Selective Alkylation of Ketones with a Bulky Aluminum Reagent-the THF-TBSOTf System

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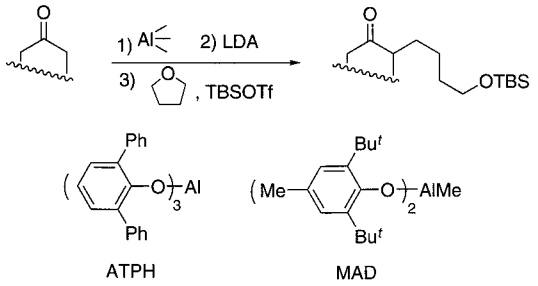
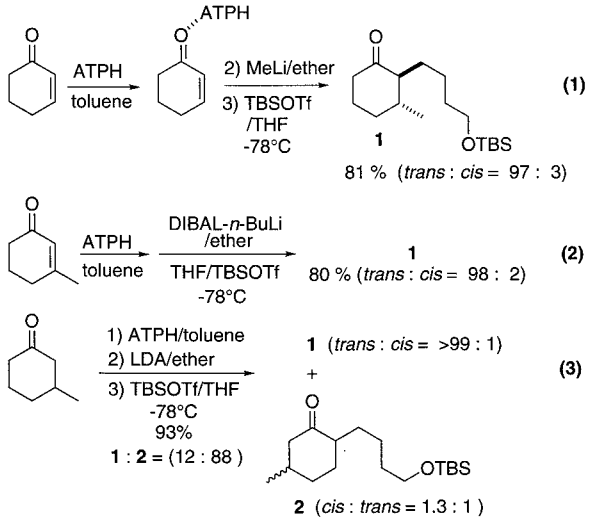
Abstract: Various ketones can be alkylated with tetrahydrofuran (THF) to provide α-siloxybutylated ketones in the presence of a bulky aluminum reagent, lithium diisopropylamide (LDA), and *t*-butyldimethylsilyl triflate (TBSOTf).

We report here an unprecedented one-pot alkylation of carbonyl compounds complexed with the bulky aluminum reagents aluminum tris(2,6-diphenylphenoxide) (ATPH)[1] or methylaluminum bis(2,6-di-*t*-butyl-4-methylphenoxide) (MAD),[2] by sequential treatment with LDA and *t*-butyldimethylsilyl triflate (TBSOTf) in THF to yield mono- or dialkylated ketones.[3]

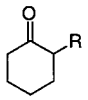


Treatment of the lithium enolate of 3-methylcyclohexanone, generated from the corresponding trimethylsilyl enol ether (MeLi, THF, 0 °C),[4] with ATPH, followed by addition of TBSOTf, resulted in no silylation or siloxybutylation of the enolate intermediate to give 3-methylcyclohexanone (>95%). Precomplexation of 2-cyclohexenone with ATPH, followed by Michael addition of MeLi (ether solution),[5] and sequential treatment with THF and TBSOTf gave, after chromatography on silica gel, a 81 % yield of **1** as a mixture of *cis* and *trans* isomers in a ratio of 3 : 97 (Equation 1).[6] Reductive alkylation of 3-methyl-2-cyclohexenone with THF and TBSOTf was also achieved using diisobutylaluminum hydride-butyllithium complex (DIBAL-BuLi) as a reducing agent in the presence of ATPH (80 % yield, *cis* : *trans* = 2 : 98) (Equation 2).[7] An even more generally useful and interesting result was obtained by the regioselective alkylation of the 3-methylcyclohexanone/ATPH complex with LDA, THF, and TBSOTf, which provided **2** as a major product in a *cis*/*trans* ratio of 1.3 : 1 (Equation 3).[8] Apparently, these reactions, depicted in Equations 1 ~ 3, should proceed *via* the same enolate intermediate.



