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Palladium-Catalyzed Direct α-C(sp3) Heteroarylation of Ketones under Microwave Irradiation

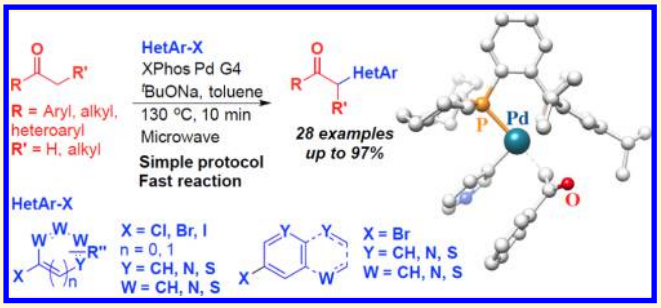
Andrew Quillen,[†] Quynh Nguyen,[†] Matthew Neiser,[†] Kara Lindsay,[†] Alexander Rosen,[†] Stephen Ramirez,[†] Stefana Costan,[†] Nathan Johnson,[†] Thuy Donna Do,[†] Oscar Rodriguez,[‡] Diego Rivera,[‡] Abdurrahman Atesin,[‡] Tülay Aygan Ateşin,[‡] and Lili Ma*[,†]

[†]Department of Chemistry & Biochemistry, Northern Kentucky University, Nunn Drive, Highland Heights, Kentucky 41099, United States

[‡]Department of Chemistry, The University of Texas Rio Grande Valley, Edinburg, Texas 78541, United States

Supporting Information

ABSTRACT: Heteroaryl compounds are valuable building blocks in medicinal chemistry and chemical industry. A palladium-catalyzed direct α-C(sp3) heteroarylation of ketones under microwave irradiation is developed and reported in this study. Under optimized conditions, twenty-eight (28) heteroarylated ketones were prepared in this study to demonstrate the substrate scope of this reaction. The ground-state optimized structure of Pd(0) active catalyst with 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos) in toluene, and the products of its reaction with 3-bromopyridine and acetophenone were studied using all-atom density functional theory. This study provided insightful information for palladium catalytic system design to generate heteroaryl compounds.



INTRODUCTION

Palladium catalysis is becoming more and more important in organic chemistry, medicinal chemistry, and chemical industries.[1] In particular, recent developments in palladium-catalyzed α-arylation of C(sp3)-H bonds in ketones, aldehydes, esters, and other carbonyl compounds have provided a general route to make α-arylated carbonyl compounds.[2] Compared to the conventional methods, the palladium-catalyzed α-arylation of carbonyl compounds has many advantages. For example, the aryl halide substrates are not limited to highly reactive halides only. Also, it utilizes a catalytic amount instead of a stoichiometric amount of transition metal reagents.[3] Therefore, several catalytic systems have been developed for this transformation. Among them, the catalytic systems developed by the research groups of Miura,[4] Buchwald,[5] Hartwig,[6] and Rossi[7] are the most commonly utilized for the α-arylation of carbonyl compounds.

In contrast, the α-heteroarylation of carbonyl compounds is rarely reported in the literature. Because of the difficulty in their synthesis, these compounds tend to be prohibitively expensive despite their simple scaffold (e.g., **HetAr-1** and **HetAr-2** in Figure 1). Heteroaryl compounds are valuable building blocks in medicinal chemistry and chemical industry. Compound *N*-methyl-2-oxo-1-(pyridin-3-yl)-cyclohexanecarbothioamide[8] **HetAr-3** (Figure 1) is a potassium channel opener, and it was developed as an antihypertensive and antianginal agent. Metyrapone[9] and its analogues have been used in the treatment of Cushing's syndrome by inhibiting the 11β-hydroxylase CYP11B1 with very low IC_{50} value (15 nM). The heteroaryl compounds are thought to be difficult substrates due to the coordination of the heteroarenes to the transition metal catalyst that can obstruct the catalytic cycle or lead to catalyst poisoning.[10] In addition to the potential poisoning effect, α-heteroarylation also suffers from two other problems commonly reported in the Pd-catalyzed α-arylation of the carbonyl compounds. First, (bishetero)arylation or (multihetero)arylation are frequently encountered since the α-H in the mono(hetero)arylation product is more acidic than those in the starting material. Second, the self-condensation of carbonyl compounds could occur, especially when more than 1 equiv of carbonyl compounds are used. This may be suppressed by using excess

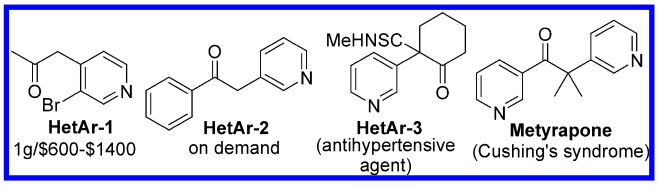


Figure 1. Selected α-heteroaryl ketones as important synthetic building blocks or bioactive molecules.

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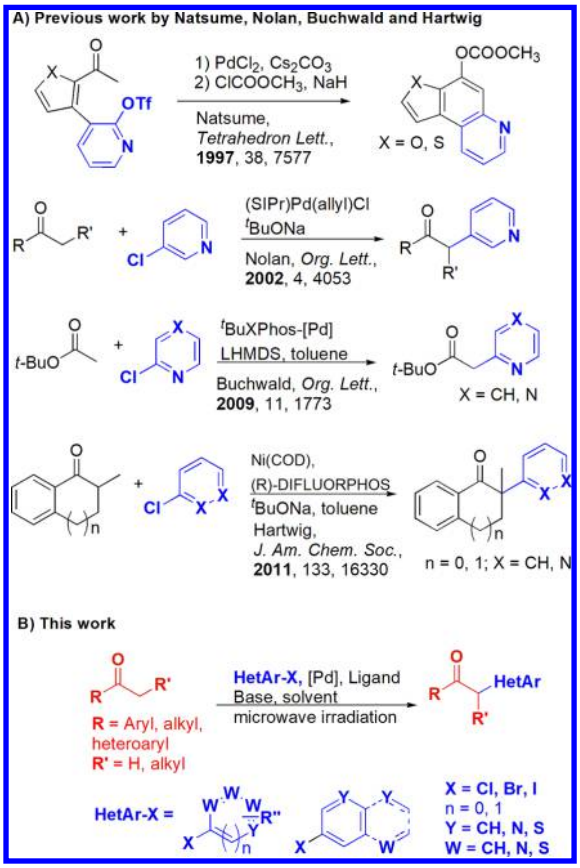
base to convert ketones to enolates. Historically, relevant problems in the α-heteroarylation reactions of carbonyl compounds have been solved using Si, Zn, Sn, and Cu enolates.[11] Many of these reactions suffered from a narrow substrate scope; for example, copper-catalyzed heteroarylation is limited to active methylene ($-COCH_2CO-$) carbons only. Also, the requirement of stoichiometric amounts of tin reagents and/or preparation of an enol ether limit their application as a general method. An early example of direct α-arylation of a ketone using an intramolecular reaction and $PdCl_2$ as a catalyst was reported by Natsume in 1997.[12] In 2002, Nolan reported an arylation reaction using (SIPr)Pd(allyl)Cl as a catalyst, which also works on a few heteroaryl substrates.[13] Biscoe and Buckwald reported a monoarylation of aryl methyl ketones and acetate esters using *t*BuXPhos-[Pd] catalyst in 2009.[5b] This catalytic system also works for some heteroaryl halides such as pyridyl, pyrazinyl, and benzothiazole chlorides. This system represents the closest example of palladium-catalyzed direct α-heteroarylation of ketones. Following this discovery, several new catalysts and ligands were investigated in palladium-catalyzed coupling reactions (Scheme 1).[14]

Scheme 1. α-Heteroarylation of C(sp^3)-H Bond in Ketones



Recent mechanistic studies on palladium catalysis have shed light on the role of ligands: the more electron-rich ligands tend to facilitate the oxidative addition of the (hetero)aryl halide by stabilizing the palladium(II) intermediate, while the sterically hindered ligands make the reductive elimination more facile by pushing the aryl and enolate groups at the palladium center closer together in space so that they coordinate in a cis mode.[15] Inspired by these findings, the discovery of sterically bulky phosphine ligands and a pretreated catalyst/ligand complex has been an active field of study. First, it is possible that strongly coordinating and sterically bulky ligands could shield the active metal catalyst and lead to effective catalyst systems for α-heteroarylation.[16] Second, the use of a bulky ligand could potentially slow down the bisheteroarylation of the monoheteroarylated product and therefore favor the monoheteroarylation reaction. Third, pretreated catalysts or precatalysts will provide the highly active form of palladium/ligand complex to rapidly convert the starting materials, preventing potentially undesirable decomposition of enolates or ketone self-condensation products.

In this project, we investigated the palladium-catalyzed direct α-heteroarylation of ketones under microwave irradiation. Specifically, a variety of palladium catalysts, ligands, bases, and solvents were investigated for the proposed catalytic system. The substrate scope for this catalytic system was examined on a range of ketones and heteroaryl halides. Microwave irradiation was utilized to facilitate the reactions since α-heteroarylation of ketones normally requires high temperature and long reaction times. This work provided useful knowledge to expand the palladium catalysis scope, to understand the roles of palladium catalysts, ligands, and bases, and to facilitate the functionalization of ketones or heteroaryl compounds. Additionally, the development of an efficient catalytic system under microwave irradiation is important for green chemistry since it requires less chemicals, produces fewer byproducts, and generates less chemical waste.

