Regioselective *ortho* Substitution of Diphenyl Sulfoxide Chromium Tricarbonyl: Complementary Stereoselectivities for the Mono- and Di-anions

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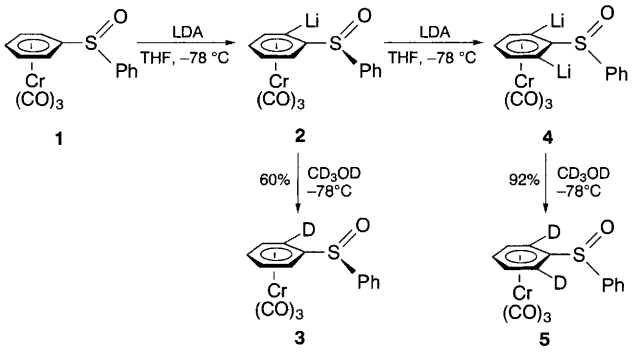
The mono- and di-anions derived from diphenyl sulfoxide chromium tricarbonyl and lithium diisopropylamide show complementary stereoselectivities in their reactions with electrophiles (D^+, MeI, Me_3SiCl).

The regioselective *ortho*-deprotonation of arene chromium tricarbonyl complexes bearing σ-electron withdrawing or chelating substituents is well established.[1] For example, anisole chromium tricarbonyl has been shown to undergo completely regioselective *ortho*-lithiation with butyllithium.[2,3] Of particular relevance was the observation of some di-*ortho* lithiation, although such dianions have received scant attention to date. Since 1,2-differentially substituted arene chromium tricarbonyl complexes are chiral and have been shown to undergo a variety of highly stereoselective reactions, attention has been recently focused on two approaches to their asymmetric synthesis both involving the stereoselective *ortho*-substitution of a phenyl chromium tricarbonyl complex. The two approaches involve either the attachment of a chiral auxiliary to achieve diastereoselective *ortho*-deprotonation[4] or the use of a homochiral lithium amide base to achieve enantioselective *ortho*-deprotonation.[5,6] We considered that a sulfoxide substituent would make a useful extension to this area since it should be capable of inducing regio- and stereo-selective *ortho*-deprotonation whilst being a latent source of its *ipso* anion thus being removable or replaceable at a subsequent stage. We were also intrigued by the possibility of generating mono- and di-anions since these might be expected to exhibit complementary stereoselectivities. We describe herein our initial results in this area.

Diphenyl sulfoxide chromium tricarbonyl **1** was readily prepared *via* lithiation of benzene chromium tricarbonyl[3,7] with butyllithium and quenching with methyl phenylsulfinate (Scheme 1). The diastereotopic *ortho* hydrogens in **1** were clearly distinguishable at δ 5.88 and δ 5.43 in the 500 MHz ^1H NMR spectrum. Treatment of complex **1** with less than 1 equiv. of lithium diisopropylamide (LDA; 0.9 equiv.) at −78 °C in THF followed by quenching with CD_3OD gave only the mono-*ortho*-deuteriated complex **3** as a single diastereoisomer together with the starting complex **1** (10%). ^2H NMR spectroscopic analysis showed that the deuterium had only been exchanged for the hydrogen at δ 5.88. Similar treatment of complex **1** with more than 2 equiv. of LDA (2.8 equiv.) followed by a CD_3OD quench led to the formation of the di-*ortho*-deuteriated complex **5**. These deuteriation experiments are consistent with the sequential formation of the mono-**2** and di-**4** anions from diphenyl sulfoxide chromium tricarbonyl with both deprotonations being completely *ortho*-regioselective and with the first being completely stereoselective.

