Asymmetric Synthesis of Functionalized Tertiary Homoallyl Alcohols by Diastereoselective Allylation of Chiral α-Keto Amides Derived from (*S*)-Proline Esters. Control of Stereochemistry Based on Saturated Coordination of Lewis Acid

Kenso Soai* and Miyuki Ishizaki

Department of Applied Chemistry, Faculty of Science, Science University of Tokyo, Kagurazaka, Shinjuku-ku, Tokyo 162, Japan

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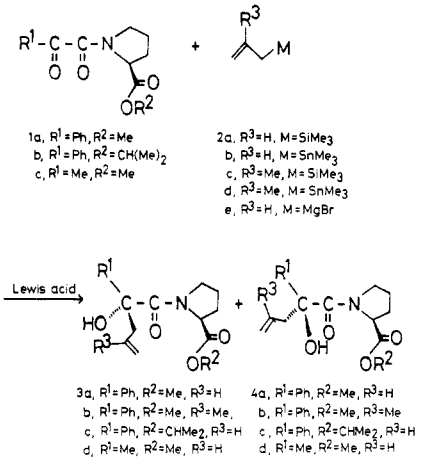
Diastereoselective additions of allylsilanes and -stannanes to chiral α-keto amides **1a–c** derived from esters of (*S*)-proline in the presence of Lewis acids afforded optically active tertiary homoallyl alcohols of high diastereomeric excesses (up to 92% de). Reaction conditions were examined in detail. The order of the effectiveness of Lewis acids on diastereoselectivity was $SnBr_4 > SnCl_4 > TiCl_4 > BF_3{\cdot}OEt_2 >> AlCl_3$. At least 3 mol equiv of $SnCl_4$ were required to achieve the high diastereoselection. The coordination of Lewis acids with the oxygen atom(s) of **1** may be one of the reasons for the high diastereoselectivity. When $SnCl_4$ was used, dichloromethane was the best solvent. In the case of $TiCl_4$, a heterogeneous reaction mixture in *n*-hexane and CH_2Cl_2 led to higher diastereoselectivity than a homogeneous solution in CH_2Cl_2 alone. Both allylsilane and -stannane led to homoallyl alcohols of predominant *R* configuration. The reaction was faster with allylstannane than with allylsilane. Allylation with allylmagnesium bromide showed the opposite diastereoselectivity. From a study of the effect of temperature, the enthalpy factor was found to be more important than the entropy factor. Some of the diastereomers (**3a,b**) were found to cyclize spontaneously to afford the corresponding lactones (**5a,b**). This lactonization process was highly stereoselective. Compounds **5a,b** were separated from **4a,b**, respectively, by preparative TLC. Removal of the chiral auxiliaries by methyllithium afforded essentially enantiomerically pure acyloins (**6** and **9**) (>98% ee) of both enantiomers.

Increasing interest has recently been centered on asymmetric synthesis.[1] Concerning allylation of carbonyl compounds, enantioselective allylation of prochiral aldehydes with chiral allylboranes,[2a–d] allylsilanes,[2e,f] allylstannanes,[2g,h] and allyldialkylaluminum derivatives[2i] affords simple secondary homoallyl alcohols in moderate to high enantiomeric excesses. As to diastereoselective allylation of chiral aldehydes, control of relative stereochemistry has been reported (1,2- and 1,3-asymmetric induction).[3] However, most of the products are optically *inactive* because the starting aldehydes are usually racemic. Only few reports have appeared on diastereoselective asymmetric allylation of optically active ketones to afford optically active diastereomers.[4] Allylation with allyltrimethylsilane in the presence of $TiCl_4$ of chiral menthyl phenylglyoxylate causes moderate diastereomeric induction [23–56% diastereomeric excesses (de)].[4,5]

Scheme I



Meanwhile, a few reports have appeared on the asymmetric syntheses of tertiary α-hydroxy ketones using Grignard reagents or the lithium derivative of formamide.[6]

In connection with our continuing study on asymmetric synthesis using proline[7] or cystine[8] derivatives as chiral auxiliaries, we recently reported diastereoselective reductions of chiral α-keto amides derived from (*S*)-proline esters.[9]

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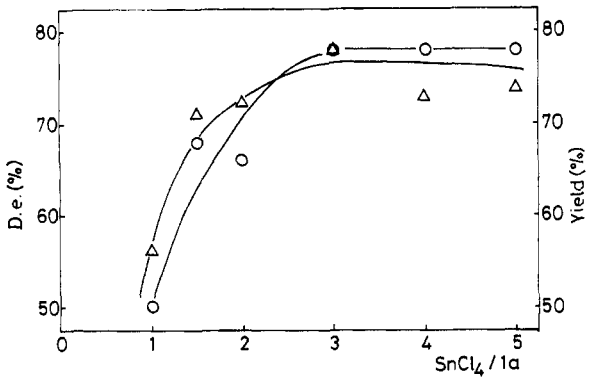


Figure 1. Effect of molar ratio of Lewis acid ($SnCl_4$) to **1a** on diastereoselectivity (○) and yield (△) in diastereoselective allylation of **1a** with **2a** using $SnCl_4$.

In this paper, we describe the diastereoselective allylations of chiral α-keto amides **1a–c** derived from (*S*)-proline esters with allylsilanes, -stannanes, and -magnesium bromide **2a–e** in the presence of Lewis acids (1,4-asymmetric induction)[10] (Scheme I).

The present approach originates from the consideration that minimizing the number of possible transition states is essential for high diastereoselection. Utilization of coordination effect of metal salts with oxygen atoms has often been found suitable for this purpose.

