Arene Chromium Tricarbonyl Catalyzed Reactions in Organic Synthesis

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Arene chromium tricarbonyl complexes have been widely used in synthetic organic chemistry. In this article, catalytic activities of these complexes in hydrogenation and isomerization are discussed. Furthermore, their application to the syntheses of biologically significant compounds such as prostaglandins, sex pheromones and antitumor antibiotics is also reviewed.

1. Introduction

A growing interest in transition metal chemistry has led to a number of discoveries that have significantly influenced the course of synthetic organic chemistry among which are the reactions of arylene(tricarbonyl)chromium complexes [arene · $Cr(CO)_3$]. Coordination of the strongly electron withdrawing "$Cr(CO)_3$" group to an arene ring activates the ring to metallation and nucleophilic reaction and the benzylic position to metallation, making possible conversions not previously accessible. These reactions have been extensively studied and as a result have been widely used by synthetic organic chemists. Arene · $Cr(CO)_3$ complexes have also been found to be quite reactive as catalysts for a number of synthetic transformations. Since the stoichiometric reactions of arene · $Cr(CO)_3$ complexes have been widely reviewed,[1] this paper will focus on recent advances in the catalytic reactions of these complexes.[2]

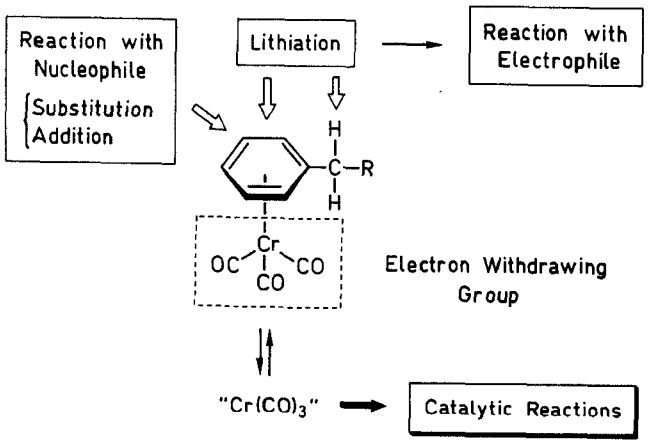


Figure 1

The arene · $Cr(CO)_3$ catalyzed hydrogenation of conjugated dienes was first reported in 1968,[3,4] but in spite of its unique selectivity, synthetic organic chemists had initially paid little attention to this catalyst. In recent years, however, many applications of this reaction to the synthesis of complex molecules have been reported. In addition, new, synthetically useful catalytic activities of arene · $Cr(CO)_3$ complexes have been found including the hydrogenation of alkynes and enones and the stereoselective isomerization of conjugated dienes. This review will attempt to demonstrate the scope of arene · $Cr(CO)_3$ catalyzed reactions with a view to practical synthesis of complex molecules and to briefly address some of the mechanistic issues which make these chromium catalysts useful reagents for synthetic chemistry.

2. Hydrogenation of Conjugated Dienes

2.1. Catalytic Activity and Reaction Mechanism

The regio- and stereospecific 1,4-hydrogenation of conjugated dienes to *Z*-olefins catalyzed by an arene · $Cr(CO)_3$ complex was first reported by two groups (Frankel et al. and Cais et al.)[3,4] in 1968, and their succeeding studies have elucidated the unique characteristics of this hydrogenation. Using methyl sorbate as a substrate, the catalytic activity of various arene · $Cr(CO)_3$ complexes was tested (Tables 1 and 2).[5–13] In all cases, methyl (*Z*)-3-hexenoate was obtained with excellent selectivity, but the reaction conditions required for the hydrogenation to proceed depended significantly on the arene ligand and solvent. However, when arene · $Mo(CO)_3$ or arene · $W(CO)_3$ complexes, similar group VIb metal complexes, were employed as the catalyst, regio- and stereoselectivities of products were low. Since other chromium complexes such as cycloheptatriene · $Cr(CO)_3$, tricarbo-

Table 1. Hydrogenation of Methyl Sorbate with Arene · $Cr(CO)_3$ Catalysts

Entry	Catalyst Arene (mol%)	Solvent	Temp. (°C)	Time (h)	H_2 (atm)	Yield (%)	Ref.
1	mesitylene (5)	cyclohexane	175	6	31	76	5
2	mesitylene (20)	cyclohexane	165	4.5	31	96	5
3	benzene (5)	cyclohexane	165	8	48	94	4
4	benzene (5)	CH_2Cl_2	165	0.5	48	94	4
5	benzene (5)	acetone	165	0.5	48	92	6
6	toluene (5)	cyclohexane	150	7	48	94	4
7	methyl benzoate (5)	cyclohexane	150	2	48	99	4
8	methyl benzoate (5)	acetone	100	16	70	94	13
9	phenanthrene (5)	cyclohexane	150	0.3	48	97	6
10	cycloheptatriene (5)	cyclohexane	120	1	31	98	5
11	anisole (1)	THF	120	5	60	100	9
12	1,4-dimethoxybenzene (1)	THF	120	5	60	100	9
13	1,2-dimethoxybenzene (1)	THF	90	5	60	100	9
14	1,2,3-trimethoxybenzene (1)	THF	80	5	60	100	9
15	methyl 4-methoxybenzoate (1)	THF	90	5	60	100	9

Table 2. Reaction Rate of Hydrogenation of Methyl Sorbate with Arene · $Cr(CO)_3$ Catalysts

Entry	Catalyst Arene (mol%)	Solvent	Temp. (°C)	H_2 (atm)	Induction Period (min)	$10^4\ k_{obs}$ (sec^{-1})	Ref.
1	benzene (5)	cyclohexane	165	48	285	40	6
2	benzene (5)	acetone	165	48	–	246	6
3	benzene (5)	benzene	175	48	150	0.63	6
4	phenanthrene (2)	decalin	120	4	14	34	8
5	phenanthrene (3)	THF	40	4	100	5	8
6	phenanthrene (3)	acetone	40	4	29	36	8
7	naphthalene (2)	decalin	120	4	1	96	8
8	naphthalene (3)	THF	40	4	8	39	8
9	naphthalene (3)	acetone	~27	4	4	96	8

nyltris(acetonitrile)chromium $[CH_3CN)_3Cr(CO)_3]$, and hexacarbonylchromium $[Cr(CO)_6]$ (under irradiation) have catalytic activity similar to the arene · $Cr(CO)_3$ complexes,[14-18] the active species of the hydrogenation reaction is believed to be the coordinatively unsaturated "$Cr(CO)_3$" fragment which is formed by dissociation of

Biographical Sketches

Mikiko Sodeoka joined Sagami Chemical Research Center in 1983, and moved to Hokkaido University in 1986. She obtained her Ph.D. from Chiba University. She spent 1990–1992 as a postdoctoral fellow at Harvard University with Professor E.J. Corey and Professor G.L. Verdine, and then moved to the University of Tokyo as an assistant professor.

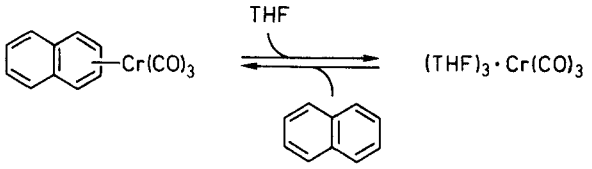
Masakatsu Shibasaki received his Ph.D. from the University of Tokyo in 1974 and did postgraduate studies with Professor E.J. Corey at Harvard University (1974–1977). He taught at Teikyo University (1977–1983), at Sagami Chemical Research Center (1983–1986), and at Hokkaido University (1986–1991), and moved to the University of Tokyo as a professor in 1991.

the arene ligand. The induction period (ca. 1 h) which is usually observed in this hdyrogenation is thought to be the time required to generate this active species. These facts suggest that those chromium complexes with readily dissociable arene ligands will have high catalytic activity.

As can be seen in Table 2, the chromium tricarbonyl complexes of polyaromatic compounds such as naphthalene, anthracene, and phenanthrene show high catalytic activity. Interestingly, X-ray structures of these complexes indicate disparity in Cr–C(ring) distances (for example in the naphthalene complex, the $Cr-C_{1,2,3,4}$ bond distances are ca. 2.20 Å, whereas the $Cr-C_{5,6}$ bond distances are ca. 2.32 Å).[8] It has been suggested that the high catalytic activity of these complexes is a result of this difference in bond lengths; the longer bond should be displaced more easily by the incoming diene ligand or solvent facilitating dissociation of the "$Cr(CO)_3$" moiety. In the case of benzene derivatives, it again seems reasonable to correlate disparity in Cr–C(ring) distances with catalytic activity. Chromium tricarbonyl complexes of the unsymmetrically substituted benzene derivatives have high catalytic activity. For example 1,2,3-trimethoxybenzene which shows noticeable disparity in the Cr–C (ring) bond distances in the X-ray molecular structure[7] has higher catalytic activity than 1,4-dimethoxybenzene (Table 1, entry 12 vs. 14).

In addition to the complexes shown in Tables 1 and 2, the catalytic activity of other arene · $Cr(CO)_3$ complexes has been screened. Among them, the chromium tricarbonyl complexes of polystyrene and poly(vinyl benzoate) are interesting. In contrast to the aforementioned catalysts, all of which are homogeneous, these are heterogeneous catalysts which can be recycled.[19,20]

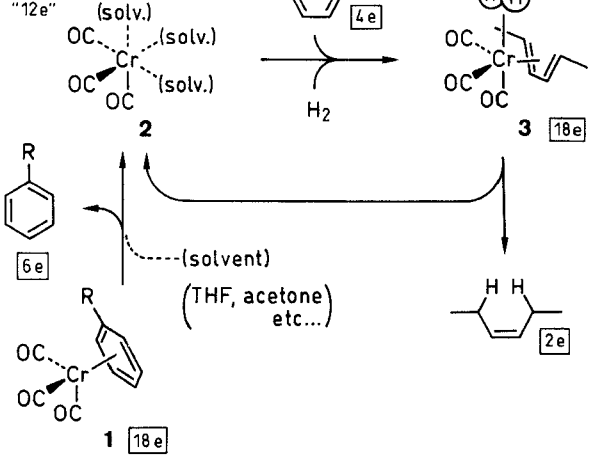
As mentioned, another factor which significantly affects the reaction rate is solvent. Benzene, which can itself coordinate to the "$Cr(CO)_3$" and suppress generation of the active species, slows the reaction, but those solvents which coordinate weakly to the $Cr(CO)_3$ moiety such as acetone and tetrahydrofuran (THF) enhance dissociation of the arene ligand and accelerate the reaction. In fact, by employing the highly reactive naphthalene complex with THF as the solvent, the hydrogenation of methyl sorbate proceeds at ambient temperature (30 °C) and atmospheric pressure (H_2, 1 atm). In these weakly coordinative solvents the arene ligand is believed to be displaced by solvent molecules resulting in the formation of a second labile complex which has high catalytic activity. This is supported by the fact that rapid formation of tricarbonyltris(tetrahydrofuran)chromium [$(THF)_3Cr(CO)_3$] from the naphthalene · $Cr(CO)_3$ complex in THF at room temprature has been observed by IR experiments (Scheme 1).[12] Dichloromethane has also been reported to be as effective a solvent as acetone (Table 1, entries 4 and 5); however, our experiments using highly purified dichloromethane indicate that the reaction rate is considerably slower than previously noted. Moreover, addition of 1% methanol to dichloromethane resulted in acceleration of the reaction suggesting that methanol, which frequently contaminates dichloromethane, can accelerate the reaction by its coordination to "$Cr(CO)_3$". Acetonitrile is also a good solvent for this reaction; however, it is less effective than acetone and THF due to its stronger affinity for "$Cr(CO)_3$".



