# Methylaluminum Bis(4-bromo-2,6-di-tert-butylphenoxide) as a Key Reagent for Effecting Primary α-Alkylation of Carbonyl Compounds

Keiji Maruoka, Junko Sato, and Hisashi Yamamoto*

*Department of Applied Chemistry, Nagoya University
Chikusa, Nagoya 464-01, Japan*

The α-alkylation of carbonyl compounds is one of the most fundamental and important C–C bond-forming reactions in organic synthesis.[1] Many useful procedures developed so far involve the S_N2 alkylation of enolate anions (or their synthetic equivalents such as deprotonated imines, oximes, or hydrazones)[2] with the appropriate alkyl halides or tosylates.[3] Here, only S_N2-active components such as methyl, allyl, benzyl, and some primary alkyl halides are employable, and many secondary and tertiary alkyl halides are subjected to competing base-induced HX elimination.[4] More recently, Lewis acid-induced α-alkylation of carbonyl compounds has been developed via the corresponding enol silyl ethers using S_N1-active alkyl halides (i.e., secondary, tertiary, and α-heterosubstituted alkyl halides) in the presence of certain Lewis acids.[5] This alkylation, however, fails to react with primary alkyl halides except allylic and benzylic halides. In this context, we have been interested for some time in *a new, yet unexplored primary α-alkylation of carbonyl compounds under nonbasic conditions* to allow the chemo- and stereoselective α-alkylation of complex carbonyl substrates possessing various base-sensitive functional groups. Here we wish to report a new type of oxygenophile-promoted primary α-alkylation of carbonyl compounds under mild conditions.
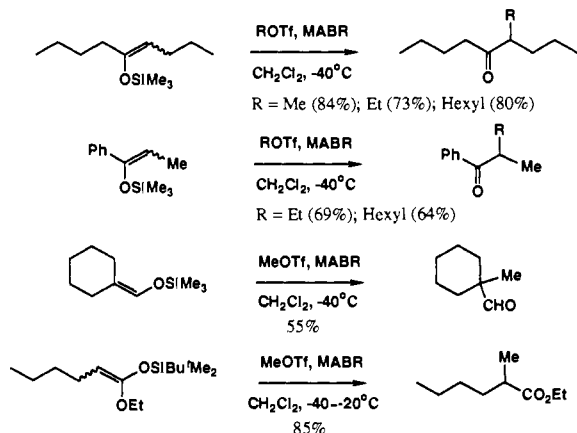
Our method involves the organoaluminum-promoted α-alkylation of carbonyl compounds via the corresponding enol silyl ethers in combination with primary alkyl triflate. Among the various modified organoaluminum reagents used as oxygenophiles, exceptionally bulky methylaluminum bis(4-bromo-2,6-di-tert-butylphenoxide) (MABR)[6] is the reagent of choice. For example,

(1) Reviews: (a) Stork, G. *Pure Appl. Chem.* **1975**, *43*, 553. (b) House, H. O. *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972. (c) Caine, D. *Carbon–Carbon Bond Formation*; Marcel Dekker: New York, 1979; Vol. 1.

(2) Whitesell, J. K.; Whitewell, M. A. *Synthesis* **1983**, 517.

(3) Naked enolates: (a) Noyori, R.; Nishida, I.; Sakata, J. *J. Am. Chem. Soc.* **1983**, *105*, 1598. (b) Kuwajima, I.; Nakamura, E.; Shimizu, M. *Ibid.* **1982**, *104*, 1025. (c) Gingras, M. *Tetrahedron Lett.* **1991**, *32*, 7381.

(4) Zook, H. D.; Kelly, W. L.; Posey, I. Y. *J. Org. Chem.* **1968**, *33*, 3477.

