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Direct Dehydrogenative Arylation of Benzaldehydes with Arenes Using Transient Directing Groups

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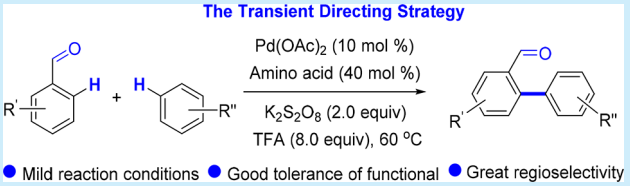
Supporting Information

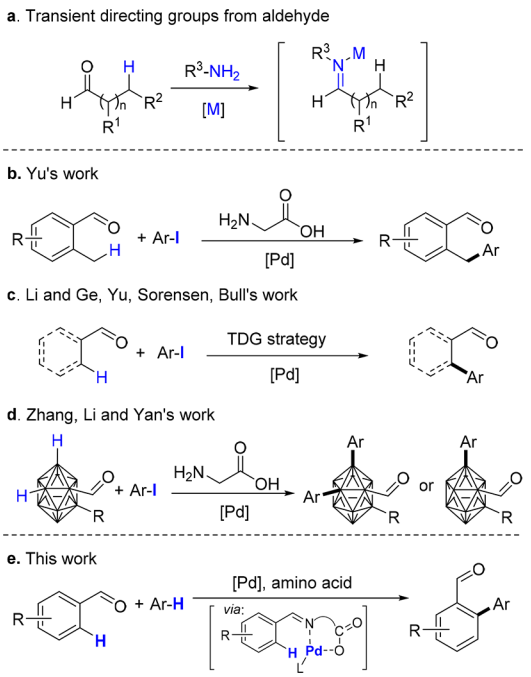
ABSTRACT: The utilization of the transient directing strategy into the direct oxidative dehydrogenative arylation of aldehydes with arenes was reported for the first time. Featured by mild reaction conditions, good functional group compatibility, and great regioselectivity, the method should find broad applications in new medicine and material development and discovery processes.



Aldehyde is a ubiquitous structural unit in biologically active compounds and organic functional materials, and the key intermediate in chemical synthesis.[1] Therefore, the development of direct C−H functionalization with an aldehyde group as a directing group is highly valuable. But such a promising transformation is a challenge due to the aldehyde's susceptibility toward oxidation,[2] undesired metal insertion into an acyl C−H bond,[3] and weak coordinating ability that allow the aldehyde group to be easily outcompeted by a wide range of functional groups, including amide, ester, and even ketone.[4] To address these issues, recently, a significant transient directing group (TDG) strategy, namely, the transient imine formed from the condensation of aldehyde substrate with an amine catalyst as a temporary directing group, was exploited (Scheme 1a).[5,6] With the TDG strategy, Yu reported the first transient imine linkage with α-amino acids to promote β-arylation of aliphatic ketones and benzylic arylation of o-tolualdehydes with aryl iodides as aryl reagents in 2016 (Scheme 1b).[7] Then, Lei and Hu,[8] Li and Ge,[9] Yu,[10] Sorensen,[11] and Bull[12] accomplished the arylations of diverse aldehydes with aryl iodides using different TDGs (Scheme 1c). Very recently, Zhang, Li, and Yan described a B−H arylation of o-carboranyl aldehydes with aryl iodides by the help of glycine to generate a TDG in situ (Scheme 1d).[13] Despite these important advances, all arylations of aldehydes with TDGs reported using highly active aryl iodides as partners via a dehydroiodination process. To the best of our knowledge, the utilization of the transient directing strategy into the direct oxidative dehydrogenative arylation of aldehyde with arene has not been reported to date, although it possesses obvious step- and atom-economical advantages. Herein, we describe the development of direct oxidative dehydrogenative arylation of benzaldehydes with arenes using natural amino acids as TDGs via palladium catalysis (Scheme 1e).

