Organozinc-promoted ring opening of cyclopropanols

Pragna Pratic Das, Bibhuti Bhusan Parida and Jin Kun Cha*

Department of Chemistry, Wayne State University, 5101 Cass Ave, Detroit, Michigan 48202
E-mail: jcha@chem.wayne.edu

Dedicated to Professor Anthony J. Arduengo, III on the occasion of his 60th birthday

Abstract
Regioselective ring opening of cyclopropanols by the use of organozinc reagents or ZnI_2 is presented. Mechanistic studies are discussed with respect to the possible involvement of zinc ketone homoenolates.

Keywords: Cyclopropanol, ring opening, organozinc, homoenolate

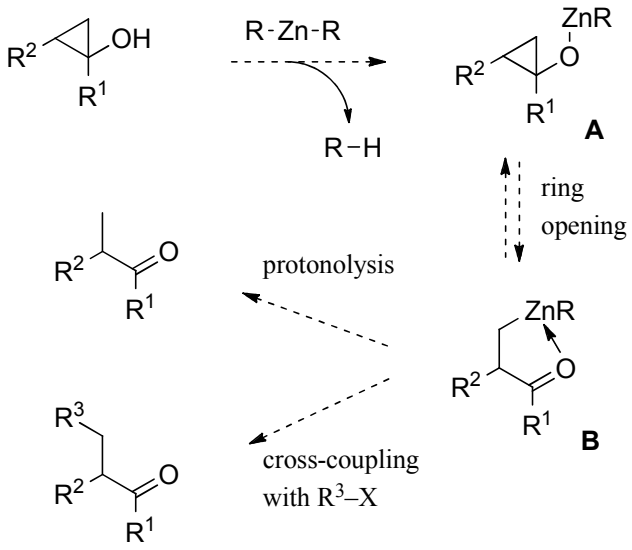
Introduction

Cyclopropanes are useful building blocks in organic synthesis.[1] A number of ring opening and expansion reactions of cyclopropanes are available by taking advantage of release of ring strain. Incorporation of electron-donating and/or withdrawing groups not only activates cyclopropanes toward ring scission, but also provides useful functionalities for subsequent elaboration.[2] Cyclopropanols are most frequently utilized among heteroatom-substituted cyclopropanes and are easily prepared by several reliable methods including the Kulinkovich cyclopropanation of esters.[3,4] Ring opening of cyclopropanols can be induced by electrophiles, such as Brönsted acid, halogens, oxocarbenium ions, and transition- or non-transition-metal salts, in addition to strong base.[3] Conspicuously absent is the use of organozinc reagents for ring opening of cyclopropanols,[5] except for one unusual rearrangement of hydroxyl-substituted cyclopropanols.[6] As part of research programs on synthetic applications of the Kulinkovich reagent,[7] we report herein regioselective ring opening of cyclopropanols promoted by organozinc reagents for the preparation of α-methyl substituted ketones.

Results and Discussion

We were intrigued by the possibility of preparing functionalized zinc homoenolates from ring opening of cyclopropanols triggered by sacrificial dialkylzinc reagents (Scheme 1). Treatment of a cyclopropanol with a dialkylzinc reagent could provide the corresponding zinc alkoxide **A** and

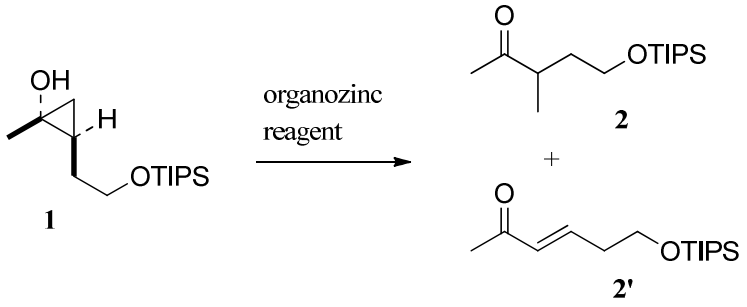
the alkane by-product (R–H) by analogy with a widely accepted mechanism of the Simmons-Smith cyclopropanation of allylic alcohols.[8] Initial formation of the zinc alkoxide **A** could be accompanied by ring opening to generate a zinc homoenolate **B**. However, little was known about zinc homoenolates of ketones in sharp contrast to those of esters and amide derivatives. We were particularly concerned about the known propensity of metal homoenolates to cyclize to the corresponding cyclopropoxides, which would become more pronounced for electrophilic ketones.[9] Matsubara's attractive synthesis of cyclopropanols by the action of $CH_2(ZnI)_2$ was supportive of facile cyclization of **B** to **A**.[10] Nonetheless, we thought that a suitable method could be devised to drive the otherwise unfavorable equilibrium. It would also be useful to gain information about the stability and reactivity of zinc ketone homoenolates.



