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Catalytic C−H Arylation of Aliphatic Aldehydes Enabled by a Transient Ligand

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Supporting Information

ABSTRACT: The direct arylation of aliphatic aldehydes has been established via Pd-catalyzed sp^3 C−H bond functionalization in the presence of 3-aminopropanoic acids as transient directing groups. The reaction showed excellent functional group compatibility and chemoselectivity in which a predominant preference for functionalizing unactivated β-C−H bonds of methyl groups over others was achieved. In addition, C−H bonds of unactivated secondary sp^3 carbons can also be functionalized. The extreme popularity and importance of aliphatic aldehydes would result in broad applications of this novel method in organic chemistry and medicinal sciences.

Transition-metal-catalyzed carbon−hydrogen bond functionalization is one of most efficient tools for selective carbon−carbon and carbon−heteroatom bond constructions in organic chemistry. Toward the development of synthetically invaluable methods, two principal challenges arise in this approach: the inert feature of most C−H bonds and site selectivity in reactions with multiple analogous C−H bonds. To address these issues, chemists have typically relied on the use of substrates that contain various directing groups.[1] The reactivity of the C−H bonds as well as the positional selectivity can be greatly promoted by the close proximity of C−H bonds to the metal centers. In the past decade, great progress on transition-metal-catalyzed selective activation of either $C(sp^2)$−H or $C(sp^3)$−H bonds has been achieved by using directing groups on substrates,[2,3] but this approach includes limitations. Additional steps are required for the preconstruction of the substrates and for removal of the directing groups, which diminishes the efficiency and compatibility of the reactions.

A promising solution to this problem would be to introduce a well-designed temporary directing group that binds reversibly to the substrate and the metal center. In the process, the desired site-selective activation would be accomplished with a catalytic amount of this transient directing group without changing the substrate function after the catalysis is finished. Some early pioneering strategies by utilizing reversibly formed covalent bonds have proven to be successful.[4] Jun and co-workers reported Rh-catalyzed functionalization of aldehyde C−H bonds using 2-aminopyridine as the transient directing group.[5] Besides, selective $C(sp^2)$−H functionalizations of phenols, alcohols, anilines, or sulfonamides have also been realized with a catalytic amount of phosphinite ligands through reversible transesterification.[6,7] Recently, Mo and Dong showed that the addition of ketone α-$C(sp^3)$−H bonds to olefins can be performed by rhodium(I) catalysis with a catalytic transient directing group.[8] In the proposed catalytic cycle, a rationally designed secondary amine containing a pyridine moiety reacts with the ketone substrate to form an enamine and simultaneously coordinates the low-valent rhodium complex. Thus, the ketone α sp^3 C−H bond can be converted into a more reactive sp^2 C−H bond, while the insertion of the rhodium into this C−H bond is facilitated by the directing group. Despite the success in Rh(I)-catalyzed sp^2 C−H activation reactions, the direct functionalization of unactivated sp^3 C−H bonds with transient directing groups has remained a big challenge. In a very recent report, Yu and co-workers described the palladium-catalyzed arylation of *o*-alkyl benzaldehydes and ketones with catalytic amounts of natural amino acids, but aliphatic aldehydes failed in their system.[9]

Aliphatic aldehydes are ubiquitous structural units in biologically active natural products and pharmaceuticals, and the key intermediates in chemical synthesis.[10] Therefore, the derivatization of aliphatic aldehydes has attracted much attention in the organic community. Methods for the functionalization at the *ipso*- and α-positions of C═O moieties have been well documented.[11] The β-functionalization of aliphatic aldehydes relies primarily on the addition of soft nucleophiles to α,β-unsaturated aldehydes which often requires prefunctionalization of the saturated precursors.[12] But the direct β-functionalization of aliphatic aldehydes is rare. In 2011, Wang et al. reported the enantioselective β-functionalization of simple aldehydes in the presence of a simple chiral amine catalyst and the nontoxic oxidant IBX, involving a sequential enamine formation, oxidation, and nucleophilic addition process (Scheme 1A).[13] Very recently, MacMillan et al. developed the direct functionalization of unactivated β-C−H bonds of aliphatic aldehydes by merging the organocatalysis and photoredox catalysis; and electron-deficient (hetero)arenes and Michael acceptors proven to be effective substrates in the process (Scheme 1B).[14] In our continuous efforts to develop efficient C−H functionalization

