Investigations into the Regioselective *C*-Deuteration of Acyclic and Exocyclic Enolates

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Keywords: Deuterium / Kinetic deuteration / Ketones / Lithium / Isotopic labeling

Results are reported on the regioselective *C*-deuteration of a series of related acyclic and exocyclic enolates derived from substituted aryl ketones. We comment on factors, such as the presence of additives and the structural nature of the enolate, that influence the observed *C*-deuteration and discuss the role of the deuterium donor.

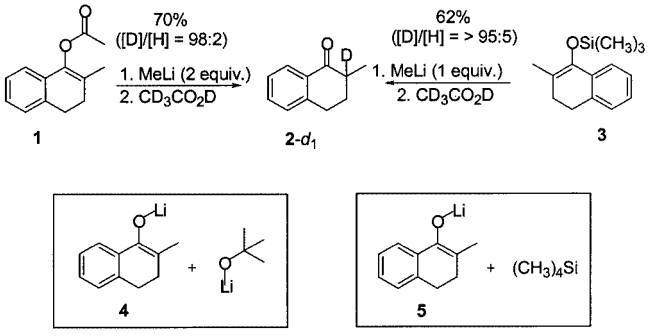
Introduction

Regioselective *C*-deuteration of enolates to give perdeuterated ketones is well documented.[1] The most popular methods involve deuteration under thermodynamic control,[2] which usually means using a large excess of a deuterium donor (e.g., D_2O and $[D_4]$MeOH) in the presence of a sub-stoichiometric amount of base or acid.[3] By comparison, efficient *C*-deuteration under kinetic control[4] has been shown to be far more difficult to achieve.[5] In particular, the method chosen to generate the required kinetic enolate has been shown to have a detrimental effect on the overall level of D-incorporation in some cases; for example, the presence of a base like diisopropylamine[6] has been shown to lower deuterium incorporation through competitive internal proton return.[7]

We have recently reported an efficient method for the regioselective *C*-deuteration of endocyclic enolates by addition of MeLi to a stirred solution of an enol acetate (e.g., **1**)[8] or silyl enol ether (e.g., **3**)[9] and quenching the resulting "base" and "base-free" enolates **4** and **5** with $[D_4]$acetic acid to give the required 2-methyl tetralone **2**-d_1 with near perfect D-incorporation (Scheme 1). We concluded from this study that the structural nature of the endocyclic "base-free" enolate played a minor role in the overall deuteration pathway for efficient *C*-deuteration.[10]

Results and Discussion

We now report our investigation into the study of the kinetic deuteration of acyclic and exocyclic enolates and comment on the acceptable substitution pattern for efficient regioselective *C*-deuteration. For this study, we were required to synthesise a series of related substituted enols, enol acetates **12**−**17** and silyl enol ethers **18**−**23**. These enol derivatives were synthesised from the parent phenyl ketones **6**−**11**, by either refluxing a solution of isopropenyl acetate[8] in the presence of a catalytic amount of *p*TsOH to give the enol acetates **12**,[11] **13**,[12] **14**,[13] **15**, **16**[14] and **17**, or by deprotonation with lithium diisopropylamide (LDA), followed by addition of chlorotrimethylsilane to give the required silyl enol ethers **18**,[15] **19**,[16] **20**,[17] **21**, **22**[18] and **23**[19] (Scheme 2).[10] It should be noted here that, for sterically hindered ketones like cyclobutyl, cyclopentyl and cyclohexyl phenyl ketones **9**, **10** and **11**, a competitive reduction involving β-hydride transfer (from the lithium diisopropylamide) occurs to give the silyl ethers **27**, **28** and **29** in low to moderate yield (Scheme 2, Entries 4−6). This type of competitive reduction using lithium diisopropylamide as a hydride donor has been documented previously.[20]



Scheme 1

We initially probed the deuteration of a series of acyclic and exocyclic enolates derived from enol acetates **12**−**17** by direct addition of MeLi (2 equiv.) to generate the lithium *tert*-butoxide enolate complex. Slow addition of $[D_4]$acetic acid at −78 °C gave the deuterated ketones **6**−**11**-d_1 with

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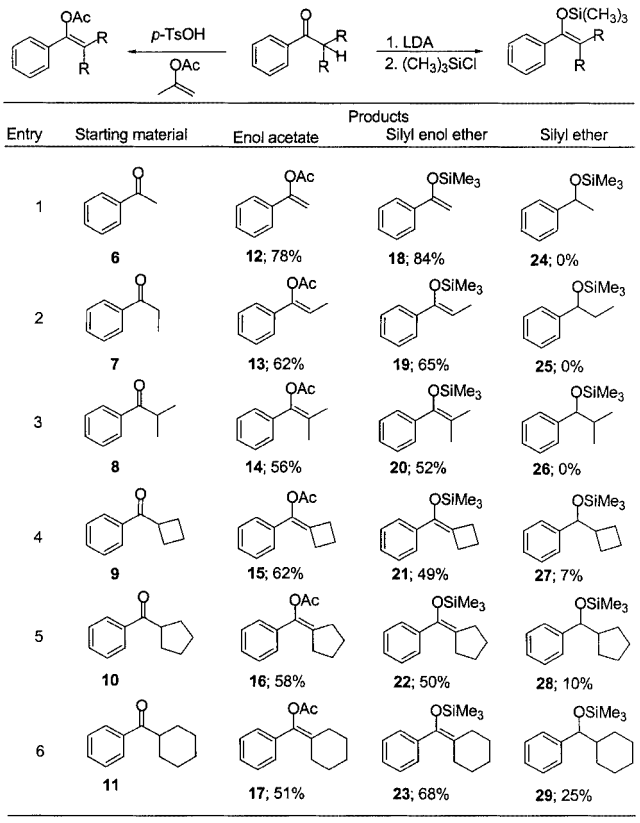
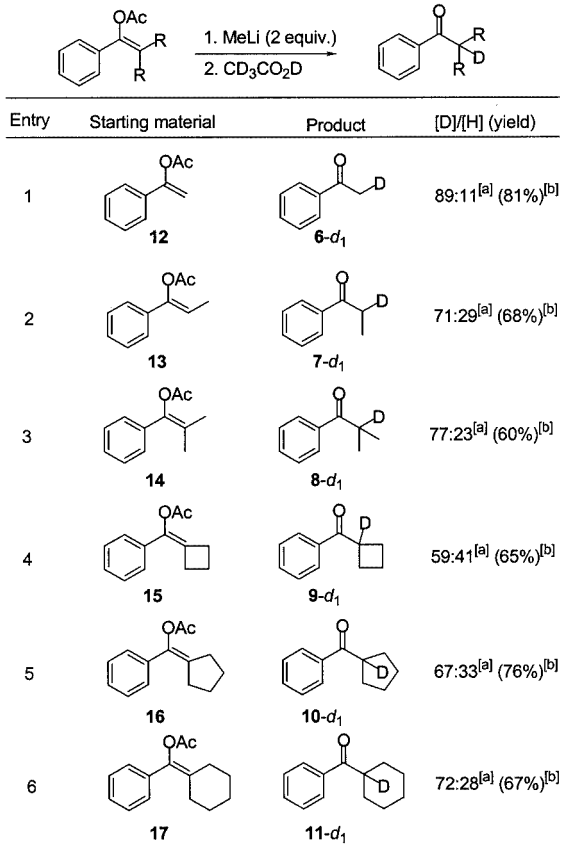


