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An Anionic Strategy for Three- and Four-Component Coupling Reactions Leading to Ketone Frameworks Based on Vinylogous Conversion of Dilithio Ketone α,*β*-Dianions

Shin-ya Yamato,[‡] Go-hei Yamamura,[‡] Mitsuo Komatsu,[‡] Masashi Arai,[†]
Takahide Fukuyama,[†] and Ilhyong Ryu*,[†]

Department of Chemistry, Graduate School of Science, Osaka Prefecture University,
Sakai, Osaka 599-8531, Japan, and Department of Applied Chemistry, Graduate
School of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

ryu@c.s.osakafu-u.ac.jp

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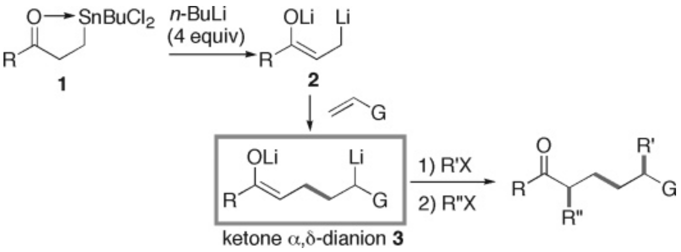
ABSTRACT



Ketone α,*δ*-dianions are generated by vinylogous extension of ketone α,*β*-dianions with alkenes such as vinylarenes, vinylsilanes, and vinyl sulfides, which then undergo reactions at the *δ* and α positions with different electrophiles, creating ketone frameworks. This work represents a cascade-type anion method that achieved three- and four-carbon component assembly reactions leading to ketones.

The ubiquitous nature of ketones in the structures of a wide variety of pharmaceutical and material science target molecules has resulted in extensive efforts to uncover efficient cascade strategies for their synthesis.[1] We report herein a unique dianionic strategy,[2,3] which is based on the vinylogous extension reaction of dilithio ketone α,*β*-dianions to dilithio α,*δ*-dianions as a platform for the construction of ketone frameworks.

We have recently shown that dilithio ketone α,*β*-dianions, having enolate/allyl anion structure **2** with *Z* geometry, can be conveniently generated by treating *β*-dichlorobutylstannyl ketones **1** with 4 equiv of *n*-BuLi.[4] Once prepared, these structures participate in a variety of synthetic transformations.[4,5] We believed that ketone α,*β*-dianions **2** thus formed would also serve as precursors for ketone α,*δ*-dianions, whose synthetic potential is yet to be explored.[6] If the ketone α,*β*-dianion **2** would undergo carbolithiation to alkenes,[7] the envisaged ketone α,*δ*-dianion **3** would be formed (Scheme

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[‡] Osaka University.

[†] Osaka Prefecture University.

(1) For general aspects of cascade reactions, see the thematic issue of *Chem. Rev.* **1996**, *96* (1). Also see: *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley Science: Amsterdam, 2005.

(2) For reviews on anion chemistry, see: (a) Najera, C.; Yus, M. *Curr. Org. Chem.* **2003**, *7*, 867. (b) Katritzky, A. R.; Piffl, M.; Lang, H.; Anders, E. *Chem. Rev.* **1999**, *99*, 665. (c) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2282. (d) Marek, I.; Normant, J. F. *Chem. Rev.* **1996**, *96*, 3241. (e) Beak, P.; Basu, A.; Gallagher, D. J.; Park, T. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552.

(3) For reviews on dianion chemistry, see: (a) Langer, P.; Freiberg, W. *Chem. Rev.* **2004**, *104*, 4125. (b) Thompson, C. M. *Dianion Chemistry in Organic Synthesis*; CRC Press: Boca Raton, FL, 1994.

