

## Lithium Benzenetelluroate-induced Reformatsky-type Reaction in the Presence of Cerium Trichloride

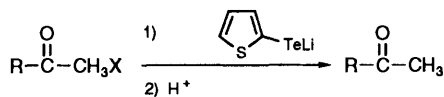
Shin-ichi Fukuzawa\* and Katsuhiko Hirai

Department of Applied Chemistry, Faculty of Science and Engineering, Chuo University, Bunkyo-ku, Tokyo 112, Japan

Reformatsky-type reactions with PhTeLi in the presence of CeCl<sub>3</sub> proceeded smoothly under mild conditions. The PhTeLi–CeCl<sub>3</sub> reagent was particularly efficient for the reactions of sterically hindered and enolizable ketones; in the absence of CeCl<sub>3</sub> unsatisfactory yields of the desired β-hydroxy ketone were obtained. It is assumed that CeCl<sub>3</sub> reactions involve a cerium enolate intermediate. The stereoselectivity of the reaction between ethyl 2-bromopropionate and benzaldehyde is also described.

The Reformatsky reaction, in its original form zinc-induced condensation of a carbonyl compound and an α-halogeno ester to give a β-hydroxy ester, is important in organic synthesis.<sup>1</sup> In addition to zinc, other metals and metal salts are now routinely used in this reaction, *e.g.* tin,<sup>2</sup> cerium,<sup>3</sup> chromium dichloride,<sup>4</sup> and samarium diiodide<sup>5</sup> have all given satisfactory results; further, combined reagents such as diethylaluminium chloride/tributylstannyl lithium,<sup>6</sup> trialkylantimony/iodine,<sup>7</sup> and cerium trichloride/sodium iodide<sup>8</sup> have allowed the reaction to be carried out under relatively mild conditions.

In 1982, Engman and Cava reported that lithium thiophene-2-telluroate reductively dehalogenated α-halogeno ketones (Scheme 1),<sup>9</sup> a reaction which highlights the potential



Scheme 1

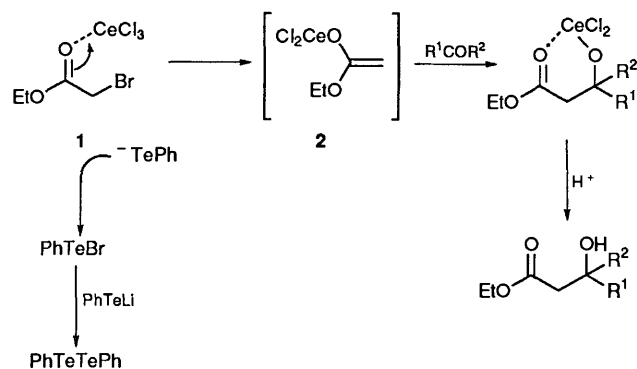
synthetic utility of the telluroate anion in the generation of a lithium enolate from α-halogeno ketones. However, only the condensation of benzaldehyde and phenacyl bromide was described. We have found that the more easily accessible lithium benzenetelluroate (PhTeLi) can replace lithium thiophene-2-telluroate, thereby increasing the potential of modifications to the Reformatsky reaction. Furthermore, concomitant use of cerium trichloride with PhTeLi (*i.e.* transmetalation to a less basic organocerium reagent<sup>10</sup>) improves yields and extends the scope of the reaction.

### Results and Discussion

PhTeLi may be readily prepared from the reaction of tellurium powder and phenyllithium in diethyl ether *in situ*.<sup>11</sup> Treatment of an equimolar mixture of ethyl bromoacetate and benzaldehyde with either PhTeLi alone or with PhTeLi and cerium trichloride (CeCl<sub>3</sub>) in diethyl ether affords the β-hydroxy ester in good to excellent yield. Similarly, PhTeLi promoted the Reformatsky-type reaction with several ketones under mild conditions. In each reaction, the presence of CeCl<sub>3</sub> afforded a better yield than in its absence; the results are summarized in Table 1. Reactions with enolizable ketones (Table 1, entries 6–9) and with sterically hindered ketones, *e.g.* diisopropyl ketone (entry 10), highlight the effect of added CeCl<sub>3</sub>, the difference in yields between its presence or its absence being > 10%. Simultaneous addition of the bromo ester and ketone to the PhTeLi–CeCl<sub>3</sub> mixture is essential to obtain good yields. Stepwise addition of the bromo ester followed by the ketone

decreases the yield. The choice of solvent is also important, diethyl ether being superior to tetrahydrofuran (THF) (Table 1 entries 7, 9). Use of lithium benzeneselenolate (PhSeLi) instead of PhTeLi in the reaction of ethyl bromoacetate with benzaldehyde gave a product yield not exceeding 80%.

