Transformations of Chiral (η^6-Arene)chromium Complexes in Organic Synthesis: Aldol Reactions of (Ortho-substituted acetophenone)chromium Complexes

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The aldol reaction of (*o*-alkoxyacetophenone)chromium complexes with boron enolates gave predominantly one diastereomeric product as a result of attack at the *re*-face of the aldehydes. The selectivity of the aldol reactions was remarkably dependent on the ortho substituents of the acetophenone complexes and the ligands on the chromium metal. In the case of the *o*-methoxy substituent, high diastereoselectivity in the boron enolate aldol condensation was achieved. (*o*-Methoxyacetophenone)$Cr(CO)_3$ exists in an anti form with respect to the methoxy and the carbonyl oxygen; thus, the corresponding anti boron enolate was formed via coordination of the boron with the benzylic carbonyl oxygen. The resulting anti boron enolate attacked the *re*-face of the aldehydes through a six-membered cyclic twist-boat transition state. The diastereoselective aldol condensations provide a new method for remote stereocontrol at the 1,5-position of the side chain in optically active forms, combined with stereoselective alkylation of chromium-complexed benzylic ketones.

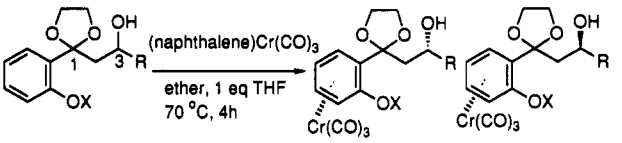
Introduction

(η^6-Arene)chromium complexes can exist in two enantiomeric forms when the phenyl ring is substituted with two different substituents at the ortho or meta positions. Some of these chromium complexes could be easily obtained in optically active forms via recrystallization[1] or column chromatography[2,3] of suitable diastereomers prepared by reaction with optically active resolution reagents. Chiral ortho-substituted benzaldehydechromium complexes can be prepared by an enantioselective lithiation of chiral (benzaldehyde acetal)chromium tricarbonyl.[4] Also, biocatalysts[5] provides a kinetically controlled resolution of (1,2-disubstituted arene)chromium complexes with high enantioselectivity. (η^6-Arene)chromium complexes possess characteristic properties due to the electronic effects and steric bulkiness of the $Cr(CO)_3$ group, and significant applications in organic synthesis have been developed.[6] The benzylic carbonyl group of (*o*-alkoxyphenyl alkyl ketone)chromium complexes can be caused to react stereoselectively with nucleophiles such as alkyllithiums or hydride reagents to produce predominantly one of several diastereomeric (benzyl alcohol)chromium complexes.[7] Furthermore, the resulting benzylic hydroxy or acetoxy group of the chromium complexes can be substituted by some carbon nucleophiles in the presence of Lewis acids with stereochemical retention.[8,9] We report herein the diastereoselective aldol reaction of (*o*-substituted acetophenone)chromium complexes via boron enolates and a new approach to remote chiral induction utilizing (η^6-arene)chromium complexes as temporary templates to relay stereochemical information into conformationally flexible molecules.

Results and Discussion

We previously reported[9] that ortho-substituted phenyl derivatives 1 possessing a hydroxy group at the C-3 position and an ethylene acetal at the C-1 position in the side chain reacted with (naphthalene)$Cr(CO)_3$ to afford predominantly one diastereomer of chromium complex 2 (Scheme I). These complexes could be easily converted to stereodefined compounds at the remote positions. However, this diastereoselective chromium complexation method has some disadvantages, such as the following: (1) Many steps are required for the preparation of the starting material. (2) Synthesis of optically active forms is not easy.

Scheme I. Diastereoselective Complexation of 1 with (Naphthalene)$Cr(CO)_3$



1 — 2 — 3

R=Et, ^{i}Pr, CH=CHMe
X=Me, Et, ^{i}Pr

ratio (89–98) : (11–2)

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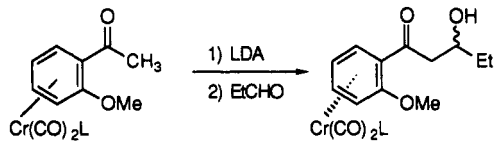
Table I. Aldol Reactions of (o-Methoxyacetophenone)Cr(CO)$_2$L (4) via Lithium Enolates



4 5

complex	ratio of diastereomers	yield (%)
L = CO	55:45	10
L = PPh_3	60:40	95
L = $P(OPh)_3$	62:38	95

(3) Starting arene compounds 1 to be complexed with (naphthalene)chromium should be prepared independently. Since the above chromium complexes 2 obtained by the diastereoselective complexation method are equivalent to the aldol condensation products of (ortho-substituted acetophenone)chromium complexes with aldehydes, the directed diastereoselective aldol reactions of (o-alkoxyacetophenone)chromium would provide a more versatile method which addresses the shortcomings of the chromium complexation method outlined above. Various excellent methods for achieving high stereoselectivity using α-substituted enolates[10] have been developed; good stereoselection in the aldol reactions of chiral enolates lacking α-substituents, however, remains a challenging problem.[11] Recently, transition metal-based aldol reactions have become a focus of interest with respect to synthetic applications and mechanistic studies.[12] Particularly, chiral acyliron complexes have been utilized for diastereoselective aldol reactions and further stereoselective carbon–carbon bond forming reactions developed by Davies's and Liebeskind's groups.[12a,b] We have studied the directed aldol reactions of (ortho-substituted acetophenone)chromium complexes.[13]

Treatment of tricarbonyl(o-methoxyacetophenone)-chromium (4, L = CO) with LDA in THF, followed by reaction with propionaldehyde, gave unsatisfactory results with respect to both yield (less than 10%) and diastereoselectivity (Table I, entry 1). This low yield of the aldol condensation could be attributed to a remarkable stabilization of the chromium-complexed enolate anion due to the strong electron-withdrawing ability of $Cr(CO)_3$ group. The formation of lithium enolate from the tricarbonyl ligand complex 4 was confirmed by quenching with chlorotrimethylsilane to produce the corresponding enolsilyl ether chromium complex in quantitative yield. Thus, it would be desirable to find solutions to the general unreactivity of these enolate anions. One conceptually straightforward solution of this problem would be to increase the reactivity either of the electrophiles or the chromium complexed enolate anions. It should be possible to enhance the reactivity of the enolate anions by replacing one of the three CO ligands with a more electron-releasing phosphine or phosphite ligand on the chromium metal. Dicarbonyl(triphenylphosphine)- or dicarbonyl(triphenyl phosphite)(o-methoxyacetophenone)chromium complexes (4, L = PPh_3, $P(OPh)_3$) have been prepared by photoinduced ligand exchange of the corresponding tricarbonyl complex with PPh_3 or $P(OPh)_3$ in benzene by use of a high-pressure mercury lamp.[14] As expected, the aldol condensation of complexes 4 (L = PPh_3, $P(OPh)_3$) with propionaldehyde via lithium enolate gave a quantitative yield of the condensation products. However, the diastereoselectivities were still low (Table I, entries 2,3).

