

RADICAL CYCLIZATION TO THE IMINO FUNCTIONAL GROUP

By

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RADICAL CYCLIZATION TO THE IMINO FUNCTIONAL GROUP

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ABSTRACT

Aryl radicals, generated by abstraction of Br from ortho-substituted bromoarenes, add to an imino functional group (C=N) in the ortho substituent in a competition involving 6-endo closure to the C and 5-exo closure to the N-atom. Absolute rate constants for the 6-endo closure were measured for two systems; $k_{6\text{-endo}} > 10^8 \text{ s}^{-1}$ (80 °C). Rate constants for the competing 5-exo closure were estimated to be 10-100 fold smaller. The utility of the 6-endo closure for the synthesis of tetrahydroisoquinolines was demonstrated with eight aldimine systems. Moreover, 1,2-asymmetric induction with up to 57% of diastereomeric excess was discovered for the 6-endo closure to the C-atom of the CN double bond derived from glyceraldehyde acetonide.

Radical cyclization in the lower homologue, wherein the choice was between 4-exo closure to the N-atom and 5-endo closure to the C-atom, was not competitive with either 1,5 H-atom transfer of the azomethine proton (aldimine) or transfer of H-atom from Bu_3SnH (ketimine).

In the isomeric imines, wherein the choice was between 5-exo closure to the C-atom and 6-endo to the N-atom, aryl radical closure was shown to be exclusively in the 5-exo sense. The absolute rate constant for the 5-exo closure to the C-atom was measured to be $5.3 \times 10^8 \text{ s}^{-1}$ (80 °C).

Finally, bis(tributylstannyl)benzopinacolate (TBBP) was found to be a novel source of canned tributylstannyl radicals.

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CHAPTER ONE

INTRODUCTION

The last decade has witnessed an explosion in the application of radical chemistry to synthesis culminating in many elegant and novel approaches to natural products and other interesting compounds.¹ Most of the radical reactions that are the foundation of these synthetic triumphs, however, have been known to physical organic chemists since the early 1970's, but their employment in synthesis was quite slow in coming.^{2,3} This delay has been attributed to some commonly held misconceptions by synthetic chemists that highly reactive radicals show low chemo-, regio-, and stereoselectivity.

One class of radical reactions that generally exhibits low selectivities is radical-radical reactions, and some of the reluctance by synthetic chemists to employ radical chemistry may be attributed to these reactions. As radicals are odd electron species without charge, there is virtually no barrier to their coupling for all but the sterically shielded radicals, and so it occurs with diffusion controlled rate constants, 10^9 - 10^{10} M⁻¹s⁻¹

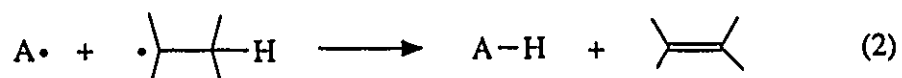
(1) For leading review articles, see: (a) Jasperse, C.P.; Curran, D.P.; Fevig, T.L. *Chem. Rev.* **1991**, *91*, 1237. (b) Thebtaranonth, C.; Thebtaranonth, Y. *Tetrahedron* **1990**, *46*, 1385. (c) Curran, D.P. *Synthesis* **1988**, 417 (Part 1); 489 (Part 2). (d) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541.

(2) *Free Radicals*; Kochi, J.K., Ed.; Wiley: New York, 1973: Vol. 1 and 2.

(3) Walling, C. *Tetrahedron* **1985**, *41*, 3887.

Scheme 1

Radical-Radical Reactions



Radical-Molecule Reactions

Addition:



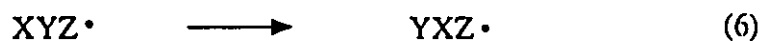
Substitution (abstraction):



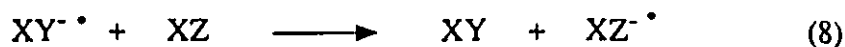
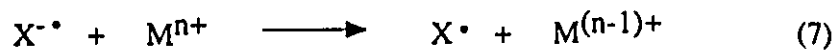
Elimination (fragmentation):



Rearrangement:



Electron Transfer:



(eq. 1, Scheme 1).⁴ Disproportionation of two radicals by transfer of an H-atom from one

(4) Ingold, K.U. In *Free Radicals*; Kochi, J.K., Ed.; Wiley: New York, 1973; Vol 1, p39.

to the other is also an extremely fast process (eq. 2).⁵ These high rates lead to low selectivities. Another severe drawback of radical-radical reactions is that they are radical destroying, non-chain processes, that require an equivalent of radical initiator and consequently are inefficient.

Radical chain processes are possible with the radical-nonradical reactions shown in Scheme 1 (eq. 3-8). As these do not destroy the radical character, they are radical propagating reactions requiring just catalytic amounts of initiator and are synthetically useful.

Chain reactions consist of three stages: initiation, propagation, and termination. Competing with radical propagating reactions (eq. 3-8) are the terminating radical-radical coupling reactions (eq. 1 and 2) and for a favourable outcome, the rate of propagation must be greater than that for termination. The rate equations for a typical propagating step, $A\cdot + YZ \rightarrow AYZ\cdot$ (eq. 3) and for the competing coupling reaction, $A\cdot + B\cdot \rightarrow AB$, are:

$$\text{Rate of propagation} = \text{Rate}_p = k_p[A\cdot][YZ]$$

$$\text{Rate of termination} = \text{Rate}_t = k_t[A\cdot][B\cdot]$$

$$1 < \text{Rate}_p/\text{Rate}_t = k_p[YZ]/k_t[B\cdot]$$

Substituting approximate values for the termination rate constant, $k_t \sim 10^9$ to $10^{10} \text{ M}^{-1}\text{s}^{-1}$, for radical concentration, $[B\cdot] = [A\cdot] \sim 10^{-7}$ to 10^{-8} M and for concentration of substrate, $[YZ] \sim 1 \text{ M}$, yields a lower limit for k_p ($k_p \geq 10^2 \text{ M}^{-1}\text{s}^{-1}$) for successful chain propagating

(5) Sheldon, R.A.; Kochi, J.K. *J. Am. Chem. Soc.* 1970, 92, 4395.

steps.⁶ A similar calculation for the unimolecular processes in Scheme 1, namely elimination and rearrangement reactions, places the lower limit of their k values at 10^2 s^{-1} .

One of the most studied rearrangements is that of the 5-hexenyl radical (2), which undergoes ring closure predominately in the contra-thermodynamic exocyclic mode to the cyclopentylmethyl radical(3) (Scheme 2).⁷ The radical propagating steps in this chain reaction (Scheme 2, eq. 2-5) have rate constants that are $\geq 10^5$ at 25°C, well above the calculated lower limit necessary for a viable chain reaction. Azobisisobutyronitrile (AIBN) is a very common and convenient radical initiator. The 5-hexenyl radical (2) is generated from the 5-hexenyl bromide (1) by bromine-atom abstraction with tri-*n*-butylstannyl radical ($Bu_3Sn\bullet$). There are two competing pathways available to the 5-hexenyl radical (2): cyclization to the cyclopentylmethyl radical (3) (eq. 3) or its reduction by Bu_3SnH to the acyclic compound 4 (eq. 4). As the latter step is bimolecular and dependent on tin hydride concentration, the concentration of Bu_3SnH can greatly influence the product outcome either toward cyclized material (5) or to the less desirable acyclic product (4). The partitioning of 2 depends upon the relative rates for cyclization (k_c) and H-atom abstraction ($k_H[Bu_3SnH]$). At $[Bu_3SnH] = 5$ M, the ratio of cyclic to acyclic product (ratio of 5 to 4) is very low, ca. 1:50. At tin hydride concentrations less than 0.05

(6) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: Oxford, 1986, p.12.

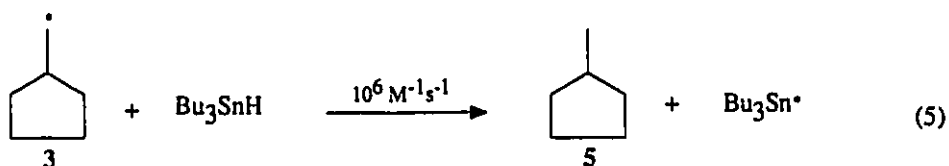
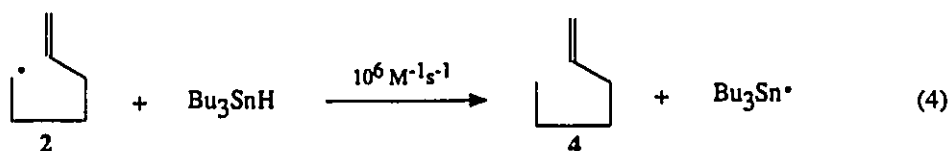
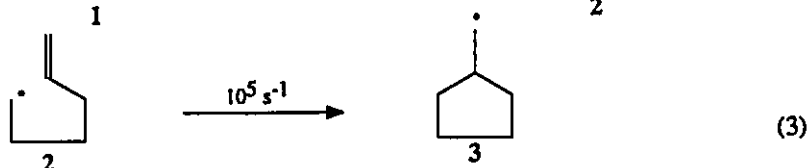
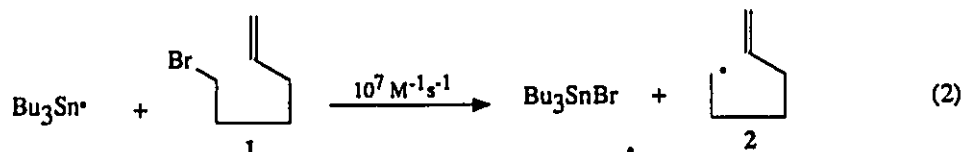
(7) Beckwith, A.L.J.; Ingold, K.U. In *Rearrangements in Ground and Excited States*; deMayo, P., Ed.; Academic Press: New York, 1980; Vol. 1, pp 162-283.

Scheme 2

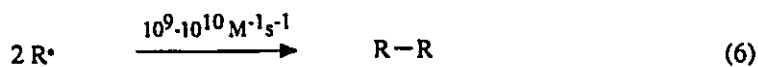
Initiation



Propagation



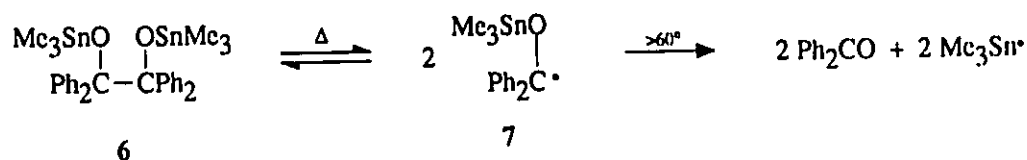
Termination



M, however, the ratio of 5 to 4 is much more favourable as it is more than 2:1, and on the side of ring closed product 5. The concentration of tin hydride determines the lifetime of intermediary radicals such as 5-hexenyl (2) and is therefore crucial to the outcome. There is a limit, however, as at very low concentrations of Bu_3SnH the bimolecular propagating steps, eqs. 4 and 5, fail and thereby collapse the chain. Competing processes such as radical-radical coupling reactions and radical-solvent attack are more prevalent at very low tin hydride concentrations.

Methods often employed in intramolecular radical cyclization reactions to maximize the yields of cyclized products, keeping a low $[\text{Bu}_3\text{SnH}]$, include working under conditions of high dilution or adding the reducing agent slowly via a syringe-pump. Alternatively, if the functionality in the substrate permits, one could generate the tin hydride in situ by reacting catalytic amounts of tin halide with a standard hydride reducing agent (NaCNBH_3 or NaBH_4).⁸ Polymer bound tin hydrides have also been used.⁹ Neumann and co-workers developed a novel source of stannyl radicals that is free of the corresponding hydride (Scheme 3).¹⁰ They found that bis-trimethylstannyl benzopinacolate (6), upon warming, splits reversibly into stannyl ketyls 7, but irreversibly into benzophenone and trimethylstannyl radicals above 60 °C. In principle, one could combine this source of stannyl radicals with an H-donor of desired strength, such as

Scheme 3



(8) Gerth, D.B.; Stork, G. *J. Org. Chem.* **1986**, *51*, 3726.

(9) (a) Gerlach, M.; Jordens, F.; Kuhn, H.; Neumann, W.P.; Peterseim, M.; *J. Org. Chem.* **1991**, *56*, 5971. (b) Ueno, Y.; Moriya, O.; Chino, K.; Watanabe, M.; Okawara, M. *J. Chem. Soc., Perkin Trans.* **1986**, 1351.

(10) (a) Neumann, W.P.; Hillgartner, H.; Baines, K.M.; Dicke, R.; Vorspohl, K.; Kobs, U.; Nussbeutel, U. *Tetrahedron* **1989**, *45*, 951. (b) Hillgartner, H.; Neumann, W.P.; Schroeder, B. *Liebigs Ann. Chem.* **1975**, 586.

cumene or THF, and carry out very effective cyclizations.^{10a} As attractive as this approach may seem there have been very few applications of this process in carbon-carbon bond formation.¹¹ The well known high toxicity of trimethylstannyl derivatives makes this procedure unattractive.¹²

Another approach aimed at increasing the proportion of cyclized to reduced material, involves replacing tin hydrides by poorer H-atom donors. Tri-n-butylgermanium hydride for example, donates its H-atom to carbon radicals about one order of magnitude slower than the corresponding tin derivative,^{1c} and therefore the lifetime of radicals such as the 5-hexenyl (2) is extended.¹³ Although most compounds with Si-H bonds are too poor as H-atom donors to propagate radical chain reactions well, the new silicon based reducing reagent, tris(trimethylsilyl)silane ((Me₃Si)₃SiH) looks quite promising. Its bond dissociation energy is only ca.5 kcal/mol higher than that for Bu₃SnH.¹⁴ Alkyl radical abstraction of the H-atom from (Me₃Si)₃SiH is ca. 10 times slower than from Bu₃SnH,

(11) For an example of intermolecular addition of alkyl radicals to oximes, see: Hart, D.J.; Seely, F.L. *J. Am. Chem. Soc.* **1988**, 110, 1631.

(12) The following are LD₅₀ for oral administration to rats: 9-20 mg/kg for Me₃SnCl versus 122-349 mg/kg for Bu₃SnCl. Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths; London, 1987.

(13) For an example of a tandem cyclization that benefitted from tributylgermane, see: Beckwith, A.L.J.; Roberts, D.H.; Schiesser, C.H.; Wallner, A. *Tetrahedron* **1985**, 26, 3349.

(14) The BDE(Si-H or Sn-H) for Et₃SiH (90.1 kcal/mol), (Me₃Si)₃SiH (79.0 kcal/mol) and Bu₃SnH (74 kcal/mol): Kanabus-Kaminska, J.M.; Hawari, J.A.; Griller, D.; Chatgililoglu, C. *J. Am. Chem. Soc.* **1987**, 109, 5267.

giving intermediary alkyl radicals sufficient time to undergo addition or rearrangement reactions before they are reduced. For example, the ratio (cyclized/uncyclized) of products obtained for reduction of 5-hexenyl bromide (1) by $(\text{Me}_3\text{Si})_3\text{SiH}$ is 24:1, while under the same conditions Bu_3SnH gave only 6:1.¹⁵ Further synthetic applications¹⁶ of this silane derivative as well as the corresponding kinetic data¹⁷ have been forthcoming.

Radical Cyclization To C=C

The addition of alkyl radicals to alkenes, as in the case of the 5-hexenyl radical (2), is energetically favourable since a strong CC σ -bond (81 kcal/mol) is made at the expense of a weak CC π -bond (67 kcal/mol).¹⁸ The preferred sense of attack by the 5-hexenyl radical (2), however, is not driven by thermodynamic factors (Scheme 4). Closure is largely in the 5-exo sense, yielding the less stable primary radical 3 rather than the more stable secondary radical 8. After the H-atom transfer, the ratio of methylcyclopentane 5 to cyclohexane 9 is in the order of 60:1 at 25°C.¹⁹ Additional

(15) Giese, B.; Kopping, B.; Chatgililoglu, C. *Tetrahedron Lett.* 1989, 30, 681.

(16) Ballestri, M.; Chatgililoglu, C.; Clark, K.B.; Griller, D.; Giese, B.; Kopping, B. *J. Org. Chem.* 1991, 56, 678.

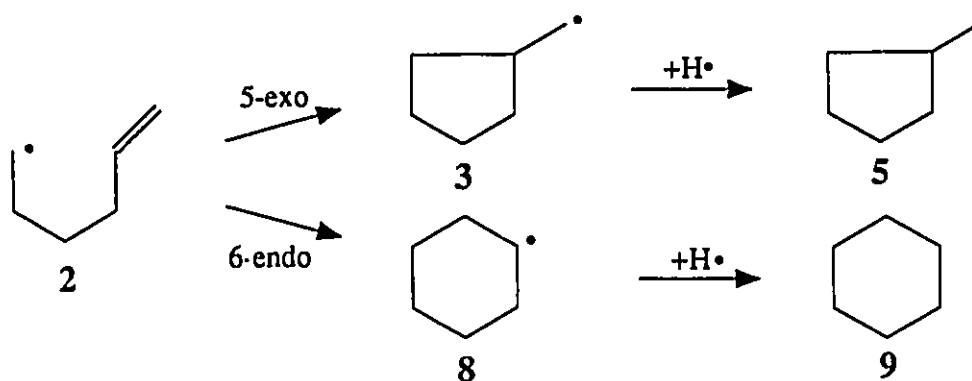
(17) (a) Chatgililoglu, C.; Dickhaut, J.; Giese, B. *J. Org. Chem.* 1991, 56, 6399. (b) Chatgililoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.* 1989, 54, 2492.

(18) Bond energies from: Lowry, T.H.; Richardson, K.S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987; p.162.

(19) Beckwith, A.L.J.; Schiesser, C.H. *Tetrahedron* 1985, 41, 3925.

studies in which cyclopentylmethyl (3) and cyclohexyl radicals (8) were generated independently demonstrated the irreversibility of the cyclization of the 5-hexenyl radical (2).⁷

Scheme 4



Three theories have been advanced to account for the formation of the less stable product of cyclization of the 5-hexenyl radical (2). The first, proposed by Capon and Rees,²⁰ suggests that a difference in ΔS^\ddagger for the 2 pathways in Scheme 4 accounts for the regiochemistry. A more favourable entropy of activation comes from the formation of a smaller ring, the cyclopentylmethyl ring system. Bischof²¹ calculated the activation parameters for the cyclization of the 5-hexenyl radical (2) using statistical thermodynamics and MINDO/3UHF. He found that $\Delta S^\ddagger_{5\text{-exo}}$ for 5-exo closure of 2 is 3.3

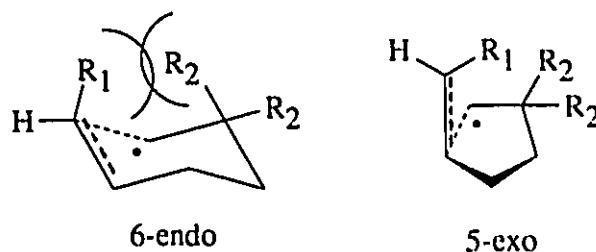
(20) Capon, D.; Rees, C.W. *J. Chem. Soc., Annu. Rep.* 1964, 61, 221.

(21) Bischof, P. *Helv. Chim. Acta.* 1980, 63, 1434.

cal/mol·K (25 °C) more favourable than $\Delta S^\ddagger_{6\text{-endo}}$ for the 6-endo closure of 2. This value for $\Delta\Delta S^\ddagger$ is, nevertheless, far too small to account for the large regioselectivity found, and therefore the favourable value for ΔS^\ddagger contributes to the preference for 5-exo closure but it is unlikely to be the dominant factor.²²

The second hypothesis **Scheme 5**

put forward to explain the contra-thermodynamic ring closure of the 5-hexenyl radical (2), is a steric argument advanced by Julia²³ and LeBel.²⁴ They propose that there



are unfavourable non-bonded interactions between the pseudo-axial group at C-2 ($R_2=H$) and the syn proton at C-6 ($R_1=H$) in the transition leading to 6-endo ring closure (Scheme 5). By comparison, the 5-exo ring closure is relatively free of such interactions and hence the preferred mode of cyclization. Beckwith,²⁵ however, based on a kinetic analysis of a series of methyl substituted 5-hexenyl radicals found the contribution of the 2,6-non-bonded interactions on the transition state free energies to be only ca. 0.8 kcal/mol, even

(22) Beckwith, A.L.J. *Tetrahedron* 1981, 37, 3073.

(23) Julia, M.; Descoins, C.; Baillarge, M.; Jacquet, D.; Uguen, D.; Groeger, F.A. *Tetrahedron* 1975, 31, 1737.

(24) LeBel, N. quoted in Julia, M. et al. reference 23

(25) Beckwith, A.L.J.; Lawrence, T. *J. Chem. Soc., Perkin Trans. II* 1979, 1535.

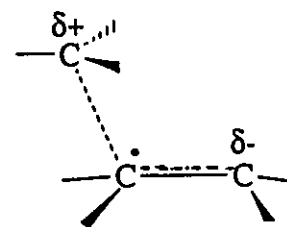
with the sterically larger methyl group at C-2. Like the entropic argument of Capon and Rees, the steric hypothesis of Julia and LeBel, involving 2,6-non-bonded interaction, may play a role in the regioselectivity of the 5-hexenyl radical (2). This, however, is not thought to be the dominant factor.

The third, and most widely accepted, hypothesis for the 5-exo closure of 5-hexenyl radical (2) is based on stereo-electronic effects and was developed by Beckwith.²² The transition state for an inter- or intramolecular attack of an alkyl radical on C=C, as Beckwith predicted, consists of the three atoms at the vertices of an obtuse triangle orthogonal to the nodal plane of the π system (Scheme 6). The incoming alkyl radical with its semioccupied 2p orbital (SOMO) overlaps with the lowest unoccupied molecular orbital (LUMO) of the alkene. The transition state complex

is further described as being dipolar with the attacking radical acting as a nucleophile. Various theoretical calculations, most recently by Houk et al.,²⁶ support this transition state model and indicate it to be reactant-like.

The attainment of this geometry at the transition state is more readily accommodated in the transition complex for 5-exo ring closure of 5-hexenyl radical (2) than in the 6-endo closure. This hypothesis contends that the 5-exo regioselectivity for the 5-hexenyl radical (2) is attributed to a strain difference at the

Scheme 6



(26) Houk, K.N.; Paddon-Row, M.N.; Spellmeyer, D.C.; Rondan, N.G.; Nagase, S. *J. Org. Chem.* 1986, 51, 2874., and references therein.

transition state for 5-exo and 6-endo ring closure that outweighs the thermochemical factors favouring the formation of the more stable product. The difference in enthalpy of activation between 5-exo and 6-endo closure must therefore be mainly responsible for the regioselectivity of cyclization of the 5-hexenyl radical (2). Experimental results indicate that the 5-exo closure has a more favourable enthalpy of activation ($\Delta H^\ddagger_{6\text{-endo}} - \Delta H^\ddagger_{5\text{-exo}} \sim 1.7$ kcal/mol).^{22,27}

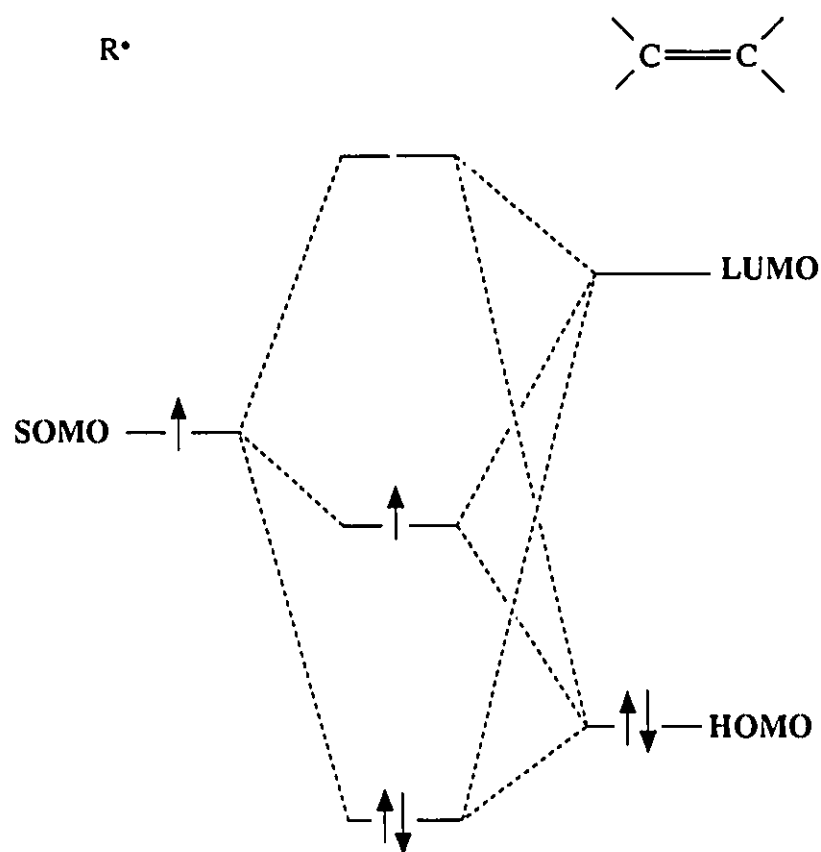
Frontier Orbitals and Radical Additions

Since the addition of alkyl radicals is a highly exothermic process the transition state should lie early on the reaction coordinate, with small changes in bonding, according to the Hammond postulate. Theoretical calculations by Houk and co-workers,²⁶ using ab initio UHF theory and the 3-21G basis set, show that in the intermolecular methyl radical addition to a simple olefin, the newly forming σ -bond is 46% longer than in the fully formed product, in support of the early transition state model. On account of the early transition state, intra- and intermolecular additions of free radicals have been described in terms of Frontier Orbital Theory. Briefly, this theory states that the energy difference between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of the reacting species largely determines the rate

(27) If $\Delta\Delta H^\ddagger$ is ca. 1.7 kcal/mol, then $k_{5\text{-exo}}/k_{6\text{-endo}}$ is ca. 20 assuming $\Delta\Delta H^\ddagger \sim \Delta E_a \sim 1.37 \log k_{5\text{-exo}}/k_{6\text{-endo}}$ at constant ΔS^\ddagger .

of the reaction (Scheme 7).^{28,29} The frontier orbital of a free radical is the SOMO. Radicals with high lying SOMO's, alkyl, alkoxyalkyl and aminoalkyl radicals, interact preferentially with the LUMO of the alkene. The rate of addition is further enhanced by

Scheme 7



(28) Fujimoto, H.; Yamabe, S.; Minato, T.; Fukui, K. *J. Am. Chem. Soc.* 1972, 94, 9205.

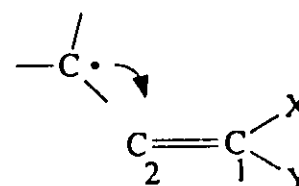
(29) Giese, B. *Angew. Chem. Int. Ed. Eng.* 1983, 22, 753., and references therein.

placing electron withdrawing substituents on the alkene, which lowers its LUMO energy. For example, the nucleophilic t-butyl radical adds some 8500 times faster to 2-propenal than to 1-hexene.²⁹ In radicals with electron withdrawing groups, however, the SOMO energy is lowered and the SOMO-HOMO interaction predominates. This reaction is sped up by using electron rich olefins because the SOMO-HOMO gap is reduced.

The regioselectivity of intermolecular alkyl radical addition to olefins has recently been studied by Pasto³⁰ and shown to be, in most cases studied, Frontier Molecular Orbital (FMO) controlled. The relative magnitudes of the coefficients on the sp² carbon atoms in the LUMO of the alkene determine the site of radical attack. This was particularly true for a series of mono-substituted and 1,1-disubstituted electron poor and capto-dative olefins which have their largest coefficients at C(2), the terminus of intermolecular alkyl radical addition (Scheme 8). Other

researchers have explained this regioselectivity with either a polar, a steric, or a bond strength argument.²⁹ The preferred site of intermolecular alkyl radical attack on mono-substituted electron rich olefins (Scheme 8, where X=H; Y=OH, NH₂, SH, or CH₃) is also to the terminal

Scheme 8



carbon atom, but in this system the largest coefficient in the LUMO appears at C(1), and not at the terminal C(2)-atom. The difference in magnitudes of orbital coefficients between C(1) and C(2), however, is quite small, and considerably smaller than in the case

(30) Pasto, D.J. *J. Org. Chem.* 1992, 57, 1139.

of electron withdrawing groups on the olefin. Perhaps steric effects in the mono-substituted electron rich olefins reverse the regioselectivity from that based solely on relative magnitudes of the coefficients.³⁰

It is anticipated that in the case of intramolecular radical closures, the geometric constraints of the ring can reverse the regioselectivity from that based singularly on the relative magnitudes of the orbital coefficients. Nonetheless, the propensity of the 5-hexenyl radical (2) to cyclize in the 5-exo mode to the non-terminal carbon atom, can only be aided by the larger coefficient at that carbon.

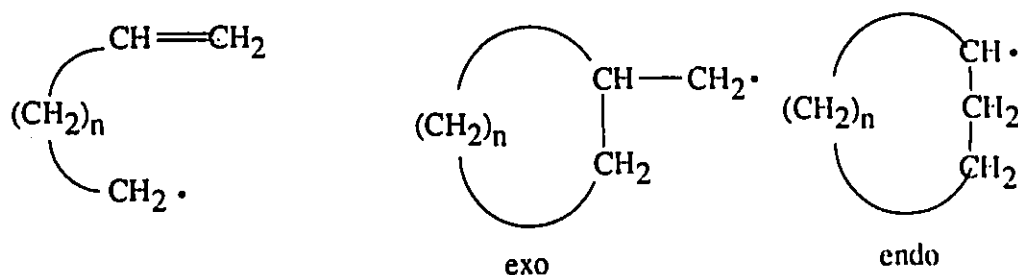
Guidelines For Intramolecular Radical Cyclizations

Based on the stereo-electronic hypothesis, Beckwith, Easton, and Serelis formulated a set of guidelines for predicting the outcome of radical cyclization reactions.³¹ These generalizations have quite strong predictive value especially when used in conjunction with a thermochemical argument. The first states that *intramolecular addition under kinetic control in lower alkenyl and alkynyl radicals and related species occurs preferentially in the exo-mode*. This prediction is true for ring closure in the series of homologous alkenyl radicals, namely, 3-butenyl (n=1), 4-pentenyl (n=2), 5-hexenyl (n=3), and 6-heptenyl (n=4) radical (Scheme 9). Further examples include various substituted alkenyl radicals, vinyl radicals, alkynyl radicals, alkenylaryl radicals, and O-

(31) Beckwith, A.L.J.; Easton, C.J.; Serelis, A.K. *J. Chem. Soc., Chem. Commun.* 1980, 482.

