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Palladium-catalyzed regio- and chemoselective *ortho*-benzylation of C–H bond using a functionalizable primary amide directing group: a concise synthesis of dibenzo[*b*,*e*]azepin-6-ones†

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A palladium-catalyzed regio- and chemoselective direct benzylation of primary benzamides with 2-bromobenzyl bromides under a mild basic condition has been developed affording various substituted diarylmethanes in good yields. Furthermore, the directing amide group (–$CONH_2$) was subjected to intramolecular N-arylation with the aryl bromide moiety present in diarylmethanes leading to a concise synthesis of dibenzoazepinones.

Diarylmethanes are privileged structures ubiquitously found in pharmaceuticals and biologically active compounds[1] and employed in the design of supramolecular structures.[2] Consequently, development of an efficient method for the construction of substituted diarylmethanes has spurred intense interest. As a result, Friedel–Crafts benzylations,[3] transition metal-catalyzed cross-coupling reactions of a stoichiometric organometallic aryl with benzyl halides,[4] and transition metal-catalyzed directed benzylations of electron-deficient arenes and heteroarenes have been successfully developed.[5] While a wide variety of functional groups have been evaluated as directing groups in arene C–H functionalizations, only the use of a secondary amide directing group containing an 8-aminoquinoline moiety in direct *ortho*-benzylation has been realized so far. The palladium[6] or nickel-catalyzed[7] direct alkylations of the *ortho* C–H bond in secondary benzamides containing an 8-aminoquinoline moiety as a bidentate directing group have been developed, wherein a few examples of *ortho*-benzylations have been included (see ESI†). While bidentate-chelation assistance of the directing group makes these directed *ortho*-benzylations more attractive, the directing group requires prior installation of the 8-aminoquinoline moiety and subsequent removal for further transformation.

The development of new types of directing groups continues to be important, in terms of exploring novel regio- and chemoselective direct C–H functionalizations that cannot be achieved when conventional directing groups are used. The regio- and chemoselective direct C–H functionalization would present a challenge especially when more than one of both nucleophiles and electrophiles are present. These challenges are further exacerbated by the requirement of the directing group to be functionalizable after the desired operation. Very recently, a primary amide group (–$CONH_2$) has been demonstrated for the first time to act as a directing group in the palladium-catalyzed *ortho*-arylation of primary benzamides with aryl iodides under acidic condition in the presence of silver oxide affording biaryls in 33–84% yields.[8] To the best of our knowledge, no other report of direct C–H functionalization *via* C–H bond activation employing a directing primary amide group is available. Herein we report a method for palladium-catalyzed regio- and chemoselective *ortho*-benzylation of primary benzamides with 2-bromobenzyl bromides under a mild basic condition. Our continued efforts to develop concise (one or two-step) syntheses of nitrogen-containing fused heterocycles[9] led us to explore the application of this protocol to the synthesis of dibenzo-fused azepinones that are prevalent in biologically active molecules.[10] Notably, this constitutes a rare example of regio- and chemoselective direct C–H functionalization using a transformable directing group.

At the outset, the choice of the appropriate benzylic electrophile for palladium-catalyzed direct benzylation of primary benzamides was crucial (see ESI†). We chose 3-methoxybenzyl bromide in our optimization study. When the reaction of benzamide (**1**) and 3-methoxybenzyl bromide (**2**) was carried out in the presence of 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3 and 1.2 equiv. of Cs_2CO_3 in toluene at 110 °C for 18 h, the desired benzylated product **3** was isolated as a major product in 30% yield together with formation of *N*-benzyl benzamide, and *C*,*N*-dibenzylated and 2,6-dibenzylated derivatives (Table 1, entry 1). Noticeably, a significant amount of starting material remained unreacted even after prolonging the reaction to 36 h. Subsequent efforts to improve upon the reaction using other ligands, bases, and solvents were ineffective (see ESI†). Gratifyingly, the yield of **3** was increased to 45% using dioxane as the solvent (entry 2). A lower catalyst loading (5 mol%) was beneficial in reducing the amount of undesired products. Thus, compound **3** was best obtained in 60% yield by heating **1** and **2** in the presence of

