

Iron-Catalyzed Decarboxylative Olefination of Cycloketone Oxime Esters with α,β -Unsaturated Carboxylic Acids via C–C Bond Cleavage

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Supporting Information

ABSTRACT: An iron-catalyzed redox-neutral, decarboxylative olefination of cycloketone oxime esters with α_{β} unsaturated carboxylic acids has been developed. This reaction involves an iminyl radical mediated C-C bond cleavage/radical addition/decarboxylation cascade. This protocol is highlighted by its low-cost catalytic system and readily accessible starting materials, as well as broad substrate scope, thus providing facile access to structurally diverse cyanocontaining alkenes.

wing to their easy availability, low toxicity, and high stability, decarboxylative cross-couplings of $\alpha_{,\beta}$ -unsaturated carboxylic acids have provided an efficient and promising strategy for $C(sp^2)-C$ and $C(sp^2)-X$ (X = N, P, S, Si) bond formations.¹ Compared with traditional transition metal catalysis, radical decarboxylative couplings have attracted much attention from chemists in recent years.² In general, these transformations are enabled by a sequential radical addition and decarboxylation process. A range of carbon- and heteroatom-centered radicals generated in situ were engaged in this procedure successfully to afford versatile alkenes, which are useful and important building blocks in organic synthesis.³ For instance, a series of decarboxylative alkylations of cinnamic acids have been reported by Mao, Liu, and Chen et al., respectively.⁴ However, strong and external stoichiometric oxidants were usually required in most cases. Lately, several redox-neutral radical decarboxylative transformations of $\alpha_{j}\beta_{j}$ unsaturated carboxylic acids have been developed.⁵ In this aspect, our group demonstrated a redox-neutral decarboxylative alkylation of α,β -unsaturated carboxylic acids with the alkyl NHP esters under visible-light photocatalysis.^{5e} However, to the best of our knowledge, direct decarboxylative cyanoalkylations of $\alpha_{,\beta}$ -unsaturated carboxylic acids under a redox-neutral catalytic system have not yet been reported to date.4,5

On the other hand, the radical C-C bond cleavage of cycloketone oxime derivatives has recently emerged as an efficient strategy to construct $C(sp^3)-C$ and $C(sp^3)-X$ (X = O, S, F) bonds, which allows incorporation of important cyanoalkyl moieties, especially those bearing longer aliphatic chains into structurally diverse molecules.^{6,7} Very recently, the group of Shi reported a copper-catalyzed Heck-type coupling of cyclobutanone oxime esters with alkenes via C-C bond cleavage.^{7b} Later, Xiao and Chen et al. also achieved this



similar transformation through visible-light photocatalysis.⁷¹ During this time, our group presented a copper-catalyzed, redox-neutral cyanoalkylation/cyclization of functionalized alkenes with cycloketone oxime esters, furnishing a variety of cyanoalkylated oxindoles, dihydroquinolin-2(1H)-ones, and dihydrofurans.^{8a,b} As is well-known, the cycloketone oxime esters could produce the reactive γ -cyanoalkyl radicals through a single-electron reduction, which theoretically enables the redox-neutral decarboxylative coupling of cycloketone oxime esters with $\alpha_{,\beta}$ -unsaturated carboxylic acids. As part of our interest in radical decarboxylation^{2b,5e} and C-C bond cleavage,^{8,9} we herein disclose a redox-neutral decarboxylative olefination of cycloketone oxime esters with easily available cinnamic acids under low-cost iron catalysis,¹⁰ which offers an attractive alternative to cyanoalkylated alkenes.¹

Initially, the decarboxylative olefination of cyclobutanone Operfluorobenzoyl oxime (1a) with (E)-cinnamic acid (2a) was investigated using low-cost iron catalysis in MeCN at 100 °C (Table 1). A variety of iron catalysts such as $Fe(acac)_{2}$, $Fe(OAc)_{2}$, $FeCl_{2}$, and Fe powder all showed good catalytic activity, while $FeCl_3$ was inefficient (entries 1–6). Among them, $Fe(OAc)_2$ proved to be the best catalyst, affording the desired 1,2-disubstituted alkenes 3a in 70% isolated yield (entry 3). Other metal catalysts such as $Cu(OAc)_2$, $Ni(OAc)_2$, $Mn(OAc)_2$, and $Pd(OAc)_2$ displayed lower catalytic activity (entries 7-10). Solvent screenings indicated that DMF, DCE, acetone, toluene, and dioxane were also suitable solvents. but inferior to MeCN (entries 11-15). Notably, the reaction in PhCF₃ also provided product 3a in a comparable yield with MeCN (entry 16). Furthermore, O-acyl oximes bearing different leaving groups such as BzO, 4-CF₃BzO, 4-NO₂BzO,

