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# Hydrogen Atom Transfer (HAT)-Mediated Remote Desaturation Enabled by Fe/Cr−H Cooperative Catalysis

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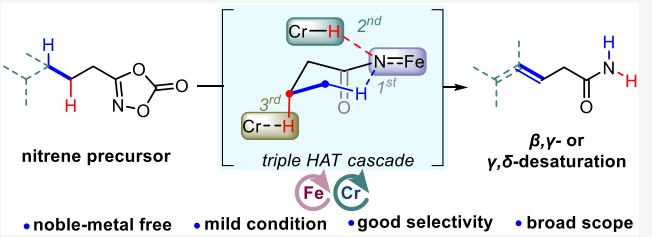
**ABSTRACT:** An iron/chromium system ($Fe(OAc)_2$, $CpCr(CO)_3H$) catalyzes the preparation of $\beta,\gamma$- or $\gamma,\delta$-unsaturated amides from 1,4,2-dioxazol-5-ones. An acyl nitrenoid iron complex seems likely to be responsible for C−H activation. A cascade of three H• transfer steps appears to be involved: (i) the abstraction of H• from a remote C−H bond by the nitrenoid N, (ii) the transfer of H• from Cr to N, and (iii) the abstraction of H• from a radical substituent by the Cr•. The observed kinetic isotope effects are consistent with the proposed mechanism if nitrenoid formation is the rate-determining step. The Fe/Cr catalysts can also desaturate substituted 1,4,2-dioxazol-5-ones to 3,5-dienamides.




## INTRODUCTION

Amides are found widely in biological, pharmaceutical, and natural product molecules.[1−5] The site-selective modification of amide C($sp^3$)−H bonds is an attractive route to many bioactive compounds.[6] The resulting carbon−carbon double bonds permit the chemo- and regioselective installation of many functional groups.[7,8] Unsaturated amides have been prepared by $\alpha,\beta$-desaturation,[9] with a transition-metal-catalyzed redox cascade widely used; it involves the formation of a metal enolate, $\beta$-hydrogen elimination, and catalyst reoxidation (Figure 1a).[10−14] The photoinduced or electrochemically driven $\alpha,\beta$-desaturation of amides has become popular in recent years.[15−18]

The site-selective removal of hydrogen atoms from nonactivated $\gamma$- or $\delta$-C($sp^3$)−H bonds in amides has been rarely achieved because of the strength of such bonds. However, hydrogen atom transfer (HAT) has shown an exceptional capability for desaturations. High-energy radicals can not only effectively overcome the thermodynamic obstacles to C−H bond cleavage but also face only a small kinetic barrier. Oxygen, nitrogen, and carbon radicals should be able to remove the remote H•, leaving carbon-centered radicals (Figure 1b).[19−26] These radicals can be trapped by metal catalysts, resulting in desaturation via $\beta$-hydrogen elimination, or they can be oxidized, which leads to the production of olefins via proton transfer.

State-of-the-art amide desaturation methods have often involved photolysis or noble metal catalysts. The sustainability of these methods, however, is often diminished by their reliance on noble metals such as Pd or Ag. Metal nitrenoid complexes offer a robust method for the generation of the initial carbon radicals, via the abstraction of H• from a remote C($sp^3$)−H bond (Figure 1c left).[27−30] However, the transformation of these radicals into carbon−carbon double bonds has been hampered by the lack of catalysts for that step. To address this challenge, we have turned our attention to the use of transition-metal radicals M• for the second H• abstraction (Figure 1c, right).[31] C($sp^3$)−H bonds that adjoin radicals are relatively weak, around 35 kcal/mol,[32] whereas metal−hydrogen bonds (M−H) range from 55 to 83 kcal/mol,[31] making H• abstraction by metal radicals M• thermodynamically favorable. In recent years, the combination of photoredox catalysis and biomimetic cobaloxime complexes has emerged as a promising option in this field.[33−35] The Norton group has examined many applications of transition-metal hydrides to unsaturated systems (the kinetics of H• transfer, and hydrogenation, hydrofunctionalization, cyclization, and isomerization reactions).[36−43] Our previous report on the epoxide hydrogenation has proven the feasibility of H• abstraction by $CpCr(CO)_3$• from C($sp^3$)−H bonds $\alpha$ to radicals.[44]

