Tetrahedron 65 (2009) 752–756

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Regiochemical observations depending on electrophiles in directed lithiation of 1,3-diheteroatom substituted arene tricarbonylchromium complexes

Christophe Michon, Masato Murai, Mai Nakatsu, Jun'ichi Uenishi, Motokazu Uemura *

Kyoto Pharmaceutical University, Yamashina, Kyoto 607-8412, Japan

ARTICLE INFO

Article history:
Received 22 October 2008
Received in revised form 20 November 2008
Accepted 20 November 2008
Available online 25 November 2008

ABSTRACT

Directed lithiation of 1,3-diheteroatom substituted arene chromium complexes gave regioisomeric compounds depending on the nature of quenching electrophiles. Quenching of lithiated intermediate generated from 3-methoxybenzaldehyde ethyleneacetal chromium complex with aldehyde, 1,2-dibromotetrafluoroethane, ethyl formate, etc. gave regioselectively 2-functionalized chromium complexes, while trap with DMF afforded 4-formylated chromium complex.

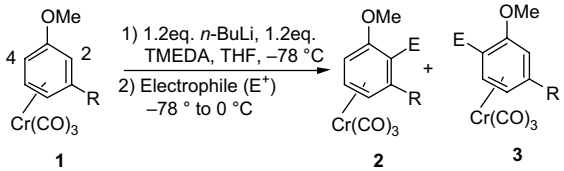
1. Introduction

Directed ortho lithiation has been one of the most effective tools for the regioselective construction of functionalized arenes and aryl metal building blocks.[1] The directing groups used for the lithiation of arenes are functional groups such as amides, amines, imines, ether, oxazolines, imidazoles, etc. When these directing groups are substituted at 1,3-positions of the arene ring, the directed lithiation occurred predominantly at 2-position. The corresponding arene tricarbonylchromium complexes are facilitated the directed lithiation due to strong electron withdrawing effect of the tricarbonylchromium fragment.[2] Directed lithiation of the arene chromium complexes is a significant useful reaction for organic synthesis combined with other characteristic properties of the chromium complexes.[3] Diastereoselective- or enantioselective lithiation of the arene chromium complexes at distinguished ortho position is employed for the preparation of optically active planar chiral arene chromium complexes.[4,5] In the course of our other project of planar chiral arene chromium complex, we found[6] that some 1,3-diheteroatom substituted arene chromium complexes gave regioisomeric products depending on the nature of quenching electrophiles. In this paper, we wish to report regiochemical results of the directed lithiation of 1,3-diheteroatom substituted arene chromium complexes followed by quenching with electrophiles.

2. Results and discussion

The regiochemistry of the directed lithiation of 3-methoxybenzaldehyde ethyleneacetal chromium complex (**1a**) was initially examined (Table 1). We reported previously that quenching of the

Table 1
Directed lithiation of 1,3-disubstituted arene chromium complexes **1**



1 **2** **3**

a: R =  **b**: R = CH_2OMe; **c**: R = Cl; **d**: R = OMe

Entry	Complex	Electrophile (E^+)	E	Yield (%)	Ratio **2**/**3**
1	**1a**	$BrCF_2CF_2Br$	Br	82	100/0
2[a]	**1a**	PhCHO	CH(OH)Ph	82	100/0
3	**1a**	$ClCO_2Et$	CO_2Et	69	100/0
4	**1a**	HCO_2Et	CHO	48	93/7
5	**1a**	MeOD	D	89	100/0
6	**1a**	DMF	CHO	80	0/100
7	**1a**	PhN(Me)CHO	CHO	33	20/80
8[b]	**1a**	$MeOCO_2Me$	CO_2Me	8 (38)	0/100
9[b]	**1a**	$ClCONMe_2$	$CONMe_2$	7 (37)	0/100
10	**1b**	$BrCF_2CF_2Br$	Br	67	100/0
11	**1b**	HCO_2Et	CHO	31	66/34
12	**1b**	DMF	CHO	64	0/100
13[c]	**1c**	$BrCF_2CF_2Br$	Br	54	100/0
14[d]	**1c**	HCO_2Et	CHO	46	100/0
15[e]	**1c**	DMF	CHO	34	0/100
16	**1d**	$BrCF_2CF_2Br$	Br	71	100/0
17	**1d**	HCO_2Et	CHO	45	100/0
18[f]	**1d**	DMF	CHO	85	0/100

[a] Diastereomeric mixture at benzylic position (ratio; 3:2).
[b] Yields of parentheses are those under the conditions of 3 equiv of BuLi.
[c] 2-Bromoanisole chromium complex was obtained in 14% yield.
[d] *o*-Anisaldehyde chromium complex was obtained in 17% yield.
[e] *o*-Anisaldehyde chromium complex was obtained in 8% yield.
[f] Ref. 10.

* Corresponding author.
E-mail address: muemura@mb.kyoto-phu.ac.jp (M. Uemura).

