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Benzyl bromides as aroyl surrogates in substrate directed Pd catalysed *o*-aroylation†

Ahalya Behera, Wajid Ali, Srimanta Guin, Nilufa Khatun, Prakash R. Mohanta and Bhisma K. Patel*

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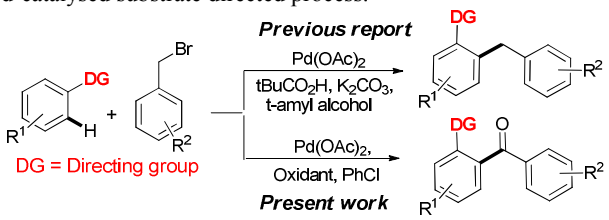
An oxidative cross-coupling between directing substrates and benzyl bromides *via* the combined effect of oxidants TBHP and NMO, catalysed by Pd(II) has been investigated. Benzyl bromides served as efficient aroyl surrogates in this substrate directed C–H functionalisation. The *in situ* generated benzaldehyde originating from benzyl bromide is the active aroylating source.

Introduction

In last two decades, an extensive exploration of Pd-catalysed regioselective C–H functionalisation has been investigated to transform simple precursors into products of significant importance, particularly for the synthesis of complex molecules and natural products.[1,2] Most of these Pd-catalysed reactions have been intended for the C–C bond forming processes involving sp, sp^2 or sp^3 hybridised C–H's as a mutual or a cross-coupling partners.[2d,g,3] The classical synthesis of aryl ketones mainly rely on the Friedel-Crafts acylation of aromatics in the presence of corrosive $AlCl_3$ or by the oxidation of corresponding secondary alcohols.[4] Compared to the classical Friedel-Crafts acylation, the direct introduction of carbonyl functionality into aromatic motifs *via* C–H bond cleavage is more eco-friendly alternative. The acylation of 2-phenylpyridines *via ortho*-C–H bond activation has been previously reported by our group and others using aldehydes,[5a] α-oxocarboxylic acids,[5b] alcohols,[5c] α-diketones,[5d] toluenes,[5e,f] benzylamines[5g] and alkenes[5h,i] / alkynes[5i] as aroyl surrogates. The process of aroylation is of significant importance because aryl ketones are useful in pharmaceuticals, fragrance, dye and agrochemical industries.[6] However, the cross-dehydrogenative coupling (CDC) strategy of converting sp^2 C–H bonds of aryl moiety into C–C bonds are challenging.[7] Generally, most of the developed approaches on regioselective C–H activation involve suitable catalysts, functionalised partners and oxidants.[8] In search of an alternative aroyl source, we envisaged that benzyl bromides which under an oxidative condition can be converted into benzaldehyde may serve as the aroylating source. With this in mind, an initial trial reaction was performed between 2-phenylpyridine (**1**) (0.5 mmol) and benzyl bromide (**a**) (1 mmol) in the presence of $Pd(OAc)_2$ (5 mol%) and oxidant TBHP (5–6 M in decane) (4 equiv.) in chlorobenzene (2 mL) at 120 °C (Table 1, entry 1). The reaction led to the exclusive formation of an *ortho*-aroylated product (**1a**) (37%) as expected. It may be mentioned here that in an auxillary assisted Pd catalysed C–C bond forming reaction benzyl bromide served as the benzylating agent for the sp^2 and sp^3 C–H bonds.[9] Herein we illustrate the first report on the use of benzyl bromides as aroylating agent in Pd-catalysed substrate directed process.[10]



Scheme 1 Differential reactivities of benzyl bromides towards directing substrates.

Results and Discussion

With the finding of benzyl bromide serving as a new aroyl surrogate we probed the effect of aroylating agent, catalysts, oxidants, additives, and solvents to obtain the best yield of the *o*-aroylated product. Increasing the quantity of benzyl bromide from 2 to 3 equiv., the yield of the product (**1a**) improved up to 48% (Table 1, entry 2). The oxidant *N*-methyl morpholine *N*-oxide (NMO) is reported to be quite effective in converting benzyl halides to their corresponding aldehydes, which we presume to be the active aroylating agent.[11] Taking cues from this report, when 1 equiv. of NMO was used in the reaction, the yield of the desired product improved to 55% (Table 1, entry 3). A further improvement in the yield (66%) was observed when the quantity of NMO was increased to 2 equiv. (Table 1, entry 4). Since the other oxidant NMO (2 equiv.) is also used along with the primary oxidant TBHP (4 equiv.), thus the reaction is expected to proceed with a lesser quantity of TBHP. With this in mind, keeping all other parameters as such, a reaction was performed with a combination of TBHP (2 equiv.) and NMO (2 equiv.). The reaction furnished a comparable yield of 62% for (**1a**) (Table 1, entry 5). Interestingly, under a TBHP free condition, using NMO as the sole oxidant, formation of the

