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Iminoxyl radicals *vs. tert*-butylperoxyl radical in competitive oxidative C–O coupling with β-dicarbonyl compounds. Oxime ether formation prevails over Kharasch peroxidation†

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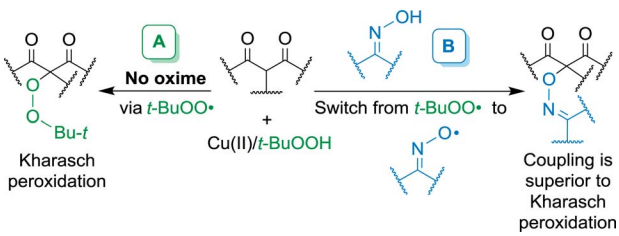
Oxidative coupling of oxime and β-dicarbonyl compounds dominates in a β-dicarbonyl compound/oxime/Cu(II)/*t*-BuOOH system; in the absence of oxime, oxidative coupling of *t*-BuOOH and a β-dicarbonyl compound (Kharasch peroxidation) takes place. The proposed conditions for oxidative coupling of oximes with dicarbonyl compounds require only catalytic amounts of copper salt and *t*-BuOOH serves as a terminal oxidant. The C–O coupling reaction proceeds *via* the formation of *tert*-butoxyl, *tert*-butylperoxyl and iminoxyl radicals. Apparently, *tert*-butylperoxyl radicals oxidize oxime into iminoxyl radical faster than they react with β-dicarbonyl compounds forming the Kharasch peroxidation product. Iminoxyl radicals are responsible for the formation of the target C–O coupling products; the yields are up to 77%.

Introduction

The development of selective processes of C–H functionalization and oxidative coupling (cross-dehydrogenative coupling, CDC) is one of the most rapidly developing areas of modern organic chemistry.[1–19] While cross-coupling reactions involving functional groups (–Hal, $-B(OR)_2$, $-SnR_3$, –ZnHal, MgHal, *etc.*) have already become classic methods for the formation of C–C and C–heteroatom bonds (heteroatom = S, N, O, P), cross-dehydrogenative coupling is a relatively new direction in the methodology of coupling, which meets such principles of green chemistry as atom-economy and step-economy.[3] CDC allows one to form the target chemical bond between molecules owing to selective cleavage of C–H and heteroatom–H bonds in the reagents without carrying out prefunctionalization.[4–19]

One of the most important problems in the realization of CDC is the selection of an oxidant that selectively cleaves certain C–H and heteroatom–H bonds. Stoichiometric or excess amounts of transition metal salts,[8–12] hypervalent iodine compounds[13–17] and DDQ[20,21] are often used as oxidants. The use of such oxidants increases the waste formation and cost of the product thus limiting the scalability of synthetic process. Important fundamental task in the development of CDC methods is the changeover from stoichiometric reagents to catalytic systems based on accessible and environmentally friendly oxidants, such as molecular oxygen and peroxides.[18,19] The use of low-cost and less-toxic transition metal salts of the 3d series as catalysts is preferable. An example of the implementation of these principles is the Cu(II)/*t*-BuOOH system, which was applied for the radical peroxidation of β-dicarbonyl compounds and their heteroanalogues through the formation of *tert*-butylperoxyl radicals (Kharasch reaction, Scheme 1, route A).[22,23] In the present work, it has been shown that a selective cross-dehydrogenative C–O coupling of β-dicarbonyl compounds with oximes occurs in the oxime/Cu(II)/*t*-BuOOH system (Scheme 1, route B) with an almost complete suppression of the competitive peroxidation process.

The proposed system is a convenient source of oxime radicals, which have found wide application in various processes of cyclization[24–38] and C–O coupling recently.[8,39] It should be noted that oxime radicals remain one of the least studied class of *N*-



Scheme 1 Kharasch peroxidation (A) and the discovered cross-dehydrogenative C–O coupling of β-dicarbonyl compounds with oximes (B).

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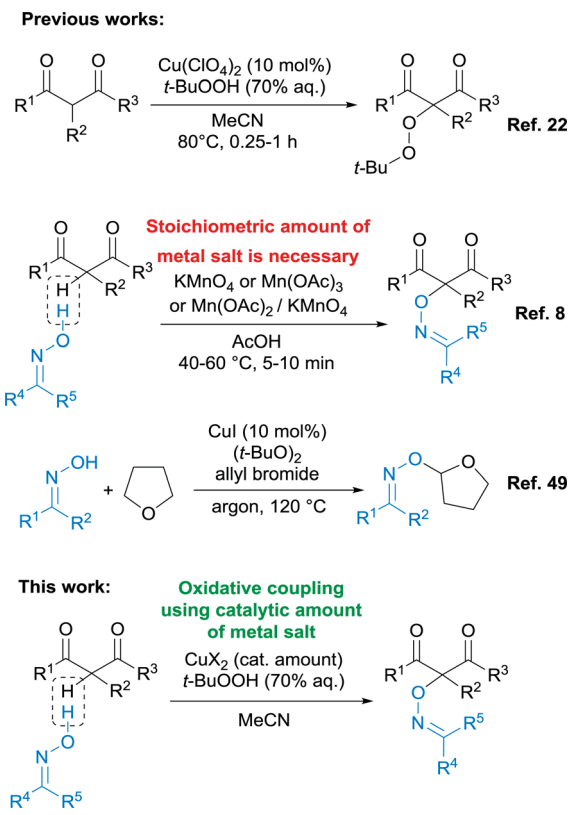
oxyl radicals, whereas amine-*N*-oxyl radicals and imide-*N*-oxyl radicals are used in numerous fields of chemistry, including oxidation methodology,[40–42] living radical polymerization,[40,43] spin-labeling,[44,45] organic magnetic materials design.[46]

