# Synthesis of α-Hydroxy Ketones by Direct, Low-Temperature, in Situ Nucleophilic Acylation of Aldehydes and Ketones by Acyllithium Reagents

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The reaction of *n*-, *sec*-, and *tert*-butyllithium with CO at atmospheric pressure at −110 and −135 °C in the appropriate solvent system in the presence of ketones and aldehydes generates the acyllithium, RC(O)Li, which reacts with the carbonyl compound to give the α-hydroxy ketone, generally in good yield. Reactions with aldehydes are limited in scope, working well with the *t*-BuLi-derived acyllithium reagents, but not with *n*-BuC(O)Li.

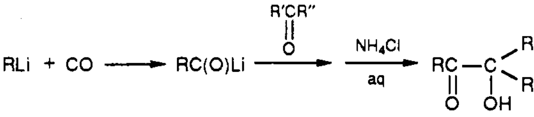
## Introduction

During the period 1983–1986, in a number of preliminary communications,[1-9] we reported the direct nucleophilic acylation of a number of different classes of organic electrophiles by acyllithium reagents, RC(O)Li. Such reagents, according to earlier studies by others, undergo a variety of reactions—with themselves, with the RLi used to generate them via RLi carbonylation, and with intermediates generated during the course of these reactions, and so stable RC(O)Li solutions were not available.[10] As a result, an extensive methodology of "acyl anion equivalents" was developed,[11] and organic chemists even today are reporting new reagents of this class.[12] In our studies of the carbonylation of alkyllithium reagents, we found that acyllithiums could be useful reagents for direct nucleophilic acylation reactions if they are generated at low temperatures (−135 to −110 °C) *in the presence of the organic electrophile*. Why this approach is successful has been discussed in two reviews[13,14] and need not be repeated here. Suffice it to say that at such low temperatures, in many cases the carbonylation of RLi (an electron transfer process[15]) is fast, while alkylation of the organic substrate by RLi is much slower. Also, in many cases, the reaction of the RC(O)Li reagent thus formed with the organic substrate is faster than those reactions of RC(O)Li which occur when no substrate is present.

Among the useful organic products that we have been able to prepare by direct nucleophilic acylation are the α-hydroxy ketones. In view of the utility of the latter as intermediates in organic synthesis, we report here full details of the reactions of RC(O)Li with aldehydes and ketones. This investigation was restricted to the low-temperature, in situ carbonylation of *n*-, *sec*- and *tert*-butyllithium since these are commercially available, but other alkyllithiums also may be used (but not $CH_3Li$).[1a]

## Results and Discussion

The direct nucleophilic acylation of ketones by the low-temperature, in situ reaction of acyllithium reagents with diverse ketones works very well (eq 1). The procedure is a simple and convenient one.



$$\mathrm{RLi} + \mathrm{CO} \longrightarrow \mathrm{RC(O)Li} \xrightarrow{\mathrm{R'C(O)R''}} \xrightarrow[\mathrm{aq}]{\mathrm{NH_4Cl}} \mathrm{RC(O)C(OH)R'R''} \qquad (1)$$

A solution of the ketone in a 4:4:1 (by volume) mixture of tetrahydrofuran (THF), diethyl ether, and pentane is cooled to −110 °C while carbon monoxide is bubbled through the solution. (The reaction can be carried out at −135 °C if the reaction at −110 °C does not proceed well, but in that case a different solvent system, three parts by volume of dimethyl ether to one of THF,[16] must be used.) The CO stream is continued through the solution at these low temperatures for about 30 min. Subsequently, the alkyllithium solution is added very slowly, at a constant rate, by means of a syringe pump. After the addition has been completed, the reaction mixture is stirred for 2 h at low temperature. It then is allowed to warm to room temperature in a stream of CO. Hydrolytic workup is followed by isolation of the product from the organic layer. Alternatively, $Me_3SiCl$ may be added. In that case, the trimethylsilyl ether, $RC(O)C(OSiMe_3)R'R''$, is isolated.

Initially, a reactant stoichiometry of 2 molar equiv of ketone to one of RLi was used, and the reactions were carried out at −110 °C. The results, on the whole, were satisfactory (eq 1, Table IA) in that the α-hydroxy ketones were obtained in fair to good yield. In some cases, low yields of the product of RLi addition to the ketone were obtained in addition to the desired product. The highest yield of such a byproduct was obtained with the least hindered ketone used, $CH_3C(O)C_2H_5$, and in the case of more hindered ketones such as $Me_3CC(O)CH_3$, the yields of such byproducts were minimal. In the case of aceto-

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0022-3263/92/1957-5620$03.00/0

phenone, enolization, not steric factors, was the problem. This was demonstrated when the reaction mixture was quenched with trimethylchlorosilane rather than with aqueous $NH_4Cl$. This procedure, applied to a reaction carried out with a $2PhC(O)CH_3/1n\text{-}BuLi$ stoichiometry at −110 °C, gave $Ph(Me_3SiO)C{=}CH_2$ in 50% yield and $n\text{-}BuC(O)C(OSiMe_3)(CH_3)(C_6H_5)$ in 43% yield. The formation of the former indicated that deprotonation of the relatively acidic (compared to dialkyl ketones) acetophenone was the cause of the low yield of the desired product.

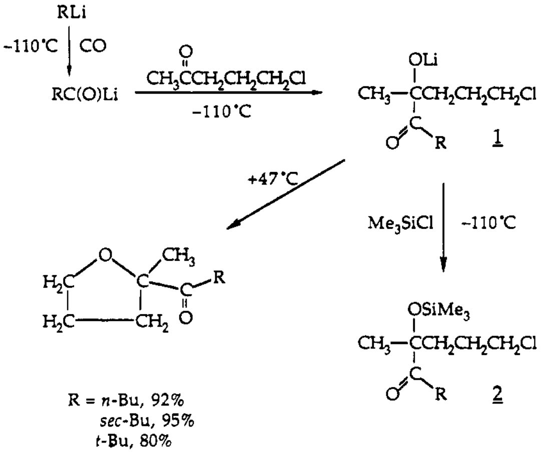
The two main experimental variables in our process are reactant stoichiometry and reaction temperature. The effect of both of these was examined with the objective of improving the yields of the desired product. Both variables were found to be important.

In the hope of minimizing or even preventing the formation of the ketone alkylation byproduct, the effect of using a 1:1 ketone to RLi stoichiometry at −110 °C was investigated. A substantial improvement in product yield was the result, and the formation of the ketone/RLi byproduct (RLi/ketone addition product in the case of cyclohexanone, the lithium enolate in the case of acetophenone) was correspondingly decreased (Table II). Further improvement resulted when the reaction temperature in such 1:1 ketone/RLi reactions was decreased from −100 to −135 °C. Apparently, the RLi/CO reactions are not affected adversely when the temperature is decreased to −135 °C, but the RLi/ketone reactions are. The use of increased reaction temperatures was not productive. Significantly lower yields of the acylation product were obtained in reactions carried out at −78 °C.

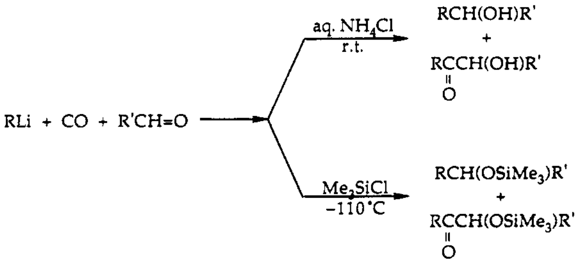
That a decrease in the ketone concentration would result in diminished attack of RLi on the ketone was expected, but it was surprising that the corresponding increase in the RC(O)Li/ketone product yield was as great as it was. One might have expected that in the absence of excess ketone the usual side reactions that consume the acyllithium reagent in the absence of an external electrophile would become more important. However, the rates of the RC(O)Li/ketone reactions must be substantially greater so that high α-hydroxy ketone yields result. An added benefit of the 1:1 stoichiometry is that product isolation is much easier. There is no excess of ketone that has to be separated, and in favorable cases, a solution of the product remains at the end.

Another variable that was investigated was the solvent system. The 4:4:1 $THF/Et_2O$/pentane mixture was used because it remained fluid at −110 °C. Using diethyl ether with only a small amount of added THF (300 mL of $Et_2O$, 10 mL of THF) in such RLi/CO/ketone reactions with a 1:1 RLi/ketone stoichiometry gave reasonably good results. For example, such a reaction of *t*-BuLi with CO in the presence of 2-butanone resulted in formation of $t\text{-}BuC(O)C(OH)(CH_3)(C_2H_5)$ in 69% yield, with only a trace of the RLi/ketone product. However, when diethyl ether alone was used as solvent, the results were not satisfactory: the yield of $t\text{-}BuC(O)C(OH)CH_3)(C_2H_5)$ was only 12% and $t\text{-}BuC(OH)(CH_3)(C_2H_5)$ was formed in 52% yield. Similar experiments were carried out with pentane alone as solvent and with pentane containing a small amount of THF. In pentane alone, the α-hydroxy ketone yield was minimal (5%), while the RLi/ketone product, $t\text{-}BuC(OH)(CH_3)(C_2H_5)$, was produced in 47% yield. In a solvent system of 300 mL of pentane and 10 mL of THF only a trace yield of $t\text{-}BuC(OH)(CH_3)(C_2H_5)$ was formed and the yield of $t\text{-}BuC(O)C(OH)(CH_3)(C_2H_5)$ was 75%. It would appear that THF is essential for a successful RLi/CO/ketone reaction but that large amounts are not required.

