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Palladium(II)-Catalyzed C–H Acylation with Arylglycine Derivatives

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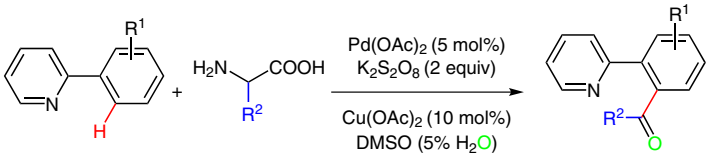

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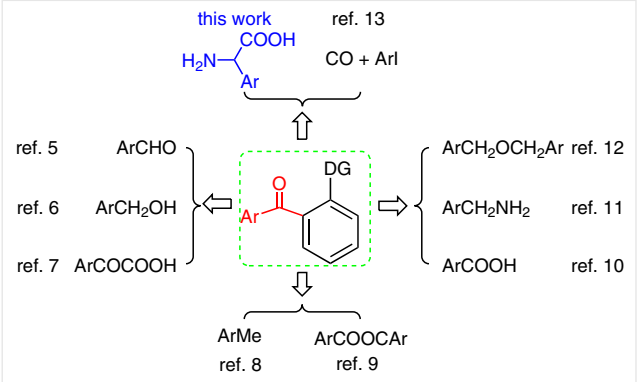
Abstract A novel palladium(II)-catalyzed *ortho* acylation of arenes with arylglycines in the presence of $Cu(OAc)_2$ and $K_2S_2O_8$ to afford the benzophenones was developed. This direct C–H acylation is suitable for a broad range of substrates. The control experiments suggested a possible oxidative addition mechanism.

Key words palladium(II)-catalyzed, *ortho* acylation, arylglycine, C–H activation, oxidative addition

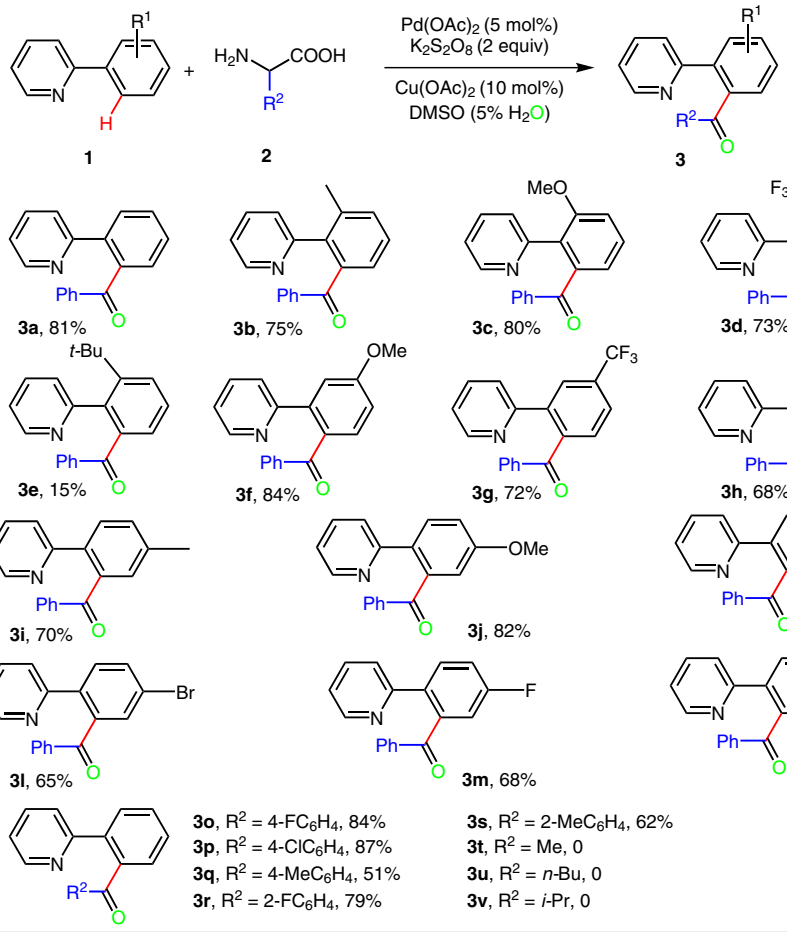
Transition-metal-catalyzed direct selective functionalization of arenes via C–H activation has attracted considerable attention due to the ecological and economical advantages in comparison to traditional cross-coupling methods with the pre-activated starting materials.[1] Benzophenones are prominent structural motifs of many pharmaceuticals, fragrances, and agrochemicals.[2] Regarding their synthesis, many effective methods have been developed, including the traditional Friedel–Crafts acylation[3] and some catalytic Friedel–Crafts acylations.[4] But these methods showed poor selectivity with isomeric mixtures. In order to solve the selectivity issue, metal-catalyzed oxidative *ortho* acylations were developed bearing conventional directing groups (Scheme 1).[5–13] The acyl sources included aldehydes,[5] alcohols,[6] α-oxocarboxylic acids,[7] toluenes,[8] diketones,[9] carboxylic acids,[10] arylmethyl amines,[11] benzylic ethers,[12] and CO with PhI.[13]

Despite the significant advances made with respect to the substrate scope, the quest for new methods of unactivated C–H acylations remains a challenge. Inspired by Wang's recent work,[14] which used amino acids as the direct arylation source to construct the benzothiazoles and suggested an oxidative mechanism involving the transformation from phenylglycine to phenylglyoxylic acid, we attempted to employ the same phenylglycine to achieve *ortho* acylation. Herein, we present a novel palladium(II)-catalyzed *ortho* acylation of arenes with arylglycine in the presence of $Cu(OAc)_2$ and $K_2S_2O_8$ to afford the benzophenones.



