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COMMUNICATION

Benzylamine as arylcarboxy surrogate: A copper catalysed *o*-benzoylation of 2-phenylpyridines using benzyl amines

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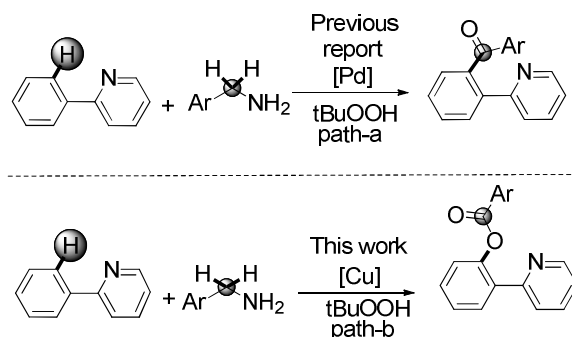
Differential reactivities and selectivities of Cu and Pd catalysts have been demonstrated in the reactions of benzylamines with 2-phenylpyridines. While Pd is reported to give *o*-arylation (ArCO-), Cu introduces an arylcarboxy group (ArCOO-) at the proximal site of the directing group. For the first time benzylamine has been utilised as a synthetic equivalent of arylcarboxy group.

Metal catalysed direct transformation of C–H bonds into C–C or C–heteroatom bonds is one of the reliable and facile tools in current organic chemistry.¹ It renders step and atom economic strategy compared to traditional cross-coupling reactions via circuitous use of prefunctionalised starting materials. Even more attractive is the new disconnection approach, which would greatly enhance the number of retrosynthetic steps to build complex molecular scaffolds. Pertinent to this, our group has developed CDC protocols for C–C and C–O bond forming reactions using various precursors such as alkylbenzenes,² terminal alkenes and alkynes³ which act as unconventional synthetic equivalents of ArCH₂O–,^{2a} ArCO–,^{2b,c} ArCOO–.^{2d,3} In continuation to the search for suitable precursor that can serve as an unorthodox surrogate of various functionalities, in the present case we took up benzyl amine as the potential candidate. Benzyl amines are highly susceptible to imine formation under

oxidative conditions. This imine on subsequent hydrolysis under the reaction conditions can generate aldehyde.⁴ The *in situ* generated aldehyde can be further manipulated in various ways to achieve C–C^{4a} and C–N^{4b} bonds. Recently, Wu group developed a Pd catalysed protocol for *ortho*-arylation of 2-phenylpyridine using benzyl amines as ArCO– surrogates^{4a} (path-a, Scheme 1). Although Pd and Cu show similar reactivities in coupling reactions there are instances where they behave differently for the same reaction. In one of our recent report on the synthesis of 2-aminobenzothiazoles from 2-halothioureas it was observed that copper prefers dehalogenative path while palladium favors C–H activation strategy.⁵ Also copper⁶ and palladium^{2b} behave differently in the reaction between alkylbenzenes and 2-phenylpyridines giving *o*-benzoylated (–OCOAr) and *o*-arylated (–COAr) products respectively. Thus it would be interesting to see how copper catalyst influences the reaction between 2-phenylpyridine and benzyl amine. To seek an answer to this, an initial trial was performed by reacting 2-phenylpyridine (**1**) and *p*-methylbenzyl amine (**c**) in the presence of Cu(OAc)₂ (20 mol %) and oxidant TBHP (5–6 M in decane) (5 equiv) in chlorobenzene at 120 °C (Table 1, entry 1). The reaction led to an exclusive formation of *o*-benzoylated (–OCOAr) product (**1c**) rather than an *o*-arylated (–COAr) product observed using Pd-catalyst.^{5a} This observation highlights the divergence in the selectivity achieved with the change of transition metal catalyst. Also present protocol for the formation of an ester C–O bond using benzyl amine as the new unconventional ArCOO– equivalents like alkylbenzenes,^{2d} terminal alkenes and alkynes³ is unparalleled in the literature (path-b, Scheme 1)

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Scheme 1 Selectivity achieved in the presence of different transition metal catalyst