**Scheme I**



**Scheme II**



After the studies relating to the effect of reactant stoichiometry, reaction temperature, and solvent on the RLi/CO/ketone reactions had been completed, some more α-hydroxy ketone syntheses using optimum conditions were carried out. The results are summarized in Table IB. The case of the α,β-unsaturated ketones merits special mention. Only with methyl vinyl ketone was any 1,4 addition of the acyllithium observed and, in fact, 1,2 addition was the major process. In the case of cyclohexenone and cyclopentenone only 1,2 addition occurred. (Exclusive 1,4-addition to α,β-unsaturated carbonyl compounds, however, occurs with acylcuprate reagents.[17])

The reactions listed in Tables I and II were carried out on a small scale (generally 8–10 mmol of RLi was used), and it is important to note that they may be carried out on a larger preparative scale with good success. Thus such reactions on a 75–100-mmol scale, with or without the use of a syringe pump, led to distilled product of >96% purity in 65–75% yield. The synthesis of $n\text{-}BuC(O)C(OH)(CH_3)(t\text{-}Bu)$ by the reaction of 78.43 mmol of *n*-BuLi with CO in the presence of 79.1 mmol of pinacolone in 73% distilled yield has been described in ref 18. On this scale a syringe pump is not essential. The *n*-butyllithium solution was added by syringe over an 80-min period. The increased rate of addition (ca. 1 mmol/min) did not affect the yield. A pressure-equalizing funnel cannot be used for the addition because the carbon monoxide would react with the lithium reagent solution in the funnel.

The RLi/CO/ketone reaction can be coupled with further useful intramolecular chemistry of the intermediate. An example is given in Scheme I. The intermediate 1, while stable at −110 °C, undergoes intramolecular attack by the alkoxide function at the C–Cl bond on warming to give an α-acyltetrahydrofuran. Intermediate 1 could be

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**Table I. Direct Nucleophilic Acylation of Ketones by the Low-Temperature, in Situ RLi/CO/Ketone Procedures**

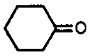
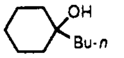
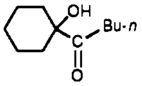
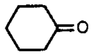
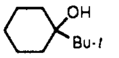
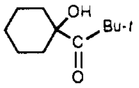
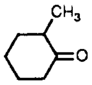
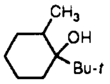
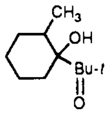
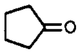
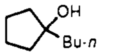
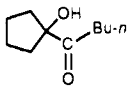
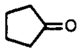
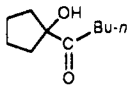
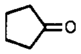
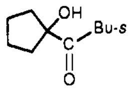
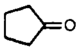
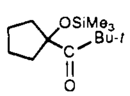
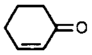
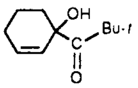
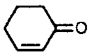
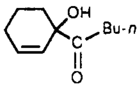
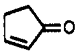
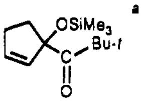
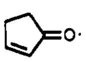
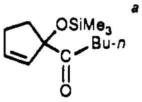
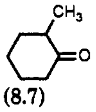
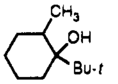
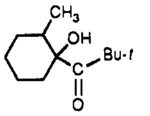
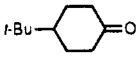
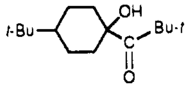
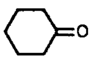
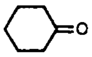
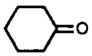
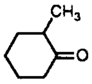
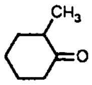
| RLi (mmol) | ketone (mmol) | reaction temp, °C | products (yield, %) |
|---|---|---|---|
| A. 2:1 Ketone/RLi Stoichiometry | | | |
| *n*-BuLi (9.5) | CH$_3$C(O)C$_2$H$_5$ (18.0) | −110 | *n*-BuC(OH)(CH$_3$)(C$_2$H$_5$) (13)<br>*n*-BuC(O)C(OH)(CH$_3$)(C$_2$H$_5$) (71) |
| *n*-BuLi (9.4) | CH$_3$C(O)CH(CH$_3$)$_2$ (18.4) | −110 | *n*-BuC(OH)(CH$_3$)(CH(CH$_3$)$_2$) (5)<br>*n*-BuC(O)C(OH)(CH$_3$)(CH(CH$_3$)$_2$) (92) |
| *n*-BuLi (9.05) | CH$_3$C(O)C(CH$_3$)$_3$ (18.0) | −110 | *n*-BuC(OH)(CH$_3$)(C(CH$_3$)$_3$) (2)<br>*n*-BuC(O)C(OH)(CH$_3$)(C(CH$_3$)) (90) |
| *n*-BuLi (8.8) | (C$_2$H$_5$)$_2$CO (18.0) | −110 | *n*-BuC(OH)(C$_2$H$_5$)$_2$ (4)<br>*n*-BuC(O)C(OH)(C$_2$H$_5$)$_2$ (67) |
| *n*-BuLi (9.05) | CH$_3$C(O)CH$_2$CH(CH$_3$)$_2$ (18.0) | −110 | *n*-BuC(OH)(CH$_3$)(CH$_2$CH(CH$_3$)$_2$ (6)<br>*n*-BuC(O)C(OH)(CH$_3$)(CH$_2$CH(CH$_3$)$_2$) (73) |
| *n*-BuLi (9.05) | C$_2$H$_5$C(O)C$_3$H$_7$-*n* (18.0) | −110 | *n*-BuC(O)C(OH)(C$_2$H$_5$)(C$_3$H$_7$-*n*) (81) |
| *n*-BuLi (9.05) | (*n*-C$_3$H$_7$)$_2$CO (18.0) | −110 | *n*-BuC(O)C(OH)(C$_3$H$_7$-*n*)$_2$ (90) |
| *n*-BuLi (9.05) | CH$_3$C(O)C$_6$H$_5$ (18.0) | −110 | *n*-BuC(O)C(OH)(CH$_3$)(C$_6$H$_5$) (35) |
| *n*-BuLi (9.05) | CH$_3$C(O)C$_6$H$_5$ (18.0) | −110 | (Me$_3$SiO)(C$_6$H$_5$)C═CH$_2$ (50)[a]<br>*n*-BuC(O)C(OSiMe$_3$)(CH$_3$)(C$_6$H$_5$) (43) |
| *n*-BuLi (9.05) |  (18.0) | −110 |  (31)<br> (54) |
| *s*-BuLi (9.0) | CH$_3$C(O)C(CH$_3$)$_3$ (18.0) | −110 | *s*-BuC(O)C(OH)(CH$_3$)(C(CH$_3$)$_3$) (55) |
| *t*-BuLi (9.12) | CH$_3$C(O)C(CH$_3$)$_3$ (18.0) | −110 | *t*-BuC(O)C(OH)(CH$_3$)(C(CH$_3$)$_3$) (69) |
| *t*-BuLi (9.0) |  (18.0) | −110 |  (22)<br> (74) |
| *t*-BuLi (8.7) |  (17.4) | −110 |  (26)<br> (66) |
| *n*-BuLi (9.7) |  (10.0) | −110 |  (8)<br> (72) |
| *n*-BuLi (16.0) |  (17.2) | −135 |  (82) |
| *s*-BuLi (11.8) |  (11.9) | −110 |  (88) |
| *t*-BuLi (13.4) |  (13.1) | −110 |  [a] (84) |
| *t*-BuLi (13.8) | CH$_3$C(O)C$_2$H$_5$ (14.4) | −110 | *t*-BuC(O)(CH$_3$)(C$_2$H$_5$) (12)<br>*t*-BuC(O)C(OH)(CH$_3$)(C$_2$H$_5$) (87) |
| *t*-BuLi (15.12) |  (15.2) | −110 |  (80) |
| *n*-BuLi (12.35) |  (12.4) | −110 |  (68) |

**Table I** (Continued)

| RLi (mmol) | ketone (mmol) | reaction temp, °C | products (yield, %) |
|---|---|---|---|
| *t*-BuLi<br>(8.35) | <br>(8.36) | -110 |  (56)[a] |
| *n*-BuLi<br>(7.87) | <br>(8.6) | -110 |  (55)[a] |
| *t*-BuLi<br>(11.04) | $CH_3C(O)CH{=}CH_2$<br>(11.1) | -110 | *t*-$BuC(O)CH_2CH_2C(O)CH_3$ (25)<br>*t*-$BuC(O)C(OH)(CH_3)(CH{=}CH_2)$ (52) |
| *t*-BuLi<br>(8.7) | <br>(8.7) | -110 |  (8)<br> (92) |
| *t*-BuLi<br>(8.7) | <br>(8.7) | -110 |  (84) |

[a] Reaction mixture quenched with $Me_3SiCl$.

**Table II. Effect of Reactant Stoichiometry and Reaction Temperature on the Product Yield of the Low-Temperature, in Situ RLi/CO/Ketone Reaction**

| RLi | ketone | ketone/RLi ratio | reaction temp, °C | RLi/ketone byproduct (yield, %) | RC(O)C(OH)R'R" (yield, %) |
|---|---|---|---|---|---|
| *n*-BuLi |  | 1.99 | -110 | 31[a] | 54 |
| *n*-BuLi |  | 1.0 | -110 | 15[a] | 66 |
| *n*-BuLi |  | 1.0 | -135 | 9[a] | 73 |
| *n*-BuLi | $CH_3C(O)C_6H_5$ | 1.99 | -110 | 37[b] | 32 |
| *n*-BuLi | $CH_3C(O)C_6H_5$ | 1.0 | -110 | 31[b] | 66 |
| *n*-BuLi | $CH_3C(O)C_6H_4$ | 1.0 | -135 | 15[b] | 77 |
| *t*-BuLi |  | 2.0 | -110 | 26[a] | 74 |
| *t*-BuLi |  | 1.0 | -110 | 8[a] | 92 |

[a] Tertiary carbinol. [b] $Ph(OSiMe_3)_2C{=}CH_2$, after $Me_3SiCl$ quench.

trapped at low temperature by $Me_3SiCl$ to give, in the case of *n*-BuLi, silyl ether **2** (R = *n*-Bu) in 67% yield.

