Thieme Chemistry Journal Awardees– Where are They Now? Intermolecular Cross-Acyloin Reactions by Fluoride-Promoted Additions of *O*-Silyl Thiazolium Carbinols

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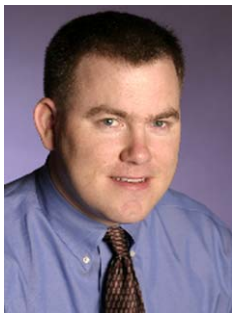
Abstract: The addition of acyl anion equivalents to aliphatic aldehydes (crossed-acyloin reaction) has been developed. Cesium fluoride with isopropanol as solvent promotes the addition of *O*-silyl thiazolium carbinols to various aliphatic aldehydes in moderate to good yields. These reactions represent a general procedure for the selective coupling of aliphatic aldehydes by an acyl anion reaction which have been problematic until now.

Key words: acyloin reaction, carbinols, cesium fluoride, acyl anions, thiazolium

The construction of carbon–carbon bonds through inverse reactivity patterns, or Umpolung, fuels potential strategies for the syntheses of biologically active molecules.[1,2] The benzoin[3–7] and Stetter reactions[8–12] are two transformations that utilize the in situ generation of acyl anion equivalents for the formation of new C–C bonds. The acyloin reaction is related to the benzoin condensation and entails the addition of an acyl anion to an aliphatic aldehyde. This process is another potentially useful Umpolung transformation that allows for direct formation of α-hydroxy ketones, a useful motif in organic chemistry.

While there are reports describing catalytic intramolecular additions of aldehydes to ketones,[13,14] the literature has very few examples of successful cross-acyloin reactions in which both reactive components are aliphatic aldehydes (Scheme 1, R^1, R^2 = alkyl).[15–19] To the best of our knowledge, there is only one example of a selective cross-acyloin reaction of this type reported by Johnson which involves an acylsilane and cyanide as a catalyst.[20] Alternatively, the deprotonation of protected cyanohydrins[21,22] or dithianes[23–25] with strong bases (e.g., LDA, *n*-BuLi) has generated acyl anion equivalent as suitable nucleophiles with aldehyde acceptors. While the cyanohydrin strategy can be an effective acyl anion equivalent, the liberation of cyanide to generate a ketone renders the use of cyanohydrins undesirable. Additionally, the use of cyanohydrins and dithianes as acyl anion equivalents requires a further deprotection step after completion of the key carbon–carbon bond-forming process. Lastly, a potential liability for these two approaches is the generation of a nucleophilic acyl anion equivalent under strongly basic conditions. To increase the effectiveness in natural product synthesis,[26–31] an alternative is desirable to directly form the α-hydroxyketones without the need for strong base, or further unmasking of the carbonyl functionality.

In our investigations aimed at developing new unconventional nucleophiles, we have discovered that the combination of azolium salts and acylsilanes generates unique acyl anion equivalents for additions to electrophiles, including α,β-unsaturated ketones (sila-Stetter reaction) and *N*-diphenylphosphinoyl imines.[32–34] However, use of these N-heterocyclic carbene (NHC) catalysts for cross-acyloin reactions has two major problems which are primarily responsible for the current dearth of solutions to accomplish this transformation: a) rapid and undesired aldol side reactions through deprotonation of the aldehyde and b) self-acyloin reactions (dimerization of aldehyde electrophile) in the presence of a Lewis base catalyst (Scheme 1). While the development of catalytic acyl anion equivalents continues to undergo a resurgence,[35–40] the basic conditions to generate acyl anion equivalents or catalysts in situ



Professor Karl Scheidt received his B.Sc. degree from the University of Notre Dame in 1994 while working in the laboratory of Professor Marvin J. Miller. Under the direction of Professor William R. Roush, Karl earned his Ph.D. from Indiana University in 1999. Following his graduate research, he was a National Institutes of Health Postdoctoral Fellow in the laboratory of Professor David Evans at Harvard University where he developed asymmetric reactions catalyzed by chiral Lewis acids. In 2002, he joined the faculty of Northwestern University where he is currently an Associate Professor and holds the Irving M. Klotz Research Chair in Chemistry. Professor Scheidt's contributions to the areas of carbene catalysis, organosilicon methodology, and total synthesis have been highly recognized by awards from Abbott Laboratories, Amgen, AstraZeneca, Boehringer-Ingelheim, 3M, GlaxoSmithKline and Novartis. He is also the recipient of a National Science Foundation CAREER award, an Alfred P. Sloan Fellowship, an American Cancer Society Scholar Award, and a Distinguished Teaching Award from Northwestern University.

