Cooperative Fe/Co Catalyzed Remote Desaturation for the Synthesis of Unsaturated Amide Derivatives

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ABSTRACT: Unsaturated amides represent common functional groups found in natural products and bioactive molecules, serving as versatile synthetic building blocks. Here, we report an iron(II)/cobalt(II) dual catalytic system for the syntheses of distally unsaturated amide derivatives. The transformation proceeds through an iron nitrenoid-mediated 1,5-hydrogen atom transfer (1,5-HAT) mechanism. Subsequently, the radical intermediate undergoes hydrogen atom abstraction from the vicinal methylene by a cobaloxime catalyst, efficiently yielding β,γ- or γ,δ-unsaturated amide derivatives under mild conditions. The efficiency of Co-mediated HAT is tunable by varying different auxiliaries, highlighting the generality of this protocol. Remarkably, this desaturation protocol is also amenable to practical scalability, enabling the synthesis of unsaturated carbamates and ureas which can be readily converted into various valuable molecules.

Carbon-carbon double bonds are ubiquitous in natural products and functional materials,[1-3] while olefins stand out as versatile functional groups with significant synthetic utility.[4-8] Classical methods for olefin synthesis,[9-16] such as halide or alcohol elimination,[9] the Wittig reaction,[16, 17] *etc.*, usually rely on prefunctionalized starting materials. The direct conversion of feedstock aliphatic molecules into privileged alkenyl structures could offer a more practical and appealing approach,[18, 19] despite the inherent challenge associated with the controlling of selectivity in those transformations.[20] To date, transition metal-catalyzed oxidative desaturation of α-carbonyl alkanes at weak acidic C(sp^3)–H bonds has witnessed much progress.[21-25] In sharp contrast, the remote desaturation of carbonyl aliphatics involving strong C(sp^3)–H bonds remains scarcely investigated.[26, 27] Among the rare examples of remote and catalytic desaturation, the hydrogen atom transfer (HAT) process, instigated by radicals generated *in situ* from either the oxidized or reduced precursors, is particularly notable (Figure 1a).[26, 28-34] The seminal biomimetic desaturation of steroids via intramolecular HAT enabled C(sp^3)–H activation was first reported by Breslow and co-workers,[35] which convincingly demonstrated the potential of such a strategy for the late-stage remote desaturation of natural or bioactive molecules. Collectively, the precursors of radicals can be strategically chosen to access radicals centered on oxygen (*via* O–O bond),[28] nitrogen (*via* N–F or N–O bonds),[29, 32] and carbon (*via* Ar–N_3R, Ar–I, SiCH_2I or C=C) (Figure 1a).[26, 27, 30, 31, 33] Utilizing the HAT-strategy, Čeković and co-workers showcased a direct remote desaturation of alkyl hydroperoxides based on oxygen-centered radicals. Following these pioneering studies, nitrogen- and carbon-centered radical-initiated HAT processes for desaturation have also been employed to overcome the thermodynamic obstacle of C(sp^3)–H abstraction by forming a stronger N–H or C–H bond.

Photochemistry has evolved as a valuable technique for achieving milder reaction conditions and facilitating transformations of double bonds.[36] The cutting-edge approach in metallaphotoredox catalysis has garnered significant attention in desaturation reactions. Notably, photoredox catalysis in conjunction with biomimetic cobaloxime complexes has emerged as a distinctive and promising option in this field (Figure 1b).[37-45] A photoredox catalyst mediates an oxidative process to form a carbon-centered radical, while the cobaloxime complex functions as a proton reduction catalyst.

