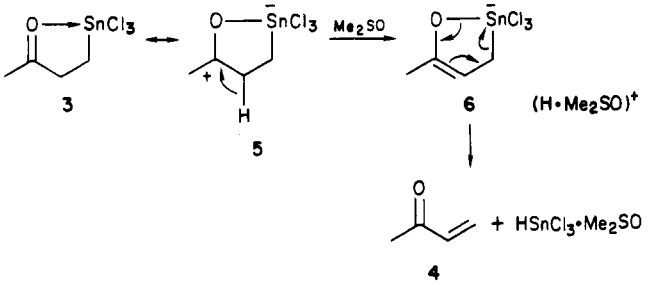
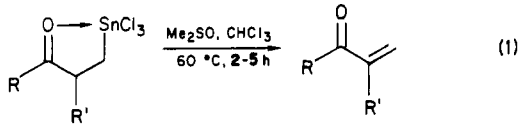
Scheme I



3 5 6 4

concomitantly, 2-methylene ketone **4g** was formed (monitored by ^{1}H NMR). After 4 h, dehydrostannation was complete, and the precipitate was filtered off. Aqueous workup of the filtrate (pentane/aqueous NH_4Cl) followed by evaporation of the solvents and bulb-to-bulb distillation afforded 2-methylenecycloheptanone (**4g**) in 80% yield. Similarly, essentially quantitative conversion of **3** to **4** (eq 1) was observed in the reaction of **3** with Me_2SO-d_6/$CDCl_3$

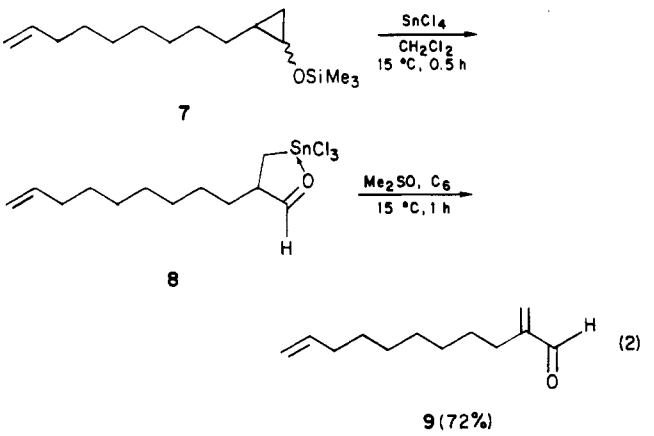


(1)

3 4

at 60 °C (by ^{1}H NMR) except for **3f** which did not bear hydrogen β to the stannyl group.[9] The results are shown in Table I. The dehydrostannation of **3d,e,g,h** proceeded with shorter reaction time than **3a–c**. It seems that for dehydrostannation to occur, the intramolecular coordination of the carbonyl oxygen to the Sn atom (as indicated by IR) may play a key role. In fact, dehydrostannation did not take place with simple *n*-$BuSnCl_3$ even under more forcing conditions (60 °C, 1 day). One plausible explanation for the present reaction is shown in Scheme I. The initial role of Me_2SO may be the one as a base toward β-hydrogen[10] which may be sufficiently acidic due to the inductive effect of the adjacent carbonyl coordinated to the Sn. Thus, the deprotonation from **5** and subsequent destannylation via **6** would occur to lead to **4** and $HSnCl_3(Me_2SO)_n$ complex.[11,12]

Interestingly, the reaction of siloxycyclopropane **7** with $SnCl_4$ in CH_2Cl_2 proceeded similarly and afforded β-trichlorostannyl aldehyde **8** (semisolid, $\nu_{C=O}$ 1680 cm^{-1}). The resulting crude **8** (4 mmol) was treated with Me_2SO (1 mL) in hexane (5 mL)[13] at 15 °C for 1 h, followed by separation of a white precipitate and aqueous treatment (Et_2O/aqueous NH_4Cl). After removal of the solvents, the residue was chromatographed on silica gel to give a 72% yield of 2-methylene-10-undecenal (**9**) (eq 2).



7 8

(2)

9 (72%)

Further synthetic application of β-stannyl ketones and aldehydes is now in progress.

Acknowledgment. We thank Shin-Etsu Chem. Ind. Co. Ltd. for a gift of trimethylchlorosilane.

