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Palladium-Catalyzed β-Acyloxylation of Simple Amide *via* sp^3 C−H Activation

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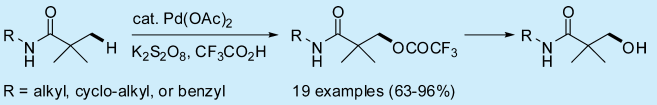
Supporting Information

ABSTRACT: β-Acyloxy amides are prepared in moderate to high yields by palladium-catalyzed acyloxylation of primary sp^3 C−H bonds from simple amides without any special directing group. A catalytic system of $Pd(OAc)_2/CF_3CO_2H/K_2S_2O_8$ is available to various amides with *N*-substituted by linear alkanes, cyclic alkanes, and electron-deficient benzyl compounds in this reaction. Acyloxylated products could be transformed easily to the corresponding β-hydroxy amides.



Transition-metal-catalyzed functionalization of C−H bonds assisted by directing groups has developed rapidly in recent years and has emerged as a powerful tool in organic synthesis.[1] Various common functional groups, such as amines, amides, hydroxyls, carboxylic acids, etc., were found as the directing group to improve the reactivity and regioselectivity in transition-metal-catalyzed sp^2 C−H functionalizations. However, inert sp^3 C−H bonds were reluctant to cleave in the presence of these simple directing groups compared to their sp^2 counterparts. For example, in the transition-metal-catalyzed oxygenation of sp^3 C−H bonds to give alcohols, ethers, or esters, special directing groups, which could bind to catalysts to enhance their reactivity, were often required in these reactions (Scheme 1).[2] *O*-Methyl oxime,[2a] pyridine,[2a] and oxazoline groups[2b] were the early class of directing groups (DG) applied in these oxygenation reactions of sp^3 C−H bonds. Recently, removable or transformable directing groups such as amides 8-aminoquinolines[2c] or *o*-acetyl oximes[2d] were also found to be effective. However, using common functional groups (FG), which exist naturally in both reactants and products, as directing groups esepcially in the selective oxygenation of sp^3 C−H bonds are of considerable interest. In 2012, Hartwig reported that oxygenation of sp^3 C−H bonds by the assistance of a hydroxyl group could be achieved in the presence of an iridium catalyst with a stoichiometric dihydridosilane reagent in a tandem reaction.[2f] On the other hand, the amide group, which is prevalent in natural products and pharmaceuticals, has received much more attention in sp^3 C−H functionalization. Yu disclosed a series of β-functionalizations of some amides, including arylation, alkylation, carbonylation, alkenylation, alkynylation, and chlorination.[3] In the β-oxygenation of amide, however, special directing groups were still necessary.[2h,j] Here, we report that simple amide groups could serve as the directing groups in palladium-catalyzed acyloxylation of unactivated sp^3 C−H bonds to afford β-acyloxy amides, which could be converted to their corresponding β-hydroxy amides easily without loss of the amide motif during this transformation.

In our previous work, we found that the $Pd(OAc)_2/CF_3CO_2H$ system was very effective in activating simple aryl sp^2 C−H bonds in both electron-rich and -deficient arenes, and simple benzylic sp^3 C−H bonds as well.[4] Thus, we attempted to apply this system to the catalytic oxygenation of sp^3 C−H bonds from simple amides. A monosubstituted amide, *N*-butylpivalamide, was selected as the model substrate to test the reaction conditions (Scheme 2). In the presence of 10 mol % $Pd(OAc)_2$, 5 equiv of CF_3CO_2H, and air (1 atm) at 80 °C, no acyloxylated product was detected by ^1H NMR analysis (entry 1). After a series of oxidants were screened, $K_2S_2O_8$ was found to be the most effective one, giving only β-trifluoroacetoxylated amide in 91% yield (entry 2). $PhI(OAc)_2$ was less effective (entry 3), and oxone or O_2 was not completely suitable in this reaction (entries 4, 5). A control test showed that $Pd(OAc)_2$ was essential to ignite this reaction (entry 6). Selecting an appropriate oxidant both to promote the formation of high valent palladium species and to be compatible with this $Pd(OAc)_2/CF_3CO_2H$ system was crucial in this acyloxylation. Different carboxylic acids were also studied, showing that trichloroacetic acid, difluoroacetic acid, or acetic acid with the exception of pavilic acid, a weak acid, was effective in this reaction to give the corresponding acyloxylated products in moderate to good yields respectively (entries 7−10). The effects of $Pd(OAc)_2$, $K_2S_2O_8$, and temperature were further studied, showing that decreasing any one of these decreased the yields significantly (entries 11−13). Moreover, neither non-substituted nor disubstituted simple amides were available in this reaction (entries 14, 15). Overall, the $Pd(OAc)_2/CF_3CO_2H/K_2S_2O_8$ system was quite beneficial to the β-acyloxylation of simple mono-*N*-substituted amides through unactivated sp^3 C−H bond cleavage.