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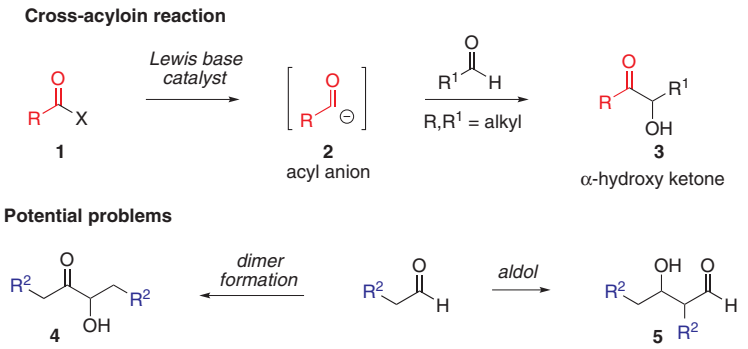
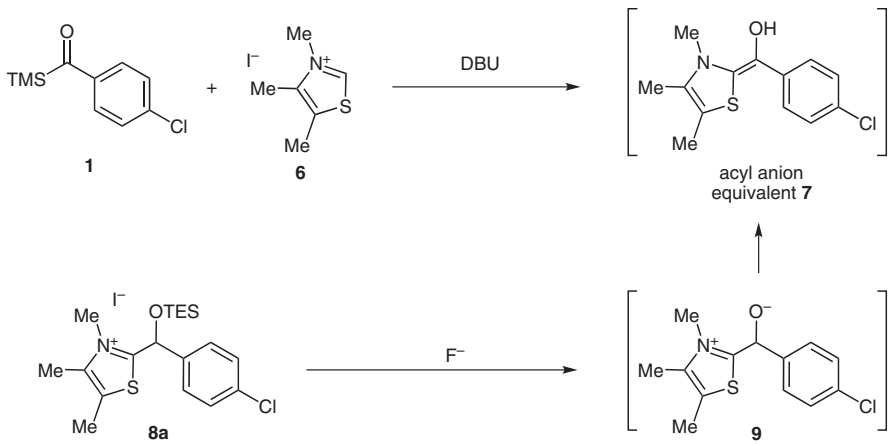


Scheme 1 Cross-acyloin reaction



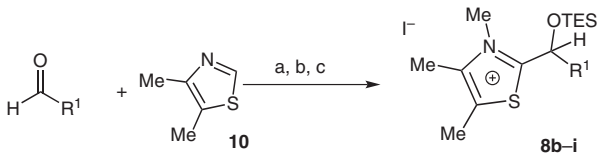
Scheme 2 Azolium and fluoride-induced acyl anion equivalents

(e.g., NHC) have limited new directions that utilize sensitive acceptors, such as enolizable aldehydes.

Our current mechanistic understanding of our NHC-catalyzed Stetter reaction invokes the generation of an acyl anion equivalent **7**, commonly referred to as the 'Breslow intermediate' due to the early work by Breslow on the thiazolium-catalyzed benzoin reaction. Accessing this acyl anion equivalent without the use of an aldehyde is accomplished through interaction of the deprotonated thiazolium salt **6** with an acyl silane (**1**, X = SiR_3, Scheme 2). However, an amine base (typically DBU) is necessary to generate the requisite thiazolium zwitterion/carbene. Our initial attempts to employ an NHC–acylsilane strategy to solve the cross-acyloin challenge proved fruitless due to the anticipated aldol side reaction.

We have developed an alternative strategy to access acyl anion reactivity without the use of amine bases involving fluoride activation of *O*-silyl thiazolium carbinols.[41,42] The desilylation of a carbinol such as **8a**, followed by a formal 1,2-proton shift would presumably generate the acyl anion equivalent **7**. We have used these *O*-silyl thiazolium carbinols in successful direct nucleophilic acylations of nitroalkenes and *o*-quinone methides. Key to the success compared to previous studies is that less-basic conditions are used to promote additions of *O*-silyl thiazolium carbinols.

Table 1 Formation of *O*-Silyl Thiazolium Carbinols

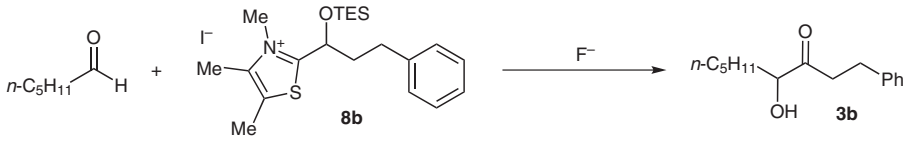


Entry	Carbinol	R^1	Yield (%)
1	**8b**	CH_2CH_2Ph	74
2	**8c**	$(CH_2)_4Me$	48
3	**8d**	$(CH_2)_4OBn$	56
4	**8e**	Me	46
5	**8f**	$CHMe_2$	45
6	**8g**	Cyclohexyl	52
7	**8h**	Cyclopropyl	76
8	**8i**	CH_2CHMe_2	50

[a] *n*-Butyllithium, THF, –78 °C.
[b] TESCl, imidazole, THF, 23 °C.
[c] MeI, reflux.

