

Addition of Dialkylzinc to Ketones in the Presence of Silylating Agents: Synthesis of Functionalized Tertiary Silyl Ethers

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Tertiary alcohols are generally prepared in good yields by the addition of alkyllithium or alkylmagnesium halide reagents to ketones; their acidic hydroxyl function, on the other hand, often requires protection if further chemical transformation is to be undertaken in a multistep reaction sequence, and silylation is often the protection of choice. The major drawback to this classic procedure is the limited number of functional groups compatible with the high reactivity of organolithium and magnesium reagents; the ester, halo, nitrile, and other electrophilic moieties must be avoided either in the substrate or in the organometallic reagent.

Dialkylzinc compounds are stable, poorly reactive, organometallic compounds.¹ Although only Me₂Zn and Et₂Zn are commercially available, simple alkyl or functionalized R₂Zn can be prepared by several methods which tolerate the presence of a variety of functionalities, like halo, ester, nitrile, etc.² R₂Zn reagents are generally inert toward carbonyl compounds, but methods to pro-

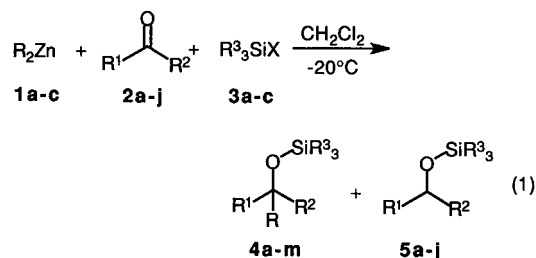
Table 1. Addition of Et₂Zn to Acetophenone^a

solvent	time (h)	yield (%) ^b
hexane	28	83
Et ₂ O	24	50
toluene	2	70
CH ₂ Cl ₂	2	81

^a All the reactions were carried out at -20 °C with a ratio **1a**:**2a**:**3a** = 1:1:1.2. ^b Yield of **4a** containing less than 2% of 1-[(trimethylsilyloxy)-1-phenylethane (**5a**) as the only contaminant.

mote their reaction with aldehydes are well defined;³ the addition of dialkylzinc to ketones, however, has remained practically unexplored.⁴

We present here the simple and chemoselective reaction of R₂Zn **1a–c** [**a**, R = Et; **b**, R = (CH₂)₄OAc; **c**, R = (CH₂)₄OPiv] with a series of ketones **2a–j** containing various functional groups promoted by trialkylsilyl chlorides or triflates **3a–c** (**a** Me₃SiCl; **b** Et₃SiCl; **c** *t*-BuMe₂-SiOTf), to give the corresponding tertiary silyl ethers **4a–n** in good yields (eq 1).



A first set of experiments showed that dichloromethane is the best solvent (Table 1); then the different ketones (**2a–j**) were tested using Et₂Zn **1a** and the silyl promoters **3a–c**. The crude products obtained were contaminated almost only by the secondary trialkylsilyl ethers **5a–j**, which are unavoidable byproducts in the case of aliphatic substrates. The products can be purified by column chromatography or distillation, but in the case of TMS ether products distillation was sometimes preferred.⁵ Data are collected in Table 2¹ and show that almost any kind of ketone⁶ affords the additon product in very good yield in combination with Me₃SiCl, the formation of **5** ranging from less than 2% with aromatics to ca. 10% with aliphatic ketones.

The chemoselectivity of the addition is very good. The ester, chloroaryl, nitroaryl, α-bromo, and α-chloro functions are unaffected by the nucleophile (entries 2–5, 9, 10). This makes our procedure very useful for the transformation of complex, multifunctional substrates. The direct synthesis of triethylsilyl and TBS ethers (entries 10–12) in even better yields than the corresponding TMS ethers is also an important finding; TBSOTf is preferred to the corresponding chloride in the latter case to achieve a comparably fast reaction. The high chemical stability of the TBS ethers makes their direct preparation attractive for use in multistep syntheses. When the addition involves chiral ketones, diastereomeric mixtures of products are obtained; a certain degree of facial selectivity was observed with

(7) No attempt has been made to determine the configuration of the diastereomeric products.