Oximes are difficult substrates for CDC, since under the action of oxidants they give a complex mixtures of products, including dimers of oxime radicals,[47] or ketones.[48] Previously, the oxidative C–O coupling of oximes with β-dicarbonyl compounds and their heteroanalogues was carried out only with the use of stoichiometric amounts of metal-containing oxidants (Scheme 2).[8,9]

CDC processes of oximes with isochromanes[20] and derivatives of 1-phenylpropene[21] in the presence of stoichiometric amounts of DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) were also reported. The only example of a catalytic cross-dehydrogenative coupling involving oximes is CuI-mediated CDC with THF in the presence of an excess of allyl bromide and di-*tert*-butyl peroxide as a oxidant (Scheme 2).[49] The method is limited to the single structure of the CH-reagent (THF), which also plays the role of solvent.

The development of a convenient and green oxidative system for C–O coupling reactions involving oximes as O-reagents opens the short way to the synthesis of compounds containing a C=N–O fragment; such structures exhibit a wide range of biological activity and are valuable intermediates for organic synthesis and medical chemistry.[50–52]



Scheme 2 The present work is in the context of the development of a methodology for oxidative C–O coupling involving β-dicarbonyl compounds and oximes.

Results and discussion

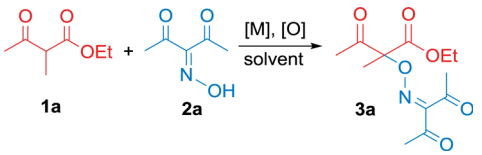
In the model coupling reaction of ethyl 2-methylacetoacetate **1a** with 3-(hydroxyimino)pentan-2,4-dione **2a** Cu(I, II), Mn(II, III), Fe(III) and Ni(II) salts were tested as catalysts. Molecular oxygen, organic and inorganic peroxides were used as oxidants for the reaction (Table 1).

The best results were obtained with $Cu(BF_4)_2 \cdot 6H_2O$ as catalyst (Table 1, entries 1–6). O_2, H_2O_2 and Oxone were ineffective oxidants in combination with this salt, the yield of **3a** did not exceed 40% (Table 1, entries 1, 2 and 4).

Possible reasons for the relatively low yields include oxidative cleavage of C–C bonds in the starting **1a**,[53–57] as well as hydroxylation of **1a** at α-position.[58–60] Satisfactory yield of **3a** (46%) were observed with $K_2S_2O_8$ (Table 1, entry 3).

The highest yield of **3a** (up to 64%) was achieved using *t*-BuOOH (Table 1, entry 5). Di-*tert*-butyl peroxide did not show

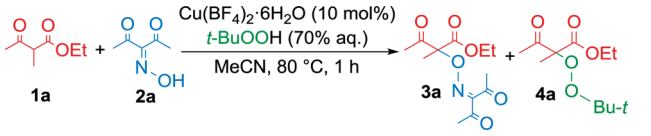
Table 1 Optimization of reaction conditions for the C–O coupling of β-keto ester **1a** with oxime **2a**[a]



Entry	Metal salt	Oxidant (molar ratio: mol per mol of **1a**)	Yield of **3a**[b] (%)
1	$Cu(BF_4)_2 \cdot 6H_2O$	O_2	14
2	$Cu(BF_4)_2 \cdot 6H_2O$	H_2O_2 (2)	38
3[c]	$Cu(BF_4)_2 \cdot 6H_2O$	$K_2S_2O_8$ (2)	46
4	$Cu(BF_4)_2 \cdot 6H_2O$	Oxone (2)	28
5	**$Cu(BF_4)_2 \cdot 6H_2O$**	***t*-BuOOH (3)**	**64**
6	$Cu(BF_4)_2 \cdot 6H_2O$	(*t*-BuO)$_2$ (2)	39
7	$Cu(ClO_4)_2 \cdot 6H_2O$	O_2	24
8	$Cu(ClO_4)_2 \cdot 6H_2O$	H_2O_2 (2)	21
9[c]	$Cu(ClO_4)_2 \cdot 6H_2O$	$K_2S_2O_8$ (2)	54
10[c]	$Cu(ClO_4)_2 \cdot 6H_2O$	$(NH_4)_2S_2O_8$ (2)	56
11	$Cu(ClO_4)_2 \cdot 6H_2O$	*t*-BuOOH (3)	51
12	$CuCl_2$	*t*-BuOOH (3)	58
13	CuCl	*t*-BuOOH (3)	40
14[c]	$CuSO_4 \cdot 5H_2O$	$K_2S_2O_8$ (2)	43
15	$CuSO_4 \cdot 5H_2O$	*t*-BuOOH (3)	11
16[c]	$Cu(OAc)_2$	$(NH_4)_2S_2O_8$ (2)	Trace
17	$Cu(OAc)_2$	*t*-BuOOH (3)	27
18	$Cu(OTf)_2$	*t*-BuOOH (3)	50
19[d]	$Mn(OAc)_3 \cdot 2H_2O$	*t*-BuOOH (3)	26
20[e]	$Mn(OAc)_3 \cdot 2H_2O$	*t*-BuOOH (3)	20
21	$Mn(ClO_4)_2 \cdot 6H_2O$	*t*-BuOOH (3)	n.d.
22	$Fe(ClO_4)_3 \cdot 11H_2O$	*t*-BuOOH (3)	34
23	$Ni(OAc)_2 \cdot 4H_2O$	*t*-BuOOH (3)	n.d.

