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Organocatalytic Redox Isomerization of Electron-Deficient Allylic Alcohols: Synthesis of 1,4-Ketoaldehydes

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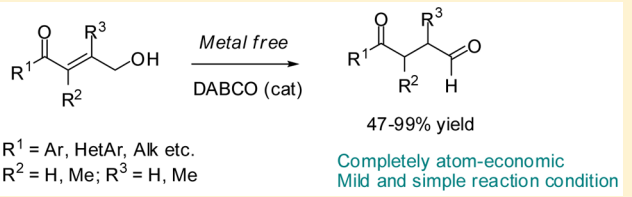
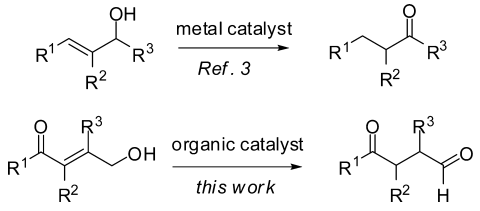
Supporting Information

ABSTRACT: An organocatalytic redox isomerization strategy has been developed for the synthesis of 1,4-ketoaldehydes. DABCO was found to be the best catalyst for the isomerization of γ-hydroxy enones. With 20 mol % of DABCO as catalyst and DMSO as the solvent high yields have been achieved for different 1,4-ketoaldehydes.



One of the current challenges in organic chemistry is to develop reactions that provide products with high levels of efficiency, selectivity, and atom economy.[1] Isomerization reactions are considered one of the perfect atom economic methods that do not generate byproducts. Redox isomerization is an intrinsically efficient process as it avoids external oxidants and reductants, and formation of unwanted byproducts is avoided.[2] The redox isomerization of readily available allylic alcohols to saturated carbonyl compounds is an attractive and atom-economic process that circumvents use of highly reactive and expensive reagents and also reduces the number of protection−deprotection steps often required for such transformations (Scheme 1).[3]

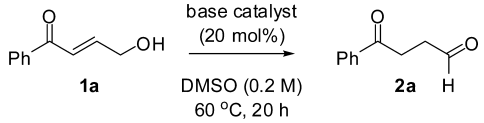
Scheme 1. Redox Isomerization of Allylic Alcohols



A variety of transition metal complexes have been utilized for the transformations of allylic alcohols to ketones, aldehydes and 1,4-diketones.[3] Interestingly, literature survey did not reveal the synthesis of 1,4-ketoaldehydes using this strategy. In addition, organocatalytic redox isomerization[4,5] of allylic alcohols, an attractive alternative strategy, has been less studied. Previously, few acid- and base-catalyzed redox isomerization of γ-hydroxy enones to 1,4-diketones have been reported.[6] Taylor et al. also observed formation of 1,4-diketones and 1,4-ketoaldehydes during the reaction of 1,2-dioxines and phosphorus ylide though lower yields (∼30%) were observed for 1,4-ketoaldehydes.[7] Miles and co-workers disclosed DABCO catalyzed isomerization of 6-hydroxy-2*H*-pyranones to 1,2,5-triketones.[8] Realizing the potential of 1,4-ketoaldehydes as important building blocks,[9] we embarked in a redox isomerization strategy for the synthesis of 1,4-ketoaldehydes (Scheme 1).

We started our investigation by stirring 3-benzoylprop-2-en-1-ol (**1a**)[10] in DMSO at 60 °C with various organic base catalysts (Table 1). As can be seen, 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) could not promote the isomerization reaction after 20 h (entry 1). Pleasingly, a moderate yield (45%) of the isomerized product 3-benzoylpropanal (**2a**) was obtained with Et_3N (entry 2). A small improvement in the yield was observed with DIPEA (entry 3). However, 1,1,3,3-tetramethylguanidine (TMG), pyridine, and inorganic base such as potassium carbonate (K_2CO_3) failed to react under identical conditions (entries 4−6). Gratifyingly, DMAP

Table 1. Catalyst Screening and Optimization of Reaction Conditions



entry[a]	catalyst	yield[b] (%)
1	DBU	0
2	Et_3N	45
3	DIPEA	52
4	TMG	0
5	pyridine	0
6	K_2CO_3	0
7	DMAP	71
8	DABCO	93
9[c]	DABCO	95

[a]Reaction conditions: 0.2 mmol of **1a** in 1.0 mL of solvent using 20 mol % of catalyst. [b]Isolated yield after silica gel column chromatography. [c]Reaction temperature 90 °C and reaction time 5 h.

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J. Org. Chem. XXXX, XXX, XXX−XXX

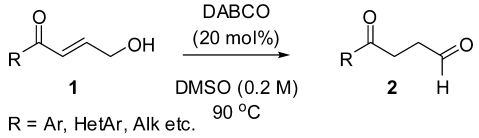
provided the product **2a** in a better yield of 71% (entry 7). Finally, the best catalyst turned out to be 1,4-diazabicyclo[2.2.2]octane (DABCO), which afforded 93% yield of the product **2a** (entry 8). The yield was further enhanced to 95% by running the reaction at higher temperature and the reaction time was shortened (entry 9). A lower yield (89%) was observed with 10 mol % of the catalyst. Other solvents were also screened, but DMSO was found to be the best solvent (see the Supporting Information for details).