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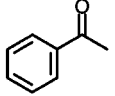
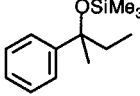
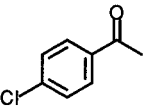
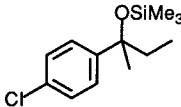
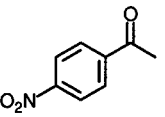
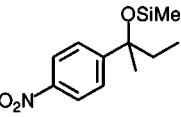
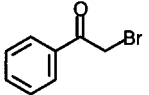
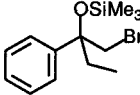
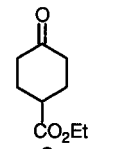
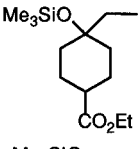
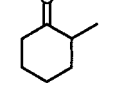
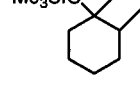

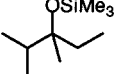
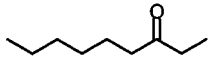
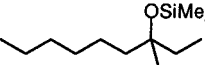
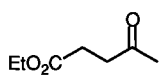
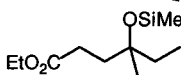

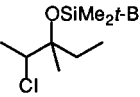
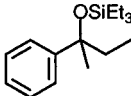
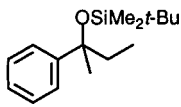
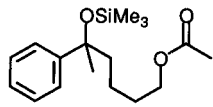
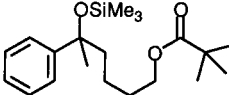
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(5) Some of the TMS ethers are not perfectly stable to prolonged contact with silica gel, leading to partial decomposition. Their thermal stability, on the other hand, is generally good.

(6) The behavior of α,β-unsaturated ketones is intriguing: while 1,3-diphenylpropanone (chalcone) undergoes clean conjugate addition of **1a** in the presence of **3a** under usual conditions to afford the corresponding 1-[(trimethylsilyloxy)-1,3-diphenylpentene, cyclohexenone gives rise to a more complex mixture of products, partially coming from successive 1,4-addition of the initially formed silyl enol ether to the substrate. On the other hand, the Michael addition of R₂Zn to enones has been described: (a) DeVries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2374. (b) Reddy, C. K.; Devasagayaraj, A.; Knochel, P. *Tetrahedron Lett.* **1996**, *37*, 4495. Also the addition of alkyl- and alkynylzinc halides is known: (c) Kim, S.; Lee, J. M. *Tetrahedron Lett.* **1990**, *31*, 7627. (d) Hanson, M. V.; Rieke, R. D. *J. Am. Chem. Soc.* **1995**, *117*, 10775. The conjugate addition of R₂Zn to nitroolefins has also been reported: (e) Schäfer, H.; Seebach, D. *Tetrahedron* **1995**, *51*, 2305.

Table 2. Reactions of R_2Zn with Ketones in the Presence of Silylating Agents R^3_3SiX

Entry	Ketone ^a	R_2Zn	R^3_3SiX	Time (h)	Product	Yield % ^b	5 (%) ^c		
1		2a	1a	3a	4		4a	77 (93)	1
2		2b	1a	3a	6		4b	65 (76)	0
3		2c	1a	3a	2		4c	65 (92)	0
4		2d	1a	3a	1		4d	87 ^d	1
5		2e	1a	3a	6		4e	60 (85) ^e	8
6		2f	1a	3a	7		4f	53 (70) ^f	11
7		2g	1a	3a	22		4g	60 (75)	10
8		2h	1a	3a	6		4h	65 (72)	10
9		2i	1a	3a	32		4i	70 (84)	10
10		2j	1a	3c	6		4j	63 ^{d,g}	10
11	2a	1a	3b	7		4k	85 (95)	2	
12	2a	1a	3c	4		4l	87 ^d	2	
13 ^h	2a	1b	3a	36		4m	52 ^d	0	
14 ^h	2a	1c	3a	36		4n	47 ^d	0	

