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Ring opening reactions of 2-methyleneoxetanes

Ying Wang, Henri Bekolo and Amy R. Howell*

Department of Chemistry, University of Connecticut, 55 North Eagleville Road, Unit 3060, Storrs, CT 06269-3060, USA

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Abstract—Ring opening of 2-methyleneoxetanes with stabilized carbanion nucleophiles provides substituted ketones. The intermediate enolate can be trapped as its silylenol ether. If the 2-methyleneoxetane is exposed to more strongly basic carbanions, the corresponding homopropargylic alcohol is isolated in excellent yield. A variety of heteroatom nucleophiles also open the 2-methyleneoxetane in good to excellent yields. © 2002 Elsevier Science Ltd. All rights reserved.

Until our preparation of 2-methyleneoxetanes (e.g. **1**) by the reaction of dimethyltitanocene with β-lactones[1] there had been few descriptions on the preparation of these ring systems. Those reports had involved either photochemical transformations[2,3] or were restricted to a few specific substitution patterns.[4,5] These novel ring systems appear to contain a number of elements of potential reactivity—ring strain, an exocyclic double bond, an electron rich enol ether and a latent enolate leaving group—which would suggest a high level of, as yet, under-exploited utility. This has been confirmed by more recent work from our laboratory which demonstrated that 2-methyleneoxetanes undergo successful ring opening[6,7] and alkene addition reactions[8,9] as well as serving as biologically active β-lactone isosteres.[10]

In one of our early projects, we had anticipated, based on limited literature precedent,[11] that treatment of 2-methyleneoxetanes with organolithium reagents would lead to ring opening at C-4 with potential for further elaboration of the resultant enolate (e.g. **2**) in a tandem process (Fig. 1). However, no reaction was observed between **1** and *n*-butyllithium or phenyllithium at temperatures from −78°C to room temperature. Unexpectedly, in the presence of trimethylaluminum **1** was converted by either *n*-butyllithium or phenyllithium to homopropargylic alcohol **3**. Indeed, we discovered that a range of 2-methyleneoxetanes could be converted to homopropargylic alcohols in high yields with LDA.[7] In spite of this serendipitous discovery of a novel approach to homopropargylic alcohols, we continued to be interested in achieving the nucleophile-promoted ring opening of 2-methyleneoxetanes at C-4. In this communication we report a realization of this goal.

Our first breakthrough came in studies directed at exploiting

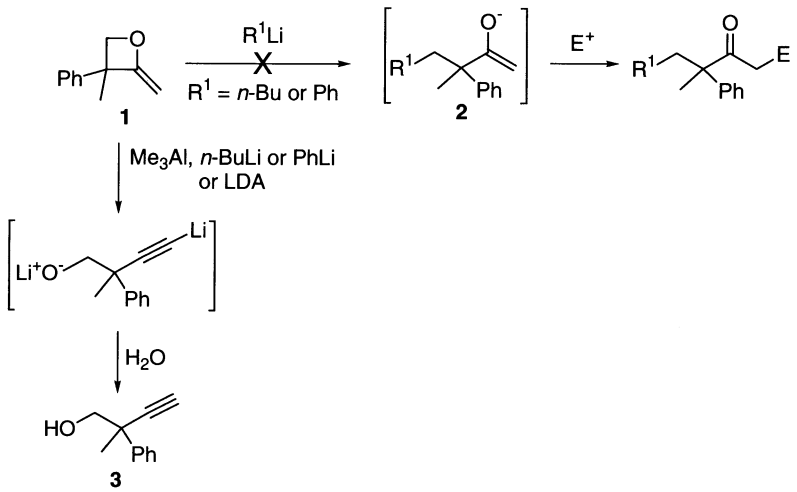

Figure 1. Unexpected formation of a homopropargyl alcohol.

Keywords: ring opening; 2-methyleneoxetane; nucleophiles; homopropargyl alcohol.

* Corresponding author. Tel.: +1-860-486-3460; fax: +1-860-486-2981; e-mail: amy.howell@uconn.edu

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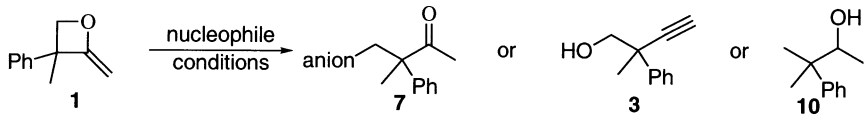
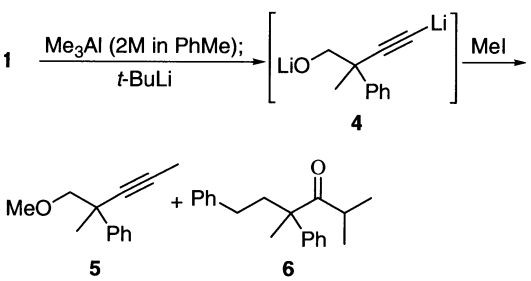
Table 1.



