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TETRAHEDRON: *ASYMMETRY*

Stereoselective hetero Diels–Alder reactions of chiral tricarbonyl (η^6-benzaldehyde)chromium complexes

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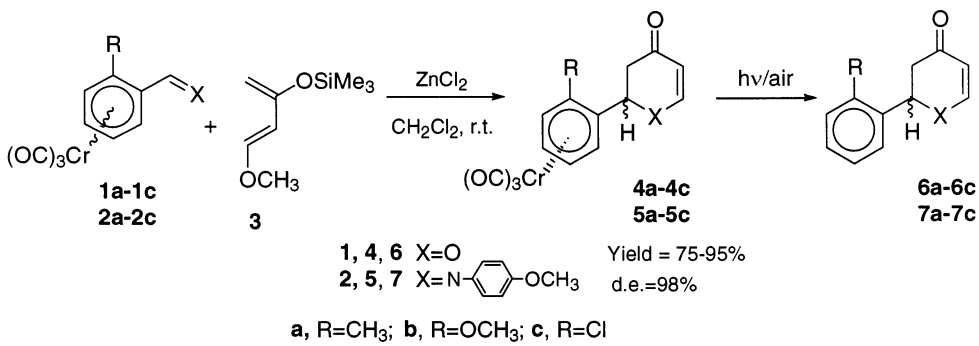
Abstract—The $ZnCl_2$-promoted cycloaddition of a series of enantiopure *ortho*-substituted benzaldehyde–$Cr(CO)_3$ complexes and Danishefsky's diene gave the corresponding 2-aryl pyranones in good yields and complete enantiospecificity. Some of the mechanistic aspects of the cycloaddition were investigated and the reaction extended to different dienes.

1. Introduction

The Lewis acid-promoted cycloaddition of electron-rich dienes to heterodienophiles is an effective synthetic method for the construction of six-membered heterocyclic systems.[1] As up to four stereocentres may be created during the reaction, much effort has been directed toward developing efficient chiral auxiliaries and catalysts for achieving stereoselective cycloadditions.[2]

In previous papers, we[3] and other authors[4] have reported some preliminary experiments on the Lewis acid-promoted stereoselective hetero Diels–Alder reaction between Danishefsky's diene **3** and chiral racemic benzaldehyde and benzaldimine chromium tricarbonyl complexes **1** and **2** (Scheme 1).

The reactions of the racemic complexes **1a**–**1c** and **2a**–**2c** with **3** were completed in CH_2Cl_2 at room temperature in the presence of $ZnCl_2$ as catalyst, and gave a series of 2-aryl-pyranone and pyridinones derivatives **4a**–**4c** and **5a**–**5c** with almost complete diastereoselectivity. The tricarbonylchromium fragment was removed by oxidation to air and sunlight, thus giving high yields of the 2-aryl pyranones **6a**–**6c** and pyridinones **7a**–**7c**,



Scheme 1.

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which are heterocyclic fragments of various biologically relevant molecules.[5]

As the formation of the dihydropyran nucleus plays an important synthetic role, the potential of the reaction of complexed benzaldehydes was further exploited[6] by means of the cycloaddition of Danishefsky's diene on enantiomerically pure complexes (+)-(1*S*)-**1a**–**1c**.

2. Results and discussion

The reactions of enantiomerically pure **1a**–**1c** with an equimolar amount of **3** and $ZnCl_2$ were completed in CH_2Cl_2 at room temperature and, after a standard work-up, complexed pyranones **4a**–**4c** were obtained in good yields as single diastereoisomers (Scheme 2, Table 1). Decomplexation by exposure to air and sunlight gave products **6a**–**6c** in quantitative yields and almost complete enantiospecificity (Table 1). Enantiomeric excesses were determined by ^1H NMR using $Eu(hfc)_3$ as the chiral shift reagent, following the signals of the *ortho*-methyl group in **6a** and the C(2)-vinyl proton for **6b** and **6c**.

Table 1.

Prod. **4**	Yield (%)	Mp (°C)	$[\alpha]_D$
a, R = CH_3	95	144–145	−12.6
b, R = OCH_3	86	146–148	−275
c, R = Cl	94	126–128	−73.8

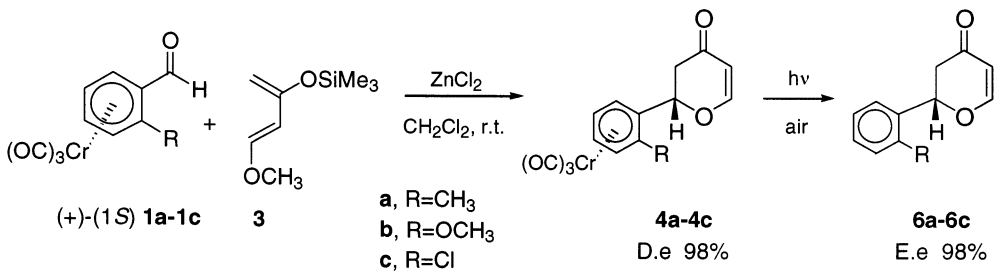
Pyranones **6a**–**6c**[7,8] are known in optically active form, but no correlation between the $[\alpha]_D$ sign and the absolute configuration has been reported. We first checked that all pyranones **6a**–**6c** have the same absolute configuration by comparing their CD spectra, which showed the same negative Cotton effect. Furthermore, determination of the crystal structure of the racemic complexed pyranone **4c** by X-ray diffraction showed the (*RS*,*RS*)-configuration for the obtained diastereoisomer.

The structure of the (*S*,*S*)-enantiomer is shown in Fig. 1, together with the atomic numbering system. Selected bond distances and angles in **4c** are given in Table 2. The coordination around the Cr atom is of three legged piano stool type with the metal interacting in a slightly asymmetric η^6-fashion with the arene ligand (Cr–C bond lengths in the range 2.195(8)–2.237(8) Å) and the arene ligand is in a staggered position with respect to the three terminal carbonyls. In fact the torsion angles C(1)–Cr–CE–C(9), C(2)–Cr–CE–C(7) and C(3)–Cr–CE–C(5), −24.1(5), −25.3(6) and −24.7(5)°, respectively, are close to the theoretical value of 30° (CE is the centroid of the arene). The pyranone ring adopts a half-chair conformation with the C(10) and C(11) atoms out of the mean plane through the other four atoms by −0.424(9) and 0.242(8) Å, respectively. The two double bonds of the pyranone ligand are partially delocalised, as shown by the C–C and C–O bond lengths (Table 2). A weak intermolecular interaction C(14)–H(14)···O(5) determines helicoidal chains of the (*S*,*S*) or (*R*,*R*) complexes parallel to the crystallographic *b* axis.

