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Iron-Catalyzed α,β-Dehydrogenation of Carbonyl Compounds

Xiao-Wei Zhang,[§] Guo-Qing Jiang,[§] Shu-Hui Lei, Xiang-Huan Shan, Jian-Ping Qu,* and Yan-Biao Kang*

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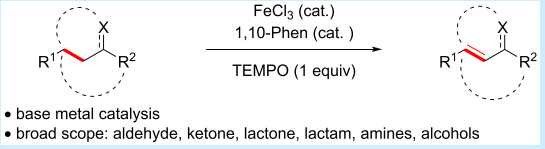
ABSTRACT: An iron-catalyzed α,β-dehydrogenation of carbonyl compounds was developed. A broad spectrum of carbonyls or analogues, such as aldehyde, ketone, lactone, lactam, amine, and alcohol, could be converted to their α,β-unsaturated counterparts in a simple one-step reaction with high yields.



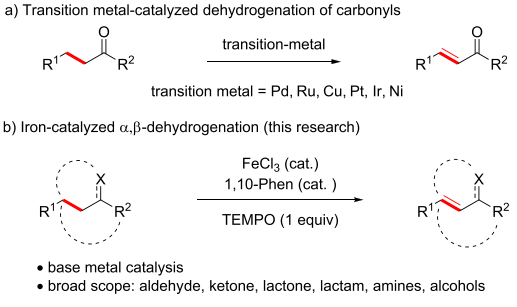
In organic synthesis, α,β-unsaturated carbonyl compounds are useful building blocks. α,β-Dehydrogenation of carbonyl compounds is among the most straightforward and practical processes for the construction of α,β-unsaturated carbonyl compounds. In earlier reports, either two- or multiple-step procedures or the involvement of stoichiometric halogen-containing oxidants, such as DDQ and hypervalent iodine reagents, was necessary.[1,2]

Recently, catalytic approaches using transition metals, especially palladium, have been well demonstrated as efficient and powerful tools for the α,β-desaturation of a wide range of carbonyl compounds.[3−15] Other transition metals including copper,[16,17] ruthenium,[18] platinum,[19] iridium,[20] and nickel[21] have also been successfully applied as the catalyst (Scheme 1a).

The economical and ample supply of iron salts make them ideal catalysts in both academic research and industrial applications.[22] Recently, iron-catalyzed dehydrogenation reactions of organic molecules, such as formic acid, alcohols, and amines, for the alternative energy storage systems or ecofriendly synthetic methods have been reported (Scheme 1b).[23−28] However, the utilization of this earth-abundant metal for the catalysts of α,β-dehydrogenation is exceedingly rare.

As part of our ongoing research interest in developing a practical method to access α,β-unsaturated carbonyl compounds via a dehydrogenation process,[3,29] we envisioned that it is possible to use iron as a bifunctional catalyst, in which it serves as both a Lewis acid and a redox catalyst. Herein, we report the recent results in detail.

Scheme 1. α,β-Dehydrogenation of Carbonyl Compounds



Our investigations started with the reaction of 3-phenylpropanal **1a** to cinnamaldehyde **2a** in the presence of 10 mol % $FeCl_3$, 10 mol % 1,10-phenanthroline **3a**, and 1 equiv of TEMPO; 81% of **2a** was obtained (Scheme 2). After evaluations of a series of iron salts (see the Supporting Information), $FeCl_3$ proved to be best catalyst. Additives, oxidants, and solvents were also investigated (see the Supporting Information), and the conditions stated in Scheme 2 were finally chosen as the standard conditions for further investigations.