1,4,2-Dioxazol-5-ones, easily made from carboxylic acids, have been used with $Ru^{II}$ porphyrins and copper salts in the synthesis of oxazoles and oxazolines,[45] and a Ru nitrenoid complex appears to be involved. Chang has identified, by EPR and with calculations, an acyl nitrenoid iron complex from the reaction of PcFe(III)Cl with the dioxazolone **S1**.[28] Arnold has shown that acyl nitrenoid iron complexes are generated in the presence of $Fe^{II}$.[46] Bao has trapped acyl nitrenoid iron complexes from dioxazolones with $PPh_3$.[47] The iron nitrenoids generated in these ways have been able to remove H• from

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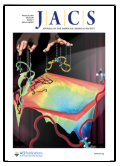


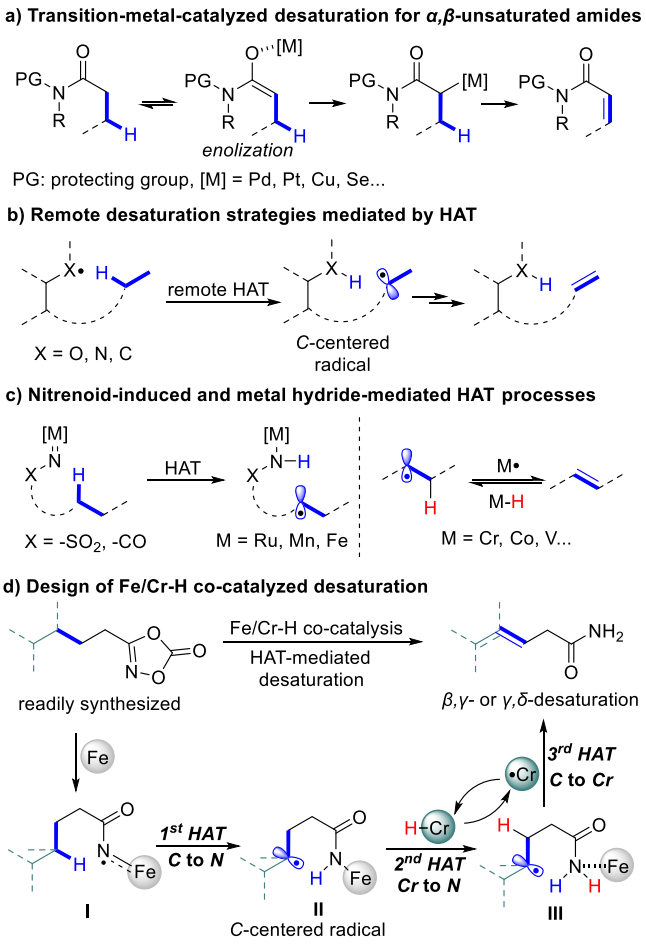



**Figure 1.** Strategies for desaturation. (a) Transition-metal-catalyzed $\alpha,\beta$-desaturation of amides. (b) Hydrogen atom transfer (HAT)-mediated remote C($sp^3$)−H desaturation. (c) Nitrenoid-induced HAT (left) and MHAT (right). (d) An iron/chromium cooperative catalysis for remote C($sp^3$)−H desaturation.

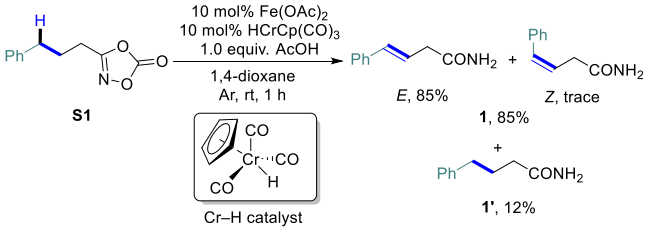
remote C($sp^3$)−H bonds. The use of an Fe(II)Pc catalyst for remote H• removal has been reported recently by the Li group.[47]

