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A convergent regiospecific synthesis of zirconium enolates

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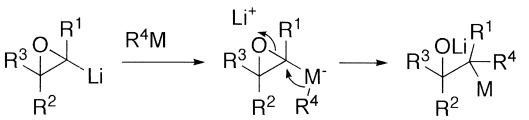
Abstract—α-Lithiated phenylsulphonyloxiranes insert into alkenylzirconocene chlorides with loss of phenylsulphinate to give zirconyloxiranes which smoothly rearrange by either α- or β- C–O cleavage to afford regiodefined zirconium enolates which may be further elaborated.

1. Introduction

Metallated oxiranes are widely used as nucleophiles, and as sources of carbenes, but their use as carbenoids is much less studied.[1] The term 'carbenoid' was initially used for 1-halo-1-metallo (usually lithio) species.[2] The ring-strain present in metallated oxiranes renders the alkoxide a sufficiently good leaving group that carbenoid properties may be observed.[1] We are interested in the insertion of carbenoids into carbon–metal bonds to afford new organometallic species—an inherently iterative reaction ideally suited to the development of novel multi component couplings. Lithiated oxiranes react with excess organolithium reagent to give products formally derived by such an insertion, although the reaction is normally drawn as occurring via a free carbene formed by α-elimination.[1,3] A 'carbenoid' mechanism for the addition is via nucleophilic[4] ring opening of the oxirane, probably best drawn as occurring via 1,2-rearrangement of a 'lithium-ate' intermediate[5] (Eq. (1), M=Li). The reaction of lithiated oxiranes with organoaluminium compounds almost certainly occurs via such a 1,2-metallate rearrangement of an 'ate' complex (Eq. (1), M=AlR_2).[6] Negishi has demonstrated the insertion of α-lithio-α-halo species into a variety of transition metal species.[7] Insertion into organozirconocenes was particularly facile, probably because these exist as co-ordinatively unsaturated '16 electron' complexes which readily add the carbenoid to afford an 18 electron 'ate' complex which may undergo a 1,2-metallate rearrangement to afford the product (Eq. (2)).



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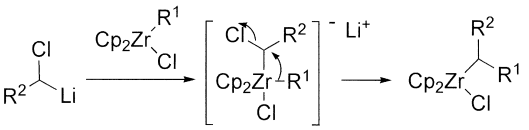

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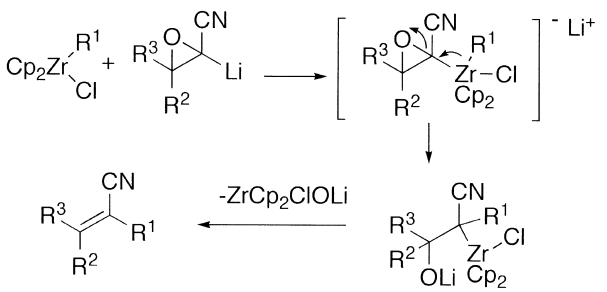
We have developed the insertion of a wide variety of carbenoids into zirconacycles and acyclic organozirconocene chlorides to provide useful multi component coupling methods.[8–11] As part of this work we have demonstrated the insertion of lithiated oxiranes into zirconacycles[10] and acyclic organozirconocene chlorides.[11] For example we recently reported the addition of lithiated cyanooxiranes to organozirconocene chlorides with opening of the oxirane ring to afford α,β-unsaturated nitriles after elimination of zirconocene oxide (Scheme 1).[11] We now report the



Scheme 1. Insertion of lithiated cyanooxiranes into organozirconocene chlorides.

Keywords: zirconium enolate; carbenoid; lithiated oxirane; multi-component; rearrangement.

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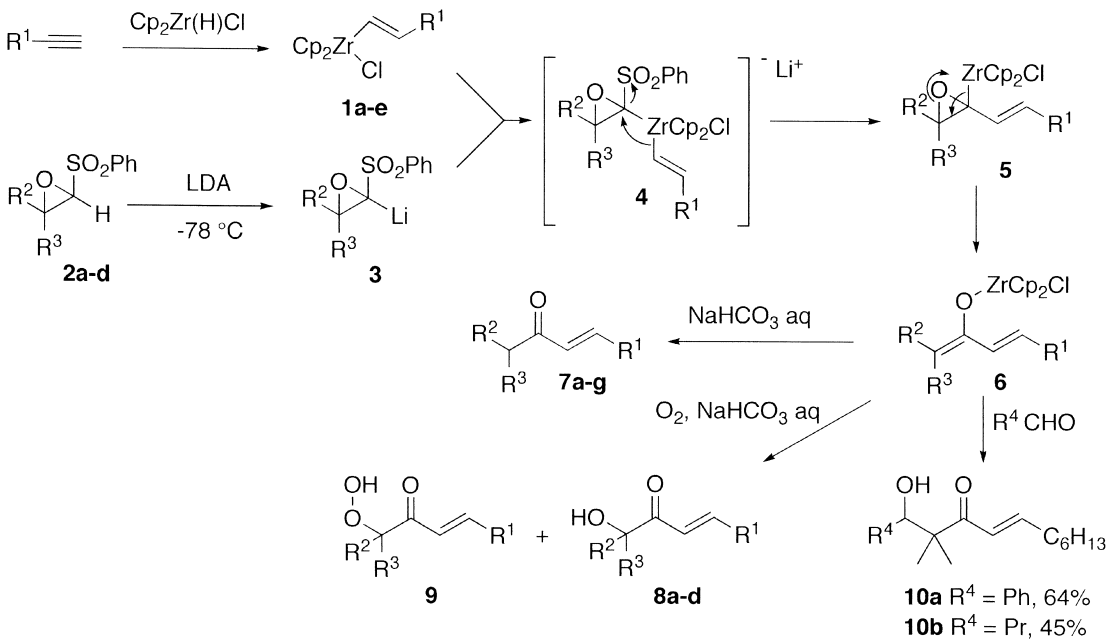
remarkably different course taken by the insertion when lithiated phenylsulphonyloxiranes are used.

