Organic LETTERS

Letter

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Direct Oxidation of Aliphatic C−H Bonds in Amino-Containing Molecules under Transition-Metal-Free Conditions

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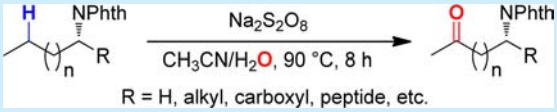
Supporting Information

ABSTRACT: By employing a simple, inexpensive, and transition-metal-free oxidation system, secondary C−H bonds in a series of phthaloyl protected primary amines and amino acid derivatives were oxidized to carbonyls with good regioselectivities. This method could also be applied to oxidize tertiary C−H bonds and modify synthetic dipeptides.



Direct oxidation of an unactivated aliphatic C−H bond in a chemo-, site-, and stereoselective manner is a challenging task and has been a long-term aspiration in organic synthesis.[1] With great effort made by generations of chemists, several successful and valuable models have been well established. By using stoichiometric active oxygen-atom donor reagents, such as DMDO,[2] TFDO,[3] and high-valent metal oxides,[4] the aliphatic C−H bonds in simple starting materials can be successfully oxidized, though these protocols often produce mixtures of regioisomers. Recently, as the alternatives to those highly active oxygen-atom donor reagents, hypervalent iodine reagents[5] and catalytic amounts of oxaziridines[6] have been successfully used in selective C−H oxidation reactions. Another successful strategy to approach this goal mainly relies on the application of well-defined oxidase mimics or nonheme metal−oxo complex catalysts in combination with less active oxidants such as H_2O_2.[7−11] For example, White and co-workers have developed a practical iron catalyst/H_2O_2 system to predictably oxidize aliphatic C−H bonds in a series of compounds.[8a,b,16a] In addition, the "directing" strategy was applied by Baran,[12a] Yang,[12b,c] and other groups.[12d−f] In those cases, the targeted C−H bonds were oxidized efficiently by well-designed pathways.[12]

Amino groups are ubiquitous in organic molecules. The oxo-/hydroxyl-containing amines and amino acid derivatives have also been found in a series of pharmaceuticals, natural compounds, and biomolecules (Figure 1A).[13] Apparently, the direct C−H oxidation of amino-containing substrates is the most straightforward synthetic pathway to obtain these bioactive compounds. Although numerous protocols for C−H functionalizations in complicated molecules have been established,[14] direct C−H oxidations in amino-containing molecules are still challenging. The existing protocols include C−H bond acetoxylation (Figure 1B, pathway a)[15] and

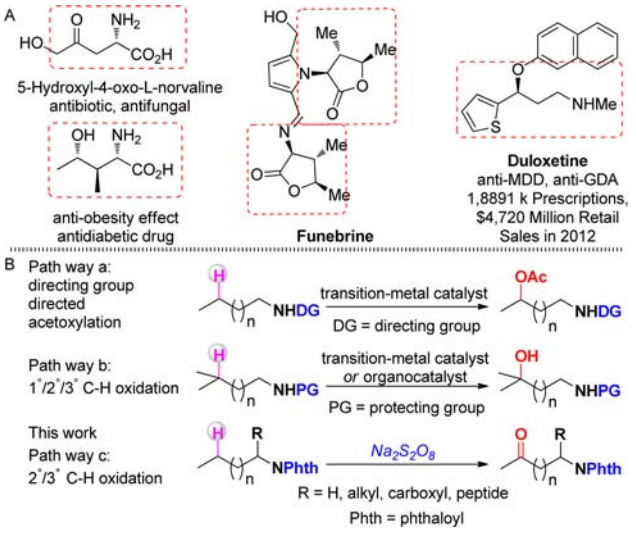


Figure 1. Bioactive molecules and strategies on C−H oxidation of amino-containing compounds.

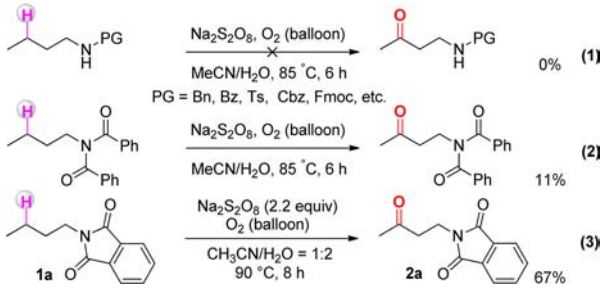
transition-metal-catalyzed or organocatalytic C−H bond oxidation (Figure 1B, pathway b).[16,17] We herein report a simple oxidation system to perform the site-selective oxidation of remote aliphatic 2°/3° C−H bonds in amino-containing molecules using sodium persulfate as oxidant (Figure 1B, pathway c).