RESULTS AND DISCUSSION

Optimization of Reaction Conditions for the Palladium-Catalyzed α-Heteroarylation of Ketones. As a starting point to investigate the palladium-catalyzed direct α-heteroarylation of ketones, the reaction between acetophenone and 3-bromopyridine was used as a model reaction to optimize the reaction conditions. These reactions were carried out at 0.1 mmol scale in valved pressure NMR tubes (Wilmad-LabGlass, 528-LPV-8) in toluene-d_8. Several inert compounds such as diethyl phthalate, benzyl ether, bibenzyl, and mesitylene were tested, and bibenzyl (δ = 2.80 ppm in Tol-d_8, δ = 2.91 ppm in $CDCl_3$) was used as an internal NMR reference for yield calculation. This model reaction was utilized to screen various catalysts, ligands, and bases (Table 1). The optimal reaction conditions for the direct α-heteroarylation of ketones were 1 equiv of 3-bromopyridine, 1.1 equiv of acetophenone, 1 mol % XPhos Palladacycle Gen. 4 catalyst (XPhos Pd G4), 2.4 equiv of NaO*t*Bu, and toluene. Decent yields were obtained after 4 h at 100 °C or 16–22 h at 60 °C.

The major findings for these reactions are as follows: (1) The ligands that possess bulky groups such as *t*BuXPhos (**L1**), XPhos (**L2**), and JackiePhos (**L4**) showed good activities, which is in agreement with the literature report on similar reaction systems.[17] From XPhos Pd G1 to XPhos Pd G4 catalysts, the steric hindrance of the ligand is getting larger. In our experiments, the best results were obtained with XPhos Palladacycle Generation 4 catalyst (Table 1, entry 17), which is in agreement with our hypothesis. (2) The effective catalyst/ligand system for this reaction included $Pd_2(dba)_3$·*t*BuPHBF$_4$ (Sigma 718246), $Pd_2(dba)_3$/XPhos, XPhos Pd G1 (STREM 46-0268), XPhos Pd G2 (STREM 46-0281), XPhos Pd G3 (STREM 46-0320), and XPhos Pd G4 (STREM 46-0327), with yields in the range of 60–90%. Some catalysts such as (SIPr)Pd(allyl)Cl, $PdCl_2$, and $Pd(OAc)_2$ showed some

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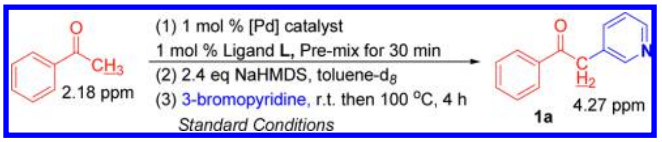
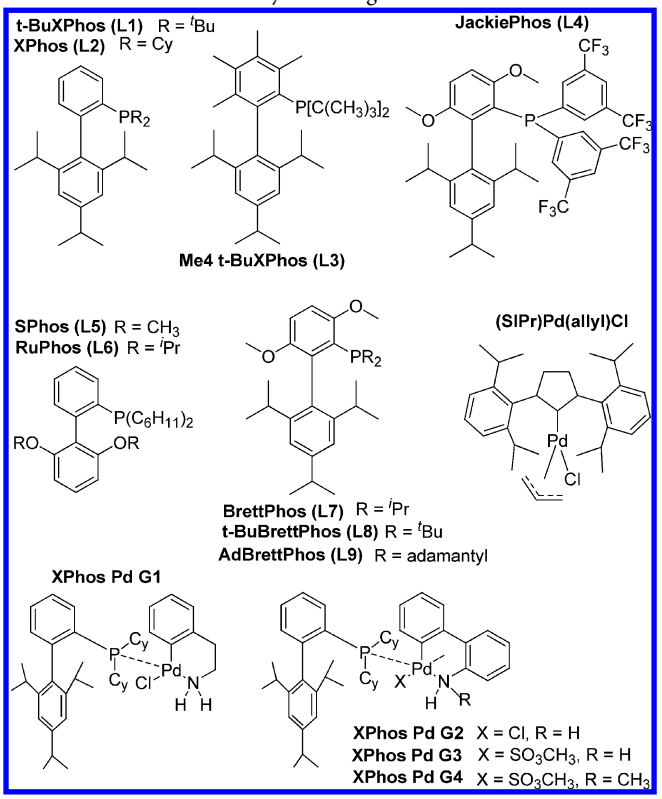
Table 1. Reaction Condition Optimization for the Direct α-Heteroarylation of Ketones[a]



entry	catalyst and ligand (L)[b]	base	yield (%)[c]
1	$Pd(OAc)_2$, **L1**	NaHMDS	36
2	$PdCl_2$, **L1**	NaHMDS	26
3	$Pd_2(dba)_3$, **L1**	NaHMDS	65
4	$Pd_2(dba)_3$·*t*BuPHBF$_4$, **L1**	NaHMDS	68
5	(SIPr)Pd(allyl)Cl, **L1**	NaHMDS	24
6[d]	$Pd_2(dba)_3$, **L1**	NaHMDS	46
7	$Pd_2(dba)_3$, **L2**	NaHMDS	68
8	$Pd_2(dba)_3$, **L2**	NaO*t*Bu	78
9	$Pd_2(dba)_3$, **L2**	K_2CO_3 or DABCO or Et_3N	N.A.
10[e]	$Pd_2(dba)_3$, **L2**	KO*t*Bu	56
11[e]	$Pd_2(dba)_3$, **L3**	NaO*t*Bu	44
12[e]	$Pd_2(dba)_3$, **L4**	NaO*t*Bu	52
13	$Pd_2(dba)_3$, **L5** or **L6** or **L7** or **L8**	NaO*t*Bu	<5
14	XPhos Pd G1	NaO*t*Bu	82
15	XPhos Pd G2	NaO*t*Bu	76
16	XPhos Pd G3	NaO*t*Bu	84
17	XPhos Pd G4	NaO*t*Bu	90

[a]Reaction conditions are as follows unless otherwise noted: 1.0 equiv of heteroaryl halide, 1.1 equiv of ketone, 1 mol % Pd catalyst/1 mol % ligand (or 1 mol % precatalyst), 2.4 equiv of base, and toluene. [b]Structures of selected catalysts and ligands are as follows:



[c]NMR yields using bibenzyl as internal reference compounds. Average of two runs. N.A., not available. [d]No premixing. [e]Similar yields were obtained when the reactions were performed at 60 °C for 16–22 h.

catalytic reactivity with yields between 20 and 40%. The rest catalysts such as $Pd(PPh_3)_2Cl_2$ and $Pd(PPh_3)_4$ had poor or no catalytic ability for this transformation. (3) Premixing of catalysts and ligands for 30 min (Table 1, entry 3 vs entry 6) before the addition of the substrate or the use of precatalysts (Table 1, entries 14–17) showed enhanced reactivity. The pretreatment lets the palladium coordinate to ligands before they are exposed to heteroaryl halides to avoid the potential inhibitory effect of heteroatoms on the in situ formation of the catalytically active Pd(0)/ligand complex.[18] (4) The basicity and equivalents of bases were important for the success of heteroarylation. A strong base such as NaHMDS or *t*BuONa is necessary since the reaction is believed to involve the activation of precatalyst by base and the coupling of heteroarylpalladium species with enolate generated in situ.[3a] More than 2 equiv of bases was used in the model reaction to suppress the ketone self-condensation side product. No heteroarylation products were observed in the NMR spectra when weak bases such as K_2CO_3 or 1,4-diazabicyclo[2.2.2]-octane (DABCO) or Et_3N were utilized, possibly due to their inability to generate enolates (Table 1, entry 9). Low yields and too many side products were noticed when a stronger base such as KO*t*Bu was used (Table 1, entry 10). These results provided important insights into the direct α-heteroarylation of carbonyl compounds, and this information could be used to guide the development of more general and robust catalyst systems.

Microwave-Assisted Palladium-Catalyzed Direct α-Heteroarylation of Ketones. Microwave irradiation has been applied in palladium-catalyzed cross-coupling reactions recently to enhance the reaction efficiency.[19] Microwave irradiation can be expedient to the synthetic process, especially for reactions that require a high activation energy such as cyclizations and the construction of sterically hindered sites.[20] The direct α-heteoarylation of ketones normally took 16–22 h at 60 °C or 4 h at 100 °C under thermal conditions in our study. For unactivated or sterically hindered substrates, it was necessary to increase the reaction temperature or to use prolonged reaction time, which is disadvantageous for monoheteroarylation reaction since thermodynamic conditions favor the bisheteroarylation side product. Therefore, we decided to utilize our recently acquired microwave reactor (Anton Paar Multiwave Pro) to facilitate the reaction process. This microwave reactor has two magnetrons that provide a very high maximum microwave power of 1500 W. The reactions were run in sealed vials in 0.5–1 mmol scale. Up to 96 parallel reactions can be set up on four silicon carbide (SiC) plates. Silicon carbide, an inert stable material, has high microwave absorbance and excellent heat capacity; therefore, it is used to efficiently heat low-absorbing solvents in a microwave environment.[21] The combination of the high microwave power and SiC plates make it possible for nonpolar, low microwave-absorbing solvents such as toluene to achieve the desired reaction temperature in a relatively short time (5–10 min).