Since diphenyl ditelluride (PhTeTePh) was formed in the reaction, 2 equiv. of PhTeLi to the bromo ester were needed; the use of 1 equiv. of PhTeLi leaves > 50% of the starting bromo ester unchanged. Such observations suggest that the first step in these reactions is halogen reduction by PhTeLi to generate PhTeBr, followed by nucleophilic attack by a second molecule of telluroate anion on the latter to yield PhTeTePh. The reaction with CeCl<sub>3</sub> is expected to proceed *via* the cerium enolate 2. High nucleophilicity (*i.e.* low basicity) to sterically hindered and enolizable ketones is consistent with the known alkylation by an organocerium reagent and the aldol reaction with a cerium enolate.<sup>12–15</sup> This process is illustrated in Scheme 2.



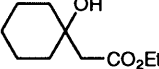
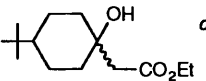
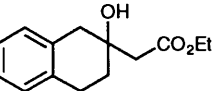
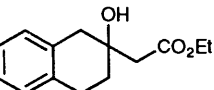
Scheme 2

The possibility of these reactions being diastereoselective was examined for the reaction of ethyl 2-bromopropionate with benzaldehyde (Scheme 3). No selectivity was, however, observed only a 50:50 mixture of *threo* and *erythro* isomers being formed.

### Experimental

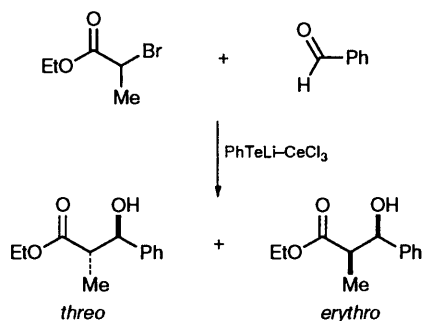
**General.**—<sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Fourier transform NMR system (JEOL JNM A-400) (400 MHz) spectrometer as solutions in CDCl<sub>3</sub>. Chemical shifts are reported in δ units downfield from the internal reference Me<sub>4</sub>Si. Assignment of carbon-13 resonance was aided by use of the DEPT delayed pulse sequence. IR spectra were obtained from

**Table 1** The reaction of ethyl bromoacetate with carbonyl compounds by PhTeLi in the presence of CeCl<sub>3</sub><sup>a</sup>

Entry	Ketone	Product	Yield (%) <sup>b</sup> (without CeCl <sub>3</sub> )
1	Acetophenone	PhC(OH)(Me)CH <sub>2</sub> CO <sub>2</sub> Et	95 (73)
2	Propiophenone	PhC(OH)(Et)CH <sub>2</sub> CO <sub>2</sub> Et	80 (73)
3	Heptan-2-one	BuC(OH)(Et)CH <sub>2</sub> CO <sub>2</sub> Et	80 (76)
4	Cyclohexanone		95 (89)
5	4- <i>tert</i> -Butylcyclohexanone	 <sup>c</sup>	95 (90)
6	2-Tetralone		63 (53)
7 <sup>d</sup>	2-Tetralone		47 (37)
8	Dibenzyl ketone	(PhCH <sub>2</sub> ) <sub>2</sub> C(OH)CH <sub>2</sub> CO <sub>2</sub> Et	87 (73)
9 <sup>d</sup>	Dibenzyl ketone	(PhCH <sub>2</sub> ) <sub>2</sub> C(OH)CH <sub>2</sub> CO <sub>2</sub> Et	58 (48)
10	Diisopropyl ketone	Pr <sub>2</sub> C(OH)CH <sub>2</sub> CO <sub>2</sub> Et	65 (27)

<sup>a</sup> Ethyl bromoacetate (2.0 mmol), ketone (2.0 mmol), PhTeLi (5.0 mmol) and CeCl<sub>3</sub> (2.5 mmol) in diethyl ether (20 cm<sup>3</sup>), 0 °C–room temp., 1 h.