^a The reactions were carried out in CH_2Cl_2 at $-20^\circ C$, as described in the experimental section. ^b Yield of the distilled or chromatographed products; in brackets yield of the crude **4** reduced by the amount of **5**. ^c Calculated by GC and/or NMR. ^d Product purified by column chromatography. ^e A 1:1 diastereomeric ratio was found. ^f A 5:1 diastereomeric ratio was found. ^g A 3.2:1 diastereomeric ratio was found. ^h Reactions carried out at $0^\circ C$.

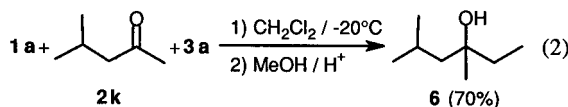
α -substituted ketones (entries 6, 10), reaching a 5:1 dr for 3-chloro-2-butanone.⁷

Having verified the chemoselective addition of simple diethylzinc to functionalized ketones, we checked the

possibility of reacting *functionalized dialkylzinc reagents*. The organometallic reagents **1b,c** were prepared according to Knochel² and allowed to react with **2a** in the presence of Me_3SiCl . The reactivity of these reagents is

significantly lower with respect to that of diethylzinc, and higher temperatures and longer reaction times are required to accomplish the addition. Nevertheless, acceptable yields of **4n,o** are obtained⁸ (Table 2, entries 13, 14), and this result greatly extends the applicability of our procedure to many combinations of reagents.

Finally, if tertiary alcohols are the desired products, they can be easily obtained upon desilylation of **4** by standard procedures.⁹ The process can be also carried out in a single pot, upon quenching with methanol followed by acid treatment (eq 2).



In conclusion, we believe that our findings significantly extend the potential of dialkylzinc reagents. Indeed, we have demonstrated that a variety of functional groups can be present either in the electrophilic substrate or in the organometallic reagent, offering to organic chemists a useful tool for the synthesis of multifunctional molecules and reducing the necessity of extensive protection–deprotection sequences.

We are currently working to control the absolute stereochemistry of the addition reaction. These results will be reported in due course.

Experimental Section

All reactions were carried out under Ar in anhydrous solvents: CH_2Cl_2 was distilled from CaH_2 , toluene, Et_2O , and hexane from sodium and benzophenone. ^1H NMR and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively, in CDCl_3 and are reported in δ units. Mass spectra were obtained through GC-MS at 70 eV EI ionization and are given as m/z (rel int). Boiling points are in $^\circ\text{C}$ (pressure in mmHg). All compounds gave correct C, H analysis.

Addition of Diethylzinc 1a. In a 25 mL flask under Ar a solution of the ketone **2a–j** (5 mmol) and the silyl promoter **3a–c** (5 mmol) in CH_2Cl_2 (6 mL) is cooled at -20°C . To this stirred mixture is added Et_2Zn **1a** (1 M in hexanes, 6 mL) within 2 min. The resulting solution is kept at -20°C until GC analysis shows that the ketone is no longer present, and then water (3 mL) is added; the mixture is filtered, extracted with ether (3 \times 5 mL), dried, and concentrated by rotary evaporation. The crude product is analyzed by GC to establish the content of the tertiary (**4**) and secondary (**5**) silyl ethers, and the products **4a–n** are purified by distillation or silica gel chromatography.

If the free alcohol is desired, after completion of the addition, methanol (3 mL) is added to the CH_2Cl_2 /hexane solution, followed by Amberlyst 15 (H) resin (1 g), and the mixture is stirred until no silyl ether can be seen by TLC analysis. After filtration to remove the resin, the product is recovered and purified by usual workup.