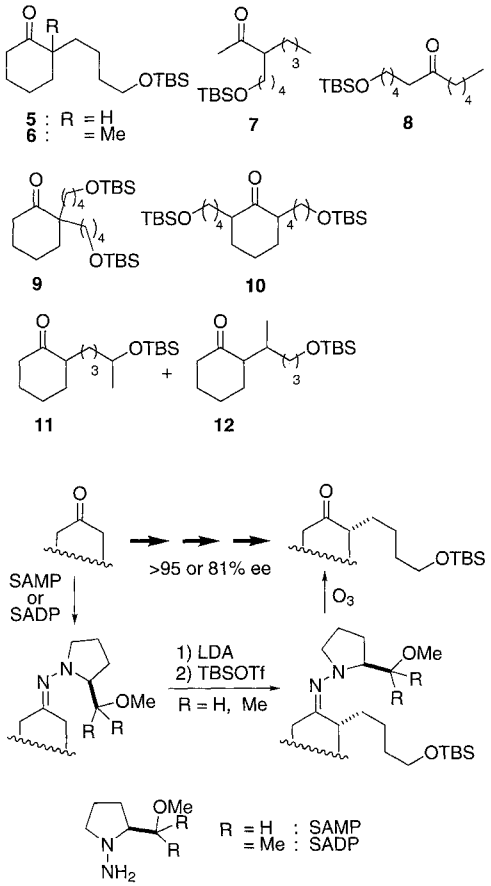
We next investigated the reaction shown in Equation 3 with other cyclohexanone derivatives, and the results are summarized in Table 1. Several characteristic features of this reaction were noted. (1) Selective monosiloxybutylation was achieved by the combined use of 1.1 equiv of ATPH and 1.1 equiv of LDA[9,10] without the formation of bissiloxybutylated products (Entries 1 ~ 4). The more-substituted site of the starting ketones was alkylated regioselectively when unsymmetrical ketones were used (Entries 2 and 3).[11,12] (2) A combination of 1.1 equiv of ATPH and 2.2 equiv of LDA for **3** led to the selective second alkylation at the more-hindered α-carbon of intermediate **5** to give α,α-dialkylated ketone **9** preferentially. Thus, formation of the ATPH-**3** complex in toluene at -78 °C, followed by successive addition of 2.2 equiv of LDA, THF, and TBSOTf gave, after 88 h, a mixture of **5**, **9**, and **10** in a ratio of 39 : 41 : 20 (Entry 5). It is interesting to note that α,α'-dialkylated ketone[13] **10** was predominant with the combined use of 1.1 equiv of MAD and 2.2 equiv of LDA (Entry 6). (3) Unsymmetrical THF 2-methyltetrahydrofuran underwent selective ring-opening at the less-substituted carbon to furnish the monoalkylated ketone in high yield (Entry 7). This result suggests that the present reaction is unlikely to proceed by an S_N1 mechanism. (4) Overall, the second alkylation was much slower than the first alkylation in our system, so that the monoalkylation was predominant with 1.1 equiv of LDA.

Table 1. Alkylation of ketones by an aluminum reagent, LDA, THF and TBSOTf [a]

entry	ketone	conditions (°C, h)	major product	yield (%)[b]
				
1	**3** : R = H	-78, 1.5	**5**	95
2	**4** : = Me	-40, 0.5	**6**	94
3		-78, 4	**7**	47[f]
4	**5**	-78, 60	**9**	21[g]
5[c]	**3**	-78, 88	**9**	37[h]
6[c,d]	**3**	-78, 23	**10**	94
7[e]	**3**	-40, 9	**11**	77[i]

[a] Unless otherwise specified, the reaction was carried out using ATPH (1.5 equiv), LDA (1.1 equiv), THF (excess), and TBSOTf (4.0 equiv). [b] Isolated yield of the major product. [c] 2.2 equiv of LDA was used. [d] MAD (1.1 equiv) was used in place of ATPH. [e] 2-methyltetrahydrofuran was used in place of THF. [f] **8** was obtained in 3% yield. [g] **10** was obtained in 8% yield. [h] **5** and **10** were obtained in 35% and 18% yield, respectively. [i] **12** was obtained in 5% yield.

