmol scale according to General Procedure B. The crude residue was purified by preparative TLC (60% EtOAc/hexanes). Purification afforded **5e** as an off-white solid (29.4 mg, 58%). ^1H NMR (600 MHz, CDCl_3) δ 7.42–7.36 (m, 4H), 7.36–7.30 (m, 3H), 7.06 (broad s, 1H), 6.84–6.79 (m, 2H), 3.78 (s, 3H), 3.72 (q, $J = 7.1$ Hz, 1H), 1.62 (d, $J = 7.2$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 171.74, 155.93, 140.64, 130.53, 128.66, 127.16 (d, $J = 31.1$ Hz), 121.18, 113.59, 55.01, 47.45, 18.15. HRMS calcd. for $\text{C}_{16}\text{H}_{17}\text{NO}_2^+$ $[\text{M}+\text{H}]^+$: 256.1338, Found: 256.1336.

N-isopropyl-2-phenylpropanamide (5f): The title compound was prepared on an 0.200 mmol scale according to General Procedure B. The crude residue was purified by preparative LCMS. Purification afforded **5f** as an off white solid. (x mg, x%). ^1H NMR (600 MHz, CDCl_3) δ 7.39–7.33 (m, 2H), 7.33–7.24 (m, 3H), 5.29 (d, $J = 22.2$ Hz, 1H), 4.06 (dhept, $J = 8.2, 6.5$ Hz, 1H), 3.58 (q, $J = 7.2$ Hz, 1H), 1.53 (d, $J = 7.2$ Hz, 3H), 1.09 (d, $J = 6.6$ Hz, 3H), 1.04 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 173.21, 141.65, 128.87, 127.60, 127.15, 47.21, 41.39, 22.64, 22.55, 18.66. HRMS calcd. for $\text{C}_{12}\text{H}_{17}\text{NO}^+$ $[\text{M}+\text{H}]^+$: 192.1388, Found: 192.1388.

N-cyclobutyl-2-phenylpropanamide (5g): The title compound was prepared on a 0.200 mmol scale according to General Procedure B. The crude residue was purified by preparative TLC (20% EtOAc/hexanes). Purification afforded **5g** as an off-white solid. (22.8 mg, 56%). ^1H NMR (600 MHz, CDCl_3) δ 7.39–7.34 (m, 2H), 7.31–7.26 (m, 2H), 5.48 (s, 1H), 4.46–4.25 (m, 1H), 3.52 (q, $J = 7.2$ Hz, 1H), 2.36–2.20 (m, 2H), 1.80–1.59 (m, 4H), 1.52 (d, $J = 7.2$ Hz, 3H). ^{13}C NMR (150 MHz, CDCl_3) δ 172.70, 141.05, 128.44, 127.18, 126.75, 46.59, 44.37, 30.67, 30.61, 18.16, 14.50. HRMS calcd. for $\text{C}_{13}\text{H}_{17}\text{NO}^+$ $[\text{M}+\text{H}]^+$: 204.1388, Found: 204.1389.

2-phenyl-*N*-(thiophen-2-ylmethyl)propanamide (5h): The title compound was prepared on a 0.200 mmol scale according to General Procedure B. The crude residue was purified by preparative TLC (60% EtOAc/hexanes). Purification afforded **5h** as an off-white solid (23.3 mg, 48%). ¹H NMR (600 MHz, CDCl₃) δ 7.39–7.33 (m, 2H), 7.33–7.26 (m, 3H), 7.20 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.92 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.87 (dt, *J* = 3.5, 1.1 Hz, 1H), 5.74 (s, 1H), 4.64–4.52 (m, 2H), 3.61 (q, *J* = 7.2 Hz, 1H), 1.57 (s, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 173.36, 140.65 (d, *J* = 3.3 Hz), 128.51, 128.33, 127.26, 126.90, 126.33, 125.15, 124.57, 46.62, 38.04, 18.03. HRMS calcd. For C₁₄H₁₅NOS⁺ [M+H]⁺: 246.0953, Found: 246.0952.

***N*-(furan-2-ylmethyl)-2-phenylpropanamide (5i):** The title compound was prepared on a 0.200 mmol scale according to General Procedure B. The crude residue was purified by preparative TLC (60% EtOAc/hexanes). Purification afforded **5i** as an off-white solid. (34.5 mg, 75%). ¹H NMR (600 MHz, CDCl₃) δ 7.39–7.33 (m, 2H), 7.33–7.25 (m, 4H), 6.29 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.12 (dd, *J* = 3.2, 0.9 Hz, 1H), 5.73 (d, *J* = 6.9 Hz, 1H), 4.44 (dd, *J* = 15.6, 5.7 Hz, 1H), 4.39–4.33 (m, 1H), 3.60 (q, *J* = 7.2 Hz, 1H), 1.55 (d, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 173.45, 150.88, 141.61, 140.75, 128.48, 127.21, 126.86, 109.91, 106.67, 46.59, 36.23, 18.10. HRMS calcd. for C₁₄H₁₅NO₂⁺ [M+H]⁺: 230.1181, Found: 230.1179.

***N*-(2-(1H-indol-3-yl)ethyl)-2-phenylpropanamide (5j):** The title compound was prepared on a 0.200 mmol scale according to General Procedure B. The crude residue was purified by preparative TLC (60% EtOAc/hexanes). Purification afforded **5j** as an off-white solid. (30.2 mg, 52%). ¹H NMR (600 MHz, CDCl₃) δ 7.95 (s, 1H), 7.55 (dq, *J* = 7.8, 0.9 Hz, 1H), 7.37 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.34–7.25 (m, 3H), 7.22 (ddt, *J* = 9.2, 6.9, 1.5 Hz, 3H), 7.12 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.72 (d, *J* = 2.3 Hz, 1H), 5.41 (s, 1H), 3.58 (dq, *J* = 12.9, 6.4 Hz, 1H), 3.54–3.46 (m, 2H), 2.95–2.84 (m, 2H), 1.52 (d, *J* = 7.2 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 174.04, 141.52, 136.31, 128.84, 127.69, 127.22, 127.13, 122.17, 121.99, 119.49, 118.71, 112.88, 111.14, 47.21, 39.70, 25.10, 18.40. HRMS calcd. for C₁₉H₂₀N₂O⁺ [M+H]⁺: 293.1654, Found: 293.1654.