Scheme 2

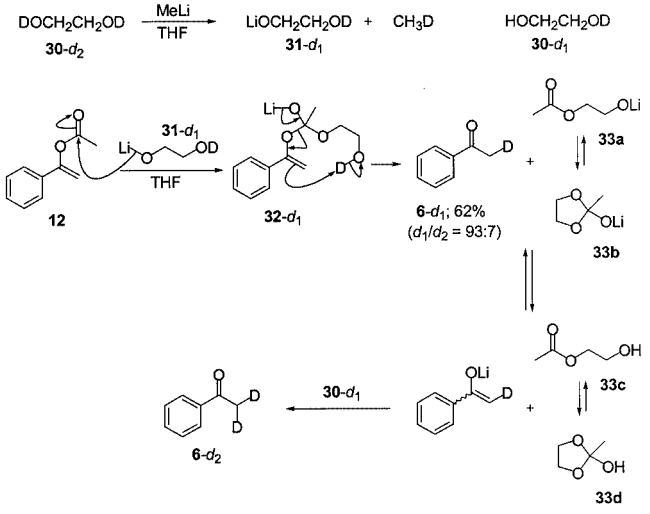
moderate to good D-incorporation (Scheme 3). The simplest case involving the acyclic enolate of acetophenone **6** (derived from the enol acetate **12**) gave the best level of D-incorporation ([D]/[H] = 89:11; 81% yield; Scheme 3, Entry 1). Structural variation of acetophenone **6** at the C-2 position by incorporation of a methyl group (in propiophenone **7**), two methyl groups (in isobutyrophenone **8**) or a carbocyclic ring (in cyclobutyl, cyclopentyl and cyclohexyl phenyl ketone **9**, **10** and **11**, respectively) lowered the level of deuterium incorporation (Scheme 2, Entries 2−6). Presumably, this is in part due to the increased steric demand of a substituted enolate, promoting *O*-deuteration to give the corresponding [D]enol. Loss of this deuterium label has been shown to occur in related cases through tautomerisation under aqueous workup to give the more thermodynamically stable unlabelled starting ketone.[10] This "enol effect" has been shown to occur with sterically hindered enolates.[21] The presence of an additional ring at the C-2 position is slightly more intriguing. The cyclohexyl enol acetate **17** behaves similarly to its noncyclic analogue isobutyrophenone **14**, whereas the smaller carbocyclic analogues cyclobutyl and cyclopentyl enol acetates **15** and **16** gave slightly lower D-incorporation. It is not surprising that a cyclopentyl ketone **10** gave lower *C*-deuteration than its cyclohexyl homologue **11**, since formation of an exocyclic enolate is known to be more kinetically[22] and thermodynamically[23] favoured. However, for cyclobutyl phenyl ketone it appears that regioselective *C*-deuteration is a minor deuteration pathway, which may be due to competitive *O*-deuteration (to give the corresponding [D]enol) being a more efficient pathway (Scheme 3, Entry 4). This at first seems surprising, however, it has been documented that *C*-proton transfer involving cyclobutyl phenyl ketone is more favoured than that of cyclopentyl phenyl ketone under both kinetic[22] and thermodynamic control due to the α-carbon atom (at C-2) having intermediate sp^2/sp^3 hybridisation.[24]



Scheme 3. [a] Isotopic $[D_1]/[D_0]$ ratio. [b] Chemical yield.

In an attempt to increase the level of deuterium incorporation, we probed an alternative method for the removal of the acetate motif by using a nucleophilic deuterium donor, the lithium alkoxide **31**-d_1. We had originally assumed that direct addition of lithium alkoxide **31**-d_1 (formed by addition of MeLi to a stirred solution of ethanediol **30**-d_2 in THF) to the acetate **12** would give the required deuterated ketone (e.g. **6**-d_1) and acetate **33a**+**b** by intramolecular deuterium transfer within the tetrahedral intermediate alkoxide **32**-d_1 (Scheme 4). However, using this methodology gave a slight over-incorporation of deuterium for the enol acetates **12** and **13** (Scheme 5, Entries 1 and 2) and moderate to low D-incorporation for the remaining substituted enol acetates **14**−**16**-d_1 (Scheme 5, Entries 3−5). This excess D-incorporation in acetophenone must come from subsequent deprotonation of the resulting monodeuterated product (e.g., **6**-d_1) with lithium alkoxide **31**-d_1 or **33a**+**b** followed by deuterium exchange involving the intermediate

