Stereo- and Regio-controlled Aldol Synthesis using Relative 1,2-Asymmetric Induction

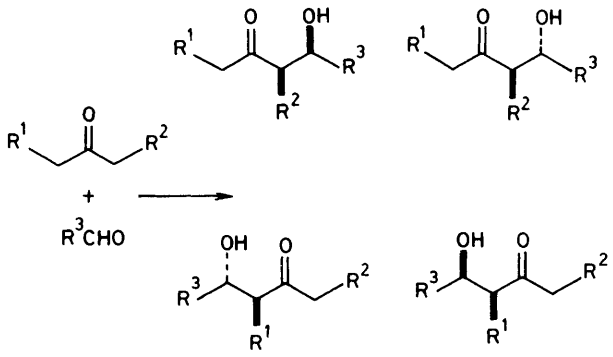
Fumie Sato,* Yoshiyuki Takeda, Hiroshi Uchiyama, and Yuichi Kobayashi

Department of Chemical Engineering, Tokyo Institute of Technology, Meguro, Tokyo 152, Japan

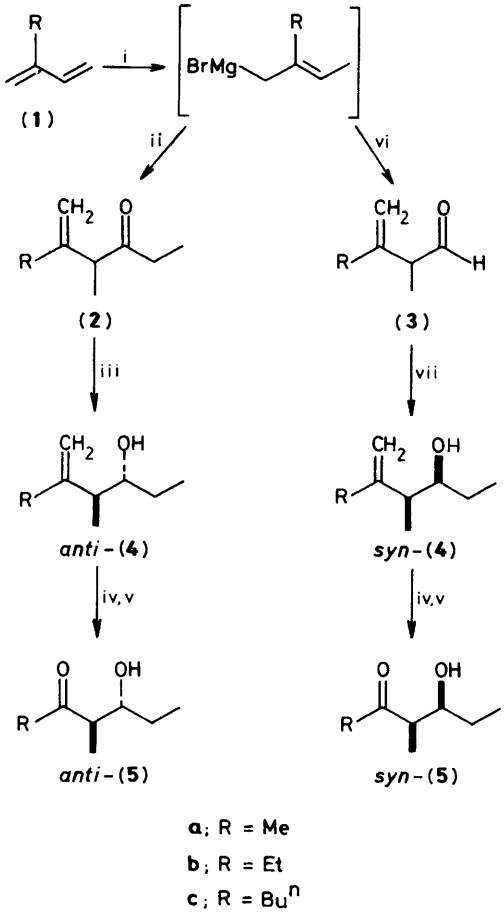
Highly stereoselective addition of nucleophiles to α-methyl-β-methylene carbonyl compounds combined with the hydromagnesiation reactions of 2-alkyl-substituted 1,3-dienes affords a practical, efficient stereo- and regio-controlled aldol synthesis.

In the crossed aldol condensations between aldehydes and ketones having two different types of methylene groups adjacent to their carbonyl group, regio- and stereo-chemical effects play a part in the reaction (Scheme 1). Although there are many methods for the control of either the regio- or stereo-chemistry of the reaction,[1] few methods for the control of both have been reported.[2]

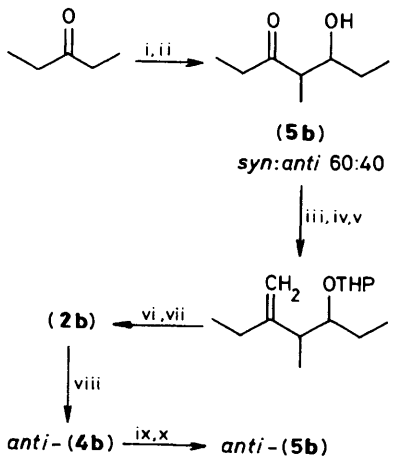
In this communication, we delineate a highly expedient solution to this synthetic problem which allows the synthesis of both *syn*- and *anti*-β-hydroxy-α-methyl ketones,[3] a fundamental structural unit present in macrolide and ionophore antibiotics.[4] The new process is shown in Scheme 2. The key feature of the process is highly stereoselective nucleophilic addition to α-methyl-β-methylene carbonyl compounds.



Scheme 1



Scheme 2. i, Bu^{i}MgBr, $(\eta\text{-}C_5H_5)_2TiCl_2$; ii, EtCN; iii, M–H; iv, O_3; v, Me_2S; vi, HCO_2MgBr; vii, EtMgBr.



Scheme 3. THP = tetrahydropyran-2-yl. i. Lithium di-isopropylamide, ii, EtCHO; iii, dihydropyran, H^+; iv, Me_3SiCH_2MgCl; v, KH, THF; vi, H^+, vii, pyridinium chlorochromate; viii, L-Selectride; ix, O_3; x, Me_2S.

