# Direct *ortho*-C−H Functionalization of Aromatic Alcohols Masked by Acetone Oxime Ether via *exo*-Palladacycle

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Ⓢ *Supporting Information*

ABSTRACT: A simple and practical *exo*-oxime ether auxiliary for *ortho*-C−H functionalization of aromatic alcohols has been developed. Selective olefination of aromatic alcohols were first achieved via a six- or seven-membered *exo*-acetone oxime ether palladacycle with broad substrate scope. In addition, the crystal of the *exo*-palladacycle intermediate was obtained for the first time, and the application of this method in total synthesis of 3-deoxyisoochracinic acid was accomplished via a novel retro-synthetic disconnection approach, thus demonstrating the utility of this transformation.
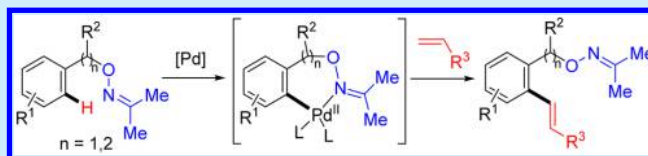
Transition-metal-catalyzed selective functionalization of C−H bonds has become a powerful strategy in the synthesis of natural products and pharmaceuticals.[1] So far, the primary strategy to achieve high site-selective C−H transformation is the employment of directing groups,[2] apart from the electronically activated substrates.[3] However, there are still a few examples of extensive applicable directing groups for functionalization of widely used alcohols.[4] In 2010, Yu[5] reported hydroxy-directed *ortho*-C−H olefination of tertiary phenethyl alcohols in the presence of palladium catalyst promoted by monoprotected amino acid ligands (Scheme 1A). Due to competitive decomposition, primary and secondary alcohol substrates gave lower yield. Meanwhile, Hartwig developed a practical hydroxyl-directed *ortho*-silylation of benzyl alcohols by employing Ir
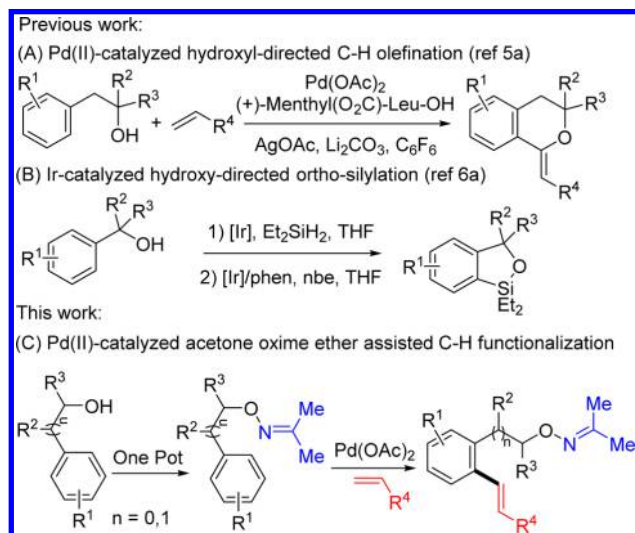
catalyst.[6] However, this reaction was limited in intramolecular C−H transformation (Scheme 1B).

Benzyl alcohols are important versatile synthetic precursors in synthetic chemistry and usually are the omnipresent component of many natural products and drug molecules.[7] Herein, we used a simple and potential *exo*-oxime ether directing group for direct C−H functionalization of benzyl alcohols at *ortho*-positions. Phenethyl alcohols were also effective despite their relatively remote coordination[8] (Scheme 1C). Moreover, a crystal of six-membered *exo*-palladacycle intermediate was successfully prepared. Finally, we demonstrated the utility of *ortho*-C−H olefination by total synthesis of a rare fungal metabolite, 3-deoxyisoochracinic acid, from commercially available 2-benzyloxybenzyl alcohol.