Herein, we report a triple HAT cascade that uses iron and chromium cooperative catalysis for remote C($sp^3$)−H desaturations (Figure 1d). An intramolecular 1,5-HAT onto the N of the iron nitrenoid **I** should release the carbon-centered radical **II**; the N-atom in **II** should accept a hydrogen atom from the chromium hydride $CpCr(CO)_3$−H (BDE(Cr−H) is about 61.5 kcal/mol)[48] to form intermediate **III**. The chromium radical Cr• should now abstract an $\alpha$ hydrogen atom from **III** via the thermodynamically favorable HAT process described above, generating the desaturation product and regenerating the chromium hydride (Cr−H).

## RESULTS AND DISCUSSION

We have tried several iron/chromium co-catalysts (Table 1). We have found that a combination of iron$^{II}$ acetate, H−$CrCp(CO)_3$, and acetic acid in 1,4-dioxane gives an optimal yield (entry 1, 85%) of desaturated product **1** from 3-(3-phenylpropyl)-1,4,2-dioxazol-5-one (**S1**). Other iron catalysts (entries 2−5) proved less effective at desaturation; apparently direct decomposition of some **S1** results in the saturated formamide **1′** and a Curtius rearrangement by-product **1″** (see Table S1 for more details). Manganese,

**Table 1. Optimization of Remote C($sp^3$)−H Desaturation with Fe/Cr Co-catalysis**[a]




| entry | deviation from standard condition | yield[b] (%) |
|---|---|---|
| 1[c] | 10 mol % $Fe(OAc)_2$, 10 mol % $HCrCp(CO)_3$, 1.0 equiv. AcOH, 1 mL 1,4-dioxane, rt, Ar, 1 h | 85 |
| 2 | $FeCl_2$ instead of $Fe(OAc)_2$ | 45 |
| 3 | $FeBr_2$ instead of $Fe(OAc)_2$ | 32 |
| 4 | $Fe(OTf)_2$ | 13 |
| 5 | FePc[d] | trace |
| 6 | $MnCl_3$/$RuCl_3$/$IrCl_3$ | trace |
| 7[e] | $HCrCp^*(CO)_3$ or $HCrCp^{\#}(CO)_3$ | 31 or 52 |
| 8 | $NaCrCp(CO)_3$ instead of Cr−H | 10 |
| 9 | w/o AcOH | 30 |
| 10 | 0.2 equiv AcOH | 55 |
| 11 | 2.0 equiv TFA instead of AcOH | trace |
| 12 | THF instead of 1,4-dioxane | 35 |
| 13 | DCE instead of 1,4-dioxane | 72 |
| 14 | 60 °C for 0.5 h | 78 |
| 15 | under air | 0 |

[a]Reaction conditions: substrate (0.1 mmol), catalysts (10 mol %), and acetic acid in 1 mL of solvent, conducted for 1 h at room temperature under an argon atmosphere, unless otherwise noted. [b]Yields were determined by $^1$H NMR using internal standard. [c]Standard conditions. [d]Phthalocyanine iron$^{II}$. [e]Cp* ($-C_5Me_5$), $Cp^{\#}$ ($-C_5Ph_5$).

ruthenium, and iridium catalysts (entry 6), used to generate nitrenoid complexes in previous research,[49−51] have proven ineffective at replacing $Fe(OAc)_2$ in our desaturation chemistry. Variation of the Cp in the chromium hydride co-catalyst (entry 7) shows that the more congested ligands Cp* and $Cp^{\#}$ lead to a decrease in yield (to 31% and 52%, respectively), while the $[CrCp(CO)_3]^-$ anion is even less effective at desaturation (entry 8, 10%). Acetic acid is indispensable when dioxazolones are employed as substrates; when it was omitted, entry 9, or decreased, entry 10, lower yields were obtained. Stronger acids (entry 11) are not tolerated, presumably because they decompose **S1**. No improvement in the yield was obtained with other solvents, such as tetrahydrofuran or 1,2-dichloroethane (entries 12 and 13). A lower yield was obtained when the reaction was conducted at 60 °C (entry 14), presumably because substrate **S1** decomposed slowly at that temperature. The desaturation reaction is so sensitive to air that no product is formed from **S1** in the presence of air (entry 15).