Entry	Nucleophile ([a])	Conditions	Product (anion)	Yield (%)[b]
1	$PhCH_2Li$ (1.2)	*n*-BuLi, $PhCH_3$, TMEDA, 0°C, 2 h	**7a** ($PhCH_2$)	81
2	$PhCH_2MgCl$ (1.2)	THF, reflux, overnight	**7a**	76
4	CH_2CHCH_2MgCl (1.2)	THF, reflux, overnight	**7b** (CH_2CHCH_2)	86
5	MeMgCl (5)	THF, reflux, overnight	No reaction	
6	*n*-BuLi	THF, reflux, 6 h	**3**	76
7	MeLi	THF, reflux, 6 h	**3**	84
8	TMS (or Ph) CCLi	$AlMe_3$ or $BF_3{\cdot}OEt_2$, THF, −78–0°C	No reaction	
9	*n*-Bu(2-C_4H_3S)Cu(CN)Li_2 or *n*-Bu(Me)Cu(CN)Li_2	Various conditions	No reaction	
10	**9**[c] (2)	NaH, 18-crown-6, DMF, 100°C, 13 h	**7c**[c]	45
11	NaCN (6)	DMF/H_2O (4:1), 100°C, 3 h	**7d** (NC)	53
12	NaN_3 (10)	DMF/H_2O (3:1), 100°C, 8 h	**7e** (N_3)	65
13	NaI (10)	DMF/H_2O (3:1), 100°C, 9 h	**7f** (I)	40
14	*p*-$MeOC_6H_4OH$ (5)	NaH, DMF, 100°C, 20 h	**7g** (*p*-MeOPhO)	80
15	PhOH (5)	NaH, DMF, 100°C, 20 h	**7h** (PhO)	70
16	PhSH (3)	NaH, DMF, 60°C, 4 h	**7i** (PhS)	98
17	PhSeH (2)	NaH, DMF, rt, 14 h	**7j** (PhSe)	71
18	Ph_2PH (1.5)	NaH, DMF, rt, 30 min	**7k** (Ph_2P)	50
19	DIBAL	CH_2Cl_2, −78°C–rt, 48 h	**10**	59
20	LAH	THF, 0°C–rt, 48 h	**10**	66
21	$MgBr_2$	CH_2Cl_2, rt, 3 h	**7l** (Br)	78

[a] Equivalents of nucleophile.
[b] Isolated yields.
[c] See text for structure.

the presumed alkynyl dianion intermediate **4** in the reaction of 2-methyleneoxetane **1** with trimethylaluminum (as a solution in toluene) and *tert*-butyllithium. The reaction was quenched with methyl iodide, and alkylated ketone **6** was isolated in 29% yield, as well as the expected homopropargylic ether **5** (eq. (1)).[12] We recognized that we were generating benzyllithium under the reaction conditions and that this was reacting with **1** at C-4. Mixing *tert*-butyllithium and toluene, followed by the addition of 2-methyleneoxetane **1**, provided ketone **7a** (see Table 1) in a modest 50% yield, along with homopropargyl alcohol **3** and recovered **1** (noted even with excess *tert*-butyllithium). However, generation of benzyllithium under conditions described by Taylor and co-workers[13] provided **7a** in an excellent 81% yield (entry 1, Table 1). Benzylmagnesium chloride gave a similar result (entry 2), although the reaction conditions were considerably more stringent. Subsequent to these successful results attention was turned to other carbon-based nucleophiles.



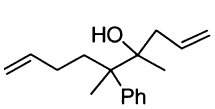
(1)

Allylmagnesium chloride provided ring-opened product **7b** when the reaction was conducted in refluxing THF. If an excess of the allylic Grignard reagent was employed, the bis-allylated species **8** was observed. In contrast, methylmagnesium bromide left **1** untouched (entry 5), even after prolonged heating. The elevated temperatures required for reaction of the Grignard reagents led us to try the stronger bases, *n*-butyllithium and methyllithium, at elevated temperatures in the absence of Lewis acids (entries 6 and 7). These strongly basic nucleophiles provided clean conversion to the homopropargylic alcohol **3**, demonstrating that reaction outcome between ring opening at C-4 or deprotonoation at the exocyclic methylene was governed by the nature of the nucleophile.

Lithium acetylides failed to react with 2-methyleneoxetane **1** (entry 8), even at elevated temperatures. Attempts to promote the ring opening by these acetylides employing additives traditionally used with oxetanes,[14–16] such as boron trifluoride diethyl etherate or trimethylaluminum, did not alter the result.

Organocuprates have been widely used for the ring opening of epoxides although their use for the opening of oxetanes has not been as widely reported. For the reaction with epoxides, higher order cuprates are generally found to be more reactive than lower order ones.[17,18] Neither a thienyl cuprate[19] nor a mixed higher order cuprate[20] (entry 9, Table 1) provided ring-opened products.

