8,8′-Dialkyl-1,1′-biisoquinolines: preparation, absolute configuration and unexpected racemization behaviour†

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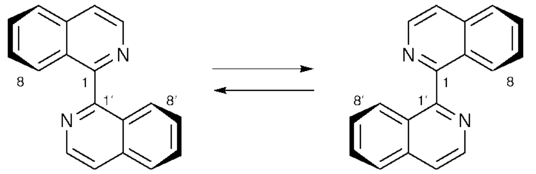
Received (in Cambridge, UK) 28th June 1999, Accepted 7th October 1999

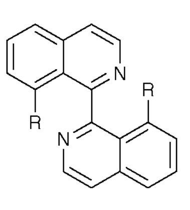
A series of 8,8′-dialkyl-1,1′-biisoquinolines, in which methyl, ethyl and isopropyl groups are introduced for enhancing the transannular steric hindrance, are synthesized. The atropisomeric biisoquinolines are separated into both enantiomers, of which the absolute configurations and the optical stabilities are determined. Contrary to prior expectations, the racemization behaviour is inversely proportional to the steric size of the alkyl groups.

Introduction

Optical activity based on a high barrier to rotation about σ-bonds is designated as 'atropisomerism',[1] that is exemplified by a wide range of biaryl compounds, both natural and synthetic. One of the important factors making such molecules dissymmetric is substituents adjacent to the rotational axes, and the steric size, shape and hybridization of these substituents exert a large influence upon the optical stability of the molecules.[2] Admittedly, increasing bulkiness of substituents tends to cause an enhancement of the configurational stability as a result of steric hindrance. For instance, 1,1′-binaphthyl shows slow racemization at ambient temperature (half-life of *ca.* 10 h),[3] whereas the 2,2′-diol or 2,2′-diphosphine derivatives, which act as useful chiral inducers in asymmetric syntheses,[4,5] give rise to no racemization at the corresponding temperature.

Another illustration of this kind of substituent-induced stabilization can be seen in 1,1′-biisoquinoline **1a**. The parent compound **1a** shows quite rapid racemization owing mainly to the very small transannular steric hindrance between H-8 (8′) and N-2′ (2), and therefore isolation as the optically active form is known to be substantially impossible.[6] By contrast, the *N*,*N*′-dioxide derivative retains enough steric hindrance to be resolved into both enantiomers.[7] Successful enhancement of the optical stability has been also achieved independently by both us[8] and Chelucci[9] with the aid of two methyl groups introduced at the 8- and 8′-position; the dimethyl derivative **1b** revealed a half-life of 17 h at 20 °C in toluene.[10] However, **1b** does show gradual racemization at room temperature, probably due to the small contribution of the nitrogen lone pairs to the rotational resistance about the pivotal bond, although the optical stability is increased in comparison with that of the parent compound **1a**. This foregoing finding led us to prepare biisoquinolines **1c**–**e** with a series of alkyl substituents at the 8,8′-positions and to study how bulky alkyl groups are required to freeze the rotation. However, on the other hand, we encountered unexpected racemization behaviour in **1b**–**d**, such that the bulkier the alkyl substituent, the lower the optical stability. In this paper, we report a full account of the syntheses and the absolute configurations of the biisoquinolines **1b**–**d**. Furthermore, we report the unexpected reversal of the optical stability observed in **1b**–**d**, and the racemization mechanism.





1a : R = H
1b : R = Me
1c : R = Et
1d : R = Pr^i
1e : R = Bu^t

Results and discussion

Synthesis

Preparation of biisoquinolines **1b**–**e** was carried out as shown in Scheme 1. Starting from the condensation reaction of *o*-alkylbenzaldehydes **2b**–**e** with aminoacetaldehyde dimethyl acetal, the resultant imines were converted to 8-alkylisoquinolines **3b**–**e** by the application of Hendrickson's procedure,[11] *i.e.*, treatment successively with ethyl chloroformate, trimethyl phosphite and titanium(IV) chloride. *N*-Oxidation was accomplished either by MCPBA or by hydrogen peroxide. Acetylation of **4b**–**e** with acetic anhydride and subsequent hydrolysis with aqueous sodium hydroxide[12] afforded isoquinolones **5b**–**e**, which were then converted to **6b**–**d** by phosphoryl trichloride in moderate yields with the exception of **6e** (*vide infra*). Final homocoupling of 1-chloroisoquinolines **6b**–**d** using nickel(0) complex generated *in situ* by reduction of nickel chloride with activated zinc[13] gave the required 1,1′-biisoquinolines **1b**–**d** in which a series of alkyl substituents was introduced at the 8- and 8′-position. The structures of the new compounds were determined by a combination of spectral data and an elemental analysis.

In the course of the attempted synthesis of *tert*-butyl derivative **1e**, however, the intermediate **5e** was not chlorinated, but

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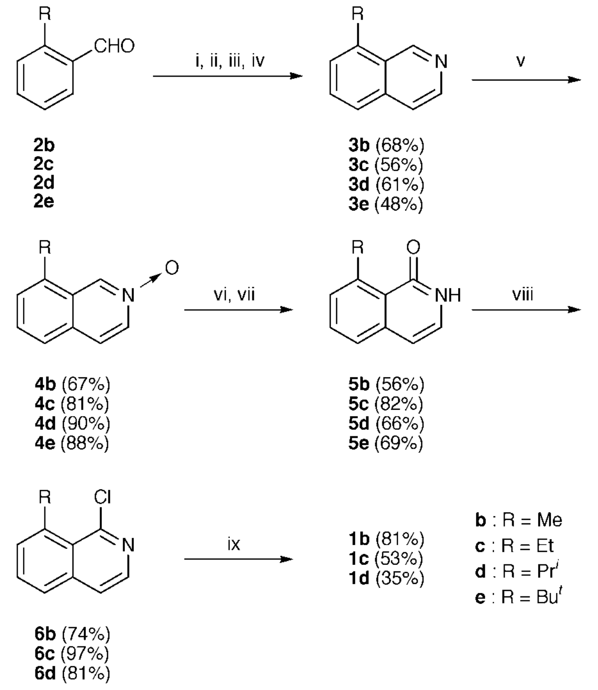
† CD and UV-VIS spectra, primary kinetic data of racemization and PM3-calculations are available as supplementary data. For direct electronic access see http://www.rsc.org/suppdata/p1/1999/3677, otherwise available from BLDSC (SUPPL. NO. 57675, pp. 12) or the RSC Library. See Instructions for Authors available *via* the RSC web page (http://www.rsc.org/authors).



