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Cross-Dehygrogenative C-O Coupling of Oximes with Acetonitrile, Ketones and Esters

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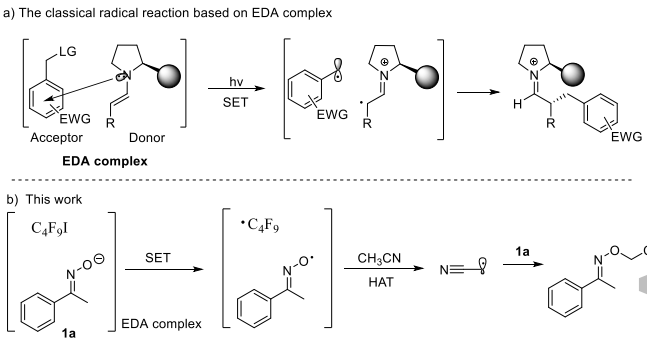
Abstract: A transition metal-free approach for the generation of radical intermediates via EDA complexes had been developed. This approach enables a cross-dehydrogenative C-O coupling of oximes with acetonitrile, ketones and esters with high yields and regioselectivities. Perfluorobutyl iodide was used as the unique electron acceptor to trigger a new radical formation. The radical pathway was confirmed by UV-Vis spectroscopy, radical inhibiting, trapping and kinetics experiments.

Keywords: C-O coupling; cross-dehydrogenative coupling; oxime ether; electron donor-acceptor complex; C(sp3)−H functionalization

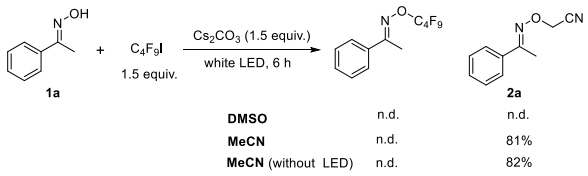
Direct transformations of C−H bonds to C−X (X = C, O, N, S) bonds with high atom/step-economy are powerful and robust strategies for the synthesis of valuable compounds such as pharmaceuticals, natural products and materials.[1] However, the activation of less reactive C(sp3)−H bonds remains challenging because of high bond-dissociation energy (BDE).[2] Usually, transition metal catalyzed activation of C(sp3)−H bonds assisted by the directing groups of the substrates is one of the most straightforward method.[3] Cross-dehydrogenative-coupling (CDC) reactions which avoid the prefunctionalization and defunctionalization of substrates are also attractive for the direct C−H bond functionalization.[4] However, most of the reactions require the use of transition metal catalysts. As a complementary method, transition-metal free CDC reactions via homolytic cleavage of C(sp3)−H bonds had been well developed in recent decades.[5] Even so, the use of strong oxidants, strong bases, highly toxic organotins and explosive peroxides still hampers their applications.

Melchiorre group found that electron-rich enamines can act as strong reductants upon light excitation. The subsequent single electron transfer (SET) to electron-deficient organic halides generates the radical intermediates.[6] It was proposed that electron donor-acceptor (EDA) complexes are formed between enamines and organic halides (Scheme 1a). Lately, Miyake,[7] Yu,[8] Chen,[9] Aggarwal[10] etc.[11] developed a series of visible-light promoted radical coupling reactions via the formation of EDA complexes. In these cases, the two radicals generated from EDA complexes are usually coupled to provide the products. If new radical species are generated from the original radical intermediates, the new transformations can be developed.[12] Herein, we report a transition metal-free approach for the generation of radical intermediates via EDA complexes. The approach enables a cross-dehydrogenative C-O coupling of oximes with acetonitrile, ketones and esters with high yields and regioselectivities.

Initially, the C-O cross-dehydrogenative coupling reaction of oxime **1a** and C_4F_9I[13] was studied. No coupling product was observed in DMSO with the irradiation of white LED. When acetonitrile was used as the solvent, the reaction gave the product **2a** in a good yield. Further experiment revealed that **2a** could be obtained in a similar yield without the irradiation of white LED (Scheme 2).



Scheme 1. EDA complexes enable radical coupling reactions.



