Enantioselective α-Hydrogen-atom Abstraction from an Ester by an Optically Active Amine-Boryl Radical

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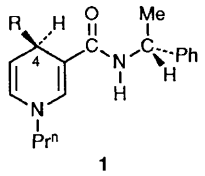
The optically active amine-boryl radical $Ipc\dot{B}H{\leftarrow}NMe_2CH_2CH_2NMe_2{\rightarrow}BH_2Ipc$ (Ipc = isopinocampheyl) abstracts hydrogen enantioselectively from the α-C–H group of methyl 2-phenylpropanoate; partial kinetic resolution of the ester has been achieved in a catalytic manner.

Although numerous stereoselective radical reactions are known, very few enantioselective homolytic processes have been identified. The only reported enantioselective hydrogen-atom transfer reaction is that which takes place from the 4-position of the optically active dihydronicotinamides **1** to the radical anion of a prochiral ketone.[1] The radical anion derived from phenyl trifluoromethyl ketone [$PhC(\bar{O})CF_3$] reacts with **1** (R = H) or **1** (R = Me) to give predominantly the (*S*)-alkoxide [$PhCH(\bar{O})CF_3$] with an enantiomeric excess (e.e.) of *ca.* 22% and *ca.* 67%, respectively.[1] In this



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communication we report the first example of enantioselective abstraction of hydrogen by an optically active radical.

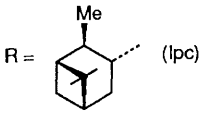
We have shown previously that α-hydrogen-atom abstraction from esters by *tert*-butoxyl radicals is subject to polarity reversal catalysis by amine-alkylborane complexes, via the cycle of reactions (1) and (2).[2-4] When an oxirane solution containing di-*tert*-butyl peroxide (DTBP) (20% v/v) and *tert*-butyl 2-phenylpropanoate **6** (R = Bu^t) (1 mol dm^{-3}) was irradiated with UV light at 190 K while the sample was in the microwave cavity of an ESR spectrometer,[2] the spectrum of the oxiranyl radical was observed [eqns. (3) and (4)]. However, when the experiment was repeated in the presence of either amine-borane **2**[5] or **4**[6] (*ca.* 0.15 mol dm^{-3}), an ESR spectrum, which we ascribe to the radical **7** (R = Bu^t) [a(3H$_\beta$) 16.77, a(2H$_o$) 4.15, a(2H$_m$) 1.46, a(1H$_p$) 4.60 G and g 2.0031]† was detected in place of that of the oxiranyl radical. The *tert*-butoxyl radical now abstracts hydrogen from the amine-borane in preference to oxirane and hydrogen abstraction from the ester is brought about by the amine-boryl radical so produced [eqns. (1) and (2)].

Similar results were obtained with the methyl ester **6** (R = Me), although the ESR spectrum of **7** (R = Me) was more complex[7] and consequently weaker than that of its *O-tert*-butyl counterpart. When 1-bromopropane (1 mol dm^{-3}) was present along with the methyl ester (1 mol dm^{-3}), DTBP and the amine-borane **2** or **4** (0.17 mol dm^{-3}), only the ESR spectrum of the propyl radical was observed during UV irradiation.‡ Again, this result shows that, at the concentrations employed, *tert*-butoxyl radicals are efficiently scavenged by the amine-borane to give the corresponding amine-boryl radical, which now abstracts halogen from the alkyl bromide [2b] in preference to abstracting hydrogen from the ester.

$$XNMe_2{\rightarrow}BH_2R \xrightarrow[-Bu^tOH]{Bu^tO^\cdot} XNMe_2{\rightarrow}\dot{B}HR \qquad (1)$$

2 X = Me, R = Bu^n **3**

4 X = $CH_2CH_2NMe_2{\rightarrow}BH_2R$ **5**



$$XNMe_2{\rightarrow}\dot{B}HR + R^1R^2CHCO_2R^3 \rightarrow R^1R^2\dot{C}CO_2R^3 + XNMe_2{\rightarrow}BH_2R \qquad (2)$$