(4) (a) Ryu, I.; Nakahira, H.; Ikebe, M.; Sonoda, N.; Yamato, S.; Komatsu, M. *J. Am. Chem. Soc.* **2000**, *122*, 1219. (b) Nakahira, H.; Ikebe, M.; Oku, Y.; Sonoda, N.; Fukuyama, T.; Ryu, I. *Tetrahedron* **2005**, *61*, 3383. (c) Nakahira, H.; Ryu, I.; Ikebe, M.; Kambe, N.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 177.

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Scheme 1. Concept for Ketone Framework Construction by an Anionic Four-Component Cascade Approach

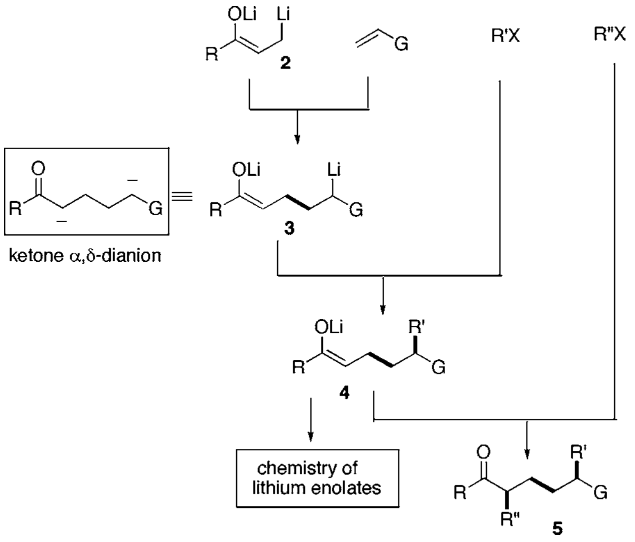
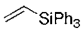
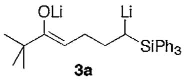
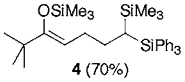
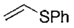
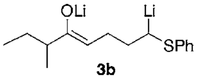
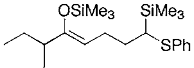
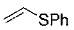
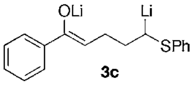
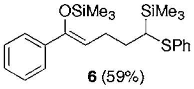
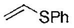
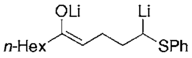
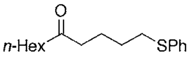
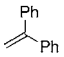
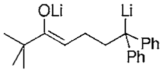
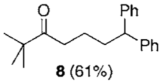
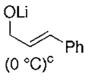
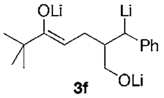
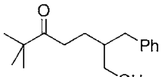
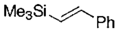
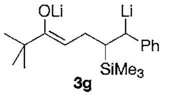
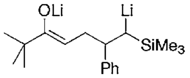
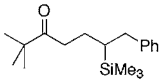
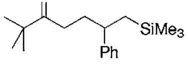
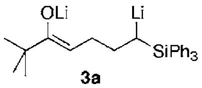
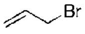
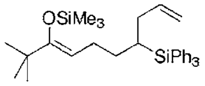
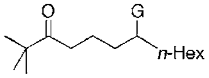
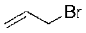
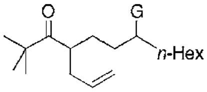
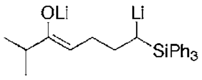
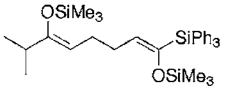
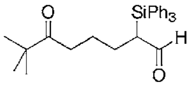


Table 1. Conversion of Ketone α,β-Dianions **2** to Ketone α,δ-Dianions **3** by Vinylogous Extension[a]