Recently, our group reported a remoted γ-C(sp^3)–H bond functionalization of 1,4,2-dioxazol-5-one substrates. The reaction was initiated by an iron nitrenoid via a 1,5-HAT process,[46] which offers a facile route to rapidly access carbon-centered radicals that enables further functionalizations. Inspired by the efficient radical generation through metal nitrenoid systems,[46-57] along with the recent advancements in direct desaturation of aliphatics through cobaloxime-based photoredox catalysis, we envision that the carbon radical generated in this manner could, in principle, be integrated with the hydrogen atom abstraction reactivity of cobaloximes to achieve remote desaturation of amide derivatives.[58-60] Very recently, the Chang group reported an Ir-catalyzed desaturation of electron-rich 1,4,2-dioxazol-5-ones via an Ir nitrenoid intermediate. However, that reaction proceeded via a hydride transfer process mediated by an iridium nitrenoind followed by E_1 elimination.[61] Here, we present an iron/cobalt cocatalyzed remote desaturation for the syntheses of unsaturated amide derivatives (Figure 1c). A simple iron salt reacts with the nitrene precursor (*N*-acyloxy amide) to form an iron nitrenoid species. This iron nitrenoid species abstracts a remote hydrogen atom (H•) via 1,5-HAT process to yield the crucial carbon-centered radical. A cobaloxime catalyst [$L_2Co(dmgBF_2)_2$] can subsequently abstract a second H• from the adjacent C(sp^3)–H bond to provide the desaturated amide derivatives (Figure 1c).

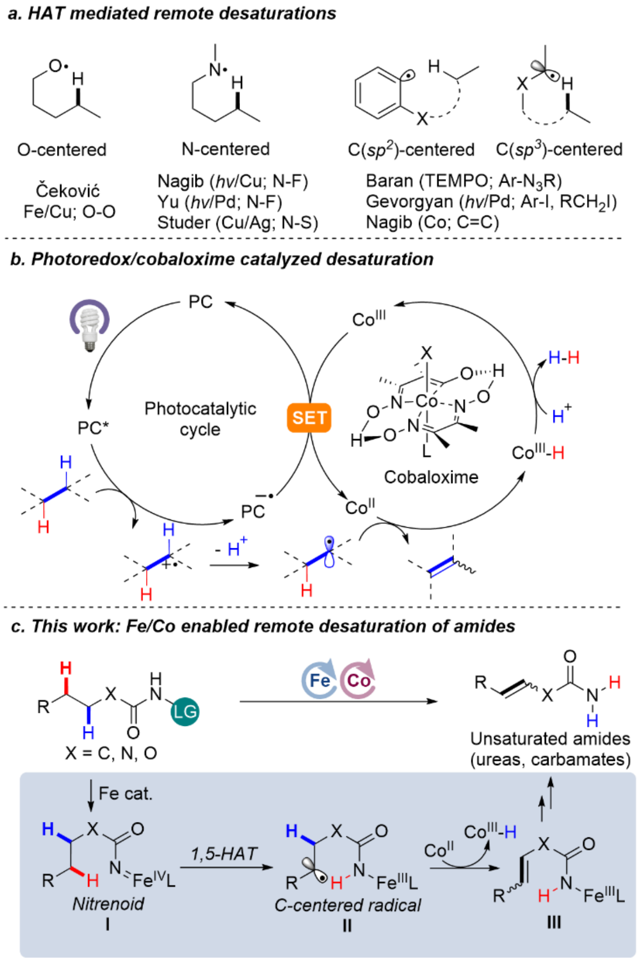
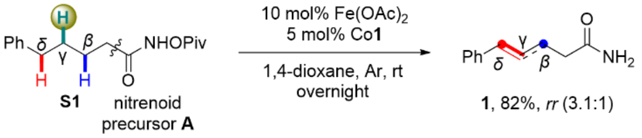


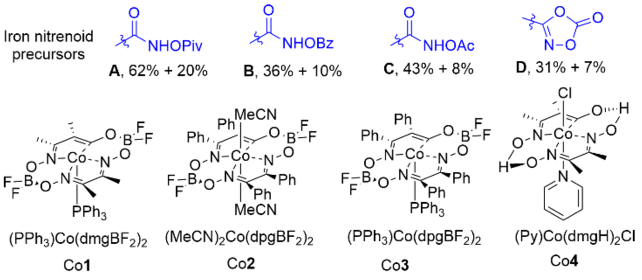
Figure 1. HAT strategy for desaturation. **a**. HAT mediated remote desaturations. **b.** Photoredox/cobaloxime catalyzed desaturations. **c.** This work: Fe/Co enable remote desaturation of amide derivatives.