Registry No. **2a**, 38858-75-2; **2b**, 101653-02-5; **2c**, 54781-38-3; **2d**, 56011-29-1; **2e**, 50338-51-7; **2f**, 50338-50-6; **2g**, 50338-48-2; **2h**, 50338-49-3; **3a** (coordinate), 101653-11-6; **3a** (stannane), 101653-04-7; **3b** (coordinate), 101653-12-7; **3b** (stannane), 101653-05-8; **3c** (coordinate), 101653-13-8; **3c** (stannane), 101653-06-9; **3d** (coordinate), 101653-14-9; **3d** (stannane), 101653-07-0; **3e** (coordinate), 101653-15-0; **3e** (stannane), 101653-08-1; **3f** (coordinate), 101653-16-1; **3f** (stannane), 101653-09-2; **3g** (coordinate), 101653-17-2; **3g** (stannane), 101653-10-5; **3h**, 101653-18-3; **3h** (stannane), 101670-94-4; **4a**, 2177-30-2; **4b**, 1606-47-9; **4c**, 62672-77-9; **4d**, 769-60-8; **4e**, 42858-50-4; **4g**, 3045-99-6; **4h**, 3045-71-4; **7**, 101653-03-6; **8**, 101653-19-4; **9**, 22414-69-3; $SnCl_4$, 7646-78-8.

(9) As the preparative method of β-stannyl ketones **3**, hydrostannation of α,β-unsaturated ketones with $HSnCl_3$ (in situ generated under acidic conditions: HCl and $SnCl_2$) has been known. The observed dehydrostannation promoted by Me_2SO formally corresponds to its reverse reaction. See: Hutton, R. E.; Burley, J. W.; Oakes, B. *J. Organomet. Chem.* **1978**, *156*, 369.

(10) The use of some amines such as pyridine, instead of Me_2SO, was also effective. DMF and methylformamide also promoted the dehydrostannation to some extent. For examples of Me_2SO promoted 1,2-elimination, see, pp 328–329 in a review: Martin, D.; Weise, A.; Niclas, H. J. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 318.

(11) Colorless crystals were obtained (mp >300 °C). The IR spectra (KBr) of this compound showed strong absorption at 900 cm^{-1}, which should be ascribed to the coordinated $\nu_{S=O}$. The spectra was identical with that of the Me_2SO complex separately prepared according to the reaction of Me_2SO with in situ generated $HSnCl_3$[9] (by treating $SnCl_2 \cdot 2H_2O$ with Me_3SiCl in ether). The number of coordinated Me_2SO molecules is not clear at the present time (1 and/or 2). Cf. Wayland, B. B.; Schramm, R. F. *J. Chem. Soc., Chem. Commun.* **1968**, 1465. Nametkin, N. S.; Kuz'min, O. V.; Korelov, V. K.; Kobrakov, K. I.; Patrikeev, A. V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1978**, 676; *Chem. Abstr.* **1978**, *89*, 42292q.

(12) We have also shown previously that bicyclic siloxycyclopropanes **2** can be converted to the corresponding 2-methylenecycloalkanones **4** based on a β-metallo ketone approach involving the ring cleavage reaction of **2** with $Hg(OAc)_2/PdCl_2$[2] or CuF_2.[4] As referred to in our previous reports, these methods were often bothered by the contamination of side products (endocyclic alkenones or coupling dimers, respectively).

(13) The use of hexane instead of $CHCl_3$ was advantageous for the formation of an easily separable hydrostannane precipitate.

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Received November 12, 1985

New C4-Chiral 1,3-Thiazolidine-2-thiones: Excellent Chiral Auxiliaries for Highly Diastereocontrolled Aldol-Type Reactions of Acetic Acid and α,β-Unsaturated Aldehydes

Summary: Diastereocontrolled aldol-type reactions between tin(II) enolates of 3-acetyl-4(*S*)-ETT (**6a**) and 3-acetyl-4(*S*)-IPTT (**6b**) and α,β-unsaturated aldehydes **7a–c** were successfully carried out to give, with high diastereoselectivity, compounds **9a–e** (major products) and **10a–e** (minor products). The reaction conditions were also investigated in detail.