ethyl 2-(4-bromophenyl)phenylpropanoate (5k): The title compound was prepared on a 0.200 mmol scale according to General Procedure B. The crude residue was purified by preparative TLC (10% EtOAc/hexanes). Purification afforded **5k** as an off-white solid. (32.7 mg, 64%). ¹H NMR (600 MHz, CDCl₃) δ 7.49–7.44 (m, 2H), 7.23–7.18 (m, 2H), 4.20–4.08 (m, 2H), 3.68 (q, *J* = 7.2 Hz, 1H), 1.50 (d, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 174.07, 139.64, 131.68, 129.27, 121.01, 60.92, 45.04, 18.47, 14.10. HRMS calcd. for C₁₂H₁₃BrO₂⁺ [M+H]⁺: 257.0177, Found: 257.0182.

tert-butyl 2-(4-bromophenyl)phenylpropanoate (5l): The title compound was prepared on a 0.200 mmol scale according to General Procedure B. The crude residue was purified by preparative TLC (10% EtOAc/hexanes). Purification afforded **5l** as an off-white solid in a 16:1 mixture of isomers. (33.6 mg, 59%). ¹H NMR (600 MHz, CDCl₃) δ 7.48–7.43 (m, 2H), 7.22–7.16 (m, 2H), 3.59 (q, *J* = 7.1 Hz, 1H), 1.44 (d, *J* = 3.9 Hz, 3H), 1.41 (s, 9H). ¹³C NMR (150 MHz, CDCl₃) δ 173.34, 140.15, 131.56, 129.21, 120.76, 80.78, 45.97, 27.91, 18.39. HRMS calcd. for C₉H₈BrO₂⁺ [M-tBu]⁺: 228.9864, Found: 228.9861.

1-morpholino-2-phenylbutan-1-one (5m): The title compound was prepared on a 0.100 mmol scale according to General Procedure C. The crude residue was purified by preparative LCMS. Purification afforded **5m** as an off-white solid. (11 mg, 47%). ¹H NMR (600 MHz, CDCl₃) δ 7.37–7.29 (m, 2H), 7.26 (dtd, *J* = 7.2, 2.1, 1.1 Hz, 3H), 3.80 (dd, *J* = 11.1, 5.7 Hz, 1H), 3.67 (ddd, *J* = 12.1, 9.1, 4.4 Hz, 1H), 3.57 (t, *J* = 7.2 Hz, 1H), 3.54–3.48 (m, 3H), 3.48–3.43 (m, 1H), 3.41–3.34 (m, 1H), 3.12 (ddd, *J* = 10.9, 7.3, 2.9 Hz, 1H), 2.14 (dt, *J* = 13.7, 7.3 Hz, 1H), 1.78 (dt, *J* = 13.6, 7.2 Hz, 1H), 0.90 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 171.69, 140.10, 128.84, 127.77, 126.96, 66.83, 66.38, 50.63, 46.05, 42.39, 27.90, 12.39. HRMS calcd. for C₁₄H₁₉NO₂⁺ [M+H]⁺: 234.1494, Found: 234.1498.

1-morpholino-2-phenylhexan-1-one (5n): The title compound was prepared on a 0.100 mmol scale according to General Procedure C. The crude residue was purified by preparative LCMS. Purification afforded **5n** as an off-white solid. (11 mg, 42%). ¹H NMR (600 MHz, CDCl₃) δ 7.35–7.30 (m, 2H), 7.27–7.24 (m, 3H), 3.79 (dd, *J* = 11.2, 5.7 Hz, 1H), 3.71–3.61 (m, 2H), 3.58–3.43 (m, 4H), 3.38 (ddd, *J* = 13.5, 5.9, 3.0 Hz, 1H), 3.12 (ddd, *J* = 10.9, 7.3, 2.9 Hz, 1H), 2.12 (dddd, *J* = 13.5, 10.6, 7.5, 4.6 Hz, 1H), 1.83–1.62 (m, 2H), 1.43–1.24 (m, 3H), 1.24–1.10 (m, 1H), 0.93–0.84 (m, 3H). ¹³C NMR (150 MHz, CDCl₃) δ 171.78, 140.34, 128.84, 127.71, 126.91, 66.82, 66.38, 48.83, 46.06, 42.41, 34.59, 30.01, 22.69, 13.98. HRMS calcd. for C₁₆H₂₃NO₂⁺ [M+H]⁺: 262.1807, Found: 262.1813.

4-methyl-1-morpholino-2-phenylpentan-1-one (5o): The title compound was prepared on a 0.100 mmol scale according to General Procedure C from the corresponding *Z*-alkene starting material. The crude residue was purified by preparative LCMS. Purification afforded **5o** as an off-white solid. (4.2 mg, 16%). ¹H NMR (600 MHz, CDCl₃) δ 7.33 (td, *J* = 7.4, 1.4 Hz, 2H), 7.28–7.22 (m, 3H), 3.79 (q, *J* = 8.4, 7.8 Hz, 2H), 3.68 (d, *J* = 11.0 Hz, 1H), 3.52 (ddd, *J* = 16.3, 11.3, 7.0 Hz, 4H), 3.42 (d, *J* = 13.4 Hz, 1H), 3.15 (dd, *J* = 13.3, 5.7 Hz, 1H), 1.62 (dt, *J* = 13.7, 6.9 Hz, 1H), 1.51 (dp, *J* = 13.5, 6.7 Hz, 2H), 0.93 (dd, *J* = 26.0, 6.6 Hz, 6H). ¹³C NMR (150 MHz, CDCl₃) δ 171.75, 140.38, 128.87, 127.71, 126.90, 66.83, 66.40, 46.23, 46.07, 43.88, 42.43, 25.62, 22.74, 22.56. HRMS calcd. for C₁₆H₂₃NO₂⁺ [M+H]⁺: 262.1807, Found: 262.1815.

4-methyl-1-morpholino-2-phenylpentan-1-one (5p): The title compound was prepared on a 0.100 mmol scale according to General Procedure C from the corresponding *E*-alkene starting material. The crude residue was purified by preparative LCMS. Purification afforded **5p** as an off-white solid. (4.8 mg, 18%). ¹H NMR (600 MHz, CDCl₃) δ 7.33 (td, *J* = 7.4, 1.4 Hz, 2H), 7.28–7.22 (m, 3H), 3.79 (q, *J* = 8.4, 7.8 Hz, 2H), 3.68 (d, *J* = 11.0 Hz, 1H), 3.52 (ddd, *J* = 16.3, 11.3, 7.0 Hz, 4H), 3.42 (d, *J* = 13.4 Hz, 1H), 3.15 (dd, *J* = 13.3, 5.7 Hz, 1H), 1.62 (dt, *J* = 13.7, 6.9 Hz, 1H), 1.51 (dp, *J* = 13.5, 6.7 Hz, 2H), 0.93 (dd, *J* = 26.0, 6.6 Hz, 6H). ¹³C NMR (150 MHz, CDCl₃) δ 171.75, 140.38, 128.87, 127.71, 126.90, 66.83, 66.40, 46.23, 46.07, 43.88, 42.43, 25.62, 22.74, 22.56. HRMS calcd. for C₁₆H₂₃NO₂⁺ [M+H]⁺: 262.1807, Found: 262.1814.

