Development of Highly Chemoselective Oxidative Transformations by Designing Organoradicals

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To conduct organic synthesis in the field of pharmaceutical science, methodologies that can easily and quickly supply compounds with high drug-likeness are highly desirable. Based on the original catalyst design concept “Radical-Conjugated Redox Catalysis (RCRC)” established during my research, various C(sp³)–H functionalizations and protein modifications have been developed, taking advantage of the high reactivity and chemoselectivity of the single-electron transfer process. This review focuses on the eight-year research efforts by my collaborators and me, from conception to results.

Key words radical; redox catalysis; late-stage functionalization; C–H functionalization; bioconjugation; chemoselectivity

1. Introduction

Given the continuously decreasing success rate for the pharmaceutical development of small-molecule drugs in recent years,¹ synthetic organic chemistry is facing tough challenges. However, late-stage diversification (LSD) is a promising method that quickly increases structural diversity and endows lead compounds with new functionality, while simultaneously ensuring their ongoing biocompatibility and medicinal efficacy.² The application of LSD to carbon–hydrogen (C–H) bond functionalization processes should have a significant impact on addressing global obstacles in both medicinal and process chemistry. Moreover, the facile incorporation of sp³ carbons into existing drug structures via LSD would be especially attractive, as this often improves the survival rate of small-molecule drugs in clinical trials.³ Moreover, the scope of LSD is not limited to the derivatization of small-molecule drugs. For example, antibody–drug conjugates (ADCs),⁴ which are obtained from the conjugation of small-molecule drugs to antibody drugs, serve as a good example of how LSD may improve the original medicinal functionality of biomacromolecules.

C(sp³)–H functionalizations and protein modifications require high selectivity and reactivity, as well as biocompatibility (aqueous solvents, neutral pH, room temperature, and atmospheric conditions). Furthermore, the selective transformation of a specific C–H bond or functional group in the presence of several similar such moieties is currently a challenging academic issue.

In order to simultaneously realize these reaction types, which look different at a glance, I have paid attention to the “single electron transfer process” for the strategic discovery of various catalytic reaction systems that satisfy such criteria (Fig. 1). In this review, I have introduced in three chapters the current results of my research over the last eight years.

2. Cross-Dehydrogenative Coupling Reactions Promoted by “Radical-Conjugated Redox Catalysis (RCRC)”

Development of a methodology to convergently supply compounds having an enriched number of sp³ carbons is an important research subject which, from the standpoint of basic science, can contribute to improving the success rate of drug development.²,⁵ Cross-dehydrogenative coupling (CDC) reactions⁶ that can oxidatively convert two C(sp³)–H bonds to a C–C bond is particularly attractive for this purpose. However, when I began my research, the field of CDC reactions was immature, especially in view of its applicability to functional group-enriched substrates, the functionalization of chemically inert C–H bonds, the utilization of molecular oxygen as a terminal oxidant, and in...
controlling chemo-, site-, and stereoselectivity.

For the strategic development of reactions with high chemoselectivity and reactivity, I focused on single-electron-transfer processes and the design of organoradical species. As a result of my research, I have proposed "radical-conjugated redox catalysis (RCRC)" (Fig. 2) as a new concept for the design of catalytic systems. Here, the conceptual importance is the generation of electrophilic species via a mechanism that involves two orthogonal one-electron oxidations ([1e+1e] oxidation), which is accomplished by cooperation between a first-row transition metal and an organoradical. A catalyst screening based on this concept should lead to the discovery of various LSD-type reactions that are highly reactive, tolerant towards functional groups, and encourage the strategic use of inexpensive first-row transition metal catalysts.

The catalyst-development research encouraged by the discovery of the RCRC concept furnished various catalytic CDC reactions that target C(sp^3)–H bonds to produce functional-group-enriched molecules. Some representative examples are described below.

