JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Communication

Iridium-Catalyzed Oxidant-Free Transfer Dehydrogenation of Carboxylic Acids

Yin Xu, Rui Zhang, Bo Zhou, and Guangbin Dong*

Cite This: J. Am. Chem. Soc. 2024, 146, 22899−22905
Read Online
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Direct dehydrogenation of carboxylic acids to their unsaturated counterparts represents a valuable transformation for complex molecule synthesis, which, however, has been challenging to achieve. In addition, the current carbonyl desaturation methods are almost all based on oxidative conditions. Here we report an Ir-catalyzed redox-neutral transfer dehydrogenation approach to directly convert carboxylic acids to either α,β- or β,γ-unsaturated counterparts. These reactions avoid using oxidants or strong bases, thus, tolerating various functional groups. The combined experimental and computational mechanistic studies suggest that this transfer hydrogenation reaction involves directed C−H oxidative addition, β-H elimination, and dihydride transfer to an alkene acceptor with C(sp^3)−H reductive elimination as the turnover-limiting step.

Unsaturated carbonyl moieties are often found in bioactive compounds that exhibit a broad range of functions, such as antioxidants, radical scavengers, or covalent inhibitors.[1] In addition, they also serve as valuable intermediates or precursors to access β or remote functionalized products.[2] Among various synthetic strategies, those that directly convert saturated carbonyl compounds to their unsaturated counterparts via dehydrogenation are highly attractive and have been widely utilized in the complex molecule synthesis.[3] However, compared to the diverse ways of desaturating aldehydes,[4] ketones,[5] amides,[6] and esters,[7] direct dehydrogenation of free carboxylic acids remains largely underdeveloped (Scheme 1A). The seminal work of Newhouse employed zinc enediolates as the key intermediate and achieved the Pd-catalyzed dehydrogenation of carboxylic acids with allyl acetate as the oxidant.[8] Later, the Yu group realized an elegant ligand-promoted Pd-catalyzed direct desaturation of carboxylic acids, which employed Ag_2CO_3, *tert*-butyl hydroperoxide, or 1,4-benzoquinone/O_2 as the oxidants.[9] In 2018, Huang and co-workers reported a Cp*Ir-catalyzed desaturation of γ,δ-unsaturated carbonyl compounds to 1,3-dienes using air as the oxidant,[10] and the γ,δ-olefin is critical for forming the key π-allyl intermediate.

On the other hand, the transition-metal-catalyzed dehydrogenation of aliphatic hydrocarbons, particularly promoted by pincer-ligated complexes,[11] represents an oxidant-free approach to transfer two hydrogens from the substrate to an acceptor alkene (Scheme 1B). While this type of catalysis typically does not tolerate polar functional groups, such as carboxylates, due to catalyst inhibition,[12,13] the unique nonoxidative feature of this H_2-transfer approach motivated us to explore an alternative strategy for dehydrogenation of free carboxylic acids.

Based on our continued interest in carbonyl desaturation and its related transformations, particularly the recent development of an Ir-catalyzed byproduct-free β-alkenylation of ketones with alkynes,[14] here we describe our preliminary development of an Ir-catalyzed transfer-dehydrogenation of carboxylic acids (Scheme 1C). It was hypothesized that the carboxylate moiety first directs oxidative addition of Ir(I) into the β or γ C−H bond, and followed by β-H elimination, the resulting Ir(III) dihydride species then undergoes a hydride-transfer process with an acceptor alkene to deliver the desired unsaturated product and to regenerate the Ir(I) catalyst. It is anticipated that this transfer dehydrogenation approach would avoid strong bases to form enolates and avoid stoichiometric oxidants to turnover the catalyst.

To examine the feasibility of the proposed strategy, *N*-Me-3-indolepropionic acid (**1a**) was employed as the model substrate. After systematic evaluation of various reaction parameters, the desired α,β-unsaturated carboxylic acid **2a** was formed in 78% yield with >50:1 *E*/*Z* diastereoselectivity (Table 1, entry 1), with NBE as the hydrogen acceptor, 10 mol % [Ir(COD)$_2$]BArF as the catalyst, 24 mol % tri(3,5-dimethylphenyl)phosphine **L1** as the ligand, Cs_2CO_3 as the base, and NaOAc as the additive. A series of control experiments was then performed to understand the role of each component. In the absence of the iridium catalyst, NBE or the ligand, the reaction gave almost no conversion (entries 2, 5 and 7), suggesting their critical roles in this reaction. Substitution of [Ir(COD)$_2$]BArF with [Ir(COD)$_2$]OTf or [Ir(COD)$_2$]NTf_2 led to a decreased yield (entries 3 and 4). In addition, a good yield was still obtained when reducing the NBE loading to 4 equiv (entry 6); but other alkenes or substituted NBEs gave almost no desired product (see Supporting Information). A much lower yield was observed