While the direct, low-temperature, in situ acylation procedure is broadly applicable to the acylation of ketones, it is not broadly applicable in the case of aldehydes for the preparation of acyloins. Good to excellent yields of acyloins were obtained when the *s*-BuLi/CO and *t*-BuLi/CO systems were used to acylate aldehydes (Scheme II, Table III). However, with the *n*-BuLi/CO reagent the direct addition of *n*-BuLi to the aldehyde was the favored process. No acylation of an aldehyde was observed with *n*-BuLi/CO except with the very hindered pivaldehyde, which gave 2,2-dimethyl-3-hydroxyoctan-4-one in 62% yield. No acylation product was obtained with the *n*-BuLi/CO reagent on reaction with a hindered benzaldehyde. With the more hindered *s*-BuLi/CO and *t*-BuLi/CO reagents lowering the reaction temperature from -110 to -135 °C did not result in improved acylation product yields.

While the low-temperature, in situ process for direct nucleophilic acylation of organic electrophiles works well with selected electrophiles, it was of interest to investigate the possibility of a two-step process, i.e., one in which the acyllithium reagent is generated first and the organic electrophile added subsequently. In fact, such a procedure had given the first evidence that acyllithiums might be accessible and useful reagents (eq 2).[19] In these experiments the solvent mixture was kept saturated with CO at -100 °C, and then the alkyllithium solution was added slowly (conditions under which the RLi/CO reaction is rapid). Upon completion of the addition, 1 molar equiv of the ketone or aldehyde was added (still at -110 °C), and the reaction mixture was maintained at -110 °C for 2 h while CO was bubbled through the reaction mixture. The results obtained are given in Table IV. These results demonstrate that it is indeed possible to prepare a solution of an acyllithium (R = *n*-Bu and *s*-Bu) at -110 °C in the appropriate solvent and use it subsequently to acylate aldehydes, ketones, and esters. While the yields of the

$$t\text{-BuLi} + CO \xrightarrow[\text{rt}]{\text{hexane}} \xrightarrow[\text{Et}_2\text{O/THF}]{\text{Me}_3\text{SiCl}} \text{Me}_3\text{SiC(O)Bu-}t \quad (2)$$

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[19] Jutzi, P.; Schröder, F.-W. *J. Organomet. Chem.* **1970**, *24*, 1.

**Table III. Direct Nucleophilic Acylation of Aldehydes by the Low-Temperature, in Situ RLi/CO/Aldehyde Procedure**

| RLi (mmol) | aldehyde (mmol) | reaction temp, °C | products (yield, %) |
|---|---|---|---|
| *n*-BuLi (8.8) | $(CH_3)_3CCHO$ (18.0) | −110 | *n*-BuCH(OH)C$(CH_3)_3$ (50)<br>*n*-BuC(O)CH(OH)C$(CH_3)_3$ (17) |
| *n*-BuLi (8.74) | $(CH_3)_3CCHO$ (9.0) | −110 | *n*-BuCH(OH)C$(CH_3)_2$ (34)<br>*n*-BuC(O)CH(OH)C$(CH_3)_3$ (45) |
| *n*-BuLi (12.2) | $(CH_3)_3CCHO$ (12.3) | −135 | *n*-BuCH(OH)C$(CH_3)_3$ (18)<br>*n*-BuC(O)CH(OH)C$(CH_3)_3$ (62) |
| *s*-BuLi (11.4) | $(CH_3)_3CCHO$ (11.6) | −110 | *s*-BuC(O)CH(OH)C$(CH_3)_3$ (77) |
| *s*-BuLi (10.0) | $(CH_3)_3CCHO$ (10.1) | −135 | *s*-BuC(O)CH(OH)C$(CH_3)_3$ (86) |
| *t*-BuLi (14.8) | $(CH_3)_3CCHO$ (14.9) | −110 | *t*-BuC(O)CH(OH)C$(CH_3)_3$ (85) |
| *t*-BuLi (16.0) | $(CH_3)_3CCHO$ (16.1) | −135 | *t*-BuC(O)CH(OH)C$(CH_3)_3$ (90) |
| *n*-BuLi (9.66) | $(CH_3)_2CHCHO$ (9.64) | −135 | *n*-BuCH(OH)CH$(CH_3)_2$ (49) |
| *s*-BuLi (8.94) | $(CH_3)_2CHCHO$ (9.01) | −110 | *s*-BuC(O)CH(OSiMe$_3$)CH$(CH_3)_2$ (76)[a] |
| *s*-BuLi (9.17) | $(CH_3)_2CHCHO$ (9.01) | −135 | *s*-BuC(O)CH(OSiMe$_3$)CH$(CH_3)_2$ (77)[a] |
| *t*-BuLi (8.7) | $(CH_3)_2CHCHO$ (8.8) | −110 | *t*-BuC(O)CH(OSiMe$_3$)CH$(CH_3)_2$ (74)[a] |
| *t*-BuLi (9.90) | $(CH_3)_2CHCHO$ (10.0) | −135 | *t*-BuC(O)CH(OSiMe$_3$)CH$(CH_3)_2$ (72)[a] |
| *n*-BuLi (10.34) | *n*-$C_3H_7CHO$ (11.33) | −135 | *n*-BuCH(OH)$C_3H_7$-*n* (58) |
| *s*-BuLi (10.8) | *n*-$C_3H_7CHO$ (11.36) | −110 | *s*-BuC(O)CH(OSiMe$_3$)$C_3H_7$-*n* (70)[a] |
| *s*-BuLi (9.86) | *n*-$C_3H_7CHO$ (9.98) | −135 | *s*-BuC(O)CH(OSiMe$_3$)$C_3H_7$-*n* (65)[a] |
| *t*-BuLi (7.74) | *n*-$C_3H_7CHO$ (7.86) | −135 | *t*-BuC(O)CH(OSiMe$_3$)$C_3H_7$-*n* (65)[a] |
| *t*-BuLi (12.14) | $CH_3CHO$ (12.88) | −110 | *t*-BuC(O)CH(OSiMe$_3$)$CH_3$ (70)[a] |
| *t*-BuLi (9.36) | *n*-$C_6H_{13}CHO$ (9.48) | −110 | *t*-BuC(O)CH(OSiMe$_3$)$C_6H_{13}$ (80)[a] |
| *t*-BuLi (7.2) | $C_6H_5CHO$ (7.4) | −110 | *t*-BuC(O)CH(OH)$C_6H_4$ (86) |
| *t*-BuLi (7.3) | $C_6H_5CHO$ (7.4) | −110 | *t*-BuC(O)CH(OSiMe$_3$)$C_6H_4$ (95)[a] |
| *n*-BuLi (7.1) | $C_6H_5CHO$ (7.3) | −135 | *n*-BuCH(OH)$C_6H_5$ (45) |
| *s*-BuLi (7.2) | $C_6H_4CHO$ (7.3) | −135 | *s*-BuC(O)CH(OH)$C_6H_5$ (78) |
| *n*-BuLi (9.44) | *o*-$CH_3C_6H_4CHO$ (9.46) | −135 | *n*-BuCH(OH)$C_6H_4CH_3$-*o* (68) |
| *s*-BuLi (8.58) | *o*-$CH_3C_6H_4CHO$ (8.66) | −110 | *s*-BuC(O)CH(OSiMe$_3$)$C_6H_4CH_3$-*o* (86)[a] |
| *t*-BuLi (9.18) | *o*-$CH_3C_6H_4CHO$ (9.23) | −110 | *t*-BuC(O)CH(OSiMe$_3$)$C_6H_4CH_3$-*o* (80)[a] |
| *n*-BuLi (8.47) | *o*-$BrC_6H_4CHO$ (8.57) | −110 | *n*-BuCH(OH)$C_6H_4$Br-*o* (81) |
| *n*-BuLi (9.44) | 2,4,6-$(CH_3)_3C_6H_2CHO$ (9.50) | −135 | *n*-BuCH(OH)$C_6H_2(CH_3)_3$-2,4,6 (88) |

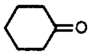
[a] Reaction mixture quenched with Me$_3$SiCl.

acylation products are much lower than those obtained in the in situ procedure, it must be noted that the reaction conditions are not optimized. If improved conditions could be determined, then the two-step procedure would be useful in the nucleophilic acylation of highly electrophilic substrates such as diethyl carbonate[20] with which the in situ nucleophilic acylation procedure was not successful.

The result obtained with *t*-BuLi, formation only of Me$_3$CC(O)CH$_2$OC(O)CMe$_3$, is of interest. When the benzaldehyde was added, *t*-BuC(O)Li must no longer have been present, and this underscores the importance of the in situ procedure. In all the in situ reactions of the *t*-BuLi/CO reagent with organic electrophiles, the acylation products were obtained in 70–95% yield and were free of side products.

