JOC The Journal of Organic Chemistry

Article

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Palladium Catalyzed Carbonylative Coupling for Synthesis of Arylketones and Arylesters Using Chloroform as the Carbon Monoxide Source

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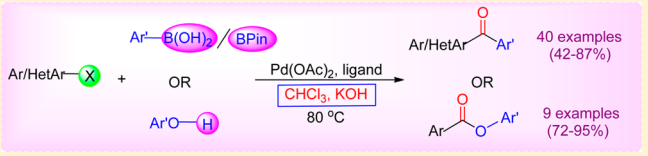
Supporting Information

ABSTRACT: We describe a modular, palladium catalyzed synthesis of aryl(hetero)aryl benzophenones and aryl benzoates from aryl(hetero)aryl halides using $CHCl_3$ as the carbonyl source in the presence of KOH. The reaction occurs in tandem through an initial carbonylation to generate an aroyl halide, which undergoes coupling with arylboronic acids, bornonates, and phenols. Direct carbonylative coupling of indoles at the third position has also been accomplished under slightly modified reaction conditions by *in situ* activation of the C−H bond. Notably, $CHCl_3$ is a convenient and safe alternation of CO gas, provides milder reaction conditions with high functional group tolerance, and gives the products in moderate to good yields.



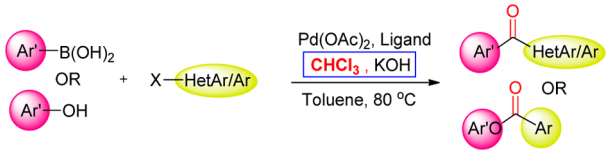
INTRODUCTION

Transition-metal catalyzed insertion of a carbonyl group directly into an organic molecule has evolved as one of the most powerful methods for synthesizing diverse carbonyl compounds due to high atom economy, functional group tolerance, regioselectivity, and easy availability of the starting materials.[1] Carbonyl installation can be achieved by using carbon monoxide (CO), which represents an economical and attractive C1 building block. The challenge, however, is the handling of CO, since it is a toxic gas available in pressurized cylinders which limits its practical utility. To avoid its direct use, alternative CO sources such as transition metal carbonyl complexes,[2] carbamoylsilane,[3] *N*-formylsaccharin,[4] amoylstannanes,[5] oxalyl chloride,[6] and others have been developed. In a recent report, Skrydstrup and co-workers have elaborated on two new CO releasing molecules referred to as COgen and SilaCOgen in a two-chamber reactor for various carbonylation reactions.[7] Although each of these precursors has its own merits, it is still important to find CO sources that are inexpensive, less toxic, easily available, and do not require multistep synthesis or complex reaction setup. In this context, generation of CO by hydrolysis of $CHCl_3$ in the presence of a strongly basic aqueous hydroxide solution is a well-known practical approach.[8] Since $CHCl_3$ is inexpensive and easy to handle, its use as a CO source is quite attractive in organic synthesis. In the past few years, there have been some reports in which CO generated from $CHCl_3$ has been used for Pd-catalyzed carboxylation,[9] aminocarbonylations,[10] Heck-type domino cyclization,[11] and carbonylative Sonogashira coupling.[12]

Arylketones are important structural building blocks present in a wide variety of molecules such as pharmaceutical drugs, natural products, and sunscreen agents.[13] Their conventional synthesis starting from acid halides can be executed via Friedel−Crafts reaction,[14] acylation of premetalated precursors,[15] or Pd-mediated cross-coupling with boronic acids.[16] Direct carbonyl insertion into aryl halides via a Pd catalyzed carbonylative Suzuki pathway has been achieved with carbon monoxide gas,[17] metal carbonyl precursors,[2a] or other CO surrogates.[18] However, these reactions are challenged by competing side reactions, such as noncarbonylative Suzuki coupling, and homocoupling.[19] To the best of our knowledge, Pd catalyzed biaryl ketone synthesis via CO insertion using chloroform as a source has not been investigated yet, though a recent report demonstrates this transformation in PEG-400 using $FeCl_2$ as the catalyst and pivalic acid and NaCl as additives.[20]

Inspired by the pioneering works of Hull, Gu, and Wang, and continuing our efforts toward developing efficient synthetic protocols using Pd,[21] we explored the synthesis of benzophenones via carbonylative cross-coupling of aryl iodides with arylboronic acids using CO generated *in situ* from $CHCl_3$ (Scheme 1). The method could also be successfully applied to phenols as coupling partners yielding aryl esters in high yields. The previous literature on Pd-catalyzed ester synthesis with aryl halide precursors has been reported using phenylformates or formic acid,[22] decarboxylative coupling using potassium oxalate monoesters,[23] and carbonylative coupling with phenols,

Scheme 1. Synthesis of Arylketones and Arylesters Using $CHCl_3$



Received: November 10, 2016
Published: December 21, 2016

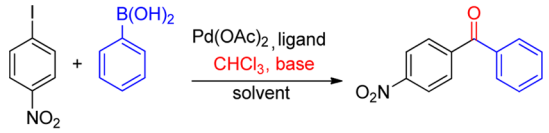
DOI: 10.1021/acs.joc.6b02711
J. Org. Chem. 2017, 82, 1105−1113

wherein CO is delivered using a CO balloon[24] or a metal carbonyl source.[25] Phenyl esters are known to serve as useful acylating agents and can deliver libraries of carbonyl derivatives, including alkyls, allyls, and thioesters under mild conditions.[26]

RESULTS AND DISCUSSION

The work initiated with a carbonylative Suzuki coupling for the synthesis of a benzophenone derivative. For this, 4-iodonitrobenzene (**1d**, 1.0 equiv), phenylboronic acid (**2a**, 1.2 equiv), KOH (6.0 equiv), $CHCl_3$ (3.0 equiv), $Pd(OAc)_2$ (2 mol %), and PPh_3 (20 mol %) were taken in toluene as the solvent. The contents were heated at 80 °C for 12 h, and the desired product, 4-nitrobenzophenone (**3i**), was isolated in 64% yield (Table 1, entry 1). Motivated by this initial success, we optimized the reaction with respect to solvent, base, catalyst, ligand, and temperature.

Table 1. Optimization of the Reaction Conditions[a]



1d **2a** **3i**

entry	solvent	base	catalyst	ligand	yield (%)[b]
1	toluene	KOH	$Pd(OAc)_2$	PPh_3	64
2	$CHCl_3$	KOH	$Pd(OAc)_2$	PPh_3	10
3	DMSO	KOH	$Pd(OAc)_2$	PPh_3	23
4	DCE	KOH	$Pd(OAc)_2$	PPh_3	11
5	CH_3CN	KOH	$Pd(OAc)_2$	PPh_3	34
6	dioxane	KOH	$Pd(OAc)_2$	PPh_3	59
7	H_2O	KOH	$Pd(OAc)_2$	PPh_3	0
8	DMF	KOH	$Pd(OAc)_2$	PPh_3	29
9	toluene	KOH	$Pd(OAc)_2$	Pyridine	63
10	toluene	KOH	$Pd(OAc)_2$	BINAP	5
11	toluene	KOH	$Pd(OAc)_2$	glucose	0
12	**toluene**	**KOH**	**$Pd(OAc)_2$**	**DMAP**	**85**, 43,[c] 64[d]
13	toluene	KOH	$Pd(PPh_3)_2Cl_2$	DMAP	trace
14	toluene	KOH	$PdCl_2$	DMAP	47
15	toluene	KOH	$Pd(OAc)_2$	DMAP	79,[e] 81,[f] 64[g]
16	toluene	NaOH	$Pd(OAc)_2$	DMAP	53
17	toluene	LiOH	$Pd(OAc)_2$	DMAP	29
18	toluene	$Mg(OH)_2$	$Pd(OAc)_2$	DMAP	15
19	toluene	$CsOH·H_2O$	$Pd(OAc)_2$	DMAP	86

[a]Reaction conditions: **1d** (0.5 mmol, 1.0 equiv), **2a** (0.6 mmol, 1.2 equiv), base (6.0 equiv), $Pd(OAc)_2$ (2 mol %), ligand (20 mol %), $CHCl_3$ (3.0 equiv) and solvent (3 mL) were heated at 80 °C for 12 h. [b]HPLC yield. [c]DMAP (10 mol %). [d]DMAP (40 mol %). [e]Temp 70 °C. [f]Temp 90 °C. [g]Temp 100 °C.

