Chiral Induction in Aryl Radical Cyclization to the Aldimino Functional Group

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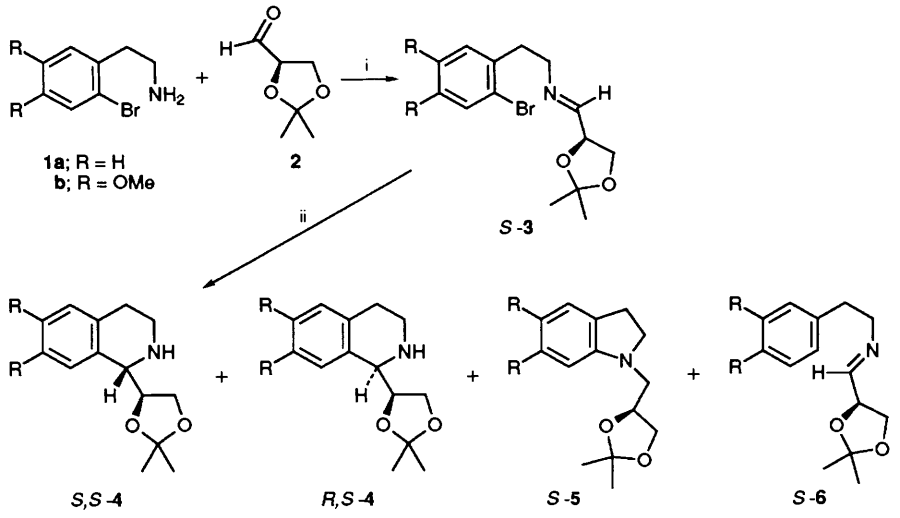
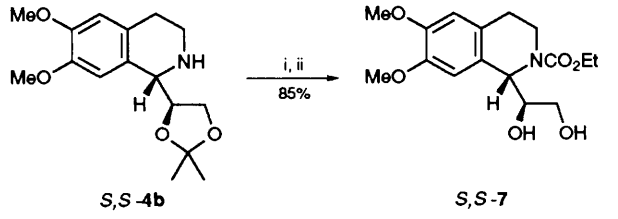
6-*endo* Cyclization of aryl radicals to carbon of aldimino double bonds (N-5/C-6) in chiral *ortho*-substituents afforded 1,2,3,4-tetrahydroisoquinolines in yields to 69%, with 58% d.e. and 97% e.e., while 5-*exo* cyclization to carbon in isomeric radicals (C-5/N-6 aldimine), leading to indanamines, was highly regioselective and fast, $k_{5\text{-}exo} = 3.9 \times 10^8\ s^{-1}$ at 80 °C.

Intramolecular radical cyclization reactions have emerged as a powerful synthetic tool for the construction of both carbocyclic and heterocyclic rings.[1] For example, aryl radical cyclization to the imino group, wherein the choice is between 5-*exo* closure to the N-atom and 6-*endo* closure to the C-atom (N-5/C-6), is regioselective in the endocyclic mode and gives tetrahydroisoquinolines in good to moderate yields.[2,3] In this communication, we report on the diastereoselectivity of the 6-*endo* closures to the C-atom of an aldimino group, leading to chiral isoquinolines. The regioselectivity and the kinetics of aryl radical cyclization to the isomeric imino group, wherein the choice is between 5-*exo* closure to the C-atom and 6-*endo* closure to the N-atom (C-5/N-6) are also reported. Finally, the potential for cyclization to the imino functionality in the lower homologue, wherein the choice is between 4-*exo* ring closure to the N-atom and 5-*endo* closure to the C-atom (N-4/C-5), was also investigated.

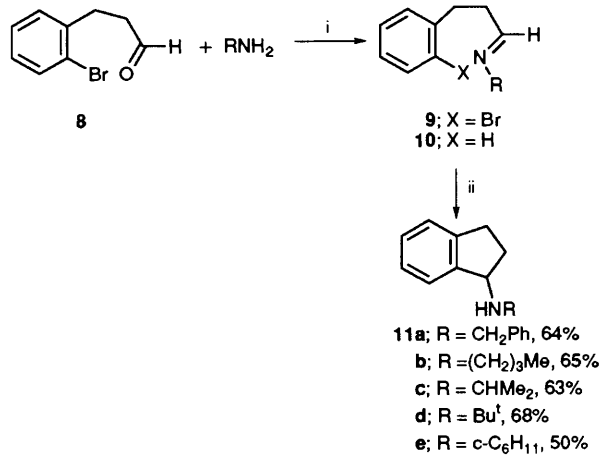
Syringe-pump addition of tri-n-butyltin hydride (TBTH) (2.0 mmol) and azoisobutyronitrile (AIBN) (0.36 mmol) in PhH (9 cm^3) over 9 h to the unisolated aldimine (*S*)-**3a** (1.6 mmol in 31 cm^3 of PhH at reflux), prepared in 95% yield from amine **1a** and (*R*)-2,3-*O*-isopropylideneglyceraldehyde **2**,[4] gave the following product ratios: *S,S*-**4a** : *R,S*-**4a** : *S*-**5a** : *S*-**6a** = 37 : 9.8: *ca.* 1 : 5.7 (GC and ^1H NMR) (Scheme 1). The diastereoisomeric tetrahydroisoquinolines, *S,S*- and *R,S*-**4a**, were isolated in 69% yield (from **1a**) and the diastereoisomeric excess (d.e.) was 58%. That diastereoselectivity could be improved moderately by running the reaction at a lower



