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Thiazolylidene-Catalyzed Cleavage of Methyl Oleate-Derived α-Hydroxy Ketone to the Corresponding Free Aldehydes

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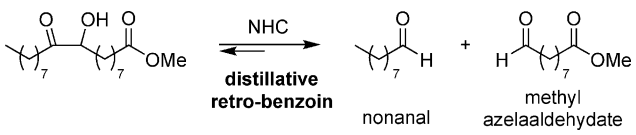
The thiazolylidene-catalyzed cleavage of the α-hydroxy ketone derived from methyl oleate gave the corresponding aldehydes under nonoxidative conditions through a retro-benzoin process. The aldehydes produced are in equilibrium with their corresponding acyloins. To illustrate the synthetic utility of this protocol, the aldehydes were recovered by distillation.

Among the primary components of biomass, triglycerides (vegetable oils and animal fats) are of great interest as, unlike carbohydrates and lignin, they exhibit low oxygen content. Consequently, they can be transformed readily into biofuels,[1] platform chemicals,[2] and biopolymers.[3] Methyl oleate produced by the methanolysis of vegetable oils is probably one the most interesting starting materials owing to the presence of a single internal double bond. First, the double bond can be functionalized to an epoxide,[4] diol,[5] ketone, or diketone group,[6] among others, and these intermediates can be used as such or further transformed. The C=C bond can be also cleaved to give shorter fragments such as C_9 acids or aldehydes though oxidative[7] or reductive[8] ozonolysis, respectively. The double bond of methyl oleate is also a suitable site for metathesis reactions. For example, methyl oleate can undergo cross-metathesis with ethylene (ethenolysis) to give C_{10} compounds with a terminal double bond that can be further transformed.[9] Moreover, methyl oleate can undergo self-metathesis to give C_{18} compounds, which could be of great interest for the polymer or biofuel industries.[10] A saturated C_{19} diester can also be prepared through isomerization of the internal double bond to the terminal position followed by transformation to the corresponding methyl ester by methoxycarbonylation.[11] Of these transformations, the reductive ozonolysis is the only direct route that provides fatty aldehydes, which are of great interest for various applications. For example, nonanal can be used as such or for the preparation of 100% biobased surfactants through the reductive alkylation of polyols.[12] Methyl azelaaldehydate can be transformed to monomers for the preparation of polyesters and polyamides through reduction or reductive amination, respectively.[8] However, although this method offers excellent atom economy, it requires the use of ozone (O_3), which is highly toxic and explosive. In this context, alternatives to prepare these biobased fatty aldehydes will be of great interest.

The utilization of renewable feedstocks has recently boosted the use of organocatalysts for biorefining.[13] In this context, N-heterocyclic carbenes (NHCs) are particularly suitable for the conversion of biomass-derived furaldehydes, such as furfural and 5-hydroxymethylfurfural (HMF),[14] through the well-established benzoin condensation. This strategy has also been applied to upgrade bioethanol-based acetaldehyde to acetoin.[15] The (asymmetric) benzoin condensation has been studied extensively,[16] and its reversibility has been demonstrated in some occasions.[17,18] This retro-benzoin process occurs in a biochemical reaction catalyzed by vitamin B1 (thiamine) in the transketolase (TK) enzyme involved in the metabolism of carbohydrates.[19] However, this reversibility has been underexploited,[20] and examples of its synthetic utility are scarce. Miyashita et al. first reported that ketones could be produced from α-substituted benzoins with cyanide ion or a range of NHCs as catalysts, exploiting the fact that ketones are usually more stable than aldehydes.[21] More recently, Chi et al. have elegantly shown that formaldehyde equivalents could be generated from carbohydrates through a retro-benzoin process catalyzed by a thiazolium salt.[22] This very reactive one-carbon acyl anion was trapped by enones to give β-formyl ketones, taking advantage of the irreversible character of the Stetter reaction. Although these two methodologies give access to the retro-benzoin products, they do not allow the isolation of the free aldehydes.