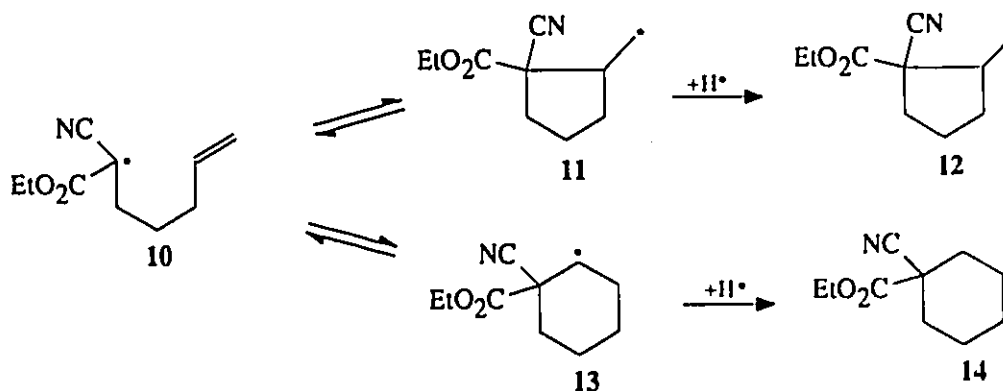
and N-centered radicals.⁷ Baldwin reached a similar conclusion on the regioselectivity of radical closure to unsaturated functionalities, based on a vector approach.³²

Scheme 9



Radical cyclizations that fall under thermodynamic control are outside Beckwith's guidelines. Julia accomplished one of the classical studies on reversible ring closure with radical **10**, derived from pentenylmalononitrile (Scheme 10).³³ The product

Scheme 10



(32) Baldwin, J.E. *J. Chem. Soc., Chem. Commun.* 1976, 734.

(33) Julia, M.; Salard, J.M.; Chottard, J.C. *Bull. Soc. Chim. Fr.* 1973, 2478.

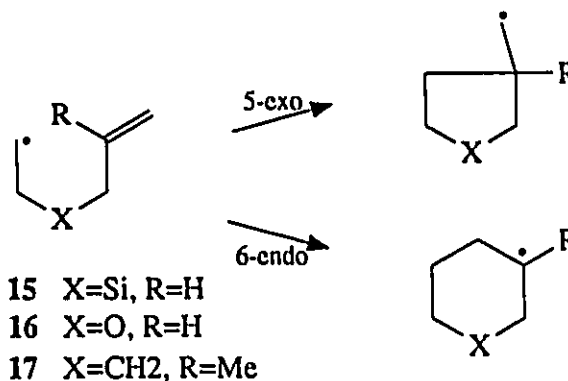
outcome, whether 5-exo or 6-endo derived, depends largely on the conditions of the reaction. For a reaction carried out at 81°C, the favoured product comes from 6-endo closure, and the ratio of **12** to **14** is 14:86, while at the lower temperature of -70°C, the exocyclic pathway predominates so that ratio **12** to **14** is 80:20. In addition, the strength of the H-donor has an appreciable effect on the product ratio. Reactions carried out in toluene at 11°C give a 5-exo to 6-endo product ratio (**12** to **14**) of 80:10, while in the presence of the poorer H-donating solvent cyclohexane thermodynamic control appears and the ratio of **12** to **14** is 67:33 at 11°C.³⁴ Therefore, the presence of radical stabilizing groups at C-1 results in a reversible reaction pathway to the 5-exo and 6-endo radicals, **11** and **13**, respectively. These observations are not totally inconsistent with the stereo-electronic hypothesis. As in the 5-hexenyl radical (**2**), radical **10**, under kinetic control affords the 1,5 cyclized product **12**, in accord with the first guideline. The process in Scheme 10, however, is reversible and under thermodynamic control radical **10** gives the more stable 6-membered product **14**. Nonetheless, stereo-electronic effects may not be as important in the ring closure of the stabilized radical **10**, as they are in the 5-hexenyl radical (**2**), because the former process is likely to be less exothermic and hence the transition state lies more toward the product side.

Wilt³⁵ in his studies on 3-sila-5-hexenyl radical, (**15**), discovered a clear contradiction to the first guideline. The ring closure of 3-sila-5-hexenyl radical, although

(34) Julia, M.; Mauray, M. *Bull. Soc. Chim. Fr.* 1969, 2427.

(35) Wilt, J.W. *Tetrahedron* 1985, 41, 3979.

not reversible, occurs almost exclusively in the 6-endo sense. This regiochemistry is totally opposite to that found in the 5-hexenyl radical (2), and is explained by comparing the geometry of the silyl substituted radical 15 to that of the 5-hexenyl



radical (2). The replacement of C-C bonds (1.53 Å) by longer C-Si bonds (1.91 Å) increases the distance between C-1 and C-5 and may result in a poorer overlap between the SOMO and LUMO in the transition state for 5-exo closure of 15. Stemming from the failure of the first guideline to account for these observations, Beckwith proposed an addendum, which states that *any structural features which affect the ability to accommodate the intimate transition state complex will necessarily affect also the rate and regioselectivity of the cyclization.*²²

Beckwith used a similar argument based on altered geometry at the transition state to explain the 5-exo regioselectivity of the 3-oxa-5-hexenyl radical (16).²² While the 5-exo to 6-endo ratio for 5-hexenyl radical (2) is ca. 56:1 and $k_{5\text{-exo}} = 2.3 \times 10^5 \text{ s}^{-1}$, in the case of the 3-oxa substituted system 16, the ratio of 5-exo to 6-endo is greater than 85:1 and $k_{5\text{-exo}} = 8.5 \times 10^6 \text{ s}^{-1}$, all at 25°C.¹⁹ Since radical 16 has the shorter C-O bonds (1.41 Å) and a smaller bond angle C-O-C (106.8°) in comparison to the 5-hexenyl radical (2) (C-C bond 1.52 Å, C-C-C angle 109.5°), the C-1 to C-5 distance in 16 is less than what it is

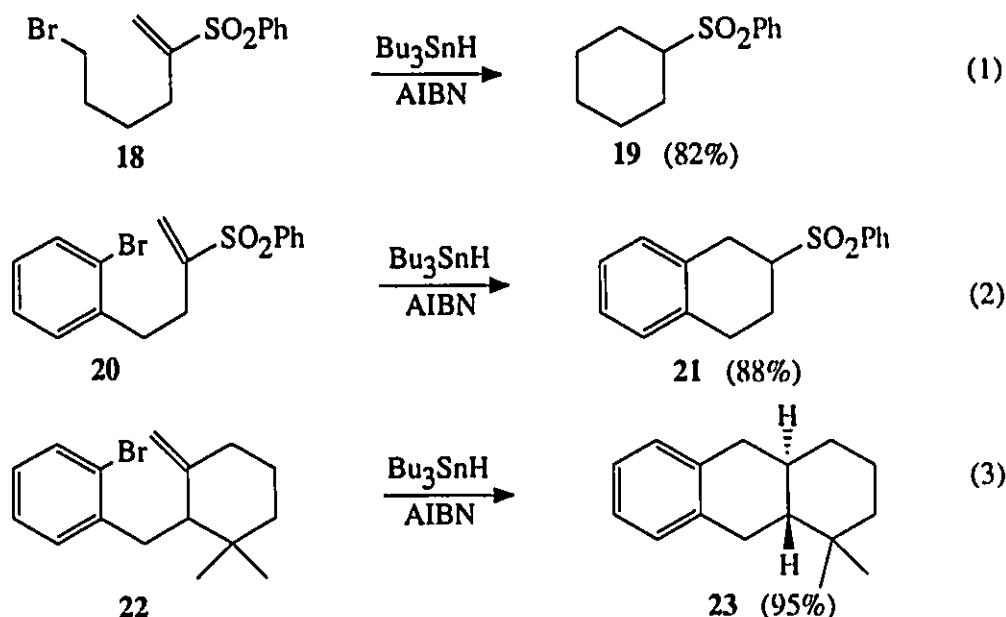
in the 5-hexenyl radical (2) and the C-1 to C-6 distance is greater. Consequently, the ring closure of the 3-oxa-5-hexenyl radical (16) is both faster and more regioselective than in the analogous all carbon system, 5-hexenyl radical (2).

Beckwith's second guideline for ring closure, is based mainly on steric effects and states that *substituents on an olefinic bond disfavour homolytic addition at the substituted position*. The 5-methyl-5-hexenyl radical (17), for example, gives approximately equal amounts of 5-exo and 6-endo products, whereas in the case of the 5-hexenyl radical (2) this ratio is ca.50:1, both at 65-70°C.⁷ It could be argued that the regiochemistry of cyclization by the 5-methyl substituted radical 17 is the result of the thermodynamic driving force favouring the formation of the more stable tertiary radical over the primary radical. Kinetic studies, nevertheless, clearly show that the preference for the endocyclic closure of 17 reflects a drop in the 5-exo cyclization rate constant and not an enhancement of the rate constant for the 6-endo pathway.

Recent examples from the groups of Padwa and Ghatak demonstrate the predicted effect of substitution at the 5-exo terminus of an olefin on the regiochemistry of cyclization (Scheme 11). Padwa and co-workers³⁶ found that both alkyl and aryl radicals, derived from the corresponding halides, 18 and 20, cyclize exclusively in the 6-endo sense to sulfones 19 and 21 respectively in yields over 80%. In another recent

(36) Padwa, A.; Murphee, S.S.; Yeske, P.E. *Tetrahedron Lett.* 1990, 2983.

Scheme 11

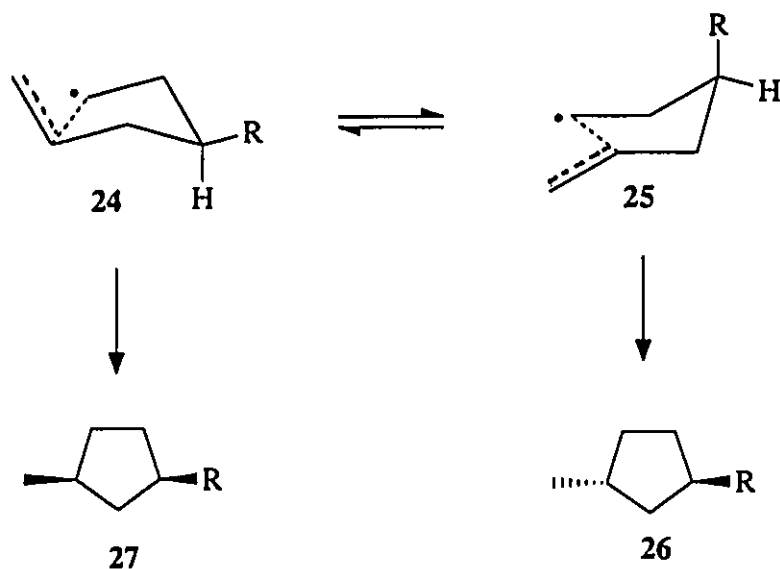


example of 6-endo closure to olefins Ghatak and co-workers³⁷ reported the synthesis of the tricyclic compound, trans-octahydroanthracene **23**, from the aryl bromide **22** in 95% isolated yield.

Beckwith's third guideline predicts the stereochemical outcome of radical cyclization reactions: *5-exo ring closure of substituted 5-hexenyl (2) and related radicals are stereoselective: 1- or 3-substituted systems afford mainly cis-disubstituted products, whereas 2- or 4-substituted systems give mainly trans-products.* This model proposes that the early transition state of a 5-exo radical cyclization is actually like the chair of a cyclohexane ring, and therefore has clearly distinguishable axial and equatorial positions

(37) Pal, S.; Mukherjee, M.; Podder, D.; Mukherjee, A.K.; Ghatak, U.R. *J. Chem. Soc., Chem. Commun.* **1991**, 1591.

Scheme 12



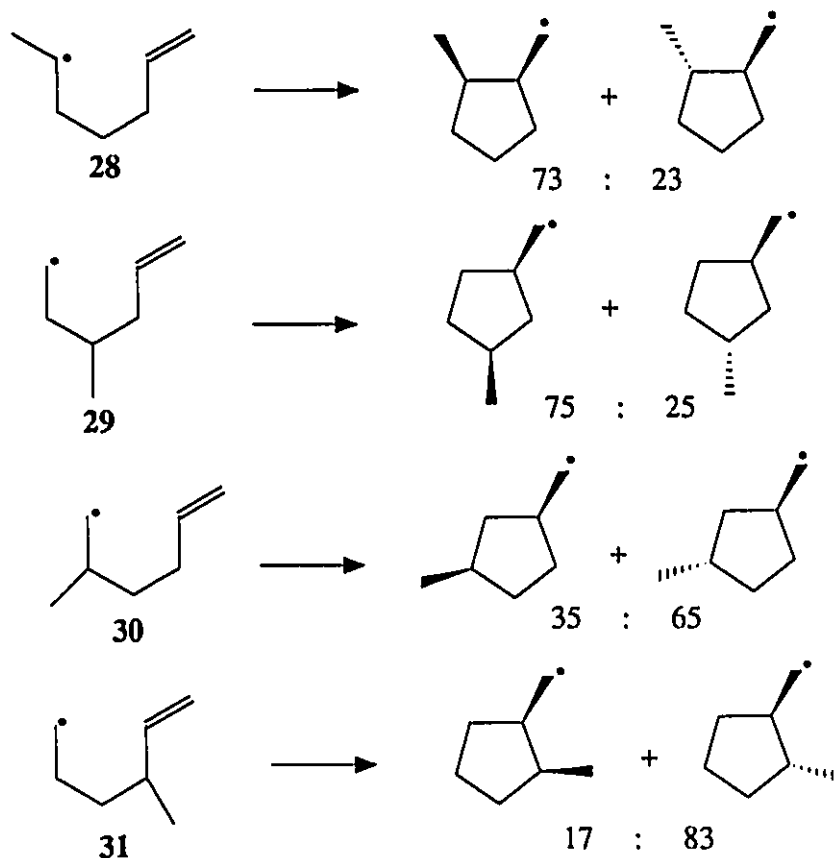
(Scheme 12). The preferred or lower in energy chair-like conformer at the transition state will place the substituents in the equatorial position. For example, when R is larger than an H-atom, the preferred conformer will be 24. The series of methyl substituted 5-hexenyl radicals in Scheme 13 demonstrates the expected pattern: 1- or 3-substituted systems 28 and 29, afford mainly cis-disubstituted products, whereas 2- or 4-substituted systems 30 and 31 give mainly trans product.^{38,39}

Stereoselectivity in inter- and intramolecular radical additions has received

(38) Beckwith, A.L.J.; Lawrence, T.; Serelis, A.K. *J. Chem. Soc., Chem. Commun.* 1980, 484.

(39) reference 6 p.148.

Scheme 13



considerable attention as is evident from the number of recent reviews⁴⁰ and articles⁴¹

(40) (a) Porter, N.A.; Giese, B.; Curran, D.P. *Acc. Chem. Res.* **1991**, *24*, 296. (b) RajanBabu, T.V. *Acc. Chem. Res.* **1991**, *24*, 139. (c) Giese, B. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 969. (d) Tedder, J.M. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 401.

(41) (a) Giese, B.; Damm, W.; Dickhaut, J.; Wetterich, F.; Sun, S.; Curran, D.P. *Tetrahedron Lett.* **1991**, *32*, 6097. (b) Smadja, W.; Zahouily, M.; Journet, M.; Malacria, M. *Tetrahedron Lett.* **1991**, *32*, 3683. (c) Koreeda, M.; Hamann, L.G. *J. Am. Chem. Soc.* **1990**, *112*, 8175. (d) RajanBabu, T.V.; Fukunaga, T.; Reddy, G.S. *J. Am. Chem. Soc.* **1989**, *111*, 1759.

published. There is now a considerable body of experimental and theoretical treatments^{42,19} that allows the planning of stereoselective radical ring closures. There is widespread support for the Beckwith's chair-like cyclohexane transition state model and exceptions to it can be anticipated.^{1a,40b}

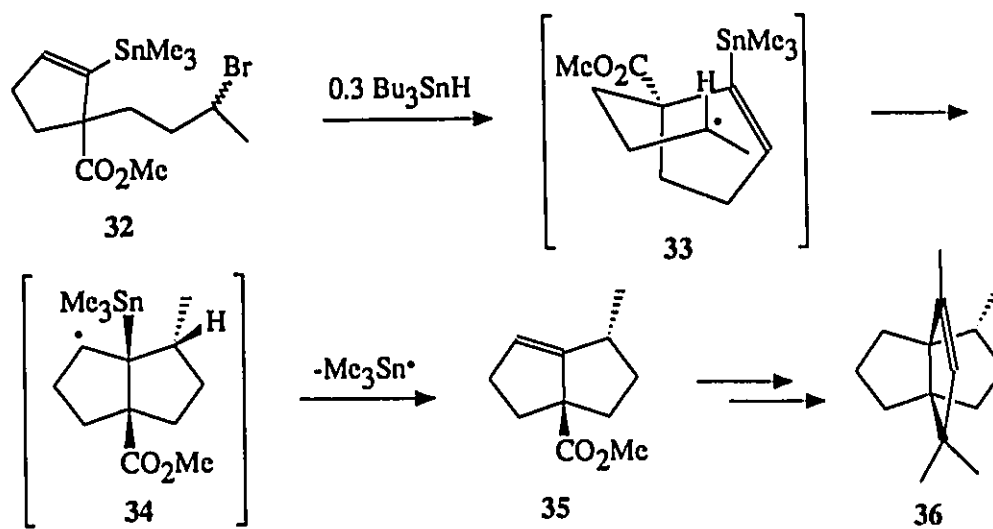
Radical reactions, in particular intramolecular radical cyclizations, contrary to the once prevalent view, are well suited for synthesis. Carbon radicals exhibit high chemoselectivity and consequently many functional groups do not require protection. For instance, alcohols and amines need not be masked as the O-H and N-H bonds are strong. Ketones and esters are also safe from intermolecular addition of carbon radicals. As is plainly evident from the above discussion, carbon radicals, in ring closing reactions, often exhibit good regio- and stereoselectivity in an often predictable sense.

Although the most common approach to conducting radical chain cyclization reactions involves the tin hydride method of Scheme 2, fragmentation and atom- or group transfer methods have been utilized as well.^{1a,b,c} In the tin hydride method, the chain-transfer agent ($\text{Bu}_3\text{Sn}^\bullet$) is generated by H-atom abstraction from Bu_3SnH . An alternative method of generating the chain-transfer agent is by fragmentation (Scheme 1, eq. 5), which Curran and Jasperse used in their synthesis of the fused triquinane modhephene (**36**) (Scheme 14).⁴³ Radical cyclization to the vinyl stannane functionality in **32** gave the bicyclic compound **35** in an amazing 90% yield, as a single diastereomer. The β

(42) Spellmeyer, D.C.; Houk, K.N. *J. Org. Chem.* **1987**, *52*, 959.

(43) Jasperse, C.P.; Curran, D.P. *J. Am. Chem. Soc.* **1990**, *112*, 5601.

Scheme 14



stereochemistry of the methyl group is consistent with the Beckwith cyclohexane, chair-like transition state in **33**. The secondary alkyl radical **34** undergoes a rapid fragmentation to generate the chain-transfer agent Me₃Sn•. The Bu₃SnH used in the above sequence was for initiation purposes only and hence was used in low concentration. The obvious advantage of the fragmentation method as compared to the tin hydride method is that there is no need for a strong H-donating reagent. Consequently, intermediate radicals are not intercepted by Bu₃SnH. Moreover, the fragmentation approach was highly desirable in this particular synthesis, because it regenerated the double bond for later usage.

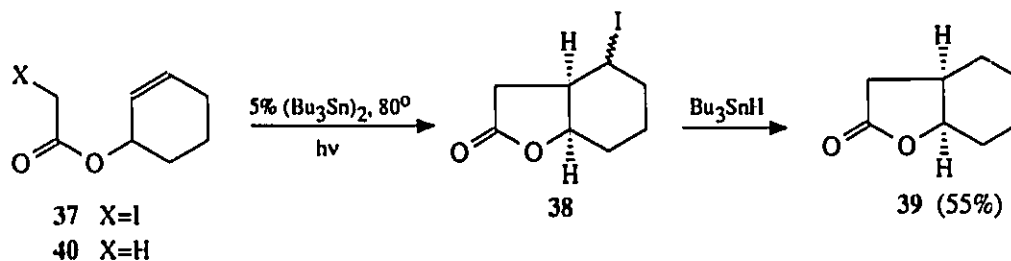
The atom-transfer method involves the common radical chain reaction of adding a reagent X-Y across a C-C double or triple bond (Scheme 15). The classical intermolecular example is the anti-Markovnikov hydrobromination of olefins. Curran's group actively pursued this approach to constructing intramolecular C-C bonds and found

Scheme 15



it to be particularly useful for systems that undergo relatively slow radical closures.^{1a,c} For example, sun lamp irradiation of iodo ester **37** with a catalytic amount of hexabutylditin afforded the bicyclic iodide **38** (Scheme 16). Reduction with Bu_3SnH resulted in lactone **39** in 55% yield from **37**.⁴⁴ In contrast, this same cyclization, when attempted by the tin hydride method even at the moderately low Bu_3SnH concentration of 0.02 M, formed only reduced uncyclized material **40**. In the presence of a strong H-donor such as Bu_3SnH , the relatively slow cyclization of the ester stabilized radical cannot compete with the H-atom transfer.

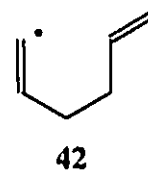
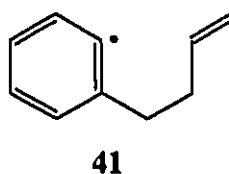
Scheme 16

Aryl Radicals

Aryl radicals, as compared to alkyl radicals, are more reactive so that intramolecular aryl radical additions have rate constants that are two to three orders of

(44) Curran, D.P.; Chang, C.-T. *Tetrahedron Lett.* 1987, 28, 2477.

magnitude greater than those of the comparable alkenyl radicals.⁴⁵ Comparing the Arrhenius equation for 5-exo cyclization of the 5-hexenyl radical



(2)⁴⁶ $\log k_{5\text{-hexenyl}}/s^{-1} = 10.4 - 6.8/\theta$ to the aryl radical analogue, o-butenylphenyl radical (41),⁴⁵ $\log k_{\text{aryl}}/s^{-1} = 11.1 - 3.51/\theta$, suggests that the higher rate of cyclization by aryl radicals is mainly due to a lower E_a . The lower E_a for aryl radicals could in turn be attributed to the high intrinsic reactivity of σ radicals, and the absence of protons at C(1) and C(2) which sterically hinder ring-closure of related alkenyl radicals. This latter observation arose from a comparison of strain energy components to the transition state for the exo ring closure of hexenyl and o-butenylphenyl radicals using MM2 force-field calculations.¹⁹ The data reveal that the o-butenylphenyl radical (41) has more favourable bending and van der Waals (VDW) components, which in turn are associated with the absence of protons at C(1) and C(2) that give rise to non-bonded interactions in the 5-hexenyl radical (2). The primary hydrogen/deuterium isotope effect casts further support for the high reactivity of aryl radicals. Beckwith found the effect of deuterium isotopic substitution on the rate of the abstraction reaction, $\text{Ph}\cdot + \text{Bu}_3\text{SnH}$, to be $k_H/k_D = 1.3$ at 25°C.⁴⁵ This value is considerably smaller than that found for the corresponding alkyl radical 2, k_H/k_D

(45) Abeywickrema, A.N.; Beckwith, A.L.J. *J. Chem. Soc., Chem. Commun.* 1986, 464.

(46) Chatgililoglu, C.; Ingold, K.U.; Scaiano, J.C. *J. Am. Chem. Soc.* 1981, 103, 7739.

– 1.9,⁴⁷ and is consistent with an earlier transition state for these reactive aryl radicals.

Even though the H-atom abstraction from Bu₃SnH is very fast by aryl radicals, with k_{II} greater than 10⁸ M⁻¹s⁻¹ at 50°C, cyclization of the o-butenylphenyl radical (41) is still more efficient than that in the analogous 5-hexenyl radical (2). The ratio k₅+k₆/k_{II} (M), fundamental in determining product outcome, is ca. 6 times larger for the aryl radical 41 than for the 5-hexenyl radical (2) at 50°C.⁴⁸ The rate constant for 5-exo closure of the o-butenylphenyl radical is 3.1x10⁸ s⁻¹, at 25°C.¹⁹ Unfortunately, there is some concern that the rate constant, k_{II}, for aryl radical abstraction from Bu₃SnH as determined by Ingold, is erroneous. In 1985 Ingold and co-workers⁴⁹ published the Arrhenius equation for the reaction Ph• + Bu₃SnH, as log k_{II}/M⁻¹s⁻¹ = (10.0±0.2) - (1.7±0.3)/θ. In their study, the source of phenyl radicals was benzoyl peroxide plus light. This approach, however, was questioned in a subsequent report by Ingold⁵⁰ in which they discovered that ArCO₂• made from aroyl peroxide also reacts with Bu₃SnH. The earlier report, therefore did not pertain to a clean Ph• + Bu₃SnH reaction. Nevertheless, studies since then by Beckwith

(47) Strong, H.J.; Brownawell, M.L.; San Filippo, J. *J. Am. Chem. Soc.* **1983**, 105, 6526. and reference 45.

(48) **5-hexenyl radical (2)**: k₅+k₆/k_{II} is 0.14 M at 50°C from references 46, 22, and 49. **o-butenylphenyl radical (41)**: k₅+k₆/k_{II} is 0.81 M at 50°C, from reference 45.

(49) Johnston, L.J.; Lusztyk, J.; Wayner, D.D.M.; Abeywickrema, A.N.; Beckwith, A.L.J.; Scaiano, J.C.; Ingold, K.U. *J. Am. Chem. Soc.* **1985**, 107, 4594.

(50) Chateauneuf, J.; Lusztyk, J.; Ingold, K.U. *J. Am. Chem. Soc.* **1988**, 110, 2877 and 2888.

and co-workers,⁵¹ gave the similar Arrhenius equation, $\log k_{\text{H}}/\text{M}^{-1}\text{s}^{-1} = 9.6 - 1.7/\theta$, by a nitroxide-trapping technique, which suggests that the Ingold equation cannot be grossly in error. The more appropriate rate constant for these aryl radical cyclizations, that for an o-alkylphenyl radical, was recently determined by laser-flash photolysis⁵² to be ca. $4.0 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ at 50°C which at 80°C is ca. $5.0 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$. At 80°C, the rate constant from the Beckwith laboratories is very similar, $k_{\text{H}} = 3.5 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$, while Ingold's is approximately twice as large, ca. $8.9 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$. It is not unreasonable that the rate constants for H-abstraction from Bu_3SnH by the phenyl radical and the o-substituted phenyl radical are similar, because the effects of steric crowding are sometimes minimal in radical reactions. For example, the rate constant for the reactions of primary, secondary, and tertiary alkyl radicals with Bu_3SnH are essentially equal, and all are ca. $2 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ at 25°C.⁴⁶ The rate constants for aryl radical cyclization to the CN double bond reported in this thesis are based on this recently determined value for k_{H} ($5.0 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$).

Vinyl radicals show reactivity comparable to their aryl counterparts. The rate constant for 5-exo closure of the vinyl radical **42** is⁵³ $k_{5\text{-exo}} = 3 \times 10^8 \text{ s}^{-1}$ at 60°C and is

(51) Abeywickrema, A.N.; Beckwith, A.L.J.; Gerba, S. *J. Org. Chem.* 1987, 52, 4072.

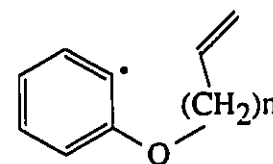
(52) Luszyk, J., personal communication. An Arrhenius equation is currently not available but extrapolating from the Arrhenius equations from references 49 and 51 gives k_{H} ca. $5.0 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ at 80°C for an ortho-substituted aryl radical.

(53) Beckwith, A.L.J.; O'Shea, D.M. *Tetrahedron Lett.* 1986, 27, 4525.

almost identical to that found for the *o*-butenylphenyl radical (41). The rate of H-atom abstraction by vinyl radical 42 from Bu₃SnH is similar as well, with $k_H = 3 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$. The efficiency of closure of vinyl radical 42 is quite high, with $k_c/k_H (\text{M}) \sim 1$, and there are numerous applications of vinyl radical cyclizations in synthesis.⁵⁴

Aryl Radical Cyclization to C=C

The regiochemistry of aryl radical closure to an olefinic functional group resembles that found in the analogous alkenyl radicals.⁵⁵ The aryl equivalent of the 5-hexenyl system, the *o*-butenylphenyl radical (41), ring closes predominately in the 5-exo sense. Intramolecular closure in the oxy derivative 44, as in the alkyl system 16, is regiospecific in the 5-exo mode. Aryl radical 45, with an olefinic bond in the 6,7 position with respect to the radical centre, cyclizes more slowly than radical 44, and the 6-exo mode is highly favoured.^{45,56} The system with an olefinic bond in the 6,7 position is further complicated by a competing pathway involving the 1,5-H-atom transfer resulting



43 n=0
44 n=1
45 n=2

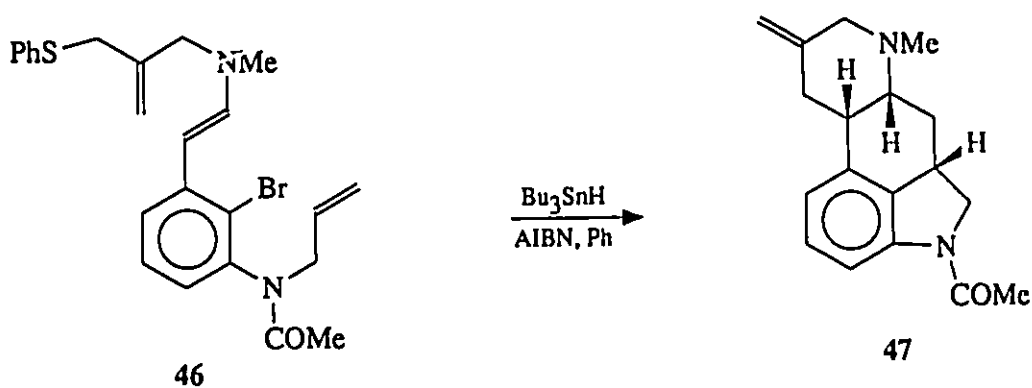
(54) For synthetic applications of intramolecular vinyl radical closures, see: (a) Dulcere, J.P.; Mihoubi, M.N.; Rodriguez, J. *J. Chem. Soc., Chem. Commun.* **1988**, 237. (b) Stork, G.; Mook, R. *J. Am. Chem. Soc.* **1987**, 109, 2829.

(55) Surzur, J.-M. In *Reactive Intermediates*; Abramovitch, A.A., Ed.; Plenum Press: New York, **1981**, Vol. 2, Chapt. 3.

