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Highly efficient amphiphilic cleavage of γ-iodo carbonyl substrates with aluminum tris(2,6-diphenylphenoxide)/*t*-BuLi system

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Abstract

A conceptually new amphiphilic cleavage of the αβ C–C bonds of γ-iodo carbonyl substrates has been realized by the effective use of a combined Lewis acid/base system consisting of aluminum tris(2,6-diphenylphenoxide) (ATPH)/*t*-BuLi. This new amphiphilic bond cleavage reaction can be applied to a wide variety of γ-iodo carbonyl substrates and therefore serves as a highly efficient and general route to both cyclic and acyclic unsaturated carbonyl compounds. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: aluminum; aluminum compounds; cleavage reaction; lithium; lithium compounds; carbonyl compounds.

We recently disclosed a novel fragmentation reaction of enones via the successive conjugate addition–cleavage sequence by the use of $Ph_3Sn(PhS)CHLi$ followed by the aluminum tris(2,6-diphenylphenoxide) (ATPH)/MeLi system (Eq. 1).[1,2] This new synthetic transformation, however, has one drawback on the limited use of starting α,β-unsaturated carbonyl substrates, and indeed α,β-unsaturated aldehydes and esters are not employable for the present amphiphilic cleavage reaction.[1] This is mainly due to the use of sulfur- or selenium-stabilized carbanions. Accordingly, we were interested in the possibility of utilizing non-stabilized pure carbanions in order to effect the facile αβ C–C bond cleavage by enhancing the push effect of the carbanion parts. Here we wish to report our successful results on highly efficient, amphiphilic cleavage of the αβ C–C bonds of γ-iodo carbonyl substrates to generate pure carbanions by treatment with *t*-BuLi via the facile metal–halogen exchange (Eq. 2), thereby allowing hitherto difficult cleavage of αβ C–C bonds of aldehydes and esters in the presence of ATPH.[3]

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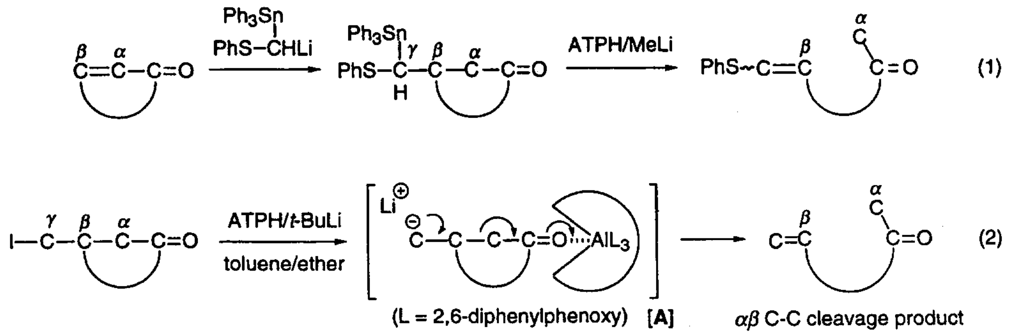
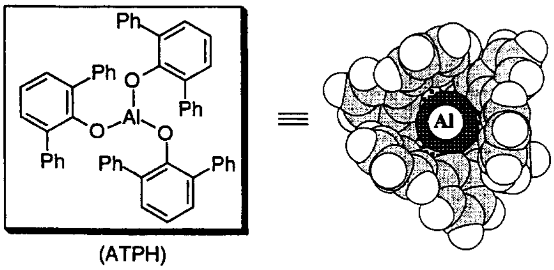


Scheme 1.



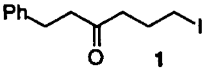
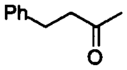
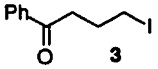
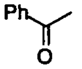
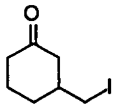
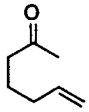
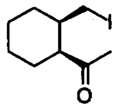
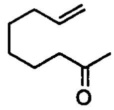
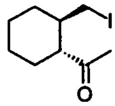
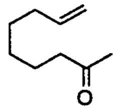
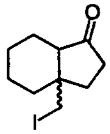
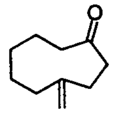
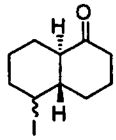
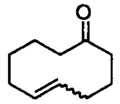
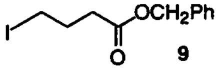
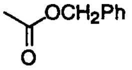
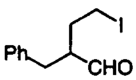
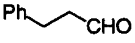
(ATPH)

The starting γ-iodo carbonyl substrates can be readily prepared by the following synthetic methods: (A) γ-iodo ketones: iodination of γ-hydroxyketones with $Ph_3P/Py/I_2$; (B) γ-iodo ketones: cyclopropanation of enones with dimethyloxosulfonium methylide,[4] and subsequent ring opening of the resulting cyclopropyl ketones with Me_3SiI; (C) γ-iodo esters: cleavage of γ-butyrolactone derivatives with MeSiI in the presence of alcohol; and (D) γ-iodo aldehydes: reduction of γ-iodo esters with DIBAH.

