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ARTICLE TYPE

Palladium-Catalyzed Oxygenation of C(sp^2)-H and C(sp^3)-H Bonds under the Assistance of Oxalyl Amide

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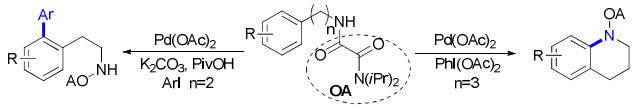
A practical palladium-catalyzed γ-oxygenation of C(sp^2)-H and C(sp^3)-H bonds under the assistance of oxalyl amide with PhI(OAc)$_2$ as oxidant was developed. Selective alkoxylation or acetoxylation of oxalyl amide protected benzyl amine was achieved in high yield. The oxalyl amide protected α-substituted propylamines could be transformed into acetoxylated products in good to excellent yield.

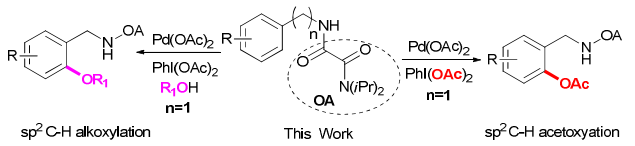
Directing-group assisted high site selective C-H functionalization has aroused considerable attention in the last decades and a significant number of transformations have emerged as powerful methods in organic synthesis.[1-2] Among the reports, a variety of functional groups, such as oximes,[3] pyridine,[4] oxazolines,[5] amides,[6] carboxylic acids,[7] amines,[8] hydroxyls,[9] esters,[10] etc.[11] were developed as directing groups to improve regioselectivity and reactivity in the transition-metal-catalyzed C-H functionalizations. The selective oxygenation of C-H bonds has regained much attention because of its important application in biosynthesis and post-synthetic modification.[12-13] In a ground-breaking report, Sanford and co-workers developed oxime-directed acetoxylation of the C(sp^3)-H bonds via palladium catalyst using PhI(OAc)$_2$ as oxidant.[14] Later, they found the pyridine was also a powerful directing group on the site selective oxygenation of C-H bonds.[15] Yu and co-workers reported the palladium-catalyzed oxazoline directed stereoselective acetoxylation of methyl group by employing inexpensive *t*-BuOO$_2$Me as oxidant.[16] Palladium-catalyzed picolinamide-directed oxygenation of C(sp^2)-H and C(sp^3)-H bonds using PhI(OAc)$_2$ as oxidant was demonstrated by Chen and co-workers in a mild condition.[17] Interestingly, Shaoo and co-workers discovered the *β*-C(sp^3)-H acetoxylation could happen at room temperature by applying S-methy-S-2-pyridylsulfoximine as the directing group.[18] Recently, the *β*-alkoxylation of methylene even could be achieved under the assistance of 8-aminoquinlone with cyclic hypervalent Iodine (I^{3+}) as oxidant by Rao and co-workers.[19] Although the significant progress has already achieved, the further development of practical oxygenation C-H bonds to synthesize useful molecules remains an important task. Herein, we report a practical protocol for palladium-catalyzed γ-oxygenation of C(sp^2)-H and C(sp^3)-H bonds under the assistance of oxalyl amide (Scheme 1).

Oxalyl amide, which was made from two general reagents of diisopropylamine and oxalyl chloride through S_N type reaction, was discovered by our group and emerged as a powerful directing group for amine derivatives.[20] It was demonstrated that it not only had an ability to enable rarely reported C-C bond formation at δ and ε positions,[20a, b] but also promoted the intramolecular amination to form six-membered heteroatom rings (Scheme 1A).[20c] Based on previous work, we tried to prepare the four-membered azetidine with oxalyl amide protected valine. However, only acetoxylated product was observed by GC-MS. It was possible that the steric effect of diisopropylamine inhibited the intramolecular C-N formation (Scheme 2). Inspired by this result, we tried to develop a selective protocol for the palladium-catalyzed oxalyl amide-directed γ-oxygenation of amine derivatives.