Sir: A chiral synthon, α-nonsubstituted-β-hydroxy-γ,δ-unsaturated carbonyl system (**1**) would be remarkably useful for construction of synthons **2–5** (eq 1). Chiral synthons **1–5** have often appeared in the complicated

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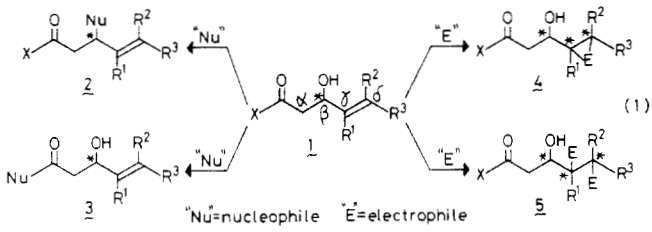


molecules of biologically active natural products such as virginiamycins, compactin, nystatin A1, borrelidin, leucomycins, and so on.[1] Synthon **2** (X = OH or its equivalent group, Nu = protected amino group) is particularly useful for β-lactam synthesis.

In spite of the utility of synthon **1**, nobody has reported its chiral synthesis utilizing an aldol-type reaction with α,β-unsaturated aldehydes, because of its remarkable sensitivity toward base or acid under the reaction conditions.[2] A few asymmetric aldol-type reactions employing saturated aldehydes and acetyl derivatives have been reported by Evans,[3] Mukaiyama,[4] and us.[5] However, these reaction conditions cannot be used without any improvement for chiral aldol-type reactions with α,β-unsaturated aldehydes because of the following reasons. High diastereoselectivity is not expected.[3,5] Excess of additive amine may cause troubles: dehydration of the product and/or decrease of the diastereoselectivity (vide infra).[4,5] Therefore, we investigated carefully the chiral aldol-type reactions of acetic acid and α,β-unsaturated aldehydes employing new C4-chiral 1,3-thiazolidine-2-thiones, 4-(*S*)-ethyl-1,3-thiazolidine-2-thione [4(*S*)-ETT][6] and 4-(*S*)-isopropyl-1,3-thiazolidine-2-thione [4(*S*)-IPTT],[6] and enolate forming reagent system, tin(II) trifluoromethanesulfonate [tin(II) triflate],[4] and *N*-ethylpiperidine (Scheme I).[7] Divalent tin atoms can possess at least 2–4 ligands.[8] We assumed a most likely transition state (**8**) having four ligands and expected alcohol **9** as the major product for this diasterocontrolled aldol-type reaction.[9]

First, we examined the amounts of enolating reagents, which must be the most important factor and should control the stereoselectivity of this aldol-type reaction.

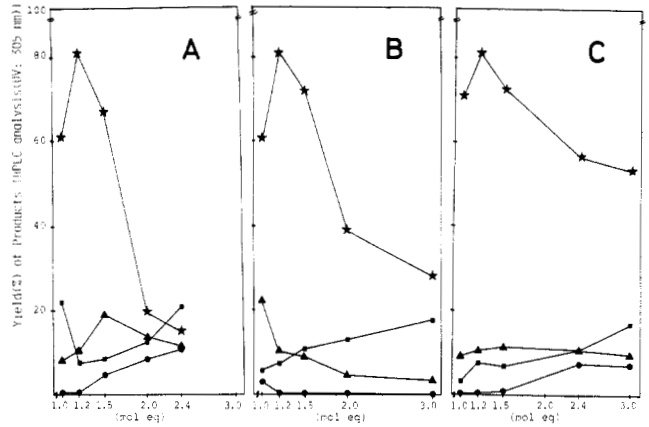
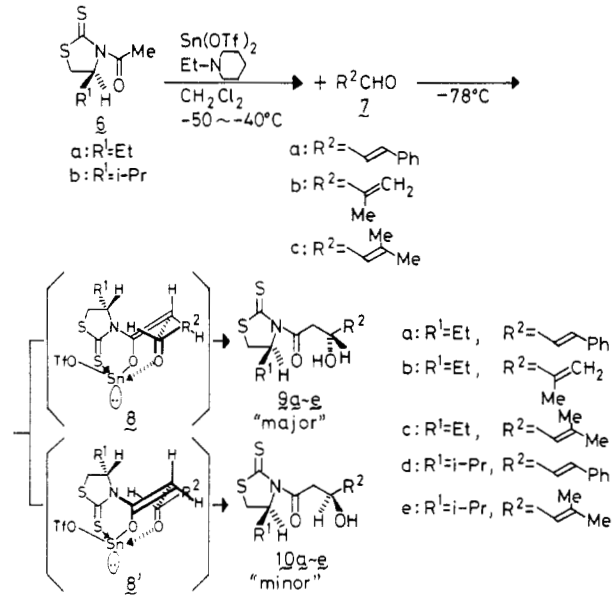