The oxidation of N-protected primary amines was selected as model reaction to actualize our plan. At first, N-monoprotected primary amines all failed to give the desired products, while

Received: December 28, 2015
Published: March 7, 2016

DOI: 10.1021/acs.orglett.5b03690
Org. Lett. 2016, 18, 1234−1237

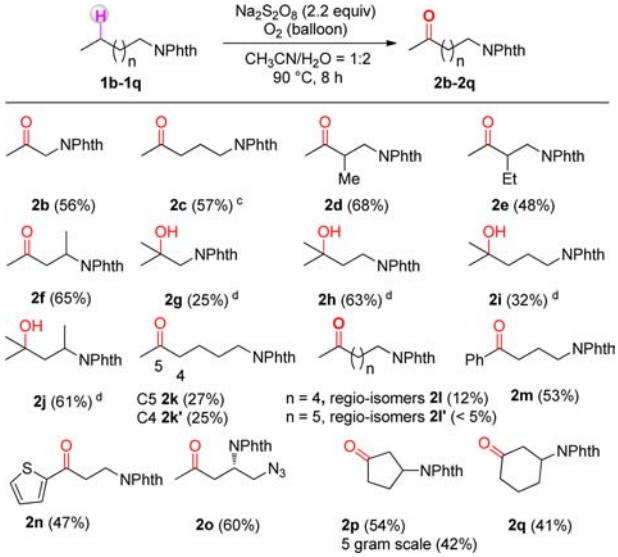
N,*N*-dibenzoylamine afforded the target product albeit in a low yield (eqs 1 and 2). After further structural modification and



condition optimizations, the phthaloyl (Phth)-protected *n*-butylamine **1a** was successfully oxidized to 3-oxobutylamine **2a** in water/acetonitrile mixed solvents by using sodium persulfate as an oxidant (eq 3).[18]

Next, a range of *N*-Phth-protected amines with different carbon chains were subjected to the standard conditions. As shown in Scheme 1, methylenes were oxidized to carbonyls

Scheme 1. Selective C−H Oxidation of Amines[a,b]

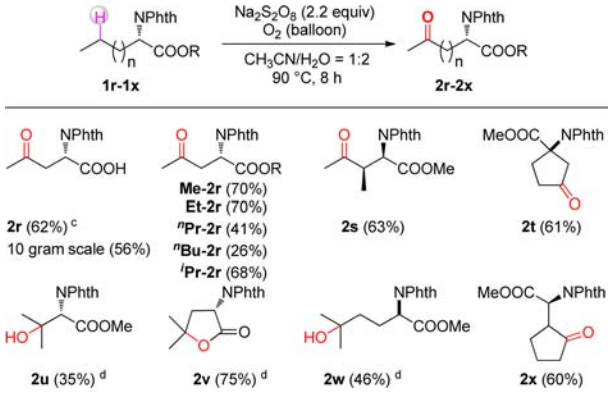


[a]Reaction conditions: *N*-Phth-protected amines (0.10 mmol), sodium persulfate (0.22 mmol), water (2.0 mL), acetonitrile (1.0 mL), O_2, 90 °C, 8 h. [b]Isolated yield. [c]ω-1/ω-2 is >16:1. [d]Under N_2.

(**2a**−**f**), while tertiary C−H bonds were oxidized to hydroxyl groups (**2g**−**j**). Furthermore, the oxidation held a high ω-1 site selectivity when linear substrates with three to five carbon chains were used, even if the substrates incorporated a tertiary C−H bond at the ω-2 position (**2d** and **2e**).[19] When 1-hexylamine was used, however, the ω-1 selectivity was not maintained and a mixture of regioisomers with almost 1:1 ratio was obtained (**2k** and **2k**′). Probably due to low solubility in water/acetonitrile, when *n*-heptyl- and *n*-octylamine derivatives were submitted, low conversions were obtained with the mixture of regioisomers as products (**2l** and **2l**′). Substrates containing benzylic C−H bonds were oxidized to benzoyl products (**2m** and **n**). Further investigation showed that the azide group could be tolerated under the standard conditions with a satisfying yield and ω-1 selectivity (**2o**). Moreover, cycloalkyl primary amines were also oxidized, affording the γ-oxo products (**2p** and **2q**), exhibiting the potential applications in cyclic system.