Received: May 24, 2024
Revised: August 3, 2024
Accepted: August 6, 2024
Published: August 8, 2024

https://doi.org/10.1021/jacs.4c07115
J. Am. Chem. Soc. 2024, 146, 22899−22905

Scheme 1. Transition-Metal-Catalyzed Dehydrogenation Reactions

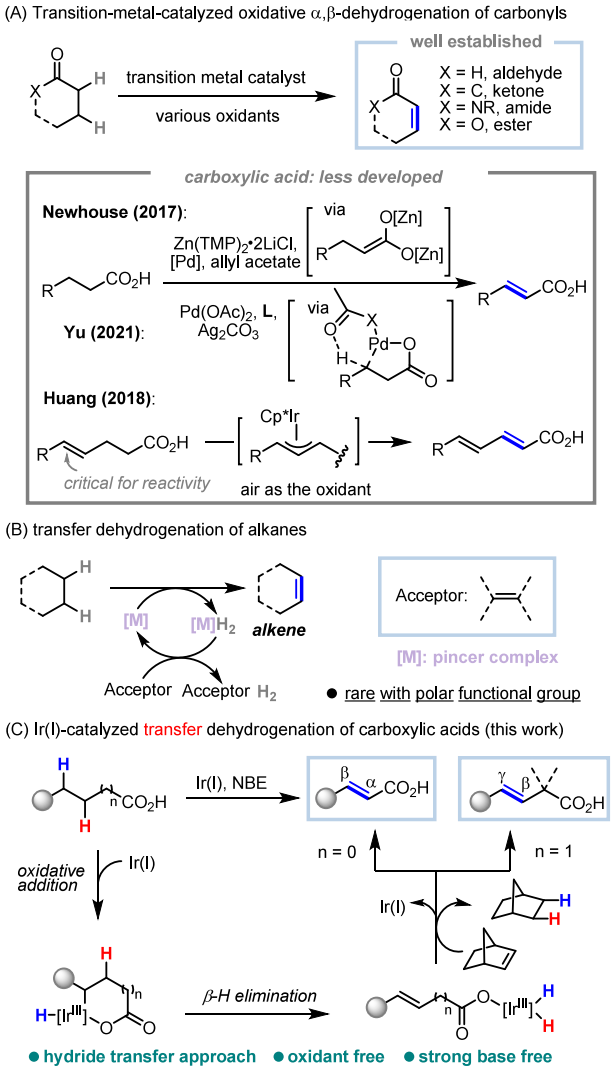
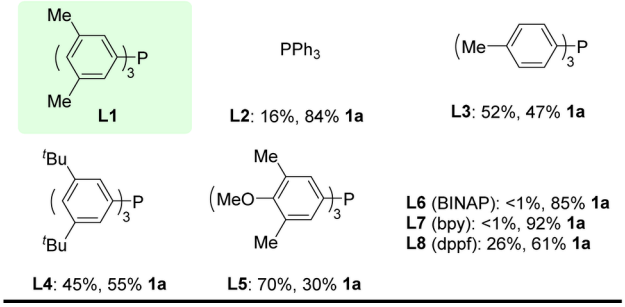


Table 1. Selected Reaction Optimization with Substrate 1a[a]

entry	variation from the "standard conditions"	yield (%)[b]	unreacted **1a** (%)[b]
1	**none**	**78**	**21**
2	w/o $[Ir(COD)_2]BArF$	<1	99
3	$[Ir(COD)_2]OTf$ instead of $[Ir(COD)_2]BArF$	48	51
4	$[Ir(COD)_2]NTf_2$ instead of $[Ir(COD)_2]BArF$	65	35
5	w/o NBE	<1	95
6	NBE (4 equiv) instead of NBE (8 equiv)	68	31
7	w/o **L1**	<1	97
8	**L1** (12 mol %) instead of **L1** (24 mol %)	29	62
9	other ligands instead of **L1**	-- see below --	
10	CsOAc instead of Cs_2CO_3	7	40
11	K_2CO_3 instead of Cs_2CO_3	26	73
12	w/o NaOAc	52	45
13	PhMe instead of PhF	64	35
14	$PhCF_3$ instead of PhF	75	24
15	150 °C instead of 160 °C	67	33