Oxime ethers which were first disclosed by Sanford[9a] present an excellent directing ability for carbonyl compounds and have been employed in C−O, C−N, C−X, and C−C bond formation via a five-membered *endo*-palladacycle intermediate (Scheme 2A). However, Dong[9b] made a brilliant modification of oxime ethers and achieved an opposite selective C−H transformation of aliphatic alcohols at β position affording the chemically differentiated 1,2-diols. The catalytic cycle might go through a five-membered *exo*-palladacycle, and the site selectivity in this protocol was achieved by blocking the potential reactive position of aldehyde (Scheme 2B).
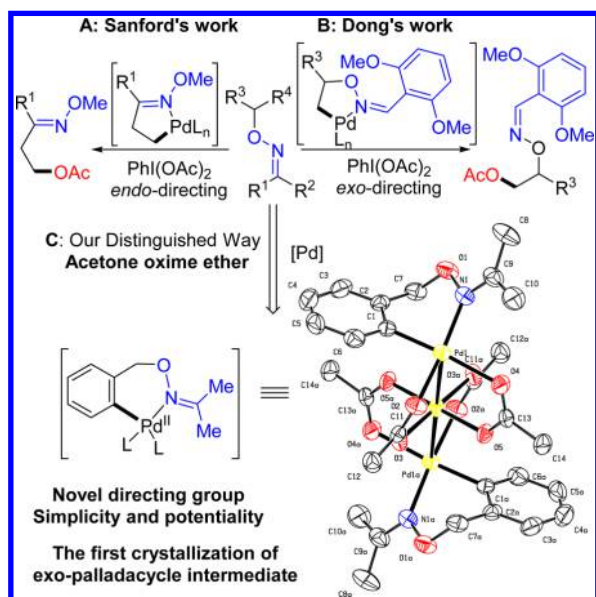
Inspired by these oxime ether directed reactions, we speculated that if the competitive C−H transformation of *endo* pathway could be avoided by employing a concise acetone oxime ether which lacks β-C−H bonds at the ketone side then the unanswered challenge of six-membered *exo*-cyclopalladation[10] should be overcome (Scheme 2C). Based on our development of new directing groups for amine compounds,[11] we might get a

Scheme 1. Hydroxyl-Assisted C−H Transformation

Scheme 2. Pd-Catalyzed Oxime Ether Directed C−H Transformation

Table 1. Optimization of Reaction Conditions[a]

entry	ligand	oxidant	yield[b] (%) (mono/di)
1		AgOAc	8 (8/0)
2	Ac-Gly-OH	AgOAc	41 (36/5)
3	Ac-Ala-OH	AgOAc	58 (51/7)
4	Ac-Val-OH	AgOAc	92 (62/30)
5	Ac-Leu-OH	AgOAc	67 (56/11)
6	PivOH	AgOAc	trace
7	HO$_2$P(OBn)$_2$	AgOAc	11(11/0)
8	1,10-phenanthroline	AgOAc	trace
9[c]	Ac-Val-OH	Cu(OAc)$_2$	15 (15/0)
10	Ac-Val-OH	O$_2$ (1 atm)	7 (7/0)
11[d]	Ac-Val-OH	O$_2$/Cu(OAc)$_2$	11 (11/0)
12	Ac-Val-OH	open air	5 (5/0)
13	Ac-Val-OH	BQ	0
14	Ac-Val-OH	K$_2$S$_2$O$_8$	37 (31/6)
15[e]	Ac-Val-OH	AgOAc	79 (63/16)
16[f]	Ac-Val-OH	AgOAc	85 (67/18)
17[g]	**Ac-Val-OH**	**AgOAc**	**93 (73/20)**
18[h]	Ac-Val-OH	AgOAc	0

[a]Conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), Pd(OAc)$_2$ (5 mol %), ligand (10 mol %), oxidant (0.5 mmol), 1,4-dioxane (1 mL), 90 °C, 20 h. [b]GC yield determined using tridecane as internal standard. [c]Cu(OAc)$_2$ (0.4 mmol). [d]Cu(OAc)$_2$ (0.04 mmol). [e]4 h. [f]8 h. [g]12 h. [h]Without Pd(OAc)$_2$. Ac = acetyl, Gly = glycine, Ala = L-alanine, Val = L-valine, Leu = L-leucine, BQ = 1,4-benzoquinone.

simple and powerful directing group for site selective functionalization of alcohol substrates.

Initially, we treated oxime **1a** with ethyl acrylate **2a** by employing Pd(OAc)$_2$ (5 mol %) as catalyst and AgOAc as oxidant in 1,4-dioxane at 90 °C under an atmosphere of air in a sealed tube to develop an easily accessible olefination protocol for benzyl alcohols. However, in the first run of the experiment, only less than 10% mono-olefinated product **3a** was detected by GC (Table 1, entry 1). To our delight, the mono-N-protected amino acid ligand,[12a] which had been proven to have the ability to enhance many C−H activations, turned out to have better reactivity than PivOH[12b] and HO$_2$P(OBn)$_2$[12c] (Table 1, entries 2−8). Under the optimized reaction conditions, the satisfactory yield of olefinated products was in total 92% (mono/di = 2.1/1) with N-acetyl-L-valine as ligand (entry 4). AgOAc was shown to be the best oxidant in this Pd-catalyzed direct olefination (entries 9−14). Further optimization was also carried out to reduce the diolefinated products (entries 15−17). Slightly higher mono-selectivity could be achieved by reducing the reaction time to 12 h (entry 17).