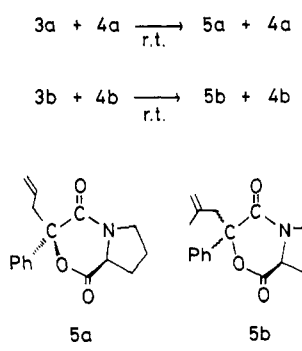
Results and Discussions

Chiral α-keto amides **1a–c** were synthesized from the corresponding α-keto acids and esters of (*S*)-proline by using dicyclohexylcarbodiimide (DCC).[9] The ketone carbonyl of **1** was diastereoselectively allylated with various organometallic reagents in the presence of Lewis acids. As a model compound, compound **1a** was chosen, and various conditions (Lewis acids, solvents, allylating agents, molar ratios of reagents, and temperatures) were examined. Diastereomeric excesses (de) were determined by GLC (capillary column) analyses of the reaction mixtures.

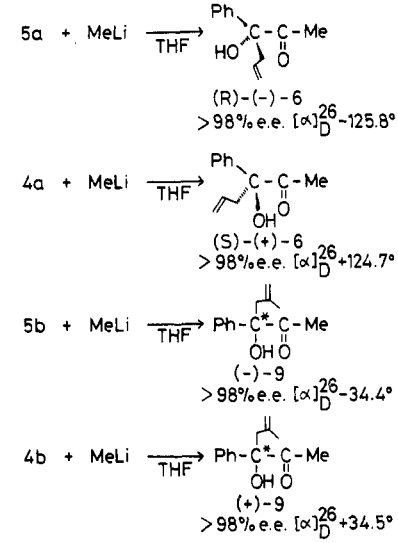
Effect of Lewis Acid, Solvent, and Allylating Agent. The effect of various Lewis acids is summarized in Table I. Their order of effectiveness is $SnBr_4 > SnCl_4 > TiCl_4 > BF_3{\cdot}OEt_2 >> AlCl_3$. Both tin tetrachloride ($SnCl_4$) and tin tetrabromide ($SnBr_4$) catalyzed high diastereoselectivity in allylation of **1a**. The configuration of the predominant homoallyl alcohol was determined to be *R* (vide infra). The diastereomeric excess was found to be as high as 92% (entry 26). Although reaction with $SnBr_4$ was slower than with $SnCl_4$, the de was generally higher with $SnBr_4$. The selectivity of $TiCl_4$ in CH_2Cl_2 was only moderate but higher in a heterogeneous reaction mixture (mixed solvent of *n*-hexane and CH_2Cl_2, entry 5) than in a homogeneous one (solvent CH_2Cl_2 only, entry 2). The reaction was very slow with $BF_3{\cdot}OEt_2$; stereoselectivity was moderate. With $AlCl_3$, low stereoselectivity was observed.

As to the effect of allylating agents, allylsilane and -stannane showed comparable stereoselectivity; however, allylstannane was more reactive.[11] Thus the synthetic yield and de reached 89% and 97:6 with $SnBr_4$ and allylstannane. Diastereoselectivities were higher with simple allylating reagents than with substituted ones such as methallyl reagents. Interestingly, allylmagnesium bromide showed opposite diastereoselectivity to that of allylsilanes and -stannanes.

Scheme II



Scheme III



Effect of the Molar Ratio of Lewis Acid and Temperature. The molar ratio of $SnCl_4$ to **1a** had a considerable effect on the diastereoselectivities and synthetic yields considerably. As shown in Figure 1, both synthetic yield an de were only moderate when equimolar amounts of $SnCl_4$ and **1a** were used. However, stereoselectivities increased with increase in the mole ratio of $SnCl_4$; 3 mol equiv of $SnCl_4$ suffices to achieve maximum stereoselectivity, and further excess was not helpful. The optimum for the high diastereoselectivities and synthetic yields was found to be 3 mol equiv of $SnCl_4$.

With regard to temperature effects, high diastereoselectivity (92% de) was attained at low temperature (−100 °C). Moreover, a linear relation was observed between ln [(*R*,*S*)/(*S*,*S*)] and the reciprocal of the temperature, $1/T$, from +30 to −100 °C. Thus, in this system, enthalpy factors appear to determine the free-energy difference in diastereomeric transition states. By plotting ln [(*R*,*S*)/(*S*,*S*)] against $1/T$, the difference in the activation energy of the present diastereoselective reaction was estimated to be 1.0 kcal/mol.

Stereoselective Cyclization of Diastereomers 3a,b to Lactones 5a,b and Conversion to Enantiomerically Pure Acyloins of Both Configurations. During the workup of the allylation product of **1a**, it was found that one of the diastereomers formed (**3a**) cyclized readily to the lactone **5a** whereas the other (**4a**) remained unchanged

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(10) Preliminary communication: Soai, K.; Ishizaki, M. *J. Chem. Soc., Chem. Commun.* **1984**, 1016.

(11) Double bond of allylstannane is known to be more nucleophilic than that of allylsilane. Hartman, G. D.; Traylor, T. G. *Tetrahedron Lett.* **1975**, 939. The different nucleophilicity of these reagents is explained by the first ionization potential of allylstannanes being lower than that of the corresponding allylsilanes: Weidner, U.; Schweig, A. *J. Organomet. Chem.* **1972**, *39*, 261. Brown, R. S.; Eaton, D. F.; Hosomi, A.; Traylor, T. G.; Wright, J. M. *Ibid.* **1974**, *66*, 249.

