ChemComm

Stereocontrolled substitution of benzylic ethers complexed to tricarbonylchromium(0)

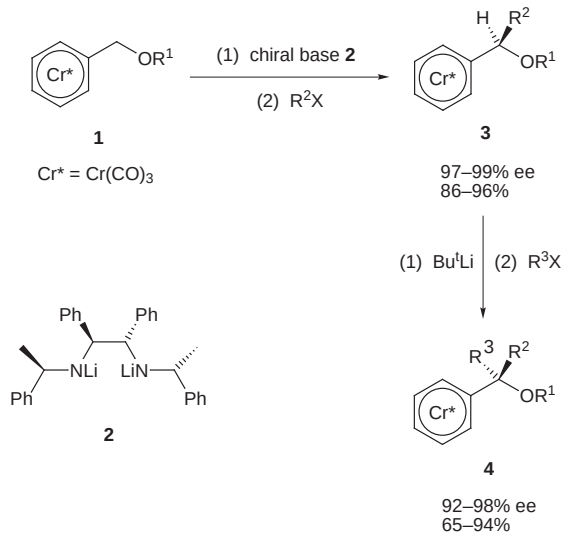
Domenico Albanese, Susan E. Gibson (née Thomas)* and Ellian Rahimian

Department of Chemistry, Imperial College of Science, Technology and Medicine, South Kensington, London, UK SW7 2AY. E-mail: s.gibson@ic.ac.uk

Received (in Liverpool, UK) 2nd September 1998, Accepted 14th October 1998

The nitrogen nucleophile HN(OH)C(O)OBu^t reacts with non-racemic chiral tricarbonylchromium(0) complexes of benzylic ethers with retention of configuration to provide a novel approach to non-racemic *N*-hydroxycarbamates and amines.

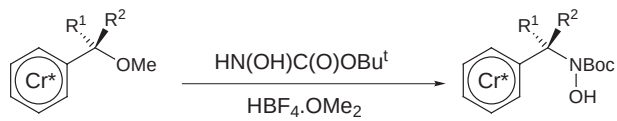
We recently demonstrated that the benzylic methylene group in tricarbonylchromium(0) complexes of benzyl ethers **1** may be functionalised asymmetrically using the non-racemic chiral base **2** (Scheme 1). Deprotonation followed by an electrophilic quench gives the substituted ethers **3** in high yield and enantiomeric excess.[1] Moreover, deprotonation of **3** with the achiral base Bu^{t}Li followed by an electrophilic quench produces the heavily substituted ethers **4** again in good yield and enantiomeric purity.[2] In view of the importance of amines as natural products, pharmaceuticals, and chiral ligands for asymmetric catalysis, we decided to determine whether or not the reliable and robust chemistry used to generate **3** and **4** could be exploited in the synthesis of chiral non-racemic amines. In principle, this could be achieved by nucleophilic substitution using a nitrogen nucleophile, but literature precedent was unpromising: although substitution of α-oxygenated arene tricarbonylchromium(0) complexes with acid/nucleophile combinations *via* a chromium-stabilised carbocation intermediate is well established for carbon, hydrogen, and oxygen nucleophiles,[3] the use of nitrogen nucleophiles is rare and inefficient. Thus, reactions of NH_3, $MeNH_2$ and Me_2NH with benzyl alcohol complexes in the presence of HPF_6 give low yields of substitution products,[4] and although introduction of nitrogen *via* the Ritter reaction works well for complexes of primary benzylic alcohols, it is inefficient for secondary alcohols and fails for tertiary alcohols.[5] We thus report herein that the nitrogen nucleophile *tert*-butyl *N*-hydroxycarbamate facilitates the introduction of nitrogen into α-oxygenated arene tricarbonylchromium(0) complexes **3** and **4** and in doing so provides a novel synthesis of non-racemic chiral *N*-hydroxycarbamates and amines.



