193. A New Asymmetric Synthesis of Tricarbonylchromium Complexes of *ortho*-Substituted Benzaldehydes

Preliminary Communication

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ortho-Substituted [Cr(CO)$_3$(benzaldehyde)] complexes are obtained *via* nucleophilic addition of alkyl- and aryllithium reagents to a [Cr(CO)$_3$(phenylmethaneimine)] complex followed by *endo*-hydride abstraction with triphenylmethyl cation. This sequence, when carried out with a [Cr(CO)$_3$(benzaldehyde SAMP hydrazone)] complex affords substituted derivatives (Me, Bu, Ph, vinyl) with high ($\geqslant 97\%$) diastereoselectivity and, after hydrolysis, *ortho*-substituted [Cr(CO)$_3$(benzaldehyde)] ((*S*)-**1**) complexes of high enantiomeric purity.

Chiral tricarbonylchromium complexes of *ortho*-substituted benzaldehydes **1** are attractive for asymmetric synthesis, because reactions at the aldehyde function in **1** can be carried out with very high diastereoselectivity [1]. This has stimulated much interest in the development of synthetic routes to enantiomerically enriched or enantiomerically pure complexes **1**. These include classic [1a,e,g,j] [2a–b] or kinetic [2c–f] resolution of racemic mixtures, chromatography on chiral solid supports [3], and asymmetric syntheses [2a–b] [4].

Reported asymmetric syntheses of **1** center on the diastereoselective complexation of chiral 1,2-substituted benzene derivatives [2a–b] [4a] and the diastereoselective *ortho*-lithiation of chiral monosubstituted benzene complexes [4b]. In this communication, we describe a new synthesis of *rac*-**1** and a highly asymmetric version, both based on the addition of C-nucleophiles to [Cr(CO)$_3$(benzaldehyde)] derivatives.

Carbanions react with arenes bound to the electron-withdrawing Cr(CO)$_3$ group by *exo*-addition, to afford anionic [Cr(CO)$_3$(η^5-cyclohexadienyl)] complex intermediates. Oxidative decomplexation delivers the substituted arene, the overall reaction being the formal replacement of an aromatic H-atom by a C-nucleophile [5]. The same transformation but without detaching the metal fragment requires the abstraction of H_{endo}–C(6) as a hydride from the η^5-cyclohexadienyl ligand. This conversion has not met with success so far[1]. Although there is some precedent for *endo*-hydride abstraction in transition-metal η^5-cyclohexadienyl complexes [7a–d], the literature shows that the preferred – and with the Cr(CO)$_3$ group exclusive – reaction with electrophilic reagents is the removal of the (*exo*) carbanion unit to give back the starting arene complex [5] [7] [8].

We recently found that [Cr(CO)$_3$(phenylmethaneimine)](**2**) and [Cr(CO)$_3$(2-phenyl-4,5-dihydrooxazole)](**3**) complexes react with organolithium nucleophiles with high

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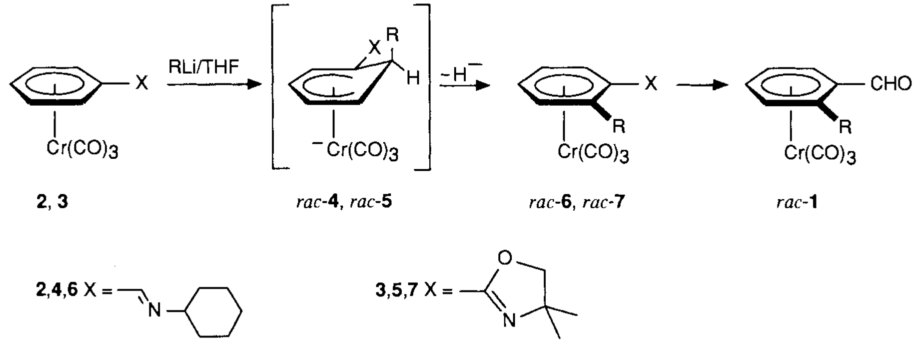
[1] All previous examples of synthesis of [Cr(CO)$_3$(η^6-RC$_6$H$_5$)] complexes *via* nucleophilic addition require the presence of a leaving group on the arene [5] [6].

Scheme 1



ortho-regioselectivity [9], leading to *rac*-**4** and *rac*-**5**. We were intrigued by the possibility of accomplishing hydride abstraction from *rac*-**4** or *rac*-**5** as the sequence would give direct access to complexes of planar chirality as shown in *Scheme 1*[2]). We have demonstrated previously that chirally modified dihydrooxazole complexes **3** undergo carbanion addition with very high diastereoselectivity [10]. Combined with the hydride abstraction this would present an asymmetric variant of the above strategy.

Attempts to induce hydride abstraction from the intermediate complex *rac*-**5** with triphenylmethyl cation did not produce satisfactory results. Reactions with complex **2** proved more successful. The addition of RLi (R = Me, Bu, Ph) to **2** in dry THF was carried out under inert atmosphere as reported in [9a]. Solvent evaporation gave the air-sensitive intermediates **4a–c** as amorphous solids. They readily dissolved in dry CH_2Cl_2 at room temperature to afford dark-red solutions which were treated, *via* cannula transfer, with a CH_2Cl_2 solution of $[Ph_3C][BF_4]$ (2 equiv., freshly crystallized from MeCN). After stirring the mixture overnight, aqueous workup and flash chromatography on a short silica-gel column afforded *rac*-**1a–c** (*Table 1*).