In the context of the valorization of vegetable oils, we envisioned that the retro-benzoin condensation of methyl oleate-derived α-hydroxy ketone (methyl 9-hydroxy-10-oxostearate) would produce the corresponding aldehydes, that are, nonanal and methyl azelaaldehydate (Scheme 1). We also hypothesized that the removal of the products from the reaction mixture by distillation would shift the equilibrium towards their formation.



Scheme 1. NHC-catalyzed distillative retro-benzoin condensation of methyl oleate derived α-hydroxy ketone (methyl 9-hydroxy-10-oxostearate).

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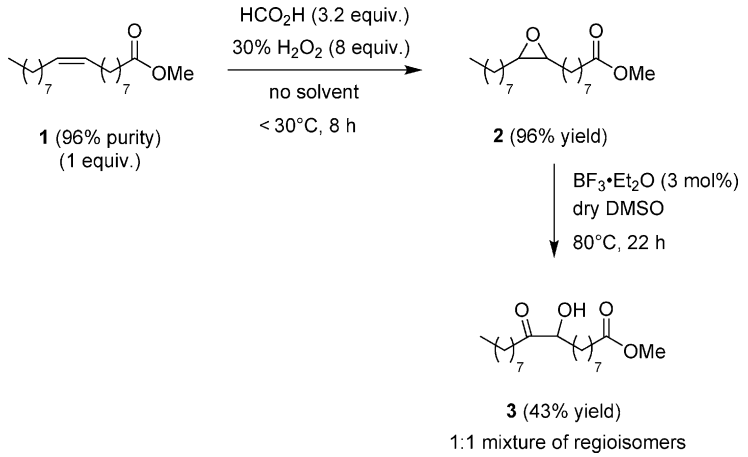


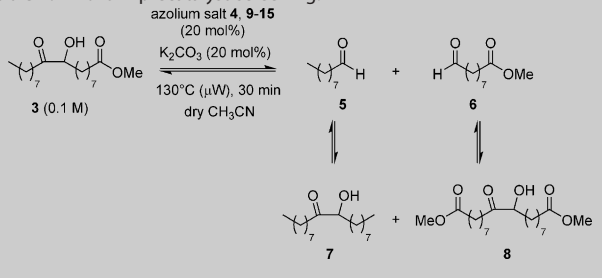
Scheme 2. Preparation of methyl oleate-derived α-hydroxy ketone.

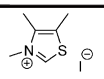
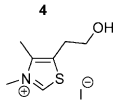
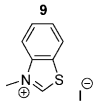
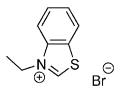
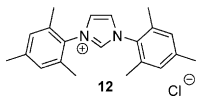
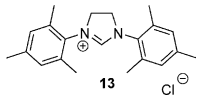
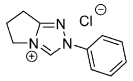
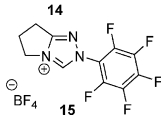
Herein, we report, to the best of our knowledge, the first retro-benzoin method that allows the generation and isolation of aliphatic free aldehydes from renewable resources.

To test our hypothesis, the α-hydroxy ketone of methyl oleate was prepared from commercially available methyl oleate in a two-step sequence involving epoxide formation and subsequent oxidative ring-opening (Scheme 2). First, methyl oleate (**1**, 96% purity) was converted to methyl 9,10-epoxystearate (**2**) in 96% isolated yield according to the procedure reported by Doll et al.[6] Then, the epoxide underwent oxidative ring-opening by dimethyl sulfoxide (DMSO), according to the procedure of Brousse and Lefort[23] to afford the desired α-hydroxy ketone **3** as a 1:1 mixture of regioisomers in 43% isolated yield after flash chromatography. The unreacted starting material **2** was also recovered in 41% isolated yield. Although the original procedure has not been optimized,[24] it allows the preparation of sufficient material for our studies.