With the optimized reaction conditions (catalyst, ligand, and base) under thermal heating in hand, we set out to optimize the conditions under microwave irradiation to speed up and improve the reaction efficiency. The only factors being optimized at this stage were reaction temperature and time. Among the reaction temperatures (100, 110, 120, 130, and 140 °C) and times tested (5, 10, 20, and 30 min), the combination of 130 °C for 10 min provided the best isolated yields for

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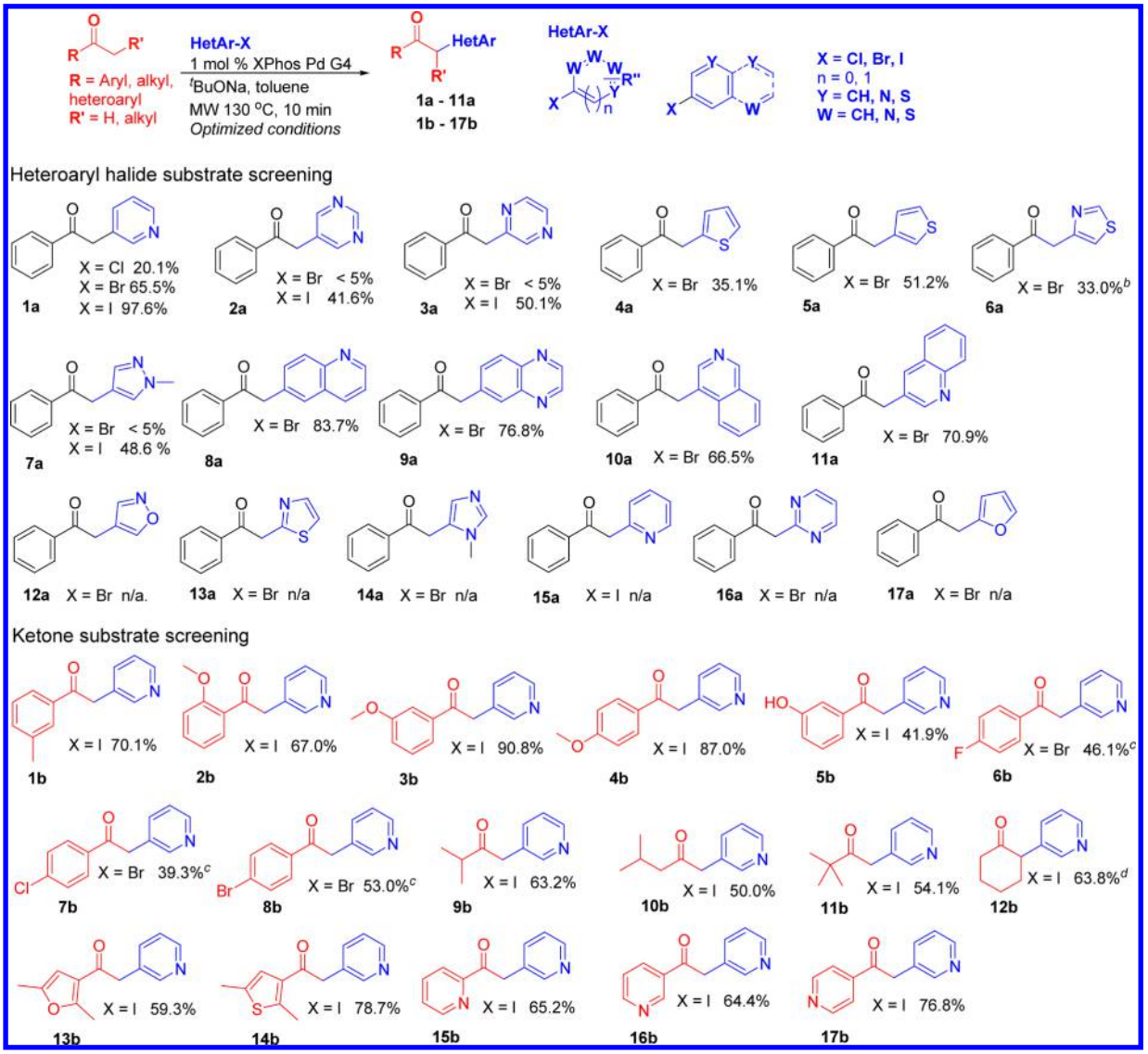
Scheme 2. Substrate Scope for Pd-Catalyzed Heteroarylation of Ketones[a]



[a]Reaction conditions are as follows unless otherwise noted: 1.0 equiv of heteroaryl halide, 1.1 equiv of ketone, 1 mol % XPhos Pd G4 catalyst, 2.4 equiv of *t*BuONa, toluene, and microwave irradiation at 130 °C for 10 min. [b]Reaction was conducted at room temperature for 3 days. [c]$Pd_2(dba)_3$ was used as the catalyst, and XPhos was used as the ligand. The catalyst and ligand were premixed in toluene for 30 min under Ar before the addition of the remaining reagents. Reactions were conducted under microwave irradiation at 120 °C for 20 min. [d]Reaction was conducted at 130 °C for 20 min.

compound **1a** in the range of 75 to 98%. Low conversions occurred when the temperature was below 120 °C or the time was shorter than 10 min. More side products were observed on the ^{1}H NMR spectra when the reaction temperature was over 140 °C. Using the optimized reaction time and temperature under microwave irradiation, we further examined other solvents such as tetrahydrofuran (THF), dimethoxyethane (DME), dioxane, and *n*-butanol for the heteroarylation reaction. These solvents did not provide better reaction outcomes than toluene.

Compared to the traditional thermal conditions for the direct α-heteoarylation of ketones, the microwave-assisted heteroarylation provide the following advantages: (1) It is rapid and efficient. The total reaction time was reduced from 4 h at 100 °C or 16−22 h at 60 °C to only 10 min at 130 °C. This is very important for the rapid screening of reaction conditions and efficient synthesis of a pool of diversity-oriented bioactive molecules. (2) This heteroarylation is more selective and has less side products. Because of the rapid heating and cooling process under microwave conditions, the starting materials and reagents have less chance to be exposed to high temperature for a long time; thus, the condensation or polymerization side products were reduced. The comparison between the NMR spectra for the crude products obtained under traditional heating and under microwave irradiation revealed much higher purity for the heteroarylated ketones, which were produced under microwave irradiation. Overall, the microwave-assisted palladium-catalyzed heteroarylation reaction enabled the establishment of a rapid and efficient approach to functionalize the ketone α-carbons with various heteroaryl moieties.

Investigation of Ketone and Heteroaryl Halide Substrate Scopes. With the reaction conditions optimized and the microwave-assisted synthetic method established, we

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set off to investigate the ketone and heteroaryl halides substrate scopes. The heteroaryl halide and ketone substrates were chosen to represent a diverse range of structures: (1) aromatic and aliphatic substrates; (2) sterically hindered substrates; (3) electron-poor or electron-rich substrates; and 4) substrates with different halides, different ring sizes, or different number of heteroatoms.[5g] Twenty-eight (28) heteroarylation products were successfully prepared and isolated in good to excellent yields (Scheme 2).

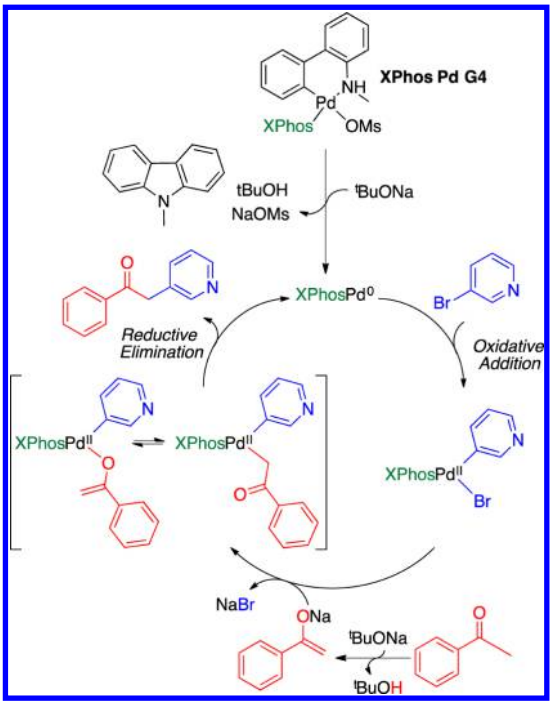
For heteroaryl substrate reactivity, the results are complicated yet interesting. First, heteroaryl halides with only one heteroatom generally gave good to excellent yields under the optimized reaction conditions established above (Scheme 2, compounds **1a**, **5a**, **8a**, **9a**, **10a**, and **11a**). Although there were a few successful examples (Scheme 2, compounds **2a**, **3a**, **6a**, and **7a**), heteroaryl halides with two heteroatoms such as 4-bromoisoxazole, 2-bromothiazole, and 5-bromo-1-methyl-1*H*-imidazole tended to decompose and were not able to form the desired products (compounds **12a**, **13a**, and **14a**). Second, better yields were achieved when the N atom is one or more carbon atoms away from the carbon with the halide attached (Scheme 2, compounds **1a**, **8a**, **9a**, **10a**, and **11a**). Low yields (compounds **3a**, **4a**, and **6a**) or no yields (compounds **15a**, **16a**, and **17a**) were observed when the N atom is adjacent to the carbon with the halide. This is probably due to the increased chances of catalyst poisoning when the N atom is getting closer to the metal center. Third, the effect of different leaving groups (Cl, Br, and I) on heteroaryl substrate reactivity was investigated in this catalytic system. Heteroaryl iodides demonstrated higher yields than heteroaryl bromides, which showed higher reactivity than heteroaryl chlorides (Scheme 2, compound **1a**, X = Cl, Br, and I). Additionally, some heteroarylation only happened when the corresponding iodides were used (Scheme 2, compounds **2a**, **3a**, and **7a**). Last, when the heteroaryl atoms are not on the ring directly attached to the ketone, the reactions went smoothly, and the products were easily purified and isolated (Scheme 2, compounds **8a** and **9a**). This observation inspired us to test the current catalytic system on aryl halides such as bromobenzene and iodobenzene. High isolated yields were obtained for these reactions, broadening the applicable area of the palladium catalytic system developed in this study.