Scheme 1 Acyl sources for the preparation of directed benzophenones

We began our investigation by allowing 2-phenylpyridine (**1a**) and phenylglycine (**2a**) to react in the presence of different palladium catalysts, oxidants, additives, and solvents. To our delight, when the reaction was conducted with $Pd(OAc)_2$ (5 mol%) and $K_2S_2O_8$ (2 equiv) in DMSO (including 5% H_2O) at 120 °C, **3a** was formed in 52% yield (Table 1, entry 1). Other palladium catalysts gave lower yields (Table 1, entries 2–4). Oxygen, the ideal oxidant, was also tested to replace $K_2S_2O_8$, but only a trace amount of the product was detected (Table 1, entry 5). Using other oxidants did not afford good results (Table 1, entries 6–10). A slightly higher yield was observed when $Cu(OAc)_2$ was introduced into the reaction (Table 1, entry 12), compared with other additives (Table 1, entries 11, 13 and 14). Compound **3a** was not obtained in the absence of $Pd(OAc)_2$ (Ta-



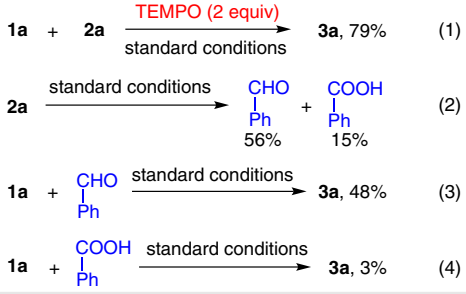
Scheme 2 Evaluation of the substrate scope. *Reagents and conditions*: **1a** (0.5 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (5 mol%), $K_2S_2O_8$ (2 equiv), $Cu(OAc)_2$ (10 mol%) in DMSO (5 mL) at 120 °C for 24 h under Ar atmosphere (1 atm).

ble 1, entry 15). When dry DMSO was used as solvent (Table 1, entry 16), a very poor yield of **3a** was obtained, suggesting that water was the O-atom source. The use of other solvents or increasing the catalyst loading led to no significant improvement in yield (see Supporting Information, SI-Tables 1, 2).

With the optimized reaction conditions in hand [$Pd(OAc)_2$, $K_2S_2O_8$, and $Cu(OAc)_2$], we turned our attention to the evaluation of the substrate scope. The results of the compatibility studies with respect to the substituted 2-phenylpyridines **1a**–**v** are presented in Scheme 2. A series of functional groups including methyl, methoxyl, chloro, trifluoromethyl, bromo, and fluoro on the phenyl ring were compatible under standard conditions, affording the target products **3a**–**n** in good yields.[18] There was no significant electronic effect observed, but the presence of an *ortho*-positioned *tert*-butyl group in **1e** reduced the yield of **3e** to 15%, indicating a steric effect.

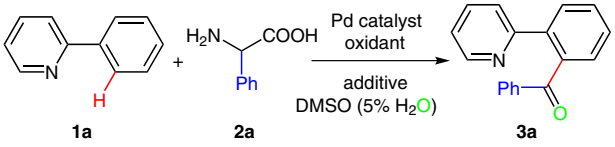
Subsequently, the substituent effects of phenylglyoxylic acid on this transformation were studied. In summary, electron-withdrawing substituents showed higher activity (**3o**,**p**,**r** > **3q**,**s**). Aliphatic amino acids afforded no products (**3t**–**v**).

More experiments were carried out to gain a better understanding of the mechanism of this transformation. Firstly, addition of the radical scavenger TEMPO did not reduce the yield under standard conditions. This suggests that a radical process is not involved (Scheme 3, eq. 1). Secondly,



