Benzylic Activation and Stereochemical Control in Reactions of Tricarbonyl(arene)chromium Complexes

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Abstract

This chapter covers reactions of (η^6-arene) chromium complexes that occur in the side chain of arene, and reactions that exhibit stereocontrol as a result of complexation. Reactions that focus on nucleophilic additions to the chromium-coordinated aromatic ring and on directed lithiation of the arene ring are not covered.

The tricarbonyl(η^6-arene) complexes are readily prepared by several convenient methods, and these complexes are relatively stable to air and moisture. Most arenes will coordinate to the tricarbonyl fragment. Certain functional groups are incompatible and electron withdrawing groups, such as CHO and CO_2H, retard complexation. Protection of these functional groups as acetals or esters followed by chromium complexation and hydrolysis procedures give the corresponding tricarbonylchromium complexes of benzaldehyde or benzoic acid in good yields. Electron-donating substituents accelerate the rate of complexation. The chemical consequences of chromium complexation include (1) the activation of the aromatic ring to nucleophilic addition; (2) enhancement of acidity in the side chain; (3) enhancement of the rate of solvolysis in the side chain; (4) enhancement of acidity of aromatic hydrogens: (5) control of reactions by steric effects of the tricarbonylchromium fragment. After the reaction, the tricarbonylchromium fragment can be easily removed by mild oxidation. When the arene ring is disubstituted with different substituents at the ortho and meta positon, the complexes are planar chiral and the substrates are useful for asymmetric synthesis.

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1. Introduction

Although a wide range of (η^6-arene)transition-metal compounds, including those of Cr, Mo, W, Ru, V, Mn, and Rh, are known, those of chromium are especially useful in synthetic organic chemistry. This chapter covers reactions of (η^6-arene)-chromium complexes that occur in the side chain of the arene, and reactions that exhibit stereocontrol as a result of the complexation. Reactions that focus on nucleophilic additions to the chromium-coordinated aromatic ring and on directed lithiation of the arene ring have been reviewed (1-15) and are not covered here.

The tricarbonyl(η^6-arene)chromium complexes are readily prepared by several convenient methods, and these complexes are relatively stable to air and moisture. Most arenes will coordinate to the tricarbonylchromium fragment. However, certain functional groups are incompatible (e.g., NO_2 and CN), (16) and electron-withdrawing groups such as CHO and CO_2H retard complexation. Protection of these functional groups as acetals or esters followed by chromium complexation and hydrolysis procedures gives the corresponding tricarbonylchromium complexes of benzaldehyde or benzoic acid in good yields. Electron-donating substituents accelerate the rate of complexation. The chemical consequences of chromium complexation include (Figure 1): (1) activation of the aromatic ring to nucleophilic addition; (2) enhancement of acidity in the side chain; (3) enhancement of the rate of solvolysis in the side chain; (4) enhancement of acidity of aromatic hydrogens; and (5) control of reactions by steric effects of the tricarbonylchromium fragment. After the reaction, the tricarbonylchromium fragment can be removed easily by mild oxidation (e.g., air, cerium(IV), iodine, electrochemical oxidation) to generate the substituted arenes. When the arene ring is disubstituted with different substituents at the ortho or meta position, the (arene)chromium complexes are planar-chiral and the substrates are useful for asymmetric synthesis.

Figure 1. Chemical consequences of chromium complexation.
[Full View]

The bond types used in the structural representations of the tricarbonylchromium complexes indicate the relative configuration of the complex. A solid bond **A** indicates that the configuration is undefined, or that the complex has no incident planar chirality; a squiggle bond **B** indicates a racemic mixture; a dotted line **C**, and a wedge **D** are obvious for the complexes shown with absolute configuration, but are principally used to designate relative configuration within a molecule when additional elements of chirality are present. In such examples, the bond type does not necessarily represent absolute configuration.

$Cr(CO)_3$	$Cr(CO)_3$	$Cr(CO)_3$	$Cr(CO)_3$
A	**B**	**C**	**D**

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2. Mechanism and Stereochemistry

1^6-(Arene)chromium complexes have considerable utility in organic synthesis. Useful organic reactions have been developed on the basis of the strong electron-withdrawing ability of the tricarbonylchromium fragment. Thus nucleophilic additions to the chromium-complexed arene ring take place regioselectively. This reaction is now at a fairly advanced stage of exploitation. Both anions and cations are stabilized at the benzylic positions of the chromium-complexed arenes by the tricarbonylchromium unit, and organic reactions based on this stabilization have been developed. Furthermore, the $Cr(CO)_3$ fragment is often used as a stereoface-directing group, whereby a reagent preferentially approaches the substrates from the face opposite to the metal (exo-approach). The steric bulk of the tricarbonylchromium is sufficient to make such stereocontrol effective. This effect is observed even two or three carbon atoms away from the chromium-coordinated arene ring. However, in some reactions, endo-approach of the reagents has been observed.

1^6-(Arene)chromium complexes that bear an unsymmetrical 1,2- or 1,3-disubstituted arene ligand are no longer superimposable on their mirror images. These enantiomers have been termed *planar chiral compounds*. The stereochemical description of planar chirality is normally determined by following Schlögl's rule: (17, 18) the arene ring is viewed from the side that is not coordinated to the chromium fragment. The priority of the substituents is determined by the Cahn-Ingold-Prelog rules. If the priority order is clockwise, the absolute configuration is denoted as R_p, and in the opposite case as S_p. For example, if the priority order for the groups on the complex **A** is A > B, the absolute planar chirality is S_p (Figure 2).

Figure 2. Stereochemical description of planar chirality, where priority order is $A > B$.
[Full View]

In 1^6-(arene)chromium complexes, the following nomenclature of absolute configuration is used for better clarity. The bonds from the chromium atom to the arene ring are regarded as single bonds and all carbons of the ring are considered to be sp^3 carbons. Thus, enantiomer **B** is called (1*S*,2*R*) as shown in Figure 3 (priority a > b > c > d). (19, 20)

Figure 3. Nomenclature of absolute configuration in (aryl)chromium complex B.
[Full View]

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3. Scope and Limitations

3.1. Preparation of Tricarbonyl(arene)chromium Complexes
A general preparation of tricarbonyl(arene)chromium complexes under simple thermal conditions using $Cr(CO)_3L_3$ is shown in Eq. 1. (21) Electron-poor arenes possessing electron-withdrawing and t-acceptor substituents (e.g., NO_2) do not form complexes. Chromium complexes of disubstituted and more highly substituted arenes

$$\tag{1}$$

possessing stereogenic centers on a side chain are formed as mixtures of diastereomers. Ligand exchange with tricarbonyl(naphthalene)chromium for the complexation of such arenes gives significant diastereoselectivity. (22-24) The yellow-red tricarbonyl(arene)chromium complexes can be purified easily by crystallization from nonpolar solvents or by column chromatography. Tricarbonyl(arene)chromium complexes are somewhat sensitive to air in solution, but the solutions can be handled in air briefly and crystalline solids can be stored without special precautions.

3.1.1. Planar Chiral Tricarbonyl(arene)chromium Complexes
3.1.1.1. Resolution of Racemates
Racemic chromium complexes of benzoic acids, **1**, and anilines, **2**, have been resolved by fractional crystallization of the diastereomeric ammonium salts obtained with enantiomerically pure chiral amines (25-27) or chiral acids. (28) Brucine, quinidine, cinchonidine, and ɛ-methylbenzylamine can be employed as the chiral amine sources, and camphorsulfonic acid is used for the resolution of substituted aniline complexes. However, these resolution methods sometimes encounter difficulties in crystallization and recrystallization of the salts.

Substituted (benzaldehyde)chromium complexes are easily separated into pure enantiomers by column chromatography of suitable derivatives. Thus, the mixtures of diastereomers obtained by treatment of the complexes with L-valinol (Eq. 2) (29-31) or *S*-(–)-(ɛ-phenethyl)semioxamazide (Eq. 3) (32, 33) are easily separated in this way. Acid hydrolysis affords the substituted (benzaldehyde)chromium complexes in high optical purity.

(2)

(3)

3.1.1.2. Enzymatic Resolution

Biocatalysts can also be used for the resolution of racemic tricarbonyl(arene)chromium complexes. Tricarbonylchromium-complexed orthosubstituted benzyl alcohols are easily resolved into the chromium-complexed acetates and unreacted alcohols in high enantioselectivities and yields by treatment with lipase in the presence of acylating agents (Eq. 4). (34-36) Racemic ortho-substituted (benzaldehyde)chromium complexes can also be reduced with biocatalysts to the corresponding optically active tricarbonylchromium-complexed benzyl alcohols (Eq. 5). (37, 38)

(4)

(5)

3.1.1.3. Diastereoselective Tricarbonylchromium Complexation

Diastereoselective tricarbonylchromium complexation with face discrimination of the arene ring is

a useful method for the preparation of optically active chromium complexes. This discrimination arises via chelation control through an initial interaction between the chromium and the benzylic oxygen. For example, enantiomerically pure e-tetralol **3** undergoes diastereoselective complexation via an interaction with the benzylic oxygen to give the (*endo*-tetralol)chromium complex **4** with high selectivity (Eq. 6). (39, 40) Compound **4** is converted in good yield into planar chiral tricarbonyl(tetralin)-chromium (**5**) or tricarbonyl(tetralone)chromium by hydrogenolysis or oxidation.

(6)

In addition to cyclic compounds, highly diastereoselective complexation is also achieved even with acyclic secondary benzyl alcohols. Ligand-transfer reactions of ortho-substituted secondary benzyl alcohols **6** with tricarbonyl(naphthalene)-chromium or hexacarbonylchromium produce predominantly one diastereomer **7** (Eq. 7). (41, 42) Complementary diastereoselectivities in meta-substituted benzyl alcohols **8** and **9** can be achieved by temporary introduction of a TMS group at either the 2- or the 6-position (Eqs. 8a and 8b). (42)

(7)

The hydroxy group does not have to be at the benzylic position for efficient, diastereoselective complexation. Thus, under kinetic conditions with tricarbonyl(naphthalene)chromium, complexation of the ethylene acetals of 3-hydroxy ketones **10** gives the diastereomers **11** with high diastereoselectivity (Eq. 9). (43) The steric effect of the acetal is important in this reaction.

(8a)

(8b)

9 R = Me, OPr-i

(88–97%) 100% de

(9)

10

11 (80–95%) 80–96% de

Some chiral acetals or aminals derived from ortho-substituted benzaldehydes form the corresponding chromium complexes with moderate to excellent selectivity depending on the substrates and reaction conditions. Thus, the chiral aminal **12** derived from (*R,R*)-1,2-*bis*-(*N*-methylamino)cyclohexane is complexed under kinetic conditions producing predominantly one isomer, whereas under thermodynamic conditions with $Cr(CO)_6$ the other diastereoisomer is formed as the major product (Eq. 10). (44) Hydrolysis of the aminals produces the optically active ortho-substituted tricarbonyl(benzaldehyde)chromium complexes with high enantiomeric purity.

(10)

	R	I:II	
(naphthalene)Cr(CO)₃, rt	Me	97:3	(80%)
	OMe	98:2	(—%)
Cr(CO)₆, *n*-Bu₂O, 140°	Me	12:88	(60%)
	OMe	9:91	(55%)

3.1.1.4. Ortho-Lithiation

Enantioselective ortho lithiation of monosubstituted tricarbonyl(benzene)chromium complexes in the presence of a chiral base provides a useful method for the preparation of optically enriched disubstituted (benzene)-chromium complexes. For example, tricarbonyl(anisole)chromium is lithiated with a chiral lithium amide base in the presence of an electrophile, e.g., chlorotrimethylsilane, to give the ortho-silylated complex in 84% ee (Eq. 11). (45) Formation of the anion intermediate, prior to adding the electrophile, results in lower enantioselectivity.

(11)

(83%) 84% ee

Diasteroselective ortho deprotonation has also been observed with enantiopure (arene)chromium complexes to afford the planar chiral (arene)chromium complexes. (3) The chromium complexes of *N,N*-dimethyl-1-phenylethylamine and chiral benzaldehyde acetals are deprotonated smoothly by *tert*-butyllithium, and the resulting ortho-lithio derivatives are trapped with various electrophiles with high selectivity to produce planar chiral (arene)chromium complexes (Eqs. 12 and 13). (46-49)

$$\text{EX = MeOSO}_2\text{F, TMSCl, Ph}_2\text{PCl; E = Me, TMS, Ph}_2\text{P}$$

Note: EX = electrophile, where X = the displaced ion or functional group.

(12)

EX = TMSCl, MeI, Bu₃SnCl, PhCOPh, Ph₂PCl, CH₂=CHCH₂Br
E = TMS, Me, Bu₃Sn, Ph₂C(OH), Ph₂P, CH₂=CHCH₂

(13)

3.1.1.5. Nucleophilic Addition-Hydride Abstraction

Diasteroselective nucleophilic addition of organolithium reagents takes place regioselectively at one of the ortho positions of the chiral hydrazones derived from the (benzaldehyde)chromium complex and (*S*)-1-amino-2-(methoxymethyl)pyrolidine (SAMP). The anionic cyclohexadienylchromium intermediate generated gives the planar chiral ortho-substituted (benzaldehyde)chromium complex with high optical purity by endo-hydride abstraction with triphenylmethyl cation followed by acidic hydrolysis (Eq. 14). (50) This type of reaction is further extended to the preparation of planar chiral orthosubstituted (benzaldehyde)chromium complexes from non-chiral (arene)chromium complexes in the presence of (+)-(1*S*,2*S*)-1,2-dimethoxy-1,2-diphenylethane as a chiral ligand (Eq. 15). (51)

R = Me, Ph, *n*-Bu

(14)

(15)

1. RLi, L* (2 eq), THF, −78°, 6 h
2. Ph₃C⁺ PF₆⁻, CH₂Cl₂, −78° to rt, 12 h
3. H⁺, H₂O

(60-68%) 58-95% ee

$$L^* =$$ Ph, OMe / Ph, OMe 1S,2S

3.2. Additions to the Carbonyl Group of Coordinated Arylaldehydes and Aryl Alkyl Ketones
3.2.1. Nucleophlic Additions to Tricarbonyl(arylaldehyde)chromium Complexes

Tricarbonyl(arylaldehyde)chromium complexes react with Grignard reagents, organolithiums, and phosphorus (52) and arsenic ylides (53) to produce the expected products as well as chromium-free parent compounds (Eqs. 16 and 17). The chromium-complexed carbonyl compounds also take part in Reformatsky reactions (Eq. 18) (52) and Baylis-Hillman reactions (Eq. 19). (54)

$$\frac{CH_3\overset{+}{P}Ph_3\ Br^-}{n\text{-BuLi, ether}}$$

(73%)

(16)

$$\frac{\overset{+}{AsPh_3}\ Br^-}{LDA,\ THF,\ -78°}$$

(55%)

cis, trans mixture

(17)

1. BrZnCH₂CO₂Et, DME
2. H⁺

$$\frac{P_2O_5}{benzene,\ reflux}$$

(61%)

(18)

$$\frac{Z}{DABCO,\ rt}$$
Z = CO₂Me, CN
R = Me, OMe, F, Cl

(85-97%) >95% de

$$\frac{h\nu,\ air}{MeCN}$$

(19)

Diastereoselectivity and enantioselectivity in nucleophilic addition reactions to the carbonyl group are different from those of the uncomplexed parent arenes in some cases. For example, the optical purity in the asymmetric allylboration of tricarbonyl(benzaldehyde)chromium (13) to give chromium complex 14a is significantly improved (83% ee) compared with that of benzaldehyde

itself (55% ee). The corresponding asymmetric E-crotyl boration produces complex **14b** with high antiselectivity and enantiomeric excess (Eq. 20). (55) In $BF_3 \cdot OEt_2$ catalyzed aldol reactions of complex **13** with trimethylsilyl enol ethers derived from cycloalkanones, the diastereoselectivity is reversed compared to that of free benzaldehyde (Eq. 21). (56) Addition of crotylmagnesium bromide in the presence of triethylaluminum is not diastereoselective, whereas treatment with 2-butenylchromium(II) gives the corresponding anti-adducts exclusively. (57)

14a R = H, (90%) 83% ee
14b R = Me, (90%) 96% de, 92% ee

$$(20)$$

(65-98%)

$$(21)$$

Tricarbonyl(arylaldehyde)chromium complexes having an ortho or a meta substituent are chiral and exist in two enantiomeric forms. In general, nucleophilic additions to the benzylic carbonyl of ortho-substituted tricarbonyl(benzaldehyde)chromium complexes proceed with extremely high diastereoselectivity. Additions of Grignard or organolithium reagents to tricarbonyl(*o*-methylbenzaldehyde)chromium (**15**) afford predominantly one diastereomer (Eq. 22). (19, 58-64) The observed diastereoselectivity can be rationalized in terms of approach of the nucleophile from the exo

I (70-99%)   II

RMgX	I:II
EtMgBr	100:0
≡—MgBr	100:0
C_2H_5Li	94:8
MeLi	100:0
TMS—≡—Li	>98:2

$$(22)$$

side to a preferred conformation, in which the carbonyl oxygen is anti to the ortho methyl group because of a steric effect (Figure 4). Similarly, tricarbonyl(*o*-methoxy-benzaldehyde)chromium reacts with Grignard and organolithium reagents to generate e-substituted benzyl alcohols via exo-attack of nucleophiles on the carbonyl groups. As expected, the meta-substituted benzaldehyde complexes exhibit very low asymmetric induction on the basis of this model (Eq. 23). (58)

(23)

Nuc⁻

Figure 4. Exo-face attack of a nucleophile to the anti-conformation (R/C ✕O) of an (aryl) chromium complex.
[Full View]

The reactions of nucleophiles with enantiomerically pure ortho-substituted (benzaldehyde) chromium complexes provide an asymmetric synthesis of secondary benzyl alcohols. For example, (1R)-(–)-tricarbonyl(o-methylbenzaldehyde)chromium (**16**) is condensed with tosylmethyl isocyanide in the presence of potassium carbonate to give only one diastereomer of the oxazoline, which is converted into the enantiomerically pure (+)- £-amino alcohol **17** by oxidative demetalation in the presence of air, followed by reduction (Eq. 24). (65)

(24)

(–)-(1R,2S)-**16**   trans   (+)-(S)-**17**
              (95%) 100% de   (60%) 100% ee

A variety of nucleophiles can be used in the addition reactions of tricarbonyl-chromium-complexed ortho-substituted benzaldehydes, and the reactions proceed with high selectivities. Additions of organozinc reagents occur with somewhat lower selectivity. (66) Reformatsky reagents add to the chromium-complexed benzaldehyde with moderate to good selectivities. (67, 68) Reaction of **18** with lithium ethyl isocyanoacetate produces the trans oxazoline **19**, but diastereoselectivity at the benzylic position is moderate (80%) (Eq. 25). (69) Addition of the formamidine anion to chromium

(25)

18 R = Me, OMe   **19** (95-98%) >96% de
                      80% de (α-position)

complex **18** in the presence of MgBr$_2$ proceeds with high diastereoselectivity (70) (Eq. 26).

Trimethylsilylcyanation of the chromium complex **18** in the presence of a Lewis acid is also highly diastereoselective (Eq. 27). (71) Base-catalyzed addition of nitromethane occurs although the diastereoselectivity is lower (Eq. 28). (72) Similarly, the Darzens reaction of chromium complex **18** with phenacyl chloride affords trans-epoxide **20** with high diastereoselectivity at the benzylic stereogenic center (Eq. 29). (73, 74) Additions of tosylmethyl isocyanide in the presence of base, (75) or reactions with methyl acrylate or acrylonitrile, (54) are also highly diastereoselective. A

combination of chloromethyl iodide and methyllithium is used for stereoselective epoxide formation. This reaction is useful for the synthesis of axially chiral vancomycin A-B ring systems. (76) The high diastereoselectivity in these addition reactions is the result of the anti orientation of the ortho carbonyl groups.

$$(26)$$

$$(27)$$

$$(28)$$

$$(29)$$

The enantiomerically pure tricarbonyl(*o*-trialkylsilylbenzaldehyde)chromium complex is potentially useful for asymmetric synthesis, since the trialkylsilyl group is readily removed from the products by treatment with fluoride ion. However, nucleophilic additions occur with complementary diastereoselectivity depending on the presence (or absence) of a Lewis acid. Thus, (+)-(1*S*)-tricarbonyl(*o*-triisopropyl-silylbenzaldehyde)chromium (**21**) reacts with methyllithium to give (*R*)-1-phenyl-ethyl alcohol, while the addition of Grignard reagent in the presence of magnesium bromide etherate affords the corresponding antipode (*S*)-phenylethyl alcohol (Eq. 30). (30, 77)

$$(30)$$

The anti and syn conformations of the carbonyl oxygen in complex **21** are in thermal equilibrium in

the absence of Lewis acids, and the bulky triisopropylsilyl group in the anti conformation sterically hinders nucleophilic attack at the carbonyl group. Therefore, the major product under these conditions arises from the addition of nucleophiles to the syn conformation. On the other hand, the carbonyl oxygen favors the anti conformation because of coordination in the presence of Lewis acids, and the complementary diastereomer is formed from addition to the anti-conformer (Eq. 31, models shown for enantiomers of **21**).

$$\text{(31)}$$

anti $R_3Si/C=O$ syn $R_3Si/C=O$ anti

The reactions of silyl enol ethers with chromium complex **22** in the presence of Lewis acids give the aldol adducts with high stereoselectivities resulting from addition to the anti carbonyl oxygen conformation (Eq. 32). (56, 78, 79) o-Tifluoromethyl-, (71, 75) fluoro-, (70, 80) dimethylamino-, and e-*N,N*-dimethylaminoethyl- (81) substituted tricarbonyl(benzaldehyde)chromium complexes undergo such highly diastereoselective additions via the anti conformation of the carbonyl group.

$$\text{(32)}$$

(+)-(1*S*)-**22**   (96%)

anti:syn = 96:4; anti = 98% ee

3.2.2. Pinacol and Related Coupling Reactions

One-electron reductive coupling of benzaldehyde or benzaldimine with lanthanoid or low-valent transition metals, giving the corresponding pinacols or 1,2-diamines, is a well-known reaction. (82, 83) However, this reductive coupling usually affords diastereomeric mixtures of dl (threo) and meso (erythro) products. Similarly, tricarbonyl(benzaldehyde)chromium complexes couple to produce the corresponding pinacols in good yields via tricarbonylchromium-stabilized ketyl radicals by reduction with samarium iodide. Racemic ortho-substituted benzaldehyde tricarbonylchromium complexes afford a mixture of tricarbonylchromium-complexed threo- and erythro-pinacols in variable ratios depending upon the nature of the ortho substituents and the reaction conditions (Eq. 33). (84) (Benzaldehyde)chromium or (*o*-methylbenzaldehyde)chromium complexes

$$\text{(33)}$$

afford mainly threo-pinacol products on reduction with SmI_2, whereas (*o*-bromobenzaldehyde) chromium produces predominantly the erythro isomer. Addition of HMPA to the reaction mixture leads to mostly erytho products in both cases.

Interestingly, each tricarbonylchromium-complexed threo- or erythro-pinacol isomer is obtained as a single stereoisomer from among three possible diastereomers from racemic ortho-substituted tricarbonyl(benzaldehyde)chromium complexes. (84) Racemic tricarbonyl(*o*-bromobenzaldehyde) chromium is coupled with SmI_2 in THF to afford tricarbonylchromium-complexed threo pinacol **23** and erythro complex **24** (Eq. 34). The threo-tricarbonyl(pinacol)chromium complex **23** is formed by a homocoupling of tricarbonyl(benzaldehyde)chromium complexes having the same planar

(34)

chirality, while the erythro isomer **24** is obtained by a hetero-coupling of different planar chiral chromium complexes. As expected, enantiomerically pure tricarbonyl-(*o*-bromobenzaldehyde) chromium (**25**) produces the corresponding chromium-coordinated threo pinacol **26** stereoselectively without formation of the erythro isomer (Eq. 35). (85)

(35)

An intramolecular reductive coupling of mono-chromium-complexed biaryls **27** affords trans 1,2-diols stereoselectively on treatment with samarium diodide (Eq. 36). (86)

(36)

27 (79-85%) (96-98%)

R^1 = H, OMe, R^2 = H, Me, R^3 = H, Me

The ketyl radicals generated from tricarbonylchromium-complexed ortho-substituted benzaldehydes react with methyl acrylate producing single diastereomers of к-butyrolactones (Eq. 37). (87, 88) This radical-mediated reaction has also been applied to an intramolecular cyclization. The tricarbonylchromium complex **28**, when treated with SmI$_2$, undergoes an 8-endo-radical cyclization to afford a single diastereomer of the cyclization product, **29**, a key intermediate for the synthesis of steganone (Eq. 38). (89)

(37)

R = Me, OMe (53-72%)

(38)

28 **29** (73%)

3.2.3. Nucleophilic Additions to Tricarbonyl(alkyl aryl ketone)chromium Complexes

3.2.3.1. Acyclic Systems

Few examples of nucleophilic additions to simple achiral tricarbonyl(alkyl aryl ketone)chromium complexes that take advantage of chromium complexation for stereoselection have been reported. For example, oxazaborolidine-catalyzed asymmetric reduction of mono tricarbonylchromium-complexed benzophenone **30** is achieved with high enantioselectivity via coordination of the boron to the lone pair of the oxygen anti to the chromium-complexed ring (Eq. 39). (90) Baker's yeast reduction of tricarbonyl(acetophenone)chromium provides (*S*)-tricarbonyl(e-phenethylalcohol) chromium with 99% ee. (91) Unfortunately, similar reductions of higher homologs are unsatisfactory in both yield and enantioselectivity.

(39)

30   (99%) 98% ee

Diastereoselectivity is usually not observed in the reactions of crotyl metals with uncomplexed alkyl aryl ketones. However, when the corresponding chromium complexes are treated with crotylmagnesium chloride in the presence of triethylaluminum, the anti adducts are formed predominantly with high diastereoselectivity (Eq. 40). (57) In the presence of triethylborane, the diastereoselectivity is reversed.

(40)

R	Et$_3$M	I + II	I:II
Me	Et$_3$Al	(95%)	89:11
Et	Et$_3$Al	(96%)	85:15
i-Pr	Et$_3$Al	(65%)	84:16
Me	Et$_3$B	(70%)	33:67

The tricarbonylchromium complexes of ortho-substituted alkyl phenyl ketones have planar chirality, and, therefore, the carbonyl faces are diastereotopic. High diastereoselectivities are generally observed in nucleophilic additions to the benzylic positions of these chromium complexes via addition to the anti conformation with respect to the carbonyl oxygen. Tricarbonyl(o-anisyl) chromium alkyl ketones **31** give nucleophilic addition products with extremely high selectivities (Eq. 41). (20, 43, 58, 61, 92-98) By contrast, the corresponding ortho-hydroxy complexes **32** produce addition products by attack on the syn conformation resulting from chelation of the magnesium ion with the oxygens (Eq. 42). (58, 93)

(41)

31 R = Me, Et, Pr   anti OMe/C=O

NuX = KBH$_4$, LiAlH$_4$, NaBH$_4$, MeLi
Note: NuX = nucleophile, where X = the displaced ion or functional group

(42)

32 R = Me, Et

Treatment of the chiral (1-phenylsulfinyl-2-pentanoylbenzene)chromium **33** with dimethylsulfonium methylide affords a single diastereomer of the epoxide (Eq. 43). (99)

$$(43)$$

(50%) >92% de

Nucleophilic addition to a distal-positioned carbonyl group shows good diastereoselectivity. Prelog-type nucleophilic addition of Grignard reagents to the e-keto esters derived from optically pure 1-(*o*-methylphenyl)propanol (or pentafluoro-1-phenylpropanol) chromium complexes **34** followed by basic hydrolysis leads to optically active e-hydroxy carboxylic acids with high selectivities (Eq. 44). (60, 100)

$$(44)$$

34 R = Et, C₂F₅;
R¹ = Ph, Me   R²M = MeMgI, C₃H₇C≡CMgBr,
C₂F₅Li, L-selectride

(65-90%)

84-100% ee

3.2.3.2. Cyclic Systems

In tricarbonylchromium-complexed cyclic alkyl aryl ketones such as e-tetralone, e-indanone, and benzocyclobutanone, nucleophiles usually attack the carbonyl group from the anti face to generate endo-hydroxy compounds. Thus, reduction with hydride reagents, and additions of Grignard or organolithium reagents, afford exclusively the endo alcohols (Eq. 45). (101-104) Therefore, enantiomerically pure indanols and tetralols are obtained starting from optically pure

$$(45)$$

R¹, R² = Me, Et   NuX = LiAlH₄, NaBH₄, MeLi,
n = 0, 1   MeMgBr, PhMgBr

35 R = Me, Et, CH(OH)Me

36

chromium-complexed cyclic ketones by nucleophilic addition to the carbonyl group followed by oxidative demetallation. (104, 105) 2-Alkyl substituents on the tricarbonyl-chromium-complexed ℮-indanone and ℮-tetralone do not affect the stereoselectivity of the nucleophilic additions to the carbonyl group even in the case of an exo-2-alkyl substituent. Related substituted (℮-tetralone) chromium complexes **35** are also reduced stereoselectively to the endo alcohol derivatives. (106, 107) Similarly, the 4-exo-isopropyl derivative **36** provides the corresponding endo alcohols upon treatment with hydride or MeLi. (102, 103)

Although the addition of crotylmagnesium chloride to (℮-tetralone)chromium complex **37** is a stereoselective exo-addition with respect to the $Cr(CO)_3$ fragment, it is nonselective for the generation of new stereogenic centers in the crotyl fragment. However, in the presence of one equivalent of triethylaluminum, one diastereomer is obtained predominantly (Eq. 46). (57) The reversed selectivity at the stereogenic center generated is observed in the presence of triethylborane.

additive	I + II	I:II
none	(75%)	50:50
Et₃Al	(73%)	93:7
Et₃B	(30%)	28:72

(46)

Tricarbonyl(f-tetralone)chromium complexes also show high exo-selectivity in nucleophilic additions generating the endo-hydroxy derivatives. For example, reduction of ketone **38** with $LiAlH_4$ or $NaBH_4$ gives *endo*-tricarbonyl(2-tetralol)chromium with good diastereoselectivity (Eq. 47). (108) The tricarbonyl(f-indanone)chromium complex, when treated with sodium borohydride or alkyllithium, produces the corresponding endo alcohols as well. (109)

(47)

Nucleophilic additions to both the tricarbonyl(indoxyl)chromium and tricarbonyl (benzocyclobutanone)chromium complexes produce the corresponding endo alcohol complexes. (110, 111, 92) (Benzocyclobutanedione)chromium complex **39**, when treated with a large excess of ethylmagnesium bromide, gives the normal exo-addition product (Eq. 48). (112) Reaction of the chromium complex **39** with an excess of isopropenyllithium affords benzocyclooctane-1,4-diones by a double oxy-Cope rearrangement along with an intramolecular condensation product (Eq. 49). (113-115)

(48)

$$\text{(49)}$$

Complex **39** undergoes asymmetric Horner-Wadsworth-Emmons reaction with the optically active phosphonate anion derived from axially chiral BINOL derivative **40**, affording mono-Z-olefination with induction of planar chirality in high selectivity (Eq. 50). (116)

$$\text{(50)}$$

The tricarbonylchromium-complexed, lactone-bridged, biaryl **41** is stereoselectively reduced with achiral reducing agents, such as sodium borohydride, leading to only one detectable atropo-diastereomer (Eq. 51). (117)

$$\text{(51)}$$

DMAP = 4-(dimethylamino)pyridine

Tricarbonylchromium-complexed aryl ketones react with samarium(II) iodide, yielding the corresponding ketyl radicals, which can be trapped with methyl acrylate in the presence of *t*-BuOH

to produce к-lactones as single diastereomers (Eq. 52). (87, 88)

$$CH_2=CHCO_2Me \quad (65\%) \tag{52}$$
$$SmI_2, THF, t\text{-}BuOH, -78°$$

The asymmetric catalytic oxazaborolidine-catalyzed borane reduction (Itsuno-Corey reduction) of racemic (е-tetralone)chromium complexes takes place with kinetic resolution. At 50 ~ 56% conversion, the recovered (е-tetralone)chromium complex shows only 40 ~ 48% enantiomeric excess. However, on complete conversion, a 52:48 mixture of the endo- and exo-tetralol complexes is obtained in good enantiopurity (Eq. 53). (118) The formation of the exo isomer **II** involves an unprecedented hydride attack on the carbonyl group from the chromium-complexed face. It appears that the asymmetric reduction in the presence of oxazaborolidine-BH_3 catalyst is governed by reagent control.

$$BH_3 \cdot SMe_2 \text{ (6 eq)} \tag{53}$$

racemic

I endo   **I:II** = 51:49   **II** exo
93% ee   99% ee

3.3. Additions to Imines and Related Compounds
3.3.1. Nucleophilic Additions
A high degree of asymmetric induction is observed in nucleophilic additions to C ⋉N double bonds of imines derived from orthosubstituted (aniline)chromium complexes and aldehydes. For example, the E-imine chromium complexe **42**, when treated with an appropriate nucleophile, provides aniline derivatives with high diastereoselectivity (Eq. 54). (119, 120) A cyclic analog, tricarbonyl(4a-methyl-2,3,4a-tetrahydro-1*H*-carbazole)chromium, undergoes stereoselective addition to the C ⋉N double bond with an organolithium reagent (Eq. 55). (121)

$$BnMgX \quad (92\%) \ 100\% \text{ de} \tag{54}$$
$$-76°$$

42

$$n\text{-BuLi, toluene, rt} \quad (36\%) \tag{55}$$

The chiral chelated imine complex **44** is converted into the (–)-amine in 94% ee by stereoselective addition of methyllithium to the C⚋N double bond followed by workup, whereas addition of methyllithium to the non-chelated ketimine complex **43** gives no asymmetric induction (Eq. 56). (122) Similarlly, tricarbonylchromium-complexed benzaldimines undergo nucleophilic addition to the C⚋N double bond

(56)

with various organic and organometallic reagents. (119, 122-126) Addition of allylmagnesium bromide to the imine double bond in the presence of zinc chloride takes place with high diastereoselectivity (Eq. 57). (126) Reformatsky reagents react with chromium-complexed imines under activation by ultrasound affording nucleophilic addition products, which are cyclized into ß-lactams. This reaction proceeds with high diastereoselectivity (Eq. 58). (127)

(57)

I + II (97%), I:II = 65:35

(58)

Baylis-Hillman type reaction of (*N*-tosyl benzaldimine)chromium complex **45** with activated olefins, such as methyl acrylate, in the presence of a catalytic amount of DABCO, proceeds smoothly to afford benzylamine **46** as a single diastereomer (Eq. 59). (54)

(59)

The Strecker reaction of chromium-complexed benzaldimines is useful for the synthesis of arylglycine derivatives. Thus, the planar and axially chiral disulfinilimine complex (+)-**47** obtained by reaction of (+)-(*S*)-sulfinylamine with the corresponding aldehyde, when treated with diethylaluminum cyanide affords a nitrile complex, which is useful for the synthesis of the vancomycin A-B ring system (Eq. 60). (128) Condensation of a trans-benzaldimine complex **48** with the lithium enolate derived from ethyl 2-methylpropanoate gives a ƒ-lactam as a single diastereomer (Eq. 61). (129)

(60)

(21%)

(64-77%) >98% de

(61)

48 R = Me, OMe
X = H, OMe

3.3.2. Cycloadditions
[2 + 2]-Cycloaddition of (+)-tricarbonylchromium-complexed *N*-(2-methoxybenzylidene)aniline **49** with ketenes generated in situ from an acid chloride affords cis ƒ-lactams with high diastereoselectivity (Eq. 62). (130)

>98% de

R = CH$_3$CO$_2$ (92%)
R = PhO (98%)

(62)

Lewis acid mediated hetero-Diels-Alder reactions of the planar chiral ortho-substituted (benzaldimine)chromium complex **50** with Danishefsky's diene affords the 2,3-dihydro-4-pyridinone derivatives with high diastereoselectivity (Eq. 63). (54, 131) An intramolecular hetero-Diels-Alder reaction of chromium-complexed E-imine derivative **51** affords the trans-fused (η^6-octahydroacridine)chromium complex **52** diastereoselectively without formation of any cis-fused isomer (Eq. 64). (132)

$$ (63) $$

$$ (64) $$

N-Lithiated azomethine ylides, generated from ɛ-imino esters **53** by treatment with Lewis acids and an amine base, undergo highly diastereoselective cycloadditions with ɛ, ʄ-unsaturated esters and ketones to give pyrrolidine derivatives **54** (Eq. 65). (133)

$$ (65) $$

Similarly, 1,3-dipolar cycloadditions of tricarbonylchromium-complexed nitrone **55** with olefins to give cis-3,5-disubstituted isoxazolidines **56** proceed with much more stereoselectivity than with the corresponding uncomplexed substrates (Eq. 66). (134, 135) An intramolecular version of the 1,3-dipolar addition of chromium-complexed nitrone has also been reported. (136)

$$ (66) $$

3.3.3. Reductive Coupling Reactions

Tricarbonylchromium-coordinated benzaldimine complexes are reduced with samarium(II) diiodide to produce the corresponding 1,2-diamino coupling products. Enantiomerically pure ortho-substituted tricarbonyl(benzaldimine)chromium complexes **57** afford, diastereoselectively, chromium-complexed threo-1,2-diamines **58** without formation of erythro-1,2-isomers (Eq. 67). (137, 85) Radical intermediate **59**, generated by an exo-attack of samarium on the anti-oriented C✂N double bond, has a substantial amount of exocyclic double bond character owing to an interaction of the d-orbitals of chromium with a p-orbital at the benzylic carbon. This exocyclic double bond structure inhibits rotation of the C_e-C_{ipso} bond, and therefore, no racemization at the benzylic position is observed. On the other hand, the corresponding racemic complex gives a mixture of chromium-coordinated single threo- and single erythro-1,2-diamino coupling products, respectively, under the same conditions. (137)

$$(67)$$

3.4. Reactions of Tricarbonylchromium-Stabilized Benzylic Cations

Chromium -complexed benzylic carbocations are stabilized relative to the parent chromium free-ions by overlap of a filled d-orbital on the chromium with the empty p-orbital at the benzylic carbon. Solvolysis of benzyl chloride tricarbonylchromium is $\sim 10^5$ times faster than that of the corresponding uncomplexed chloride. (138) The benzyl cations thus formed are stabilized by the tricarbonylchromium fragment. These cations undergo facile reactions with various carbon or heteroatom nucleophiles, and with hydrides. (139)

3.4.1. Cyclic Systems

In tricarbonylchromium complexes of arenes with a fused ring, the benzylic carbocations generated do not have multiple conformations, and nucleophiles always attack from the exo-side. For example, 2-substituted *endo*-tricarbonyl(1-indanol)chromium (Eq. 68) and *endo*-tricarbonyl(1-tetralol)chromium complexes are stereoselectively converted into the corresponding exo 1-substituted chromium complexes via nucleophilic attack on the carbocations with inversion at the benzylic positions. (140-143) These reactions proceed via a S_N1 mechanism, and the exo-substituent at the vicinal position does not influence the stereochemical outcome of these reactions. Exo-leaving groups are displaced much more readily than are the corresponding endo groups, (141) and produce the same intermediate carbocation, which is trapped with nucleophiles giving the exo substitution products.

$$(68)$$

Carbon nucleophiles can also react with chromium-stabilized benzyl cations. Enol silyl ethers in the presence of zinc chloride give the exo-substitution complexes in good yields, regardless of the configuration of the leaving group (e.g., the exo- or endo-acetates shown in Eq. 69). (144, 145)

$$R = R^1 = H, R^2 = t\text{-Bu } (91\%)$$
$$R = R^1 = Me, R^2 = OMe \ (87\%)$$

(69)

Other nucleophiles such as electron-rich arenes, (146) ß-dicarbonyl compounds, organosilanes, (147) and organometallic and hydride reagents (102) show the same behavior with respect to stereocontrol in the fused cyclic (arene)chromium complexes. The presence of an additional substituent at the C_e position leads to asymmetric synthesis of quaternary centers. However, a competing olefin is sometimes observed. This problem can be circumvented by employing stronger nucleophiles. Both exo and endo 1-substituted (tetralin)chromium complexes are stereoselectively prepared from a common (e-tetralone)chromium complex by changing the addition order of the two nucleophiles (Eqs. 70a and 70b). (147) Thus, tricarbonyl(1-*exo*-methyl-1-*endo*-tetralol) chromium (61), which is obtained by reaction of tricarbonyl(e-tetralone)chromium (60) with methyllithium, is treated with trimethylallylsilane in the presence of titanium tetrachloride to afford stereoselectively tricarbonyl(1-*exo*-allyl-1-*endo*-methyl-tetralin)chromium (62) (Eq. 70a). On the other hand, tricarbonyl(1-*exo*-allyl-1-*endo*-tetralol)chromium (63), prepared by treatment of chromium complex 60 with allylmagnesium bromide, reacts with trimethylaluminum to give diastereoisomeric tricarbonyl(1-*endo*-allyl-1-*exo*-methyltetralin)chromium (64) (Eq. 70b).

