J. Am. Chem. Soc. **2000,** *122,* 1219−1220 1219

Chelation-Aided Generation of Ketone α,β-Dianions and Their Use as Copper Ate Complexes. Unprecedented Enolate Intervention in the Conjugate Addition to Enones

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Received October 5, 1999

In this paper, we report (i) a novel method for the regio- and stereoselective generation of ketone α,β-dianions having an allyl/*Z* structure by an unprecedented chelation-aided approach using β-dichlorobutylstannyl ketones and (ii) the unique reactivity of the corresponding lithium cuprates. Remarkably, conjugate addition of these species to enones yielded products resulting from two consecutive C−C bond-forming reactions at both α- and β-positions of the dianion cuprates.

Anion chemistry has continuously produced versatile tools in organic synthesis.[1] Some years ago, we reported that ketone α,β-dianions (lithium enolates of β-lithio ketones) can be efficiently generated from lithium enolates of β-tributylstannyl ketones by Sn−Li exchange.[2] Sequential alkylation at β- and α-positions to a carbonyl group has been achieved with the dianions.[2] To make these α,β-dianions more practical and useful, the regio- and stereochemical issues regarding the generation of their enolate precursors need to be clarified. As expected from current knowledge about enolate chemistry, treatment of β-tributylstannyl ketones having two methylene groups α and α' to the carbonyl such as **1a** with LDA yielded a nearly 1:1 mixture of regioisomeric lithium enolates without stereochemical control (Figure 1). It is known that highly hindered bases such as LHMDS favor the formation of *Z* enolates and can differentiate α-methylene from α'-methine[3] but this attractive base cannot override the regiochemical issues associated with α,α'-dimethylene differentiation (Figure 1).

Seeking a novel approach for stereo- and regioselective enolate formation, we became curious about the use of coordinated species such as β-halostannyl ketones[4] (Figure 2). In principle the reaction of β-halostannyl ketone with organolithium reagents can proceed through three different pathways: ***a***, substitution at Sn; ***b***, carbonyl addition; and ***c***, abstraction of α and/or α'-proton. We envisioned that α-deprotonation to form a *Z* enolate would precede nucleophilic attack on the carbonyl.

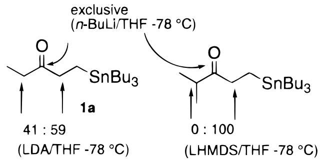


Figure 1.

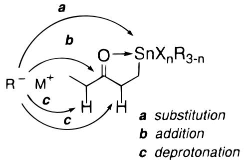
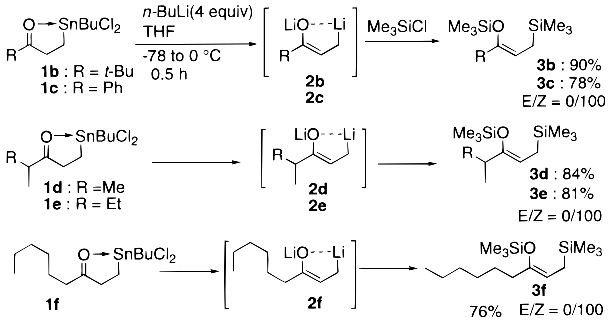


Figure 2.

Scheme 1



The chelation-free substrate, ethyl β-(tributylstannyl)ethyl ketone (**1a**), undergoes exclusive nucleophilic attack on the carbonyl in the presence of *n*-BuLi. However, in sharp contrast, when β-dichlorobutylstannyl ketone **1b**[5] was treated with *n*-BuLi (4 equiv) in THF (-78 to 0 °C, 30 min), clean reaction took place to give the desired dianion **2b**, which was transformed to the disilylated product **3b** in 90% yield by quenching with trimethylchlorosilane (Scheme 1). This result suggests that abstraction of an α-proton by *n*-BuLi precedes the two-step alkylation at the Sn atom and the chelated structure predisposes the system to *Z*-form enolate formation.[6] Methyllithium, which is more nucleophilic and less basic than *n*-BuLi, reacted predominantly via carbonyl attack and a trichlorostannyl analogue **1b′** suffered from an undesirable β-SnH elimination reaction.[7]