The directing group assisted C–O bond formation mostly concentrated on acetoxylation⁷ and hydroxylation^{7d–f,8} via C–H bond activation. However reports on benzylation via same strategy are comparatively fewer in spite of their importance in the synthesis of natural products and pharmacological compounds.⁹ Initially *o*-benzylation of 2-phenylpyridine was achieved by Sanford group using benzoate iodonium salts as the mutual coupling partner.¹⁰ Later, the same was demonstrated using various transition metal catalysts with carboxylic acids/salts¹¹ or its derivatives such as acid chlorides¹² anhydrides¹³ or peroxides¹⁴ as the arylcarboxy sources. Further, Huang *et al.* used aldehydes and alkylbenzenes as alternative benzyloxy surrogates during *o*-benzylation of 2-phenylpyridine⁶ Similar *o*-benzylation has been achieved with other directing groups such as ketoxime ether,¹⁵ acetanilides¹⁶ and benzamides¹⁷ using carboxylic acids in the presence of Pd and Ru catalysts respectively. Very recently our group has developed a protocol for *o*-benzylation of 2-phenylpyridine using terminal alkenes and alkynes as the new arylcarboxy surrogates.³

Table 1 Screening of Reaction Conditions^a

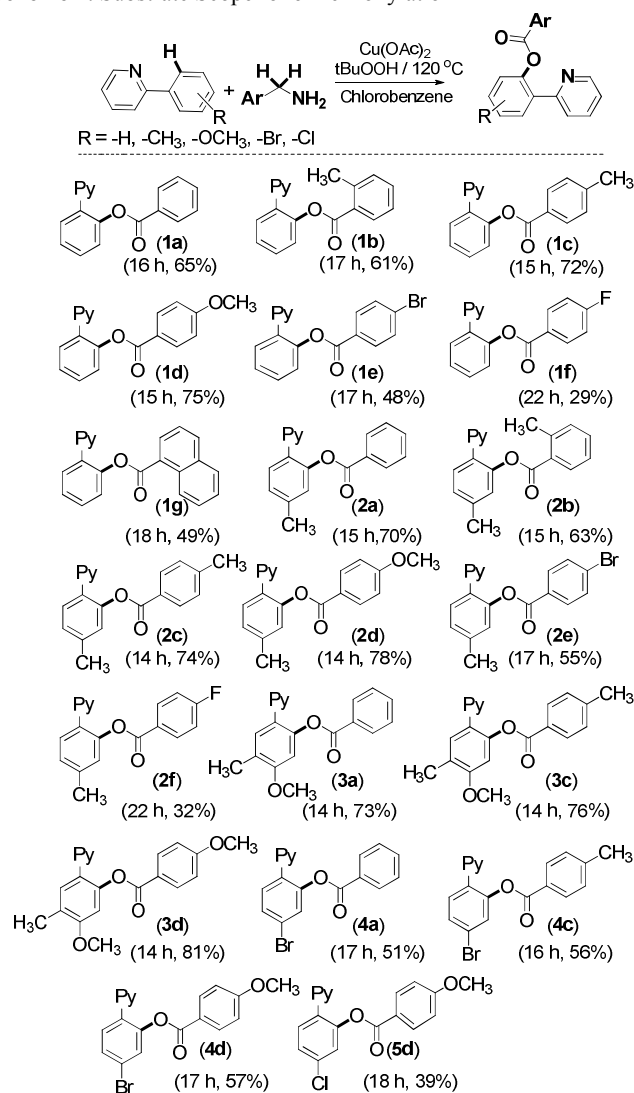
Entry	Catalyst (mol%)	Oxidant (Equiv.) ^c	Temp (°C)	Yield ^b (%)
1	Cu(OAc) ₂ (20)	TBHP (5)	120	66
2	CuBr (20)	TBHP (5)	120	37
3	CuBr ₂ (20)	TBHP (5)	120	51
4	CuCl (20)	TBHP (5)	120	28
5	CuCl ₂ (20)	TBHP (5)	120	45
6	Cu(OTf) ₂ (20)	TBHP (5)	120	25
7	CuI (20)	TBHP (5)	120	23
8	Cu(OAc)₂ (20)	TBHP (6)	120	72
9	Cu(OAc) ₂ (20)	TBHP (7)	120	73
10	Cu(OAc) ₂ (10)	TBHP (6)	120	58
11	Cu(OAc) ₂ (30)	TBHP (6)	120	75
12	Cu(OAc) ₂ (20)	TBHP (6)	140	63
13	Cu(OAc) ₂ (20)	aq.TBHP (6)	120	47
14	None	TBHP (6)	120	0
15	Cu(OAc) ₂ (20)	None	120	0

^aReaction conditions: 2-phenylpyridine (**1**) (0.5 mmol), *p*-methylbenzylamine (**e**) (1 mmol), chlorobenzene (2 mL), time 15 h. ^bIsolated yield.

