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Allyl-Palladium Catalyzed α,β-Dehydrogenation of Carboxylic Acids via Enediolates

Yizhou Zhao, Yifeng Chen, Timothy R. Newhouse*

Abstract: *A highly practical and step-economic α,β-dehydrogenation of carboxylic acids via enediolates is reported through the use of allyl-palladium catalysis. Dianions underwent smooth dehydrogenation when generated using Zn(TMP)$_2$•2LiCl as base in the presence of excess ZnCl$_2$, avoiding the typical decarboxylation pathway of these substrates. Direct access to 2-enoic acids allows for derivatization by numerous approaches.*

In biological systems, dehydrogenation of fatty acids is a pivotal metabolic step to generate ATP.[1] Fatty acid dehydrogenase effects β-oxidation of a carboxylic acid derivative, the acyl-CoA thioester, via deprotonation of the α-position by a catalytically active glutamate residue and subsequent hydride transfer from the β-position to a flavin adenine dinucleotide co-factor.[2] The resulting α,β-unsaturated fatty acid derivatives are degraded further via oxidative cleavage to release ATP and a two-carbon chain-shortened fatty acid that can undergo further oxidative degradation (Figure 1a).

While α,β-dehydrogenation of carboxylic acid derivatives is utilized in catabolic metabolism, and also cellular signaling,[3] the availability of carboxylic acids renders their conversion to higher value dehydrogenated materials beneficial for chemical synthesis. Although dehydrogenation of carboxylic acid derivatives is well-established by numerous mechanistic approaches,[4] dehydrogenation of carboxylic acids instead requires multistep sequences (e.g. ester formation, dehydrogenation by one- or two-step methods, and ester hydrolysis)[5-7] to navigate the reactivity of the nefarious carboxylic acid functionality. Numerous complicating factors arise in attempts to dehydrogenate acids directly: their acidity, nucleophilicity, and ability to ligate metals impede their direct transformation.

Some success has come from attempts to employ biological synthesis[8] or through biomimetic reaction development.[9] Employing biological synthesis, 2-*trans*-hexadecenoic acid was obtained in low synthetic yield by dehydrogenation of palmitate in a yeast enzyme system,[8a] and a mixture of 2-*trans*-hexadecenoic acid and 9-*cis*-hexadecenoic acid were found to be formed by palmitic acid dehydrogenation using rat liver particulates.[8b] Mechanistic mimic of flavin dependent fatty acid dehydrogenation has also resulted in limited success: subjection of a preformed sodium carboxylate to basic conditions and DDQ resulted in at best a 30% GC yield of enoic acids.[9]

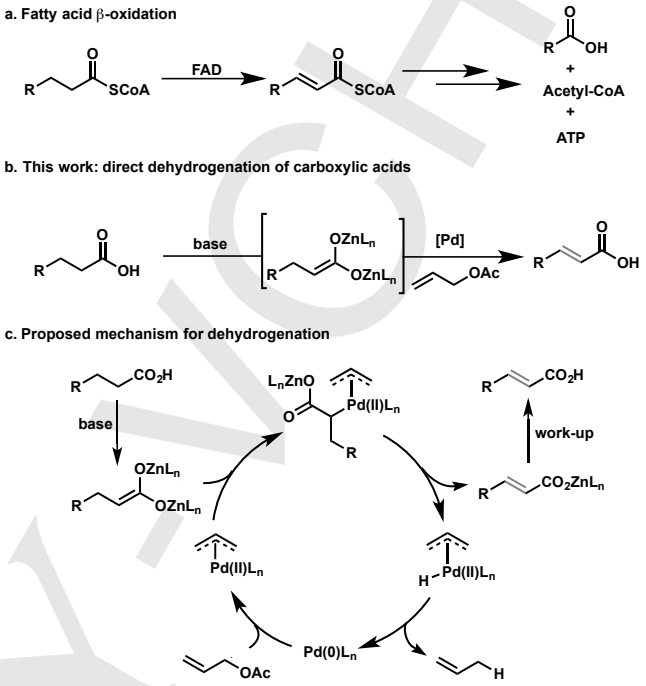

Figure 1. Fatty acid β-oxidation and carboxylic acid dehydrogenation.

Although recent reports describing dehydrogenation of carboxylic acid derivatives via allyl-palladium catalysis[10] suggested the possibility of using this approach, carboxylic acids are a particularly challenging substrate class owing to the aforementioned challenges and also due to specific problems that arise from employing palladium catalysis. One obstacle is the difficulty in generating the necessary C-bound palladium-enolate given the tendency of palladium to coordinate at the carboxylate oxygen.[11] Further complications to the direct transformation of acids includes the propensity for palladium to effect decarboxylation of the carboxylic acid starting materials or vinyl carboxylic acid products.[12-13] Herein, a direct carboxylic acid dehydrogenation is reported using allyl-palladium catalysis and in situ formed enediolate intermediates (Figure 1b).