2. Results and discussion

2.1. Insertion of β,β-disubstituted α-lithiated phenylsulphonyloxiranes

Hydrozirconation of 1-octyne gave the alkenylzirconium species **1a**. After cooling to −78°C addition of the β-disubstituted phenylsulphonyloxirane **2a** followed by lithium diisopropylamide (LDA) to generate the lithiated oxirane **3**[12] in situ, warming to −60°C, then quenching by pouring into aqueous sodium bicarbonate solution gave a mixture of the ketone **7a** and α-hydroxyketone **8a** in 13 and 63% isolated yields, respectively. The formation of **7a** and **8a** implies the intermediate formation of the zirconium enolate **6a**.[13] A reasonable mechanism is attack of the lithiated phenylsuphonyloxirane **3** on the alkenylzirconocene chloride **1** to form an 'ate' complex **4** which undergoes a 1,2-metallate rearrangement with loss of phenylsulphinate to afford the zirconyloxirane **5**. This is the first example of reaction of a metallated oxirane with a nucleophile which does not directly cleave the oxirane ring. Presumably the difference in behaviour compared with cyanooxiranes (Scheme 1) is due to the much greater stability of the phenylsulphinate anion compared with cyanide (p*K*a values of phenylsulphinic acid and hydrogen cyanide in water are 2.1 and 9.2, respectively). The presence of the oxirane oxygen is essential for sulphinate to act as a leaving group in the 1,2-metallate rearrangement. For example lithiated alkylsulphones do not insert into alkenylzirconocene chlorides, but lithiated methoxymethylenesulphone does.[9] Rearrangement of the zirconyloxirane **5** then affords the zirconium enolate **6** which may be protonated to afford the ketone **7**.

Rearrangements of lithiated oxiranes to carbonyl compounds are known but these generally occur by cleavage of the α-C–O bond and a mechanism involving a carbene intermediate is usually postulated.[1,14] Often yields and selectivity are poor, and there are few examples of the proposed intermediate enolates being productively trapped.[15] The only rearrangements of metallated oxiranes to enolates which unambiguously involve cleavage of the β



Scheme 2. Formation and reactions of zirconium dienolates derived from β,β-disubstituted α-lithiated phenylsulphonyloxiranes.

Table 1. Formation and reaction of zirconium enolates derived from β,β-disubstituted phenylsulphonyloxiranes

Entry	Zirconocene **1**		Phenylsulphonyloxirane **2**			Ketone **7**		α-Hydroxyketone **8**	
	R^1		R^2	R^3		Yield (%)[a]		Yield (%)[a]	
1	n-C_6H_{13}	**1a**	Me	Me	**2a**	87	**7a**	63	**8a**
2	n-C_6H_{13}	**1a**	$-(CH_2)_5-$		**2b**	84	**7b**	60	**8b**
3	$(CH_2)_2OBn$	**1b**	$-(CH_2)_5-$		**2b**	40	**7c**		
4	$(CH_2)_2OSi^tBuMe_2$	**1c**	$-(CH_2)_5-$		**2b**	79	**7d**	51	**8c**
5	$SiMe_3$	**1d**	$-(CH_2)_5-$		**2b**	50	**7e**	38	**8d**
6	n-C_6H_{13}	**1a**	$-(CH_2)_2C(O(CH_2)_2O)(CH_2)_2-$		**2c**	77	**7f**		
7	n-C_6H_{13}	**1a**	Me	Bu	**2d**	77	**7g**		

[a] Isolated yields based on phenylsulphonyloxirane.

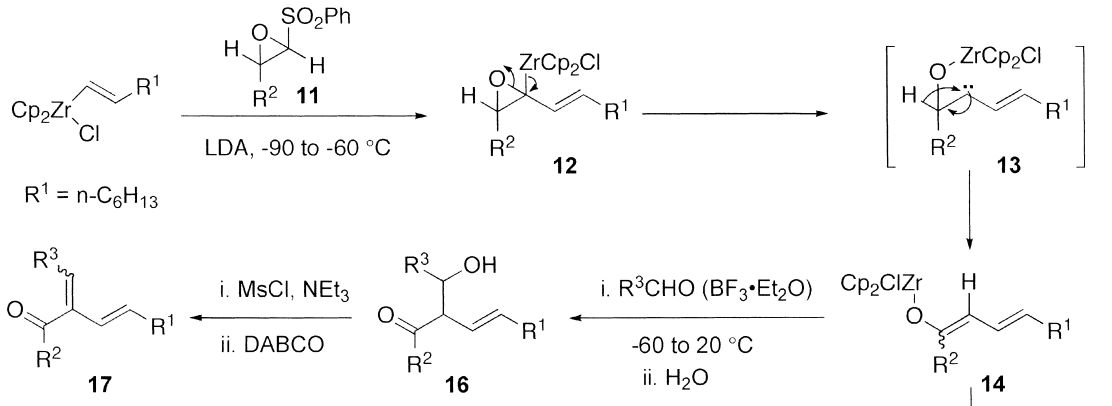
C–O bond of which we are aware is of terminally lithiated monosubstituted oxiranes, and lithiated oxazolinyl oxiranes.[16] The mechanism of β C–O bond cleavage of lithiated oxiranes to afford an enolate may be viewed as an electrocyclic ring opening,[1,14,16] but for **5** to **6** we believe a 1,2-elimination more reasonable. The very poor overlap between the σ* orbital of the breaking C–O bond and C–Zr σ-bond in the starting oxirane implies that substantial electron donation from the latter can only occur late on the reaction pathway i.e. when the C–O bond is largely/completely cleaved. A very similar mechanism is suggested for Lewis acid catalysed rearrangements of β,β-disubstituted silyloxiranes.[17a,b] With the 1,2-elimination mechanism formation of the enolate should be stereospecific, though we have not yet investigated this aspect of the reaction.