In an initial attempt, α-hydroxy ketone **3** was heated at 130 °C for 24 h in the presence of the commercially available thiazolium salt **4** (20 mol%) and K_2CO_3 (20 mol%). The ^1H NMR spectrum of the crude reaction mixture revealed the formation of the desired aldehydes **5** and **6** (10% yield based on the conversion of α-hydroxy ketone **3**) and, thus, validated our approach that α-hydroxy ketone could be cleaved under nonoxidative conditions. Encouraged by this preliminary result, we quickly turned our attention to the use of microwave activation. Under these conditions, the conversion reached 24% after only 30 min, and the desired aldehydes **5** and **6** were both obtained in 19% yield along with 5% of each of the symmetric acyloins **7** and **8** (Table 1, entry 1).[25] We hypothesized that these products were formed by the thiazolium-catalyzed self-benzoin condensation of the previously generated aldehydes **5** and **6** and that the whole system is in equilibrium. Interestingly, by analogy with the olefin self-metathesis of methyl oleate, acyloins **7** and **8** could be seen as the benzoin self-metathesis products of α-hydroxy ketone **3**. Other commercially available azolium salts **9**–**15** were next screened as precatalysts. The thiamine-derived thiazolium salt **9** was also active, but the aldehydes were formed in a slightly lower yield (14%), and almost no acyloins were produced (Table 1, entry 2). Surprisingly, NHCs derived from the structurally-related benzothiazolium salts **10** and **11** were almost inactive (Table 1, entries 3 and 4). Other precatalysts such as imidazolium salt **12**, imidazolinium salt **13**, and triazolium salts **14** and **15** were also screened; similarly, none of these species led to the efficient formation of the cleavage products (Table 1, entries 5–8). Finally, only the thiazolium-based catalysts **4** and **9** were sufficiently active for this transformation. These results corroborate the findings of Chi, who also proved the superiority of thiazolium salts as

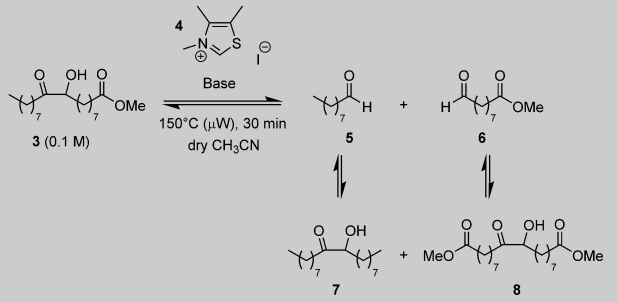
Table 1. Azolium precatalyst screening.[a]



Entry	Azolium salt	Conversion [%]	Yield [%] 5	6	7	8
1	 4	24	19	19	5	5
2	 9	16	14	14	2	2
3	 10	2	2	2	0	0
4	 11	2	2	2	0	0
5	 12	2	2	2	0	0
6	 13	0	0	0	0	0
7	 14	0	0	0	0	0
8	 15	3	3	3	0	0

[a] Conditions: microwave tube, α-hydroxy ketone **3** (1:1 mixture of regioisomers, 0.2 mmol), azolium salt (20 mol%), K_2CO_3 (20 mol%), dry CH_3CN (2 mL), 130 °C, 30 min; the conversions and yields were determined by GC using hexadecane as internal standard.

Table 2. Screening of bases and reaction parameters.[a]



Entry	4 [mol%]	Base	[mol%]	Conversion [%]	GC yields [%] 5	6	7	8
1	20	Et_3N	20	7	7	7	0	0
2	20	iPr_2NEt	20	7	7	7	0	0
3	20	Li_2CO_3	20	2	2	2	0	0
4	20	Na_2CO_3	20	13	13	13	0	0
5	20	K_2CO_3	20	39	28	28	11	11
6	20	Rb_2CO_3	20	30	24	24	6	6
7	20	Cs_2CO_3	20	30	16	16	14	14
8	20	$KHCO_3$	20	29	23	23	6	6
9	20	KOAc	20	32	24	24	8	8
10	20	KOH	20	35	27	27	8	8
11	10	K_2CO_3	10	33	27	27	6	6
12	5	K_2CO_3	5	23	19	19	4	4
13	20	K_2CO_3	10	32	23	23	8	8
14[b]	20	K_2CO_3	20	56	40	40	16	16
15[c]	20	K_2CO_3	20	60	40	40	20	20
16	20	–	–	0	0	0	0	0
17	–	K_2CO_3	20	0	0	0	0	0
18	–	–	–	0	0	0	0	0

