Study on Ru(bpga)-Catalyzed Practical C-H Oxidation: Using Water as an Oxygen Source and Acid-Cooperative Oxygen Atom Transfer

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- Using Water as an Oxygen Source and

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Abstract

Direct oxygenation of C–H bonds is considered to strongly contribute to the development of step-, atom-, and redox-economic synthetic strategy because C–H bonds are stable for the various organic transformation conditions and no-requiring pre-functionalization. Thus, this class of oxygenation has received much attention and has been intensively studied in recent four decades. However, C–H bonds, ubiquitous and abundant in the molecule, are still difficult to be oxygenated to the desired functional group with the site-, chemo-, and stereoselectivity. Although recently, several groups demonstrated selective unreactive C–H bond oxygenation using non-heme-enzyme inspired transition-metal complexes as a catalyst, these oxygenations have points needing improvement such as low site-selectivity, narrow substrate scope, and poor catalyst durability. Thus, the author realized truly practical and useful catalytic C–H oxygenation and found that Ru(bpga) complexes, a model of non-heme enzyme, present efficient and unique catalysis in C–H oxidation under acidic conditions. Ru(bpga) catalysis with PhIO as the oxidant was dramatically encouraged by the addition of TFA. Based on the found acid's acceleration on Ru(bpga)-catalyzed C–H oxygenation, the author has brought further developments in this field: one is the C–H oxygenation using an almost stoichiometric amount of water as the oxygen source, and the other is the intramolecular carboxylic acid-cooperative C–H oxygenation.

Based on mechanistic studies of the preliminary research, the author hypothesized that oxygen of water can insert into a C–H bond via hydrolysis of iodobenzene(dicarboxylate) and subsequent oxygen atom transfer from resulting ruthenium(oxo) intermediate in a site- and chemoselective manner and demonstrated the highly practical and economic protocol to the synthesis of oxygen-isotope labeling compounds. The oxygen-isotope labeling method consumed only 1.5 to 5.0 equivalents of labeling water and gave an oxygenation compound that exhibited a high isotopic retention ratio from water.

Furthermore, a newly synthesized Ru(bpga)(H-maleate)$_2$ complex based on the acid-cooperative oxygen atom transfer concept, discovered by the author's group, presented excellent turnover frequency in this field (TOF: up to 600 rph) in site-selective C–H oxygenation using hydrogen peroxide as the terminal oxidant. Acid-cooperative ruthenium catalyst system allowed a wide tolerance of functional groups and converted methine and methylene C–H bonds on even complex natural compounds to desired hydroxy and carbonyl groups with high site- and chemoselectivity in good to high yield. The author believed that the concept and catalytic system will lead to further progress in this field.

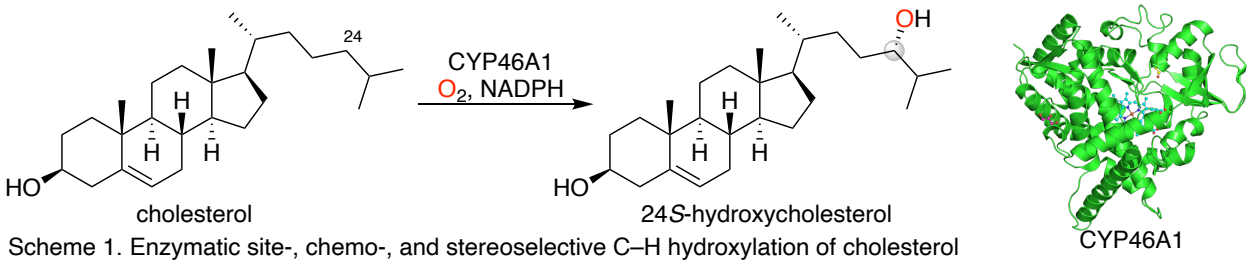
Contents

Chapter 1

Introduction

Since the late last century, organic material transformations have been strongly developed for the synthesis of targeting molecules and have been an essential technology for our society to produce various kinds of organic materials such as dyes, perfumes, electronic devices, pharmaceuticals, and agrochemicals. However, most organic synthesis of target molecules has consumed a lot of time, materials, and energy, unfortunately, because most organic transformation has required pre-functional chemicals as the starting materials. From the synthetical economic point of view, introducing more efficient methodologies is required for the step, redox, and atom-economic synthesis of target molecules.[1] According to this perspective, direct C–H bond functionalization is an ideal transformation because C–H bonds, ubiquitous and abundant on the molecule, don't need to pack lots of things before use.[2-4] Accordingly, C–H bond functionalization has been a recent major topic in organic chemistry. Although direct C–H bond functionalization has been intensively studied and developed, most C–H functionalization have limited substrate scope to C(sp^2)–H bonds and required the directing group for the high site-selectivity.[4] Especially, the functionalization of unreactive C(sp^3)–H bond on complicate compounds such as natural products is still difficult.[3c]

On the other hand, enzymatic oxidation converts even extremely unreactive C–H bonds to desired oxygen functional group with the almost complete site-, chemo-, and stereoselectivity, albeit with quite a narrow substrate scope and low versatile reaction conditions (Scheme 1).[5-8] Highly reactive enzymatic oxygen atom transfers have attracted scientific attention to its mechanistic and model studies due to its high utility.[6-9] These studies, especially heme-type-enzyme models such as cytochrome P450, have strongly contributed to the development of catalytic oxidative oxygenation.[7-9] P450-catalyzed C–H oxygenation involves the two electrons and two protons consuming activation of molecular oxygen to high valent iron(oxo) species, followed by the oxygen atom transfer (Figure 1).



Scheme 1. Enzymatic site-, chemo-, and stereoselective C–H hydroxylation of cholesterol

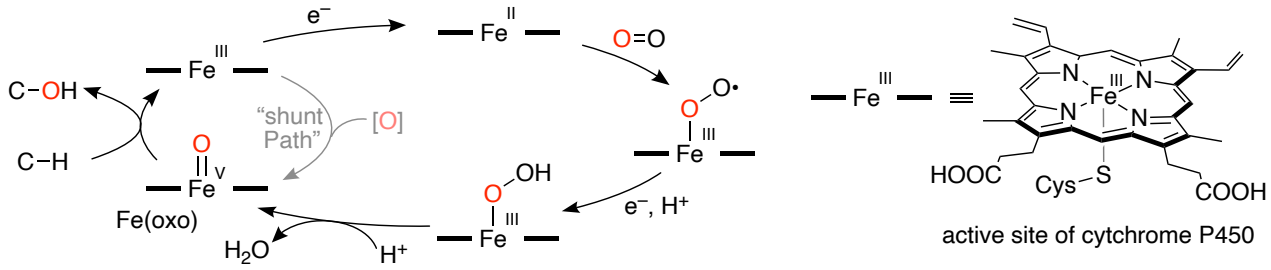
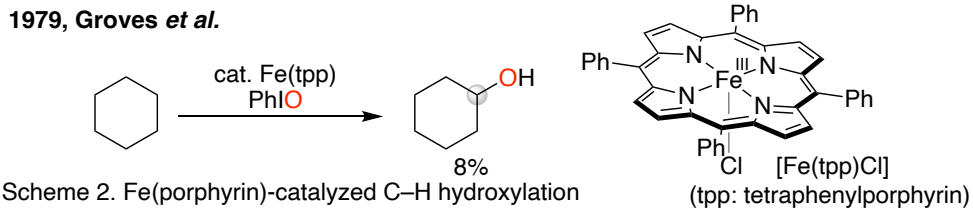


Figure 1. Mechanism of C–H oxidation catalyzed by cytchrome P450

However, biological molecular oxygen activation is extremely complicated and difficult to realize artificially. Thus, to exploit the advantages of biological oxygen atom transfer, the new strategy, the so-called "shunt path", has been introduced by Groves *et al.* in 1979.[10] They succeeded in omitting the complicated biological activation of molecular oxygen by using iodosylbenzene (PhIO) as the terminal oxidant. Metalloporphyrin, inspired by the active site of P450, with PhIO can oxidize cyclohexane to cyclohexanol (Scheme 2). Thereafter, heme enzyme model complexes with shunt path protocol have led to the development of catalytic oxygen atom transfer such as oxygenation of C–H bonds and epoxidation of olefins (Figure 2).[11]



Scheme 2. Fe(porphyrin)-catalyzed C–H hydroxylation

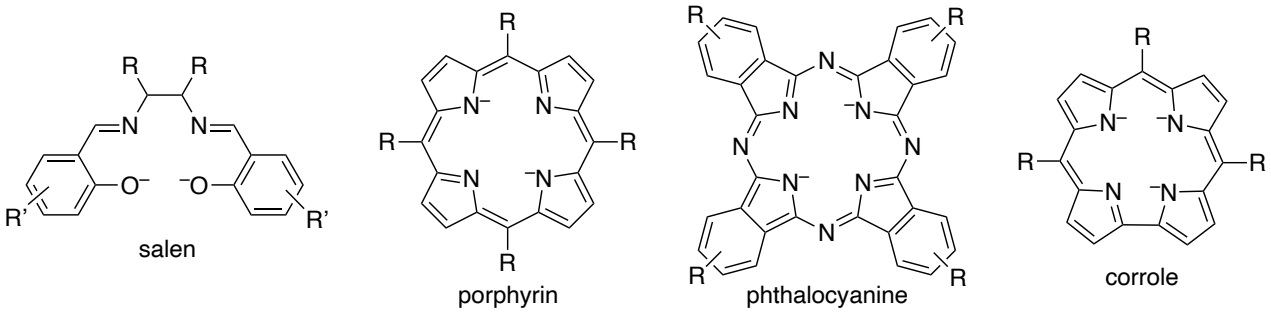
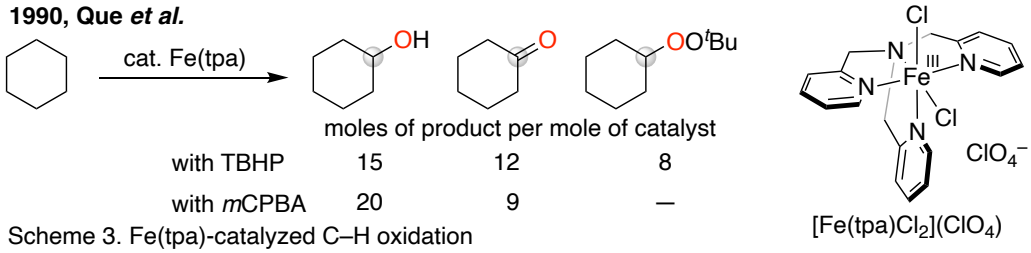


Figure 2. Ligands of catalysts inspired by heme enzyme for oxygen atom transfer reaction

Furthermore, non-heme enzyme model studies also strongly contributed to recent development in this field. In 1990, Que and co-workers presented Fe(tpa) [tpa: tris(2-pyridylmethyl)amine], non-heme-model, catalyzed C–H oxygenation of cyclohexane using *tert*-butyl hydroperoxide (TBHP)

or *meta*-chloroperbenzoic acid (*m*CPBA) as the terminal oxidant (Scheme 3).[12] Since that, various transition-metal complexes ligated with non-heme model ligands such as tpa and bpy (bipyridine) derivatives have been introduced in this field (Figure 3).[13] However, most of these attempts are only model studies and impractical for use in actual organic synthesis.



Scheme 3. Fe(tpa)-catalyzed C–H oxidation

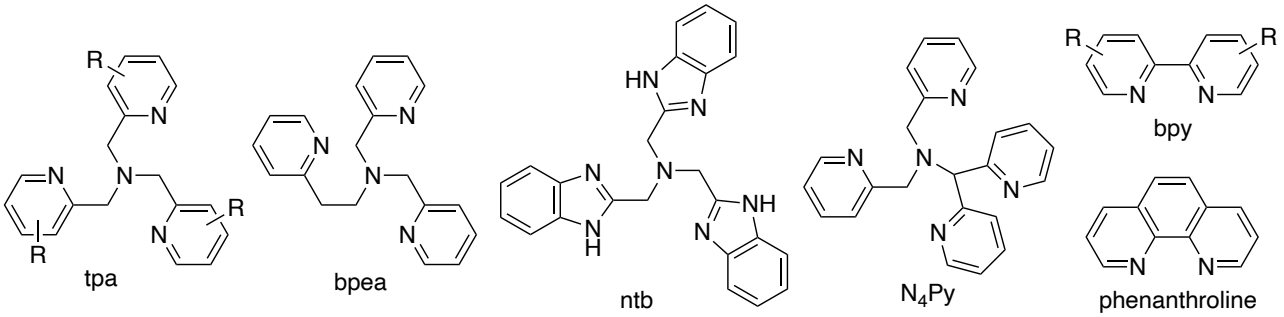
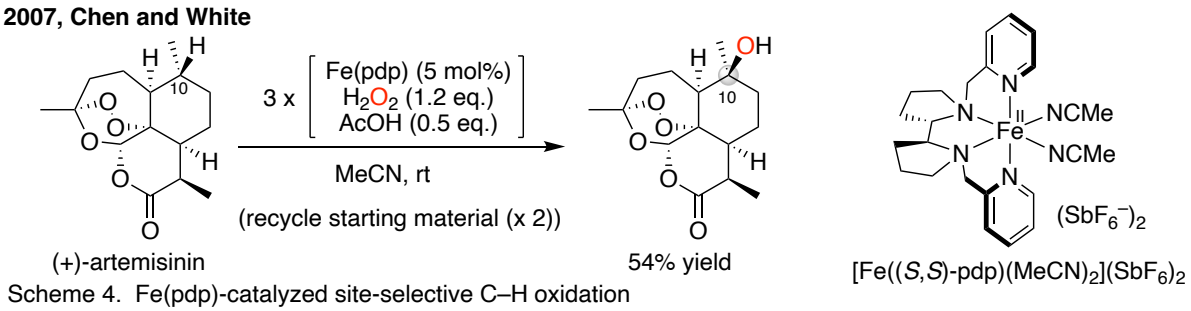


Figure 3. Non-heme enzyme-inspired N-polydentate ligands of catalysts for C–H oxidation

Then, in 2007, Chen and White led the important successes, which is referred to as a milestone, in this field.[14] They found that non-heme-inspired iron(pdp) [pdp: *N*,*N'*-bis(2-pyridylmethyl)-2,2'-bipyrrolidine] complex can catalyze unactivated C(sp^3)–H bond oxygenation using hydrogen peroxide (H_2O_2) as the co-oxidant in a site-selective manner (Scheme 4). Iron(pdp) complex-catalyzed C–H oxidation underwent at the electrically and sterically predictable position in even complicated natural products under acidic conditions.



Scheme 4. Fe(pdp)-catalyzed site-selective C–H oxidation

Subsequently, various non-heme type iron catalysts have been introduced and brought many developments in this field (Figure 4).[15,16] Nowadays, various C–H bonds such as even electrically unfavored methylene C–H bonds due to the original nature of the substrate and C–H bonds in easily oxidizable *N*-containing compounds were converted to the desired oxygen functional groups by using non-heme-type iron complexes as the catalyst (Scheme 5,6).[16d,f,g,j] Moreover, complicated organic compounds such as natural products and pharmaceutical compounds can be oxidized in a site-selective manner (Figure 5).[3c,14,16b,f-j]

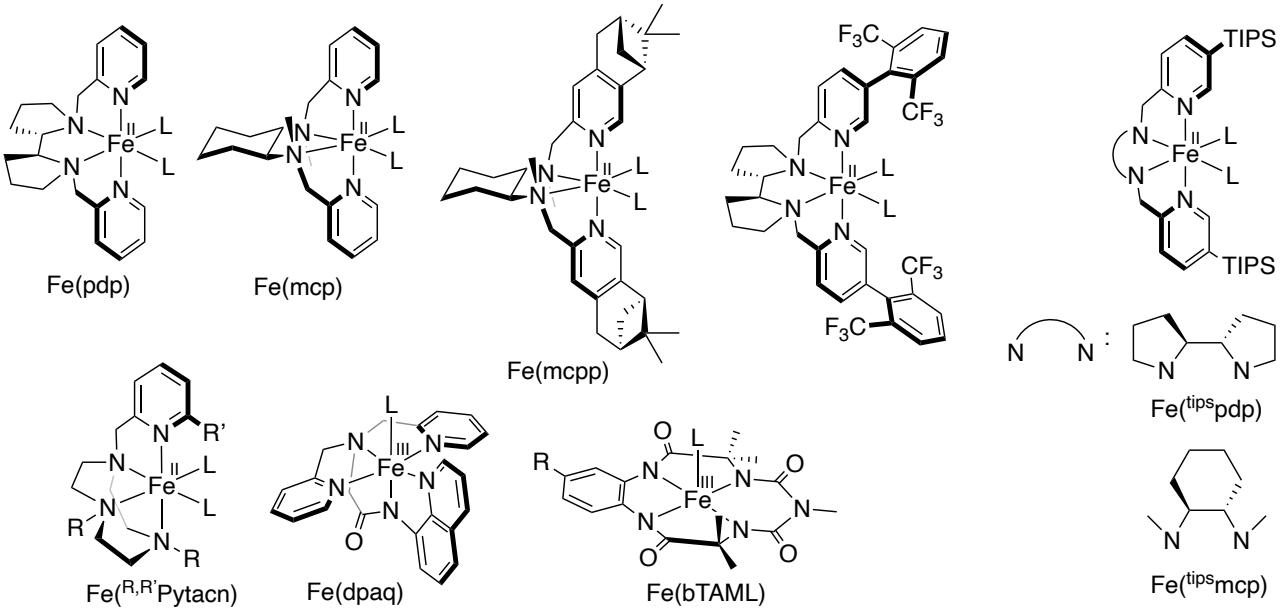
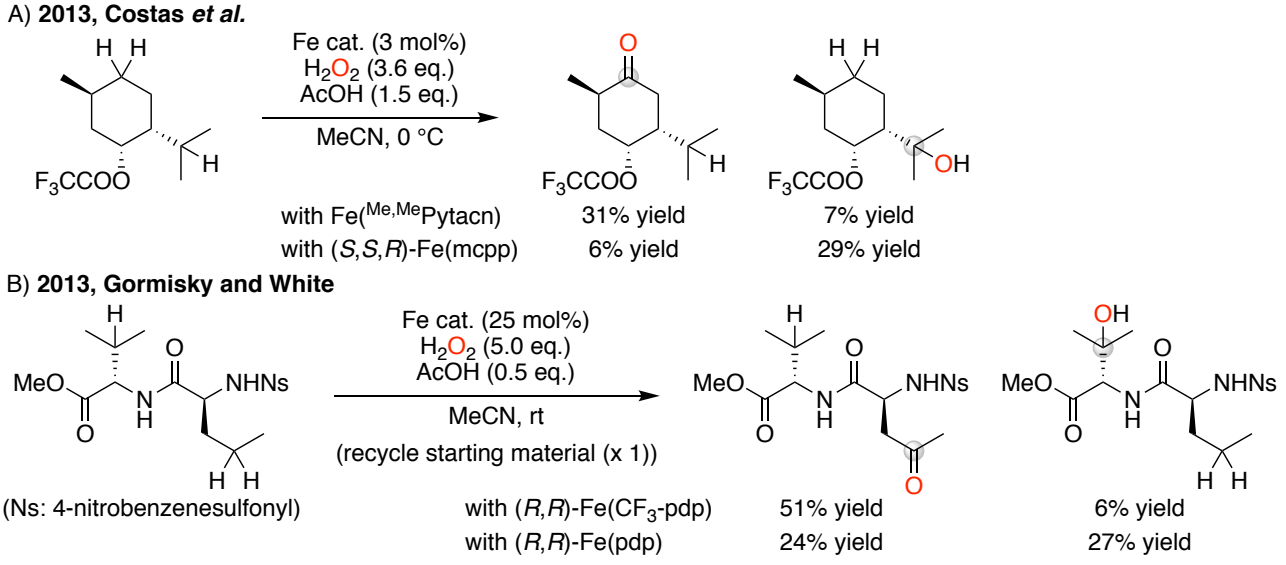
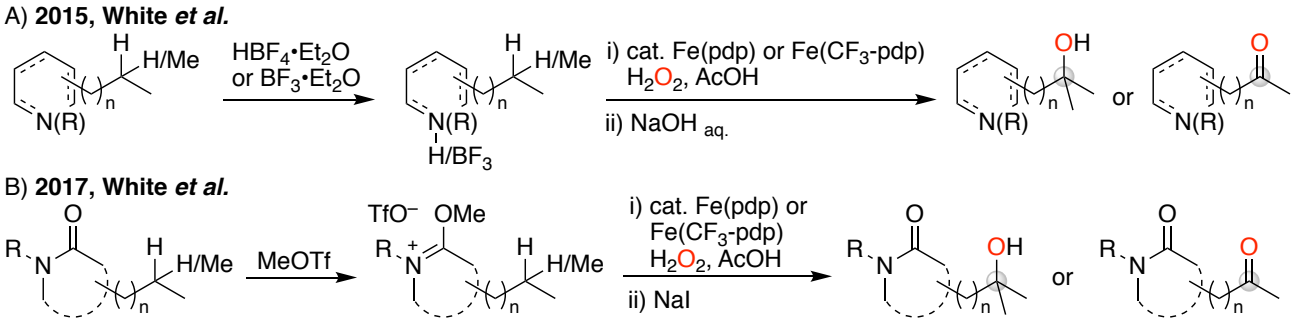


Figure 4. Iron catalysts for site-selective aliphatic C–H oxidation



Scheme 5. Iron-catalyzed methylene selective C–H oxidation



Scheme 6. Iron-catalyzed C–H oxidation of N-containing substrates

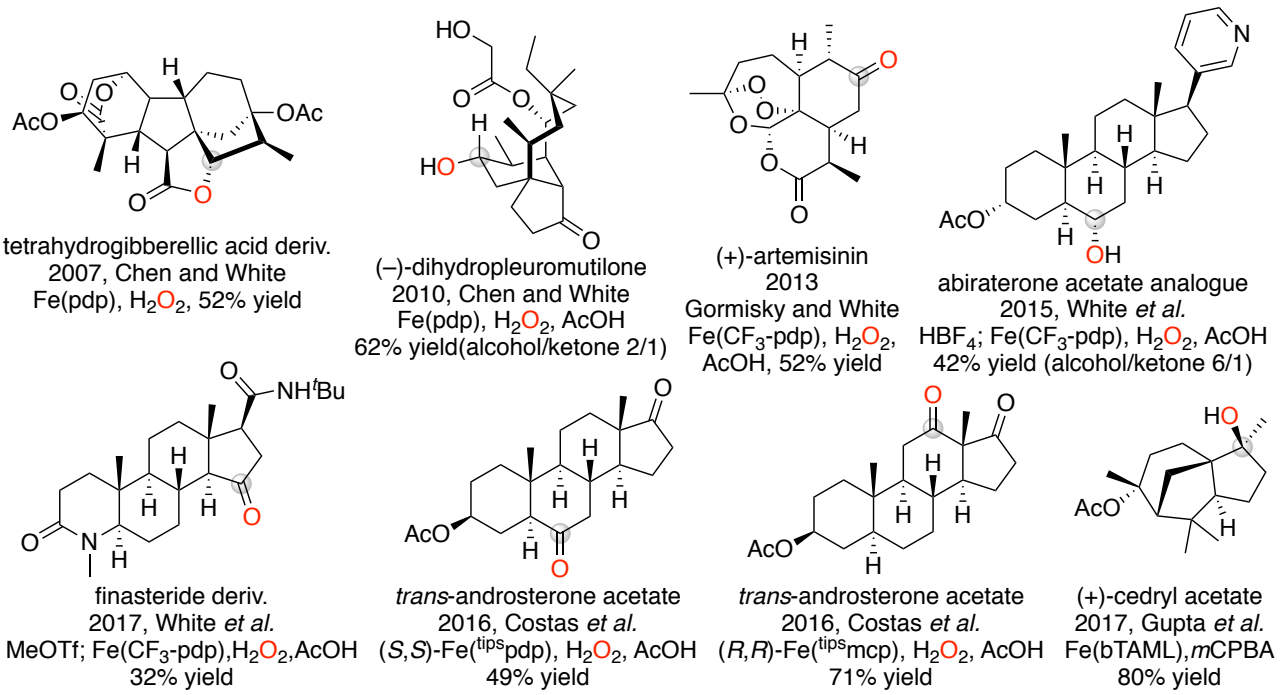
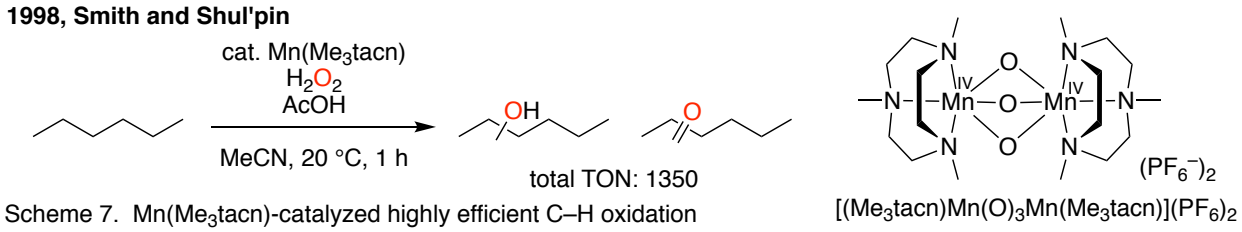


Figure 5. Site-selective late-stage C–H oxygenation using iron catalysts

Although non-heme-type iron complexes have been able to open the fields of the site-selective oxidation of unactivated C–H bond, iron complexes-catalyzed oxidation required high catalysts loading (3-25 mol% in most cases) due to the catalyst durability and the reaction rate, unfortunately. In addition to the development of non-heme-type iron complexes-catalyzed C–H oxidation, bio-inspired manganese complexes also have received attention due to their high robustness under oxidation conditions.[17,18] In 1998, Smith and Shul'pin described excellent catalyst turnover number (up to a total of 1350) in the oxidation of hexane using Mn(Me_3tacn)-μ-oxo-dimer (Me_3tacn: 1,4,7-trimethyl-l,4,7-triazacyclononane) complex as the catalyst (Scheme 7).[19] It was thought that Mn(Me_3tacn)-catalyzed oxidation underwent via hydrogen abstraction and related oxygen-rebound process, but a part of alkyl radical was released from the solvent cage of the reaction site, so the

corresponding alkyl hydroperoxide was observed.



Scheme 7. Mn(Me$_3$tacn)-catalyzed highly efficient C–H oxidation

In 2012, highly selective and practical manganese-catalyzed unreactive C–H oxidation was achieved by Bryliakov and co-workers (Figure 6).[18a] They found that non-heme-type manganese(pdp) and (pmpp) [pmpp: *N*,*N'*-bis(2-pyridylmethyl)-*N'*-methyl-2-aminomethylpyrrolidine] complexes can catalyze tertiary C–H bond selective oxygenation with excellent TON (up to 970).

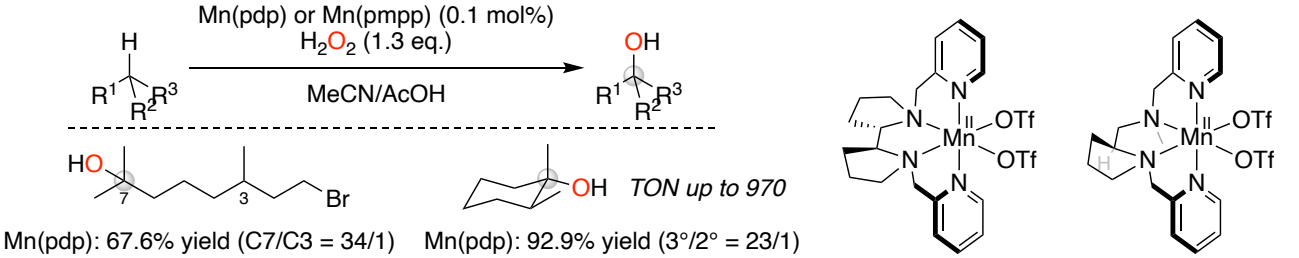
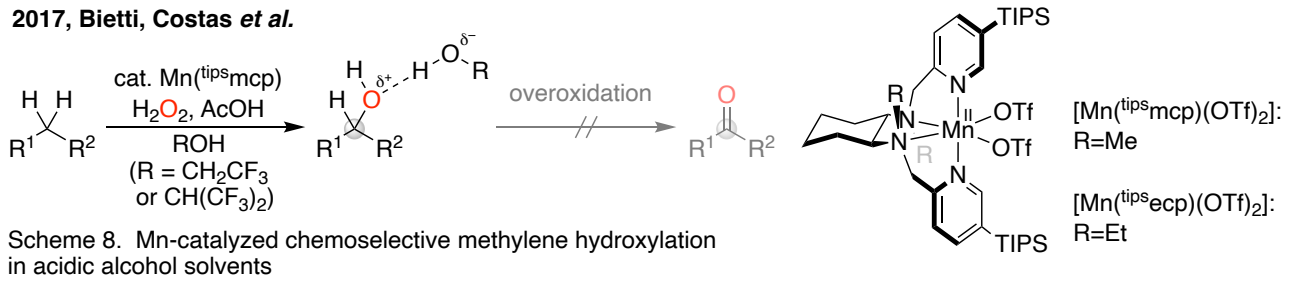
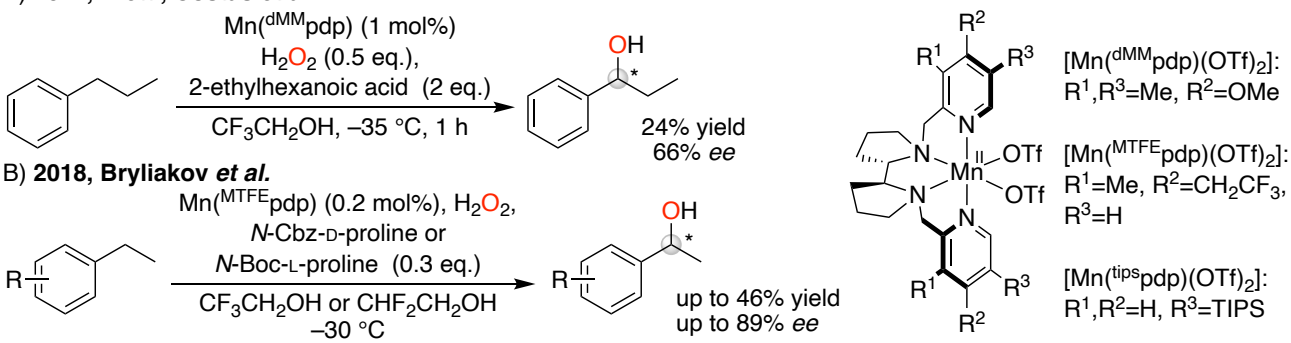


Figure 6. Mn(pdp)- and Mn(pmpp)-catalyzed highly efficient site-selective C–H oxidation

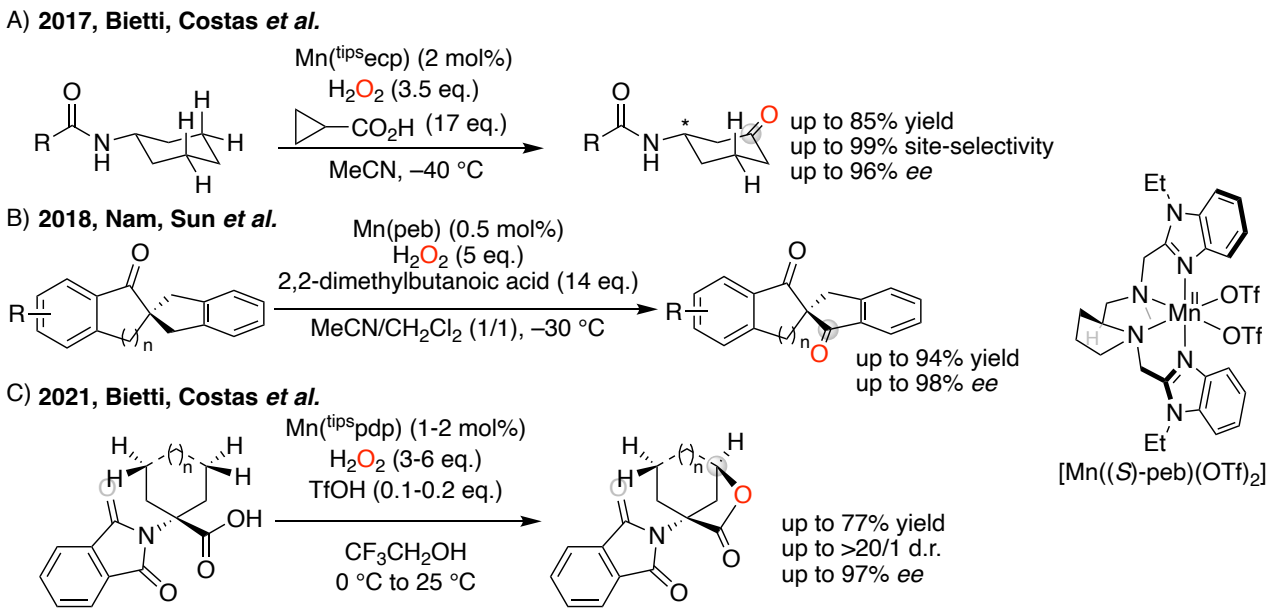
Furthermore, the important development of C–H oxidation, that is chemoselective methylene hydroxylation, has been achieved by using acidic fluorinated alcohol such as 1,1,1,3,3,3-hexafuloro-2-propanol (HFIP). Bietti and Costas *et al.* hypothesized that HFIP can reverse the electronic nature of α C–H bond of a generated hydroxy group (Scheme 8).[18e] Subsequent to this, Bryliakov group and Bietti and Costas group reported asymmetric methylene C–H hydroxylation, albeit with reactive benzylic C–H bonds, catalyzed by non-heme type manganese complexes, respectively (Scheme 9).[18e,i] Furthermore, highly enantioselective oxidative desymmetrization of prochiral *N*-cyclohexylamides, spiro compounds, and amino acid derivatives have been reported (Scheme 10).[18c,f,m]



Scheme 8. Mn-catalyzed chemoselective methylene hydroxylation in acidic alcohol solvents



Scheme 9. Mn(pdp)-catalyzed asymmetric C–H hydroxylation of arylalkanes



Scheme 10. Enantioselective desymmetrization using Mn-catalyzed C–H oxidation

Parallel to these developments of based-metal catalyzed C–H oxidations, non-heme-type ruthenium complexes have also attracted attention and have been studied (Figure 7).[20-22] Most of these complexes showed insufficient catalysis in C–H oxidation, unfortunately. In 2012, McNeill and Du Bois presented an effective method by using non-heme-type ruthenium complexes in this field.[22a] They found that Ru(Me$_3$tacn) using ceric (IV) ammonium nitrate (CAN) as the co-oxidant can catalyze C–

H oxidation with broad substrate scope including natural products in a high site-selective manner (Figure 8A). Du Bois and Sigman *et al.* also reported ruthenium-catalyzed methine selective C–H hydroxylation under electrochemical oxidation conditions (Figure 8B).[22d]