The remarkably facile oxidation of the enolate **6** to afford the alcohol **8** on aqueous quench in air is notable.[18] Quenching with deoxygenated water under argon gave only the ketone **7**. Quenching the reaction mixture under an oxygen atmosphere slightly improved the selectivity for **8** over **7**, but also gave a little (5–10%) of the hydroperoxide **9**. The small amounts of hydroperoxide **9** formed could be converted to the alcohol **8** in situ by addition of dimethylsulphide. Stirring the enolate **6** under an oxygen atmosphere for 30 min followed by careful purging (via freeze/evacuate/thaw cycles) of all the oxygen before quenching with oxygen free aqueous sodium bicarbonate solution gave only the ketone **7**. The simultaneous presence of oxygen and aqueous sodium bicarbonate is thus necessary for the formation of **8** and **9**. The predominant formation of the alcohol **8** rather than hydroperoxide **9** in the reaction has some precedent,[18] but could also be due to the presence of phenylsulphinic acid, a competent reducing agent, from the initial elimination. By variation of the starting alkyne, and phenylsulphonyloxirane, a range of ketones **7** and α-hydroxyketones **8** were formed in reasonable yield (Table 1). Formation of the β-silylenones **7d** and **8c** are notable.

We further demonstrated the utility of the enolate **6** derived from zirconocene **1a** and phenylsulphonyloxirane **2a** by quenching the reaction with benzaldehyde and butanal to afford aldol products **10a** and **10b** in reasonable overall yields for a three component coupling reaction (Scheme 2).

2.2. Insertion of β-monosubstituted α-lithiated phenylsulphonyloxiranes

The reaction of α-lithiated β-monosubstituted-(*E*)-phenylsulphonyloxiranes **11** with (*E*)-1-octenylzirconocene chloride followed by aqueous quench gave the β,γ-unsaturated ketones **15** implying the enolates **14** as intermediates (Scheme 3). The reaction thus follows a similar course to that shown in Scheme 2 as far as the zirconyloxirane **12**, but then opening of the oxirane occurs with cleavage of the bond between oxygen and the metallated carbon (α-cleavage). There are several ways to describe the mechanism for the rearrangement of **12** to **14**. Initial α-elimination of zirconium alkoxide to afford the carbene **13** which inserts into the β C–H bond to afford the enolate **14** (Scheme 3) is favoured by the strong affinity of zirconium for oxygen. It is also the mechanism usually drawn for rearrangement of lithiated oxiranes to enolates.[1,14] Alternatively cleavage of the α C–O bond accompanied by 1,2-hydride migration to afford the α-zirconylketone **18**, which may rearrange to the enolate **14** (Eq. (3)) has precedent in the Lewis acid catalysed rearrangement of many oxiranes,[19] in particular of silyloxiranes to β-silylketones.[17a,c] The above are two extreme forms of a mechanism in which α-elimination of zirconium alkoxide is concerted with migration of the β-hydride to afford **14** directly (Eq. (4)). The transition state **19** for this process



16/17	R^2	R^3	Yield **16** (ds ratio)	Yield **17** (*Z*,*E* : *E*,*E*)
a	Pr	Ph	65% (74 : 26)	57% (72 : 28)[a]
b	Pr	Pr	54% (71 : 29)	60% (84 : 16)[a]
				60% (92 : 8)[b]
c	^{i}Pr	Ph	68% (60 : 40)	65% (72 : 28)[a]
				62% (95 : 5)[b]

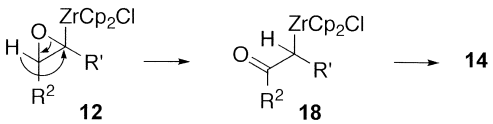
[a] From major diastereoisomer of **16**. [b] From minor diastereoisomer of **16**.

15	R^2	Yield **15**[a]
a	Pr	72%
b	^{i}Pr	85%
c	Ph	12% (23%[b])

[a] isolated yield based on sulphonyloxirane.
[b] Using (*Z*)-sulphonyloxirane

Scheme 3. Formation and reactions of zirconium dienolates derived from β-monosubstituted α-lithiated phenylsulphonyloxiranes.

resembles that well established for Simmons Smith cyclopropanation,[20] however, initial orbital alignment is very poor implying a late transition state with much of the character of **13**. Cope demonstrated that in rearrangements of lithiated oxiranes via α C–O bond cleavage to afford carbonyl compounds it is the group *cis* to the metal which migrates.[21] The Lewis acid induced rearrangement of silyloxiranes to β-silyl ketones has also been shown to involve selective 1,2-migration of the group *cis* to the silicon.[17a,c] It is thus surprising that we found that the yield of ketone **15c** from (*Z*)-β-phenyl phenylsulphonyloxirane was higher than from the (*E*)-isomer **11** (R^2=Ph), though both were poor.



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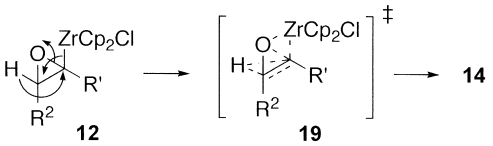

(4)

It is interesting that even when the aqueous quench of enolates **14** was carried out in an atmosphere of oxygen there was no formation of α-hydroxyketones analogous to **8**. Work-up of the enolates with aldehydes gave the aldol products **16** in good overall yield but poor diastereoselectivity. Alkyl aldehydes required the addition of $BF_3{\cdot}Et_2O$ for clean reaction. Although the aldol products could be separated by column chromatography they were rather unstable and elimination to the α,β-unsaturated ketones **17** was used to provide more stable derivatives. The *E*/*Z* composition of the products **17** was influenced by the diastereoisomer of the aldol product **16** used, but was not stereospecific.

2.3. Explanation of reactivity and regioselectivity

The remarkably facile rearrangement of α-zirconyl oxiranes to zirconium enolates, and the difference in behaviour of β-monosubstitituted and β,β-disubstituted phenylsulphonyloxiranes in giving regioisomeric dienolates **6** and **14**, respectively requires explanation. We believe that action of the zirconium as a Lewis acid towards the oxirane oxygen during these rearrangements is important. The structure of $Cp_2Zr(Cl)(CH_2OMe)$ shows strong bonding between the oxygen and zirconium, and its reactivity is consistent with an 'oxonium ion' depiction.[22] The rearrangements of zirconyloxiranes to enolates could thus be considered to be both 'pushed' by the anionic character of the carbon to which zirconium is attached, and 'pulled' by Lewis acid interaction of the zirconium with the oxirane oxygen.