(70a)

(70b)

3.4.2. Acyclic Systems

Stabilization of tricarbonylchromium-coordinated benzylic cations has its origin in the delocalization of the positive charge from the benzylic carbon to the chromium metal as represented by resonance structures. It can be expected that the carbocation exhibits a substantial amount of exocyclic double bond character (see for example, structure **65**) and this, in turn, causes rotation about the C_e-C_{ipso} bond to be restricted. Thus, no racemization at the benzylic position is observed even in acyclic systems (Eq. 71). (139) Therefore, optically pure tricarbonyl-chromium-complexed benzyl alcohols, when treated with sulfuric acid in acetonitrile, give Ritter-type products with complete retention of configuration at the benzylic position (Eq. 72). (148)

(71)

65

(72)

optically pure   (96%) 100% retention

This phenomenon can be used for stereoselective asymmetric carbon-carbon bond formation at the benzylic position. Thus, two diastereomers of tricarbonyl(o-2-butylanisol)chromium (**66** and **67**) are prepared stereoselectively with retention at the benzylic position via the chromium-stabilized benzylic carbocations by treatment of the corresponding allylic acetates with trialkylaluminums at low temperature (Eq. 73). (42)

(73)

66

67

An interconversion of the syn conformer to the thermodynamically more stable anti conformer of the chromium-complexed carbocation intermediates is observed at higher reaction temperatures. Thus, syn carbocation **69**, generated from ether **68**, is isomerized to the corresponding anti conformer **70** at higher temperature and then trapped with methanol, giving diastereoisomer **71** predominantly (Eq. 74). (139)

Time before addition of MeOH	Temp	**68:71**
3 min	0°	41:59
4 min	20°	8:92
4 min	40°	6:94

(74)

When combined with the stereoselective exo nucleophilic attack on tricarbonylchromium-complexed aryl ketones having an ortho methoxy group, this stereospecific substitution with nucleophiles via benzylic carbocations controls the configuration at the benzylic position with respect to the remote positions. With the choice of appropriate nucleophiles, different diastereomers can be prepared with high diastereoselectivity. Thus, addition of methyllithium at –78° to complex **72** followed by reduction with triethylsilane in the presence of a Lewis acid affords 1,5-syn dimethyl complex **73**, whereas the corresponding 1,5-anti dimethyl compound **74** is obtained by reduction with NaBH$_4$, acetylation, and subsequent treatment with trimethylaluminum (Eq. 75). (24)

(75)

In the acid-catalyzed cyclization of complex **75**, an intramolecular trapping of the chromium-stabilized carbocation proceeds with stereochemical retention, giving isoquinoline alkaloid **76** (Eq. 76). (149, 150)

$$(76)$$

75 → **76** (75%) >98% de

This carbon-carbon bond formation with retention of configuration of the benzylic carbocation has been applied to the total synthesis of a complex natural product, (–)-macrocarpal C. In a key step, the coupling of chromium-complexed chloroacetate **77** with a cyclic silyl enol ether in the presence of zinc chloride in dichlotromethane gives predominantly one diastereomeric chromium complex, which is converted into the chromium-free compound **78** in good overall yield (Eq. 77). (151, 152)

$$(77)$$

77 → **78** (61%)

The dimethylamino group at the chromium-complexed benzylic position is a useful leaving group for substitution with a variety of P-, N-, and O-nucleophiles via a chloride intermediate. (153-155) Thus, treatment of tricarbonyl[1-(e-dimethylamino)-ethylbenzene]chromium with 2-chloroethyl chloroformate affords a benzylic chloride with stereochemical retention. The resulting (benzyl chloride)chromium complex is further reacted with HPR_2 or amines in the presence of $TlPF_6$ to afford the corresponding substitution products (Eq. 78).

$$(78)$$

3.4.3. Benzylic Oxonium Ions

Tricarbonylchromium-stabilized benzylic oxonium ions generated from acetals react with nucleophiles in the presence of a Lewis acid with retention of configuration. For example, treatment

of chiral (benzaldehyde acetal)chromium complex **79** derived from (R,R)-butane-2,3-diol with a Lewis acid, followed by trimethylaluminum gives chromium complex **80** with high selectivity (Eq. 79). (156) The product **80** undergoes the same retentive substitution reaction with acetonitrile and acid to yield the Ritter product **81**.

Reactions of oxonium ions derived from the acetals of tricarbonyl(o-tolualdehyde)chromium or tricarbonyl(o-anisaldehyde)chromium proceed through the more

(79)

stable anti conformer **82** even if the syn conformer is generated initially (Eq. 80). (157) Rotation of the C_e-C_{ipso} bond takes place more easily in these oxonium ion intermediates than in other chromium-complexed benzylic carbocations.

NuX = Me₃Al, EtO⁻
Nu = Me (90%), 99% de; OEt (85%), 96% de

(80)

This methodology could be extended to the asymmetric synthesis of 2-aryltetrahydropyran **83** by intramolecular cyclization of an olefin with the oxonium ion (Eq. 81). (158) The reaction proceeds by ionization of the acetal with titanium(IV) tetrachloride, trapping the oxonium ion thus formed with a homoallylic alcohol, re-ionization with loss of the methoxy group to generate the oxonium ion, and cyclization via the more stable anti-conformation.

(81)

83 R = Me (94%)
R = OMe (83%)

3.4.4. σ-Propargyl Cations

Tricarbonyl(arene)chromium-substituted propargyl cations are generated by ionization of chromium-complexed propargyl alcohols or acetates with Lewis acids. (159) Chromium-complexed 1,1,3-triphenylpropargyl cations **84** ($R^1 = R^2 = Ph$) are formed as stable intermediates (<20°) that can be characterized in solution by NMR and UV/Vis spectroscopy. These propargyl cations are trapped with C-, S-, O-, and N-nucleophiles to give propargylated products **85** with high diastereoselectivity (Eq. 82). (160-162) The regioselectivitity of the trapping reactions strongly depends on the substitution pattern at the γ-position. Only the highly stable chromium-complexed triphenylpropargyl cation **84** ($R^1 = R^2 = Ph$) gives rise to the regioselective formation of allenes **86** in good yields with C- and soft nucleophiles. Other propargyl alcohols or acetates leading to less-stable propargyl cations have to be reacted under in situ ionization conditions and furnish exclusively the propargyl compounds **85** (Eq. 82) (159-161, 163)

(82)

Likewise, irreversible ionization of chromium-complexed σ-propargyl acetate **87** is achieved with $BF_3 \cdot OEt_2$ complex at –78°. The reactive site is largely dependent on the nature of the nucleophile. Alcohols and C-nucleophiles give exclusively propargyl ethers, whereas thiols and triphenylphosphine afford solely allenyl thioethers and phosphonium salts (Eq. 83). (160-163)

Tricarbonyl(arene)chromium-complexed propargyl cations derived from diastereomerically pure, planar chiral propargyl acetate **88** with TMSOTf, $SnCl_4$, or $TiCl_4$, are trapped with various C-, sulfur, oxygen, and nitrogen nucleophiles giving propargyl compounds **89** with remarkably high diastereoselectivity (Eq. 84). (164)

$$(83)$$

$$(84)$$

3.4.5. Remotely Positioned Cations

Even tricarbonyl(η^6-arene)chromium complexes having leaving groups at the f-or k-positions undergo nucleophilic substitution reactions with enhanced rates. (165-167) Reaction of chromium-complexed 1,1-dideuterio-1-iodoethylbenzene with nucleophiles in the presence of $AgBF_4$

produces substitution products via a chromacyclic cation without positional scrambling (Eq. 85). (168) The stereochemical outcome of the substitution is net retention. Treatment of chromium complex **90** with 1-methylpyrrole under the same conditions affords the substitution product **91** with 86% retention of stereochemistry (Eq. 86). (168) Moreover, (arene)chromium complex **92** with a leaving group positioned at the k-position undergoes substitution with 74% retention of configuration (Eq. 87). (168)

$$(85)$$

$$(86)$$

90
erythro:threo = 96:4

91 (43%)
erythro:threo = 83:17

$$(87)$$

92

74% retention
26% inversion

3.5. Reactions of Tricarbonylchromium-Stabilized Benzylic Anions
3.5.1. Cyclic Systems

The tricarbonylchromium fragment also stabilizes benzylic carbanions by delocalization of the negative charge onto the chromium because of its strong electron-withdrawing ability. A number of bases have been used for deprotonation at the benzylic position. Only the exo-benzylic protons are removed in (indane)- or (tetralin)chromium complexes by treatment with a base. Treatment of tricarbonyl(indane)chromium with potassium *tert*-butoxide in deuterodimethylsulfoxide results in the stereoselective incorporation of deuterium at the exo-benzylic position. Tricarbonyl(*endo*-1-methylindane)chromium (**93**) has two exo-benzylic protons whereas the corresponding tricarbonyl(*exo*-1-methylindane)chromium (**94**) has only one. Complexes **93** and **94** stereoselectively incorporate two and one deuterium atoms, respectively (Eq. 88). (169)

$$(88)$$

93

94

In tricarbonyl(1-methoxycarbonylindan)complexes, the proton ε to the ester is selectively removed. Both the exo- and endo-isomers are deprotonated at the 1-position but subsequently produce a single product by stereoselective exo-attack of electrophiles regardless of the configuration of the ester (Eq. 89). (170)

$$(89)$$

endo or exo

(~100%)

RX = MeI, PhCH₂CH₂Br,
CH₂=CHCH₂Br

Similarly, the oxime of (ꜰ-tetralone)chromium complex **95**, when treated with an excess of base

followed by alkylation, produces the exo-alkylation product at the C-1 position stereoselectively (Eq. 90). (171)

(90)

Sequential regioselective deprotonation of the aryl ring and two benzylic methylenes of substituted (tetralin)chromium complexes can be achieved by using different lithium bases. For example, (tetralin)chromium complex **96** initially gives trimethylsilylated compound **97** via lithiation on the ring by treatment with lithium hexamethylpiperidide at low temperature. Continued sequential deprotonations at the two benzylic positions of complex **97** using *n*-BuLi followed by quenching with electrophiles afford, stereo- and regioselectively, the exo-(bis)-alkylated compound **98** with different alkyl groups at the benzylic positions (Eq. 91). (172, 173)

(91)

Although the benzylic deprotonation and subsequent alkylation of tricarbonyl(arene)chromium complexes usually proceed in a stereospecific fashion anti to the tricarbonylchromium fragment, the tricarbonylchromium complex of (*exo*-3-diisopropylamino)chroman **99** affords predominantly alkylated products syn to the Cr(CO)$_3$ fragment, probably because of steric hindrance by the diisopropylamino group (Eq. 92). (174) The corresponding [(*endo*-3-diisopropylamino)chroman] chromium complex affords the usual exo substitution products under the same conditions.

Tricarbonylchromium complexes of e-indanone **100**, and e-tetralone **101**, with carbonyl groups in the sidechain, undergo base-catalyzed stereocontrolled cyclization to give tricyclic compounds via removal of the exo benzylic protons (Eqs. 93a

(92)

and 93b). In both cases, Robinson-type products are formed in less than 10% yields. (175-177)

(93a)

(93b)

Although attack of electrophiles on chromium-complexed benzylic carbanions generally takes place from the exo face in cyclic compounds owing to the steric bulk of the tricarbonylchromium fragment, tricarbonyl(indene)chromium or tricarbonyl(fluorene)chromium complexes undergo endo alkylation under higher temperatures. The intermediate anion **102** undergoes 1^6–1^5 slippage to generate anion **103**, which, on addition of the electrophiles, affords the endo-alkylation product **104** via Cr✐R bond formation and subsequent reductive coupling (Eq. 94). (178, 179)

(94)

3.5.2. Acyclic Systems

Chromium-complexed benzylic carbanions are considered to have substantial exocyclic carbon-carbon double bond character with the benzyl ligand coordinated in an 1^5-mode with tricarbonylchromium analogous to chromium-stabilized benzylic carbocations and radicals. This character inhibits rotation about the C_{ipso}-$C_{benzylic}$ bond, and the stereochemical configuration at the benzylic position is resistant to epimerization. (4, 180, 181) The benzylic proton of tricarbonyl

(toluene)chromium or tricarbonyl(ethylbenzene)chromium can be easily abstracted by bases, and the resulting benzylic carbanions can be trapped with a variety of electrophiles (Eq. 95).

$$(95)$$

R = H, Me   EX = alkyl halides, aldehydes, ketones, esters, etc.

A number of bases have been used for deprotonation. The choice of correct base and conditions is crucial in order to avoid either deprotonation at the arene positions (3) or nucleophilic addition to the ring. (2) The most widely used systems for benzylic deprotonation are *t*- BuOK in DMSO or THF, potassium hydride in THF, sodium hydride in DMF, *n*-BuLi in THF or ether, KOH in DME, and amide bases such as LDA, NaN(TMS)$_2$, or sodium amide. Usually, reactions are carried out under thermodynamic conditions at ambient temperature. Treatment of tricarbonyl(toluene) chromium with *n*-BuLi in THF at –60° followed by quenching with CO$_2$ produces a mixture of tricarbonyl(*m*- and *p*-toluic acid)chromium, while tricarbonyl(phenylacetic acid)chromium is exclusively formed at 0°. (182) The carbanions also react with diethyl oxalate (183) and *tert*-butyl nitrite (184) producing an enol ether and an oxime, respectively (Eqs. 96 and 97).

$$(96)$$

R = H, Me, Et

$$(97)$$

mixture of E and Z isomers

The enhancement of benzylic acidity upon complexation with the tricarbonylchromium fragment is obvious from the reaction of mono-chromium-complexed diphenylalkanes. Complex **105** gives a mono-methylated complex at the chromium-stabilized benzylic position with MeI and *t*-BuOK (Eq. 98). (185)

$$(98)$$

105

Chromium-complexed phenylacetic ester **106** undergoes base-induced dialkylation reactions with an excess of NaH and alkyl halides (Eq. 99). (185, 186) Similarly, ɵ-substituted methyl

phenylacetate complexes afford the corresponding quaternary carbon products by treatment with alkyl halides in the presence of base. The same reaction on the chromium-free arenes under phase-transfer conditions results in ester hydrolysis without alkylation. (170) The related κ-lactone complex **107** undergoes analogous benzylic alkylation (Eq. 100). (170)

(99)

(100)

Tricarbonylchromium-complexed xylene is similarly deprotonated at the benzylic position giving both ℮-substitution and ℮, ℮′-disubstitution products. Whereas the use of *t*-BuOK as a base leads to the benzylic deprotonation of tricarbonyl-(toluene)chromium, kinetic deprotonation with a strong base such as *n*-BuLi affords a mixture of arene ring- and benzylic-deprotonated products (Eq. 101). (183, 187-189)

(101)

The ℮-anion derived from tricarbonyl(2-ethylpyridine)chromium (**108**) undergoes stereoselective allylation and aldol reactions (Eq. 102). (190) The chelation of the lithium cation to the pyridine nitrogen is necessary for the achievement of high stereocontrol.

(102)

Prochiral tricarbonylchromium complexes of 2,6-dimethylbenzamides and anilides are deprotonated at one of the diastereotopic benzylic methyl groups by treatment with a chiral lithium amide followed by quenching with electrophiles to afford planar chiral (arene)chromium complexes. Thus, prochiral (*N*-methyl-*N*-acyl-2,6-dimethylaniline)chromium complexes **109** give preferential substitution at the Me^b group by treatment with a combination of *n*-BuLi and chiral amine **110** followed by quenching with electrophiles to give products **111**, which have axial chirality because of a barrier about the *N*-aryl and *N*-carbonyl bonds. Oxidative demetalation of the complex **111** affords the axially chiral anilides **112** with up to 99% ee (Eq. 103). (191, 192) Similarly, axially chiral benzamides are prepared by the same reaction sequence. (193)

(103)

3.5.3. Effect of Substituents on Benzylic Deprotonation
3.5.3.1. meta-or Para-Substituents
Regioselective deprotonation at the benzylic position occurs in tricarbonylchromium-complexed xylene and related cyclic compounds, such as tetralin or indane with substituents on the aromatic ring. The position of deprotonation is controlled by the electronic nature of the substituents on the chromium-complexed arene ring. It has been noted that t-electron donor substituents such as NMe_2 or OMe reduce the acidity of the para benzylic protons, whereas t-electron acceptor substituents such as CO_2R or TMS increase the acidity of the para benzylic protons. These effects appear to arise solely from electronic effects rather than from the influence of the substituents on the conformation of the tricarbonylchromium tripod. (194, 195-188) Thus, the position of benzylic deprotonation is controlled by the nature of the substituent in 4-substituted (*o*-xylene)chromium and related complexes. If the substituent X is a t-electron donor in 4-substituted (*o*-xylene)chromium **113**, deprotonation occurs at the 2-position, but if X = CO_2Bu-*t* or TMS, it occurs exclusively at the 1-position (Eq. 104)

(104)

For example, both tricarbonyl(4-methoxy-*o*-xylene)chromium (**114**) (188, 194-196) and tricarbonyl (6-methoxytetralin)chromium complexes (**115**) (197) undergo regioselective deprotonation at the meta-benzylic position by *t*-BuOK leading to substitution at the position meta to the methoxy group (Eqs. 105 and 106). Sometimes ketones derived from air oxidation of the initial products are formed as side products. Similarly, estradiol derivatives produce the corresponding alkylated compounds at the position meta to the methoxy group via tricarbonylchromium complexation, followed by a deprotonation-alkylation sequence. (196, 198, 199)

(105)

(106)

Removal of the meta benzylic proton takes place in tricarbonyl(1,2-diethyl-4-dimethylaminobenzene)chromium (**116**) on treatment with *t*-BuOK in the presence of formaldehyde. Alkylation products are formed with high stereoselectivity at the newly created stereogenic center (Eq. 107). (198) Because the chlorine acts as a net electron donor, the benzylic deprotonation reaction of tricarbonyl(4-chloro-*o*-xylene)chromium occurs regioselectively at the C-2 methyl position. (189, 194)

(107)

In contrast to the above results, tricarbonylchromium complexes possessing t-electron-withdrawing groups undergo deprotonation regioselectively at the position para to the substituents. For example, treatment of tricarbonyl(4-*tert*-butoxycarbonyl-*o*-xylene)chromium (**117**) with *t*-BuOK results in deprotonation at the C-1 methyl group (Eq. 108). (188, 194, 195) Similarly, the trimethylsilyl group activates the para benzyl proton of tricarbonyl(4-trimethylsilyl-*o*-xylene)chromium (**118**) for deprotonation (Eq. 109). (180) However, treatment of the corresponding tricarbonyl(4-*tert*-butyl-*o*-

xylene)chromium with *t*-BuOK and benzaldehyde results in an approximately equimolar mixture of the two possible e-substituted products. (188)

(108)

117

138

R^1	base	EX	R^2	
TMS	*n*-BuLi	MeI	Me	**I** (99%)
t-Bu	*t*-BuOK	PhCHO	CH(OH)Ph	**I + II** (55%)

I:II:α,α'-disubstituted product = 1:1:1

(109)

In meta-substituted (toluene)chromium complexes, the substitutents have no influence on the benzylic deprotonation reaction regardless of their electronic effects. In para-substituted (toluene) chromium complexes, the substituents influence the acidity of the methyl protons. t-Electron-withdrawing groups facilitate benzylic deprotonation, whereas electron-donating groups retard the deprotonation reaction resulting in low yields of substitution products. (183, 184, 194-196, 200, 201) Tricarbonyl(4-methoxy-1-ethylbenzene)chromium and tricarbonyl(4-methoxy-1-isopropylbenzene)chromium complexes are inert to benzylic deprotonation under conditions where the analogous (3-methoxy)ethylbenzene, (3-methoxy)isopropylbenzene, or (4-*tert*-butoxycarbonyl) ethylbenzene complexes are easily deprotonated (Eq. 110). (195, 196)

(110)

3.5.3.2. Ortho Substituents

The effect of an ortho substituent on the acidity of benzylic protons in chromium complexes of toluene and related arenes parallels that observed for para substituents. The acidity is increased by t-electron acceptors and decreased by t-donors. More interestingly, ortho substituents affect the stereochemistry of the deprotonation at diastereotopic benzylic positions. For example, sequential treatment of ortho-substituted ethylbenzene complex **119** with *t*-BuOK and formaldehyde produces the ortho-substituted (phenylpropanol)chromium complex **121** stereoselectively (Eq. 111). (198) The relative configuration of product **121** is derived from the configurationally most stable intermediate **120** having the methyl group of the sidechain anti to the ortho substituent.

(111)

119 → **120** → **121** R = OMe (60%),
NMe₂ (82%)

In contrast, alkylation of tricarbonyl(methyl *o*-methoxyphenylacetate)chromium (**122**) with methyl iodide in the presence of sodium hydride affords a mixture of products **123** and **124** in a ratio of 88:12 (Eq. 112). (170) However, on alkylation of complexes **123** and **124** with benzyl bromide, only one of the two diastereomers, **125**, is obtained. (170) An identical stable enolate is formed via equilibration of the anion derived from complexes **123** and **124**.

122 → **123**   123:124 = 82:18   **124**

1. NaH
2. BnBr

125

(112)

3.5.4. *ɐ*-Heteroatom-Substituted Tricarbonyl(arene)chromium Complexes

Tricarbonyl(alkyl benzyl ether)chromium complexes are easily deprotonated at the benzylic position, giving ɐ-substituted products rather than substitution on the ring, without undergoing the Wittig rearrangement (Eq. 113). (202) With chiral lithium amide bases, enantioselective benzylic functionalization of (alkyl benzyl ether)chromium complexes and tricarbonyl(1,3-dihydroisobenzofuran)chromium can be achieved with moderate to good enantioselectivity. (203-205) Treatment of the chromium complex of methyl benzyl ether or dibenzyl ether with chiral dilithium amide base **126** in the presence of lithium chloride followed by alkylation with methyl iodide produces complex **127** in high enantiomeric excess (Eq. 114). (203, 206, 207) Intramolecular cyclization of (alkyl benzyl ether)chromium complex **128** having a remote leaving group takes place on base treatment (Eq. 115). (202)

EX = MeOH, MeI, BnBr, MeCO₂Et, MeCHO, TMSCl
E = H, Me, Bn, MeCO, MeC(OH)H, TMS

(113)

$$(114)$$

$$(115)$$

A single-electron reduction of the (ethyl benzyl ether)chromium complex with LiDBB generates a radical anion intermediate that loses the ethoxy group. This radical intermediate is reduced by a second electron transfer to an anionic species that is configurationally stable and can be trapped with a variety of electrophiles with stereochemical retention (Eq. 116). (208)

RX = TMSCl, BnBr, MeOCOCl, Me$_2$NCOCl

$$(116)$$

Tricarbonyl[1,2-(dimethoxymethyl)benzene]chromium (**129**) affords monomethylated compound **130** diastereoselectively by treatment with *n*-BuLi followed by alkylation with methyl iodide (Eq. 117). (47) Compound **130** is formed by exo attack on the most stable conformation of the anion derived by removal of the exo proton, in which two methoxy groups are oriented anti to each other. Subsequent methylation of **130** under basic conditions gives meso complex **131** as the only product.

$$(117)$$

Similarly, the (methyl *o*-methoxybenzyl ether)chromium complex affords ꞓ-substituted complexes stereoselectively by treatment with *t*-BuLi and subsequent quenching with electrophiles (Eq. 118). (180) In contrast, the corresponding meta isomer gives the product functionalized on the arene ring without deprotonation at the benzylic position. (209)

$$(118)$$

The Wittig rearrangement is suppressed even with tricarbonyl(allyl benzyl ether)chromium by deprotonation at low temperature. Subsequent rapid quenching of the anion gives alkylated products. (202) However, a 2,3-Wittig rearrangement occurs if the benzylic anion solution warms or is left standing. The diastereoselectivity of this 2,3-Wittig rearrangement is affected by tricarbonylchromium complexation of crotyl benzyl ethers. Thus, treatment of [(E)-crotyl benzyl ether]chromium complex **132** with n-BuLi for 7 hours produces the 2,3-Wittig rearrangement product with high syn-selectivity (Eq. 119). (210) The corresponding chromium complex of the Z-isomer shows poor selectivity. These stereochemical results are contrasted with

$$(119)$$

those of the 2,3-Wittig rearrangement of chromium-free crotyl benzyl ethers: the rearrangement of (Z)-crotyl benzyl ether provides high syn stereoselection, whereas the corresponding E-substrate results in poor stereoselection. (211) Furthermore, asymmetric [2,3]-Wittig rearrangements of (allyl benzyl ether)chromium complexes can be achieved with high asymmetric induction via asymmetric deprotonation at the benzylic position by treatment with a chiral lithium amide base (Eq. 120). (212)

$$(120)$$

The regioselectivity of the deprotonation of tricarbonyl(4-methoxychroman)chromium is dependent on the configuration of the methoxy group with respect to the tricarbonylchromium fragment. Thus, tricarbonyl(endo-4-methoxychroman)-chromium complex **133** is deprotonated at the exo-benzylic position by treatment with n-BuLi, but the corresponding exo-isomer **134** is selectively lithiated on the arene ring (Eqs. 121a and 121b). (180)

$$(121a)$$

(121b)

Similarly, the (ethyl benzyl thioether)chromium complex is selectively deprotonated at the benzylic position generating the benzylic anion intermediate (Eq. 122). (202) The cyclic (1,3-dihydroisobenzothiophene)chromium complex undergoes asymmetric deprotonation with high enantiomeric selectivity by treatment with a chiral lithium amide base (Eq. 123). (213) However, tricarbonyl(*N,N*-dimethylbenzylamine)chromium undergoes exclusive ortho-lithiation with *t*-BuLi via an intramolecular coordination of the lithium with the proximate nitrogen (cf. Eq. 12). (47, 214)

(122)

(123)

With tricarbonyl(benzaldimine)chromium, deprotonation takes place at the benzylic position, and the enantiopure ortho-substituted analog **135** gives optically pure e-substituted benzylamine derivatives upon trapping with alkyl halides and subsequent hydrolysis (Eq. 124). (125)

(124)

Tricarbonyl(isochroman)chromium complex **136** undergoes deprotonation at the C-1 exo-position with *n*-BuLi . The benzylic anion generated gives the (*exo*-1-methylisochroman)chromium by treatment with methyl iodide (Eq. 125). (180) The 1-exo proton is more acidic than the 4-exo proton because of activation by both the

(125)

oxygen atom and the tricarbonylchromium fragment. In contrast, in the corresponding nitrogen analog, tricarbonyl(*N*-methyltetrahydroisoquinoline)chromium (**137**), the deprotonation takes place exclusively at the 4-exo position and a single diastereomeric compound **138** is obtained on quenching with a variety of electrophiles (Eq. 126). (215, 216) The regio- and stereoselectivity of this reaction is the result of chelation of *n*-BuLi with an axial nitrogen lone pair, thereby delivering the base to the proximate pseudoaxial 4-exo-hydrogen. Further treatment of the 4-exo-substituted derivatives **138** with *t*-BuLi followed by addition of an electrophile produces 1,4-disubstituted complexes with exo-configurations at both positions.

$$E^1X = MeI, EtI, BnBr, MoOPH, TMSCl, Me_2CO$$
$$E^2X = EtI, BnBr$$

(126)

The related chromium complex **139** derived from (–)-canadine is initially lithiated at the position ortho to the methoxy group. In order to obtain the benzylic deprotonation product, this position has to be protected with trimethylsilyl chloride (Eq. 127). The trimethysilyl group not only protects the arene ring but also activates the 8-position. Treatment of intermediate **140** with *t*-BuLi and then methyl iodide affords the exo-methyl derivative **141** in isomerically pure form. (217)

(127)

Horner-Emmons-Wadsworth reaction of the tricarbonylchromium-complexed benzylphosphonate **142** with aldehydes produces E-alkenyl-substituted (arene)-chromium complexes without formation of the corresponding Z-isomers (Eq. 128). (218)

(128)

3.5.5. ƒ-Heteroatom-Substituted Tricarbonyl(arene)chromium Complexes

Chromium complexes of arenes possessing ƒ-hetero-substituents such as alkoxy or dialkylamino groups generally undergo benzylic deprotonation along with subsequent elimination of the ƒ-leaving group producing the corresponding styrene derivatives. For example, tricarbonyl (dihydrobenzofuran)chromium (**143**) undergoes cleavage with base to afford an (*o*-methoxyvinylbenzene)chromium complex (Eq. 129). (198) The (dihydroindole)chromium complex undergoes a similar reaction to produce the corresponding (styrene)chromium complex. (110)

(129)

Similarly, the (ƒ-*N,N*-dialkylaminoethylbenzene)chromium complex undergoes ƒ-elimination from the benzylic anion at ambient temperature. However, these benzylic carbanions are stable toward elimination at low temperature and can be trapped with electrophiles. Treatment of (–)-(*S*)-tricarbonyl(*N,N*-dimethylamphetamine)chromium (**144**) with a base at –78° generates the benzylic anion, which can be trapped by a variety of electrophiles at low temperature yielding ᴇ-substituted *N,N*-dimethylamphetamine derivatives with complete stereoselectivity (Eq. 130). (219)

(130)

Cyclic compounds containing a nitrogen atom are smoothly lithiated at the benzylic position at low temperature. For example, tricarbonyl(*N*-methyltetrahydrobenzazepine)chromium (**145**) undergoes facile C-1 deprotonation followed by alkylation or other electrophilic quenching (Eq. 131). (180)

EX	
MeI	(76%)
EtI	(81%)
BnBr	(71%)
MeSSMe	(91%)

(131)

Chromium complexation of codeine is completely stereoselective as are the benzylic deprotonation and subsequent alkylation reactions. Complex **146** affords exo-alkyl-substituted codeine **147** stereoselectively (Eq. 132). (220)

$$(132)$$

3.5.6. e-Propargyl Anions

Propargyl anions are stabilized by tricarbonylchromium complexation of the arene ring. The chromium-complexed propargyl anion **149** derived from **148** can be trapped with electrophiles such as methyl iodide to give the corresponding propargyl derivative **150**. With trimethylsilyl chloride, the allenyl compound **151** is produced (Eq. 133). (162)

$$(133)$$

3.6. Reactions of Alkenes, Alkynes, and Allenes

3.6.1. Addition to Tricarbonyl(styrene)chromium Complexes

The tricarbonylchromium fragment stabilizes both benzylic carbanions and carbocations, and, therefore, the chromium complexes of styrene and the related arenes are susceptible to both nucleophilic and electrophilic addition at the f-position of the double bond. The conjugate addition of a nucleophile at the f-position generates a tricarbonylchromium-stabilized benzylic carbanion, which can be trapped with a variety of electrophlies resulting in the functionalization of both the e- and f-positions. Alkyllithiums and stabilized carbanions can add at the f-position. Addition of 2-lithio-2-methylpropanenitrile to the tricarbonyl(styrene)chromium and subsequent proton quenching affords a Michael addition product. (221) Both nucleophilic additions to (1,2-dihydronaphthalene)chromium **152** and subsequent trapping with electrophiles take place stereoselectively from an exo-side to give complex **153** (Eq. 134). (221-223)

(134)

EX	E	
MeOH	H	(95%)
MeI	Me	(65%)
PhCOCl	PhCO	(32%)

An intramolecular nucleophilic addition to the conjugated double bond of the chromium-complex **154** proceeds with complete stereoselectivity to form a bridged product (Eq. 135). (224)

(135)

Electrophiles can also add to the f-position of styrene and related (arene)-chromium complexes to generate tricarbonylchromium-stabilized benzylic carbocation intermediates. For example, Friedel-Crafts acylations of (dihydronaphthalene)-chromium complexes have been explored. Acylation of (dihydronaphthalene)-chromium complex **152** leads to the generation of the benzylic carbocation, which eliminates a proton to produce e, f-unsaturated ketone complex **155** on addition of ethanol (Eq. 136). (225)

(136)

Electrochemical reduction of tricarbonyl(stilbene)chromium produces a dimerization product as a diastereomeric mixture via radical-anion intermediates (Eq. 137). (226)

(137)

The double bonds of tricarbonylchromium-complexed styrene and related compounds **156** are reduced with SmI_2, but an isolated double bond in the molecule is not affected by this reagent (Eq. 138). (227)

(138)

An intramolecular radical addition to the double bond of a tricarbonylchromium-complexed dihydronaphthalene has also been explored. (6,7-Dimethoxy-3,4-dihydronaphthalene)chromium complex **157** bearing a remote ketone functional group is reduced with SmI_2 to produce the 5-endo-trig cyclization product **158** via a ketyl radical intermediate with high diastereoselectivity (Eq. 139). (228) However, reduction of the corresponding saturated (tetralin)chromium complex **159** with SmI_2 affords an intramolecular radical addition to the arene ring. The product, in which an ortho methoxy group is lost, is formed as a single diastereomer (Eq. 140). (228) Similar cyclization of the corresponding ketimine complex **160** gives a diastereomeric mixture of chromium-complexed cyclic amines (Eq. 141). (229)

(139)

(140)

(141)

Tricarbonylchromium complexes of styrene, indene, and related compounds undergo highly regioselective hydroformylation with rhodium catalysts (Eq. 142). (230) In the presence of a chiral phosphine, the hydroformylated compound is obtained in up to 46% ee.

$$\text{(142)}$$

I + II (96%), I:II = >98:<2

Reduction of the double bond of tricarbonyl(indole)chromium complexes is achieved with NaBH$_3$CN or NaBH$_4$ in the presence of trifluoroacetic acid to give the corresponding (indoline) chromium complexes in good yields. (231) With certain substrates, this reduction proceeds with good to excellent levels of stereoselectivity through a reaction manifold apparently involving preferential addition of a hydride to the sterically more hindered endo face. Thus, (2,3-dimethylindole)chromium complex **161** gives predominantly the (*exo*-methylindoline)chromium complex along with the formation of the endo methyl isomer as the minor product (Eq. 143). This unusual exo methyl isomer results from endo hydride addition to a putative indolenium ion.

$$\text{(143)}$$

I + II (87%), I:II = 4.5:1

3.6.2. Cycloadditions of the Styrene Double Bond

Tricarbonyl(styrene)chromium undergoes Diels-Alder reaction with cyclopentadiene to give the expected cyclo-addition product (Eq. 144). (232) Similarly, 1,3-dipolar cycloaddition of an ortho-substituted (styrene)chromium complex with a nitrile oxide produces adduct **162**

$$\text{(144)}$$

(Eq. 145). (233) The reaction of a (dihydronaphthalene)chromium complex with diazomethane gives the cycloaddition product **163** with high diastereoselectivity (Eq. 146). (234)

$$\text{(145)}$$

162   Ar = 3,5-Cl$_2$-2,4,6-Me$_3$C$_6$
R = OMe, 60% de; Me >96% de;
Cl, >92% de

163

(146)

Cycloaddition of chiral tricarbonylchromium-complexed styrenes with 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide proceeds with high stereoselectivity, offering a new synthetic route to optically active 3,5-disubstituted 4,5-dihydroisoxazoles (Eq. 147). (233) The preferred formation of the cycloadduct **I** implies that the reactive conformer of the styrene chromium has an s-trans (C$_1$-C$_e$) configuration.

I + II (65-70%),
I:II = 98-80:2-20

(147)

Reactions of tricarbonyl(styrene)chromium with sulfur or phosphorus ylides give the corresponding cyclopropanes **164** (Eq. 148) (235)

164   R = OMe (72%), 60% de
R = SO$_2$Ph (91%), >95% de

(148)

3.6.3. *Additions to Remotely Positioned Double Bonds*

Conjugate addition of organocopper reagents to e, f–unsaturated enone chromium complexes and cycloaddition reactions to double bonds proceed stereoselectively even when these functionalities are at remote positions. Conjugate addition of organocuprates to ortho-substituted (propenyl phenyl

ketone)chromium complexes takes place with fair selectivity depending on the nature of the copper reagents and the ortho substituent. Gilman reagents such as $(n\text{-Bu})_2\text{CuLi}$ attack one face of the double bond in the conjugated enone complex **165**, whereas the BuCu · BF$_3$ reagent adds to the opposite face giving the other diastereomer as the major product (Eq. 149). (236) In a matched pair combination of the chiral R-enone complex **166** and enantiomerically pure (S)-2-methyl-3-(1-butoxy)propylcopper boron trifluoride reagent **167**, high diastereoselectivity (>98% de) is achieved at the remote position in the conjugate addition product **168** (Eq. 150). In the mismatched pair of the S-enone complex with copper reagent **167**, the diastereomeric excess is only 32%. The benzylic carbonyl group of the conjugate addition product **168** is stereoselectively converted into the 1,3,5-trimethyl derivative **169** via stereoselective reduction of the ketone, acetylation, and subsequent treatment with trimethylaluminum. (236)

[RCu]	I:II
$(n\text{-Bu})_2\text{CuLi}$	76:24
$n\text{-BuCu}\bullet\text{BF}_3$	8:92

(149)

(150)

Unusual endo-selectivity at the ƒ-position is observed in the reaction of tricarbonyl(2-arylidene- ε-tetralone)chromium complex **170** with allyltrimethylsilane (Sakurai-Hosomi reaction) in the presence of TiCl$_4$ (Eq. 151). (237) The configuration at the ƒ-position of the 1,4-addition products **171** is opposite that of product **172** obtained by the exo-addition of allylmagnesium bromide to complex **170** followed by anionic oxy-Cope rearrangement. Conjugate addition of organolithium or organomagnesium reagents to complex **170** proceeds with endo selectivity in the presence of excess TiCl$_4$ in methylene chloride. (238) On the other hand, cuprates in ether afford the expected exo-adducts, and organolithiums give predominantly 1,2-addition products without Lewis acids.

(151)

Similary, endo approach of dimethylsulfonium methylide under phase-transfer conditions is observed in the cyclopropanation of 2-arylidene- e-tetralone complex **170** giving the complex **173** (Eq. 152). (239)

(152)

Chiral e, f-unsaturated (enone)chromium complexes can be employed effectively as chiral auxiliaries to achieve high diastereoselectivity in asymmetric Diels-Alder reactions. Acrylates **174** show t-face selectivities in Lewis acid catalyzed Diels-Alder reactions with cyclopentadiene (Eq. 153). (240) Similarly, Lewis acid catalyzed Diels-Alder reactions of chromium-complexed e, f-unsaturated esters**175** and **176** result in higher selectivities. (241)

(153)

175

176

L = CO, (PhO)$_3$P, (EtO)$_3$P, Ph$_3$P

Palladium(0)-catalyzed substitution on allylic acetate **177** with sodium diethy malonate proceeds with high regio- and stereoselectivity (Eq. 154). Adduct **178** can be functionalized stereospecifically at the benzylic position to give the syn- or antimethyl derivatives by stereoselective conversions of the benzylic ketone as shown in Eq. 75. (24) Enolate formation from methoxyacetate **179** with LDA followed by addition of trimethylsilyl chloride and subsequent warming to room temperature results in stereoselective Ireland-Claisen rearrangement, yielding product **180** (Eq. 155). (24)

(154)

(155)

Planar chiral (*o*-chlorobutenylbenzene)chromium complexes undergo intramolecular palladium(0)-catalyzed carbonylative Heck cyclizations stereoselectively. When the reaction of complex **181** is carried out in the presence of CO and methanol, an anti-cyclization product (relation between the Cr(CO)$_3$ fragment and CH$_2$CO$_2$Me group) is obtained as a single isomer (Eq. 156). (242-244) The diastereoselectivity of this alkene carbopalladation is controlled by the planar chirality of the starting material.