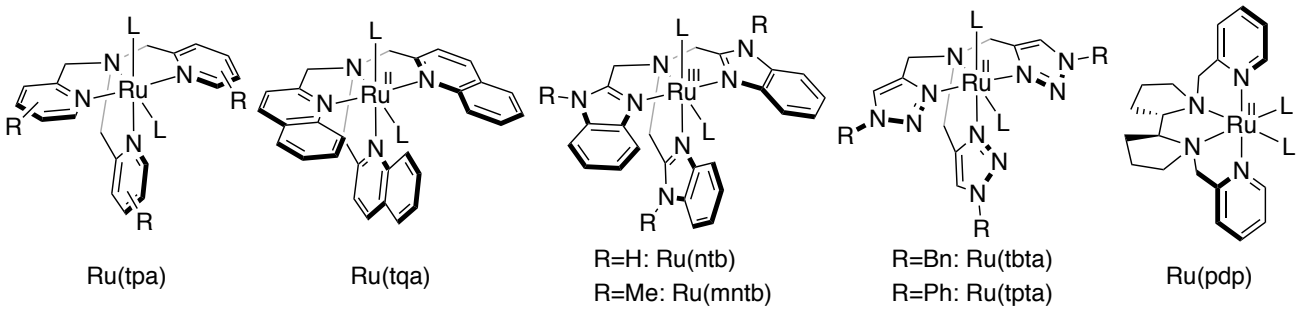


Figure 7. Ruthenium catalysts for aliphatic C–H oxidation

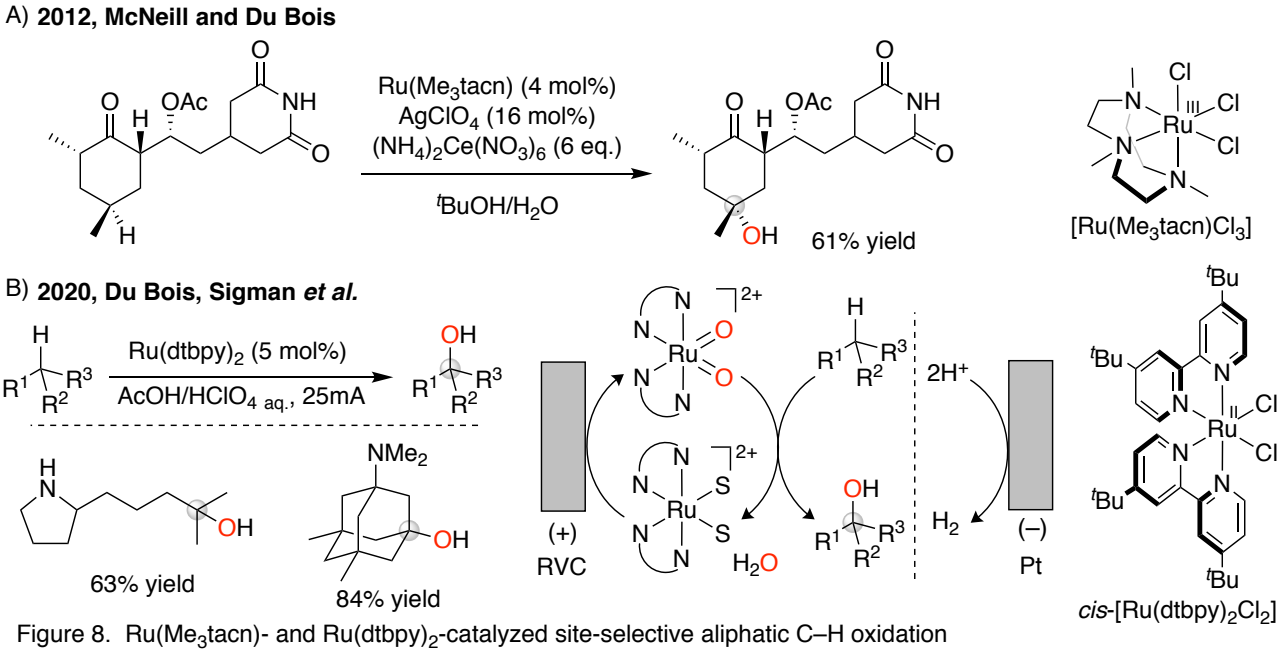


Figure 8. $Ru(Me_3tacn)$- and $Ru(dtbpy)_2$-catalyzed site-selective aliphatic C–H oxidation

As mentioned above, non-heme-type transition-metal complexes led to the recent developments in unreactive $C(sp^3)$–H oxidation. Nowadays, various C–H bonds on even complicated natural products can be converted into desired oxygen functional groups with chemo-, site- and stereoselectivity by using these bio-inspired transition-metal catalysts with hydrogen peroxide, an atom-economic, and environment-friendly reagent, as the terminal oxidant. However, there is still room for improvements such as substrate scope and catalyst durability under oxidation conditions, individually. Introducing truly practical site- and chemo-selective C–H oxidation methods have been

required. That is, a method with wide substrate scope and high catalyst durability under oxidation conditions was wanted to be developed. The author was intrigued by the efficient catalysis of non-heme complexes in C–H oxidation and began to develop a practical and strong method by introducing a new class of non-heme catalysts. Consequently, the author also found that non-heme-type ruthenium(bpga)(PPh_3) **1a** [bpga: *N*,*N*-bis(2-pyridylmethyl)glycinamide] is an efficient catalyst for site-selective C–H oxygenation (Figure 9).[3e,23] Ru(bpga) **1a** presented efficient catalysis using iodosylbenzene (PhIO) as the terminal oxidant under acidic conditions. Ruthenium-catalyzed C–H oxidation could be dramatically accelerated with excellent site-selectivity by the addition of trifluoroacetic acid (TFA) (Figure 9A). Furthermore, under oxidation conditions, the catalyst was stable and present an unparalleled high turnover number (up to 26,000) in the reaction of adamantane. The ruthenium(bpga)-catalyzed C–H oxidation could oxidize various substrates including even complicated natural compounds with excellent site-selectivity (Figure 9B) and be considered to be a practical oxygen functionalization. However, ruthenium(bpga)-catalyzed oxygenation required PhIO, a low atom-economic and unstable oxidant that causes disproportionation even under 4 °C.[24] If more stable and atom-economic reagents could be used as the terminal oxidant while leaving its excellent site-selectivity and catalyst durability, the reaction system would be truly ideal and practical oxygenation.

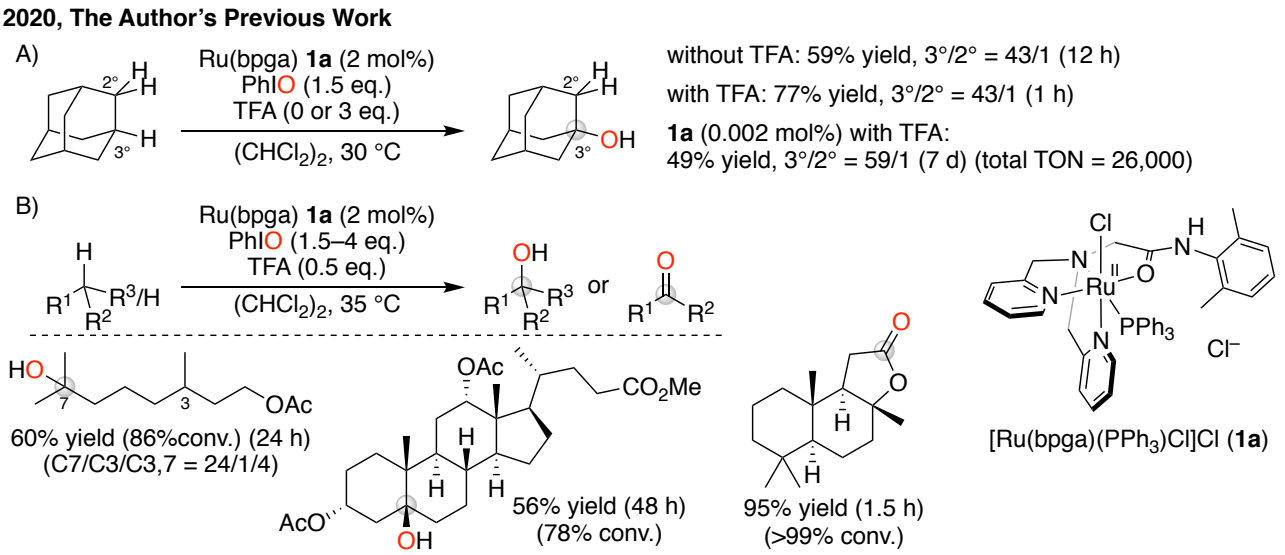


Figure 9. Ru(bpga)-catalyzed site-selective C–H oxidation with broad substrate scope

Chapter 2

C–H Oxidation Using Water as the Stoichiometric Oxygen Source: Activation of Water's Oxygen vis Hydrolysis of Iodobenzene(dicarboxylate)

2.1. Mechanistic Insight of Acceleration with Carboxylic Acid and Working Hypothesis of Its Applicable Water Activation

As mentioned above, ruthenium(bpga) complexes showed efficient catalysis in site-selective C–H oxygenation with unideal PhIO under acidic conditions. These observations have raised a concern about the role of carboxylic acid in the ruthenium-catalyzed C–H oxidation. To get mechanistic insight into the carboxylic acid, the author began ^{1}H NMR studies of PhIO with TFA (Figure 10). In the absence of TFA, no signal resulting from PhIO was observed because PhIO is an oligomer and insolvable in a non-protonic solvent such as tetrachloroethane [$(CHCl_2)_2$] and chloroform ($CHCl_3$). On the other hand, in the presence of TFA, oligomeric PhIO was completely soluble in $CDCl_3$ and produced several signals, assigned to the corresponding iodobenzene[bis(trifluoroacetate)] [$PhI(OCOCF_3)_2$], iodobenzene, and monomeric PhIO or hydroxyiodobenzene(trifluoroacetate) [$PhI(OH)(OCOCF_3)$], in ^{1}H NMR spectrum (Figure 10A).[25] These observations indicated that, under acidic conditions, oligomeric PhIO reversibly produced $PhI(OCOR)_2$, H_2O, and monomeric PhIO or PhI(OH)(OCOR) and contaminated by the disproportionation of PhIO. Further NMR study using $PhI(OCOR)_2$ was conducted in $CDCl_3$. It was observed that treatment of $PhI(OCOCF_3)_2$ with 2.0 equivalent of water produced monomeric PhIO or $PhI(OH)(OCOCF_3)$ without the formation of iodobenzene (Figure 10B). It was indicated that the reversible hydrolysis of $PhI(OCOR)_2$ with water molecules can in situ generate monomeric-PhIO or its derivatives. That is, an oxygen atom of a water molecule could be activated to the putative ruthenium(oxo) intermediate via hydrolysis of [$PhI(OCOR)_2$], a more stable and easy-handling hypervalent iodine reagent than PhIO (Figure 10C).

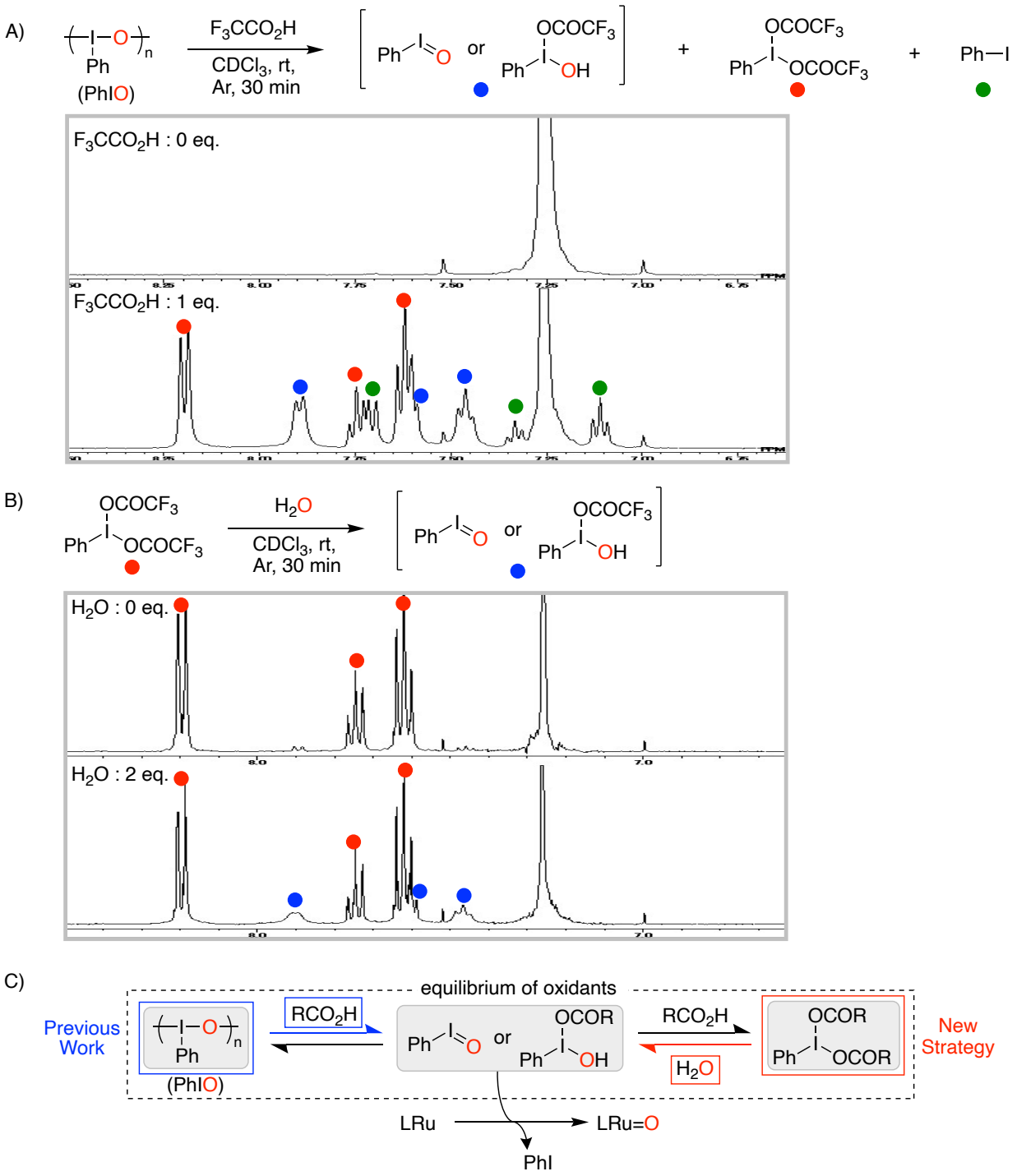


Figure 10. ^{1}H NMR experiment of hypervalent iodine derivatives

A water molecule, the most easily available and low-cost reagent on the earth, is a typical and useful oxygen source for organic synthesis. Due to the abundance of water, a lot of typical oxygenation such as hydration of alkenes and hydrolysis of esters have used a large excess of water as the reagent. However, the recent growing population and developments in the chemical industry would lead to an increase in the consumption of water. The efforts of water resource conservation are also becoming to

be extremely important in organic synthesis.[26] Moreover, due to the recent development of imaging technologies such as secondary ionization mass spectrometry (SIMS) and multinuclear magnetic resonance imaging (MRI), isotopic-labeled compounds have been expected to be used as imaging tags.[27] Especially, isotopic labeling of oxygen functional groups, ubiquitous and abundant in most bio-active compounds, has been attractive.

Most conventional isotopic labeling of oxygen functional groups is formed through the hydration of carbonyl compounds using >500 equivalents of a rare and expensive isotopic-labeled water molecule ($H_2{}^{18}O$ and $H_2{}^{17}O$) (Figure 11A).[28] If more ideal isotopic-labeled oxygen functionalization would be realized, it would strongly contribute to the progress of the isotopic bio-imaging. For the improvement of the construction of the isotopic-labeled oxygen functional group, the method that uses labeled water as the stoichiometric oxygen source is ideal.

For the purpose of isotopic oxygen functionalization, it was considered that C–H oxygenation would be a strong and useful tool if water molecules could be used as a stoichiometric oxygen source. Although several catalytic oxygen atom transfer reactions including C–H oxidation used water molecules as the oxygen source, these reactions are only model or mechanistic studies, not practical (Figure 11B).[16m,22d,29] On the other hand, mentioned hydrolysis of $PhI(OCOR)_2$ in ruthenium-catalyzed C–H oxidation was considered to be an effective tool (Figure 12). That is, in the presence of labeled water, $PhI(OCOR)_2$ reversely produces labeled-PhIO and the corresponding carboxylic acid. In-situ obtained labeled-PhIO can be decomposed to the ruthenium(oxo) intermediate, which can oxidize C–H bonds in a site-selective manner.

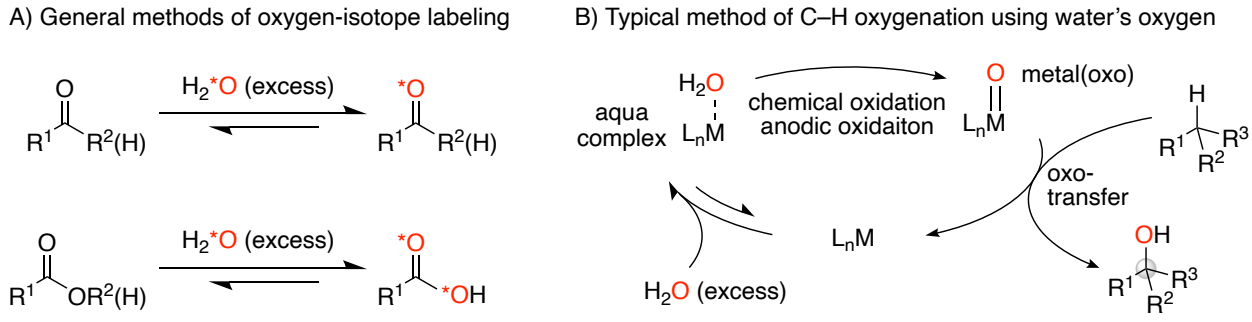


Figure 11. Previous reports for oxygen-isotope labeling and C–H oxidation using water's oxygen

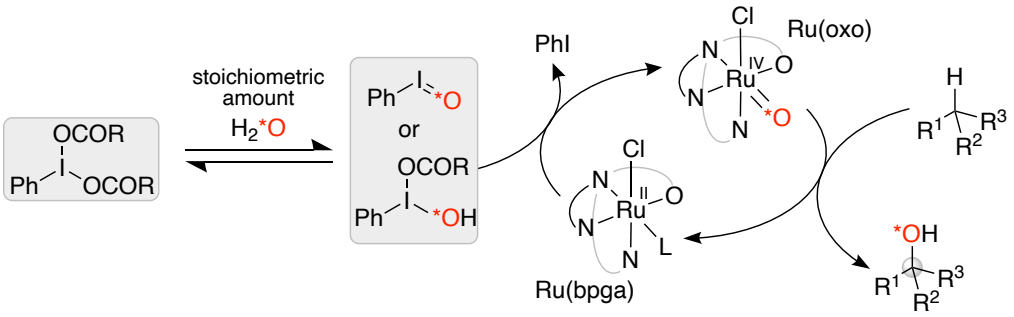
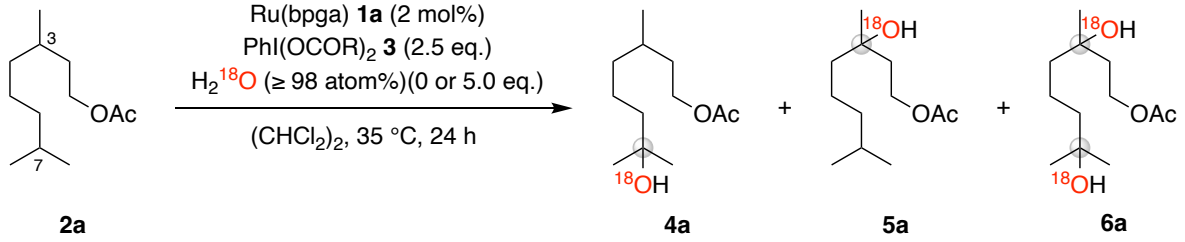


Figure 12. Working hypothesis of C–H oxidation using oxygen-isotope labeled water as the oxygen source

2.2. Results and Discussion

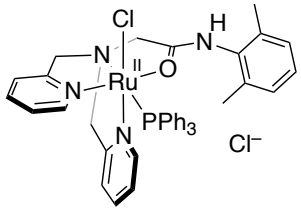
Based on the hypothesis, the author conducted the preliminary investigation on Ru(bpga) **1a**-catalyzed aliphatic C–H oxidation using water as the oxygen source and 3,7-dimethylocthyl acetate **2a** as the model substrate with iodobenzene(diacetate) **3a** as the terminal oxidant (Table 1). The reaction without the addition of water rarely worked out (entry 1). On the other hand, a much better result was observed on the reaction in the presence of 5.0 equivalents of ^{18}O-water. The reaction selectively underwent at the C7, electrically favored distal side, to give **4a** in 38% yield without significantly decreasing isotopic content of ^{18}O-water as the oxygen source (entry 2). The reaction using iodobenzene[bis(trifluoroacetate)] **3b** instead of **3a** consumed the substrate in 35% conversion but an extremely little amount of desired alcohols was observed (entry 3). It was thought to be due to the dehydration of the generated alcohol.

Table 1. Preliminary investigation of Ru(bpga) **1a**-catalyzed C–H oxidation using water as the oxygen source[a]



2a **4a** **5a** **6a**

entry	$PhI(OCOR)_2$	$H_2{}^{18}O$ (eq.)	conv. (%)[b]	**4a** yield (%)[b]	**4a/5a/6a**[b]
1	$PhI(OAc)_2$ **3a**	–	14	5	7/1/-
2	$PhI(OAc)_2$ **3a**	5.0	48	38 (^{18}O: 96 atom%)	13/1/1
3	$PhI(OCOCF_3)_2$ **3b**	5.0	35	1	1/-/-



[Ru(bpga)(PPh_3)Cl]Cl (**1a**)

[a] The reaction was performed with **2a** (0.1 mmol), **1a** (2.0 mol%), **3** (2.5 eq.), and $H_2{}^{18}O$ (≥98 atom%)(0 or 5.0 eq.) at 35 °C in $(CHCl_2)_2$ (0.4 M) for 24 h. [b] Determined by GC analysis.

With these preliminary results in hand, the author further conducted the reaction using $PhI(OAc)_2$ **3a** under wet conditions with a variety of carboxylic acids (Figure 13).[30] These observations indicated that the acidity of the added carboxylic acids correlated with the reaction rates. The reaction rate of Ru(bpga) **1a**-catalyzed C–H oxidation gradually elevated with a more acidic carboxylic acid and reached a peak by the addition of pentafluorobenzoic acid (F_5-BzOH) bearing pKa value 1.72 (in water) with high site-selectivity. In contrast, more acidic acids than F_5-BzOH diminished the

conversion and chemo-selectivity, and the decomposition of substrate **2a** and products was observed. Additionally, acceleration with too strong carboxylic acids appeared to exceed catalyst durability.

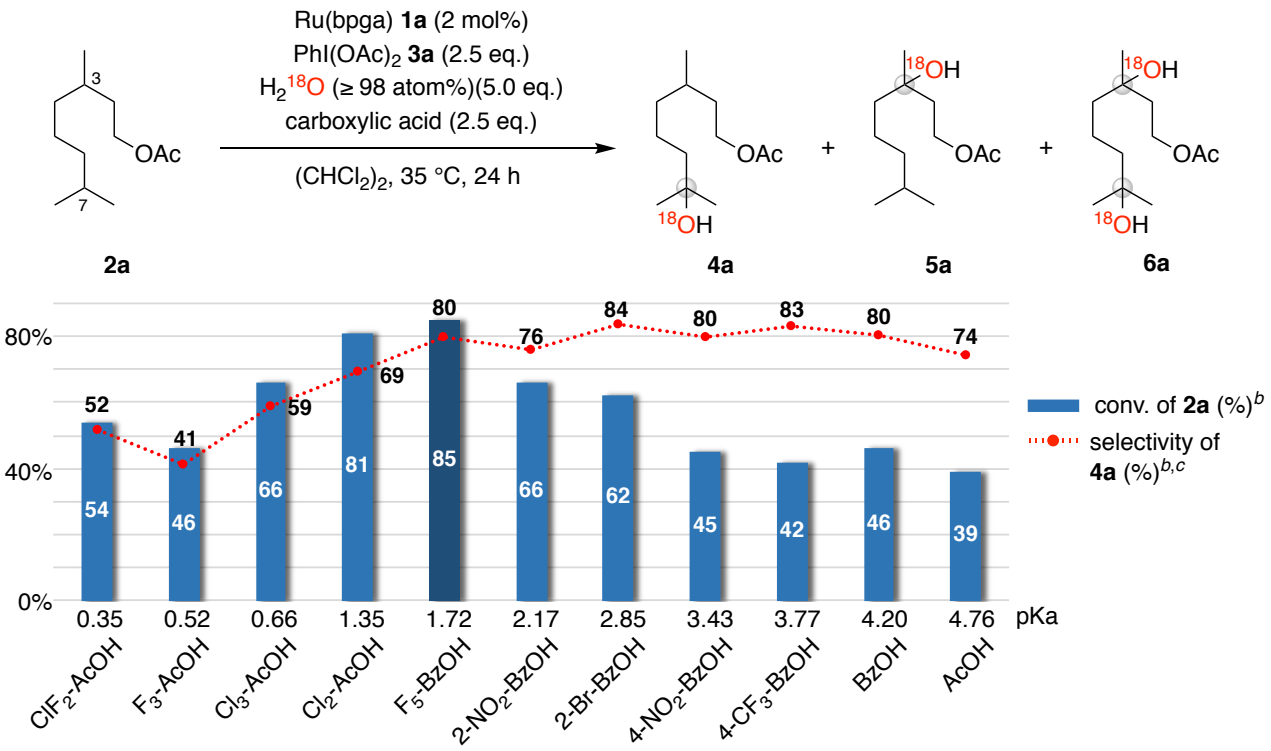


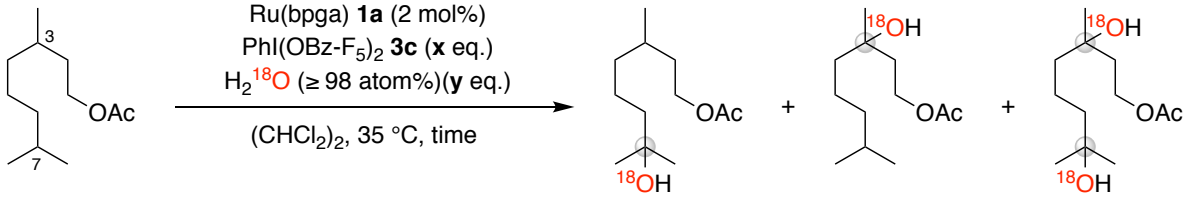
Figure 13. Ru(bpga) **1a**-catalyzed C–H oxidation using water and **3a** with various carboxylic acids[a]

[a] The reaction was performed with **2a** (0.1 mmol), **1a** (2.0 mol%), **3a** (2.5 eq.), $H_2{}^{18}O$ (≥98 atom%)(5.0 eq.) and carboxylic acid (2.5 eq.) at 35 °C in $(CHCl_2)_2$ (0.4 M) for 24 h. [b] Determined by GC analysis. [c] Based on conversion of **2a**.

Under these reaction conditions, two kinds of carboxylic acids, an added one and another in-situ generated one from hypervalent iodine reagent, were mixed, which was suspected to dampen the activation effect by the higher acidic carboxylic acid. Therefore, the author was intrigued by the activation effect on the reaction by a single carboxylic acid and conducted the reaction using iodobenzene(dicarboxylate) **3c** bearing F_5-BzOH,[31] which presented better results than others, under wet conditions (Table 2). Consequently, the reaction using PhI(OBz-F_5)$_2$ **3c** with 5.0 equivalents of water presented one-half shorten reaction times compared to previous conditions, using PhI(OAc)$_2$ with additional F_5-BzOH (entry 1), in almost complete conversion with high site-selectivity (entry 2). Reactions using 2.5-2.0 equivalents of PhI(OBz-F_5)$_2$ or 2.0-1.5 equivalents of water showed roughly similar catalysis (entries 2-3 and 5-6). On the other hand, reducing the oxidant to 1.5 equivalents or water to 1.0 equivalent showed diminished reaction rates but gave the corresponding alcohol in acceptable yields (entries 4 and 7). During these studies, high ^{18}O content (93 atom%) of the product

4c was observed in the reaction with even 1.5 equivalents of $H_2{}^{18}O$ (≥98 atom%) (entry 6). The observation indicated that the catalytic C–H oxygenation with PhI(OBz-F_5)$_2$ **3c** as the terminal oxidant can use water as the almost stoichiometric oxygen source. This protocol, ruthenium-catalyzed oxidation using reversible hydration of iodobenzene(dicarboxylate), was considered to be an economic, useful, and valuable method for the construction of an isotopic oxygen functional group.

Table 2. Optimization of Ru(bpga) **1a**-catalyzed C–H oxidation with water and PhI(OBz-F_5)$_2$ **3c**[a]



2a **4a** **5a** **6a**

entry	**3c** **x** (eq.)	$H_2{}^{18}O$ **y** (eq.)	time (h)	conv. (%)[b]	**4a** yield (%)[b]	**4a/5a/6a**[b]
1[c]	**3a** (2.5) + F_5-BzOH (2.5)	5.0	24	85	68	27/1/3
2	2.5	5.0	12	95	68	45/1/8
3	2.0	5.0	12	92	68	33/1/5
4	1.5	5.0	12	75	57	20/1/2
5	2.0	2.0	12	97	69	49/1/10
6	2.0	1.5	12	93	65 (^{18}O: 93 atom%)	35/1/6
7	2.0	1.0	12	73	53	19/1/1

[a] The reaction was performed with **2a** (0.1 mmol), **1a** (2.0 mol%), **3c**, and $H_2{}^{18}O$ (≥98 atom%) at 35 °C in $(CHCl_2)_2$ (0.4 M) for 12 h. [b] Determined by GC analysis. [c] Run with **3a** (2.5 eq.) and F_5-BzOH (2.5 eq.) instead of **3c** for 24 h.

Encouraged by these results, the author conducted the ruthenium-catalyzed reaction with various substrates under reversible hydration of PhI(OBz-F_5)$_2$ **3c** protocols (Figure 14). Under the reaction with 2.0 mol% loading of Ru(bpga) **1a** in the presence of 2.0 equivalents of PhI(OBz-F_5)$_2$ and 1.5 equivalents of ^{18}O-water (≥98 atom%), 4-methylpenthyl benzoate **2b** selectively produced the desired ^{18}O-isotopic-labeled alcohol **4b** with 95 atom% in 91% conversion and 83% yield. The reaction of adamantane **2c** gave 1-adamantanol **4c** in 82% yield with high site-selectivity. The C–H oxygenation showed wide functional group tolerance; substrates **2d-h** bearing bromine, ester, alcohol, as well as nitro group afforded the corresponding tertiary alcohols **4d-h** with good to high yields. Moreover, the oxygenation process underwent stereospecifically providing tertiary alcohols. No racemization was

observed in the reaction at chiral methine carbon, and (*S*)-3-methylpentenyl benzoate **2i** afforded the corresponding chiral alcohol **4i** while completely retaining stereochemistry. *cis*-Decalin **2j** also stereospecifically gave *cis*-decalin-9-ol **4j**. The C–H oxidation of 1,2-*O*-isopropylidene-*cis*-cyclohexanediol **2k** at 15 °C produced 2-hydroxycyclohexanone **4k** via hemiacetal formation through proximal site C–H oxidation of oxygen atom and followed deacetalization. Methylene C–H bonds at benzylic and α position of oxygen atom could also oxidize to the corresponding carbonyl compounds with good yields by using 2.5 to 3.0 equivalents of $PhI(OBz\text{-}F_5)_2$ **3c**. It was noteworthy that even complex natural products such as cedrol **2m**, deoxycholic acid derivative **2n**, and (–)-ambroxide **2o** could be oxidized at a sterically less-hindered and electrically favorable position in a high site-selective

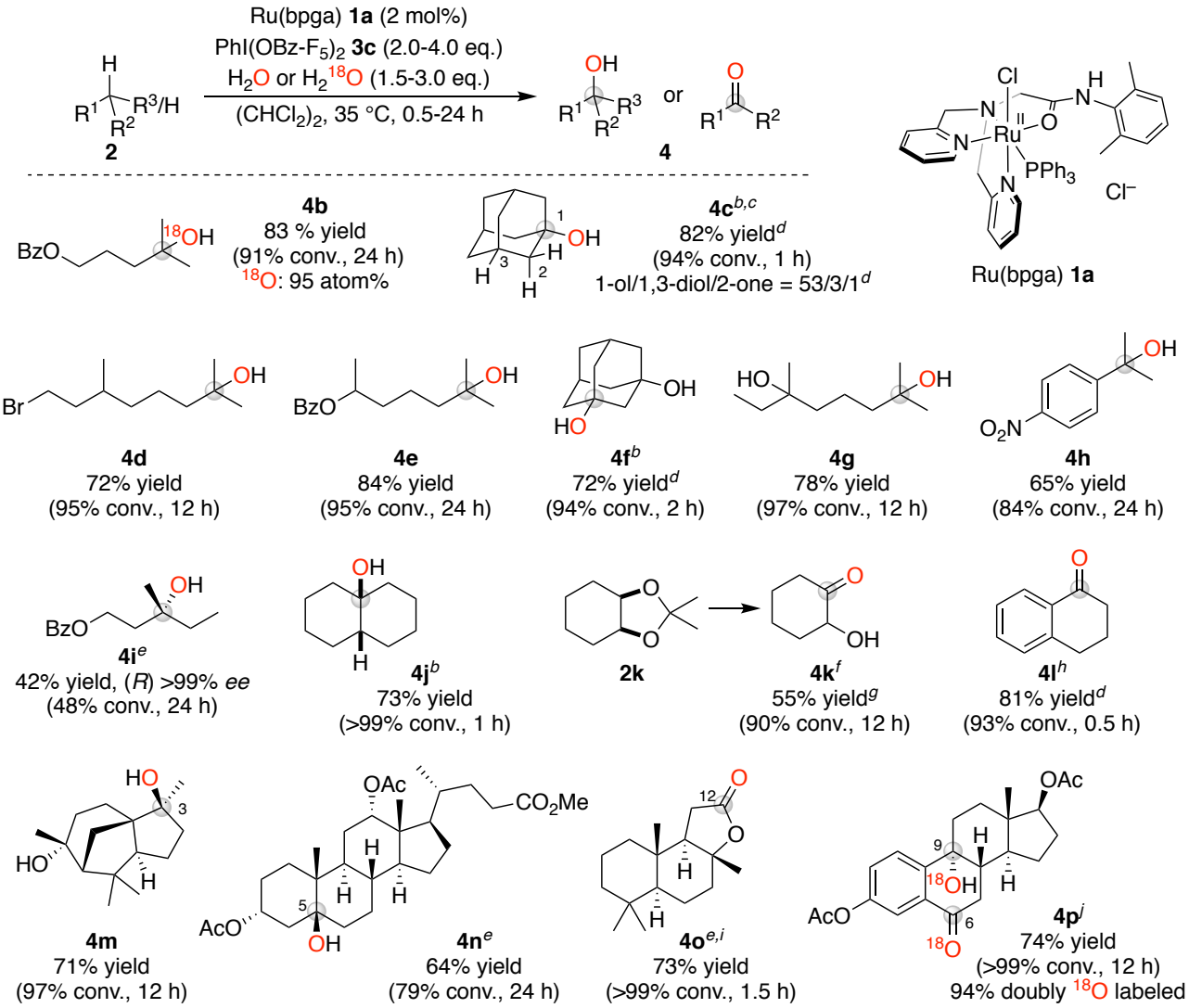


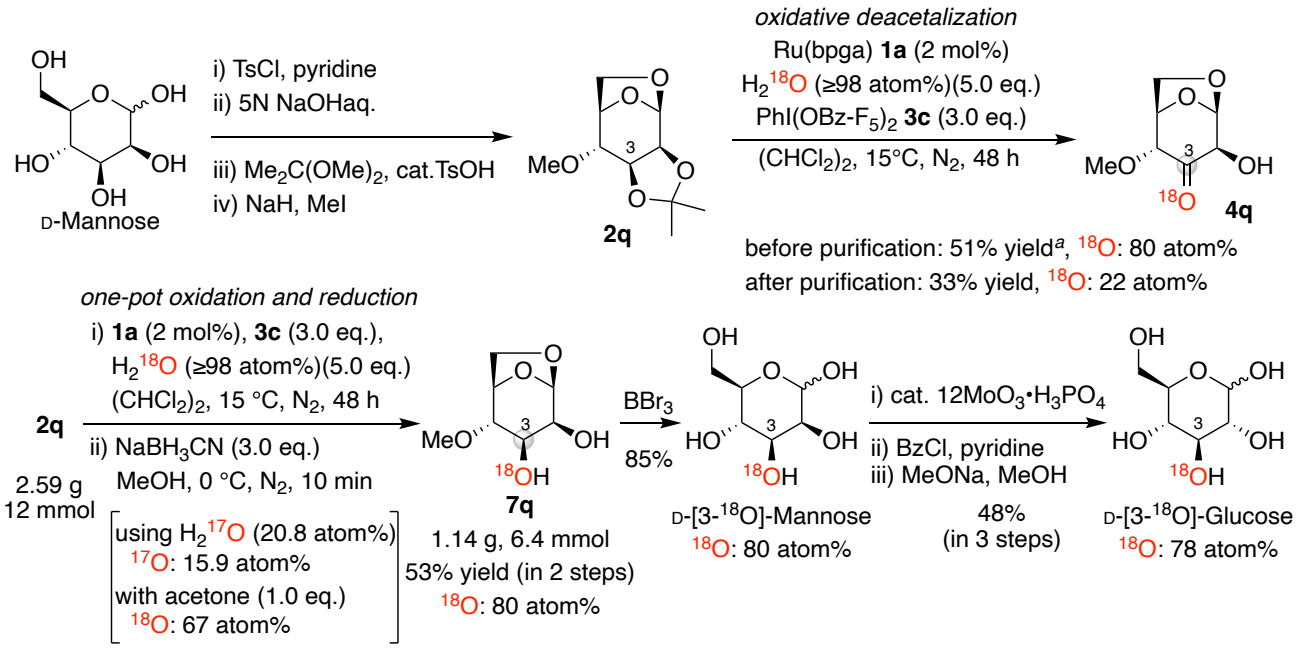
Figure 14. Substrate scope of Ru(bpga) **1a**-catalyzed C–H oxidation using water as the oxygen source[a]

[a] The reaction was performed with **2** (0.2 mmol), **1a** (2.0 mol%), **3c** (2.0 eq.), and H_2O or $H_2{}^{18}O$ (≥98 atom%) (1.5 eq.) at 35 °C in $(CHCl_2)_2$ (0.4 M). Conversion was determined by GC analysis. Yield was isolated yield. [b] Using **3c** (1.5 eq.). [c] Run in $(CHCl_2)_2$ (0.2M). [d] Determined by GC analysis. [e] Using H_2O (2.0 eq.). [f] Run at 15 °C in $(CHCl_2)_2$ (0.05 M). [g] Determined by converting to the corresponding benzoate ester **4k'**. [h] Using **3c** (2.5 eq.). [i] Using **3c** (3.0 eq.). [j] Using **3a** (4.0 eq.) instead of **3c** and $H_2{}^{18}O$ (3.0 eq.).

manner. Moreover, the reactivity of the catalytic system can be easily tuned by simply changing an iodine reagent. For instance, the reaction of reactive estradiol diacetate **2p** in the presence of PhI(OBz-F_5)$_2$ **3c** gave a complex mixture, but PhI(OAc)$_2$ **3a**, bearing lower acidic acetic acid as a ligand, produced the corresponding hydroxy ketone **4p**, which is selective oxidation product at benzylic position, in 74% yield.

