

## Efficient $\alpha$ -Alkylation and Silylation of Aromatic *O*-*tert*-Butyldimethylsilyl Ketoximes

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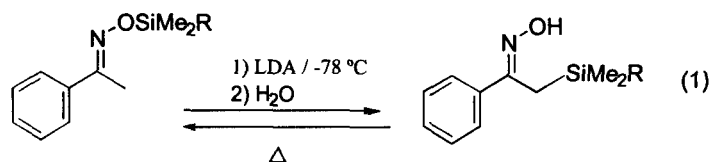
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**Abstract:** The  $\alpha$ -alkylation and silylation of *para* substituted acetophenones, 1- and 2-indanone (*O*-TBS) oximes at various reaction conditions, were studied. Optimum conversions from 82% to 100% were afforded for the alkylation and silylation of these (*O*-TBS) ketoximes with LDA at  $-78$  °C, using electrophiles, such as, methyl iodide, ethylbromide, benzyl bromide and trimethylchlorosilane. © 1999 Elsevier Science Ltd. All rights reserved.

Reactions of metal enolates and azaenolates are well-known methods for the construction of C-C and C-Si bonds.<sup>1,2</sup> The study of these systems for the synthesis of biologically active molecules, is presently a most productive endeavor.<sup>3</sup> However, a similar approach for the  $\alpha$ -functionalization of oximes has been overlooked.<sup>4a</sup> Oximes and oxime ethers are important intermediates in organic synthesis, especially for protection, alkylation and regeneration of carbonyl compounds,<sup>4b</sup> in the synthesis of hydroxylamines and primary amines,<sup>4c,d</sup> nitrones,<sup>4e</sup> and also in the preparation of pharmaceutical derivatives.<sup>4f</sup> It is well known that the alkylation of oxime dianions produces mixtures of nitrones, and *O*- and *C*-alkyl oximes.<sup>5a</sup> The resulting product distribution depends on the geometrical isomers, alkylating reagent and reaction conditions.<sup>5b,c</sup> There has been much effort in the last twenty years towards the development of an efficient methodology for the  $\alpha$ -functionalization of protected oximes.<sup>4a</sup> However, the difficulties associated with the synthesis and purification of *O*-alkyl ketoximes,<sup>6a</sup> the possibility that isomerization of the azaenolate to form the more stable anion does not

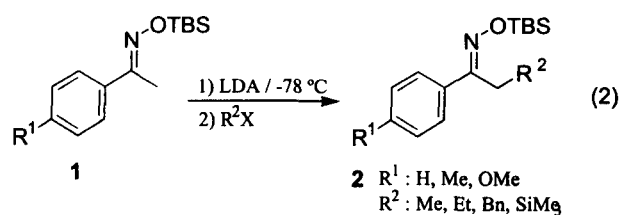
occur,<sup>6b,c,d</sup> and the harsh conditions required for the deprotection of oxime ethers,<sup>6f</sup> have limited the use of oximes for regio- and stereocontrolled alkylations. Recently,<sup>7a,b</sup> we described a convenient method for the large scale synthesis of aromatic substituted *O*-*tert*-butyldimethylsilyl acetophenone oximes, yielding more than 93% of the *E* isomeric form. The *O*-TBS oximes are very stable compounds, easier to purify than the trimethylsilyl protected oximes, and with the further advantage that they can be smoothly reverted to the oxime. Consequently, *O*-TBS oximes have been used for the synthesis of nitriles,<sup>7c</sup> amines,<sup>7a</sup> chiral amino alcohols,<sup>8a</sup> nitrosoalkenes,<sup>8b,c</sup> and as azadienes for Diels-Alder reactions.<sup>8d,e</sup> Based on our previous work, we became interested in studying the alkylation and silylation of aromatic *O*-TBS oximes, which were envisioned as convenient precursors for the synthesis of other important intermediates.<sup>9</sup>

Mora and coworkers<sup>10</sup> were the first to study the stability of azaenolates derived from ketoxime *O*-silyl ethers, finding a 1,4-anionic shift of the silyl moiety from oxygen to carbon (eq 1). A 98% yield of the rearranged product was obtained when the monoanion of the *O*-TMS acetophenone oxime ether was generated by the treatment of the *O*-silylated oxime with LDA followed by protonation with water. However, under the same reaction conditions, they reported only a 5% yield for the *O*-TBS  $\alpha$ -silylated oxime. The only other  $\alpha$  alkylation reaction of *O*-TBS ketoximes reported, is an *O*-TBS- $\beta$ -oximophosphine oxide (64/36 *E/Z* ratio) regio-selectively methylated at the  $\alpha$ -phosphine oxide position.<sup>11a</sup> However, this alkylation process required three days under reflux to obtain 67% yield of the desired methylated product.