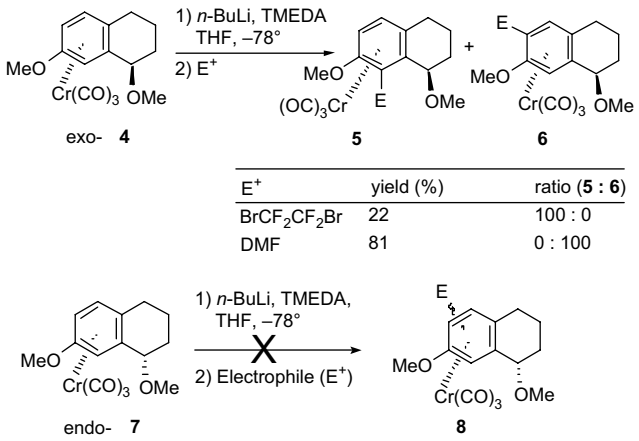
0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.11.056

lithiated intermediate with 1,2-dibromo-1,1,2,2-tetrafluoroethane gave regioselectively 2-brominated chromium complex **2a** (E=Br) (entry 1).[7] Similarly, benzaldehyde and ethyl chloroformate afforded regioselectively functionalized products at the 2-position in good yields (entries 2 and 3). Quenching with ethyl formate gave predominantly 2-formylated chromium complex **2a** (E=CHO) along with small amount formation of 4-formylated complex (entry 4). Regioselective introduction of these electrophiles at 2-position is based on 2-lithiated intermediate, in which the lithium atom is coordinated with two proximal oxygen atoms.

However, quenching of the lithiated intermediate with DMF gave surprisingly 4-formyl-3-methoxybenzaldehyde ethyleneacetal chromium complex (**3a**) (E=CHO) in 80% yield without formation of expected 2-formyl complex (entry 6). By quenching with sterically bulky *N*-methyl-*N*-phenylformamide, 4-formylated, and 2-formylated arene chromium complexes were obtained with a ratio of 80:20 in 33% yield (entry 7). Similarly, quenching with dimethyl carbonate or dimethylcarbamoyl chloride gave 4-substituted arene chromium complexes in low yield without formation of regioisomers (entries 8 and 9). It is noteworthy that both regioisomers can be obtained regioselectively by only changing of electrophiles. Thus, quenching of the lithiated intermediate with ethyl formate gave 2-formyl complex **2a** (E=CHO), while 4-formyl chromium complex **3a** (E=CHO) was obtained by trapping with DMF (entries 4 vs 6). Also, an ester group was regioselectively introduced at 2- or 4-position by quenching with different electrophiles (entries 3 vs 8). Different regioselectivity on the directed lithiation depending on the nature of the electrophiles is quite useful for the construction of functionalized arenes. It is normally known that regioselectivity change of the directed lithiation is based on kinetic or thermodynamic conditions depending on the reaction temperature, solvents, the nature of employing bases, and the steric size of the coordinating heteroatom directing groups.[8] Few examples reported that arenes with poly-substituents of an inductive acceptor group with lone pair such as chlorine showed different regioselectivity depending on the nature of quenching electrophiles in the directed lithiation. Unusual regioselectivity was observed by quenching with DMF of lithium intermediate generated from 1,2,4-trichlorobenzene and 3,4-dichloro-1-trifluoromethylbenzene.[9] This unusual regioselectivity might be based on reduced electron density of the arene ring.

We next examined the regiochemistry on the directed lithiation of other 1,3-disubstituted arene chromium complexes. Tricarbonylchromium complexes of methyl 3-methoxybenzylether and 3-chloroanisole (**1b** and **1c**) showed the same behavior on the quenching of generated lithium intermediates. Thus, quenching of the lithiated intermediates with 1,2-dibromo-1,1,2,2-tetrafluoroethane gave 2-brominated complexes **2b** and **2c** (E=Br), while trapping with DMF afforded 4-formylated complexes **3b** and **3c** (E=CHO) without formation of regioisomeric products, respectively (entries 10 vs 12; 13 vs 15). Quenching of lithiated intermediates generated from **1c** or **1d** with ethyl formate afforded regioselectively 2-formylated chromium complexes **2c** and **2d** (E=CHO) (entries 14 and 17), and trapping of lithiated intermediate from benzyl methyl ether chromium complex (1b) with ethyl formate afforded 2-formylated complex as major product (entry 11). With 3-chloroanisole chromium complex (**1c**), de-chlorinating products were obtained as minor product (entries 13–15). Unusual regioselectivity by quenching of generated lithiated intermediate from 1,3-dimethoxybenzene chromium complex (**1d**) with DMF was also reported by Schmalz et al. (entry 18).[10]

We further examined directed lithiation of cyclic tetraline chromium complexes. *exo*-Methyl ether of 7-methoxyteralol chromium complex (**4**) gave a similar result (Scheme 1). Quenching of lithiated intermediate with 1,2-dibromo-1,1,2,2-tetrafluoroethane gave 8-bromo chromium complex **5** (E=Br), while trapping with DMF afforded 6-formylated compound **6** (E=CHO) without regioisomeric products, respectively. However, the corresponding *endo*-isomer **7** gave no functionalized products at the arene ring under the same conditions. In this case, the benzylic *exo*-hydrogen at C-1 position was removed with *n*-BuLi.