The scope of aldehydes was first investigated. Both alkyl- and aryl-substituted aldehydes could be converted to their α,β-unsaturated counterparts (Scheme 2). When α-disubstituted aldehyde **1b** was subjected to the standard conditions, the dehydrogenation product **2b** was isolated in 61% yield. Aldehydes bearing heterocyclic substituents, such as 2-, 3-, or 4-pyridyl (**1c−1e**), thiophenyl (**1f**), and methylfuryl (**1g**), were all suitable. Aldehydes bearing either electron-rich or electron-deficient aryl substituents (**1h−1u**) could also be oxidized to the corresponding products. Dehydrogenation of *N*-methyl-6-oxo-*N*-phenylhexanamide **1v** with 2 equiv of TEMPO afforded α,β-, γ,δ-dehydrogenation product **2v**. When cyclohexanecarbaldehyde **1w** was treated with 3 equiv of TEMPO, benzaldehyde **2w** was obtained. Dehydrogenation of 3-cyclohexylpropanal **1x** under standard conditions produced the corresponding α,β-dehydrogenation product **2x** in 67% yield. When the straight-chain aliphatic aldehyde dodecanal **1y** was subjected to the standard conditions, α,β-dehydrogenation occurred albeit with low yield. The α,β-, γ,δ-unsaturated product **2z** was observed with prolonged reaction time. After 17 h of reaction in the presence of 2 equiv of

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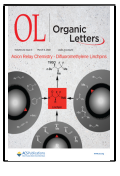

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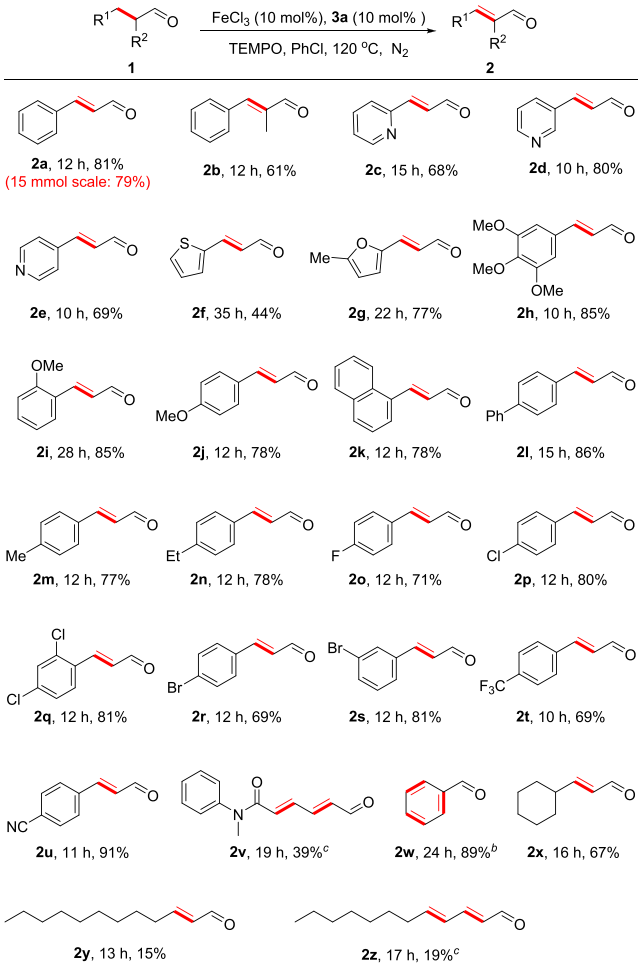
Scheme 2. α,β-Dehydrogenation of Aldehydes[a]



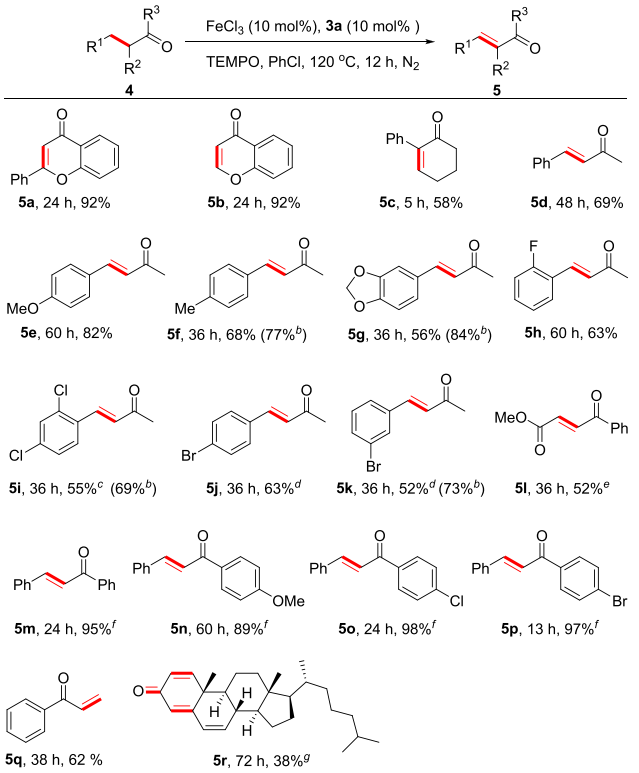
[a]Standard conditions: **1** (1 mmol), $FeCl_3$ (0.1 mmol), **3a** (0.1 mmol), TEMPO (1 mmol), PhCl (2 mL) (DMSO for **2c**), 120 °C, under N_2, isolated yields. [b]$FeCl_3$ (20 mol %), **3a** (20 mol %), pyridine (20 mol %), *p*-TsOH (10 mol %), TEMPO (3 mmol), DMSO (2 mL). [c]TEMPO (2 mmol).

