Palladium-Catalyzed Oxime Ether Directed Regioselective C-H Alkoxylation of Arenes

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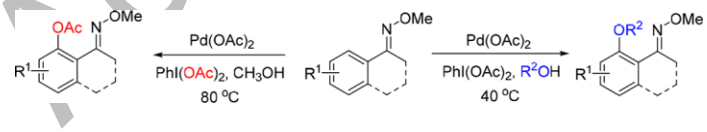
Abstract

A palladium-catalyzed high regioselective *ortho*-C(sp^2)-H alkoxylation of oxime ethers with $PhI(OAc)_2$ as the oxidant and alcohols as the alkoxylation reagents has been developed. *Mono*-alkoxylated and acetoxylated products could be selectively obtained via tuning the reaction conditions. A series of oxime ethers were tolerated, affording the corresponding products in moderate to good yields. Both primary and secondary alcohols survived the reaction conditions. Moreover, the directing group can be easily removed, thereby providing a straightforward access to substituted aryl ketones.

GRAPHICAL ABSTRACT:



KEYWORDS: C-H activation, oxime ethers, alkoxylation, acetoxylation, palladium catalysis

1. INTRODUCTION

Aryl ethers are very important structural motifs in many natural products, pharmaceuticals, and materials.[1] Generally, these compounds were synthesized via classical methods such as Ullmann coupling reactions,[2] Chan-Evans-Lam reactions,[3] Williamson reactions,[4] and Buchwald-Hartwig couplings.[5] However, some disadvantages including harsh reaction conditions, the use of expensive reagents, low atom-economy, as well as the generation of wastes (HX, *etc.*) may limited their synthetic applications in some extent.

Over the past decades, catalytic C-H bond functionalization has emerged as a powerful tool to construct complex chemical frameworks.[6] Particularly, the directing group (DG) assisted C-H activation is considered as one of the most useful strategies to achieve C-C and C-X couplings with good regioselectivity, especially for C(sp^2)-H bonds.[7] Recently, the direct alkoxylation of inert C(sp^2)-H bond with alcohols using this strategy provides a feasible route to access aryl ethers. A series of directing groups such as carbonyl, carbamoyl, acylamino, cyano, azo, triazole, 2-pyridyl, 2-pyridyloxyl, *etc*. have been successfully employed for the alkoxylations.[8] Compared with the classical C-O bond formations mentioned above, no preactivation of arenes is required and wasteful byproducts are minimized. Despite the remarkable success in this field, there are still two issues should be pointed out: (1) the alkoxylation of inert C(sp^2)-H remains a challenging

topic because alkanols are easily oxidized; and (2) some of the reported DGs cannot be removed, thus resulting in a big drawback for the practical application in organic synthesis. Thus, development of simple and efficient route for C-H alkoxylation is still highly desirable.

Recently, our work focused on developing removable DGs-assisted C-O bond formations. A regioselective palladium-catalyzed *ortho*-C(sp^2)-H acetoxylation of 2-aryloxypyridines with $PhI(OAc)_2$ as both the oxidant and acetate source was achieved.[9] However, tedious workup was required for the removal of 2-pyridyloxyl. Our interest led us to explore substrates with readily removable DGs. In another aspect, oxime ether as a directing group shows widespread applications in C-H activations.[10] They are readily available or prepared, and meanwhile, they can be easily removed via simple hydrolysis workup after C-H activations, thereby providing a facile route to deliver functionalized ketones. Motivated by previous studies and our interest in this field, we herein report a palladium-catalyzed regioselective C-H alkoxylation of aryl oxime ethers. Alkoxylation and acetoxylation products could be selectively obtained via tuning the reaction conditions (Scheme 1).

2. RESULTS AND DISCUSSION

Our initial studies investigated the methoxylation of the corresponding *O*-methyl oxime derivative **1a** in methanol (1). Encouragingly, product **3a** was obtained in 71% yield in