In this paper, we report the first efficient procedure for the  $\alpha$ -alkylation and silylation of 4-substituted acetophenone *O*-(TBS) oxime ethers affording exclusively the  $\alpha$ -*C* substituted product (eq 2). In addition, a mixture of the *E* and *Z* isomers of the acetophenone *O*-(TBS) oxime, in a 93/7 ratio was treated with LDA at  $-78^{\circ}\text{C}$  for two hours followed by reaction with methyl iodide. Only the *E* isomer was observed, as determined by capillary GC<sup>11b</sup> and <sup>13</sup>C NMR.<sup>11c,d</sup> Similar results were also observed for other *O*-(TBS) oxime *E/Z* isomeric mixtures. Hence, the formation of the *O*-(TBS) oxime

*syn* anion is both kinetically and thermodynamically favored, as reported by Ensley *et al.*<sup>6b</sup> for the deprotonation of *O*-tetrahydropyranyl oximes with LDA.<sup>6b</sup> Notwithstanding the above, deprotonation of oximes<sup>5a</sup> and *O*-methylated ketoxime<sup>5b,c</sup> has been reported to occur regio-specifically *syn* to the oxygen and it has been attributed to the ability of the Li cation to coordinate with the oxygen and the carbanion. Thus, no generalizations for the regio-control of oxime ethers can be made, since kinetic and thermodynamic considerations depend on diverse factors such as, oxime structure, base, electrophiles, solvent and temperature.<sup>6a</sup>



In general, one equivalent of the aromatic (*O*-TBS)-ketoxime was added to LDA (1.25 - 2.0 equiv) in THF solution at -78 °C. After 1 - 2 h, the reaction mixture had a bright orange color and the anion was reacted with an excess of the corresponding halide (3-5 equiv). The progress of the reaction was followed by GC or TLC. After the reaction was complete, the resulting mixture was allowed to warm at room temperature, diluted with cold pentane, washed with cold sodium bicarbonate and dried over MgSO<sub>4</sub>. Under these conditions, the resulting product from the previously mentioned 1,4-silicon migration<sup>10a</sup> was not observed, neither desilylation of the starting material, or of the product.<sup>11</sup> The isolated product yields and GC conversion percentages for the  $\alpha$ -alkylation and silylation (TMS) of representative 4-substituted acetophenone-*O*-(TBS) oximes are shown in table 1.

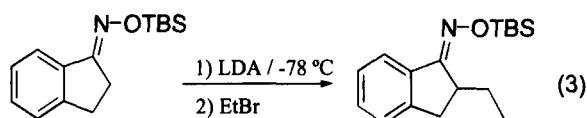
The methylation and silylation reactions were usually complete after 1 h. The benzylation and ethylation reactions were slower, about 2-3 h. Overall, the yields were good, but an orange-brown polymeric material was occasionally observed when the azaenolate was allowed to stand for more than 4 h, or the temperature was allowed to rise above -50 °C. Attempts to generate the anion using *n*-butyl lithium gave lower conversion yields and intractable dark orange side products. The use of *sec*-butyl lithium and the presence of TMEDA did not improve the yield of the desired products.

**Table 1:  $\alpha$ -Alkylation and Silylation of Aromatic *O*-TBS Ketoximes**

entry	<i>O</i> -TBS ketoxime 1 R <sup>1</sup>	LDA (equiv)	electrophile (equiv)	product 2	Yield (%) <sup>a,b</sup> (Conversion) <sup>c</sup>
1	H	1.25	MeI (3.0)	2a	81 (93)
2	H	1.30	BnBr (3.0)	2b	56 (91)
3	H	1.40	EtBr (4.0)	2c	69 (87)
4	Me	2.00	MeI (3.0)	2d	82 <sup>b</sup> (98)
5	Me	2.00	BnBr (3.0)	2e	68 (97)
6	Me	2.00	EtBr (4.0)	2f	78 (87)
7	Me	1.30	TMSCl (3.0)	2g	60 (92)
8	MeO	1.30	MeI (3.1)	2h	69 (97)
9	MeO	1.25	EtBr (3.1)	2i	56 (82)
10	MeO	1.30	TMSCl (2.3)	2j	79 (97)

