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Base-Mediated Cascade Aldol Addition and Fragmentation Reactions of Dihydroxyfumaric Acid and Aromatic Aldehydes: Controlling Chemodivergence via Choice of Base, Solvent, and Substituents

George Ward[a], Charles L. Liotta[a,]*, Ramanarayanan Krishnamurthy[b,]*, and Stefan France[a,]*

[a] School of Chemistry and Biochemistry, Georgia Institute of Technology, Atlanta, Georgia, 30332, United States

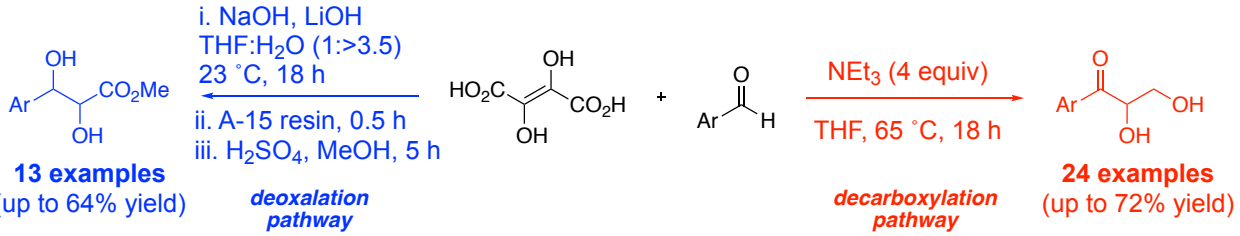
[b] Department of Chemistry, The Scripps Research Institute, La Jolla, California 92037, United States

[c] Petit Institute for Bioengineering and Bioscience, Georgia Institute of Technology, Atlanta, Georgia 30332, United States

stefan.france@chemistry.gatech.edu

rkrishna@scripps.edu

charles.liotta@carnegie.gatech.edu



Abstract

The diester derivative of dihydroxyfumaric acid (DHF) has been used exclusively as an electrophile in organic synthesis. However, the synthetic utility of DHF's nucleophilic reactivity, contained in the ene-diol moiety, has been underexplored. Inspired by recently observed pH-dependent chemodivergent nucleophilic aldol reactions of dihydroxyfumarate (DHF^{2-}) with glyoxylate and formaldehyde, we report herein the control and synthetic application of base-controlled chemodivergent reactions between dihydroxyfumarate and aromatic and heteroaromatic aldehydes. With hydroxide as the base in a predominantly aqueous medium, aldol addition followed by deoxalation occurs to provide various 3-aryl-2,3-dihydroxypropanoic acids. With triethylamine as the base in THF, 1-aryl-2,3-dihydroxypropanones are the products of the reaction. In order to understand the difference in reactivity between DHF, its dicarboxylate and its dimethyl ester, we undertook computational and experimental studies that provide a rationale as to why the dihydroxyfumarate (DHF^{2-}) is a nucleophile while the corresponding diester reacts as an electrophile.

INTRODUCTION

The reactivity of DHF, a molecule that was reported by Fenton in the 1890s,[1,2] has been the subject of recent studies (Figure 1). While it has been primarily reported as a reducing agent (oxidation to di-oxosuccinic acid), DHF has also been shown to undergo reduction to tartaric acid.[3,4] Due to its inherent propensity toward oxidation, DHF has been used as an additive in various food and wine preparations as an anti-oxidant.[5] DHF also undergoes CO_2^- group migration (benzilic acid-type rearrangement) upon oxidation with O_2 and hydroxide to form di- and trisubstituted methoxide anions, which have been used to make ligand complexes and coordination polymers.[6] Until recently, aside from oxidation/reduction of the ene-diol moiety, the only examples reflecting the

electrophilic character of DHF involved the conjugate addition of nucleophiles to the α,β-unsaturated ester portion of DHF.[7,8,9] In all cases, the carboxylic acids were derivatized as alkyl esters.

The physical and chemical properties of dihydroxyfumaric acid vary significantly as one proceeds from the diacid to the conjugate base of the diacid to the diester. Depending on the specific form, it can: (a) exhibit nucleophilic or electrophilic character; and/or (b) behave as an oxidizing or a reducing agent (Figure 1A). For instance, aryl amines provided nitrogen-containing heterocycles after nucleophilic attack and subsequent ring closure.[10] Moreover, protection of the hydroxy groups has also been used to facilitate nucleophilic (1,4-) attack on the unsaturated ester portion.[7] In contrast, the latent nucleophilic behavior of DHF has been relatively underexplored.

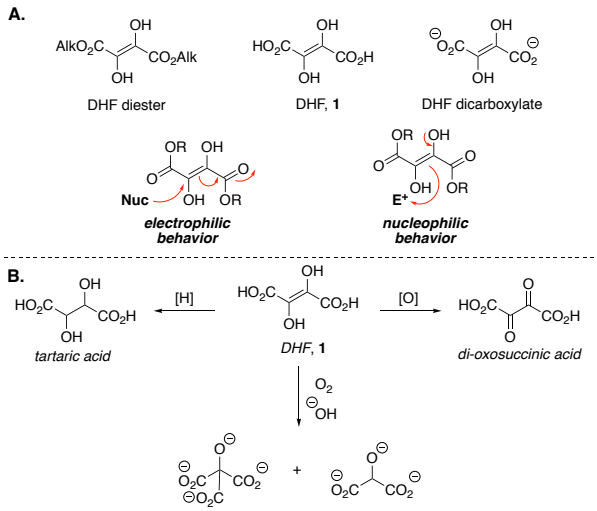


Figure 1. Amphoteric reactivity of dihydroxyfumaric acid (DHF), its diester, and its dicarboxylate

Coincidentally, the nucleophilic behavior of DHF lies at the heart of its importance in prebiotic chemistry. Eschenmoser[11] originally hypothesized a "glyoxylate scenario," in which

DHF (as the formal dimer of glyoxylate) is a central starting material that serves as a source molecule for the formation of a variety of biogenic molecules (such as sugars, α-amino acids, and pyrimidines), and various constituents of the citric acid cycle (or their primordial equivalents). Experimentally, this hypothesis has begun to be explored. It has recently been reported that the reaction of DHF with glyoxylate (**2**) in water proceeds by two completely different reaction pathways depending on the pH of the medium (Figure 2A). The reaction of DHF with glyoxylate at pH 7-8 produces dihydroxyacetone (**4**) and pentulosonic acid (**5**) via the formation of 2,3-dihydroxy-oxalosuccinate **3** (aldol reaction) followed by decarboxylation.[12] Conducting the reaction at pH 13-14 produces tartrate (**6**) and oxalate (**7**) via a hydroxide-mediated deoxalation of the same intermediate **3**.[13] The divergent product formation based on the different pH has been rationalized based on the proclivity of decarboxylation pathway at lower pH verus the dominance of deoxalation pathway at high pH.[14] The reaction of glycolaldehyde and glyceraldehyde as electrophiles, in place of glyoxylate, with DHF at pH 7-8 was found to produce efficiently the corresponding ketoses, tetrulose and pentuloses respectively.[12]

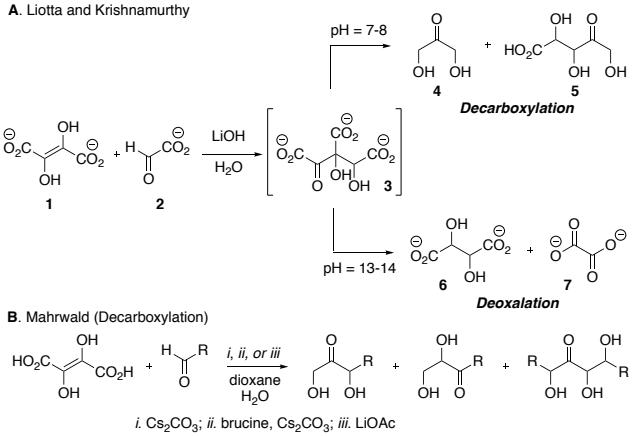
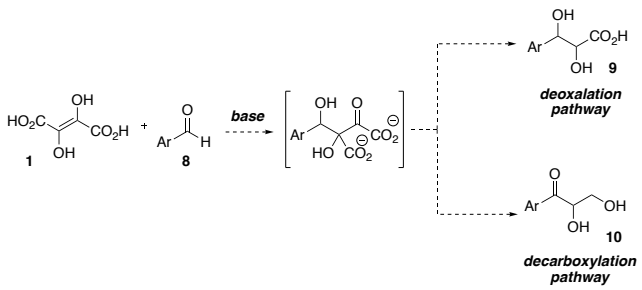


Figure 2. Previous examples of nucleophilic DHF chemistry.

Mahrwald et al. have used these observations to explore the synthetic utility of the decarboxylative aldol reactions of DHF with a variety of aromatic aldehydes, hydroxyacetaldehyde, and several chiral oxygen-containing enolizable aldehydes (Figure 2B).[15] Several synthetic protocols were presented, of which *in situ* generation of the dihydroxyfumarate salt employing a variety of lithium or cesium bases proved to be the most promising. In the presence of a slight excess of aldehyde, mono-decarboxylative aldol reactions were observed. Conversely, in the presence of a large excess of aldehyde, a second addition of aldehyde occurred. The mechanistic pathways for the mono- and di-decarboxylative aldol processes were discussed. They also reported that: (1) in many cases mixtures of carbonyl regioisomers were produced; (2) the yields of the product varied from very good to marginal, and especially for aryl products the yields were particularly low; and (3) the reactions did not result in clean isolable products for many of the examples.

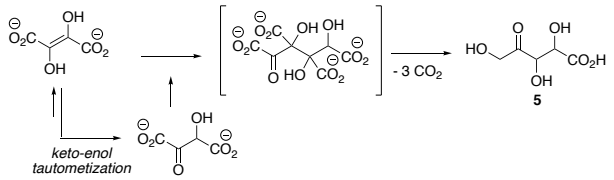
While some of the synthetic possibilities of the decarboxylative aldol pathway have been demonstrated by Mahrwald *et al.,* the synthetic utility and generalization based on the chemodivergence reported by Sagi et al.[12] and Butch et al.[13] have not yet been realized. Herein, we describe our efforts toward controlling chemodivergence in the reactions of aryl and heteroaryl aldehydes with DHF by the careful choice of base and solvent and the applicability in organic synthesis (Scheme 1). We also provide rationale for the disparate physical properties and reactivity of DHF and dihydroxyfumarate (DHF^{2-}) when compared to DHF-diester derivatives, which exhibit significant deviations ranging from solubility to propensity for self-condensation and aerobic oxidation.