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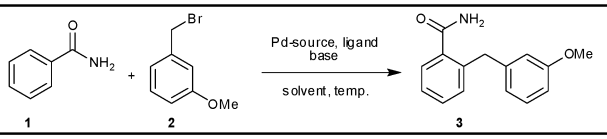
† Electronic supplementary information (ESI) available: Additional information on this study, detailed experimental procedure and analytical data for all new compounds. See DOI: 10.1039/c3cc43835j

Table 1 Optimization study for the direct benzylation[a]



1 2 3

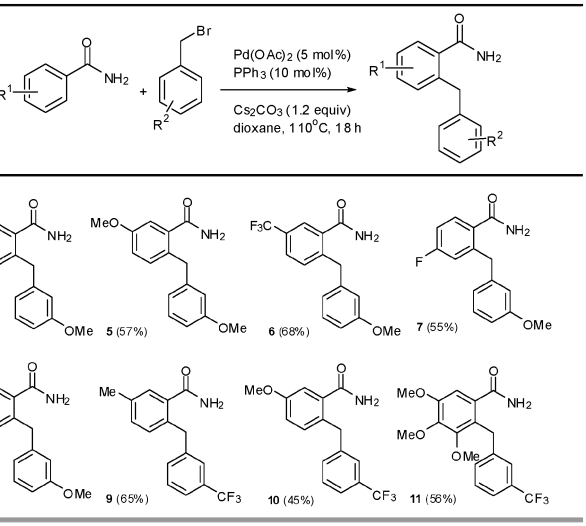
Entry	Pd-source	Ligand	Base	Solvent	Yield (%)
1	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	Toluene	30
2	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	Dioxane	45
3[b]	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	Dioxane	**60**[c]
4[d]	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	Dioxane	38
5[e]	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	Dioxane	30–35
6[f]	$Pd(PPh_3)_4$	—	Cs_2CO_3	Dioxane	52
7	$Pd(OAc)_2$	—	Cs_2CO_3	Dioxane	38
8[g]	$Pd(OAc)_2$	—	K_2CO_3	*t*-Amyl-OH	20
9[h]	$Pd(OAc)_2$	PPh_3	Cs_2CO_3	Dioxane	0

[a] *Reagents and conditions*: **1** (0.2 mmol), **2** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), base (0.24 mmol), solvent (500 mM), 110 °C, 18 h. [b] Used $Pd(OAc)_2$ (5 mol%) and PPh_3 (10 mol%). [c] Also isolated *N*-benzyl benzamide (8%). [d] Used **2** (2 equiv.). [e] Used $Pd(OAc)_2$ (1.25–2.50 mol%) and PPh_3 (2.5–5.0 mol%). [f] Used $Pd(PPh_3)_4$ (10 mol%). [g] Ref. 6. [h] Employed secondary benzamide (*N*-methylbenzamide or *N*-phenylbenzamide) as one of the coupling partners using 5 mol% $Pd(OAc)_2$ and 10 mol% PPh_3.

5 mol% $Pd(OAc)_2$, 10 mol% PPh_3 and 1.2 equiv. Cs_2CO_3 in dioxane at 110 °C (entry 3). It should be noted here that in addition to the desired diarylmethane **3**, the formation of *N*-benzyl benzamide (8%), *C*,*N*-dibenzylated derivatives, and other unidentified products account for the mass balance of the conversion of benzamide into products. The use of excess **2** (2 equiv.) in this reaction was detrimental (entry 4). Similarly, further lowering of the catalyst loading to 2.5 mol% or 1.25 mol% was deleterious (entry 5). Replacing $Pd(OAc)_2$ by $Pd(PPh_3)_4$ resulted in slightly reduced yield of **3** (entry 6). However, the optimized condition excluding PPh_3 gave the desired *ortho*-benzylated benzamide in reduced yield (38% *vs.* 60%, entry 7). Interestingly, we observed that the reaction of **1** and **2** could give **3** in 20% yield under the conditions described in the literature,[6] however, the *N*-benzyl benzamide was found to be a major compound in this reaction (entry 8). Similarly to previous observations,[6,7] the reaction of a secondary benzamide (*N*-methylbenzamide or *N*-phenylbenzamide) with **2** did not produce the corresponding direct benzylated product under the best conditions (entry 9, see ESI†).