1-morpholino-2,3-diphenylpropan-1-one (5q): The title compound was prepared on a 0.100 mmol scale according to General Procedure C. The crude residue was purified by preparative LCMS. Purification afforded **5q** as an off-white solid. (7.0 mg, 24%). ¹H NMR (600 MHz, CDCl₃) δ 7.35–7.29 (m, 3H), 7.28–7.15 (m, 5H), 7.14–7.05 (m, 2H), 3.97 (td, *J* = 7.1, 3.1 Hz, 1H), 3.70 (dt, *J* = 11.4, 5.2 Hz, 1H), 3.54 (tq, *J* = 16.6, 8.0 Hz, 4H), 3.40–3.22 (m, 3H), 3.14–3.05 (m, 1H), 2.99 (dt, *J* = 13.2, 5.0 Hz, 1H). ¹³C NMR (150 MHz, CDCl₃) δ 171.15, 139.81, 139.51, 129.22, 128.81, 128.25, 127.88, 127.16, 126.24, 66.74, 66.24, 50.84, 46.13, 42.48, 40.98. HRMS calcd. for C₁₉H₂₁NO₂⁺ [M+H]⁺: 296.1651, Found: 296.1653.

Unsuccessful Coupling Partners

The following substrates gave less than 15% yield and/or poor selectivity for α -hydroarylation

Figure S3. Unsuccessful coupling partners.

Racemization Experiment

Scheme 5. Racemization test with additive **9**

General Procedure: To a two-dram vial containing a stir bar was added K_3PO_4 (85 mg, 0.40 mmol). Using a micropipette, aryl iodide (0.240 mmol), 4-acryloylmorpholine (28.2 mg, 25.2 μ L, 0.200 mmol), tetramethylammonium formate (30 wt%, 100 μ L, 0.290 mmol), and premixed solution of palladium (4.58 mg, 0.005 mmol) and tris(4-fluoro-phenyl)phosphane (12.7 mg, 0.040 mmol) in 1,4-dioxane (0.133 mL) were added sequentially to the vial. To this vial was added **9** (27.9 mg, 0.100 mmol, >99% ee). The vial was sealed and placed in a pre-heated heating block at 60 $^{\circ}C$ for 1 h. After 1 h, the vial was cooled to room temperature. A small aliquot was removed and dissolved in $CDCl_3$ for 1H NMR analysis (600 MHz). The NMR sample was recombined with the reaction mixture, and the solution was diluted with MeCN to approximately 1 mg/mL and run on 2D chiral-SFC to determine ee. Retention time 1.61 min (minor) and 1.74 min (major).

Figure S4. SFC traces for racemic **9** (A), enantiopure **9** (B), and enantioenriched recovered **9** after reaction conditions (C).

Base-Sensitive Procedure and NMR Spectra

General Procedure for Base-Sensitive Substrates

Scheme S6. General procedure for base-sensitive substrates **4s** and **4t**

To a one-dram vial containing a stir bar was added K₃PO₄ (43 mg, 0.20 mmol) and 1,3,5-trimethoxybenzene (11.2 mg, 0.067 mmol). Using a micropipette, aryl iodide (0.240 mmol), alkene (0.200 mmol), tetramethylammonium formate (30 wt%, 100 μ L, 0.290 mmol), and Pd/Ligand stock solution (133 μ L) were added sequentially to the vial. The vial was sealed and placed in a pre-heated heating block at 80 °C for 1 h. After 1 h, the vial was cooled to room temperature and the contents were dissolved in CDCl₃ for ¹H NMR analysis (600 MHz). Yields are referenced to 1,3,5-trimethoxybenzene as internal standard.

NMR Spectra of Base Sensitive Substrates

Figure S5. Crude NMR spectra of (A) **5r** and (B) **5s**

MECHANISTIC EXPERIMENTS

Synthesis of Compounds 6–8

6⁸ and **7**⁹ were prepared according to literature procedures.

Synthesis and Characterization of Complex **8**

To a 20-mL screw cap vial was added Pd₂(dba)₃ (458 mg, 0.500 mmol), tris(4-fluorophenyl)phosphane (648 mg, 2.05 mmol), and DCM (12 mL). Once homogeneous, this solution was layered with a solution of iodobenzene (613 μ L, 5.50 mmol) in Et₂O and kept in a -10 °C freezer overnight. The precipitate was filtered and dried under vacuum to give 187 mg (0.20 mmol, 40% yield) of monomeric oxidative addition complex as yellow crystals of x-ray diffraction quality. ¹H NMR (600 MHz, CDCl₃) δ 7.44 (ddt, *J* = 10.4, 5.3, 3.7 Hz, 11H), 7.02–6.95 (m, 11H), 6.56 (dtd, *J* = 7.8, 2.3, 1.1 Hz, 2H), 6.53–6.46 (m, 1H), 6.36 (t, *J* = 7.4 Hz, 2H). ¹³C NMR (150 MHz, CDCl₃) δ 163.82 (d, *J* = 252.4 Hz), 159.34, 136.70 (q, *J* = 7.5 Hz), 135.76 (t, *J* = 5.0 Hz), 128.32, 127.26 (td, *J* = 24.5, 3.4 Hz), 122.53, 115.41 (dt, *J* = 21.3, 5.8 Hz). ¹⁹F NMR (376 MHz, CDCl₃) δ -109.52. HRMS calcd. for C₄₂H₂₉F₆P₂Pd⁺ [M-I]⁺: 811.0705, Found: 811.0712. X-ray (single-crystal) If insufficiently pure, crystals of X-ray quality can be grown by recrystallization from hexanes (CCDC 1987658).¹³

General Procedure for Stoichiometric Study

Scheme S7. Stoichiometric study.

To a one-dram vial containing a stir bar was added K₃PO₄ (43 mg, 0.20 mmol) and 1,3,5-trimethoxybenzene (5.6 mg, 0.033 mmol). Using a micropipette, aryl iodide (0.140 mmol), 4-acryloylmorpholine (14.1 mg, 12.6 μ L, 0.100 mmol), tetramethylammoniumformate (30 wt%, 53 μ L, 0.150 mmol), and **8** (106 mg, 0.110 mmol in 66 μ L Dioxane) was added sequentially to the vial. The vial was sealed and placed in a pre-heated heating block at 80 °C for 60 minutes. After 60 minutes, the vial was cooled to room temperature and the contents were dissolved in CDCl₃ for ¹H NMR analysis (600 MHz). Yields are referenced to 1,3,5-trimethoxybenzene as internal standard.