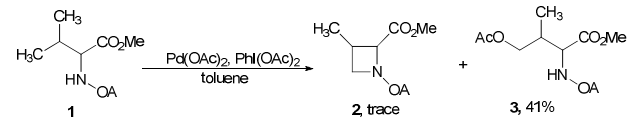
A: Oxalyl amide assisted bond formations



B: The new application in C-O bonds formations



Scheme 1. Oxalyl amide assisted C-H functionalization



Scheme 2. Functionalization of C(sp^3)-H Bonds

At the outset of our study, we first treated the oxalyl amide protected benzyl amine **4a**, PhI(OAc)$_2$, and Pd(OAc)$_2$ (5 mol%) in a mixture of methanol and toluene (1:6) at 100 °C in a sealed tube to explore the alkoxylation reaction. It's not surprising that the product of **5a** was observed in 71% yield analysed by GC (Table1, entry 1) and the rare dialkoxylated product was observed in 24% yield. Encouraged by the preliminary result, the reaction condition was further optimized to achieve selective transformation (entry 2). The alkoxylation reaction could afford mono-alkoxylated product in 83% yield at 60 °C. The less expensive oxidants, such as $K_2S_2O_8$, BQ and DDQ, were tested

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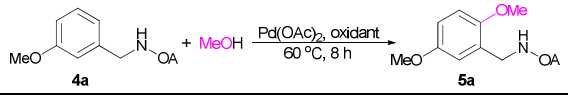
and failed to give any desired products, along with starting material recovered (entries 3-5, 14). Solvents screening revealed that toluene was the best solvent, providing excellent yield of **5a** (entries 2, 6-9). The additives of PivOH, $(BuO)_2PO_2H$ and AcOH had a slightly suppression effect on this transformation. Amino acid (Ac-Gly-OH), which was a super ligand in many transformations,[21] also had the similar result as PivOH on this oxalyl amide assisted C-H oxygenation (entries 10-13). Controlling experiments confirmed that no reaction happened without palladium catalyst, indicating the irreplaceable role of $Pd(OAc)_2$ for this transformation (entry 15).

Table 1. Optimization of reaction condition.



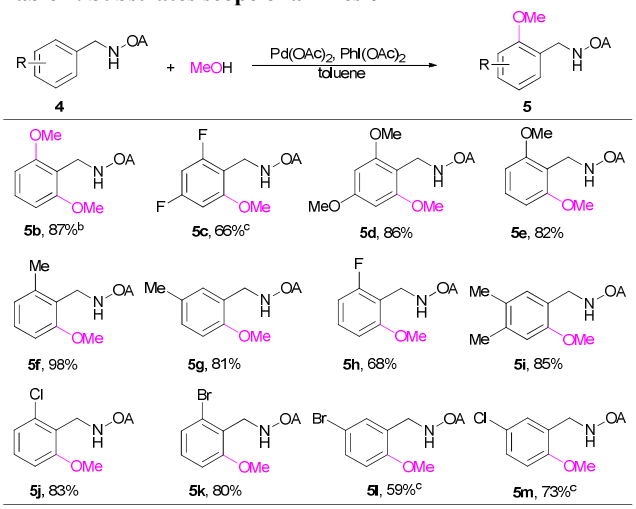
Entry[a]	Oxidant	Additive	Solvent	Yield(%)
1[b]	$PhI(OAc)_2$	-	toluene	71
2	**$PhI(OAc)_2$**	**-**	**toluene**	**90(83)**
3	DDQ	-	toluene	-
4	$Cu(OAc)_2$	-	toluene	-
5	BQ	-	toluene	-
6	$PhI(OAc)_2$	-	CH_3OH	44
7	$PhI(OAc)_2$	-	CH_3CN	40
8	$PhI(OAc)_2$	-	PhCl	88
9	$PhI(OAc)_2$	-	*m*-xylene	84
10	$PhI(OAc)_2$	PivOH	toluene	86
11	$PhI(OAc)_2$	$(BuO)_2PO_2H$	toluene	82
12	$PhI(OAc)_2$	AcOH	toluene	85
13	$PhI(OAc)_2$	Ac-Gly-OH	toluene	82
14	$K_2S_2O_8$	-	toluene	-
15[c]	$PhI(OAc)_2$	-	toluene	-

[a]**4a** (0.1 mmol), MeOH (0.05 mL), $Pd(OAc)_2$ (5 mol%), oxidant (0.15 mmol), additive (0.03 mmol), solvent (0.3 mL), in a 25 mL sealed tube; yields were based on GC using tridecane as standard. [b]100 °C. [c]No $Pd(OAc)_2$ was used.