(56) For a recent report of 6- and 7-exo aryl radical closure to C=C, see: Clark, A.J.; Jones, K.; McCarthy, C.; Storey, J.M.D. *Tetrahedron Lett.* **1991**, 32, 2829.

in an allylic radical. Finally, in the lower homologue **43**, in which the olefinic bond is in the 4,5 position, the closure is inefficient so that less than 1% of the isolated product is from 5-endo cyclization; the remaining 94% corresponds to the uncyclized reduced material.⁵⁷ Although the kinetic data for aryl radical closure to an ortho-situated C=C functionality may not be as well known as those for the alkenyl radicals, there are many recent syntheses that utilize these reactive radicals.⁵⁸ In 1990 Cladingboel and Parsons⁵⁹ constructed the lysergic acid derivative **47** by a triple radical cyclization starting with the

Scheme 17



highly functionalized aryl bromide **46** (Scheme 17). After stannyl radicals abstract the Br-atom the tandem cyclization commences with an aryl radical 5-exo attack on C=C, that

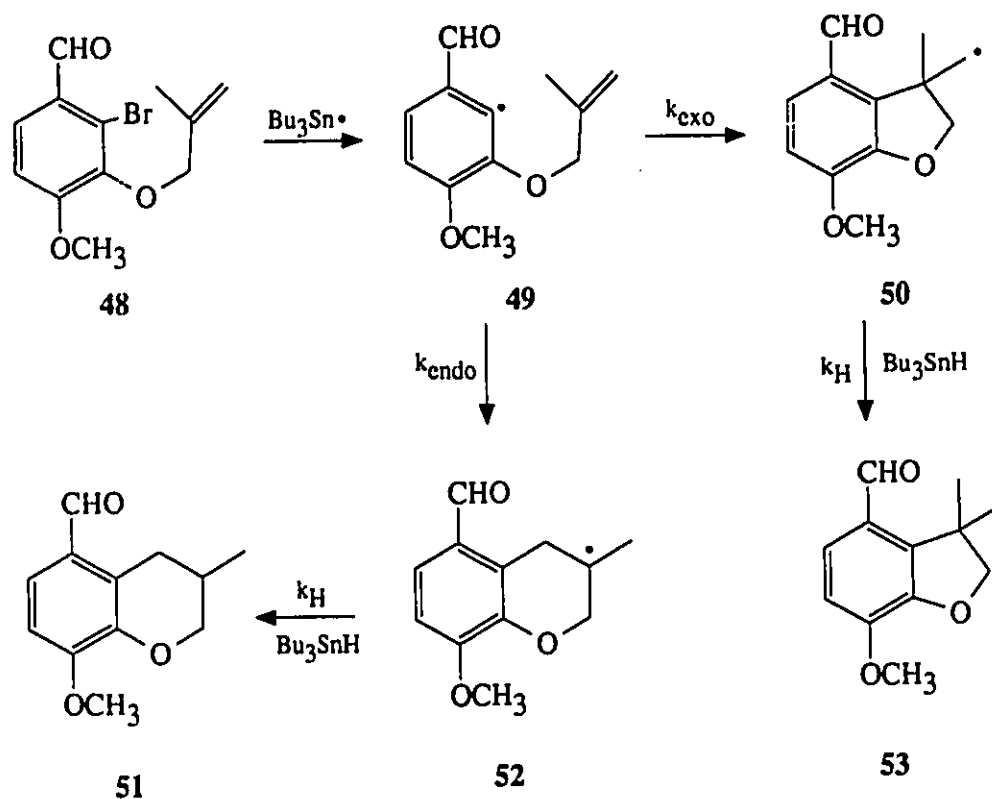
(57) Beckwith, A.L.J.; Gara, W.B. *J. Chem. Soc., Perkin Trans. II* 1975, 795

(58) For additional examples, see: (a) Dittami, J.P.; Ramanathan, H. *Tetrahedron Lett.* 1988, 29, 45. (b) Bowman, W.R.; Heaney, H.; Jordan, B.M. *Tetrahedron Lett.* 1988, 29, 6657.

(59) Cladingboel, D.E.; Parsons, P.J. *J. Chem. Soc., Chem. Commun.* 1990, 1543.

is followed by two consecutive 6-endo alkyl radical closures to C=C bonds. The second ring closure can only occur in the endocyclic mode because of the 6,5 fused ring system formed from the chain.

Scheme 18

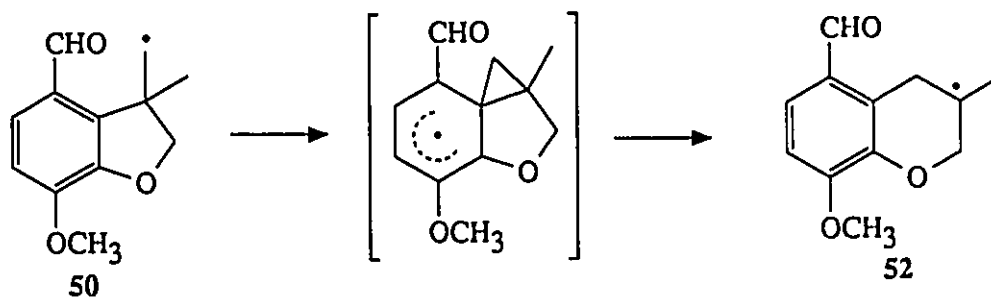


Parker⁶⁰ and Beckwith⁵¹ independently discovered aryl radical systems that gave surprisingly large amounts of 6-endo cyclized products (Scheme 18). In addition, the ratio of cyclized products, 5-membered to 6-membered, depended on the concentration of Bu_3SnH . Subjecting the aryl bromide 48 to a tin hydride concentration of 0.02 M (used

(60) Parker, K.A.; Spero, D.M.; Inman, K.C. *Tetrahedron Lett.* 1986, 27, 2833.

in large excess) resulted in a 5-exo to 6-endo product ratio (53 to 51) of 44:56 but at a Bu_3SnH concentration of 0.5 M (large excess) the ratio changed to 90:10.⁵¹ This finding is not consistent with the general mechanism as shown in Scheme 18, which is based on direct closure of the intermediary radical 49 to 5-exo and 6-endo products. As the ring closures are unlikely to be reversible, it was proposed that an additional pathway involving the neophyl rearrangement of 5-exo radical 50 to the 6-endo radical 52 was operative at low tin hydride concentrations (Scheme 19). At the low tin hydride concentrations the lifetime of the 5-exo radical 50 is extended allowing the unimolecular rearrangement to compete with its trapping by Bu_3SnH . The driving force for this 1,2 aryl shift includes the formation of a more stable six-membered ring, and a more stable tertiary radical from a primary one. The acceleration of neophyl rearrangements by electron withdrawing substituents on the aromatic nucleus has been well documented.⁷

Scheme 19

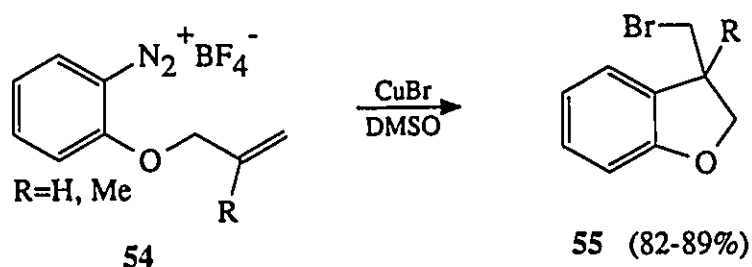


Although radical cyclization reactions are most often carried out by the tin hydride method, this approach has some significant drawbacks. Aside from the fact that yields of cyclized product suffer because of the formation of reduced uncyclized material,

commercial application of the tin method carried out with molar quantities of tin compounds presents a disposal problem. In addition, the tin hydride method is often done well above ambient temperature to initiate radical formation from AIBN. This heating may decompose thermally unstable compounds and it diminishes the regioselectivity of the ring closure. For example, the 5-exo/6-endo regioselectivity of the 5-hexenyl radical (2) drops from ca. 60:1 at 25°C to ca. 30:1 at 100°C.^{19,22}

In light of these observations, Meijs and Beckwith⁶¹ used a non-stannyl generated source of aryl radicals, one derived from arenediazonium tetrafluoroborates **54** and copper(II) bromide (Scheme 20). Dihydrobenzofurans **55** were formed at room temperature in excellent yields of 82-89%, using this copper-based "Sandmeyer" dediazonation reagent with DMSO as solvent. The reaction mixture was free of 6-endo

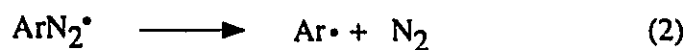
Scheme 20



product and uncyclized material. This reaction is believed to follow a radical chain mechanism (Scheme 21), as traces of copper(I) initiate the reaction by donating an

(61) Meijs, G.F.; Beckwith, A.L.J. *J. Am. Chem. Soc.* 1986, 108, 5890.

Scheme 21



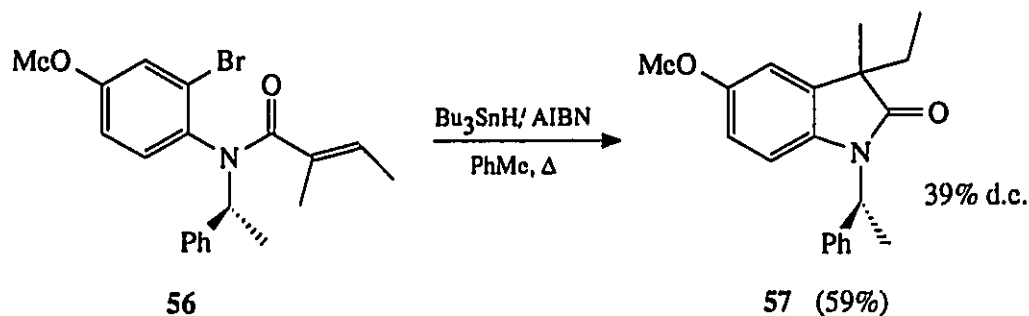
electron to the diazonium salt forming the diazenyl radical (eq 1), a rather labile species that in turn gives up dinitrogen to form an aryl radical (eq 2). The aryl radical can now undergo an intramolecular cyclization to generate the cyclized radical R• (eq 3). In the chain-transfer step (eq. 4), copper(II) bromide undergoes a ligand transfer to the cyclized radical R• to yield RBr and regenerate copper(I), which may further propagate the chain (eq 4). The many ways of generating aryl radicals from arenediazonium ions are reviewed by Galli.⁶²

Jones and McCarthy have published recently an example of chiral induction in aryl radical cyclization to olefins (Scheme 22).⁶³ They found that optically active ortho-haloacryloyl anilide **56** undergoes radical cyclization to produce oxindoles **57** with diastereomeric excess (d.e.) of 39%. In the absence of methyl groups on the olefinic carbons, the diastereoselectivity dropped to only 2%, indicating that there are important interactions between the methyl group(s) and the chiral auxiliary that aid the diastereoselectivity.

(62) Galli, C. *Chem. Rev.* **1988**, *88*, 765.

(63) Jones, K.; McCarthy, C. *Tetrahedron Lett.* **1989**, *30*, 2657.

Scheme 22



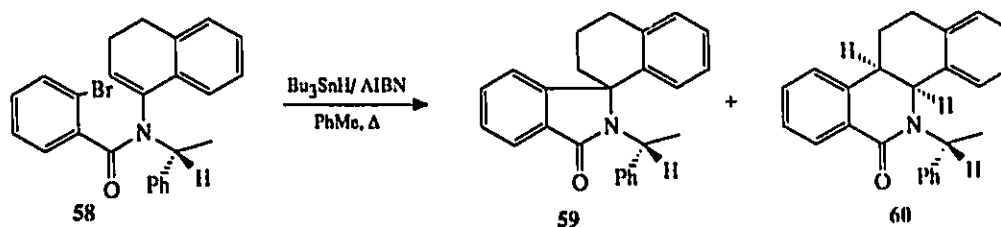
The only other example of chiral induction in aryl radical cyclization to C=C is that by Takano and co-workers.⁶⁴ The optically active enamide **58** undergoes both 5-exo and 6-endo cyclizations (Scheme 23). The exocyclic pathway affords the indoline derivative **59** in 20% yield with a diastereomeric excess (d.e.) of 43% while the endocyclic route gives a 20% yield of isoquinoline **60** with d.e. of 33%. The stereochemistry of the B/C ring juncture in the latter product is *cis* as deduced from the magnitude of the coupling constant in the ^1H NMR spectrum. The absolute stereochemistry, however, was not determined.

Aryl Radical Cyclization to C≡C

The regiochemistry of closure of alkyl and aryl radicals to C≡C functionality is very similar to that found with the C=C group, but the rates of ring closure are generally slower with the alkynes.⁵⁵ The process is most efficient in the 5-exo/6-endo case,

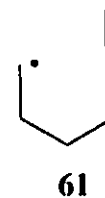
(64) Takano, S.; Suzuki, M.; Kijima, A.; Ogasawara, K. *Tetrahedron Lett.* 1990, 31, 2315.

Scheme 23



less so in the 6-*exo*/7-*endo* systems, and does not operate well for the lower homologues. The regiochemistry, in accord with Beckwith's first guideline, is in the exocyclic sense. The rate constant for cyclization of 5-hexynyl radical⁶⁵ (**61**) is $k_{5\text{-exo}} = 2.6 \times 10^5 \text{ s}^{-1}$ at 80°C, and is almost one order of magnitude slower than that for 5-hexenyl⁴⁶ (**2**), $k_{5\text{-exo}} = 1.5 \times 10^6 \text{ s}^{-1}$, at the same temperature. This difference in rates may be explained in terms of Frontier Molecular Orbitals. As alkynes possess higher LUMO's and HOMO's of lower energies in comparison to alkenes (Scheme 7), the interaction between the SOMO and these frontier orbitals of the π -system is considerably poorer in the case of the alkynes.²⁹

Although there are relatively few examples of aryl radical cyclizations to alkynes,^{66,67} the work of Boger and co-workers,⁶⁸



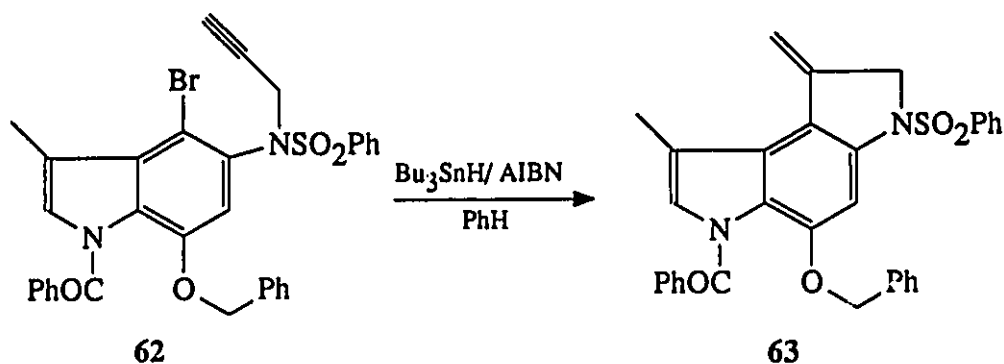
(65) Barton, D.H.R.; Crich, D.; Kretzschmar, G. *J. Chem. Soc., Perkin Trans. I* 1986, 39.

(66) For an example of aryl radical cyclization to the α -position of α,β -unsaturated (C \equiv C) N-alkylamides, see: reference 58b.

(67) For an example of aryl radicals generated from arenediazonium salts cyclizing to C \equiv C, see: Beckwith, A.L.J.; Meijs, G.F. *J. Org. Chem.* 1987, 52, 1922.

(68) Boger, D.L.; Coleman, R.S. *J. Am. Chem. Soc.* 1988, 110, 4796.

Scheme 24



demonstrates well the potential of this particular ring closure. En route to their total synthesis of antibiotic CC-1065, Boger subjected the alkynyl substituted aryl bromide **62** to Bu_3SnH and AIBN and produced the tricyclic compound **63** in 72% yield.

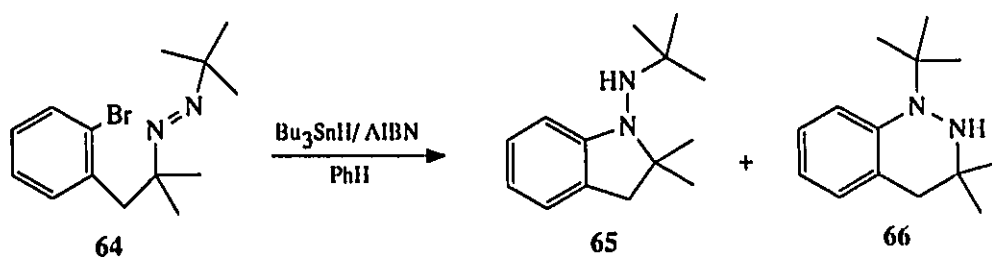
Aryl Radical Cyclization to N=N

Closures to the azo group by aryl radicals have been examined most recently by Beckwith, Wang and Warkentin.⁶⁹ Aryl radicals, given the choice of a 5-exo or 6-endo intramolecular attack on an azo functionality, surprisingly favoured a 6-endo attack (Scheme 25). This is in striking contrast to the analogous closure of aryl radicals to olefins. For the aryl azo system **64**, the ratio of rate constants for closure, k_5/k_6 is 0.65 at 82°C, while for the *o*-butenylphenyl radical (**41**), k_5/k_6 is greater than 50, at 82°C.¹⁹ Furthermore, the aryl radical closures to both termini of the azo functionality, giving **65** and **66**, are rapid with $k_{6\text{-endo}} = 1.3 \times 10^9 \text{ s}^{-1}$ and $k_{5\text{-exo}} = 8.4 \times 10^8 \text{ s}^{-1}$ at 82°C, based⁵² on k_{11}

(69) Beckwith, A.L.J.; Wang, S.; Warkentin, J. *J. Am. Chem. Soc.* 1987, 109, 5289.

= $5.0 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$. These rate constants are in the same region as those for 5-exo closure of the *o*-butenyl phenyl radical for which k_5 is ca. $8.4 \times 10^8 \text{ s}^{-1}$ at 80°C using the slightly different $k_{11} = 8.0 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ at 80°C .⁴⁵

Scheme 25



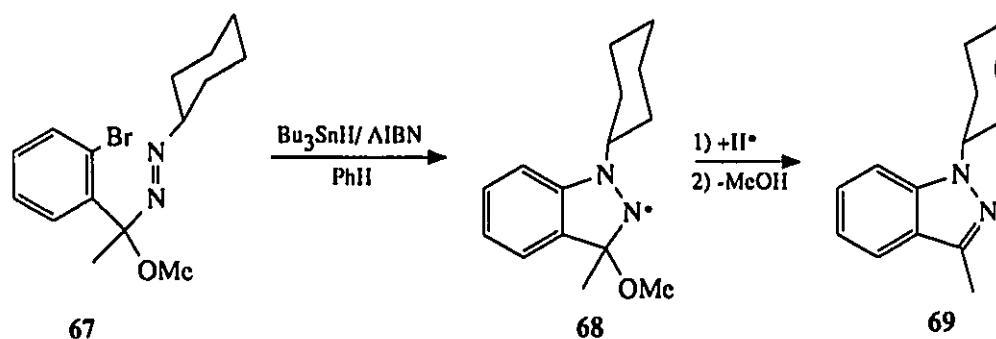
This dramatic change in regioselectivity is attributed to the particular geometry associated with the azo functionality. Firstly, the azo double bond (1.22 \AA) is shorter than that in alkenes (1.34 \AA), and secondly, the bond angle $\text{N}=\text{N}-\text{C}$ of $114\text{--}115^\circ$ is smaller than that in alkenes ($\text{C}=\text{C}-\text{C}$ is ca. 120°). Double bond shortening and angle tightening in the azo system improves the interorbital alignment in the transition state between the SOMO and LUMO. As well, the high rates are likely due in part to gem-dimethyl substitution which is known to increase k_5 by ca. one order of magnitude in the alkenyl radicals.²² The gem-dimethyl effect, otherwise known as the Thorpe-Ingold effect, is believed to accelerate rates by introducing extra gauche interactions in the ground state which are relieved at the cyclic transition state.²²

Kunka and Warkentin,⁷⁰ have demonstrated another interesting aspect of the

(70) Kunka, C.P.K.; Warkentin, J. *Can. J. Chem.* 1990, 68, 575.

azo group, that of free radical acceptor in the little found 5-endo sense (Scheme 26). Treatment of aryl bromide **67** with Bu_3SnH , and a catalytic amount of AIBN in refluxing benzene, gave the indazole **69** in 92% yield. The intermediate hydrazyl radical **68**, after abstracting an H-atom, eliminates methanol producing indazole **69**. The propensity for closure by the aryl radical derived from **67** is huge, as $k_{5\text{-endo}}/k_{\text{H}}$ (M) is ca. 15 at 80°C and is similar to that found for the *o*-butenyloxy aryl radical (**44**).⁴⁵ The facility of 5-endo aryl

Scheme 26

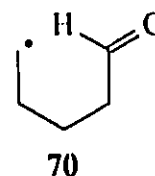


radical closures to the azo group, as shown by the magnitude of $k_{5\text{-endo}}$ which is $7.5 \times 10^9 \text{ s}^{-1}$ at 80°C ,⁷¹ is in large contrast to the analogous closure to C=C in **40**. For example, radical **43** yields less than 1% of cyclized product even though the resulting radical from 5-endo closure would be stabilized by the adjacent lone pairs on oxygen.⁵⁷

(71) Calculated using Luszyk's k_{H} , see reference 52.

Cyclization to C=O

Based on thermochemical grounds, alkyl or aryl radical closure to C=O is surmised to be unfavourable. A strong CO π bond (88 kcal/mol) is broken and a weaker CC σ bond (82 kcal/mol) is formed.⁷² Not surprisingly then, the ΔG° for the 5-exo ring closure of 4-formyl butyl radical (70), as calculated by the group additivity method, is endoergonic by 7.1 kcal/mol, while the closure of the 5-hexenyl radical (2) is exoergonic, $\Delta G^\circ = -12.6$ kcal/mol.⁷³ In fact, the reverse reaction, β -scission of alkoxy radicals to generate the carbonyl group is well known and has been utilized in synthesis.⁷⁴



Nonetheless, some recent syntheses of carbohydrate derivatives involve efficient alkyl radical closures to C=O,⁷⁵ predominately 6-exo closures to the C-atom of aldehydes. For example, Fraser-Reid and Tsang⁷⁶ carried out the 6-exo cyclization of the carbohydrate-derived iodoaldehyde 71 to the cyclohexanol derivative 72 in 85% yield (Scheme 27). An in-depth study of the kinetics of radical closures to aldehydes by Beckwith,⁷³ and confirmed more recently by Fraser-Reid⁷⁵, explains the preponderance of

(72) Average bond energies taken from reference 18 p.162.

(73) Beckwith, A.L.J.; Hay, B.P. *J. Am. Chem. Soc.* **1989**, 111, 2674.

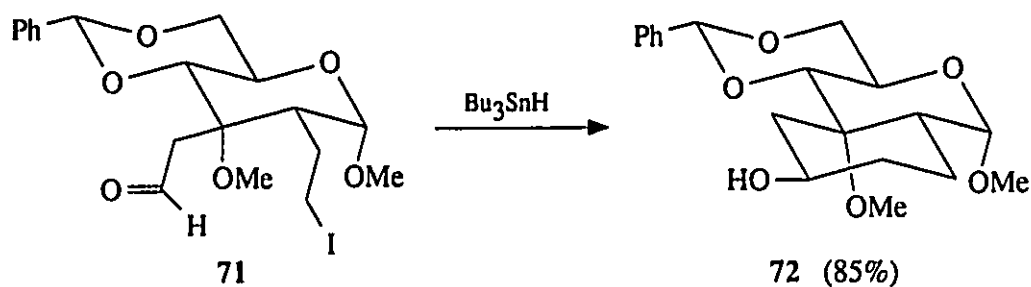
(74) For example, see: Schreiber, S.L.; Liew, W.-F. *J. Am. Chem. Soc.* **1985**, 107, 2980.

(75) Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1991**, 113, 5791., and references therein.

(76) Tsang, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1986**, 108, 2116.

6-exo closures as well as the inefficacy of the 5-exo route.

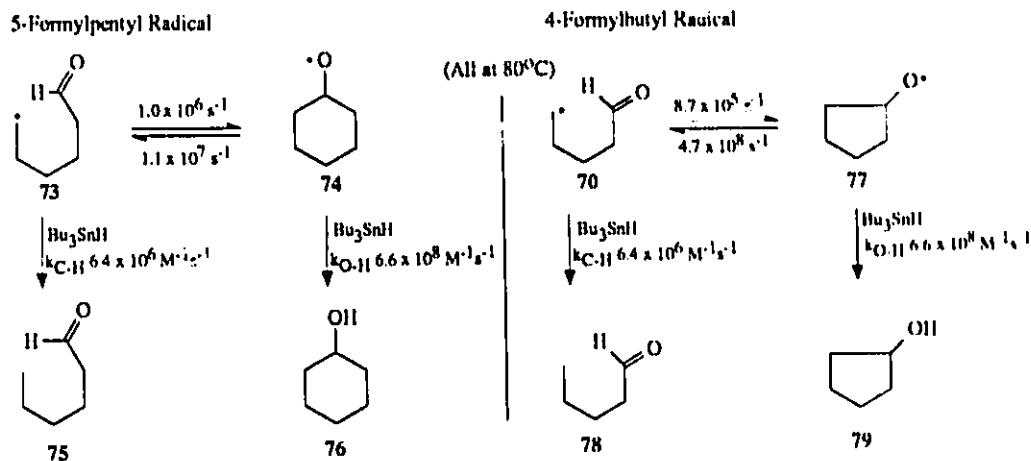
Scheme 27



Beckwith and Hay carried out their kinetic studies on the 4-formylbutyl radical (70) and the 5-formylpentyl radical (73). Both were generated from the corresponding bromides by the tin hydride method (Scheme 28). Radical cyclization of the 5-formylpentyl radical (73) proceeds quite readily in the 6-exo mode with rate constant, $k_{6\text{-exo}}$ of $1.0 \times 10^6 \text{ s}^{-1}$ at 80°C , yielding the reactive alkoxy radical 74. This rate constant is almost identical to that for the 5-hexenyl radical⁴⁶ (2), $k_{5\text{-exo}} = 1.5 \times 10^6 \text{ s}^{-1}$ at 80°C . Although, the cyclohexyloxy radical (74) reverts back with a rate constant that is one order of magnitude greater than that leading to it, the higher reactivity of alkoxy radicals as compared to alkyl radicals (some two orders of magnitude) means that the majority of product will be cyclohexanol (76).

The greater amount of ring closed product from the 5-formylpentyl radical (73) as compared to its lower homologue, 4-formylbutyl radical (70), is explained by comparing the relative rates for their ring closures and β -scissions (Scheme 28). The rate constant for 6-exo closure of 5-formylpentyl radical (73) is slightly larger than that for

Scheme 28

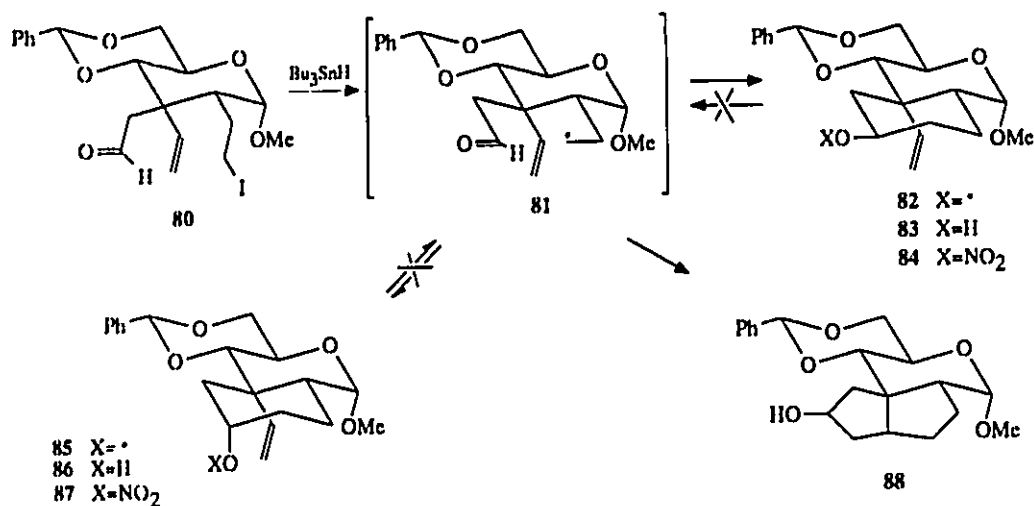


5-exo closure in 4-formylbutyl radical (70). The rate constant for β -scission of the cyclopentoxy radical (77), however, is substantially larger than that for the cyclohexoxy radical (74), and hence a greater amount of cyclized product is derived from the 5-formylpentyl radical (73). This difference in rate constants for β -scissions has been attributed to the estimated 6.5 kcal/mol ring strain associated with the cyclopentyl ring. Intramolecular 1,5 H-atom transfer, through a six-membered transition state, is an additional competing pathway in the 4-formylbutyl radical which decreases the amount of cyclized product.

Recent experiments by Fraser-Reid and co-workers,^{75, 77} on 6-exo alkyl closure to aldehydes, have shown that under appropriate reaction conditions (relatively high $[\text{Bu}_3\text{SnH}]$) closure to the aldehyde group is irreversible (Scheme 29). The primary alkyl radical 81, generated by iodine atom abstraction by $\text{Bu}_3\text{Sn}^\bullet$ from 80, produced

(77) Fraser-Reid, B.; Vite, G.D.; Yeung, B.A.; Tsang, R. *Tetrahedron Lett.* 1988, 29, 1645.

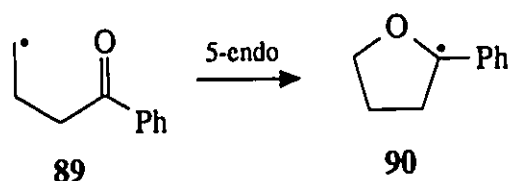
Scheme 29



cyclohexanol derivative **83** (78%) and the diquinane **88** (18%). However, when the cyclohexyloxy radical **82** was generated independently from the nitrate **84** with Bu_3SnH , the only product was **83**. Furthermore, the epimeric alkoxy radical **85**, formed independently from the nitrate **87**, gave only the corresponding alcohol **86**. These results strongly imply that this particular closure to $\text{C}=\text{O}$ is not reversible!

Cyclization to the oxygen atom Scheme 30

of $\text{C}=\text{O}$ functionality have likewise been observed.^{7,78} In a competition involving 4-exo to C-atom and 5-endo to O-atom cyclization in radical **89**, the latter takes



place exclusively yielding the highly stabilized radical **90**. The ratio of cyclized furan product to acyclic reduced phenyl ketone is 4:1, when the reaction is conducted by the

(78) Menapace, L.W.; Kuivila, H.G. *J. Am. Chem. Soc.* 1964, 86, 3047.

tin hydride method (Scheme 30). The utility of this system of closure is further advanced by the relatively high ratio for $k_{5\text{-endo}}/k_{11}$ (M) which is ca. 1.6.⁷

Examples of aryl radical closures to C=O are scarce. Beckwith⁷⁹ has studied intramolecular aryl radical closure to methyl ketones in which the radical **92**, obtained from the bromide **91**, undergoes 5-exo closure giving the cyclopentoxy radical **94** (Scheme 31). This intermediary alkoxy radical **94** undergoes β -scission affording **95** rather than abstracting from Bu_3SnH so that none of the cyclized product **93** was detected. In light of the high dissociation energy of C-C_{aryl} bonds in comparison to C-C_{alkyl} bonds, the β -scission forms the thermodynamically more stable alkyl radical **95**. An additional driving force for this mode of ring opening is stabilization offered by the ester functionality. Overall, this reaction sequence has resulted in a 1,4-acyl group migration, albeit in a relatively low yield of 26%. The tendency for 5-exo closure to methyl ketones (k_5/k_{11} (M) = ca. 0.01 M at 80°C) is considerably lower than that for the related *o*-butenylphenyl radical (**41**),⁴⁵ in which k_5/k_{11} (M) is ca. 1.1 at 80°C.