General Procedure for Determination of Kinetic Isotope Effect

Scheme S8. Determination of kinetic isotope effect

To a one-dram vial containing a stir bar was added K_3PO_4 (43 mg, 0.20 mmol), sodium formate (2.72 mg, 0.040 mmol), sodium formate-D (2.73 mg, 0.040 mmol), TBABF_4 (16.5 mg, 0.050 mmol), and 1,3,5-trimethoxybenzene (5.6 mg, 0.033 mmol). Using a micropipette, aryl iodide (0.140 mmol), 4-acryloylmorpholine (14.1 mg, 12.6 μL , 0.100 mmol), tetramethylammonium formate (30 wt%, 53 μL , 0.150 mmol), and Pd/Ligand stock solution (66.5 μL) was added sequentially to the vial. The vial was sealed and placed in a pre-heated heating block at 80 $^\circ\text{C}$ for 20 minutes. After 20 minutes, the vial was cooled to room temperature and the contents were dissolved in CDCl_3 for ^1H NMR analysis (600 MHz). The NMR sample was recombined with the reaction mixture, and the solution was loaded directly onto a preparative TLC plate (40% EtOAc/Hexanes) to yield **3a** (2.7 mg, 12%). This was analyzed by high resolution mass spectrometry to determine a KIE of 1.5.

MassWorks 5.0 idealized Gaussian peaks (black) and best fit of 0–2 deuteriums (green).

MassWorks calculated mixture composition:

Mixture Results:

0.598 C₁₃H₁₈NO₂

0.400 C₁₃H₁₇NO₂[2H]

0.001 C₁₃H₁₆NO₂[2H]₂

Overall Mass Error (mDa): 0.3822

Figure S9. MassWorks determination of kinetic isotope effect

KINETICS PROCEDURES

General Procedure for Reaction Kinetics

All analysis unless otherwise noted is performed via LCMS.

Different/Same Excess:

Pd. Stock: 57 mg Pd₂(dba)₃, 158 mg ligand, and 420 mg 1,3,5-trimethoxybenzene (internal standard, IS) in 1.17 mL DMF.

Alkene Stock: 315 μ L alkene in 250 μ L DMF.

212 mg of tripotassium phosphate was added to a 2-dram vial followed by alkene stock, iodobenzene, and formate in that order. Pd/ligand/IS stock was added and the vial was then placed in a preheated block. 10 μ L aliquots were taken at their respective time points and diluted with 700 μ L MeCN directly into a LCMS plate.

Standard: 113 μ L alkene stock, 250 μ L formate, 67 μ L PhI, 234 μ L palladium stock, 100 μ L DMF

DE-1: 113 μL alkene stock, **125 μL formate**, **100 μL DI water**, 67 μL PhI, 234 μL palladium stock, 100 μL DMF

DE-2: **223 μL alkene stock**, 250 μL formate, 67 μL PhI, 234 μL palladium stock

DE-3: 113 μL alkene stock, 250 μL formate, **134 μL PhI**, 234 μL palladium stock, 100 μL DMF

SE-1: 41.2 μL alkene (neat), 195 μL formate, 65 μL DI water, 50.2 μL PhI, 234 μL palladium stock, 116 μL DMF

SE-2: 41.2 μL alkene (neat), 195 μL formate, 65 μL DI water, 50.2 μL PhI, 234 μL palladium stock, 116 μL DMF, **27.4 mg product**

Palladium Order:

A palladium ligand stock solution was prepared using 183.2 mg $\text{Pd}_2(\text{dba})_3$, 508 mg ligand, and 0.664 mL of DMF. This was allowed to stir for 5 minutes until dissolved. An acrylamide, iodobenzene, internal standard stock was prepared using 315 μL of alkene, 335 μL of PhI, and 420 mg of 1,3,5-trimethoxybenzene in 830 μL of DMF. 212 mg of tripotassium phosphate was weighed into a 2-dram vial and 296 μL of alkene stock was added followed by 260 μL of formate. Pd/ligand stock was added followed by DMF to dilute to the proper concentration. The vial was then placed in a preheated block. 5 μL aliquots were taken at their respective time points and diluted with 450 μL MeCN directly into a filter vial.

A: to this vial was added 66 μL of palladium stock followed by 200 μL of DMF to reach palladium concentration of 0.046 M

B: to this vial was added 166 μL of palladium stock followed by 100 μL of DMF to reach palladium concentration of 0.116 M

C: to this vial was added 266 μL of palladium stock to reach palladium concentration of 0.185 M

Kinetics Results

Same/Different Excess

Figure S6. (A) Same excess experiment for reaction shown in eq. 1. (B) Different excess experiments of the reaction shown in eq. 1.

Determining Order in Palladium

[3a] vs Time		0.046 M	0.116 M	0.185 M
induction period	0 min	0 M	0 M	0 M
	1 min	0 M	0.006 M	0.006 M
	2 min	0.005 M	0.012 M	0.018 M
	3 min	0.015 M	0.023 M	0.074 M
	4 min	0.065 M	0.215 M	0.145 M
	5 min	0.048 M	0.302 M	0.489 M
	7 min	0.155 M	0.492 M	0.695 M

Figure S7. Determination of order in palladium using initial rates.

Full Reaction Profile

Figure S8. Graphical representation the speciation during the course of the reaction.

Ligand Loadings

Kinetics performed followed Palladium Order general procedure with the exception that palladium, ligand, and base are weighed individually into each vial, allowed to premix, and then charged with alkene/ArI/IS stock, and formate.

Figure S9. Different excess experiment varying ligand loadings.

In Situ NMR Study

To an NMR tube was added 4-acryloylmorpholine (62.9 μL , 0.500 mmol), iodobenzene (66.9 μL , 0.600 mmol), tetramethylammonium formate (260 μL , 30 wt %, 0.750 mmol), tripotassium phosphate (212 mg, 1.00 mmol), and 400 μL of DMF-d_7 . This was placed in a 400 MHz spectrometer and brought to 70 $^\circ\text{C}$. Once at temperature, the sample was locked and shimmed. To this warm NMR tube was added premixed $\text{Pd}_2(\text{dba})_3$ (11.4 mg, 0.0125 mmol) and triphenylphosphine (26.2 mg, 0.100 mmol) in 100 μL DMF-d_7 . This was placed back in the spectrometer and spectra was collected every two minutes for 18 minutes.

Figure S10. *In situ* NMR spectrum.