Having identified the optimized conditions, we ventured toward the scope and generality of the reaction. Initially, different γ-hydroxy aryl enones were prepared and treated under the reaction conditions (Table 2). It turned out that the reaction is quite general for a variety of electron-rich and electron-poor aryl enones. Substitutions at the *ortho*, *para*, and *meta* positions of the phenyl group are also well tolerated. 4-Methyl-substituted aryl enone provided 90% yield of the product **2b** (entry 2). A similar yield was observed with 4-isopropyl-substituted aryl enone (entry 3), but a lower yield was obtained with 4-*tert*-butyl-substituted aryl enone (entry 4). Consequently, 4-methoxy-substituted aryl enone **1e** was found to be the best substrate, providing the product **2e** in 99% yield (entry 5). Then 4-halo-substituted aryl enones were examined under the reaction conditions, and the desired products were obtained in acceptable yields (entries 6–8). While 4-chloro- and 4-fluoro-substituted enones provided similar yields, 4-bromo-substituted enone **1h** afforded an enhanced yield of 92% (entry 8). Aryl enones having *meta*-substitutions were then prepared and subjected to the reaction conditions. Excellent yield (98%) was obtained with 3-methoxyaryl enone **1i** (entry 9). 3-Chloro-substituted and 3-methyl-substituted aryl enones afforded products **2j** and **2k** in moderate yields (entries 10 and 11). Interestingly, *ortho*-substitution on the aryl group also did not change the outcome of the reaction, and a good yield of 82% was attained with 2-methyl-substituted aryl enone **1l** (entry 12). 1-Naphthyl-substituted enone **1m** was also engaged in the reaction, and good yield of 75% was achieved for the desired product **2m** (entry 13). 4-Biphenyl-substituted enone **1n** provided product **2n** in a much higher yield of 95% (entry 14). Interestingly, 2,4-dimethylphenyl-substituted keto aldehyde **2o** was obtained in 97% yield after the treatment of the corresponding enone (entry 15). Then, a heteroaromatic group was incorporated in the enone moiety, and product **2p** was isolated in 89% yield (entry 16). Finally, aliphatic enones were examined under the reaction conditions, and gratifyingly, the products are obtained in good yields although higher reaction times were required (entries 17 and 18). Enone **1q** having hydrocinnamyl moiety provided product **2q** in 65% yield (entry 17), whereas a higher yield of 77% was achieved for the cyclohexyl-substituted product **2r** (entry 18). Finally, enone **1s** having an isovaleryl moiety was used in our reaction, and a good yield of 80% was obtained (entry 19).

The next phase of experiments concerned the preparation and screening of different α-substituted enones. After some experiments were performed, it was found that the α-methyl group could be tolerated in this reaction. Thus, a variety of α-methyl enones (**1t–x**) was prepared and engaged in the reaction (Table 3, entries 1–5). In general, longer reaction times were required for significant conversion to the products. Product **2t** was isolated in 51% yield after 48 h (entry 1). Substitutions at the *meta* and *para* positions of the aryl group did not alter the fate of the reaction. Moderate yields were achieved for 3- and 4-chloro-substituted aryl ketoaldehydes **2u** and **2v** (entries 2 and 3). Product **2w** having a 4-bromo-substituted aryl group was isolated in a similar yield of 59% (entry 4). 4-Methyl-substituted aryl ketone **1x** was found to undergo isomerization slowly, and product **2x** was attained in 47% yield after 72 h (entry 5). This indicates that electron deficiency of the double bond is important for the rate of the reaction for α-substituted substrates. Pleasingly, our method is also applicable for β-methyl-substituted enones such as **1y**, providing a moderate yield of 48% for the product **2y** (entry 6).

To understand the mechanism of our reaction, kinetic experiments were performed using **1a** in DMSO-d_6 at 90 °C, and the conversions were determined by ^{1}H NMR spectroscopy (Figure1a,b). The rate of the reaction was found to be second order overall (Figure 1a) and first order with respect to

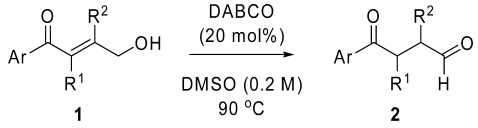
Table 2. Substrate Scope: α-Unbranched Enone



entry[a]	R	time (h)	2	yield[b] (%)
1	Ph	5	**2a**	95
2	4-MeC_6H_4	3.5	**2b**	90
3	4-^{i}PrC_6H_4	5	**2c**	88
4	4-^{t}BuC_6H_4	4.5	**2d**	66
5	4-OMeC_6H_4	6	**2e**	99
6	4-FC_6H_4	3	**2f**	75
7	4-ClC_6H_4	3	**2g**	79
8	4-BrC_6H_4	3	**2h**	92
9	3-OMeC_6H_4	4.5	**2i**	98
10	3-ClC_6H_4	3	**2j**	74
11	3-MeC_6H_4	4	**2k**	68
12	2-MeC_6H_4	3.5	**2l**	82
13	1-naphthyl	2.5	**2m**	75
14	4-biphenyl	5	**2n**	95
15	2,4-$(Me)_2C_6H_3$	4	**2o**	97
16	2-thiophene-yl	2	**2p**	89
17	hydroxycinnamyl	10	**2q**	65
18	cyclohexyl	20	**2r**	77
19	isovaleryl	24	**2s**	80

[a]Reaction conditions: 0.2 mmol of **1** in 1 mL of solvent using 20 mol % of DABCO. [b]Isolated yield after silica gel column chromatography.