[a] General reaction conditions: β-keto ester **1a** (1 mmol), oxime **2a** (1 mmol), metal salt (0.1 mmol, 10 mol%), oxidant (2–3 mmol), MeCN (5 mL) at 80 °C for 1 h. [b] Yield of isolated product. [c] MeCN–H_2O (5 mL; v/v = 3/2) mixture was used as solvent. [d] AcOH (5 mL) was used as solvent. [e] β-keto ester **1a** (1 mmol), oxime **2a** (1.5 mmol), $Mn(OAc)_3 \cdot 2H_2O$ (0.1 mmol, 10 mol%), *t*-BuOOH (70% aq.) (3 mmol), MeCN (2.5 mL), 20–25 °C, 48 h. *t*-BuOOH was used as 70% aqueous solution. H_2O_2 was used as 34% aqueous solution. n.d. – not detected.

Table 2 The effect of molar ratio of β-keto ester **1a**, oxime **2a** and *t*-BuOOH on yields of the reaction products **3a** and **4a**[a]



Entry	Molar ratio of **1a**, **2a** and *t*-BuOOH	Yield of **3a**[b] (%)	Yield of **4a**[b] (%)
1	1 : 1 : 2	61	Trace
2	1 : 1 : 3	70 (64)	Trace
3	**1 : 1.5 : 2**	**81 (77)**	**n.d.**
4	1 : 2 : 2	76	Trace
5	1 : 3 : 2	60	n.d.
6	1 : 3 : 3	57	Trace
7	1.5 : 1 : 2	74	18
8	1.5 : 1 : 3	76	20
9	2 : 1 : 3	51	34

[a] General reaction conditions: β-keto ester **1a** (1–2 mmol), oxime **2a** (1–3 mmol), $Cu(BF_4)_2 \cdot 6H_2O$ (0.1 mmol, 10 mol%), *t*-BuOOH (70% aq.) (2–3 mmol), MeCN (5 mL) at 80 °C for 1 h. [b] Yields of **3a** and **4a** were determined based on ^{1}H NMR using *p*-methoxyacetophenone as an internal standard; in the entries 2 and 3 isolated yields of **3a** based on β-dicarbonyl compound are given in parenthesis. n.d. – not detected.

sufficient oxidizing capacity in this reaction (Table 1, entry 6), probably because its optimal temperature range of activation lies above the boiling point of acetonitrile.

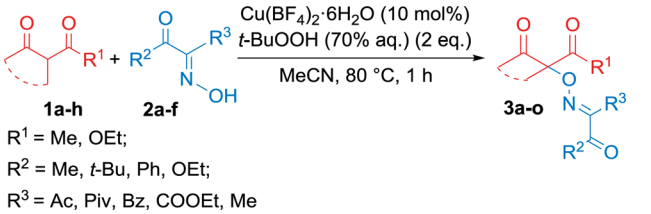
$Cu(ClO_4)_2 \cdot 6H_2O$, $CuCl_2$ and $Cu(OTf)_2$ showed a moderate activity (Table 1, entries 7–12 and 18) that was comparable to the activity of $Cu(BF_4)_2 \cdot 6H_2O$. The other copper salts (Table 1, entries 13–17), as well as Mn(II), Mn(III), Fe(III) and Ni(II) salts (Table 1, entries 19–23) in combination with peroxydisulfates and *t*-BuOOH were not sufficiently effective. A combination of $Mn(OAc)_3 \cdot 2H_2O$, *t*-BuOOH and MeCN was previously used to generate *t*-BuOO$^{\bullet}$ radicals at rt.[61] Using this combination **3a** was obtained with yield of only 20% (entry 20) and conversion of β-keto ester **1a** was about 27%.

