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Stereoselective α-Methylation of N-Methyl Benzylamine *via* a Combination of Chromium Tricarbonyl and Chiral Formamidine Methodologies.

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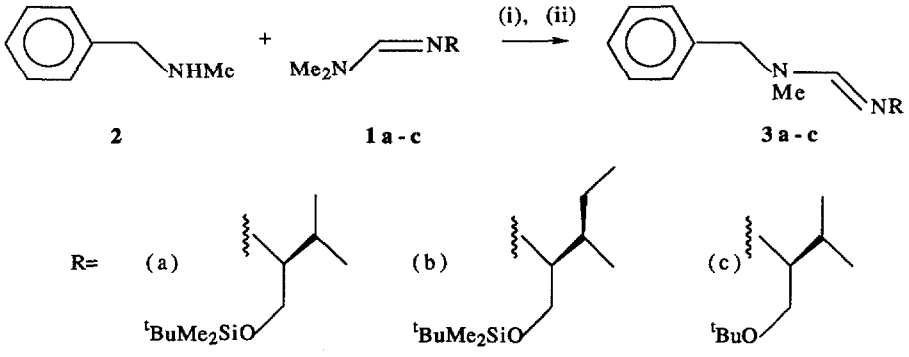
Abstract: Whereas carbanions of formamidines derived from N-methyl benzylamine and L-valinol or L-leucinol undergo electrophilic benzylic methylation with poor stereoselectivities (d.e. 17-26%), enhanced stereoselectivities (d.e. 74-84%) are observed for the corresponding chromium tricarbonyl complexes.

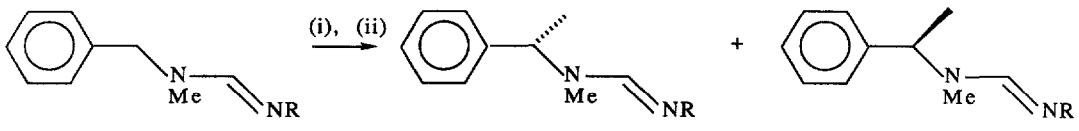
The application of arene chromium tricarbonyl chemistry to the stereoselective elaboration of benzylic centres *via* the corresponding carbanions has been previously established.[1] We were interested in extending the available methodologies to the asymmetric synthesis of α-substituted benzylamines. The elegant work of Meyers *et.al.*[2] on the use of formamidine chiral auxiliaries to achieve the stereoselective α-alkylation of secondary amines has, however, to date been restricted to cyclic secondary amines, for example tetrahydroisoquinolines.[3] We describe here the extension of the formamidine methodology to an acyclic case, N-methyl benzylamine, and the enhancement of the observed stereoselectivities on complexation to chromium tricarbonyl. Recently Gawley *et. al.* reported the use of aminooxazoline and oxazolidinone chiral auxiliaries to achieve such acyclic stereocontrol. In the former case the stereoselectivity was moderate while in the latter it was excellent but the chiral auxiliary could only be removed destructively.[4]

L-Valinol and L-leucinol were converted to the corresponding N,N-dimethylformamidines **1a-c** by sequential treatment with N,N-dimethylformamide dimethyl acetal and O-protection according to the literature procedure.[3c,5] Treatment of N-methylbenzylamine **2** with **1a-c** afforded the homochiral formamidines (S)-**3a-c** in 60-80% yields.



Reagents: (i) $(NH_4)_2SO_4$ catalyst (ii) 120°C, 5 days

Benzylic deprotonation of the homochiral formamidines (S)-**3a-c** with lithium di-isopropylamide at -48°C followed by alkylation with methyl iodide gave, in each case, mixtures of the two α-methylated diastereoisomers **4** and **5.** In all cases the stereoselectivities were poor.