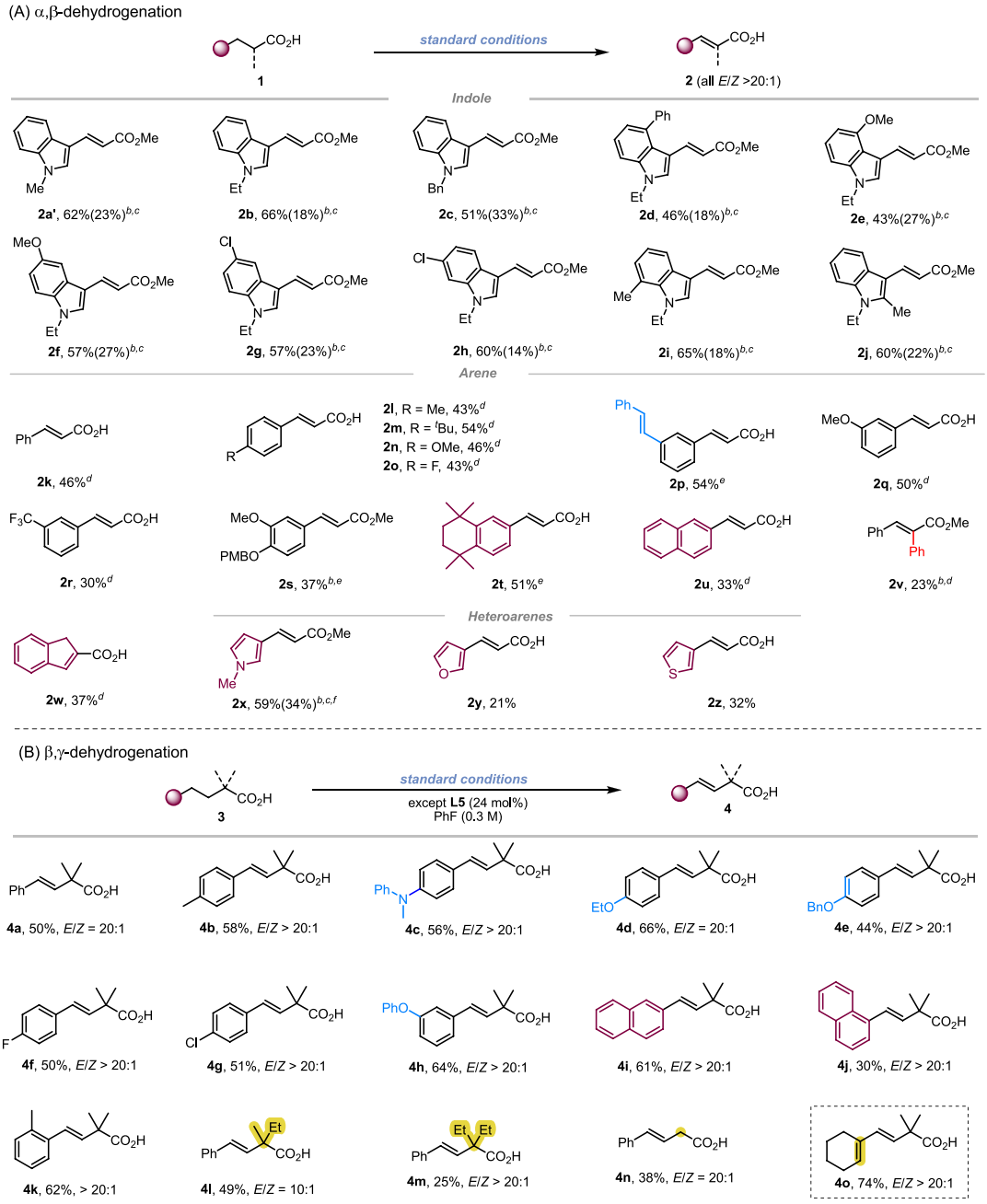
[a]Standard condition: **1a** (0.1 mmol), $[Ir(COD)_2]BArF$ (0.01 mmol), **L1** (0.024 mmol), NBE (0.8 mmol), Cs_2CO_3 (0.1 mmol), NaOAc (0.1 mmol) in 0.5 mL PhF at 160 °C for 24 h. [b]Determined by ^1H NMR with 1,1,2,2-tetrachloroethane as the internal standard. NBE, norbornene; BArF, tetrakis(3,5-bis(trifluoromethyl)phenyl)borate; COD, 1,5-cyclooctadiene.

when reducing the ligand loading to 12 mol %, suggesting that a 1:2 metal-to-ligand ratio is likely important for high catalyst efficiency. While the exact reason for the ligand effect remains to be uncovered, compared to the optimal ligand (**L1**), other monodentate phosphines without the 3,5-dimethyl groups (**L2**–**L4**) were significantly less efficient (see Supporting Information); in contrast, **L5** with the additional 4-methoxy group gave comparable yield. Moreover, bidentate ligands (**L6**–**L8**), except dppf, exhibited almost no reactivity (entry 9 and Table S1), likely due to the sensitivity to the electronic and steric properties of the ligand. A survey of different bases suggested that Cs_2CO_3 was much better than the others (entries 10 and 11). NaOAc is an effective additive, though it is not essential to the reactivity (entry 12).[15] PhF proved to be a better solvent, and slightly lower yields were observed with toluene and $PhCF_3$ (entries 13 and 14). Finally, lowering the reaction temperature led to a lower conversion (entry 15).

The scope of the Ir-catalyzed α,β-dehydrogenation was subsequently explored (Table 2A). It should be mentioned that some products were converted to the corresponding methyl esters for convenience of purification. For the indole-derived substrates, first we found the substituent on the nitrogen does not significantly influence the reactivity (**2a**–**2c**). In addition, the substrates with substituents at the C2, C4, C5, C6, and C7 positions, including methyl (**2i** and **2j**), phenyl (**2d**), methoxy (**2e** and **2f**), and chloro (**2g** and **2h**) groups, were all compatible in this transformation. Besides the indole framework, substrates bearing aryl rings (**2k**–**2t**) are also suitable for this transformation. 3-Arylpropanoic acids containing electron-donating or -withdrawing groups on the arene can afford the desired α,β-unsaturated carboxylic acids (**2l**–**2s**) in moderate yields. In general, these reactions were very clean, showing high mass balances. Note that compound **2m** is the precursor for the synthesis of vanilloid receptor-1 antagonist RPV-1.[16] Moreover, a styrenyl group (**2p**) was tolerated under the transfer dehydrogenation conditions, indicating that the hydride transfer process is much faster with NBE than with other alkenes. In addition to simple phenyl rings, products **2t** and **2u** bearing bicyclic moieties could also be synthesized. Gratifyingly, α-substituted carbox-

https://doi.org/10.1021/jacs.4c07115
J. Am. Chem. Soc. 2024, 146, 22899−22905

Table 2. Substrate Scope of the Transfer Dehydrogenation of Free Carboxylic Acids[a]



[a]Unless mentioned otherwise, all reactions were carried out with 0.1 mmol of **1** or **3** for 24 h under the standard conditions. All yields are isolated yields. [b]The subsequent esterification was carried out with MeI (2 equiv), Cs_2CO_3 (2 equiv), acetone, 60 °C, 4 h. [c]The recovered amount of the unreacted ester of **1** is given within parentheses. [d]In PhF (0.33 M). [e]In 1,4-dioxane (0.33 M). [f]At 150 °C.