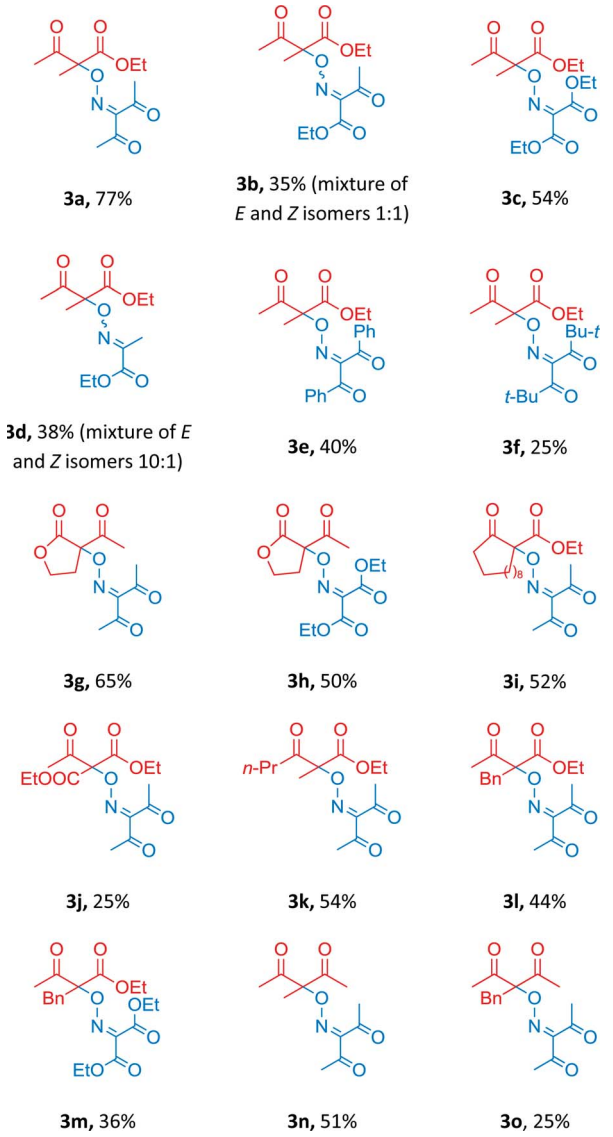
It was found, that the product yields were substantially dependent on the molar ratio of the starting reagents **1a**, **2a** and *t*-BuOOH (Table 2). The yield of product **3a** increased in the case of a 1.5-2-fold excess of the oxime **2a** with respect to β-keto ester **1a** (Table 2, entries 3–6). Presumably, the excess of oxime enhanced the trapping of the peroxyl radicals generated in the system of Cu(II) and *t*-BuOOH. When the reaction was carried out with an excess of β-keto ester **1a**, in addition to the main product **3a**, significant quantities of peroxidation by-product **4a** were observed (Table 2, entries 7–9).

Thus, the optimal reaction conditions under which the yield of the target product **3a** reached 77%, are the molar ratio of β-keto ester **1a** : oxime **2a** : *t*-BuOOH = 1 : 1.5 : 2 in the presence of 10 mol% of $Cu(BF_4)_2 \cdot 6H_2O$ in MeCN at 80 °C (Table 2, entry 3). These conditions were used for coupling of a number of β-dicarbonyl compounds with various oximes (Table 3).

The cross-coupling reaction proceeded with oximes bearing one (compound **3d**, yield 38%) or two (**3a–c**, **3e–o**, yields 25–77%) electron-withdrawing ester- or keto-groups.

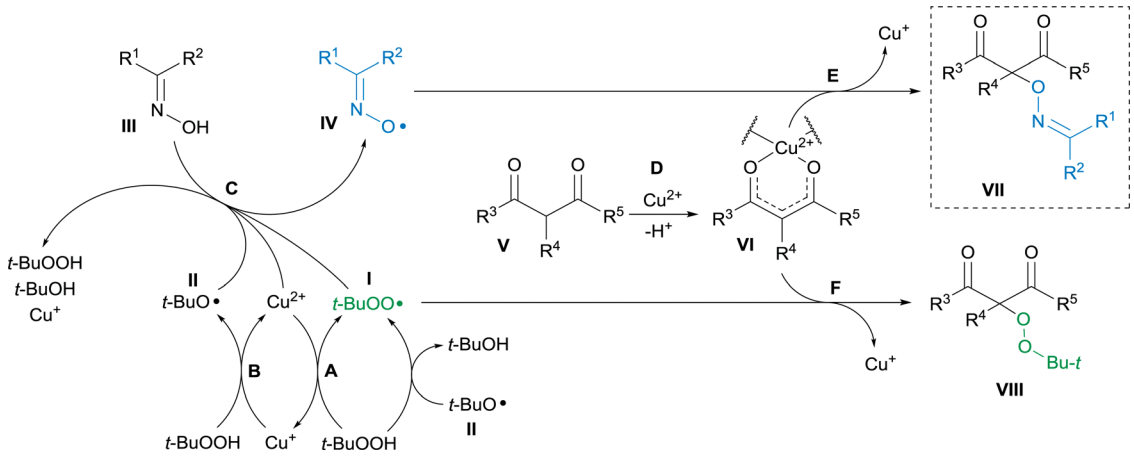
Table 3 Cross-dehydrogenative coupling of β-dicarbonyl compounds **1a–h** with oximes **2a–f**[a,b]





[a] General reaction conditions: β-dicarbonyl compound **1** (1 mmol), oxime **2** (1.5 mmol), $Cu(BF_4)_2 \cdot 6H_2O$ (0.1 mmol, 10 mol%), *t*-BuOOH (70% aq.) (2 mmol), MeCN (5 mL) at 80 °C for 1 h. [b] Isolated yields of **3a–o** based on β-dicarbonyl compound are given.