**Table IV. "Two-Step" Reactions**

$$\text{RLi} + \text{CO} \xrightarrow{-110\ ^\circ\text{C}} \text{“RC(O)Li”} \xrightarrow{\text{E}^+} \text{RC(O)E} + \text{RE}$$

| RLi | E$^+$ | % yield of RC(O)E | % yield of RE | % yield of others[a] |
|---|---|---|---|---|
| *n*-BuLi | Me$_3$CCHO | 37 | 26 | 7 |
| *n*-BuLi |  | 56 | 18 | 8 |
| *n*-BuLi | $C_6H_4CO_2Me$ | 48 |  | 24 |
| *s*-BuLi | Me$_3$CCHO | 38 |  | *b* |
| *t*-BuLi | $C_6H_5CHO$ |  |  | *c* |

[a] Other products include the acyllithium dimer and the α-diketone derived from it. [b] Four other products, as yet unidentified, were formed in this reaction. [c] Me$_3$CC(O)OCH$_2$C(O)CMe$_3$ was formed in 65% yield.

The formation of Me$_3$CC(O)OCH$_2$C(O)CMe$_3$ as the sole product in substantial yield when the Me$_3$CLi/CO reagent

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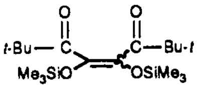
(20) Seyferth, D.; Weinstein, R. M.; Hui, R. C.; Wang, W.-L.; Archer, C. M. *J. Org. Chem.* **1991**, *56*, 5768.

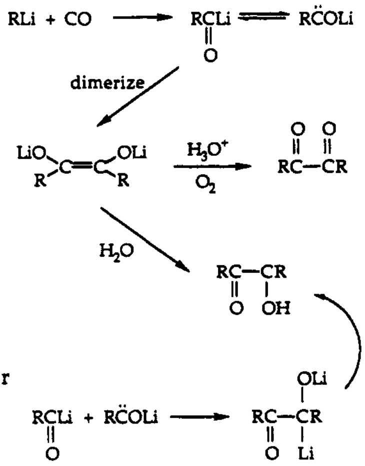
**Table V. Reactions between Butyllithium Reagents and Carbon Monoxide**

$$RLi + CO \xrightarrow{-110\ ^\circ C} \xrightarrow{\text{quenching}} P$$

| R in RLi | quenched with | product(s) (yield, %) |
|---|---|---|
| *n*-Bu | $NH_4Cl$ at rt | *n*-BuC(O)C(O)Bu-*n* (19)<br>*n*-BuC(O)CH(OH)Bu-*n* (21) |
| *s*-Bu | $NH_4Cl$ at rt | *s*-BuC(O)CH(OH)Bu-*s* (27)[a] |
| *t*-Bu | $NH_4Cl$ | *t*-BuC(O)$CH_2$OC(O)Bu-*t* (70) |
| *t*-Bu | $Me_3SiCl$ | *t*-BuC(O)CH($OSiMe_3$)C(O)Bu-*t* (22)<br>+  (51) |
| *t*-Bu | $Ac_2O$ | *t*-BuC(O)CH(OAc)C(O)Bu-*t* (72) |

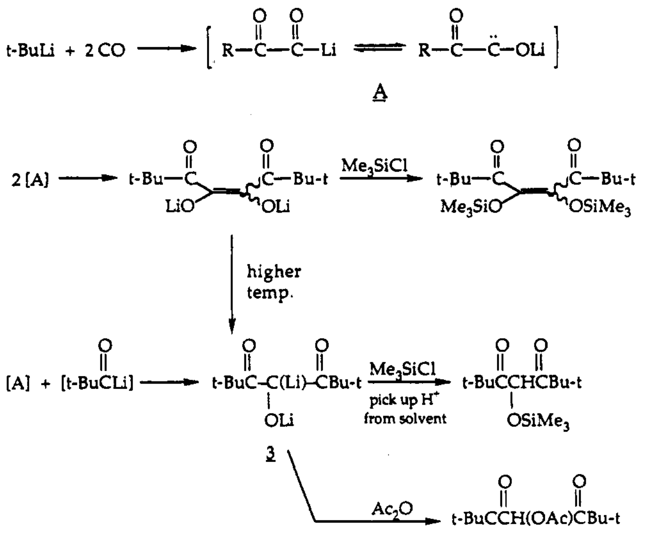
[a] Along with three other minor products not yet identified.

**Scheme III**

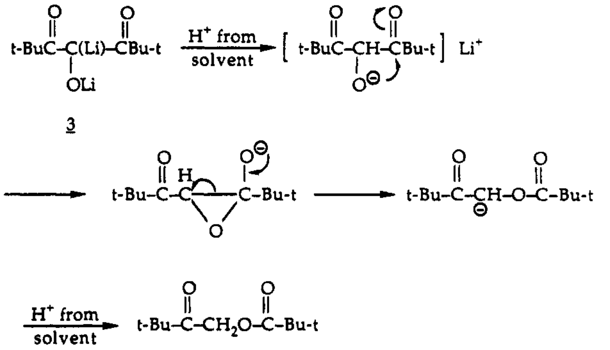


was used in the two-step procedure led us to investigate the reactions of *n*-, *sec*-, and *tert*-butyllithium with CO at −110 °C in the absence of an organic electrophile. In these experiments the organolithium solution was added to the CO-saturated solvent mixture at −110 °C. The solution was maintained at −110 °C for 2 h and then was allowed to warm to room temperature and treated with aqueous $NH_4Cl$ or with $Me_3SiCl$. The results of these experiments are shown in Table V. It is noteworthy that the products differ as the alkyllithium increases in bulk from *n*-BuLi to *s*-BuLi to *t*-BuLi. Only with *n*-BuLi was the α-diketone observed. With *s*-BuLi only the acyloin was formed, and the product obtained with *t*-BuLi is unique to that reagent. There is precedent for the formation of acyloins and α-diketones in ArLi/CO systems.[10] A possible mechanism for their formation is shown in Scheme III. It may be noted that oxidative hydrolysis of the 1-naphthyllithium-/CO reaction mixture at 0 °C gave $1\text{-}C_{10}H_7C(O)C(O)C_{10}H_7\text{-}1$, while treatment of the $1\text{-}C_{10}H_7Li$/CO reagent with acetic anhydride gave 1,2-diacetoxy-1,2-di(1-naphthyl)ethene in 65% yield.[21] The results obtained with the *n*-BuLi/CO and *s*-BuLi/CO systems thus can be understood in terms of known RLi/CO chemistry. The formation of the products obtained when the *t*-BuLi/CO reaction mixture is quenched with $Me_3SiCl$ and $Ac_2O$ can be rationalized in terms of the intermediates shown in Scheme IV. The product obtained when the *t*-BuLi/CO reaction mixture is hydrolyzed, *t*-BuC(O)$OCH_2$C(O)Bu-*t*, could be formed by way of rearrangement of intermediate **3** in Scheme IV as shown in Scheme V. The reaction of *t*-BuLi with CO, in contrast to those of *n*- and *s*-BuLi with CO, appears to consume 2 mol of CO per *t*-BuLi. The reaction of *t*-BuC(O)Li with CO must be much slower than that of *t*-BuLi with CO or else the in situ *t*-BuLi/CO/electrophile reactions would not work as well as they do.

**Scheme IV. Reaction of *tert*-Butyllithium with CO**



**Scheme V**



In conclusion, the low-temperature, in situ nucleophilic acylation of ketones and aldehydes with the alkyllithium-/CO reagent constitutes a useful synthesis of α-hydroxy ketones and of acyloins. There are limitations in the case of reactions in which aldehydes are the organic substrates, and this procedure did not work with methyllithium, the least reactive alkyllithium. The reactions of aryllithiums with CO are more complicated and will be the subject of a later paper.

## Experimental Section

**General Comments.** *All reactions involving the use of CO were carried out in a good hood; CO is toxic so due caution should be exercised.*

All glassware was flame-dried prior to use under a stream of prepurified nitrogen. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl, and pentane was distilled from lithium aluminum hydride prior to use. Dimethyl ether (Matheson) was passed through a drying tower of Drierite and condensed directly into the reaction flask. Carbon monoxide (Matheson) was used directly as received. *n*-Butyllithium (Alfa/Ventron, in hexane) and *tert*-butyllithium (Aldrich, in pentane) were used as received. *sec*-Butyllithium (Alfa-Ventron) was purchased as a solution in cyclohexane. However, cyclohexane freezes at the reaction temperature that was used, so cyclohexane was removed by trap-to-trap distillation (1.0 Torr) at room temperature and replaced with pentane. All alkyllithium solutions were assayed prior to use by the Gilman method. Addition of alkyllithium solutions was effected with a syringe pump (Orion Research, Inc., Model 341 A). Melting points were uncorrected.

Total-immersion-type, low-temperature pentane thermometers (Kesler) were used to measure the temperature in the partial

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[21] Nudelman, N.; Outumuro, P. *J. Org. Chem.* **1982**, *47*, 4347.