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X-RAY CRYSTALLOGRAPHY

Experimental Summary for Crystal_8 (CCDC 1987658)

Figure S11. Single crystal X-ray structure of **8**

The single crystal X-ray diffraction studies were carried out on a Bruker APEX II ULTRA CCD diffractometer equipped with Mo K α radiation ($\lambda = 0.71073 \text{ \AA}$). Crystals of the subject compound were used as received (grown from DCM/Et₂O). A 0.170 x 0.060 x 0.050 mm colorless block crystal was mounted on a Cryoloop with Paratone N oil.

Data were collected in a nitrogen gas stream at 100(2) K using π scans. Crystal-to-detector distance was 45 mm using an exposure time of 1.0 second with a scan width of 0.65°. Data collection was 100.0% complete to 25.242° in θ . A total of 32138 reflections were collected. 7932 reflections were found to be symmetry independent, with an R_{int} of 0.0419. Indexing and unit cell refinement indicated a **Primitive Monoclinic** lattice. The space group was found to be ***P2₁/c***. The data were integrated using the Bruker SAINT Software program and scaled using the SADABS software program. Solution by direct methods (SHELXT) produced a complete phasing model consistent with the proposed structure.

All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All carbon bonded hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Notes: Excellent data and refinement. The crystal lattice contains one molecule of CH₂Cl₂ (disordered) per formula unit.

Table S2. Crystal data and structure refinement for Engle213.

Report date	2019-10-03	
Identification code	Engle213	
Empirical formula	C ₄₃ H ₃₁ Cl ₂ F ₆ I P ₂ Pd	
Formula weight	1027.82	
Temperature	100.0 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 1 2 ₁ /c 1	
Unit cell dimensions	a = 14.9867(6) Å	α = 90°.
	b = 11.4710(5) Å	β = 104.3650(10)°.
	c = 24.2026(10) Å	γ = 90°.
Volume	4030.6(3) Å ³	
Z	4	
Density (calculated)	1.694 Mg/m ³	
Absorption coefficient	1.497 mm ⁻¹	
F(000)	2024	
Crystal size	0.17 x 0.06 x 0.05 mm ³	
Theta range for data collection	1.737 to 26.021°.	
Index ranges	-18 ≤ h ≤ 18, -14 ≤ k ≤ 14, -29 ≤ l ≤ 29	
Reflections collected	32138	
Independent reflections	7932 [R(int) = 0.0419]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.4908 and 0.4379	
Refinement method	Full-matrix least-squares on F ²	

Data / restraints / parameters	7932 / 2 / 503
Goodness-of-fit on F^2	1.030
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0239$, $wR2 = 0.0541$
R indices (all data)	$R1 = 0.0288$, $wR2 = 0.0565$
Extinction coefficient	n/a
Largest diff. peak and hole	0.475 and -0.338 e. $\text{\AA}^{-3}$

Table S3. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for Engle213. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
I(1)	4142(1)	3606(1)	2402(1)	15(1)
Pd(1)	2784(1)	5052(1)	2543(1)	10(1)
P(1)	3264(1)	4899(1)	3527(1)	11(1)
P(2)	2271(1)	5408(1)	1568(1)	11(1)
F(1)	7290(1)	5593(1)	4397(1)	25(1)
F(2)	1951(1)	473(1)	4308(1)	38(1)
F(3)	1739(1)	8403(1)	4850(1)	28(1)
F(4)	-118(1)	9565(1)	932(1)	25(1)
F(5)	448(1)	1405(1)	204(1)	24(1)
F(6)	5494(1)	6225(1)	609(1)	32(1)
C(1)	4508(2)	5036(2)	3798(1)	13(1)
C(2)	5023(2)	4367(2)	4244(1)	15(1)
C(3)	5967(2)	4541(2)	4442(1)	18(1)
C(4)	6370(2)	5399(2)	4194(1)	17(1)
C(5)	5891(2)	6087(2)	3752(1)	18(1)
C(6)	4955(2)	5884(2)	3550(1)	16(1)
C(7)	2915(2)	3518(2)	3780(1)	14(1)
C(8)	2558(2)	2642(2)	3388(1)	16(1)
C(9)	2235(2)	1608(2)	3564(1)	22(1)
C(10)	2277(2)	1473(2)	4137(1)	24(1)

C(11)	2616(2)	2316(2)	4534(1)	23(1)
C(12)	2936(2)	3339(2)	4354(1)	18(1)
C(13)	2832(2)	5959(2)	3958(1)	13(1)
C(14)	3304(2)	6996(2)	4142(1)	16(1)
C(15)	2937(2)	7822(2)	4439(1)	20(1)
C(16)	2098(2)	7608(2)	4553(1)	19(1)
C(17)	1610(2)	6603(2)	4380(1)	20(1)
C(18)	1978(2)	5789(2)	4078(1)	17(1)
C(19)	1533(2)	6671(2)	1328(1)	12(1)
C(20)	645(2)	6673(2)	1414(1)	17(1)
C(21)	82(2)	7649(2)	1279(1)	18(1)
C(22)	422(2)	8603(2)	1056(1)	17(1)
C(23)	1275(2)	8626(2)	949(1)	19(1)
C(24)	1835(2)	7652(2)	1089(1)	16(1)
C(25)	1636(2)	4207(2)	1160(1)	12(1)
C(26)	1134(2)	4367(2)	595(1)	16(1)
C(27)	724(2)	3423(2)	272(1)	18(1)
C(28)	827(2)	2335(2)	521(1)	18(1)
C(29)	1296(2)	2150(2)	1078(1)	18(1)
C(30)	1711(2)	3099(2)	1397(1)	15(1)
C(31)	3246(2)	5641(2)	1258(1)	13(1)
C(32)	3918(2)	6453(2)	1512(1)	14(1)
C(33)	4668(2)	6665(2)	1291(1)	17(1)
C(34)	4753(2)	6018(2)	827(1)	19(1)
C(35)	4129(2)	5185(2)	575(1)	20(1)

C(36)	3364(2)	5004(2)	794(1)	17(1)
C(37)	1662(2)	5876(2)	2668(1)	14(1)
C(38)	895(2)	5205(2)	2683(1)	18(1)
C(39)	103(2)	5735(3)	2771(1)	27(1)
C(40)	76(2)	6923(3)	2848(1)	34(1)
C(41)	840(2)	7588(2)	2838(1)	29(1)
C(42)	1632(2)	7072(2)	2746(1)	19(1)
C(43)	3628(2)	10182(2)	2694(1)	26(1)
Cl(1)	3638(5)	9253(5)	3276(2)	27(1)
Cl(2)	2536(3)	10198(5)	2192(1)	37(1)
Cl(1A)	3622(14)	9089(11)	3205(5)	27(1)
Cl(2A)	2675(5)	9890(8)	2130(3)	37(1)

Table S4. Bond lengths [Å] and angles [°] for Engle213.