Addition of Functionalized Dialkylzinc Reagents 1b,c. The organometallic reagents have been prepared from pure Et_2Zn and 1-acetoxy-4-iodobutane (for **1b**) or 1-pivaloxy-4-iodobutane (for **1c**) according to the literature.^{2c} In the same reaction flask containing 4 mmol of **1b** or **1c**, cooled at 0°C , CH_2Cl_2 (3 mL) is added, followed by **2a** (0.38 mL, 3.3 mmol) and TMSCl **3a** (0.42 mL, 3.3 mmol). After 36 h, the reaction is quenched and worked up as above. The products **4m** and **4n** are purified by chromatography on silica gel.

The following products were prepared:

2-[(Trimethylsilyloxy)-2-phenylbutane (4a): bp 33 (0.08). MS 222 (1), 207 (7), 193 (100), 105 (5), 73 (53). ^1H NMR 0.10 (s, 9H); 0.72 (t, 3H, $J = 7.5$ Hz); 1.60 (s, 3H); 1.78 (q, 2H, $J = 7.5$ Hz); 7.12–7.42 (m, 5H). ^{13}C NMR 2.4, 8.5, 29.2, 38.3, 77.7, 125.3, 126.1, 127.7, 145.1.

2-[(Trimethylsilyloxy)-2-(4-chlorophenyl)butane (4b): bp 94 (0.7). MS 243 (1.5), 241 (4), 229 (32), 227 (100), 127 (4), 125 (14), 75 (40), 73 (87). ^1H NMR 0.10 (s, 9H), 0.69 (t, 3H, $J = 7.4$ Hz), 1.57 (s, 3H), 1.74 (q, 2H, $J = 7.4$ Hz), 7.20–7.35 (m, 4H). ^{13}C NMR 2.3, 8.3, 29.5, 38.2, 77.5, 126.7, 128.0, 129.6, 147.1.

2-[(Trimethylsilyloxy)-2-(4-nitrophenyl)butane (4c): MS 252 (9), 238 (100), 73 (55). ^1H NMR 0.17 (s, 9H), 0.69 (t, 3H, $J = 7.4$ Hz), 1.64 (s, 3H), 1.80 (q, 2H, $J = 7.4$ Hz), 7.55 (m, 2H), 8.19 (m, 2H). ^{13}C NMR 2.3, 8.2, 29.3, 38.0, 77.8, 123.0, 126.2, 146.3, 156.2.

2-[(Trimethylsilyloxy)-2-phenyl-1-bromobutane (4d): MS 273 (53), 271 (52), 207 (79), 91 (37), 73 (100). ^1H NMR 0.30 (s, 9H), 0.77 (t, 3H, $J = 7.3$ Hz), 2.05 (ABX₃, 2H), 3.69 (d, 1H, $J = 10.2$ Hz), 3.72 (d, 1H, $J = 10.2$ Hz), 7.20–7.45 (m, 5H). ^{13}C NMR 4.9, 10.9, 35.3, 45.9, 82.2, 128.5, 129.6, 130.5, 146.5.

4-[(Trimethylsilyloxy)-4-ethylcyclohexanecarboxylic acid ethyl ester (4e) (1:1 isomers mixture): bp 74 (30). MS 272 (3), 242 (78), 169 (55), 157 (100), 73 (73). ^1H NMR (first isomer) 0.11 (s, 9H), 0.85 (t, 3H, $J = 7.3$ Hz), 1.25 (t, 3H, $J = 7.1$ Hz), 4.12 (q, 2H, $J = 7.1$ Hz); (second isomer) 0.12 (s, 9H), 0.88 (t, 3H, $J = 7.3$ Hz), 1.26 (t, 3H, $J = 7.1$ Hz), 4.13 (q, 2H, $J = 7.1$ Hz); (both isomers) 1.4–1.9 (m), 2.35 (m, 1H). ^{13}C NMR (both isomers) 2.4, 2.6, 7.3, 7.9, 14.1, 24.3, 25.3, 35.7, 35.9, 36.1, 41.5, 42.8, 59.9, 60.0, 75.1, 76.6, 175.5, 175.8.