Based on the pioneering research mentioned above, we reasoned that the amino acid could be reversibly condensed with benzaldehyde into an imine.[14] The imine moiety combined with the carboxyl group of the amino acid to form a transient bidentate directing group that bound reversibly to the substrate and the metal center to assist the activation of aryl C−H bond (Scheme 1e).[6] Thus, we estimated that the amino acid would be helpful for the accomplishment of the direct oxidative dehydrogenative arylation of benzaldehydes with arenes. We also realized that an appropriate oxidant was key for avoiding the overoxidation of benzaldehydes and other undesired oxidation reactions, while meanwhile ensuring its

Scheme 1. C−H Arylation of Aldehydes with Transient Directing Groups



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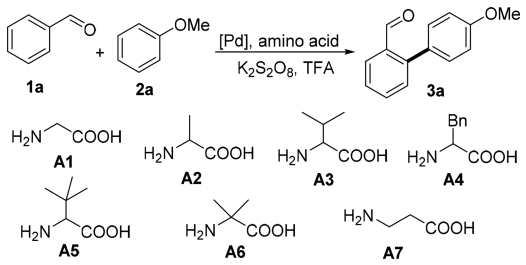
compatibility with the TDG. With these considerations in mind, a palladium-catalyzed oxidative dehydrogenative arylation of benzaldehyde with an arene using the TDG strategy was envisioned.

Initially, we focused on the amino acid screening with simple benzaldehyde (**1a**) and anisol (**2a**) as the model substrates, $Pd(OAc)_2$ as the catalyst, and $K_2S_2O_8$ as the oxidant (Table 1).

Table 1. Optimization of Dehydrogenative Arylation of Benzaldehyde with Anisol[a]



entry	Pd source	amino acid	oxidant	temp (°C)	yield (%)[b]
1[c]	$Pd(OAc)_2$	**A1**	$K_2S_2O_8$	70	0
2[d]	$Pd(OAc)_2$	**A1**	$K_2S_2O_8$	70	30
3[d]	$Pd(OAc)_2$	**A2**	$K_2S_2O_8$	70	42
4[d]	$Pd(OAc)_2$	**A3**	$K_2S_2O_8$	70	43
5[d]	$Pd(OAc)_2$	**A4**	$K_2S_2O_8$	70	23
6[d]	$Pd(OAc)_2$	**A5**	$K_2S_2O_8$	70	54
7[d]	$Pd(OAc)_2$	**A6**	$K_2S_2O_8$	70	57
8[d]	$Pd(OAc)_2$	**A7**	$K_2S_2O_8$	70	35
9[d]	$Pd(OAc)_2$	**A6**	$K_2S_2O_8$	60	58
10[e]	$Pd(OAc)_2$	**A6**	$K_2S_2O_8$	60	63
11[e]	$Pd(TFA)_2$	**A6**	$K_2S_2O_8$	60	53
12[e]	$PdCl_2$	**A6**	$K_2S_2O_8$	60	57
13[e]	PdI_2	**A6**	$K_2S_2O_8$	60	10
14[e]	$Pd(PPh_3)_2Cl_2$	**A6**	$K_2S_2O_8$	60	40
15[e]	$Pd(OH)_2$	**A6**	$K_2S_2O_8$	60	15
16[e]	$Pd(OAc)_2$	**A6**	$Na_2S_2O_8$	60	20
17[e]	$Pd(OAc)_2$	**A6**	$(NH_4)_2S_2O_8$	60	34
18[e]	$Pd(OAc)_2$	**A6**	BQ	60	trace
19[e]	$Pd(OAc)_2$	**A6**	$PhI(OAc)_2$	60	10
20[e]	$Pd(OAc)_2$	**A6**	Ag_2CO_3	60	trace
21[e]	$Pd(OAc)_2$	**A6**	O_2[f]	60	trace
22[e,g]	$Pd(OAc)_2$	AcOH	$K_2S_2O_8$	60	0
23[e,h]	$Pd(OAc)_2$	*n*-$C_4H_9NH_2$	$K_2S_2O_8$	60	0
24[e,i]	$Pd(OAc)_2$	AcOH + *n*-$C_4H_9NH_2$	$K_2S_2O_8$	60	trace

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.5 mL, 4.6 mmol), [Pd] (10 mol %), amino acid (40 mol %), oxidant (0.4 mmol), for 24 h. [b]Isolated yield. [c]0.5 mL of AcOH was added, without TFA. [d]5.0 equiv of TFA was used. [e]8.0 equiv of TFA was used. [f]O_2 (1 atm). [g]AcOH (40 mol %). [h]*n*-$C_4H_9NH_2$ (40 mol %). [i]AcOH (40 mol %) + *n*-$C_4H_9NH_2$ (40 mol %). BQ: *p*-benzoquinone.

