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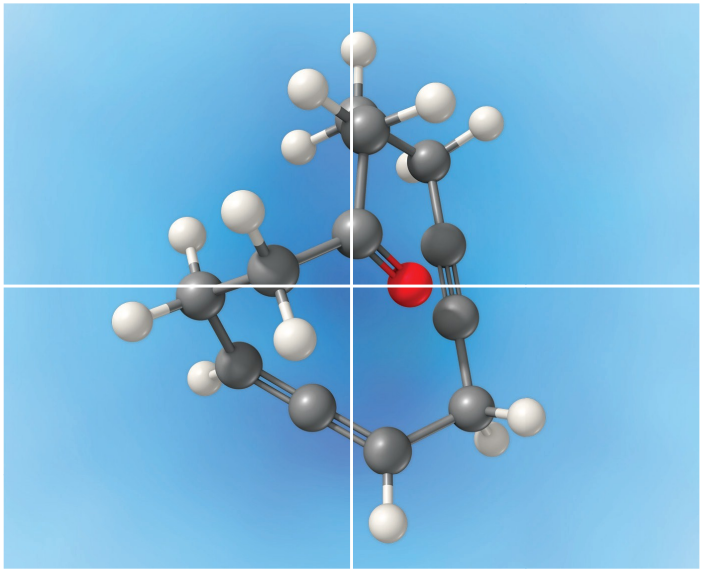

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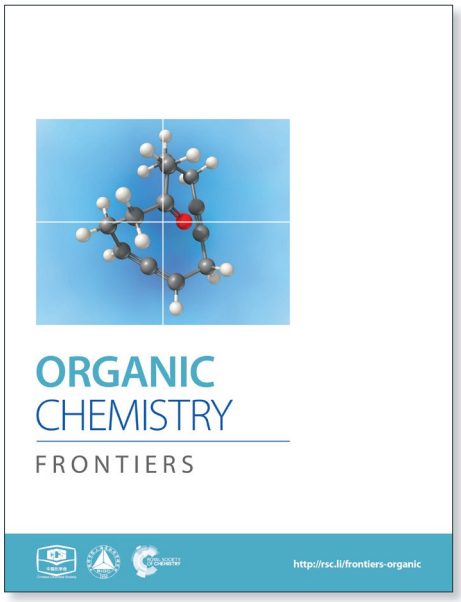

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RESEARCH ARTICLE

Pd(II)-Catalyzed *β*-C-H Arylation of *O*-Methyl Ketoximes with Iodoarenes†

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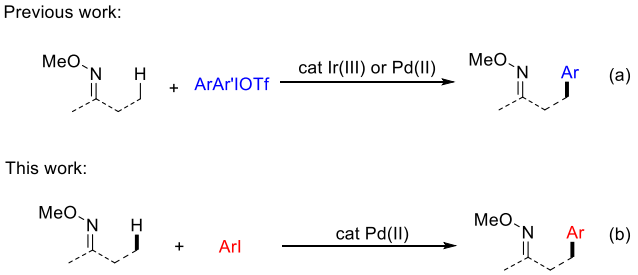
Pd(II)-catalyzed selective *β*-arylation of *O*-methyl ketoximes was developed using iodoarenes as the coupling partners. This transformation has good functional group compatibility and can serve as a powerful synthetic tool for late-stage C-H arylation of complex compounds. Moreover, when employing 2-iodobenzoic acids as the substrates in this developed catalytic system, a type of unexpected five-membered lactones could be formed by tandam sp^3 C-H arylation and oxygenation.

Introduction

Compared with traditional coupling reactions, the direct functionalization of C-H bonds gains more advantages due to its atom and step economy, especially when introduction of halides in a specific synthesis intermediate is difficult.[1] In particular, transition metal catalysis has emerged as a powerful tool for the functionalization of otherwise unreactive sp^2 C-H in the past decades.[2] The aliphatic C-H bonds, which are ubiquitous in organic molecules are most challenging targets for effective and selective functionalization.[3] Among them, notable advances have been made in the direct C-H arylation reactions through a variety of developed strategies. Initial studies focused on the direct arylation of 8-methylquinoline due to its good chelating abilities.[4] Later on, external ligands were added to facilitate the Pd-catalyzed direct arylation of aliphatic acids, amides, amino acid derivatives and peptides.[5] In addition, utilization of bidentate chelating groups such as 8-aminoquinoline and picolinamide was also a powerful strategy to promote the C-H arylations.[6] Despite the great progress made in this field, the current substrates are still limited to aliphatic acids, amides and the related compounds. Therefore, new catalytic systems need to be developed to expand the scope to other types of compounds.

