Chlorination of enantiomerically pure 1,1′-bis(hydroxyalkyl)-3,3′-biindolizines: conservation of chirality by thermal treatment

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Enantiomerically pure 1,1′-bis(hydroxyalkyl)-3,3′-biindolizines 1 racemize unexpectedly by reaction with tetrachloromethane–triphenylphosphine at room temperature affording the corresponding dichloro compounds 2, whereas the chirality is preserved at higher reaction temperatures.

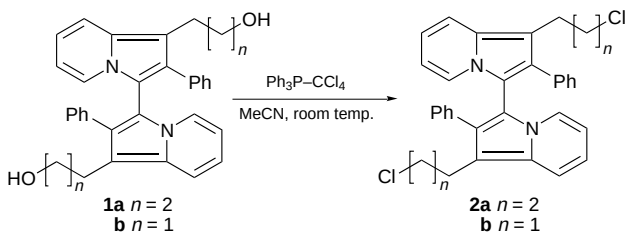
Axial-chiral ligands, especially binaphthyls, play an important role in asymmetric synthesis.[1] Recently, we reported the chirality of biindolizines[2] and the enzyme-catalysed kinetic resolution of racemic bis(hydroxyalkyl)biindolizines.[3] To further extend the utility of this new chiral source, *e.g.* as chiral modifiers and complex ligands in homogeneous catalysis, we attempted the preparation of derivatives of the non-racemic chiral diols **1a** and **1b**.

First attempts using the racemic diols (±)-**1a** and (±)-**1b** showed that the chlorination with triphenylphosphine and tetrachloromethane[4] is a useful method for the synthesis of the corresponding racemic bis(chloroalkyl)biindolizines (±)-**2a** and (±)-**2b**, respectively. By addition of acetonitrile to the reaction mixture the conversion takes place at room temperature.

Application of these mild conditions to the conversion of the enantiomerically pure diols (−)-**1a** and (+)-**1b** to the corresponding dichloro compounds surprisingly resulted in complete racemization‡ affording (±)-**2a** and (±)-**2b**, respectively, despite the fact that there are four or five bonds between the chirality axis and the reacting carbon atom.

The reaction at higher temperatures revealed an unusual and unexpected behaviour of the enantiomerically pure diols (−)-**1a** and (+)-**1b** depending on the reaction conditions. Reaction of (−)-**1a** with an ee of 98% in refluxing tetrachloromethane in the absence of acetonitrile furnished the dichloro compound (−)-**2a**§ with an ee of 96%. In order to investigate the influence of acetonitrile on the outcome of the reaction, acetonitrile was added to the refluxing solution of the diol (−)-**1a** and triphenylphosphine in tetrachloromethane. This treatment did not influence the enantiomeric excess of the dichloro compound (−)-**2a** (ee 98%) formed, but as expected, the reaction rate was drastically increased.

In comparison with (±)-**1a** the diol (±)-**1b** is less reactive. Only in the presence of acetonitrile does the chlorination proceed in good yields. In contrast to the results described before, the conversion of the diol (+)-**1b** with an ee of 98% led, in the presence of triphenylphosphine in refluxing tetrachloromethane and subsequent addition of acetonitrile, to a partial racemization affording the dichloro compound (+)-**2b**§ with an ee of only 63%. Therefore, it seemed promising to enhance the reaction temperature to suppress further racemization. This was realised by addition of triphenylphosphine to a refluxing solution of (+)-**1b** in tetrachloromethane–toluene–acetonitrile (2:5:1) yielding (+)-**2b** with an ee of 87%. These results clearly demonstrate that increased reaction temperatures suppress the racemization during the chlorination of (−)-**1a** and (+)-**1b** to (−)-**2a** and (+)-**2b**, respectively, under the described conditions. The results are summarized in Table 1.



1a *n* = 2
b *n* = 1

2a *n* = 2
b *n* = 1

Scheme 1 Chlorination of **1a** and **1b** by PPh_3–CCl_4

Results published recently by K. Fuji *et al*. on the unexpected racemization of 8-diphenylphosphinoyl-8′-methoxy-1,1′-binaphthyl[5] illustrate the difficulties in explaining such a surprising loss of axial chirality. Based on the crystal structure, the authors suggest that a strong destabilisation of the ground state of this compound is responsible for the racemization.

The different substitution of the biindolizines **1** and **2** should not have an influence on the configurational stability as a result of the different torsion angles between the coupled heterocyclic systems. Each enantiomer of **2a** and **2b** exists independently. There is every indication that in our case both the twisted and normally rotation-hindered aromatic systems are each forced to occupy coplanar configurations during the time-scale of the conversion of the biindolizines. Such a coplanar transition state or intermediate could be explained by intramolecular interactions between the 'α- and ω-end' of the molecule. Particularly, a strong strained cyclic species is imaginable, cancelling the twisting of the coupled indolizines.

