unusually facile rearrangement can be expected. This should be the case when an electron-donating substituent is placed on C_4, and indeed there is evidence that such a rearrangement will proceed with ease.[17]

Acknowledgment. We thank Professor K. N. Houk for numerous helpful discussions. We also thank Professor B. K. Carpenter for communication of unpublished results.

(17) (a) Reed, S. F., Jr. *J. Org. Chem.* **1965**, *30*, 1663. (b) Cressin, P.; Buncel, S. *C. R. Hebd. Sceances Acad. Sci. Ser. C* **1968**, *266*, 409. (c) Coates, R. M.; Hobbs, S. J. *J. Org. Chem.* **1984**, *49*, 140 (see ref 20 in this paper).

Unprecedented Regio- and Stereochemical Control in the Addition of Organoaluminum Reagents to Chiral α,β-Unsaturated Acetals

Junya Fujiwara, Yoshimi Fukutani, Masaichi Hasegawa, Keiji Maruoka, and Hisashi Yamamoto*

Department of Applied Chemistry, Nagoya University Chikusa, Nagoya 464, Japan

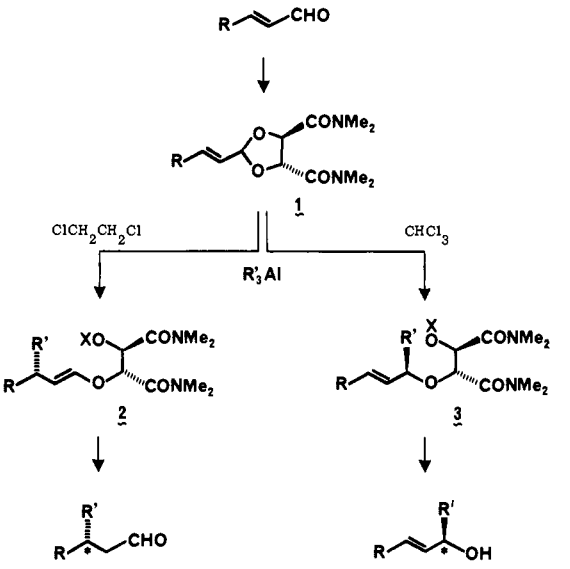
Received May 9, 1984

A highly effective method for the synthesis of optically active alcohols has been recently developed based on a strategy of utilizing a chiral protecting group that is subjected to activation by electrophiles[1] or nucleophiles.[2] Here we wish to report either the nucleophilic 1,4- or 1,2-addition of organoaluminum reagents to chiral α,β-unsaturated acetals with remarkably high asymmetric induction, thus providing an easy access to β-substituted aldehydes or allylic alcohols, respectively, in optically active forms (Scheme I).[3,4]

Chiral α,β-unsaturated acetal **1** was readily accessible by transacetalization of α,β-unsaturated aldehyde diethyl acetal with (*R,R*)-(+)-*N,N,N',N'*-tetramethyltartaric acid diamide[5] in quantitative yield.

The course of the reaction appeared to be highly dependent on the nature of substrates, solvents, and temperature as revealed in Table I. A typical experimental procedure is exemplified by the 1,4-addition of Me_3Al to the acetal **1** (R = *n*-Pr; entry 1). To a solution of the acetal **1** (R = *n*-Pr; 0.5 mmol; $[\alpha]^{18}_D$ −42.69° (*c* 2.15, MeOH)) in 1,2-dichloroethane (10 mL) was added a 2