Table 3. Substrate Scope: α- and β-Branched Enones



entry[a]	Ar	R^1	R^2	time (h)	2	yield[b] (%)
1	Ph	Me	H	48	**2t**	51
2	3-ClC_6H_4	Me	H	30	**2u**	67
3	4-ClC_6H_4	Me	H	30	**2v**	62
4	4-BrC_6H_4	Me	H	48	**2w**	59
5	4-MeC_6H_4	Me	H	72	**2x**	47
6	Ph	H	Me	30	**2y**	48

[a]Reaction conditions: 0.2 mmol of **1** in 1 mL of solvent using 20 mol % of DABCO. [b]Isolated yield after silica gel column chromatography.

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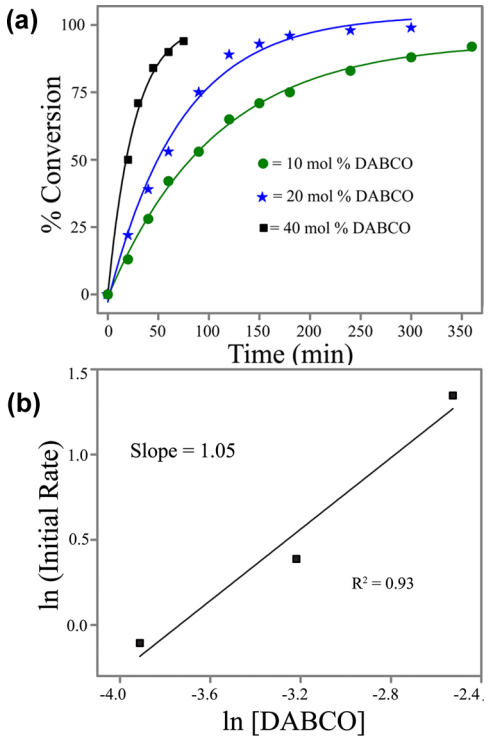


Figure 1. (a) Percent conversion vs time. (b) Initial reaction rate vs ln [DABCO].

DABCO (Figure 1b). Thus, the rate-determining step involves one molecule of **1** and one molecule of DABCO in the transition state.

To gain further insight into the mechanism of our redox isomerization reaction, we performed a deuterium incorporation experiment with **1a**. After treatment of **1a** with 20 mol % of DABCO in DMSO-d_6/D_2O (16:1),[5b] the exclusive formation of 2,3-d_2-**2a** was observed (Scheme 2, eq 1).[11] This result eliminated the possibility of 1,2-hydride shift from C4 to C3 induced by the 4-OH deprotonation by DABCO as in this case product 3-*d*-**2a** will be formed (eq 2). Similarly, any mechanism involving the abstraction of 4-H of **1a** by DABCO was also ruled out since in this case the resulting enolate would be quenched by more acidic protonated DABCO (pK_a = 9 in DMSO) than H_2O (or D_2O; pK_a = 32 for H_2O in DMSO)[5b,12] as was found to operate in the isomerization of secondary propargylic alcohol[5b] (eq 3). Thus, the remaining possibility was the conjugate addition by DABCO to the enone to generate intermediate **3** (eq 4). This intermediate would create **4** after quenching with D_2O.

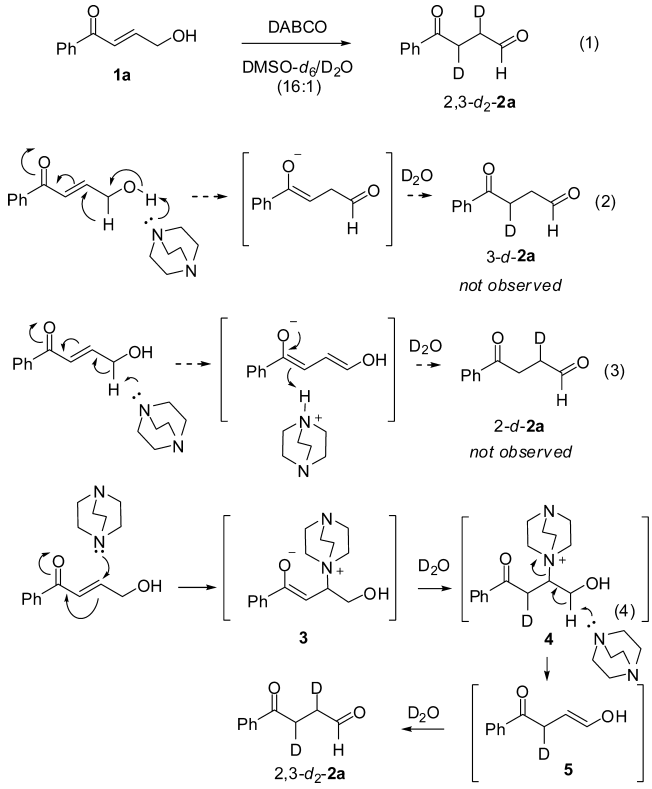
An E2 elimination of DABCO from **4** assisted by the general base catalysis of another molecule of DABCO leaded to the formation of enol **5**, which then tautomerized after abstracting a proton from residual H_2O or a deuterium from D_2O to afford 2,3-d_2-**2a**.

In summary, we have developed a facile synthesis of 1,4-ketoaldehydes by redox isomerization strategy. DABCO was found to be the best catalyst for this purpose. The 1,4-ketoaldehyde motifs are difficult to obtain, and our method will be very useful in natural product synthesis and drug discovery.

EXPERIMENTAL SECTION

General Information. All reactions were carried under air in oven-dried glassware with magnetic stirring. Organic solvents were dried

Scheme 2. Plausible Mechanism



over anhydrous Na_2SO_4 and concentrated in a rotary evaporater under reduced pressure. For column chromatography, silica gel (60−120 mesh size) were used. For TLC analyses precoated silica gel plates were used.