Formation of *O*-silyl thiazolium carbinols **8b–i** for utilization as acyl anion equivalents can be accomplished in three easy steps from 4,5-dimethylthiazole (**10**) and various aldehydes (Table 1). This method is compatible with

Table 2 Optimization of Acyl Anion Additions to Aldehydes



Entry	Fluoride source	Aldehyde (equiv)	Solvent	Temp (°C)	Yield (%)
1	Me_4NF	2	CH_2Cl_2 (0.2 M)	0 to 23	38
2	Me_4NF	1	CH_2Cl_2 (0.2 M)	0 to 23	27
3	Me_4NF	4	CH_2Cl_2 (0.2 M)	0 to 23	64
4	Me_4NF	4	CH_2Cl_2 (0.2 M)	0 to 23	58[a]
5	Me_4NF	4	CH_2Cl_2 (0.2 M)	23	61
6	CsF	4	CH_2Cl_2 (0.2 M)	23	38
7	CsF	4	DMF (0.2 M)	23	64
8	CsF	4	*i*-PrOH (0.2 M)	23	70
9	Me_4NF	4	*i*-PrOH (0.2 M)	23	48
10	CsF	2	*i*-PrOH (1 M)	23	39
11	CsF	2	*i*-PrOH (0.4 M)	23	52

[a] Three equiv *i*-PrOH added.

straight chain and branched aldehydes as well as aldehydes bearing a benzyl ether (entry 3).[43] These thiazolium salts are crystalline, easily purified (involving one column, a filtration, and a crystallization for the three steps), and bench-top stable.

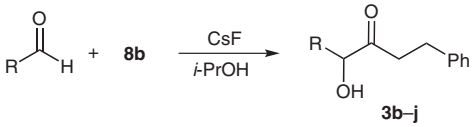
With a collection of *O*-silyl carbinols in hand, we began a survey with the addition of the hydrocinnamaldehyde-derived carbinol **8b** to hexanal (Table 2). Use of tetramethylammonium fluoride (Me_4NF) at 0 °C to generate the acyl anion equivalent resulted in addition in 38% yield (entry 1). Altering the equivalents of aldehyde, however, increased the yield to 64% (entry 3). The major byproduct in these reactions was the dimerization that results from the liberated thiazolium carbene interacting with the aldehyde in solution under the thiazolium-catalyzed self-acyloin reaction.

In addition to Me_4NF, several other fluoride sources were examined. Tetrabutylammonium fluoride (TBAF) produced similar results as with Me_4NF. Copper fluoride, indium fluoride, and magnesium fluoride promoted only the aldol condensation of the aldehyde, producing none of the desired hydroxy ketone. Cesium fluoride as the desilylating reagent was successful in producing the desired product and showed a low amount of observed dimer (**4**, Scheme 1) and no aldol product **5**. However, diminished yields in dichloromethane were observed (entry 6). It was noted that the solubility of CsF was poor in dichloromethane, thereby prompting a change of solvent to DMF (entry 7). Further examination of the solvent choice was then considered. Due to the limited solubility of the carbinol in THF, diethyl ether, and benzene, additional solvents were examined. In our previously published NHC-catalyzed additions to chalcone, the addition of isopropanol increased the yield of the reaction, and we were inspired to investigate this additive as the actual solvent. Hence, we discovered that CsF as well as the carbinol are soluble in isopropanol. The combination of isopropanol as solvent with the Me_4NF conditions, however, had little effect on the overall yield of the reaction (entry 4). Upon submission of the carbinol to cesium fluoride in isopropanol, a 70% yield was observed (entry 8). Further attempts to increase concentration and vary reaction temperatures produced inferior yields. Moreover, the use of other alcohols (such as *tert*-amyl alcohol and methanol) as well as water affords little or no desired addition products, and many decomposition products are observed. Prolonged exposure of the silyl-protected carbinol to isopropanol also results in decomposition. Due to this degradation process, the immediate addition of the cesium fluoride showed slight increases in yield.

To expand the scope of this addition, several aldehyde acceptors were examined (Table 3). Initial experiments with aldehydes lacking α-substitution resulted in good to high yield, with the addition to the β-branched isovaleraldehyde producing 77% of the desired compound (entry 3). Additions to α-branched aldehydes such as cyclohexanecarboxaldehyde, isobutyraldehyde, and cyclopropylcarboxaldehyde (entries 4–6) resulted in moderate to good yields in 41%, 49%, and 71%, respectively. Interestingly, additions to O-protected 4-hydroxyaldehydes afford good yielding additions with benzyl and benzoyl protection

(entries 7 and 8), as well as selective desilylation of the TES group over a TIPS-protected alcohol (entry 9).

