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ENANTIOSELECTIVE SYNTHESIS OF CHIRAL BENZYLIC AMINES.

(A STEREOSPECIFIC TRANSAMINATION-ALKYLATION REACTION)

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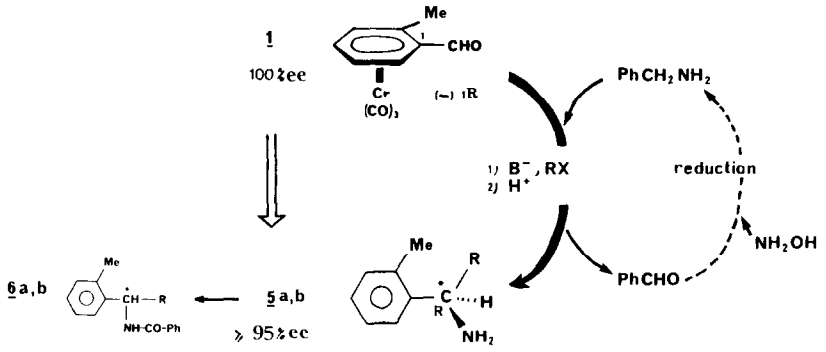
Abstract : *Optically pure arene-chromium-tricarbonyl complex 1 leads to almost optically pure (⩾95% ee) benzylic amines in good yields (∿85%) during a 3-step-reaction involving transfer of a nitrogen atom from a trivial reactant (benzylamine).*

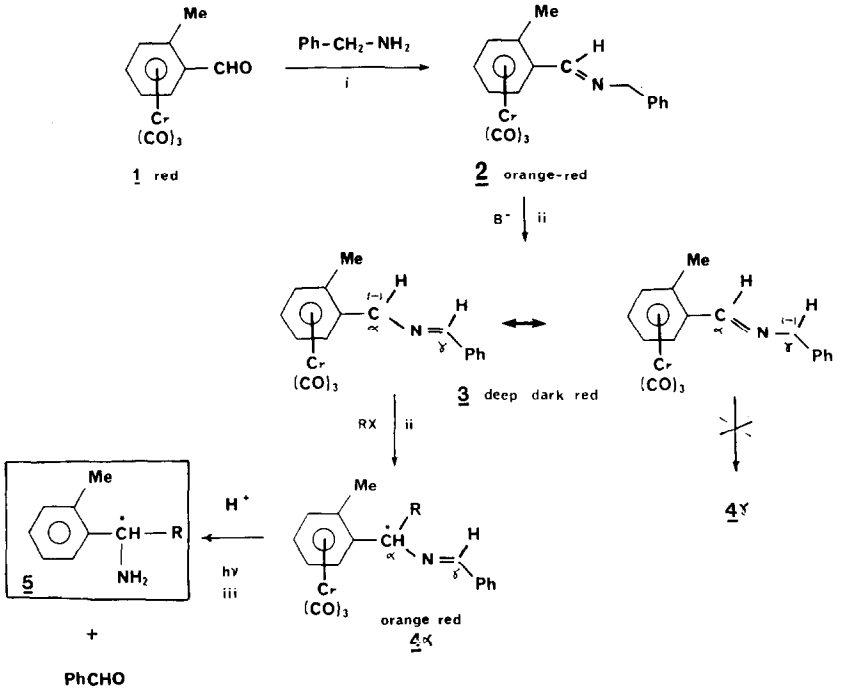
We want to report some results dealing with an enantioselective synthesis of chiral benzylic amines which can be considered as a transamination reaction (scheme 1). The nitrogen atom is transfered from a trivial reactant (benzylamine) to a chiral and optically pure[1] arene-chromium tricarbonyl complex 1 which is converted into a chiral benzylic amine with ⩾95% e.e. Transamination reactions used to synthesize α-amino acids either mimic vitamin B_6-dependent transamination or transform an optically pure α-amino acid to another one. Optical yields range form 5-10%[2], 29-54%[3] to 60-95%[4] and to 25-70%[5].

Scheme 1

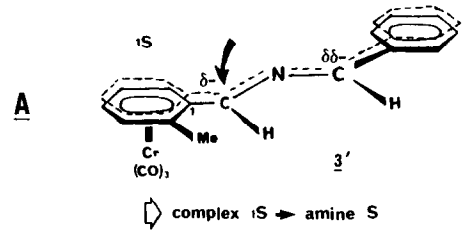


The reaction presented here proceeds in three steps, scheme 2, but can be performed as a one-pot reaction.