Scheme 1 *Reagents and conditions*: (i) $H_2NCH_2CH(OMe)_2$, benzene, reflux, 15 h; (ii) $ClCO_2Et$, THF, −10 °C, 5 min; (iii) $P(OMe)_3$, THF, rt, 20 h; (iv) $TlCl_4$, CH_2Cl_2, reflux, 41 h; (v) MCPBA, CH_2Cl_2, rt, 4 h or H_2O_2, AcOH, 80 °C, 12 h; (vi) Ac_2O, reflux, 5 h; (vii) 1.3 M NaOH, 80 °C for 40 min and then rt for 12 h; (viii) $POCl_3$, reflux, 3 h; (ix) $NiCl_2$, Zn, PPh_3, DMF, 50 °C, 5 h.

recovered almost quantitatively. Furthermore, direct dimerization of **3e** to **1e** by using lithium diisopropylamide according to Meth-Cohn's procedure[14] also failed. Considerations based on the Corey–Pauling–Koltun molecular model suggested that *tert*-butyl groups were too bulky to be incorporated into the *peri*-positions of the biisoquinoline framework, and this might be responsible for the failure of the synthesis. Indeed, this result is consistent with the fact that the yields of the final homo-coupling reaction **6** ⟶ **1** decreased gradually with a rise in steric size of the alkyl substituents.

Absolute configuration

Enantiomeric enrichment of **1b**–**d** was performed by two kinds of well known methods, *i.e.*, (1) high-performance liquid chromatography (HPLC) using a chiral stationary-phase column and (2) enantiomeric resolution through transformation into a diastereomeric salt by using a chiral binuclear palladium complex was reported by both Dai[15] and Chelucci.[9] All the biisoquinolines were resolved into both enantiomers and isolated as optically active forms of 68–86% ee. This incomplete enantiomeric resolution was caused by experimental difficulties mainly due to the moderately easy racemization of **1b**–**d** (full particulars are given in the next section).

The absolute configurations of a series of biisoquinolines **1b**–**d** were successfully determined by applying the exciton chirality method.[16] Almost the same CD and UV–visible spectra were obtained for optically active **1b**–**d**, and those of **1b** are shown in Fig. 1 as a typical example. Transition moments along the long axes of the isoquinoline rings, which appeared as an intense absorption at 219 nm in the UV spectrum, interact with each other to give the exciton-split CD spectra. Cotton effects for (−)-**1b** were observed positively at 235 nm and negatively at 220 nm, indicating positive exciton chirality. On the other hand, the mirror image was obtained for (+)-**1b**. In addition to the CD spectra, the specific rotations of $[\alpha]_D$ +60 ‡ for (+)-**1b** of 78% ee and $[\alpha]_D$ −53 ‡ for (−)-**1b** of 68% ee ensure that these are a pair of enantiomers. The cotton effect is known to depend strongly on the dihedral angle between chromophores; in analogous 1,1′-binaphthyl systems positive and negative signs are exchanged at a dihedral angle of 110°.[17] X-Ray structural elucidation using racemic single crystals revealed an almost perpendicular conformation for **1b** and **1c**, of which dihedral angles between the two isoquinoline rings were found to be 102.1° for **1b** and 93.8° for **1c** (Fig. 2). Despite a great deal of effort, a single crystal of **1d** appropriate for X-ray crystallography was not obtained. However, the AM1-

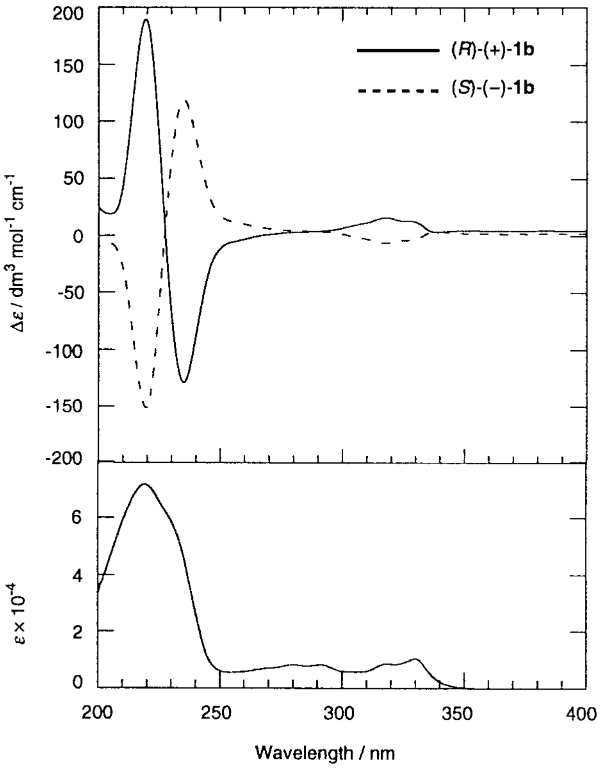


Fig. 1 CD (upper panel) and UV–visible (lower panel) spectra of biisoquinoline **1b** in ethanol. Enantiomeric excesses of the samples were 78% ee for (*R*)-(+)-**1b** and 68% ee for (*S*)-(−)-**1b**.

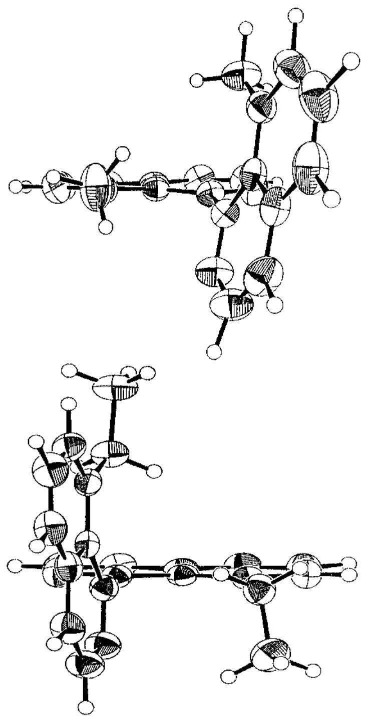


Fig. 2 ORTEP drawings of biisoquinolines **1b** (top) and **1c** (bottom).

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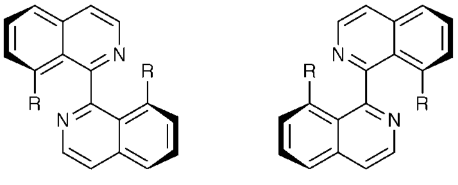
‡ In this paper, $[\alpha]_D$-values are given in units of 10^{-1} deg cm^2 g^{-1}.

