

Chiral Base-Mediated Asymmetric Synthesis of Tricarbonyl(η^6 -arene)chromium Complexes

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Summary: Enantiomerically enriched tricarbonyl(η^6 -arene)chromium complexes can be obtained in up to 84% ee from the reaction of certain monosubstituted complexes with Me_3SiCl , mediated by a chiral lithium amide base.

Tricarbonyl(η^6 -arene)chromium complexes have emerged as important intermediates for organic synthesis, the presence of the transition metal facilitating regio- and stereoselective substitution of positions on or adjacent to the aromatic ring.¹ The availability of these complexes as single enantiomers has usually depended on resolution methods or on the diastereoselective complexation of arenes bearing chiral auxiliaries.² Recently, alternative asymmetric approaches to tricarbonyl(η^6 -arene)chromium complexes have appeared,³ and one such report, involving diastereoselective deprotonation,⁴ prompts us to describe our own asymmetric metalation approach to these compounds.

We anticipated a novel and direct approach to chiral, nonracemic tricarbonyl(η^6 -arene)chromium complexes would be possible by treatment of a monosubstituted (and therefore prochiral) complex with an enantiomerically pure chiral lithium amide base.⁵ A kinetically controlled discrimination between the two enantiotopic *ortho*-hydrogens available would lead directly to a nonracemic product, following reaction with a suitable electrophile.⁶ The viability of this approach was demonstrated on treatment of the anisole complex **1** with the chiral base **2**,

in the presence of Me_3SiCl (*in situ* quench conditions), which resulted in the formation of *ortho*-silylated complex (+)-**3** in 83% yield and 84% ee,⁷ along with minor amounts (ca. 4%) of the disilylated product **4**, Scheme 1.

The use of a slight excess of the chiral base (1.1 equiv) under relatively dilute conditions (0.04 M) resulted in the maximum optical rotation observed for **3** and minimized the formation of **4**. Alternative protocols, involving the addition of Me_3SiCl to the reaction mixture subsequent to chiral base metalation (conventional external quench method), gave (+)-**3** with significantly lower levels of asymmetric induction.⁸ In order to establish the absolute configuration of (+)-**3** we further transformed nonracemic material as indicated in Scheme 2.⁹

Thus, *ortho*-lithiation of (+)-**3** at the remaining free site, using $^n\text{BuLi}$, followed by addition of benzaldehyde, gave the two diastereoisomeric addition products (+)-**5** and (+)-**6** in yields of 50% and 44%, respectively. Both of these complexes were easily desilylated by treatment with Bu_4NF to give (-)-**7** (84%) and (-)-**8** (53%), respectively,¹⁰ and in addition, (+)-**5** was decomplexed by exposure to sunlight to give (+)-**9** (83%).¹¹ Both of the complexes (-)-**7** and (-)-**8** were also decomplexed to give the corresponding diarylcarbinol products (+)-**10** and (-)-**10**, having equal and opposite optical rotations at a level of 82% optical purity.¹⁰

An alternative, more direct approach for the preparation of aldehyde addition products from silylated complex (+)-**3** involved treatment of this compound with $\text{CsF}/18$ -crown-6 in the presence of PhCHO .¹² This resulted in direct *ipso*-substitution of the silicon substituent, resulting in the formation of a mixture of (+)-**7** and (+)-**8**, isolated in 19% and 24% yields, respectively, these complexes having optical rotations equal in magnitude but opposite in sign

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(1) For reviews, see: (a) *Transition Metal Organometallics for Organic Synthesis*; McQuillin, F. J., Parker, D. G., Stephenson, G. R., Eds.; Cambridge University Press: Cambridge, 1991. (b) Semmelhack, M. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 517.

(2) See: (a) Alexakis, A.; Mangeney, P.; Marek, I.; Rose-Munch, F.; Rose, E.; Semra, A.; Robert, F. *J. Am. Chem. Soc.* 1992, 114, 8288 and references cited therein. For more recent reports, see: (b) Baldoni, C.; Maiorana, S.; Carrea, G.; Riva, S. *Tetrahedron: Asymmetry* 1993, 4, 767. (c) Uemura, M.; Miyake, R.; Nakayama, K.; Shiro, M.; Hayashi, Y. *J. Org. Chem.* 1993, 58, 1238.

(3) See, for example: (a) Kündig, E. P.; Liu, R.; Ripa, A. *Helv. Chim. Acta* 1992, 75, 2657. (b) Uemura, M.; Nishimura, H.; Hayashi, T. *Tetrahedron Lett.* 1993, 34, 107. (c) Schmalz, H.-G.; Millies, B.; Bats, J. W.; Dürner, G. *Angew. Chem., Int. Ed. Engl.* 1992, 31, 631.

(4) (a) Kondo, Y.; Green, J. R.; Ho, J. *J. Org. Chem.* 1991, 56, 7199. (b) Kondo, Y.; Green, J. R.; Ho, J. *J. Org. Chem.* 1993, 58, 6182.

