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Enantioselective ortho-Lithiation of Benzaldehyde Chromiumtricarbonyl Complex

Alexandre Alexakis[a], Tonis Kanger[a] and Pierre Mangeney[a]
Françoise Rose-Munch[b], Anne Perrotey[b] and Eric Rose[b]

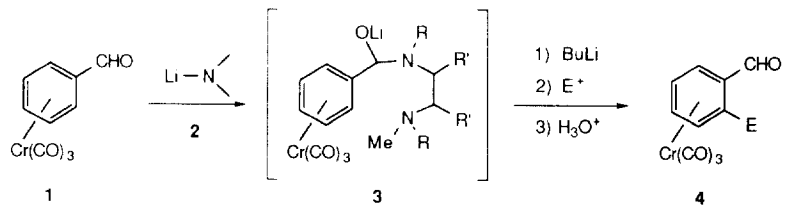
[a] Laboratoire de Chimie des Organo-Eléments, CNRS URA 473
[b] Laboratoire de Chimie Organique, CNRS URA 408

Université P. et M. Curie, 4, Place Jussieu , F-75252 Paris Cedex 05, France

Abstract : *The asymmetric ortho lithiation of benzaldehyde chromiumtricarbonyl complex is performed by in situ temporary protection of the aldehyde functionality with a chiral amide and BuLi as metallating agent. Reaction with an electrophile followed by acidic hydrolysis leads to the enantiomerically enriched ortho substituted benzaldehyde chromiumtricarbonyl complex.*

Chiral arenechromium tricarbonyl derivatives are useful tools in asymmetric synthesis.[1] The particularly interesting problem of asymmetric ortho deprotonation of a monosubstituted arenechromium tricarbonyl derivative has been recently actively studied by several groups and by us. Chiral ethers,[2] sulfoxides,[3] acetals[4] or aminals[5] have been used, as well as chiral bases[6] or chiral complexing agents such[7] as sparteine. We disclose herein our first results of a new concept where tricarbonylchromium benzaldehyde is *in situ* protected, ortho deprotonated and reacted with an electrophile in a one pot procedure.

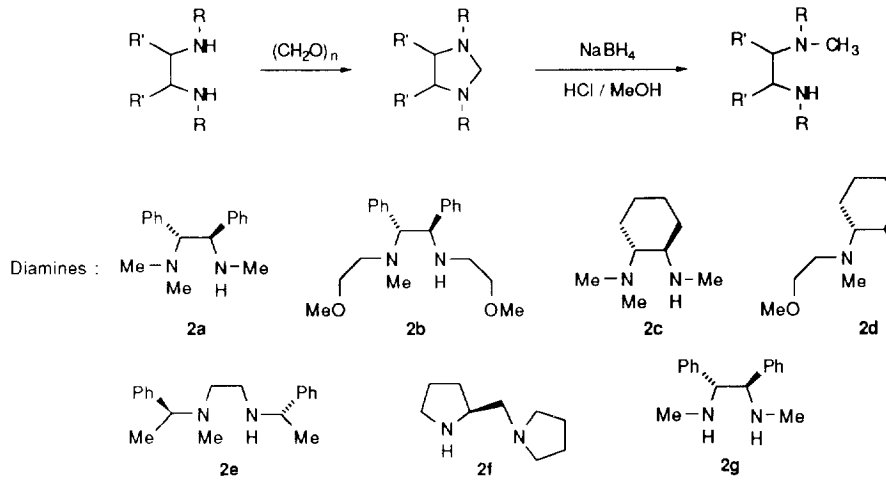
The method, developed by Commins[8], where an aromatic aldehyde is temporarily protected as amino-alcoholate, while the amino appendage facilitates the ortho deprotonation, is an essentially achiral process. When applied to an aromatic compound, with a potential planar chirality, it allows the unprecedented asymmetric version of this process :



1 3 4

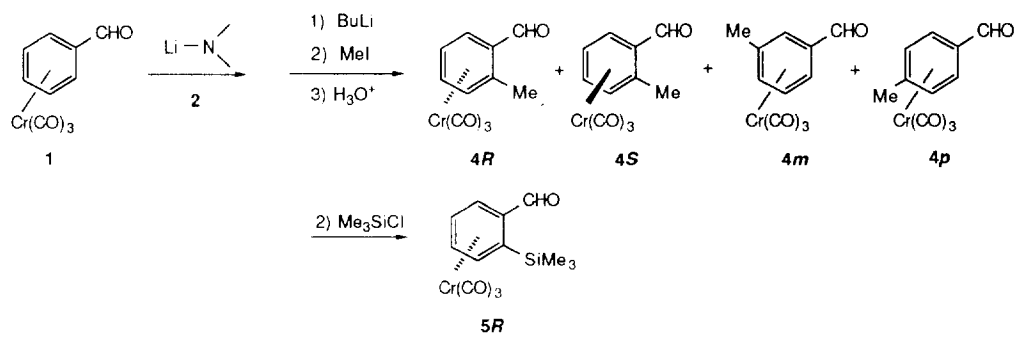
Scheme 1

Several diamines were used in this approach, most of them derived from a C2 symmetrical diamine by an N-methylation (diamines **2a-2e**). In addition, commercially available diamine **2f**, derived from L-proline, was tested.