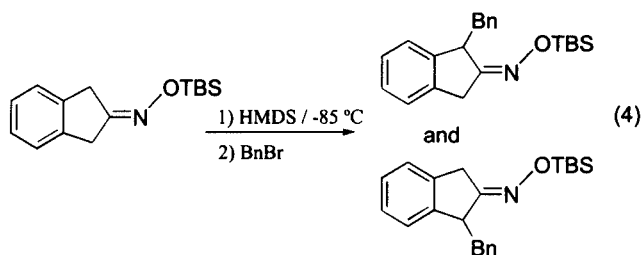
<sup>a</sup> Isolated crude product containing traces of starting material, which was purified by vacuum distillation and/or column chromatography, and characterized by spectroscopic methods. <sup>b</sup> Isolated yield of pure product. <sup>c</sup> Conversion percentages determined by capillary G.C.

The *O*-(TBS) oxime derivative of 1-indanone was also successfully  $\alpha$ -ethylated with up to 94% conversion by GC, and a 60% isolated yield (eq 3).



Under similar reaction conditions the benzylation of 2-indanone silyloxime ether produced a 97% conversion of two regio-isomers in an equal ratio (eq 4). As expected for both benzylic positions, the formation of the azaenolates was faster than the previously studied acetophenone oximes and consequently no kinetic differentiation was allowed. When the same reaction was carried out at -85 °C with HMDS as a base, an initial regio-selective alkylation (34/66) was observed. However, since a

54:46 ratio of E/ Z products was obtained by GC at the end of the reaction, isomerization could have occurred.



On the other hand, attempts to obtain  $\alpha$ -ethylated and benzylated cyclopentanone and cyclohexanone *O*-(TBS) oximes under similar conditions, as previously indicated, failed to provide the expected products with an acceptable yield. A possible lower reactivity<sup>6b,d</sup> and/or competing *N*-alkylation of the oxime,<sup>4</sup> followed by product hydrolysis during the aqueous treatment may have occurred, producing a complex mixture of secondary products. Further studies on the  $\alpha$ -functionalization of cyclic substrates are presently under consideration.

In summary, the  $\alpha$ -alkylation and silylation of aromatic *O*-TBS ketoximes were studied at various reaction conditions. By formation of the azaenolate with LDA at  $-78^\circ\text{C}$ , and using alkyl halides and trimethylchlorosilane as electrophiles, excellent conversion yields to one major product were observed for the first time. This methodology offers a simple and straightforward access to the synthesis of new  $\alpha$ -substituted *O*-TBS aromatic ketoximes, which are useful for other organic transformations.<sup>8</sup>

### Experimental Section

All experiments were carried out under an atmosphere of dry nitrogen, and using standard procedures for handling air sensitive compounds.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a GE 500 MHz in  $\text{CDCl}_3$  solution using TMS as internal reference. Mass spectra were measured at 70 eV on a HP 5996 instrument. Analytical gas chromatography (GC) was performed using a flame ionization detector and a capillary column (25 mm X 0.33 mm bonded methylsilicone). Elemental analysis was performed by Galbraith Laboratories. Commercial grade reagents and solvents were used after standard purification. Dry THF was distilled from sodium benzophenone ketyl. DMF and diisopropylamine were

distilled over CaH<sub>2</sub>, prior to use.

**O-Silylation of Ketoximes. General Method.** To a solution of the corresponding oxime<sup>12</sup> (100 mmol), *tert*-butyldimethylchlorosilane (15.9 g, 106 mmol) in dry DMF (10 mL) at rt under nitrogen, was added a solution of imidazole (14.4 g, 212 mmol) in dry DMF (40 mL). The resulting mixture was stirred and heated between 80–120 °C for 4–6 h. After the reaction was complete, as monitored by GC and IR, the mixture was allowed to cool to rt and extracted with pentane (3 x 150 mL). The combined pentane layers were cooled at 0 °C, washed first with cold NaHCO<sub>3</sub> (3 x 50 mL), then with cold water (50 mL) and dried over MgSO<sub>4</sub>. After the solvent was removed under reduced pressure on a rotoevaporator, the residue was fractionally distilled *in vacuo*, and further purified by column chromatography on silica gel (hexane as eluent), or by crystallization to give the pure silyl oxime. The physical properties and analytical data for acetophenone derivatives used as starting material, were identical to those given in the references 7a and 7b.