Scheme 1. Base-mediated Chemodivergent Aldol Additions of DHF to Aromatic Aldehydes

RESULTS AND DISCUSSION

DHF Nucleophilic Reactivity. From the current literature, there is evidence that deprotonation of DHF to provide its dicarboxylate (DHF^{2-}) is critical to unveiling its nucleophilicity. Deprotonation effectively minimizes the orbital overlap between the delocalized carboxylate anions and the electron-rich ene-diol portion of the molecule. To the best of our knowledge, in cases where DHF behaves as an electrophile, the carboxylic acids of DHF existed as alkyl esters.[6-10] Whereas when reacting as a nucleophile, the carboxylic acid groups of DHF were always ionized using basic media.[12-15] Even with this clear trend in the literature there has been no focused study on why seemingly minor changes to the carboxylic acid moieties of DHF have a profound effect on its reactivity. The relative stabilities of the DHF derivatives, especially toward reaction with atmospheric oxygen (to form di-oxosuccinic acid) and self-condensation (via the putative keto form of DHF^{2-} to form sugar acid **5**, Scheme 2)[16] also seem to be affected by state of ionization of DHF versus its ester derivatives.



Scheme 2. Self-condensation of DHF^{2-} in H_2O.[16] Reproduced with permission from Sagi, V. N.; Karri, P.; Hu, F.; Krishnamurthy, R. Diastereoselective Self-Condensation of Dihydroxyfumaric Acid in Water: Potential Route to Sugars. *Angew. Chem. Int. Ed*. **2011**, *50*, 8127-8130. Copyright 2011 John Wiley and Sons.

For example, DiMeDHF (**11**) is stable under air for months with no degradation or self-condensation as observed by NMR in the solid state or in solution. It is also surprisingly insoluble in most common organic solvents giving rise to dilute solutions in dichloromethane or chloroform at room temperature. Heating at reflux is required to dissolve DiMeDHF in THF or 1,4-dioxane. Upon cooling, DiMeDHF can be recovered quantitatively. Treating DiMeDHF with an electrophile, such as benzaldehyde or 4-nitrobenzaldehyde, in chloroform-*d* at room temperature resulted in no observed reaction (Figure 3A). Conducting the reaction in THF at reflux or with added base (i.e., NEt_3) also failed to provide any observable reaction by crude NMR. With H_2SO_4 as the aldehyde activator, only degradation of the starting materials was observed. This suggests that the ene-diol moiety in ester **11** is unreactive as a nucleophile towards reactive electrophiles such as aryl aldehydes.

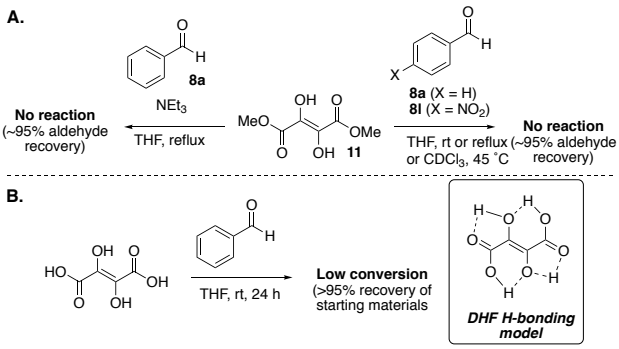


Figure 3. Probing DiMeDHF (**A**) vs DHF free acid (**B**) nucleophilic reactivity

When compared to DiMeDHF, DHF (as the free acid) is oxidized by oxygen but it still can be stored in a refrigerator without rigorous degassing of the container. DHF is much more soluble than DiMeDHF in organic solvents which is odd as, in general, esters are more soluble. The differences in solubility between DiMeDHF and DHF can be rationalized by the fact that in DHF, the molecule is expected to adopt a very ordered intramolecular hydrogen bond arrangement[17] which, ultimately, hides the multiple highly polar functional groups and increases organic solubility[18] (Figure 3B). The reactivity of DHF as the free acid in organic solvents has not been studied. To probe this, we performed a control reaction in which DHF (free acid) was stirred in THF and the solution monitored daily by ^{1}H NMR (Figure 3B). After 3 days, only ~10% of DHF was consumed forming a trace amount of pentulosonic acid via self-condensation. As further proof of DHF acid's poor nucleophilic behavior, extremely low conversion (<5%) was observed by ^{1}H NMR when DHF (free acid) was stirred with an electrophile (i.e., benzaldehyde) in THF after 24 h.

Finally, in contrast, the dicarboxylate can be rapidly oxidized by O_2 so it needs to be stored in a freezer and ideally under a nitrogen balloon to retain its purity for any length of time. The self-condensation of DHF^{2-} in water has been shown by Sagi et. al.[16] to proceed cleanly to sugar

acid **5** in only a few hours.

In order to gain insights into the relative reactivities of dimethyl dihydroxyfumarate (DiMeDHF), the free acid (DHF), and the dicarboxylate (DHF^{2-}), DFT calculations [B3LYP; 6-311+G(2*df*,2*p*)][19] were employed to determine the physical and electronic structure associated with each of these species in aqueous media. Figure 4 illustrates the structure of each of these molecules, the energies of their HOMO and LUMO, and the corresponding molecular orbitals. A common structural feature is that the three structures are held in a planar conformation by the presence of strong hydrogen bonds. The di-deprotonation of dihydroxyfumaric acid to form the corresponding dianion raises the HOMO from -7.53 ev to -5.33 ev suggesting that the nucleophilicity of the dianion should be enhanced compared to the protonated species. In contrast, the respective LUMOs for both dihydroxyfumaric acid and the corresponding dimethyl ester are -2.94 ev and -2.21 ev suggesting that these species are stronger electrophiles than dihydroxyfumarate (LUMO = -0.76 ev). These relative energies also suggest that the dicarboxylate (DHF^{2-}) can behave as a reducing agent or nucleophilic agent while the acid and the diester cannot. These results support the hypothesis that the formation of the dianionic structure is important in order to facilitate reactions where DHF acts as a nucleophile.

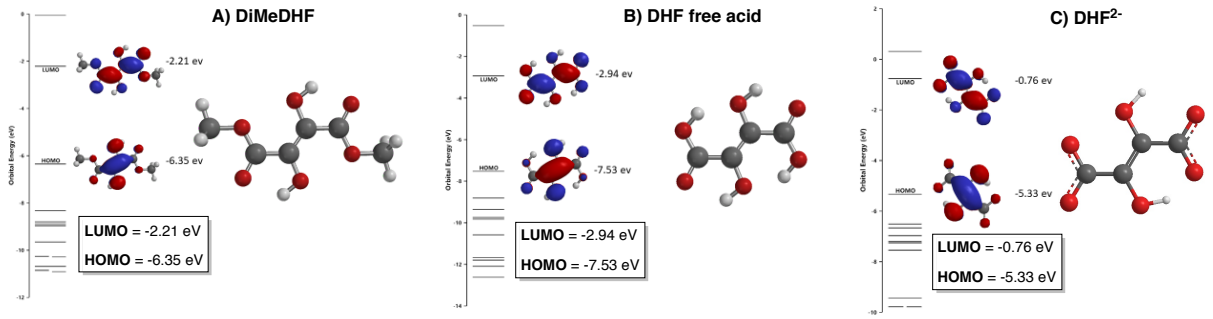
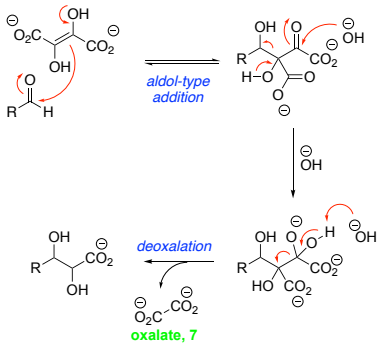


Figure 4. Calculated Frontier Molecular Orbitals of DHF-Diester, DHF Free Acid and DHF Dicarboxylate

Optimization the Reaction of DHF with Benzaldehyde and Hydroxide Bases- The Deoxalation Pathway. With this understanding of the nucleophilic behavior of the dicarboxylate form of DHF, we sought to expand the scope of the work by Sagi et al.[12] and Butch et al.[13] by exploring the reactivity of aryl and heteroaryl aldehydes toward the observed chemodivergence. Benzaldehyde was selected as the substrate for optimization and various bases and solvent systems (e.g., organic, aqueous, and mixed) were screened to first determine conditions selective for the deoxalation pathway. The results are summarized in Table 1. It was previously shown by Sagi et al.[12] and Butch et al.[13] that two hydroxide molecules (one as a nucleophile, one as a base) are necessary to promote the deoxalation pathway (Scheme 3).[14]

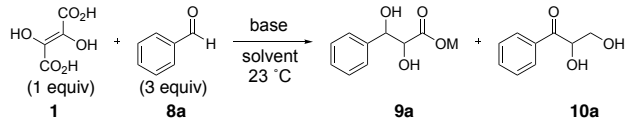


Scheme 3. Deoxalation Pathway and the Importance of Hydroxide

When 4 equivalents (2 equiv to form dicarboxylate and 2 equiv to promote deoxalation) of either TBAH, NaOH, or LiOH were included in the THF reaction, only Cannizzaro reaction products[20,21] (e.g., benzoic acid, benzyl alcohol, etc.) were observed (Table 1, entries 1-3). Addition of 1 equivalent of 15-crown-5 (to activate the hydroxide) with NaOH in THF gave the desired deoxalation product **9a** in 56% yield as a diastereomeric mixture of the sodium carboxylate complexed to the crown ether (entry 4). Reducing the amount of 15-crown-5 to 0.5 equiv resulted in a severe drop in yield (23%, entry 5). Using of 2 equiv of NaH (to form the DHF dicarboxylate)

and 2 equiv of NaOH with 1 equiv of the crown ether improved the yield of the deoxalation product **9a** to 75% yield (entry 6). Unfortunately, efforts to remove the 15-crown-5 by acidification or ion exchange either resulted in degradation or substantial loss of material. Moreover, the presence of the crown ether made characterization using NMR extremely difficult due to overlapping aliphatic signals with the product. Given the difficulty in purification of the product and the requirement of a full equivalent of crown ether, we abandoned this approach and looked for other conditions that would facilitate the deoxalation reaction without the necessity of crown ether.

Table 1. Deoxalation Reaction Optimization[a]



entry[a]	Base (equiv)	Solvent	%Yield (**9a**/**10a**)
1	TBAH (4)	THF	0/0[c]
2	NaOH (4)	THF	0/0[c]
3	LiOH (4)	THF	0/0[c]
4	NaOH:15-c-5 (4:1)	THF	56[d]/0
5	NaOH:15-c-5 (4:0.5)	THF	23[d]/0
6	NaH:NaOH:15-c-5 (2:2:1)	THF	75[d]/0
7	NaOH (4)	H_2O	0/0[c]
8	NaOH (4)	THF:H_2O (1:1)	0/0[c]
9	NaOH:LiOH (4:2)	H_2O	0/0[c]
10	NaOH:LiOH (4:2)	THF:H_2O (1:1)	0/0[c]
11	NaOH:LiOH (4:2)	THF:H_2O (1:3.5)	25[e]/0
12	NaOH:LiOH (4:2)	THF:H_2O (1:30)	45[e]/0
13	**NaOH:LiOH (4:2)**	**THF:H_2O (1:47)**	**72[e]/0**

[a] Reactions were performed with 1 equiv. of DHF, 3 equiv. of benzaldehyde, and indicated base in indicated solvent and temperature for 18 h. [b] Yields determined by quantitative ^{1}H NMR of the crude reaction mixture with dimethyl sulfone as an internal standard. [c] No desired products. Only products from Cannizzaro reaction observed. [d] Isolated yield of the 15-crown-5 sodium carboxylate complex. [e] Yield determined by quantitative ^{1}H NMR with dimethyl sulfone as an internal standard following acidification with Amberlyst 15 resin and extraction of organic soluble byproducts.