Replacing toluene with other solvents such as $CHCl_3$, DMSO, DCE, CH_3CN, dioxane, water, and DMF (entries 2−8) lowered the product yield suggesting a strong influence of the solvent on this transformation. Screening of ligands such as pyridine, BINAP, glucose, and DMAP (entries 9−12) showed that while pyridine exerted a similar effect as PPh_3 (entries 1 and 9), BINAP and glucose were ineffective in promoting the reaction (entries 10 and 11). DMAP was found to be the best ligand giving **3i** in 85% yield (entry 12). Lowering or raising the amount of DMAP to 10 or 40 mol % decreased the product yield (entry 12). Other palladium precursors such as $Pd(PPh_3)_2Cl_2$ and $PdCl_2$ were also examined, but relatively lower yields were obtained with them (entries 13, 14). Blank experiments carried out without the addition of phenylboronic acid or a palladium catalyst did not yield any product. Varying the temperature to 70, 90, or 100 °C gave the product in 64−81% yields (entry 15) suggesting 80 °C to be the optimum reaction temperature. Since a base is vital for this reaction, other hydroxide bases such as NaOH, LiOH, and $Mg(OH)_2$ were tested, but all were found to be inferior to KOH and gave a lower yield of **3i** (12−53%, entries 16−18), except $CsOH·H_2O$ which gave **3i** in 86% yield (entry 19). In view of the higher cost and hygroscopic nature of $CsOH·H_2O$, we chose KOH. It is noteworthy to mention that the reaction kinetics enabled carbonylation to outcompete the noncarbonylative couplings reported previously as side reactions, when CO gas is used directly.[19a−c] We noticed that the reaction atmosphere did not have any effect, and similar yields were obtained under both air and nitrogen.

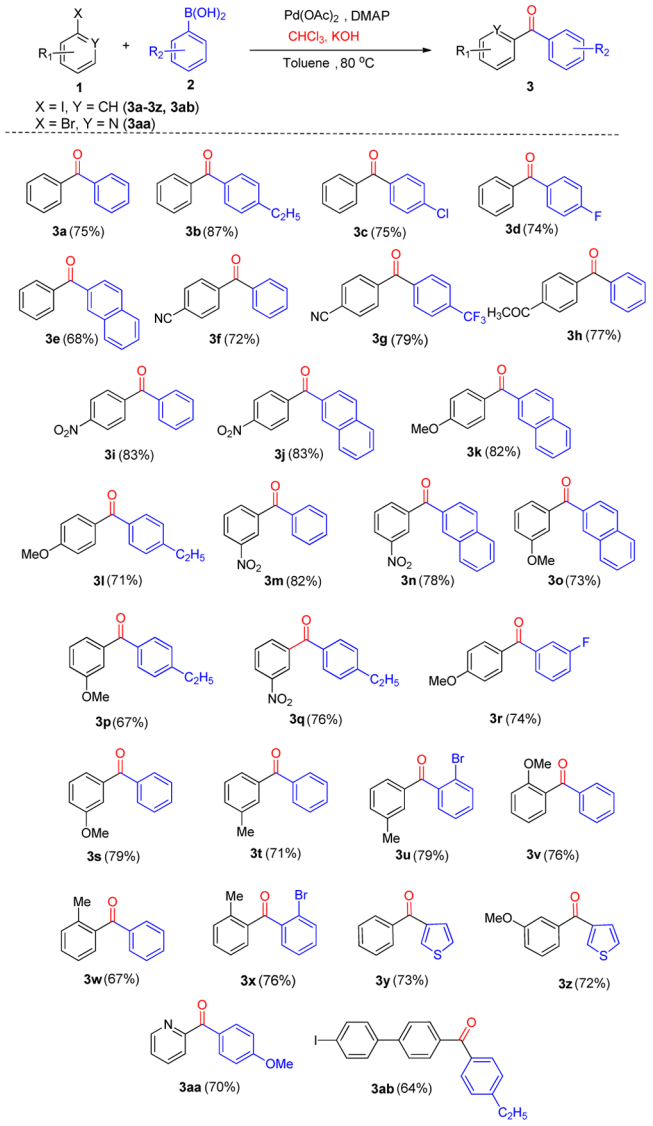
Employing the best optimized reaction conditions, a variety of aryl and heteroaryl halides were treated with substituted and unsubstituted arylboronic acids to establish the versatility of this protocol. The results are summarized in Table 2. In general, all the investigated arylboronic acids underwent smooth carbonylative coupling with iodobenzene (**1a**) to provide the diarylketones in moderate to good yields (**3a−3e**, 68−87%). The effect of substituents on aryl iodides was also examined. It was found that aryl iodides with substituents at the *para*-position afforded slightly better yields (**3i−3l**) compared to their *meta*-substituted analogues (**3m−3p**). A similar pattern was seen while comparing the *meta*-substituted derivatives (**3s−3u**) with their corresponding *ortho*-substituted counterparts (**3v−3x**) probably due to the prevalent steric effects. Notably, with 2-bromoboronic acid, chemoselectivity was observed with carbonylation occurring exclusively on aryl iodide to afford the corresponding bromosubstituted ketone (**3u**, **3x**) with an intact bromine handle for further functionalization. The electronic effect of substituents present on aryl iodides and arylboronic acids did not influence the reaction significantly. It was found that similar yields were obtained whether electron-donating (methyl, ethyl, methoxy) or electron-withdrawing (fluoro, nitro, cyano, trifluoromethyl, acetyl) groups were present on aryl iodides and arylboronic acids.

This offers a significant improvement over the conventional carbonylative Suzuki couplings with unpressurized CO gas, where electron-deficient aryl halides show poor reactivity.[22] Even heteroaryl substrates such as 2-bromopyridine and thiophene-3-boronic acid survived the reaction conditions and gave **3y**, **3z**, and **3aa** in moderate yields. The reaction of 4,4′-diiodo-1,1′-biphenyl with (4-ethylphenyl) boronic acid yielded the monocarbonylated product, (4-ethylphenyl)(4′-iodo-[1,1′-biphenyl]-4-yl)methanone (**3ab**) exclusively in 64% yield. This is in contrast to the previous report on carbonylative Suzuki coupling of 4,4′-diiodo-1,1′-biphenyl using a CO balloon or metal carbonyls and a Pd(NHC) complex, where a mixture of mono- (**3ab**) and dicarbonylated products [biphenyl-4,4′-diyl bis(phenylmethanone)] was obtained in varied yields.[27] This method, therefore, offers better selectivity for synthesizing the monocarbonylated ketone derivatives. The reaction was also applied for gram-scale synthesis starting from 1 g of iodobenzene and 883 mg of 4-ethylboronic acid to yield **3b** in an 84% yield (870 mg).

The substrate scope was further examined with boronic acid esters as shown in Table 3. The reaction of 4-(4-phenyl-1-piperazinylmethyl)benzeneboronic acid pinacol ester (**4a**) with

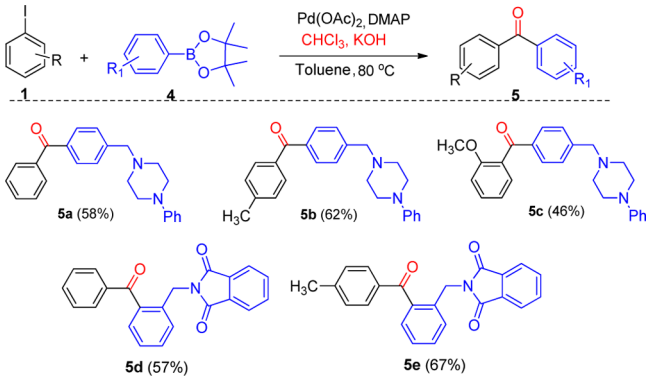
DOI: 10.1021/acs.joc.6b02711
J. Org. Chem. 2017, 82, 1105−1113

Table 2. Substrate Scope of Aryl Halides and Aryl Boronic Acids[a]



[a]Reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), $Pd(OAc)_2$ (2 mol %), DMAP (20 mol %), $CHCl_3$ (3.0 equiv), KOH (6.0 equiv) in toluene at 80 °C for 12 h.

Table 3. Scope with Aryl Boronates[a]



[a]Reaction conditions: **1** (1.0 mmol), **4** (1.2 mmol), $Pd(OAc)_2$ (2 mol %), DMAP (20 mol %), $CHCl_3$ (3.0 equiv), KOH (6.0 equiv) in toluene at 80 °C for 12 h.

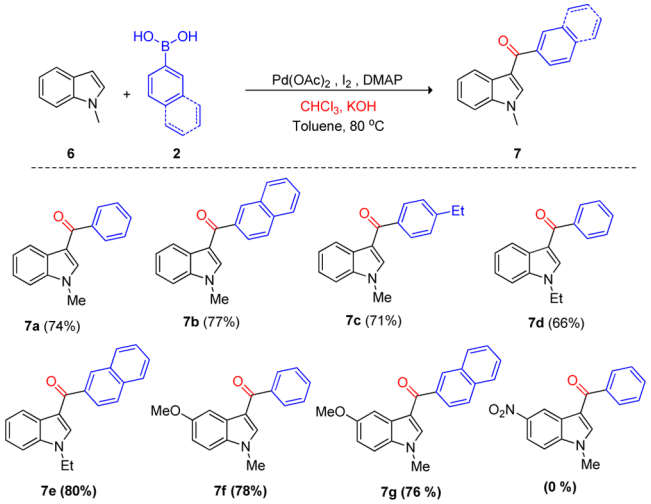
unsubstituted iodobenzene, as well as iodobenzene substituted with 4-methyl or 2-methoxy groups, proceeded well under the optimized conditions to yield the piperazinyl substituted aromatic ketones (**5a**–**5c**) in 46–62% yields. These compounds are medicinally important, as their analogues are being developed as potent p38-alpha MAPK inhibitors for treatment of Alzheimer's disease.[28] With 2-(*N*-phthalimidomethyl)-benzeneboronic acid pinacol ester (**4b**), the corresponding phthalimide substituted aromatic ketones **5d** and **5e** were obtained in 57% and 67% yields, respectively. In general, the reaction failed with electron-withdrawing aryl iodides. The reaction of 4-nitroiodo benzene with **4b** under optimized conditions did not yield the desired carbonylative coupled product, and the corresponding Suzuki coupled biaryl was obtained instead.