Scheme 1

Generally, arene · $Cr(CO)_3$ complexes are stable in crystalline form and can be handled in air, but they are quite unstable in solution. The $(THF)_3Cr(CO)_3$ complex is readily oxidized by trace amounts of oxygen in solvent resulting in the formation of Cr_2O_3, and it can be converted to other species such as $(THF)_2Cr(CO)_4$ via disproportionation. In order to avoid side reactions at high temperature in practical synthetic applications, it is recommended that naphthalene · $Cr(CO)$[21,22] is used as the catalyst and rigorously degassed acetone or THF as the solvent. Commercially available arene · $Cr(CO)_3$ complexes are as follows: anisole, benzene, mesitylene, *N*-methylaniline, methyl benzoate, and 1,2,3,4-tetrahydronaphthalene.

The extremely high regio- and stereoselectivities of this hydrogenation have been explained by a unique reaction mechanism. Using various diene hydrocarbons[23–26] and unsaturated fatty acids,[27–33] the influence of the stereochemistry of the conjugated diene on the reaction rate was studied. The reactivity was found to decrease in order of *E,E* > *E,Z* > > *Z,Z* suggesting that coordination of the diene as a bidentate ligand in the *s-cis* conformation is an important factor. Moreover, reduction of methyl sorbate with deuterium (D_2) yielded methyl (*Z*)-(2,5-$^2H_2$)-3-hexenoate, excluding the possibility of a 1,2-hydrogen addition–isomerization pathway.

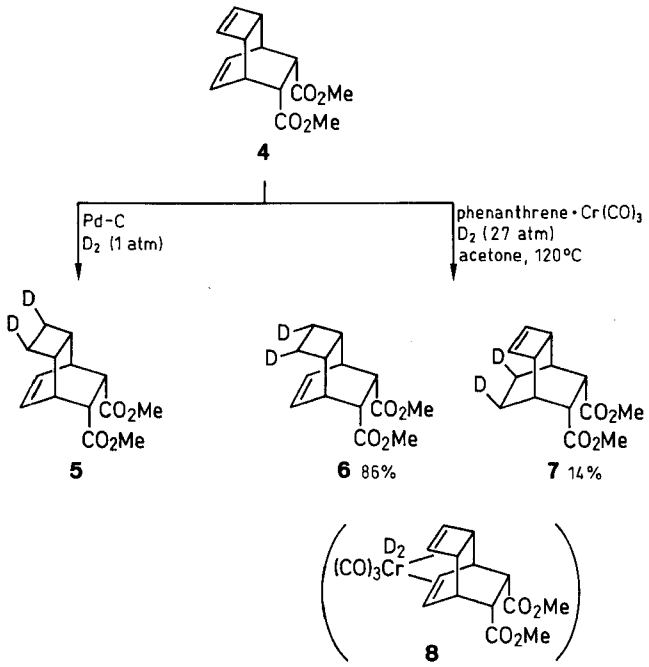


Scheme 2

The proposed reaction mechanism is shown in Scheme 2. As described above, the arene ligand (6-electron donor) first dissociates from the stable 18-electron arene · $Cr(CO)_3$ complex **1** to give a coordinatively unsaturated fragment, "$Cr(CO)_3$" (**2**). Because the solvent coordinates weakly, this fragment **2** can formally be regarded as a

"12-electron" complex having three vacant coordination sites. A conjugated diene then coordinates to the complex **2** in the *s-cis* conformation donating four electrons and filling two coordination sites. The remaining site is occupied by hydrogen to form the stable intermediate **3** with an 18-electron configuration. In the final step, the two hydrogen atoms on chromium are added in a 1,4-fashion to the conjugated diene yielding a (*Z*)-olefin. Since this simple olefin has no affinity for the chromium tricarbonyl, it dissociates to regenerate the active species **2**. The strong affinity of the "$Cr(CO)_3$" fragment for the bidentate ligand distinguishes this catalyst from other transition metal catalysts which can catalyze the hydrogenation and isomerization of isolated olefins.

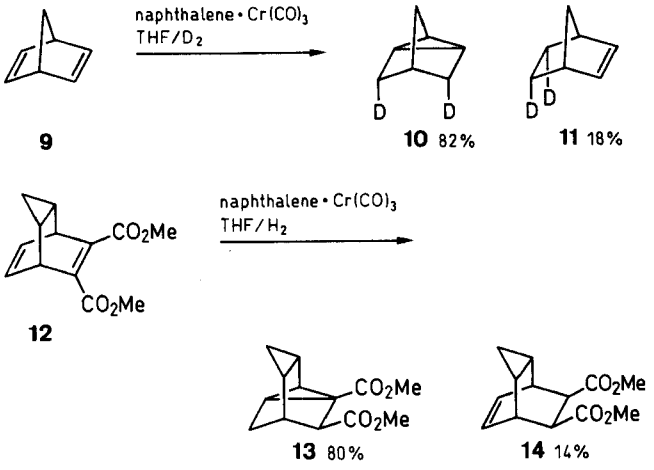
As shown in Scheme 3, hydrogenations of nonconjugated olefins catalyzed by arene · $Cr(CO)_3$ complexes have been reported, but the systems are notable. The arene · $Cr(CO)_3$ catalyzed reaction of **4** with deuterium (D_2) gave the *endo*-adducts **6** and **7**.[34] In contrast, the palladium on charcoal (Pd–C) catalyzed hydrogenation gave only the *exo*-adduct **5**, suggesting that the 1,2-deuteration catalyzed by the arene · $Cr(CO)_3$ complex proceeded via the η^4-diene intermediate **8**.



Scheme 3

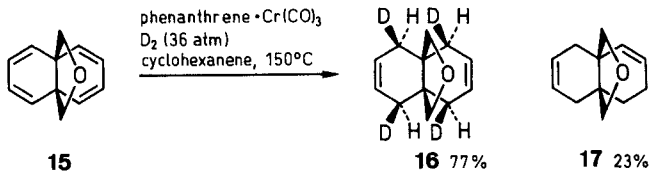
In the case of norbornadiene **9**, 1,5-hydrogen addition and C–C-bond formation occurred to afford primary nortricyclene **10** and a small amount of **11**.[35] Again the substrate can act as a bidentate ligand, and this reaction is considered to proceed via coordination of the two sterically fixed double bonds to chromium. As can be seen, this reductive cyclization provides a synthetically useful route to nortricyclene derivatives (Scheme 4).

Another interesting example has been reported by Cais et al. (Scheme 5)[36] in which the naphthalene · $Cr(CO)_3$ catalyzed reduction of **15** with D_2 gave **16** stereoselectively. They suggested that this selectivity was due to the interaction of the ether oxygen with the chromium



Scheme 4

tricarbonyl complex. Recently, Uemura et al. reported the stereoselective synthesis of arene · $Cr(CO)_3$ complexes and it appears that the selectivity achieved was due to the directing effect of the hydroxyl group in the substrate.[37] This affinity of "$Cr(CO)_3$" for oxygen is quite interesting and promises to be very useful in the synthesis of highly functionalized molecules.



Scheme 5

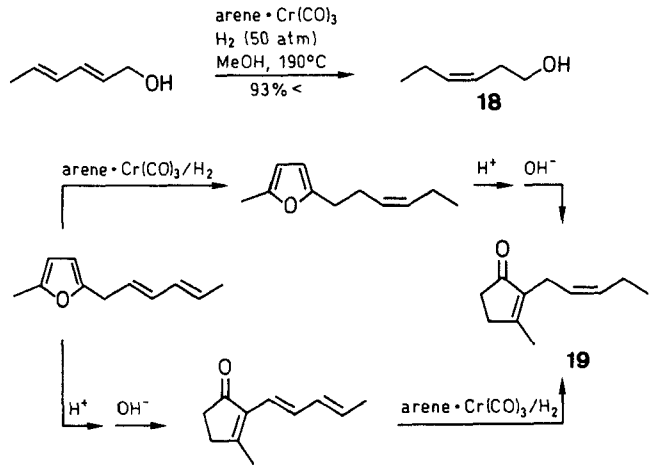
2.2. Application to Organic Synthesis

The 1,4-hydrogenation of conjugated dienes has been applied to the syntheses of various biologically active compounds. In all of the following examples, excellent regio- and stereoselectivity have been achieved in the presence of a variety of functional groups.

2.2.1. Stereocontrol of Acyclic Olefins

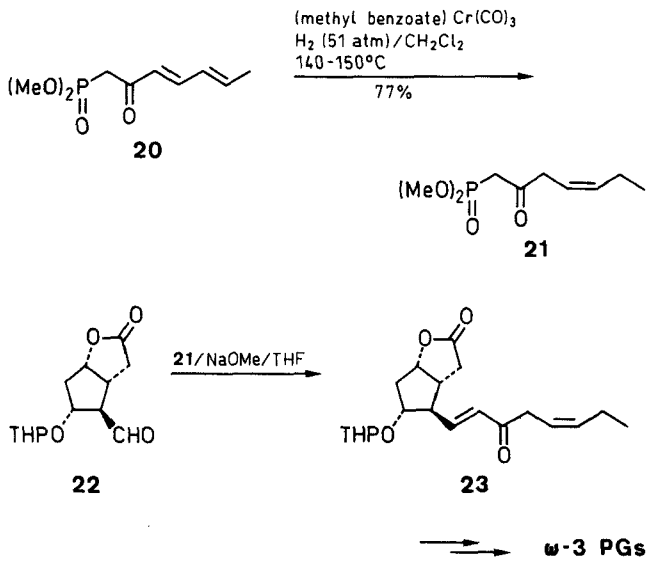
There are several well-known methods for the construction of (*Z*)-olefins including the hydrogenation of alkynes with the Lindlar catalyst and the Wittig reaction; however, in some cases formation of a significant amount of the (*E*)-olefin is observed. Since the separation of (*Z*)- and (*E*)-olefin isomers is often difficult, the control of olefin geometry can be a critical point in a synthesis.

