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# [Fe(diene)(CO)<sub>3</sub>] complexes as a guide in stereocontrol. Applications to the asymmetric synthesis of natural products

### Chuzo Iwata\* and Yoshiji Takemoto

Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamad-Oka, Suita, Osaka 565, Japan

The ability of iron tricarbonyl units to control the regio- and stereo-chemistry of nucleophilic addition to a neighbouring C=X (X = O, N) double bond and 1,5-nucleophilic substitution via a  $\eta^5$ -cation intermediate are described. We investigated the potential of acyclic [Fe(diene)(CO)<sub>3</sub>] complexes as chiral auxiliaries for the asymmetric synthesis of natural products. The asymmetric syntheses of (+) and (-)-frontalin, a hydroxyethylidene dipeptide isostere, a piperidine alkaloid (SS20846A), and N-Boc-O-Me-(2R,3S,5E,7E)-2-aminotetradeca-5,7-dien-3-ol were achieved by using the stereodirecting ability and mobility of the Fe(diene)(CO)<sub>3</sub> group. In addition, we developed an efficient method for synthesizing chiral dienal Fe(CO)<sub>3</sub> complexes, which are versatile starting materials for the asymmetric synthesis of the biologically active natural products described above.

### Introduction

Fe(CO)<sub>3</sub> complexes enjoy widespread use in organic synthesis<sup>1</sup> because they are synthetically equivalent to free dienes and yet are more stable and possess markedly different chemical properties. Complexation and decomplexation of Fe(diene)- $(CO)_3$  compounds is readily accomplished and provides high yields in most cases. In addition, unsymmetrically substituted dienes are prochiral and, therefore, the corresponding Fe(CO)<sub>3</sub> complexes are chiral. Considerable attention has been directed towards the efficient use of this temporarily introduced chirality to construct neighbouring stereogenic centres.<sup>2</sup> Indeed, this is the main subject of [Fe(CO)<sub>3</sub>] complex chemistry, along with research on a practical method for synthesizing chiral [Fe(diene)(CO)<sub>3</sub>] complexes.



Another fascinating aspect of these complexes is the mobility of the Fe(CO)<sub>3</sub> unit, which has received less attention than its stereodirecting ability. The Fe(CO)<sub>3</sub> moiety, which attaches to dienyl compounds by coordination, can move one carbon unit accompanied by isomerization of the diene *via* an  $\eta^5$ -cation intermediate (1,2-migration)<sup>3</sup> and can also migrate two carbon units on conjugated triene compounds (1,3-migration).<sup>4</sup> We recently became interested in using this mobility of Fe(CO)<sub>3</sub> compleses to construct contiguous stereogenic centres in acyclic natural products. This article reports some recent results obtained in our laboratory.



#### Use of the Fe(CO)<sub>3</sub> complex as a stereodirecting group

# (a) Nucleophilic addition of organometallics to [Fe(Z-dienone)(CO)<sub>3</sub>] complexes<sup>5</sup>

Over the past decade, several chiral auxiliaries have been developed for the highly stereocontrolled addition of organometallics to acyclic aldehydes and ketones.<sup>6</sup> Recent attention has been directed towards changing the diastereoselectivity of the reaction via a different transition state, which would enable different stereoisomers to be stereoselectively obtained starting from the same substrate.7 Fujisawa<sup>7a</sup> and Utimoto<sup>7b</sup> reported independently that such reversible stereoselectivity could be achieved by simply changing the metal species of the organometal. We became interested in the diastereoselective nucleophilic addition of organometallics to (Z)- and (E)-(diene)  $Fe(CO)_3$  complexes for a totally different approach to this goal. Neumann previously reported that reaction of the (E)-dienone  $Fe(CO)_3$  complex 4 with alkyllithiums gave exclusively the (1RS,2SR)-(E)-alcohol **3**.<sup>8</sup> Therefore, if nucleophilic addition to (Z)-dienone Fe(CO)<sub>3</sub> complex 1, which is a synthetic precursor of 4, proceeds stereoselectively to give (1SR, 2RS)-(Z)-alcohol 2 as a major product, we can obtain both diastereoisomers of the tertiary alcohol from the same starting material 1. To clarify this point, we first examined the nucleophilic 1,2-addition of several organometals to 1a-b.9 Representative results are summarized in Table 1, which demonstrates the differences between 1 and 4 and also shows high stereoselectivity in all of the entries. The addition of organolithium and organocuprate reagents to 1a-b occurred very quickly to give normal (Z)-alcohol complexes 2a-c as a sole product, respectively (runs 1, 3 and 4). However similar treatment of 1a with Et<sub>3</sub>Al produced 3b as a single product, which was also obtained by reacting 4 with Et<sub>3</sub>Al (run 6). Furthermore, using Grignard reagents (runs 2, 5 and 7), the related reactions gave unpredictable results; *i.e.* either 2b or **3a.c** was obtained exclusively depending on the nucleophile  $(R^2)$  of the reagent. This abnormal outcome may be due to the