With the optimized catalyst system in hand, we investigated the scope of the HAT-mediated C($sp^3$)−H desaturation of amide derivatives (Table 2). The reaction tolerates a wide range of electron-donating and electron-withdrawing substituents on the aromatic ring of 3-(3-phenylpropyl)-1,4,2-dioxazol-5-ones (Table 2A), including methoxy (**2**), methyl (**3**), isopropyl (**4**), phenyl (**5**), halides (**6**−**8**), nitro (**9**), trifluoromethyl (**10**), and 2,4-dimethoxy (**11**). In all cases, the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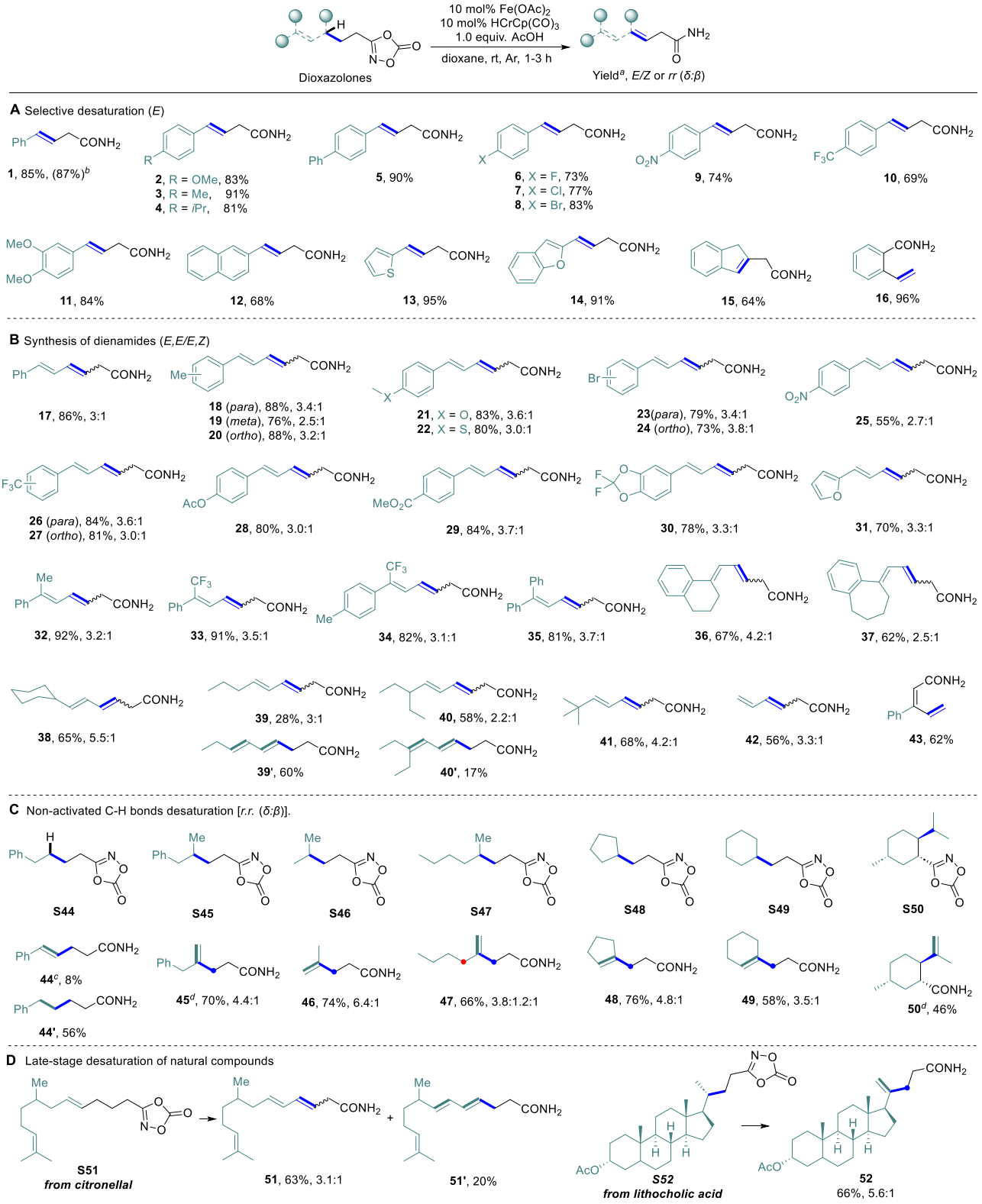
## Table 2. Substrate Scope of Cr−H/Fe Co-catalyzed Desaturation[a]