**Table VI. Characterization Data for Nucleophilic Acylation Products**

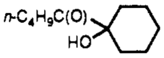
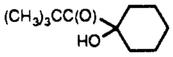
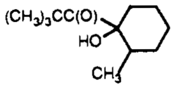
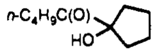
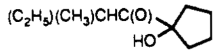
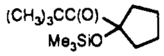
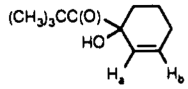
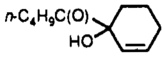
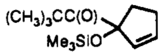
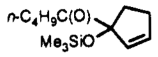
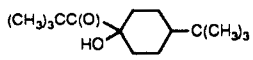
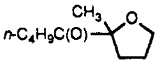
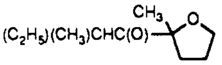
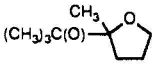
| α-hydroxy ketone or α-trimethylsiloxy ketone | $n^{20}{}_D$ | anal. calcd (found) | | $^1$H NMR (δ, ppm) (* = $CDCl_3$, ≠ = $CCl_4$, # = $C_6D_6$, x = $CD_2Cl_2$) | IR ν(C=O) (cm$^{-1}$) |
|---|---|---|---|---|---|
| | | carbon | hydrogen | | |
| n-$C_4H_9C(O)C(OH)(CH_3)(C_2H_5)$ | 1.4316 | 68.31 (68.22) | 11.47 (11.45) | * 0.7–1.8 (m, 15 H, alkyl), 2.45 (t, *J* = 6.5 Hz, 2 H, $CH_2C(O)$), 3.80 (s, 1 H, OH) | 1705 |
| n-$C_4H_9C(O)C(OH)(CH_3(C(CH_3)_3)$ | 1.4444 | 70.92 (70.93) | 11.90 (11.88) | # 0.8=1.82 (m, 19 H, alkyl with s at 0.89 ($C(CH_3)_3$) and 1.11 ($C(OH)CH_3$)), 2.26 (t, *J* = 7.3 Hz, $CH_2C(O)$), 3.32 (s, 1 H, OH) | 1695 |
| n-$C_4H_9C(O)C(OH)(C_2H_5)_2$ | 1.4335 | 69.72 (69.82) | 11.70 (11.79) | ≠ 0.8–1.7 (m, 17 H, alkyl), 2.4 (t, *J* = 7 Hz, 2 H, $CH_2C(O)$), 3.6 (s, 1 H, OH) | 1705 |
| n-$C_4H_9C(O)C(OH)(CH_3)CH_2CH(CH_3)_2$ | 1.4362 | 70.92 (70.99) | 11.90 (11.88) | # 0.75–1.70 (m, 19 H, alkyl with s at 1.08 ($C(CH_3)(OH)$), 2.10 (t, *J* = 6.6 Hz, 2 H, $CH_2C(O)$), 3.8 (s, 1 H, OH) | 1702 |
| n-$C_4H_9C(O)C(OH)(C_2H_5)(C_3H_7$-n) | 1.4368 | 70.92 (71.33) | 11.90 (11.93) | # 0.7–1.5 (m, 19 H, alkyl), 2.02–2.15 (m, 2 H, $CH_2C(O)$), 3.96 (s, 1 H, OH) | 1700 |
| n-$C_4H_9C(O)C(OH)(C_3H_7$-n$)_2$ | 1.4386 | 71.95 (72.15) | 12.08 (12.12) | # 0.85–1.57 (m, 21 H, alkyl), 2.43 (t, *J* = 7.08 Hz, 2 H, $CH_2C(O)$), 3.88 (s, 1 H, OH) | 1700 |
| n-$C_4H_9C(O)C(OH)(CH_3)(C_6H_5)$ | 1.5089 | 75.69 (75.79) | 8.79 (8.91) | × 0.7–1.47 (m, 7 H, $C_3H_7$), 2.07 (s, 3 H, $C(CH_3)OH$), 2.56 (t, *J* = 6.8 Hz, 2 H, $CH_2C(O)$), 4.4 (s, 1 H, OH), 7.0–7.4 (m, 5 H, Ph) | 1710 |
| n-$C_4H_0C(O)(OSiMe_3)(CH_3)(C_6H_5)$ | 1.4802 | 69.01 (68.98) | 9.41 (9.43) | * 0.16 (s, 9 H, $Me_3Si$), 0.8–1.3 (m, 7 H, $C_3H_7$), 1.70 (s, 3 H, $CH_3C(OSiMe_3)$), 2.41 (t, *J* = 7.0 Hz, 2 H, $CH_2C(O)$), 7.32–7.35 (m, 5 H, Ph) | 1715 |
|  | 1.4660 | 71.70 (71.95) | 10.94 (11.00) | # 0.83 (t, *J* = 7.0 Hz, 3 H, $CH_3$ of n-Bu), 1.1–1.9 (m, 14 H, alkyl), 2.63 (t, *J* = 6.83 Hz, 2 H, $CH_2C(O)$), 3.45 (broad s, 1 H, OH) | 1700 |
| $(C_2H_5)(CH_3)CHC(O)C(OH)CH_3)(C(CH_3)_3)$ | 1.4370 | 70.92 (71.03) | 11.90 (11.93) | (2 diastereomers in equal amounts) 0.89–1.13 (m, 17 H, alkyl, incl s at 0.95 ($CMe_3$)), 1.38 and 1.365 (2 s, 3 H, $CH_3COH$), 2.85 (m, 1 H, CHC(O)), 3.31, 3.63 (2 s, 1 H, OH) | 1703 |
| $(CH_3)_3CC(O)C(OH)(CH_3)(C(CH_3)_3)$ | mp 56.5–58 °C | 70.92 (70.94) | 11.90 (11.94) | ≠ 1.30 and 1.07 (2 s, 9 H each, $CMe_3$), 1.37 (s, 3 H, $C(O)CH_3$), 1.52 (s, 1 H, OH) | 1679 |
|  | | 71.70 (71.74) | 10.94 (11.01) | 1.25 (s, 9 H, $Me_3C$), 1.50 (m, 10 H, alkyl), 2.67 (s, 1 H, OH) | 1685 |
|  | | 72.68 (72.68) | 11.18 (11.21) | * 0.65 (d, *J* = 6.9 Hz, 3 H, $CH_3$), 1.22, 1.25 (2 s, 9 H, $CMe_3$, axial and equatorial), 1.3–2.2 (m, 9 H, alkyl), 2.8 (s, 1 H, OH) | 1680 |
|  | 1.4633 | 70.55 (70.29) | 10.66 (10.71) | * 0.86–2.63 (m, 15 H, alkyl), 3.93 (m, 2 H, $CH_2C(O)$) | 1704 |
|  | 1.4652 | 70.55 (70.61) | 10.66 (10.69) | * 0.62–2.55 (m, 16 H, alkyl), 3.81 (m, 1 H, CH of *s*-Bu) | 1702 |
|  | 1.4459 | 64.41 (64.38) | 10.81 (10.85) | * 0.15 (s, 9 H, $Me_3Si$), 1.23 (s, 9 H, $Me_3C$), 1.52–2.15 (m, 8 H, alkyl) | 1693 |
|  | mp 38–40 °C | 72.49 (72.72) | 9.95 (9.91) | * 1.25 (s, 9 H, $Me_3C$), 1.5–2.3 (m, 6 H, cyclohexyl), 4.14 (s, 1 H, OH), 5.64 (d, *J* = 9.8 Hz, 1 H, vinyl $H_a$), 6.1 (m, 1 H, $H_b$) | 1687 |
|  | 1.4793 | 72.49 (72.30) | 9.95 (9.80) | * 0.89 (t, *J* = 6.4 Hz, 3 H, $CH_3$), 1.10–1.20 (m, 10 H, alkyl), 2.58 (t, *J* = 7.2 Hz, 2 H, $CH_2C(O)$), 4.0 (s, 1 H, OH), 5.6, 6.1 (m, 1 H each, CH=CH) | 1705 |
|  | 1.4520 | 64.95 (65.18) | 10.06 (10.19) | * 0.10 (s, 9 H, $Me_3Si$), 1.25 (s, 9 H, $Me_3C$), 1.60–2.52 (m 4 H, alkyl), 5.7, 6.0 (m, 1 H each, CH=CH) | 1700 |
|  | 1.4530 | 64.95 (65.19) | 10.06 (10.06) | * 0.10 (s, 9 H, $Me_3Si$), 0.89 (t, *J* = 7.5 Hz, 3 H, $CH_3C$), 1.10–1.190 (m, 6 H, $CCH_2CH_2C$), 2.20–2.61 (m, 4 H, $CH_2C(O)$), 5.7–6.0 (m, 2 H, CH=CH) | 1720 |
| $(CH_3)_3CC(O)C(OH)(CH_3)(CH{=}CH_2)$ | | 69.20 (69.24) (mixture analyzed) | 10.32 (10.27) | 1.24 (s, 9 H, $Me_3C$), 1.50 (s, 3 H, $CH_3$), 3.84 (s, 1 H, OH), 6.2 (m, 2 H, $=CH_2$), 6.5 (m, 1 H, =CH) | 1685 |
| $(CH_3)_3CC(O)CH_2CH_2C(O)CH_3$ | | | | * 1.14 (s, 9 H, $Me_3C$), 2.17 (s, 3 H, $CH_3$), 2.66 (t, *J* = 4.6 Hz, $C(O)CH_2$), 2.78 (t, *J* = 4.6 Hz, 2 H, $C(O)CH_2$) | 1710 |
|  | solid | 74.95 (74.84) | 11.74 (11.73) | * 0.83 (s, 9 H, ring-$CMe_3$), 1.26 (s, 9 H, $Me_3CC(O)$), 1.3–1.8 (m, 9 H, ring), 2.70 (s, 1 H, OH) | 1700 |
| n-$C_4H_9C(O)CH(OH)C(CH_3)_3$ | 1.4376 | 69.72 (69.51) | 11.70 (11.70) | # 0.87 (s, 9 H, $Me_3C$), 0.91–1.47 (m, 7 H, $C_3H_7$), 2.04 (t, *J* = 6.89 Hz, $CH_3C(O)$), $3.08^b$ (d, *J* = 6.64 Hz, 1 H, OH), $3.59^c$ (d, *J* = 6.64 Hz, C*H*OH) | 1705 |
| $(C_2H_5)(CH_3)CHC(O)CH(OH)C(CH_3)_3$ | 1.4369 | 69.72 (69.84) | 11.70 (11.79) | (2 diastereomers in equal amounts) * 0.6–1.6 (m, 17 H, alkyl, incl s at 0.96 ($Me_3C$)), 2.7 (m, 1 H, $C_H(CH_3)$), 3.1–$3.3^b$ (m, 1 H, OH), 3.94, $3.94^c$ (2 d, *J* = 7.8, 7.3 Hz, C*H*OH) | 1701 |
| $(CH_3)_3CC(O)CH(OH)C(CH_3)_3$ | mp 79–80 °C (lit.$^a$ mp 80–80.5 °C) | | | * 0.96, 1.18 (2 s, 9 H each, $Me_3C$), $2.21^b$ (d, *J* = 10.74 Hz, 1 H, OH), $4.18^c$ (d, *J* = 10.74 Hz, 1 H, C*H*OH) | 1700 |
| $(C_2H_5)(CH_3)C(O)CH(OSiMe_3)CH(CH_3)_2$ | | 62.55 (62.61) | 11.37 (11.55) | * 0.1 (s, 9 H, $Me_3Si$), 0.6–2.1 (m, 15 H, alkyl), 2.6–2.9 (m, 1 H, $CH_3C(O)$), 3.9 (m, 1 H, CH of iPr) | 1710 |
| $(CH_3)_3CC(O)CH(OSiMe_3)CH(CH_3)_2$ | | 62.55 (62.63) | 11.37 (11.43) | * 0.08 (s, 9 H, $Me_3Si$), 0.9 (d, *J* = 6.8 Hz, 6 H, $CHMe_2$), 1.16 (s, 9 H, $Me_3C$), 2.0 (m, 1 H, CH of iPr), 4.3 (d, *J* = 4.9 Hz, $CHOSiMe_3$) | 1710 |

