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Enantioselective ortho-Lithiation of Aminals of Benzaldehyde Chromiumtricarbonyl Complex

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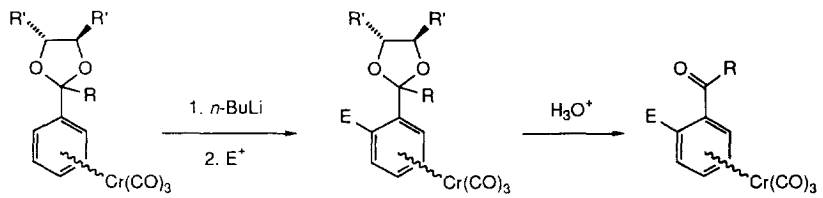
Abstract *: The asymmetric ortho lithiation of aminals of benzaldehyde chromiumtricarbonyl complex is described. The best regioisomeric composition is attained with aminal* ***2d****. Quenching with an electrophile and hydrolysis of the aminal back to the aldehyde afford a single enantiomer of the o-substituted benzaldehyde chromiumtricarbonyl complex.*

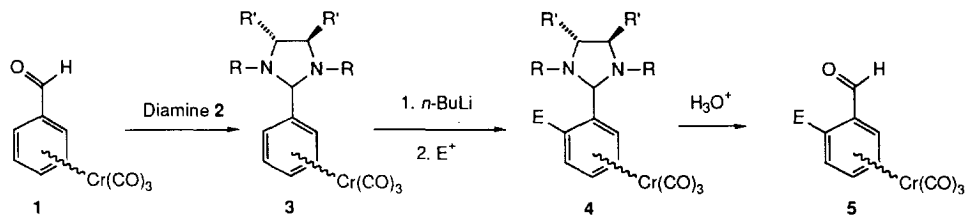
Chiral chromiumtricarbonyl arene complexes are useful synthons in asymmetric synthesis.[1] Their preparations lie usually in the resolution of diastereomeric derivatives[2] or enzymatic enantioselection.[3] We have recently demonstrated that enantioselective complexation of o-substituted chiral aminal derivatives of the corresponding aldehydes is a viable way to achieve this goal.[4]

Recent interest in the selective o-metallation (versus o'-metallation) of arene chromiumtricarbonyl complexes led to highly diastereoselective preparation of o-substituted arene complexes.[5] The overall enantioselective process has been reported using either a chiral base as deprotonation reagent,[6] or a chiral acetal derivative of benzaldehyde or acetophenone chromiumtricarbonyl complex :[7]



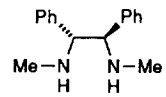
The main problem with acetals lies in the difficulties in the preparation of these derivatives and in the final hydrolysis step where extensive decomplexation occurs.[7]

For our part, we were interested by the same approach using chiral aminals as auxiliaries, in light of the ease of preparation and hydrolysis of such derivatives.[4] We report herein our preliminary results in this field :

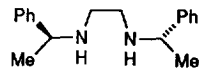


Starting from benzaldehyde chromiumtricarbonyl **1** we have prepared several aminals **3a-3d** by reaction of **1** with chiral diamines **2a-2d** (in 83-95% yield).

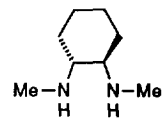
Diamines :



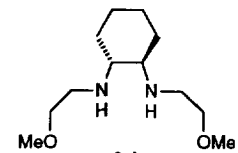
2a



2b



2c

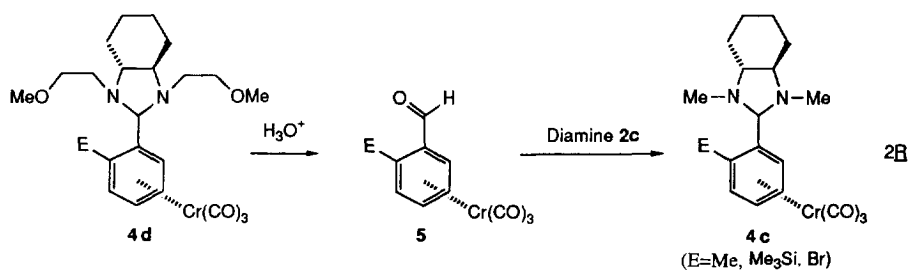


2d

Aminals **3** were treated with different RLi under various conditions, and then methylated with MeI (Table). The lithiation is best performed with *n*-BuLi, in THF solvent, and the crude yield of methylated product **4** (mixture of regioisomers) is quantitative. The presence of lithium salt has neither deleterious nor beneficial effect (compare entries 5 and 7). Deprotonation with LDA was unsuccessful and a strong base such as *t*-BuLi gave an intractable mixture of (polymethylated ?) products. In Et_2O solvent (entry 4), a poor yield of **4** was obtained.