With optimized conditions in hand, a wide range of the acetone oxime ether masked benzyl alcohols were synthesized and tested, and representative data are shown in Scheme 3. Various functional groups, such as Me, ^{t}Bu, MeS, MeO, F, Cl, CF$_3$, COOMe, and NO$_2$, were all tolerated. Generally, olefination of the *para*-position substituted substrates (Scheme 3, **3b−i**) afforded the mono-olefinated products in good yields (56−67%) and gave the corresponding diolefinated products in 14−32% yield that could be easily separated by silica gel chromatography. The *ortho*-substituted arenes gave good yields (**3j−o**). It is worth mentioning that the α-substituted alcohol **1p−r** gave the mono-olefinated products in 65−86% yield, and the further olefinated products were observed in less than 10% yield as analyzed by ^{1}H NMR (**3p−r**). It is probable that the steric effect inhibited further olefination, which resulted in a highly selective mono-olefination reaction. The electron-withdrawing group substituted arene reacted smoothly and afforded olefinated products in good yield by increasing the catalyst loading to 10 mol % (**3f−i**). The substrates bearing a secondary

alcohol (**1v−x**) were also transformed into the corresponding olefinated products (**3v−x**) in good yields, which might be further applied in construction of bioactive molecules. Generally, the olefination tended to happen at less hindered positions and afforded the mono-olefinated products in moderate to good yields (**3t−u**).

Under the optimized reaction conditions, diverse olefins were tested, and the representative data are listed in Scheme 4. A variety of electron-deficient olefins were compatible in this acetone oxime ether directed C−H transformation. Notably, the olefin of **2g−i** selectively gave the mono-olefinated products **4g−i** in moderate to good yields, implicating the potential application in construction of complex molecules. Acetone oxime ether protected phenethyl alcohols were also tested under the optimized reaction conditions. Gratifyingly, moderate to good yield of *ortho*-olefinated products were achieved, even though those substrates maybe undergo a seven-membered palladacycle intermediate (Scheme 5).

The ideal directing group should have sufficient ability to tolerate C−H activation/functionalization conditions and be easily removed from the substrate or directly converted into diverse functional groups. Indeed, acetone oxime ether fulfilled all of these requirements[10,13] (see the Supporting Information). First, gram-scale reactions were easily achieved in good yields (Scheme 6). Second, selective cleavage of the N−O bond in the products could be accomplished by Mo(CO)$_6$[14a] (Scheme 7A). Alternatively, cleavage of the N−O bond by Raney Ni[14b] afforded the fascinating alkylated benzyl alcohol products (Scheme 7B).

