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Planar Chiral Arene Tricarbonylchromium Complexes via Enantioselective Deprotonation / Electrophile Addition Reactions

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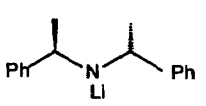
Abstract: Sequential reaction of prochiral (η^6-arene)$Cr(CO)_3$ complexes with chiral amide bases and electrophiles yielded planar chiral complexes. Benzaldehyde acetal and phenyl carbamate complexes gave *o*-substituted products with 64 to 81% enantiomeric excess. With the benzaldehyde acetal complex, competitive benzylic deprotonation occured. Enantiomeric purity of the substituted carbamate complexes could be increased to >90% ee by fractional crystallization. The racemate crystallized selectively, leaving the enantiomerically enriched complex in solution.

1,2-disubstituted (arene)$Cr(CO)_3$ complexes with different substituents are chiral molecules. The planar chirality and the reactivity changes due to complexation, make these readily accessible and stable complexes attractive intermediates and catalysts for asymmetric synthesis.[1] This has stimulated much interest in the development of synthetic routes to enantiomerically enriched or pure planar chiral (arene)$Cr(CO)_3$ complexes. Practical routes exist notably for *ortho*-substituted benzaldehyde complexes. They have been obtained by classic or kinetic resolution of racemic mixtures, chromatography on chiral solid supports, and asymmetric synthesis.[2] This paper reports our results on asymmetric lithiation reactions of substituted (arene)$Cr(CO)_3$ complexes. Our approach differs from previous work in this area[2c,3] in that the chiral information is not contained in the substituent but in the base used for deprotonation. Chiral bases have not been used previously in asymmetric lithiation of (arene)$Cr(CO)_3$ complexes.



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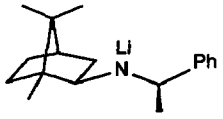

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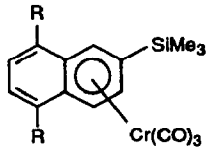


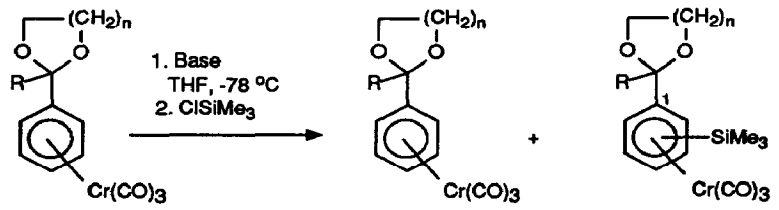
5 : R=H
6 : R=OMe

We chose the two chiral amides **1** and **2** for their reported efficiency in other asymmetric deprotonations.[4] A potential problem with their use with (arene)$Cr(CO)_3$ complexes is the small pKa difference between the complex hydrogens and the conjugate acids of **1** and **2**.[5] We have shown earlier that while tetramethylpiperidyl lithium (LTMP) reacts irreversibly with (naphthalene)$Cr(CO)_3$ at the β-position, rapid equilibration takes place when diisopropylamine is added. This is accompanied by loss of regioselectivity.[6] Steric interactions between substituents and base are another potential source of problems. In order to evaluate the regiochemistry we performed first reactions with LTMP.

Initial reactions with (naphthalene)$Cr(CO)_3$ (**3**) and (1,4-OMe-η^6-(4a,5-8a)-naphthalene)$Cr(CO)_3$ (**4**) with base **2** and $ClSiMe_3$ gave $SiMe_3$ substituted complexes **5** (yield 56 %) and **6** (yield 68 %) with excellent β-regioselectivity but very low enantioselectivity. The increase in induction in going from **3** to **4**, albeit very modest (from 8 to 20% ee), suggested that coordination of the incoming Li-base enhances enantioselectivity. Reactions with the benzaldehyde acetal complex **7** (Scheme 1) also support this argument. Entries 2 and 3

show both bases to give *ortho* substituted product **9** with considerably better ee's than obtained for the naphthalene compounds. Unfortunately, benzylic deprotonation was a major side reaction with both **1** and **2**. Lower temperatures and/or additives (HMPA, LiCl) failed to bring about the desired improvements. The *in-situ* quench procedure (ISQ)[7], while improving selectivity (entries 4 and 5), also failed to give results competitive with other routes to non racemic chiral *o*-substituted benzaldehyde complexes.[2]