Moreover, in order to prove that **1a**-catalyzed C–H oxidation using water as the oxygen source could be applied to practical preparation of isotopic-oxygen labeled compounds for using a bio-imaging probe, mannose, a major component of glycan chain, was chosen as the target (Scheme 11). For the purpose of the synthesis of oxygen-isotope-labeled mannose, first, pyranose derivative **2q** was prepared from D-mannose in 4 steps according to reported procedures.[32] Treatment of obtained mannopyranose **2q**, bearing multi-reactive sites, under ruthenium-catalyzed C–H oxidation conditions afforded to the corresponding α-hydroxy ketone **4q** with 80 atom% of the ^{18}O content in 51% yield. Unfortunately, under purification using silica gel chromatographed preparation conditions, ^{18}O content of **4q** was reduced to 22 atom% due to the hydration with bulk water. It was considered that the intramolecular hydrogen bond of α-hydroxy ketone would activate the hydration of the carbonyl group. To avoid degradation of the ^{18}O content of the product, the author assumed that the initial C–H oxygenation product **4q** should be directly converted to the diol **7q** without isolation. Based on this consideration, highly isotopically-oxygen-labeled diol **7q** (80 atom% at C3) was successfully produced in 53% yield even in multi-gram scale reaction via ruthenium-catalyzed oxidative deacetalizaition and subsequent diastereoselective reduction of ketone with $NaBH_3CN$ in methanol at 0 °C. This one-pot protocol could also be applied to ^{17}O-labeling to give 15.9 atom% ^{17}O-labeled **7q** in the reaction with $H_2{}^{17}O$ (20.8 atom%). During these investigations, a slightly reduced ^{18}O content of a product was observed compared to the original oxygen source. The observation led to suspect that something other than added water was also present as the oxygen source for the C–H oxygenation. Based on the control experiment, in-situ generated acetone through oxidative deacetalizaition was indicated as the consequential oxygen source via reversible hydration. Obtained ^{18}O-labeled **7q** could be converted into D-[3-^{18}O]-mannose in 85% yield without the reducing oxygen-isotope labeling ratio by treatment with BBr_3. Furthermore, molybdate-catalyzed aldose rearrangement of D-[3-^{18}O]-mannose could produce D-[3-^{18}O]-glucose with a slight reduction of ^{18}O content.[28b,33] Therefore, the author could demonstrate the high synthetic usefulness and practicality of Ru(bpga)-catalyzed C–H oxygenation using hydrolysis of iodobenzene(dicarboxylate) in organic synthesis. In fact, the C–H oxygenation

protocol has begun to be used for the synthesis of natural products by several groups.[34] Especially, it was believed that this C–H oxygenation protocol would strongly contribute to the development of isotope-labeled bio-imaging such as SIMS and multinuclear MRI. The research of SIMS bio-imaging using oxygen-isotope labeled sugars is now in progress.



Scheme 11. Short-step synthesis of oxygen-isotope labeled sugars using Ru(bpga) **1a**-catalyzed C–H oxidation

[a] Determined by ^{1}H NMR analysis.

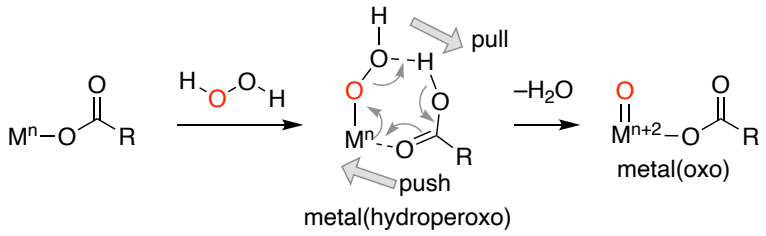
Chapter 3

Acid-Cooperative Highly Efficient C–H Oxidation Using H_2O_2 as the Oxidant

3.1. Mechanistic Insights of C–H Oxidation with $PhI(OCOR)_2$ and H_2O and Working Hypothesis of Acid-Cooperative C–H Oxidation with H_2O_2

As mentioned above, the author achieved highly practical site-selective unreactive C(sp^3)–H oxygenation by using Ru(bpga) **1a** as the catalyst. However, a significant challenge still remained in the catalytic system. Unfortunately, due to the important requirement, that is, the reaction uses hypervalent iodine reagent as the terminal oxidant, the catalytic system is lower atom economic. If Ru(bpga)-catalyzed C–H oxygenation can use an atom-economic oxidant such as hydrogen peroxide and molecular oxygen while maintaining the high site- and chemoselectivity and catalyst durability under the conditions, it was considered that the catalytic oxygenation system would be truly practical and useful oxygen functionalization in organic synthesis.

Although the non-heme enzymimic model's iron and manganese(pdp) derivatives can use hydrogen peroxide as a matter of course, it was considered that carboxylic acids served an important role in the using that terminal oxidant. Based on the non-heme-enzyme model studies, it was considered that ligated carboxylic acid can reduce the redox potential by the metal center (push-effect) and activate O–O bond cleavage to the putative metal(oxo) intermediate (pull-effect) via intramolecular hydrogen bond formation (Scheme 12).[35] These carboxylic acid's cooperative "push-pull" effects prompt the reactive species formation. However, non-heme-type model catalysts durability is unsatisfactory under oxidation conditions, the maximum turnover number is 970.[18a] High durability of the ruthenium(bpga) complex under oxidation conditions is attractive.



Scheme 12. Carboxylic acid assisted O–O bond heterolysis to generate metal(oxo)

Mechanistic studies of Ru(bpga)-catalyzed C–H oxygenation provided tips for utilizing hydrogen peroxide as the terminal oxidant. Shimoda, a collaborator, investigated kinetic studies of Ru(bpga) complex **1a**-catalyzed C–H oxidation of 3,7-dimethyloctyl acetate with $PhI(OBz\text{-}F_5)_2$ and water, and found that the deactivation process involves tautomerization of the putative ruthenium(oxo)

intermediate (Figure 15A) and ligand exchange between chloride and carboxylate ligands, reversibly (Figure 15B). Furthermore, the correlation between reaction rates and pKa of an in-situ generated carboxylic acid is not linear, but the reaction rate was dramatically enhanced in the range of pKa 3.0 to 0.6 (Figure 15C). These mechanistic observations indicated that in-situ obtained carboxylic acids formed a hydrogen bond to the oxo-intermediate and improved the electrophilicity of the reactive species through that hydrogen bond (Figure 15D).[36]

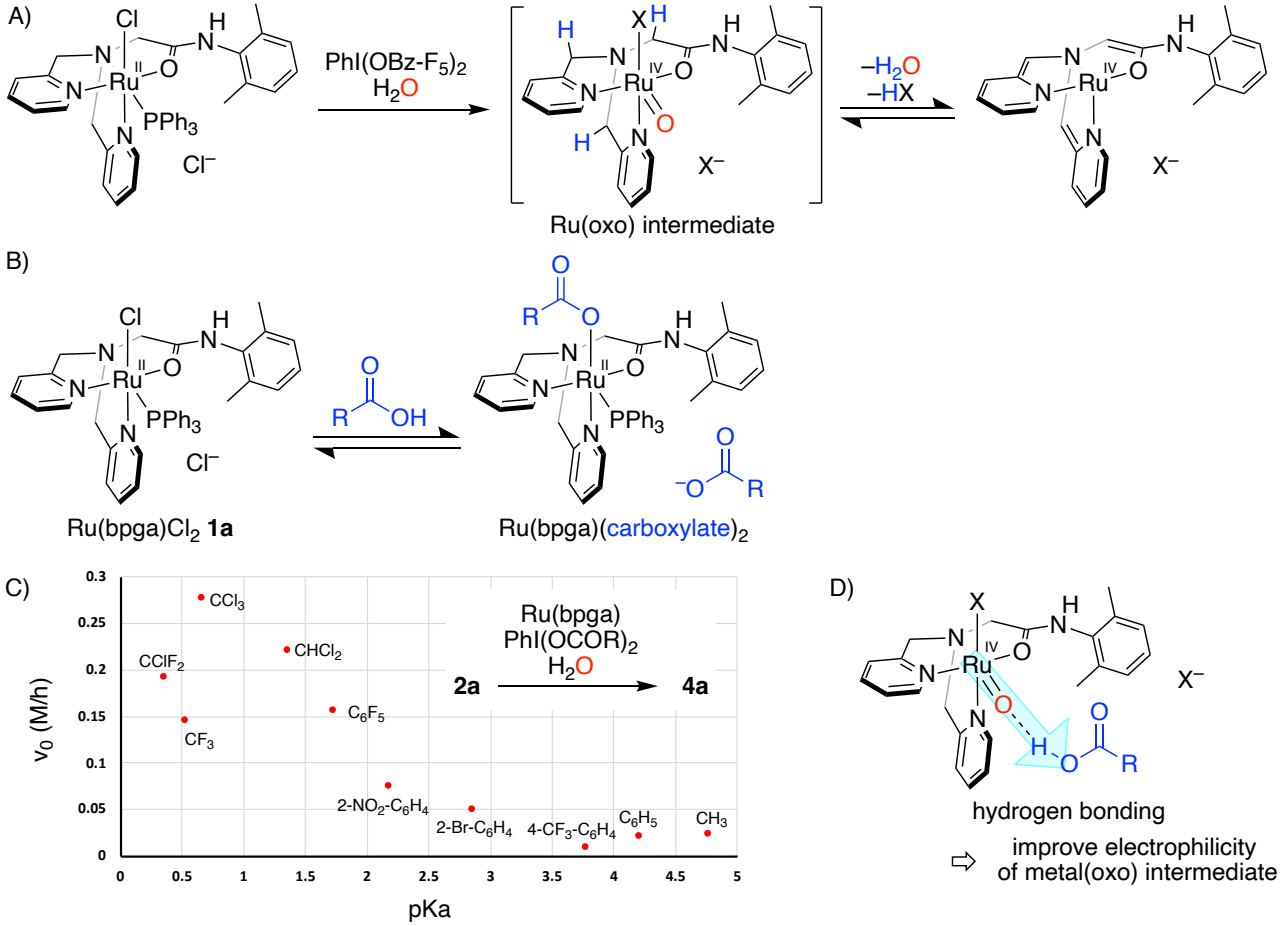


Figure 15. Mechanistic insights of Ru(bpga)-catalyzed C–H oxidation using $PhI(OCOR)_2$ and water

Based on these mechanistic observations and consideration, the author hypothesized that, under acidic conditions, Ru(bpga) complex can use hydrogen peroxide as the terminal oxidant by the cooperative "push-pull" effect of carboxylic acid (Figure 16); the first, reversible ligand exchange between chloride and carboxylate produced the carboxylate complex, then obtained carboxylate complex would be able to decompose hydrogen peroxide to the corresponding metal(oxo) intermediates, which would be further activated through a hydrogen bond.

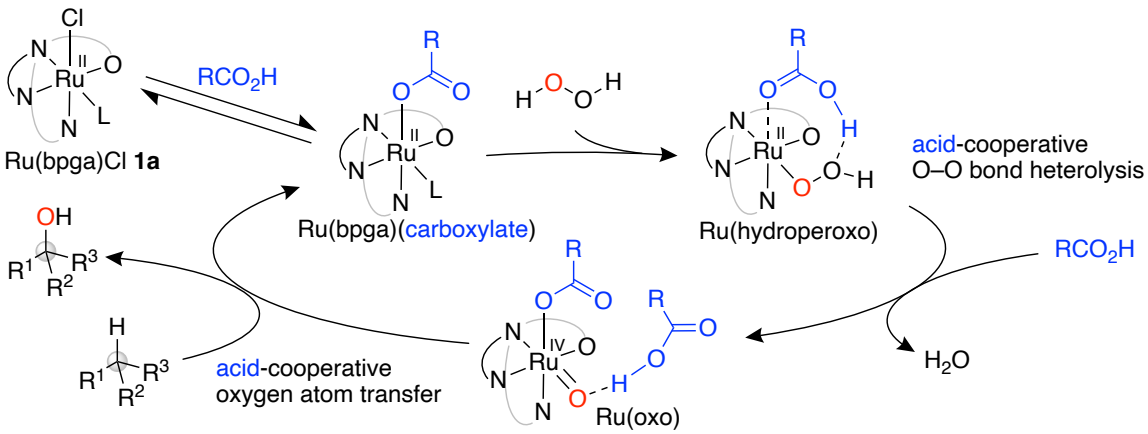
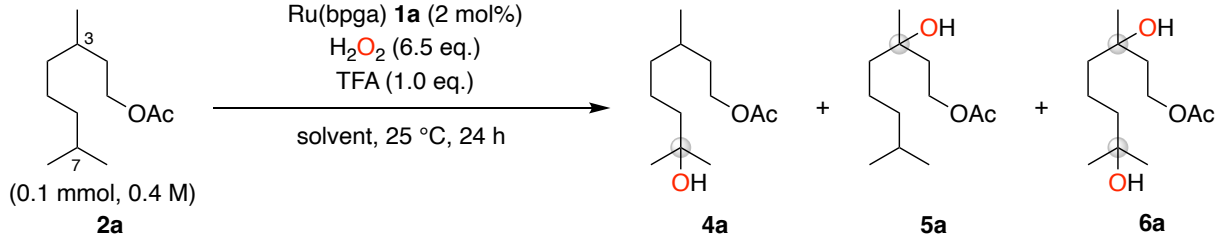


Figure 16. Working hypothesis of carboxylic acid-cooperative C–H oxidation using Ru(bpga) catalyst and H_2O_2

3.2. Results and Discussion

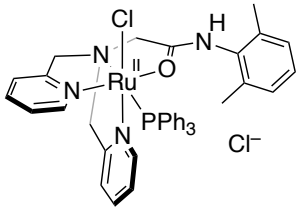
Based on these considerations, the author started Ru(bpga) **1a**-catalyzed C–H oxidation of 3,7-dimethyloctyl acetate using H_2O_2 as the terminal oxidant under acidic conditions (Table 3). The reaction in the presence of 1.0 equivalent of trifluoroacetic acid (TFA) in 1,1,2,2-tetrachloroethane at 25 °C for 24 h produced the C7-hydroxylated product **4a** in 13% yield with excellent site-selectivity (entry 1). On the other hand, no reaction was observed in the reaction in the absence of the TFA (entry 2). Encouraged by these preliminary results, the author surveyed the effective solvent for using hydrogen peroxide (entries 3-11). Less polar chlorinated solvents such as dichloromethane, chloroform, and 1,2-dichloroethane were sluggish (entries 3-5). Reactions in polar solvents such as ethyl acetate, acetonitrile, methanol, and *tert*-butanol did not give the desired alcohol (entries 6-9). To the author's delight, amphiphilic and acidic solvents such as 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) improved conversion, especially in HFIP, 81% conversion and 39% yield was observed (entries 10 and 11). On the other hand, during these studies, it was suspected that TFA decomposed the substrate and the product via alcoholysis and/or dehydration.

Table 3. Screening of solvents in Ru(bpga)-catalyzed C–H oxidation with H_2O_2[a]



(0.1 mmol, 0.4 M) **2a** | **4a** | **5a** | **6a**

entry	solvent	conv. (%)[b]	yield of **4a** (%)[b]	**4a/5a/6a**[b]	TOF (rph)
1	$(CHCl_2)_2$	19	13	5/1/0.1	0.3
2[c]	$(CHCl_2)_2$	0	0	-/-/-	0
3	CH_2Cl_2	20	14	5/1/0.1	0.4
4	$CHCl_3$	10	8	5/1/-	0.2
5	$(CH_2Cl)_2$	18	12	4/1/0.1	0.3
6	AcOEt	5	0	-/-/-	0
7	MeCN	15	0	-/-/-	0
8	MeOH	47	0	-/-/-	0
9	^{t}BuOH	8	0	-/-/-	0
10	TFE	50	25	9/1/0.4	0.6
11	**HFIP**	**81**	**39**	**11/1/2**	**1.1**

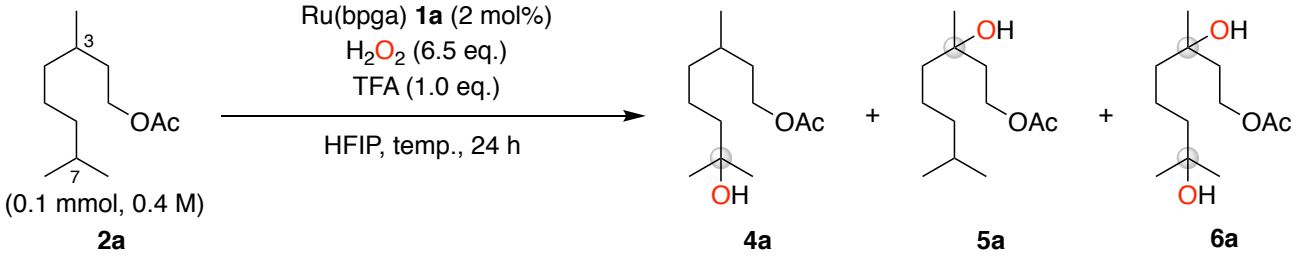


Ru(bpga) **1a**

[a] The reaction was performed with **2a** (0.1 mmol), **1a** (2.0 mol %), H_2O_2 (6.5 eq.), and TFA (1.0 eq.) at 25 °C in solvent (0.4 M) for 24 h. [b] Determined by GC analysis. [c] Run without TFA.
TFA: trifluoroacetic acid, TFE: 2,2,2-trifluoroethanol, HFIP: 1,1,1,3,3,3-hexafluoro-2-propanol

Subsequently, the author optimized the reaction temperature of Ru(bpga)-catalyzed C–H oxidation with H_2O_2 in HFIP (Table 4). Consequently, conversion and chemo-selectivity were gradually improved with reducing reaction temperature and reached a peak in 94% conversion and 60% yield at 10°C (entries 1-4). These improvements were thought to be caused by the inhibition of acidic autolysis of catalyst, substrate, product, and hydrogen peroxide. In contrast, a lower temperature than 10°C reduced the conversion and yield and gave unsatisfactory results (entries 5 and 6).

Table 4. Screening of temperature in Ru(bpga)-catalyzed C–H oxidation with H_2O_2[a]

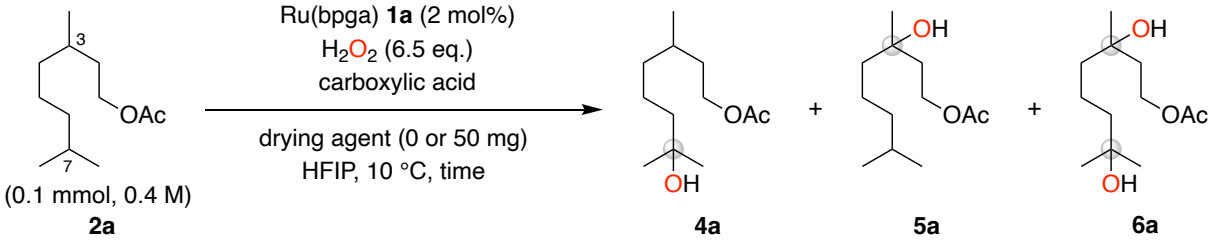


entry	temp. (°C)	conv. (%)[b]	yield of **4a** (%)[b]	**4a/5a/6a**[b]	TOF (rph)
1	25	81	39	11/1/2	1.1
2	20	85	46	14/1/2	1.3
3	15	88	51	18/1/2	1.4
4	**10**	**94**	**60**	**26/1/3**	**1.6**
5	5	76	51	17/1/1	1.3
6	0	60	41	17/1/0.9	1.0

[a] The reaction was performed with **2a** (0.1 mmol), **1a** (2.0 mol %), H_2O_2 (6.5 eq.), and TFA (1.0 eq.) in HFIP (0.4 M) for 24 h. [b] Determined by GC analysis.

Furthermore, the use of an aqueous H_2O_2 solution as the terminal oxidant made the author think about the effect of water on the reaction. To remove water, the addition of drying agents was conducted (Table 5).[37] Interestingly, $MgSO_4$ could enhance the turnover frequency (TOF) almost twice (entries 1-3). Na_2SO_4 presented almost the same TOF as the reaction in the absence of drying agent (entries 2 vs 4). On the other hand, molecular sieve 3Å hampered the reaction (entry 5). Further improvement of TOF as well as chemoselectivity was observed in the reaction with F_5-BzOH instead of TFA in the presence of $MgSO_4$ (entry 3 vs 7). The reaction with 1.5 equivalents of F_5-BzOH using H_2O_2 reached to same reactivity and yield comparable to the previous $PhI(OBz\text{-}F_5)_2$/water system (entry 7 vs 9).

Table 5. Survey of drying agents in Ru(bpga)-catalyzed C–H oxidation with H_2O_2[a]



entry	acid (eq.)	drying agent	time (h)	conv. (%)[b]	yield of **4a** (%)[b]	**4a/5a/6a**[b]	TOF (rph)
1	TFA (1.0)	—	24	94	60	26/1/3	1.6
2	TFA (1.0)	—	12	73	49	17/1/1	2.4
3	TFA (1.0)	$MgSO_4$	12	93	52	20/1/2	2.8
4	TFA (1.0)	Na_2SO_4	12	63	43	15/1/0.9	2.2
5	TFA (1.0)	MS3Å	12	6	5	12/1/-	0.2
6	F_5-BzOH (1.0)	$MgSO_4$	12	78	55	22/1/1	2.7
7	**F_5-BzOH (1.5)**	**$MgSO_4$**	**12**	**96**	**66**	**41/1/5**	**3.5**
8	F_5-BzOH (2.0)	$MgSO_4$	12	98	65	56/1/8	3.6
9[c]	$PhI(OBz\text{-}F_5)_2$ + $H_2{}^{18}O$		12	93	65	35/1/6	3.6

[a] The reaction was performed with **2a** (0.1 mmol), **1a** (2.0 mol %), H_2O_2 (6.5 eq.), carboxylic acid, and drying agent (0 or 50 mg) at 10 °C in HFIP (0.4 M). [b] Determined by GC analysis. [c] The reaction was performed with **2a** (0.1 mmol), **1a** (2.0 mol%), $PhI(OBz\text{-}F_5)_2$ (2.0 eq.), and $H_2{}^{18}O$ (1.5 eq.) at 35 °C in $(CHCl_2)_2$ (0.4 M) for 12 h.

Using $MgSO_4$ in the presence of carboxylic acids has paved the way for the use of hydrogen peroxide as the terminal oxidant on ruthenium-catalyzed C–H oxygenation. However, under that condition, it is essentially impossible to completely bring out the potential of complex **1a** because of the reaction through reversible ligand exchange for H_2O_2 activation. Realize the irreversible formation

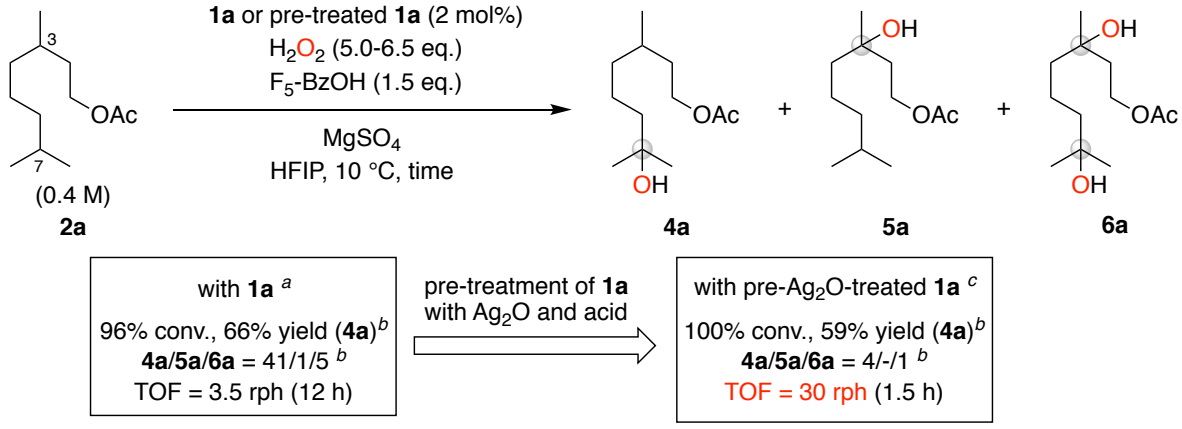


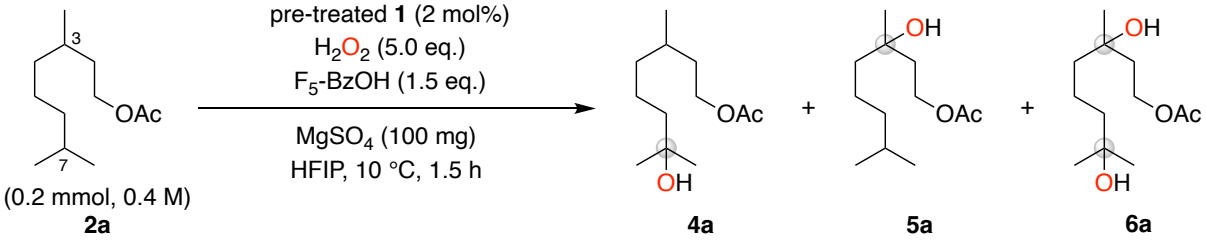
Figure 17. Improvement of TOF in Ru(bpga)-catalyzed C–H oxidation with H_2O_2 by pre-treatment of the catalyst

[a] The reaction was performed with **2a** (0.1 mmol), **1a** (2.0 mol %), H_2O_2 (6.5 eq.), F_5-BzOH (1.5 eq.), and $MgSO_4$ (50 mg) at 10 °C in HFIP (0.4 M) for 12 h. [b] Determined by GC analysis. [c] Pre-treatment of **1a** (2.0 mol%) was performed with F_5-BzOH (10 mol%), and Ag_2O (1.6 mol%) at room temperature in HFIP under N_2 for 1 h, and then the reaction of **2a** (0.2 mmol) was started with H_2O_2 (5.0 eq.), F_5-BzOH (1.4 eq.), and $MgSO_4$ (100 mg) at 10 °C in HFIP (0.4 M) for 1.5 h.

of the desired Ru(bpga)(carboxylate) complex, **1a** was pre-treated with silver oxide (Ag_2O) as the chloride trapping reagent and F_5-BzOH. The reaction using pre-treated complex **1a** dramatically improved the TOF to 30 rph, surprisingly (Figure 17).

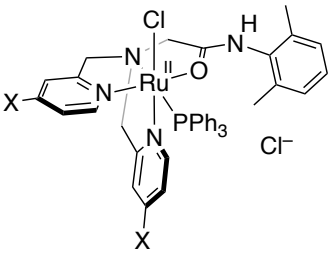
Under that condition, the author investigated the reaction using several Ru(bpga) complexes, bearing substituent groups as C4 position on the pyridine unit, as a catalyst (Table 6). However, the introduction of substituent groups such as methoxy, chloride, bromide, and trifluoromethyl group on pyridine rings did not show a positive effect on the reaction. It was considered that the electron-donating methoxy group reduced the electrophilicity of the putative Ru(oxo) species, and electron-withdrawing chloride, bromide, and trifluoromethyl group increased the redox potential of metal ions, as the result, slowed down the formation of the reactive species.

Table 6. Survey of catalysts in Ru(bpga)-catalyzed C–H oxidation with H_2O_2[a]



entry	Ru(bpga) **1** [X]	conv. (%)[b]	yield of **4a** (%)[b]	**4a/5a/6a**[b]	TOF (rph)
1	**1a** [H]	**100**	**59**	**4/-/1**	**30**
2	**1b** [OMe]	57	38	17/1/0.6	14
3	**1c** [Cl]	70	43	19/1/0.9	17
4	**1d** [Br]	71	48	22/1/1	19
5	**1e** [CF_3]	27	16	15/1/0.2	5.9

[a] Pre-treatment of **1** (2.0 mol%) was performed with F_5-BzOH (10 mol%), and Ag_2O (1.6 mol%) at room temperature in HFIP under N_2 for 1 h, and then the reaction of **2a** (0.2 mmol) was started with H_2O_2 (5.0 eq.), F_5-BzOH (1.4 eq.), and $MgSO_4$ (100 mg) at 10 °C in HFIP (0.4 M) for 1.5 h. [b] Determined by GC analysis.



Ru(bpga) **1**

With these results in hand, the author conducted the optimization of carboxylic acid (Figure 18). In Figure 18, the results of the reaction for each 30 min were summarized. The correlation between the acidity of the carboxylic acids and conversion and TOF was similar to that of the Ru(bpga)/PhI(OCOR)$_2$/H_2O system (see Figure 13 and 15C). These investigations also observed a gradual improvement in the TOF and conversion as decreasing a pKa value of about 3.0 to 1.0, and more acidic conditions diminished TOF.

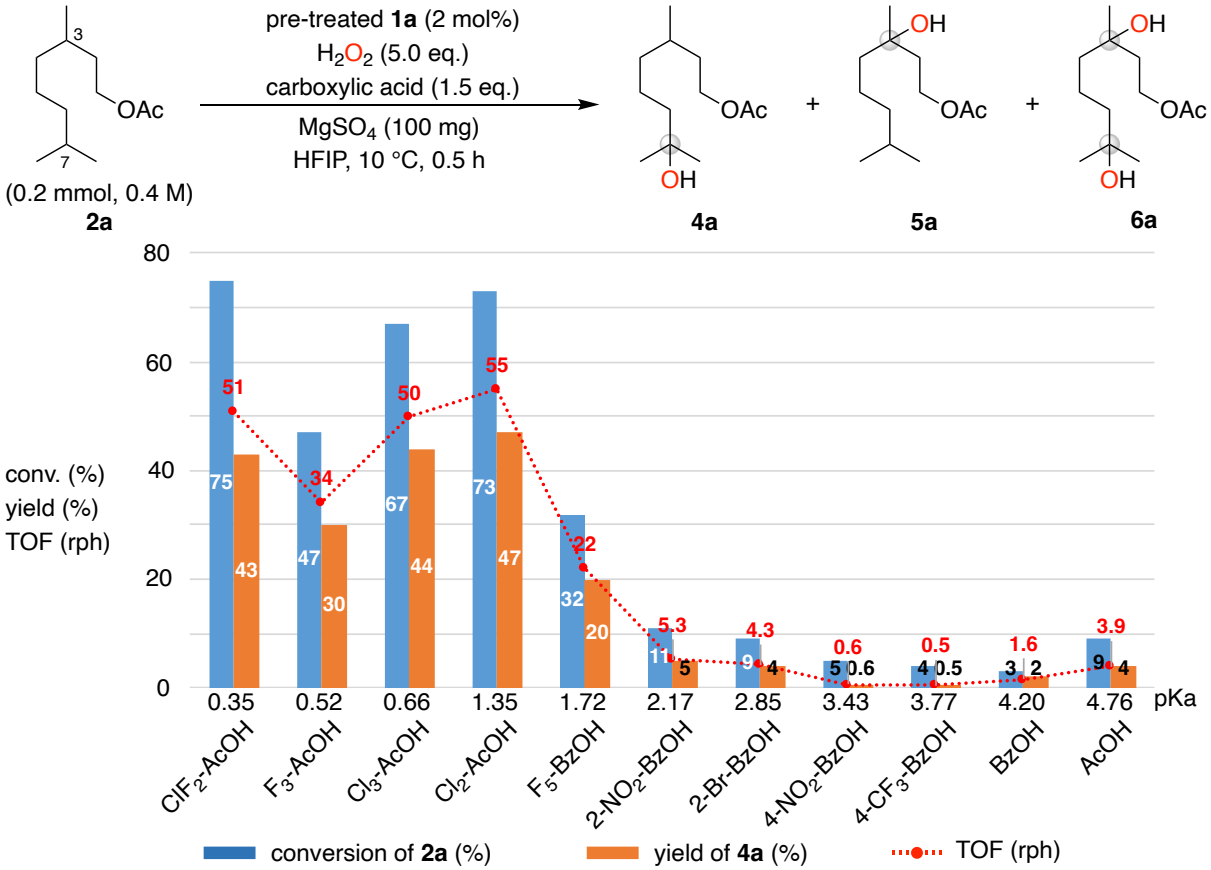


Figure 18. Screening of carboxylic acids in pre-treated Ru(bpga)-catalyzed C–H oxidation with H_2O_2[a]

[a] Pre-treatment of **1a** (2.0 mol%) was performed with carboxylic acid (10 mol%), and Ag_2O (1.6 mol%) at room temperature in HFIP under N_2 for 1 h, and then the reaction of **2a** (0.2 mmol) was started with H_2O_2 (5.0 eq.), carboxylic acid (1.4 eq.), and $MgSO_4$ (100 mg) at 10 °C in HFIP (0.4 M) for 0.5 h. [b] Determined by GC analysis.