(5) Review: Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 96. For alkylations using metal complex-stabilized carbocations and iodinium salts, see: (a) Padmanabhan, S.; Nicholas, K. M. *Tetrahedron Lett.* **1982**, *23*, 2555. (b) Mikaelian, G. S.; Gybin, A. S.; Smith, W. A.; Caple, R. *Ibid.* **1985**, *26*, 1269. (c) Zhdankin, V. V.; Tykwinski, R.; Caple, R.; Berglund, B.; Koz'min, A. S.; Zefirov, N. S. *Ibid.* **1988**, *29*, 3703. (d) Green, J. R.; Carroll, M. K. *Ibid.* **1991**, *32*, 1141. (e) Chen, K.; Koser, G. F. *J. Org. Chem.* **1991**, *56*, 5764.

(6) (a) Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 316. (b) Maruoka, K.; Ooi, T.; Nagahara, S.; Yamamoto, H. *Tetrahedron* **1991**, *47*, 6983.

Table I. MABR-Promoted Primary α-Alkylation of Enol Silyl Ethers[a]

entry	enol silyl ether	alkyl triflate (ROTf)	product (major isomer)	yield[b] % (ratio)[c]	ratio by enolates[d]
1		R = Me		78	
2		R = Et		78 (13:87)	|53:47|[f]
3		R = Hexyl		81 (9:91)	|62:38|[f]
4		R = Me		65 (86:14)	|24:76|[f]
5		R = Me		62 (12:88)	|18:82|[e]
6		R = Et		57 (6:94)	|14:86|
7		R = Hexyl		53 (6:94)	|34:66|
8		R = Et		51 (40:60)	|79:21|[h]
9		R = Me		83 (58:42)	|32:68|[f]
10		R = Me		59 (63:37)	|12:88|[i]
11		R = Me		83[e]	

[a] Unless otherwise noted, the α-alkylation of enol silyl ethers with alkyl triflate (2 equiv) was carried out with 1.1–2 equiv of MABR in CH_2Cl_2 at –40 to –20 °C. [b] Isolated yield. [c] Ratio of cis/trans (entries 2–9) and dl/meso (entry 10). [d] Isomeric ratios by alkylation of the corresponding lithium enolates. [e] Use of each 3 equiv of MABR/MeOTf. [f] The stereochemical assignment was made by the base-catalyzed conversion of the cis/trans mixtures to the thermodynamically stable isomers. [g] Posner, G. H.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 107. [h] House, H. O.; Umen, M. J. *J. Org. Chem.* **1973**, *38*, 1000. [i] Baretz, B. H.; Turro, N. J. *J. Am. Chem. Soc.* **1983**, *105*, 1309.

treatment of 5-(trimethylsiloxy)-4-nonene with alkyl triflate (2 equiv)[7] under the influence of MABR (1.1–2 equiv) in CH_2Cl_2 at –40 °C for 1.5–3 h gave rise to a monoalkylation product, 4-alkyl-5-nonanone exclusively in 73–84% yield. Little or no dialkylation product was detected. Other examples are shown in the text and in Table I. Several characteristic features of the reaction have been noted. (1) A combination of MABR and alkyl triflates for a variety of enol silyl ethers is one of the best, and only monoalkylation products are obtained. Attempted alkylation of 4-tert-butyl-1-(trimethylsiloxy)-1-cyclohexene with conventional Lewis acids such as $BF_3 \cdot OEt_2$, $TiCl_4$, and Me_3SiOTf gave none of the alkylation products. (2) Enol silyl ethers of a variety of ketones, esters, and certain aldehydes can be successfully utilized for the present alkylation. tert-Butyldimethylsilyl groups are recommended in the case of ketene silyl acetals, and use of trimethylsilyl and triethylsilyl groups leads to a mixture of monoalkylation products and rearranged α-silyl esters.[8] (3) Methyl iodide and dimethyl sulfate are not employable as other methylation agents. (4) α-Branched alkyl triflates are not suitable in view of the facile carbocation rearrangement under the MABR-promoted alkylation conditions. Reaction of 5-(trimethylsiloxy)-4-nonene and isobutyl triflate with MABR in CH_2Cl_2 at –78 to –40 °C generated, via the rearrangement of isobutyl cation, tert-butyl cation which was trapped by (4-bromo-2,6-di-tert-butylphenoxy)aluminum ligands in preference to the enol silyl ether. (5) Since unsymmetrical ketones are selectively convertible into

(7) (a) Howells, R. D.; McCown, J. D. *Chem. Rev.* **1977**, *77*, 69. (b) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85.