### 2.1. Catalytic Migratory Oxidative Coupling of Nitrones

The RCRC concept is inspired by the copper-catalyzed CDC reaction of benzyl nitrones and ethers/amines, found serendipitously in 2011^8–10^ (Fig. 3). This CDC reaction proceeded quickly, with high functional group tolerance at room temperature, convergently producing functionalized building blocks, even in aqueous media. In particular, substrates that formed continuous tetrasubstituted carbons (3bb), the introduction of a strained ring (3bg), and substrates having unstable functional groups under oxidizing conditions such as terminal alkyne (3ap), an unprotected hydroxyl group (3ar), indole (3au), and phenol (3av), were found to be acceptable. These examples demonstrate that the catalyst system shows high reactivity under mild conditions.

Various experiments were carried out to pursue this reaction mechanism (Fig. 4). Experiments using radical clock substrates 2m and 2n revealed that any product with an opened cyclopropane ring could not be isolated. In substrate 2w, which has an unprotected hydroxyl group at four carbons apart from the reaction site, the coupling reaction did not proceed: only the intramolecular cyclization occurred to form the five-membered spiroorthoester. When the substrate 2j was treated in the absence of nitrones, a dimerized product through C–H arylation at the p-methoxyphenyl (PMP) group was obtained. Under standard conditions, the CDC reaction proceeded between diethyl malonate and 2a. All these results support the idea that a carbocation intermediate was generated at the reaction site rather than carbon radicals.

Based on these results, a catalyst cycle shown in Fig. 5 was proposed. Initially, Cu(I) and tert-butylhydroperoxide (TBHP) underwent a Fenton reaction, producing Cu(II) and an alkoxyl (or hydroxy) radical. The thus-generated alkoxyl radical homolytically cleaved the C–H bond of ethers/amines, and Cu(II) oxidized the lone pair on the heteroatom in a single electron manner, thereby producing a carboxylation intermediate and Cu(I). Kinetic isotope effect experiments suggest that cleavage of the C–H bond of ethers/amines is the rate-determining step (rds). The C–C bond formation occurred following a nucleophilic attack of the nitrones toward the carbocation.

Key to this catalytic cycle is the cooperative work of oxyl radicals and Cu(II), which respectively promoted one-electron oxidations, leading to a two-electron oxidation of the substrate ([1e+1e] mechanism).

### 2.2. Catalytic β-C–H Functionalization of Amines

The catalytic β-C–H functionalization of amines should open new research avenues toward concise synthetic pathways of β-substituted (cyclic)amines, a ubiquitous structural motif in small-molecule drugs. The above-mentioned reaction can be regarded as a catalytic reaction that promotes the transformation of an α-C(sp^3)–H bond of ethers/amines to a C–C bond in the presence of the nucleophile (nitrone). If the iminium cation generated from the amine substrate by the RCRC system can be converted to a nucleophilic enamine via deprotonation, substituents can be introduced to the β-position with proper electrophiles (Fig. 6).

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**Biography**

Kounosuke Oisaki was born in 1980 in Tokushima, Japan, and received his B.Sc. (2003), M.Sc. (2005) and Ph.D. (2008) from the University of Tokyo under the direction of Professor Masakatsu Shibasaki. He then moved to the University of California, Los Angeles as a JSPS postdoctoral fellow under Professor Omar M. Yaghi. In 2010, he returned to Japan and joined Professor Motomu Kanai's group at the University of Tokyo as an assistant professor. In 2016, he was promoted as a lecturer. Dr. Oisaki has received several awards, including the SSOCJ FUJIFILM Award (2012), the Chemical Society of Japan Presentation Award [Academic] (2014), the Chemical Society of Japan Lecture Award for Young Chemists (2017), the Pharmaceutical Society of Japan Award for Young Scientists (2018), and Mitsui Chemicals Catalysis Science Award of Encouragement (2018). His current research interests include catalytic methodologies for complex organic molecule syntheses, peptide and protein chemistry, biorientational transformations, and medicinal chemistry of small organic molecules and chemically modified biologics.
After several investigations, the dehydrogenative β-functionalization of amines bearing a bulky substituent (mesityl group) could be achieved using nitroalkene catalyzed by a Fe–peroxide system \(^{11}\) (Fig. 7). The reaction proceeded with good yield for β-aryl nitroalkene (5a–5j), β-alkyl nitroalkene (5k–5l), and α,β-disubstituted nitroalkene (5m). If a substrate is prone to overoxidation (4b–4d), excessive use is required to produce high yield. If the substrate includes a γ,γ-dimethyl substitution (4g), the unreacted enamine was able to be isolated under this condition, suggesting that this reaction proceeded via an enamine intermediate. Since the product from acyclic amine (4k–4m) was unstable, reduction of the product enamine was essential in order to isolate the β-functionalized amines. The reaction proceeded even on 4n, having a 2,6-dimethyl-4-methoxyphenyl group which can be removed under oxidation conditions, producing a β-substituted secondary amine 7 after reduction and deprotection. When amine 8, having a N-cyclopropyl group, was subjected to the conditions, cinnamaldehyde was obtained via cyclopropane opening. This result suggested that the aminyl radical cation was generated by one electron oxidation of amine.