**Propiophenone-*O*-(*tert*-butyldimethylsilyl)oxime (2a).** Compound **2a** was prepared from the propiophenone oxime (5 g, 35.5 mmol) using the general procedure for silylation. The clear oil (5.8 g, 66%) was purified by fractional distillation and flash column chromatography on silica/hexane (4.48 g, 51% yield, 97% purity by GC) obtaining the *E* isomer: bp. 81 °C/ 0.178 mmHg; FT-IR (neat, cm<sup>-1</sup>) 3060; 2949, 2931, 2848, 1600, 1563, 1461, 1250 (vs), 927 (vs); <sup>1</sup>H NMR δ: 7.72 (m, 2H), 7.41 (m, 3H), 2.86 (q, *J* = 7.6 Hz, 2H), 1.19 (t, *J* = 7.6 Hz, 3H), 1.05 (s, 9H), 0.30 (s, 6H); <sup>13</sup>C NMR δ: 163.5, 135.9, 128.9, 128.3, 126.3, 26.2, 19.6, 18.2, 11.1, -5.1; HRMS *m/z*: 263 (M<sup>+</sup>), 248, 206, 132, 77.

**4-Methoxypropiophenone-*O*-(*tert*-butyldimethylsilyl)oxime (2h).** Compound **2h** was prepared from the 4-methoxypropiophenone oxime (1.8 g, 10 mmol) using the general procedure for silylation. The cloudy oil was purified by flash column chromatography on silica/hexane (0.8 g, 30%), as the *E* isomer: FT-IR (neat, cm<sup>-1</sup>) 1610 (C=N), 1255 (vs); <sup>1</sup>H NMR δ: 7.64 (d, *J* = 8.8, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 3.84 (s, 3H), 2.80 (q, *J* = 7.6 Hz, 2H), 1.15 (t, *J* = 7.6 Hz, 3H), 1.09 (s, 9H), 0.25 (s, 6H); <sup>13</sup>C NMR δ: 163.0, 160.3, 128.4, 127.8, 113.7, 55.6, 26.2, 19.5, 18.2, 11.2, -5.2; HRMS *m/z*: 293 (M<sup>+</sup>), 236, 162 (100), 134, 92, 75; Anal. Calcd. for C<sub>16</sub>H<sub>27</sub>NO<sub>2</sub>Si: C, 65.48; H, 9.27; N, 4.77. Found: C, 65.75; H, 9.36; N, 4.58.

**1-Indanone-*O*-(*tert*-butyldimethylsilyl)oxime.** This compound was obtained from 1-indanone oxime (2.35 g, 16 mmol) using the general procedure for silylation in 86 % yield (3.6 g, 97% conversion by GC). After purification by fractional distillation, the *E* isomer was obtained (2.9 g, 69% yield, 94% purity): bp 82.5 °C/0.16 mmHg; IR (film, cm<sup>-1</sup>) 3071, 2927, 1637, 1600, 1463, 1387, 1264 (vs), 937,

756;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , TMS)  $\delta$ : 7.73 (d, 1H), 7.32 (m, 3H), 3.04 (t, 2H), 2.95 (t, 2H), 1.00 (s, 9H), 0.25 (s, 6H);  $^{13}\text{C NMR}$   $\delta$ : 167.0, 149.3–121.6, 28.6, 26.4, 26.2, 18.5, -4.9; HRMS  $m/z$ : 246 ( $\text{M}^+ - \text{Me}$ ), 204 (100), 190, 130, 103, 75.

**2-Indanone-*O*-(*tert*-butyldimethylsilyl)oxime.** The pure compound was obtained from 2-indanone oxime (2.5 g, 17 mmol) in 95 % yield (4.2 g), after purification by column chromatography on silica gel in hexane and crystallization in hexane: mp 44–46; IR (KBr,  $\text{cm}^{-1}$ ) 3013, 2922, 2857, 1475, 1401, 1250 (vs), 941 (vs), 821, 789;  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , TMS)  $\delta$ : 7.28 (m, 2H), 7.22 (m, 2H), 3.85 (s, 2H), 3.81 (s, 2H), 0.98 (s, 9H), 0.23 (s, 6H);  $^{13}\text{C NMR}$   $\delta$ : 166.6, 139.4, 139.3, 127.0, 126.9, 125.1, 124.7, 36.32, 34.7, 26.1, 18.1, -5.2; HRMS  $m/z$ : 246 ( $\text{M}^+ - \text{Me}$ ), 204, 190, 130, 103, 75.