Department of Chemistry, Indian Institute of Technology Guwahati, 781 039, Assam, India. Fax no. +91-3612690762; E-mail: patel@iitg.ernet.in
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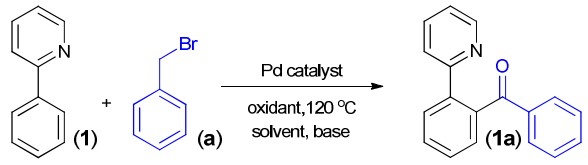
desired product (**1a**) was not observed (Table 1, entry 6) suggesting the essential requirement of TBHP in bringing about the transformation. Next, various other salts of Pd such as $PdCl_2$ (56%), $PdBr_2$ (53%), $Pd(PPh_3)_2Cl_2$ (39%), $Pd(OCOCF_3)_2$ (43%) (Table 1, entries 7–10), were examined to check their efficacy, from which $Pd(OAc)_2$ was found to be the superior (Table 1, entry 5). When $PdCl_2$ and $PdBr_2$were used as the catalysts along with the formation of the desired *o*-aroylated product, traces of *o*-brominated product was also observed. It may be mentioned here that in an analogous reaction reported by Wu's group (using benzyl chloride and $PdCl_2$) exclusive formation of the corresponding *o*-chlorinated product was observed with no formation of *o*-acylated product.[10] However the *o*-brominated product so generated in our case is converted to its corresponding *o*-acylated product on prolonging the reaction time. A two fold increase in the catalyst loading had no significant effect on the product yield (Table 1, entry 11). The effects of different oxidants for this transformation were also screened as shown in Table 1. All the primary oxidants such as 70% aq. TBHP (59%), DTBP (45%), $K_2S_2O_8$ (05%) and H_2O_2 (00%) were found to be inferior compared to the use of a decane solution of TBHP (Table 1, entries 12–15). Among various solvents tested such as THF (00%), dioxane (30%), DMSO (27%), DMF (52%), DCE (49%) (Table 1, entries 16–20), chlorobenzene (62%) was found to be the most appropriate (Table 1, entry 5).

Table 1 Screening of the reaction conditions[a,b]