(5) (a) Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* 1991, 2, 1. For more recent contributions, see: (b) Cox, P. J.; Simpkins, N. S. *Synlett* 1991, 321. (c) Coggins, P.; Simpkins, N. S. *Synlett* 1991, 515. (d) Wild, H.; Born, L. *Angew. Chem., Int. Ed. Engl.* 1991, 30, 1685. (e) Cox, P. J.; Persad, A.; Simpkins, N. S. *Synlett* 1992, 194. (f) Coggins, P.; Simpkins, N. S. *Synlett* 1992, 3, 313. (g) Majewski, M.; Zheng, G.-Z. *Can. J. Chem.* 1992, 70, 2618. (h) Majewski, M.; Gleave, M. *J. Org. Chem.* 1992, 57, 3599. (i) Sato, D.; Kawasaki, H.; Shimada, I.; Arata, Y.; Okamura, K.; Date, T.; Koga, K. *J. Am. Chem. Soc.* 1992, 114, 761. (j) Underiner, T. L.; Paquette, L. A. *J. Org. Chem.* 1992, 57, 5438. (k) Bambridge, K.; Simpkins, N. S.; Clark, B. P. *Tetrahedron Lett.* 1992, 33, 8141. (l) Honda, T.; Kimura, N.; Tsubuki, M. *Tetrahedron: Asymmetry* 1993, 4, 21. (m) Honda, T.; Kimura, N.; Tsubuki, M. *Tetrahedron: Asymmetry* 1993, 4, 1475.

(6) Dr. D. A. Widdowson of Imperial College, London, has informed us of his independent studies in this area.

(7) Determined by HPLC (Hewlett-Packard HP 1090M) using a Chiralcel OJ or Chiralpak AD column (Diacel Chemical Industries Ltd., Japan), with UV detection at 324 nm, and using EtOH in hexane (between 3% and 10% EtOH) as mobile phase.

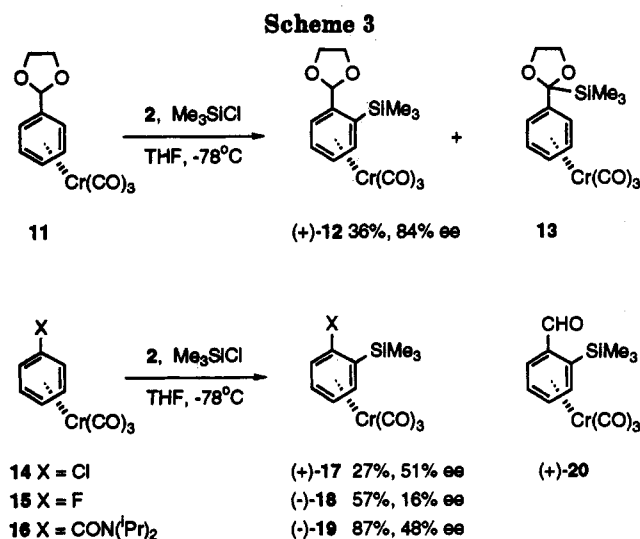
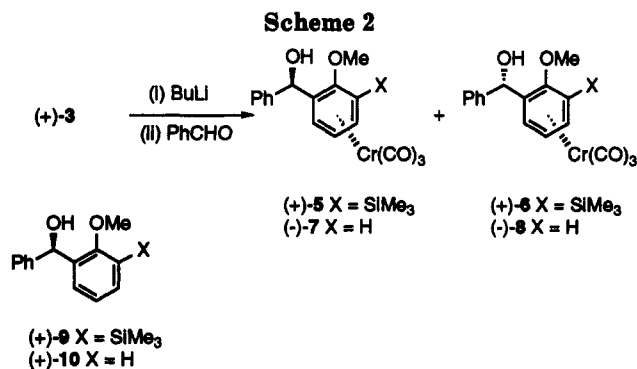
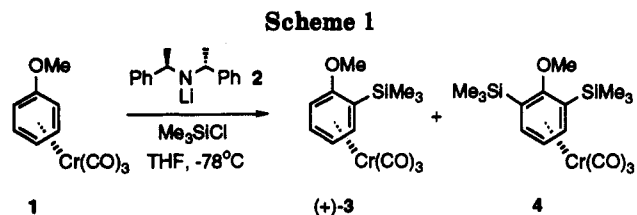
(8) We believe that the asymmetric induction in external quench reactions is compromised by an intermolecular equilibration process; thus, in external quench reactions using Me_3SiCl , the level of asymmetric induction decreases on increasing the time allowed before addition of the electrophile. Further study of this behavior is underway; we thank Dr. D. A. Widdowson of Imperial College, London, for making available unpublished results of this type of anion equilibration.