Employing the optimized reaction conditions, we then explored the scope of benzyl amines, and representative data were listed in Table 2. To our great delight, a remarkable broad substrates scope of benzyl amines was achieved. The electron-donating functional groups were tolerated in this transformation, and gave the corresponding alkoxylated products in good to excellent yields (**5b, d-5i**). The electron-withdrawing groups such as F, Cl, Br were also tolerated, affording the corresponding products in good yields. The steric effect had an important influence on the regioselectivity of this transformation. As all the results were observed selectively taking place at the less hindered site (**5h**, **5i**, **5**l, **5m**).

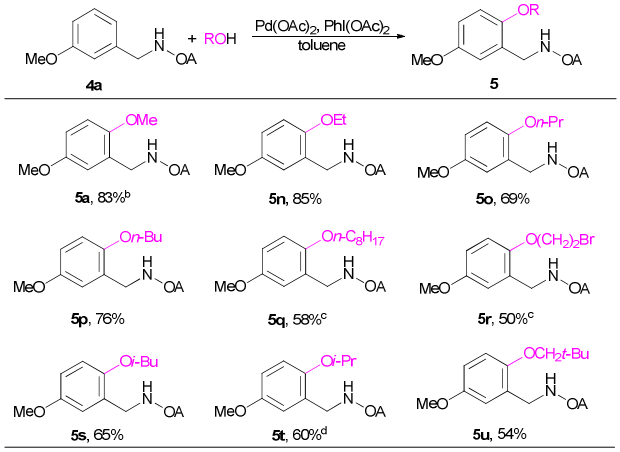
The scope of alcohols turned out to be very broad. A variety of alcohols was tolerated and gave well to excellent yields (Table 3, **5a**, **5n-5u**). Generally, the primary alcohols, such as ethanol, *n*-propanol and *n*-octanol, were all transformed into the corresponding ethers in good yields. It's worthy to mention that the 2-bromoethanol generated the corresponding ether in moderate yield, which was a useful synthon for further transformation (**5r**). Delightfully, bulk alcohol could also be employed, affording corresponding ethers in moderate yields (**5s-5u**). The more hindered isopropyl alcohol reacted slowly, yielding the product **5t** in acceptable yield. Unfortunately, some other alcohols, such as tertiary alcohol, phenol and cyclic alcohol, were also tested and failed to give corresponding products.

Table 2. Substrates scope of amines[a].



[a]**4a** (0.3 mmol), MeOH (0.15 mL), $Pd(OAc)_2$ (5mol%), $PhI(OAc)_2$ (0.45 mmol), and 0.9 mL toluene in a 25 mL sealed tube, 100 °C, 8 h; isolated yields. [b]$Pd(OAc)_2$ (10 mol%), 130 °C, 12 h. [c]130 °C, 20 h.

Table 3. Substrates scope of alcohol[a].



[a]**4a** (0.3 mmol), ROH (0.15 mL), $Pd(OAc)_2$ (5 mol%), $PhI(OAc)_2$ (0.45 mmol) and 0.9 mL toluene in a 25 mL sealed tube, 100 °C, 8 h; isolated yields. [b]60 °C. [c]130 °C, 20 h. [d]8 h.