^cWith respect to benzylamine.

To arrive at the best possible yield various counter anions of Cu(I) [CuBr, CuCl and CuI] and Cu(II) [Cu(OAc)₂, CuBr₂, CuCl₂, Cu(OTf)₂] salts (Table 1, entries 1–7) were screened. Among all the catalysts screened Cu(OAc)₂ (Table 1, entry 1) was found to be the best. Increasing the quantity of TBHP (5–6 M in decane) from 5 to 6 equivalents enhanced the product yield from 66% to 72% (Table 1, entry 8), while no significant change in the yield was observed using 7 equivalents of the same. A decrease in the catalyst loading from 20 to 10 mol% lowered the product yield (Table 1, entry 10) while only a marginal improvement in the yield occurred with the use of Cu(OAc)₂ (30 mol%) (Table 1, entry 11). The reaction when performed at 140 °C was counterproductive (Table 1, entry 12). Among all the other solvents examined such as toluene (0%), THF (30%), dioxane (8%), DMSO (17%), DCE (45%) and DMF (12%), chlorobenzene (74%) was found to give superior yield. The use of an aq. TBHP (47%) was less effective compared to that of a decane solution of TBHP (Table 1, entry 13). Control experiments suggest that both catalyst and oxidant combination is indispensable for this transformation (Table 1, entries 14–15). Thus the use of Cu(OAc)₂ (20 mol %), TBHP (5-6 M in decane) (6 equiv) and chlorobenzene (2 mL) at 120 °C was found to be the best condition for this transformation.

Scheme 2. Substrate Scope for *o*-Benzylation^{a,b}



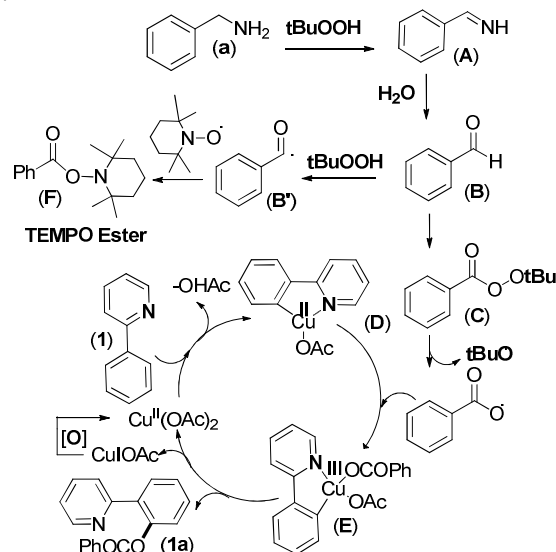
^aReaction conditions: 2-phenylpyridine (**1–5**) (0.5 mmol), arylmethanamines (**a–g**) (1 mmol), Cu(OAc)₂ (0.1 mmol), TBHP (5–6 M) (6 mmol),

temperature 120 °C, in chlorobenzene (2 mL), time 14–22 h. ^bYield of isolated pure product.

