Advanced Synthesis & Catalysis

Accepted Article

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Authors: Junliang Wang, Cong Dong, Liangfei Wu, Mingkai Xu, Jun Lin, and kun wei

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201800489

Link to VoR: http://dx.doi.org/10.1002/adsc.201800489

10.1002/adsc.201800489

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Palladium-Catalyzed β-C–H Arylation of Ketones Using Amino Amide as a Transient Directing Group: Applications to Synthesis of Phenanthridinone Alkaloids

Junliang Wang,[a] Cong Dong,[a] Liangfei Wu,[a] Mingkai Xu,[c] Jun Lin*[b] and Kun Wei*[a]

[a] School of Chemical Science and Technology, Yunnan University, Kunming, 650091 (P. R. China). E-mail: kunwei@ynu.edu.cn
[b] Key Laboratory of Medicinal Chemistry for Natural Resource (Ministry of Education), Yunnan University. Kunming, 650091 (P. R. China). E-mail: linjun@ynu.edu.cn
[c] Institute of Applied Ecology, Chinese Academy of Science. Shenyang, 110016 (P. R. China).

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. The direct arylation of aromatic and aliphatic ketones was carried out via palladium-catalyzed inert C–H bond functionalization with 2-amino-*N*-isopropyl-acetamide as a new catalytic transient directing group. The reaction showed excellent functional group compatibility and site selectivity. We demonstrated that α-amino amide forming N,N-bidentate coordination with Pd catalyst is more favorable for the β-arylation of ketones than α-amino acid forming N,O-bidentate coordination with Pd catalyst under relatively mild conditions. This elegant approach provides straightforward access to important structural motifs in organic and medicinal chemistry and is demonstrated here in the efficient synthesis of phenanthridinone alkaloids.

Keywords: palladium-catalyzed; arylation of ketones; transient directing group; phenanthridinone alkaloids

Introduction

In the past two decades, there has been great interest in C–H bond functionalization carried out by using transition metal complexes in organic chemistry, because these reactions can convert unactivated C–H bonds into new C–C and C–heteroatom bonds.[1-6] However, the development of transition metal complexes capable of selective, catalytic functionalization of C–H bonds is a principal challenge.

In order to control selectivity and facilitate reactivity in C–H activation reactions, the strategy of introducing directing groups into the substrate is usually exploited.[7-15] Through coordination of the metal with the directing group, cyclometalation processes have proceeded to realize C–H bond activation as well as positional selectivity. However, this approach still includes some limitations for synthetic applications, because the substrate is firstly connected with the directing group before it can be coordinated with the metal and it is necessary to remove the directing group at the end of the reaction, which diminishes the efficiency of the reaction. In addition, the conditions for installation or removal of the directing groups are sometimes incompatible with other functional groups present in advanced synthetic intermediates. A reasonable solution to this problem would be to devise a transient directing group (TDG) that can be reversibly linked to the substrate and the metal center. Upon C–H activation and subsequent functionalization, the TDG would dissociate from the product after the activation is accomplished with a catalytic amount of this temporary directing group. This strategy allows shorter reaction sequences, resulting in environmental advantages, unique regioselectivities, and use of easily accessible starting materials.

The strategy has been successfully implemented in C–H bond functionalization of ketones and aldehydes.[16-20] Recently, through employing an amino acid as a TDG, Yu and co-workers described palladium-catalyzed arylation of *o*-alkyl benzaldehydes and aliphatic ketones.[21] Soon after, a similar transformation was also realized by using 3-aminopropanoic acids,[22] acetohydrazide,[23] 2-amino-2-methyl-propionic acid,[24] anthranilic acid[24, 25], or *α*-benzyl *β*-alanine,[26] which form N,O-bis-coordinated complexes with Pd(II) catalyst and promote the C–H activation process. In addition, *N*-tosylethylene-diamine was shown to form a N,N-bidentate directing group with an imine linkage for arylation of aldehydes, which was limited to utilization of tertiary aldehydes and afforded poor selectivity of the monoarylated product.[27] Nevertheless, mild and selective transformations of this type remain to be further exploited, and direct inert C–H functionalization of ketones using transient N,N-bidentate coordination with Pd(II) has not yet been reported, even for the efficient synthesis of natural products. One of the most used and versatile