Table I. Diastereoselective Allylation of 1a with 2a–e

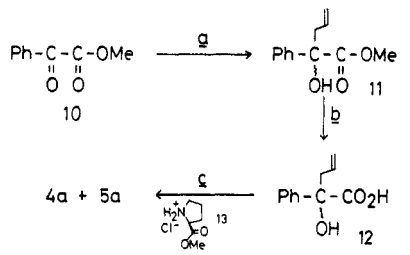
entry	2	Lewis acid	temp,[f] °C	solvent	time, h	yield,[a] %	molar ratio,[b] 3(5):4
1	a	$TiCl_4$	0	CH_2Cl_2	1	84	49:51
2	a	$TiCl_4$	−40	CH_2Cl_2	3	69	62:38
3[c]	a	$TiCl_4$	−40	CH_2Cl_2	1	71	64:36
4	a	$TiCl_4$	−40	CH_3CH_2Cl	3	70	72:28
5	a	$TiCl_4$	−40	mix[d]	3	72	89:11
6	a	$TiCl_4$	−78	CH_2Cl_2	6	56	76:24
7	a	$TiCl_4$	−78	Mix[d]	5	13	86:14
8	b	$TiCl_4$	−78	CH_2Cl_2	5	(96)	82:18
9	a	$AlCl_3$	−40	CH_2Cl_2	3	71	73:27
10	a	$BF_3{\cdot}OEt_2$	rt → reflx	CH_2Cl_2	12	e	80:20
11	a	$BF_3{\cdot}OEt_2$	−40 → rt	CH_2Cl_2	24	5	83:17
12	a	$SnCl_4$	30	CH_2Cl_2	1	81	86:14
13	a	$SnCl_4$	0	CH_2Cl_2	3	78	89:11
14	a	$SnCl_4$	0	$CHCl_3$	3	0	
15	a	$SnCl_4$	0 → rt	$CHCl_3$	5	(3)	87:13
16	a	$SnCl_4$	0 → rt	CCl_4	5	(51)	74:26
17	a	$SnCl_4$	0	CH_2ClCH_2Cl	3	65	86:14
18	a	$SnCl_4$	0	$CH_2ClCHCl_2$	2	43	82:18
19	a	$SnCl_4$	0	$C_6H_5CH_3$	3	43	88:12
20	a	$SnCl_4$	10	C_6H_6	3	(66)	87:13
21	a	$SnCl_4$	−40	CH_2Cl_2	3	44	91:9
22	a	$SnCl_4$	−40	mix[d]	2	30	88:12
23	a	$SnCl_4$	−78	CH_2Cl_2	4	36	94:6
24[c]	a	$SnCl_4$	−78	CH_2Cl_2	4	28	93:7
25	b	$SnCl_4$	−78	CH_2Cl_2	5	(78)	89:11
26	b	$SnCl_4$	−100	CH_2Cl_2	7	46	96:4
27	a	$SnBr_4$	0	CH_2Cl_2	24	55	94:6
28	a	$SnBr_4$	0 → rt	mix[d]	47	19	93:7
29	a	$SnBr_4$	−40 → rt	CH_2Cl_2	44	59	92:8
30	b	$SnBr_4$	−20 → rt	CH_2Cl_2	24	89	94:6
31	e		−78	Et_2O	3	46	38:62
32	c	$TiCl_4$	−78	CH_2Cl_2	1	63	72:28
33	d	$TiCl_4$	−78	CH_2Cl_2	1	85	72:28
34	c	$SnCl_4$	−78	CH_2Cl_2	6	(50)	56:44
35	d	$SnCl_4$	−78	CH_2Cl_2	6	(49)	58:42
36	c	$SnBr_4$	−20 → rt	CH_2Cl_2	24	90	65:35
37	d	$SnBr_4$	−20 → rt	CH_2Cl_2	24	99	60:40

[a] Isolated total yields of 3 and 5. Yields parentheses are those determined by GLC. [b] Determined by GLC (capillary column) analyses. [c] Before adding allylsilane, the reaction mixture was refluxed for 30 min. [d] CH_2Cl_2/*n*-hexane, (2:1, v/v). [e] Trace not isolated. [f] Room temperature, rt; reflux, reflx.

under the same conditions (Scheme II). A similar observation was made for the mixture of **3b** and **4b**: Isomer **3b** cyclized quantitatively to **5b** whereas the accompanying **4b** remained untouched. When **4a** and **5a** were treated with methyllithium to remove the chiral auxiliary, opposite enantiomers of the methyl ketone **6** were obtained: (*S*)-(+)-**6** ($[\alpha]^{26}_D$ +124.7°) (for configurational assignment see ref 12) from **4a** and (*R*)-(−)-**6** ($[\alpha]^{26}_D$ −125.8°) from **5a** each in 54% yield (Scheme III). NMR analyses of (+)- and (−)-**6** using a chiral shift reagent [Eu(hfc)$_3$] showed only one peak for the each methyl singlet respectively. Thus both enantiomers of **6** are essentially enantiomerically pure (>98% ee, Scheme III). On the other hand, racemic **6**[12] showed two separated singlet peaks of equal integral in the presence of Eu(hfc)$_3$. This is expected if, as a result of a high degree of kinetic stereoselection, **3a** is cyclized to **5a** whereas its diastereomer **4a** remains unchanged. In a similar manner, essentially enantiomerically pure (−)-**9** and (+)-**9** were obtained from **5b** and **4b**, respectively. Thus the cyclizations of **3a** and **3b** are highly stereoselective.

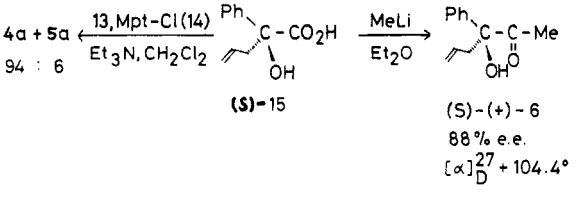
Synthesis of Authentic Diastereomers. The above results were further confirmed by comparisons with racemic and optically active authentic samples. Racemic α-hydroxy acid **12** and a mixture of **4** and **5** were prepared as shown in Scheme IV. Methyl benzoylformate (**10**) was allylated with **2a** by using $TiCl_4$ to give **11**, whose hydrolysis afforded racemic α-allylmandelic acid (**12**). Condensation of **12** with (*S*)-methyl prolinate (**13**) using DCC failed because of the formation of many byproducts. However, dimethylphosphinothioic chloride (Mpt-Cl, **14**),[13]

Scheme IV[a]



[a] (a) $TiCl_4$, **2a**, CH_2Cl_2, −78 °C; (b) KOH, MeOH, room temperature; (c) **13**, $Me_2P(=S)Cl$ (**14**), Et_3N, CH_2Cl_2, 0 °C.

