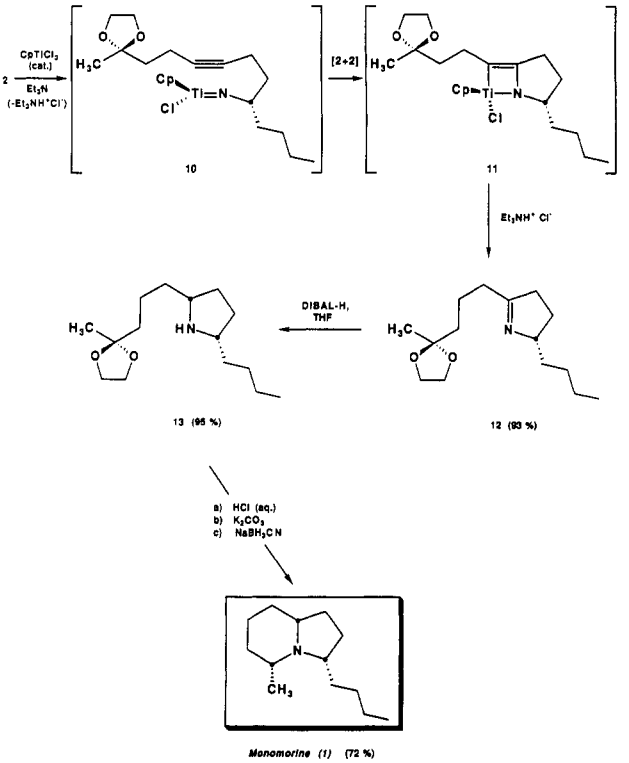
pyrroline **12** *in 93% isolated yield* by way of a [2 + 2] cycloaddition sequence involving the transient imido complex **10** and the titanetine **11**.[7] The latter transformation is most prominently characterized by its extraordinary facility and functional group compatibility. The stereoselective reduction of **12** to the *cis*-pyrrolidine **13** was efficiently accomplished by exposure to DIBALH (4 equiv, THF, $-78 \rightarrow 0$ °C) in 95% yield. The conversion of pyrrolidine **13** into (±)-monomorine (**1**) was subsequently achieved by the procedure of Stevens and Lee.[9b] Accordingly, hydrolysis of the 1,3-dioxolane moiety of **13** (aq HCl–THF) followed by treatment with K_2CO_3 and immediate reduction (THF, $NaBH_3CN/CH_3OH$, 5% aq HCl) furnished (±)-monomorine (**1**) in 72% overall yield from **13**. The spectroscopic (^1H NMR, ^{13}C NMR, IR, and mass spectral) characteristics of synthetic **1** that was prepared in the above manner were identical in all respects to those reported for synthetic[9] samples of the alkaloid.

In summary, a catalytic imidotitanium–alkyne [2 + 2] cycloaddition has been successfully exploited as the key transformation in an efficient (53% overall yield from the point of convergence) total synthesis of the indolizidine alkaloid (±)-monomorine (**1**). The utilization of this and related transition-metal-based methodologies for the synthesis of more structurally intricate ring systems will be described in future accounts from these laboratories.



(14) *Experimental procedure for the preparation of* (±)-**2-butyl-3,4-dihydro-5-[4,4-(ethylenedioxy)pentyl]-2*H*-pyrrole** (**11**). To Et_3N (260 μL, 1.9 mmol) and $CpTiCl_3$ (208 mg, 0.95 mmol) in THF (10 mL) at 25 °C was added **2** (1.20 g, 4.74 mmol) in THF (10 mL). After 1 h, 5% methanolic NaOH (4 mL) was added, and the reaction mixture was brought to dryness. The residue was triturated with hexane (3 × 10 mL) which was then filtered through powdered K_2CO_3. Concentration of the filtrate yielded **11** (1.12 g, 93%) as a slightly colored oil: ^1H NMR (300 MHz, $CDCl_3$) δ 3.88 (m, 4 H, OCH_2CH_2O), 2.55–2.2 (m, 5 H, $N{=}C(CH_2)_2$, NCH), 2.1–1.7 (m, 1 H), 1.7–1.55 (m, 5 H), 1.45–1.1 (m, 9 H), 0.86 (m, J = 7, 3 H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.70, 109.83, 72.48, 64.56, 38.71, 36.81, 36.36, 33.90, 28.82, 28.55, 23.69, 22.80, 21.14, 14.02; IR (film) 2956, 2928, 2872, 1644, 1458, 1376, 1256, 1218, 1132, 1060; high-resolution mass spectrum calcd for $C_{15}H_{27}NO_2$ (M^+) 253.2042, found 253.2034.