[a] Conditions: microwave tube, α-hydroxy ketone **3** (1:1 mixture of regioisomers, 0.2 mmol), thiazolium **4**, base, dry CH_3CN (2 mL), 150 °C, 30 min; yields were determined by GC using hexadecane as internal standard and refer to the conversion of α-hydroxy ketone **3**. [b] 170 °C, 30 min. [c] 170 °C, 60 min.

catalysts for the retro-benzoin condensation of carbohydrate derivatives.[22]

The influence of the base was next probed using thiazolium salt **4** as the catalyst at 150 °C under microwave irradiation (Table 2). Among the organic bases tested, Et_3N and iPr_2NEt gave poor results (Table 2, entries 1 and 2). Using a range of carbonates, the conversion of α-hydroxy ketone **3** increased gradually from 2% with Li_2CO_3 to 39% with K_2CO_3 (Table 2, entries 3–5). However, these results could not be improved using other carbonates such as Rb_2CO_3 and Cs_2CO_3 (Table 2, entries 6 and 7). Other potassium bases such as $KHCO_3$, KOAc, and KOH also promoted the reaction but to a lesser extent than K_2CO_3 (Table 2, entries 8–10). The effect of the catalyst loading was then probed. Predictably, decreasing the loading of both thiazolium **4** and K_2CO_3 from 20 to 5 mol% led to a moderate drop of conversion from 39 to 23% (Table 2, entries 5, 11, and 12). Interestingly, the selectivity of aldehydes **5** and **6** was higher (82%) when using 5 and 10 mol% of the NHC than with 20 mol% (72%). This property could be used advantageously for the selective recovery of aldehydes by distillation. The reaction was also performed with 20 mol% of precatalyst **4** and 10 mol% of K_2CO_3, but neither the conversion of **3** nor the selectivity of the aldehydes improved under these conditions (Table 2, entry 13). To find the equilibrium of this system, the reaction was performed at a higher temperature. At 170 °C under microwave irradiation, the conversion reached 56 and 60% after 30 and 60 min, respectively (Table 2, entries 14 and 15). Under these conditions, aldehydes **5** and **6** both formed in 40% yield, and acyloins **7** and **8** both formed in 20% yield. These results could not be improved by prolonged reaction times; therefore, the equilibrium was probably reached. Satisfyingly, the reaction mixture was relatively clean, which indicates that few side-reactions occurred under these optimized conditions (Figure 1).

Finally, control experiments were performed to verify that the NHC derived from **4** is the active catalytic species. The addition of α-hydroxy ketone **3** to either thiazolium precatalyst **4** (20 mol%) or K_2CO_3 (20 mol%) gave no conversion to the corresponding aldehydes (Table 2, entries 16 and 17). Moreover, heating α-hydroxy ketone **3** in CH_3CN under microwave irradiation also returned the starting material exclusively (Table 2, entry 18). These control experiments confirm that the thiazolylidene species generated from **4** is responsible for the catalytic cleavage of the α-hydroxy ketone derived from methyl oleate.