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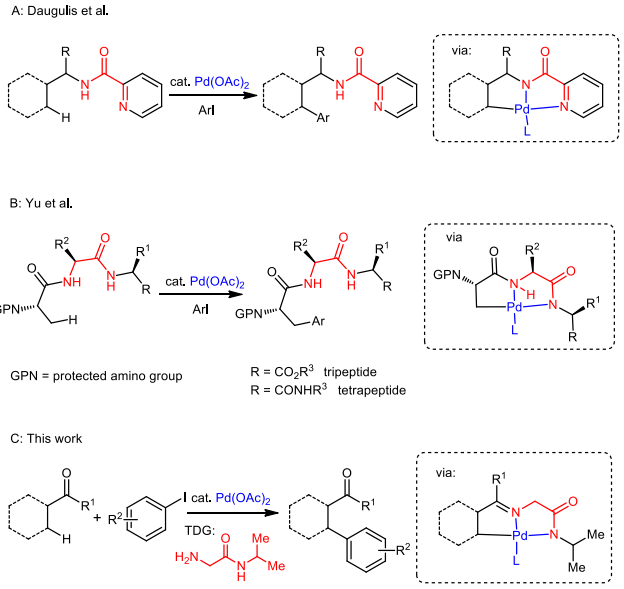


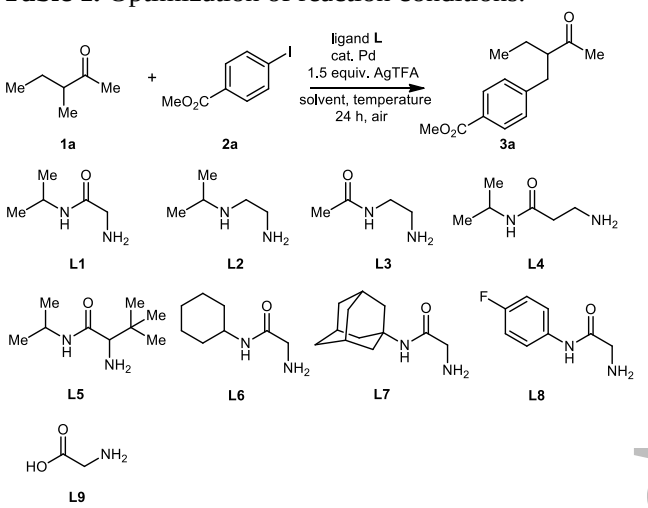
Scheme 1. Pd-catalyzed C–H arylation of ketones.

aminoquinolines and picolinic acid presented catalytic action by N,N-bidentate coordination with Pd(II) (Scheme 1A).[28-32] Significantly, the use of the N,N-bis-coordination of the peptide backbone in C–H functionalizations of tri- and tetrapeptides[33] (Scheme 1B) led us to speculate that an α-amino amide could serve as a suitable transient directing group. We envisioned that an elaborated TDG, e.g., α-amino amide, could be reversibly tethered to ketones via an imine linkage under appropriate conditions, which might effectively facilitate inert C–H arylation of ketones by N,N-bidentate coordination with Pd(II). Herein, we report a new class of TDG utilized to promote β-arylation of ketones that will greatly enrich the toolbox for synthesis of key intermediates in chemical synthesis and ubiquitous structural units in biologically active natural products and pharmaceuticals[34] (Scheme 1C). Preliminary mechanistic studies have been performed. In addition, we have developed a one-pot method for the efficient synthesis of phenanthridinone alkaloids.