Scheme 2. Initial results.

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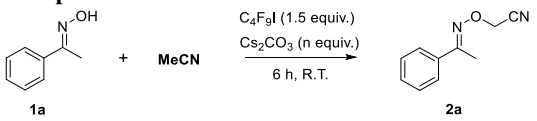
Table 1. Optimization of reaction conditions.[a]

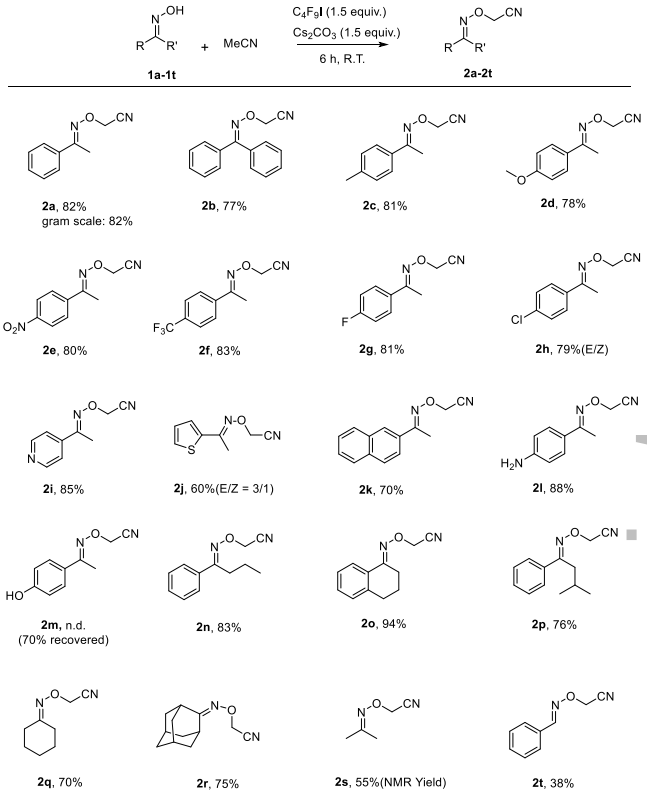


Entry	Base	n (equiv.)	Yield (%)[a]
1	Cs_2CO_3	1.5	82
2	CsF	1.5	50
3	K_3PO_4	1.5	40
4	K_2CO_3	1.5	15
5	Na_2CO_3	1.5	n.d.
6	CsOAc	1.5	n.d.
7	NaOH	1.5	trace
8	NaO*t*-Bu	1.5	trace
9	Et_3N	1.5	n.d.
10	DMAP	1.5	n.d.
11	DBU	1.5	n.d.
12	Cs_2CO_3	1.2	75
13	Cs_2CO_3	2.0	82
14	-	-	n.d.
15[c]	Cs_2CO_3	1.5	n.d.
16[d]	Cs_2CO_3	1.5	80

[a] Reaction conditions: **1a** (0.2 mmol), C_4F_9I (0.3 mmol), base (0.3 mmol) and CH_3CN (1.0 mL) at RT under air.
[b] Isolated yield.
[c] The reaction was conducted in the absence of C_4F_9I.
[d] The reaction was conducted under argon.

The effect of different base was investigated and the results are summarized in Table 1. CsF, K_3PO_4 and K_2CO_3 were also applicable, but lower yields were obtained in comparison with that using Cs_2CO_3 as the base (Table 1, entries 1-4). Other bases such as Na_2CO_3, CsOAc, KOH, NaO*t*-Bu and organic bases (Et_3N, DMAP and DBU) were inefficient (Table 1, entries 5-11). The loading of Cs_2CO_3 was also examined. The yield of **2a** was slightly decreased while using 1.2 equivalents of Cs_2CO_3 (Table 1, entry 12). Increasing the loading of Cs_2CO_3 to 2.0 equivalents did not improve the yield (Table 1, entry 13). The reaction was also carried out in the absence of Cs_2CO_3 or C_4F_9I, however, no product **2a** was obtained (Table 1, entries 14-15).[14] The reaction under the protection of argon gave the similar result. The experiment indicated that the oxygen is not the oxidant for this reaction (Table 1, entry 16).

