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Asymmetric Synthesis of Amines by the Reductive Amination of Ketones Using (+) and (-) Norephedrine Followed by Periodate Oxidation.

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Abstract: A new route for the synthesis of aralkyl primary amines is reported, where the commercially available (+) or (-) norephedrine is condensed with aralkyl ketones followed by hydrogenation of the Schiff base using platinum catalyst. The chiral β-aminoalcohols thus obtained were oxidized by periodate to yield the aralkyl primary amines in 54-66% enantiomeric excess.

Reductive amination of carbonyl compounds is a useful method for the preparation of amines [1,2]. This reaction can be adopted for the preparation of chiral amines in one of two ways, namely (i) conversion of the prochiral ketone to the prochiral imine (Schiff base) followed by reduction using a chiral catalyst or chiral reagent[3]; or (ii) conversion of the prochiral ketone to a chiral Schiff base using a chiral amine followed by reduction by an achiral catalyst or reagent. In the latter approach, after the reduction step, the chiral auxiliary may be regenerated for reuse or it may be destroyed by a chemical reaction, in which case it has been referred to as 'self-immolative' chiral auxiliary [4].

The present paper reports the chiral synthesis of aralkyl amines from aralkyl ketones by reductive amination using the commercially available (+) or (-) norephedrine followed by the oxidative removal of the norephedrine carbons using periodate (Scheme 1), a methodology for reductive amination developed in our laboratory [5].

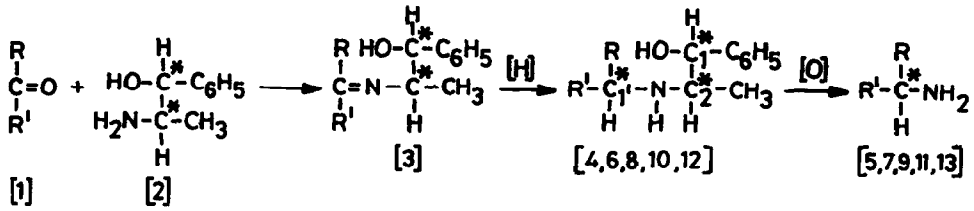
There are several reports on the use of norephedrine in asymmetric synthesis. The reaction of norephedrine and other β-aminoalcohols with aldehydes or ketones can give rise to the Schiff base or the isomeric oxazolidine, which have been shown to exist in equilibrium with each other [6-8]. The norephedrine Schiff base/oxazolidine has been used for the asymmetric aldolization of ketones [8,9] and in the enantioselective synthesis of the carbapenem antibiotics [10].

The oxidative cleavage of β-aminoalcohols by glycol cleaving regents (lead tetracetate [11], periodate [5,12]) for the generation of amines has been reported.

Results and Discussion

For the present study the commercially available, (1S,2R)-(+)-norephedrine [2] and (1R,2S)-(-)-norephedrine [2'] (Aldrich), were used as chiral auxiliaries.

The general procedure was to condense the prochiral ketone with norephedrine in benzene in the presence of 4A molecular sieve (to remove the water formed in the reaction). The condensation



R,R': [4] & [5], -C_6H_5, -CH_3 ; [6] & [7], -C_6H_5, -C_2H_5; [8] & [9], p-$CH_3C_6H_4$, -CH_3; [10] & [11], p-$CH_3OC_6H_4$, -CH_3; [12] & [13] correspond to [1] = 

Scheme 1

product was not analysed. From the literature reports [7], it is clear that the product is a mixture of the Schiff base and the oxazolidine, in dynamic equilibrium. The mixture was hydrogenated using platinum catalyst. The benzylic hydroxy group and benzyl C–N bond are potentially hydrogenolyzable. But there was no evidence that under the present reaction conditions there was any appreciable hydrogenolysis. It was assumed that the imine tautomer of the condensation product was the one hydrogenated to yield the N-alkylamine, the equilibrium shifting away from the oxazolidine. It is known that C=N is very rapidly hydrogenated over platinum [2]. The following discussions are based on the assumption that the C=N is the functionality getting hydrogenated, though there is no clear evidence that the oxazolidine C–O bond is also not hydrogenolyzed. If the oxazolidine is hydrogenolysed, the product would be the same, but the model suggested for asymmetric induction will have to be modified.