With the optimized condition [5 mol% $Pd(OAc)_2$, 10 mol% PPh_3, 1.2 equiv. of Cs_2CO_3, dioxane (500 mM), 110 °C, 18 h] in hand, we next examined the scope of the reaction to the extent for regioselective direct *ortho*-benzylation (Table 2). To our delight, the reaction of 3-methylbenzamide and **2** under the optimized conditions gave diarylmethane **4** in 65% yield indicating complete regiocontrol in terms of C-benzylation prevailed in this reaction. The effect of an electron-donating or -withdrawing group at the 3-position of benzamide was also investigated. While an electron-donating group as in 3-methoxybenzamide resulted the formation of **5** in slightly reduced yield (57%), the electron-withdrawing group present in 3-trifluoromethylbenzamide restored the yield (68%) of diarylmethane **6**. Instead, an electron-withdrawing group at the 4-position (as in 4-fluorobenzamide) afforded the direct benzylation product **7** in reduced yield (55%). The C–H bond adjacent to the amide group in 3,5-difluorobenzamide undergoes regioselective *ortho*-benzylation giving the diarylmethane **8** in 52% yield.

Table 2 Regioselective direct *ortho*-benzylation of primary benzamides with benzyl bromides



We also investigated the reactions of 3-substituted benzamides with 3-trifluoromethylbenzyl bromide under the optimized condition. Pleasantly, both 3-methylbenzamide and 3-methoxybenzamide reacted with 3-trifluoromethylbenzyl bromide affording diarylmethanes **9** and **10** in 65% and 45% yields, respectively. Similarly, 3,4,5-trimethoxybenzamide gave highly substituted diarylmethane **11** in 56% yield. It is noteworthy that in several instances the yields of diarylmethanes obtained in palladium-catalyzed *ortho*-benzylation directed by a primary amide group are comparable to that obtained using a secondary amide group containing an 8-aminoquinoline moiety.[6]

After successfully developing the protocol for regioselective benzylation, our subsequent efforts were directed to the development of more challenging regio- and chemoselective direct benzylation of benzamides with 2-bromobenzyl bromides involving more than one competitive nucleophile and electrophile (Table 3). Taking advantage of the different reactivity of the two bromo-groups present in 2-bromobenzyl bromide, Suzuki or Stille cross-coupling reactions employing 2-bromobenzyl bromides have been described, wherein chemoselective C-benzylation has been achieved over C-arylation.[11] However, regio- and chemoselective direct C–H functionalization using 2-bromobenzyl bromide is unprecedented. Under the optimized conditions, 3-methylbenzamide reacts with 2-bromobenzyl bromide yielding **12** in 81% yield. Benzamides with an electron-donating or -withdrawing group at the 3-position sustain similar reactivity to 2-bromobenzyl bromide, affording **13** and **14** in 56% and 52% yields, respectively. 4-Methoxybenzamide was also found to react with 2-bromobenzyl bromide to give **15** in 48% yield. Similarly to our previous observation, 3,5-difluorobenzamide reacted with 2-bromobenzyl bromide regioselectively yielding compound **16** in 65% yield. A similar trend of reactivity was observed with benzamide, 3-methylbenzamide, or 4-methoxybenzamide and 5-bromo-6-bromomethyl-1,3-benzodioxole, yielding diarylmethanes **17**, **18**, and **19** in 50%, 53%, and 64% yields, respectively. In addition, 4-fluorobenzamide and 3,5-difluorobenzamide reacted with 5-bromo-6-bromomethyl-1,3-benzodioxole to give **20** and **21** in 60% and 62% yields, respectively.