Scheme 1. A working hypothesis on organozinc-mediated ring opening of cyclopropanols.

Toward ring scission of cyclopropanol **1**, we surveyed several common organozinc reagents that were prepared according to known methods (Table 1).[11-13] Treatment of **1** with a THF solution of EtZnI at reflux resulted in clean ring opening to afford **2** in 72% yield (entry 1). Not surprisingly, methylene chloride was unsuitable as solvent due to the limited solubility of EtZnI (entry 2). Furukawa's modification, $EtZnCH_2I$ (prepared from CH_2I_2 + Et_2Zn), was also effective for the preparation of **2** (entries 3 and 4), whereas high temperature was necessary (Cf. entry 5).[14] Ring opening proceeded smoothly with *gem*-dizinc $CH_2(ZnI)_2$ (entries 6 and 7). Interestingly, the use of $Zn(CH_2I)_2$ delivered a mixture of both regioisomers **2** and **2'** (entry 8). Diethylzinc also induced ring opening to provide **2**, but the reaction was sluggish and suffered from low conversion (entry 9). Finally, the formation of **2** was also possible by the action of ZnI_2, albeit in low conversion even after longer reaction times.

Table 1. Organozinc-mediated ring opening of cyclopropanol **1**

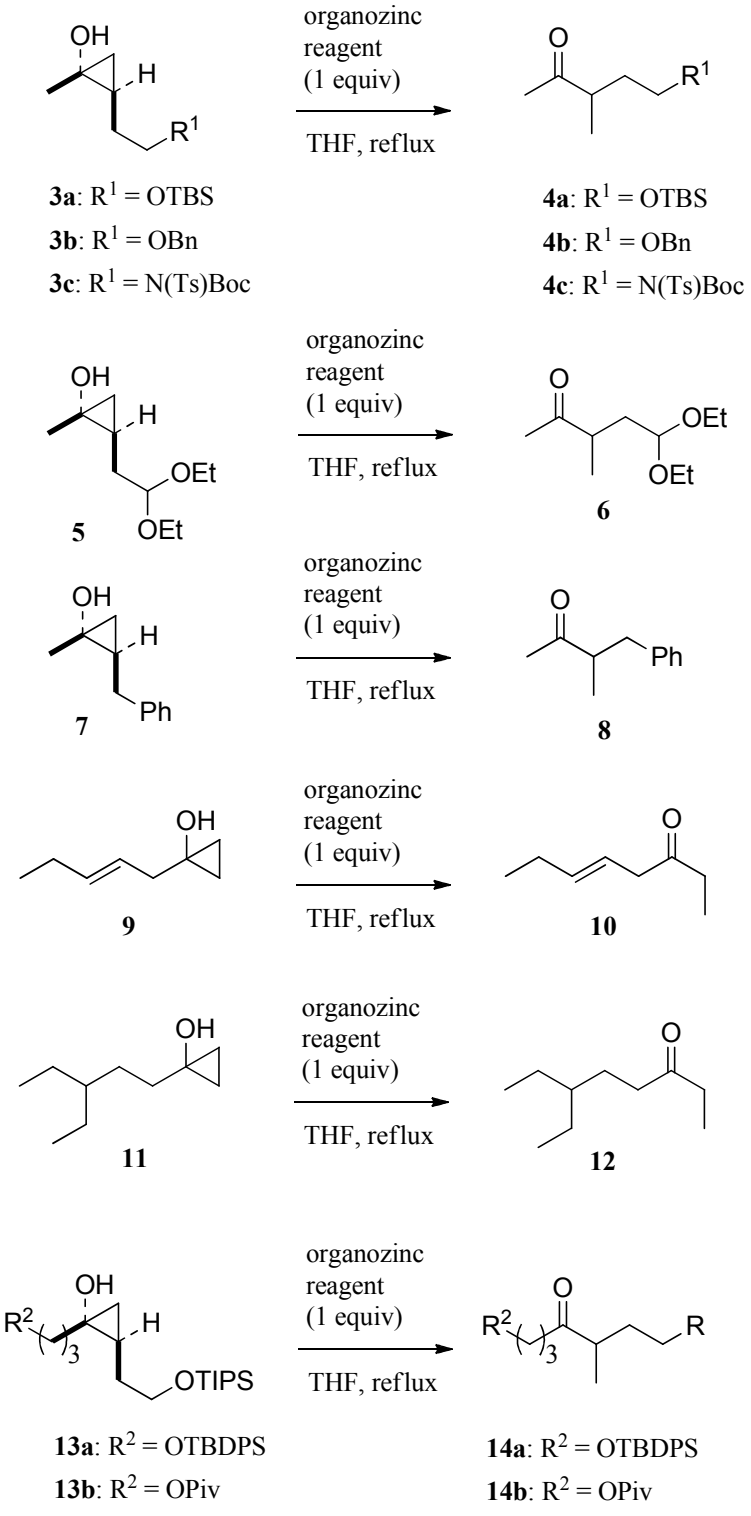


Entry	Organozinc	Conditions[a]	Product yields (%)
1	EtZnI (1 equiv)[c]	reflux, 8 h	**2** (72)
2	EtZnI (1 equiv)[c]	CH_2Cl_2[b] reflux, 3 h	**2** (30) (72 brsm)[h]
3	$EtZnCH_2I$ (1 equiv)[d]	reflux, 8 h	**2** (70)
4	$EtZnCH_2I$ (2 equiv)[d]	reflux, 3 h	**2** (82)