^1H, ^{13}C NMR spectroscopy: 400 MHz (at 298 K) and 600 MHz. Chemical shifts, δ (in ppm), are reported in ppm relative to TMS δ (^1H) 0.0 ppm, δ (^{13}C) 0.0 ppm, which was used as the inner reference with multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet). Otherwise, the solvents residual proton resonance and carbon resonance ($CHCl_3$, δ (^1H) 7.26 ppm, δ (^{13}C) 77.23 ppm were used for calibration. IR: spectra were recorded on an FT-IR Instrument at normal temperature making KBr pellet grinding the sample with KBr (IR grade). Mass spectra were recorded on a Q-TOF mass spectrometer. Melting points were obtained with a Mel-Tem capillary melting point apparatus and are uncorrected.

General Procedure for the Synthesis of α-Unbranched *trans*-γ-Hydroxy Enones 1a−s. α-Unbranched *trans*-γ-hydroxy enones were prepared according to the reported procedure.[10b,13]

To a stirred solution of $SnCl_2{\cdot}2H_2O$ (1.5 equiv) and KI (3 equiv) in H_2O were added allyl bromide and aldehydes, satd aqueous NH_4Cl solution was added, and the resulting solution was stirred for 5 h at room temperature to obtain the homoallylic alchol. β,γ-Unsaturated ketone was obtained by PCC (1.5 equiv) oxidation. Then β,γ-epoxy ketone was prepared from β,γ-unsaturated ketone using *m*-CPBA (1.1 equiv). Finally, ring opening occurred to afford the *trans*-γ-hydroxyenones.

General Procedure for the Synthesis of α-Branched *trans*-γ-Hydroxy Enones 1t−y. α-Branched *trans*-γ-hydroxy enones were prepared according to the reported procedure.[10a]

To a stirred solution of the appropriate stabilized keto ylide (1.2 mmol) in THF (5 mL) was added glycoaldehyde dimer (1 mmol), and the resulting solution was heated under reflux for 3 h. The solution was cooled and the solvent evaporated in vacuo. The product was purified by silica gel column chromatography.

Ylides were prepared by reacting the appropriate haloalkanone with triphenylphosphine and deprotonating with 2 N NaOH solution.[14,15]

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General Procedure for the Synthesis of Products 2a−y. In a 10 mL round-bottom-flask were combined compound **1** (0.2 mmol) and DABCO (20 mol %), and 1 mL of DMSO solvent was added. The round bottom flask was sealed with a glass stopper and placed in a heating block at 90 °C. After completion of the reaction, as determined by TLC, the reaction mixture was allowed to cool at room temperature and diluted with EtOAc. The organic layer was washed with water and brine and dried (Na_2SO_4). The solvents were concentrated in vacuo and purified by silica gel column chromatography (15% EtOAc/hexane) to afford the title compound **2**.

*4-Oxo-4-phenylbutanal (**2a**).* This compound was prepared according to the general procedure. Reaction was completed after 5 h. Analytical TLC on silica gel, 15% ethyl acetate/hexane (R_f = 0.55). Brown liquid (31 mg, yield: 95%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.91 (s, 1H), 7.99 (d, J = 7.2 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 4.8 Hz, 2H), 3.33 (t, J = 6.3 Hz, 2H), 2.94 (t, J = 6.3 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.8, 198.0, 136.7, 133.6, 128.9, 128.3, 37.9, 31.3. FT-IR (thin film): 1716, 1685, 1597, 1449, 1364, 1240, 983, 759, 691 cm^{-1}. HRMS (+APCI): calcd for $C_{10}H_{11}O_2$ [M + H]$^+$ 163.0754, found 163.0748.

*4-Oxo-4-p-tolylbutanal (**2b**).* This compound was prepared according to the general procedure. Reaction was completed after 3.5 h. Analytical TLC on silica gel, 15% ethyl acetate/hexane (R_f = 0.57). Brown solid (32 mg, yield: 90%). Mp: 45−47 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.91 (s, 1H), 7.89 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 3.31 (t, J = 6.4 Hz, 2H), 2.93 (t, J = 6.4 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.9, 197.6, 144.3, 134.2, 129.5, 128.4, 37.8, 31.1, 21.9. FT-IR (thin film): 1709, 1681, 1607, 1382, 1239, 1182, 977, 875, 814, 548 cm^{-1}. HRMS (+ESI): calcd for $C_{11}H_{13}O_2$ [M + H]$^+$ 177.0910, found 177.0908.

*4-(4-Isopropylphenyl)-4-oxobutanal (**2c**).* This compound was prepared according to the general procedure. Reaction was completed after 5 h. Analytical TLC on silica gel, 15% ethyl acetate/hexane (R_f = 0.60). Yellow oil (36 mg, yield: 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.91 (s, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 3.31 (t, J = 6.4 Hz, 2H), 2.95−3.00 (m, 1H), 2.93 (t, J = 6.4 Hz, 2H), 1.27 (d, J = 6.8 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.9, 197.7, 155.1, 134.5, 128.5, 126.9, 37.8, 34.4, 31.1, 23.8. FT-IR (thin film): 1722, 1685, 1607, 1460, 1419, 1362, 1243, 1182, 1055, 981, 830 cm^{-1}. HRMS (+APCI): calcd for $C_{13}H_{17}O_2$ [M + H]$^+$ 205.1223, found 205.1213.