To assess the viability of the proposed strategy, our investigation commenced with the desaturation of 5-phenyl-*N*-(pivaloyloxy)pentanamide **S1** bearing challenging non-activated γ-C(sp^3)–H bonds (Table 1). Our evaluation revealed the combination of 10 mol% iron(II) acetate and 5 mol% $(PPh_3)Co(dmgBF_2)_2$ catalyst (Co**1**)[60] in 1,4-dixoane was optimal for the production of the desaturation product **1** (82%, *rr* 3.1:1). Variations in iron catalysts highlighted the significant impact of electronic effects on the yield of the desaturation product **1** (Table 1, entries 1-4). Either electron-deficient catalyst $Fe(OTf)_2$ or electron-rich catalyst FePc (iron phthalocyanine) resulted in drastical decrease in yields (< 5%). We next investigated the effect of the cobaloxime catalysts (Table 1, entries 5-7). Both $(MeCN)_2Co(dpg\ BF_2)_2$ (Co**2**) and $(PPh_3)Co(dpgBF_2)_2$ (Co**3**) proved less effective in the desaturation process. In addition, the more electron-deficient catalyst $(Py)Co(dmgH)_2Cl$ (Co**4**) was ineffective in replacing Co**1** in the desaturation process, indicating that electron-rich ligands can enhance the reactivity of cobaloxime in abstracting H•.[60] The yield was not improved in the presence of 2.0 equivalent acetic acid (Table 1, entry 8). Some other commonly used nitrene precursors, including *N*-acyloxy amides (**B** and **C**), dioxazolone **D**, were also investigated (Table 1, entry 9). However, all three precursors provided the desaturation products in lower yields (38% - 51%). No further improvement in yield was achieved upon changing the solvent (Table 1, entries 10-11). Moreover, air is proved deleterious to the desaturation protocol (Table 1, entry 12. see Table S1 and S2 in the Supporting Information for full data of reaction optimization).

Table 1. Optimization of iron/cobalt co-catalyzed remote desaturation.[a]