The transition state for rearrangement of the zirconyl oxiranes **5** to enolates **6** (β-C–O cleavage) must involve substantial positive charge build-up on the carbon β to the zirconium since the zirconium-carbon bond is initially close to orthogonal to the breaking C–O bond's σ* orbital. The β-C–O bond cleavage will thus be strongly favoured when the β-position is tertiary, as in **5** (cf. secondary as in **12**). The Lewis acid catalysed rearrangement of silyloxiranes shows the same regiochemical preference.[17] In **12** breaking of the β C–O bond is disfavoured as positive charge build-up would be on a secondary centre, and the observed 1,2-shift favoured by the good migrating group ability of hydride.

3. Conclusions

Reaction of in situ generated α-lithio phenylsulphonyloxiranes with alkenylzirconocene chlorides derived by hydrozirconation of alkynes affords zirconyloxiranes which incorporate the alkenyl fragment via a 1,2-metallate rearrangement with loss of phenylsulphinate. Subsequent rearrangement to zirconium enolates through cleavage of either α- or β-oxirane C–O bonds is facile, probably due to promotion by the Lewis acidity of the zirconium. The enolates so formed may be further elaborated by aldol reaction to provide a novel one-pot three component coupling reaction. The exceptionally facile oxidation of 1,1-disubstututed-2-(chloro(biscyclopentadienyl)zirconyl)-oxydienes with air to afford α-hydroxyketones is also notable.

4. Experimental

4.1. General techniques

^1H and ^{13}C NMR spectra were recorded on a Bruker AC300 spectrometer (300 MHz proton, 75 MHz carbon) in $CDCl_3$. Chemical shifts are reported as values in ppm relative to tetramethylsilane, referenced to solvent ($CHCl_3/CDCl_3$). The following abbreviations are used in proton spectra to denote multiplicity and shape of signal and may be compounded: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. ^{13}C spectra were proton decoupled. Atmospheric pressure chemical ionisation (APCI) mass spectra were recorded on a VG Platform spectrometer in acetonitrile. *m/z* signals are reported as values in atomic mass units followed by the peak intensity relative to the base peak. High Resolution Mass Spectra (HRMS) were recorded on a VG Analytical 70-250-SE double focusing mass spectrometer using either electron impact (EI) (70 eV) or chemical ionisation (CI) (using ammonia as the reagent gas) as indicated. Infra-red spectra were recorded on a Perkin–Elmer 1600 FT-IR spectrometer as films between sodium chloride plates. Elemental analyses were performed by the University College London Microanalysis Service. Organometallic reactions were performed under argon using standard Schlenk techniques. Boiling points (bp) refer to oven temperatures in Kugelrohr distillation at the pressure specified.

4.2. Materials

$Cp_2Zr(H)Cl$ (Schwartz reagent) was purchased from Aldrich and weighed out in a glovebag under nitrogen. The phenylsulphonyloxiranes were prepared by the reaction of phenyl chloromethyl sulphone with acetone, cyclohexanone, 1,4-cyclohexanedione mono-ethylene ketal, methyl pentyl ketone, butanal, and isobutanal, respectively, in 50% aq. NaOH–triethylbenzylammonium chloride (cat.) system.[23,24] *Trans*- and *cis*-2-phenyl-1-phenylsulphonyloxiranes were prepared by stereoselective epoxidation of

trans- and *cis*-β-styryl phenyl sulphones with lithium *tert*-butyl hydroperoxide.[25] Tetrahydrofuran was freshly distilled from sodium/benzophenone. Petrol refers to the fraction of petroleum ether that has a boiling range 40–60°C and was distilled before use.

4.3. General procedure for the formation of zirconium enolates

To a stirred suspension of $Cp_2Zr(H)Cl$ (0.297 g, 1.15 mmol) in THF (9.0 mL) was added 1-octyne (0.110 g, 1.00 mmol). The mixture was stirred at 20°C for 1 h to give a clear yellow solution of (*E*)-octenylzirconocene chloride. After cooling to −90°C a solution of the phenylsulphonyloxirane **2a** (0.163 g, 0.77 mmol) in THF (2.5 mL) was added followed by a solution of LDA (1.00 mmol, 0.50 mL, 2.0 M in heptane/THF/ethylbenzene). The reaction mixture was stirred at −90 to −60°C for 1 h to afford a solution of the zirconium enolate ready for the next reactions.

4.4. Protonation of enolates

To the solution of the zirconium enolate prepared above was added degassed saturated $NaHCO_3$ aq. (6 mL) at −60°C. The cooling bath was immediately removed, and the mixture was stirred at 20°C for 1 h. After extraction with ether (2×6 mL) the organic layer washed with 2 M HCl aq. (5 mL), brine (2×10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (40–60 petrol ether/EtOAc mixtures) to give the product α,β- or β,γ-unsaturated ketone as colourless to very pale yellow oils in the yields given in the tables.

4.4.1. (*E*)-2-Methyl-4-undecen-3-one (7a). Bp 110–115°C/0.5 mm Hg). Proton and carbon NMR, and IR data consistent with the literature.[26] Anal. calcd for $C_{12}H_{22}O$: C 79.06, H 12.16; found: C 78.82, H 12.37.

4.4.2. (*E*)-1-Cyclohexyl-2-nonen-1-one (7b). Bp 140–145°C/0.5 mm Hg. ^{1}H NMR: δ 0.80 (m, 3H), 1.10–1.45 and 1.55–1.80 (m, 18H), 2.11 (m, 2H), 2.46 (m, 1H), 6.07 (d, J=15.8 Hz, 1H), 6.78 (dt, J_1=15.8 Hz, J_2=7.0 Hz, 1H). ^{13}C NMR: δ 14.18, 22.68, 25.90, 26.04, 28.24, 28.86, 29.01, 31.73, 32.62, 48.66, 128.70, 147.31, 203.62, IR: 1692, 1665, 1626, 1450, 977, 756 cm^{-1}. Anal. calcd for $C_{15}H_{26}O$: C 81.02, H 11.79; found: C 81.10, H 11.95.