Table 3 Regio- and chemoselective direct *ortho*-benzylation of primary benzamides with 2-bromobenzyl bromides

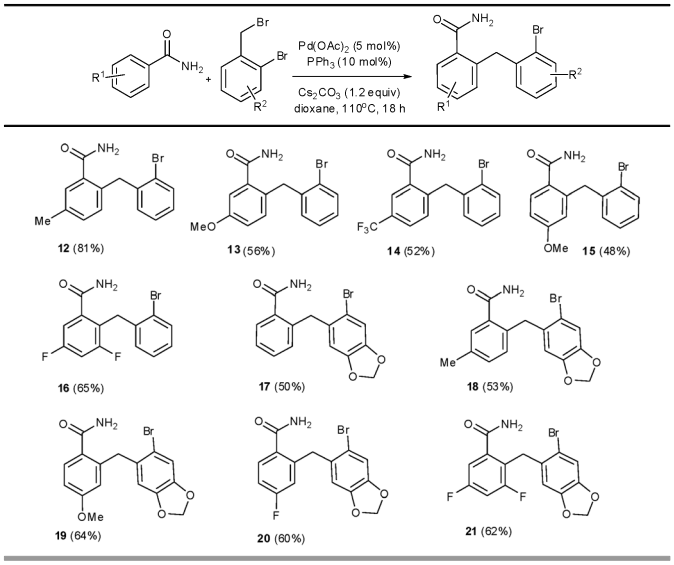
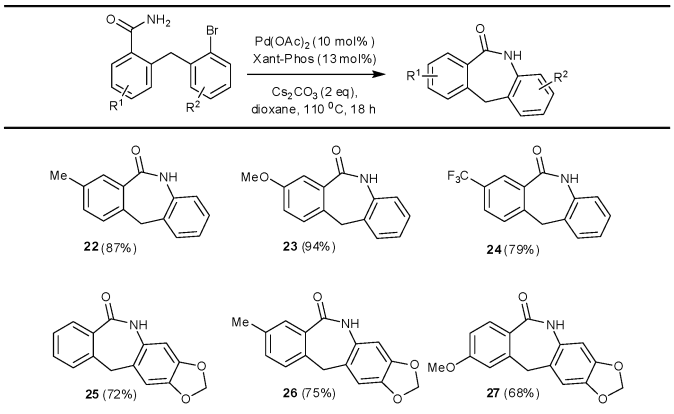


Table 4 Convergent synthesis of dibenzoazepinones



Furthermore, the application of regio- and chemoselective direct benzylation was demonstrated in the synthesis of dibenzoazepinones. Dibenzoazepinones display interesting biological activities including being anticancer and anticonvulsant.[10] Despite its widespread importance, methods to prepare the dibenzoazepinone skeleton are scarce.[12] The methods to prepare these skeletons largely rely on multi-step strategies involving initial lactam formation followed by intramolecular nucleophilic aromatic substitution,[12a] or *vice versa*.[12b] The diarylmethanes (**12–14**, **17–19**) thus obtained were subjected to the intramolecular N-arylation[13] in the presence of 10 mol% $Pd(OAc)_2$, 13 mol% Xant-Phos and 2 equiv. Cs_2CO_3 in dioxane at 110 °C for 18 h, which upon isolation by column chromatography afforded dibenzoazepinones **22–27** in good to excellent yields (Table 4).

A palladium-catalyzed direct *ortho*-benzylation has been developed for the first time in the presence of an easily functionalizable directing group ($-CONH_2$). Furthermore, regio- and chemoselective direct *ortho*-benzylation of primary benzamides with 2-bromobenzyl bromides was also achieved. Finally, the application of this novel protocol has been demonstrated in the concise synthesis of fused dibenzoazepinone heterocycles that are invariably obtained in multi-step synthesis. Taken together, these novel findings confer a new direction towards the development of regio- and chemoselective direct C–H functionalization.

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