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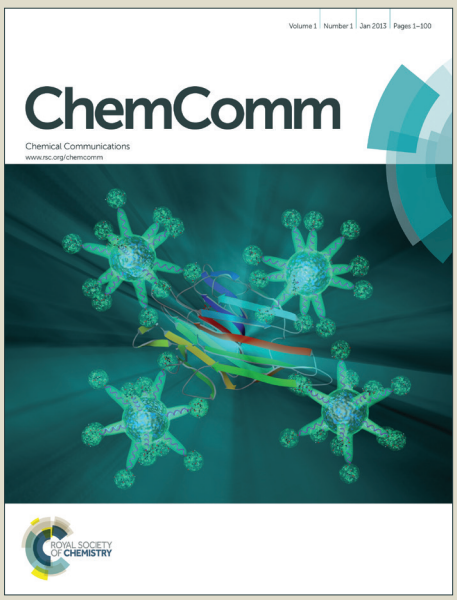

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ARTICLE TYPE

Pd(II)-Catalyzed Arylation of Unactivated Methylene C(sp^3)–H bonds with Aryl Halides Using a Removable Auxiliary

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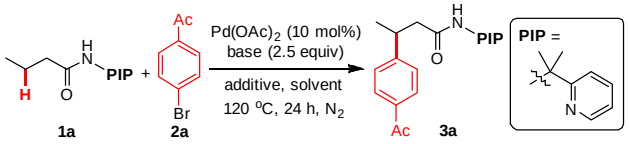
A Pd(II)-catalyzed arylation of methylene C(sp^3)–H bonds in aliphatic amides directed by our newly developed PIP directing group with aryl iodides/bromides has been achieved. Arylation occurs efficiently with a broad range of aryl halides and amides.

In recent years, transition-metal-catalyzed C-H arylation has emerged as an attractive alternative to traditional cross-coupling reactions due to the minimization of stoichiometric metallic waste and the avoidance of multi-step sequences to prepare the starting materials.[1] Compared to the significant progress made with the arylation of C(sp^2)–H bonds of arenes and heteroarenes, general strategies for the arylation of unactivated C(sp^3)–H bonds, especially methylene C(sp^3)–H bonds, remain relatively rare.[2] An isolated example of methylene C(sp^3)–H arylation of 2-ethylpyridine with aryl iodides was first reported by Daugulis in 2005.[3] Shortly after, the seminal work by the same group described a removable bidentate directing group (DG) derived from 8-aminoquinoline for the effective arylation with broad substrate scope.[4] In 2006, Corey reported the β-arylation of phthalimide protected α-amino acids with aryl iodides assisted by the same DG.[5] Recently, Yu reported a ligand-enabled arylation of methylene C(sp^3)–H bond using a weakly coordinating perfluorinated arylamides DG (CONHAr$_F$).[6a] Very recently, Yu *et al*. have extended this elegant strategy to the β-arylation of α-amino acids with aryl iodides.[6b] Besides, Shi has reported the arylation of methylene C(sp^3)–H bonds with diarylhyperiodonium salts using 8-aminoquinoline DG.[8] However, the above mentioned arylation reactions mainly depended on the use of aryl iodides[4-7] or diarylhyperiodonium salts.[8] Thus, extending arylation reactions of methylene C(sp^3)–H bonds to other unreactive, yet readily available and cost-effecitve arylating reagents, such as aryl bromides, is highly desirable.