These results indicated that the introduced carboxylic acid cooperation protocol strongly affected TOF on Ru(bpga)-catalyzed C–H oxygenation without reducing site-selectivity. In addition, to perform an entropically favorable intramolecular acid cooperative activation, the author was intrigued to introduce the carboxylic acid on the catalyst molecule. The author came up with the use of dicarboxylic acids instead of monocarboxylic acid. It was thought that introducing hydrogen dicarboxylate ligand could reduce the redox potential of the ruthenium ion by carboxylate unit and activate in-situ

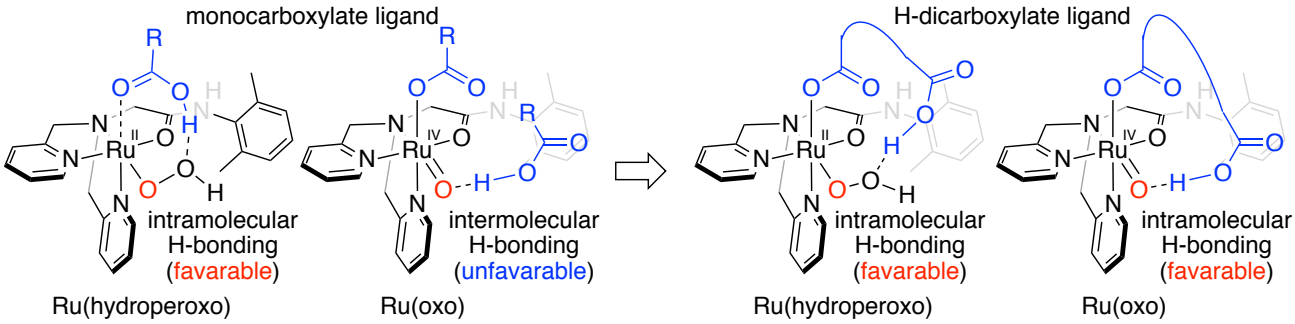


Figure 19. Concept of intramolecular acid-cooperative system using H-dicarboxylate ligand

generating Ru(OOH) and Ru(oxo) intermediate through intramolecular hydrogen bonding with the other remaining carboxylic acid unit (Figure 19).

Based on this consideration, the author further investigated the reaction with a dicarboxylic acid and Ag_2O for realizing the intramolecular acid-cooperative C–H oxidation (Figure 20). Consequently, oxalic acid, malonic acid, and maleic acid specifically and dramatically improved TOF. These carboxylic acid's pKa values are 1.27, 2.83, and 1.83, respectively.[38] These results and pKa values indicated that these drastic improvements were probably caused by the carboxylic acid's structure, not the pKa.

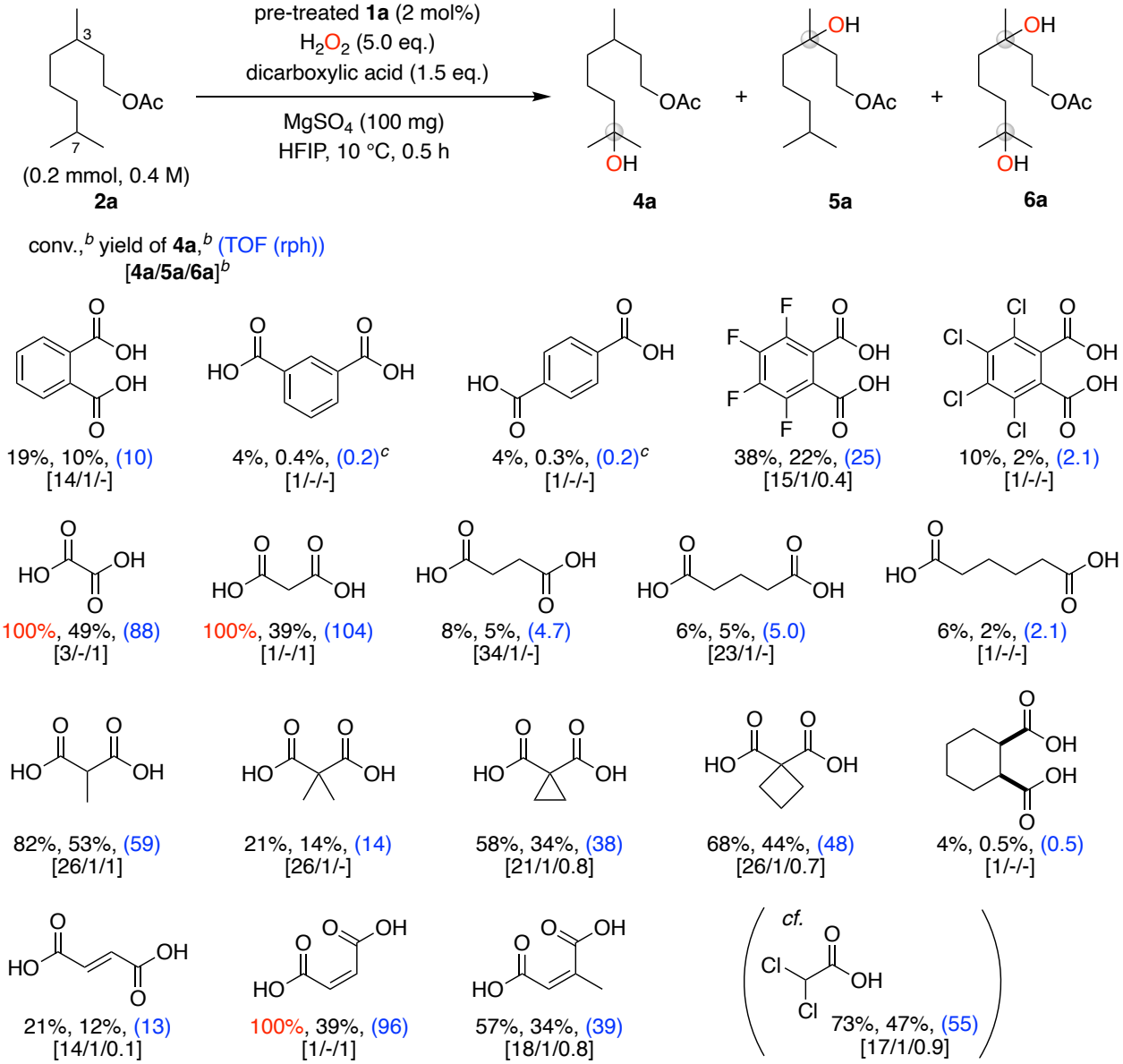
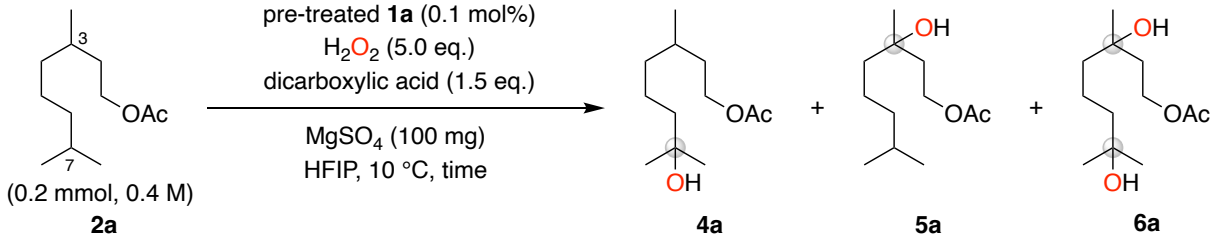


Figure 20. Screening of dicarboxylic acids in acid-cooperative Ru(bpga)-catalyzed C–H oxidation with H_2O_2[a]

[a] Pre-treatment of **1a** (2.0 mol%) was performed with dicarboxylic acid (10 mol%), and Ag_2O (1.6 mol%) at room temperature in HFIP under N_2 for 1 h, and then the reaction of **2a** (0.2 mmol) was started with H_2O_2 (5.0 eq.), dicarboxylic acid (1.4 eq.), and $MgSO_4$ (100 mg) at 10 °C in HFIP (0.4 M) for 0.5 h. [b] Determined by GC analysis. [c] Run for 1 h.

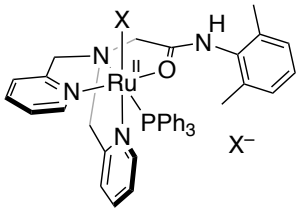
Further investigation using these three carboxylic acids was conducted with only 0.1 mol% catalyst loading (Table 7). Interestingly, all of these catalytic systems presented excellent TOF (> 100 rph) (entries 1-3). Especially, maleic acid showed higher TOF (560 rph) than others and, for only 1.5h, fully converted the substrate and yielded the desired alcohol **4a** in 64% yield with high site-selectivity (entry 4). Desired Ru(bpga)(H-maleate)$_2$ **1f** could be isolated with simple extraction and presented the highest TOF (600 rph) in the model reaction (entry 5). It is noted that, as far as the author knows, this TOF value is the world's best in this field of site-selective aliphatic C–H oxidation using a molecular catalyst.[18k] In addition, reducing the added maleic acid and H_2O_2 to 0.4 and 2.0 equivalents, respectively, presented acceptable TOF with excellent site-selectivity (entry 6). Truly practical, strong, and atom-economic catalytic C–H oxygenation could be achieved by using acid-cooperative Ru(bpga)(H-maleate)$_2$ complex **1f** as the catalyst.

Table 7. Survey of dicarboxylic acids in acid-cooperative Ru(bpga)-catalyzed C–H oxidation with H_2O_2[a]



entry	acid	time (h)	conv. (%)[b]	yield of **4a** (%)[b]	**4a/5a/6a**[b]	TOF (rph)
1	oxalic acid	1	31	19	11/1/0.2	210
2	malonic acid	1	62	45	31/1/0.8	490
3	maleic acid	1	70	48	21/1/1	560
4	maleic acid	1.5	99	64	83/1/13	560
5[c]	maleic acid	1.5	100	62	4/-/1	600
6[c,d]	maleic acid	3	95	61	42/1/8	280

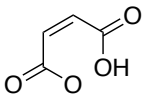
[a] Pre-treatment of **1a** (0.1 mol%) was performed with dicarboxylic acid (0.5 mol%), and Ag_2O (0.08 mol%) at room temperature in HFIP under N_2 for 1 h, and then the reaction of **2a** (0.2 mmol) was started with H_2O_2 (5.0 eq.), dicarboxylic acid (1.5 eq.), and $MgSO_4$ (100 mg) at 10 °C in HFIP (0.4 M). [b] Determined by GC analysis. [c] Using **1f** (0.1 mol%) instead of **1a**. [d] Run with H_2O_2 (2.0 eq.), maleic acid (0.4 eq.), and $MgSO_4$ (40 mg) in HFIP (1 M).



Ru(bpga) **1**

1a: X= Cl

1f: X=



The acid-cooperative C–H oxygenation allowed wide tolerance of functional groups (Figure 21). Benzoate derivatives bearing nitro and nitrile groups and sulfonate produced the desired tertiary alcohols **4r-t** in high yield with even 0.1-0.5 mol% catalyst loading. Alkyl bromide **2d** and tertiary alcohol **2g** also yielded the desired alcohols with good chemoselectivity. Carboxylic acid **2u** selectively produced the corresponding lactone **4u**.[39a] Under acid-cooperative conditions, the oxidation of chiral

substrate **2i** also underwent complete stereospecifically to give the corresponding chiral alcohol **4i** with retentional stereochemistry in 58% yield with 99% *ee* and ketone **4i'** in 12% yield, respectively. Under that conditions, no-epimerization of chiral tertiary carbon at α-position of ketone **4i'** was observed. This acid-cooperative protocol can oxidize various types of N-containing compounds in a site- and chemoselective manner. Imide **2v** and sulfonamide **2w** with even 0.1 mol% of **1f** loading also produced the corresponding *tert*-alcohols in good to high yield with high site-selectivity. *tert*-Butoxycarbonyl (Boc) group, well reactive N-protecting group under acidic conditions, was also tolerated under the present reaction conditions and produced the corresponding *tert*-alcohol **4x** in 74% yield. Moreover, nucleophilic nitrogen functional groups such as pyridine and amine, ubiquitous in bio-active compounds and oxidizable functional groups, were allowed on the reaction but required an extra step, meaning nucleophilic nitrogen atom was protected by forming the corresponding salt with strong acids in advance.[16g,22b,c] After the surveying acid and optimizing conditions for protonation,[39b] one-pot

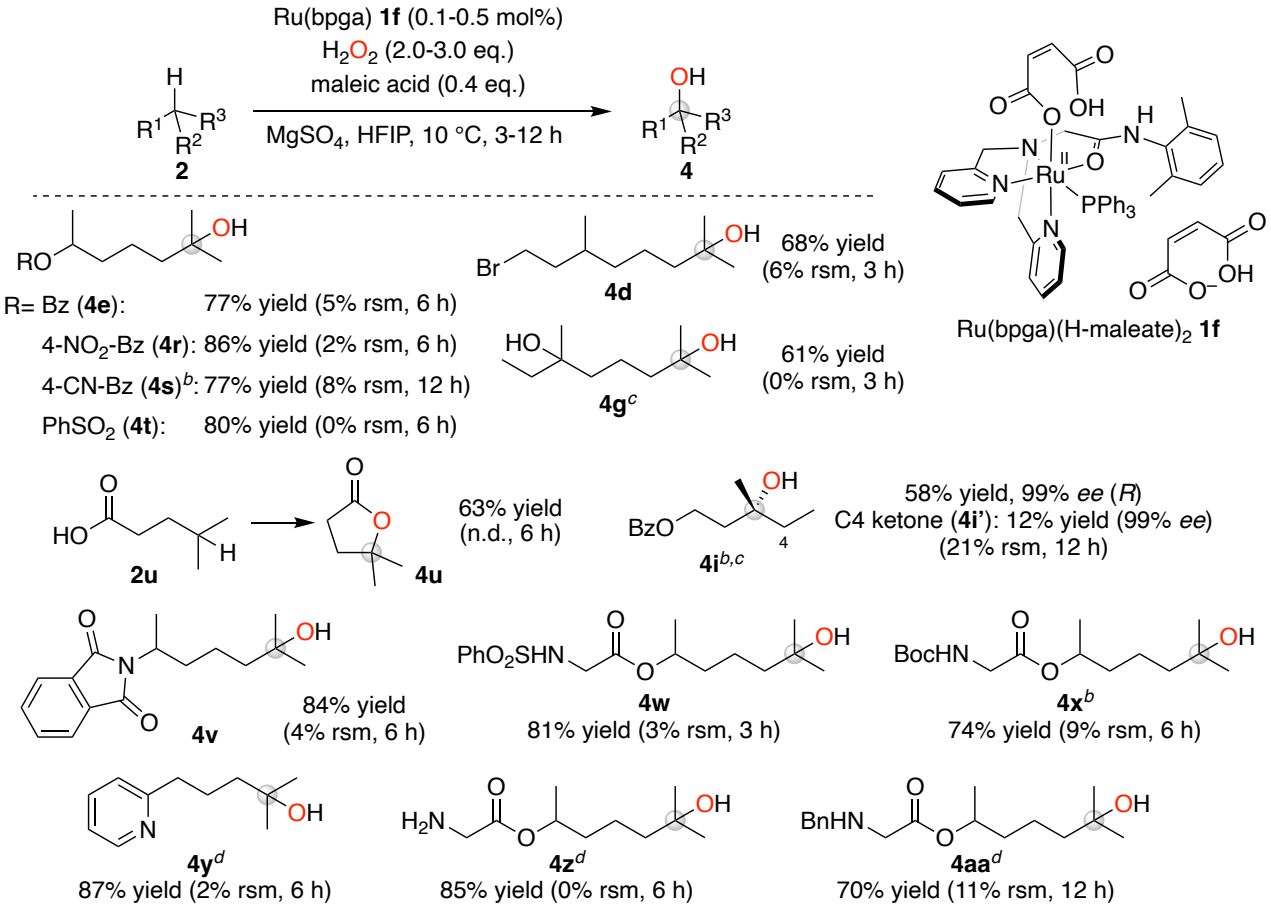


Figure 21. Substrate scope of Ru(bpga) **1f**-catalyzed methyne C–H oxidation with H_2O_2[a]

[a] The reaction was performed with **2** (0.2 mmol), **1f** (0.1 mol%), H_2O_2 (2.0 eq.), meleic acid (0.4 eq.), and $MgSO_4$ (40 mg) at 10 °C in HFIP (1 M). Yield (%) was isolated yield. Rsm (%) was recovered starting material. [b] Using **1f** (0.5 mol%). [c] Using H_2O_2 (3.0 eq.) and $MgSO_4$ (60 mg). [d] Pre-treatment of **2** (0.2 mmol) was performed with aq. HBF_4 (1.1 eq.), and $MgSO_4$ (60 mg) at 0 °C to room temperature in HFIP, and then the reaction was started at 10 °C.

protocol combining pre-treatment with 1.1 equivalents of HBF_4 aqueous solution in HFIP and C–H oxidation with Ru(bpga) catalyst and H_2O_2 could achieve excellent chemo- and site-selectivity on the reaction of pyridine, primary, and secondary amine-containing compounds **2y**-**aa**.

Unactivated methylene C–H bonds could be oxidized by using the acid-cooperative Ru(bpga) **1f** catalytic system (Figure 22). Under typical methine C–H oxidation conditions, the reaction of *n*-pentyl benzoate **2ab** was sluggish. Fortunately, batch-wise addition of H_2O_2 with 2 mol% loading of **1f** improved conversion and yielded 4-ketone **4ab** and 3-ketone **4ab'** with a 4.3/1 ratio. *n*-Hexyl benzoate **2ac** using 1 mol% of **1f** with the addition of 6.0 equivalents of H_2O_2 in 3 batches also produced ketones in 82% yield, although there is room for improvement in site-selectivity. Cyclohexane **2ad** selectively gave cyclohexanone **4ad** in good yield by using 4.0 equivalents of H_2O_2 in 1 batch protocol. Cyclopentylmethyl benzoate **2ae** under batch protocol was converted to 3-ketone **4ae** in 42% yield. In this reaction, it was suspected that the retro-Michael reaction of the C2-oxidized product proceeded due to the observation of benzoic acid formation.

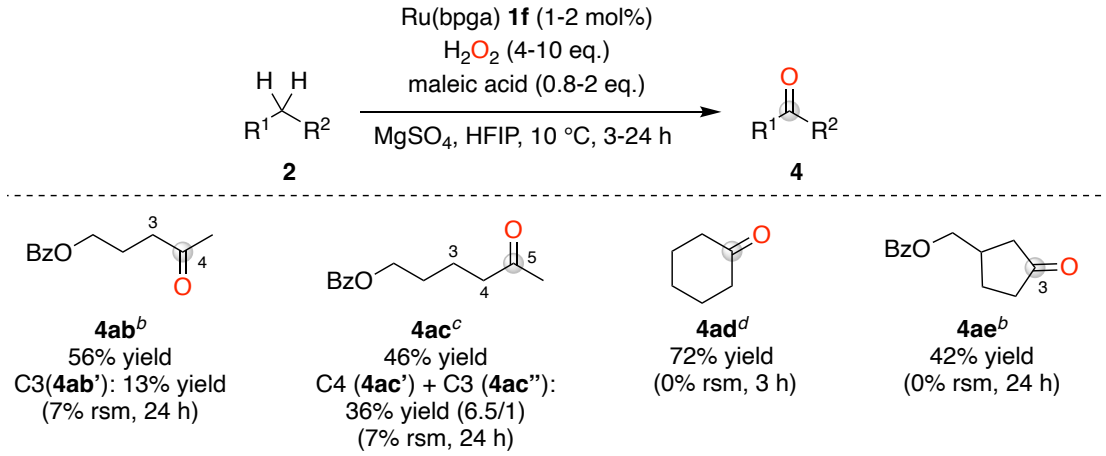


Figure 22. Substrate scope of Ru(bpga) **1f**-catalyzed methylene C–H oxidation with H_2O_2[a]

[a] Run on a 0.2 mmol scale at 10 °C. Yield (%) was isolated yield. Rsm (%) was recovered starting material. [b] Run with **1f** (2 mol%), H_2O_2 (10 eq., in 5 batches), meleic acid (2.0 eq.), and $MgSO_4$ (200 mg) in HFIP (0.2 M). [c] Run with **1f** (1 mol%), H_2O_2 (6.0 eq., in 3 batches), meleic acid (1.0 eq.), and $MgSO_4$ (100 mg) in HFIP (0.4 M). [d] Run with **1f** (1 mol%), H_2O_2 (4.0 eq.), meleic acid (0.8 eq.), and $MgSO_4$ (80 mg) in HFIP (0.5 M). Yield (%) was determined by GC analysis.

Finally, the author conducted the late-stage C–H oxidation by using Ru(bpga)(H-maleate)$_2$ **1f**-catalyzed acid-cooperative oxygen atom transfer (Figure 23). Under the standard using 0.1 mol% of **1f** loading conditions, deoxycholic acid derivative **2n** was selectively oxidized at the C5 position to afford the corresponding *tert*-alcohol **4n** in 81% yield with stereospecifically. The oxidation of sulbactam derivative **2af**, which was a multi-functional compound, with 0.5mol% of **1f** occurred at the

sterically and electronically favored tertiary C–H bond in high yield. Citalopram **2ag** bearing a tertiary amine and cyano groups produced the corresponding lactol **4ag** as the major product by using pre-treatment with HBF_4 and one batch addition of 4.0 equivalents of H_2O_2. The reaction of (+)-sclareolide **2ah**, bearing multiple methylene C–H bonds, using 2 mol% of **1f** with batch-wise addition of 10 equivalents of H_2O_2 underwent at sterically and electronically favored C2 and C3 in 48% and 33% yields, respectively.

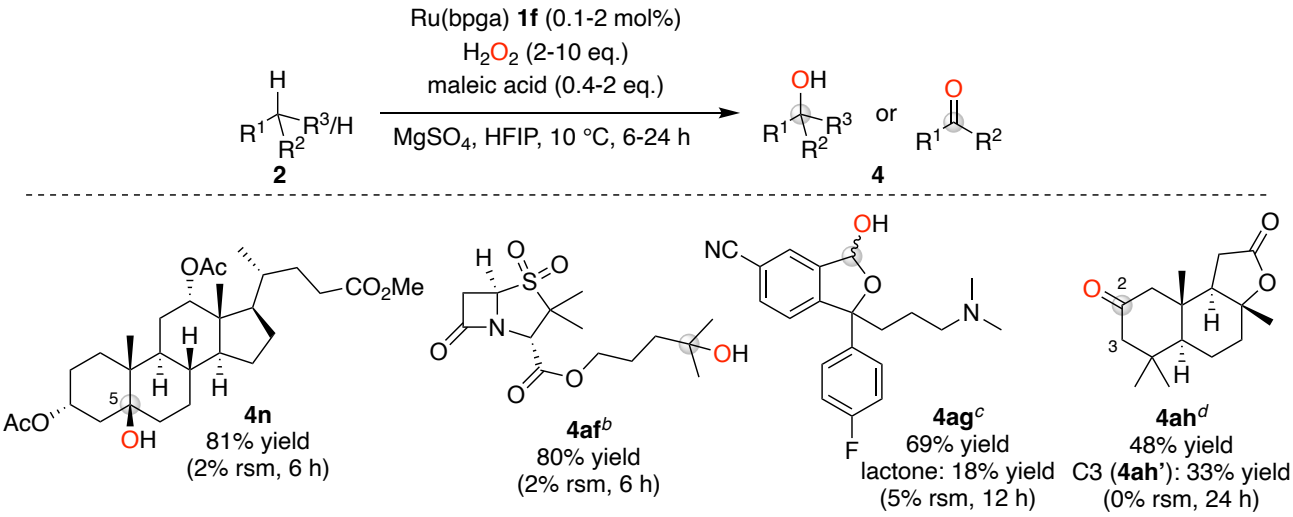


Figure 23. Substrate scope of Ru(bpga) **1f**-catalyzed late-stage C–H oxidation with H_2O_2[a]

[a] The reaction was performed with **2** (0.2 mmol), **1f** (0.1 mol%), H_2O_2 (2.0 eq.), meleic acid (0.4 eq.), and $MgSO_4$ (40 mg) at 10 °C in HFIP (0.4 M). Yield (%) was isolated yield. Rsm (%) was recovered starting material. [b] Using **1f** (0.5 mol%), H_2O_2 (3.0 eq.) and $MgSO_4$ (60 mg). [c] Pre-treatment of **2ai** (0.2 mmol) was performed with aq. HBF_4 (1.1 eq.), and $MgSO_4$ (100 mg) at 0 °C to room temperature in HFIP, and then the reaction was started with **1f** (0.5 mol%), H_2O_2 (4.0 eq.), and maleic acid (0.4 eq.) at 10 °C in HFIP (0.4 M). [d] Run with **1f** (2 mol%), H_2O_2 (10 eq., in 5 batches), meleic acid (2.0 eq.), and $MgSO_4$ (200 mg) in HFIP (0.2 M).

Chapter 4

Conclusion

In conclusion, the author has done highly practical two types of C–H oxygenations by using non-heme-type ruthenium(bpga) complexes as a catalyst with carboxylic acid-cooperation protocols found by the author and co-worker: i) C–H oxidation using water as the stoichiometric oxygen source through hydrolysis of iodobenzene(dicarboxylate), and ii) highly site-selective C–H oxidation using H_2O_2 as the terminal oxidant with the new intramolecular acid-cooperation system. These ruthenium(bpga)-catalyzed oxidations can convert tertiary as well as secondary C–H bonds on even complex natural compounds to corresponding alcohols or ketones with good to high site-selectivity under acidic conditions, respectively. The characters of each C–H oxygenation are as follows.

Oxidative oxygen atom transfer of water using a ruthenium catalyst is saving water resources that can use an almost stoichiometric amount of water molecular as the oxygen source for direct C–H oxygen functionalization. Especially, this method would be a strong tool for the synthesis of isotopic-oxygen labeled compounds, which are anticipated as a next-generation bio-imaging probe for SIMS and multinuclear MRI. It was noted that the method could be to tune the reactivity to fit the substrate by choosing a carboxylate ligand on a hypervalent iodine reagent. Moreover, the protocol could be applied to multigram scale synthesis. In fact, isotopic-oxygen-labeled sugars such as D-mannose and D-glucose were achieved by using the protocol within acceptable short synthetic steps.

On the other hand, a ruthenium-catalyst bearing a carboxylate ligand, especially H-maleate, can use hydrogen peroxide as the terminal oxidant and showed excellent TOF with high site-selectivity. Introduced hydrogen-dicarboxylate ligands were thought to be able to assist the formation of the putative reactive ruthenium(oxo) intermediate from hydrogen peroxide and activate the oxo-intermediate through a hydrogen bond. The mechanistic details of the carboxylic acid-cooperation are still uncleared, but the new activation method would be able to contribute to the development of oxygen atom transfer reactions via metal(oxo) intermediate.

Chapter 5

Experimentals

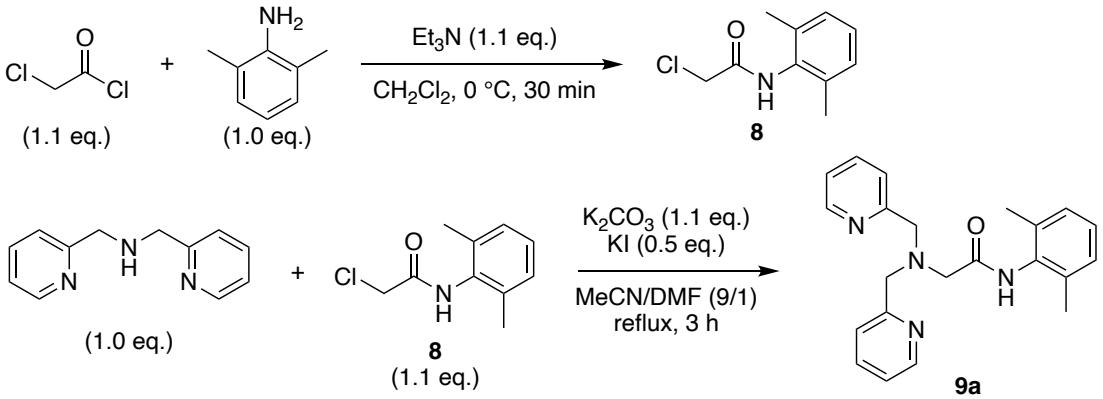
5.1. General Information

^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL JNM-AL-400 spectrometer at 400 and 100 MHz, respectively. Chemical shifts were expressed in parts per million (ppm) with respect to tetramethylsilane (TMS) as the internal standard (0 ppm) for ^{1}H NMR, and $CDCl_3$ as internal standard (77.0 ppm) for ^{13}C NMR. Coupling constants were reported as Hertz (Hz), signal shapes and splitting patterns were indicated as follows: s, singlet; br, broad; d, doublet; t, triplet; q, quartet; quin, quintet; sext, sextet; dd, doublet doublet; m, multiplet. Mass spectra were recorded on a BRUKER DALTONICS MICRO TOF-KS1 focus (HR-ESI); peaks are given in m/z (% of basis peak). Infrared spectra were obtained with SHIMADZU IRAffinity-1 FTIR spectrophotometer, and only diagnostic signals are listed below. Optical rotations were recorded on an ANTON PAAR MCL-300. Gas chromatography was performed on SHIMADZU GC-2025 with COATING CP-SELECT 624 CB column (30 m, 0.25 mm, 1.4 μm, for **4a**-**m**, **4o**, and **4ad**) or HP-5 column (30 m, 0.32 mm, 0.25 μm, for **4p** and **4y**). Thin layer chromatography was performed on Merck silica gel 60 F^{254} coated glass plates and visualized by fluorescence quenching under UV light or staining with the standard solution of $12MoO_3•H_3PO_4$, *p*-anisaldehyde and ceric ammonium molybdate. Column chromatography was conducted on Cica (Kanto Chemical Co., INC.) silica gel 60N (spherical, neutral, 63-210 μm), or Fuji Silysia Chemical Ltd. Chromatorex NH silica gel (spherical, basic, 100-200 μm). Ru(bpga) complex **1a** was prepared according to the reported procedure[23a] or following modified procedure. Ru(bpga) complexes **1b**-**f** was synthesized by following procedure. (±)-3,7-Dimethyloctyl acetate **2a**,[16a] 4-methylpentyl benzoate **2b**,[40] (±)-3,7-dimethyloctyl bromide **2d**,[41] (*S*)-3-methylpentyl benzoate **2i**,[22c] *cis*-1,2-isopropylidenedioxycyclohexane **2k**,[42] deoxycholic acid derivative **2n**,[43] 17β-estradiol diacetate **2p**,[44] 6-methylheptan-2-yl 4-cyanobenzoate **2s**,[45] *N*-(6-methylheptan-2-yl)phthalimide **2v**,[46] 2-(4-methylpentyl)pyridine **2y**,[16g] sulbactam derivative **2af**,[45] iodosylbenzene,[47] iodobenzene[bis(pentafluorobenzoate)] **3c**[31] and Ag_2O[48] were prepared according to the literature procedure. Starting materials (adamantane **2c**, 1-adamantanol **2f**, 3,7-dimethyloctan-3-ol **2g**, 1-isopropyl-4-nitrobenzene **2h**, *cis*-decalin **2j**, 1,2,3,4-tetrahydronaphthalene **2l**, cedrol **2m**, (–)-ambroxide **2o**, 4-methylpentanoic acid **2u**, *n*-pentyl benzoate **2ab**, *n*-hexyl benzoate **2ac**, cyclohexane **2ad**, citalopram **2ag**, and (3a*R*)-(+)-sclareolide **2ah**) and sample of products for GC (1-adamantanol **4c**, 1,3-adamantanediol **4f**, 1-tetralone **4l**, cyclohexanone **4ad**) were commercially available, which were distilled or passed on silica gel column before use. Other starting materials were synthesized by following procedure. Iodobenzene(diacetate) **3a**, iodobenzene[bis(trifluoroacetate)] **3b**, and

carboxylic acids were commercially available, which were used without purification. Hydrogen peroxide (H_2O_2) was commercially available, and the concentration of H_2O_2 was determined by redox titration with $KMnO_4$.