Scheme 3 Control experiments

Table 1 Optimization of the Conditions



1a 2a 3a

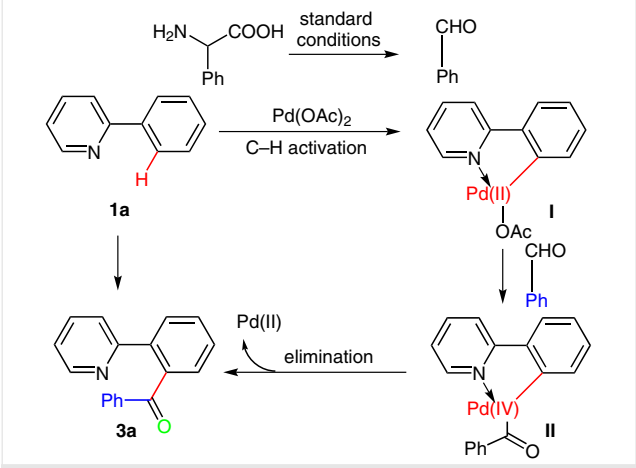
Entry[a]	Catalyst (5 mol%)	Oxidant (2 equiv)	Additive (10 mol%)	Yield (%)[b]
1	$Pd(OAc)_2$	$K_2S_2O_8$	–	52
2	$PdCl_2$	$K_2S_2O_8$	–	8
3	$Pd_2(dba)_3$	$K_2S_2O_8$	–	0
4	$Pd(OTf)_2$	$K_2S_2O_8$	–	47
5	$Pd(OAc)_2$	O_2 (1 atm)	–	<5
6	$Pd(OAc)_2$	$PhI(OAc)_2$	–	0
7	$Pd(OAc)_2$	TBHP	–	<5
8	$Pd(OAc)_2$	$Na_2S_2O_8$	–	33
9	$Pd(OAc)_2$	Oxone	–	41
10	$Pd(OAc)_2$	Ag_2CO_3	–	28
11	$Pd(OAc)_2$	$K_2S_2O_8$	AgOTf	61
12	$Pd(OAc)_2$	$K_2S_2O_8$	$Cu(OAc)_2$	81
13	$Pd(OAc)_2$	$K_2S_2O_8$	CuCl	43
14	$Pd(OAc)_2$	$K_2S_2O_8$	HOAc	49
15	–	$K_2S_2O_8$	$Cu(OAc)_2$	0
16[c]	$Pd(OAc)_2$	$K_2S_2O_8$	$Cu(OAc)_2$	<5

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), catalyst (5 mol%), oxidant (2 equiv), additive (10 mol%), in DMSO (5 mL) at 120 °C for 24 h under Ar atmosphere (1 atm).
[b] Isolated yields.
[c] Dry DMSO solvent.

when **2a** reacted under standard conditions for only for one hour, 56% yield of PhCHO and 15% yield of PhCOOH were isolated, respectively (Scheme 3, eq. 2). This result is in agreement with the fact that the α-amino acids are easily oxidized to aldehydes.[14,15] Moreover, **1a** reacted with PhCHO affording compound **3a** in 48% yield, but PhCOOH showed poor reactivity (Scheme 3, eq. 3 and 4).[14] Finally, the additional parallel experiments to oxidize the α-amino acids with or without $Cu(OAc)_2$ in the presence of $K_2S_2O_8$ suggested that $Cu(OAc)_2$ accelerated the oxidation of **2a** (Supporting Information, Scheme 1D).

Based upon the experimental and literature results,[5–13] a mechanism is proposed in Scheme 4. The active palladium catalyst reacts with **2a** by chelation-directed C–H activation to generate intermediate **I**.[16] Meanwhile, **2a** is oxidized to PhCHO,[14,15] followed by oxidative addition to form acyl palladium(IV) intermediate **II**.[17] Finally, elimination results in **3a** and the active palladium(II) species is regenerated.

In summary, we have developed a novel palladium(II)-catalyzed *ortho* acylation of arenes with arylglycine in the presence of $Cu(OAc)_2$ and $K_2S_2O_8$ to afford benzophenones. This direct C–H acylation is suitable for a broad range of substrates. The control experiments suggested a possible oxidative addition mechanism. Further studies concerning the detailed mechanism and a broader investigation of substrate scope are currently in progress in our laboratory.



Scheme 4 Proposed mechanism

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380440.

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(18) **Synthesis of 3a–v**

A mixture of **1** (0.5 mmol), **2** (0.6 mmol), DMSO (5% H_2O aq, 5 mL), $Pd(OAc)_2$ (5 mol%), $Cu(OAc)_2$ (10 mol%), and $K_2S_2O_8$ (2 equiv) was stirred at 120 °C under Ar atmosphere for 24 h. The reaction mixture was washed with H_2O, and the aqueous phase was extracted with EtOAc (3×). The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was purified by silica gel column chromatography to give the corresponding products (**3a**–**d**,[7b] **3f**–**k**,[7b] **3n**–**s**[7b]).

Compound **3e**: yield 15%, white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 4.6 Hz, 1 H), 7.68 (m, 2 H), 7.52 (m, 2 H), 7.50 (m, 1 H), 7.41 (t, *J* = 7.2 Hz, 1 H), 7.25 (m, 2 H), 7.18 (m, 2 H), 7.0 (m, 1 H), 1.13 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 197.2, 158.0, 155.2, 148.5, 140.2, 136.8, 135.9, 131.5, 129.9, 129.3, 128.4, 127.8, 126,9, 121.3, 119.5, 114.1, 34.5, 15.8. HRMS: *m/z* calcd for $C_{22}H_{21}NO$: 315.1623; found: 315.1626.