Despite the well-established arylation of C(sp^3)–H bonds with ArI under the Pd(II)/Pd(IV) catalytic cycle,[4-7] the use of aryl bromides as arylating reagents was mainly limited to the Pd(0)/Pd(II) catalytic cycle initiated by the oxidative addition of ArBr to palladium(0).[10] Recently, the You group has reported the first nickel-catalyzed arylation of C(sp^3)–H with aryl bromides assisted by 8-aminoquinoline DG.[11] However, this reaction protocol was limited to the arylation of methyl C(sp^3)–H bonds adjacent to quanternary centers. We have recently developed a removable bidentate DG derived from 2-(pyridine-2-yl)isopropylamine (PIP-amine), which exhibited superior reactivity in the activation of unactivated methylene C(sp^3)–H bonds.[12] Compared to Daugulis' 8-aminoquinoline DG, the nitrogen atom on this DG is more electron-rich and sterically bulky. We hypothesized that this may not only facilitate the C-H activation but also promote the oxidative addition of the less reactive aryl bromides to the Pd(II) intermediates. Herein we report an efficient Pd(II)-catalyzed arylation of secondary C(sp^3)–H bonds with aryl bromides and/or iodides directed by our newly developed PIP DG. The reaction could tolerate a broad range of aryl halides and aliphatic amides, providing an efficient protocol for the synthesis of β-arylated aliphatic carboxylic acids and their derivatives.[13]

Table 1 Optimization of the reaction conditions



1a 2a 3a

Entry	Base	Additive (equiv)	Solvent	Yield (%)[b]
1	K_2CO_3	$(BnO)_2PO_2H$ (0.2)	*t*-Amyl-OH	39
2	K_2CO_3	MesCOOH (0.2)	*t*-Amyl-OH	41
3	K_2CO_3	PivOH (0.2)	*t*-Amyl-OH	53
4	AgF	-	*t*-Amyl-OH	trace
5	$KHCO_3$	PivOH (0.2)	*t*-Amyl-OH	17
6	K_3PO_4	PivOH (0.2)	*t*-Amyl-OH	43
7	$CsCO_3$	PivOH (0.2)	*t*-Amyl-OH	23
8	$NaHCO_3$	PivOH (0.2)	*t*-Amyl-OH	trace
9	K_2CO_3	PivOH (0.2)	DCM	36
10	K_2CO_3	PivOH (0.2)	toluene	25
11	K_2CO_3	PivOH (0.2)	*t*-BuOH	**75**[c]
12[d]	K_2CO_3	PivOH (0.2)	*t*-Amyl-OH	41

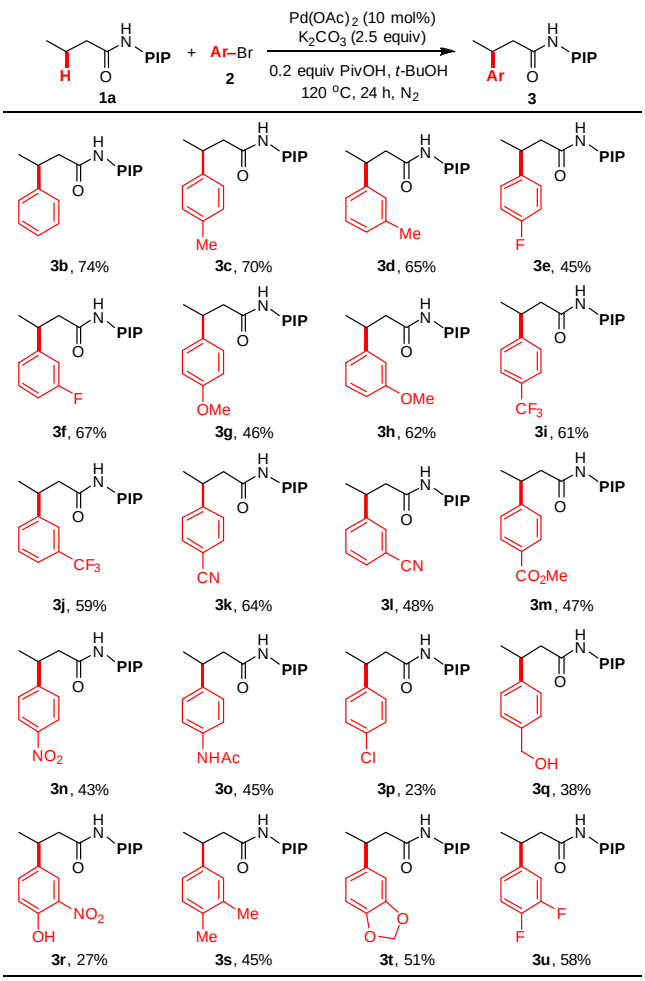
[a] Reaction conditions: **1a** (0.15 mmol), $Pd(OAc)_2$ (10 mol%), base and additive in 1.5 mL solvent at 120 °C for 36 h. [b] ^{1}H NMR yield using CH_2Br_2 as the internal standard. [c] Isolated yield. [d] $Pd(TFA)_2$ (10 mmol%) was used.