Considering the reaction mechanism, the acetoxylation of amines at γ positions might be realized without the alcohol as solvent. Reaction optimization quickly, the excellent yields of acetoxylated products was observed with acetic acid (2 equiv) as additive, using $PhI(OAc)_2$ as oxidant in toluene under palladium catalyst. Remarkable functional groups, such as Cl-, Br-, I-, Me, and MeO-, were well tolerated, and afforded the corresponding products in moderate to good yields. Interestingly, the substrate of **4a** gave the diacetoxylated product at higher reaction temperature in moderate yield (**6i**). Although the role of acetic was unclear, on the basis of preliminary studies and pioneering

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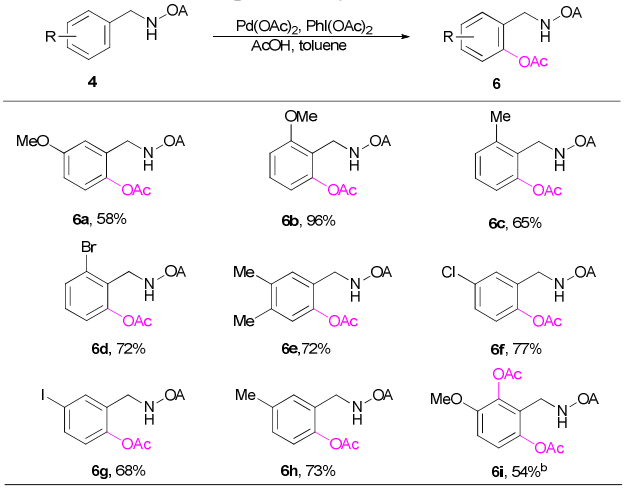
reports, acetic acid might act as a stabilizer during the catalytic cycle (SI).

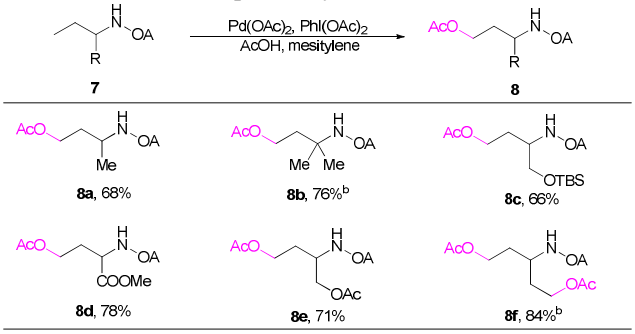
Encouraged by the success of oxalyl amide assisted oxygenation of C(sp^2)-H bonds, we tried to expand the alkoxylation to unactive C(sp^3)-H bonds. Gratifyingly, γ-acetoxylation of C(sp^3)-H bonds can proceed slowly under the assistance of oxalyl amide with acetic acid as additive (Table 5). Interestingly, the substrate of **7f** could be converted into diacetoxylated product **8f** in good yield.

Table 4. Substrates scope of benzylamine[a].

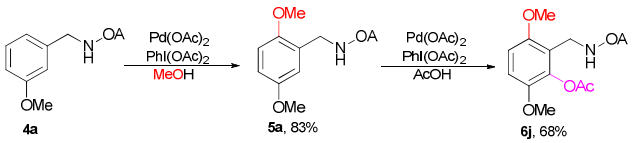


[a]**4** (0.3 mmol), $Pd(OAc)_2$ (5 mol%), $PhI(OAc)_2$ (0.6 mmol), AcOH (0.6 mmol) and 0.9 mL toluene in a 25 mL sealed tube, 100 °C, 22 h; isolated yields. [b]$PhI(OAc)_2$ (1.2 mmol), 140 °C.

Table 5. Substrates scope of alkylamine[a].



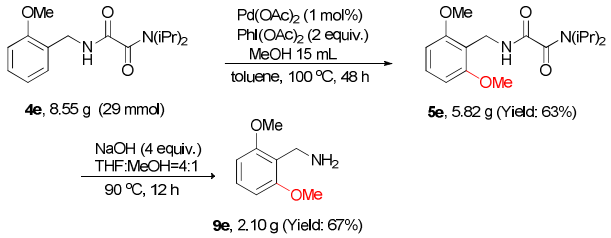
[a]**7** (0.3 mmol), $Pd(OAc)_2$ (5 mol%), $PhI(OAc)_2$ (1.2 mmol), AcOH (0.3 equiv.) and 0.9 mL mesitylene in a 25 mL sealed tube, 140 °C, 24 h; isolated yields. [b]160 °C.