the presence of 10 mol% of $Pd(OAc)_2$ and three equivalents of $PhI(OAc)_2$ at 40 ^oC. Meanwhile, 10% yield of *di*-methoxylated product **3a'** was also isolated. No acetoxylated product **3a** was observed under this condition (Table 1, entry 1). Other palladium salts including $PdCl_2$, $Pd(PPh_3)_4$, $PdCl_2(CH_3CN)_2$ and $Pd(TFA)_2$ gave inferior results (Table 1, entries 2~5). A series of oxidants were then tried. Much lower yields were obtained when oxone and $K_2S_2O_8$ were used, while the BQ (benzoquinone), $Cu(OAc)_2$ and oxygen were completely ineffective for this reaction (Table 1, entries 6, 9 and 10). No improvement was observed when increasing the amount of $PhI(OAc)_2$ to five equivalents, while 52% yield of **3a** was obtained when using two equivalents of the oxidant. The mixed solvents such as MeOH/DCE, MeOH/CH_3CN and MeOH/dioxane were also tested, and the results clearly showed that addition of other solvents reduced the yields obviously (Table 1, entries 13~15), which was might attributed to the fact that a low concentration of alcohol was unfavorable for this reaction. Moreover, the addition of AcOH, TFA and TsOH still did not improve the yields (Table 1, entries 16~18). The temperature significantly affect this reaction, especially for the $Pd(OAc)_2$/$PhI(OAc)_2$ system, since the acetoxylated product could be easily generated.[8b,8g,9] As expected, reaction at 60 ^oC afforded only 51% yield of the desired product **3a**, while a satisfactory yield (74%) of acetoxylated product **4a** was obtained when performing the reaction at a higher temperature (80 ^oC). Finally, decreasing the catalyst amount to 5 mol% also provided a low yield of **3a**.

Having established the optimized reaction conditions, the substrates scope was next examined. The results are summarized in Table 2. For the methoxylation, a series of *O*-methyl oxime ethers with substituents such as methyl, methoxyl, halogens (Cl, Br) survived the reaction conditions, affording the corresponding products in moderate to good yields. However, substrate with strong electron-withdrawing group, for example, the nitro group, failed to provide the desired product. For the *meta*-substituted substrates, the reaction selectively took place on the side with smaller steric hindrance (**3g** and **3h**). Interestingly, no reaction occurred for the *ortho*-substituted substrates with the present reaction conditions; while moderate yields were obtained (**3i**: 64%; **3j**: 51%) by switching the oxidant to oxone. This phenomenon was also observed for (*E*)-benzaldehyde *O*-methyl oxime (**3k**). Moreover, a high yield (85%) of product **3l** was obtained by employing oxime ether **1l** which was derived from 3,4-dihydronaphthalen-1(2*H*)-one. Other alcohols, such as ethanol, isopropanol, *n*-butanol and *tert*-butyl alcohol were also checked as the alkoxylation reagents. The desired *ortho*-alkoxylation products **3m**~**3o** were obtained in acceptable to moderate yields, while *tert*-butyl alcohol showed no reactivity towards this reaction. It should be pointed out that *mono*-alkoxylated products were identified as the major products in all cases, together with trace amounts of *di*-alkoxylated ones.

As mentioned above, acetoxylation reaction was observed as the major reaction at an elevated temperature. Therefore, a selected number of oxime ethers was tested. Pleasingly,

all of them tolerated the reaction conditions to afford the corresponding acetoxylated products in good yields (Table 3).

The synthetic utilities of present protocol was also demonstrated in Scheme 2. Using compounds **3a** and **4a** as examples (0.5 mmol scale), both the oxime ether and the acetyl group can be removed by the treatment with HCl in Et_2O at room temperature, thereby providing a feasible route to access *ortho*-methoxy or *ortho*-hydroxy aryl ketones (**5**, 92% and **6**, 84%, respectively).

On the basis of the literatures[8b,11] and our previous experimental results,[9] a plausible mechanism was outlined in Scheme 3. First, the reaction may involve the formation of a C-Pd bond to generate the five-membered palladacycle intermediate **A**. Then, the oxidation of intermediate **A** in the presence of $PhI(OAc)_2$ and an alcohol will form Pd(IV) intermediate **B** . Finally, the formation of the C-O bond affords the alkoxylated product and regenerates the catalyst via reductive elimination.

3. CONCLUSION

In summary, a palladium-catalyzed high regioselective *ortho*-C(sp^2)-H alkoxylation of oxime ethers with $PhI(OAc)_2$ as the oxidant and alcohols as the alkoxylation reagents has been developed. *Mono*-alkoxylated products were indentified as the major products at 40 ^oC, while a higher temperature (80 ^oC) favored the C-H acetoxylation reaction. A series

of functional groups survived the reaction conditions, affording the corresponding products in moderate to good yields. This protocol is also available for both primary and secondary alcohols. Importantly, the directing group can be easily removed, thereby providing a straightforward access to substituted aryl ketones.

