Communications to the Editor

Highly Regioselective Alkylation at the More-Hindered α-Site of Unsymmetrical Ketones by the Combined Use of Aluminum Tris(2,6-diphenylphenoxide) and Lithium Diisopropylamide

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An unsymmetrical dialkyl ketone can form two regioisomeric enolates upon deprotonation.[1] To exploit the synthetic potential of enolate ions, the regioselectivity of their formation must be controlled. By adjusting the conditions under which an enolate mixture is formed from a ketone, it is possible to establish either kinetic or thermodynamic control. Ideal conditions for kinetic control of the formation of less-substituted enolate are those in which deprotonation is irreversible, such as those with lithium diisopropylamide (LDA). On the other hand, at equilibrium, the more-substituted enolate is the dominant species with moderate selectivity.[2] Although there exists a method to generate the more-substituted enolate using magnesium reagents,[3] the selectivity is not always high. We report here a third, hitherto unknown, method for the kinetically controlled generation of the more-substituted enolate by the combined use of aluminum tris(2,6-diphenylphenoxide) (ATPH)[4] and LDA (Scheme 1).

Precomplexation of ATPH with methylcyclohexanone (**1a**) at −78 °C in toluene, followed by sequential treatment with

Scheme 1
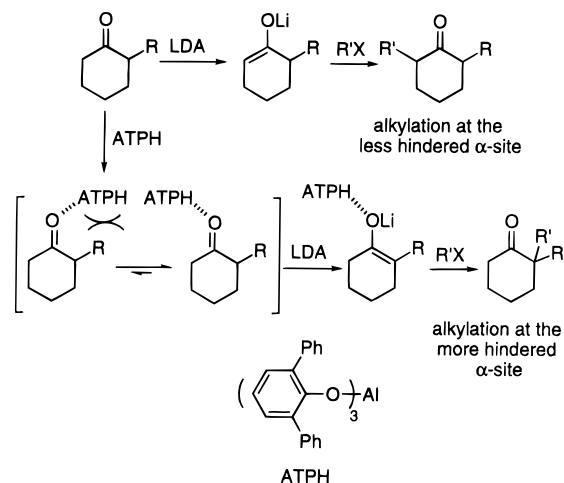
LDA in tetrahydrofuran and methyl trifluoromethanesulfonate[5] (MeOTf), furnished, after 2 h, 2,2-dimethylcyclohexanone (**2a**) and 2,6-dimethylcyclohexanone (**3a**) in an isolated yield of 53% in a ratio of 32:1.[6] Other alkylating agents, such as octyl triflate[7] (OctOTf), allyl bromide (Allyl-Br), allyl iodide (Allyl-I), and propargyl bromide, were also used for highly selective alkylation at the more encumbered α-site of **1a** to give **2b**−**d** exclusively (entries 2−5). In general, the reaction with the halides required
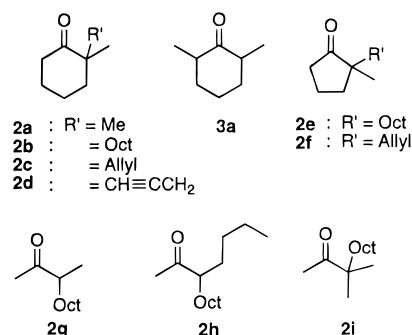
a higher temperature (−20 to 0 °C) than that with the alkyl triflates (−78 to −40 °C). This alkylation method was also successfully applied to other unsymmetrical ketones, and the results are summarized in Table 1. It should be emphasized that a high level of discrimination of α-methine over α-methylene (entries 1−8), α-methylene over α-methyl (entries 9 and 10), and α-methine over α-methyl (entry 11) was achieved using ATPH to give **2b**−**i** in reasonable yields.

The generation of the kinetically deprotonated more-substituted enolate could be interpreted in terms of the influence

(1) (a) House, H. O. In *Modern Synthetic Reactions*; Breslow, R., Ed.; W. A. Benjamin, INC.: Menlo Park, NY 1972; Chapter 9 and references cited therein. (b) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: San Diego, CA, 1984; Vol. 3, Chapter 1 and references cited therein. (c) Caine, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, Chapter 1.1 and references cited therein. (d) Mekelburger, H. B.; Wilcox, C. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 1.4 and references cited therein. (e) Heathcock, C. H. In *Modern Synthetic Methods 1992*; Scheffold, R., Ed.; VHCA and VCH: Basel, Weinheim, and New York, 1992; Vol. 6, Chapter 1 and references cited therein.