Table 1 Racemization-rate constants at 30 °C and activation parameters for racemization in biisoquinolines **1b**–**d**

Compound	k_{rac}/s^{-1}	E_a/kJ mol^{-1}	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}	$\Delta G^{\ddagger}_{303}$/kJ mol^{-1}
1b	5.8×10^{-6}	113(2)[a]	110(2)[a]	19(7)[a]	105
1c	2.2×10^{-5}	103(1)[a]	100(1)[a]	−3.9(3.2)[a]	101
1d	5.3×10^{-5}	95(1)[a]	92(1)[a]	−22(4)[a]	99

[a] Numbers in parentheses are standard deviations of this variable.

optimized[18] geometry of **1d** showed a dihedral angle of 73.3°, and those of **1b** and **1c** were estimated to be 90.2° and 88.6°, respectively. The X-ray and AM1 results showed slightly different structures, but the dihedral angles for each compound were found to be less than 110°. Hence, the exciton chirality method should be applicable to **1b**–**d** in a similar way to that for 1,1′-binaphthyl systems, and led to a conclusive assignment that all the (+)-forms corresponded to (*R*)-configurations and all (−)-forms to (*S*) ones as shown in Chart 1. Although the methodologies are different, the assignment thus obtained was identical with that reported by Chelucci,[9] who succeeded in determining the absolute configuration of **1b** by using ^{1}H NMR spectroscopy.



(*R*)-(+)-**1** (*S*)-(−)-**1**

Chart 1 Absolute configurations of 8,8′-dialkyl-1,1′-biisoquinolines.

Racemization

The rate constants (k_{rac}) for the conversion from one enantiomer to the other in **1b**–**d** were determined in methanol over the range of +10 to +50 °C. Optically active biisoquinolines **1b**–**d** of 52 to 92% ee were used for the kinetic measurements, and the changes in the concentration of both enantiomers were followed by using HPLC equipped with a chiral stationary phase column. Although continuous chiroptical techniques such as CD and optical rotatory dispersion should be superior candidates for these kinetic measurements, a chiral HPLC technique was used in the present study owing to experimental circumstances. Fig. 3 represents a typical example of the concentrational changes with the passage of time in **1b** at +40 °C. Under the described conditions, both the enantiomers, of which absolute configurations were identified in the preceding section, were well resolved. The initial enantiomeric excess of 92% was gradually decreased to 14% ee after 11 h. Contrary to prior expectations, the bulkier the alkyl substituents, the greater the rate constants. As summarized in Table 1, the rate constants were found to be largest in **1d** and smallest in **1b**, and this unexpected racemization behaviour in **1b**–**d** was clearly reflected in the systematic decrease in activation parameters such as the Arrhenius activation energy (E_a), the heat of activation ($\Delta H^{\ddagger}$) and the Gibbs energy of activation ($\Delta G^{\ddagger}$); these thermodynamic parameters were inversely proportional to the size of the alkyl groups. However, it is difficult to present a detailed discussion on the decrease in the entropy of activation ($\Delta S^{\ddagger}$) at this moment.

In order to clarify the unexpected reversal of the sequence in **1b**–**d**, PM3-calculations[19] were carried out for the ground state (GS) and the transition state (TS) during the racemization process, in which a more favourable *anti*-pathway was taken into consideration between two kinds of possible pathways such as *syn* and *anti*. Harmonic vibrational frequency calculations gave only one imaginary frequency for each TS structure. The GS and TS geometries of **1c** are shown in Fig. 4 as a typical example. As seen in Fig. 4, the two isoquinoline rings were nearly perpendicular in the GS, but almost coplanar in the TS though both rings were much distorted. The calculated barrier heights ($\Delta\Delta H_f$), deduced from the heat of formation in the GS and TS, were nearly in accordance with the experimental findings as summarized in Tables 1 and 2.

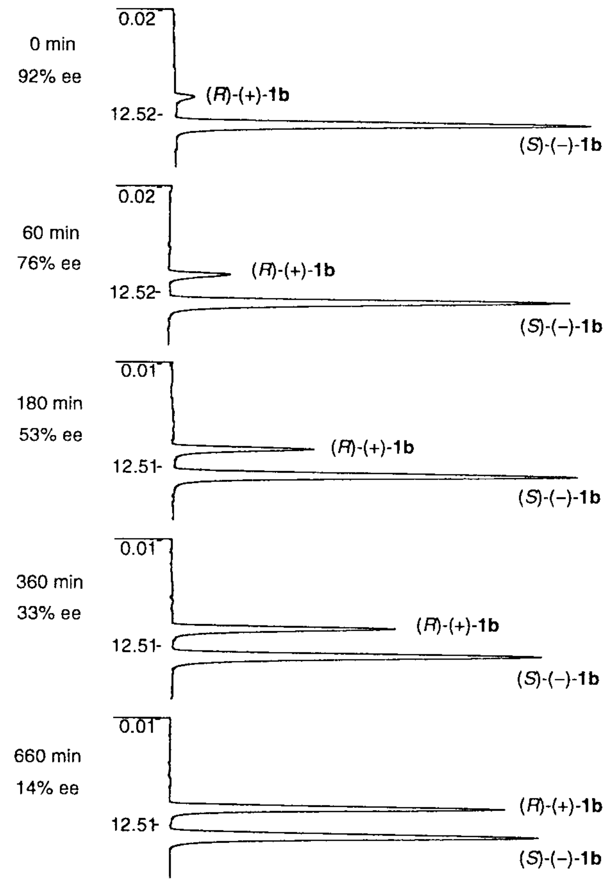


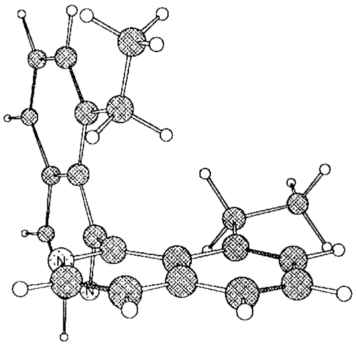
Fig. 3 Concentrational changes of (*R*)- and (*S*)-**1b** in methanol at 40 °C. Column Chiralcel OD; mobile phase 30% EtOH–hexane; flow rate 0.5 ml min^{-1}; $\lambda = 280$ nm.

Optically active rotational isomers have sometimes been reported to be more optically labile than would be expected from the structures.[2a,20] As a good example, Fuji *et al.*[21] recently reported this kind of behaviour in 8,8′-disubstituted 1,1′-binaphthyl compounds. From considerations based on X-ray crystallography and theoretical calculations, they concluded that the relatively easy racemization of a compound with a bulkier substituent originated from the destabilization of the ground state. On the theoretical side, the methodology used in Schleyer's study[22] is helpful to us in examining this possibility. Using the PM3-optimized GS and TS geometries of **1b**–**d**, their distortional energies were evaluated according to the described procedures.[22] The results of the calculations are summarized in Table 2.