5.2. Preparation of Bpga Ligands

5.2.1. Modified procedure for preparation of *N'*-2,6-dimethylphenyl *N*,*N*-bis(2-pyridylmethyl)glycinamide (9a)



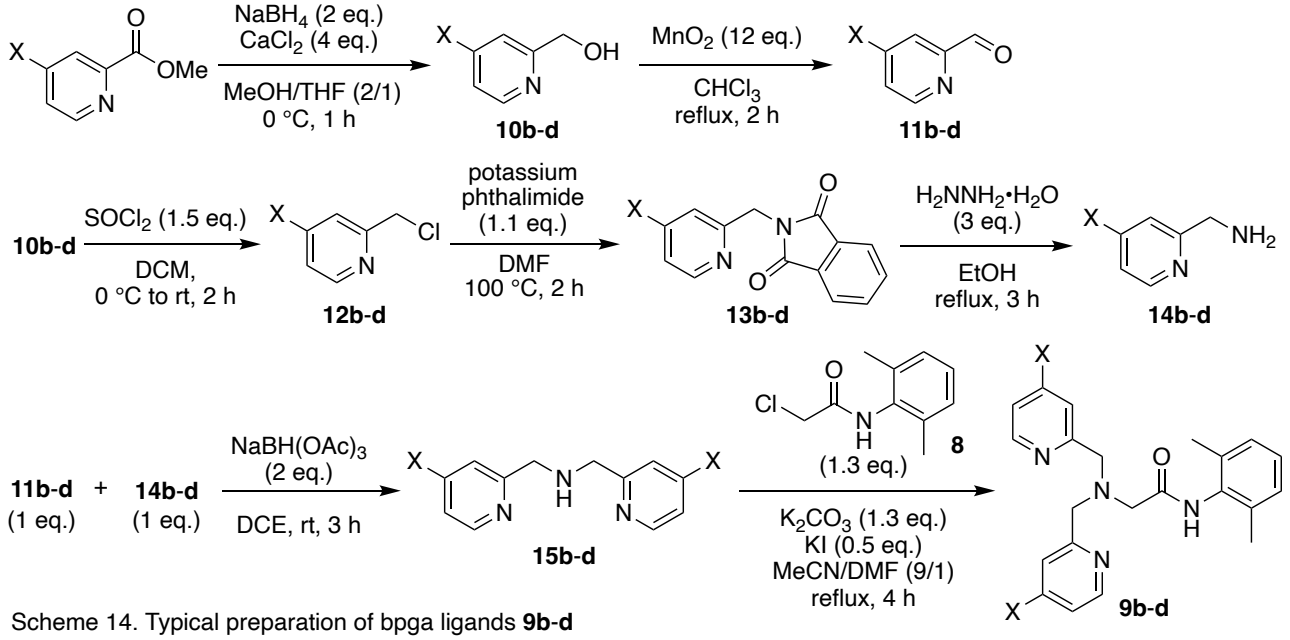
Scheme 13. Modified preparation of bpga ligand **9a**

(Step 1): 2,6-Dimethylaniline (3.03 g, 3.08 mL, 25.0 mmol), CH_2Cl_2 (50 mL), and triethylamine (2.78 g, 3.83 mL, 27.5 mmol) were placed in a 100 mL flask and cooled at 0 °C using an ice-water bath. At that temperature, chloroacetyl chloride (3.11 g, 2.19 mL, 27.5 mmol) was added slowly to the mixture. After stirred for 30 min at that temperature, the reaction was quenched by addition of sat. $NaHCO_3$ aq. (30 mL) and extracted with CH_2Cl_2 (30 mL x 3). The organic layers were washed with 1N HCl and brine, and then dried over anhydrous Na_2SO_4. The crude mixture was concentrated under reduced pressure. Resulting residue was submitted to silica gel chromatography (CH_2Cl_2/MeOH = 1/0 to 49/1) to give 2-chloro-*N*-(2,6-dimethylphenyl)acetamide **8** (4.79 g, 24.3 mmol, 97.0% yield) as a colorless solid.

(Step 2): 2-Chloro-*N*-(2,6-dimethylphenyl)acetamide **8** (2.17 g, 11.0 mmol), MeCN (90 mL), and DMF (10 mL), potassium carbonate (1.52 g, 11.0 mmol), potassium iodide (830 mg, 5.00 mmol), and bis(2-pyridylmethyl)amine (1.99 g, 1.80 mL, 10.0 mmol) were placed in a 300 mL flask and heated at reflux using an aluminum bath. After stirred for 3 h at that temperature, the resulting mixture was diluted by AcOEt (100 mL) and passed through Celite pad with AcOEt, and then the filtrate was concentrated under reduced pressure. AcOEt (50 mL) and sat. $NaHCO_3$ aq. (100 mL) were added to the resulting mixture and organic compounds were extracted with AcOEt (50 mL x 3). The organic

layers were washed with brine, and then dried over anhydrous Na_2SO_4. The crude mixture was concentrated under reduced pressure. Resulting residue was submitted to NH silica gel chromatography (*n*-hexane/AcOEt = 2/1 to 0/1) to give *N'*-2,6-dimethylphenyl *N*,*N*-bis(2-pyridylmethyl)glycinamide **9a** (2.25 g, 6.25 mmol, 62.5% yield) as a light brown solid.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.13 (br-s, 1H), 8.54 (d, *J* = 4.9 Hz, 2H), 7.62 (td, *J* = 1.5, 7.4 Hz, 2H), 7.37 (d, 2H, *J* = 7.8 Hz), 7.17 (dd, *J* = 4.9, 7.3 Hz, 2H), 7.10-7.06 (m, 3H), 3.99 (s, 4H), 3.53 (s, 2H), 2.17 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 158.3, 149.5, 136.5, 135.4, 134.5, 128.0, 126.9, 123.0, 122.4, 60.4, 57.9, 18.5 ppm; FT-IR (KBr): 3262, 3011, 2920, 2841, 1676, 1585, 1504, 1435, 1369, 1271, 1140, 1043, 991, 766, 619 cm^{-1}; HRESI-MS (m/z) [M + H$^+$], calcd. for $[C_{22}H_{25}N_4O]^+$ 361.2023, found: m/z = 361.2024.

5.2.2. Typical procedure for preparation of *N'*-2,6-dimethylphenyl *N*,*N*-bis(4-substituted-2-pyridylmethyl)glycinamide (9b-d)[49-53]



Scheme 14. Typical preparation of bpga ligands **9b-d**

(Step 1)[49]: Methyl 4-chloro-2-pyridinecarboxylate (9.55 g, 55.7 mmol), MeOH (50 mL), THF (25 mL), and calcium chloride (24.7 g, 223 mmol) were placed in a 300 mL flask and cooled at 0 °C using an ice-water bath. At that temperature, sodium borohydride (4.21 g, 111 mmol) was added slowly to the mixture. After stirred for 1 h at that temperature, the reaction was quenched by addition of water (100 mL) and extracted with AcOEt (100 mL x 3). The organic layers were washed with brine, and then dried over anhydrous Na_2SO_4. The crude mixture was concentrated under reduced pressure. Resulting residue was submitted to silica gel chromatography (n-hexane/AcOEt = 2/1 to 1/2) to give 4-chloro-

2-pyridinemethanol **10c** (7.73 g, 53.8 mmol, 96.7% yield).

(Step 2)[50]: 4-Chloro-2-pyridinemethanol **10c** (1.44 g, 10.0 mmol), $CHCl_3$ (20 mL), and MgO_2 (10.4 g, 120 mmol) were placed in a 100 mL flask and heated at reflux using an aluminum bath. After stirred for 2 h at that temperature, the reaction was cooled to room temperature and passed through Celite pad with $CHCl_3$. The crude mixture was concentrated under reduced pressure. Resulting residue was submitted to silica gel chromatography (CH_2Cl_2/MeOH = 1/0 to 9/1) to give 4-chloro-2-pyridinecarboxaldehyde **11c** (947 mg, 6.69 mmol, 66.9% yield).

(Step 3)[51]: 4-Chloro-2-pyridinemethanol **10c** (1.72 g, 12.0 mmol) and CH_2Cl_2 (60 mL) were placed in 100 mL flask under nitrogen atmosphere and cooled at 0 °C using an ice-water bath. At that temperature, thionyl chloride (2.14 g, 1.31 mL, 18.0 mmol) was added dropwise to the mixture and allowed to warm up to room temperature. After stirred for 2 h at that temperature, the reaction was quenched by addition of sat. $NaHCO_3$ aq. (50 mL) and extracted with CH_2Cl_2 (50 mL x 3). The organic layers were washed with brine, and then dried over anhydrous Na_2SO_4. The crude mixture was concentrated under reduced pressure. Resulting residue was submitted to silica gel chromatography (n-hexane/AcOEt = 4/1) to give 4-chloro-2-(chloromethyl)pyridine **12c** (1.71 g, 10.5 mmol, 87.8% yield).

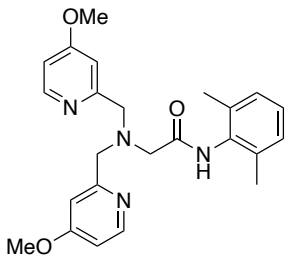
(Step 4)[52]: 4-Chloro-2-(chloromethyl)pyridine **12c** (1.71 g, 10.5 mmol), DMF(21 mL), and potassium phthalimide (2.15 g, 11.6 mmol) were placed in 100 mL Schlenk tube under nitrogen atmosphere and heated at 100 °C using an aluminum bath. After stirred for 2 h at that temperature, the reaction was cooled to room temperature, quenched by addition of sat. $NaHCO_3$ aq. (50 mL), and extracted with CH_2Cl_2 (50 mL x 3). The organic layers were washed with brine, and then dried over anhydrous Na_2SO_4. The resulting mixture was concentrated under reduced pressure to give crude mixture including 2-((4-chloropyridin-2-yl)methyl)isoindoline-1,3-dione **13c**, which was used for following step without purification.

(Step 5)[52]: Crude mixture including 2-((4-Chloropyridin-2-yl)methyl)isoindoline-1,3-dione **13c** was dissolved in EtOH (100 mL). Hydrazine monohydrate (1.58 g, 1.54 mL, 31.6 mmol) was added to the mixture and heated at reflux using an aluminum bath. After stirred for 2 h at that temperature, the reaction was cooled to room temperature and the resulting precipitate was removed from the solution by filtration. The filtrate was concentrated under reduced pressure. Resulting residue was submitted to NH silica gel chromatography (CH_2Cl_2/MeOH = 1/0 to 99/1) to give 4-chloro-2-pyridinemethanamine **14c** (1.22 g, 8.53 mmol, 80.9% yield in 2 steps from **12c**).

(Step 6)[53]: 4-Chloro-2-pyridinemethanamine **14c** (713 mg, 5.00 mmol), 1,2-dichloroethane (10 mL), and 4-chloro-2-pyridinecarboxaldehyde **11c** (708 mg, 5.00 mmol) were placed in 50 mL flask and cooled at 0 °C using an ice-water bath. At that temperature, sodium triacetoxyborohydride (2.12 g, 10.0 mmol) was added slowly to the mixture and allowed to warm up to room temperature. After stirred for 3 h at that temperature, the reaction was quenched by addition of sat. $NaHCO_3$ aq. (20 mL) and extracted with CH_2Cl_2 (20 mL x 3). The organic layers were washed with brine, and then dried over anhydrous Na_2SO_4. The crude mixture was concentrated under reduced pressure. Resulting residue was submitted to NH silica gel chromatography (n-hexane/AcOEt = 4/1 to 2/1) to give bis(4-chloro-2-pyridylmethyl)amine **15c** (1.16 g, 4.34 mmol, 86.8% yield).

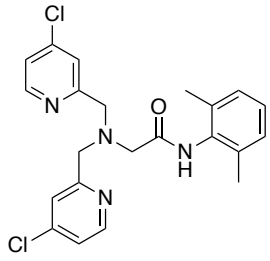
(Step 7): Bis(4-chloro-2-pyridylmethyl)amine **15c** (804 mg, 3.00 mmol), MeCN (27 mL), DMF (3 mL), 2-Chloro-*N*-(2,6-dimethylphenyl)acetamide **8** (771 mg, 3.90 mmol), potassium carbonate (539 mg, 3.90 mmol), and potassium iodide (249 mg, 1.50 mmol) were placed in a 100 mL flask and heated at reflux using an aluminum bath. After stirred for 4 h at that temperature, the resulting mixture was diluted by AcOEt (30 mL) and passed through Celite pad with AcOEt, and then the filtrate was concentrated under reduced pressure. AcOEt (15 mL) and sat. $NaHCO_3$ aq. (30 mL) were added to the resulting mixture and organic compounds were extracted with AcOEt (15 mL x 3). The organic layers were washed with brine, and then dried over anhydrous Na_2SO_4. The crude mixture was concentrated under reduced pressure. Resulting residue was submitted to NH silica gel chromatography (*n*-hexane/AcOEt = 4/1 to 1/2) to give *N'*-2,6-dimethylphenyl *N*,*N*-bis(4-chloro-2-pyridylmethyl)glycinamide **9c** (1.04 g, 2.43 mmol, 80.8% yield) as a light brown solid.

5.2.2.1. *N'*-2,6-dimethylphenyl *N*,*N*-bis(4-mehthoxy-2-pyridylmethyl)glycinamide (9b)



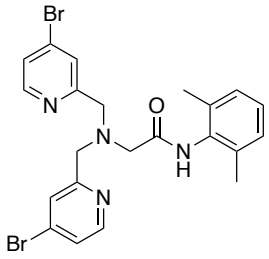
This compound was synthesized according to typical procedure to be given as a light brown solid [step 1: 91.3% yield, step 2: 83.4% yield, step 3: quantitative yield, step 4+5: 74.7% yield (in 2 steps), step 6: 49.0% yield, step 7: 50.7% yield].; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.25 (br-s, 1H), 8.35 (d, *J* = 5.6 Hz, 2H), 7.11-7.05 (m, 3H), 6.93 (d, *J* = 2.4 Hz, 2H), 6.69 (dd, *J* = 5.6, 2.4 Hz, 2H), 3.95 (s, 4H), 3.81 (s, 6H), 3.53 (s, 2H), 2.17 (s, 6H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 166.2, 160.1, 150.6, 135.5, 134.6, 128.0, 126.8, 109.3, 108.3, 60.5, 58.1, 55.1, 18.5 ppm.; HRESI-MS (m/z) [M + H$^+$], calcd for $[C_{24}H_{29}N_4O_3]^+$ 421.2234, found: m/z = 421.2235.

5.2.2.2. *N'*-2,6-dimethylphenyl *N*,*N*-bis(4-chloro-2-pyridylmethyl)glycinamide (9c)



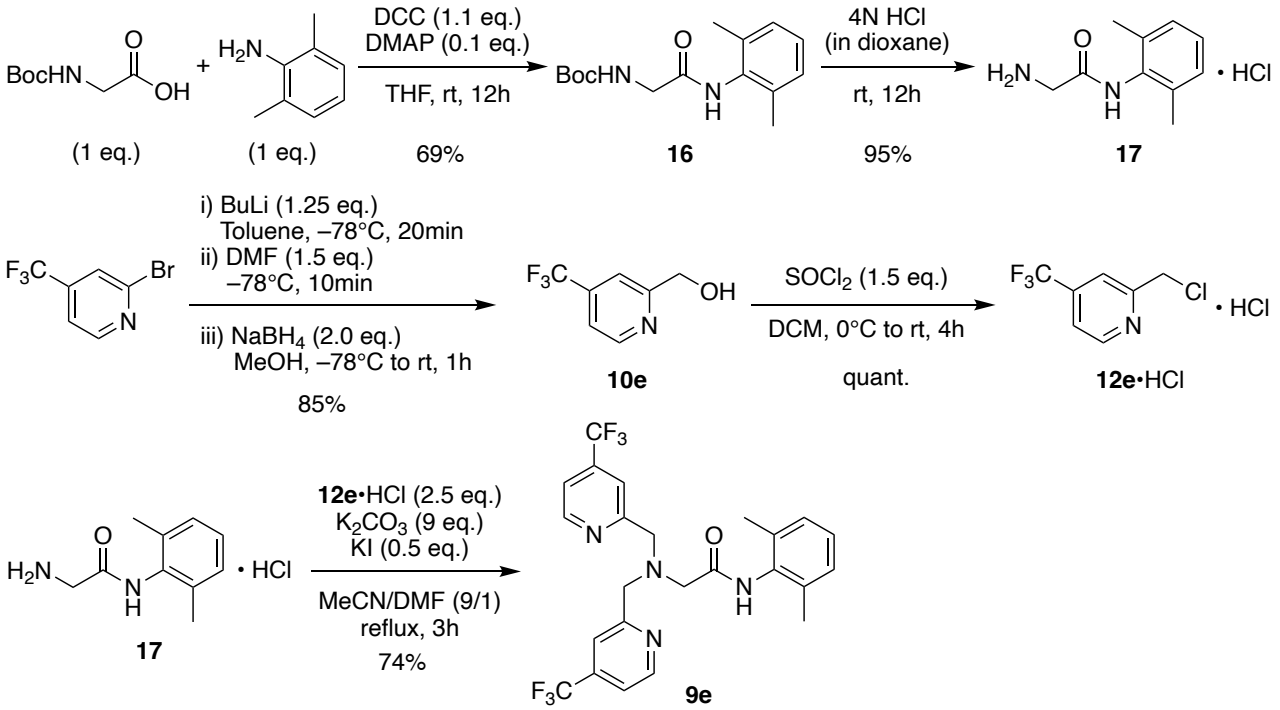
This compound was synthesized according to typical procedure to be given as a light brown solid [step 1: 96.7% yield, step 2: 66.9% yield, step 3: 87.8% yield, step 4+5: 80.9% yield (in 2 steps), step 6: 86.8% yield, step 7: 80.8% yield].; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.07 (br-s, 1H), 8.45 (d, *J* = 5.4 Hz, 2H), 7.36 (d, *J* = 2.0 Hz, 2H), 7.20 (dd, *J* = 5.4, 2.0 Hz, 2H), 7.14-7.08 (m, 3H), 3.97 (s, 4H), 3.54 (s, 2H), 2.20 (s, 6H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 159.8, 150.4, 144.7, 135.4, 134.3, 128.1, 127.1, 123.4, 123.0, 60.1, 58.1, 18.6 ppm.; HRESI-MS (m/z) [M + Na^+], calcd for $[C_{22}H_{22}Cl_2N_4NaO]^+$ 451.1063, found: m/z = 451.1061.

5.2.2.3. *N'*-2,6-dimethylphenyl *N*,*N*-bis(4-bromo-2-pyridylmethyl)glycinamide (9d)



This compound was synthesized according to typical procedure to be given as a light brown solid [step 1: 93.4% yield, step 2: 70.4% yield, step 3: 97.5% yield, step 4+5: 94.4% yield (in 2 steps), step 6: 88.4% yield, step 7: 82.5% yield].; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.06 (br-s, 1H), 8.37 (d, *J* = 5.4 Hz, 2H), 7.51 (d, *J* = 1.7 Hz, 2H), 7.36 (dd, *J* = 5.4, 1.7 Hz, 2H), 7.14-7.06 (m, 3H), 3.97 (s, 4H), 3.55 (s, 2H), 2.21 (s, 6H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 159.6, 150.2, 135.4, 134.3, 133.5, 128.1, 127.1, 126.4, 126.0, 60.1, 58.2, 18.6 ppm.; HRESI-MS (m/z) [M + Na^+], calcd for $[C_{22}H_{22}Br_2N_4NaO]^+$ 541.0033, found: m/z = 541.0036.

5.2.3. Preparation of *N'*-2,6-dimethylphenyl *N*,*N*-bis(4-trifuluoromethyl-2-pyridylmethyl)glycinamide (9e)



Scheme 15. Preparation of bpga ligand **9e**

(Step 1): (*tert*-Butoxycarbonyl)glycine (1.75 g, 10.0 mmol), THF (25 mL), 2,6-dimethylaniline (1.21 g, 1.23 mL, 10.0 mmol), and 4-(dimethylamino)pyridine (122 mg, 1.00 mmol) were placed in a 100 mL flask and cooled at 0 °C using an ice-water bath. At that temperature, *N*,*N'*-dicyclohexylcarbodiimide (2.27 g, 11.0 mmol) was added to the mixture and allowed to warm up to room temperature. After stirred for 12 h, the resulting mixture was passed through Celite pad with AcOEt. 0.1N HCl (25 mL) was added to the filtrate, and the organic layer was extracted with AcOEt (25 mL x 3). The mixture was washed with sat. $NaHCO_3$ aq. and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Resulting residue was submitted to silica gel chromatography (*n*-hexane/AcOEt = 4/1 to 1/1) to give *N*′-2,6-dimethylphenyl *N*-(*tert*-butoxycarbonyl)glycinamide **16** (1.93 g, 6.94 mmol, 69.4% yield).

(Step 2): *N*′-2,6-Dimethylphenyl *N*-(*tert*-butoxycarbonyl)glycinamide **16** (1.43 g, 5.15 mmol) and 4N HCl (1,4-dioxane solution, 20 mL) were placed in a 100 mL flask, and then the mixture was stirred for 12 h at room temperature. Et_2O (50 mL) was added to the resulting mixture, and then the resulting precipitate was separated from the solution by filtration. The precipitate was washed with Et_2O and dried under reduced pressure to give *N*′-2,6-dimethylphenyl glycinamide hydrochloride **17** (1.05 g, 4.88 mmol, 94.8% yield).

(Step 3)[54]: 2-Bromo-4-(trifluoromethyl)pyridine (2.26 g, 1.31 mL, 10.0 mmol) and toluene (30 mL) were placed in a 100 mL Schlenk tube under nitrogen atmosphere and cooled at –78 °C using a dry

ice-methanol bath. At that temperature, *n*-butyllithium (2.6 M in hexane, 4.81 mL, 12.5 mmol) was added dropwise to the mixture. After stirred for 20 min at that temperature, *N*,*N*-dimethylformamide (1.10 g, 1.16 mL, 15.0 mmol) was added dropwise to the mixture. After stirred for 10 min at that temperature, methanol (5.6 mL) and sodium borohydride (757 mg, 20.0 mmol) were added to the mixture, and then the reaction was allowed to warm up to room temperature. After stirred for 1 h, the reaction was quenched by addition of water (30 mL) and extracted with AcOEt (30 mL x 3). The organic layers were washed with brine, and then dried over anhydrous Na_2SO_4. The crude mixture was concentrated under reduced pressure. Resulting residue was submitted to silica gel chromatography (*n*-hexane/ AcOEt = 4/1 to 1/2) to give 4-trifluoromethyl-2-pyridinemethanol **10e** (1.51 g, 8.54 mmol, 85.4% yield).

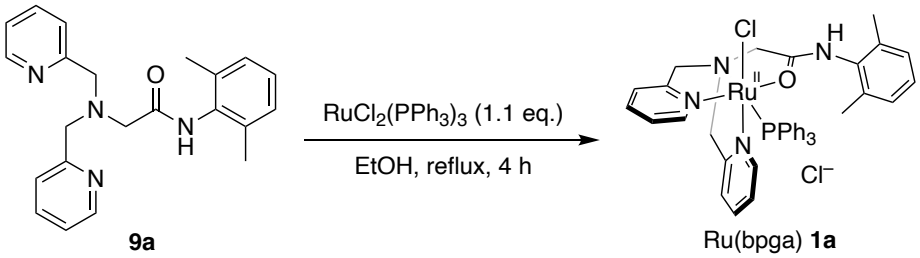
(Step 4): 4-Trifluoromethyl-2-pyridinemethanol **10e** (709 mg, 4.00 mmol) and CH_2Cl_2 (20 mL) were placed in 50 mL Schlenk tube under nitrogen atmosphere and cooled at 0 °C using an ice-water bath. At that temperature, thionyl chloride (714 mg, 438 μL, 6.00 mmol) was added dropwise to the mixture and allowed to warm up to room temperature. After stirred for 4 h at that temperature, the crude mixture was concentrated under reduced pressure to give 4-trifluoromethyl-2-(chloromethyl)pyridine hydrochloride **12e**•HCl (928 mg, 4.00 mmol, quantitative yield), which was used for following step without purification.

(Step 5): 4-Trifluoromethyl-2-(chloromethyl)pyridine hydrochloride **12e**•HCl (928 mg, 4.00 mmol), MeCN (14 mL), DMF (1.6 mL), *N*′-2,6-dimethylphenyl glycinamide hydrochloride **17** (344 mg, 1.60 mmol), potassium carbonate (1.99 g, 14.4 mmol), and potassium iodide (133 mg, 800 μmol) were placed in a 50 mL flask and heated at reflux using an aluminum bath. After stirred for 3 h at that temperature, the resulting mixture was diluted by AcOEt (20 mL) and passed through Celite pad with AcOEt, and then the filtrate was concentrated under reduced pressure. AcOEt (10 mL) and sat. $NaHCO_3$ aq. (20 mL) were added to the resulting mixture and organic compounds were extracted with AcOEt (10 mL x 3). The organic layers were washed with brine, and then dried over anhydrous Na_2SO_4. The crude mixture was concentrated under reduced pressure. Resulting residue was submitted to NH silica gel chromatography (*n*-hexane/AcOEt = 4/1 to 1/1) to give *N'*-2,6-dimethylphenyl *N*,*N*-bis(4-trifluoromethyl-2-pyridylmethyl)glycinamide **9e** (587 mg, 1.18 mmol, 73.9% yield) as light brown solid.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (br-s, 1H), 8.72 (d, *J* = 4.9 Hz, 2H), 7.49 (s, 2H), 7.39 (d, *J* = 4.9 Hz, 2H), 7.14-7.07 (m, 3H), 4.10 (s, 4H), 3.62 (s, 2H), 2.18 (s, 6H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 159.8, 150.6, 138.9 (q, *J* = 34.2 Hz), 135.3, 134.2, 128.2, 127.1, 122.6 (q, *J* = 273.4

Hz), 118.7 (q. J = 4.1 Hz), 118.3 (q, J = 3.3 Hz), 60.7, 58.8, 18.4 ppm.; HRESI-MS (m/z) [M + H^+], calcd for $[C_{24}H_{23}F_6N_4O]^+$ 497.1771, found: m/z = 497.1767.

5.3. Preparation of Ru(bpga) complexes

5.3.1. Modified procedure for preparation of Ru(bpga) 1a

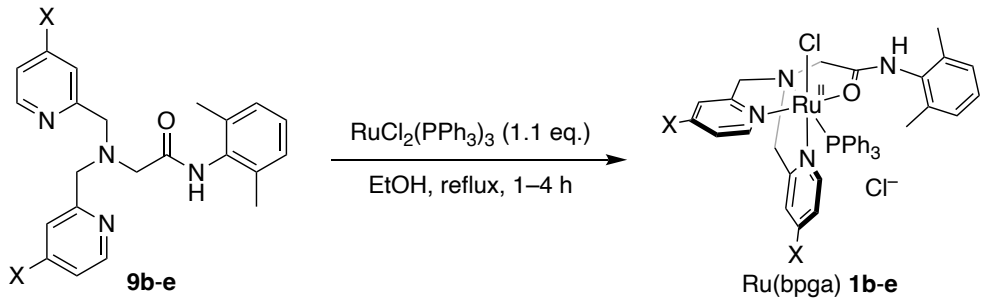


9a Ru(bpga) **1a**

Scheme 16. Modified preparation of Ru(bpga) **1a**

To the solution of *N'*-2,6-dimethylphenyl *N*,*N*-bis(2-pyridylmethyl)glycinamide **9a** (901 mg, 2.50 mmol) in EtOH (80 mL), $RuCl_2(PPh_3)_3$ (2.64 g, 2.75 mmol) was added at room temperature, and the mixture was heated at reflux. After stirred for 4 h at that temperature, the reaction mixture was concentrated on a rotary evaporator. The crude mixture was dissolved in CH_2Cl_2 (5 mL), and MeOH (10 mL) was added to the mixture. The resulting mixture was cooled at 0 °C using an ice-water bath, and then the resulting orange precipitate was separated from the solution by filtration. The precipitate was washed with cold methanol (5 mL x5) and *n*-hexane (5 mL x5). Then, the precipitate was dissolved in CH_2Cl_2 (500 mL) and concentrated under reduced pressure to give Ru(bpga) **1a** (970 mg, 1.22 mmol, 48.8% yield) as an orange solid.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.49 (br-s, 1H), 8.10 (d, J = 5.9 Hz, 1H), 7.99 (d, J = 5.9 Hz, 1H), 7.45 (t, J = 8.8 Hz, 6H), 7.39-7.25 (m, 7H), 7.16 (t, J = 6.8 Hz, 6H), 7.05-6.83 (m, 3H), 6.61-6.53 (m, 2H), 6.25 (d, J = 14.6 Hz, 1H), 5.86 (dd, J = 2.7, 15.6 Hz, 1H), 5.39 (d, J = 15.6 Hz, 1H), 5.17 (d, J = 2.0, 16.9 Hz, 1H), 4.88 (dd, J = 3.9, 14.6 Hz, 1H), 4.77 (d, J = 16.9 Hz, 1H), 2.07 (br-s, 3H), 1.49 (br-s, 3H) ppm; FT-IR (KBr): 3431, 3049, 2916, 2849, 1611, 1582, 1476, 1435, 1034, 1005, 762, 696, 525 cm^{-1}; HRESI-MS (m/z) [M – Cl^-], calcd for $[C_{40}H_{39}ClN_4OPRu]^+$ 759.1595, found: m/z = 759.1595.

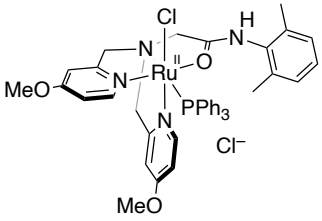
5.3.2. Typical procedure for preparation of Ru(bpga) 1b-e



Scheme 17. Preparation of Ru(bpga) complexes **1b-e**

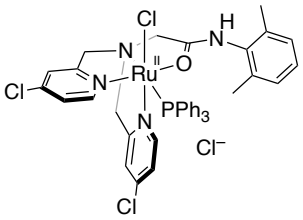
To the solution of *N'*-2,6-dimethylphenyl *N*,*N*-bis(4-chloro-2-pyridylmethyl)glycinamide **9c** (350 mg, 815 μmol) in EtOH (32 mL), $RuCl_2(PPh_3)_3$ (860 mg, 897 μmol) was added at room temperature, and the mixture was heated at reflux. After stirred for 4 h at that temperature, the reaction mixture was concentrated on a rotary evaporator. The residue was submitted two times to silica gel chromatography (CH_2Cl_2/MeOH: 19/1 to 4/1, then $CHCl_3$/MeOH: 14/1 to 4/1) to give Ru(bpga) **1c** (168 mg, 195 μmol, 23.9% yield) as an orange solid.

5.3.2.1. Ru(bpga) 1b



This compound was synthesized according to typical procedure for 1 h to give 39.4% yield as an orange solid.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.08 (br-s, 1H), 7.78 (d, *J* = 6.3 Hz, 1H), 7.72 (d, *J* = 6.3 Hz, 1H), 7.43 (t, *J* = 8.3 Hz, 6H), 7.33-7.25 (m, 4H), 7.19-7.10 (m, 7H), 7.05-6.97 (m, 1H), 6.90-6.78 (m, 2H), 6.24 (d, *J* = 15.1 Hz, 1H), 6.19 (d, *J* = 6.3 Hz, 1H), 6.09 (d, *J* = 6.3 Hz, 1H), 5.83 (d, *J* = 16.1 Hz, 1H), 5.37 (d, *J* = 15.1 Hz, 1H), 5.27 (d, *J* = 14.6 Hz, 1H), 4.87 (d, *J* = 14.6 Hz, 1H), 4.69 (d, *J* = 16.1 Hz, 1H), 3.78 (s, 6H), 2.03 (br-s, 3H), 1.49 (br-s, 3H) ppm.; HRESI-MS (m/z) [M – Cl^-], calcd for $[C_{42}H_{43}ClN_4O_3PRu]^+$ 819.1807, found: m/z = 819.1803.

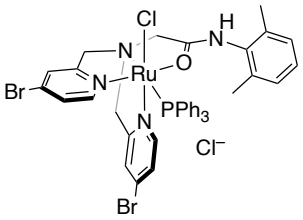
5.3.2.2. Ru(bpga) 1c



This compound was synthesized according to typical procedure for 4 h to give 23.9% yield as a reddish orange solid.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.50 (br-s, 1H), 7.90 (d, *J* = 6.3 Hz, 1H), 7.69 (d, *J* = 6.3 Hz, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.43 (t, *J* = 8.8 Hz, 6H), 7.34-7.31 (m, 4H), 7.18 (t, *J* = 7.1 Hz, 6H), 7.08-6.95 (m, 2H), 6.93-6.81 (m, 1H), 6.58 (dd, *J* = 6.3, 2.0 Hz, 1H), 6.56 (dd, *J* = 6.3, 2.0 Hz, 1H), 6.15 (d, *J* = 14.6 Hz, 1H), 5.89 (d, *J* = 15.9 Hz, 1H), 5.41 (d, *J* = 17.3 Hz, 1H), 5.38 (d, *J* =

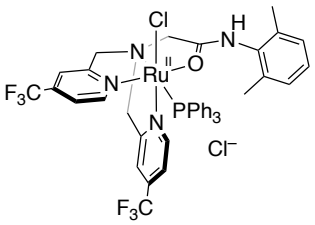
15.9 Hz, 1H), 5.15 (dd, *J* = 14.6, 2.9 Hz, 1H), 4.86 (d, *J* = 17.3 Hz, 1H), 2.07 (br-s, 3H), 1.63 (br-s, 3H) ppm.; HRESI-MS (m/z) [M – Cl^-], calcd for $[C_{40}H_{37}Cl_3N_4OPRu]^+$ 829.0800, found: m/z = 829.0795.

5.3.2.3. Ru(bpga) 1d



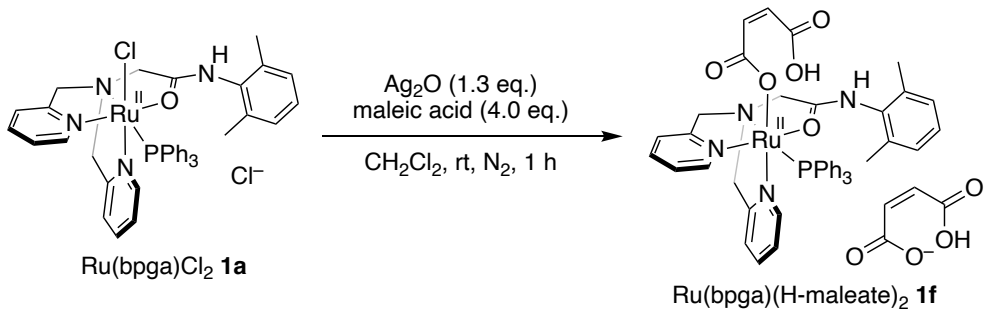
This compound was synthesized according to typical procedure for 3 h to give 18.8% yield as a reddish orange solid.; ^1H NMR (400 MHz, $CDCl_3$): δ 11.61 (br-s, 1H), 7.82 (d, *J* = 6.3 Hz, 1H), 7.64 (d, *J* = 1.7 Hz, 1H), 7.61 (d, *J* = 5.9 Hz, 1H), 7.43 (t, *J* = 8.8 Hz, 7H), 7.33 (t, *J* = 7.1 Hz, 3H), 7.18 (t, *J* = 7.1 Hz, 6H), 7.08-6.94 (m, 2H), 6.94-6.82 (m, 1H), 6.74 (dd, *J* = 6.3, 1.7 Hz, 1H), 6.72 (dd, *J* = 5.9, 1.7 Hz, 1H), 6.15 (d, *J* = 14.6 Hz, 1H), 5.89 (dd, *J* = 16.1, 2.4 Hz, 1H), 5.38 (d, *J* = 16.1 Hz, 1H), 5.32 (d, *J* = 16.6 Hz, 1H), 5.10 (dd, *J* = 14.6, 3.4 Hz, 1H), 4.86 (d, *J* = 16.6 Hz, 1H), 2.08 (br-s, 3H), 1.63 (br-s, 3H) ppm.; HRESI-MS (m/z) [M – Cl^-], calcd for $[C_{40}H_{37}Br_2ClN_4OPRu]^+$ 916.9788, found: m/z = 916.9789.