Scheme 1

The first complex to be examined was (*R*)-**5a** (R^1 = H, R^2 = Me),[1] which was synthesised in high enantiomeric purity (99% ee) from the tricarbonylchromium(0) complex of benzyl methyl ether and MeI using the chiral base **2**. Initial reactions of **5a** with a range of nitrogen nucleophiles (*e.g.* RNH_2, R_2NH, $BocNH_2$, BocNHR, BocNHOTBDMS) in the presence of $HBF_4{\cdot}OMe_2$ were disappointing, providing only very low levels of nitrogen incoroporation and complex mixtures of products. In contrast,

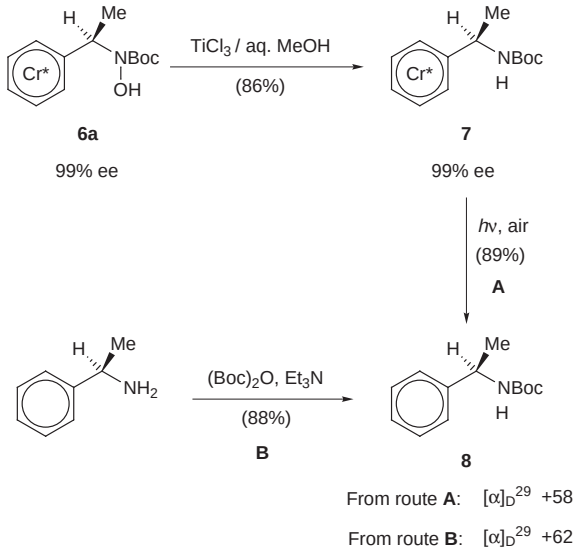
Table 1 Addition of HN(OH)C(O)OBu^t to ether complexes **5** and **7**[a]



5a–c, 9a,b **6a–c, 10a,b**

Entry	Substrate	R^1	R^2	Ee (%)[b]	$[\alpha]_D$[c]	Product	Yield (%)	Ee (%)[b]	$[\alpha]_D$[c]
1	**5a**	H	Me	99	+53	**6a**	85	99	−68
2	**5b**	H	Et	96	+66	**6b**	53	96	−40
3	**5c**	H	Pr^i	98	+43	**6c**	43	91	+18
4	**9a**	D	Me	99	+53	**10a**	79	88	−53
5	**9b**	Et	Me	99	−10	**10b**	48	80	+6

[a] The experimental procedure for the conversion of **5a** to **6a** (entry 1) is typical: $HBF_4{\cdot}OMe_2$ (0.20 cm^3, 0.26 g, 2.0 mmol) was added dropwise to a yellow solution of **5a** (0.272 g, 1.00 mmol) in CH_2Cl_2 (10 cm^3) at −40 °C under an atmosphere of nitrogen. To the resulting deep blue solution, a precooled solution of HN(OH)C(O)OBu^t (0.532 g, 4.00 mmol) in CH_2Cl_2 (5 cm^3) was added immediately *via* a cannula. The yellow mixture was stirred for 25 min at −40 °C, after which saturated aqueous $NaHCO_3$ (5 cm^3) was added and the mixture allowed to warm to room temperature. Addition of water (5 cm^3), extraction with pentane (3 × 20 cm^3), drying ($MgSO_4$), filtration through Celite and solvent removal *in vacuo* gave a yellow solid. Column chromatography [SiO_2; Et_2O–light petroleum (bp 40–60 °C) 1:5–1:1] gave **6a** as a yellow solid (0.316 g, 85%). [b] Ees measured by HPLC (Chiralcel OD-H); accuracy ±1%. [c] All values measured within the range 20–31 °C (*c* 0.5–1.0) in CH_2Cl_2.



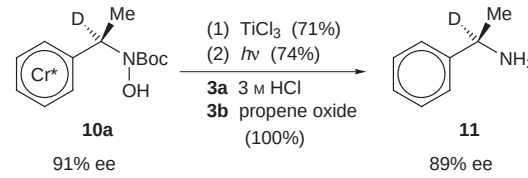
Scheme 2

protonation of **5a** at −40 °C with $HBF_4{\cdot}OMe_2$ followed by addition of commercially available *tert*-butyl *N*-hydroxycarbamate [HN(OH)C(O)OBu^t] gave the nitrogen substitution product **6a** in 85% yield. Moreover the ee of the novel† complex **6a** was measured by chiral HPLC‡ and found to be 99% (Table 1, entry 1).