Counterion effects have been documented to exert a dramatic influence on the stereochemistry of organic enolate reactions.[15] Furthermore, the stereochemistry of aldol condensation products from chiral acyliron complexes

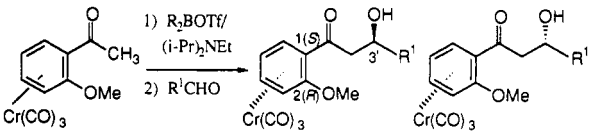
Table II. Influence of Counterions on Aldol Reactions

6 5

entry	L	MX	ratio of diastereomers	yield (%)
1[a]	CO	Me_3SiCl	30:70	15
2	CO	Et_2AlCl	50:50	13
3	PPh_3	Et_2AlCl	70:30	70
4	PPh_3	$SnCl_2$	65:35	40
5	PPh_3	Ph_3SnCl	65:35	60
6	PPh_3	Cp_2ZrCl_2		0

[a] Aldol reaction with propionaldehyde was carried out in the presence of borontrifluoride etherate. The major product is diastereomer with aldol condensation product via boron enolate.

Table III. Aldol Reactions via Boron Enolate of Tricarbonyl(o-methoxyacetophenone)chromium (7)



7 8 9

1	R_2BOTf	R^1CHO	ratio of 8:9	yield (%)
1	$(^nBu)_2BOTf$	EtCHO	90:10	80
2	$(c\text{-}C_5H_9)_2BOTf$	EtCHO	91:9	45
3	9-BBNOTf	EtCHO	92:8	35
4	$(^nBu)_2BOTf$	C_6H_5CHO	92:8	75
5	$(^nBu)_2BOTf$	(E)-MeCH=CHCHO	88:12	77
6	$(^nBu)_2BOTf$	(E)-PhCH=CHCHO	89:11	78
7	$(^nBu)_2BOTf$	Me_2CHCHO	95:5	81

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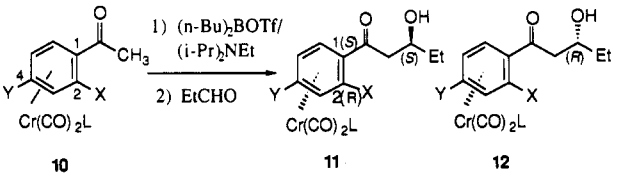
is remarkably influenced by the nature of the additive metal salts to the lithium enolate solution.[12a,b] Following this lead, we added a variety of metal salts to a THF solution of the lithium enolate 6 and performed the aldol reaction with EtCHO. Unfortunately, the diastereoselectivity of the aldol condensation products was not increased by the other metal enolates. Also, the aldol reaction via enolsilyl ether in the presence of $BF_3{\cdot}OEt_2$ resulted in low yield and selectivity (Table II).

After several attempts, the aldol reaction via the corresponding boron enolate of (*o*-methoxyacetophenone)-$Cr(CO)_3$ was found to produce satisfactory results. The boron enolate generated from racemic tricarbonyl(*o*-methoxyacetophenone)chromium (7), dibutyl trifluoromethanesulfonate, and diisopropylethylamine in ether at −78 °C gave Ar(1*S**,2*R**),3′(*S**)[16]-condensation product product 8 (R^1 = Et) and Ar(1*S**,2*R**),3′(*R*)[16]-complex 9 (R^1 = Et) in a ratio of 90:10 after a treatment with propionaldehyde (Table III, entry 1). The diastereomeric isomer could easily be separated by SiO_2 colum chromatography. The assignment of relative stereochemistry of the major aldol condensation product 8 (R^1 = Et) was determined as the Ar(1*S**,2*R**),3′(*S**)-configuration after chemical interconversion to the corresponding acetate complex by comparison of the ^1H NMR spectrum and melting point with the stereodefined authentic compound. The ^1H NMR spectrum of the acetate complex (mp 92 °C) derived from the major aldol reaction product 8 (R^1 = Et) was consistent with that of the corresponding compound derived from a minor product 3 (R = Et, X = Me) obtained by the chromium complexation method illustrated in Scheme I. On the other hand, the corresponding stereoisomeric acetate complex (mp 121 °C) obtained from the complex 2 (R = Et, X = Me), in which the relative stereochemistry[9] has been unambiguously determined by X-ray crystallography, was cleanly distinguished from the above acetate complex of the major aldol condensation product 8 in the ^1H-NMR spectrum. Reaction results with other aldehydes are summarized in Table III. The aldol reaction with sterically bulky Me_2CHCHO gave high diastereoselectivity. The ratio of diastereomers was determined by integration of the well-resolved acetate or methylene proton resonances of the high-field ^1H NMR spectra of the corresponding crude acetate complexes. In order to confidently assign the relative stereochemistry of predominant diastereomers from the other aldehydes, a careful analysis of high-field ^1H NMR spectra was undertaken. This analysis showed a general pattern for the appearance of the methylene hydrogens adjacent to the acyl carbon. The stereochemistries of the other products were assigned by analogy to 8 (R^1 = Et). The use of other dialkylboron reagents resulted in lower yields (entries 2, 3). These two reactions (chromium complexation and aldol condensation) give different stereoisomeric chromium complexes at the C-3′ position as the major product and are complementary to each other with respect to the further development of remote stereocontrol.

Both the nature of the substituents on the chromium-complexed aromatic ring and the ligands on the chromium

(16) This nomenclature is based on the Cahn–Ingold–Prelog rule; see the following references: (a) Schlögl, K. *Topics in Stereochemistry*; Eliel, E. L., Allinger, N. L., Eds.; Wiley-Interscience: New York, 1967; Vol. 1. (b) Paiaro, G.; Panuzi, A. *J. Am. Chem. Soc.* **1964**, *86*, 5148. (c) Solladié-Cavallo, A. Chiral-Arene-Chromium-Carbonyl Complexes in Asymmetric Synthesis. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Eds.; JAI Press: Greenwich, CT, 1989; Vol 1, p 99. The symbol * indicates a racemate, and one enantiomer is illustrated for clarity. The first symbol shows a configuration at the chromium-complexed aromatic carbon and the second symbol indicates the configuration at the chiral center in the side chain; see ref 16c.

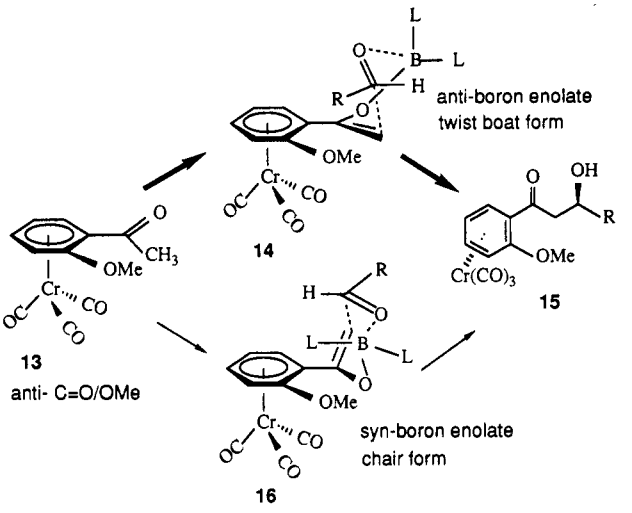
Table IV. Influence of Ligand L and Substituents X, Y on Aldol Reactions



entry	L	X	Y	ratio of 11:12	yield (%)
1	CO	OMe	H	90:10	80
2	CO	O^{i}Pr	H	85:15	75
3	CO	Me	H	40:60[a]	45
4	PPh_3	OMe	H	88:12	50
5	PPh_3	O^{i}Pr	H	70:30	30
6	PPh_3	Me	H	50:50	40
7	$P(OPh)_3$	OMe	H	88:12	85
8	$P(OMe)_3$	OMe	H	86:14	60
9	CO	OMe	OMe	90:10	85
10	PPh_3	OMe	OMe	50:50	30
11	$P(OPh)_3$	OMe	OMe	50:50	80
12	$P(OMe)_3$	OMe	OMe	80:20	55

[a] The ratio may be reversed.