Table 3 Fluoride-Promoted Additions to Aldehydes

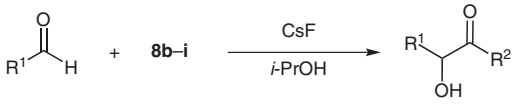


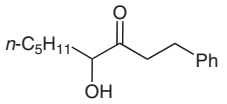
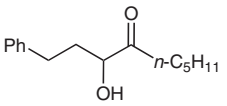
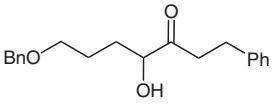
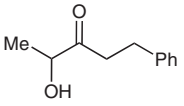
Entry	R	Yield (%)
1	$(CH_2)_4Me$	70
2	Me	80
3	CH_2CHMe_2	77
4	Cyclohexol	41
5	$CHMe_2$	49
6	Cyclopropyl	71
7	$(CH_2)_3OBz$	70
8	$(CH_2)_3OBn$	67
9	$(CH_2)_3OTIPS$	72

Variations of the carbinol were also explored (Table 4). Addition of carbinol **8c** to hydrocinnamaldehyde (**3k**) successfully produced the regioisomer of the addition of **8b** to hexanal (**3b**). With this result, regioselective syntheses of α-hydroxyketones can be imagined. Other additions of unbranched *O*-silyl carbinols **8d** and **8e** produced similar results with good additions to hexanal.

Our proposed reaction pathway is shown in Scheme 3 and begins with the desilylation promoted by cesium fluoride (**I**). A formal 1,2-proton shift results in formation of the Breslow intermediate (**III**), which is the reactive acyl anion equivalent.[44,45] Recent MP2/6-31+G(d,p) level calculations by Gronert[46] explored the possibility of a

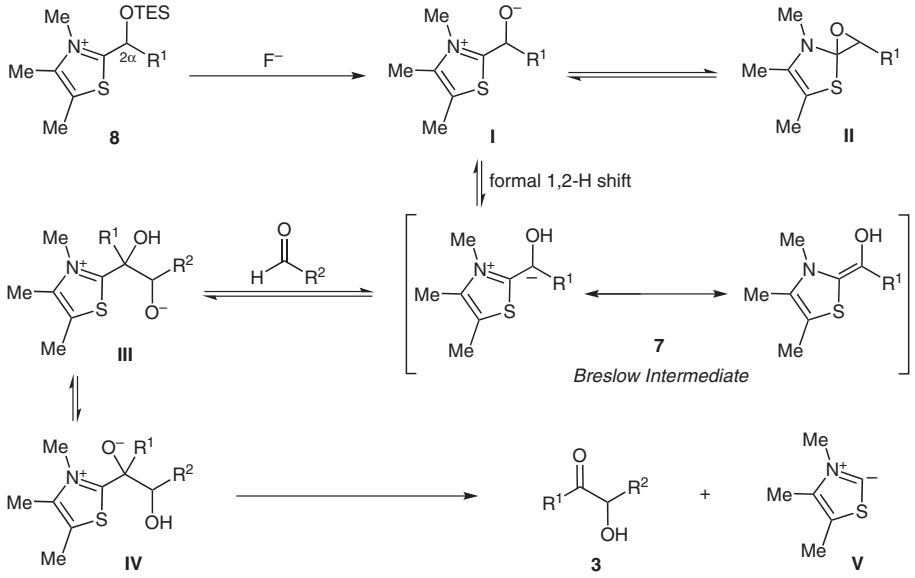
Table 4 Survey of Silyl-Protected Carbinols



Entry	Carbinol	Product	Yield (%)
1	**8a**	 **3b**	70
2	**8c**	 **3k**	62
3	**8d**	 **3l**	49
4	**8e**	 **3m**	56

spiroepoxide intermediate arising from cyclization of the alkoxide anion onto the thiazolium ring (**II**). It is interesting to note that the presence of the isopropanol does not hinder the reaction of aliphatic carbinols, but produces no product with aryl carbinols.[47–50] A possible explanation is that protic solvents further stabilize the intermediates (**I** and **II**), thereby minimizing possible elimination of the carbene to form the aldehyde.

Upon formation of the acyl anion equivalent **7**, addition to the aldehyde (**III**), a proton shift (**IV**), and subsequent elimination of the thiazolium carbene (**V**) completes the



Scheme 3 Proposed reaction pathway

synthesis of the α-hydroxy ketones **3**. Further reactions of the generated thiazolium carbene (**V**) can occur with aldehyde in solution producing the self-acyloin product. Isopropanol as the solvent seems to reduce this side reaction.

In summary, cross-acyloin reactions have been accomplished employing *O*-silyl thiazolium carbinols and aliphatic aldehydes. Due to the relatively mild reaction conditions compared to other catalytic conditions, side reactions have been minimized. A variety of branched and unbranched aldehydes as well as *O*-silyl thiazolium carbinols have been explored, showing compatibility with several different O-protecting groups. This process is an important addition to the synthetic methods available for Umpolung transformations.

The ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian Inova 500 (operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C), or a Mercury 400 (operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C). The FT-IR spectra were obtained on a Perkin Elmer 1600 series FT-IR. Mass spectra data were obtained on a Varian 1200 Quadrupole Mass Spectrometer. Laser desorption mass spectra were obtained with PE BioSystems time-of-flight MALDI mass spectrometer with 2,5-dihydroxybenzoic acid as matrix.