*4-(4-Tert-butylphenyl)-4-oxobutanal (**2d**).* This compound was prepared according to the general procedure. Reaction was completed after 4.5 h. Analytical TLC on silica gel, 10% ethyl acetate/hexane (R_f = 0.50). Brown liquid (29 mg, yield: 66%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.90 (s, 1H), 7.93 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 3.31 (t, J = 6.2 Hz, 2H), 2.92 (t, J = 6.2 Hz, 2H), 1.34 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.1, 197.7, 157.3, 134.0, 128.2, 125.8, 37.8, 35.3, 31.3, 31.1. FT-IR (thin film): 1720, 1682, 1605, 1407, 1364, 1247, 1192, 1108, 1018, 986, 828 cm^{-1}. HRMS (+APCI): calcd for $C_{14}H_{19}O_2$ [M + H]$^+$ 219.1380, found 219.1372.

*4-(4-Methoxyphenyl)-4-oxobutanal (**2e**).* This compound was prepared according to the general procedure. Reaction was completed after 6 h. Analytical TLC on silica gel, 18% ethyl acetate/hexane (R_f = 0.52). Pale yellow oil (38.5 mg, yield: 99%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.91 (s, 1H), 7.97 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 9.0 Hz, 2H), 3.87 (s, 3H), 3.28 (t, J = 6.3 Hz, 2H), 2.91 (t, J = 6.3 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 201.1, 196.5, 163.9, 130.6, 129.7, 114.0, 55.7, 37.9, 30.9. FT-IR (thin film): 1720, 1675, 1601, 1575, 1511, 1419, 1363, 1246, 1212, 1171, 1028, 834 cm^{-1}. HRMS (+ESI): calcd for $C_{11}H_{13}O_3$ [M + H]$^+$ 193.0859, found 193.0857.

*4-(4-Fluorophenyl)-4-oxobutanal (**2f**).* This compound was prepared according to the general procedure. Reaction was completed after 3 h. Analytical TLC on silica gel, 12% ethyl acetate/hexane (R_f = 0.53). Colorless oil (27 mg, yield: 75%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.89 (s, 1H), 8.00 (dd, J = 5.1, 8.7 Hz, 2H), 7.13 (t, J = 8.7 Hz, 2H), 3.28 (t, J = 6.3 Hz, 2H), 2.92 (t, J = 6.3 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.7, 196.4, 166.0 (d, J = 103.4 Hz), 133.1 (d, J = 3 Hz), 130.9 (d, J = 9.3 Hz), 115.9, 37.8, 31.1. FT-IR (thin film): 1721, 1685, 1597, 1506, 1410, 1363, 1233, 1209, 1158, 986, 838 cm^{-1}. HRMS (+ESI): calcd for $C_{10}H_{10}FO_2$ [M + H]$^+$ 181.0659, found 181.0660.

*4-(4-Chlorophenyl)-4-oxobutanal (**2g**).* This compound was prepared according to the general procedure. Reaction was completed after 3 h. Analytical TLC on silica gel, 12% ethyl acetate/hexane (R_f = 0.52). Brown solid (31 mg, yield: 79%). Mp: 51−53 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.90 (s, 1H), 7.92 (d, J = 8.4 Hz, 2H), 7.45 (d, J = 8.4 Hz, 2H), 3.28 (t, J = 6.3 Hz, 2H), 2.94 (t, J = 6.3 Hz, 2H);. ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.5, 196.8, 140.0, 134.9, 129.7, 129.2, 37.8, 31.1. FT-IR (thin film): 1710, 1682, 1589, 1400, 1244, 1207, 1091, 983, 833 cm^{-1}. HRMS (+ESI): calcd for $C_{10}H_{10}ClO_2$ [M + H]$^+$ 197.0364, found 197.0363.

*4-(4-Bromophenyl)-4-oxobutanal (**2h**).* This compound was prepared according to the general procedure. Reaction was completed after 3 h. Analytical TLC on silica gel, 12% ethyl acetate/hexane (R_f = 0.53). White solid (44 mg, yield: 92%). Mp: 59−61 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.90 (s, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 3.29 (t, J = 6.0 Hz, 2H), 2.95 (t, J = 6.0 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.6, 197.0, 135.3, 132.2, 129.8, 128.7, 37.7, 31.1. FT-IR (thin film): 1713, 1681, 1582, 1407, 1296, 1202, 1067, 998, 822, 715, 666 cm^{-1}. HRMS (+ESI): calcd for $C_{10}H_{10}BrO_2$ [M + H]$^+$ 240.9859, found 240.9858.

*4-(3-Methoxyphenyl)-4-oxobutanal (**2i**).* This compound was prepared according to the general procedure. Reaction was completed after 4.5 h. Analytical TLC on silica gel, 18% ethyl acetate/hexane (R_f = 0.51). Pale yellow oil (38 mg, yield: 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.90 (s, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.50 (s, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.12 (dd, J = 2.4, 8.4 Hz, 1H), 3.85 (s, 3H), 3.31 (t, J = 6.4 Hz, 2H), 2.93 (t, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.8, 197.8, 160.0, 137.9, 129.8, 120,.9, 119.9, 112.5, 55.6, 37.8, 31.3. FT-IR (thin film): 1720, 1685, 1596, 1576, 1487, 1431, 1293, 1263, 1169, 1045, 788 cm^{-1}. HRMS (+APCI): calcd for $C_{11}H_{13}O_3$ [M + H]$^+$ 193.0859, found 193.0858.