The arene · $Cr(CO)_3$ catalyzed hydrogenation of acyclic dienes to (*Z*)-olefins was first applied to the preparation of biologically active compounds with the synthesis of (*Z*)-3-hexen-1-ol **(18)** and *cis*-jasmone **19**, key components in the characteristic odors of tea leaves and jasmine oil, respectively. Since our sense of smell is very keen, the regio- and stereocontrol of double bond geometry is quite important in the synthesis of fragrant compounds; a trace amount of the undesired stereoisomer can affect the scent drastically (Scheme 6).[38,39]

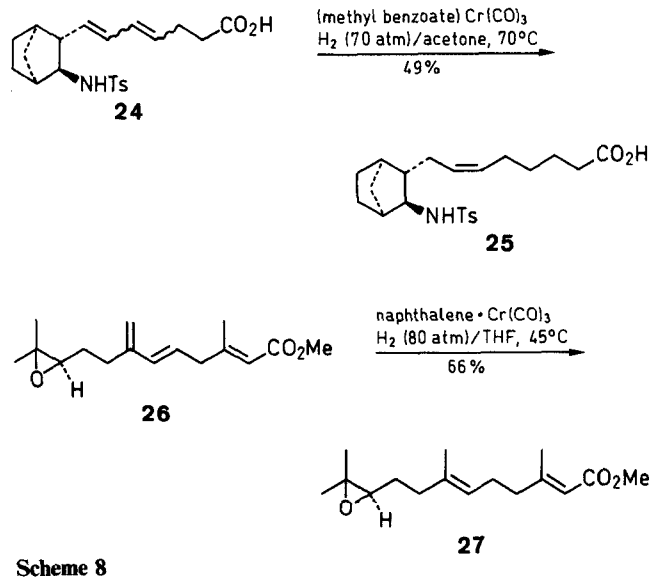


Scheme 6

Corey et al. employed the arene · $Cr(CO)_3$ catalyzed 1,4-hydrogenation in the preparation of the nonconjugated (*Z*)-2-oxo-4-heptenylphosphonate **21**, a key reagent in the synthesis of ω-3 prostaglandins (Scheme 7).[40]



Scheme 7

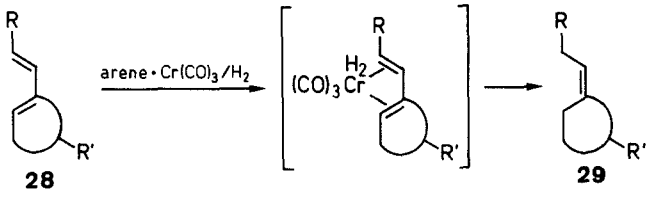


Scheme 8

Yamamoto et al also used this reaction in the final step of their synthesis of thromboxane receptor antagonist **25** and their synthesis of C_{16}-juvenile hormone **27** (Scheme 8).[41,42] While these examples illustrate the elegant application of this reaction to the synthesis of natural products, they also demonstrate that the arene · $Cr(CO)_3$ catalyzed hydrogenation of dienes is not affected by the presence of other functional groups such as nonconjugated olefins, esters, ketones, phosphonate esters, carboxylic acids, sulfonamides and epoxides.

2.2.2. Stereocontrol of Exocyclic Olefins

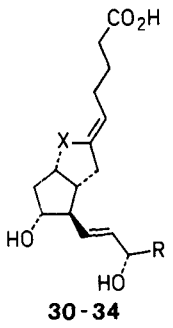
The stereocontrolled construction of exocyclic olefins is an interesting challenge in synthetic chemistry, and it was the thought of these authors that the arene · $Cr(CO)_3$ catalyzed 1,4-hydrogenation reaction described in Chapter 2.1. should be a powerful, general solution to this problem. Since the arene · $Cr(CO)_3$ catalyzed hydrogenation of conjugated dienes proceeds via a conformationally fixed intermediate, the 1,4-hydrogenation of diene **28** should be expected to give **29** with complete regio- and stereocontrol, regardless of its thermodynamic stability (Scheme 9). The following results demonstrate that this approach is quite efficient for the stereocontrolled syntheses of biologically significant molecules.



Scheme 9

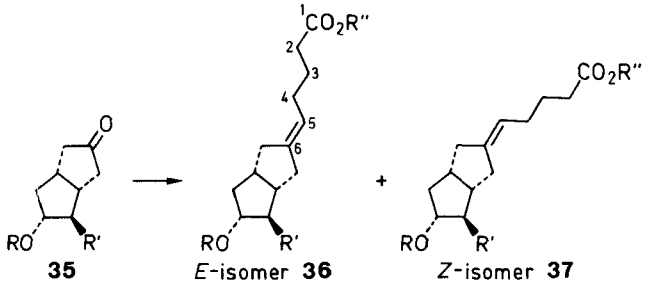
The compound which first made us aware of the difficulty of obtaining exocyclic olefins in a stereocontrolled fashion was carbacyclin **31**. Carbacyclin **31** is one of the potent, chemically stable analogs of prostacyclin (PGI_2, **30**), a naturally occurring bioregulator having remarkable platelet aggregation-inhibiting activity. A large number of ω-chain derivatives of **31** had been synthesized when this research began, and some of them (e. g. **33**) were being studied in clinical trials as therapeutic agents for cardiovascular and circulatory diseases. Although many groups had succeeded in the synthesis of these important compounds, most of them had used the Wittig reaction to construct the crucial exocyclic olefin with little control of its stereochemistry (**35** → **36** + **37**). The formation of a considerable amount of the pharmacologically much less active (5*Z*)-isomer **37** and the extremely troublesome separation of the olefin stereoisomers were unavoidable problems that made the industrial scale preparation of the carbacyclin analogs fairly difficult. We began our research with the aim of developing a practical synthetic route to these compounds which involved the construction of the exocyclic olefin with complete stereocontrol.

Our approach to this problem is outlined in Scheme 11. As described in section 2.1., the arene · $Cr(CO)_3$ catalyzed 1,4-hydrogenation requires that the diene adopt the *s-cis*

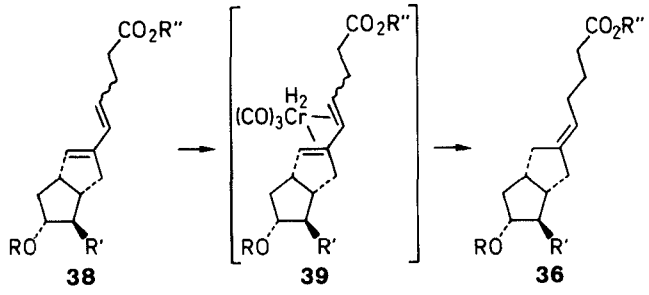


30-34

	X	R
30 prostacyclin (PGI_2)	O	
31 carbacyclin	CH_2	
32 OP-41483	CH_2	
33 iloprost	CH_2	
34 CS-570	CH_2	

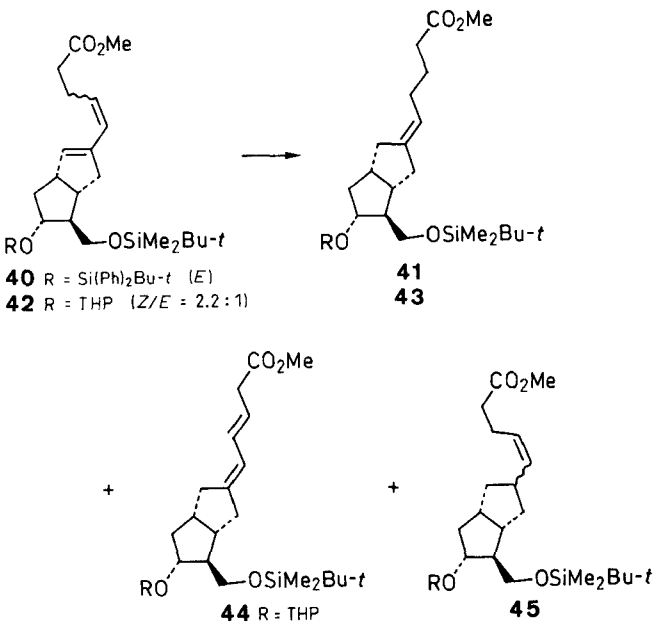


Scheme 10



Scheme 11

conformation, and the diene stereochemistry that is best able to adopt this conformation is *E*, *E*. With this in mind, the conjugated diene with an (*E*)-disubstituted olefin **40** was prepared stereospecifically in ca. 27% overall yield using the well-known Corey lactone and an intramolecular thermal ene reaction in the key step.[43] Hydrogenation of this diene **40** in acetonitrile (70 kg/cm^2 of H_2 pressure, 130°C, 12 h) using (methyl benzoate)$Cr(CO)_3$ as the catalyst gave the desired (*E*)-exocyclic olefin **41** stereospecifically in 66% yield along with the starting diene **40** (21%) (Scheme 12, Table 3, entry 1). No other product was observed. When acetone was used as a solvent, **41** was obtained in quantitative yield (entry 2).[44,45]