Results and Discussion

To establish the viability of the β-C–H arylation of ketones, we synthesized a series of TDGs that were designed to offer potential N,N-bidentate coordination through varied amides (**L1-L8**) (Table 1). We commenced our investigation of palladium-catalysed β-arylation of 3-methyl-2-pentanone (**1a**) with methyl 4-iodobenzoate (**2a**) in the presence of 10 mol% of $Pd(OAc)_2$ and 1.5 equiv. of AgTFA with 2-amino-*N*-isopropylacetamide **L1** as a transient directing group at 100 °C for 24 hours (Table 1). Initially, a series of different volume ratios of hexafluoroisopropyl alcohol (HFIP) and acetic acid

Table 1. Optimization of reaction conditions.



Entry	Pd source (10 mol%)	Ligand (50 mol%)	Solvent (HFIP/AcOH)	Yield (%)[a]
1	$Pd(OAc)_2$	**L1**	HFIP	12
2	$Pd(OAc)_2$	**L1**	AcOH	20
3	$Pd(OAc)_2$	**L1**	HFIP/AcOH (1 : 1)	34
4	$Pd(OAc)_2$	**L1**	HFIP/AcOH (3 : 1)	41
5	$Pd(OAc)_2$	**L1**	HFIP/AcOH (5 : 1)	48
6	$Pd(OAc)_2$	**L1**	HFIP/AcOH (9 : 1)	53
7	$Pd(OAc)_2$	**L1**	HFIP/AcOH (14 : 1)	16
8[b]	$Pd(OAc)_2$	**L1**	HFIP/AcOH (9 : 1)	85(80)[e]
9[c]	$Pd(OAc)_2$	**L1**	HFIP/AcOH (9 : 1)	32
10[d]	$Pd(OAc)_2$	**L1**	HFIP/AcOH (9 : 1)	6
11	$Pd(TFA)_2$	**L1**	HFIP/AcOH (9 : 1)	5
12	$Pd(acac)_2$	**L1**	HFIP/AcOH (9 : 1)	8
13	$PdCl_2$	**L1**	HFIP/AcOH (9 : 1)	11
14	$Pd(PPh_3)_2Cl_2$	**L1**	HFIP/AcOH (9 : 1)	45
15	$Pd(CH_3CN)_2Cl_2$	**L1**	HFIP/AcOH (9 : 1)	20
16	$Pd(OAc)_2$	**L2**	HFIP/AcOH (9 : 1)	trace
17	$Pd(OAc)_2$	**L3**	HFIP/AcOH (9 : 1)	0
18	$Pd(OAc)_2$	**L4**	HFIP/AcOH (9 : 1)	0
19	$Pd(OAc)_2$	**L5**	HFIP/AcOH (9 : 1)	trace
20	$Pd(OAc)_2$	**L6**	HFIP/AcOH (9 : 1)	29
21	$Pd(OAc)_2$	**L7**	HFIP/AcOH (9 : 1)	trace
22	$Pd(OAc)_2$	**L8**	HFIP/AcOH (9 : 1)	4
23	$Pd(OAc)_2$	**L9**	HFIP/AcOH (9 : 1)	5

Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), Pd source (0.02 mmol), ligand (0.1 mmol), silver trifluoroacetate (AgTFA) (0.3 mmol), solvent (1 mL), 100 °C, 24 h. [a] Yields were determined by ^{1}H NMR using dibromomethane as the internal standard. [b] 80 °C, 24 h. [c] 60 °C, 24 h. [d] Reaction performed using 30 mol% ligand. [e] Isolated yield.