Diacetyloxime **1a** (product **3a** in comparison with **3b–f**) proved to be the most effective OH-substrate in the coupling reaction, probably owing to increased stability of corresponding iminoxyl radical.[39] Coupling with β-diketones proceeded with



Scheme 3 Proposed mechanism of oxidative C–O coupling of β-dicarbonyl compounds with radicals generated in the oxime/Cu(II)/*t*-BuOOH system.

yields lower than those in the case of β-keto esters (products **3n** and **3o** in comparison with **3a** and **3l**).

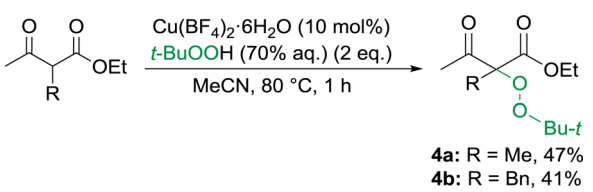
Proposed reaction mechanism

Based on the literature data the mechanism of cross-dehydrogenative coupling of β-dicarbonyl compounds with oximes under the action of Cu(II)/*t*-BuOOH system was proposed. It consists of three key parts: formation of alkoxyl and peroxyl radicals **I** and **II** derived from *t*-BuOOH in the presence of Cu^{2+},[22,23,62–65] oxidation of oxime **III** leading to the radical **IV** (ref. 8 and 47) and coupling of β-dicarbonyl compound **V** with radicals **I** and **IV** giving products **VII** and **VIII** (Scheme 3).[22]

In stage A, *tert*-butylhydroperoxide interacts with Cu^{2+} to form Cu^{+} and *tert*-butylperoxyl radical **I**.[62–65] *t*-BuOOH oxidizes Cu^{+} with the formation of Cu^{2+} and *tert*-butoxyl radical **II** (stage B).[22,23,62–65] Furthermore, generation of *tert*-butylperoxyl radical **I** can occur *via* abstraction of hydrogen atom from *t*-BuOOH by *t*-BuO˙ radical **II**.[63,65,66]

Generation of iminoxyl radical **IV** (stage C) can occur *via* oxidation of oxime **III** with Cu^{2+},[8] as well as with radicals **I** and **II** formed from *t*-BuOOH.[47,67] At stage D, β-dicarbonyl compound **V** forms a Cu^{2+} chelate complex **VI**,[22,68] which reacts with iminoxyl radical **IV** to form the final coupling product **VII** (stage E).

Formation of peroxidation byproduct **VIII** takes place in stage F by the interaction of complex **VI** with *tert*-butylperoxyl radical **I**.[22] In the absence of oxime, peroxidation products **4a**,**b** were obtained with moderate yields (Scheme 4).



4a: R = Me, 47%
4b: R = Bn, 41%

Scheme 4 Reaction of β-keto esters with Cu(II)/*t*-BuOOH (in the absence of oxime) with the formation of peroxidation products **4a**,**b**.

Redox properties of oxime **2a** in the presence of $Cu(BF_4)_2$ were studied by cyclic voltammetry (Fig. 1). In the absence of copper, only a slight reversible peak of oxidation of oxime into the radical was observed at 0.32 V. When copper salt was added, oxime oxidation peak increased significantly, and the peak of Cu^{+}/Cu^{2+} oxidation appeared in the more anodic region (0.97 V).

Thus, $Cu(BF_4)_2$ is a strong oxidizing agent for oxidation of oxime **2a** to iminoxyl radical **IV**, and it also can serve as an effective mediator for the electrochemical generation of iminoxyl radicals.

Conversion of oxime **2a** into radical **IV** under the action of $Cu(BF_4)_2$ and *t*-BuOOH separately or in combination was studied by EPR spectroscopy (Fig. 2). The concentrations of reagents were the same as in the general conditions of the C–O coupling (Table 3). The highest amount of iminoxyl radical was formed in the presence of $Cu(BF_4)_2$ (Run 1). Mixing the reagents at room temperature led to a rapid change in color from almost colorless to the red which is typical of radical **IV**.[39] The concentration of **IV** was estimated using a 0.002 M solution of 4-

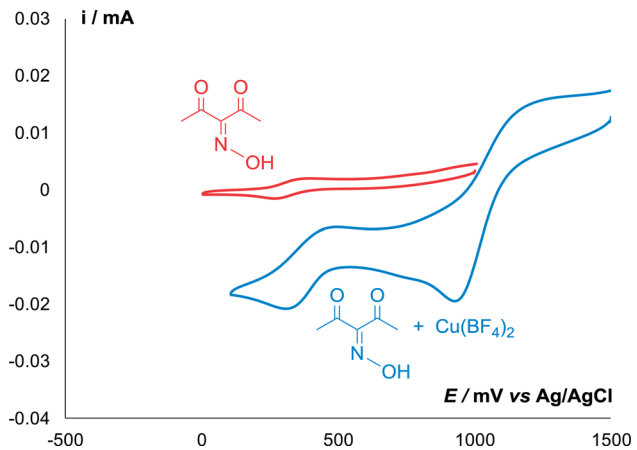


Fig. 1 CV curves of 5 mmol L^{-1} of oxime **2a** in the presence (blue) and absence (red) of equimolar amount of $Cu(BF_4)_2$ in 0.1 M *n*-Bu_4NBF_4/MeCN at a scan rate of 0.1 V s^{-1} at 298 K.