Typical Procedure for Formation of *O*-Silyl Thiazolium Carbinols (8)

To a –78 °C solution of 4,5-dimethylthiazole (1.0 mL, 9.5 mmol) in THF (50 mL) was added a 1.4 M solution of *n*-BuLi (7 mL, 9.45 mmol). After 1 h, hydrocinnamaldehyde (3.7 mL, 28 mmol) was slowly added to the reaction flask and the mixture warmed to 23 °C. After 4 h, the reaction was quenched with H_2O (50 mL) and extracted with Et_2O (3 × 25 mL). The organic layers were combined, dried over anhyd Na_2SO_4, and then concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 5% to 30% Et_2O–hexane) to produce 2.264 g (91%) of a yellow oil. To the thiazole product (1.057 g, 4.03 mmol) and imidazole (330 mg, 4.84 mmol) in THF (40 mL) was added triethylchlorosilane (1.1 mL, 6.1 mmol). After 4 h, the reaction was diluted with Et_2O (50 mL) and washed with sat. aq $NaHCO_3$ (2 × 25 mL) and brine (25 mL). The organic layer was dried over anhyd Na_2SO_4 then concentrated in vacuo. The residue oil was dissolved in MeI (5 mL) and heated at reflux for 16 h. The reaction was cooled and the excess MeI removed in vacuo. Diethyl ether (25 mL) was added to the unpurified oil and stirred 1 h producing a solid. Filtration afforded 1.635 g (81%) of a yellow solid (**8b**).

3,4,5-Trimethyl-2-[3-phenyl-1-(triethylsilyloxy)propyl]thiazole-3-ium Iodide (8b)

Isolated in 74% yield over three steps as a pale yellow solid; mp 138–139.5 °C. IR (film): 2954, 2885, 1604, 1454, 1100, 734 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.14 (m, 5 H), 5.76 (dd, *J* = 4.4, 4.4 Hz, 1 H), 4.09 (s, 3 H), 2.92–2.86 (m, 1 H), 2.76–2.70 (m, 1 H), 2.43 (s, 3 H), 2.41 (s, 3 H), 2.38–2.32 (m, 2 H), 1.00 (t, *J* = 7.8 Hz, 9 H), 0.78 (q, *J* = 7.8 Hz, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.0, 143.6, 139.9, 130.0, 128.5, 128.4, 126.2, 70.0, 40.9, 38.0, 29.3, 13.2, 12.5, 6.9, 4.9. LRMS (MALDI-TOF): m/z calcd for $C_{21}H_{34}NOSSi$ [M]$^+$: 376.2; found: 377.0.

3,4,5-Trimethyl-2-[1-(triethylsilyloxy)hexyl]thiazol-3-ium Iodide (8c)

Isolated in 48% yield over three steps as a white solid; mp 106–107 °C. IR (film): 2951, 1606, 1458, 1241, 1092, 1009 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.55 (t, *J* = 5.5 Hz, 1 H), 4.25 (s, 3 H), 2.60 (s, 3 H), 2.50 (s, 3 H), 1.96–1.87 (m, 2 H), 1.51–1.50 (m, 2 H), 1.30–1.26 (m, 4 H), 0.97 (t, *J* = 7.6 Hz, 9 H), 0.88 (m, 3 H), 0.72 (q, *J* = 7.6 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.3, 143.9, 130.2, 70.8, 41.1, 37.1, 31.4, 23.8, 22.6, 14.1, 13.8, 13.1, 6.9, 4.9. LRMS (MALDI-TOF): *m/z* calcd for $C_{18}H_{36}NOSSi$ [M]$^+$: 342.2; found: 342.7.

2-[4-(Benzyloxy)-1-(triethylsilyloxy)butyl]-3,4,5-trimethylthiazol-3-ium Iodide (8d)

Isolated in 56% yield over three steps as a yellow oil. IR (film): 2953, 1713, 1603, 1097 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.18 (m, 5 H), 5.58 (t, *J* = 5.4 Hz, 1 H), 4.38 (s, 2 H), 4.05 (s, 3 H), 3.46 (t, *J* = 6.3 Hz, 2 H), 2.41 (s, 3 H), 2.40 (s, 3 H), 2.07–1.99 (m, 1 H), 1.95–1.88 (m, 1 H), 1.79–1.73 (m, 1 H), 1.55–1.49 (m, 1 H), 0.86 (t, *J* = 7.8 Hz, 9 H), 0.62 (q, *J* = 7.8 Hz, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.6, 143.3, 137.8, 129.8, 128.0, 127.5, 127.3, 72.8, 70.1, 69.4, 40.2, 33.9, 23.6, 13.1, 12.5, 6.4, 4.4. LRMS (MALDI-TOF): *m/z* calcd for $C_{23}H_{38}NO_2SSi$ [M]$^+$: 420.2; found: 421.4.