(156)

Aryl radicals at the chromium-coordinated ring generated from bromo- or iodo(benzene)chromium complexes with AIBN and Bu$_3$SnH undergo intramolecular cyclizations affording (indan)

chromium complexes as diastereomeric mixtures (Eq. 157). (244)

(157)

3.6.4. Reactions of Alkynes

Carbon-carbon triple bonds in the side chain of tricarbonylchromium-complexed arenes react with various reagents. Tricarbonyl-(phenylacetylene)chromium undergoes Sonogashira coupling with aryl halides (Eq. 158). (245) Diastereoselective cobalt complexation and hydride reduction of the diastereotopic carbon-carbon triple bonds of chromium-complexed ortho-substituted arenes have been observed. Treatment of diyne chromium complex **182** with $Co_2(CO)_8$ in ether at room temperature gives predominantly mono-cobalt complexation (Eq. 159). (246)

(158)

(159)

$R^1 = Me, OMe$
$R^2 = H, Ph, TMS$
$R^3 = H, TMS$

Heating of tricarbonylchromium-complexed phenylpropargylic alcohol in the presence of triethylamine gives rise to rapid formation of the chalcone complex by isomerization (Eq. 160). (247)

(160)

Tricarbonylchromium-complexed phenylpropargylic alcohols react with thionyl chloride or diethoxychlorophosphite, yielding chloroallenyl- and allenylphosphonate arene complexes, respectively (Eq. 161). (248, 249)

(161)

3.6.5. Reactions of Allenes

Organocuprate addition to (arene)chromium-substituted phosphorylallenes gives rise to the regioselective formation of chromium-complexed allylphosphine oxide derivatives in good yields (Eq. 162). (250)

(162)

Allenylphosphonate arene complex **183**, on reaction with a number of 1,2- or 1,3-difunctional carbonyl compounds in the presence of NaH in refluxing THF, affords heterocyclic tricarbonyl (arene)chromium complexes **184** via a consecutive Michael addition and intramolecular Horner-Emmons-Wadsworth olefination (Eq. 163). (249)

(163)

The chloroallene-substituted (arene)chromium complex **185** can be coupled with terminal alkynes under palladium/copper catalysis to give arene complexes **186** carrying both allene and yne functionalities in good yields (Eq. 164). (248)

(164)

3.7. Cross-Coupling Reactions
3.7.1. Cross-Coupling of Tricarbonyl(arene)chromium Complexes

Oxidative addition of aryl halides to palladium(0) is accelerated by coordination with the electron-withdrawing tricarbonylchromium fragment. (251-257) Even chlorobenzene and fluorobenzene (258, 259) can be made susceptible to oxidative addition by utilizing tricarbonylchromium complexation to give cross-coupling products. For example, palladium(0)-catalyzed cross-coupling of tricarbonyl(chlorobenzene)chromium with a vinylstannane gives vinylbenzene in good yield after oxidative demetallation (Eq. 165). (251) Palladium-catalyzed carbonylation of tricarbonyl (chlorobenzene) chromium gives the corresponding esters, aldehydes, amides, or ɛ-oxo-amides depending on the conditions (Eq. 166). (252)

$$(165)$$

$$(166)$$

The cross-coupling of substituted (halobenzene)chromium complexes with amino acid-derived organozinc compounds in the presence of a palladium(0) catalyst affords the corresponding chromium-complexed phenylalanine derivatives without racemization (Eq. 167). (257)

$$(167)$$

Prochiral tricarbonyl(1,2-dichlorobenzene)chromium produces an optically active planar chiral (2-chlorobiphenyl)chromium complex (ee up to 69%) via a Suzuki-Miyaura cross-coupling reaction with phenylboronic acid and other reagents in the presence of a chiral palladium complex (Eq. 168). (260, 256) Carbomethoxylation also can be carried out enantioselectively (Eq. 169). (261) The enantioselectivity strongly

$$(168)$$

RM = CH₂=CHZnCl, CH₂=C(Me)B(OH)₂, ArB(OH)₂

depends on the reaction time. The initial enantioselectivity is enhanced by subsequent kinetic resolution during formation of the (bis)methoxycarbonylated product.

(169)

The tricarbonyl(chlorobenzene)chromium complex undergoes smooth Sonogashira coupling with alkynes in the presence of a catalytic amount of Pd(II) and copper iodide to give alkynylated (benzene)chromium complexes (Eq. 170). (262, 248) However, Sonogashira coupling of tricarbonylchromium-coordinated chlorobenzene

(170)

with 1-arylpropargyl alcohols under the same conditions gives (aryl)chromium-complexed chalcones by base-catalyzed isomerization of the alkyne coupling products (Eq. 171). (247) The facility of the reaction is attributed to the strong electron-withdrawing

(171)

ability of the chromium fragment. Furthermore, this mild enone synthesis enables the development of novel one-pot reactions to take advantage of an in situ generated enone functionality. Addition of N-methyhydrazine is compatible with the reaction conditions, and after Sonogashira coupling a pyrazoline skeleton is generated (Eq. 172). (247)

(172)

3.7.2. Axially Chiral Biaryls
Axially chiral biaryls can be obtained stereoselectively by palladium(0)-catalyzed Suzuki-Miyaura cross-coupling of 2,6-disubstituted tricarbonyl(bromobenzene)chromium complexes with ortho-substituted phenylboronic acids under basic conditions in refluxing aqueous methanol. The axial chirality of the mono-tricarbonylchromium complexes of biaryls so obtained by cross-coupling with phenylboronic acids is greatly influenced by the steric bulk of the ortho substituents of phenylboronic acids and the reaction conditions. For example, the cross-coupling of chromium

complexes **187** with ortho-alkyl-, ortho-methoxy- or ortho-hydroxymethyl-substituted (R^2-groups) phenylboronic acids in the presence of a Pd(0) catalyst and sodium carbonate in aqueous methanol at 75° diastereoselectively affords the cross-coupling products **188**, in which the R^2-groups are oriented in a syn-configuration with respect to the tricarbonylchromium fragments (Eq. 173). (263, 264) On the other hand, the cross-coupling with *o*-formylphenylboronic acid produces the diastereoisomeric coupling product **189** with anti-orientation of the formyl group with respect to the tricarbonylchromium fragment (Eq. 174). (264)

(173)

(174)

This reaction is useful for the synthesis of axially chiral biaryl natural products, and can be further applied to an intramolecular cyclization. When the mono-tricarbonylchromium complex **190**, in which the uncomplexed A-ring bears a bromine atom and the complexed B-ring has a chlorine atom, is treated with 1 equivalent of *n*-BuLi at –78°, followed by quenching with B(OMe)$_3$, the corresponding boronic acid derivative is produced. Without isolation, this arylboronic acid intermediate affords the intramolecular cyclization product in moderate yield upon palladium-catalyzed cross-coupling (Eq. 175). (265)

(175)

3.7.3. Axial Isomerization
syn-Biphenyl tricarbonylchromium complexes, which are presumably kinetically controlled products of the above coupling reactions, can be isomerized to the thermodynamically more stable anti-biphenyl tricarbonyl-chromium complexes by either of two methods: (1) modification of the ortho substituents to less bulky ones; or (2) application of thermal conditions to assist the central bond rotation. When *syn*-tricarbonyl[(1,2,3,4,5,6- 1^6)-2-methoxy-2′-hydroxymethyl-6-methylbiphenyl]chromium (**191**) is oxidized with DMSO/Ac$_2$O at room temperature, rotation of the

central bond takes place to afford the anti-product **192** in 53% yield with no contamination from the syn complex (Eq. 176). (266)

(176)

Several tricarbonylchromium-complexed syn-biaryls would be expected to isomerize to the thermodynamically more stable anti-complexes on refluxing in a high-boiling solvent. Refluxing of complex **193** (R^1 = CHO, R^2 = Me) in toluene for 2 hours facilitates the central bond isomerization to produce the thermodynamically more stable complex **194** (R^1 = CHO, R^2 = Me) in good yield with only small amounts of the starting material remaining (Eq. 177). (266) No migration of the $Cr(CO)_3$ fragment to the other arene ring or to the solvent is observed under the isomerization conditions. The axial isomerization is largely dependent on the reaction temperature (Eq. 177). Similarly, tricarbonyl[naphthyl(1^6-phenyl)]chromium complexes give the corresponding axially-isomerized products under thermal conditions.

R^1	R^2	solvent		193:194
CHO	Me	toluene	(98%)	2:98
Me	OMe	toluene	(98%)	42:58
Me	OMe	xylene	(98%)	9:91
Me	Me	xylene	(98%)	80:20
Me	Me	mesitylene	(79%)	2:98

(177)

A combination of diastereoselective cross-coupling reactions and subsequent axial isomerizations can be used for the preparation of both enantiomers of axial biphenyls. Enantiopure (–)-tricarbonyl (2-bromo-3-methoxybenzaldehyde)chromium (**195**) is coupled with 2-methylphenylboronic acid to give (+)-chromium complex **196**. Aldehyde **196** is reduced with $NaBH_4$ and acetylated with acetic anhydride to give (–)-(R)-2-methoxy-2′-methyl-6-(acetoxymethyl)biphenyl (**197**), after photooxidative demetalation. On the other hand, axial isomerization of cross-coupling product **196** by refluxing in xylene for 2 hours affords the diastereomeric (S)-**198**, which is converted into the corresponding antipode (+)-(S)-biphenyl **199** by the same reaction sequences (Eq. 178). (265) Furthermore, both syn- and anti-coupling products can be obtained stereoselectively by changing only the reaction temperature starting from an identical planar chiral (aryl halide)chromium complex. (265)

(178)

3.7.4. Biaryls by Nucleophilic Addition of Aryl Grignard Reagents

Nucleophilic substitution of an ortho-alkoxy group of arenes activated with electron-withdrawing groups such as oxazoline, ester, sulfinyl, sulfonyl, or diphenylphosphinyl groups by aryl Grignard or lithium reagents produces biaryl compounds. (267-269) The strong electron-withdrawing ability of the $Cr(CO)_3$ fragment accelerates the nucleophilic reaction to the chromium-complexed arene ring. Nucleophilic substitution by orthotolyl Grignard reagents on tricarbonylchromium complexes of 2-methoxybenzoate in refluxing benzene has also been employed for asymmetric synthesis of axially chiral biphenyls. (270) A sterically hindered 2,4,6-trimethylphenyl ester **200** is used to prevent the Grignard addition to the benzoate (Eq. 179).

(179)

3.8. Reactions of Enolates of Tricarbonyl(alkyl aryl ketone)chromium Complexes

Alkylation of enolates generated from chromium-complexed cyclic ketones such as tricarbonyl(ɛ-tetralone)chromium or tricarbonyl(ɛ-indanone)chromium is completely stereoselective; the electrophiles attack from the exo-side. Methylation of (indanone)chromium or (tetralone)chromium complex using NaH/MeI in DMF/benzene at room temperature gives the 2-exo-methyl complex along with a small amount of dimethylation product (Eq. 180). (105, 176) Despite the basic conditions favoring an exo-endo equilibration of the ketones, only the exo-methylation products

(180)

are obtained. Further alkylations to form quaternary carbon centers proceed stereo-selectively in

some cases. A mixture of exo and endo (2-methyl-1-indanone)-chromium complexes is treated with benzyl chloride and NaH to give a single exo-benzyl-endo-methyl (indanone)chromium complex. (176) Exo-alkylated (indanone)- or (tetralone)chromium complexes are easily isomerized to endo-alkylated ones by exo-proton addition under basic conditions (Eq. 181). (105) Similarly, Michael addition of methyl vinyl ketone to the (indanone)chromium complex proceeds predominantly via exo-attack (Eq. 182). (176) Tricarbonyl(7-methoxy-1-tetralone)chromium undergoes complete exo-alkylation and -aldol reactions. (107)

(181)

(182)

Base-catalyzed condensation of tricarbonyl(indanone)chromium complexes with benzaldehydes affords chalcone derivatives **201** in good yields (Eq. 183). (271) These chromium complexes can be converted into (2,2′-spiroindan)chromium complexes as mixtures of cis- and trans-isomers **202** and **203** by reduction of the double bond, hydrolysis of the ester, and subsequent cyclization (Eq. 184). (271)

(183)

(184)

The aldol reaction of boron enolates of ortho-substituted (acetophenone)-chromium complexes with

aldehydes is highly stereoselective (Eq. 185). (96, 95) Use of the corresponding lithium enolates results in low yields of aldol products because of stabilization of the chromium-complexed lithium enolate, and hence the lack of reactivity.

$$(185)$$

(75-81%) 76-90% de

3.9. Miscellaneous Side-Chain Reactions and Stereocontrol in Tricarbonyl(arene)chromium Complexes

Tricarbonyl(1-benzocyclobutanol)chromium (204) undergoes facile ring opening on base treatment to generate (o-quinodimethane)chromium intermediate 205 at low temperature. This intermediate can be trapped by electron-deficient dienophiles to produce cycloaddition products 206 (Eq. 186). (92, 111, 258, 272-274) The corresponding acetate of complex 204 can be converted to the ortho-quinodimethane intermediate

$$(186)$$

Z = CO$_2$Me, CN, SO$_2$Ph   206
R^1 = H, Me, Ph, CO$_2$Me

under thermal conditions. High diastereoselectivity in its cycloaddition with dienophiles is observed as well. The corresponding endo-ethoxy chromium complex 207 undergoes an isomerization to the exo-isomer 209 at 160° via the o-quinodimethane intermediate 208. Treatment of complex 207 with the unusual dienophile *trans*-bis-(1,2-trimethylsilyl)ethene at 160° affords cycloadduct 210 with high diastereoselectivity (Eq. 187). (275, 273)

$$(187)$$

(53%)

The lithium salt of a related cyclobutanol complex 211 undergoes ring opening to the *o*-quinodimethane, which is trapped with dimethyl fumarate to produce 212 as a diastereomeric

mixture (Eq. 188). (92) However, a completely different ring-opening product, **213**, is obtained on protonation of the intermediate.

(188)

Treatment of [1-*endo*-hydroxy-1-*exo*-(methoxyallenyl)benzocyclobutene]-chromium complex **214** with trifluoroacetic acid induces an ɇ-ketol rearrangement, leading to (ɇ-indanone)chromium complex **215** as a single diastereomer (Eq. 189). (276) An intermediate in this rearrangement is an ɇ, ſ-conjugated enone derivative, which is formed on hydrolysis of the methoxyallenyl group. The analogous [2-*endo*-hydroxy-2-*exo*-(methoxyallenyl)benzocyclobuten-1-one]chromium complex affords the corresponding (1,3-indandione)chromium complex under the same conditions. Ring expansions of this kind have been observed in the corresponding chromium-free benzocyclobutene derivatives. (277) (2-Hydroxy-1-indanone)chromium complex **216** is converted to [1-hydroxy-2-indanone]chromium complex **217** by an ɇ-ketol rearrangement under basic conditions (Eq. 190). (276)

(189)

(190)

Usually, tricarbonyl(arene)chromium complexes are sensitive to oxidizing agents, which render chromium-free arenes by oxidative demetalation. However, some functional groups on tricarbonyl (arene)chromium complexes are smoothly oxidized without decomplexation. Benzylic hydroxy groups are easily oxidized in good yields to the corresponding carbonyl groups with DMSO/Ac$_2$O (278) or active MnO$_2$ (105) (Eq. 191). The tolualdehyde tricarbonylchromium complex is converted into the (methyl toluate)chromium complex by treatment with MnO$_2$ and NaCN in AcOH and methanol (Eq. 192). (193, 279) Chromium-complexed phenyl thio ethers are easily oxidized to the corresponding sulfoxide complexes. (280-284) Asymmetric oxidation of

(thioanisole)chromium complexes is achieved by cumene hydroperoxide in the presence of diethyl tartrate and tetraisopropoxytitanium reagent with high optical purity (Eq. 193).

$$(191)$$

$$(192)$$

R = H, Me, OMe

(60-73%) 81-86% ee

$$(193)$$

Benzylic tertiary amino groups are removed under mild conditions. (*N*,*N*-Dimethyl ℮-phenylethylamine)chromium complexes **218** are smoothly converted to the corresponding *N*-oxides by treatment with dimethyldioxirane at low temperature. The resulting *N*-oxides undergo a Cope elimination to give substituted tricarbonyl(styrene)chromium complexes (Eq. 194). (285, 286) In this procedure, enantiopure ortho-substituted (styrene)chromium complexes are obtained.

218 R = SMe, PPh₂, TMS, I, CH₂=CHCH₂

$$(194)$$

Ethylene acetals of chromium-complexed aryl ketones undergo oxidative deprotection by treatment with trityl cation to generate the parent carbonyl compounds without isomerization of the double bond to give ℮, f-enones (Eq. 195). (24)

$$(195)$$

The tricarbonylchromium complexes of ℮-tetralone, ℮-indanone, and acetophenone are oxidized with hypervalent iodine reagents to give the corresponding ℮-hydroxy derivatives without oxidative demetalation. Interestingly, in cyclic ketones, endo-2-hydroxy complexes are formed exclusively rather than the expected exohydroxy complexes (Eq. 196). (287, 288)

$$ (196) $$

$$ n = 1 \ (60\%), \ n = 2 \ (40\%) $$

A diphenylphosphine oxide substituent on the (arene)chromium complexes **219** is reduced to diphenylphosphine with polymethylhydrosiloxane in good yields (Eq. 197). (289, 290) This reduction is significant for the preparation of planar chiral (diphenylphosphine)chromium complexes as chiral ligands for asymmetric catalysis.

$$ (197) $$

$$ R = TMS \ (74\%), \ SnBu_3 \ (93\%) $$

(*N*-Hydroxybenzylamine)chromium complex **220** gives the corresponding (benzylamine)chromium complex without racemization by treatment with titanium trichloride (Eq. 198). (291)

$$ (198) $$

The chiral iron carbene complex **221**, derived from enantiomerically pure tricarbonyl(*o*-anisaldehyde)chromium and the CpFe(CO)$_2$ anion, followed by treatment with trimethylsilyl triflate, can be trapped with styrene to produce the cis isomer of cyclopropane chromium complex **223** via iron carbene complex **222** (Eq. 199). (292)

$$ (199) $$

(Arene)chromium complexes with a (tetracarbonyliron)acylya group such as **224**, obtained from

tricarbonyl(*o*-lithiochlorobenzene)chromium and pentacarbonyliron, are moderately air-stable. They react with electrophiles to give the corresponding (acyl)chromium complexes. For example, protonation performed with $HBF_4 \cdot OEt_2$ under 1 atmosphere of CO gives (*o*-chlorobenzaldehyde) chromium complex **225** (E ✂ H) in 80% yield (Eq. 200). (293)

EX	E	
$HBF_4 \cdot OEt_2$, CO (1 atm)	H	(80%)
MeI	Me	(—%)
$NCCH_2I$	CH_2CN	(—%)

(200)

Tricarbonyl(arene)chromium complexes undergo electrophilic attack, for example, Friedel-Crafts acylation, but less readily so than the uncomplexed aromatic system because of the electron-withdrawing effect of the $Cr(CO)_3$ unit. However, intramolecular reactions are promising. For example, the tricarbonylchromium complex of 4-isopropyl-4-(*p*-methoxyphenyl butyric acid (**226**) affords predominantly the exo (4-isopropyl- e-tetralone)chromium complex along with small amounts of the corresponding endo isomer (Eq. 201). (103)

I + II (63%), I:II = 96:4

(201)

Attachment of (arene)chromium complexes to polymer supports as traceless linkers has been devised for efficient solid-phase synthesis. (294-296) The polystyrene-supported (arene)chromium complex **227** undergoes organic transformations in high overall yield (Eq. 202). (296)

(202)

3.10. Catalytic Asymmetric Reactions Utilizing Chiral Tricarbonyl(arene)chromium Complexes as Chiral Ligands

Tricarbonyl(arene)chromium complexes can be functionalized easily at the side chain and arene ring, and some of these complexes have been utilized as chiral ligands in catalytic asymmetric reactions. Unlike ferrocenyl complexes, (arene)chromium complexes have been used rarely as chiral ligands in catalytic asymmetric reactions. (297, 15) One example is the cross-coupling of vinyl bromides with benzylzinc or benzyl Grignard reagents using the complexed arenephosphine ligand **228**, which proceeds with up to 61% ee (Eq. 203). (298)

Chiral amino alcohols not only accelerate the reaction of aldehydes with diorganozinc compounds but also direct the stereochemical outcome in an absolute sense. Tricarbonylchromium complexes such as **229** having amine and hydroxy

(203)

groups at two benzylic positions, obtained by ortho lithiation of tricarbonyl(*N,N*-dimethylphenylethylamine)chromium followed by trapping with aldehydes or ketones, catalyze the asymmetric reaction of benzaldehyde with alkylzinc reagents with high enantioselectivity (Eq. 204). (81, 299) The catalytic asymmetric reaction of organozinc reagents with both aliphatic (Eq. 205) (300-303) and aromatic aldehydes proceeds with higher enantioselectivity using the chromium-complexed norephedrine **230** than with the chromium-free ligand. Chromium-complexed h-amino alcohol **229** is used as a ligand for the asymmetric conjugate addition of diethylzinc to chalcone in the presence of Ni(acac)$_2$ with a moderate enantioselectivity (Eq. 206). (304)

(204)

(205)

$$(206)$$

Chiral tricarbonyl(arene)chromium complexes can also be employed as chiral ligands in catalytic asymmetric Diels-Alder reactions. Thus, cyclopentadiene reacts with methacrolein in the presence of 10 mol% of the chiral (arene)chromium complex **231** giving the exo-adduct in high yield and 61% ee (Eq. 207). (305)

$$(207)$$

The highly enantioselective allylic alkylation of 1,3-diphenyl-1-acetoxypropene is achieved by reaction with sodium malonate in the presence of a palladium catalyst of diphosphine ligands **232**, amino phosphine ligand **233**, (306) or mono-dentate phosphine ligand **234** (307) (Eq. 208).

$$(208)$$

The palladium-catalyzed substitution reaction of allylic derivatives with a sulfur nucleophile is achieved by using chromium-complexed diphosphine ligand, *ent*-**232** (R ✂Ph), giving a sulfonation product in moderate optical purity (Eq. 209). (155)

$$\text{(209)}$$

Rhodium-catalyzed asymmetric hydrogenation can also be achieved using chromium-complexed diphosphine compounds as chiral ligands. Hydrogenation of (*Z*)-methyl acetamidocrotonate in the presence of 0.2 mol% of a Rh-catalyst (prepared in situ from [(COD)RhCl]$_2$ and diphosphine ligand, *ent*-**232** (R ✂Cy), gives the product in quantitative yield and >95% ee (Eq. 210). (155)

$$\text{(210)}$$

The tricarbonylchromium complex **235** of the tricyclic oxazaborolidine derived from (*S*)-indoline-2-carboxylic acid can be used for asymmetric reduction of ketones, giving up to 91% ee for secondary alcohols (Eq. 211). (308) The enantioselectivity of the asymmetric reduction is largely dependent upon the face topology, and the equivalents used, of the chiral ligand. Use of one equivalent of the chiral reagent gives a secondary alcohol with high enantioselectivity (Eq. 211). Use of the corresponding chromium-free compound as the chiral reagent in the Itsuno-Corey reaction results in lower enantioselectivity.

$$\text{(211)}$$

A planar chiral (arene)chromium complex carrying amine and phosphine groups (e.g., **236**) has been used in the asymmetric hydroboration of styrene derivatives to provide 1-arylethanols with moderate enantioselectivity (Eq. 212). (309)

$$\text{(212)}$$

Reagents:
1. catecholborane, Rh(COD)$_2$BF$_4$ (2 mol%), **236** (2.4 mol%), THF, −25°, 18 h
2. 3 M NaOH, H$_2$O$_2$ (30%), rt, 3 h

Ar = 4-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$, 2,4-Me$_2$C$_6$H$_3$, 3,4-(MeO)$_2$C$_6$H$_3$

19–81% ee

Palladium-catalyzed asymmetric hydrovinylation of styrene with ethylene can also be accomplished using phosphino-substituted chromium complex **237**, giving 3-phenyl-1-butene with 78.5 % ee (Eq. 213). (153)

CH$_2$=CH$_2$ (30 bar), CH$_2$Cl$_2$
237, (C$_3$H$_7$)Pd(cod)BF$_4$, rt, 15 min

(62%) 78.5% ee

(213)

Tricarbonyl(arene)chromium complexes are also useful as catalysts in the 1,4-hydrogenation of conjugated dienes to cis-olefins, in isomerization of conjugated dienes, and in hydrosilation of conjugated dienes. This type of reaction has been reviewed (310, 15) and is not covered here because the complexes [e.g., tricarbonyl(naphthalene)chromium] used for these purposes have no side chains.

Benzylic Activation and Stereochemical Control in Reactions of Tricarbonyl(arene)chromium Complexes

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4. Applications to Natural Product Synthesis

Tricarbonyl(1^6-arene)chromium complexes are useful for the synthesis of natural products containing fused benzene, biaryl, cyclohexane, or cyclohexenone skeletons. These types of natural products have been synthesized regio- and stereoselectively utilizing the unique properties of these complexes. Several natural products have been synthesized in optically active form starting with non-racemic planar chiral (arene)chromium complexes.

4.1. Natural Product Synthesis Utilizing Nucleophilic Addition Processes as Key Steps
Nucleophilic additions to chromium-coordinated arene rings (1, 2, 6-9) have been exploited in key steps for the synthesis of several natural products.

4.1.1. Deoxyfrenolicin
The naphthoquinone derivative, deoxyfrenolicin methyl ester (**241**), can be synthesized using nucleophilic addition/oxidation of an appropriate (arene)chromium complex as a key step. Directed lithiation of tricarbonyl[2-(trimethylsilyl)anisole]chromium (**238**) followed by alkylation gives tricarbonyl[2-(2-(*E*)-hexenyl)-6-(trimethylsilyl)anisole)]chromium (**239**). Regioselective nucleophilic addition of the nitrile-stabilized carbanion to chromium complex **239** followed by oxidation with an excess of iodine gives chromium-free 2,3-disubstituted anisole derivative **240** (Scheme 1). (311) Compound **240** is subsequently converted into deoxyfrenolicin methyl ester (**241**).

Scheme 1. [Full View]

4.1.2. (+)-Ptilocaulin
(+)-Ptilocaulin nitrate (**243**) has been synthesized from optically active tricarbonyl[2-(trimethylsilyl)anisole]chromium. This complex is produced by enantioselective ortho-lithiation of tricarbonyl(anisole)chromium with a chiral lithium amide in the presence of trimethylsilyl chloride as shown in Eq. 11. Regioselective nucleophilic addition of 2-lithio-1,3-dithiane followed by protonation, acid hydrolysis, and photo-oxidation affords optically active 1,2-cis-disubstituted cyclohexenone derivative **242** (Scheme 2). (312) Cyclohexenonea **242** is subsequently converted into (+)-ptilocaulin nitrate.

Scheme 2. [Full View]

4.1.3. Clavicipic Acid
This indole alkaloid has been prepared using an intramolecular nucleophilic addition/oxidation process (Scheme 3) in a key step. (313)

Scheme 3. [Full View]

4.1.4. Acorenone A and Acorenone B
The spiro-sesquiterpenoids acorenone A and acorenone B have been synthesized by a regioselective intramolecular nucleophilic addition/protonation process (Scheme 4). (314) Chromium complexation of nitrile **244** with $Cr(CO)_6$ affords a diastereomeric mixture of chromium complexes **245** and **246** in a ratio of 60:40. The chromium complex **245** is treated with LDA to generate a nitrile-stabilized carbanion intermediate, which attacks at the position meta to the electron-donating methoxy group. After protonation of the intermediate with trifluoroacetic acid and hydrolysis with acid, spirocyclohexenone derivative **247** is obtained in 45% yield. Intermediate **247** is converted to acorenone B (**248**) in several additional steps. The diastereomeric chromium compound **246** is converted to acorenone A by a similar reaction sequence.

Scheme 4. [Full View]

Diastereomers **245** and **246** can be prepared stereoselectively as shown in Scheme 5. (42) Diastereoselective chromium complexation of ortho-substituted secondary benzyl alcohol derivatives (e. g., **250**), followed by stereoselective carbon-carbon bond formation via a chromium-complexed benzyl cation intermediate, with stereochemical retention at the benzylic position, gives a single diastereomeric chromium complex. (42) Thus, ligand transfer of ortho-substituted secondary benzyl alcohol **249** with tricarbonyl(naphthalene)chromium followed by desilylation gives exclusively one diastereomeric chromium complex **250** via chelation of the chromium to the benzylic oxygen in the most stable conformation. Directed lithiation of complex **250** and quenching with methyl iodide affords a single complex **251** at the least hindered position ortho to the methoxy group. (209) Treatment of complex **251** with methyl 2-(trimethylsilyl)but-3-enoate in the presence of a Lewis acid affords substitution product **252** with retention at the benzylic position. Complex **252** is converted into key intermediate complex **246** for acorenone A. On the other hand, the ortho-substituted secondary benzyl alcohol **253** gives the chromium complex **245** by the same sequence of reactions.

Scheme 5. [Full View]

4.1.5. Anthraquinone Antibiotics

The A-B ring system of aklavinone (**258**) is synthesized by a tandem addition process involving both a nucleophile and an electrophile (Scheme 6). (315) Nucleophilic addition of tris(methylthio) methyl lithium to tricarbonyl(1-methoxynaphthalene)chromium (**254**), and subsequent trapping with methyl iodide in the presence of CO gives the corresponding chromium complex. Decomplexation with triphenylphosphine affords 1,2-addition products **255** and **256** with the nucleophile and acyl groups in a trans orientation in a ratio of 6:1, respectively. The functionalized dihydronaphthalene **255** is converted into the anthraclinone A-B ring system **257**.

Scheme 6. [Full View]

The double bond of tricarbonyl(dihydronaphthalene)chromium complexes reacts with nucleophiles to give conjugate addition products as shown in Eq. 134. The carbanion of a protected acetaldehyde cyanohydrin adds to the double bond of tricarbonyl(methoxydihydronaphthalene)chromium (**259**) to give the 2-exo-substituted (5-methoxytetralin)chromium complex **260** (Scheme 7). (222, 316) Directed lithiation of **260** followed by quenching with 2-formyl-3-methoxy-*N,N*-diethylbenzamide and oxidative decomplexation gives a diastereomeric mixture of the ketophthalide derivative **261**. Reductive ring cleavage followed by cyclization and oxidation produces an anthraclinone derivative.

Scheme 7. [Full View]

4.2. Synthesis of Sesqui- and Diterpenoid Natural Products with Tetralin Skeletons

Hydroxycalamenenes (**262** and **263**) and related sesquiterpenoids, diterpenoids, pseudopterosins, and dihydroxyserrulatic acid (**264–267**) all have a 1,4-disubstituted tetralin skeleton (Figure 5). Some of these natural products have been synthesized stereo- and regioselectively using tricarbonylchromium complexes. Stereoselective introduction of the proper substituents at the benzylic position is achieved by exo-attack on chromium-stabilized benzylic anion or cation intermediates.

Figure 5. Natural products having a 1,4-disubstituted tetralin skeleton. [Full View]

4.2.1. Dihydroxyserrulatic Acid

Reduction of (ꬲ-tetralone)chromium complex **268**, followed by reaction with (*E*)-crotyltrimethylsilane in the presence of $BF_3 \cdot OEt_2$, gives the exo-substitution product **269** as a mixture of diastereomers in a ratio of 75:25 via a tricarbonylchromium-stabilized benzylic cation

(Scheme 8). (317) Addition of methyllithium to the carbonyl group of complex **269** followed by stereoselective hydride reduction of the resulting alcohol with triethylsilane affords 1,4-transdisubstituted (tetralin)chromium complex **270**. Nucleophilic addition of 2-lithio-1,3-dithiane at the position meta to the methoxy group followed by treatment with iodine gives the intermediate **271**, which is subsequently transformed into dihydroxyserrulatic acid (**264**).

Scheme 8. [Full View]

4.2.2. Analog of Dihydropseudopterosin G

The aglycone of dihydropseudopterosin G is synthesized by two successive regio- and diastereoselective benzylic deprotonation/alkylation reactions (Scheme 9). (173) ɛ-Methylation of the planar chiral (ɛ-tetralone)chromium complex **272** followed by reduction and dehydration affords the (dihydronaphthalene)chromium complex **273**. Reduction of the double bond in **273** affords an (*endo*-methyltetralin)chromium complex, which is protected at the arene ring by introduction of two TMS group to afford **274**. The C-4 benzylic position of complex **274** is selectively deprotonated and alkylated, affording complex **275**. Further deprotonation at the C-1 position followed by treatment with methyl ɛ-trimethylsilylacrylate gives 1-exo-2-endo-4-exo-trisubstituted tetralin complex **276** as a single diastereomer after fluoride-induced desilylation. Hydrolysis of the ester and Friedel-Crafts cyclization of the derived carboxylic acid provides (ɛ-tetralone)chromium complex **277**. Reduction of the carbonyl group and subsequent treatment with Me$_3$Al gives exo-methyl-substituted chromium complex **278**. Finally, introduction of a methyl group in the arene ring and oxidative demetalation affords dihydropseudopterosin G dimethyl ether (**279**). (318-320)

Scheme 9. [Full View]

4.2.3. seco-Pseudopterosin

The agylycone of seco-pseudopterosin is synthesized by stereoselective functionalization at the benzylic position of planar chiral (ɛ-tetralone)chromium complex **280** (Scheme 10). (321) The absolute configuration at the exocyclic position is controlled by a diastereoselective hydroboration/oxidation process. Treatment of complex **281** with borane dimethylsulfide followed by oxidation and dehydration gives **282** as a single diastereomer; the oxidation with basic hydrogen peroxide proceeds without removal of the chromium fragment. Introduction of a methyl group ortho to the methoxy group in the aromatic ring followed by stereoselective reduction of the double bond in complex **283** with SmI$_2$ gives **284** with the requisite configuration of the natural product.

Scheme 10. [Full View]

The aglycones of related diterpenoids have been synthesized via diastereoselective alkylation at the benzylic position of various chromium complexes. (223, 322, 323) Analogous sesquiterpenoids, 7- and 8-hydroxycalamenenes, have also been synthesized by means of stereoselective functionalization at the corresponding benzylic positions. (102, 103, 316)

4.3. Synthesis of Axially Chiral Biaryl Compounds

Palladium(0)-catalyzed diastereoselective cross-coupling of planar chiral aryl halide chromium complexes with arylboronic acids has been used as a key step in the synthesis of axially chiral, biaryl natural products such as (–)-steganone (285), korupensamines A (286) and B, and the A-B ring system of vancomycin (287).

285

(–)-steganone

286

korupensamine A

korupensamine B

287

vancomycin

4.3.1. (–)-Steganone

The planar chiral (2-bromobenzaldehyde)chromium complex **289** is obtained by diastereoselective ortho-lithiation (removal of H^a-proton) of chiral (benzaldehyde acetal)chromium complex **288** derived from (S)-1,2,4-butanetriol (Scheme 11). (324, 89) After reduction of the formyl group in

complex **289**, palladium(0)-mediated cross-coupling with 2-formyl-4,5-methylenedioxyphenylboronic acid in aqueous methanol gives, stereoselectively, the anti-coupling [CHO vs $Cr(CO)_3$] product **290**. The hydroxymethyl group of **290** is then converted into the butenolide to give complex **291**. Treatment of the butenolide with SmI_2 in THF using *t*-BuOH as a proton source gives a single diastereomer of product **292** via 8-endo radical cyclization. Decomplexation and oxidation of the secondary alcohol followed by equilibration of the stereocenter ε to the ketone produce (–)-steganone (**285**).

Scheme 11. [Full View]

4.3.2. A-B Ring System of Vancomycin

Vancomycin (**287**) and related antibiotics have attracted multidisciplinary interest for decades because of their clinical use. They have been enlisted as a drug of last resort for the treatment of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA). The axially chiral A-B ring system can be prepared stereoselectively from both enantiomers of a planar chiral (bromobenzene)chromium complex (Schemes 12 and 13). (76, 128) Both enantiomers of planar chiral (3,5-dimethoxy-2-bromobenzaldehyde)chromium, (+)-**294** and (–)-*ent*-**294**, are obtained in high enantiopurity by diastereoselective ortho-lithiation and subsequent bromination of chiral (acetal)chromium complexes **293** and **299**, derived from *S*)-1,2,4-butanetriol and methyl ε-D-glucopyranoside, respectively. (325) Treatment of complex (+)-**294** with trimethylsilyl cyanide in the presence of zinc iodide gives a single diastereomer of the cyanohydrin derivative which is subsequently converted into complex **295**. Formation of a single diastereomer of the cyanohydrin chromium complex is based on exo-attack of the reagent on the antioriented carbonyl oxygen ortho to the bromo group. Palladium(0)-catalyzed cross-coupling of complex **295** with arylboronic acid **296** in aqueous methanol at 80° affords the syn-coupling product **297** without formation of any other stereoisomers. Product **297** is converted into key intermediate **298** for vancomycin synthesis. (326) The antipode (–)-*ent*-**295** is also converted into key intermediate **302** as shown in Scheme 13. Cross-coupling of (–)-*ent*-**295** with arylboronic acid **296** under the same conditions affords the anti-coupling product **300**. Treatment of product **300** with MeLi and $ClCH_2I$ gives a single epoxide **301**.

Ring opening of the epoxide with the nitrogen nucleophile trimethylsilyl azide is required to achieve the desired configuration of the vancomycin intermediate. Thus, treatment of **301** with $TMSN_3$ in the presence of $BF_3 \cdot OEt_2$ gives a single azide **302** with retention of configuration via a chromium-stabilized benzylic cation intermediate.

Scheme 12. [Full View]

Scheme 13. [Full View]

Korupensamine A (**286**) has been prepared by stereoselective cross-coupling of a planar chiral (aryl bromide)chromium complex with an arylboronic acid. (327)

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Benzylic Activation and Stereochemical Control in Reactions of Tricarbonyl(arene)chromium Complexes

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5. Comparison with Other Methods

Arene compounds are converted into the corresponding neutral (η^6-arene)- $M(CO)_3$ complexes (M ⋊ Cr, Mo, W) and their cationic analogs (e.g., $FeCp^+$, $RuCp^+$, $Mn(CO)_3{}^+$) (328-331) by transition-metal coordination. Among these η^6-arene transition-metal complexes, the η^6-(arene) chromium complexes have been widely employed for organic synthesis because of their stability and ease of preparation. The electron-withdrawing ability and the steric bulk of the tricarbonylchromium fragment impart some unique properties to (η^6-arene)chromium complexes; therefore, the chemistry exhibited by these complexes does not have any parallel. Since the electron density of the aromatic ring is decreased, facile nucleophilc addition to the aromatic ring takes place at low temperature. Positions meta to an electron-donating group are selectively attacked by nucleophiles. Depending on the quenching method used, the (η^5-cyclohexadienyl)chromium intermediates give substituted benzene, dihydrobenzene, or 1,2-trans-disubstituted dihydrobenzene derivatives. It is difficult to prepare these compounds from benzene by direct procedures. Since one face of the arene ring is blocked by coordination with the tricarbonyl-chromium fragment, the usual approach of the attacking reagent to the benzene ring or side chain is from the side opposite the metal fragment. Therefore, the configuration at the side chain of benzene derivatives can be controlled. Furthermore, the corresponding tricarbonylchromium complexes of di- or polysubstituted benzene derivatives having different substituents at the 1,2- or 1,3-positions can exist in two enantiomeric planar chiral forms, although the chromium-free arenes themselves are non-chiral. Planar chiral (arene)chromium complexes can become useful synthetic precursors or chiral ligands and auxiliaries in asymmetric reactions. By using these properties, optically active natural products can be synthesized stereoselectively.

Both carbocations and carbanions are stabilized at the benzylic positions of tricarbonylchromium-complexed arenes by delocalization of the charge onto the chromium. The chromium-complexed benzylic carbanions and carbocations are considered to have substantial exocyclic carbon-carbon double bond character with the benzyl ligand coordinated in a η^5-mode to the

Therefore, both nucleophiles and electrophiles react by stereoselective bond formation. In cyclic systems, reagents react with chromium-complexed benzylic anions or cations from the side opposite to the chromium fragment to give exo-substituted cyclic complexes. In acyclic systems, reactions of chromium-complexed benzylic cations or anions with nucleophiles or electrophiles proceed with stereochemical retention because of the exocyclic carbon-carbon double bond character.

In a complementary approach, an aromatic system can be activated toward organic transformations by η^2-coordination. Of the handful of transition-metal systems that are known to form stable η^2-arene complexes with aromatic molecules, only pentaamine(η^2-arene)osmium(II) has been shown to enhance the reactivity of the aromatic ligand. (332) The (arene) $[Os]^{2+}$ complexes are most commonly prepared by reducing the Os(III) precursor $Os(NH_3)_5(OTf)_3$. Typically, the reduction is

carried out with magnesium in DMA or a DMA/DME mixture. Using this simple procedure, pentaamine(arene)osmium(II) complexes including those derived from benzene, anisole, aniline, phenol, naphthalene, pyridine, pyrrole, furan, and thiophene have been prepared in high yields. (333-338) As a general rule, the osmium selects a binding site on monosubstituted arenes where it causes the minimum disruption to the π-system. Osmium preferentially binds at the C-5 and C-6 double bonds, allowing linear conjugation of the substituent and the unbound portion of the arene ring for both electron-rich (e.g., anisole, aniline, phenol) and electron-deficient (e.g., adiphenylacetylene, benzophenone) arenes. Whereas the η^6-arene transition-metal complexes are susceptible to nucleophilic substitution or addition, ultimately leading to the formation of substituted arenes or cyclohexadienes respectively, the (η^2-arene)osmium complexes take part in electrophilic additions. η^2-Osmium complexes of phenols, anilines, acetanilides, and anisoles undergo electrophilic substitution with high regioselectivities at the C-4 position (Eq. 214). (332, 339) An electrophilic addition to the (phenol)osmium complex is typically carried out in the presence of a tertiary amine base. With less reactive electrophiles such as methyl acrylate, a Lewis acid cocatalyst is employed for conjugate addition. Electrophilic addition reactions to

(214)

osmium(II) complexes of anilines and anisoles are carried out in the presence of Lewis acids. The reaction takes place predominantly at the C-4 position of these osmium complexes. Furthermore, dienone, anilinium, and anisolium intermediates derived from benzene, aniline, and anisole take part in nucleophilc addition to the double bond at the C-3 position (Eq. 215). (332, 339)

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6. Experimental Conditions

The arene transition-metal complexes should be handled under an inert atmosphere such as argon or nitrogen, since they are easily oxidized in solution. Hexacarbonylchromium is volatile and sublimes easily. Compounds of chromium are toxic and must be used in a well-ventilated fume hood. The aqueous layers from the chromium-mediated reactions and any other waste materials should be disposed of properly.

