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Highly regio- and stereo-controlled hydroformylation of *ortho*-substituted (η^6-styrene)chromium complexes

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Abstract

The rhodium-catalyzed hydroformylation of *ortho*-substituted tricarbonyl(η^6-styrene)-chromium occur with high regio- and diastereo-selectivities; a similar regioselectivity is also observed with tricarbonyl (η^6-indene)chromium, but with a lower diastereoselectivity.

Keywords: Chromium; Hydroformylation; Regioselectivity; Stereoselectivity; Arene complexes

Since the development of homogeneous catalytic asymmetric synthesis, olefin hydroformylation has been the subject of numerous studies [1–4]. Much work has been devoted to the use of optically active phosphorus ligands as chiral modifies to induce enantioselectivity. However, the use of the tricarbonyl(η^6-styrene)chromium for this reaction is possible at a rather low temperature, avoiding the decomplexation of the arene. The first example was published recently, and showed that the complexation of styrene derivatives with the $Cr(CO)_3$ moiety has a beneficial influence on the regioselectivity of the branched product [5].

We now report that *ortho*-substituted styrenes, when complexed to tricarbonylchromium, can be hydroformylated with a rhodium complex with asymmetric induction, leading to a diastereoselectivity in the aldehyde products (Scheme 1). In a typical experiment, **1a** was submitted to the catalytic hydroformylation using $[HRhCO(PPh_3)_3]$ [5] under 28 bar CO/H_2 (1:1) at 50°C for 72 h. After cooling, the reaction mixture was immediately reduced with an excess of $Li[AlH_4]$. The results obtained with three different *ortho*-substituted complexes are summarized in Table 1.

Table 1 shows that complexation by $Cr(CO)_3$ decreases the chemoselectivity, as the direct hydrogenation of the double bond occurs to a larger extent than with the uncomplexed olefin (chemoselectivity 79% versus 99% for **1a** and 83% versus 98% for **1b** [7]). In contrast, regioselectivity favouring the branched aldehyde is strongly enhanced, as no linear aldehyde was observed by HPLC under our experimental conditions although bulky substituents, such as the isopropyloxy group, are present *ortho* to the vinyl bond.

Hydroformylation of complexes **1a**, **1b** and **1c** leads to mixtures of diastereoisomeric aldehyde complexes which are immediately reduced to the corresponding alcohols with $Li[AlH_4]$. This procedure is essential, since the benzylic proton of the aldehyde might be the subject of a rapid epimerization, especially when labilized by complexation of the aromatic ring to the $Cr(CO)_3$. A diastereoisomeric excess is observed in each case. The relative configuration of these products was determined by ^1H NMR, spectroscopy by comparison with the hydroxymethylation products of *ortho*-substituted tricarbonyl(η^6-ethylbenzene) chromium, already described in the literature [8]. The relative configuration *RR-SS* has been attributed to the major products **5** and *RS-SR* to compounds **6**.

The observed diastereofacial control of this reaction is fully consistent with a mechanism in which olefin complexation occurs on the anti face of the chromium