5.3.2.4. Ru(bpga) 1e



This compound was synthesized according to typical procedure for 3 h to give 18.2% yield as a red solid.; ^1H NMR (400 MHz, $CDCl_3$): δ 11.75 (br-s, 1H), 8.30 (d, *J* = 6.3 Hz, 1H), 8.09 (d, *J* = 5.9 Hz, 1H), 7.69 (d, *J* = 1.5 Hz, 1H), 7.48 (d, *J* = 1.5 Hz, 1H), 7.43 (t, *J* = 8.5 Hz, 6H), 7.36 (td, *J* = 7.3, 1.0 Hz, 3H), 7.20 (td, *J* = 7.7, 1.6 Hz, 6H), 7.08-6.96 (m, 2H), 6.92-6.82 (m, 1H),6.78 (dd, *J* = 5.9, 1.5 Hz, 1H), 6.77 (dd, *J* = 6.3, 1.5 Hz, 1H), 6.19 (d, *J* = 15.1 Hz, 1H), 5.93 (dd, *J* = 16.1, 2.9 Hz, 1H), 5.51 (dd, *J* = 17.8, 2.4 Hz, 1H), 5.43 (d, *J* = 16.1 Hz, 1H), 5.38 (dd, *J* = 15.1, 3.4 Hz, 1H), 4.98 (d, *J* = 17.8 Hz, 1H), 2.11 (br-s, 3H), 1.52 (br-s, 3H) ppm.; HRESI-MS (m/z) [M – Cl^-], calcd for $[C_{42}H_{37}ClF_6N_4OPRu]^+$ 895.1343, found: m/z = 895.1344.

5.3.3. Preparation of Ru(bpga)(H-maleate)$_2$ 1f



Ru(bpga)Cl_2 **1a**

Ru(bpga)(H-maleate)$_2$ **1f**

Scheme 18. Preparation of Ru(bpga) complex **1f**

Ru(bpga) Cl_2 **1a** (159 mg, 0.20 mmol), maleic acid (92.9 mg, 0.80 mmol), and CH_2Cl_2 (5 mL) were placed in a 10 mL Schlenk tube under nitrogen atmosphere. At the room temperature, the mixture was stirred for 5 min. To the mixture, Ag_2O (60.3 mg, 0.26 mmol) was added, and then the suspension was stirred vigorously for 1 h at room temperature under photo-shielding condition (during the stirring, the suspension was sonicated 5 times for 1 min at 10 min intervals). The resulting mixture was passed through Celite pad with CH_2Cl_2. Deionized water (5 mL) was added to the solution, and a ruthenium complex was extracted with CH_2Cl_2 (10 mL x 3). The organic layers were washed with deionized water, and then dried over anhydrous Na_2SO_4. The solution was concentrated under reduced pressure to give Ru(bpga)(H-maleate)$_2$ **1f** (163.3 mg, 0.171 mmol, 85.6% yield) as an orange solid.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.68 (br-s, 1H), 8.46 (d, J = 5.4 Hz, 1H), 7.45-7.29 (m, 13H), 7.25 (d, J = 7.8 Hz, 1H), 7.16(dt, J = 7.7, 1.6 Hz, 6H), 7.06-6.89 (m, 3H), 6.68 (t, J = 6.8 Hz, 1H), 6.57 (t, J = 6.1 Hz, 1H), 6.29 (s, 2H), 5.67 (d, J = 12.7 Hz, 1H), 5.62 (d, J = 12.7 Hz, 1H), 5.51 (dd, J = 15.9, 2.4 Hz, 1H), 5.29 (d, J = 17.6 Hz, 1H), 5.07 (d, J = 15.0 Hz, 1H), 5.01 (dd, J = 15.0, 3.2 Hz, 1H), 4.90 (d, J = 15.9 Hz, 1H), 4.83 (d, J = 17.6 Hz, 1H), 2.26 (br-s, 3H), 1.56 (br-s, 3H) ppm.; HRESI-MS (m/z) [M – $(C_4H_3O_4)^-$], calcd for $[C_{44}H_{42}N_4O_5PRu]^+$ 839.1943, found: m/z = 839.1944.

5.3.4. Cyclic Voltammetries of Ruthenium Complexes

All cyclic voltammetries were carried out under the following conditions: CH_2Cl_2 solvent, 10mM samples (ruthenium complexes), 100mM tetra-*n*-butylammonium perchlorate (^{n}Bu$_4$NClO$_4$) as supporting electrolyte, total volume 2mL, a glassy carbon working electrode, an Ag^+/Ag reference electrode, a Pt wire counter electrode, sweep rate 100mV/s, 5cycles, at room temperature, ^{n}Bu$_4$NClO$_4$ was recrystallized from hot ethanol before use, Before the measurement, de-aeration of the solution was carried out using N_2 gas (through CH_2Cl_2) bubbling during at least 10 minutes. The potential value obtained for the Ag^+/Ag reference electrode scale was converted to the ferroceium/ferrocene (Fc^+/Fc) scale using the redox potential of Fc^+/Fc obtained in the same conditions as an internal reference.

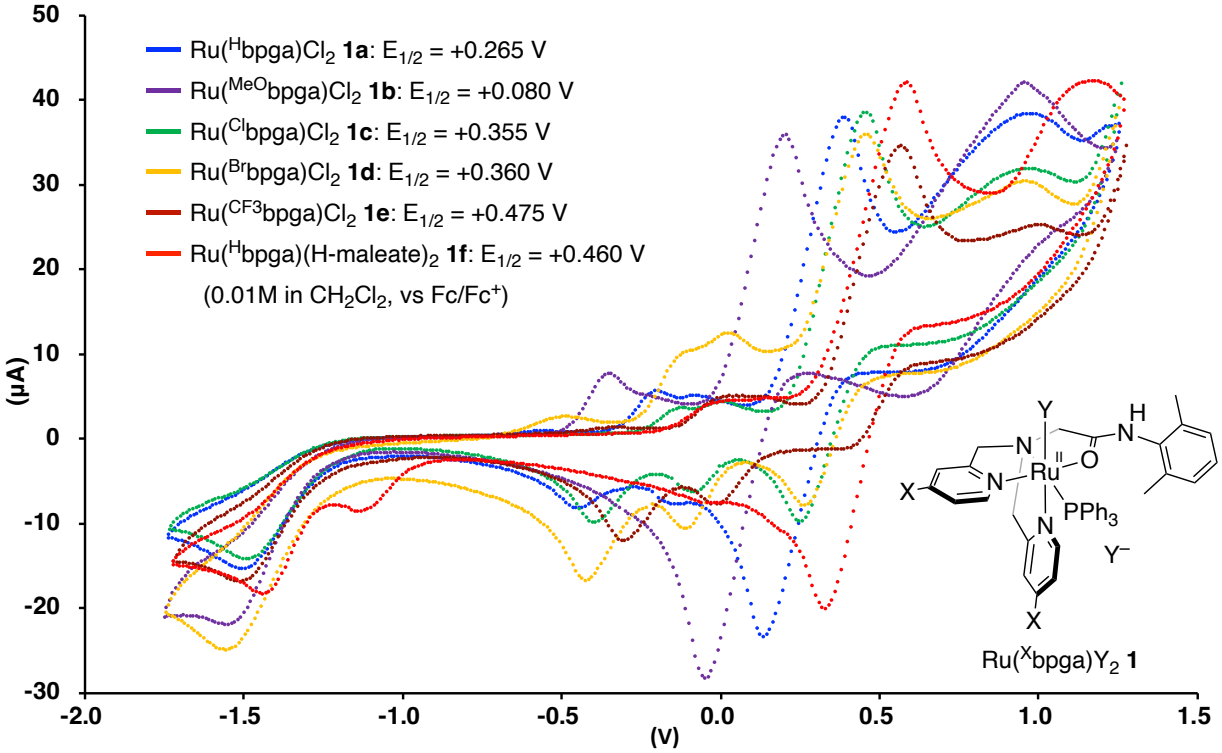
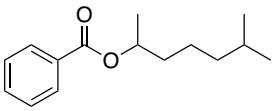


Figure 24. Cyclic Voltammetry of ruthenium(II) complexes **1** vs. Fc/Fc^+ in CH_2Cl_2

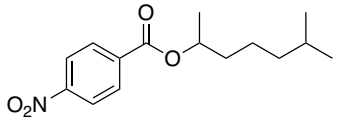
5.4. Preparation of Substrates 2

5.4.1. 6-Methylheptan-2-yl benzoate (2e)



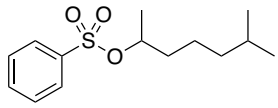
4-Dimethylaminopyridine (19.2 mg, 158 mmol) was charged to a 10 mL round bottom flask and dissolved in pyridine (5 mL), and then 6-methylheptan-2-ol (410 mg, 3.13 mmol) was added at 0 ˚C. Benzoyl chloride (1.33 g, 9.45 mmol) was dropwise to the mixture at that temperature. The reaction was allowed to warm to room temperature and stirred for 12h. The reaction was quenched with sat. NH_4Cl aq. and extracted with diethyl ether (20 mL x3), dried with $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified via column chromatography on silica gel (*n*-hexane/AcOEt = 19/1 to 4/1) to give 6-methylheptan-2-yl benzoate **2e** (578.5mg, 78.4%) as a colorless oil.; ^1H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, J = 8.3 Hz, 2H), 7.54 (t, J = 6.8 Hz, 1H), 7.43 (pseudo-t, J = 7.6 Hz, 2H), 5.16 (td, J = 6.3, 12.8Hz, 1H), 1.78-1.68 (m, 1H), 1.62-1.47 (m, 2H), 1.44-1.30 (m, 2H), 1.34 (d, J = 6.4 Hz, 3H), 1.25-1.41 (m, 2H), 0.87 (s, 3H), 0.85 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 132.6, 130.9, 129.5, 128.2, 71.7, 38.7, 36.3, 27.8, 23.2, 22.6, 22.5, 20.1 ppm.

5.4.2. 6-Methylheptan-2-yl 4-nitrobenzoate (2r)



6-Methyl-heptan-2-ol (521 mg, 649 μL, 4.0 mmol), CH_2Cl_2 (40 mL), and triethylamine (1.01 g, 1.39 mL, 10.0 mmol) were placed in a 100 mL Schlenk tube under nitrogen atmosphere and cooled at 0 °C using an ice-water bath. At that temperature, 4-nitrobenzoyl chloride (1.11 g, 6.0 mmol) was added to the mixture and allowed to warm up to room temperature. After stirred for 4 h, the reaction was quenched by addition of sat. $NaHCO_3$ aq. (20 mL) and extracted with CH_2Cl_2 (20 mL x 3). The organic layers were washed with 1N HCl, water, and brine, and then dried over anhydrous Na_2SO_4. The crude mixture was concentrated under reduced pressure. Resulting residue was submitted to silica gel chromatography (*n*-hexane/ CH_2Cl_2 = 2/1 to 1/1) to give 6-methylheptan-2-yl 4-nitrobenzoate **2r** (665 mg, 2.48 mmol, 59.5% yield) as a colorless oil.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, *J* = 9.1 Hz, 2H), 8.20 (d, *J* = 9.1 Hz, 2H), 5.19 (tq, *J* = 12.7, 6.3 Hz, 1H), 1.80-1.71 (m, 1H), 1.66-1.49 (m, 2H), 1.45-1.31 (m, 2H), 1.37 (d, *J* = 6.3 Hz, 3H), 1.28-1.17 (m, 2H), 0.87 (d, *J* = 6.8 Hz, 6H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 150.4, 136.3, 130.6, 123.4, 73.1, 38.6, 36.1, 27.8, 23.2, 22.5, 22.5, 20.0 ppm.; HRESI-MS (m/z) [M + Na^+], calcd for $[C_{15}H_{21}NNaO_4]^+$ 302.1363, found: m/z = 302.1362.

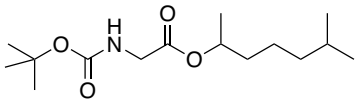
5.4.3. 6-Methylheptan-2-yl benzenesulfonate (2t)



6-Methyl-heptan-2-ol (521 mg, 649 μL, 4.0 mmol), CH_2Cl_2 (16 mL), and 4-(dimethylamino)pyridine (147 mg, 1.20 mmol) were placed in a 50 mL Schlenk tube under nitrogen atmosphere and cooled at 0 °C using an ice-water bath. At that temperature, triethylamine (607 mg, 836 μL, 6.0 mmol) and benzenesulfonyl chloride (777 mg, 564 μL, 4.4 mmol) was added to the mixture and allowed to warm up to room temperature. After stirred for 24 h, the reaction was quenched by addition of sat. NH_4Cl aq. (20 mL) and extracted with CH_2Cl_2 (20 mL x 3). The organic layers were washed with brine, and then dried over anhydrous Na_2SO_4. The crude mixture was concentrated under reduced pressure. Resulting residue was submitted to silica gel chromatography (*n*-hexane/ CH_2Cl_2 = 2/1 to 1/1) to give 6-methylheptan-2-yl benzenesulfonate **2t** (894 mg, 3.31 mmol, 82.6% yield) as a colorless oil.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 7.3 Hz, 2H), 7.64 (dd, *J* = 7.8, 7.5 Hz, 1H), 7.54 (pseudo-t, *J* = 7.8 Hz, 2H), 4.64 (dq, *J* = 12.7, 6.3 Hz, 1H), 1.64-1.54 (m, 1H), 1.50-1.37 (m, 2H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.25-1.17 (m, 1H), 1.15-1.00 (m, 3H), 0.80 (dd, *J* = 6.6, 2.4 Hz, 6H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.6, 133.4, 129.1, 127.6, 81.1, 38.3, 36.7, 27.7, 22.7, 22.4, 22.4, 20.9 ppm.; HRESI-MS (m/z) [M + Na^+], calcd for

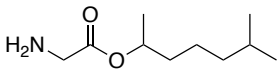
$[C_{14}H_{22}NaO_3S]^+$ 293.1182, found: m/z = 293.1185.

5.4.4. 6-Methylheptan-2-yl *N-tert*-butoxycarbonylglycinate (2x)



(*tert*-Butoxycarbonyl)glycine (3.85 g, 22.0 mmol), CH_2Cl_2 (50 mL), 6-methyl-heptan-2-ol (2.60 g, 3.24 mL, 20.0 mmol), and 4-(dimethylamino)pyridine (244 mg, 2.00 mmol) were placed in a 100 mL flask and cooled at 0 °C using an ice-water bath. At that temperature, *N*,*N'*-dicyclohexylcarbodiimide (4.54 g, 22.0 mmol) was added to the mixture and allowed to warm up to room temperature. After stirred for 2 h, the resulting mixture was passed through Celite pad with CH_2Cl_2. 0.1N HCl (50 mL) was added to the filtrate, and the organic layer was extracted with CH_2Cl_2 (50 mL x 3). The mixture was washed with sat. $NaHCO_3$ aq. and brine, and then dried over anhydrous Na_2SO_4. And concentrated under reduced pressure. Resulting residue was submitted to silica gel chromatography (*n*-hexane/AcOEt = 19/1 to 4/1) to give 6-methylheptan-2-yl (*tert*-butoxycarbonyl)glycinate **2x** (5.74 g, 20.0 mmol, 99.9% yield) as a colorless oil.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.6 (comb br-s and tq, *J* = 12.6, 6.2 Hz, 2H), 3.88 (d, *J* = 5.4 Hz, 2H), 1.66-1.49 (m, 3H), 1.45 (s, 9H), 1.32-1.26 (m, 2H), 1.22 (d, *J* = 5.9 Hz, 3H), 1.19-1.13 (m, 2H), 0.86 (d, *J* = 6.8 Hz, 6H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 155.6, 79.8, 72.5, 42.6, 38.6, 36.0, 28.3, 27.8, 23.1, 22.5, 22.5, 19.9 ppm.; HRESI-MS (m/z) [M + Na^+], calcd for $[C_{15}H_{29}NNaO_4]^+$ 310.1989, found: m/z = 310.1989.

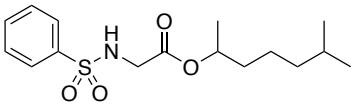
5.4.5. 6-Methylheptan-2-yl glycinate (2z)



6-Methylheptan-2-yl (*tert*-butoxycarbonyl)glycinate **2x** (575 mg, 2.00 mmol) and 4N HCl (1,4-dioxane solution, 5.0 mL) were placed in a 100 mL flask, and then the mixture was stirred for 1 h at room temperature. The resulting mixture was diluted by AcOEt (30 mL), and then the reaction was quenched by addition of sat. $NaHCO_3$ aq. (30 mL) and extracted with AcOEt (20 mL x 3). The organic layers were washed with brine, and then dried over anhydrous Na_2SO_4. The crude mixture was concentrated under reduced pressure. Resulting residue was submitted to NH silica gel chromatography (*n*-hexane/AcOEt = 9/1 to 2/1) to give 6-methylheptan-2-yl glycinate **2z** (221 mg, 1.18 mmol,58.9% yield) as a colorless oil.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.96 (tq, *J* = 12.7, 6.3 Hz, 1H), 3.40 (s, 2H), 1.63-1.41 (m, 5H), 1.35-1.13 (m, 4H), 1.22 (d, *J* = 6.3 Hz, 3H), 0.86 (d, *J* = 6.3 Hz, 6H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 71.8, 44.2, 38.7, 36.1, 27.8, 23.1, 22.5, 22.5, 20.0 ppm.; HRESI-MS (m/z) [M + H^+], calcd for $[C_{10}H_{22}NO_2]^+$

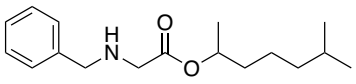
188.1645, found: m/z = 188.1642.

5.4.6. 6-Methylheptan-2-yl *N*-phenylsulfonylglycinate (2w)



6-Methylheptan-2-yl (*tert*-butoxycarbonyl)glycinate **2x** (862 mg, 3.00 mmol) and 4N HCl (1,4-dioxane solution, 6.0 mL) were placed in a 50 mL flask, and then the mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure. The crude mixture was dissolved in CH_2Cl_2 (12 mL) and cooled at 0 °C using an ice-water bath. At that temperature, triethylamine (759 mg, 1.05 mL, 7.50 mmol) and benzenesulfonyl chloride (583 mg, 423 μL, 3.3 mmol) were added to the mixture and allowed to warm up to room temperature. After stirred for 1 h, the reaction was quenched by addition of sat. $NaHCO_3$ aq. (10 mL) and extracted with CH_2Cl_2 (10 mL x 3). The organic layers were washed with 1N HCl, sat. $NaHCO_3$ aq., and brine, and then dried over anhydrous Na_2SO_4. The crude mixture was concentrated under reduced pressure. Resulting residue was submitted to silica gel chromatography (*n*-hexane/AcOEt = 9/1 to 4/1) to give 6-methylheptan-2-yl (phenylsulfonyl)glycinate **2w** (951 mg, 2.90 mmol, 96.8% yield) as a colorless oil.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 7.3 Hz, 2H), 7.59 (dd, *J* = 7.6, 7.3 Hz, 1H), 7.52 (pseudo-t, *J* = 7.3 Hz, 2H), 5.06 (t, *J* = 5.3 Hz, 1H), 4.82 (tq, *J* = 12.6, 6.2 Hz, 1H), 3.76 (d, *J* = 5.3 Hz, 2H), 1.52-1.34 (m, 3H), 1.28-1.08 (m, 4H), 1.11 (d, *J* = 6.3 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 6H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 139.2, 132.9, 129.1, 127.2, 73.4, 44.3, 38.5, 35.8, 27.7, 23.0, 22.5, 19.7 ppm.; HRESI-MS (m/z) [M + Na^+], calcd for $[C_{16}H_{25}NNaO_4S]^+$ 350.1397, found: m/z = 350.1396.

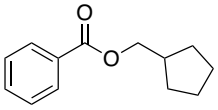
5.4.7. 6-Methylheptan-2-yl *N*-benzylglycinate (2aa)



6-Methylheptan-2-yl (*tert*-butoxycarbonyl)glycinate **2x** (862 mg, 3.00 mmol) and 4N HCl (1,4-dioxane solution, 6.0 mL) were placed in a 50 mL flask, and then the mixture was stirred for 1 h at room temperature. The resulting mixture was concentrated under reduced pressure. The crude mixture was dissolved in MeCN (12 mL) at room temperature. At that temperature, potassium carbonate (1.04 g, 7.50 mmol), benzyl bromide (564 mg, 392 μL, 3.3 mmol), *N*,*N*-diisopropylethylamine (969 mg, 1.30 mL, 7.5 mmol), and potassium iodide (249 mg, 1.5 mmol) were added to the mixture, and then the mixture was heated at reflux using an aluminum bath. After stirred for 2 days at that temperature, the reaction was quenched by addition of water (30 mL) and extracted with AcOEt (30 mL x 3). The organic layers were washed with brine, and

then dried over anhydrous Na_2SO_4. The crude mixture was concentrated under reduced pressure. Resulting residue was submitted to silica gel chromatography (*n*-hexane/AcOEt = 9/1 to 4/1) to give 6-methylheptan-2-yl benzylglycinate **2aa** (227 mg, 817 μmol, 27.2% yield) as a colorless oil.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.23 (m, 5H), 4.98 (tq, *J* = 12.7, 6.3 Hz, 1H), 3.80 (s, 2H), 3.38 (s, 2H), 1.74 (br-s, 1H), 1.63-1.42 (m, 3H), 1.36-1.25 (m, 2H), 1.23 (d, *J* = 6.3 Hz, 3H), 1.20-1.12 (m, 2H), 0.86 (d, *J* = 6.3 Hz, 6H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 139.6, 128.4, 128.3, 127.1, 71.7, 53.3, 50.3, 38.7, 36.1, 27.8, 23.2, 22.5, 20.0 ppm.; HRESI-MS (m/z) [M + H$^+$], calcd for $[C_{17}H_{28}NO_2]^+$ 278.2115, found: m/z = 278.2118.

5.4.8. Cyclopentylmethyl benzoate (2ae)[55]



Cyclopentylmethyl benzoate **2ae** was prepared in the same procedure as described for the synthesis of **2r**, except for using cyclopentylmethanol (501 mg, 541 μL, 5.0 mmol), triethylamine (1.26 g, 1.74 mL, 12.5 mmol), and benzoyl chloride (1.05 g, 869 μL, 7.5 mmol), and purified by column chromatography on silica gel (*n*-hexane/ CH_2Cl_2 = 4/1 to 1/1) to give cyclopenthylmethyl benzoate **2ae** (916 mg, 4.5 mmol, 89.7%) as a colorless oil.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 7.3 Hz, 2H), 7.54 (dd, *J* = 7.6, 7.3 Hz, 1H), 7.43 (pseudo-t, *J* = 7.6 Hz, 2H), 4.22 (d, *J* = 6.8 Hz, 2H), 2.40-2.29 (m, 1H), 1.87-1.79 (m, 2H), 1.71-1.52 (m, 4H), 1.42-1.30 (m, 2H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 132.7, 130.5, 129.5, 128.3, 68.8, 38.7, 29.4, 25.3 ppm.

5.5. ^{1}H NMR Studies of High-Valent Iodine Derivatives

5.5.1. ^{1}H NMR analysis of iodosylbenzene with trifluoroacetic acid in $CDCl_3$

Under argon atmospheric conditions, iodosylbenzene (44.0 mg, 0.2 mmol), and dry $CDCl_3$ (1 mL) were combined in an oven-dried Schlenk tube equipped with a stir-bar. An aliquot (50 μL) of obtained supernatants was taken out of a NMR tube as the zero-point sample (or at each point). The after, trifluoroacetic acid (7.7 μL, 0.10 mmol, 15.4 μL, 0.20 mmol, or 30.8 μL, 0.40 mmol) was added to the suspension and stirred for 30 min. The aliquot (50 μL) was diluted by $CDCl_3$ (0.6 mL) and submitted to ^{1}H NMR analysis.

5.5.2. ^{1}H NMR analysis of iodobenzene[bis(trifluoroacetate)] with H_2O in $CDCl_3$

Under argon atmospheric conditions, iodobenzene[bis(trifluoroacetate)] (86.0 mg, 0.2 mmol),

and dry $CDCl_3$ (1 mL) were combined in an oven-dried Schlenk tube equipped with a stir-bar. An aliquot (50 μL) of obtained supernatants was taken out of a NMR tube as the zero-point sample (or at each point). The after, H_2O (1.8 μL, 0.10 mmol, 3.6 μL, 0.20 mmol, or 7.2 μL, 0.40 mmol) was added to the suspension and stirred for 30 min. The aliquot (50 μL) was diluted by $CDCl_3$ (0.6 mL) and submitted to ^1H NMR analysis.

5.6. General Procedure for Ru(bpga) 1a-Catalyzed C–H Oxidation with H_2O or $H_2{}^{18}O$ as an Oxygen Source

5.6.1. Typical procedure for Ru(bpga) 1a-catalyzed C–H oxidation of 3,7-dimethyloctyl acetate with $H_2{}^{18}O$ as an oxygen source (Table 1-2, Figure 13)

Under nitrogen atmosphere, 3,7-dimethyloctyl acetate **2a** (23.1 μL, 0.1 mmol), Ru(bpga) complex **1a** (1.6 mg, 2.0 μmol, 2 mol%), carboxylic acid (0 or 2.5 equiv.), $H_2{}^{18}O$ (1.0–5.0 equiv.), 1,3,5-trichlorobenzene (3.6 mg, 0.02 mmol) as an internal standard for GC analysis, and 1,1,2,2-tetrachloroethane (0.25 mL) were placed in a 5 mL Schlenk tube in an aluminum block at 35 °C. Then, iodobenzene(dicarboxylate) **3** (1.5–5.0 equiv.) was added to the mixture and stirred for 12–24 h. An aliquot (2.5 μL) of the resulting mixture was taken out of the test tube as the zero-time sample (or at each time point). The aliquot (2.5 μL) was diluted by CH_2Cl_2 (0.5 mL) and submitted to GC analysis with a COATING CP-SELECT 624 CB column to determine conversion and yields of products.

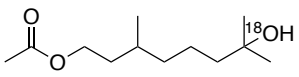
5.6.2. General procedure for Ru(bpga) 1a-catalyzed C–H oxidation of various alkanes 2 with H_2O or $H_2{}^{18}O$ as an oxygen source (Figure 14)

Under ambient air (or nitrogen atmosphere using $H_2{}^{18}O$ as the oxygen source), substrate **2** (0.2 mmol), Ru(bpga) complex **1a** (3.2 mg, 4.0 μmol, 2 mol%), H_2O (or $H_2{}^{18}O$) (5.4 μL, 0.3 mmol), 1,3,5-trichlorobenzene (7.2 mg, 0.04 mmol) as an internal standard for GC analysis, and 1,1,2,2-tetrachloroethane (0.5 mL) were placed in a 5 mL Schlenk tube in an aluminum block at 35 °C . Then, iodobenzene[bis(pentafluorobenzoate)] **3c** (250.4 mg, 0.4 mmol) was added to the mixture. An aliquot (1.0 μL) of this was taken out of the test tube as the zero-time sample (or at each time point). The aliquot (1.0 μL) was diluted by CH_2Cl_2 (0.2 mL) and submitted to GC analysis with a COATING CP-SELECT 624 CB column to determine conversion (and yields of products). Resulting mixture was passed through a short pad of NH-silica gel with AcOEt and evaporation of the solvents under reduced pressure gave crude mixture. Resulting residue was submitted on silica gel with *n*-hexane/AcOEt to

afford the desired product **4**.

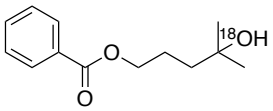
5.7. Characterization of Products in Ru(bpga) 1a-Catalyzed C–H Oxidation with H_2O or $H_2{}^{18}O$ as an Oxygen Source

5.7.1. [7-^{18}O]-7-Hydroxy-3,7-dimethyloctyl acetate (4a)[16a]



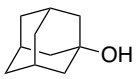
This compound was obtained in 69% yield (97% conversion) as a colorless oil.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.15-4.05 (m, 2H), 2.04 (s, 3H), 1.67 (dt, *J* = 7.2, 13.0 Hz, 1H), 1.60-1.50 (m, 1H), 1.48-1.29 (m, 7H), 1.28-1.13 (comb-s and m, 7H), 0.92 (d, *J* = 6.3 Hz, 3H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 70.9, 63.0, 44.1, 37.3, 35.4, 29.8, 29.3, 29.2, 21.6, 21.0, 19.4 ppm.; HRESI-MS (m/z) [M + Na^+], calcd for $[C_{12}H_{24}NaO_2{}^{18}O]^+$ 241.1660, found: m/z = 241.1666.; ^{18}O content: 96 atom%.

5.7.2. [4-^{18}O]-4-Hydroxy-4-methylpentyl benzoate (4b)[22c]



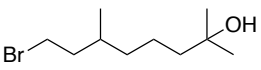
This compound was purified by column chromatography on silica gel (hexane/ethyl acetate, 4/1 to 2/1) to give 83% yield (91% conversion) as a colorless oil.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.3 Hz, 2H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.44 (pseud-t, *J* = 7.8 Hz, 2H), 4.35 (t, *J* = 6.6 Hz, 2H), 1.91-1.84 (m, 2H), 1.71 (br-s, 1H), 1.64-1.60 (m, 2H), 1.26 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 132.8, 130.3, 129.5, 128.3, 70.6, 65.3, 40.0, 29.3, 23.9 ppm.; HRESI-MS (m/z) [M + Na^+], calcd for $[C_{13}H_{18}NaO_2{}^{18}O]^+$ 247.1191, found: m/z = 247.1194.; ^{18}O content: 95 atom%.

5.7.3. 1-Adamantanol (4c)



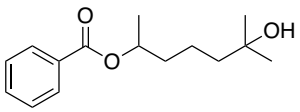
This compound was obtained in 82% yield (94% conversion), where commercially available **4c** (colorless solid) was used as a reference product.

5.7.4. 7-Hydroxy-3,7-dimethyloctyl bromide (4d)[16a]



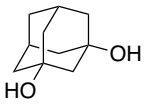
This compound was purified by column chromatography on silica gel (hexane/ ethyl acetate, 9/1 to 4/1) to give 72% yield (95% conversion) as a colorless oil.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.50-3.37 (m, 2H), 1.93-1.84 (m, 1H), 1.72-1.60 (m, 2H), 1.48-1.29 (m, 6H), 1.22-1.13 (comb-s and m, 7H), 0.91 (d, *J* = 5.9 Hz, 3H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 70.9, 44.0, 40.0, 36.9, 32.1, 31.6, 29.3, 29.2, 21.5, 18.9 ppm.

5.7.5. 6-Hydroxy-6-methylheptan-2-yl benzoate (4e)[16i]



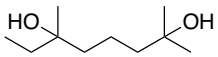
This compound was purified by column chromatography on silica gel (hexane/ethyl acetate, 4/1 to 3/1) to give 84% yield (95% conversion) as a colorless oil.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 7.3 Hz, 2H), 7.54 (pseudo-t, *J* = 7.3 Hz, 1H), 7.43 (pseudo-t, *J* = 7.6 Hz, 2H), 5.18 (dq, *J* = 12.6, 6.2 Hz, 1H), 1.82-1.73 (m, 1H), 1.67-1.58 (m, 1H), 1.54-1.42 (m, 5H), 1.35 (d, *J* = 6.3 Hz, 3H), 1.20 (s, 6H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.2, 132.7, 130.8, 129.5, 128.2, 71.4, 70.8, 43.5, 36.5, 29.2, 29.1, 20.2, 20.0 ppm.

5.7.6. 1,3-Adamantanediol (4f)



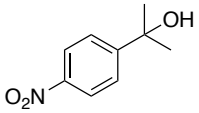
This compound was obtained in 72% yield (94% conversion), where commercially available **4f** (colorless solid) was used as a reference product.

5.7.7. 2,6-Dimethyloctane-2,6-diol (4g)[14]



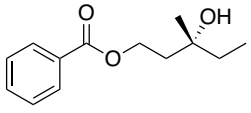
This compound was purified by column chromatography on silica gel (hexane/ethyl acetate, 1/1 to 0/1) to give 78% yield (97% conversion) as a colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54-1.38 (m, 10H), 1.22 (s, 6H), 1.16 (s, 3H), 0.90 (t, *J* = 7.6 Hz, 3H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 72.9, 71.0, 44.3, 41.7, 34.3, 29.3, 26.3, 18.5, 8.2 ppm.

5.7.8. 2-(4-Nitrophenyl)propan-2-ol (4h)[22c]



This compound was purified by column chromatography on silica gel (hexane/ethyl acetate, 9/1 to 2/1) to give 65% yield (84% conversion) as a colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J* = 9.1 Hz, 2H), 7.66 (d, *J* = 9.1 Hz, 2H), 1.94 (br-s, 1H), 1.62 (s, 6H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 146.7, 125.5, 123.5, 72.5, 31.7 ppm.

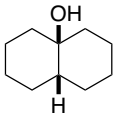
5.7.9. (*R*)-3-Hydroxy-3-methylpentyl benzoate (4i)[22c]



This compound was purified by column chromatography on silica gel (hexane/ethyl acetate, 4/1 to 2/1) to give 42% yield with >99% *ee* (48% conversion) as a colorless oil. Enantiomeric excess were determined by HPLC (Daicel Chiralcel OB-H, hexane/2-propanol=95/5, flow rate 0.5 mL/min, λ=254 nm, t_R=26.3 min (major), t_S=29.1 min (minor).); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.3 Hz, 2H), 7.55 (t, *J* = 6.8 Hz, 1H), 7.44

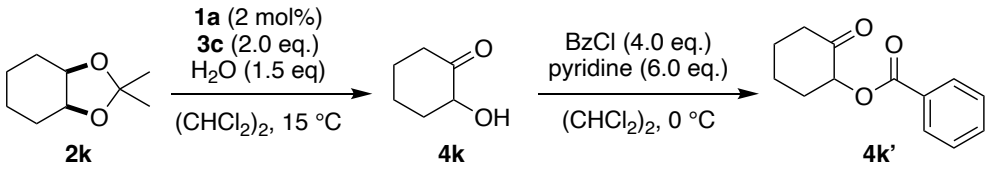
(pseudo-t, J = 7.8 Hz, 2H), 4.50 (t, J = 7.1 Hz, 2H), 2.08 (br-s, 1H), 2.02-1.91 (m, 2H), 1.59 (q, J = 7.6 Hz, 2H), 1.26 (s, 3H), 0.95 (t, J = 7.6 Hz, 3H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 132.9, 130.3, 129.5, 128.4, 72.2, 61.8, 39.3, 35.0, 26.6, 8.2 ppm.

5.7.10. *cis*-9-Decalinol (4j)[16i]



This compound was purified by column chromatography on silica gel (hexane/diethyl ether, 4/1 to 3/1) to give 73% yield (>99% Conversion) as a colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.72-1.31 (m, 18H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 71.7, 42.8, 28.0 (br), 23.0 (br) ppm.

5.7.11. 1-Hydroxycyclohexanone (4k)[56]



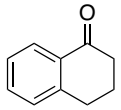
Scheme 19. Oxidative deacetarization of **2k** and estelification of corresponding product

The reaction of 1,2-*O*-isopropylidene-*cis*-cyclohexanediol with 2.0 equivalent of iodobenzene(dicalboxylate) **3c** using 1.5 equivalent of H_2O as the oxygen source at 15 °C in $(CHCl_2)_2$ (0.05M) was underwent with high conversion. However, obtained 2-hydroxycyclohexanone **4k** was difficult to the isolation, due to its highly sublimable nature. Thus, **4k** was directly converted to the corresponding benzoyl ester **4k'** under following protocol.