**Synthesis of *O*-TBS Ketoximes by  $\alpha$ -Alkylation and Silylation. General Method.** To a stirred solution of diisopropylamine (4.65 mmol, 0.65 mL) in dry THF (5 mL) under  $\text{N}_2$ , cooled at  $-78^\circ\text{C}$  was added *n*-BuLi (2.32 mL, 2.0 M in hexanes, 4.65 mmol). The reaction mixture was warmed to  $0^\circ\text{C}$  and left to stir for 45 min to complete the LDA formation. After the solution was cooled to  $-78^\circ\text{C}$ , the corresponding *O*-silylated oxime (3.6 mmol) in dry THF (5 mL) was added dropwise and the resulting light orange solution was stirred for 2–3 h to ensure the complete formation of the azaenolate. The corresponding halide (14.3 mmol, 3 equiv), distilled and purified by filtration on a short silica gel column, was added dropwise to the solution, and the mixture was stirred at  $-78^\circ\text{C}$  until the reaction was complete, as shown by GC analysis. The reaction mixture was left to warm overnight to rt, diluted with cold pentane (15 mL), extracted with cold aqueous  $\text{NaHCO}_3$  (2 x 10 mL) and dried with anhydrous  $\text{Na}_2\text{SO}_4$ . After the solvent was removed *in vacuo*, a light yellow residue was obtained which was then analyzed by GC and GC/MS. The crude product was subsequently purified by fractional distillation on a spinning band and/or by silica gel (60 Å) column chromatography (1.0 x 20 cm) using hexane and hexane/ethyl acetate to remove traces of starting material in order to have analytical pure samples. The fractions with the same GC were combined and the solvent removed to yield the pure product.

**Propiophenone-*O*-(*tert*-butyldimethylsilyl)oxime (2a).** Prepared as described above from the azaenolate of acetophenone *O*-(*tert*-butyldimethylsilyl)oxime (1.0 g, 4 mmol) and methyl iodide (0.75 mL, 12 mmol). GC and GC/MS analyses of the crude product (0.86 g, 81%) showed only the product **2a** and the starting material in a 93/7 ratio. After purification by column chromatography on silica gel in hexane, **2a** was obtained as a clear liquid (0.31 g, 29%) with a similar spectroscopical data than the compound derived from the corresponding oxime, prepared previously.

**3-Phenylpropiophenone-*O*-(*tert*-butyldimethylsilyl)oxime (2b).** Prepared as described above

from the azaenolate of acetophenone *O*-(*tert*-butyldimethylsilyl)oxime (2.5 g, 10 mmol) and benzyl bromide (3.58 mL, 30 mmol). GC and GC/MS analyses of the crude product (1.9 g, 56%) showed the benzylated product **2b** and the starting material in a 91/9 ratio: After purification by column chromatography on silica gel in hexane, the title compound was obtained as a clear liquid (0.45 g, 13%): IR (film,  $\text{cm}^{-1}$ ): 3023, 2931, 2857, 1604, 1494, 1452, 1250 (vs), 932 (vs), 836;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , TMS)  $\delta$ : 7.68 (m, 2H), 7.32 (m, 8H), 3.12 (m, 2H), 2.82 (m, 2H), 1.04 (s, 9H), 0.27 (s, 6H);  $^{13}\text{C}$  NMR  $\delta$ : 161.6, 141.7, 134.0, 129.0, 128.4, 128.4, 128.3, 126.3, 126.1, 32.6, 28.6, 26.2, 26.1, 18.1, -5.1; HRMS  $m/z$ : 324 ( $\text{M}^+ - \text{Me}$ ), 282, 208 (100), 105, 75.

