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Aerobic Direct Dioxygenation of Terminal/Internal Alkynes to form α-Hydroxyketones by Fe Porphyrin Catalyst

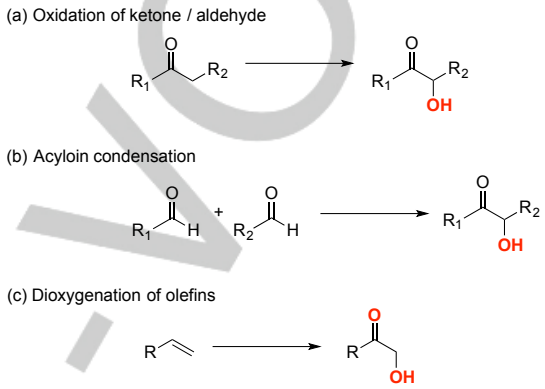
Kento Kimura, Takuya Kurahashi,* and Seijiro Matsubara*

Abstract: We herein report a new synthetic method for the preparation of α-hydroxyketones by the dioxygenation of alkynes. The reaction proceeds at room temperature under the action of Fe porphyrin and pinacolborane under air as a green oxidant to produce α-hydroxyketones. The mild reaction conditions allow chemoselective oxidation with functional group tolerance. Terminal alkynes in addition to internal alkynes are applicable, affording unsymmetrical α-hydroxyketones that are difficult to obtain by any reported dioxygenation of unsaturated C–C bonds.

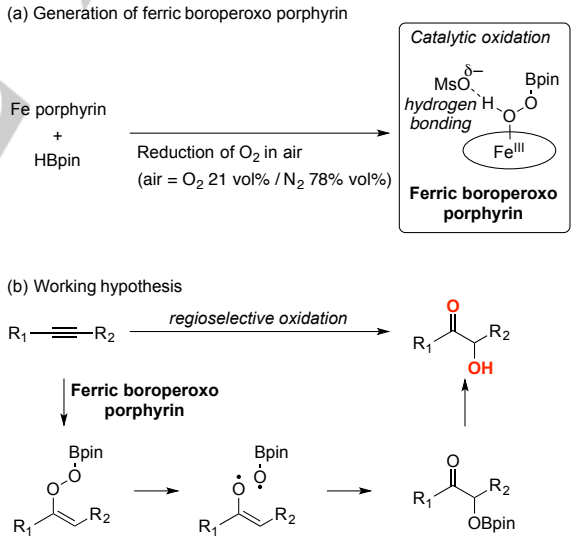
α-Hydroxyketones are important structural motifs in natural products[1] and drug molecules,[2] as well as useful intermediates in organic chemistry.[3] Various methods have been reported for the synthesis of the α-hydroxyketone moiety.[4-6] Among these, methodologies using carbonyl compounds as starting materials for transformations such as α-hydroxylation[4] and the acyloin condensation[5] are widely known, although unsymmetrical α-hydroxyketone synthesis with full regiocontrol remains challenging (Scheme 1a, 1b). On the other hand, the direct dioxygenation of a carbon–carbon unsaturated bond could be considered one of the most reasonable strategies from the perspective of step economy. Indeed, the dioxygenation of olefins to α-hydroxyketones has been developed through the use of noble metal catalysts such as osmium,[6a,6b] ruthenium,[6c,6d] tungsten,[6e] and palladium.[6f] For environmentally friendly oxidation reactions, metal-free conditions employing iodine[7] and *N*-bromosuccinimide[8] were recently reported (Scheme 1c). However, the oxidation of internal olefins to unsymmetrical internal α-hydroxyketones is very limited due to the difficulty of regioselective oxidation. Alkynes are another class of compounds containing unsaturated C–C bonds. Although α-acetoxyketone synthesis by the oxidation of alkynes has been reported,[9] the oxidation of alkynes to α-hydroxyketones has not been described, to the best of our knowledge.

Dioxygen in ambient air is an ideal oxidant for green chemistry by virtue of its nominal cost and ready availability; it has been used for various oxidation reactions.[10,11] However, the aerobic oxidation of alkynes is generally difficult owing to the generation of unstable radical/ionic intermediates during the reaction compared to alkenes.[12] Iron-catalyzed oxidations are well known in enzymatic reactions *in vivo* and are also attractive in terms of eco-friendliness because of their low toxicity and

Scheme 1. Direct synthesis of α-hydroxyketone moiety.