Although simple enolates have, thus far, failed to react with **1**, even at elevated temperatures, the stabilized enolate from dimedone (**9**) provided **7c** in modest yield (entry 10). The conditions were rather harsh, and best results were achieved with the addition of 18-crown-6. Sodium cyanide also provided ring-opened **7d**, again, in modest yield (entry 11).



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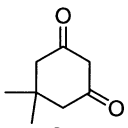

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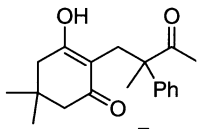
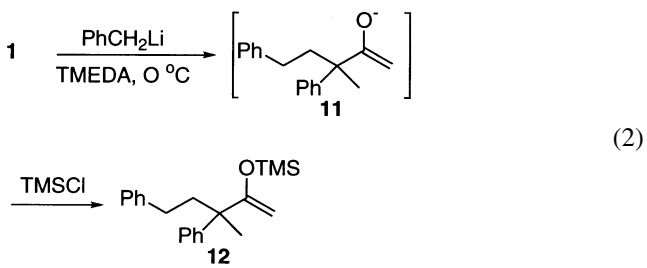


7c

We also explored the reaction of **1** with a range of heteroatom nucleophiles (entries 12–18, Table 1). The conditions required for successful ring opening mirrored the nucleophilicity of the heteroatomic anions. On the whole, the yields were good to excellent. However, amine nucleophiles under a variety of conditions either did not react or did not provide isolable and identifiable products. For example, benzylamine in the presence of silver tetrafluoroborate did not react. With lithium tetrafluoroborate or boron trifluoride diethyl etherate added to the reaction mixture, as the temperature was gradually increased, **1** disappeared, but the reactions were messy. Similarly, aniline and corresponding nucleophilic anions (e.g. PhNHMgBr, *p*-MeOPhNHMgBr, PhNHLi, *p*-MeOPhNHLi) under a variety of conditions failed to give significant quantities of ring-opened product.

Hydride nucleophiles, diisobutylaluminium hydride (DIBAL) and lithium aluminum hydride (LAH), both reacted at C-4, providing alcohol **10** (entries 19 and 20, Table 1). These reactions were surprisingly slow. Obviously, ring opening at C-4 has occurred. However, it is difficult to demonstrate conclusively how the subsequent reduction to the alcohol proceeded.

Once we had established that 2-methyleneoxetanes were labile to nucleophilic attack at C-4 with stabilized carbon-based nucleophiles and with heteroatom nucleophiles, we were anxious to explore tandem reactions of the presumed enolate intermediate with electrophiles. The mildest condition for generating an enolate from **1** (see **11**) were those for the reaction with benzyllithium. However, intermediate **11** failed to react directly with methyl- or allyl iodide or acetaldehyde, although it could be quantitatively trapped as the silyl enol ether **12** (eq. (2)). It was apparent that the conditions for generating the benzyllithium were not ideal for subsequent in situ reactions with electrophiles. Moreover, the time required for complete reaction and the harshness of the reaction conditions for the other nucleophiles suggested that Lewis acid activation of the oxetane would be required to achieve ring opening at C-4 under sufficiently mild conditions to permit subsequent in situ reaction of the enolate.



(2)

Significantly, when **1** was treated with magnesium bromide.etherate (entry 21), ring opening to β-bromoketone **7k** proceeded at room temperature in approximately 3 h. This result demonstrates that Lewis acids can promote the ring opening under milder conditions. We are currently examining Lewis acids to determine those that will promote ring opening at C-4 under mild conditions and that will contain appropriate counterions so that the enolate will undergo in situ reaction with electrophiles.

In summary, we have found that 2-methyleneoxetanes can be opened at C-4 by both carbon-based and heteroatom nucleophiles. In the absence of Lewis acids, only stabilized carbanionic nucleophiles, such as benzyllithium, benzylmagnesium chloride, allyl magnesium chloride and the enolate of dimedone, provided C-4 ring opening. Strongly basic carbanionic nucleophiles deprotonated the enol ether, resulting in the products of elimination, homopropargylic alcohols. Surprisingly, acetylide anions, even in the presence Lewis acids, and organocuprates which have worked well with oxiranes and oxetanes did not react with methyleneoxetane **1**. A variety of heteroatom nucleophiles reacted with 2-methyleneoxetane **1** to give β-substituted ketones. Current efforts are targeted at determining Lewis acids that will both promote ring opening of the 2-methyleneoxetanes at C-4 under milder conditions and provide appropriate activation for subsequent reaction of the resultant enolate anions.