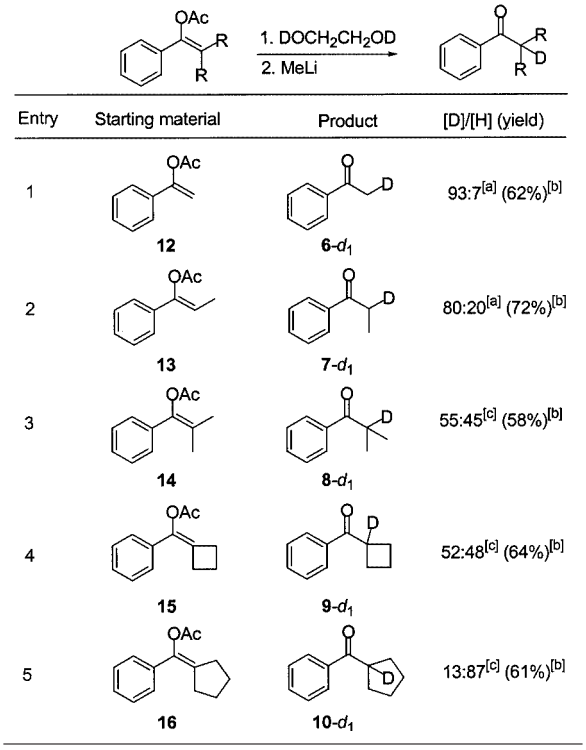
ethane-1,2-diol **30**-d_1. Incomplete D-incorporation may illustrate competitive deuterium exchange resulting in *O*-deuteration leading to the corresponding [D]enol, tautomerisation of which upon aqueous workup would allow the D-label to be exchanged and lost. This lack of D-incorporation presumably illustrates the rate difference between efficient D-transfer involving an oxygen atom based deuteron donor and acceptor to form the corresponding [D]enol and the less-favoured D-transfer pathway involving an oxygen-based deuteron donor and the carbon atom acceptor of an enol in **32**-d_1.[25] For related proton transfer processes, it has been shown that proton transfer between highly electronegative atoms, such as two oxygen atoms, is at least a thousand times faster than that between an oxygen atom and a carbon atom.[25]



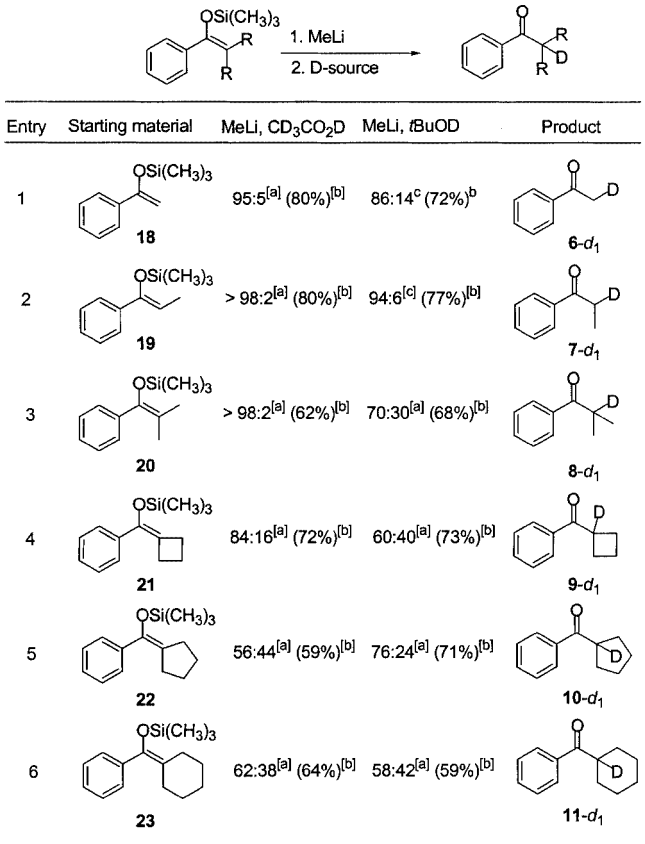
Scheme 4

We have also focused on the use of silyl enol ethers **18**−**23** as a precursor for generating "base-free" lithium enolates to probe the effect of lithium *tert*-butoxide as an additive in these processes. This additive is generated in situ as a by-product from the addition of 2 equiv. of MeLi to the corresponding enol acetate (e.g. **4**). Addition of MeLi to a stirred solution of silyl enol ethers **18**−**23** in THF, followed by addition of [D_4]acetic acid at −78 °C, gave the required deuterated ketones **6**−**11**-d_1 with excellent to moderate D-incorporation (Scheme 6).

The acyclic silyl enol ethers **18**, **19** and **20** [derived from acetophenone (**6**), propiophenone (**7**) and isobutyrophenone (**8**), respectively] gave near perfect deuterium incorporation (> 95%) (Scheme 6, Entries 1−3). The levels of D-incorporation were found to be slightly higher when using a "base-free" enolate (derived from a silyl enol ether) than with a "base" enolate (derived from an enol acetate) as the enolate precursor (Schemes 3 and 6). This difference presumably reflects the more Lewis acidic nature of the lithium counterion present in a "base-free" enolate than that of a "base" enolate (due to the presence of lithium *tert*-butoxide) which presumably assists efficient *C*-deuteration when using a (carbonyl-) directing deuterium source like



Scheme 5. [a] Isotopic [D_1]/[D_2] ratio. [b] Chemical yield. [c] Isotopic [D_1]/[D_0] ratio.



Scheme 6. [a] Isotopic [D_1]/[D_0] ratio. [b] Chemical yield. [c] Isotopic [D_1]/[D_2] ratio.

[D_4]acetic acid.[10] No over-incorporation of deuterium occurs when using [D_4]acetic acid due to the low basicity of the intermediate conjugate base, lithium acetate.

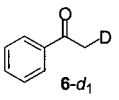
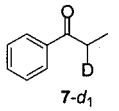
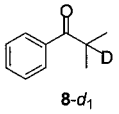
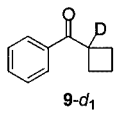
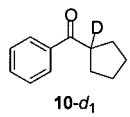
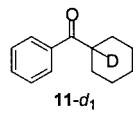
The exocyclic silyl enol ethers **21**, **22** and **23** with a cycloalkane positioned at C-2 (synthesised from cyclobutyl, cyclopentyl and cyclohexyl phenyl ketones **9**, **10** and **11**) gave significantly lower levels of *C*-deuteration (Scheme 6, Entries 4−6). The presence of a cycloalkane ring at the C-2 position must promote regioselective *O*-deuteration to account for the loss of the deuterium label. Of these derivatives, the smaller cyclobutane ring in **21** appears to favour *C*-deuteration under "base-free"conditions (Scheme 6, Entry 4) more so than under "base" conditions (Scheme 3, Entry 4). This increase in D-selectivity may be due to tighter deuterium transfer (within the transition state) promoted by the minimal re-hybridisation[24] at the C-2 position.