Given this issue, we went back to the drawing board and decided to directly adapt the published aqueous method from Sagi et al.[12] and Butch et al.[13] NaOH (6 equivalents) in H_2O or in a 1:1 THF-H_2O mixture only provided Cannizzaro reaction products (entries 7 and 8). Previous work had indicated that a combination of both LiOH (2 equiv) and NaOH (4 equiv) afforded better results as the DHF dilithium salt is much more soluble in water than the sodium salt. Unfortunately, initial combination of these bases either in H_2O or in a 1:1 THF-H_2O mixture continued to produce Cannizzaro products (entries 9 and 10). Interestingly, employing a lower THF to H_2O ratio and changing the order of addition was key in the development of a successful process. Benzaldehyde dissolved in THF (2 mL) was added to a solution of NaOH in H_2O (5 mL) followed by slow addition of DHF and LiOH in H_2O (2 mL) to give a 1:3.5 THF-H_2O mixture. Using this sequence, deoxalation product **9a** was observed (entry 11). Since the product could not

be extracted into the organic phase, the reaction mixture was treated with Amberlyst 15 resin[22] to acidify the solution and remove the sodium and lithium cations and the organic soluble byproducts were removed by extraction. Upon concentration of the aqueous phase, a 25% yield of deoxalation product **9a** was observed by quantitative ^{1}H NMR along with a collection of other unidentified peaks. Reducing the amount of THF used to dissolve the benzaldehyde to ~0.23 mL resulted in a 1:30 THF-H_2O ratio and gave a 45% ^{1}H NMR yield (entry 12). In the end, the addition of a minimal amount of THF (0.15 mL) to dissolve benzaldehyde (providing a 1:47 THF-H_2O solution) proved to be the best conditions, with a 72% ^{1}H NMR yield observed for deoxalation the product **9a** (entry 13).

Deconvoluting Deoxalation from DHF Self-Condensation Pathways. We hypothesized that the undesired peaks in the deoxalation reaction arose from DHF self-condensation. To test that hypothesis, we exposed DHF to the deoxalation reaction conditions in the absence of benzaldehyde (Figure 5A). Through spiking studies as well as comparison to literature precedent[14] we determined that the signal at 174.3 ppm is glycolic acid (**13**), the pair of peaks at 173.3 and 172.8 ppm are the two diastereomers (D/L and *meso*) of tartaric acid (**6**), and the peak at 170.8 ppm is tartronic acid (**12**). 2-D NMR experiments and DEPT further confirm these identifications. Comparing the control reaction against the same reaction with 3 equiv of benzaldehyde, the signals at 174.1 and 174.0 ppm represent the diastereomers of the deoxalation product while the same peaks from DHF self-condensation are also observed (Figure 5B). A signal for oxalic acid can also be observed at 162.2 ppm.

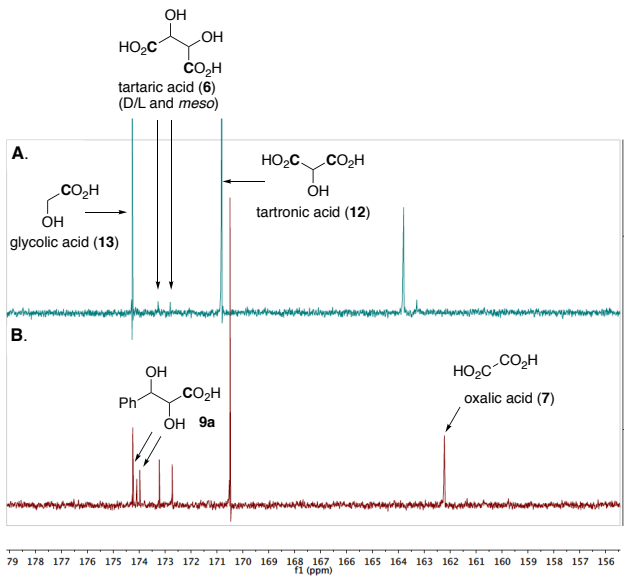


Figure 5. Crude ^{13}C NMR (DMSO-d_6) of Reactions of (**A**) DHF with NaOH:LiOH (4:2) in THF:H_2O (1:3.5) and (**B**) with 3 equiv of benzaldehyde added after acidification.

We envision a range of different pathways that DHF can undergo to form the observed byproducts under strong basic conditions (Figure 6). These pathways are distinct from the previously published self-reactivity of DHF under slightly basic conditions (pH 8). A single DHF molecule can fragment to form glycolate (**13**) and glyoxylate (**2**). Glyoxylate is a highly reactive species that has already been shown to react with DHF to form tartrate (**6**) through a deoxalative mechanism.[13] Dimerization of DHF forms the tetra-carboxy intermediate **I**, which undergoes decarboxylation to form **II**. **II** can also tautomerize to **III** then proceed through a deoxalation-like cleavage mechanism to release tartronate (**12**) and tartrate. Tartronate can also decarboxylate to produce glycolate. The three observed products are the only non-volatile, stable products from the self-reactivity of DHF at high pH after acidification. It is important to mention that the observed peak ratios do not accurately represent how much condensation products are formed. Based on the proposed mechanism, tartrate should be generated in a greater amount than tartronate. However, the NMR shows a much larger amount of tartronic acid than tartaric acid. This discrepancy is an

artifact of the workup procedure. Some tartrate is extracted into the organic phase and some undergoes degradation following the acidic workup.

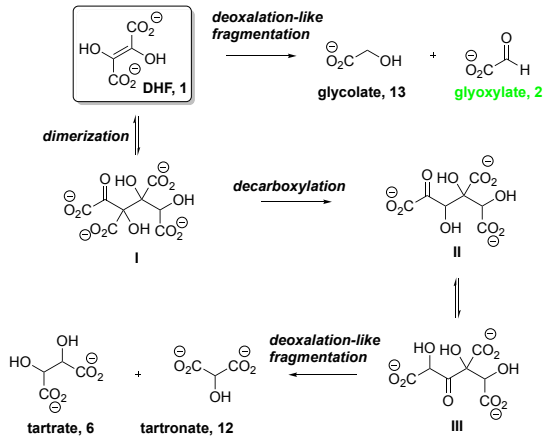
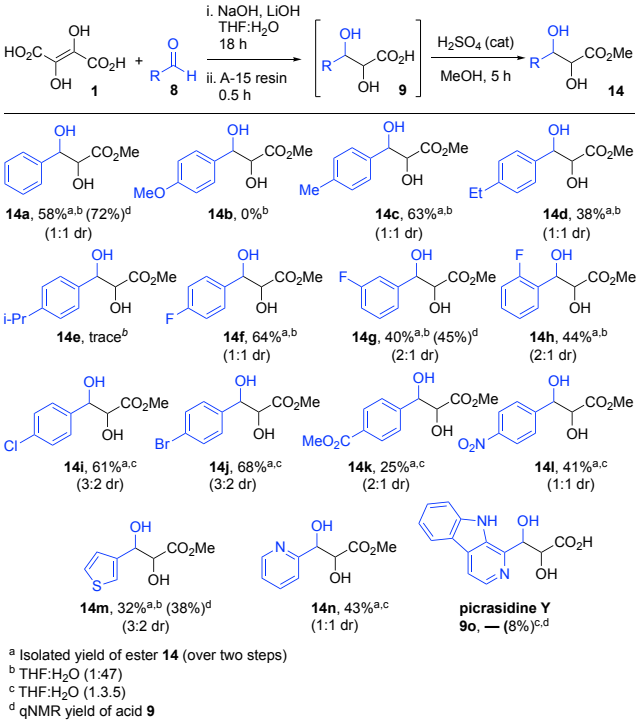


Figure 6. Proposed mechanism for the origin of tartronic acid (**12**), tartaric acid (**6**), and glycolic acid (**13**)

Examination of Substrate Scope of Deoxalation Reaction. With working conditions for the deoxalation reaction in place, we next examined the scope and limitations of employing various aryl and heteroaryl aldehydes (Scheme 4). Instead of relying on quantitative NMR, we decided to derivatize the products to the corresponding methyl esters for easy isolation via column chromatography. Heating the crude mixture with catalytic H_2SO_4 in MeOH readily afforded esterification products in greater than ~80% yield. For instance, the deoxalation product from benzaldehyde was converted to its methyl ester in 81% yield. This gave an overall yield of 58% for the two steps upon isolation. The ester **14a** was isolated as a 1:1 mixture of diastereomers.

Scheme 4. Hydroxide-Mediated Cascade Aldol-Deoxalation Reactions



[a] Isolated yield of ester **14** (over two steps)
[b] THF:H_2O (1:47)
[c] THF:H_2O (1.3.5)
[d] qNMR yield of acid **9**

We then probed electronic effects on the reaction by looking at 4-substituted benzaldehydes. The reaction with 4-anisaldehyde failed to provide any desired deoxalation product, whereas 63% yield of dihydroxyester **14c** was obtained with 4-tolualdehyde (**8c**). In contrast to tolualdehyde, the 4-ethylbenzaldehyde **8d** gave 38% yield of **14d** whereas only trace product was observed with 4-isopropylbenzaldehyde **8e**. 4-Fluorobenzaldehyde **(8e)** was similarly compatible with the reaction sequence forming dihydroxy ester **14e** in 64% yield. Both 3-fluoro- and 2-fluorobenzaldehydes (**8f** and **8g**) similarly gave their corresponding methyl esters **14f** and **14g** in 40% and 44% yield, respectively. 4-Chloro- and 4-bromobenzaldehydes (**8i** and **8j**) are solids and were not readily solubilized in the amount of THF (0.15 mL) used in the 1:47 THF-H_2O mixture. To ensure solubility, 2 mL of THF was used to dissolve the solids before addition to the aqueous DHF/base solution (resulting in a 1:3.5 THF-H_2O mixture). In this solvent system, the respective

chloro and bromo ester products **14i** and **14j** were obtained in 63% and 68% yield. Stronger electron-withdrawing groups on the phenyl ring, such as 4-CO_2Me and 4-NO_2,[23] were also amenable to the reaction, albeit with reduced yields. 4-CO_2Me-benzaldehyde (**8k)** only gave 25% yield of the ester product **14k** while 41% yield of ester **14l** was obtained with the 4-NO_2-benzaldehyde (**8l)**. In both cases, increased amounts of Cannizzaro reaction products were observed.

