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View Article Online
DOI: 10.1039/C8CC00980E

Journal Name

COMMUNICATION

Palladium-Catalyzed Site-Selective Arylation of Aliphatic Ketones Enabled by A Transient Ligand

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Lei Pan[a†], Ke Yang[a,b†], Guigen Li[b,c]* and Haibo Ge[a]*

Transition metal-catalyzed direct C–H bond functionalization enabled by transient ligands has become an attractive topic. Here we report a palladium-catalyzed site-selective arylation of β-C(sp^3)–H bonds in aliphatic ketones with β-alanine as the transient ligand.

Aliphatic ketones are key intermediates in chemical synthesis and ubiquitous structural units in biologically active natural products and pharmaceuticals, such as the marketed drugs nabumetone[1], warfarin[2] and loxoprofen[3] (Figure 1). Among various synthetic methods for aliphatic ketones, transition metal-catalyzed C–H bond functionalization has become one of the most efficient tactics in organic synthesis. In the past decade, the auxiliary group-based strategy has been extensively explored to achieve a series of C–H bond functionalization reactions with high site-selectivity[4]. Despite the great progress has been made in this area, this approach is still far from satisfaction because installation and removal of the directing ligands on substrates add additional synthetic steps, and thus diminish the overall efficiency of the reaction process. For this reason, the development of novel and powerful methodologies without attaching an internal directing group is highly desirable.

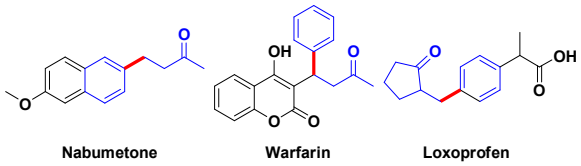
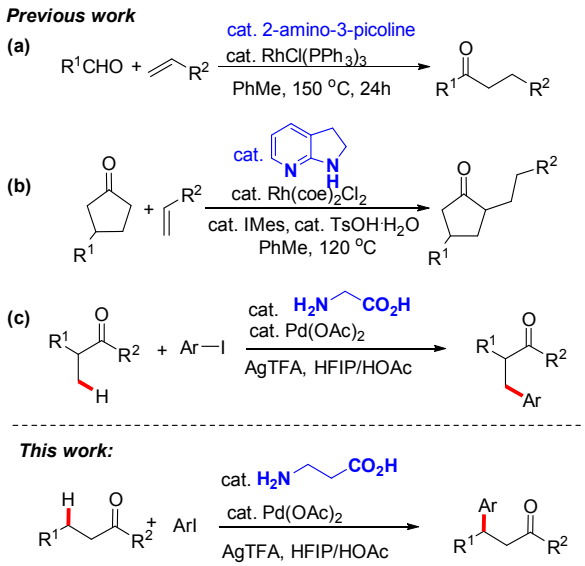


Figure 1. Selected examples of biologically active drugs.



Scheme 1. Transition metal-catalyzed C–H bond functionalization of aldehydes/ketones enabled by transient ligands.

A strategy based on the *in situ* generated directing groups has proven successful in transition metal-catalyzed C–H bond functionalization reactions. In 1997, Jun's group demonstrated for the first time the Rh(I)-catalyzed functionalization of C–H bonds of aldehydes by employing 2-amino-3-picoline as a transient ligand (Scheme 1a)[5]. Recently, Dong's group established a novel Rh(I)-catalyzed alkylation process of ketones with a secondary amine as a transient ligand (Scheme 1b)[6]. In the meanwhile, the use of catalytic amounts of

[a] Department of Chemistry and Chemical Biology, Indiana University-Purdue University Indianapolis, Indianapolis, IN 46202, USA.

[b] Institute of Chemistry & BioMedical Sciences, Nanjing University, Nanjing 210093, P. R. China.

[c] Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX 79409-1061, USA.

† They contributed equally to this research.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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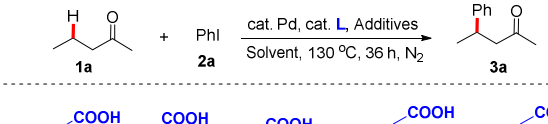
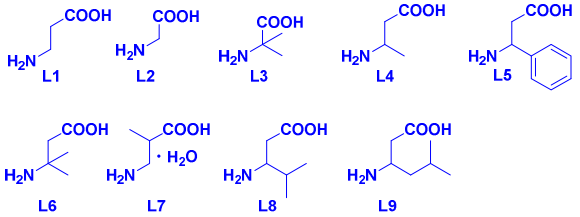
DOI: 10.1039/C8CC00980E