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7. Experimental Procedures

The most convenient method for decomplexation of the reaction products is to expose a solution of the chromium-complexed product in an organic solvent (e.g., ether) to sunlight until the solution changes from a yellow or red color to colorless. Filtration and evaporation of the solvent give chromium-free compounds. Oxidizing agents (I_2 or Ce(IV)) can also be employed for the decomplexation.

7.1.1. Tricarbonyl(η^6-anisole)chromium (*21*)

The reaction should be carried out in a well-ventilated hood, as hexacarbonylchromium is toxic and carbon monoxide evolves during the reaction. In a 250-mL round-bottomed flask fitted with a gas inlet and simple reflux condenser (not a spiral or similar type from which subliming $Cr(CO)_6$ was washed back less efficiently) were placed hexacarbonylchromium (4 g, 18 mmol), anisole (25 mL), dibutyl ether (120 mL), and THF (10 mL). A bubbler was placed at the top of the condenser to prevent access of air. The apparatus was thoroughly purged with nitrogen. The nitrogen stream was stopped and the mixture was then heated at reflux for 24 hours. The yellow solution was cooled with ice (most of the unreacted $Cr(CO)_6$ separated out in 10–15 minutes) and filtered through kieselguhr or a small pad of similar material on a sintered-glass filter, which was then washed with additional solvent. The solvents were removed on a rotary evaporator using a water bath held at 60° (an oil pump may be required to remove the solvents completely). A deep-yellow oil remained to which dry light petroleum ether (bp 40–60°) or hexane (20 mL) was added with subsequent crystallization of tricarbonyl(η^6-anisole)chromium (4.1 g, 92%). A small amount of unreacted $Cr(CO)_6$ may have been recoverable from the condenser; the remainder was distilled with the solvent. Recrystallization of the crude product from benzene or Et_2O with added light petroleum ether gave the title product (3.53 g, 80%), mp 84–85°; IR (C_6H_{12}) 1980, 1908 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.6 (s, 3H), 4.77 (t, 1H), 5.03 (d, 2H), 5.4 (d, 2H).

7.1.2. Resolution of Racemic Tricarbonyl(η^6-o-anisaldehyde)chromium with L-Valinol (31)

L-Valinol (379 mg, 3.68 mmol) was added to an ether (10 mL) solution of racemic tricarbonyl
o-anisaldehyde)chromium (1.00 g, 3.68 mmol) and the mixture was stirred for 4.5 hours under an
inert atmosphere, the initial red solution turning orange. Column chromatography on deactivated
alumina (grade V) gave two fractions. The first fraction, which eluted with Et_2O , was concentrated
to a red solid, and the second fraction ($MeOH/CH_2Cl_2$ 1 : 10) gave an orange oil. Both products
were separately dissolved in THF (8 mL). Water (2 mL) was added, followed by conc. HCl (5
drops), and the resulting darkened solutions were stirred until they turned crimson (ca. 30 minutes).
The solvents were removed, the residues were taken up in Et_2O (10 mL), and the solutions were
filtered through plugs of alumina to give both products as red solids. The first fraction was
identified as (–)-tricarbonyl(η^6-o-anisaldehyde)chromium (460 mg, 46%); $[\alpha]^{23}_D$ –1015° (c

$CHCl_3$). The second fraction was the (+)-isomer (380 mg, 38%); $[\alpha]^{23}_D$ + 1016° (c 0.06, $CHCl_3$).

7.1.3. Resolution of Racemic Tricarbonyl(o-methylbenzyl alcohol)chromium with Lipase (Amano PS) (36)

A mixture of racemic tricarbonyl(o-methylbenzyl alcohol)chromium (52 mg, 0.2 mmol) and lipase
Amano PS (100 mg) in isopropenyl acetate (0.35 mL) was stirred under nitrogen at room
temperature for 6 hours. Methylene chloride (3 mL) was added, and the resulting mixture was
filtered through a short column of silica gel to remove the lipase. The filtrate was evaporated under
reduced pressure and the residue was purified by silica gel chromatography (Et_2O /hexane 1:4) to
give 28.1 mg (47%) of the acetate complex and 25.2 mg (47%) of the alcohol chromium complex.
The absolute configurations of both chromium complexes were determined by comparison of the
optical rotations with those of authentic samples. Optical purities were determined by ^{1}H NMR in
the presence of Pr[hfc]$_3$. (Benzyl acetate)chromium complex, $[\alpha]^{25}_D$ + 38.9° (c 0.61, $CHCl_3$),
ee. (Benzyl alcohol)chromium complex, $[\alpha]^{25}_D$ –5.2° (c 0.56, $CHCl_3$), 99% ee.

7.1.4. (S*,S*)-Tricarbonyl-[1-(3-Methoxyphenyl)ethyl alcohol]chromium [Preparation of an (Arene)Chromium Complex by Diastereoselective Tricarbonylchromium Complexation] (42)

Racemic 2-trimethylsilyl-3-methoxy- ⍺-methylbenzyl alcohol (224 mg, 1.0 mmol), tricarbonyl (naphthalene)chromium (320 mg, 1.2 mmol), THF (0.16 mL), and Et_2O (6 mL) were placed in a heavy-wall glass tube with a valve and gas inlet. The mixture was degassed by a freeze/pump/thaw cycle and then heated at 70° for 4 hours in a closed system. The reaction mixture was cooled to room temperature, and the organic solvents were removed under vacuum. The residue was purified by silica gel chromatography with Et_2O /petroleum ether to give (S*,S*)-tricarbonyl(2-trimethylsilyl-3-methoxy- ⍺-methylbenzyl alcohol)chromium (250 mg); mp 127°; ^{1}H NMR ($CDCl_3$) ⍺ 0.38 (s, 9H), 1.42 (d, J = 6 Hz, 3H), 1.97 (br s, 1H), 3.69 (s, 3H), 4.90 (br s, 1H), 4.99 J = 7 Hz, 1H), 5.15 (d, J = 7 Hz, 1H), 5.75 (t, J = 7 Hz, 1H). The product (214 mg, 0.59 mmol) in THF (2 mL) was treated with n-Bu_4NF (1.8 mL, 0.4 M in THF, 0.72 mmol) at 0° for 4 hours under argon. After addition of water, the reaction mixture was extracted with Et_2O , the extracts were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by silica gel chromatography with Et_2O /petroleum ether to give the title product, mp 66°; ^{1}H NMR ($CDCl_3$) ⍺ 1.50 (d, J = 7 Hz, 3H), 2.16 (d, J = 5 Hz, 1H), 3.68 (s, 3H), 4.40–4.73 (br, 1H), 4.95–5.16 (m, 3H), 5.56 (t, J = 6 Hz, 1H).

7.1.5. (1R)-(–)-Tricarbonyl(o-methylbenzaldehyde)chromium [Preparation of an (Arene) chromium Complex by Diastereoselective Ortho-Lithiation] (49)

The chromium complex **303** (0.20 g, 0.45 mmol) derived from methyl ⍺-glucopyranoside was dissolved in Et_2O (20 mL) at –78°, and a hexane solution of n-BuLi (0.54 mmol) was added dropwise within 30 seconds. The resulting solution was stirred for 1 hour at –78° and then treated with 5 equivalents of MeI at –78°. After stirring for an additional 1 hour at –78°, the solution was left to warm to room temperature and quenched with 1 M aqueous NaOH. The organic layer was separated and chromatographed (hexane/ Et_2O 2:1) to yield 65% of the ortho-methylated compound, [⍺]$^{23}_D$ + 85° (c 0.34, $CHCl_3$); IR 1955, 1874 cm^{-1}; ^{1}H NMR ($CDCl_3$) ⍺ 2.26 (s, 3.25 (dd, J = 3.8, 12.9 Hz, 1H), 3.45 (s, 3H), 3.55 (s, 3H), 3.58 (s, 3H), 3.60 (m, 1H), 3.70–3.80 (m, 3H), 4.31 (dd, J = 3.9, 9.5 Hz, 1H), 4.84 (d, J = 3.6 Hz, 1H), 5.11 (d, J = 6.4 Hz, 1H), 5.17 (t, J = 6.4 Hz, 1H), 5.31 (s, 1H), 5.40 (t, J = 5.4 Hz, 1H), 5.87 (d, J = 6.6 Hz, 1H). After the product (0.13 mmol) was dissolved in THF (5 mL), 50% aqueous H_2SO_4 solution (0.5 mL) was added, and the resulting solution was heated at reflux for 2 hours under an inert atmosphere. After cooling followed by neutralization with aqueous $NaHCO_3$, the organic layer was separated and

chromatographed (hexane/ Et$_2$O 20:1) to give the title compound, $[\alpha]^{20}_D$ –665° (c 0.1, CHCl$_3$); 1965, 1891 cm^{-1}; ^{1}H NMR (CDCl$_3$) $\hat=$ 2.53 (s, 3H), 5.03 (d, J = 6.5 Hz, 1H), 5.22 (t, J = 6.3 Hz, 1H), 5.72 (t, J = 6.4 Hz, 1H), 6.05 (d, J = 6.6 Hz, 1H).

7.1.6. (+)-(R)-Tricarbonyl(2-trimethylsilylanisole)chromium [Preparation of an (Arene) Chromium Complex by Enantioselective Ortho-Lithiation] (340, 45)

Into a solution of (R,R)-bis(phenylethyl)amine (248 mg, 1.10 mmol) in dry THF (22 mL) was added n-BuLi (0.69 mL, 1.6 M in hexane, 1.10 mmol) at –78° under nitrogen. The reaction mixture was warmed to room temperature for 15 minutes, and the resulting chiral lithium amide base solution was then cooled to –78°, and TMSCl (0.38 mL, 3.00 mmol) was added in one portion. A solution of tricarbonyl-(anisole)chromium (1.00 mmol) in THF (3 mL) was immediately added in one portion. After stirring the solution at –78° for 30 minutes, saturated aqueous NaHCO$_3$ solution (5 mL) was added and the reaction mixture left to warm to room temperature. The mixture was extracted with CH$_2$Cl$_2$ (40 mL), the extract was washed with water (15 mL), dried over MgSO$_4$, and the solvent was evaporated under reduced pressure. The resulting yellow oil was purified by flash column chromatography on silica gel to give 18 mg (4%) of tricarbonyl[2,6-bis(trimethylsilyl) anisole]chromium as the first fraction and then (+)-(R)-tricarbonyl(2-trimethylsilylanisole) chromium (264 mg, 83%) as a yellow crystalline solid, mp 79–80°; $[\alpha]^{29}_D$ + 205° (c 1.10,

IR (CHCl$_3$) 1966, 1897 1330, 841 cm^{-1}; ^{1}H NMR (CDCl$_3$) $\hat=$ 0.32 (s, 9H), 3.74 (s, 3H), 4.78 (dd, J = 6.1, 6.1 Hz, 1H), 4.97 (d, J = 6.1 Hz, 1H), 5.58 (d, J = 6.1 Hz, 1H), 5.56 (dd, J = 6.1, 6.1 Hz, 1H).

7.1.7. 3-(o-Anisyl)-2-cyano-3-hydroxy-1-Propene [Baylis-Hillman Reaction of an Arylaldehyde Coordinated to Chromium] (54)

(+)-Tricarbonyl(o-methoxybenzaldehyde)chromium (272 mg, 1 mmol) and DABCO (56 mg, 0.5 mmol) were dissolved in acrylonitrile (0.7 mL) under nitrogen, and the reaction mixture was stirred at room temperature for 11 hours. The excess olefin was removed under vacuum, the remaining mixture was taken up in Et$_2$O , and the solution was washed with 10% aqueous HCl and water. The organic layer was dried over MgSO$_4$ and taken to dryness. Column chromatography on silica (hexane/ Et$_2$O 2:1 to 1:1) gave a yellow crystalline complex (88%), mp 129–133° (dec.);

$^{20}_D$ –197° (c 0.06, CHCl$_3$); IR (CH$_2$Cl$_2$) 1969, 1889 cm^{-1}; ^{1}H NMR (C$_6$D$_6$) $\hat=$ 2.25 (d,

1H), 3.77 (s, 3H), 4.96 (dt, $J = 0.8, 6.3$ Hz, 1H), 5.05 (dd, $J = 0.8, 6.8$ Hz, 1H), 5.47 (br d, $J = 3.4$ Hz, 1H), 5.60 (ddd, $J = 1.4, 6.3, 6.8$ Hz, 1H), 5.95 (dd, $J = 1.4, 6.3$ Hz, 1H), 6.03 (d, $J = 0.8$ Hz, 1H), 6.12 (d, $J = 1.2$ Hz, 1H).

7.1.7.1. Decomplexation

A solution of the complex (0.5 mmol) as produced above in MeCN (10 mL) was exposed to sunlight and air at room temperature for 5 hours. The volatiles were removed by vacuum, and the product was chromatographed on silica gel to give the title compound (93%) as a colorless oil; $^{20}_{D} - 68°$ (c 0.23, CHCl$_3$); ^{1}H NMR (C$_6$D$_6$) $\triangleq$ 3.45 (d, $J = 6.0$ Hz, 1H), 3.82 (s, 3H), 5.48 (t, $J = 6.0$ Hz, 1H), 5.96 (d, $J = 1.2$ Hz, 1H), 5.98 (d, $J = 1.2$ Hz, 1H), 6.90 (d, $J = 8.0$ Hz, 1H), 6.98 (t, $J = 7.5$ Hz, 1H), 7.25–7.40 (m, 2H).

(95%)

7.1.8. (–)-(2R,4S,5R)-5-[Tricarbonyl(o-tolyl)chromium]-4-(p-toluenesulfonyl)oxazoline [Cycloaddition Reaction] (65)

To a mixture of (–)-tricarbonyl(o-tolualdehyde)chromium (128 mg, 0.5 mmol) and p-toluenesulfonylmethyl isocyanide (98 mg, 0.5 mmol) in MeOH (5 mL) at 0° was added K$_2$CO$_3$ (69 mg, 0.5 mmol). After the reaction mixture was stirred at 0° for 30 minutes, glacial acetic acid (0.58 mL, 0.5 mmol) was added dropwise. The methanol was removed under vacuum (without heating) and the residue was dissolved in CH$_2$Cl$_2$ (20 mL). After washing with water (2 × 5 mL), the organic phase was dried over MgSO$_4$, the solvent was evaporated, and the crude title product was analyzed by ^{1}H NMR before and after purification (by flash chromatography), 95% yield; [2] $_D - 299°$ (c 2.9, CHCl$_3$); IR (CHCl$_3$) 1975, 1900, 1620 cm^{-1}; ^{1}H NMR (CDCl$_3$) $\triangleq$ 2.48 (s, 6H), 5.03 (dd, $J = 5.5, 1.7$ Hz, 1H), 5.13 (m, 3H), 5.44 (td, $J = 6, 2$ Hz, 1H), 5.91 (d, $J = 5.5$ Hz, 1H), 7.22 (d, $J = 1.7$ Hz, 1H), 7.41 (d, $J = 8.5$ Hz, 2H), 7.83 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (CDCl$_3$) $\triangleq$ 19.7, 22.4, 76.2, 89.3, 90.1, 93.0, 93.1, 94.7, 104.5, 108.6, 130.2, 130.6, 132.9, 160.0, 235.5.

7.1.9. S-tert-Butyl (2R,3S)-3-Hydroxy-2-methyl-3-[2-(trimethylsilyl)phenyl]propane(thioate) [Aldol Reaction of an Arylaldehyde Coordinated to Chromium] (79)

To a solution of (+)-tricarbonyl(o-trimethylsilylbenzaldehyde)chromium (41 mg, 0.13 mmol) and E-trimethylsilylketene thioacetal (39.5 mg, 0.16 mmol) in dry CH$_2$Cl$_2$ (5 mL) was added dropwise a solution of TiCl$_4$ in dry CH$_2$Cl$_2$ (1 M, 1.2 eq) at –78°, after which the reaction mixture was stirred for 30 minutes while being monitored by TLC. The reaction was quenched by addition of saturated aqueous NH$_4$Cl solution (0.5 mL) and the solution was gradually warmed to room temperature. The organic layer was washed with water and brine, dried, and concentrated. The

residue was dissolved in MeOH (5 mL), then CAN (3.0 equiv) was added portionwise at 0°. The mixture was stirred until the decomplexation of the chromium moiety was complete (monitored by TLC, 10–20 minutes). The methanol was removed and the residue was taken up in CH_2Cl_2. The solution was washed with water, brine, dried, and concentrated to dryness. Chromatography of the residue (CH_2Cl_2/hexane 1:1) afforded the title product (40.5 mg, 96%; anti:syn 96:4).

Chromatography was repeated several times to provide pure anti product, $[\alpha]^{26}_D$ – 61.5° (c 0.50, $CHCl_3$) (96 %ee); IR (neat) 3550, 1670 cm^{-1}; ^{1}H NMR ($CDCl_3$) $\triangleq$ 0.38 (s, 9H), 0.93 (d, J = 7.3 Hz, 3H), 1.42 (s, 9H), 2.61 (br s, 1H), 3.05 (quin-like, J = 8.3 Hz, 1H), 5.11 (d, J = 8.3 Hz, 1H), 7.28 (t, J = 7.8 Hz, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.51 (d, J = 7.8 Hz, 1H).

7.1.10. (1S,2S)-Bis[1,2-tricarbonyl(o-bromophenyl)chromium]ethanediol [Pinacol Coupling] (85)

A solution of (+)-tricarbonyl(*o*-bromobenzaldehyde)chromium (100 mg, 0.31 mmol) and SmI_2 (0.1 M in THF, 10 mL, 1.0 mmol) was stirred under argon at –78° for 30 minutes. The mixture was warmed to 0° over 30 minutes, quenched with saturated aqueous NH_4Cl, then filtered through a pad of Celite. The filtrate was extracted with Et_2O, and the extract was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with Et_2O /hexane) to give enantiomerically pure threo pinacol (75 mg), $[\alpha]^{23}_D$ + 58.2° (c 0.27, MeOH); IR ($CHCl_3$) 3390, 1970, 1910 cm^{-1}; ^{1}H NMR ($CDCl_3$) $\triangleq$ 2.25 (br s, 2H), 4.33 (s, 2H), 5.25 (d, J = 6.7 Hz, 2H), 5.39 (d, J = 6.6 Hz, 2H), 5.46– (m, 4H); MS *m/z* (relative intensity) 644 (M$^+$ 0.6), 588 (7), 476 (20), 390 (18), 338 (15), 178 (37), 52 (100).

7.1.11. Tricarbonyl(tetrahydrobenzocyclooctene-5,10-dione)chromium [Double Oxy-Cope Rearrangement] (112)

A solution of tricarbonyl(1,2-dioxobenzocyclobutene)chromium (421 mg, 1.57 mmol) in Et_2O /THF (1:1, 120 mL) was added to a cooled (–78°) solution of vinyllithium (0.48 M in THF, 20 mL, 9.6 mmol) over a period of 6 hours. The resulting intensely dark red solution was stirred for a further 16 hours at –78°. After addition of aqueous hydrochloric acid (2 M, 10 mL) at –78°, the organic layer was diluted with Et_2O and the layers were separated. The aqueous layer was extracted with Et_2O until the extract remained colorless. The combined organic layers were washed with

water and dried over $MgSO_4$. After filtration, the volatile components were evaporated in vacuo. The crude oily residue was crystallized from a concentrated solution in acetone at –78°. After a second recrystallization from Et_2O , the pure product was obtained as orange-red needles (442 mg, 87%), mp 145–146°; IR (THF) 1984, 1919, 1682 cm^{-1}; ^{1}H NMR (CD_3COCD_3) ≙ 1.95 (m, 4H), 2.73 (m, 4H), 5.87 (m, 4H); MS (70 eV, EI) m/z 324 (M$^+$, 12), 268 (8), 241 (25), 240 (100).

7.1.12. Tricarbonyl[1-N-(p-toluenesulfonyl)-1-(η^6-2-methylphenyl)but-3-enyl]-chromium [Organometallic Addition to an Arylaldimine Coordinated to Chromium] (126)

Allylmagnesium bromide (1 M in Et_2O , 1 mL, 1 mmol) was added dropwise to a solution of the chromium-complexed benzaldimine (0.6 mmol) and of $ZnCl_2$ (0.1 eq) in THF (6 mL) at –20°. The color of the solution rapidly changed from orange to yellow, and after 20 minutes the mixture was quenched by adding H_2O/MeOH (1:1, 15 mL). The mixture was passed through a pad of Celite, extracted with CH_2Cl_2 (3 × 15 mL) and the solvent was evaporated. The crude product was purified by column chromatography (petroleum ether/ Et_2O 3:2), affording the title product (80%), mp 103–104°; IR (nujol) 3410, 1880, 1860, 1600 cm^{-1}; ^{1}H NMR (CD_3COCD_3) ≙ 2.3 (s, 3H), 2.5 (m, 2H), 3.75 (br s, 1H), 4.38 (t, J = 6.1 Hz, 1H), 4.98 (d, J = 6.2 Hz, 1H), 5.06 (dd, J = 6.3, 6.4 Hz, 1H), 5.15 (d, J = 17.0 Hz, 1H), 5.16 (d, J = 10.7 Hz, 1H), 5.49 (dd, J = 6.2, 6.3 Hz, 1H), 5.78 (m, 1H), 5.76 (d, J = 6.4 Hz, 1H), 6.75 (m, 3H), 7.2 (m, 2H).

7.1.13. Tricarbonyl[N-(4-methoxyphenyl)-(3R)-acetoxy-(4R)-(2-fluorophenyl)azetidin-2-one] chromium [Cycloaddition of a (Benzaldimine)chromium Complex with Acetoxyketene] (341)

A solution of acetoxyacetyl chloride (0.41 mL, 3.82 mmol) in CH_2Cl_2 (5 mL) was carefully added to a solution of the (–)-(1R)-(benzaldimine)chromium complex (400 mg, 1.09 mmol) and Et_3N (0.91 mL, 6.53 mmol) in CH_2Cl_2 (8 mL) at 0°. The reaction mixture was maintained for 6 hours at 0° and then overnight at room temperature. The reaction was quenched with water (10 mL) and the organic layer was dried over Na_2SO_4. After evaporation of the solvent at reduced pressure, the remaining brown solid was purified by chromatography (silica gel, eluent Et_2O /petroleum ether 3/1) to give the title compound as a pale yellow solid (93%), mp 199° (dec.); [☺]$_D$ – 25.5° (c CHCl$_3$); IR (nujol) 1975, 1880, 1744 cm^{-1}; ^{1}H NMR (CDCl$_3$) ≙ 1.9 (s, 3H), 3.8 (s, 3H), 4.7 (m, 1H), 5.22 (m, 1H), 5.6 (d, J = 5 Hz, 1H), 5.65–5.6 (m, 2H), 6.5 (d, J = 5 Hz, 1H), 7.0–7.5 (m, 4H).

7.1.14. N-Methyl-3-o-trimethylsilylphenyl-5-phenylisoxazolidine [Cycloaddition of a Chromium-Coordinated Nitrone with Styrene] (342)

A solution of tricarbonyl(2-trimethylsilylbenzaldehyde)chromium (569 mg, 1.81 mmol) and *N*-methylhydroxylamine hydrochloride (181 mg, 2.17 mmol) in CH_2Cl_2 (15 mL) was heated at reflux in the presence of $NaHCO_3$ (482 mg, 5.74 mmol) for 9 hours. After cooling, the $NaHCO_3$ was removed by filtration and the filtrate was concentrated to dryness. Chromatography of the residue (hexane acetone 10:3) gave tricarbonyl[η^6-(*Z*)-*N*-(2-trimethylsilylbenzylidene)methylamine *N*-oxide]chromium (609 mg, 98%) as red needles, mp 108–110°; IR ($CHCl_3$) 1980, 1900, 1580 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.41 (s, 9H), 3.86 (s, 3H), 5.25 (t, *J* = 6.2 Hz, 1H), 5.44 (d, *J* = 6.9 Hz, 1H), 5.62 (t, *J* = 6.4 Hz, 1H), 6.91 (d, *J* = 6.9 Hz, 1H), 7.22 (s, 1H); ^{13}C NMR δ 0.4, 55.0, 91.0, 91.9, 93.9, 98.9, 99.0, 101.8, 132.0, 232.7.

A mixture of the chromium-complexed nitrone (76 mg, 0.22 mmol) and styrene (3 mL) was heated in a sealed tube at 90° for 6 hours. The excess of styrene was removed by evaporation. The residue was dissolved in MeOH, CAN (3 eq) was added portionwise at 0°, and the mixture was stirred at 0° for 30 minutes. The residue left after methanol removal was treated with water and extracted several times with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with water and brine, dried, and then concentrated to dryness. Chromatography of the residue (hexane/ EtOAc 20:1) gave the title compound (47 mg, 69%) as a colorless oil, ^{1}H NMR ($CDCl_3$) δ 0.39 (s, 9H), 2.35 (ddd, *J* = 7.7, 9.8, 12.5 Hz, 1H), 2.71 (s, 3H), 3.12 (ddd, *J* = 6.7, 7.7, 12.5 Hz, 1H), 4.05 (dd, *J* = 6.7, 9.8 Hz, 1H), 5.26 (t, *J* = 7.7 Hz, 1H), 7.23–7.29 (m, 2H), 7.33–7.39 (m, 3H), 7.46–7.51 (m, 3H), 7.64 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR δ 1.0, 43.5, 50.4, 73.0, 78.2, 125.9, 126.8, 127.0, 127.2, 128.4, 129.9, 134.2, 138.4, 143.4, 145.1.

7.1.15. N-Allyl-[2-tricarbonyl(o-iodophenyl)chromium]-2,3-dihydro-4-pyridone [Hetero-Diels-Alder Reaction of a Chromium-Coordinated Arylaldimine with Danishefsky's Diene] (243)

Allylamine (0.61 mL, 8.2 mmol) and molecular sieves (4 Å) were added to a solution of (–)-(1*R*)-tricarbonyl(*o*-iodobenzaldehyde)-chromium [2.94 g, 8.0 mmol, [α]$_D$ – 741°(*c* 0.15, $CHCl_3$)] in Et_2O . The mixture was stirred overnight, then filtered through Celite and concentrated to give crude (–)-aldimine complex as an orange oil. The oil was dissolved in THF (50 mL), cooled to –78°, and $SnCl_4$ (1.04 mL, 8.45 mmol) was added dropwise. After 15 minutes, Danishefsky's diene (2.70 mL, 14.1 mmol) was added, and stirring was continued for 18 hours while gradually raising

the temperature to 0°. The crude reaction mixture was filtered through Celite and volatiles were removed under vacuum. The residue was taken up in EtOAc and washed with aqueous $NaHCO_3$ solution. Column chromatography (SiO_2, Et_2O /hexane 7:3) gave the title compound as a yellow solid (3.78 g, 90%), $[\alpha]_D$ + 55.6°(c 0.185, $CHCl_3$); IR (hexane) 1983, 1926, 1911, 1749 cm^{-1}; ^{1}H NMR (C_6D_6) δ 2.55 (d, J = 16.4 Hz, 1H), 2.84 (dd, J = 8.4, 16.4 Hz, 1H), 3.3–3.45 (m, 1H), 3.88 (m, 1H), 4.15 (t, J = 6.4 Hz, 1H), 4.17 (t, J = 8 Hz, 1H), 4.33 (d, J = 8 Hz, 1H), 4.75 (d, J = 5.6 Hz, 1H), 4.95–5.10 (m, 2H), 5.17 (m, 2H), 5.2–5.45 (m, 1H), 6.19 (d, J = 7.6 Hz, 1H); ^{13}C NMR (C_6D_6) δ 41.9, 56.8, 60.9, 78.1, 88.4, 90.6, 96.6, 99.5, 100.4, 118.9, 133.4, 152.0, 186.3, 232.7.

7.1.16. Tricarbonyl(1-exo-isopropyl-4-endo-methyl-6-methoxy-7-methyl-tetralin)chromium [Ionic Reduction of a Chromium-Complexed Benzylic Alcohol] (103)

To a mixture of the chromium complex **304** (200 mg, 0.50 mmol) and triethylsilane (350 mg, 3.0 mmol) was added trifluoroacetic acid (350 µL, 4.5 mmol) at 0° under nitrogen. The reaction mixture was heated with stirring at 50–60° for 4.5 hours, decomposed with water, and extracted with Et_2O . The extract was washed with saturated aqueous $NaHCO_3$ solution and brine, dried, and then concentrated to dryness. The residue was purified by silica gel chromatography to give the title compound (151 mg, 82%), IR ($CHCl_3$) 1970, 1800 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.72 (d, J = 7 Hz, 3H), 0.96 (d, J = 7 Hz, 3H), 1.38 (d, J = 6 Hz, 3H), 2.17 (s, 3H), 3.71 (s, 3H), 5.26 (s, 1H), 5.43 (s, 1H).

7.1.17. 2-[Tricarbonyl(o-anisyl)chromium]butane [Stereoselective Carbon-Carbon Bond Formation via a Complexed-Carbocation] (42)

To a solution of chromium complex **305** (100 mg, 0.3 mmol) in dry CH_2Cl_2 (6 mL) was added Et_3Al (1.0 M in hexane, 1.2 mL, 1.2 mmol) under argon at –78°. The mixture was warmed to 0° for 3 hours, then quenched with dilute cold aqueous HCl, and extracted with CH_2Cl_2. The extract was washed with saturated aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. Evaporation of the solvent and purification of the residue by silica gel chromatography gave the title compound (89 mg, 90%), mp 61°; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7 Hz, 3H), 1.22 (d, J = 7 Hz, 3H), 1.32–1.66 (m, 2H), 2.78–3.12 (m, 1H), 3.70 (s, 3H), 4.84 (d, J = 7 Hz, 1H), 4.95 (d, J = 7 Hz, 1H), 5.36–5.50 (m, 2H).

7.1.18. Tricarbonyl([2-(1-chloroethyl)phenyl]diphenylphosphine oxide)chromium [Stereoselective Benzylic Carbon-Halogen Bond Formation via a Complexed Carbocation] (112)

A stirred solution of the chromium complex **306** (2.95 g, 6.08 mmol) in THF was treated dropwise with 1-chloroethyl chloroformate (3.48 g, 24.31 mmol) at –40°. The solution was stirred overnight without cooling. It was subsequently concentrated, and the residue dissolved in EtOAc, then filtered through silica gel. The title compound was isolated as yellow crystals from an EtOAc solution at –30° (2.24 g, 77%), IR ($CHCl_3$) 1986, 1925 cm^{-1}; ^{1}H NMR (C_6D_6) $\triangleq$ 1.44 (d, J = 6.5 Hz, 3H), (t, J = 6 Hz, 12H), 4.51 (br d, J = 10.0, 6.5 Hz, 1H), 4.56 (t, J = 6.5 Hz, 1H), 4.60 (m, 1H), 6.91 (q, J = 7.0 Hz, 1H), 7.04–7.07 (m, 6H), 7.74–7.82 (m, 4H); ^{31}P NMR (C_6D_6) $\triangleq$ 28.76.

7.1.19. 1-Phenyl-1-isopropylthio-3-tricarbonyl(phenyl)chromium-1,2-propadiene [Reaction of a Chromium-Coordinated Benzyl-Propargyl Cation] (160)

To a solution of chromium complex **307** (150 mg, 0.39 mmol) in CH_2Cl_2 (18 mL), cooled to –78°, was added dropwise $BF_3 \cdot OEt_2$ (1.4 equiv). The purple red solution was stirred at –78° for 50 minutes, and then 2-propanethiol (0.08 mL, 0.85 mmol) was added dropwise. The color of the solution turned from purple red to yellow, and the reaction mixture was stirred for 30 minutes. Ether (20 mL) and water (20 mL) were added successively to the reaction mixture, which was gradually warmed to room temperature. After several extractions with Et_2O , the combined organic phases were dried over $MgSO_4$, the solvent evaporated in vacuo, and the residue purified by flash chromatography on silica gel (Et_2O /pentane 1:2). Crystallization from pentane gave the title compound (112 mg, 72%), mp 108–111°; ^{1}H NMR (DMSO-d_6) $\triangleq$ 1.27 (d, J = 6.89 Hz, 3H), 1.30 (d, J = 6.6 Hz, 3H), 3.15 (m, 1H), 5.72–5.79 (m, 3H), 5.86 (d, J = 6.2 Hz, 1H), 5.92 (d, J = 6.3 Hz, 1H), 7.09 (s, 1H), 7.30 (t, J = 6.9 Hz, 1H), 7.36–7.43 (m, 4H); ^{13}C NMR $\triangleq$ 22.9, 23.1, 37.9, 93.2, 94.3, 94.4, 94.6, 101.2, 103.6, 105.4, 124.6, 128.5, 129.2, 132.4, 204.6, 233.7; MS (EI, 70 eV) *m/z*: M$^+$ 402 (4), 346 (12), 318 (44), 244 (100), 243 (6), 191 (50), 52 (22).

7.1.20. Tricarbonyl(1-exo-methyl-1,3-dihydroisobenzothiophene)chromium [Asymmetric Deprotonation and Alkylation of a Prochiral (Arene)chromium Complex] (290)

A solution of the bis-lithium amide base was prepared by addition of *n*-BuLi (1.6 M in hexane, 0.5 mL, 0.80 mmol) to a solution of the chiral diamine (0.17 g, 0.40 mmol) in THF (10 mL) under an atmosphere of nitrogen at –78°. The solution was left to warm to room temperature with stirring and then cooled to –100°. To the resulting pink solution was added a solution of LiCl (7.7 mg, 0.18 mmol) in THF (5 mL) via cannula, followed by dropwise addition of a solution of the (1,3-dihydroisobenzothiophene)chromium complex (100 mg, 0.37 mmol) in THF (10 mL). The red solution was stirred at –100° for an additional hour. Methyl iodide (0.12 mL, 1.9 mmol) was added in one portion, the reaction mixture was warmed to –78° and stirred for another hour. Methanol (1 mL) was added with subsequent warming to room temperature before the solvents were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel (10% EtOAc in light petroleum) to give the title compound (100 mg, 95%), mp 118°,[α]$^{23}_D$ –

(*c* 0.53, CHCl$_3$); IR (CHCl$_3$) 1971, 1897 cm^{-1}; ^{1}H NMR (CDCl$_3$) $\triangleq$ 1.59 (d, *J* = 7 Hz, 3H), 3.86 (d, *J* = 14 Hz, 1H), 4.24 (d, *J* = 14 Hz, 1H), 4.34 (q, *J* = 7 Hz, 1H), 5.26 (m, 2H), 5.42–5.48 (m, 2H); ^{13}C NMR (CDCl$_3$) $\triangleq$ 26.4, 35.8, 47,6, 89.7, 90.3, 91.4, 91.6, 111.0, 116.6, 232.8.

The enantiomeric excess of the product was determined to be 94% ee using a Chiralcel OD column (hexane/2- PrOH 95:5, flow rate 1 mL/minute; UV detection at 256 nm). The products had retention times of 18.7 minutes (major) and 23.7 minutes (minor).

308 (89%)   (82%)

7.1.21. Tricarbonyl(N-methyl-cis-1-ethyl-4-methyl-1,2,3,4-tetrahydroisoquionoline)chromium [Stereoselective Alkylation of a Tricarbonylchromium-Stabilized Benzylic Anion] (215)

n-BuLi (1.6 M in hexane, 1.2 mL, 1.95 mmol) was added to a stirred solution of tricarbonyl(*N*-methyl-1,2,3,4-tetrahydroisoquinoline)chromium (500 mg, 1.77 mmol) in THF (30 mL) at –78°. The initial yellow solution rapidly became crimson. After the reaction mixture had been stirred at –78° for 2 hours, methyl iodide (>3 equiv) was added, and the mixture was stirred at –78° for 2 hours. After the addition of MeOH (1 mL), the solution was warmed to room temperature and concentrated. Column chromatography (Al$_2$O$_3$ Grade V; hexane/ Et$_2$O 3:1) of the residue followed by evaporation and crystallization from CH$_2$Cl$_2$/hexane gave the chromium complex **308** as yellow needles (467 mg, 89%), mp 74–75°; IR (nujol) 1970, 1940, 1900 cm^{-1}; ^{1}H NMR (CDCl$_3$) $\triangleq$ 1.36 (d, *J* = 7 Hz, 3H), 2.34 (s, 3H), 2.45 and 2.59 (AB system, *J* = 12 Hz, 2H), 2.78–2.84 (m, 1H), 3.25 and 3.57 (AB system, *J* = 15 Hz, 2H), 5.34–5.52 (m, 4H).

To a stirred solution of complex **308** (760 mg, 2.56 mmol) in THF (30 mL) at –78° was added *t*-BuLi (1.4 mL, 2.8 mmol). The initial yellow solution rapidly became orange. After the mixture had been stirred at –78° for 2 hours, ethyl iodide (0.85 mL, 10.6 mmol) was added and stirring was continued at –78° for 4 hours. Methanol (6 mL) was added, and the reaction mixture worked up and purified as described above, giving the title complex (680 mg, 82%) as a yellow solid, mp 97–98°; IR (nujol) 1965, 1890 cm^{-1}; ^{1}H NMR (CDCl$_3$) $\triangleq$ 0.78 (t, *J* = 7.4 Hz, 3H), 1.37 (d, *J* = 6.9 Hz, 1.74 (ddq, *J* = 3.8, 7.4, 14.7 Hz, 1H), 2.00 (ddq, *J* = 4.0, 7.4, 14.7 Hz, 1H), 2.42 (s, 3H), 2.58–2.64 (m, 1H), 2.58 and 2.83 (ABX system, *J* = 12 Hz, 2H), 3.32 (t, *J* = 3.8 Hz, 1H), 5.26–5.32 (m, 4H).

7.1.22. Tricarbonyl[1,1,3-trimethyl-3-(2-trimethylsilylphenyl)propionitrile]chromium [Conjugate Addition to and Alkylation of a Tricarbonyl(vinylarene)chromium Complex] (286)

To a cooled (–78°) solution of n-BuLi (1.5 M in hexane, 1.75 mL, 2.63 mmol) in THF (8 mL) was added dropwise with stirring isobutyronitrile (182 mg, 2.63 mmol). The reaction mixture temperature was increased to –20° over 30 minutes. To this solution was added (–)-(1S,2R)-tricarbonyl(2-trimethylsilylstyrene)chromium (674 mg, 1.88 mmol) in THF (5 mL) at –78°. The reaction mixture was brought to –20° quickly and subsequently stirred for 2 hours as it warmed from –20 to 0°. After cooling again to –78°, methyl iodide (441 mg, 3.10 mmol) was added dropwise. After warming from –20 to 0° with stirring over 2 hours, the reaction mixture was left to reach room temperature. The solvent was removed under reduced pressure and the residue dissolved in Et$_2$O (30 mL), washed with saturated aqueous NH$_4$Cl solution (10 mL) and brine (10 mL), dried over MgSO$_4$, and concentrated. Purification by column chromatography (SiO$_2$, light petroleum/ CH$_2$Cl$_2$ 2:1 to 1:1) followed by crystallization (hexane/ CH$_2$Cl$_2$), yielded yellow crystals of the title compound (453 mg, 61%), mp 112–114°; [᪲]^{23}$_D$ – 25.6° (c 1.36, CHCl$_3$); IR (CH$_2$Cl$_2$) 1963, 1885 cm^{-1}; ^{1}H NMR ᪲ 0.41 (s, 9H), 1.45 (d, J = 6 Hz, 3H), 1.46 (s, 3H), 1.49 (s, 3H), 1.88 (dd, J = 10, 14 Hz, 1H), 1.95 (dd, J = 3, 14 Hz, 1H), 2.89 (dqd, J = 3, 6, 10 Hz, 1H), 4.98 (dd, J = 1, 6 Hz, 1H), 5.19 (dt, J = 1, 6 Hz, 1H), 5.44 (dd, J = 1, 6 Hz, 1H), 5.57 (dt, J = 1, 6 Hz, 1H); ^{13}C NMR ᪲ 25.5, 25.8, 30.0, 30.6, 34.0, 45.7, 88.4, 90.4, 95.4, 99.0, 100.4, 125.4, 127.4, 233.2.