Lewis acidity of the organometallic reagents, which promotes an initial Z to E isomerization of the starting materials 1a-b.<sup>10</sup>

We next planned the asymmetric syntheses of (+)- and (-)-frontalin starting from a chiral diene Fe(CO)<sub>3</sub> complex. Frontalin<sup>11,12</sup> is the aggregation pheromone of the southern pine beetle, *Dendorctonus frontalis*, and the western pine bark beetle, *Dendorctonus brevicomis*. Although frontalin contains two asymmetric centres, only the stereochemistry of C-1 needs to be specifically addressed in the planning stage of frotalin synthesis since the correct configuration of C-5 is dictated by that of C-1 during formation of the bicyclic ketal system. Thus, 2-methylhept-6-ene-1,2-diol **10**<sup>12</sup> would be a good target for the formal synthesis of frontalin (Scheme 1).

For this purpose, the chiral (Z)-dienone complex **6** was prepared from a known chiral pentadiene iron tricarbonyl complex  $5^{13}$  by the Friedel–Crafts reaction. As expected, the diastereoselective addition of MeLi to **6** gave the desired (Z)tertiary alcohol complex **7** in 86% yield. Sequential ozonolysis and hydride-reduction of the optically active tertiary dienol **8**,

Table 1 Diastereoselective addition of organometallics to (Z)-dienone complex 1a, b

Fe	(ÇO) <sub>3</sub>	Fe(CO) <sub>3</sub>					
// o		<sup>2-metal</sup> R <sup>2</sup> R <sup>1</sup>	+ // Fe(4	; \ CO)₃	R <sup>2</sup> OH		
	R'	ÓН					
1a R1 = Me		2a R <sup>1</sup> = Me, R <sup>2</sup> =	= Bu <b>3a</b> R	$R^1 = Me, R^2 = Bu$			
<b>b</b> R <sup>1</sup> = Bu		<b>b</b> R <sup>1</sup> = Me, R <sup>2</sup> =	allyl bR	<b>b</b> $R^1 = Me, R^2 = Et$			
		<b>c</b> R' = Bu, R <sup>2</sup> =	Me CR	' = Bu,	R² = Me		
			/F	e(CO) <sub>3</sub>	O Me		
	0.1			Yield	d (%)		
Dum	Substrate	D2 Matel	Product 2	2	2		
Kun	1	KMicial	Floduct 2				
1a	a	BuLi	2a	51	0		
2 <i>a</i>	а	(allyl)MgBr	2b	53	0		
3 <i>a</i>	a	(allyl) <sub>2</sub> CuMgBr·BF <sub>3</sub>	2ь	63	0		
<b>4</b> <i>a</i>	b	MeLi	2c	96	0		
5 <i>a</i>	а	BuMgBr	3a	0	97		
6 <sup>b</sup>	a	Et <sub>3</sub> Al	3b	0	81		
7a	L	MaMaDr	30	0	90		

<sup>a</sup> The reactions were carried out in tetrahydrofuran at -78 °C. <sup>b</sup> The reaction was carried out in benzene at room temp.

which was obtained from 7 in 98% yield by decomplexation with ammonium cerium(IV) nitrate (CAN), gave (R)-9 in 79% yield. Finally, the desired product (R)-10 was obtained from (R)-9 by treatment with potassium tert-butoxide (Bu<sup>t</sup>OK) in Me<sub>2</sub>SO. The specific rotation of (R)-10,  $[\alpha]_{D}^{25}$  +2.38 (c 0.405, CHCl<sub>3</sub>) [lit.,  ${}^{12b} [\alpha]_D^{25} - 2.6 (c \ 1.4, CHCl_3)$  for (S)-10], confirms the (R) assignment of the absolute configuration at C-2 in (R)-10. On the other hand, (E)-tertiary alcohol complex 11 was obtained in 88% yield as a single product by treatment of 6 with MeMgBr. Unfortunately, the same treatment of 11 with CAN gave the optically active tertiary dienol 12 in low yield. The yield of 12 increased to 100% by reacting 11 with H<sub>2</sub>O<sub>2</sub> in MeOH. Similarly, ozonolysis and hydride-reduction of 12 gave (S)-9, which was subjected to elimination with Bu'OK in  $Me_2SO$  to give the desired product (S)-10. The specific rotation of (S)-10,  $[\alpha]_D^{24} - 2.55$  (c 0.185, CHCl<sub>3</sub>), confirms the (S) assignment of the absolute configuration at C-2 in (S)-10. Thus, we achieved the formal synthesis of (+)- and (-)-frontalin from sole chiral (Z)-dienone complexes, with which we could determine the relative configuration of the nucleophilic addition adducts 2 and 3.