*4-(3-Chlorophenyl)-4-oxobutanal (**2j**).* This compound was prepared according to the general procedure. Reaction was completed after 3 h. Analytical TLC on silica gel, 12% ethyl acetate/hexane (R_f = 0.54). Pale yellow oil (29 mg, yield: 74%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.89 (s, 1H), 7.95 (s, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 9.0 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 3.29 (t, J = 6.0 Hz, 2H), 2.94 (t, J = 6.0 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.4, 196.8, 138.2, 135.2, 133.4, 130.2, 128.4, 126.4, 37.7, 31.3. FT-IR (thin film): 1717, 1689, 1572, 1420, 1237, 1206, 1018, 997, 869, 789, 680 cm^{-1}. HRMS (+ESI): calcd for $C_{10}H_{10}ClO_2$ [M + H]$^+$ 197.0364, found 197.0363.

*4-Oxo-4-m-tolylbutanal (**2k**).* This compound was prepared according to the general procedure. Reaction was completed after 4 h. Analytical TLC on silica gel, 15% ethyl acetate/hexane (R_f = 0.60). Brown liquid (24 mg, yield: 68%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.91 (s, 1H), 7.78 (d, J = 9.0 Hz, 2H), 7.34−7.40 (m, 2H), 3.32 (t, J = 6.6 Hz, 2H), 2.93 (t, J = 6.6 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.9, 198.2, 138.7, 136.7, 134.3, 128.8, 128.7, 125.5, 37.9, 31.3, 21.6. FT-IR (thin film): 1722, 1685, 1603, 1587, 1362, 1255, 1161, 875, 785 cm^{-1}. HRMS (+ESI): calcd for $C_{11}H_{13}O_2$ [M + H]$^+$ 177.0910, found 177.0900.

*4-Oxo-4-o-tolylbutanal (**2l**).* This compound was prepared according to the general procedure. Reaction was completed after 3.5 h. Analytical TLC on silica gel, 15% ethyl acetate/hexane (R_f = 0.59). Pale yellow oil (29 mg, yield: 82%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.90 (s, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.38 (t, J = 7.5 Hz, 1H), 7.25−7.29 (m, 2H), 3.23 (t, J = 6.3 Hz, 2H), 2.91 (t, J = 6.3 Hz, 2H), 2.49 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 201.9, 200.8, 138.5, 137.5, 132.2, 131.7, 128.8, 125.9, 38.1, 33.9, 21.5. FT-IR (thin film): 1718, 1686, 1456, 1384, 1237, 1207, 1018, 977, 760 cm^{-1}. HRMS (+ESI): calcd for $C_{11}H_{13}O_2$ [M + H]$^+$ 177.0910, found 177.0915.

*4-(Naphthalen-5-yl)-4-oxobutanal (**2m**).* This compound was prepared according to the general procedure. Reaction was completed after 2.5 h. Analytical TLC on silica gel, 15% ethyl acetate/hexane (R_f = 0.50). Brown oil (32 mg, yield: 75%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.95 (s, 1H), 8.58 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.97

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J. Org. Chem. XXXX, XXX, XXX−XXX

(d, J = 6.6 Hz, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.59 (t, J = 7.8 Hz, 1H), 7.50−7.55 (m, 2H), 3.39 (t, J = 6.0 Hz, 2H), 3.02 (t, J = 6.3 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 202.2, 200.9, 135.6, 134.1, 133.1, 130.3, 128.6, 128.2, 127.9, 126.7, 125.9, 124.6, 38.3, 34.5. FT-IR (thin film): 1717, 1677, 1595, 1509, 1394, 1235, 1178, 1104, 940, 805, 773 cm^{-1}. HRMS (+ESI): calcd for $C_{14}H_{13}O_2$ $[M + H]^+$ 213.0910, found 213.0912.

*4-(Biphenyl)-4-oxobutanal (**2n**).* This compound was prepared according to the general procedure. Reaction was completed after 5 h. Analytical TLC on silica gel, 15% ethyl acetate/hexane (R_f = 0.51). Pale yellow solid (45 mg, yield: 95%). Mp: 93−95 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.93 (s, 1H), 8.06 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 7.2 Hz, 2H), 7.48 (t, J = 7.8 Hz, 2H), 7.41 (t, J = 7.2 Hz, 1H), 3.37 (t, J = 6.3 Hz, 2H), 2.97 (t, J = 6.3 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.9, 199.6, 146.2, 140.0, 135.3, 129.1, 128.9, 128.8, 127.6, 127.4, 37.8, 31.2. FT-IR (thin film): 1711, 1680, 1448, 1405, 1384, 1245, 1197, 981, 766, 724, 690 cm^{-1}. HRMS (+APCI): calcd for $C_{16}H_{15}O_2$ $[M + H]^+$ 239.1067, found 239.1068.

*4-(2,4-Dimethylphenyl)-4-oxobutanal (**2o**).* This compound was prepared according to the general procedure. Reaction was completed after 4 h. Analytical TLC on silica gel, 15% ethyl acetate/hexane (R_f = 0.59). Brown liquid (37 mg, yield: 97%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.90 (s, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.07 (d, J = 11.4 Hz, 2H), 3.24 (t, J = 6.3 Hz, 2H), 2.89 (t, J = 6.0 Hz, 2H), 2.48 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 201.1, 200.9, 142.5, 139.2, 134.3, 133.2, 129.4, 126.6, 38.2, 33.6, 21.9, 21.6. FT-IR (thin film): 1720, 1680, 1611, 1566, 1448, 1234, 1206, 1140, 981, 814 cm^{-1}. HRMS (+APCI): calcd for $C_{12}H_{15}O_2$ $[M + H]^+$ 191.1067, found 191.1068.