Scheme I



M hexane solution of Me_3Al (2.5 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 12 h. The mixture was poured into 10% NaOH and extracted with CH_2Cl_2. The combined extracts were concentrated in vacuo to give the crude oil, which was acetylated by using Ac_2O–Py in the presence of catalytic 4-(dimethylamino)pyridine at room temperature for 1 h.[6] Evaporation of excess Ac_2O–Py followed by silica gel column chromatography (MeOH–AcOEt as eluant) of the residue afforded 1,4-adduct **2** (R = *n*-Pr, R' = Me, X = Ac) preferentially in 84% yield accompanied by 13% of 1,2-adduct **3**.[7] The optical purity of the 1,4-adduct **2** was substantiated by GC analysis after converting to the acetal of (−)-2(*R*),4(*R*)-pentanediol (catalytic TsOH, toluene reflux, 2 h; 93%).[8,9] In sharp contrast, however, the use of $CHCl_3$ as sovlent under the comparable conditions gave rise to 1,2-adduct **3** (R = *n*-Pr, R' = Me, X = H) exclusively in 85% yield (entry 7). Cleavage of the 1,2-adduct **3** with potassium *tert*-butoxide in isopropyl alcohol produced (*R*)-(+)-hepten-2-ol, $[\alpha]^{19}_D$ +10.68° (*c* 3.58, $CHCl_3$)[10] in 57% yield, the optical purity of which was determined by GC analysis of the (*S*)-(−)-MTPA ester.[11]

In connection with regio- and stereochemical control, the characteristic features observed in the 1,4-addition of Me_3Al to **1** (R = *n*-Pr) follow (entries 1-7):[12,13] (1) By manipulating the solvents, either addition mode appears feasible. (2) Nonpolar solvents such as toluene produced higher diastereofacial selectivity at the expense of regiocontrol than polar solvents such as 1,2-dichloroethane. (3) The high optical yield (~95% ee) was ob-

(1) (a) McNamara, J. M.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7371. (b) Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *Ibid.* **1983**, *105*, 2088. (c) Johnson, W. S.; Elliott, R.; Elliott, J. D. *Ibid.* **1983**, *105*, 2904. (d) Elliott, J. D.; Choi, V. M. F.; Johnson, W. S. *J. Org. Chem.* **1983**, *48*, 2294. (e) Choi, V. M. F.; Elliott, J. D.; Johnson, W. S. *Tetrahedron Lett.* **1984**, *25*, 591.

(2) (a) Mori, A.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4581. (b) Mori, A.; Maruoka, K.; Yamamoto, H. *Ibid.*, in press.

(3) Asymmetric Synthesis of β-substituted aldehydes via 1,4-addition of organometallics to chiral α,β-unsaturated aldehyde derivatives: (a) Hashimoto, S.; Yamada, S.; Koga, K. *Chem. Pharm. Bull.* **1979**, *27*, 771. (b) Hashimoto, S.; Komeshima, N.; Yamada, S.; Koga, K. *Ibid.* **1979**, *27*, 2437. (c) Kogen, H.; Tomioka, K.; Hashimoto, S.; Koga, K. *Tetrahedron* **1981**, *37*, 3951. (d) Mangeney, P.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1983**, *24*, 373. (e) Huche, M.; Aubouet, J.; Pourcelot, G.; Berlan, J. *Ibid.* **1983**, *24*, 585. (f) Besace, Y.; Berlan, J.; Pourcelot, G.; Huche, M. *J. Organomet. Chem.* **1983**, *247*, C11. For relevant reactions, see: (g) Tsuchihashi, G.; Mitamura, S.; Ogura, K. *Tetrahedron Lett.* **1976**, 855. (h) Meyers, A. I. *Acc. Chem. Res.* **1978**, *11*, 375. (i) Mukaiyama, T.; Takeda, T.; Fujimoto, K. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3368. (j) Meyers, A. I.; Smith, R. K.; Whitten, C. E. *J. Org. Chem.* **1979**, *44*, 2250. (k) Asami, M.; Mukaiyama, T. *Chem. Lett.* **1979**, 569. (l) Mukaiyama, T.; Iwasawa, N. *Ibid.* **1981**, 913. (m) Posner, G. H.; Mallamo, J. P.; Hulce, M.; Frye, L. L. *J. Am. Chem. Soc.* **1982**, *104*, 4180. (n) Posner, G. H.; Hulce, M. *Tetrahedron Lett.* **1984**, *25*, 379. (o) Posner, G. H.; Kogan T. P.; Hulce, M. *Ibid.* **1984**, *25*, 383. (p) Mioskowski, C. *Ibid.* **1984**, *25*, 519. (q) Bailey, W. F.; Zartun, D. L. *J. Chem. Soc., Chem. Commun.* **1984**, 34.