(2) Recent methods for the generation of more-substituted enolates have been reported. KH and BEt₃ system: (a) Negishi, E.; Chatterjee, S. *Tetrahedron Lett.* **1983**, *24*, 1341. (b) Negishi, E.; Matsushita, H.; Chatterjee, S.; John, R. A. *J. Org. Chem.* **1982**, *47*, 3190. Unsymmetrical imines with RLi; (c) Hosomi, A.; Araki, Y.; Sakurai, H. *J. Org. Chem.* **1982**, *104*, 2081. The regiochemistry of α-alkylation of unsymmetrical ketones depends on the combination of the metal cation and electrophiles rather than on regioselective enolate formation. (d) Duhamel, P.; Cahard, D.; Quesnel, Y.; Poirier, J.-M. *J. Org. Chem.* **1996**, *61*, 2232. Preparation of thermodynamic trimethylsilyl enol ethers: (e) Krafft, M. E.; Holton, R. A. *J. Org. Chem.* **1984**, *49*, 3669. (f) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462. (g) House, H. O.; Czuba, L. J.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324. (h) Nakamura, E.; Murofushi, T.; Shimizu, M.; Kuwajima, I. *J. Am. Chem. Soc.* **1976**, *98*, 2346. (i) Miller, R. D.; Mckean, D. R. *Synthesis* **1979**, 730. (j) Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913.

(3) (a) Krafft, M. E.; Holton, R. A. *Tetrahedron Lett.* **1983**, *24*, 1345. (b) Crisp, G. T.; Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 7500. A referee has suggested that in the Krafft−Holton procedure, complexation of an acidic Mg species with the carbonyl groups of ketones might occur prior to deprotonation, based on our results described here. In fact, they used more than 1 equiv of the magnesium reagent (<1.25 equiv) for deprotonation.

(4) ATPH was prepared as follows: To a solution of 2,6-diphenylphenol (3 equiv) in toluene was added a 1 M hexane solution of Me₃Al (1 equiv) at room temperature under argon. The resulting pale yellow solution was stirred at this temperature for 30 min and used without further purification.

(a) Maruoka, K.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 9091. (b) Maruoka, K.; Saito, S.; Yamamoto, H. *Ibid.* **1995**, *117*, 1165. (c) Maruoka, K.; Imoto, H.; Yamamoto, H. *Ibid.* **1994**, *116*, 12115. (d) Maruoka, K.; Imoto, H.; Saito, S.; Yamamoto, H. *Ibid.* **1994**, *116*, 4131.

(5) For alkylation of ketone enolates with alkyl triflates, see: (a) Bates, R. B.; Taylor, S. R. *J. Org. Chem.* **1993** *58*, 4469. (b) Bates, R. B.; Taylor, S. R. *Ibid.* **1994**, *59*, 245.

(6) Monitoring the reaction by GC-MS analysis using dodecane as an internal standard revealed that **2a** (94%) and **3a** (0.5%) were generated along with unreacted **1a** (5%) after 1 h at −78 °C. The relatively low isolated yield with low observed regioselectivity (entry 1, Table 1) should be due to more volatile nature of **2a**. The tri- and tetramethylated products could not be detected by the GC-MS analysis.

(7) Prepared as described in the literature procedure: Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85.