7.1.23. Tricarbonyl[η⁶-1-(1-[2,2-dimethyl-1,3-dioxane-4,6-dion-5-yl]ethyl)-5,6-dimethoxy-4-methyl-7-trimethylsilanyl-1,2,3,4-tetrahydronaphthalene]-chromium [Conjugate Addition of a Chromium-Complexed Benzylic Anion] (318)

In a 10-mL Schlenk tube the chromium complex **309** (100 mg, 0.24 mmol) was dissolved in dry THF (2 mL) and cooled to –65°. s-BuLi (0.27 mL, 1.35 M in cyclohexane/hexane, 0.36 mmol) was added and the mixture was warmed to –20° over a period of 45 minutes. The initial yellow solution turned orange. A second Schlenk tube was charged with freshly distilled 5-ethylidene-2,2-dimethyl-1,3-dioxane-4,6-dione (50 mg, 0.29 mmol) in dry THF (0.5 mL). This solution was transferred to the deprotonated complex via cannula at –60°. The color of the reaction mixture changed back to yellow. The solution was warmed to room temperature over a period of 1 hour, diluted with hexane/ EtOAc (4:1, 25 mL), and transferred to a separatory funnel. The mixture was washed with saturated aqueous NH$_4$Cl solution, water, and brine, dried over MgSO$_4$, and concentrated in vacuo. The crude product was separated from the remaining starting material by flash chromatography (hexane/

EtOAc 4:1, then methyl *tert*-butyl ether/ CH$_2$Cl$_2$ 4:1) to give racemic title compound (68 mg, 48%), mp 140°; ^{1}H NMR (CDCl$_3$) ≙ 0.31 (s, 9H), 1.10 (d, J = 7.0 Hz, 3H), 1.37 (d, J = 7.0 Hz, 3H), 1.47–1.58 (m, 1H), 1.69 (s, 3H), 1.77 (s, 3H), 1.75–1.84 (m, 1H), 1.88–1.96 (m, 1H), 2.19–2.28 (m, 1H), 2.74- 2.88 (m, 2H), 3.25 (qd, J = 7.0, 2.0 Hz, 1H), 3.53 (d, J = 2.0 Hz, 1H), 3.79 (s, 3H), 3.84 (s, 3H), 5.44 (s, 1H).

7.1.24. Tricarbonyl[3′,4′-dihydro-2-phenylspiro(cyclopropane-1,2′(1′H)-naphthalen)-1′-one] chromium [Remote Stereoselectivity in the Cyclopropanation of an (Arene)chromium Complex] (*239*)

To a solution of benzylidene- ⌖-tetralone chromium (1 mmol), trimethylsulfoxonium iodide (1 mmol), and tetrabutylammonium bromide (2 mol%) in degassed CH$_2$Cl$_2$ (10 mL) was added 50% aqueous NaOH (10 mL) under argon. The mixture was heated under reflux for 16 hours. The usual work-up followed by flash chromatography on silica gel (20% EtOAc in hexane) afforded the endo-cyclopropanation product as orange crystals (83%), IR (CHCl$_3$) 1990, 1920, 1670 cm^{-1}; ^{1}H NMR (CDCl$_3$) ≙ 1.35–1.55 (m, 2H), 2.15–2.80 (m, 5H), 5.1 (d, J = 6 Hz, 1H), 5.3 (d, J = 6 Hz, 1H), 5.1 (t, J = 7 Hz, 1H), 5.6 (dt, J = 1, 6 Hz, 1H), 7.3 (m, 5H); ^{13}C NMR (CDCl$_3$) ≙ 18.3, 24.6, 26.4, 33.3, 37.1, 89.4, 90.2, 90.6, 93.1, 94.0, 115.2, 127.1, 128.2. 128.9, 136.0, 195.0, 230.9.

7.1.25. (–)-Tricarbonyl[2-methoxyphenyl (3R,5R) Dimethyl-6-(1′,1′-dimethyl-ethoxy)-1-hexanone]chromium [Stereoselectivity in Conjugate Addition at a Remote Double Bond of an (Arene)chromium Complex] (*236*)

To a suspension of CuI (76 mg, 0.4 mmol) in Et$_2$O (2 mL) was added 2-methyl-3-*tert*-butoxypropyl-lithium (10.08 M in Et$_2$O , 0.37 mL, 0.4 mmol), which was prepared from Li metal and (*S*)-2-methyl-3-*tert*-butoxy-1-bromopropane at –45° under argon. The reaction mixture was stirred for 30 minutes and then BF$_3$ · OEt$_2$ (0.05 mL, 0.4 mmol) was added to the suspension at –78°. A solution of chromium complex **310** (30 mg, 0.01 mmol) in Et$_2$O (2 mL) was added at –78° and the reaction mixture was stirred for 1 hour, then quenched with saturated aqueous sodium thiosulfite solution and extracted with Et$_2$O . The extract was washed with saturated aqueous NaHCO$_3$ solution and brine, dried over MgSO$_4$, and evaporated in vacuo. The residue was purified by silica gel chromatography with Et$_2$O /hexane to afford the title compound as a yellow oil (37 mg, 86%), [⌖]$^{18}_D$ –197° (*c* 0.1, CHCl$_3$); IR (CHCl$_3$) 1975, 1890, 1660, 1460 cm^{-1}; ^{1}H NMR CDCl$_3$) ≙ 0.91 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.7 Hz, 3H), 1.05–1.15 (m, 1H), 1.17 (s, 9H),

1.30 (m, 1H), 2.30–2.38 (m, 1H), 2.71 (dd, J = 6.7, 16.5 Hz, 1H), 2.88 (dd, J = 6.7, 17.1 Hz, 1H), 3.07 (dd, J = 7.3, 8.6 Hz, 1H), 3.17 (dd, J = 6.1, 8.5 Hz, 1H), 3.85 (s, 3H), 4.92 (t, J = 6.1 Hz, 1H), 5.00 (d, J = 6.7 Hz, 1H), 5.78 (t, J = 6.1 Hz, 1H), 6.22 (d, J = 6.7 Hz, 1H).

7.1.26. Tricarbonyl(1-exo-methoxy-3-exo-methoxycarbonylmethylindan)chromium [Palladium-Catalyzed Heck Cyclization/Carbonylation of an (Arene)chromium Complex] (242, 244)

The reaction was carried out in a heavy-walled 80-mL Schlenk tube fitted with an 8-mm O-ring tap and rubber septum. To a suspension of Pd(PPh$_3$)$_4$ (51 mg, 0.0443 mmol) and complex **311** (295 mg, 0.887 mmol) in MeCN (15 mL) was added Et$_3$N (0.18 mL, 1.33 mmol) and MeOH (0.14 mL, 3.5 mmol). The rubber septum was replaced by an adapter with a small pressure gauge. Carbon monoxide (3.5 bar) was pressed onto the mixture, which was then heated with magnetic stirring at 80° for 12 hours. Excess CO was vented and the volatiles were evaporated in vacuo. After filtration of the crude reaction mixture through Celite® and removal of the volatiles under vacuum, the ^{1}H NMR spectrum showed the presence of a single diastereomer. Purification by flash chromatography on silica gel (Et$_2$O /hexane) afforded the title compound (226 mg, 73%), [⚲] $^{20}_D$ + 12° (c 0.15, CHCl$_3$); IR (CHCl$_3$) 1971, 1896, 1732 cm^{-1}; ^{1}H NMR (C$_6$D$_6$) ≙ 1.64 (d, J = 14.5 Hz, 1H), 2.23 (ddd, J = 5.7, 7.5, 14.5 Hz, 1H), 2.42 (d, J = 7.5 Hz, 2H), 2.88 (s, 3H), 3.24 (q, J = 7.5 Hz, 1H), 3.30 (s, 3H), 3.99 (d, J = 5.7 Hz, 1H), 4.29 (t, J = 6.5 Hz, 1H), 4.47 (t, J = 6.5 Hz, 1H), 4.87 (d, J = 6.5 Hz, 1H), 4.98 (d, J = 6.5 Hz, 1H); ^{13}C NMR (C$_6$D$_6$) ≙ 36.7, 39.8, 42.0, 51.2, 56.6, 83.4, 89.9, 91.0, 91.6, 93.6, 109.6, 117.5, 171.8, 233.2.

7.1.27. 2,3-Dimethyl-4-diethylphosphono-4-[tricarbonyl(2-methylphenyl)chromium]-2-butene [Nucleophilic Addition to an (Allenylarene)chromium Complex] (250)

A stirred suspension of CuI (104 mg, 0.55 mmol) in THF (10 mL) was cooled to 0° and MeLi (1.6 M in Et$_2$O , 0.68 mL, 1.1 mmol) was added over a period of 1 minute by syringe. The resulting cuprate solution was stirred for an additional 40 minutes at 0°, and a solution of chromium complex **312** (0.21 g, 0.5 mmol) in THF (5 mL) was added at –78° over a period of 5 minutes. Stirring was continued at the same temperature for 7 hours. Saturated aqueous NH$_4$Cl solution (20 mL) was added, and the aqueous layer was extracted several times with Et$_2$O . The combined organic phases were dried over MgSO$_4$, filtered, and concentrated under reduced pressure. After chromatography on silica gel, a diastereomeric mixture of the title compound was obtained (151 mg, 70%, dr 5:1). Major diastereomer: mp 108–111°; IR (KBr) 3084, 2982, 2928, 1967, 1889, 1872, 1629, 1445, 1380 cm^{-1};^{1}H NMR (DMSO-d$_6$) ≙ 1.18 (t, J = 6.9 Hz, 3H), 1.29 (t, J = 6.9 Hz, 3H), 1.49 (s, 3H), 1.69 (d, J = 5.3 Hz, 3H), 1.78 (s, 3H), 1.96 (s, 3H), 3.73–4.15 (m, 5H), 5.52 (d, J = 6.1 Hz, 1H),

5.61 (d, $J = 6.3$ Hz, 1H), 5.74 (t, $J = 6.4$ Hz, 1H), 6.36 (d, $J = 6.5$ Hz, 1H); ^{13}C NMR $\triangleq$ 15.7, 16.1, 16.6, 18.4, 21.0, 21.3, 42.8, 61.3, 63.2, 91.5, 95.2, 95.6, 97.3, 107.8, 109.8, 119.6, 132.1, 234.2. Minor diastereomer: mp 93–95°; ^{1}H NMR (DMSO-d_6) $\triangleq$ 1.06 (t, $J = 6.9$ Hz, 3H), 1.16 (t, $J = 7.0$ Hz, 3H), 1.66 (d, $J = 3.3$ Hz, 3H), 1.79 (s, 3H), 2.01 (s, 3H), 2.28 (s, 3H), 3.82–3.99 (m, 4H), 4.15 (d, $J = 26.5$ Hz, 1H), 5.44–5.49 (m, 2H), 5.83 (t, $J = 6.4$ Hz, 1H), 6.06 (d, $J = 5.8$ Hz, 1H); ^{13}C NMR $\triangleq$ 16.3, 16.4, 17.7, 19.6, 20.9, 21.3, 40.8, 61.9, 62.6, 90.2, 93.5, 97.3, 98.9, 109.8, 112.4, 122.7, 131.3, 234.0.

7.1.28. Trimethylsilylethynyl Dicarbonyltriphenylphosphine(benzene)chromium [Sonogashira Coupling of a (Chloroarene)chromium Complex] (262)

To a degassed solution of (chlorobenzene)Cr(CO)$_2$PPh$_3$ (1.0 g, 2.07 mmol), PdCl$_2$(PPh$_3$)$_2$ (30 mg, 0.04 mmol), and CuI (9 mg, 0.04 mmol) in a mixture of THF (40 mL) and Et$_3$N (20 mL) was added dropwise over a period of 1 hour a solution of trimethylsilylacetylene (0.59 mL, 4.14 mmol) in THF (10 mL). The reaction mixture was heated at reflux for 24 hours, then cooled to room temperature. Ether (50 mL) was added, the mixture was filtered, and the filtrate was evaporated in vacuo. The residue was chromatographed on silica gel (Et$_2$O /pentane) to give the title compound (1.0 g, 89%) as a red solid, mp 58–61°; IR (KBr) 2158, 1972, 1900, 1842, 1667 cm^{-1};^{1}H NMR (DMSO-d_6) $\triangleq$ 0.17 (s, 9H), 4.72 (m, 2H), 4.83–4.89 (m, 15H); ^{13}C-NMR (DMSO-d_6) $\triangleq$ 0.07, 89.38, 89.91, 92.39, 92.91, 103.82, 128.16, 129.34, 132.68, 138.66, 240.20; MS (70 eV, EI) m/z: M$^+$ 544 (6), 488 (39), 314 (100), 262 (77), 226 (5), 52 (32).

syn-313 (80%)

7.1.29. syn-(+)-(1R$_p$,R$_a$)-Tricarbonyl[(1–6-$\widetilde{\eta}$)-2-methoxy-2′-methyl-6-formyl-biphenyl] [Stereoselective Palladium-Catalyzed Biaryl Synthesis using a (Bromoarene)chromium Complex] (264)

A mixture of enantiopure (1R)-tricarbonyl(2-methoxy-6-formylbromobenzene)chromium (400 mg, 1.20 mmol), 2-methylphenylboronic acid (325 mg, 2.40 mmol), and Pd(PPh$_3$)$_4$ (69 mg, 0.06 mmol) in aqueous 2 M Na$_2$CO$_3$ (1 mL) and MeOH (10 mL) was degassed by three freeze/vacuum/thaw cycles and heated at 75° for 30 minutes under argon. The reaction mixture was quenched with saturated aqueous NH$_4$Cl solution and extracted with Et$_2$O . The extract was washed with aqueous NaOH and brine, dried over MgSO$_4$, and evaporated under reduced pressure. The residue was purified by silica gel chromatography (20 g, eluted with 10% Et$_2$O in hexane) to give the title compound (348 mg, 80%), mp 118°;$[\circlearrowleft]^{23}_{D}$ + 199.7° (*c* 0.51, CHCl$_3$); IR (CHCl$_3$) 1980, 1910, 1690, 1520 cm^{-1}; ^{1}H NMR (CDCl$_3$) $\triangleq$ 2.62 (s, 3H), 3.80 (s, 3H), 5.39 (d, $J = 6.7$ Hz, 1H), 5.53

$J = 6.1$ Hz, 1H), 5.79 (dd, $J = 6.1, 6.7$ Hz, 1H), 7.06 (d, $J = 7.3$ Hz, 1H), 7.17–7.23 (m, 1H), 7.36 (d, $J = 7.3$ Hz, 2H), 9.48 (s, 1H).

syn-**313**   anti-**313** (89%)

7.1.30. anti-(–)-(1R$_p$,S$_a$)-Tricarbonyl[(1–6- ⚌)-2-methoxy-2′-methyl-6-formyl-biphenyl] [Axial Isomerization of a Chromium-Coordinated Biaryl under Thermal Conditions] (264)

A solution of complex syn- **313** (80 mg, 0.22 mmol) in xylene (3 mL) was heated at reflux for 2 hours under argon. The solvent was removed under vacuum, and the residue was purified by silica gel chromatography to give the title compound (78 mg, 97%), mp 130°;[⚌]$^{23}_D$ – 275.5° (c 0.51, CHCl$_3$); IR (CHCl$_3$) 1980, 1910, 1690, 1520 cm^{-1}; ^{1}H NMR (CDCl$_3$) ⚌ 2.09 (s, 3H), 3.67 (s, 5.27 (d, $J = 6.7$ Hz, 1H), 5.43 (d, $J = 6.7$ Hz, 1H), 5.80 (t, $J = 6.7$ Hz, 1H); 7.26 (d, $J = 7.3$ Hz, 1H), 7.31–7.38 (m, 2H), 7.57 (d, $J = 7.3$ Hz, 1H), 9.41(s, 1H).

314 (89%)   (60%)

7.1.31. (–)-(R)-2-Methoxy-2′-methyl-6-(acetoxymethyl)biphenyl [Reduction and Decomplexation of a Chromium-Coordinated Biaryl Aldehyde] (264)

A solution of NaBH$_4$ (13.6 mg, 0.36 mmol) in MeOH (5 mL) was added slowly to a solution of (+)-(R,R)-tricarbonyl[(1–6- ⚌)-2-methoxy-2′-methyl-6-formylbiphenyl]chromium (65.0 mg, 0.36 mmol) in MeOH (4 mL) at 0°, and the mixture was stirred under nitrogen at 0° for 30 minutes. The mixture was quenched with water and extracted with Et$_2$O , and the extract was washed with brine, dried over MgSO$_4$, and evaporated in vacuo to give yellow crystals. To a solution of the crude product in pyridine (2 mL) were added a catalytic amount of DMAP and acetic anhydride (2 mL), with stirring at room temperature for 3 hours under nitrogen. The mixture was extracted with Et$_2$O , and the extract was washed with aqueous 1 M HCl, saturated aqueous NaHCO$_3$ solution, and brine, and then dried over MgSO$_4$. The solvent was removed under vacuum, and the residue was purified by silica gel chromatography (hexane/ Et$_2$O) to give yellow crystals. Crystallization from hexane/ Et$_2$O gave chromium-complexed acetoxy compound **314** (65.0 mg, 89%), mp 104°;[⚌]$^{27}_D$ + 235.1° (c 0.51, CHCl$_3$); IR (CHCl$_3$) 1980, 1905, 1745 cm^{-1}; ^{1}H NMR (CDCl$_3$) ⚌ 2.04 (s, 3H), 2.64 (3H, s), 3.70 (s, 3H), 4.60 (d, $J = 12.8$ Hz, 1H), 4.65 (d, $J = 12.8$ Hz, 1H), 5.02 (d, $J = 6.1$ Hz, 1H), 5.13 (d, $J = 6.7$ Hz, 1H), 5.72 (dd, $J = 6.1, 6.7$ Hz, 1H), 7.05 (d, $J = 7.3$ Hz, 1H), 7.16 (t, $J = 7.3$ Hz, 1H), 7.26–7.32 (m, 2H). The purity (>99.9%) was determined by HPLC on a Chiralcel OF column (hexane/2-PrOH 50:1; flow rate 1.0 mL/min; column temperature 40°); retention time 43.13 minutes; antipode = 37.33 minutes.

A solution of complex **314** (45.0 mg, 0.11 mmol) in Et$_2$O (20 mL) was exposed to sunlight at 0° for 30 minutes until the yellow solution became colorless. The precipitate was removed by filtration, the solvent was evaporated in vacuo, and the residue was purified by silica gel chromatography to give the title compound (20 mg, 60%), [α]$^{21}_D$ – 24.1° (*c* 0.45, CHCl$_3$); IR (CHCl$_3$) 1720, 1460 cm^{-1}; ^{1}H NMR (CDCl$_3$) ≙ 1.98 (s, 3H), 2.02 (3H, s), 3.72 (s, 3H), 4.71 (d, *J* = 7.9 Hz, 1H), 4.78 (d, *J* = 12.8 Hz, 1H), 6.95 (d, *J* = 7.9 Hz, 1H), 7.07 (t, *J* = 6.7 Hz, 2H), 7.21–7.27 (m, 3H). The optical purity (>99.9% ee) was determined by HPLC [Ceramospher RU-1 (Shiseido Ltd.), eluted with MeOH, flow rate 0.5 mL/minute; retention times 18.98 minutes for the (–)-(*R*)-isomer and 16.76 minutes for the (+)-(*S*)-isomer].

7.1.32. Tricarbonyl[1-exo-hydroxy-2-exo-3-endo-bis(methoxycarbonyl)tetralin]chromium [Base-Initiated Ring-Opening and Cycloaddition of a (Benzocyclobutanol)chromium Complex] (*272*)

n-BuLi (1.6 M in hexane, 4.03 mL, 6.44 mmol) was added dropwise to a solution of racemic *syn*-(1-hydroxybenzocyclobutene)Cr(CO)$_3$ (1.5 g, 5.85 mmol) in THF (120 mL) at –78°. The color of the solution became yellow-orange. After the reaction mixture was stirred for 1 hour at –78°, a solution of dimethyl fumarate (6.44 mmol) in THF (18 mL) was added dropwise. The mixture was warmed to room temperature over 14 hours; the color of the mixture became more intense. The mixture was cooled to –78° and hydrolyzed by addition of saturated aqueous NH$_4$Cl solution. After warming to room temperature, the mixture was diluted with Et$_2$O and water, the layers were separated, and the aqueous layer was extracted with Et$_2$O until the extract remained colorless. The combined organic layers were dried over MgSO$_4$, and the solvent was evaporated into a cold trap under reduced pressure. The residue was taken up in a small amount of THF. Cold pentane was added, and the mixture was stored at –30° for 14 hours until precipitation was complete. The mother liquor was separated from the precipitate, and the precipitation procedure was repeated twice with the mother liquor. The collected precipitates were dried at 0.001 mbar to give the title compound (2.08 g, 89%), IR (THF) 1966, 1890, 1744 cm^{-1}; ^{1}H NMR (THF-d$_8$) ≙ 2.73 (dd, *J* = 11.9, 17.0 Hz, 1H), 3.04 (dd, *J* = 6.3 Hz, 1H), 3.12 (dd, *J* = 3.4, 12.0 Hz, 1H), 3.24 (ddd, 1H), 3.65 (s, 3H), 3.68 (s, 3H), 4.79 (dd, *J* = 3.4 Hz, 1H), 5.16 (d, 1H), 5.36 (dd, 1H), 5.43 (d, 1H), 5.58 (dd, 1H), 5.63 (d, 1H); ^{13}C NMR (THF-d$_8$) ≙ 31.4, 34.7, 47.9, 52.0, 52.3, 69.8, 92.5, 93.1, 94.7, 95.9, 107.5, 171.7, 174.5, 233.7.

7.1.33. Tricarbonyl(4-isopropoxy-7-methoxy-1-tetralone)chromium [Friedel-Crafts Cyclization of a Tricarbonyl(Arene)chromium Complex] (*103*)

A mixture of 4-tricarbonyl(*p*-methoxyphenyl)chromium-5-methylhexanoic acid (6.01 g, 16.1 mmol) and oxalyl chloride (12.0 g, 94.5 mmol) in dry benzene (500 mL) was heated under nitrogen at 50° for 2 hours. The solvent and excess reagent were evaporated in vacuo to give the acid chloride chromium complex as a yellow oil, which was used for the next step without purification. To a solution of the complex in dry CH_2Cl_2 (400 mL) was added anhydrous $AlCl_3$ (25 g, 18.4 mmol) all at once at 0° under nitrogen. The reaction mixture was stirred at 0° for 30 minutes and then at room temperature for 2 hours. After addition of water (300 mL) at 0°, the reaction mixture was extracted with CH_2Cl_2. The extract was washed with aqueous $NaHCO_3$ and brine, and dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave a red oil, which showed two spots on TLC. Column chromatography (SiO_2, 200 g, Et_2O /petroleum ether 1:3) gave 3.45 g of product **I** as the first fraction and 166 mg of product **II** as the second fraction. Product **I**: mp 90°; IR ($CHCl_3$) 1980, 1900, 1690, 1540 cm^{-1}; ^{1}H NMR ($CDCl_3$) $\hat{=}$ 1.02 (d, J = 6.3 Hz, 3H), 1.02 (d, J = 6.3 Hz, 3H), 1.08 (d, J = 6.3 Hz, 3H), 1.62–3.63 (m, 6H), 3.72 (s, 3H), 5.44 (s, 2H), 5.60 (s, 1H). Product **II**: mp 133°; IR ($CHCl_3$) 1980, 1910, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) $\hat{=}$ 1.06 (d, J = 6.3 Hz, 3H), 1.18 (d, J = 6.3 Hz, 3H), 1.24–2.74 (m, 6H), 3.66 (s, 3H), 5.32 (dd, J = 2, 5 Hz, 1H), 5.64 (d, J = 2 Hz, 1H), 5.68 (d, J = 5 Hz, 1H).

7.1.34. 5-Formyl-5-methylbicyclo[2,2,1]hept-2-ene [Asymmetric Diels-Alder Reaction Catalyzed by an Aluminum(III) Lewis Acid Carrying a Tricarbonyl(arene)-chromium Complex] (343)

Diethylaluminum chloride (0.33 mmol) was added slowly to a pre-cooled (–78°) solution of tricarbonyl[(R_p,1R,2S)-1,2,3,4-tetrahydro-1,2-naphthalenediol]chromium (0.33 mmol) in CH_2Cl_2 (5 mL). The mixture was warmed to ambient temperature over a period of 3 hours, then it was re-cooled to –78°. Freshly distilled methacrolein (1.67 mmol) was added rapidly by syringe and the mixture was stirred for 15 minutes, then freshly distilled cyclopentadiene (8.3 mmol) was added, and the mixture was stirred an additional 3 hours at –78°. The reaction mixture was warmed to 0°, quenched by addition of saturated aqueous $NaHCO_3$ solution (2 × 20 mL), and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), concentrated under vacuum, and the residue was purified by silica gel chromatography (hexane/ Et_2O 9:1) to give the title compound (81%). The exo/endo ratio of the title compound was determined by NMR spectroscopy. The enantiomeric excess was calculated either by NMR analysis using Eu(hfc)$_3$ as chiral shift reagent or by derivatization with (–)-(2R,4R)-pentane diol followed by GC analysis.

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Benzylic Activation and Stereochemical Control in Reactions of Tricarbonyl(arene)chromium Complexes

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8. Tabular Survey

The literature has been covered throughly through the end of March 2003. The tables are organized by reaction type as discussed in the text, where the substrate is the chromium-complexed aryl compound. The entries in each table are arranged in order of carbon count of the starting complex, and the tricarbonyl chromium fragment and protecting groups are included in the count.

A few entries appear in more than one table since they are legitimately described by the reactions described in the titles, and cannot be assigned exclusively to one or the other.

The yields of the products are given in parentheses. A dash in parentheses (—) indicates that no yields were provided by the author; similarly, a non-enclosed dash in sub-tables indicates that no relevant data were provided.

The following abbreviations are used in the tables:

Ac	acetyl
acac	acetylacetone
AcOH	acetic acid
Ac_2O	acetic anhydride
AIBN	azo(bis)diisobutyronitrile
Alox B	aluminum oxide basic
9-BBN	9-borabicyclo[3,3,1]nonane
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthalene
BIPHEP	2,2′-bis(diphenylphosphino)-1,1′-biphenyl
Boc	*tert*-butoxycarbonyl
BPPFA	1-(⟲-*N,N*-dimethylaminoethyl)-1,2-bis(diphenylphosphino) ferrocene
BPPM	(2*S*,4*S*)-*N*-(*tert*-butoxycarbonyl)-4-(diphenylphosphino)-2-(diphenylphosphinomethyl)pyrrolidine
BSA	*N,O*-bis(trimethylsilyl)acetamide
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CCL	*Candida cylindracea* lipase
Cp	cyclopentadienyl
CTAB	cetyltrimethylammonium bromide
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane

DMA	*N,N*-dimethylacetamide
dba	dibenzylidene acetone
DBN	1,5-diazabicyclo[3.4.0]nonene
de	diastereomeric excess
DIBALH	diisobutylaluminum hydride
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino) butane
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1′-bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
ee	enantiomeric excess
EX	electrophile, where X = displaced ion or functional group
E	functional group corresponding to EX when X is displaced
Gly	glycine
HMPA	hexamethylphosphoric triamide
LDA	lithium diisopropylamide
LiDBB	lithium 4,4′-di-*tert*-butylbiphenyl
MEM	methoxyethoxymethyl
Mes	2,4,6-trimethylphenyl
MOM	methoxymethyl
MoOPH	(hexamethylphosphoric amide)oxodi(peroxo)pyridinemolybdenum
Ms_2O	methanesulfonic anhydride
NuX	nucleophile, where X = displaced ion or functional group
Nu	functional group corresponding to NuX when X is displaced
NMP	*N*-methyl-2-pyrrolidone
PMHS	polymethylhydrosiloxane
PMP	*p*-methoxyphenyl
PPA	polyphosphoric acid
PPFA	*N,N*-dimethylaminoethyl-1-(2-diphenylphosphino)ferrocene
pyr	pyridine
SAMP	(*S*)-1-amino-2-(methoxymethyl)pyrolidine
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethysilyl
TBDPS	*tert*-butyldiphenylsilyl
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFP	trifluoropropanol
THA	tri-*n*-hexylamine
THAB	tetrahexylammonium bromide

TIPS   triisopropylsilyl
TMEDA   *N*,*N*,*N*′,*N*′-tetramethylethylenediamine
TMS   trimethylsilyl
TMSOTf trimethylsilyl triflate
TOAB   tetra-octylammonium bromide
TosMic   4-toluenesulfonylmethyl isocyanide
Ts   *p*-toluenesulfonyl

Table 1A. Resolution of Racemic (Arene)chromium Complexes

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Table 1B. Resolution of Racemic (Arene)chromium Complexes with Lipase

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Table 1C. Asymmetric Reductions of Racemic (Arene)chromium Complexes with Baker's Yeast

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Table 1E. Enantioselective ortho-Lithiations of (Arene)chromium Complexes

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Table 2E. Nucleophilic Addition Reactions of (Benzaldehyde)chromium Complexes

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Table 2F. Aldol Reactions of (Benzaldehyde)chromium Complexes

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Table 3C. Reduction Reactions of Cyclic (Alkyl Aryl Ketone and Lactone)chromium Complexes

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Table 3D. Nucleophilic Addition Reactions of Acyclic (Alkyl Aryl Ketone and Ester) chromium Complexes

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Table 3E. Nucleophilic Addition Reactions of Cyclic (Alkyl Aryl Ketone)chromium Complexes

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Table 3F. Radical-Mediated Reactions of (Aryl Ketone)chromium Complexes

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Table 4A. Additions of (Arene)chromium Complexes to Imines

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Table 4B. Cycloadditions of (Arene)chromium Complexes to Imines

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Table 4C. Radical-Mediated Reactions of Imines of (Arene)chromium Complexes

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Table 5A. Reactions of Chromium-Complexed Benzylic Cations Derived from Cyclic (Arene)chromium Complexes

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Table 5B. Reactions of Chromium-Complexed Benzylic Cations Derived from Acyclic (Arene)chromium Complexes

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Table 5C. Reactions of Chromium-Complexed Benzylic Oxonium Ions Derived from (Arene)chromium Complexes

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Table 5D. Reactions of Chromium-Complexed Propargyl Cations

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Table 5E. Reactions of Chromium-Complexed Remotely-Positioned Cations

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Table 6A. Reactions of Chromium-Complexed Benzylic Anions Derived from Cyclic (Arene) chromium Complexes

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Table 6B. Reactions of Chromium-Complexed Benzylic Anions Derived from Acyclic (Arene) chromium Complexes

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Table 6C. Reactions of Chromium-Complexed Benzylic Anions Having ♋- and ♌- Substituents

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Table 7A. Reductions of Double Bonds in (Arene)chromium Complexes

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Table 7B. Nucleophilic Additions to Double Bonds in (Arene)chromium Complexes

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Table 7C. Electrophilic Additions to Double Bonds in (Arene)chromium Complexes

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Table 7D. Cycloadditions to Double Bonds in (Arene)chromium Complexes

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Table 7E. Allylic Alkylation and Rearrangement Reactions of Double Bonds in (Arene) chromium Complexes

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Table 7F. Radical-Mediated Additions to Double Bonds in (Arene)chromium Complexes

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Table 7G. Palladium-Catalyzed Heck Reactions of (Arene)chromium Complexes

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Table 7H. Hydroformylation Reactions of Double Bonds in (Arene)chromium Complexes

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Table 7I. Protection Reactions of Double Bonds and Triple Bonds in (Arene)chromium Complexes

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Table 8B. Reactions of Allenyl(Arene)chromium Complexes

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Table 9B. Axially Chiral Biaryls from Cross-Coupling Reactions of Planar Chiral (Arene) chromium Complexes

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Table 10A. Axially Chiral Biaryls from Nucleophilc Addition of Grignard Reagents to (Arene)chromium Complexes

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Table 11A. Reactions of Chromium-Complexed Acyclic Enolates

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Table 11B. Reactions of Chromium-Complexed Cyclic Enolates

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Table 12A. Cycloadditions to Chromium-Complexed *o*-Quinodimethane Intermediates

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Table 12B. Rearrangements of Chromium-Complexed Benzocyclobutan-1-ols and Related Compounds

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Table 13A. Oxidations of Hydroxy Groups of (Arene)chromium Complexes

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Table 13B. Oxidations of Nitrogen- and Sulfur-Containing Groups in (Arene)chromium Complexes

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Table 13C. Oxidations of Carbonyl and Related Groups in (Arene)chromium Complexes

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Table 14. Reductive Cleavage Reactions of Functional Groups in (Arene)chromium Complexes

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Table 15. Friedel-Crafts Reactions of (Arene)chromium Complexes

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Table 16. Reductive Aminations with (Arene)chromium Complexed Amines

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Table 17. Miscellaneous Side-Chain Reactions of (Arene)chromium Complexes

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Table 18. Catalytic Asymmetric Reactions using (Arene)chromium Complexes as Chiral Ligands

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Benzylic Activation and Stereochemical Control in Reactions of Tricarbonyl(arene)chromium Complexes

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Catalytic Enantioselective Aldol Addition Reactions

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Abstract

The aldol addition reaction has become a strategically important, reliable transformation that is widely employed in the asymmetric synthesis of complex molecules. It can be counted on not only to provide access to polyketide fragments with their characteristic 1,3-oxygenation pattern, but also to numerous other classes of compounds, such as oxo-heterocycles, alpha and beta-amino acids, and nucleosides.

Two general approaches have emerged for aldol reaction: (1) diastereoselective additions, wherein stoichiometric quantities of a covalently bound, chiral controlling element shepherds the stereochemical course of the reaction and, alternatively, (2) enantioselective methods wherein a chiral catalyst functions as the stereochemical controlling element. Diastereoselective methods remain dominant. Enantioselective methods are new on the scene. However, explosive development has led to complex molecule assembly via catalytic asymmetric aldol transformations. Such reactions are described here.

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1. Introduction

The aldol addition reaction has become a strategically important, reliable transformation that is widely employed in the asymmetric synthesis of complex molecules (Eq. 1). (1-17) It can be counted upon not only to provide access to polyketide fragments with their characteristic 1,3-oxygenation pattern, (18) but also to numerous other classes of compounds, such as oxo-heterocycles, (19) ℧- and ℧-amino acids, (20-22) and nucleosides. (23) Indeed, its numerous applications in synthesis attest to the versatile role of this reaction in the pantheon of organic transformations. (12)

$$R^2 = H \quad \text{Acetate Aldol}$$
$$R^2 = Me \quad \text{Propionate Aldol}$$

(1)

Two general approaches have emerged for the asymmetric aldol reaction: (1) diastereoselective additions, wherein stoichiometric quantities of a covalently bound, chiral controlling element shepherds the stereochemical course of the reaction, (3-8, 11, 14) and, alternatively, (2) enantioselective methods, wherein a chiral catalyst functions as the stereochemical controlling element, preferably in substoichiometric amounts. (15, 24-29)

Given the intensive research activities in this area by numerous groups over the last three decades, diastereoselective methods remain dominant in practice to date with respect to the frequency of use. This is hardly surprising as such methods have enjoyed a long period of intense scrutiny and possess a high degree of predictability and reliability. By comparison, useful catalytic, enantioselective methods are fairly recent arrivals on the scene. Nonetheless, explosive developments in the field are beginning to provide the practitioner with additional useful tools for complex molecule assembly via catalytic asymmetric aldol transformations. (30-40) In this respect, it is important to note that enantioselective asymmetric, catalytic aldol addition methods can furnish ketide fragments such as polyacetate or unsubstituted skipped polyol fragments that have not otherwise been conveniently accessible through more traditional diastereoselective approaches.

Enantioselective aldol methods use small-molecule (often termed chemical catalysts) as well as macromolecule catalysis (commonly referred to as biological catalysts, such as enzymes or antibodies). (41-48) The origins of the differentiation between chemical or biological is likely historical. It is debatable whether such a categorization is at all reasonable, because the only obvious differentiation between catalysts of either group is molecular weight or, correspondingly, size, properties that vary continually. Moreover, the advances in mutagenesis techniques, library synthesis, and high-throughput screening methods (49-54) for the generation of non-natural catalysts in both classes serve to further blur the distinction between bio- and abiological catalysis.

It is certainly the case that members of either group share many more features in common than an artificial designation would suggest. Thus examples of catalytic processes in both types can be found that are metal-mediated as well as metal-free, operate in organic or aqueous media, and exhibit both high and low efficiencies.

The early work with isocyanoacetates and ferrocenyl *bis*-phosphine **1** established that catalytic enantioselective aldol additions could be carried out with in-situ generation of an enolate (Eq. 2), (55-64) and the commonly held distinction that only

$$ \text{I:II} \quad 94{:}6, \quad 95\% \text{ ee} \tag{2} $$

biocatalytic aldol additions would be tolerant of nucleophilic substrate partners possessing polar unprotected groups (e.g., hydroxyls) is no longer tenable (Eq. 3). (65) The two approaches (biological and chemical) are complementary in scope. Certain classes of reactions are at present best effected with macromolecular catalysts, whereas others are best effected with small-molecule catalysts such as **2–9** (Eqs. 3-13). (22, 39, 66-75) Given the immense breadth of the field, a compilation of catalytic methods for asymmetric aldol reactions is best when it is focused. Consequently, the coverage in this chapter is limited to catalytic enantioselective aldol addition methods using small-molecule catalysts, wherein the products in general

$$ \text{I:II} = 81{:}19, \text{ I } 98\% \text{ ee, II } 79\% \text{ ee} \tag{3} $$

(47%) 96% ee $\tag{4}$

(5)

(6)

retain β-hydroxycarbonyl functionality. For historical reasons there are three exceptions to such boundary conditions on the topical discussion, namely the aldol addition reactions leading to oxazoline products (Eq. 2), (55-64, 76) aldehyde ene addition reactions of enol silanes, (77) and domino processes (cf Eq. 5). (65) In the aldol reactions that form the basis of this compilation, catalytic turnover is a necessary requirement, with reactions in which the turnover number is unity excluded, as these are considered best classified with processes that rely on the use of chiral auxiliaries or stoichiometric controlling groups or additives.

(7)

(8)

Cl, N, H, O, MOMO + OTMS, OMe

5 (1.1 mol%)

Et$_2$O, −10°

TMSO, O, Cl, N, OMe, MOMO

(90%) 94% ee

(9)

Ph, O, H + OTMS, Ph

1. *i*-PrO, O, CO$_2$H, O, CO$_2$H, OH, OPr-*i*

6

2-PhOC$_6$H$_4$B(OH)$_2$ (20 mol%), EtCN, −78°

2. HCl

Ph, OH, O, Ph

(93%) 94% ee

(10)

EtO, O, O, H + OTMS, SPh

1. [structure] $^{2+}$, O, O, N, Sn, N, Bn, Bn, 2 OTf$^-$

7 (10 mol%)

CH$_2$Cl$_2$, −78°

2. aq. HCl

EtO, OH, O, O, SPh

(90%) 98% ee

(11)

BnO, CHO + OTMS, O

1. [structure] $^{2+}$, O, N, Cu, N, O, Ph, Ph, 2 SbF$_6$$^-$

8 (10 mol%)

CH$_2$Cl$_2$, −78°

2. aq. HCl, THF

BnO, OH, O, O

(95%) dr = 96:4, 95% ee

(12)

Ph, O, H + C$_5$H$_{11}$, OSiCl$_3$

1. [structure] Me, O, N, P, N, N, (CH$_2$)$_5$, Me, Me, $_2$

9 (5 mol%),

CHCl$_3$/CH$_2$Cl$_2$ (4:1), −78°, 6 h

2. MeOH

Ph, OH, CHO, C$_5$H$_{11}$ + Ph, OH, CHO, C$_5$H$_{11}$

(92%) dr = 99:1, 90% ee

(13)

1.1. Background

The use of catalysts to channel the stereochemical outcome of the aldol addition reaction process is feasible because the aldol addition reaction is overall an atom-transfer reaction (Fig. 1). (78) In the reactions involving enolate additions to aldehydes, an O ⸚ Si or C ⸚ Sn bond in the starting material is exchanged for another O ⸚ Si or O ⸚ Sn bond in the product with concomitant trade of the C ⸗ O bond in the electrophile and C ⸗ C in the enolate component for a C ⸚ C bond and a new C ⸗ O in the adduct. (79) In aldol additions involving direct addition of enolizable carbonyls, the C ⸚ H and C ⸗ O bonds in the educts are exchanged for C ⸚ C and O ⸚ H bonds in the adduct.