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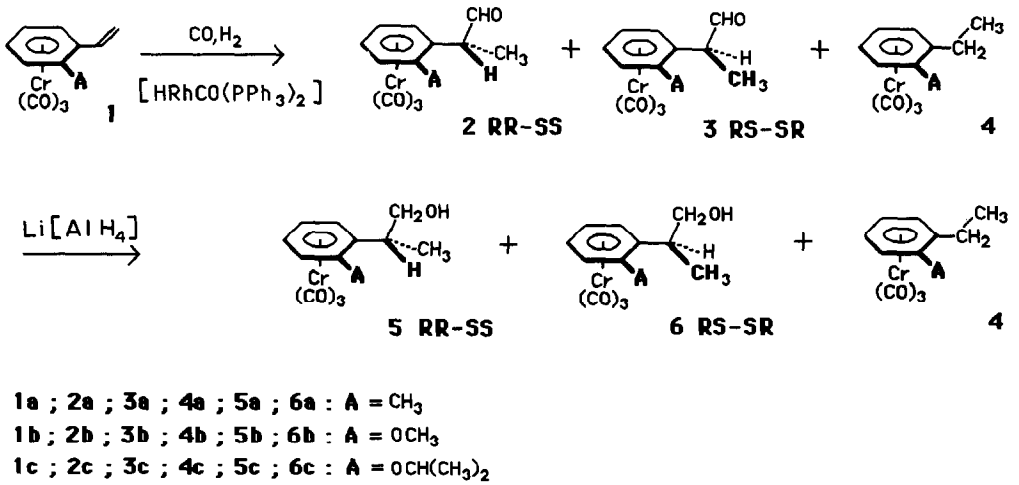
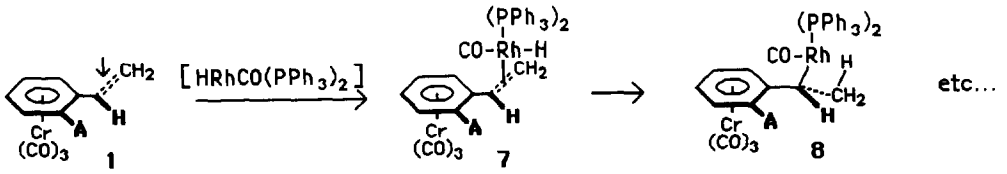


1a ; 2a ; 3a ; 4a ; 5a ; 6a : A = CH_3
1b ; 2b ; 3b ; 4b ; 5b ; 6b : A = OCH_3
1c ; 2c ; 3c ; 4c ; 5c ; 6c : A = $OCH(CH_3)_2$

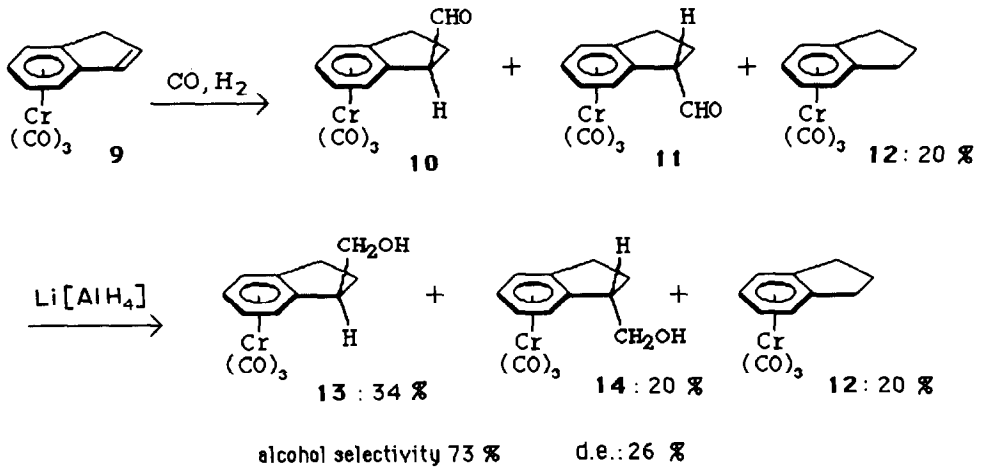
Scheme 1.

Table 1
Hydroformylation of tricarbonyl (η^6-*ortho*-substituted styrene)chromium complexes with $[HRhCO(PPh_3)_3]$

Substrate	5 *RR-SS* (mol%)	6 *RS-SR* (mol%)	4 (mol%)	Alcohol selectivity (%)	d.e. (5 − 6/5 + 6) 100
1a	69	8	20	79	80
1b	72	8	16	83	80
1c	56	8	19	77	75



Scheme 2.



Scheme 3.

styrene complex, in which, for steric reasons, the vinyl group is opposite to the *ortho*-substituent (Scheme 2). The olefin insertion then gives compounds **7** and **8**, which the CO insertion provide the aldehyde whose relative configuration *RR-SS* is the same as that of the rhodium-olefin intermediate. This is consistent with the diastereocontrol reported for tricarbonyl(η^4-unsaturated ketone), where an adjacent chiral centre gave rise to a 100% d.e. [9].

