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Authors: Daiki Doiuchi, Tatsuya Nakamura, Hiroki Hayashi, and Tatsuya Uchida

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Non-Heme-Type Ruthenium Catalyzed Chemo- and Site-Selective C–H Oxidation

Daiki Doiuchi,[b] Tatsuya Nakamura,[b] Hiroki Hayashi[a] and Tatsuya Uchida*[a,c]

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[a] Prof. Dr. T. Uchida: 0000-0002-6511-5752, Dr. H. Hayashi: 0000-0003-2081-6886
Faculty of Arts and Science
Kyushu University
744, Motooka, Nishi-ku, Fukuoka, 819-0395, Japan
E-mail: uchida.tatsuya.045@m.kyushu-u.ac.jp
[b] D. Doiuchi, T, Nakamura
Department of Chemistry, Graduate School of Science
Kyushu University
744, Motooka, Nishi-ku, Fukuoka, 819-0395, Japan
[c] Prof. Dr. T. Uchida
International Institute for Carbon-Neutral Energy Research (WPI-I2CNER)
Kyushu University
744, Motooka, Nishi-ku, Fukuoka, 819-0395, Japan

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Abstract: Herein, we developed a Ru(II)(BPGA) complex that could be used to catalyze chemo- and site-selective C–H oxidation. The described ruthenium complex was designed by replacing one pyridyl group on tris(2-pyridylmethyl)amine with an electron-donating amide ligand that was critical for promoting this type of reaction. More importantly, higher reactivities and better chemo-, and site-selectivities were observed for reactions using the *cis*-ruthenium complex rather than the *trans*-one. This reaction could be used to convert sterically less hindered methyne and/or methylene C–H bonds of a various organic substrates, including natural products, into valuable alcohol or ketone products.

Since C–H bonds are the stable and ubiquitous backbones of every organic molecule, their functionalization *via* chemo- and site-selective methods has been the focus of research interest. C–H bond functionalization is an extremely powerful and useful tool in organic synthesis because C–H bond oxidation reactions offer a step-economic strategy for the construction of organic molecules.[1,2] It is well known that various enzymes, such as iron-containing heme- and non-heme proteins, are capable of catalyzing C–H oxidation reactions with almost complete chemo- and site selectivity (Scheme 1, a).[3-8] As a result, various bio-inspired catalysts have been developed (Scheme 1, b), in particular, metalloporphyrins, which are typical heme oxygenase enzymes; one such well-documented example is the *cytochrome* P450 family of enzymes.[3,5] Non-heme enzymes, such as methane monooxygenase and α-ketoglutarate-dependent oxygenase, are also known to activate aliphatic C–H bonds.[4,6-8] Que and coworkers reported using a non-heme model complex, namely, (μ-oxo)diferric(TPA) [TPA: tris(2-pyridylmethyl)amine], to catalyze alkane C–H oxidation.[6] As a remarkable demonstration of artificial non-heme-type catalysts, iron-PDP [PDP: N,N′-bis(2-pyridylmethyl)-2,2′-bipyrrolidine] complexes were shown to exhibit superb site selectivity during the C–H hydroxylation of complex molecules and natural products.[7] Since the publication of this pioneering report, numerous methods utilizing iron and manganese complexes to effect change have been developed.[4,8] However, these reactions often suffer from catalyst degradation via oxidative decomposition or dimerization, necessitating the use of a high catalyst load in order to accomplish results.[9] An alternative method for achieving high reactivity, selectivity, and catalytic durability for C–H bond oxidations is sorely needed. As such, various types of catalytic methods, structures, and the electronic nature of non-heme enzymes have become attractive targets for research and development in this field. Moreover, biomimetic oxidation mechanisms, hydrogen atom transfer (HAT) reactivity of metal(oxo) intermediates, and putative reactive species in a reaction are all enhanced by the presence of better electron-donating axial ligands on the catalyst.[10] Typical non-heme model catalysts have an electron-donating nitrogen atom at the apical site and are thus expected to improve HAT reactivity. Major advancements have been made in the development of iron or manganese catalysts in this field,[6-8] and ruthenium complexes[11,12] have also attracted much attention owing to their extensive redox and coordination chemistry. Thus, we were intrigued by the use of non-heme-type ruthenium complexes as catalysts for C–H oxidation. In this study, we found that the newly designed ruthenium(II)[bis(2-pyridylmethyl)glycinamide] [Ru(II)(BPGA)] complex exhibited excellent catalytic activity and site selectivity (Scheme 1, c).