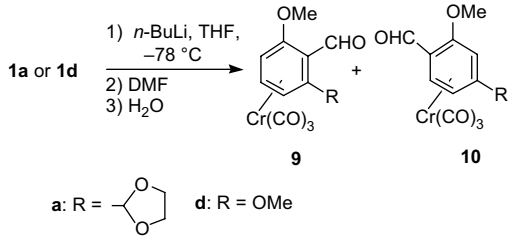


E^+	yield (%)	ratio (**5 : 6**)
$BrCF_2CF_2Br$	22	100 : 0
DMF	81	0 : 100

Scheme 1. Directed lithiation of tetralin chromium complexes.

To understand the reaction mechanism for the quenching of lithiated intermediate with DMF, we examined the selectivity change with variation of the reaction conditions. The position of the formyl group introduced by quenching of the generated lithiated intermediates with DMF was found to be affected by the quantity of *n*-butyl lithium and reaction temperature. Under the conditions with 1.2 equiv of *n*-BuLi and large excess of DMF as shown in Table 1 (entries 1 and 4), 4-formylated chromium complexes were regioselectively obtained in good yields. However, when 1.0 equiv of *n*-BuLi was treated with 1,3-dimethoxybenzene chromium complex (**1d**) in THF at −78 °C followed by addition of excess DMF, a mixture of 2-formylated chromium complex **9a** and 4-formylated complex **10a** was obtained by quenching with water at low temperature (−60 °C) in a ratio of 44:56 (Table 2, entry 5). With use of 0.7 equiv *n*-BuLi, 2- and 4-formylated chromium complexes were obtained with 76:24 ratio in 40% yield (entry 6). Similarly,

Table 2
Effect of *n*-BuLi amount for regioselectivity



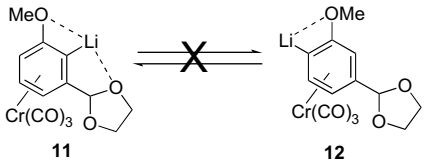
Entry	Complex	Equiv of *n*-BuLi	Ratio **9**/**10**	Yield (%)
1[a]	**1a**	1.2	0/100	80
2[b]	**1a**	1.0	9/91	84
3[b]	**1a**	0.7	16/84	40
4[a]	**1d**	1.2	0/100	85
5[b]	**1d**	1.0	44/56	57
6[b]	**1d**	0.7	76/24	40
7[a]	**1d**	0.7	0/100	43
8[b]	**1d**	0.5	69/31	29

[a] Reaction mixture after addition of DMF was warmed to 0 °C and quenched with water at 0 °C.

[b] Reaction temperature with DMF was −76 °C and quenching took place with water at −60 °C.

3-methoxybenzaldehyde ethyleneacetal chromium complex gave 16:84 mixture of 4- and 2-formylated chromium complexes in 40% yield under the conditions of 0.7 equiv *n*-BuLi and quenching with water at low temperature (Table 2, entry 3). The conditions under use of excess *n*-BuLi and quenching with water at higher temperature (0 °C) increased the 4-formylated chromium complexes, whereas a proportion of 2-formylated complexes increased under the conditions of small quantity of *n*-Buli and quenching with water at low temperature.

Unusual regioselectivity obtained by quenching of the lithiated intermediate with DMF may be related to an isomerization of the initially formed lithium intermediate **11** to nonhindered lithium intermediate **12** prior to the quenching under the reaction conditions (Scheme 2). An equilibrium mechanism of the lithiated intermediate for quenching with DMF was proposed by Schmalz.[10] Therefore, we examined equilibrium of the lithium intermediate **11** under thermal conditions. A solution of the generated lithium intermediate **11** warmed to 0 °C before addition of electrophile, and then 1,2-dibromo-1,1,2,2-tetrafluoroethane or D_2O was added to the above solution at the same temperature. The obtained compounds were 2-brominated chromium complex **2a** (E=Br) and 2-deuterio complex **2a** (E=D), respectively, without formation of products incorporating these electrophiles at the 4-position. Thus, no equilibrium between the 2-lithio and 4-lithio intermediates was observed and the initially generated 2-lithio intermediate **11** is thermodynamically stable due to the coordination of the lithium atom with two proximal oxygen atoms.



Scheme 2. Equilibrium between lithiated intermediates.

Therefore, we speculated the reaction mechanism giving 4-formyl complex by trapping with DMF as follows (Fig. 1). The generated lithium intermediate **11** reacts with DMF to afford *O*-lithiated aminoacetal intermediate **13**, in which takes place further deprotonation at the C-4 position with an excess of *n*-BuLi (or lithium dimethylamide) to produce C-4 lithiated complex **14**. The sterically more congested aminoalkoxy acetal at the C-2 position of bis-aminoalkoxy acetal intermediate **15** is reversible to C-2 lithio complex **16** with loss of DMF, while the corresponding aminoalkoxy acetal group at the C-4 position is formed in an irreversible manner. The generated aryl lithium **16** would act as base for deprotonation at the C-4 position of the intermediate **13**. Finally, 4-formyl chromium complex **3a** (E=CHO) was obtained by hydrolysis. In contrast, the corresponding *O*-lithiated hemiacetal intermediate **17** generated by trapping of the lithiated intermediate **11** with ethyl formate eliminated spontaneously lithium ethoxide to give 2-formyl complex **18**. These distinct results might be contributed to the value of electron-negativities of oxygen and nitrogen atoms. In the case of trap with DMF, elimination of DMF from aminoalkoxy intermediate is preferred due to the small electron-negativity of the nitrogen atom generating the chromium-coordinated aryl lithium intermediate **16**.