1. Experimental

1.1. General experimental

Toluene was distilled from sodium; tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled under nitrogen from a dark blue solution of sodium benzophenone ketyl. Deuterated chloroform ($CDCl_3$) was dried over 3 Å molecular sieves. Methylene chloride (CH_2Cl_2) and triethylamine (Et_3N) were distilled from CaH_2. Dimethylformamide (DMF) was dried over CaH_2 prior to distillation. The concentrations of solutions of MeLi and *n*-BuLi were determined by titrations with *sec*-butyl alcohol using 1,10-phenanthroline as the indicator. Petroleum ether was purchased from JT Baker and distilled from $CaCl_2$. With the exceptions noted, all starting reagents were purchased from Aldrich and used without further purification. A literature procedure was followed for the preparation of 3-methyl-2-methylene-3-phenyloxetane (**1**).[1]

NMR spectra were obtained on a Bruker Avance DRX-400 (400 MHz ^{1}H, 100 MHz ^{13}C) NMR spectrometer. The ^{1}H and ^{13}C chemical shifts (δ) are reported in units of parts per million (ppm) from TMS. Infrared spectra were recorded on a JASCO FT/IR-410 spectrometer as a thin film on a polished NaCl plate and are reported in cm^{-1}. Combustion analyses were performed by NuMega Resonance Labs, Inc., San Diego, California. Melting points were observed in open Pyrex capillary tubes and are uncorrected. Low resolution mass spectra were obtained on an HP 5970 series GC–MSD system and are reported in units of mass/charge (m/z). High resolution mass spectra were obtained on a JEOL JMS-AX505HA instrument at the University of Notre Dame. Flash chromatography was performed on Silica Gel, 40 μm, 32-63 flash silica from Scientific Adsorbent Inc. Thin layer chromatography was performed on silica gel (EM Science Silica Gel 60 F_{254}) glass plates, and the compounds were visualized by UV, 5% phosphomolybdic

acid in ethanol or 0.5% potassium permanganate in 0.1 M aqueous NaOH.

1.1.1. 2-Methyl-2-phenyl-3-butyn-1-ol (3). *Method a*. *n*-Butyllithium (1.6 M in hexane, 0.49 mL, 0.78 mmol) was added dropwise to a stirred solution of of 3-methyl-2-methylene-3-phenyloxetane (**1**) (25 mg, 0.16 mmol) in dry THF (ca. 1 mL) at 0°C under N_2. The reaction was heated at reflux for 6 h, cooled to 0°C, diluted with THF (ca. 5 mL), and quenched with saturated aqueous NH_4Cl (3 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3×15 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 80:20) afforded **3** as a colorless oil (19 mg, 76%): mp 57.5–59°C; IR (KBr) 3500, 3250, 2900, 2130, 1500, 1490, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (m, 5H), 3.72 (m, 2H), 2.47 (s, 1H), 1.81 (dd, J=7.1, 7.1 Hz, 1H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 128.5, 127.2, 126.4, 87.3, 72.7, 71.8, 43.3, 25.0; MS (EI) m/z 160 (M^+) 145, 129 (100), 115, 77, 51; HRMS (EI) calcd for $C_{11}H_{11}$ (M^+-OH) 143.0861. Found: 143.0863; Anal. calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.08; H, 7.15.

Method b. Methyllithium (1.4 M in Et_2O, 0.56 mL, 0.78 mmol) was added dropwise to a stirred solution of of 3-methyl-2-methylene-3-phenyloxetane (**1**) (25 mg, 0.16 mmol) in dry THF (ca. 1 mL) at 0°C under N_2. The reaction was heated at reflux for 6 h, cooled to 0°C, diluted with THF (ca. 5 mL), and quenched with saturated aqueous NH_4Cl (3 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3×15 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 80:20) afforded **3** as a colorless oil (21 mg, 84%).

1.1.2. 3-Methyl-3,5-diphenylpentan-2-one (7a). *Method a*. *n*-Butyllithium (1.6 M in hexane, 0.23 mL, 0.37 mmol) was added dropwise to a stirred solution of dry toluene (2 mL) containing TMEDA (0.089 mL, 0.59 mmol) at 0°C under N_2. After stirring for 30 min, the resulting solution turned orange. 3-Methyl-2-methylene-3-phenyloxetane (**1**) (0.05 g, 0.31 mmol) in a small amount of toluene (0.2 mL) was added dropwise to the reaction mixture, and stirring was continued for 1 h at 0°C. The reaction mixture was treated with saturated aqueous NH_4Cl (2 mL). The separated aqueous layer was extracted with Et_2O (5×15 mL), and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography of the crude product on silica gel (petroleum ether/EtOAc 97:3) gave **7a** (0.06 g, 81%) as a colorless oil: IR (film) 3026, 2950, 1708, 1600, 1497, 1447, 1352, 764, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.12 (m, 10H), 2.47–2.30 (m, 2H), 2.29–2.18 (m, 2H), 1.94 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.6, 142.9, 142.5, 129.0, 128.5, 128.4, 127.2, 126.6, 126.0, 56.1, 39.9, 31.1, 26.0, 21.4; MS (EI) m/z 209 (M^+-CH_3CO), 148, 105, 91 (100), 77; Anal. calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.55; H, 8.13.