For the ketone substrate scope investigation, the palladium-catalyzed direct heteroarylation reaction went smoothly in general. First, aryl methyl ketones, represented by acetophenone, showed great compatibility with many substituents such as methyl, methoxy, hydroxyl, and halides on the benzene ring (Scheme 2, compounds **1b**−**8b**). Alkyl methyl ketones were also reactive in this reaction, with expected regioselectivity due to steric effect; the reactions occurred exclusively on the methyl side instead of the alkyl side (Scheme 2, compounds **9b**−**11b**). Second, when a primary carbon ($-CH_3$) is not available on the α-position of the ketone, higher reaction temperature or longer reaction time was required to drive the reaction to completion due to the increased steric hindrance for secondary carbon (compounds **12b**). Third, it was exciting to find out that this catalytic system also worked well for heteroaryl methyl ketones including 3-acetyl-2,5-dimethylfuran (Scheme 2, compound **13b**), 3-acetyl-2,5-dimethylthiophene (compound **14b**), 2-acetylpyridine (compound **15b**), 3-acetylpyridine (compound **16b**), and 4-acetylpyridine (compound **17b**). Last, the ketones with active methylene groups (1-phenyl-1,3-butanedione, 1,3-cyclohexanedione, ethyl levulinate, etc.) did not give expected products, probably due to the strong basicity of *t*BuONa. For these reactions, the use of a weaker base such as NaOEt might give improved results. For ketones bearing cyano or nitro groups, no α-heteroarylation was observed possibly due to their reactions with strong bases and nucleophiles. Overall, most ketones reacted smoothly in the palladium-catalyzed direct heteroarylation reactions, demonstrating that the palladium-catalyzed direct heteroarylation of ketones is of great value to access synthetically or pharmaceutically important molecules.

Investigation on the Mechanism of Palladium-Catalyzed Heteroarylation of Acetophenone with 3-Bromopyridine. Palladium catalysis is used in a wide range of coupling reactions. The understanding of the mechanistic steps involved in the catalytic cycle is very important for mechanism-driven reaction design.[22] The actual mechanism for palladium catalysis requires the consideration of many factors such as palladium aggregates and palladium stereoisomers. Even though the mechanistic steps are not clear and still need further investigation, it has been proposed that the catalytic cycle for Pd-catalyzed (hetero)arylation typically involves the following steps: oxidative addition of (hetero)aryl halides to generate the Pd(II) intermediate, the transmetallation with enolates, and the reductive elimination to form the α-(hetero)arylation product and regenerate the Pd(0) active catalyst.[3a] The (hetero)aryl-Pd(II) enolate was considered as the reactive intermediate. On the basis of this understanding, the mechanism shown in Scheme 3 is proposed for the Pd-catalyzed heteroarylation of acetophenone with 3-bromopyridine.[2a,3a,4,5,10a,12]

The precatalyst XPhos Pd G4 is an amine-ligated oxidative addition complex. After being activated by a strong base, this precatalyst undergoes reductive elimination to produce a monoligated XPhos Pd(0) active catalyst along with other side products such as indoline, *t*BuOH, and NaOMs. We first

Scheme 3. Proposed Mechanism for Pd-Catalyzed Heteroarylation of Acetophenone with 3-Bromopyridine



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reexamined the ground-state structure of the XPhos Pd(0) active catalyst in toluene by an all-atom DFT approach using SMD(toluene) M06/SDD(d,f)-6-311++G(d,p)//SMD-(toluene) M06/SDD(d,f)-6-31G(d,p) (see Computational Methods for details). It was established previously that inclusion of the entire ligand structure in these types of calculations is important to obtain accurate results.[23] The lowest-energy rotamer of XPhos Pd(0), **1c1**, has a C1-C2-P-Pd dihedral angle of −157° and an asymmetrical Pd η^2-arene interaction of the nonphosphine-containing ring of the ligand with Pd−C(ortho) and Pd−C(meta) distances of 2.23 and 2.42 Å, respectively (Figure 2). In the previously reported gas-phase optimized structure, this interaction was described as an η^1-arene coordination due to a much longer Pd−C(meta) distance of 2.58 Å compared to Pd−C(ortho) distance of 2.31 Å.[23b] The second lowest-energy rotamer has a C1-C2-P-Pd dihedral angle of 162° and Pd η^2-arene interaction on the opposite side of the C2-P-Pd plane (see the Supporting Information). The energy difference between these two rotamers is 0.9 kcal/mol. The other two high-energy isomers have C1-C2-P-Pd dihedral angles of −32° and 71° and relative energies of 11.0 and 12.6 kcal/mol, respectively. The isomers with C1-C2-P-Pd dihedral angles of −32°, **1c2**, is shown in Figure 2. The Pd metal center in the XPhos Pd(0) active catalyst is stabilized by being positioned proximal to the nonphosphine-containing ring of the ligand prior to the oxidative addition of 3-bromopyridine by the Pd−arene interactions in the two lowest-energy rotamers.

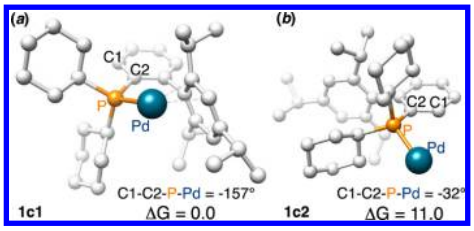

Figure 2. Optimized geometries of (a) the lowest-energy rotamer and (b) a higher-energy rotamer of active catalyst XPhos Pd(0) in toluene. Relative energies (ΔG) are shown in kcal/mol. Silver: carbon; orange: phosphorus; ocean green: palladium. Hydrogen atoms are omitted for clarity.

Oxidative Addition of 3-Bromopyridine to XPhos Pd(0). The Pd(0) active catalyst undergoes oxidative addition reaction with 3-bromopyridine to produce a palladium(II) intermediate. By performing ground-state energy optimizations, we located two possible isomers of the oxidative addition product resulted from the reaction of the lowest-energy rotamer of XPhos Pd(0) with 3-bromopyridine (Figure 3). One of these isomers, **2c1**, has the bromide ligand trans to the phosphine atom, while the other one, **2c2**, has a cis orientation. The interchange of the bromide and 3-pyridiyl groups results in a 5.6 kcal/mol energy difference, the trans isomer being more stable than the cis isomer. The trans orientation of the phosphine and bromide has been previously observed in the X-ray crystal structures of various monoligated Pd(aryl)X species[24] and anticipated to be a result of the trans influence of the phosphine.[25] Trans influence means the tendency of a ligand to selectively weaken the bond trans to itself.[26]

The Pd metal center is directly above the ipso carbon of the nonphosphine-containing ring of the ligand (Pd-C(ipso) distance of 2.63 and 2.41 Å in trans and cis isomers of the oxidative addition product, respectively). The Pd−arene interactions get weaker upon formation of the oxidative addition products. It was proposed that the ability of XPhos to stabilize the Pd(II) center of oxidative addition complexes through labile Pd−arene interaction is partially responsible for the effectiveness of XPhos as a supporting ligand in Pd-catalyzed cross-coupling reactions.[23]

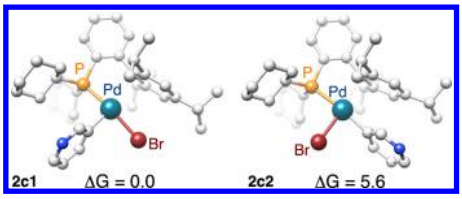

Figure 3. Optimized geometries of two possible trans and cis isomers of the oxidative addition product resulted from the reaction of the lowest-energy rotamer of XPhos Pd(0) with 3-bromopyridine. Relative energies (ΔG) are shown in kcal/mol. Silver: carbon; orange: phosphorus; ocean green: palladium; brown: bromine; blue: nitrogen. Hydrogen atoms are omitted for clarity.

Transmetallation with Sodium Enolate. The XPhos Pd(II) oxidative addition product subsequently reacts with the sodium enolate to afford the (hetero)aryl-Pd(II) enolate. The optimized geometries of three possible isomers of the transmetallation products resulted from the reaction of the trans isomer of the oxidative addition product (hetero)aryl-Pd(II) bromide with enolate are shown in Figure 4.

The lowest-energy isomer, **3c1**, is a Pd(II) η^1-alkyl complex. The η^3-Pd(II) complex, **3c2**, is 4.4 kcal/mol higher in energy, and the Pd(II) η^1-oxo complex, **3c3**, is 9.6 kcal/mol higher in energy. The relative stabilities of these isomers depend on the Pd metal center being proximal or distal to the nonphosphine-containing ring of the ligand. As it was postulated before, we propose that the reductive elimination would be more facile when the Pd center is proximal to the nonphosphine-containing ring of the ligand than the distal one due to increased steric pressure caused by this ring.

In the final step of the catalytic cycle, the (hetero)aryl-Pd(II) enolate undergoes reductive elimination through transition state **4c** (Figure 4) to produce the final product and regenerate the active Pd(0) catalyst. The relative free energies of the optimized structures on the PES for the Pd-catalyzed heteroarylation of acetophenone with 3-bromopyridine are calculated with respect to the most stable isomer of XPhos Pd(0), **1c1**, acetophenone, and 3-bromopyridine (Figure 5). The transition state energy is 22.3 kcal/mol, and the reaction is overall exothermic by −3.9 kcal/mol. Recent studies revealed that the electronic properties, geometry, flexibility, and distance of the ligands are very important for their function in the active palladium intermediates.[27] The electron-poor or electron-rich nature of the substrates, especially the heteroaryl halides, might change their reactivity significantly.[28] On the basis of our observations so far, the distance of heteroatoms from the metal center also seems very important. Further investigation on the reaction mechanism for the palladium-catalyzed direct α-heteroarylation of ketone is currently in progress.