The optimised conditions were then implemented for *o*-benzoylation of 2-arylpyridines (**1–5**) using various substituted benzylamines and the results are summarised in Scheme 2. Initially benzyl amine (**a**) and benzyl amines possessing various electron-rich groups *viz.* *o*-Me (**b**), *p*-Me (**c**) and *p*-OMe (**d**) were treated with 2-phenylpyridine (**1**) for *o*-benzoylation at the proximal site of *N*-atom. All the benzyl amines served as their respective ArCOO–surrogates to provide good to moderate yields of their *o*-benzoylated products (**1a–1d**) as shown in Scheme 2. Moderately electron-deficient groups such as *p*-Br (**f**) and *p*-F (**g**) when present in phenyl ring of the benzyl amine coupled with (**1**) to give *o*-esters (**1e**) and (**1f**) in lower yields of 48% and 29% (Scheme 2). Arylmethyl amines bearing electron-deficient substituents gave lower yields compared to substrates possessing electron-rich groups suggesting the importance of their electronic effects on the overall process. Notably, 1-naphthylmethylamine (**g**) having a fused ring reacted smoothly with (**1**) yielding naphthylcarboxylated (**1g**) in 49%. In addition to 2-phenylpyridine (**1**), *o*-benzoylation of 2-(*p*-tolyl)pyridine (**2**) were also investigated with various arylmethyl amines (Scheme 2). The selectivity and reactivity trends of substituted benzyl amines towards *o*-benzoylation of (**2**) were found to be identical as was observed for (**1**). Marginally better yields were obtained for *o*-benzoylated products (**2a–2f**) with (**2**) than (**1**) could be attributed to its better chelation ability with metal catalyst due to presence of electron-donating *o*-tolyl group. Directing arene possessing two electron donating groups (–Me and –OMe) as in 2-(4-methoxy-3-methylphenyl)pyridine (**3**) showed identical reactivity and yield trends as that of (**2**) toward *o*-benzoylation when reacted with various benzylamines (**a**), (**c**) and (**d**) as shown in Scheme 2. The scope of *o*-benzoylation for 2-(4-bromophenyl)pyridine (**4**) with benzyl amine (**a**) and substituted benzyl amines *viz.* *p*-Me (**c**), and *p*-OMe (**d**) were also investigated. All provided *o*-benzoylated products (**4a–4d**) in moderate yields ranging from 51% to 57% (Scheme 2). Lower yields obtained in 2-(4-bromophenyl)pyridine (**4**) could possibly arise from poor chelating ability of (**4**) as compared to its neutral and electron-rich analogues (**1**, **2** and **3**). Finally, reaction of 2-(4-chlorophenyl)pyridine (**5**) with *p*-methoxybenzylamine (**d**) afforded *o*-benzoylated products (**5d**) in a modest yield of 39%. Unfortunately, aliphatic amines such as butyl amine and cyclohexylmethylamine failed to undergo any *o*-acetoxylation with any of the directing arenes under the optimised condition.

To find out a possible reaction pathway for this protocol systematic investigations were carried out. Analysis of the reaction mixture between (**1**) and (**a**) divulges the presence of benzaldehyde and benzoic acid in the medium suggesting their intermediacy. A control experiment carried out by reacting (**1**) with an equimolar mixture of *p*-methylbenzyl amine (**c**) and *p*-methoxybenzoic acid under the optimised condition gave product (**1a**) predominantly (53%) along with a trace of (**1d**); suggesting arylcarboxylic acid is not the main coupling partner. The coupling partner is most likely *tert*-butyl benzoperoxate generated *in situ* by the reaction of aldehyde and TBHP; similar to our recent *o*-benzoylation of (**1**) using terminal alkenes and alkynes.³ The aldehyde is obtained by the hydrolysis of imine which in turn is formed by the oxidation of benzylamine.^{4b} To ascertain the nature of reaction mechanism a reaction was performed in the presence of radical inhibitor TEMPO (see Scheme S2, ESI†). Substantial quenching of product formation and isolation of TEMPO ester (**F**) suggest a radical mechanism. From the above experimental observations a tentative mechanism has been proposed for this protocol as depicted in Scheme 3. Benzyl amine oxidises to imine (**A**) which on hydrolysis gives benzaldehyde

(**B**). In the presence of excess of TBHP, (**B**) or (**B'**) is transformed to *tert*-butyl benzoperoxate (**C**). A loss of ¹BuO radical from (**C**) gives benzoxy radical. The radical species on subsequent ligation with the Cu(II) complex (**D**) gives the Cu(III) intermediate (**E**). The reductive elimination in the final step leads to the *o*-benzoylated product (**1a**) while the Cu(I) generated is reoxidised to Cu(II) for next catalytic cycle.



Scheme 3 Proposed Mechanism for *ortho*-Benzoylation

In conclusion this protocol demonstrates the use of benzyl amines as an unconventional synthetic equivalent of arylcarboxy groups (ArCOO–) which has been employed for the *o*-benzoylation of 2-phenylpyridine derivatives. A plausible reaction mechanism involves the *in situ* generation of intermediates such as imine and aldehyde from arylmethylamine. The radical nature of the reaction has been established by isolation of TEMPO ester. This protocol shows the differential selectivities and reactivities of Cu and Pd catalysts for the same reaction.

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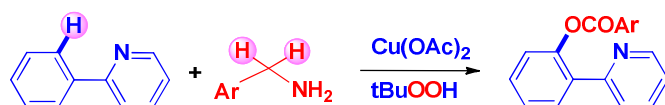
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