Scheme 12

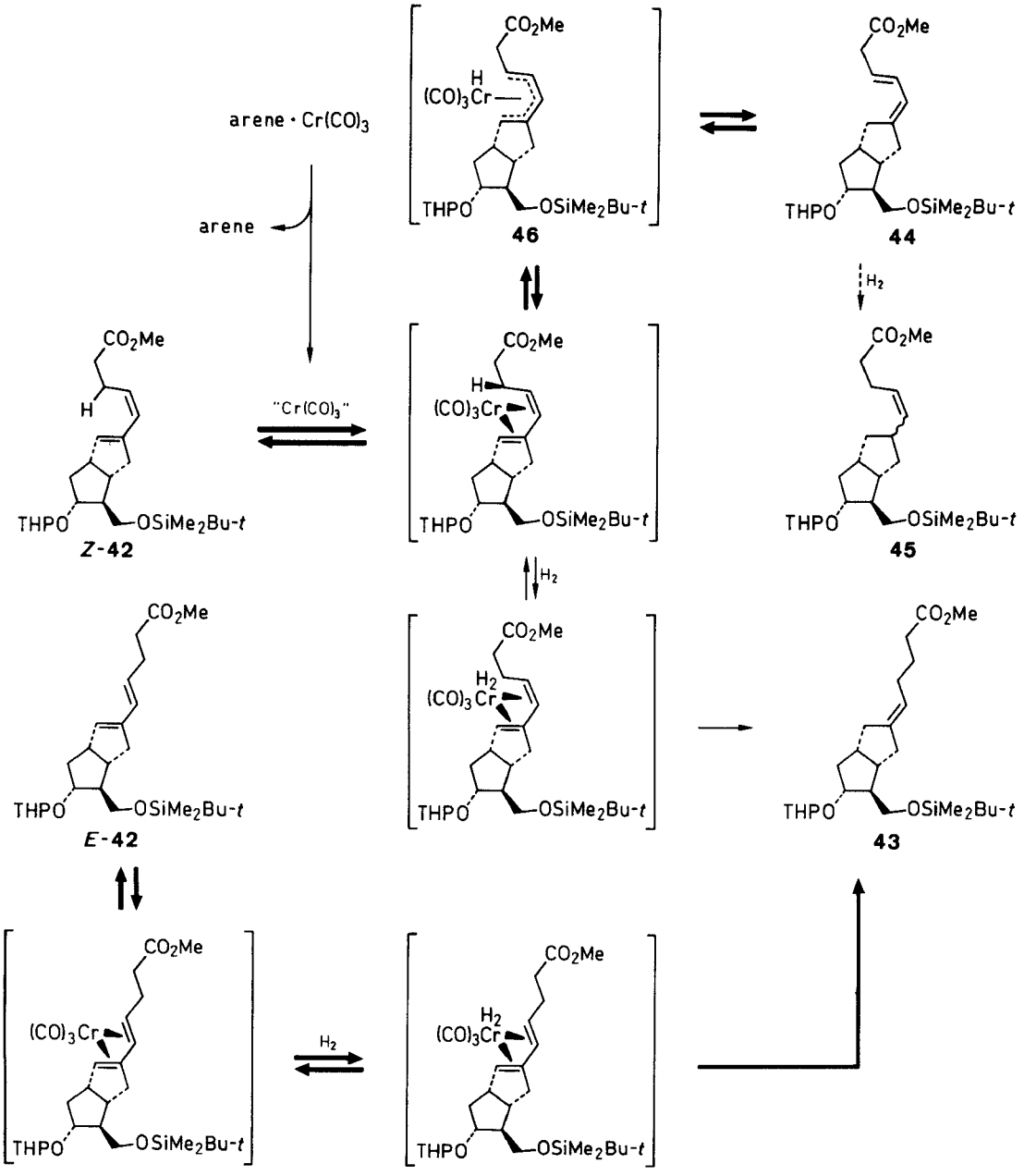
We then turned our attention to the (*Z*)-rich 1,3-diene **42** (*Z*/*E* = 2.2:1), which was also prepared from the Corey lactone with a better overall yield of 69%. Here an intramolecular aldol condensation was used in the key step.[43,46] Hydrogenation of the (*Z*)-rich diene **42** in acetone (70 kg/cm^2 of H_2 pressure, 120°C, 12 h) using (methyl benzoate)$Cr(CO)_3$ as the catalyst gave the desired (*E*)-exocyclic olefin **43** in nearly quantitative yield (entry 3).[45,47] No (*Z*)-isomer was detected. Careful GLC analysis of the hydrogenated product, however, indicated contamination by a trace amount of the regioisomer **45** (< 2%). This was readily separated from the (*E*)-olefin after removal of *tert*-butyldimethylsilyl group. Furthermore, when the naphthalene · $Cr(CO)_3$ complex was used as the catalyst in THF, the hydrogenation proceeded smoothly at 45°C to give **43** stereospecifically in 95% yield (entry 4). Again no (*Z*)-isomer was detected. The exocyclic olefins **41** and **43** were converted to carbacyclin analogs (**31**–**34**) efficiently. Thus, the stereospecific synthesis of an (*E*)-trisubstituted olefin as found in carbacyclin **31** was realized for the first time, and the arene · $Cr(CO)_3$ catalyzed 1,4-hydrogenation of dienes was shown to be a successful approach to the stereocontrolled synthesis of exocyclic olefins.

In contrast to the aforementioned results, hydrogenation of **42** in acetonitrile (70 kg/cm^2 of H_2 pressure, 130°C, 12 h) using (methyl benzoate)$Cr(CO)_3$ as the catalyst gave two main products (entry 5). One was the desired 1,4-reduction product **43** (28%), and the second was the stereochemically homogeneous (3*E*,5*E*, PG numbering) exocyclic conjugated diene **44** (27%), formed presumably via a 1,5-hydrogen shift. In addition, the recovered starting material (37%) contained only the 4*Z*-stereoisomer. When a higher hydrogen pressure (130 kg/cm^2) was used, **44** was not detected (entry 6), but when the less labile toluene · $Cr(CO)_3$ complex was used as the catalyst in acetone, a small amount of **44** (4%) was obtained (entry 7). Two control experiments indicated that the exocyclic conjugated diene **44** was formed in direct

Table 3. Hydrogenation of the Dienes

Entry	Diene	Catalyst[a,b]	Solvent	Pressure (kg/cm^2)	Temp. (°C)	Time (h)	Yield (%) **41** or **43**	**44**	**45**	Recovery **40** or **42** (*Z*/*E*)	Ref.
1	**40**	MBZ · $Cr(CO)_3$	MeCN	H_2 70	130	12	66	–	–	–/21	44, 45
2	**40**	MBZ · $Cr(CO)_3$	acetone	H_2 70	120	15	100	–	–	–/–	44, 45
3	**42**	MBZ · $Cr(CO)_3$	acetone	H_2 70	120	16	98	–	+[c]	–/–	45, 47
4	**42**	NP · $Cr(CO)_3$	THF	H_2 70	45	23	95	–	+[c]	–/–	45, 47
5	**42**	MBZ · $Cr(CO)_3$	MeCN	H_2 70	130	12	28	27	+[c]	37/–	44, 45
6	**42**	MBZ · $Cr(CO)_3$	MeCN	H_2 130	120	24	83	–	+[c]	–/–	44, 45
7	**42**	TOL · $Cr(CO)_3$	acetone	H_2 70	130	13	81	4	+[c]	–/–	45, 47
8	**42**	MBZ · $Cr(CO)_3$	MeCN	Ar 70	130	12	–	32	–	25/29	45, 47
9	**42**	MBZ · $Cr(CO)_3$	acetone	Ar 70	130	25	–	28	–	17/21	45, 47
10	**42**	no catalyst	MeCN	Ar 70	130	26	–	–	–	62/28	47
11	**44**	MBZ · $Cr(CO)_3$	acetone	Ar 1	130	20	–	62	–	38/–	47
12	**44**	MBZ · $Cr(CO)_3$	acetone	H_2 70	120	16	94	–	+[c]	–/–	44, 45

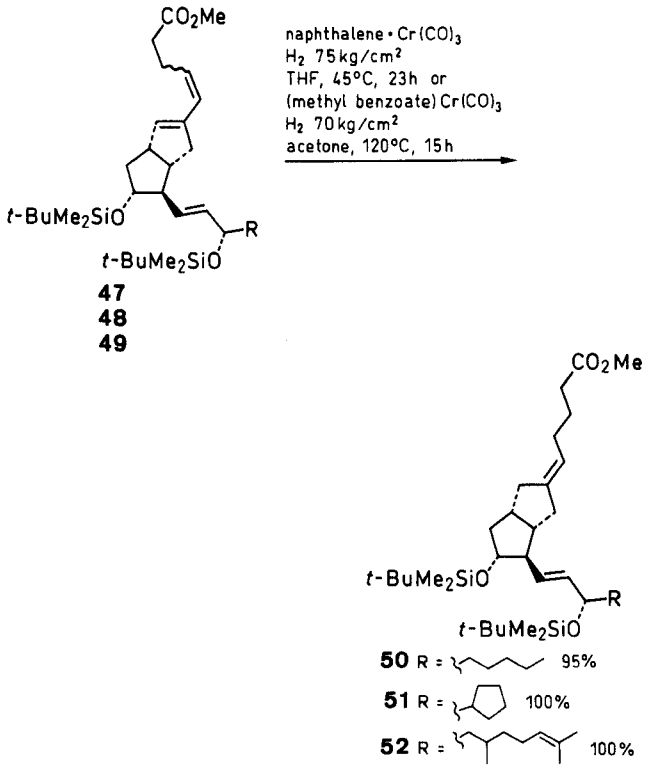
[a] Catalyst = 20%.
[b] MBZ = methyl benzoate, NP = naphthalene, TOL = toluene.
[c] TLC analysis showed the presence of an extremely small amount of **45**.



Scheme 13

proportion to the amount of (4*Z*)-isomer of **42** consumed simply by heating **42** in the presence of a catalytic amount of (methyl benzoate)$Cr(CO)_3$ in acetonitrile or acetone under an argon atmosphere (entry 8 and 9). This was not observed in the absence of the catalyst (entry 10). Treatment of **44** with a catalytic amount of (methyl benzoate)$Cr(CO)_3$ in acetone under argon atmosphere for 20 hours at 130 °C, however, afforded the (4*Z*)-isomer of **42** (38%) together with **44** (62%). These results strongly imply that only the (4*Z*)-isomer of the conjugated diene **42** and the exocyclic conjugated diene **44** were in equilibrium, presumably via the η^5-pentadienylhydridochromium intermediate **46** (Scheme 13). No other isomerized product was obtained in any case, showing that this 1,5-hydrogen shift catalyzed by (methyl benzoate)$Cr(CO)_3$ proceeded in a strictly stereocontrolled manner.

It is quite interesting to consider why the exocyclic conjugated diene **44** or its 1,4-hydrogenated product **45** was scarcely formed from **42** under the reaction conditions noted in entries 3 and 4. We propose the following mechanism (Scheme 13). Under the hydrogenation conditions used, the (4*E*)-isomer of **42** is exclusively hydrogenated to give the desired product **43**, but the (4*Z*)-isomer of **42** is rapidly isomerized, entering into a state of equilibrium with **44**. However, because of the slow rate of conversion of **44** to **45**, the (4*Z*)-isomer of **42** is transformed to **43** in high yield. The fact that hydrogenation of the exocyclic conjugated diene **44** in acetone using (methyl benzoate)$Cr(CO)_3$ as a catalyst (70 kg/cm^2 of H_2 pressure, 120 °C, 16 h) gave the (5*E*)-trisubstituted olefin **43** in 94% yield and only trace amounts of **45** supports this assumption.

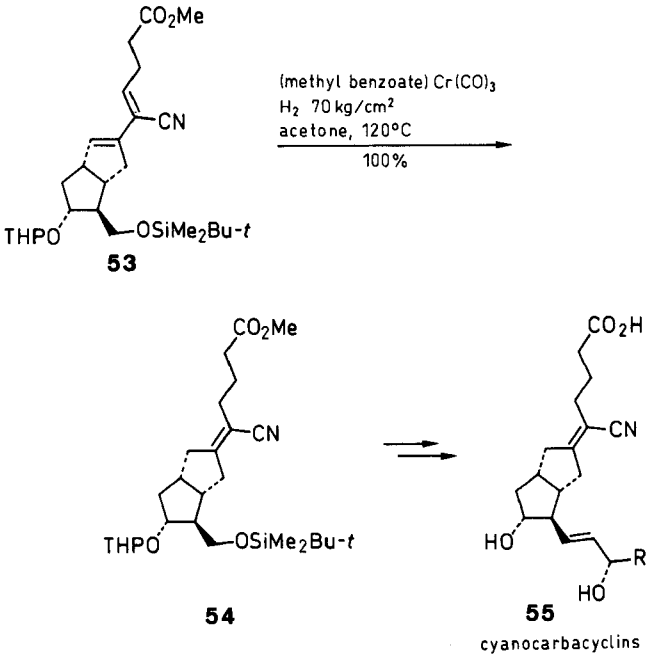


Scheme 14

It should be noted that the formation of **44** led us to investigate the isomerization of dienes catalyzed by arene · $Cr(CO)_3$ complexes. This will be described in section 4.