5	$EtZnCH_2I$ (2 equiv)[d]	rt, 24 h	**2** (10)
6	$CH_2(ZnI)_2$ (1 equiv)[e]	reflux, 6 h	**2** (69)
7	$CH_2(ZnI)_2$ (2 equiv)[e]	reflux, 6 h	**2** (65)
8	$Zn(CH_2I)_2$ (1 equiv)[f]	reflux, 8 h	**2** (30) + **2'**(25)
9	Et_2Zn (1 equiv)	reflux, 8 h	**2** (32) (76 brsm)[h]
10	ZnI_2 (1 equiv)[g]	reflux, 2 d	**2** (42) (72 brsm)[h]
11	ZnI_2 (2 equiv)[g]	reflux, 1d	**2** (45) (73 brsm)[h]

[a]THF was employed as solvent, except for entry 2. [b]CH_2Cl_2 was employed as solvent for entry 2. [c]Prepared from Et_2Zn (1 equiv) + I_2 (1 equiv). [d]Prepared from Et_2Zn (1 equiv) + CH_2I_2 (1 equiv). [e]Prepared from Zn (2 equiv) + CH_2I_2 (1 equiv). [f]Prepared from Et_2Zn (1 equiv) + CH_2I_2 (2 equiv). [g]Prepared from Et_2Zn (1 equiv) + I_2 (2 equiv). [h]brsm: based on recovered SM.

We next examined the generality of this ring scission procedure by employing $EtZnCH_2I$, $CH_2(ZnI)_2$, or Et_2Zn (Table 2): two zinc carbenoid reagents were equally effective for opening of cyclopropanols bearing a range of common functional groups. Ring opening was found to be complete in 3 h, and it was thus unnecessary to keep the reaction at reflux overnight. As was the case for ring opening of **1**, low conversion was observed when Et_2Zn was employed (entries 3, 6, 13, and 16). Ring opening of **9** and **11** was markedly faster than other more substituted cyclopropanols. When the reaction was quenched in 15 min, **10** was obtained in 61% yield, free from double bond isomerization (entry 14).