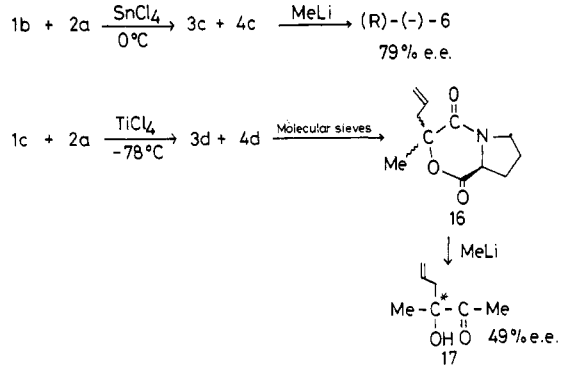
Scheme V



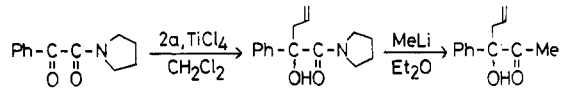
(12) The absolute configuration of **6** was correlated with (*S*)-**15** and was determined as *S*-(+). For the synthesis of racemic **6**, *N*-(benzoylformyl)pyrrolidine (**7**) was allylated with **2a** in the presence of $TiCl_4$ to give **8**. Subsequent reaction of **8** with MeLi afforded racemic **6** (Scheme VII).

(13) Ueki, M.; Inazu, T. *Chem. Lett.* **1982**, 45.

Scheme VI



Scheme VII



a dehydrating reagent known to be compatible with alcoholic hydroxyl groups, cleanly afforded a mixture of **4a** and **5a**. If the cyclization proceeds with a high degree of kinetic stereoselection, the molar amount of **4a** and **5a** should be equal within experimental error. In fact GLC analysis showed a 49.4:50.6 (molar ratio) mixture of **4a** and **5a**.[14] In a similar manner, the corresponding mixture of **4b** and **5b** was prepared by using **2c** instead of **2a**. GLC analysis showed that the ratio of **4b**/**5b** was 49.4:50.6.

Optically active authentic samples were prepared as follows (Scheme V). Optically active (*S*)-α-allylmandelic acid (**15**) was prepared according to the literature procedure.[15] When (*S*)-**15** was reacted with MeLi, (*S*)-**6** was obtained ($[\alpha]^{27}_D$ +104.4°, 88% ee by NMR analysis using Eu(hfc)$_3$). On the other hand, condensation of (*S*)-**15** with **13** (using **14**) afforded a mixture of **5a** and **4a** of 94:6 (by GLC), which corresponds to 88% de. In a similar manner, starting from (*R*)-**15**, (*R*)-**6** (>95% ee by NMR, $[\alpha]^{27}_D$ −119.6°) and a mixture of **5a** and **4a** (1.5:98.5, by GLC, corresponding to 97% de) were obtained. Therefore the absolute configuration at the α-carbon of **5a** (as well as **3a**) and **4a** were determined as *R* and *S*, respectively. These results confirm the stereospecific cyclization of **3a** to **5a**.

Effect of the Structure of Ketone and Ester of 1. Isopropyl ester **1b** was allylated with $SnCl_4$, and unlike in the case of methyl ester **1a**, no cyclization was observed according to NMR analysis. This may be explained by the relatively slower reaction rate of isopropyl as compared to methyl esters. Reaction of MeLi with a diastereomeric mixture of **3c** and **4c** afforded (*R*)-**6** of 79% ee (Scheme VI).

In the case of methyl ketone **1c**, it was not possible to separate cyclic and acyclic allylated products. When the mixture was heated in benzene in the presence of molecular sieves, lactone **16** was obtained in 56% yield. Treatment of **16** with MeLi afforded the corresponding acyloin **17** in 49% ee as determined by NMR using Eu(hfc)$_3$.

We interpret the general difficulty in obtaining a high level of the stereoselectivity with menthyl phenylglyoxylate as mainly due to the presence of various conformations[16]

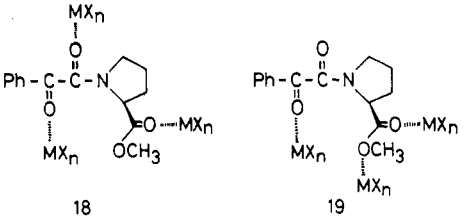


Figure 2.

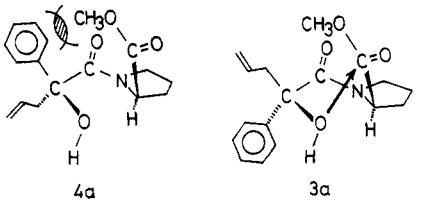


Figure 3. Stereospecific lactonization of **3a**.

that may lead to various competing transition states.

On the other hand, the high diastereoselectivities in the present system may be attributed to the coordination of Lewis acids to the oxygen atom(s) of **1a**. Of the 3 mol equiv of $SnCl_4$ (Figure 1), one is considered to be required to allylate the ketone of **1a**. The other 2 mol equiv may coordinate with the ester and/or amide oxygen atom(s) of **1a**, probably in the manner (**18** or **19**) shown in Figure 2. This *saturated coordination* may reduce the number of possible conformations of **1a**.[17]

As to the stereoselective cyclization of **3a** to **5a**, examination of Dreiding models of **3a** and **4a** show the presence of steric repulsion between the phenyl substituent and the methoxy group of **4a**. Thus only **3a** can cyclize to afford **5a** (Figure 3). Although the number of examples is limited, the present stereoselective cyclization suggests the possibility of a unique optical resolution of tertiary alcohols.