Table 2. Selected bond lengths (Å) and angles (°) for **4c**

Cr–C(1)	1.842(11)	C(6)–C(7)	1.415(11)
Cr–C(2)	1.840(12)	C(7)–C(8)	1.391(12)
Cr–C(3)	1.844(10)	C(8)–C(9)	1.414(12)
Cr–C(4)	2.195(8)	C(4)–C(9)	1.397(12)
Cr–C(5)	2.237(8)	Cl–C(4)	1.750(9)
Cr–C(6)	2.206(8)	C(5)–C(10)	1.491(11)
Cr–C(7)	2.207(8)	C(10)–C(11)	1.513(11)
Cr–C(8)	2.222(9)	C(11)–C(12)	1.508(12)
Cr–C(9)	2.213(9)	C(12)–C(13)	1.442(13)
O(1)–C(1)	1.167(11)	C(13)–C(14)	1.318(12)
O(2)–C(2)	1.148(12)	O(4)–C(14)	1.357(10)
O(3)–C(3)	1.153(10)	O(4)–C(10)	1.442(10)
C(4)–C(5)	1.423(11)	O(5)–C(12)	1.226(10)
C(5)–C(6)	1.406(11)		
C(2)–Cr–C(1)	89.1(4)	C(2)–Cr–C(9)	149.8(4)
C(3)–Cr–C(1)	87.7(4)	C(3)–Cr–C(7)	151.2(4)
C(2)–Cr–C(3)	89.5(5)	C(3)–Cr–C(8)	157.7(4)
C(1)–Cr–C(5)	151.8(4)	O(1)–C(1)–Cr	177.1(8)
C(1)–Cr–C(6)	158.3(4)	O(2)–C(2)–Cr	178.8(10)
C(2)–Cr–C(4)	156.0(4)	O(3)–C(3)–Cr	177.1(10)

The (*S*)-configuration for the cycloadducts **4c** is also that expected on the basis of the well-known stereochemical model[9] operating on such chiral complexes, involving approach of the diene from the side opposite to $Cr(CO)_3$ on the preferred *anti* conformation of the carbonyl group (*Si*-face) with respect to the *ortho*-substituent, as shown for (+)-(1*S*)-**1** in Fig. 2.



Scheme 2. Stereoselective Diels–Alder cycloaddition of (+)-(1*S*)-benzaldehyde complexes **1a**–**1c**.

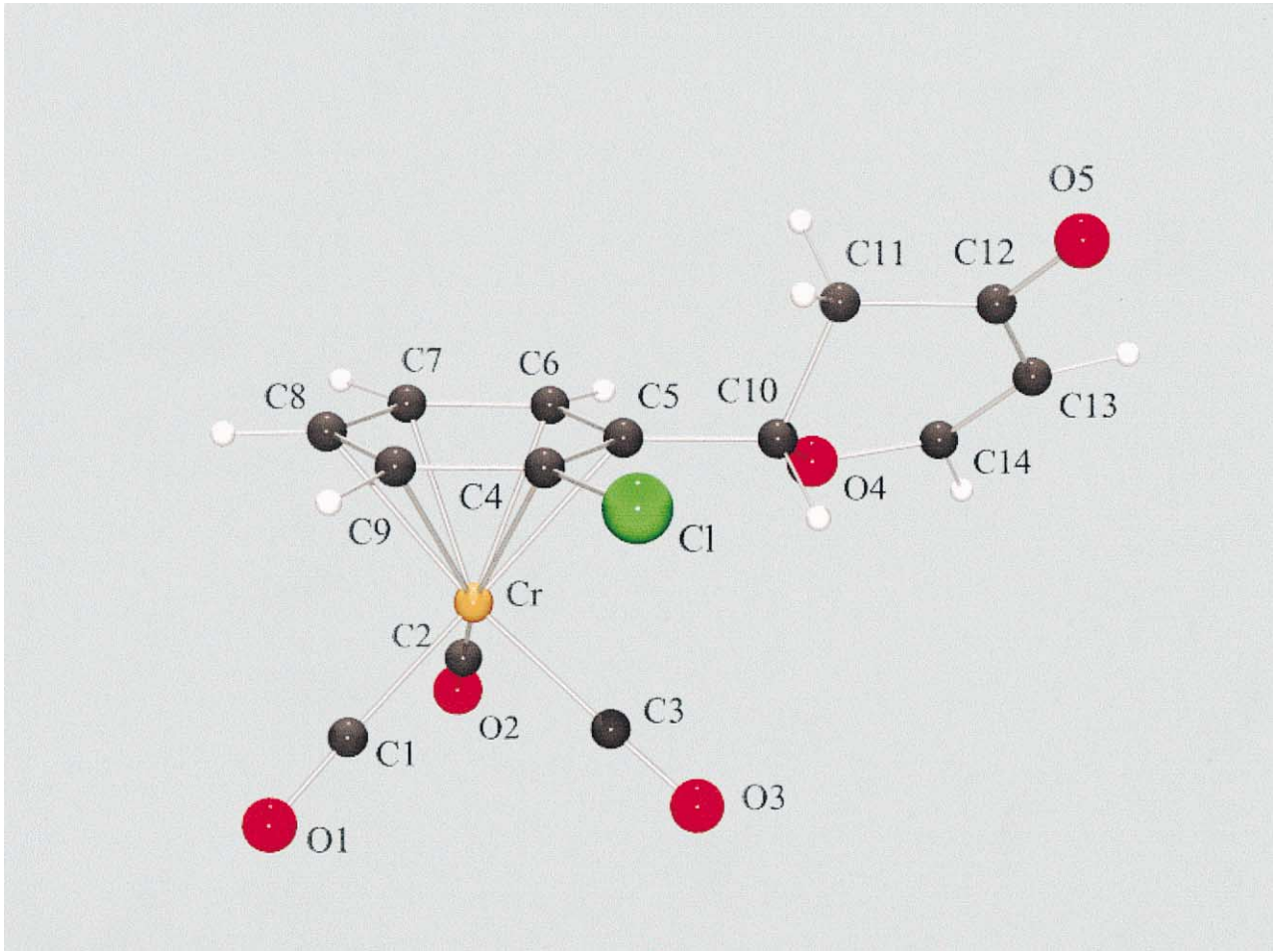
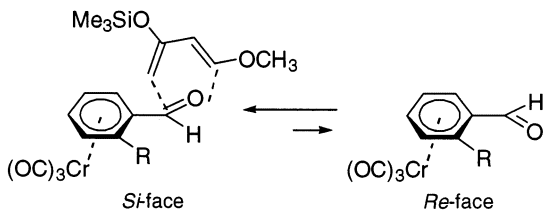


Figure 1. View of the structure of the (*S*,*S*)-enantiomer of the diastereoisomer of **4c**. The ellipsoids are drawn at the 30% probability level.