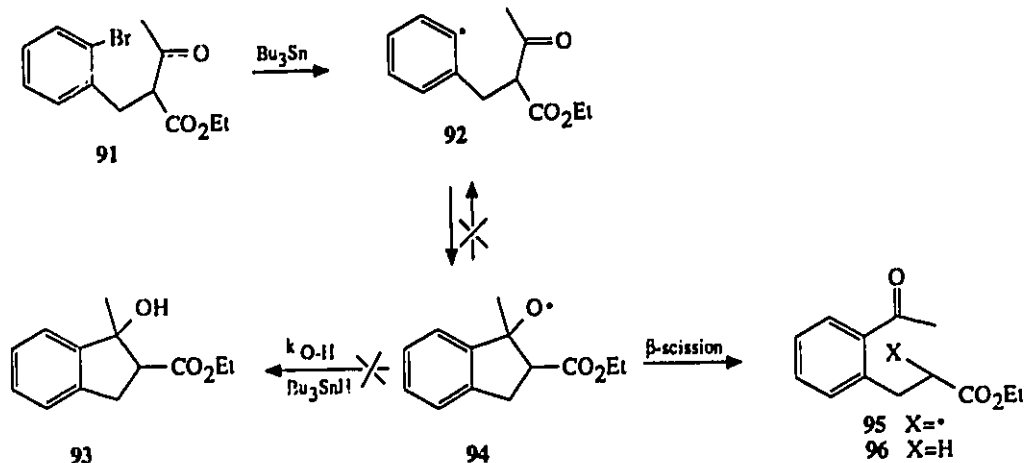
Cyclization to C \equiv N

The rate constant for 5-exo cyclization of the 4-cyanobutyl radical (**97**) is $k_{5\text{-exo}} = 3.9 \times 10^3 \text{ s}^{-1}$ at 25°C,⁸⁰ and it is some two orders of magnitude smaller than that found

(79) Beckwith, A.L.J.; O'Shea, D.M.; Westwood, S.W. *J. Am. Chem. Soc.* **1988**, *110*, 2565.

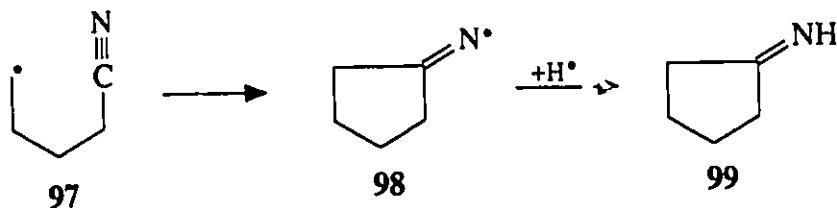
(80) Griller, D.; Schmid, P.; Ingold, K.U. *Can. J. Chem.* **1979**, *57*, 831.

Scheme 31



for the 5-hexenyl radical (2) (Scheme 32). Alkyl radical closure to $\text{C}\equiv\text{N}$ leads to an iminyl radical 98 which in the presence of a good H-donor leads to the easily hydrolyzable imine 99.⁸¹ Cyclizations other than to the C-atom of $\text{C}\equiv\text{N}$ have not been found.⁸²

Scheme 32



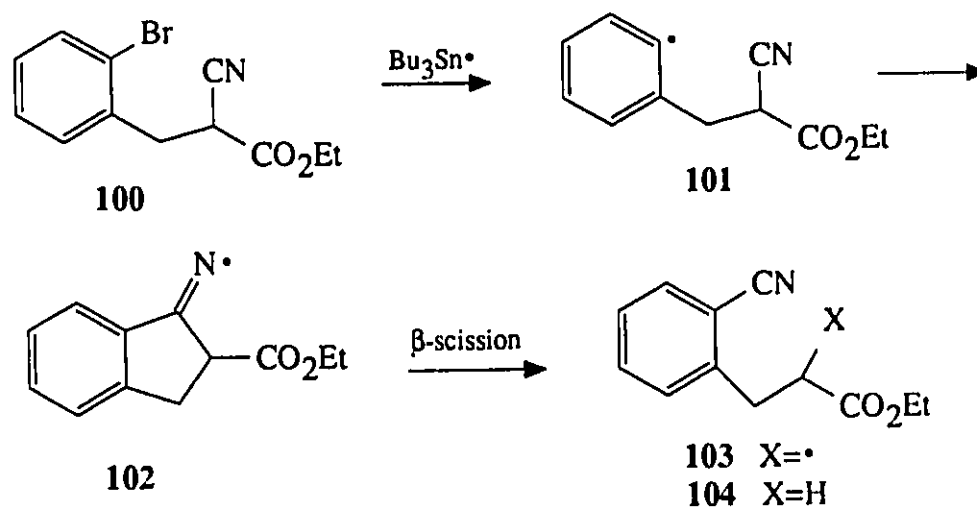
In contrast the intramolecular aryl radical cyclization to $\text{C}\equiv\text{N}$, as studied by

(81) For other examples of cyclizations to $\text{C}\equiv\text{N}$, see: (a) Clive, D.L.J.; Beaulieu, P.L.; Set, L. *J. Org. Chem.* 1984, 49, 1313. (b) reference 76.

(82) reference 55 p.210.

Beckwith and co-workers,⁷⁹ does not afford a ring closed product (Scheme 33). For example, aryl radical **101** derived from the bromide **100**, cyclizes to the iminyl radical **102**. The iminyl radical **102** effectively ring opens to migrate the cyano group 1,4 and gives the ester stabilized radical **103** which, after H-atom abstraction, yields **104**. The absence of bicyclic product derived from **102** suggests that H-atom transfer by Bu_3SnH (1.2 equiv, 0.05 M) occurs too slowly to compete with ring opening of **102**. The tendency for ring closure to the cyano group in aryl radical **101**, $k_{5-\text{exo}}/k_{\text{H}}$ (M), is ca. 0.15 and is between that found for closure to C=C in *o*-butenylphenyl radical (**41**) ($k_{\text{c}}/k_{\text{H}}$ (M) \sim 1.1) and to C=O in arylacyl radical **92**, $k_{\text{c}}/k_{\text{H}}$ (M) \sim 0.01, all at 80°C.

Scheme 33



Cyclizations to C=N-X, where X is an O or N-atom

In the last three to four years, there have been numerous reports concerning

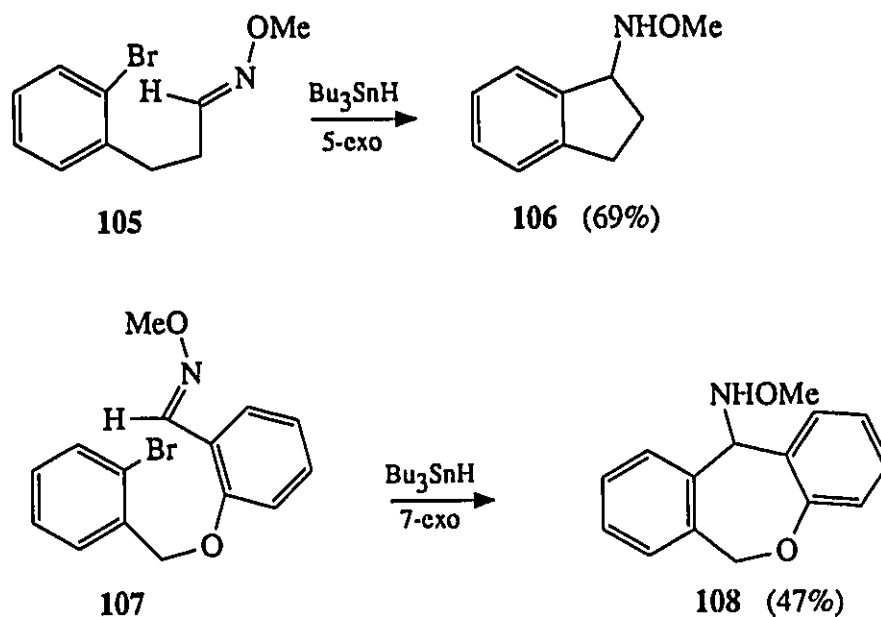
radical cyclization to oximes⁸³ and one to N-aziridinyl imines.⁸⁴ All reported cyclizations to the hydroxyimino functionality are in the exocyclic mode and are exclusively to the C-atom. The majority have involved alkyl radical attack in either the 5-exo^{83d,f} or the 6-exo sense.^{83b,d,e} There are several examples involving cyclization of the reactive vinyl radical in 5-exo^{83c} and 6-exo^{83a,c} modes and only two examples of aryl radical^{83a} closure to oximes. For example, the aryl radical derived from bromide **105** closes in the 5-exo sense to the oxime methyl ether producing indane **106** in 69% yield. By a similar process, ether **107** provides the 7-exo product **108** in 47% yield (Scheme 34).

Bartlett and co-workers,^{83d} studied alkyl radical closures to benzyloxime ether functionality and compared aldoximes (**109**, R₃=H) to ketoximes (**109**, R₃=Me) as radical acceptors, as well as the effect of chain length (**109**, n=1 or 2) on product distribution; the ratio of **110** to **111** (Scheme 35). They found that regardless of whether it was an aldoxime or a ketoxime, the shorter chain system (**109**, n=1) resulted in more cyclized material **110**. Furthermore, for a given chain length, the aldoximes (**109**, R₃=H) cyclized more readily than the ketoximes (**109**, R₃=Me). This result is in accord with Beckwith's

(83) (a) Booth, S.E.; Jenkins, P.R.; Swain, C.J. *J. Chem. Soc., Chem. Commun.* 1991, 1248. (b) Marco-Contellas, J.; Martinez-Grau, A.; Bernabe, M.; Martin, N.; Seoane, C. *Synlett* 1991, 165. (c) Enholm, E.J.; Burroff, J.A.; Jaramillo, L.M. *Tetrahedron Lett.* 1990, 31, 3727. (d) Bartlett, P.A.; McLaren, K.L.; Ting, P.C. *J. Am. Chem. Soc.* 1988, 110, 1633. (e) Parker, K.A.; Spero, D.M.; Van Epp, J. *J. Org. Chem.* 1988, 53, 4628. (f) Corey, E.J.; Pyne, S.G. *Tetrahedron Lett.* 1983, 24, 2821.

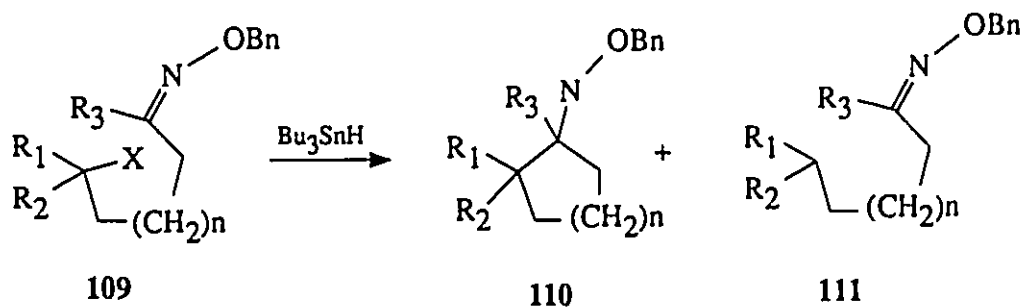
(84) Kim, S.; Kee, I.S.; Lee, S. *J. Am. Chem. Soc.* 1991, 113, 9882.

Scheme 34



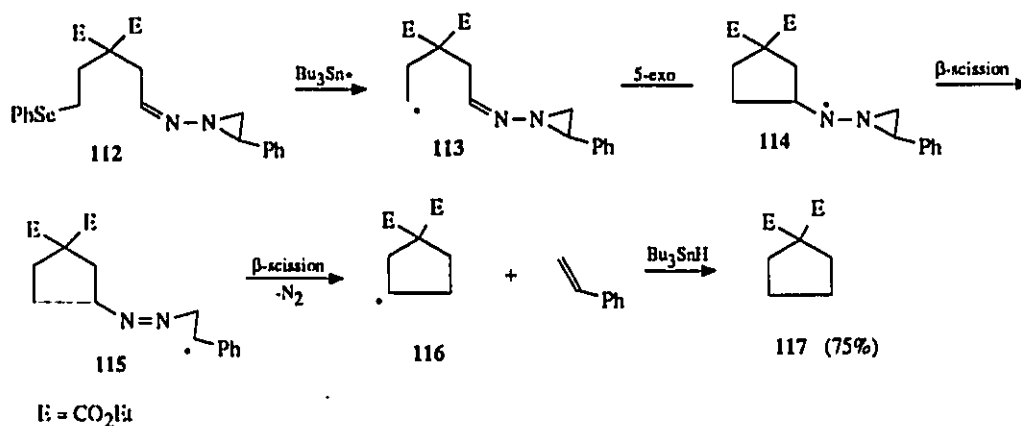
second guideline, and the predicted retardation in rate due to the presence of the Me group at the terminus of alkyl radical attack. However, the stereoselectivity in cyclic product **110** was generally quite low and favoured the *cis* product in the cyclopentane series and the *trans* product in the cyclohexane series, consistent with the chair-like transition state proposed by Beckwith (Scheme 12).³¹

Scheme 35



A novel cyclization approach recently published by Kim and co-workers⁸⁴ deals with intramolecular alkyl and vinyl radical attack on N-aziridinyl imines (Scheme 36). For example, the alkyl radical **113** derived from the phenyl selenide **112**, ring closes by attacking the C-atom of the C=N-N functionality in the 5-exo mode to form the cyclopentanylhazyl radical **114**. The first β -scission, that in hazyl radical **114**, relieves the strain of the three-membered aziridine ring to produce **115**, and the second β -scission ejects dinitrogen, styrene, and the cyclopentyl radical **116**. The yield of cyclopentane derivative **117** was 75%.

Scheme 36

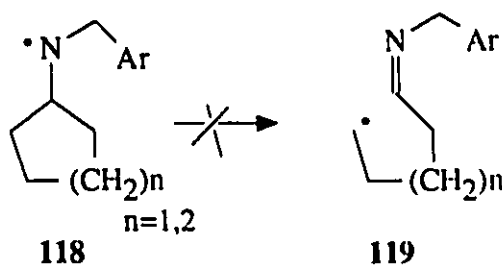


Cyclization to C=N

It is not unreasonable to expect radical closure to imines to be effective. Closure to the C-atom of the imino group creates an aminyl radical which, unlike an alkoxy radical, is not prone to β -scissions. For example, the cyclopentyl- and

Scheme 37

cyclohexylaminyl radicals **118** ($n=1$ and $n=2$, respectively), created from Bu_3SnH and the corresponding phenylsulfides, supply none of the ring opened imine **119** nor any product derived from it.⁸⁵



Radical closure in the other sense, to the N-atom of an imine, creates an α -aminoalkyl radical, whose stability is well known.⁸⁶ Hence, the thermochemistry of radical addition to the imino group is expected to be quite favourable. This point may be illustrated by comparing the thermochemistry of five related model reactions; H atom addition to ethylene, acetylene, acetonitrile, methanimine, and formaldehyde. The heats of formation,^{80,87,88} ΔH_f° in kcal/mol (and corresponding references) are: H^\bullet , 52.1 (80); C_2H_4 , 12.4 (88); $\text{C}_2\text{H}_3^\bullet$, 25.9 (87); C_2H_2 , 54.3 (87); $\text{H}_2\text{C}=\dot{\text{C}}\text{H}$, 70.4 (88); $\text{CH}_3\text{C}\equiv\text{N}$, 19.0 (80); $\text{H}_3\text{C}-\text{HC}=\text{N}^\bullet$, 34.4 (80); $\text{H}_2\text{C}=\text{NH}$, 26.4 (87); $\text{H}_3\text{C}-\dot{\text{N}}\text{H}$, 42.4 (88); $\text{H}_2\dot{\text{C}}-\text{NH}_2$, 35.7 (88); $\text{H}_2\text{C}=\text{O}$, -27.3, (87); $\text{H}_3\text{C}-\text{O}^\bullet$, 4.2 (88); $\text{H}_2\dot{\text{C}}-\text{OH}$, -6.2 (88). Scheme 38 shows the calculated exothermicities of these five model reactions. The thermochemistries for H^\bullet addition to the C-atom of $\text{C}=\text{N}$, to $\text{C}=\text{C}$, and to $\text{C}\equiv\text{C}$ are comparable and more favourable

(85) Bowman, W.R.; Clark, D.N.; Marmon, R.J. *Tetrahedron Lett.* **1991**, 32, 6441.

(86) Griller, D.; Lossing, F.P. *J. Am. Chem. Soc.* **1981**, 103, 1586.

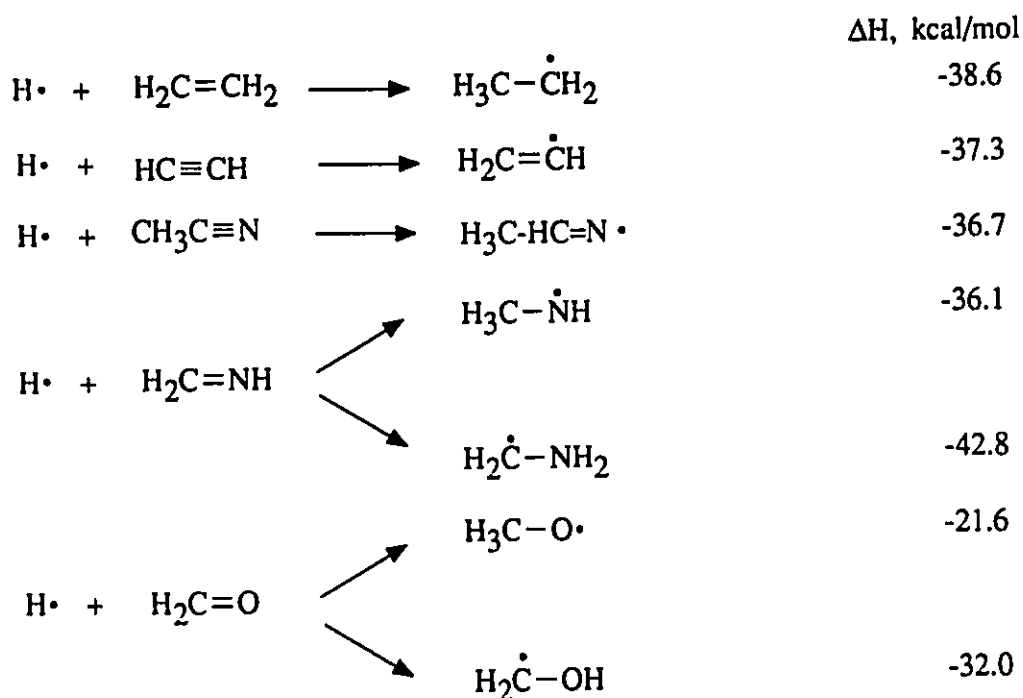
(87) Olivella, S.; Urpi, F.; Vilarrasa, J. *J. Comput. Chem.* **1984**, 5, 230.

(88) McMillen, D.F.; Golden, D.M. *Ann. Rev. Phys. Chem.* **1982**, 33, 493.

than that for addition to C of the C=O functionality. The most exothermic process, however, is the addition to the N-atom of C=N creating the stable α -aminoalkyl radical.

The ring opening of strained three- and four-membered rings affording imines are known to be fast.⁸⁹ Photolysis of N-methylaziridine (120) in cyclopropane with *t*-butyl peroxide (10-30%) at -130 to -140°C produced an esr spectrum consistent with the

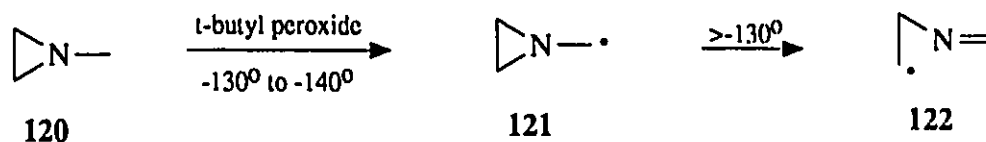
Scheme 38



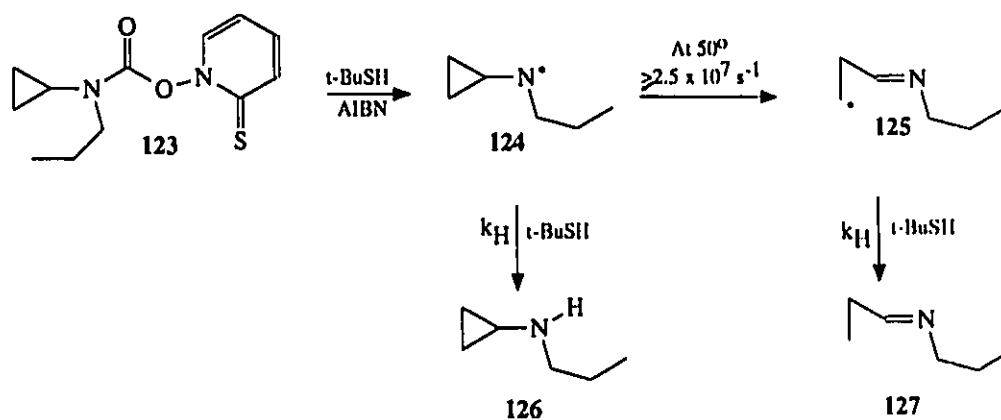
1-aziridylcarbiny radical (121) (Scheme 39). At temperatures above -130°C, on the other hand, the esr spectrum fit the ring opened iminoalkyl radical 122. Newcomb and co-

(89) Danen, W.C.; West, C.T. *J. Am. Chem. Soc.* 1974, 96, 2447.

Scheme 39



Scheme 40

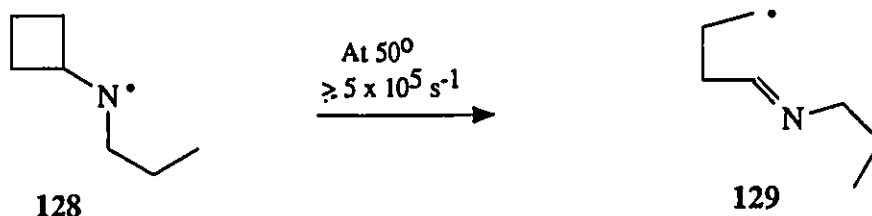


workers⁹⁰ generated the cyclopropylamino radical **124** from the carbamate **123** and in the presence of a large excess of t-BuSH could trap some of **124** before it opened to **125** (Scheme 40). From the ratio of **126** to **127** they could estimate the lower limit for k_R as $2.5 \times 10^7 \text{ s}^{-1}$ at 50°C . Using the same approach, the ring opening of the cyclobutylaminy radical **128** to the imine **129**, was found to be approximately 50 times slower ($k \geq 5 \times 10^5$)

(90) Newcomb, M.; Park, S.-U.; Kaplan, J.; Marquardt, D.J. *Tetrahedron Lett.* 1985, 26, 5651.

s^{-1} at $50^{\circ}C$, Scheme 41).⁹¹ Radical cyclizations to the imino functional group have been little explored in the past and kinetic studies involving the imino group are scarce. Roberts and Winter,⁹² back in 1978, found that the intermolecular addition of methyl or propyl radicals to N-methylene-t-butylamine ($BuN=CH_2$) is a relatively rapid process with k_{add} ca. 10^2 - $10^3 M^{-1}s^{-1}$ at $-3^{\circ}C$ and the addition is strictly to the C-atom.⁹³ This rate constant is comparable to, or even larger than, that for addition of ethyl radical to ethylene ($k_{add} \sim 2 \times 10^2 M^{-1}s^{-1}$ at $-3^{\circ}C$).⁹⁴

Scheme 41



Some indirect evidence for the intramolecular addition to C=N comes from the pyrolytic studies on 3-alkylindoles (Scheme 42).⁹⁵ Heating 3-benzylindole (130) to

(91) Maeda, Y.; Ingold, K.U. *J. Am. Chem. Soc.* 1980, 102, 328.

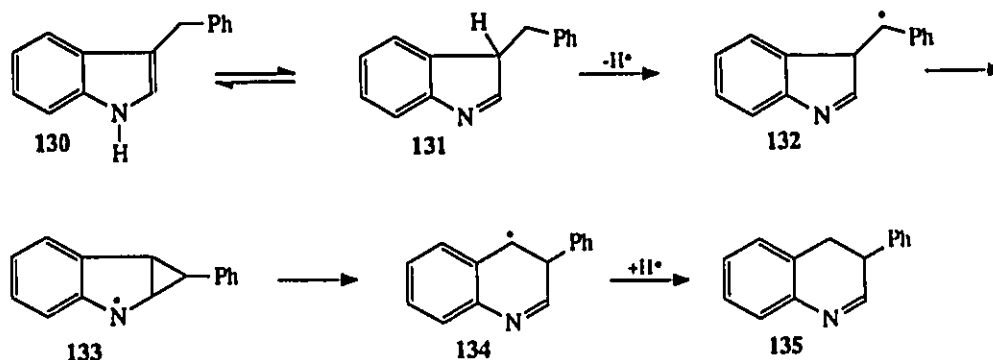
(92) Roberts, B.P.; Winter, J.N. *J. Chem. Soc., Chem. Commun.* 1978, 960.

(93) For a more recent example of intermolecular attack on C-atom of Schiff bases and anils, see: Russell, G.A.; Yao, C.-F.; Rajaratnam, R.; Kim, B.H. *J. Am. Chem. Soc.* 1991, 113, 373.

(94) Nonhebel, D.C.; Tedder, J.M.; Walton, J.C. *Radicals*; Cambridge University Press; London, 1979; p.90.

(95) Patterson, J.M.; Mayer, C.F.; Smith, W.T. *J. Org. Chem.* 1975, 40, 1511.

Scheme 42



650°C gave among numerous other products, the 3-phenyldihydroquinoline 135 in 5% yield. The formation of 135 was accounted for by an initial C-H bond cleavage in 131 to form the benzyl radical 132. This was followed by an intramolecular radical attack onto the C=N functional group producing the cyclopropylamino radical 133. Ring opening of this strained system to 134, and H-atom abstraction formed the 3-phenylquinoline 135.

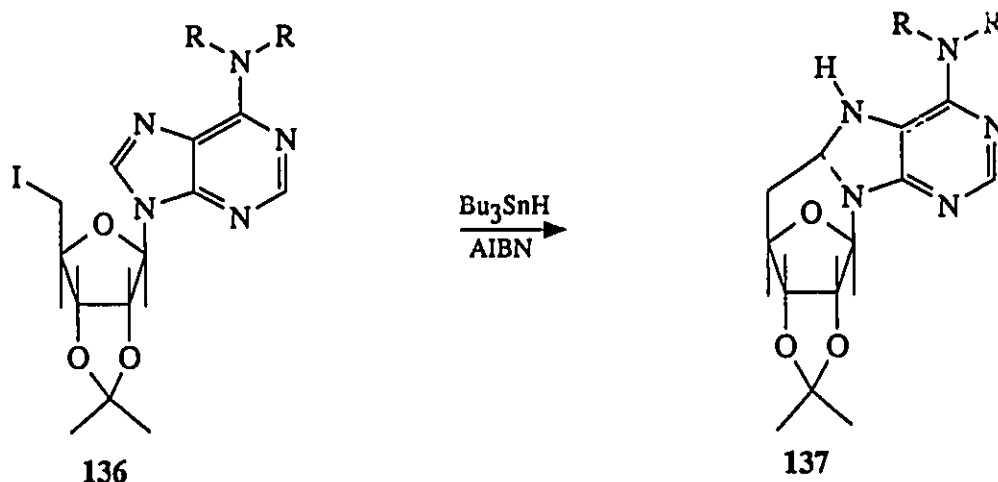
A more convincing example of intramolecular addition to C=N comes from Duong and co-workers⁹⁶ and their alkyl radical cyclization to the C=N of the aromatic base adenosine (Scheme 43). The nucleotide derivative 136, after loss of the I-atom, cyclizes the ribose portion to the purine base giving product 137 in 52% yield.

The third example of cyclization to imines from Tanner and Rahimi⁹⁷ provides some indirect evidence for 5-endo closure to the N-atom (Scheme 44). The

(96) Duong, K.N.V.; Gaudemer, A.; Johnson, M.D.; Quillivic, R.; Zylber, J. *Tetrahedron Lett.* 1975, 2997.

(97) Tanner, D.D.; Rahimi, P.M. *J. Org. Chem.* 1979, 44, 1674.

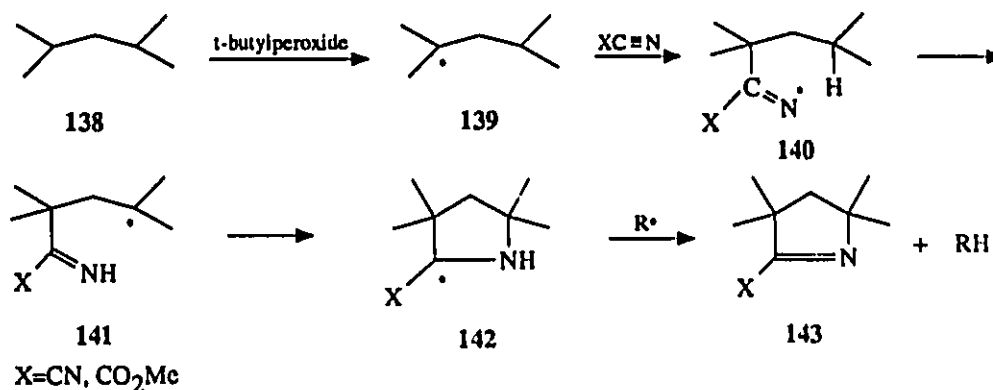
Scheme 43



reaction of methyl cyanoformate or cyanogen with 2,4-dimethylpentane (**138**) and benzoyl peroxide as initiator, gives the azacyclopentene **143** in 22% yield. The proposed mechanism involves H-atom abstraction to the tertiary radical **139**, which then adds to the C-atom of $\text{XC}\equiv\text{N}$ (X is CN or CO_2Me) creating the iminyl radical **140**. A 1,5 H-atom transfer regenerates a tertiary alkyl radical (**141**), which subsequently cyclizes in the 5-endo sense to the N-atom of the imino group affording **142**. Termination by disproportionation results in the azacyclopentene **143**. This 5-endo radical cyclization to the N-atom of the imino group is favourable, perhaps because of the relatively high stability of radical **142**. Radicals substituted by capto-dative groups as is **142**, are known to be highly stabilized.⁹⁸

(98) Merenyi, R.; Janousek, Z.; Viehe, H.G. In *Substituent Effects in Radical Chemistry*; Viehe, H.G.; Janousek, Z.; Merenyi, R., Eds.; Reidel Publishers: Boston, 1986; p.301.