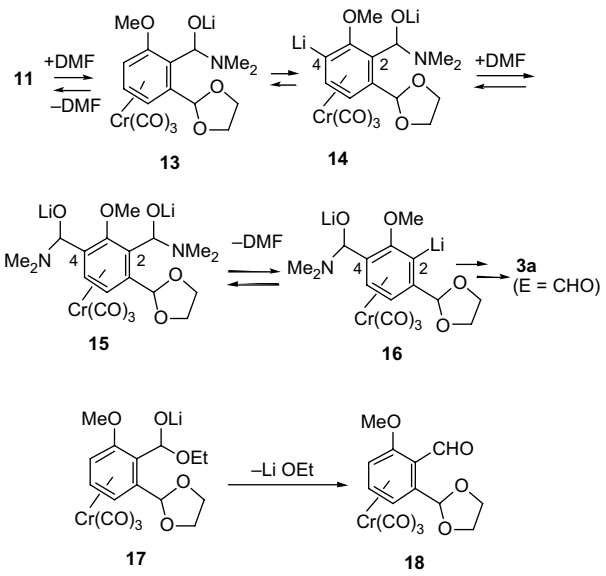
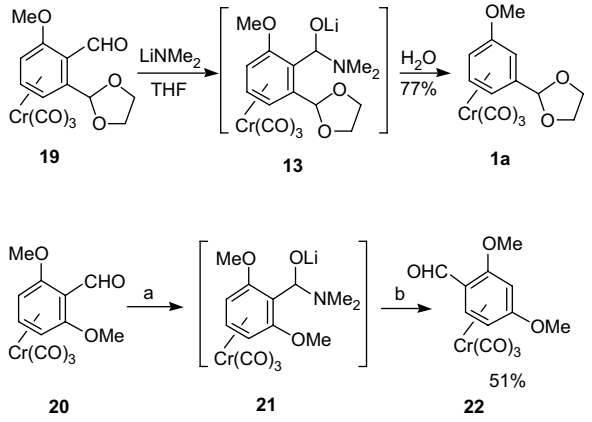


Figure 1. Reaction mechanism for quenching with DMF.

In order to confirm the presence of *O*-lithiated aminoacetal adduct **13** as an intermediate in the reaction path, 2-formylated complex **19** was treated with lithium dimethylamide (Scheme 3). When a solution of 2-formylated chromium complex **19** was added to lithium dimethylamide solution at −78 °C, a red color of the solution changed immediately to a yellow solution, in which would generate *O*-lithiated aminoacetal adduct **13** in solution.[11] By quenching with water at 0 °C, the obtained product was 3-methoxybenzaldehyde ethyleneacetal chromium complex **1a** with loss of the formyl group at 2-position in 77% yield. Furthermore, generated *O*-lithiated aminoacetal adduct **21** from 2-formyl-1,3-dimethoxybenzene chromium complex (**20**) in THF was further treated with 3.0 equiv *n*-BuLi followed by quenching with DMF to give 4-formylated 1,3-dimethoxybenzene chromium complex (**22**) in 51% yield along with formation of deformylated 1,3-dimethoxybenzene chromium complex in 26% yield. On the other hand, quenching of the intermediate with 1,2-dibromo-1,1,2,2-tetrafluoroethane afforded 2-bromo-1,3-dimethoxybenzene chromium complex in 52% yield. These results support that *O*-lithiated aminoacetal adducts **13** and **21** would be intermediates for 4-formylated chromium complexes.



Scheme 3. (a) 1.2 equiv $LiNMe_2$, THF, −78 °C. (b) (1) 3 equiv *n*-BuLi, −78 °C; (2) DMF, −78–0 °C; (3) H_2O.

The reaction mechanism of introduction of ester or dimethylamide group at 4-position of 3-methoxybenzaldehyde ethyleneacetal chromium complex (**1a**) by quenching with dimethyl carbonate or dimethylcarbamoyl chloride seems to be distinct from the mechanism of quenching with DMF. The yield of these products was largely depended on the equivalent of *n*-BuLi (Table 1). Indeed, the use of 3 equiv *n*-BuLi increased the yields up to 37–38% (entries

8 and 9). 2,4-Di-deuterio product was obtained in 38% yield by quenching with MeOD under this conditions. The formation of the complexes **3a** (E=CO_2Et, $CONMe_2$) might be resulted from 2,4-dilithiated intermediate,[12] in which sterically less hindered and more reactive C-4 lithium reacts selectively with these electrophiles to give 4-substituted complexes in low yields.

3. Conclusions

The directed lithiation of arene chromium complexes with heteroatom at 1,3-positions gave regioselectively 2- or 4-functionalized arene chromium complexes depending on the nature of electrophile. Regioselective introduction of functional groups at different position of arene ring would be a significant useful tool for organic synthesis.

4. Experimental

4.1. General

All manipulations involving organometallics were carried out under an atmosphere of nitrogen or argon and using inert gas/vacuum double manifold techniques. All NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as an internal reference. Mass spectra were determined with EI or FAB mode. Diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone ketyl immediately before use.