The plausible catalytic cycle is shown in Fig. 8. First, Fe(II) and di-tert-butylperoxide (TBP) underwent a Fenton reaction, producing Fe(III) and an alkoxy radical. Fe(III) oxidized a lone pair of amine 4 in a single electron manner to give an aminyl cation radical intermediate. The alkoxy radical cleaved...
an α-C–H bond, by which an iminium cation intermediate and Fe(II) were reproduced, indicating an RCRC cycle involving [1e+1e] oxidation. Thus-generated iminium cation isomerized to enamine, then a β-substituted product was formed through Michael addition with nitroalkene.

2.3. Catalytic Aerobic Production of Imines Enabling an Asymmetric CDC Reaction

Although peroxide is used as the terminal oxidant in the above-mentioned reactions, the use of an environmentally benign and readily available molecular oxygen instead is a pressing, cutting-edge issue in the field of CDC reaction. A study based on the RCRC concept realized CDC-type carbon elongation at the α-position of amines using oxygen as the terminal oxidant.12)

The development of catalytic aerobic oxidation of amines to imines13) as a key process is challenging because the highly Lewis basic starting/target materials and byproduct water often cause deactivation of the metallic catalyst. Such aerobic oxida-
tion catalysts that proceed under mild conditions around room temperature with the aid of a first-row transition metal catalyst were almost unprecedented at the starting point of our research. As a prototype of a catalyst enabling this reaction, the Cu/TEMPO system\(^{14,15}\) which has been proven effective in the aerobic oxidation of alcohol, looked promising. To make the \(\text{N-oxyl radical conjugated with copper metal more active, keto-ABNO as an electron deficient N-oxyl radical with smaller steric hindrance was developed, inspired by the study of Iwabuchi}\(^{16}\) (Fig. 9). Keto-ABNO is a yellow crystalline solid that can be synthesized from commercially available compounds within three steps in a multigram scale. According to X-ray structural analysis, the N–O bond length in keto-ABNO is between the typical N–O single bond length (about 1.45 Å) and the N=O double bond length (about 1.20 Å). From

![Fig. 7. Catalytic Dehydrogenative \(\beta\)-Functionalization of Amines](image)

![Fig. 8. Plausible RCRC Cycle of \(\beta\)-C–H Functionalization of Amines](image)
the waveform and g value of ESR measurement, keto-ABNO was proven to exist as a stable N-oxyl radical, even under air. Cyclic voltammetry (CV) measurement of keto-ABNO also proved its reversible redox behavior and increased redox potential due to the inductive effect of the carbonyl group.

Once this new organoradical was available, aerobic oxidation of amines to imines was investigated based on the RCRC concept. Adding 2.5 to 10 mol% of CuBr, bulky \( \text{Bu}_2\text{bipy} \) (or \( \text{iPr-PyBox} \)) as a ligand, keto-ABNO, and 4-(dimethylamino)-pyridine (DMAP) (three equivalents to copper), while suppressing deactivation by highly Lewis-basic and coordinating substrates, various amines, including aliphatic amines and...
Fig. 11. Direct Oxidative Transformation of Amines Catalyzed by the Cu/Keto-ABNO/O\textsubscript{2} System

Fig. 12. Plausible RCRC Cycle for the Cu/Keto-ABNO/O\textsubscript{2} System
primary amines, were able to be oxidized with high generality under mild conditions (room temperature to 50°C) (Fig. 10). Under these conditions, a tertiary amine was not oxidized. The product imines were highly sensitive to hydrolysis, so the isolated yield was significantly lower than the NMR yield.