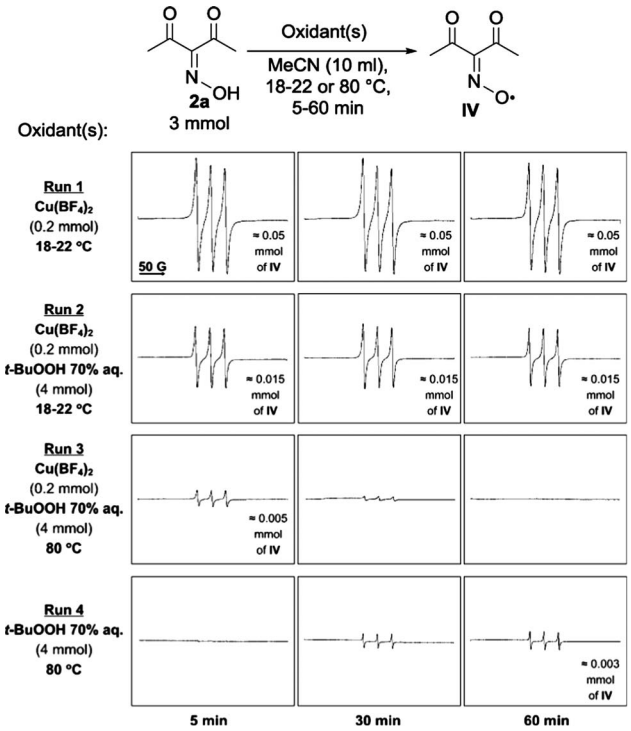


Fig. 2 EPR monitoring of formation of iminoxyl radical **IV** from oxime **2a** under action of $Cu(BF_4)_2$ and *t*-BuOOH.

benzoyloxy-2,2,6,6-tetramethylpiperidine 1-oxyl in MeCN as external standard. The concentration of **IV** according to EPR did not varied in time interval of 5–60 min after the beginning of the reaction. The estimated amount of iminoxyl radical **IV** was 0.05 mmol which corresponds to a 25% conversion of $Cu(BF_4)_2$ (reduction of Cu^{2+} to Cu^{+}).

Surprisingly, the amount of iminoxyl radical formed in the presence of both $Cu(BF_4)_2$ and *t*-BuOOH (Run 2, *ca.* 0.015 mmol of **IV**) was lower than in the presence of $Cu(BF_4)_2$ alone (Run 1, *ca.* 0.05 mmol of **IV**). Apparently, addition of *t*-BuOOH 70% aq. affected the coordination environment of Cu^{2+} ions, which caused a decrease in Cu^{2+} oxidative potential, which was confirmed by the CV method (Fig. 3). Addition of *t*-BuOOH 70% aq. to a solution of the oxime **2a** and $Cu(BF_4)_2$ leads to a negative shift of the copper reduction peak by 170 mV.

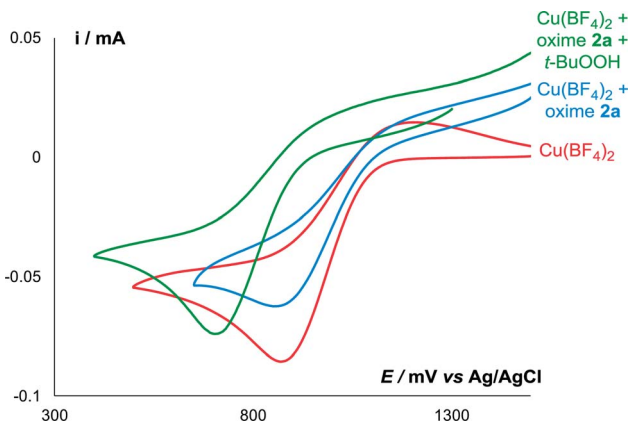


Fig. 3 CV curves of $Cu(BF_4)_2$ (red), $Cu(BF_4)_2$ in the presence of oxime **2a** (blue), and $Cu(BF_4)_2$ in the presence of oxime **2a** and *t*-BuOOH (70% aq.) (green) in 0.1 M *n*-Bu_4NBF_4/MeCN at a scan rate of 0.1 V s^{-1} at 298 K.

Reoxidation of Cu^{+} to Cu^{2+} by *t*-BuOOH is supposed to be rather slow at room temperature, and therefore EPR experiment with $Cu(BF_4)_2$/*t*-BuOOH system at 80 °C was performed (Fig. 2, Run 3). In this case the concentration of **IV** decreased significantly, presumably, due to decomposition.[69–74] In the presence of *t*-BuOOH without $Cu(BF_4)_2$, iminoxyl radicals **IV** formed very slowly at 80 °C; maximum concentration was observed after 60 min (Run 4, *ca.* 0.003 mmol of **IV**). The formation of **IV** in this run can be explained by the interaction of oxime **2a** with radicals formed by a homolytic cleavage of O–O bond in *t*-BuOOH.

The results of EPR monitoring and CV experiments indicate a complex character of the interaction between oxime, $Cu(BF_4)_2$ and *t*-BuOOH, but iminoxyl radical **IV** is the dominating O-centered radical in all cases.