In the investigation of the substrate scope, we found that various monosubstituted amides could be employed in this acyloxylation (Scheme 3). Not only linear aliphatic substituted amides including *n*-butyl, cyclohexylmethyl, 1-ethylpropyl, and *tert*-butyl amides but also cyclic aliphatic substituted amides especially containing five to eight member rings performed very

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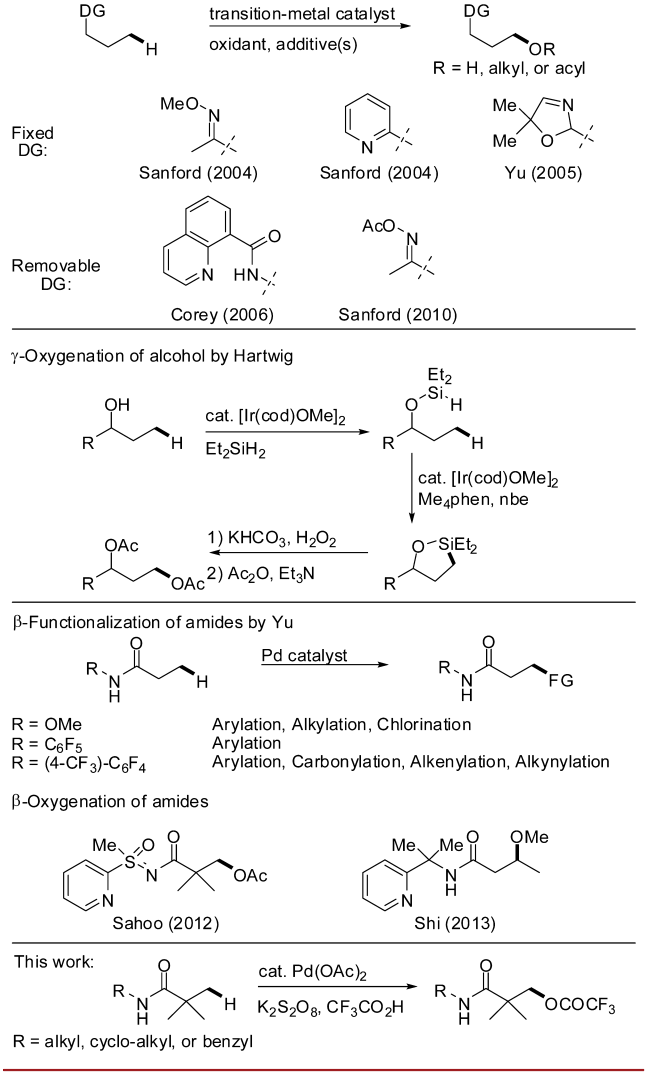
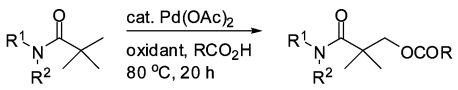
Scheme 1. Transition-Metal-Catalyzed Functionalization of sp^3 C−H Bonds Assisted by Directing Groups