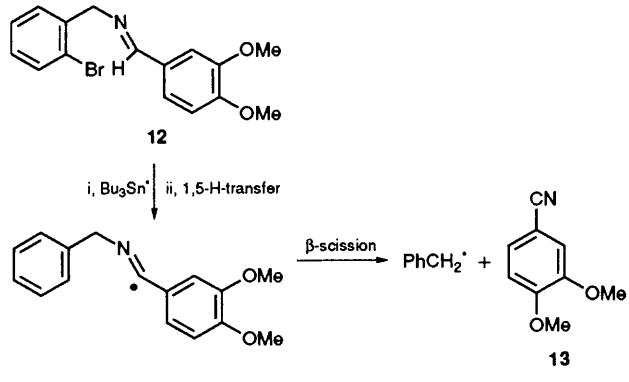
Scheme 1. *Reagents and conditions*: i, 4 Å sieves, CH_2Cl_2 or Et_2O, 5–20 °C, 2 h; ii, Bu_3SnH, AIBN, PhH, reflux



Scheme 2. *Reagents and conditions*: i, $ClCO_2Et$, 1% NaOH (aq), CH_2Cl_2, 5 °C, 1.5 h; ii, 80% HOAc, room temp., 14 h



Scheme 3. *Reagents and conditions*: i, 4 Å sieves, PhH, 6–10 °C; ii, Bu_3SnH (1.3 equiv.), 15% AIBN, PhH, reflux (**9a–9d**, all at once addition of Bu_3SnH and AIBN; **9e**, syringe-pump addition of Bu_3SnH and AIBN over 9 h)



Scheme 4

temperature. Heating of aldimine *S*-**3a**, TBTH (1.4 equiv., 0.58 mol dm^{-3}), and excess AIBN (1.8 equiv., a small fraction decomposes) in a degassed sealed tube at 60 °C for 2 h resulted in a d.e. of 65% (GC).

The stereochemistry of the new stereocentre, C-1, in the tetrahydroisoquinolines was assigned by conversion to a compound of known absolute configuration. Syringe-pump addition of TBTH (5.7 mmol) and AIBN (1.4 mmol) in PhH (18 cm^3) to aldimine *S*-**3b** (4.1 mmol) in PhH (50 cm^3, 80 °C) gave the diastereoisomeric isoquinolines **4b** (62%, from **1b**) with 53% d.e. The amino group of the major diastereoisomer was protected and the 1,2-diol function was unmasked (85% overall, Scheme 2). Comparison of the optical rotations and the ^1H NMR data of the MacLean isoquinoline,[5] *R,S*-**7** ($[\alpha]_D^{23}$ = +72.8 (*c* = 0.81 g/100 cm^3, $CHCl_3$), to those of ours, *S,S*-**7**, ($[\alpha]_D^{22}$ = −25.4 (*c* = 0.835 g/100 cm^3; −25.6, *c* = 0.242 g/100 cm^3, $CHCl_3$) showed that the relationship is one of diastereoisomers.

To prove that chiral integrity had been maintained throughout the route to *S,S*-**4b**, *S,S*-**4b** (1 part) was mixed with the chiral solvating agent (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)-ethanol (3 parts) and the ^1H NMR (500 MHz) spectrum was recorded.[6] A similar mixture with scalemic **4b**, prepared from scalemic **2**, was shown to have a pronounced nonequivalence in chemical shifts, Δδ, for the H-1′ and the methyl groups of the acetonide. By comparison of the spectra from scalemic **4b** and *S,S*-**4b**, the % e.e. for the major isoquinoline *S,S*-**4b** was found to be 97%. Based on the sense of the nonequivalence observed, the proposed interaction between the chiral solvating agent and *S,S*-**4b** is as shown in Fig. 1 with the H-1′ atom *cis* to the anthryl group and shielded by it. The acetonide methyl groups are affected as well.