(9) Optical rotation data for compounds described in this paper (all $[\alpha]_D$ in CHCl_3 at c values of 1-1.5 and temperatures of 27-29 °C unless otherwise stated): **3** (+205), **5** (+28), **6** (+13), **7** (-37), **8** (-118; lit.^{10b} -178), **9** (+79), **10** (+28; lit.^{10b} 34), **12** (+22), **17** (+6.4), **18** (-4.4), **19** (-48.4), **20** [+122 (c 0.1); lit.^{10a} +146].

(10) The assignments of absolute and relative configuration are based upon comparison of optical rotation data for the known compounds **8**, **10**, and **20**; see: (a) Davies, S. G.; Goodfellow, C. L. *J. Chem. Soc., Perkin Trans. 1* 1990, 393. (b) Bromley, L. A.; Davies, S. G.; Goodfellow, C. L. *Tetrahedron: Asymmetry* 1991, 2, 139.

(11) The enantiomeric excess of (+)-**9** was checked by examination of its ^1H NMR spectrum in the presence of $\text{Eu}(\text{tfc})_3$ and also by the preparation of Mosher ester derivatives using (*R*)-MTPACl, both methods giving a value of 81% ee.

(12) Effenburger, F.; Schöllkopf, K. *Chem. Ber.* 1985, 118, 4356.



to those for their enantiomers prepared earlier according to Scheme 2. Thus, either enantiomeric series of benzaldehyde addition complexes can be accessed by this route.

In order to demonstrate some generality in this approach to enantiomerically enriched tricarbonyl(η^6 -arene)chromium complexes we carried out chiral base reactions using complexes 11 and 14–16 as shown in Scheme 3.

Under the usual Me_3SiCl *in situ* quench conditions the *ortho*-silylated dioxolane complex (+)-12 was formed in 36% yield, accompanied by 13, the product of substitution at the benzylic position, in 34% yield. The substitution reactions of 14 under Me_3SiCl *in situ* quench conditions proved to be difficult to control, with mixtures of polysilylated products being obtained when LDA was used as base. With chiral base 2 the reaction was a little improved, and we were able to isolate the desired product (+)-17 in a modest 27% yield. The silylation reactions of the fluoro

and carboxamide derivatives 15 and 16 proved more straightforward, the desired products (–)-18 and (–)-19 being isolated in 57% and 87% yields, respectively. The enantiomeric excess of each of these products is indicated in Scheme 3, the *ortho*-silylated dioxolane complex (+)-12 being formed in comparable ee to that for (+)-3, whereas 14 and 16 give products of intermediate (*ca.* 50%) ee, and the fluoro complex 15 gives product of low ee. The absolute configuration of (+)-12 was determined by simple acid hydrolysis to give the known aldehyde (+)-20.¹³ Correlation of (+)-17 with other products shown in Scheme 1 also proves the absolute stereochemistry shown.¹⁴ To date we have been unable to prove the absolute stereochemistry shown for (–)-18 and (–)-19, but have assumed that the sense of asymmetric induction is consistent with the proven cases.

As yet we are unable to provide a rationale for the sense of asymmetric induction observed in the above reactions or to fully explain the disparate levels of induction seen with the different complexes. However, from the few examples tried, it appears that the asymmetric deprotonation works best when one or more oxygen atoms are present in the original ring substituent. Since most of these complexes are nicely crystalline, this new asymmetric approach should enable many complexes to be prepared in high optical purity via enantiomeric enrichment by recrystallization. Indeed, we have found that one recrystallization of complex (+)-3 from hexane gave material of >97% ee.

These results show for the first time that enantiomerically enriched tricarbonyl(η^6 -arene)chromium complexes are available directly via the asymmetric deprotonation approach. The method should be applicable to many other chromium complexes, and may also be of use in similar reactions with other types of metal complexes, such as ferrocenes.¹⁵

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Supplementary Material Available: General experimental procedure for asymmetric deprotonation and ^1H NMR spectra of (+)-3, (+)-12, (+)-17, (–)-18, (–)-19, and a chlorobenzene complex (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(13) The enantiomeric excess of aldehyde (+)-20 was shown to be *ca.* 80% by HPLC and by ^1H NMR experiments using the chiral shift reagent $[\text{Eu}(\text{hfc})_3]$.

(14) We have been unable to correlate (+)-17 with any of the other compounds shown in satisfactory yield. However, metalation of (+)-17 with BuLi, followed by addition of PhCHO, gave the expected mixture of diastereomeric adducts. The less polar isomer was treated with NaOMe and 18-crown-6 in benzene to give small amounts of (–)-8 (resulting from *ipso*-substitution and desilylation) along with decomplexed arene.

(15) For a recent example of stereoselective ferrocene lithiation, see: Rebiere, F.; Riant, O.; Ricard, L.; Kagan, H. B. *Angew. Chem., Int. Ed. Engl.* 1993, 32, 568.