Method b. Benzylmagnesium chloride (2.0 M in THF, 0.56 mL, 1.12 mmol) was added dropwise to a stirred solution of **1** (0.15 g, 0.94 mmol) in anhydrous THF (ca. 2 mL) at 0°C under N_2. The reaction mixture was stirred for 10 min at 0°C, allowed to warm to rt, and, then, heated at reflux overnight. The mixture was cooled to rt, and THF (5 mL) was added. Saturated aqueous NH_4Cl (5 mL) was then added, and the layers were separated. The aqueous layer was further extracted with Et_2O (5×15 mL), and the combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The orange residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 98:2) to give **7a** (0.18 g, 76%) as a colorless oil.

1.1.3. 3-Methyl-3-phenylhept-6-en-2-one (7b). Allylmagnesium chloride (2.0 M in THF, 0.75 mL, 1.50 mmol) was added dropwise to a stirred solution of 3-methyl-2-methylene-3-phenyloxetane (**1**) (0.20 g, 1.25 mmol) in anhydrous THF (ca. 2 mL) at 0°C under N_2. The reaction mixture was stirred for 10 min at 0°C, allowed to warm to rt, and, then, heated at reflux overnight. The mixture was cooled to rt, and THF (ca. 5 mL) was added. Saturated aqueous NH_4Cl (5 mL) was then added, and the layers were separated. The aqueous layer was further extracted with Et_2O (5×15 mL), and the combined organic layers were washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The orange residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc 99.5:0.5) to give **7b** (0.22 g, 86%) as a colorless oil: IR (film) 3062, 2978, 1710, 1642, 1353, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.21 (m, 5H), 5.78 (dddd, J=17.1, 10.3, 6.8, 6.8 Hz, 1H), 4.99 (dddd, J=17.1, 1.7, 1.7, 1.7 Hz, 1H), 4.93 (dddd, J=10.3, 1.9, 1.2, 1.2 Hz, 1H), 2.06 (m, 2H), 1.90 (s, 3H), 1.92–1.74 (m, 2H), 1.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.6, 142.8, 138.5, 128.8, 126.9, 126.4, 114.5, 55.7, 36.7, 28.7, 25.8, 21.2; MS (EI) m/z 159 (M^+-CH_3CO), 148, 117, 105 (100), 91, 81; Anal. calcd for $C_{14}H_{18}O$: C, 83.11; H, 8.97. Found: C, 83.36; H, 9.12.

1.1.4. 5,5-Dimethyl-2-(2-methyl-3-oxo-2-phenylbutyl)-cylclohexane-1,3-dione (7c). Dry DMF (0.50 mL) was added to NaH (0.02 g, 0.8 mmol). Solutions of 5,5-dimethyl-1,3-cyclohexanedione (**9**) (0.12 g, 0.8 mmol) in dry DMF (0.50 mL) and 3-methyl-2-methylene-3-phenyloxetane (**1**) (0.066 g, 0.4 mmol) in DMF (0.50 mL) were added successively. 18-Crown-6 (0.22 g, 0.8 mmol) was then added. The mixture was stirred for 13 h at 100°C, then cooled to rt. H_2O (6 mL) was added, and the mixture was extracted with Et_2O (3×6 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 70:30) afforded **7c** (0.055 g, 45%) as a yellowish oil: IR (film) 1709, 1655, 1606, 1220 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.23 (m, 5H), 5.39 (s, 1H), 4.33 (d, J=9.7 Hz, 1H), 4.00 (d, J=9.7 Hz, 1H), 2.23 (d, J=17.3 Hz, 1H), 2.18 (s, 2H), 2.16 (d, J=17.4 Hz, 1H), 1.99 (s, 3H), 1.67 (s, 3H), 1.04 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 207.8, 199.1, 175.7, 139.0, 129.0, 127.7, 126.2, 101.9, 73.1, 55.7, 50.7, 42.5, 32.3, 28.2, 28.1, 25.8, 19.5; MS (EI) m/z 300 (M^+), 118 (100), 91, 67; HRMS (FAB) calcd for $C_{19}H_{25}O_3$ (M^++H) 301.1805, found 301.1788.