Conclusion

Diastereoselective allylation of chiral α-keto amides **1** was examined by using various allylating reagents in the presence of various Lewis acids. Choice of the appropriate allylating reagent and Lewis acid, the presence of an excess of Lewis acid, and a low reaction temperature were all essential to achieve high diastereoselectivity. Removal of the chiral auxiliary with methyllithium afforded highly enantiomerically pure α-hydroxy ketones **6** and **9**.

Experimental Section

General. Melting and boiling points were uncorrected. IR spectra were recorded with a Hitachi 260-10 spectrophotometer. ^{1}H NMR spectra were taken at 60 MHz by using either a JEOL JMN-PMX-60 spectrometer or a Varian EM-360A spectrometer and are reported parts per million downfield from tetramethylsilane as an internal standard. Mass spectra were measured on Hitachi RMU-7M spectrometer. Optical rotation was obtained by JASCO DIP-181 polarimeter. GLC analysis was carried out with either a Shimadzu GC-4C or a Hitachi 263-70 instrument.

Materials. Allyltrimethylsilane was purchased from Aldrich Chemical Co. or Wako Chemical Co. Allyltrimethylstannane, methallyltrimethylsilane and -stannane were prepared according to the reported method.[18] Methyllithium in Et_2O was purchased

(14) The area ratio of GLC analysis of the mixture of **4a** and **5a** revealed the molar ratio. The area ratio was 53:47 in GLC analysis of a mixture of **4a** and **5a** of molar ratio 53:47 (prepared by mixing pure **4a** and **5a**).

(15) Fráter, Gy.; Müller, U.; Günther, W. *Tetrahedron Lett.* **1981**, *22*, 4221.

(16) The dihedral angle between the carbonyls of menthyl (*p*-bromophenyl)glyoxylate in the crystal is known to vary from 92° to 111°. Parthasarathy, R.; Ohrt, J.; Horeau, A.; Vigneron, J. P.; Kagan, H. B. *Tetrahedron* **1970**, *20*, 4705.

(17) For a chelation effect in asymmetric alkylation of chiral oxo-1,3-oxathiane with Grignard reagents, see: Eliel, E. L.; Soai, K. *Tetrahedron Lett.* **1981**, *22*, 2859.

from Merck, and its activity was measured by the method of Watson and Eastham[19] prior to use. Dichloromethane was purified by the literature procedure[20] and was stored over 4A molecular sieves. Tetrahydrofuran (THF), diethyl ether, and *n*-hexane were distilled from lithium aluminum hydride ($LiAlH_4$) prior to use. Lewis acids were distilled prior to use and were prepared as 1.0 M solution of reaction solvent except for the case of aluminum chloride.

General Procedure for the Diastereoselective Reaction of Allylsilanes and -stannanes 2a–d with Methyl (*S*)-*N*-(Benzoylformyl)prolinate (1a) in the Presence of Lewis Acid (Table I). Preparation of the Mixture of 5 and 4. To a dichloromethane solution (2 mL) of **1a** (0.131 g, 0.5 mmol) under an argon atmosphere was added a 1.0 M Lewis acid solution of dichloromethane (1.5 mL, 1.5 mmol) over a few minutes. After the mixture was stirred for 5 min, **2a–d** (0.75 mmol) in dichloromethane (3 mL) was added to the mixture with sirring being continued for several hours. The reaction was quenched by the addition of pH 7 phosphate buffer solution (5 mL). After the organic layer was separated, the aqueous layer was extracted with dichloromethane (15 mL × 3). The combined extracts were dried over anhydrous sodium sulfate and concentrated on a rotary evaporator. Purification of the residual oil on silica gel TLC (60:1:trace CH_2Cl_2/MeOH/AcOH as developing solvent) afforded the mixture of **5** and **4**.

The ratios of **5** and **4** were determined by GLC analyses. Analytical condition: Silicon SE-30 25-m capillary column; column temperature, 178 °C; flame ionization detector; t_r, (**4a**) 18.3, (**5a**) 15.6, (**4b**) 22.4, (**5b**) 18.4 min.

Reaction of Allylmagnesium Bromide (2e) with Methyl (*S*)-*N*-(Benzoylformyl)prolinate (1a) (Table I, Entry 31). To an ether solution (5 mL) of **1a** (0.131 g, 0.5 mmol) at −78 °C under an argon atmosphere was added **2e** (1.5 mmol) in 2.3 mL of ether over a period of 23 min. After the reaction mixture was stirred for 3 h, the reaction was quenched with saturated aqueous NH_4Cl (5 mL). The usual workup afforded the mixture of **5a** and **4a** (0.070 g, 46%). GLC analysis showed that the ratio of **5a** and **4a** was 62:38.

Separation of 5a or 5b and 4a or 4b. Separation of **5a(b)** and **4a(b)** was performed on preparative silica gel TLC [80:1 (v/v) CH_2Cl_2/MeOH as developing solvent).

(3*R*,8a*S*)-3-Phenyl-3-(2-propenyl)-1,4-dioxo-3,4,6,7,8,8a-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine (5a): IR (KBr) 3025, 2980, 2920, 1760, 1680, 1460 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.63–2.47 (m, 4 H), 2.91 (t, 2 H), 3.43–3.87 (m, 3 H), 4.82–4.93 (m, 2 H), 5.37–6.13 (m, 1 H), 7.34 (s, 5 H); EIMS, *m/e* calcd for $C_{16}H_{17}NO_3$ 271.1209, found 271.1228; mp 103.0 °C.