Scheme II. Proposed Mechanism of Boron Enolate Aldol Reaction



exert a significant influence on the stereoselectivity of the aldol reactions. For instance, (*o*-methylacetophenone)-$Cr(CO)_2L$ (10, L = CO, PPh_3; X = Me; Y = H), lacking the *o*-methoxy substituent, gave low diastereoselection in the aldol reaction (Table IV, entries 3, 6); thus, an alkoxy substituent at the ortho position is required for the achievement of high selectivity. Interestingly, monophosphine or -phosphite (*o*-methoxyacetophenone)chromium complexes 10 (L = PPh_3, $P(OPh)_3$, $P(OMe)_3$; X = OMe; Y = H) exhibited a slightly lower selectivity when compared with the corresponding tricarbonylchromium complex (enteries, 1, 4, 7, and 8), while 2,4-dimethoxy chromium complexes with sterically bulky phosphine or phosphite ligands showed no selectivity (entries 10, 11). Since the tricarbonyl ligand of (2,4-dimethoxyacetophenone)chromium gave predominantly Ar(1*S**,2*R**),3′-(*S**)-complex 11 (entry 9), the electron-donating phosphine or phosphite ligand in the (2,4-dimethoxyacetophenone)-chromium was shown to dramatically affect stereoselectivity. The fact that no diasteroselection was observed in the aldol condensation products via the boron enolate in (2,4-dimethoxyacetophenone)$Cr(CO)_2L$ (10, L = PPh_3, $P(OPh)_3$; X = Y = OMe) may be attributed to the conformation of the chromium complexes and stereoelectronic effects. However, a visual comparison of the two com-

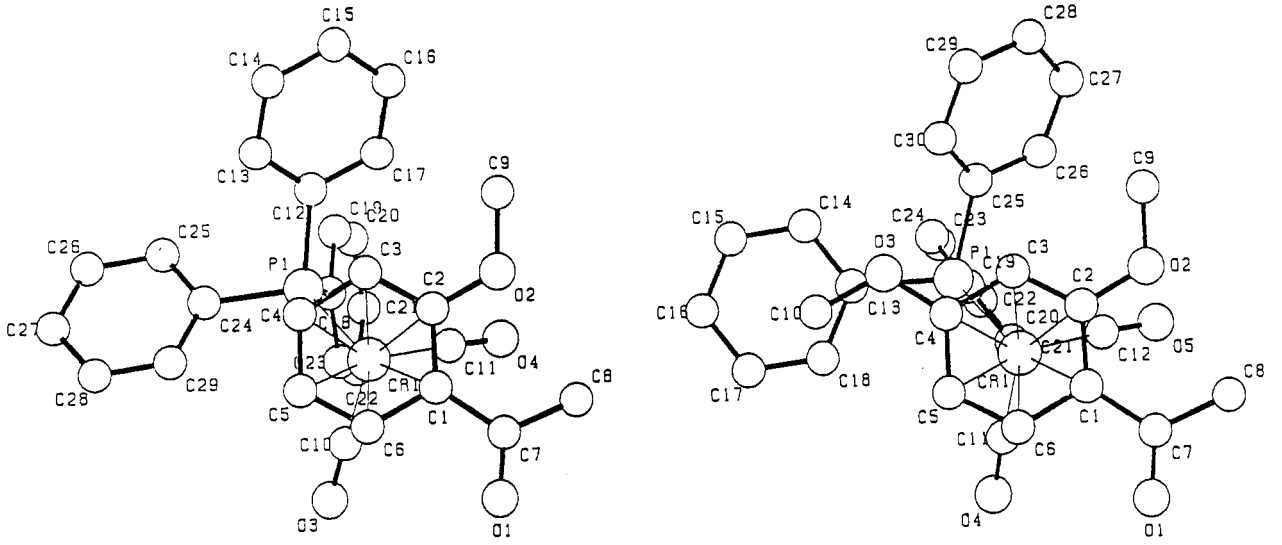


Figure 1. Molecular structures of (2-methoxyacetophenone)$Cr(CO)_2PPh_3$ and (2,4-dimethoxyacetophenone)$Cr(CO)_2PPh_3$.

plexes $(2\text{-}MeOC_6H_4COCH_3)Cr(CO)_2PPh_3$ and $[2,4\text{-}(MeO)_2C_6H_3COCH_3]Cr(CO)_2PPh_3$ does not suggest a significant difference between the conformations of the methyl ketone regions or their environments. The molecular structures of the both complexes are shown in Figure 1. Further investigations should be undertaken in order to find an explanation for the distinct selectivities observed between (2-methoxyacetophenone) and (2,4-dimethoxyacetophenone)chromium complexes with triphenylphosphine or triphenyl phosphite ligands.

The transition state depicted in Scheme II is assumed for the aldol condensation of the chromium complexes. (*o*-Methoxyacetophenone)$Cr(CO)_3$ (**13**) exists in an anti form[16c,17] with respect to the methoxy and the carbonyl oxygen owing to stereoelectronic effects in the solid state. Furthermore, the anti conformation of complex **13** is evidenced even in solution by stereoselective addition[7,18] of nucleophiles such as hydride or alkyllithiums to the chromium-complexed benzylic carbonyl group. Therefore, the formation of anti boron enolate is postulated via coordination of the boron with the carbonyl oxygen and followed by deprotonation with amine. The resulting anti boron enolate would attack a *re*-face of the aldehydes from an exo side of the chromium ligand through a six-membered cyclic twist boat transition state **14** to produce the complex **15** (Scheme II). In the case of (*o*-methylacetophenone)$Cr(CO)_3$ a lack of diastereoselectivity in the aldol reaction as mentioned above would contribute to the syn-disposed conformation[16c] with respect to the C=O and Me groups.

Recent ab initio calculations[19] and asymmetric inductions[20] in simple boron enolate transition states suggest that the twist boat is easily accessible, if there is no α-substituent as with methyl ketone derivatives. However, it still remains a possibility that syn boron enolate is generated to form the cyclic chair transition state **16** (see Scheme II). At this point, it cannot be determined whether only one enolate is formed or whether both anti or syn enolates rapidly interconvert under the reaction conditions in which the enolate is generated and the condensation with aldehyde is carried out.