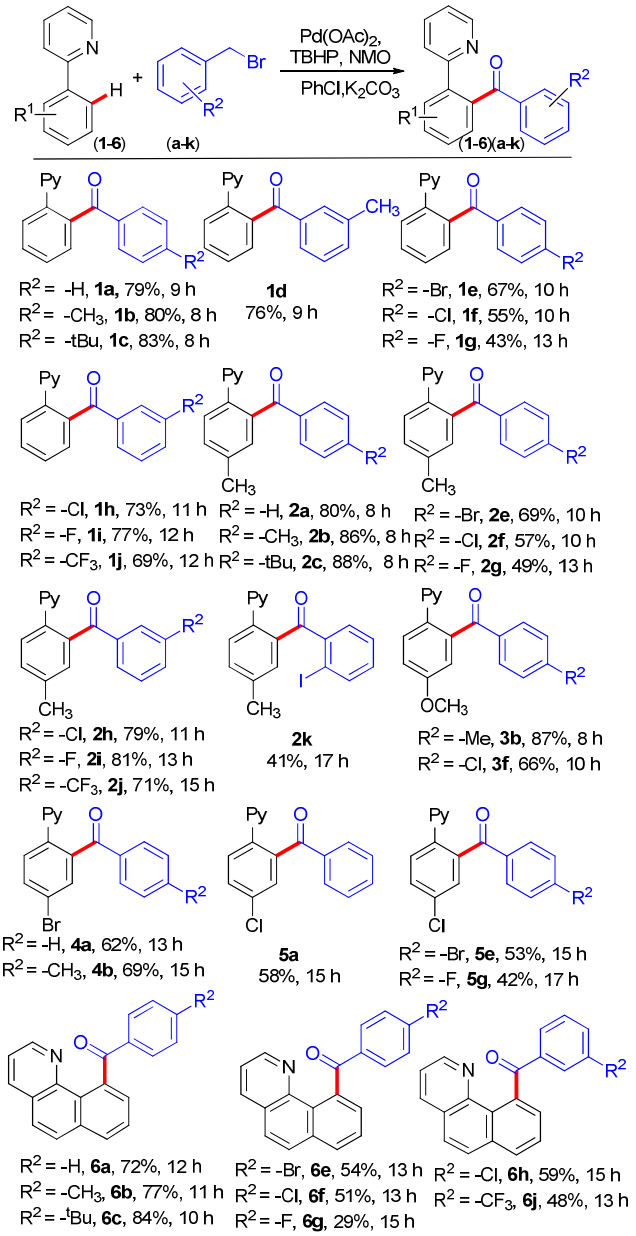


Sl. No	Catalyst (mol%)	Oxidant (equiv.)	Additive (equiv.)	Solvent	Yield (%)
1	$Pd(OAc)_2$ (5)	TBHP (4)	-	PhCl	37
2	$Pd(OAc)_2$ (5)	TBHP (4)	-	PhCl	48[c]
3	$Pd(OAc)_2$ (5)	TBHP (4)	NMO (1)	PhCl	55[c]
4	$Pd(OAc)_2$ (5)	TBHP (4)	NMO (2)	PhCl	66[c]
5	$Pd(OAc)_2$ (5)	TBHP (2)	NMO (2)	PhCl	62[c]
6	$Pd(OAc)_2$ (5)	-	NMO (2)	PhCl	00[c]
7	$PdCl_2$ (5)	TBHP (2)	NMO (2)	PhCl	56[c]
8	$PdBr_2$ (5)	TBHP (2)	NMO (2)	PhCl	53[c]
9	$Pd(PPh)_3Cl_2$ (5)	TBHP (2)	NMO (2)	PhCl	39[c]
10	$Pd(OCOCF_3)_2$ (5)	TBHP (2)	NMO (2)	PhCl	43[c]
11	$Pd(OAc)_2$ (10)	TBHP (2)	NMO (2)	PhCl	64[c]
12	$Pd(OAc)_2$ (5)	TBHP (2)	NMO (2)	PhCl	59[c,d]
13	$Pd(OAc)_2$ (5)	DTBP (2)	NMO (2)	PhCl	45[c]
14	$Pd(OAc)_2$ (5)	$K_2S_2O_8$ (2)	NMO (2)	PhCl	05[c]
15	$Pd(OAc)_2$ (5)	H_2O_2 (2)	NMO (2)	PhCl	00[c]
16	$Pd(OAc)_2$ (5)	TBHP (2)	NMO (2)	THF	00[c]
17	$Pd(OAc)_2$ (5)	TBHP (2)	NMO (2)	Dioxane	30[c]
18	$Pd(OAc)_2$ (5)	TBHP (2)	NMO (2)	DMSO	27[c]
19	$Pd(OAc)_2$ (5)	TBHP (2)	NMO (2)	DMF	52[c]
20	$Pd(OAc)_2$ (5)	TBHP (2)	NMO (2)	DCE	49[c]
21	**$Pd(OAc)_2$ (5)**	**TBHP (2)**	**NMO (2)**	**PhCl**	**79**[c,e]

[a]Reaction conditions: arenes (**1**) (0.5 mmol), solvent (2 mL) at 120 °C [b]Yields of isolated pure product. [c]1.5 mmol of benzyl bromide. [d]aq. TBHP. [e]K_2CO_3 (1.5 equiv.).

The catalytic activity of Pd is often hampered in acidic medium. Since an equivalent amount of HBr is liberated in the medium during the conversion of benzyl bromide to active aroylating species, it was decided to perform the reaction in the presence of a mild base. The use of K_2CO_3 (79%) (Table 1, entry 21) was found to be superior compared to other inorganic bases such as Cs_2CO_3 (71%), $NaHCO_3$ (73%) and Na_2CO_3 (56%). Finally, the optimum condition was the use of 2-phenyl pyridine (**1**) (0.5 mmol), benzyl bromides (**a**) (1.5 mmol), $Pd(OAc)_2$ (5 mol%), TBHP (2 equiv.), *N*-methyl morpholine *N*-oxide (2 equiv.), K_2CO_3 (1.5 equiv.) in chlorobenzene (2 mL) at 120 °C (Table 1, entry 21).