Inorganic bases and silver(I) salts have been widely used as halide scavengers in the direct arylation of C-H bonds under a Pd(II)/Pd(IV) catalytic cycle.[4-7] Moreover, carboxylate counteranions also play a key role in the C-H activation reactions.[14] Therefore, initial experiments were performed in *t*-Amyl alcohol with K_2CO_3 (2.5 equiv) as halide scavenger and $(BnO)_2PO_2H$ (0.2 equiv) as ligand, which has been found to facilitate the C(sp^3)–H alkylation reactions.[12b] To our delight, the desired product **3a** was obtained in 39% yield (Table 1, entry 1). Further investigation revealed that **3a** was given in 53% yield

when PivOH was used as ligand (entry 3).[4b,d] Other inorganic bases and silver salts gave reduced yields (entries 4-8). *t*-BuOH was found to be the ideal solvent for the reaction providing arylated product **3a** in 75% yield (entries 9-11 and see ESI†). The yield decreased to 41% when $Pd(TFA)_2$ was used as catalyst (entry 12).

With the optimized conditions in hand, we explored the scope of the aryl bromide coupling partners (Table 2). The reaction conditions were compatible with a wide range of aryl bromides with different functional groups, such as alkyl, fluoro, methoxy, trifluoromethyl, cyano, methoxycarbonyl, nitro, acetylamino and chloro. It is worth noting that aryl bromides bearing strong electron-withdrawing groups, such as nitro, methoxycarbonyl and cyano, were also tolerated under the optimized reaction conditions, affording the desired products in moderate yields (**3k-3n**, 43%-64% yields). Notably, aryl bromides bearing free hydroxyl groups were also survived, albeit affording the products in reduced yields (**3q** and **3rb**). Moreover, disubstituted aryl bromides bearing synthetically useful functional groups were also good arylating reagents and gave the desired products in reasonable yields (**3r-3u**).

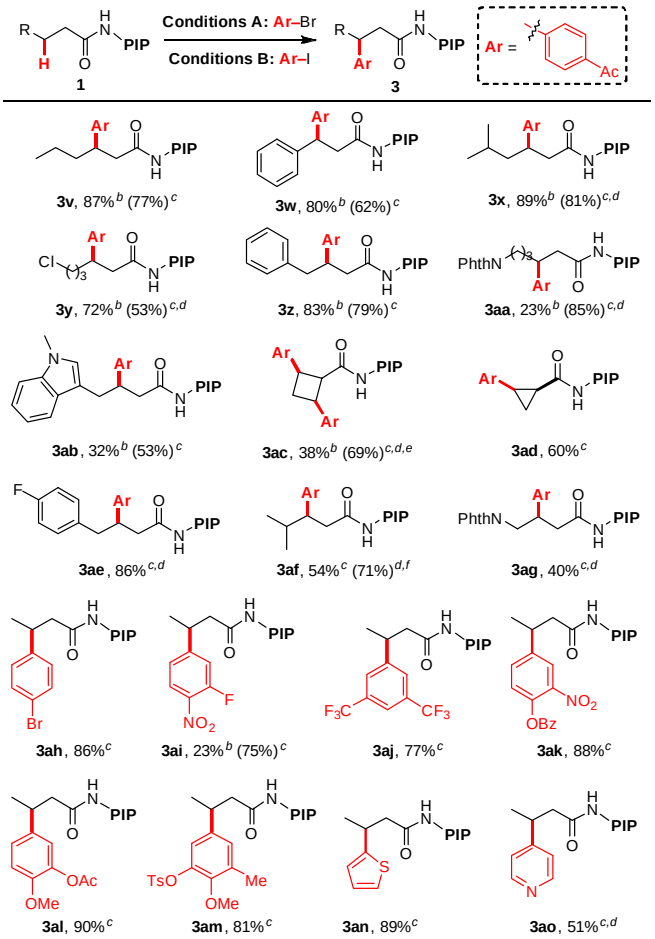
Table 2 Pd(II)-Catalyzed arylation of methylene C(sp^3)–H bonds with ArBr[a,b]