Glycine **A1** was first investigated with acetic acid as an additive at 70 °C. Unfortunately, there was no obvious reaction observed (entry 1). Considering that trifluoroacetic acid (TFA) and $Pd(OAc)_2$ can facilitate the generation of more active $[Pd(II)O_2CCF_3]^+$ species in situ,[15] the same reaction was set up again just with TFA (5 equiv) instead of acetic acid. To our delight, the reaction gave the desired product **3a** in 30% yield (entry 2). Then the effect of the amino acid structure was tested with TFA as the additive. While α-amino acids **A1**−**A4** gave similar results, quaternary amino acids **A5** and **A6** proved to be the better TDGs, with the latter being the best one (entries 3−7). A β-amino acid **A7** was also tested providing an inferior result (entry 8). Recently, Yu reported a Pd-catalyzed olefination of arenes using 2-pyridone as the ligand to promote the reaction. Therefore, the reaction was carried out with 2-pyridone or 3-(trifluoromethyl)-2-pyridone instead of an amino acid, but no reaction occurred [see Supporting Information (SI)]. Reducing the loading of **A6** led to a slow reaction, while increasing the loading of **A6** did not improve the yield evidently (see SI). Temperature had a noticeable effect on the reaction, and 60 °C was preferred (entry 9; see SI). Next, the amount of TFA was investigated, and 8 equiv of TFA gave the best result (entry 10; see SI). By using other palladium sources, oxidants, and amounts of $K_2S_2O_8$, the same reaction proceeded but less efficiently (entries 11−20; see SI). It should be mentioned that reaction efficiency was obviously affected when the air atmosphere was replaced by an oxygen or argon atmosphere. A series of control experiments were also conducted. The reaction did not proceed in the absence of the $Pd(OAc)_2$, **A6**, or TFA. Significantly, acetic acid and *n*-butyl amine respectively did not give any product, and a simple mixture of acetic acid and butyl amine only provided trace product (entries 22−24). These results confirmed the importance of the bidentate chelation mode of the imine and carboxyl moieties in **A6**. Accordingly, the reaction conditions were optimized as follows: $Pd(OAc)_2$ (10 mol %), amino acid **A6** (40 mol %), TFA (8.0 equiv) at 60 °C.

With the optimal reaction conditions in hand, the direct oxidative dehydrogenative arylation was applied to different benzaldehydes and arenes (Scheme 2). First, the scope of benzaldehydes was tested with **2a** as the partner. Benzaldehydes bearing substituents at the *otho*-, *meta*-, or *para*-positions smoothly underwent dehydrogenative arylation with **2a** to provide the products (**3a**−**3p**) in good yields. Both electron-withdrawing (**3b**−**3d**, **3g**−**3m**) and electron-donating substituents (**3e**, **3f**, **3n**−**3p**) were well tolerated, and their reactivities did not show a significant difference. A broad range of substituent groups with diverse steric and electronic properties (ether, alkyl, halide, ester, and nitro groups) were compatible with this procedure, and could be versatile handles for further transformations. Particularly noticeable is the performance of *p*-iodobenzaldehyde (**1l**) in the reaction. Based on the literature,[10,11] the carbon center bearing I is also a possible arylation site (via dehydroiodination homocoupling of benzaldehyde). Surprisingly, it only provided the cross-dehydrogenative coupling product (**3l**) in good yield. Interestingly, disubstituted benzaldehydes and naphthyl aldehydes were also suitable substrates for the reaction to give the corresponding products (**3q**−**3t**) in good yields. It should be mentioned that all reactions possessed complete *ortho*-position selectivity for benzaldehyde and *para*-position selectivity for anisole, and no product at other positions could be detected on analyzing the reaction mixtures. The structures of **3j**, **3k**, and **3l** were confirmed by single-crystal X-ray diffraction (see SI).