The generality of this straightforward method for generation of ketone α,β-dianions was studied with some other β-dichlorobutylstannyl ketones **1c**−**f** and the results are also given in Scheme 1. In each case dianion formation was conducted by simply adding ca. 4 equiv of *n*-BuLi to a THF solution of β-dichlorobutylstannyl ketones **1** at -78 °C and warming up to 0 °C and the regio- and stereochemical outcomes of the dianion **2** were confirmed by silylative derivatization to **3**. The α-regio- and *Z*-stereoselective deprotonation was observed when substrates **1d** and **1e**, having α-methylene and α'-methine groups, were examined. Although the regioselective deprotonation of substrates having two methylene groups α and α' to the carbonyl is particularly difficult to achieve,[3] it is noteworthy that the α-selective deprotonation was achieved with **1f**.

With this operationally simple method for ketone α,β-dianions in hand, we then examined their conversion to the corresponding copper organometallic species. The resulting cuprates should be capable of adding a β-acylalkyl group to enones in 1,4-fashion but we also anticipated a hitherto unknown reactivity inherent to the unique dianion structure of these reagents. Thus, conversion to the cuprate was carried out by treating the dianion with 0.5 mol equiv of copper cyanide in THF at -78 °C, as exemplified by the case of **2b** to **4** (Scheme 2). 2-Cyclohexenone (0.5 mmol) was added to the solution containing **4** at -78 °C and the solution was stirred

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(1) For recent reviews, see: (a) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282. (b) Marek, I.; Normant, J. F. *Chem. Rev.* **1996**, *96*, 3241. (c) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552.

(2) Nakahira, H.; Ryu, I.; Ikebe, M.; Kambe, N.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 177.

(3) For a pertinent review on enolate chemistry, see: Heathcock, C. H. In *Modern Synthetic Methods*; Scheffold, R., Ed.; VCH: New York, 1992; pp 3−102.

(4) Nakahira, H.; Ryu, I.; Ikebe, M.; Oku, Y.; Ogawa, A.; Kambe, N.; Sonoda, N.; Murai, S. *J. Org. Chem.* **1992**, *57*, 27.

(5) β-Dichlorobutylstannyl ketones are readily available from siloxycyclopropanes and butyltrichlorotin, see ref 4.

(6) Treatment of **1b** with 3 equiv of *n*-BuLi at -78 °C and the subsequent chlorosilane quenching at that temperature gave the *Z*-enol silyl ether of the corresponding β-tributylstannyl ketone in 72% yield, supporting the idea that the β-tributylstannyl ketone enolate is a precursor of the dianion **2b**.

(7) With the trichlorostannyl analogue of **1b′**, **3b** was formed in 44% yield**.** Side reaction to give the lithium enolate of *tert*-butyl hexyl ketone, which is most likely formed via β-elimination of the stannyl ketone[4] and the subsequent Michael addition of *n*-BuLi, was difficult to suppress.

10.1021/ja993577t CCC: $19.00

Scheme 2

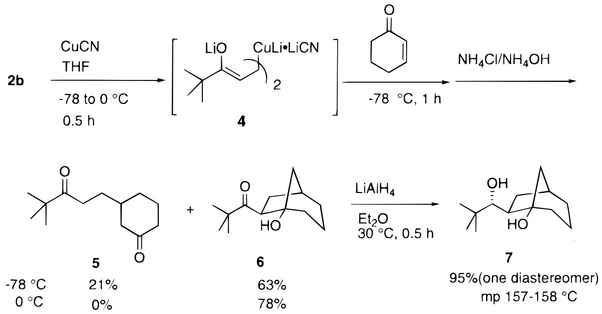
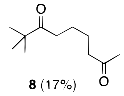
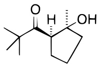
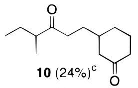
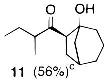
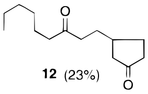
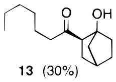
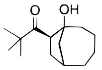
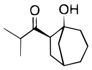


Table 1. Reactions of Dianion Cuprates with Enones[a]