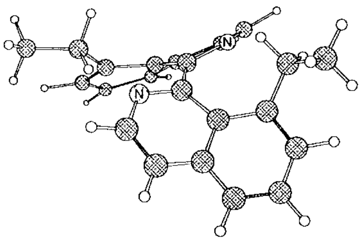
What is significant in Table 2 is that the calculated distortional energies in the GS were proportional to the steric size

Table 2 PM3-calculated activation barriers for racemization and distortional energies inherent in biisoquinoline frameworks

		Distortional energy/kJ mol^{-1}	
Compound	$\Delta\Delta H_f$/kJ mol^{-1}	Ground state	Transition state
1b	111.6	10.1	94.7
1c	104.9	19.9	89.4
1d	97.9	25.6	94.7



Ground State



Transition State

Fig. 4 PM3-optimized geometries of the ground and transition states during the racemization process in **1c**.

of the alkyl groups, whereas this was not the case for the TS. Corey–Pauling–Koltun molecular models suggested that there exists a small space around the nitrogen lone pairs at the 2,2′-positions, enough to slightly accommodate the alkyl groups in the TS, where the alkyl substituents lie in close proximity to the nitrogen lone pairs. This might result in little influence to effectively enhance the steric hindrance, and therefore the distortional energies in the TS should become almost constant irrespective of the alkyl groups, while those in the GS should increase in proportion to the steric size of the substituents. The systematic increase in the distortional energies in the GS is evident from the X-ray structural elucidation, by which bond angles N2–C1–C1′ were found to be reduced to 112.1° for **1b** and 110.9° for **1c** due to the steric interaction between the isoquinoline ring and the alkyl group at the *peri*-position (Fig. 2). As mentioned in the preceding section, a single crystal of **1d** was not obtained, but the PM3-optimized geometries of **1b**–**d** showed a similar decrease in the relevant angles that were estimated to be 112.7° for **1b**, 112.2° for **1c** and 111.3° for **1d**. Here, it is worth noting that the increase in the distortional energies in the GS (+9.8 kJ mol^{-1} for **1b** $\longrightarrow$ **1c**, and +15.5 kJ mol^{-1} for **1b** $\longrightarrow$ **1d**) is approximately reflected on the decrease in the PM3-calculated barrier heights (−6.7 and −13.7 kJ mol^{-1}, respectively), as can be seen from Tables 1 and 2. Equally importantly, the calculated relative values are in good agreement with the experimental findings such as E_a and $\Delta H^\ddagger$ (−10 kJ mol^{-1} for **1b** $\longrightarrow$ **1c**, and −18 kJ mol^{-1} for **1b** $\longrightarrow$ **1d**), although the distortional energies were roughly estimated. This moderate coincidence between the experimental and calculated values means that the unexpected racemization observed in **1b**–**d** would be caused predominantly by the destabilization in the GS. One extensive experiment[23] has so far been reported on the transition-state stabilization which acts as an alternative mechanism to lower the racemization barrier. The simple racemization *via* an unfavourable *syn*-pathway in the chiral ruthenium(II) complex of the parent compound **1a** is accounted for by the metal-assisted favourable coordination in the TS,[24] but this kind of special interaction is completely eliminated in the present system. Further work on the non-distortional contribution may be needed to allow us to fully understand the mechanism, nonetheless the present result clearly demonstrates that destabilization in the GS would be the most plausible mechanism for the unexpected racemization behaviour observed in biisoquinolines **1b**–**d**.

Conclusions

Summarizing the present study, we have arrived at the following conclusions: (1) a series of 8,8′-dialkyl-1,1′-biisoquinolines, in which methyl, ethyl and isopropyl groups are introduced, have been prepared in nine steps from readily available *o*-alkylbenzaldehydes. (2) Enantiomeric resolution into both enantiomers was achieved by two kinds of well known techniques, and then the absolute configurations were successfully determined by application of the exciton chirality method. (3) Although the optical stabilities of the 8,8′-dialkyl derivatives were largely enhanced in comparison with that of the parent compound, the racemization behaviour was found to be inversely proportional to the steric size of the alkyl groups. On the basis of PM3 and X-ray analyses, the unexpected racemization was ascribed to destabilization of the ground state. Although the detailed mechanism is being investigated in our laboratory, the present work affords one example that shows the curious relationship between molecular structure and atropisomerism.

Experimental

General

Mps were determined on a Yanako melting point apparatus MP-500D and are uncorrected. ^{1}H NMR spectra were obtained at 400 MHz with a JEOL EX-400 spectrometer for samples in $CDCl_3$ solution with tetramethylsilane as an internal standard. *J*-Values are given in Hz. IR and mass spectra were recorded on JEOL FT/IR-230 and JEOL JMS DX-300 spectrometers, respectively. UV–visible spectra were recorded on a Shimadzu UV-2400PC spectrometer at a concentration of 9.67–9.83 × 10^{-6} mol dm^{-3} in ethanol at 20 °C. Elemental analyses were performed on a Yanako MT-5. CD spectra were measured on a JEOL J-720 spectrometer in a 1 cm path-length cell at a concentration of 1.96–2.28 × 10^{-5} mol dm^{-3} in ethanol at 10 °C. Optical rotations were measured in a 1 dm path-length cell on a JASCO DIP-370 polarimeter. Merck Kieselgel #7734 was used for column chromatography. For analytical thin-layer plates Merck #5715 and #5721 were used. HPLC analyses were carried out with a JASCO instrument equipped with an 870-UV detector, an 880-PU pump and a Chromatocorder 12 recorder. Shiseido Ceramospher Chiral RU-1 and Daicel Chiralcel OD were used as chiral stationary-phase columns. All chemicals were reagent grade and were used without further purification. Organic solvents were purified by standard procedures. Compound **2b** is commercially available and used without further purification. Compounds **2c**–**e** were prepared according to the described procedures.[25] Semiempirical calculations based on AM1[18] and PM3[21] methods were carried out using the MOPAC97 program package implemented in WinMOPAC Version 2.0, Fujitsu Limited, 1998.