As far as the regioselectivity of metallation is concerned, the results with aminals **3a**, **3b** and **3c** (entries 1-3) were quite disappointing as the main products were the ones arising from meta and para metallation.[8] The steric bulk of the aminal moiety overcomes the chelating ability of the nitrogen of the imidazolidine ring. However, aminal **3d**, having the additional CH_2-CH_2-OMe side chain on the nitrogen, is particularly efficient as the ortho metallation product becomes the major one. *Moreover in all the cases (except entry 6) the selectivity of o-metallation versus o'-metallation was total.* This enhanced regioselectivity is ascribed to the bidentate structure of the oxygen of the side chain and the nitrogen of the imidazolidine ring (see scheme on the following page).

The ratio of ortho to meta and para products was determined after hydrolysis of the obtained aminals **4** (0.5 N aqueous HCl) back to the aldehyde **5** and integrating the CHO signal by ^1H NMR spectroscopy. The overall yield of isolated (by column chromatography on SiO_2) aldehydes is 53-64%. The absolute configuration of the ortho methylated product was ascribed to be R on the basis of the sign of its rotation,[9] and the enantiomeric excess was measured by formation of the diastereomeric aminals with excess diamine **2c**, and integration (by ^1H NMR) of the aminal proton on **4c** (singlet).[10]



4d **5** **4c**
(E=Me, Me_3Si, Br)

Once the best conditions of selective o-metallation were set, some other electrophiles were reacted with the lithio-arene derivative. Thus, silylation with TMSCl gave the o-silylated product (entry 9) and bromination with 1,2-dibromoethane gave the o-bromo derivative (entry 10) in 53 and 64% isolated yield respectively. In both cases the ratio of ortho to meta and para was higher than in the methylation experiments, a fact already observed in the case of acetals of benzaldehyde chromiumtricarbonyl.[7]

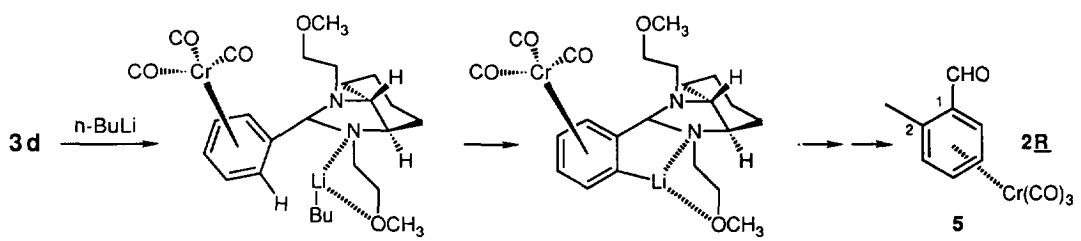
TABLE

Lithiation of aminals of benzaldehyde chromiumtricarbonyl complex, followed by reaction with an electrophile.

Entry	Aminal	Metallation conditions	Solvent	E+	Crude overall yield %	Ratio[a] ortho : m and p	de of ortho 4 %
1	**3a**	3 *n*-BuLi; -30°C; 0.5h	THF	MeI	>95	0 : 100	-
2	**3b**	"	"	"	>95	10 : 90	>99
3	**3c**	"	"	"	>95	10 : 90	>99
4	**3d**	3 *n*-BuLi; -30°C; 0.5h	Et_2O[b]	"	<10	73 : 27	not determined
5	"	"	THF	"	>95	76 : 24	>99
6	"	"	toluene[c]	"	40	100 : 0	0
7	"	3 *n*-BuLi, LiBr; -30°C	THF	"	>95	77 : 23	>99
8	"	3 MeLi, LiBr; -30°C	"	"	>95	80 : 20	95
9	**3d**	3 *n*-BuLi; -30°C; 0.5h	THF	Me_3SiCl	>95	90 : 10	>99
10	"	"	"	$(CH_2Br)_2$	>95	95 : 5	>99

a. Ratio determined on the hydrolyzed aldehyde **5**, by ^1H NMR on the CHO signal.
b. The whole sequence (lithiation and methylation) was done in this solvent.
c. Only the lithiation was performed in toluene. THF was added for the methylation step.

The stereochemical outcome of this asymmetric deprotonation may be ascribed to a bidentate chelation of lithium as suggested tentatively in the following scheme :



In summary, we have demonstrated that the chiral aminal auxiliary may be quite efficient when the appropriate diamine is used. Usually, chiral aminals act as steric controllers,[11] although some chelation controlled diastereoselective reactions were known.[12] In the present case the imidazolidine nitrogen alone is not sufficient and the additional methoxy group on the side chain helps to maintain a tight chelation of the metal.

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8. The meta metallation products were racemic materials. The chiral auxiliary was unable to discriminate the meta from the meta' positions. For meta-metallation, see for example :
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9. ortho-Tolualdehyde chromiumtricarbonyl complex was levorotatory (-475 for a 77:23 mixture of ortho and meta + para regioisomers) and was assigned the R configuration.[2a] Purified ortho-trimethylsilyl benzaldehyde chromiumtricarbonyl complex had $[\alpha]_D$ = -157, lit -154 (Davies, S. G.; Goodfellow, C.L. *J. Chem. Soc., Perkin Trans. 1* **1990**, 393-407)
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