1.1.5. 3-Methyl-4-oxo-3-phenylpentanenitrile (7d). Sodium cyanide (0.12 g, 2.4 mmol) was dissolved in distilled water (0.20 mL). A solution of 3-methyl-2-methylene-3-phenyloxetane (**1**) (0.07 g, 0.4 mmol) in DMF (0.80 mL) was added. The mixture was stirred for 3 h at 100°C, then cooled to rt. Water (6 mL) was added, and the mixture was extracted with Et_2O (3×6 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 90:10) afforded **7d** (0.043 g, 53%) as a colorless oil: IR (film) 2245, 1709, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.24 (m, 5H), 2.90 (d, J=16.9 Hz, 1H), 2.78 (d, J=16.9 Hz, 1H), 1.98 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 207.0, 138.6, 129.2, 128.2, 125.9, 117.4, 53.7, 28.3, 24.9, 20.3; MS (EI) m/z 187 (M^+), 144 (100), 118, 103, 91, 77; HRMS (FAB) calcd for $C_{12}H_{14}NO$ (M^++H) 188.1075, found 188.1085.

1.1.6. 4-Azido-3-methyl-3-phenylbutan-2-one (7e). Sodium azide (0.27 g, 4.2 mmol) was dissolved in distilled water (0.2 mL). A solution of 3-methyl-2-methylene-3-phenyloxetane (**1**) (0.066 g, 0.4 mmol) in DMF (0.6 mL) was added. The mixture was stirred for 8 h at 100°C then cooled to rt. H_2O (6 mL) was added, and the reaction mixture was extracted with Et_2O (3×6 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 97:3) afforded **7e** (0.054 g, 65%) as a colorless oil: IR (film) 2099, 1705, 1598 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.23 (m, 5H), 3.80 (d, J=12.4 Hz, 1H), 3.56 (d, J=12.4 Hz, 1H), 1.97 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 208.8, 139.4, 129.0, 127.8, 126.3, 58.8, 56.3, 25.7, 19.2; MS (EI) m/z 147, 118 (100), 105, 91, 77; Anal. calcd for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.68. Found: C, 65.23; H, 6.28; N, 20.82.

1.1.7. 4-Iodo-3-methyl-3-phenylbutan-2-one (7f). The title compound was prepared by the above method using sodium iodide instead of sodium azide. The reaction mixture stirred for 9 h at 100°C in the dark and yielded **7f** (0.048 g, 40%) as a colorless oil: IR (film) 1703, 1352, 1209 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.20 (m, 5H), 3.73 (d, J=10.3 Hz, 1H), 3.57 (d, J=10.3 Hz, 1H), 2.00 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 207.1, 140.1, 129.0, 127.8, 126.2, 55.6, 26.3, 22.9, 16.7; MS (EI) m/z 245 (M^+-CH_3CO), 161 (M^+-I), 118 (100), 91; Anal. calcd for $C_{11}H_{13}IO$: C, 45.85; H, 4.55. Found: C, 46.10; H, 4.48.

1.1.8. 3-Methyl-4-(4-methoxyphenoxy)-3-phenylbutan-2-one (7g). Dry DMF (0.70 mL) was added to NaH (0.050 g, 2.0 mmol). A solution of 4-methoxyphenol (0.26 g, 2.0 mmol) in dry DMF (0.30 mL), and a solution of 3-methyl-2-methylene-3-phenyloxetane (**1**) (0.066 g, 0.4 mmol) in dry DMF (0.25 mL) were successively added dropwise. The mixture was stirred for 20 h at 100°C. The solution was then cooled to rt, and H_2O (6 mL) was added. The reaction mixture was extracted with Et_2O (3×6 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 95:5) afforded **7g** (0.094 g, 80%) as a colorless oil: IR (film) 1707, 1507, 1227, 1042, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.24 (m, 5H), 6.80 (m, 4H); 4.46 (d, J=8.9 Hz, 1H), 4.15 (d, J=8.9 Hz, 1H), 3.74 (s, 3H), 2.02 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 208.8, 154.1, 153.2, 140.3, 128.9, 127.4, 126.4, 115.8, 114.6, 73.9, 56.4, 55.7, 26.1, 20.4; MS (EI) m/z 284 (M^+), 241, 124 (100), 95, 77; Anal. calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.25; H, 7.34.

1.1.9. 3-Methyl-4-phenoxy-3-phenylbutan-2-one (7h). The title compound was prepared by the above method, using phenol instead of 4-methoxyphenol. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 97:3) afforded **7h** (0.073 g, 70%) as a colorless oil: IR (film) 1708, 1598, 1495, 1240 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.22 (m, 7H), 6.90 (m, 3H), 4.50 (d, J=9.0 Hz, 1H), 4.19 (d, J=9.0 Hz, 1H), 2.02 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 208.7, 158.9, 140.1, 129.3, 128.8, 126.3, 125.8, 120.9, 114.7, 72.9, 56.3, 26.1, 20.3; MS (EI) m/z 254 (M^+), 118 (100), 94, 77; Anal. calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.14. Found: C, 80.48; H, 7.38.