A variety of oximes **1a**-**1t** were examined in the reaction with acetonitrile and the results are summarized in Scheme 3. The reaction of benzophenone oxime gave nitrile compound **2b** in good yield. The substitutions on the benzene ring with electron-donating groups (**1c**, **1d**), electron-withdrawing groups (**1e**, **1f**) and halides (**1g**, **1h**) were tolerated very well. The corresponding products were obtained in good yields (77-83%). Pyridinyl, thienyl and naphthyl ketone oximes (**1i**-**1k**) were also applicable and moderate to good yields were obtained. Oxime (**1l**) with a reactive group of NH_2 on the aromatic ring was also tolerated



Scheme 3. Reactions of acetonitrile with oximes.[a]
[a] Reaction conditions: oximes (0.2 mmol), C_4F_9I (0.3 mmol), Cs_2CO_3 (0.3 mmol) and CH_3CN (1.0 mL) at RT under air.

under our C-O coupling conditions. However, when NH_2 was replaced by OH (**1m**), the reaction was inhibited completely and most of **1m** was recovered. The acidic OH group may be incompatible with the reaction. The reaction is not limited to aryl methyl ketone oximes. Other aryl alkyl ketone oximes **1n**-**1p** afforded the products **2n**-**2p** in good to excellent yields too. The dialkyl ketone oximes (**1q**-**1s**) were also successfully applied. The products **2q**-**2s** were obtained in moderate to good yields. The benzaldehyde oxime (**1t**) was applicable, however, with lower yield. To further demonstrate the utility of this reaction, a gram-scale reaction of **1a** was examined. The product **2a** was obtained in a good yield (1.14 g, 82%).

The reactions of oxime **1a** with esters and ketones were also explored and the results are summarized in Scheme 4. The reactions of ethyl acetate and methyl acetate with oxime **1a** gave **4a** and **4b** in good yields. Other alkyl acetates (**4c**, **4d**) were also applicable, however, the higher reaction temperature (50 °C) was required. The reaction of 2-methoxyethyl acetate gave **4e** in a 74% yield at room temperature. In these reactions, the methyl group adjacent to carbonyl group was the sole reaction site. When this site was substituted by an alkyl group or ether group, the reaction still gave the expected products **4f** and **4g**, however with lower yields at higher reaction temperature. The lactone **3h** was also applicable and the C-O coupled product **4h** was obtained with a 38% yield. Furthermore, ketones **3i**-**3h** were examined. Acetone (**3i**), 2,4-dimethylpentan-3-one (**3j**), and 2,6-dimethylcyclohexan-1-one (**3k**) gave the C-O coupled products in good yields. When asymmetric methyl alkyl ketones (**3l**-**3n**) were used, the C-O bonds were preferentially formed on the *sec*- (**4l**,

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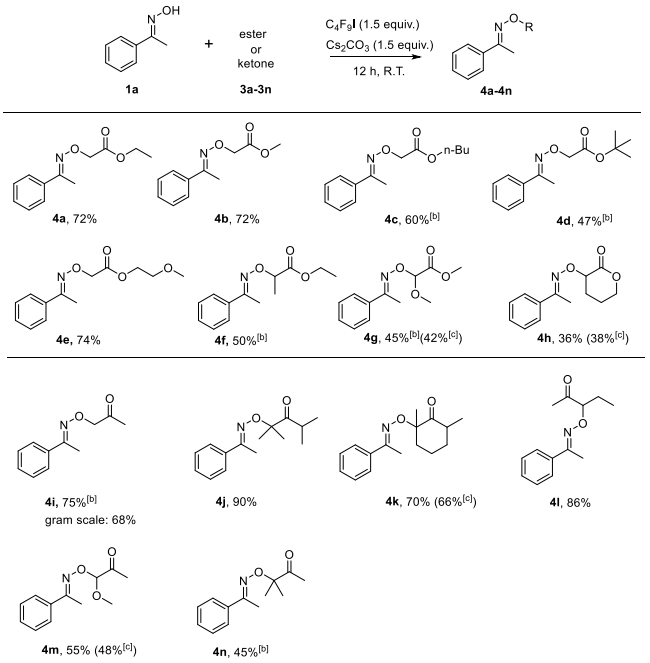