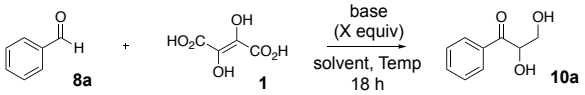
Several heteroaryl aldehydes were also examined under the reaction conditions. 3-Thiophencarboxaldehyde **8m** gave 38% qNMR yield of **9m** and a 32% yield of ester **14m** over the two steps. 2-Formylpyridine (**8n**) performed similarly and gave 43% yield of ester **14n**. Finally, 1-formyl β-carboline (**8o**) was subjected to the reaction conditions to form the natural product, picrasidine Y[24] (**9o**). **9o** was formed in 8% yield by qNMR along with several undesired side products (including Cannizzaro products). Protection of the carboline would most likely improve the product yield given the strong basic conditions and the acidic carboline proton. Picrasidine Y has been previously synthesized in 7 steps[24a] using tartaric acid. Despite the low yield, this synthesis thus represents a one-step approach to picrasidine Y which could offer a rapid opportunity for compound library development by employing substituted 1-formyl-β-carbolines.

Optimization of the Reaction of DHF with Benzaldehyde and Tertiary Amine Bases- The Decarboxylation Pathway. While searching for a viable protocol for the deoxalation reaction, we simultaneously probed for conditions to selectively promote the decarboxylation reaction (Table 2). Given that trace decarboxylation products were detected in the reaction of DHF and benzaldehyde with no added base in THF at room temperature (entry 1), we started by increasing the reaction temperature. Upon heating the reaction at reflux, 2,3-dihydroxypropanone **10a** was

obtained in 15% yield as the only decarboxylation product (entry 2). This observation runs counter to what was expected based on Mahrwald's decarboxylation work.[15] In that report for aryl aldehydes, the isomeric aryl-substituted dihydroxyacetones or diaryl trihydroxybutanones were predominantly formed. Only three examples of aryl 2,3-dihydroxypropanone formation were shown. To affect the transformation, brucine (50 mol %) and Cs_2CO_3 (1.5 equivalents) were employed, but the yields were low (13-38% yield) in each case. In contrast, our reaction provides selective mono-aldol additions (despite using excess aldehyde) and formation of the dihydroxypropanones. It is also important to note that the transformation represents a formal C(sp^2)-H alkylation of the aromatic aldehyde without involving any transition metal-based chemistry.

Next, bases were screened to facilitate the decarboxylation reaction at 65 ˚C. The use of hydroxides, alkoxides, or carbonate bases resulted in Cannizzaro reaction (entries 3-5). Next, tertiary amine bases were added. With Hünig's base (iPr_2NEt, 4 equiv), **10a** was obtained in 25% yield (entry 6). While no product formation was detected with DBU (entry 7), NEt_3 afforded **10a** in 68% yield (entry 8). Increasing the amount of NEt_3 to 6 equivalents resulted in a 62% yield (entry 9), whereas reducing the amount of NEt_3 to 3 equivalents provided 72% yield of **10a** (entry 10). Further efforts to lower the amount of NEt_3 failed to improve the yield (entries 11 and 12). Changing the relative amounts of aldehyde and DHF from 3:1 to either 2:1 or 1:1 resulted in reduced yields (entries 13 and 14). Other solvents such as dioxane and methylene chloride also failed to improve the product yield (entries 15 and 16).

Table 2. Decarboxylation Optimization[a]

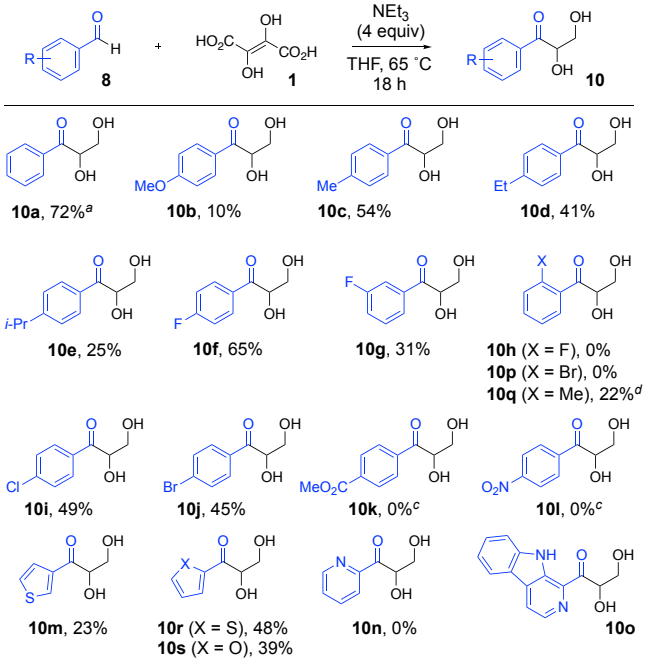


entry	8a:1	base (equiv)	solvent (Temp [˚C])	yield (%)[b]
1	3:1	None	THF (23)	trace
2	3:1	None	THF (65)	15
3	3:1	NaOH (4)	THF (65)	--[c]
4	3:1	K_2CO_3 (4)	THF (65)	--[c]
5	3:1	NaOEt (4)	THF (65)	--[c]
6	3:1	*i*-Pr_2NEt (4)	THF (65)	25
7	3:1	DBU (4)	THF (65)	—[d]
8	3:1	NEt_3 (4)	THF (65)	68
9	3:1	NEt_3 (6)	THF (65)	62
10	3:1	**NEt_3 (3)**	**THF (65)**	**72**
11	3:1	NEt_3 (2)	THF (65)	64
12	3:1	NEt_3 (1)	THF (65)	55
13	2:1	NEt_3 (4)	THF (65)	45
14	1:1	NEt_3 (4)	THF (65)	28
15	3:1	NEt_3 (4)	CH_2Cl_2 (40)	23
16	3:1	NEt_3 (4)	dioxane (100)	20

[a] Reaction performed with indicated amounts of DHF, benzaldehyde **8a**, and base in indicated solvent at the listed temperature. [b] Isolated yields after column chromatography. [c] Formation of benzoic acid via Cannizzaro-type reaction of **8a**. [d] No desired product. Degradation of DHF observed.

Examination of Substrate Scope of the Decarboxylation Reaction. Having optimized the conditions for the decarboxylation reaction with benzaldehyde, the scope and limitations of the transformation were initially examined with the same substituted aryl aldehydes that were previously utilized in the deoxalation study (Scheme 5). Whereas no deoxalation product was formed with 4-anisaldehyde (**8b**), a 10% isolated yield of decarboxylation product **10b** was obtained under the triethylamine conditions. 4-Methyl-, 4-ethyl-, and 4-isopropyl-benzaldehydes (**8c**-**e**) gave dihydroxy-1-phenylpropanones **10c**-**e** in 54%, 41%, and 25% yield, respectively.

Scheme 5. Triethylamine-mediated Decarboxylative Aldol Cascade Reactions of DHF with Aryl Aldehydes



For the mono-substituted fluorobenzene series, 4-fluoro- and 3-fluoro-benzaldehydes (**8f** and **8g**) provided decarboxylation products **10f** and **10g** in 65% and 31% yield, respectively. A complex mixture of the isomeric diaryl trihydroxybutanones (**16h** and **17h**) was obtained with 2-fluorobenzaldehyde (**8h)** (Figure 7). Despite using excess aldehyde, this was the first instance that double aldol addition products were observed under our conditions. Intrigued by the observation of the double aldol addition products, we employed 2-bromobenzaldehyde (**8p**) and 2-tolualdehyde (**8q**) and to probe steric and electronic effects. 2-Bromobenzaldehyde gave a similar complex mixture of double aldol isomers (**15p** and **16p**) as seen with the 2-fluoro derivative. 2-Tolualdehyde instead produced 22% yield of a 2:1 mixture of carbonyl isomers **10q** and **17q**.

Beyond these complex substrates, 4-chloro- and 4-bromobenzaldehydes (**8i-8j**) were more amendable and each gave their respective dihydroxypropanones **10i-10j** in 49% and 45% yield.

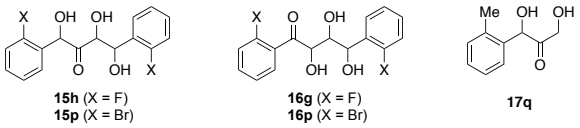
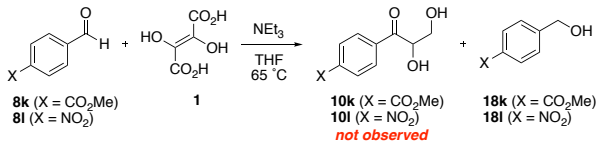


Figure 7. Dihydroxyacetone and Isomeric Diaryl Trihydroxybutanones Products Obtained from 2-Substituted Benzaldehydes

Interestingly, products **10k** and **10l** were not observed with 4-CO_2Me- and 4-NO_2-benzaldeyde (**8k** and **8l**). Instead, only reduction to form benzyl alcohols **18k** and **18l** were observed (Scheme 6). The benzyl alcohols do not arise from Cannizzaro reactions as there are no hydroxide (or alkoxy) bases present. Therefore, DHF must be playing a direct role in their formation.

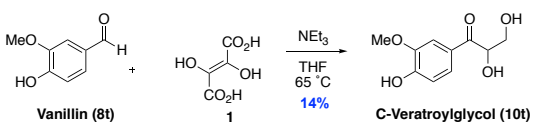


Scheme 6. Unexpected Aldehyde Reduction

Heteroaryl aldehydes were next explored, but proved troublesome upon initial screening; substantial degradation of starting materials and/or products was observed and no dihydroxypropanone products were detected. After some optimization, it was found that products could be isolated when the reaction was performed in CH_2Cl_2 at reflux. Under these conditions, 3-thienyl-, 2-thienyl-, and 2-furyl-2,3-dihydroxypropanones (**10m**, **10r**, and **10s)** were obtained in 23%, 48%, and 39% yield, respectively. In contrast, nitrogen-containing heteroaryl rings were

problematic for the method. Reduction to the benzyl alcohols took place with both pyridine-2-carbaldehyde (**8n**) and 1-formyl-β-carboline (**8o**).

Application of the Decarboxylation: Synthesis of *C*-Veratroylglycol. Aryl 2,3-dihydroxypropanones (**10**) represent a class of highly oxidized alkyl chains that have garnered the attention of synthetic chemists for many years.[25] They represent a diverse set of compounds that include both pharmaceutically-relevant lignan and non-lignan natural products and synthetically-derived compounds.[26] Despite the prevalence of (hetero)aryl 2,3-dihydroxylpropanones in nature, only a small subset has been examined for biological activity due to the low abundance of the individually isolated compounds.[27] For instance, *C*-veratroylglycol (**10t**) is a naturally-occurring 2,3-dihydroxy-1-phenylpropanone that has been isolated from a variety of plants, fruits, and tree saps (Scheme 7).[28] It has been shown to demonstrate modest antioxidant,[29] antiproliferative (against human colon cancer cells),[30] and COX-2 inhibitory activity[31] in various studies. The key issues in studying the activity of **10t** are its low abundance in natural sources which gives rise to poor isolated yields. For example, <75 mg can be isolated from 1 kg of hazelnut shells after extensive grinding, milling, sequential extractions, and column fractionations.[28] Similarly, while one study reported that 1.5 mg of **10t** was isolated from 20 L of maple syrup, another claimed that only 0.5 mg was obtained from 1 kg of syrup.[29,30,32] *C*-Veratroylglycol can also be purchased primarily from contract companies at a cost of >$100/mg.[33] Therefore, a cheaper approach toward *C*-veratroylglycol would be an enabling endeavor for the scientific community.