The reaction was quenched with 1N NaS_2O_3 aq. (1 mL) and sat. $NaHCO_3$ aq. (4 mL). The organic product was extracted with 5 mL portions of CH_2Cl_2 three times. The combined organic layer was washed with brine, and then dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated by rotary evaporator. The resulting mixture was purged with nitrogen gas and cooled at 0 °C. At that temperature, pyridine (97 μL, 1.2 mmol) was added to the mixture, and then benzoyl chloride (93 μL, 0.80 mmol) was added dropwise under nitrogen atmosphere. The reaction mixture was allowed to warm up to room temperature. After stirred for 6h, the resulting mixture was passed through a short pad of silica gel with CH_2Cl_2 and evaporation of the solvent under reduced pressure. Resulting residue was submitted on silica gel (hexane/ethyl acetate, 9/1 to 4/1) to give 2-oxocyclohexyl benzoate **4k'** 55% yield (90% conversion) as a colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 7.3 Hz, 2H), 7.57 (t, J = 7.3 Hz, 1H), 7.45 (pseudo-t, J = 7.3 Hz, 2H), 5.41 (dd, J = 11.2, 6.0 Hz,

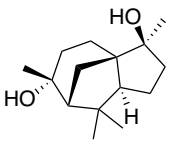
1H), 2.60-2.54 (m, 1H), 2.51-2.40 (m, 2H), 2.17-2.09 (m, 1H), 2.07-2.00 (m, 1H), 1.99-1.78 (m, 2H), 1.75-1.63 (m, 1H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.3, 165.5, 133.1, 129.8, 129.7, 128.3, 77.0, 40.7, 33.2, 27.2, 23.8 ppm.

5.7.12. 1-Tetralone (4l)



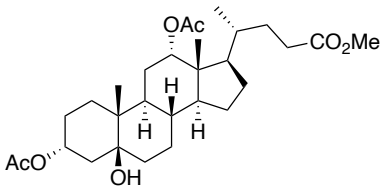
This compound was obtained in 81% yield (93% conversion), where commercially available **4l** (colorless liquid) was used as a reference product.

5.7.13. (3*S*,3a*R*,6*R*,7*R*,8*aS*)-3,6,8,8-Tetramethyloctahydro-1*H*-3a,7-methanoazulene-3,6-diol (4m)[22c]



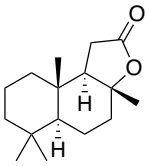
This compound was purified by column chromatography on silica gel (hexane/ethyl acetate, 4/1 to 2/3) to give 71% yield (97% conversion) as a colorless solid; $[\alpha]_D^{25}$ +11.8 (c = 1.24, $CHCl_3$);[ref.57] $[\alpha]_D^{25}$ +10.52 (c = 12.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.00-1.33 (m, 14H), 1.30 (s, 3H), 1.28 (s, 3H), 1.18 (s, 3H), 1.05 (s, 3H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 79.6, 74.9, 59.1, 57.5, 53.5, 44.9, 41.2, 36.6, 35.5, 30.3, 30.0, 28.4, 27.5, 24.3, 21.5 ppm.

5.7.14. (3*R*,5*S*,8*S*,9*S*,10*R*,12*S*,13*R*,14*S*,17*R*)-5-Hydroxy-17-((*R*)-5-methoxy-5-oxo-pentan-2-yl)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[a]phenanthrene-3,12-diyl diacetate (4n)[58]



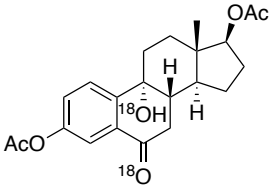
This compound was purified by column chromatography on silica gel (hexane/ethyl acetate, 7/1 to 2/1) to give 64% yield (79% conversion, conversion was determined from recovered starting material) as a colorless solid; $[\alpha]_D^{25}$ +78.0 (c = 1.29, $CHCl_3$);[ref.59] $[\alpha]_D^{22}$ +77.3 (c = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.10-5.02 (m, 2H), 3.66 (s, 3H), 2.38-2.31 (m, 1H), 2.42-2.15 (m, 1H), 2.11 (s, 3H), 2.03 (s, 3H), 2.11-1.01 (m, 24H), 0.88 (s, 3H), 0.81 (d, *J* = 6.3 Hz, 3H), 0.73 (s, 3H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.5, 170.4, 170.3, 75.5, 75.1, 71.1, 51.5, 49.4, 47.4, 44.8, 39.0, 38.1, 37.1, 36.6, 34.8, 34.8, 30.9, 30.8, 29.1, 28.1, 27.2, 26.1, 25.9, 23.4, 21.4, 21.3, 17.4, 16.0, 12.3 ppm.

5.7.15. (3a*R*)-(+)-Sclareolide (4o)[60]



This compound was purified by column chromatography on silica gel (hexane/ethyl acetate, 9/1 to 4/1) to give 73% yield (> 99% conversion) as a colorless solid; $[\alpha]_D^{25}$ +44.7 (c = 1.13, $CHCl_3$);[ref.60] $[\alpha]_D^{25}$ +42.6 (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.41 (pseudo-t, *J* = 15.4 Hz, 1H), 2.23 (dd, *J* = 6.4, 16.1 Hz, 1H), 2.08 (dt, *J* = 3.2, 11.7 Hz, 1H), 1.97 (dd, *J* = 6.4, 14.9 Hz, 1H), 1.88 (dq, *J* = 3.2, 6.9 Hz, 1H), 1.73-1.65 (m, 2H), 1.46-1.35 (m, 4H), 1.35 (s, 3H), 1.20 (td, *J* = 13.7, 4.2 Hz, 1H), 1.06 (dd, *J* = 2.4, 12.7 Hz, 1H) 1.06-1.02 (m, 1H), 0.91 (s, 3H), 0.89 (s, 3H), 0.84 (s, 3H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.8, 86.3, 59.0, 56.6, 42.1, 39.4, 38.6, 36.0, 33.1, 33.1, 28.6, 21.5, 20.9, 20.5, 18.0, 15.0 ppm.

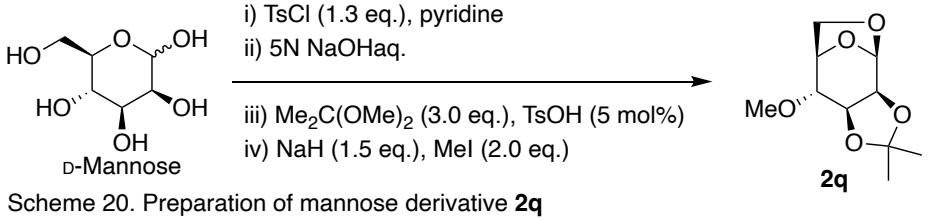
5.7.16. [6,9-^{18}O]-9-Hydroxy-6-keto-17β-estradiol diacetate (4p)[23a]



The crude mixture was directly submitted on silica gel (hexane/ethyl acetate, 4/1 to 1/1) to give the product **4p** in 74% yield (>99% conversion) as a colorless solid; $[\alpha]_D^{25}$ -13.3 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, *J* = 2.4 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.29 (dd, *J* = 2.4, 8.8 Hz, 1H), 4.76 (t, *J* = 8.3 Hz, 1H), 2.81 (dd, *J* = 13.2, 17.6 Hz, 1H), 2.49 (dd, *J* = 4.1, 17.8 Hz, 1H), 2.39 (dt, *J* = 2.9, 14.1 Hz, 1H), 2.32 (s, 3H), 2.27-2.20 (m, 2H), 2.06 (s, 3H), 2.02-1.90 (m, 2H), 1.84-1.53 (m, 5H), 1.37 (qd, *J* = 6.3, 12.0 Hz, 1H), 0.84 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.0, 171.1, 169.3, 150.6, 144.8, 133.1, 127.1, 125.6, 120.6, 82.0, 69.2, 43.0, 42.7, 41.0, 37.3, 32.5, 32.2, 27.5, 22.7, 21.1, 21.0, 11.2 ppm.; HRESI-MS (m/z) [M + Na^+], calcd for $[C_{22}H_{26}NaO_4{}^{18}O_2]^+$ 413.1707, found: m/z = 413.1706.; ^{18}O content: 94% doubly ^{18}O labeled, 6% singly ^{18}O labeled.

5.8. Synthesis of Oxygen-Isotope Labeled Sugars

5.8.1. Synthesis of 1,6-anhydro-4-*O*-methyl-2,3-*O*-isopropylidene-β-D-mannopyranose 2q[32]



Scheme 20. Preparation of mannose derivative **2q**

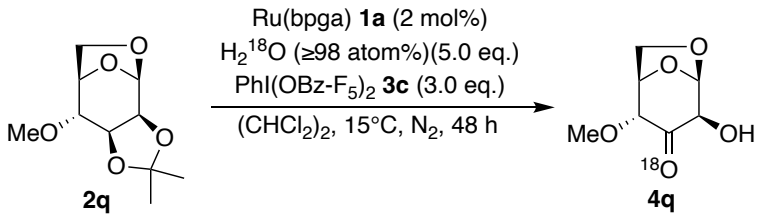
Under nitrogen atmosphere, D-mannose (4.0 g, 22.2 mmol) and pyridine (40 mL) were placed in a 100 mL Schlenk tube equipped with a stir-bar. Resulting mixture was cooled at 0 °C using an ice-water bath. To the suspension, solution of *p*-toluenesulfonyl chloride (5.5 g, 28.9 mmol) in pyridine (8 mL) was added dropwise at that temperature. After stirring for 2h, 5N aqueous NaOH (12 mL, 60

mmol) was added dropwise to the mixture at 0 °C. The mixture was allowed to room temperature and stirred for addition 2h. After that, the pH of the reaction was carefully raised to 7 by addition of 2N aqueous HCl, and the solvents were eliminated under reduced pressure. Residual pyridine was removed by azeotropic distillation with toluene (20 mL x 2). Obtained reside was suspended into ethanol and filtered through Celite pad. The filtrate was concentrated on a rotary evaporator.

Resulting crude 1,6-anhydro-β-D-mannopyranose was suspended in 70 mL of acetone and treated with 2,2-dimethoxypropane (8.3 mL, 66.6 mmol) and *p*-toluenesulfonic acid monohydrate (211 mg, 1.1 mmol). After stirred for 12h at room temperature, the reaction was treated with triethylamine (0.16 mL, 1.1 mmol). The mixture was passed through a short pad of silica gel with AcOEt and evaporation of the solvents under reduced pressure gave crude acetonide. The residue was submitted to silica gel chromatography (*n*-hexane/AcOEt = 1/1 to 1/2) to give 1,6-anhydro-2,3-isopropylidene-β-D-mannopyranose (2.33 g, 11.5 mmol, 51.8% yield)

Under nitrogen atmosphere, 1,6-anhydro-2,3-isopropylidene-β-D-mannopyranose (1.0 g, 5.0 mmol) was dissolved in 25 mL of tetrahydrofuran/*N*,*N*-dimethylformamide (4/1) and cooled at 0 °C using an ice-water bath. NaH (60% in oil, 300 mg, 7.50 mmol) was added to the solution and stirred for 1h at that temperature. At that temperature, methyl iodide (0.63 mL, 10.0 mmol) was added dropwise to the mixture and allowed to warm up to room temperature. After stirred for 1.5 h, the reaction was quenched by addition of sat. NH_4Cl aq. (20 mL) and extracted with AcOEt (30 mL x 3). The organic layers were washed with brine, and then dried over anhydrous Na_2SO_4. After the crude mixture was concentrated under reduced pressure. Resulting residue was submitted to silica gel chromatography (*n*-hexane/AcOEt = 9/1 to 2/1) to give 1,6-Anhydro-4-*O*-methyl-2,3-*O*-isopropylidene-β-D-mannopyranose **2q** (1.0 g, 4.7 mmol, 94% yield) as a colorless solid.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.35 (d, *J* = 2.9 Hz, 1H), 4.63 (d, *J* = 6.3 Hz, 1H), 4.23 (d, *J* = 6.3 Hz, 1H), 4.07 (dd, *J* = 6.3, 2.9 Hz, 1H), 3.95 (d, *J* = 7.3 Hz, 1H), 3.77 (pseudo-t, *J* = 6.6 Hz, 1H), 3.50 (s, 3H), 3.48 (s, 1H), 1.54 (s, 3H), 1.34 (s, 3H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.7, 99.1, 78.6, 73.2, 72.7, 72.2, 64.4, 57.4, 25.9, 25.8 ppm.; HRESI-MS (m/z) [M + Na^+], calcd for $[C_{10}H_{16}O_5Na]^+$ 239.0890, found: m/z = 239.0892.

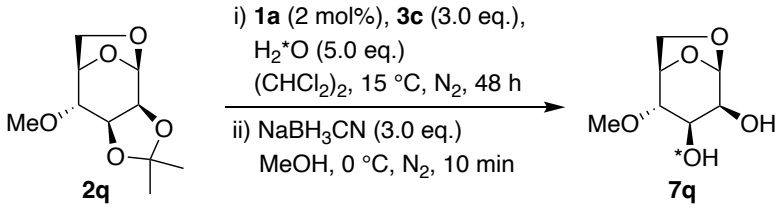
5.8.2. Ru(bpga) 1a-Catalyzed Oxidation of 1,6-Anhydro-4-*O*-methyl-2,3-*O*-isopropylidene-β-D-mannopyranose 2q



Scheme 21. Ru(bpga) **1a**-catalyzed oxidation of mannose derivative **2q**

1,6-Anhydro-4-*O*-methyl-2,3-*O*-isopropylidene-β-D-mannopyranose **2q** (43.2 mg, 0.2 mmol), Ru(bpga) complex **1a** (3.2 mg, 4.0 μmol), $H_2{}^{18}O$ (≥98 atom%) (18 μL, 1.0 mmol), 4'-chloroacetophenone (15.5 mg, 0.1 mmol) as an internal standard for NMR analysis, and 1,1,2,2-tetrachloroethane (4 mL) were take a placed in a 10 mL Schlenk tube in an aluminum block under nitrogen atmosphere at 15 °C. At that temperature, iodobenzene[bis(pentafluorobenzoate)] **3c** (375.7 mg, 0.6 mmol) was added to the mixture and stirred for 48h. An aliquot (40 μL) of the resulting mixture was taken out of the Schlenk tube as the zero-time or 48 h sample. The aliquot (40 μL) was diluted by $CDCl_3$ (0.6 mL) and submitted to ^{1}H NMR analysis to determine conversion and yields of products (85% conversion, 51% yield, ^{18}O content: 80 atom%). Resulting reaction mixture was directly submitted to silica gel chromatography (*n*-hexane/AcOEt = 2/1 to 1/2) to give (1*R*,2*R*,4*R*,5*R*)-[3-^{18}O]-4-hydroxy-2-methoxy-6,8-dioxabicyclo[3.2.1]octan-3-one **4q** (11.4 mg, 66.0 μmol, 33% yield, ^{18}O content: 22 atom%) as a colorless oil.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.64 (d, *J* = 2.4 Hz, 1H), 4.89-4.87 (m, 1H), 4.47 (d, *J* = 3.4 Hz, 1H), 3.86 (dd, *J* = 8.3, 5.9 Hz, 1H), 3.67 (d, *J* = 2.0 Hz, 1H), 3.64 (dd, *J* = 8.3, 1.0 Hz, 1H), 3.43 (s, 3H), 3.27 (d, *J* = 6.3 Hz, 1H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.5, 103.6, 85.1, 76.9, 76.6, 65.4, 58.0 ppm.; HRESI-MS (m/z) [M + Na^+], calcd for $[C_7H_{10}O_4{}^{18}ONa]^+$ 199.0463, found: m/z = 199.0467.

5.8.3. One-pot protocol of synthesis of [3-^{18}O/^{17}O]-1,6-anhydro-4-*O*-methyl-β-D-mannopyranose 7q



Scheme 22. One-pot protocol of oxidation and reduction from **2q** to **7q**

5.8.3.1. [3-^{18}O]-1,6-Anhydro-4-*O*-methyl-β-D-mannopyranose [3-^{18}O]-7q

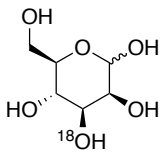
1,6-Anhydro-4-*O*-methyl-2,3-*O*-isopropylidene-β-D-mannopyranose **2q** (2.59 g, 12.0 mmol),

Ru(bpga) complex **1a** (191 mg, 0.24 mmol), $H_2{}^{18}O$ (≥98 atom%) (1.08 mL, 60.0 mmol), and 1,1,2,2-tetrachloroethane (240 mL) were take a placed in a 500 mL flask equipped three-way cock in a water bath under nitrogen atmosphere at 15 °C. At that temperature, iodobenzene[bis(pentafluorobenzoate)] **3c** (22.5 g, 36.0 mmol) was added to the mixture and stirred for 48h. After that, the reaction mixture was cooled at 0 °C using an ice-water bath. Then, MeOH (60 mL), and $NaBH_3CN$ (2.26 g, 36.0 mmol) was added to the mixture and stirred for additional 10 min. The reaction was quenched by addition of sat. NH_4Cl aq. (20 mL). Resulting mixture was passed through a short pad of NH-silica gel with CH_2Cl_2/MeOH = 19/1-4/1 and evaporation of the solvents under reduced pressure gave crude mixture. Resulting residue was submitted to silica gel chromatography (CH_2Cl_2/MeOH = 19/1 to 9/1) to give [3-^{18}O]-1,6-anhydro-4-*O*-methyl-β-D-mannopyranose **[3-^{18}O]-7q** (1.14 g, 6.40 mmol, 53.3% yield, ^{18}O content: 80 atom%) as a colorless oil.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.38 (s, 1H), 4.62 (d, *J* = 5.9 Hz, 1H), 4.18 (d, *J* = 7.3 Hz, 1H), 4.03 (br-s, 1H), 3.81-3.73 (m, 2H), 3.48 (s, 3H), 3.43 (s, 1H), 3.25 (br-s, 2H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 101.5, 81.0, 73.4, 68.2, 66.7, 64.8, 57.5 ppm.; HRESI-MS (m/z) [M + Na^+], calcd for $[C_7H_{12}O_4{}^{18}ONa]^+$ 201.0619, found: m/z = 201.0615.

5.8.3.2. [3-^{17}O]-1,6-Anhydro-4-*O*-methyl-β-D-mannopyranose [3-^{17}O]-7q

Preparation of **[3-^{17}O]-7q** was carried out in 0.2 mmol scale reaction with $H_2{}^{17}O$ (^{17}O content: 20.8%, ^{18}O content: 19.9%) (18 μL, 1.0 mmol) as the oxygen source. [3-^{17}O]-1,6-Anhydro-4-*O*-methyl-β-D-mannopyranose **[3-^{17}O]-7q** was obtained in 51% yield (18.1 mg, 102 μmol, ^{17}O content: 15.9 atom%, ^{18}O content: 16.0 atom%) as a colorless oil.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.38 (s, 1H), 4.62 (d, *J* = 5.4 Hz, 1H), 4.18 (d, *J* = 7.3 Hz, 1H), 4.04 (d, *J* = 4.4 Hz, 1H), 3.83-3.74 (m, 2H), 3.49 (s, 3H), 3.44 (s, 1H), 3.25 (br-s, 2H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 101.5, 81.0, 73.4, 68.2, 66.7, 64.8, 57.5 ppm.; HRESI-MS (m/z) [M + Na^+], calcd for $[C_7H_{12}O_4{}^{17}ONa]^+$ 200.0619, found: m/z = 200.0623.

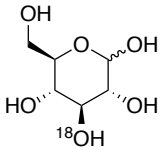
5.8.4. Synthesis of [3-^{18}O]-D-mannose[61]



Under nitrogen atmosphere, [3-^{18}O]-1,6-Anhydro-4-*O*-methyl-β-D-mannopyranose **7q** (276 mg, 1.55 mmol) was dissolved in a 15.5 mL of CH_2Cl_2 and cooled at 0 °C using an ice-water bath. At that temperature, the solution was treated with CH_2Cl_2 solution of BBr_3 (1 M, 4.65 mL, 4.65 mmol) and stirred for 30 min. After that, the reaction was quenched by addition of water (15 mL) and organic layer was removed. Aqueous layer was neutralized with Amberlite IRA-67 and concentrated under reduced pressure. Resulting residue was

submitted to silica gel chromatography (CH_2Cl_2/MeOH = 9/1 to 2/1) to give [3-^{18}O]-D-mannose (239 mg, 1.31 mmol, 85% yield, ^{18}O content: 80 atom%) as a colorless oil. Recrystallization of the product from ethanol solution gave a colorless solid.; $[\alpha]_D^{25}$ +14.3 (c = 0.38, H_2O); [ref.61] $[\alpha]_D^{20}$ +13.9 (c = 10, H_2O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.23 (d, *J* = 4.4 Hz, 1H), 6.15 (d, *J* = 8.3 Hz, 0.4H), 4.87 (d, *J* = 3.9 Hz, 1H), 4.67 (d, *J* = 4.4 Hz, 0.4H), 4.61 (d, *J* = 5.4 Hz, 1H), 4.56-4.50 (m, 1.8H), 4.45-4.41 (m, 1.8H), 4.33 (pseudo-t, *J* = 5.9 Hz, 1H), 3.70-3.61 (m, 1.4H), 3.54-3.23 (m, 6.6H), 3.01 (pseudo-t, *J* = 6.8 Hz, 0.4H) ppm.; ^{13}C NMR (100 MHz, DMSO-d_6): δ 94.2, 94.1, 77.3, 73.9, 73.3, 71.7, 71.5, 70.7, 67.5, 67.2, 61.6, 61.6 ppm.; HRESI-MS (m/z) [M + Na^+], calcd for $[C_6H_{12}O_5{}^{18}ONa]^+$ 205.0569, found: m/z = 205.0564.

5.8.5. Synthesis of [3-^{18}O]-D-gulcose[62,63]



[3-^{18}O]-D-Mannose (36.4 mg, 0.20 mmol) and phosphomolybdic acid (0.61 mg, 0.33 μmol) were dissolved in a 1.0 mL of water and the mixture was heated at reflux using an aluminum bath. After stirred for 3h at that temperature, the reaction mixture was concentrated under reduced pressure to give crude [3-^{18}O]-D-mannose and [3-^{18}O]-D-glucose mixture (mannose/glucose = 30/70).

Under nitrogen atmosphere, the resulting residue was dissolved in a 1.0 mL of pyridine and cooled at 0 °C using an ice-water bath. At that temperature, benzoyl chloride (186 μL, 1.60 mmol) was added dropwise to the mixture and allowed to warm up to room temperature. After stirred for 12h, the reaction was quenched by addition of sat. $NaHCO_3$ aq. (3 mL) and extracted with CH_2Cl_2 (3 mL x 3). The organic layers were washed with 4N HCl and brine, and then dried over anhydrous Na_2SO_4. After the crude mixture was concentrated under reduced pressure. Resulting residue was purified by flush column chromatography (silica gel, *n*-hexane/$CHCl_3$ = 3/2 to 0/1) and preparative TLC (silica gel, $CHCl_3$/ethyl acetate: 99/1) to give [3-^{18}O]-D-glucopyranose pentabenzoate (77.6 mg, 110 μmol, 55% yield from [3-^{18}O]-D-mannose).

Under nitrogen atmosphere, the [3-^{18}O]-D-glucopyranose pentabenzoate (70.3 mg, 0.10 mmol) was dissolved in a 1.0 mL of methanol and cooled at 0 °C using an ice-water bath. At that temperature, sodium methoxide (10.8 mg, 0.20 mmol) was added to the mixture and allowed to warm up to room temperature. After stirred for 2h, the reaction mixture was neutralized with Dowex 50X8 and concentrated under reduced pressure. Resulting residue was submitted to silica gel chromatography (CH_2Cl_2/MeOH = 9/1 to 2/1) to give [3-^{18}O]-D-glucose (15.9 mg, 87 μmol, 87% yield, (48% yield

from [3-^{18}O]-D-mannose), ^{18}O content: 78 atom%) as a colorless oil. Recrystallization of the product from ethanol solution gave a colorless solid.; $[\alpha]_D^{25}$ +48.6 (c = 1.43, H_2O); [ref.64] $[\alpha]_D^{24}$ +49.8 (c = 1.6, H_2O); ^{1}H NMR (400 MHz, D_2O): δ 5.22 (d, *J* = 3.4 Hz, 1.0H), 4.63 (d, *J* = 8.3 Hz, 1.5H), 3.91-3.69 (m, 7.0H), 3.54-3.37 (m, 7.0H), 3.24 (pseudo-t, *J* = 8.5 Hz, 1.5H) ppm.; ^{13}C NMR (100 MHz, D_2O): δ 96.5, 92.7, 76.5, 76.3, 74.7, 73.3, 72.1, 72.0, 70.2, 70.2, 61.3, 61.2 ppm.; HRESI-MS (m/z) [M + Na^+], calcd for $[C_6H_{12}O_5{}^{18}ONa]^+$ 205.0569, found: m/z = 205.0564.

5.9. General Procedure for Ru(bpga)-Catalyzed C–H Oxidation of 3,7-Dimethyloctyl Acetate 2a with H_2O_2 as the Terminal Oxidant

5.9.1. General procedure for Ru(bpga) 1a-catalyzed C–H oxidation of 3,7-dimethyloctyl acetate with H_2O_2 under acidic conditions (Table 3-5)

Under ambient air, 3,7-dimethyloctyl acetate **2a** (20.0 mg, 23.1 μL, 0.10 mmol), Ru(bpga) complex **1a** (1.59 mg, 2.00 μmol, 2 mol%), carboxylic acid (1.0–2.0 eq.), drying agent (0 or 50 mg), and solvent (250 μL) were placed in a 5 mL test tube in an aluminum block at indicated reaction temperature. Then, hydrogen peroxide (11.48M in water, 56.6 μL, 0.65 mmol) was added to the mixture and stirred for 12 or 24 h. To the resulting mixture, 1,3,5-trichlorobenzene (0.2M in 1,1,2,2-tetrachloroethane, 250 μL, 0.05 mmol) as a standard material for GC analysis and CH_2Cl_2 (24.5 mL) was added, and then the mixture was submitted to GC analysis with a COATING CP-SELECT 624 CB column to determine conversion and yields of products.

5.9.2. General procedure for C–H oxidation of 3,7-dimethyloctyl acetate with H_2O_2 using pre-generated Ru(bpga)(carboxylate) (2 mol%) as the catalyst (Table 6, Figure 18, 20)

Ru(bpga) **1** (12.0 μmol), carboxylic acid (60.0 μmol), and HFIP (1.50 mL) were take a placed in a 5 mL Schlenk tube under nitrogen atmosphere. At the room temperature, the mixture was stirred for 5 min. To the mixture, Ag_2O (2.23 mg, 9.60 μmol) was added, and then the suspension was vigorously stirred for 1 h at room temperature under photo-shielding condition (during the stirring, the suspension was sonicated 5 times for 1 min at 10 min intervals). The resulting mixture was passed through filter (HLC-DISK® 3 (0.45μm) hydrophobic, Kanto Chemical) to give the solution of pre-treated **1**.

C–H oxidation was performed by following procedure. Under ambient air, 3,7-dimethyloctyl acetate **2a** (40.1 mg, 46.2 μL, 0.20 mmol), carboxylic acid (280 μmol), $MgSO_4$ (100 mg), and pre-treated **1** solution [500 μL, containing 4 μmol (2 mol%) of catalyst and 20 μmol of carboxylic acid]

were placed in a 5 mL test tube in an aluminum block at 10 °C. Then, hydrogen peroxide (11.48 M in water, 87.1 μL, 1.0 mmol) was added to the mixture and the reaction mixture was stirred for 0.5–1.5 h. To the resulting mixture, 1,3,5-trichlorobenzene (0.2 M in 1,1,2,2-tetrachloroethane, 500 μL, 0.1 mmol) as a standard material for GC analysis and CH_2Cl_2 (49 mL) was added, and then the mixture was submitted to GC analysis with a COATING CP-SELECT 624 CB column to determine conversion and yields of products.

5.9.3. General procedure for C–H oxidation of 3,7-dimethyloctyl acetate with H_2O_2 using pre-generated Ru(bpga)(H-dicarboxylate)$_2$ (0.1 mol%) or isolated Ru(bpga)(H-maleate)$_2$ 1f (0.1 mol%) as the catalyst (Table 7)

Pre-treatment of Ru(bpga) **1a** was performed in the same procedure as section 5.9.2. The resulting mixture was used without filtration.

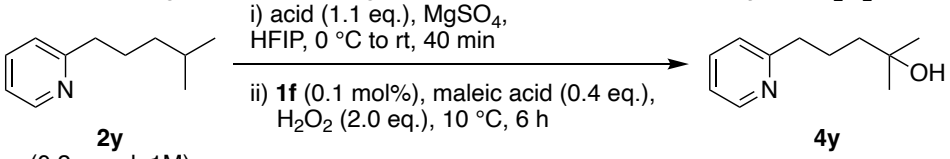
C–H oxidation was performed by following procedure. Under ambient air, 3,7-dimethyloctyl acetate **2a** (40.1 mg, 46.2 μL, 0.20 mmol), carboxylic acid [299 μmol (or 300 μmol for the reaction with **1f**)], $MgSO_4$ (100 mg), and HFIP (475 μL) were placed in a 5 mL test tube in an aluminum block at 10 °C. At that temperature, pre-treated **1a** solution [25 μL, containing 0.2 μmol (0.1 mol%) of catalyst and 1 μmol of carboxylic acid] [or solution of **1f** (8 mM in HFIP under N_2, 25 μL, 0.2 μmol, 0.1 mol%)] was added to the mixture. Then, hydrogen peroxide (11.48 M in water, 87.1 μL, 1.0 mmol) was added to the mixture and the reaction mixture was stirred for 1–3 h. To the resulting mixture, 1,3,5-trichlorobenzene (0.2 M in 1,1,2,2-tetrachloroethane, 500 μL, 0.1 mmol) as a standard material for GC analysis and CH_2Cl_2 (49 mL) was added, and then the mixture was submitted to GC analysis with a COATING CP-SELECT 624 CB column to determine conversion and yields of products.

5.10. Optimization of C–H Oxygenation of 2-(4-Methylpentyl)pyridine 2y with H_2O_2 as the Terminal Oxidant Using Ru(bpga)(H-maleate)$_2$ 1f as the Catalyst

2-(4-Methylpentyl)pyridine **2y** (32.7 mg, 36.4 μL, 0.20 mmol), $MgSO_4$ (40 or 60 mg), and HFIP (175 μL) were placed in a 5 mL test tube and cooled at 0 °C using an ice-water bath under air. At that temperature, acid (1.1 equiv) was added to the mixture and stirred 10 min, then warm up to at room temperature and stirred for 30 min. To the resulting mixture, maleic acid (9.29 mg, 80.0 μmol) was added and cooled at 10 °C using an aluminum block. At that temperature, **1f** solution (8 mM in HFIP under N_2, 25 μL, 0.2 μmol, 0.1 mol%) was added to the mixture. Then, hydrogen peroxide (11.48 M

in water, 34.8 μL, 0.40 mmol) was added to the mixture and stirred for 6 h. The resulting mixture was diluted by $CHCl_3$ (1 mL) and passed through cotton-plug with $CHCl_3$ (4 mL). 1N $Na_2S_2O_3$ aq. (1 mL) was added to the obtained filtrate, the resulting mixture was stirred for 5 min at room temperature. The organic layer was concentrated under reduced pressure. To the resulting residue, CH_2Cl_2 (5 mL) and 1N NaOH aq. (4 mL) were added and stirred for 10 min at room temperature. To the mixture, 1,3,5-trichlorobenzene (0.2M in 1,1,2,2-tetrachloroethane, 0.5 mL, 0.1 mmol) was added as a standard material for GC analysis, after that, extracted with CH_2Cl_2 (5 mL x 3). The organic layer was washed with brine, and then dried over anhydrous Na_2SO_4. The resulting mixture was diluted by CH_2Cl_2 until total volume reached to 50 mL, and then the mixture was submitted to GC analysis with a HP-5 column to determine conversion and yields of products. The extraction was concentrated under reduced pressure. Resulting residue was submitted to silica gel chromatography (CH_2Cl_2/MeOH = 1/0 to 19/1) to determine isolated yield of the product and recovered starting material.

Table 8. Screening of acids in Ru(bpga) **1b**-catalyzed C–H oxidation of **2y** with H_2O_2



2y (0.2 mmol, 1M) → **4y**

entry	acid	$MgSO_4$ (mg)	conv. (%)[a]	yield (%)[a]	TOF (rph)[a]
1	maleic acid	40	21	13	22
2	CF_3CO_2H	40	37	29	49
3	CF_3SO_3H	40	93	86	143
4	$HClO_4$ (60% in water)	60	99	89	149
5	HBF_4 (42% in water)	60	97 (98)[b]	91 (87)[c]	151 (146)[d]

[a] Determined by GC analysis. [b] Determined by recovering starting material. [c] Isolated yield. [d] Determined by isolated yield.

5.11. Typical Procedure for Ru(bpga)(H-maleate)$_2$ 1f-Catalyzed C–H Oxygenation of Alkanes 2 with H_2O_2 as the Terminal Oxidant (Figure 21-23)

5.11.1. Typical procedure for 1f-catalyzed C–H hydroxylation with H_2O_2

Alkane **2** (0.20 mmol), maleic acid (9.29 mg, 80.0 μmol), $MgSO_4$ (40 mg), and HFIP (175 μL) were placed in a 5 mL test tube in an aluminum block at 10 °C. At that temperature, Ru(bpga)(H-maleate)$_2$ **1f** (8 mM in HFIP under N_2, 25 μL, 0.2 μmol, 0.1 mol%) and hydrogen peroxide (11.48 M in water, 34.8 μL, 0.40 mmol) were added to the mixture and stirred for 3–12 h. The resulting mixture

was diluted by CH_2Cl_2 (1 mL) and passed through cotton-plug with CH_2Cl_2 (4 mL). 1N $Na_2S_2O_3$ aq. (1mL) and sat. $NaHCO_3$ aq. (4 mL) were added to the filtrate, and then resulting organic layer were extracted with CH_2Cl_2 (5 mL x 3). The organic layer was washed with brine, and then dried over anhydrous Na_2SO_4. The crude mixture was concentrated under reduced pressure. Resulting residue was submitted to silica gel chromatography with *n*-hexane/AcOEt to afford the desired product **4**.