Methyl (2*S*,1′*S*)-*N*-[(1-hydroxy-1-phenyl-3-butenyl)-formyl]prolinate (4a): IR (KBr) 3350 (OH), 2975, 1745, 1620, 1470, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48–2.25 (m, 4 H), 2.91 (t, 2 H), 3.01–3.53 (m, 2 H), 3.76 (s, 3 H, $COOCH_3$), 4.03–4.78 (m, 1 H), 4.82–5.38 (m, 2 H), 5.40–6.23 (m, 1 H), 7.13–7.65 (m, 5 H); EIMS, *m/e* calcd for $C_{17}H_{21}NO_4$ 303.1471, found 303.1446; mp 113.0 °C. Anal. Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.22; H, 6.96; N, 4.62.

(8a*S*)-3-Phenyl-3-(2-methyl-2-propenyl)-1,4-dioxo-3,4,6,7,8,8a-hexahydro-1*H*-pyrrolo[2,1-*c*][1,4]oxazine (5b): IR (neat) 3080, 2980, 2920, 1760, 1680, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38–3.52 (m, 7 H), 2.88 (dd, 2 H), 3.05–3.82 (m, 3 H), 4.68 (d, 2 H), 7.32 (s, 5 H); EIMS, *m/e* calcd for $C_{17}H_{19}NO_3$ 285.1366, found 285.1336; oil.

Methyl (2*S*)-*N*-[(1-hydroxy-1-phenyl-3-methyl-3-butenyl)formyl]prolinate (4b): IR (KBr) 3350 (OH), 2975, 1745, 1620, 1470, 1450, 1410 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46–2.15 (m, 7 H), 2.53–3.46 (m, 4 H), 3.70 (s, 3 H, $COOCH_3$), 4.10 (s, 1 H, OH), 5.23–5.66 (m, 1 H), 5.82 (d, 2 H), 7.17–7.62 (m, 5 H); EIMS, *m/e* calcd for $C_{18}H_{23}NO_4$ 317.1628, found 317.1621; mp 154.0 °C.

(*R*)-(−)-3-Hydroxy-3-phenyl-5-hexen-2-one (6). To 1.75 mmol of MeLi in 3 mL of THF in an ice–salt bath was added **5a** (0.186 g, 0.69 mmol) in THF (1 mL) over 5 min. The reaction mixture was stirred overnight. Then 3 mL of pH 7 phosphate buffer solution was added to the mixture. After the organic layer was separated, the aqueous layer was extracted with ethyl acetate (10 mL × 5). The combined organic extracts were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The oily residue was purified on preparative silica gel TLC ($CHCl_3$ as developing solvent). Subsequent bulb-to-bulb distillation [160 °C (27 mmHg), bath temperature] afforded (*R*)-(−)-**6** was colorless oil (0.070 g, 54%), $[\alpha]^{26}_D$ −125.8° (*c* 0.865, benzene).

NMR analysis of (*R*)-**6** using the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium-(III) [Eu(hfc)$_3$] showed presence of only one peak of the singlet methyl group: >98% ee; IR (neat) 3460, 3080, 1715, 1650, 1600, 1360 cm^{-1}; ^1H NMR (CCl_4) δ 2.01 (s, 3 H, $COCH_3$), 2.83 (d, 2 H, CH_2), 3.76 (s, 1 H, OH), 4.88–5.33 (m, 2 H, C=CH_2), 5.37–5.88 (m, 1 H, CH=C), 7.09–7.52 (m, 5 H, Ph). NMR and IR spectra were identical with those of racemic **6**.[21]

(*S*)-(+)-3-Hydroxy-3-phenyl-5-hexen-2-one (6). To 1.10 mmol of MeLi in 2 mL of THF in an ice–salt bath was added **4a** (0.106 g, 0.35 mmol) in THF (0.5 mL) was added over 4 min. The same procedure described in the preceding paragraph afforded 0.036 g (54%) of (*S*)-(+)-**6**: $[\alpha]^{26}_D$ +124.7° (*c* 0.635, benzene); >98% ee by NMR analysis using Eu(hfc)$_3$; IR (neat) 3460, 3080, 1715, 1650, 1600, 1360 cm^{-1}; ^1H NMR (CCl_4) δ 2.01 (s, 3 H, $COCH_3$), 2.83 (d, 2 H, CH_2), 3.76 (s, 1 H, OH), 4.88–5.33 (m, 2 H, C=CH_2), 5.37–5.88 (m, 1 H, CH=C), 7.09–7.52 (m, 5 H, Ph). NMR and IR spectra were identical with those of racemic **6**.[21]

(±)-3-Hydroxy-3-phenyl-5-hexen-2-one (6). *N*-(Benzoylformyl)pyrrolidine was allylated with **2a** in the presence of $TiCl_4$ in CH_2Cl_2 in a similar manner as described before. Following reaction with MeLi afforded (±)-**6** in 57% overall yield. NMR and IR spectra were in good accordance with those of the literature.[21] In NMR analysis using Eu(hfc)$_3$, singlet peak of methyl group split into two sets of singlet peaks of equal integration.

(−)-3-Hydroxy-5-methyl-3-phenyl-5-hexen-2-one (9). To 0.93 mmol of MeLi in 1.5 mL of THF in an ice–salt bath was added **5b** (0.066 g, 0.23 mmol) in THF (0.5 mL) over 4 min. The usual workup as described above afforded 0.022 g (46%) of (−)-**9**: $[\alpha]^{26}_D$ −34.4° (*c* 0.593, benzene); $[\alpha]^{26}_{Hg365}$ −151.3° (*c* 0.593, benzene); IR (neat) 3460, 3080, 2980, 1715, 1650, 1610, 1500 cm^{-1}; ^1H NMR (CCl_4) δ 1.60 (s, 3 H, C=CCH_3), 2.01 (s, 3 H, $COCH_3$), 2.85 (dd, 2 H, CH_2), 3.58 (s, 1 H, OH), 4.82 (d, 2 H, CH_2=C), 7.12–7.60 (m, 5 H, Ph); EIMS, *m/e* calcd for $C_{13}H_{14}O$ ($M^+ - H_2O$) 186.1045, found 186.1022 ($M^+ - H_2O$). NMR analysis using Eu(hfc)$_3$ showed only one singlet peak (acetyl group) to be present, >98% ee. In another, the signal of the acetyl group of racemic **9** split into two peaks of equal integral upon addition of Eu(hfc)$_3$.