Scheme 7. One-step Decarboxylative Synthesis of *C*-Veratroylglycol (**10t**)

We were pleased to find that the reaction of vanillin (**8t**), DHF, and triethylamine (7 equivalents)[34] afforded *C*-veratroylglycol (**10t**) in 14% yield from the single step reaction (Scheme 7). One true value of this decarboxylation approach lies in the financial savings. Based on raw material and solvent pricing,[35] we can synthesize 25-30 mg of *C*-veratroylglycol for ~$2.36/mg, which is ~50-fold cheaper than purchasing it from current commercial sources. To complement this synthesis, we have begun to assemble a small compound library of various substituted aryl 2,3-dihydroxypropanones by using the decarboxylation method (see Supporting Information for more details).

Complete Mechanistic Picture of Chemodivergence. The complete mechanistic landscape for the reactions of DHF with aryl aldehydes is shown in Figure 8. The reaction can take place along various pathways depending on the choice of base, solvent, and the electron-donating or electron-withdrawing substituents on the aryl aldehyde component. Upon aldol addition of DHF to the aldehyde to form intermediate **19**, three possible pathways for fragmentation are plausible. In the first pathway, nucleophilic attack on the carbonyl by hydroxide occurs. Subsequent deprotonation (mediated by hydroxide) leads to the deoxalative fragmentation pathway to generate 1-aryl 2,3-dihydroxypropanoates **9** (see Figure 5). In the second pathway, NEt_3 mediates the transformations as a proton transfer agent (NEt_3/$^+NEt_3H$). Following aldol addition of DHF, aldol addition intermediate **19** then undergoes decarboxylation to form enediol **21**. NEt_3-mediated tautomerization provides **22** followed by another decarboxylation to form enediol intermediate **23**, which can tautomerize to dihydroxyacetone **17**. Further isomerizations mediated by NEt_3 and its

conjugate acid provide the observed 2,3-dihydroxypropanone **10**. Alternatively, a second aldol-type reaction can take place between enediol **23** and another aldehyde molecule to provide diaryl trihydroxybutanones **15** and **16** (after carbonyl isomerization). This second addition arises when the isomerization from **24** to **10** is slower than tautomerization to enediol **23**. In the cases of electron-poor arenes with NEt_3, fragmentation of intermediate **19** can occur such that a resonance-delocalized benzylic anion is generated along with 2,3-dioxosuccinate (**26**). Subsequent protonation yields the alcohols **18**. The major impediment toward higher yield is presumably the complications that can result from self-condensation of DHF (see Figure 6).

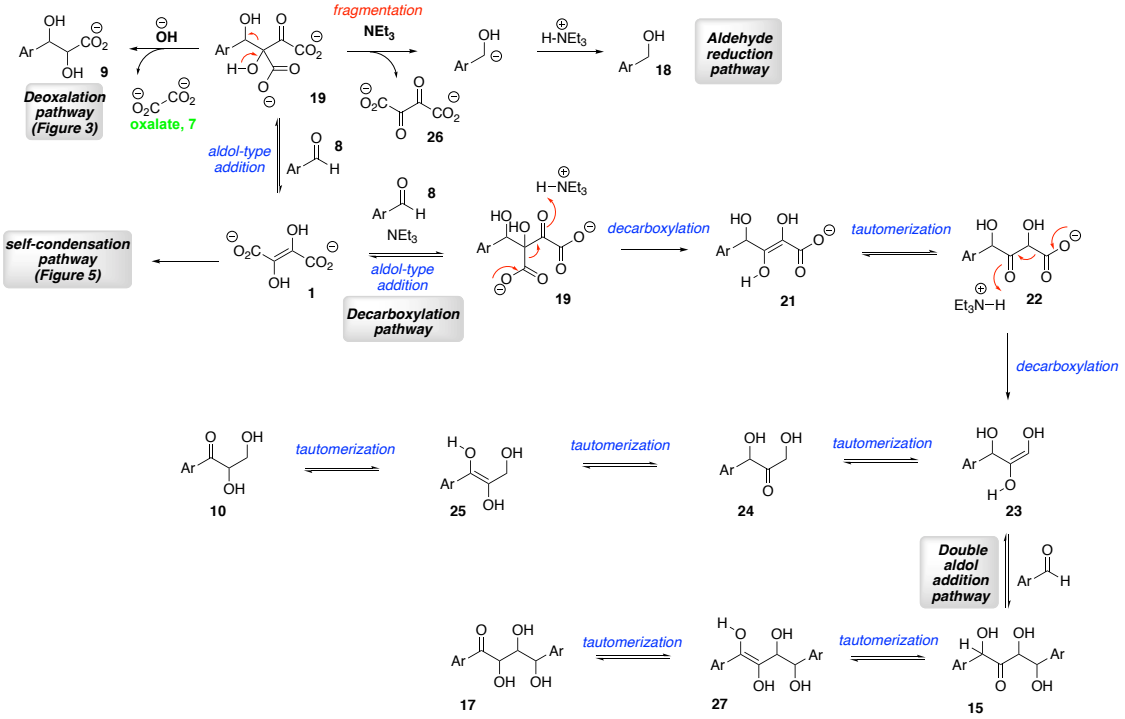
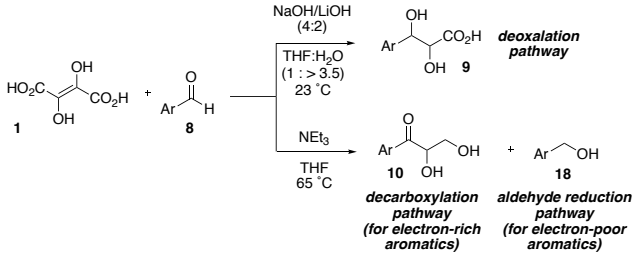


Figure 8. Integrated Mechanistic Proposal for Product Formation

CONCLUSIONS

In summary, through a combination of control reactions and DFT calculations, we have demonstrated that DHF is nucleophilic in its dicarboxylate form and electrophilic in both its free acid form and when derivatized as a diester. The DHF dicarboxylate, under the high pH conditions, readily undergoes self-condensation to afford tartronic acid, glycolic acid, and tartaric acid. In contrast, the diester is completely stable and unreactive even at elevated temperatures, while the free acid undergoes very slow self-condensation. This represents the first efforts to understand and codify the reactivity of DHF in order to harness its greater synthetic potential.



Scheme 8. Summary of Observed Chemodivergence

In particular, the reactions of DHF with aryl aldehydes display remarkable base-mediated chemodivergence (Scheme 8). With excess hydroxide in a THF:H_2O (1:47) mixture, DHF reacts with aryl aldehydes by aldol addition followed by a deoxalative fragmentation to form 3-aryl-2,3-dihydroxypropanoates. The propanoates were isolated as their methyl esters in up to 64% yield following esterification of the crude mixture. The nature of the base used to form the dicarboxylate plays a central role in the nucleophilic reactions of DHF. Hydroxide acts as both a base and a nucleophile to promote deoxalation. Conversely, with excess NEt_3 in THF, the same aldol intermediate undergoes a series of decarboxylations and carbonyl isomerizations to form 1-aryl-2,3-dihydroxypropanones in up to 72% yield. NEt_3 acts as a proton shuttle to mediate the various

transformations. Compared to the literature precedent for the DHF reaction with aryl aldehydes (which predominantly forms substituted dihydroxyacetones or the disubstituted trihydroxybutanones), selective formation of the 1-aryl-2,3-dihydroxypropanones is achieved. The overall reaction represents a formal C(sp^2)-H alkylation of an aldehyde to form the propanone products. In both cases, the reaction is generally amenable to 3- and 4-substituted benzaldehydes, although strongly electron-rich substituents give very low yields or no reaction at all. While strongly electron-withdrawing substituents are tolerable in the deoxalation reactions with hydroxide, the desired propanones are not formed with NEt_3 and reduction to the corresponding benzyl alcohols are observed instead. Heteroaryl aldehydes are amenable to the deoxalation reactions but those containing basic nitrogens give reduction products or other side reactions with NEt_3. Finally, in an application of the decarboxylation method toward target synthesis, *C*-veratroylglycol- an expensive, bioactive, and naturally-occurring 2,3-dihydroxy-1-phenylpropanone- was synthesized cheaply in one step from vanillin with a 14% overall yield.

EXPERIMENTAL SECTION

General Information. Chromatographic purification was performed as flash chromatography with Silicycle SiliaFlash P60 silica gel (40-63 μm) or preparative thin-layer chromatography (prep-TLC) using silica gel F254 (1000 μm) plates and solvents indicated as eluent with 0.1-0.5 bar pressure. For quantitative flash chromatography, technical grades solvents were utilized. Analytical thin-layer chromatography (TLC) was performed on Silicycle SiliaPlate TLC silica gel F254 (250 μm) TLC glass plates. Visualization was accomplished with UV light.

Infrared Spectra were obtained on a Thermo Nicolet 6700 FTIR and analyzed using OMNIC software. The IR bands are characterized as broad (br), weak (w), medium (m), and strong (s). Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Bruker 500 MHz spectrometer with solvent resonances as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). MestraNova was used to analyze NMR spectra. ^{1}H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, t = triplet, m = multiplet, br = broad), coupling constants (Hz), and integration. High resolution mass spectrometry (HRMS) measurements were obtained either through EI on a Micromass AutoSpec M [forward geometry (EBE) three sector tandem MS] or through ESI on a Thermo Orbitrap XL. The accurate mass analyses run in EI mode were at a mass resolution of 10,000 and were calibrated using PFK (perfluorokerosene) as an internal standard. The accurate mass analyses run in ESI mode were at a mass resolution of 30,000 using the calibration mixture supplied by Thermo. Uncorrected melting points were measured with a digital melting point apparatus (DigiMelt MPA 160). DFT calculations performed using B3LYP functional with 6-31G* in the gas phase as the basis set.