[a]Reaction conditions: substrates (0.2 mmol), 10 mol % $Fe(OAc)_2$, 10 mol % $HCrCp(CO)_3$, and 1.0 equiv acetic acid in 1,4-dioxane (1 mL) at room temperature for 1−3 h under argon; yields were determined by $^1H$ NMR using 2-nitrobenzaldehyde as internal standard; unless noted, only the *E*-isomer was obtained. [b]Large scale: substrate (10 mmol), 5 mol % $Fe(OAc)_2$, 5 mol % $HCrCp(CO)_3$, and 1.0 equiv acetic acid in 1,4-dioxane (10 mL) at room temperature for 1 h under argon. [c]30 mol % $Fe(OAc)_2$, 30 mol % $HCrCp(CO)_3$ were used. [d]1,2-Dichloroethane as reaction solvent.



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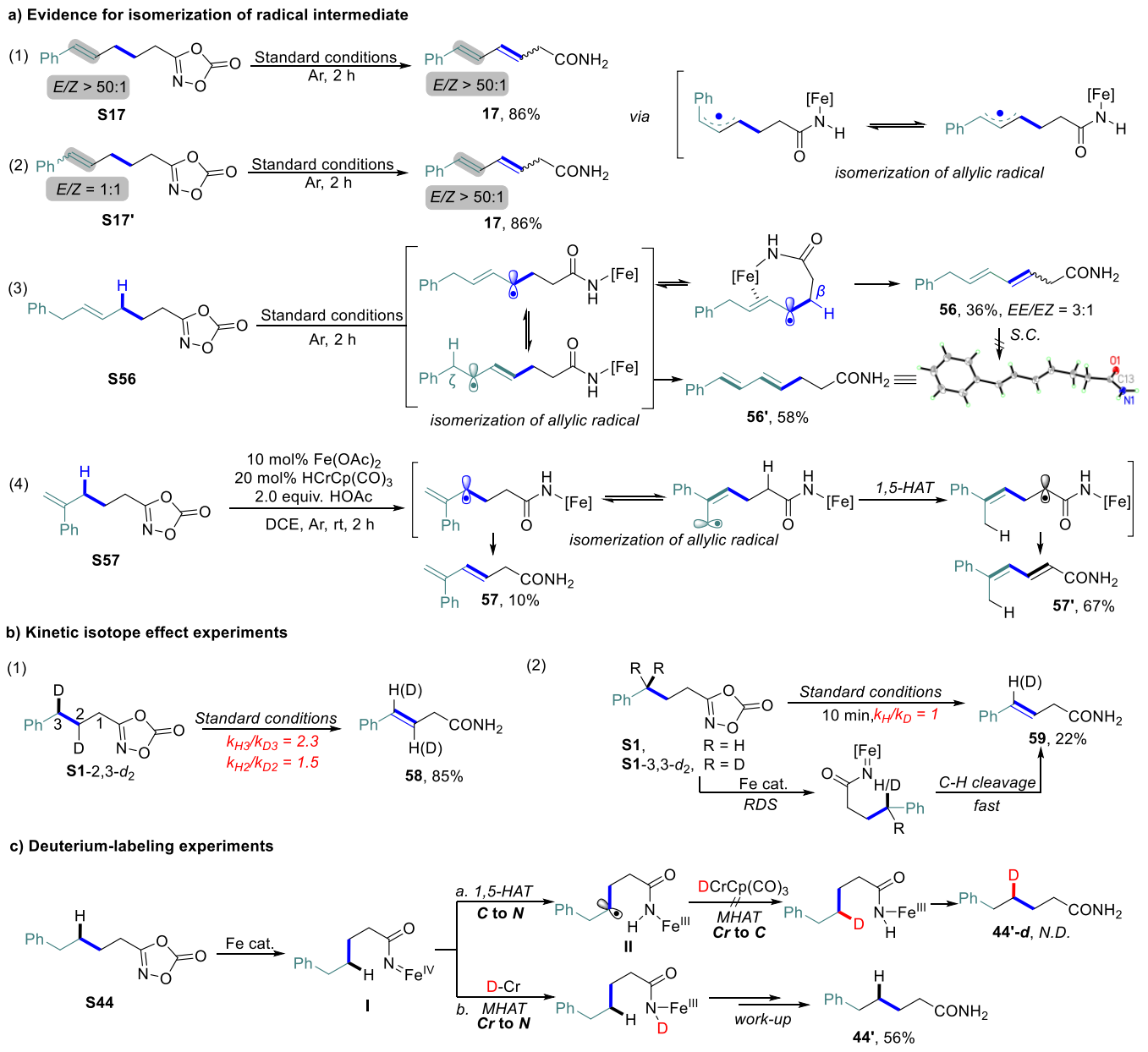