entry	α,β-dianion	conditions	α,δ-dianion	product (yield[b])
1	**2a** (R = *t*-Bu)	1)  (0 °C) 2) Me$_3$SiCl (-78 to 0 °C)	 **3a**	 **4** (70%)
2	**2b** (R = *sec*-Bu)	1)  (0 °C) 2) Me$_3$SiCl (-78 to 0 °C)	 **3b**	 **5** (61%)
3	**2c** (R = Ph)	1)  (0 °C) 2) Me$_3$SiCl (-78 to 0 °C)	 **3c**	 **6** (59%)
4	**2d** (R = *n*-Hex)	1)  (0 °C) 2) H$_2$O (0 °C)	 **3d**	 **7** (65%)
5	**2a**	1)  (-78 to 0 °C) 2) H$_2$O (0 °C)	 **3e**	 **8** (61%)
6	**2a**	1)  (0 °C)[c] 2) H$_2$O (0 °C)	 **3f**	 **9** (70%)
7	**2a**	1)  (0 °C) 2) H$_2$O (0 °C)	 **3g**  **3g'**	 **10** (75%)  **10'**(15%)

[a] Reactions were conducted on a 1 mmol scale. [b] Isolated yield by column chromatography on silica gel. [c] Generated in situ from β-(hydroxymethyl)styrene and *n*-BuLi.

Table 2. Three- and Four-Carbon Component Coupling Reactions Based on Ketone Dianions[a]

entry	α,δ-dianion	electrophile (conditions)	product (yield[b])
1	 **3a**	1)  (1.2 equiv) (-78 °C) 2) Me$_3$SiCl (1.2 equiv) (-78 to 0 °C)	 **11** (63%)
2	**3a**	1) *n*-Hex−Br (2 equiv) (-78 to -20 °C) 2) MeOH (-20 °C)	 **12** (63%) G = Ph$_3$Si $\xrightarrow{c}$ **13** (88%) G = OH
3	**3a**	1) *n*-Hex−Br (2 equiv) (-78 to -20 °C) 2)  (3 equiv) HMPA (-78 to 20 °C)	 **14** (62%) (60/40) G = Ph$_3$Si $\xrightarrow{c}$ **15** (70%) (60/40) G = OH
4	 **3h**	1) CO (1 atm) (20 °C) 2) Me$_3$SiCl (2.2 equiv) (-78 to 0 °C)	 **16** (53%)
5	**3a**	1) Me$_2$NCHO (1.1 equiv) (-78 to 0 °C) 2) H$_2$O (0 °C)	 **17** (53%)

[a] Reactions were conducted on a 1 mmol scale. [b] Isolated yield by column chromatography on silica gel. [c] (1) Bu$_4$NF (5 equiv), THF, reflux, 1.5 h; (2) KF (2 equiv), H$_2$O$_2$ (3 equiv), NaHCO$_3$ (1 equiv), THF/MeOH = 1/1, reflux, 2 h.

1). If carbon electrophiles attack the δ position of the resulting dianions preferentially, the *Z*-lithium enolate **4** would then result. This structure can then participate in the rich metal enolate based synthetic chemistry.[8] Alkylation of the enolate **4** would lead to four-component coupling product **5**. Thus, we launched this study in the hope of exploring a novel anionic cascade-type strategy available for the construction of ketone frameworks.

We began by studying the carbolithiation reactions of ketone α,β-dianions **2** with several alkenes, such as vinyl-

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(5) (a) Ryu, I.; Ikebe, M.; Sonoda, N.; Yamato, S.; Yamamura, G.; Komatsu, M. *Tetrahedron Lett.* **2000**, *41*, 5689. (b) Ryu, I.; Ikebe, M.; Sonoda, N.; Yamato, S.; Yamamura, G.; Komatsu, M. *Tetrahedron Lett.* **2002**, *43*, 1257.

(6) Ketone α,δ-dianions are a very rare class of dianions, see: Lansbury, P. T.; Spagnuolo, C. J.; Zhi, B.; Grimm, E. L. *Tetrahedron Lett.* **1990**, *31*, 3965.

(7) For a review on carbolithiation, see: Knochel, P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 4, pp 865−911.