Scheme 2. Optimization of the Reaction Conditions



entry	R^1	R^2	$Pd(OAc)_2$ (mol %)	RCO_2H (5 equiv)	oxidant (equiv)	yield[a] (%)
1	*n*-Bu	H	10	CF_3CO_2H	air (1 atm)	0
2	***n*-Bu**	**H**	**10**	**CF_3CO_2H**	**$K_2S_2O_8$ (2)**	**91**
3	*n*-Bu	H	20	CF_3CO_2H	$PhI(OAc)_2$ (2)	50
4	*n*-Bu	H	10	CF_3CO_2H	oxone (2)	0
5	*n*-Bu	H	10	CF_3CO_2H	O_2 (1 atm)	0
6	*n*-Bu	H	0	CF_3CO_2H	$K_2S_2O_8$ (2)	0
7	*n*-Bu	H	10	CCl_3CO_2H	$K_2S_2O_8$ (2)	40
8	*n*-Bu	H	10	CHF_2CO_2H	$K_2S_2O_8$ (2)	90
9	*n*-Bu	H	10	CH_3CO_2H	$K_2S_2O_8$ (2)	48
10	*n*-Bu	H	10	$C(CH_3)_3CO_2H$	$K_2S_2O_8$ (2)	0
11	*n*-Bu	H	5	CF_3CO_2H	$K_2S_2O_8$ (2)	53
12	*n*-Bu	H	10	CF_3CO_2H	$K_2S_2O_8$ (1)	56
13	*n*-Bu	H	10	CF_3CO_2H	$K_2S_2O_8$ (2)	32[b]
14	H	H	10	CF_3CO_2H	$K_2S_2O_8$ (2)	trace
15	Et	Et	10	CF_3CO_2H	$K_2S_2O_8$ (2)	0

[a]Yields based on substrate and detected by ^1H NMR analysis in situ using CH_2Br_2 as internal standard. Alcoholysis of the *β*-acyloxylated amides occurred to the corresponding *β*-hydroxy amides, which were isolated by flash chromatography. For details, see Supporting Information. Conditions: substrate (1.0 mmol), $Pd(OAc)_2$ (0.1 mmol), $K_2S_2O_8$ (2.0 mmol), CF_3CO_2H (5.0 mmol), 80 °C, 20 h. [b]60 °C.

well to give their corresponding products in high yields. Although no desired product was detected in the case of cyclopropyl substituted amide, an acyloxylated product from highly strained cyclobutyl substituted amide was obtained in 63% yield. Notably, all acyloxylated products were *β*-substituted ones for the carbonyl group rather than for the amino group of amides and the chemical selectivity was good, giving only mono-*β*-acyloxylated products in this reaction. For benzyl substituted amides, strong electron-deficient benzyl substituted amides such as *N*-(4-nitrobenzyl)pivalamide and *N*-(4-trifluorobenzyl)pivalamide could afford the corresponding acyloxylated products in high yield. Halogen atoms such as fluorine, chlorine, or bromine attached to arenes were also tolerated during reactions. However, either a benzyl amide without electron-deficient groups or an aryl amide such as *N*-(4-nitrophenyl)pivalamide gave biaryls as products, indicating that activation of aryl sp^2 C−H bonds was more easily compared to that of sp^3 C−H bonds under the same reaction conditions. For the sp^3 C−H bond at the *β*-position of the carbonyl group, primary sp^3 C−H bonds from ethyl dimethyl amides were also effective in giving high product yields in these reactions. However, a mono-*N*-alkyl substituted dimethyl amide gave its corresponding acid as the detected product (Scheme 4). After installation of an ester methylene group to the amide linkage, which may make the nitrogen of the amide less electron-rich and coordinate to the Pd catalyst firmly, and further optimization of the reaction conditions especially in raising the reaction temperature and replenishing $K_2S_2O_8$ in a timely manner, a *β*-primary sp^3 C−H acyloxylated amide from dimethyl amide was obtained in 48% yield. Acyloxylation of the secondary sp^3 C−H bonds of amides was more hindered compared to their primary counterparts since decomposition of amides happened readily.