Scheme 44

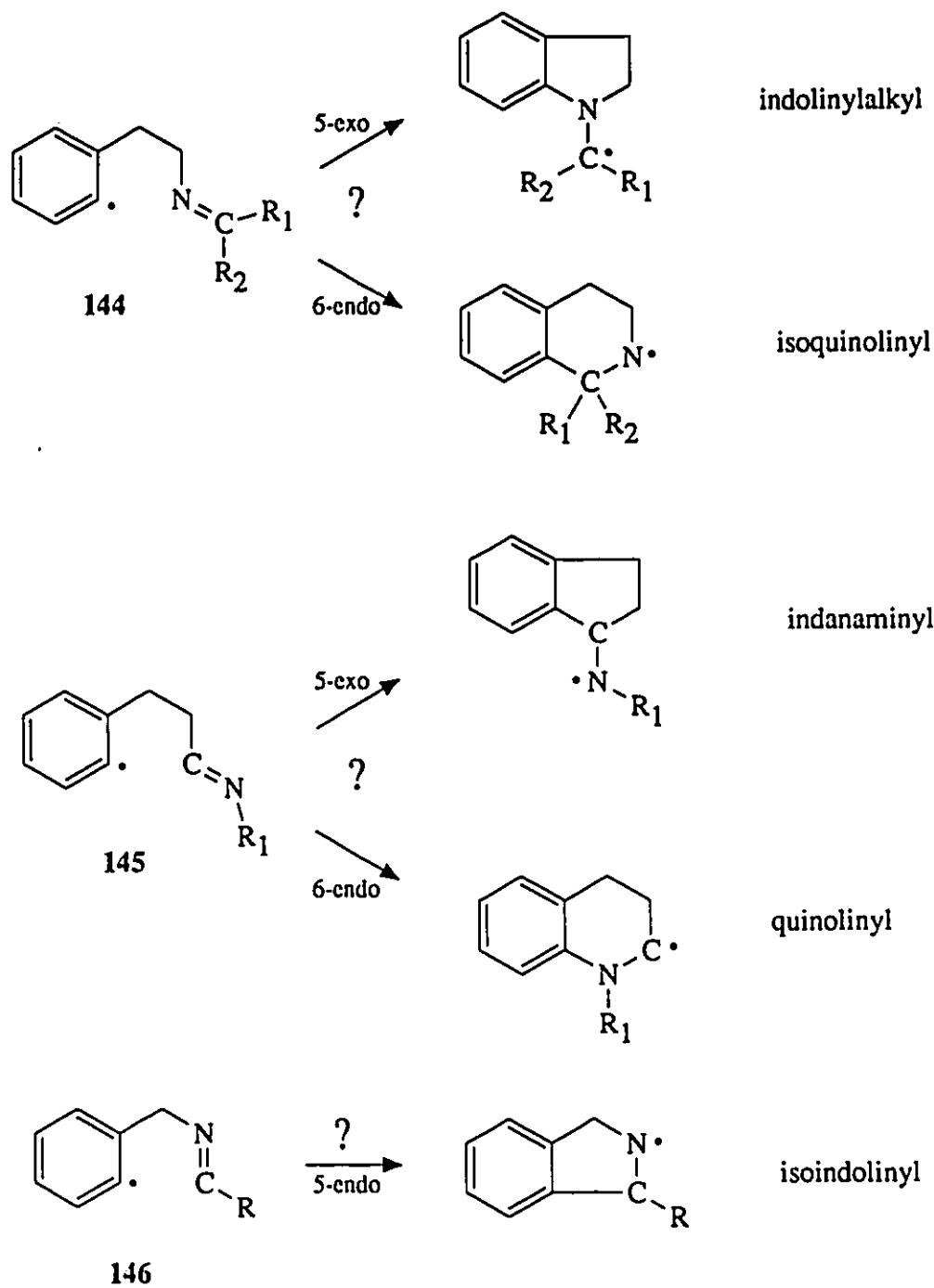


Objectives

The regioselectivity of aryl radical cyclization to an imino group, wherein the competition is between closure in the 5-exo sense to the N-atom and 6-endo sense to the C-atom, was unknown at the outset of this project (144, Scheme 45). Based on Beckwith's first guideline for radical cyclization reactions, preferred closure should be in the 5-exo mode, analogous to the *o*-butenylphenyl radical (41). However, as was discovered in aryl radical cyclizations to the azo functionality,⁶⁹ geometric constraints may alter the regioselectivity. The question of regioselectivity is equally interesting for the reverse imines, wherein the choice is between 5-exo closure to the C-atom and 6-endo closure to the N-atom (145, Scheme 45). Depending upon the mode of closure to an imino group, either an aminyl and an α -aminoalkyl radical is formed. Another objective was to determine the rate constants for cyclization to C=N in Scheme 45. Aryl radical cyclizations to the unsaturated groups, C=C, C=O, and N=N, are known to be rapid.

Aside from some indirect evidence for 5-endo closure of alkyl radicals to the

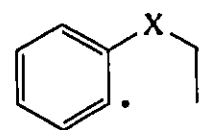
Scheme 45



N-atom of imines,⁹⁷ the alkyl or aryl closure to a 4,5 situated imino group was not known.

In particular, do the isomeric imines **146** undergo 5-endo aryl radical closure to the C-atom of the imino group? The analogous alkenylaryl radical, *o*-propenylphenyl radical (**147**), is known to be very resistant to cyclization as is the 3-oxa derivative **40**.^{7, 57} However, closure to the azo group in the 5-endo mode is extremely facile (Scheme 26).⁷⁰

As a result of the great interest in synthesizing enantiomerically pure compounds the question of diastereoselectivity afforded by a chiral auxiliary attached to an imino group was examined.



40 X=O
147 X=CH₂

Finally, although the tin hydride method is the most popular for carrying out radical chain reactions in synthesis, the high H-donating ability of Bu₃SnH, as discussed earlier, often reduces intermediary radicals before they undergo the desired rearrangement. Approaches to generating Bu₃Sn• from a source other than Bu₃SnH were therefore investigated.

While our work was well in progress,⁹⁹ a short report was published by Takano and co-workers¹⁰⁰ that dealt with the question of regioselectivity of aryl radical cyclization to Schiff bases, wherein the choice is between 5-exo closure to the N-atom or 6-endo closure to the C-atom **144** (R₁=H, R₂=Ar) Scheme 45. They found that the

(99) The regioselectivity and rate constants for intramolecular aryl radical closure 5-exo to N or 6-endo to C of an imino group were presented at the 72nd Canadian Chemical Conference and Exhibition, Victoria, British Columbia, June 1989; 611 OR-G3.

(100) Takano, S.; Suzuki, M.; Kijima, A.; Ogasawara, K. *Chem. Lett.* **1990**, 315.

product mixture from the thermolysis of Schiff bases with Bu_3SnH and catalytic AIBN in refluxing toluene consisted of two isomers, indoline and isoquinoline in a ratio of ca. 1 to 5. The yields of tetrahydroisoquinolines ranged from 36 to 56%.

CHAPTER TWO

RESULTS AND DISCUSSION

Synthesis of Imines with N-5/C-6

In this study aryl radical cyclizations to the imino group with the N-atom in the 5-position and the C-atom in the 6-position relative to the latent radical site were investigated. Aryl radicals are amongst the most reactive carbon radicals and therefore likely to exhibit high rates in ring closure. The heterocycles, which result from ring closure in the 5-exo sense to the N-atom, indoline **148**, or the 6-endo sense to the C-atom, isoquinoline **149**, are well known ring systems and therefore product analysis is simplified (Scheme 46). Furthermore, the synthesis of the precursor of radical **144** was deemed to be relatively straightforward.

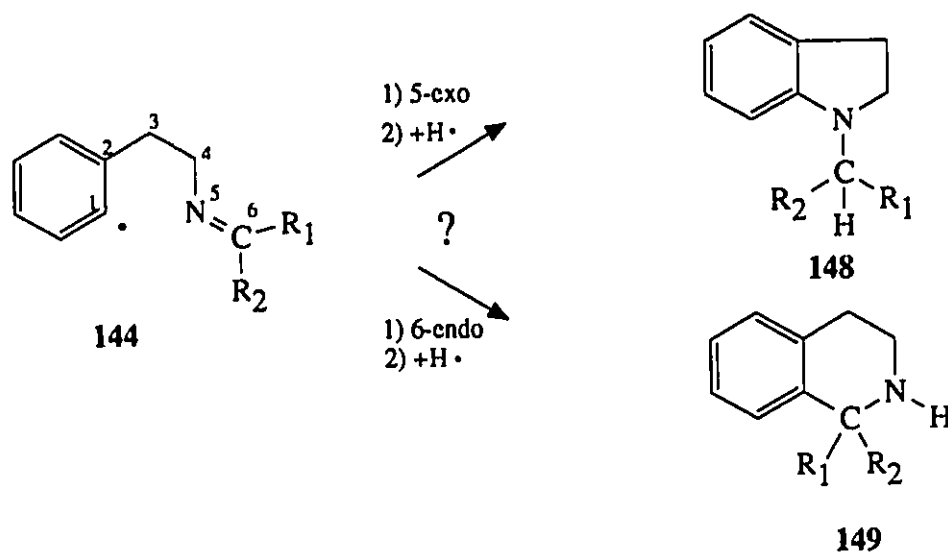
Two commonly employed routes to 2-bromophenethylamine (**154**) are found in the literature (Scheme 47). Reaction of nitromethane with 2-bromobenzaldehyde under basic conditions gives the nitrostyrene derivative **150** which may be reduced to the amine **154** in an overall yield of 37%.^{101,102} An alternate route to the primary amine **154** is based on the classical Gabriel synthesis. Alkylation of the phthalimide with the dibromide

(101) Bradsher, C.K.; Hunt, D.A. *J. Org. Chem.* 1981, 46, 327.

(102) Mori, M.; Chiba, K.; Ban, Y. *J. Org. Chem.* 1978, 43, 1684.

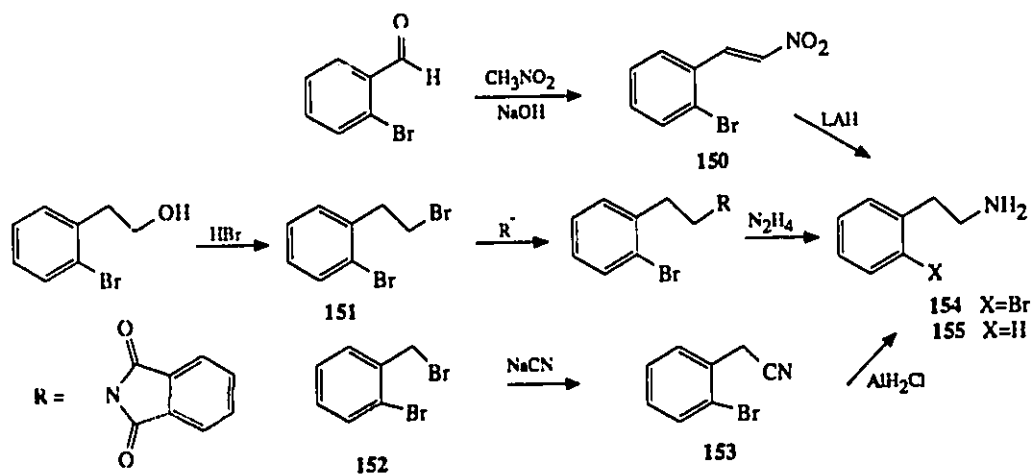
151, followed by deprotection of the amino group with hydrazine, gives the desired

Scheme 46



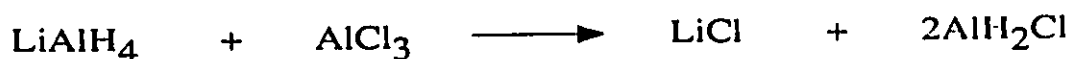
product **154** in three steps and 35% yield from the alcohol.¹⁰¹

Scheme 47



These relatively low yielding approaches led us to investigate a more direct

synthesis of 2-bromophenethylamine (154), the one step reduction of the commercially available 2-bromophenylacetonitrile (153). Initially, some difficulty was encountered in cleanly converting the nitrile 153 to the amine 154. Reduction with B_2H_6 (THF)¹⁰³ or $NaBH_3(OCOFCF_3)$ ¹⁰⁴ produces the amine 154 in low yields. Usage of $NaBH_4-CoCl_2$ ¹⁰⁵ results in a mixture of amine 154 and the dehalogenated amine 155. Aryl bromides have been dehalogenated in the past with $LiAlH_4$.¹⁰⁶ The less reactive aluminium hydride, AlH_2Cl , however, has been used to reduce nitriles selectively in the presence of an aryl bromide.¹⁰⁷ This mixed hydride may be prepared *in situ* from $LiAlH_4$ and $AlCl_3$.¹⁰⁸



In accordance, 2-bromophenylacetonitrile (153) is reduced with AlH_2Cl at ambient temperature in 35 min, affording the 2-bromophenethylamine (154) in 82% isolated yield. The starting nitrile 153 was either purchased or prepared from o-bromobenzylbromide

(103) Anhoury, M.-L.; Crooy, P.; De Neys, R.; Eliaers, J. *J. Chem. Soc. Perkin Trans I* 1974, 1015.

(104) Umino, N.; Iwakuma, T.; Itoh, N. *Tetrahedron Lett.* 1976, 33, 2875.

(105) Heinzman, S.W.; Ganem, B. *J. Am. Chem. Soc.* 1982, 104, 6801.

(106) Brown, H.C.; Krishnamurthy, S. *J. Org. Chem.* 1969, 34, 3918.

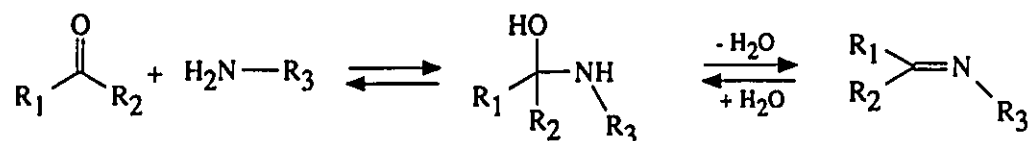
(107) Miller, S.M.; Klinman, J.P. *Biochemistry* 1985, 24, 2114.

(108) Nystrom, R.F. *J. Am. Chem. Soc.* 1955, 77, 2544.

(152) by nucleophilic displacement reaction in 72% yield.¹⁰⁹

The condensation of a primary amine, such as 2-bromophenethylamine (154), with a carbonyl compound is a reversible reaction that proceeds via the carbinolamine intermediate (Scheme 48). Imine formation is, in general, acid catalyzed and may be driven toward the product side by removal of water.

Scheme 48



The nomenclature of imines is often not consistent in the literature. The terms aldimine and ketimine will be used for imines that are derived from aldehydes and ketones, respectively. The more specific term, Schiff base, applies to aldimines of benzaldehyde and its derivatives, whereas anils are imines in which the amine precursor is anilino. These definitions are consistent with the latest review on imines.¹¹⁰

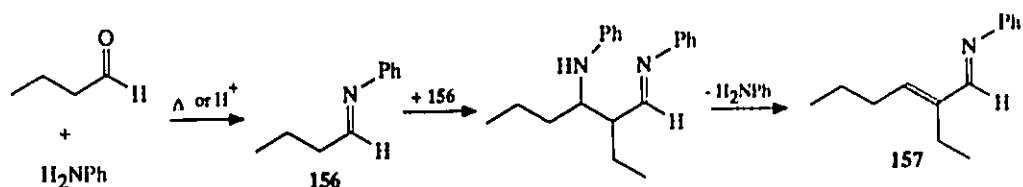
The success of imine synthesis depends largely on the choice of carbonyl compound. In general, the condensation of amines with primary aliphatic aldehydes, aldehydes with an α -methylene functionality, gives polymeric materials. Imines are

(109) Smiley, R.A.; Arnold, C. *J. Org. Chem.* 1960, 25, 257.

(110) Layer, R.W. *Chem. Rev.* 1963, 63, 489.

formed but they quickly undergo aldol type condensation.^{110,111} For example, the reaction of 1-butanal with aniline yielded the dimeric α,β -unsaturated compound **157** instead of N-butylideneaniline (**156**) (Scheme 49).¹¹² Condensations with secondary aliphatic aldehydes, however, occur readily and cleanly. The absence of a second α -hydrogen prevents the elimination of amine and the formation of α,β -unsaturated imines. Likewise, tertiary aliphatic and aromatic aldehydes react swiftly and in high yields with amines even at room temperature. Condensations with aliphatic ketones, although not as fast as with aldehydes, are still viable. Elevated temperatures, acid catalysis, and water removal improve the yields. Aromatic ketones, on the other hand, generally require forcing conditions, as proton or Lewis acid are essential as are high temperatures for prolonged periods of time.¹¹⁰

Scheme 49

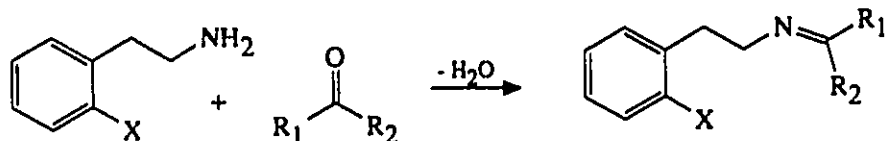


Depending on the volatility of the starting aldehyde or ketone, one of two general procedures was used to synthesize the imine. The condensations of higher boiling carbonyl compounds, including benzaldehyde, benzaldehyde-1-d (**162**), 4-tolualdehyde,

(111) Dayagi, S. In *The Chemistry of the Carbon-Nitrogen Double Bond*; Patai, S.; Ed.; Interscience Publishers: London, 1970; p.61.

(112) Kharasch, M.S.; Richlin, J.; Mayo, F.R. *J. Am. Chem. Soc.* 1940, 62, 494.

Scheme 50



154 X=Br

155 X=H

164 R₁ = CH(CH₃)₂, R₂ = H, X = Br

165 R₁ = CH(CH₃)₂, R₂ = D, X = Br

168 R₁ = CH(CH₃)₂, R₂ = H, X = H

169 R₁ = CH(CH₃)₂, R₂ = D, X = H

176 R₁ = C₆H₅, R₂ = H, X = Br

179 R₁ = C₆H₅, R₂ = H, X = H

181 R₁ = p-C₆H₄CH₃, R₂ = H, X = Br

186 R₁ = C₆H₅, R₂ = D, X = Br

189 R₁ = C₆H₅, R₂ = D, X = H

208 R₁ = R₂ = CH₂CH₃, X = Br

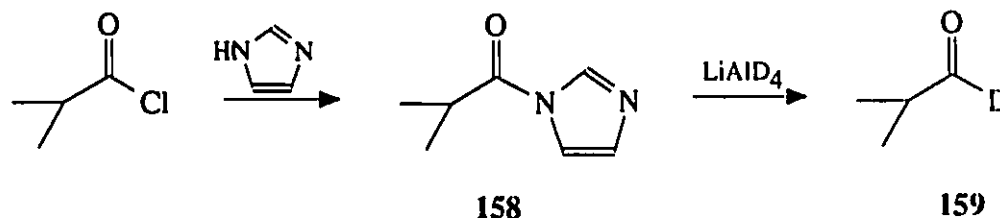
233 R₁ = p-C₆H₄N(CH₃)₂, R₂ = H, X = Br

4-(dimethylamino)benzaldehyde, and 3-pentanone with 2-bromophenethylamine (**154**) or phenethylamine (**155**) were done in refluxing benzene or toluene. The water was removed as an azeotrope in a Dean-Stark apparatus. In the case of the low boiling aldehydes, isobutyraldehyde and isobutyraldehyde-1-d (**159**), condensation with 2-bromophenethylamine (**154**) or phenethylamine (**155**) was effected most often at room temperature in dry diethyl ether. Molecular sieves were used to remove the water. ¹H NMR, ¹³C NMR, MS, and IR spectroscopy served to characterize the imines in Scheme 50. The isolated yields of imines ranged from 67 to 95%.

The deuterated imines **165** and **186** were prepared by condensation of 2-bromophenethylamine (**154**) with isobutyraldehyde-1-d (**159**) and benzaldehyde-1-d (**162**), respectively. Isobutyraldehyde-1-d (**159**) was synthesized from the imidazolidine **158** by

reduction with LiAlD_4 (Scheme 51).¹¹³ Since the reduction of the imidazolidine is faster than that of the resulting aldehyde, there was relatively little further reduction to the alcohol.¹¹⁴ The imidazolidine **158** in turn was prepared in 72% from the acid chloride and two equivalents of imidazole.¹¹⁵ The reaction of benzil with cyanide in the presence of

Scheme 51



D_2O furnished benzaldehyde-1-d (**162**) (Scheme 52).¹¹⁶ The key step was the rearrangement of the adduct **160** to the carbanion **161**. The carbanion was trapped by D_2O and the product was hydrolyzed to benzoic acid and benzaldehyde-1-d (**162**).

Geometric Isomerism in Imines

Geometric isomers are possible in imines by virtue of the presence of a

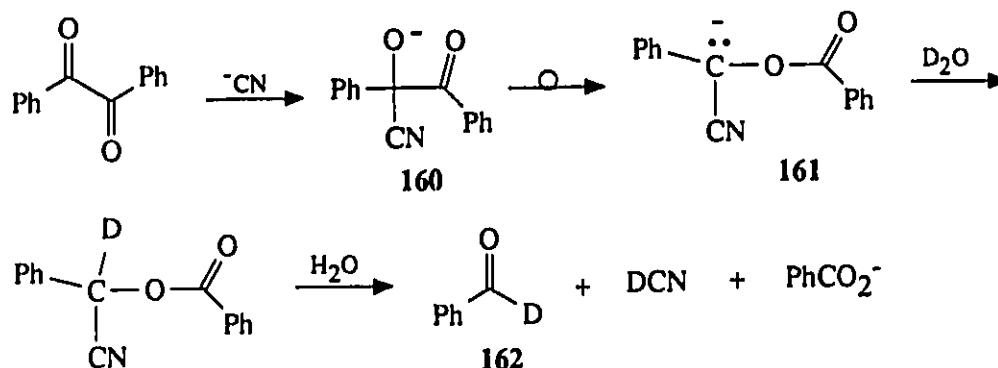
(113) Staab, H.A.; Braunling, H. *Liebigs Ann. Chem.* **1962**, 654, 119.

(114) Staab, H.A. *Angew. Chem. Intl. Ed. Engl.* **1962**, 1, 351.

(115) Staab, H.A.; Rohr, W. In *Newer Methods of Preparative Organic Chemistry*; Foerst, W., Ed. Verlag Chemie, New York, Vol V, 1968; p61.

(116) Burgstahler, A.W.; Walker, D.E.; Kuebrich, J.P.; Schowen, R.L. *J. Org. Chem.* **1972**, 37, 1272.

Scheme 52



carbon-nitrogen double bond. The early reports of the discrete existence and isolation of E- and Z-isomeric forms of Schiff bases, however, have been discredited and attributed to other phenomena such as polymorphism.¹¹⁷ Based on extensive studies, mainly by NMR, N-alkyl- and N-aryl-aldimines have been shown to exist exclusively in the thermodynamically more stable E-isomeric form.^{118,119,120} The unstable aldimines in the Z-configuration, nevertheless, have been detected by low temperature ¹³C NMR and their spectra have been compared to those of the E-isomers. Fraser and co-workers¹²¹

(117) McCarty, C.G. In *The Chemistry of the Carbon-Nitrogen Double Bond*; Patai, S., Ed.; Interscience Publishers: London, 1970, p363.

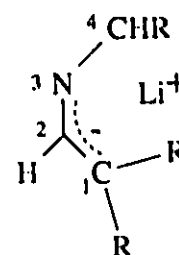
(118) Fraser, R.R.; Chuaqui-Offermans, N. *Can. J. Chem.* 1981, 59, 3007.

(119) Bjorgo, J.; Boyd, D.R.; Watson, C.G.; Jennings, W.B.; Jerina, D.M. *J. Chem. Soc. Perkin Trans. II* 1974, 1081.

(120) Kobayashi, M.; Yoshida, M.; Minato, J. *J. Org. Chem.* 1976, 41, 3322.

(121) Fraser, R.R.; Banville, J.; Akiyama, F.; Chuaqui-Offermans, N. *Can. J. Chem.* 1981, 59, 705.

found that the lithiated aldimine **163** adopted the Z-configuration.¹²² Alkylation of these lithiated aldimines in turn gave transient Z-isomeric imines that were detected by ¹³C NMR at -20 to -40°C. Fraser and co-workers found that the chemical shift for C-1 or C-4 in aldimines in the Z-configuration was consistently upfield by 5-11 ppm.¹²¹

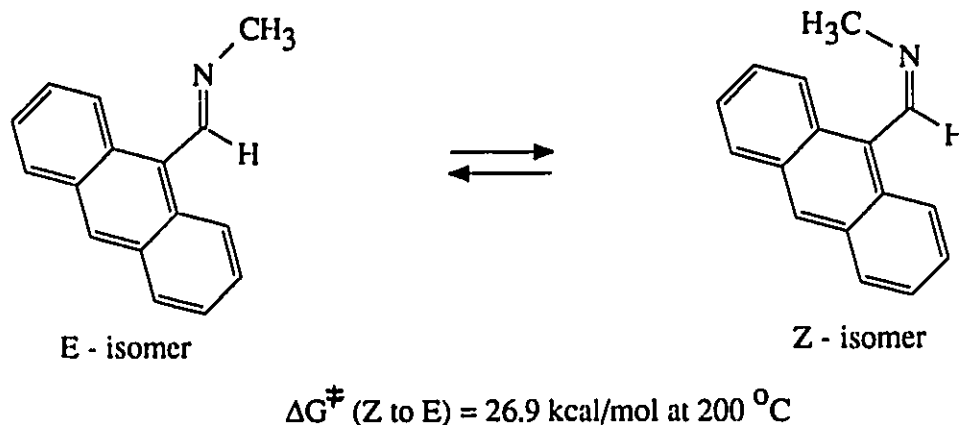
**163**

Based on precedents in the literature and analysis of ¹H NMR, ¹³C NMR, and ²H NMR spectra, we concluded that the aldimines and Schiff bases in Scheme 50 exist predominately in the E-configuration at room temperature. At 80°C, the temperature used for radical cyclizations of imines, the ratio of E- to Z-isomer is not expected to change drastically from that at room temperature. The equilibrium constant for the interconversion of E- and Z-imines of N-(9-anthrylidene)methylamine shows a small temperature dependence (Scheme 53).¹²³ Boyd and co-workers found 7% of Z-isomer at 42°C and 12% at 200°C. The presence of the Z-isomer in equilibrium with the E-isomer is ascribed to a lone pair repulsion between the nitrogen lone pair electrons and the π-electrons of the anthryl ring in the E-configuration.

(122) The preference for the Z-configuration of lithiated imines has been estimated to be at least 4 kcal/mol: Fraser, R.R.; Bresse, M.; Chuaqui-Offermanns, N.; Houk, K.N.; Rondan, N.G. *Can. J. Ch. m.* **1983**, 61, 2729. For an explanation, see: Houk, K.N.; Strozier, R.W.; Rondan, N.G.; Fraser, R.R.; Chuaqui-Offermanns, N. *J. Am. Chem. Soc.* **1980**, 102, 1426.

(123) Boyd, D.R.; Watson, C.G.; Jennings, W.B.; Jerina, D.M. *J. Chem. Soc., Chem. Commun.* **1972**, 183.

Scheme 53



Radical Cyclizations to Isobutyraldimine with N-5/C-6

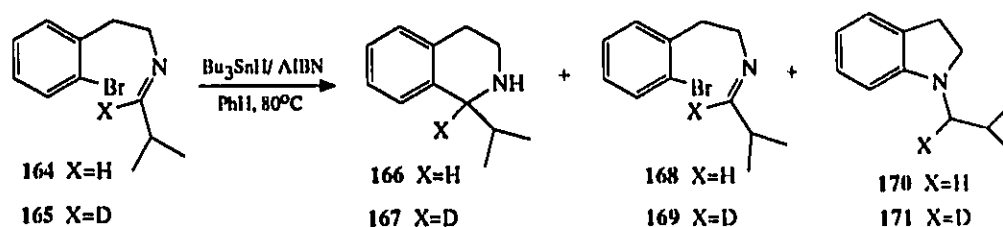
Regiochemistry

Aryl radical cyclization to the aldimine of isobutyraldehyde **164** is highly regioselective in the 6-endo sense to the C-atom (Scheme 54). Syringe-pump addition of Bu_3SnH and AIBN to the aldimine **164** afforded tetrahydroisoquinoline **166** as the major product in 60% isolated yield. The isomeric product arising from the exocyclic closure, indoline **170**, was present but in much lower concentrations, so that the ratio of isoquinoline **166** to indoline **170** was ca. 55/1 at 80°C. The identity of minor isomer **170** was confirmed by the independent synthesis of indoline **170** (Scheme 55).¹²⁴

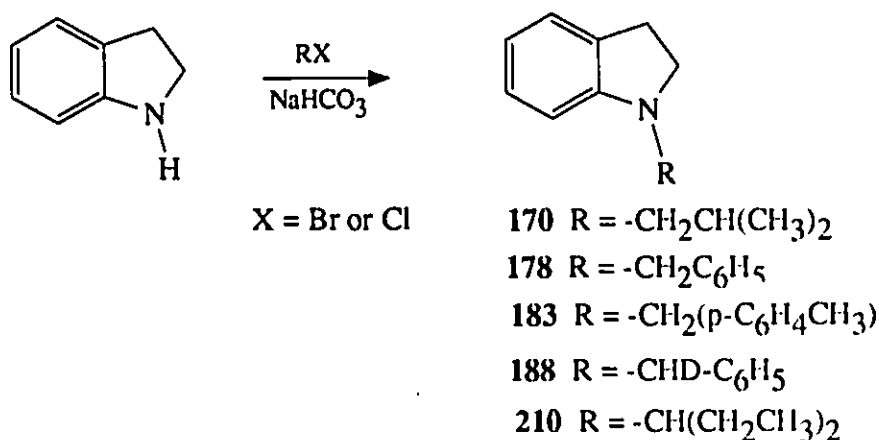
The 6-endo regioselectivity of the aryl radical closure to C=N clearly contradicts Beckwith's first guideline on radical closures. For example, the analogous

(124) Belsky, I.; Gertner, D.; Zilkha, A. *J. Org. Chem.* 1968, 33, 1348.