From these results, the following mechanism could be proposed (Scheme 3). First, thiazolium salt **4** could be deprotonated with K_2CO_3 to generate thiazolylidene **I** as the active catalyst. The addition of thiazolylidene **I** to α-hydroxy ketone **3** (1:1 mixture of regioisomers) would lead to intermediate **II**. Then, proton transfer from **II** to **III** would produce the Breslow intermediate[26] **IV** with the concomitant release of aldehyde **6** (or **5** with the other regioisomer). Finally, further proton transfer would generate intermediate **V**, which would release aldehyde **5** (or **6** for the other regioisomer) and the active thiazolylidene catalyst **I**. As the reaction is reversible, aldehydes **5** or **6** could re-enter the catalytic cycle to produce a Breslow intermediate that would react with a second aldehyde to finally produce symmetrical α-hydroxy ketones **7** and **8**. The fact that this retro-benzoin process could only be catalyzed efficiently by thiazolium precursors could be attributed to the relative stability of the Breslow intermediate. Indeed, Hollóczki and Nyulászi have recently shown that the Breslow intermediate generated from thiazol-2-ylidene is more stable (by ca. 10 kcal mol^{-1}) than those produced from other NHC precursors such as imidazolium and triazolium salts and, thus, the reversibility of the reaction increases.[27]

To prove the synthetic utility of this method, we envisioned that the removal of aldehydes **5** and **6** from the reaction mixture by distillation would shift the equilibrium towards their formation and would also limit the formation of acyloins **7** and **8**. To avoid the formation of potential aldol byproducts, the pregeneration of the NHC was favored, and the aldehydes were distilled simultaneously. Neat α-hydroxy ketone **3** (4.00 g) was heated at 180 °C (oil bath) in the presence of 10 mol% of the thiazolylidene active species [pregenerated from thiazolium salt **4** (10 mol%) and K_2CO_3 (10 mol%)]. The distillate was collected from 58 to 91 °C under reduced pressure (4–6 mbar). After 3 h, aldehydes **5** and **6** were recovered (1.42 g, 36% yield; Table 3, entry 1) as a 63:37 mixture as determined by GC

