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Triethylgallium as a Nonnucleophilic Base to Generate Enolates from Ketones

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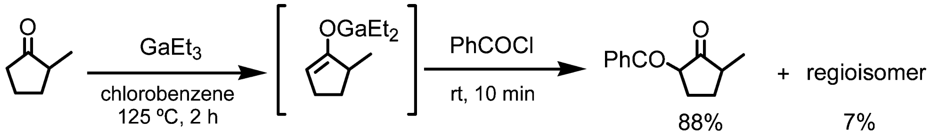
ABSTRACT



Triethylgallium deprotonated cyclic and acyclic ketones at 125–175 °C without forming carbonyl addition products, and the resulting gallium enolates underwent facile C-benzoylation and an aldol reaction. Unsymmetrical ketones were preferentially enolized at the methylene moiety, which was under kinetic control.

Reaction of metal enolates is one of the most fundamental transformations in organic synthesis, and various methods have been developed to generate the nucleophilic intermediate from ketones.[1] Stepwise methods that involve the initial formation of metal enolates at high concentrations and a subsequent reaction with electrophilic reagents are often used. Compared with the methods of equilibrating enolate formation,[2] each step of a stepwise method can be more readily controlled. Bulky alkalimetal dialkylamides, typically lithium diisopropylamide (LDA) generated from butyllithium and diisopropylamine, are employed as the base because butyllithium adds to ketones. A combination of Lewis acid metal halides or triflates and tertiary amines was also developed for this purpose.[3] These methods, however, require stoichiometric amounts of amines, which are not essential for the transformation, and the coordination of the amines to the metal enolates often complicates the analysis of the reaction.

The development of nonnucleophilic bases, which do not form excessive byproducts for the stepwise method, is desirable. Potassium hydride and sodium hydride forming hydrogen are sometimes used,[4] although it is not easy to control their reactivities because they are insoluble in organic solvents. Soluble alkylmetal bases are attractive because the operation to form an enolate using them is simple, and the byproducts generated are volatile alkanes. The alkylmetal base method enables the control of transformation by changing the alkyl moiety. In addition, the resulting enolates might exhibit reactivities different from those for conventional metal enolates. Few studies, however, have been conducted on such an enolate formation because of competitive carbonyl addition. The reaction of triphenylmethyl ketones with trialkylaluminum or butyllithium for the generation of the aluminum or lithium enolates was reported by Seebach and others.[5] Triphenylmethyllithium and potassium were used in some cases.[6] These methods required the use of either hindered ketones or hindered bases to avoid

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[1] Reviews, see: (a) House, H. O. In *Modern Synthetic Reactions*, 2nd ed.; Benjamin: Menlo Park, 1972; Chapter 9, p 492. (b) d'Angelo, J. *Tetrahedron* **1976**, *32*, 2979. (c) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. (d) Mekelburger, H. B.; Wilcox, C. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 1.4, p 99. (e) Caine, D. In *Comprehensive Organic Synthesis*, Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 3, Chapter 1.1, p. 1. (f) Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 1, p. 1.

[2] Heathcock, C. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 1.5, p. 133.

[3] For example, see: (a) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324. (b) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174. (c) Mukaiyama, T.; Stevens, R. W.; Iwasawa, N. *Chem. Lett.* **1982**, 353. (d) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1.

[4] For example, see: (a) Groenewegen, P.; Kallenberg, H.; van der Gen, A. *Tetrahedron Lett.* **1978**, *19*, 491. (b) Iseki, K.; Yamazaki, M.; Shibasaki, M.; Ikegami, S. *Tetrahedron* **1981**, *37*, 4411.

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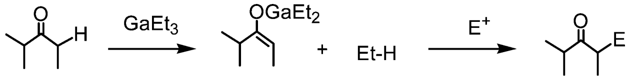
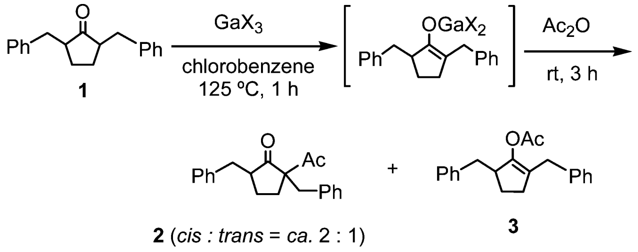
carbonyl addition. During our investigations on the use of gallium enolates in organic synthesis,[7–9] α-ethynylation reaction of ketones, which involved in situ generation of enolates from ketones and trialkylgalliums, was developed.[10] Described here is a study of the stepwise method using triethylgallium as a nonnucleophilic base for ketone enolization (Scheme 1). The regioselectivity in this enolization was compared with that in conventional methods.