4.2. Directed lithiation of arene chromium complexes

*4.2.1. Preparation of tricarbonyl(2-formyl-3-methozxybenzaldehyde ethyleneacetal)chromium (**2a**) (E=CHO)*

To a solution of tricarbonyl(3-methoxybenzaldehyde ethyleneacetal)chromium (**1a**) (316 mg, 0.1 mmol) and TMEDA (139 mg, 0.12 mmol) in THF (15 mL) was added *n*-BuLi (1.6 M in hexane, 0.75 mL, 0.12 mmol) at −78 °C under argon. The mixture was stirred for 1 h at the same temperature. To the mixture was added ethyl formate (0.5 mL) and reaction mixture was warmed to 0 °C over 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with ether. The extract was washed with brine, dried over $MgSO_4$. Filtration and evaporation of organic solvent under reduced pressure and subsequent purification of the residue with silica gel column chromatography gave red crystals of title complex **2a** (E=CHO) (165 mg, 48% yield). Mp 145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (3H, s), 4.04–4.22 (4H, m), 5.06 (1H, d, *J*=6.5 Hz), 5.30 (1H, d, *J*=6.5 Hz), 5.85 (1H, t, *J*=6.5 Hz), 6.44 (1H, s), 10.13 (1H, s); IR ($CHCl_3$) 1987, 1680, 1920 cm^{-1}. Anal. Calcd for $C_{14}H_{12}O_7Cr$: C, 48.85; H, 3.52. Found: C, 48.72; H, 3.55.

*4.2.2. Tricarbonyl[2-(α-hydroxybenzyl)-3-methoxybenzaldehyde ethyleneacetal]chromium (**2a**) (E=CH(OH)Ph)*

Yellow crystals; recrystallization from ether/hexane; mp 122–124 °C; diastereomeric mixture (ratio 2:3); ^{1}H NMR (300 MHz, $CDCl_3$) major isomer δ 3.28 (1H, d, *J*=7.2 Hz), 3.73 (3H, s), 3.95–4.18 (4H, m), 5.03 (1H, d, *J*=6.5 Hz), 5.27 (1H, d, *J*=6.5 Hz), 5.59 (1H, t, *J*=6.5 Hz), 6.05 (1H, s), 6.25 (1H, d, *J*=7.2 Hz), 7.30–7.50 (5H, m); minor isomer 3.53 (1H, d, *J*=10.8 Hz), 3.69 (3H, s), 3.95–4.18 (4H, m), 5.03 (1H, d, *J*=6.5 Hz), 5.21 (1H, d, *J*=6.5 Hz), 5.59 (1H, t, *J*=6.5 Hz), 5.84 (1H, s), 5.85 (1H, d, *J*=10.5 Hz), 7.30–7.50 (5H, m); IR ($CHCl_3$) 3436 (br), 1970, 1895 cm^{-1}. Anal. Calcd for $C_{20}H_{18}O_7Cr$: C, 56.86; H, 4.30. Found: C, 57.02; H, 4.14.

*4.2.3. Tricarbonyl(2-ethoxycarbonyl-3-methoxybenzaldehyde ethyleneacetal)chromium (**2a**) (E=CO_2Et)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (3H, t, *J*=7.0 Hz), 3.76 (3H, s), 3.97–4.15 (4H, m), 4.29–4.39 (2H, m), 5.01 (1H, d, *J*=6.7 Hz), 5.07 (1H, d, *J*=6.7 Hz), 5.53 (1H, t, *J*=6.7 Hz), 5.94 (1H, s); IR (KBr) 1966, 1885, 1731 cm^{-1}; EIMS (relative intensity) *m*/*z*: 388 (M^+ 4), 332 (M^+−2CO, 14), 304 (M^+−3CO, 25), 186 (42), 52 (100). HRMS calcd for $C_{16}H_{16}O_8Cr$: 388.0250. Found: 388.0241.

*4.2.4. Tricarbonyl(4-formyl-3-methoxybenzaldehyde ethyleneacetal)chromium (**3a**) (E=CHO)*

Red crystals; mp 109 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (3H, s), 4.04–4.22 (4H, m), 5.14 (1H, d, *J*=6.4 Hz), 5.20 (1H, s), 5.74 (1H, s), 6.25 (1H, d, *J*=6.4 Hz), 10.03 (1H, s); IR ($CHCl_3$) 1987, 1923, 1682 cm^{-1}. Anal. Calcd for $C_{14}H_{12}O_7Cr$: C, 48.85; H, 3.52. Found: C, 48.92; H, 3.54.

*4.2.5. Tricarbonyl(4-methoxycarbonyl-3-methoxybenzaldehyde ethyleneacetal)chromium (**3a**) (E=CO_2Me)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.47 (3H, s), 3.49 (3H, s), 4.06–4.20 (4H, m), 5.04 (1H, d, *J*=6.6 Hz), 5.19 (1H, s), 5.70 (1H, s), 6.24 (1H, d, *J*=6.6 Hz); IR (KBr) 1957, 1872, 1640 cm^{-1}; EIMS (relative intensity) *m*/*z*: 374 (M^+, 4), 318 (M^+−2CO, 2), 290 (M^+−Cr(CO)$_3$−58), 52 (100). HRMS calcd for $C_{15}H_{14}CrO_8$: 374.0094. Found: 374.0086.