ylic acids can also be used as the substrate (**1v**); although the yield is low, only the *E* isomer of the product was observed. The application of 2,3-dihydro-1*H*-indene-2-carboxylic acid as the starting material resulted in forming indene **2w**. Finally, substrates featuring other heteroarenes, such as pyrrole, furan, and thiophene (**2x**–**2z**), were competent for this transformation. Note that attempts to desaturate esters and amides were not fruitful under the current reaction conditions (see Supporting Information).[17]

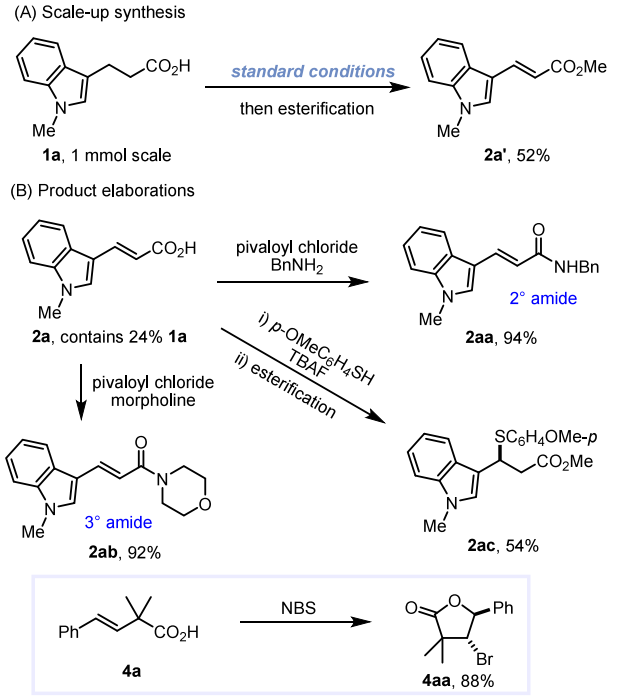
When one-carbon elongated carboxylic acids were used as the substrates, this method can be extended to realize the *β*,*γ*-transfer dehydrogenation (Table 2B).[9c] The *α*,*α*-disubstituted substrates worked notably better; however, the one without any *α*-substituent also delivered the desired product (**4n**), albeit in a lower conversion. This suggests that the Thorpe–Ingold effect likely benefits the C–H activation step in this reaction. The substrates bearing an electron-rich arene gave higher conversion than electron-deficient ones, although the exact reason is unclear. In addition, carboxylic acids bearing diverse functional groups, such as tertiary amine (**4c**), ethoxy (**4d**), benzyl ether (**4e**), phenyl ether (**4h**) and naphthalene (**4i** and **4j**), could give the desired *β*,*γ*-unsaturated carboxylic acids in excellent *E*/*Z* diastereoselectivity. Moreover, besides *α*-dimethyl groups, diethyl- or unsymmetrically *α*-disubstituted

https://doi.org/10.1021/jacs.4c07115
J. Am. Chem. Soc. 2024, 146, 22899–22905

substrates (**4l** and **4m**) also worked. Like in the former α,β-dehydrogenation, the β,γ-dehydrogenation reactions typically do not form side products, and the modest yields were mainly due to incomplete conversions.[18] Furthermore, apart from the aryl-substituted carboxylic acids, the cyclohexene-derived substrate **3o** is also competent to afford the corresponding diene product **4o** in 74% yield.

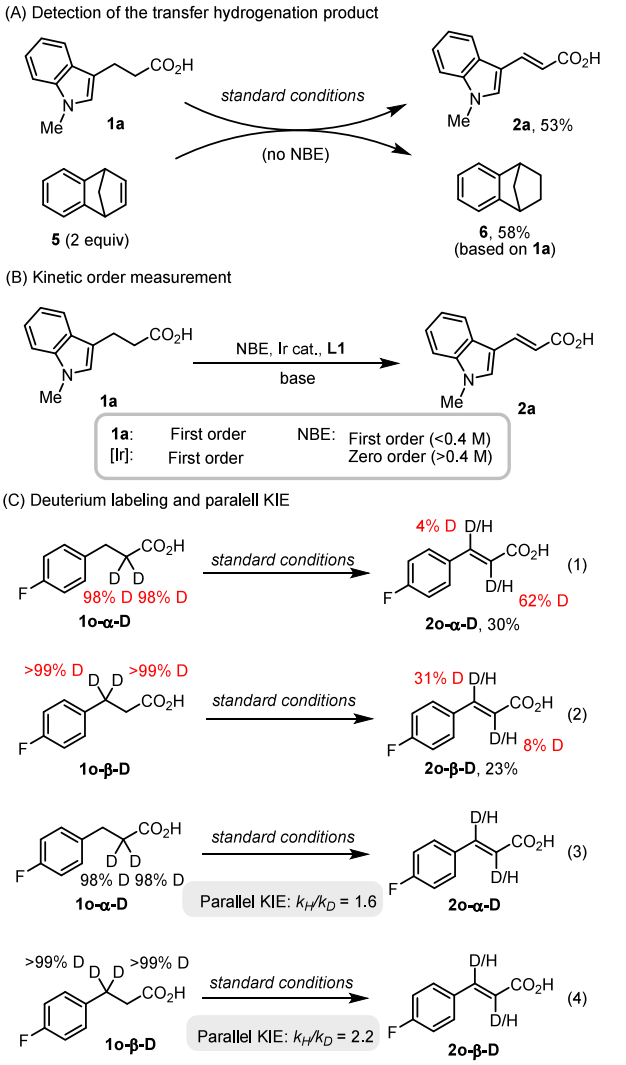
To explore the potential utility of this method, first a scale-up reaction was carried out, and the desired product was obtained in good yield on a 1 mmol scale (Scheme 2A). In addition, simple transformations of the dehydrogenated products were demonstrated (Scheme 2B). For example, the α,β-unsaturated carboxylic acid (**2a**) can be converted to the corresponding secondary amide **2aa** and tertiary amide **2ab** uneventfully. In addition, Michael addition of a thiophenol followed by esterification furnished β-functionalized ester **2ac**. Furthermore, treatment of a β,γ-unsaturated carboxylic acid (**4a**) with *N*-bromosuccinimide (NBS) led to bromolactonization in 88% yield with excellent diastereoselectivity.