Acknowledgment. Support for this research by grants from the Alfred P. Sloan Foundation, the Petroleum Research Fund administered by the American Chemical Society and the National Science Foundation is gratefully acknowledged.

Supplementary Material Available: Experimental procedures complete with spectroscopic data as well as ^1H and ^{13}C NMR spectra (26 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Stereoselective Synthesis of Both Diastereomers of the α-Methyl-β-hydroxy-β-alkyl(aryl) Units by Use of Tin(II) Triflate-Mediated Aldol Reaction

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Summary: Both diastereomers of the α-methyl-β-hydroxy-β-alkyl(aryl) units are prepared by the tin(II) triflate-mediated aldol reaction of 1-(ethylthio)-1-(trimethylsiloxy)propene with α-keto esters in high selectivities.

Recently, a series of pyrrolizidine alkaloids has attracted much attention due to their potent hepatotoxic, carcinogenic, and mutagenic properties.[1] These alkaloids, especially 11- or 12-membered pyrrolizidine dilactones such as integerrimine, senecionine, fulvine, crispatine, etc., possess unique common structures of the α-methyl-β-hydroxy-β-alkyl units, and rather complicated multistage transformations have often been required for the stereoselective construction of these successive asymmetric centers including quaternary carbons.[2] In the course of our investigations to develop novel efficient synthetic routes to pyrrolizidine alkaloids, we were confronted with the above problem. In this paper, we would like to describe a general method for the preparation of both diastereomers of the α-methyl-β-hydroxy-β-alkyl(aryl) units by using the tin(II) triflate-mediated aldol reaction and to discuss a unique character of tin(II) triflate as a Lewis acid in order to realize the high diastereoselectivities. Enantioselective

(1) Robins, D. J. *Fortschr. Chem. Org. Naturst.* **1982**, *41*, 115 and references cited therein.

(2) For the recent synthesis of pyrrolizidine alkaloids: Mulzer, J.; Kirstein, H. M.; Buschmann, J.; Lehmann, C.; Luger, P. *J. Am. Chem. Soc.* **1991**, *113*, 910. Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367. White, J. D.; Jayasinghe, L. R. *Ibid.* **1988**, *29*, 2139. Niwa, H.; Miyachi, Y.; Uosaki, Y.; Yamada, K. *Ibid.* **1986**, *27*, 4601. Narasaka, K.; Sakakura, T.; Uchimaru, T.; Guēdin-Vuong, D. *J. Am. Chem. Soc.* **1984**, *106*, 2954 and references cited therein.

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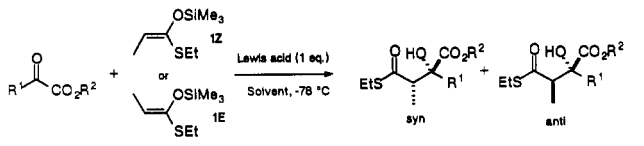
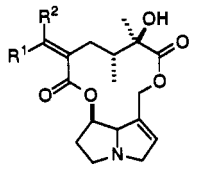
Table I. Effect of Lewis Acids (R^1 = Ph, R^2 = Me, Solvent: CH_2Cl_2)

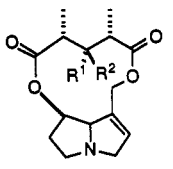


entry	Lewis acid		yield/%	syn/anti
1	$TiCl_4$	*Z*	79	28/72
2		*E*	88	30/70
3	$SnCl_4$	*Z*	79	28/72
4		*E*	90	34/66
5	BF_3OEt_2	*Z*	41	23/77
6		*E*	18	43/57
7	$EtAlCl_2$	*Z*	88	38/62
8		*E*	86	38/62
9	$Sn(OTf)_2$	*Z*	91	83/17
10		*E*	89	22/78

synthesis of the α-methyl-β-hydroxy-β-alkyl units is also reported.



integerrimine (R^1=H, R^2=Me)
senecionine (R^1=Me, R^2=H)