Possible causes of the incomplete diastereoselectivity include a non-stereospecific rhodium chelation process and/or an equilibration process that occurs under reaction conditions before reduction. To find out whether racemization takes place during the asymmetric hydroformylation, the reaction has been carried out in triethyl *ortho*-formate. We expected the formation of acetals [10]. In contrast with results reported in reference [10], but consistent with those in reference [11], we could not detect any acetals. To obtain further proof for the racemization we added the aldehydes **2b** *RR-SS* and **3b** *RS-SR* of known diastereomeric excess (44%) to rhodium catalyst under reaction conditions. After 72 h, a diastereomeric excess of 22% was observed. Contrary to the findings in reference [11], the lower d.e. indicates that racemization takes place during hydroformylation. The tricarbonylchromium moiety is responsible for the increased acidity of benzylic hydrogenatoms in alkylarene complexes [12] and a plausible explanation, consistent with this effect, is that enolization and racemization are relatively easier than in an uncomplexed arene. From this result, it is obvious that the aldehydes formed are prone to racemization and the diastereoselectivity of the hydroformylation is more than 80%.

A similar reaction was carried out with tricarbonyl(η^6-indene)chromium (**9**). The results are described in Scheme 3.

The observed d.e. is rather unexpected, since similar indane and indanone $Cr(CO)_3$ complexes revealed an exclusive *anti* regioselectivity during both electrophilic attack and nucleophilic attack followed by deprotonation [13]. In this case, more than one-third of the *syn* configuration **14** is obtained. The d.e. with the indene complex is lower than observed with the styrene derivatives, but can be related to that obtained by the free substrates with chiral ligands on platinum-based catalysts, where 1-formyl indane is formed with a 45% ee compared to 85% with styrene [4].

Induction with the styrene complexes is at least as efficient as that obtained with most conventional chiral catalysts [14] where sophisticated chelating phosphorus ligands generally are necessary. Together with the excellent regioselectivity of branched product, this asymmetric induction opens an alternative way for the synthesis of chiral synthons from substituted styrenes. The aldehydes formed are prone to racemization and the diastereselectivity of hydroformylation is higher than 80% before racemization.

1. Experimental section

^1H NMR spectra were measured in $CDCl_3$ solution on Bruker WP 60 and AM 300 spectrometers. Mass spectra were recorded on a Riber 10-10 spectrometer. Liquid chromatography analyses were run on Shimatzu LC-8A apparatus with an SPD-6A spectrophotometric detector.

THF was distilled from sodium benzophenone ketyl immediately before use. Dibutyl ether was dried over sodium and distilled. DMSO was distilled over CaH_2 and stored on to 4 Å molecular sieves. $[Cr(CO)_6]$ was obtained from Strem Chemicals and used as received.

1.2. General procedure of hydroformylation and reduction

The complex (1.3 mmol) and the precursor $[HrhCO(PPH_3)_3]$ (1 mol%) were dissolved in 20 ml of toluene and introduced into a stainless steel autoclave (100 ml). The mixture was stirred under 28 bars CO/H_2 (1 : 1) at 50°C. After 72 h the mixture was immediately reduced with an excess of $Li[AlH_4]$ for 1 h at room temperature. Water was added dropwise and the aqueous mixture was extracted with ether (3 × 10 ml). The extract was dried over $MgSO_4$ and evaporated under reduced pressure. The complexes were separated by column chromatography on silica gel (hexane, ether). The percentage of the diastereoisomers was determinated by HPLC and verified with the isolated products.

Tricarbonyl(η^6-2-methylstyrene)chromium (**1a**)

A mixture of 2-methylstyrene (1.18 g, 10 mmol) and chromium hexacarbonyl (2.4 g, 11 mmol) in dibutylether (25 ml) and THF (5 ml) was heated at 130°C for 24 h under nitrogen. After filtration the solution was evaporated. Column chromatography (hexane, ether as eluant) gave complex **1a** as yellow cristals (450 mg, 18%). ^1H NMR ($CDCl_3$, 300 MHz); 6.6 (1 H, $-CH=$, dd, $J = 11$ Hz, 17 Hz), 5.64–5.38 (2 H, $=CH_2$, 2d, $J = 11$ Hz, 12 Hz), 5.66–5.19 (2 H, ArH, 2d, $J = 6$ Hz), 5.37–5.23 (2 H, ArH, 2t, $J = 6$ Hz).