Scheme 1



2,5-Dibenzylcyclopentanone **1** and triethylgallium (1.5 equiv) were treated in chlorobenzene at 125 °C for 1 h. After being cooled to room temperature, acetic anhydride (2 equiv) was added, and the reaction for 3 h gave C-acetylated **2** (cis/trans = 2:1) and O-acetylated **3** in 37 and 59% yields, respectively (Table 1, entry 1). The yield of this enolate formation then was calculated to be 96%. The enolization required a high temperature, and the combined yields decreased to 52 and 4% at 100 and 75 °C, respectively (entries 2 and 3). Carbonyl addition products, namely, cyclopentanol **4** and ethylcarbinol **5**, were not detected. The reaction of trimethylgallium and triisopropylgallium gave **2** and **3** in modest yields (entries 4 and 5). For comparison, **1** was reacted with triethylaluminum, which after acetylation gave only a 16% yield of **3** accompanied by considerable amounts of **4** and **5** (Scheme 2). Although triethylgallium is a nonnucleophilic base for ketone enolization, the corresponding aluminum compound exhibits nucleophilic and reducing characteristics.

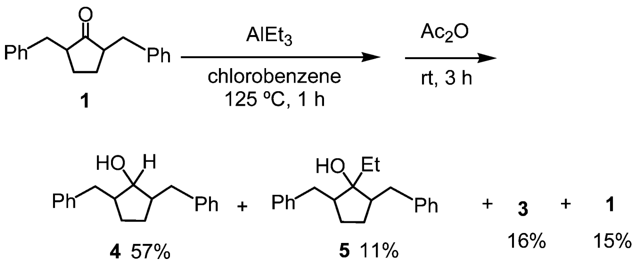
Table 1. Deprotonation and Acetylation of **1**



entry	GaX$_3$	temp/°C	yield/% **2** + **3** (**2**:**3**)	recovery of **1**/%
1	GaEt$_3$	125	96 (37:59)	0
2		100	52 (12:40)	41
3		75	4 (**3** only)	95
4	GaMe$_3$	125	67 (23:44)	33
5	Ga^{i}Pr$_3$	125	28 (23:5)	27[a]

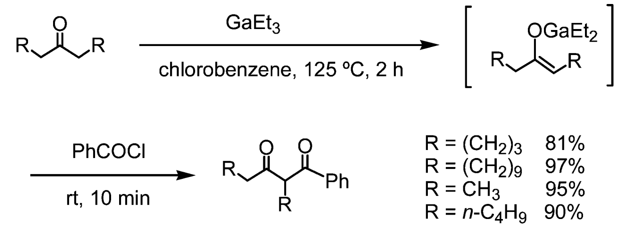
[a] Reduced ketone **4** was obtained in 28% yield.

Scheme 2

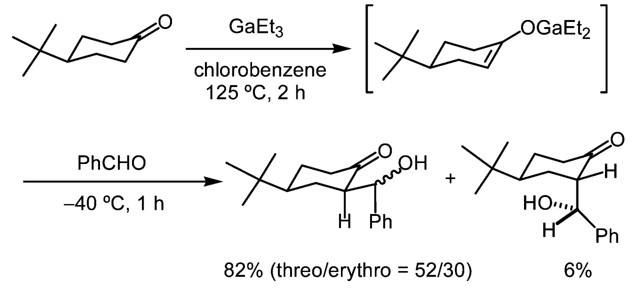


Several symmetrical ketones possessing α-methylene groups were converted to enolates employing the above conditions, and the intermediates were trapped with benzoyl chloride giving C-benzoyl derivatives in high yields (Scheme 3). The reaction of 4-(*tert*-butyl)cyclohexanone with triethylgallium followed by reaction of benzaldehyde gave aldol products with equatorial isomers (82%) predominating (Scheme 4). The stereochemistry is highly contrasted with those of the lithium enolates exhibiting axial preferences.[11]

Scheme 3



Scheme 4



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(5) (a) Jeffery, E. A.; Meisters, A. *J. Organomet. Chem.* **1972**, *82*, 307. (b) Seebach, D.; Ertas, M.; Locher, R.; Schweizer, W. B. *Helv. Chim. Acta* **1985**, *68*, 264. (c) Ertas, M.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 961.

(6) For example, see: (a) House, H. O.; Kramar, V. *J. Org. Chem.* **1963**, *28*, 3362. (b) House, H. O.; Trost, B. M. *J. Org. Chem.* **1965**, *30*, 1341.