(4) Recent preparation of optically active allylic alcohols: (a) Noyori, R. *Pure Appl. Chem.* **1981**, *53*, 2315. (b) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

(5) Seebach, D.; Kalinowski, H.-O.; Langer, W.; Crass, G.; Wilka, E.-M. *Org. Synth.* **1983**, *61*, 24.

(6) The 1,4- and 1,2-adducts were converted into the corresponding acetates because of their easy separation by column chromatography and the efficient acetalization of the 1,4-adduct with (−)-2(*R*),4(*R*)-pentanediol.

(7) The reaction gave entirely the trans isomers **2** and **3** as judged by 200-MHz ^{1}H NMR spectroscopy.

(8) Optically active (−)-2(*R*),4(*R*)-pentanediol is available from Aldrich Chemical Co. and Wako Pure Chemical Industries, Ltd., and its $[\alpha]_D$ value should be checked before use.

(9) For determination of enantiomeric purity by using chiral acetals, see: (a) Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2183. (b) Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S. K.; Druelinger, M. *J. Am. Chem. Soc.* **1981**, *103*, 3081. See also: (c) Eliel, E. L.; Ko, K.-Y. *Tetrahedron Lett.* **1983**, *24*, 3547. (d) Meyers, A. I.; White, S. K.; Fuentes, L. M. *Ibid.* **1983**, *24*, 3551.

(10) Terashima, S.; Tanno, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1980**, 1026.

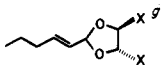
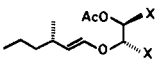
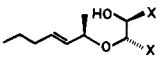
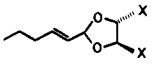
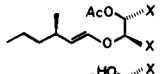
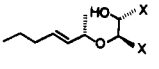
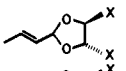
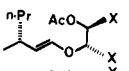
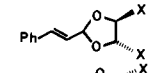
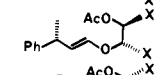
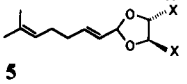
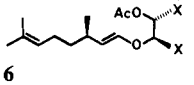
(11) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(12) Attempted reaction of α,β-unsaturated acetal derived from (−)-2(*R*),4(*R*)-pentanediol with Me_3Al resulted in formation of 1,2-adduct exclusively with loss of diastereoselectivity.

(13) Treatment of the cis isomer of **1** (R = *n*-Pr) with Me_3Al in toluene furnished a mixture of 1,4- and 1,2-adducts in 23% yield (ratio, 4:1). The optical purity of the 1,4-adduct was found to be 77% ee with the *R* configuration.

0002-7863/84/1506-5004$01.50/0

Table I. Asymmetric 1,4- and 1,2-Additions of Aluminum Reagents to α,β-Unsaturated Acetals[a]