(+)-(*1S*)-**1**

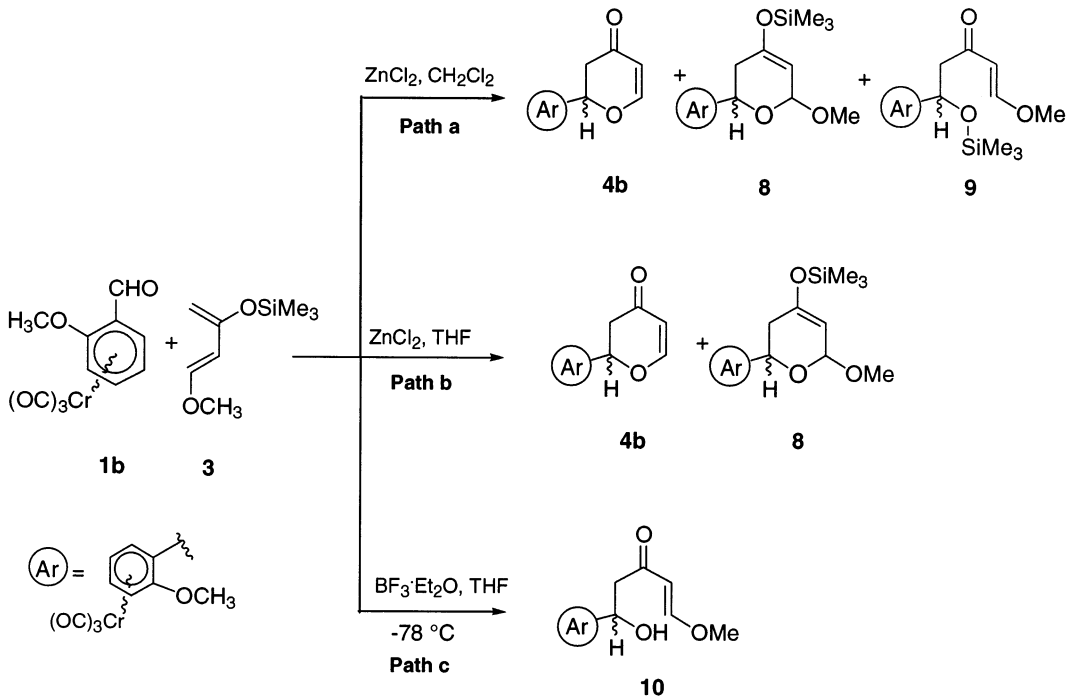
Figure 2. Stereochemical model for chiral *ortho*-substituted benzaldehyde complexes.

The mechanism of the hetero Diels–Alder reaction is a matter of debate.[2a] In our case, during the set-up of the reaction conditions, the cycloaddition of benzaldehyde complexes with Danishefsky's diene **3** was studied in detail and this allowed us to elucidate some mechanistic aspects of the reaction.

Two mechanistic pathways have been formulated for the Lewis acid-mediated hetero Diels–Alder reactions of carbonyl compounds: a traditional DA cycloaddition mechanism or a Mukaiyama-like aldol reaction. The reaction pathway often depends on the substrate structure and the type of solvent and catalyst. Danishefsky et al. concluded that, in the presence of BF_3, the reaction of benzaldehyde with diene **3** proceeds by a stepwise aldol mechanism, whereas a concerted reaction takes place when $ZnCl_2$ or lanthanides are used as catalysts.[2a,10,11]

In our case, the $Cr(CO)_3$ complex of 2-methoxybenzaldehyde **1b** was used as a model compound, and a series of experiments were run at different temperatures using CH_2Cl_2 or THF as solvent and $ZnCl_2$ or $BF_3{\cdot}Et_2O$ catalysts (Scheme 3). This study showed that the two mechanistic pathways were observed even when using $ZnCl_2$ as the catalyst.

The first reaction of **1b** with **3** was run in CH_2Cl_2 at −78°C (Scheme 3, path a) and gave a mixture of the cycloadduct **4b**, its precursor **8** and open compound **9** (98% d.e., from the Mukaiyama-like aldol reaction) in a ratio of about 15:25:60, as determined by ^1H NMR of the crude reaction mixture. Allowing the reaction temperature to rise to 25°C, the intermediate **8** completely converted into **4b**, and compounds **4b** and **9** were the only isolated products. A series of experiments further ascertained that a variable amount of compound **9** is always formed in CH_2Cl_2 at temperatures of between −78 and 0°C, but the reaction follows the cycloadditive pathway when run at higher temperature. This set of experiments determined the choice of room temperature for running the reaction on optically active benzaldehyde complexes **1a**–**1c** (Scheme 2).



Scheme 3.

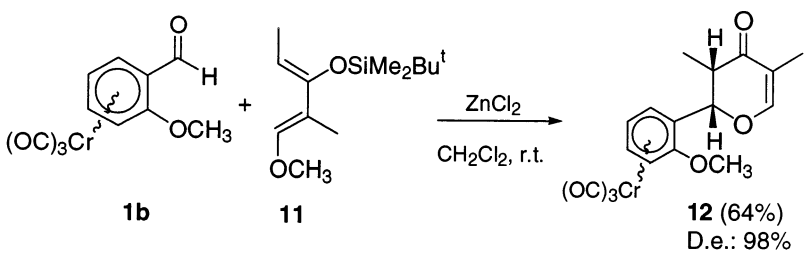
To the best of our knowledge, aldol condensation products have not previously been isolated in $ZnCl_2$-catalysed reactions and so, in order to verify the role of the solvent, we repeated the reaction between complex **1b** and **3** at −78°C in THF (Scheme 3, path b), the solvent used by Danishefsky for most of his studies.[11] In this case, a concerted mechanism always operates even at low temperatures. Only **4b** and its precursor **8** were formed (in agreement with Danishefsky's results). It is worth noting that running the reaction at −20°C allowed us to isolate and fully characterise the silylated intermediate **8**. The study was completed by running the reaction in THF at −78°C using BF_3 as the catalyst: in this case, and as expected, only the Mukaiyama-like aldol product **10** was obtained in 89% yield with complete diastereoselectivity.