Scheme 54



Scheme 55



cyclization to C=C in the o-butenylphenyl radical (**41**) has a regioselectivity almost completely reversed so that the 6-endo to 5-exo product ratio is $<1/50$ at 25°C .¹⁹

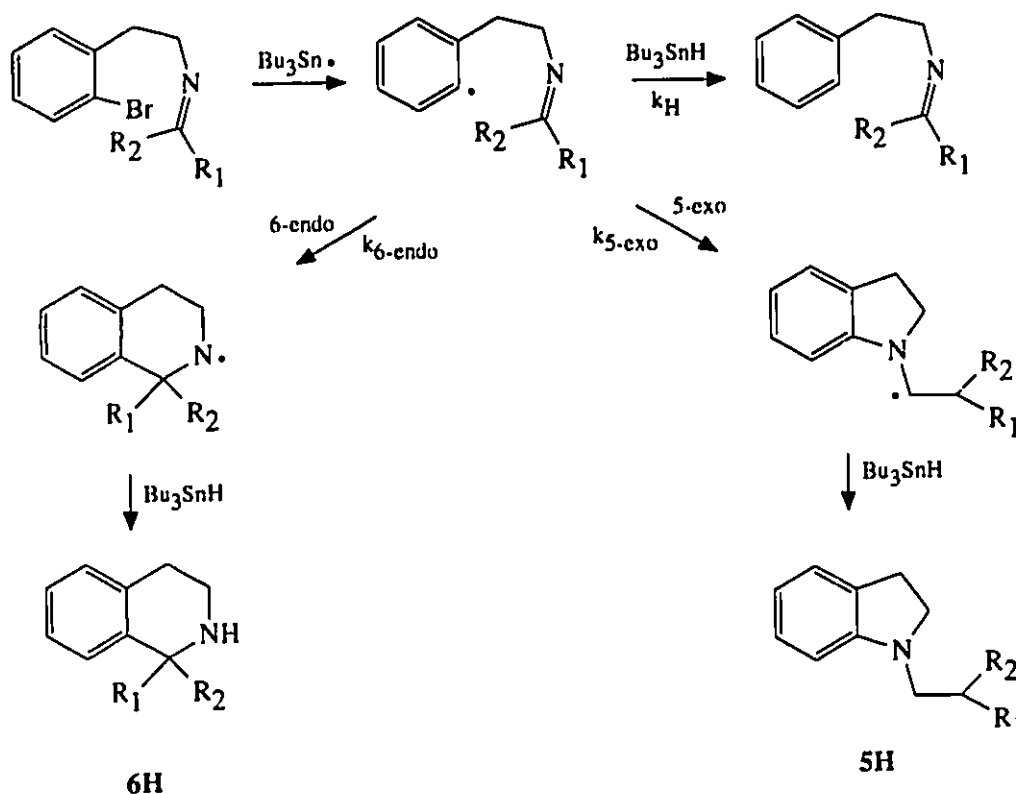
Kinetics of Ring Closure in Isobutyraldimine

Based on the general mechanism for radical cyclizations in Scheme 56, analysis of cyclized (c) and uncyclized (u) products at a known Bu_3SnH concentration should give k_c/k_{H} from the integrated rate equation $k_c/k_{H} = c/u [\text{Bu}_3\text{SnH}]$, where k_{H} is the rate constant for H-atom abstraction from Bu_3SnH , and k_c is the rate constant for cyclization.

Table 1 shows ratios of products and rate constants at three different

concentrations of tin hydride for the radical cyclization of isobutyraldimine **164**. Reactions

Scheme 56



were carried out with 8% AIBN and a tenfold excess of Bu₃SnH. The product ratios were obtained from integrals in the ¹H NMR spectra. Reproducibility of the integrals, however, was poor and hence the ratio of rate constants was not constant. The high concentration of tributyltin hydride in the reaction mixture made phasing and baseline correction of the ¹H NMR spectra formidable.

Product analysis could be simplified, however, by monitoring a different nucleus by the NMR spectrometer: deuterium. The availability of high field FT

Table 1. Kinetic Data for Cyclization of Isobutyraldimine **164** at 80 °C.

[HSn] ^a ,	Product Ratios ^b	Rate Csts
	166/168 (6H/RH)	k_d/k_H
0.68	0.24	0.16
0.07	1.9	0.13
0.005	11.	0.06

^a Bu₃SnH was used in 10 fold excess. The numbers are average concentrations, based on a 1:1 stoichiometry. Reactions were conducted in degassed sealed tubes containing 8% AIBN and the solvent was PhH.

^b Product ratios from integrals in ¹H NMR (500 MHz) spectra.

spectrometers has made the detection of deuterium routine. The ²H chemical shifts are essentially identical in ppm to those of the corresponding ¹H shifts.¹²⁵ The ²H NMR scale, however, is some six times smaller than that of ¹H, and consequently the signals of interest must be well separated in the ¹H NMR spectrum. This is compensated, in part, by a large reduction in spin-spin coupling due to the lower magnetogyric ratio of ²H.

Integration is the most widely used method of obtaining product ratios from NMR spectra. In theory, the integral over the spectral lines is directly proportional to the number of spins. In practice integrals, although accurate, are difficult to reproduce as was discovered in analysing data for Table 1. User specified baseline correction, phase correction and the integration limits affect integrals. An alternate approach to extracting quantitative information from the NMR spectra is the measurement of peak heights. Peak

height measurements are believed to be more robust and less sensitive to operator bias than integrals.^{126, 127, 128} One drawback of relying on peak heights is that the direct connection to the number of spins is destroyed and therefore a calibration is necessary.¹²⁷

Saturation effects, the nuclear Overhauser effect (NOE), and variations in linewidths affect peak height measurements.¹²⁹ Saturation of spins may be avoided by ensuring that the spin system relaxes fully between pulses. This is achieved by waiting between acquisitions for at least five times the longest spin-lattice relaxation time in the system. By waiting for at least five time constants between pulses, the exponential relaxation is 99.3% complete. Quantitative analyses for nuclei having dipole-dipole interactions, such as ^{13}C and ^1H , are greatly affected by the NOE. In the case of ^2H , however, the NOE may be ignored as deuterium relaxation is governed by quadrupolar relaxation. Finally, linewidths in ^2H NMR spectra are in general similar because the dominant factor in line-broadening of deuterium signals is quadrupolar relaxation and the other line broadening factors, such as field inhomogeneity, are negligible.

The standard approach of collecting many scans (N) to obtain one averaged

(126) Fulton, D.B.; Sayer, B.G.; Bain, A.D.; Malle, H.V. *Anal. Chem.* 1992, 64, 349.

(127) Bain, A.D.; Lao, L. In *Isotopes in the Physical and Biochemical Sciences*; Buncel, E.; Jones, J.R., Eds.; Elsevier: Amsterdam, 1991, vol 2, p411.

(128) Bain, A.D.; Fahie, B.J.; Kozluk, T.; Leigh, W.J. *Can. J. Chem.* 1991, 69, 1189.

(129) Bain, A.D.; Lao, L.; Bartoszek, F.E.; Robins, J. Article prepared for submission to *Anal. Chem.*

Table 2. Kinetic Data for Cyclization of Isobutyraldimine-d 165 at 80 °C.

[SnH] ^a , M	Product Ratios ^b	Rate Csts
	167/169 (6H/RH)	k_d/k_{11} (M)
0.760	0.27±0.08	0.21±0.06
0.381	0.62±0.16	0.24±0.06
0.191	1.5±0.4	0.29±0.08
0.191	1.5±0.4	0.29±0.08
0.096	2.5±0.8	0.24±0.06
0.048	4.6±1.4	0.22±0.06
0.048	5.0±1.4	0.24±0.08

^a Effective concentration of Bu₃SnH (9.4 fold excess). The numbers are average concentrations, based on a 1:1 stoichiometry.

^b Product ratios from peak heights in the ²H NMR (76.8 MHz) spectra. The error bars reflect 95.5% confidence limits ($\pm 2\sigma$) as determined from the ²H NMR spectra. A pulse delay of 1.5 s was used. A gravimetric calibration was done.

spectrum was modified to collect the data in a series of blocks. Since the total number of scans is unchanged the average spectra are identical. By collecting the data in blocks, however, in addition to the average spectrum a statistical analysis of the data is possible at no cost in acquisition time.

The results of radical cyclization of the deuterated isobutyraldimine 165 are given in Table 2. Reactions were conducted at 80°C in degassed sealed tubes containing Bu₃SnH (9.4 equivalents), aldimine-d 165, and 5% of AIBN in PhH. Reactions were monitored by ¹H NMR spectroscopy and were stopped when the starting imine was

consumed. The ratios of 6-endo derived product **167** to dehalogenated aldimine **169** were determined from the peak heights in the ^2H NMR spectra and were corrected. Typical average (bottom) and the standard deviation (top) spectra are shown in Figure 1. Independently synthesized deuterated aldimine **169** was used for the gravimetric calibration.

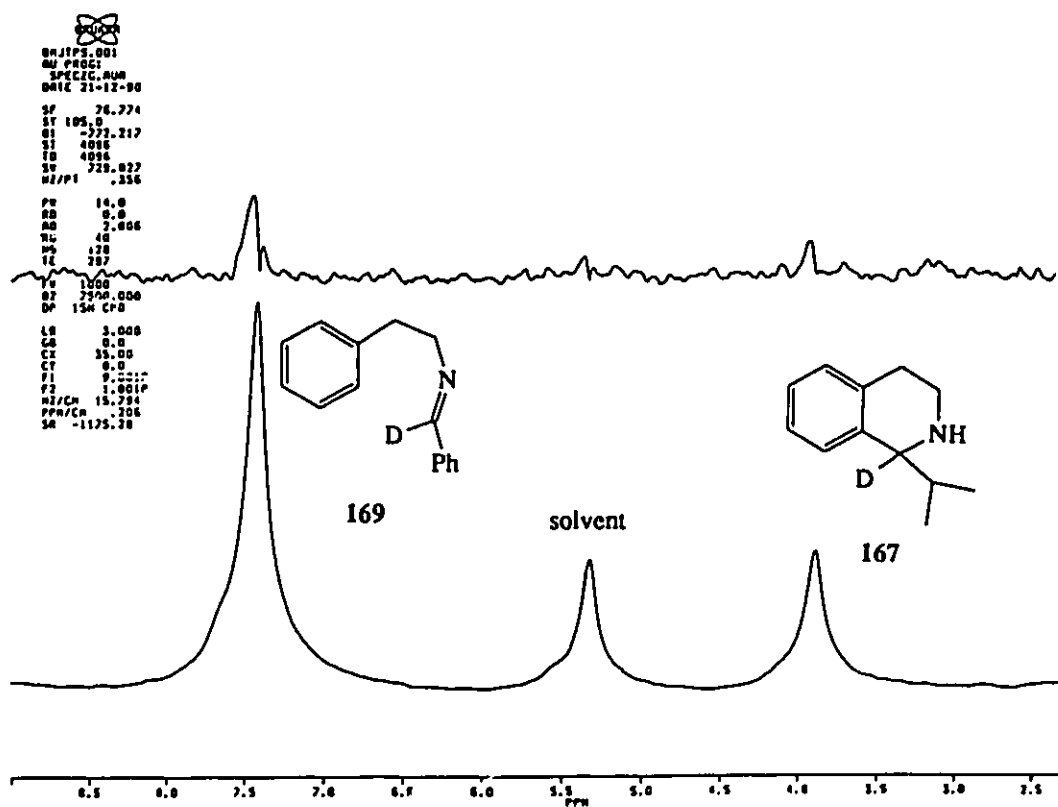
Aryl radical closure to isobutyraldimine is an efficient process (Table 2). The tendency for ring closure to the isobutyraldimino group by the aryl radical, k_f/k_{11} (M) is 0.24 (± 0.03) at 80°C, which is twice as large as that for the aryl closure to $\text{C}\equiv\text{N}$ in **101**⁷⁹ and some twenty times greater than the aryl closure to $\text{C}=\text{O}$ in **92**,⁷⁹ all at 80°C. The ratio k_f/k_{11} for ring closure to $\text{C}=\text{C}$ in the *o*-butenylphenyl radical (**41**), however, is larger as k_f/k_{11} is ca. 1.1 at 80°C.⁴⁵

The high 6-endo regioselectivity of the aryl radical derived from **165** stands in large contrast to the preferred 5-exo closure in $\text{C}=\text{C}$, $\text{C}=\text{O}$ and $\text{C}\equiv\text{C}$. Substituting the recently determined value⁵² for k_{11} ($5.0 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ at 80°C) into k_f/k_{11} for isobutyraldimine **165** yields $k_{6\text{-endo}}$ of $1.2(\pm 0.2) \times 10^8 \text{ s}^{-1}$. The value of $k_{5\text{-exo}}$ is $k_{6\text{-endo}}/55$ or $2.2 \times 10^6 \text{ s}^{-1}$ at 80°C. The high regioselectivity and the large rate constants make this an attractive route for the synthesis of tetrahydroisoquinolines.

Reactions under High Dilution

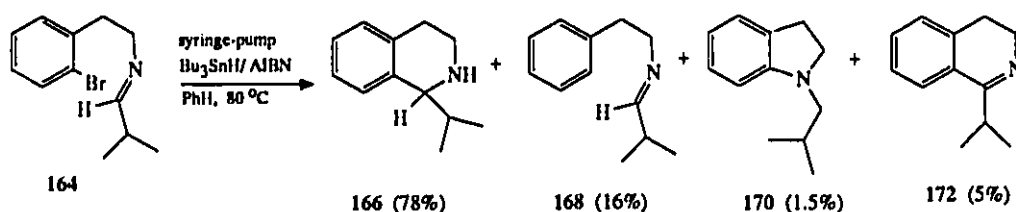
In an effort to optimize the amount of tetrahydroisoquinoline product **166**, thermolyses of isobutyraldimine **164** were conducted with slow addition of Bu_3SnH and

Figure 1. ^1H NMR (76.8 MHz, CH_2Cl_2) average (bottom) and standard deviation (top) spectra from the thermolysis of aldimine 165 [0.043 M], Bu_3SnH [0.402 M], and AIBN (5%) in PhH. The natural abundance deuterium in the solvent, CH_2Cl_2 , was set to 5.32 ppm.



AIBN via a syringe-pump (Scheme 57). Surprisingly, in addition to the expected tetrahydroisoquinoline **166** (60% isolated yield), dehalogenated imine **168**, and a trace of indoline **170**, the product mixture contained some oxidized isoquinoline, 3,4-dihydroisoquinoline **172**. The product mixture typically contained some 5% of the 3,4-dihydroisoquinoline **172** (GC).

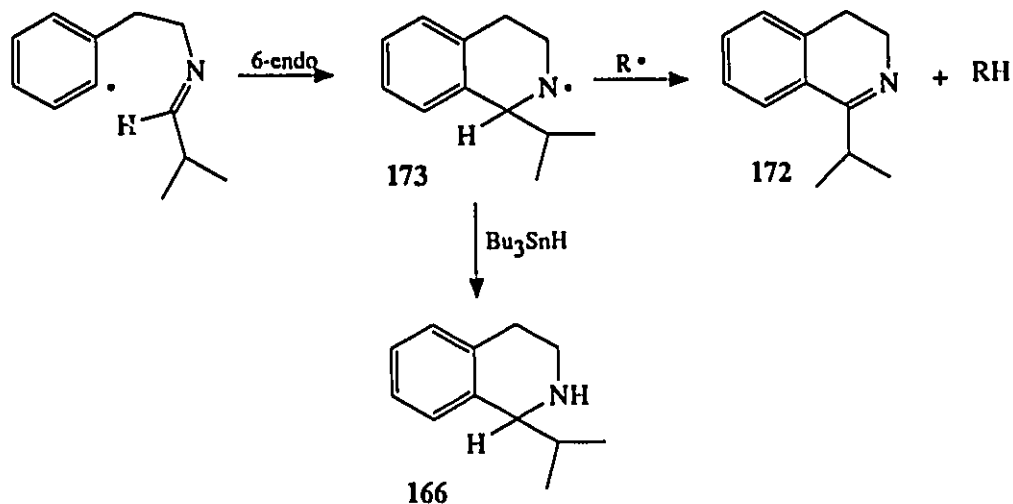
Scheme 57



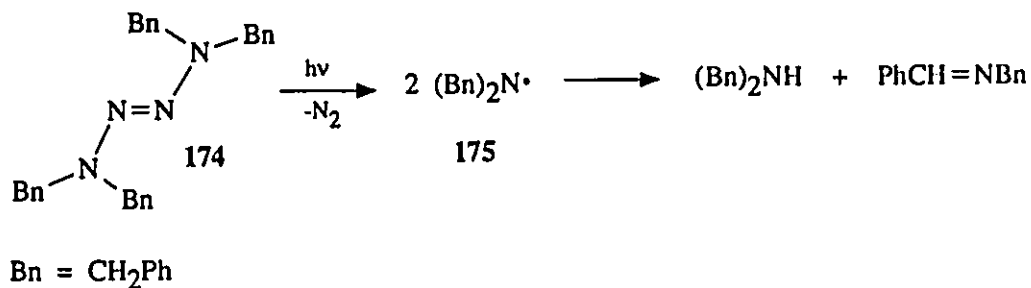
The formation of the 3,4-dihydroisoquinoline **172** may be attributed to the low concentration of tin hydride employed in the reaction. At low $[\text{Bu}_3\text{SnH}]$, the isoquinolinyl radical **173** may engage in radical-radical reactions in competition with an attack on tin hydride (Scheme 58). Although the exact value of the rate constant for aminyl radical abstraction from Bu_3SnH is not known, the lowest that it may be is $8 \times 10^4 \text{ M}^{-1}\text{s}^{-1}$ at 50°C .⁹⁰ A likely route to the 3,4-dihydroisoquinoline **172**, therefore, involves the disproportionation of the tetrahydroisoquinolinyl radical **173**. Ratcliff and Kochi¹³⁰ found that the dibenzylaminyl radical (**175**), generated by the photolysis of tetrabenzyltetrazene (**174**) at 310 nm, undergoes disproportionation exclusively (Scheme 59).

(130) Ratcliff, M.A.; Kochi, J.K. *J. Org. Chem.* **1972**, *37*, 3268.

Scheme 58



Scheme 59



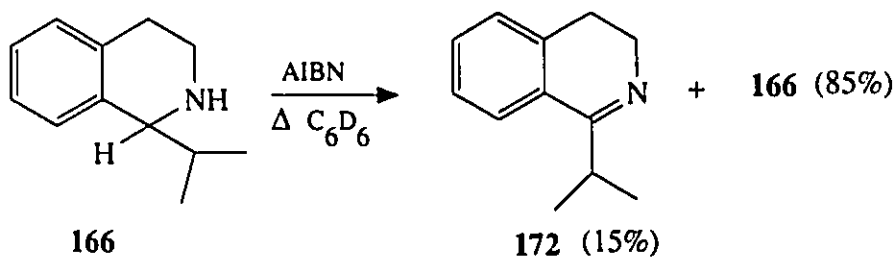
It was also found that aryl radical cyclization in the corresponding deuterated aldimine **165** carried out under very similar reaction conditions as for **164** in Scheme 57, gives a lower proportion of the 3,4-dihydroisoquinoline **172**, less than 3%. This may be attributed to an isotope effect. There is precedent for a kinetic isotope effect on disproportionation. Gibian and Corley¹³¹ compared the disproportionation of $\text{Ph}\dot{\text{C}}\text{HCH}_3$,

(131) Gibian, M.J.; Corley, R.C. *J. Am. Chem. Soc.* 1972, 94, 4178.

to $\text{Ph}\dot{\text{C}}\text{HCD}_3$ and found that k_1/k_D is 1.87. Griller and Ingold,¹³² likewise, reported a primary kinetic isotope effect of 1.4 for the disproportionation of $(\text{CH}_3)_3\text{C}\cdot/(\text{CD}_3)_3\text{C}\cdot$.

A second possible route to the 3,4-dihydroisoquinoline **172** may be from the reaction of tetrahydroisoquinoline **166** with AIBN. A correlation was found between the amount of AIBN used in a thermolysis with isobutyraldimine **164** and Bu_3SnH and the amount of 3,4-dihydroisoquinoline **172** formed. Syringe-pump addition of 0.22 equivalents of AIBN relative to the isobutyraldimine **164** resulted in a product mixture of which 5% was 3,4-dihydroisoquinoline **172**. When 0.35 equivalents of AIBN were employed, however, the proportion of 3,4-dihydroisoquinoline **172** increased to 7.5%. A control experiment showed that heating tetrahydroisoquinoline **166** in the presence of AIBN for 6 h gave some 15% of **172** (Scheme 60). A possible mechanism involves the abstraction of the benzylic H-atom yielding the stabilized α -aminoalkyl radical that then undergoes disproportionation to give the 3,4-dihydroisoquinoline **172**.

Scheme 60



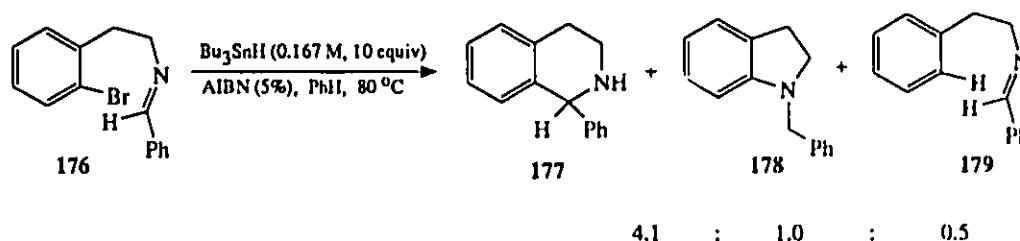
(132) Griller, D.; Ingold, K.U. *J. Am. Chem. Soc.* **1975**, *97*, 1813.

Radical Cyclization to Schiff Bases with N-5/C-6

Regiochemistry

The preferred mode of aryl radical cyclization to Schiff bases is also in the 6-endo sense to the C-atom as discovered for the isobutyraldimine **164**. The selectivity of closure to the Schiff base, however, is lower than that found for the isobutyraldimine **164**. For example, cyclization of the benzaldimine **176**, in the presence of excess Bu_3SnH (10 equivalents) and 5% AIBN, gave an tetrahydroisoquinoline **177** to indoline **178** ratio of ca. 4:1 (taken from Table 4 below) while for the isobutyraldimine **164** this ratio was ca. 55:1 (Scheme 61). Spectral data for the minor isomer **178**, matched well with the authentic indoline **178** (Scheme 55). In addition to tetrahydroisoquinoline **177**, indoline **178** and reduced starting material **179**, some thermolysis mixtures from benzaldimine **176** contained N-benzylphenethylamine (**180**).

Scheme 61



Explanation of Regiochemistry in Cyclization to C=N with N-5/C-6

The regiochemistry of aryl radical cyclization to C=N is in stark contrast to that found in aryl radical cyclization of alkenes. For example, *o*-butenylphenyl radical (**41**) yields mainly 5-exo product with less than 5% of 6-endo product.⁴⁵ An examination

of bond energies and geometries of imines compared to those of alkenes provides a potential explanation for the 6-endo regioselectivity in radical cyclization to C=N. Endocyclic ring closure for these imines results in a C—C bond which is inherently ca. 10 kcal/mol stronger than a C—N bond.¹³³ This difference is presumably enhanced by ring strain and reduced by resonance stabilization of α -anilinoalkyl. The stabilization of α -aminoalkyl radicals relative to aminyl radicals is estimated at ca. 5 kcal/mol.⁸⁸ Although the 6-membered radical is likely to be somewhat more stable, there are important features other than product stability that affect the relative energies of the transition states for cyclizations. The geometry of imino compounds (C=N bond length 1.30 Å, C-N bond length 1.44 Å, C—N=C angle 116.9°)¹³⁴ compared to that of alkenes (C=C bond length 1.336 Å, Csp¹-Csp² bond length 1.501 Å, C—C=C bond angle 124.3°)¹³⁵ may be largely responsible for the facile 6-endo cyclization to C=N. Single and double bond shortening as well as angle tightening in the imino aryl radicals improve the interorbital alignment between the SOMO and π LUMO of the imine in the transition structure for 6-endo closure.¹⁹ Moreover, calculated coefficients (AM1, version 2.1) for the imine π LUMO of isobutyraldimine **168** are 0.70 (C) and 0.62 (N) and for benzaldimine **179** are 0.60 (C)

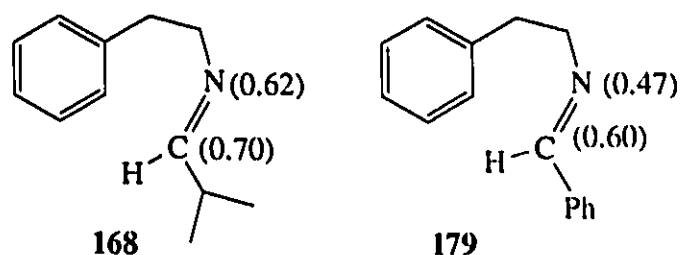
(133) Sandorfy, C. In *The Chemistry of the Carbon-Nitrogen Double Bond*; Patai, S., Ed.; Interscience Publishers: London, 1970; p6.

(134) Values for N-methylenemethanamine as determined by microwave spectroscopy: Sastry, K.V.L.N.; Curl, R.F. *J. Chem. Phys.* 1964, 41, 77.

(135) Values for propene as determined by microwave spectroscopy, see: Lide, D.R.; Christensen, D. *J. Chem. Phys.* 1961, 35, 1374.

and 0.47 (N), which would favour an attack at the carbon atom kinetically (Figure 2).¹⁰

Figure 2. π LUMO Coefficients of the Imino Group (AM1).



Other Reactions of C=N

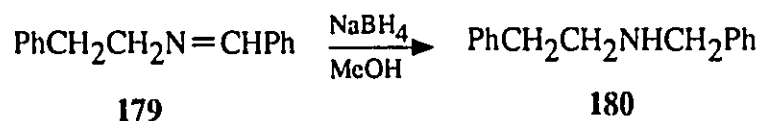
Before undertaking a thorough study of the kinetic data for the cyclization in the Schiff bases, it was deemed necessary to examine reduction of the carbon-nitrogen double bond by tin hydride. The greatest proportion of the reduced product is found in cyclization reactions carried out with high concentrations of Bu_3SnH . For example, changing the Bu_3SnH concentration from 0.29 to 1.42 M in the thermolysis of *p*-tolylaldimine **181** increased the ratio of amine **185** to tetrahydroisoquinoline **182** from ca. 0.01 to 0.97 (Scheme 62 and Table 3). ^2H NMR spectroscopy also revealed that the concentration of Bu_3SnH is tied to amine formation. The deuterated benzaldimine **186** was heated with two different concentrations of Bu_3SnH (Scheme 63). The solution containing a Bu_3SnH concentration of 0.52 M gave a product mixture in which some 7% was assignable to the amine **190**. When the concentration of Bu_3SnH was 0.06 M, however,

Table 3. Kinetic Data for Cyclization of p-Tolylaldimine 181 at 80 °C.

[SnH] ^a , M	Pdt Ratios ^b		
	182/184 (6H/5H)	182/189 (6H/RH)	185/182
1.42	3.4	0.32	0.97
0.892	4.1	0.43	0.44
0.535	3.8	0.63	0.19
0.287	4.2	1.1	<0.01
0.072	4.6	3.5	
0.043	5.0	5.0	
0.014	6.3	13.	

^a Effective concentration of Bu₃SnH, in 10 fold excess. The numbers are average concentrations, based on a 1:1 stoichiometry.

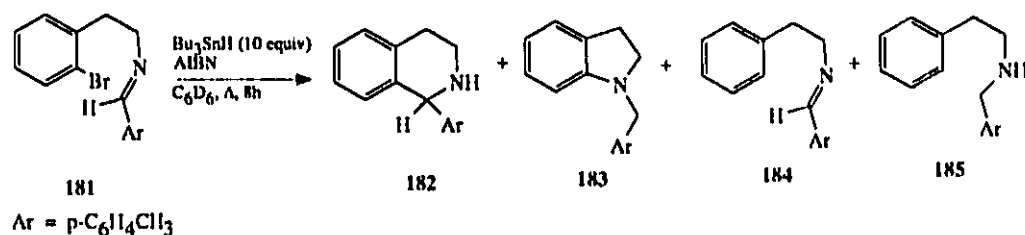
^b Product ratios determined by integration of the ¹H NMR (500 MHz) spectra. Reactions were run in PhH with 5% AIBN. The presence of 184 and 183 was verified by their independent synthesis (Schemes 50 and 55).



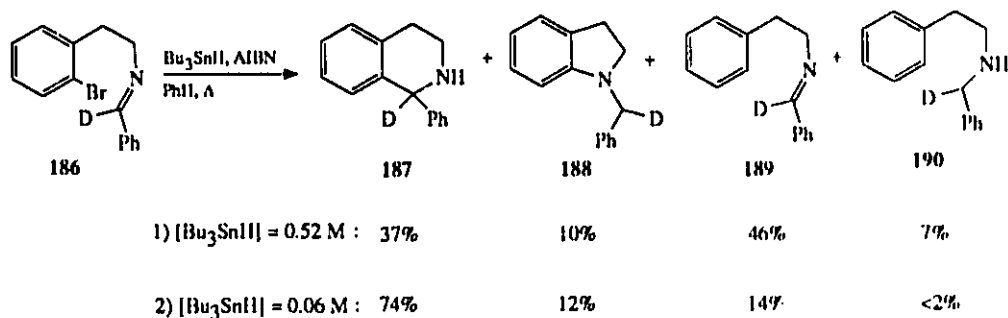
none of the amine 190 could be detected (<2%). The identity of the amine was checked by independent synthesis¹³⁶ of the nondeuterated analogue 180 and by comparing the ¹H NMR spectra and GC retention times to those of the reduction product from 186.

(136) Billman, J.H.; Dising, A.C. *J. Org. Chem.* 1957, 22, 1068.

Scheme 62



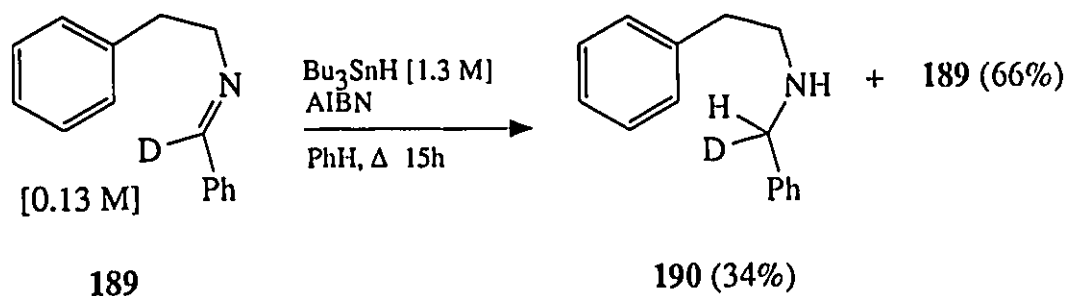
Scheme 63



The question of whether reduction of the C=N by Bu₃SnH competes effectively with bromine-atom abstraction by Bu₃Sn• was investigated next. If the reduction of the imino group is slower than Br-atom abstraction, it may be possible to complete the cyclization reactions before a substantial amount of amine is formed. A solution containing benzaldimine-d **186** (0.05 M), a catalytic amount of AIBN, and Bu₃SnH (0.51 M) was heated at 80°C. The progress of the reaction was monitored by ²H NMR and ¹H NMR spectroscopy. After 23 min, the ratio of starting material **186** to dehalogenated imine **189** was ca. 1 and no amine **190** was detected. After 75 min, the cyclization reaction was complete as no starting material **186** was evident and, most importantly, none of the amine **190** could be found (²H NMR). The ratio of **189** to **187**

was 1.4. After heating for a total of 43 h, however, some 5% of the product mixture was assignable to the amine **190** (^2H NMR). The ratio of **189** to **187** accordingly decreased slightly to 1.2. The ratio of tetrahydroisoquinoline **187** to indoline **188** was ca. 4.4 throughout. Heating a mixture of the deuterated benzaldimine **189**, Bu_3SnH and AIBN for 15 h, gave the amine **190** (^2H NMR) (Scheme 64). These data clearly show that bromine atom abstraction is faster than reduction of the Schiff base.