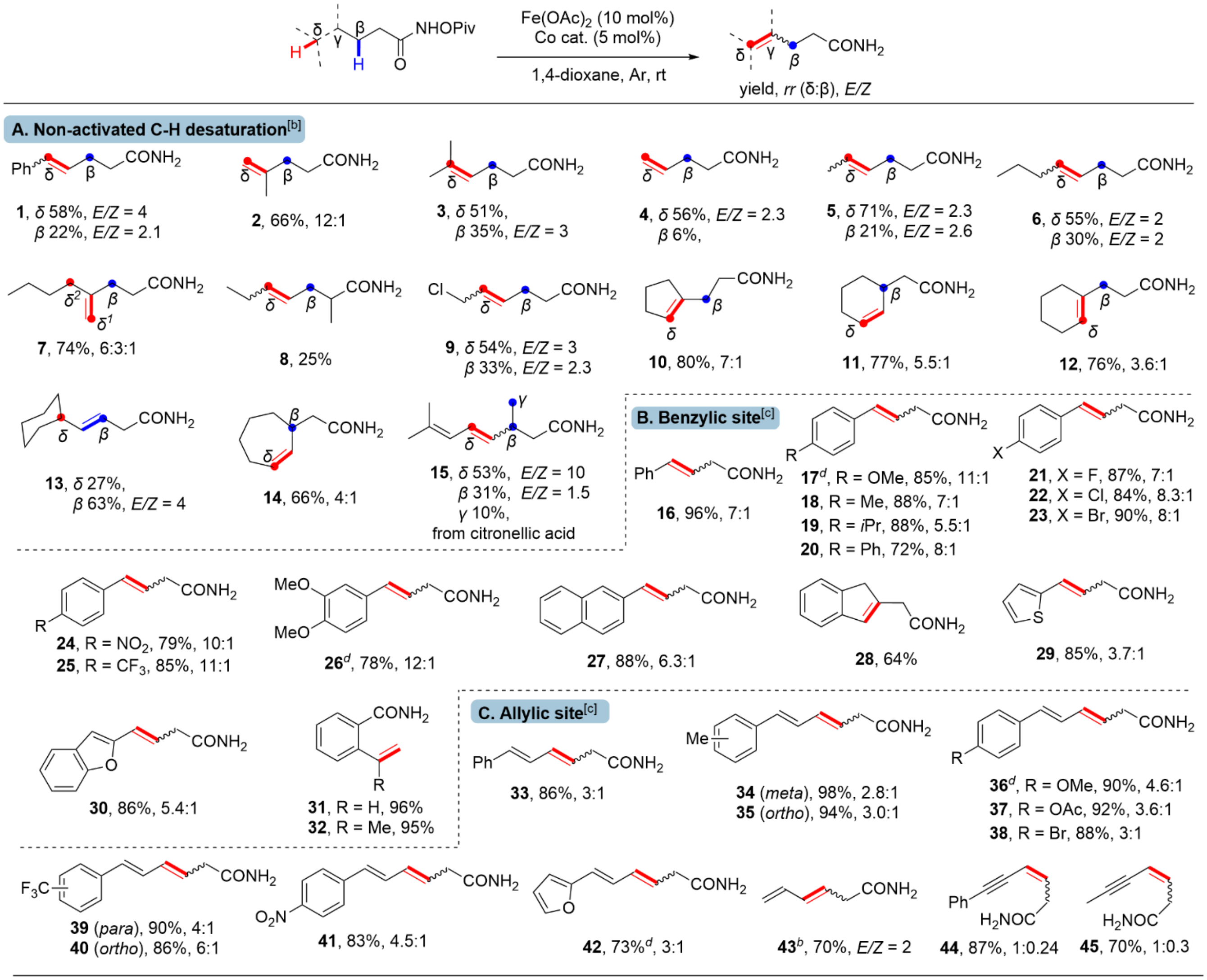
Entry	Deviation from standard condition	Yield[b] (%)	
		γ,δ-	β,γ-
1	none	62	20
2	$FeCl_2$ instead of $Fe(OAc)_2$	45	15
3	$Fe(OTf)_2$ instead of $Fe(OAc)_2$	trace	trace
4	FePc instead of $Fe(OAc)_2$	< 5	< 5
5	Co**2** instead of Co**1**	61	8
6	Co**3** instead of Co**1**	52	13
7	Co**4** instead of Co**1**	-	-
8	2.0 equiv. AcOH as additive	62	18
9	Precursors **B**, **C**, **D** instead of **A**	38-51	
10	THF instead of 1,4-dioxane	12	< 5
11	DCE instead of 1,4-dioxane	45	13
12	Under air	-	-



[a] *rr* is regioselectivity ratio; reaction conditions: substrate (0.1 mmol), Fe catalyst (10 mol%), Co catalyst (5 mol%) in solvent (1 mL) at room temperature under argon overnight. [b] NMR yields with internal standard (4-bromobenzaldehyde).

Under the optimized condition, we evaluated the scope of this Fe/Co co-catalyzed desaturation of amide derivatives (Table 2). Simple linear aliphatic substrates were tested first and found to be compatible with the current conditions, yielding more preferable γ,δ-desaturated products than β,γ-desaturations in good to excellent yields (**1**-**15**) due to the weaker electronic effect on the δ position (Table 2A). Various substituents (chloride, phenyl, alkyls, *etc.*) on the carbon chain were well-tolerated, though an α-methyl substituted substrate gave desaturated **8** in 25% yield, which can be attributed to the Curtius rearrangement. Similarly, various cycloalkyl substrates provide majority γ,δ-desaturated products (**10**-**12**, **14**) in good regioselectivities (up to *rr* 7:1). If a bulky cyclohexyl group is present at the δ position, the formation of γ,δ-desaturated products will be rendered and a much higher yield of β,γ-desaturated product is obtained instead (**13**, 90%, *rr* 1:2.3). Olefin substrates, which can undergo late-stage diversifications in drug discovery,[62] are usually vulnerable due to the electron-rich C=C bonds. However, they are well tolerated in this reaction. A citronellic acid derivative was successfully desaturated under optimal conditions in an excellent total yield with three isomers (**15**, 94%).