CONCLUSIONS

In conclusion, we have developed a highly efficient palladium-catalyzed direct α-C(sp3) heteroarylation of ketones under microwave irradiation. The optimized conditions were 1 mol %

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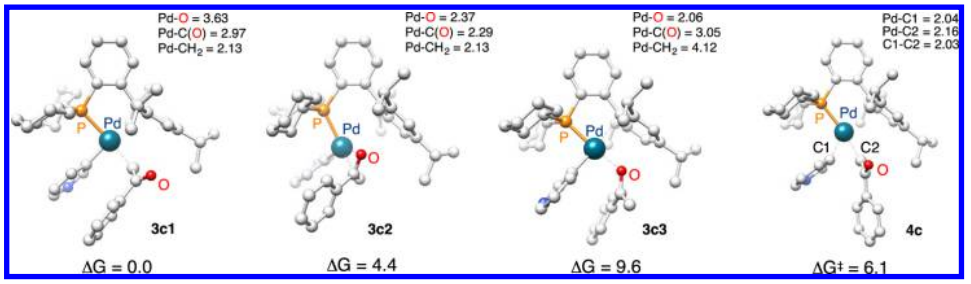

Figure 4. Optimized geometries of three possible isomers of (hetero)aryl-Pd(II) enolate resulted from the transmetallation of the trans isomer of the oxidative addition product (hetero)aryl-Pd(II) bromide with enolate and reductive elimination transition state. Relative energies (ΔG) are shown in kcal/mol, and distances are shown in Å. Silver: carbon; orange: phosphorus; ocean green: palladium; brown: bromine; blue: nitrogen; red: oxygen. Hydrogen atoms are omitted for clarity.

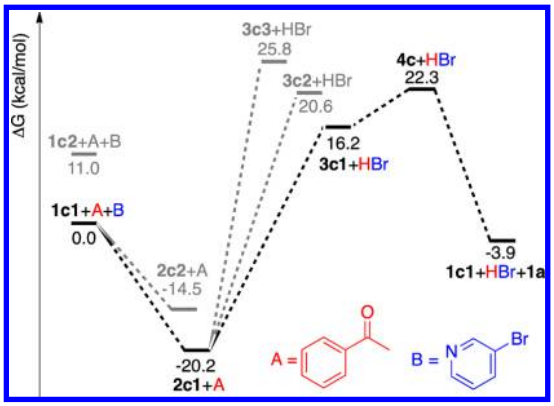

Figure 5. Free energy diagram of the Pd-catalyzed heteroarylation of acetophenone with 3-bromopyridine. The structures on the lowest-energy pathway are shown in black. Energies (ΔG) are reported in kcal/mol.

XPhos Pd G4, 2.2 equiv of NaO*t*Bu, toluene, and microwave irradiation at 130 °C for 10 min. Twenty-eight (28) heteroarylation compounds with various functional groups were prepared at 0.5−1.0 mmol scale. It is feasible to scale up these reactions by using large reaction vessels (e.g., Rotor 16HF100) or a kilolab microwave reactor (e.g., Masterwave BTR from Anton Paar Inc.). The structural analyses were conducted on the Pd(0) active catalyst and Pd(II) intermediates with the XPhos ligand in toluene using an all-atom DFT approach. The Pd−arene interactions in the lowest-energy structures contribute to the stability of the XPhos Pd complexes in the catalytic cycle. Efforts to further investigate the reaction mechanism with complete energy profiles and to apply this reaction in bioactive molecule synthesis are currently underway and will be reported in the near future.

EXPERIMENTAL SECTION

General Information. The chemicals and solvents were obtained from commercial vendors and used without further purification, unless otherwise noted. Toluene was vigorously purged with argon for 2 h before use. Pd catalysts and NaO*t*Bu were stored in a glove box under N_2. The microwave-assisted reactions were conducted on a MultiwavePro microwave reaction system from Anton Paar Instruments. The pressure vessels consist of disposable Wheaton glass vials (item # 224882) with a special PEEK screw cap and a PTFE seal (reaction volume, 0.3−3 mL; operation pressure, 20 bar). Rotor (4x24MG5) and four SiC well plates were used for homogeneous heating of up to 96 g-scale experiments in parallel. Thin-layer chromatography was performed using precoated silica gel F254 plates (Whatman). Column chromatography was performed using pre-packed RediSep Rf Silica columns on a CombiFlash Rf Flash Chromatography system (Teledyne Isco). NMR spectra were obtained on a Joel 500 MHz spectrometer. Chemical shifts were reported in parts per million (ppm) relative to the tetramethylsilane (TMS) signal at 0.00 ppm. Coupling constants, J, were reported in Hertz (Hz). The peak patterns were indicated as follows: s, singlet; d, doublet; t, triplet; dt, doublet of triplet; dd, doublet of doublet; m, multiplet; q, quartet. High-resolution mass spectra were recorded on a Micromass Q-TOF 2 or a Thermo Scientific LTQ-FT mass spectrometer operating in electrospray (ES) mode.

Computational Methods. All quantum mechanical calculations were performed using the Gaussian 16[29] suite of programs. The previously reported optimized structures of palladium complexes, when available, were used as a starting point for the calculations.[23] Ground-state geometries were fully optimized in redundant internal coordinates without any symmetry constraints,[30] with all-atom DFT and a wave function incorporating the hybrid functional of Truhlar and Zhao's M06.[31] The Pd, P, and Br atoms were represented with the effective core pseudopotentials of the Stuttgart group, and the associated basis sets were improved with a set of *f*-polarization functions for Pd (α = 1.472)[32] and a set of d-polarization functions for P (α = 0.387) and Br (α = 0.428).[33] The remaining atoms (C, H, N, and O) were represented with the 6-31G(d,p) basis sets.[34] Solvent effects on the geometries and the relative stabilities of the stationary points were evaluated by reoptimizing the stationary points using the Solvation Model based on Density (SMD)[35] and toluene as the solvent. Frequency calculations were performed on the optimized geometries using the same basis sets to confirm that each optimized ground state has zero imaginary frequencies. The zero-point energies, thermal corrections, and entropic corrections were calculated from the frequency calculations. Single-point energy calculations on the optimized geometries were performed using the M06 density functional with the same basis set detailed above for Pd, P, and Br and the polarized and diffuse 6-311++G(d,p)[36] basis set for all other atoms. The free energy corrections were calculated by adding the thermal corrections calculated from the SMD(toluene) M06/SDD(d,f)-6-31G(d,p) unscaled vibrational frequencies to the SMD-(toluene) M06/SDD(d,f)-6-311++G(d,p) electronic energies. The energies discussed throughout the text are the Gibbs free energies at 298.15 K and 1 atm. Optimized structures are illustrated using UCSF Chimera.[37]

General Procedure for Synthesis of Heteroarylated of Ketones via Palladium Catalysis under Microwave Irradiation. To an oven-dried microwave reaction vial (standard Wheaton glass vials, item # 224882) containing a stirring bar was charged with 1 mol % XPhos Pd G4 catalyst, 2.4 equiv of NaO*t*Bu, 1.1 equiv of ketone, and 2.0 mL of toluene. The reaction mixture was stirred at room temperature for 10 min before the addition of 1.0 equiv of heteroaryl halide. The reaction vial was then secured with a Teflon seal and PEEK cap. The reaction mixture was subject to microwave irradiation at 130 °C for 10 min. After cooling down to room temperature, the reaction mixture was transferred to a separatory funnel, followed by the addition of saturated NH_4Cl solution (2 mL). The crude product was extracted with ethyl acetate three times (3 × 10 mL). The combined organic layer was dried over anhydrous $MgSO_4$. After

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rotatory evaporation to remove the solvents, the product was purified using column chromatography (0−100% ethyl acetate/hexanes or 0−20% $MeOH/CH_2Cl_2$).

*1-Phenyl-2-(pyridin-3-yl)ethanone (**1a**).*[9] **1a** was synthesized from acetophenone (0.55 mmol, 1.1 equiv, 64.36 μL) and 3-iodopyridine (0.50 mmol, 1 equiv, 48.2 μL) according to the general procedure described above, yielding a pale yellow solid. Yield, 192 mg, 97.6%. ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.53 (1H, s), 8.49 (1H, d, *J* = 5.05 Hz), 8.00 (2H, d, *J* = 7.6 Hz), 7.58 (1H, d, *J* = 6.85 Hz), 7.56 (1H, t, *J* = 7.8 Hz), 7.46 (2H, t, *J* = 7.8 Hz), 7.24 (1H, dd, *J* = 7.8,4.6 Hz), 4.27 (2H, s). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz, ppm): δ 196.5, 150.7, 148.4, 137.3, 136.3, 133.6, 130.3, 128.9, 128.5, 123.5, 42.4. HRMS calcd for $C_{13}H_{12}NO$ [M + H], 198.0919; found, 198.0921.

*1-Phenyl-2-(pyrimidin-5-yl)ethanone (**2a**).* **2a** was synthesized from acetophenone (0.55 mmol, 1.1 equiv, 64.36 μL) and 5-iodopyrimidine (0.5 mmol, 1 equiv, 102.99 mg) according to the general procedure described above, yielding a yellow solid. Yield, 82.4 mg, 41.6%. ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 9.14 (1H, s), 8.65 (2H, s), 8.02 (2H, d, *J* = 7.35 Hz), 7.63 (1H, t, *J* = 7.8 Hz), 7.52 (2H, t, *J* = 7.8 Hz), 4.31 (2H, s). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz, ppm): δ 195.1, 157.9, 157.6, 136.0, 134.0, 129.0, 128.4, 128.2, 39.7. HRMS calcd for $C_{12}H_{11}N_2O$ [M + H], 199.0871; found, 199.0879.

*1-Phenyl-2-(pyrazin-2-yl)ethanone (**3a**).* **3a** was synthesized from acetophenone (0.5 mmol, 1 equiv, 58.50 μL) and 2-iodopyrimidine (0.5 mmol, 1 equiv, 79.49 mg) according to the general procedure described above, yielding a brown solid. Yield, 99.2 mg, 50.1%. ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.62 (1H, s), 8.54 (1H, d, *J* = 7.3 Hz), 8.48 (1H, d, *J* = 2.7 Hz), 8.06 (2H, d, *J* = 6.9 Hz), 7.60 (1H, t, *J* = 7.3 Hz), 7.50 (2H, t, J = 7.8 Hz), 4.54 (2H, s). $^{13}C\{^1H\}$ NMR($CDCl_3$, 125 MHz, ppm):δ 195.8, 151.3, 146.0, 144.3, 143.0, 133.8, 128.9, 128.7, 128.6, 45.5. HRMS calcd for $C_{12}H_{11}N_2O$ [M + H], 199.0871; found, 199.0876.