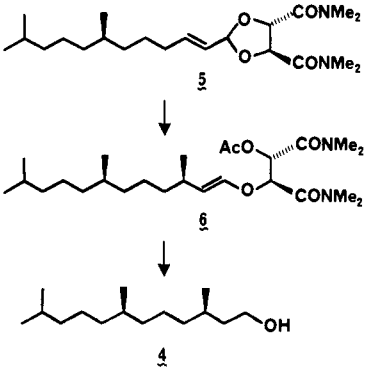
						1,4- or 1,2-adduct		
entry	acetal[b]	R_3Al	solvent	condtn[c]	yield, % (ratio)[d]	product	$[\alpha]^{19}_D$, deg (*c*)[e]	opt yield, % ee[f] (confign)
1		Me_3Al	$ClCH_2CH_2Cl$	A	97 (6.5:1)		+74.75 (2.00)	88 (*S*)[i]
2			$ClCH_2CH_2Cl$	C	92 (2.8:1)			94 (*S*)
3			*n*-PrCl	A	96 (6.5:1)			91 (*S*)
4			CH_2Cl_2	A	91 (3.3:1)		+75.93 (2.04)	95 (*S*)
5			toluene	A	79 (1.5:1)			95 (*S*)
6			toluene	B	81 (1.7:1)		+76.08 (2.00)	96 (*S*)[i]
7			$CHCl_3$	A	85 (0:1)		+65.30 (2.00)	88 (*R*)[j]
8		Me_3Al	CH_2Cl_2	A	82 (3.5:1)		−67.28 (2.09)	93 (*R*)
9			toluene	B	80 (2.8:1)		−69.19 (2.03)	96 (*R*)[i]
10			$CHCl_3$	A	83 (0:1)		−59.10 (1.90)	86 (*S*)[j]
11		*n*-Pr_3Al	CH_2Cl_2	B	96 (2.1:1)		+43.57 (2.01)	87 (*R*)
12			toluene	B	83 (1:1)		+42.08 (2.02)	93 (*R*)[i]
13		Me_3Al	CH_2Cl_2	B	62 (1:0)			94 (*R*)[k]
14			toluene	B	91 (5.7:1)		+36.68 (2.04)	98 (*R*)[k]
15		Me_3Al	toluene	C	76 (4:1)		−75.17 (2.07)	96 (*R*)[l]
16	**5**	Me_3Al	*n*-PrCl	C	74 (4.5:1)	**6**	−63.34 (2.08)	95[m]
17			toluene	C	81 (2.1:1)		−60.37 (2.11)	96[m]

[a] The reaction was carried out using 5 equiv of trialkylaluminum. [b] X = $CONMe_2$. [c] Condition A: reaction at room temperature for 12–15 h. Condition B: reaction at 5 °C (in a refrigerator) for 3 days. Condition C: reaction at −15 °C (in a freezer) for 1 week. [d] Isolated ratio of 1,4- and 1,2-adducts. [e] In MeOH. [f] Unless otherwise stated, the optical yield was determined by GC on a 25-m PEG-HT capillary column as described in text. [g] The ratio of trans and cis isomers was found to be 96.5:3.5 by GC analysis. [h] Ratio of trans and cis isomers = 94:6 by GC analysis. [i] Determined by conversion to (*S*)- or (*R*)-3-methyl-1-hexanol (2 N HCl/THF; $NaBH_4$): Levene, P. A.; Rothen, A. *J. Org. Chem.* **1936**, *1*, 76. [j] See text and ref 10. [k] The absolute configuration has proven by transformation to (*R*)-3-phenylbutan-1-ol.[l] [l] Compared with optically pure D-(+)-citronellal. [m] Optical yield after correction for the starting D-(+)-citronellal of 97% optical purity.[15,16] The diastereomeric ratio of **4** and its 3*S*,7*R* isomer was found to be 96:4 (entry 16) or 96.5:3.5 (entry 17) by the 90.54-MHz ^{13}C NMR measurement according to ref 14o. The ^{13}C NMR peaks at δ 40.00 and 40.08 for the isomers were used for the diastereomeric distinction, although a base-line separation of the two peaks was not completely obtained.

tained even at room temperature, although the optical yield appeared to increase by lowering the reaction temperature (20 to −15 °C).

Some other examples are listed in Table I. Apparently the present method gave exceptionally high optical yields in production of 1,4- and 1,2-adducts without resorting to impractically low temperature. Since both (*R*,*R*)- and (*S*,*S*)-tartaric acid diamide are readily obtainable in optically pure form,[5] this method allows the synthesis of both enantiomers of β-substituted aldehydes and allylic alcohols from α,β-unsaturated aldehydes in a predictable manner.

It seems clear that the asymmetric process described herein has a vast potential in natural product synthesis as illustrated in the short synthesis of the side-chain alcohol **4** of biologically important vitamine E and K.[14] The requisite acetal **5** ($[\alpha]^{20}_D$ + 28.90° (*c* 2.05, MeOH)) was readily available from D-(+)-citronellal[15] (entry 15) via a five-step sequence in 56% overall yield.[16] The critical alkylation of **5** in toluene with Me_3Al proceeded smoothly to yield 1,4-adduct **6** (entry 17). Hydrolysis (6 N HCl/dioxane) followed by reduction with $NaBH_4$ produced the alcohol **4** ($[\alpha]^{18}_D$



+3.49° (*c* 0.98, $CHCl_3$))[17] in 92% yield. Its optical purity was established by 90.54-MHz ^{13}C NMR spectroscopy to be 96% ee.[18]

Further studies on the origin of the eminent regiochemical control as well as the high diastereofacial differentiation arising from the unique influence of the functionalized acetal moiety of the substrates are in progress.