Attempts at ensuring efficient *C*-deuteration using a weakly D-acidic source, such as [D_1]*tert*-butyl alcohol (to disfavour *O*-deuteration), resulted in only moderate D-incorporation (Scheme 6). The structural nature and D-acidity of the D-source is additionally important; [D_4]acetic acid was found to give better levels of single *C*-deuteration than [D_1]*tert*-butyl alcohol. Over-incorporation of deuterium was shown to occur for the enolate derived from the silyl enol ether **18** (to give the acetophenone **6**-d_1/**6**-d_2 = 86:14); this must occur by competitive deprotonation of **6**-d_1 by the conjugate base (lithium *tert*-butoxide) and subsequent re-deuteration with [D_1]*tert*-butyl alcohol. The presence of an *exo*-carbocyclic ring at the C-2 position in **9**, **10** and **11** appears to be a dominant factor preventing efficient *C*-deuteration. Nevertheless, it is still surprising that thermodynamic D-tautomerisation does not appear to occur under these conditions to promote regioselective *C*-deuteration and thus re-formation of the more favourable *exo*-double bond.

Conclusion

In conclusion, we have reported the kinetic deuteration of a series of related acyclic and exocyclic enolates and have commented on the similarities and differences of using "base-free" and "base" enolates. We have concluded that increasing substitution at the C-2 position decreases the likelihood of efficient regioselective *C*-deuteration. The presence of a ring at the C-2 position significantly lowers the overall level of D-incorporation. This is due to increased *O*-deuteration allowing competitive [D]enol formation. This unwanted pathway is presumably responsible for the loss of deuterium incorporation during the workup procedure, due to thermodynamic tautomerisation giving the unlabelled parent ketone.[21] The structural nature and D-acidity of the D-source was also found to be important: [D_4]acetic acid gave better levels of single *C*-deuteration than [D_1]*tert*-butyl alcohol.

During the course of this study, we have noticed a number of characteristic features due to the presence of a deuterium atom within these ketones **6**−**11**-d_1: a) the presence of an infrared C−D stretching frequency at approximately 2100 cm^{-1};[26] b) the presence of a C−D triplet (1:1:1, $J_{C,D}$ = 19.6 Hz) in the ^{13}C NMR spectra, and c) a negative isotope shift for the C−D bond (with respect to the analogous C−H bond) in the ^{13}C NMR spectra between 0.25 and 0.47 ppm (Scheme 7).[27]

Product	$^2J_{CD}$ [Hz]	Isotope shift [Hz]/[ppm]
 **6**-d_1	19.6	24.5/0.44
 **7**-d_1	19.6	25.9/0.25
 **8**-d_1	19.6	29.0/0.42
 **9**-d_1	19.6	28.9/0.27
 **10**-d_1	19.6	25.9/0.25
 **11**-d_1	19.6	32.3/0.47

Scheme 7

Experimental Section

General Remarks: All solvents were distilled before use. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from sodium wire. Benzophenone was used as the indicator for THF. All reactions were carried out under nitrogen using oven-dried glassware. Flash column chromatography was carried out using Merck Kieselgel 60 (230−400 mesh). Thin layer chromatography (TLC) was carried out on commercially available pre-coated plates (Merck Kieselgel 60F_{254} silica). Proton and carbon NMR spectra were recorded with a JEOL EX 270 and Bruker AM 250, AMX 400 and AM 600 Fourier transform spectrometers (using an internal deuterium lock). Chemical shifts are quoted in ppm downfield from tetramethylsilane. Carbon NMR spectra were recorded with broad proton decoupling. Infrared spectra were recorded with a Shimadzu 8300 FTIR machine and mass spectra were recorded with a Kratos 50MSTC machine using a DS503 data system for high-resolution analysis. The levels of D-incorporation were determined by a combination of mass, proton and carbon NMR spectra.

Acetophenone 6-d_1: A solution of MeLi (0.43 mL, 1.6 M in diethyl ether, 0.68 mmol) was added dropwise to the enol acetate **12** (0.10 g, 0.62 mmol) at room temperature. This resulting solution was stirred for 1 h at room temperature and then cooled to −78 °C. [D_4]Acetic acid (80 mg, 70 μL, 1.24 mmol) in THF (1 mL) was

added dropwise to this solution and stirred for a further 30 min. The reaction was quenched by the addition of water (10 mL). The solution was extracted with diethyl ether (3 × 20 mL), dried ($MgSO_4$) and the solvents were evaporated under vacuum. The residue was purified by flash chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1) to give **6**-d_1 [28] (61 mg, 81%) as an oil; R_F [light petroleum ether (40−60 °C)/diethyl ether, 9:1] = 0.31. IR (film): $\tilde{\nu}_{max}$ = 2231 (CD), 1685 (C=O) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 8.04 (d, J = 8.2 Hz, 2 H, 2 × CH, Ar), 7.62−7.47 (m, 3 H, 3 × CH, Ar), 2.62 (m, 2 H, CH_2D) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 198.1, 137.1, 133.1, 128.5, 128.3, 26.3 [1 C, t (1:1:1), $^1J_{CD}$ = 19.6, *C*DCO] ppm. The isotopic shift was 0.44 ppm (24.5 Hz at 62.5 MHz). C_8H_8DO requires 122.0716; found [M + H] 122.0710.

A solution of MeLi (0.36 mL, 1.6 M in diethyl ether, 0.57 mmol) was added dropwise to the silyl enol ether **18** (0.10 g, 0.52 mmol) at room temperature. This resulting solution was stirred for 1 h at room temperature and then cooled to −78 °C. [D_4]Acetic acid (66 mg, 60 μL, 1.04 mmol) in THF (1 mL) was added dropwise to this solution and stirred for a further 30 min. The reaction was quenched by the addition of water (10 mL). The solution was extracted with diethyl ether (3 × 20 mL), dried ($MgSO_4$) and the solvents were evaporated under vacuum. The residue was purified by flash chromatography on silica gel eluting with light petroleum ether (40−60 °C)/diethyl ether (19:1) to give **6**-d_1 [28] (50 mg, 80%) as an oil identical to that reported above.

A solution of MeLi (0.36 mL, 1.6 M in diethyl ether, 0.57 mmol) was added dropwise to the silyl enol ether **18** (0.10 g, 0.52 mmol) at room temperature. This resulting solution was stirred for 1 h at room temperature and then cooled to −78 °C. [D_1]*tert*-Butyl alcohol (78 mg, 98 μL, 1.04 mmol) in THF (1 mL) was added dropwise to this solution and stirred for a further 30 min. The reaction was quenched by the addition of water (10 mL). The solution was extracted with diethyl ether (3 × 20 mL), dried ($MgSO_4$) and the solvents were evaporated under vacuum. The residue was purified by flash chromatography on silica gel eluting with light petroleum ether (40−60 °C)/diethyl ether (19:1) to give **6**-d_1/**6**-d_2[28] (49 mg, 72%) as an oil identical to that reported above.