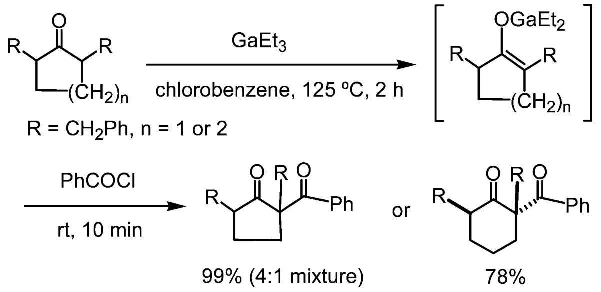
(7) (a) Yamaguchi, M. In *Main Group Metals In Organic Synthesis*; Yamamoto, H.; Oshima, K., Eds.; Wiley-VCH Verlag: Weinheim, 2004; Chapter 7, p. 307. (b) Amemiya, R.; Yamaguchi, M. *Eur. J. Org. Chem.* **2005**, 5145.

(8) For gallium enolates by transmetalation, see: (a) Yamaguchi, M.; Tsukagoshi, T.; Arisawa, M. *J. Am. Chem. Soc.* **1999**, *121*, 4074. (b) Arisawa, M.; Amemiya, R.; Yamaguchi, M. *Org. Lett.* **2002**, *4*, 2209. (c) Amemiya, R.; Fujii, A.; Arisawa, M.; Yamaguchi, M. *Chem. Lett.* **2003**, 298. (d) Amemiya, R.; Fujii, A.; Arisawa, M.; Yamaguchi, M. *J. Organomet. Chem.* **2003**, *686*, 94. Also see references cited.

Such stereoselectivity was observed in reactions of gallium enolate generated from gallium trichloride[9] and appears to be a general feature of gallium enolate.

Symmetrical cyclic ketones possessing α-methine groups, namely, 2,5-dibenzylcyclopentanone and 2,6-dibenzylcyclohexanone, were C-benzoylated in high yields (Scheme 5).

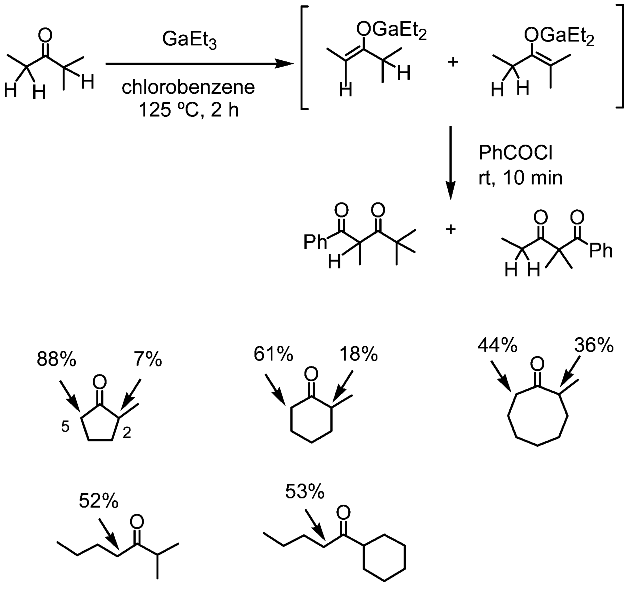
Scheme 5



A 4:1 mixture of diastereomers was formed in the former reaction, whereas a 2,6-*cis*-dibenzyl isomer was obtained selectively in the latter. Acyclic ketones, diisopropyl ketone, and 5,7-dibutyl-6-undecanone did not give these products. The reason enolate formation took place with cyclic ketones but not with acyclic ketones can be ascribed to steric factors.

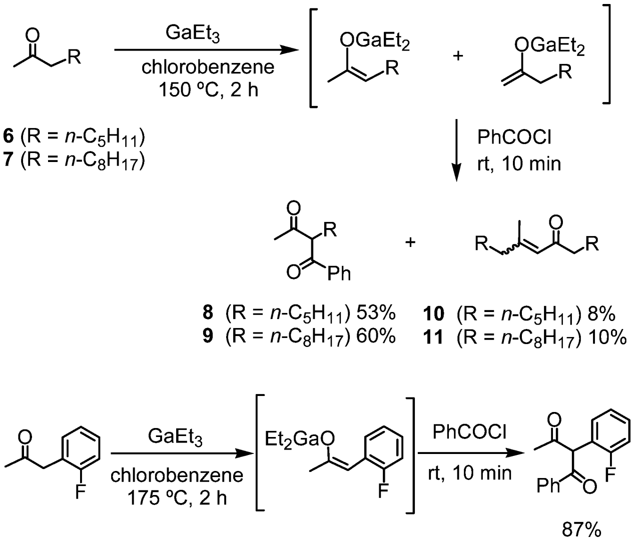
Regioselectivity in the enolization of unsymmetrical ketones has been the focus of considerable interest[1] and was examined here for gallium enolates. The reaction of 2-methylcyclopentanone with triethylgallium at 125 °C for 2 h followed by reaction with benzoyl chloride gave 5-benzoyl and 2-benzoyl derivatives in 88 and 7% yields, respectively, indicating that deprotonation took place at a less-hindered site (Scheme 6). A similar result was obtained for 2-methylcyclohexanone, and the selectivity decreased for 2-methylcyclooctanone. Acyclic ketones, namely, 2-methyl-3-heptanone and 1-cyclohexyl-1-pentanone, exclusively provided enolate at the less-hindered site. The regioselectivities were consistent with kinetic enolate formation.