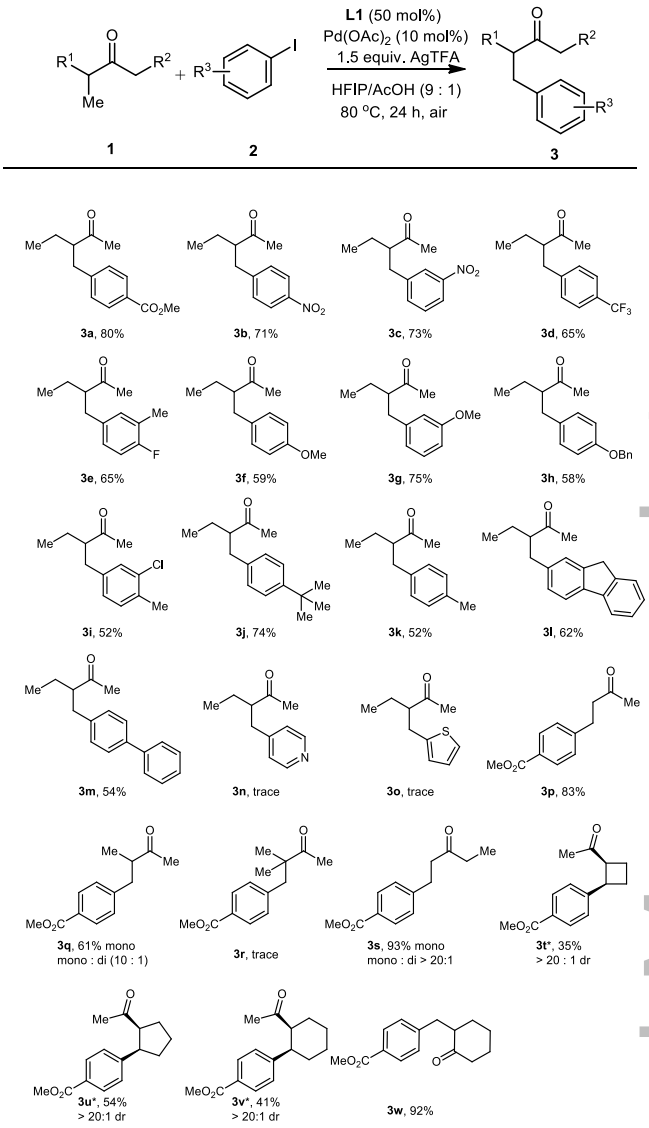
10.1002/adsc.201800489

(AcOH) as the cosolvent were tested, and the results were summarized in Table 1 (entries 1-7). When a 9:1 mixture of HFIP and acetic acid as the cosolvent was used, a relatively high yield (53%) of the desired arylated product **3a** was achieved (entry 6). Next, other reaction parameters, including temperatures and amounts of TDG, were screened. As revealed in Table 1 (entries 8 and 9), the temperature has a significant impact on the catalytic effect. It was then noticed that the yield was obviously improved by decreasing the reaction temperature from 100 °C to 80 °C. In addition, the TDG loading screening showed that low loading is not beneficial for the reaction (entry 10). Then, the examination of different palladium catalysts revealed that this reaction can be catalyzed by $Pd(TFA)_2$, $Pd(acac)_2$, $PdCl_2$, $Pd(PPh_3)_2Cl_2$, $Pd(CH_3CN)_2Cl_2$, albeit with lower efficiency compared with $Pd(OAc)_2$ (entries 11-15).

Following the above investigation, the screening of TDGs was conducted, (entries 16-23). When commercially available *N*-isopropylethylene-diamine (**L2**) was used, only a trace amount of **3a** was obtained (entry 16). The data suggested that the carbonyl group is very important. When TDG **L3** was investigated, the product was not observed (entry 17), which suggested that the carbonyl group must be located between two nitrogen atoms. Also, **L4** was completely ineffective, which indicated that the 6-membered palladacycle intermediate is not suitable for this process (entry 18). Furthermore, the presence of an *α-tert*-butyl group had negative effects on C(sp^3)–H arylation (entry 19). To further investigate the role of the directing groups, several TDGs containing bulky groups were synthesized, but rather poor yields were observed (entries 20-22). As a comparison, when glycine (**L9**) was used as a TDG,[19] only 5% yield was achieved (entry 23). This result suggested that the 2-amino-*N*-isopropylacetamide **L1** rather than its hydrolysate facilitates the transformation, and N,N-bidentate coordination between Pd and TDG is more favorable for the *β*-arylation of ketones than that of N,O-bidentate coordination under optimal reaction conditions. According to the above results, the highest NMR yield (85%) was obtained when the reaction was carried out to 24 h with 10 mol% of $Pd(OAc)_2$, 50 mol% of **L1**, and 1.5 equiv. of AgTFA in HFIP/AcOH (9:1) at 80 °C.