(8) For reviews on lithium enolate chemistry, see: (a) Heathcock, C. H. In *Modern Synthetic Methods*; Scheffold, R., Ed.; VCH: New York, 1992; Vol. 3, pp 3−102. (b) Caine, D. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 1−63.

arenes, vinyl sulfides, and vinylsilanes, as described in Table 1. The reaction of **2a** with trimethylvinylsilane was problematic, since abstraction of a methyl proton competed to some extent. However, triphenylvinylsilane worked without difficulty. Thus, when 1 equiv of triphenylvinylsilane was treated with a THF solution containing **2a** at 0 °C for 1 h and the resulting reaction mixture was quenched with 2.2 molar equiv of trimethylchlorosilane, the corresponding bis-silylated product **4**, a *Z*-enol silyl ether, was obtained in 70% isolated yield (entry 1). This result suggests that dianion **2a** underwent efficient carbolithiation to vinylsilane to give the envisaged δ-silyl-α,δ-dianion **3a**. Addition of α,β-dianion **2b** (R = *sec*-Bu) to vinyl phenyl sulfide also took place to give δ-sulfur functionalized α,δ-dianion **3b**, which was transformed into the corresponding bis-silylated product **5** after quenching with chlorosilane (entry 2). Although treatment of dianion **2a** with styrene caused anionic polymerization, substituted vinylarenes, such as 1,1-diphenylethylene and 2-hydroxymethylstyrene, underwent smooth carbolithiation to give the corresponding ketone α,δ-dianions (entries 5 and 6). When a styrylsilane was used as the alkene component, an 83:17 mixture of regioisomeric dianions was formed in favor of phenyl-stabilized dianion **3g** (entry 7).

With this vinylogous route to ketone α,δ-dianions optimized, we then focused our attention on C−C bond formation at δ and α. We employed δ-silicon functionalized α,δ-dianions as models, with the results summarized in Table 2. Treatment of α,δ-dianion **3a** with allyl bromide at −78 °C resulted in δ-selective allylation to yield a lithium enolate, which was then transformed to an enol silyl ether **11** through treatment with trimethylchlorosilane (entry 1). Similarly selective alkylation by hexyl bromide took place exclusively at the δ-position (entry 2). In this case, the resulting enolate was quenched by methanol to give **12**. The treatment of thus generated enolate with allyl bromide/HMPA gave a four-component coupling product **14** as a 60/40 mixture of diastereomers (entry 3). In all cases, the C−Si bond was easily converted to a C−OH bond by Tamao−Fleming oxidation.[9]

One-carbon extension reactions using carbon monoxide[10] and DMF were also examined (entries 4 and 5). Thus, the reaction of a δ-silicon-functionalized ketone α,δ-dianion, derived from dianion **2e** (R = *i*-Pr) and vinyltriphenylsilane, with carbon monoxide gave the corresponding bis(lithium enolate), whose stereochemistry was *Z* for the ketone enolate portion and *E* for the acylsilane enolate portion (entry 4). On the other hand, reaction with DMF resulted in selective δ-formylation without a silicon shift (entry 5).

In summary, we have shown that a new class of ketone α,δ-dianions **3** are easily accessible by vinylogous extension reactions of ketone α,β-dianions **2**. Based on this key transformation, an unprecedented anionic method for assembling three- or four-carbon components to construct diverse ketone structures was achieved. Further work on ketone dianion chemistry is now ongoing in this laboratory.

Acknowledgment. I.R. is grateful for a Grant-in-Aid for Scientific Research on Priority Areas (A) “Reaction Control of Dynamic Complexes” from the Ministry of Education, Culture, Sports, Science and Technology, Japan, for financial support.

Supporting Information Available: Experimental procedure and spectral data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050813Y

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[9] Wanzl, G.; Knölker, H. J. *Synlett* **1995**, 378. For a review on the oxidation of C−Si bonds, see: Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599.

[10] (a) Murai, S.; Ryu, I.; Iriguchi, J.; Sonoda, N. *J. Am. Chem. Soc.* **1984**, *106*, 2440. (b) Ryu, I.; Yamamoto, H.; Sonoda, N.; Murai, S. *Organometallics* **1996**, *15*, 5459.