phosphinite ligands was also proven effective in Rh(I)-catalyzed selective C–H functionalization of phenols, alcohols and anilines[7]. However, the catalytic site-selective functionalization of unactivated C(sp^3)–H bonds is a challenge process[8]. Very recently, Yu and co-workers established the Pd-catalyzed arylation of *o*-alkyl benzaldehydes and aliphatic ketones with α-amino acids as transient ligands (Scheme 1c)[8a]. In spite of a powerful approach, this method suffers from a restricted substrates scope, and only terminal -C(sp^3)–H bonds could be functionalized with linear ketones. On the basis of previous study in our group, herein we report a palladium-catalyzed arylation of unactivated β-methylene C–H bonds of aliphatic ketones with 3-aminopropanoic acid as the transient ligand[9].

Table 1. Optimization of Reaction Conditions[a]



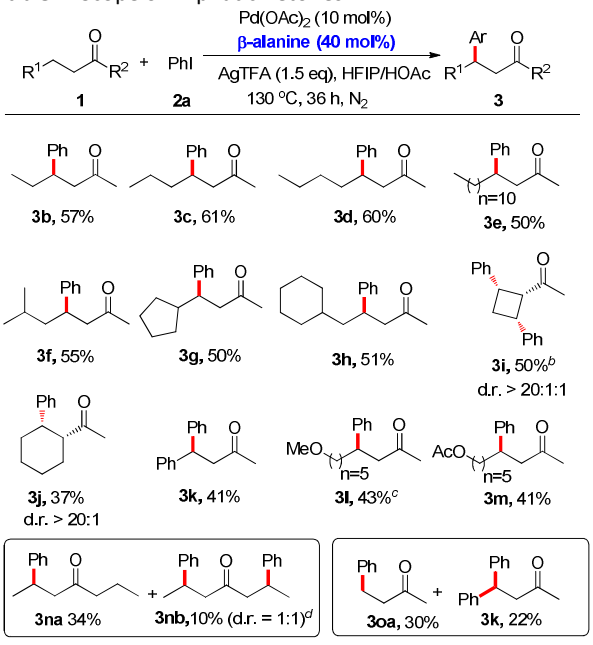


Entry	Pd source	Ligand	Additives	Solvent	Yield(%)[b]
1	$Pd(OAc)_2$	**L1**	AgTFA	AcOH	5
2	$Pd(OAc)_2$	**L1**	AgTFA	HFIP	15
3	$Pd(OAc)_2$	**L1**	AgTFA	HFIP/AcOH (1/1, v/v)	43
4	$Pd(OAc)_2$	**L1**	AgTFA	HFIP/AcOH (1/3, v/v)	44
5	$Pd(OAc)_2$	**L1**	AgTFA	HFIP/AcOH (3/1, v/v)	70(62)[d]
6	$Pd(OAc)_2$	**L2**	AgTFA	HFIP/AcOH (3/1, v/v)	15
7	$Pd(OAc)_2$	**L3**	AgTFA	HFIP/AcOH (3/1, v/v)	trace
8	$Pd(OAc)_2$	**L4**	AgTFA	HFIP/AcOH (3/1, v/v)	12
9	$Pd(OAc)_2$	**L5**	AgTFA	HFIP/AcOH (3/1, v/v)	4
10	$Pd(OAc)_2$	**L6**	AgTFA	HFIP/AcOH (3/1, v/v)	53
11	$Pd(OAc)_2$	**L7**	AgTFA	HFIP/AcOH (3/1, v/v)	5
12	$Pd(OAc)_2$	**L8**	AgTFA	HFIP/AcOH (3/1, v/v)	10
13	$Pd(OAc)_2$	**L9**	AgTFA	HFIP/AcOH (3/1, v/v)	21
14	$Pd(OAc)_2$	**L1**	AgOAc	HFIP/AcOH (3/1, v/v)	54
15	$Pd(OAc)_2$	**L1**	Ag_2CO_3	HFIP/AcOH (3/1, v/v)	30
16	$Pd(OAc)_2$	**L1**	Ag_2O	HFIP/AcOH (3/1, v/v)	32
17	$Pd(TFA)_2$	**L1**	AgTFA	HFIP/AcOH (3/1, v/v)	54
18	$PdCl_2$	**L1**	AgTFA	HFIP/AcOH (3/1, v/v)	33
19	$Pd(acac)_2$	**L1**	AgTFA	HFIP/AcOH (3/1, v/v)	19
20	$Pd(PhCN)_2Cl_2$	**L1**	AgTFA	HFIP/AcOH (3/1, v/v)	43
21	$Pd(OAc)_2$	**L1**	-	HFIP/AcOH (3/1, v/v)	-
22	$Pd(OAc)_2$	-	AgTFA	HFIP/AcOH (3/1, v/v)	-
23[c]	$Pd(OAc)_2$	**L1**	AgTFA	HFIP/AcOH (3/1, v/v)	64

[a] Reaction conditions: **1a** (0.2 mmol), Pd source (10 mol%), **2a** (0.4 mmol), additives (0.3 mmol), ligands (40 mol%), solvent (2.0 mL), 130 °C, N_2, 36 h. [b] Yields are based on **1a**, determined by ^{1}H-NMR using dibromomethane as internal standard. [c] 110 °C. [d] Isolated yields.