In any event, the directed aldol reactions of (*o*-alkoxyacetophenone)chromium complexes with aldehydes and chromium complexations of *o*-alkoxyarene compounds having an ethylene acetal and a hydroxy group can be useful for organic syntheses, since the major products in both reactions are diastereomers at the C-3′ position. Also, diastereoselective aldol reactions of the chromium complexes can be applied in order to gain stereocontrol at the remote 1,5-position in optically active forms because both enantiomers of (*o*-methoxyacetophenone)chromium could be easily obtained. Racemic (*o*-alkoxybenzaldehyde)$Cr(CO)_3$ can be resolved to give optically active forms by column chromatography of the diastereomers derived from L-valinol or (*S*)-5-(α-phenylethyl)semioxamazide as developed by the two groups of Davies[2] and Solladié-Cavallo,[3] respectively. Optically active (*o*-methoxybenzaldehyde)-$Cr(CO)_3$ was converted to optically active (*o*-methoxyacetophenone)$Cr(CO)_3$ by treatment with methyllithium followed by oxidation[21] with DMSO/acetic anhydride. The optical purity of the (*o*-methoxyacetophenone)chromium complex was determined by HPLC with Daicel Chiralcel OD (eluted with 10% 2-propanol in hexane). The optically active (*o*-methoxyacetophenone)chromium complex was also obtained by a diastereoselective chromium complexation[22] as follows: (*S*)-α-(*o*-Methoxyphenyl)ethyl alcohol was treated with (naphthalene)$Cr(CO)_3$ in ether containing 1 equiv of THF at 70 °C in a sealed tube to give exclusively one diastereomer, the Ar(1*S*,2*R*),(*S*)-chromium complex, which was oxidized to afford the Ar(1*S*,2*R*)-(*o*-methoxyacetophenone)$Cr(CO)_3$ complex. The optically active (+)-Ar(1*S*,2*R*)-(*o*-methoxyacetophenone)chromium (**17**) gave Ar(1*S*,2*R*),3′(*R*)-aldol condensation product **18** ($[\alpha]_D$ +305, $CHCl_3$) in 72% yield, along with a stereoisomeric

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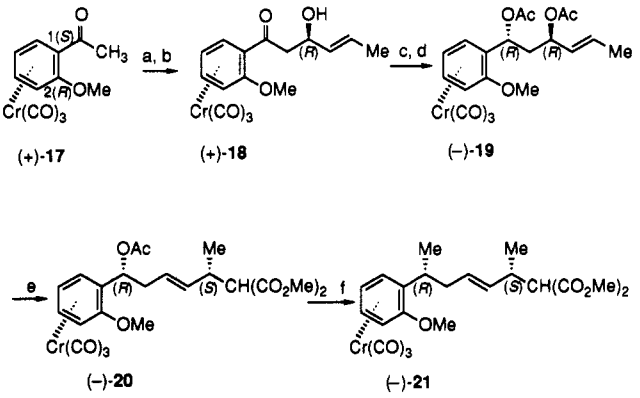
Scheme III. Stereoselective Synthesis of Optically Active 1,5-*syn*-Dimethyl Complex[a]



[a] Reagents: (a) $(^nBu)_2BOTf/(^iPr)_2NEt$; (b) (*E*)-MeCH=CHCHO (72% from **17**); (c) $LiAlH_4$; (d) Ac_2O/pyr (84% from **18**); (e) $NaCH(CO_2Me)_2/[PdCl(C_3H_5)]_2$/dppe/THF (99%); (f) Me_3Al/CH_2Cl_2 (87%).

Ar(1*S*,2*R*),3′(*S*)-complex ($[\alpha]_D$ +262, $CHCl_3$) in 8% yield by the reaction of the corresponding boron enolate and (*E*)-crotonaldehyde (Scheme III). The (+)-complex **18** was easily converted into (−)-1,5-*syn*-dimethyl complex **21** as follows. Stereoselective reduction[7,18d,e] with $LiAlH_4$ followed by acetylation gave (−)-1,3-*anti*-diacetoxy complex **19** in 84% overall yield. The diacetoxy complex **19** was treated with sodium dimethyl malonate in the presence of palladium catalyst to give (−)-1,5-syn rearranged complex **20** in 99% yield by regio- and stereoselective chirality transfer via a π-allylpalladium complex. The stereoselective conversion of the benzylic acetoxy group of the resulting chirality transferred chromium complex **20** to the methyl group was achieved by treatment with trimethylaluminum in 87% yield with stereochemical retention.[8,9] In this way, 1,5-stereocontrol in the acyclic systems was easily achieved by aldol reaction of (*o*-methoxyacetophenone)chromium and subsequent chirality transfer and further stereoselective conversion of the benzylic ketone to the methyl group in optically active forms. These reaction sequences incorporate significant flexibility with regard to stereochemistry at the remote centers, since a simple variation in the allylic olefin geometry would result in effective stereocontrol at the remote chiral centers.

Experimental Section

All manipulations involving organometallics were carried out under an atmosphere of nitrogen or argon and using inert gas/vacuum double-manifold techniques. $Cr(CO)_6$ was obtained from Strem Chemicals and used as received. Ether and tetrahydrofuran were distilled from sodium/benzophenone ketyl immediately before use, and methylene chloride was distilled from P_2O_5. Diisopropylamine and diisopropylethylamine were distilled from CaH_2. Dibutylboron triflate was freshly prepared and used neat. ^1H NMR spectra were measured on Hitachi R-90 and JEOL GX-400 spectrometers. Chemical shifts are recorded in parts per million on the δ scale from tetramethylsilane, and coupling constants are given in Hz. IR spectra were determined on a JASCO A-100 spectrometer. Mass spectra were taken on JEOL D-300 and JEOL AX-500 spectrometers. Elemental analysis was performed on a Perkin-Elmer Model 240 elemental analyzer. All melting points were determined on a Yanagimoto MPJ-2 micromelting point apparatus and are uncorrected. Optical rotations were obtained on a JASCO DIP-370 automatic polarimeter at wavelength 589 nm (sodium D line) using a 1.0-dm cell with a total volume of 3 mL. Tricarbonyl(substituted acetophenone)chromium complexes were prepared by thermolysis of $Cr(CO)_6$ and the corresponding acetal compounds, followed by hydrolysis according to the standard method.[23]

Preparation of (*o*-Methoxyacetophenone)$Cr(CO)_2PPh_3$ (4) (L = PPh_3) from (*o*-Methoxyacetophenone)$Cr(CO)_3$ by Ligand-Exchange Reaction. A typical procedure for ligand exchange from tricarbonyl to phosphine or phosphite is as follows. A solution of (*o*-methoxyacetophenone)$Cr(CO)_3$ (500 mg, 1.75 mmol) and PPh_3 (920 mg, 2.9 mmol) in benzene (30 mL) was irradiated with a high-pressure mercury lamp for 1.5 h under nitrogen at room temperature. The precipitate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was purified with silica gel chromatography (elution solvents; hexane/ether) to produce (*o*-methoxyacetophenone)-$Cr(CO)_2PPh_3$ (800 mg, 80%) as red crystals, mp 206 °C (recrystallization from methylene chloride/ether): ^1H NMR ($CHCl_3$) δ 2.52 (3 H, s), 3.58 (3 H, s), 3.94 (1 H, br d, J = 6), 4.38 (1 H, tt, J = 1.5, 6), 4.83 (1 H, ABX, J_{AB} = 1.5 J_{AX} = J_{BX} = 6), 5.70 (1 H, dt, J = 1.5, 6), 7.27–7.55 (15 H, m); IR ($CHCl_3$) 1900, 1840, 1660, 1285 cm^{-1}. Anal. Calcd for $C_{29}H_{25}O_4PCr$: C, 66.93; H, 4.84. Found: C, 66.34; H, 6.97. Other ligand-exchange reactions were carried out under similar reaction conditions. The data of some ligand exchanged chromium complexes are as follows.

(*o*-Methoxyacetophenone)$Cr(CO)_2P(OPh)_3$ (4) (L = $P(OPh)_3$): yield 60%; mp 174 °C; ^1H NMR ($CDCl_3$) δ 2.46 (3 H, s), 3.35 (3 H, s), 3.40 (1 H, d, J = 7), 3.75 (1 H, d, J = 7), 5.32 (1 H, dq, J = 2, 7), 5.78 (1 H, dt, J = 2, 7), 7.05–7.48 (15 H, m); IR ($CHCl_3$) 1920, 1870, 1660, 1595 cm^{-1}. Anal. Calcd for $C_{29}H_{25}O_7PCr$: C, 61.27; H, 4.43. Found: C, 61.26; H, 4.29.