Scheme 1. Enantioselective Deprotonation/Silylation Reactions with (Benzaldehyde Acetal) and (Acetophenone Acetal)$Cr(CO)_3$ Complexes



7 : n=1, R=H
10: n=2, R=H
13: n=1, R=Me

8 : n=1, R=$SiMe_3$

9 : n=1, R=H, ortho
11: n=2, R=H, meta. **12** : n=2, R=H, para
14: n=1, R=Me, meta. **15** : n=1, R=Me, para

Entry	Complex	Base[a]	Products[b] benzyl.	*ortho*	*meta*	*para*	Distribution (ee)[c]	Config.[d]	Yield[e] [%]
1	**7**	LTMP	**9**	0	100	0	0		79
2	**7**	**1**	**8,9**	74	26 (77)	0	0	1S[f]	67
3	**7**	**2**	**8,9**	47	53 (70)	0	0	1S[f]	87
4	**7**	**1** (ISQ)[g]	**8,9**	52	48 (81)	0	0	1S[f]	90
5	**7**	**2** (ISQ)[g]	**8,9**	35	65 (76)	0	0	1S[f]	85
6	**10**	LTMP	**11,12**	0	0	76	24		91
7	**13**	**1**	**14,15**	0	0	50 (6)	50		55

[a]The complex was added as a solid to 1.15 equiv.base in THF at -78°C. After 1.5h, $ClSiMe_3$ (1.2 equiv) was added. [b]Products were isolated and characterized by ^1H NMR, IR, and MS and elem. analysis or HRMS. [c]Enantiomeric excess was determined by HPLC (Chiralcel OD column, hexane/isopropanol 99.5:0.5). [d]The $[\alpha]_D$ of the aldehyde complex obtained on acetal hydrolysis matched that of the known complex[8]. [e]Yields of isolated products after chromatography. [f]Refers to the chiral center carrying the acetal substituent. [g]Lithiation in the presence of $ClSiMe_3$[7].

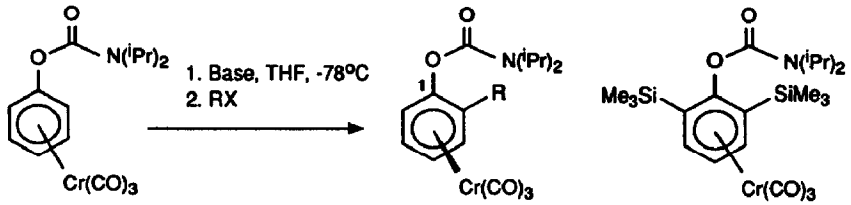
With the 6-membered ring acetal complex **10**, regioselectivity in deprotonation changed to give *meta*- and *para*- products **11** and **12** only (Scheme 1, entry 6). Similarly, the acetophenone acetal complex **13**, when reacted with the chiral base **1** and $ClSiMe_3$ gave a 1:1 mixture of *meta*- and *para*- products **14** and **15** with a very low ee for **14** (entry 7).

We then turned our attention to the carbamate complex **16**.[9] Asymmetric deprotonation would be very useful in this case because, different from (benzaldehyde)$Cr(CO)_3$ complexes, asymmetric methodologies or resolution procedures for $Cr(CO)_3$ complexes of *ortho*-substituted phenol derivatives have not been reported previously. Also, the carbamate function offers numerous synthetic possibilities.[10]

The carbamate complex **16** gave high *ortho* regioselectivity with LTMP as well as with the chiral bases **1** and **2** (Scheme 2).[11] Surprisingly, base **1**, when used in ca. equimolar quantity gave racemic product **17**. Excess of base **1** produced **17** with 67% ee (entries 3 and 4) but at the expense of yield as the *o*-disubstituted

product **22** is also formed. Base **2** deprotonates **16** with moderate enantioselectivity and the lithiated intermediate was reacted with five different electrophiles (entries 5-10).[12] Enantiomeric excess in this series varied little because asymmetric induction is controlled in the lithiation step. The products are solids and this prompted us to investigate the possibility of increasing enantiomeric purity further by fractional recrystallization. This was successful as the racemic product precipitated first, leaving in solution the enantiomerically enriched complex.

Scheme 2. Enantioselective Deprotonation/Electrophile Addition Reactions with (Phenyl Carbamate)$Cr(CO)_3$ Complex 16.