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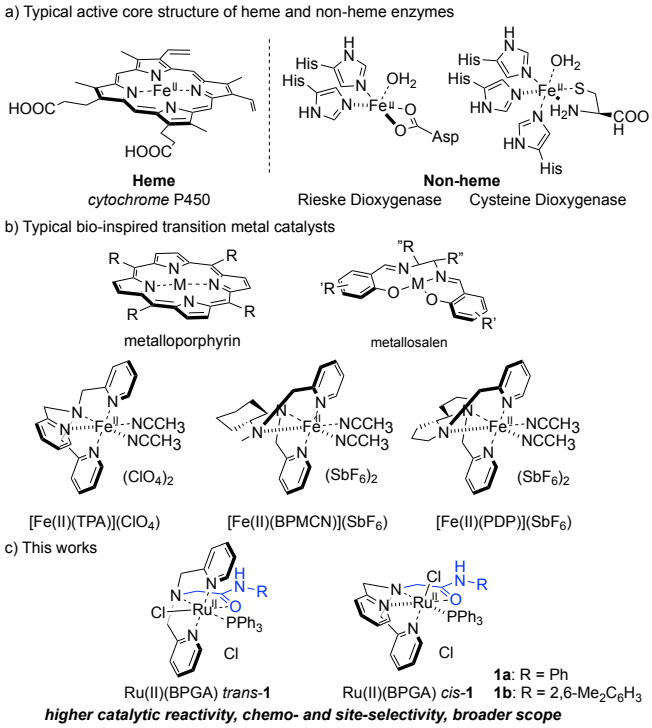
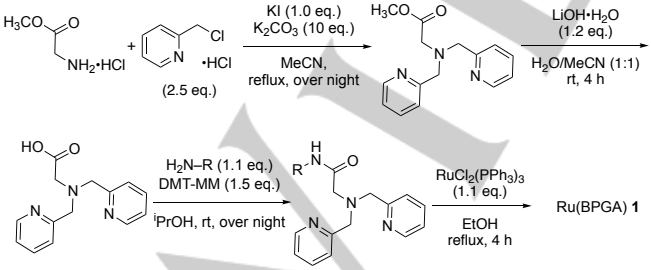


Scheme 1. Bio-inspired transition metal catalyst.

To prepare the ruthenium complexes, a series of BPGA ligands was synthesized from 2-chloromethylpyridine hydrochloride, glycine methyl ester hydrochloride, and various anilines in three steps: 1) *N*,*N*-2-pyridylmethylation,[13] 2) hydrolysis of the ester, and 3) a dehydrating condensation (Scheme 2). Then, *trans*- and *cis*-Ru(II)(BPGA) complexes **1** were obtained *via* the simple treatment of the ligand with $RuCl_2(PPh_3)_3$ in ethanol under reflux conditions. Single-crystal X-ray analysis of the *trans*- and *cis*-Ru(II)(BPGA) complexes of **1** clearly revealed that the two nitrogen atoms of the pyridine units were in *cis* or *trans*-positions relative to each other (Figure 1). The resulting *trans*- and *cis*-**1a** complexes exhibited the ability to reversibly couple reaction with Ru(II)/Ru(III) in 0.24 and 0.27 V *versus* Fc/Fc^+ in CH_2Cl_2, respectively.[14]



Scheme 2. Preparation of Ru(II)(BPGA) complexes **1**.

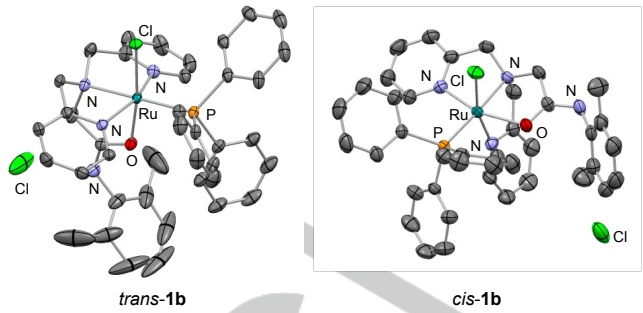
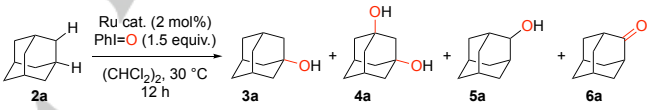


Figure 1. ORTEP diagram of *cis*-**1b** and *trans*-**1b**.