Table 2. Substrate Scope of Fe/Co co-catalyzed desaturaion.[a]



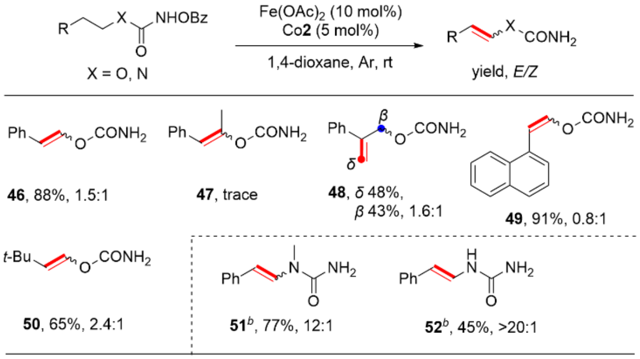
[a]Reaction conditions: Substrates (0.2 mmol), 10 mol% $Fe(OAc)_2$ and 5 mol% Co catalyst in 1,4-dioxane (1 mL) under argon at room temperature overnight; Yields were determined by ^1H NMR. [b]Using 5 mol% $PPh_3Co(dmgBF_2)_2$ (Co**1**). [c]Using 5 mol% $(MeCN)_2Co(dmpBF_2)_2$ (Co**2**). [d]Using 10 mol% $Fe(OTf)_2$, 10 mol% Co**2** and 20 mol% sodium iodide (NaI) as additive.

Benzylic substrates are next examined under the optimal condition. We were delightful to discover that a diverse range of substrates (**S16** - **S30**) encompassing various aryl substitutients exhibit excellent susceptibility to the Fe/Co co-catalyzed desaturation reaction, resulting in consistently high yields of desaturated products (up to 96%) predominantly favoring the *E*-configuration (Table 2B). This reactivity extends across a broad scope of substrates with diverse electronic properties and proves compatible with commonly encountered organic functional groups, including electron-rich arenes (**17**-**20**, **26**), aryl halides (**21**-**23**), nitro- (**24**) and CF_3-substituated (**25**) phenyls as well as naphthyl (**27**) and heteroaryls (**29**, **30**). It is noted that the desaturation of substrates featuring strong electron-donating groups (**17**, 85%, *E/Z* = 11, and **25**, 78%, *E/Z* = 12) were conducted under slightly modified conditions where $Fe(OTf)_2$ was used as the catalyst and NaI was used as an additive to enhance the desaturation process. It is noteworthy that highly valuable vinyl derivatives vinylbenzamides (**31** and **32**), which are typically produced using iron oxide catalysts under extremely high temperatures in industry,[63] can be obtained through our Fe/Co cocalayzed desaturation protocol in nearly quantitative yields under mild conditions.

In stark contrast to alkene formation, methods for synthesizing conjugated diene or enyne derivatives via hydrogen atom transfer remain significantly underexplored.[27, 64] Our system presents a mild process for generating the corresponding 1,3-conjugated dienes and enynes with excellent yields (**33**-**45**) (Table 2C). The functionalized dienes bearing electron-rich aryls (**34**-**36**, **42**) and electron-withdrawing aryls (**37**-**41**) can all be successfully synthesized with high to excellent yields (73%-98%). Moreover, a terminal diene (**43**) can also be obtained in 70% yield. It is worth mentioning that substrates with alkynyl group interestingly give the thermodynamically unfavorable *Z*-configuration enynes as major products (**44**, 87%, *E/Z* = 0.24 and **45**, 70%, *E/Z* = 0.3 respectively), which can be attributed to the coordination between the iron and carbon-carbon triple bonds that poses a more accessible H atom on a *cis* C(sp^3)–H bond for the cobaloxime to abstract.