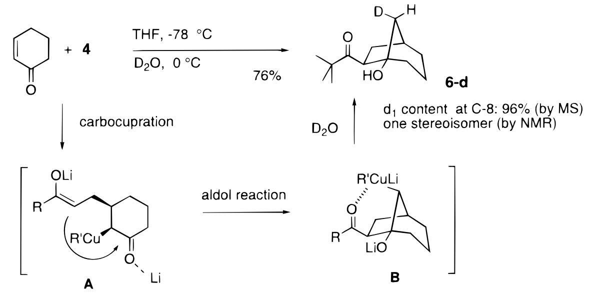
run	α,β-dianion **2** (from **1**)	reagents (conditions)	product (yield[b])	
1	**2b**	1) CuCN (-78 to 0 °C) 2) 2-cyclohexenone (-78 °C) 3) NH_4Cl/NH_4OH (-78 °C)	**5** (21%)	**6** (63%)
2		(0 °C)	**5** (-)	**6** (78%)
3	**2b**	1) $CuBr•Me_2S$ (-78 °C) 2) 2-cyclohexenone (-78 °C) 3) NH_4Cl/NH_4OH (-78 °C)	**5** (10%)	**6** (63%)
4	**2b**	1) $CuC{\equiv}CSiMe_3$ (1 equiv, -78 °C) 2) 2-cyclohexenone (-78 °C) 3) NH_4Cl/NH_4OH (-78 °C)	**5** (16%)	**6** (42%)
5	**2b**	1) CuCN (-78 to 0 °C) 2) methyl vinyl ketone (-78 °C) 3) NH_4Cl/NH_4OH (-78 °C)	 **8** (17%)	 **9** (35%)
6	**2e**	1) CuCN (-78 to 0 °C) 2) 2-cyclohexenone (-78 °C) 3) NH_4Cl/NH_4OH (-78 °C)	 **10** (24%)[c]	 **11** (56%)[c]
7		(0 °C)	**10** (-)	**11** (68%)[c]
8	**2f**	1) CuCN (-78 to 0 °C) 2) 2-cyclopentenone (-78 °C) 3) NH_4Cl/NH_4OH (-78 °C)	 **12** (23%)	 **13** (30%)
9	**2b**	1) CuCN (-78 to 0 °C) 2) 2-cycloheptenone (-78 °C) 3) NH_4Cl/NH_4OH (0 °C)	–	 **14** (70%)
10	**2d**	1) CuCN (-78 to 0 °C) 2) 2-cyclohexenone (-78 °C) 3) NH_4Cl/NH_4OH (0 °C)	–	 **15** (64%)

[a] Reactions were conducted on a 1 mmol scale. For experimental procedures, see Supporting Information. [b] Isolated yield by column chromatography on silica gel. [c] Obtained as a 1:1 mixture of diastereomers.

for 1 h at that temperature and then the reaction mixture was quenched by aqueous NH_4Cl/NH_4Cl (1:1) solution. Interestingly, the keto alcohol **6** having a bicyclo[3.2.1]octane structure was formed as the major product in 63% yield along with 21% yield of the Michael addition/protonation product **5**. The proton quenching at an elevated temperature (0 °C) gave **6** as the sole product with a significant increase in the yield (78%). Bicyclic alcohol **6** was obtained as a single stereoisomer and its exo-structure was unambiguously determined by an X-ray analysis of the diol **7** which was derived by diastereoselctive reduction of **6** by $LiAlH_4$.

Some other results of the conjugate addition of the dianion cuprates are summarized in Table 1. The major formation of keto alcohols, which should involve two consecutive C−C bond-forming reactions at both α- and β-positions of the dianion structure, was general irrespective of the types of cuprates employed (**2b** plus $CuBr{\cdot}Me_2S$ (run 3) and **2b** plus $CuCCSiMe_3$ (run 4)) and was also observed with other enones, such as methyl vinyl ketone (run 5), 2-cyclopentenone (run 8), and 2-cycloheptenone (run 9), each of which gave a single stereoisomer of the corresponding keto alcohol.