The imine 2 is readily available in quantitative yield[6]. Alkylation (step 2) is performed following Stork's method[7] using, as RX, methyl iodide, ethyl iodide and butyl iodide. Examination of 200MHz ^1H NMR spectra of the crude products 4 (before hydrolysis) shows that the alkylation occurs exclusively at c-α carbon, the double bond being shifted towards the c-γ carbon. This is based on the fact that the uncomplexed aromatic ring exhibits a ~ 0.4ppm non-equivalence between the ortho protons and the (meta + para) protons, which is characteristic of a ring substituted by a C=X group. In accord with this conclusion type 5 amine[8] is the only one isolated after hydrolysis (step 3).



Scheme 2 : i) C_6H_6, p-Tol SO_3H, reflux - ii) THF/HMPT 20%, LDA, RX at -78°c, -20°c or 0°c, 3 hrs - iii) Ethyl ether/HCl 10%, room t°.



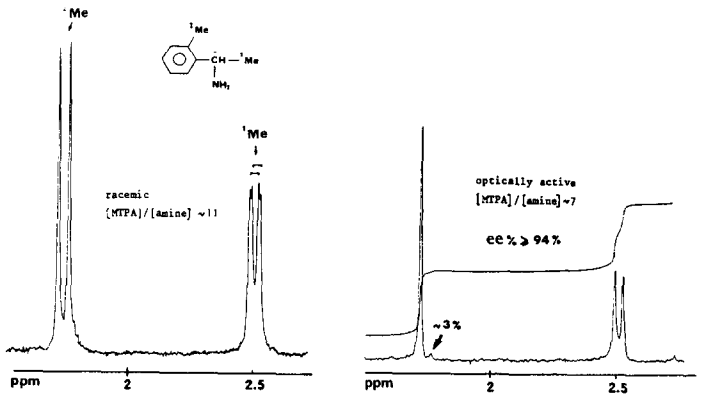


Figure 1

It is clear that mainly one diastereomer of 4α imines[9] is formed according to complexed-aromatic-protons signals. In accord with this observation, amines 5a ($R=CH_3$) and 5b ($R=CH_3CH_2$), obtained from optically pure (-) 1R complex 1, are found to be almost optically pure.

(+) MTPA is used as chiral reagent for determination of enantiomeric purity. Non-equivalences ranging from 0.03ppm to 0.05ppm are obtained for the aromatic methyl groups, figure 1, which leads to e.e.% $\geqslant$ 94% when $R=CH_3$[10].

Because of their rapid carbonation the optically pure amines have been isolated as their amide derivatives 6a and 6b[11], for better identification. When R=butyl the amine 5c has not been isolated yet by GC, however NMR (200MHz) spectra of 4c and 5c are correct.

The chemical yields, as determined on ^1H NMR spectra (200MHz) of crude products 4, range from 85 to 100% at -20°C and/or 0°C. No change in diastereoselectivity is observed when the reaction temperature increases.

The results are given in Table 1.

It must be noticed (Table 1) that addition of isopropyl iodide on carbanion 3 leads, at -78°C, to 20% addition at C-γ carbon (80/20 mixture of 4α and 4γ), and to 90% addition at C-α at 0°C. Steric effect might be implied in this change of regioselectivity.

Since the very first works (1972) by Trahanovsky[12], Ceccon[13] and Knox[14] it is well known and often used for synthetic purpose[15], that complexation of a phenyl-ring with $Cr(CO)_3$ increases the acidity of the benzylic protons or accelerates reactions which tend to develop a negative charge at the α-carbon. As early as 1967, results from Tirouflet[16] show that the $Cr(CO)_3$ group participated to the asymetric induction obtained in reactions occuring at the α-carbon even in acyclic complexes. But it was not before 1977 that des Abbayes[17] joining the two observations obtained 70% and 100% diastereoselection on alkylation of the anion of a racemic complexed arylacetic ester. However, there was no obvious way to get the starting material optically pure and here lies, in fact, the main difficulty when one tries to use these complexes as sources of optically active/pure synthons.

In our case, optically pure imine 2 is readily obtained from optically pure complex 1[1]. One proton is then easily removed from the γ-carbon leading to the anion 3.

An aza-allylic anion was already postulated as intermediate[18,19] during base catalyzed imines double bond shifts. However, in this case, the intensely colored carbanion 3 will be better represented by the highly delocalised species 3'.

The very high regioselectivity, with 90 to 100% addition at c-α, implies a much larger orbital coefficient at C-α for the HOMO'S (frontier orbital control) or a much larger electron-density at C-α (charge control) which is more consistent with the fact that the net electron-attracting effect of the $Cr(CO)_3$ group has been shown to involve mainly the σ-frame work[20,21].

The very high disatereoselectivity obtained, with 97 to 100% of one diastereomer during addition of the "small" methyl group, is consistant with but higher than previous results dealing with additions at C-α on ortho substituted acyclic complexes.