Scheme 2 Substrate scope for the *o*-aroylation[a,b]



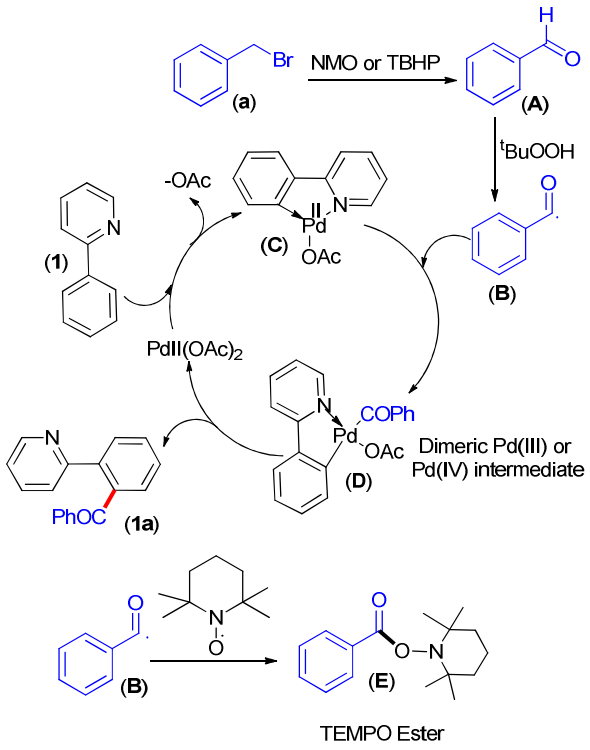
[a]Reaction conditions: **1–6** (0.5 mmol), **a–k** (1.5 mmol), $Pd(OAc)_2$ (5 mol%), TBHP (5–6 M in decane) (2 equiv.), NMO (2 equiv.), K_2CO_3 (1.5 equiv.) at 120 °C in chlorobenzene (2 mL), time 8–17 h. [b]Yield of isolated pure product reported.

The optimised conditions were then implemented for the *o*-aroylation of 2-phenyl pyridine (**1**) using various substituted benzyl bromides and the results are summarised in Scheme 2. Benzyl bromides having electron-donating groups such as *p*-Me (**b**), *p*-^{t}Bu (**c**) and *m*-Me (**d**) when treated with 2-phenylpyridine

(**1**) afforded corresponding *o*-aroylated products (**1b**–**1d**) in moderate to good yields. Benzyl bromides substituted with moderately electron-withdrawing groups such as *p*-Br (**e**), *p*-Cl (**f**) and *p*-F (**g**) served as less effective acylating agent giving their *o*-aroylated products (**1e**), (**1f**) and (**1g**) in 67%, 55% and 43% yields respectively which are slightly less compared to benzyl bromides possessing electron-donating substituents. However, the influence of electron-withdrawing substituents such as –Cl (**h**), –F (**i**) and $-CF_3$ (**j**) when present at the *m*-position had no effect on the products (**1h**–**1j**) yield. To further explore the scope of this protocol, aroylation of other 2-aryl pyridines were carried out with a set of substituted benzyl bromides. The reactivity of substituted benzyl bromides with 2-(*p*-tolyl)pyridine (**2**) were found to be similar to that of (**1**). A slight increase in the product yields (**2a–2c** and **2e**–**2j**) with 2-(*p*-tolyl)pyridine (**2**) could be attributed due to the better chelation of the metal catalyst with the electron rich *p*-tolyl ring in (**2**). 2-Iodo benzyl bromide (**k**) when treated with (**2**), a lower yield of 41% of (**2k**) was observed while its reaction with (**1**) is completely unproductive. The non-reactivity of 2-iodo benzyl bromide (**k**) with (**1**) could be due to the electronic and steric hindrance imparted by the bulky *o*-iodo substituent. However due to the better chelation ability of (**2**) leads to the formation of product (**2k**) in 41% yield. Similarly when 2-(4-methoxyphenyl)pyridine (**3**) was treated with benzylbromides (**b**) and (**f**) provide the acylated product in 87% and 66% yield respectively (**3b** and **3f**). 2-(4-Bromophenyl)pyridine (**4**), a moderately deactivated substrate when treated with benzyl bromides (**a** and **b**) provided corresponding *o*-aroylated products (**4a**) and (**4b**) in 62% and 69% yields respectively as shown in Scheme 2. Furthermore, electron neutral (**a**) and electron deficient benzyl bromides (**e** and **g**) provided *o*-aroylated products (**5a**), (**5e**) and (**5g**) in moderate yields when reacted with 2-(4-chlorophenyl)pyridine (**5**). Lesser reactivity of directing arenes possessing electron-withdrawing groups –Br (**4**) and –Cl (**5**) as compared to electron neutral –H (**1**) and electron rich $-CH_3$ (**2**) and $-OCH_3$ (**3**) analogues may be due to their poor chelating ability with the metal catalyst.