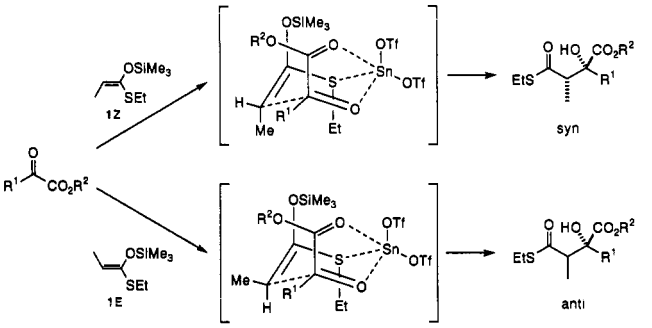
fulvine (R^1=OH, R^2=Me)
crispatine (R^1=Me, R^2=OH)

We intended to construct the α-methyl-β-hydroxy-β-alkyl(aryl) units by the stereoselective aldol reaction of the enolate components derived from propionic acid derivatives with α-ketoesters.[3] First, the lithium enolate, prepared from *S*-ethyl propanethioate and LDA in THF according to the conventional procedure, was allowed to react with methyl phenylglyoxylate. The reaction smoothly proceeded at −78 °C to give the corresponding aldol-type adduct in 80% yield; however, the diastereoselectivity was low (syn/anti = 47/53). Second, the Lewis acid-mediated aldol reaction[4] was examined by serving the reaction of (*Z*)-1-(ethylthio)-1-(trimethylsiloxy)propene (1*Z*)[5] with methyl phenylglyoxylate as a model system. After screening several Lewis acids, it was made clear that the anti aldol-type adduct was obtained in moderate diastereoselectivity by employing the typical Lewis acid such as $TiCl_4$, $SnCl_4$, BF_3OEt_2, or $EtAlCl_2$, etc., while the syn aldol-type adduct was predominantly produced in good yield when tin(II) triflate (tin(II) trifluoromethanesulfonate, $Sn(OTf)_2$)[6] was used as a Lewis acid. On the other hand, in the reaction of (*E*)-1-(ethylthio)-1-(trimethylsiloxy)-propene (1*E*),[7] the anti aldol-type adduct was preferentially obtained by employing every Lewis acid shown in Table I including $Sn(OTf)_2$. It is noteworthy to refer that, in the case of the tin(II) triflate-mediated reaction, the stereoselectivity depends on the geometry of the silyl enol ether and both diastereomers are prepared starting from *Z* and *E* isomers, while the anti aldol-type adduct was obtained independent of the geometry of the silyl enol ether in the cases when the other typical Lewis acids were employed (Table I). Furthermore, the diastereoselectivity was improved by using propionitrile as a solvent[8] instead of dichloromethane. Several examples of this reaction are listed in Table II, and in every case, syn aldol-type products are obtained from the (*Z*)-silyl enol ether, while anti isomers are produced from the (*E*)-silyl enol ether.[9]

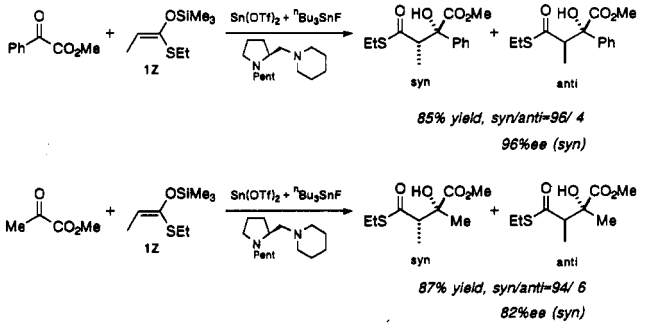
Table II. Synthesis of Syn and Anti 2,3-Disubstituted Malates (Lewis Acid = $Sn(OTf)_2$)

entry	R^1	R^2	solvent		yield/%	syn/anti
1	Me	Me	CH_2Cl_2	*Z*	84	90/10
2	Me	Me	CH_2Cl_2	*E*	81	9/91
3	Me	Et	C_2H_5CN	*Z*	89	91/9
4	Me	Et	C_2H_5CN	*E*	88	9/91
5	Ph	Me	C_2H_5CN	*Z*	95	96/4
6	Ph	Me	C_2H_5CN	*E*	71	10/90

Scheme I



Scheme II



The present tin(II) triflate-mediated aldol reaction is proposed to proceed via the cyclic (chelated) transition states shown in Scheme I. It is known that most of the

(3) To our knowledge, there was no example of the stereoselective aldol reaction of propionate derivatives with α-keto esters before this report. Quite recently, stereoselective addition reaction of crotylboronates with α-oxocarboxylic acids have been reported: Wang, Z.; Meng, X-J.; Kabalka, G. W. *Tetrahedron Lett.* **1991**, *32*, 5677.