Oxime ethers as the precursor of ketones, amines, amides and cyanos are among the most useful functional building blocks available to the synthetic chemists. The *β*-oxygenation[7] and amination[8] of aliphatic C-H bonds in ketoxime derivatives have been exploited. Considering the wide existence of *β*-arylated ketones in natural products and pharmaceuticals,[9] it's worth well developing a method to introduce a phenyl group in the *β*-position of oxime ethers *via* aliphatic C-H activation. In 2015, our group first developed a versatile method for direct arylation of sp^3 C-H bonds in *O*-methyl ketoximes and nitrogen-containing heterocycles.[10] The key to this success depends on the appropriate choice of an Ir(III) catalyst and the use of diaryliodonium triflate salts as the coupling partners (Scheme 1a, Ir catalysis). Very recently, Chen and co-workers uncovered that the same transformation can occur in the presence of Pd catalysis (Scheme 1a, Pd catalysis).[11] In view of the diaryliodonium salts, as costly and less available reagents with low atom economy, we are encouraged to discover a milder catalytic system using more accessible phenyl source. Herein, we report the Pd-catalyzed intermolecular direct arylation of sp^3 C-H bonds in *O*-methyl ketoximes with iodoarenes (Scheme 1b). Our latest method demonstrates a perfect adaptability of a wide range of substrates and proceeds smoothly in late-stage C-H functionalization, which provides a meaningful perspective in future research.



Scheme 1 Iridium- and palladium-catalyzed direct C-H arylation of *O*-methyl ketoximes.

Results and discussion

We started our research on Pd-catalyzed C-H arylation of the readily available 2,3-dimethylcyclohex-2-en-1-one oxime (**1a**) and iodobenzene (**2a**) for the optimization of reaction conditions (Table 1). Initial studies focused on the sources of silver oxidants (entries 1-3). It was found that AgTFA was very critical to the reaction and provided the desired product **3aa** in 31% yield at 100°C using DCE as the solvent. The effects of various solvents were also examined and $PhCF_3$ demonstrated the best effects (entry 4). Notably, lowering the temperature to 80 °C led to an improvement in the reaction outcome (entries 5-6). We also screened several different kinds of ligands from **L1** to **L7**, and found only organic phosphate **L5-L6** can give positive effects (entries 7-8).[12] Simple phosphate $BINPO_2H$, commercially available at low cost, was most effective affording **3aa** in 80% yield. Under these conditions, reducing the amount of AgTFA or $Pd(OAc)_2$ led to lower yields (entries 9-10). In addition, other palladium sources including $Pd(TFA)_2$ and $Pd_2(dba)_3$ showed comparatively poor yields and obviously,

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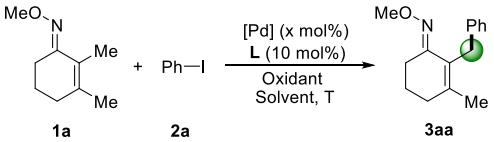
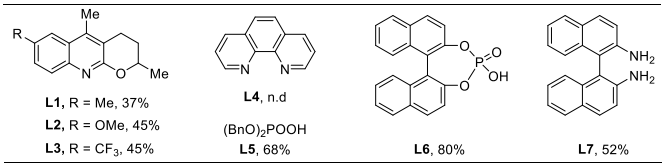
†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Table 1 Optimization of the reaction conditions[a]



entry	[Pd] (mol%)	L	Oxidant (equiv)	Solvent	T	Yield[b] (%)
1	$Pd(OAc)_2$ (5)	-	Ag_2CO_3(2.0)	DCE	100	trace
2	$Pd(OAc)_2$ (5)	-	AgOAc (2.0)	DCE	100	5
3	$Pd(OAc)_2$ (5)	-	AgTFA (2.0)	DCE	100	31
4	$Pd(OAc)_2$ (5)	-	AgTFA (2.0)	$PhCF_3$	100	42
5	$Pd(OAc)_2$ (5)	-	AgTFA (2.0)	$PhCF_3$	80	65
6	$Pd(OAc)_2$ (5)	-	AgTFA (2.0)	$PhCF_3$	60	54
7	$Pd(OAc)_2$ (5)	**L1**	AgTFA (2.0)	$PhCF_3$	80	37
8	**$Pd(OAc)_2$ (5)**	**L6**	**AgTFA (2.0)**	**$PhCF_3$**	**80**	**80 (73)[c]**
9	$Pd(OAc)_2$ (5)	**L6**	AgTFA (1.0)	$PhCF_3$	80	47
10	$Pd(OAc)_2$ (2.5)	**L6**	AgTFA (2.0)	$PhCF_3$	80	56
11	$Pd(TFA)_2$ (5)	**L6**	AgTFA (2.0)	$PhCF_3$	80	63
12	$Pd(dba)_2$ (5)	**L6**	AgTFA (2.0)	$PhCF_3$	80	53
13	-	**L6**	AgTFA (2.0)	$PhCF_3$	80	0