**1-Phenylbutanone *O*-(*tert*-butyldimethylsilyl)oxime (2c).** Prepared as described above from the azaenolate of acetophenone *O*-(*tert*-butyldimethylsilyl)oxime (1.5 g, 6.0 mmol) and ethyl bromide (1.35 mL, 2.0 g, 18 mmol). GC and GC/MS analyses of the crude residue (1.2 g, 69%) showed **2c** and the starting material in an 87/13 ratio. After purification by column chromatography on silica gel in hexane, the title compound was obtained as a clear liquid (0.35 g, 21%): IR (film,  $\text{cm}^{-1}$ ): 2942, 2855, 1608, 1513, 1464, 1251 (vs), 1178, 924, 835;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , TMS)  $\delta$ : 7.66 (m, 2H), 7.36 (m, 2H), 2.79 (t, 2H), 1.57 (m, 2H), 0.99 (s, 9H), 0.96 (t, 3H), 0.23 (s, 6H);  $^{13}\text{C}$  NMR  $\delta$ : 162.4, 136.2, 128.9, 128.3, 126.3, 27.3, 26.1, 20.0, 18.1, 14.3, -5.1; HRMS  $m/z$ : 277 ( $\text{M}^+$ ), 262 ( $\text{M}^+ - \text{Me}$ ), 220, 146 (100), 91, 75.

**1-(4-Tolyl)propanone-*O*-(*tert*-butyldimethylsilyl)oxime (2d).** Prepared as described above from the azaenolate of 1-(4-tolyl)ethanone *O*-(*tert*-butyldimethylsilyl)oxime (2.5 g, 9.4 mmol) and methyl iodide (1.9 mL, 31 mmol). GC and GC/MS analyses of the crude product (2.4 g, 91%) showed the product **2d** and the starting material in a 98/2 ratio. After purification by column chromatography on silica gel in hexane, the title compound was obtained as a clear liquid (2.15 g, 82%): IR (film,  $\text{cm}^{-1}$ ): 3050, 2928, 1614, 1506, 1463, 1250 (vs);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , TMS)  $\delta$ : 7.67 (d, 2H), 7.22 (d, 2H), 2.80 (q, 2H), 2.35 (s, 3H), 1.18 (t, 3H), 1.00 (s, 9H), 0.25 (s, 6H);  $^{13}\text{C}$  NMR  $\delta$ : 164, 140, 134, 130, 127, 26, 20, 18, 11, -5.1; HRMS  $m/z$ : 277 ( $\text{M}^+$ ), 262 ( $\text{M}^+ - \text{Me}$ ), 220, 146 (100), 91, 75.

**3-Phenyl-1-(4-tolyl)propanone-*O*-(*tert*-butyldimethylsilyl)oxime (2e).** Prepared as described above from the azaenolate of 1-(4-tolyl)ethanone *O*-(*tert*-butyldimethylsilyl)oxime (1.0 g, 3.8 mmol) and benzyl bromide (1.8 mL, 15.2 mmol). GC and GC/MS analyses of the crude residue (0.91 g, 68%) showed the compound **2e** and the starting material in a 97/3 ratio. After purification by fractional distillation, only the E isomer (GC/MS and  $^{13}\text{C}$  NMR) was obtained (0.83 g, 45%): bp. 136°C/0.07 mmHg; IR (film,  $\text{cm}^{-1}$ ): 3023, 2921, 1604, 1452, 1250 (vs), 932, 835;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , TMS)  $\delta$ : 7.59



(d,  $J = 8.2$ , 2H), 7.27 (m, 7H), 3.10 (m, 2H), 2.88 (m, 2H), 2.43 (s, 3H), 1.04 (s, 9H), 0.27 (s, 6H);  $^{13}\text{C}$  NMR  $\delta$ : 161.5, 141.3, 139.0, 133.1, 129.1, 128.5, 128.4, 128.4, 128.3, 126.2, 126.0, 126.2, 32.7, 28.6, 26.2, 21.3, 18.2, -5.1; HRMS  $m/z$ : 338 ( $\text{M}^+ - \text{Me}$ ), 296, 222 (100), 91, 75

**1-(4-Tolyl)butanone *O*-(*tert*-butyldimethylsilyl)oxime (2f).** Prepared from the azaenolate of 1-(4-tolyl)ethanone-*O*-(*tert*-butyldimethylsilyl)oxime (1.5 g, 5.7 mmol) and ethyl bromide (1.8 mL, 23 mmol). GC and GC/MS analyses of the crude product (1.3 g, 78 %) showed the product **2f** and the starting material in an 87/13 ratio. The oily mixture was purified twice by flash column chromatography on silica/hexane (0.6 g, 36 %), as the E isomer (determined by GC/MS and  $^{13}\text{C}$  NMR): IR (film,  $\text{cm}^{-1}$ ): 3027, 2955, 1611, 1250 (vs);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , TMS)  $\delta$ : 7.56 (d, 2H), 7.17 (d, 2H), 2.78 (t, 2H), 2.36 (s, 3H), 1.57 (m, 2H), 0.99 (s, 9H), 0.96 (t, 3H), 0.23 (s, 6H);  $^{13}\text{C}$  NMR:  $\delta$  162.4, 133.4, 138.8, 129.0, 124.3, 27.9, 26.3, 21.2, 18.1, 16.2, 14.3, -5.1; HRMS  $m/z$ : 276 ( $\text{M}^+ - \text{Me}$ ), 234, 160 (100), 91, 75.