**Figure 2.** Mechanistic experiments. (a) Evidence for isomerization of allylic radical intermediates. (b) Kinetic isotope effect measurements, (1) intramolecular KIE, (2) intermolecular KIE. (c) Deuterium-labeling experiments for the pathway of byproducts.

yields of $\beta,\gamma$-unsaturated amides were satisfactory (69−91%). Desaturation is not limited to chains with phenyl substituents but works with other aromatic rings, such as naphthyl (**12**, 68%), thiophenyl (**13**, 95%), benzofuranyl (**14**, 91%), and indenyl (**15**, 64%). The preferential formation of *E* products (**1**−**14**) is ascribed to the exceptionally rapid H• transfer mediated by the chromium complex.[48] Vinyl derivatives like **16**, which are valuable feedstocks and synthetic intermediates, are available industrially with iron oxide catalysts, but only at extremely high temperatures;[52] our HAT-mediated cooperative desaturation gives the vinylbenzamide **16** in 96% yield.

Methodologies for the preparation of conjugated dienamides have been even less available[10,53] than methods for the preparation of but-3-enamides. Our HAT-based desaturation reaction can make **17**−**43** (Table 2B), which are found in various natural products and their metabolites.[54−57] The substrates required for dienamide synthesis (**17**−**43**) are readily obtained from aldehydes or ketones via Wittig reactions. Compatible functional groups are the electron-donating ones in **18**−**22**, the bromines in **23** and **24**, the electron-withdrawing ones in **25**−**29**, and the sterically hindered ones in **20** and **27**. In general, conjugated dienamides are obtained in good to excellent yields (55−88%) with good *E,E* selectivity, although some *E,Z*-isomers were observed, attributed to weak coordination of the initial double bond to the iron (Figure 2a, eq 3). Particularly good yields have been obtained for 2,2-difluoro-1,3-dioxole (**30**) and furanyl (**31**)-substituted and 6,6-disubstituted (**32**−**35**) products, and for dienamides (**38**−**41**) containing alkyl substituents in distal positions. Terminal dienes like **42** and **43** are available in moderate yields, and cyclic structures like **36** and **37** are available in lower yields, presumably as a result of steric hindrance.