The catalysis of Ru(II)(BPGA) **1a** and Ru(II)(TPA) complexes for the C–H oxidation of adamantane **2a** as the model substrate was conducted (Scheme 3). In this case, both *trans*- and *cis*-Ru(II)(BPGA) **1a** exhibited better catalytic activity than Ru(II)(TPA), in particular, *cis*-**1a**, which produced 1-adamantanol **3a** in much higher yields with excellent chemoselectivity and site selectivity when compared with its *trans*-**1a**. Initial reaction analysis indicated that C–H oxidation using *trans*- and *cis*-**1a** as the catalyst experienced different reaction rates. There was no interconversion between *trans*-**1a** and *cis*-**1a** during C–H oxidation; this indicated that the ruthenium(oxo) derivatives from the *cis*-isomer and iodosylbenzene (PhI=O), which acted as the terminal oxidant, were the primary active species in this reaction (Figure 2).[11c]



[Ru(TPA)(PPh$_3$)Cl]Cl; **3a**: 11%, **4a**: 0%, **5a**: 0%, **6a**: 0.4%, 3°/2° = 24/1
trans-**1a**; **3a**: 26%, **4a**: 0.4%, **5a**: 0.4%, **6a**: 1.1%, 3°/2° = 25/1
cis-**1a**; **3a**: 53%, **4a**: 2.1%, **5a**: 0%, **6a**: 1.4%, 3°/2° = 42/1

Scheme 3. Preliminary studies ruthenium-catalyzed C–H oxidation. Reactions were conducted with **2a** (0.1 mmol), Ru-cat. (2.0 μmol), and PhI=O (0.15 mmol, 1.5 equiv.) in $(CHCl_2)_2$ (0.2 M) at 30 °C for 12 h.

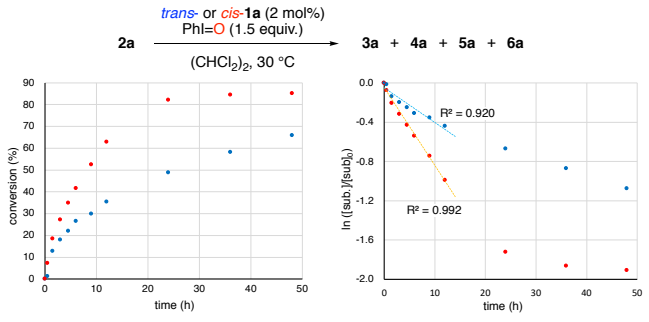


Figure 2. Monitoring *trans*-**1a** and *cis*-**1a**-catalyzed C–H hydroxylation of adamantane **2a**.

Based on these results, the optimization of C–H oxidation of adamantane **2a** was conducted (Table 1). Initial examination of the catalyst revealed that the ruthenium complex *cis*-**1b** bearing 2,6-dimethylaniline unit exhibited slightly higher reactivity than all the other ruthenium complexes (entry 1).[14] Moreover, the