This high diastereoselectivity can be explained as follows (Fig. 1). Based on enhancement of the nuclear Overhauser effect (NOE) between C(3)–H and Me, the *s*-*cis* conformer **B** would be more stable than the *s*-*trans* conformer **A** due to severe steric hindrance between C(6)–H and Me in the latter case. Therefore, when non-Lewis acidic and strong nucleophiles such as allylmagnesium bromide and diallylcuprate reagent are used, nucleophiles attack from the opposite side of the bulky Fe(CO)<sub>3</sub> unit in the *s*-*cis* conformer **B** to stereoselectively yield **2**. On the other hand, when the Lewis acidic and weak nucleophiles such as alkylmagnesium halides and Et<sub>3</sub>Al are used, initial isomerization of the (Z)-dienone complex **1** to the (E)-dienone complex **4** occurs, and nucleophiles similarly attack from the opposite side of the bulky Fe(CO)<sub>3</sub> unit in the more stable *s*-*cis* conformer **C** to yield **3** stereoselectively.

# (b) Nucleophilic addition of organometallics to 1-azatriene Fe(CO)<sub>3</sub> complexes<sup>14</sup>

The diastereoselective addition of organometallic reagents to the C=N double bond of chiral imines offers an attractive approach for the asymmetric synthesis of chiral amines. Several stereoselective nucleophilic additions to chiral imines derived from 1-phenylethylamine<sup>15a</sup> and amino acid derivatives<sup>15b</sup> as chiral auxiliaries have been reported. In contrast to the 1,2-nucleophilic additions to the [Fe(dienone)(CO)<sub>3</sub>] complexes described above,<sup>5,8</sup> there are no reports on the stereoselectivity of the nucleophilic addition of organometallics to the 1-iminodiene complex **13**. In connection with our goal of developing a highly stereoselective reaction mediated by the [Fe(diene)(CO)<sub>3</sub>] complex, we investigated the dia-



Scheme 1 Reagents and conditions: i, ClCO(CH<sub>2</sub>)<sub>5</sub>Cl, AlCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 74%; ii, CH<sub>3</sub>Li, THF, -78 °C, 86%; iii, CAN, K<sub>2</sub>CO<sub>3</sub>, MeCN, -40 °C, 98%; iv, O<sub>3</sub>, MeOH, -78 °C; then Me<sub>2</sub>S, 89 and 65%; v, NaBH<sub>4</sub>, PrOH, 0 °C, 89 and 82%; vi, BuOK-Me<sub>2</sub>SO, 68 and 69%; vii, MeMgBr, THF, -78 to -30 °C, 88%; viii, H<sub>2</sub>O<sub>2</sub>, NaOH<sub>aq</sub>, MeOH, 100%

Racemic 1-iminodiene complexes 13a were prepared by condensing a known dienal complex<sup>17</sup> and benzylamine in the presence of 4 Å molecular sieves in benzene at room temperature. The results of the 1,2-nucleophilic addition of several organometallics to 13a are summarized in Table 2. Whereas the reaction of 13a with organolithium, Grignard reagent and diallylcuprate reagent<sup>18</sup> gave disappointing results in terms of chemical yield and diastereoselectivity (runs 1-4), treatment of 13a with butylcerium reagent,<sup>19a</sup> prepared in situ from butyllithium and cerium(III) chloride (CeCl<sub>3</sub>) at -78 °C, gave the alkylated secondary amine complex ( $\psi$ -endo 14a) not only in good yield (74%) but also with excellent diastereoselectivity (runs 5). Similar treatment of 13a with methyl- and phenyl-cerium reagents as nucleophiles provided the corresponding amine complexes 14c--d in good yields and with high stereoselectivity, respectively (runs 6, 7). Furthermore, organocerium reagents can be replaced by a mixed system<sup>19b</sup> prepared from the corresponding Grignard reagents (5 equiv.) and CeCl<sub>3</sub> (5 equiv.) without loss of stereoselectivity (runs 8-10). The stereochemistries of the secondary amines  $\psi$ -endo 14b and  $\psi$ exo 14b were predicted from  $R_f$  values according to Lillya's method,<sup>20</sup> which had been applied to secondary alcohols. Those of the other  $\psi$ -endo amine complexes 14a, c-d were estimated by mechanistic analogy of 14b (Fig. 2).