Initial complexation of 6-iodo-1-phenyl-3-hexanone (**1**) with ATPH (1.1 equiv.) in toluene/ether (volume ratio=1:1) at −78°C and subsequent addition of *t*-BuLi (2 equiv.) in pentane cleanly afforded 4-phenyl-2-butanone (**2**) as an αβ C–C bond cleavage product in almost quantitative yield (entry 1 in Table 1). The clean and rapid halogen–lithium exchange takes place in a toluene–ether solvent at −78°C, while in only toluene solvent the lithiation proceeds reluctantly. The simultaneous push–pull effect of the intermediary γ-lithio carbonyl substrates by complexation with Lewis acidic ATPH as a carbonyl protector seems to be crucial for effecting the smooth αβ C–C bond cleavage reaction as shown in [**A**] of Scheme 1. Indeed, in the absence of ATPH, treatment of γ-iodo ketone **1** with *t*-BuLi gave deteriorated reaction mixtures without formation of the desired **2**. Attempted use of ordinary Lewis acids such as $BF_3 \cdot OEt_2$ and $TiCl_4$ in place of ATPH gave unsatisfactory results mainly due to the facile attack of *t*-BuLi to the Lewis acids.

Other selected examples, which are shown in Table 1, concerning the novel fragmentation reaction of γ-iodo carbonyl substrates with the ATPH/*t*-BuLi system, clearly indicate the effectiveness of our approach.[5] Although aromatic ketones on treatment with ATPH are reported to give the corresponding 1,6-adduct as a nucleophilic aromatic substitution product,[3c] acetophenone was obtainable exclusively from γ-iodobutyrophenone (**3**) without concomitant formation of Michael addition products on the benzene ring under these reaction conditions (entry 2). β-Iodomethylcyclohexanone (**4**), *cis*-(2-iodomethyl)cyclohexyl methyl ketone (**5**), and its *trans*-isomer **6** experienced clean ring-cleavage by treatment with the ATPH/*t*-BuLi system to furnish the corresponding alkenyl methyl ketones in good yields (entries 3–5). Bicyclic ketone **7** possessing an iodomethyl moiety underwent smooth ring expansion to furnish a large-membered cyclic ketone with *exo* double bond (entry 6), which represents

Table 1
Selective cleavage of γ-iodo carbonyl substrates with ATPH/*t*-BuLi System[a]

entry	substrate[b]	cleavage product	% yield[c]
1	 **1**	 **2**	>99%[d]
2	 **3**		>99%
3	 **4**		80%[d]
4	 **5**		93%
5	 **6**		70%[e]
6	 **7**		85%
7	 **8**		50%[f]
8	 **9**		84%
9	 **10**		58%[e]

[a] The reaction was carried out with ATPH (1.1 equiv) and *t*-BuLi (2 equiv) in toluene/ether (volume ratio = 1:1) at -78 °C for 20 min. [b] Prepared according to the method A (entries 1, 2, and 7), B (entries 3-6), C (entry 8), and D (entry 9), respectively. [c] Isolated yield. [d] Isolated yield after conversion of fragmentation product to the corresponding alcohol by DIBAH reduction in toluene at -78 °C. [e] Cyclobutanol derivatives, which arised from intramolecular nucleophilic addition of the initially generated carbanion to carbonyl moiety, were also obtained as side products (10~20% yields). [f] *E*/*Z* ratio of the product was determined to be 1:1.6 by ^{1}H NMR analysis .

an attractive method for the construction of otherwise difficult nine-membered carbocycles. Formation of ten-membered carbocycles also appears feasible starting from a *secondary* iodo decalone **8** (entry 7). γ-Iodo ester **9** and aldehyde **10** were also susceptible to the new amphiphilic bond cleavage reaction, producing the corresponding fragmentation products (entries 8 and 9).

The new amphiphilic cleavage of γ-iodo carbonyl substrates described herein serves as a highly efficient and general route to a variety of both cyclic and acyclic unsaturated carbonyl compounds, and, therefore, further expands utility in selective organic synthesis.

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