*4-Oxo-4-(thiophene-2-yl)butanal (**2p**).* This compound was prepared according to the general procedure. Reaction was completed after 2 h. Analytical TLC on silica gel, 15% ethyl acetate/hexane (R_f = 0.45). Brown oil (30 mg, yield: 89%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.88 (s, 1H), 7.77 (d, J = 4.2 Hz, 1H), 7.65 (d, J = 4.8 Hz, 1H), 7.14 (t, J = 4.2 Hz, 1H), 3.26 (t, J = 6.6 Hz, 2H), 2.93 (t, J = 6.6 Hz, 2H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 200.5, 190.9, 143.7, 134.0, 132.3, 128.4, 37.8, 31.7. FT-IR (thin film): 1723, 1662, 1518, 1416, 1246, 1054, 928, 854, 728 cm^{-1}. HRMS (+ESI): calcd for $C_8H_9O_2S$ $[M + H]^+$ 169.0318, found 169.0319.

*4-Oxo-6-phenylhexanal (**2q**).* This compound was prepared according to the general procedure. Reaction was completed after 10 h. Analytical TLC on silica gel, 12% ethyl acetate/hexane (R_f = 0.52). Brown liquid (25 mg, yield: 65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 (s, 1H), 7.28 (t, J = 7.6 Hz, 2H), 7.19 (t, J = 8.0 Hz, 3H), 2.91 (t, J = 7.2 Hz, 2H), 2.80 (t, J = 7.2 Hz, 2H), 2.77−2.74 (m, 2H), 2.71−2.68 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.9, 200.6, 141.0, 128.7, 128.5, 126.3, 44.4, 37.6, 35.0, 29.9. FT-IR (thin film): 1712, 1599, 1435, 1409, 1263, 1100, 877, 751, 700 cm^{-1}. HRMS (+ESI): calcd for $C_{12}H_{15}O_2$ $[M + H]^+$ 191.1067, found 191.1066.

*4-Cyclohexyl-4-oxobutanal (**2r**).* This compound was prepared according to the general procedure. Reaction was completed after 20 h. Analytical TLC on silica gel, 15% ethyl acetate/hexane (R_f = 0.55). Pale yellow oil (26 mg, yield: 77%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.80 (s, 1H), 2.73−2.77 (m, 4H), 2.39 (t, J = 11.1 Hz, 1H), 1.88 (d, J = 11.4 Hz, 2H), 1.78 (d, J = 13.2 Hz, 2H), 1.23−1.37 (m, 5H), 1.20 (t, J = 12.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 212.1, 200.9, 50.9, 37.6, 32.8, 28.7, 26.0, 25.8. FT-IR (thin film): 1705, 1632, 1448, 1386, 1146, 1018 cm^{-1}. HRMS (+ESI): calcd for $C_{10}H_{17}O_2$ $[M + H]^+$ 169.1223, found 169.1223.

*6-Methyl-4-oxoheptanal (**2s**).* This compound was prepared according to the general procedure. Reaction was completed after 24 h. Analytical TLC on silica gel, 15% ethyl acetate/hexane (R_f = 0.49). Yellow oil (23 mg, yield: 81%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.80 (s, 1H), 2.72 (d, J = 16.8 Hz, 4H), 2.33 (d, J = 6.0 Hz, 2H), 2.18−2.10 (m, 1H), 0.91 (d, J = 3.6 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 208.7, 200.7, 51.9, 37.6, 35.4, 24.9, 22.7. FT-IR (thin film): 1712, 1468, 1386, 1368, 1170, 1140, 1080, 1033, 872 cm^{-1}. HRMS (+APCI): calcd for $C_8H_{15}O_2$ $[M + H]^+$ 143.1067, found 143.1068.

*3-Methyl-4-oxo-4-phenylbutanal (**2t**).* This compound was prepared according to the general procedure. Reaction was completed after 48 h. Analytical TLC on silica gel, 15% ethyl acetate/hexane (R_f = 0.51). Colorless oil (18 mg, yield: 51%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.81 (s, 1H), 7.98 (d, J = 7.8 Hz, 1H), 7.58 (t, J = 7.2 Hz, 1H), 7.48 (t, J = 7.2 Hz, 2H), 4.03−3.97 (m, 1H), 3.17 (dd, J = 18.3, 7.8 Hz, 1H), 2.62 (dd, J = 18.6, 4.8 Hz, 1H), 1.24 (d, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 202.7, 200.7, 135.8, 133.4, 128.9, 128.7, 47.3, 35.3, 18.2. FT-IR (thin film): 1711, 1681, 1596, 1449, 1380, 1240, 1179, 979, 794, 704 cm^{-1}. HRMS (+APCI): calcd for $C_{11}H_{13}O_2$ $[M + H]^+$ 177.0910, found 177.0909.