Scheme 2. Catalytic aerobic oxidation by ferric porphyrin catalyst.



cheapness compared with other rare metals.[13] In our previous work, we reported the generation of a ferric boroperoxoporphyrin species by use of a ferric porphyrin complex and pinacolborane in air atmosphere (Scheme 2a).[14,15] Following upon our previous study, we envisioned the oxidation of alkynes by the ferric porphyrin complex to obtain α-hydroxyketones. As shown in Scheme 2b, the ferric boroperoxoporphyrin that is formed from ferric porphyrin, pinacolborane, and oxygen was expected to add to an alkyne regioselectively to form a boroperoxo alkynyl complex. This species can undergo homolytic scission of the O–O bond to yield the corresponding alkoxy radicals that recombine at the α-position of the carbonyl moiety to form the α-hydroxyketone.

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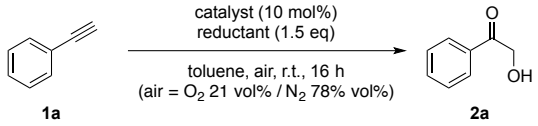
To prove our hypothesis, we initially examined the oxidation of phenylacetylene (**1a**) using [Fe(TPP)]Cl (iron(III) tetraphenylporphyrin chloride) as the catalyst and pinacolborane (HBpin) as the reductant in toluene at room temperature in air (Table 1). Unfortunately, the reaction did not proceed, although a trace amount of 2-hydroxy-1-phenylethan-1-one (**2a**) was obtained (entry 1). However, upon changing the counter anion of the catalyst from Cl to mesylate (OMs), the yield of **2a** was dramatically increased to 78% (entry 2). Other iron porphyrin catalysts were not suitable for the reaction (entries 3–5). Using more reactive boron and silane reducing agents gave poor yields of **2a** due to over reduction of the resulting product (entries 6–9). $FeCl_3$, the efficient catalyst used in the aerobic olefin oxidation reaction,[16] did not promote this reaction (entry 10). Finally, control experiments in the absence of an iron catalyst, reductant, or air atmosphere resulted in no product formation (entries 11–13).

Table 1. Optimization of the reaction conditions for Fe porphyrin-catalyzed oxidation of alkynes.[a]

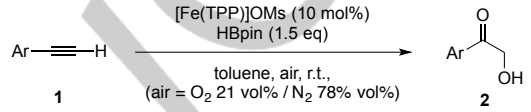


Entry	Catalyst	Reductant	Yield (%)[b]
1	[Fe(TPP)Cl]	HBpin	<5
2	[Fe(TPP)OMs]	HBpin	78
3	[Fe(TMP)OMs]	HBpin	31
4	[Fe(TPFPP)OMs]	HBpin	51
5	[Fe(OEP)OMs]	HBpin	<5
6	[Fe(TPP)OMs]	9-BBN	21
7	[Fe(TPP)OMs]	$NaBH_4$	<5
8	[Fe(TPP)OMs]	TESH	<5
9	[Fe(TPP)OMs]	PMHS	<5
10	$FeCl_3$	HBpin	<5
11	–	HBpin	<5
12	[Fe(TPP)OMs]	–	<5
13[c]	[Fe(TPP)OMs]	HBpin	<5