To definitely determine the relative configurations of the resulting secondary amines, we planned the asymmetric synthesis of hydroxyethylidene dipeptide isostere **15**. Hydroxy-



Fig. 1 Reaction mechanism of organometallic addition to (E)- and (Z)dienone complexes

ethylidene dipeptide isostere 15, first reported by Hanson and Lindberg, is an interesting dipeptide analogue which was designed to restrict conformational flexibility and to be susceptible to attack by enzyme nucleophiles such as cysteine thiol.<sup>21,22</sup>

A chiral imine complex 17 was synthesized from a known chiral pentadienal complex 16<sup>23</sup> (Scheme 2). Exposure of 17 to the diastereoselective nucleophilic addition of benzylcerium reagents gave the desired amine complex 18 as a single isomer in high yield. At this stage, we undertook the stereoselective intrroduction of the C(4)-hydroxy group of 15 by the intramolecular iodocarbamation of the methyl carbamate 19, which was obtained from 18 by methylcarbamoylation.<sup>16</sup> Treatment of 19 with iodine in the presence of potassium iodine in CH<sub>2</sub>Cl<sub>2</sub> induced decomplexation of the Fe(CO)<sub>3</sub> moiety and sequential iodocyclocarbamation to give the desired product 20a with high regio- and stereo-selectivity (trans 20a/cis 20b = 97/3). This inseparable mixture of 20a,b was converted to the pure transalcohol 21 as follows. Acetoxylation and subsequent hydrolysis of 20a,b gave the corresponding alcohols as a diastereomixture, from which trans-21 was separated as a single isomer by recrystallization from Pri<sub>2</sub>O. Birch reduction of 21 gave the monobenzyl compound 22 in 94% yield. Successive treatment of 22 by Jones oxidation and protection with di-tert-butyl dicarbonate gave the acid 23, which was converted to the desired hydroxyethylidene dipeptide isostere 15 in 78% yield by treatment with caesium carbonate in MeOH. The specific rotation of 15,  $[\alpha]_{D}^{25}$  -98.2 (c 0.185, MeOH) [*lit.*,<sup>21a</sup>  $[\alpha]_{D}^{25}$ -100

Table 2 Diastereoselective addition of organometallic reagents to 1-iminodiene-iron complex 13a



a Isolated yields.



Fig. 2 Preferred conformations of 13a and plausible reaction mechanism

# (c) Diastereoselective [4+2] cycloaddition of $[Fe(1-azatriene)(CO)_3]$ complex<sup>24</sup>

To establish a method for the diastereoselective synthesis of several heterocycles from secondary amines, the construction of a piperidine skeleton by [4+2]cycloaddition between iminedienophile Fe(CO)<sub>3</sub> complex and a diene were examined. The piperidine ring system, which is found in nojirimycin, porantheridine and swainsonine, has attracted much interest due to its varied and clinically useful biological actions.<sup>25</sup>

After unsuccessful experiments using the benzylidene imine 13a with Danishefsky's diene in various solvents in the presence of various Lewis acids, we found that when the pmethoxyphenylimine (PMP-imine) complex 13b was treated with Danishefsky's diene in the presence of a catalytic or stoichiometric amount of LiClO<sub>4</sub><sup>26</sup> at room temperature, [4+2]cycloaddition proceeded smoothly to give 24b diastereoselectively in good yields (Table 3, runs 1-3). This LiClO<sub>4</sub>-promoted cycloaddition requires a less-than-equivalent addition of LiClO<sub>4</sub> and the use of CH<sub>2</sub>Cl<sub>2</sub> for high stereoselectivity (runs 3–7). To investigate the electronic effect of the aromatic ring of 13b, cycloaddition of 13c and 13d with Danishefsky's diene was conducted under optical conditions, and resulted in a diastereoisomeric mixture of 24c/25c and 24d/ 25d with lower stereoselectivity (81 and 79% de) (runs 8, 9). Since a more electron-rich aldimine complex (13b: p-MeOC<sub>6</sub>H<sub>4</sub> > 13c:Ph > 13d: p-ClC<sub>6</sub>H<sub>4</sub>) tends to exhibit higher stereoselectivity, the PMP substituent of 13b holds the key to success in this diastereoselective [4+2]cycloaddition. This trend in stereoselectivity might be attributed to the coordinating ability of the aldimine nitrogen.

To completely establish the stereochemistry, an X-ray analysis of **24b** was carried out which revealed that **24b** is the  $\psi$ -*endo* diastereoisomer; *i.e.* it has an (6*RS*, 1'S*R*)-configuration.<sup>27</sup> Based on the stereochemistry of the major products, the reaction process can be described by analogy to the nucleophilic addition of organometals to **13a**.