The yield, specific rotation, ee% and absolute configuration of primary amines synthesized are shown in Table 1 and Table 2.

Table 1
Experiments using (1S,2R)-(+)-norephedrine

β-Amino-alcohol	Sp. rotation $[\alpha]_D^{30}$ (1N HCl)	Yield (%)	Amines	Sp. rotation $[\alpha]_D^{30}$	Yield (%)	ee %	Absolute configuration [13]
[4]	+10.6	90	[5]	−20.4 (Benzene)	78	59	S
[6]	+1.8	85	[7]	−14.1 (Ethanol)	73	66	S
[8]	+3.2	79	[9]	−20.4 (Ethanol)	81	64	S
[10]	+4.2	82	[11]	−15.1 (Methanol)	69	57	S
[12]	−4.5	88	[13]	−26.5 (Methanol)	71	64	S

The enantiomeric excess obtained in these reactions ranges from 54 to 66%. Partial loss of enan-

tioselectivity could have happened at either the catalytic hydrogenation stage or at the oxidation stage. The diastereoselectivity of the hydrogenation step was not ascertained. The enantiomeric excess at this stage is expected to be no less than that of the final amines. On the basis of the absolute configuration of the final amines (assigned by comparison with literature [13]), the configuration of **[4,6,8,10** and **12]** are assigned as 1S,2R,1'S and that of **[4',6'** and **8']** as 1R,2S,1'R.

Reaction of Acetophenone with (1S, 2R)-(+)-norephedrine

The β-aminoalcohol **[4]** was prepared by treating acetophenone with (1S,2R)-(+)-norephedrine **[2]** followed by the hydrogenation of the Schiff base formed using platinum catalyst in benzene in an atmosphere of hydrogen. The spectra (IR, ^{1}HNMR, ^{13}CNMR and mass) were in full agreement with the proposed structure.

The standard protocol developed for effecting destructive removal of the chiral auxiliary from the β-aminoalcohol was the oxidative cleavage with sodium metaperiodate in methanol at room temperature followed by hydrolysis with HCl. The amine was recovered in good yield. It was not ascertained whether the N-acetyl derivative was formed (cf. formation of N-formylamine in the oxidation of N-benzylethanolamine) [5] initially to any extent. The amines formed were characterized by their spectra. The results of the asymmetric amination of acetophenone, 3-phenylpropanone, p-methylacetophenone, p-methoxyacetophenone and α-tetralone using (+) norephedrine are given in Table 1.

Amination of some of these prochiral ketones was done with (1R,2S)-(-)-norephedrine **[2']**. This time, as expected the amines formed were the R isomers, with nearly the same enantiomeric excess. The results of the experiments with chiral auxiliary (1R,2S)-(-)-norephedrine are summarized in Table 2.

Table 2
Experiments using (1R,2S)-(-)-norephedrine

β-Amino-alcohol	Sp. rotation $[\alpha]_D^{30}$ (1N HCl)	Yield (%)	Amines	Sp. rotation $[\alpha]_D^{30}$	Yield (%)	ee %	Absolute configuration [13]
[4']	-14.5	86	**[5']**	+19.2 (Benzene)	73	54	R
[6']	+2.4	89	**[7']**	+12.6 (Ethanol)	71	59	R
[8']	-7.6	85	**[9']**	+18.9 (Ethanol)	76	60	R
Structures **[4' – 9']** correspond to the stereoisomers of **[4 – 9]** of Table 1.							