Figure 1. Aldol addition reactions as atom transfer reactions.
[Full View]

Although the larger number of catalytic enantioselective aldol processes involve the use of enoxysilanes, the direct addition of enolizable ketones and esters to aldehydes and ketones in aldol additions have been documented as well. The classic in this respect is rooted in the proline-catalyzed Robinson annulation reaction (Eq. 14)

$$(14)$$

for the preparation of the Wieland-Miescher ketone (80-82) and the direct addition of isocyanoacetates to aldehydes to give isoxazolines catalyzed by gold complexes prepared from **1** (Eq. 2). (55-64) More recently, impressive advances have been made in catalytic, enantioselective aldol reactions involving the direct addition of enolizable carbonyls to aldehydes (Eqs. 15-18), mediated by chiral metal phenoxides such as **10** or alkoxides (**11**) as well as by amines, such as proline or derivatives like **11**. (15, 55-65, 82-87)

$$(15)$$

$$(16)$$

(17)

(18)

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2. Mechanism and Stereochemistry

2.1. General Aspects

The diastereoselective aldol addition reactions that are best understood and provide adducts with a high degree of stereochemical control and predictability are those proceeding from a metal enolate through closed, Zimmerman-Traxler-like transition states, such as those derived from alkali or alkaline earth metals or boron. (1-8, 12, 88-91) By contrast, catalytic enantioselective counterparts lack thorough mechanistic understanding. Earlier analyses suggesting open transition states (Fig. 2, A-C), (92-96) despite their historical importance and utility, are likely oversimplifications, because at the very least they tend to ignore the fate of the silyl group in the course of C & O addition and C ‰ C bond formation. Given the inherent high energy of a trialkylsilyl cation, its formation in the course of the aldol process is unlikely. In this respect, it is interesting to note that more recent models (D-H) take into account the silicon in the transition state. (97-101) Indeed, focusing on the fate of the silyl group can lead to useful new catalytic processes. (102-110)

Figure 2. Proposed transition states for aldol addition reactions.
[Full View]

Under typical conditions, most enoxysilanes are unreactive toward aldehydes, notable exceptions being silyl enolates derived from amides, enoxy-silacyclobutanes, (105-109) and trihalosilyl enolates. (102) The typical lack of reactivity for the parent trialkylsilyl enolates is critical, as it ensures that the uncatalyzed background aldol additions are precluded. The enoxytrihalosilanes represent an interesting exception. Thus, although their reactions with aldehydes are fast even at low temperature, the Lewis base catalyzed processes are even faster. (75)

In the simplest analysis, the enoxysilanes and aldehydes can be induced to react by either of two fundamentally different mechanisms: electrophilic activation of the C & O component (25) or nucleophilic activation of the enolate (15, 57, 69, 111-114) or enol surrogate (Fig. 3). (71) In reality, it is likely that mechanistic pathways form a continuum of possibilities and possess some component of both activation modes. (115-117) Recent reports involving the use of enolizable carbonyl substrates that undergo in situ conversion to the corresponding enolate or enamine provide new mechanistic options for this transformation. Moreover, these add to the class of traditional closed cyclic transition-state arrangements found in the aldol addition reactions such as those of alkali, alkaline earth, and boron enolates.

Figure 3. Electrophilic vs. nucleophilic activation of an enolate intermediate.
[Full View]

Close inspection of the few cases that have been studied in some detail reveals that the mechanistic possibilities are as numerous as the catalysts and conditions that have been described for this venerable reaction. Given the complexity of the reaction, there are a number of important issues that can be examined in the process: substrate binding and activation (C & O electrophile, enolate nucleophile, or both), C & O face differentiation, as well as catalyst turnover.

With respect to the activation and facial differentiation of the electrophilic C & O component, little detailed structural information is available at the kind of resolution that would permit generalization and/or understanding at a fundamental level. (118) However, a number of binding modes of aldehydes to Lewis acidic centers have been proposed and are worth examining because of their great value in formulating the binding event (Fig. 4). (119-124) In the most general mode of C & O activation, a Lewis acidic center (or Brønsted acid) binds to an aldehyde (**A** in Fig. 4), for example, through the lone pair of the oxygen syn to the formyl proton (Fig. 4). Although this arrangement sets the position of the metal in the plane defined by the aldehyde, it leaves ill-defined the dihedral angle X ‰ M ‰ O & C, which is critical to understanding the facial differentiation event, assuming that C & O addition is the stereochemically determining step. A number of intriguing hypotheses have been proffered dealing with factors that may be operating in constraining the critical dihedral angle. These include secondary contacts between the polarized coordinated aldehyde and aromatic surfaces on the ligand (**A1** in Fig. 4). (125, 126) Indeed, examination of the crystal structure of benzyloxyacetaldehyde bound to a bisoxazoline-copper complex strongly implicates aromatic/aromatic ◻ interactions as an organizational element. (39) An additional control element can be stereoelectronic in nature such as a putative interaction between the aldehyde C & O lone pair and an M ‰ X antibonding orbital (**A2** in Fig. 4). (127) An intriguing model implicates a hydrogen bond between the formyl C ‰ H and a heteroatom ligating group (**A3** in Fig. 4). (128-132)

Figure 4. Possible binding modes of aldehydes to Lewis acid centers.
[Full View]

Special classes of substrates such as ☺-alkoxy or ☺-amino carbonyls and 1,2-dicarbonyls that to activating metal centers via chelate formation have been investigated and developed to furnish aldol adducts in high selectivity. (133) The details of how the chiral metal complex binds and activates substrates have been the subject of structural studies. It has been suggested that the subtle differences in the various binding modes arise from the differences in the Lewis basicity between the carbonyl and ether oxygens. The more basic ether oxygen is bound at the site that displays the complementary greater electron deficiency, with the less basic carbonyl oxygen coordinating in the corresponding complementary site. The study illustrates that numerous subtle features need to be considered in order to fully understand the details of the coordination complexes formed between substrates and Lewis acidic catalysts. It is an analysis that goes beyond simple consideration of ligand steric effects, but also must include analysis of stereoelectronic effects at the metal center.

As new types of asymmetric, catalytic aldol addition processes are identified and studied, such as those proceeding via metalloenolates and those catalyzed by Lewis bases or amines (e.g., proline), the collection of transition states for the aldol addition processes is dramatically augmented (Fig. 5). Reactions proceeding through metalloenolate intermediates have numerous options available that require additional study. Thus, for the systems that have been examined, metals are typically employed in which at least three structures are possible: O- (**A, C, F**), C ☺- (**B, D**), or C ℽ- (**E**) regioisomeric enolates. Additionally, there is the possibility of the involvement of multiple metal

sites. Much remains to be learned about the new Lewis base catalyzed processes of trihalosilyl enolates. In this respect, the reactions of trichloroenoxysilanes are currently believed to proceed through hexavalent silicon intermediates **G**, wherein the high degree of stereoselectivity results from a closed Zimmerman-Traxler-like arrangement with the silicon serving as an organizational locus. (134) Although the amine-catalyzed aldol addition reactions have been known for some time, it is only recently that computational studies have shed some light on the nature of the transition state in these processes. Thus, it has been suggested that the hydrogen bond formed between the carboxylic acid and the ensuing aldol alcohol in structure **H** is critical to the organization in the transition state and accounts for the sense of induction. (135, 136)

Figure 5. Transition states for asymmetric, catalytic aldol addition processes.
[Full View]

2.2. Catalyst Turnover

The general aspects of turnover in the catalytic, enantioselective aldol addition reaction have been discussed (Figs. 6 and 7). (25) Depending on the aldol type, namely electrophile versus nucleophile activation, various possibilities for turnover exist. The proline-catalyzed processes provide additional features to consider in the catalytic turnover. For the aldol additions involving enoxysilanes that undergo additions via Lewis acid coordinated aldehydes, three distinct mechanistic possibilities may be postulated. In the first of these, silyl transfer takes place from a silylated oxonium species, the first formed adduct, to the newly installed δ-alkoxide in a distinct step subsequent to the C % C bond formation. Such silicon transfer may be imagined to occur via either direct transfer of the silicon moiety from C & O to the metal alkoxide in the product in an intramolecular manner (**A**, Fig. 6), or alternatively, in an intermolecular process (from **B** or **C** and R$_3$SiX, Fig. 6). The intramolecular transfer of the silyl unit has been suggested to be operating in the reaction involving titanium-BINOL catalysts, (137, 138) and, more recently, in simple R$_3$SiNTf$_2$-catalyzed additions. (104) In a related process (Fig. 7), the intramolecular transfer of the silyl group is suggested to occur through an intermediate, wherein the ligand associated with the metal complex serves as a shuttle, undergoing silylation transiently. (139, 140) This option has been hypothesized to occur in the aldol addition reactions involving boron and titanium complexes. The alternative third option, wherein silyl transfer occurs in an intermolecular fashion has been proffered in the context of aldol addition reactions catalyzed by chiral copper-bisoxazoline complexes (Fig. 8). (74, 141) The silylating species is presumably R$_3$SiOTf. The Cu-catalyzed process (74) is rather interesting, as it represents a case wherein the metal activation of the aldehyde substrate and the subsequent turnover is faster than a potentially competing stereorandom silicon-catalyzed process. This situation may be the result of two key features of the system. The fact that chelating substrates are employed in this reaction may considerably favor activation of the substrate by the metal complex over the silyl triflate. Indeed, it is well known that chelation of electrophilic substrates leads to significant rate acceleration as compared to the monodentate substrates. (142) Additionally, the metal aldolate that is first formed in these addition reactions is a copper alkoxide, which may be silylated at considerably faster rates than harder metal alkoxides derived from early transition metals such as titanium(IV). The operation of intermolecular silylation in the turnover event is consistent with double-labeling experiments. (97)

Figure 6. Catalytic cycle of the Lewis acid catalyzed aldol reaction.
[Full View]

Figure 7. Intramolecular silyl group transfer in boron- and titanium-catalyzed aldol reactions.
[Full View]

Figure 8. Intermolecular silyl group transfer in copper-catalyzed aldol reactions.
[Full View]

When the reactions involve the use of enolsilanes that in turn produce an intermediate metalloenolate, the key turnover event is likely the silylation of the aldolate product by the starting enoxysilane (Fig. 9). (114) Such an event is necessarily intermolecular; given the metals that are involved in such systems (e.g., soft metals such as platinum, (143) copper, (69) and palladium (144, 145)) the process is driven by the exchange of a weak metal oxygen bond in the first formed adduct for a strong Si ‰ O bond in the silylated product.

Figure 9. Catalytic cycle of the aldol reaction of enoxysilane.
[Full View]

Commentary on the turnover step in the recently reported systems involving direct addition of ketones and aldehydes to aldehyde electrophiles is warranted. These generally fall into two categories: metal-mediated enolization and addition or, alternatively, amine-mediated additions via formation of an enamine. Turnover in the first of these systems is possible, because the pK_a values of the alcohol adducts are within range of the starting ketone or aldehyde. Thus, for the lanthanide BINOL complexes (65) and zinc(II)-mediated aldol additions (84) involving the direct addition of ketones to aldehydes, the product metal alkoxide may effect direct deprotonation of the ketone subsequent to aldol addition to furnish the aldol product and regenerate a ketone enolate. For the amine-catalyzed aldol addition processes (Fig. 10), modeling suggests that the proton transfer that occurs from the carboxylic acid to the aldol adduct is crucial for selectivity. (80-82, 135, 136) Thus, in the course of the enamine addition to aldehyde substrates, a carboxylic acid surrenders its proton to the more basic oxygen acceptor in the adduct. Of greater significance in these processes with respect to turnover is the hydrolytic cleavage of the enamine in the adduct to release the amine for a subsequent round of C ‰ C bond formation. The precarious balance in these systems is manifest in the conditions that are used in the amine-catalyzed crossed aldol addition reactions, where it is worth noting that the experimental procedures prescribe long reaction times and highlight the

importance in proper selection of polar solvents, where presumably the requisite enamine forming and cleavage steps are facilitated. The prescription for slow addition of aldehyde substrates in some of the reported processes highlights another aspect of these systems, wherein the adduct as an enamine could itself participate in aldol addition chemistry, as such slow addition of substrate is necessary to allow sufficient time for enamine exchange between product and reactant. Nonetheless, it is important to note that even in the earliest reports of this process in the 1970's, aldol addition reactions could be conducted with low catalytic loadings of proline.

Figure 10. Amine-catalyzed aldol addition processes.
[Full View]

< Previous   Next >

Catalytic Enantioselective Aldol Addition Reactions

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3. Scope and Limitations

3.1. Acetate, Methyl Ketone, and Unsubstituted Dienolates

Reports of catalytic, enantioselective aldol addition reactions involving unsubstituted enolates (acetate aldol) are far fewer than the corresponding additions involving substituted enolates (e.g., propionates). Some of the more prominent examples for both categories are selected in this section for discussion.

3.1.1. Enoxysilanes and Stannanes

The classic examples in the area of catalytic enantioselective aldol addition methodology originate from the work involving the addition of enol silanes under the influence of tin catalysts. (146-165) The tin(II) complexes are typically assembled from $Sn(OTf)_2$ and optically active diamine ligands such as **12**, in particular, in the early work those derived from proline. These early examples involve the addition of thioacetate-derived *O*-silyl ketene acetals to a wide range of aldehydes (Eqs. 19-21). (141, 153) The additions are typically conducted at low

(19)

temperature (–78°) with 20–30 mol% loadings of catalysts **12** or ent-**12**. The thioester-derived enoxysilanes are optimal for these systems. Of additional benefit is the presence of a thioester in the product as it is conveniently converted directly into an aldehyde. (166, 167) This catalytic system has been extensively studied, and much information is available concerning the effect of numerous additives and variations in a number of reaction parameters on the reaction selectivity, rates, and catalyst turnover. One particular aspect of the process that is worth noting is the fact that the reactions can be carried out under reagent control. Thus, in additions to the enantiomers of 2-silyloxypropionaldehyde, both diastereomeric adducts can be obtained in high selectivities (Eqs. 20 and 21). (141)

(20)

$$\text{(21)}$$

R		dr
Me	(85%)	94:6
Ph	(86%)	94:6

Aldol addition reactions employing BINOL/TiCl$_x$(OPr-i)$_{4-x}$ complexes as catalysts are highly attractive because of the convenient access to the catalyst components (BINOL, Ti(OPr – i)$_4$, and/or TiCl$_4$) along with the simplicity of their preparation. (67, 77, 168-174) Two general formulations have been reported to be effective in the acetate aldol addition reaction: a catalyst prepared from BINOL and either TiCl$_2$(OPr-i)$_2$ (137) or Ti(OPr-i)$_4$ (171) in the absence or presence of molecular sieves. Both formulations have been documented to give aldol adducts in excellent yields and enantioselectivities (Eqs. 22 and 23). A particularly attractive feature of the

$$\text{(22)}$$

(80%) 96% ee

$$\text{(23)}$$

(82%) >98% ee

TiCl$_2$(OPr – i)$_2$ system is the fact that the addition to a wide range of functionalized aldehydes has been documented, such as trifluoro- (Eq. 24), (67) chloro- (Eq. 25), (137) and azido acetaldehydes, all of which are rare substrates in catalytic, enantioselective aldol addition reactions. It is worth noting that these titanium catalysts are also quite general with respect to the enolate component, thus both silyl ketene and thioketene acetals in addition to ketone-derived enol ethers have been employed

$$\text{(24)}$$

(38%) 96% ee

$$\text{(25)}$$

(61%) 91% ee

(Eq. 26). (77, 175, 176) They have been utilized in the context of a complex natural product synthesis, namely that of dermostatin A (Fig. 11). (177) These reactions are best considered as aldehyde ene additions in which the C & C of the ketone-derived enol ether has undergone a shift in the product. The ease with which the product silyl enol ethers are hydrolyzed to the corresponding hydroxycarbonyl compound renders these synthetically equivalent to aldol addition reactions. (178) The addition reactions are reported to give adducts in high selectivity in a procedure that prescribes

–20 to 0° with 10–20 mol% catalyst loadings. For the processes employing Ti(OPr-*i*)$_2$/BINOL complexes, certain peculiarities of the process have been noted, with the reaction rate and product selectivity not only being dramatically sensitive to solvent and reaction temperature, but also to catalyst concentration and loading.

(26)

Figure 11. Application of the titanium-catalyzed aldol to the synthesis of dermostatin A. [Full View]

There has been an interesting report of chiral Zr(IV) complexes that mediate enantioselective aldol addition reactions of thioester-derived silyl ketene acetals (Eq. 27). (179, 180) The catalyst is readily assembled from 3,3′-diiodo-2,2′-BINOL derivatives and Zr(OBu-*t*)$_4$. Using as little as 10 mol% of this convenient catalyst, adducts are isolated in useful yields and high enantioselectivity. It is noteworthy that the reactions are carried out under optimal conditions in aqueous 2-propanol/toluene solvent mixtures. As such, it is remarkable that the process is tolerant and indeed thrives in the presence of water.

(27)

Another popular family of catalysts for the acetate aldol addition reaction of unsubstituted silyl ketene acetals utilizes simple ligands derived from tartaric acid or amino acids as donors for metals, such as boron or zinc, with the former being most common (Eqs. 28-32). (72, 73, 140, 181-184) The typical boron catalyst is assembled upon mixing diol or amide acid ligands with BH$_3$·THF (with concomitant release of hydrogen gas), RB(OH)$_2$ (with azeotropic removal of the released water), or RBCl$_2$ (in the presence of base). The use of monosubstituted boronic acids offers the opportunity to vary the nature of the substituents for reaction optimization. Indeed, there can be benefits to the use of 3,5-bis(trifluoromethyl)phenylboron, (185) which offers advantages with corresponding reduction of reaction time. The fact that the ligands are straightforward and convenient to access permits a number of ligand variations to be used, allowing an optimal system to be found for a given substrate. These have included ligands derived from tartrate (**6**, Eq. 28), natural (**13**, Eq. 29) and non-natural amino acids, such as C ⊘-substituted ⊘ amino acids (**14**, Eqs. 30, 31). (140) In general, the addition reactions are conducted at –78° with 20–30 mol% of catalyst to give adducts in useful levels of enantioselectivity. One particularly attractive feature of these catalysts is that they allow considerable flexibility in the types of enolates that can be employed, such as enol silanes derived from methyl ketones (Eq. 29), alkyl thioacetates (Eq. 30), and phenyl acetate (Eq. 31).

$$ (28) $$

$$ (29) $$

$$ (30) $$

$$ (31) $$

The related complexes prepared from Et$_2$Zn have also been reported. (186) Although these do not have the broad substrate scope displayed by the boron complexes, there are some remarkable aldol addition reactions that have been described, such as those with trihaloacetaldehydes (Eq. 32).

R		% ee
CCl$_3$	(61%)	88
CBr$_3$	(66%)	93

$$ (32) $$

A complex derived from titanium(IV), a tridentate Schiff base ligand, and di-*tert*-butylsalicylic acid is effective in catalyzing the addition of the trimethylsilyl ketene acetal derived from methyl acetate or other simple alkyl acetates (Eqs. 33 and 34). (187, 188)

(33)

R value table:

R		% ee
(E)-PhCH=CH	(81)	98
TBSOCH$_2$C≡C	(95)	99

The reaction is typically conducted at 0° with 2–5 mol% catalyst loadings to give acetate aldol adducts in high selectivities for a broad range of aldehydes. There are a number of unique features of this catalyst system that are worth noting: (1) the reaction does not require the use of low temperatures, (2) the additions can be conducted

(34)

(88%) 97% ee

with as little as 0.5 mol% catalyst, and (3) the additions are effected with methyl or ethyl ester-derived enoxysilanes and aliphatic, aromatic, and unsaturated aldehydes. The tridentate ligand from which the complex is prepared is readily obtained from (+)- or (–)-2-amino-2′-hydroxy-1,1′-binaphthyl and 3-bromo-5-tert-butylsalicylaldehyde. Treatment of the Schiff base with Ti(OPr-i)$_4$ and di-tert-butylsalicylic acid followed by evaporation of the solvent with concomitant azeotropic removal of 2-propyl alcohol affords an orange crystalline solid which can be used as a catalyst in the reactions. The reaction can be carried out in a variety of solvents such as toluene, benzene, chloroform, or diethyl ether; with solvents such as dichloromethane and dichloroethane significant reduction in the reaction enantioselectivity is observed. The catalytic aldol addition reaction may be conducted between the temperature range of –20 to 23° without adversely affecting the reaction rate (2–8 hours) or enantioselectivity (>90% ee). For the aldol addition reaction of the methyl acetate-derived silyl ketene acetal and aldehydes mediated by **5**, no diminution in the optical purity of the aldol products is observed throughout the catalyst range of 0.5–10 mol%. The complex **5** has been shown to perform well in the synthesis of a variety of natural products including the antitumor depsipeptide FR-9001,228 (Fig. 12), (33) the polyene macrolide antibiotic roflamycoin (Fig. 13), (32) kedarcidin (Fig. 14), (22) phorboxazole A (Fig. 15), (189) and the polyol fragment of amphotericin. (190)

Figure 12. Application of the titanium-catalyzed aldol reaction to the synthesis of FR-9001,228.
[Full View]

Figure 13. Application of the titanium-catalyzed aldol reaction to the synthesis of roflamycoin.
[Full View]

Figure 14. Application of the titanium-catalyzed aldol reaction to the synthesis of kedarcidin.
[Full View]

Figure 15. Application of the titanium-catalyzed aldol reaction to the synthesis of phorboxaxole A.
[Full View]

The protocol most widely employed for the preparation of catalyst **5** prescribes the co-mixing of the various catalyst components, as described above, followed by evaporation of solvent and released isopropanol. A simplified experimental protocol for the preparation of the active catalyst has been developed. (191) Thus, the addition of 20 mol% TMSCl and one equivalent of Et$_3$N to a solution of 2 mol% of catalyst **5** (generated from ligand **15**) gives a catalyst solution which can be directly utilized in the aldol addition reaction (Eq. 35). This in situ procedure leads to substantial simplification of the overall protocol, because it obviates the need to remove isopropanol. Importantly, the efficiency of the catalytic process (high ee's and yields with low catalyst loads) is not jeopardized by the presence of the Et$_3$NHCl and TMSOPr-*i* byproducts. Moreover, the in situ procedure described provides in principle a useful alternative to the more commonly employed methods for the removal of isopropanol released in the preparation of Ti(IV) complexes with Ti(OPr-*i*)$_4$ (evaporation and addition of 4 Å sieves). As an application of the catalytic, enantioselective aldol addition employing the in situ catalyst preparation procedure, the synthesis of (*R*)-(–)-epinephrine has been carried out through a convenient sevenstep sequence from commercially available veratraldehyde (Eq. 35). (191)

(35)

Aldehyde and ketone substrates incorporating an oxygenated C substituent that can participate metal chelation, such as -alkoxyacetaldehydes, pyruvates, and -diketones, have been shown to ideal substrates in a class of highly selective aldol addition reactions employing bisoxazoline-derived ligands and copper(II), (37, 67, 192-197) tin(II), (39, 194) scandium(III), (198, 199) and zinc(II) catalytic systems (Eqs. 36 and 37). (38) Two general ligand classes have been examined: bidentate bisoxazolines prepared from malonate esters, and the complementary tridentate bisoxazoline-derived ligands accessed from 2,6-dicarboxypyridine (PYBOX). (200) Some general

comments can be made about these ligand classes and their corresponding metal complexes as catalysts for the aldol addition reaction. (133, 201) Interestingly, for the copper-mediated reactions, glyoxylates cannot be used as substrates, despite the fact that, in principle, these meet the structural criteria for this general class of catalysts. Typically, triflates

(36)

(37)

are the counterions accompanying the metal centers, although other non-participating counterions such as the corresponding hexafluoroantimonate have been examined. Of additional importance for this process is the fact that the additions are tolerant of a wide range of enolic partners including thioester-, ester-, and ketone-derived enol silanes. The typical protocol for catalyst generation proceeds by addition of ligand to a solution of a metal triflate; after allowing a brief time for complexation the subtrates are then added. A highly attractive feature of this system is the fact that a meticulous study of the process and a range of reaction parameters have been undertaken. In this respect, catalyst preparation time, catalyst hydration state, catalyst loading, time, solvent, and temperature, along with the typical scope has been the subject of in-depth investigations, which are well worth consulting for the practical and mechanistic insight they provide. (133) For a broad range of complexation times, 15 minutes to 4 hours, no difference in catalytic efficiency or selectivity was observed. Only at extended complexation times (>12 hours) were some deleterious effects in efficiency observed. The fact that catalyst activity and efficiency can be regained on addition of molecular sieves strongly implies catalyst hydration as the culprit in deactivation; indeed, studies have revealed that the bishydrates are less efficient catalysts than their anhydrous counterparts. The reactions are exceptional for the high level of enantioselectivity, and for the fact that in certain cases that have been investigated, the additions can be carried out with as little as 0.5 mol% catalyst without detriment to product selectivities. In a typical reaction, the additions are conducted at –78° with 5–10 mol% complex. A careful study of the copper-bisoxazoline complexes has revealed that for a range of solvents such as THF, Et$_2$O, CH$_2$Cl$_2$, toluene, hexane, and

trifluoromethylbenzene, the enantioselectivity of the adducts is maintained at >95% ee. For all but hexane, yields of more than 88% have been noted with reaction times of 1–3 hours. Only in hexane is a slight decrease in product yield observed as well as a dramatic increase in reaction time (3 days), presumably because of partial insolubility of the catalyst in this solvent. Nonetheless, the

(38)

1. 7 (10 mol%)

CH$_2$Cl$_2$, –78°

2. aq. HCl

(90%) 98% ee

(39)

1. 16 (10 mol%)

CH$_2$Cl$_2$, –78°

2. aq. HCl

(92%) 90% ee

use of THF is optimal, as it routinely provides high yields and selectivities in the shortest amount of time over a broad temperature range. For example, in the addition of *tert*-butyl thioacetate *O*-trimethylsilyl ketene acetal in Et$_2$O the enantioselectivity fluctuates between 98 and 85% ee in the temperature range –78 to 20°; by contrast, in THF over the same range of temperature the enantioselectivities are between 92 and 99% ee. Over a range of electrophile concentration (0.3 M–1.5 M) no change in product selectivity is observed. Studies aimed at gaining mechanistic insight have revealed the beneficial effects of added TMSOTf, which leads to considerable acceleration of the reaction. Thus the addition reaction of pyruvate and trimethylsilyl *tert*-butyl thioketene acetal mediated by 2 mol% of copper(bisoxazoline) affords product in 97% ee over the course of 14 hours; interestingly, when the same addition is conducted with one equivalent of TMSOTf and Cu catalyst under otherwise identical conditions, reaction is observed to reach completion in 35 minutes with no diminution in product enantioselectivity. This represents a rare example where the TMSOTf-catalyzed reaction in the absence of Cu complex is considerably slower than the metal-mediated process, a feature that is intimately related to the ability of the substrates to undergo significant activation by chelate formation. The benefits of chelate formation leading to highly organized transition states with concomitant high selectivities also result in some limitations. (202) Thus, carbonyl substrates forming chelates greater than five-membered rings (e.g., 3-benzyloxypropionaldehyde) are not good substrates. The process can display significant matching/mismatching with chiral substrates. In particular, when the configuration at C$_\infty$

with chelation by the substrate, diminished product diastereoselectivity can be observed (Fig. 16).

Figure 16. Matching and mismatching in the copper-catalyzed aldol reaction. [Full View]

The extensive structural and mechanistic studies to which the process has been subjected has permitted an in-depth understanding of not only the detailed aspects of the aldol process, but also the structural and coordination chemistry of the corresponding metal complexes. Consequently, of particular significance is the fact that a high level of predictability is possible in this process; moreover, the insight afforded by these studies is sure to impact the evolution of metal-based complexes for enantioselective catalysis. Key applications of a tin catalyst and copper complex **8**

can be found in the synthesis of phorboxazole A and altohyrtin C, respectively (Figs. 17 and 18). (196, 203-205)

Figure 17. Application of the tin-catalyzed aldol reaction to the synthesis of phorboxaxole A.
[Full View]

Figure 18. Application of the copper-catalyzed aldol reaction to the synthesis of altohyrtin C.
[Full View]

The aldol addition reactions of enoxysilanes are not limited to the use of trialkyl substituted silyl ketene acetals. Indeed, recent studies describe the use of enoxytrichlorosilanes in enantioselective addition reactions to aldehydes (Eq. 40). (102, 134, 206-212) These processes are noteworthy for a number of reasons, not the least of which is the

(40)

fact that they are at present rare examples of Lewis base catalyzed asymmetric reactions. Interestingly, the background rate of aldol addition between such enolates and aldehydes in the absence of additives has been shown to be rapid, even at low temperature. Nonetheless, stereoselective additions are possible since the Lewis base catalyzed processes are markedly faster. In this respect, the basic oxygen of chiral phosphoramides interacts with silicon leading to the formation of a hypervalent siliconate species with enhanced Lewis acidity that is subsequently poised to activate an aldehyde. The resulting cyclic arrangement of aldehyde, enoxysilane, and phosphoramide leads to selective addition processes. A key advance in this exciting area is the use of chiral silicon Lewis acids that are generated from $SiCl_4$ and chiral Lewis basic phosphoramides.

Such processes that rely on chiral Si-Lewis acids employ the more conventional trialkylenoxysilanes as reacting partners (Eqs. 41 and 42). Studies of the mechanism of activation have led to the design of bisphosphoramides for silicon, resulting in even more highly selective additions.

(41)

$$\text{(42)}$$

Despite the numerous documented examples of the catalytic, enantioselective aldol addition reactions to aldehydes, addition reactions to ketones are rare. The difficulty faced by investigators working in this area are manifold, not only because ketones are less reactive than aldehydes, but also because differentiation of the two alkyl groups flanking the ketone C & O on the basis of sterics alone presents a more difficult challenge in comparison to the corresponding differentiation that must occur with aldehyde involving alkyl versus proton. Nonetheless, with Lewis base catalysts such as **18** there are some noteworthy examples (Fig 19). The addition reaction of trichlorosilyl enolates to aryl ketones is impressive in that products are obtained in high yields and useful levels of induction. (102) Given the fact that little else can be relied upon to access such compounds, the results are remarkable. (75, 134, 154-156, 209-211, 213)

Figure 19. *N*-oxide-catalyzed aldol reaction of aryl ketones.
[Full View]

An additional departure from the traditional aldol addition reaction of enol silanes catalyzed by Lewis acid activation of the electrophilic aldehyde component is the use of complexes that lead to activation of the enoxysilane component via transient formation of metalloenolates. One of the earliest examples in catalytic asymmetric synthesis is the report that acetophenone-derived trimethylsilyl enol ethers can be activated by BINAP/palladium(II) complexes to afford putative palladium enolates. (144, 145) These are generated from a mixture of enol silane and a complex formed between palladium(II) and *p*-Tol-BINAP (5 mol%) in the presence of molecular sieves and have been shown to undergo aldol additions in up to 89% ee (Eq. 43).

$$\text{(43)}$$

By comparison to enol silanes, there is a paucity of catalytic, enantioselective aldol addition reactions involving the corresponding stannanes. Stannyl enolates derived from methyl ketones have been shown to participate in enantioselective addition reactions to a wide range of aldehydes at –20° in THF in the presence of a novel silver(I)/BINAP complex. The adducts can be isolated in up to 95% ee and useful yields (Eq. 44). (94) Control experiments have led to the conclusion that the systems behave in analogy to the typical reaction of enol silanes with electrophilic activation of the aldehyde component, without proceeding through a silver(I) enolate.

$$\text{(44)}$$

(78%) 95% ee

3.1.2. Direct Aldol Addition Reactions of Unsubstituted Systems

In parallel with reactions involving the generation of metal enolates from stannylated or silylated precursors, there have been recent developments on the use of ketones that undergo in situ enolization or activation by transient conversion into enamines and participate in aldol addition reactions. (214) In the first of these, lanthanum binaphthoxide complexes (LLB) are able to effect deprotonation of ketones and activation of aldehydes to afford aldol adducts in high selectivities and yields (Eqs. 45 and 46). (65, 215, 216) This process has been utilized elegantly in the synthesis of epothilones A and B (Fig. 20). (40) The reactions proceed at 0°, giving products in high enantioselectivity. Related processes utilizing barium, (217) zinc, (83, 218) and calcium (Eq. 47) (219) have been documented.

(71%) 94% ee

(45)

(85%) I:II = 86:14, I 99% ee, II 93% ee

(46)

(76%) 91% ee

(47)

Figure 20. Application of the hetero-bimetallic-catalyzed aldol reaction to the synthesis of epothilone A.
[Full View]

The easily accessible ligand **11** and its bimetallic zinc complex have also been used in aldol addition reactions of methyl ketones and aldehydes that proceed via in situ enolization (Eq. 48). (84, 220, 213)

(48)

11 (10 mol%)

Et$_2$Zn (20 mol%), 4 Å MS, THF, 5°

c-C$_6$H$_{11}$ H

(85%) 93% ee

Another way that ketones can undergo activation and participate in stereoselective aldol additions is through their in situ conversion to the corresponding enamines. Proline is remarkably effective in this process. Indeed, the enantioselective synthesis of Wieland-Miescher ketone using proline had been established as early as 1973. (80-82) Recent dramatic advancements in this area have taken the proline-catalyzed processes in new directions to include other amine catalysts (Eqs. 49-52). (85, 66, 221, 222) The addition can be conducted with acetone (223, 85) in DMSO, a solvent which appears to be critical, utilizing 30 mol% of proline at ambient temperatures giving adducts in up to 99% ee. The proline-catalyzed aldol addition reaction of acetaldehyde can be carried out in a domino process proceeding by a double aldol addition and elimination to give useful building blocks for asymmetric synthesis (Eqs. 51 and 52).

L-proline (30 mol%)

DMSO, rt

i-Pr H

(97%) 96% ee

(49)

L-proline (30 mol%)

DMSO, rt

dr = 99:1

(50)

L-proline (1.7 mol%)

THF, rt, 14 h

CHO

(10%) 90% ee

(51)

(3 mol%)

2,4-(O$_2$N)$_2$C$_6$H$_3$SO$_3$H·2H$_2$O (3 mol%), acetone, rt

O$_2$N

(72%) 93% ee

(52)

3.2. Propionates and Substituted Enolates
3.2.1. Enoxysilanes and Stannanes
The addition reactions of propionate-derived silyl ketene acetals and other substituted enolates or their equivalents can be effected with a broader range of catalysts than that of the unsubstituted

systems described in the previous section. In principle, two kinds of stereochemical families of reaction processes can be identified: (1) those processes in which each geometrical isomer of the enolate gives divergent, complementary diastereomeric products and (2) those in which both enolates stereoselectively lead to convergent formation of a preferred diastereomer. Examples of both types have been documented. For the first of these in which the additions are stereospecific, stereoselective generation of enolates is of great importance to the selectivity of the process. In such cases, the ability to generate a particular enolate from a given carbonyl precursor may be limiting to the process. The convergent process obviates such concerns, but in turn can provide limitations as to the type of stereochemical relationships in the product that can be accessed.

As with the additions of acetates and other unsubstituted enolates, the classics in this area are the enantioselective aldol additions mediated by tin(II) diamine complexes (Eq. 52). These complexes are conveniently prepared from $Sn(OTf)_2$ and proline-derived diamines. (31, 146-165, 224-231)

There are numerous studies of these systems and careful scrutiny of these can be rewarding because this system represents one in which the effect of many different variables on reaction selectivity and rate have been carefully examined. Moreover, there is an equally large amount of mechanistically relevant data making the careful study of these reports a fruitful venture. In the typical procedure the reactions employ thioester-derived silyl ketene acetals and are carried out with 20 mol% catalyst at –78° in propionitrile. The selection of this unusual solvent rests on two key observations: (1) the ability of nitriles to lead to effective turnover in the addition reactions and (2) the fact that, unlike acetonitrile, this solvent permits reactions to be carried out at low temperature where the enantioselectivity is maximized. Optimal selectivities are obtained when the aldehyde is added slowly to the reaction mixture, minimizing stereorandom, background reactions while allowing for concomitant catalyst turnover. Both *O*-trimethylsilyl and *O*-dimethyl-*tert*-butylsilyl enol ethers give adducts in equally good selectivities. The propionate additions using these complexes have been conducted with the Z-enolates and afford products displaying syn simple diastereoselectivity and high enantiomeric purity (Eq. 53). The use of ester-derived enol silanes has been examined for alkoxyacetate-derived enolates (Eqs. 54 and 55). (225, 230, 232) High anti or syn selectivity was shown to be a function of whether the Z- or E-starting enolate was employed, respectively. (227)

(53)

R		dr	% ee
$n\text{-}C_7H_{15}$	(76%)	99:1	98
Ph	(86%)	93:7	91

(54)

(80%) dr = 98:2, 96% ee

$$(55)$$

Catalysts derived from titanium(IV) or zirconium(IV) and BINOL or its substituted derivatives mediate the addition of propionate enolates to aldehydes (Eqs. 56-60). The use of the complex derived from BINOL and $TiCl_2(OPr-i)_2$ has been studied extensively in the addition of substituted ester (137, 67) as well as ketone-derived (77, 233) silyl enolates to chelating aldehydes, such as benzyloxyacetaldehyde and ethyl glyoxylates. The addition of the E-enol silanes preferentially affords syn adducts in up to 98% ee (Eq. 56). (137) By comparison, addition of the Z-enol silanes furnishes the complementary anti adduct in 90% ee (Eq. 57). A particularly attractive feature of these titanium-catalyzed reactions is the fact that trifluoroacetaldehyde

$$(56)$$

$$(57)$$

can be utilized, albeit the products exhibit poor diastereoselectivity (Eqs. 58 and 59). (67) There have been some interesting studies involving the enol silane derived from 3-pentanone (Eq. 60), wherein a highly selective aldehyde addition is observed. (77) Although the process is best classified as an ene addition, the products isolated after exposure to acid are β-hydroxy ketones. In this process the addition of either the Z- or E-trimethylsilyl enolate of 3-pentanone to glyoxaldehyde gives syn adducts in up to 99% ee.

$$(58)$$

$$(59)$$

(48%) **I:II** = 44:56, **I** 89% ee, **II** 83% ee

$$(60)$$

(54%) Z:E = 96:4,
dr = 98:2, 99% ee

Catalysts prepared from $Zr(OBu\text{-}t)_4$ and 3,3′-diiodo-BINOL in the presence of propanol and water are effective at mediating the addition of primarily phenyl propionate-derived E-enolates to aldehydes. Thus 12 mol% of the putative zirconium complex affords products in excellent diastereo- and enantioselectivities (99% ee), favoring the anti product (95:5 dr) (Eq. 61). (179, 180, 234) In addition to propionates,

$$(61)$$

(94%) dr = 95.5, 99% ee

isobutyrate-derived silyl ketene acetals have been reported to participate in the addition reaction (Eq. 62), (179, 180) furnishing adducts in equally high enantioselectivity (98% ee). The fact that the catalytic process prescribes the use of water/isopropyl alcohol mixtures renders the complex unique as a rare example of an early group-(IV) transition-metal catalyst displaying wide tolerance to moisture.

$$(62)$$

(95%) 98% ee

Enantioselective aldol addition reactions employing boron catalysts were some of the earliest processes reported for propionate aldol addition reactions. A particularly attractive feature of the reported catalysts is the ease with which the ligands and the corresponding complexes are generally accessible. The optically active ligand on boron is typically derived from either ℘-amino acids or tartrates. (181) As such, the process is notable because of the large library of structurally and functionally related boron catalysts that have been described. The aldehyde addition reaction of the E-silyl ketene acetal prepared from phenyl propionate at –78° employing 20 mol% catalyst affords predominantly the syn adduct in up to 92% ee (Eq. 63). (73)

(63)

This versatile catalytic system can also be employed in the aldol addition reaction of ketone-derived silyl enol ethers. Irrespective of the enolate geometry, these systems afford the syn aldol adduct in useful levels of relative and absolute stereocontrol (Eqs. 64 and 65). (72, 177, 182, 32) The addition of enol silanes derived from cyclic ketones and aldehydes is also possible, with the formation of the syn aldol adduct

(64)

(65)

once again favored in impressive diastereo- and enantioselectivity (Eqs. 66 and 67). (181, 235) The reaction has been employed in the asymmetric synthesis of cheimonophyllal (Fig. 21). (235)

(66)

(67)

(71%) **I:II** = 94:6, 92% ee

Figure 21. Application of the boron-catalyzed aldol reaction to the synthesis of cheimonophyllal.
[Full View]

In addition to catalysts derived from natural amino acids, the use of C2-substituted 2-amino has been examined and yielded notable results (Eqs. 68-70). (140)

(68)

(84%) **I:II** = 55:45, **I** >98% ee

Additions of the ethyl thiopropionate-derived E-silyl enolate afford products in good enantioselectivities (98% ee), albeit modest diastereoselection (syn/anti 55:45). By contrast, the use of the Z-silyl enolate furnishes a mixture of syn and anti adducts wherein the anti is preferred in up to 94:6 ratio and in up to 82% ee (Eq. 69). When the E-silyl enolate prepared from phenyl propionate is utilized, the absolute selectivity is improved (87% ee) in comparison to that observed for the same substrate with thioproprinate enoxysilanes. However, for the phenyl ester the simple diastereoselectivity of the addition is somewhat diminished (Eq. 70). (140)

(69)

R		I:II	% ee I
Ph	(78%)	94:6	82
2-C4H3O	(54%)	88:12	79

(70)

(77%) **I:II** = 77:23, **I** 87% ee

One particularly interesting aspect of the boron Lewis acid catalysts derived from amino acids like **19** is that dichloro-, difluoro-, (236) and dithio- (237) substituted enoxysilanes have been employed to give adducts that are otherwise not easily accessed in useful levels of induction (Eqs. 71-73).