Figure 1. Effect of amount of (A) *N*-ethylpiperidine, (B) tin(II) triflate, and (C) *N*-ethylpiperidine plus tin(II) triflate; (■) compound **6a**, (★) compound **9c**, (▲) compound **10c**, (●) compound **11**.

Scheme I



Thus, all the reactions were carried out as follows: A required amount of *N*-ethylpiperidine was added dropwise to a suspension of a required amount of tin(II) triflate in anhydrous CH_2Cl_2 (2.6 mL) at −50 °C to −40 °C under argon. Then, a CH_2Cl_2 (1.2 mL) solution of 3-acetyl-4-(*S*)-ETT (**6a**) (1 mmol) was added and the mixture was stirred at −50 °C to −40 °C for 4 h. After addition of 3-methyl-2-butenal (**7c**) (1.2 mmol) at −78 °C, the mixture was stirred at the same temperature for 30 min and treated as usual to give a mixture of products and some starting compounds, which was subjected to HPLC analysis. All results are exhibited in Figure 1A–C.

From the results, we realized some interesting facts. Diastereoselectivity and yield of this aldol-type reaction are remarkably susceptible to *N*-ethylpiperidine (Figure 1A). Relative yield ratio between diastereoisomers **9c** and **10c** apparently decreases in proportion to the increasing amount of *N*-ethylpiperidine from 1.2 molar equiv of the reagent. This may be due to the coordination of *N*-ethylpiperidine to the tin(II) enolates of 3-acetyl-4(*S*)-ETT, from the less hindered side, which would interfare stereoselective approach of aldehyde **7c**. Excess *N*-ethylpiperidine also promoted dehydration of the resulting alcoholic product and gave a conjugated diene compound **11**. A small excess of tin(II) triflate does not affect strongly

(1) (a) Cocito, C. *Microbiol. Rev.* **1979**, *43*, 145. (b) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiot.* **1976**, *29*, 1346. (c) Brown, A. G.; Smale, T. C.; King, T. J.; Hasenkamp, R.; Thompson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1165. (d) Takahashi, N.; Marumo, S.; Otake, N. Eds. *Chemistry of Biologically Active Natural Products* (in Japanese); Univ. of Tokyo Press: Tokyo, 1973.

(2) For preparations of stable a α-substituted-β-hydroxyl-γ,δ-unsaturated enone system, see: (a) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099. (b) Harada, T.; Mukaiyama, T. *Chem. Lett.* **1982**, 161.

(3) The aldol-type reactions of the boron enolate of 2-acetyl-4(*S*)-isopropyl-1,3-oxazolidin-2-one with acetaldehyde and isobutyraldehyde gave low diastereoselectivities of 52:48 and 72:28, respectively. See: Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(4) Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1983**, 297.

(5) Nagao, Y.; Yamada, S.; Kumagai, T.; Ochiai, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1985**, 1418.

(6) 4(*S*)-ETT and 4(*S*)-IPTT were readily prepared by refluxing a solution of the corresponding amino alcohols, 2(*S*)-amino-1-butanol and 2(*S*)-amino-3-methyl-1-butanol, in aqueous ethanol, CS_2 (2 molar equiv), and KOH (2 molar equiv). 4(*S*)-ETT: 82.5% yield, colorless needles (CH_2Cl_2): mp 41 °C; $[\alpha]^{23}_D$ −35.4° (*c* 0.64, $CHCl_3$). 4(*S*)-IPTT: 65.3% yield, colorless needles (CH_2Cl_2); mp 67–68 °C; $[\alpha]^{22}_D$ −36.81° (*c* 1.16, $CHCl_3$).