To further generalize the application of this protocol, we examined if the carbonyl generated from $CHCl_3$ and KOH could be inserted directly into the relatively inert C–H bonds. This was explored with indoles as substrates, through an *in situ* iodination followed by palladium catalyzed sequential carbonylation and coupling in one pot. A similar carbonylative coupling of indoles has been reported earlier using CO gas as the carbonyl source.[29] The reaction of *N*-methylindole (1.0 mmol) with phenylboronic acid in the presence of $Pd(OAc)_2$ (2.0 mol %), iodine (1.2 equiv), chloroform (3.0 equiv), KOH (6.0 equiv), and DMAP (20 mol %) in toluene at 80 °C yielded the desired product (**7a**) in 24% yield. To improve the reaction yield, the amount of DMAP was increased up to 1.0 equiv, which facilitated the reaction and gave **7a** in 74% yield.

After determining the optimal conditions, different *N*-alkylated indoles as substrates were screened. The reaction served well with an unsubstituted as well as a methoxy substituted *N*-methylindole derivative to give the carbonylated products (**7a**–**7g**) in moderate to good yields (Table 4). However, with 5-nitro substituted *N*-methylindole, the reaction failed and did not yield any product.

After successful execution of the carbonylative coupling strategy for benzophenone synthesis, we implemented it on

Table 4. Substrate Scope of *N*-Alkyl Indoles and Arylboronic Acids[a]

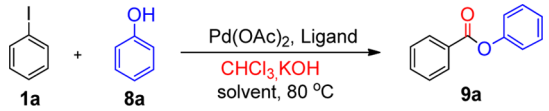


[a]Reaction conditions: **6** (1.0 mmol), **2** (1.2 mmol), $Pd(OAc)_2$ (2 mol %), DMAP (1.0 equiv), $CHCl_3$ (3.0 equiv), KOH (6.0 equiv), I_2 (1.2 equiv) in toluene at 80 °C for 12 h.

DOI: 10.1021/acs.joc.6b02711
J. Org. Chem. 2017, 82, 1105–1113

oxygen nucleophiles for the synthesis of aryl esters. To establish this, we attempted the reaction of phenol (**8a**) with iodobenzene (**1a**) under the optimized conditions, but failed to obtain any product (Table 5, entry 1). Replacing DMAP with PPh_3 as the ligand favored the reaction and gave the desired product phenylbenzoate (**9a**) in 30% yield (Table 5, entry 2). To further improve the yield, the reaction was attempted with an excess of KOH (10 equiv) in a biphasic solvent system comprised of water and $CHCl_3$ in the ratio 3:1. Surprisingly, under these conditions, the reaction did not proceed at all. However, utilizing a nitrogen atmosphere enabled a facile and smooth coupling, and **9a** was obtained in 80% yield (Table 5, entry 4).

Table 5. Optimization of Reaction Conditions for Aryl Ester Synthesis[a]

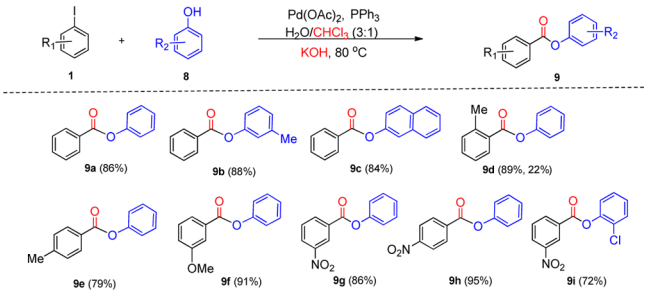


entry	solvent	KOH (equiv)	ligand	yield (%)[b]
1	toluene	6	DMAP	–
2	toluene	6	PPh_3	30
3	$H_2O/CHCl_3$ (3:1)	10	PPh_3	–
4	$H_2O/CHCl_3$ (3:1)	10	PPh_3	80[c]

[a]Reaction conditions: **1a** (0.5 mmol, 1.0 equiv), **8a** (0.6 mmol, 1.2 equiv), $Pd(OAc)_2$ (2 mol %), ligand (20 mol %), $CHCl_3$ (3.0 equiv), KOH, solvent at 80 °C for 12 h under an air atmosphere. [b]Isolated yield. [c]Under a N_2 atmosphere.

Subsequently, a library of aryl esters was synthesized using PPh_3 as the ligand in $H_2O/CHCl_3$ (3:1) under a nitrogen atmosphere (Table 6). Aryl iodides substituted with methyl, methoxy, and nitro groups at varied positions underwent facile reaction with substituted phenols as well as β-naphthol to yield the aryl esters (**9a**–**9i**) in moderate to good yields (72–95%). As was observed in the benzophenone series, the electronic influence of the substituents was not quite significant with esters as well. The structure of **9g** was also confirmed by single crystal X-ray analysis (Supporting Information, Figure S1). Notably, no product resulting from O-arylation was observed.

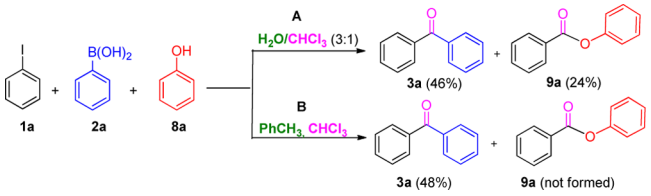
Table 6. Scope of Carbonylative Coupling with Phenols[a]



[a]Reaction conditions: **1** (1.0 mmol), **8** (1.2 mmol), $Pd(OAc)_2$ (2 mol %), PPh_3 (20 mol %), $CHCl_3$ (3.0 equiv), KOH (10.0 equiv), in 4 mL of $H_2O/CHCl_3$ (3:1) at 80 °C for 12 h under a N_2 atmosphere.

To ascertain the relative reactivity of arylboronic acids and phenols toward a competitive coupling with the intermediate carbonylated aryl iodide, a mixed experiment was carried out (Scheme 2). Equimolar amounts of **2a** and **8a** were added to $H_2O/CHCl_3$ (3:1) containing **1a**, $Pd(OAc)_2$, PPh_3, and KOH, and the contents were heated at 80 °C for 12 h under a N_2 atmosphere (Scheme 2A). Chemoselectivity was not observed under biphasic conditions, and a mixture of ketone **3a** and ester **9a** was obtained in 46% and 24% yields respectively, suggesting faster kinetics for boronic acids compared to phenols. However, replacing H_2O with toluene selectively gave the ketone **3a**, and no traces of **9a** were seen (Scheme 2B).

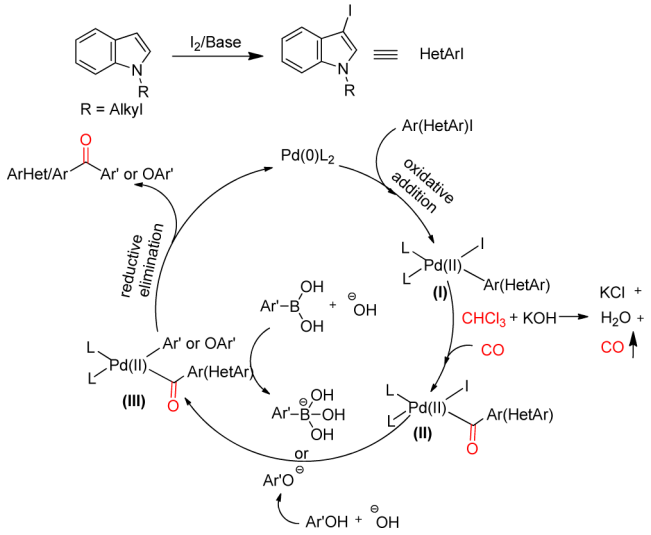
Scheme 2. Competitive Palladium Catalyzed Carbonylative Coupling for Synthesis of Ketone versus Ester[a]



[a]Reaction conditions: **1a** (1.0 mmol), **2a** (0.6 mmol), **8a** (0.6 mmol), $Pd(OAc)_2$ (2 mol %), PPh_3 (20 mol %), $CHCl_3$ (3.0 equiv), KOH (10.0 equiv) in 4 mL of [A]$H_2O/CHCl_3$ (3:1), and [B]toluene at 80 °C for 12 h under a N_2 atmosphere.