Notwithstanding the potential problems, the ability to alkylate enediolates at the α-position[14] suggested these dianion intermediates[15] may react with a palladium-allyl species to form a C-bound palladium enolate that could subsequently undergo β-hydride elimination. A catalytic process could be realized after propene-forming reductive elimination and reformation of the allyl-palladium species by oxidative addition to the stoichiometric oxidant allyl acetate (Figure 1c).

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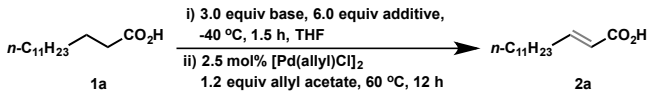
Table 1. Optimization of carboxylic acid dehydrogenation.



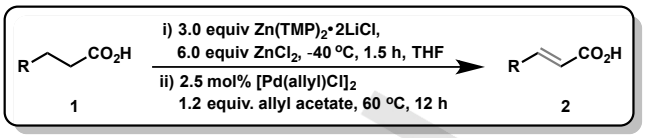
entry	base	additive	yield (%)[a]
1 (ref 10a)	LiTMP	$ZnCl_2$	40 (48)
2 (ref 10b)	LiCyan	$ZnCl_2$	<5 (<5)
3 (ref 10c)	$Zn(TMP)_2$	-	52 (55)
4	$Zn(TMP)_2$•2LiCl	-	51 (55)
5	$Zn(TMP)_2$•2LiCl	LiCl	19 (68)
6	$Zn(TMP)_2$•2LiCl	$ZnCl_2$	85[b] (99)

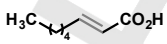
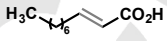
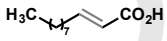
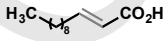
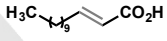
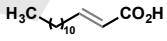
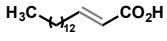
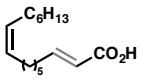
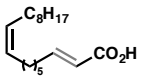
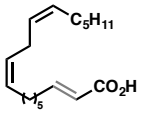
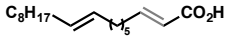
[a] Yield of **2a** was determined by ^{1}H-NMR analysis after aqueous work-up using CH_2Br_2 as an internal standard. The conversion of **1a** is in parentheses. [b] Isolated yield of **2a**.

Our initial attempts to dehydrogenate carboxylic acids began by using the several reaction conditions we previously reported for α,β-dehydrogenation of various carbonyl compounds (Table 1). Although it was encouraging that myristic acid (**1a**) could be dehydrogenated using excess base, the conversion was poor. Employment of the ester dehydrogenation conditions effecting the deprotonation with LiTMP[10a] resulted in 40% yield as observed by ^{1}H NMR (entry 1), and use of the hindered anilide LiCyan, optimized for amide dehydrogenation in the presence of acidic functionality,[10b] resulted in only trace product formation (entry 2). Slightly improved yields could be obtained using our recently disclosed procedure that avoids transmetallation utilizing commercial $Zn(TMP)_2$ (entry 3, 52%)[10c] or $Zn(TMP)_2$ prepared as the LiCl adduct from LiTMP and $ZnCl_2$ (entry 4, 51%). While addition of 6.0 equiv LiCl to these reaction conditions resulted in a depreciated yield of 19% (entry 5), the optimal protocol involved pre-mixing $Zn(TMP)_2$•2LiCl with excess $ZnCl_2$,[16] remarkably resulting in complete conversion and 90% ^{1}H-NMR yield with an isolated yield of 85% obtained in >20:1 *E*:*Z* diastereoselectivity (entry 6). It is noteworthy that the analogous procedure using commercial $Zn(TMP)_2$ with added $ZnCl_2$ results in comparable ^{1}H-NMR yield (88%). The cause of the heightened yield obtained utilizing $Zn(TMP)_2$ with added $ZnCl_2$ is difficult to ascertain at this juncture, but may be the result of influencing the aggregation state of the enediolate or impacting the coordination sphere of one of the palladium intermediates.[17]

With the optimized conditions in hand, a variety of natural fatty acids were examined as substrates for dehydrogenation (Table 2). Linear even- and odd-numbered saturated fatty acids underwent efficient dehydrogenation to give *trans*-α,β-unsaturated carboxylic acids with up to 93% isolated yield (**2a**-**2g**) and in all cases >20:1 *E*:*Z* diastereoselectivity. Interestingly, the dehydrogenation of unsaturated linear fatty acids, bearing *cis* or *trans* internal alkenes, proceeded more readily (**2h**-**2k**), and less forcing conditions were required to prevent product decomposition (3 h reaction time, 2.3 equiv of base, and no added $ZnCl_2$). With these milder conditions, even the skipped diene present in linoleic acid (**1j**) remained intact in the product. In addition to the natural fatty acids, various unnatural carboxylic acids were suitable substrates for this process (Table 3). An

Table 2. Scope of natural fatty acid dehydrogenation.