To demonstrate the efficiency of this [4+2]cycloaddition using an [Fe(azatriene)(CO)<sub>3</sub>] complex, we attempted the first asymmetric synthesis of SS20846A, the absolute configuration of which had not yet been determined.<sup>28</sup> The chiral non-racemic cycloadduct (+)-24 was synthesized from the known chiral complex 26<sup>13</sup> in 5 steps (Scheme 3). Hydrolysis and chlorination of 26 was followed by reduction with (PPh<sub>3</sub>)<sub>2</sub>CuBH<sub>4</sub> to give (-)-27<sup>29a</sup> in an overall yield of 72%. The desired product (+)-24, obtained as a single isomer by the catalytic LiClO<sub>4</sub>mediated cycloaddition of the PMP-imine derivative of (-)-27 was reduced by L-Selectride to give the 1,4-reduction product (-)-28 in 80% yield. Subsequently, reduction by NaBH<sub>4</sub> in methanol in the presence of cerium chloride at 0 °C gave the desired (+)-29a as a major product (77%: 29a: 29b = 70:30). Finally, simultaneous deprotection of the iron-tricarbonyl and PMP-group with CAN gave SS20846A in 64% yield in an optically active form. The synthesized sample,  $[\alpha]_D^{24} - 15.2$  (*c* 0.53, CHCl<sub>3</sub>), was identical to the natural product based on a comparison of their spectral data, including the sign of  $[\alpha]_D$ , which indicates that natural SS20846A,  $[\alpha]_D^{20} - 15$  (*c* 1.00, CHCl<sub>3</sub>),<sup>28a</sup> has a (2*S*,4*S*)-configuration. This is the first successful synthesis and determination of the absolute configuration of SS20846A.

Table 3 Aza-Diels-Alder reaction of 1-azatriene- $Fe(CO)_3$  complexes 13 mediated by Lewis acids



**a** R = Bn; **b** R = p-MeOC<sub>6</sub>H<sub>4</sub>; **c** R = Ph; **d** R = p-ClC<sub>6</sub>H<sub>4</sub>

Run	Substrate	Reaction conditions	Yield <sup>a</sup> (%)	De (24/25)		
1	13b	AlCl <sub>3</sub> (1.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , $-78 \rightarrow -30$ °C, 6 h	59	63 <sup>b</sup>		
2		Me <sub>3</sub> SiOTf (1.1 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , $-78 \rightarrow -30$ °C, 8 h	77	74 <sup>6</sup>		
3		LiClO <sub>4</sub> ( $\overline{0.2}$ equiv.), CH <sub>2</sub> Cl <sub>2</sub> , room temp., 8 h	93	$> 98^{b}$		
4		LiClO <sub>4</sub> (0.2 equiv.), THF, room temp., 8 h	73	77 <sup>ь</sup>		
5		LiClO <sub>4</sub> (1.1 equiv.), $CH_2Cl_2$ , room temp., 3 h	80	> 98 <sup>b</sup>		
6		LiClO <sub>4</sub> (2.0 equiv.), $CH_2Cl_2$ , room temp., 3 h	87	81 <sup>b</sup>		
7		LiClO <sub>4</sub> (5 mol dm <sup>-3</sup> solution), ether, room temp., 1 h	89	86 <sup><i>b</i></sup>		
8	13c	LiCl <sub>4</sub> (0.2 equiv.), $CH_2Cl_2$ , room temp., 2 h	92	81 <sup>c</sup>		
9	13d	LiClO <sub>4</sub> (0.2 equiv.), CH <sub>2</sub> Cl <sub>2</sub> , room temp., 0.5 h	82	79¢		

 $^a$  Isolated yields of cycloadducts 24 and 25.  $^b$  Deduced from the 500 MHz  $^1\mathrm{H}$  NMR spectra of the diastereoisomeric mixture.  $^c$  Determined from the isolated yields.



Scheme 2 Reagents and conditions: i, BnNH<sub>2</sub>, 4 Å MS, benzene, quant.; ii, BnMgCl, CeCl<sub>3</sub>, THF, -30 °C, 90%; iii, ClCO<sub>2</sub>Me, K<sub>2</sub>CO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 98%; iv, I<sub>2</sub>, Kl, CH<sub>2</sub>Cl<sub>2</sub>, 90%; v, AgOAc, DMF, AcOH; 1.0 mol dm<sup>-3</sup> NaOH<sub>aq</sub>, MeOH, 94%; vi, Li, NH<sub>3</sub>, THF, -78 °C, 94%; vii, Jones reagent, acetone, 84%; viii, (Boc)<sub>2</sub>O, DMAP, Et<sub>3</sub>N, THF, 74%; ix, CsCO<sub>3</sub>, MeOH, 78%