The carbonylative coupling is believed to follow the mechanistic path shown in Scheme 3. It begins with the oxidative addition of aryl(heteroaryl)iodide on $Pd(0)L_2$ to yield complex **I**, which undergoes insertion of carbon monoxide generated *in situ* from chloroform and KOH to form complex **II**. Thereafter, a phenyl anion or phenoxide ion generated from arylboronic acid(pinacol ester) or phenol, respectively, undergoes ligand displacement, resulting in the formation of complex **III**.[27,30]

Scheme 3. Proposed Mechanism for Palladium Catalyzed Carbonylative Coupling



In the final step, **III** undergoes reductive elimination to yield the product and regenerate Pd(0) for the next catalytic cycle. The faster insertion of CO into the Ar(HetAr)PdX intermediate (**I**) allows a tandem reaction and prevents the formation of Ar(HetAr)–Pd–Ar′(OAr′) species responsible for generating biaryls as side products. To confirm that the ester formation goes via this route, and not through esterification of benzoic acid with phenol, the reaction was monitored at different time intervals. Stopping the reaction at 2, 5, and 12 h did not reveal any traces of benzoic acid, confirming

DOI: 10.1021/acs.joc.6b02711
J. Org. Chem. 2017, 82, 1105–1113

that the reaction did not involve an intermediate benzoic acid which could subsequently become esterified.

CONCLUSIONS

In summary we have developed a "CO-free", Pd catalyzed carbonylative coupling of aryl halides with arylboronic acids, aryl boronates, and phenols using $CHCl_3$. The protocol is an extremely convenient and safe alternative to CO balloons or pressured CO reactors essentially required for carbonylations. The method allows the modular synthesis of an array of benzophenones and arylesters with high functional group tolerance in good yields from available substrates and is directly amenable to structural diversification. The strategy can also be applied for a direct carbonylative coupling of *N*-alkylindoles with arylboronic acids. The protocol is effective with a cheap base such as KOH in contrast to $CsOH{\cdot}H_2O$ reported previously for aminocarbonylations.[10] Also, isotopically enriched organic compounds can be prepared by direct incorporation of ^{13}CO and ^{14}CO from the corresponding labeled $CHCl_3$ available commercially.

EXPERIMENTAL SECTION

General Methods. All reagents and solvents were of pure analytical grade. Thin layer chromatography (TLC) was performed on 60 F_{254} silica gel, precoated on aluminum plates and revealed with either a UV lamp (λ_{max} = 254 nm) or iodine vapors. The products were purified by column chromatography on silica gel 230−400 mesh. ^1H, ^{19}F, and ^{13}C NMR spectra were recorded on a 300 MHz (^1H 300 MHz, ^{19}F 282 MHz, ^{13}C 75 MHz) and 400 MHz spectrometer (^1H 400 MHz) using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as the internal standard at room temperature. Chemical shifts are in δ (ppm) relative to TMS. The coupling constants (J) are in Hz. High resolution mass spectra (HRMS) were recorded on a mass spectrometer using electrospray ionization-time-of-flight (ESI-TOF) reflectron experiments.

General Procedure for Synthesis of Benzophenones (3a−3ab) and (5a−5e). Iodobenzene (204 mg, 1 mmol), phenylboronic acid (heteroarylboronic acid pinacol ester) (146.32 mg, 1.2 mmol), chloroform (250 μL, 3 mmol), KOH (336.7 mg, 6 mmol), DMAP (24.4 mg, 20 mol %), $Pd(OAc)_2$ (4.5 mg, 2 mol %), and toluene (4 mL) were added to an 8 mL ace pressure tube, sealed tightly, and stirred vigorously at 80 °C for 12 h. After completion of the reaction, the combined organic layer was extracted with ethyl acetate, washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography to afford benzophenone (**3a**) in 75% yield.

General Procedure for the Synthesis of N-Protected Indole. Indole (1 g, 8.54 mmol) and DMF (25 mL) were added to a round-bottom flask, stirred, and cooled in an ice bath, simultaneously purging with nitrogen gas (15 min) to create an inert atmosphere. After that sodium hydride (0.82 g, 34.2 mmol) was added and stirred for 20 min under a N_2 atmosphere. Then methyl iodide (1.82 g, 12.8 mmol) was added, and the flask was kept at room temperature for 15 min and then was heated at 120 °C for 12 h under a nitrogen atmosphere. The protected indole was isolated using column chromatography on silica and hexane as an eluent to give the product in 90% yield.

General Procedure for Carbonylation of Indoles with Arylboronic Acids (7a−7g). *N*-Methylindole (131 mg, 1 mmol), phenylboronic acid (146.3 mg, 1.2 mmol), chloroform (250 μL, 3 mmol), KOH (336.7 mg, 6 mmol), DMAP (122 mg, 1.0 equiv), $Pd(OAc)_2$ (4.5 mg, 2 mol %), iodine (151.2 mg, 1.2 mmol), and toluene (4 mL) were added to an 8 mL ace pressure tube sealed tightly and stirred vigorously at 80 °C for 12 h. After completion of the reaction, the combined organic layer was extracted with ethyl acetate, washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography to afford phenylbenzoate (**7a**) in a 74% yield.

General Procedure for Synthesis of Phenylbenzoate (9a−9i). Iodobenzene (204 mg, 1 mmol), phenol (112.8 mg, 1.2 mmol), 4 mL chloroform/water (1:3), KOH (56 mg, 10 mmol), PPh_3 (55.6 mg, 20 mol %), and $Pd(OAc)_2$ (4.5 mg, 2 mol %) were added to an 8 mL ace pressure tube, followed by nitrogen flushing for 10 min, then sealed tightly, and stirred vigorously at 80 °C for 12 h. After completion of the reaction, the combined organic layer was extracted with ethyl acetate, washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography to afford phenylbenzoate (**9a**) in an 86% yield.

Procedure for Competitive Palladium Catalyzed Carbonylative Coupling for Synthesis of Ketone versus Ester. Iodobenzene (204 mg, 1 mmol), phenyl boronic acid (73 mg, 0.6 mmol), phenol (56 mg, 0.6 mmol), $Pd(OAc)_2$ (4.5 mg, 2 mol %), PPh_3 (55 mg, 20 mol %), $CHCl_3$ (250 μL, 3.0 equiv), and KOH (561 mg, 10.0 equiv) were added to 4 mL of $H_2O/CHCl_3$ (3:1) in an 8 mL ace pressure tube and heated at 80 °C for 12 h under a N_2 atmosphere. After completion of the reaction, the combined organic layer was extracted with ethyl acetate, washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography. **3a** and **9a** were obtained in 46% (83 mg) and 24% (48 mg) yields, respectively. The same experiment was repeated by replacing 4 mL of $H_2O/CHCl_3$ (3:1) with 4 mL of toluene as solvent.

Physical Properties and Characterization Data of the Synthesized Compounds. *Benzophenone (**3a**):*[31] White solid, Hexane/EtOAc = 98/2, yield 75% (136 mg); ^1H NMR (300 MHz, $CDCl_3$): δ 7.81 (d, J = 7.2 Hz, 4H), 7.57 (d, J = 6.6 Hz, 2H), 7.48 (d, J = 6.9 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.8, 137.6, 132.5, 130.1, 128.3; MS (ESI) m/z 183 $[M + H]^+$; HRMS calcd for $C_{13}H_{11}O^+$, 183.0804; found, 183.0806 $[M + H]^+$.

*(4-Ethylphenyl)(phenyl)methanone (**3b**):*[32] White solid, Hexane/EtOAc = 98/2, yield 87% (182 mg); ^1H NMR (300 MHz, $CDCl_3$): 7.69−7.63 (m, 4H), 7.46 (t, J = 7.2 Hz, 1H), 7.35 (t, J = 7.5 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H), 2.62 (q, J = 7.5 Hz, 2H), 1.71 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.3, 149.4, 138.0, 135.2, 132.1, 130.4, 129.9, 128.2, 127.8, 29.0, 15.2; MS (ESI) m/z 211 $[M + H]^+$; HRMS calcd for $C_{15}H_{15}O^+$, 211.1117; found, 211.1121 $[M + H]^+$.

*(4-Chlorophenyl)(phenyl)methanone (**3c**).*[31] White solid, Hexane/EtOAc = 97/3, yield 75% (162 mg); ^1H NMR (300 MHz, $CDCl_3$): 7.77−7.71 (m, 4H), 7.60−7.55 (m, 1H), 7.48−7.41 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 195.4, 138.9, 137.2, 135.9, 132.7, 131.5, 129.9, 128.6, 128.4; MS (ESI) m/z 217 $[M + H]^+$; HRMS calcd for $C_{13}H_{10}ClO^+$, 217.0420; found, 217.0415 $[M + H]^+$.

*(4-Fluorophenyl)(phenyl)methanone (**3d**).*[31] Colorless oil, Hexane/EtOAc = 97/3, yield 74% (148 mg); ^1H NMR (400 MHz, $CDCl_3$): δ 7.76−7.71 (m, 2H) 7.69−7.66 (m, 2H), 7.49 (t, J = 7.6 Hz, 1H), 7.38 (t, J = 7.6 Hz, 2H), 7.08−7.03 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.2, 165.4 (d, J = 252.5 Hz), 137.5, 133.8 (d, J = 3 Hz), 132.7 (d, J = 9.2 Hz), 132.5, 132.4, 129.9, 115.5 (d, J = 21.8 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −106.0 (s, 1F); MS (ESI) m/z 201 $[M + H]^+$; HRMS calcd for $C_{13}H_{10}FO^+$, 201.0710; found, 201.0713 $[M + H]^+$.