16 **17 - 21** **22**

Entry	Base	RX	Products[a]	ee[b] [%]	Yield[c] [%]	ee[d] [%]	Yield[e] [%]
1	LTMP	$ClSiMe_3$	**17**		86		
2	**1**, 1.15 eq.	$ClSiMe_3$	**17**	2	83		
3	**1**, 1.53 eq	$ClSiMe_3$	1R-**17** + **22**[f]	66	88		
4	**1**, 1.73 eq.	$ClSiMe_3$	1R-**17** + **22**[g]	67	90		
5	**2**, 1.15 eq.	$ClSiMe_3$	1R-**17**	67	86	93	44
6	**2**, 1.15 eq.	$ClSiMe_3$ (ISQ)	1R-**17**	64	80		
7	**2**, 1.15 eq.	$ClCO_2Me$	1R-**18**	73	71	91	41
8	**2**, 1.15 eq.	$ClCONMe_2$	1R-**19**	68	85		
9	**2**, 1.15 eq.	MeI	1R-**20**	64	93	87	46
10	**2**, 1.15 eq.	$HCONMe_2$[h]	1R-**21**	69[i]	93	95[i]	47

[a]The absolute configuration refers to the major isomer. It was determined for 1R-(+)-**21** by X-ray of the SAMP hydrazone complex. 1R refers to the chiral center carrying the carbamate function. [b]Enantiomeric excess was determined by HPLC (Chiralcel OD column, hexane/isopropanol). [c]Isolated products, characterized by ^1H NMR, IR, MS, and elem. analysis or HRMS. [d]Enantiomeric excess of product isolated from the mother liquor after a single crystallization from ether/hexane of the less soluble racemic (or low ee) complex. [e]Isolated yield of high ee complex after chromatography. Yield based on **16**. [f]**17**/**22** = 6:4. [g]**17**/**22** = 1:1. [h]Aqueous work up, aldehyde product. [i]Determined by ^1H NMR of the SAMP hydrazone complex.

In summary, we have shown that chiral amide bases can be used to differentiate between the enantiotopic C(H) in prochiral (arene)$Cr(CO)_3$ complexes. Although enantiomeric purity is modest, in the carbamate complexes, a simple crystallization procedure provides the more soluble enantiomerically enriched complexes in enantiomeric purities above 90 %. Studies aimed at an interpretation of observed enantioselectivity and at the use of this new methodology in synthesis are in progress.

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12 **Procedure:** Under nitrogen, a hexane solution of n-BuLi (2.3 mmol) was added to a solution of exo-(1R)-N-(1-phenylethyl)boranamine (590 mg, 2.3 mmol) in 7 ml of dry THF at -78 °C. The reaction mixture was brought to 10°C, stirred for 1h, then recooled to -78 °C and complex **16** (714 mg, 2 mmol) was added. The solution was stirred at -78°C for 2.5 h, then treated with methyl chloroformate (0.46 ml, 6 mmol). After 0.5 h volatiles were removed in vacuum while warming to room temperature. Flash chromatography on silica (hexane/ether 1:1) yielded orange **18** (593 mg, 71%). An e.e. of 73% was determined for **18** by HPLC (Chiralcel OD column, eluent hexane/isopropanol 95:5; flow rate 0.8ml/min, retention times: minor enantiomer 40.0 min, major 45.5 min). Crystallization from ether/hexane gave 208 mg (25% based on **16**) of a **18** with an ee of 15 %. From the mother liquor were isolated 347 mg (41% based on **16**) of **18** with an e.e. of 91%.
Complex (+)-**18**: Orange crystals, M.p. 113-115 °C. $[\alpha]^{20}_D$ = +82° (c=0.20, CH_2Cl_2). IR ($CHCl_3$): 1959, 1918, 1720. ^{1}H-NMR (200 MHz, C_6D_6): 5.74 (*dd*, J=1.3, 6.6 Hz, 1H, ArH), 4.49-4.64 (*m*, 2H, ArH), 4.0-4.17 (*m*, 1H), 3.89 (*ddd*, 1H, J=1.4, 5.5, 6.6 Hz, ArH), 3.57-3.74 (*m*, 1H), 3.32 (*s*, 3H, Me), 1.1-1.27 (*m*, 12H, 4Me). Anal.: calc for $C_{18}H_{21}CrNO_7$: C 52.05, H 5.10, N 3.37; found C 52.06, H 5.14, N 3.52.

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