The known antibacterial activity compound 3-deoxyisoochracinic acid[15] **14** was synthesized from the commercial available compounds **12** in five steps with a total yield of 40%, which
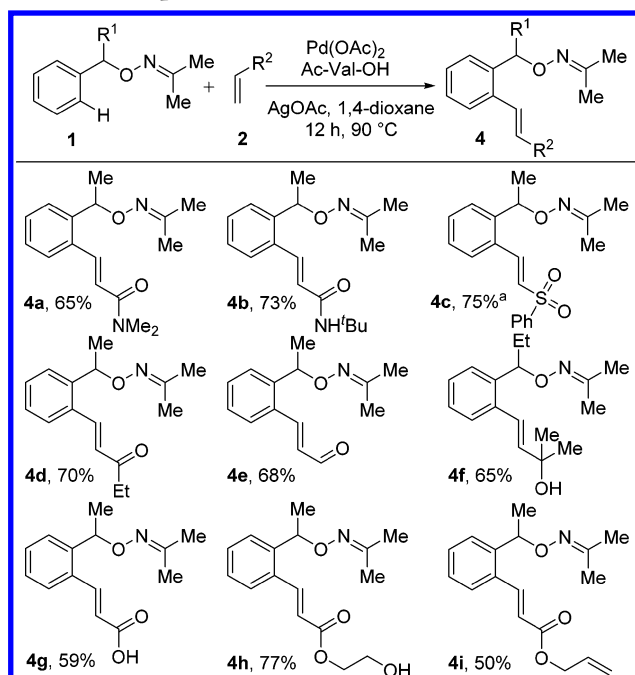
Scheme 3. Scope of Benzyl Alcohols*
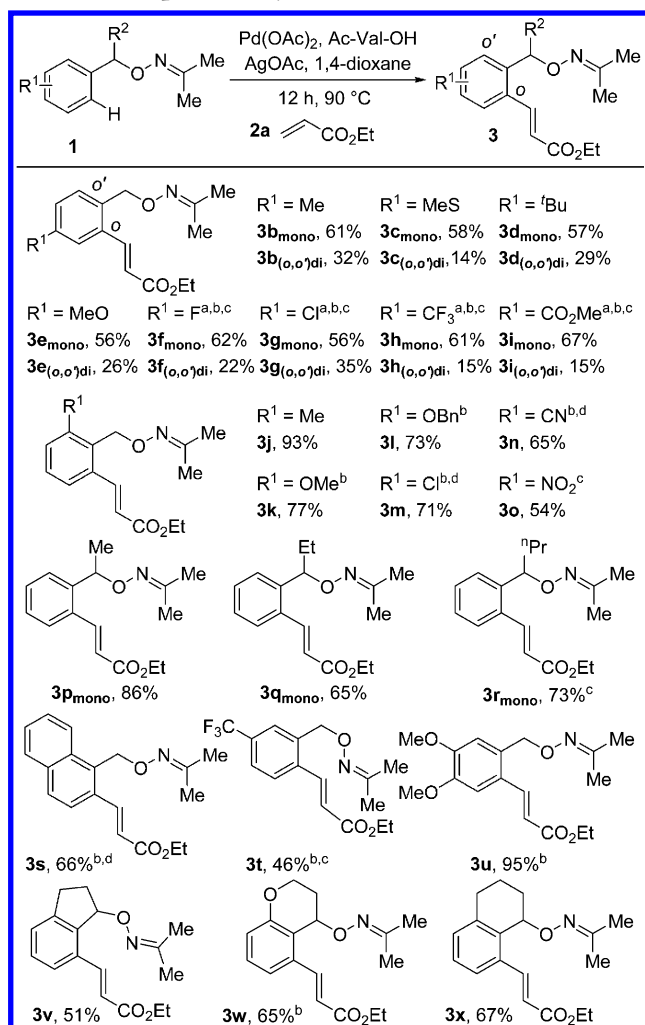
*Conditions: **1** (0.2 mmol), **2a** (0.3 mmol), Pd(OAc)$_2$ (5 mol %), Ac-Val-OH (10 mol %), AgOAc (0.5 mmol), 1,4-dioxane (1 mL), 90 °C, 12 h. o,o′-Diolefinated products **3p–r** were observed but not isolated. [a]Pd(OAc)$_2$ (10 mol %) and Ac-Val-OH (20 mol %) used. [b]20 h. [c]100 °C. [d]120 °C.

Scheme 4. Scope of Olefins*

*Conditions: **1** (0.2 mmol), **2** (0.3 mmol), Pd(OAc)$_2$ (5 mol %), Ac-Val-OH (10 mol %), AgOAc (0.5 mmol), 1,4-dioxane (1 mL), 90 °C, 12 h. Trace o,o′-diolefinated products were observed but not isolated. [a]**2** (0.18 mmol).

Scheme 5. Scope of Phenethyl Alcohols[a]
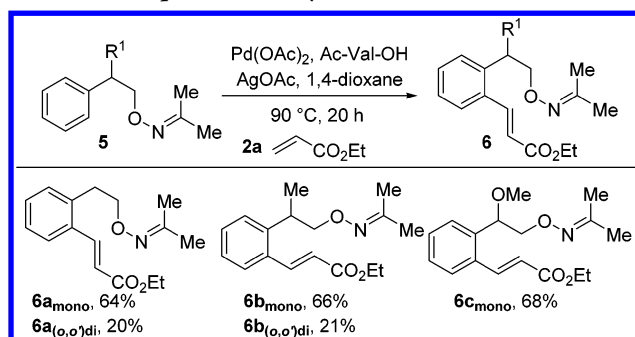
[a]Conditions: **5** (0.2 mmol), **2a** (0.3 mmol), Pd(OAc)$_2$ (5 mol %), Ac-Val-OH (10 mol %), AgOAc (0.5 mmol), 1,4-dioxane (1 mL), 90 °C, 20 h. o,o′-Diolefinated products **6c** were observed but not isolated.