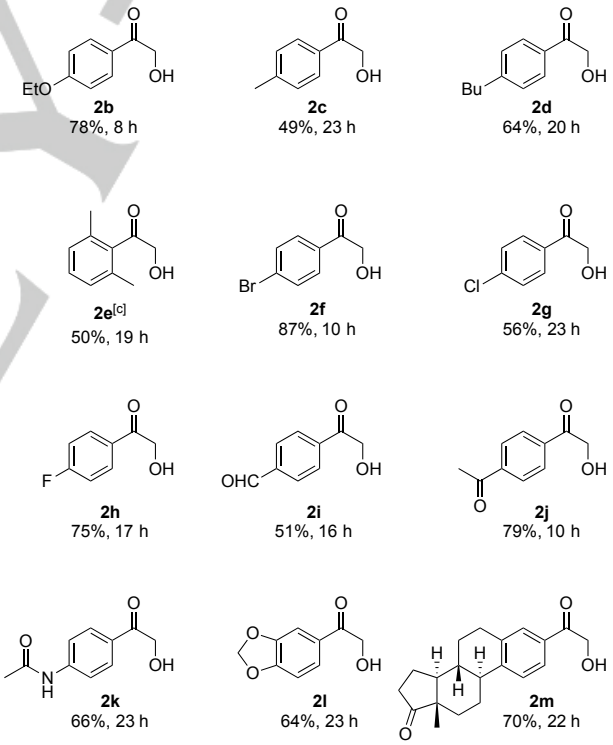
[a] Reaction conditions: **1** (0.1 mmol), catalyst (10 mol%), reductant (1.5 equiv), solvent (2 mL, 0.05 M), room temperature, air (1 atm; O_2, 21 vol%), 16 h. [b] ^{1}H NMR yield using 1,1,2,2-tetrachloroethane as internal standard. [c] Reaction under N_2. TPP: 5,10,15,20-tetraphenylporphyrin. TMP: 5,10,15,20-tetramesitylporphyrin. TPFPP: 5,10,15,20-tetrapentaflurophenylporphyrin. OEP: 2,3,7,8,12,13,17,18-octaethyl-21H,23H-porphine. TESH: triethylsilane. PMHS: polymethylhydrosiloxane.

With optimized reaction conditions in hand, we first tested various types of terminal alkynes (Figure 1). Substituted aromatic terminal alkynes with electron-donating ether (**2b**) or alkyl moieties (**2c**, **2d**), and electron-withdrawing groups such as halides (**2f**–**2h**) or carbonyl groups (**2i**–**2k**), were oxidized to furnish the corresponding α-hydroxyketones. These products would be difficult to obtain by the previously reported reaction that oxidized the α-position of a carbonyl compound.[4] In addition, a sterically hindered aromatic terminal alkyne (**2e**) was suitable for the reaction. Moreover, polycyclic aromatic alkynes with an acetal (**2l**) or estrone (**2m**) moiety were compatible and provided the desired products.

Figure 1. Substrate scope for the Fe porphyrin-catalyzed oxidation of aromatic terminal alkynes.[a]

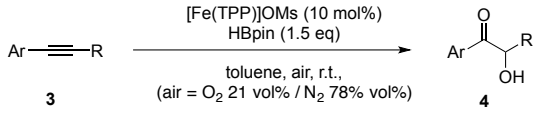


Product (%)[b]