1-[(Trimethylsilyloxy)-1-ethyl-2-methylcyclohexane (4f) (3:1 isomers mixture): bp 72 (30). MS 214 (6), 185 (70), 157 (57), 144 (44), 73 (100). ^1H NMR (major isomer) 0.08 (s, 9H), 0.76 (d, $J = 6.2$ Hz, 3H), 0.80 (t, 3H, $J = 7.6$ Hz); (minor isomer) 1.70 (ABX₃, 2H), 0.10 (s, 9H), 0.83 (t, 3H, $J = 7.6$ Hz), 0.85 (d, 3H, $J = 6.8$ Hz); (both isomers) 1.10–1.65 (m). ^{13}C NMR (major isomer) 2.6, 8.9, 14.9, 22.0, 26.1, 30.3, 33.5, 36.0, 36.9, 77.7; (minor isomer) 2.7, 6.9, 15.1, 23.6, 24.6, 31.4, 35.3, 41.7, 78.3.

3-[(Trimethylsilyloxy)-2,3-dimethylpentane (4g): bp 77 (3). MS 187 (0.1), 173 (12), 159 (47), 145 (74), 73 (100). ^1H NMR 0.10 (s, 3H), 0.83 (d, 3H, $J = 6.8$ Hz), 0.86 (d, 3H, $J = 6.8$ Hz), 0.87 (t, 3H, $J = 8.1$ Hz), 1.10 (s, 3H), 1.47 (ABX₃, 2H), 1.70 (hept, 1H, $J = 6.8$ Hz). ^{13}C NMR 2.6, 8.1, 17.3, 17.4, 23.5, 32.4, 36.2, 78.4.

3-[(Trimethylsilyloxy)-3-ethylnonane (4h): bp 100 (2.5). MS 244 (17), 215 (88), 159 (100), 103 (15), 73 (46). ^1H NMR 0.10 (s, 9H), 0.81 (t, 6H, $J = 7.5$ Hz), 0.89 (m, 3H), 1.20–1.35 (m, 8H), 1.35–1.45 (m, 2H), 1.45 (q, 4H, $J = 7.5$ Hz). ^{13}C NMR 1.0, 8.8, 14.1, 22.7, 24.2, 30.3, 31.9, 33.4, 40.2, 77.2.

4-[(Trimethylsilyloxy)-4-methylhexanoic acid ethyl ester (4i): bp 75 (4.8). MS 231 (18), 217 (35), 185 (16), 145 (92), 99 (96), 73 (100). ^1H NMR 0.10 (s, 9H), 0.86 (t, 3H, $J = 7.4$ Hz), 1.18 (s, 3H), 1.27 (t, 3H, $J = 7.1$ Hz), 1.48 (q, 2H, $J = 7.4$ Hz), 1.65–1.85 (m, 2H), 2.35 (t, 2H, $J = 7.6$ Hz), 4.13 (q, 2H, $J = 7.1$ Hz). ^{13}C NMR 2.5, 8.6, 14.2, 26.6, 29.3, 34.9, 36.2, 60.2, 75.5, 172.2.

3-[(*t*-Butyldimethylsilyloxy)-2-chloro-3-methylpentane (4j) (5:1 isomers mixture): MS 237 (1), 235 (3), 223 (5), 221 (17), 195 (38), 197 (12), 187 (42), 139 (31), 137 (90), 93 (65), 75 (80), 73 (100). ^1H NMR 0.11 (s, 3H), 0.12 (s, 3H), 0.88 (s, 9H), 0.90 (t, 3H, $J = 7.6$ Hz), 1.28 (s, 3H), 1.48 (d, 3H, $J = 6.7$ Hz), 1.79 (ABX₃, 2H), 3.86 (q, 1H, $J = 6.7$ Hz). ^{13}C NMR (major isomer) -2.5, -2.0, 7.5, 18.4, 19.3, 25.9, 33.1, 62.2, 77.8; (minor isomer) 8.2, 18.4, 19.7, 23.9, 25.9, 32.0, 65.0, 78.6.