*4.2.6. Tricarbonyl(4-N,N-dimethylaminocarbonyl-3-methoxybenzaldehyde ethyleneacetal)chromium (**3a**) (E=$CONMe_2$)*

Recrystallization from ether/hexane; mp 133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00 (3H, s), 3.06 (3H, s), 3.83 (3H, s), 4.04–4.18 (4H, m), 4.99 (1H, dd, *J*=6.4, 0.7 Hz), 5.15 (1H, d, *J*=0.7 Hz), 5.63 (1H, s), 5.75 (1H, d, *J*=6.4 Hz); IR (KBr) 1963, 1870, 1656 cm^{-1}. Anal. Calcd for $C_{16}H_{17}NO_7Cr$: C, 49.62; H, 4.42; N, 3.62. Found: C, 49.75; H, 4.53; N, 3.59.

*4.2.7. Tricarbonyl(methyl 2-bromo-3-methoxybenzylether)-chromium (**2b**) (E=Br)*

Recrystallization from ether/hexane; mp 68 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.55 (3H, s), 3.85 (3H, s), 4.40 (1H, d, *J*=12.8 Hz), 4.60 (1H, d, *J*=12.8 Hz), 5.10 (1H, d, *J*=6.4 Hz), 5.22 (1H, d, *J*=6.4 Hz), 5.44 (1H, t, *J*=6.4 Hz); IR (KBr) 1955, 1877 cm^{-1}. Anal. Calcd for $C_{12}H_{11}O_5BrCr$: C, 39.26; H, 3.02. Found: C, 39.49; H, 3.12.

*4.2.8. Tricarbonyl(methyl 2-formyl-3-methoxybenzylether)-chromium (**2b**) (E=CHO)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.52 (3H, s), 3.83 (3H, s), 4.65 (1H, d, *J*=15.0 Hz), 4.91 (1H, d, *J*=15.0 Hz), 5.00 (1H, d, *J*=6.6 Hz), 5.35 (1H, d, *J*=6.6 Hz), 5.87 (1H, t, *J*=6.6 Hz), 10.15 (1H, s); IR ($CHCl_3$) 1969, 1889, 1680 cm^{-1}; EIMS (relative intensity) *m*/*z*: 316 (M^+ 4), 260 (M^+−2CO, 28), 232 (M^+−3CO, 30), 202 (M^+−3CO−2Me, 38), 187 (66), 180 (M^+−Cr(CO)$_3$, 84), 165 (M^+−Cr(CO)$_3$−Me, 97), 148 (M^+−Cr(CO)$_3$−OMe, 79), 52 (100). HRMS calcd for $C_{13}H_{12}O_6Cr$: 316.0039. Found: 316.0030.

*4.2.9. Tricarbonyl(methyl 4-formyl-3-methoxybenzylether)-chromium (**3b**) (E=CHO)*

Recrystallization from ether/hexane; mp 128–129 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.53 (3H, s), 3.88 (3H, s), 4.37 (1H, d, *J*=12.0 Hz), 4.43 (1H, d, *J*=12.0 Hz), 4.99 (1H, d, *J*=6.6 Hz), 5.16 (1H, s), 6.24 (1H, d, *J*=6.6 Hz), 10.03 (1H, s); IR (KBr) 1963, 1892, 1677 cm^{-1}. Anal. Calcd for $C_{13}H_{12}O_6Cr$: C, 49.38; H, 3.82. Found: C, 49.64; H, 3.80.

*4.2.10. Tricarbonyl(2-bromo-3-chloroanisole)chromium (**2c**) (E=Br)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85 (3H, s), 4.93 (1H, d, *J*=6.4 Hz), 5.28 (1H, dd, *J*=6.4, 1.0 Hz), 5.44 (1H, t, *J*=6.4 Hz); IR (KBr) 1965, 1892 cm^{-1}; EIMS (relative intensity) *m*/*z*: 356 (M^+ 2), 322 (M^+−Cl, 2), 300 (M^+−2CO, 2), 272 (M^+−3CO, 7), 238 (M^+−3CO−Cl), 222 (5), 76 (24), 52 (100). HRMS calcd for $C_{10}H_6BrClCrO_4$: 355.8542. Found: 355.8539.

4.2.11. Tricarbonyl(2-chloro-3-methoxybenzaldehyde)chromium (**2c**) (E=CHO)

Recrystallization from ether/hexane; mp 130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (3H, s), 4.90 (1H, d, J=6.6 Hz), 5.14 (1H, d, J=6.6 Hz), 5.79 (1H, t, J=6.6 Hz), 10.14 (1H, s); IR ($CHCl_3$) 1974, 1889, 1694 cm^{-1}. Anal. Calcd for $C_{11}H_7O_5CrCl$: C, 43.09, H, 2.30. Found: C, 43.12; H, 2.21.

4.2.12. Tricarbonyl(4-chloro-2-mthoxybenzaldehyde)chromium (**3c**) (E=CHO)

Recrystallization from ether/hexane; mp 74 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (3H, s), 5.11 (1H, d, J=6.3 Hz), 5.34 (1H, s), 6.23 (1H, d, J=6.3 Hz), 9.91 (1H, s); IR (KBr) 1965, 1898, 1686 cm^{-1}. Anal. Calcd for $C_{11}H_7ClO_5Cr$: C, 43.09; H, 2.30. Found: C, 43.04; H, 2.59.