Tricarbonyl(η^6-2-[1-formylethyl]toluene)chromium (**2a–3a**)

The reaction of hydroformylation on complex **1a** (330 mg, 1.3 mmol) according to the general procedure gave a mixture (386 mg) which could not be separated. Aldehyde **2a**: ^1H ($CDCl_3$, 300 MHz): 9.72 (1 H, CHO, s), 5.47–5.15 (4 H, ArH, m), 3.62 (1 H, Ar–CH, q, $J = 7$ Hz), 2.15 (3 H, $Ar-CH_3$, s), 1.49 (3 H, $C-CH_3$, q, $J = 7$ Hz). Aldehyde **3a**: ^1H ($CDCl_3$, 300 MHz): 9.74 (1

H, CHO, s), 5.47–5.15 (4 H, ArH, m), 3.5 (1 H, Ar–CH, q, $J = 7$ Hz), 2.23 (3 H, Ar–CH_3, s), 1.34 (3 H, C–CH_3, d, $J = 7$ Hz). MS: m/z 284 (M^+) 228 ($M^+ - 2$ CO), 200 ($M^+ - 3$ CO).

(Tricarbonyl(η⁶-2-[1-hydroxyprop-2-yl]-toluene)chromium **(5a–6a)**

Reduction by $LiAlH_4$ and the separation on column chromatography gave complexs **5a** (256 mg, 69%) and **6a** (29 mg, 8%). Alcohol **5a**: ^1H ($CDCl_3$, 300 MHz): 5.44–5.12 (4 H, ArH, m), 3.71–3.62 (2 H, CH_2O, m), 2.98 (1 H, Ar–CH, s, $J = 6.5$ Hz), 2.24 (3 H, Ar–CH_3, s), 1.29 (3 H, C–CH_3, d, $J = 7$ Hz). MS: m/z 286 (M^+), 230 ($M^+ - 2$ CO), 202 ($M^+ - 3$ CO). Alcohol **6a**: ^1H ($CDCl_3$, 300 MHz): 5.58–5.12 (4 H, ArH, m), 3.89 (2 H, CH_2O, m), 2.8 (1 H, Ar–CH, s, $J = 6.5$ Hz), 2.22 (3 H, Ar–CH_3, s), 1.26 (3 H, C–CH_3, d, $J = 7$ Hz). MS: m/z 286 (M^+), 202 ($M^+ - 3$ CO).

Tricarbonyl (η⁶-2,3-dihydrobenzofuran)chromium

A mixture of 2,3-dihydrobenzofuran (1.2 g, 10 mmol) and hexacarbonylchromium (2.4 g, 11 mmol) in dibutyl ether (20 ml) and THF (3 ml) was heated at 130°C for 54 h under nitrogen. The cooled solution was filtered through Celite and the solvent evaporated to give the crude complex. The residue was purified by silica gel chromatography with hexane/ether to produce the corresponding chromium complex (1.11 g, 43%). ^1H NMR ($CDCl_3$, 60 MHz): 5.74–4.35 (4 H, ArH, m), 3.19–2.94 (4 H, CH_2, m).

Tricarbonyl (η⁶-2-methoxystyrene)chromium **(1b)**

A mixture of tricarbonyl(2,3-dihydrobenzofuran)-chromium (375 mg, 1, 1 mmol) and KO^{t}Bu (214 mg, 1.4 mmol) was dissolved in 4 ml of DMSO. Methyl iodide (0.145 ml, 2.3 mmol) was added and the solution was stirred for 1.7 h. Aqueous HCl (0.1 N, 10 ml) was added to quench the reaction. The resulting mixture was extracted with ether (3 × 15 ml) and the extract was washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane, ether) to given 287 mg (73%) of chromium complex **1b**. ^1H NMR ($CDCl_3$, 60 MHz): 6.77 (1 H, Ar–CH=, dd, $J = 11.9$ Hz, 17.7 Hz), 5.9–4.86 (6 H, ArH + $=CH_2$, m), 3.8 (3 H, OCH_3, s).