(+)-3-Hydroxy-5-methyl-3-phenyl-5-hexen-2-one (9). To 0.99 mmol of MeLi in 1.5 mL of THF in an ice–salt bath was added **4b** (0.064 g, 0.20 mmol) in THF (0.5 mL) over 4 min. The same workup as before afforded 0.017 g (43%) of (+)-**9**: $[\alpha]^{26}_D$ +34.5° (*c* 0.580, benzene); $[\alpha]^{26}_{Hg365}$ +151.4° (*c* 0.580, benzene). NMR and IR spectra were identical with those of (−)-**9**, >98% ee, by NMR analysis using Eu(hfc)$_3$.

Condensation of (±)-2-Hydroxy-2-phenyl-4-pentenoic Acid (12) and Methyl (*S*)-Prolinate (13). Preparation of the Mixture of Equimolar Amounts of 4a and 5a. To a mixture of (±)-**12** (0.192 g, 1.0 mmol) and Et_3N (0.102 g, 1.0 mmol) in CH_2Cl_2 was added dimethylphosphinothioic chloride[13] (**14**, Mpt-Cl, 0.13 g, 1.0 mmol) in CH_2Cl_2 (0.5 mL) under an argon atmosphere. The mixture was stirred for 30 min in an ice bath. A mixture of (*S*)-methyl prolinate hydrochloride (**13**, 0.168 g, 1.0 mmol) and Et_3N (0.102 g, 1.0 mmol) in CH_2Cl_2 (0.5 mL) was added to the mixture over a period of 5 min. The reaction mixture was stirred overnight. Then CH_2Cl_2 was removed under reduced pressure, and 10 mL of AcOEt was added to the residue. The resulting suspension was washed with 0.5 M citric acid, water, saturated $NaHCO_3$, water, and brine, successively, and was dried over anhydrous Na_2SO_4. The organic solvent was evaporated under reduced pressure. GLC analysis showed that the molar ratio of **4a**/**5a** was 49.4:50.6 (Silicone SE-30 25-m capillary column; column temperature, 180 °C; flame ionization detector; t_r, (**4a**) 20.8, (**5a**) 16.8 min).

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(21) Chantrapromma, K.; Ollis, W. D.; Sutherland, I. O. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1049.

Preparation of a Mixture of Equimolar Amounts of 4b and 5b. This was performed in a similar manner as described above using methallyltrimethylsilane (**2c**) instead of **2a**. The molar ratio of **4b**/**5b** was 49.4:50.6 by GLC analysis (Silicone SE-30 25-m capillary column; column temperature, 178 °C; flame ionization detector; t_r, (**4b**) 22.4, (**5b**) 18.4 min).

(*S*)-3-Hydroxy-3-phenyl-5-hexen-2-one (6) from (*S*)-15. To an ether solution of (*S*)-**15**[15] (0.077 g, 0.40 mmol) in an ice bath was added MeLi (0.5 mL, 1.0 mmol) under atmoshere of an argon. After the reaction mixture was stirred for 3 h, a phosphate buffer solution (1.5 mL, pH 7) was added. The aqueous layer was extracted with ethyl acetate. The extract was dried over anhydrous Na_2SO_4 and was evaporated under reduced pressure. Purification of oily residue on silica gel TLC ($CHCl_3$ as developing solvent) afforded (*S*)-**6** (0.032 g, 41%), $[\alpha]^{27}_D$ +104.4° (*c* 1.01, benzene), 88% ee by NMR analysis using a chiral shift reagent [Eu(hfc)$_3$].

(*R*)-3-Hydroxy-3-phenyl-5-hexen-2-one (6) from (*R*)-15. In a similar manner, from (*R*)-**15**,[15] (*R*)-**6** was obtained in 40% yield, $[\alpha]^{27}_D$ −119.6° (*c* 0.854, benzene).

Condensation of (*S*)-2-Hydroxy-2-phenyl-4-pentenoic Acid (15) and Methyl (*S*)-Prolinate (13). To a solution of (*S*)-**15**[15] (0.115 g, 0.60 mmol) and triethylamine (0.061 g, 0.60 mmol) in CH_2Cl_2 (1 mL) was added Mpt-Cl (**14**, 0.078 g, 0.61 mmol) in 0.3 ml of CH_2Cl_2 under an argon atmosphere. Then the reaction mixture was cooled in an ice bath and was stirred for 30 min. A mixture of (*S*)-methyl prolinate hydrochloride (**13**, 0.109 g, 0.60 mmol) and Et_3N (0.067 g, 0.66 mmol) in 0.4 mL of CH_2Cl_2 was added to the mixture over a period of 2 min. After the reaction mixture was stirred overnight, the solvent was removed in vacuo. Then 10 mL of ethyl acetate was added and was washed with 0.5 M citric acid, water, saturated $NaHCO_3$, water, and brine, successively. The solvent was dried over anhydrous Na_2SO_4 and was evaporated under reduced pressure. GLC analysis (for the conditions, see the preceding paragraphs) showed that the ratio of **4a**/**5a** was 94:6 (corresponding to 88% de).