We have no evidence concerning the nature of such a cyclic species and thus can only speculate. Possibly, the low reactivity of **1a** and **1b** is responsible for the formation of a cyclic transition state or intermediate. Therefore, only the bifunctional intermediate $Ph_3P^+CCl_2P^+Ph_3$, $2Cl^-$ **3**[4] reacts with the diol to give the dichloro compounds **2a** and **2b** quickly at room temperature. Fig. 1 shows the imaginable addition product **4**—formed by reaction of the diol **1b** with the described dication **3**—causing a small torsion angle between the two heterocyclic systems. At higher temperatures this intermediate is unfavoured because the system reacts before **4** is formed. This assumption is in accordance with our observation that the less reactive diol **1b** tends to racemize even at higher temperatures. Obviously, even in refluxing tetrachloromethane the reaction partially takes place *via* a coplanar intermediate such as **4**. Only more drastic conditions allowed an almost complete chirality conservation.

Table 1 The influence of the reaction conditions on the degree of racemization by chlorination of non-racemic **1a** and **1b**

		Product ees under various reaction conditions (%)		
Product **2**	Ee of starting material (%)	CCl_4–MeCN (5:1), room temperature	CCl_4–MeCN (30:1), reflux	CCl_4–MeCN–PhMe (2:1:5), reflux
a	98	0	98	—
b	98	0	63	87

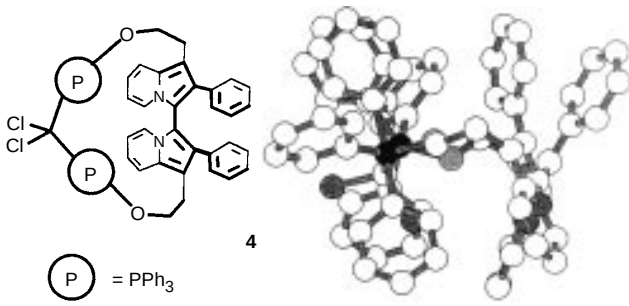


Fig. 1 Structures of the assumed cyclic intermediate **4** generated through HYPERCHEM (release 4, MM^+, optimised by Polak-Ribiere)

Nevertheless, we have found a possible method to prevent the unexpected racemization and to obtain the 1,1′-bis(chloroalkyl)-3,3′-biindolizines **2a** and **2b** in high enantiomeric excess. We are also looking for other chlorination methods to obtain enantiomerically pure dichloro compounds.

Footnotes

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‡ The ee was determined by HPLC on Chiralpak AD with heptane–propan-2-ol (95 : 5).

§ The dichlorides were successfully characterised by ^1H and ^{13}C NMR spectroscopy, MS and elemental analysis. *Selected data* (NMR in $CDCl_3$/$SiMe_4$, *J* in Hz): for (±)-**2a**: ^1H NMR δ 7.46 (d, *J* 9.1, 2 H), 7.24 (d, *J* 6.4, 2 H), 7.08 (m, 6 H), 6.79 (dd, *J* 7.8 and 1.7, 4 H), 6.70 (dd, *J* 8.6 and 6.8, 2 H), 6.37 (ddd, *J* 6.8 and 0.9, 2 H), 3.40 (t, *J* 6.5, 4 H), 2.97 (t, *J* 7.3, 4 H) and 1.92 (t, *J* 7.3, 4 H). ^{13}C NMR δ 135.2 (s), 131.4 (s), 130.9 (s), 129.7 (d), 127.9 (d), 126.2 (d), 122.9 (d), 117.3 (d), 116.9 (d), 111.5 (s), 110.5 (d), 109.9 (s), 44.7 (t), 33.9 (t) and 21.3 (t). *m/z* (CI): 536 [$(M + H)^+$, 100%]. (−)-**2a**: $[\alpha]_D^{20}$ −4.5, (*c* 0.4, THF), 96% ee. For (±)-**2b**: ^1H NMR δ 7.46 (td, *J* 9.0 and 1.0, 2 H), 7.26 (td, *J* 6.9 and 1.0, 2 H), 7.10 (m, 4 H), 6.76 (m, 6 H), 6.42 (dt, *J* 6.8 and 1.2, 4 H), 3.52 (m, 4 H) and 3.25 (m, 4 H). ^{13}C NMR δ 134.6 (s), 131.8 (s), 131.2 (s), 129.0 (d), 128.0 (d), 126.5 (d), 123.1 (d), 117.5 (d), 117.2 (d), 111.6 (s), 110.9 (d), 107.4 (s), 44.5 (t) and 28.2 (t). *m/z* (FAB-MS): 508 [$M + H^+$), 100%]. (+)-**2b**: $[\alpha]_D^{20}$ + 17.2, (*c* 1, THF), ee 87%.

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