Very recently, our group discovered the palladium-catalyzed direct β-arylation of aliphatic aldehydes with β-alanine as a transient ligand in hexafluoro-2-propanol and acetic acid[8b]. On the basis of this report, we commenced our investigation on the cross coupling of 2-pentanone (**1a**) and iodobenzene (**2a**) in the presence of catalytic $Pd(OAc)_2$ and stoichiometric amounts of AgTFA with β-alanine (**L1**) as a transient ligand at 130 °C under nitrogen atmosphere (Table 1). Initial solvent screening showed that mixture of hexafluoro-2-propanol and acetic acid at the volume ratio of 3:1 could provide the desired arylated product **3a** in decent yield (entry 5). It is believed that this co-solvent system facilitates the ligand association and dissociation, and cyclopalladation in the process.[10] Next, the effect on selected ligands towards the process was examined. It turned out that the reactions gave low yields with an α-amino acid (**L2** or **L3**) as the ligand, indicating that a [5,5]-bicyclic palladium intermediate may not be suitable in this process (entries 6-7). Following the above investigations, screening of silver salts was conducted, and low yields were observed with AgOAc, Ag_2CO_3 or Ag_2O (entries 14-16). Further study showed that this reaction could also be catalyzed by $PdCl_2$, $Pd(TFA)_2$, $Pd(acac)_2$ or $Pd(PhCN)_2Cl_2$ with moderate yields (entries 17-20). It is noteworthy that no desired product **3a** was obtained in the absence of a silver salt or a ligand (entries 21-22). Moreover, a lower yield was obtained at a lower reaction temperature (entry 23).

Table 2. Scope of Aliphatic Ketones[a]



[a] Reaction conditions: **1** (0.20 mmol), $Pd(OAc)_2$ (10 mol%), **2a** (0.4 mmol), AgTFA (0.3 mmol), β-alanine (40 mol%), HFIP (1.5 mL), HOAc (0.5 mL), 130 °C, N_2, 36 h. Isolated yields. [b] PhI (0.8 mmol). [c] HFIP (1.6 mL), HOAc (0.4 mL). [d] β-alanine (0.14 mmol).

As shown in Scheme 2, this strategy could be used for the unsymmetric double C–H arylation of ketones. Two different aryl groups could be consecutively installed to provide compound **4** with glycine and β-alanine as the transient ligands respectively.

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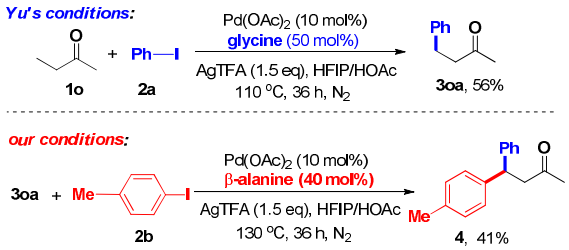
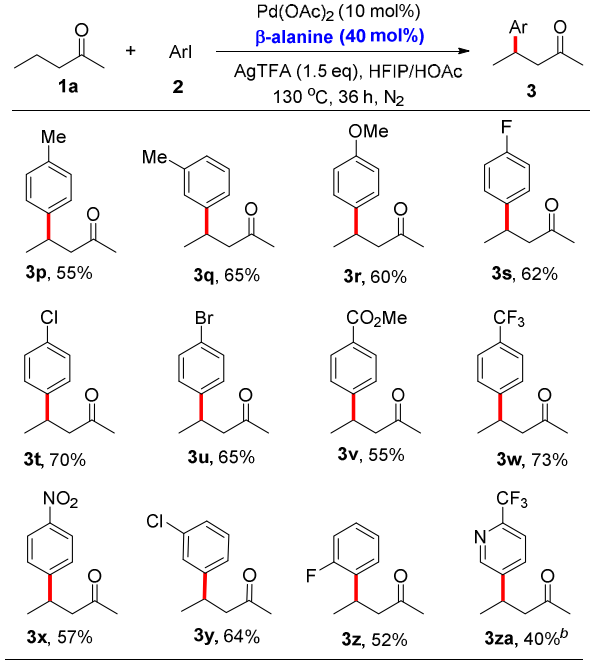