(8) Yields and ratios of the methylation products and α-silyl esters were as follows: ketene tert-butyldimethylsilyl acetal, 85% (100:0); ketene triethylsilyl acetal, 97% (72:28); ketene trimethylsilyl acetal, 95% (36:64). The rearranged α-silyl esters can be generated via 1,3-rearrangement of silyl groups on treatment of ketene silyl acetals with certain organoaluminum reagents. See: Maruoka, K.; Banno, H.; Yamamoto, H. *Synlett* **1991**, 253.

"kinetic" or "thermodynamic" enol silyl ethers,[9] regioselective primary α-alkylation can be easily realized (entries 5–8 and 10). (6) A salient feature of the MABR-promoted alkylation is that the alkylation of chiral enol silyl ethers shows opposite diastereomeric ratios compared to those with the corresponding metal enolates (entries 2–4 and 8–10).[10] In particular, the trimethylsilyl ethers of 2,6-disubstituted cyclohexanones exhibited high cis selectivity (entries 2–4) hitherto not observable in metal–enolate chemistry. (7) The selective alkylation of enol silyl ethers possessing base-sensitive functional groups appears feasible under the present reaction conditions (entry 11).[3] The mild reactivity of the oxygenophilic MABR is primarily responsible for the chemoselectivity of the reaction. For example, reaction of 5-(trimethylsiloxy)-4-nonene and methyl triflate with MABR proceeded smoothly at −40 °C in the presence of 2-undecanone to furnish 4-methyl-5-nonanone in 81% yield with 90% recovery of unreacted 2-undecanone.

The present alkylation has vast synthetic potential, as demonstrated by the regiocontrolled alkylation of allylic stannanes with alkyl triflates. For example, treatment of (*E*)-cinnamyltributylstannane (1) with methyl triflate in CH₂Cl₂ at −20 °C under the influence of MABR gave rise to the γ-methylation product, 3-phenyl-1-butene, exclusively in 72% yield. Since preparation of functionalized allylic stannanes has already been well-established,[11] the present method would be equally applicable to allylic systems possessing various base-sensitive functional groups.
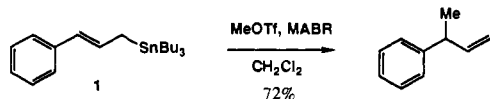
(9) (a) Rasmussen, J. K. *Synthesis* **1977**, 91. (b) Emde, H.; Simchen, G. *Ibid.* **1977**, 867. (c) Colvin, E. W. *Silicon in Organic Synthesis*; Butterworths: London, 1981. (d) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: New York, 1983.

(10) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3B, p 1.

(11) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: London, 1987. See also: Trost, B. M.; Herndon, J. W. *J. Am. Chem. Soc.* **1984**, *106*, 6835.

Photon-Promoted Chemiionization Reactions

X. H. Wang, Y. F. Yen,† R. J. Cross,* and M. Saunders*

*Department of Chemistry, Yale University
Box 6666, New Haven, Connecticut 06511*

One of the "holy grails" of chemical physics has been the photon-promoted chemical reaction: a case where the course of a bimolecular chemical reaction is altered by the absorption of a photon *during* the reactive collision,[1] not where a reactant is excited before the collision. We have found a photon-promoted chemiionization reaction involving a large organic molecule. These reactions may be more common than previously thought, and the place to look for them may be in reactive systems with many degrees of freedom rather than the two- and three-atom cases studied to date.[1] We have been studying the dynamics of a series of organic chemiionization reactions, where the two reactants are neutral but the products are ions.[2] One example is the reaction of an acid and a base to produce a salt,[3,4] such as