1.1.10. 3-Methyl-3-phenyl-4-phenylsulfanyl-butan-2-one (7i). Dry DMF (0.45 mL) was added to NaH (0.030 g, 1.2 mmol). Benzenethiol (0.13 mL, 1.2 mmol) was added dropwise; then, a solution of 3-methyl-2-methylene-3-phenyloxetane (**1**) (0.066 g, 0.4 mmol) in dry DMF (0.30 mL) was added. The mixture was stirred for 4 h at 60°C, then cooled to rt. H_2O (6 mL) was added, and the reaction mixture was extracted with Et_2O (3×6 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 97:3) afforded **7i** (0.11 g, 98%) as a colorless oil which crystallized in the freezer: mp 38°C; IR (film) 1703, 1481, 1088 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.11 (m, 10H), 3.52 (d, J=13.0 Hz, 1H), 3.48 (d, J=13.0 Hz, 1H), 1.95 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 209.1, 140.8, 137.4, 129.7, 128.8, 127.5, 126.4, 126.0, 125.9, 56.5, 43.8, 25.8, 20.8; MS (EI) m/z 270 (M^+), 227, 149 (100), 118, 91, 77; Anal. calcd for $C_{17}H_{18}OS$: C, 75.51; H, 6.71. Found: C, 75.20; H, 6.41.

1.1.11. 3-Methyl-4-phenylselanyl-3-phenylbutan-2-one (7j). Dry DMF (0.60 mL) was added to NaH (0.034 g, 1.4 mmol). Solutions of benzeneselenol (0.09 mL, 0.8 mmol) in dry DMF (0.25 mL) and 3-methyl-2-methylene-3-phenyloxetane (**1**) (0.066 g, 0.4 mmol) in dry DMF (0.25 mL) were added successively. The mixture was stirred for 14 h in the dark at rt. Water (6 mL) was then added, and the reaction mixtures was extracted with Et_2O (3×6 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 95:5) afforded **7** (0.092 g, 71%) as a colorless oil: IR (film) 1704, 1476, 1436, 1351 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.17 (m, 10H), 3.49 (d, J=12.2 Hz, 1H), 3.39 (d, J=12.2 Hz, 1H), 1.95 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 209.3, 141.3, 133.0, 131.6, 128.9, 128.8, 127.5, 126.8, 126.3, 56.7, 38.8, 25.8, 21.4; MS (EI) m/z 318 (M^+), 275, 197 (100), 157, 117, 91, 77; Anal. calcd

for $C_{17}H_{18}OSe$: C, 64.35; H, 5.72. Found: C, 63.96; H, 5.65.

1.1.12. 4-Diphenylphosphanyl-3-methyl-3-phenylbutan-2-one (7k). Dry DMF (0.50 mL) was added to NaH (0.015 g, 0.6 mmol). Diphenylphosphine (0.11 mL, 0.6 mmol) was then added dropwise. A solution of 3-methyl-2-methylene-3-phenyloxetane (**1**) (0.066 g, 0.4 mmol) in dry DMF (0.50 mL) was then added, and the mixture was stirred for 30 min at rt. Water (6 mL) was added, and the reaction mixture was extracted with Et_2O (3×6 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 97:3) afforded **7k** (0.071 g, 50%) as a viscous, colorless oil that crystallized upon standing: mp 73°C; IR (KBr) 1699, 1434, 1350 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.17 (m, 15H), 2.80 (dd, J=14.6, 4.5 Hz, 1H), 2.73 (dd, J=14.6, 2.8 Hz, 1H), 1.91 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 210.3 (d, J=15.6 Hz), 142.2 (d, J=18.8 Hz), 139.9 (d, J=48.0 Hz), 139.3 (d, J=48.4 Hz), 133.3 (d, J=81.2 Hz), 132.9 (d, J=76.4 Hz), 128.8, 128.5, 128.4, 128.3 (d, J=7.2 Hz), 127.0, 126.7 (d, J=4.4 Hz), 55.7 (d, J=72.5 Hz), 39.4 (d, J=57.7 Hz), 25.9 (d, J=11.3 Hz), 22.5 (d, J=52.6 Hz); MS (EI) m/z 346 (M^+), 331, 202 (100), 183, 121, 91, 77; Anal. calcd for $C_{23}H_{23}OP$: C, 79.75; H, 6.69; Found: C, 80.08; H, 6.57.

1.1.13. 4-Bromo-3-methyl-3-phenyl-2-butanone (7l). Freshly prepared magnesium bromide diethyl etherate[21] (0.65 g, 2.50 mmol) was added to a stirred solution of 3-methyl-2-methylene-3-phenyloxetane (**1**) (0.20 g, 1.25 mmol) in dry CH_2Cl_2 (35 mL) at rt under N_2. The suspension was left to stir for 3 h at rt. Brine was added (25 mL), and the reaction mixture was stirred for 20 min. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (5×15 mL). The combined organic extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 99:1) afforded **7l** as a colorless oil (0.24 g, 78%): IR (film) 3059, 2981, 1709, 1496, 1449, 1354, 1245, 761, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.23 (m, 5H), 3.95 (d, J=10.5 Hz, 1H), 3.72 (d, J=10.5 Hz, 1H), 2.00 (s, 3H), 1.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 139.7, 129.0, 127.9, 126.3, 56.3, 40.9, 26.0, 20.9; MS (EI) m/z 199 ($M^+-{}^{79}Br$), 197 ($M^+-{}^{81}Br$), 118 (100), 103, 91, 77; Anal. calcd for $C_{11}H_{13}BrO$: C, 54.79; H, 5.43. Found: C, 55.03; H, 5.32.