*Naphthalen-2-yl(phenyl)methanone (**3e**).*[31] White solid, Hexane/EtOAc = 98/2, yield 68% (157 mg); ^1H NMR (300 MHz, $CDCl_3$): δ 8.36−8.30 (m, 1H), 8.02−7.89 (m, 6H), 7.65- 7.55 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.1, 137.9, 135.3, 134.9, 132.4, 132.3, 131.9, 131.8, 130.1, 129.4, 128.4, 127.8, 126.8, 125.9, 125.8; MS (ESI) m/z 233 $[M + H]^+$; HRMS calcd for $C_{17}H_{13}O^+$, 233.0961; found, 233.0964 $[M + H]^+$.

*4-Benzoylbenzonitrile (**3f**).*[33] White solid, Hexane/EtOAc = 97/3, yield 72% (149 mg); ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 8.4 Hz, 2H), 7.81−7.78 (m, 4H), 7.65 (t, J = 7.6 Hz, 1H), 7.52 (t, J = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.0, 141.2, 136.3, 133.3, 132.2, 130.2, 130.1, 128.6, 118.0, 115.6; MS (ESI) m/z 208 $[M + H]^+$; HRMS calcd for $C_{14}H_{10}NO^+$, 208.0757; found, 208.0760 $[M + H]^+$.

*4-(4-(Trifluoromethyl)benzoyl)benzonitrile (**3g**).*[34] White solid, Hexane/EtOAc = 97/3, yield 79% (217 mg); ^1H NMR (400 MHz, $CDCl_3$): δ 8.39 (d, J = 8.8 Hz, 2H), 7.98 (d, J = 8.8 Hz, 2H), 7.93 (d, J = 8.4 Hz, 2H), 7.83 (d, J = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$):

DOI: 10.1021/acs.joc.6b02711
J. Org. Chem. 2017, 82, 1105−1113

δ 193.0, 139.3, 138.5, 133.5 (q, J = 30 Hz), 131.4, 129.3, 129.2, 126.0 (q, J = 4.0 Hz), 124.7 (q, J = 3.4 Hz), 116.8, 115.3; ^{19}F NMR (282 MHz, $CDCl_3$) δ −63.2 (s, 1F); MS (ESI) m/z 276 $[M + H]^+$; HRMS calcd for $C_{15}H_9F_3NO^+$, 276.0631; found, 276.0634 $[M + H]^+$.

1-(4Benzoylphenyl)ethanone (**3h**).[27] Brown liquid, Hexane/EtOAc = 96/4, yield 77% (172 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.98 (d, J = 6.9 Hz, 2H), 7.79 (d, J = 8.1 Hz, 2H),7.73 (d, J = 6.3 Hz, 2H), 7.62−7.52 (m, 1H), 7.44 (d, J = 6.6 Hz, 2H), 2.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.5, 196.0, 141.4, 139.6, 136.9, 133.0, 130.1, 130.0, 128.5, 128.2, 26.8; MS (ESI) m/z 247 $[M + Na]^+$; HRMS calcd for $C_{15}H_{12}NaO_2^+$, 247.0730; found, 247.0733 $[M + Na]^+$.

(4-Nitrophenyl)(phenyl)methanone (**3i**).[27] Yellow solid, Hexane/EtOAc = 96/4, yield 83% (189 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 8.8 Hz, 2H), 7.81 (d, J = 7.6 Hz, 2H), 7.66 (t, J = 7.2 Hz, 1H), 7.53 (t, J = 7.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.9, 149.8, 142.9, 136.3, 133.5, 130.7, 130.1, 128.7, 123.6; MS (ESI) m/z 228 $[M + H]^+$; HRMS calcd for $C_{13}H_{10}NO_3^+$, 228.0655; found, 228.0663 $[M + H]^+$.

Naphthalen-2-yl(4-nitrophenyl)methanone (**3j**).[35] Yellow solid, Hexane/EtOAc = 96/4, yield 83% (230 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (d, J = 7.2 Hz, 2H), 8.25 (s, 1H), 8.01−7.94 (m, 6H), 7.68−7.60 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ193.7, 148.8, 142.2, 134.6, 132.5, 131.4, 131.2, 129.7, 128.5, 128.0, 127.8, 126.9, 126.2, 124.2, 122.6; MS (ESI) m/z 278 $[M + H]^+$; HRMS calcd for $C_{17}H_{12}NO_3^+$, 278.0812; found, 278.0818 $[M + H]^+$.

(4-Methoxyphenyl)(naphthalen-2-yl)methanone (**3k**).[36] White solid, Hexane/EtOAc = 97/3, yield 82% (215 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44−8.42 (s, 1H), 8.3 (m, 6H), 7.60 (t, J = 8.4 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 3.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.6, 163.2, 135.5, 135.1, 132.6, 132.3, 131.1, 130.5, 129.3, 128.2, 128.0, 127.8, 126.7, 125.9, 113.7, 55.5; MS (ESI) m/z 263 $[M + H]^+$; HRMS calcd for $C_{18}H_{15}O_2^+$, 263.1067; found, 263.1062 $[M + H]^+$.

(4-Ethylphenyl)(4-methoxyphenyl)methanone (**3l**).[37] White solid, Hexane/EtOAc = 97/3, yield 71% (171 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.76−7.71 (m, 2H), 7.63−7.61 (m, 2H), 7.22−7.20 (m, 2H), 6.90−6.86 (m, 2H), 3.80 (s, 3H), 2.65 (q, J = 7.5 Hz, 2H), 1.20 (t, J = 7.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 195.3, 163.1, 148.8, 135.8, 132.4, 130.6, 130.1, 127.7, 113.5, 55.5, 28.9, 15.2; MS (ESI) m/z 241 $[M + H]^+$; HRMS calcd for $C_{16}H_{17}O_2^+$, 241.1223; found, 241.1224 $[M + H]^+$.

(3-Nitrophenyl)(phenyl)methanone (**3m**).[38] Yellow solid, Hexane/EtOAc = 96/4, yield 82% (186 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (s, 1H), 8.45 (d, J = 8.0 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 7.6 Hz, 2H), 7.73−7.65 (m, 2H), 7.54 (t, J = 8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.1, 148.1, 139.1, 136.3, 135.4, 133.3, 130.0, 129.6, 128.7, 126.7, 124.7; MS (ESI) m/z 228 $[M + H]^+$; HRMS calcd for $C_{13}H_{10}NO_3^+$, 228.0655; found, 228.0658 $[M + H]^+$.

Naphthalen-2-yl(3-nitrophenyl)methanone (**3n**). Yellow solid, Hexane/EtOAc = 96/4, mp: 110−125 °C, yield 78% (216 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.71 (s, 1H), 8.50 (d, J = 8.7 Hz, 1H), 8.35−8.20 (m, 2H), 8.01−7.95 (m, 4H), 7.78−7.61 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.2, 148.4, 139.4, 135.6, 135.5, 133.6, 132.3, 132.1, 129.7, 129.6, 128.9, 128.9, 127.9, 127.2, 126.7, 125.3, 124.7; MS (ESI) m/z 278 $[M + H]^+$; HRMS calcd for $C_{17}H_{12}NO_3^+$, 278.0810; found, 278.0823 $[M + H]^+$.

(4-Methoxyphenyl)(naphthalen-2-yl)methanone (**3o**).[36] White solid, Hexane/EtOAc = 97/3, yield 82% (215 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H), 7.94−7.90 (m, 4H), 7.61−7.55 (m, 2H), 7.40 (d, J = 6.0 Hz, 3H), 7.18−7.15 (m, 1H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.6, 163.2, 135.5, 135.1, 132.6, 132.3, 131.1, 130.5, 129.3, 128.2, 128.0, 127.8, 126.7, 125.9, 113.7, 55.5; MS (ESI) m/z 285 $[M + Na]^+$; HRMS calcd for $C_{18}H_{14}NaO_2^+$, 285.0886; found, 285.0875 $[M + Na]^+$.

(4-Ethylphenyl)(3-methoxyphenyl)methanone (**3p**).[39] Yellow oil, Hexane/EtOAc = 97/3, yield 67% (161 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76−7.74 (m, 2H), 7.37−7.29 (m, 5H), 7.13−7.10 (m, 1H), 3.86 (s, 3H), 2.74 (q, J = 7.6 Hz, 2H), 1.29 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.2, 159.6, 149.4, 139.3, 135.2, 130.4, 129.1, 127.8, 122.7, 118.6, 114.3, 55.5, 29.0, 15.2; MS (ESI) m/z 263 $[M + Na]^+$; HRMS calcd for $C_{16}H_{16}NaO_2^+$, 263.1043; found, 263.1048 $[M + Na]^+$.