Finally, in order to evaluate the general applicability of chiral benzaldehyde complexes in hetero Diels–Alder reactions, two different dienes **11** and **13** were reacted with complexes **1b** (Scheme 4) and **1c** (Scheme 5). After being catalysed by $ZnCl_2$ in CH_2Cl_2 at room temperature, the reaction of complex **1b** with **11** afforded only the *cis*-isomer of cycloadduct **12**[12] (64%, d.e. 98%) arising from the expected cycloadditive pathway (Scheme 4).

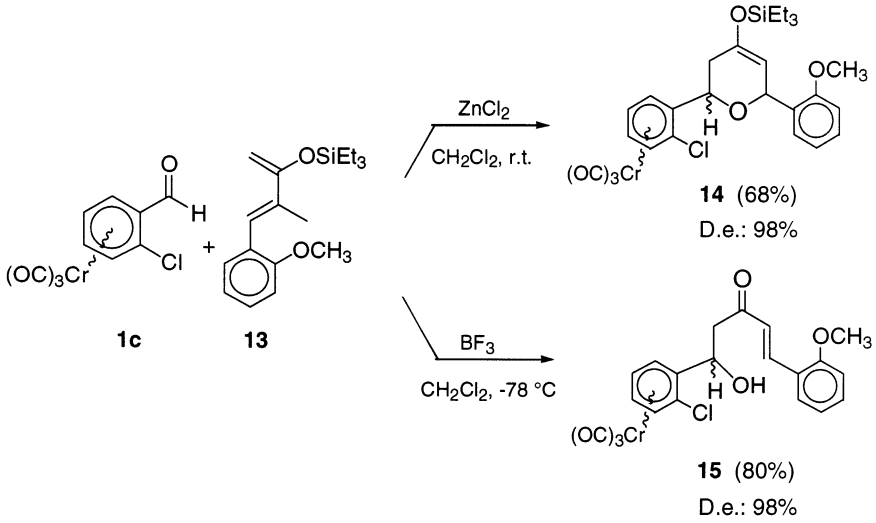
Analogously, 2-chlorobenzaldehyde complex **1c** reacted with diene **13** in CH_2Cl_2 and $ZnCl_2$ at room temperature to give the cycloadduct **14** in 68% yield and with complete diastereoselectivity (Scheme 5). The reaction with **13** was also repeated at −78°C using BF_3 as the catalyst: as expected, only the aldol-addition product **15** was isolated in 80% yield and 98% d.e.

The choice of the rather unusual 2-methoxyphenyl substituted diene **13** was made considering that an interesting extension of the work could be the use of a chiral $Cr(CO)_3$ complexed diene in stereoselective Diels–Alder reactions. We therefore synthesised the $Cr(CO)_3$ complexed racemic diene **17**, starting from ketone **16**, as shown in Scheme 6. In turn, complex **16** was prepared through Wittig reaction of the 2-methoxybenzaldehyde complex **1b** with acetonyltriphenylphosphonium bromide.

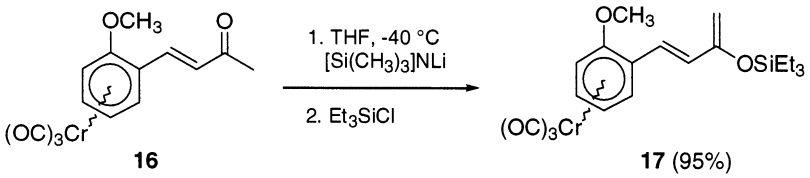
The reactivity of diene **17** was first tested in the $ZnCl_2$-catalysed cycloaddition with both benzaldehyde and



Scheme 4.



Scheme 5.



Scheme 6.

2-chlorobenzaldehyde. No reaction was observed in either case, probably because of the reduced electron density on the diene caused by complexation to the $Cr(CO)_3$ group. The experiment performed using benzaldehyde as the dienophile was then repeated with $BF_3{\cdot}Et_2O$ in THF at −78°C (Scheme 7). In this case, the Mukaiyama-like aldol product **18** and compound **19** (from dehydration of **18**) were obtained. The NMR of compound **18** disappointingly revealed the presence of an equimolar mixture of two diastereoisomers: the complexed stereogenic fragment is probably too far from the reactive site to affect the diastereoselectivity of the reaction.

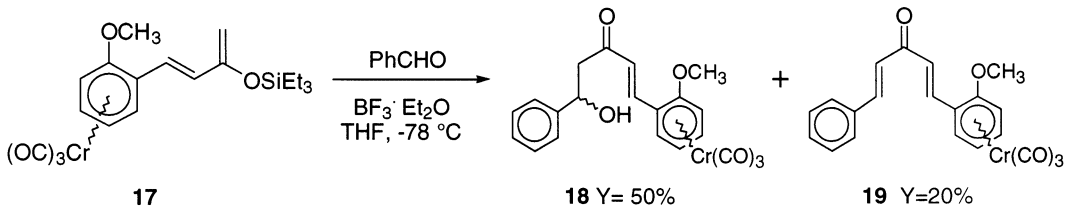
3. Conclusions

The results presented in this paper complete our study of the potential of benzaldehyde chromium tricarbonyl complexes as efficient chiral dienophiles in stereoselective hetero Diels–Alder cycloadditions. The reaction of the Danishefsky's diene with a series of enantiopure benzaldehyde complexes **1a**–**1c** is completely enantioselective and, after decomplexation, gave (*S*)-pyranones **6a**–**6c** in good yields. In addition some mechanistic aspects of the reaction have been elucidated.

4. Experimental

4.1. General

All reactions were carried out in a dry nitrogen atmosphere. The reagents and solvents available from commercial sources were used as received unless otherwise noted. Tetrahydrofuran was distilled from a Na/benzophenone ketyl. Column chromatography was performed using Merck silica gel 60 (70–230 mesh). The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, using a Bruker AC300 spectrometer. Chemical shifts (δ) are given in ppm, and coupling constants (J) in hertz. The melting points were measured on a Buchi 510 M.P. apparatus and are uncorrected. The IR spectra were recorded on a Perkin–Elmer 1725 FTIR; $[\alpha]_D$, deter-



Scheme 7.

mined using a Perkin–Elmer 243 polarimeter. The homochiral complexes **1a**–**1c** were prepared as previously reported.[9] Diene **11** was prepared according to a published procedure.[13]

4.2. General procedure for the synthesis of 2-aryl pyranone complexes 4a–4c

Zinc chloride (1 mL 0.3 M soln in THF) was added at 0°C to a solution of **1a**–**c** (0.3 mmol) in CH_2Cl_2 (5 mL); diene **3** (0.3 mmol) was then added at room temperature, and the mixture stirred at 25°C for 24 h. After dilution with a saturated solution of $NaHCO_3$ (10 mL), the mixture was filtered over a Celite pad. The aqueous phase was extracted using CH_2Cl_2 (3×10 mL), separated and, after washing with H_2O (10 mL), the organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude yellow product thus obtained was purified by column chromatography using the appropriate eluent.