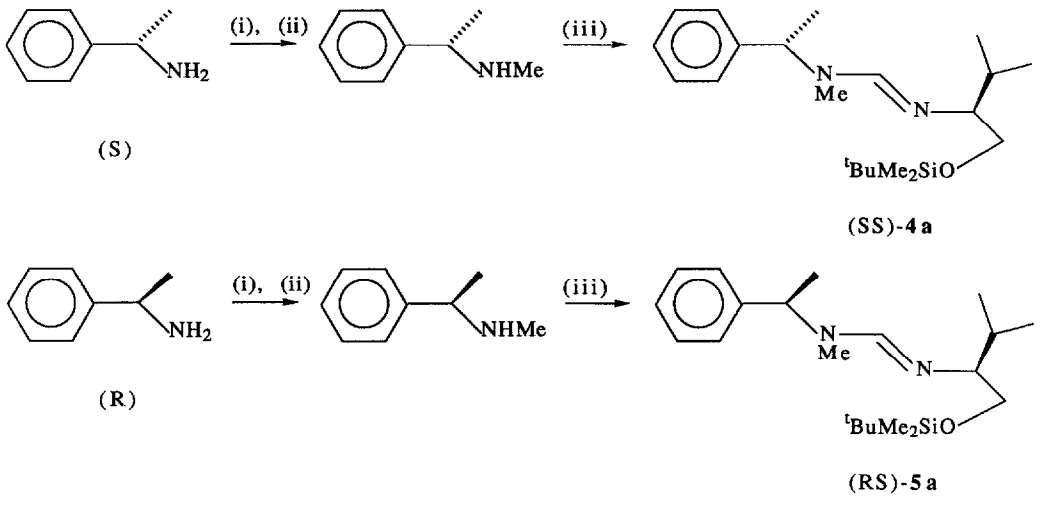
3a-c **4a-c** **5a-c**

Major	d.e.(%)	Minor
(SS)-4a	17	(RS)-5a
(SS)-5b	25	(RS)-5b
(SS)-5c	26	(RS)-5c

Reagents: (i) LDA, 5eq., 4h, -48°C (ii) MeI, 20eq., 2h, -48°C

The relative configurations within **4a** and **5a** were unambiguously assigned by independent syntheses. N-Methylation of commercial S-α-methylbenzylamine followed by treatment with the (S)-formamidine **1a** generated (SS)-**4a** as a single diastereoisomer by 300 Mz ^{1}H nmr (>99%)[6], indicating that both the S-α-methylbenzylamine and the L-(S)-valinol must be homochiral. Similar conversion of commercial (R)-α-methyl benzylamine with homochiral **1a** gave (RS)-**5a**[7] containing a small amount of **4a** (*ca.* 2%) consistent with this sample of R-α-methyl benzylamine not being homochiral.[8] The relative configurations within **4b-c** and **5b-c** were assigned by analogy. The ratio of **4a** to **5a** could be estimated by ^{1}H nmr spectroscopy by integration of

the PhCH(CH_3)- signals whilst the ratios of **4b-c** and **5b-c** were determined by integration of the -CH=N- signals. Consistent with Meyers' results for the tetrahydroisoquinolines[3], the major diastereoisomers **4** have the S-configuration at the new benzylic chiral centre.