# Use of the Fe(CO)<sub>3</sub> complex as a mobile chiral auxiliary<sup>30</sup>

Over the past decade,  $\eta^5$ -dienyl tricarbonyliron(+1) cation complexes have been proven to be extremely useful as intermediates in organic synthesis, and highly diastereoselective addition reactions to  $\eta^5$ -cation complexes are well documented.31 Although U-shaped cation complexes are conveniently generated from the corresponding alcohol or acetate complexes I, they react with various nucleophiles in a stereoselective but non-regioselective manner, giving rise to four possible regiochemical isomers II-V in ratios depending on the electronic and steric effects of the  $R^1$ ,  $R^2$  and  $R^3$  groups, even without considering the stereochemistry (Scheme 4). Two groups recently reported regio- and stereo-specific nucleophilic substitutions via S-shaped cation complexes, which open a route for (E,E)-1,1-disubstituted adducts IV.<sup>32</sup> However, it is still unclear how to predominantly obtain isomers II, III and V. In view of an iterative chiral induction<sup>3</sup> which uses the iron tricarbonyl moiety, the (E,E)- and (E,Z)-1,5-substituted adducts II and III are very promising intermediates, since 1,2-migration of the Fe(CO)<sub>3</sub> in pentadienyl cations should occur in these products.

In the course of our studies on the 1,2-migration of  $[Fe(diene)(CO)_3]$  complexes, we become interested in cyanohydrin derivatives **B** for two reasons: (i) nucleophiles would predominantly attack the C-5 position of the cation complex **C** due to an electronic effect of the nitrile group; and (ii) the resulting nitriles **D** could be easily converted into aldehydes, from which another cyanohydrin **B** could be prepared for the second manipulation (Scheme 5).

We first examined the effect of the leaving groups (LG) of the cyanohydrin derivatives **30a-d** and **31a-d** which include acetate, 3,5-dinitrobenzoate (DNB), 2,4,6-trichlorobenzoate (TCB) and diethylphosphonate (DEP) (Scheme 6). These cyanohydrins were synthesized from **27** as diastereoisomeric mixtures under standard conditions. From the reaction of **30a-d** and **31a-d** with acidic ion exchange-resin in MeOH, we found that (i) cyanophosphates **30d** and **31d**<sup>33</sup> are the most suitable substrates for the desired 1,5-substituted reaction, and (ii) the same products (*E*,*E*)-**32** are always obtained regardless of the C-2 chirality of the starting materials (**30** vs. **31**).

We next directed our attention toward the stereoselective preparation of both the (E,E)-isomer 32 and the (E,Z)-isomer 33 from the cyanophosphates 30d and 31d (Table 4). After many experiments with various solvents and Lewis acids, we found that treatment of a mixture of 30d/31d and several alcohols (10 equiv.) with a catalytic amount of BF<sub>3</sub> diethyl ether in THF at 0 °C led to the exclusive formation of the (E,Z)-isomers 33a–c in good yields with the notable exception of run 3, which only a small amount of 32c is detected (runs 1–3). When benzenethiol and trimethylsilyl azide are used as nucleophiles, the LiClO<sub>4</sub>-catalysed reaction of 30d/31d gave the desired products **33d** and **33e** in good yields (runs 4, 5), while **33a–c**, which bore an oxygen atom, were always obtained as a diastereoisomeric mixture (66–68% de) under these conditions. During these experiments, we found that trityl perchlorate effectively promoted the isomerization reaction of **33** to **32**, through which the stereoselective synthesis of the (*E*,*E*)-isomers **32a** and **32d** could be achieved accompanied by the introduction of oxygen and nitrogen heteroatoms (runs 6 and 7).

With these preliminary results in hand, we investigated the extension of this method to the iterative chiral induction shown in Scheme 7, and succeeded in constructing three contiguous stereogenic centres ( $32d \rightarrow 34 \rightarrow 35$ ) and in converting 35 into the racemic *N*-Boc-*O*-Me derivative 36 of (2R,3S,5E,7E)-2-aminotetradeca-5,7-dien-3-ol, isolated from a Pacific sponge.<sup>34</sup>

#### Synthesis of chiral acyclic [Fe(diene)(CO)<sub>3</sub>] complexes<sup>35</sup>

One problem in the asymmetric synthesis of natural products is how to develop a practical method for synthesizing chiral  $[Fe(dienal)(CO)_3]$  complexes such as **A** in Scheme 5, which are suitable for the iterative methodology.