(4) Mukaiyama, T. *Org. React.* **1982**, *28*, 203.

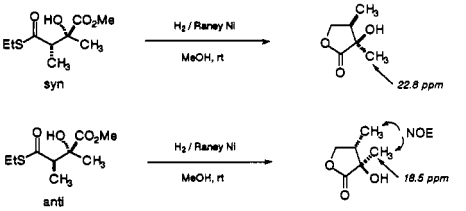
(5) *Z*/*E* = 96/4. The stereochemical descriptors *Z* and *E* of silyl enol ethers derived from thioesters are opposite to those of silyl enol ethers derived from ketones and esters due to change of sequence rule priority associated with sulfur atom.

(6) Cf. Mukaiyama, T.; Iwasawa, N.; Stevens, R. W.; Haga, T. *Tetrahedron* **1984**, *40*, 1381. See also ref 16.

(7) *Z*/*E* = 6/94.

(8) Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem. Lett.* **1990**, 1455.

(9) A typical experimental procedure is described for the reaction of (*Z*)-1-(ethylthio)-1-(trimethylsiloxy)propene (1*Z*) with methyl pyruvate: to a dichloromethane solution (1 mL) of tin(II) triflate (0.38 mmol) was added a mixture of 1*Z* (0.4 mmol) and methyl pyruvate (0.36 mmol) in dichloromethane (1.5 mL) at −78 °C. The mixture was stirred at this temperature for 4 h and then poured into aqueous saturated sodium hydrogen carbonate. After usual workup, the crude product was chromatographed on silica gel to afford the pure aldol-type adduct in 84% yield (syn/anti = 90/10. The diastereomers were separated). Relative configuration assignments were made after derivation to the γ-butyrolactones by comparison of the ^{13}C NMR chemical shifts of the methyl groups. This assignment was supported by the observation of NOE in the lactone derived from the anti isomer.



aldol reactions of silyl enolates with carbonyl compounds proceed via the acyclic (nonchelated) transition states.[10] In the present case, the use of tin(II) triflate as a promoter is essential for the cyclic transition states,[11] and one of the most characteristic points in these transition states is that the divalent tin predominantly coordinates to the sulfur atom rather than the oxygen atom of the enolates,[12] forming the six-membered transition state consisting of three carbon, oxygen, sulfur, and tin atoms. Consequently, syn aldols are obtained from (*Z*)-enolates while anti aldols from (*E*)-enolates, *which are opposite selectivities to those observed in the conventional cyclic transition states in the aldol reaction.*[13-15]

Finally, enantioselective synthesis of α-methyl-β-hydroxy-β-methyl units was surveyed by using a chiral tin(II) promoter.[16] When 1*Z* was treated with methyl phenylglyoxylate in the presence of tin(II) triflate, (*S*)-1-pentyl-2-[(piperidin-1-yl)methyl]pyrrolidine, and tributyltin fluoride, the reaction smoothly proceeded to give the syn isomer in high yield with high diastereo- and enantioselectivities. Similarly, 1*Z* smoothly reacted with methyl pyruvate to give the corresponding syn adduct in high ee (Scheme II). On the other hand, 1*E* reacted with methyl phenylglyoxylate or methyl pyruvate very slowly under the same reaction conditions.[17]

In summary, a novel general method for the preparation of the α-methyl-β-hydroxy-β-alkyl(aryl) units including their optically active forms has been developed by use of the tin(II) triflate-mediated aldol reaction of 1-(ethylthio)-1-(trimethylsiloxy)propene with α-keto esters. In the course of this study, a unique character of tin(II) triflate as a Lewis acid to realize high selectivities has also been found.

Further progress to apply the present methodology to the synthesis of pyrrolizidine alkaloids as well as to utilize the unique character of tin(II) triflate as a Lewis acid are now under investigation.