Propiophenone 7-d_1: In the same way as acetophenone **6**-d_1, enol acetate **3** (55 mg, 0.32 mmol), MeLi (0.22 mL, 1.6 M in diethyl ether, 0.35 mmol) and [D_4]acetic acid (44 mg, 40 μL, 0.64 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1), **7**-d_1 [29] (29 mg, 68%) as an oil; R_F [light petroleum ether (40−60 °C)/diethyl ether, 9:1] = 0.40.IR (film): $\tilde{\nu}_{max}$ = 2241 (CD), 1687 (C=O) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.98 (d, J = 8.2 Hz, 2 H, 2 × CH, Ar), 7.58−7.42 (m, 3 H, 3 × CH, Ar), 3.05−3.00 (m, 1 H, CHD), 1.25 (d, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 201.5, 137.6, 133.5, 129.2, 128.6, 32.1 [1 C, t (1:1:1), $^1J_{CD}$ = 19.6, *C*DCO]. The isotopic shift was 0.25 ppm (25.9 Hz at 100 MHz). $C_9H_{10}DO$ requires 136.0873; found [M + H] 136.0867.

In the same way as acetophenone **6**-d_1, silyl enol ether **19** (0.10 g, 0.48 mmol), MeLi (0.33 mL, 1.6 M in diethyl ether, 0.53 mmol) and [D_4]acetic acid (31 mg, 30 μL, 0.96 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1), **7**-d_1 [29] (50 mg, 80%) as an oil identical to that reported above.

In the same way as acetophenone **6**-d_1, silyl enol ether **19** (0.10 g, 0.48 mmol), MeLi (0.33 mL, 1.6 M in diethyl ether, 0.53 mmol) and [D_1]*tert*-butyl alcohol (72 mg, 90 μL, 0.96 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1), **7**-d_1 [29] (50 mg, 80%) as an oil identical to that reported above.

2-Isobutyrophenone 8-d_1: In the same way as acetophenone **6**-d_1, enol acetate **14** (76 mg, 0.39 mmol), MeLi (0.27 mL, 1.6 M in diethyl ether, 0.43 mmol) and [D_4]acetic acid (51 mg, 50 μL, 0.78 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1), **8**-d_1 [30] (35 mg, 60%) as an oil; R_F [light petroleum ether (40−60 °C)/diethyl ether, 9:1] = 0.45.IR (film): $\tilde{\nu}_{max}$ = 2210 (CD), 1618 (C=O) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.4 Hz, 2 H, 2 × CH, Ar), 7.58−7.43 (m, 3 H, 3 × CH, Ar), 1.25 (s, 6 H, 2 × CH_3) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 204.6, 136.3, 132.8, 128.6, 128.4, 35.3 [1 C, t (1:1:1), $^1J_{CD}$ = 19.6, *C*DCO], 19.1 ppm. The isotopic shift was 0.43 ppm (29.0 Hz at 67.5 MHz). $C_{10}H_{11}DO$ requires 149.0951; found M 149.0958.

In the same way as acetophenone **6**-d_1, silyl enol ether **20** (0.2 g, 0.91 mmol), MeLi (0.62 mL, 1.6 M in diethyl ether, 0.99 mmol) and [D_4]acetic acid (0.12 g, 0.10 mL, 1.82 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1), **8**-d_1 [30] (83 mg, 62%) as an oil identical to that reported above.

In the same way as acetophenone **6**-d_1, silyl enol ether **20** (0.20 g, 0.91 mmol), MeLi (0.62 mL, 1.6 M in diethyl ether, 0.99 mmol) and [D_1]*tert*-butyl alcohol (0.14 g, 0.17 mL, 1.82 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1), **8**-d_1 [30] (83 mg, 62%) as an oil identical to that reported above.

Cyclobutyl Phenyl Ketone 9-d_1: In the same way as acetophenone **6**-d_1, enol acetate **15** (0.10 g, 0.62 mmol), MeLi (0.42 mL, 1.6 M in diethyl ether, 0.68 mmol) and [D_4]acetic acid (87 mg, 80 μL, 1.36 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1), **9**-d_1 [31] (65 mg, 65%) as an oil; R_F [light petroleum ether (40−60 °C)/diethyl ether, 9:1] = 0.49.IR (film): $\tilde{\nu}_{max}$ = 2209 (CD), 1682 (CO) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.87 (d, J = 7.2 Hz, 2 H, 2 × CH, Ar), 7.51−7.39 (m, 3 H, 3 × CH, Ar), 2.41−2.23 (m, 4 H, 2 × CH_2), 2.10−2.04 (m, 1 H, CH_AH$_B$), 1.91−1.87 (m, 1 H, CH$_A$$H_B$) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 201.1, 135.7, 132.9, 128.6, 128.4, 41.9 [1 C, t (1:1:1), $^1J_{CD}$ = 19.6. *C*DCO], 25.1, 18.3 ppm. The isotopic shift was 0.29 ppm (28.9 Hz at 100 MHz). $C_{11}H_{11}DO$, requires 161.0903; found [M^+] 161.0898.

In the same way as acetophenone **6**-d_1, silyl enol ether **21** (0.10 g, 0.49 mmol), MeLi (0.3 mL, 1.6 M in diethyl ether, 0.54 mmol) and [D_4]acetic acid (63 mg, 60 μL, 0.98 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1), **9**-d_1 [31] (50 mg, 72%) as an oil identical to that reported above.

In the same way as acetophenone **6**-d_1, silyl enol ether **21** (0.10 g, 0.49 mmol), MeLi (0.3 mL, 1.6 M in diethyl ether, 0.54 mmol) and [D_1]*tert*-butyl alcohol (73 mg, 92 μL, 0.98 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1), **9**-d_1 [31] (50 mg, 72%) as an oil identical to that reported above.

Cyclopentyl Phenyl Ketone 10-d_1: In the same way as acetophenone **6**-d_1, enol acetate **16** (0.10 g, 0.45 mmol), MeLi (0.28 mL, 1.6 M in diethyl ether, 0.45 mmol) and [D_4]acetic acid (52 mg, 50 μL, 0.81 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1), **10**-d_1 [32] (54 mg, 76%) as an oil; R_F [light petroleum ether (40−60 °C)/diethyl ether,

9:1] = 0.47.IR (film): $\tilde{\nu}_{max}$ = 2119 (CD), 1679 (CO) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.1 Hz, 2 H, 2 × CH, Ar), 7.63−7.32 (m, 3 H, 2 × CH, Ar), 2.02−1.91 (m, 4 H, 2 × CH_2), 1.89−1.61 (m, 4 H, 2 × CH_2) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 202.8, 137.0, 132.7, 128.5, 128.4, 45.9 [1 C, t (1:1:1), $^1J_{CD}$ = 21.1, *C*DCO], 29.9, 26.3 ppm. The isotopic shift was 0.26 ppm (25.9 Hz at 100 MHz). $C_{12}H_{13}DO$, requires 175.1107; found [M] 175.1115.