*1-Phenyl-2-(thiophen-2-yl)ethanone (**4a**).* **4a** was synthesized from acetophenone (0.83 mmol, 1.1 equiv, 95.0 μL) and 2-bromothiophene (0.75 mmol, 1 equiv, 75.0 μL) according to the general procedure described above, yielding a brown solid. Yield, 70.1 mg, 35.1%. ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.03 (2H, d, *J* = 8.3 Hz), 7.57 (1H, t, *J* = 7.8 Hz), 7.48 (2H, t, *J* = 7.4 Hz), 7.22 (1H, d, *J* = 5.1 Hz), 6.97 (1H, t, *J* = 5.1 Hz), 6.94 (1H, d, *J* = 3.0 Hz), 4.49 (2H, s). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz, ppm): δ 195.8, 135.6, 133.5, 130.3, 128.8, 128.7, 127.0, 126.9, 125.2, 39.5. HRMS calcd for $C_{12}H_{11}OS$ [M + H], 203.0531; found, 203.0532.

*1-Phenyl-2-(thiophen-3-yl)ethanone (**5a**).* **5a** was synthesized from acetophenone (0.83 mmol, 1.1 equiv, 95.0 μL) and 3-bromothiophene (0.75 mmol, 1 equiv, 70.0 μL) according to the general procedure described above, yielding brown crystals. Yield, 103.6 mg, 51.2%. ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.01 (2H, d, *J* = 8.2 Hz), 7.57 (1H, t, *J* = 7.3 Hz), 7.47 (2H, t, *J* = 7.8 Hz), 7.30 (1H, dd, *J* = 5.0, 2.8 Hz), 7.13 (1H, d, *J* = 2.8 Hz), 7.03 (1H, d, *J* = 5.0 Hz), 4.32 (2H, s). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz, ppm): δ 197.2, 136.5, 134.2, 133.4, 128.8, 128.7, 128.6, 125.9, 123.0, 40.2. HRMS calcd for $C_{12}H_{11}OS$ [M + H], 203.0531; found, 203.0531.

*1-Phenyl-2-(thiazol-4-yl)ethanone (**6a**).* **6a** was synthesized from acetophenone (0.55 mmol, 1.1 equiv, 64.36 μL) and 4-bromothiazole (0.50 mmol, 1 equiv, 45.0 μL) according to the general procedure described above, with the exception of no microwave step being used. When the microwave was used, no product was obtained. The product is a brown oil. Yield, 67.0 mg, 33.0%. ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.79 (1H, s), 8.06 (2H, d, *J* = 8.2 Hz), 7.60 (1H, t, *J* = 7.3 Hz), 7.48 (2H, t, *J* = 7.8 Hz), 7.27 (1H, s), 4.56 (2H, s). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz, ppm): δ 196.32, 152.67, 150.30, 136.48, 133.48, 128.79, 128.76, 116.29, 41.15. HRMS calcd for $C_{11}H_{10}NOS$ [M + H], 204.0483; found, 204.0482.

*2-(1-Methyl-1H-pyrazol-4-yl)-1-phenylethanone (**7a**).* **7a** was synthesized from acetophenone (0.55 mmol, 1.1 equiv, 64.2 μL) and 4-iodo-1-methyl-1*H*-pyrazole (0.5 mmol, 1 equiv, 104 mg) according to the general procedure described above, yielding a yellow solid. Yield, 97.4 mg, 48.6%. ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.01 (2H, dd, *J* = 6.8, 0.9 Hz), 7.58 (1H, t, *J* = 7.4 Hz), 7.48 (2H, t, *J* = 7.8 Hz), 7.42 (1H, s), 7.37 (1H, s), 4.16 (2H, s), 3.88 (3H, s). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz, ppm): δ 197.3, 139.3, 136.5, 133.4, 129.9, 128.8, 128.5, 113.6, 39.0, 34.6. HRMS calcd for $C_{12}H_{13}N_2O$ [M + H], 201.1028; found, 201.1025.

*1-Phenyl-2-(quinolin-6-yl)ethanone (**8a**).*[38] **8a** was synthesized from acetophenone (0.55 mmol, 1.1 equiv, 64.36 μL) and 6-bromoquinoline (0.5 mmol, 1 equiv, 104.0 mg) according to the general procedure described above, yielding a yellow solid. Yield, 207.0 mg, 83.7%. ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.87 (1H, s), 8.08−8.03 (4H, m), 7.68 (1H, s), 7.61 (1H, d, *J* = 8.7 Hz), 7.55 (1H, d, *J* = 7.3 Hz), 7.45 (2H, t, *J* = 6.8 Hz), 7.36−7.34 (1H, m), 4.46 (2H, s). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz, ppm): δ 197.31, 150.37, 147.47, 135.90, 133.50, 133.14, 131.50, 129.80, 128.86, 128.66, 128.40, 128.15, 127.32, 121.38, 45.35. HRMS calcd for $C_{17}H_{14}NO$ [M + H], 248.1075; found, 248.1072.

*1-Phenyl-2-(quinoxalin-6-yl)ethanone (**9a**).* **9a** was synthesized from acetophenone (0.55 mmol, 1.1 equiv, 64.36 μL) and 6-bromoquinoxaline (0.5 mmol, 1 equiv, 104 mg) according to the general procedure described above, yielding a yellow solid. Yield, 190.8 mg, 76.8%. ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.81 (2H, s), 8.09−8.05 (3H, m), 7.99 (1H, s), 7.70 (1H, dd, *J* = 8.7, 1.0 Hz), 7.58 (1H, t, *J* = 7.3 Hz), 7.48 (2H, t, *J* = 7.3 Hz), 4.54 (2H, s). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz, ppm): δ 196.8, 145.21, 144.91, 143.11, 142.25, 137.22, 136.1, 133.65, 132.21, 129.91, 129.67, 128.91, 128.66, 45.47. HRMS calcd for $C_{16}H_{13}N_2O$ [M + H], 249.1028; found, 249.1028.

*2-(Isoquinolin-4-yl)-1-phenylethanone (**10a**).* **10a** was synthesized from acetophenone (0.5 mmol, 1 equiv, 58.50 μL) and 4-bromoisoquinoline (0.5 mmol, 1 equiv, 104.0 mg) according to the general procedure described above, yielding a brown solid. Yield, 164.4 mg, 66.5%. ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 9.18 (1H, s), 8.41 (1H, s), 8.08 (2H, d, *J* = 7.3 Hz), 7.96 (1H, d, *J* = 8.25 Hz), 7.78 (1H, d, *J* = 8.25 Hz), 7.66 (1H, t, *J* = 8.7 Hz), 7.60−7.56 (2H, m), 7.48 (2H, t,J = 7.8 Hz), 4.66(2H, s). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz, ppm): δ 192.0, 155.2, 139.5, 132.6, 129.2, 128.7, 128.6, 128.4, 126.6, 122.2, 19.0. HRMS calcd for $C_{17}H_{14}NO$ [M + H], 248.1028; found, 248.1022.

*1-Phenyl-2-(quinolin-3-yl)ethanone (**11a**).* **11a** was synthesized from acetophenone (0.55 mmol, 1.1 equiv, 64.36 μL) and 3-bromoquinoline (0.5 mmol, 1 equiv, 68.0 μL) according to the general procedure described above, yielding a yellow solid. Yield, 175.3 mg, 70.9%. ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.83 (1H, s), 8.10 (1H, d, *J* = 8.7 Hz), 8.06 (1H, s), 8.04−8.03 (2H, m), 7.77 (1H, d, *J* = 8.2 Hz), 7.68 (1H, t, *J* = 7.4 Hz), 7.59 (1H, t, *J* = 7.3 Hz), 7.54−7.47 (3H, m), 4.47(2H, s). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz, ppm): δ 196.6, 152.1, 147.3, 136.4, 133.7, 129.4, 129.3, 128.9, 128.6, 128.1, 127.7, 127.5, 126.9, 42.6. HRMS calcd for $C_{17}H_{14}NO$ [M + H], 248.1075; found: 248.1073.

*2-(Pyridin-3-yl)-1-(m-tolyl)ethanone (**1b**).* **1b** was synthesized from *m*-methyl acetophenone (1.1 mmol, 1.1 equiv, 147.6 mg, 149.7 μL) and 3-iodopyridine (1.0 mmol, 1 equiv, 205.0 mg) according to the general procedure described above, yielding a yellow oil. Yield, 148.1 mg, 70.1%. ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.45 (1H, s), 8.44 (1H, d, *J* = 4.6 Hz), 7.76 (1H, s), 7.75 (1H, d, *J* = 8.2 Hz), 7.53 (1H, d, *J* = 7.7 Hz), 7.34−7.29 (1H, m), 7.22−7.16 (1H, m), 4.22 (2H, s), 2.35 (3H, s). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz, ppm): δ 196.7, 150.7, 148.3, 138.7, 136.4, 134.4, 130.4, 129.0, 128.7, 125.7, 123.5, 42.4, 21.4. HRMS calcd for $C_{14}H_{14}NO$ [M + H], 212.1075; found, 212.1070.