3,4,5-Trimethyl-2-[1-(triethylsilyloxy)ethyl])thiazol-3-ium Iodide (8e)

Isolated in 46% yield over three steps as a pale yellow solid; mp 115–115.5 °C. IR (film): 2955, 2877, 1607, 1109, 1016, 745 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.67 (d, *J* = 6.4 Hz, 1 H), 4.25 (s, 3 H), 2.57 (s, 3 H), 2.49 (s, 3 H), 1.72 (d, *J* = 6.4 Hz, 3 H), 0.99 (t, *J* = 7.8 Hz, 9 H), 0.74 (q, *J* = 7.8 Hz, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.0, 143.7, 129.9, 67.3, 40.8, 24.4, 13.4, 12.6, 6.8, 4.8. LRMS (MALDI-TOF): *m/z* calcd for $C_{14}H_{28}NOSSi$ [M]$^+$: 286.2: found: 287.0.

3,4,5-Trimethyl-2-[2-methyl-1-(triethylsilyloxy)propyl]thiazol-3-ium Iodide (8f)

Isolated in 45% yield over three steps as a white solid; mp 159–160 °C. IR (film): 2959, 2875, 1609, 1463, 1058, 799, 733 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.32 (d, *J* = 2.9 Hz, 1 H), 4.28 (s, 3 H), 2.63 (s, 3 H), 2.51 (s, 3 H), 2.28–2.26 (m, 1 H), 1.15 (d, *J* = 6.8 Hz, 3 H), 0.97 (t, *J* = 8.3 Hz, 9 H), 0.89 (d, *J* = 6.3 Hz, 3 H), 0.72 (q, *J* = 7.8 Hz, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.0, 144.0, 130.3, 75.2, 41.6, 34.2, 20.2, 15.8, 14.0, 13.1, 7.1, 5.1. LRMS (MALDI-TOF): *m/z* calcd for $C_{16}H_{32}NOSSi$ [M]$^+$: 314.2; found: 315.3.

2-[Cyclohexyl(triethylsilyloxy)methyl]-3,4,5-trimethylthiazol-3-ium Iodide (8g)

Isolated in 52% over three steps as a pale yellow solid; mp 158–159 °C. IR (film): 2928, 2870, 1605, 1450, 1110, 1008 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.25 (d, *J* = 3.7 Hz, 1 H), 4.28 (s, 3 H), 2.63 (s, 3 H), 2.50 (s, 3 H), 1.88–1.01 (m, 1 H), 0.97 (t, *J* = 7.9 Hz, 9 H), 0.70 (q, *J* = 7.9 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.4, 144.1, 130.3, 75.0, 43.8, 41.5, 30.1, 26.1, 25.9, 25.7, 14.0, 13.1, 7.1, 5.0. LRMS (MALDI-TOF): *m*/z calcd for $C_{19}H_{36}NOSSi$ [M]$^+$: 354.2; found: 354.9.

2-[Cyclopropyl(triethylsilyloxy)methyl]-3,4,5-trimethylthiazol-3-ium Iodide (8h)

Isolated in 78% yield over three steps as a pale yellow solid; mp 110–111 °C. IR (film): 2955, 2877, 1605, 1458, 1072, 734 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.26 (d, *J* = 6.8 Hz, 1 H), 4.26 (s, 3 H), 2.57 (s, 3 H), 2.51 (s, 3 H), 1.41–1.38 (m, 1 H), 0.95 (t, *J* = 7.8 Hz, 9 H), 0.92 (m, 1 H), 0.78 (m, 1 H), 0.71 (q, *J* = 7.8 Hz, 6 H), 0.62 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 176.0, 143.8, 130.2, 71.8, 41.6, 17.2, 13.7, 13.0, 7.1, 5.3, 4.7, 4.5. LRMS (MALDI-TOF): *m*/z calcd for $C_{16}H_{30}NOSSi$ [M]$^+$: 312.2; found: 313.0.

3,4,5-Trimethyl-2-[3-methyl-1-(triethylsilyloxy)butyl]thiazol-3-ium Iodide (8i)
Isolated in 50% yield over three steps as a pale yellow solid; mp 143–144 °C. IR (film): 2956, 2876, 1607, 1462, 1096, 1004, 748 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.44 (dd, *J* = 6.8, 4.4 Hz, 1 H), 4.23 (s, 3 H), 2.62 (s, 3 H), 2.51 (s, 3 H), 1.87–1.76 (m, 3 H), 1.05 (d, *J* = 6.3 Hz, 3 H), 0.97 (t, *J* = 5.9 Hz, 9 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 0.73 (q, *J* = 5.9 Hz, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.5, 144.2, 130.2, 69.8, 47.0, 41.0, 24.5, 23.7, 22.2, 14.0, 13.1, 7.05, 5.10. LRMS (MALDI-TOF): *m*/z calcd for $C_{17}H_{34}NOSSi$ $[M]^+$: 328.2; found: 328.8.