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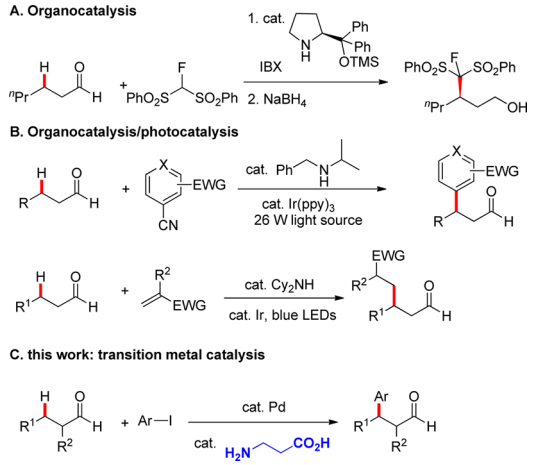
Scheme 1. Direct β-Functionalization of Aliphatic Aldehydes

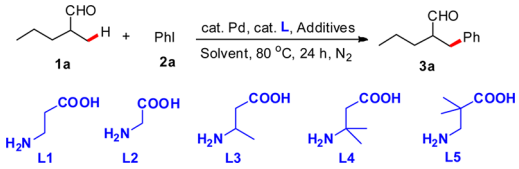


processes, here we report the Pd-catalyzed arylation of unactivated β-C−H bonds of aliphatic aldehydes with 3-aminopropanoic acids as novel transient directing groups (Scheme 1C).

Very recently, our group discovered the palladium-catalyzed direct γ-arylation of primary amines with glyoxylic acid as a transient directing group and acetic acid as the solvent.[15] On the basis of this study, we commenced our investigation on the cross coupling of 2-methylpentanal (**1a**) and iodobenzene (**2a**) in the presence of catalytic $Pd(OAc)_2$ and stoichiometric amounts of AgTFA with 3-aminopropanoic acid (**L1**) as a transient directing group at 80 °C (Table 1). Initial solvent screening showed that the desired arylated product **3a** could be obtained in AcOH, TFE or HFIP (entries 1−3). It was then noticed that the reaction was significantly improved with HFIP and AcOH as the cosolvent at the volume ratio of 5:1 (entries 4−6). Next, the effect on selected ligands toward the process was examined. It turned out that the reaction failed with natural amino acid glycine (**L2**) as the ligand, indicating a [5,5]-bicyclic palladium intermediate is not suitable in this process (entry 7). In contrast, all substituted 3-aminopropanoic acids **L3**-**L5** led to the formation of the desired arylated product **3a**, albeit with lower efficiency compared with **L1** (entries 8−10). Then, the examination on different palladium catalysts revealed that this reaction can also be catalyzed by $PdCl_2$, $Pd(TFA)_2$ or $Pd(acac)_2$ with moderate yields (entries 11−13). Following the above investigation, the screening of silver salts was conducted, and a low yield was observed with AgF, AgF_2, or AgOAc (entries 14−16). Interestingly, a lower yield was observed with either increased or decreased loading of the ligand **L1** (entries 17 and 18). To our delight, the isolated yield was improved to 71% by increasing the reaction concentration from 0.1 M to about 0.14 M (entry 19). It is noteworthy that no desired product **3a** was obtained in the absence of a silver salt or ligand (entries 20 and 21).

Next, we carried out the substrate scope study of aliphatic aldehydes under the optimized reaction conditions. As shown in Table 2, α-methyl-α-alkyl substituted acetaldehyde derivatives provided the corresponding products in good yields with excellent site selectivity (**3a**−**g**). In all cases, the functionalization of the β-C−H bonds of α-methyl groups is predominantly favored over γ- or δ-C−H bonds of the methyl groups, indicating that the kinetic barrier toward functionalizing the β-C−H bond is lower than the γ- or δ-C−H bond. It was also found that with isobutyraldehyde employed as the substrate, both β-mono- and