Because simple olefins are left intact by this arene · $Cr(CO)_3$ catalyzed hydrogenation, the method was successively applied to other dienes having an isolated olefin in the ω-chain **47**–**49**.[44,45] In fact by using this methodology, kilogram-scale preparation of these therapeutically useful compounds and their synthetic intermediates are now being performed (by Nissan Chemical Industries, Japan).

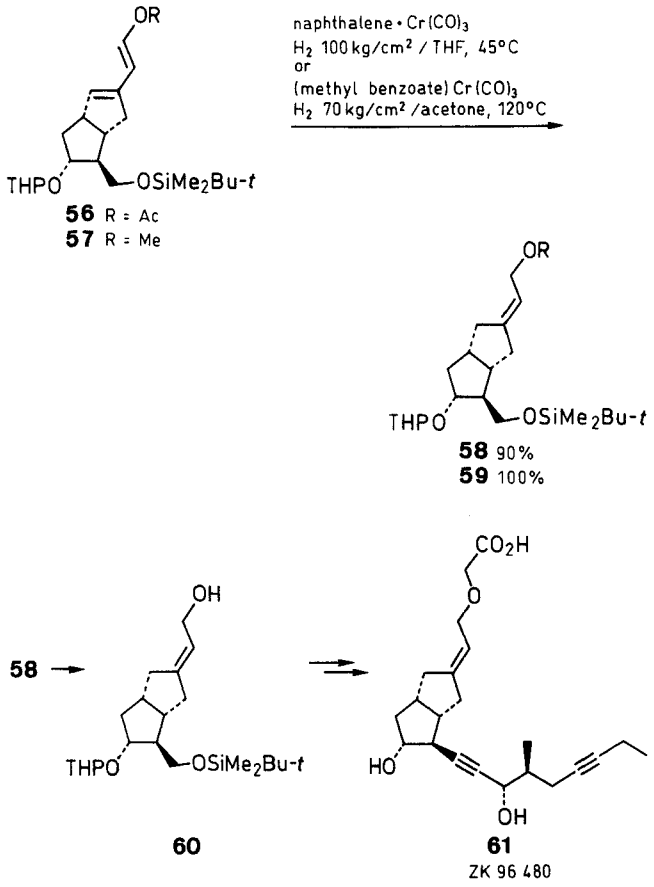
Encouraged by the success of the carbacyclin synthesis, we applied this methodology to the hydrogenation of other functionalized diene systems. The cyano-substituted diene **53** was examined first. Although the cyano group is known to coordinate to the chromium tricarbonyl species, the desired 1,4-hydrogenation proceeded without difficulty to afford the tetra-substituted exocyclic olefin **54** [(*Z*)-isomer] regio- and stereospecifically. The cyanoolefin **54** was subsequently converted to the cyanocarbacyclin analogs **55**. It is notable that the Pd–C catalyzed hydrogenation of **53** gave the opposite stereoisomer of **54** [(*E*)-isomer] as the major product.[49]



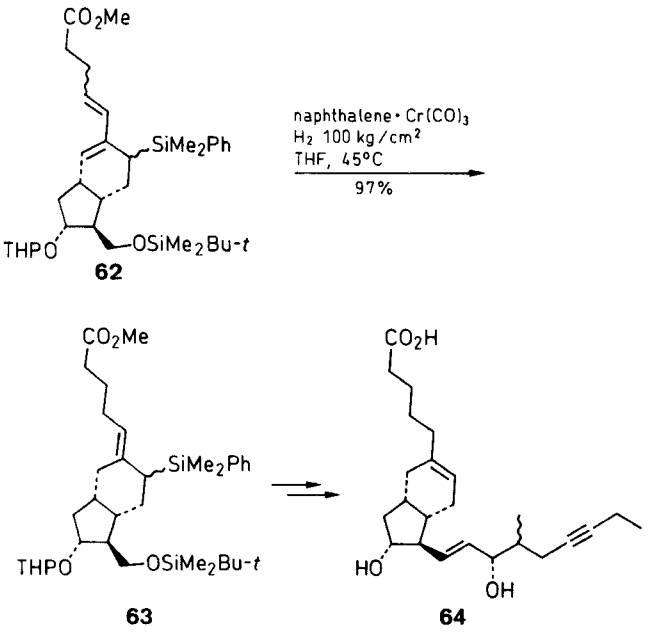
Scheme 15

We have also found that the hydrogenation of the dienol acetate **56** and the dienol ether **57** proceed smoothly, providing access to the 3-oxacarbacyclin analogs such as ZK 96480 **(61)**, a potent, metabolically stable member of this group.[50]

Furthermore, the hydrogenation of dienes bearing an allylic silyl group, **62** has been carried out. This reaction was used in the regiocontrolled synthesis of the homoisocarbacyclin analog **64**.[51]

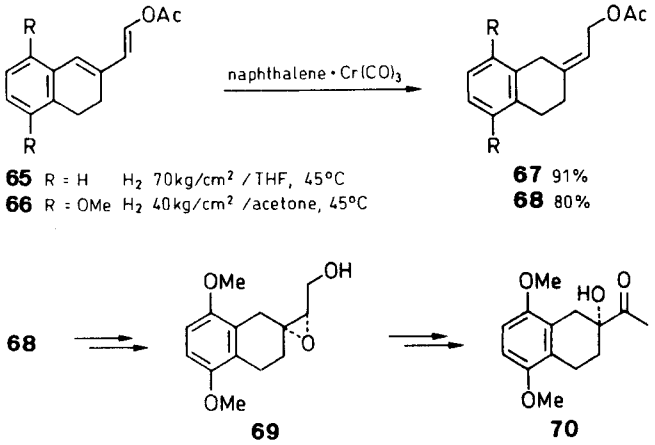


Scheme 16



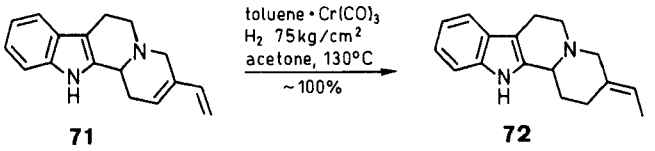
Scheme 17

As described, this methodology has contributed to the synthesis of various prostacyclin analogs; however, its use is not limited to this type of substrate. Scheme 18 illustrates an application of the arene · $Cr(CO)_3$ catalyzed hydrogenation to a diene that is further conjugated with an aromatic ring. The asymmetric synthesis of **70**, a common synthetic intermediate in the preparation of anthracyclins, has been accomplished stereoselectively via the stereocontrolled conversion of **66** to the exocyclic allylic alcohol, the Sharpless epoxidation, and further transformations.[52,53]



Scheme 18

The 1,4-hydrogenation of **71** reported by Rosenmund et al. is also an interesting example which demonstrates neither the amine nor indole group affect this reaction.[54]



Scheme 19

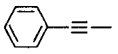
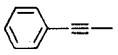
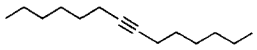
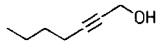
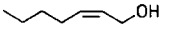
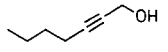
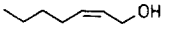
3. Scope and Limitation of Arene · $Cr(CO)_3$ as a Hydrogenation Catalyst

Coordination of the substrate diene to the chromium as a 4-electron donor ligand is crucial to the success of the arene · $Cr(CO)_3$ catalyzed hydrogenation, and this fact prompted us to examine the hydrogenation of other unsaturated functional groups which might act as 4-electron donors. As a result, several new functions for arene · $Cr(CO)_3$ complexes were found.

3.1. Hydrogenation of Alkynes

Since it is known that alkynes can coordinate to transition metals as 4-electron donors, we first investigated the catalytic hydrogenation of these substrates with arene · $Cr(CO)_3$ complexes. As shown in Table 4, alkynes were found to be hydrogenated to (*Z*)-olefins with 100% stereoselectivity.[55] A number of transition metal catalysts (Pd, Ni, Rh, etc.) which catalyze the hydrogenation of acetylenes to (*Z*)-olefins have been reported; however, most of them can also catalyze the hydrogenation of olefins to saturated compounds and the isomerization of (*Z*)-olefins to (*E*)-olefins. As a result, the desired (*Z*)-olefin is often unavoidably contaminated with the over-reduced product and the (*E*)-isomer. For example, the hydrogenation of 1-phenyl-1-propyne with Lindlar

Table 4. Hydrogenation of Alkynes

Entry	Substrate	Catalyst[a]	Solvent	H_2 (kg/cm^2)	Temp. (°C)	Time (h)	Product	Yield (%)
1		MBZ · $Cr(CO)_3$	acetone	70	120	23		92
2		NP · $Cr(CO)_3$	THF	20	45	24		92
3		MBZ · $Cr(CO)_3$	acetone	70	120	15		100
4		MBZ · $Cr(CO)_3$	acetone	70	120	8		95
5		NP · $Cr(CO)_3$	THF	50	45	8		87

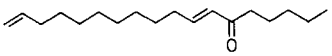
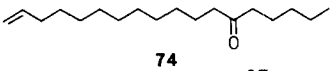
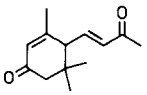
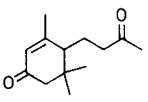
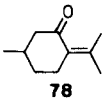
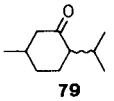
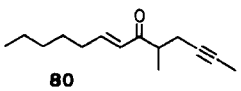
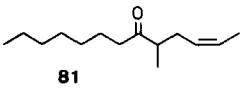
[a] Catalyst = 20 mol%. MBZ = methyl benzoate. NP = naphthalene.

catalyst in the presence of quinoline (hexane solvent, 1 kg/cm^2 of H_2 pressure, 4.5 h) gave a mixture of (*Z*)-β-methylstyrene (83%), (*E*)-β-methylstyrene (4%), propylbenzene (10%), and the starting material (3%); however, hydrogenation of 1-phenyl-1-propyne with an arene · $Cr(CO)_3$ complex afforded (*Z*)-β-methylstyrene as the sole product (Table 4). In contrast to the other transition metal catalysts used for hydrogenation, arene · $Cr(CO)_3$ complexes have no affinity for isolated olefins. As a result, neither the over-reduced product nor the (*E*)-isomer is formed even after prolonged reaction time with the chromium catalyst. Because this hydrogenation does not require strict control of reaction conditions (monitoring hydrogen consumption, reaction temperature, reaction time, additives for modifying catalytic activity, etc.), it is predicted that it will find wide application in the large scale preparation of pure (*Z*)-olefins.