Next, the scope of arenes was tested (Scheme 3). Considering *meta*-bromide benzaldehyde **1g** possessed more broad utility in the further transformation, it was chosen as the arylation substrate. Arenes bearing alkyl (Me, Et, *i*-Pr, and Ph; **2v**−**2y**), ether (OEt and OPh; **2z** and **2aa**), and halides (F and Cl; **2bb** and **2cc**) all reacted smoothly, affording the corresponding products in good yields. Disubstituted arenes were also effective substrates to give dehydrogenative arylation

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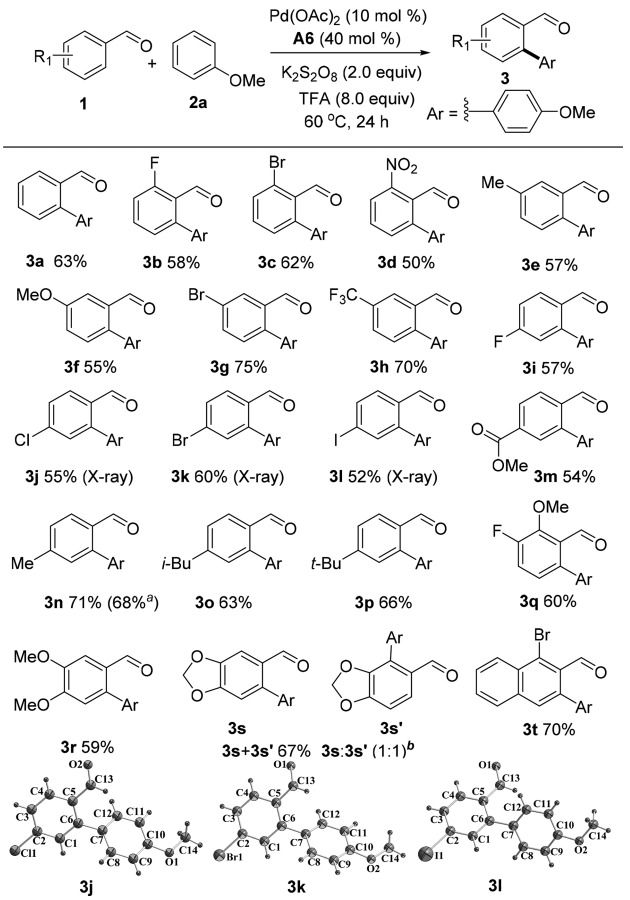
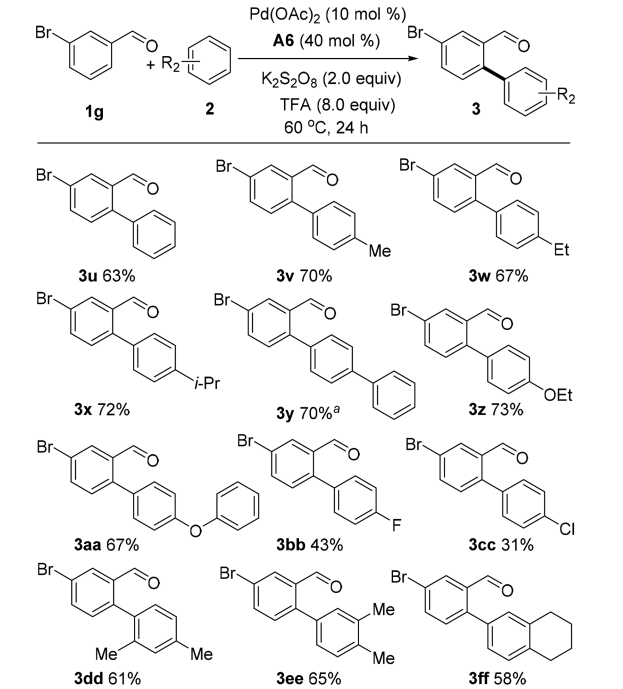
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Scope of Aldehydes