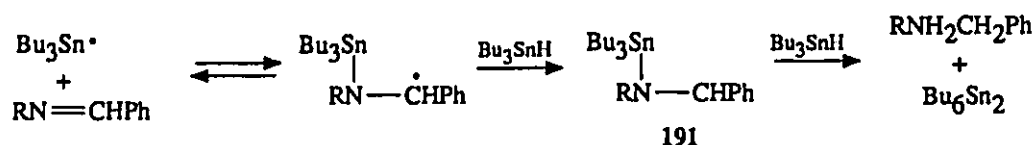
Scheme 64



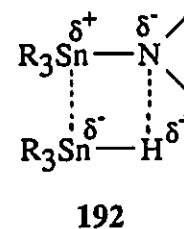
The first step in the reduction of the carbon-nitrogen double bond by Bu_3SnH is thought to involve the reversible addition of stannyl radicals to the N-atom of the C=N functional group (Scheme 65). Abstraction of an H-atom from Bu_3SnH gives the aminostannane **191**. Attempts to observe the aminostannane by ^{119}Sn NMR were unsuccessful,¹³⁷ which is likely due to a fast subsequent reaction between the aminostannane and Bu_3SnH . The reactivity of aminostannanes has been compared to that of Grignard reagents and may be attributed to a combination of a weak and highly polar

(137) For some ^{119}Sn NMR chemical shifts, see: Wrackmeyer, B. *Annu. Rep. NMR spectrosc.* 1985, 16, 73.

Scheme 65



$\text{Sn}^{\delta+}-\text{N}^{\delta-}$ bond.¹³⁸ The Sn-N bond in aminostannanes is readily cleaved by protic species with pKa values of less than ~ 25 .¹³⁹ Although the exact mechanism for the reaction of aminostannane with Bu_3SnH is not known, the polar mechanism, involving transition structure 192 has been proposed.¹⁴⁰



The reactivity of aminostannanes with Bu_3SnH was briefly explored using the model compound $\text{Bu}_3\text{SnNEt}_2$ (193). Aminostannane 193 was prepared from LiNEt_2 and Bu_3SnCl (Scheme 66).¹⁴¹ Mixing $\text{Bu}_3\text{SnNEt}_2$ (193) and Bu_3SnH at room temperature gave 60% of the amine within 30 min (^1H NMR).

The reduction of C=N by Bu_3SnH may also explain the previous finding that the 3,4-dihydroisoquinolines were consistently detected only at low concentrations of Bu_3SnH . At the high $[\text{Bu}_3\text{SnH}]$, the 3,4-dihydroisoquinolines 172 and 194 may be reduced

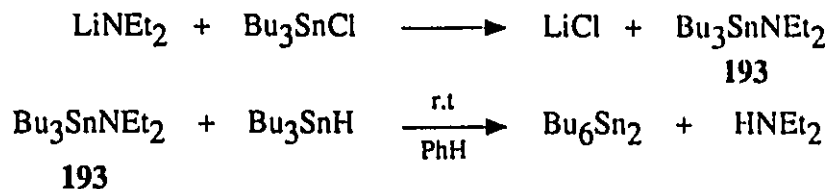
(138) Jones, K.; Lappert, M.F. *Organomet. Chem. Rev.* 1966, 1, 67.

(139) Jones, K.; Lappert, M.F. In *Organotin Compounds*; Sawyer, A.K., Ed.; Marcel Dekker: New York, Vol. 2, 1971; p509.

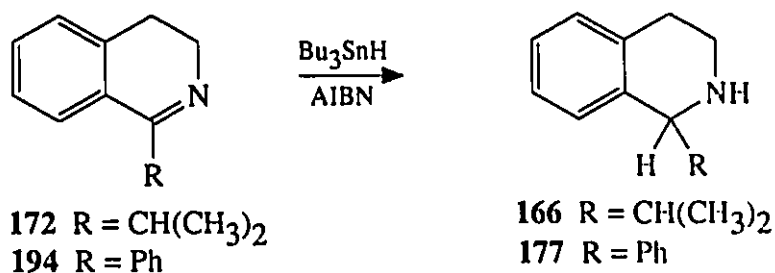
(140) Creemers, H.M.J.C.; Verbeck, F.; Noltes, J.G. *J. Organometal. Chem.* 1967, 8, 469.

(141) Jones, K.; Lappert, M.F. *J. Chem. Soc.* 1965, 1944.

Scheme 66



Scheme 67



back to the tetrahydroisoquinolines **166** and **177**, respectively (Scheme 67). Furthermore, the rate of addition of $\text{Bu}_3\text{Sn}\cdot$ to the 1-phenyl-3,4-dihydroisoquinoline (**194**) may be faster than to the 1-isopropyl-3,4-dihydroisoquinoline (**172**) because of the additional resonance stabilization afforded by the phenyl group. This may explain the fact that less of the 3,4-dihydroisoquinoline product was typically found from the cyclization of the benzaldimine **176** as compared to the isobutyraldimine **164**.

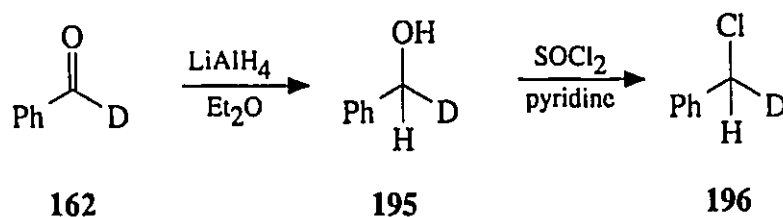
Kinetics of Radical Cyclization to Schiff Bases

Table 4 gives the product ratios for the cyclization of the deuterated benzaldimine **186**. Thermolyses were conducted at 80°C with 9.8-fold excess of Bu_3SnH and 6% AIBN. The reactions were monitored by ^1H NMR and the heating was stopped

upon depletion of the starting Schiff base **186**. The product ratios **187/188** (6H/5H) were determined from the peak heights in the ^2H NMR (76.8 MHz) spectra and are recorded along with error limits ($\pm 2\sigma$). Authentic deuterated indoline **187** was prepared by alkylation of indoline with benzyl- α -d chloride (**196**) (Scheme 55). Benzyl- α -d chloride (**196**), in turn, was prepared in two steps from benzaldehyde-1-d (**162**) (Scheme 68).^{142, 143}

The dependence of the **193/194** (6H/5H) product ratio on $[\text{Bu}_3\text{SnH}]$, in Table 4, does not agree with the general mechanism in Scheme 56. Application of the usual steady state approach shows that if exo and endo derived products are generated solely by unimolecular 5-exo and 6-endo cyclizations, respectively, then their ratio should be independent of the tin hydride concentration at any fixed temperature. The ratio **187/188** (6H/5H) was ca. 4.1 at $[\text{Bu}_3\text{SnH}] \geq 0.167$ M, while at the concentration of 0.021 M the ratio of **187/188** increased to 5.2 (Table 4). Interconversion between the cyclized products,

Scheme 68



tetrahydroisoquinoline **177** and indoline **178**, was checked by heating them in the presence

(142) Kwart, H.; Brechbiel, M.W. *J. Org. Chem.* 1982, 47, 461.

(143) Gannon, W.F.; House, H.O. In *Organic Synthesis Collective Volume 5*; Baumgarten, H.E., Ed.; John Wiley: New York, 1973; p294.

Table 4. Kinetic Data for Cyclization of Benzaldimine-d **186** at 80 °C.

[SnH] ^a (M)	Product Ratios ^c			Rate Csts (M)	
	187/188 (6H/5H)	187/189 (6H/RH)	188/189 (5H/RH)	k _d /k ₁₁	k ₂ /k ₁₁ x 10 ²
0.666	4.2±0.2	0.48±0.04	0.12±0.01	0.32±0.02	7.7±0.6
0.333	4.1±0.2	0.96±0.06	0.23±0.02	0.32±0.02	7.8±0.6
0.167	4.1±0.2	2.0±0.1	0.49±0.02	0.33±0.02	8.2±0.4
0.083	4.4±0.2	4.2±0.2	0.94±0.04	0.35±0.02	7.9±0.4
0.042	4.8±0.2	≥ 7.0	≥ 1.4	≥0.29	≥6.1
0.021	5.2±0.2	≥13.	≥ 2.6	≥0.28	≥5.4
0.021	5.2±0.2	≥14	≥ 2.8	≥0.30	≥5.8
0.021	5.4±0.4	≥20	≥ 3.7	≥0.42	≥7.8
0.19 ^b	16.	18	1.1		

^a Except for 0.19 M run, Bu₃SnH in 9.8 fold excess and the concentrations are averages based on a 1:1 stoichiometry. Solvent was PhH with 6% AIBN and solutions were degassed and flame sealed.

^b Bu₃SnH in 1.4 fold excess added with AIBN (0.35 equiv) via a syringe-pump over 18 h to **186** [0.05 M] all in PhH.

^c Ratios from peak heights and 95.5% confidence limits ($\pm 2\sigma$) from ²H NMR (76.8 MHz) spectra. For full relaxation between pulses, the pulse delay was set at 1.5 s; T₁ values (s): **187** (0.21), **188** (0.30), **189** (0.27). A gravimetric calibration was done. At [Bu₃SnH] < 0.083 M, the natural abundance ²H in PhH interferes with the signal from **189**.

of Bu₃SnH and catalytic amount of AIBN. No interconversion was found after heating for 22 h at 80°C.

That the trend in product ratios was real was shown by thermolysis of

benzaldimine-d 186 with dilute tin hydride (Table 4). Syringe-pump addition of Bu_3SnH to benzaldimine-d 186 gave a 187/188 ratio of 16/1 (^2H NMR and GC). The same trend in the ratio of 6H to 5H product was evident from the cyclization of the p-tolylaldimine 181, as determined by integrating the ^1H NMR spectra (Table 3). Photolysis of Me_6Sn_2 in the presence of benzaldimine 176 gave a 177/178 (6H/5H) ratio of ca. 20/1. Furthermore, thermolyses carried out in the presence of a different H-donor, namely tris(trimethylsilyl)silane, showed the same trend in the ratio of 6H to 5H (Table 5).

Table 5. Product Ratios for Cyclization of 176 with $(\text{Me}_3\text{Si})_3\text{SiH}$ at 80 °C.

[SiH] ^a , M	Product Ratios ^b		Conversion %
	177/178 (6H/5H)	177/179 (6H/RH)	
0.628	3.4	1.4	46
0.126	5.2	2.1	35
0.063	7	1.7	31

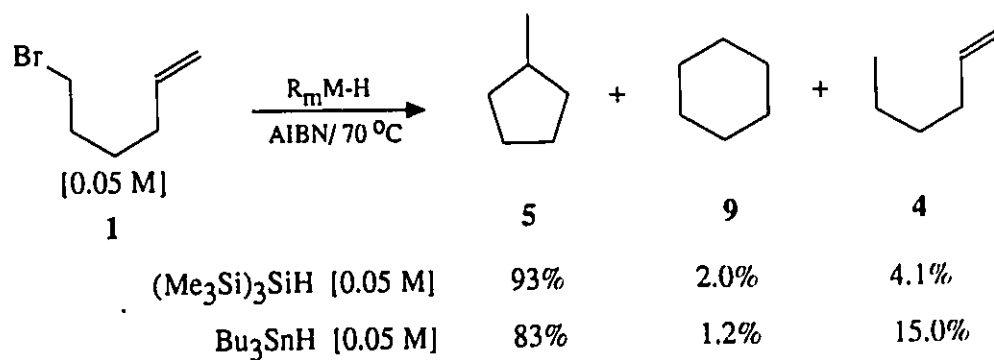
^a $(\text{Me}_3\text{Si})_3\text{SiH}$ was used in 10 fold excess. The concentrations are at time 0. Solvent was C_6D_6 with 11% AIBN and the solutions were degassed and flame sealed. The samples were heated for 20 h.

^b Ratios were determined from ^1H NMR (200 MHz) spectra and are only approximate.

It is not totally clear, however, why the cyclizations reactions conducted with silane showed low conversions, ca. 40%. Giese and co-workers found that the cyclization of 1-bromo-5-hexene (1) with $(\text{Me}_3\text{Si})_3\text{SiH}$ gave more cyclic product than when Bu_3SnH was used as the H-donor (Scheme 69).¹⁵ Silyl radicals are known to be excellent Br-atom

abstractors. The rate constant for bromine atom abstraction from an aryl bromide by $(\text{Me}_3\text{Si})_3\text{Si}\cdot$ is^{17b} $k_{\text{Br}}^{\text{Si}} = 4.6 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ and is higher than that by $\text{Bu}_3\text{Sn}\cdot$,¹⁴⁴ $k_{\text{Br}}^{\text{Sn}} = 2.4 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$, both at 80°C . The rate constant for attack of alkyl radicals on $(\text{Me}_3\text{Si})_3\text{SiH}$, however, is ca. 10 times smaller than attack on Bu_3SnH .^{17a} For example, the rate constant for the reaction of a secondary alkyl radical with $(\text{Me}_3\text{Si})_3\text{SiH}$ is^{17a} $k_{\text{SiH}} = 1.38 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$, while that for Bu_3SnH is⁴⁶ $k_{\text{SnH}} = 1.47 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ at 25°C . A small rate constant for the H-abstraction from $(\text{Me}_3\text{Si})_3\text{SiH}$ by the aminyl radical **197** and the α -aminoalkyl radical **198** would collapse the radical chain reaction, resulting in low conversion of the starting material.

Scheme 69

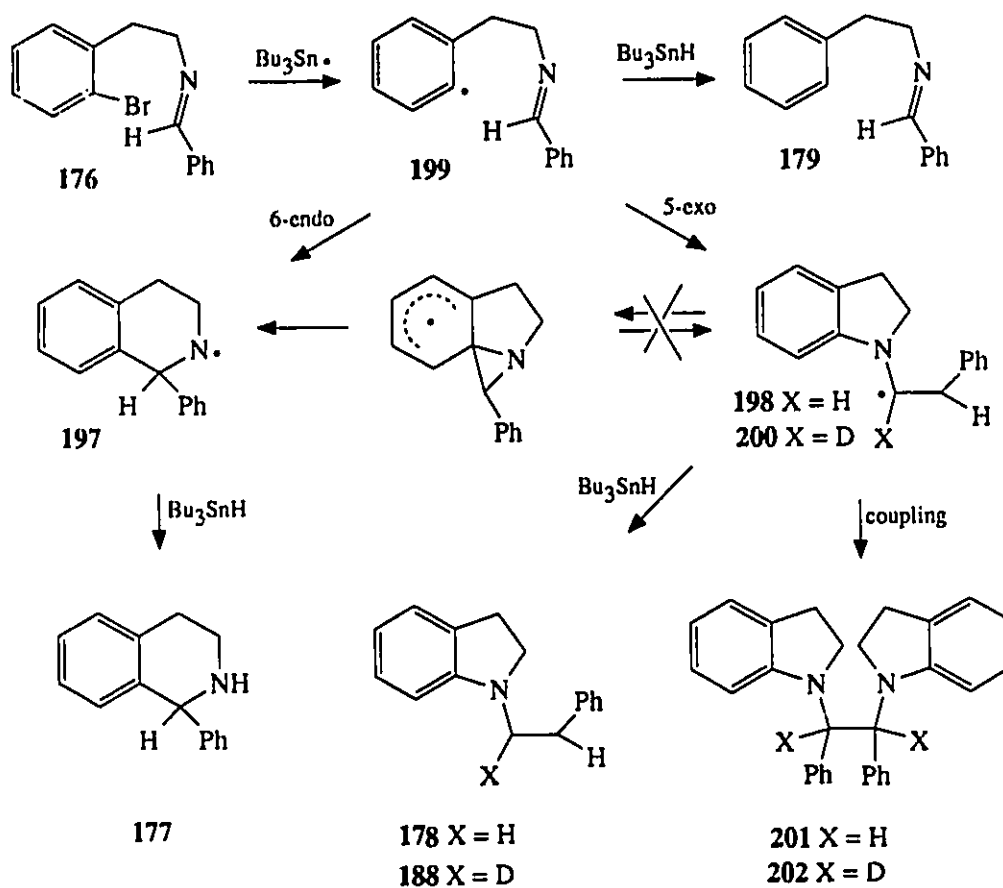


The kinetic data in Tables 3 and 4 are consistent with any process that results in the conversion of the 5-membered exo-radicals into their 6-membered endo counterparts. Two such processes are: (i) the neophyl rearrangement and (ii) ring

(144) Curran, D.P.; Jasperse, C.P.; Totleben, M.J. *J. Org. Chem.* **1991**, *56*, 7169.

opening followed by recyclization in the endo mode. Ring opening of the highly stabilized indoliny radical **198** to either the primary alkyl radical or the aryl radical would be highly endothermic. Therefore, reversibility of cyclization need not be considered.

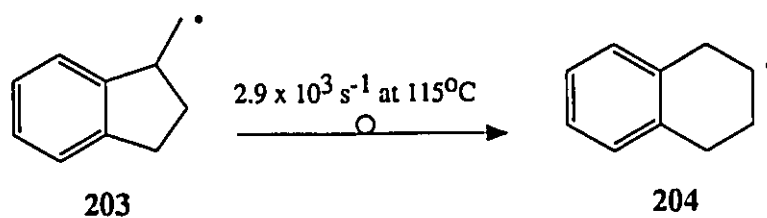
Scheme 70



Beckwith and co-workers have explained a similar trend in product ratios to that found in Tables 3 and 4 in terms of the neophyl rearrangement (Schemes 18 and 19). At the high concentrations of Bu_3SnH , the indoliny radical **198** and tetrahydroisoquinoliny radical

radicals **197** would be formed by direct closure of the intermediate aryl radical **199**, according to Scheme 70. At the lower concentrations of Bu_3SnH , and the longest lifetime of the indolinyl radical **198**, the neophyl rearrangement of 5-membered indolinyl radical **198** to the 6-membered isoquinolinyl radical **197** would be most likely. The thermodynamic driving force for rearrangement of **198** to **197**, however, is quite small. This reaction would be only mildly exothermic and therefore slow, like other neophyl rearrangements. The rate constant for rearrangement of the primary radical **203** to the secondary radical **204** is only ca. $2.9 \times 10^3 \text{ s}^{-1}$ at 115°C (Scheme 71).⁵¹ Moreover, attempts to rearrange indoline **178** to the isoquinoline **177**, in the presence of decomposing initiators, AIBN, and di-*t*-butyl peroxide, all failed.

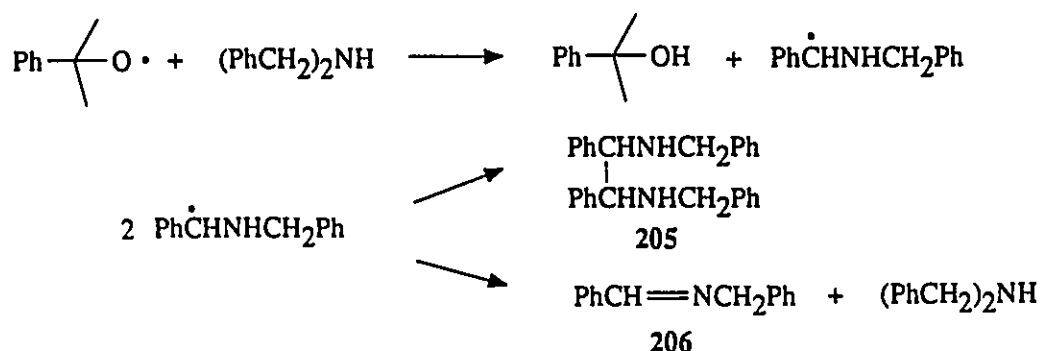
Scheme 71



The most likely explanation for the trends in Tables 3 and 4 is that the isoquinolinyl **197** and the indolinyl **198** radicals are both formed directly from aryl radical **199**, but at the low $[\text{Bu}_3\text{SnH}]$, indolinyl radicals **198** are lost to radical-radical coupling reactions (Scheme 70). The rate constant for H-atom abstraction from Bu_3SnH by the indolinyl radical **198** is anticipated to be relatively small. The indolinyl radical **198** is highly stabilized by virtue of being both benzylic and an α -aminoalkyl radical. The

maximum value for the rate constant in the attack of benzyl radical on Bu_3SnH is $3 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$, which is at least tenfold less than the rate constant for reaction of ethyl radical with Bu_3SnH ($k_{11} = 2.3 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$) both at room temperature.⁴⁶ It is not unreasonable, therefore, to expect indolyl radicals **198** to engage in radical-radical reactions at low Bu_3SnH concentrations. Ratcliff and Kochi¹³⁰ prepared the analogous radical by thermolysis of dibenzylamine with dicumyl peroxide (Scheme 72). The predominant products were the dimer **205** and N-(benzylidene)benzylamine (**206**) in 2 to 1 ratio, respectively. The absence of an proton α to the radical site in the indolyl radical **198** rules out the disproportionation reaction. Evidence of coupling products was found in the MS. Mass spectrometric analysis of the crude reaction mixtures, from the reactions in Table 4 carried out at low $[\text{Bu}_3\text{SnH}]$, showed a peak of the correct mass to correspond to indoline dimer **202**. From the isotopic distribution in the species the presence of tin atoms could be ruled out.

Scheme 72

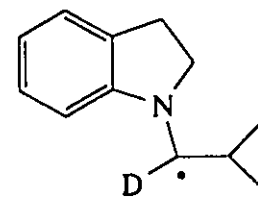


The question of why the products of coupling were not evident in the ^2H

NMR spectra (Table 4) was also investigated. Dropping the tin hydride concentration from 0.666 M to 0.021 M, changed the **187/188** (6H/5H) product ratio from 4.1 to 5.2. This corresponds to a reduction of the yield of indoline by some 4% or to a dimer concentration of ca. 4×10^{-5} M. The limit for detectability in the ^2H NMR spectra was calculated to be very close to the above dimer concentration, ca. 3.5×10^{-5} M. Although these calculations are only approximate, it is not surprising that the coupling product **202** was not evident in the ^2H NMR spectra.

Rate constants for the 6-endo and 5-exo cyclizations of the aryl radicals to the benzaldimino group in **186** were calculated in the usual way from the product ratios in Table 4 (6H/RH and 5H/RH, respectively, obtained with Bu_3SnH in large excess). The rate constant for attack of ortho substituted aryl radicals on Bu_3SnH (k_{11}^{Ar}), estimated to be⁵² $5.0 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ at 80°C , gives $k_6 = 1.6 \times 10^8 \text{ s}^{-1}$, at 80°C . The corresponding rate constant for 5-exo closure, determined from $k_{5\text{-exo}}/k_{11} (\text{M}) = 0.08$ at $[\text{Bu}_3\text{SnH}] > 0.083 \text{ M}$, is $4.0 \times 10^7 \text{ s}^{-1}$, at 80°C .

The rate constant for endocyclic closure to the isobutyraldimino group in **165**, $k_{6\text{-endo}} = 1.2 \times 10^8 \text{ s}^{-1}$, is similar to that for the closure to the benzaldimine **186**, $k_6 = 1.6 \times 10^8 \text{ s}^{-1}$, both at 80°C . The rate constant $k_{5\text{-exo}}$ for addition in the benzaldimine **186** is $k_5 = 4.0 \times 10^7 \text{ M}^{-1}\text{s}^{-1}$, while the analogous

**207**

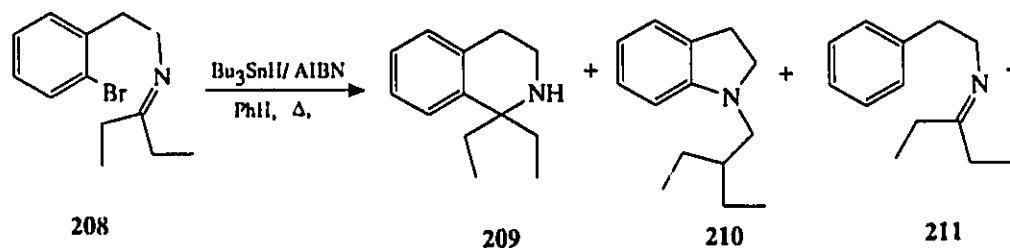
closure in isobutyraldimine **165** is slower, with $k_5 = 2.2 \times 10^6 \text{ s}^{-1}$, both at 80°C . This is probably a reflection of stability afforded by the phenyl group in the product from

exocyclic closure in the Schiff base (200 versus 207).

Cyclization to Ketimine of 3-Pentanone with N-5/C-6

The results of a series of thermolyses of ketimine 208 with Bu_3SnH and catalytic AIBN are summarized in Table 6. Degassed solutions were heated at 80°C in sealed tubes with 1.9 equivalents of Bu_3SnH and 5% AIBN in PhH. When higher concentrations of tin hydride were employed the proportions of cyclized products 209 and 210 were low and the reactions were dirty. These data are in stark contrast to those found for radical cyclization reactions in the isobutyraldimine 165 (Table 2) and benzaldimine

Scheme 73



186 (Table 4). By increasing the steric bulk at the C-6 atom of the imino group, the product distribution has been completely altered. Even in the most dilute solution studied, $[\text{Bu}_3\text{SnH}] = 0.008 \text{ M}$, the major product was the dehalogenated starting material 211 (Table 6). Furthermore, by making the 6-endo terminus more sterically hindered, the regioselectivity of the ring closure, the ratio of 209/210 (6H/5H), had dropped to ca. 1 at 80°C . This is in agreement with Beckwith's second guideline: substituents on an olefinic bond disfavour homolytic addition at the substituted position. The rate constant for 5-exo

closure of the 5-methyl-5-hexenyl radical (17) is some 40 fold lower than that in the 5-hexenyl radical (2) (Scheme 74).¹⁹ Bartlett and co-workers,^{8,3d} in their study of radical cyclization to oxime ethers, also found that the placement of a methyl substituent at the C-atom of the hydroxyimino group, the site of radical attack, had a pronounced effect on the regioselectivity of that reaction (Scheme 75).

Table 6. Product Ratios and Rate Csts for Cyclization of Ketimine 208 at 80 °C.

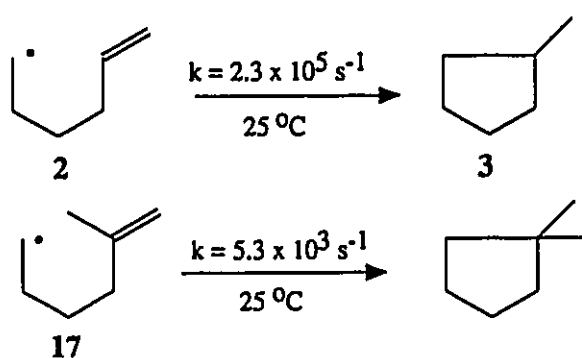
[SnH] ^a , M	Product Ratios ^b			Ratios of Rate Csts (M), x 10 ³	
	209/210	209/211	210/211	k ₆ /k ₁₁	k ₅ /k ₁₁
	(6H/5H)	(6H/RH)	(5H/RH)		
0.057	0.1	0.1	0.1	5.7	5.7
0.043	0.92	0.12	0.13	5.2	5.6
0.034	0.87	0.13	0.15	4.4	5.1
0.034	0.88	0.14	0.16	4.8	5.4
0.17	1.0	0.19	0.19	3.2	3.2
0.008	0.6	0.4	0.7	3.2	5.6

^a Effective concentration of Bu₃SnH, in 1.9 fold excess. The numbers are average concentrations, based on a 1:1 stoichiometry. Reactions were run in PhI with 5% AIBN and the solutions were degassed and flame sealed.

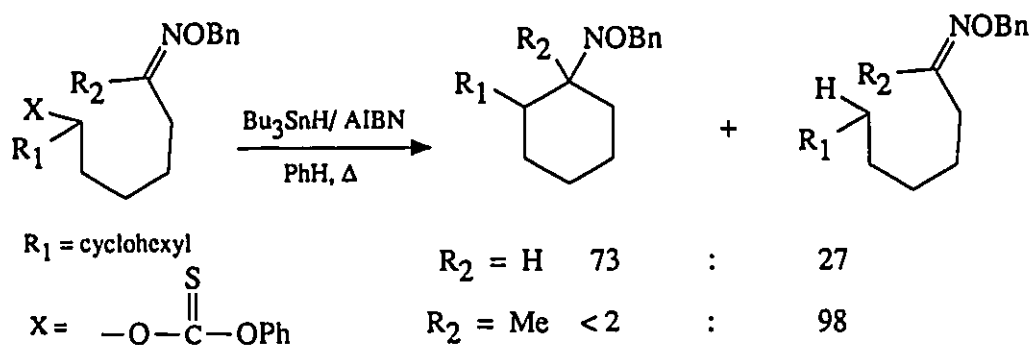
^b Approximate ratios as determined from the integrals in the ¹H NMR (500 MHz) spectra.

Based on the expected mechanism illustrated in Scheme 56, the standard kinetic expression may be used to calculate the rate constants:

Scheme 74



Scheme 75



$$k_c/k_{ii} = c/u [\text{Bu}_3\text{SnH}] \quad [1]$$

where c and u are the concentrations of the cyclized and uncyclized products and $[\text{Bu}_3\text{SnH}]$ is the average stannane concentration. A more accurate method of estimating k_c/k_{ii} involves solving the integrated rate expression:⁵⁷

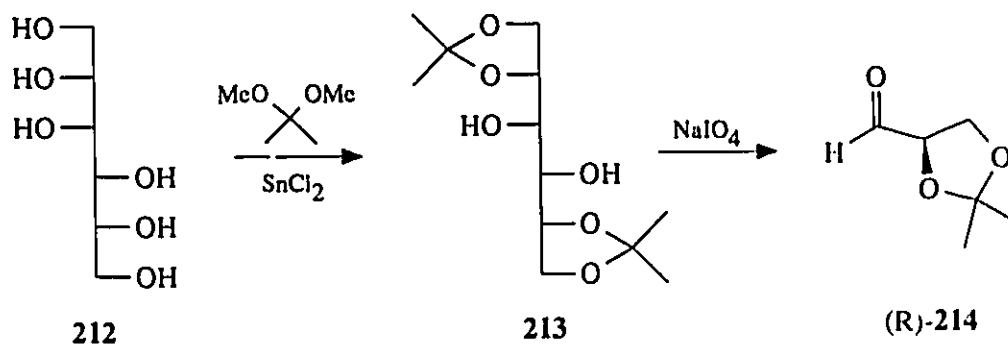
$$c = k_c/k_{ii} \{ \ln([\text{SnH}]_0 + k_c/k_{ii}) - \ln([\text{SnH}]_f + k_c/k_{ii}) \} \quad [2]$$

in which $[\text{SnH}]_0$ and $[\text{SnH}]_f$ are the initial and final values for $[\text{Bu}_3\text{SnH}]$, respectively. Beckwith, however, found the results obtained from equation 1 to be in good agreement with those from the more accurate rate equation 2.

Substituting into equation 1 the rate constant for the attack of ortho substituted aryl radicals on Bu_3SnH (k_{H}^{\wedge}), estimated⁵² to be $5.0 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ at 80°C , into $k_{\text{6}}/k_{\text{H}} = 0.0044$ and $k_{\text{5}}/k_{\text{H}} = 0.0051$, gives $k_{\text{6-endo}}$ ca. $2.2 \times 10^6 \text{ s}^{-1}$, and $k_{\text{5-exo}}$ ca. $2.5 \times 10^6 \text{ s}^{-1}$ at 80°C . The 5-exo rate constant is identical to that found for 5-exo closure on the isobutyraldimino group in **165**. The 6-endo rate constant for closure to the ketimino group, in turn, is some 60 fold smaller than that found in the isobutyraldimino group in **165**.