<sup>b</sup> Isolated yield. <sup>c</sup> A mixture of diastereoisomers. <sup>d</sup> The reaction was carried out in THF.



solutions in chloroform with a Hitachi 260-56 spectrometer. GLC analyses were carried out on a Shimadzu GC-14A gas chromatograph equipped with capillary column (CBP1-25) (25 m) (helium as carrier gas). Column chromatography was performed by a Yamazen YFLC-540 and Michael Miller column equipped with a UV detector by using Wakogel C-300. Thin layer chromatography (TLC) separation was conducted using 20 × 20 cm aluminium sheet coated with a 0.2 mm thick layer of Merck Kieselgel 60 PF<sub>254</sub>. Elemental analyses were carried out at the Microanalytical Center of Kyoto University, Kyoto, Japan.

**Materials.** Anhydrous CeCl<sub>3</sub> was obtained by drying the commercial hydrate with SOCl<sub>2</sub> at reflux and heating it at 150 °C *in vacuo* for 2 h over KOH. Tetrahydrofuran (THF) and diethyl ether were distilled under nitrogen from sodium benzophenone ketyl just before use. Tellurium powder was purchased from Aldrich. Phenyllithium was prepared from the reaction of bromobenzene and lithium in diethyl ether and its concentration was determined by the Gilman method. All organic compounds were commercially available and used without further purification unless otherwise noted.

**Reaction of Ethyl Bromoacetate with Carbonyl Compounds induced by PhTeLi in the Presence of CeCl<sub>3</sub>.**—All reactions were carried out under nitrogen using standard techniques for air-sensitive materials. The following example provides a general procedure for the reaction of ethyl bromoacetate with carbonyl compounds. Anhydrous cerium trichloride (0.62 g, 2.5 mmol) was placed in a 50 cm<sup>3</sup> two-neck round-bottom flask equipped with a three-way cock. The flask was heated at 150 °C *in vacuo* for 1 h. After the flask had been cooled to room temperature, tellurium powder (0.64 g, 5 mmol) and a magnetic stirring bar were placed in the flask, which was flushed with nitrogen. Dry diethyl ether (15 cm<sup>3</sup>) was added by a syringe through a rubber septum with stirring. After the mixture had been stirred at room temperature for 10 min, the flask was cooled in an ice-bath and an ethereal solution of phenyllithium (1.0 mol cm<sup>-3</sup>; 5 cm<sup>3</sup>, 5 mmol) was injected slowly at 0 °C into the suspension. The tellurium powder reacted with phenyllithium immediately and the solution became grey and turbid (CeCl<sub>3</sub>–PhTeLi reagent prepared). The resulting suspension was stirred at room temperature for 20 min, and then a mixture of ethyl bromoacetate (0.33 g, 2.0 mmol) and benzaldehyde (0.21 g, 2.0 mmol) in diethyl ether (5 cm<sup>3</sup>) was added to it at 0 °C. The solution immediately became reddish brown and stirring was continued at 0 °C to room temperature for 1 h. The resulting solution was treated with diluted HCl (3%; 20 cm<sup>3</sup>), and then extracted with diethyl ether (20 cm<sup>3</sup> × 3). The extracts were combined, washed with brine, dried (MgSO<sub>4</sub>) and evaporated to give a reddish brown residue which was subjected to short column chromatography on silica gel (3 × 5 cm). TLC (SiO<sub>2</sub>) analysis showed the presence of the organic product with diphenyl ditelluride. Hexane eluted the diphenyl ditelluride and diethyl ether eluted the desired ethyl 3-hydroxy-3-phenylpropionate (0.38 g, 2.0 mmol, >99%). Further purification by Kugelrohr distillation (oven temp. 180 °C/5 mmHg) gave pure products; δ<sub>H</sub>(CDCl<sub>3</sub>; 400 MHz) 1.24 (3 H, t, OCH<sub>2</sub>CH<sub>3</sub>), 2.67 (1 H, dd, *J* 4.2, 16.1, CH<sub>2</sub>CO<sub>2</sub>Et), 2.74 (1 H, dd, *J* 8.8, 16.1,