Due to its mild conditions and exceptional functional group compatibility, this Fe/Co cooperatively catalyzed method shows promise for the concise and efficient synthesis of desaturated carbamates and carbamides (Table 3). To our delight, this Fe/Co co-catalytic system proves effective in the desaturation of carbamides when *N*-(benzoyloxy)amide is employed as the iron-nitrenoid precursor. The corresponding products (**46**-**50**) are obtained in good yields. Particularly, the *tert*-butyl substrate exhibits robust tolerance under the conditions, yielding the desaturated carbamate derivative **50** in a 65% yield (*E/Z* 2.4:1). Likewise, the desaturation of carbamides occurs at 80 °C in just 1 hour to rapidly deliver **51** (77%, *E/Z* 12:1) and *N*-unprotected carbamide **52** in 45% yield, respectively. These results demonstrated the potential application of this Fe/Co cocatalytic system in the efficient synthesis of diverse desaturated carbamates and carbamides.

Table 3. Fe/Co co-catalyzed desaturation for synthesis of unsaturated carbamates and carbamides. [a]



[a]Substrates (0.2 mmol), $Fe(OAc)_2$ (10 mol%) and Co2 (5 mol%) in 1,4-dioxane (1 mL) under argon for overnight. [b]At 80 °C for 1 h; Yields were determined by ^{1}H NMR.

To gain insight into the mechanism of this dual metal-catalyzed desaturation process, various mechanistic studies were conducted. Kinetic isotope effect (KIE) experiments were employed to investigate the rate-determining step (RDS) (Figure 2a). In an intramolecular competition experiment involving **S16-*d*₁** with 2,3-dideuterium, KIE values of 2.5 and 1.3 were determined (Figure 2a, eq 1). In sharp contrast, no KIE was observed in an intermolecular competition between **S16** and **S16-*d*₂** (Figure 2a, eq 2). These results can be attributed to the fact that an irreversible binding between the substrate and catalyst is not involved in the cleavage of the C–H bond.[46, 65] In other words, the C–H bond cleavage is an irreversible process and occurs after RDS. Consequently, we infer that the rate-determining step is the formation of the iron nitrenoid species.[46]

To experimentally explore the generation of Co^{III}–H species, we carried out the deuterium-labeling and crossover experiments starting with a mixture of **S16-*d*₁** and **S29** in the presence of deuterated acetic acid (AcOD, 0.1 mL) (Figure 2b). Notably, no intermolecular H/D exchange product **29-D** was detected. The absence of H/D exchange suggests that both the iron nitrenoid-initiated 1,5-HAT process and the hydrogen abstraction process by cobaloxime are irreversible, aligning with the conclusions drawn from the KIE experiments. These findings further support the notion that the Co-mediated *β*-H abstraction involves a radical pathway rather than a concerted *β*-H elimination.[40] Furthermore, a concerted *β*-H elimination pathway requires a vacant coordination site *cis* to the alkyl group.[66] The hypothetical [$L_2Co(dmgBF_2)_2$] alkyl complex evidently fails to meet this criterion, as four equatorial coordination sites *cis* to the alkyl are already occupied by two coplanar ($dmgBF_2$) anion ligands.[67]