4.4.3. (*E*)-1-Cyclohexyl-5-benzyloxy-2-penten-1-one (7c). ^{1}H NMR: δ 1.10–1.40 and 1.55–1.80 (m, 10H), 2.46 (m, 3H), 3.52 (t, J=6.4 Hz, 2H), 4.45 (s, 2H), 6.13 (d, J=15.8 Hz, 1H), 6.80 (dt, J_1=15.8 Hz, J_2=7.0 Hz, 1H), 7.24 (m, 5H). ^{13}C NMR: δ 25.90, 26.05, 28.83, 33.02, 48.65, 68.52, 73.21, 127.86, 128.58, 130.25, 138.24, 143.39, 203.43. IR: 1738, 1692, 1664, 1626, 1451, 1365, 1100, 735, 698 cm^{-1}. MS (APCI) 273 (M+H, 51%), 272 (62), 165 (100), 145 (69), 132 (36). HRMS (EI) calcd for $C_{18}H_{24}O_2$ (M): 272.1776, found: 272.1783.

4.4.4. (*E*)-1-Cyclohexyl-5-*tert*-butyldimethylsilyloxy-2-penten-1-one (7d). ^{1}H NMR: δ 0.00 (s, 6H), 0.85 (s, 9H), 1.15–1.40 and 1.55–1.80 (m, 10H), 2.37 (m, 2H), 2.52 (m, 1H), 3.68 (t, J=6.4 Hz, 2H), 6.14 (d, J=15.8 Hz, 1H), 6.80 (dt, J_1=15.8 Hz, J_2=7.0 Hz, 1H). ^{13}C NMR: δ 18.42, 25.89, 26.00, 28.86, 36.07, 48.53, 61.77, 130.37, 143.76, 203.46. IR: 1694, 1669, 1629, 1253, 1102, 835, 776 cm^{-1}. Anal. calcd for $C_{17}H_{32}O_2Si$: C 68.86, H 10.88; found: C 68.77, H 10.89.

4.4.5. (*E*)-1-Cyclohexyl-3-trimethylsilyl-2-propen-1-one (7e). ^{1}H NMR: δ −0.02 (s, 9H), 1.05–1.70 (m, 10H), 2.53 (m, 1H), 6.40 (d, J=19.1 Hz, 1H), 6.95 (d, J=19.1 Hz, 1H). ^{13}C NMR: δ −1.62, 25.88, 26.03, 28.82, 47.91, 140.91, 146.47, 203.15. IR: 1682, 1249, 1219, 1101, 987, 868, 843, 750 cm^{-1}. Anal. calcd for $C_{12}H_{22}OSi$: C 68.51, H 10.54, Si 13.35; found: C 68.40, H 10.51, Si 13.53.

4.4.6. (*E*)-1-(1.4-Dioxaspiro[4.5]dec-8-yl)-2-nonen-1-one (7f). Bp 180–185°C/0.5 mm Hg. ^{1}H NMR: δ 0.88 (m, 3H), 1.20–1.85 (m, 16H), 2.20 (m, 2H), 2.58 (m, 1H), 3.92 (s, 4H), 6.17 (d, J=15.8 Hz, 1H), 6.88 (dt, J_1=15.8 Hz, J_2=7.0 Hz, 1H). ^{13}C NMR: δ 14.20, 22.68, 26.23, 28.21, 29.01, 31.72, 32.63, 34.15, 47.23, 64.44, 108.31, 128.29, 147.71, 202.52. IR: 1692, 1666, 1625, 1458, 1364, 1102, 1035, 929 cm^{-1}. Anal. calcd for $C_{17}H_{28}O_3$: C 72.82, H 10.06; found: 72.47, H 10.17.

4.4.7. (*E*)-6-Methyl-8-pentadecen-7-one (7g). Bp 140–145°C/0.5 mm Hg. ^{1}H NMR: δ 0.82 (m, 6H), 1.00 (d, J=7.0 Hz, 3H), 1.15–1.65 (m, 16H), 2.15 (m, 2H), 2.68 (tq, J_1=J_2=7.0 Hz, 1H), 6.07 (d, J=15.8 Hz, 1H), 6.80 (dt, J_1=15.8 Hz, J_2=7.0 Hz, 1H). ^{13}C NMR: δ 14.17, 16.74, 22.66, 27.13, 28.24, 28.99, 31.73, 32.04, 32.62, 33.39, 43.94, 129.03, 147.49, 204.38. IR: 1696, 1670, 1627, 1459, 1377, 977, 737 cm^{-1}. Anal. calcd for $C_{16}H_{30}O$: C 80.61, H 12.68; found: C 80.38, H 12.76.

4.4.8. (*E*)-6-Tridecen-4-one (15a). Bp 95–100°C/0.5 mm Hg. ^{1}H NMR: δ 0.82 (m, 6H), 1.10–1.35 (m, 10H), 1.52 (tq, J_1=J_2=7.0 Hz, 2H), 1.97 (m, 2H), 2.35 (t, J=7.0 Hz, 2H), 3.02 (d, J=5.2 Hz, 2H), 5.45 (m, 2H). ^{13}C NMR: δ 13.85, 14.21, 17.28, 22.75, 28.95, 29.32, 31.83, 32.72, 44.14, 47.00, 121.99, 135.32, 209.81. IR: 1714, 1464, 1408, 1366, 1124, 967, 725 cm^{-1}. Anal. calcd for $C_{13}H_{24}O$: C 79.53, H 12.32; found: C 79.15, H 12.28.

4.4.9. (*E*)-2-Methyl-5-dodecen-3-one (15b). Bp 90–93°C/0.5 mm Hg. ^{1}H NMR: δ 0.88 (m, 3H), 1.10 (d, J=7.0 Hz, 6H), 1.20–1.40 (m, 8H), 2.02 (m, 2H), 2.67 (qq, J_1=J_2=7.0 Hz, 1H), 3.12 (d, J=5.2 Hz, 2H), 5.52 (m, 2H). ^{13}C NMR: δ 14.07, 18.18, 22.60, 28.80, 29.19, 31.69, 32.58, 40.15, 44.47, 121.99, 134.90, 213.18. IR: 1714, 1466, 1382, 967 cm^{-1}. Anal. calcd for $C_{13}H_{24}O$: C 79.53, H 12.32; found: C 79.44, H 12.30.