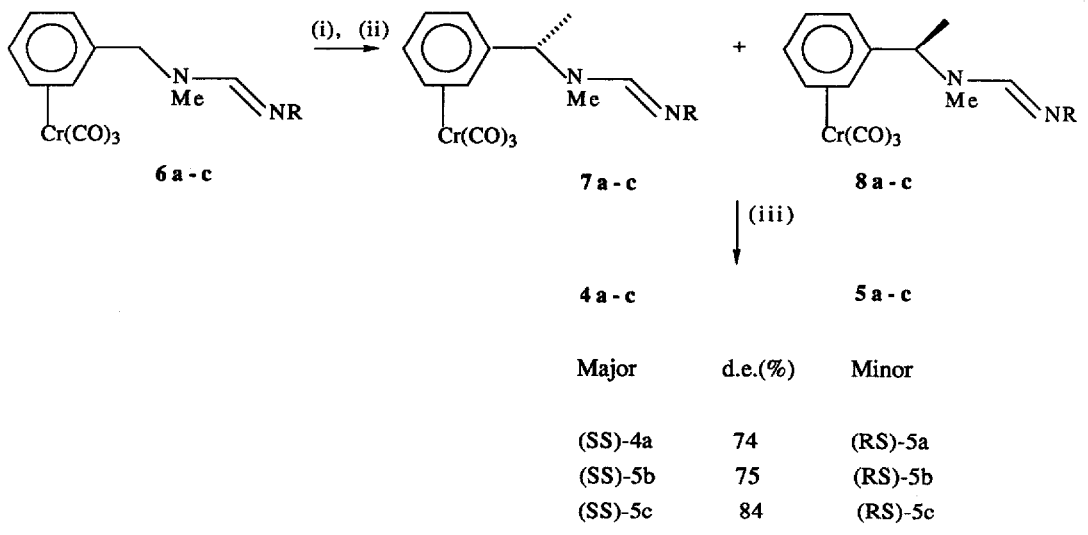


Reagents: (i) HCO_2Et (ii) $LiAlH_4$ (iii) 1a, $(NH_4)_2SO_4$ catalyst, 120°C, 5 days

Coordination of arenes to the electron withdrawing chromium tricarbonyl moiety renders the arene sterically more bulky and results in an increased acidity of benzylic protons with a corresponding stabilisation of benzylic carbanions.[9] All of these factors were expected to influence the stereoselectivities of the above methylation reactions.

Thermolysis of chromium hexacarbonyl in the presence of the (S)-formamidines **3a-c** in a mixture of dibutyl ether-tetrahydrofuran (10:1) gave the corresponding chromium tricarbonyl complexes **6a-c** in up to 55% yield. Complexes **6a-c** were unstable red oils but complete complexation was indicated by the characteristic upfield shift of the aryl protons in the ^1H nmr spectrum by *ca.* 2 ppm. Under the optimal conditions (tetrahydrofuran, -48°C) deprotonation of complexes **6a-c** with lithium di-isopropylamide followed by quenching of the resultant anion with methyl iodide gave the α-methylated complexes **7a-c** and **8a-c** in 50-60% yield, always accompanied by unreacted starting formamidine complexes **6a-c**. Oxidative decomplexation of the crude reaction products liberated the α-methylated compounds **4a-c** and **5a-c** and allowed the stereoselectivities of the alkylation reactions to be assessed. In all three cases a significant improvement in the stereoselectivity for the complexed over the uncomplexed formamidines was observed.

Although the precise mechanisms and origins of stereocontrol in the above reactions are still to be elucidated, we have demonstrated the beneficial effect of complexation to chromium hexacarbonyl in formamidine mediated benzylic methylations. Work is in progress to determine whether this effect is general for other chiral auxiliaries.



Reagents: (i) LDA, 5eq., 4h, -48°C (ii) MeI, 20eq., 2h, -48°C (iii) O_2/ sunlight, 2 days

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6. (S,S)-4a: ^{1}H nmr ($CDCl_3$, 500 MHz): 7.48 (1H, s), 7.38-7.24 (5H, m), 4.90-4.70 (1H, m), 3.78 (1H, dd, J=9.9, 4.5 Hz), 3.48 (1H, dd, J= 9.8, 9.7 Hz), 2.73-2.70 (1H, m), 2.61 (3H, s), 1.80-1.74 (1H, m), 1.55 (3H, d, J=7.0 Hz), 0.90-0.87 (15H, m), 0.06 (3H, s), 0.05 (3H, s). Anal. Calc. for $C_{21}H_{38}SiN_2O$: C, 69.55; H, 10.6. Found: C, 69.5; H, 10.9.

7. (R,S)-5a: ^{1}H nmr ($CDCl_3$, 500 MHz): 7.46 (1H, s), 7.38-7.24 (5H, m), 5.00-4.80 (1H, m), 3.78 (1H, dd, J=9.9, 4.5 Hz), 3.48 (1H, dd, J=9.8, 9.7 Hz), 2.73-2.70 (1H, m), 2.62 (3H, s), 1.80-1.74 (1H, m), 1.54 (3H, d, J=7.0 Hz), 0.90-0.87 (15H, m), 0.06 (3H, s), 0.05 (3H, s). Anal. Calc. for $C_{21}H_{38}SiN_2O$: C, 69.55; H, 10.6. Found: C, 69.5; H, 10.7.

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