$\text{CH}_2\text{CO}_2\text{Et}$ ), 3.40 (1 H, br s, OH), 4.15 (2 H, q,  $\text{OCH}_2\text{CH}_3$ ), 5.11 (1 H, dd,  $J$  8.8, 4.2,  $\text{CH}(\text{OH})\text{CH}_2\text{CO}_2\text{Et}$ ), 7.3 (5 H, m, Ph);  $\delta_{\text{C}}$  14.0, 43.3, 60.8, 70.2, 125.6, 127.7, 128.4, 142.5 and 172.2;  $\nu_{\text{max}}/\text{cm}^{-1}$  3550 (OH) and 1720 (C=O) (Found: C, 67.9; H, 7.5.  $\text{C}_{11}\text{H}_{14}\text{O}_3$  requires C, 68.02; H, 7.27%).

**Ethyl 3-hydroxy-3-phenylpentanoate.** The title compound was obtained from the reaction of ethyl bromoacetate with propiophenone;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ; 400 MHz) 0.77 (3 H, t,  $\text{CH}_3\text{CH}_2$ ), 1.08 (3 H, t,  $\text{OCH}_2\text{CH}_3$ ), 1.7–1.8 (2 H, m,  $\text{CH}_3\text{CH}_2$ ), 2.77 (1 H, d,  $J$  15.9,  $\text{CH}_2\text{CO}_2\text{Et}$ ), 2.95 (1 H, d,  $J$  15.9,  $\text{CH}_2\text{CO}_2\text{Et}$ ), 4.01 (2 H, q,  $\text{OCH}_2\text{CH}_3$ ), 4.2 (1 H, br s, OH) and 7.1–7.4 (5 H, m, Ph);  $\delta_{\text{C}}$  7.7, 13.8, 35.6, 44.9, 60.6, 75.1, 125.1, 126.6, 128.0, 145.1 and 172.9;  $\nu_{\text{max}}/\text{cm}^{-1}$  3510 (OH) and 1720 (C=O) (Found: C, 70.5; H, 8.4.  $\text{C}_{13}\text{H}_{18}\text{O}_3$  requires C, 70.24; H, 8.16%).

**Ethyl 3-ethyl-3-hydroxyheptanoate.** The title compound was obtained from the reaction of ethyl bromoacetate with heptan-3-one;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ; 400 MHz) 0.91 (3 H, t,  $\text{CH}_3\text{CH}_2$ ), 0.92 (3 H, t,  $\text{OCH}_2\text{CH}_3$ ), 1.3–1.6 (11 H, m, alkyl-H), 2.46 (2 H, s,  $\text{CH}_2\text{CO}_2\text{Et}$ ), 3.3 (br s, 1 H, OH) and 4.18 (2 H, q,  $\text{OCH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  7.9, 13.9, 14.1, 23.1, 25.7, 31.6, 38.3, 42.6, 60.5, 73.1 and 173.2;  $\nu_{\text{max}}/\text{cm}^{-1}$  3500 (OH) and 1717 (C=O) (Found: C, 65.1; H, 11.1.  $\text{C}_{11}\text{H}_{22}\text{O}_3$  requires C, 65.31; H, 10.96%).

**1-Ethoxycarbonylmethylcyclohexanol.** The title compound was obtained from the reaction of ethyl bromoacetate with cyclohexanone;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ; 400 MHz) 1.2–1.8 (15 H including methyl group of ester, m), 2.47 (2 H, s,  $\text{CH}_2\text{CO}_2\text{Et}$ ), 3.4 (1 H, br s, OH), 4.17 (2 H, q,  $\text{OCH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  14.1, 21.9, 25.5, 37.4, 45.2, 60.5, 69.9 and 172.8;  $\nu_{\text{max}}/\text{cm}^{-1}$  3520 (OH) and 1716 (C=O) (Found: C, 64.4; H, 9.9.  $\text{C}_{10}\text{H}_{18}\text{O}_3$  requires C, 64.49; H, 9.74%).