Typical Procedure for Cesium Fluoride Activated Addition of Silylcarbinols to Aldehydes
To a flask charged with carbinol **8b** (117 mg, 0.233 mmol) was added hexanal (112 mL, 0.932 mmol) in 2-PrOH (1.1 mL). Immediately, CsF (53 mg, 0.35 mmol) was added to the reaction flask and the mixture stirred. After 16 h, 1 mL of water was added. After 1 h, CH_2Cl_2 (10 mL) was added and the layers separated. The aqueous phase was washed with CH_2Cl_2 (2 × 10 mL) and the combined organic layers washed with brine (25 mL). The solution was dried and concentrated. Flash chromatography (5% to 25% Et_2O–hexane) afforded 38 mg (70%) of a yellow oil (**3b**).

4-Hydroxy-1-phenylnonan-3-one (3b)
Isolated in 70% yield as a pale clear oil. IR (film): 3480, 2927, 2857, 1712, 1454, 1081 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.31–7.18 (m, 5 H), 4.14 (dd, *J* = 7.0, 3.5 Hz, 1 H), 3.43 (d, *J* = 4.9 Hz, 1 H), 2.99–2.93 (m, 2 H), 2.86–2.74 (m, 2 H), 1.79–1.75 (m, 1 H), 1.52–1.41 (m, 3 H), 1.29–1.22 (m, 4 H), 0.88 (t, *J* = 6.8 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 211.4, 140.5, 128.5, 128.3, 126.3, 76.5, 39.6, 33.5, 31.6, 29.5, 24.4, 22.4, 13.9. LRMS (ES): *m*/z calcd for $C_{15}H_{22}O_2$ $[M + 23]^+$: 257.2; found: 257.6.

4-Hydroxy-1-phenylpentan-3-one (3c)
Isolated in 77% yield as a clear oil. IR (film): 3479 (br), 2955, 2927, 1711, 1080 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.14 (m, 5 H), 4.15 (dd, *J* = 10.2, 10.2 Hz, 1 H), 3.37 (s, 1 H), 3.02–2.94 (m, 2 H), 2.92–2.72 (m, 2 H), 1.94–1.88 (m, 1 H), 1.50–1.46 (m, 1 H), 1.45–1.36 (m, 1 H), 0.97 (d, *J* = 6.4 Hz, 3 H), 0.94 (d, *J* = 6.7 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 211.8, 140.5, 128.6, 128.8, 126.4, 75.3, 42.7, 39.6, 29.6, 24.7, 23.6, 21.2. LRMS (ES): *m*/z calcd for $C_{14}H_{20}O_2$ $[2 M + Na]^+$: 463.3; found: 463.5.

1-Cyclohexyl-1-hydroxy-4-phenylbutan-2-one (3e)
Isolated in 41% yield as a clear oil. IR (film): 3470 (br), 2927, 2851, 1715, 1455, 1084 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.15 (m, 5 H), 3.97 (ap s, 1 H), 3.23 (ap s, 1 H), 2.95–2.90 (m, 2 H), 2.81–2.72 (m, 2 H), 1.77–0.85 (m, 11 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.3, 140.5, 128.6, 128.3, 126.3, 80.9, 41.2, 39.9, 30.1, 29.5, 26.5, 26.0, 25.8, 25.0. LRMS (ES): *m*/z calcd for $C_{16}H_{22}O_2$ $[2 M + Na]^+$: 515.3; found: 516.0.

4-Hydroxy-5-methyl-1-phenylhexan-3-one (3f)
Isolated in 49% yield as a clear oil. IR (film): 3476 (br), 2962, 2924, 1709, 1455, 1026 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.15 (m, 5 H), 4.05 (dd, *J* = 4.9, 2.4 Hz, 1 H), 3.36 (d, *J* = 4.9 Hz, 1 H), 3.00–2.96 (m, 2 H), 2.84–2.76 (m, 2 H), 2.19–2.21 (m, 1 H), 1.11 (d, *J* = 6.8 Hz, 3 H), 0.68 (d, *J* = 2.8 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 211.2, 140.4, 128.5, 128.3, 126.4, 80.8, 39.8, 31.2, 29.4, 20.0, 14.6. LRMS (ES): *m*/z calcd for $C_{13}H_{18}O_2$ $[M]^+$: 206.1; found: 206.2.

1-Cyclopropyl-1-hydroxy-4-phenylbutan-2-one (3g)
Isolated in 71% yield as a clear oil. IR (film): 3475 (br), 2922, 2850, 1712, 1602, 1453, 1028, 749, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.21 (m, 5 H), 3.62 (dd, *J* = 7.6, 4.9 Hz, 1 H), 3.50 (d, *J* = 4.6 Hz, 1 H), 3.21–2.98 (m, 3 H), 2.86–2.81 (m, 1 H), 0.93–0.89 (m, 1 H), 0.64–0.55 (m, 3 H), 0.46–0.43 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.5, 140.6, 128.6, 128.3, 126.3, 78.9, 39.9, 29.5, 14.3, 2.9, 2.1. LRMS (ES): *m/z* calcd for $C_{13}H_{16}O_2$ $[2 M + 23]^+$: 431.2; found: 431.8.