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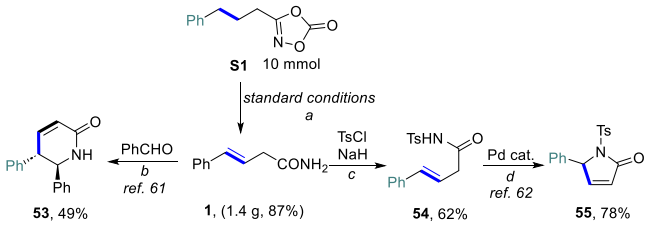
We have tested our desaturation reaction on nonactivated aliphatic substrates like **S44**–**S50**, with C($sp^3$)–H bonds ranging from 96 to 101 kcal/mol.[58] Disappointingly, with 30 mol % of the catalysts little *γ,δ*-desaturated amide **44** was formed, along with 56% of the byproduct **44′** (Table 2C). An additional methyl substituent, which makes the C–H bonds in substrates **S45**–**S47** tertiary, gives appreciably better yields of the *γ,δ*-unsaturated products **45**–**47**. Cycloalkyl substrates are selectively desaturated at their *δ* C–H bonds, giving *γ,δ*-desaturated derivatives (**48**, **49**) with useful regioselectivities (up to 4.8:1). The yields of **45** and **50** are much higher in 1,2-dichloroethane than in 1,4-dioxane.

Carbon–carbon double bonds are easily transformed into many other functional groups,[59,60] and the late-stage desaturation of pharmaceutics may prove useful. Our iron/chromium cooperative catalysts easily convert the citronellal derivative **S51** to **51** in 63% yield (Table 2D), although the reaction is accompanied by some formation of the isomeric dienamide **51′** (20%). We have also been able to convert dioxazolone **S52**, derived from lithocholic acid, to unsaturated steroid derivative **52**.

**Scheme 1. Synthetic Utility of Unsaturated Amides**[a]




[a]Reaction conditions: [b]**1** (0.2 mmol), benzaldehyde (0.2 mmol) in polyphosphate ester (1 mL) at 10 °C under argon for overnight; [c]**1** (0.2 mmol), TsCl (0.2 mmol) and NaH (0.4 mmol) in THF (1 mL) at 40 °C for 5 h; [d]for **55**, see ref 62.

Our iron/chromium co-catalyst is effective on a large scale. With 5 mol % of each catalyst we can convert 10 mmol of **S1** to **1** in 87% yield, eventually allowing the highly stereocontrolled, efficient preparation of the 5,6-dihydro-2(1*H*) pyridinone **53** in 49% yield[61] and of the 3-pyrrolin-2-one **55**[62] in 78% yield (Scheme 1). Compounds **53** and **55** model the core structures of many natural products, drugs, and agrochemicals.[63,64]

Radical mechanisms have been established by earlier work on the H• transfer chemistry of oxo and nitrene iron complexes.[65−67] Evidence in the present case is offered by the configuration of the gray double bond in diene **17** (Figure 2a). An *E* configuration in substrate **S17** gives **17** that retains the *E* configuration of the gray double bond (Figure 2a, eq 1); **S17′**, with a mixture of the *E* and *Z* configurations, gives **17** with entirely an *E* configuration for the gray double bond (Figure 2a, eq 2). Both *E* configurations are consistent with the *Z*/*E* isomerization of an allyl radical intermediate.[27,68]

Additional evidence is offered by the formation of double-bond isomers **39′**, **40′**, **56′**, and **57′** along with the expected dienamides **39** and **40** (Table 2B), **56**, and **57** (Figure 2a, eqs 3 and 4). The positions of the double bonds in **39′**, **40′**, **56′**, and **57′** are consistent with the isomerization of allyl radical intermediates. (The structure of **56′** has been confirmed (details in the SI) by X-ray crystallography.) The dienamide originally expected, **56**, does not isomerize to **56′** under the reaction conditions (Figure 2a, eq 3).