TEMPO, **2z** was obtained in 19% yield without the observation of **2y**.

The dehydrogenation of less reactive ketones can also proceed well to give corresponding α,β-unsaturated ketone products in up to 98% yields (Scheme 3). Both cyclic (**5a**−**5c**) and noncyclic ketones were suitable. With respect to the cyclic ketones, the reaction is not sensitive to the β-substituents (**5a** vs **5b**), whereas the α-substituent has negative effects (**5c**). Either alkyl (**5d**−**5k**) or aryl α,β-unsaturated ketones (**5l**−**5q**) were obtained in moderated to excellent yields. Unsaturated 1,4-dicarbonyl compound **5l** was achieved in 52% yield. The cholesterol analogue could also be oxidized to the corresponding unsaturated counterpart **5r**.

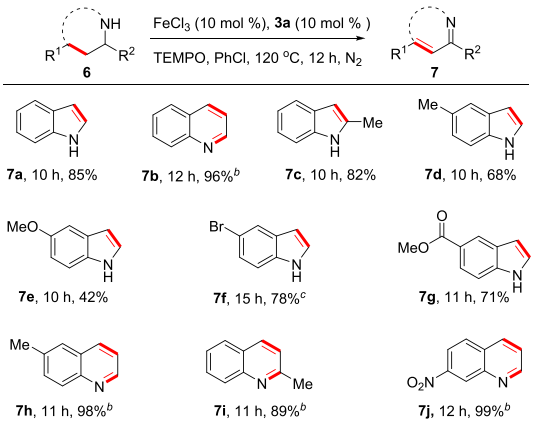
Besides carbonyl compounds, this iron-catalyzed dehydrogenative desaturation can be applied to *N*-heterocycles **6** under standard conditions, affording corresponding aromatic *N*-heterocycles in up to 99% yields (Scheme 4). For examples, indoline **6a** and 1,2,3,4-tetrahydroquinoline **6b** could be converted to indole **7a** and quinolone **7b** in 85% and 96% yields, respectively. Substituted indolines (**6c**−**g**) and tetrahydroquinolines (**6h**−**j**) bearing either electron rich or electron

Scheme 3. α,β-Dehydrogenation of Ketones[a]



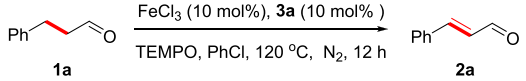
[a]Under standard conditions. [b]Yields were calculated based on recovered starting materials. [c]$FeCl_3$ (20 mol %), **3a** (20 mol%). [d]$FeCl_3$ (15 mol %), **3a** (15 mol%). [e]130 °C. [f]DMSO as solvent. [g]$FeCl_3$ (20 mol %), **3a** (20 mol%), TEMPO (3 equiv).

Scheme 4. Dehydrogenative Desaturation of *N*-Heterocycles



[a]Under standard conditions. [b]TEMPO (2 mmol). [c]DMSO as solvent.