General procedure for compounds 3b–e

8-Methylisoquinoline 3b. A solution of **2b** (10.22 g, 85 mmol) and aminoacetaldehyde dimethyl acetal (8.75 g, 85 mmol) in dry benzene (50 ml) was refluxed for 15 h; during this period water was removed by using a Dean–Stark trap. After removal of the solvent, the resultant viscous oil was dissolved in dry THF. To the solution was added ethyl chloroformate (8.7 ml, 85 mmol) at −10 °C with vigorous stirring. After stirring of the mixture for 5 min, 12 ml (100 mmol) of $P(OMe)_3$ was added at room temperature. The mixture was stirred for 20 h at room temperature and was then concentrated under reduced pressure. In order to remove trace amounts of $P(OMe)_3$, evaporation with toluene was repeated twice. The resulting oil was dissolved in dry CH_2Cl_2 (110 ml), and 6 molar equiv. (56 ml, 0.51 mol) of $TiCl_4$ were added. The mixture was heated under reflux for 41 h. The reaction mixture was basified by adding 10% aq. NaOH, whereupon TiO_2 precipitated as a white solid. The mixture was filtered though Celite and the filtrate was acidified with 3 mol dm^{-3} HCl. After washing with CH_2Cl_2, the aqueous layer was basified strongly with 10% aq. NaOH and extracted with CH_2Cl_2. The organic layer was washed successively with water and brine, dried over Na_2SO_4, and evaporated *in vacuo* to afford **3b** (8.2 g, 68%) as a *pale yellow oil* (Found: C, 83.94; H, 6.48; N, 9.65. $C_{10}H_9N$ requires C, 83.88; H, 6.34; N, 9.78%); ν_{max}(neat)/cm^{-1} 1615, 1580, 1570; δ_H 2.78 (3 H, s, CH_3), 7.38 (1 H, dd, *J* 1.0 and 6.8, 7-H), 7.56 (1 H, dd, *J* 6.8 and 7.8, 6-H), 7.63 (1 H, d, *J* 5.4, 4-H), 7.66 (1 H, dd, *J* 1.0 and 7.8, 5-H), 8.55 (1 H, d, *J* 5.4, 3-H), 9.45 (1 H, s, 1–H); *m*/*z* (EI) 143 (M^+).

8-Ethylisoquinoline 3c. Yield 56%. *Colourless oil* (Found: C, 79.77; H, 7.03; N, 8.29. $C_{11}H_{11}N{\cdot}0.5H_2O$ requires C, 79.48; H, 7.28; N, 8.43%); ν_{max}(neat)/cm^{-1} 1621, 1583; δ_H 1.42 (3 H, t, *J* 7.5, CH_2CH_3), 3.21 (2 H, q, *J* 7.5, CH_2CH_3), 7.42 (1 H, d, *J* 7.1, 7-H), 7.60 (1 H, dd, *J* 7.1 and 8.3, 6-H), 7.64 (1 H, d, *J* 5.9, 4-H), 7.67 (1 H, d, *J* 8.3, 5-H), 8.53 (1 H, d, *J* 5.6, 3-H), 9.50 (1 H, s, 1-H); *m*/*z* (EI) 157 (M^+) (Found: M^+, 157.0905. $C_{11}H_{11}N$ requires *M*, 157.0891).

8-Isopropylisoquinoline 3d. Yield 61%. *Colourless oil* (Found: C, 84.08; H, 7.79; N, 8.26. $C_{12}H_{13}N$ requires C, 84.17; H, 7.65; N, 8.18%); bp 111–112 °C (2 mmHg); ν_{max}(neat)/cm^{-1} 1617, 1587, 1572; δ_H 1.43 (6 H, dd, *J* 6.8 and 1.0, 2 × CH_3), 3.89 [1 H, m, $CH(CH_3)_2$], 7.49 (1 H, dd, *J* 6.2 and 2.1, 7-H), 7.59–7.65 (3 H, m, 4-, 5- and 6-H), 8.52 (1 H, d, *J* 5.6, 3-H), 9.59 (1 H, s, 1-H); *m*/*z* (EI) 171 (M^+).

8-*tert*-Butylisoquinoline 3e. Yield 48%. *Pale yellow oil* (Found: C, 83.47; H, 8.36; N, 7.10. $C_{13}H_{15}N{\cdot}0.1H_2O$ requires C, 83.47; H, 8.19; N, 7.49%); ν_{max}(neat)/cm^{-1} 2982, 1739; δ_H 1.66 (9 H, s, 3 × CH_3), 7.57–7.61 (2 H, m, 7- and 6-H), 7.66–7.68 (2 H, m, 4- and 5-H), 8.49 (1 H, d, *J* 5.4, 3-H), 9.94 (1 H, s, 1-H); *m*/*z* (EI) 185 (M^+) (Found: M^+, 185.1192. $C_{13}H_{15}N$ requires *M*, 185.1204).

General procedure for compounds 4b–d

8-Methylisoquinoline *N*-oxide 4b. A mixture of **3b** (332 mg, 2.3 mmol) and 30% H_2O_2 (0.3 ml, 3.0 mmol) in AcOH (10 ml) was stirred for 3 h at 80 °C. After an additional amount of 30% H_2O_2 (0.3 ml, 3.0 mmol) was added, stirring was continued for 9 h. The mixture was concentrated *in vacuo*, diluted with CH_2Cl_2, and washed with saturated aq. $NaHCO_3$. After the aqueous layer had been extracted again with CH_2Cl_2, the organic layers were combined, and dried over Na_2SO_4. Removal of the solvent gave crude **4b**, which was subjected to column chromatography on SiO_2 with hexane–EtOAc–MeOH (6 : 3 : 1) as a eluent. Recrystallization from MeOH afforded **4b** (246 mg, 67%) as colourless needles (Found: C, 74.72; H, 5.78; N, 8.69. Calc. for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80%); mp 137–139 °C (from MeOH) (lit.,[9] 137 °C).

8-Ethylisoquinoline *N*-oxide 4c. Yield 81%. *Colourless plates* (Found: C, 69.61; H, 6.90; N, 7.41. $C_{11}H_{11}NO{\cdot}0.9H_2O$ requires C, 69.75; H, 6.81; N, 7.39%); mp 38–39 °C (from EtOAc); ν_{max}(Nujol)/cm^{-1} 1604, 1260; δ_H 1.38 (3 H, t, *J* 7.6, CH_2CH_3), 3.01 (2 H, q, *J* 7.6, CH_2CH_3), 7.46 (1 H, d, *J* 7.1, 7-H), 7.52 (1 H, dd, *J* 7.1 and 8.1, 6-H), 7.64 (1 H, d, *J* 8.1, 5-H), 7.67 (1 H, d, *J* 7.1, 4-H), 8.14 (1 H, dd, *J* 1.2 and 7.1, 3-H), 8.99 (1 H, d, *J* 1.2, 1-H); *m*/*z* (EI) 173 (M^+) (Found: M^+ 173.0847. $C_{11}H_{11}NO$ requires *M*, 173.0840).

