(*R*)- and (*S*)-Enantioselective lithiation of (arene)tricarbonylchromium acetal complexes with chiral alkyllithiums

Michael J. Siwek and James R. Green*

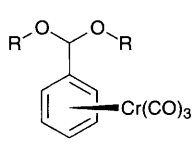
Department of Chemistry and Biochemistry, University of Windsor, Windsor, Ontario, N9B 3P4, Canada

The lithiation of (arene)tricarbonylchromium acetal complexes with the organolithium reagents derived from (1*R*)-menthyl chloride and (1*R*)-8-phenylmenthyl chloride occurs at the *pro-R* site (up to 70% ee) and the *pro-S* (up to 80% ee), respectively.

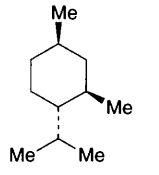
The chemistry of (arene)tricarbonylchromium complexes has enjoyed much recent attention, due in part to the ability of the transition metal fragment to enable highly stereoselective reactions on attached functional groups.[1] Full use of this chemistry requires the arene complexes to be available in enantiomerically enriched form, and several excellent methods have been reported for this purpose.[1] In particular, there has been increasing use of diastereoselective *ortho* lithiation reactions of complexes bearing a chiral auxiliary for access to these compounds.[2] While highly effective for the preparation of enantiomerically pure complexes, this approach often suffers from the incorporation of an auxiliary which is difficult or impractical to remove.

It has been reported recently that chiral bases, most commonly lithium amides, have shown promise in the enantioselective *ortho* functionalization of (arene)tricarbonylchromium complexes.[3–5] Unfortunately, for one of the most synthetically useful classes of compounds, that of benzaldehyde acetal complexes **1a,b**, lithium amides abstract the benzylic hydrogen atom in competition with *ortho* lithiation.[3,6]†

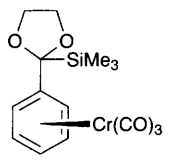
Based on literature reports on the lithiation of both metal-free systems[7] and (arene)tricarbonylchromium complexes,[8] it was our belief that chiral alkyllithium reagents would be far less likely than the amides to induce benzylic lithiation.‡ Consequently, we have investigated several chiral alkyllithium bases, including **2a** ('menthyllithium'), in lithiation reactions of **1**. Although the preparation of menthyllithium **2a** has been reported to occur through the mixing of lithium sand and (−)-menthyl chloride **2b** in pentane at reflux,[9] we have found greater reproducibility by employing LiDBB[10] (lithium 4,4′-di-*tert*-butylbiphenylide, 3.0 equiv.) and **2b** (1.5 equiv.) in THF at −78 °C for 5 min.



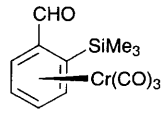
1a R = –$(CH_2)_2$–
b R = –$(CH_2)_3$–
c R = Me
d R = Et



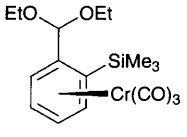
2a R = Li
b R = Cl



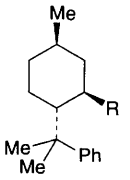
3



5



6



7a R = Li
b R = Cl

Initial results were disappointing. Subjecting acetal complex **1a** to a THF solution of **2a** (−78 °C, 0.5 h) resulted in benzylic lithiation, as quenching with Me_3SiCl gave **3** in 72% yield. The use of acyclic acetal complexes as substrates, however, proved to be much more successful. At −78 °C (0.5 h, THF), menthyllithium caused dimethyl acetal complex **1c** to undergo clean *ortho* lithiation; the resulting intermediate was trapped with Me_3SiCl to give silylated arene **4a** in 85% yield. The only observable material other than **4a** was a trace of starting **1c**; neither benzylic silylation nor *meta* functionalization had occurred at detectable levels.

The enantiomeric enrichment of **4a** could be determined by its ^1H NMR spectrum in the presence of the chiral shift reagent $Eu(hfc)_3$ (by integration of methyl groups of the acetal). For determination of the direction of asymmetry in **4a**, samples were hydrolysed (H_2SO_4, THF, room temp.) to benzaldehyde complex **5**, whose ^1H NMR spectral behaviour in the presence of chiral shift reagents has been established.[1,11] This showed that (1*R*)-**4a** had been produced in 35% ee.