(7) The aldol-type reactions of the tin(II) enolate of 3-acetyl-4(*S*)-ETT (**6a**) and 3-acetyl-4(*S*)-IPTT (**6b**) with saturated aldehydes proceeded smoothly by employing 1.5 molar equiv of tin(II) triflate and 1.6 molar equiv of *N*-ethylpiperidine. Superior diastereoselectivities in the range of 92.3:7.7–98.5:1.5 ratios were gained (unpublished results by us). Compare with the cases (diastereoselectivities 81.8:18.2–91.4:8.6)[5] of chiral 3-acetyl-1,3-oxazolidine-2-thiones.

(8) Zubieta, J. A.; Zuckerman, J. J. *Prog. Inorg. Chem.* **1978**, *24*, 251.

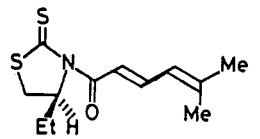
(9) We thank Dr. K. Tamao (Kyoto University) for his kind discussion about chemical structure of the species involving tin(II) metal.

Table I. Diastereocontrolled Aldol-Type Reactions between C4-Chiral 3-Acetyl-1,3-thiazolidine-2-thiones (ATT) and α,β-Unsaturated Aldehyde

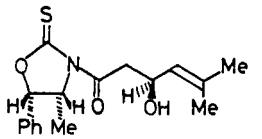
ATT	aldehyde	diastereoisomer selectivity[a]	isolated yield[b] (%)
6a	**7a**	92.7:7.3 (**9a**:**10a**)	77.0
6a	**7b**	93.1:6.9 (**9b**:**10b**)	74.2
6a	**7c**	88.6:11.4 (**9c**:**10c**)	72.4
6b	**7a**	97.1:2.9 (**9d**:**10d**)	81.2
6b	**7c**	97.3:2.7 (**9e**:**10e**)	70.2

[a] Determined by HPLC analysis (UV: 305 nm). [b] Total yields of both stereoisomers.

the relative yield ratio between **9c** and **10c**. Dehydration of **9c** is not observed (Figure 1B). Recovery of **6a** and the decrease of yields of both products **9c** and **10c** were observed, however, according to the increase of the amount of tin(II) triflate. Hence, it may be speculated that excess tin(II) triflate may act on the aldehyde and/or *N*-ethylpiperidine but not on tin(II) enolate of **6a**. Simultaneous increase of equimolar amount of *N*-ethylpiperidine and tin(II) triflate affects to a small extent both the product ratio and their yields but a considerable increase of recovery of **6a** and dehydration to **11** were observed (Figure 1C). Consequently, the conditions under which 1.2 molar equiv of *N*-ethylpiperidine and tin(II) triflate were used were shown to give the best result.



