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Enantioselective Ortho Lithiation of Tricarbonyl(Masked Phenol and Aniline)Chromium Complexes

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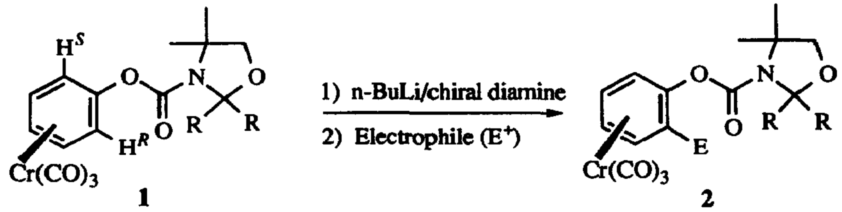
Abstract: Tricarbonyl(η^6-phenylcarbamate)chromium complexes were lithiated in the presence of chiral diamine followed by quenching with electrophiles to afford optically active (*o*-substituted phenylcarbamate)chromium complexes up to 82% ee.

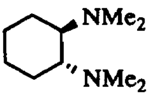
(η^6-Disubstituted arene)chromium complexes exist in two enantiomeric forms due to a planar chirality when the phenyl ring is substituted in the *ortho*- or *meta* positions with different substituents. This fact coupled with the ability of the tricarbonylchromium function to effectively block one face of the ring, has led to a rapid increase in the use of chiral (arene)chromium complexes as synthetic intermediates[1] and as catalysts[2] for the asymmetric synthesis. Generally, preparation of enantiomerically enriched complexes has been accomplished by the resolution of racemic mixtures of the corresponding diastereomers. Thus, *ortho* substituted benzaldehyde chromium complexes have been resolved by column chromatography of diastereomeric mixtures derived from (*S*)-5-(α-phenylethyl)semioxamazide[3] or *L*-valinol.[4] Enzymatic[5] and nonenzymatic[6] catalysts can be used for the kinetic resolution. In addition, diastereoselective chromium complexation[7] of the chiral *o*-substituted benzaldehyde aminals and diastereoselective *ortho* lithiation[8] of the chiral benzaldehyde acetal chromium complexes have been developed. These methods for the preparation of optically active complexes are limited to the compounds with an aldehyde or its equivalents as a functional group. Homochiral chromium complexes of *o*-substituted phenol derivatives are promising compounds in the asymmetric reactions, but no practical methods for the preparation of this type complexes have been reported.[1] We now report an *enantioselective ortho lithiation* of masked phenol and aniline chromium complexes.[9]

Thus masked phenol chromium complexes were reacted with *n*-BuLi in ether at –78 °C in the presence of (1*R*,2*R*)-*N*,*N*,*N'*,*N'*-tetramethyl-1,2-cyclohexanediamine[10] (3) followed by quenching with DMF. Tricarbonylchromium complexes of phenyl methoxymethylether and phenyl methoxyethoxymethyl ether resulted in low enantioselectivities (4% ee, respectively) under these conditions, while the corresponding tricarbonyl(phenyl *N*,*N*-diethylcarbamate)chromium[11] produced (1*R*,2*S*)-(2-formyphenyl carbamate)chromium complex in 43% ee. The results show definitely that coordination of the lithium with carbonyl oxygen of the carbamate is essential for enantioselective *ortho* lithiation. Therefore, our attention was next focused on the lithiation of some carbamate chromium complexes bearing an oxazolidine group with chiral bases for the achievement of high enantioselectivity in the *ortho* lithiation.

Phenyl carbamate complexes **1a**, **1b** and **1c** derived from the corresponding oxazolidine[12] were reacted with *n*-BuLi[13] in the presence of chiral diamine **3** in ether to give the corresponding complexes (+)-**2** (E = CHO) in 41~43% ee (entries 1,2,4). The absolute configuration of the products was determined by a comparison of



a: R=Et, **b**: R R= -(CH$_2$)$_4$-, **c**: R R= -(CH$_2$)$_5$-



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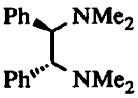

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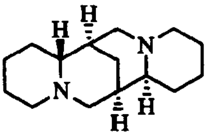

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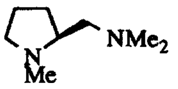

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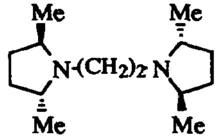

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Table 1 Enantioselective *ortho* lithiation of phenylcarbamate chromium complexes

entry	complex	diamine	solvent	E$^+$	yield (%)	% ee (abs. config.)
1	**1a**	**3**	ether	DMF	94	43 (1*R*,2*S*)[a]
2	**1b**	**3**	ether	DMF	73	43 (1*R*,2*S*)[a]
3	**1b**	**3**	toluene	DMF	83	53 (1*R*,2*S*)[a]
4	**1c**	**3**	ether	DMF	90	41 (1*R*,2*S*)*a*
5	**1c**	**3**	toluene	DMF	69	59 (1*R*,2*S*)[a]
6	**1c**	**4**	ether	DMF	73	53 (1*R*,2*S*)[a]
7	**1c**	**4**	toluene	DMF	84	72 (1*R*,2*S*)[a]
8	**1c**	**5**	toluene	DMF	62	17 (1*S*,2*R*)[a]
9	**1c**	**6**	toluene	DMF	74	36 (1*S*,2*R*)[a]
10	**1c**	**7**	toluene	DMF	62	9 (1*S*,2*R*)[a]
11	**1c**	**4**	toluene	ClCOMe	31	82 (1*R*,2*S*)[b]
12	**1c**	**4**	toluene	PPh$_2$Cl	85	75 (1*R*,2*S*)[c]
13	**1c**	**4**	toluene	ClCO$_2$Me	84	68 (1*R*,2*S*)[c]
14	**1c**	**4**	toluene	BrCF$_2$CF$_2$Br	90	65 (1*R*,2*S*)[b]