Scheme 2. Scale-up and Product Transformations



To gain some insight into the dehydrogenation mechanism, several control experiments were next conducted. First, to elucidate the role of NBE, less volatile benzo-fused NBE **5** was used as the hydrogen acceptor (Scheme 3A). As expected, under the standard conditions, the corresponding hydrogenated product **6** was detected in a comparable yield to that of the dehydrogenated product (**2a**), strongly supporting the idea that NBE serves as the hydrogen acceptor in this reaction. Next, the kinetic orders of the soluble components of the reaction were measured (Scheme 3B). The reaction exhibits a first-order dependence on the concentration of the Ir catalyst and substrate **1a**, and a first-order dependence on NBE at low NBE concentration (<0.4 M), which dropped to zero when the concentration of NBE was higher than 0.4 M. These kinetic data suggest that the iridium catalyst, **1a** and NBE should be involved in the turnover limiting step (TLS). Moreover,

Scheme 3. Experimental Mechanistic Studies



deuterium labeling experiments were conducted. The reaction of the α-deuterated substrate **1o-α-D** gave product **2o-α-D** with 4% D at the β position and 62% D at the α position (eq 1), while the β-deuterated substrate **1o-β-D** gave product **2o-β-D** with 31% D at the β position and 8% D at the α position (eq 2). These experiments suggest that C−H activation and β-hydrogen elimination are likely reversible processes; otherwise, deuterium loss and scrambling should have not taken place. Subsequently, parallel kinetic isotope effect (KIE) was investigated, which showed a small KIE value (1.6) at the α position and a slightly higher value (2.2) at the β position (eqs 3 and 4). Altogether, these experiments collectively imply that cleavage of the α- and β-C−H bonds may occur before the TLS.[19]

Finally, the complete reaction profile was calculated by density functional theory (DFT) study, and a tentative mechanism is proposed (Figure 1). The initial ligand exchange of $[Ir(COD)_2]^+$ with the two phosphine ligands and the substrate is downhill by 17.3 kcal/mol, leading to a stable intermediate (**Int1**).[20] It is also possible to have NBE coordination to the Ir center to give **Int1-nbe** under high NBE concentration, which could explain the observed saturation kinetics of NBE. The subsequent sp^3 C−H oxidative addition forms the five-membered iridacycle **Int3**, followed by

https://doi.org/10.1021/jacs.4c07115
J. Am. Chem. Soc. 2024, 146, 22899−22905

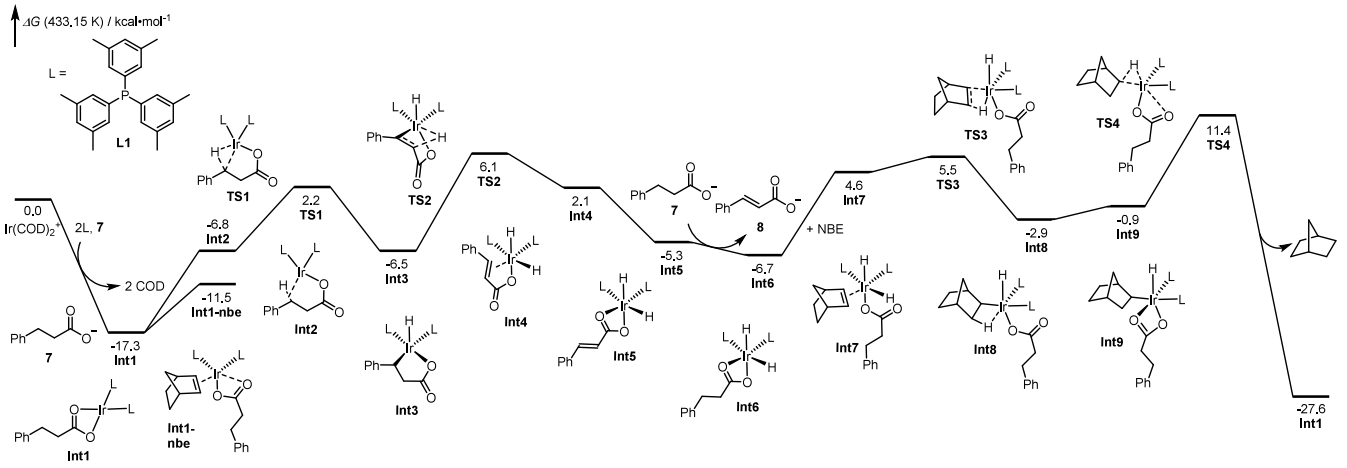


Figure 1. Computational mechanistic study and a tentative proposed reaction pathway. DFT calculations were performed at the M06-D3/def2-TZVP/SMD(PhF)//B3LYP-D3(BJ)/6-31G(d)-Lanl2dz level of theory at 433.15 K. Free energy changes are shown in kcal/mol.