I(1)-Pd(1)	2.7114(2)
Pd(1)-P(1)	2.3175(6)
Pd(1)-P(2)	2.3302(6)
Pd(1)-C(37)	2.016(2)
P(1)-C(1)	1.824(2)
P(1)-C(7)	1.821(2)
P(1)-C(13)	1.823(2)
P(2)-C(19)	1.828(2)
P(2)-C(25)	1.820(2)
P(2)-C(31)	1.820(2)
F(1)-C(4)	1.363(3)
F(2)-C(10)	1.352(3)
F(3)-C(16)	1.354(3)
F(4)-C(22)	1.357(3)
F(5)-C(28)	1.355(3)
F(6)-C(34)	1.363(3)
C(1)-C(2)	1.392(3)
C(1)-C(6)	1.398(3)
C(2)-H(2)	0.9500
C(2)-C(3)	1.390(3)
C(3)-H(3)	0.9500
C(3)-C(4)	1.369(4)
C(4)-C(5)	1.378(3)

C(5)-H(5)	0.9500
C(5)-C(6)	1.386(3)
C(6)-H(6)	0.9500
C(7)-C(8)	1.394(3)
C(7)-C(12)	1.399(3)
C(8)-H(8)	0.9500
C(8)-C(9)	1.387(3)
C(9)-H(9)	0.9500
C(9)-C(10)	1.381(4)
C(10)-C(11)	1.370(4)
C(11)-H(11)	0.9500
C(11)-C(12)	1.378(3)
C(12)-H(12)	0.9500
C(13)-C(14)	1.400(3)
C(13)-C(18)	1.393(3)
C(14)-H(14)	0.9500
C(14)-C(15)	1.383(3)
C(15)-H(15)	0.9500
C(15)-C(16)	1.374(3)
C(16)-C(17)	1.374(3)
C(17)-H(17)	0.9500
C(17)-C(18)	1.383(3)
C(18)-H(18)	0.9500
C(19)-C(20)	1.397(3)
C(19)-C(24)	1.391(3)

C(20)-H(20)	0.9500
C(20)-C(21)	1.391(3)
C(21)-H(21)	0.9500
C(21)-C(22)	1.374(3)
C(22)-C(23)	1.365(3)
C(23)-H(23)	0.9500
C(23)-C(24)	1.388(3)
C(24)-H(24)	0.9500
C(25)-C(26)	1.399(3)
C(25)-C(30)	1.388(3)
C(26)-H(26)	0.9500
C(26)-C(27)	1.387(3)
C(27)-H(27)	0.9500
C(27)-C(28)	1.378(3)
C(28)-C(29)	1.373(3)
C(29)-H(29)	0.9500
C(29)-C(30)	1.389(3)
C(30)-H(30)	0.9500
C(31)-C(32)	1.397(3)
C(31)-C(36)	1.389(3)
C(32)-H(32)	0.9500
C(32)-C(33)	1.381(3)
C(33)-H(33)	0.9500
C(33)-C(34)	1.378(3)
C(34)-C(35)	1.371(3)

C(35)-H(35)	0.9500
C(35)-C(36)	1.392(3)
C(36)-H(36)	0.9500
C(37)-C(38)	1.392(3)
C(37)-C(42)	1.388(3)
C(38)-H(38)	0.9500
C(38)-C(39)	1.396(3)
C(39)-H(39)	0.9500
C(39)-C(40)	1.376(4)
C(40)-H(40)	0.9500
C(40)-C(41)	1.381(4)
C(41)-H(41)	0.9500
C(41)-C(42)	1.393(4)
C(42)-H(42)	0.9500
C(43)-H(43A)	0.9900
C(43)-H(43B)	0.9900
C(43)-H(43C)	0.9900
C(43)-H(43D)	0.9900
C(43)-Cl(1)	1.762(5)
C(43)-Cl(2)	1.779(4)
C(43)-Cl(1A)	1.762(12)
C(43)-Cl(2A)	1.746(8)
P(1)-Pd(1)-I(1)	91.800(16)
P(1)-Pd(1)-P(2)	174.10(2)

P(2)-Pd(1)-I(1)	92.824(16)
C(37)-Pd(1)-I(1)	170.22(7)
C(37)-Pd(1)-P(1)	86.52(6)
C(37)-Pd(1)-P(2)	89.53(6)
C(1)-P(1)-Pd(1)	113.08(8)
C(7)-P(1)-Pd(1)	111.68(8)
C(7)-P(1)-C(1)	107.93(11)
C(7)-P(1)-C(13)	102.43(11)
C(13)-P(1)-Pd(1)	118.30(7)
C(13)-P(1)-C(1)	102.33(10)
C(19)-P(2)-Pd(1)	118.77(7)
C(25)-P(2)-Pd(1)	114.45(8)
C(25)-P(2)-C(19)	103.56(10)
C(25)-P(2)-C(31)	104.70(10)
C(31)-P(2)-Pd(1)	110.20(7)
C(31)-P(2)-C(19)	103.75(10)
C(2)-C(1)-P(1)	123.50(18)
C(2)-C(1)-C(6)	119.0(2)
C(6)-C(1)-P(1)	117.47(17)
C(1)-C(2)-H(2)	119.7
C(3)-C(2)-C(1)	120.6(2)
C(3)-C(2)-H(2)	119.7
C(2)-C(3)-H(3)	120.8
C(4)-C(3)-C(2)	118.3(2)
C(4)-C(3)-H(3)	120.8

F(1)-C(4)-C(3)	118.5(2)
F(1)-C(4)-C(5)	118.2(2)
C(3)-C(4)-C(5)	123.3(2)
C(4)-C(5)-H(5)	121.1
C(4)-C(5)-C(6)	117.7(2)
C(6)-C(5)-H(5)	121.1
C(1)-C(6)-H(6)	119.5
C(5)-C(6)-C(1)	121.0(2)
C(5)-C(6)-H(6)	119.5
C(8)-C(7)-P(1)	119.52(18)
C(8)-C(7)-C(12)	118.7(2)
C(12)-C(7)-P(1)	121.63(18)
C(7)-C(8)-H(8)	119.6
C(9)-C(8)-C(7)	120.8(2)
C(9)-C(8)-H(8)	119.6
C(8)-C(9)-H(9)	121.0
C(10)-C(9)-C(8)	118.1(2)
C(10)-C(9)-H(9)	121.0
F(2)-C(10)-C(9)	118.2(2)
F(2)-C(10)-C(11)	118.9(2)
C(11)-C(10)-C(9)	122.9(2)
C(10)-C(11)-H(11)	120.8
C(10)-C(11)-C(12)	118.4(2)
C(12)-C(11)-H(11)	120.8
C(7)-C(12)-H(12)	119.5