[a]Reaction conditions: **1a** (0.15 mmol), $Pd(OAc)_2$ (10 mol%), K_2CO_3 (2.5 equiv) and PivOH (0.2 equiv) in 1.5 mL *t*-BuOH at 120 °C for 24 h. [b]Isolated yields.

The present reaction was next applied to various aliphatic amides (Table 3). A variety of functional groups, such as chloro, indolyl and Phth-protected amine, were tolerated under the reaction conditions. Arylation of cyclobutanecarboxamide gave the diarylated product **3ac** in 38% yield. To our delight, some specific carboxamides and aryl bromides, which were ineffective for arylation under **Conditions A**, were compatible with the reaction conditions established by Daugulis (**Conditions B**)[4] using ArI as the arylating reagents (**3ad-3ao**). Thus, aryl iodides with strong electron-withdrawing groups and heteroaryl iodides, proceed smoothly under **Conditions B** to give the desired products in good yields (**3ai-3ao**, 51%-90%). Interestingly, bromo was survived under **Conditions B** (**3ah**, 86%). It is also worth noting that heteroaryl iodides such as 2-iodothiophene and 4-iodopyridine were also tolerated under the arylation conditions, affording the desired products in good yields (**3an**, 89% and **3ao**, 51%, respectively).

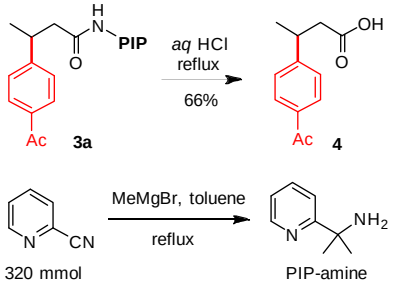
Table 3 Pd(II)-Catalyzed arylation of methylene C(sp^3)–H bonds with aryl halides[a]



[a]Isolated yields. [b] **Condations A**. [c] **Conditions B**: **1** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (1.5 equiv) and ArI (1.5 equiv) in 2 mL *t*-BuOH at 120 °C for 24 h. [d] Work-up by treating with 0.5 mL Et_3N for 5 h. [e] 60 °C, 3 equiv ArI. [f] **Conditions B**, AgF (1.5 equiv).

Finally, the PIP directing group was removed under acidic conditions (eqn (1)). The corresponding carboxylic acid **6** was obtained in 66% yield. Most importantly, the 2-(pyridine-2-yl)isopropylamine (PIP-amine) is readily prepared from the

reaction of 2-cyanopyridine with MeMgBr on large scale following an improved procedure (eqn (2), see ESI†).[15]



In conclusion, we have developed a Pd(II)-catalyzed direct arylation of methylene C(sp^3)–H bonds with aryl bromides and/or aryl iodides. Good structural versatility in both aryl halides and aliphatic amides and high functional group tolerance were achieved, providing an efficient protocol for the synthesis of β-arylated carboxylic acid derivatives. Unlike the arylation reactions proceeded under palladium/phosphine ligand catalytic system, this reaction protocol was believed to go through a Pd(II)/Pd(IV) catalytic cycle. Further studies to elucidate the mechanistic details are currently underway.

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† Electronic Supplementary Information (ESI) available: Experimental details and characterization data for new compounds. See DOI: 10.1039/b000000x/

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