After determining the optimal conditions, we carried out a substrate scope study of aliphatic ketones and aryl iodides. The results were summarized in Table 2. Firstly, the substrate scope of the aryl iodides was examined for arylation, using 3-methyl-2-pentanone as the model substrate. Electron-deficient aryl iodides bearing ester, nitrotrifluoromethyl, and fluorine substituents were well tolerated to give the arylated products in good to moderate yields (**3a**-**3e**). Electron-rich aryl iodides with alkoxy, methyl, and *tert*-butyl substituents afforded the corresponding products in moderate yields (**3f**-**3k**). When we changed the placement of the methoxyl group from the *para*-position to the *meta*-position, a significant improvement in the yield was observed (**3f**, **3g**). Also, aryl iodides containing biphenyl units were tolerated, providing moderate yields (**3l**, **3m**). Lastly, screening of arylation with heteroaryl iodides showed that no product was obtained (**3n**, **3o**).

Table 2. Palladium-catalyzed C(sp^3)–H arylation of ketones.



Conditions: ketones **1** (0.4 mmol, 2.0 equiv), ArI **2** (0.2 mmol, 1.0 equiv), $Pd(OAc)_2$ (10 mol%), AgTFA (1.5 equiv), HFIP : AcOH = 9 : 1 (0.2 M), under air, 80 °C, 24 h. Yields correspond to the yields of isolated products.
*Reaction performed at 100 °C.

Next, we surveyed the aliphatic ketone scope of the *β*-C(sp^3)–H arylation (Table 2). A variety of simple linear ketones were well tolerated, giving excellent to good yields (**3p**, **3q**, **3s**). Significantly, when 3-methylbutan-2-one (**1q**) and symmetrical 3-pentanone (**1s**) bearing two unactivated C–H sites were used, high

monoselectivity was observed. Also, the arylation of branched ketone only provided a trace yield (**3r**). Furthermore, we found that *β*-arylation of methylene C(sp^3)–H bonds of cyclic ketones provided the corresponding *syn* products with excellent diastereoselectivity (**3t**-**3v**).[35]

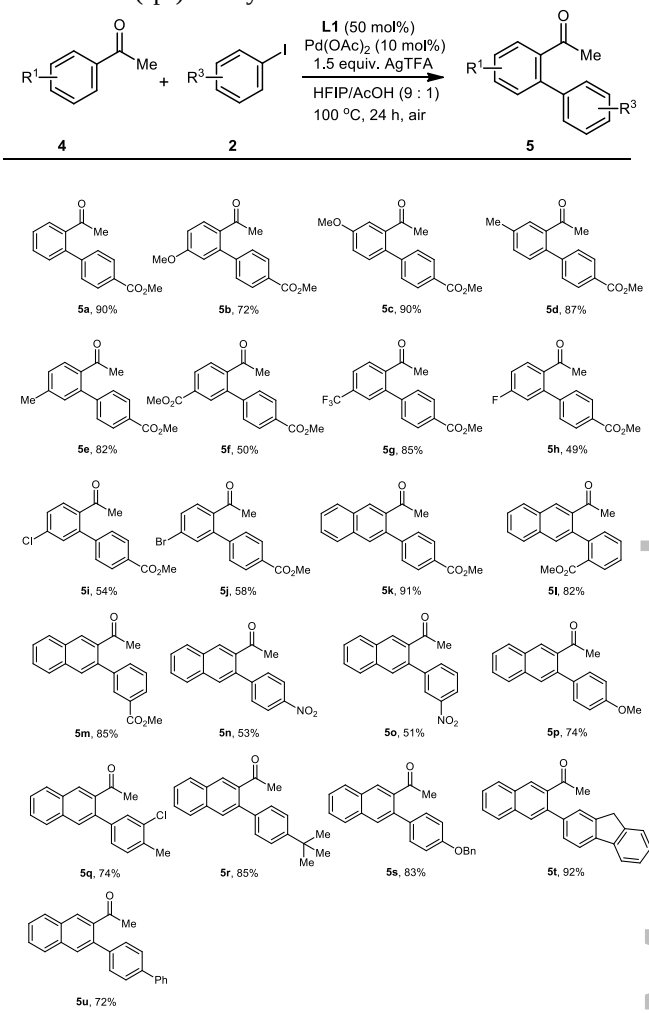
We also surveyed the scope of aromatic ketones and aryl iodides under optimized conditions. As illustrated in Table 3, acetophenones with electron-donating or -withdrawing substituents and different halogen substitutions underwent arylation to give the products in excellent to moderate yields (**5a**-**5j**). Also, the *ortho*-C–H arylation of 2-acetonaphthone with a variety of aryl iodides was achieved to afford the target products in excellent to moderate yields (**5k**-**5s**). Furthermore, aryl iodides containing biphenyl units were tolerated, providing excellent to good yields (**5t**, **5u**).