**Table VI** (Continued)

| α-hydroxy ketone or α-trimethylsiloxy ketone | $n^{20}_D$ | anal. calcd (found) |  | $^1$H NMR (δ, ppm) (* = $CDCl_3$, ≠ = $CCl_4$, = $C_6D_6$, x = $CD_2Cl_2$) | IR ν(C=O) (cm$^{-1}$) |
|---|---|---|---|---|---|
|  |  | carbon | hydrogen |  |  |
| $(C_2H_5)(CH_3)CHC(O)CH(OSiMe_3)C_3H_7$-*n* |  | 62.55 (62.78) | 11.37 (11.60) | * 0.1 (s, 9 H, $Me_3Si$), 0.6–2.5 (m, 15 H, alkyl), 2.9 (m, 1 H, C*H*C(O)), 4.0 (m, 1 H, C*H*$OSiMe_3$) | 1710 |
| $(CH_3)_3CC(O)CH(OSiMe_3)C_3H_7$-*n* |  | 62.55 (62.81) | 11.37 (11.35) | * 0.09 (s, 9 H, $Me_3Si$), 0.90 (t, *J* = 7.2 Hz, 3 H, $CH_3$), 1.17 (s, 9 H, $Me_3C$), 1.20–1.80 (m, 4 H, $CH_2CH_2$ of *n*-Pr), 4.5 (m, 1 H, C(O)C*H*) | 1715 |
| $(CH_3)_3CC(O)CH(OSiMe_3)CH_3$ |  |  |  | * 0.12 (s, 9 H, $Me_3Si$), 1.18 (s, s, 9 H, $Me_3C$), 1.25 (d, *J* = 6.3 Hz, 3 H, $CH_3$), 4.8 (q, *J* = 6.5 Hz, 1 H, C*H*C(O)) | 1705 |
| $(CH_3)_3CC(O)CH(OSiMe_3)C_6H_{13}$-*n* |  | 66.12 (66.21) | 11.84 (11.80) | * 0.10 (s, 9 H, Me*4Si*), 0.6–1.7 (m, 22 H, alkyl incl s at 1.17 ($Me_3C$)), 4.5 (m, 1 H, CHC(O)) | 1710 |
| $(CH_3)_3CC(O)CH(OH)C_6H_5$ | mp 45–46 °C (lit.[d] mp 46–47 °C) |  |  | (acetone-$d_6$) 1.05 (s, 9 H, $Me_3C$), 4.59[b] (d, *J* = 6.83 Hz, 1 H, OH), 5.52[c] (d, *J* = 6.83 Hz, 1 H, C*H*OH), 7.34 (s, 5 H, Ph) | 1690 |
| $(CH_3)_3CC(O)CH(OSiMe_3)C_6H_5$ | mp 43–44 °C | 68.13 (68.44) | 9.15 (9.28) | (acetone-$_{d6}$) 0.05 (s, 9 H, $Me_3Si$), 1.09 (s, 9 H, $Me_3C$), 5.67 (s, 1 H, C*H*$OSiMe_3$), 7.29–7.45 (m, 5 H, Ph) | 1711 |
| $(CH_3)_3CC(O)CH(OSiMe_3)C_6H_4CH_3$-*o* |  | 69.01 (69.31) | 9.41 (9.35) | * 0.05 (s, 9 H, $Me_3Si$), 1.09 (s, 9 H, $Me_3C$), 2.37 (s, 3 H, *o*-$CH_3$), 5.66 (s, 1 H, CHC(O)), 7.20 (m, 4 H, $C_6H_4$) | 1717 |
| $(C_2H_5)(CH_3)CHC(O)CH(OSiMe_3)C_6H_4CH_3$-*o* |  | 69.01 (69.30) | 9.41 (9.32) | * (mixture of 2 diastereomers) 0.068, 0.070 (2 s, 9 H, $Me_3Si$), 0.62, 0.72 (2 t, *J* = 7.4 Hz, 3 H, $CH_3$ of Et), 0.86, 0.93 (2 d, 3 H, $CH_3CH$), 1.2, 1.4 (2 m, 2 H, $CH_2$ of Et), 0.23 (s, 3 H, *o*-$CH_3$), 2.8 (m, 1 H, C*H*MeEt), 5.28 (2 s, 1 H, $CHOSiMe_3$) | 1715 |
| *n*-$C_4H_9C(O)C(CH_3)(OSiMe_3)(CH_2)_3Cl$ | 1.4459 | 55.99 (56.62) | 9.76 (9.78) | * 0.15 (s, 9 H, $OSiMe_3$), 1.0–1.8 (m, 14 H, alkyl; contains 1.32 (s) (C-$CH_3$)), 2.55 (t, *J* = 7.33 Hz, 2 H, $CH_2C(O)$), 3.47 (t, *J* = 5.4 Hz, 2 H, $CH_2Cl$) | 1712 |
|  | 1.4400 | 70.55 (70.46) | 10.66 (10.52) | * 0.88 (t, *J* = 7.35 Hz, 3 H, $CH_3$ of $C_4H_9$), 1.21–1.35 (m, 5 H, contains 1.30 (s) (C-$CH_3$)), 1.45–1.94 (m, 5 H), 2.19 (m, 1 H), 2.58 (complex m, 2 H, $CH_2C(O)$), 3.82, 3.96 (m, 1 H each, $CH_2O$) |  |
|  | 1.4388 | 70.55 (70.59) | 10.66 (10.55) | * 0.74–1.1 (m, 6 H, $CH_3$s of *s*-$C_4H_9$), 1.29, 1.31 (2 s, 3 H, diastereotopic C-$CH_3$ (ring)), 1.53–1.77 (m, 6 H, $CH_2CH_2$ (ring)), 2.15 (m, 1 H, CH of *s*-$C_4H_9$), 3.88 (m 2 H, $CH_2O$) |  |
|  | 1.4405 | 70.55 (70.50) | 10.66 (10.83) | * 1.21 (s, 9 H, $Me_3C$), 1.33 (s, 3 H, C-$CH_3$), 1.6–2.3 (m, 4 H, $CH_2CH_2$ (ring)), 3.92 (m, 2 H, $CH_2O$) |  |
| $(CH_3)_3CC(O)CH_2OC(O)C(CH_3)_3$ | mp 47–48 °C | 65.97 (65.84) | 10.01 (9.94) | * 1.18 (s, 9 H, $Me_3C$), 1.25 (s, 9 H, $Me_3C$), 4.84 (s, 2 H, $CH_2$) | 1725<br>(ketone)<br>1740<br>(ester) |
| $(CH_3)_3CC(O)CH(OSiMe_3)C(O)C(CH_3)_3$ |  | 61.72 (61.90) | 10.36 (10.33) | * 0.13 (s, 9 H, $Me_3Si$), 1.17 (s, 18 H, $Me_3C$), 5.40 (s, 1 H, C(O)CHC(O)) | 1730 |
| $(CH_3)_3CC(O)CH(O_2CCH_3)C(O)C(CH_3)_3$ |  | 64.44 (64.57) | 9.15 (9.15) | * 1.19 (s, 18 H, $Me_3C$), 2.17 (s, 3 H, $C(O)CH_3$), 6.19 (s, 1 H, C(O)CHC(O)) | 1732<br>1730,<br>1710<br>(ketone)<br>1760<br>(ester) |

[a] Leonard, N. J.; Mader, P. M. *J. Am. Chem. Soc.* **1950**, *72*, 5388. [b] Signal disappears upon addition of $D_2O$. [c] Signal reduced to a singlet upon addition of $D_2O$. [d] Fuson, R. C.; Gray, H.; Gouza, J. J. *J. Am. Chem. Soc.* **1939**, *61*, 1937.

immersion mode. The readings usually are 7–8 °C higher compared to the actual temperature under our reaction conditions. The temperatures reported here all are corrected by subtracting 7 °C from the thermometer readings.