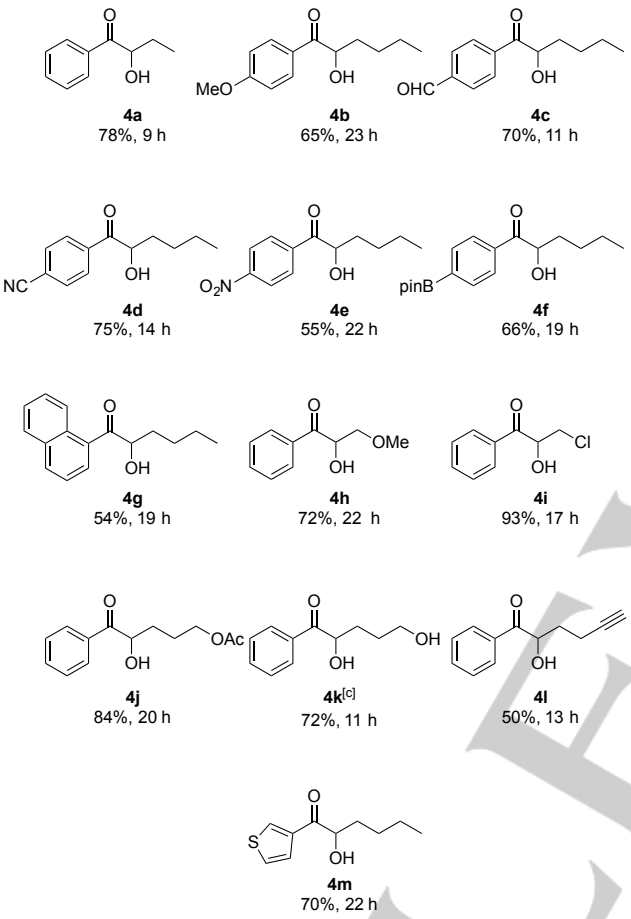


[a] Reaction conditions: **1** (0.1 mmol), catalyst (10 mol%), reductant (1.5 equiv), solvent (2 mL, 0.05 M), room temperature, air (1 atm; O_2, 21 vol%), indicated time. [b] ^{1}H NMR yield using 1,1,2,2-tetrachloroethane as internal standard. [c] 3.0 equivalents of HBpin were used.

Figure 2. Substrate scope for the Fe porphyrin-catalyzed oxidation of aromatic internal alkynes.[a]



Product (%)[b]

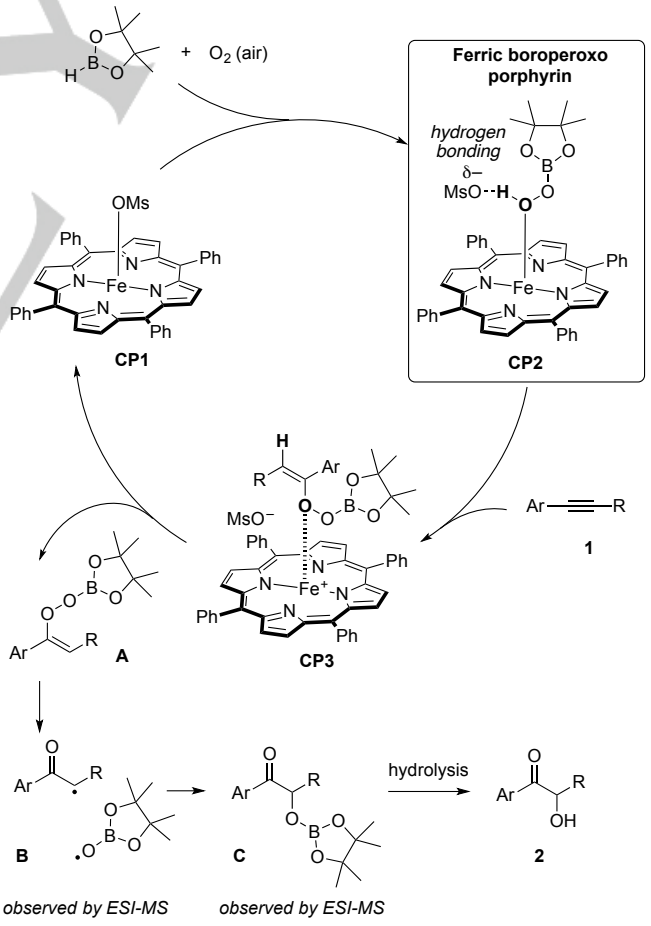


[a] Reaction conditions: **1** (0.1 mmol), catalyst (10 mol%), reductant (1.5 equiv), solvent (2 mL, 0.05 M), room temperature, air (1 atm; O_2, 21 vol%), indicated time. [b] ^{1}H NMR yield using 1,1,2,2-tetrachloroethane as internal standard. [c] 3.0 equivalents of HBpin were used.

We next expanded the scope of the oxidation reaction with aromatic internal alkynes; the products from these reactions would be challenging to access from the dioxygenation of olefins[6] (Figure 2). Gratifyingly, each alkyne underwent oxidation with full regioselectivity. 1-Phenylhexyne with aromatic ring substituents such as an electron-donating methoxy group (**4b**), electron-withdrawing cyano (**4d**) and nitro substituents (**4e**), and easily oxidized formyl (**4c**) and boronic acid groups (**4f**) underwent oxidation. Heteroaromatic alkyne (**4m**) was applicable in the reaction. Functional groups on the alkyl chain portion of the alkyne, including methoxy (**4h**), chloro (**4i**), acetoxy (**4j**), and hydroxyl groups (**4k**), also afforded the corresponding α-hydroxyketones. In particular, the chemoselective oxidation of an aromatic internal alkyne bearing a terminal aliphatic alkyne moiety gave **4l**. This result highlights the good chemoselectivity of the oxidative transformation.