Acknowledgment. The authors are grateful to Professor Teruaki Mukaiyama, Science University of Tokyo, for his helpful discussion.

Supplementary Material Available: Experimental procedures (2 pages). Ordering information is given on any current masthead page.

(10) Heathcock, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, 3027. Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44*, 4259 and references cited therein. The cyclic transition states in the reaction of ketene silyl acetals with aldehydes were reported: Chan, T. H.; Aida, T.; Lau, P. W. K.; Gorys, V.; Harpp, D. N. *Tetrahedron Lett.* **1979**, *20*, 4029. Gong, L.; Streitwieser, A. *J. Org. Chem.* **1990**, *55*, 6235.

(11) Other Lewis acid ($TiCl_4$, $SnCl_4$, BF_3OEt_2, $EtAlCl_2$) mediated reactions would proceed via the acyclic transition states: Gennari, C.; Beretta, M. G.; Bernardi, A.; Moro, G.; Scolastico, C.; Todeschini, R.; *Tetrahedron* **1986**, *42*, 893.

(12) Yura, T.; Iwasawa, N.; Narasaka, K.; Mukaiyama, T. *Chem. Lett.* **1988**, 1025.

(13) Heathcock, C. H. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Part B, Chapter 2. Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

(14) In the recent report on the diastereoselective aldol reactions using β-keto imide derived tin(II) enolates, four-coordinated tin(II) is postulated: Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866. See also ref 15.

(15) For five-coordinated tin(II): Shields, K. G.; Seccombe, R. C.; Kennard, C. H. L. *J. Chem. Soc., Dalton Trans.* **1973**, 741. See also: Mukaiyama, T.; Kobayashi, S.; Uchiro, H.; Shiina, I. *Chem. Lett.* **1990**, 129.

(16) The aldol reactions of the acetic acid enolates with α-keto esters for the synthesis of 2-substituted malates including their optically active forms were reported. Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem. Lett.* **1989**, 2069.

(17) Similar results had also been observed in the reactions of 1*Z* and 1*E* with achiral aldehydes. These enantioselective reactions may not proceed via the six-membered cyclic transition state shown in Scheme I, probably due to the strong coordination of the chiral diamine to tin(II) metal.[18]

(18) Kobayashi, S.; Uchiro, H.; Fujishita, Y.; Shiina, I.; Mukaiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 4247.

Stereocontrolled Formation of Cis and Trans Ring Junctions in Hydrindane and Decalin Systems by Palladium-Catalyzed Regioselective and Stereospecific Hydrogenolysis of Allylic Formates

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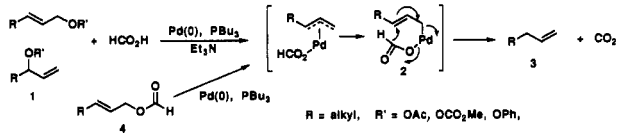
Summary: Both cis and trans ring junctions can be generated selectively in hydrindane, decalin, and steroid systems by the palladium-catalyzed regioselective and stereospecific hydrogenolysis of allylic formates.

Stereocontrolled generation of cis or trans ring junctions in hydrindane or decalin derivatives is a desirable but elusive synthetic goal. An elegant method for stereospecific generation of cis and trans ring junctions via free-radical cyclization using stereo-defined allylic alcohols in decalin and hydrindane systems has been reported.[1] In this case, however, a carbon unit is introduced. We now wish to report a solution to this general problem based on π-allylpalladium chemistry. We have reported that the palladium-catalyzed hydrogenolysis of terminal allylic compounds **1** with ammonium formate proceeds regioselectively to afford 1-olefins **3**.[2] This regioselective hydrogenolysis can be explained by the attack of the hydride generated from σ-allylpalladium formate **2** on the more substituted end of the allylic system to afford terminal olefins **3**. We also found that allylic formates **4** can be used for the same transformation without use of ammonium formate.



We hoped to apply this regioselective hydrogenolysis reaction to hydrindane and decalin systems, expecting high regio- and stereoselectivities, if the hydride attacks the

(1) (a) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500. (b) Stork, G.; Sofia, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 6826.

(2) (a) Tsuji, J.; Yamakawa, T. *Tetrahedron Lett.* **1979**, 613. (b) Tsuji, J.; Shimizu, I.; Minami, I. *Chem. Lett.* **1984**, 1017.

0022-3263/92/1957-1326$03.00/0