3.2. Hydrogenation of Enones

Arene · $Cr(CO)_3$ complexes catalyze another synthetically useful reaction in that α,β-unsaturated carbonyl groups are chemoselectively hydrogenated in the presence of nonconjugated double bonds.[55] For example, in contrast to the nonselective hydrogenation of the 7,17-octadecadien-6-one (**73**) catalyzed by Pd–C which gave a mixture of the saturated product (6-octadecanone, 78%), the

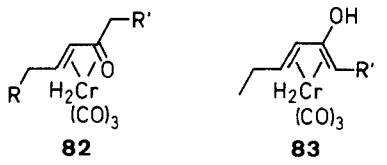
Table 5. Hydrogenation of Enones

Entry	Substrate	Catalyst[a]	Solvent	Pressure (kg/cm^2)	Temp. (°C)	Time (h)	Product	Yield (%)	Ref.
1	 **73**	MBZ · $Cr(CO)_3$	acetone	70	120	12	 **74**	97	55
2	**73**	NP · $Cr(CO)_3$	THF	30	45	3	**74**	94	55
3	**73**	NP · $Cr(CO)_3$	THF	1	45	12	**74**	78	13
4	 **75**	MBZ · $Cr(CO)_3$	acetone	70	120	20	[b]	[b]	55
5	 **76**	NP · $Cr(CO)_3$	THF	70	45	26	 **77**	96	55
6	 **78**	NP · $Cr(CO)_3$	THF	100	40	24	 **79**	83	13
7	 **80**	MBZ · $Cr(CO)_3$	THF	70	120	24	 **81**	93	55

[a] Catalyst = 20 mol%. MBZ = methyl benzoate. NP = naphthalene.
[b] No reaction.

isomerized products (16-octadecen-6-one and other isomers, 19%), and the enone (7-octadecen-6-one, 3%), the hydrogenation of **73** catalyzed by an arene · $Cr(CO)_3$ complex gave the hydrogenated ketone **74** in nearly quantitative yield without any hydrogenation or isomerization of the terminal double bond (Table 5, entries 1–3).

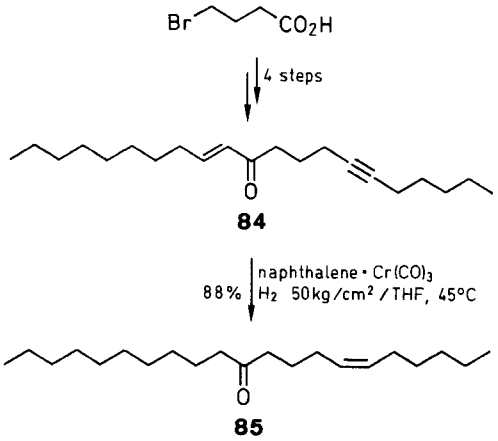
In contrast, cyclic α,β-unsaturated ketones in which the enone system is rigidly constrained to a transoid geometry, as in 2-cyclohexenone (**75**), were found to remain unchanged under the hydrogenation conditions (entry 4). Although it might be argued that enones could coordinate to the chromium atom in the enol form, **83**, the fact that **75** is not reduced suggest that this is not occurring and that the π-orbitals of C=C and C=O double bonds must adopt the cisoid conformation **82**. It follows that arene · $Cr(CO)_3$ complexes can discriminate between those enones capable of adopting the *s-cis* conformation and those that cannot. The chemoselective hydrogenation of **76** illustrates this fact (entry 5).



82 **83**

Figure 2

In another example two functional groups were reduced in a single operation. The hydrogenation of **80** having both an enone and a triple bond gave ketone **81** with (Z)-double bond stereoselectively. This simultaneous hydrogenation was also applied in the total synthesis of (Z)-6-heneicosen-11-one (**85**), the principal sex pheromone of the Douglas fir tussock moth (Scheme 20).[55]

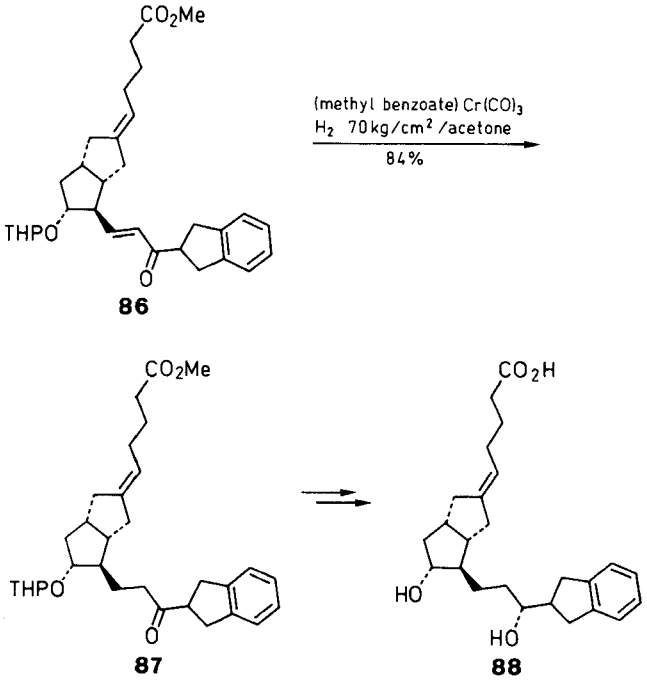


Scheme 20

Scheme 21 illustrates a final example of the arene · $Cr(CO)_3$ catalyzed enone hydrogenation in the synthesis of the 13,14-dihydrocarbacyclin analog **88**.[56]

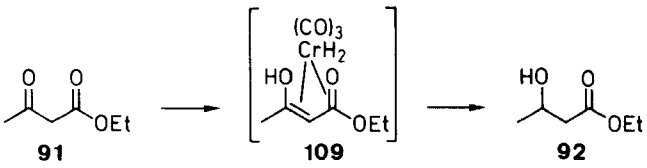
3.3. Hydrogenation of Other Functional Groups

Table 6 summarizes the results obtained from the arene · $Cr(CO)_3$ catalyzed hydrogenation of a number of other functional groups which might act as 4-electron donor ligands. The α,β-unsaturated ester **89**, though less reactive



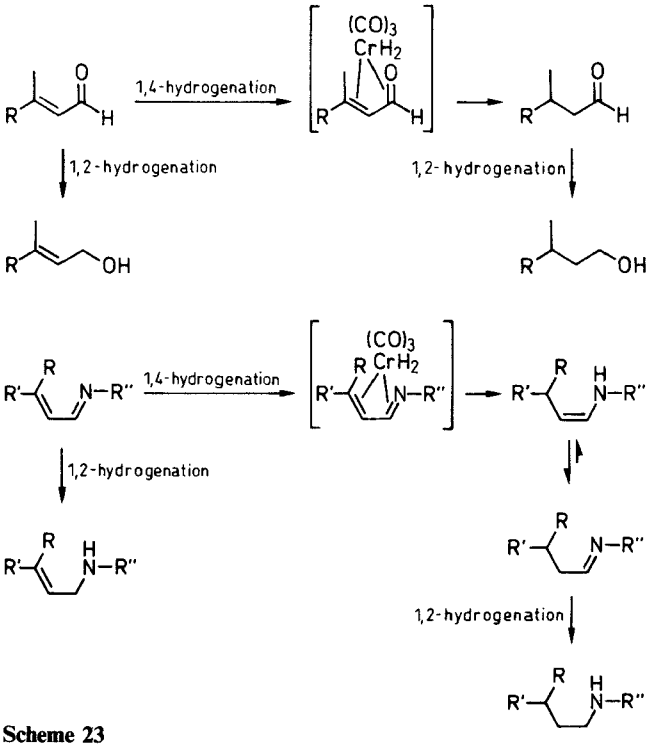
Scheme 21

than the α,β-unsaturated ketones examined, was hydrogenated to its saturated analog **90** in good yield (entry 1).[55] Likewise, the β-oxo ester **91** was found to undergo hydrogenation at 120°C probably via the enol form **109** to give the hydroxy ester **92**, albeit in low yield (entry 2).[55]



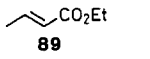
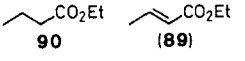
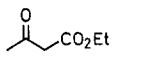
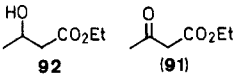
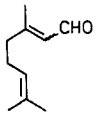
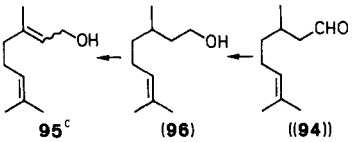
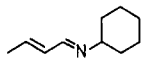
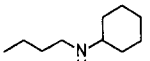
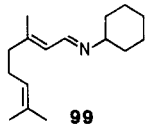
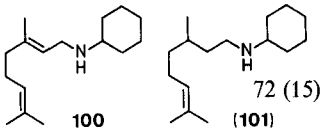
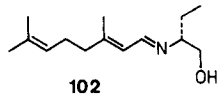
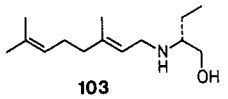
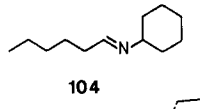
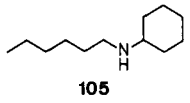
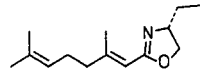
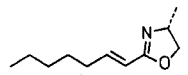
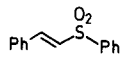
91 **109** **92**

Scheme 22



Scheme 23

Table 6. Hydrogenation of Other Unsaturated Compounds

Entry	Substrate	Catalyst[a]	Solvent	Pressure (kg/cm^2)	Temp. (°C)	Time (h)	Product	Yield (%)	Ref.
1	 **89**	NP · $Cr(CO)_3$	THF	95	45	30	 **90** (**89**)	99.5 (0.5)	55
2	 **91**	NP · $Cr(CO)_3$	THF	80	120	12	 **92** (**91**)	11 (69) 21 (5) ((70))	55 13
3	 **93**[b]	NP · $Cr(CO)_3$	THF	120	45	18	 **95**[c] (**96**) ((**94**))		
4	 **97**	NP · $Cr(CO)_3$	THF	70	60	19	 **98**	100	13
5	 **99** (+ **93** <20%)	NP · $Cr(CO)_3$	THF	135	45	19	 **100** +((**94**)) (**101**)	72 (15) ((15))	13
6	 **102**	NP · $Cr(CO)_3$	THF	110	45	18	 **103**	58	13
7	 **104**	NP · $Cr(CO)_3$	THF	130	45	21	 **105**	100	13
8	 **106**	NP · $Cr(CO)_3$	THF	115	45	17.5	no reaction		13
9	 **107**	NP · $Cr(CO)_3$	acetone	150	45	20	no reaction		13
10	 **108**	MBZ · $Cr(CO)_3$	acetone	70	120	15	no reaction		13

[a] Catalyst = 20 mol%. MBZ = methyl benzoate. NP = naphthalene.
[b] $E/Z = 98:2$.
[c] $E/Z = 91:9$.