Scheme 5. Control Experiments



no $FeCl_3$	no TEMPO	100 °C	$FeCl_3$ (99%)	$FeCl_3$ (99.9%)	$FeCl_3$ (99.99%)
19%	trace	25%	82%[b]	85%[b]	89%[b]

[a]Under standard conditions, and the yields were determined by GC analysis of the crude products. [b]Average yield of three parallel reactions.

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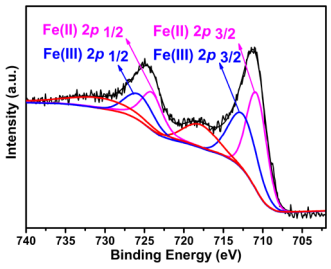


Figure 1. Detection of Fe(III) and Fe(II) by XPS experiment. XPS Instrument type, Thermo ESCALAB 250Xi; X- ray excitation source, monochromatic Al Kα ($h\nu$ = 1486.6 eV); power, 150 W; X-ray beam, 500 μm; energy analyzer fixed transmission energy, 30 eV.

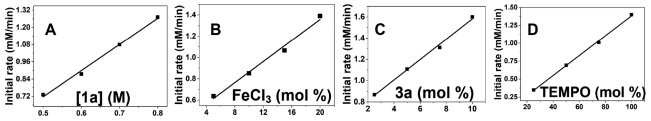
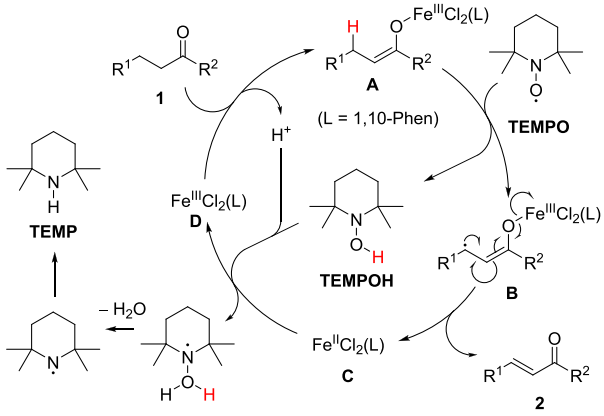


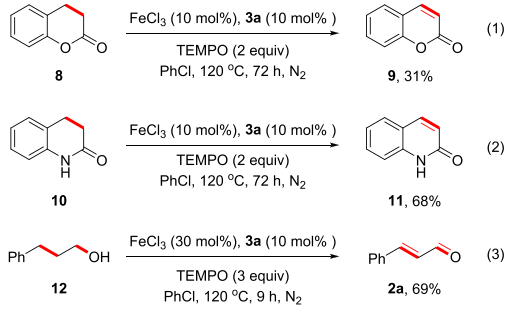
Figure 2. Kinetic studies.

Scheme 6. Proposed Mechanism



deficient groups could be transformed to the corresponding heterocycles.

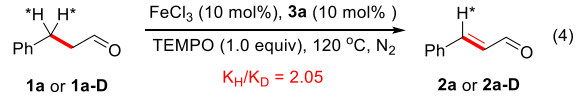
The iron-catalyzed α,β-dehydrogenation of other carbonyl analogues were investigated. Dehydrogenation of lactone **8** afforded α,β-unsaturated lactone **9** in 31% yield (eq 1), while lactam **10** could also be oxidized to α,β-unsaturated lactam **11** in 68% yield (eq 2). Alcohol **12** was subjected to the dehydrogenation conditions and α,β-unsaturated aldehyde **2a** was obtained in 69% yield (eq 3).



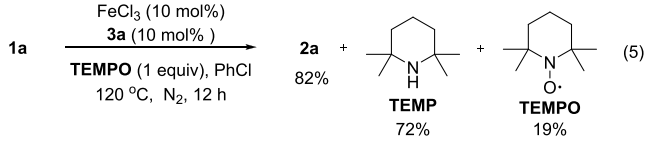
The reaction mechanism has been investigated with experimental evidence. As demonstrated in Scheme 5, either $FeCl_3$ or TEMPO is necessary for the completion of reaction. Effects on the purity of $FeCl_3$ were then investigated. The fact that yield of **2a** increased along with the growth of purity indicates that iron salt has been involved in this α,β-dehydrogenation reaction. The XPS experiments for the reaction under standard conditions demonstrated both Fe(III) and Fe(II). This further confirms that iron salts have been involved in the reaction as a catalyst (Figure 1).