Kinetic isotope effect (KIE) experiments (Figure 2b) have suggested the rate-determining steps in these desaturation reactions. An intramolecular competition experiment on **S1**-2,3-$d_2$, with each carbon bearing a deuterium, gave a KIE of 2.3 for C3 and a KIE of 1.5 for C2. In contrast, no KIE was observed for the intermolecular competition between **S1** and **S1**-3,3-$d_2$. These results show that C–H bond cleavage is *irreversible*, consistent with the formation of a nitrenoid in the rate-determining step (Figure 2b, eq 2).[47,69]

Finally, we wanted to explore the extent of H• transfer from Cr to the *reactive* radicals **II** formed from *unweakened* C–H bonds, for example, the radical formed from **S44** in Figure 2c. The use of $CpCr(CO)_3D$ and AcOD *did not* give any deuterium incorporation into **44′** (no **44′**-*d* was detected by HRMS or $^1$H NMR), which means *pathway a* (Figure 2c) can be ruled out for the generation of **44′**. Presumably the D• is transferred instead to the nitrenoid *N* (*pathway b*) and exchanged during workup in the presence of excess acid. The same result—lack of D incorporation into **44′**—confirms that cleavage of C–H bonds is *irreversible*, which is consistent with our conclusion from the KIE experiments.

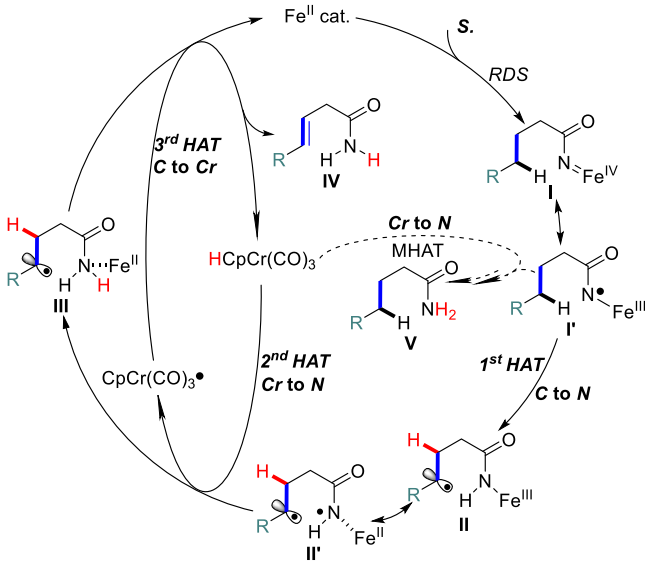



**Figure 3.** Proposed mechanism for desaturation enabled by Fe/Cr–H cooperative catalysis.

On the basis of these experiments and previous reports,[28,47,70,71] we propose the catalytic cycle in Figure 3 for the remote C($sp^3$)–H desaturation of amides. There are good precedents for the decarboxylation of dioxazolones by $Fe^{II}$ to $Fe^{IV}$ nitrenoid intermediates like **I**. By intramolecular 1,5-HAT from the *γ* carbon to the nitrenoid nitrogen, these intermediates generate carbon-centered radicals **II**, which have *β*-C–H bonds of only 35 kcal/mol. (Another possibility is an intermolecular MHAT between Cr–H and the nitrenoid **I**, which—after removal of the *N* from the *Fe*—would explain the observed byproduct **V**.) The transfer of a H• from Cr to the N of **II**, releasing •$CrCp(CO)_3$, gives intermediate **III**. Removal of the *β* hydrogen from **III** by •$CrCp(CO)_3$, and protic cleavage of the ligand from the iron complex, gives the unsaturated product **IV**, and the iron catalyst is regenerated.



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## CONCLUSION

We have demonstrated the remote $\beta,\gamma$- or $\gamma,\delta$-desaturation of amides by iron and chromium hydride cooperative catalysis. The reaction seems likely to involve a triple HAT process: (i) a 1,5-HAT from a remote C−H bond to an iron nitrenoid (C to N); (ii) a chromium-hydride-mediated HAT to the N-center (Cr to N); (iii) the abstraction of a second H• from the C−H bond close to the radical by the chromium radical Cr• (C to Cr). Most tertiary C−H bonds and activated secondary C−H bonds are subject to the desaturation reaction. Because the substrates are readily available, the metal catalysts are cheap, and the conditions are mild, we hope that our reaction can be applied to the manufacture of pharmaceuticals.

## ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c13085.

Experimental details, materials and methods, characterization data, NMR spectra for all compounds (PDF)

### Accession Codes

CCDC 2288241 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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