(14) Review: Yamada, S.; Takeshita, T.; Tanaka, J. *J. Synth. Org. Chem., Jpn.* **1982**, *40*, 268. For recent synthesis of the vitamin E side chain, see: (a) Fuganti, C.; Grasselli, P. *J. Chem. Soc., Chem. Commun.* **1979**, 995. (b) Schmid, M.; Barner, R. *Helv. Chim. Acta* **1979**, *62*, 464. (c) Zeil, R. *Ibid.* **1979**, *62*, 474. (d) Kabbea, H. J.; Heitzer, H. *Synthesis* **1979**, 888. (e) Trost, B. M.; Klun, T. P. *J. Am. Chem. Soc.* **1979**, *101*, 6756. (f) Takahashi, J.; Mori, K.; Matsui, M. *Agric. Biol. Chem.* **1979**, *43*, 1605. (g) Trost, B. M.; Klun, T. P. *J. Org. Chem.* **1980**, *45*, 4256. (h) Saucy, G.; Cohen, N.; Banner, B. L.; Trullinger, D. P. *J. Org. Chem.* **1980**, *45*, 2080. (i) Still, W. C.; Darst, K. P. *J. Am. Chem. Soc.* **1980**, *102*, 7385. (j) Gora, J.; Antczak, U. *Perfum. Flavor.* **1980**, *5*, 31, 37. (k) Fujisawa, T.; Sato, T.; Kawara, T.; Ohashi, K. *Tetrahedron Lett.* **1981**, *22*, 4823. (l) Cohen, N.; Scott, C. G.; Neukom, C.; Lopresti, R. J.; Webber, G.; Saucy, G. *Helv. Chim. Acta* **1981**, *64*, 1158. (m) Trost, B. M.; Klun, T. P. *J. Am. Chem. Soc.* **1981**, *103*, 1864. (n) Heathcock, C. H.; Jarvi, E. T. *Tetrahedron Lett.* **1982**, *23*, 2825. (o) Koreeda, M.; Brown, L. *J. Org. Chem.* **1983**, *48*, 2122.

(15) D-(+)-Citronellal ($[\alpha]^{24}_D$ + 16.3° (neat), *d* = 0.851) was kindly supplied from Takasago Perfumery Co., Ltd. Its optical purity was determined to be 97% ee by GC analysis after conversion to the acetal of (−)-2-(*R*),4(*R*)-pentanediol.

(16) Preparation of **5** follows: (i) conversion of D-(+)-citronellal to α,β-unsaturated aldehyde **7** (90%) with the lithio enaminophosphonate $(EtO)_2POCH{=}CHNLi$-*t*-Bu (**8**) (Meyers, A. I.; Tomioka, K.; Fleming, M. P. *J. Org. Chem.* **1978**, *43*, 3788); (ii) hydrogenation of **7** with 10% Pd/C in THF (92%); (iii) transformation of the resulting aldehyde into homologated α,β-unsaturated aldehyde **9** with the reagent **8** (85%); (iv) acetalization of **9** using $HC(OEt)_3$–NH_4NO_3 in EtOH (90%); (v) transacetalization with (*S*,*S*)-(−)-*N*,*N*,*N*′,*N*′-tetramethyltartaric acid diamide in the presence of catalytic Py·TsOH (88%).

(17) Lit. $[\alpha]^{23}_D$ +3.35° (*c* 0.955, $CHCl_3$).[14e]

(18) We are indebted to Dr. T. Iwashita of Suntory Institute for Bioorganic Research and Ono Pharmaceutical Co. for ^{13}C NMR measurement.