In the same way as acetophenone **6**-d_1, silyl enol ether **22** (0.10 g, 0.41 mmol), MeLi (0.30 mL, 1.6 M in diethyl ether, 0.45 mmol) and [D_4]acetic acid (53 mg, 50 μL, 0.82 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1), **10**-d_1 [32] (59 mg, 59%) as an oil identical to that reported above.

In the same way as acetophenone **6**-d_1, silyl enol ether **22** (0.10 g, 0.41 mmol), MeLi (0.30 mL, 1.6 M in diethyl ether, 0.45 mmol) and [D_1]*tert*-butyl alcohol (61 mg, 76 μL, 0.82 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1), **10**-d_1 [32] (59 mg, 59%) as an oil identical to that reported above.

Cyclohexyl Phenyl Ketone 11-d_1: In the same way as acetophenone **6**-d_1, enol acetate **17** (50 mg, 0.21 mmol), MeLi (0.15 mL, 1.6 M in diethyl ether, 0.24 mmol) and [D_4]acetic acid (28 mg, 30 μL, 0.43 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1), **11**-d_1 [33] (28 mg, 67%) as an oil; R_F [light petroleum ether (40−60 °C)/diethyl ether, 9:1] = 0.42.IR (film): $\tilde{\nu}_{max}$ = 2201 (CD), 1678 (CO) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 8.0 (d, *J* = 7.8 Hz, 2 H, 2 × CH, Ar), 7.61−7.39 (m, 3 H, 3 × CH, Ar), 1.98−1.64 (m, 5 H, 2 × CH_2, CH_AH_B), 1.61−1.23 (m, 5 H, 2 × CH_2, CH_AH_B) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 204.5, 137.1, 133.4, 129.2, 128.9, 45.8 [1 C, t (1:1:1), $^1J_{CD}$ = 19.5, *C*DCO], 30.0, 26.5 ppm. The isotopic shift was 0.48 ppm (32.3 Hz at 67.5 MHz). $C_{13}H_{15}DO$, requires 189.1264; found [M] 189.1258.

In the same way as acetophenone **6**-d_1, silyl enol ether **23** (0.10 g, 0.39 mmol), MeLi (0.27 mL, 1.6 M in diethyl ether, 0.43 mmol) and [D_4]acetic acid (50 mg, 40 μL, 0.78 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1), **11**-d_1 [33] (45 mg, 64%) as an oil identical to that reported above.

In the same way as acetophenone **6**-d_1, silyl enol ether **23** (0.10 g, 0.39 mmol), MeLi (0.27 mL, 1.6 M in diethyl ether, 0.43 mmol) and [D_1]*tert*-butyl alcohol (58 mg, 73 μL, 0.78 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1), **11**-d_1 [33] (45 mg, 64%) as an oil identical to that reported above.

1-Phenylvinyl Acetate (12): Acetophenone (**6**) (2.00 g, 1.9 mL, 17.0 mmol) and *p*-toluenesulfonic acid (0.30 g, 1.57 mmol) were added to neat isopropenyl acetate (72 mL, 0.54 mol). The resulting solution was refluxed at 110 °C for 12 h. The solution was cooled to room temperature and extracted with diethyl ether (2 × 100 mL). This solution was washed with water (3 × 50 mL) and the solvents were evaporated under reduced pressure to give a dark orange oily residue. This residue was purified by flash column chromatography eluting with light petroleum ether/diethyl ether (19:1) to give **12**[11] (2.70 g, 78%) as an oil; R_F [light petroleum ether (40−60 °C)/diethyl ether, 9:1] = 0.38. IR (film): $\tilde{\nu}_{max}$ = 1685 (C=O), 1598 (C=C) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.49−7.44 (m, 2 H, 2 × CH, Ar), 7.38−7.29 (m, 3 H, 3 × CH, Ar), 5.50 (d, *J* = 2.4 Hz, 1 H, CH_AH_B), 5.05 (d, *J* = 2.4 Hz, 1 H, CH_AH_B), 2.26 (s, 3 H, CH_3) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 169.0, 152.9, 133.4, 130.4, 128.9, 124.8, 102.1, 20.9 ppm. $C_{10}H_{10}O_2$ requires 162.0573; found [MH^+] 162.0572.

1-Phenylprop-1-enyl Acetate (13): In the same way as enol acetate **12**, propiophenone (**7**) (1.00 g, 7.45 mmol, 0.99 mL), isopropenyl acetate (32 mL, 0.29 mol) and *p*-toluenesulfonic acid (0.14 g, 0.73 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1) **13**[12] (0.81 g, 62%) as an oil; R_F [light petroleum ether (40−60 °C)/diethyl ether, 9:1] = 0.43. IR (film): $\tilde{\nu}_{max}$ = 1712 (C=O), 1687 (C=C) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.42−7.28 (m, 5 H, 5 × CH; Ar), 5.91 (q, *J* = 7.1 Hz, 1 H, CH), 2.32 (s, 3 H, CH_3), 1.72 (d, *J* = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 167.2, 146.4, 134.6, 128.8, 127.6, 126.0, 95.5, 17.9, 6.5 ppm. $C_{11}H_{12}O_2$ requires 176.0837; found [M^+] 176.0829.

2-Methyl-1-phenylprop-1-enyl Acetate (14): In the same way as enol acetate **12**, isobutyrophenone (**8**) (2.00 g, 13.5 mmol, 2.0 mL), isopropenyl acetate (58 mL, 0.53 mol) and *p*-toluenesulfonic acid (0.24 g, 1.26 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1), **14**[13] (1.43 g, 56%) as an oil; R_F [light petroleum ether (40−60 °C)/diethyl ether, 9:1] = 0.55. IR (film): $\tilde{\nu}_{max}$ = 1716 (C=O), 1600 (C=C) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.71−7.24 (m, 5 H, 5 × CH, Ar), 2.13 (s, 3 H, CH_3), 1.79 (s, 3 H, CH_3), 1.76 (s, 3 H, CH_3) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 169.2, 141.3, 135.9, 128.9, 128.0, 127.8, 121.9, 20.7 19.8, 18.3 ppm. $C_{12}H_{14}O_2$ requires 190.0994; found [M^+] 190.0989.