The *β*-acyloxy amide products could be mildly turned to their corresponding *β*-hydroxy amides by using a regular alcoholysis method (Scheme 5).

A reaction mechanism is proposed as follows (Figure 1). There are three main steps involved in the catalytic cycle: (1) a Pd(II) species coordinates with an amide group and attacks its sp^3 C−H bond to produce an alkyl−Pd(II) intermediate. Since the highly cationic $Pd(OAc)_2/CF_3CO_2H$ system performs very well in the reaction, an eletrophilic metalation process is probably involved in this C−H activation step; (2) the formed alkyl−Pd(II) intermediate is oxidized to its Pd(IV) state by an oxidant $K_2S_2O_8$. (3) A *β*-acyloxy amide product is formed by reductive elimination from the high valent Pd(IV) species, and

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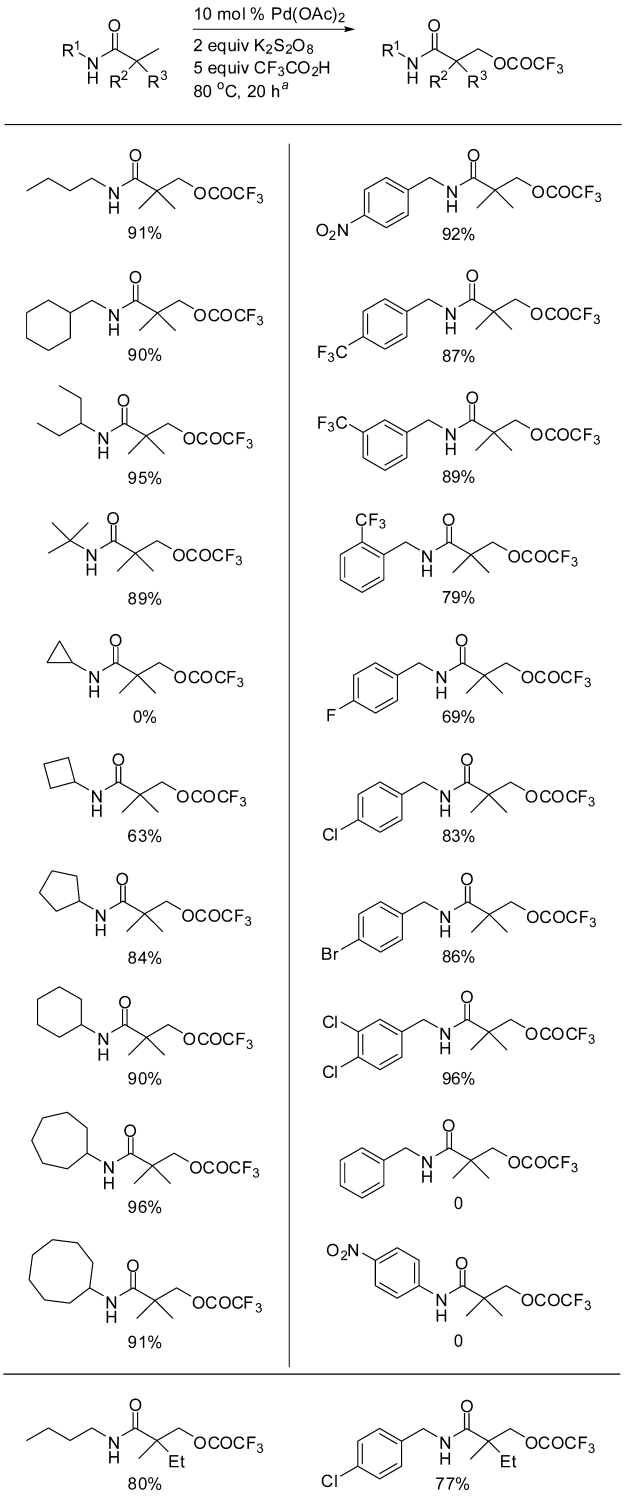
Scheme 3. Investigation of the Reaction Scope (1)