Scheme 6. Gram-Scale Reactions

demonstrated the utility of the acetone oxime ether assisted C–H olefination (Scheme 8).

To gain a deep understanding of this *exo*-directing group assisted C–H transformation, we treated acetone oxime ether protected **1a** with 1.2 equiv of Pd(OAc)$_2$ in CHCl$_3$ and stirred the mixture at room temperature for 5 h, an orange red palladium complex was obtained. Single-crystal X-ray diffraction analysis demonstrated that the six-membered *exo*-palladacycle intermediate was successfully synthesized, which could give a clear insight of these *exo*-directing group directed C–H functionalization reactions (Scheme 2C). Based on the preliminary experimental data, we deduced that the acetone oxime ether assisted C–H functionalization reaction had a tendency to move from Pd(II) to Pd(0) in the catalytic cycle. Hence, a series of C–H transformations could potentially be developed for acetone oxime ether masked aromatic alcohols.
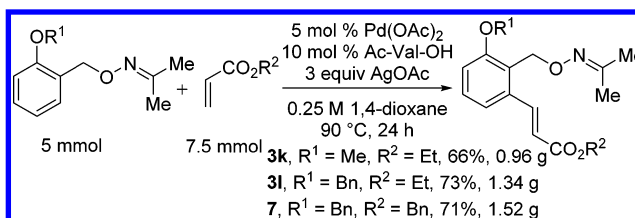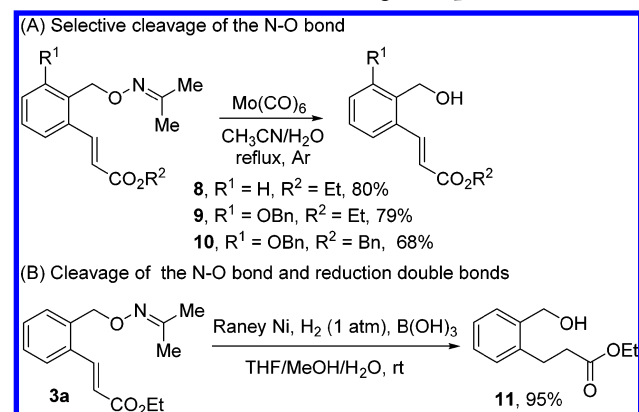
In conclusion, we have developed a versatile and readily transformable directing group for aromatic alcohols. Direct olefination of aromatic alcohols masked by acetone oxime ether were first developed with a broad substrate scope. The mechani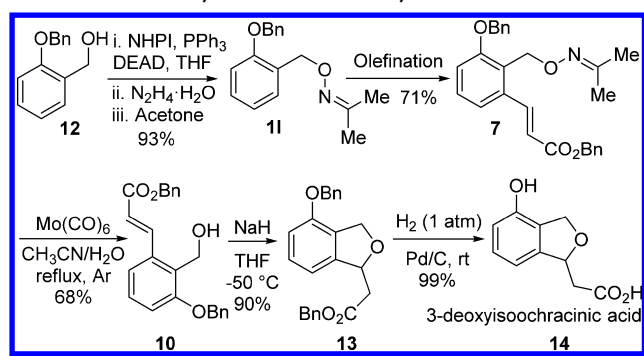sm study gave the first example of an *exo*-palladacycle intermediate crystal, which provided a clear understanding of the *exo*-directed C–H transformation. To demonstrate the utility of this transformation, total synthesis of the antibacterial activity compound 3-deoxyisoochracinic acid was accomplished in five steps. More detailed mechanistic studies are underway in our laboratory.

Scheme 7. Removal of the Directing Group

(A) Selective cleavage of the N–O bond

8, R^1 = H, R^2 = Et, 80%
9, R^1 = OBn, R^2 = Et, 79%
10, R^1 = OBn, R^2 = Bn, 68%

(B) Cleavage of the N–O bond and reduction double bonds

11, 95%

Scheme 8. Total Synthesis of 3-Deoxyisoochacinic Acid

3-deoxyisoochracinic acid

■ ASSOCIATED CONTENT

S Supporting Information

Experimental procedures, X-ray crystallographic analysis, and ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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