$$HI + Qn \rightarrow I^- + HQn^+ \qquad (1)$$

(1) Brooks, P. R. *Chem. Rev.* **1988**, *88*, 407.
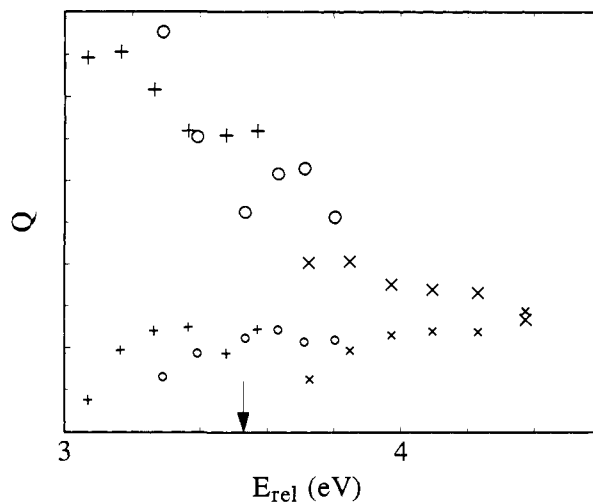(2) Cross, R. J.; Saunders, M. *Acc. Chem. Res.* **1991**, *24*, 104.

Figure 1. The large symbols show the cross section Q for the photochemical reaction of HI and quinuclidine (light on minus light off), and the small symbols show the cross section for the residual dark reaction. The HI beam is seeded in H₂, and the quinuclidine beam is seeded in He (+), a mixture of 40% H₂ and 60% He (O), and H₂ (×). The arrow gives the thermodynamic threshold for the dark reaction at 3.53 eV. Data are shown for the cation product.

where Qn is the bicyclic amine quinuclidine.

The experimental setup is similar to the one used previously.[2–4] Each reactant is made into a seeded supersonic nozzle beam. The quinuclidine beam is made by passing inert carrier gas, e.g., H₂, He, or a mixture of 40% H₂ and 60% He, through crystals of the solid at 25 °C to produce a mixture of 0.16% quinuclidine in ~1 atm of carrier gas. The resulting mixture passes through a heated nozzle 40 μm in diameter. Two sources are used for HI. In one, the carrier gas is bubbled through *tert*-butyl iodide at −42 °C. The resulting mixture is then pyrolyzed at 260 °C to give HI and isobutene either in the heated nozzle or in a small chamber behind the nozzle. Because this source contains impurities, we also used a 5-L bulb containing 1% HI in H₂. Both sources give similar results. The relative energy is controlled by varying the nozzle temperature and the type of carrier gas for Qn. The light source is a 350-W high-pressure mercury arc lamp. The light is focused on the beam intersection region by a crown glass lens which cuts off all light below 300 nm. A beam flag turns the light off and on. Product ions are extracted with an electric field, focused with an ion lens, mass selected, and detected with an electron multiplier.

Figure 1 shows the data for the reaction of HI and Qn. There is only one cation at mass 112 (HQn⁺), and there is only one anion at mass 127 (I⁻). At each energy the cross section is measured with the light on and off several times in succession. Cross sections for the dark and the photochemical reactions are shown for reaction 1. The arrow gives the thermodynamic threshold for the dark reaction at 3.53 eV.[5] The small amount of the dark signal below this energy is due to the finite energy width in the beam and possibly to reactions of dimers in the beams. The signal for the dark reaction increases by over 1 order of magnitude[4] at energies above 4.0 eV. The photochemical signal is many times the background and requires both beams to be on. The photochemical cross section decreases with increasing energy as expected, since the lifetime of the reaction complex decreases with increasing energy.

We must make sure that the signal is due to reaction 1 and not to another process. Because we need to extract the product ions with a potential of ~75 V, the ions travel through the quadrupole mass filter at ~40 eV, and this degrades the resolution.

(3) Huh, Y. D.; Cross, R. J.; Saunders, M. *J. Am. Chem. Soc.* **1990**, *112*, 3774.
(4) Yen, Y. F.; Huh, Y. D.; Cross, R. J.; Saunders, M. *J. Phys. Chem.* **1991**, *95*, 8753.
(5) Lias, S. G.; Bartmess, J. E.; Liebman, J. F.; Holmes, J. L.; Levin, R. D.; Mallard, W. G. *J. Phys. Chem. Ref. Data* **1988**, *17*, Suppl. 1.