**4-tert-Butyl-1-ethoxycarbonylmethylcyclohexanol.** The title compound was obtained from the reaction of ethyl bromoacetate with 4-tert-butylcyclohexanone;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ; 400 MHz) 0.86 (9 H, s, Bu'), 1.1–1.9 (14 H, m, including methyl group of ester), 2.56 (2 H, s,  $\text{CH}_2\text{CO}_2\text{Et}$ ), 3.8 (1 H, br s, OH) and 4.18 (2 H, q,  $\text{OCH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  14.1, 24.3, 25.2, 27.6, 32.1, 38.3, 40.6, 47.4, 60.6, 70.8 and 172.8;  $\nu_{\text{max}}/\text{cm}^{-1}$  3520 (OH) and 1716 (C=O) (Found: C, 69.2; H, 10.9.  $\text{C}_{14}\text{H}_{26}\text{O}_3$  requires C, 69.38; H, 10.81%).

**Ethyl 3-benzyl-3-hydroxy-4-phenylbutanoate.** The title compound was obtained from the reaction of ethyl bromoacetate with dibenzyl ketone;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ; 400 MHz) 1.22 (3 H, t,  $\text{OCH}_2\text{CH}_3$ ), 2.32 (2 H, s,  $\text{CH}_2\text{CO}_2\text{Et}$ ), 2.84 (4 H, d,  $J$  13.4,  $\text{CH}_2\text{Ph}$ ), 3.80 (1 H, s, OH), 4.04 (2 H, q,  $\text{OCH}_2\text{CH}_3$ ) and 7.1–7.4 (10 H, m, Ph);  $\delta_{\text{C}}$  14.1, 41.1, 46.5, 60.6, 73.3, 126.5, 128.1, 130.8, 137.0 and 173.1;  $\nu_{\text{max}}/\text{cm}^{-1}$  3500 (OH) and 1710 (C=O) (Found: C, 76.4; H, 7.4.  $\text{C}_{19}\text{H}_{22}\text{O}_3$  requires C, 76.48; H, 7.43%).

**Ethyl 3-hydroxy-3-isopropyl-4-methylpentanoate.** The title compound was obtained from the reaction of ethyl bromoacetate with diisopropyl ketone;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ; 400 MHz) 0.85 [6 H, d,  $J$  6.9,  $(\text{CH}_3)_2\text{CH}$ ], 0.93 [6 H, d,  $J$  6.9,  $(\text{CH}_3)_2\text{CH}$ ], 1.28 (3 H, t,  $\text{OCH}_2\text{CH}_3$ ), 1.94 [2 H, septet,  $J$  6.9,  $(\text{CH}_3)_2\text{CH}$ ], 2.42 (2 H, s,  $\text{CH}_2\text{CO}_2\text{Et}$ ), 3.80 (1 H, s, OH) and 4.20 (2 H, q,  $\text{OCH}_2\text{CH}_3$ );  $\delta_{\text{C}}$  14.0, 17.2, 17.4, 34.8, 35.7, 39.4, 60.8, 75.1 and 174.8;  $\nu_{\text{max}}/\text{cm}^{-1}$  3500 (OH) and 1710 (C=O) (Found: C, 65.25; H, 11.1.  $\text{C}_{11}\text{H}_{22}\text{O}_3$  requires C, 65.31; H, 10.96%).

**2-Ethoxycarbonylmethyl-1,2,3,4-tetrahydronaphthalen-2-ol.**—The title compound was obtained from the reaction of ethyl bromoacetate with 2-tetralone;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ; 400 MHz) 1.29 (t, 3 H,  $\text{CH}_3$ ), 1.7–2.0 (2 H, m,  $\text{CH}_2\text{CH}_2\text{COH}$ ), 2.58 (s, 2 H,  $\text{CH}_2\text{CO}_2\text{Et}$ ), 2.7–3.1 (2 H, m,  $\text{CH}_2\text{CH}_2\text{COH}$ ), 2.85 (1 H, d,  $J$  16.5, benzyl  $\text{CH}_2\text{C}-\text{OH}$ ), 2.95 (d, 1 H,  $J$  16.5, benzyl  $\text{CH}_2\text{C}-\text{OH}$ ), 3.7 (1 H, br s, OH), 4.20 (2 H, q,  $\text{CH}_3\text{CH}_2\text{O}$ ), 7.0–7.2 (4 H, m, aromatic H);  $\delta_{\text{C}}$  14.2, 26.2, 34.0, 41.7, 43.9, 60.7, 69.4, 125.9, 126.0, 128.6, 129.4, 134.0, 135.0 and 172.8;  $\nu_{\text{max}}/\text{cm}^{-1}$  3510 (OH) and 1720 (C=O) (Found: C, 71.8; H, 7.7.  $\text{C}_{14}\text{H}_{18}\text{O}_3$  requires C, 71.77; H, 7.74%).