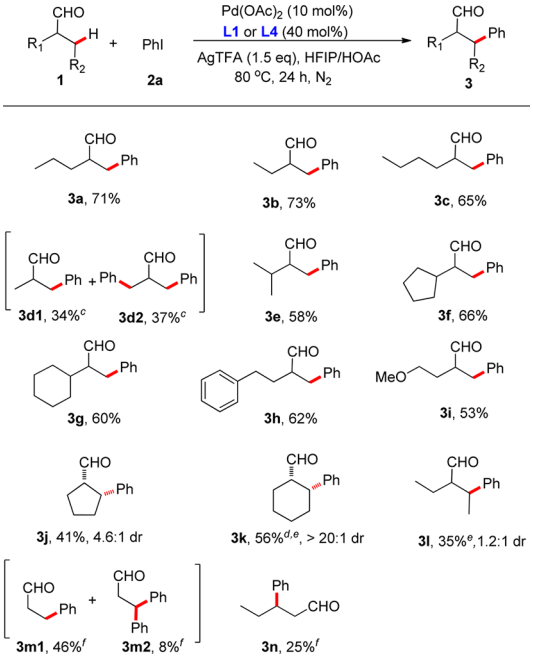
Table 1. Optimization of Reaction Conditions



entry	Pd source	Ligand(mol%)	Additives	Solvent	Yield(%)[b]
1	$Pd(OAc)_2$	**L1** (40)	AgTFA	AcOH	16
2	$Pd(OAc)_2$	**L1** (40)	AgTFA	TFE	6
3	$Pd(OAc)_2$	**L1** (40)	AgTFA	HFIP	29
4	$Pd(OAc)_2$	**L1** (40)	AgTFA	HFIP/AcOH (1/1, v/v)	45
5	$Pd(OAc)_2$	**L1** (40)	AgTFA	HFIP/AcOH (3/1, v/v)	53
6	$Pd(OAc)_2$	**L1** (40)	AgTFA	HFIP/AcOH (5/1, v/v)	63
7	$Pd(OAc)_2$	**L2** (40)	AgTFA	HFIP/AcOH (5/1, v/v)	0
8	$Pd(OAc)_2$	**L3** (40)	AgTFA	HFIP/AcOH (5/1, v/v)	38
9	$Pd(OAc)_2$	**L4** (40)	AgTFA	HFIP/AcOH (5/1, v/v)	21
10	$Pd(OAc)_2$	**L5** (40)	AgTFA	HFIP/AcOH (5/1, v/v)	37
11	$PdCl_2$	**L1** (40)	AgTFA	HFIP/AcOH (5/1, v/v)	48
12	$Pd(TFA)_2$	**L1** (40)	AgTFA	HFIP/AcOH (5/1, v/v)	54
13	$Pd(acac)_2$	**L1** (40)	AgTFA	HFIP/AcOH (5/1, v/v)	55
14	$Pd(OAc)_2$	**L1** (40)	AgF	HFIP/AcOH (5/1, v/v)	44
15	$Pd(OAc)_2$	**L1** (40)	AgF_2	HFIP/AcOH (5/1, v/v)	27
16	$Pd(OAc)_2$	**L1** (40)	AgOAc	HFIP/AcOH (5/1, v/v)	5
17	$Pd(OAc)_2$	**L1** (60)	AgTFA	HFIP/AcOH (5/1, v/v)	50
18	$Pd(OAc)_2$	**L1** (20)	AgTFA	HFIP/AcOH (5/1, v/v)	47
19[c]	$Pd(OAc)_2$	**L1** (40)	AgTFA	HFIP/AcOH (5/1, v/v)	75(71)[d]
20[c]	$Pd(OAc)_2$	**L1** (40)	-	HFIP/AcOH (5/1, v/v)	0
21[c]	$Pd(OAc)_2$	-	AgTFA	HFIP/AcOH (5/1, v/v)	0

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), Pd source (0.03 mmol), ligand, additives (0.45 mmol), solvent (3 mL), 80 °C, N_2, 24 h. [b]Yields are based on **1a**, determined by ^1H NMR using dibromomethane as the internal standard. [c]HFIP (1.8 mL), HOAc (0.36 mL). [d]Isolated yields.