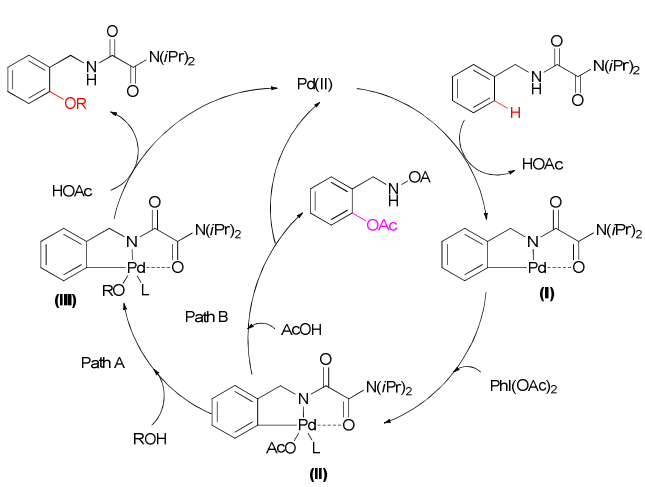
Scheme 3. Sequential C-H alkoxylation/acetoxylation reaction.

Inspired by the high regioselectivity of mono-alkoxylation (Table 2, 3), and exceptive example of **6i**, we might construct the complex arene by two steps. Delightfully, sequential oxygenation was successfully achieved in total 56% yields in two steps (Scheme 3).

The synthetic utility of this new developed protocol was also examined in the gram-scale reaction. The catalyst loading could be reduced to 1 mol% and the desired product was obtained in 5.8 g. Under the basic condition, the auxilixary could be removed to furnish the potential useful product **9d** (Scheme 4).



Scheme 4. Scale up and removal of directing group.



Scheme 5. Proposed catalytic cycle.

Although the mechanistic detail of this palladium-catalyzed oxalyl amide directed-oxygenation still remains uncertain, based on experimental results and pioneering works,[22] we proposed a possible mechanism showed in Scheme 5. The first step involved a chelate-directed C-H activation of the substrate to generate the five-membered cyclopalladium intermediate (I) through a CMD pathway. The Pd^{II} was further oxidized to a Pd^{IV} intermediate (II) by $PhI(OAc)_2$. When the alcohol was added, the ligand of AcO- could be replaced with alcohol to form intermediate (III). Reductive elimination afforded the oxygenated products.

In summary, we have developed a practical palladium-catalyzed γ-oxygenation of C(sp^2)-H and C(sp^3)-H bonds under the assistance of oxalyl amide using $PhI(OAc)_2$ as oxidant. Alkoxylation of benzyl amine derivative could be achieved with 10-20 equivalent amount of alcohol at a mild condition. Both C(sp^2)-H and C(sp^3)-H bonds of oxalyl amide protected amine derivatives were converted into corresponding acetoxylated products in moderate to excellent yields. Sequential oxygenation of 4a was also successful observed in moderate yield. Gram scale reaction was examined via 1 mol% palladium catalyst affording the desired product in 5.8 g. This new developed approach is an expandation of oxalyl amide assisted C-H functionalization in synthetic chemistry.

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Notes and references

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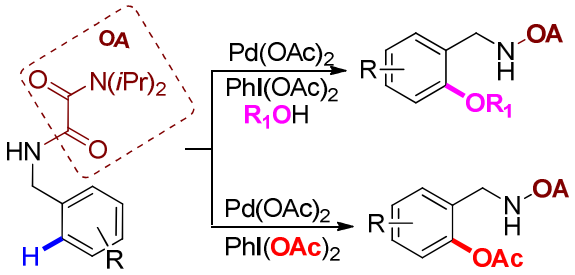

A general Palladium catalyzed selective γ-oxygenation of oxalyl amide protected amines is accomplished under mild condition.

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