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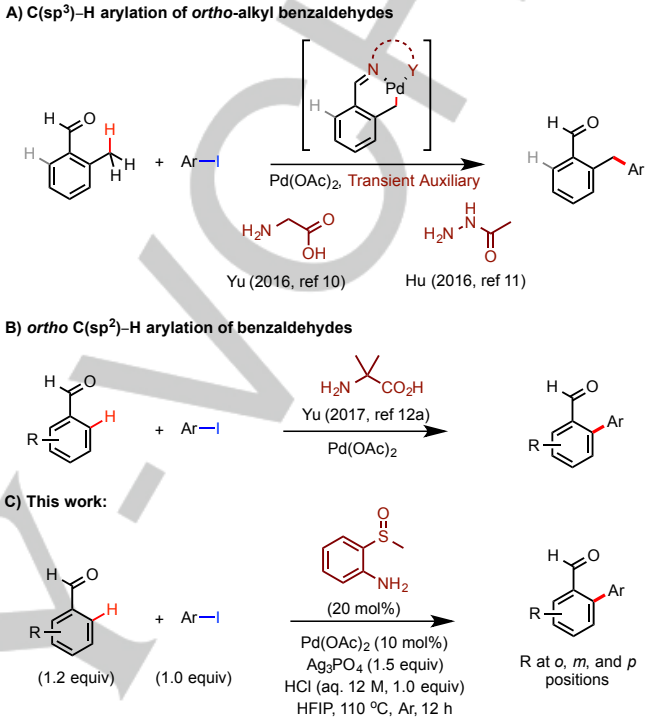
Palladium-Catalyzed *ortho* C−H Arylation of Benzaldehydes Using *ortho*-Sulfinyl Aniline Transient Auxiliary

Delong Mu,[a] Gang He*[a] and Gong Chen*[a,b]

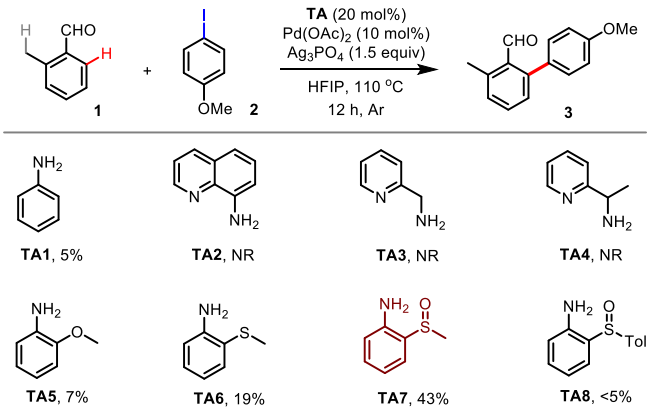
Abstract: A Pd^{II}-catalyzed *ortho*-(Csp^2)−H arylation reaction of benzaldehydes using catalytic amount of 2-methylsulfinyl-aniline as transient auxiliary was developed. This reaction is compatible with a broad range of benzaldehyde and aryl iodide substrates. Compared with other related reaction systems, an excellent regioselectivity for *ortho*-C(sp^2)−H bonds over benzylic C(sp^3)−H bonds was obtained for *ortho*-alkyl-benzaldehyde substrates.

2-Arylbenzaldehyde compounds are frequently encountered in organic synthesis. While various metal-catalyzed cross coupling reactions such as Suzuki−Miyaura coupling have been widely utilized to prepare these compounds,[1] direct *ortho* C−H arylation of benzaldehydes with suitable aryl coupling partners would provide a more streamlined synthetic strategy. Despite the significant advance of metal-catalyzed C−H functionalization chemistry[2, 3], practical method for *ortho* C−H functionalization of benzaldehydes remain challenging due to the relatively weak coordinating ability of aldehyde group.[4] An alternative solution is to convert the carbonyl group into imine or oxime, thus taking advantage of the stronger directing ability of sp^2 nitrogen to facilitate the desired C−H functionalization.[5, 6] However, the need to install and remove the directing group diminishes the overall operational economy. Recently, a more attractive strategy using catalytic amount of amine-based transient auxiliary (TA) has been reported for C−H functionalization of benzaldehydes.[7-9] In these reaction systems, an imine directing group was in situ generated to facilitate metal-catalyzed *ortho* C−H activation and subsequently hydrolyzed to release the functionalized products and the transient auxiliary. For example, Yu[10] and Hu[11] reported palladium-catalyzed C−H arylation reactions of 2-alkyl benzaldehydes using unprotected glycine or acetohydrazone as transient auxiliary respectively (Scheme 1A). Notably, the arylation reactions preferentially take place at the benzylic C(sp^3)−H bonds over the *ortho*-(Csp^2)−H bonds. More recently, Yu reported a protocol for arylation of *ortho*-C(sp^2)−H bond of benzaldehydes using a 2-aminoisobutyric acid transient auxiliary (Scheme 1B)[12]. Herein, we report a new protocol of Pd^{II}-catalyzed *ortho*-C(sp^2)−H arylation reaction of benzaldehydes using a catalytic amount of 2-methylsulfinyl-aniline as transient auxiliary group. A variety of benzaldehydes were arylated in good yields and excellent regioselectivity. An exclusive selectivity for *ortho*-C(sp^2)−H bonds was observed for *ortho*-alkyl-benzaldehyde substrates.