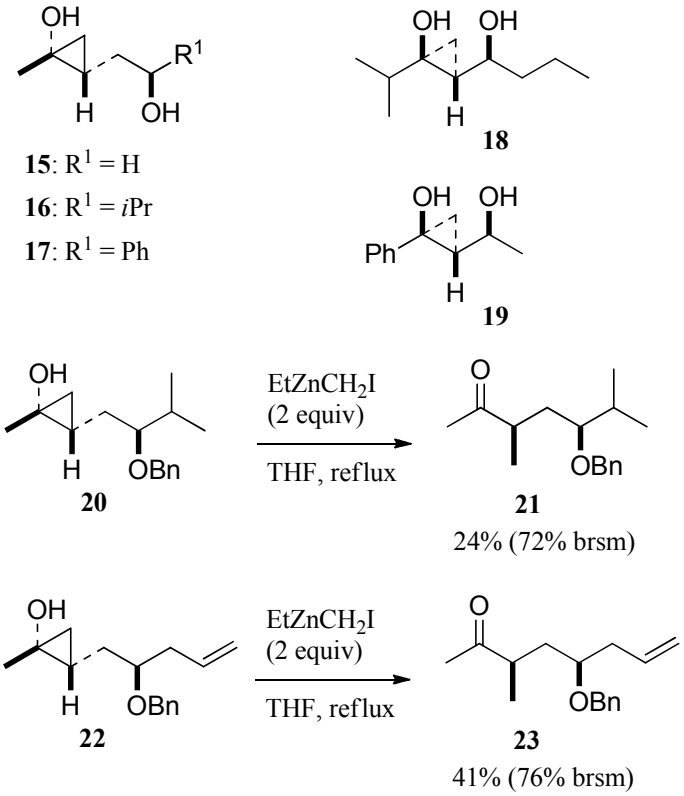
Table 2. Additi onal ring opening examples



Entry	SM	Organozinc	Time (h)	Yield (%)
1	**3a**	$EtZnCH_2I$	3	**4a** (71)
2	**3a**	$CH_2(ZnI)_2$	3	**4a** (75)
3	**3a**	Et_2Zn	12	**4a** (42)[a]
4	**3b**	$EtZnCH_2I$	3	**4b** (81)
5	**3b**	$CH_2(ZnI)_2$	3	**4b** (71)
6	**3b**	Et_2Zn	12	**4b** (45)[a]
7	**3c**	$EtZnCH_2I$	3	**4c** (68)
8	**3c**	$CH_2(ZnI)_2$	3	**4c** (68)
9	**5**	$EtZnCH_2I$	3	**6** (55)
10	**5**	$CH_2(ZnI)_2$	3	**6** (58)
11	**7**	$EtZnCH_2I$	3	**8** (69)
12	**7**	$CH_2(ZnI)_2$	3	**8** (62)
13	**7**	Et_2Zn	8	**8** (40)[a]
14	**9**	$EtZnCH_2I$	15 min[b]	**10** (61)
15	**11**	$CH_2(ZnI)_2$	3	**12** (68)
16	**11**	Et_2Zn	12	**12** (36)[a]
17	**13a**	$EtZnCH_2I$	3	**14a** (76)
18	**13a**	$CH_2(ZnI)_2$	3	**14a** (72)
19	**13b**	$EtZnCH_2I$	3	**14a** (75)
20	**13b**	$CH_2(ZnI)_2$	3	**14a** (73)

[a]In ring opening reactions with Et_2Zn, the starting cyclo -propanol was recovered unreacted in 17–21% yields. [b]A short reaction time was necessary to avoid formation of a complex mixture.