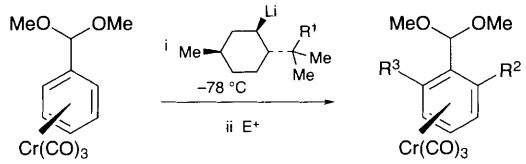
Methylation of the lithiated species was more sluggish, as MeI gave only small amounts of (1*R*)-**4b**. Dimethyl sulfate was more successful, and with it, (1*R*)-**4b** could be obtained in 51% yield and 30% ee. Diethyl acetal **1d** behaved in a manner similar to **1c**, as reaction with menthyllithium followed by Me_3SiCl afforded (1*R*)-**6** in 71% yield and 30% ee.

The effect of the solvent on the deprotonation reactions of **1c** was explored. Although lithiation did not occur in Et_2O, it was found that in 4:1 Et_2O–THF, deprotonation of **1c** with **2a** (−78 °C, 0.5 h) and subsequent reaction with Me_3SiCl gave (1*R*)-**4a** in 57% chemical yield and 70% ee.§ Methylation now could be accomplished with MeI, giving (1*R*)-**4b** in 61% yield and 56% ee (Table 1).

Given the dramatic effects observed in chiral auxiliaries containing appropriately situated aryl groups,[12] we also chose to investigate **7a** ('8-phenylmenthyllithium'), derived from (1*R*)-(−)-8-phenylmenthol,[13] as base. This required the corresponding chloride **7b** [(1*R*)-(−)-8-phenylmenthyl chloride] {$[\alpha]_D$ −40.1 (*c* 0.67, CH_2Cl_2)}, which was prepared in 82% yield from (1*R*)-(−)-8-phenylmenthol by treatment with neat $SOCl_2$. The equatorial nature of the chlorine substituent was evident from the ^1H NMR spectrum of **7b**, which revealed a resonance at δ 3.83 (d of apparent t, J = 4.3, 10.9 Hz) for the chlorine-bearing methine group.

Reaction of **7b** with LiDBB to afford organolithium **7a** occurred under conditions similar to those of **2a** (THF, −78 °C, 5 min).¶ Lithiation of **1c** by this alkyllithium solution, in 4:1 Et_2O–THF (−78 °C, 0.5 h), followed by silylation gave **4a** in 74% chemical yield. The ^1H NMR spectrum of this sample of **4a** in the presence of $Eu(hfc)_3$ showed a 54% ee in favour of the opposite enantiomer, (1*S*)-**4a**. Contrary to the results with menthyllithium **2a**, switching to THF as the reaction solvent gave superior results, as use of **7a** now led to a 77% yield of (1*S*)-**4a** in 80% ee {$[\alpha]_D$ +41.9 (*c* 0.28, CH_2Cl_2)}. Methylation of the aryllithium complex could be accomplished only in modest yield [MeI, (1*S*)-**4b**, 21%], but with a 73% ee {$[\alpha]_D$ −30.0 (*c* 0.08, CH_2Cl_2)} (Table 1).

Table 1 Enantioselective lithiation reactions of **1c**



1c **2a** R^1 = H; **7a** R^1 = Ph

(*R*)-**4a** R^2 = Me_3Si, R^3 = H; (*S*)-**4a** R^2 = H, R^3 = Me_3Si; (*R*)-**4b** R^2 = Me, R^3 = H; (*S*)-**4b** R^2 = H, R^3 = Me

Alkyllithium	E^+	Solvent	Product	Yield (%) (ee, %)
2a	Me_3SiCl	THF	(*R*)-**4a**	85 (35)
2a	Me_2SO_4	THF	(*R*)-**4b**	51 (30)
2a	Me_3SiCl	4 : 1 Et_2O : THF	(*R*)-**4a**	51 (70)
2a	MeI	4 : 1 Et_2O : THF	(*R*)-**4b**	61 (56)
7a	Me_3SiCl	4 : 1 Et_2O : THF	(*S*)-**4a**	74 (56)
7a	Me_3SiCl	THF	(*S*)-**4a**	77 (80)
7a	MeI	THF	(*S*)-**4b**	21 (73)

This demonstrates that both antipodes of *ortho* substituted acetal complexes may be obtained from the same enantiomeric series of bases. The dramatic change in the nature of asymmetric induction based on the structural differences in these two bases is surprising; definitive statements regarding the source of this change require knowledge of the solution structure of **7a** and the testing of other functionalized menthyllithium reagents. This, along with generalization of these substitution reactions, in terms of both electrophiles and substrates, is under current study and will be reported in due course.

We are grateful to NSERC (Canada) and the University of Windsor for support of this research.