To provide insight into the reaction mechanism, a series of deuteration experiments were performed (Scheme 2). The intramolecular kinetic isotope effect (KIE) of the palladium-catalyzed C–H functionalization was found to be k_H/k_D = 2.2 [Scheme 2 (1)]. Moreover, the intermolecular KIE of k_H/k_D = 2.3 was investigated with independent reactions of substrates **4a** and **4a**-d_5 [Scheme 2 (2)]. These experimental results are indicative of a kinetically relevant C–H metalation step.[36]

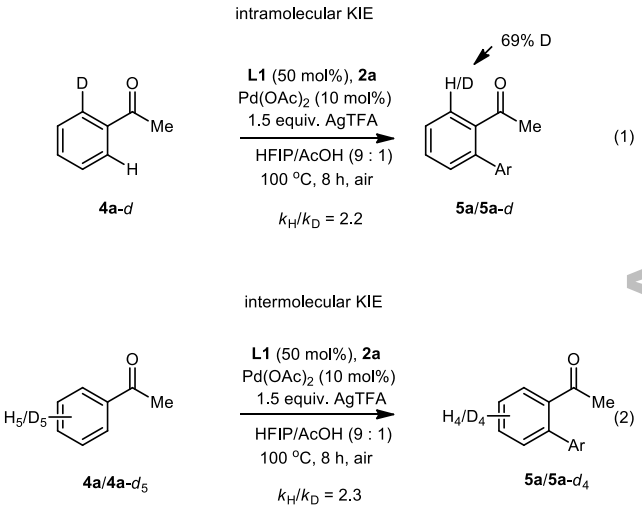
Based on the above results and the previous reports,[27, 33, 37-39] we propose a plausible reaction mechanism for the *β*-C–H arylation of aliphatic ketones and aromatic ketones (Scheme 3). Condensation of ketones with the ligand 2-amino-*N*-isopropylacetamide provides the imine intermediate **A**. Coordination of this *α*-imino amide to a palladium species followed by a ligand exchange process generates palladium complex **B**. Cyclopalladation of intermediate **B** gives rise to the [5,5]-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**. Reductive elimination of this palladium complex followed by a ligand dissociation process and iodide abstraction by AgTFA provides the *α*-imino amide **E**, which releases the desired product, and ligand 2-amino-*N*-isopropylacetamide.

To further demonstrate the potential application of this transformation, we selected phenanthridinone and phenaglydon (natural products) as synthetic targets, and successfully synthesized the two compounds based on a one-pot method (Scheme 4). Using phenanthridinone as an example, after the arylation of compound **4a** based on the above optimized conditions was completed, the reaction mixture was concentrated *in vacuo*. Subsequently, sodium azide and silica sulfuric acid were added.[40,41] The reaction mixture was stirred for