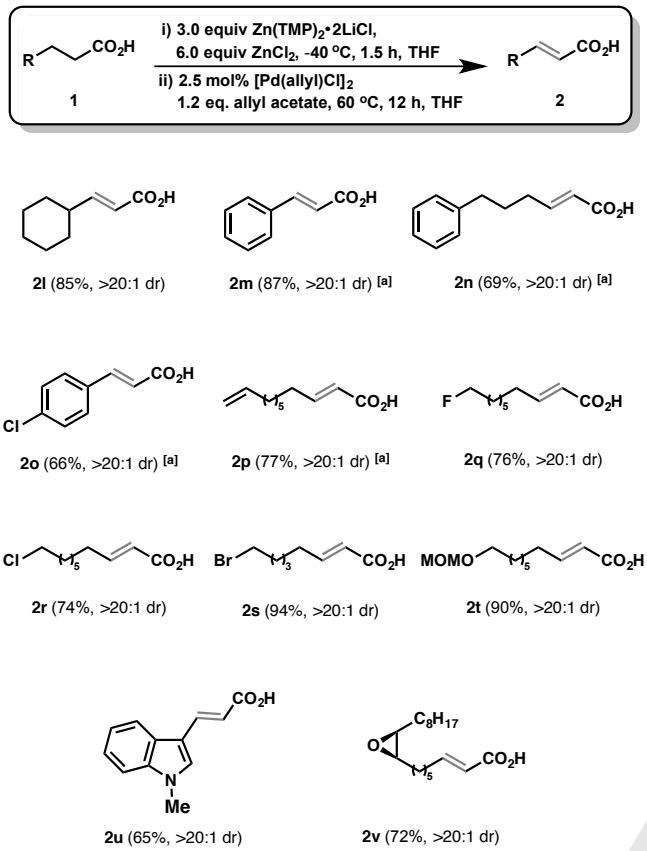


substrate	product	isolated yield
caprylic acid (1b)		93% (>20:1 dr)
capric acid (1c)		89% (>20:1 dr)
undecylic acid (1d)		82% (>20:1 dr)
lauric acid (1e)		89% (>20:1 dr)
tridecylic acid (1f)		85% (>20:1 dr)
myristic acid (1a)		85% (>20:1 dr)
palmitic acid (1g)		81% (>20:1 dr)
palmitoleic acid (1h)		72% (>20:1 dr) [a]
oleic acid (1i)		79% (>20:1 dr) [a]
linoleic acid (1j)		66% (>20:1 dr) [a]
elaidic acid (1k)		82% (>20:1 dr) [a]

[a] 2.3 equiv $Zn(TMP)_2$•2LiCl, $ZnCl_2$ not added, and reaction was quenched after 3 h.

arene or cyclohexyl group at the β-position provided similar outcomes (**2l**-**2m**) and more distal arenes were also tolerated (**2n**). Byproducts derived from competitive oxidative addition of palladium to aryl chloride were not observed (**2o**), and the terminal monosubstituted alkene was not isomerized to the more thermodynamically stable internal alkene (**2p**). Terminal fluoro-, chloro-, and bromo-substituted 2-enoic acids were obtained in 76%, 74%, and 94% isolated yield, respectively (**2q**-**2s**). It is remarkable that dehydrogenation was the most favorable process for these substrates considering the host of undesired pathways that could occur with the electrophilic alkyl halides by either catalyzed or uncatalyzed manifolds, including those that originate with oxidative addition,[18] inter- or intramolecular

Table 3. Scope of unnatural carboxylic acid dehydrogenation.