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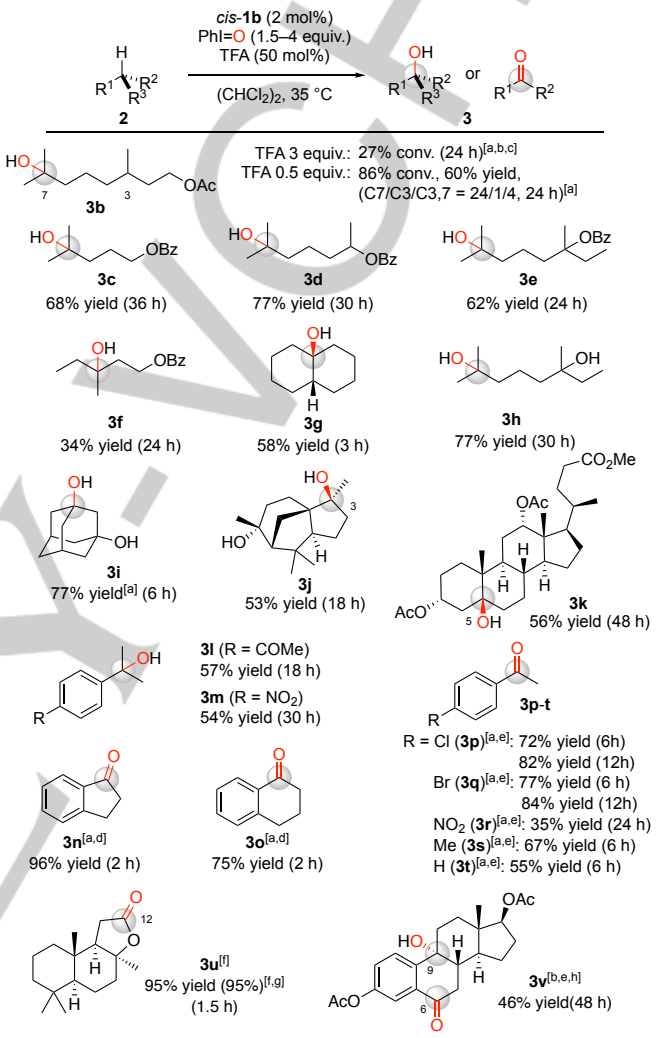
addition of trifluoroacetic acid (TFA) enhanced reaction rate without the diminishing chemo- and site-selectivities (entry 2). Although the exact mechanistic details of how the addition of acid affects the reaction are unclear at present, it is theorized that the acids disassemble the relatively less-soluble oligomeric PhI=O to generate a soluble monomer,[15] and enhance the reactivity of the putative ruthenium(oxo) species.[16] Increasing the amount of TFA in the reaction dramatically improved the desired C–H hydroxylation process (entries 3-5).

Table 1. Investigation of Ru(II)(BPGA) *cis*-**1b**-catalyzed C–H hydroxylation of adamantane **2a**.[a]

entry	Ru-cat.	additive	**3a** / **4a** / **5a** /**6a** (%)[b]	3°/2°[c]
1[d]	*cis*-**1b**	–	59 / 2.9 / 0 / 1.5	43/1
2	*cis*-**1b**	CF_3CO_2H (0.25 equiv.)	46 / 1.7 / 0 / 1.1	44/1
3	*cis*-**1b**	CF_3CO_2H (0.50 equiv.)	61 / 4.6 / 0 / 1.7	41/1
4	*cis*-**1b**	CF_3CO_2H (1.0 equiv.)	71 / 12 / 0 / 2.2	43/1
5	*cis*-**1b**	CF_3CO_2H (3.0 equiv.)	77 / 8.4 / 0.6 / 1.6	43/1

[a] Reaction were run with **2a** (0.1 mmol), *cis*-**1b** (2.0 μmol), and PhI=O (0.15 mmol, 1.5 equiv.) in $(CHCl_2)_2$ (0.2 M) at 30 °C for 1 h, unless otherwise noted. [b] Yields were determined by GC Analysis. [c] Regioselectivities were determined as follows; 3°/2° = **3a**(%) + 2x**4a**(%) / **5a**(%) + **6a**(%). [d] Run for 12h.

We conducted further the C–H oxidation of various substrates using *cis*-**1b** as the catalyst with PhI=O as the terminal oxidant (Scheme 4). The reaction of (±)-dihydrocitronellol acetate **2b** with 3.0 equiv. of TFA and 1.5 equiv. of PhI=O at 30 ˚C gave the 7-hydroxy compound **3b** as the major product in a good site-selective manner in 27% conversion. Fortunately, the chemical yield of **3b** could be improved to 60% in a C7/C3/C3,7 = 24/1/4 by the loading 0.5 equiv. of TFA and using 2.5 equiv. of PhI=O at 35 ˚C. Under these conditions, various carbohydrates could be oxidized at the sterically less-hindered 3˚ C–H bonds to hydroxy group with excellent site-selectivities. From alkylbenzoate derivatives (**2c**-**2f**), the corresponding *tert*-alcohols (**3c**-**f**) could be obtained with acceptable yields, respectively. The sterically less-hindered **2c**-**e** exhibited better reactivity than its counterpart **2f**. Cyclic substrate such as *cis*-decalin **2g** was underwent stereospecific 3˚ selective C–H oxidation. The reactions of *tert*-alcohols (**2h** and **2i**) also contained methyne C–H bonds and underwent transformation. Moreover, complex **1b**-catalyzed C–H oxidations could be applied to late-stage functionalization of highly complicated natural products. Cedrol **2j** could be oxidized at the C3 position in 53% yield, whereas the hydroxylation of the deoxycholic acid derivative **2k** was proceeded at the C5 in 56% yield. This type of C–H oxidation also converted benzylic methyne and methylene C–H bonds to their corresponding *trat*-alcohols and ketones. Cumene derivatives (**2l** and **2m**) could be obtained the corresponding *tert*-alcohols in good yields. The catalytic C–H bond oxidation can convert methylene C–H bonds to the corresponding ketones. Indan **2n** and 1,2,3,4-tetrahydronaphthalene **2o** were also compatible with the reaction conditions and could be converted to 1-indanone **3n** and 1-tetralone **3o** in a chemoselective manner, respectively. Under *cis*-**1b**-catalyzed oxidation, overoxidation products such as hydroxyketones and diketones were observed in only trace amounts. A series of ethyl benzene derivatives **2p–t** could be afforded to the corresponding ketone products **3p–t** in good to high yields. Under the catalytic conditions, (–)-ambroxide **2u** obtained (+)-sclareolide **3u** as a sole product even on 1.0 mmol scale. β-Estradiol diacetate **2v** could be oxidized benzylic methyne and methylene C–H and gave 9-hydroxy-6-keto β-estradiol derivatives as the major product.[17]