4.4.10. (*E*)-1-Phenyl-3-decen-1-one (15c). ^{1}H NMR: δ 0.88 (m, 3H), 1.20–1.40 (m, 8H), 2.05 (m, 2H), 3.70 (d, J=5.1 Hz, 2H), 5.65 (m, 2H), 7.42–7.60 and 7.98 (m 5H). IR: 1686, 1448, 1207, 967, 754, 690 cm^{-1}. MS (APCI) 231 (M+H, 100%). HRMS (CI) calcd for $C_{16}H_{23}O$ (M+H): 231.1749, found: 231.1728.

4.5. Oxidation of enolates

The solution of the zirconium enolate prepared above was

added dropwise to saturated $NaHCO_3$ aq. (20 mL) at 20°C with vigorous stirring under an oxygen atmosphere. The resulting mixture was stirred at 20°C for 1 h and extracted with ether (2×6 mL). The organic layer was washed with brine (2×10 mL), then Me_2S (0.095 g, 1.54 mmol) was added and the mixture was kept at 20°C overnight. After drying over $MgSO_4$ and concentration under reduced pressure the residue was purified by column chromatography on silica gel (40–60 petrol ether/EtOAc, mixtures) to give the product α-hydroxyketones as colourless oils in the yields given in Table 1.

4.5.1. (*E*)-2-Methyl-2-hydroxy-4-undecen-3-one (8a). ^{1}H NMR: δ 0.79 (m, 3H), 1.15–1.45 (m, 8H), 1.30 (s, 6H), 2.20 (m, 2H), 3.95 (br s, 0H), 6.35 (d, J=15.4 Hz, 1H), 7.07 (dt, J_1=15.4 Hz, J_2=7.0 Hz, 1H). ^{13}C NMR: δ 14.44, 22.93, 26.72, 28.34, 29.25, 31.95, 33.18, 75.51, 122.54, 151.66, 202.78. IR: 3450 br, 1688, 1625, 1465, 1362, 1163, 1081, 971 cm^{-1}. MS (APCI) 199 (M+H, 100%), 181 (14), 153 (30). HRMS (CI) calcd for $C_{12}H_{23}O_2$ (M+H): 199.1698, found: 199.1693.

4.5.2. (*E*)-1-(1-Hydroxycyclohexyl)-2-nonen-1-one (8b). ^{1}H NMR: δ 0.90 (m, 3H), 1.20–1.80 (m, 18H), 2.25 (m, 2H), 3.87 (br s, 0H), 6.50 (d, J=15.4 Hz, 1H), 7.16 (dt, J_1=15.4 Hz, J_2=7.0 Hz). ^{13}C NMR: δ 14.19, 21.25, 22.67, 25.49, 28.13, 29.01, 31.71, 32.95, 33.76, 77.03, 122.56, 151.07, 202.63. IR: 3450 br, 1682, 1622, 985 cm^{-1}. MS (APCI) 239 (M+H, 100), 221 (12), 139 (32). HRMS (EI) calcd for $C_{15}H_{27}O_2$ (M+H): 239.2011, found: 239.2011.

4.5.3. (*E*)-1-(1-Hydroxycyclohexyl)-5-*tert*-butyldimethylsilyloxy-2-penten-1-one (8c). ^{1}H NMR: δ 0.02 (s, 6H), 0.85 (s, 9H), 1.20–1.75 (m, 10H) 2.43 (m, 2H), 3.74 (t, J=6.4 Hz, 2H), 3.80 (br s, 0H), 6.53 (d, J=15.4 Hz, 1H), 7.08 (dt, J_1=15.4 Hz, J_2=7.0 Hz, 1H). ^{13}C NMR: 18.38, 21.22, 25.47, 25.98, 33.70, 36.30, 61.43, 77.05, 124.25, 147.51, 202.40. IR: 3450 br, 1684, 1626, 1255, 1096, 984, 835, 776 cm^{-1}. MS (APCI) 313 (M+H, 100), 295 (8), 213 (16). HRMS (EI) calcd for $C_{17}H_{33}O_3Si$ (M+H): 313.2199, found: 313.2204.

4.5.4. (*E*)-1-(1-Hydroxycyclohexyl)-3-trimethylsilyl-2-propen-1-one (8d). ^{1}H NMR: δ 0.03 (s, 9H), 1.10–1.65 (m, 10H), 3.52 (s, 0H), 6.76 (d, J=19.1 Hz, 1H), 7.25 (d, J=19.1 Hz, 1H). ^{13}C NMR: δ −1.68, 21.16, 25.41, 33.65, 77.17, 134.35, 151.10, 201.81. IR: 3400 br, 1681, 1249, 1219, 987, 868, 844, 750 cm^{-1}. HRMS (CI) calcd for $C_{12}H_{23}O_2Si$ (M+H): 227.1467, found: 227.1455.

4.6. Reaction of enolates with aldehydes

To the solution of the zirconium enolate prepared above was added the aldehyde (1.16 mmol) at −60°C. The mixture was allowed to warm to 20°C over 2 h, stirred at 20°C for 1 h and hydrolysed with $NaHCO_3$ aq. (6 mL). After extraction with ether (2×6 mL) the organic layer was washed with 2 M HCl aq. (5 mL), brine (2×10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (40–60 petrol ether/EtOAc mixtures) to give the aldol products in the yields given in the Schemes and Tables.

4.6.1. (*E*)-1-Phenyl-1-hydroxy-2,2-dimethyl-4-undecen-3-one (10a). ^{1}H NMR: δ 0.91 (m, 3H), 1.07 (s, 3H), 1.17 (s, 3H), 1.25–1.55 (m, 8H), 2.25 (m, 2H), 3.37 (br s, 0H), 4.96 (s, 1H), 6.56 (d, J=15.4 Hz, 1H), 7.04 (dt, J_1=15.4 Hz, J_2=7.0 Hz, 1H), 7.33 (m, 5H). ^{13}C NMR: δ 14.23, 18.19, 22.71, 22.80, 28.24, 29.04, 31.74, 32.78, 51.01, 78.38, 124.87, 127.70, 127.83, 128.10, 140.28, 149.32, 205.65. IR: 3450 br, 1738, 1681, 1619, 1365, 1228, 1217, 703 cm^{-1}. MS (APCI) 287 (M+H, 9%), 271 (8), 224 (100), 183 (71), 139 (37). HRMS (EI) calcd for $C_{19}H_{28}O_2$ (M): 288.2089, found: 288.2093.