We endeavored to elucidate the catalytic cycles involving a Co^{III} hydride and an intermediate **III** (Figure 1c and 2c). The protonation of Co^{III}–H can result in the release of dihydrogen (Figure 1b). Nevertheless, no H_2 evolution was detected using gas chromatography in our reaction. This result suggests another possibility where a Co^{III}–H species may undergo proton transfer to result a Co^{I} species.[68-72] Accordingly, a mechanistic outline is depicted in eq 1 and eq 2 (Figure 2c). The intermediate **III** is protonated to give the desaturated product and $PivOFe^{III}(OAc)_2$ (eq 1). The Co^{III}–H can tautomerize to provide a Co^{I} center and an exchangeable proton (Figure 2c, eq 2).[68] The Co^{I} species ($E^{red}[Co^{II}/Co^{I}] = -0.28$ V versus SCE in MeCN)[69] then undergoes a single-electron transfer with the Fe^{III} species ($E^{red}[Fe^{III}/Fe^{II}] = 0.53$ V versus SCE)[73], thus simultaneously facilitating turnover in both the iron and cobalt cycles (Figure 2c, eq 2).

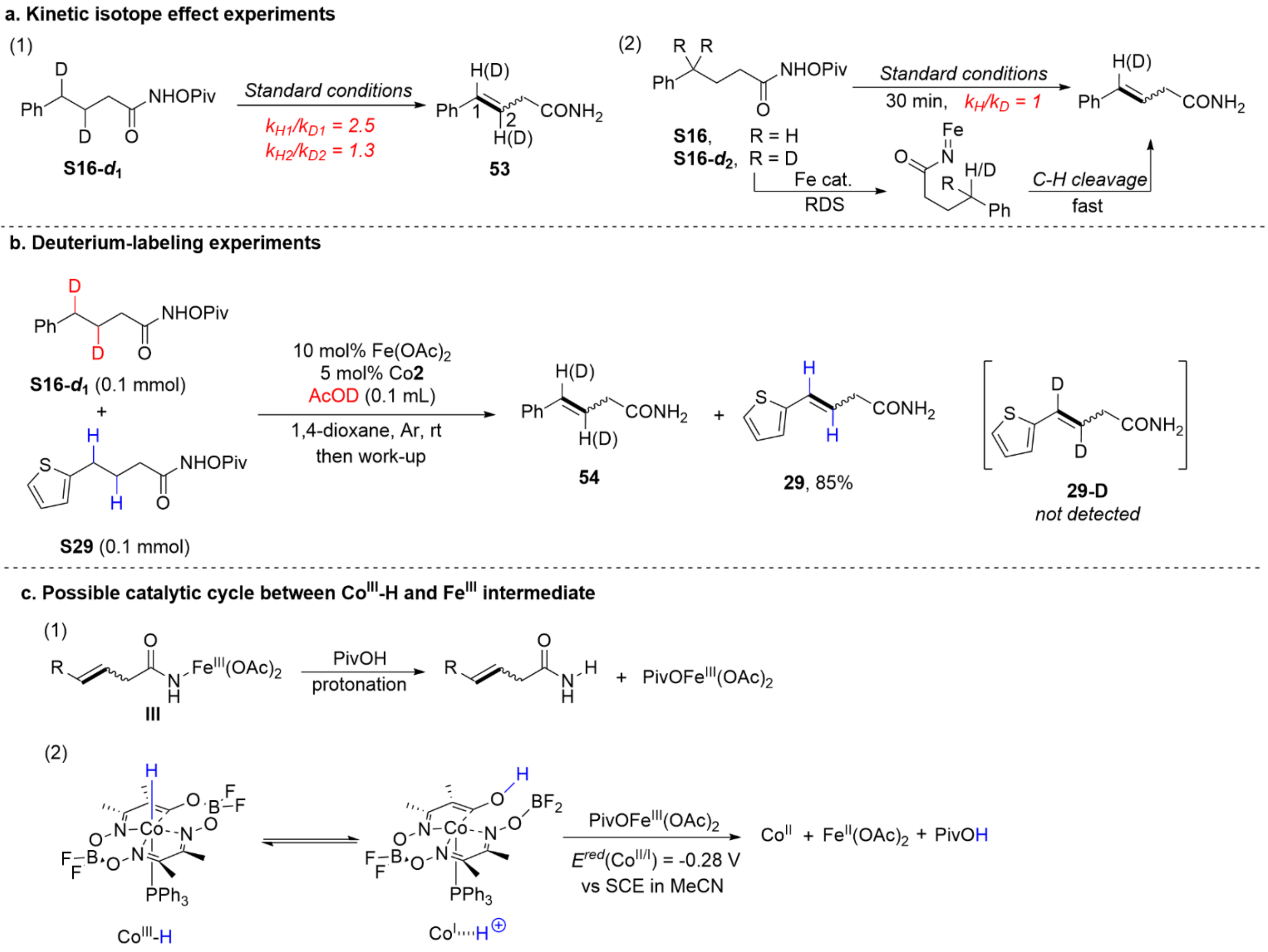


Figure 2. Mechanistic experiments. **a.** Kinetic isotope effect experiments. **b.** Deuterium-labeling and D/H exchange experiments. **c.** Possible catalytic cycle for Co^{III}-H and Fe^{III} intermediate.

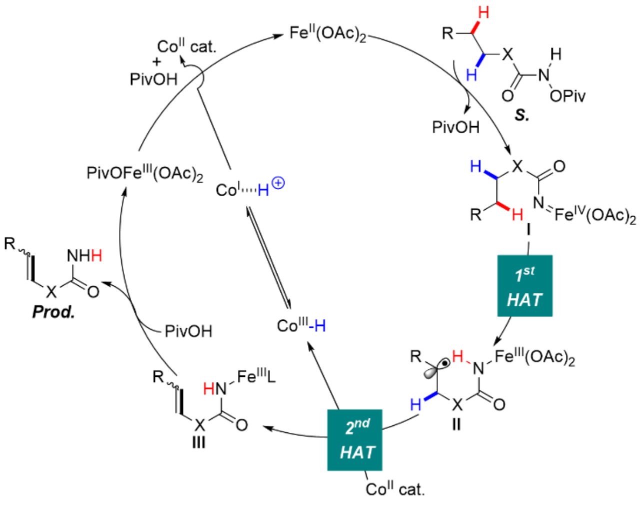


Figure 3. Proposed mechanism for Fe/Co co-catalyzed desaturation of amides derivatives.

Based on these experiments and precedents, a plausible mechanism for the Fe/Co cocatalyzed remote desaturation is outlined in Figure 3. The iron catalyst first reacts with the nitrene precursor to form an iron-nitrenoid intermediate **I**. The highly active metal nitrenoid can readily and selectively abstract a hydrogen atom via 1,5-HAT process, leading to the formation of the carbon-centered radical