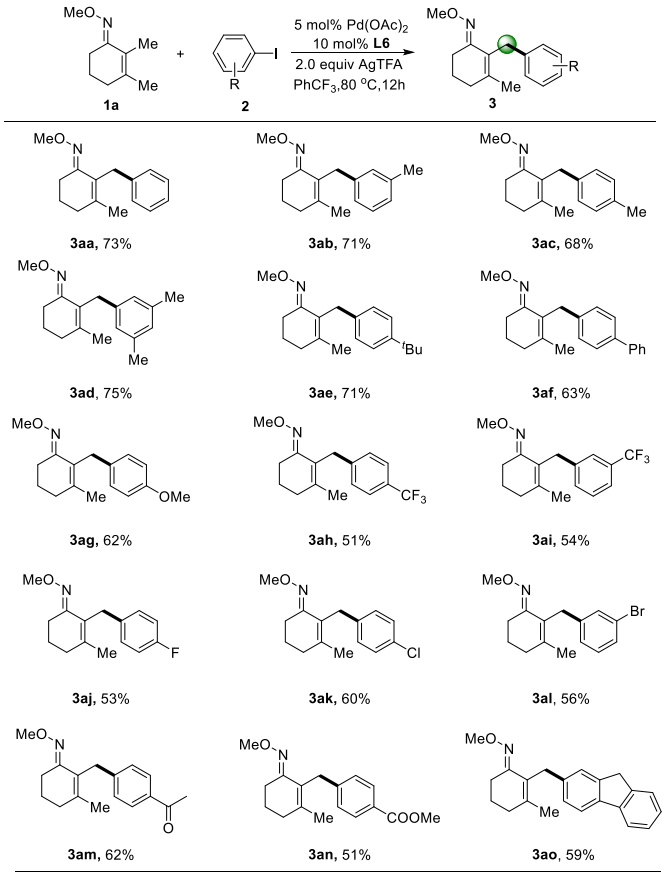
[a] Reaction conditions: all the reactions were run at a 0.20 mmol scale with **1a** (1.0 equiv), **2a** (2.0 equiv), palladium catalyst (5 mol%), ligand (10 mol%) and silver oxidant (2.0 equiv) in 1.0 mL solvent, 12h. [b] Crude ^{1}H NMR yield using CH_2Br_2 as the internal standard. [c] Isolated yield in parentheses.

the absence of catalyst failed to provide the corresponding product (Table 1, entries 11-13). Based on the above results, it was revealed that entry 8 illustrated the optimal conditions for the Pd-catalyzed arylation of *O*-methyl ketoxime **1a**.

With the best conditions in hand, we sought to expand this transformation to the transfer of diverse aryl groups and we found that a range of substituted iodoarenes worked well with 2,3-dimethylcyclohex-2-en-1-one oxime (**1a**) (Table 3). Aromatic groups displaying electron-neutral and electron-rich substituents at the *meta*- and *para*-position (**3ab**-**3ad** & **3ae**-**3ag**) were transferred in particularly good yields from the corresponding iodoarenes. Useful halogenated iodoarenes such as trifluoromethyl-(**3ah**-**3ai**), fluoro-(**3aj**), chloro-(**3ak**) and even bromo-(**3al**) groups were accommodated, thereby providing possibilities for subsequent chemical transformations. Electron-withdrawing substituted group such as acetyl- (**3am**) and methyl ester (**3an**) groups could be tolerated in this protocol. We were pleased that the coupling of the polycyclic aromatic motif was possible and proceeded in moderate yield (**3ao**), thus further enhancing the scope of our reaction.