4-Hydroxy-5-oxo-7-phenylheptyl Benzoate (3h)[51]
Isolated in 70% yield as a clear oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 7.3 Hz, 1 H), 7.58 (t, *J* = 7.6 Hz, 1 H), 7.45 (t, *J* = 7.9 Hz, 2 H), 7.38–7.06 (m, 5 H), 4.38–4.29 (m, 2 H), 4.22 (dd, *J* = 7.6, 2.1 Hz, 1 H), 3.00–2.72 (m, 4 H), 2.00–1.60 (m, 4 H), LRMS (ES): *m/z* calcd for $C_{20}H_{22}O_4$ $[2 M + Na]^+$: 675.3; found: 675.4.

7-(Benzyloxy)-4-hydroxy-1-phenylheptan-3-one (3i)
Isolated in 67% yield as a clear oil. IR (film): 3448 (br), 2925, 2857, 1712, 1450, 1093, 739, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.12 (m, 10 H), 4.51 (s, 2 H), 4.15 (dd, *J* = 7.3, 3.9 Hz, 1 H), 3.64 (brs, 1 H), 3.54–3.49 (m, 2 H), 2.98–2.93 (m, 2 H), 2.88–2.75 (m, 2 H), 2.00–1.89 (m, 1 H), 1.81–1.57 (m, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 211.8, 140.8, 138.5, 128.8, 128.7, 128.6, 127.9, 127.9, 126.6, 76.6, 73.2, 69.9, 39.9, 30.8, 29.8, 25.4. LRMS (ES): *m*/z calcd for $C_{20}H_{24}O_3$ $[M + Na]^+$: 335.2; found: 335.9.

4-Hydroxy-1-phenyl-7-(triisopropylsilyloxy)heptan-3-one (3j)
Isolated in 72% yield as a clear oil. IR (film): 3484 (br), 2943, 2866, 1712, 1604. 1458, 1103, 883, 682 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.31–7.19 (m, 5 H), 4.19 (dd, *J* = 7.3, 3.2 Hz, 1 H), 3.76–3.69 (m, 3 H), 2.98–2.77 (m, 4 H), 2.00–1.95 (m, 1 H), 1.72–1.53 (m, 3 H), 1.09–0.88 (m, 21 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 211.8, 140.6, 128.5, 128.4, 126.4, 76.5, 62.8, 39.5, 30.4, 29.5, 28.2, 18.0, 11.9. LRMS (ES): *m*/z calcd for $C_{22}H_{38}O_3Si$ $[2 M + 23]^+$: 779.5; found: 779.8.

3-Hydroxy-1-phenylnonan-4-one (3k)
Isolated in 62% yield as a clear oil. IR (film): 3468 (br), 2928, 2859, 1712, 1602, 1454, 1072, 700 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.33–7.20 (m, 5 H), 4.17 (dd, *J* = 8.3, 4.4 Hz, 1 H), 3.61 (d, *J* = 4.9 Hz, 1 H), 2.84–2.72 (m, 2 H), 2.49–2.37 (m, 2 H), 2.19–2.12 (m, 1 H), 1.86–1.79 (m, 1 H), 1.64–1.58 (m, 2 H), 1.35–1.24 (m, 4 H), 0.90 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 212.3, 141.1, 128.6, 128.5, 126.1, 75.6, 37.8, 35.6, 31.3, 31.2, 23.3, 22.4, 13.8. LRMS (ES): *m*/z calcd for $C_{15}H_{22}O_2$ $[2 M + Na]^+$: 491.3; found: 491.9.

1-(Benzyloxy)-5-hydroxydecan-4-one (3l)
Isolated in 49% yield as a clear oil. IR (film): 3479 (br), 2929, 2858, 1715, 1455, 1361, 1100 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.39–7.29 (m, 5 H), 4.49 (s, 2 H), 4.18–4.17 (m, 1 H), 3.51 (t, *J* = 5.9 Hz, 2 H), 3.46 (d, *J* = 3.4 Hz, 1 H), 2.66–2.53 (m, 2 H), 1.99–1.94 (m, 2 H), 1.85–1.80 (m, 1 H), 1.65–1.42 (m, 3 H), 1.40–1.21 (m, 4 H), 0.90 (t, *J* = 6.4 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 212.2, 138.2, 128.4, 127.7, 127.6, 76.5, 72.9, 67.0, 34.5, 33.7, 31.6, 24.5, 23.8, 22.5, 14.0. LRMS (ES): *m*/z calcd for $C_{17}H_{26}O_3$ $[2 M + Na]^+$: 579.4; found: 579.9.

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