Contrary to our expectations, however, the hydrogenation of α,β-unsaturated aldehydes and imines was complicated.[13] The major products of these reactions were not the expected 1,4-hydrogenation product (saturated aldehyde or imine), but either the 1,2-hydrogenation product (allylic alcohol or amine) or the over-reduced product (saturated alcohol or amine), depending on the substrate. These results can be explained by the fact that arene · $Cr(CO)_3$ complexes can catalyze the 1,2-hydrogenation of simple aldehydes and imines (entry 7). Therefore, those substrates which could easily adopt the cisoid conformation such as **97** were converted to the fully saturated products through the sequential 1,4- and 1,2-hydrogenations, but those substrates which preferred the transoid conformation, such as **93**, **99**, and **102**, gave the allylic compound through a 1,2-hydrogenation pathway (Scheme 23).

In contrast to the examples shown above, no hydrogenation of the α,β-unsaturated dihydrooxazoles **106** and **107** and the α,β-unsaturated sulfone **108** was observed under the reaction conditions shown in Table 6.

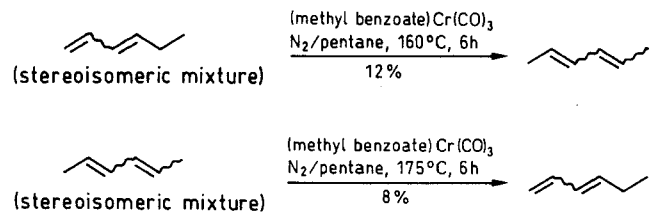
The unique properties of arene · $Cr(CO)_3$ complexes described in this section distinguish this catalyst from other hydrogenation catalysts. Given the scope of the arene · $Cr(CO)_3$ catalyzed hydrogenation, it is expected that this reaction will find wide application to the synthesis of a variety of complex molecules.

4. Isomerization of Conjugated Dienes

4.1. Stereocontrolled 1,5-Hydrogen Shift of Conjugated Dienes

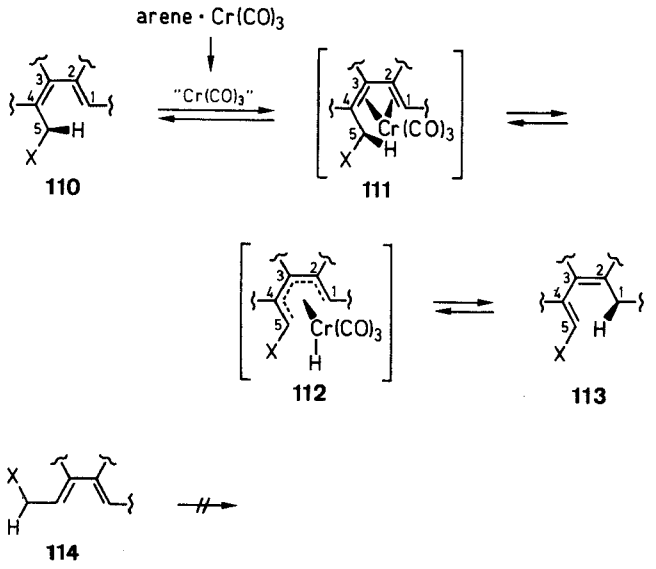
The ability of arene · $Cr(CO)_3$ complexes to catalyze the isomerization of conjugated dienes was first studied by Frankel et al. who observed that under a nitrogen atmosphere in the presence of (methyl benzoate)$Cr(CO)_3$ complex, conjugated hexadienes underwent a 1,5-hydrogen shift (Scheme 24).[23] Although at that time they considered the thermal 1,5-sigmatropic rearrangement a

result of the high reaction temperature (> 160 °C), our studies, as described in section 2, clearly demonstrate that this 1,5-hydrogen shift is catalyzed by arene · $Cr(CO)_3$ complexes and proceeds in a stereospecific manner. Scheme 25 shows the proposed mechanism of this reaction.



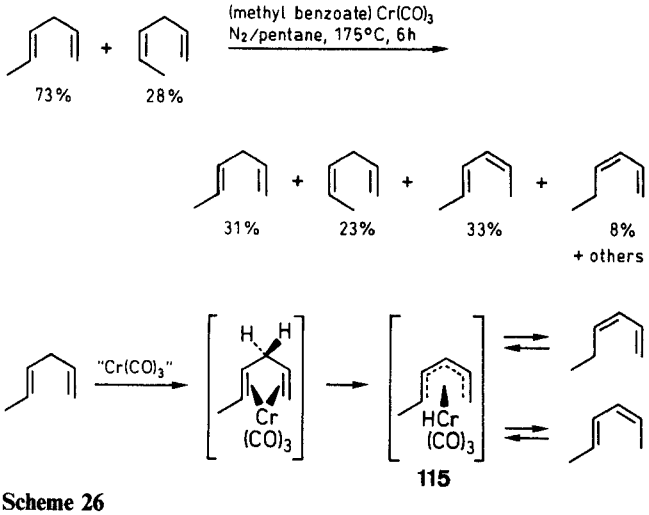
Scheme 24

The conjugated diene **110** first coordinates to the "$Cr(CO)_3$" fragment formed on dissociation of the arene ligand from the arene complex. The complex formed, **111**, is believed to have the hydrogen atom at the C-5 position in close proximity to the chromium atom. Oxidative addition of this C–H bond to the chromium atom then affords the stable η^5-pentadienylhydridochromium intermediate **112** with an 18-electron configuration. Since the pentadienyl moiety is fixed in a U-shape by the chromium atom in the complex **112**, the substituent X should be orientated towards the outside, avoiding severe steric interactions with the hydrogen atom at the C-1 position. The hydrogen atom on the chromium is then believed to move to the C-1 position yielding the diene **113** with the stereochemistry of the newly formed double bonds controlled by the U-shape of the intermediate **112**. It is this latter fact that explains why no isomerization is observed for the dienes with no "inside" methylene group such as **114**. It is known that the conformation of pentadienyl anions can vary from a U-shape to a S- and W-shape depending on the substituents, the counter cation (e. g. K, Na, Li, etc.), and the reaction conditions, and therefore the protonation of these pentadienyl anions usually give a mixture of the stereoisomers. In contrast to these ordinary metals, the "$Cr(CO)_3$" fragment can hold the pentadienyl group in a U-shape, and it is the rigidity of the pentadienyl intermediate that affords the arene · $Cr(CO)_3$ catalyst high regio- and stereoselectivities. Fortunately, the authors have found that this 1,5-hydrogen shift proceeds smoothly even at room temperature in acetone with the naphthalene · $Cr(CO)_3$ complex as the catalyst. This finding has made it possible to avoid the undesired thermal side reactions, which might occur under the previous conditions, and makes this isomerization an attractive method for organic synthesis.



Scheme 25

Frankel et al. have also reported the isomerization of 1,4-hexadiene (stereoisomeric mixture) to a mixture of (*Z*)-1,3-hexadiene and (*Z,E*)-2,4-hexadiene at 175 °C (Scheme 26). Furthermore, they have observed that the isomerization of 1,4-cyclohexadiene to 1,3-cyclohexadiene occurred under milder conditions than that of linear 1,4-dienes. Under the same reaction conditions, however, no isomerization was observed in the case of 1,5-hexadiene. The isomerization of simple olefins was also examined, and no isomerization of 2- or 3-hexene was detected with (methyl benzoate)$Cr(CO)_3$ under hydrogen pressure at 170 °C. These facts may indicate that these reactions are initiated by coordination of both double bonds and proceed through the η^5-pentadienylhydridochromium intermediate **115**.[23,57,58,59] However, 1-hexene was isomerized slowly to a mixture of the 2- and 3-hexenes at high temperature (> 160 °C).



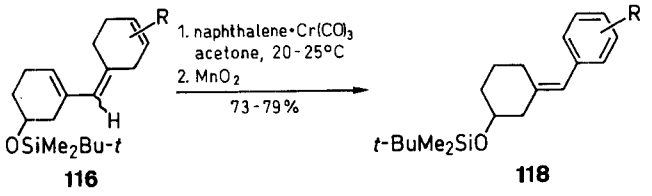
Scheme 26

As shown in Scheme 25, this 1,5-hydrogen shift is believed to be a reversible process, and therefore it is conceivable that a mixture of **110** and **113** might be obtained. However, if the substituent X can stabilize the product **113** by entering into conjugation with the diene, the thermodynamic equilibrium will lie far to the side of **113**. The following applications of this stereospecific isomerization to organic synthesis have been achieved by the careful design of the reaction systems.

4.2. Application to Organic Synthesis

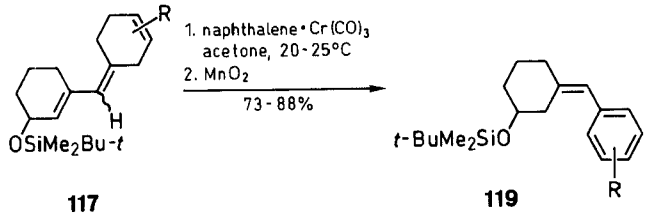
The first synthetic application of the arene · $Cr(CO)_3$ catalyzed isomerization is found in the stereocontrolled

synthesis of aryl-substituted exocyclic olefins.[60] In these systems the equilibrium is driven toward the product by the further conjugation which results on formation of the fully conjugated triene. As shown in Scheme 27, treatment of the partially conjugated trienes **116** and **117** (stereoisomeric mixtures) with naphthalene · $Cr(CO)_3$ and subsequent oxidation yielded the aryl-substituted olefin **118** and **119** stereospecifically regardless of the substrate stereochemistry.



