Pergamon

Tetrahedron Letters, Vol. 35, No. 33, pp. 6159-6162, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01221-0

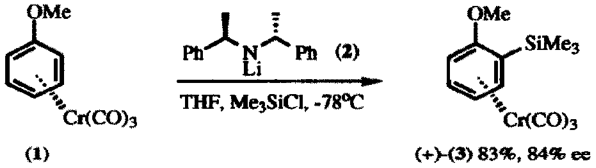
A Study of the Synthesis and Racemisation of a Chiral Lithiated Tricarbonyl(η^6-anisole)chromium Complex

David A. Price and Nigel S. Simpkins*
Department of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, UK

and Angus M. MacLeod and Alan P. Watt
Merck Sharp and Dohme Research Laboratories, Terlings Park, Harlow, Essex CM20
2QR, UK

Abstract: The non-racemic metallated complex derived from tricarbonyl(η^6-anisole)chromium **1**, formed using the homochiral lithium amide base **2**, undergoes rapid racemisation by intermolecular proton transfer if the neutral chromium complex is present, this problem being minimised if the deprotonation is conducted in the presence of LiCl.

We recently reported a novel method for the asymmetric synthesis of tricarbonyl(η^6-arene)chromium complexes, which involves asymmetric deprotonation of a monosubstituted complex by a homochiral lithium amide base, Scheme 1.[1]



Scheme 1

Best results were obtained by treatment of the anisole complex **1** with the base **2** in the presence of Me_3SiCl (*in situ* quench conditions – Me_3SiCl-ISQ), which resulted in the formation of the desired *ortho*-silylated complex **3** in 83% yield and 84 % ee. Two aspects of this study were initially puzzling. Firstly, the Me_3SiCl-ISQ procedure gave optimal asymmetric induction, whereas external quenching (EQ) with Me_3SiCl gave product **3** with an ee which decreased on increasing the metallation time allowed (see below). Secondly, although the Me_3SiCl-EQ protocol gave non-racemic product in good chemical yield (albeit of reduced ee), the use of other electrophiles under identical conditions gave very low yields of racemic products.

In this paper we clarify the origins of these effects, and in particular it is shown that: (i) the non-racemic lithium derivative of **1** is configurationally stable in the absence of proton donors; (ii) asymmetric metallation of **1** under the previously described EQ conditions is undermined by a rapid racemisation process involving proton transfer between **1** and Li–**1**; (iii) modified EQ conditions allow the use of electrophiles other than Me_3SiCl in this chemistry with good levels of asymmetric induction; (iv) the more rapid rates of reactions involving Me_3SiCl, compared to other electrophiles, is due to an acceleration caused by the liberation of LiCl as the electrophilic quench proceeds.

Since chiral base reactions involving Me_3SiCl under either EQ or ISQ conditions gave good yields of product **3** after a reaction period of 5 minutes at -78°C, we were perplexed by the very low yields of adducts (*ca.* 10%) with electrophiles such as PhCHO under the same conditions. A deuteration study (Fig. 1) showed that the metallation of **1** by base **2** is rather slow, requiring about three hours to reach completion, this making the high yields obtained after 5 minutes using Me_3SiCl seemingly anomalous.