8-Isopropylisoquinoline *N*-oxide 4d. Yield 90%. *Light yellow oil* (Found: C, 71.69; H, 7.08; N, 6.78. $C_{12}H_{13}NO{\cdot}0.75H_2O$ requires C, 71.80; H, 7.28; N, 6.98%); ν_{max}(neat)/cm^{-1} 1626, 1600, 1566, 1256; δ_H 1.40 (6 H, dd, *J* 6.8 and 2.9, 2 × CH_3), 3.51 [1 H, m, $CH(CH_3)_2$], 7.52–7.57 (2 H, m, 6- and 7-H), 7.63 (1 H, dd, *J* 6.7 and 2.6, 5-H), 7.67 (1 H, d, *J* 7.1, 4-H), 8.13 (1 H, dd, *J* 7.1 and 1.7, 3-H), 9.06 (1 H, d, *J* 1.7, 1-H); *m*/*z* (EI) 187 (M^+) (Found: M^+, 187.1010. $C_{12}H_{13}NO$ requires *M*, 187.0996).

8-*tert*-Butylisoquinoline *N*-oxide 4e

A solution of MCPBA (4.23 g, 24.5 mmol) in CH_2Cl_2 (12 ml) was added to **3e** (1.85 g, 9.99 mmol). After stirring for 4 h, the mixture was poured onto dilute aq. $NaHSO_3$, and then the reaction mixture was extracted with CH_2Cl_2. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Recrystallization from EtOAc afforded **4e** (1.77 g, 88%) as *brown columns* (Found: C, 77.55; H, 7.56; N, 6.93. $C_{13}H_{15}NO$ requires C, 77.58; H, 7.52; N, 6.96%); mp 197–198 °C (from EtOAc); ν_{max}(KBr)/cm^{-1} 1179; δ_H 1.60 (9 H, s, 3 × CH_3), 7.49 (1 H, dd, *J* 8.5 and 8.1, 6-H), 7.60–7.65 (2 H, m, 5-H and 7-H), 7.67 (1 H, d, *J* 7.1, 4-H), 8.13 (1 H, d, *J* 7.1, 3-H), 9.40 (1 H, s, 1-H); *m*/*z* (EI) 201 (M^+).

General procedure for compounds 5b–e

8-Methylisoquinolin-1(2*H*)-one 5b. A mixture of **4b** (246 mg, 1.5 mmol) and Ac_2O (5 ml) was refluxed for 5 h. After removal of Ac_2O *in vacuo*, the resulting residue was heated to 80 °C with 1 mol dm^{-3} NaOH (4.1 ml) for about 40 min and stored at room temperature for 12 h. The mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography on SiO_2 with hexane–EtOAc–MeOH (6 : 3 : 1). Recrystallization from MeOH gave **5b** (137 mg, 56%) as *colourless plates* (Found: C, 75.76; H, 5.83; N, 8.56. $C_{10}H_9NO$ requires C, 75.45; H, 5.70; N, 8.80%); mp 139–141 °C (from MeOH); ν_{max}(Nujol)/cm^{-1} 3130, 1660, 1640, 1590; δ_H 2.93 (3 H, s, CH_3), 6.44 (1 H, d, *J* 6.8, 4-H), 7.01 (1 H, d, *J* 6.8, 3-H), 7.22 (1 H, dd, *J* 1.0 and 7.3, 5-H), 7.35 (1 H, dd, *J* 1.0 and 7.8, 7-H), 7.48 (1 H, dd, *J* 7.3 and 7.8, 6-H), 9.54 (1 H, s, NH); *m*/*z* (EI) 159 (M^+).

8-Ethylisoquinolin-1(2*H*)-one 5c. Yield 82%. *Colourless columns* (Found: C, 76.36; H, 6.45; N, 8.08. $C_{11}H_{11}NO$ requires C, 76.28; H, 6.40; N, 8.09%); mp 169–170 °C (from MeOH); ν_{max}(KBr)/cm^{-1} 3162, 1642, 1598; δ_H 1.32 (3 H, t, *J* 7.3, CH_2CH_3), 3.44 (2 H, q, *J* 7.3, CH_2CH_3), 6.47 (1 H, d, *J* 7.0, 4-H), 7.07 (1 H, d, *J* 7.0, 3-H), 7.26 (1 H, d, *J* 5.9, 5-H), 7.37 (1 H, d, *J* 7.8, 7-H), 7.52 (1 H, dd, *J* 5.9 and 7.8, 6-H), 10.82 (1 H, br s, NH); *m*/*z* (EI) 173 (M^+).

8-Isopropylisoquinolin-1(2*H*)-one 5d. Yield 66%. *Colourless needles* (Found: C, 77.14; H, 7.19; N, 7.46. $C_{12}H_{13}NO$ requires C, 76.98; H, 7.00; N, 7.48%); mp 112–113 °C (from EtOAc–hexane); ν_{max}(KBr)/cm^{-1} 3173, 1653; δ_H 1.33 (6 H, d, *J* 6.8, 2 × CH_3), 4.96 [1 H, m, $CH(CH_3)_2$], 6.47 (1 H, d, *J* 7.0, 4-H), 7.06 (1 H, d, *J* 7.0, 3-H), 7.36 (1 H, dd, *J* 7.8 and 1.0, 5-H), 7.47 (1 H, dd, *J* 7.8 and 1.0, 7-H), 7.57 (1 H, t, *J* 7.8, 6-H), 10.54 (1 H, br s, NH); *m*/*z* (EI) 187 (M^+).

8-*tert*-Butylisoquinolin-1(2*H*)-one 5e. Yield 69%. Colourless columns (Found: C, 77.80; H, 7.60; N, 6.92. $C_{13}H_{15}NO$ requires C, 77.58; H, 7.52; N, 6.96%); mp 166–168 °C (from hexane);

ν_{max}(KBr)/cm^{-1} 2952, 1636; δ_H 1.63 (9 H, s, 3 × CH$_3$), 6.45 (1 H, d, *J* 6.7, 4-H), 7.03 (1 H, dd, *J* 6.7 and 3.8, 3-H), 7.38 (1 H, dd, *J* 7.8 and 1.3, 5-H), 7.52 (1 H, dd, *J* 7.8 and 7.9, 6-H), 7.62 (1 H, dd, *J* 7.9 and 1.3, 7-H), 9.40 (1 H, s, NH); *m*/*z* (EI) 201 (M$^+$).

General procedure for compounds 6b–d

1-Chloro-8-methylisoquinoline 6b. A mixture of **5b** (6.58 g, 43 mmol) and POCl$_3$ (100 ml, 1.07 mmol) was refluxed for 3 h. After the excess of POCl$_3$ was evaporated *in vacuo*, saturated aq. NaHCO$_3$ and CH$_2$Cl$_2$ were added. The organic layer was dried over Na$_2$SO$_4$ and evaporated under reduced pressure. Column chromatography on SiO$_2$ with CH$_2$Cl$_2$ and recrystallization from MeOH gave **6b** (5.68 g, 74%) as brown prisms (Found: C, 67.72; H, 4.61; N, 8.00. Calc. for C$_{10}$H$_8$ClN: C, 67.62; H, 4.54; N, 7.89%); mp 144–146 °C (from MeOH) (lit.,[9] 78 °C); *m*/*z* (EI) 177 (M$^+$).