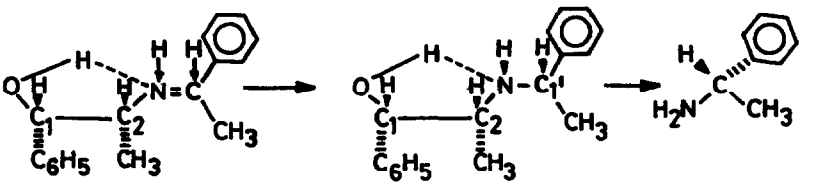
The enantioselectivity during the hydrogenation of the Schiff base using platinum catalyst could be due to the cyclic structure originating from the intramolecular H-bonding in the Schiff base, which causes some steric effect in the orientation of the phenyl and the methyl group (in the case of the Schiff base formed from acetophenone and (1S, 2R)-(+)-norephedrine) connected to the olefinic carbon atom. Due to this reason the preferred orientation of the bulkier phenyl group will be anti to the side heavily substituted with the bulky groups of the chiral auxiliary part (Scheme 2).

This Schiff base can be adsorbed comfortably in such a way that the bulky groups are away from the catalytic surface. Here cis hydrogenation occurs as shown in Scheme 2. The in-

tramolecular H–bonding and the steric factors in the Schiff base favour the formation of the S-isomer of the primary amines when (1S,2R)–(+)–norephedrine [2] was the chiral auxiliary and R–isomer when (1R,2S)–(-)–norephedrine [2'] was the chiral auxiliary.

Experimental

Adams Catalyst was prepared from chloroplatinic acid according to the reported procedure [14].



C_1=S, C_2=R, C_1'=S

Scheme 2

Model for the hydrogenation of the Schiff base obtained from (1S,2R)–(+)–norephedrine and acetophenone.

(+)–N–(α–phenylethyl)norephedrine [4]

About 1 g of (1S,2R)–(+)–norephedrine (Aldrich) $\left[[\alpha]_D^{20} = +40\,(1N\,HCl)\right]$, 0.81 g of acetophenone, 10 g of molecular sieve 4A and 50ml of dry benzene were taken in a 100ml R.B. flask. The mixture was stirred for 24 hours at room temperature to yield the Schiff base. The asymmetric hydrogenation of the Schiff base was done using Adams catalyst (0.3g) in benzene at atmospheric pressure. The optical activity of the resultant β–aminoalcohol was recorded after purification.

Yield : 90% I.r. (CCl_4) : 3640, 3320, 2992, 1878, 1644, 1488, 1366, 1286, 1075 and 950 cm^{-1}. ^{1}HNMR (400MHz, $CDCl_3$/TMS) : δ 0.8 (d, 3H), 1.4 (d, 3H), 2.88 (m, 1H), 3.15 (b.s., 2H), 4.33 (d, 1H), 4.75 (q, 1H) and 7.16–7.3 (m, 10H). ^{13}C NMR (400MHz, $CDCl_3$/TMS) : δ 17.75 (q), 25.19 (q), 51.89 (d), 69.68 (d), 77.29 (d), 125.39 (d), 126.57 (d), 127.09 (d), 127.32 (d), 128.00 (d), 128.06 (s), 128.18 (s), and 128.26 (s). Mass spectrum (m/z) : 122 (50), 121 (18), 107 (50), 105 (22), 79 (100), 77 (64) and 51 (84). Specific rotation, $[\alpha]_D^{30}$ = + 10.6 (1N HCl).

α–Phenylethylamine [5]

The β–aminoalcohol [4] was oxidized using sodium metaperiodate in methanol. About 1g of the compound [4], sodium metaperiodate (1.5g) and 100ml methanol were taken in a flask fitted with a water condenser and was stirred for 4–5h at room temperature. Then the reaction mixture was treated with 3N HCl (15ml) and extracted with dichloromethane (25ml). The aqueous layer was neutralized with aq. NaOH, extracted with dichloromethane (50ml). Drying and solvent removal furnished compound [5].

Yield : 78%. I.r. (CCl_4) : 3456, 2960, 1795, 1609, 1485, 1443, 1360, 1177 and 912 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$/TMS) : δ 1.38 (d, 3H), 1.78 (s, 2H), 4.05 (q, 1H) and 7.3 (s, 5H). ^{13}CNMR (400 MHz, $CDCl_3$/TMS) : δ 25.57 (q), 51.24 (d), 125.63 (d), 126.76 (d), 128.43 (s) and 147.63 (s).