(71)

(72)

(73)

The addition of isobutyrate-derived enoxysilanes has also been documented, (184, 238) with products obtained in high selectivities and useful yields (Eqs. 74 and 75). (184, 195, 236) An unusual catalyst derived from optically active O-trimethylsilyl- O-hydroxyacetic acid functions in such additions (Eq. 76), affording adducts in up to 90% ee. (239)

(74)

(75)

(76)

There has been a single report of the use of allenyl enolates in enantioselective aldol addition reactions. The phenylalanine-derived ligand has been used in the synthesis of a boronate complex which has been shown to mediate aldol additions, giving products in up to 97% ee (Eq. 77). (240)

(77)

As discussed in the section above on acetate-type additions, substrates such as benzyloxyacetaldehyde and glyoxal have unique structural features that allow them to chelate with Lewis acidic metal centers. This has been elegantly capitalized upon in the development of highly stereoselective propionate-type aldol addition reactions catalyzed by copper-, tin-, and scandium-bisoxazoline complexes. The two ligand families that have been reported include either bidentate bisoxazolines derived from malonate or tridentate bis-oxazolines prepared from 2,6-pyridinedicarboxylic acids. For copper(II), for example, the two ligands afford complementary products, giving adducts with opposite face selectivity (Eqs. 78-80). (37)

(78)

This family of catalysts includes a wide selection of complexes that can be used in enantioselective aldol additions, which is the key advantage of these systems. This versatility, when coupled to the range of aldehydes that can be employed, such as glyoxylates and benzyloxyacetaldehyde, provides access to a broad range of substituted aldol adducts possessing the various permutations of complementary, diverse stereochemical patterns. The typical reaction calls for the use of 5–10 mol% catalyst loadings with the reaction conducted at –78°. The strict requirement for the substrate to form five-membered chelated adducts with the metal center leads to a system that is impressive in its high selectivity, reaction rate, and yield for a wide range of enoxysilanes. These silanes include those derived from esters, (197) thioesters, (70) ketones, (37, 197, 199) and lactones. (74)

$$(79)$$

$$(80)$$

In additions mediated by copper complexes, the correlation between enolate geometry and product diastereoselectivity has been studied and found to be ligand and substrate dependent. Thus, for example, for the tridentate bisoxazoline copper complexes the E- and Z-silyl thioketene acetals derived from thiopropionate afford syn adducts (Eqs. 79 and 80). The additions of the latter are, however, considerably more selective (Eq. 79). (37) In a study involving ketone additions mediated by the tridendate copper-bisoxazoline complexes, the Z-silyl enolates afford exceptional levels of induction, whereas the corresponding E-enol silanes lead to preferential formation of the anti adduct, albeit in low yield and selectivity (Eq. 80). (37)

The tin complexes function equally well in the aldol addition reactions of bidentate aldehydes. In this regard, the addition of the Z-thioketene acetal derived from thiopropionate gives the anti aldol adduct in high selectivities (Eq. 81). (39) Importantly, the adducts can be obtained in equally good selectivities for a wide range of C꞊O substituents and are thus not limited to the propionate Scandium(III) catalyst **16** affords the complementary products resulting from addition with opposite facial selectivity (Eq. 82). (198)

$$(81)$$

(82)

These addition reactions have been examined with alkoxy-substituted silyl enolates as well as cyclic enolates. The former are reported to work particularly well with the scandium catalysts (Eq. 83). (198) The use of copper-bisoxazoline complexes in the addition of the butyrolactone-derived enoxysilanes provide access to useful adducts in a 93:7 syn/anti mixture and 96% ee (Eq. 84). (74) In addition to propionate-derived enolates, isobutyrate and related silyl enolates have been examined (Eqs. 85-87). (199)

(83)

(84)

(85)

Eq. 85 scheme (first reaction):

1. Scandium bisoxazoline catalyst (10 mol%), SbF_6^-, t-Bu, Bu-t
TMSCl (2 equiv), CH_2Cl_2, $-78°$
2. aq. HCl

EtO_2C–CHO + silyl enol ether (R, Ar, OTMS) → EtO–C(=O)–CH(OH)–C(R)(R)–C(=O)–Ar

Ar	R		% ee
Ph	Me	(85%)	95
4-FC$_6$H$_4$	Me	(85%)	95
Ph	n-C$_5$H$_{11}$	(80%)	97
Ph	n-C$_4$H$_9$	(81%)	98

Eq. (86):

1. **8** (10 mol%), CH_2Cl_2, $-78°$, 16 h
2. H^+

→ product (61%) 98% ee

Eq. (87):

16 (10-15 mol%), CH_2Cl_2, $-78°$, 16 h

→ product (90%) 95% ee

In addition to the traditional enoxysilanes derived from ketones and esters, the bisoxazoline catalysts have been shown to mediate an aldol-type addition between aldehydes and 5-alkoxy-substituted oxazoles to afford substituted oxazolines (Eq. 88). (241) In the initial reports on these unusual addition reactions, wherein copper-bisoxazoline complexes are employed, it was necessary to use aldehydes that can chelate the metal center (Eq. 88). Interestingly, the use of a new class of aluminum complexes permits the use of a wider range of aryl-substituted aldehydes for which chelation is not a prerequisite (Eq. 89), (241) affording adducts not only possessing high relative, but also absolute stereocontrol. For the typical reaction, 20 mol% of aluminum catalyst is prescribed and the addition reactions can be carried out at ambient temperature.

Eq. (88):

Copper bisoxazoline catalyst, 2^+, 2 OTf$^-$, t-Bu, Bu-t, **4** (1 mol%), THF, $-40°$

R		dr	% ee
H	(99%)	95:5	97
Me	(94%)	94:6	99

The bisoxazoline-derived complexes of tin(II) and copper(II) which have proven so successful in

additions to aldehydes that display the ability to form a five membered-ring chelate, are also effective in pyruvate and 1,2-diketone additions (Eqs. 90 and 91). (70, 197) Thus, at 10 mol% loading, additions of enol silanes to such ketones can be effected in 84–96% yield and up to 99% ee. It is worth noting that the tin(II)- and copper(I)-catalyzed additions provide access to products possessing complementary simple stereochemical patterns.

$$(89)$$

X	Y		I:II	% ee I
F	Cl	(100%)	89:11	98
OMe	Br	(90%)	91:9	98
Cl	NO$_2$	(99%)	74:26	92

$$(90)$$

X = SEt, OEt, Ph, Me

R^1, R^2 = Me, Me; Bn, Me; t-Bu, Me; Me, Et; Me, t-Bu; Et, i-Pr

$$(91)$$

Recent advances in the use of chiral phosphoramides have permitted the use of chiral silicon Lewis acid catalysts, which are generated in situ from SiCl$_4$. The reaction can be effected with as little as 1 mol% of bisphosphoramide as promoter at –78°. In these additions neither the absolute nor the relative stereochemical outcome of the addition reaction is affected by the geometry of the starting enolate (Eq. 92). This is, of course, a highly desirable feature of the process. Thus, as exemplified by the addition of tert-butyl propionate, both E- and Z-enol silanes afford the anti aldol products in

>99:1 enantioselectivity and 99 : 1 diastereoselectivity, with preference for the anti-substituted product. Accompanying mechanistic studies are consistent with an open transition state and rule out isomerization of the starting enolate.

$$E:Z \qquad dr \qquad \% \text{ ee}$$

95:5 (93%) 99:1 >99

12:88 (73%) 99:1 >99

(92)

A significant departure from the use of traditional enoxysilanes involves the chemistry of trichlorosilyl enolates prepared from the corresponding silyl or stannyl enolates. (208) The use of trichlorosilyl enolates in aldol addition reactions results in a process that is quite general with respect to aldehyde as well as enolate components. Thus, in addition to enolates from esters, ketone-derived enoxysilanes can be employed (Eq. 93). (207) The addition of the Z-trichlorosilyl enolate prepared from propiophenone to a wide range of aldehydes yields adducts in high simple induction

I   II

(95%) I:II = 18:1, 95% ee

(93)

(syn/anti up to 18 : 1) and absolute selectivity (up to 96% ee). Trichlorosilyl enolates prepared from cyclohexanone have also been examined in additions to aldehydes (Eqs. 94 and 95). (134) Both syn and anti aldol products can be produced at will by selection of the chiral phosphoramide, wherein a simple change in the N-substituent for a given enantiomer of a phosphoramide catalyst can lead to generation of the diastereomeric product.

I   II

(94%) dr = 1:99, 97% ee

(94)

(95)

The studies of these systems have included an examination of enolates derived from chiral ketones (Eq. 96). (210) For the ketone-derived Z-enolate examined, the syn aldol is formed preferentially. Further studies employing chiral ketones have revealed interesting results. (209, 210, 242) The addition can show excellent catalyst control but having the requisite starting enolate geometry is critical (Eqs. 97 and 98).

(96)

Z:E	cat		I:IV	I+IV:II+III
16:1	ent-17	(84%)	1:16	30:1
16:1	17	(80%)	10:1	26:1
1:15	17	(86%)	1:1	3:1

(97)

R	cat		I:IV	I+IV:II+III
Ph	ent-17	(84%)	24:1	53:1
Ph	17	(82%)	1:8	32:1
1-C₁₀H₇	ent-17	(71%)	89:1	14:1
1-C₁₀H₇	17	(79%)	1:17	14:1

(98)

A particularly noteworthy feature of these Lewis base catalyzed additions of trichlorosilyl enolates is the fact that crossed aldol addition reactions can be effected (Eqs. 99 and 100). (75) This rather remarkable process utilizes both E- and Z-enolates from an aldehyde, with each showing complementary relative diastereoselectivity.

$$\text{(99)}$$

(92%) dr = 99:1, 90% ee

$$\text{(100)}$$

(91%) dr = 97:3, 82% ee

Catalysts derived from complexes prepared with metals such as lead, (243) silver, (244, 245) platinum, (143) and lanthanides (246) mediate catalytic, enantioselective propionate aldol addition reactions. The addition of propiophenone to benzaldehyde mediated by a praseodynium complex prepared with a chiral macrocyclic ether is noteworthy, as it is a rare example of the use of a lanthanide in such aldol addition reactions and constitutes the successful use of a macrocyclic ligand (Eq. 101). The addition of isobutyrate-derived enoxysilanes catalyzed by platinum(II) complexes is also interesting for a number of reasons (Eq. 102). (143) Firstly, the additions afford a mixture of both silylated product and free alcohol, with both adducts formed with identical enantioselectivity. Secondly, the enantioselectivity of the process actually benefits from the inclusion of oxygen and water during catalyst preparation. It is also intriguing as it represents one of the few processes in which an isobutyrate addition is proposed to proceed by way of a metalloenolate intermediate. The reaction prescribes the use of 20 mol% catalyst, furnishing adducts in up to 95% ee.

$$\text{(101)}$$

(85%) dr = 91:9, 82% ee

$$\text{(102)}$$

(94%) **I:II** = 51:49, 95% ee

Simple chiral bisphosphine silver(I) complexes catalyze enantioselective addition reactions of stannyl enolates, (244) trimethoxysilyl enolates, (245) and diketene (247) with aldehydes. Under typical conditions, the addition reaction is catalyzed by 5–10 mol% of silver-BINAP complexes at –20°. The additions involving tin(II) enolates prescribe the use of a complex prepared from AgOTf and BINAP. The requisite tin enolates for the aldol addition can be prepared prior to use (Eq. 103) or can be generated in situ from the corresponding enol acetates (Eq. 104) or diketene (Eq. 105) upon treatment with Me₃SnOMe. In such addition reactions, adducts are formed in up to

(90%) **I:II** = 85:15, **I** 96% ee

(103)

96:4 anti:syn diastereoselectivity and up to 96% ee. Alternatively, ketone-derived trimethoxysilyl enol ethers have been employed in MeOH with the complex prepared from BINAP and AgF (Eq. 106). This represents a noteworthy example of a transition metal catalyzed process involving aldol addition that can be carried out successfully in a polar, protic solvent.

(86%) **I:II** = 94:6, **I** 96% ee

(104)

(59%) 84% ee

(105)

(77%) **I:II** = 1:99, **I** 97% ee

(106)

There have been some recent exciting advances in asymmetric phase-transfer catalysis that make possible the addition of substituted ketone-derived enol silanes to aldehydes with useful levels of relative and absolute induction (Eq. 107). (248)

(107)

3.2.2. Direct Aldol Addition Reactions of Substituted Systems

The direct aldol addition reactions of enolizable carbonyl compounds have been of interest for some time and are known for a wide range of C & O activated C ‰ H acids, including esters, ketones, and aldehydes. One of the earliest examples from this class involves the addition of isocyanoacetates to aldehydes mediated by bis-phosphine gold complexes (Eqs. 2, 108, and 109). (55, 56, 58-60) Despite the fact that the process is now well over 25 years old, it remains noteworthy because of the high levels of relative and absolute stereocontrol that can be obtained. Additionally, the process can be conducted with low catalytic loadings. The addition of substituted ♋-isocyanoacetates is possible, with the phenyl-substituted derivative affording products in the highest levels of relative and absolute induction (Eq. 109). Since its original disclosure the enolate precursor can be widely varied to include amides (63, 249) and other esters. (250, 251) Additional developments in ligand innovation and design, (252, 253) as well as the use of other metals (e.g. platinum), (254) have also yielded improvements.

(108)

(109)

(97%) I:II = 93:7, I 94% ee, II 53% ee

The first of the more recent advances in the in situ enolization of carbonyl C ‰ H acids and the subsequent stereocontrolled addition of the derived enolates to aldehydes was documented with lanthanide binaphthoxide catalysts, a class of bifunctional catalysts notable for their convenient synthesis and ready accessibility. These catalysts make possible the direct addition of ketones and hydroxy ketones to aldehydes in useful levels of relative and absolute stereoselectivity (Eqs. 110 and 111). (65, 83, 216)

(110)

(95%) I:II = 93:7, I 76% ee, II 88% ee

(111)

(50%) dr = 81:19, I 98% ee, II 79% ee

There have also been advances in this area involving the use of zinc(II) complexed to chiral alkoxy or phenoxy ligands (Eqs. 112 and 113, and Fig. 22). (83, 213, 214)

10 (1 mol%)

THF, −30°, 16-24 h

C_5H_9 ... H ... OMe ... OH

(112)

(88%) **I:II** = 88:12, **I** 95% ee, **II** 91% ee

11 (5 mol%)

Et_2Zn (10 mol%), 4 Å MS, THF, −35°, 24 h

(113)

$c\text{-}C_6H_{11}$ ... H ... OH

(90%) dr = 6:1, 96% ee

The ligands are derived from linked BINOL or bisprolinols anchored around a phenol. The typical addition reactions are conducted at reduced temperature and provide adducts in impressive levels of selectivity. For the BINOL-derived systems catalytic loadings as low as 1 mol% have been documented, while for the prolinol-derived systems slightly higher loadings are prescribed. (65, 218, 222) A zinc(II) catalyst has been used in the synthesis of boronolide 1 (Fig. 22). (213)

Figure 22. Application of the zinc-catalyzed aldol reaction to the synthesis of boronolide 1. [Full View]

There has been an intriguing report of titanium-catalyzed in situ aldol addition reactions involving ketones and non-enolizable aldehydes (Eq. 114). It is particularly noteworthy that a racemic titanium/BINOL complex is employed, which in the presence of optically active mandelic acid produces the aldol adducts as a 91 : 9 mixture of diastereomers with the major syn isomer formed in 91% ee. (255)

rac-BINOL$_2$-Ti$_2$(OPr-*i*)$_3$

(*R*)-mandelic acid (10 mol%), rt

(114)

(85%) dr = 91:9, 91% ee

There are reports of in situ enolization and aldol addition reactions mediated by catalytic phase-transfer catalysts. (256) The addition of glycinate Schiff bases to aldehydes under basic conditions

in the presence of a chiral tetraalkylammonium phase transfer agent furnishes protected amino alcohol products in 2:1 dr and 95% ee (Eq. 115).

(115)

Proline has been investigated in the addition reactions of substituted ketones to aldehydes. These proline-mediated reactions, as well as other amine-catalyzed aldol addition reactions, are remarkable because of the high level of regio- and enantioselectivity they display. Thus, in an early example, the addition of cyclohexanone to isopentanal using 20 mol% of proline affords a 7:1 mixture of anti/syn adducts in 86 and 89% ee, respectively (Eq. 116). (257) Hydroxyacetone has also been demonstrated to undergo facile, regioselective aldol addition reactions. (66, 258) The addition of excess hydroxyacetone to isobutyraldehyde mediated by 20–30 mol% of L-proline in DMSO at ambient temperature affords the adducts as a >20:1 mixture favoring the anti diol, itself isolated in >99% ee (Eq. 117). The ability to access 1,2-anti diol products complements the more conventional method involving asymmetric dihydroxylation of unsaturated ketones. (259) These reactions have also been carried out in ionic liquids (71, 260, 261) and with polymer-bound 4-hydroxyproline. (262, 263)

(116)

(117)

Recent studies in this area have subsequently shown that it is possible to effect crossed aldol addition reactions between two aldehydes to give adducts in useful levels of simple diastereoselectivity and high enantioselectivity (Eq. 118). (86) For the addition of propionaldehyde to isobutyraldehyde or cyclohexanecarboxaldehyde the simple induction can be as high as 24:1; however, for additions to aldehydes such as propionaldehyde and isopentanal the selectivity is 3–4:1, with a preference for the anti adduct. The key to the success of this process appears to be the selection of the appropriate reactive components and the reaction conditions; thus, slow addition of the nucleophilic aldehyde component to the electrophilic aldehyde counterpart and 10 mol% of proline in DMSO at 4° constitute the optimal conditions for the cross-aldol addition reaction. The addition reaction of aldehydes to non-enolizable ketones has also been documented, affording

adducts in 90% yield and up to 90% ee (Eq. 119) (264, 265)

(118)

(119)

3.2.3. Enoxysilanes of Acetoacetate and Furan

The addition reactions of dienolates are gaining increased attention, as they provide access to densely functionalized building blocks for asymmetric synthesis. These additions offer a unique advantage in molecule assembly as a C4 carbon unit is appended to the aldehyde in the course of aldol addition. Consequently, they offer enhanced efficiency over an iterative aldol process that would otherwise require two sequential aldol addition reactions with concomitant protections and oxidation-state adjustments.

One of the earliest examples of the use of a dienolate, namely 1-methoxy-3-trimethylsilyloxy-1,3-butadiene, is the aldol addition reaction mediated by 20 mol% of a tryptophan-derived oxazaborolidine catalyst at –78° in propionitrile (Eq. 120). (181) The first-formed aldol adducts are converted upon treatment with mild acid into the corresponding 4*H*-pyran-4-ones with optical purity of up to 82% ee.

(120)

Pioneering examples of the use of acetoacetate-derived dienoxysilanes in aldehyde additions were reported using both boron- and titanium(IV)-derived catalysts (Eqs. 121 and 122). (266, 267) In these reactions large loadings of catalyst were necessary along with slow addition of the aldehyde substrate and the products were isolated in 38–69% yield and 67–92% ee. (267)

(121)

$$(122)$$

Advances in the enantioselective addition of acetoacetate-derived dienolates has been reported with the titanium(IV) complex **5** and its enantiomer. The adducts are formed with as little as 2 mol% catalyst loading (Eq. 123). (35, 139) The fact that δ-stannylpropenal can be used successfully as a substrate permits access to aldol adducts that can be subsequently extensively functionalized, providing convenient building blocks for complex molecule assembly. This ability significantly facilitates the assembly of polyacetate-derived natural products, as exemplified in the synthesis of macrolactin A (Fig. 23). (35)

$$(123)$$

Figure 23. Use of δ-stannylpropenal as starting material in the synthesis of macrolactin [Full View]

Bisphosphine copper(I) complexes are also efficient in mediating dienolate additions to aldehydes. Thus, the complex that is generated upon mixing Tol-BINAP, Cu(OTf)$_2$, and (Bu$_4$N)Ph$_3$SiF$_2$ effects the rapid addition reaction of acetoacetate-derived dienolates to aldehydes to give adducts in high yield and with high selectivity (Eq. 124). (69, 190, 268, 269) The addition of these dienolates to crotonaldehyde and other unsaturated aldehydes serves as an important launching point in a total synthesis of leucascandrolide A (Fig. 24), (270) salicylhalamide A (Fig. 25), (271) and madumycin 1 (Fig. 26). (268)

(124)

Figure 24. Application of the copper-catalyzed aldol reaction to the synthesis of leucascandrolide A.
[Full View]

Figure 25. Application of the copper-catalyzed aldol reaction to the synthesis of salicylhalamide A.
[Full View]

Figure 26. Application of the copper-catalyzed aldol reaction of enoxysilane to the synthesis of madumycin 1.
[Full View]

The copper-BINAP system has been examined in the addition reactions of ∞-substituted 3-pentenoic acid-derived dienolates (Eq. 125). (272) In these addition reactions, useful levels of stereoinduction are observed, thus considerably expanding the scope of the acetoacetate aldol addition reactions. In studies aimed at the synthesis of octalactin A, the catalytic system afforded a useful intermediate (Eq. 126). (273)

(125)

(126)

The catalytic systems that have been shown to effectively mediate additions to chelating aldehydes, such as benzyloxyacetaldehyde, have also been examined in the context of dienolate additions. (37, 74) The additions have been investigated with both acetoacetate-derived enoxysilanes (Eq. 127) as well as the bis-silyldienolate prepared directly from acetoacetate derivatives **20** and **21**. The addition has been used in the preparation of the C4-C9 subunit of phorboxazole B (Eq. 128) (274) as well as a key fragment in bryostatin 2 (Fig. 27). (275, 276)

(127)

(128)

Figure 27. Application of the copper-catalyzed aldol reaction of dienolate in the synthesis of bryostatin 2.
[Full View]

Silyloxyfurans are synthetically useful equivalents of γ-alkoxysubstituted α, β-unsaturated ester enolates. Their use in aldehyde additions has been documented using simple catalyst systems derived from titanium(IV) and BINOL (Eq. 129). (277-280) The adducts are obtained in modest levels of simple diastereoselectivity and up to 90% ee. The use of this system has been documented in a total synthesis of 4-deoxygigantecin (Fig. 28). (281) Bisoxazoline copper(II) complexes are effective in mediating these addition reactions as well. Thus, the addition of 1-trimethylsilyloxyfuran to pyruvate (Eq. 130) and benzyloxyacetaldehyde (Eq. 131) employing 10 mol% copper(II) catalyst affords adducts in high diastereoselectivity and 99% ee. (197)

(129)

(130)

$$(131)$$

Figure 28. Use of silyloxyfurans in the synthesis of 4-deoxygigantecin. [Full View]

3.2.4. Domino Reactions Involving Aldol Additions

Among the various exciting new developments involving enantioselective aldol addition reactions is their use in the context of domino processes. Although there are only a few examples, these are quite innovative and promising, as a consequence of the ability of such processes to potentially lead to powerful simplifications in synthetic planning and execution. Domino enantioselective processes involving aldol additions can be grouped into two general classifications on the basis of whether the aldol reaction is the first step or the subsequent in a series.

There are several reports of domino sequences in which an aldol addition is the leading step. In these, aldolization is followed by either C & O reduction or ring formation. In the first of these, 2 mol% of a chiral yttrium complex effects the crossed aldol addition reaction between non-enolizable aldehydes and isobutyraldehyde. (282) In the presence of excess aldehyde, the β-hydroxyaldehyde aldol adduct subsequently undergoes Tishchenko reduction to afford a selectively protected 1,3-diol which is isolated in up to 84% ee (Eq. 132).

$$(132)$$

Another process in which an asymmetric aldol addition leads the sequence is the intramolecular version of the catalytic, enantioselective Wynberg β-lactone synthesis, giving rise to bicyclic lactones through a sequence involving intramolecular aldol and lactone formation (Eq. 133). (283) Thus, the formylacid initially undergoes conversion into the corresponding formylketene via chemoselective formation of the acid chloride. The ketene is then suggested to undergo reaction with the cinchona alkaloid catalyst to form a chiral enolate, which subsequently participates in aldol addition and ring closure. The products formed from these reactions are isolated enantioselectively in up to 92% ee.

(133)

A third example of aldehyde addition as the leading step in a domino sequence involves the addition of two equivalents of diethylketene acetal to phenyl pyruvate in the presence of 20 mol% of a copper-bisoxazoline catalyst (Eq. 134). (284) Aldol-like addition to the ketone by the electron-rich diethyl ketene acetal leads to the formation of an oxonium intermediate, which is attacked by a second equivalent of the nucleophile to give yet another oxonium intermediate, which is trapped by the newly formed copper alkoxide, leading to the formation of a densely funtionalized pyran in up to 93% ee.

(134)

There are a number of processes wherein aldol addition follows a different initial reaction whose outcome is the generation of an enolate intermediate. Such processes have been documented in the context of conjugate additions. The reduction of enones and enoates generally proceeds through the intermediacy of metal enolates. When the conjugate additions are carried out with chiral metal complexes, they provide chiral metal enolates which can subsequently participate in enantioselective aldol addition reactions. In this respect, the reaction of methyl acrylate with benzyloxyacetaldehyde, in the presence of a chiral tridentate bisoxazoline ligand **22**, and Ir(COD) Cl dimer, and a silane reductant leads to formation of propionate aldol adducts (Eq. 135). (285, 286) The adduct is formed diastereoselectively with a preference for the syn diastereomer (up to 10:1) in up to 96% ee. With certain chiral substrates the reaction process can display a significant amount of matching/mismatching. Thus, the addition of the acrylate-derived propionate enolate to both enantiomers of 3-benzyloxybutyraldehyde using the same catalyst affords complementary products

(135)

BnO—CHO + acrylate OMe → **22** (3 mol%), [(COD)IrCl]$_2$ (1 mol%), Et$_2$MeSiH, rt, 24 h; 2. aq. HCl → BnO—CH(OH)—CH(Me)—CO$_2$Me

(84%) dr = 8:1, 96% ee

in equally good selectivities (Eq. 136). However, for a given catalyst enantiomer only one enantiomer of the chiral 2-benzyloxypropionaldehyde undergoes addition. The reaction process has been applied in the synthesis of borrelidin 1 (Fig. 29), a complex natural product macrolide isolated from *Streptomyces*. (287)

R—CHO + acrylate OMe → 1. **22** (7.5 mol%), [(COD)IrCl]$_2$ (2.5 mol%); Et$_2$MeSiH, rt, 24 h; 2. aq. HCl → R—CH(OH)—CH(Me)—CO$_2$Me (syn$_a$) + syn$_b$ + anti

(136)

R		syn$_a$:syn$_b$	syn:anti
(R)-MeCH(OBn)	(50%)	>95:5	>95:5
(S)-MeCH(OBn)	(<5%)	n.d.	n.d.
(R)-MeCH(OBn)CH$_2$	(65%)	89:11	2.7:1
(S)-MeCH(OBn)CH$_2$	(57%)	88:12	3.0:1

Figure 29. Conjugate reduction/aldol sequence in the synthesis of borrelidin 1. [Full View]

Enone acceptors can also lead to the formation of enolates through asymmetric metal-mediated conjugate addition reactions of carbon nucleophiles. The rhodiumcatalyzed addition reaction of phenylboronic acid to aryl enones affords an intermediate rhodium enolate which participates in a subsequent intramolecular aldol addition reaction, giving cyclic adducts in high yield and up to 95% ee (Eq. 137). (288)

Ph(BOH)$_2$ + Ph—enone → [Rh(COD)Cl]$_2$ (2.5 mol%), (R)-BINAP (7.5 mol%), H$_2$O (5 equiv), dioxane, 95° → cyclic adduct

(137)

(88%) 94% ee

In another domino process involving conjugate addition followed by aldol addition, the enolate formed upon asymmetric 1,4-addition of diethyl methylmalonate carbanion to cyclopentanone participates in an intermolecular aldol addition, affording adducts in up to 89% ee and good yields

(Eq. 138). (68, 289) The catalyst used in this process is the multifunctional complex **23** conveniently formed from LiAlH$_4$ and BINOL. This cascade process has been elegantly employed in a synthesis of 11-deoxy-PGF$_1$♋ (Fig. 30).

(138)

(75%) dr = 12:1, 97% ee

Figure 30. Conjugate addition/aldol reaction sequence in the synthesis of 11-deoxy-PGF$_1$♋.

[Full View]

Catalytic Enantioselective Aldol Addition Reactions

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4. Comparison with Other Methods

The advances in asymmetric synthesis have been so dramatic and pervasive that there are typically numerous approaches available for the synthesis of any given building block. This should not be perceived as unnecessary duplication or overlap, but is, on the contrary, indispensable for the field and the synthesis of complex organic molecules. Despite the general desire of every methods chemists to develop reactions that display broad substrate scope, in reality no method can provide access to the endless structural space of chiral building blocks. In this respect, even when a method displays the broadest scope, access to subclasses of starting materials may be sufficiently laborious that the use of the method may be precluded. In considering the preparation of aldol fragments, one cannot escape considering the use of diastereoselective chiral auxiliary-based methods. The development of asymmetric aldol addition processes has been most thoroughly and successfully studied in the context of diastereoselective methods, wherein the stereochemical induction is derived from previously existing stereogenic centers in the nucleophilic enolate, electrophilic aldehyde or ketone component, (290, 291) or metal fragment. (292-302) In this respect, addition reactions in which the stereochemical outcome of the reaction is derived from a chiral enolate component are most common. In particular, chiral carboxylic acid derivatives have proven most versatile and general. Hydrolysis of the aldol product affords the β-hydroxy carboxylic acid (or ester) and the conjugate acid of the chiral controlling group. The most common of these relies on the use of chiral imides (Eq. 139). (303-306) Recent exciting developments in such processes have permitted considerable expansion in the stereochemical outcome of the reaction by subtle variations in the nature of the auxiliary and conditions employed (Eq. 140) (307-309) Additionally, the use of readily available ester-derived auxiliaries

(139)

(140)

has made possible convenient access to anti aldol adducts (Eqs. 141 and 142). (310, 311) A particularly attractive feature of the use of a chiral auxiliary is undeniable: the fact that the products are diastereomeric allows for ease of isomer purification by simple chromatographic means.

(141)

(90%) dr >96:4

(142)

I

II

(63%) I:II = 99:1

In parallel with the developments in imide-derived chiral auxiliaries, there have been exciting advances in the use of chiral boron reagents which allow for the formation of chiral enolates (Eqs. 143 and 144). (312-314) These permit efficient stereoselective coupling of ketone enolate and aldehyde fragments and are particularly noteworthy in the context of complex fragment couplings, imparting a great degree of convergency in the assembly of polyketides.

$(-)$-Ipc$_2$BCl

$(i$-Pr$)_2$NEt, Et$_2$O

(143)

(68%) 78% ee

(144)

Ar = 4-O$_2$NC$_6$H$_4$O$_2$S

(85%) 96% ds

There has been a dramatic increase in the understanding of the various factors in the aldol addition reaction involving chiral enolate and chiral aldehyde coupling reactions. The nature of these processes makes them particularly amenable to mechanistic studies and analysis, and consequently it is possible to carry out numerous fragment coupling reactions that lead to stereochemically dense polyketide fragments (Eqs. 145-147). (292, 314) However, it should be noted that periodically one finds unexpected results even in chiral auxiliary-mediated aldol addition reactions, which require reevaluation of the accepted models in this area (Eq. 148). (315, 316)

n-Bu$_2$BOTf

$(i$-Pr$)_2$NEt, Et$_2$O, $-78°$

(145)

(89%) anti:syn = 95:5

$$(146)$$ (97%) dr = 98:2

$$(147)$$ (84%) syn:anti = 82:18

$$(148)$$ I   (68%) I:II = 5:1   II

An overview of the aldol reaction in its various incarnations reveals an interesting dichotomy in the development of the two general class types for stereocontrol with respect to the family of ketides they provide access to. Thus, although chiral-auxiliary controlled diastereoselective aldol processes that afford syn or anti ℒ-substituted ℛ-hydroxy carbonyl compounds allow the ready synthesis of propionate fragments, they in general do not work well, with some exceptions (Eqs. 149 and 150), (317-320) in furnishing acetate adducts. Yet, this latter case of aldol processes can be effected by employing a number of different enantioselective catalysts. It can be said with some confidence that further developments in the field will fill in the respective gaps of each strategy providing versatile, enabling reactions for the synthetic chemist.

$$(149)$$ (89%) dr = 50:1

$$(150)$$ (62%) dr >99:1

There are alternatives in catalytic asymmetric synthesis methods that do not involve aldol coupling

reactions and furnish access to hydroxycarbonyl compounds. These can be highly effective means of accessing polyketide fragments. The preparation of both acetate and propionate fragments can be effected by catalytic, asymmetric hydrogenation of β-diketones and β-keto esters (Eq. 151). (321, 322) Applications of these highly effective processes are numerous. A particularly innovative application involves the asymmetric reduction of 1,5-dichloro-2,4-pentanone to an optically active diol and conversion of the diol product to the corresponding diepoxide, which serves as a useful starting material (Eq. 152). (323) Optically active monosubstituted epoxides can be directly converted into β-hydroxycarbonyl compounds (Eq 153). (324) These serve as entry points for the preparation of anti-propionate subunits via the alkylation of β-alkoxyenolate dianions. (325-328)

(151)

(152)

(153)

The allylation reaction of aldehydes leading to the formation of homoallylic alcohols has long been recognized as a useful, practical alternative for the generation of aldol fragments. (329, 330) Convenient access to β-hydroxycarbonyl compounds is available from optically active homoallylic alcohols by oxidative olefin functionalization. These alcohols are readily accessed through asymmetric allylation reactions of aldehydes. (331-340) The use of chiral allylboron reagents is most common (Eqs. 154 and 155). (341-343) Chiral allyllithium reagents generated in the presence of sparteine have also been documented (Eq. 156). (344) Optically active allylsilanes have been cleverly utilized in the synthesis of complex polyketides (Eqs. 157 and 158). (345, 337) A particularly attractive feature of these processes is that alteration of the reaction conditions can lead to divergent stereochemical patterns in the products. Related methods commencing with chiral propargyl mesylates (Eq. 159) and allenylstannanes (Eq. 160) have been described and elegantly employed in complex molecule assembly. (346)

(154)

(155)

TESO O

TBDPSO

+ allyl-B reagent with N-CF3 groups

PhMe, sieves, −78° →

TESO OH

TBDPSO

I

+

TESO OH

TBDPSO

II

I:II = 9:1

$$\text{(−)-sparteine, } s\text{-BuLi} \quad \text{then } i\text{-Pr-CHO} \tag{156}$$

(95%) 83% ee

$$\text{BnO-CHO} + \text{SiPhMe}_2\text{-CO}_2\text{Me} \xrightarrow[\text{CH}_2\text{Cl}_2,\ -78°]{\text{BF}_3\cdot\text{OEt}_2} \tag{157}$$

(68%) syn:anti = 6.5:1

$$\text{BnO-CHO} + \text{SiPhMe}_2\text{-CO}_2\text{Me} \xrightarrow[\text{CH}_2\text{Cl}_2,\ -78°]{\text{MgBr}_2} \tag{158}$$

(59%) syn:anti = 1:12.2

$$\text{TBSO aldehyde} + \text{OMs} \xrightarrow[\text{Et}_2\text{Zn, THF}]{\text{Pd(OAc)}_2,\ \text{Ph}_3\text{P}} \tag{159}$$

(76%)

$$\text{BnO aldehyde} + n\text{-Bu}_3\text{Sn allene} \xrightarrow[\substack{1.\ \text{BF}_3\cdot\text{OEt}_2,\ \text{CH}_2\text{Cl}_2,\ -78° \\ 2.\ \text{TESOTf, Et}_3\text{N}}]{} \tag{160}$$

(88%) syn:anti = 94:6

The catalytic, enantioselective allylation of aldehydes has been examined and documented. The use of allyl stannanes in combination with a catalyst system derived from BINOL and Ti(IV) has proven highly effective for the synthesis of homoallylic alcohols (Eq. 161). (338, 347) The catalytic, enantioselective addition of allyltrimethylsilane has been effected with a catalyst derived from TiF$_4$ · BINOL. (348, 349)

$$\tag{161}$$

(162)

There are new developments in the use of homoallylic alcohols for the synthesis of polyketide fragments. Treatment of a homoallylic alcohol with acetone in the presence of mercury leads to the formation of an alkyl mercurial intermediate that can subsequently undergo carbonylation to afford an aldehyde (Eq. 163). (350-352) The silyl

(163)

ethers derived from homoallylic alcohols and diallylchlorosilane participate in a domino sequence of reactions involving directed hydrocarbonylation and intramolecular allylation of the aldehyde product, providing rapid entry into polyketides subunits (Eq. 164). (353)

(164)

The ability to prepare optically active epoxy alcohols as well as glycidate derivatives provides additional access to ketide fragments (Eqs. 165-167). (354-358) Chiral epoxy alcohols have been shown to undergo pinacol rearrangements to furnish β-hydroxy aldehydes. (359-362) Regioselective nucleophilic opening by carbon nucleophiles (or hydride) subsequently affords useful ketides. (363-366)

(165)

(166)

(167)

A number of alternative approaches provide access to polyketide fragments and subunits. The recent development of highly diastereoselective dipolar cycloaddition reactions of nitrile oxides and chiral allylic alcohols furnishes a wide range of substituted isoxazolines that can be easily reductively opened to the corresponding hydroxy ketones (Eq. 168). (367-369) The cycloaddition reaction of aldehydes with ketenes derived from acid bromides is catalyzed by a chiral aluminum complex, which furnishes δ-lactones in high selectivity and yield (Eq. 169). (370) These lactones have been converted into the corresponding aldol fragments. (371) Propargylic alcohols have also been converted into hydroxy carbonyl compounds in high optical purity. (372) The alkylation of acetonides has been effectively employed in the synthesis of skipped polyols and can be relied upon to provide polyol stretches efficiently with high levels of induction (Eq. 170). (373) In a unique approach to δ-hydroxy ketone and ester fragments, oxabicyclooctanes have been functionalized cleverly manipulated to furnish long stretches of polyketide subunits (Eq. 171). (374-376) The

(168)

(169)

(170)

(45%)

(90%) 88% ee

(171)

tandem sequence of reactions involving the diastereoselective conjugate addition reaction of cuprates to γ-alkoxy-α, β-unsaturated enoates followed by stereoselective oxidation of the enolate is also a powerful approach to polyketides (Eq. 172). (376, 377)

(86%) ds >50:1

(172)

Advances in bioorganic chemistry and biochemistry have resulted in the identification and engineering of novel enzymatic (Eq. 173 and 174) (42-44, 378) and antibody (45-47) catalysts that provide access to aldolate fragments. The processes are notable by the fact that they are carried out under aqueous conditions and that they furnish polar products rich in functionality free of protecting groups.

(70%)

(173)

(35%) dr >99:1

(174)

A number of the aldol addition reactions presented in this chapter are unique in that other direct routes to hydroxycarbonyl compounds are not easily envisioned because they would require laborious, multi-step synthetic sequences. In this category are found the acetoacetate and furan

aldol addition reactions, additions affording isoxazolines, and, significantly, the domino processes that incorporate an aldol addition reaction as part of a multi-step sequence of reactions.

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Catalytic Enantioselective Aldol Addition Reactions

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5. Experimental Conditions

The traditional catalytic aldol addition reactions have involved the use of enoxytrialkylsilanes. These are conveniently prepared from the corresponding ketone, ester, or thioester for which a number of procedures have been described: ketones (379) and esters, (37) halo esters, (237) acetoacetate, (380) substituted acetoactetates, (271) and dioxolinone. (266) The preparation of the corresponding trialkoxyenoxysilanes has been described. (246) Trichlorosilyl enolates of aldehydes, ketones, and esters are accessed from the corresponding enoxysilane or stannyl derivates and have been carefully documented. (75, 207, 208, 381) The stannane-derived enolates are prepared from the corresponding *O*-enol acetates. (381, 382) Small amounts of the C-silylated derivative can accompany the desired *O*-enoxysilane; however, few reports comment on this and, in general, no additional manipulation is undertaken to remove this by-product prior to use. The enol silanes tend to be moisture sensitive and are used unpurified or following distillation under reduced pressure.

The experimental conditions and catalysts vary widely. Although some of the transition-metal-catalyzed processes can be sensitive to moisture, it is difficult to generalize, as some are tolerant of moisture and benefit from the addition of small amounts of water. The amine-catalyzed aldol addition reactions can provide useful alternatives to the transition-metal-catalyzed processes that form the majority of processes that have been documented. They offer a particular advantage in that the additional steps typically required to prepare the enoxysilanes are obviated.

So fundamental a reaction as the aldol addition can expect to be the subject of additional scrutiny and study for the foreseeable future. When compared to other well-studied processes in catalytic asymmetric synthesis, catalytic, enantioselective aldol addition reactions are in general far from ideal. In this respect, although impressive enantioinduction has been achieved (>99%), the important reaction parameters such as catalytic loading, turn-over numbers, and volumetric efficiency require additional improvement. Advances in this respect will necessitate mechanistic insight and reaction innovation.