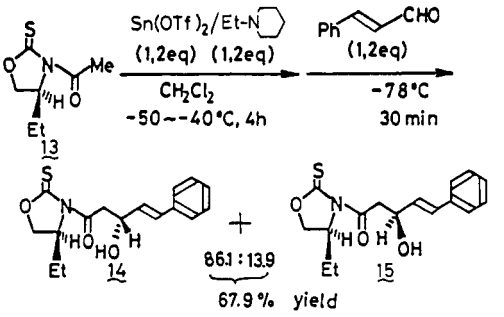
11



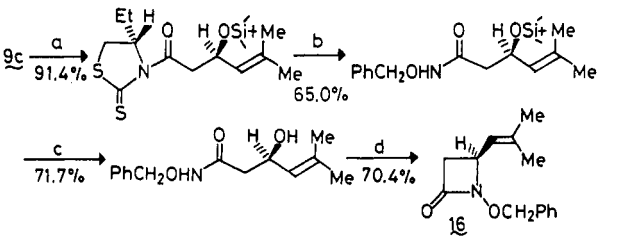
12

Thus, all aldol-type reactions employing 3-acetyl-4(*S*)-ETT (**6a**) and 3-acetyl-4(*S*)-IPTT (**6b**) with α,β-unsaturated aldehyde **7a–c** were performed under such conditions to afford **9a–e** as major products in a highly diastereoselective manner. The minor products **10a–e** might be obtained predominantly via a transition state (8') because of the bulkiness of the R^1 group of the thiazolidine-2-thione moiety which apparently controls the diastereoselectivity (see Table I). Chromatographic separation of the major product **9** and the corresponding minor product **10** on a silica gel column can be readily monitored by the yellow color due to the 3-acyl-1,3-thiazolidine-2-thione structure.[10] All results are summarized in Table I. Absolute configuration of aldol products **9c**, **9e**, **10c**, and **10e** was confirmed by chemical correlation with compound **12**,[11] whose stereochemistry had been determined by X-ray analysis. Stereochemistry of other compounds **9a**, **9b**, **9d**, **10a**, **10b**, and **10d** was determined by the similarlity in characteristic ABX-type peaks pattern (400-MHz ^{1}H NMR spectrum) which is assignable to α-CH_2 in the major products **9c** and **9e** and their corresponding minor products **10c** and **10e**, respectively. We have compared the relative merits between C4-chiral 1,3-thiazolidine-2-thione and C4-chiral 1,3-oxazolidine-2-thiones in this diastereocontrolled aldol-type reaction. We realized 3-acetyl-4(*S*)-ethyl-1,3-oxazolidine-2-thione (**13**) to be slightly less stereoselective than 3-acetyl-4(*S*)-ETT (**6a**) (Scheme II and Table I). In the former case, the separation of **13** and both products **14** and **15** on a silica gel column cannot be monitered because of their colorless nature. Thus, new C4-chiral-1,3-thiazolidine-2-thiones [4(*S*)-IPTT and 4(*S*)-ETT] proved to be excellent chiral auxiliaries for chiral aldol-type reactions of acetic acid with α,β-unsaturated aldehydes.

Scheme II



Scheme III[a]



[a] (a) TBDMS-chloride, imidazole, CH_2Cl_2, 0 °C; (b) *O*-benzylhydroxylamine hydrochloride, Et_3N, CH_2Cl_2; (c) Bu_4NF, THF; (d) Ph_3P, DEAD, THF.

Finally, we synthesized a chiral β-lactam **16** [colorless oil, $[\alpha]^{20}_D$ +49.9° (*c* 0.85, $CHCl_3$)] by utilizing active amide **9c**, which is shown in Scheme III.[12]

Registry No. **6a**, 101979-44-6; **6b**, 101979-45-7; **7a**, 104-55-2; **7b**, 78-85-3; **7c**, 107-86-8; **9a**, 101979-46-8; **9b**, 101979-47-9; **9c**, 101979-48-0; **9d**, 101979-49-1; **9e**, 101979-50-4; **10a**, 101979-51-5; **10b**, 101979-52-6; **10c**, 101997-90-4; **10d**, 101979-53-7; **10e**, 101979-54-8; **11**, 101979-55-9; **13**, 98290-54-1; **14**, 101979-56-0; **15**, 101979-57-1; **16**, 101979-58-2; 4(*S*)-ETT, 42163-68-8; 4(*S*)-IPTT, 76186-04-4; (*R*)-$PhCH_2ONHC(O)CH_2CH(OSiMe_2$-*t*-Bu)$CH{=}C(CH_3)_2$, 101979-59-3; (*R*)-$PhCH_2ONHC(O)CH_2CH(OH)CH{=}C(CH_3)_2$, 101979-60-6; 2(*S*)-amino-1-butanol, 5856-62-2; 2(*S*)-amino-3-methyl-1-butanol, 2026-48-4; 3-[1-oxo-3(*R*)-[(*tert*-butyldimethylsilyl)oxy]-5-methylhex-4-enyl]-4(*S*)-ethyltetrahydrothiazole-2-thione, 101997-91-5.

(10) (a) Nagao, Y.; Ikeda, T.; Yagi, M.; Fujita, E.; Shiro, M. *J. Am. Chem. Soc.* **1982**, *104*, 2079. (b) Nagao, Y.; Inoue, .; Fujita, E.; Terada, S.; Shiro, M. *J. Org. Chem.* **1983**, *48*, 132.

(11) Nagao, Y.; Yamada, S.; Hagiwara, Y.; Hasegawa, Y.; Ochiai, M.; Shiro, M.; Fujita, E., to be published.

(12) Cf. (a) Mattingly, P. G.; Kerwin, J. F. Jr.; Miller, M. J. *J. Am. Chem. Soc.* **1979**, *101*, 3983 and ref 5.

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