Condensation of (*R*)-2-Hydroxy-2-phenyl-4-pentenoic Acid (15) and Methyl (*S*)-Prolinate (13). In a similar manner, condensation reaction of (*R*)-**15**[15] and (*S*)-**13** hydrochloride using Mpt-Cl (**14**) afforded mixture of **4a** and **5a**. GLC analysis showed that the ratio of **4a**/**5a** was 1.5:98.5.

Reaction of Allyltrimethylsilane (2a) with Isopropyl (*S*)-*N*-(Benzoylformyl)prolinate (1b). Preparation of (*R*)-(−)-6. **1b** was made to react with **2a** in the presence of $SnCl_4$ in CH_2Cl_2 at 0 °C. The usual workup as described before afforded **3c** + **4c** in 63%. **3c** + **4c**: IR (neat) 3425 (OH), 3080, 3000, 2900, 1750, 1630, 1460, 1440 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (br, 6 H), 1.45–2.30 (m, 4 H), 2.67–3.67 (m, 4 H), 3.90 (s, 1 H), 4.08–4.58 (m, 1 H), 4.75–5.40 (m, 3 H), 5.45–6.28 (m, 1 H), 7.12–7.62 (m, 5 H); EIMS, *m*/*e* calcd for $C_{19}H_{25}NO_4$ 331.1785, found 331.1776.

MeLi reacted with **3c** + **4c** in a similar manner as described to afford (*R*)-(−)-**6**, 79% ee by NMR analysis with Eu(hfc)$_3$.

Reaction of Allyltrimethylsilane (2a) with Methyl Pyruvoylprolinate (1c). (8a*S*)-3-Methyl-3-(2-propenyl)-1,4-dioxo-3,4,6,7,8,8a-hexahydro-1*H*-pyrrol[2,1-*c*][1,4]oxazine (16). To a dichloromethane solution (6 mL) of **1c** (0.389 g, 1.95 mmol) under an argon atmosphere was added 5.9 mmol of $TiCl_4$ (6.0 mL of 0.99 M CH_2Cl_2 solution) over 8 min. After the mixture was stirred for 5 min, **2a** (0.376 g, 2.9 mmol) in dichloromethane (3 mL) was added to the mixture. Then the reaction mixture was stirred for 3 h. The reaction was quenched with a pH 7 phosphate buffer solution (5 mL). After the organic layer was separated, the aqueous layer was extracted with dichloromethane (15 mL × 3). The combined extracts were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The residue was purified on silica gel TLC (40:1 CH_2Cl_2/MeOH as developing solvent). The mixture obtained was dissolved in benzene and refluxed with 4A molecular sieves for 5 h. Lactonization occurred to form **16** (0.231 g, 56%): IR (KBr) 3000, 1750, 1690, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 3 H), 1.76–2.87 (m, 6 H), 3.45–3.85 (m, 2 H), 4.03–4.42 (m, 1 H), 4.93–5.37 (m, 2 H), 5.47–6.20 (m, 1 H); EIMS, *m*/*e* calcd for $C_{11}H_{15}NO_3$ 209.1053, found 209.1030; mp 113.5–114.5 °C.

3-Hydroxy-3-methyl-5-hexen-2-one (17). To 0.231 g of **16** (1.10 mmol) in 5 mL of THF in an ice–salt bath was added 2.7 mL of methyllithium (4.43 mmol) over 10 min. The reaction mixture was stirred overnight and was quenched with 5 mL of pH 7 phosphate buffer solution. The aqueous layer was extracted with dichloromethane (10 mL × 5). The combined extracts were dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The oily residue was purified by preparative silica gel TLC (CH_2Cl_2 as developing solvent), followed by bulb-to-bulb distillation [105 °C (42 mmHg) bath temperature]. Compound **17** was obtained as a clear oil (0.047 g, 33%). NMR analysis using Eu(hfc)$_3$ showed 49% ee: $[\alpha]^{23}_D$ +31.0° (*c* 0.933, benzene); $[\alpha]^{26}_{Hg365}$ +132.9° (*c* 0.933, benzene); IR (neat) 3475, 3100, 3000, 2960, 1720, 1655 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.28 (s, 3 H, CH_3), 2.17 (s, 3 H, $COCH_3$), 2.37 (d, 2 H, CH_2), 3.42 (s, 1 H, OH), 4.78–5.23 (m, 2 H, C=CH_2), 5.28–5.98 (m, 1 H, CH=C).

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Stereochemistry and Conformation of a Nitrogen-Containing, Medium-Sized Ring: Hexahydro-1-phenyl-3-benzazonine Derivatives. High 1,4-Diastereoselectivity in Hydrogenation of an Exocyclic Alkene

Bruce E. Maryanoff* and Harold R. Almond, Jr.

Chemical Research Department, McNeil Pharmaceutical, Spring House, Pennsylvania 19477

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Hydrogenation of olefin **2** or **4** (as a perchlorate salt) over platinum afforded in each case almost exclusively (at least 95%) one diastereomeric, saturated product, **3** or **5**, respectively. The other diastereomer corresponding to **5** was obtained by sodium/ammonia reductive cleavage of **6**. Stereochemical assignments for **5** and **7** were founded on proton NMR data in conjunction with elaborate conformational analysis assisted by empirical force field calculations (MM2). For this, we have explored the conformational space of this medium-sized ring to find all structures that define local energy minima. Base treatment of **5** (in attempted equilibration) produced a mixture of **7** and ring-opened amine **8**, a retro-Michael product. Although equilibrium is violated by (probably) irreversible formation of **8**, this experiment suggests that **7** is more thermodynamically stable than **5**, a point that is supported by the force field calculations. The diastereofacial selectivity of the hydrogenation is rationalized with the aid of computations (MMP1) on **4**.

Stereochemical control in the generation of specific relative configurations at nonadjacent carbon centers has recently attracted a great deal of interest.[1,2] Classically, such remote asymmetric induction has been successfully

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