Proton NMR spectra were obtained using either JEOL FX-90Q (90-MHz) or Bruker WM-250 (250-MHz) spectrometers, with samples in $CDCl_3$ solution. They are reported in δ units. Analytical gas chromatography was carried out using a Perkin-Elmer 5754 Research chromatograph equipped with a 6-ft × $^1/_4$-in. 15% SE-30 on Chromosorb P column and a Gow Mac 550P Model chromatograph with a similar column. The program used for the separation of the compounds was 100–275 °C, heating at 6 °C/min. Yields by GLC were obtained using the internal standard method ($C_8$–$C_{12}$). Analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark.

Tables I–III provide experimental details of the preparative experiments. Table VI details product characterization.

**Nucleophilic Acylation of Aldehydes and Ketones. (A) Small-Scale Procedure at −110 °C.** A 500-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, a Claisen adapter (fitted with a low temperature thermometer and a gas outlet tube), and a no-air stopper which held a coarse-fritted gas dispersion tube (which was connected to a carbon monoxide cylinder) was charged with 130 mL each of dry THF and diethyl ether, 40 mL of pentane, and the ketone (about 9–12 mmol). This solution was cooled to −110 °C with the aid of a liquid nitrogen-filled Dewar flask (which could be raised or lowered with a laboratory jack to maintain the desired temperature), and carbon monoxide was bubbled through the solution for 30 min. Subsequently, while the CO gas stream through the solution was continued, the alkyllithium solution (9–12 mmol for 1:1 reactions, 4.5–6 mmol for 2:1 reactions, in hexane) was added through a 15-gauge syringe needle that was inserted through the no-air stopper and was connected to a syringe pump via polyethylene tubing. The tip of the syringe needle was about 1 in. above the surface of the solvent. The alkyllithium solution was added at a controlled rate, generally about 0.5 mmol/min with vigorous stirring. Upon completion of the addition, the reaction mixture was stirred at −110 °C for 2 h while the CO stream was continued. Subsequently, the mixture was allowed to warm to room temperature; CO was bubbled through the solution during this time. Hydrolysis was affected with 75 mL of saturated aqueous $NH_4Cl$. The aqueous layer was separated and extracted twice with diethyl ether. The ether extracts were combined with the organic layer.

Drying with anhydrous $MgSO_4$ was followed by filtration and removal of solvents by fractional distillation (9-in. Vigreux column) or by trap-to-trap distillation at 15–20 Torr. The residue was analyzed by GLC (6 ft × $^1/_4$ in. DE-30 silicone rubber gum on Chromosorb P). Solid products were recrystallized from appropriate solvent mixtures.

In some experiments the reaction mixtures were quenched with an excess of trimethylchlorosilane while the temperature was still at −110 °C instead of being hydrolyzed. In those cases, the reaction mixture then was allowed to warm to room temperature and filtered. The filtrate was distilled to remove solvents and the product isolated by GLC as above, or by crystallization.

**(B) Small-Scale Procedure at −135 °C.** The reaction flask (as in A) was charged with 75 mL of dry THF and the substrate (9–12 mmol) and cooled to −40 to −50 °C. Dimethyl ether (ca. 220 mL of liquid) then was condensed (from a lecture bottle) into the flask. The resulting solution was cooled to −135 °C with the aid of a liquid nitrogen-filled Dewar flask, and carbon monoxide was bubbled into the solution for about 30 min. Subsequently, the alkyllithium solution was added at a controlled rate (ca. 0.5 mmol/min by syringe pump) with stirring. After the addition had been completed, the reaction mixture was stirred at −135 °C (continuing the stream of CO) for 2 h and then was allowed to warm (still in a CO stream) to ca. −30 °C, at which temperature the dimethyl ether began to evaporate. A cold water bath was placed around the flask to facilitate this process. When most of the $Me_2O$ had evaporated (~2 h), hydrolysis and further workup were continued as in A.

**(C) Larger Scale Procedure at −110 °C.** We have described the synthesis of 3-hydroxy-2,2,3-trimethyloctan-4-one on a 78-mmol scale by the $n$-$C_4H_9Li/CO/CH_3C(O)C(CH_3)_3$ reaction at −110 °C in detail in an *Organic Synthesis* preparation.[18] Isolated yields of 67–73% were obtained in several experiments.

**Reaction between *n*-Butyllithium, Carbon Monoxide, and Acetophenone at −110 °C: Subsequent Quenching of the Reaction Solution with Trimethylchlorosilane.** Via the procedure outlined in A, $n$-BuLi (hexane solution, 2.32 M, 3.9 mL, 9.05 mmol) was added at a rate of 0.24 mL/min (0.57 mmol/min) to a solution of $PhC(O)CH_3$ (2.1 mL, 18.0 mmol) in THF (133 mL), $Et_2O$ (133 mL), and pentane (33 mL) at −110 °C. After complete addition of $n$-BuLi, the reaction mixture was maintained at −110 °C for 2 h, $Me_3SiCl$ (2.0 mL, 15.8 mmol) was then added at −110 °C, and the solution was allowed to warm to room temperature over 1 h under a nitrogen atmosphere.

The reaction mixture was cannulated into a flame-dried 1-L round bottomed flask, and the solvents and the excess of $Me_3SiCl$ were removed. Pentane (50 mL) was added to precipitate the salts, the mixture was centrifuged, and the supernatant liquid was decanted. The later was concentrated and analyzed by GLC (100–270 °C at 6 °C/min, IS = $C_{10}$) which showed the presence of two products: 1-phenyl-1-(trimethylsiloxy)ethylene, [0.645 g, 3.35 mmol, 37%, 50% based on recovered acetophenone, NMR (90 MHz, acetone-$d_6$): $\delta$ 0.26 (s, 9 H, $OSiMe_3$), 4.43 and 4.99 (2 s, 1 H each, $=CH_2$), 7.3–7.6 (m, 5 H, phenyl protons); IR (thin film, NaCl, $cm^{-1}$) 1610 (s, $\nu(C=C)$), 1250 (s, $Me_3Si$)] and 2-phenyl-2-(trimethylsiloxy)-3-heptanone (0.805 g, 2.89 mmol, 32%, 43% based on recovered acetophenone).

**Reaction between *n*-Butyllithium, Carbon Monoxide, and 5-Chloro-2-hexanone at −110 °C: Subsequent Trimethylsilylation of the Reaction Mixture.** Via the procedure outlined in A, $n$-BuLi (hexane solution, 2.1 M, 4.0 mL, 8.2 mmol) was added to a solution of 5-chloro-2-hexanone (2.1 mL, 18 mmol) in THF (133 mL), $Et_2O$ (133 mL), and pentane (33 mL) at a rate of 0.24 mL/min (0.50 mmol/min) at −110 °C. After 2 h at −110 °C, $Me_3SiCl$ (4.0 mL, 32.0 mmol) was added (at −110 °C) and the reaction mixture was gradually warmed to room temperature over 1 h under a nitrogen atmosphere. The reaction mixture then was cannulated into a flame-dried, nitrogen-flushed, 1-L, round-bottomed flask and concentrated under a nitrogen atmosphere. Pentane (30 mL) was added to the concentrate to precipitate LiCl. The resulting suspension was filtered through a pad of Celite to remove the salts, and the clear filtrate was concentrated under a nitrogen atmosphere. The residue was analyzed by GLC (100–240 °C at 6 °C/min, IS = $C_{12}$), which showed the presence of one product which was identified as 4-(trimethylsiloxy)-4-methyl-1-chloro-5-nonanone (1.53 g, 5.5 mmol, 67%).

**Reaction between the Isomeric Butyllithiums, Carbon Monoxide, and 5-Chloro-2-hexanone at −110 °C: Cyclization of the Intermediate Alkoxide to a Tetrahydrofuran. (1) *n*-Butyllithium.** Via the procedure outlined in A, $n$-BuLi (hexane solution, 2.1 M, 4.0 mL, 8.2 mmol) was added to a solution of 5-chloro-2-hexanone (2.1 mL, 18.0 mmol) in THF (133 mL), $Et_2O$ (133 mL), and pentane (33 mL) at a rate of 0.24 mL/min (0.50 mmol/min) at −110 °C. After 2 h at −110 °C, the reaction mixture was warmed to room temperature over 1 h with carbon monoxide bubbling through the solution. Under a nitrogen atmosphere, the overhead stirrer was replaced with a reflux condenser, the gas dispersion tube with a glass stopper, and the low-temperature thermometer with a regular thermometer, and the reaction mixture subsequently was refluxed for 2 h at +47 °C. The solution then was cooled to room temperature and concentrated under reduced pressure. Pentane (50 mL) was added to precipitate the LiCl, and the resulting solution was filtered through a pad of Celite to remove the salts. The clear filtrate was concentrated, and the liquid residue was analyzed by GLC (100–250 °C at 6 °C/min, IS = $C_{11}$). One product was present which was identified as 2-pentanoyl-2-methyltetrahydrofuran (1.28 g, 7.5 mmol, 92%).

**(2) *sec*-Butyllithium.** The same procedure was used but with $s$-BuLi, 8.75 mmol, 1.75 M pentane. The single product was identified as 2-(2-methylbutanoyl)-2-methyltetrahydrofuran, (1.41 g, 8.3 mmol, 95%).