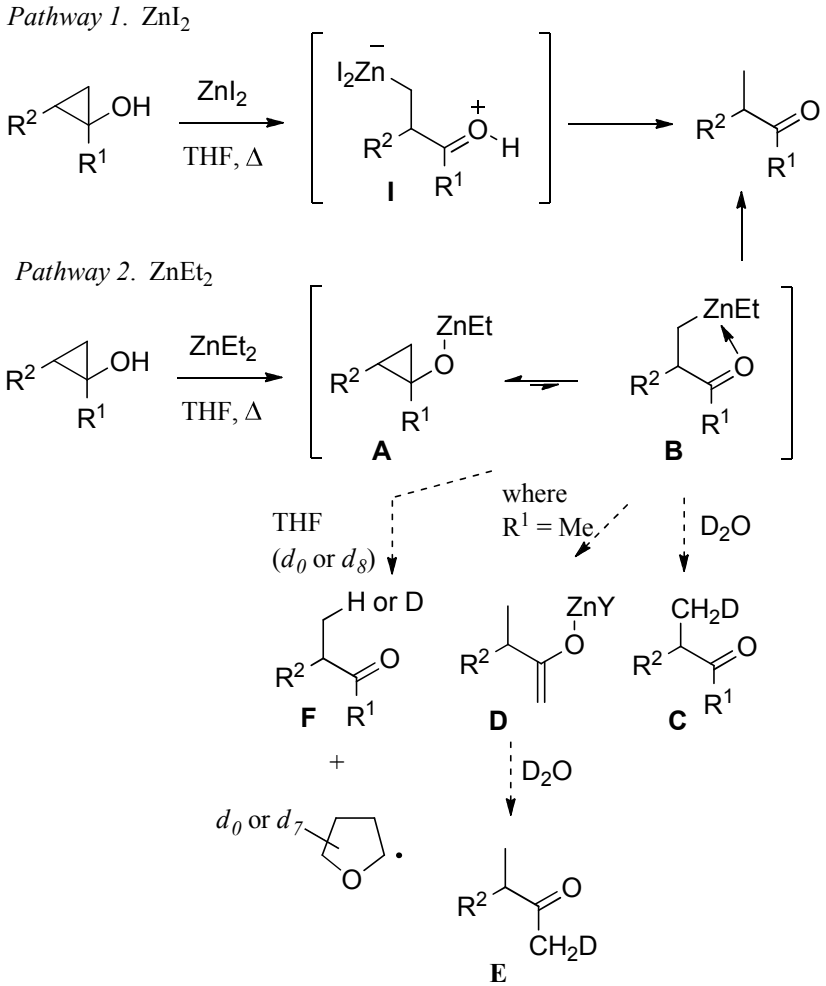
With regard to limitations, cyclopropanols **15–19** containing a free hydroxyl group in the side chain did not undergo ring opening, but were recovered presumably due to formation of a chelate, even with the use of 2–3 equivalents of $EtZnCH_2I$, $CH_2(ZnI)_2$, or Et_2Zn (Scheme 2). The ring scission procedure seemed to be sensitive to steric effects: ring opening of **20** and **22** proved to be conspicuously slower than that of **3a**-**c**.[15]



Scheme 2. Ring opening examples comparison.

The free cyclopropanol functionality is required for ring opening, as the corresponding TBS ethers were found to be stable toward alkylzinc reagents under identical reaction conditions. However, zinc iodide induced ring opening, albeit in low conversion: ketone **8** was isolated in 40% (82% brsm) yield from the TBS ether of **7**.[5] The observed regiochemistry (i.e., opening at the less substituted C–C bond), except for formation of **2'** (Table 1, entry 8), rules out the involvement of alkoxy radical-induced β-fragmentation. At the outset the nature of zinc reagents was believed to affect the reaction mechanism. Isomerization of a cyclopropanol by ZnI_2 to the corresponding ketone is assumed to occur via intermediate **I** (*Pathway 1*, Scheme 3), in part because no gas evolution was observed upon addition of ZnI_2. On the other hand, addition of diethylzinc results in vigorous evolution of gas from a reaction mixture in accord with formation of zinc cyclopropoxide **A** (Pathway 2). Alkoxide **A** could be in equilibrium with homoenolate **B**, where the former is expected to be strongly favored.[16] Deuterium-labeling experiments were carried out to probe the presumed intermediacy of a zinc homoenolate by using cyclopropanol **7**. No deuterium incorporation into the methyl group (e.g., $–CH_2D$ in **C**: R^1 = Me, $R^2 = CH_2Ph$) was detected upon addition of D_2O, MeOD, or AcOD (Scheme 3). As a plausible fate of **B**, we considered proton transfer leading to enolate **D**, protonolysis of which would afford **E**. The regioisomeric zinc enolate (structure not shown) was discounted in view of exclusive formation of **21** and **23**. Regardless of the position of equilibrium between **A** and **B**, ring scission would be