*4-(3-Chlorophenyl)-3-methyl-4-oxobutanal (**2u**).* This compound was prepared according to the general procedure. Reaction was completed after 30 h. Analytical TLC on silica gel, 15% ethyl acetate/hexane (R_f = 0.53). Yellow oil (28 mg, yield: 67%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.78 (s, 1H), 7.94 (s, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.42 (d, J = 7.8 Hz, 1H), 3.95−3.89 (m, 1H), 3.19 (dd, J = 18.6, 8.4 Hz, 1H), 2.64 (dd, J = 18.6, 4.8 Hz, 1H), 1.22 (d, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 201.5, 200.4, 137.5, 135.3, 133.3, 130.3, 128.8, 126.7, 47.3, 35.4, 18.0. FT-IR (thin film): 1726, 1685, 1570, 1239, 1198, 1075, 801, 736, 670 cm^{-1}. HRMS (+ESI): calcd for $C_{11}H_{12}ClO_2$ $[M + H]^+$ 211.0520, found 211.0522.

*4-(4-Chlorophenyl)-3-methyl-4-oxobutanal (**2v**).* This compound was prepared according to the general procedure. Reaction was completed after 30 h. Analytical TLC on silica gel, 15% ethyl acetate/hexane (R_f = 0.52). Yellow oil (26 mg, yield: 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 (s, 1H), 7.92 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H), 3.98−3.89 (m, 1H), 3.18 (dd, J = 18.8, 8.4 Hz, 1H), 2.62 (dd, J = 18.8, 4.8 Hz, 1H), 1.22 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.5, 200.5, 139.8, 134.2, 130.1, 129.3, 47.3, 35.2, 18.1. FT-IR (thin film): 1724, 1681, 1590, 1488, 1459, 1401, 1238, 1092, 1013, 980, 842, 748, 525 cm^{-1}. HRMS (+ESI): calcd for $C_{11}H_{12}ClO_2$ $[M + H]^+$ 211.0520, found 211.0522.

*4-(4-Bromophenyl)-3-methyl-4-oxobutanal (**2w**).* This compound was prepared according to the general procedure. Reaction was completed after 48 h. Analytical TLC on silica gel, 15% ethyl acetate/hexane (R_f = 0.51). Yellow oil (30 mg, yield: 59%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.78 (s, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 3.95−3.89 (m, 1H), 3.17 (dd, J = 18.6, 8.4 Hz, 1H), 2.63 (dd, J = 18.6, 4.8 Hz, 1H), 1.22 (d, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 201.7, 200.5, 134.7, 132.3, 130.2, 128.6, 47.3, 35.2, 18.1. FT-IR (thin film): 1713, 1681, 1585, 1397, 1071, 1010, 978, 838 cm^{-1}. HRMS (+ESI): calcd for $C_{11}H_{12}BrO_2$ $[M + H]^+$ 255.0015, found 255.0017.

*3-Methyl-4-oxo-4-p-tolylbutanal (**2x**).* This compound was prepared according to the general procedure. Reaction was completed after 72 h. Analytical TLC on silica gel, 15% ethyl acetate/hexane (R_f = 0.54). Yellow oil (18 mg, yield: 47%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.80 (s, 1H), 7.88 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 3.99−3.96 (m, 1H), 3.14 (dd, J = 18.3, 8.1 Hz, 1H), 2.60 (dd, J = 18.6, 5.4 Hz, 1H), 2.42 (s, 3H), 1.23 (d, J = 8.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 202.3, 200.8, 144.2, 133.3, 129.6, 128.8, 47.3, 35.3, 21.9, 18.3. FT-IR (thin film): 1724, 1680, 1608, 1456, 1381, 1261, 1183, 1019, 801, 747 cm^{-1}. HRMS (+ESI): calcd for $C_{12}H_{15}O_2$ $[M + H]^+$ 191.1067, found 191.1065.

*2-Methyl-4-oxo-4-phenylbutanal (**2y**).* This compound was prepared according to the general procedure. Reaction was completed after 30 h. Analytical TLC on silica gel, 15% ethyl acetate/hexane (R_f = 0.51). Brown oil (17 mg, yield: 48%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.80 (s, 1H), 7.98 (d, J = 7.8 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.48 (t, J = 8.4 Hz, 2H), 3.50 (dd, J = 18.0, 7.2 Hz, 1H), 3.16−3.10 (m, 1H), 3.26 (dd, J = 17.7, 6.0 Hz, 1H), 1.25 (d, J = 7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 203.7, 199.0, 136.7, 133.6, 128.9, 128.3, 48.9, 39.6, 14.0. FT-IR (thin film): 1725, 1683, 1597, 1448, 1359, 1263, 1217, 1003, 913, 751, 690 cm^{-1}. HRMS (+ESI): calcd for $C_{11}H_{13}O_2$ $[M + H]^+$ 177.0910, found 177.0912.

*Spectral data for compound 2,3-**d**$_2$-**2a**.* This compound was prepared according to the general procedure. Reaction was completed after 5 h. Analytical TLC on silica gel, 15% ethyl acetate/hexane (R_f = 0.55). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.91 (s, 1H), 7.99 (d, J = 7.8 Hz, 2H), 7.58 (t, J = 7.2 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 3.32(t, J = 6.6 Hz, 1H), 2.92 (t, J = 6.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ

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J. Org. Chem. XXXX, XXX, XXX−XXX

200.9, 198.0, 136.6, 133.5, 128.9, 128.3, 37.4 (t, J = 7.8 Hz), 30.9 (t, J = 7.8 Hz). FT-IR (thin film): 1724, 1682, 1597, 1448, 1280, 1220, 753, 690 cm^{-1}. HRMS (+ESI): calcd for $C_{10}H_{19}D_2O_2$ $[M + H]^+$ 166.0957, found 166.0953

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00243.

Optimization table and spectra of all the products (PDF)

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Notes

The authors declare no competing financial interest.

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