Mass spectrum (m/z) : $M^{+\cdot}$ 121 (14), 120 (10), 106 (100), 105 (8), 91 (4), 79 (36), 77 (20) and 65 (4).
Specific rotation, $[\alpha]_D^{30}$ = − 20.4 (Benzene). ee% = 59. Absolute configuration [13] = S.

Compounds [6]−[13] were prepared by the same procedure as for [4] and [5] using the same molar proportions of reagents. The yields and optical activity data of the products were as in Table 1. The spectroscopic data are listed below.

[6] i.r. (CCl_4) : 3584, 3280, 2992, 2880, 1680, 1443, 1340, 1276, 1177, 1040, 944 and 918 cm^{-1}.
^{1}HNMR (400 MHz, $CDCl_3$/TMS) : δ 0.85−0.95 (m, 5H), 1.4 (d, 3H), 2.5 (b.s., 2H), 2.9 (t, 1H), 4.4 (d, 1H), 4.55 (m, 1H) and 7.1−7.3 (m, 10 H). ^{13}CNMR (400MHz, $CDCl_3$/TMS) : δ 8.21 (q), 10.18 (t), 18.09 (q), 52.01 (d), 75.57 (d), 76.83 (d), 126.00 (d), 126.60 (d), 127.36 (d), 127. 95 (d), 128.11 (d), 128.41 (s), 128.53 (s) and 132. 87 (s). Mass spectrum (m/z) : 136 (12), 134 (18), 107 (80), 105 (100), 70 (56) and 77 (70). [7] i.r. (CCl_4) : 3440, 3376, 3040, 1718, 1670, 1616, 1481, 1446, 1366, 1283, 1056 and 912 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$/TMS) : δ 0.85 (t, 3H), 1.7 (m, 4H), 3.78 (t, 1H) and 7.28 (m, 5H). ^{13}C NMR (400 MHz, $CDCl_3$/TMS) : δ 10.95 (q), 32.37 (t), 57.80 (d), 126.38 (d), 126.83 (d), 128.36 (s) and 146.37 (s). Mass spectrum (m/z) : $M^{+\cdot}$ 135 (10), 134 (6), 120 (8), 107 (18), 106 (100), 91 (12) and 77 (24).
[8] i.r. (CCl_4) : 3616, 3291, 2880, 1747, 1686, 1484, 1446, 1363, 1283, 1084, 1033, 947 and 694 cm^{-1}.
^{1}HNMR (400 MHz, $CDCl_3$/TMS) : δ 0.85 (d, 3H), 1.4 (d, 3H), 2.3 (s, 3H), 2.98 (m, 1H), 3.1 (b.s., 2H), 4.37 (d, 1H), 4.77 (m, 1H) and 7.1−7.34 (m, 9H). ^{13}C NMR (400 MHz, $CDCl_3$/TMS) : δ 17.79 (q), 21.03 (q), 25.15 (q), 51.94 (d), 69.68 (d), 77. 38 (d), 125.37 (d), 126. 57 (d), 127.33 (d), 128.06 (d), 128.97 (d), 129.20 (s), 136.64 (s), and 143.19 (s). Mass spectrum (m/z) : 136 (18), 134 (10), 121 (100), 93 (70), 91 (20) and 77 (44). [9] i.r. (CCl_4) : 3410, 2978, 1782, 1667, 1616, 1500, 1443, 1363, 1100 and 912 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$/TMS) : δ 1.3 (d, 3H), 2.15 (b.s., 2H), 2.27 (s, 3H), 3.98 (q, 1H) and 7.0−7.2 (m, 4H). ^{13}CNMR (400 MHz, $CDCl_3$/TMS) : δ 20.94 (q), 25.44 (q), 50.83 (d), 125.56 (d), 129.06 (d), 136.15 (s) and 144.53 (s). Mass spectrum (m/z) : $M^{+\cdot}$ 135 (8), 134 (10), 120 (100), 93 (30) and 65 (8). [10] i.r. (CCl_4) : 3604, 3405, 2992, 1673, 1596, 1449, 1350, 1171 and 954 cm^{-1}.