Table 1. Regioselective Alkylation of Unsymmetrical Ketones[a]

entry	ketone[b]	R'X	major product	yield[c] (%) (2:3)[d]
1	1a	MeOTf	2a	53% (32:1)
2		OctOTf	2b	88% (>99:1)
3		Allyl-Br	2c	53% (>99:1)
4		Allyl-I	2c	69% (>99:1)
5		CH≡CCH₂Br	2d	61% (>20:1)
6		OctOTf	2e	99% (>20:1)
7		Allyl-I	2f	55% (>99:1)
8		MeOTf	2e	75% (5.1:1)
9		OctOTf	2g	69% (24:1)
10		OctOTf	2h	89% (>20:1)
11		OctOTf	2i	71% (>99:1)

[a] Unless otherwise noted, deprotonation of ketones with LDA in the presence of ATPH at −78 °C for 30 min was followed by treatment with alkylating agent (R′X), and the mixture was stirred at −78 °C to room temperature. [b] The carbons indicated with arrows are the more-hindered α-site. [c] Yields are of isolated, purified products. [d] Product ratios are determined by 300 MHz ¹H NMR, HPLC, or GC analysis against authentic samples.

of ATPH on the inherent coordination preferences of unsymmetrical ketones. The X-ray crystal structure of the ATPH−dimethylformamide complex[4d] revealed that the three arene rings of ATPH form a propeller-like arrangement around the aluminum, producing a pocket for accepting a carbonyl compound. It is reasonable to suggest that the bulky aluminum reagent ATPH prefers coordination with one of the lone pairs of the carbonyl oxygen *anti* to the more-hindered α-carbon of the unsymmetrical ketone.[8,9] As a consequence, the pocket surrounds the less-hindered site of the carbonyl group, thus

(8) Coordination aptitude of a variety of Lewis acids toward carbonyl compounds is discussed in the following review: (a) Schreiber, S. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 1, Chapter 1.10 and references cited therein. (b) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 256.
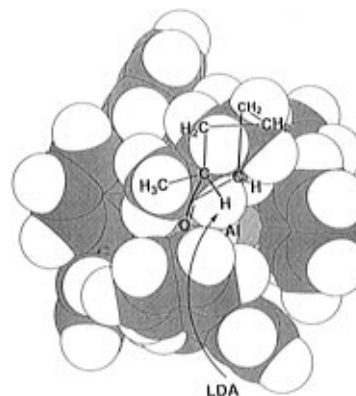
Figure 1. Space-filling model of the ATPH-**1a** complex. LDA attacking is more feasible at the more substituted α-carbon.

obstructing the trajectory of the nucleophilic LDA attacking at this position (Scheme 1 and Figure 1).

Figure 1 also shows that upon *anti* complexation with ATPH, the α-methylene proton of **1a** lays behind the α-methine proton, which is more accessible for deprotonation. The crucial role of the pocket in obtaining the present regioselectivity and high yields was further demonstrated by an alkylation experiment with **1a** in the presence of methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD),[10] a less-hindered aluminum reagent lacking a pocket. Complexation of **1a** with MAD at −78 °C was followed by addition of LDA. After 1 h, the resulting enolate was treated with MeOTf, and the mixture was stirred continuously for 19 h at the same temperature to give **2a** and **3a** in a ratio of ∼1:1.

In conclusion, the synthetically useful, highly selective alkylation at the more-substituted α-carbon of unsymmetrical ketones was realized by extending the Lewis acid−base complexation system to the ordinary ketone alkylation method using LDA and electrophilic alkylating agents.

Supporting Information Available: A representative experimental procedure, spectral data for all new compounds, and the determination of regioisomeric ratios (5 pages). See any current masthead page for ordering and Internet access instructions.

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(9) The MM2 calculation for the ATPH-**1a** complex using the CAChe system indicates that the *anti* coordination of ATPH to **1a** is 7.6 kcal/mol more stable than the *syn* coordination.

(10) The bulky Lewis acid methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) selectively chelates to the less-hindered oxygen functionalities of ethers, ketones, and esters. (a) MAD for ethers: Maruoka, K.; Nagahara, S.; Yamamoto, H. *Tetrahedron Lett.* **1990**, *31*, 5475. (b) MAD for ketones: Maruoka, K.; Araki, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 6225. (c) MAD for esters: Maruoka, K.; Saito, S.; Yamamoto, H. *Ibid.* **1992**, *114*, 1089. (d) Selective coordination to one of the lone pairs of the epoxide oxygen *anti* to the migration group, with the MAD analogue methylaluminum bis(4-bromo-2,6-di-*tert*-butyl-4-methylphenoxide) (MABR): Maruoka, K.; Ooi, T.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 6505.