**Ethyl 3-hydroxy-2-methyl-3-phenylpropionate.** The title compound was obtained from the reaction of ethyl 2-bromopropionate with benzaldehyde;  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ ; 400 MHz) showed the presence of a mixture of *threo* and *erythro* isomers; 1.00 (1.5 H, d, *threo*  $\text{CH}_3$ ), 1.11 (1.5 H, d, *erythro*  $\text{CH}_3$ ), 1.18 (1.5 H, t, *threo*  $\text{OCH}_2\text{CH}_3$ ), 1.25 (1.5 H, t, *erythro*  $\text{OCH}_2\text{CH}_3$ ), 2.6–3.0 (1 H, m,  $\text{CHCO}_2\text{Et}$ ), 3.2 (1 H, br s, OH), 4.10 (1 H, q, *threo*  $\text{OCH}_2\text{CH}_3$ ), 4.17 (1 H, q, *erythro*  $\text{OCH}_2\text{CH}_3$ ), 4.73 (0.5 H, d,  $J$  8.3, *threo*  $\text{CHOH}$ ), 5.05 (0.5 H, d,  $J$  4.4, *erythro*  $\text{CHOH}$ ) and 7.1–7.4 (5 H, m, Ph);  $\delta_{\text{C}}$  showed the presence of a mixture of *threo* and *erythro* isomers;  $\delta_{\text{C}}$  10.9, 14.0, 14.1, 46.5, 47.1, 60.6, 60.7, 73.7, 76.3, 125.9, 126.6, 127.4, 128.0, 128.2, 129.5, 141.5, 141.6, 175.7 and 175.9;  $\nu_{\text{max}}/\text{cm}^{-1}$  3510 (OH) and 1720 (C=O) (Found: C, 69.4; H, 7.5.  $\text{C}_{12}\text{H}_{16}\text{O}_3$  requires C, 69.21; H, 7.74%).

## References

- 1 A. Fürstner, *Synthesis*, 1989, 571.
- 2 T. Harada and T. Mukaiyama, *Chem. Lett.*, 1982, 161; 462.
- 3 T. Imamoto, T. Kusumoto, Y. Tawarayama, Y. Sugiura, T. Mita, Y. Hatanaka and M. Yokoyama, *J. Org. Chem.*, 1984, **49**, 3904.
- 4 J. E. Dubois, G. Axiotis and E. Bertouneque, *Tetrahedron Lett.*, 1985, **26**, 4371.
- 5 T. Tabuchi, K. Kawamura, J. Inananaga and M. Yamaguchi, *Tetrahedron Lett.*, 1986, **27**, 3889.
- 6 S. Matubara, N. Tuboniwa, Y. Morizawa, K. Oshima and H. Nozaki, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 3242.
- 7 Y. Z. Huang, C. Cheng and Y. Shen, *J. Chem. Soc., Perkin Trans. 1*, 1988, 2855.
- 8 S. Fukuzawa, T. Tsuruta, T. Fujinami and S. Sakai, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1473.
- 9 L. Engman and M. P. Cava, *J. Org. Chem.*, 1982, **47**, 3946.
- 10 For reviews, T. Imamoto, in *Organocerium Reagents; Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon Press, Oxford, 1991, vol. 1, pp. 231–250.
- 11 J. L. Piette and M. Renson, *Bull. Soc. Chim. Belg.*, 1970, **79**, 383.
- 12 T. Imamoto, T. Kusumoto and M. Yokoyama, *Tetrahedron Lett.*, 1983, **24**, 5233.
- 13 H.-J. Liu and N. H. Al-Said, *Tetrahedron Lett.*, 1991, **32**, 5473.
- 14 H.-J. Liu and B.-Y. Zhu, *Can. J. Chem.*, 1991, **68**, 2008.
- 15 K. Nagasawa, H. Kanbara, K. Matsushita and K. Ito, *Chem. Lett.*, 1985, 6477.

Paper 3/02667A

Received 11th May 1993

Accepted 19th May 1993