the β-H elimination to realize the desaturation process. Both steps are reversible with relatively low barriers, which is consistent with the deuterium labeling results. The reversibility of the dehydrogenation process also suggests the product can serve as a competing hydrogen acceptor (see the Supporting Information). The following NBE-hydrogenation process starts with ligand exchange between the α,β-unsaturated carboxylate (**8**) and the substrate (**7**), which is thermodynamically favored by 1.4 kcal/mol. The reason is probably because the unsaturated carboxylic acid is notably more acidic than the saturated counterpart (pK_a in water: 4.44 for **2k** versus 4.66 for **1k**[21]), thus the unsaturated carboxylate is a better leaving group. This also corroborates the observation that adding an unsaturated carboxylic acid to this reaction system does not inhibit the α,β-dehydrogenation process (see the Supporting Information). The subsequent NBE coordination and migratory insertion of the Ir−H intermediate from the *exo* face of NBE gives **Int8**. The final sp^3 C−H reductive elimination step requires an overall activation barrier of 28.7 kcal/mol, which is considered as the TLS of the whole transformation. Hydrogenation with the unsaturated carboxylate as the ligand was also considered, albeit with a ca. 3 kcal/mol higher barrier in the final reductive elimination step (see Supporting Information). The fact that the ligand exchange takes place prior to the hydrogenation step is also supported by the first-order kinetics of the substrate. The overall transformation is thermodynamically favored by 10.3 kcal/mol.

In summary, we have realized the first transfer dehydrogenation of free carboxylic acids that also provides a new strategy for carbonyl desaturation. This protocol is redox neutral and strong base free, thus, complementary to all the previous desaturation approaches. Such a nonoxidative reaction condition allows tolerance of diverse functional groups. The mechanistic insights obtained here suggest the sp^3 C−H reductive elimination as a surprising TLS, which could be valuable for designing a more efficient catalytic system in the future. While the current substrate scope is limited, efforts to expand this strategy to more general carboxylic acid and other carbonyl substrates are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c07115.

Experimental procedures and spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Guangbin Dong − *Department of Chemistry, University of Chicago, Chicago, Illinois 60637, United States;* orcid.org/0000-0003-1331-6015; Email: gbdong@uchicago.edu

Authors

Yin Xu − *Department of Chemistry, University of Chicago, Chicago, Illinois 60637, United States*

Rui Zhang − *Department of Chemistry, University of Chicago, Chicago, Illinois 60637, United States*

Bo Zhou − *Department of Chemistry, University of Chicago, Chicago, Illinois 60637, United States;* orcid.org/0000-0002-5551-678X

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.4c07115

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank University of Chicago and NSF (CHE-2154632) for financial support. Umicore AG & Co. K.G. is acknowledged for a generous donation of Ir salts. Dr. Jie Yan (Peking University) is thanked for the assistance in DFT calculations. Mr. Kezhi Chen from University of Chicago is thanked for checking the experimental procedure.

■ REFERENCES

(1) For recent selected reviews, see: (a) Amslinger, S. The Tunable Functionality of α,β-Unsaturated Carbonyl Compounds Enables Their Differential Application in Biological Systems. *ChemMedChem.* **2010**, *5*, 351−356. (b) Arshad, L.; Jantan, I.; Bukhari, S. N. A.; Haque, M. A. Immunosuppressive Effects of Natural α,β-Unsaturated Carbonyl Based Compounds, and Their Analogs and Derivatives, on Immune Cells: A Review. *Front Pharmacol.* **2017**, *8*, 1−22.

(c) Hossain, M.; Das, U.; Dimmock, J. R. Recent Advances in α,β-Unsaturated Carbonyl Compounds as Mitochondrial Toxins. *Eur. J. Med. Chem.* **2019**, *183*, 111687.

(2) For recent selected reviews, see: (a) Xavier, N. M.; Rauter, A. P. Sugars Containing α,β-Unsaturated Carbonyl Systems: Synthesis and Their Usefulness as Scaffolds in Carbohydrate Chemistry. *Carbohydr. Res.* **2008**, *343*, 1523−1539. (b) Huang, Z.; Lim, H. N.; Mo, F.; Young, M. C.; Dong, G. Transition Metal-Catalyzed Ketone-Directed or Mediated C−H Functionalization. *Chem. Soc. Rev.* **2015**, *44*, 7764−7786. (c) Keiko, N. A.; Vchislo, N. V. Synthesis of Diheteroatomic Five-Membered Heterocyclic Compounds from α,β-Unsaturated Aldehydes. *Asian J. Org. Chem.* **2016**, *5*, 1169−1197. (d) Jackson, P. A.; Widen, J. C.; Harki, D. A.; Brummond, K. M. Covalent Modifiers: A Chemical Perspective on the Reactivity of α,β-Unsaturated Carbonyls with Thiols via Hetero-Michael Addition Reactions. *J. Med. Chem.* **2017**, *60*, 839−885. (e) Zhuang, C.; Zhang, W.; Sheng, C.; Zhang, W.; Xing, C.; Miao, Z. Chalcone: A Privileged Structure in Medicinal Chemistry. *Chem. Rev.* **2017**, *117*, 7762−7810. (f) Desimoni, G.; Faita, G.; Quadrelli, P. Forty Years after "Heterodiene Syntheses with α,β-Unsaturated Carbonyl Compounds": Enantioselective Syntheses of 3,4-Dihydropyran Derivatives. *Chem. Rev.* **2018**, *118*, 2080−2248. (g) Brenninger, C.; Jolliffe, J. D.; Bach, T. Chromophore Activation of α,β-Unsaturated Carbonyl Compounds and Its Application to Enantioselective Photochemical Reactions. *Angew. Chem., Int. Ed.* **2018**, *57*, 14338−14349. (h) Wang, C.; Dong, G. Catalytic β-Functionalization of Carbonyl Compounds Enabled by α,β-Desaturation. *ACS Catal.* **2020**, *10*, 6058−6070.