Tricarbonyl(η⁶-2-[1-formylethyl]anisole)chromium **(2b–3b)**

The reaction of hydroformylation on complex **1b** (281 mg, 1 mmol) gave a mixture of the aldehyde **2b–3b** and the tricarbonyl(η⁶-2-methoxyethylbenzene)-chromium (**4b**) which could not be separated by column chromatography on silica gel. Aldehyde **2b**: ^1H ($CDCl_3$, 300 MHz): 9.73 (1 H, CHO, s), 5.59–4.93 (2 H, ArH, 2 t, $J = 6$ Hz), 5.49–4.89 (2 H, ArH, 2 d, $J = 6$ Hz), 3.83–3.67 (1 H, Ar–CH, m), 3.73 (3 H, OCH_3, s), 1.44 (3, H, C–CH_3, d, $J = 7.3$ Hz). Aldehyde **3b**: ^1H ($CDCl_3$, 300 MHz): 9.73 (1 H, CHO, s), 5.59–4.85 (2 H, ArH, 2 t, $J = 6$ Hz), 5.29–4.89 (2 H, ArH, 2 d, $J = 6$ Hz), 3.83–3.67 (1 H, Ar–CH, m), 3.77 (3 H, OCH_3, s), 1.37 (3 H, C–CH_3, d, $J = 7$ Hz). MS: m/z 300 (M^+).

Tricarbonyl(η⁶-2-[1-hydroxyprop-2-yl]anisole)chromium **(5b–6b)**

The reduction of the mixture of hydroformylation and the separation on column chromatography gave the alcohol **5b** (226 mg, 72%), **6b** (25 mg, 8%) and the tricarbonyl(η⁶-2-methoxyethylbenzene)-chromium (**4b**) (47 mg, 16%). These products were described in a previous publication (15).

Tricarbonyl(η⁶-2-isopropoxystyrene)chromium **(1c)**

A mixture of *o*-isopropyloxystyrene (1 g, 6 mmol) and chromium hexacarbonyl (1.49 g, 6, 7 mmol) in dibutyl ether (20 ml) and THF (3 ml) was heated at 130°C for 24 h under nitrogen. After filtration, the solution was evaporated. Column chromatography (hexane, ether as eluant) gave complex **1c** (180 mg, 10%). ^1H NMR ($CDCl_3$, 60 MHz): 6.78 (1 H, –CH=, dd, $J = 10.7$ Hz, 19 Hz), 5.94–4.82 (6 H, ArH + CH_2, m), 4.43 (1 H, OCH, h, $J = 6.2$ Hz), 1.44 – 1.35 (6 H, CH_3, 2 d, $J = 6.2$ Hz). MS: m/z 298 (M^+).

Tricarbonyl(η⁶-1-isopropoxy-2-[1-formylethyl]benzene)-chromium **(2c–3c)**

The reaction of hydroformylation on the complex **1c** (169 mg) gave a mixture of aldehydes **2c–3c**. ^1H ($CDCl_3$, 60 MHz): 9.77 (1 H, CHO, s), 5.7–4.87 (4 H, ArH, m), 4.39 (1 H, O–CH, s, $J = 6$ Hz), 3.6 (1 H, Ar–CH, q, $J = 7$ Hz), 1.4 (3 H, C–CH_3, d, $J = 7$ Hz), 1.37–1.30 (6 H, O–$C(CH_3)_2$, 2d, $J = 6$ Hz). MS: m/z 328 (M^+), 272 ($M^+ - 2$ CO), 244 ($M^+ - 3$ CO).