4.2.1. (−)-(*S*,*S*)-2,3-Dihydro-2-(2-methylphenylchromiumtricarbonyl)-4*H*-pyran-4-one 4a. Eluent: CH_2Cl_2/Et_2O (20:1). Yellow solid (95%) recrystallised from di-*iso*-propylether, mp 144–145°C (racemic 169–170°C). $[\alpha]_D=-12.6$ ($c=0.1$, $CHCl_3$) IR ν_{max}/cm^{-1} (Nujol) 1834, 1949, 1654, 1461. ^1H NMR (δ): 2.19 (s, 3H, CH_3), 2.58–2.73 (m, 2H, CH_2), 5.1 (d, 1H, arom., $J=6.3$), 5.19–5.26 (m, 2H, CH arom.+CH), 5.4 (dd, 1H arom., $J=6.5$), 5.54 (d, 1H, CH=, $J=6.1$), 5.62 (d, 1H, arom., $J=6.5$), 7.52 (d, 1H, CH=, $J=6.1$). Found: C, 55.82; H, 3.60; $C_{15}H_{12}O_5Cr$ requires C, 55.56; H, 3.73%.

4.2.2. (−)-(*S*,*S*)-2,3-Dihydro-2-(2-methoxyphenylchromiumtricarbonyl)-4*H*-pyran-4-one 4b. Eluent: CH_2Cl_2/Et_2O (10:1). Yellow solid (86%) recrystallised from petroleum ether/di-*iso*-propyl ether (10:1), mp 146–148°C (racemic 118–119°C). $[\alpha]_D=-275$ ($c=0.1$, $CHCl_3$). IR ν_{max}/cm^{-1} (Nujol) 1954, 1871, 1678, 1466. ^1H NMR (δ): 2.6 (dd, 1H, CH_2, $J=16.7$, 14.2), 2.77 (dd, 1H, CH_2, $J=16.7$, 4.4), 3.75 (s, 3H, OCH_3), 4.92 (dd, 1H, arom., $J=6.3$), 5.05 (d, 1H, arom., $J=6.8$), 5.45 (dd, 1H, CH, $J=14.2$, 4.4), 5.48–5.56 (m, 2H, arom.+CH=), 5.8 (d, 1H, arom., $J=6.3$), 7.53 (d, 1H, CH=, $J=6.1$). Found: C, 52.99; H, 3.53; $C_{15}H_{12}O_6Cr$ requires C, 52.95; H, 3.55%.

4.2.3. (−)-(*S*,*S*)-2-(2-Chlorophenylchromiumtricarbonyl)-2,3-dihydro-4*H*-pyran-4-one 4c. Eluent: CH_2Cl_2. Yellow solid (94%) recrystallised from di-*iso*-propyl ether, mp 127–128°C; (racemic 151–152°C). $[\alpha]_D=-74$ ($c=0.14$, $CHCl_3$). IR ν_{max}/cm^{-1} (Nujol) 1968, 1885, 1678, 1465. ^1H NMR (δ): 2.65 (dd, 1H, CH_2, $J=16.7$, 14.4), 2.85 (dd, 1H, CH_2, $J=16.7$, 3.6), 5.09–5.13 (m, 1H, CH), 5.42–5.58 (m, 2H, arom.+CH=), 5.57 (d, 1H, arom., $J=6.2$), 5.69 (d, 1H, arom., $J=6.4$), 7.54 (d, 1H, CH=, $J=6.3$). Found: C, 48.83; H, 2.62; $C_{14}H_9O_5ClCr$ requires C, 48.79; H, 2.63%.

4.3. Decomplexation of compounds 4a–4c

A solution of complex **4a**–**4c** in CH_2Cl_2 was exposed to air and sunlight until the yellow colour had completely disappeared. The solvent was evaporated and the residue was taken up in Et_2O, the mixture was filtered through a pad of Celite® to give quantitative yields of pyranones **6a**–**6c**, respectively, as near-analytically pure oils.

4.3.1. (+)-(*S*)-2,3-Dihydro-2-(2-methylphenyl)-4*H*-pyran-4-one 6a. $[\alpha]_D^{25}=+46.3$ ($c=0.38$, $CHCl_3$). ^1H NMR (δ): 2.4 (s, 3H, CH_3), 2.6 (dd, 1H, CH_2, $J=3.4$, 16.9), 2.9 (dd, 1H, CH_2, $J=14.6$, 16.9), 5.6 (d, 1H, CH=, $J=5.9$), 5.7 (dd, 1H, CH, $J=14.6$, 3.4), 7.2–7.3 (m, 3H, arom.), 7.5–7.6 (m, 2H, arom.+CH=).

4.3.2. (−)-(*S*)-2,3-Dihydro-2-(2-methoxyphenyl)-4*H*-pyran-4-one 6b. $[\alpha]_D^{25}=-63.5$ ($c=0.37$, $CHCl_3$). ^1H NMR (δ): 2.7–2.8 (m, 2H, CH_2), 3.8 (s, 3H, OCH_3), 5.5 (d, 1H, CH=, $J=6.1$), 5.8 (dd, 1H, CH, $J=11.3$, 6.4), 6.9 (d, 1H, arom., $J=8.1$), 7.0 (dd, 1H, arom. $J=7.5$), 7.3 (dd, 1H, arom. $J=8.1$), 7.4–7.5 (m, 2H, arom.+CH=).

4.3.3. (−)-(*S*)-2-(2-Chlorophenyl)-2,3-dihydro-4*H*-pyran-4-one 6c. $[\alpha]_D^{25}=-127$ ($c=0.24$, $CHCl_3$). ^1H NMR (δ): 2.7–2.9 (m, 2H, CH_2), 5.6 (d, 1H, CH=, $J=6.1$), 5.85 (dd, 1H, CH, $J=13.4$, 4.4), 7.2–7.4 (m, 3H, arom.), 7.55 (d, 1H, CH=, $J=6.1$), 7.65 (dd, 1H, arom., $J=7.3$, 1.9).