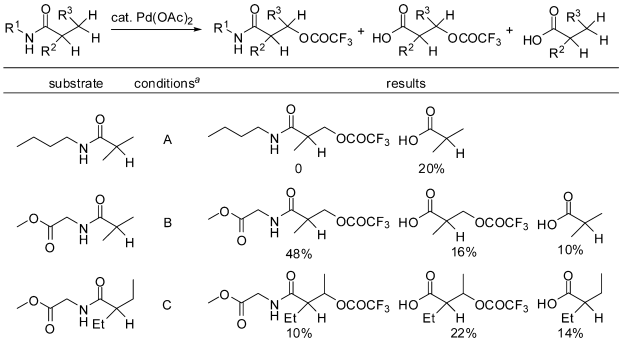


[a]Yields based on substrate and detected by ^{1}H NMR analysis in situ using CH_2Br_2 as internal standard. Alcoholysis of the β-acyloxylated amides occurred to the corresponding β-hydroxy amides, which were isolated by flash chromatography. For details, see Supporting Information.

the Pd(IV) species is reduced to a Pd(II) species to fulfill the catalytic cycle.

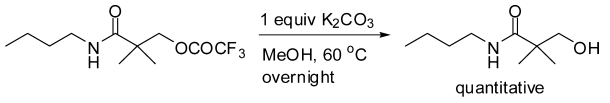
In this work, we reported a palladium-catalyzed acyloxylation of unactivated sp^3 C−H bonds from simple amides. Primary sp^3 C−H bonds at the β-position of amides were more suitable than secondary ones for activation in the $Pd(OAc)_2/CF_3CO_2H$ system. Selection of an appropriate oxidant $K_2S_2O_8$ was very important to promote this reaction and to complete the catalytic cycle. Various amides *N*-substituted by linear alkanes, cyclic alkanes, and electron-deficient benzyl compounds were employed successfully to produce their β-acyloxy amides in this reaction. These acyloxylated products could be easily converted to their corresponding β-hydroxy amides using common methods. Further research on the scope, mechanism, and application of this acyloxylation reaction is ongoing.

Scheme 4. Investigation of the Reaction Scope (2)



[a]Yields based on substrate and detected by ^{1}H NMR analysis in situ. Conditions A: substrate (1.0 mmol), $Pd(OAc)_2$ (0.1 mmol), $K_2S_2O_8$ (2.0 mmol), CF_3CO_2H (5.0 mmol), 80 °C, 20 h. Conditions B: substrate (0.5 mmol), $Pd(OAc)_2$ (0.1 mmol), $K_2S_2O_8$ (2.0 mmol), CF_3CO_2H (10.0 mmol), 105 °C, 2 h; then added substrate (0.5 mmol), $K_2S_2O_8$ (2.0 mmol), CF_3CO_2H (10.0 mmol), 105 °C, 4 h. Conditions C: substrate (0.5 mmol), $Pd(OAc)_2$ (0.1 mmol), $K_2S_2O_8$ (2.0 mmol), CF_3CO_2H (10.0 mmol), 110 °C, 4 h.

Scheme 5. Alcoholysis of β-Acyloxylated Amides to the Corresponding β-Hydroxy Amides



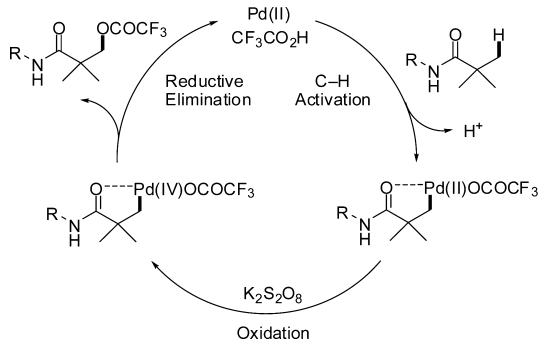


Figure 1. Proposed reaction mechanism.

■ ASSOCIATED CONTENT

Supporting Information

Text and figures giving experimental details and characterization data for simple amides, acyloxy amides, and hydroxy amides. 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.

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