C(11)-C(12)-C(7)	121.1(2)
C(11)-C(12)-H(12)	119.5
C(14)-C(13)-P(1)	121.67(18)
C(18)-C(13)-P(1)	120.05(18)
C(18)-C(13)-C(14)	118.1(2)
C(13)-C(14)-H(14)	119.6
C(15)-C(14)-C(13)	120.8(2)
C(15)-C(14)-H(14)	119.6
C(14)-C(15)-H(15)	120.5
C(16)-C(15)-C(14)	118.9(2)
C(16)-C(15)-H(15)	120.5
F(3)-C(16)-C(15)	119.4(2)
F(3)-C(16)-C(17)	118.4(2)
C(17)-C(16)-C(15)	122.3(2)
C(16)-C(17)-H(17)	120.8
C(16)-C(17)-C(18)	118.3(2)
C(18)-C(17)-H(17)	120.8
C(13)-C(18)-H(18)	119.2
C(17)-C(18)-C(13)	121.5(2)
C(17)-C(18)-H(18)	119.2
C(20)-C(19)-P(2)	118.56(17)
C(24)-C(19)-P(2)	122.63(18)
C(24)-C(19)-C(20)	118.7(2)
C(19)-C(20)-H(20)	119.6
C(21)-C(20)-C(19)	120.7(2)

C(21)-C(20)-H(20)	119.6
C(20)-C(21)-H(21)	121.0
C(22)-C(21)-C(20)	118.1(2)
C(22)-C(21)-H(21)	121.0
F(4)-C(22)-C(21)	118.3(2)
F(4)-C(22)-C(23)	118.6(2)
C(23)-C(22)-C(21)	123.1(2)
C(22)-C(23)-H(23)	120.8
C(22)-C(23)-C(24)	118.4(2)
C(24)-C(23)-H(23)	120.8
C(19)-C(24)-H(24)	119.5
C(23)-C(24)-C(19)	120.9(2)
C(23)-C(24)-H(24)	119.5
C(26)-C(25)-P(2)	120.83(18)
C(30)-C(25)-P(2)	119.40(17)
C(30)-C(25)-C(26)	119.6(2)
C(25)-C(26)-H(26)	119.9
C(27)-C(26)-C(25)	120.3(2)
C(27)-C(26)-H(26)	119.9
C(26)-C(27)-H(27)	120.8
C(28)-C(27)-C(26)	118.3(2)
C(28)-C(27)-H(27)	120.8
F(5)-C(28)-C(27)	118.7(2)
F(5)-C(28)-C(29)	118.4(2)
C(29)-C(28)-C(27)	123.0(2)

C(28)-C(29)-H(29)	120.9
C(28)-C(29)-C(30)	118.3(2)
C(30)-C(29)-H(29)	120.9
C(25)-C(30)-C(29)	120.6(2)
C(25)-C(30)-H(30)	119.7
C(29)-C(30)-H(30)	119.7
C(32)-C(31)-P(2)	118.83(17)
C(36)-C(31)-P(2)	122.16(18)
C(36)-C(31)-C(32)	118.9(2)
C(31)-C(32)-H(32)	119.5
C(33)-C(32)-C(31)	121.0(2)
C(33)-C(32)-H(32)	119.5
C(32)-C(33)-H(33)	121.0
C(34)-C(33)-C(32)	118.0(2)
C(34)-C(33)-H(33)	121.0
F(6)-C(34)-C(33)	118.1(2)
F(6)-C(34)-C(35)	118.7(2)
C(35)-C(34)-C(33)	123.2(2)
C(34)-C(35)-H(35)	121.0
C(34)-C(35)-C(36)	118.0(2)
C(36)-C(35)-H(35)	121.0
C(31)-C(36)-C(35)	120.8(2)
C(31)-C(36)-H(36)	119.6
C(35)-C(36)-H(36)	119.6
C(38)-C(37)-Pd(1)	118.05(18)

C(42)-C(37)-Pd(1)	122.73(18)
C(42)-C(37)-C(38)	119.2(2)
C(37)-C(38)-H(38)	119.9
C(37)-C(38)-C(39)	120.1(2)
C(39)-C(38)-H(38)	119.9
C(38)-C(39)-H(39)	119.8
C(40)-C(39)-C(38)	120.4(3)
C(40)-C(39)-H(39)	119.8
C(39)-C(40)-H(40)	120.2
C(39)-C(40)-C(41)	119.6(2)
C(41)-C(40)-H(40)	120.2
C(40)-C(41)-H(41)	119.7
C(40)-C(41)-C(42)	120.7(3)
C(42)-C(41)-H(41)	119.7
C(37)-C(42)-C(41)	120.0(2)
C(37)-C(42)-H(42)	120.0
C(41)-C(42)-H(42)	120.0
H(43A)-C(43)-H(43B)	107.9
H(43C)-C(43)-H(43D)	108.8
Cl(1)-C(43)-H(43A)	109.2
Cl(1)-C(43)-H(43B)	109.2
Cl(1)-C(43)-Cl(2)	112.1(3)
Cl(2)-C(43)-H(43A)	109.2
Cl(2)-C(43)-H(43B)	109.2
Cl(1A)-C(43)-H(43C)	110.6

Cl(1A)-C(43)-H(43D)	110.6
Cl(2A)-C(43)-H(43C)	110.6
Cl(2A)-C(43)-H(43D)	110.6
Cl(2A)-C(43)-Cl(1A)	105.5(6)

Table S5. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for Engle213. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U ¹¹	U ²²	U ³³	U ²³	U ¹³	U ¹²
I(1)	15(1)	16(1)	14(1)	0(1)	4(1)	3(1)
Pd(1)	11(1)	11(1)	9(1)	0(1)	3(1)	0(1)
P(1)	12(1)	12(1)	9(1)	0(1)	3(1)	0(1)
P(2)	12(1)	12(1)	9(1)	1(1)	2(1)	-1(1)
F(1)	13(1)	36(1)	24(1)	1(1)	1(1)	-1(1)
F(2)	51(1)	17(1)	56(1)	12(1)	31(1)	-3(1)
F(3)	46(1)	17(1)	28(1)	-4(1)	22(1)	7(1)
F(4)	24(1)	20(1)	31(1)	2(1)	6(1)	11(1)
F(5)	30(1)	19(1)	21(1)	-7(1)	2(1)	-8(1)
F(6)	22(1)	47(1)	31(1)	-7(1)	17(1)	-11(1)
C(1)	14(1)	15(1)	10(1)	-4(1)	3(1)	0(1)
C(2)	19(1)	13(1)	13(1)	0(1)	5(1)	-2(1)
C(3)	20(1)	18(1)	14(1)	1(1)	0(1)	6(1)
C(4)	12(1)	24(1)	16(1)	-6(1)	2(1)	0(1)
C(5)	19(1)	21(1)	16(1)	2(1)	6(1)	-3(1)
C(6)	17(1)	19(1)	13(1)	2(1)	5(1)	1(1)
C(7)	17(1)	12(1)	16(1)	2(1)	7(1)	2(1)
C(8)	17(1)	16(1)	19(1)	0(1)	8(1)	1(1)
C(9)	22(1)	14(1)	32(2)	-2(1)	11(1)	0(1)
C(10)	23(1)	14(1)	40(2)	10(1)	19(1)	4(1)