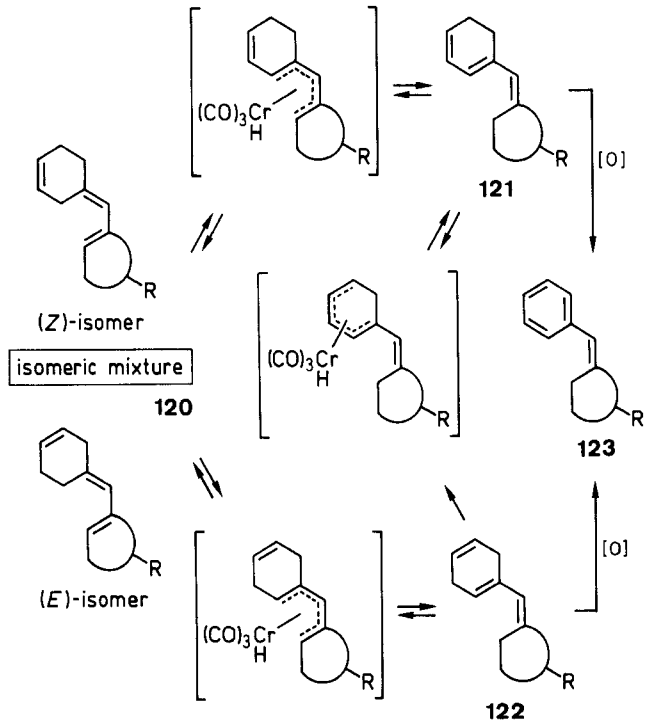
116 **118**

R = *p*-$OSiMe_2Bu$-*t*, *m*-CH_2OAc, *p*-Me, H



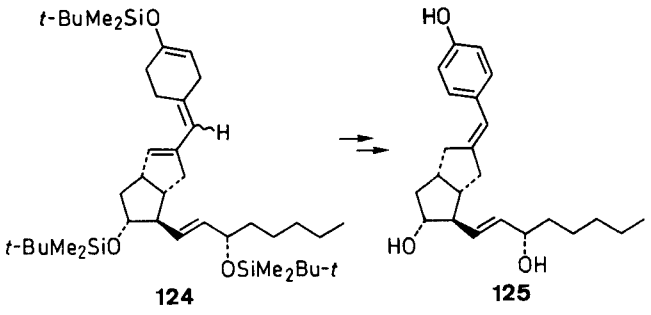
117 **119**

Scheme 27



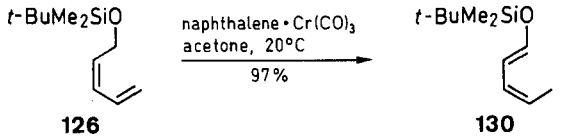
Scheme 28

It is important to note that both (*E*)- and (*Z*)-isomers of the partially conjugated triene **120** afford the same fully conjugated triene **121** through a stereospecific 1,5-hydrogen shift, and in the case of the (*E*)-isomer a second isomerization. Thus, aromatization of the fully conjugated triene **121** (or the intermediate **122**) gives **123** in sterically pure form (Scheme 28). This methodology has been applied to the synthesis of the prostacyclin analog **125**.

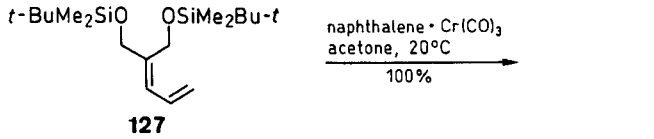


124 **125**

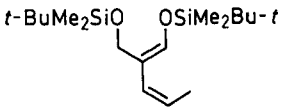
Scheme 29



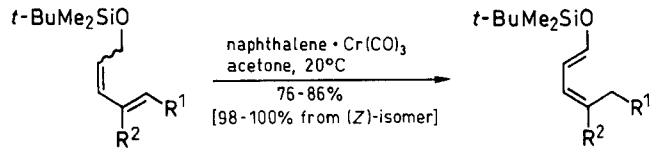
126 **130**



127

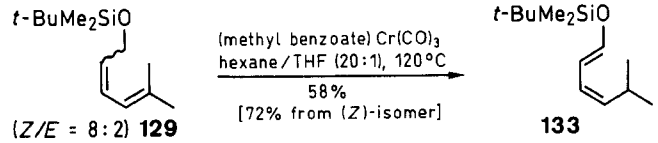


131

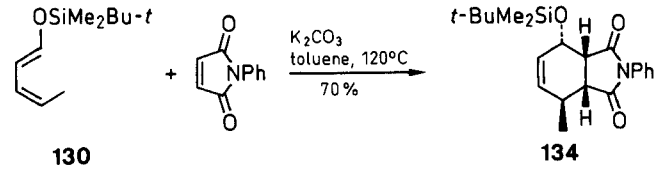


(*Z*/*E* = 8:2) **128** **132**

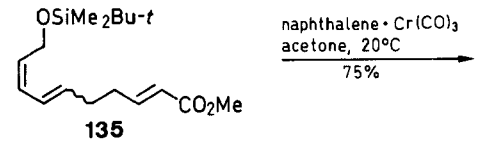
R^1 = H, Me, Bu
R^2 = H, Me



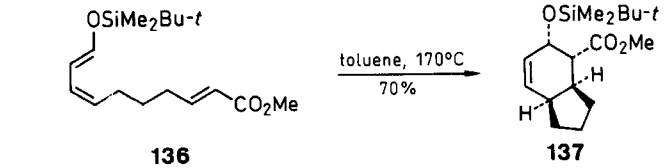
(*Z*/*E* = 8:2) **129** **133**



130 **134**



135

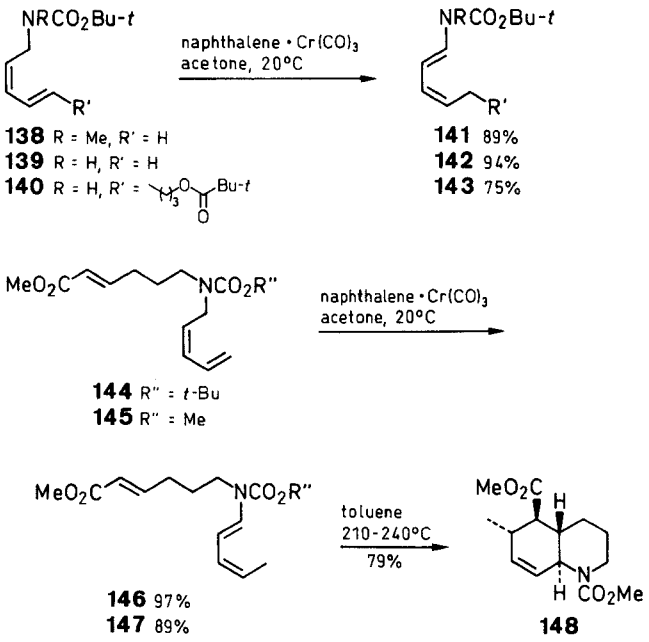


136 **137**

Scheme 30

The stereocontrolled synthesis of silyl dienol ethers has also been achieved using this methodology.[61] With the readily prepared dienes **126–128** (X = $OSiMe_2Bu$-*t* in **110**), nearly quantitative yields of the silyl dienol ethers **130–132** were obtained using the naphthalene · $Cr(CO)_3$ catalyst. It is interesting to note that although the diene **128** contained ca. 20% of the (*E*)-isomer, only the (*Z*)-isomer was consumed; the less polar dienol ether **132**, stereospecifically formed in this reaction, was readily separated from the unreacted (*E*)-isomer of **128**. In the case of diene **129**, no isomerization was observed under the standard reaction conditions [naphthalene · $Cr(CO)_3$, acetone, 20°C], presumably because of the difficulty encountered by this substrate in adopting the required cisoid conformation at this temperature. However, the isomerized product **133** was obtained when the thermostable (methyl benzoate)$Cr(CO)_3$ complex was used in hexane/THF (20:1) at 120°C. These silyl dienol ethers, which cannot be prepared stereoselectively by ordinary methods, are valuable substrates for the Diels–Alder reaction. Moreover, because the arene · $Cr(CO)_3$ catalyzed isomerization leaves isolated olefins intact, this methodology is also useful for the preparation of substrates for the intramolecular Diels–Alder reaction, such as **136**.

The stereocontrolled synthesis of dienamides **141–143** (X = NRCOR′ in **110**) has also been accomplished with this reaction.[62] Moreover by combining this methodology with the Diels–Alder reaction, the construction of alkaloid skeletons such as hydroquinolines has been achieved.



Scheme 31

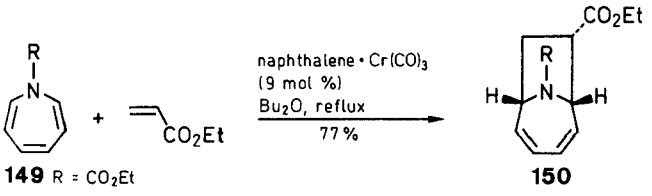
As described above, the arene · $Cr(CO)_3$ catalyzed 1,5-hydrogen shift has been successfully applied to the stereocontrolled synthesis of a variety of compounds, and further applications of this methodology to organic synthesis are anticipated.

Recently we have found that acetoxymethyldienes (X = OAc in **110**) demonstrate distinct reactivity to arene · $Cr(CO)_3$ from siloxymethyl- (X = $OSiMe_2Bu$-*t* in **110**) and alkoxycarbonylaminomethyldienes (X = $NRCO_2R'$ in **110**). Oxidative addition of the C–OAc bond to chromium(0) occurred, and the resulting η^5-pentadienylacetoxychromium intermediates reacted with carbonyl compounds at the C-3 position of the pentadienyl group to give bishomoallylic alcohols. Further investigations of this unique C–C bond forming reaction are now under progress.[63]

5. Conclusion and Outlook

We have reviewed the arene · $Cr(CO)_3$ catalyzed hydrogenation and isomerization reactions, and in conclusion we note the most striking characteristics of these reactions: i) high functional group selectivity, ii) high regioselectivity, and iii) high stereoselectivity. The origin of these high selectivities lies in the fact that the active "$Cr(CO)_3$" species strongly prefers the 18-electron configuration and catalyzes these reactions by filling all of its vacant coordination sites in a selective manner. Specifically, the bidentate coordination of the substrate results in a conformationally rigid intermediate and high selectivity.

Although not discussed in this review, arene · $Cr(CO)_3$ complexes are also known to catalyze the trimerization[64] and polymerization[2] of alkynes, the addition of carbon tetrachloride to olefins,[65,66] and the dehydrohalogenation of alkyl halides.[67] Furthermore, Rigby et al. have recently found that naphthalene · $Cr(CO)_3$ can catalyze the $6\pi + 2\pi$ cycloaddition reactions (Scheme 32). This new catalytic C–C bond forming reaction will be very useful in the synthetic field.[68]



Scheme 32

Moreover, chiral arene · $Cr(CO)_3$ complexes have been reported to be useful ligands for other transition metal catalyzed reactions. Interestingly, the $Cr(CO)_3$ complexed ligands gave better enantioselectivity than the corresponding uncomplexed ligands in the addition of dialkylzincs to aldehydes[69–71] and in palladium catalyzed cross-coupling reactions.[72] Though these are not "$Cr(CO)_3$" catalyzed reactions, this is another practical use for arene · $Cr(CO)_3$ complexes.

In summary, it should be emphasized that arene · $Cr(CO)_3$ complexes have a number of unique characteristics which distinguish it from other group VIII–XI transition metal catalysts. We anticipate the further growth of this field with the development of new useful catalytic reactions and the application of these reactions to organic synthesis.

We thank Professor J. H. Rigby for the information about his reactions prior to publication.

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