Scheme 2. Unsymmetric double C–H arylation of butan-2-one

Next, we carried out the substrate scope study on aryl iodides (Table 3). As expected, unactivated β-secondary C–H bond of 2-pentanone could be arylated with different aryl iodides with great functional group compatibility. Aryl iodides bearing an electron-withdrawing or electron-donating group on phenyl ring at the *o*-, *m*- or *p*-positions underwent arylation smoothly to produce the desired products in good yields (**3p-z**). It is also noteworthy that halogens (F, Cl, or Br) were well tolerated, enabling further manipulations of the initial products. Furthermore, 5-iodo-2-(trifluoromethyl)pyridine was also a suitable substrate for this reaction (**3za**).

Table 3. Scope of Aryl Iodides[a]



[a] Reaction conditions: **1a** (0.20 mmol), $Pd(OAc)_2$ (10 mol%), **2** (0.4 mmol), AgTFA (0.3 mmol), β-alanine (40 mol%), HFIP (1.5 mL), HOAc (0.5 mL), 130 °C, N_2, 36 h. Isolated yields. [b] β-alanine (0.12 mmol), HFIP (1.6 mL), HOAc (0.4 mL).

On the basis of the above obtained results and previous reports[8b,11], a plausible reaction mechanism is proposed (Figure 2). It is believed that this process is initiated by the reversible imine formation from aliphatic ketone **1** with the catalytic transient ligand β-alanine, providing the imine intermediate **A**. Then, coordination of the imine intermediate **A** to a palladium species generates the corresponding six-membered palladium complex **B**. Cyclometalation of intermediate **B** activates the β-C(sp^3)–H bond, giving rise to a [5,6]-bicyclic palladium intermediate **C**. Then, oxidative addition of the intermediate **C** with an aryl iodide produces the palladium (IV) species **D**. Finally, reductive elimination of the palladium complex **D** will occur, followed by ligand dissociation and iodide abstraction to give the β-imino acid **F**, which releases the desired product **3** and the ligand β-alanine.

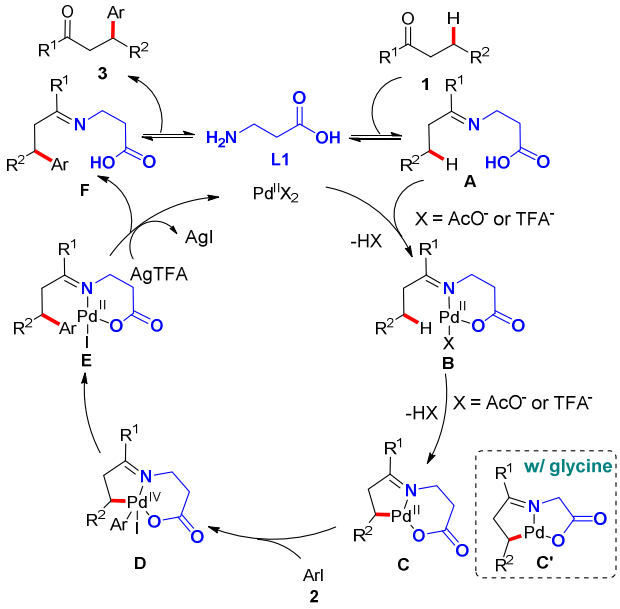


Figure 2. Proposed catalytic cycle.

In summary, a direct arylation of β-C(sp^3)–H bonds of aliphatic ketones has been developed via a palladium catalysis under atmospheric nitrogen with cheap and commercially available β-alanine as the transient ligand with good functional group compatibility. A great preference for functionalizing the C–H bonds of β-sp^3 carbons over those of γ-carbons and relatively reactive α-carbons is observed. The detailed mechanistic study of this transformation is currently undergoing in our laboratory.

Acknowledgements

We greatly appreciate the financial support for this work by NSF (CHE-1350541) and Indiana University Purdue University Indianapolis. G. L. is also grateful for financial support from Robert Welch Foundation (D-1361).

Conflicts of interest

There are no conflicts to declare.

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DOI: 10.1039/C8CC00980E

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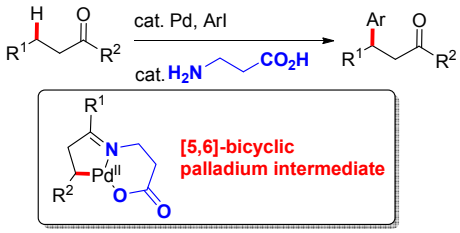

C-H Arylation of ketones enabled by a cheap and commercially available transient ligand with high site-selectivity and functional group compatibility.