C(11)	26(1)	25(1)	22(1)	11(1)	13(1)	8(1)
C(12)	22(1)	17(1)	16(1)	1(1)	6(1)	4(1)
C(13)	15(1)	14(1)	9(1)	2(1)	1(1)	2(1)
C(14)	19(1)	15(1)	14(1)	3(1)	5(1)	-2(1)
C(15)	30(2)	12(1)	17(1)	-1(1)	5(1)	0(1)
C(16)	31(2)	15(1)	14(1)	2(1)	9(1)	7(1)
C(17)	22(1)	22(1)	18(1)	2(1)	9(1)	3(1)
C(18)	17(1)	17(1)	15(1)	-2(1)	2(1)	-1(1)
C(19)	14(1)	13(1)	8(1)	0(1)	2(1)	0(1)
C(20)	18(1)	21(1)	12(1)	4(1)	4(1)	-1(1)
C(21)	12(1)	27(1)	15(1)	2(1)	3(1)	2(1)
C(22)	20(1)	15(1)	14(1)	-1(1)	1(1)	6(1)
C(23)	22(1)	13(1)	20(1)	1(1)	5(1)	-1(1)
C(24)	15(1)	18(1)	17(1)	-1(1)	6(1)	-1(1)
C(25)	10(1)	16(1)	11(1)	-2(1)	4(1)	-1(1)
C(26)	19(1)	14(1)	15(1)	4(1)	4(1)	1(1)
C(27)	18(1)	24(1)	11(1)	0(1)	-1(1)	0(1)
C(28)	16(1)	19(1)	18(1)	-6(1)	7(1)	-5(1)
C(29)	20(1)	12(1)	20(1)	2(1)	4(1)	-2(1)
C(30)	16(1)	19(1)	11(1)	1(1)	3(1)	-1(1)
C(31)	13(1)	14(1)	11(1)	3(1)	2(1)	3(1)
C(32)	17(1)	13(1)	11(1)	0(1)	3(1)	0(1)
C(33)	14(1)	18(1)	17(1)	2(1)	2(1)	-3(1)
C(34)	14(1)	26(1)	19(1)	4(1)	7(1)	-1(1)
C(35)	20(1)	25(1)	17(1)	-6(1)	9(1)	-1(1)

C(36)	16(1)	18(1)	15(1)	-2(1)	1(1)	-3(1)
C(37)	15(1)	20(1)	9(1)	1(1)	3(1)	3(1)
C(38)	16(1)	24(1)	16(1)	2(1)	4(1)	1(1)
C(39)	16(1)	44(2)	22(1)	7(1)	8(1)	4(1)
C(40)	28(2)	50(2)	26(2)	9(1)	12(1)	23(1)
C(41)	38(2)	26(2)	21(1)	-1(1)	6(1)	18(1)
C(42)	23(1)	20(1)	14(1)	0(1)	3(1)	4(1)
C(43)	19(1)	27(2)	31(2)	9(1)	5(1)	-2(1)
Cl(1)	32(1)	22(1)	24(1)	3(1)	1(1)	-5(1)
Cl(2)	27(1)	49(2)	28(1)	9(1)	-4(1)	-4(1)
Cl(1A)	32(1)	22(1)	24(1)	3(1)	1(1)	-5(1)
Cl(2A)	27(1)	49(2)	28(1)	9(1)	-4(1)	-4(1)

Table S6. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^{-3}$) for Engle213.

	x	y	z	U(eq)
H(2)	4727	3788	4416	18
H(3)	6323	4076	4741	22
H(5)	6192	6680	3592	22
H(6)	4611	6329	3238	19
H(8)	2535	2755	2996	20
H(9)	1991	1009	3298	26
H(11)	2630	2199	4925	28
H(12)	3176	3931	4625	22
H(14)	3884	7136	4061	19
H(15)	3259	8526	4562	24
H(17)	1034	6470	4467	24
H(18)	1641	5098	3948	20
H(20)	423	6000	1566	20
H(21)	-521	7656	1340	22
H(23)	1480	9292	782	22
H(24)	2433	7655	1022	20
H(26)	1074	5126	432	19
H(27)	380	3524	-112	22
H(29)	1337	1392	1241	21

H(30)	2048	2989	1781	18
H(32)	3858	6865	1841	17
H(33)	5112	7240	1454	20
H(35)	4215	4744	260	24
H(36)	2918	4438	623	20
H(38)	910	4384	2634	22
H(39)	-420	5274	2778	33
H(40)	-464	7282	2906	40
H(41)	826	8407	2895	34
H(42)	2151	7539	2737	23
H(43A)	4103	9920	2501	31
H(43B)	3786	10983	2837	31
H(43C)	3574	10964	2856	31
H(43D)	4203	10149	2564	31

4g. 1.fid

cyclobutyl acrylamide

C=CC(=O)N1CCC1

4g

6.30, 6.28, 6.09, 6.07, 6.06, 5.66, 5.64, 5.62, 5.52, 5.51, 5.45, 5.40, 5.38, 5.36, 5.34, 5.32, 5.30, 5.28, 5.26, 5.24, 5.22, 5.20, 5.18, 5.16, 5.14, 5.12, 5.10, 5.08, 5.06, 5.04, 5.02, 5.00, 4.98, 4.96, 4.94, 4.92, 4.90, 4.88, 4.86, 4.84, 4.82, 4.80, 4.78, 4.76, 4.74, 4.72, 4.70, 4.68, 4.66, 4.64, 4.62, 4.60, 4.58, 4.56, 4.54, 4.52, 4.50, 4.48, 4.46, 4.44, 4.42, 4.40, 4.38, 4.36, 4.34, 4.32, 4.30, 4.28, 4.26, 4.24, 4.22, 4.20, 4.18, 4.16, 4.14, 4.12, 4.10, 4.08, 4.06, 4.04, 4.02, 4.00, 3.98, 3.96, 3.94, 3.92, 3.90,

4g.2.fid
cyclobutyl acrylamide

AV-A-277-A2-X.2.fid
A2

8.2.fid
ari complex

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