driven to completion by the proton transfer step. However, the proton transfer scenario was ruled out by negative trapping experiments of enolate **D** (with D_2O, MeOD, and PhCHO). Another possibility was next considered that **B** might abstract a hydrogen atom from the solvent in light of the known use of dialkylzincs as a source of alkyl radicals (albeit typically in the presence of oxygen).[17] This H-transfer pathway was discounted by no deuterium incorporation (e.g., **F**) from the use of THF-d_8. Similarly, the cognate labeling studies revealed no deuterium incorporation in the ring opening reactions of **7** by $EtZnCH_2I$, to which either pathway could be applicable.[18] Unfortunately, the exact "proton" source remains unclear to date. With respect to the possible intermediacy of a zinc homoenolate, it is noteworthy that **B** can be trapped in situ by transmetalation at low temperatures.[19]



Scheme 3. Plausible pathways for organozinc-mediated ring opening of cyclopropanols.

Conclusions

We have described the regioselective preparation of α-methyl substituted ketones by organozinc reagent-promoted ring opening of cyclopropanols. Mechanistic studies and other methods for trapping the zinc homoenolates are currently underway to achieve C–C bond formation.

Experimental Section

General. All reactions were conducted under an inert atmosphere of argon. Anhydrous tetrahydrofuran and diethyl ether were purified on alumina columns by Innovative Technology's purification system. Other reagents were purchased from commercial sources and used as received. FT infrared spectra were obtained as neat films. Proton NMR spectra were recorded at 400 MHz, and carbon NMR spectra were recorded at 100 MHz (on Varian spectrometers). GC/MS analyses were performed on an Agilent Model 6890N. Analytical thin-layer chromatography (TLC) was performed on 0.2 mm precoated silica gel plates (60 F_{254}). Column chromatography was carried out with Merck (Kieselgel 60, 63-200 ⌈m) or SiliCycle silica gel.

Representative procedure for ring opening of cyclopropanols with organozinc reagents
To a solution of CH_2I_2 (103 mg, 0.4 mmol) in anhydrous THF (0.3 mL) was added at rt under an atmosphere of nitrogen a 1 M hexane solution of Et_2Zn (0.4 mL, 0.4 mmol). After the mixture had been stirred for 5 min, a solution of cyclopropanol **1** (50 mg, 0.18 mmol) in anhydrous THF (0.5 mL) was added at rt. The reaction mixture was then refluxed for 3 h, and TLC showed complete disappearance of the starting material. The mixture was cooled to rt and quenched with sat NH_4Cl (2 mL). The organic layer was diluted with Et_2O (10 mL), washed with sat NH_4Cl (2 x 10 mL) and brine (1 x 10 mL), and evaporated under reduced pressure. Purification of the crude product by silica gel column chromatography using 2:98 EtOAc/hexane afforded pure **2** (41 mg, 82%) as a colorless liquid.
3-Methyl-5-triisopropylsiloxypentan-2-one (2). IR (neat, cm^{-1}) 2941, 2866, 1714, 1461, 1100. ^1H NMR (400MHz, $CDCl_3$) δ 3.69 (t, *J* = 6.5 Hz, 2H), 2.80–2.71 (m, 1H), 2.16 (s, 3H), 1.98–1.89 (m, 1H), 1.54–1.46 (m, 1H), 1.10 (d, *J* = 6.5 Hz, 3H), 1.08–1.00 (m, 21H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.9, 61.1, 43.7, 36.0, 28.5, 18.2, 16.4, 12.1; MS (GC/MS) *m/z* 229 (M^+–*i*Pr, 100%), 199, 187, 131, 103.
5-*tert*-Butyldimethylsiloxy-3-methylpentan-2-one (4a). IR (neat, cm^{-1}) 2857, 1713, 1255, 1097, 835. ^1H NMR (400MHz, $CDCl_3$) δ 3.62–3.59 (t, *J* = 6.5 Hz, 2H), 2.68 (m,1H), 2.10 (s, 3H), 1.94–1.86 (m, 1H), 1.56–1.48 (m, 1H), 1.09 (d, *J* = 7.3 Hz, 3H), 0.88 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.5, 60.9, 43.9, 35.8, 28.5, 26.1, 18.5, 16.4, −5.2; MS (GC/MS) *m/z* 230 (M^+), 173 (100%), 155, 143, 129, 115, 99, 75.
5-Benzyloxy-3-methylpentan-2-one (4b). IR (neat, cm^{-1}) 3030, 2880, 1706, 1453, 1027. ^1H NMR (400MHz, $CDCl_3$) δ 7.40–7.22 (m, 5H), 4.41 (s, 2H), 3.50–3.40 (t, *J* = 6.5 Hz, 2H), 2.70