*Synthesis of DiMeDHF (**11**)*. In a flame dried flask, DHF hydrate[36] (5.0 g, 27.2 mmol) was dissolved in anhydrous MeOH (35 mL) under an inert atmosphere. The resulting solution was cooled to 0 ˚C and thionyl chloride (8.8 g, 59.7 mmol, 2.2 equiv) was added. The reaction was warmed to room temperature and stirred for 2 d while a white precipitate was formed. The precipitate was recovered by filtration to provide DiMeDHF (**11**) as a white solid (4.4 g, 74%). Characterization matches previously published results.[37]

DHF Derivative Self-Reactivity Studies. To determine the relative stability of DHF and DiMeDHF, 150 mg of both were separately dissolved in refluxing THF (7 mL) for 3 d. At which point the reactions were cooled to room temperature and concentrated to dryness. The crude mixture was then analyzed by NMR. DiMeDHF was completely recovered while only 10% of DHF had reacted to give pentulosonic acid and other side products. The di-lithiated DHF stability was confirmed according to the published self-reactivity of DHF work by Sagi *et al.*[16]

General Procedures for the Synthesis of (Hetero)aryl 2,3-dihydroxypropanoic Methyl Esters

Deoxalation Procedure: A dried round bottom flask is charged with nitrogen and NaOH (130 mg, 3.26 mmol, 4 equiv). To this, deionized water (5 mL) is added and stirred to fully dissolve the salt. A 16 M solution of aldehyde (2.44 mmol) in distilled THF (0.15 mL) was prepared in a vial. In a second separate vial, 1 eq of DHF and 2 eq of $LiOH•H_2O$ (68 mg, 1.63 mmol) are dissolved in water to bring the concentration of LiOH to 1M (2 mL). The aldehyde solution is added to the reaction flask followed by slow addition of DHF/LiOH solution via syringe pump. Volume is added over 30 min. The reaction is then allowed to stir overnight. After ~18 h, Amberlyst-15 cationic exchange resin is added to the flask. Stirring is continued until the pH of the solution reaches ~4. Usual equilibration of pH takes approximately 20 min depending on amount of resin beads added. The mixture was poured over a Buchner funnel to remove the beads and washed with both water and EtOAc. The biphasic mixture was separated via a separatory funnel and the aqueous phase was extracted with EtOAc (3x) to remove all undesired Cannizzaro reaction products. The aqueous phase contains both the dihydroxy acid products as well as DHF dimerization/fragmentation products (tartrate, glycolate, hydroxy malonate).

Esterification Procedure: After concentration of the aqueous phase through rotatory evaporation, the crude mixture was suspended in MeOH and transferred into another round bottom flask. Catalytic concentrated sulfuric acid (5 drops) was added and the reaction mixture refluxed for 5 h. After completion by TLC, the reaction was concentrated onto silica and purified via flash chromatography (5 % MeOH/DCM).

Methyl 2,3-dihydroxy-3-phenylpropanoate (**14a**). The general deoxalation and esterification procedures were followed using DHF dihydrate (150 mg, 0.814 mmol), benzaldehyde **8a** (259 mg, 2.44 mmol) in 0.15 mL of THF, NaOH (130 mg, 3.26 mmol) and LiOH•H_2O (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, R_f = 0.2), compound **14a** was afforded as a clear oil (93 mg, 58% yield) as a 1:1 mixture of diastereomers. Characterization matches previously published results.[38]

Methyl 2,3-dihydroxy-3-(p-tolyl)propanoate (**14c**). The general deoxalation and esterification procedures were followed using DHF dihydrate (150 mg, 0.814 mmol), 4-methyl benzaldehyde **8c** (294 mg, 2.44 mmol) in 0.15 mL of THF, NaOH (130 mg, 3.26 mmol) and LiOH•H_2O (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, R_f = 0.25), compound **14c** was afforded as a clear oil (108 mg, 63% yield) in a 1:1 mixture of diastereomers. Characterization matches previously published results.[38]

Methyl 3-(4-ethylphenyl)-2,3-dihydroxypropanoate (**14d**). The general deoxalation and esterification procedures were followed using DHF dihydrate (150 mg, 0.814 mmol), 4-ethyl benzaldehyde **8d** (328 mg, 2.44 mmol) in 0.15 mL of THF, NaOH (130 mg, 3.26 mmol) and

LiOH•H_2O (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, R_f = 0.25), compound **14d** was afforded as a clear oil (69 mg, 38% yield) as a 1:1 mixture of diastereomers. **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.2 Hz, 2H), 7.41 – 7.38 (m, 2H), 7.36 – 7.33 (m, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 5.15 (dd, *J* = 7.2, 3.3 Hz, 1H), 4.55 (d, *J* = 3.3 Hz, 1H), 3.79 (d, *J* = 7.2 Hz, 1H), 2.76 (q, *J* = 7.6 Hz, 2H), 2.66 (q, *J* = 7.6 Hz, 2H), 1.31 (t, *J* = 7.6 Hz, 3H), 1.24 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 150.9, 150.7, 144.2, 129.0, 128.9, 128.7, 128.2, 128.2, 127.9, 127.8, 127.6, 127.5, 127.4, 85.5, 84.3, 76.2, 57.3, 29.7, 29.0, 28.58, 28.55, 15.5, 15.4, 15.09, 15.06. **IR** 3419 (br), 1975 (s), 2128 (w), 1738 (w), 1685 (s), 1614 (w) **HRMS** (ESI) *m/z*: [M+Na^+] Calcd for $C_{12}H_{16}O_4Na$ 247.0941; Found 247.0941.

Methyl 2,3-dihydroxy-3-(4-isopropylphenyl)propanoate (**14e**). The general deoxalation procedure was followed using DHF dihydrate (150 mg, 0.814 mmol), 4-isopropyl benzaldehyde **8e** (362 mg, 2.44 mmol) in 0.15mL of THF, NaOH (130 mg, 3.26 mmol) and LiOH•H_2O (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, R_f = 0.25), compound **14e** was afforded in a trace amount (<5% yield).

Methyl 3-(4-fluorophenyl)-2,3-dihydroxypropanoate (**14f**). The general deoxalation and esterification procedures were followed using DHF dihydrate (150 mg, 0.814 mmol), 4-fluoro benzaldehyde **8f** (303 mg, 2.44 mmol) in 0.15 mL of THF, NaOH (130 mg, 3.26 mmol) and LiOH•H_2O (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, R_f = 0.15), compound **14f** was afforded as a pale-yellow oil (112 mg, 64% yield) as a 1:1 mixture of diastereomers. Characterization matches previously published results.[39]

Methyl 3-(3-fluorophenyl)-2,3-dihydroxypropanoate (**14g**). The general deoxalation and esterification procedures were followed using DHF dihydrate (150 mg, 0.814 mmol), 3-fluoro benzaldehyde **8g** (303 mg, 2.44 mmol) in 0.15 mL of THF, NaOH (130 mg, 3.26 mmol) and LiOH•H_2O (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, R_f = 0.15), compound **14g** was afforded as a pale-yellow oil (69 mg, 40% yield) as a 1:2 mixture of diastereomers. **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.35 (m, 1H), 7.32 (m, 0.51H), 7.17 (m, 1.95H), 7.08 (m, 1H), 7.02 (m, 1.32H), 5.04 (d, *J* = 2.9 Hz, 1H), 5.03 (d, *J* = 4.7 Hz, 0.44H), 4.50 (d, *J* = 4.2 Hz, 0.46H), 4.38 (d, *J* = 2.8 Hz, 1H), 3.84 (s, 3H), 3.71 (s, 1.33H), 3.28 (s, 1H), 3.18 (s, 0.73H), 2.99 (s, 1H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 173.0, 172.2, 162.9 (d, *J* = 246.3 Hz), 162.8 (d, *J* = 246.3 Hz), 142.6 (d, *J* = 7.1 Hz), 141.3 (d, *J* = 7.2 Hz), 130.0 (d, *J* = 8.3 Hz), 129.8 (d, *J* = 8.1 Hz), 122.0 (d, *J* = 3.1 Hz), 121.8 (d, *J* = 2.8 Hz), 115.1, 114.94 (d, *J* = 20.9 Hz), 113.5 (d, *J* = 22.3 Hz), 113.4 (d, *J* = 22.2 Hz), 74.7, 74.5, 74.4 (d, *J* = 1.7 Hz), 73.8 (d, *J* = 1.7 Hz), 53.0, 52.6. **IR** 3425 (br), 2955 (m), 1734 (s), 1613 (m), 1591 (s). **HRMS** (ESI) *m/z*: [M+Na^+] Calcd for $C_{10}H_{11}O_4FNa$ 237.0534; Found 237.0536.

Methyl 3-(2-fluorophenyl)-2,3-dihydroxypropanoate (**14h**). The general deoxalation and esterification procedures were followed using DHF dihydrate (150 mg, 0.814 mmol), 2-fluoro benzaldehyde **8h** (303 mg, 2.44 mmol) in 0.15 mL of THF, NaOH (130 mg, 3.26 mmol) and LiOH•H_2O (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, R_f = 0.15), compound **14h** was afforded as a pale-yellow oil (77 mg, 44% yield) as a 1:2 mixture of diastereomers: **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.54 (td, *J* = 7.6, 1.7 Hz, 1H), 7.48 (td, *J* = 7.6, 1.7 Hz, 0.41H), 7.31 (tdd, *J* = 8.6, 4.1, 1.5 Hz, 1.26H), 7.20 (td, *J* = 7.5, 1.1 Hz, 1H), 7.17 (td, *J* = 7.5, 1.1 Hz, 0.45H), 7.08 – 7.02 (m, 1.32H), 5.36 (d, *J* = 2.9 Hz, 1H), 5.33 (d, *J* = 3.9 Hz, 0.42H), 4.56

(d, J = 3.9 Hz, 0.45H), 4.42 (d, J = 2.9 Hz, 1H), 3.86 (s, 3H), 3.66 (s, 1.32H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 173.0, 172.5, 159.7 (d, J = 245.4 Hz), 159.6 (d, J = 245.2 Hz), 129.6 (d, J = 8.3 Hz), 129.5 (d, J = 8.4 Hz), 128.0 (d, J = 4.0 Hz), 127.9 (d, J = 3.9 Hz), 127.1 (d, J = 13.0 Hz), 124.2 (d, J = 3.5 Hz), 124.1 (d, J = 3.5 Hz), 115.1 (d, J = 21.5 Hz), 115.1 (d, J = 22.0 Hz), 73.9, 73.7, 69.6 (d, J = 1.4 Hz), 68.8 (d, J = 2.3 Hz), 53.0, 52.4. **IR**: 3434 (br), 2953 (m), 1745 (s), 1620 (m), 1587 (m). **HRMS** (ESI) *m/z*: [M+Na$^+$] Calcd for $C_{10}H_{11}O_4FNa$ 237.0534; Found 237.0533.