1.1.14. 3-Methyl-3-phenylbutan-2-ol (10). *Method a*. A solution of 3-methyl-2-methylene-3-phenyloxetane (**1**) (0.25 g, 1.56 mmol) in anhydrous THF (ca. 8 mL) was added slowly to a stirred suspension of lithium aluminum hydride (0.19 g, 95% purity, 4.68 mmol) in anhydrous THF (ca. 3 mL) at 0°C under N_2. After the addition the mixture was stirred for 1 h at 0°C and, subsequently, allowed to reach rt. After 48 h, TLC showed that the starting material was consumed. The reaction was quenched with 2 M sulfuric acid (4 mL), followed by saturated NaCl (10 mL). The layers were separated, and the aqueous layer was further extracted with Et_2O (5×20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography on silica gel (petroleum ether/EtOAc 85:15) afforded alcohol **10**[22] (0.17 g, 66%) as a colorless oil: IR (film) 3429, 3060, 2975, 1600, 1497, 1444, 1373, 1086, 1065, 761, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.19 (m, 5H), 3.87 (qd, J=6.4, 4.4 Hz, 1H), 1.34 (s, 3H), 1.32 (s, 3H), 1.25 (d, J=4.4 Hz, 1H), 1.07 (d, J=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 128.3, 126.6, 126.2, 75.4, 42.6, 24.5, 22.8, 17.6; MS (EI) m/z 163 (M^+-H), 149, 120, 105 (100), 91, 77.

Method b. DIBAL (1.0 M in toluene, 3.75 mL, 3.75 mmol) was added dropwise to a stirred solution of 3-methyl-2-methylene-3-phenyloxetane (**1**) (0.20 g, 1.25 mmol) in dry CH_2Cl_2 (10 mL) at −78°C under N_2. The mixture was stirred at −78°C for 1 h. Then, the reaction was allowed to warm to rt and stirred for two days. Water (5 mL) was added dropwise by syringe, and ice-cold 1 M HCl was then added until the precipitated aluminum hydroxide had dissolved. The layers were separated. The aqueous layer was further extracted with Et_2O (5×15 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. Flash chromatography on silica gel (petroleum ether/EtOAc 90:10) gave **10** (0.12 g, 59%) as a colorless oil.

1.1.15. 3-Methyl-3,5-diphenyl-2-[(trimethylsilyl)oxy]-1-pentene (12). *n*-Butyllithium (1.6 M in hexane, 2.34 mL, 3.74 mmol) was added dropwise to a stirred solution of dry toluene (2 mL) containing TMEDA (0.89 mL, 5.93 mmol) at 0°C under N_2. After stirring for 30 min, the resulting solution turned orange. 3-Methyl-2-methylene-3-phenyloxetane (**1**) (0.50 g, 3.12 mmol) in a small amount of toluene (1 mL) was added dropwise to the reaction mixture. It was left to stir for 1 h at 0°C. Neat TMSCl (1.19 mL, 9.36 mmol) was added dropwise over 3 min; then, the reaction mixture was stirred for 30 min at 0°C. A saturated aqueous $NaHCO_3$ solution (10 mL) was added, the layers were separated. The aqueous layer was extracted with Et_2O (5×20 mL). The Et_2O extracts were combined with the toluene layer, and the solution was washed with saturated aqueous NaCl, dried ($MgSO_4$), filtered, and evaporated in vacuo to afford an orange residue. The resulting oily residue was quickly purified by short column chromatography on silica gel (petroleum ether/triethylamine 99:1). A pale yellow oil (**12**) (0.83 g, quant.) was isolated: IR (film) 3027, 2959, 1620, 1603, 1497, 1252, 1103, 844, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.15 (m, 10H), 4.30 (d, J=1.6 Hz, 1H), 4.18 (d, J=1.6 Hz, 1H), 2.58 (ddd, J=12.8, 12.8, 4.7 Hz, 1H), 2.42 (ddd, J=12.8, 12.8, 4.7 Hz, 1H), 2.23 (ddd, J=12.8, 12.8, 4.7 Hz, 1H), 2.09 (ddd, J=12.8, 12.8, 4.7 Hz, 1H), 1.49 (s, 3H), 0.04 (s, 9H); MS (EI) m/z 309 (M^+-CH_3), 220 (100), 205, 91, 77, 73, 51.

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