Scheme 1. Pd-catalyzed C−H arylation of benzaldehydes using a transient auxiliary.

We commenced our study by evaluating various alkyl and arylamine-based transient auxiliaries for the arylation reaction of 2-methylbenzaldehyde **1** with 4-iodoanisole **2** in the presence of 10 mol% of $Pd(OAc)_2$ catalyst and 1.5 equiv of Ag_3PO_4 in hexafluoroisopropanol (HFIP) (Scheme 2). The reaction without any additives gave no detectable arylated product **3**. The addition of 20 mol% of plain aniline (**TA1**) formed trace amount of **3**. The



Scheme 2. Evaluation of transient auxiliaries for Pd-catalyzed *ortho*-C(sp^2)−H arylation of benzaldehyde **1**. Yields are based on ^{1}H-NMR analysis of crude reaction mixture on a 0.2 mmol scale using 1,1,2,2-tetrachloroethane as internal standard. NR: no reaction.

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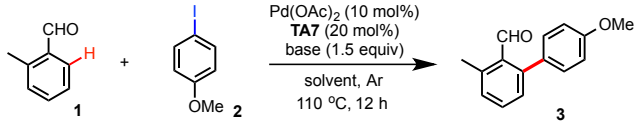
Table 1. Pd-catalyzed *ortho*-C(sp^2)−H arylation of benzaldehyde **1**



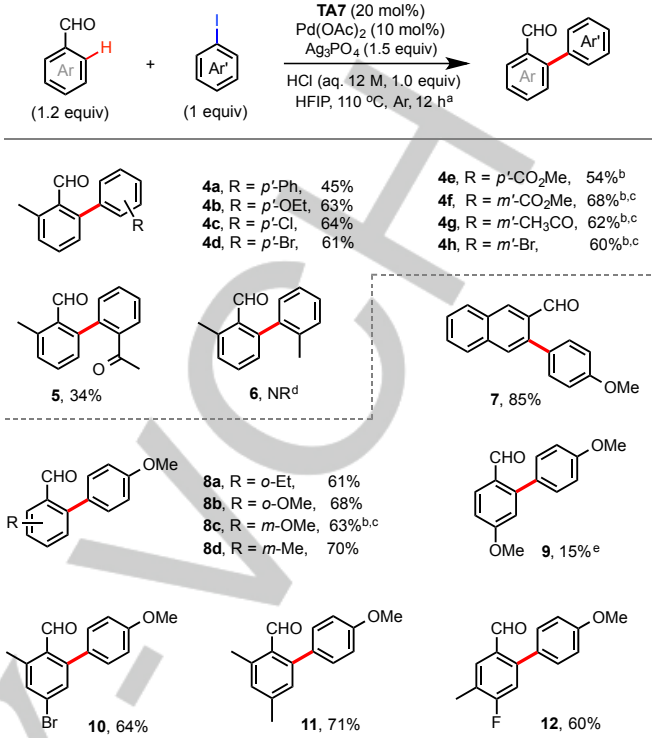
Entry	Base	Additive (equiv)	Solvent	Yield (%)[a]
1	Ag_3PO_4	NONE	HFIP	43
2	Ag_3PO_4	NONE	dioxane	<5
3	Ag_3PO_4	NONE	toluene	<5
4	Ag_3PO_4	NONE	*t*-AmylOH	<5
5	Ag_2CO_3	NONE	HFIP	<5
6	AgOAc	NONE	HFIP	<5
7	AgOTf	NONE	HFIP	<5
8	AgF	NONE	HFIP	6
9	AgOTFA	NONE	HFIP	22
10	K_2CO_3	NONE	HFIP	<5
11	Cs_2CO_3	NONE	HFIP	<5
12	Ag_3PO_4	HCl (12 M, 1.0)	HFIP	80 (75)[b]
13	Ag_3PO_4	HCl (12 M, 2.0)	HFIP	65
14	Ag_3PO_4	H_3PO_4 (1.0)	HFIP	20
15	Ag_3PO_4	HOAc (1.0)	HFIP	18
16	Ag_3PO_4	$ZnCl_2$ (1.0)	HFIP	<5
17	Ag_3PO_4	$FeCl_3$ (1.0)	HFIP	<5