(*o*-Methoxyacetophenone)$Cr(CO)_2P(OMe)_3$ (4) (L = $P(OMe)_3$): yield 48%; mp 92 °C (recrystallization from ether/hexane); ^1H NMR ($CDCl_3$) δ 2.50 (3 H, s), 3.45 (9 H, d, J = 11), 3.74 (3 H, s), 4.45–4.72 (2 H, m), 5.25–5.55 (1 H, m), 5.88 (1 H, ddd, J = 2, 5, 7); IR ($CHCl_3$) 1910, 1850, 1665 cm^{-1}. Anal. Calcd for $C_{14}H_{19}O_7PCr$: C, 43.99; H, 5.01. Found: C, 43.86; H, 4.76.

(*o*-Isopropoxyacetophenone)$Cr(CO)_2PPh_3$ (10) (X = O^iPr, Y = H, L = PPh_3): yield 60%; mp 189 °C (recrystallization from ether/methylene chloride); ^1H NMR ($CDCl_3$) δ 1.20 (3 H, d, J = 6), 1.36 (3 H, d, J = 6), 2.53 (3 H, s), 3.92 (1 H, d, J = 7), 4.12 (1 H, t, J = 7), 4.33 (1 H, t, J = 7), 4.82 (1 H, dq, J = 1, 7), 5.78 (1 H, dt, J = 2, 7), 7.20–7.60 (15 H, m); IR ($CHCl_3$) 1900, 1845, 1660 cm^{-1}. Anal. Calcd for $C_{31}H_{29}O_4PCr$: C. 67.87; H, 5.33. Found: C, 67.73; H, 5.27.

(*o*-Methylacetophenone)$Cr(CO)_2PPh_3$ (10) (X = Me, Y = H, L = PPh_3): yield 60%; mp 164 °C (recrystallization from ether/methylene chloride); ^1H NMR ($CDCl_3$) δ 2.32 (3 H, s), 2.40 (3 H, s), 3.94 (1 H, dt, J = 4, 7), 4.46–4.75 (2 H, m), 5.45 (1 H, d, J = 7), 7.25–7.55 (15 H, m); IR ($CHCl_3$) 1900, 1840, 1665 cm^{-1}. Anal. Calcd for $C_{29}H_{25}O_3PCr$: C, 69.04; H, 4.99. Found: C, 68.63; H, 4.90.

(*o*,*p*-Dimethoxyacetophenone)$Cr(CO)_2PPh_3$ (10) (X = Y = OMe, L = PPh_3): yield 65%; mp 172 °C (recrystallization from ether/methylene chloride); ^1H NMR ($CHCl_3$) δ 2.46 (3 H, s), 3.38 (3 H, s), 3.72 (3 H, s), 3.82 (1 H, dt, J = 5, 7), 4.60 (1 H, br s), 5.47 (1 H, dd, J = 5, 7), 7.28–7.55 (15 H, m); IR ($CHCl_3$) 1890, 1830, 1260 cm^{-1}. Anal. Calcd for $C_{30}H_{27}O_5PCr$: C, 65.45; H, 4.97. Found: C, 65.25, H, 4.97.

(*o*,*p*-Dimethoxyacetophenone)$Cr(CO)_2P(OPh)_3$ (10) (X = Y = OMe, L = $P(OPh)_3$): yield 65%; mp 152 °C (recrystallization from methylene chloride/ether); ^1H NMR ($CDCl_3$) δ 2.40 (3 H, s), 3.34 (3 H, s), 3.50 (1 H, d, J = 7), 3.68 (3 H, s), 4.75 (1 H, br s), 5.95 (1 H, t, J = 7), 6.95–7.40 (15 H, m): IR ($CHCl_3$) 1920, 1860, 1670, 1590, 1490 cm^{-1}. Anal. Calcd for $C_{30}H_{27}O_8PCr$: C, 60.20; H, 4.55. Found: C, 60.21; H, 4.41.

(*o*,*p*-Dimethoxyacetophenone)$Cr(CO)_2P(OMe)_3$ (10) (X = Y = OMe, L = $P(OMe)_3$): yield 45%; mp 117 °C (recrystallization from ether/methylene chloride); ^1H NMR ($CDCl_3$) δ 2.45 (3 H, s), 3.47 (9 H, d, J = 12), 3.72 (3 H, s), 3.78 (3 H, s), 4.60 (1 H, dt, J = 2, 7), 4.86 (1 H, t, J = 2), 5.95 (1 H, dd, J = 7, 7); IR ($CHCl_3$) 1900, 1840, 1660, 1530 cm^{-1}. Anal. Calcd for $C_{15}H_{21}O_8PCr$: C, 43.70; H, 5.13. Found: C, 43.43; H, 5.14.

Aldol Reaction of (*o*-Methoxyacetophenone)$Cr(CO)_2L$ (4, L = PPh_3) with Propionaldehyde via Lithium Enolate. *n*-BuLi (0.15 mL, 1.6 M in hexane, 0.24 mmol) was added to a solution of diisopropylamine (25 mg, 0.25 mmol) in THF (5 mL) at 0 °C under argon, and the mixture was stirred for 15 min. To

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the above-prepared LDA solution was added a solution of (*o*-methoxyacetophenone)$Cr(CO)_2PPh_3$ (105 mg, 0.20 mmol) in THF (5 mL) at −78 °C under argon. After being stirred for 30 min, a solution of propionaldehyde (17 mg, 0.3 mmol) in THF (2 mL) was added to the above reaction mixture at the same temperature, and the mixture was stirred for 30 min. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The extract was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to afford a diastereomeric mixture of aldol condensation products (109 mg). A ratio of diastereomers was determined by the area of OMe protons after conversion to the corresponding acetate complexes under standard conditions with acetic anhydride, and a catalytic amount of (dimethylamino)pyridine in pyridine (δ, 3.58 and 3.61 ppm, respectively).

Influence of Counterions on Aldol Reaction of (*o*-Methoxyacetophenone)$Cr(CO)_2L$ (4, L = PPh_3). To the above-prepared solution of the lithium enolate of (*o*-methoxyacetophenone)$Cr(CO)_2PPh_3$ was added diethylaluminum chloride (0.67 mL, 0.6 M in hexane, 0.40 mmol) at −78 °C under argon, and the mixture was stirred for 15 min. The reaction mixture was condensed with propionaldehyde under the same conditions, and the ratio was determined after conversion to the acetate complexes by the above-mentioned method. The other metal enolates were prepared by similar techniques.