Scheme 6



Unsymmetrical ketones possessing α-methyl and α-methylene groups were also enolized by triethylgallium. The reaction of 2-octanone **6** with triethylgallium at 150 °C for 2 h followed by benzoylation gave the C-benzoylated product **8** reacted at the methylene moiety in 53% yield (Scheme 7).

Scheme 7



6 (R = n-C_5H_{11})
7 (R = n-C_8H_{17})

8 (R = n-C_5H_{11}) 53%
9 (R = n-C_8H_{17}) 60%

10 (R = n-C_5H_{11}) 8%
11 (R = n-C_8H_{17}) 10%

Small amounts of the self-aldol product **10** were formed, which were generated by deprotonation at the methyl moiety. The enolization of **6** predominantly took place at the hindered methylene moiety. The result, however, suggests kinetic enolate formation because the initial deprotonation at the methyl group predominantly provides the self-aldols. Similar results were obtained with 2-undecanone **7**. A benzyl methyl ketone was deprotonated selectively at the methylene moiety, and a C-benzoylated product was obtained in 87% yield.

Regiochemistry in the enolate formation using triethylgallium showed a notable methylene preference. Both methylene−methine and methyl−methylene ketones were deprotonated at the methylene moiety. To determine the mechanism, 1,1,1-trideutero-2-octanone **6**-d_3 was reacted with triethylgallium at 150 °C for 2 h and quenched with water. Recovered **6**-d_3 (81%) contained 90%-*d* at the methyl group and 3%-*d* at the methylene group (Scheme 8). When the reaction was quenched with benzoyl chloride, **8**-d_3 was obtained in 54% yield with 87%-*d* at the methyl group and

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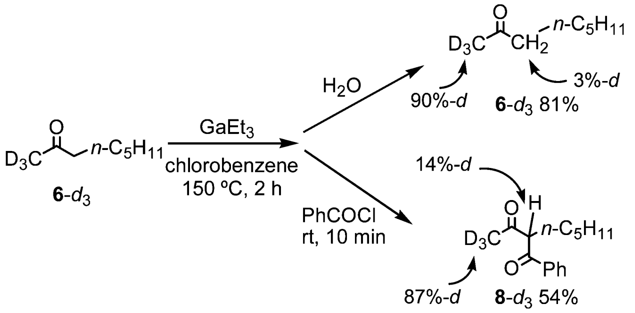
(9) For gallium enolates from ketones and $GaCl_3$, see: (a) Amemiya, R.; Nishimura, Y.; Yamaguchi, M. *Synthesis* **2004**, 1307. (b) Amemiya, R.; Miyake, Y.; Yamaguchi, M. *Tetrahedron Lett.* **2006**, *47*, 1797. Deprotonation reactions of 1,4-enynes were also reported. (c) Amemiya, R.; Suwa, K.; Toriyama, J.; Nishimura, Y.; Yamaguchi, M. *J. Am. Chem. Soc.* **2005**, *127*, 8252.

(10) Nishimura, Y.; Amemiya, R.; Yamaguchi, M. *Tetrahedron Lett.* **2006**, *47*, 1839.

(11) Majewski, M.; Gleave, D. M. *Tetrahedron Lett.* **1989**, *30*, 5681.

Scheme 8



14%-*d* at the methine group. The lack of serious deuterium scrambling indicated the formation of a kinetic enolate. Methylene deprotonation at a high temperature under kinetic control is another interesting aspect of this method.

Compared with the LDA method, the triethylgallium method has several notable properties in the enolate formation from ketones: (1) simple operation of heating with a reagent; (2) formation of volatile ethane as the byproduct; (3) preferential enolization of symmetrical cyclic ketones possessing an α-methine group over that of acyclic ketones; (4) methylene preference in the enolization of unsymmetrical ketones; (5) kinetic enolate formation.

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Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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