Reaction conditions: **1** (0.24 mmol, 1.2 equiv), **2** (0.2 mmol, 1.0 equiv), **TA7** (0.04 mmol, 0.2 equiv), base (0.3 mmol, 1.5 equiv), solvent (2 mL), 110 °C, Ar, 12 h. [a] Yields are based on ^{1}H-NMR analysis of crude reaction mixture on a 0.2 mmol scale using 1,1,2,2-tetrachloroethane as internal standard. [b] Isolated yield.

use of *N,N*-bidentate compounds **TA2**-**4**, which have demonstrated excellent directing ability in metal-catalyzed C−H functionalization reactions of the corresponding carboxamide substrates, did not give any desired product.[13] We were pleased to find that 2-methylsulfinyl aniline (MSOA, **TA7**) gave the best performance, forming **3** in 43% yield. Interestingly, *ortho*-tolylsulfinyl aniline (TSOA, **TA8**) showed much lower reactivity. In our previous study, we have shown that these two *ortho*-sulfinyl aniline auxiliary group are particularly effective at facilitating Pd-catalyzed β-C(sp^3)-H arylation of the corresponding alkyl carboxamides with sterically hindered aryl iodides.[14, 15]

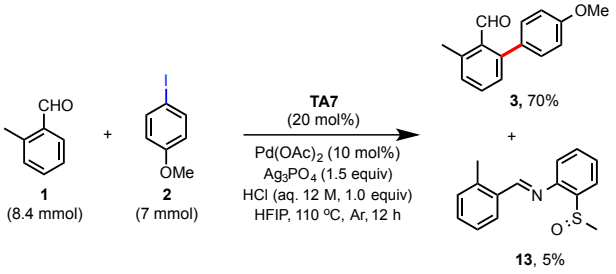
The arylation conditions of **1** with **2** and **TA7** were further optimized (Table 1). Both HFIP solvent and Ag_3PO_4 base were critical to obtain good yield (entries 1-11). Importantly, the addition of 1 equiv of concentrated aqueous HCl solution significantly improved the yield of **3** to 80% (75% isolated yield, entry 12). [10-12] The amount and type of acid was crucial, as the addition of 2 equiv of aq. HCl (entry 13) and other brønsted or Lewis acids (entries 14-17) gave lower yield. Notably, no benzylic C(sp^3)−H arylation side product was observed under the conditions tested above.

With the optimized conditions in hand, we next explored the scope of aryl iodides and benzaldehydes (Scheme 3). Arylation of 2-methylbenzaldehyde **1** with electron rich aryl iodides proceeded well, affording the desired products in moderate to good yields (**4a**, **4b**). Electron deficient aryl iodides showed lower reactivity under the standard conditions; synthetic useful yields could be obtained at slightly higher temperature (**4e**-**4h**). Chloro and bromo groups



Scheme 3. Substrate scope of Pd-catalyzed *ortho*-C(sp^2)−H arylation of benzaldehydes. [a] Isolated yield. [b] 120 °C. [c] benzaldehyde (0.2 mmol, 1.0 equiv), ArI (0.24 mmol, 1.2 equiv). [d] NR: no reaction. [e] 9% of *ortho* di-arylated product and 55% of benzaldehyde starting material were obtained.

on arenes were tolerated (**4c**, **4d**). The steric effect of aryl iodide also has a strong impact on their reactivity. Reaction of **1** with 2-iodoacetophenone gave low yield (**5**). Product **6** with 2-iodotoluene was not observed. As seen in compounds **8a**-**8d**, reactions of 4-iodoanisole **2** with *ortho*- and *meta*-substituted benzaldehydes proceeded smoothly. The arylation of *meta*-substituted benzaldehydes took place at the less hindered position. For unclear reasons, *para*-substituted benzaldehydes showed low reactivity under the standard conditions, forming a mixture of mono- and di-arylated products in low yield along with considerable amount of unreacted starting material (see **9**). Multi-substituted benzaldehydes were compatible (**10**-**12**). 2-Naphthaldehyde was arylated selectively at the C$_3$ position to give **7** in 85% yield.