The absolute configuration of the nitrogen substitution product **6a** was determined by chemical correlation. Reduction of the nitrogen–oxygen bond using $TiCl_3$ in aqueous MeOH[6] proceeded smoothly to give the novel complex **7** without loss of stereochemistry (Scheme 2).§ Oxidative removal of the tricarbonylchromium(0) unit from **7** gave carbamate **8**, the optical rotation of which was essentially identical to a sample prepared from authentic (*R*)-α-methylbenzylamine. Thus the absolute configuration of **6a** is *R* and the conversion of **5a** to **6a** proceeds with retention of configuration, presumably *via* a chromium stabilised carbocation.

In order to probe the effect on the nitrogen substitution reaction of increasing steric hindrance around the benzylic position, complexes **5b**[7] (R^1 = H, R^2 = Et) and **5c**[7] (R^1 = H, R^2 = Pr^i) were prepared and reacted with HN(OH)C(O)OBu^t. The reactions led to the novel products **6b** and **6c** in 53 and 43% yield and 96 and 91% ee respectively (Table 1, entries 2 and 3). Thus increasing steric hindrance leads to notable yield reductions and a small but significant stereochemical leakage. These effects are attributed to a reduced rate of addition of the nitrogen nucleophile to the intermediate carbocation, the increased lifetime of the latter leading to byproducts and rotation about the *ipso* carbon–benzylic carbon bond.

Subsequently, in order to test whether α,α-disubstituted benzylic ethers may be used as substrates in the reaction, complex **9a**[2] and the novel complex **9b** were synthesised from



Scheme 3

5a by Bu^{t}Li deprotonation–electrophilic quench sequences.[2] Reaction of **9a** and **9b** with HN(OH)C(O)OBu^t gave the novel complexes **10a** and **10b** in 79 and 48% yield, 88 and 80% ee respectively (Table 1, entries 4 and 5). Thus steric hindrance around the tertiary carbocation generated in the conversion of **9b** to **10b** appears to reduce the rate of nucleophilic attack by HN(OH)C(O)OBu^t allowing significant rotation around the *ipso* carbon–benzylic carbon bond to occur and hence some loss of enantiomeric purity. Finally, the deuterated product **10a** was converted into the labelled amine **11** in good overall yield and without loss of enantiomeric purity (Scheme 3).¶

The authors thank the EPSRC for a studentship (E. R.), and The Accademia Nazionale dei Lincei/The Royal Society for funding a study visit (D. A.) under the auspices of the European Science Exchange Programme.

Notes and references

† The novel complexes **6a–c**, **7**, **9b**, **10a** and **10b** all gave satisfactory spectroscopic (IR, ^{1}H NMR, ^{13}C NMR and low resolution MS) and microanalytical or high resolution MS data.

‡ Racemic products for HPLC analysis were generated by addition of HN(OH)C(O)OBu^t to ether substrates produced by Bu^{t}Li deprotonation–electrophilic quench of the tricarbonylchromium(0) complex of benzyl methyl ether.

§ The ee of **7** was measured by Boc removal, replacement with Z and HPLC analysis (Chiralcel OD-H)

¶ The ee of **11** was measured by derivatisation with 3,5-dinitrobenzoyl chloride and HPLC analysis (Phenomenex - Phase 3014).

1 E. L. M. Cowton, S. E. Gibson (née Thomas), M. J. Schneider and M. H. Smith, *Chem. Commun*., 1996, 839.
2 S. E. Gibson (née Thomas), P. C. V. Potter and M. H. Smith, *Chem. Commun*., 1996, 2757.
3 S. G. Davies and T. D. McCarthy, in *Comprehensive Organometallic Chemistry II*, ed. E.W. Abel, F. G. A. Stone and G. Wilkinson, Pergamon, Oxford, 1995, vol. 12, p. 1048.
4 S. Top, B. Caro and G. Jaouen, *Tetrahedron Lett*., 1978, 787.
5 S. Top and G. Jaouen, *J. Org. Chem*., 1981, **46**, 78.
6 A. Dondoni, S. Franco, F. Merchan, P. Merino and T. Tejero, *Synlett*, 1993, 78; S.-I. Murahashi and Y. Kodera, *Tetrahedron Lett*., 1985, **26**, 4633.
7 The racemic complexes have been reported previously: J. Blagg, S. G. Davies, N. J. Holman, C. A. Laughton and B. E. Mobbs, *J. Chem. Soc., Perkin Trans. 1*, 1986, 1581.

Communication 8/06832A