Aldol Reaction of (*o*-Methoxyacetophenone)$Cr(CO)_3$ (7) via Boron Enolate. To a solution of $(n\text{-}Bu)_2BOTf$ (110 mg, 0.40 mmol) and $(i\text{-}Pr)_2NEt$ 52 mg, 0.40 mmol) in ether (3 mL) was added a solution of (*o*-methoxyacetophenone)$Cr(CO)_3$ (57 mg, 0.29 mmol) in ether (3 mL) at −78 °C. After being stirred for 30 min, a solution of propionaldehyde (23 mg, 0.40 mmol) in ether (0.5 mL) was added to the above mixture. The reaction mixture was stirred for 30 min at −78 °C and then quenched with a buffer of phosphoric acid and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. Purification by SiO_2 column chromatography gave a diastereomeric mixture of **8** (R^1 = Et) and **9** (R^1 = Et) (55 mg, 80%) as red crystals. The ratio of diastereomers was determined by 400 MHz ^1H NMR. Recrystallization of the crude complex from ether/hexane afforded pure **8** (R^1 = Et): mp 70 °C; ^1H NMR ($CDCl_3$) δ 1.00 (3 H, t, *J* = 7), 1.55 (2 H, m), 2.94 (1 H, dd, *J* = 10, 18), 3.11 (1 H, d, *J* = 4), 3.14 (1 H, dd, *J* = 3, 18), 3.86 (3 H, s), 4.10 (1 H, m), 4.97 (1 H, t, *J* = 7), 5.04 (1 H, d, *J* = 7), 5.82 (1 H, dt, *J* = 1, 7), 6.27 (1 H, dd, *J* = 1, 7); IR ($CHCl_3$) 1980, 1810, 1660, 1460 cm^{-1}. Anal. Calcd for $C_{15}H_{16}O_6Cr$: C, 52.33; H, 4.68. Found: C, 52.33; H, 4.72. The corresponding acetate complex was prepared by the usual methods: mp 92 °C; ^1H NMR ($CDCl_3$) δ 0.95 (3 H, t, *J* = 7), 1.67 (2 H, m), 2.05 (3 H, s), 3.10 (1 H, dd *J* = 6, 18), 3.22 (1 H, dd *J* = 6, 18), 3.86 (3 H, s), 4.95 (1 H, t, *J* = 6), 5.02 (1 H, d, *J* = 6), 5.32 (1 H, m), 5.80 (1 H, dt, *J* = 1, 6), 6.26 (1 H, dd, *J* = 1, 6); IR ($CHCl_3$) 1980, 1810, 1725, 1680 cm^{-1}. Anal. Calcd for $C_{17}H_{18}O_7Cr$: C, 52.85; H, 4.70. Found: C, 52.81, H, 4.73.

Stereoisomeric Ar(1*S,2*R**),(*R**)-Acetate Complex of 9 (R^1 = Et).** Stereoisomeric acetate complex **9** (R^1 = Et) as an authentic sample for the comparison of stereochemistry was prepared from the stereodefined complex **2** (X = Me, R = Et), which was obtained as the major product by complexation with (naphthalene)$Cr(CO)_3$ as mentioned in Scheme I, by acetylation (Ac_2O/pyridine), and following hydrolysis of the acetal group (H_2SO_4/acetone) under the standard conditions: mp 121 °C; ^1H NMR ($CDCl_3$) δ 0.95 (3 H, t, *J* = 7), 1.68 (2 H, m), 2.03 (3 H, s), 3.03 (1 H, dd, *J* = 4, 17), 3.17 (1 H, dd, *J* = 9, 17), 3.87 (3 H, s), 4.94 (1 H, t, *J* = 6), 5.03 (1 H, d, *J* = 6), 5.40 (1 H, m), 5.80 (1 H, dt, *J* = 1, 6), 6.24 (1 H, dd, *J* = 1, 6); IR ($CHCl_3$) 1980, 1810, 1725, 1680 cm^{-1}. Anal. Calcd for $C_{17}H_{18}O_7Cr$: C, 52.85; H, 4.70. Found: C, 52.85, H, 4.71.

The aldol reactions of the complexes **7** and **10** via the boron enolates were carried out under the same conditions as the above-mentioned procedure. The physical data of some representative complexes are as follows. **8** (R^1 = Ph): mp 109 °C; ^1H NMR ($CDCl_3$) δ 3.36 (1 H, dd, *J* = 9, 18), 3.35 (1 H, d, *J* = 3), 3.43 (1 H, dd, *J* = 3, 18), 3.80 (3 H, s), 4.97 (1 H, t, *J* = 7), 5.03 (1 H, d, *J* = 7), 5.31 (1 H, td, *J* = 3, 9), 5.82 (1 H, dt, *J* = 1, 7), 6.30 (1 H, dd, *J* = 1, 7), 7.20 (1 H, d, *J* = 7), 7.38 (2 H, t, *J* = 7), 7.40 (2 H, d, *J* = 7); IR ($CHCl_3$) 1980, 1810, 1660, 1460 cm^{-1}. Anal. Calcd for $C_{18}H_{16}O_6Cr$: C, 58.17; H, 4.11. Found: C, 58.18, H, 4.11.

8 (R^1 = (*E*)-CH=CHCH$_3$): ^1H NMR ($CDCl_3$) δ 1.72 (3 H, d, *J* = 8), 2.99 (1 H, br s), 3.06 (1 H, dd, *J* = 8, 18), 3.14 (1 H, dd, *J* = 4, 18), 3.85 (3 H, s), 4.66 (1 H, m), 4.96 (1 H, t, *J* = 7), 5.04 (1 H, d, *J* = 7), 5.55 (1 H, m), 5.79 (1 H, dd, *J* = 6, 15), 5.81 (1 H, dt, *J* = 1, 7), 6.27 (1 H, dd, *J* = 1, 7); IR ($CHCl_3$) 1980, 1810, 1660, 1460 cm^{-1}; MS *m/e* 356 (M^+), 338 ($M^+ - H_2O$), 254 ($M^+ - H_2O - 3CO$).

8 (R^1 = (*E*)-CH=CHPh): mp 105 °C; ^1H NMR ($CDCl_3$) δ 3.17 (1 H, dd, *J* = 9, 18), 3.24 (1 H, d, *J* = 4), 3.28 (1 H, dd, *J* = 4, 18), 3.85 (3 H, s), 4.98 (1 H, t, *J* = 7), 5.04 (1 H, d, *J* = 7), 5.83 (1 H, dt, *J* = 1, 7), 6.27 (1 H, dd, *J* = 1, 7), 6.31 (1 H, d, *J* = 6), 6.72 (1 H, d, *J* = 16), 7.24 (1 H, d, *J* = 7), 7.32 (2 H, t, *J* = 7), 7.41 (2 H, d, *J* = 7); IR ($CHCl_3$) 1980, 1810, 1660, 1460 cm^{-1}. Anal. Calcd for $C_{21}H_{18}O_6Cr$: C, 60.29; H, 4.34. Found: C, 60.44, H, 4.35.

8 (R^1 = CH(CH$_3$)$_2$): mp 85 °C; ^1H NMR ($CDCl_3$) δ 0.97 (3 H, d, *J* = 7), 0.99 (3 H, d, *J* = 7), 1.71 (1 H, m), 2.92 (1 H, dd, *J* = 10, 18), 3.03 (1 H, br s), 3.15 (1 H, dd, *J* = 3, 18), 3.85 (3 H, s), 3.95 (1 H, m), 4.96 (1 H, t, *J* = 7), 5.04 (1 H, d, *J* = 7), 5.82 (1 H, dt, *J* = 1, 7), 6.26 (1 H, dd, *J* = 1, 7); IR ($CHCl_3$) 1980, 1810, 1660, 1460 cm^{-1}. Anal. Calcd for $C_{16}H_{18}O_6Cr$: C, 53.63; H, 5.06. Found: C, 53.65, H, 5.10.