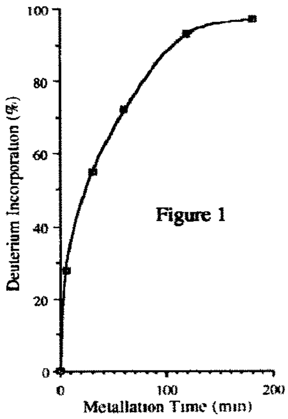


Figure 1

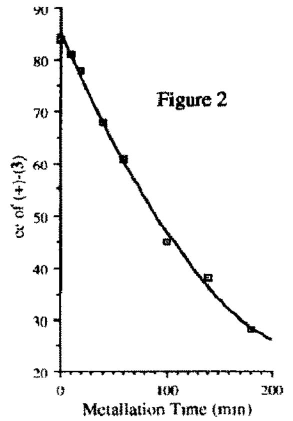
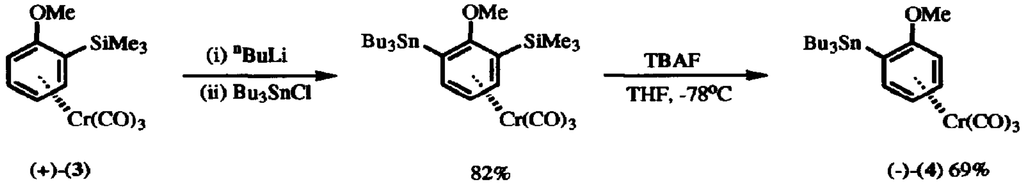


Figure 2

A possible cause of this effect was thought to be the LiCl which is liberated on reaction of the metallated complex with Me_3SiCl, and which could then affect the rate of deprotonation. To test this idea we carried out deuteration experiments in the presence of added LiCl (0.5 equiv.), and found that metallation is *complete within only one minute.*[2] The high yields obtained only with Me_3SiCl as electrophile can therefore be rationalised, since the LiCl generated on reaction with Li–**1** allows subsequent rapid completion of the metallation (effectively under ISQ conditions), possibly due to the formation of a more reactive mixed lithium amide–lithium chloride aggregate.

Figure 2 shows the variation in the ee of (+)-**3** obtained under traditional EQ-type conditions, with increasing metallation time (i.e. time before addition of Me_3SiCl). With knowledge of the metallation rates from Fig. 1 an explanation for the trend shown in Fig. 2 presented itself – namely, that in the absence of an *in situ* quench an equilibration process was eroding the enantiomeric excess of Li–**1**.[3] A typical result in Fig. 2, say the *ca.* 45 % ee result achieved using Me_3SiCl-EQ after 100 minutes, therefore represents an initial 100 minute period of slow metallation (no salt present) in which racemisation occurs, due to the absence of an electrophile, followed by a second period of rapid metallation and *in situ* quench after addition of Me_3SiCl. Clearly, the shorter the initial period allowed before addition of Me_3SiCl the more the overall reaction approximates an *in situ* quench. The low yields of racemic product obtained using PhCHO as electrophile could now be fully understood.

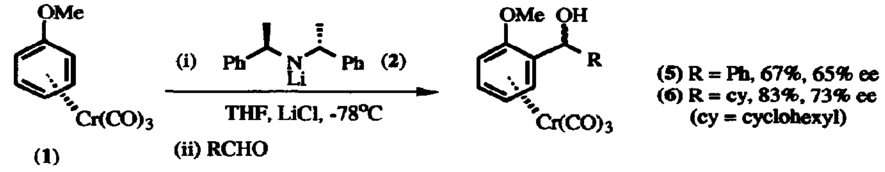
We next decided to probe the nature of the equilibration process involving Li–1, which in our asymmetric reactions results in racemisation under EQ conditions. Reaction of a sample of (+)-3 of 82% ee as shown in Scheme 2 allowed the preparation of the stannyl derivative (-)-4 without loss of stereochemical integrity.[4]



Scheme 2

Addition of a sample of (-)-4 to a solution of ⁿBuLi in THF at -78°C resulted in rapid transmetallation (monitored by TLC) to give the intermediate lithiated complex. After one hour at -78°C the mixture was quenched by addition of Me_3SiCl to give (-)-3 with an optical rotation equal and opposite to that of the sample of (+)-3 used to make the tin derivative (-)-4. This shows that under these conditions the intermediate Li–1 is configurationally stable. However, in similar reactions we added the neutral complex 1 (0.5 equiv.) to the intermediate Li–1, generated from (-)-4 as described above, and found that subsequent quenching with Me_3SiCl after only five minutes gave racemic product 3. These experiments clearly reveal the source of the racemisation process seen in the chiral base reactions under EQ conditions, which can be seen to involve non-stereoselective proton transfer between 1 and Li–1.[5]