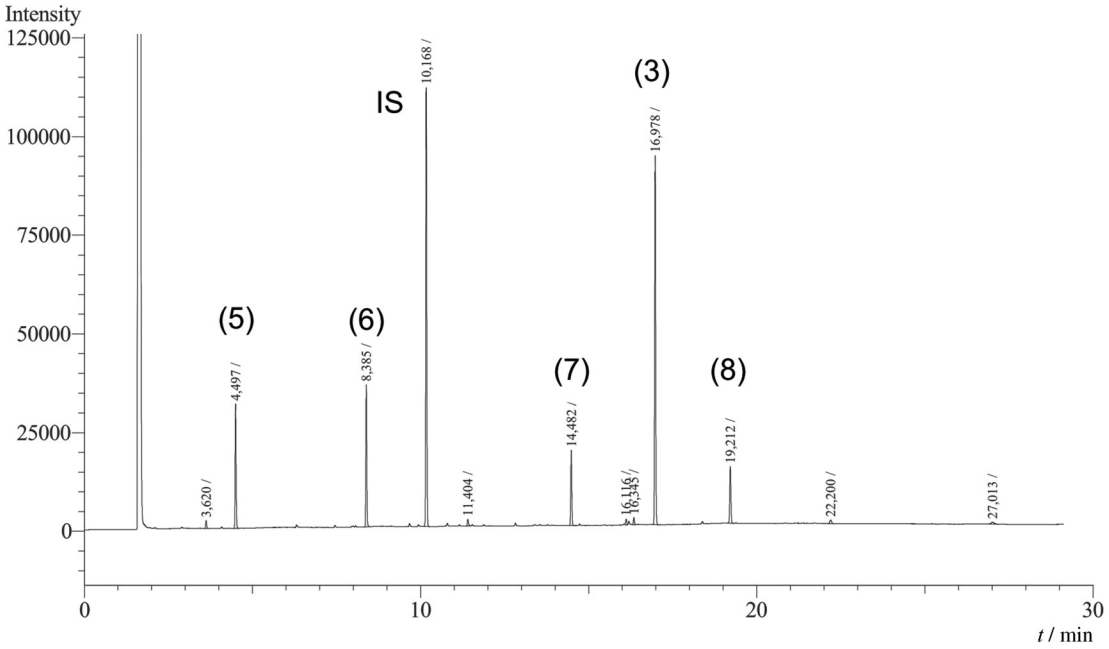
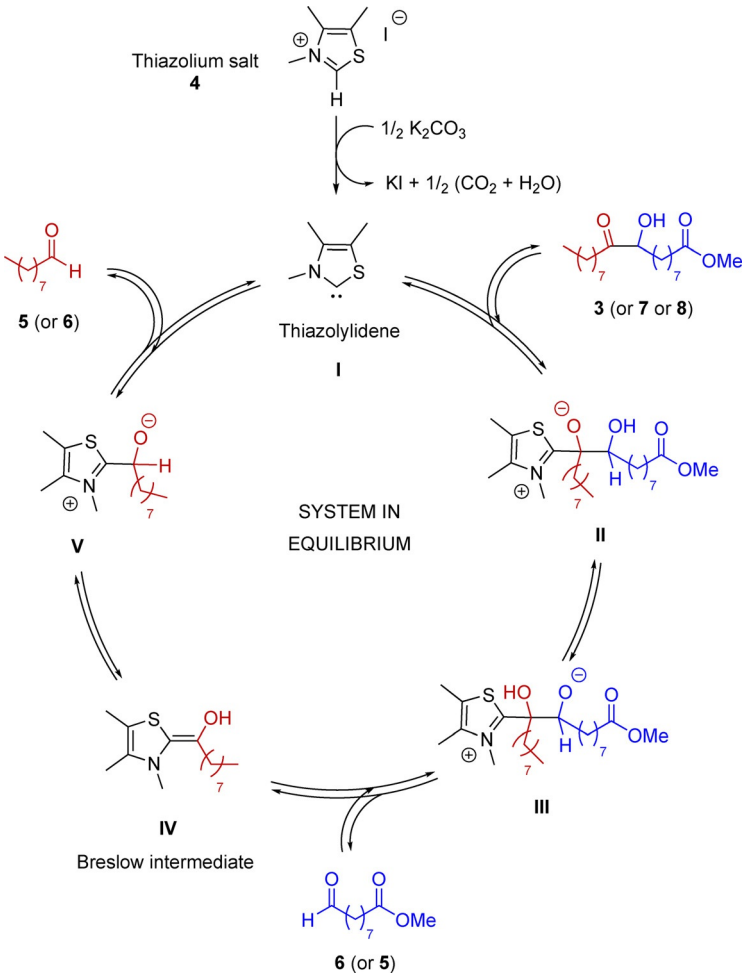


Figure 1. GC chromatogram of the crude reaction mixture after 60 min. at 170 °C. IS = internal standard (hexadecane).

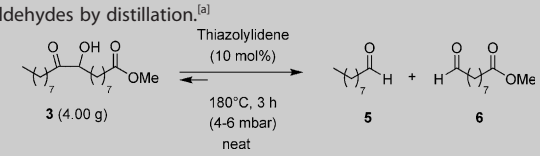


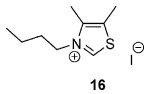
Scheme 3. Proposed mechanism (only one regioisomer of **3** is represented).

analysis. Encouragingly, the residue showed no significant signs of degradation, and only starting material **3** and acyloin **8** were recovered. However, we noticed that the slight degradation of precatalyst **4** to 4,5-dimethylthiazole resulted in a low yield. Therefore, thiazolium salt **16** with an ionic-liquid-like structure was designed specifically to prevent the degradation. Satisfyingly, under these conditions, aldehydes **5** and **6** were recovered as a 66:34 mixture in an improved 58% global yield (Table 3, entry 2). In that case, the residue showed a significant proportion (24%) of acyloin **8**. The further addition of freshly pregenerated catalyst (10 mol%) to the residue did not improve the yield of the aldehydes. This result indicates that the conversion was limited by the lack of material in the distillation setup rather than by catalyst deactivation and, thus, encourages the development of a continuous distillation process.