2-[(Triethylsilyloxy)-2-phenylbutane (4k): bp 98 (1). MS 264 (1), 235 (46), 115 (20), 103 (100), 75 (40). ^1H NMR 0.70 (q, 6H, $J = 7.6$ Hz), 0.78 (t, 3H, $J = 7.4$ Hz), 1.05 (t, 9H, $J = 7.6$ Hz), 1.69 (s, 3H), 1.85 (ABX₃, 2H), 7.23–7.53 (m, 5H).

2-[(*tert*-Butyldimethylsilyloxy)-2-phenylbutane (4l): MS 249 (0.2), 235 (21), 207 (22), 115 (4), 75 (100). ^1H NMR 0.00 (s, 3H), 0.12 (s, 3H), 0.71 (t, 3H, $J = 7.4$ Hz), 0.97 (s, 9H), 1.60 (s, 3H), 1.79 (ABX₃, 2H), 7.15–7.45 (m, 5H). ^{13}C NMR -1.9, 8.6, 18.6, 26.2, 29.6, 38.4, 77.7, 125.4, 126.1, 127.7, 148.5.

5-[(Trimethylsilyloxy)-5-phenylhexan-1-ol acetate (4m): MS 293 (0.5), 194 (21), 193 (100), 177 (4), 117 (17), 91 (8), 73 (36). ^1H NMR 0.88 (s, 9H), 1.0–1.6 (m, 4H), 1.57 (s, 3H), 1.65–1.8 (m, 2H), 1.96 (s, 3H), 3.94 (t, 2H, $J = 6.7$ Hz), 7.1–7.4 (m,

(8) RZnI reagents have also been tested: an attempted reaction with $\text{R} = (\text{CH}_2)_4\text{OAc}$ showed the formation of some **4m**; however, the rate is too slow to make the reaction synthetically useful.

(9) For example, treatment of **4a** (Table 2, entry 1) with Amberlyst 15 (H) in MeOH gave the corresponding tertiary alcohol in 94% yield.

5H). ¹³C NMR 2.4, 20.4, 20.9, 28.7, 29.7, 45.3, 64.3, 77.4, 125.1, 126.2, 127.8, 148.4, 171.1.

5-[(Trimethylsilyl)oxy]-5-phenylhexan-1-ol pivaloate (4n): MS 335 (0.3), 193 (100), 159 (6), 117 (5), 73 (33). ¹H NMR 0.11 (s, 9H), 1.14 (s, 9H), 1.2–1.6 (m, 4H), 1.61 (s, 3H), 1.65–1.85 (m, 2H), 3.97 (t, 2H, *J* = 6.5 Hz), 7.1–7.4 (m, 5H). ¹³C NMR 2.4, 20.4, 27.1, 28.7, 29.7, 40.1, 45.4, 64.1, 77.3, 125.1, 126.1, 127.7, 148.3, 173.9.

3,5-Dimethyl-3-hexanol (6): MS 115 (8), 101 (19), 73 (100), 57 (33). ¹H NMR 0.91 (t, 3H, *J* = 7.4 Hz), 0.97 (d, 3H, *J* = 6.7 Hz), 0.98 (d, 3H, *J* = 6.7 Hz), 1.17 (s, 3H), 1.26 (br s, 1H), 1.38 (d, 2H, *J* = 7.4 Hz), 1.51 (q, 2H), 1.80 (hept, 1H, *J* = 6.7 Hz).

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Supporting Information Available: Elemental analysis data for compounds **4a–n**, **6** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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