The kinetic studies show that the dependences of initial rate on the concentration of [**1a**], [$FeCl_3$], [**3a**], and [TEMPO] are all first-order, suggesting that under the standard reaction conditions each component participates in the rate determining step (Figure 2).

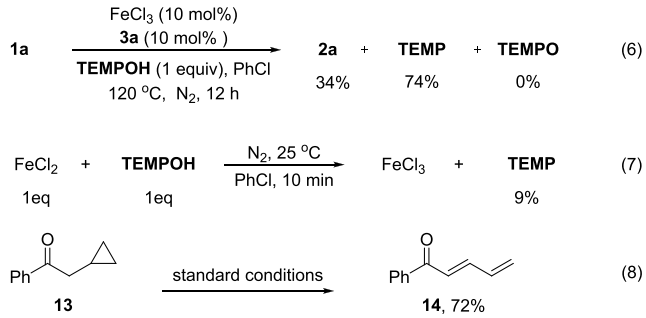
In the kinetic isotope experiments, a KIE of 2.05 for the β-H of PhCH_2CH_2CHO (**1a**) was observed (eq 4). This KIE indicates that in the iron-catalyzed dehydrogenation reaction the β-C−H bond cleavage should be the rate-limiting step. Therefore, a process that undergoes an α oxygenation with TEMPO followed by elimination was possible. However, no α oxygenation intermediate could be observed under the standard conditions. Other attempts to find such an intermediate failed, too.



The yield of **2a** depended linearly on the amount of TEMPO indicating that TEMPO works as a stoichiometric oxidant (see the Supporting Information). The form of TEMPO after the dehydrogenation reaction was determined. TEMP (2,2,6,6-tetramethylpiperidine) was obtained in 72% yield (eq 5), whereas no TEMPOH (2,2,6,6-tetramethylpiperidin-1-ol) was detected.



When 1 equiv of TEMPOH was used instead of TEMPO, **2a** was obtained in 34% yield with 74% of TEMP (eq 6). Reaction of ferrous chloride with TEMPOH at room temperature gave TEMP (eq 7), and the iodometric titration confirms the generation of Fe(III). These suggested that TEMPOH might be involved in the catalytic cycle. The radical clock experiment with **13** yields ring opening product **14** in 72% yield which confirms the radical nature of this reaction (eq 8).



Although the details of this reaction are unclear, a preliminary mechanism has been proposed based on above-mentioned experimental evidence. In the reaction model in Scheme 6, enolization of **1** promoted by $FeCl_3$ as a Lewis acid generates intermediate **A**. The following abstraction of the hydrogen atom by TEMPO forms radical intermediate **B**. **B** is quickly oxidized to **2** via the SET reduction of Fe(III)

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affording Fe(II) species **C**, wherein Fe(III) acts as a redox catalyst. The oxidation of **C** regenerates Fe(III).

In conclusion, we have developed a general $FeCl_3$-catalyzed α,β-dehydrogenation for the construction of α,β-unsaturated compounds. A broad spectrum of carbonyls or analogues can be converted to their α,β-unsaturated counterparts in a simple one-step reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00043.

Effect of the variation of reaction parameters, experimental procedures, analysis data for compounds, and copies of ^{1}H NMR and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Jian-Ping Qu − *Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing 211816, China;* orcid.org/0000-0002-5002-5594; Email: ias_jpqu@njtech.edu.cn

Yan-Biao Kang − *Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, China;* orcid.org/0000-0002-7537-4627; Email: ybkang@ustc.edu.cn

Authors

Xiao-Wei Zhang − *Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing 211816, China; Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, China*

Guo-Qing Jiang − *Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing 211816, China*

Shu-Hui Lei − *Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Nanjing Tech University, Nanjing 211816, China*

Xiang-Huan Shan − *Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00043

Author Contributions

§X.-W.Z. and G.-Q.J. contributed equally.

Notes

The authors declare no competing financial interest.

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