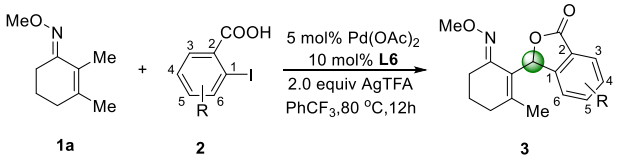
When 2-iodobenzoic acid (**2p**) was employed as an *ortho*-substituted substrate, an unexpected five-membered lactone **3ap** was observed in 62% yield under the optimized conditions (Scheme 2). Other substrates involving methyl-, chloro- and bromo-groups were well-tolerated, and the corresponding products **3aq**-**3as** were isolated in 50%-63% yields. In addition, 2-iodo-4,5-dimethoxybenzoic acid (**2t**) was also compatible affording the cyclization product **3at** in 54% yield. We

Table 2 Substrate scope of iodoarenes **2**[a]



[a] Reaction conditions: all the reactions were run at a 0.20 mmol scale with **1a** (1.0 equiv), **2** (2.0 equiv), $Pd(OAc)_2$ (5 mol%), **L6** (10 mol%) and AgTFA (2.0 equiv) in 1.0 mL $PhCF_3$, 12h; Isolated yields.

speculated that *β*-C-H arylation of *O*-methyl ketoximes with 2-iodobenzoic acids could afford the C-H arylation products as shown in Table 2, which occurred the further intramolecular C-H oxygenation in the presence of *ortho*-carboxylic acid groups. Although the cyclization reactions *via* multiple palladium-catalyzed C-H activation of arenes have been developed,[13] this tandem sp^3 C-H arylation and oxygenation process is seldom to report.

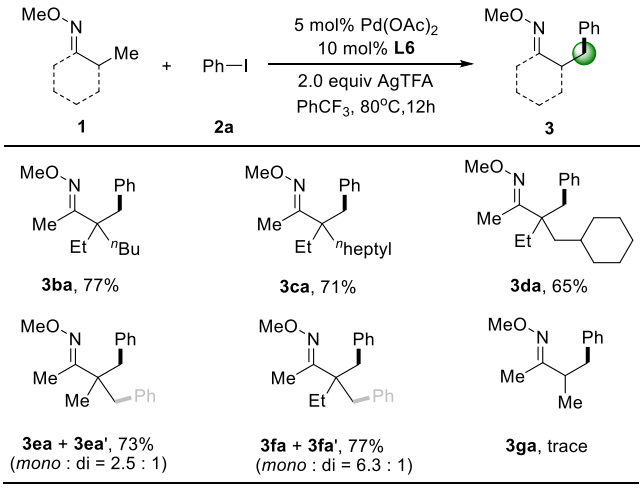


R = H, **2p**	R = H, **3ap**, 62%
R = 4-Me, **2q**	R = 4-Me, **3aq**, 63%
R = 4-Cl, **2r**	R = 4-Cl, **3ar**, 58%
R = 4-Br, **2s**	R = 4-Br, **3as**, 50%
R = 4, 5-OMe, **2t**	R = 4, 5-OMe, **3at**, 54%

Scheme 2 Cyclization of 2-iodobenzoic acids **2p**-**2t** by dual C-H activation[a]

We next investigated the substrate scope of *O*-methyl ketoximes with iodobenzene (**2a**) in Table 3. *β*-Arylation of ketoxime **1b**, which contains a quaternary α-carbon atom, gave the monoarylated product **3ba** in 77% yield. In the case of substrates **1c**-**1d**, with the increasing of steric bulk from *n*-heptyl to cyclohexyl adjacent to the quaternary centers, the yield of the corresponding products gradually decreased. It

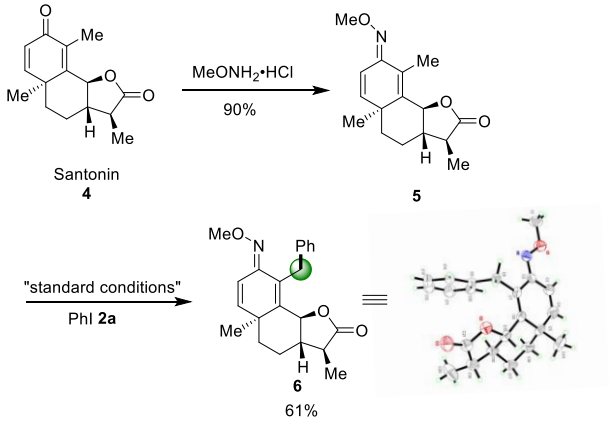
Table 3 Substrate scope of *O*-methyl ketoximes **1**[a]



[a] Reaction conditions: all the reactions were run at a 0.20 mmol scale with **1** (1.0 equiv), **2a** (2.0 equiv), $Pd(OAc)_2$ (5 mol%), **L6** (10 mol%) and AgTFA (2.0 equiv) in 1.0 mL $PhCF_3$, 12h; Isolated yields.