Conclusions

In the reaction system containing β-dicarbonyl compounds, iminoxyl and peroxyl radicals, the reaction conditions were found which allow to synthesize C–O coupling products with iminoxyl radicals preferably over peroxyl radicals. It was shown that the system consisting of oxime, Cu(II) and *t*-BuOOH is a convenient source of iminoxyl radicals. The first cross-dehydrogenative C–O coupling of β-dicarbonyl compounds with α-keto oximes was accomplished using the proposed system with catalytic amounts of metal-containing oxidant. Kharasch peroxidation of β-dicarbonyl compounds with *tert*-butylperoxyl radicals was observed in the absence of oxime. Apparently, oximes are effective scavengers of peroxyl radicals in the discovered process, which leads to a change of the process route.

It appears that the ability of oximes to scavenge O-centered radicals found in this work opens the new way for their application as reagents for C–O coupling, inhibitors of radical processes and test reagents for confirmation of the radical mechanism of various reactions.

Experimental

Experimental for Table 1

2-Methylacetoacetate **1a** (144 mg, 1 mmol), 3-(hydroxyimino) pentan-2,4-dione **2a** (129 mg, 1 mmol), MeCN (5 mL), and metal salt (10–55 mg, 0.1 mmol) were successively loaded into a round bottom flask. The mixture was heated on oil bath (80 °C) with stirring by a magnetic bar and an oxidant (200–615 mg, 2–3 mmol) was added for 10 seconds; stirring was continued for 1 h at 80 °C. In the entries 1 and 7 oxygen gas was bubbled through the reaction mixture (0.3 mL s^{-1}) until the end of the synthesis; entries 2–6, 8–23 were carried out in air atmosphere. In the entry 20 mixture of β-keto ester **1a** (144 mg, 1 mmol), oxime **2a** (194 mg, 1.5 mmol), $Mn(OAc)_3 \cdot 2H_2O$ 95% (28 mg, 0.1 mmol, 10 mol%), *t*-BuOOH 70% aq. (386 mg, 3 mmol) and MeCN (2.5 mL) was stirred for 48 h at 20–25 °C.

Reaction mixture was cooled to the room temperature, diluted with CH_2Cl_2 (10 mL) and water (30 mL) and shaken. Organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). All the organic extracts were combined, washed with aqueous solution of $Na_2S_2O_4$ (200 mg in 20 mL of water), then with water (20 mL), dried over Na_2SO_4, rotary evaporated at 40–60 °C under water-jet vacuum (20–30 mmHg). C–O coupling product **3a** was isolated by column chromatography on silica gel using CH_2Cl_2/EtOAc eluent with volume part of EtOAc 2.5%.

Experimental for Table 2

2-Methylacetoacetate **1a** (144–288 mg, 1–2 mmol), 3-(hydroxyimino)pentan-2,4-dione **2a** (129–387 mg, 1–3 mmol), MeCN (5 mL), and $Cu(BF_4)_2 \cdot 6H_2O$ (35 mg, 0.1 mmol) were successively loaded into a round bottom flask. The mixture was heated on oil bath (80 °C) with stirring by a magnetic bar and *t*-BuOOH (70% aqueous solution, 257–386 mg, 2–3 mmol) was added for 10 seconds; stirring was continued for 1 h at 80 °C.

Reaction mixture was cooled to the room temperature, diluted with CH_2Cl_2 (10 mL) and water (30 mL) and shaken. Organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). All the organic extracts were combined, washed with aqueous solution of $Na_2S_2O_4$ (200 mg in 20 mL of water), then with water (20 mL), dried over Na_2SO_4, rotary evaporated at 40–60 °C under water-jet vacuum (20–30 mm Hg). Yields of **3a** and **4a** were determined by ^{1}H NMR using *p*-methoxyacetophenone as an internal standard. In the entries 2 and 3 product **3a** was isolated by column chromatography on silica gel using CH_2Cl_2/EtOAc eluent with volume part of EtOAc 2.5% (isolated yields are given in parenthesis).

Experimental for Table 3

β-Dicarbonyl compound **1a–h** (114–254 mg, 1 mmol), oxime **2a–f** (194–380 mg, 1.5 mmol), MeCN (5 mL), and $Cu(BF_4)_2 \cdot 6H_2O$ (35 mg, 0.1 mmol) were successively loaded into a round bottom flask. The mixture was heated on oil bath (80 °C) with stirring by a magnetic bar and *t*-BuOOH (70% aqueous solution, 257 mg, 2 mmol) was added for 10 seconds; stirring was continued for 1 h at 80 °C.

Reaction mixture was cooled to the room temperature, diluted with CH_2Cl_2 (10 mL) and water (30 mL) and shaken. Organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). All the organic extracts were combined, washed with aqueous solution of $Na_2S_2O_4$ (200 mg in 20 mL of water), then with water (20 mL), dried over Na_2SO_4, rotary evaporated at 40–60 °C under water-jet vacuum (20–30 mmHg). C–O coupling product **3a–o** was isolated by column chromatography on silica gel using CH_2Cl_2/EtOAc eluent.