[a]; determined by HPLC with Chiralcel OJ-H (10% 2-propanol in hexane) after conversion to tricarbonyl(*o*-anisaldehyde)chromium. [b]; determined with Chiralcel OD (10% 2-propanol in hexane). [c]; determined with Chiralpak AD (10% 2-propanol in hexane).

rotation value of (*o*-anisaldehyde)Cr(CO)$_3$ obtained by basic hydrolysis followed by treatment with diazomethane with that of the authentic compound.[3,4] By use of toluene instead of ether as solvent, the enantiomeric excesses in the *ortho* lithiation of the spirocyclic oxazolidine derived complexes **1b** and **1c** were increased to 53 and 59% ee, respectively, under the same conditions (entries 3,5). But, (phenyl *N*,*N*-diethylcarbamate)chromium and **1a** resulted in unchanged enantioselectivity in both ether and toluene. The enantioselection of *ortho* lithiation of the complex **1c** was next examined with other chiral diamines. With (–)-sparteine (**5**) and chiral pyrrolidine type diamine **6**[14] and **7**[15], enantioisomeric (1*S*,2*R*)-complex **1c** (E = CHO) was obtained in 17%, 36% and 9% ee, respectively. *Ortho* lithiation of **1c** with C_2 symmetry (1*R*,2*R*)-*N*,*N*,*N'*,*N'*-tetramethyl-1,2-diphenylethylenediamine[16] (**4**) in toluene produced the (1*R*,2*S*)-complex in 72% ee (entry 7). The use of acetylchloride as an electrophile produced 82% ee of *o*-acetyl compound albeit low yield (entry 11). But, enantioselectivities by an addition of 1.5 eq of HMPA before quenching with DMF or use of ether as solvent decreased to 2% and 53% ee, respectively. It has become apparent from the reaction results that the spirocyclic phenyl carbamate complex **1c** results in higher enantioselectivity of the *ortho* lithiation in toluene solvent in the presence of the chiral diamine **4**. Coordination of the lithium atom with the chiral diamine, and an aggregation of the resulting lithium compounds in solution are significant for the asymmetric *ortho* lithiation. In hydrocarbon solvent, a polymeric structure (tetra- or hexameric) of alkyllithium upon addition of the chiral diamine changes to a less bulky dimeric structure[17] which abstracts enantioselectively the *ortho* H^R proton. In ether, butyllithium can coordinate with both ether oxygen and the diamine to form the other structural lithium reagent, which results in low enantioselectivity in the *ortho* lithiation.

The related chromium complex of *N*-methyl *N*-Boc protected aniline **8** was next examined for the enantioselective *ortho* lithiation (Table 2). It is known[18] that tricarbonyl(*N*,*N*-dimethylaniline)chromium is predominantly lithiated at the *meta* position of the substituents along with *ortho* and *para* lithiated products. However, for the chromium complex **8**[19] only *o*-lithiation takes place in good yields in spite of the sterically bulky protecting group. In the presence of the chiral diamine **4**, the reaction with n-BuLi at –78 °C in toluene followed by quenching with methyl chlorocarbonate to afford (+)-(1*R*,2*S*)-2-carbomethoxylated chromium complex **9** (E = CO_2Me) in 46% ee. Among the butyllithiums, deprotonation with *t*-BuLi resulted in a highest enantioselectivity of the *ortho* lithiation (entry 3). Reaction of the *ortho* lithiated complex with DMF produced 2-formyl chromium complex with a deprotection of the Boc group as the major product through an intramolecular nucleophilic addition of the resulting intermediate benzyl oxide anion to the Boc (entry 4). This reaction is significant for the preparation of an optically enriched *ortho* substituted aniline chromium complexes.

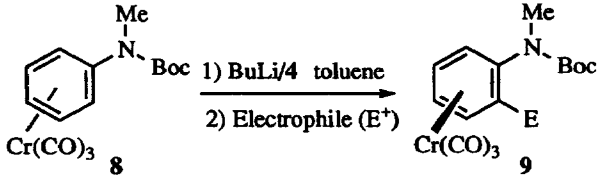

Table 2 Enantioselective lithiation of chromium complex **8**

entry	buthyllithium	E^+	yield (%)	% ee of **9** (abs config.)
1	*n*-BuLi	$ClCO_2Me$	79	46 (1*R*,2*S*)[c]
2	*s*-BuLi	$ClCO_2Me$	49	10 (1*R*,2*S*)
3	*t*-BuLi	$ClCO_2Me$	59	59 (1*R*,2*S*)
4[a]	*t*-BuLi	DMF	14[b]	61 (1*R*,2*S*)[d]
5	*t*-BuLi	Ac_2O	48	65 (1*R*,2*S*)[e]
6	*t*-BuLi	Me_3SiCl	50	57 (1*R*,2*S*)[e]
7	*t*-BuLi	PPh_2Cl	96	54 (1*R*,2*S*)[e]

[a]; reaction in ether gave 35% ee of **13** (E=CHO) in 35% yield and 33% ee of the corresponding de-Boc product in 32% yield. [b]; corresponding de-Boc product was obtained in 34% yield with 58% ee. [c]; determined by HPLC with Chiralpak AD (10% 2-propanol in hexane). [d]; determined with Chiralcel OJ-H (10% 2-propanol in hexane). [e]; determined with Chiralcel OD (10% 2-propanol in hexane).

We are now attempting to improve the enantioselectivity in the lithiation, and the chirality transfer from planar chirality of the (arene)chromium complexes to stereogenic center(s).

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