(4-Ethylphenyl)(3-nitrophenyl)methanone (**3q**). Yellow oil, Hexane/EtOAc = 96/4, yield 76% (194 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.62 (s, 1H), 8.44 (d, J = 8.1 Hz, 1H), 8.13 (d, J = 7.8 Hz, 1H), 7.76−7.67 (m, 3H), 7.35 (d, J = 8.1 Hz, 2H), 2.76 (q, J = 7.8 Hz, 2H), 1.30 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.7, 150.6, 148.1, 139.5, 135.3, 133.8, 130.4, 129.6, 128.3, 126.5, 124.6, 29.0, 15.1; MS (ESI) m/z 256 $[M + H]^+$; HRMS calcd for $C_{15}H_{14}NO_3^+$, 256.0968; found, 256.0967 $[M + H]^+$.

(4-Fluorophenyl)(3-methoxyphenyl)methanone (**3r**).[40] Yellow oil, Hexane/EtOAc = 96/4, yield 74% (170 mg); ^{1}H NMR (300 MHz, $CDCl_3$):δ 7.84−7.81 (m, 2H), 7.55−7.44 (m, 3H), 7.28−7.26 (m, 1H), 7.00−6.96 (m, 2H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.0, 163.5, 162.4 (d, J = 246.4), 140.4 (d, J = 6.3 Hz), 132.5, 129.9 (d, J = 7.7 Hz), 129.6, 125.4 (d, J = 2.9 Hz), 118.8 (d, J = 21.2 Hz), 116.5 (d, J = 22.2 Hz), 113.7, 55.50; ^{19}F NMR (282 MHz, $CDCl_3$) δ −106.0 (s, 1F); MS (ESI) m/z 231 $[M + H]^+$; HRMS calcd for $C_{14}H_{12}FO_2^+$, 231.0816; found, 231.0828 $[M + H]^+$.

(3-Methoxyphenyl)(phenyl)methanone (**3s**).[41] White solid, Hexane/EtOAc = 97/3, yield 79% (167 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.81 (d, J = 7.2 Hz, 2H), 7.59 (t, J = 7.2 Hz, 2H), 7.51−7.46 (m, 2H), 7.41−7.33 (m, 2H), 7.14 (d, J = 6.9 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.4, 159.8, 139.0, 137.8, 132.4, 130.1, 129.2, 128.3, 122.9, 118.9, 114.4, 55.5; MS (ESI) m/z 235 $[M + Na]^+$; HRMS calcd for $C_{14}H_{12}NaO_2^+$, 235.0730; found, 235.0737 $[M + Na]^+$.

Phenyl(m-tolyl)methanone (**3t**).[31] White solid, Hexane/EtOAc = 98/2, yield 71% (139 mg); ^{1}H NMR (300 MHz, $CDCl_3$): 7.79 (d, J = 6.6 Hz, 2H), 7.62 (s, 1H), 7.56 (d, J = 2.4 Hz, 2H), 7.46 (d, J = 6.3 Hz, 2H), 7.35 (d, J = 6.6 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.9, 138.2, 137.8, 137.7, 133.2, 132.4, 130.5, 130.1, 128.3, 128.1, 127.4, 21.4; MS (ESI) m/z 197 $[M + H]^+$; HRMS calcd for $C_{14}H_{13}O^+$, 197.0961; found, 197.0959 $[M + H]^+$.

(2-Bromophenyl)(m-tolyl)methanone (**3u**).[42] Yellow semisolid, Hexane/EtOAc = 98/2, yield 79% (216 mg); ^{1}H NMR (300 MHz, $CDCl_3$): 7.59−7.55 (m, 2H), 7.49 (d, J = 7.2 Hz, 1H), 7.34−7.28 (m, 4H), 7.19 (s, 1H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.2, 138.1, 137.8, 134.6, 133.1, 131.0, 130.4, 128.9, 128.5, 128.0, 127.7, 127.3, 127.1, 21.7; MS (ESI) m/z 275 $[M + H]^+$; HRMS calcd for $C_{14}H_{12}BrO^+$, 275.0066; found, 275.0092 $[M + H]^+$.

(2-Methoxyphenyl)(phenyl)methanone (**3v**).[30] White solid, Hexane/EtOAc = 97/3, yield 76% (161 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 (d, J = 7.2 Hz, 2H), 7.58−7.38 (m, 5H), 7.09−7.01 (m, 2H), 3.75 (s, 3H); ^{13}C NMR: δ (75 MHz, $CDCl_3$): δ 196.5, 157.4, 137.9, 132.9, 131.9, 129.8, 129.6, 128.9, 128.2, 120.5, 111.5, 55.6; MS (ESI) m/z 235 $[M + Na]^+$; HRMS calcd for $C_{14}H_{12}NaO_2^+$, 235.0730; found, 235.0741 $[M + Na]^+$.

Phenyl(o-tolyl)methanone (**3w**).[31] White solid, Hexane/EtOAc = 98/2, yield 67% (135 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83 (d, J = 7.2 Hz, 2H), 7.59 (d, J = 6.3 Hz, 1H), 7.50−7.40 (m, 3H), 7.33−7.27 (m, 3H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.7, 138.6, 137.8, 136.8, 133.2, 131.0, 130.3, 130.1, 128.5, 128.5, 125.2, 20.0; MS (ESI) m/z 197 $[M + H]^+$; HRMS calcd for $C_{14}H_{13}O^+$, 197.0961; found, 197.0960 $[M + H]^+$.

(2-Bromophenyl)(o-tolyl)methanone (**3x**).[43] Colorless oil, Hexane/EtOAc = 98/2, yield 76% (208 mg); ^{1}H NMR (400 MHz, $CDCl_3$): (400 MHz, $CDCl_3$): 7.62 (d, J = 8.0 Hz, 1H), 7.44−7.42 (m, 1H), 7.40−7.39 (m, 2H), 7.34−7.30 (m, 3H), 7.19 (t, J = 7.6 Hz, 1H), 2.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.0, 141.7, 139.9, 136.5, 133.5, 132.1, 131.9, 131.6, 131.4, 129.8, 127.2, 125.5, 120.2, 21.3; MS (ESI) m/z 296 $[M + Na]^+$; HRMS calcd for $C_{14}H_{11}BrNaO^+$, 296.9886; found, 296.9873 $[M + Na]^+$.

Phenyl(thiophen-3-yl)methanone (**3y**).[31] Yellow oil, Hexane/EtOAc = 98/2, yield 73% (137 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03−7.93 (m, 1H), 7.86−7.84 (m, 1H), 7.75−7.64 (m, 1H), 7.62−7.57 (m, 1H), 7.55−7.44 (m, 3H), 7.40−7.38 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.2, 141.3, 138.7, 133.9, 132.3, 129.4, 128.8, 128.6, 126.2; MS (ESI) m/z 189 $[M + H]^+$; HRMS calcd for $C_{11}H_9OS^+$, 189.0369; found, 189.0368 $[M + H]^+$.

DOI: 10.1021/acs.joc.6b02711
J. Org. Chem. 2017, 82, 1105−1113

(3-Methoxyphenyl)(thiophen-3-yl)methanone (**3z**).[44] Yellow oil, Hexane/EtOAc = 97/3, yield 72% (157 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.54 (d, J = 12.9 Hz, 1H), 7.31 (d, J = 7.8 Hz, 4H), 7.05 (d, J = 6 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.7, 159.7, 141.3, 139.9, 133.9, 129.3, 128.6, 126.2, 122.0, 118.7, 113.9, 55.5; MS (ESI) m/z 241 $[M + Na]^+$; HRMS calcd for $C_{12}H_{10}NaO_2S^+$, 241.0294; found, 241.0298 $[M + Na]^+$.

(4-Methoxyphenyl)(pyridin-2-yl)methanone (**3aa**).[45] White solid, Hexane/EtOAc = 96/4, yield 70% (149 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.61−8.60 (m, 1 H), 8.06−8.03 (m, 2H), 7.9 (d, J = 7.8 Hz, 1H), 7.81−7.78 (m, 1H), 7.39−7.35 (m, 1H), 6.90−6.87 (m, 2H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 192.2, 163.6, 155.8, 148.3, 137.0, 133.5, 129.0, 125.8, 124.5, 113.5, 55.5; MS (ESI) m/z 236 $[M + Na]^+$; HRMS calcd for $C_{13}H_{11}NNaO_2^+$, 236.0682; found, 236.0682 $[M + Na]^+$.

(4-Ethylphenyl)(4′-iodo-[1,1′-biphenyl]-4-yl)methanone (**3ab**). White solid, Hexane/EtOAc = 97/3, mp: 221−234 °C, yield 64%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, J = 8.4 Hz, 2H), 7.83−7.76 (m, 4H), 7.39 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 2.75 (q, J = 7.5 Hz, 2H), 1.30 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.0, 149.6, 143.8, 139.6, 138.2, 137.1, 135.2, 130.7, 130.4, 129.1, 127.9, 126.7, 94.1, 29.0, 15.3; MS (ESI) m/z 413 $[M + H]^+$; HRMS calcd for $C_{21}H_{18}IO^+$, 413.0397; found, 413.0409 $[M + H]^+$.

