$RuCl_3$–NaOH as a Reagent for Chirality Transfer. Synthesis of Chiral β-Deuteriated Ketones by Asymmetric Induction

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Summary Chiral β-deuteriated acyclic ketones have been quantitatively obtained by a 37% stereospecific isomerisation of the corresponding allylic alcohols.

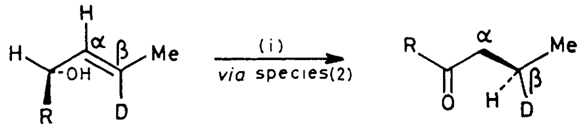
It is well known that the isomerisation of allylic alcohols to the corresponding saturated aldehydes and ketones is induced by a variety of transition metal catalysts:[1] iron,[2] cobalt,[3] osmium,[4] iridium,[5] platinum,[6] palladium,[7] rhodium,[5a,8] and ruthenium.[5a,8,9] Studies using pentacarbonyl iron suggest that the reaction is intramolecular[2c] and requires a *syn*-relationship between the transferred hydrogen and the catalyst[2f] in a 1,3- *suprafacial*-hydrogen shift.[2h]

In preliminary work, we found that an equimolar mixture of ruthenium chloride and sodium hydroxide is a very efficient reagent for promoting this type of isomerisation of the allylic alcohols $RCHOHCH{=}CH_2$ (R = Me, Et, Pr^i, Bu^i, and Bu^t). The reaction was shown to be quantitative and rapid. Since no solvent was used and no side products were formed the pure ketone was easily recovered.

In a further attempt to study the stereochemistry of this overall 1,3-hydrogen transfer in an acyclic system, we investigated the isomerisation of the chiral (*E*)-[4-$^2H_1$]-pent-3-en-2-ol (**1a**) and (*E*)-[5-$^2H_1$]hex-4-en-3-ol (**1b**). These secondary allylic alcohols were chosen since their *prochiral* β-trigonal carbon can serve as a convenient probe for the detection of 1,3-chirality transfer (Scheme).

Using the $RuCl_3$–NaOH (1 : 1) reagent the chiral allylic alcohols (**1**) were isomerised to the chiral β-deuteriated aliphatic ketones (**3**) of opposite configuration (Scheme and Table).

The optical activity of the ketone (**3a**) was shown not to be due to any chiral contaminant since purification of its crystalline semicarbazone (m.p. 110—110·5 °C; lit.[10] 112 °C) led to a retention of the optical activity, $[\alpha]_{365}$ 0·57° (*c* 4·6; EtOH).



(*E*)-(*S*)-(+)-(**1**)
a ; R = Me
b ; R = Et

(*R*)-(+)-(**3**)
a ; R = Me
b ; R = Et

Scheme. 1,3-Chirality transfer by $RuCl_3$–NaOH catalyst. (i) 3×10^{-3} equiv. of $RuCl_3$–NaOH (1 : 1), 5 min, 130 °C.

Furthermore the o.r.d. curves of the (*R*) and (*S*) enantiomers of (**3a**), are mirror images, with $[\phi]_R$ $2{\cdot}1 \times 10^{-2}$ (*c* 1·1; dioxan) and $[\phi]_S$ $-2{\cdot}8 \times 10^{-2}$ (*c* 0·9; dioxan) at 310 nm, and $[\phi]$ 0 at λ_{max} 290 nm, the ketone (*S*)-(−)-(**3a**) exhibiting a negative Cotton effect.[11] Therefore the optical activity must originate in the chiral ketone.

Finally the chirality of the ketones (**3**) can be attributed to the asymmetry of the β-carbon atom since the (*R*)-(+)-[5-$^2H_1$]hexan-3-one (**3b**), with $[\alpha]_D$ 0·101°, retains its optical rotation after treatment with 1 M NaOH in H_2O–MeOH (9 : 1) for 16 h.

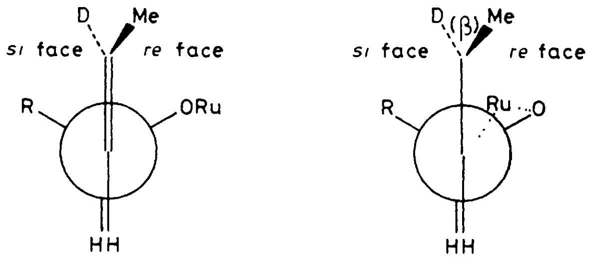
As the data in the Table show, a hydrogen atom is transferred to the β-carbon atom of the allylic alcohols (**1**) by a 37% stereospecific process, the transition metal acting predominantly *via* the *si* face of the double bond of the alcohol (*S*)-(**1**).