(m, 1H), 2.10 (s, 3H), 2.06–1.98 (m, 1H), 1.66–1.58 (m, 1H), 0.95 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.7, 138.5, 128.6, 127.9, 119.2, 73.2, 68.1, 44.2, 32.9, 28.6, 16.6; MS (GC/MS) *m/z* 206 (M^+), 178, 119, 99, 91 (100%).

***tert*-Butyl *N*-3-methyl-4-oxopentyl-*N*-tosylcarbamate (4c).** IR (neat, cm^{-1}) 3070, 2985, 1709, 1729, 1356, 1157. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.1Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 3.79 (t, *J* = 6.5 Hz, 2H), 2.69–2.62 (m, 1H), 2.42 (s, 3H), 2.20 (s, 3H), 2.19–1.99 (m, 1H), 1.81–1.72 (m, 1H), 1.33 (s, 9H), 1.1 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.8, 151.2, 144.4, 137.5, 129.5, 128.0, 84.6, 45.6, 44.6, 32.8, 28.2, 28.1, 21.8, 16.8; MS (GC/MS) *m/z* 369 (M^+), 251, 186, 155, 96 (100%); ESI-HRMS *m/z* calcd. for $C_{18}H_{27}NO_5SNa$ $[M+Na]^+$ 392.1508, found 392.1506.

5,5-Diethoxy-3-methylpentan-2-one (6). IR (neat, cm^{-1}) 2978, 1711, 1461, 1114. ^{1}H NMR (400MHz, $CDCl_3$) δ 4.51 (t, *J* = 6.5 Hz, 1H), 3.63–3.60 (m, 2H), 3.50–3.45 (m, 2H), 2.67 (m, 1H), 2.10 (s, 3H), 2.07–1.96 (m, 1H), 1.83–1.75 (m, 1H), 1.20 (t, *J* = 6.9 Hz, 6H), 1.09 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7, 102.5, 61.3, 35.7, 28.4, 26.1, 16.3, 15.5.

3-Methyl-4-phenylbutan-2-one (8). IR (neat, cm^{-1}) 3040, 2971, 2931, 1710, 1454, 1359. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.78–7.15 (m, 5H), 2.99 (dd, *J* = 6.4, 13.0 Hz, 1H), 2.83 (m, 1H), 2.56 (dd, *J* = 7.3, 13.0 Hz, 1H), 2.08 (s, 3H), 1.09 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.5, 139.9, 129.2, 129.1, 128.7, 126.5, 49.1, 39.1, 29.1, 16.5; MS (GC/MS) *m/z* 162 (M^+), 147, 119, 91 (100%).

(*E*)-Oct-5-en-3-one (10). IR (neat, cm^{-1}) 2971, 2931, 1710, 1455, 1267. ^{1}H NMR (400MHz, $CDCl_3$) δ 5.60–5.48 (m, 2H), 3.10 (d, *J* = 6.5 Hz, 2H), 2.45 (q, *J* = 7.3 Hz, 2H), 2.13–2.08 (m, 2H), 1.41 (t, *J* = 7.3 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.1, 136.8, 121.2, 46.6, 35.5, 25.4, 13.8, 7.9; MS (GC/MS) *m/z* 126 (M^+), 111, 69 (100%).

6-Ethyloctan-3-one (12). IR (neat, cm^{-1}) 2985, 1717, 1459, 1102. ^{1}H NMR (400MHz, $CDCl_3$) δ 2.40–2.25 (m, 4H), 1.45–1.22 (m, 7H), 1.01 (t, *J* = 7.3 Hz, 6H), 0.95 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.0, 43.6, 40.1, 35.8, 28.7, 25.4, 13.8, 7.9; MS (GC/MS) *m/z* 156 (M^+), 125, 109, 85 (100%).