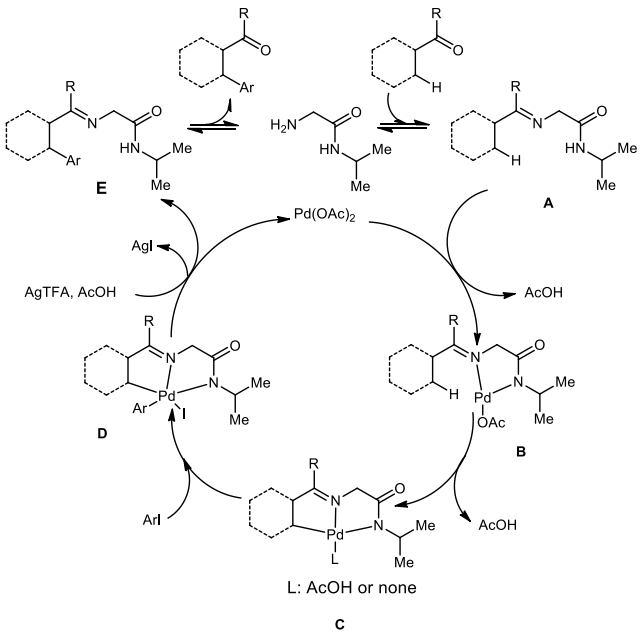
Table 3. C(sp^2)–H arylation of aromatic ketones.



Conditions: ketones (0.2 mmol, 1.0 equiv), ArI (0.4 mmol, 2.0 equiv), $Pd(OAc)_2$ (10 mol %), AgTFA (1.5 equiv), HFIP : AcOH = 9 : 1 (0.2 M), under air, 100 °C, 24 h. Yields correspond to the yields of isolated products.

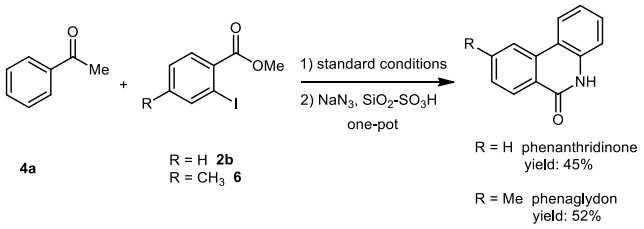


Scheme 2. Deuteration experiments.



Scheme 3. Proposed reaction mechanism.

12 h at 70 °C. After continuous Schmidt reaction, deacetylation, and amination, a 45% yield of phenanthridinone, the desired product, was obtained.



Scheme 4. Synthetic applications.

Conclusion

In summary, palladium-catalyzed arylation of ketones was achieved via a *β*-C–H bond functionalization process with 2-amino-*N*-isopropylacetamide as a new transient directing group. A range of unactivated methyl as well as cyclic methylene C–H bonds were efficiently functionalized. The transformation showed excellent functional group compatibility and diastereoselectivity under relatively mild conditions. Compared with glycine, the α-amino amide produced better results via N,N-bidentate coordination between Pd and TDG. Furthermore, we developed a one-pot method and successfully completed the synthesis of two phenanthridinone alkaloids based on the arylation of ketones. This study offers valuable insight for the future development of transient directing groups to promote inert C–H functionalization, which should find broad applications in the synthesis of drug molecules and natural products. Further efforts to enable enantioselective selectivity with this reaction using chiral amides are currently underway in our laboratory.

Experimental Section

General Methods and Materials

Melting points were obtained on a XT-4 melting-point apparatus and were uncorrected. The infrared (IR) spectra were measured on a Nicolet Avatar iS10 Fourier transform infrared (FTIR) spectrometer with 4 cm^{-1} resolution and 32 scans between wavenumber of 4000 cm^{-1} and 400 cm^{-1}. Samples were prepared as KBr disks with 1 mg of samples in 100 mg of KBr. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Avance 400 or 500 spectrometer at 400 or 500 MHz. Carbon-13 nuclear magnetic resonance (^{13}C NMR) was recorded on a Bruker Avance 400 or 500 spectrometer at 100 or 125 MHz. High resolution mass spectral (HRMS) data were obtained with an ionization mode of electrospray ionization (ESI). All the solvents and commercially available reagents were purchased from commercial sources and used directly. Ligands **L2**, **L3,** and **L9** were purchased from TCI, and the other ligands **L1**[42], **L4**[42], **L5**[42], **L6**[42], **L7**[43], **L8**[44] and starting materials **6**[45], **4a**-*d*[46], and **4a**-d_5[46] were prepared according to literature procedures

(see the supporting information for more details).