1-Chloro-8-ethylisoquinoline 6c. Yield 97%. *Colourless oil* (Found: C, 69.04; H, 5.47; N, 7.25; Cl, 18.37. C$_{11}$H$_{10}$ClN requires C, 68.94; H, 5.26; N, 7.31; Cl, 18.50%); ν_{max}(Nujol)/cm^{-1} 1609, 1591, 1558; δ_H 1.36 (3 H, t, *J* 7.5, CH$_2$C*H*$_3$), 3.48 (2 H, q, *J* 7.5, C*H*$_2$CH$_3$), 7.46 (1 H, d, *J* 7.1, 7-H), 7.52 (1 H, d, *J* 5.4, 4-H), 7.56 (1 H, dd, *J* 7.1 and 8.1, 6-H), 7.64 (1 H, d, *J* 8.1, 5-H), 8.18 (1 H, d, *J* 5.4, 3-H); *m*/*z* (EI) 191 (M$^+$) (Found: M$^+$, 191.0484. C$_{11}$H$_{10}$ClN requires *M*, 191.0501).

1-Chloro-8-isopropylisoquinoline 6d. Yield 81%. *Colourless oil* (Found: C, 70.13; H, 6.00; N, 6.86; Cl, 17.32. C$_{12}$H$_{12}$ClN requires C, 70.07; H, 5.88; N, 6.81; Cl, 17.24%); bp 111–112 °C (2 mmHg); ν_{max}(neat)/cm^{-1} 1610, 1591, 1556; δ_H 1.39 (6 H, d, *J* 6.0, 2 × CH$_3$), 4.79 [1 H, m, C*H*(CH$_3$)$_2$], 7.54 (1 H, d, *J* 5.4, 4-H), 7.61–7.68 (3 H, m, 5-, 6- and 7-H), 8.19 (1 H, d, *J* 5.4, 3-H); *m*/*z* (EI) 205 (M$^+$).

Preparation of 8,8′-dimethyl-1,1′-biisoquinoline 1b. Typical procedure

Zinc powder (25 mg, 0.37 mmol) was added to a stirred solution of NiCl$_2$·6H$_2$O (90 mg, 0.37 mmol) and PPh$_3$ (390 mg, 1.5 mmol) in DMF (6 ml) under argon atmosphere at 50 °C. After stirring for 1 h, **6b** (66 mg, 0.37 mmol) was added to the solution. After 5 h, the mixture was poured onto 28% aq. NH$_3$ and extracted with CH$_2$Cl$_2$. The organic layer was washed successively with water and brine, dried over Na$_2$SO$_4$, and evaporated. Column chromatography on SiO$_2$ with hexane–EtOAc–MeOH (5 : 4 : 1) as eluent gave crude **1b**, which was recrystallized from MeOH to yield **1b** (32 mg, 81%) as colourless prisms (Found: C, 84.65; H, 5.67; N, 9.76. Calc. for C$_{20}$H$_{16}$N$_2$: C, 84.48; H, 5.67; N, 9.85%); mp 210.0–213.5 °C (from MeOH) (lit.,[9] 207–210 °C); *m*/*z* (EI) 284 (M$^+$).

8,8′-Diethyl-1,1′-biisoquinoline 1c. Yield 53%. *Colourless needles* (Found: C, 84.75; H, 6.67; N, 8.95. C$_{22}$H$_{20}$N$_2$ requires C, 84.58; H, 6.45; N, 8.97%); mp 125–126 °C (from EtOAc–hexane); λ_{max}(EtOH)/nm 220, 319 and 330 (ε/dm^3 mol^{-1} cm^{-1} 71 800, 8930 and 10 400); ν_{max}(KBr)/cm^{-1} 1613, 1594, 1557; δ_H 0.90 (6 H, t, *J* 7.3, 2 × CH$_2$C*H*$_3$), 2.14 (2 H, m, C*H*$_2$CH$_3$), 2.27 (2 H, m, C*H*$_2$CH$_3$), 7.43 (2 H, d, *J* 7.1, 7- and 7′-H), 7.65 (2 H, dd, *J* 7.1 and 7.8, 6- and 6′-H), 7.74 (2 H, d, *J* 5.6, 4- and 4′-H), 7.79 (2 H, d, *J* 7.8, 5- and 5′-H), 8.52 (2 H, d, *J* 5.6, 3- and 3′-H); *m*/*z* (EI) 312 (M$^+$).

8,8′-Diisopropyl-1,1′-biisoquinoline 1d. Yield 35%. *Colourless prisms* (Found: C, 84.65; H, 7.20; N, 8.04. C$_{24}$H$_{24}$N$_2$ requires C, 84.67; H, 7.10; N, 8.23%); mp 211–212 °C (from EtOAc); λ_{max}(EtOH)/nm 223, 320 and 331 (ε/dm^3 mol^{-1} cm^{-1} 63 700, 7850 and 8670); ν_{max}(KBr)/cm^{-1} 1606, 1555; δ_H 0.93 [6 H, d, *J* 6.8, 2 × CH(C*H*$_3$)$_2$], 1.05 [6 H, d, *J* 6.6, 2 × CH(C*H*$_3$)$_2$], 2.98 [2 H, m, 2 × C*H*(CH$_3$)$_2$], 7.61 (2 H, dd, *J* 7.1 and 1.4, 7- and 7′-H), 7.67 (2 H, d, *J* 5.5, 4- and 4′-H), 7.71 (2 H, dd, *J* 8.1 and 7.1, 6- and 6′-H), 7.76 (2 H, dd, *J* 8.1 and 1.4, 5- and 5′-H), 8.93 (2 H, d, *J* 5.5, 3- and 3′-H); *m*/*z* (EI) 340 (M$^+$).