The availability of chiral [Fe(diene)(CO)<sub>3</sub>] complexes as single enantiomers usually depends on the resolution method, such as recrystallization or column chromatographic separation of diastereoisomers.<sup>36</sup> Recently, however, more direct methods, involving auxiliary-directed<sup>37</sup> and reagent- controlled<sup>29,38</sup> stereoselective complexation, have been developed. Bifunctional meso-diene Fe(CO)<sub>3</sub> complexes would be ideal and useful starting materials for the asymmetric synthesis of natural products, since Fe(CO)<sub>3</sub> complexation of meso-dienes does not give diastereoisomers and two-directional functionalization<sup>39</sup> using the Fe(CO)<sub>3</sub> chirality is possible. Despite the synthetic versatility of meso complexes, there have been only two reports







Scheme 3 Reagents and conditions: i, KOH, EtOH, H<sub>2</sub>O, reflux, 89%; ii, (COCl)<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C; (PPh<sub>3</sub>)<sub>2</sub>CuBH<sub>4</sub>, Ph<sub>3</sub>P, acetone, 81%; iii, *p*-MeOC<sub>6</sub>H<sub>4</sub>NH<sub>2</sub>, 4 Å MS benzene; Danishefsky's diene, cat. LiClO<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 93%; iv, L-Selectride, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 80%; v, NaBH<sub>4</sub>, CeCl<sub>3</sub>·7H<sub>2</sub>O, MeOH, 0 °C, 77%; vi, CAN, MeCN, -30 °C, 64%

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Scheme 6 a: LG = Ac, b: LG = 3,5-DNB, c: LG = 2,4,6-TCB, d: LG = DEP

Table 4 The reaction of 30d and 31d with several nucleophiles under Lewis acidic conditions



Run	Nu (10 equiv.)	Reaction conditions	Product (Ratio)	Yield <sup>a</sup> [de] <sup>b</sup> (%)	
1	MeOH	BF <sub>3</sub> ·OEt <sub>2</sub> (0.1 equiv.), THF, 0 °C	33a	48 [>98]	
2	EtOH	BF <sub>3</sub> ·OEt <sub>2</sub> (0.1 equiv.), THF, 0 °C	33b	41 [>98]	
3	i-PrOH	BF <sub>3</sub> ·OEt <sub>2</sub> (0.1 equiv.), THF, 0 °C	<b>33c : 32c</b> (96 : 4) <sup>a</sup>	45 [>98]	
4	TMSN <sub>3</sub>	LiClO <sub>4</sub> (1.1 equiv.), ether, room temp.	33d	60 [>98]	
5	PhSH	LiClO <sub>4</sub> (1.1 equiv.), ether, room temp.	33e	39 [>98]	
6	MeOH	TrClO <sub>4</sub> (1.1 equiv.), THF, room temp.	32a	49 [>98]	
7	TMSN <sub>3</sub>	TrClO <sub>4</sub> (1.1 equiv.), THF, room temp.	32d	56 [>98]	

<sup>a</sup> Isolated yields of cycloadducts **32** and **33**. <sup>b</sup> Deduced from the 500 MHz <sup>1</sup>H NMR spectra of the diastereoisomeric mixture. <sup>c</sup> Determined from the isolated yields.

on the differentiation of enantiotopic functionality: biochemical reduction,<sup>29</sup> acetylation<sup>38a</sup> and allylboration using stoichiometric chiral reagents.<sup>38b</sup> This encouraged us to investigate a more efficient approach; *i.e.* the catalytic enantioselective alkylation of meso-( $\eta^4$ -hexa-2,4-dien-1,6-dial) iron tricarbonyl **37**<sup>38b</sup> with several dialkylzincs in the presence of chiral ligands **38a–c** (Table 5).<sup>40</sup> If one formyl group remained in the products **39**, further transformations and iterative reactions of **39** using the remained formyl moiety could be performed.

The reaction of **37** under the standard conditions reported by Soai *et al.* [Et<sub>2</sub>Zn (2.5 equiv.), ligand (0.1 equiv.), toluene,  $0 \,^{\circ}C$ ]<sup>40a</sup> gave the desired mono-alkylated products **39** and **40** in 60% yield (>90% de) together with the over-reaction products **41** and **42**. The enantiomeric excess of the major product **39** was determined to be 94% ee by the MTPA method using the corresponding diol complex. The additional chiral ligand and careful selection of the solvent used are important for good chemical yield and high stereoselectivity. The reaction of **37** in toluene in the presence of 0.5 equiv. of **38a** gave **39** in 78% yield (>98% ee). In addition, although the enantioselective alkylation of **37** with dimethylzinc gave disappointing results, the reaction with dipentylzinc, a bulkier nucleophile, gave **39** as the major product with high enantio- and diastereo-selectivity (76% yield, 95% de, >98% ee).

The most interesting result of asymmetric alkylation is the high group-selectivity; *i.e.* excellent differentiation of the two enantiotopic aldehyde groups of **37**. The origin of such high group-selectivity is not entirely clear but can be attributed to a plausible transition state assembly, as shown in Fig. 3. The chiral zinc metallocycle coordinates both the incoming aldehyde complex and dialkylzinc such that their transition state assumes a six-membered chair conformation. This coordinated alkylzinc, which would become polarized by this process, is stabilized by attractive dipole–dipole interaction with the Fe(CO)<sub>3</sub> group,<sup>41</sup> which would enable intramolecular delivery of the alkyl group in a controlled manner to give **39** regio- and stereo-selectively.