(3) For recent selected reviews, see: (a) Muzart, J. One-Pot Syntheses of α,β-Unsaturated Carbonyl Compounds through Palladium-Mediated Dehydrogenation of Ketones, Aldehydes, Esters, Lactones, and Amides. *Eur. J. Org. Chem.* **2010**, *2010*, 3779−3790. (b) Stahl, S. S.; Diao, T. Oxidation Adjacent to C = X bonds by Dehydrogenation. *Comp. Org. Synth.* **2014**, *7*, 178−212. (c) Turlik, A.; Chen, Y.; Newhouse, T. R. Dehydrogenation Adjacent to Carbonyls Using Palladium-Allyl Intermediates. *Synlett* **2016**, *27*, 331−336. (d) Hirao, T. Synthetic Strategy: Palladium-Catalyzed Dehydrogenation of Carbonyl Compounds. *J. Org. Chem.* **2019**, *84*, 1687−1692. (e) Chen, H.; Liu, L.; Huang, T.; Chen, J.; Chen, T. Direct Dehydrogenation for the Synthesis of α,β-Unsaturated Carbonyl Compounds. *Adv. Synth. Catal.* **2020**, *362*, 3332−3346. (f) Gnaim, S.; Vantourout, J. C.; Serpier, F.; Echeverria, P.-G.; Baran, P. S. Carbonyl Desaturation: Where Does Catalysis Stand? *ACS Catal.* **2021**, *11*, 883−892. (g) Huang, D.; Newhouse, T. R. Dehydrogenative Pd and Ni Catalysis for Total Synthesis. *Acc. Chem. Res.* **2021**, *54*, 1118−1130. (h) Dai, P.-F.; Li, Q.-Q.; Qu, J.-P.; Kang, Y.-B. Recent Developments on the Earth-Abundant-Metal-Catalyzed α,β-Dehydrogenation of Carbonyl Compounds. *Synthesis* **2024**, *56*, 2213.

(4) For recent representative works for aldehydes, see: (a) Zhu, J.; Liu, J.; Ma, R.; Xie, H.; Li, J.; Jiang, H.; Wang, W. A Direct Amine-Palladium Acetate Cocatalyzed Saegusa Oxidation Reaction of Unmodified Aldehydes to α,β-Unsaturated Aldehydes. *Adv. Synth. Catal.* **2009**, *351*, 1229−1232. (b) Liu, J.; Zhu, J.; Jiang, H.; Wang, W.; Li, J. Direct Oxidation of β-Aryl Substituted Aldehydes to α,β-Unsaturated Aldehydes Promoted by an *o*-Anisidine−$Pd(OAc)_2$ Co-catalyst. *Chem.—Asian J.* **2009**, *4*, 1712−1716. (c) Wang, M. M.; Ning, X. S.; Qu, J. P.; Kang, Y. B. Dehydrogenative Synthesis of Linear α,β-Unsaturated Aldehydes with Oxygen at Room Temperature Enabled by *t*-BuONO. *ACS Catal.* **2017**, *7*, 4000−4003.

(5) For recent representative works for ketones, see: (a) Diao, T.; Stahl, S. S. Synthesis of Cyclic Enones via Direct Palladium-Catalyzed Aerobic Dehydrogenation of Ketones. *J. Am. Chem. Soc.* **2011**, *133*, 14566−14569. (b) Shang, Y.; Jie, X.; Jonnada, K.; Zafar, S. N.; Su, W. Dehydrogenative Desaturation-Relay via Formation of Multicenter-Stabilized Radical Intermediates. *Nat. Commun.* **2017**, *8*, 2273. (c) Huang, D.; Zhao, Y.; Newhouse, T. R. Synthesis of Cyclic Enones by Allyl-Palladium-Catalyzed α,β-Dehydrogenation. *Org. Lett.* **2018**, *20*, 684−687. (d) Chen, M.; Dong, G. Platinum-Catalyzed α,β-Desaturation of Cyclic Ketones through Direct Metal−Enolate Formation. *Angew. Chem., Int. Ed.* **2021**, *60*, 7956−7961. (e) Li, H.; Yin, C.; Liu, S.; Tu, H.; Lin, P.; Chen, J.; Su, W. Multiple Remote $C(sp^3)$−H Functionalizations of Aliphatic Ketones via Bimetallic Cu−Pd Catalyzed Successive Dehydrogenation. *Chem. Sci.* **2022**, *13*, 13843−13850.

(6) For recent representative works for amides and lactams, see: (a) Chen, Y.; Turlik, A.; Newhouse, T. R. Amide α,β-Dehydrogenation Using Allyl-Palladium Catalysis and a Hindered Monodentate Anilide. *J. Am. Chem. Soc.* **2016**, *138*, 1166−1169. (b) Chen, M.; Dong, G. Direct Catalytic Desaturation of Lactams Enabled by Soft Enolization. *J. Am. Chem. Soc.* **2017**, *139*, 7757−7760. (c) Teskey, C. J.; Adler, P.; Goncalves, C. R.; Maulide, N. Chemoselective α,β-Dehydrogenation of Saturated Amides. *Angew. Chem., Int. Ed.* **2019**, *58*, 447−451.