Footnotes

† The aldehydes themselves have recently been shown to undergo enantioselective *ortho* lithiation in the presence of butyllithium and a chiral diamine.[4]

‡ It has been suggested that the size of the base also plays an important role in the competition between benzylic and *ortho* lithiation.[6]

§ *General Procedure*: To a −78 °C solution of 4,4′-di-*tert*-butylbiphenylide, generated from 4,4′-di-*tert*-butylbiphenyl (277 mg) and lithium metal (with the removal of the excess metal with a syringe needle) in THF (3 ml), was added (+)-menthyl chloride (91 mg). The solution was stirred for 2 min, and Et_2O (10 ml) and complex **1c** (100 mg in 2 ml Et_2O) were added sequentially. After stirring for 0.5 h, the appropriate electrophile (1.5 equiv.) was added, and the solution stirred at −78 °C for a further 1 h. The mixture was then subjected to a conventional workup.

¶ Carboxylation experiments demonstrated that the alkyllithium reagent had not undergone intramolecular proton transfer to form an aryllithium under the conditions of reaction.

References

1 A. Solladié-Cavallo, *Adv. Met. Org. Chem.*, 1989, **1**, 99; S. G. Davies, S. J. Coote and C. L. Goodfellow, *Adv. Met. Org. Chem.*, 1991, **2**, 1; M. Uemura, *Adv. Met. Org. Chem.*, 1991, **2**, 195; S. G. Davies and T. J. Donohue, *Synlett*, 1993, 323.

2 Y. Kondo, J. R. Green and J. Ho, *J. Org. Chem.*, 1993, **58**, 6182 and references cited therein; J. Aubé, J. A. Heppert, M. L. Milligan, M. J. Smith and P. Zenk, *J. Org. Chem.*, 1992, **57**, 3563; S. G. Davies, T. Loveridge and J. M. Clough, *J. Chem. Soc., Chem. Commun.*, 1995, 817; A. Alexakis and K. Tonis, *Tetrahedron: Asymmetry*, 1995, **6**, 47; M. Uemura, A. Daimon and Y. Hayashi, *J. Chem. Soc., Chem. Commun.*, 1995, 1943.

3 D. A. Price, N. S. Simpkins, A. M. MacLeod and A. P. Watt, *J. Org. Chem.*, 1994, **59**, 1961; E. P. Kündig, and A. Quattropani, *Tetrahedron Lett.*, 1994, **35**, 3497; D. A. Price, N. S. Simpkins, A. M. MacLeod and A. P. Watt, *Tetrahedron Lett.*, 1994, **35**, 6159; H.-G. Schmalz and K. Schellhaas, *Tetrahedron Lett.*, 1995, **36**, 5515.

4 A. Alexakis, T. Kanger, P. Mangeney, F. Rose-Munch and E. Rose, *Tetrahedron: Asymmetry*, 1995, **6**, 2135.

5 For the use of alkyllithiums with chiral diamines, see: M. Uemura, Y. Hayashi and Y. Hayashi, *Tetrahedron: Asymmetry*, 1994, **5**, 1427.

6 Recent work has also demonstrated the effectiveness of chiral lithium amides at enantioselective benzylic lithiation of benzylic ether complexes: R. A. Ewin and N. S. Simpkins, *Synlett*, 1996, 317; E. L. M. Cowton, S. E. Gibson, M. J. Schneider and M. H. Smith, *Chem. Commun.*, 1996, 839.

7 V. Snieckus, *Chem. Rev.*, 1990, **90**, 879.

8 S. G. Davies and C. L. Goodfellow, *J. Chem. Soc., Perkin Trans. 1*, 1990, 393; J. A. Heppert, J. Aubé, M. E. Thomas-Miller, M. L. Milligan and F. Takusagawa, *Organometallics*, 1990, **9**, 727; J. Blagg, S. G. Davies, C. L. Goodfellow and K. H. Sutton, *J. Chem. Soc., Perkins Trans 1*, 1987, 1805.

9 W. H. Glaze and C. M. Selman, *J. Org. Chem.*, 1968, **33**, 1987; A. Maercker, R. Schuhmacher, W. Buchmeier and H. D. Lutz, *Chem. Ber.*, 1991, **124**, 2489.

10 P. K. Freeman and L. L. Hutchinson, *J. Org. Chem.*, 1980, **45**, 1924; P. K. Freeman and L. L. Hutchinson, *J. Org. Chem.*, 1983, **48**, 4705.

11 A. Solladié-Cavallo and J. Suffert, *Magn. Reson. Chem.*, 1985, **23**, 739.

12 J. K. Whitesell, *Chem. Rev.*, 1992, **92**, 953.

13 O. Ostwald, *Org. Synth.*, 1987, **65**, 203.

Received, 12th June 1996; Com. 6/04144B