Scheme 4. Reactions of oxime **1a** with esters and ketones. [a]

[a] Reaction conditions: **1a** (0.2 mmol), C_4F_9I (0.3 mmol), Cs_2CO_3 (0.3 mmol) and solvent (1.0 mL) at RT under air. [b] The reaction was heated at 50 °C. [c] DMSO (1.0 mL) was used as co-solvent, and the corresponding ester or ketone (10 equiv.) was added.

4m) and *tert*- (**4n**) carbons adjacent to carbonyl groups. The reaction pattern accords with a radical pathway. A gram-scale reaction of **1a** with acetone was also examined, and **4i** was obtained in 68% yield. To enhance the practicability of the reaction, we can also employ DMSO as co-solvent to decrease the using amount of expensive ester or ketone (see the yields in the parentheses).

To gain the insight into the reaction mechanism, we firstlyperformed UV-vis spectroscopic measurements on various combinations of **1a**, C_4F_9I and Cs_2CO_3 in CH_3CN (Figure 1). We observed a red shift of absorption when oxime **1a**, C_4F_9I and Cs_2CO_3 were combined in acetonitrile. The color change of this mixture was also observed. The red shift and color change are proposed to result from the formation of an electron donor-acceptor (EDA) complex between the oxime anion and C_4F_9I.

The control experiments with free radical scavengers such as TEMPO, DPPH (1,1-diphenyl-2-picrylhydrazyl) and BHT (butylated hydroxytoluene) were carried out (Scheme 5a). The reactions with DPPH and BHT were totally inhibited and 90% of

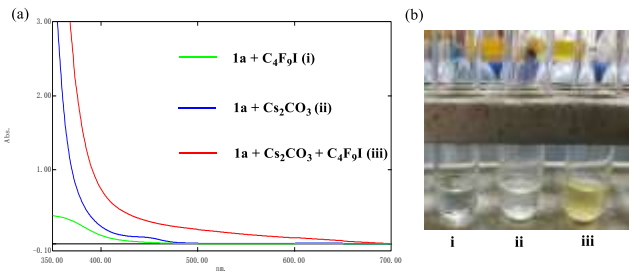
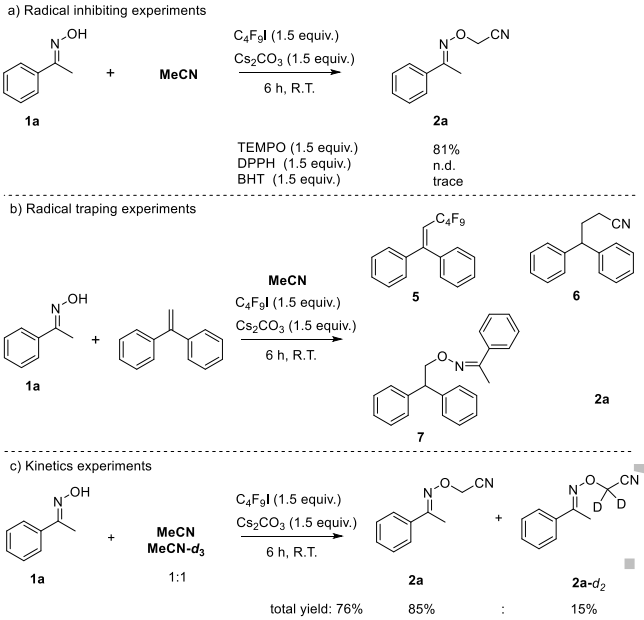