Next, various oxidative C–C bond-forming reactions were developed through rapidly trapping the intermediate imines with a carbon nucleophile without isolation (Fig. 11). In the oxidative Friedel–Crafts reaction, an addition of indole and pyrrole proceeded by using co-existing silica gel as an imine activator (eqs 2, 3). A Danishefsky diene sensitive to oxidative conditions could also be used in the same vessel, proceeding to an unprecedented oxidative aza-Diels–Alder reaction in moderate yield (eq 4). Oxidative Strecker reaction also progressed by allowing the co-existence of HCN (eq 5). These conditions could also be extended to catalytic asymmetric reactions. The first catalytic asymmetric CDC reaction between amine and nitroalkane was carried out using a tertiary amine (Et₃N) as a co-catalyst, and (−)-Ph-Box as a chiral ligand with high diastereo- and enantioselectivity, to afford an α,β-diaminoacid surrogate (eq 6).

The catalytic cycle of amine oxidation in this reaction is proposed (Fig. 12, left). Cu(I), bulky bipyridyl ligand, and keto-ABNO formed a ternary complex in the system, and the copper was oxidized by molecular oxygen to produce A. After the copper amide intermediate B was formed via ligand exchange by an acid-base reaction between A and the substrate amine, the Cu–N bond was homolytically cleaved to give the aminyl radical intermediate C. This is also supported by radiocal clock experiments using 9p and 9r (Fig. 12, right). Subsequently, the α-hydrogen atom was transferred to keto-ABNO, forming an imine. As in Figs. 5 and 8, this amine oxidation also proceeded with a [1e+1e] mechanism of Cu(II)–N-oxyl radical conjugate, in accordance with the RCRC concept. 19)

The resulting complexes, D through E, were subjected to oxidation by molecular oxygen, and the catalytically active species A was regenerated. Adding DMAP improved the catalyst turnover by making the resting state, i.e., F, dominant, thus suppressing deactivation of the catalyst.20)

3. Site-Selective Aerobic C(sp³)–H Oxygenation Using N-Oxyl Radical Directing Activators

Site-selective functionalization of inert C–H bonds, especially at a remote site from functional groups, is one of the biggest academic challenges in developing new pharmaceuticals. The attempted approaches so far have relied mainly on metal-catalyzed conditions targeting C(sp²)–H bonds of substrates having directing groups.21) However, organoradical species activating C(sp³)–H bonds by a hydrogen atom transfer (HAT) process have increasingly been reported.22)

In our group, site-selective C(sp³)–H activation was investigated based on a strategy of using a directing activator (DA, a chemically reactive directing group) for an alcohol substrate.
Especially, DA with an electron-deficient N-oxyl radical showing HAT activity\(^{23}\) was designed, which is expected to be capable of being driven by molecular oxygen (Fig. 13).

After many investigations, the CF\(_3\)-substituted \(N\)-hydroxyisoindolinone DA was proved to be suitable for \(C(sp^3)\)–H oxygenation of aliphatic alcohol substrates under Co/Mn/O\(_2\).
conditions. The oxidation mainly proceeds at the γ-C–H bonds to produce ketones (K)\textsuperscript{23} (Fig. 14). Reactions proceeded more mildly at tertiary and benzylic C–H bonds. However, in Fig. 14, examples of oxidizing inert secondary C–H bonds are primarily represented. In the case of substrates having a longer alkyl chain, such as 11d, the δ-position also becomes a reaction site, but electron-withdrawing substituents deactivated neighboring C–H bonds, resulting in exclusive γ-selective oxygenation (11e–11g).