The regioselectivity of aryl radical cyclization to the isomeric aldimino group (choice of 5-*exo* closure to the C-atom or 6-*endo* closure to the N-atom), in contrast, was found to be exclusively in the 5-*exo* sense (Scheme 3). In a one-pot procedure, the primary aldimine **9**, formed by the condensation of **8** with an amine, was used directly, after filtration from molecular sieves, in the radical cyclization with TBTH (1.3 equiv.) and 15% AIBN. The only products of cyclization detected by ^1H NMR spectroscopy were 1-indanamines **11** with overall isolated yields in the range 50–68%,

Table 1 Kinetic data for cyclization of *N*-benzylaldimine **9a** at 80 °C

[SnH][a]/ mol dm^{-3}	Product ratio[b] (**11a**/**10a**)	Ratios of rate csts/mol dm^{-3} (k_5/k_H)	Integrals relative to TMS: **9a**/TMS	Integrals relative to TMS: (**10a** + **11a**)/ TMS
0.473	2.4	1.1	0.9	0.9
0.473	2.4	1.1	0.7	0.8
0.237	4.8	1.1	0.9	1.0
0.118	8.5	1.0	1.0	1.0
0.059	14	0.8	1.0	1.0
0.059	14	0.8	1.0	1.0

[a] Bu_3SnH was in 8.6 fold excess, and the concentrations are averages based on expected 1 : 1 stoichiometry. Solvent was PhH (7% AIBN) and solutions were degassed and flame sealed. [b] Ratios from the integrals in ^1H NMR (500 MHz) spectra.

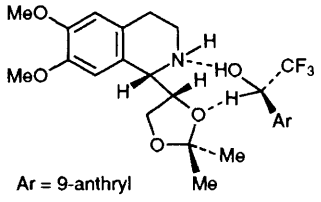
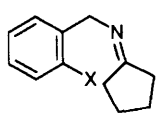


Fig. 1 Interaction between the chiral solvating agent and *S,S*-**4b**

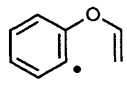
from **8**. This preference for 5-*exo* closures to the C-atom of the imino group (C-5/N-6) is the same as that reported for closures to the hydroxyimino[7] and *N*-aziridinylimino[8] functionalities.

Table 1 summarizes product ratios and derived rate constants for cyclization of *N*-benzylaldimine **9a**. Reactions were found to proceed cleanly to the indanamine **11a** and the reduced starting material **10a**, as evident from the equivalence of the ratios **9a**/TMS and (**10a** + **11a**)/TMS. The best value for the ratio k_5/k_H/mol dm^{-3} of 1.1 indicates that the closure of the aryl radical derived from **9a** is highly efficient. Substituting the value for k_H^{Ar} (80 °C) = 3.5×10^8 dm^3 mol^{-1} s^{-1}, calculated from[9] $\log k_H^{Ar} = 9.6 - 1.7/\theta$, gave $k_{5\text{-}exo} = 3.9 \times 10^8$ s^{-1}, at 80 °C. This is the fastest ring closure to the aldimino group known to date. The regioselectivity and the value of the 5-*exo* rate constant for cyclization of the radical from **9a** are, in fact, similar to those for the *o*-butenylphenyl radical.[10] This is probably due to the fact that the geometry of the imine (Csp^3–Csp^2 bond length 1.50 Å, C=N bond length 1.30 Å, C–C=N bond angle 121.5°) resembles that of the alkene (Csp^3–Csp^2 bond length 1.508 Å, C=C bond length 1.347 Å, C–C=C bond angle 123.8°).[11]

Radical cyclization to imines (N-4/C-5) in which the only likely closure would be in the 5-*endo* sense to the C-atom, was also investigated.[12] Syringe-pump addition of TBTH (1.3 equiv.) and AIBN (0.35 equiv.) to the Schiff base **12** gave 3,4-dimethoxybenzonitrile **13** and toluene, but none of the product of radical cyclization. In a reasonable mechanism (Scheme 4) the aryl radical, formed by removal of the Br-atom, abstracts the azomethine H-atom forming the imidoyl radical, which subsequently fragments[13] to **13** and the benzyl radical. Although the intramolecular 1,5-H-atom transfer of the azomethine proton is apparently unprecedented, the analogous process is well known in aldehydes.[14] As the 1,5-H-atom transfer was clearly faster than the 5-*endo*



14; X = Br
15; X = H



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cyclization to the C-atom in Schiff base **12**, cyclization in ketimine **14** was attempted. When treated under conditions of dilute TBTH (1.2 equiv.) and catalytic amounts of AIBN (10%) in refluxing PhH, **14** was cleanly converted to the dehalogenated ketimine **15**, and none of the product of cyclization was detected (^1H NMR). Based on the assumption that 4% or less would not have been detected by ^1H NMR spectroscopy, the ratio k_c/k_H is ≤0.0016 mol dm^{-3} at 80 °C, assuming a mean stannane concentration of 0.039 mol dm^{-3}. Substituting the value of 3.5×10^8 dm^3 mol^{-1} s^{-1} for k_H gives an upper limit for the 5-*endo* ring closure rate constant of 5.6×10^5 s^{-1} at 80 °C. The 5-*endo* cyclization of the *o*-propenyloxyphenyl radical[15] **16** is also poor, the ratio k_c/k_H being <0.01 mol dm^{-3} at 130 °C.

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