11 (L = PPh_3, X = OMe, Y = H): mp 154 °C; ^1H NMR ($CDCl_3$) δ 1.00 (3 H, t, *J* = 7), 1.56 (2 H, m), 2.88 (1 H, dd, *J* = 10, 18), 3.24 (1 H, dd, *J* = 3, 18), 3.49 (1 H, br s), 3.62 (3 H, s), 3.97 (1 H, t, *J* = 7), 4.07 (1 H, m), 4.48 (1 H, dt, *J* = 1, 7), 4.91 (1 H, dt, *J* = 6, 7), 5.88 (1 H, d, *J* = 6), 7.35 (9 H, m), 7.47 (6 H, m); IR ($CHCl_3$) 1900, 1840, 1660, 1285 cm^{-1}. Anal. Calcd for $C_{32}H_{31}O_5PCr$: C, 66.43; H, 5.40. Found: C, 66.43; H, 5.42.

11 (L = $P(OPh)_3$, X = OMe, Y = H): mp 127 °C; ^1H NMR ($CDCl_3$) δ 0.97 (3 H, t, *J* = 7), 1.52 (2 H, m), 2.82 (1 H, dd, *J* = 9, 18), 3.13 (1 H, dd, *J* = 3, 18), 3.38 (3 H, s), 3.42 (1 H, t, *J* = 7), 3.74 (1 H, d, *J* = 7), 4.05 (1 H, m), 5.40 (1 H, dt, *J* = 7, 7), 5.85 (1 H, d, *J* = 7), 7.35 (9 H, m), 7.47 (6 H, m); IR ($CHCl_3$) 1930, 1870, 1650, 1490, 1190, 910 cm^{-1}. Anal. Calcd for $C_{32}H_{31}O_8PCr$: C, 61.34; H, 4.99. Found: C, 61.27; H, 5.02.

11 (L = $P(OMe)_3$, X = OMe, Y = H): mp 75 °C; ^1H NMR ($CDCl_3$) δ 0.99 (3, H, t, *J* = 7), 1.56 (2 H, m), 2.85 (1 H, dd, *J* = 10, 18), 3.23 (1 H, dd, *J* = 2, 18), 3.52 (9 H, d, *J* = 11), 3.81 (3 H, s), 4.05 (1 H, m), 4.67 (1 H, dt, *J* = 2, 7), 4.76 (1 H, dd, *J* = 1, 7), 4.53 (1 H, dt, *J* = 4, 7), 5.97 (1 H, dd, *J* = 4, 7); IR ($CHCl_3$) 1920, 1860, 1650, 1020 cm^{-1}. Anal. Calcd for $C_{17}H_{25}O_8PCr$: C, 46.37; H, 5.72. Found: C, 45.68; H, 5.80.

Some aldol condensation products via boron enolates were characterized as the corresponding acetate complexes. Physical data of the acetate complexes of the following major aldol products **11** are as follows.

11 (L = CO, X = O^{i}Pr, Y = H): mp 93 °C; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t, *J* = 7), 1.33 (3 H, d, *J* = 7), 1.42 (3 H, d, *J* = 7), 1.50–1.80 (2 H, m), 1.98 (3 H, s), 3.00 (1 H, dd, *J* = 6, 16), 3.20 (1 H, dd, *J* = 6, 16), 4.45 (1 H, m), 4.81 (1 H, t, *J* = 7), 4.91 (1 H, d, *J* = 7), 5.30 (1 H, m), 5.70 (1 H, dt, *J* = 1, 7), 6.16 (1 H, dd, *J* = 1, 7); IR ($CHCl_3$) 1975, 1900, 1730, 1675 cm^{-1}. Anal. Calcd for $C_{19}H_{22}O_7Cr$: C, 55.07; H, 5.35. Found: C, 54.98; H, 5.42.

11 (L = CO, X = Y = OMe): mp 118 °C; ^1H NMR ($CDCl_3$) δ 0.88 (3 H, t, *J* = 7), 1.50–1.80 (2 H, m), 1.95 (3 H, s), 2.95 (1 H, dd, *J* = 6, 16), 3.10 (1 H, dd, *J* = 6, 16), 3.70 (3 H, s), 3.81 (3 H, s), 4.85 (1 H, dd, *J* = 2, 7), 5.05 (1 H, d, *J* = 2), 5.10–5.40 (1 H, m), 6.22 (1 H, d, *J* = 7); IR ($CHCl_3$) 1975, 1895, 1730, 1675 cm^{-1}. Anal. Calcd for $C_{18}H_{20}O_8Cr$: C, 51.93; H, 4.84. Found: C, 51.89; H, 4.90.

Preparation of (1*S*)-(+)-(*o*-Methoxyacetophenone)Cr(CO)$_3$ (17). Ar(1*S*,2*R*),1′(*S*)-(+)-[α-)*o*-methoxyphenyl)ethyl alcohol]$Cr(CO)_3$ (640 mg, 2.2 mmol),[18d] which was prepared by the diastereoselective complexation of (*S*)-α-(*o*-methoxyphenyl)ethyl alcohol with (naphthalene)$Cr(CO)_3$, was oxidized with DMSO (9 mL)/Ac_2O (6 mL) for 2.5 h at room temperature under argon, and then the reaction mixture was poured into water. The reaction mixture was extracted with ether. The extract was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated under reduced pressure. Purification with SiO_2 column chromatography gave **17** (515 mg, 80%) as red crystals: mp 77 °C; ^1H NMR ($CDCl_3$) δ 2.54 (3 H, m), 3.82 (3 H, s), 4.88 (1 H, dt, *J* = 1, 7), 4.97 (1 H, dd, *J* = 1, 7), 5.72 (1 H, dt, *J* = 1, 7), 6.29 (1 H, dd, *J* = 1, 7); IR ($CHCl_3$) 1980, 1810, 1670, 1280 cm^{-1}; $[\alpha]^{25}_D$

= +464 (c = 1.00, $CHCl_3$). Anal. Calcd for $C_{12}H_{10}O_5Cr$: C, 50.36; H, 3.52. Found: C, 50.30, H, 3.47.

(+)-Ar(1*S*,2*R*)-Tricarbonyl[*o*-methoxyphenyl 2(*R*)-hydroxy-3(*E*)-pentenyl ketone]chromium (18). To a solution of $(^nBu)_2BOTf$ (330 mg, 2.4 mmol) and $(^iPr)_2NEt$ (307 mg, 2.4 mmol) in ether (10 mL) was added a solution of (1*S*)-(*o*-methoxyacetophenone)$Cr(CO)_3$ (340 mg, 1.2 mmol) in ether (10 mL) at -78 °C under argon. After the solution was stirred for 30 min, (*E*)-crotonaldehyde(170 mg, 2.4 mmol) in ether (0.5 mL) was added at the same temperature. The reaction mixture was stirred for 30 min at -78 °C and then quenched with buffer of phosphoric acid and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified with SiO_2 column chromatography to give Ar(1*S*,2*R*),(*R*)-(+)-18 (350 mg, 72%) as red oil and the corresponding stereoisomeric Ar(1*S*,2*R*),(*S*)-complex (15 mg, 8%). Ar(1*S*,2*R*),(*R*)-(+)-18: ^1H NMR ($CDCl_3$) δ 1.72 (3 H, d, J = 8), 2.96 (1 H, br s), 3.07 (1 H, dd, J = 8, 18), 3.15 (1 H, dd, J = 4, 18), 3.85 (3 H, s), 4.68 (1 H, m), 4.96 (1 H, t, J = 7), 5.04 (1 H, d, J = 7), 5.56 (1 H, m), 5.79 (1 H, dd, J = 6, 15), 5.82 (1 H, dt, J = 1, 7), 6.27 (1 H, dd, J = 1, 7); IR ($CHCl_3$) 1980, 1810, 1660, 1460 cm^{-1}; MS m/e 356 (M^+), 338 ($M^+ - H_2O$); $[\alpha]^{25}_D$ = +305 (c = 1.00, $CHCl_3$). **Stereoisomeric Ar(1*S*,2*R*),(*S*)-complex:** ^1H NMR ($CDCl_3$) δ 1.72 (3 H, d, J = 8), 3.04 (1 H, m), 3.12 (2 H, m), 3.85 (3 H, s), 4.59 (1 H, m), 4.95 (1 H, t, J = 7), 5.02 (1 H, d, J = 7), 5.59 (1 H, m), 5.77 (1 H, m), 5.81 (1 H, dt, J = 1, 7), 6.37 (1 H, dd, J = 1, 7); IR ($CHCl_3$) 1980, 1810, 1660, 1460 cm^{-1}; MS m/e 356 (M^+), 338 ($M^+ - H_2O$); $[\alpha]^{25}_D$ = +262 (c = 1.00, $CHCl_3$).