If this method could selectively produce oxygenation products with the oxidation state of alcohols, rather than ketones, it would be a more straightforward polyol synthesis. However, the alcohol moiety produced by secondary C(sp\textsuperscript{3})–H oxygenation exhibits much higher reactivity than the starting alkanes, and thus rapidly furnishes overoxidized ketones. Changing the reaction conditions of the DA-promoted aerobic C–H oxygenation from a metal catalyst system to a NO\textsubscript{x}–based system allowed the γ-selective installation of a nitroxy group (N), which can be regarded as an alcohol surrogate.\textsuperscript{25} Although the generality and selectivity of nitroxy/ketone (N/K) could still be improved, this proof-of-principle may help to solve the aforementioned problems regarding alcohols versus ketones.

Switching site-selectivity by modifying the structure of DA was also possible (Fig. 15). For example, when the oxygenation of 10m, which is a combination of 3-(4-ethylphenyl)-propan-1-ol and DA used in Fig. 14, was carried out under the co-catalyzed aerobic oxygenation condition, only the C–H bonds of the γ-position were selectively oxidized to produce 11m. On the other hand, if the substrate bound with long-arm DA 13 was placed under similar oxygenation conditions, ultra-remote C–H bonds were selectively oxidized to produce 14. Furthermore, the involvement of DA in site-selectivity

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Fig. 17. Serine-Selective Aerobic Cleavage of Peptide/Protein
(Color figure can be accessed in the online version.)
was also demonstrated. When intermolecular oxidation of the hydroxyl-protected 10m–Me or 13–TMES occurred with the corresponding N-hydroxyl activator (1 equiv), different site-selectivities were observed.

A plausible reaction mechanism is shown in Fig. 16. First, one-electron oxidation of N-hydroxy DA of starting material 10 was caused by the Co/O₂ system or NOₓ to produce the N-oxyl radical G. This species promoted HAT in proximity to a γ- (or δ-) C–H bond to generate the carbon radical H. After capturing H by molecular oxygen, alkyl peroxyradical I was produced. In the Co/O₂ system, decomposition by a cobalt catalyst finally produced 11(K) as the major product. In the NOₓ system, I was trapped by NO to produce the nitrosyl peroxide L. After homolytic cleavage, recombination produced 11(N) (route a), or HAT produced 11(K) (routes b and b').

After reporting these results, we tried to develop catalytic site selective C–H functionalization using a N-hydroxy HAT catalyst having a recognition group which holds alcohol substrates through dynamic covalent bonding. However, due to difficult synthesis of the N-hydroxy catalyst, such an optimization study has not yet been completed. In recent years, we...
have developed structurally novel HAT catalysts driven by a visible-light photoredox catalyst, which is more easily synthesized. Based on these new findings, investigations into the extended use of the organoradical as a site-selective C–H oxygennation catalyst are currently ongoing.

4. Chemoselective Protein Modifications Based on Organoradicals and Their Medicinal Application

Chemical transformation of proteins targeting proteinogenic amino acids is a powerful methodology that can append supranatural functions to biocompatible scaffolds or properly truncate/degrade unnecessary domains, with a wide range of possible applications such as biological control, analysis of biological phenomena, creation of biocompatible materials, and new modalities of therapeutics. However, a variety of reaction patterns are still insufficient to chemically transform proteins at will. Development of such chemical transformation of proteins will be the challenge of synthetic chemists, who are often accustomed to running reactions in organic solvents.

Proteins must be handled under physiological conditions, which are characterized by an aqueous solvent, at near neutral pH, ambient temperature and in a diluted concentration (mM or less). Furthermore, the development of protein modifications with high amino acid selectivity and positional selectivity remains a cutting-edge task, since proteins contain a number of polar functional groups with structural similarities.

We focused on the previously mentioned RCRC concept (Fig. 2), taking advantage of its high functional group tolerance and reactivity. By considering its further tolerance to Lewis base and water, a Cu/keto-ABNO/NO \(_2\) system was adapted to peptide substrates. As a result, we succeeded in developing a serine-selective oxidative peptide/protein cleavage reaction (Fig. 17). The optimized Cu/keto-ABNO/NO/NO \(_2\) system, with a water-soluble phenanthroline ligand, cleaves a peptide chain at serine residues, even to a small native protein (ubiquitin). This catalytic system selectively oxidizes the hydroxyl group of a serine side chain to produce an oxalimide intermediate, leading to mild hydrolysis (Fig. 18). However, because amide bonds are one of the most stable chemical bonds in nature, site-selective cleavage under nonenzymatic (artificial catalyst) conditions with high fidelity remains an ongoing challenge. Our newly proposed system makes such hydrolysis easier through the intermediate formed by chemoselective side chain oxidation.