Benzo[*h*]quinoline (**6**), a rigid directing system has similar structural frame to that of 2-phenyl pyridine (**1**) where the sp^2 C–H at C10 can be aroylated. When (**6**) was reacted with benzyl bromide (**a**), and those possessing electron-donating groups such as *p*-CH_3 (**b**), *p*-^{t}Bu (**c**) all provided their respective *o*-aroylated products (**6a**), (**6b**) and (**6c**) (Scheme 2). Similarly benzyl bromides having electron-withdrawing substituents such as –Br (**e**), –Cl (**f**) and –F (**g**) also resulted in their corresponding aroylated products (**6e**), (**6f**) and (**6g**) respectively but in slightly lesser yields compared to their electron-donating counterparts. When moderately –Cl (**h**) or even strongly $-CF_3$ (**j**) electron-withdrawing substituents are present in the *meta* position of benzyl bromides, corresponding C10 aroylated products (**6h**) and (**6j**) were obtained in 59% and 48% yields respectively. In order to broaden the scope of this methodology when the present conditions were applied to substrates having other directing groups such as 2-phenylbenzo[*d*]thiazole, 2,3-diphenylquinoxaline and ketoxime ether, the reactions were completely unproductive giving no desired acylated products.

A plausible mechanism for this palladium catalysed carbo-acylation reaction of 2-phenyl pyridine (**1**) with benzyl bromide (**a**) *via* directed C–H bond activation is depicted in Scheme 3. The detection of benzaldehyde (**A**) in the crude reaction mixture suggests its intermediacy for this transformation. Furthermore, to deduce the nature of this coupling, a reaction between (**1**) and (**a**) was performed in the presence of a radical quencher TEMPO under otherwise identical conditions. The formation of product (**1a**) (< 10%) and isolation of TEMPO ester (**E**) in 67% yield suggests a radical pathway. Taking cues from these experimental results and related literature reports,[5i,12] a proposed mechanism is shown in Scheme 3. In the presence of oxidants NMO[11] and TBHP benzyl bromide is first oxidised to benzaldehyde (**A**). This *in situ* generated benzaldehyde (**A**) is then converted to benzoyl radical (**B**) with the aid of TBHP. Subsequent ligation of this radical species (**B**) with the chelated complex of Pd(II) (**C**) gives either a dimeric Pd(III) or Pd(IV) intermediate (**D**). Finally, C–C bond formation *via* reductive elimination of Pd formed complex (**D**) afforded the *o*-aroylated product (**1a**) and releasing Pd(II) catalyst in the medium to maintain the catalytic cycle.



Scheme 3 Proposed mechanism for *o*-aroylated product from benzyl bromide and 2-phenyl pyridine.

Conclusion

This protocol demonstrates a convenient and efficient synthesis of aryl ketones via Pd-catalysed *ortho*-C–H activation of 2-phenyl pyridines and benzo[*h*]quinoline using commercially available benzyl bromides as unconventional synthetic equivalents of aroyl group (ArCO–). All the benzyl bromides having activating or deactivating groups efficiently gave the desired product with 2-aryl pyridines and benzo[*h*]quinoline.

General procedure for the synthesis of phenyl(2-(pyridin-2-yl)phenyl)methanone (1a)

A mixture of 2-phenyl pyridine (77.5 mg, 0.5 mmol), $Pd(OAc)_2$ (5.6 mg, 5 mol%), benzyl bromide (256.5 mg, 1.5 mmol), *N*-methyl morpholine *N*-oxide (NMO) (351 mg, 3 mmol, 2equiv. *w.r.t.* benzyl bromide), chlorobenzene (2 mL) were taken in an oven dried round bottom flask (10 mL). To this mixture, K_2CO_3 (103.5 mg, 0.75 mmol) and decane solution of TBHP (5−6 M) (600 µL, 3 mmol, 2 equiv. *w.r.t.* benzyl bromide) were added. Then the flask was fitted with a condenser and heated for

9 h in a pre-heated oil bath maintained at 120 °C. During this period, the progress of the reaction was monitored by TLC at regular intervals. After completion of the reaction, it was cooled to room temperature and admixed with ethyl acetate (30 mL) and filtered. The ethyl acetate layer was washed successively with water (3 x 5 mL). The organic layer was then dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified over a column of silica gel and eluted with a mixture of hexane/ethyl acetate (9.3:0.7) to afford phenyl(2-pyridin-2-yl)phenyl methanone (**1a**) (102 mg, 79% yield).

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