Methyl 3-(4-chlorophenyl)-2,3-dihydroxypropanoate (**14i**). The general deoxalation and esterification procedures were followed using DHF dihydrate (150 mg, 0.814 mmol), 4-chloro benzaldehyde **8i** (344 mg, 2.44 mmol) in 2 mL of THF, NaOH (130 mg, 3.26 mmol) and LiOH•H_2O (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, R_f = 0.15), compound **14j** was afforded as a pale-yellow oil (152 mg, 68% yield) as a 3:2 mixture of diastereomers. Characterization matches previously published results.[38]

*Methyl 3-(4-bromophenyl)-2,3-dihydroxypropanoate (**14j**)*. The general procedure was followed using DHF dihydrate (150 mg, 0.814 mmol), 4-bromo benzaldehyde **8j** (452 mg, 2.44 mmol) in 2 mL of THF, NaOH (130 mg, 3.26 mmol) and LiOH•H_2O (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, R_f = 0.15), compound **14j** was afforded as a pale-yellow oil (152 mg, 68% yield) as a 3:2 mixture of diastereomers. Characterization matches previously published results.[40]

Methyl 4-(1,2-dihydroxy-3-methoxy-3-oxopropyl)benzoate (**14k**). The general deoxalation and esterification procedures were followed using DHF dihydrate (150 mg, 0.814 mmol), 4-

methylcarboxy benzaldehyde **8k** (401 mg, 2.44 mmol) in 2 mL of THF, NaOH (130 mg, 3.26 mmol) and LiOH•H_2O (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, R_f = 0.15), compound **14k** was afforded as a pale-yellow wax (51 mg, 25% yield) as a 2:1 mixture of diastereomers. **^{1}H NMR** (700 MHz, DMSO-d_6) δ 7.86 (d, *J* = 7.7 Hz, 3H), 7.36 (dd, *J* = 8.1, 3.6 Hz, 3H), 4.87 (d, *J* = 3.9 Hz, 1H), 4.67 (d, *J* = 7.2 Hz, .87H), 4.18 (d, *J* = 3.9 Hz, 1H), 4.02 (d, *J* = 7.2 Hz, .93H), 3.62 (s, 2H), 3.59 (s, 3H), 3.38 (s, 6H). **^{13}C NMR** (176 MHz, DMSO) δ 173.4, 173.1, 129.1, 129.0, 127.0, 126.5, 75.92, 75.86, 74.4, 74.3, 53.3, 51.9, 51.7. **IR** 3365 (br), 2956 (m), 1699 (m), 1612 (m). **HRMS** (ESI) *m/z*: [M+Na^+] Calcd for $C_{12}H_{14}O_6Na$ 277.0683; Found 277.0684.

Methyl 2,3-dihydroxy-3-(4-nitrophenyl)propanoate (**14l**). The general deoxalation and esterification procedures were followed using DHF dihydrate (150 mg, 0.814 mmol), 4-nitro benzaldehyde **8l** (369 mg, 2.44 mmol) in 2 mL of THF, NaOH (130 mg, 3.26 mmol) and LiOH•H_2O (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, R_f = 0.15), compound **14l** was afforded as a yellow wax (81 mg, 41% yield) as a 4:3 mixture of diastereomers. Characterization matches previously published results.[39]

Methyl 2,3-dihydroxy-3-(thiophen-3-yl)propanoate (**14m**). The general deoxalation and esterification procedures were followed using DHF dihydrate (150 mg, 0.814 mmol), 3-thiophene carboxyaldehyde **8m** (274 mg, 2.44 mmol) in 0.15 mL of THF, NaOH (130 mg, 3.26 mmol) and LiOH•H_2O (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, R_f = 0.15), compound **14m** was afforded as a pale-yellow oil (53 mg, 32% yield) as a 3:2 mixture of diastereomers. Characterization matches previous published results.[41]

Methyl 2,3-dihydroxy-3-(pyridin-2-yl)propanoate (**14n**). The general procedure was followed using DHF dihydrate (150 mg, 0.814 mmol), 2-pyridyl carboxyaldehyde **8n** (261 mg, 2.44 mmol) in 0.15 mL of THF, NaOH (130 mg, 3.26 mmol) and LiOH•H_2O (68 mg, 1.63 mmol) in deionized water. After purification (5% MeOH/DCM, R_f = 0.15), compound **14n** was afforded as a pale-yellow oil (69 mg, 43% yield) as a 2:1 mixture of diastereomers. **^{1}H NMR** (700 MHz, $CDCl_3$ & MeOD) δ 8.55 (dt, *J* = 4.9, 1.4 Hz, 1H), 8.52 (dt, *J* = 4.9, 1.3 Hz, 0.49H), 7.76 (td, *J* = 7.7, 1.7 Hz, 1H), 7.71 (ddd, *J* = 19.0, 7.7, 1.7 Hz, 0.54H), 7.44 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1.45H), 7.26 (m, 1.4H), 5.13 (d, *J* = 2.2 Hz, 1H), 5.05 (d, *J* = 4.2 Hz, 0.5H), 4.60 (d, *J* = 2.2 Hz, 1H), 4.57 (d, *J* = 4.2 Hz, 0.59H), 3.85 (s, 3H), 3.67 (s, 1.7H). **^{13}C NMR** (176 MHz, $CDCl_3$ & MeOD) δ 173.03, 172.33, 158.03, 157.84, 148.42, 148.11, 137.09, 136.95, 122.99, 122.90, 121.50, 120.84, 75.04, 74.10, 73.91, 73.30, 52.73, 52.23. **IR** 3307 (br), 2925 (m), 2856 (w), 1641 (m). **HRMS** (ESI) Calcd for $C_9H_{12}O_4N$ [M+H^+] 198.0761; Found 198.0762.

Picrasidine Y (**9o**). The general deoxalation procedure was followed using DHF dihydrate (100 mg, 0.814 mmol), 9*H*-pyrido [3,4-*b*]indole-1-carbaldehyde **8o** (479 mg, 2.44 mmol) in 2mL of THF, NaOH (130 mg, 3.26 mmol) and LiOH•H_2O (68 mg, 1.63 mmol) in deionized water. Obtained in 8% quantitative NMR yield as a crude mixture from the aqueous phase. Crude NMR shows peaks that match with published literature.[24] Esterification was attempted without success isolating pure product.

Deconvolution of Deoxalation and Self Condensation Pathways. Using the standard deoxalation conditions, 150 mg (0.814 mmol) of DHF and benzaldehyde **8a** (259 mg, 2.44 mmol), NaOH (130

mg, 3.26 mmol) and LiOH•H_2O (68 mg, 1.63 mmol). After acidification by Amberlyst-15 resin, the crude aqueous residue was analyzed by 2D NMR.

DHF Fragmentation Control and Spiking Studies. Using a variation standard deoxalation conditions, 150 mg (0.814 mmol) of DHF was dissolved in 7mL of distilled water. 4 eq (130 mg, 3.26 mmol) of NaOH and 2 eq (68 mg, 1.68 mmol) of LiOH hydrate were added and the reaction was stirred for 18 h at room temperature. At which point, Amberlyst-15 resin was added until the pH of the solution was ~4. The resin was then filtered off using a Buchner funnel and rotovapped to dryness at ~70 ˚C. The residue was then analyzed by NMR. *D,L* tartrate was added to the NMR sample to determine the location of the tartrate peaks. *meso*-Tartrate was determined by comparison to known literature. Pure glycolate was added to the NMR sample to confirm its location and tartronate was assigned by comparison to previously published results.[14]

General Decarboxlation Procedure for Synthesis of (Hetero)aryl 2,3propanones (10). A dry round-bottom flask was charged with a stir-bar, and DHF dihydrate (1 equiv) was added, followed by freshly distilled solvent. The respective aldehyde **8** (3 equiv) was added followed immediately by the addition of triethylamine (3 or 4 equiv). A reflux condenser was attached to the flask and the reaction was heated at reflux. As determined by TLC, after 18 h, the reaction was diluted with CH_2Cl_2, concentrated under reduced pressure, and purified by flash column chromatography on silica gel using EtOAc/Hexanes as the mobile phase.

2,3-Dihydroxy-1-phenylpropan-1-one (**10a**). The general decarboxylation procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), benzaldehyde **8a** (173 mg, 1.63 mmol), triethylamine

(220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10a** was afforded as a pale-yellow oil (65 mg, 72% yield). Characterizations were consistent with previously reported literature.[42]

2,3-Dihydroxy-1-(4-methoxyphenyl)propan-1-one (**10b**). The general decarboxylation procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 4-methoxy benzaldehyde **8b** (222 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10b** was afforded as a pale-yellow oil (10.6 mg, 10% yield). Characterizations were consistent with previously reported literature.[42]

2,3-Dihydroxy-1-(p-tolyl)propan-1-one (**10c**). The general decarboxylation procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 4-tolualdehyde **8c** (196 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10c** was afforded as a pale-yellow oil (53 mg, 54% yield). **^{1}H NMR** (501 MHz, $CDCl_3$) δ = 7.86 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 5.16 (dd, *J* = 5.1 Hz, 3.3 Hz, 1H), 4.03 (dd, *J* = 11.7 Hz, 3.3 Hz, 1H), 3.75 (dd, *J* = 11.7 Hz, 5.1 Hz, 1H), 2.46 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 198.8, 145.5, 130.8, 129.7, 128.7, 74.3, 65.5, 29.7. **IR** 3434 (m), 3394 (m), 2940 (w), 1680 (s), 1595 (s), 1503 (w) cm^{-1}. **HRMS** ESI m/z [M+Na^+] Calcd. for $C_{10}H_{12}O_3Na$ 203.0679; Found 203.0678.

1-(4-Ethylphenyl)-2,3-dihydroxypropan-1-one (**10d**). The general decarboxylation procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 4-ethylbenzaldehyde **8d** (219 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50%

EtOAc/Hexanes, R_f = 0.2), compound **10d** was afforded as a pale-yellow oil (43 mg, 41% yield). **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.6 Hz, 2H), 5.14 (td, *J* = 5.1 Hz, 3.2 Hz, 1H), 4.04 (d, *J* = 5.7 Hz, 1H), 4.01 (d, *J* = 12.2 Hz, 1H), 3.73 (d, *J* = 10.1 Hz, 1H), 2.72 (q, *J* = 7.6 Hz, 2H), 2.26 (s, 1H), 1.26 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ = 198.8, 151.6, 130.9, 128.8, 128.7, 128.5, 126.9, 74.4, 65.5, 29.0, 15.1. **IR** 3348 (br), 2962 (m), 2928 (m), 2870 (w), 1675 (s), 1606 (w) cm^{-1}. **HRMS** (ESI) m/z: [M+Na^+] Calcd. For $C_{11}H_{14}O_3Na$ 217.0835; Found 217.0834.

2,3-Dihydroxy-1-(4-isopropylphenyl)propan-1-one (**10e).** The general decarboxylation procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 4-ethylbenzaldehyde **8e** (241 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10e** was afforded as a pale-yellow wax (16 mg, 14% yield). **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 5.14 (t, *J* = 4.2 Hz, 1H), 4.06 (s, 1H), 4.02 (dd, *J* = 11.7, 3.3 Hz, 1H), 3.74 (dd, *J* = 11.8, 5.2 Hz, 1H), 2.98 (hept, *J* = 6.9 Hz, 1H), 1.27 (d, *J* = 7.1 Hz, 6H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ = 198.8, 156.2, 131.1, 128.9, 127.4, 127.1, 126.9, 74.4, 65.5, 34.4, 23.6. **IR:** 3401 (br), 2960 (s), 2925 (s), 1678 (s), 1606 (w) cm^{-1}. **HRMS** (ESI) m/z: [M+Na^+] Calcd. For $C_{12}H_{16}O_3Na$ 231.0992; Found 231.0993.

