

Stereocontrolled substitution of benzylic ethers complexed to tricarbonylchromium(0)

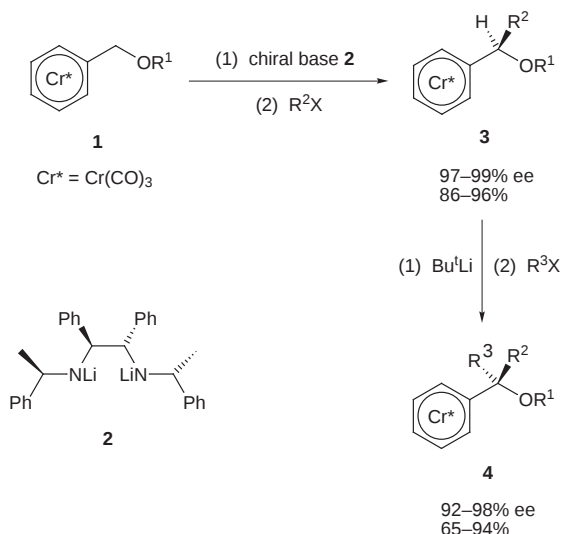
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The nitrogen nucleophile $\text{HN}(\text{OH})\text{C}(\text{O})\text{OBu}^t$ reacts with non-racemic chiral tricarbonylchromium(0) complexes of benzylic ethers with retention of configuration to provide a novel approach to non-racemic *N*-hydroxycarbamates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



Scheme 1

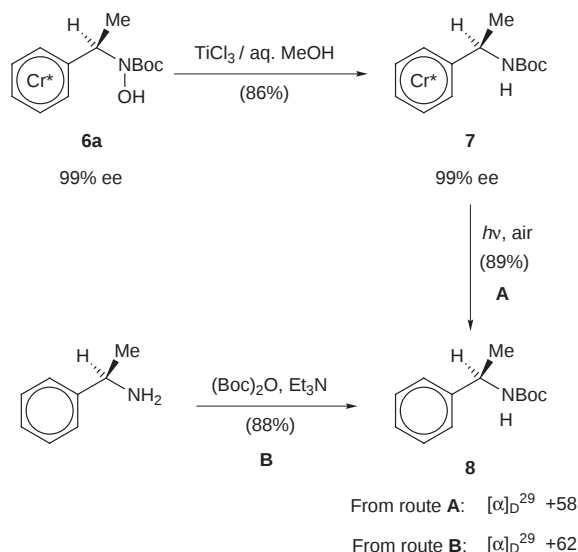
enantiomeric excess.¹ Moreover, deprotonation of **3** with the achiral base Bu^tLi followed by an electrophilic quench produces the heavily substituted ethers **4** again in good yield and enantiomeric purity.² In view of the importance of amines as natural products, pharmaceuticals, and chiral ligands 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.

The first complex to be examined was (*R*)-**5a** ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Me}$),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 $\text{HBF}_4 \cdot \text{OMe}_2$ were disappointing, providing only very low levels of nitrogen incorporation and complex mixtures of products. In contrast,

Table 1 Addition of $\text{HN}(\text{OH})\text{C}(\text{O})\text{OBu}^t$ to ether complexes **5** and **7a**

Entry	Substrate	R ¹	R ²	Ee (%) ^b	[α] _D ^c	Product	Yield (%)	Ee (%) ^b	[α] _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: $\text{HBF}_4 \cdot \text{OMe}_2$ (0.20 cm³, 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 cm³) at −40 °C under an atmosphere of nitrogen. To the resulting deep blue solution, a precooled solution of $\text{HN}(\text{OH})\text{C}(\text{O})\text{OBu}^t$ (0.532 g, 4.00 mmol) in CH_2Cl_2 (5 cm³) was added immediately via a cannula. The yellow mixture was stirred for 25 min at −40 °C, after which saturated aqueous NaHCO_3 (5 cm³) was added and the mixture allowed to warm to room temperature. Addition of water (5 cm³), extraction with pentane (3 × 20 cm³), drying (MgSO_4), filtration through Celite and solvent removal *in vacuo* gave a yellow solid. Column chromatography [SiO_2 ; Et₂O–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 .



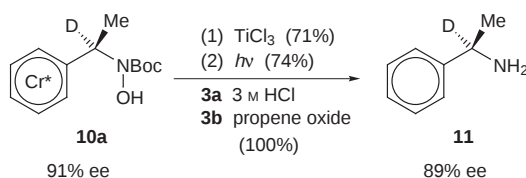
Scheme 2

protonation of **5a** at $-40\text{ }^{\circ}\text{C}$ with $\text{HBF}_4\cdot\text{OME}_2$ followed by addition of commercially available *tert*-butyl *N*-hydroxycarbamate $[\text{HN}(\text{OH})\text{C}(\text{O})\text{OBu}^t]$ 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 § proceeded smoothly to give the novel complex **7** without loss of stereochemistry (Scheme 2).§ Oxidative removal of the tricarbenylchromium(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 ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Et}$) and **5c**⁷ ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Pr}^i$) were prepared and reacted with $\text{HN}(\text{OH})\text{C}(\text{O})\text{OBu}^t$. 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^tLi deprotonation–electrophilic quench sequences.² Reaction of **9a** and **9b** with $\text{HN}(\text{OH})\text{C}(\text{O})\text{OBu}^t$ 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 $\text{HN}(\text{OH})\text{C}(\text{O})\text{OBu}^t$ 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).¶

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Notes and references

† The novel complexes **6a–c**, **7**, **9b**, **10a** and **10b** all gave satisfactory spectroscopic (IR, ^1H 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 $\text{HN}(\text{OH})\text{C}(\text{O})\text{OBu}^t$ to ether substrates produced by Bu^tLi deprotonation–electrophilic quench of the tricarbenylchromium(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).

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