[a]1.0 mmol of **1n** was used. [b]The isomers **3s** and **3s′** were not separable by column chromatography

Scheme 3. Scope of Arenes

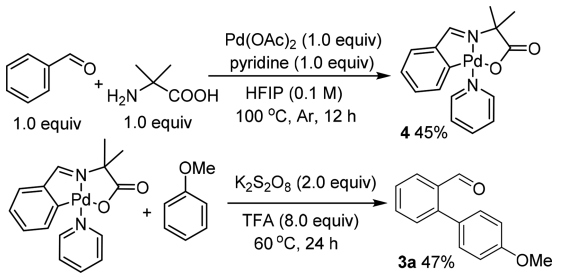


[a]At 90 °C.

products in nice yields (**3dd**–**3ff**). It is worthwhile to note that, without a directing group, the site-selective C–H functionalization of monosubstituted arenes is generally rather troublesome,[4c,16] while this reaction presented completely *para*-position selectivity for monosubstituted arenes substrates. At present, heteroarenes, such as thiophene, indole, and pyrole, as arylation reagents, could not afford satisfactory results, and a large excess of arenes were used in the reaction. Futher studies on the heteroarenes as the substrate and reducing the amount of arenes are underway.

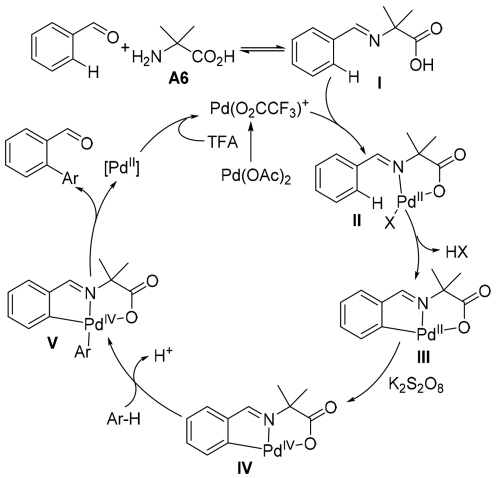
To gain insight into the reaction mechanism, we carried out a capture experiment of the cyclopalladated intermediate (Scheme 4). Pleasingly, cyclopalladated intermediate **4** was

Scheme 4. Isolation and Subsequent Arylation of Palladacycle 4



isolated from the reaction of benzaldehyde with a stiochiometric amount of $Pd(OAc)_2$, **A6**, and pyridine.[5b,6c] The intermediate was then treated with anisole, $K_2S_2O_8$, and TFA to give **3a** in 47% yield. On the basis of these results and the related literature, a tentative mechanism for the directoxidative dehydrogenative arylation of benzaldehydes with arenes is proposed as shown in Scheme 5. We propose that the first step

Scheme 5. Proposed Mechanism



is acid-promoted reversible formation of imine intermediate **I** from benzaldehyde and **A6**.[11] Simultaneously, the active $Pd(O_2CCF_3)^+$ is generated in situ by the treatment of $Pd(OAc)_2$ with TFA.[15] Coordination of an α-imino acid to a palladium species generates palladium complex **II**.[5d] An intramolecular C–H palladation of intermediate **II** gives rise to the five-membered ring intermediate **III**, probably via a concerted metalation–deprotonation (CMD) process.[17] The oxidation of intermediate **III** by persulfate gives Pd(IV) species

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Org. Lett. XXXX, XXX, XXX–XXX

IV,[4f,18] which is arylated by arene to afford intermediate **V**, and then the following reductive elimination resulted in product formation and Pd catalyst regeneration.

In summary, the transient directing strategy was successfully utilized in the direct oxidative dehydrogenative arylation of aldehydes with arenes for the first time. Featured by mild reaction conditions, good functional group compatibility, and great regioselectivity, the method should find broad applications in new medicine and material development and discovery processes. Detailed mechanism and application studies are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00292.

Experimental procedures and spectral data (PDF)

Accession Codes

CCDC 1812842 and 1812861−1812862 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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Org. Lett. XXXX, XXX, XXX−XXX