4. EXPERIMENTAL

4.1. General Remarks

Chemicals were used as received without special purification unless stated otherwise. Melting points (m.p.) are determined with an Optimelt MPA 100 apparatus and are not corrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Advance 300 analyzer in Chloroform-*d* ($CDCl_3$) using TMS as an internal standard. The coupling constants *J* are given in Hz. High-resolution mass spectrometry (HRMS) was performed on a TOF MS instrument with an ESI source.

General procedure for palladium-catalyzed alkoxylation and acetoxylation: a sealed tube equipped with a magnetic stirrer bar was charged with oxime ether **1a** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol, 10 mol%), and $PhI(OAc)_2$ (0.6 mmol, 3.0 equiv) in an alcohol **2** (1 mL). The reaction mixture was stirred at 40 ^{o}C for 24 h (for acetoxylation, reaction was performed at 80 ^{o}C). After reaction, the mixture was allowed to cool to room temperature. The solvent was then removed under vacuum, and the residue was purified by silica gel

chromatography using a mixture of petroleum ether/EtOAc to afford the desired product **3** or **4**.

*(E)-1-(2-methoxyphenyl)ethan-1-one O-methyl oxime (**3a**)*. Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.29 (m, 2H), 6.97-6.88 (m, 2H), 3.98 (s, 3H), 3.83 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.4, 156.6, 130.1, 129.5, 126.9, 120.6, 110.9, 61.6, 55.4, 15.9; HRMS (ESI): Calcd for $C_{10}H_{13}NNaO_2$ $(M + Na)^+$ 202.0838, found 202.0849.

*(E)-2-(1-(methoxyimino)ethyl)-5-methylphenyl acetate (**4b**).* Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 7.9 Hz, 1H), 7.08-7.04 (m, 1H), 6.90 (d, *J* = 0.7 Hz, 1H), 3.95 (s, 3H), 2.35 (s, 3H), 2.27 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4, 153.3, 147.6, 140.1, 129.1, 127.2, 126.8, 123.6, 61.8, 21.0 (2C), 14.9; HRMS (ESI): Calcd for $C_{12}H_{15}NNaO_3$ $(M + Na)^+$ 244.0944, found 244.0950.

General procedure for the synthesis of 3i~3k: Oxone (0.6 mmol, 3.0 equiv) and $Pd(OAc)_2$ (0.02 mmol, 10 mol%) were combined in MeOH (1 mL) in a tube. Substrate **1a** (0.2 mmol, 1.0 equiv) was then added to the mixture. The tube was sealed, and the reaction mixture was stirred at room temperature for 12 h. Then the temperature was slowly ramped to 80 ^{o}C for another 12 h. The reaction mixture was diluted with ethyl acetate and extracted with water (2 x 5 mL), $NaHCO_3$ (2 x 5 mL), and brine (2 x 5 mL).

The organic layer was dried over $MgSO_4$, filtered and concentrated. The resulting oil was purified by chromatography on silica gel to afford the desired products.

ACKNOWLEDGMENTS

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SUPPORTING INFORMATION

Full experimental detail, characterization data, ^{1}H and ^{13}C NMR spectra. This material can be found via the "Supplementary Content" section of this article's webpage.

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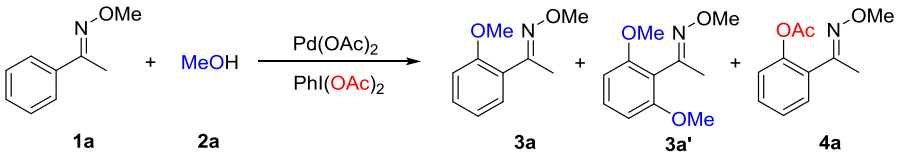
Table 1. Optimization of reaction conditions.[a]



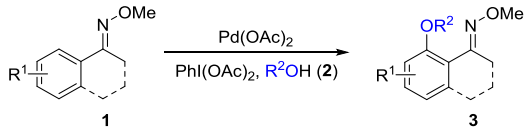
Entry	Catalyst (mol%)	Oxidant (equiv)	Solvent	Additive (equiv)	Yield(%)[b]		
					3a	3a'	4a
1	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (3)	MeOH	none	71	10	0
2	$PdCl_2$ (10)	$PhI(OAc)_2$ (3)	MeOH	none	33	<5	0
3	$Pd(PPh_3)_4$ (10)	$PhI(OAc)_2$ (3)	MeOH	none	37	<5	0
4	$PdCl_2(CH_3CN)_2$	$PhI(OAc)_2$ (3)	MeOH	none	43	<5	0
5	$Pd(TFA)_2$ (10)	$PhI(OAc)_2$ (3)	MeOH	none	47	<5	0
6	$Pd(OAc)_2$ (10)	BQ (3)	MeOH	none	0	0	0
7	$Pd(OAc)_2$ (10)	Oxone (3)	MeOH	none	35	<5	0
8	$Pd(OAc)_2$ (10)	$K_2S_2O_8$ (3)	MeOH	none	19	0	0
9	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$ (3)	MeOH	none	0	0	0