In conclusion, we have demonstrated that the α-hydroxy ketone derived from methyl oleate could be cleaved under nonoxidative conditions to give the corresponding aldehydes nonanal (**5**) and methyl azelaaldehydate (**6**). The reaction proceeds through a retro-benzoin process that is catalyzed specifically by a thiazolylidene species. The aldehydes are in equilibrium with their corresponding acyloins **7** and **8**, which could be considered as the benzoin self-metathesis products of α-hydroxy ketone **3**. To illustrate the synthetic utility of this method, the cleavage products were removed by distillation to shift the equilibrium towards the formation of the desired aldehydes. Current studies are now focused upon improving the access to the α-hydroxy ketone starting

Table 3. Recovery of aldehydes by distillation.[a]



Entry	Thiazolium salt	Distillate composition	Residue composition
1	 4	aldehydes **5**/**6** (63:37), 1.42 g (36%)	α-OH ketones **3**/**8** (95:5), 2.58 g (64%)
2	 16	aldehydes **5**/**6** (66:34), 2.31 g (58%)	α-OH ketones **3**/**8** (76:24), 1.69 g (42%)

[a] Conditions: distillation setup, pregeneration of catalyst from thiazolium salt (10 mol%), K_2CO_3 (10 mol%), dry CH_3CN (4 mL) for 10 min at RT; removal of K_2CO_3 and evaporation of CH_3CN; then, α-hydroxy ketone **3** (1:1 mixture of regioisomers, 4.00 g), 180 °C, 4–6 mbar, 3 h.

material and optimizing the structure of the catalyst. Further investigations will also focus on the development of a continuous distillation process.

Experimental Section

Methyl 9,10-epoxystearate (2): Following a modified literature procedure,[6] in a 50 mL round-bottom three-necked flask, methyl oleate (**1**, Alfa Aesar, 96%; 10 mL, 29.4 mmol, 1 equiv.) was mixed with formic acid (3.6 mL, 94.1 mmol, 3.2 equiv.). Hydrogen peroxide (7 mL, 234 mmol, 8 equiv.) was added dropwise with a dropping funnel over a 15 min period, and an ice bath was used to control the temperature. Then, the mixture was stirred magnetically at room temperature for 8 h. The reaction was followed by GC. The temperature should not exceed 30 °C. The organic layer was extracted with heptane (10 mL), neutralized with a saturated $NaHCO_3$ solution (5×10 mL), and washed with H_2O (3×10 mL) and a saturated NaCl solution (2×5 mL). The organic layer was dried using Na_2SO_4, filtered, and concentrated under reduce pressure to give the title compound **2** (8.80 g, 96%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.86$ (t, 3H, $J = 6.5$ Hz), 1.10–1.52 (m, 24H), 1.52–1.70 (m, 2H), 2.28 (t, 2H, $J = 7.4$ Hz), 2.80–2.96 (m, 2H), 3.64 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.2$ (CH_3), 22.8, 25.0, 26.6, 26.7, 27.90, 27.94, 29.1, 29.29, 29.33, 29.4, 29.6, 29.7, 32.0 (13CH_2), 34.2 (CH_2), 51.5 (CH_3), 57.28 (CH), 57.33 (CH), 174.3 ppm (C). See the Supporting Information for full characterization data.