These results suggest the model of approach A where the more stable conformation (predicted grossly on the basis of steric hindrance) is the only one populated for the anionic ligand. This model of approach is of the same type as the one we already postulated for aldehydes and ketones[22] and, knowing the absolute configuration of the starting complex 1, allows prediction of the absolute configuration of the asymetric carbon created.

This transamination thus provides a one-pot enantiospecific synthesis of α-alkyl benzylamines, which, until now, had been obtained via alkylation of azomethine double bond[23].

Table 1

	Me			Et		nBu		iPr	
react. temp. °C	-78°	-20°	0°	-78°	0°	-78°	0°	-78°	0°
yields %	60	75	85	90	95	95	95	90	90
e.e. % for amines 5			94		100				
diastereomer ratio in 4α	100/0	100/0	97/3	100/0	97/3	100/0	100/0	90/10	96/4
Cα /Cγ (4α /4γ) %	100/0	100/0	100/0	100/0	100/0	100/0	100/0	80/20	90/10

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6. Red-orange solid, mp 100-1°C. IR (C_6H_6), ν C≡O = 1970, 1900 vs, ν C=N 1630 m cm^{-1}. ^1H NMR ($CDCl_3$/TMS, 200MHz Bruker, δ ppm), 2.32 (s, CH_3), 4.72 (s, CH_2), 5.02 (d, H_4), 5.16 (t, H_2), 5.45 (t, H_3), 6.20 (d, H_1), 7.25 (m, 5H, C_6H_5), 8.20 (s, H-imine).
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8. ^1H NMR ($CDCl_3$/TMS , 200MHz Bruker, δ ppm)
   5a, R=CH_3 : 1.35 (d,CH_3), 2.36 (s,CH_3), 4.35 (q,CH), 7.20 (m,3H), 7.45 (d,1H).
   5b, R=CH_3-CH_2 : 0.92 (t,CH_3), 1.70 (m,CH_2, AB part of ABX_3), 2.35 (s,CH_3), 4.10 (t, CH), 7.17 (m,3H), 7.40 (d, 1H).
   5c, R=$CH_3(CH_2)_3$: 0.80 (t,CH_3), 1.20 (m,$2CH_2$), 1.56 (m,CH_2), 2.27 (s,CH_3), 4.06 (t,CH), 7.15 (m,3H), 7.32 (d,1H).
9. ^1H NMR ($CDCl_3$/TMS, 200MHz Bruker, δ ppm) 4α a,R=CH_3 : 1.50 (d,CH_3), 2.29 (s,CH_3), 4.37 (q,CH), 5.14 (d,H_4), 5.24 (t,H_2), 5.35 (t,H_3), 6.05 (d,H_1), 7.42 (m,3H), 7.80 (m,2H), 8.42 (s, H-imine).
   4α b, R=CH_3CH_2 : 0.90 (t,CH_3) ; 1.81 (m,CH_2 AB part of an ABX_3), 2.28 (s,CH_3), 4.05 (d.d, CH), 5.12 (d,H_4), 5.21 (t,H_2), 5.34 (t,H_3), 6.02 (d,H_1), 7.42 (m,3H), 7.80 (m,2H), 8.37 (s,H-imine).
   4α c, R=$CH_3(CH_2)_3$: 0.87 (t,CH_3), 1.29 (m,$2CH_2$), 1.79 (m,CH_2), 2.27 (s,CH_3), 4.14 (d.d, CH), 5.10 (d,H_4), 5.21 (t,H_2), 5.35 (t,H_3), 6.00 (d,H_1), 7.42 (m, 3H), 7.82 (m,2H), 8.36 (s,H-imine).
10. If the small signal detected (3%) corresponds to an impurity and not to the other enantiomer, the percentage of enantiomeric excess would be larger than 94%. This has not been checked yet.
11. 6a, R=CH_3 : mp =125-6°C, $[\alpha]_D$ = +19±1° (c 0.38, $CHCl_3$).
    ^1H NMR ($CDCl_3$/TMS, 200MHz Bruker, δ ppm), 1.6 (d, CH_3), 2.42 (s,CH_3), 5.50 (quintuplet, CH), 6.25 (broad d,NH), 7.2 (m,3H), 7.40 (m,4H), 7.75 (d,2H),
    6b, R=CH_3-CH_2 : mp =107-8°C, $[\alpha]_D$=+15±1° (C 0.26, $CHCl_3$).
    ^1H NMR ($CDCl_3$/TMS, 200MHz Bruker, δ ppm) 0.98 (t, CH_3), 1.94 (m,CH_2,AB part of ABX_3), 2.45 (s,CH_3), 5.33 (q,CH), 6.20 (broad d,NH), 7.20 (m,3H), 7.40 (m,4H), 7.75 (d,2H).
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