*1-(2-Methoxyphenyl)-2-(pyridin-3-yl)ethanone (**2b**).*[39] **2b** was synthesized from 2′-methoxyacetophenone (0.55 mmol, 1.1 equiv, 82.6 mg, 75.8 μL) and 3-iodopyridine (0.50 mmol, 1 equiv, 102.5 mg) according to the general procedure described above, yielding a yellow oil. Yield, 152.3 mg, 67.0%. ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.50 (2H, s), 7.68 (1H, d, *J* = 7.75 Hz), 7.56 (1H, d, *J* = 9.65 Hz), 7.45 (1H, t, *J* = 8.25 Hz), 7.21 (1H, t, *J* = 7.35 Hz), 6.97 (2H, q, *J* = 16.7 Hz), 4.28 (2H, s), 3.90 (3H, s). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz, ppm): δ 198.5, 158.3, 150.9, 148.1, 137.3, 134.1, 130.9, 123.3, 121.0, 111.6. HRMS calcd for $C_{14}H_{14}NO_2$ [M + H], 228.1025; found, 228.1034.

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*1-(3-Methoxyphenyl)-2-(pyridin-3-yl)ethanone (**3b**).* **3b** was synthesized from 3′-methoxyacetophenone (0.55 mmol, 1.1 equiv, 82.6 mg, 75.8 μL) and 3-iodopyridine (0.50 mmol, 1 equiv, 102.5 mg) according to the general procedure described above, yielding a yellow oil with white solid. Yield, 206.4 mg, 90.8%. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.52 (2H, s), 7.61−7.60 (2H, m), 7.52 (1H, t, *J* = 3.70 Hz), 7.40 (1H, t, *J* = 16.05 Hz), 7.28−7.26 (1H, m), 7.14 (1H, dd, *J* = 8.25 Hz), 4.28 (2H, s), 3.84 (3H, s). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz, ppm): δ 196.5, 160.1, 150.7, 137.7, 137.3, 129.9, 123.6, 121.1, 120.1, 112.8. HRMS calcd for $C_{14}H_{14}NO_2$ [M + H], 228.1025; found, 228.1023.

*1-(4-Methoxyphenyl)-2-(pyridin-3-yl)ethanone (**4b**).*[5b,40] **4b** was synthesized from 4′-methoxyacetophenone (0.55 mmol, 1.1 equiv, 80 mg) and 3-iodopyridine (0.50 mmol, 1 equiv, 102.5 mg) according to the general procedure described above, yielding a yellow solid. Yield, 197.8 mg, 87.0%. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.51−8.50 (2H, m), 7.98 (2H, d, *J* = 9.15 Hz), 7.58 (1H, d, *J* = 7.8 Hz), 7.26−7.24 (1H, m), 6.93 (2H, d, *J* = 8.7 Hz), 4.23 (2H, s), 3.85 (3H, s). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz, ppm): δ 195.1, 163.9, 150.7, 148.3, 137.3, 130.9, 130.7, 129.3, 123.5, 114.1, 55.6, 42.1. HRMS calcd for $C_{14}H_{14}NO_2$ [M + H], 228.1025; found, 228.1018.

*1-(3-Hydroxyphenyl)-2-(pyridin-3-yl)ethanone (**5b**).*[41] **5b** was synthesized from 3′-hydroxyacetophenone (0.55 mmol, 1.1 equiv, 74.9 mg, 68.1 μL) and 3-iodopyridine (0.5 mmol, 1 equiv, 102.5 mg) according to the general procedure described above, yielding a yellow oil. Yield, 89.3 mg, 41.9%. ^{1}H NMR (acetone-d_6, 500 MHz, ppm): δ 9.31 (1H, s), 8.53 (1H, s), 8.46 (1H, d, *J* = 4.6 Hz), 7.69 (1H, d, *J* = 7.8 Hz), 7.58 (1H, d, *J* = 6.9 Hz), 7.50 (1H, d, *J* = 1.8 Hz), 7.37−7.32 (2H, m), 7.10 (1H, dd, *J* = 8.3, 2.8 Hz), 4.42 (2H, s). ^{13}C{^{1}H} NMR (acetone-d_6, 125 MHz, ppm): δ 196.5, 158.1, 151.0, 147.9, 138.2, 137.4, 129.9, 123.3, 120.5, 119.6, 114.8, 42.0. HRMS calcd for $C_{13}H_{12}NO_2$ [M + H], 214.0868; found, 214.0871.

*1-(4-Fluorophenyl)-2-(pyridin-3-yl)ethanone (**6b**).* To an oven-dried microwave reaction vial (standard Wheaton glass vials, item # 224882) containing a stirring bar was charged with $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol, 1 mol %), XPhos (4.8 mg, 0.01 mmol, 1 mol %), and toluene (2.0 mL). The catalyst and ligand were premixed at r.t. for 30 min under Ar. Then, NaO*t*Bu (230.6 mg, 2.40 mmol, 2.4 equiv) and 4′-fluoroacetophenone (1.1 mmol, 1.1 equiv, 152.0 mg, 133.5 μL) were added and stirred for 10 min at r.t, followed by the addition of 3-bromopyridine (1.0 mmol, 1 equiv, 158.0 mg, 96.4 μL). The reaction vial was then secured with a Teflon seal and PEEK cap. The reaction mixture was subject to microwave irradiation at 120 °C for 20 min. After cooling down to room temperature, the reaction mixture was transferred to a separatory funnel, followed by the addition of saturated NH_4Cl solution (2 mL). The mixture was extracted with ethyl acetate three times (3 × 10 mL). The combined organic layer was dried over anhydrous $MgSO_4$. After rotatory evaporation to remove the solvents, the product was purified using column chromatography (0−100% ethyl acetate/hexanes), yielding a yellow solid. Yield, 99.2 mg, 46.1%. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.50 (1H, d, *J* = 6.4 Hz), 8.49 (1H, s), 8.04−8.01 (2H, m), 7.58 (1H, d, *J* = 7.8 Hz), 7.27−7.25 (1H, m), 7.13 (2H, t, *J* = 8.2 Hz), 4.26 (2H, s). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz, ppm): δ 194.9, 166.1, 150.6, 148.4, 137.4, 132.8, 131.2, 130.1, 123.6, 116.1, 42.3. HRMS calcd for $C_{13}H_{11}NOF$ [M + H], 216.0825; found, 216.0834.

*1-(4-Chlorophenyl)-2-(pyridin-3-yl)ethanone (**7b**).* To an oven-dried microwave reaction vial (standard Wheaton glass vials, item # 224882) containing a stirring bar was charged with $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol, 1 mol %), XPhos (4.8 mg, 0.01 mmol, 1 mol %), and toluene (2.0 mL). The catalyst and ligand were premixed at r.t. for 30 min under Ar. Then, NaO*t*Bu (230.6 mg, 2.40 mmol, 2.4 equiv) and 4′-chloroacetophenone (1.1 mmol, 1.1 equiv, 170.0 mg, 142.7 μL) were added and stirred for 10 min at r.t, followed by the addition of 3-bromopyridine (1.0 mmol, 1 equiv, 158.0 mg, 96.4 μL). The reaction vial was then secured with a Teflon seal and PEEK cap. The reaction mixture was subject to microwave irradiation at 120 °C for 20 min. After cooling down to room temperature, the reaction mixture was transferred to a separatory funnel, followed by the addition of saturated NH_4Cl solution (2 mL). The mixture was extracted with ethyl acetate three times (3 × 10 mL). The combined organic layer was dried over anhydrous $MgSO_4$. After rotatory evaporation to remove the solvents, the product was purified using column chromatography (0−100% ethyl acetate/hexanes), yielding a yellow solid. Yield, 91.0 mg, 39.3%. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.49−8.48 (2H, m), 7.92 (2 H, d, *J* = 8.7 Hz), 7.55 (1H, d, *J* = 7.8 Hz), 7.42 (2H, d, *J* = 8.3 Hz), 7.24 (1H, d, *J* = 7.8 Hz), 4.24 (2H, s). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz, ppm): δ 195.3, 150.7, 148.6, 140.1, 137.3, 134.6, 129.9, 129.2, 128.7, 123.6, 42.4. HRMS calcd for $C_{13}H_{11}NOCl$ [M + H], 232.0529; found, 232.0536.

*1-(4-Bromophenyl)-2-(pyridin-3-yl)ethanone (**8b**).* To an oven-dried microwave reaction vial (standard Wheaton glass vials, item # 224882) containing a stirring bar was charged with $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol, 1 mol %), XPhos (4.8 mg, 0.01 mmol, 1 mol %), and toluene (2.0 mL). The catalyst and ligand were premixed at r.t. for 30 min under Ar. Then, NaO*t*Bu (230.6 mg, 2.40 mmol, 2.4 equiv) and 4′-bromoacetophenone (1.1 mmol, 1.1 equiv, 218.9 mg, 150.9 μL) were added and stirred for 10 min at r.t, followed by the addition of 3-bromopyridine (1.0 mmol, 1 equiv, 158.0 mg, 96.4 μL). The reaction vial was then secured with a Teflon seal and PEEK cap. The reaction mixture was subject to microwave irradiation at 120 °C for 20 min. After cooling down to room temperature, the reaction mixture was transferred to a separatory funnel, followed by the addition of saturated NH_4Cl solution (2 mL). The mixture was extracted with ethyl acetate three times (3 × 10 mL). The combined organic layer was dried over anhydrous $MgSO_4$. After rotatory evaporation to remove the solvents, the product was purified using column chromatography (0−100% ethyl acetate/hexanes), yielding a yellow solid. Yield, 146.3 mg, 53.0%. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.55 (1H, s), 8.00−7.95 (1H, m), 7.88 (2H, d, *J* = 8.2 Hz), 7.64 (2H, d, *J* = 8.2 Hz), 7.37 (1H, d, *J* = 8.2 Hz), 7.31 (1H, dd, *J* = 7.3, 4.6 Hz), 4.30 (2H, s). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz, ppm): δ 195.4, 150.2, 148.1, 137.8, 132.3, 132.2, 130.2, 130.1, 129.0, 123.8, 42.3. HRMS calcd for $C_{13}H_{11}NOBr$ [M + H], 276.0024; found, 276.0017.