Methyl 9(10)-hydroxy-10(9)-oxostearate (3): Following a literature procedure,[23] in a 25 mL round-bottom flask, methyl 9,10-epoxystearate (**2**; 1.00 g, 3.2 mmol, 1 equiv.) was dissolved in DMSO (4 mL, 56.3 mmol, 17.6 equiv.) under an argon atmosphere. Then, $BF_3{\cdot}Et_2O$ (0.012 mL, 0.1 mmol, 0.03 equiv.) was added. The mixture was heated at 80 °C and stirred for 22 h. Water (10 mL) was added, and the organic layer was extracted with CH_2Cl_2 (4×10 mL). The organic layers were combined, dried using Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (cyclohexane/EtOAc 98:2 to 80:20) to give the unreacted starting material **2** (0.41 g, 41%, $R_f = 0.7$, cyclohexane/EtOAc 90:10) and the title compound **3** (0.45 g, 43%, $R_f = 0.4$, cyclohexane/EtOAc 90:10) as a white solid (m.p. 36–40 °C). ^{1}H NMR (300 MHz, $CDCl_3$, 1:1 mixture of regioisomers): $\delta = 0.85$ (t, 3H, $J = 6.4$ Hz), 1.15–1.38 (m, 17H), 1.38–1.70 (m, 6H), 1.70–1.88 (m, 1H), 2.28 (t, 2H, $J = 7.4$ Hz), 2.31–2.53 (m, 2H), 3.15–3.40 (m, 1H), 3.64 (s, 3H), 4.09–4.18 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 1:1 mixture of regioisomers): $\delta = 14.2$ (CH_3), 22.7, 23.6, 23.7, 24.93 and 24.96, 29.0, 29.08 and 29.11, 29.17 and 29.19, 29.32 and 29.34, 29.4, 29.52 and 29.56, 31.89 and 31.93 (11 CH_2), 33.81 and 33.87 (CH_2), 34.11 and 34.14 (CH_2), 37.88 and 37.95 (CH_2), 51.5 (CH_3), 76.45 and 76.52 (CH), 174.33 and 174.38 (C), 212.59 and 212.64 ppm (C). See the Supporting Information for full characterization data.

Procedure for the thiazolylidene-catalyzed cleavage of α-hydroxy ketone (3) under microwave conditions: In a 5 mL microwave tube, α-hydroxy ketone **3** (1:1 mixture of regioisomers; 65.7 mg, 0.2 mmol, 1 equiv.), 3,4,5-trimethylthiazol-3-ium iodide (**4**; 10.2 mg, 0.04 mmol, 20 mol%), and K_2CO_3 (5.5 mg, 0.04 mmol, 20 mol%) were combined. The tube was flushed with argon, and dry CH_3CN (2 mL) was added. The mixture was stirred under microwave irradiation at the desired temperature for a period of time. The mixture was cooled to room temperature, and the solvent was evaporated under reduced pressure. The residue was analyzed by GC with hexadecane as an internal standard.

Procedure for the thiazolylidene-catalyzed cleavage of α-hydroxy ketone (3) with recovery of aldehydes by distillation: In a 25 mL bottom flask, K_2CO_3 (1.09 mmol, 150.6 mg, 9 mol%) was added to thiazolium salt **16** (359.4 mg, 1.21 mmol, 10 mol%) in dry CH_3CN (4 mL) under an argon atmosphere. The mixture was stirred magnetically at room temperature for 10 min to give a yellow solution. Then, under argon, the resulting solution was collected using a syringe and injected into a distillation flask containing the starting material **3** (4.00 g, 12.18 mmol). The residue was washed with CH_3CN. The solvent used for the generation of the carbene was evaporated first under reduced pressure (4–6 mbar). Then, the mixture was heated at 180 °C and stirred for 3 h. The distillate was collected between 58 and 91 °C under 4–6 mbar to give nonanal (**5**) and methyl 9-oxononanoate (**6**) as a 66:34 mixture (2.31 g, 58% wt. yield) as determined by GC analysis. The residue (1.69 g, 42% wt. yield) was recovered as a 76:24 mixture of starting material **3** and acyloin **8** as determined by GC analysis. If required, the aldehydes could be separated further by flash chromatography (cyclohexane/EtOAc 99.8:0.2 to 95:5).

Keywords: aldehydes · biomass · carbenes · cleavage reactions · organocatalysis

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