10	$Pd(OAc)_2$ (10)	O_2 (1 atm)	MeOH	none	0	0	0
11	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (5)	MeOH	none	68	12	0
12	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (2)	MeOH	none	52	<5	0
13	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (3)	MeOH/DCE (1:1)	none	45	<5	0
14	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (3)	MeOH/MeCN (1:1)	none	41	<5	0
15	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (3)	MeOH/dioxane (1:1)	none	36	<5	0
16	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (3)	MeOH	AcOH (5)	63	<5	0
17	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (3)	MeOH	TFA (5)	21	<5	0
18	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (3)	MeOH	TsOH (5)	15	<5	0
19[c]	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (3)	MeOH	none	42	0	0
20[d]	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (3)	MeOH	none	51	10	6
21[e]	$Pd(OAc)_2$ (10)	$PhI(OAc)_2$ (3)	MeOH	none	5	trace	74

22	$Pd(OAc)_2$ (5)	$PhI(OAc)_2$ (3)	MeOH	none	48	<5	0

[a] Reaction conditions: **1a** (0.2 mmol), catalyst (10 mol%), solvent (1 mL), oxidant (3.0 equiv) at 40 ^oC, air, 24 h. [b] Isolated yield. [c] room temperature. [d] Reaction at 60 ^oC. [e] Reaction at 80 ^oC.

Table 2. Pd-catalyzed *ortho*-alkoxylation of oxime ethers.[a]

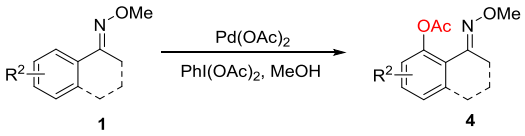


1 3

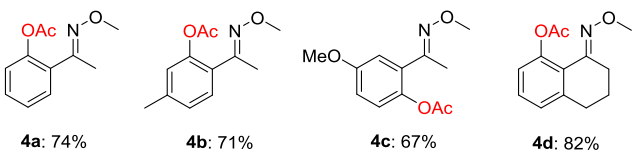
3b: 68%	**3c**: 45%	**3d**: 62%
3e: 60%	**3f**: NR	**3g**: 52%
3h: 55%	**3i**: 64%(7:1)[b,c]	**3j**: 51%[b]
3k: 55%[b]	**3l**: 85%	**3m**: 64%
3n: 41%	**3o**: 46%	**3p**: NR

[a] Reaction conditions: **1a** (0.2 mmol) and alcohol (1 mL), $Pd(OAc)_2$ (10 mol%), $PhI(OAc)_2$ (3.0 equiv), 40 °C, air, 24 h, isolated yields. [b] Oxone (3 equiv) as the oxidant, rt for 12 h; then 80 °C for 12 h. [c] Ratio of Z/E isomers determined by ^1H NMR.

Table 3. Pd-catalyzed *ortho*-acetoxylation of selected oxime ethers.[a]



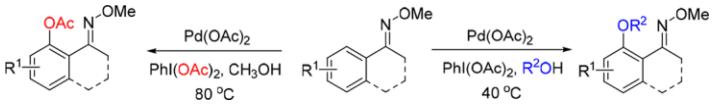
1 4



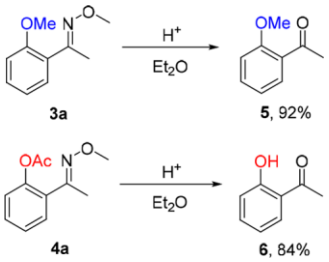
4a: 74% **4b**: 71% **4c**: 67% **4d**: 82%

[a] Reaction conditions: **1a** (0.2 mmol) and CH_3OH (1 mL), $Pd(OAc)_2$ (10 mol%), $PhI(OAc)_2$ (3.0 equiv), 80 ^oC, air, 24 h, isolated yields.

Scheme 1. Palladium-catalyzed oxime ether directed C-O bond formation



Scheme 2. Synthetic utilities of present protocol



Scheme 3. Plausible mechanism