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Table 1. Optimization of the Reaction Conditions^a

N_OCOC ↓ 1a	eF5 HOOC 2a	(10 mol %) ► NC 100 °C, 12 h	3a
entry	catalyst (mol %)	solvent	yield (%) ^b
1	FeSO ₄ ·7H ₂ O (10)	MeCN	20
2	$Fe(acac)_2$ (10)	MeCN	63
3	$Fe(OAc)_2$ (10)	MeCN	70 $(68)^c$
4	$\operatorname{FeCl}_2(10)$	MeCN	60
5	Fe powder (10)	MeCN	59
6	FeCl ₃ (10)	MeCN	trace
7	$Cu(OAc)_2$ (10)	MeCN	55
8	$Ni(OAc)_2$ (10)	MeCN	31
9	$Mn(OAc)_2$ (10)	MeCN	39
10	$Pd(OAc)_2$ (10)	MeCN	19
11	$Fe(OAc)_2$ (10)	DMF	35
12	$Fe(OAc)_2$ (10)	DCE	65
13	$Fe(OAc)_2$ (10)	acetone	60
14	$Fe(OAc)_2$ (10)	toluene	55
15	$Fe(OAc)_2$ (10)	dioxane	39
16	$Fe(OAc)_2$ (10)	PhCF ₃	69
17	-	MeCN	7 ^d

^{*a*}Reaction conditions: 10 mol % of catalyst, **1a** (0.3 mmol, 1.0 equiv), **2a** (0.45 mmol, 1.5 equiv), solvent (3 mL), 100 °C, 12 h, under N₂. ^{*b*}Isolated yields. ^cYield on a 1 mmol scale is given in parentheses. ^{*d*}40% of **1a** was recovered.

and OAc were also evaluated, albeit furnishing the product **3a** in 27%–64% yields (see Table S1 in the Supporting Information). Finally, a control experiment revealed that the catalyst crucially affected the reaction efficiency. Without a catalyst, the substrate **1a** delivered the target product **3a** in only 7% yield due to low conversion after 12 h (entry 16).

Under the above established conditions, the generality of α_{β} -unsaturated carboxylic acids 2 was investigated with the oxime ester 1a (Scheme 1). Satisfactorily, a variety of cinnamic acids bearing electron-donating or -withdrawing groups reacted well with 1a to give the corresponding cyanoalkylated alkenes 3b-q in moderate to good yields. The electronic effect and steric hindrance of the substituents on the aryl ring of the cinnamic acids did not exhibit a strong influence on the reaction reactivity. A wide range of functional groups, including dimethylamino (3c), hydroxy (3d), halogen (3e-g, 3p, 3q), trifluoromethyl (3h), cyano (3i), ester (3j), nitro (3k), and methoxy (3n, 3o), were tolerated well under the reaction conditions. 2-Furylacrylic acid was also a compatible substrate, delivering the desired product 3r in 51% yield. Treatment of 3methyl-3-phenylacrylic acid 2s with 1a furnished the corresponding trisubstituted alkene 3s in 63% yield. However, 3,3-dimethylacrylic acid failed to give the anticipated product (not shown). Besides the cinnamic acids, other acrylic acids were also found to be amenable. The reaction of 3benzoylacrylic acid with 1a proceeded smoothly to give the desired product 3t in 72% yield. Dienoic acid 2u also afforded the expected diene 3u in 41% yield with excellent regioselectivity. Remarkably, the sterically congested acrylic acid 2v derived from estrone also worked well to generate the desired product 3v in satisfactory yield. It should be mentioned that the E/Z ratio of products was independent of the α_{β} unsaturated carboxylic acids. In most cases, the alkenes were obtained as a mixture of E/Z stereoisomers with good to





^aReaction conditions: Fe(OAc)₂ (10 mol %), **1a** (0.3 mmol, 1.0 equiv), **2** (0.45 mmol, 1.5 equiv), solvent (3 mL), 100 °C, 12 h, under N₂. Isolated yields. The E/Z ratios were determined by ¹H NMR analysis and were given in parentheses. ^bFor 18 h.

excellent selectivities, wherein the *trans*-alkenes were major isomers.