intermediate **II**. Subsequently, in the second HAT step catalyzed by the cobaloxime catalyst, a second hydrogen atom is abstracted to generate the desaturated intermediate **III** and a Co^{III}–H species. This Co^{III}–H species can tautomerize to form a Co^{I} complex and a proton. Simultaneously, intermediate **III** can be protonated to release an Fe^{III} intermediate along with the desired desaturated products. The generated Co^{I} complex can then reduce Fe^{III} to Fe^{II}, thus facilitating the regeneration of the cobaloxime catalyst.

In conclusion, we have successfully demonstrated a remote desaturation of diversely functionalized aliphatics via iron and cobalt cooperative catalysis. Commercially available carboxylic acids can be readily converted to the necessary nitrenoid precursors for the desaturations. Mechanistic studies have revealed that the desaturation occurs via two hydrogen atom transfer (HAT) processes. In conjunction with investigations into the substrate scope and the catalytic process, particularly the metal-nitrenoid species, valuable insights were gained into the desaturation process. The reaction uses simple earth-abundant metal complexes as the catalysts and encompasses a broad substrate scope under mild conditions. We anticipate broader applications of this protocol in site-selective desaturation, particularly in drug derivatives and biologically relevant compounds, showcasing the potential synthetic applications of this protocol.

ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via the Internet at http://pubs.acs.org.

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

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Notes

The authors declare no conflict of interest.

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