4.4. (±)-3,6-Dihydro-6-methoxy-2-(2-methoxyphenylchromiumtricarbonyl)-4-trimethylsilyloxy-2*H*-pyran 8

Zinc chloride (1 mL 0.37 M soln in THF) was added at −78°C to a solution of **1b** (0.37 mmol) and **3** (0.4 mmol) in THF (3 mL). The mixture was stirred at the same temperature for 1 h and then stirred overnight at −20°C. The yellow mixture was quenched with H_2O (10 mL) and the aqueous phase extracted using Et_2O (3×10 mL). After washing with H_2O (10 mL), the organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude yellow product thus obtained was taken up with di-*iso*-propylether, and filtered to give compound **8** in 87% yield, mp 96–97°C. IR ν_{max}/cm^{-1} (Nujol) 1942, 1898, 1854, 1666. ^1H NMR (δ): 0.2 (s, 9H, $Si(CH_3)_3$), 2.1–2.2 (m, 1H, CH_2), 2.25–2.35 (m, 1H, CH_2), 3.58 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 4.74 (dd, 1H, CH, $J=10.5$, 3.6), 4.83 (bs, 1H, CH), 4.92 (dd, 1H, arom., $J=6.1$), 5.05 (d, 1H, arom., $J=6.8$), 5.25 (bs, 1H, CH=), 5.45 (dd, 1H, CH, $J=6.1$, 6.1), 5.98 (d, 1H, arom). Found: C, 51.99; H, 5.45; $C_{19}H_{24}O_7CrSi$ requires C, 51.34; H, 5.44%. EIMS: m/z 444 (M^+), 413 (-OCH_3), 388 (-2CO), 360 (-3CO).

4.5. (±)-1-Methoxy-5-(2-methoxyphenylchromiumtricarbonyl)-5-trimethylsilyloxy-1-penten-3-one 9

Zinc chloride (0.9 mL 2 M soln in THF) was added to a solution of **1b** (1.8 mmol) in CH_2Cl_2 (9 mL). The solution was cooled to −78°C and, after the addition of **3** (2.1 mmol), stirred at the same temperature for 4 h and then stirred overnight at 20°C. The yellow mixture was then quenched with H_2O (10 mL) and the aqueous

phase extracted using CH_2Cl_2 (3×10 mL). After washing with H_2O (10 mL), the organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. Column chromatography (CH_2Cl_2/Et_2O, 10:1) afforded cycloadduct **4b** (36%) and compound **9** (53%): IR ν_{max}/cm^{-1} (Nujol) 1956, 1850, 1690, 1620. ^1H NMR (δ): 0.2 (s, 9H, $Si(CH_3)_3$), 2.67 (dd, 1H, CH_2, $J=14.7$, 7.7), 2.79 (dd, 1H, CH_2, $J=14.7$, 3.2), 3.7 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 4.89 (dd, 1H, arom., $J=6.2$, 6.2), 4.95 (d, 1H, arom., $J=6.6$), 5.3 (dd, 1H, CH, $J=7.7$, 3.2), 5.48 (dd, 1H, arom. $J=6.6$, 6.6), 5.60 (d, 1H, CH=, $J=12.7$), 5.90 (d, 1H, arom., $J=6.2$), 7.58 (d, 1H, CH=, $J=12.7$). Found: C, 51.32; H, 5.44; $C_{19}H_{24}O_7CrSi$ requires C, 51.34; H, 5.44%. EIMS: m/z 444 (M^+), 416 (-CO), 388 (-2CO), 360 (-3CO), 308 (-$Cr(CO)_3$).

4.6. (±)-5-Hydroxy-1-methoxy-5-(2-methoxyphenylchromiumtricarbonyl)-1-penten-3-one 10

$BF_3{\cdot}Et_2O$ (0.74 mmol) was added to a solution of **1b** (0.74 mmol) in CH_2Cl_2 (5 mL) cooled to −78°C; the colour of the solution changed from orange to deep purple. After 5 min, diene **3** (0.85 mmol) was added and the mixture stirred at −78°C for 2 h following the disappearance of **1b** (Et_2O/CH_2Cl_2, 1:1). The reaction was quenched with a saturated solution of $NaHCO_3$ (10 mL), and filtered over a Celite pad. The aqueous phase was extracted using CH_2Cl_2 (3×10 mL) and separated; after washing with H_2O (10 mL), the organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude yellow product thus obtained was purified by column chromatography using CH_2Cl_2/Et_2O (7:1) as eluent. Yield 89%, mp (di-*iso*-propylether) 125–126°C. IR ν_{max}/cm^{-1} (Nujol) 1958, 1852, 1627, 1595. ^1H NMR (δ): 2.67 (dd, 1H, CH_2, $J=16.4$, 9.2), 2.92 (dd, 1H, CH_2, $J=16.4$, 2.5), 3.46 (d, 1H, OH, $J=3.4$), 3.72 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 4.90 (dd, 1H, arom., $J=6.2$), 5.04 (d, 1H, arom., $J=6.8$), 5.22 (m, 1H, CH), 5.48 (d, 1H, arom. $J=6.8$), 5.61 (d, 1H, CH=, $J=12.7$), 5.93 (d, 1H, arom., $J=6.2$), 7.65 (d, 1H, CH=, $J=12.7$). Found: C, 51.42; H, 4.32; $C_{16}H_{16}O_7Cr$ requires C, 51.62; H, 4.33%.

4.7. (±)-2,3-Dihydro-2-(2-methoxyphenylchromiumtricarbonyl) *cis*-3,5-dimethyl-4*H*-pyran-4-one 12

Zinc chloride (0.4 mmol in THF 0.3 mL) was added to a solution of **1** (0.4 mmol) in CH_2Cl_2 (5 mL). After the addition of **11**[13] (0.42 mmol), the mixture was stirred at 25°C for 24 h, diluted with a saturated aqueous $NaHCO_3$ (10 mL) and filtered through a Celite pad. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL), separated and, after washing with H_2O (10 mL), the organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude yellow product thus obtained was purified by preparative chromatography. Eluent: CH_2Cl_2/Et_2O/petr. ether (20:2:6). Yield 64%. IR ν_{max}/cm^{-1} (Nujol) 1969, 1890, 1669, 1623. ^1H NMR (δ): 0.98 (d, 3H, CH_3 $J=7.5$), 1.7 (s, 3H, CH_3), 2.67 (dq, 1H, CH, $J=3.1$, 7.5), 3.7 (s, 3H, OCH_3), 4.92 (dd, 1H, arom., $J=6.3$, 6.3), 5.05 (d, 1H, arom., 6.7), 5.4 (d, 1H, $J=3.1$), 5.5 (dd, 1H, arom., $J=6.7$, 6.7), 5.82 (d, 1H, arom., $J=6.3$), 7.4 (s, 1H, CH). Compound **11** was decomplexed as reported above to the corresponding 2,3-dihydro-2-(2-methoxyphenyl) *cis*-3,5-dimethyl-4*H*-pyran-4-one **20**.[12,13]