The mechanistic aspects of the present reaction remain unclear. However, Enders et. al. reported that the ring-opening process of THF with lithiated hydrazones and TBSOTf could be explained by the intervention of *O*-silyltetrahydrofuranium trifluoromethanesulfonate (Scheme 1).[14] Our system seems to proceed *via* the same intermediate. Further investigation and extension of the present study to other cyclic ethers[15] are currently underway in our laboratory.



Scheme 1

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References and Notes

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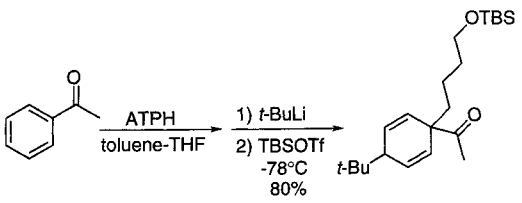
(3) This reaction was eventually found during our research on the conjugate addition of *t*-butyllithium (*t*-BuLi) to acetophenone in the presence of ATPH (in toluene-THF), followed by subsequent treatment with TBSOTf, as shown below.



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(6) The *cis*/*trans* ratio was determined by GC-MS and ^{1}H NMR (300 MHz, $CDCl_3$) analysis by measuring the coupling constant (Hz) of C(2)H of **1**. *Trans*-**1**: δ 2.38 (dt, 1H, *J* = 13.3, 4.9 Hz)

(7) Selective 1,4-reduction of α-enones with ATPH: Saito, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 2928.

(8) The *cis*/*trans* ratio was determined by ^{1}H NMR (300 MHz, $CDCl_3$) analysis and by comparing the chemical shifts (ppm) of the Me-groups of *trans*- and *cis*-**2** (*trans*-**2**: δ 1.02 (d, *J* = 6.2 Hz); *cis*-**2**: δ 0.97 (d, *J* = 6.6 Hz) with those of *trans*- and *cis*-3,5-dimethylcyclohexanone (*trans*: δ 0.99 (d, *J* = 6.8 Hz); *cis*: δ 1.02 (d, *J* = 6.0 Hz)).

(9) A typical procedure is as follows: treatment of **3** (0.5 mmol) with ATPH (0.75 mmol) in toluene (5.0 mL) was followed by the addition of an ether (2.0 mL) solution LDA (0.55 mmol, 1.1 equiv) at -78 °C. To the resulting complex was added THF (1.0 mL) and TBSOTf (2.0 mmol, 2.2 equiv). Monitoring the reaction by TLC analysis showed the complete consumption of **3** after 1 ~ 2 hours. The reaction mixture was poured into *aq.* $NaHCO_3$, and the resulting precipitates were filtered through a Celite pad. The organic layer of the filtrate was extracted with ether, dried, and concentrated. None of the silyl enol ether was detected, but alkylated product **5** was obtained in nearly quantitative yield after chromatography on silica gel. The assigned structure is consistent with the results of IR, ^{1}H and ^{13}C NMR, and elemental analysis. Preparation of ATPH: see reference 1a.

(10) Using MAD (1.1 equiv) in place of ATPH (1.1 equiv) in the same reaction sequence resulted in the immediate consumption of ketone **3**, followed by subsequent production of a mixture of **5** and **10** (~ 2.4 : 1). Preparation of MAD: see reference 2b.

(11) Alkylation at the more substituted α-site of unsymmetrical ketones using ATPH: Saito, S.; Ito, M.; Yamamoto, H., *J. Am. Chem. Soc.*, **1997**, *119*, 611.

(12) Regioselective alkylation at the more-substituted α-site of **4** under thermodynamic conditions has been reported, but the selectivity was much lower: House, H. O.; Gall, M.; Olmstead, H. D.; *J. Org. Chem.*, **1971**, *36*, 2361. (b) House, H. O; Trost, B. M.; *ibid.* **1965**, *30*, 1341. See also reference 11, and other references cited therein.

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