Scheme 4. Substrate scope of *cis*-**1b**-catalyzed C–H oxidation. Reactions were conducted with **2** (0.2 mmol), *cis*-**1b** (2 mol%), TFA (0.5 equiv.) and PhI=O (2.5 equiv.) in $(CHCl_2)_2$ (0.4 M) at 35 °C for 1.5-48 h, unless otherwise noted. [a] Determined by GC analysis. [b] Run on a 0.1 mmol scale. [c] Run with PhI=O (1.5 equiv.) in $(CHCl_2)_2$ (0.2 M) at 30 °C. [d] Run with PhI=O (2.0 equiv.). [e] Run with PhI=O (4.0 equiv.). [f] Run with PhI=O (3.0 equiv.). [g] Run on 1.0 mmol scale. [h] Run without TFA in $(CHCl_2)_2$ (0.2 M).

We investigated the oxidation of cyclobutanol in order to gain mechanistic insight into the route to the present C–H hydroxylation. Under oxidation conditions, cyclobutanone was formed as the major product, and no ring opening products were observed.[18] This observation indicated that Ru(II)(BPGA) *cis*-**1b**-catalyzed C–H oxidation was underwent via hydrogen atom transfer with a two-electron oxidation process.[18c]

In summary, a durable non-heme Ru(II)(BPGA) *cis*-**1b** was constructed with the aim of achieving high methyne C–H bond selective oxidation *via* the addition of TFA. Ru(II)(BPGA) complex

cis-**1b**-catalysed oxidation selectively proceeded at the sterically less-hindered tertiary C–H bond with high chemoselectivity. Notably, late-stage C–H oxidation of highly complicated molecules also proceeded in a highly chemo- and site-selective manner. Based on the mechanistic studies, *cis*-**1b** catalyzed the two-electron oxidation of the C–H bonds. Although further insight into the mechanism must be obtained through additional kinetic and control studies, the present research has opened a new way toward the step-economic synthesis of alcohols.

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Keywords: C–H oxidation• Non-Heme model • Hydroxylation• Ruthenium • Site-selective oxidation

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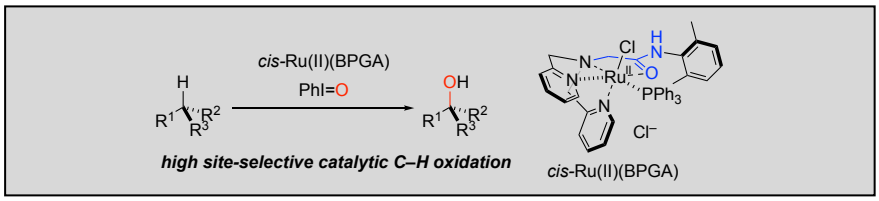

Non-heme ruthenium catalysis for selective C–H oxidation is described. The newly designed *cis*-Ru(BPGA) complex bearing a glycinamide unit promotes oxidation of methyne and methylene C–H bonds selectively with iodosylbenzene as the terminal oxidant. The catalytic system can be applied for a wide range of organic molecules including natural products to provide valuable alcohols or ketones with high chemo- and site-selectivity.