Experimental for Scheme 4

To a stirred at 80 °C mixture of β-keto ester **1a**,**f** (144–220 mg, 1 mmol), $Cu(BF_4)_2 \cdot 6H_2O$ (35 mg, 0.1 mmol) and MeCN (5 mL) *t*-BuOOH (70% aqueous solution, 257 mg, 2 mmol) was added for 10 seconds; stirring was continued at 80 °C for 1 h.

Reaction mixture was cooled to the room temperature, diluted with CH_2Cl_2 (10 mL) and water (30 mL) and shaken. Organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). All the organic extracts were combined, washed with aqueous solution of $Na_2S_2O_4$ (200 mg in 20 mL of water), then with water (20 mL), dried over Na_2SO_4, rotary evaporated at 40–60 °C under water-jet vacuum (20–30 mmHg). Peroxidation products **4a**,**b** were isolated by column chromatography on silica gel using CH_2Cl_2/EtOAc eluent with volume part of EtOAc 3%.

Experimental for Fig. 1

Oxime **2a** (3.22 mg, 0.025 mmol) and 0.1 M *n*-Bu_4NBF_4/MeCN (2.5 mL) were placed into electrochemical cell, the resultant solution was stirred by bubbling with argon at 25 °C. Then a solution of $Cu(BF_4)_2 \cdot 6H_2O$ (8.62 mg, 0.025 mmol) in 0.1 M *n*-Bu_4NBF_4/MeCN (2.5 mL) was added. The bubbling was stopped after 15 min and voltammetry curve was recorded.

Experimental for Fig. 2

EPR spectra were recorded at 18–22 °C using following parameters: microwave frequency — ≈9.6 GHz, central field — 3340 G, hf (100 kHz) field modulation amplitude — 1.0 G, microwave power — 31 mW, scan range — 300 G, receiver gain — 1.25 × 10^4. Sample solutions in 100 μL glass capillaries (inner diameter 1.2 mm) were placed into the EPR cavity. In all runs, EPR spectra were recorded after 5, 30 and 60 min of reaction. In runs 3 and 4 conducted at 80 °C, samples were taken from the reaction mixture at given times (5, 30 and 60 min), allowed to cool to 18–22 °C in air (about 5 min) and then EPR spectra were recorded. In all cases, EPR signal of diacetyliminoxyl radical **IV** (g = 2.0044, a_N = 28.1 G)[8] was observed. The amount of radical **IV** formed in the reaction was estimated by double integration of its EPR spectrum. A 0.002 M solution of 4-benzoyloxy-2,2,6,6-tetramethylpiperidine 1-oxyl (4-BzO-TEMPO) in MeCN was used as external concentration standard. Detailed procedures for runs 1–4 are given below. Run 1: to a stirred at 18–22 °C solution of oxime **2a** (387.3 mg, 3 mmol) in MeCN (5 mL) a solution of $Cu(BF_4)_2 \cdot 6H_2O$ (69.0 mg, 0.2 mmol) in MeCN (5 mL) was added. Run 2: to a stirred at 18–22 °C solution of oxime **2a** (387.3 mg, 3 mmol) in MeCN (5 mL) a solution of $Cu(BF_4)_2 \cdot 6H_2O$ (69.0 mg, 0.2 mmol) in MeCN (5 mL) was added, then *t*-BuOOH (70% aq.) (515 mg, 4 mmol) was added. Run 3: to a stirred at 18–22 °C solution of oxime **2a** (387.3 mg, 3 mmol) in MeCN (5 mL) a solution of $Cu(BF_4)_2 \cdot 6H_2O$ (69.0 mg, 0.2 mmol) in MeCN (5 mL) was added, then *t*-BuOOH (70% aq.) (515 mg, 4 mmol) was added. Then the obtained solution was stirred on the oil bath (80 °C). Run 4: to a stirred at 18–22 °C solution of oxime **2a** (387.3 mg, 3 mmol) in MeCN (5 mL) a solution of *t*-BuOOH (70% aq.) (515 mg, 4 mmol) in MeCN (5 mL) was added. Then the obtained solution was stirred on the oil bath (80 °C).

Experimental for Fig. 3

Three solutions were studied by CV with scan rate 100 mV s^{-1}. Solution of $Cu(BF_4)_2$: $Cu(BF_4)_2 \cdot 6H_2O$ (34.5 mg, 0.1 mmol) was dissolved in 0.1 M *n*-Bu_4NBF_4/MeCN (5 mL). Solution of

$Cu(BF_4)_2$ + oxime **2a:** $Cu(BF_4)_2 \cdot 6H_2O$ (34.5 mg, 0.1 mmol) was dissolved in 0.1 M *n*-Bu_4NBF_4/MeCN (5 mL), then oxime **2a** (193.7 mg, 1.5 mmol) was added. Solution of $Cu(BF_4)_2$ + oxime **2a** + *t*-BuOOH: $Cu(BF_4)_2 \cdot 6H_2O$ (34.5 mg, 0.1 mmol) was dissolved in 0.1 M *n*-Bu_4NBF_4/MeCN (5 mL), then oxime **2a** (194 mg, 1.5 mmol) and *t*-BuOOH 70% aq. (257 mg, 2 mmol) were added. Solutions were deaerated by bubbling argon for 15 min before recording a cyclic voltammogram.

Conflicts of interest

There are no conflicts to declare.

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