1-(4-Fluorophenyl)-2,3-dihydroxypropan-1-one (**10f**). The general decarboxylation procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 4-fluorobenzaldehyde **8f** (202 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10f** was afforded as a colorless oil (65 mg, 65% yield). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.9 Hz, 5.3 Hz, 2H), 7.22 (dd, *J* = 8.9 Hz, 8.3 Hz, 2H),

5.15 (q, *J* = 4.5 Hz, 4.0 Hz, 1H), 4.03 (d, *J* = 11.6 Hz, 1H), 4.00 (d, *J* = 5.8 Hz, 1H), 3.78 (d, *J* = 8.6 Hz, 1H), 2.25 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 197.8, 166.4 (d, *J* = 257.1 Hz), 131.3 (d, *J* = 9.5 Hz), 129.3 (d, *J* = 3.4 Hz), 116.3 (*d*, *J* = 22.1 Hz), 74.4, 65.3 ppm **IR**: 3340 (s), 2911 (w), 1679 (s), 1597 (s), 1507 (m) cm^{-1}. **HRMS** (ESI) m/z: [M+H$^+$] Calcd. for $C_9H_{10}O_3F$ 185.0608; Found 185.0606.

1-(3-Fluorophenyl)-2,3-dihydroxypropan-1-one (**10g**). The general decarboxylation procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 3-fluorobenzaldehyde **8g** (202 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.25), compound **10g** was afforded as a pale-yellow oil (31 mg, 31% yield). **^{1}H NMR** (700 MHz, $CDCl_3$) δ = 7.72 (dt, *J* = 7.7 Hz, 1.2 Hz, 1H), 7.65 (ddd, *J* = 9.1 Hz, 2.5 Hz, 1.6 Hz, 1H), 7.52 (td, *J* = 8.0 Hz, 5.4 Hz, 1H), 7.37 (tdd, *J* = 8.2 Hz, 2.6 Hz, 1.2 Hz, 1H), 5.14 (t, *J* = 3.8 Hz, 1H), 4.04 (q, *J* = 5.0 Hz, 1H), 3.98 (s, 1H), 3.81 (q, *J* = 5.49 Hz, 1H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ = 200.3, 162.5 (d, *J* = 244.6 Hz), 138.2, 131.3 (d, *J* = 7.60 Hz), 125.2 (d, *J* = 2.68 Hz), 120.5 (d, *J* = 21.1 Hz), 115.5 (d, *J* = 22.5 Hz), 75.3, 64.3. **IR**: 3350 (s), 2922 (s), 2854 (m), 1681 (s), 1588 (s) cm^{-1}. **HRMS** (ESI) *m/z*: [M+H$^+$] Calcd. for $C_9H_{10}O_3F$ 185.0608; Found 185.0607.

1-(4-Chlorophenyl)-2,3-dihydroxypropan-1-one (**10i**). The general decarboxylation procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 4-chlorobenzaldehyde **8i** (228 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10i** was afforded as a colorless oil (53 mg, 49% yield). Characterizations were consistent with previously reported literature.[42]

1-(4-Bromophenyl)-2,3-dihydroxypropan-1-one (**10j**). The general decarboxylation procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 4-bromobenzaldehyde **8j** (301 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10j** was afforded as a pale-yellow solid (60 mg, 45% yield). [m.p. = 143 ˚C] **^{1}H NMR** (501 MHz, DMSO) δ = 7.92 (d *J* = 8.6 Hz, 2H), 7.74 (d, *J* = 8.6 Hz, 2H), 5.38 (d, *J* = 6.5 Hz; 1H), 4.92 (dt, *J* = 6.5 Hz, 4.8 Hz, 1H), 4.83 (t, *J* = 5.8 Hz, 1H), 3.66 (m, 1H). **^{13}C NMR** (126 MHz, DMSO) δ = 200.5, 134.9, 132.1, 131.1, 127.6, 75.2, 64.3 ppm. **IR**: 3327 (s), 2984 (w), 2899 (w), 1675 (s) cm^{-1}. **HRMS** (ESI) *m/z*: [M+Na$^+$] Calcd. for $C_9H_9O_3BrNa$ 266.9627; Found 266.9628.

2,3-Dihydroxy-1-(thiophen-3-yl)propan-1-one (**10m)**. The general decarboxylation procedure was followed using DHF dihydrate (150 mg, 0.814 mmol), 3-thiophene carboxyaldehyde **8m** (274 mg, 2.44 mmol), triethylamine (330 mg, 3.26 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10m** was afforded as a clear oil (32 mg, 23% yield) **^{1}H NMR** (501 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 2.9, 1.3 Hz, 1H), 7.60 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.43 (dd, *J* = 5.2, 2.9 Hz, 1H), 4.97 (dd, *J* = 5.0, 3.4 Hz, 1H), 4.06 (dd, *J* = 11.7, 3.4 Hz, 1H), 3.84 (dd, *J* = 11.7, 5.0 Hz, 1H), 2.28 (s, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 193.2, 137.9, 133.7, 127.1, 126.9, 75.4, 65.6. **IR**: 3323 (s), 3099 (m), 2892 (w), 1664 (s), 1511 (m) cm^{-1}. **HRMS** (ESI) *m/z*: [M+Na$^+$] Calcd for $C_7H_8O_3SNa$ 195.0086; Found 195.0083.

2,3-Dihydroxy-1-(o-tolyl)propan-1-one (**10q**). The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 2-tolualdehyde **8q** (196 mg, 1.63 mmol), triethylamine (220 mg,

2.17 mmol) in THF (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.25), compound **10q** was afforded as a pale-yellow oil with its dihydroxyacetone isomer **17q** (22 mg, 22% yield). **10q**:**17q** Ratio: (2:1). **^{1}H NMR** (700 MHz, $CDCl_3$) δ = 7.55 (dd, *J* = 7.6 Hz, 1.0 Hz, 1H), 7.46 (td, *J* = 7.6 Hz, 1.0 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.28 (m, 1.20H), 7.24 (m, 0.85H), 5.43 (s, 0.73H), 5.06 (d, *J* = 2.9 Hz, 1H), 4.34 (d, *J* = 19.3 Hz, 0.36H), 4.20 (d, *J* = 19.3 Hz, 0.36H), 4.13 (d, *J* = 3.3 Hz, 0.61H), 3.93 (dd, *J* = 11.8 Hz, 3.2 Hz, 1H), 3.69 (dd, *J* = 11.8 Hz, 3.5 Hz, 1H), 2.51 (s, 3H), 2.40 (s, 1H) **^{13}C NMR** (175 MHz, $CDCl_3$) δ = 209.6, 203.1, 139.2, 136.4, 135.3, 134.0, 132.32, 132.30, 131.5, 129.2, 128.1, 128.0, 126.8, 125.8, 75.8, 65.3, 64.6, 20.7, 19.3. **IR**: 3404 (br), 2928 (m), 1690 (s) cm^{-1}. **HRMS** (ESI) *m/z*: [M+Na^+] Calcd. For $C_{10}H_{12}O_3Na$ 203.0679; Found 203.0677.

2,3-Dihydroxy-1-(thiophen-2-yl)propan-1-one (**10r**). The general decarboxylation procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 2-thiophenecarboxyaldehyde **8r** (182 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in CH_2Cl_2 (7 mL). After purification (50% EtOAc/Hexanes, R_f = 0.2), compound **10r** was afforded as a pale-yellow oil (45 mg, 48% yield). **^{1}H NMR** (501 MHz, $CDCl_3$) δ = 7.84 (dd, *J* = 3.88 Hz, 1.08 Hz, 1H), 7.78 (dd, *J* = 4.92 Hz, 1.08 Hz, 1H), 7.21 (dd, *J* = 4.92 Hz, 3.88 Hz, 1H), 4.99 (dd, *J* = 5.10 Hz, 3.45 Hz, 1H), 4.07 (dd, *J* = 11.8 Hz, 3.40 Hz, 1H), 3.88 (dd, *J* = 11.8 Hz, 5.15 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 191.7, 139.6, 135.4, 133.4, 128.5, 75.2, 66.1. **IR**: 3340 (s), 2937 (w), 1657 (s), 1516 (w) cm^{-1}. **HRMS** (ESI) *m/z*: [M+Na^+] Calcd. for $C_7H_8O_3SNa$ 195.0086; Found 195.0086.

2,3-Dihydroxy-1-(furan-2-yl)propan-1-one (**10s**). The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 2-furaldehyde **8s** (157 mg, 1.63 mmol), triethylamine (220 mg,

2.17 mmol) in CH_2Cl_2 (7 mL). After purification (50% EtOAc/Hexanes, $R_f = 0.2$), compound **10s** was afforded as a pale-yellow oil (33 mg, 39% yield). **^{1}H NMR** (501 MHz, $CDCl_3$) δ = 7.67 (dd, *J* = 1.65 Hz, 0.62 Hz, 1H), 7.40 (dd, *J* = 3.65 Hz, 0.45 Hz, 1H), 6.63 (dd, *J* = 3.65 Hz, 1.65 Hz, 1H), 4.93 (dd, *J* = 4.25 Hz, 3.50 Hz, 1H), 4.07 (dd, *J* = 11.81 Hz, 3.30 Hz, 1H), 3.96 (dd, *J* = 11.81 Hz, 4.45 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 187.6, 150.2, 147.4, 119.5, 112.8, 74.9, 64.9. **IR**: 3309 (s), 3130 (w), 2896 (w), 1662 (s), 1565 (m) cm^{-1}. **HRMS** (ESI) *m/z*: [M+Na^+] Calcd. for $C_7H_8O_4Na$ 179.0314; Found 179.0315.

C-Veratroylglycol (**10t**). The general procedure was followed using DHF dihydrate (150 mg, 0.8 mmol), vanillin **8t** (372 mg, 2.4 mmol), triethylamine (577 mg, 5.7 mmol) in THF (11 mL). After 18 h the reaction was diluted with 10%MeOH/CH_2Cl_2 and filtered over Amberlyst-15 hydrogen form resin to remove any TEA complexed with the product. The product was then purified via column chromatography on silica (10% MeOH/CH_2Cl_2, $R_f = 0.45$) to afford compound **10t** as a white solid (25 mg, 14% yield). [m.p. = 54 ˚C] Characterizations were consistent with previously reported literature.[43]

Methyl 4-(hydroxymethyl)benzoate (**18k**). The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 4-methylcarboxy benzaldehyde (268 mg, 1.63 mmol), triethylamine (220 mg, 2.17 mmol) in CH_2Cl_2 (7 mL). Only the benzyl alcohol was observed by crude NMR after 18 h.

(4-Nitrophenyl)methanol (**18l**). The general procedure was followed using DHF dihydrate (100 mg, 0.543 mmol), 4-nitro benzaldehyde (246 mg, 1.63 mmol), and triethylamine (220 mg, 2.17 mmol) in CH_2Cl_2 (7 mL). Only the benzyl alcohol was observed by crude NMR after 18 h.

ASSOCIATED CONTENT

Supporting Information

Optimization tables for the deoxalation and decarboxylation reactions, control reactions, 1H NMR for known compounds, NMR (^1H, ^{13}C, and 2D experiments where applicable) spectra for all new compounds, and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

***Email:** stefan.france@chemistry.gatech.edu; rkrishna@scripps.edu; charles.liotta@carnegie.gatech.edu

Notes

The authors declare no competing financial interest.

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