4.6.2. (*E*)-4-Hydroxy-5,5-dimethyl-7-tetradecen-6-one (10b). ^{1}H NMR: δ 0.93 (m, 6H), 1.15 (s, 3H), 1.20 (s, 3H), 1.25–1.70 (m, 12H), 2.23 (m, 2H), 2.57 (br s, 0H), 3.70 (m, 1H), 6.50 (d, J=15.4 Hz, 1H), 6.98 (dt, J_1=15.4 Hz, J_2=7.0 Hz, 1H). ^{13}C NMR: δ 14.19, 19.55, 20.07, 21.61, 22.69, 28.23, 29.01, 31.72, 32.73, 33.72, 50.60, 76.19, 124.87, 148.96, 205.45. IR: 3450 br, 1682, 1620, 1466, 977 cm^{-1}. MS (APCI) 255 (M+H, 100), 224 (61), 183 (45), 139 (28). HRMS calcd for $C_{16}H_{31}O_2$ (M+H): 255.2324, found: 255.2326.

4.6.3. (*E*)-5-[Hydroxy(phenyl)methyl]-6-tridecen-4-one (16a). ^{1}H NMR: δ 0.70 (t, J=6.8 Hz, 3H), 0.80 (m, 3H), 1.00–1.55 (m, 10H), 1.97 (m, 2H), 2.05 and 2.30 (two m, 2H), 3.07 (br s, 0H), 3.25 (dd, J_1=8.5 Hz, J_2=5.9 Hz, 1H), 4.90 (d, J=5.9 Hz, 1H), 5.40–5.55 (m, 2H), 7.20 (m, 5H) (main isomer); 0.80 (m, 6H), 1.00–1.55 (m, 10H), 1.80 (m, 2H), 2.22–2.48 (m, 2H), 3.07 (br s, 0H), 3.38 (dd, J_1=9.2 Hz, J_2=8.5 Hz, 1H), 4.85 (d, J=8.5 Hz, 1H), 5.11 (dd, J_1=15.4 Hz, J_2=9.2 Hz, 1H), 5.30 (dt, J_1=15.4 Hz, J_2=6.6 Hz, 1H), 7.20 (m, 5H) (minor isomer). ^{13}C NMR: δ 13.67, 14.23, 16.78, 22.74, 28.85, 29.16, 31.79, 32.80, 44.79, 64.09, 73.70, 123.44, 126.63, 127.67, 128.28, 138.48, 141.45, 212.43 (main isomer).

4.6.4. 1-Phenyl-2-(1-octenyl)-1-hexen-3-one (17a). To a solution of **16a** (0.151 g, 0.50 mmol) in CH_2Cl_2 (3.0 mL) was added triethylamine (0.101 g, 1.00 mmol) and MsCl (0.074 g, 0.65 mmol) at 0°C. The reaction mixture was stirred at 0 to 20°C for 3 h, then diluted with ether (6 mL) and washed with 2 M HCl aq. (5 mL) followed by saturated $NaHCO_3$ aq. (5 mL). After drying over $MgSO_4$ and concentration under reduced pressure the crude mesylate was dissolved in CH_2Cl_2 (3.0 mL). DABCO (0.084 g, 0.75 mmol) was added, the mixture was stirred at 20°C for 18 h and diluted with ether (6 mL). After washing with 2 M HCl aq. (5 mL) the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude diene was purified by column chromatography on silica gel (40–60 petrol ether/EtOAc, 20:1) to afford the title dienone **17a** (0.081 g, 57% yield) as a mixture of *Z*,*E*- and *E*,*E*-isomers. ^{1}H NMR: δ 0.82 (m, 3H), 0.91 (t, J=6.8 Hz, 3H), 1.15–1.40 (m, 8H), 1.62 (tq, J_1=J_2=6.8 Hz, 2H), 2.08 (m, 2H), 2.65 (t, J=7.4 Hz, 2H), 5.88 (dt, J_1=16.2 Hz, J_2=7.0 Hz, 1H), 6.20 (d, J=16.2 Hz, 1H), 6.93 (s, 1H), 7.10–7.40 (m, 5H) (*Z*,*E*-isomer); 0.77 (m, 3H), 0.91 (t, J=6, 8 Hz, 3H), 1.15–1.40 (m, 8H), 1.52 (tq, J_1=J_2=6.8 Hz, 2H), 2.04 (m, 2H), 2.32 (t, J=7.4 Hz, 2H), 5.56 (dt, J_1=15.8 Hz, J_2=7.0 Hz, 1H), 6.02 (d, J=15.8 Hz, 1H), 6.36 (s, 1H), 7.10–7.40 (m, 5H) (*E*,*E*-isomer). ^{13}C NMR: δ 14.01, 14.26, 18.19, 22.75, 29.08, 31.85, 33.73, 42.64, 123.61, 128.42, 128.67, 130.24, 133.86,

135.93, 138.47, 139.90, 204.67 (*Z*,*E*-isomer); 13.76, 17.03, 29.19, 33.31, 45.58, 127.95, 128.12, 129.37, 134.27, 143.25, 210.20 (*E*,*E*-isomer). IR: 1682, 1640, 1593, 1491, 1465, 1378, 963, 756, 696 cm^{-1}. HRMS (EI) calcd for $C_{20}H_{28}O$ (M): 284.2140, found: 284.2132.