4.8. 1-(2-Methoxyphenyl)-3-trimethylsilyloxy-1,3-butadiene 13

Lithium bis(trimethylsilyl)amide (3.5 mL 1 M sol in THF) was dropped into a solution of 4-(2-methoxyphenyl)but-3-en-2-one[14] (2.84 mmol, 0.5 g) in THF (5 mL) and cooled to −40°C. After 5 min, chlorotriethylsilane (3.5 mmol, 0.6 mL) was added and the solution stirred for 1.5 h. The mixture was then quenched with a saturated solution of $NaHCO_3$ (10 mL) and extracted with Et_2O (3×10 mL). After washing with H_2O (10 mL), the organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. After flash chromatography (petroleum ether/Et_2O, 2:1), silyloxy diene **13** ((*E*)-isomer) was isolated in 95% yield (yellow oil) and used in the next step without further purification. IR ν_{max}/cm^{-1} (Nujol) 1630, 1600. ^1H NMR (δ): 1.0 (q, 6H, CH_2), 1.1 (t, 9H, CH_3), 3.86 (s, 3H, OCH_3), 4.45 (d, 2H, CH_2=, $J=3.9$), 6.65 (d, 1H, CH=, $J=15.9$), 6.86–6.95 (m, 2H, arom), 7.2–7.3 (m, 2H, arom.+CH=), 7.5 (dd, 1H, $J=7.6$, 1.4).

4.9. 3,6-Dihydro-2-(2-chlorophenylchromiumtricarbonyl)-6-(2-methoxyphenyl)-4-triethylsilyloxy-2*H*-pyran 14

Zinc chloride (1 mL 0.4 M soln in THF) was added at 0°C to a solution of **1c** (0.37 mmol) in CH_2Cl_2 (3 mL). After 10 min, diene **13** (0.43 mmol) was added and the mixture stirred at room temperature for 24 h. A solution of $NaHCO_3$ (10 mL) was added and the mixture filtered over a Celite pad. The aqueous phase was extracted using CH_2Cl_2 (3×10 mL) and, after washing with H_2O (10 mL), the organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by column chromatography (Et_2O/petroluem ether, 2:1) to give **14** in 68% yield, mp 94–95°C. IR ν_{max}/cm^{-1} (Nujol) 1990, 1900, 1660. ^1H NMR (δ): 0.7 (q, 6H, $Si(CH_2CH_3)_3$), 1.0 (t, 9H, $Si(CH_2CH_3)_3$), 2.2–2.32 (m, 1H, CH), 2.5–2.58 (m, 1H, CH_2), 3.85 (s, 3H, OCH_3), 4.83 (dd, 1H, CH, $J=10.6$, 3.3), 5.04 (bs, 1H, CH), 5.1 (dd, 1H, arom., $J=6.2$, 6.2), 5.27 (dd, 1H, arom., $J=6.4$, 6.4), 5.45 (d, 1H, CH, $J=6.4$), 5.79–5.81 (m, 2H, arom.+CH=), 6.9 (d, 1H, arom., $J=7.9$), 7.0 (dd, 1H, arom., $J=7.3$, 7.4), 7.28 (dd, 1H, arom., $J=7.9$, 1.8), 7.46 (dd, 1H, arom., $J=7.3$, 1.6). Found: C, 57.09; H, 5.52; $C_{27}H_{31}O_6ClCrSi$ requires: C, 57.19; H, 5.35%.

4.10. (±)-5-(2-Chlorophenylchromiumtricarbonyl)-5-hydroxy-1-(2-methoxyphenyl)-1-penten-3-one 15

$BF_3{\cdot}Et_2O$ (0.58 mmol) was added to a solution of **1c** (0.59 mmol) in CH_2Cl_2 (5 mL) cooled to −78°C; the colour of the solution changed from orange to deep purple. After 5 min, diene **13** (0.6 mmol) was added and the mixture stirred at −78°C for 4 h following the disappearance of **1c** (Et_2O/petroleum ether, 2:3). The

reaction was quenched using a saturated solution of $NaHCO_3$ (15 mL) and filtered over a Celite pad. The aqueous phase was extracted using CH_2Cl_2 (3×10 mL), separated and, after washing with H_2O (10 mL), the organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The yellow crude product thus obtained was purified by column chromatography using Et_2O/petroleum ether 2:3 as eluent. Yield 80% (d.e. 98%), mp (pentane) 118–119°C. IR ν_{max}/cm^{-1} (Nujol) 1960, 1910, 1880, 1630, 1595. ^1H NMR (δ): 2.9 (dd, 1H, CH_2, $J=16.9$, 9.4), 3.26 (dd, 1H, CH_2, $J=16.9$, 2.2), 3.73 (d, 1H, OH, $J=3.6$), 3.9 (s, 3H, OCH_3), 5.13 (dd, 1H, arom., $J=6.2$, 6.2), 5.25–5.3 (m, 1H, CH), 5.35 (dd, 1H, arom., $J=6.2$, 6.3), 5.45 (d, 1H, arom., $J=6.4$), 5.89 (d, 1H, arom., $J=6.4$), 6.8 (d, 1H, CH=, $J=16.4$), 6.9–7.0 (m, 2H (d, 1H, arom.), 7.38 (dd, 1H, arom., $J=8.7$, 7.8), 7.55 (d, 1H, arom., $J=7.8$), 7.95 (d, 1H, CH=, $J=12.4$). Found: C, 55.82; H, 3.76; $C_{21}H_{17}O_6ClCr$ requires C, 55.70; H, 3.78%.