Scheme 3



Interestingly, quenching the reaction mixture resulting from **4** and 2-cyclohexenone with D_2O resulted in 96% incorporation of one deuterium at the bridged carbon with complete stereoselectivity (Scheme 3). Although the precise mechanism of this reaction must await further study, this result led us to postulate an anionic cascade reaction mechanism that consists of carbocupration of the C−C double bond of cyclohexenone followed by an aldol reaction of the resulting α-cuprio ketone **A** with the internal lithium enolate, where the lithioxy organocopper species **B** would be a precursor to **6-d** (Scheme 3). Alternatively, aldol reaction of the enolate portion of the dianion cuprate **4** with cyclohexenone could precede carbocupration of the internal C−C double bond, but this requires both a diastereoselective aldol reaction and a rather rigid transition state for the subsequent carbocupration of a now isolated C−C double bond. The most frequently argued mechanism for organocuprate conjugate addition to enones, which is based on a controversial Cu(III) intermediate, located β to the carbonyl preceding the formation of C−C bond,[8] does not appear to be accommodated by our results.[9,10]

In summary, we have shown that an unprecedented chelation-aided approach is particularly useful for the straightforward generation of ketone α,β-dianions having the *Z*/allyl-type structures. The thus generated dianions can be transformed into novel types of copper ate complexes containing an enolate moiety. It is noteworthy that the conjugate addition to enones is dominated by the formation of cyclic keto alcohols under a variety of conditions. We believe that the results reported herein provide new insights into the conjugate addition chemistry of organocuprates.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan. We thank Profs. T. Cohen, C. M. Crudden and M. Segi for useful discussions.

Supporting Information Available: Typical experimental procedures and characterization data for all products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For recent theoretical and mechanistic studies on the cuprate addition to enones, see: (a) Krause, N.; Wagner, R.; Gerold, A. *J. Am. Chem. Soc.* **1994**, *116*, 381. (b) Dorgio, A. E.; Wanner, J.; Schleyer, P. v. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 476. (c) Nakamura, E.; Mori, S.; Morokuma, K. *J. Am. Chem. Soc.* **1997**, *119*, 4900. (d) Kingsbury, C. L.; Smith, R. A. J. *J. Org. Chem.* **1997**, *62*, 4629. (e) Ericksson, M.; Iliefski, T.; Nilsson, M.; Olsson, T. *J. Org. Chem.* **1997**, *62*, 182. (f) Vellekoop, A. S.; Smith, R. A. J. *J. Am. Chem. Soc.* **1994**, *116*, 2902. (g) Snyder, J. P. *J. Am. Chem. Soc.* **1995**, *117*, 11025. Also see reviews: (h) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135. (i) Krause, N.; Gerold, A. *Angew. Chem., Int. Ed. Engel.* **1997**, *36*, 186.

(9) For carbocupration mechansims in the conjugate addition to α,β-unsaturated carbonyl compounds, see: (a) Nilsson, K.; Andersson, T.; Ullenius, C.; Gerold, A.; Krause, N. *Chem. Eur. J.* **1998**, *4*, 2051. (b) Nilsson, K.; Ullenius, C.; Kraus, N. *J. Am. Chem. Soc.* **1996**, *118*, 4194. (c) Eriksson, M.; Hjelmencrantz, A.; Nilsson, M.; Olsson, T. *Tetrahedron* **1995**, *51*, 12631. (d) Krause, N. *J. Org. Chem.* **1992**, *57*, 3509. (e) Berlan, J.; Battioni, J.; Koosha, K. *J. Organomet. Chem.* **1978**, *152*, 359. (f) Nakamura, E.; Yamanaka, M. *J. Am. Chem. Soc.* **1999**, *121*, 8941.

(10) Some other machansitic possibilities should also be taken into consideration. The dienolate formation, followed by chemoselective protonation at one of the enolates (cyclohexanone portion) and the rapid intramolecular aldol reaction with the other enolate portion, which occur during the aqueous workup, can account for the formation of **6**. However, as is evident from the results of D_2O quenching, this chemoselective protonation, if it occurs, should also demand high stereoselection of the re/si faces of the enolate, which we think highly unlikely. We are grateful to one referee who suggested a mechanistic possibility involving π-complexation of the copper on the enolate portion or oxo-π-allylcopper formation.