4.6.5. (*E*)-5-(1-Hydroxybutyl)-6-tridecen-4-one (16b). Method as for **16a**, except that 1 equiv. $BF_3{\cdot}Et_2O$ was added dropwise directly after the butanal. ^1H NMR: δ 0.83 (m, 6H), 1.15–1.55 (m, 14H), 2.02 (m, 2H), 2.27–2.53 (m, 2H), 2.95 (br s, 0H), 2.99 (m, 1H), 3.87 (m, 1H), 5.38 (dd, J_1=15.4 Hz, J_2=9.2 Hz, 1H), 5.60 (dt, J_1=15.4 Hz, J_2=6.6 Hz, 1H) (main isomer); 0.85 (m, 6H), 1.15–1.55 (m, 14H), 1.97 (m, 2H), 2.25–2.50 (m, 2H), 2.58 (d, J=5.9 Hz, 0H), 3.05 (dd, J_1=J_2=9.2 Hz, 1H), 3.80 (m, 1H), 5.17 (dd, J_1=15.4 Hz, J_2=9.2 Hz, 1H), 5.56 (dt, J_1=15.4 Hz, J_2=6.6 Hz, 1H) (minor isomer). ^{13}C NMR: δ 13.80, 14.15, 17.02, 18.97, 22.76, 28.91, 29.28, 31.79, 32.87, 36.44, 44.17, 61.19, 70.61, 123.21, 138.22, 213.87 (main isomer); 13.81, 14.20, 17.04, 18.75, 22.76, 28.88, 29.16, 31.78, 32.77, 36.58, 44.52, 62.99, 71.99, 124.87, 136.94, 213.32 (minor isomer). The product **16b** was converted into the 1,3-diene **17b** (mixture of *Z*,*E*- and *E*,*E*-isomers) as described for **17a**.

4.6.6. 5-(1-Octenyl)-5-nonen-4-one (17b). ^1H NMR: δ 0.75–0.92 (m, 9H), 1.15–1.65 (m, 12H), 2.08 (m, 2H), 2.21 (m, 2H), 2.55 (t, J=7.4 Hz, 2H), 5.74 (dt, J_1=15.8 Hz, J_2=7.0 Hz, 1H), 6.03 (d, J=15.8 Hz, 1H), 6.28 (t, J=7.4 Hz, 1H) (*Z*,*E*-isomer); 0.75–0.92 (m, 9H), 1.15–1.65 (m, 12H), 1.98 (m, 4H), 2.48 (t, J=7.4 Hz, 2H), 5.30 (dt, J_1=15.8 Hz, J_2=7.0 Hz, 1H), 5.38 (t, J=7.4 Hz, 1H), 5.89 (d, J=15.8 Hz, 1H) (*E*,*E*-isomer). ^{13}C NMR: δ 14.07, 14.22, 18.20, 22.59, 22.76, 29.03, 29.33, 31.00, 31.84, 41.64, 122.64, 136.97, 139.66, 139.79, 203.43 (*Z*,*E*-isomer); 13.90, 13.99, 17.08, 22.92, 28.98, 29.24, 31.36, 33.10, 45.83, 128.62, 130.91, 132.12, 142.98, 209.00 (*E*,*E*-isomer). IR: 1678, 1608, 1464, 1378, 967, 897, 739 cm^{-1}. HRMS (EI) calcd for $C_{17}H_{30}O$ (M): 250.2297, found: 250.2296.

4.6.7. (*E*)-2-Methyl-4-[hydroxy(phenyl)methyl]-5-dodecen-3-one (16c). ^1H NMR: δ 0.76 (d, J=7.0 Hz, 3H), 0.83 (m, 3H), 0.88 (d, J=7.0 Hz, 3H), 1.10–1.45 (m, 8H), 1.96 (m, 2H), 2.37 (qq, J_1=J_2=7.0 Hz, 1H), 2.98 (br s, 0H), 3.43 (dd, J_1=9.2 Hz, J_2=6.3 Hz, 1H), 4.88 (d, J=6.3 Hz, 1H), 5.40 (dd, J_1=15.4 Hz, J_2=9.2 Hz, 1H), 5.50 (dt, J_1=15.4 Hz, J_2=6.3 Hz, 1H), 7.22 (m, 5H) (main isomer); 0.79 (m, 3H), 0.88 and 0.95 (two d, J=7.0 Hz, 6H), 1.05–1.45 (m, 8H), 1.80 (m, 2H), 2.61 (qq, J_1=J_2=7.0 Hz, 1H), 3.15 (m, 0H), 3.52 (m, 1H), 4.86 (m, 1H), 5.16 (dd, J_1=15.4 Hz, J_2=9.2 Hz, 1H), 5.32 (dt, J_1=15.4 Hz, J_2=6.3 Hz, 1H), 7.22 (m, 5H) (minor isomer). ^{13}C NMR: δ 14.23, 17.74, 22.75, 28.85, 29.19, 31.79, 32.80, 40.98, 62.99, 74.01, 124.08, 126.71, 127.75, 128.28, 138.37, 141.50, 215.44 (main isomer); 14.24, 17.84, 18.11, 22.71, 28.68, 29.06, 31.78, 32.64, 41.04, 61.92, 75.87, 124.57, 126.72, 127.72, 128.30, 136.82, 142.17, 216.61 (minor isomer). The product **16c** was converted into the 1,3-diene **17c** (mixture of *Z*,*E*- and *E*,*E*-isomers) as described for **17a**.

4.6.8. 1-Phenyl-2-(1-octenyl)-4-methyl-1-penten-3-one (17c). ^1H NMR: δ 0.84 (m, 3H), 1.09 (d, J=7.3 Hz, 6H), 1.10–1.40 (m, 8H), 2.05 (m, 2H), 3.17 (qq, J_1=J_2=7.3 Hz, 1H), 5.81 (dt, J_1=16.2 Hz, J_2=7.0 Hz, 1H), 6.28 (d, J=16.2 Hz, 1H), 6.82 (s, 1H), 7.10–7.40 (m, 5H) (*Z*,*E*-isomer); 0.84 (m, 3H), 0.94 (d, J=7.3 Hz, 6H), 1.10–1.40 (m, 8H), 2.05 (m, 2H), 2.44 (qq, J_1=J_2=7.3 Hz, 1H), 5.55 (dt, J_1=16.2 Hz, J_2=7.0 Hz, 1H), 6.07 (d, J=16.2 Hz, 1H), 6.48 (s, 1H), 7.10–7.40 (m, 5H) (*E*,*E*-isomer). ^{13}C NMR: δ 14.25, 18.91, 22.79, 29.05, 31.84, 33.66, 37.78, 124.04, 128.30, 128.43, 130.13, 132.35, 135.99, 138.21, 139.98, 209.33 (*Z*,*E*-isomer). IR: 3023, 2930, 2851, 1680, 1642, 1600, 1490, 1465, 1375, 1180, 1025, 960, 922, 754 cm^{-1}. HRMS (EI) calcd for $C_{20}H_{28}O$ (M): 284.2140, found: 284.2138.

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