4.11. 4-(2-Methoxyphenylchromiumtricarbonyl)but-3-en-2-one 16

Lithium bis(trimethylsilyl)amide (3.8 mL 1 M soln in THF) was added dropwise into a solution of acetonyltriphenylphosphonium bromide (3.8 mmol, 1.3 g) in THF (8 mL) at room temperature. After stirring for 30 min, tricarbonyl(2-methoxybenzaldehyde)chromium (3.4 mmol, 0.92 g) in THF (5 mL) was added and the solution stirred at 30°C overnight. The mixture was then quenched with H_2O (10 mL) and extracted using Et_2O (3×10 mL). After washing with H_2O (10 mL), the organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude compound **16** (85%) was obtained as an E/Z (4:1) mixture. After flash chromatography (CH_2Cl_2/petroleum ether, 5:1), the (E)-isomer of complex **16** was isolated in 65% yield. Mp (pentane) 144–145°C. IR ν_{max}/cm^{-1} (Nujol) 1968, 1887, 1859, 1682, 1593. ^1H NMR (δ): 2.36 (s, 1H, CH_3), 3.83 (s, 1H, OCH_3), 4.96 (dd, 1H, arom., $J=6.3$, 6.3), 5.1 (d, 1H, arom., $J=6.8$), 5.67 (dd, 1H, arom., $J=6.8$, 6.8), 5.9 (d, 1H, arom. $J=6.3$), 6.55 (d, 1H, CH=, $J=16.4$), 7.55 (d, 1H, CH=, $J=16.4$). Found: C, 53.77; H, 3.88; $C_{14}H_{12}O_5Cr$ requires C, 53.85; H, 3.87%. (Z)-Isomer ^1H NMR (δ): 2.30 (s, 1H, CH_3), 3.7 (s, 1H, OCH_3), 4.89 (dd, 1H, arom., $J=6.4$, 6.4), 5.1 (d, 1H, arom., $J=6.8$), 5.6 (dd, 1H, arom., $J=6.8$, 6.8), 6.1 (d, 1H, arom. $J=6.4$), 6.3 (d, 1H, CH=, $J=12.3$), 6.7 (d, 1H, CH=, $J=12.3$).

4.12. 1-(2-Methoxyphenylchromiumtricarbonyl)-3-triethylsilyloxy-1,3-butadiene 17

The (E)-isomer of **17** was obtained in 93% yield from **16** following the same experimental procedure as that used for **13**. IR ν_{max}/cm^{-1} (Nujol) 1962, 1890, 1860, 1628, 1608. ^1H NMR (δ): 0.98 (q, 6H, CH_2), 1.0 (t, 9H, CH_3), 3.82 (s, 3H, OCH_3), 4.44 (s, 1H, CH_2=), 4.47 (s, 1H, CH_2=), 4.92 (dd, 1H, arom., $J=6.4$, 6.3), 5.10 (d, 1H, arom., $J=6.4$), 5.51 (dd, 1H, arom., $J=6.2$, 6.2), 6.42 (d, 1H, arom., $J=6.2$), 6.46 (d, 1H, CH=, $J=15.7$), 6.75 (d, 1H, CH=, $J=15.7$).

4.13. Cycloaddition of triethylsilyloxy diene 17 with benzaldehyde

$BF_3{\cdot}Et_2O$ (0.6 mmol) was added to a solution of benzaldehyde (0.6 mmol, 70 mg) in CH_2Cl_2 (3 mL) cooled to −78°C. After 5 min, diene **16** (0.7 mmol, 300 mg) was added, and the mixture was stirred at −78°C for 4 h following the disappearance of **1c** (CH_2Cl_2/Et_2O, 6:1). The reaction was quenched with a saturated solution of $NaHCO_3$ (15 mL). The aqueous phase was extracted using CH_2Cl_2 (3×10 mL), separated and, after washing with H_2O (10 mL), the organic phase was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude mixture was purified by column chromatography using CH_2Cl_2 as eluent, and the low-melting compounds **18** (R_f 0.05) and **19** (R_f 0.2) were isolated.

18: ^1H NMR (δ): (diast. I/II, 1:1) 3.05 (m, 2H, CH_2), 3.5 (m, 1H, OH), 3.82 (s, 3H, OCH_3), 4.94 (dd, 1H, arom., $J=6.3$, 6.3), 5.10 (d, 1H, arom., $J=6.7$), 5.2–5.3 (m, 1H, CH), 5.65 (dd, 1H, arom., $J=6.7$, 6.4), 5.87 (d, 1H, arom., $J=6.3$), 6.55 (d, 1H, CH=, $J=16.4$), 7.25–7.42 (m, 5H, arom), 7.54 (d, 1H, CH=, $J=16.4$, diast I), 7.7 (d, 1H, CH=, $J=16.4$, diast II). **19**: ^1H NMR (δ): 3.85 (s, 3H, OCH_3), 4.98 (dd, 1H, arom., $J=6.3$, 6.3), 5.13 (d, 1H, arom., $J=6.8$), 5.69 (dd, 1H, arom., $J=6.8$, 6.8), 5.98 (d, 1H, arom., $J=6.3$), 6.90 (d, 1H, CH=, $J=16.0$), 6.90 (d, 1H, CH=, $J=16.0$), 7.05 (d, 1H, CH=, $J=15.9$), 7.38–7.42 (m, 3H, arom), 7.6–7.64 (m, 2H, arom), 7.72 (d, 1H, CH=, $J=16.0$), 7.73 (d, 1H, CH=, $J=15.9$).

4.14. X-Ray structural determination and refinement of 4c

The crystallographic data are summarised in Table 3. The intensity data were collected on a Philips PW 1100 diffractometer, using the $\theta-2\theta$ scan technique at room temperature. 1761 reflections were measured (with θ in the range 3–27°) of which 1700 were independent and included in the structural refinement. The structure was solved by means of direct and Fourier methods, and refined using full-matrix least-squares procedures (based on F_o^2), with anisotropic thermal parameters in the last cycles of refinement for all of the non-hydrogen atoms. The hydrogen atoms were introduced into the geometrically calculated positions and refined riding on the parent atoms. The SHELXL-97 computer program was used.[15]

The supplementary material for the structure includes the lists of atomic coordinates for the non-H atoms, of calculated coordinates for the hydrogen atoms, of anisotropic thermal parameters. The details of the crystal structure investigation have been deposited at the Cambridge Crystallographic Data Center as supplementary publications no. CCDC-170067 (copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: int. code +44(1223)336-033; e-mail: deposit@ccdc.cam.ac.uk].

Table 3. Crystal data and structure refinement for **4c**

Empirical formula	$C_{14}H_9ClCrO_5$
Formula weight	344.66
Temperature (K)	296(2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	$P2_1/a$
Unit cell dimensions	
a (Å)	7.159(2)
b (Å)	11.313(3)
c (Å)	17.285(6)
β (°)	92.72(2)
Volume (Å^3)	1398.3(7)
Z	4
Calculated density (Mg/m^3)	1.637
Absorption coefficient (mm^{-1})	1.026
$F(000)$	696
Crystal size (mm)	$0.15 \times 0.20 \times 0.25$
Index ranges	$-7 \le h \le 7$, $0 \le k \le 11$, $0 \le l \le 18$
Reflections collected/unique	1761/1700 [$R_{int} = 0.0416$]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1700/0/190
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0386$, $wR_2 = 0.0864$
R indices (all data)	$R_1 = 0.1538$, $wR_2 = 0.1614$
Largest difference peak and hole (e Å^{-3})	0.651 and -0.547

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