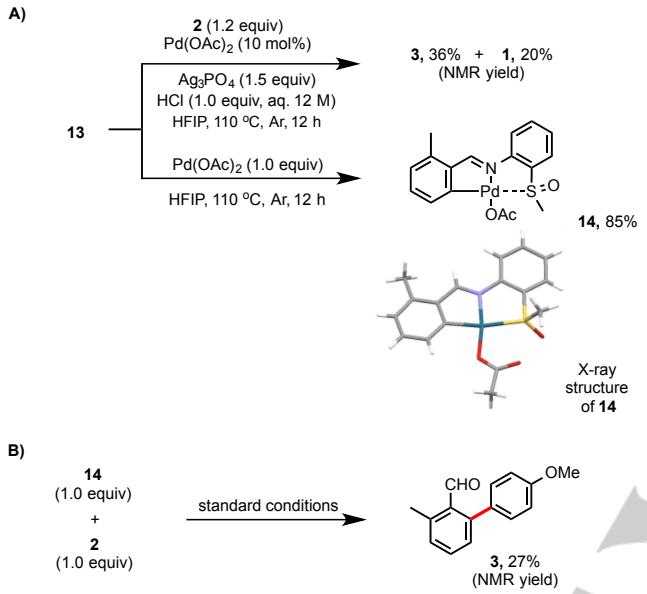


Scheme 4. Scale-up reaction.

As shown in Scheme 4, *ortho*-C(sp^2)−H arylation of **1** with **2** on a 7 mmol scale under our standard conditions gave **3** in 70%

10.1002/asia.201800581

isolated yield along with 5% of imine intermediate **13**. As shown in Scheme 5A, arylation of **13** with 4-iodoanisole **2** gave 36% yield of **3** and 20% of **1** under standard conditions. Heating **13** with 1 equiv of $Pd(OAc)_2$ in HFIP at 110 °C for 12 hours gave the palladacycle intermediate **14** in 85% yield. The structure of **14** was confirmed by X-ray crystallography (see Supporting information for details).[16] Reaction of **14** with 4-iodoanisole **2** under the standard conditions gave **3** in 27% yield along with compounds **13** and **1** (Scheme 5B).



Scheme 5. Mechanistic studies.

A $Pd^{II/IV}$ catalytic cycle has been proposed for the arylation reaction of 2-methylbenzaldehyde **1** with **2**. **1** likely first reacts with 2-methylsulfinyl aniline (**TA7**) to generate an imine intermediate **13**. C−H palladation of **13** directed by the N,S-chelation of imine gives palladacycle intermediate **14**. Oxidative addition of **14** with 4-iodoanisole **2** followed by reductive elimination gives the arylated imine intermediate, which is then hydrolyzed to give the final product **3** and release the transient auxiliary **TA7**.

In summary, we have developed a new protocol for Pd^{II}-catalyzed *ortho*-C(sp^2)−H arylation reaction of benzaldehydes with aryl iodides using a catalytic amount of 2-methylsulfinyl-aniline. The unique electron withdrawing property and metal-coordination ability of the methylsulfinyl group was found critical to the success of this aniline transient auxiliary. Compared with other related reaction systems, an excellent regioselectivity for *ortho*-C(sp^2)−H bonds over benzylic C(sp^3)−H bonds was obtained for *ortho*-alkyl-benzaldehyde substrates.

Experimental Section

A mixture of 2-methylbenzaldehyde **1** (28.8 mg, 0.24 mmol, 1.2 equiv), 4-iodoanisole **2** (46.8 mg, 0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 0.1 equiv), 2-methylsulfinyl aniline **TA7** (6.2 mg, 0.04 mmol, 0.2 equiv), Ag_3PO_4 (125 mg, 0.3 mmol, 1.5 equiv), aq. HCl (12 M, 17 μL, 0.2 mmol, 1.0 equiv) and HFIP (2 mL) was dispersed in a 8 mL vial at room temperature. The vial was purged with Ar and sealed with PTFE cap. The reaction mixture was heated at 110 °C for 12 h. After being cooled to room temperature, the reaction mixture was diluted with EtOAc (3 mL) and filtered through a pad of Celite. The filtrate was concentrated *in vacuo*, and the resulting residue was purified by flash chromatography to give the desired product **3** in 75% yield as a yellow solid (R_f = 0.7, Hexanes:EtOAc = 30:1).

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: C−H arylation • benzaldehyde •2-methylsulfinyl aniline • transient auxiliary • palladium

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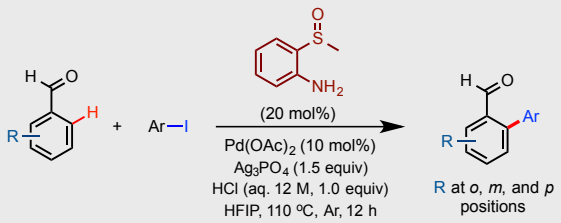

Delong Mu,[a] Gang He[a] and Gong Chen*[a,b]*

Page No. – Page No.

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