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Catalytic Enantioselective Aldol Addition Reactions

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6. Experimental Procedures

6.1. Phenyl (2*R*,3*S*)-2-(Benzyloxy)-5-(*tert*-Butyldimethylsiloxy)-3-Hydroxypentanoate (Tin-Catalyzed Aldol Reaction) (227)

To a solution of Sn(OTf)$_2$ (0.16 mmol) and SnO (0.16 mmol) in *n*-PrCN (2.0 mL) was added a solution of (*R*)-1-methyl-2-(5,6,7,8-tetrahydro-1-naphthylaminomethyl)pyrrolidine (0.19 mmol) in EtCN (2.0 mL). The mixture was cooled to –78° and the aldehyde (0.77 mmol) in EtCN (1.0 mL) and the silylenol ether (0.93 mmol) in EtCN (1.0 mL) were slowly added to the catalyst over 4 hours. The reaction mixture was further stirred for 2 hours at the same temperature and then quenched with saturated aqueous NaHCO$_3$. The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$. The combined organic layers were dried over Na$_2$SO$_4$, filtered, and evaporated. The crude product was treated with THF/1 N HCl (20: 1) at 0°. After the usual workup, the crude aldol was purified by chromatography on silica gel to afford the title compound in 70% yield. The diastereomer ratio was determined by ^{1}H NMR analysis (syn/anti = 95:5). The enantiomeric excess of the syn adduct was determined to be >96% ee by HPLC analysis using Daicel Chiralcel AD [hexane/*i*-PrOH (9:1), flow rate 1.0 mL/minutes, t_R = 8.2 minutes (2*S*,3*R*), 15.6 minutes (2*R*,3*S*)]. syn: [⌾]$^{25}_D$ + 58.0° (*c* 2.0, CHCl$_3$); IR (neat) 3478, 2928, 1771, 1594, 1493, 1093 cm^{-1};^{1}H NMR (CDCl$_3$) ≏ 0.00 (s, 6H), 0.83 (s, 9H), 1.65–1.95 (m, 2H), 2.96 (d, *J* = 5.6 Hz, 1H), 3.66–3.85 (m, 2H), 4.09 (d, *J* = 3.96 Hz, 1H), 4.26 (m, 1H), 4.52 (d, *J* = 11.6 Hz, 1H), 4.85 (d, *J* = 11.6 Hz, 1H), 7.04–7.35 (m, 10H); ^{13}C NMR (CDCl$_3$) ≏ – 5.5, 18.2, 25.8, 35.4, 60.8, 71.3, 72.9, 80.6, 121.3, 121.4, 126.0, 128.2, 128.3, 128.4, 128.5, 129.4, 136.9, 150.4, 169.6. HRMS: [M]$^+$ calcd for C$_{24}$H$_{34}$O$_5$Si , 430.2176; found, 430.2169.

6.2. Phenyl (2*S*,3*S*)-3-Hydroxy-2-Methyl-3-(4-Methoxyphenyl)Propanoate (Zirconium-Catalyzed Aldol Reaction) (180)

To a suspension of (*R*)-3,3′-diiodo-1,1′-binaphthalene-2,2′-diol (0.048 mmol) in toluene (1.0 mL) was added Zr(OBu – *t*)$_4$ (0.040 mmol) in toluene (1.0 mL) at room temperature and the solution was stirred for 30 minutes. Then *n*-PrOH (0.32 mmol) and H$_2$O (0.080 mmol) in toluene (0.5 mL) were added, and the reaction mixture was stirred for 3 hours at room temperature. After cooling at 0°, benzaldehyde (0.40 mmol) in toluene (0.75 mL) and silyl enol ether (0.48 mmol) in toluene (0.75 mL) were added successively. The mixture was stirred for 18 hours and saturated aqueous NaHCO$_3$ solution (10 mL) was added to quench the reaction. After CH$_2$Cl$_2$ (10 mL) was added the organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 × 10 mL). The organic layers were combined and dried over Na$_2$SO$_4$. After filtration and concentration under reduced pressure, the residue was treated with THF/1 N HCl (20 : 1) for 1 hour at 0°. The solution was then made alkaline with saturated NaHCO$_3$ and extracted with CH$_2$Cl$_2$. The organic layers were combined and dried over Na$_2$SO$_4$. After filtration and concentration under reduced pressure, the crude product was purified by preparative TLC [C$_6$H$_6$/EtOAc (20 : 1)] to afford the title compound. The optical purity was determined by HPLC analysis using a chiral column. HPLC (after acetylation), Daicel Chiralcel OD, hexane/*i*-PrOH (30 : 1), flow rate = 0.5 mL/minute: syn isomer t_R = 17.8 minutes (major), t_R = 22.5 minutes (minor); anti isomer t_R = 19.7 minutes (major), t_R = 24.3 minutes (minor); IR (neat) 3491, 1756, 1611, 1592, 1514, 1493, 1457, 1375, 1304, 1250 cm^{-1}; ^{1}H NMR (CDCl$_3$) anti isomer $\triangleq$ 1.14 (d, *J* = 7.0 Hz, 3H), 2.74 (br, 1H), 3.03 (dq, *J* = 8.8, 7.3 Hz, 1H), 3.81 (s, 3H), 4.82 (d, *J* = 8.6 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 7.08 (m, 2H), 7.21–7.40 (m, 5H); detectable peaks of syn isomer $\triangleq$ 1.34 (d, *J* = 7.1 Hz, 3H), 5.07 (d, *J* = 5.6 Hz, 1H); ^{13}C NMR (CDCl$_3$) anti isomer $\triangleq$ 14.3, 47.5, 55.2, 76.0, 113.8, 121.5, 125.8, 127.9, 129.3, 133.5, 150.5, 159.4, 174.4; detectable peaks of syn isomer $\triangleq$ 11.9, 47.1, 55.2, 74.0, 113.7, 121.3, 127.4, 129.3, 129.4, 133.6, 150.3, 159.1, 173.8. HRMS (*m/z*): [M]$^+$ calcd for C$_{17}$H$_{18}$O$_4$, 286.1205; found, 286.1202.

6.3. (*R*)-1-Hydroxy-1-Phenyl-3-Heptanone (Boron-Catalyzed Aldol Reaction) (181)

To a solution of catalyst (0.056 mmol) in 0.5 mL of EtCN at –78° in a dry 25-mL round-bottom flask was added benzaldehyde (0.028 mL, 0.28 mmol) followed by 2-trimethylsiloxy-1-hexene (0.080 mL, 0.41 mmol). The reaction mixture was stirred for 14 hours at –78° and then quenched by the addition of saturated aqueous NaHCO$_3$ solution (10 mL). The mixture was extracted with Et$_2$O(4 × 20 mL) and the combined organic phases were dried (MgSO$_4$) and concentrated. The residue was dissolved in THF (4 mL) and aqueous 1 M HCl (2 mL), and the resulting solution left

standing for 30 minutes. Saturated aqueous NaHCO$_3$ solution (20 mL) was added and the mixture was extracted with Et$_2$O(4 × 25 mL). The combined organic phases were dried (MgSO$_4$) and concentrated to an oily residue. Silica gel chromatography (5–20% EtOAc/hexane) afforded 0.058 g (100%) of the known title compound. HPLC analysis (Chiralcel AD column with 5% *i*-PrOH/hexane) indicated an enantiomeric excess of 90% ($t_r$major = 11.5 minutes; minor = 13.8 minutes).

6.4. Methyl (*R*)-3-Hydroxy-8-Phenyloct-4-Ynoate (Titanium-Catalyzed Aldol Reaction) (188)

To a solution of the chiral Schiff base ligand (5.0 mM, 0.066 equiv) in toluene was added Ti(OPr – *i*)$_4$ (0.030 equiv). The orange solution was stirred for 1 hour at room temperature and 3,5-di-*tert*-butylsalicylic acid (0.060 equiv, 0.1 M in toluene) was added. Stirring was continued for an additional hour at room temperature. The solvent was removed in vacuo and the orange solid was dissolved in Et$_2$O to give a 5.0 mM solution (relative to chiral ligand). After cooling the solution to 0°, 2,6-lutidine (0.40 equiv) was added, followed by the sequential addition of 6-phenylhex-2-ynal (100 mg, 0.581 mmol, 1 equiv) and (1-methoxyvinyloxy)trimethylsilane (102 mg, 0.697 mmol, 1.2 equiv). The reaction mixture was stirred at 0° for 4 hours before it was poured into water. The organic phase was dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was dissolved in THF and treated with excess Bu$_4$NF (2–3 equiv). The solution was partitioned between Et$_2$O and 1 M aqueous HCl. The organic layer was washed with 5% aqueous NaHCO$_3$ solution and then brine, dried (Na$_2$SO$_4$), and concentrated in vacuo. Purification by chromatography on silica gel using CH$_2$Cl$_2$/hexanes (10:1) to elute the ligand, followed by CH$_2$Cl$_2$/Et$_2$O (10:1) afforded 119 mg (84%) of methyl (*R*)-3-hydroxy-8-phenyloct-4-ynoate, [⍺]$_D$ + 19.3° (*c* 1.01, CHCl$_3$); IR (thin 3448, 3026, 2948, 2860, 1739, 1602, 1496, 1454, 1438, 1356, 1278, 1167, 1055, 1028, 747, 701 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) ≙ 1.82 (dt, *J* = 7.4 Hz, 7.0, 2H), 2.22 (t, *J* = 7.0 Hz, 2H), 2.70 (t, *J* = 7.4 Hz, 2H), 3.08 (d, *J* = 6.1 Hz, 2H), 3.73 (s, 3H), 4.77 (q, *J* = 6.1 Hz, 1H), 7.37–7.17 (m, 5H); ^{13}C NMR (75 MHz, CDCl$_3$) ≙ 18.0, 29.9, 34.6, 42.1, 58.9, 79.8, 85.4, 125.8, 128.3, 141.4, 171.8; HRMS-EI: [M]$^+$ calcd for C$_{15}$H$_{18}$O$_3$, 246.1256; found, 246.1243.

6.5. (*R*)-*S*-*tert*-Butyl 4-Benzyloxy-3-Hydroxybutanethioate (Copper-Catalyzed Aldol Reaction) (**74**)

To a 5-mL round-bottom flask equipped with a magnetic stirring bar and fitted with a septum was added 200 µL (2.5 µmol, 0.5 mol%) of a 0.0125 M solution of the catalyst in CH_2Cl_2. After cooling to –78°, benzyloxyacetaldehyde (74.8 mg, 0.50 mmol, 70.0 µL) was added followed by (1-*tert*-butylsulfanylvinyloxy)-trimethylsilane (122 mg, 0.60 mmol, 153 µL). The resulting solution was stirred at –78° until the aldehyde was completely consumed, as determined by TLC (30% EtOAc/hexanes). The reaction mixture was then filtered through silica gel (1.5 × 8 cm plug) with Et_2O (50 mL). Concentration of the ether solution gave a clear oil which was dissolved in THF solution (10 mL) and 1 N HCl (2 mL). After standing at room temperature for 15 minutes, the solution was poured into a separatory funnel and diluted with Et_2O (10 mL) and H_2O (10 mL). After mixing, the aqueous layer was discarded and the ether layer was washed with saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL). The resulting ether layer was dried over $MgSO_4$, filtered, and concentrated to provide pure title compound in 100% yield (141 mg, 0.50 mmol). $[\alpha]^{rt}_D$ – 10.9° (*c* 3.0, CH_2Cl_2); $[\alpha]^{26}_D$(lit.) + 10.0° (*c* 1.0, $CHCl_3$) 96% ee (R). The enantiomeric excess was determined by HPLC with a Chiralcel OD-H column [hexanes: *i*-PrOH:EtOAc (94.2:0.8:5.0), 1.0 mL/minute] R enantiomer t_r = 16.3 minutes, S enantiomer t_r = 17.9 minutes, 99% ee. ^{1}H NMR, ^{13}C NMR, IR, and HRMS were identical to that previously reported.

6.6. (*S*)-4-Hydroxy-4-Phenyl-2-Butanone (Organocatalyzed Aldol Reaction) (**383**)

The trichlorosilyl enolate (421.3 mg, 2.2 mmol, 1.1 equiv) was added quickly to a cold (–74°) solution of the S,S-catalyst (37.3 mg, 0.1 mmol, 0.05 equiv) in CH_2Cl_2 (2 mL). A solution of benzaldehyde (203 µL, 2.0 mmol) in CH_2Cl_2 (2 mL) was cooled to –78° and was added quickly via a short cannula to the first solution. During the addition the temperature rose to –67°. The reaction mixture was stirred at –75° for 2 hours, then was quickly poured into cold (0°) saturated aqueous $NaHCO_3$ solution and the resulting slurry was stirred for 15 minutes. The two-phase mixture was filtered through Celite, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2(3 × 50 mL). The organic phases were combined, dried over Na_2SO_4, filtered, and concentrated, and the residue was purified by column chromatography [SiO_2, pentane/Et_2O (1 : 1)] to give 321.6 mg (98%) of the title compound as a clear, colorless oil. TLC: R_f 0.16 [hexane/EtOAc

(3 : 1)]; $[\alpha]^{24}_{D}$ – 51.4° (c 1.47, CHCl$_3$); IR (neat) 3466, 3424, 2910, 1710, 1417, 1361, 1062, 701 cm^{-1};^{1}H NMR (500 MHz) δ 2.19 (s, 3H), 2.81 (A$\underline{B}$X, J_{AB} = 17.5 Hz, J_{BX} = 2.7 Hz,1H), 2.88 ($\underline{A}$BX, J_{AB} = 17.5 Hz, J_{AX} = 9.5 Hz, 1H), 3.30 (s, 1H), 5.15 (dd, J = 9.1, 3.3 Hz, 1H), 7.36–7.27 (m, 5H); ^{13}C NMR (126 MHz) δ 30.7, 51.6, 69.8, 125.6, 127.7, 128.5, 142.7, 209.1; MS (CI, M$^+$ 164 (19), 147 (30), 146 (18), 107 (100), 106 (21), 105(15), 79 (26), 59 (27). Anal. Calcd for C$_{10}$H$_{12}$O$_2$: C, 73.15; H, 7.37. Found: C, 72.97; H, 7.43.

6.7. (*R*)-4,4-Dimethyl-1-Hydroxyl-1-Phenyl-3-Pentanone (Silver-Catalyzed Aldol Reaction) (94)

A mixture of AgOTf (26.7 mg, 0.104 mmol) and (*R*)-BINAP (64.0 mg, 0.103 mmol) was dissolved in dry THF (3 mL) under argon atmosphere and with direct light excluded, and stirred at 20° for 10 minutes. To the resulting solution was added dropwise a THF solution (3 mL) of benzaldehyde (100 μL, 0.98 mmol), and then 3,3-dimethyl-1-tributylstannyl-2-butanone (428.1 mg, 1.10 mmol) was added over a period of 4 hours with a syringe pump at –20°. The mixture was stirred for 4 hours at this temperature and treated with MeOH (2 mL). After warming to room temperature, the mixture was treated with brine (2 mL) and solid KF (ca. 1 g). The resulting precipitate was removed by filtration and the filtrate was dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel to afford the title compound (161.7 mg, 78% yield) as a colorless oil: TLC R_f 0.22 [EtOAc/hexane (1 : 5)]; $[\alpha]^{30}_{D}$ + 61.5° (c 1.3, CHCl$_3$); IR (neat) 3625–3130, 3063, 3033, 2971, 2907, 2872, 1701, 1605, 1495, 1478, 1455, 1395, 1368, 1073, 1057, 1011, 984, 914, 878, 760, 747, 700 cm^{-1}; ^{1}H NMR(CDCl$_3$) δ 1.14 (s, 9H), 2.89 (d, J = 5.7 Hz, 2H), 3.59 (d, J = 3.0 Hz, 1H), 5.13 (m, 1H), 7.29–7.39 (m, 5H). The enantioselectivity was determined to be 95% ee by HPLC analysis using a chiral column (Chiralcel OD-H, hexane/*i*-PrOH (20 : 1), flow rate = 0.5 mL/minute) t_{minor} = 17.7 minutes, t_{major} = 20.2 minutes. The absolute configuration of the product was unknown and assigned to be R by analogy.

6.8. (*S*)-3-Hydroxy-4-Methyl-1-(3-Nitrophenyl)-1-Pentanone (Heterobimetallic-Catalyzed Aldol Reaction) (216)

To a stirred solution of potassium bis(trimethylsilyl)amide (KHMDS, 43 µL, 0.0216 mmol, 0.5 M in toluene) at 0°, was added a solution of water (48.0 µL, 0.048 mmol, 1.0 M in THF). The solution was stirred for 20 minutes at 0° and then catalyst (400 µL, 0.024 mmol, 0.06 M in THF) was added and the mixture was stirred at 0° for 30 minutes. The resulting pale yellow solution was then cooled to –20°, and 3-nitroacetophenone (175 µL, 1.5 mmol) was added. The solution was stirred for 20 minutes at this temperature, and then 2,2-dimethyl-3-phenylpropanal (49.9 µL, 0.3 mmol) was added and the reaction mixture was stirred for 28 hours at –20°. The mixture was quenched by addition of 1 N HCl (1 mL), and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography [SiO_2,Et_2O/hexane (1 : 12)] to give the title compound (72 mg, 85%, 89% ee); [☺]^{28}$_D$ – 40.8° (c 0.56, $CHCl_3$) (70% ee); IR (neat) 3541, 1688, 1535, 1351 cm^{-1};^{1}H NMR ($CDCl_3$) ≏ 1.01 (d, J = 7.0 Hz, 3H), 1.02 (d, J = 7.0 Hz, 3H), 1.82 (m, 1H), 2.85 (d, J = 3.5 Hz, 1H), 3.13 (d, J = 5.0 Hz, 1H), 3.14 (d, J = 7.0 Hz, 1H), 4.04 (m, 1H), 7.69 (m, 1H), 8.31–8.29 (m, 1H), 8.44–8.42 (m, 1H), 8.77 (m, 1H); ^{13}C NMR ($CDCl_3$) ≏ 17.7, 18.5, 33.2, 42.6, 72.3, 123.0, 127.6, 129.9, 133.6, 138.2, 148.5, 198.7; MS m/z 237 (M$^+$ – CH_3), 165 (M$^+$ – i – PrCHO), 150 (ArC ⸺O$^+$, base peak); HPLC [Chiralpak AS, 2-PrOH/hexane (1/9), flow 1.0 mL/minute] t_R = 16.1 and 18.4 minutes. Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.49; H, 6.51; N, 5.71.

6.9. (R)-3-Cyclohexyl-3-Hydroxy-1-Phenylpropan-1-One (Zinc-Catalyzed Aldol Reaction) (220)

Under an argon atmosphere, a solution of diethylzinc (1 M in hexane, 0.2 mL, 0.2 mmol) was added to the solution of ligand 11 (64 mg, 0.1 mmol) in THF (1 mL) at room temperature. After stirring for 30 minutes (evolution of ethane gas), the resulting solution was used as catalyst for the aldol reaction (ca 0.09 M solution). To a suspension of cyclohexylcarboxaldehyde (0.5 mmol), triphenylphosphine sulfide (22.1 mg, 0.075 mol), powdered 4 Å molecular sieves (100 mg, dried at 150° under vacuum overnight) and acetophenone (5 mmol) in THF (0.8 mL) was added the solution of catalyst (0.025 mmol) at 0°, and the mixture was stirred at 5° for 2 days. The resulting mixture was poured onto 1 N HCl and extracted with Et_2O. After normal workup, the crude product was purified by silica gel column chromatography using a mixture of petroleum ether and Et_2O. The title compound was obtained in 60% yield and 98% ee.

6.10. (*R*)-4-Hydroxy-5-Methylhexan-2-One (L-Proline-Catalyzed Aldol Reaction) (**85**)

L-Proline (0.03–0.04 mmol) was stirred in 1 mL of DMSO/acetone (4:1) for 15 minutes. Isobutyraldehyde (0.1 mmol) was added and the mixture was stirred for 4–24 hours. The mixture was treated with saturated aqueous NH_4Cl solution and extracted with EtOAc. The organic layer was dried ($MgSO_4$), filtered, and concentrated to give the title compound after column chromatography [hexanes/EtOAc (3:1)].

(88%) dr = 97:3, 99% ee

6.11. *S-tert*-Butyl (3*S*)-3-Hydroxy-3-Methoxycarbonyl-2-Butanethioate (Copper-Catalyzed Aldol) (**197**)

To a 10-mL round-bottom flask were added, in an inert atmosphere box, ligand (15 mg, 0.050 mmol) and $Cu(OTf)_2$ (18 mg, 0.050 mmol). The flask was charged with 1.5 mL of THF and the resulting suspension was stirred rapidly for 1 hour to give a clear dark green solution. The catalyst solution was cooled to –78° and methyl pyruvate (45 µL, 0.50 mmol) was added, followed by the silylketene thioacetal (153 µL, 0.60 mmol). The resulting solution was stirred at –78° until the pyruvate was completely consumed (0.5–24 hours), as determined by TLC (2.5% Et_2O/ CH_2Cl_2). The reaction mixture was then filtered through a 2–4 cm plug of silica gel with Et_2O (60 mL). Concentration of the solution gave the crude silyl ether, which was dissolved in THF (5 mL) and treated with 1 N HCl (1 mL). After being stirred at room temperature for 1–5 hours this solution was poured into a separatory funnel and diluted with Et_2O (20 mL) and H_2O (10 mL). After mixing, the aqueous layer was discarded and the ether layer was washed with saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL). The resulting ether layer was dried over Na_2SO_4, filtered, and concentrated to provide the title compound as a clear oil in 88% yield (112 mg, 0.48 mmol) after flash chromatography (10–20% EtOAc/hexanes). Enantiomeric excess was determined by HPLC [Chiralcel OD-H column (hexanes/2-propanol (99:1), flow = 0.5 mL/minute]: 2S,3S enantiomer t_r = 13.4 minutes, 2R,3R enantiomer t_r = 12.7 minutes, 99% ee; [☺]$^{rt}_D$ + 25.1° (*c* 5.2, $CHCl_3$); IR (CH_2Cl_2) 3534, 2967, 1738, 1678 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) ≙ 1.36 (s, 3H). 1.40 (s, 9H), 2.79 (d, *J* = 15.8 Hz, 1H), 3.02 (d, *J* = 15.8 Hz, 1H), 3.70 (br s, 1H), 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) ≙ 26.0, 29.6, 48.6, 52.7, 52.9, 175.7, 198.1; LRMS (CI/NH_3) (*m/z*): 235 (MH$^+$), 252 (M + NH_4)$^+$; HRMS (CI/ NH_3) (*m/z*): calcd for ($C_{10}H_{18}O_4S + NH_4$)$^+$, 252.1270; found, 252.1268.

(86%) I:II = 94:6, I 96% ee, II 18% ee

6.12. (2*S*,1′*R*)-2-(Hydroxyphenylmethyl)Cyclohexanone (Silver-Catalyzed Aldol Reaction) (245-247)

A mixture of AgOTf (12.9 mg, 0.050 mmol) and (*R*)-*p*-Tol-BINAP (37.3 mg, 0.055 mmol) was dissolved in dry THF (6 mL) under argon atmosphere and with direct light excluded, and stirred at 20° for 10 minutes. To the resulting solution were added dropwise MeOH (81 µL, 2.00 mmol), benzaldehyde (100 µL, 0.98 mmol), 1-trichloroacetoxycyclohexene (243.2 mg, 1.00 mmol), and trimethyltin methoxide (0.52 M in THF, 100 µL, 0.052 mmol) successively at –20°. After being stirred for 4 hours at this temperature and then for 12 hours at room temperature, the mixture was treated with MeOH (2 mL). The mixture was treated with brine (2 mL) and KF (ca. 1 g) at ambient temperature for 30 minutes. The resulting precipitate was removed by filtration using a glass filter funnel filled with Celite and silica gel. The filtrate was dried over Na_2SO_4 and concentrated in vacuo after filtration. The residual crude product was purified by column chromatography on silica gel to afford a mixture of aldol adducts **I** and **II** (172.8 mg, 86% yield) as a colorless oil. The anti/syn ratio was determined to be 94:6 by ^{1}H NMR analysis. The enantioselectivities of the anti and syn isomers were determined to be 96% ee and 18% ee, respectively, by HPLC [Chiralcel OD-H, hexane/*i*-PrOH (9:1), flow rate = 0.5 mL/ minutes]: 2S,1′S enantiomer $t_{syn–minor}$ = 14.2 minutes, 2R,1′R enantiomer $t_{syn–major}$ = 15.7 minutes, 2S,1′R enantiomer $t_{anti–major}$ = 17.4 minutes, 2R,1′S enantiomer $t_{anti–minor}$ = 24.2 minutes. Spectral data of the anti isomer (oil, 96% ee): TLC R_f 0.11 [EtOAc/hexane (1:5)]; [α]^{32}$_D$ + 19.7° (*c* 1.0, CHCl$_3$). IR (neat) 3700–3140, 2940, 2863, 1700, 1605, 1497, 1453, 1401, 1312, 1296, 1227, 1204, 1130, 1042, 702 cm^{-1}; ^{1}H NMR (300 MHz, CHCl$_3$) δ 1.22–1.37 (m, 1H), 1.47–1.81 (m, 4H), 2.05–2.13 (m, 1H), 2.31–2.42 (m, 1H), 2.45–(m, 1H), 2.57–2.67 (m, 1H), 3.96 (d, *J* = 2.8 Hz, 1H), 4.79 (dd, *J* = 2.8, 8.8 Hz, 1H), 7.28–7.40 (m, 5H,); ^{13}C NMR (75 MHz, CDCl$_3$) δ 24.5, 27.6, 30.6, 42.4, 57.3, 74.5, 126.9 (2 C), 127.7, 128.3 (2 C), 140.9, 215.3. Spectral data of the syn isomer (white solid, 18% ee): TLC R_f 0.13 [EtOAc/hexane (1:5)]; [α]^{33}$_D$ + 37.6° (*c* 1.0, CHCl$_3$); IR (KBr) 3600–3125, 2940, 2855, 1701, 1603, 1495, 1449, 1406, 1320, 1132, 1063, 986, 696 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.47–1.80 (m, 4H), 1.81–1.91 (m, 1H), 2.04–2.15 (m, 1H), 2.32–2.51 (m, 2H), 2.56–2.65 (m, 1H), 3.01 (d, *J* = 3.2 Hz, 1H), 5.40 (d, *J* = 2.4, 3.2 Hz, 1H), 7.25–7.37 (m, 5H); ^{13}C NMR (75 MHz, CDCl$_3$) 24.7, 25.9, 27.8, 42.5, 57.1, 70.5, 125.7 (2 C), 126.8, 128.0 (2 C), 141.5, 214.5.

(99%) I:II = 90:10,
I 91% ee, II 7% ee

6.13. (4*S*,5*R*)-4-(Methoxycarbonyl)-5-Phenyl-2-Oxazoline (Gold-Catalyzed Aldol Reaction) (253)

To a solution of ligand (37.5 mg, 0.055 mmol) in CH_2Cl_2 (6 mL) was added the gold complex (25.1 mg, 0.05 mmol). The reaction mixture was stirred for 10 minutes, and then to the resultant

solution were added sequentially methyl isocyanoacetate (0.45 mL, 5 mmol) and benzaldehyde (0.56 mL, 5.5 mmol). The reaction mixture was stirred for 18 hours at room temperature. The solvent was removed in vacuo, and the residue was dissolved in Et$_2$O (20 mL). Any precipitate formed was removed by filtration, and the solvent was removed in vacuo. The residue was bulb-to-bulb distilled (Kugelrohr), to give a 90:10 cis/trans mixture of the title compound in 99% combined yield, which was analyzed by GLC using a Chirasil-L-Val column and by ^{1}H NMR with the chiral shift reagent (+)-2,2,2-trifluoro-1-(9-anthryl)-ethyl alcohol.

(83%) dr = 89:11, 96% ee

6.14. (2*R*,3*S*)-2,3-Dihydroxy-2,3-*O*-Isopropylidene-1-(2-Methoxyphenyl)-5-Phenyl-1-Pentanone (Zinc-Catalyzed Aldol Reaction of a Hydroxyketone) (83)

Molecular sieves (3 Å, 200 mg, powder) in a test tube were activated prior to use under reduced pressure (ca. 0.7 kPa) at 160° for 3 hours. After cooling, a solution of (S,S)-ligand (1.54 mg, 0.0025 mmol) in THF (0.6 mL) was added under Ar. The mixture was cooled to –20°. To the mixture was added Et$_2$Zn (10 µL, 0.01 mmol, 1.0 M in hexanes) at –20°. After the mixture had been stirred for 10 minutes at –20°, a solution of hydroxyketone (182.8 mg, 1.1 mmol) in THF (1.1 mL) was added. Hydrocinnamaldehyde (1.0 mmol) was added, and the mixture was stirred at –20°. After 18 hours, the mixture was quenched with 1 M HCl (2 mL). The mixture was extracted with EtOAc and the combined organic layers were washed with saturated aqueous NaHCO$_3$ solution and brine, and dried over MgSO$_4$. Evaporation of solvent gave a crude mixture of the title compound. The diastereomeric ratio of the aldol product was determined by ^{1}H NMR of the crude product. After purification by silica gel flash column chromatography [hexanes/acetone (8:1-4:1)], the title compound was obtained (269.6 mg, 0.898 mmol, 90%, dr syn/anti = 89:11, 96% ee syn). Spectral data were collected after conversion into the acetonide. colorless oil; [$\circledcirc$]$^{21}_D$ – 39.4° (*c* 0.52, CH$_2$Cl$_2$) (92% ee). HPLC (for diol) [Daicel Chiralcel OD, *i*-PrOH/hexane (20/80), flow 1.0 mL/minute, detection at 254 nm]: t_R = 13.6 minutes (minor) and 15.9 minutes (major); IR (neat) 2936, 1685, 1598, 1247 cm^{-1}; ^{1}H NMR (CDCl$_3$) $\triangleq$ 1.34 (s, 3H), 1.49 (s, 3H), 1.87–1.99 2H), 2.65 (ddd, *J* = 6.9, 9.8 Hz, 14.1 Hz, 1H), 2.80 (ddd, *J* = 5.5, 10.0 Hz, 14.1 Hz, 1H), 3.82 (s, 3H), 4.21–4.23 (m, 1H), 4.95 (d, *J* = 6.7 Hz, 1H), 6.92 (brd, *J* = 8.3 Hz, 1H), 6.99 (ddd, *J* = 0.9, 7.5, 7.5 Hz, 1H), 7.10–7.12 (m, 2H), 7.14–7.17 (m, 1H), 7.22–7.25 (m, 2H), 7.42–7.48 (m, 2H); ^{13}C NMR (CDCl$_3$) $\triangleq$ 26.1, 27.5, 31.8, 35.6, 55.6, 77.7, 84.7, 110.3, 111.5, 120.8, 125.8, 127.5, 128.3, 128.3, 130.3, 133.3, 141.5, 157.8, 201.5. EIMS (*m/z*): 340 [M$^+$],135 [ArCO$^+$]; HRMS-FAB (*m/z*): [M + H]$^+$ calcd for C$_{21}$H$_{25}$O$_4$, 341.1753; found, 341.1743.

(62%) dr = 20:1, >99% ee

6.15. (3S,4S)-4-Cyclohexyl-3,4-Dihydroxybutan-2-One (L-Proline-Catalyzed Aldol Reaction of a Hydroxyketone) (257)

To a mixture of anhydrous DMSO (4 mL) and hydroxyacetone (1 mL) was added cyclohexanecarboxaldehyde (0.5 mmol) followed by L-proline (25 mol%), and the resulting homogeneous reaction mixture was stirred at room temperature for 60 hours. Then half-saturated NH$_4$Cl solution and EtOAc were added with vigorous stirring, the layers were separated, and the aqueous phase was extracted thoroughly with EtOAc. The combined organic phases were dried (MgSO$_4$), concentrated, and purified by flash column chromatography (silica gel, mixtures of hexanes/EtOAc) to afford the title compound. HPLC [Chiralpak AS, hexane/i-PrOH (85:15), flow rate = 1.0 mL/minute, $\bullet$ = 285 nm]: t_R = 6.22 minute; [$\circlearrowleft$]$_D$ + 83° (c 1, CHCl$_3$); IR (NaBr): 3445, 2922, 2351, 1730, 1640, 1456, 1373, 1253, 1045, 736 cm^{-1}; ^{1}H NMR: $\triangleq$ 0.99–1.37 (m, 1H), 1.58–1.84 (m, 1H), 1.92 (m, 1H), 2.31 (s, 4H), 3.52–3.60 (m, 2H), 4.24 (m, 1H); ^{13}C NMR: $\triangleq$ 25.8, 26.2, 72.4, 29.7, 39.7, 77.5, 78.3, 209.9; HRMS (m/z): [M + Na]$^+$ calcd for C$_{10}$H$_{18}$O$_3$, 209.1148; found, 209.1157.

6.16. (R)-6-(2-Hydroxy-4-Phenylbut-3-Enyl)-2,2-Dimethyl-[1,3]-Dioxin-4-One (Titanium-Catalyzed Aldol Reaction of a Dienolate) (139)

To a solution of the chiral Schiff base ligand (5.5 mM, 0.022 equiv) in toluene was added Ti(OPr–i)$_4$ (0.010 equiv). The orange solution was stirred for 1 hour at room temperature and a solution of 3,5-di-$tert$-butylsalicylic acid (0.020 equiv; 20 mM in toluene) was added. Stirring was continued for an additional hour at room temperature. The solvent was removed in vacuo and the orange solid was dissolved in Et$_2$O to give a 5.5 mM solution (relative to chiral ligand). After cooling the solution to 0°, 2,6-lutidine (0.40 equiv) was added to the solution, followed by the sequential addition of cinnamaldehyde (1.0 equiv) and the dienolate (1.5 equiv). After the reaction mixture was stirred for 4 hours at 0°, it was poured into water. The mixture was extracted with Et$_2$O. The organic extracts were dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was treated with 10% TFA in THF. After desilylation was complete the solution was partitioned between Et$_2$O and water. The organic layer was washed twice with a 5% aqueous NaHCO$_3$ solution and then with brine. The solution was dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by chromatography on silica gel [hexane/EtOAc (2:1)] afforded the aldol adduct. A portion of the aldol adduct was converted into the corresponding (S)-MTPA ester as follows. To a solution of the alcohol (0.010 mmol, 1 equiv) and DMAP (10 mg) in CH$_2$Cl$_2$ (1 mL) was added (R)-MTPA-Cl (0.011 mmol, 1.1 equiv). The MTPA ester was purified by chromatography on silica gel

[hexane/EtOAc (2:1)]. The enantiomeric excess of the product was determined by integration of the ^{1}H NMR (300 MHz, CDCl$_3$). The title compound was isolated (88%) as a white crystalline solid, mp 85–86°;[☺] + 6.2° (c 1.0, CHCl$_3$). IR (thin film) 3420, 1728 cm^{-1};^{1}H NMR (300 MHz, ☺1.68 (s, 3H), 1.68 (s, 3H), 2.24 (br s, 1H), 2.54 (m, 2H), 4.59 (q, J = 6.6 Hz, 1H), 5.36 (s, 1H), 6.20 (dd, J = 15.9, 6.6 Hz, 1H), 6.63 (d, J = 15.9 Hz, 1H), 7.38–7.27 (m, 5H); ^{13}C NMR (75 MHz, CHCl$_3$) ☺ 24.8, 25.3, 41.5, 69.7, 95.3, 106.7, 126.5, 128.1, 128.6, 130.2, 131.4, 136.0, 161.1, HRMS-FAB (m/z): [M + H]$^+$ calcd for C$_{16}$H$_{19}$O$_4$, 275.1283; found 275.1285. (S)-MTPA ester data: ^{1}H NMR(CHCl$_3$) vinyl resonances at ☺ 5.30 and 5.19 ppm in ratio of 24.4 : 1 (92% ee). crystallizing 90 mg of the title product from hexane/EtOAc (6 : 1), 55 mg (61% yield) of white needle crystals (mp 88–89°) were obtained which were found to be 99% ee by integration of the ^{1}H NMR of the (S)-MTPA ester.

6.17. (2S,3S)-Methyl-4-Benzyloxy-3-Hydroxy-2-Methylbutanoate (Iridium-Catalyzed Aldol Reaction) (286)

A flask was charged with [Ir(COD)Cl]$_2$ (20.0 mg, 0.030 mmol), the ligand (384) (35.0 mg, 0.089 mmol), and CH$_2$Cl$_2$ (850 µL). The resulting solution was stirred at room temperature. After 1 hour CH$_2$Cl$_2$ (644 µL) and diethylmethylsilane (207 µL, 1.43 mmol) were added to the mixture and the reaction mixture was stirred for an additional 30 minutes. Stock aldehyde/methyl acrylate solution (1.7 mL, 0.7 M in aldehyde and 0.84 M in acrylate, 1.19 mmol aldehyde, 1.43 mmol acrylate) was added dropwise. The vessel was then sealed and the contents stirred for 24 hours. The solvent was then evaporated from the reaction mixture and 1 mL each of THF, MeOH, and 4 N HCl were added. The solution was stirred at room temperature for an additional 30 minutes. The product was extracted with EtOAc (3 × 7 mL), and the combined organic layers were washed with saturated NaHCO$_3$ solution (2 × 20 mL), dried over MgSO$_4$, and filtered. The solvent was removed by rotary evaporation to give the crude product, which was purified via flash chromatography (10 : 1 then 8 : 1 hexanes:EtOAc) to yield 131 mg (0.6 mmol, 49% yield) of the title compound (94% ee, GC Alltech Chiraldex GTA column). IR (neat) 3462, 3032, 2950, 1961, 1869, 1731, 1203, 1101 cm^{-1};^{1}H NMR ☺ 1.22 (d, J = 7.2 Hz, 3H), 2.70 (m, 1H), 2.72 (d, J = 4.8 Hz, 1H), 3.48 (dd, J = 3.4, 7.0 Hz, 1H), 3.53 (dd, J = 1.9, 8 Hz, 1H), 3.67 (s, 3H), 4.07 (m, 1H), 4.55 (s, 2H), 7.34 (m, 5H); ^{13}C NMR: ☺ 12.2, 42.2, 52.0, 71.1, 71.8, 73.7, 128.0, 128.0, 128.7, 138.0, 175.8. Anal. Calcd for C$_{13}$H$_{18}$O$_4$: C, 65.53; H, 7.61. Found: C, 65.31; H, 7.51.

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Catalytic Enantioselective Aldol Addition Reactions

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7. Tabular Survey

The literature search for the tabular survey takes into account publications on catalytic asymmetric aldol addition reactions— meaning catalytic in the enantioinducing chiral species— until January 2003 and was effected using Beilstein and SciFinder. Given the complexity of the subject, different organizations of this tabular survey were conceivable. The finally adopted structure is based on the differentiation between direct aldol reactions and Mukaiyama-type additions. Each section is further subdivided into organocatalysis and metal-catalyzed reactions according to the nature of the metal used.

Within a subtable, entries are sorted by increasing number of carbon atoms in the nucleophilic component (not taking into consideration protective groups), followed by the increasing number of hydrogen atoms. For a given nucleophile, the same criteria were applied to the electrophiles and also for subtables within an entry.

Yields are given in parentheses, and (—) indicates that no information was given in the original report.

The following abbreviations were used in the tabular survey.

Ac	acetyl
acac	acetylacetonyl
atm	atmosphere
BBN	borabicyclo[3.3.1]nonyl
BINAP	2,2′-bis(diphenylphosphino)-1,1′-binaphthyl
BINOL	1,1′-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butyoxycarbonyl
Bu	butyl
Bz	benzoyl
cod	cyclooctadiene
de	diastereomeric excess
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
ee	enantiomeric excess
KHMDS	potassium hexamethyldisilazide
LLB	lithium lanthanum binaphthoxide complex

MOM   methoxymethyl
Ms   methanesulfonyl
MS   molecular sieves
Ns   4-nitrophenylsulfonyl
PCC   pyridinium chlorochromate
Ph   phenyl
Piv   pivaloyl
PMB   *p*-methoxybenzyl
PMP   *p*-methoxyphenyl
Py   pyridine
rac   racemic
rt   room temperature
sc   supercritical
Taddol   ♋, ♋, ♋′, ♋′-tetraaryl-1,3-dioxolan-4,5-
TBAF   tetra-*n*-butylammonium fluoride
TBAI   tetra-*n*-butylammonium iodide
TBDPS   *tert*-butyldiphenylsilyl
TBS   *tert*-butyldimethylsilyl
TES   triethylsilyl
Tf   trifluoromethanesulfonyl
TFA   trifluoroacetic acid
THF   tetrahydrofuran
TIPS   triisopropylsilyl
TMEDA *N,N,N,N*-tetramethylethylenediamine
TMS   trimethylsilyl
Tol   4-methylphenyl
Tr   trityl
Ts   4-methylbenzenesulfonyl

Table 1A. Silver-Catalyzed Mukaiyama-Type Aldol Additions

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Table 1B. Boron-Catalyzed Mukaiyama-Type Aldol Additions

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Table 1C. Copper-Catalyzed Mukaiyama-Type Aldol Additions

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Table 1D. Tin-Catalyzed Mukaiyama-Type Aldol Additions

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Table 1E. Titanium-Catalyzed Mukaiyama-Type Aldol Additions

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Table 1F. Other Metal-Catalyzed Mukaiyama-Type Aldol Additions

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Table 1G. Non-Metal-Catalyzed Mukaiyama-Type Aldol Additions

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Table 2A. Gold-Catalyzed Aldol Additions of Unmodified Nucleophiles

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Table 2B. Non-Gold Metal-Catalyzed Aldol Additions of Unmodified Nucleophiles

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Table 2C. Non-Metal-Catalyzed Aldol Additions of Unmodified Nucleophiles

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Table 3. Aldol Tandem Reactions

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Catalytic Enantioselective Aldol Addition Reactions

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