(-)-Ar(1*S*,2*R*)-Tricarbonyl[6-(*o*-methoxyphenyl)-4(*R*),6-(*R*)-diacetoxy-2(*E*)-hexene]chromium (19). To a suspended mixture of $LiAlH_4$ (24 mg, 0.63 mmol) in ether (5 mL) was added a solution of Ar(1*S*,2*R*),(*R*)-(+)-18 (105 mg, 0.29 mmol) in ether (5 mL) with stirring at -78 °C under nitrogen. After being stirred for 30 min at -78 °C, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was treated with Ac_2O (0.5 mL) and pyridine (2 mL) in the presence of a catalytic amount of *p*-(dimethylamino)pyridine. After being stirred for 2 h at room temperature, the reaction mixture was poured into cold 1 M aqueous HCl solution and extracted with ether. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated under reduced pressure. Purification with SiO_2 column chromatography gave Ar(1*S*,2*R*),(*R*)-(-)-19 (110 mg, 84%): mp 122 °C; ^1H NMR ($CDCl_3$) δ 1.72 (3 H, d, J = 8), 2.05 (3 H, s), 2.09 (3 H, s), 2.16 (2, H, m), 3.85 (3 H, s), 4.78 (1 H, t, J = 7), 4.99 (1 H, d, J = 7), 5.33 (1 H, m), 5.47 (1 H, dd, J = 7, 8), 5.58 (1 H, dt, J = 1, 7), 5.80 (2 H, m), 5.88 (1 H, dd, J = 1, 7); IR ($CHCl_3$) 1980, 1810, 1730, 1250 cm^{-1}; $[\alpha]^{25}_D$ = -45 (c = 0.10, $CHCl_3$). Anal. Calcd for $C_{20}H_{22}O_8Cr$: C, 54.30; H, 5.01. Found: C, 54.39; H, 5.11.

(-)-Ar(1*S*,2*R*)-Tricarbonyl[dimethyl 5-(*o*-methoxyphenyl)-1(*S*)-methyl-5(*R*)-acetoxy-2(*E*)-pentenylmalonate]chromium (20). Bis(μ-chloro)bis(π-allyl)dipalladium (4.1 mg, 0.011 mmol) and 1,2-bis(diphenylphosphino)ethane (dppe) (9.0 mg, 0.022 mmol) were placed in a 30-mL two-necked flask equipped with a serum cap and a three-way stopcock. The flask was filled with argon after evacuation, and to it were added through the serum cap with a syringe 5 mL of THF and 50 mg (0.11 mmol) of Ar(1*S*,2*R*),(*R*)-19 at 0 °C. The mixture was stirred at 0 °C for 5 min, and a solution of sodium dimethyl malonate was added at 0 °C, which was prepared in another flask by addition of 24 mg (0.18 mmol) of dimethyl malonate to a suspension of 5.4 mg (0.14 mmol) of 60% sodium hydride in mineral oil in THF (0.8 mL) at 0 °C. The reaction mixture was kept stirring at room temperature for 12 h, hydrolyzed with water, and extracted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. Purification of the residue by silica gel column chromatography with ether/hexane gave 60 mg (99%) of Ar(1*S*,2*R*),(*S*)-(-)-20: ^1H NMR ($CDCl_3$) δ 1.07 (3 H, d, J = 7), 2.06 (3 H, s), 2.49 (1 H, m), 2.58 (1 H, m), 2.74 (1 H, m), 3.29 (2 H, d, J = 9), 3.71 (3 H, s), 3.74 (3 H, s), 3.79 (3 H, s), 4.79 (1 H, t, J = 7), 4.98 (1 H, d, J = 7), 4.53 (1 H, m), 4.58 (1 H, dt, J = 1, 7), 5.79 (1 H, dd, J = 1, 7), 5.83 (1 H, m); IR ($CHCl_3$) 1970, 1880, 1730, 1230 cm^{-1}; MS m/e 514 (M^+), 430 (M^+ - 3CO); $[\alpha^{25}_D]$ = -68 (c = 0.10, $CHCl_3$).

(-)-Ar(1*S*,2*R*)-Tricarbonyl[dimethyl 5-(*o*-methoxyphenyl)-1(*S*),5(*R*)-dimethyl-3(*E*)-pentenylmalonate]chromium (21). To a solution of (1*S*,*R*,*S*)-20 (50 mg, 0.09 mmol) in CH_2Cl_2 (5 mL) was added trimethylaluminum in hexane (1.5 M, 0.32 mL, 0.48 mmol) at -78 °C under argon. The reaction mixture was warmed to 0 °C over 3 h, quenched with water, and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was chromatographed on silica gel with ether/hexane to afford (-)-1,5-*syn*-21 (40 mg, 87%) which was identical with authentic racemate complex[18e] by ^1H NMR spectra: ^1H NMR ($CDCl_3$) δ 1.09 (3 H, d, J = 7), 1.11 (3 H, d, J = 7), 2.00-2.18 (1 H, m), 2.35-2.42 (1 H, m), 2.75-2.85 (1 H, m), 2.88-2.98 (1 H, m), 3.30 (1 H, d, J = 8), 3.69 (3 H, s), 3.71 (3 H, s), 3.72 (3 H, s), 4.86 (1 H, t, J = 7), 5.00 (1 H, d, J = 7), 5.44-5.60 (4 H, m); IR ($CHCl_3$) 1970, 1890, 1730, 1260 cm^{-1}; MS m/e 470 (M^+), 386 (M^+ - 3CO); $[\alpha]^{25}_D$ = -120, (c = 0.10, $CHCl_3$).

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Total Synthesis of Dihydromevinolin and a Series of Related 3-Hydroxy-3-methylglutaryl Coenzyme A Reductase Inhibitors

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The natural product dihydromevinolin, **2**, and a series of structurally related 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, **3-6**, have been synthesized. The key features are an intramolecular Diels-Alder reaction to form a functionalized decalin skeleton with six asymmetric centers in a stereocontrolled manner, the selective manipulation of the functional groups, and an improved method for the introduction and elaboration of the δ-lactone portion. Analogue **6** was approximately 10-fold more potent than **2** as an inhibitor and was produced in multigram quantities.

Introduction

Coronary heart disease (CHD) and atherosclerosis are the major causes of mortality in the western world. Epidemiological studies have revealed that there is a strong correlation between the incidence of CHD and the level of cholesterol in the blood, particularly low-density lipo-

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