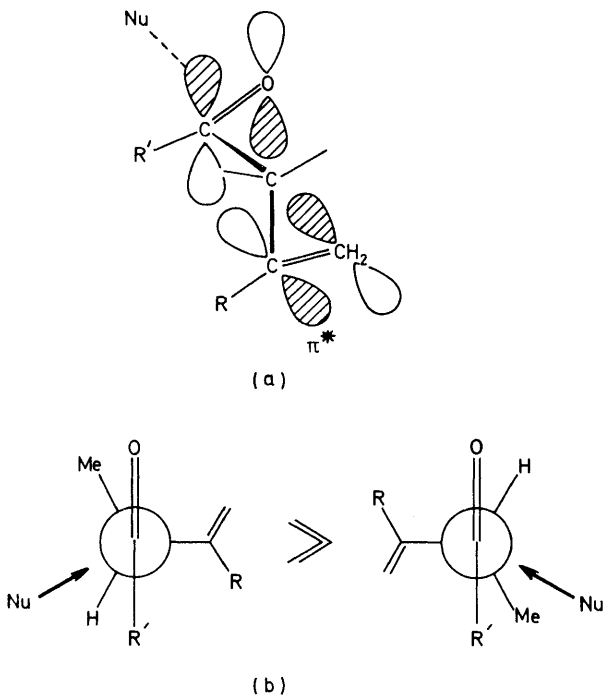


Figure 1. (a) Stereoview of the supermolecule including the π^* orbitals. (b) Direction of nucleophilic attack.

In the preceding communication, we showed that 2-methyl-3-trimethylsilylalk-3-enyl carbonyl compounds react with nucleophiles with high diastereofacial selectivity, affording 'Cram' products.[5] The initial object of the present investigation was to measure the degree of diastereoselectivity in nucleophilic addition to an aldehyde where the trimethylsilyl group has been replaced by an alkyl group; we obtained unprecedented, highly stereochemical results.[6]

The 2-alkylbuta-1,3-dienes (**1b,c**) were prepared in good yields by the coupling reaction of 2-chlorobuta-1,3-diene with the corresponding alkyl Grignard reagent in the presence of a catalytic amount of $Ni(Ph_2P[CH_2]_3PPh_2)Cl_2$.[7] Titanium-catalysed hydromagnesiation of (**1**) with isobutylmagnesium bromide[8] followed by treatment with propionitrile afforded the 5-alkyl-4-methylhex-5-en-3-one (**2**) in yields of 78%, (**2a**); 71% (**2b**); and 81% (**2c**). The aldehydes (**3**) were prepared by reaction with the magnesium salt of formic acid in tetrahydrofuran (THF) after hydromagnesiation; the yields were 33% (**3a**); 49% (**3b**); and 66% for (**3c**).[9†]

† In our hands, the use of dimethylformamide or $HC(OEt)_3$ instead of HCO_2MgBr resulted in the formation of undesired α,β-unsaturated aldehydes in addition to (**3**).

Table 1. Results of the reduction of (**2**) to give (**4**) and the ozonolysis of (**4**) to give (**5**).

	Conditions for (**2**)→(**4**)		Product (**4**)		Product (**5**)[c,d]
Ketone	Reagent	*t*/°C	*syn*:*anti*[a]	Yield (%)[b]	Yield (%)[b]
(**2a**)	$NaBH_4$	0	7 : 93	93	—
(**2a**)	$NaBH_4$	−18	5 : 95	96	—
(**2a**)	L-Selectride	−78	1 : 99	94	91
(**2b**)	L-Selectride	−78	<1 : >99	93	90
(**2c**)	L-Selectride	−78	<1 : >99	92	92

[a] Determined by g.l.c. analysis. [b] Isolated yield after chromatography on silica gel. [c] Diastereoisometric ratio as (**4**). [d] See footnote ‡.

Table 2. Results of the reaction of (**3**) with ethylmagnesium bromide[a] and the ozonolysis of (**4**) to give (**5**).

	Product (**4**)		Product (**5**)[d,e]
Aldehyde	*syn* : *anti*[b]	Yield (%)[c]	Yield (%)[c]
(**3a**)	93 : 7	89	91
(**3b**)	94 : 6	90	88
(**3c**)	94 : 6	91	92

[a] The reaction was carried out at −78 °C for 1 h and then at room temperature for 1 h. [b] Determined by g.l.c. analysis. [c] Isolated yield after chromatography on silica gel. [d] Diastereoisomeric ratio as (**4**). [e] See footnote ‡.

Table 1 summarizes the results obtained from the reduction of (**2**) with metal hydride reagents to give (**4**) and from the ozonolysis of (**4**) to give the aldols (**5**). It can be seen from Table 1 that metal hydride reduction of (**2**) occurred with high stereoselectivity to give the 'Cram' products *anti*-(**4**). As expected, an increase in the steric demand of the metal hydride reagent increased the stereoselectivity, and near-perfect diastereoselectivity was attained using L-Selectride. An estimate of the stereoselectivity was obtained from ^1H and ^{13}C n.m.r. spectroscopy, and also by g.l.c. analysis compared with the corresponding diastereoisomers (*vide infra*). Ozonolysis of *anti*-(**4**) followed by treatment with dimethyl sulphide afforded the corresponding aldols *anti*-(**5**) in excellent yields.‡

The reaction of (**3**) with a Grignard reagent also proceeded with high diastereoselectivity. Thus, (**3**) reacted with ethylmagnesium bromide to give the 'Cram' products *syn*-(**4**) selectively, thereby allowing the synthesis of the *syn*-aldols (**5**) (Table 2).