Cyclobutylidene(phenyl)methyl Acetate (15): In the same way as enol acetate **12**, cyclobutyl phenyl ketone (**9**) (1.00 g, 6.25 mmol), isopropenyl acetate (35 mL, 0.318 mol) and *p*-toluenesulfonic acid (0.14 g, 0.74 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1), **15** (0.78 g, 62%) as an oil; R_F [light petroleum ether (40−60 °C)/diethyl ether, 9:1] = 0.68. IR (film): $\tilde{\nu}_{max}$ = 1681 (C=O), 1596 (C=C) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.39−7.17 (m, 5 H, 5 × CH, Ar), 3.18 (t, *J* = 7.6 Hz, 2 H, CH_2), 2.81 (t, *J* = 7.6 Hz, 2 H, CH_2), 2.23 (s, 3 H, CH_3), 2.12 (q, *J* = 7.6 Hz, 2 H, CH_2) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 168.7, 138.6, 131.8, 128.4, 127.2, 124.9, 118.2, 30.5, 28.9, 20.6, 17.7 ppm. $C_{13}H_{14}O_2$ requires 202.0994; found [M^+] 202.0988.

Cyclopentylidene(phenyl)methyl Acetate (16): In the same way as enol acetate **12**, cyclopentyl phenyl ketone (**10**) (1.00 g, 5.74 mmol), isopropenyl acetate (32.0 mL, 0.29 mol) and *p*-toluenesulfonic acid (0.13 g, 0.68 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1), **16**[14] (0.72 g, 58%) as an oil. R_F [light petroleum ether (40−60 °C)/diethyl ether, 9:1] = 0.65. IR (film): $\tilde{\nu}_{max}$ = 1679 (C=O), 1596 (C=C) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.40−7.23 (m, 5 H, 5 × CH, Ar), 2.55 (t, *J* = 7.1 Hz, 2 H, CH_2), 2.38 (t, *J* = 7.1 Hz, 2 H, CH_2), 2.19 (s, 3 H, CH_3), 1.76−1.68 (m, 4 H, 2 × CH_2) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 169.2, 138.2, 134.2, 128.5, 128.1, 127.4, 126.7, 31.9, 31.4, 27.6, 25.7, 20.8 9 ppm. $C_{14}H_{16}O_2$ requires 216.1145; found [M^+] 216.1140.

Cyclohexylidene(phenyl)methyl Acetate (17): In the same way as enol acetate **12**, cyclohexyl phenyl ketone (**11**) (0.50 g, 2.66 mmol), isopropenyl acetate (11.4 mL, 0.10 mol) and *p*-toluenesulfonic acid (50 mg, 0.26 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1), **17** (0.31 g, 51%) as an oil. R_F [light petroleum ether (40−60 °C)/diethyl ether, 9:1] = 0.58. IR (film): $\tilde{\nu}_{max}$ = 1678 (C=O), 1596 (C=C) cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.36−7.16 (m, 5 H, 5

× CH, Ar), 2.24−2.19 (m, 5 H, 2 × CH_2, CH_AH$_B$), 2.17 (s, 3 H, CH_3), 1.68−1.51 (m, 5 H, 2 × CH_2, CH_AH$_B$) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 169.5, 135.8, 129.3, 129.1, 128.5, 128.3, 128.1, 125.6, 29.8, 28.4, 27.7, 27.2, 26.5, 20.9 ppm. $C_{15}H_{18}O_2$ requires 230.1413; found [M$^+$] 230.1409.

(β-Styryloxy)trimethylsilane (18): Acetophenone (**6**) (1.00 g, 8.32 mmol) was slowly added dropwise to a stirred solution of LDA (6.1 mL, 1.5 M in THF, 9.16 mmol) in THF (50 mL) at −78 °C and stirred for 20 min. Me_3SiCl (0.99 g, 1.2 mL, 9.16 mmol) was added and this solution was stirred for 3 h. A solution of NH_4Cl (50 mL) was added and the mixture was extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and the solvents evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1) to give **18**[15] (1.34 g, 84%) as an oil; R_F [light petroleum ether (40−60 °C)/diethyl ether, 9:1] = 0.71. IR (film): $\tilde{\nu}_{max}$ = 1627 (C=C). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.65−7.58 (m, 2 H, 2 × CH, Ar), 7.37−7.21 (m, 3 H, 3 × CH, Ar), 4.91 (d, J = 1.6 Hz, 1 H, CH_AH$_B$), 4.42 (d, J = 1.6 Hz, 1 H, CH$_A$$H_B$), 0.24 [s, 9 H, $Si(CH_3)_3$] ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 159.1, 134.1, 128.5, 127.5, 126.0, 90.2, 0.18 ppm. $C_{11}H_{16}OSi$ requires 192.0859; found [MH$^+$] 192.0863.

(1-Phenylprop-1-enyloxy)trimethylsilane (19): In the same way as silyl enol ether **18**, propiophenone **7** (1.00 g, 7.45 mmol), LDA (5.5 mL, 1.5 M in THF, 8.19 mmol) and chlorotrimethylsilane (0.89 g, 1.0 mL, 8.19 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1), **19**[16] (1.00 g, 65%) as an oil; R_F [light petroleum ether (40−60 °C)/diethyl ether, 9:1] = 0.73. IR (film): $\tilde{\nu}_{max}$ = 1686 (C=C).^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.46−7.41 (m, 2 H, 2 × CH; Ar), 7.30−7.15 (m, 3 H, 3 × CH; Ar), 5.30 (q, J = 6.9 Hz, 1 H, CH), 1.74 (d, J = 7.1 Hz, 3 H, CH_3), 0.12 [s, 9 H, $Si(CH_3)_3$]. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 156.3, 137.0, 133.6, 128.9, 127.9, 88.2, 8.2, 0.12. $C_{12}H_{19}OSi$ requires 206.1127; found [MH$^+$] 206.1135.