During investigation of the serine-selective cleavage, we confronted a second serendipitous factor: keto-ABNO binds to the tryptophan side chain. Optimization based on this finding led to the metal-free tryptophan-selective bioconjugation of proteins. Most protein modifications target lysine/cysteine residues having highly reactive side chains. However, due to the high number of surface exposures and the difficulty in distinguishing side chain reactivity, lysine/cysteine modifications often produce complex mixtures. Moreover, many of the native cysteines form crosslinked S–S bonds to stabilize the protein structure. Cysteine bioconjugation requires reductive S–S cleavage, often affecting the tertiary structure of proteins.

In contrast, tryptophan has a unique characteristic. Tryptophan is contained in 90% of natural proteins, but its primary sequence content and surface exposure numbers are the smallest among proteinogenic amino acids. Since surface-exposed tryptophans exist in various local environments with a range of solvent accessibility, each tryptophan is easily distinguishable in the bioconjugation process. Therefore, tryptophan-selective bioconjugation can produce highly homogeneous conjugates. This is particularly important from the viewpoint of medicinal application.

By using optimized conditions (for example, the ABNO-NO/NO \(_2\) system) for protein modification, various functional small molecules (fluorescent molecules, biotin, anticancer agents) could be efficiently conjugated to protein tryptophan residues (Fig. 19). Depending on the protein, these reactions did not proceed efficiently. This is partly because the protein did not have surface-exposed tryptophans. When the same reaction was carried out after denaturation (aqueous HCl treatment), the reaction yield improved (e.g., Concavalin A, Subtilisin Carlsberg). Anti-A\(_\beta\) \(_{1–16}\) antibody (6E10) can be also modified by fluorescent molecules, and a dot blot assay demonstrated that binding ability to the antigen (A\(_\beta\)) was retained even after such modification.

From lysozymes, which have particularly high crystallinity, we were able to obtain the single crystal of keto-ABNO adduct, and succeeded in solving the atomic-level structure (Fig. 20). X-Ray crystallographic structural analysis revealed that the side chain of Trp62 mainly reacted in a diastereoselective manner. Since Trp62 has maximum surface exposure among tryptophans, the solvent accessibility of each tryptophan seems highly correlated with reactivity. The orientation of the tryptophan side chain in the local environment is also important in determining stereoselectivity. The higher order structure of modified protein remained almost unchanged.

Fig. 20. Crystal Structure of Lysozyme-Keto-ABNO Adduct at Trp62 (PDB: 5B59)

(Color figure can be accessed in the online version.)
from that of the native source. These results indicate that not only the native higher order structure but also the local environment/side chain conformation is reflected in the selectivity under the very mild conditions. It is also noteworthy that this tryptophan-selective bioconjugation produced conjugates sufficiently homogeneous to meet the high-level criteria of protein crystallography, requiring a high purity sample.

Currently, we are utilizing this Trp-selective bioconjugation reaction for drug discovery, namely, by applying it to the production of homogeneous antibody–drug conjugates (ADCs).^{40}

**Conclusion**

During the last eight years of research, I have discovered various chemoselective transformations based on single-electron-transfer processes, and have been involved in the design of organoradicals. The (catalytic) reaction systems thus developed, which include CDC reactions, site-selective C(sp^2)–H oxygenation, and chemoselective protein modification, are able to transform various drug-like compounds that range from small organic molecules to biomacromolecules. In addition, I am now developing chemically modified biologics by applying a highly practical novel protein bioconjugation method. Taken together, these results clearly demonstrate that basic research and innovative reaction design can open unprecedented routes to drug discovery.

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**Conflict of Interest**

The author declares no conflict of interest.

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