This method was successfully expanded to aliphatic C−H oxidation of amino acids and their derivatives (Scheme 2). The

Scheme 2. Selective C−H Oxidation of Amino Acid Derivatives[a,b]



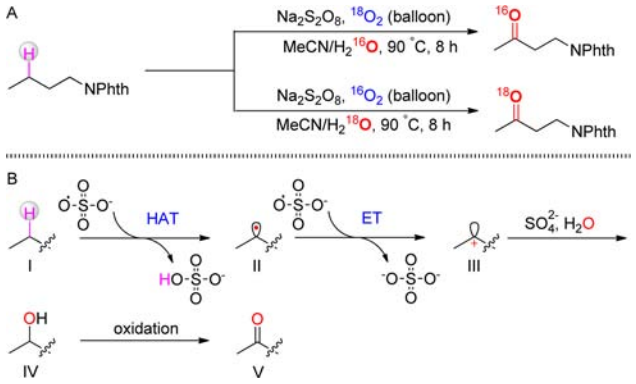
[a]Reaction conditions: *N*-Phth-protected amino acids (0.10 mmol), sodium persulfate (0.22 mmol), water (2.0 mL), acetonitrile (1.0 mL), O_2, 90 °C, 8 h. [b]Isolated yield. [c]Potassium persulfate (0.15 mmol), water (2.0 mL), acetonitrile (1.0 mL), O_2, 85 °C, 4 h. [d]Under N_2.

free acid of *N*-phth-norvaline (**2r**), as well as a series of *N*-phth-norvaline esters, were all suitable substrates. Among them, methyl (**Me-2r**), ethyl (**Et-2r**), and isopropyl esters (**^{i}Pr-2r**) were smoothly converted to the corresponding desired products, while the yields sharply dropped off with *n*-propyl/*n*-butyl esters (**^{n}Pr-2r** and **^{n}Bu-2r**). In those cases, only the amino acid oxidized products were isolated. As the regioselectivities in amine substrates, the oxidation occurred at the ω-1 position, regardless of the existence of tertiary C−H bonds in the molecules (**2s**). L-Leucine derivatives gave a γ-lactone as a sole product (**2v**), which arose from the lactonization of the produced alcohol, while L-valine and 2-aminohexanoic acid derivatives gave hydroxyl products, owing to the lower stabilities of β- and δ-lactones under the reaction conditions (**2u** and **2w**). Similarly, the oxidation also proceeded well on cyclic substituents, affording the γ-oxo products with good selectivities and yields (**2t** and **2x**). Moreover, after the oxidation reaction, good optical purity could be obtained. For example, the value of the specific optical rotation of compound **Me-2r** matches well with the literature reported value, indicating that no racemization occurred at the steric center (see the Supporting Information for details).

To confirm the source of the oxygen atom in the products, ^{18}O-labeling experiments were carried out. The results clearly showed that the oxygen atom came from water, rather than from dioxygen (O_2) or persulfates (Scheme 3A). The addition of TEMPO shut down the reaction, indicating that this reaction proceeded via a radical pathway. These data as well as the fact that the reaction also performed well under N_2 all indicated that O_2 did not play a key role in the reaction. Thus, a plausible pathway is proposed in Scheme 3B. With a thermal activation, sulfate radical anions are generated by pyrolysis of persulfate. The intermolecular H-abstraction between sulfate radical and substrate **I** forms a carbon radical **II**. Radical **II** is further oxidized by another sulfate radical to generate carbocation **III**, which reacts with O-based nucleophiles to yield the alcohol intermediate **IV**. Secondary alcohols are not stable and further

DOI: 10.1021/acs.orglett.5b03690
Org. Lett. 2016, 18, 1234−1237

Scheme 3. ^{18}O-Labeling Experiments and Plausible Mechanism



oxidized to the final product **V** under the oxidative conditions. Moreover, the possibility of single-electron transfer between phthalimide (PhthN) group and sulfate radical was also investigated. Molecular dynamics simulations, DFT calculations, and Marcus theory were used to calculate the rate of electron transfer from PhthN group to persulfate corresponding to the experimental conditions. The calculations showed that it was a fast electron transfer in the inverted region and the rate of electron transfer from PhthN group to persulfate was about 10^{10} $mol^{-1}\cdot L\cdot s^{-1}$ at room temperature (see the Supporting Information for details).