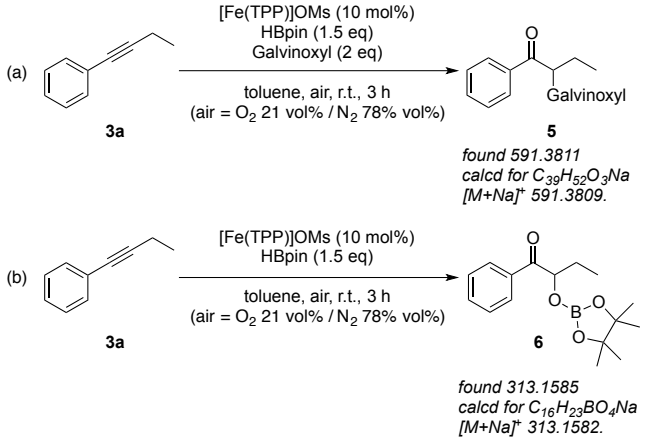
A plausible mechanism for the oxidation is postulated in Figure 3. Initially, Fe porphyrin (**CP1**) is activated by oxygen and pinacolborane to afford an Fe peroxoporphyrin complex (**CP2**). We previously reported that Fe boroperoxoporphyrin **CP2** is formed via the reduction of oxygen by **CP1** and pinacolborane.[14] The hydrogen boroperoxoate moiety on **CP2** adds to alkyne **1** in accord with the Markovnikov rule to give **CP3**. The addition likely proceeds in a stepwise process, with initial C–H bond formation via a vinyl cation-like transition state and subsequent C–O bond formation, which would lead to the selective addition of the boroperoxo moiety to the alkyne. The boroperoxyalkenyl intermediate then dissociates from the Fe porphyrin to provide **A** and regenerate **CP1**. Homolytic O–O bond scission in **A** generates corresponding radical species **B**, and radical recombination proceeds to give **C**. Finally, **C** undergoes hydrolysis to afford **2** and the pinacol ester of boric acid.

Figure 3. Plausible mechanism.



The proposed mechanism is supported by the following mechanistic study. When the reaction was conducted in the presence of galvinoxyl as a radical scavenger, the yield of product was largely decreased, and intermediate radical **B** was trapped by the addition of galvinoxyl radical; this adduct **5** was confirmed by ESI–MS (Scheme 3a). Intermediate **C** was also observed by ESI–MS (Scheme 3b,**6**), but its isolation was difficult due to its facile hydrolysis to afford final product **2**.

Scheme 3. Detection of reaction intermediate by ESI–MS.



In summary, we report the first example of the aerobic direct dioxygenation of alkynes to yield α-hydroxyketones. The reaction proceeds in the presence of oxygen in air as a green oxidant and an iron catalyst at room temperature. The protocol, with its high chemoselectivity and functional group tolerance. Efforts to expand the scope of the alkyne substrates and further application of this reaction are now in progress.

Acknowledgements

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Supporting Information

Experimental procedures, spectroscopic and analytical data for new compounds, and additional experimental data. This material is available free of charge via the Internet.

Keywords: oxidation • alkyne • α-hydroxyketone • ferric porphyrin complex • compound 0

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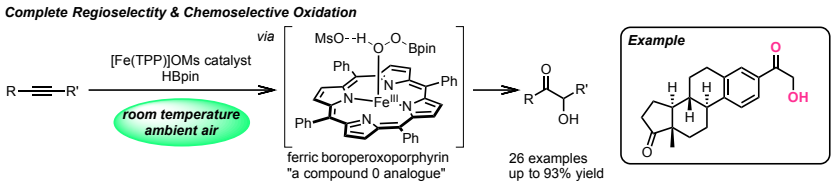

We report the first synthesis of α-hydroxyketones through the dioxygenation of alkynes. The reaction is mediated by an Fe porphyrin complex and pinacolborane at room temperature under air as a green oxidant, furnishing α-hydroxyketones in up to 93% yields. The mild reaction conditions allow chemoselective oxidation with good functional group tolerance.

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