The highly stereoselective method for the conversion of (**2**) into *anti*-(**4**) described above provides a useful extention to the conversion of *syn*-aldols into their *anti*-isomers. Thus, a *syn*–*anti* mixture of the aldol (**5b**) obtained by the reaction of pentan-3-one and propanal was converted into >99% pure *anti*-(**5b**) in 68% overall yield according to Scheme 3. This method should prove useful for the preparation of rarely obtained optically active *anti*-aldols;[11] there are several excellent methods available for the preparation of optically active *syn*-aldols.[1]

The high diastereofacial selectivity obtained in the nucleophilic addition to (**2**) [or (**3**)] described here may be explained by Anh's theory.[12] Thus, the supermolecule [nucleophile(Nu) + carbonyl compound] is most stable when the vinyl group is perpendicular to the carbonyl plane resulting in a $\pi^*_{C=O}$–$\pi^*_{C=C}$ interaction, and nucleophilic attack occurs from the less hindered side to avoid steric interactions as shown in Figure 1.

We gratefully acknowledge the generous supply of 2-chorobuta-1,3-diene from Denki Kagaku Kogyo Co. Ltd.

Received, 14th May 1984; Com. 661

‡ The stereochemistry of the aldols (**5**) was ascertained by comparison of their ^1H n.m.r. spectra (chemical shift of the alcohol protons and the coupling constant J_{ab} of $O{=}CCH_aCH_bOH$) with those of authentic *syn*–*anti* mixtures, obtained by the method of Yamamoto (ref. 10) for (**5a**) and (**5c**) and by following the procedure shown in Scheme 3 for (**5b**). The chemical shifts of the alcohol protons and J_{ab} are as follows: *syn*-(**5a**), δ 3.68, 4 Hz; *anti*-(**5a**), δ 3.48, 8 Hz; *syn*-(**5b**), δ 3.64, 4 Hz; *anti*-(**5b**), δ 3.47, 8 Hz; *syn*-(**5c**), δ 3.64, 4 Hz; *anti*-(**5c**), δ 3.46, 7 Hz.

References

1 For reviews, see ref. 4 of *J. Chem. Soc., Chem. Commun.*, 1984, preceding communication.
2 J. Hooz and J. Oudenes, *Tetrahedron Lett.*, 1983, **24**, 5695; I. Kuwajima, M. Kato, and A. Mori, *ibid.*, 1980, **21**, 4291.
3 The stereoconfiguration was classified as '*syn*' and '*anti*' according to the definition of Masamune: S. Masamune, S. A. Ali, D. L. Snitman, and D. S. Garvey, *Angew. Chem., Int. Ed. Engl.*, 1980, **19**, 557; S. Masamune, T. Kaiho, and D. S. Garvey, *J. Am. Chem. Soc.*, 1982, **104**, 5521.
4 P. A. Bartlett, *Tetrahedron*, 1980, **36**, 2; W. Wierenga, in 'The Total Synthesis of Natural Products,' ed. J. ApSimon, Wiley, New York, 1981, vol. 4, p. 263.
5 F. Sato, M. Kusakabe, and Y. Kobayashi, *J. Chem. Soc., Chem. Commun.*, 1984, preceding communication.
6 Owing to the scarcity of α-alkyl-β,γ-unsaturated carbonyl compounds, only a few nucleophilic addition reactions have been studied. Fujita *et al.* reported that 3-isopropenyl-6-methylhept-5-en-2-one reacts with vinylmagnesium bromide to give the 'Cram' addition product selectively: Y. Fujita, T. Onishi, and T. Nishida, *J. Chem. Soc., Chem. Commun.*, 1978, 972.
7 K. Tamao, K. Sumitani, Y. Kiso, M. Zembayashi, A. Fujioka, S. Kodama, I. Nakajima, A. Minato, and M. Kumada, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 1958; A. Hosomi, M. Saito, and H. Sakurai, *Tetrahedron Lett.*, 1979, 429.
8 F. Sato, H. Ishikawa, and M. Sato, *Tetrahedron Lett.*, 1980, **21**, 365.
9 F. Sato, K. Oguro, H. Watanabe, and M. Sato, *Tetrahedron Lett.*, 1980, **21**, 2869.
10 K. Maruoka, S. Hashimoto, Y. Kitagawa, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, 1977, **99**, 7705.
11 S. Masamune, T. Kaiho, and D. S. Garvey, *J. Am. Chem. Soc.*, 1982, **104**, 5521; A. I. Meyers and Y. Yamamoto, *ibid.*, 1981, **103**, 4278.
12 N. T. Anh and O. Eisenstein, *Nouv. J. Chim.*, 1977, **1**, 61.