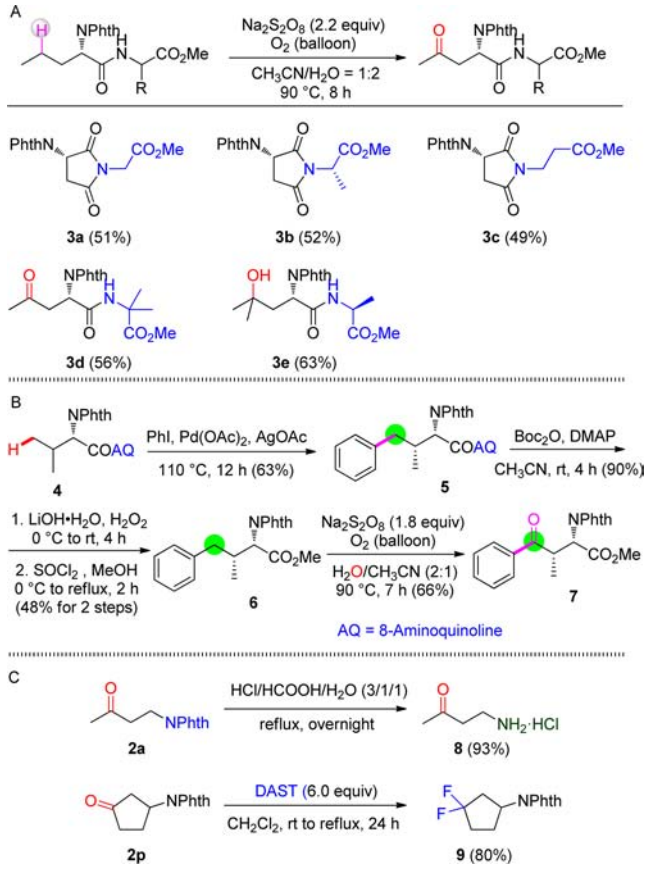
After establishing the site-selective C−H oxidation in *N*-phth-protected amine and amino acid derivatives, we moved our endeavor to the modification of synthetic peptides. To our satisfaction, the ω-1 methylene groups of the dipeptides were oxidized with an interesting chemoselectivity on the C-residues. For those with less hindered C-residues, such as Gly and Ala, the succinimide-type products were obtained (Scheme 4A, **3a-c**), which was considered to be generated via a C−H oxidation/intramolecular nucleophilic addition/hydroxyl elimination/C−C bond cleavage cascade process.[20] On the other hand, more bulky C-residues prevented the amidation process from the C−H oxidation step, thus affording the normal oxo-dipeptide products (**3d**). The methine groups were oxidized to hydroxyls, affording a new dipeptide (**3e**). In all cases, both stereogenic centers in dipeptides were well maintained.

Additionally, the herein developed protocol was combined with the protocols based on directing strategy to conduct sequential functionalization of different aliphatic C−H bonds to assemble complex molecules (Scheme 4B). After the amino group was protected with a phthaloyl group and the carboxylic acid motif with 8-aminoquinoline (AQ), the prepared substrate **4** underwent 8-AQ-directed arylation to afford a new amino acid derivative **5**.[15a] According to ref 21, the 8-AQ group was removed and the oxidation of the newly formed amino acid **6** further gave another new amino acid ester **7**.

The removal of the Phth group in the oxidized products was carried out to afford the corresponding hydrochloride salt in high yield. Moreover, the generated carboxyl group could be transferred into difluoromethylene in good yield, which further extended its applications (Scheme 4C).

In summary, we have accomplished a simple, efficient, and site-selective oxidation of remote aliphatic C−H bonds. Various amino-containing compounds, including a series of primary amines, amino acids, and their derivatives as well as dipeptides, were successfully oxidized to the corresponding oxo products.

Scheme 4. Synthetic Applications



Efforts to clearly understand the mechanisms and explore further applications are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03690.

MB simulation details (PDF)
Experimental procedures and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support of this work by the "973" Project from the MOST of China (2015CB856600) and NSFC (No. 21332001) is acknowledged. We thank Prof. Li-Zhu Wu and Dr. Qing-Yuan Meng (Technical Institute of Physics and Chemistry, Chinese Academy of Sciences), Prof. Jian Pei, Prof. Ning Jiao, Dr. Xiao-Ye Wang, Dr. Yu-Feng Liang, and Mr. Ke Shi (Peking University), and Prof. San-Zhong Luo (Institute of Chemistry, Chinese Academy of Sciences) for their generous help. We appreciate the instructive discussion and draft polishing work

DOI: 10.1021/acs.orglett.5b03690
Org. Lett. 2016, 18, 1234−1237

from Prof. Chuan He (The University of Chicago) and Prof. E. Peter Kündig (University of Geneva).

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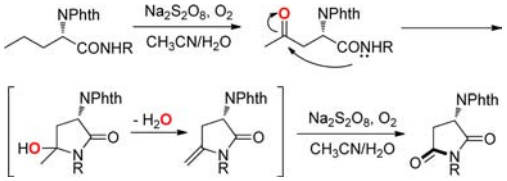
(19) After the oxidation of *n*-pentylamine substrate, a small amount of ω-2-oxidized product was found in crude ^{1}H NMR, and the ratio of ω-1/ω-2 is >16/1.

(20) The succinimide-type products may be generated via the following cascade process:



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DOI: 10.1021/acs.orglett.5b03690
Org. Lett. 2016, 18, 1234–1237