(2-Methyl-1-phenylprop-1-enyloxy)trimethylsilane (20): In the same way as silyl enol ether **18**, isobutyrophenone (**8**) (1.00 g, 6.75 mmol), LDA (5.0 mL, 1.5 M in THF, 7.42 mmol) and chlorotrimethylsilane (0.81 g, 0.94 mL, 7.42 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1), **20**[17] (0.78 g, 45%) as an oil; R_F [light petroleum ether (40−60 °C)/diethyl ether, 9:1] = 0.93. IR (film): $\tilde{\nu}_{max}$ = 1673 (C=C) ppm. ^{1}HNMR (250 MHz, $CDCl_3$): δ = 7.32−7.22 (m, 5 H, 5 × CH, Ar), 1.79 (s, 3 H, CH_3), 1.69 (s, 3 H, CH_3), 0.10 [s, 9 H, $Si(CH_3)_3$] ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 143.6, 139.1, 129.2, 127.6, 127.0, 112.8, 19.7, 18.2, 0.32 ppm. $C_{13}H_{21}OSi$ requires 221.1362; found [MH$^+$] 221.1370.

[Cyclobutylidene(phenyl)methoxy]trimethylsilane (21): In the same way as silyl enol ether **18**, cyclobutyl phenyl ketone (**9**) (0.50 g, 3.12 mmol), LDA (2.3 mL, 1.5 M in THF, 3.43 mmol) and chlorotrimethylsilane (0.37 g, 0.44 mL, 3.43 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1), **21** (0.36 g, 49%) as an oil; R_F [light petroleum ether (40−60 °C)/diethyl ether, 9:1] = 0.85; and **27**[34,35] (51 mg, 7%) as an oil; R_F [light petroleum ether (40−60 °C)/diethyl ether, 9:1] = 0.88. **21:** IR (film): $\tilde{\nu}_{max}$ = 1627 (C=C).^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.27−7.03 (m, 5 H, 5 × CH, Ar), 2.87−2.79 (m, 2 H, CH_2), 2.74−2.67 (m, 2 H, CH_2), 1.97−1.84 (m, 2 H, CH_2), 0.04 [s, 9 H, $Si(CH_3)_3$]. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 140.7, 137.8, 127.9, 126.6, 125.7, 123.2, 31.1, 29.7, 18.2, 0.6. $C_{14}H_{20}OSi$ requires 232.1170; found [M$^+$] 232.1164. **27:** ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.39−7.25 (m, 5 H, 5 × CH, Ar), 4.58 (d, J = 8.1 Hz, 1 H, CH), 2.69−2.52 (m, 1 H, CHCH$_2$), 2.15−1.69 (m, 6 H, 3 × CH_2), 0.40 [s, 9 H, $Si(CH_3)_3$]. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 143.0, 128.4, 127.6, 126.3, 78.3, 42.6, 25.0, 24.5, 17.8, 1.3 ppm.

[Cyclopentylidene(phenyl)methoxy]trimethylsilane (22): In the same way as silyl enol ether **18**, cyclopentyl phenyl ketone (**10**) (1.00 g, 5.74 mmol), LDA (4.2 mL, 1.5 M in THF, 6.31 mmol) and chlorotrimethylsilane (0.69 g, 0.80 mL, 6.31 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1), **22** (0.71 g, 50%) as an oil and **28**[34,35] (0.14 g, 10%) as an oil. **22:** R_F [light petroleum ether (40−60 °C)/diethyl ether, 9:1] = 0.92. IR (film): $\tilde{\nu}_{max}$ = 1639 (C=C) cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.69−7.05 (m, 5 H, 5 × CH, Ar), 2.59−2.38 (m, 4 H, 2 × CH_2), 2.02−1.56 (m, 4 H, 2 × CH_2), 0.06 [s, 9 H, $Si(CH_3)_3$] ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 140.9, 139.7, 127.6, 126.8, 125.9, 109.2, 31.1, 30.4, 27.7, 25.9, 0.7 ppm. $C_{15}H_{22}OSi$ requires 246.1440; found [M$^+$] 246.1432. **28:** R_F [light petroleum ether (40−60 °C)/diethyl ether, 9:1] = 0.93. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.38−7.25 (m, 5 H, 5 × CH, Ar), 4.62 (d, J = 8.4 Hz, 1 H, CH), 2.37−2.18 (m, 1 H, CHCH$_2$), 2.18−1.91 (m, 4 H, 2 × CH_2) 1.88−1.65 (m, 4 H, 2 × CH_2), 0.20 [s, 9 H, $Si(CH_3)_3$] ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 144.6, 128.4, 127.6, 126.6, 79.2, 47.7, 29.6, 29.5, 25.6, 25.5, 1.4 ppm.

[Cyclohexylidene(phenyl)methoxy]trimethylsilane (23): In the same way as silyl enol ether **18**, cyclohexyl phenyl ketone (**11**) (1.00 g, 5.31 mmol), LiHMDS (5.8 mL, 1.0 M in THF, 5.84 mmol) and chlorotrimethylsilane (0.63 g, 0.74 mL, 5.84 mmol) gave, after column chromatography on silica gel eluting with light petroleum ether/diethyl ether (19:1), **23** (0.98 g, 68%) as an oil and **29**[34,35] (0.35 g, 25%) as an oil. **23:** R_F [light petroleum ether (40−60 °C)/diethyl ether, 9:1] = 0.90. IR (film): $\tilde{\nu}_{max}$ = 1647 (C=C). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.29−7.21 (m, 5 H, 5 × CH, Ar), 2.31−2.29 (m, 2 H, CH_2), 2.12−2.08 (m, 2 H, CH_2), 1.57−1.45 (m, 6 H, 3 × CH_2), 0.20 [s, 9 H, $Si(CH_3)_3$] ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 148.9, 136.7, 128.9, 127.7, 126.4, 113.1, 32.9, 30.9, 28.9, 1.2 ppm. $C_{16}H_{24}OSi$ requires 260.1712; found [M$^+$] 260.1708. **29:** R_F [light petroleum ether (40−60 °C)/diethyl ether, 9:1] = 0.91. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.38−7.18 (m, 5 H, 5 × CH, Ar), 4.45 (d, J = 7.1 Hz, 1 H, CH), 3.35−3.13 (m, 1 H, CHCH$_2$), 1.98−1.18 (m, 10 H, 5 × CH_2), 0.20 [s, 9 H, $Si(CH_3)_3$]. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 139.4, 137.1, 128.3, 125.7, 78.2, 39.2, 27.1 25.2, 1.3 ppm.

Acknowledgments

We thank the EPSRC, the Faculty of Natural Science at Queen Mary, University of London, London University Central Research Fund, The Nuffield Foundation, The Royal Society and GOSS Scientific Instruments Ltd for their generous support.

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Received July 18, 2002
[O02408]