Typical Procedure for Palladium-Catalyzed C–H Arylation of Aliphatic Ketones

To a 15-mL reaction tube were added $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), **L1 (**11.6 mg, 0.1 mmol), silver trifluoroacetate (66.3 mg, 0.3 mmol), ketone substrate (0.4 mmol), and aryl iodide (0.2 mmol), followed by the mixture of HFIP (0.9 mL) and acetic acid (0.1 mL). The tube was then sealed, and the reaction mixture was stirred at room temperature for 15 min before being heated to 80 °C for 24 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The crude reaction mixture was purified on silica gel using hexanes/EtOAc as the eluent to afford the desired product.

General Procedure for ortho-C–H Arylation of Aromatic Ketones

To a 15-mL reaction tube were added $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), **L1 (**11.6 mg, 0.1 mmol), AgTFA (66.3 mg, 0.3 mmol), aromatic ketones (0.2 mmol), aryl iodide (0.4 mmol), HFIP (0.9 mL), and acetic acid (0.1 mL). The tube was then sealed, and the mixture was stirred at room temperature for 15 min before being heated to 100 °C for 24 h. The reaction mixture was cooled to room temperature, filtered via Celite, exhaustively washed with ethyl acetate, and then the filtrate was concentrated under reduced pressure. The resulting residue was purified on silica gel using hexanes/EtOAc as the eluent to provide the biaryl products.

Synthesis of Phenanthridine Skeletal Amaryllidaceae Alkaloids

To a 15-mL reaction tube were added $Pd(OAc)_2$ (4.5 mg 0.02 mmol), **L1 (**11.6 mg, 0.1 mmol), AgTFA (66.3 mg, 0.3 mmol), acetophenone (24 mg, 0.2 mmol), methyl 2-iodobenzoate **2b** (105 mg, 0.4 mmol) or methyl 2-iodo-4-methylbenzoate **6** (110 mg, 0.4 mmol), HFIP (0.9 mL), and AcOH (0.1 mL). The tube was then sealed, and the mixture was stirred at room temperature for 15 min before being heated to 100 °C for 24 h. The reaction mixture was then cooled to room temperature and concentrated under reduced pressure. To the crude reaction mixture was added silica sulfuric acid SSA (760 mg, 2 mmol) and NaN_3 (52 mg, 0.8 mmol). The mixture was stirred at 70 °C for 12 h, and the progress of the reaction was monitored by thin-layer chromatography (TLC). After the reaction was complete, ethyl acetate (15 mL) was added to the reaction mixture, and silica sulfuric acid was removed by filtration. The filtrate was then washed with water (10 ml), dried over

anhydrous $MgSO_4$, and the solvent evaporated in a vacuum to give the crude product. The resulting residue was purified by column chromatography (eluting with petroleum ether/ethyl acetate) to provide the phenanthridin-6(5*H*)-one or phenaglydon.

Acknowledgements

This work was supported by the Program for CAS "Light of West China". The authors gratefully acknowledge the Program for Changjiang Scholars and Innovative Research Team in University (IRT17R94), the NSFC (81760621), the Foundation of "Yunling Scholar" Program of Yunnan Province (C6183005), and Innovative Research Team (in Science and Technology) in University of Yunnan Province for financial support.

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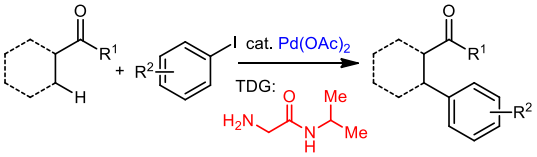
10.1002/adsc.201800489

FULL PAPER

Palladium-Catalyzed *β*-C–H Arylation of Ketones Using Amino Amide as a Transient Directing Group: Applications to Synthesis of Phenanthridinone Alkaloids



Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Junliang Wang,[a] Cong Dong,[a] Liangfei Wu,[a] Mingkai Xu,[c] Jun Lin*[b] and Kun Wei*[a]