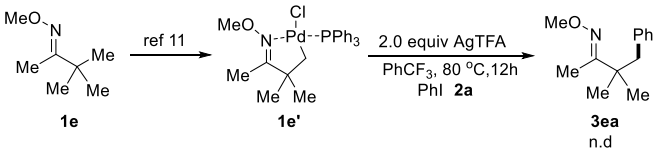
should be mentioned that these substrates contain multiple possible sites for the direct arylation, showing extremely high selectivity for activation of primary *β*-C-H bonds in lieu of those at secondary carbon centers. Later on, we tested the substrates with several primary *β*-C-H bonds that can be functionalized. Gratifyingly, we were able to functionalize pinacolone derivative **1e** and **1f** to give a mixture of mono- and diarylated products in 73% and 77% yield, respectively. It's also noticed that the methyl groups adjacent to a quaternary center is necessary for this C-H arylation and oxime ethers with *α*-hydrogens has much lower reactivity, since *O*-methyl ketoxime **3ga** only gave trace amount product.

Late-stage modification of naturally significant molecules to access new bioactive compounds have been an emerging concept in organic chemistry.[14] Encouraged by this successful sp^3 C-H arylation, we also turned our attention to utilize our method as a key step for regioselective C-H arylation of a complex molecule. *O*-methyl ketoxime **5**, derived from pharmaceutical compound Santonin **4**, a kind of roundworm repellent, was compatible to this catalytic system affording the desired product **6** in 61% yield. The structure of **6** was further confirmed by X-ray diffraction as shown in Scheme 2.



Scheme 3 Late-stage C-H arylation of Santonin.

Chen and co-workers previously uncovered that Pd-catalyzed C-H arylation of *O*-methyl ketoximes with diaryliodonium salt triggered by the palladium species inducing C-H activation of the *O*-methyl ketoxime to generate a palladacycle complex.[11, 15] However, when the complex **Ie'** was synthesized and treated with 2.0 equiv of **2a** and 2.0 equiv of AgTFA, we didn't observe any corresponding arylated products (Scheme 4). We hypothesized that oxidative addition of the palladium species to iodoarenes should take place ahead of C-H activation of *O*-methyl ketoximes in our conditions.



Scheme 4 Mechanistic investigations.

Conclusions

In summary, we have developed the examples of palladium-catalyzed C-H arylation of *O*-methyl ketoximes with iodoarenes under mild conditions. This novel method exhibited flexibility with different substrates and offered new opportunities to prepare *β*-arylated *O*-methyl ketoximes from inexpensive and available reagents. The efficient strategy not only tolerated various functional groups, but also has been applied into modification of the complex molecule. Also, a series of five-membered lactones could be generated from 2-iodobenzoic acids under standard conditions. Further studies on the mechanism and applications of this novel method are going to be researched in our group.

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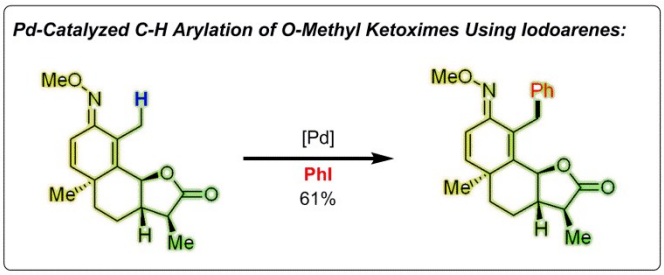
TOC



Zhuangzhi Shi was born in Jiangsu Province in 1983. He received his B.S. and M.S. degree in chemistry and organic chemistry from Yangzhou University in 2005 and 2008. Then he moved to Peking University and completed his Ph.D. degree in organic chemistry under the supervision of Prof. Ning Jiao. In 2011, he joined the group of Prof. Frank Glorius at Westfalische Wilhelms-Universitat Münster, as an Alexander von Humboldt Research Fellow studying Rh(III)-catalyzed C-H activation reactions. Since March 2014, he is working as a full professor at the Nanjing University, focusing on the development of new transition-metal catalysts and synthetic methodology.

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