Since the rate of the $RuCl_3$-catalysed isomerisation is enhanced by the addition of NaOH and the methyl ether of the racemic alcohol (**1a**) is inert under the reaction conditions, the transfer may involve an alkoxide Ru species as the reactive intermediate (**2**) which is very similar to that pro-

TABLE. Synthesis of chiral β-deuteriated ketones by asymmetric induction [all the spectral data (i.r. n.m.r.) are consistent with the structures of the compounds]

Allylic[a] alcohols	$[\alpha]_D^{22}$ (neat, l = 1)	Optical purity/%	Aliphatic ketones	$[\alpha]_D^{22}$ (neat, l = 1)	Optical purity/%	Transfer of chirality/%
(*S*)[b]-(+)[c]-(**1a**)	(?)[c]	59[b]	(*R*)-(+)[d]-(**3a**)	0·099°[e,g]	22·2[h]	37·6
(*R*)[b]-(−)[c]-(**1a**)	(?)[c]	55·4[b]	(*S*)-(−)[d]-(**3a**)	0·123°[f]	21·6	39·5
(*S*)-(+)-(**1b**)	6·51°	49·7[i]	(*R*)-(+)-(**3b**)	0·115°[e]	20·2[j]	40·7
(*S*)-(+)-(**1b**)	6·08°	46·4[i]	(*R*)-(+)-(**3b**)	0·101°[f]	17·8[j]	38·3

[a] β-Deuterated secondary allylic alcohols (**1**), with *E* configuration, have been obtained from the corresponding resolved (K. Koosha. J. Berian, M.-L. Capmau, and W. Chodkiewicz, *Bull Soc. Chem. Fr.*, 1975, **5–6**, **1294**; R. Weidman, A. Schoofs, and A. Horeau, *Bull. Soc, Chim. Fr.*; 1976, **3–4**, 645) acetylenic alcohols (M. Gaudemar, *Ann. Chim.* (*Paris*), 1956, **13**, 1, 161, and 168) by reduction, using the $AlLiH_4$, THF, and D_2O technique (B. Grant and C. Djerassi, *J. Org. Chem.*, 1974, **39**, 968). [b] The structure and the optical purity of the alcohol (**1a**) have been correlated with those of pentan-2-ol (K. Koosha, J. Berian, M.-L. Capmau, and W. Chodkiewicz, *Bull. Soc. Chem. Fr.*, 1975, **5–6**, 1294; R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, 1911, **99**, 45) obtained by the catalytic hydrogenation of the corresponding pent-3-yn-2-ol using Raney nickel (K.-K. Chang, N. Cohen, J. P. de Noble, A. C. Specian, Jr., and G. Saucy, *J. Org. Chem.*, 1976, **41**, 3450). [c] As first noted by Kenyon (H. W. J. Hill, J. Kenyon, and H. Phillips, *J. Chem. Soc.*, 1936, 576 the optical rotation of the undeuteriated alcohol (**1a**) is known to be small, its sign and magnitude varying with time. [d] The structure and rotation for the optically pure ketone (**3a**) has been established by Streitweiser (A. Streitweiser, Jr. and M. R. Granger, *J. Org. Chem.*, 1967, **32**, 1528; D. Arigoni and E. L. Eliel, *Top. Stereochem.*, 1969, **4**, 127; J. Jacques, C. Gras, and S. Bourcier in 'Stereochemistry,' ed. H. B. Kagan, G. Thieme, Stuttgart, 1977, p. **219**; L. Verbit, *Prog. Phys. Org. Chem.*, 1970, **7**, 115): (*S*)-(−)- and $[\alpha]_D^{20}$ 0·57° (neat, l = 1). [e] Corrected for fully monodeuteriated product. [f] Uncorrected for fully monodeuteriated product. [g] The chiral ketone (*R*)-(+)-(**3a**) was shown to be pure by g.l.c. on Carbowax 20M, 6 m at 40 and 100 °C and SE 30, 6 m at 40 and 100 °C. [h] The alcohol (*S*)-(**1a**) was 50% deuteriated on oxygen; we have shown that this deuterium did not lead to any transfer of chirality in the isomerisation since chiral but-1-en-3-ol deuteriated on oxygen was similarly converted into [3-$^2H_1$]butan-2-one, which was optically inactive. The deuterium scrambling at C-1 and C-3, observed during the isomerisation of 50% oxygen deuterated (**1a**), is most probably due to keto–enol equilibria. [i] The optical purity of the alcohol (**1b**) was calculated from the known value $[\alpha]_D$ 13·1° of the undeuterated (*S*)-(+)-pent-2-en-3-ol (J. Kenyon and R. Poplett, *J. Chem. Soc.*, 1945, 273). [j] These values were calculated using $[\alpha]_D$ of optically pure [4-^{2}H]pentan-2-one (**3a**). They are actually minimised because, as generally observed in a series of chiral compounds, the rotation of pure [5-^{2}H]hexan-3-one must be smaller than the rotation of [4-^{2}H]pentan-2-one (0·57°).



(2) (2′)

FIGURE. (**2**): Favoured conformational bisecting rotamer of allylic alcohol (*E*)-(*R*)-(**1**).

posed by Sharpless[12] in the epoxidation of the racemic allylic alcohol (**1a**).

The asymmetric π-ruthenium complex (**2′**) is then formed from complex (**2**) which brings a hydrogen to the *re* face of the trigonal *β-prochiral* carbon, very probably *via* an intramolecular 1,3-shift after an sp^3–sp^2 free rotation of the bond of the (*R*)-enantiomer (**1**).

The possibility of distinguishing between the intra- or inter-molecular process and π-allyl ruthenium hydride or addition–elimination ruthenium hydride mechanisms[13] is under study.

Although some examples of retention of chirality during olefin isomerisation are known,[2g,2i,3b] in our opinion this observation represents the first chirality transfer reported in an acyclic system induced by a transition metal catalyst. The $RuCl_3$–NaOH reagent is thus able to differentiate between the two double bond diastereotopic faces of chiral allylic alcohols (*vide supra*).

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