



## Digest Paper

# Chemoselective aerobic oxidation catalyzed by a metal/stable organoradical redox conjugate

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## ABSTRACT

This review summarizes recent advances of catalytic chemoselective aerobic oxidations promoted by a metal/stable organoradical redox conjugate. The sophisticated system exhibits high activity and chemoselectivity and is recently applied to late-stage transformations for complex natural product synthesis and a polypeptide transformation. The characteristics of the catalytic system are likely due to the unique mechanism ([1e + 1e] oxidation), which takes intrinsic advantages of cooperative work of first-row transition metals and stable organoradicals (radical-conjugated redox catalysis).

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## Chemoselectivity in current organic synthesis

Controlling chemoselectivity (preference of one of specific functional groups present in reactants) is one of the greatest challenges in synthetic organic chemistry.<sup>1</sup> Highly chemoselective reactions minimize the use of protective groups, realizing streamlined synthesis of complex molecules with high atom<sup>2</sup> and step economy.<sup>3</sup>

Late stage-functionalization of complex molecules<sup>4</sup> and chemical modification of biomacromolecules (including bioconjugation)<sup>5</sup> are emerging methodologies that are in high demand, and will provide new avenues for the development of medicinal leads and functional materials, as well as for chemical biology tools. These methodologies require highly sophisticated chemoselectivity.

Conventional strategies to furnish chemoselectivity include: (1) the use of protecting groups; (2) the use of innate reactivity differences between functional groups;<sup>6</sup> and (3) stoichiometric use of covalent directing groups.<sup>7</sup> Compared to such conventional strategies, catalyst-controlled chemoselectivity<sup>8</sup> has significant

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advantages, such as: (1) arbitrary control of the reaction site; (2) requirement of substoichiometric amounts of reagents, thereby minimizing waste; (3) avoidance of prefunctionalization of reactants.

In this review, we discuss catalytic chemoselective aerobic oxidation promoted by a metal/organoradical redox conjugate (aerobic version of radical-conjugated redox catalysis). Because there are several reviews of related topics,<sup>9,10</sup> here we discuss only representative reports highlighting the *chemoselectivity* of the catalytic system relying on *stable* organoradicals.

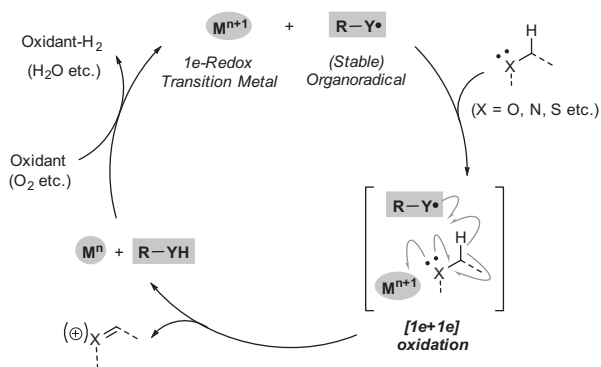
### Radical-conjugated redox catalysis

Many second- and third-row transition metal-catalyzed reactions are mediated by two-electron (2e) redox events as key processes, such as oxidative addition and reductive elimination.<sup>11</sup> Use of earth-abundant first-row transition metals in redox catalysis is less costly, but also less explored. First-row transition metals contain more one-electron (1e) transfer characteristics.

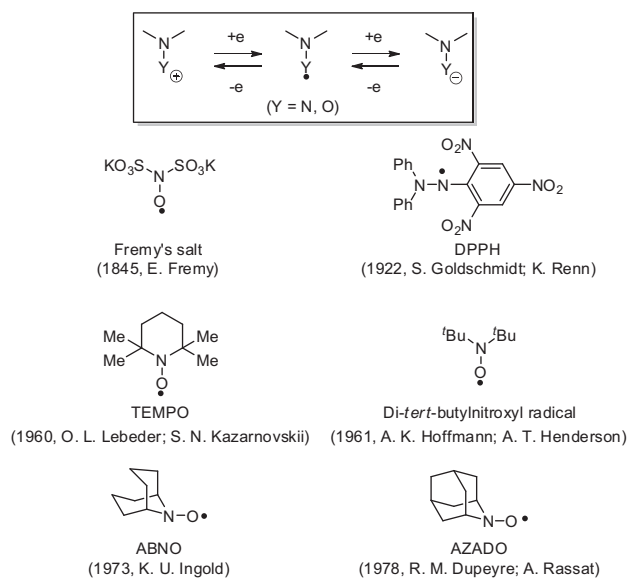
Here we describe a promising approach to deal with essential 2e redox events using first-row transition metals, *radical-conjugated redox catalysis* (RCRC). The conceptual catalytic cycle of RCRC is shown in Figure 1. If a 1e redox transition metal is conjugated with a (stable) organoradical functioning as a 1e oxidant, (orthogonal) double 1e redox events ([1e + 1e] oxidation process) will occur to form or break chemical bonds, especially a C(sp<sup>3</sup>)–H bond adjacent to a heteroatom of substrates. Subsequent reoxidation of the conjugate by terminal oxidants allows for catalyst turnover. RCRC may be categorized as an extended version of metal catalysis bearing redox non-innocent ligands.<sup>12</sup> It further provides the opportunity for more flexible and diverse catalyst design toward broader applications.<sup>13</sup>