**(3) *tert*-Butyllithium.** The same procedure was used, but with $t$-BuLi, 6.51 mmol, 1.76 M in pentane. The single product was identified as 2-(2,2-dimethylpropionyl)-2-methyltetrahydrofuran, 0.88 g, 5.2 mmol, 80%.

**Two-Step Reaction between *n*-Butyllithium, Carbon Monoxide, and Pivalaldehyde at −110 °C.** The standard reaction apparatus was charged with THF (133 mL), $Et_2O$ (133 mL), and pentane (33 mL) and cooled to −110 °C with a slow CO stream bubbling through the solution. After 30 min at −110 °C, a hexane solution of $n$-BuLi (2.3M, 4.0 mL, 9.2 mmol) was added at a rate of 0.24 mL/min (0.55 mmol/min). The reaction mixture turned a deep orange during the addition of $n$-BuLi. After the addition of $n$-BuLi was completed, pivalaldehyde (0.79 g, 9.2 mmol) was added via syringe at −110 °C. No color change was noted upon the addition of pivalaldehyde. The reaction mixture was maintained at −110 °C for 2 h with CO bubbling through the solution and then was warmed to room temperature over 1 h, at which time the reaction mixture was yellow. The reaction mixture was hydrolyzed by the addition of 75 mL of saturated aqueous $NH_4Cl$; the aqueous layer was separated and extracted with 100 mL of pentane. The combined organic layers were dried over $MgSO_4$, concentrated, and analyzed by GLC (100–270 °C at 6 °C/min, IS = $C_{11}$) which showed the presence of three products: 2,2-dimethyl-3-heptanol, $n$-$C_4H_9CH(OH)CMe_3$ (0.347 g, 2.4 mmol, 26%), 4-hydroxy-2,2-dimethyl-3-octanone, $n$-$C_4H_9C(O)CH(OH)CMe_3$ (0.591 g, 3.4 mmol, 37%), 4-hydroxy-5-nonanone, $n$-$C_4H_9C(O)$-$CH(OH)n$-$C_4H_9$ (0.054 g, 0.3 mmol, 7%).

These produces were identified by comparison of their IR spectra and GLC co-injection with those of authentic samples.

**Two-Step Reaction between *n*-Butyllithium, Carbon Monoxide, and Cyclohexanone at −110 °C.** Via the procedure outlined above, $n$-BuLi (hexane solution, 2.3 M, 4.0 mL, 9.2 mmol) was added to a CO saturated solution of THF (133 mL), $Et_2O$ (133 mL), and pentane (33 mL) at a rate of 0.24 mL/min (0.55 mmol/min) at −110 °C. After the addition of $n$-BuLi was completed, cyclohexanone (0.90 g, 9.2 mmol) was added at −110 °C. The usual reaction conditions and workup as in A, followed by GLC analysis (100–271 °C/min, IS = $C_{10}$), showed the presence of four products: 1-$n$-butylcyclohexanol (0.230 g, 1.5 mmol, 16%), 1-$n$-pentanoylcyclohexanol (0.941 g, 5.1 mmol, 56%), 5-hydroxy-6-decanone, $n$-$C_4H_9C(O)CH(OH)n$-$C_4H_9$ (0.040 g, 0.2 mmol, 4%), 5,6-decanedione, $n$-$C_4H_9C(O)C(O)n$-$C_4H_9$ (0.040 g, 0.2 mmol, 4%).

These products were identified by comparison of their IR spectra (for the cyclohexanol products) or GLC co-injection (for the dimers) with those of authentic samples.

**Two-Step Reaction between *tert*-Butyllithium, Carbon Monoxide, and Benzaldehyde at −110 °C.** Via the procedure outlined above, $t$-BuLi (pentane solution, 2.04 M, 4.4 mL, 9.0 mmol) was added to a CO-saturated solution of THF (133 mL),

$Et_2O$ (133 mL), and pentane (33 mL) at a rate of 0.24 mL/min (0.49 mmol/min) at −110 °C. The addition of *t*-BuLi resulted in an immediate deep red coloration of the reaction mixture. After the complete addition of *t*-BuLi, benzaldehyde (0.93 mL, 9.1 mmol) was added at −110 °C. This did not result in dissipation of the red color. After the 2-h reaction period at −110 °C, the reaction mixture was warmed to room temperature (reaction solution was still red) and hydrolyzed by the addition of 75 mL of saturated $NH_4Cl$ which resulted in a clear, essentially colorless reaction mixture. The usual workup and analysis by GLC (100–270 °C at 6 °C/min, IS = $C_8$) showed the presence of benzaldehyde (77% recovery) and one major product in addition to three very minor products (<5%).

The major product was collected by preparative GLC and identified as 3,3-dimethylacetonyl pivalate, $Me_3CC(O)OCH_2C(O)CMe_3$ (0.584 g, 2.92 mmol, 65%), mp 47–48 °C. $^{13}C$ NMR ($CD_2Cl_2$), gated decoupled spectrum, $\delta_C$ 26.3, 27.3 (q, $J$ = 128 Hz each, 2-$CMe_3$), 38.9, 43.0 (s, 2-$CMe_3$), 64.7 (t, $J$ = 146 Hz, $OCH_2C(O)$), 208.2 (s, ketone C=O). The ester C=O was not located with certainty; a peak at δ 170 could be ascribed to this, although it was smaller than expected.

Further characterization data are given in later experiments.

**Reaction between *n*-Butyllithium and Carbon Monoxide at 110 °C in the Absence of an Electrophile.** *n*-Butyllithium (2.37 N solution in hexane, 4.0 mL, 9.48 mmol) was added to the CO-saturated THF/$Et_2O$/pentane solvent mixture at −110 °C. The solution was kept at −110 °C for 2 h, during which time the solution was brown. The reaction mixture was allowed to warm to room temperature, which resulted in a color change to orange brown. It then was treated with 75 mL of saturated aqueous $NH_4Cl$ solution. The usual workup followed. GLC analysis of the residue showed the presence of two major products: (1) *n*-BuC(O)C(O)Bu-*n*, a yellow liquid, yield 0.15 g, 0.99 mmol, 19%, and (2) *n*-BuC(O)CH(OH)*n*-Bu, yield 0.17 g, 0.99 mmol, 21%.

These compounds were identified by the comparison of their IR and $^1H$ NMR spectra and GLC co-injection with those of the authentic materials.

**Reaction between *sec*-Butyllithium and Carbon Monoxide at −110 °C in the Absence of an Electrophile.** The same procedure used in above was used in this reaction of *sec*-butyllithium (1.46 N solution in hexane, 7.0 mL, 10.36 mmol). The color was red-brown during the reaction. Saturated aqueous $NH_4Cl$ solution (75 mL) was added at room temperature. The usual workup was followed by GLC analysis. One major product and three minor products were obtained. No attempt was made to identify the minor products. The major product was *s*-BuC(O)CH(OH)*s*-Bu, yield 0.24 g, 1.41 mmol, 27%, $n^{20}{}_D$ = 1.4385; lit.[16] $n^{20}{}_D$ = 1.4391; also IR.

**Reaction between *tert*-Butyllithium and Carbon Monoxide at −110 °C in the Absence of an Electrophile.** The same procedure as in the above reaction was used in this reaction of *tert*-butyllithium (1.96 N solution in pentane, 5.0 mL, 9.80 mmol). The reaction mixture was red-brown during the reaction and changed to orange brown when it was warmed to room temperature. It then was treated with 75 mL of saturated aqueous $NH_4Cl$. GLC analysis of the residue after the removal of the solvents showed the presence of only one product, 3,3-dimethyl-2-oxo-*n*-butyl pivalate, $Me_3CC(O)CH_2OC(O)CMe_3$, yield 0.68 g, 3.41 mmol, 70%; mp 47–48 °C (twice recrystallized from hexane).

In a second experiment, the same reaction was quenched with 1.50 mL of trimethylchlorosilane (11.80 mmol) at −110 °C. No immediate color change occurred when $Me_3SiCl$ was added at −110 °C. However, the reaction mixture changed to yellow when it was warmed to room temperature. Solvent then was removed by trap-to-trap distillation (0.5 Torr) at room temperature; 50 mL of pentane was added to the residue to precipitate the LiCl. The suspension was filtered, and the solvent was removed by trap-to-trap distillation (1.0 Torr) at room temperature. GLC analysis of the residue showed the presence of two products: (1) 2,2,6,6-tetramethyl-4-(trimethylsiloxy)heptane-3,5-dione, $Me_3CC(O)CH(OSiMe_3)C(O)CMe_3$, 0.3 g, 1.09 mmol, 22%, and (2) 1,2-bis(trimethylsiloxy)-1,2-dipivaloylethene, 0.92 g, 2.48 mmol, 51%. NMR (90 MHz, $CDCl_3$): δ 0.13 (s, 18 H, 2-$SiMe_3$), 1.14 (s 18 H, 2-$CMe_3$). IR (thin film, NaCl, $cm^{-1}$): 2960 s, 2920 m, 2860 w, 1690 s (ν(C=O)), 1610 m (ν(C=O)), 1480 s, 1460 m, 1395 w, 1365 m, 1250 s, 1210 s, 1160 s, 1060 m, 1010 w, 920 m, 850 s, 750 m, 690 w.

In another experiment, the same reaction was quenched with 1.0 mL of acetic anhydride at −110 °C. The reaction mixture was yellow when it was warmed to room temperature. GLC analysis showed the presence of only one product, 2,2,6,6-tetramethyl-4-acetoxyheptane-3,5-dione (0.76 g, 3.14 mmol, 72%).

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