4.2.13. Tricarbonyl(2,6-dimethoxybromobenzene)chromium (**2d**) (E=Br)

Recrystallization from ether/hexane; mp 138–139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89 (6H, s), 4.89 (2H, d, J=6.6 Hz), 5.50 (1H, t, J=6.6 Hz); IR ($CHCl_3$) 1952, 1876 cm^{-1}. Anal. Calcd for $C_{11}H_9O_5CrBr$: C, 37.42; H, 2.57. Found: C, 37.70; H, 2.32.

4.2.14. Tricarbonyl(2,6-dimethoxybenzaldehyde)chromium (**2d**) (E=CHO)

Recrystallization from ether/hexane; mp 147–148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.82 (6H, s), 4.82 (2H, d, J=6.9 Hz), 5.84 (1H, t, J=6.9 Hz), 10.12 (1H, s); IR ($CHCl_3$) 1968, 1879, 1683 cm^{-1}. Anal. Calcd for $C_{12}H_{10}O_6Cr$: C, 47.69; H, 3.33. Found: C, 47.59; H, 3.36.

4.2.15. exo-Tricarbonyl(1,7-dimethoxy-8-bromotetraline)chromium (**6**) (E=Br)

Recrystallization from ether/hexane; mp 134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.37 (d, J=6.8 Hz, 1H), 5.31 (d, J=6.8 Hz, 1H), 4.50 (s, 1H), 3.85 (s, 3H), 3.54 (s, 3H), 2.63–2.58 (m 2H), 2.31–2.27 (m, 1H), 1.77–1.43 (m, 3H); IR ($CHCl_3$) 1958, 1877 cm^{-1}. Anal. Calcd for $C_{15}H_{15}O_5CrBr$: C, 44.36; H, 3.72. Found: C, 44.35, H, 3.69.

4.2.16. exo-Tricarbonyl(1,7-dimethoxy-6-formyltetraline)chromium (**6**) (E=CHO)

Recrystallization from ether/hexane; mp 162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.98–1.79 (3H, m), 2.21–2.12 (1H, m), 2.45–2.35 (1H, m), 2.73–2.63 (1H, m), 3.53 (3H, s), 3.84 (3H, s), 4.36–4.40 (1H, m), 5.28 (1H, s), 6.19 (1H, s), 10.05 (1H, s); IR ($CHCl_3$) 1959, 1900, 1676 cm^{-1}. Anal. Calcd for $C_{16}H_{16}CrO_6$: C, 53.78, H, 4.80. Found: C, 53.68, H, 4.59.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research from Ministry of Education, Culture, Sports, Science and Technology, Japan. We thank also the support of COE Foundation of Kyoto Pharmaceutical University.