Enantiomeric enrichment

Racemic biisoquinolines **1b**–**d** were each partly resolved to their enantiomers by HPLC equipped with a chiral stationary-phase column (λ 280 nm). Ceramospher Chiral RU-1 (1.0 ml min^{-1}) was used for the preparative separation of **1b** and **1d** with MeOH as eluent, and Chiralcel OD (0.5 ml min^{-1}) was used for **1c** with 10% EtOH–hexane. The retention times were 25 and 34 min for **1b**, 18 and 24 min for **1c** and 10 and 12 min for **1d**. The first eluted enantiomers in **1b** and **1d** were (*R*)-forms, while that of **1c** was the (*S*)-form. Enantiomeric excesses of the obtained samples were analyzed by using Chiralcel OD (0.5 ml min^{-1}, λ 280 nm). The mobile phase for **1b**, **1c** and **1d** was 30, 20 and 10% EtOH–hexane, respectively. Under these conditions, all the first eluted enantiomers indicated positive specific rotation, and the second ones negative. (*R*)-(+)-**1b** (78% ee): $[\alpha]_D^{23}$ +60 (*c* 0.10 in CHCl$_3$); CD (EtOH) $[\Delta\varepsilon]_{318}$ +11.4, $[\Delta\varepsilon]_{235}$ −134 and $[\Delta\varepsilon]_{219}$ +184. (*S*)-(−)-**1b** (68% ee): $[\alpha]_D^{24}$ −53 (*c* 0.10 in CHCl$_3$); CD (EtOH) $[\Delta\varepsilon]_{318}$ −6.9, $[\Delta\varepsilon]_{235}$ +92.9 and $[\Delta\varepsilon]_{220}$ −125. (*R*)-(+)-**1c** (86% ee): $[\alpha]_D^{26}$ +58 (*c* 0.25 in CHCl$_3$); CD (EtOH) $[\Delta\varepsilon]_{319}$ +11.5, $[\Delta\varepsilon]_{235}$ −135 and $[\Delta\varepsilon]_{220}$ +190. (*S*)-(−)-**1c** (81% ee): $[\alpha]_D^{26}$ −55 (*c* 0.51 in CHCl$_3$); CD (EtOH) $[\Delta\varepsilon]_{319}$ −9.85, $[\Delta\varepsilon]_{235}$ +141 and $[\Delta\varepsilon]_{220}$ −186. (*R*)-(+)-**1d** (82% ee): $[\alpha]_D^{24}$ +67 (*c* 0.10 in CHCl$_3$); CD (EtOH) $[\Delta\varepsilon]_{321}$ +9.6, $[\Delta\varepsilon]_{238}$ −72.1 and $[\Delta\varepsilon]_{222}$ +162. (*S*)-(−)-**1d** (71% ee): $[\alpha]_D^{25}$ −56 (*c* 0.10 in CHCl$_3$); CD (EtOH) $[\Delta\varepsilon]_{321}$ −10.4, $[\Delta\varepsilon]_{238}$ +92.6 and $[\Delta\varepsilon]_{222}$ −188.

Kinetic measurements

A solution of **1b**–**d** in methanol (7.9–9.4 mol dm^{-3}) was heated or cooled at a given temperature in a thermostat-controlled bath. Uncertainty of temperature was ±0.1 °C. Initial enantiomeric excesses were 92% ee for (*S*)-(−)-**1b**, 82% ee for (*R*)-(+)-**1c** and 52% ee for (*R*)-(+)-**1d**. The changes in the concentration of both enantiomers were followed at appropriate intervals by using HPLC (Chiralcel OD, 0.5 ml min^{-1}, λ 280 nm). The mobile phase for **1b**, **1c** and **1d** was 30, 20 and 10% EtOH–hexane, respectively. First-order rate constants were obtained by analyzing 10–20 concentration data for each sample, and the correlation factors were >0.977. The rate constants were as follows. **1b**: 5.8×10^{-6} s^{-1} at 30 °C, 2.4×10^{-5} s^{-1} at 40 °C and 9.1×10^{-5} s^{-1} at 50 °C. **1c**: 5.5×10^{-6} s^{-1} at 20 °C, 2.2×10^{-5} s^{-1} at 30 °C and 8.3×10^{-5} s^{-1} at 40 °C. **1d**: 3.7×10^{-6} s^{-1} at 10 °C, 1.5×10^{-5} s^{-1} at 20 °C and 5.3×10^{-5} s^{-1} at 30 °C.

Crystal-structure determination §

Crystal data for compound 1b. C$_{20}$H$_{16}$N$_2$, M = 284.35, trigonal, space group $R\bar{3}$ (no. 148), hexagonal cell constants a = 31.695(2), c = 7.7985(7) Å, V = 6784.7(8) Å^3, Z = 18, D_x = 1.253 g cm^{-3}, F(000) = 2700, μ = 0.074 mm^{-1}. Specimen: colourless hexagonal prisms, 0.43 × 0.50 × 0.54 mm, 2355 reflections measured ($4.0 \leqslant 2\theta \leqslant 51.5°$), 2215 unique reflections with $|F_o| \geqslant 4\sigma|F_o|$, h,k,l $0 \longrightarrow 38$, $0 \longrightarrow 38$, ±9, R = 0.044, R_w = 0.041. Residual extrema, 0.17 and −0.17 e Å^{-3}.

Crystal data for compound 1c. C$_{22}$H$_{20}$N$_2$, orthorhombic, space group *P*bca (no. 61), cell constants a = 21.343(3), b = 20.316(2), c = 7.5398(7) Å, V = 3269.3(5) Å^3, Z = 8, D_x = 1.269 g cm^{-3}, F(000) = 1328, μ = 0.075 mm^{-1}. Specimen: colourless prisms, 0.79 × 0.32 × 0.37 mm, 7392 reflections measured ($5.0 \leqslant 2\theta \leqslant 55°$, $\pm h,k,l$), 3748 unique reflections with $I > 3\sigma|I|$, h,k,l ±26, $-27 \longrightarrow 0$, $0 \longrightarrow 9$, R = 0.037, R_w = 0.047. Residual extrema, 0.14 and −0.16 e Å^{-3}. Lattice constants and intensity

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§ CCDC reference number 207/374. See http://www.rsc.org/suppdata/p1/1999/3677 for crystallographic files in .cif format.

data of **1b** and **1c** were measured on an Enraf-Nonius CAD-4 diffractometer with graphite-monochromated Mo-Kα radiation ($\lambda = 0.710\,73$ Å). The structure of **1b** was solved by direct methods using MULTAN78[23] and refined by block-diagonal least-squares based on $|F_o|$, and that of **1c** was solved by direct methods using SAPI91[26] and refined by full-matrix least-squares. All calculations on **1b** and **1c** were performed using UNICS-III program system[27] and TeXsan,[28] respectively. Hydrogen atoms were located from a difference Fourier synthesis. Anisotropic temperature factors for all non-hydrogen atoms and isotropic temperature factors for hydrogen atoms were applied. ORTEP plots of **1b** and **1c** are shown in Fig. 2.

Acknowledgements

This work was supported by Grant-in-Aids (No. 10877347 to K. H. and No. 09740456 to H. T.) from the Ministry of Education, Science, Sports and Culture, Japan.

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Paper 9/05161I