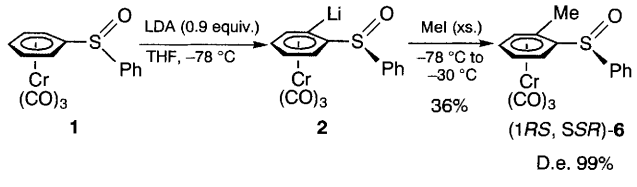


Scheme 1

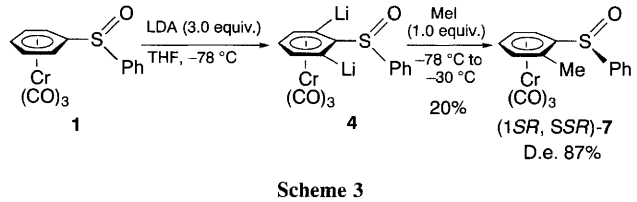
In order to ensure exclusive formation of the monoanion **2**, complex **1** was treated with 0.9 equiv. of LDA at −78 °C (45 min). Addition of an excess of methyl iodide and warming to −30 °C (2 days) gave, after work-up, the monomethylated complex (1*RS*,*SSR*)-**6**[8] (Scheme 2). 500 MHz NMR spectroscopic analysis established that **6** had been formed highly stereoselectively (d.e. 99%) and the relative configurations within **6** were established as (1*RS*,*SSR*) by single-crystal X-ray analysis.[9] The completely stereoselective formation of (1*RS*,*SSR*)-**6** is consistent with delivery of the base, *via* lithium coordination of the sulfoxide oxygen, to the proximal *ortho*-proton in the conformation which places the bulky phenyl group distal to the chromium tricarbonyl moiety.

Formation of the dianion **4** was assured by treatment of complex **1** with 3 equiv. of LDA at −78 °C (2 h). Quenching dianion **4** with only 1 equiv. of methyl iodide followed by protic work-up generated the mono-methyl complex (1*SR*,*SSR*)-**7** (Scheme 3) the diastereoisomer of **6** with a high d.e. of 87%. The yield was low in this reaction because of competitive removal of the electrophile, methyl iodide, by the excess base LDA and diisopropylamine. The complementary nature of the two mono-methylations is consistent with the second site of deprotonation being the more reactive towards electrophiles as expected.

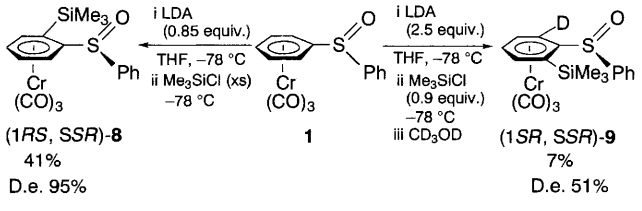
As a mechanistic probe to verify the intermediacy of the dianion **4** in the formation of complex **7** the reactions illustrated in Scheme 4 were performed. Treatment of complex **1** with 0.85 equiv. of LDA at −78 °C but quenching with trimethylsilylchloride resulted in the isolation of the complex (1*RS*,*SSR*)-**8** again as a single diastereoisomer. In addition, reaction of **1** with



Scheme 2



Scheme 3



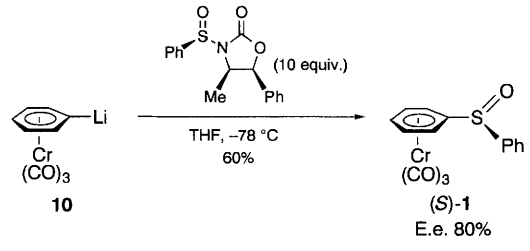
Scheme 4

2.5 equiv. of LDA at −78 °C and quenching with only 0.9 equiv. of trimethylsilylchloride followed by a CD_3OD quench led to the isolation of complexes (1*SR*,S*SR*)-**9** together with the dideuterio complex **5**. In particular, incorporation of deuterium into complex **9** confirms that this complex must be derived from the dianionic intermediate **4**.

Recent work by Thomas and coworkers[10] documents the synthesis of a range of homochiral arene sulfoxide chromium tricarbonyl complexes and prompts us to report our synthesis of the enantiomerically enriched diphenyl sulfoxide chromium tricarbonyl complex **1**. Reaction of (phenyllithium) chromium tricarbonyl **10**[3,7] with a tenfold excess of (4*R*,5*S*)-4-methyl-5-phenyl-3-[(*R*-)-phenylsulfinyl]-2-isoxazolidinone[11] at −100 °C allows isolation of complex **1** in 60% yield and with an enantiomeric excess of 80% (Scheme 5).

In summary, we have demonstrated that it is possible to obtain both diastereoisomers of *ortho* substituted diphenyl sulfoxide chromium tricarbonyl complexes selectively *via* simple alteration of the reaction conditions to generate either a mono- or di-anionic intermediate. The extension of this methodology to chiral auxiliaries other than phenyl sulfoxide is under investigation. We have unequivocally established the ease with which dianion formation can be achieved and such intermediates may offer a simple explanation for the variable stereoselectivities observed in the electrophilic quenches of the anions derived from chromium tricarbonyl complexes with homochiral lithium amide bases.[5,6]

All compounds described above have been fully characterised.



Scheme 5

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