Phenyl(4-((4-phenylpiperazin-1yl)methyl)phenyl)methanone (**5a**). Brown liquid, Hexane/EtOAc = 95/5, yield 58% (206 mg); ^{1}H NMR (400 MHz, $CDCl_3$): 7.80 (t, J = 7.6 Hz, 3H), 7.59 (t, J = 7.6 Hz, 1H), 7.50−7.47 (m, 4H), 7.28−7.24 (m, 3H), 6.93 (d, J = 8 Hz, 2H), 6.86 (t, J = 7.2 Hz,1H), 3.66 (s, 2H), 3.23 (t, J = 4.8 Hz, 4H), 2.66 (t, J = 4.8 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.4, 151.3, 143.0, 137.8, 136.6, 132.3, 130.2, 130.0, 129.0, 128.7, 128.3, 119.8, 116.2, 62.6, 53.2, 49.1; MS (ESI) m/z 357 $[M + H]^+$; HRMS calcd for $C_{24}H_{25}N_2O^+$, 357.1961; found, 357.1976 $[M + H]^+$.

(4-((4-Phenylpiperazin-1-yl)methyl)phenyl)(p-tolyl)methanone (**5b**). Brown liquid, Hexane/EtOAc = 95/5, yield 62% (229 mg); ^{1}H NMR (400 MHz, $CDCl_3$): 7.80−7.71 (m, 4H), 7.48 (d, J = 8 Hz, 2H), 7.30−7.27 (m, 3H), 7.25−7.23 (m, 1H), 6.93 (d, J = 8 Hz, 2H), 6.88−6.84 (m, 1H), 3.66 (s, 2H), 3.23 (t, J = 4.8 Hz, 4H), 2.66 (t, J = 5.2 Hz, 4H), 2.45 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 196.2, 151.3, 143.2, 137.0, 135.0, 134.9, 130.2, 130.1, 129.1, 129.0, 128.9, 119.8, 116.1, 62.6, 53.2, 49.1, 21.6; MS (ESI) m/z 371 $[M + H]^+$; HRMS calcd for $C_{25}H_{27}N_2O^+$, 371.2118; found, 371.2119 $[M + H]^+$.

(2-Methoxyphenyl)(4-((4-phenylpiperazin-1-yl)methyl)phenyl)-methanone (**5c**). Brown liquid, Hexane/EtOAc = 94/6, yield 46% (177 mg); ^{1}H NMR (400 MHz, $CDCl_3$): 7.79 (d, J = 8.0 Hz, 2H), 7.49−7.42 (m, 3H), 7.36−7.34 (m, 1H), 7.28 (s, 1H), 7.24 (s, 1H), 7.06−7.00 (m, 2H), 6.92 (d, J = 7.6 Hz, 2H), 6.85 (t, J = 6.8 Hz, 1H), 3.74 (s, 3H), 3.63 (s, 2H), 3.21 (t, J = 4.8 Hz, 4H), 2.63 (t, J = 4.8 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 196.1, 157.3, 151.3, 143.6, 136.9, 131.7, 130.0, 129.5, 129.1, 128.8, 128.4, 120.5 119.7, 116.1, 111.5, 62.7, 55.7, 53.2, 49.2; MS (ESI) m/z 387 $[M + H]^+$; HRMS calcd for $C_{25}H_{27}N_2O_2^+$, 387.2067; found, 387.2071 $[M + H]^+$.

2-(2-Benzoylbenzyl)isoindoline-1,3-dione (**5d**).[46] Brown solid, Hexane/EtOAc = 96/4, yield 57% (195 mg); ^{1}H NMR (400 MHz, $CDCl_3$): 7.85−7.83 (m, 2H), 7.81−7.78 (m, 2H), 7.71−7.67 (m, 2H), 7.56−7.55 (m, 1H), 7.47−7.42 (m, 3H), 7.39 (t, J = 6.8 Hz, 2H), 7.34−7.30 (m, 1H), 5.05 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.8, 167.9, 138.0, 137.6, 136.1, 134.0, 133.1, 132.0, 130.9, 130.4, 129.4, 128.6, 128.4, 126.8, 123.3, 38.9; MS (ESI) m/z 364.0945 $[M + Na]^+$; HRMS calcd for $C_{22}H_{15}NNaO_3^+$, 364.0944; found, 364.0946 $[M + Na]^+$.

2-(2-(4-Methylbenzoyl)benzyl)isoindoline-1,3-dione (**5e**).[47] Brown semisolid, Hexane/EtOAc = 96/4, yield 67% (237 mg); ^{1}H NMR (400 MHz, $CDCl_3$): 7.79−7.77 (m, 2H), 7.75−7.73 (m, 2H), 7.68−7.67 (m, 2H), 7.43−7.37 (m, 2H), 7.36−7.31 (m, 2H), 7.23 (d, J = 8 Hz, 2H), 5.02 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.3, 167.9, 138.4, 135.7, 135.0, 134.4, 133.9, 132.0, 131.2, 130.6, 129.1, 128.6, 126.8, 123.3, 39.0, 21.8; MS (ESI) m/z 378 $[M + Na]^+$; HRMS calcd for $C_{23}H_{17}NNaO_3^+$, 378.1101; found, 378.1108 $[M + Na]^+$.

(1-Methyl-1H-indol-3-yl)(phenyl)methanone (**7a**).[29] White solid, Hexane/EtOAc = 94/6, yield 74% (178 mg); ^{1}H NMR (400 MHz, $CDCl_3$): 8.36−8.34 (m, 1H), 7.73−7.71 (m, 2H), 7.45−7.37 (m, 4H), 7.27−7.25 (m, 3H), 3.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.8, 141.0, 137.9, 137.6, 131.1, 128.7, 128.3, 127.2, 123.6, 122.7, 122.7, 115.6, 109.6, 33.5; MS (ESI) m/z 258 $[M + Na]^+$; HRMS calcd for $C_{16}H_{13}NNaO^+$, 258.0889; found, 258.0897 $[M + Na]^+$.

(1-Methyl-1H-indol-3-yl)(naphthalen-2-yl)methanone (**7b**).[29] White solid, Hexane/EtOAc = 94/6, yield 77% (219 mg), ^{1}H NMR (400 MHz, $CDCl_3$): 8.45−8.42 (m, 1H), 8.29 (s, 1H), 7.94−7.89 (m, 4H), 7.58−7.54 (m, 3H), 7.37−7.34 (m, 3H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.8, 138.3, 137.8, 137.6, 134.7, 132.6, 129.2, 129.0, 128.2, 127.8, 127.5, 127.3, 126.6, 125.6, 123.7, 122.8, 122.7, 115.9, 109.6, 33.6; MS (ESI) m/z 286 $[M + H]^+$; HRMS calcd for $C_{20}H_{16}NO^+$, 286.1226; found, 286.1212 $[M + H]^+$.

(4-Ethylphenyl)(1-methyl-1H-indol-3-yl)methanone (**7c**). Yellow liquid, Hexane/EtOAc = 94/6, yield 71% (186 mg); ^{1}H NMR (400 MHz, $CDCl_3$): 8.43−8.41 (m, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.56 (s, 1H), 7.37−7.30 (m, 5H), 3.85 (s, 3H), 2.74 (q, J = 7.6 Hz, 2H), 1.30 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.7, 147.8, 138.4, 137.6, 137.5, 129.0, 127.8, 127.3, 123.6, 122.8, 122.6, 115.8, 109.5, 33.5, 28.9, 15.4; MS (ESI) m/z 264 $[M + H]^+$; HRMS calcd for $C_{18}H_{18}NO^+$, 264.1383; found, 264.1379 $[M + H]^+$.

(1-Ethyl-1H-indol-3-yl)(phenyl)methanone (**7d**).[29] Yellow liquid, Hexane/EtOAc = 94/6, yield 66% (164 mg); ^{1}H NMR (400 MHz, $CDCl_3$): 8.43−8.41 (m, 1H), 7.83−7.81 (m, 2H), 7.59 (s, 1H), 7.55−7.53 (m, 1H), 7.51−7.47 (m, 2H), 7.42−7.40 (m, 1H), 7.37−7.33 (m, 2H), 4.23 (q, J = 7.2 Hz, 2H), 1.52 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.9. 141.0, 136.7, 136.2, 131.0, 128.7, 128.3, 127.5, 123.6, 122.9, 122.7, 115.8, 109.8, 41.9, 15.3; MS (ESI) m/z 272 $[M + Na]^+$; HRMS calcd for $C_{17}H_{15}NNaO^+$, 272.1046; found, 272.1046 $[M + Na]^+$.

(1-Ethyl-1H-indol-3-yl)(naphthalen-2-yl)methanone (**7e**). Yellow oil, Hexane/EtOAc = 94/6, yield 80% (239 mg); ^{1}H NMR (400 MHz, $CDCl_3$): 8.44−8.42 (m, 1H), 8.3 (s, 1H), 7.96−7.91 (m, 4H), 7.65 (s, 1H), 7.60−7.55 (m, 2H), 7.43−7.41 (m, 1H), 7.37−7.35 (m, 2H), 4.23 (q, J = 7.2 Hz, 2H), 1.52 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 197.9, 138.3, 136.7, 136.2, 134.7, 132.6, 129.2, 129.1, 128.2, 127.8, 127.5, 127.5, 126.6, 125.6, 123.6, 122.9, 122.7, 116.0, 109.8, 41.8, 15.2; MS (ESI) m/z 322 $[M + Na]^+$; HRMS calcd for $C_{21}H_{17}NNaO^+$, 322.1202; found, 322.1195 $[M + Na]^+$.