(7) For recent representative works for esters and lactones, see: (a) Chen, M.; Rago, A. J.; Dong, G. Platinum-Catalyzed Desaturation of Lactams, Ketones, and Lactones. *Angew. Chem., Int. Ed.* **2018**, *57*, 16205−16209. (b) Chen, M.; Dong, G. Copper-Catalyzed Desaturation of Lactones, Lactams, and Ketones under pH-Neutral Conditions. *J. Am. Chem. Soc.* **2019**, *141*, 14889−14897.

(8) Zhao, Y.; Chen, Y.; Newhouse, T. R. Allyl-Palladium-Catalyzed α,β-Dehydrogenation of Carboxylic Acids via Enediolates. *Angew. Chem., Int. Ed.* **2017**, *56*, 13122−13125.

(9) (a) Wang, Z.; Hu, L.; Chekshin, N.; Zhuang, Z.; Qian, S.; Qiao, J. X.; Yu, J.-Q. Ligand-Controlled Divergent Dehydrogenative Reactions of Carboxylic Acids via C−H Activation. *Science* **2021**, *374*, 1281−1285. (b) Meng, G.; Hu, L.; Chan, H. S. S.; Qiao, J. X.; Yu, J.-Q. Synthesis of 1,3-Dienes via Ligand-Enabled Sequential Dehydrogenation of Aliphatic Acids. *J. Am. Chem. Soc.* **2023**, *145*, 13003−13007. (c) Sheng, T.; Kang, G.; Zhuang, Z.; Chekshin, N.; Wang, Z.; Hu, L.; Yu, J.-Q. Synthesis of β,γ-Unsaturated Aliphatic Acids via Ligand-Enabled Dehydrogenation. *J. Am. Chem. Soc.* **2023**, *145*, 20951−20958.

(10) Wang, Z.; He, Z.; Zhang, L.; Huang, Y. Iridium-Catalyzed Aerobic α,β-Dehydrogenation of γ,δ-Unsaturated Amides and Acids: Activation of Both α- and β-C−H Bonds through an Allyl−Iridium Intermediate. *J. Am. Chem. Soc.* **2018**, *140*, 735−740.

(11) For recent selected reviews, see: (a) Kumar, A.; Bhatti, T. M.; Goldman, A. S. Dehydrogenation of Alkanes and Aliphatic Groups by Pincer-Ligated Metal Complexes. *Chem. Rev.* **2017**, *117*, 12357−12384. (b) Li, H.; Gonçalves, T. P.; Lupp, D.; Huang, K. W. $PN^3(P)$-Pincer Complexes: Cooperative Catalysis and Beyond. *ACS Catal.* **2019**, *9*, 1619−1629.

(12) Kundu, S.; Choi, J.; Wang, D. Y.; Choliy, Y.; Emge, T. J.; Krogh-Jespersen, K.; Goldman, A. S. Cleavage of Ether, Ester, and Tosylate $C(sp^3)$−O Bonds by an Iridium Complex, Initiated by Oxidative Addition of C−H Bonds. Experimental and Computational Studies. *J. Am. Chem. Soc.* **2013**, *135*, 5127−5143.

(13) For a sole example on catalytic transfer dehydrogenation of a special ketone, see: Zhang, X.; Wang, D. Y.; Emge, T. J.; Goldman, A. S. Dehydrogenation of Ketones by Pincer-Ligated Iridium. Formation and Reactivity of Novel Enone Complexes. *Inorg. Chim. Acta* **2011**, *369*, 253−259. There is no example with other carbonyl substrates.

(14) Zhou, B.; Deng, S.; Xu, Y.; Qi, X.; Dong, G. Iridium-Catalyzed Intramolecular β-C−H Alkenylation of Ketones with Alkynes via a Hydride-Transfer Approach. *J. Am. Chem. Soc.* **2022**, *144* (50), 23230−23238.

(15) The addition of NaOAc may promote carboxylate anion exchange on the Ir catalyst. For control experiments, see the Supporting Information Table S2.

(16) Malkov, A. V.; Derrien, N.; Barlog, M.; Kocovsky, P. Palladium-Catalyzed Alkoxycarbonylation of Terminal Alkenes to Produce α,β-Unsaturated Esters: The Key Role of Acetonitrile as a Ligand. *Chem.—Eur. J.* **2014**, *20*, 4542−4547.

(17) Further extension of this protocol to simple long-chain aliphatic carboxylic acids resulted in almost no reactivity under the current conditions. For additional examples of unsuccessful substrates for α,β-desaturation, see the Supporting Information.

(18) For representative examples of unsuccessful substrates for β,γ-desaturation, see the Supporting Information.

https://doi.org/10.1021/jacs.4c07115
J. Am. Chem. Soc. 2024, 146, 22899−22905

(19) The relatively small KIE values could also result from the Ir−H-involved migratory insertion with NBE and the following turnover-limiting reductive elimination steps. For a similar situation, see: Campos, J.; Hintermair, U.; Brewster, T. P.; Takase, M. K.; Crabtree, R. H. Catalyst Activation by Loss of Cyclopentadienyl Ligands in Hydrogen Transfer Catalysis with Cp^*Ir^{III} Complexes. *ACS Catal.* **2014**, *4*, 973−985.
(20) For an example of various transformations involving two monodentate phosphine-coordinated Ir complexes, see: Dirnberger, T.; Werner, H. A Series of Hydrido(vinyl)iridium(III) Complexes That Are Thermodynamically More Stable than Their Olefin Iridium(I) Isomers. *Organometallics* **2005**, *24*, 5127−5139.
(21) Braude, E. A.; Nachod, F. C. *Determination of Organic Structures by Physical Methods*; Academic Press: New York, 1955.

https://doi.org/10.1021/jacs.4c07115
J. Am. Chem. Soc. 2024, 146, 22899−22905