Tricarbonyl(η⁶-1-isopropoxy-2-[1-hydroxypropy-2-yl]-benzene)chromium **(5c–6c)**

The reduction of the previous mixture by $LiAlH_4$ gave the alcohol **5c** (104 mg, 56%), **6c** (15, mg, 8%) and the tricarbonyl(η⁶-2-isopropyloxyethylbenzene)chromium **4c** (33 mg, 19%). Alcohol **5c**: ^1H ($CDCl_3$, 60 MHz): 5.63–4.77 (4 H, ArH, m), 4.37 (1 H, OCH, m) 3.68 (2 H, CH_2–O, d, $J = 4.7$ Hz), 3.27 (1 H, Ar–CH, m), 1.35–1.41 (6 H, O–$C(CH_3)_2$, 2 d, $J = 5.8$ Hz, 6.2 Hz), 1.2 (3 H, Ar–C–CH_3, d, $J = 7$ Hz). MS: m/z 300 (M^+), 246 ($M^+ - 3$ CO). Alcohol **6c**: ^1H ($CDCl_3$, 60 MHz): 6.2–4.6 (4 H, ArH, m), 4.38 (1 H, OCH, m), 3.8–3.69 (2 H, OCH_2, 2d, $J = 4.2$ Hz) 3.11 (1 H, ArCH, m), 1.41–1.35 (6H, $OC(CH_3)_2$, dd, $J = 4.2$ Hz, 4.9 Hz), 1.28 (3 H, Ar–C–CH3, d, $J = 6.8$ Hz), MS: m/z 330 (M^+), 246 ($M^+ - 3$ CO).

Tricarbonyl(η^6-indene)chromium (**9**)

A mixture of indene (1.16 g, 10 mmol) and chromium hexacarbonyl (2.4 g, 11 mmol) in dibutyl ether (25 ml) and THF (5 ml) was heated at 130°C for 24 h under dinitrogen. After filtration, the solution was evaporated. Column chromatography (hexane, ether as eluant) gave complex **9** (305 mg, 12%). ^{1}H NMR ($CDCl_3$, 300 MHz): 6.5 (2 H, −CH=CH−, s), 5.85–5.75 (2H, ArH, 2d, J = 6 Hz), 5.28–5.23 (2 H, ArH, 2t, J = 6 Hz), 3.6 (2H, CH_2, d, J = 2 Hz).

Tricarbonyl-(η^6-1-formylindane)chromium (**10–11**)

The reaction of hydroformylation on tricarbonyl(η^6-indene)chromium (**9**) 427 mg, 1.7 mmol) according to the general procedure led to a mixture (463 mg) of aldehydes **10**, **11** and tricarbonyl(η^6-indane)chromium (**12**). Aldehydes **10**, **11**: ^{1}H ($CDCl_3$, 60 MHz): 9.74–9.5 (1 H, CHO, 2s), 6–4.6 (4 H, ArH, m), 3.76–363 (1 H, Ar–CH, m), 3.1–2.04 (4 H, CH_2–CH_2, m).

Tricarbonyl(η^6-1-hydroxymethylindane)chromium (**13–14**)

The mixture was reduced by $Li[AlH_4]$. After separation on column chromatography (hexane, ether), we obtained the alcohol **13** (164 mg, 34%), **14** (96 mg, 20%) and the tricarbonyl(η^6-indane)chromium (**12**) (86 mg, 20%). Alcohol **13**: ^{1}H ($CDCl_3$, 60 MHz): 5.66–5.18 (4 H, ArH, m), 3.66 (2 H, O–CH_2, d, J = 6 Hz), 3.0 (1 H, Ar–CH, m), 2.8–1.74 (4 H, CH_2–CH_2, m). MS: m/z 284 (M^+), 288 ($M^+ - 2$ CO), 200 ($M^+ - 3$ CO). Alcohol **14**: ^{1}H ($CDCl_3$, 60 MHz): 5.98–4.92 (4 H, ArH, m), 3.9 (2, H, O–CH_2, d, J = 6.2 Hz), 3.28 (1 H, Ar–CH, m), 2.8–1.58 (4 H, CH_2–CH_2, m): MS: m/z 284 (M^+), 200 ($M^+ - 3$ CO). Tricarbonyl(η^6-indane)chromium **12**: ^{1}H ($CDCl_3$, 60 MHz): 5.5–5.18 (4 H, ArH, m), 2.75–2.03 (6 H, CH_2, m).

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