Table 1. *Syntheses of Racemic Complexes* **1** *from Complex* **2**[a])

Entry	RLi	Product	Yield [%][b])
1	MeLi	*rac*-**1a**	64
2	BuLi	*rac*-**1b**	61
3	PhLi	*rac*-**1c**	62

[a]) 1.1 equiv. of RLi and 2.0 equiv. of $[Ph_3C][BF_4]$ were used in all reactions.

[b]) After purification by flash chromatography.

For an asymmetric version, we used the new hydrazone complex **8**, readily prepared in 88% yield from $[Cr(CO)_3$(benzaldehyde)] [9a] and (*S*)-1-amino-2-(methoxymethyl)-pyrrolidine (SAMP) [11]. The nucleophile addition/hydride abstraction sequence gave the diastereoisomeric complexes **9a–d** and **10a–d** (*Scheme 2*). Although diastereoselectivity was high throughout (MeLi 97%, BuLi 96.5%, PhLi 93%, vinyllithium 99% de), yields were less satisfactory (42, 44, 21, and 42%, respectively).

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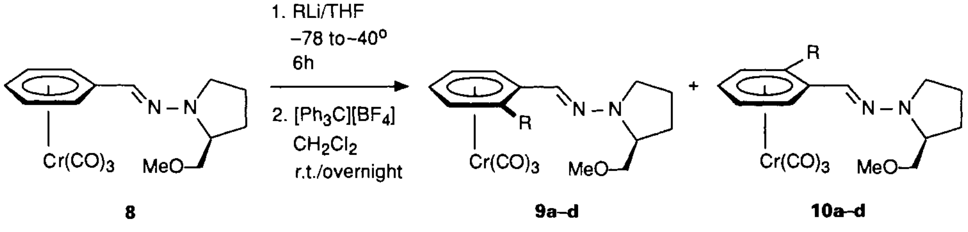
[2]) For clarity, only one of the two enantiomers of *rac*-**1**, **4–7** is shown in *Scheme 1*.

Scheme 2



8 **9a–d** **10a–d**

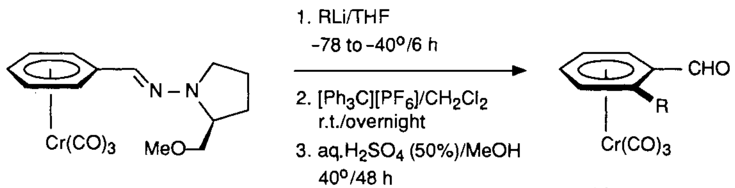
> 96.5 : < 3.5

The reaction was optimized with PhLi, the nucleophile which initially gave the lowest yield and de. Salt formation with the triphenylmethane cation was thought to be a likely cause for loss of material upon chromatography. Indeed, treatment of the crude mixture with acid (aq. H_2SO_4 (50%)/MeOH) followed by conversion of the resulting aldehyde/hydrazone mixture with SAMP back to the hydrazone gave, after chromatography, a 98.4:1.6 mixture **9c**/**10c** in 71% yield.

In all cases, the ratio of diastereoisomers formed was readily determined by ^{1}H-NMR spectroscopy *via* integration of the vinylic proton resonance signals of the two diastereoisomers. Equimolar mixtures of **9a–c** and **10a–c** were prepared from *rac*-**1a–c** and SAMP[3]. The assignment of the proton resonance signals of the minor diastereoisomer **10a–c** was unambiguous.

The relative configuration of the two new stereogenic centers in **9a–c**, with respect to the preexisting chiral center of the auxiliary, was assigned by converting pure **9a** into the

Scheme 3



8 (*S*)-**1a–c**

Table 2. *Asymmetric Syntheses of Complexes* **1** *from Complex* **8**[a])

Entry	RLi	Product	Yield [%][b])	[α]$_D$[c]) (*c*)[d])
1	MeLi	(*S*)-**1a**	55	+660 (0.23)[e])
2	BuLi	(*S*)-**1b**	56	+540 (0.44)
3	PhLi	(*S*)-**1c**	55	+380 (0.43)

[a]) 1.1 equiv. of RLi and 2.0 equiv. of [Ph$_3$C][PF$_6$] were used in all reactions.

[b]) After purification by flash chromatography; unhydrolyzed SAMP hydrazone complexes **9** and **10** were also isolated in 9–10% yield.

[c]) [α]$_D$ measurements at 20°, *Entry 1* in CHCl$_3$; other entries in CH$_2$Cl$_2$.

[d]) e.e. [%] > 97, controlled by SAMP hydrazone formation (see text).

[e]) Recrystallized product.

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[3]) Compounds **9a–c** could not be separated from **10a–c** by flash chromatography.

known complex (*S*)-**1a** ($[\alpha]_D^{20} = +660$ ($c = 0.23$, $CHCl_3$); [12]: $[\alpha]_D^{20} = +665$ ($c = 0.22$, $CHCl_3$)).

Although initially useful for the determination of the extent of asymmetric induction, the isolation of the hydrazone complex is not required, and the three-step transformation of **8** into the aldehyde complexes **1a–c** could be carried out as a one-pot procedure (*Scheme 3, Table 2*). While yields are moderate because of the limited stability of the aldehyde complexes and the requirement of a non-oxidative hydrazone-cleavage procedure demanding rather severe conditions, the methodology is new, competitive, and complementary to existing methods. Of particular interest is the finding that substitution of an aromatic H-atom by a carbanion in $[Cr(CO)_3(arene)]$ complexes can be realized without loosing the $Cr(CO)_3$ group. Further studies including asymmetric transformations of **8** into regio- and stereoselectively substituted cyclohexadienes [9b] [10] are in progress.

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