Stereospecific Conversion of *N,N*-Dimethylamphetamine into *N*-Methylpseudoephedrine

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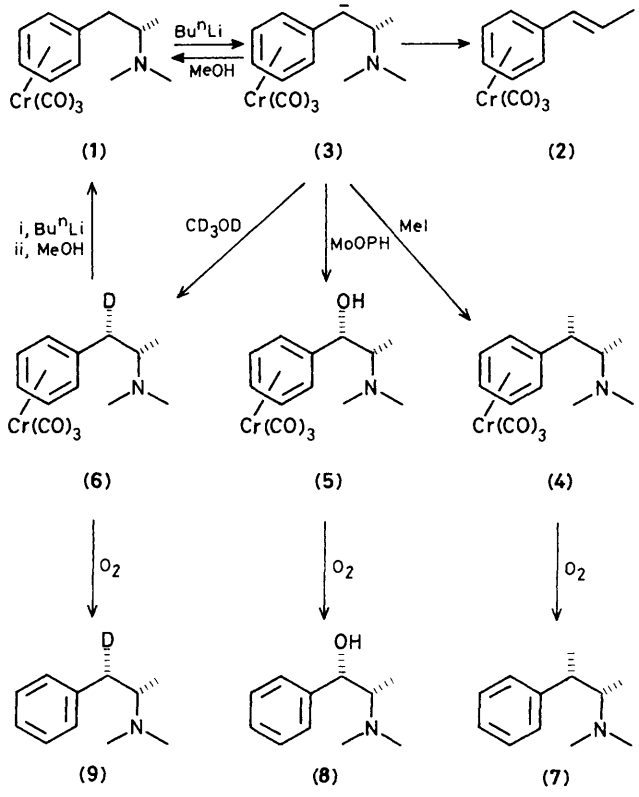
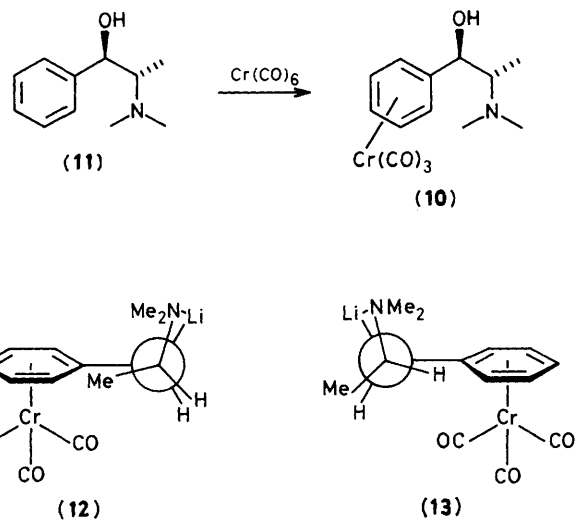
The *pro-R* hydrogen of (+)-*N,N*-dimethylamphetamine chromium tricarbonyl can be stereospecifically substituted *via* sequential treatment with Bu^{n}Li and an electrophile, with retention of configuration to give for example *N*-methylpseudoephedrine after decomplexation.

The enzyme mediated stereoselective benzylic hydroxylation of 2-arylethylamines is a very important *in vivo* process resulting in, for example, the formation of adrenalin and noradrenalin. Previous attempts to mimic this benzylic substitution reaction *via* formation of benzylic anions and trapping with suitable electrophiles have been thwarted by the ready formation of styrenes by elimination of the β-amino function.[1] We have previously reported that co-ordination of benzyl alkyl ethers to chromium tricarbonyl stabilises the corresponding α-carbanions and allows α-substitution to be achieved by suppression of the Wittig rearrangement.[2] We described here that co-ordination of *N,N*-





dimethylamphetamine to chromium tricarbonyl stabilises the corresponding benzylic carbanion towards elimination and allows benzylic substitutions to be achieved. Furthermore these substitutions are stereospecific.

Thermolysis of chromium hexacarbonyl in di-n-butyl ether in the presence of (+)-*N*,*N*-dimethylamphetamine[3] gives the yellow chromium tricarbonyl complex (**1**) ($[\alpha]_D^{20}$ −26.5°; *c* 0.1 in $CHCl_3$). Treatment of (**1**) with Bu^{n}Li at −40 °C or above results in elimination of dimethylamine and formation of (*E*-β-methylstyrene) chromium tricarbonyl (**2**). However at −78 °C the initially formed anion (**3**) is stabilised towards elimination and can be trapped by electrophiles such as MeI, oxodiperoxymolybdenum(pyridine)hexamethylphosphoramide (MoOPH),[4] and CD_3OD to yield the complexes (**4**), (**5**), and (**6**) respectively. Decomplexation of complexes (**4**), (**5**), and (**6**) by exposure of ether solutions to air and sunlight liberates (**7**), *N*-methylpseudoephedrine (**8**), and (**9**) respectively.

Each of these substitutions is stereospecific. Only one diastereoisomer could be detected by 300 MHz ^1H n.m.r. spectroscopy for compounds (**4**)—(**9**). ^2H N.m.r. spectra for compounds (**6**) and (**9**) showed deuterium to be present in only one of the diastereotopic benzylic positions. Treatment of complex (**6**) sequentially with Bu^{n}Li and MeOH regenerated (**1**) indicating that the deprotonation was also stereospecific. The possibility that racemisation of carbanion (**3**) had occurred prior to electrophilic addition was eliminated by protonation of (**3**) with methanol to regenerate (**1**) with the same specific rotation ($[\alpha]_D^{20}$ −26.5°; *c* 0.1 in $CHCl_3$) as the starting complex.

Authentic samples of (+)-*N*-methylpseudoephedrine and its chromium tricarbonyl complex were prepared from commercial (+)-pseudoephedrine. These compounds were spectroscopically identical to (**8**) and (**5**) respectively. Furthermore the specific rotations for complex (**5**) obtained by the two independent routes were identical ($[\alpha]_D^{20}$−31°; *c* 0.25 in $CHCl_3$).

An authentic sample of *N*-methylephedrine chromium tricarbonyl complex (**10**) was prepared from commercial (−)-*N*-methylephedrine (**11**). These compounds were clearly distinguishable by ^1H n.m.r. spectroscopy from complex (**5**) and compound (**8**) respectively confirming (**8**) to be pseudoephedrine and the hydroxylation reaction to be stereospecific.

The above results demonstrate that the *pro-R* hydrogen of *N*,*N*-dimethylamphetamine chromium tricarbonyl can be stereospecifically substituted with retention of configuration. The high stereospecificity observed presumably originates from unfavourable steric interactions between the 1-methyl group and the phenyl chromium tricarbonyl moiety which would arise in all transition states leading to removal of the *pro-S* hydrogen and formation of (**12**); such unfavourable interactions are avoided in transition states leading to removal of the *pro-R* hydrogen and formation of (**13**).

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