Finally, we have used the above findings to devise modified deprotonation conditions which allow direct asymmetric transformation of complex 1 by use of electrophiles other than Me_3SiCl under EQ-type conditions, Scheme 3.[6]



Scheme 3

We reasoned that the racemisation process would be less likely if rapid metallation could be achieved on mixing 1 and base 2, so that no (or little) free neutral 1 was available for proton transfer. This was achieved by gradual addition (syringe pump 15 min) of the complex 1 to an excess of 2 (3.3 equiv.) in the presence of LiCl (1.5 equiv.). Under these conditions we found that quenching the reaction mixture with PhCHO or cyclohexanecarboxaldehyde gave the expected products **5** and **6**, as mixtures of diastereomers, with levels of ee approaching those available under ISQ conditions, Scheme 3.

The findings described here shed new light on the equilibration processes available to metallated tricarbonyl(η^6-arene)chromium complexes, and broaden the utility of our chiral base approach to these intermediates in non-racemic form.[7]

Acknowledgements

We are grateful to the Science and Engineering Council and Merck Sharp and Dohme (Terlings Park, Harlow, Essex CM20 2QR, UK) for support of D.A.P. under the CASE scheme.

References and Footnotes

1. (a) Price, D. A.; Simpkins, N. S.; MacLeod, A. M.; Watt, A. P. *J. Org. Chem.* **1994**, *59*, 1961. (b) Prof. E. P. Kündig of the University of Geneva has kindly informed us of his independent work using the same approach, see E. P. Kündig and A. Quattropani, *Tetrahedron Lett.*, **1994**, *35*, 3497.
2. We have previously reported a related "salt effect" in chiral base deprotonations, see Bunn, B. J.; Simpkins, N. S. *J. Org. Chem.* **1993**, *58*, 533.
3. There is considerable evidence for equilibration in several other metallated complexes, see (a) Kundig, E. P.; Grivet, C.; Spichiger, S. *J. Organomet. Chem.* **1987**, *332*, C13; (b) Kondo, Y.; Green, J. R.; Ho, J. *J. Org. Chem.* **1993**, *58*, 6182. We also thank Dr D. A. Widdowson of Imperial College, London for informing us of unpublished work in this area.
4. The enantiomeric excess of compounds **3–6** has been determined by HPLC (Hewlett Packard HP1090M) using a Chiralcel OJ or Chiralpak AD column (Diacel Chemical Industries Ltd, Japan), with UV detection at 324nm, and using EtOH in hexane (between 3% and 10% EtOH) as mobile phase.
5. We also examined the effect of adding the chiral secondary amine corresponding to **2** to solutions of non-racemic lithiated anisole complex prepared from the tin derivative (-)-**4**. In this case (0.5 equiv. of amine) much slower equilibration of the organolithium was observed than when neutral complex **1** was added (only *ca.* 35% loss in ee over 2 hours at -78°C). We believe that the slow racemisation under these conditions is due to small amounts of neutral complex **1** being produced through protonation of some Li-**1** by the chiral amine.
6. *Typical salt-modified conditions:* A solution of LiCl (10.6 ml of a 0.14 M solution in THF, 1.5 mmol) was added to a stirred solution of base **2** (3.3 mmol) in THF at -78° C under an atmosphere of nitrogen. A solution of the chromium complex **1** (244 mg, 1.0 mmol) in THF (10 ml) was then added dropwise by syringe pump over 15 min. When addition was complete PhCHO (1.02 ml, 10 mmol) was added in one portion and the reaction mixture maintained at -78° C for 30 min before addition of saturated aqueous NH_4Cl. The aqueous mixture was extracted with CH_2Cl_2 (40 ml), the organic extract washed with water, dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the resultant yellow oil by flash chromatography gave the desired alcohol **5** as shown in Scheme 3 (see supplementary data in reference 1a for details).
7. It is apparent from the work of Kündig and coworkers[1b] that the racemisation behaviour we observe for the lithiated anisole complex is not observed with some other complexes. We are presently examining a range of complexes in order to determine the generality of the findings described here.

(Received in UK 26 *May* 1994; *accepted* 24 *June* 1994)