(5-Methoxy-1-methyl-1H-indol-3-yl)(phenyl)methanone (**7f**).[28] White solid, Hexane/EtOAc = 93/7, yield 78% (206 mg); ^{1}H NMR (400 MHz, $CDCl_3$): 7.87 (d, J = 2.4 Hz, 7.68−7.66 (m, 2H), 7.41−7.39 (m, 1H), 7.11−7.08 (m, 1H), 6.87−6.84 (m, 1H), 3.79 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 190.8, 156.6, 141.0, 138.0, 132.6, 131.0, 128.6, 128.3, 128.1, 115.2, 114.1, 110.5, 103.9, 55.8, 33.7; MS (ESI) m/z 338 $[M + H]^+$; HRMS calcd for $C_{17}H_{16}NO_2^+$, 266.1175; found, 266.1175 $[M + H]^+$.

(5-Methoxy-1-methyl-1H-indol-3-yl)(naphthalen-2-yl)-methanone (**7g**). White solid, Hexane/EtOAc = 93/7, yield 76% (239 mg), mp: 97−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.23 (s, 1H), 8.00 (d, J = 2.4 Hz, 1H), 7.95−7.89 (m, 4H), 7.56−7.52 (m, 3H), 7.25−7.24 (m, 1H), 7.01−6.98 (m, 1H), 3.92 (s, 3H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$); δ 190.8, 156.7, 139.6, 138.3, 138.0, 134.7, 132.6, 129.0, 128.1, 127.8, 127.5, 126.6, 125.5, 115.5, 114.3, 110.5, 104.0, 55.9, 34.1, 33.7, 128.6, 128.3, 128.1, 115.2, 114.1, 110.5, 103.9, 55.8, 33.7; HRMS calcd for $C_{21}H_{17}NNaO_2^+$, 338.1151; found, 338.1154 $[M + Na]^+$.

Phenyl Benzoate (**9a**).[22] Yellowish liquid, Hexane/EtOAc = 98/2, yield 86% (170 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, J = 7.2 Hz, 2H), 7.46 (t, J = 7.5 Hz, 1H), 7.35 (d, J = 7.8 Hz, 2H), 7.31 (d, J = 4.2 Hz, 1H), 7.27 (s, 1H), 7.14−7.05 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.2, 151.1, 133.7, 130.3, 129.7, 129.6, 128.7, 126.0, 121.8; MS (ESI) m/z 221 $[M + Na]^+$; HRMS calcd for $C_{13}H_{10}NaO_2^+$ 221.0573; found, 221.0572 $[M + Na]^+$.

m-Tolyl Benzoate (**9b**).[48] White liquid, Hexane/EtOAc = 98/2, yield 64% (187 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (d, J = 6.9 Hz, 2H), 7.67 (d, J = 7.2 Hz, 1H), 7.57 (d, J = 7.5 Hz, 2H), 7.37 (t, J = 7.5 Hz, 1H), 7.16−7.10 (m, 3H); ^{13}C NMR(75 MHz, $CDCl_3$): δ

DOI: 10.1021/acs.joc.6b02711
J. Org. Chem. 2017, 82, 1105−1113

165.4, 151.0, 139.7, 133.6, 130.2, 129.7, 129.3, 128.6, 126.8, 122.4, 118.7; MS (ESI) m/z 213 $[M + H]^+$; HRMS calcd for $C_{14}H_{13}O_2^+$, 213.0910; found, 213.0907 $[M + H]^+$.

*Naphthalen-2-yl Benzoate (**9c**).*[48] Brown solid, Hexane/EtOAc = 98/2, yield 84% (208 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.26 (d, J = 7.5 Hz, 2H), 7.92−7.82 (m, 3H), 7.70−7.64 (m, 1H), 7.54 (t, J = 7.8 Hz, 1H), 7.50−7.46 (m, 4H), 7.38−7.35 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.4, 148.6, 133.8, 133.7, 131.5, 130.2, 129.6, 129.5, 128.6, 127.8, 127.8, 126.6, 125.8, 121.3, 118.7; MS (ESI) m/z 271 $[M + Na]^+$; HRMS calcd for $C_{17}H_{12}NaO_2^+$, 271.0730; found, 271.0736 $[M + Na]^+$.

*Phenyl 2-Methylbenzoate (**9d**).*[23] White liquid, Hexane/EtOAc = 98/2, yield 89% (189 mg); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, J = 7.6 Hz, 1H), 7.50−7.42 (m, 3H), 7.34−7.27 (m, 2H), 7.25 (s, 1H), 7.21 (d, J = 7.6 Hz, 2H), 2.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.8, 151.0, 141.3, 132.7, 132.0, 131.2, 129.5, 128.6, 125. 9, 125.8, 121.8, 19.8; MS (ESI) m/z 235 $[M + Na]^+$; HRMS calcd for $C_{14}H_{12}NaO_2^+$, 235.0730; found, 235.0723 $[M + Na]^+$.

*Phenyl 4-Methylbenzoate (**9e**).*[23] White liquid, Hexane/EtOAc = 98/2, yield 64%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13(d, J = 6.3 Hz, 2H), 7.45 (d, J = 5.7 Hz, 2H), 7.34 (d, J = 7.5 Hz, 2H), 7.29−7.23 (m, 3H), 2.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.3, 151.1, 144.4, 130.2, 129.5, 129.3, 126.9, 125.8, 121.8, 21.8; MS (ESI) m/z 235 $[M + Na]^+$; HRMS calcd for $C_{14}H_{12}NaO_2^+$, 235.0730; found, 235.0727 $[M + Na]^+$.

*Phenyl 3-Methoxybenzoate (**9f**).*[49] White solid, Hexane/EtOAc = 97/3, yield 91% (207 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86 (d, J = 7.5 Hz, 1H), 7.76 (s, 1H), 7.50−7.43 (m, 3H), 7.34−7.21 (m, 4H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.1, 159.8, 151.0, 130.9, 129.6, 129.5, 125.9, 122.6, 121.7, 120.2, 114.6, 55.5; MS (ESI) m/z 251 $[M + Na]^+$; HRMS calcd for $C_{14}H_{12}NaO_3^+$, 251.0679; found, 251.0678 $[M + Na]^+$.

*Phenyl 3-Nitrobenzoate (**9g**).*[50] Yellow oil, Hexane/EtOAc = 96/4, yield 86% (209 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.05 (d, J = 1.5 Hz, 1H), 8.55−8.50 (m, 2H), 7.77−7.72 (m, 1H), 7.50−7.44 (m, 2H), 7.35−7.23 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.1, 150.5, 148.4, 135.8, 131.4, 129.9, 129.7, 128.0, 126.4, 125.1, 121.5; MS (ESI) m/z 266 $[M + Na]^+$; HRMS calcd for $C_{13}H_9NNaO_4^+$, 266.0424; found, 266.0427 $[M + Na]^+$.

*Phenyl 4-Nitrobenzoate (**9h**).*[51] Yellow solid, Hexane/EtOAc = 96/4, yield 95% (231 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.40−8.36 (m, 4 H), 7.49−7.44 (m, 2H), 7.33 (d, J = 7.2 Hz, 1H), 7.25−7.22 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4, 150.9, 150.5, 135.0, 131.3, 129.7, 126.5, 123.8, 121.5; MS (ESI) m/z 266 $[M + Na]^+$; HRMS calcd for $C_{13}H_9NNaO_4^+$, 266.0424; found, 266.0423 $[M + Na]^+$.

*2-Chlorophenyl 3-Nitrobenzoate (**9i**).*[52] Yellow solid, Hexane/EtOAc = 96/4, yield 72% (200 mg); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.53−8.50 (m, 1H), 7.78−7.73 (m, 2H), 7.78−7.73 (m, 1H), 7.53−7.50 (m, 1H), 7.40−7.25 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.3, 148.5, 146.8, 135.9, 130.7, 130.6, 130.0, 128.3, 128.0, 127.6, 126.8, 125.3, 123.6; MS (ESI) m/z 278 $[M + H]^+$; HRMS calcd for $C_{13}H_9ClNO_4^+$, 278.0214; found, 278.0225 $[M + H]^+$.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02711.

Copies of ^{1}H, ^{13}C NMR for all the synthesized compounds, ORTEPs (PDF)

associated X-ray crystallographic data for **9g** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank Council of Scientific and Industrial Research (CSIR), India (02(180)/14/EMR-II) for financially supporting this work and DST-FIST for funding the ESI-HRMS, and the SCXRD facility at IIT Delhi. P.S. and S.R. thank IIT Delhi and CSIR for their graduate fellowships.

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