**1-(4-Tolyl)-2-trimethylsilyletanone-*O*-(*tert*-butyldimethylsilyl)oxime (2g).** Prepared from the azaenolate of 4-methylacetophenone-*O*-(*tert*-butyldimethylsilyl)oxime (1.9 g, 7.2 mmol) and trimethylchlorosilane (2.3 g, 2.7 mL, 22 mmol). GC and GC/MS analyses of the blue crude product (1.4 g, 60%) showed **2g**, with a small amount of the starting material (92/8 ratio) that was purified by flash column chromatography on silica gel (87% purity), as the E isomer (1.1g, 45%): IR (film,  $\text{cm}^{-1}$ ) 2955, 2857, 1610, 1512, 1466, 1317, 1251 (vs, SiMe), 932, 838;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , TMS)  $\delta$ : 7.53 (d,  $J = 8.1$ , 2H), 7.15 (d,  $J = 8.0$ , 2H), 2.39 (s, 2H), 2.36 (s, 3H), 1.00 (s, 9H), 0.22 (s, 6H), 0.13 (s, 9H);  $^{13}\text{C}$  NMR  $\delta$ : 160.6, 138.7, 134.5, 128.9, 126.3, 26.3, 21.2, 18.3, 18.2, -0.38, -4.94; HRMS  $m/z$ : 278, 204, 147, 73 (100).

**4-Methoxypropiophenone *O*-(*tert*-butyldimethylsilyl)oxime (2h).** Prepared as described above from the azaenolate of 4-methoxyacetophenone-*O*-(*tert*-butyldimethylsilyl)oxime (1 g, 3.6 mmol) and methyl iodide (2.0 g, 14 mmol). GC and GC/MS analyses of the crude product (0.72 g, 69%) showed only the product **2h** and the starting material in a 97/3 ratio. The fragmentation pattern of **2h** was similar to the authentic sample prepared from the oxime and characterized previously.

**1-(4-Methoxyphenyl)butanone-*O*-(*tert*-butyldimethylsilyl)oxime (2i).** Prepared as described above from the azaenolate of 4-methoxyacetophenone-*O*-(*tert*-butyldimethylsilyl)oxime (2.0 g, 7.2 mmol) and ethyl bromide (3.1 g, 2.1 mL, 29 mmol). GC and GC/MS analyses of the crude product (0.62 g, 56%) showed the product **2i** and the starting material in an 82/18 ratio. This clear oily mixture was purified by vacuum distillation with a short path system (bp. 112 °C at 0.15 mmHg, 0.57 g, 26%) and then by flash column chromatography (hexane / ethyl acetate, 90/10 v/v) on silica gel as the E

isomer: IR (film,  $\text{cm}^{-1}$ ) 2943, 2911, 2874, 1606, 1457, 1247 (vs), 836;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , TMS):  $\delta$  7.66 (d,  $J=9.0$ , 2H), 6.93 (d,  $J=9.0$ , 2H), 3.80 (s, 3H), 2.76 (t,  $J=7.2$ , 2H), 1.56 (m, 2H), 1.00 (s, 9H), 0.96 (t, 3H), 0.25 (s, 6H);  $^{13}\text{C}$  NMR  $\delta$ : 161.8, 160.2, 128.8, 127.6, 113.7, 55.2, 27.9, 26.2, 20.1, 18.1, 14.3, -5.12; HRMS  $m/z$ : 307 ( $\text{M}^+$ ), 250, 208, 176 (100), 134, 92, 75.