Scheme 2

After screening several reaction conditions, the following typical procedure was systematically applied to the above diamines. To a solution of 0.6 mmol of Li-amide (prepared from equimolecular amounts of n-BuLi and diamine **2a-2f** by stirring at -30°C for 15 min) in THF (10 mL) Cr-benzaldehyde (0.5 mmol, in 5 mL THF) was added at -30°C . The resulting mixture was stirred at the same temperature for 15 min and n-BuLi (1.5 mmol, 1.6M solution in hexane) was added via syringe. After stirring at -30°C for 3h, the electrophile was added and the reaction was allowed to warm to room temperature for 1h. The reaction mixture was then cooled to 0°C, quenched with 10% aq. HCl and extracted three times with 30 mL Et_2O. The combined organic extracts were washed with brine and dried over $MgSO_4$. The solvent was evaporated and the product was isolated by flash chromatography on silica gel, eluting with cyclohexane/ Et_2O (7:3).



Scheme 3

As shown in the Table, most reactions gave a mixture of ortho (**4*R*** + **4*S***), meta (**4m**) and para (**4p**) methylated products, in addition to unreacted starting material (5-20%). All these aldehydes were difficult to separate. The ratio of these compounds was determined by integration (^1H NMR) of the Me and the CHO group. On the other hand, the crude mixture could be treated with excess (*R,R*) N,N'-dimethyl-1,2-cyclohexane diamine

to form the diastereomeric aminals which allowed the determination of the ortho (**4*R***) versus ortho' (**4*S***) ratio.[9] As the enantioselection is concerned, the two phenyl-substituted diamines **2a** and **2b** (entries 1 and 2) gave the best ratio (ee 78 and 72% respectively). However, only diamine **2b** having the two methoxy appendages on the nitrogen atom gave exclusively the ortho methylated products (**4*R*** + **4*S***) in 68% isolated yield. Quenching with Me_3SiCl (entry 3) afforded the ortho-silylated product **5** in 58% isolated yield and 71% enantiomeric excess.[10] Finally, it should be noted that when diamine **2g** was used as its bis-amide, the intermediate aminoalcoholate **3** was unstable and collapsed into the corresponding aminal.

TABLE

Reaction of benzaldehyde chromiumtricarbonyl complex according to Scheme 3

Entry	Amine	E^+	Ratio[a] ortho : m and p	Ratio[b] ortho : ortho' (**4*R***) : (**4*S***)
1	**2a**	MeI	3 : 1	8 : 1
2	**2b**	"	100 : 0	6 : 1[c]
3	"	Me_3SiCl	100 : 0	6 : 1[d]
4	**2c**	MeI	3 : 1	5 : 1
5	**2d**	"	4 : 1	3 : 1
6	**2e**	"	1 : 1	1.2 : 1
7	**2f**	"	3 : 1	2 : 1
8	**2g**	"	see text	see text

a. Ratio determined on the hydrolysed aldehyde **4**, by ^1H NMR on the CHO and Me signal.
b. Ratio determined on the corresponding diastereomeric aminals, by ^1H NMR.
c. Reaction optimised with 2 eq. of Li-**2b**. Isolated yield 68%; ee 72%.
d. Isolated yield of **5*R*** 58%; ee 71% (see ref 10). Absolute configuration ref 11.

The striking aspect of this enantioselective lithiation is that the first step (formation of **3**) generates a new stereogenic centre, at the starting carbonyl functionality position. The question of whether this new stereogenic centre determines the level of enantioselectivity was addressed by ^1H NMR (200 MHz) experiments with **2b** in perdeuterated THF. The CH proton of the lithium aminoalcoholate functionality appears as a single signal at 4.65 ppm (singlet) and the ortho and ortho' protons as doublets at 5.41 and 6.25 ppm.[12] Thus, it may be assumed that the origin of this enantioselective process lies in this first step.

The question of the regioselectivity is also of interest. Both structurally related diamines **2a** and **2b** give a quite good enantioselectivity (ee 78 and 72% respectively), although they differ in the regioselectivity of the lithiation step. Therefore, the clean regioselectivity with diamine **2b** should be ascribed to the two methoxy appendages on the nitrogen atom, an effect already noted in the enantioselective lithiation of aminals of benzaldehyde tricarbonylchromium.[5]

In summary, we have developed a new concept for introduction of planar chirality which has wide applicability not only with arene tricarbonylchromium derivatives but also to other systems such as ferrocenes and other metal complexes.

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