Table 2. Scope of Aliphatic Aldehydes[a]



[a]Reaction conditions: **1** (0.3 mmol), **2a** (0.45 mmol), $Pd(OAc)_2$ (0.03 mmol), AgTFA (0.45 mmol), **L1** (0.12 mmol), HFIP (1.8 mL), HOAc (0.36 mL), 80 °C, N_2, 24 h. [b]Isolated yields. [c]HFIP (2.25 mL), HOAc (0.75 mL). [d]**2a** (0.6 mmol). [e]36 h. [f]**L4** (0.12 mmol), 100 °C.

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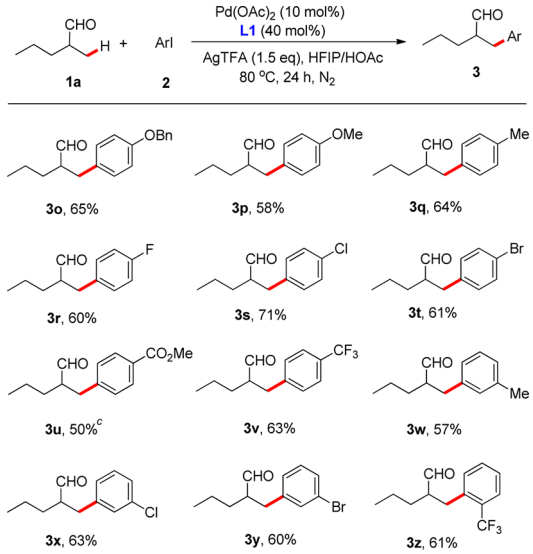
β,β'-diphenyl substituted products were generated (**3d**). This result suggests that the reaction was performed with a great preference for functionalizing the sp^3 β-C−H bond of the methyl group over the relatively reactive benzylic β-C−H bond. In addition, cyclic sp^3 C−H bonds were functionalized with high site selectivity and stereoselectivity, providing the *cis*-isomers as the major products (**3j** and **3k**). Furthermore, selective functionalization of a β-C−H bond of a methylene group was also achieved in the presence of a γ-C−H bond of a methyl group (**3l**). Moreover, unactivated methyl and methylene β-C−H bonds of linear aliphatic aldehydes could also be arylated with iodobenzene by using 3-amino-3-methylbutanoic acid (**L4**) as a transient directing group (**3m** and **3n**).

We then examined the substrate scope of aryl iodides. As shown in Table 3, great functional group compatibility was

Table 3. Scope of Aryl Iodides[a]

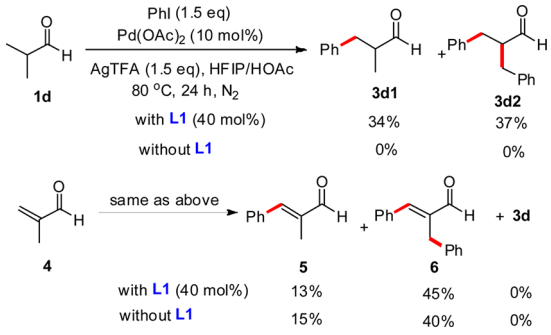


[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.45 mmol), $Pd(OAc)_2$ (0.03 mmol), AgTFA (0.45 mmol), **L1** (0.12 mmol), HFIP (1.8 mL), HOAc (0.36 mL), 80 °C, N_2, 24 h. [b]Isolated yields. [c]105 °C, 36 h.

observed in this catalytic process. Iodobenzene substituted with an electron-donating group (alkoxyl or alkyl) or moderate or strong electron-withdrawing group (ester or CF_3) were all compatible with the current catalytic system. In addition, halogens (F, Cl, or Br) were well tolerated, enabling the further manipulation of the initial products. It was also noticed that there is no an apparent electronic effect in the process.