**1-(4-Methoxyphenyl)-2-trimethylsilylethanone *O*-(*tert*-butyldimethylsilyl)oxime (2j).** Prepared as described above from the azaenolate of 4-methoxyacetophenone-*O*-(*tert*-butyldimethylsilyl)oxime (2.0 g, 7.2 mmol) and trimethylchlorosilane (2.3 g, 2.7 mL, 21 mmol). GC and GC/MS analyses of the light-blue crude product (2.3g, 79%) showed the product **2j** and the starting material in a 97/3 ratio. The mixture was purified twice by column chromatography on silica gel in hexane as the E isomer (1.13 g, 45%, 89% purity): IR (film,  $\text{cm}^{-1}$ ) 2956, 2860, 1610, 1514, 1463, 1318, 1250 (vs), 1177, 1043, 932, 835;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , TMS)  $\delta$ : 7.68 (d,  $J=8.8$ , 2H), 7.01 (d,  $J=8.8$ , 2H), 3.95 (s, 3H), 2.53 (s, 2H), 1.14 (s, 9H), 0.36 (s, 6H), 0.16 (s, 9H);  $^{13}\text{C}$  NMR  $\delta$ : 159.9, 129.7, 127.5, 113.3, 54.9, 26.1, 17.9, -0.62, -5.17; HRMS  $m/z$ : 351 ( $\text{M}^+$ ), 294, 277, 264, 220, 147, 132, 73 (100).

**2-Ethyl-1-indanone-*O*-(*tert*-butyldimethylsilyl)oxime.** Prepared as described above from the azaenolate of 1-indanone-*O*-(*tert*-butyldimethylsilyl)oxime (1.14 g, 1.38 mmol) and ethyl bromide (0.45 g, 4.14 mmol). GC and GC/MS analyses of the crude residue showed only the product and the starting material in a 94/6 ratio. This clear oily mixture was purified by column chromatography on silica gel in hexane as the E isomer (0.19 g, 60% yield, 97% purity by GC). The reaction was repeated in a larger scale (1.50 g, 5.74 mmol of silyl oxime) obtaining a crude product (1.34 g, 88% yield) with an 83/17 conversion ratio. Purification of the mixture by column chromatography on silica gel/hexane afforded a pure sample for analysis (0.74 g, 47%): FT-IR (film,  $\text{cm}^{-1}$ ) 3060, 2940, 1627, 1599, 1457, 1245 (vs, SiMe), 836, 753;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , TMS)  $\delta$ : 7.74 (d, 1H), 7.31 (m, 3H), 3.46 (m, 1H), 3.21 (dd, 2H), 1.63 (m, 1H), 2.03 (m, 1H), 1.07 (s, 9H), 0.98 (t, 3H), 0.31 (s, 6H);  $^{13}\text{C}$  NMR  $\delta$ : 168.5, 147.0, 136.7, 121.7, 41.1, 34.9, 26.2, 25.1, 18.2, 11.4, -5.17; HRMS  $m/z$ : 274 ( $\text{M}^+ - \text{Me}$ ), 232 (100), 202, 158, 116, 75.

**1-Benzyl-2-indanone-*O*-(*tert*-butyldimethylsilyl)oxime.** Prepared as described above from the azaenolate of 2-indanone-*O*-(*tert*-butyldimethylsilyl)oxime (1.5 g, 5.7 mmol) and benzyl bromide (1.3 mL, 4.14 mmol) at  $-78^\circ\text{C}$ . GC analysis of the crude (97% conversion) showed a mixture two product in 1:1 ratio. This dark brown residue was purified by vacuum distillation obtaining a 1:1 mixture of the E and Z isomeric compounds: bp. 125-127 $^\circ\text{C}$ /0.05 mmHg, FT-IR (film,  $\text{cm}^{-1}$ ) 3060, 3023, 2921, 1650, 1600, 1494, 1471, 1250 (vs, SiMe), 927, 835;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , TMS)  $\delta$ : 7.3-6.9 (m, 9H), 4.6 (m, 0.5H),

4.28 (m, 0.5H), 3.87-3.05 (m, 5H), 1.13 and 1.07 (d, 9H), 0.33-0.2 (dd, 6H);  $^{13}\text{C}$  NMR  $\delta$ : 168.6, 168.3, 143-124, 48.5, 48.7, 41.6, 38.0, 35.8, 33.8, 26.2, 25.1, 18.1, 18.0, -4.9, -5.1. When the reaction was carried out at -90 °C, a 79% yield of crude product was obtained with a 96% conversion by GC. The isomeric E/Z ratio was 57:43. Using as a base lithium hexamethyldisilazide at -85 °C to form the azaenolate, the alkylation reaction was analyzed by GC after 45 min obtaining 58% of conversion and the isomeric E/Z ratio was 34:66. When the reaction was 91% complete the ratio changed to 54:46.

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