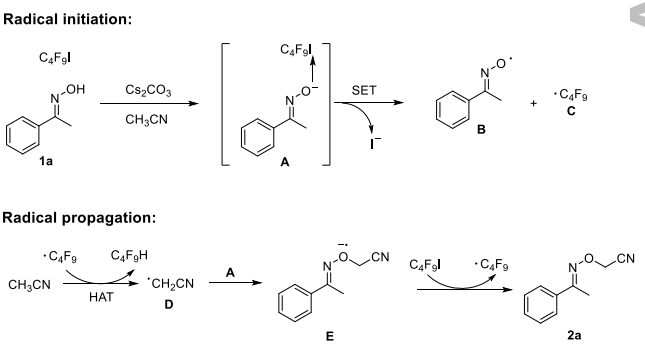
Figure 1. (a) UV-vis absorption spectra and (b) the color change of different combinations of **1a**, C_4F_9I and Cs_2CO_3 in CH_3CN.



Scheme 5. Control experiments.

substrate **1a** was recovered. The reaction was not interfered by TEMPO. However, after a careful analysis of the HRMS data of the reaction mixture, we observed the coupling product between TEMPO and C_4F_9 radical (see SI 3.3 for the details). To further understand the reaction mechanism, the trapping of the radical intermediate with 1,1-diphenylethylene was attempted (Scheme 5b). To our delight, compounds **5**, **6**, **7** were detected by HRMS. The radical trapping products were also obtained in the presence of BHT (see SI for details). All the data demonstrated the formation of the oxime radical, C_4F_9 radical and acetonitrile radical in the reaction. The kinetic isotope effect (KH/KD) was determined to be 5.67 (Scheme 5c) which showed that acetonitrile radical was proposed to be generated via a hydrogen abstraction by C_4F_9 radical. Previous studies showed that the generation of acetonitrile radical is difficult without metal catalyst and peroxide at room temperature, probably due to high bond dissociation energy of the C−H bond (96.0 kcal/mol).[1e]

A plausible mechanism is depicted in Scheme 6. The initiation of radicals was started from the deprotonation of oxime **1a** which gives oxime anion **A** (pKa = 20.1 in DMSO, ^{1}H NMR data in SI). Then an EDA complex is formed between oxime **A** and C_4F_9I. After an intermolecular electron transfer from oxime **A** to C_4F_9I, oxime radical **B** and perfluobutyl radical **C** are formed. Perfluobutyl radical **C** then abstracts a hydrogen from CH_3CN to



Scheme 6. Proposed reaction mechanism.

give acetonitrile radical **D**, which could be trapped by oximeanion **A** to form the anion radical **E**.[15] Subsequently, anion radical **E** is oxidized by C_4F_9I to give the product **2a** and regenerate the perfluobutyl radical **C**.

In summary, we have developed new cross-dehydrogenative C-O coupling of oximes with acetonitrile, ketones and esters. The reaction occurred under mild conditions without transition metal catalyst. Perfluorobutyl iodide was used as the unique oxidant. The formation of the EDA complex between oxime anion and perfluorobutyl iodide was proposed to enable the single electron transfer process. The resulting perfluorobutyl radical abstracts the hydrogen from acetonitrile, esters and ketones. The subsequent radical coupling with oxime radical provides the final products. The further applications of this strategy to other radical reactions are currently under investigation.

Experimental Section

To the mixture of 1-phenylethan-1-one oxime **1a** (27.1 mg, 0.2 mmol) and Cs_2CO_3 (97.8 mg, 0.3 mmol) in anhydrous acetonitrile (1.0 mL), nonafluoro-1-iodobutane (52 μL, 0.3 mmol) was added. The resulting reaction mixture was stirred at room temperature for 6 hours. The reaction mixture was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (petroleum/EtOAc) to give the compound **2a** as a yellow liquid (28.6 mg, 82%); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.69–7.64 (m, 2H), 7.42–7.36 (m, 2H), 4.82 (s, 2H), 2.27 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 158.33, 135.24, 129.96, 128.54, 126.38, 116.37, 58.94, 13.03; **HRMS (ESI)** calculated for $C_{10}H_{11}N_2O$ $(M+H)^+$: 175.0871, found: 175.0867.

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[15] The radical cross-coupling of the two radicals **B** and **D** may also happened but with little chance because the two open-shell radicals need to persistent for a period of time in the solvent before they meet each other.

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