13,13-Diisopropyl-2,2,9,14-tetramethyl-3,3-diphenyl-4,12-dioxa-3,13-disilapentadecan-8-one (14a). IR (neat, cm^{-1}) 2937, 2870, 1711, 1267, 1101. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.71–7.61 (m, 4H), 7.40–7.31 (m, 6H), 3.69–3.60 (m, 4H), 2.79–2.71 (m, 1H), 2.60–2.50 (m, 2H), 1.98–1.90 (m, 1H), 1.81–1.75 (pentet, *J* = 6.4 Hz, 2H), 1.50–1.42 (m, 1H), 1.10 (d, *J* = 7.3 Hz, 3H), 1.10–1.00 (m, 30H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.4, 135.7, 134.0, 129.8, 127.9, 63.2, 61.2, 42.9, 37.5, 36.1, 30.5, 27.1, 26.8, 19.4, 18.2, 16.6, 12.2; ESI-HRMS *m/z* calcd. for $C_{31}H_{50}O_3Si_2Na$ $[M+Na]^+$ 577.3507, found 577.3493.

5-Methyl-4-oxo-7-((triisopropylsilyl)oxy)heptyl pivalate (14b). IR (neat, cm^{-1}) 2938, 2866, 1713, 1750, 1459, 1157, 1099. ^{1}H NMR (400MHz, $CDCl_3$) δ 4.20 (t, *J* = 6.5 Hz, 2H), 3.68 (t, *J* = 7.3 Hz, 2H), 2.81–2.78 (m, 1H), 2.59–2.52 (m, 1H), 1.94–1.60 (m, 3H), 1.54–1.46 (m, 1H), 1.19 (s, 9H), 1.10–1.02 (m, 25 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.7, 178.7, 63.8, 61.1, 42.8, 38.9, 37.5, 36.7, 36.1, 36.0, 32.8, 27.4, 26.6, 23.3, 23.0, 18.2, 17.3, 16.6, 12.1; MS (GC/MS) *m/z* 357,

255 (100%), 215, 185, 125; ESI-HRMS *m/z* calcd. for $C_{22}H_{44}O_4SiNa$ $[M+Na]^+$ 423.2901, found 423.2897.

5-Benzyloxy-3,6-dimethylheptan-2-one (21). IR (neat, cm^{-1}) 2932, 2858, 1709, 1266, 1100. ^1H NMR (400MHz, $CDCl_3$) δ 7.40–7.25 (m, 5H), 4.66 (d, *J* = 11.3 Hz, 1H), 4.54 (d, *J* = 11.3 Hz, 1H), 3.41–3.36 (m, 1H), 2.72 (m, 1H), 2.12 (s, 3H), 1.90–1.80 (m, 1H), 1.70–1.63 (m, 1H), 1.35–1.22 (m, 1H), 1.10 (d, *J* = 6.4 z, 3H), 0.96 (d, *J* = 7.3 Hz, 3H), 0.92 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.7, 138.5, 128.6, 127.9, 127.8, 73.2, 68.1, 44.2, 32.9, 28.5, 23.6, 20.2, 19.0, 16.6; MS (GC/MS) *m/z* 248, 206, 91 (100%).

5-Benzyloxy-3-methyloct-7-en-2-one (23). IR(neat, cm^{-1}) 3027, 2881, 1709, 1494, 1452. ^1H NMR (400MHz, $CDCl_3$) δ 7.41–7.22 (m, 5H), 5.95–5.80 (m, 1H), 5.15–5.01 (m, 2H), 4.58 (s, 3H), 3.55 (m,1H), 2.50–2.30 (m, 1H), 2.01 (s, 3H), 1.80–1.71 (m, 1H), 1.63–1.52 (m, 2H), 1.11 (d, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.4,135.76, 134.1, 129.8, 127.9, 119.2, 74.9, 63.3, 37.7, 36.1, 30.5, 16.6. MS (GC/MS) *m/z* 246, 206, 203, 91 (100%).

Acknowledgements

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