The use of molecular oxygen (O<sub>2</sub>) in oxidative reactions is ideal in view of availability and economic/environmental benefits, but it remains challenging especially in industrial applications.<sup>14</sup> Safety issues are the major concern with regard to industrial applications; harsh conditions are generally required due to the kinetic inertness of ubiquitously present triplet O<sub>2</sub>, and undesired (sometimes explosive) side reactions by peroxide production are possible. RCRC might be a key basic concept for developing aerobic oxidations with high reactivity and functional group-tolerance under mild conditions, taking advantage of 1e redox events.

Stable and isolable organoradicals mediating reversible 1e redox events were developed in the 19th century,<sup>15</sup> and are utilized in catalytic aerobic oxidation (Fig. 2). The catalyst performance is tunable by structural modification. For example, changing the electron density of oxyl/nitronyl radicals can tune their oxidation potential and bond dissociation energy. Smaller steric



**Figure 1.** Catalytic cycle of (aerobic) oxidation promoted by radical-conjugated redox catalysis.



**Figure 2.** Stable radicals utilized for oxidative reactions.

hindrance around the radical is often beneficial to access substrates' reaction site. Steric tuning of oxyl/nitronyl radicals greatly affects the catalytic performance and chemoselectivity, even when a stable radical is used as a single-component oxidation catalyst.<sup>16</sup>

### Chemoselective aerobic oxidation of alcohols catalyzed by metal/stable radical conjugates

Oxidation of alcohols to aldehydes or ketones is an important transformation in organic chemistry. Practical aerobic oxidation of alcohols was recently intensively investigated.

Since the report by Brackman and Gaasbeek of aerobic oxidation of methanol to formaldehyde catalyzed by the Cu/di-*tert*-butylnitroxyl system in 1966<sup>17</sup> and the report by Semmelhack of the more general Cu/TEMPO system in 1984,<sup>18</sup> highly chemoselective aerobic oxidations of polyols and functional group-rich alcohols have been achieved by metal/stable radical conjugates.

In 2002, Knochel reported a Cu/TEMPO system using fluororous biphasic media with 2,2'-bipyridine bearing perfluorinated ponytails (P<sup>per</sup>Fbipy) as the ligand for Cu.<sup>19</sup> The primary alcohol moiety was oxidized selectively over the benzylic secondary alcohol moiety (Fig. 3). In 2003, Sheldon reported a Cu/TEMPO system in the presence of KO<sup>t</sup>Bu as a base in an aqueous solvent.<sup>20</sup> Benzylic alcohol was oxidized selectively over a secondary alcohol due to steric effects (Fig. 4). In 2005, Liang and Liu reported an Fe/TEMPO system with NaNO<sub>2</sub> as a cocatalyst.<sup>21</sup> Alcohols were oxidized selectively over sulfides, which are often reactive for transition metal-catalyzed oxidations (Fig. 5). In 2007, Sekar reported a DABCO–CuCl/TEMPO system.<sup>22</sup> The benzylic primary alcohol moiety was oxidized selectively over the benzylic secondary alcohol moiety (Fig. 6). They reported the following reactivity trend of oxidation: benzylic primary alcohols > allylic primary alcohols > benzylic secondary alcohols > aliphatic alcohols.

Recently, Stahl reported a highly practical Cu/TEMPO system using 2,2'-bipyridyl (bipy) as a ligand for Cu and *N*-methylimidazole (NMI) as a basic additive for chemoselective aerobic oxidation of primary alcohols.<sup>23</sup> This system is applicable to a broad range of primary alcohols, including allylic, benzylic, and aliphatic alcohols, to produce the corresponding aldehydes at room temperature under open air. High chemoselectivity was demonstrated by successful selective oxidation of unprotected diols (Fig. 7). In competition between primary and secondary alcohol moieties,

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