5.11.2. Typical procedure for 1f-catalyzed C–H oxidation of nucleophilic nitrogen-containing compounds with H_2O_2

Substrate **2** (0.20 mmol), $MgSO_4$ (60 mg), and HFIP (175 μL) were placed in a 5 mL test tube and cooled at 0 °C using an ice-water bath under air. At that temperature, HBF_4 (42% in water, 33.3 μL, 0.22 mmol) was added to the mixture and stirred 10 min, then warmed up to room temperature and stirred for 30 min. To the resulting mixture, maleic acid (9.29 mg, 80.0 μmol) was added and the mixture was cooled at 10 °C using an aluminum block. At that temperature, Ru(bpga)(H-maleate)$_2$ **1f** (8 mM in HFIP under N_2, 25 μL, 0.2 μmol, 0.1 mol%) and hydrogen peroxide (11.48 M in water, 34.8 μL, 0.40 mmol) were added to the mixture and stirred for 6–12 h. After that, to the resulting mixture, CH_2Cl_2 (5 mL), 1N $Na_2S_2O_3$ aq. (1mL), and sat. $NaHCO_3$ aq. (4 mL) was added and stirred for 5 min at room temperature. Then, the mixture was passed through cotton-plug with CH_2Cl_2 (5 mL). The resulting filtrate were extracted with CH_2Cl_2 (5 mL x 3). The organic layer was washed with brine, and then dried over anhydrous Na_2SO_4. The crude mixture was concentrated under reduced pressure. Resulting residue was submitted to silica gel chromatography with CH_2Cl_2/MeOH to afford the desired product **4**.

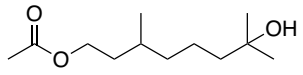
5.11.3. Typical procedure for 1f-catalyzed methylene C–H oxidation with H_2O_2

Substrate **2** (0.20 mmol), Ru(bpga)(H-maleate)$_2$ **1f** (3.82 mg, 4.0 μmol, 2 mol%), maleic acid (46.4 mg, 0.40 mmol), $MgSO_4$ (200 mg), and HFIP (1.00 mL) were placed in a 5 mL test tube in an aluminum block at 10 °C. At that temperature, hydrogen peroxide (11.48 M in water, 34.8 μL, 0.400 mmol) was added to the mixture. Hydrogen peroxide (11.48 M in water, 34.8 μL, 0.40 mmol) was added forth time to the mixture every 3 hours. After further stirred for 12h, the resulting mixture was diluted by CH_2Cl_2 (1 mL) and passed through cotton-plug with CH_2Cl_2 (4 mL). 1N $Na_2S_2O_3$ aq. (1mL) and sat. $NaHCO_3$ aq. (4 mL) were added to the filtrate. Obtained filtrate was extracted with CH_2Cl_2 (5 mL x 3). The extraction was washed with brine, and then dried over anhydrous Na_2SO_4. The crude

mixture was concentrated under reduced pressure. Resulting residue was submitted to silica gel chromatography with *n*-hexane/AcOEt to afford the desired product **4**.

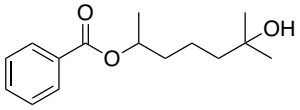
5.12. Characterization of Products in Ru(bpga)(H-maleate)$_2$ 1f-Catalyzed C–H Oxygenation with H_2O_2 as the Terminal Oxidant

5.12.1. 7-Hydroxy-3,7-dimethyloctyl acetate (4a)[16a]



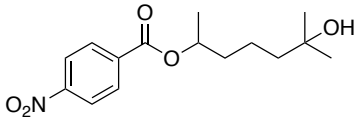
The this compound was synthesized following typical procedure 5.11.1 for 3h, and purified by column chromatography on silica gel (*n*-hexane/AcOEt, 1/0 to 4/1) to give 61% yield (95% conversion) as a colorless oil.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.15-4.05 (m, 2H), 2.04 (s, 3H), 1.67 (td, *J* = 13.4, 6.7 Hz, 1H), 1.56 (td, *J* = 12.4, 6.2 Hz, 1H), 1.48-1.29 (m, 7H), 1.24-1.11 (m, 1H), 1.22 (s, 6H), 0.92 (d, *J* = 6.3 Hz, 3H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 70.9, 63.0, 44.1, 37.3, 35.4, 29.8, 29.3, 29.2, 21.6, 21.0, 19.4 ppm.

5.12.2. 6-Hydroxy-6-methylheptan-2-yl benzoate (4e)[16i]



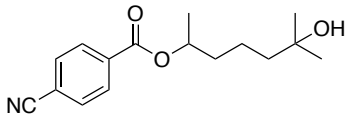
This compound was synthesized according to typical procedure 5.11.1 for 6h and purified by preparative TLC (silica gel, *n*-hexane/AcOEt: 3/2) to give 77% yield as a colorless oil (recovered starting material: 5%). NMR data was described in section 5.7.5.

5.12.3. 6-Hydroxy-6-methylheptan-2-yl 4-nitrobenzoate (4r)



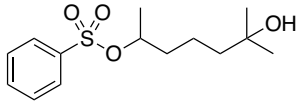
This compound was synthesized according to typical procedure 5.11.1 for 6h and purified by preparative TLC (silica gel, *n*-hexane/AcOEt: 3/2) to give 86% yield as a colorless oil (recovered starting material: 2%).; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 9.0 Hz, 2H), 8.20 (d, *J* = 9.0 Hz, 2H), 5.22 (qt, *J* = 12.7, 6.3 Hz, 1H), 1.80-1.71 (m, 1H), 1.66-1.49 (m, 2H), 1.43-1.32 (conb-m, 2H and 1.37 (d, *J* = 6.3 Hz, 3H)), 1.24-1.18 (m, 2H), 1.21 (s, 6H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 150.4, 136.3, 130.6, 123.4, 72.9, 70.8, 43.4, 36.4, 29.3, 29.2, 20.1, 20.0 ppm.; HRESI-MS (m/z) [M + Na^+], calcd for $[C_{15}H_{21}NNaO_5]^+$ 318.1312, found: m/z = 318.1309.

5.12.4. 6-Hydroxy-6-methylheptan-2-yl 4-cyanobenzoate (4s)[46]



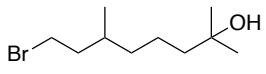
This compound was synthesized according to typical procedure 5.11.1 using **1f** (8 mM in HFIP under N_2, 125 μL, 1 μmol, 0.5 mol%) and HFIP (75 μL) for 12h, and purified by preparative TLC (silica gel, *n*-hexane/AcOEt: 2/3) to give 77% yield as a colorless oil (recovered starting material: 8%).; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, *J* = 8.8 Hz, 2H), 7.74 (d, *J* = 8.8 Hz, 2H), 5.20 (tq, *J* = 12.4, 6.2 Hz, 1H), 1.83-1.60 (m, 3H), 1.54-1.41 (m, 4H), 1.36 (t, *J* = 6.3 Hz, 3H), 1.21 (s, 6H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 134.6, 132.1, 130.0, 118.0, 116.1, 72.7, 70.7, 43.4, 36.3, 29.3, 29.2, 20.1, 19.9 ppm.

5.12.5. 6-Hydroxy-6-methylheptan-2-yl benzenesulfonate (4t)



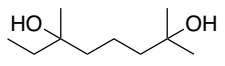
This compound was synthesized according to typical procedure 5.11.1 for 6h and purified by column chromatography on silica gel (*n*-hexane/AcOEt, 3/2 to 1/1) to give 80% yield as a colorless oil (recovered starting material: 0%).; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 7.3 Hz, 2H), 7.64 (dd, *J* = 7.6, 7.3 Hz, 1H), 7.55 (pseudo-t, *J* = 7.6 Hz, 2H), 4.67 (tq, *J* = 12.4, 6.2 Hz, 1H), 2.38 (br-s, 1H), 1.68-1.59 (m, 1H), 1.54-1.46 (m, 1H), 1.41-1.10 (m, 4H), 1.27 (d, *J* = 6.3 Hz, 3H), 1.14 (d, *J* = 2.4 Hz, 6H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 133.4, 129.1, 127.6, 80.8, 70.9, 43.1, 36.8, 29.1, 29.0, 20.9, 19.7 ppm.; HRESI-MS (m/z) [M + Na^+], calcd for $[C_{14}H_{22}NaO_4S]^+$ 309.1131, found: m/z = 309.1129.

5.12.6. 7-Hydroxy-3,7-dimethyloctyl bromide (4d)[16a]



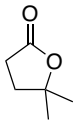
This compound was synthesized according to typical procedure 5.11.1 for 3h and purified by column chromatography on silica gel (*n*-hexane/AcOEt, 1/0 to 4/1) to give 68% yield as a colorless oil (recovered starting material: 6%). NMR data was described in section 5.7.4.

5.12.7. 2,6-Dimethyloctane-2,6-diol (4g)[14]

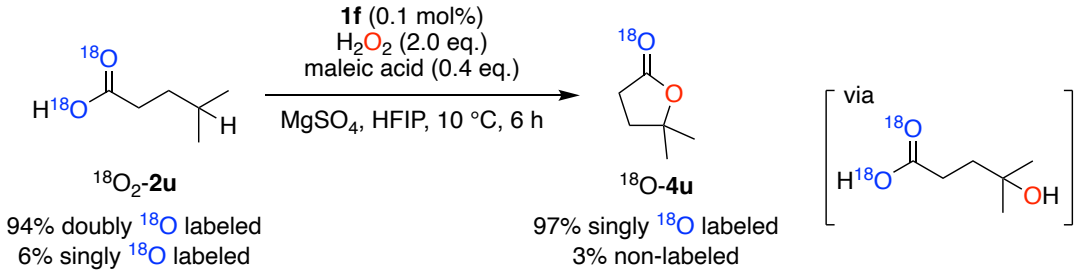


This compound was synthesized according to typical procedure 5.11.1 using H_2O_2 (3.0 equiv) and $MgSO_4$ (60 mg) for 3h, and purified by column chromatography on silica gel (*n*-hexane/AcOEt, 1/1 to 0/1) to give 61% yield as a colorless solid (recovered starting material: 0%). NMR data was described in section 5.7.7.

5.12.8. 4,4-Dimethyl-γ-butylolactone (4u)[65]



This compound was synthesized according to typical procedure 5.11.1 for 6h and purified by column chromatography on silica gel (*n*-hexane/AcOEt, 2/1) to give 63% yield as a colorless oil (recovered starting material: not determined).; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.62 (t, *J* = 8.2 Hz, 2H), 2.06 (t, *J* = 8.2 Hz, 2H), 1.43 (s, 6H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 84.6, 34.7, 29.4, 27.7 ppm.

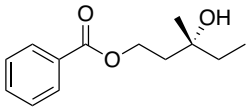


Scheme 23. Mechanistic Study of C–H lactonization

To investigate the mechanism of this C–H lactonization, doubly oxygen isotopic labeled carboxylic acid $^{18}O_2$-**2u** (^{18}O content: 94% doubly ^{18}O labeled, 6% singly ^{18}O labeled)[65] was used as a substrate. The reaction was performed according to typical procedure 5.11.1 for 6h, and then resulting reaction mixture was directly submitted to silica gel chromatography (*n*-hexane/AcOEt, 2/1) without extraction to give 59% yield as a colorless oil. ^{18}O content was determined by HRESI-MS.; HRESI-MS (m/z) [M + Na^+], calcd for $[C_6H_{10}NaO^{18}O]^+$ 139.0615, found: m/z = 139.0611.; ^{18}O content: 97% singly ^{18}O labeled, 3% non-labeled.

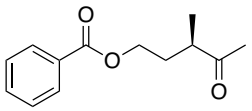
This mechanistic study suggested that C–H lactonization proceeded via methine C–H hydroxylation followed by lactone formation.[18l,65]

5.12.9. (*R*)-3-Hydroxy-3-methylpentyl benzoate (4i)[18k]



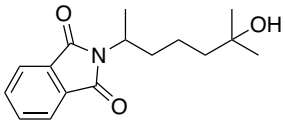
This compound was synthesized according to typical procedure 5.11.1 using **1f** (8 mM in HFIP under N_2, 125 μL, 1 μmol, 0.5 mol%), HFIP (75 μL), H_2O_2 (3.0 equiv), and $MgSO_4$ (60 mg) for 12h, and purified by column chromatography on silica gel (*n*-hexane/AcOEt, 1/0 to 4/1) to give 58% yield as a colorless oil (recovered starting material: 21%). Enantiomeric excess was determined to be 99% *ee* by HPLC (Daicel Chiralcel OB-H, hexane/2-propanol=95/5, flow rate 0.5 mL/min, λ=254 nm, t_R=28.0 min (major), t_S=30.9 min (minor)). NMR data was described in section 5.7.9.

5.12.10. (*R*)-3-Methyl-4-oxopentyl benzoate (4i')[18k]



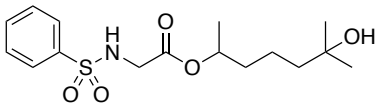
The reaction of **2i** also produced the regio-isomer **4i'** in 12% yield as a colorless oil. Enantiomeric excess was determined to be 99% *ee* by HPLC (Daicel Chiralcel OD-3, hexane/2-propanol=99/1, flow rate 0.5 mL/min, λ=254 nm, t_R=29.9 min (major), t_S=27.9 min (minor).); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 7.3 Hz, 2H), 7.57 (pseudo-t, *J* = 7.6 Hz, 1H), 7.45 (pseudo-t, *J* = 7.6 Hz, 2H), 4.34 (t, *J* = 6.6 Hz, 2H), 2.74 (ddq, *J* = 7.3, 7.0, 7.0 Hz, 1H), 2.25-2.15 (m, 1H), 2.19 (s, 3H), 1.79 (ddt, *J* = 7.0, 6.3, 6.3 Hz, 1H), 1.19 (d, *J* = 7.3 Hz, 3H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.5, 166.5, 133.0, 130.1, 129.5, 128.4, 62.9, 44.0, 31.4, 28.4, 16.6 ppm.

5.12.11. *N*-(6-Hydroxy-6-methylheptan-2-yl)phthalimide (4v)



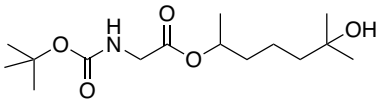
This compound was synthesized according to typical procedure 5.11.1 for 6h and purified by column chromatography on silica gel (*n*-hexane/AcOEt, 19/1 to 2/1) to give 84% yield as a colorless oil (recovered starting material: 4%).; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (dd, *J* = 6.1, 3.4 Hz, 2H), 7.70 (dd, *J* = 6.1, 3.4 Hz, 2H), 4.42-4.33 (m, 1H), 2.15-2.06 (m, 1H), 1.77-1.68 (m, 1H), 1.64-1.29 (m, 4H), 1.48 (d, *J* = 6.8 Hz, 3H), 1.16 (s, 6H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 133.8, 131.9, 123.0, 70.7, 47.2, 43.3, 34.1, 29.2, 21.3, 18.7 ppm.; HRESI-MS (m/z) [M + Na^+], calcd for $[C_{16}H_{21}NNaO_3]^+$ 298.1414, found: m/z = 298.1417.

5.12.12. 6-Hydroxy-6-methylheptan-2-yl (phenylsulfonyl)glycinate (4w)



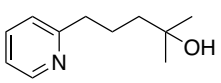
This compound was synthesized according to typical procedure 5.11.1 for 3h and purified by column chromatography on silica gel (*n*-hexane/AcOEt, 4/1 to 1/1) to give 81% yield as a colorless oil (recovered starting material: 3%).; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 6.8 Hz, 2H), 7.59 (dd, *J* = 7.6, 6.8 Hz, 1H), 7.52 (pseudo-t, *J* = 7.6 Hz, 2H), 5.49 (d, *J* = 2.9 Hz, 1H), 4.86 (tq, *J* = 12.4, 6.3 Hz, 1H), 3.76 (d, *J* = 5.9 Hz, 2H), 1.53-1.25 (m, 7H) 1.19 (s, 6H), 1.13 (d, *J* = 6.3 Hz, 3H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 139.3, 132.8, 129.1, 127.1, 73.0, 70.7, 44.3, 43.2, 36.0, 29.3, 29.1, 19.9, 19.7 ppm.; HRESI-MS (m/z) [M + Na^+], calcd for $[C_{17}H_{27}NNaO_5S]^+$ 366.1346, found: m/z = 366.1343.

5.12.13. 6-Hydroxy-6-methylheptan-2-yl (*tert*-butoxycarbonyl)glycinate (4x)



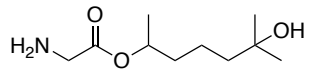
This compound was synthesized according to typical procedure 5.11.1 using **1f** (8 mM in HFIP under N_2, 125 μL, 1 μmol, 0.5 mol%) and HFIP (75 μL) for 6h, and purified by column chromatography on silica gel (*n*-hexane/AcOEt, 9/1 to 1/1) to give 74% yield as a colorless oil (recovered starting material: 9%).; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.08 (br-s, 1H), 5.00 (tq, *J* = 12.4, 6.3 Hz, 1H), 3.87 (br-s, 2H), 1.73-1.58 (m, 2H), 1.55-1.32 (m, 5H), 1.45 (s, 9H), 1.24 (d, *J* = 6.3 Hz, 3H), 1.20 (s, 6H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 155.7, 79.9, 72.1, 70.7, 43.3, 42.6, 36.2, 29.3, 29.1, 28.3, 20.0, 19.9 ppm.; HRESI-MS (m/z) [M + Na^+], calcd for $[C_{15}H_{29}NNaO_5]^+$ 326.1938, found: m/z = 326.1937.

5.12.14. 2-Methyl-5-(pyridin-2-yl)pentan-2-ol (4y)[16g]



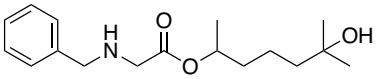
This compound was synthesized according to the procedure in section 5.10 for 6h and purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 1/0 to 19/1) to give 87% yield as a colorless oil (recovered starting material: 2%).; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51 (d, *J* = 4.9 Hz, 1H), 7.59 (dd, *J* = 7.6, 7.3 Hz, 1H), 7.15 (d, *J* = 7.3 Hz, 1H), 7.10 (dd, *J* = 7.3, 4.9 Hz, 1H), 2.81 (t, *J* = 7.6 Hz, 2H), 2.29 (br-s, 1H), 1.86-1.78 (m, 2H), 1.57-1.52 (m, 2H), 1.21 (s, 6H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, 149.0, 136.3, 122.8, 120.9, 70.7, 43.1, 38.3, 29.2, 24.5 ppm.

5.12.15. 6-Hydroxy-6-methylheptan-2-yl glycinate (4z)



This compound was synthesized according to typical procedure 5.11.2 for 6h and purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 19/1 to 4/1) to give 85% yield as a colorless oil (recovered starting material: 0%).; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.98 (tq, *J* = 12.4, 6.2 Hz, 1H), 3.40 (s, 2H), 1.61-1.20 (m, 9H), 1.20 (d, *J* = 6.3 Hz, 3H), 1.20 (s, 6H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.9, 71.5, 70.6, 44.1, 43.4, 36.3, 29.3, 29.2, 20.1, 19.9 ppm.; HRESI-MS (m/z) [M + H^+], calcd for $[C_{10}H_{22}NO_3]^+$ 204.1594, found: m/z = 204.1592.

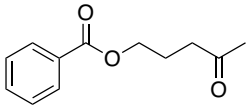
5.12.16. 6-Hydroxy-6-methylheptan-2-yl *N*-benzylglycinate (4aa)



This compound was synthesized according to typical procedure 5.11.2 for 12h and purified by preparative TLC (silica gel, CH_2Cl_2/MeOH: 14/1) to give 70% yield as a colorless oil (recovered starting material: 11%).; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.23 (m, 5H), 5.00 (tq, *J* = 12.4, 6.2 Hz, 1H), 3.80 (s, 2H), 3.38 (s, 2H),

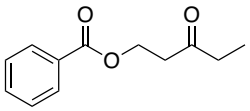
1.87 (br-s, 2H), 1.66-1.58 (m, 1H), 1.54-1.31 (m, 5H), 1.24 (d, J = 6.3 Hz, 3H), 1.20 (s, 6H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 139.4, 128.4, 128.2, 127.1, 71.5, 70.7, 53.2, 50.2, 43.4, 36.3, 29.3, 29.2, 20.1, 20.0 ppm.; HRESI-MS (m/z) [M + H^+], calcd for $[C_{17}H_{28}NO_3]^+$ 294.2064, found: m/z = 294.2065.

5.12.17. 4-Oxopentyl benzoate (4ab)[22c]



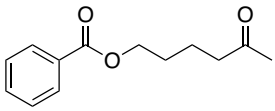
This compound was synthesized according to typical procedure 5.11.3 for 24h and purified by column chromatography on silica gel (*n*-hexane/AcOEt, 1/0 to 4/1) to give 56% yield as a colorless oil (recovered starting material: 7%).; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (d, J = 7.3 Hz, 2H), 7.57 (dd, J = 7.6, 7.3 Hz, 1H), 7.44 (pseudo-t, J = 7.6 Hz, 2H), 4.34 (t, J = 6.3 Hz, 2H), 2.61 (t, J = 7.3 Hz, 2H), 2.18 (s, 3H), 2.06 (tt, J = 7.3, 6.3 Hz, 2H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.6, 166.5, 132.9, 130.1, 129.5, 128.3, 64.1, 39.9, 30.0, 22.9 ppm.

5.12.18. 3-Oxopentyl benzoate (4ab')[22c]



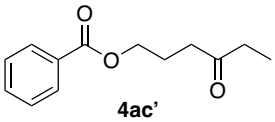
In the reaction of **2ab**, this compound was also obtained in 13% yield as a colorless oil.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, J = 7.8 Hz, 2H), 7.56 (dd, J = 7.8, 7.6 Hz, 1H), 7.43 (pseudo-t, J = 7.8 Hz, 2H), 4.60 (t, J = 6.3 Hz, 2H), 2.88 (t, J = 6.3 Hz, 2H), 2.51 (q, J = 7.3 Hz, 2H), 1.10 (t, J = 7.3 Hz, 3H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.4, 166.4, 133.0, 130.0, 129.6, 128.4, 60.0, 41.1, 36.4, 7.6 ppm.

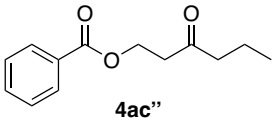
5.12.19. 5-Oxohexyl benzoate (4ac)[66]



The reaction was carried out under typical procedure 5.11.3 using **1f** (1 mol%), HFIP (500 μL), maleic acid (1 eq.), $MgSO_4$ (100 mg), and H_2O_2 (total 6.0 eq., added in 3 batch at 0, 3, 6 hours later after the start of the reaction) for 24h, and purified by column chromatography on silica gel (*n*-hexane/AcOEt, 19/1 to 4/1) to give 46% yield as a colorless oil (recovered starting material: 7%).; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, J = 6.8 Hz, 2H), 7.55 (dd, J = 7.8, 6.8 Hz, 1H), 7.44 (pseudo-t, J = 7.8 Hz, 2H), 4.33 (t, J = 6.1 Hz, 2H), 2.52 (t, J = 6.8 Hz, 2H), 2.15 (s, 3H), 1.79-1.72 (m, 4H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.4, 166.6, 132.9, 130.3, 129.5, 128.3, 64.5, 43.0, 29.9, 28.1, 20.2 ppm.

5.12.20. 4-Oxohexyl benzoate (4ac') and 3-Oxohexyl benzoate (4ac")[66]


4ac'

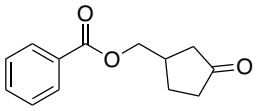

4ac"

In the reaction of **2ac**, these compounds were also obtained as the mixture in 36 % yield as a colorless oil. Respective yields were determined as **4ac'** and **4ac"** mixture with 6.5/1 ratio, determined by ^{1}H NMR analysis.; ^{1}H NMR (400 MHz, $CDCl_3$): **4ac'**; δ 8.02 (d, *J* = 8.3 Hz, 2H), 7.56 (dd, *J* = 8.3, 7.6 Hz, 1H), 7.56 (pseudo-t, *J* = 7.6 Hz, 2H), 4.33 (t, *J* = 6.3 Hz, 2H), 2.58 (t, *J* = 7.3 Hz, 2H), 2.45 (q, *J* = 7.3 Hz, 2H), 2.07 (tt, *J* = 7.3, 6.3 Hz, 2H), 1.07 (t, *J* = 7.3 Hz, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$): (**4ac'**) δ 210.3, 166.5, 132.9, 130.2, 129.5, 128.3, 64.2, 38.6, 36.0, 23.0, 7.8 ppm.

5.12.21. Cyclohexanone (4ad)

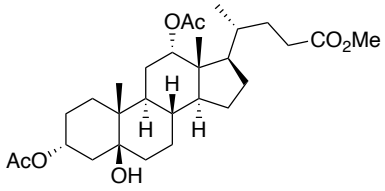
A typical procedure 5.11.3 for the reaction using **1f** (1 mol%), HFIP (400 μL), maleic acid (0.8 eq.), $MgSO_4$ (80 mg), and H_2O_2 (4.0 eq., in one batch) for 3h, this compound was obtained in 72% yield (100% conversion), determined by GC analysis.

5.12.22. (3-Oxocyclopentyl)methyl benzoate (4ae)[67]



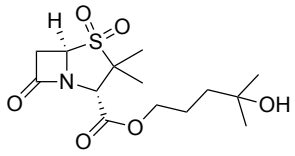
This compound was synthesized according to typical procedure 5.11.3 for 24h and purified by preparative TLC (silica gel, ^{i}Pr$_2$O) to give 42% yield as a colorless oil (recovered starting material: 0%).; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, *J* = 7.3 Hz, 2H), 7.58 (dd, *J* = 7.8, 7.3 Hz, 1H), 7.45 (pseudo-t, *J* = 7.8 Hz, 2H), 4.41-4.34 (m, 2H), 2.79-2.68 (m, 1H), 2.48 (dd, *J* = 18.5, 7.8 Hz, 1H), 2.42-2.33 (m, 1H), 2.30-2.20 (m, 2H), 2.12 (dd, *J* = 18.2, 9.1 Hz, 1H), 1.89-1.75 (m, 1H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 217.9, 166.4, 133.1, 129.9, 129.5, 128.4, 67.4, 41.8, 37.9, 36.0, 26.1 ppm.

5.12.23. (3*R*,5*S*,8*S*,9*S*,10*R*,12*S*,13*R*,14*S*,17*R*)-5-Hydroxy-17-((*R*)-5-methoxy-5-oxo-pentan-2-yl)-10,13-dimethylhexadecahydro-1*H*-cyclopenta[*a*]phenanthrene-3,12-diyl diacetate (4n)[58]



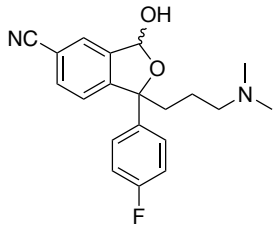
This compound was synthesized according to typical procedure 5.11.1 using HFIP (475 μL) for 6h, and purified by column chromatography on silica gel (*n*-hexane/AcOEt, 7/1 to 2/1) to give 81% yield as a colorless solid (recovered starting material: 2%). Characterization data was described in section 5.7.14.

5.12.24. 4-Hydroxy-4-methylpentyl (2*S*,5*R*)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0] heptane-2-carboxylate 4,4-dioxide (4af)[16j]



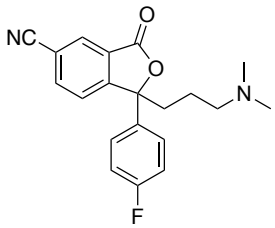
This compound was synthesized according to typical procedure 5.11.1 using **1f** (8 mM in HFIP under N_2, 125 μL, 1 μmol, 0.5 mol%), HFIP (375 μL), H_2O_2 (3.0 eq.), and $MgSO_4$ (60 mg) for 6h, and purified by column chromatography on silica gel (*n*-hexane/AcOEt, 2/1 to 1/3) to give 80% yield as a colorless oil (recovered starting material: 2%). $[\alpha]_D^{25}$ +151.2 (c = 1.05, $CHCl_3$); [ref.16j] $[\alpha]_D^{20}$ +125.9 (c = 0.83, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.64 (dd, *J* = 4.1, 2.0 Hz, 1H), 4.39 (s, 1H), 4.23 (t, *J* = 6.8 Hz, 2H), 3.51 (dd, *J* = 16.2, 4.1 Hz, 1H), 3.44 (dd, *J* = 16.2, 2.0 Hz, 1H), 1.83-1.76 (m, 2H), 1.62 (s, 3H), 1.54-1.50 (m, 3H), 1.43 (s, 3H), 1.24 (s, 6H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 166.9, 70.3, 66.8, 63.2, 62.6, 61.0, 39.5, 38.2, 29.3, 29.3, 23.5, 20.2, 18.5 ppm.

5.12.25. 1-(3-(Dimethylamino)propyl)-1-(4-fluorophenyl)-3-hydroxy-1,3-dihydroisobenzofuran-5-carbonitrile (4ag)[68]



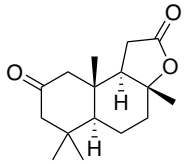
This compound was synthesized according to typical procedure 5.11.2 using **1f** (8 mM in HFIP under N_2, 125 μL, 1 μmol, 0.5 mol%), HFIP (375 μL), H_2O_2 (4.0 eq.), and $MgSO_4$ (100 mg) for 12h, and purified by column chromatography on NH silica gel (*n*-hexane/AcOEt/MeOH, 2/1/0 – 0/1/0 – 0/19/1) to give diastereo-mixed **4ag** (69% yield) as a colorless oil (recovered starting material: 5%).; ^{1}H NMR (400 MHz, $CDCl_3$): (diastereo mixture) δ 7.64-7.57 (m, 3H), 7.45 (dd, *J* = 7.8, 5.4, 1H), 7.33 (d, *J* = 7.3 Hz, 1H), 7.03-6.96 (m, 2H), 6.59-6.56 (comb-s and s, 1H), 2.49-2.06 (comb-s, s, and m, 10H), 1.64-1.26 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): (major) δ 162.0 (d, *J* = 246.6 Hz), 150.5, 141.1, 140.2, 133.1, 127.3, 126.7 (d, *J* = 7.4 Hz), 122.4, 115.4 (22.3 Hz), 112.0, 99.8, 90.1, 58.6, 44.7, 39.1, 22.0 ppm. (minor) δ 162.0 (d, *J* = 246.6 Hz), 150.3, 140.1, 139.3, 133.2, 127.4, 127.1 (d, *J* = 7.4 Hz),122.6, 118.4, 115.1 (22.3 Hz), 99.5, 90.6, 59.3, 45.1, 39.1, 22.0 ppm.; HRESI-MS (m/z) [M + Na^+], calcd for $[C_{20}H_{21}FN_2O_2]^+$ 341.1660, found: m/z = 341.1658.

5.12.26. 1-(3-(Dimethylamino)propyl)-1-(4-fluorophenyl)-3-oxo-1,3-dihydroisobenzofuran-5-carbonitrile (4ag')[69]



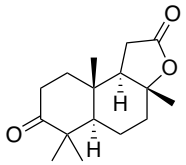
In the reaction of **2ag**, this compound was also obtained in 18% yield as a colorless oil.; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.92 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.64 (d, *J* = 7.3 Hz, 1H), 7.47-7.44 (m, 2H), 7.09-7.05 (m, 2H), 2.59-2.51 (m, 1H), 2.28-2.12 (m, 3H), 2.12 (s, 6H), 1.50-1.39 (m, 1H), 1.32-1.21 (m, 1H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.5, 162.7 (d, *J* = 248.3 Hz), 156.6, 137.4, 134.7 (d, *J* = 3.3 Hz), 130.1, 126.7 (d, *J* = 8.3 Hz), 126.5, 123.3, 117.1, 116.0 (d, *J* = 21.5 Hz), 113.9, 90.0, 58.7, 45.3, 37.6, 21.8 ppm.

5.12.27. 2-Oxo-sclareolide (4ah)[16b]



This compound was synthesized according to typical procedure 5.11.3 for 24 h, and purified by column chromatography on silica gel (CH_2Cl_2/Et_2O, 29/1 to 9/1) to give 48% yield as a colorless solid (recovered starting material: 0%).; $[\alpha]_D^{25}$ +55.53 (c = 1.52, $CHCl_3$); [ref.16b] $[\alpha]_D^{23}$ +44.3 (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.50-2.41 (m, 1H), 2.33-2.14 (m, 7H), 2.03 (dq, *J* = 14.1, 3.2 Hz, 1H), 1.80 (td, *J* = 12.4, 4.1 Hz, 1H), 1.70 (dd, *J* = 12.7, 2.4 Hz, 1H), 1.49 (qd, *J* = 13.3, 3.5 Hz, 1H), 1.35 (s, 3H), 1.09 (s, 3H), 0.93 (s, 6H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.2, 175.6, 85.6, 58.2, 56.5, 55.6, 54.9, 40.3, 38.6, 38.1, 33.2, 28.5, 22.6, 21.1, 20.7, 16.1 ppm.

5.12.28. 3-Oxo-sclareolide (4ah')[16b]



In the reaction of **2ah**, this compound was also obtained in 33% yield as a colorless solid.; $[\alpha]_D^{25}$ +82.49 (c = 1.00, $CHCl_3$); [ref.16b] $[\alpha]_D^{23}$ +64.8 (c = 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.63-2.45 (m, 2H), 2.48 (dd, *J* = 15.9, 14.4 Hz, 1H), 2.30 (dd, *J* = 16.3, 6.6 Hz, 1H), 2.14 (dt, *J* = 11.9, 2.8 Hz, 1H), 2.01 (dd, *J* = 14.9, 6.6 Hz, 1H), 1.84 (dt, *J* = 13.3, 2.8 Hz, 1H), 1.78-1.70 (m, 2H), 1.65-1.50 (m, 3H), 1.39 (s, 3H), 1.13 (s, 3H), 1.07 (s, 3H), 1.03 (s, 3H) ppm.; ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.5, 175.9, 85.6, 58.1, 54.3, 47.3, 37.7, 37.7, 35.5, 33.4, 28.6, 26.6, 21.4, 21.1, 20.7, 14.5 ppm.

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List of Publications

(1) “Iron-Catalyzed Asymmetric Inter- and Intramolecular Aerobic Oxidative Dearomatizing Spirocyclization of 2-Naphthols”
Takuya Oguma, Daiki Doiuchi, Chisaki Fujitomo, Chungsik Kim, Hiroki Hayashi, Tatsuya Uchida, and Tsutomu Katsuki
Asian J. Org. Chem. **2020**, *9*, 404–415.

(2) “Non-Heme-Type Ruthenium Catalyzed Chemo- and Site-Selective C–H Oxidation”
Daiki Doiuchi, Tatsuya Nakamura, Hiroki Hayashi, and Tatsuya Uchida
Chem. Asian J. **2020**, *15*, 762–765.

(3) “Recent Strategies in Non-Heme-Type Metal Complex-Catalyzed Site-, Chemo-, and Enantioselective C–H Oxygenations”
Daiki Doiuchi and Tatsuya Uchida
Synthesis, **2021**, *53*, 3235–3248.

(4) “Catalytic Highly Regioselective C–H Oxygenation Using Water as the Oxygen Source: Preparation of $^{17}O/^{18}O$-Isotope-Labeled Compounds”
Daiki Doiuchi and Tatsuya Uchida
Org. Lett. **2021**, *23*, 7301–7305.

(5) “Preparation of Oxysterols by C–H Oxidation of Dibromocholestane with Ru(Bpga) Catalyst”
Yui Fujii, Makoto Yoritate, Kana Makino, Kazunobu Igawa, Daiki Takeda, Daiki Doiuchi, Katsuhiko Tomooka, Tatsuya Uchida, and Go Hirai
Molecules, **2022**, *27*, 225.

(6) “Acid-Cooperative Oxygen Atom Transfer: Ruthenium(bpga) Catalyzed C–H Oxygenation”
Daiki Doiuchi, Nanako Shimoda, and Tatsuya Uchida
In preparation.

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