## Conclusion

In summary, several diastereoselective reactions have been developed using  $[Fe(diene)(CO)_3]$  complexes as a guide in stereocontrol. The stereodirecting power of the Fe(CO)<sub>3</sub> moiety is very strong in most cases, and the asymmetric synthesis of several biologically active natural products has been achieved. Furthermore, to overcome the disadvantage of the stoichiometric use of organometallic complexes, an iterative reaction system in which complete stereocontrol is always ensured by 1,2-migration of the Fe(CO)<sub>3</sub> group, has been developed. This method becomes more valuable with easy access to chiral dienal Fe(CO)<sub>3</sub> complexes. With the aim of the asymmetric synthesis of more complex natural products, further application of this iterative reaction system is under study in our laboratory.



Scheme 7 Reagents and conditions: i, DIBAL, 78%, 72%, 78%; ii, (EtO)<sub>2</sub>POCN, LiCN; iii, MeOH (10 equiv.), TrClO<sub>4</sub> (1.1 equiv.), THF, room temp., 52%; iv, EtSH (10 equiv.), TrClO<sub>4</sub> (1.1 equiv.), THF, room temp., 61%; v, H<sub>2</sub> (5 atm.), 61%; v, H<sub>2</sub> (5 atm.), 10% Pd/C, Boc<sub>2</sub>O, 71%; vi, C<sub>5</sub>H<sub>10</sub>PPh<sub>3</sub>, 73%; vii, H<sub>2</sub> (3 atm.), 10% Pd/C, 81%; viii, Me<sub>3</sub>NO, 80%

Table 5 Catalytic asymmetric alkylation of 37 with several dialkylzincs in the presence of 38a-c<sup>a</sup>



						Yiel	Yield <sup>c</sup> (%)				
Run	R	Ligand <b>38</b> (equiv.)	Solvent <sup>b</sup>	t/h	39	40	41	42	37	-Ee of <b>39</b> <sup>d</sup> (%)	
	1	Et	<b>a</b> (0.1)	T-H (4:1)	4	59	1	1	7	, 9	94
	2		<b>a</b> (0.5)	T-H (4:1)	1	78	3	3	2	9	>98
	3		<b>a</b> (0.5)	M-H (3:1)	5	53	4	e	e	28	>98
	4		<b>a</b> (0.5)	E-H (5:1)	3	29	2	<u></u> e	e	52	> 98
	5		<b>b</b> (0.5)	T-H (4:1)	2	59	3	3	1	29	96
	6		<b>c</b> (0.5)	T - H(4:1)	1	48	5	1	e	34	70
	7	$C_{5}H_{11}$	<b>a</b> (0.5)	Т	3	76	2	e	e	4	>98
	8		<b>a</b> (0.5)	M-T (3:1)	5	29	1	e	<u></u> e	39	>98
	9	Me	<b>a</b> (0.5)	T–H (4:1)	2	12	4	e	e	61	86

<sup>*a*</sup> Reactions were carried out at 0 °C in the presence of 2.5 equiv. of dialkylzinc. <sup>*b*</sup> T = toluene, H = hexane, M = methylene chloride, E = diethyl ether. <sup>*c*</sup> Isolated yield. <sup>*d*</sup> Determined by <sup>13</sup>F NMR analysis of the MTPA-derivatives of **39a–c**. <sup>*e*</sup> Not detected.



Fig. 3 Proposed transition state of the asymmetric alkylation of 37 with  $R_2 Z n$ 

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Chuzo Iwata was born in Shiga Prefecture, Japan in 1935 and received his BSc in 1958 from Osaka University, where he received his Doctor Degree of Pharmaceutical Sciences under the supervision of Professor Zen-ichi Horii in 1965. After postdoctoral work at Iowa State University at Ames with Professor D. E. Metzler from 1965 to 1967, he joined Osaka University in 1968 where he became a full professor in 1980. His research interests focus on the methodology of organic synthesis, especially enantioselective and diastereoselective synthesis aiming at biologically active natural products.

Yoshiji Takemoto was born in Osaka, Japan in 1960. He received his BSc from Osaka University in 1983 and completed his doctoral work on total synthesis of some spirovetivane-type phytoalexins under the direction of Professor C. Iwata from Osaka University in 1988. He then moved to the United States and worked as a postdoctoral researcher with Professor Robert A. Holton at the Florida State University at Tallahassee. After he served as a research associate at Sagami Chemical Research Center in Japan for a year, he joined the faculty of Osaka University in 1990, where he continues his research as a research assistant.

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