^{1}H NMR (400MHz, $CDCl_3$/TMS) : δ 0.85 (d, 3 H), 1.4 (d, 3H), 2.98 (m, 1H), 3.2 (b.s., 2H), 3.8 (s, 3H), 4.4 (d, 1H), 4.8 (m, 1H) and 6.9−7.9 (m, 9H). ^{13}CNMR (400MHz, $CDCl_3$/TMS) : δ 17.69 (q), 25.30 (q), 26.19 (q), 52.17 (d), 55. 37 (d), 69.32 (d), 113.67 (d), 126.62 (d), 128.08 (d), 130.55 (d), 130. 64 (d), 138.56 (s), 141.77 (s) and 163. 50 (s). Mass spectrum (m/z) : 136 (18), 121 (100), 93 (70) and 77 (44). [11] i.r. (CCl_4) : 3481, 3024, 1666, 1590, 1478, 1436, 1229, 1037 and 915 cm^{-1}. ^{1}HNMR (400MHz, $CDCl_3$/TMS) : δ 1.35 (d, 3H), 1.9 (s, 2H), 3.75 (s, 3H), 4.0 (q, 1H), and 6.8−7.4 (m, 4H). ^{13}C NMR (400 MHz, $CDCl_3$/TMS) : δ 25.65 (q), 50.53 (d), 55.11 (q), 113.76 (d), 126.71 (d), 139.86 (s) and 158.40 (s). Mass spectrum (m/z) : $M^{+\cdot}$ 151 (10), 136 (100), 107 (20) and 65 (8). [12] i.r. (CCl_4) : 3611, 3396, 2944, 1680, 1443, 1283, 1024 and 700 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) : δ 0.86 (d, 3H), 2.0 (m, 2H), 2.5 (q, 2H), 2.85 (t, 2H), 3.3 (m, 1H), 4.9 (m, 4H), and 7.1−7.9 (m, 9H). ^{13}C NMR (400 MHz, $CDCl_3$/TMS) : δ 23.17 (q), 26.85 (t), 29.53 (t), 38.99 (t), 52.47 (d), 74.48 (d), 76.98 (d), 126.21 (d), 126.50 (d), 126.69 (d), 127.01 (d), 127.18 (d), 128.06 (d), 128.18 (d), 128.70 (s), 133.31 (s) and 144.41 (s). Mass spectrum (m/z) : 146 (80), 118 (100), 107 (12), 91 (40) and 77 (20). [13] i.r.(CCl_4) : 3488, 2976, 1600, 1497, 1446, 1360, 1292, 1238, 1040 and 864 cm^{-1}.
^{1}HNMR (400 MHz, $CDCl_3$/TMS) : δ 1.5−2.0 (series of multiplets, 6H), 2.7 (t, 2H), 3.9 (t, 1H) and 7.0−7.35 (m, 4H).
^{13}CNMR (400 MHz, $CDCl_3$/TMS) : δ 19.49 (t), 29.47 (t), 33.34 (t), 49.18 (d), 125.92 (d), 126.47 (d), 127.94 (d), 128.9 (d), 136.55 (s) and 140.93 (s). Mass spectrum (m/z) : $M^{+\cdot}$ 147 (16), 130 (100), 119 (68) and 91 (22).

Experiments with (1R, 2S)-(-)-Norephedrine

Reductive amination of acetophenone, 3-phenylpropanone and p-methylacetophenone were done with (1R, 2S)-(-)-norephedrine (Aldrich) $\left[[\alpha]_D^{20} = -41 (1N\ HCl)\right]$. The spectra were identical to the corresponding ones with the (1S,2R)-(+)-norephedrine reaction products, except for the absolute con-

figuration and specific rotation. The yields and optical activity were as reported in Table 2.

Conclusion

A procedure for the asymmetric synthesis of aralkyl primary amines by the reductive alkylation of aralkyl ketones using the commercially available (+) or (-) norephedrine followed by oxidative removal of the sacrificial chiral auxiliary by periodate oxidation is reported. Enantiomeric excess ranging from 54–66% has been realized. The asymmetric induction can be rationalised on the basis of a model for the hydrogenation of the ketimine involving a hydrogen bonded cyclic structure.

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