References and notes

1. Representative reviews; (a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879; (b) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206; (c) Schlosser, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 376; (d) Gschwend, H.W.; Rodriguez, H.R. *Organic Reactions*; 1979; Vol. 26, p 1; (e) Clayden, J. In *Directed Metallation of Aromatic Compounds in the Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; John Wiley & Sons: Chichester, UK, 2004; part 1, p 495; (f) Hartung, C. G.; Snieckus, V. In *Modern Arene Chemistry*; Astruc, D., Ed.; Wiley, VCH: Weinheim, Germany, 2002; p 330; For some representative references; (g) McCarthy, M.; Guiry, P. J. *Tetrahedron* **2001**, *57*, 3809; (h) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345; (i) Hubbard, B. K.; Walsh, C. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 730.
2. For some representative reviews: (a) Solladié-Cavallo, A. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: Greenwich, 1989; Vol. 1, p 99; (b) Davies, S. G.; Coote, S. J.; Goodfellow, C. L. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: Greenwich, 1991; Vol. 2, p 1; (c) Uemura, M. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: Greenwich, 1991; Vol. 2, p 195; (d) Semmelhack, M. F. In *Comprehensive Organometallic Chemistry II*; Abel, E. D., Stone, F. G. A., Wilkinson, Eds.; Pergamon: Oxford, 1995; Vol. 12, p 979; (e) Davies, S. G.; McCarthy, T. D. In *Comprehensive Organometallic Chemistry II*; Abel, E. D., Stone, F. G. A., Wilkinson, Eds.; Pergamon: Oxford, 1995; Vol. 12, p 1039; (f) *Transition Metal Arene π-Complexes in Organic Synthesis and Catalysis*; Kündig, E. P., Ed.; Topics in Organometallic Chemistry; Springer: Berlin, 2004; Vol. 7; (g) Uemura, M. *Organic Reactions*; 2006; Vol. 67, p 217.
3. Some representative references on directed lithiation of arene chromium complexes; (a) Semmelhack, M. F. In *Comprehensive Organometallic Chemistry II*; Abel, E. D., Stone, F. G. A., Wilkinson, Eds.; Pergamon: Oxford, 1995; Vol. 12, p 1017; (b) Berger, A.; Djukic, J.-P.; Michon, C. *Coord. Chem. Rev.* **2002**, *225*, 215; (c) Dickens, P. J.; Gilday, J. P.; Negri, J. T.; Widdowson, D. A. *Pure Appl. Chem.* **1990**, *62*, 575.
4. Some representative enantioselective lithiation; (a) Price, D. A.; Simpkins, N. S.; MacLeod, A. M.; Watt, A. P. *J. Org. Chem.* **1994**, *59*, 1961; (b) Ewin, R. A.; MacLeod, A. M.; Price, D. A.; Simpkins, N. S.; Watt, A. L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 401; (c) Kündig, E. P.; Quattropani, A. *Tetrahedron Lett.* **1994**, *35*, 3497; (d) Uemura, M.; Hayashi, Y.; Hayashi, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 1427; (e) Wihelm, R.; Sebhat, I. K.; White, A. J. P.; Williamis, D. J.; Widdowson, D. A. *Tetrahedron: Asymmetry* **2000**, *11*, 5003.
5. Some representative diastereoselective lithiation: (a) Han, J. W.; Son, S. K.; Chung, Y. K. *J. Org. Chem.* **1997**, *62*, 8264; (b) Alexakis, A.; Kanger, T.; Mangeney, P.; Rose-Munch, F.; Perrotey, A.; Rose, E. *Tetrahedron: Asymmetry* **1995**, *6*, 47; (c) Kondo, Y.; Green, J. R.; Ho, J. *J. Org. Chem.* **1993**, *58*, 6182; (d) Bolm, C.; Muñiz, K.; Ganter, C. *New J. Chem.* **1998**, 1371.
6. Michon, C.; Liu, S.; Hiragushi, S.; Uenishi, J.; Uemura, M. *Synlett* **2008**, 1321.
7. Tricarbonylchromium complexes of 3-methoxybenzaldehyde ethyleneacetal and the related arenes are lithiated at 2-position; (a) Kamikawa, K.; Watanabe, T.; Uemura, M. *J. Org. Chem.* **1996**, *61*, 1375; (b) Watanabe, T.; Shakadou, M.; Uemura, M. *Inorg. Chim. Acta* **1999**, *296*, 80; (c) Watanabe, T.; Shakadou, M.; Uemura, M. *Synlett* **2000**, 1141; However, 3-methoxybenzylalcohol chromium complex and the related chromium complexes are predominantly lithiated at 4-position; (d) Uemura, M.; Nishikawa, N.; Hayashi, Y. *Tetrahedron Lett.* **1980**, *21*, 2069; (e) Uemura, M.; Nishikawa, N.; Take, K.; Ohnishi, M.; Hirotsu, K.; Higuchi, T.; Hayashi, Y. *J. Org. Chem.* **1983**, *48*, 2349.
8. Representative references; (a) Shimano, M.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 10815; (b) Slocum, D. W.; Jennings, C. A. *J. Org. Chem.* **1976**, *41*, 3653; (c) Katsoulos, G.; Takagishi, S.; Schlosser, M. *Synlett* **1991**, 731; (d) Marzi, E.; Mongin, F.; Spitaleri, A.; Schlosser, M. *Eur. J. Org. Chem.* **2001**, 2911; (e) Schlosser, M.; Marull, M. *Eur. J. Org. Chem.* **2003**, 1569; (f) Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2101; (g) Skowronska-Ptasinska, M.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1985**, *50*, 2690; (h) Nguyen, T.-H.; Chau, N. T. T.; Castanet, A.-S.; Nguyen, K. P. P.; Mortier, J. *J. Org. Chem.* **2007**, *72*, 3419; (i) Nguyen, T.-H.; Chau, N. T. T.; Castanet, A.-S.; Nguyen, K. P. P.; Mortier, J. *Org. Lett.* **2005**, *7*, 2445; (j) Maggi, R.; Schlosser, M. *J. Org. Chem.* **1996**, *61*, 5430; (k) Ribéreau, P.; Queguiner, G. *Tetrahedron* **1984**, *40*, 2107.
9. (a) Kasahara, I.; Sugiura, T.; Inoue, T. PCT Int. App. W09700845 (*Chem. Abstr.* **1997**, *126*, 143985F9); (b) Burton, A. J.; Cardwell, K. S.; Fuchter, M. J.; Lindvall, M. K.; Patel, R.; Packham, T. W.; Prodger, J. C.; Schilling, M. B.; Walker, M. D. *Tetrahedron Lett.* **2003**, *44*, 5653.
10. Schmalz, H.-G.; Volk, T.; Bernicke, D. *Tetrahedron* **1997**, *53*, 9219.
11. *O*-Lithiated amino acetal generated from benzaldehyde chromium complex with chiral lithium amide is performed by enantioselective ortho lithiation with BuLi and electrophilc substitution followed by acidic hydrolysis to give enantiomerically enriched ortho substituted benzaldehyde chromium complex. The formyl group in this case was not eliminated due to less steric hindrance; Alexakis, A.; Kanger, T.; Mangeney, P.; Rose-Munch, F.; Perrotey, A.; Rose, E. *Tetrahedron: Asymmetry* **1995**, *6*, 2135.
12. Dilithiated species of arene chromium complexes; see references, (a) Davies, S. G.; Loveridge, T.; Clough, J. M. *J. Chem. Soc., Chem. Commun.* **1995**, 817; (b) Tan, Y.-L.; Widdowson, D. A.; Wilhelm, R. *Synlett* **2001**, 1632; (c) Quattropani, A.; Bernardinelli, G.; Kündig, E. P. *Helv. Chim. Acta* **1992**, *82*, 90.