Then, the scope of cycloketone oxime esters was examined (Scheme 2). The reactions of cyclobutanone oxime esters bearing aryl, benzyl, and alkyl groups on the 3-position with 2a proceeded smoothly to afford the desired alkenes 4a-g in moderate to good yields. Notably, the 3-cyano cyclobutanone oxime ester was compatible and furnished the target product 4h in 79% yield. The 3,3-disubstituted oxime ester containing a -NBoc group also led to the desired product 4i in 63% yield. Satisfactorily, the 2,3-disubstituted oxime ester derived from 1H-indene afforded the desired product 4k in 76% yield. To our delight, the less-strained five-membered cycloketone oxime esters were also applicable, delivering the corresponding products 4l-4n in 52%-67% yields. The 2-phenyl cyclohexanone oxime ester was also converted to the desired product 40 in 53% yield, while the simple cyclohexanone oxime ester was inactive. It is noteworthy that the C-C bond cleavage of unsymmetrical cycloketone oxime esters always selectively occurred at the more hindered site (4k, 4m, 4n, 40), which was attributed to the formation of a more stable alkyl radical.

To gain insight into the reaction mechanism, several control experiments were carried out. When 1.0 equiv of TEMPO, a typical radical scavenger, was added to the reaction of 1a with 2a, the yield of 3a decreased to 17%, along with a 65% yield of alkyl-TEMPO adduct 5a being isolated. Increasing the amount of TEMPO to 2.0 equiv led to complete inhibition of the reaction (eq 1). These results indicate that a radical process might be involved in this reaction. On the other hand, treatment of radical clock substrates 6a and 6b containing an intramolecular C==C bond with 2a afforded the ring-closing

Scheme 2. Scope of Cycloketone Oxime Esters^a



^{*a*}Reaction conditions: $Fe(OAc)_2$ (10 mol %), **1** (0.3 mmol, 1.0 equiv), **2** (0.45 mmol, 1.5 equiv), solvent (3 mL), 100 °C, 12 h, under N₂. Isolated yields. The *E/Z* ratios were determined by ¹H NMR analysis and were given in parentheses. ^{*b*}For 18 h.



products 7a and 7b in 61% and 40% yields (eqs 2 and 3), respectively, which further verified a radical pathway for this transformation. Notably, when ethyl cinnamate 2a' was used instead of the cinnamic acid 2a, no desired product 3a was observed (eq 4). Moreover, no reaction occurred even when using the potassium of cinnamic acid instead of 2a (not shown). These results indicate that the COOH group was crucial for this decarboxylation process.

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Based on the above results, a plausible mechanism was proposed in Scheme 3. First, single-electron reduction of 1a by

Scheme 3. Proposed Mechanism



Fe(II) affords iminyl radical I, which undergoes C–C bond cleavage to give the cyanoalkyl radical II.^{6a,7,8} Subsequently, the alkyl radical II attacks the C=C bond of cinnamic acid 2a regioselectively to give the benzyl radical III.^{4,5} Deprotonation of III with aryl carboxylate occurs to give radical IV, and then radical IV is oxidized by Fe(III) to deliver the diradical intermediate V, which releases CO₂, affording the final product 3a.¹²

In conclusion, we have disclosed an efficient iron-catalyzed decarboxylative olefination of cycloketone oxime esters with α , β -unsaturated carboxylic acids via C–C bond cleavage. This facile and redox-neutral procedure is applicable to a wide variety of cycloketone oxime esters and carboxylic acids, thus constituting a useful alternative for preparing cyanoalkyl alkenes in good yields with high selectivities.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.8b01901.

Experimental procedures and spectroscopic data of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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