*3-Methyl-1-(pyridin-3-yl)butan-2-one (**9b**).* **9b** was synthesized from 3-methyl-2-butanone (0.55 mmol, 1.1 equiv, 47.4 mg, 58.8 μL) and 3-iodopyridine (0.5 mmol, 1 equiv, 102.5 mg) according to the general procedure described above, yielding a yellow oil. Yield, 103.1 mg, 63.2%. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.48 (1H, s), 8.40 (1H, s), 7.52 (1H, d, *J* = 7.8 Hz), 7.24−7.22 (1H, m), 3.74 (2H, s), 2.72 (1H, s), 0.12 (6H, d, *J* = 6.9 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz, ppm): δ 210.4, 150.5, 148.4, 137.2, 130.2, 123.5, 44.2, 40.8, 18.3. HRMS calcd for $C_{10}H_{14}NO$ [M + H], 164.1075; found, 164.1082.

*4-Methyl-1-(pyridin-3-yl)pentan-2-one (**10b**).* **10b** was synthesized from 4-methyl-2-pentanone (0.55 mmol, 1.1 ., 55.1 mg, 68.8 μL) and 3-iodopyridine (0.50 mmol, 1 equiv, 102.5 mg) according to the general procedure described above, yielding a yellow oil. Yield, 88.6 mg, 50.0%. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.46 (1H, dd, *J* = 5.0, 1.4 Hz), 8.39 (1H, d, *J* = 1.8 Hz), 7.50 (1H, m), 7.21 (1H, m), 3.64 (2H, s), 2.33 (2H, d, *J* = 6.9 Hz), 2.11 (1H, m) 0.85(6H, d, *J* = 6.5 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz, ppm): δ 206.8, 150.5, 148.4, 137.1, 129.9, 123.5, 51.5, 47.1. HRMS calcd for $C_{11}H_{16}NO$ [M + H], 178.1232; found, 178.1225.

*3,3-Dimethyl-1-(pyridin-3-yl)butan-2-one (**11b**).* **11b** was synthesized from 3,3-dimethyl-2-butanone (0.55 mmol, 1.1 equiv, 55.1 mg, 68.8 μL) and 3-iodopyridine (0.5 mmol, 1 equiv, 102.5 mg) according to the general procedure described above, yielding a yellow oil. Yield, 95.8 mg, 54.1%. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.45 (1H, d, *J* = 1.4 Hz), 8.37 (1H, s), 7.49 (1H, t, *J* = 7.3 Hz), 7.21 (1H, t, *J* = 7.8 Hz), 3.77 (2H, s), 1.21 (9H, s). ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz, ppm): δ 211.9, 150.6, 148.2, 137.4, 130.7, 123.3, 44.7, 40.2, 26.4. HRMS calcd for $C_{11}H_{16}NO$ [M + H], 178.1232; found, 178.1238.

*2-(Pyridin-3-yl)cyclohexanone (**12b**).*[42] **12b** was synthesized from cyclohexan-1-one (1.1 mmol, 1.1 equiv, 105.7 mg, 106.5 μL) and 3-iodopyridine (1.0 mmol, 1 equiv, 205.0 mg) according to the general procedure described above, yielding a yellow oil. Yield, 111.8 mg, 63.8%. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.49 (1H, d, *J* = 5.0 Hz), 8.37 (1H, s), 7.48 (1H, d, *J* = 6.0 Hz), 7.26 (1H, dd, *J* = 7.7, 3.2 Hz), 3.62 (1H, dd, *J* = 17.9, 5.5 Hz), 2.56−2.48 (2H, m), 2.30−2.26

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(1H, m), 2.20−2.26 (1H, m), 2.20−2.14 (1H, m), 1.02−1.78 (4H, m). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz, ppm): δ 209.3, 150.1, 148.4, 136.3, 134.4, 123.3, 55.0, 42.3, 35.5, 27.9, 25.5. HRMS calcd for $C_{11}H_{14}NO$ [M + H], 176.1075; found, 176.1082.

*1-(2,5-Dimethylfuran-3-yl)-2-(pyridin-3-yl)ethanone (**13b**).* **13b** was synthesized from 3-acetyl-2,5-dimethylfuran (0.55 mmol, 1.1 equiv, 76.0 mg, 73.2 μL) and 3-iodopyridine (0.50 mmol, 1 equiv, 102.5 mg) according to the general procedure described above, yielding a brown oil. Yield, 127.6 mg, 59.3%. ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.50 (1H, d, *J* = 1.35), 8.47 (1H, s), 7.57 (1H, d, *J* = 7.75 Hz), 7.27 (1H, m), 6.25 (1H, s), 3.97 (2H, s), 2.53 (3H, s), 2.25 (3H, s). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz, ppm): δ 192.7, 158.3, 150.7, 150.4, 148.3, 137.3, 130.3, 123.5, 121.0, 105.6, 44.9, 14.4, 13.3. HRMS calcd for $C_{13}H_{14}NO_2$ [M + H], 216.1025; found, 216.1021.

*1-(2,5-Dimethylthiophen-3-yl)-2-(pyridin-3-yl)ethanone (**14b**).*[5b] **14b** was synthesized from 3-acetyl-2,5-dimethylthiophene (0.55 mmol, 1.1 equiv, 84.8 mg, 78.1 μL) and 3-iodopyridine (0.50 mmol, 1 equiv, 102.5 mg) according to the general procedure described above, yielding a brown oil. Yield, 182.0 mg, 78.7%. ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.50 (1H, d, *J* = 1.35), 8.50 (1H, d, *J* = 4.6), 8.47 (1H, s), 7.58 (1H, d, *J* = 7.75), 7.27−7.26 (1H, m), 4.09 (2H, s), 2.65 (3H, s), 2.41 (3H, s). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz, ppm): δ 192.3, 150.7, 149.1, 148.3, 137.3, 135.7, 134.7, 130.5, 125.8, 123.5, 45.3, 16.3, 15.1. HRMS calcd for $C_{13}H_{14}NOS$ [M + H], 232.0796; found, 232.0799.

*1-(Pyridin-2-yl)-2-(pyridin-3-yl)ethanone (**15b**).* **15b** was synthesized from 2-acetylpyridine (0.55 mmol, 1.1 equiv, 66.7 mg, 61.1 μL) and 3-iodopyridine (0.50 mmol, 1 equiv, 102.5 mg) according to the general procedure described above, yielding a yellow oil. Yield, 129.2 mg, 65.2%. ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.72 (1H, d, *J* = 3.6 Hz), 8.59 (1H, s), 8.50 (1H, d, *J* = 5.1 Hz), 8.05 (1H, d, *J* = 7.8 Hz), 7.84 (1H, td, *J* = 7.8, 1.8 Hz), 7.71 (1H, d, *J* = 7.8 Hz), 7.51 (1H, t, *J* = 5.1 Hz), 7.30−7.18 (2H, m), 4.51 (2H, s). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz, ppm): δ 152.7, 150.4, 149.2, 147.5, 138.3, 137.2, 131.0, 127.7, 123.6, 122.5, 41.3. HRMS calcd for $C_{12}H_{11}N_2O$ [M + H], 199.0871; found, 199.0869.

*1,2-Di(pyridin-3-yl)ethanone (**16b**).*[5b] **16b** was synthesized from 3-acetylpyridine (0.55 mmol, 1.1 equiv, 66.7 mg, 60.5 μL) and 3-iodopyridine (0.50 mmol, 1 equiv, 102.5 mg) according to the general procedure described above, yielding a yellow oil. Yield, 127.6 mg, 64.4%. ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 9.24 (1H, s), 8.80 (1H, d, *J* = 5.0 Hz), 8.53 (2H, d, *J* = 8.3 Hz), 8.27 (1H, d, *J* = 5.9 Hz), 7.61 (1H, d, *J* = 7.8 Hz), 7.44 (1H, dd, *J* = 8.2, 5.0 Hz), 7.29 (1H, dd, *J* = 7.8, 5.0 Hz), 4.32 (2H, s). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz, ppm): δ 195.4, 154.0, 150.5, 149.9, 148.6, 137.5, 135.8, 131.6, 129.4, 123.9, 123.7, 42.7. HRMS calcd for $C_{12}H_{11}N_2O$ [M + H], 199.0871; found, 199.0872.

*2-(Pyridin-3-yl)-1-(pyridin-4-yl)ethanone (**17b**).* **17b** was synthesized from 4-acetylpyridine (0.55 mmol, 1.1 equiv, 66.7 mg, 60.9 μL) and 3-iodopyridine (0.50 mmol, 1 equiv, 102.5 mg) according to the general procedure described above, yielding a yellow oil. Yield, 152.2 mg, 76.8%. ^1H NMR ($CDCl_3$, 500 MHz, ppm): δ 8.83 (2H, d, *J* = 4.6 Hz), 8.54 (1H, d, *J* = 4.1 Hz), 8.50 (1H, s), 7.77 (2H, dd, *J* = 5.9, 1.3 Hz), 7.58 (1H, d, *J* = 7.8 Hz), 7.30−7.27 (1H, m). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz, ppm): δ 196.0, 151.2, 150.5, 148.7, 142.2, 137.5, 129.1, 123.7, 121.3, 42.6. HRMS calcd for $C_{12}H_{11}N_2O$ [M + H], 199.0871; found, 199.0872.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.9b00446.

^1H and $^{13}C\{^1H\}$ NMR spectra of all of the products and thermochemical corrections and solvation energies for the optimized stationary points (PDF)

Collection of .mol2 formatted files of the Cartesian coordinates for the optimized stationary points (ZIP)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mal1@nku.edu. Tel.: +1 859 572 6961. Fax: +1 859 572 5162.

ORCID

Tülay Aygan Ateşin: 0000-0001-8394-8830

Lili Ma: 0000-0002-7231-3351

Notes

The authors declare no competing financial interest.

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