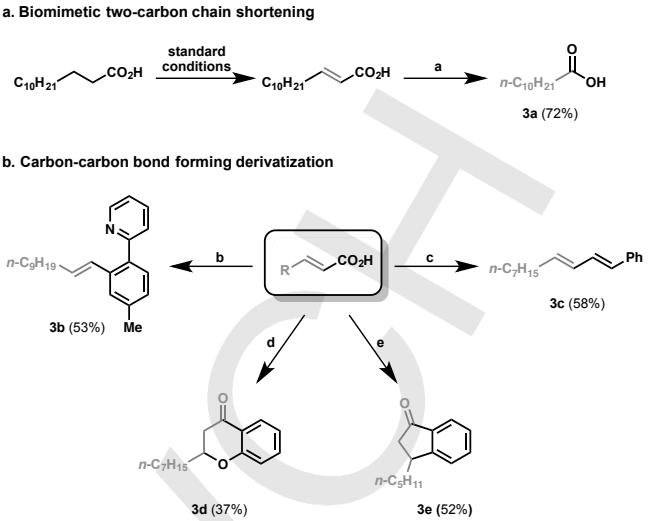


[a] 2.3 equiv $Zn(TMP)_2$•2LiCl, $ZnCl_2$ not added, and the reaction was quenched after 3 h.

substitution, or elimination. Additionally, a number of other functionalities were tolerated under the basic reaction conditions, including a methoxymethyl ether (**2t**), an *N*-methyl indole (**2u**), and an internal epoxide without the generation of epoxide ring-opening byproducts (**2v**). In all substrates examined, high levels of diastereoselectivity (>20:1) were observed. Unfortunately at present some limitations have been identified: α-branched and β,β-disubstituted carboxylic acid starting materials gave limited conversion when subjected to the reaction conditions.

Direct access to enoic acids from their saturated counterparts provides an expedient approach to these materials that are otherwise tedious to obtain, but are useful intermediates for diversification of existing libraries of carboxylic acids (Figure 2). For example, the biomimetic degradation of fatty acids to oxidatively shorten these materials by two carbon units is easily performed through ozonolytic cleavage of the enoic acid products as illustrated by the conversion of *n*-$C_{12}H_{25}CO_2H$ to **3a** (Figure 2a). Decarboxylative coupling reactions are also feasible as in the case of the Rh-catalyzed directed C-H olefination to form **3b**.[19] In addition, readily available enoic acids could undergo decarboxylative coupling[20] with β-bromosytrenes under palladium catalysis to produce the corresponding butadiene derivatives (**3c**),[21] which are commonly seen in a number of

Figure 2. Synthetic utility of aliphatic 2-enoic acids.



a. O_3, acetone, –78 °C, 1 h, then 4.0 equiv Jones reagent (2.5 M in H_2SO_4/H_2O), 72%; b. 1.0 equiv arene, 1.5 equiv enoic acid, 5 mol % $[Rh(COD)_2]OTf$, 1.5 equiv $(t\text{-BuCO})_2O$, PhMe, 120 °C, 48 h, 53%; c. 1.0 equiv β-bromostyrene, 1.2 equiv enoic acid, 5 mol % $Pd(OAc)_2$, 2.0 equiv LiOAc, 1.5 equiv LiCl, DMF, 120 °C, 12 h, 58%; d. 1.1 equiv phenol, 5.0 equiv CF_3SO_3H, CH_2Cl_2, 40 °C, 12 h, 37%; e. CF_3SO_3H/benzene (1:1), 80 °C, 6 h, 52%.

bioactive compounds and materials. Furthermore, fused ring systems such as 4-chromanone (**3d**)[22] and indanone (**3e**)[23] were also obtained through annulation by Michael addition and Friedel-Crafts acylation.

In conclusion, allyl-palladium catalysis provides exquisite chemoselectivity for dehydrogenation of carboxylic acids via in situ dianion formation with $Zn(TMP)_2$•2LiCl in the presence of excess $ZnCl_2$. Future work will focus on obtaining mechanistic insight into the specific effect that the base has on this and other carbonyl dehydrogenation processes. The availability of saturated carboxylic acids and the versatility of enoic acids in downstream transformations forecast the utility of this oxidation process for organic synthesis.

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Keywords: palladium • dehydrogenation • carboxylic acid • biomimetic synthesis • carbanion

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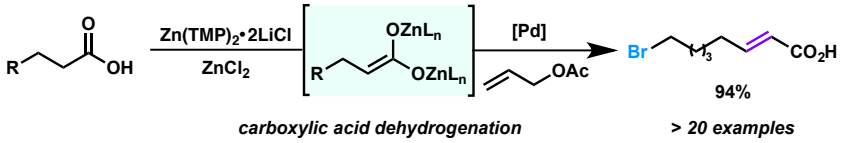

carboxylic acid dehydrogenation *> 20 examples*

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All about that dianion: Instead of decarboxylation, allyl-palladium catalysis allows for dehydrogenation of carboxylic acids to form enoic acids via enediolates.