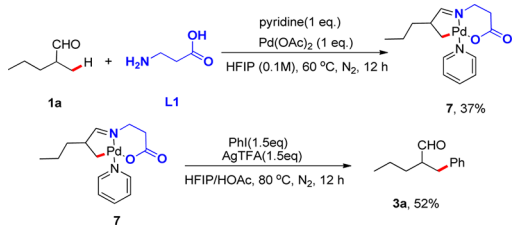
To provide some insights into the reaction mechanism, a series of control experiments were carried out (Scheme 2). It has been demonstrated that aliphatic carbonyl compounds could undergo dehydrogenation to produce the corresponding α,β-unsaturated derivatives. Therefore, a sequential oxidation/addition process would not be excluded in this reaction.[16] To clarify this, cross-coupling of methacrylaldehyde (**4**) and iodobenzene was examined under the current conditions. 2-Methyl-3-phenylacrylaldehyde (**5**) and 2-benzyl-3-phenylacrylaldehyde (**6**) were obtained in 13% and 45% yield, respectively, while the direct sp^3 C−H arylation product (**3d**) was not observed. Notably, similar results were also obtained in the absence of ligand **L1**. Additionally, we examined the reaction of isobutyraldehyde (**1d**) and iodobenzene without ligand **L1** under the current conditions, and no desired products (**3d**) were observed. These

Scheme 2. Control Experiments



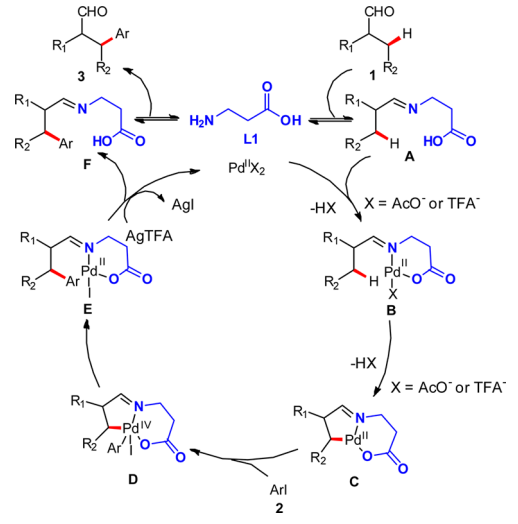
outcomes suggest that dehydrogenation of aliphatic aldehydes is not involved in the formation of the desired products. In order to further illustrate the reaction mechanism, the bicyclic palladium intermediate **7** was captured from the reaction of 2-methylpentanal with 3-aminopropanoic acid in the presence of stoichiometric amounts of $Pd(OAc)_2$ and 1 equiv of pyridine.[15,17] Next, the desired arylated product **3a** was isolated in 52% yield using the intermediate **7** and iodobenzene under the arylation conditions (Scheme 3).

Scheme 3. Synthesis of Bicyclic Palladium Intermediate 7 and Subsequent Arylation



On the basis of the above results and the previous literature reports,[9,15,18] a plausible reaction pathway of this process is proposed as shown in Scheme 4. Condensation of aliphatic aldehyde **1** with the ligand 3-aminopropanoic acid provides the imine intermediate **A**. Coordination of the imine intermediate **A** to a palladium species produces the corresponding six-member cyclic palladium complex **B**. Next, the cyclometalation gives rise

Scheme 4. Plausible Reaction Mechanism



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to a [5,6]-bicyclic palladium intermediate **C** via a site-selective C−H bond activation process, and oxidative addition of the intermediate **C** with an aryl iodide generates the palladium(IV) species **D**. Finally, reductive elimination of the palladium complex **D** followed by the ligand dissociation and iodide abstraction processes gives the β-imino acid **F**, which releases the desired product **3**, and ligand 3-aminopropanoic acid.

In summary, a highly site-selective arylation reaction of an aliphatic aldehyde with an aryl iodide was developed via a palladium-catalyzed sp^3 C−H bond functionalization process with 3-aminopropanoic acid as a novel transient directing group. A great preference for functionalizing unactivated β-sp^3 C−H bonds of methyl groups over the unactivated β-methylene, γ- or δ-terminal C−H bonds was observed. In addition, the cyclic aldehydes could be functionalized in a diastereoselective manner by favoring the *cis* products. Furthermore, the direct C−H functionalization of unactivated secondary β-C−H bonds has also been achieved, albeit with lower efficiency. Moreover, good functional group compatibility was observed in the process, and both electron-rich and electron-deficient aromatic rings can be efficiently incorporated into the aliphatic aldehydes in a highly site-selective manner. Considering the vital importance of aliphatic aldehyde in organic and pharmaceutical research, this reaction would have great potential for broad applications in organic and medicinal chemistry. The detailed mechanistic studies and synthetic applications of this process are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08478.

Experimental details and compound characterizations (PDF)

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Notes

The authors declare no competing financial interest.

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