Next an oxirane solution containing racemic ester **6** (R = Me) (0.80 mol dm^{-3}), DTBP (18% v/v), and *tert*-butylbenzene (0.32 mol dm^{-3}) as an internal concentration standard was irradiated through quartz with UV light from a high-pressure mercury discharge lamp at 190 K for 3 h. Oxirane was allowed to evaporate from the sample at room temperature, after which GLC analysis showed that 98% of the ester remained. However, when the experiment was repeated in the presence of the amine-borane **4** (0.15 mol dm^{-3}), under otherwise identical conditions, 26% of the ester was consumed; both results are in accord with the ESR spectroscopic observations.§ The recovered ester was examined by 400 MHz ^{1}H NMR spectroscopy in the presence of the optically active shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III)[Eu(hfc)$_3$] and shown to be enriched in one enantiomer (14% e.e.). Comparison with the NMR spectra obtained from ester of known e.e., prepared from authentic (*R*)-**6** (R = Me) and racemic ester, showed that the optically active amine-boryl radical **5** abstracts hydrogen more rapidly from the (*R*)-ester, leaving the residual compound enriched in the (*S*)-enantiomer. Reaction mixtures developed a pale-yellow colouration during UV irradiation and it appears that progressively less light is absorbed by the peroxide as the reaction proceeds. When the DTBP concentration was increased to 28% v/v under otherwise similar conditions, 41% of the ester was consumed after 5 h UV irradiation and the recovered ester contained a 22% e.e. of the (*S*)-enantiomer.¶ The concentration of DTBP could not be increased further without causing the catalyst **4** to come out of solution. Assuming that none of the radicals **7** (R = Me) goes on to abstract hydrogen and thus to regenerate racemic ester **6**, an e.e. of 22% after 41% consumption of the ester implies[8] that the (*R*)-enantiomer is *ca.* 2.4 times more reactive than the (*S*)-enantiomer towards α-hydrogen transfer to the radical **5** at 190 K. As a control for the experimental procedures used, it was shown that racemic ester remained after 49% consumption of **6** (R = Me) in the presence of the achiral amine-borane **2**.

$$PhMeC(H)CO_2R \qquad PhMe\dot{C}CO_2R$$
6 **7**

$$Bu^tOOBu^t \xrightarrow{h\nu} 2Bu^tO^\cdot \qquad (3)$$

$$Bu^tO^\cdot + \overbrace{CH_2CH_2O} \rightarrow {}^\cdot\overbrace{CHCH_2O} + Bu^tOH \qquad (4)$$

The enantiomerically pure *N,N,N',N'*-tetramethylenediamine (TMEDA) complex **4** was prepared[6] from (+)-α-pinene. When similar experiments were carried out with the TMEDA complex prepared from (−)-α-pinene, hydrogen was abstracted more rapidly from (*S*)-**6** (R = Me). After 36% consumption of the ester, NMR analysis showed that the remaining material contained a 19% e.e. of (*R*)-**6** (R = Me).

The major fate of the radicals **7** (R = Me) appears to be coupling to give[9] *meso*- and (±)-diester **8**, although it is possible that a small amount of disproportionation could take place to give racemic starting material **6** and the α,β-unsaturated ester **9**.

$$Ph(MeO_2C)MeC{-}CMe(CO_2Me)Ph \qquad Ph(MeO_2C)C{=}CH_2$$
8 **9**

Although enantioselective hydrogen-atom abstraction mediated by *tert*-butoxyl radicals under conditions of polarity reversal catalysis by optically active amine-boranes has been clearly demonstrated, the e.e. obtained so far is only modest and a difference in enantiomer reactivity of at least a factor of 5 is needed if efficient kinetic resolution is to be achieved.[8] It should prove possible to design sterically more demanding enantiomerically pure amine-borane complexes which, while

† In principle, two rotational isomers of **7**, which differ in configuration about the C–C(O) bond, could be present. A few weak lines, which might be associated with a minor isomer, were detected alongside the main spectrum, but it is also possible that the spectra of the two rotamers could be indistinguishable.

‡ Only the oxiranyl radical was detected when the amine-borane was omitted, showing that this radical does not abstract halogen from 1-bromopropane under the experimental conditions.

§ These experiments were carried out with 0.2–1 mmol of ester.

¶ In the absence of DTBP, with or without added *tert*-butyl alcohol (which would be formed from the peroxide), the recovered ester was racemic.

still functioning as effective catalysts for abstraction of hydrogen from electron-deficient C–H groups,[2–4] will exhibit improved chiral discrimination.

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