Chiral Induction in Aryl Radical Cyclization to C=N

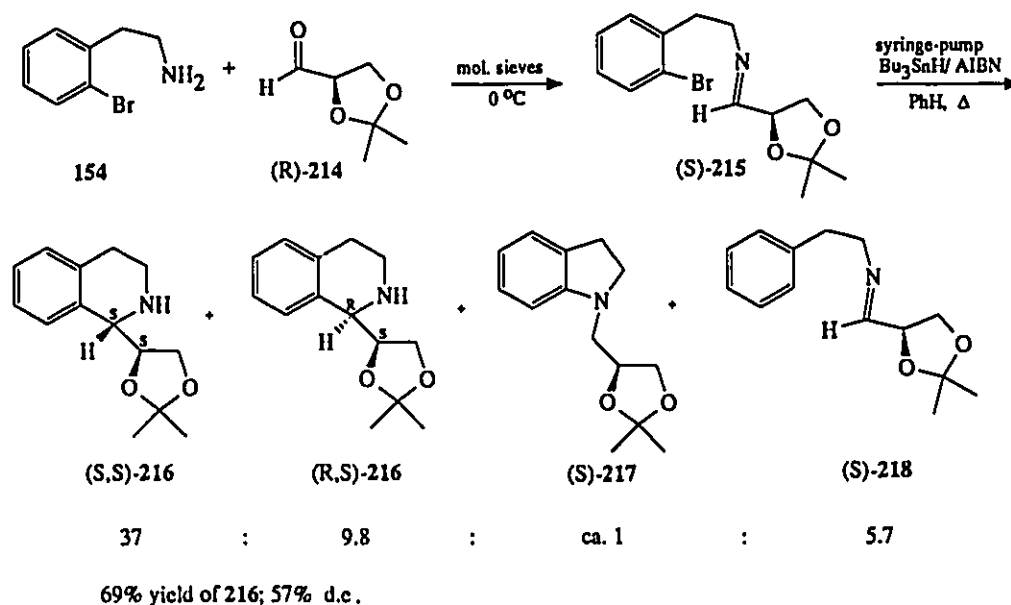
Scheme 76



Having found that the highest regioselectivity of aryl radical closures to C=N are to C-alkylaldimines, we investigated next the diastereoselectivity of radical cyclizations to C=N. The chiral functionality was positioned close to the site of radical attack in order to increase the likelihood of observing diastereoselectivity on radical closure. Sugars are a common and inexpensive source of chiral building blocks. The

chiral aldehyde utilized was (R)-2,3-O-isopropylidene-D-glyceraldehyde ((R)-214) which was prepared in two steps from D-mannitol (212) (Scheme 76).¹⁴⁵ Ketalization of D-mannitol (212) with 2,2-dimethoxypropane, in the presence of catalytic stannous chloride, afforded 1,2:5,6-diisopropylidene-D-mannitol (213) in 48% yield. Sodium periodate oxidation of the glycol 213 gave the desired aldehyde (R)-214 in 80% yield. Condensation of (R)-2,3-O-isopropylidene-D-glyceraldehyde ((R)-214) with the 2-bromophenethylamine (154) at 0°C in the presence of molecular sieves gave the chiral aldimine (S)-215 (Scheme 77). It was shown to be of high purity by ¹H NMR, ¹³C NMR and GC analysis.

Scheme 77



Attempts to distill aldimine (S)-215 led to considerable decomposition.

(145) Schmid, C.R.; Bryant, J.D.; Dowlatzedah, M.; Phillips, J.L.; Prather, D.E.; Schantz, R.D.; Sear, N.L.; Vianco, C.S. *J. Org. Chem.* 1991, 56, 4056.

Thermolysis of chiral aldimine (S)-**215** at 80°C with syringe-pump addition of Bu₃SnH and AIBN gave the following ratio of products; (S,S)-**216** : (R,S)-**216** : (S)-**217** : (S)-**218** = 37:9.8:ca. 1.0:5.7 (GC and ¹H NMR) (Scheme 77). In all cases the absolute configuration at C-1 is specified first, and that of C-1' is given second. The diastereomeric isoquinolines (S,S)-**216** and (R,S)-**216** were separable by chromatography. The isolated yield of isoquinoline diastereomers was 69% in a diastereomeric excess (de) of 57% (ratio of (S,S)-**216**/(R,S)-**216** = 3.7:1).¹⁴⁶ The diastereoselectivity of this cyclization was improved moderately by lowering the reaction temperature. Thermolysis of chiral aldimine (S)-**215** at 60°C, gave a de of 65% (ratio of (S,S)-**216**/(R,S)-**216** = 4.7:1). An excess of AIBN was required in the lower temperature reactions, as the half-life of AIBN is ca. 60h at 60°C.³

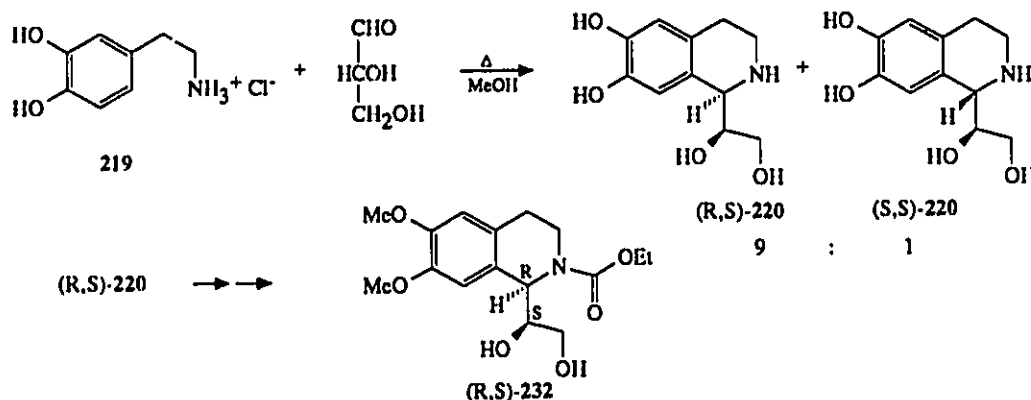
The stereochemistry at C-1 in the tetrahydroisoquinoline **216** was assigned by conversion to a compound of known absolute configuration. In 1986, MacLean and co-workers,¹⁴⁷ in their enantioselective synthesis of isoquinoline alkaloids, prepared the similar isoquinoline derivative (R,S)-**232** for which they reported the optical rotation and ¹H NMR spectrum (Scheme 78). MacLean and co-workers prepared diastereomeric isoquinolines (R,S)-**220** and (S,S)-**220** in a 9 to 1 ratio, respectively, by a Pictet-Spengler condensation of the dopamine hydrochloride **219** with R-(+)-glyceraldehyde. Although the

(146) Percent stereoselectivity = $(1-r)/(1+r) \times 100$, where r is the ratio of isomers.

(147) Czarnocki, Z.; MacLean, D.B.; Szarek, W.A. *Can. J. Chem.* **1986**, *64*, 2205.

conversion of radical derived isoquinoline **216** to the MacLean isoquinoline **232** was not feasible, it was possible from the dimethoxy isoquinoline **224**.

Scheme 78

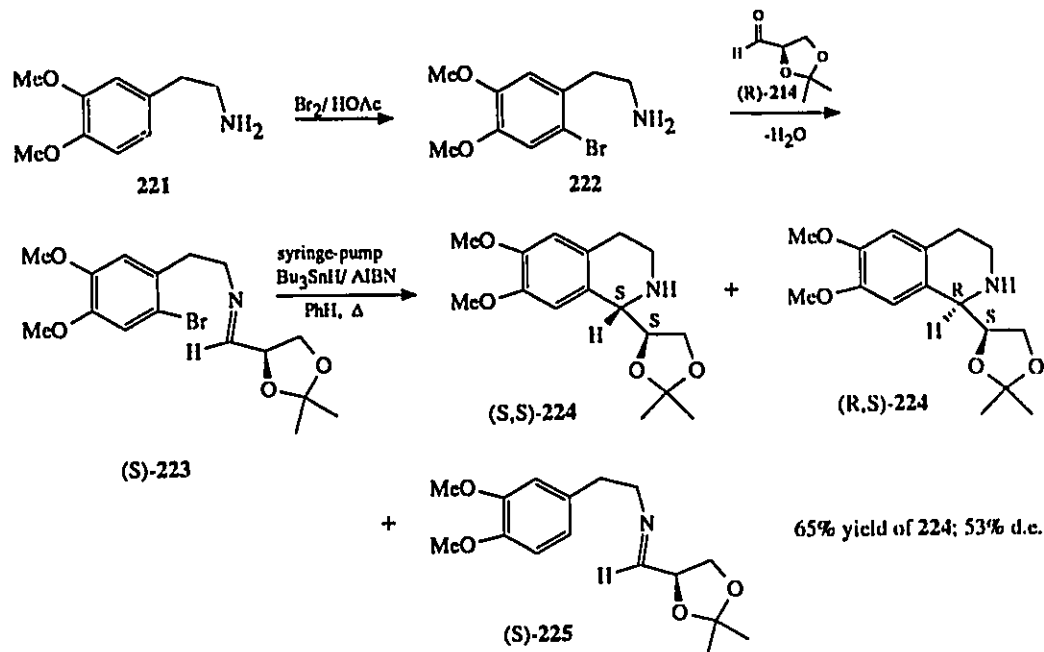


Bromination of 3,4-dimethoxybenzeneethanamine (**221**) in glacial acetic acid gave the required amine **222** (Scheme 79).¹⁴⁸ Condensation of amine **222** with (R)-2,3-*O*-isopropylidene-D-glyceraldehyde ((R)-**214**) gave the dimethoxyaldimine **223**, which was used immediately in the radical cyclization. Thermolysis of aldimine (S)-**223** with syringe-pump addition of Bu_3SnH and AIBN gave the product ratio of (S,S)-**224** : (R,S)-**224** : (S)-**225** = 3.3:1:0.8 (^1H NMR and GC). The diastereomeric isoquinolines (S,S)-**224** and (R,S)-**224** were separated by chromatography. The isolated yield of isoquinoline diastereomers was 65% in a diastereomeric excess of 53%.

To check for racemization in either the synthesis of aldimine (S)-**223** and/or the radical cyclization, the enantiomeric purity of the major diastereomer (S,S)-**224** was determined. The common NMR methods used to determine %ee involve chiral

(148) Harley-Mason, J. J. *Chem. Soc.* 1953, 200.

Scheme 79



derivatizing reagents,¹⁴⁹ chiral solvating agent (CSA)¹⁵⁰ or chiral lanthanide shift reagents.¹⁵¹ Many nitrogenous solutes have been successfully studied with chiral solvating agents (CSA).¹⁵² This approach is very direct requiring only the mixing of the solute, CSA, and an achiral cosolvent, such as benzene d^6 or deuteriochloroform, and recording the NMR spectrum. The solute may be recovered from the CSA by

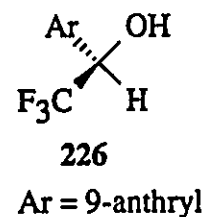
(149) Yamaguchi, S. In *Asymmetric Synthesis*; Morrison, J.D., Ed.; Academic Press: New York, Vol 1, 1983; p125.

(150) Weisman, G.R. In *Asymmetric Synthesis*; Morrison, J.D., Ed.; Academic Press: New York, Vol 1, 1983; p153.

(151) Fraser, R.R. In *Asymmetric Synthesis*; Morrison, J.D., Ed.; Academic Press: New York, Vol 1, 1983; p173.

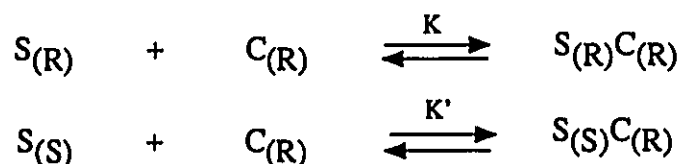
(152) Pirkle, W.H.; Hoover, D.J. In *Topics in Stereochemistry*; Interscience: New York, Vol 13, 1982; p263.

chromatography. The CSA employed was (R)-(-)-2,2,2-trifluoro-1-(9-anthryl) ethanol ((R)-226).



The enantiomers do not form true diastereomers with the solvating agent but there are diastereomeric interactions between the solute ($S_{(S)}$ and $S_{(R)}$) and the CSA ($C_{(R)}$) (Scheme 80).¹⁵² As these equilibria are established rapidly, the average species are observed by NMR. The primary

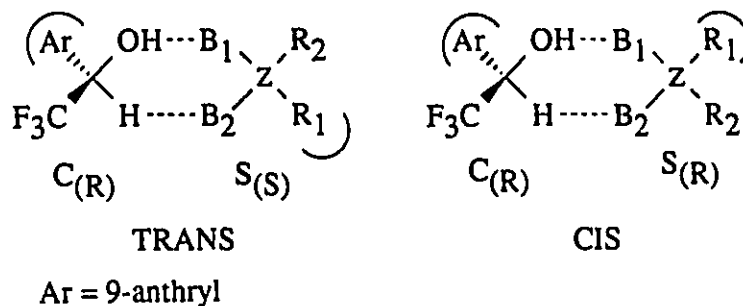
Scheme 80



solute binding force is believed to be H-bonding. Fluoro alcohol (R)-226 has two acidic sites. The acidic alcohol portion of fluoro alcohols H-binds to the most basic site in the solute. The carbinyl hydrogen of the fluoro alcohol is slightly acidic, due to the trifluoromethyl substituent, and seeks interaction with a less basic site in the solute. This site could be the π -electrons of the aromatic ring, multiple bonds, or unshared pairs of electrons. A three-point interaction between the solute and the solvating agent has been proposed (Scheme 81).¹⁵² When R_1 and the anthryl group are cis, as they are in $C_{(R)}S_{(R)}$, R_1 is shifted upfield because of the magnetic anisotropy of the anthryl group. In fact, correlations have been developed between the absolute configuration of the solute and the

sense of the nonequivalence.¹⁵³ This is possible only for solutes in which there are just two basic sites, as in the case of $\text{PhCHNH}_2\text{CH}_3$ and $\text{RCHOHC}\equiv\text{CH}$.

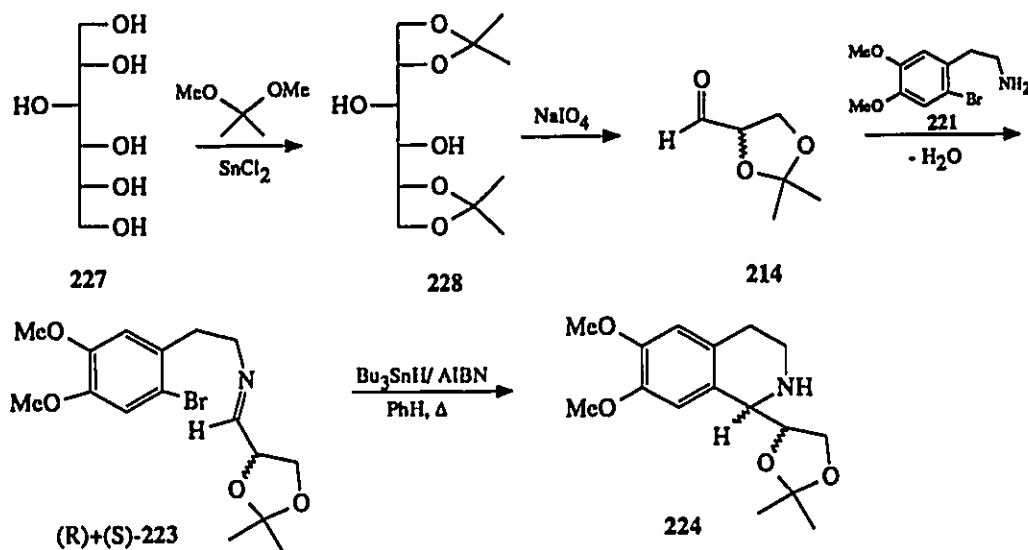
Scheme 81



The racemic mixture of the isoquinolines (S,S)- and (R,R)-224 was first examined to demonstrate nonequivalence in chemical shifts, $\Delta\delta$, in the ^1H NMR. Racemic glyceraldehyde 214 was prepared from the sugar D-sorbitol (227) (Scheme 82). The pyrolysis of the racemic aldimine 223 gave the four stereoisomeric isoquinolines (S,S)-, (R,S)-, (R,R)- and (S,R)-224. This mixture was separated into two racemic mixtures, (S,S)+(R,R)-224 and (R,S)+(S,R)-224, by chromatography. A 1.9 to 1.0 mixture of the chiral solvating agent (R)-(-)-2,2,2-trifluoro-1-(9-anthryl)ethanol (226) and racemic isoquinolines (S,S)+(R,R)-224, showed nonequivalent chemical shifts for Me's of the acetonide group and for H-1'. Unfortunately, the methyl signals were overlapping, as were the quartets corresponding to H-1'. Increasing the proportion of (R)-226 so that there was a 3 to 1 ratio of chiral solvating agent (R)-226 to racemic isoquinoline (S,S)+(R,R)-224, however, was sufficient to separate the quartets corresponding to H-1' and the methyl

(153) Pirkle, W.H.; Sikkenga, D.L.; Pavlin, M.S. *J. Org. Chem.* 1977, 42, 384.

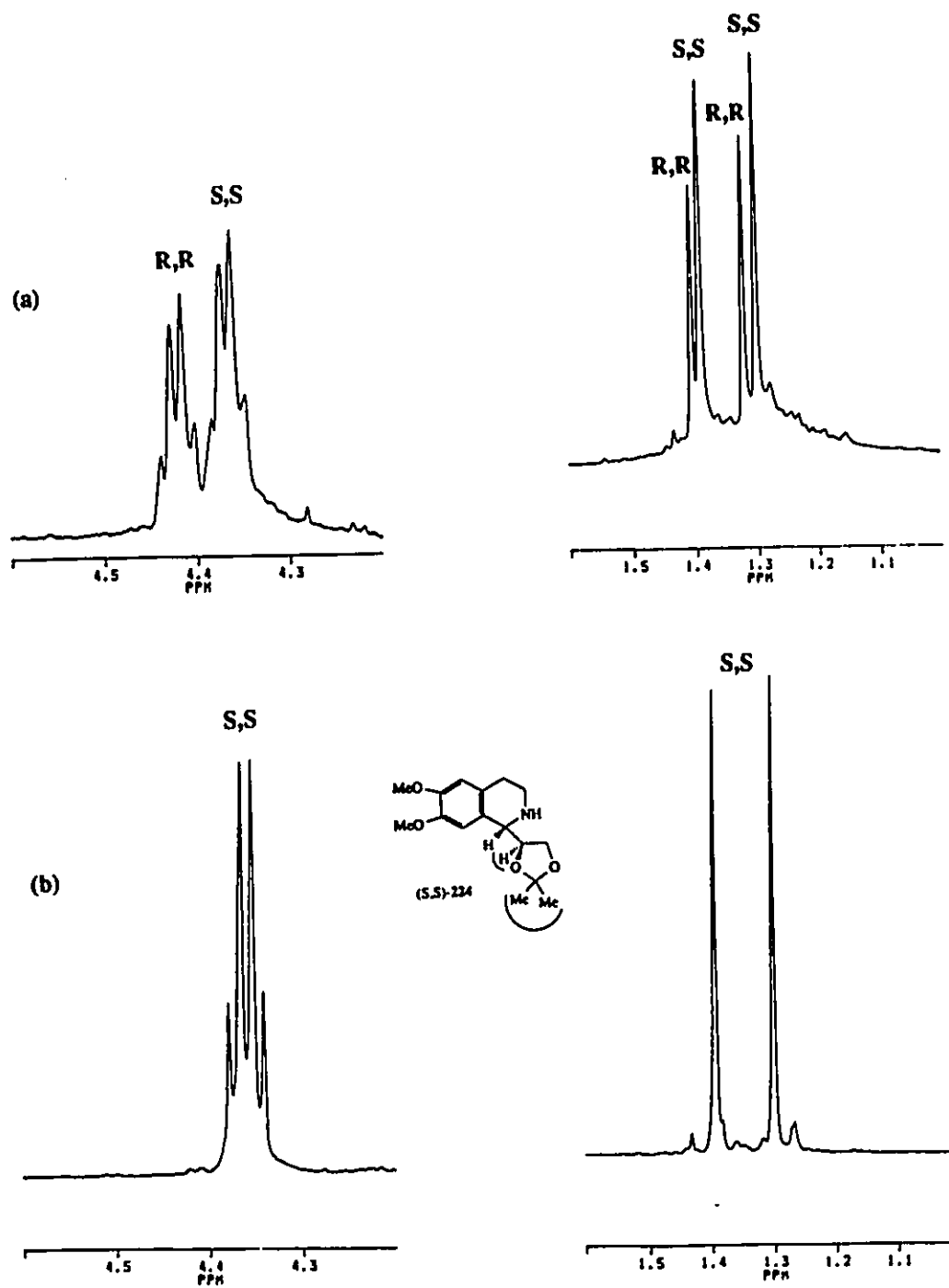
Scheme 82



singlets completely (Figure 3a). The slight excess of the (S,S) enantiomer of 224 is likely due to an excess of the R-enantiomer of glyceraldehyde in the condensation reaction (Scheme 82). The ketalization of D-sorbitol (227) probably gave, in addition to the diacetonide, some monoacetonide. The oxidation of this unpurified mixture gives a mixture of R and S glyceraldehydes that is not racemic. The ketalization of D-mannitol (212) is known to yield monoacetonides in addition to the diacetonides.¹⁴⁵

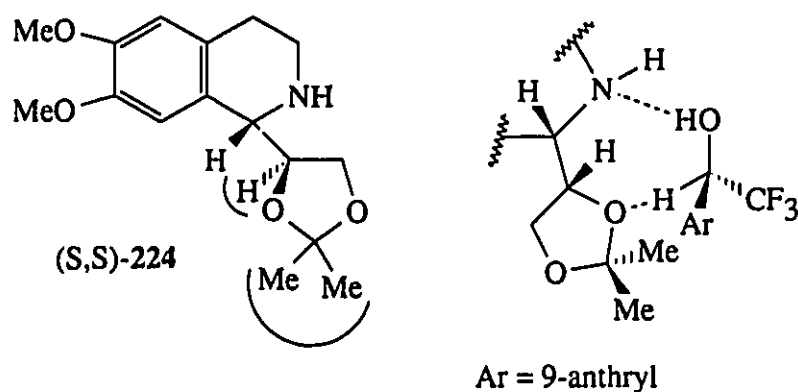
Having determined the conditions for observing nonequivalence in the ¹H NMR spectrum, the isoquinoline product (S,S)-224 from the cyclization of the chiral aldimine (S)-223 was investigated next. The result of mixing the chiral solvating agent (R)-226 (3 parts) with the major isoquinoline diastereomer (S,S)-224 (1 part) is shown in Figure 3b. Only a trace of the (R,R) enantiomer 224 is evident. From the ratio of the peak heights in the ¹H NMR spectrum (500 MHz), the % enantiomeric excess (%ee) is 97%.

Figure 3. ^1H NMR (500 MHz, CDCl_3) spectra of (a) (R,R)+(S,S)-224 (1 part) and chiral solvating agent (R)-226 (3 parts); (b) (S,S)-224 (1 part) and (R)-226 (3 parts).



Therefore, no appreciable racemization takes place in the formation of the aldimine (S)-223 nor during its radical cyclization.

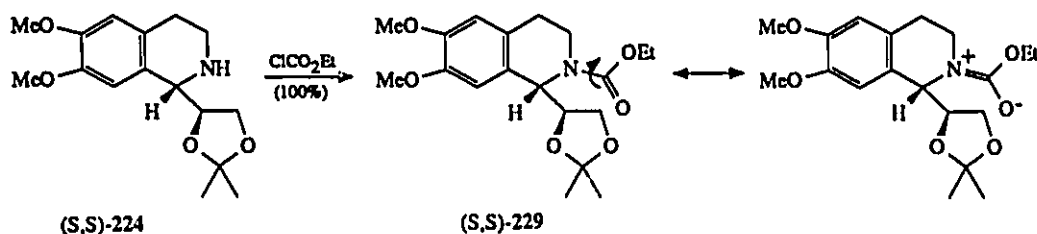
Figure 4. Interaction between the chiral solvating agent (R)-226 and tetrahydroisoquinoline (S,S)-224.



The interaction between the isoquinoline (S,S)-224 and the chiral solvating agent 226 is considerably more complicated than in solutes having just two basic sites. The amine functionality is likely the most basic and so it should H-bond to the hydroxy group. There are five possible sites on the isoquinoline 224 for H-bonding to the carbonyl H-atom: four ether oxygens and the π -electrons of the aromatic ring. The protons that exhibit the largest nonequivalence are H-1' and the acetonide Me's. Based on this the most likely interaction between the chiral solvating agent 226 and the isoquinoline (S,S)-224 is as shown in Figure 4. The alcohol and carbonyl proton of the CSA (R)-226 interact with the amine and ether O-1' of the isoquinoline (S,S)-224, respectively. In this way, the H-1' atom is cis to the anthryl group and thereby shielded due to its anisotropy. The isopropylidene Me's would be affected strongly as well.

Conversion of the enantiomerically pure isoquinoline (S,S)-224 to the compound of known absolute stereochemistry, the MacLean isoquinoline (R,S)-232, required protection of the amine as the carbamate and the deprotection of the diol. Accordingly, the reaction of the isoquinoline (S,S)-224 with ethylchloroformate under basic conditions was undertaken.¹⁴⁷ It gave a quantitative yield of the carbamate (S,S)-229 (Scheme 83).

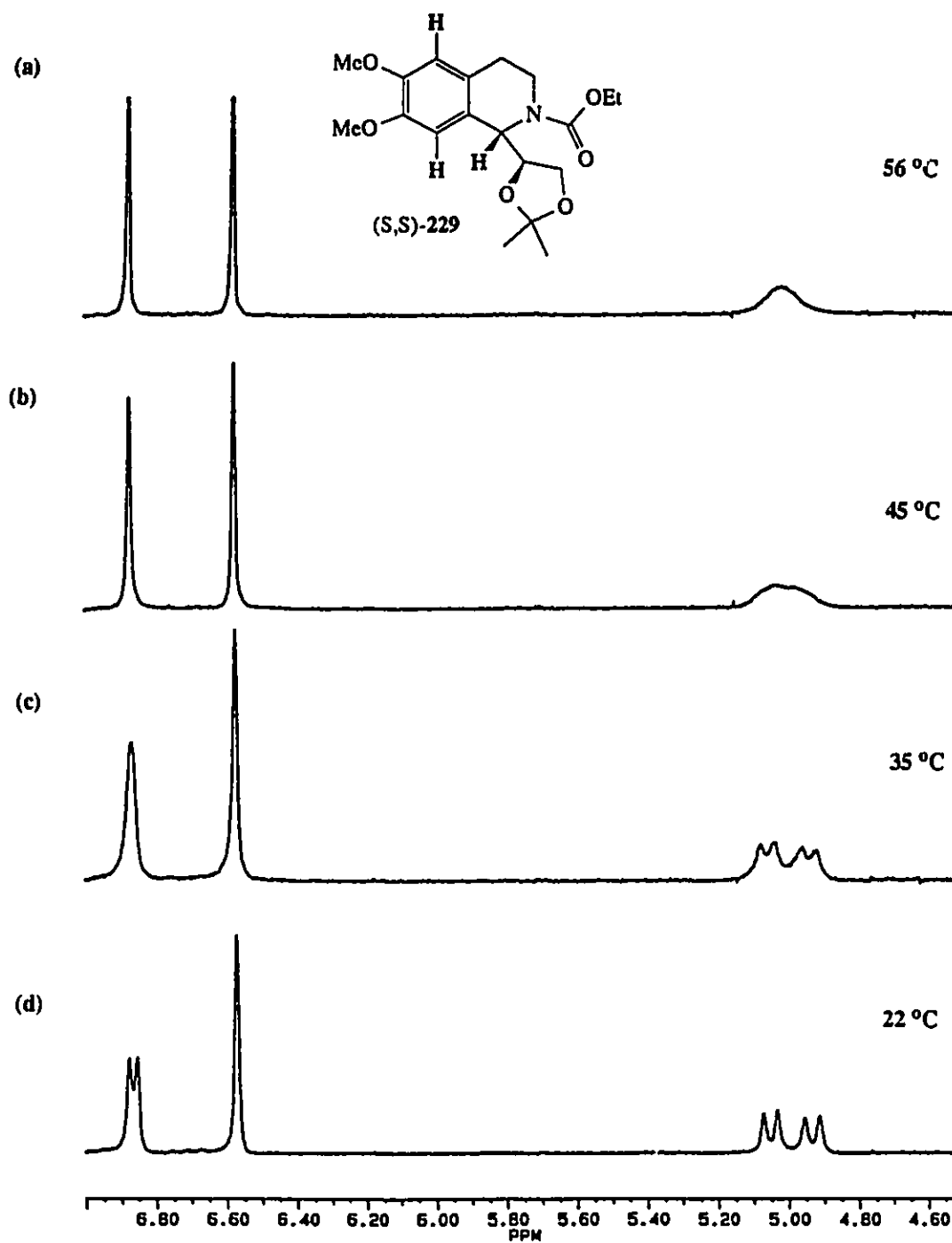
Scheme 83



The carbamate (S,S)-229 showed interesting ¹H NMR spectra by virtue of the restricted rotation about the N-CO bond. When the N-CO group is planar, the molecule (S,S)-229 is stabilized by electron delocalization as represented by the dipolar canonical structure. Dislodging the N-CO bond from this planar ground state requires energy. At room temperature, the rotation or interconversion about the carbamate moiety in (S,S)-229 is slow on the NMR timescale and consequently two sets of signals are evident for the rotational isomers (Figure 5d). A pronounced chemical shift difference is evident for the benzylic H-atom for the two rotational isomers.

From a series of ¹H NMR (200 MHz, CDCl₃) spectra of the carbamate (S,S)-229 at variable temperature, the coalescence temperature, T_c, was determined to be 50±3

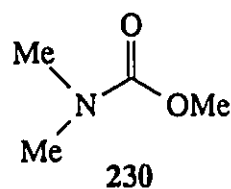
Figure 5. Variable temperature ^1H NMR (200 MHz, CDCl_3) spectra for the carbamate (S,S)-229.



°C (Figure 5). The coalescence temperature is the temperature at which the two signals merge and no observable valley between the signals exists. From the coalescence temperature, the rate constant and the free energy of activation for the exchange were calculated. The rate constant for the exchange at the coalescence temperature, k_c , is given by the equation $k_c = 2.22 \times \Delta\nu$, where $\Delta\nu$ is the difference in the chemical shifts of the two sites in Hz. Substituting the $\Delta\nu$ value of 60.0 Hz, obtained from Figure 5d, yields $k_c = 133 \text{ s}^{-1}$ at $50 \pm 3^\circ\text{C}$. The free energy of activation for the exchange, ΔG_c^\ddagger , is given by:

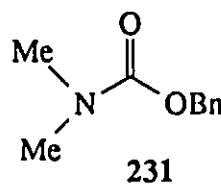
$$\Delta G_c^\ddagger = 4.57 T_c \{9.97 + \log_{10}(T_c/\Delta\nu)\}$$

As the populations of the rotational isomers are nearly equal, this equation strictly applies. Substituting the values for T_c ($50 \pm 3^\circ\text{C}$) and $\Delta\nu$ (60.0 Hz) into the above equation gives $\Delta G_c^\ddagger = 15.8 \pm 0.15 \text{ kcal/mol}$. This value is in line with the reported free energies of Figure 6. The free energies of activation for the isomerization of carbamates.



$$\Delta G^\ddagger = 15.5 \text{ kcal/mol}$$

$$T_c = 27^\circ\text{C}$$



$$\Delta G^\ddagger = 15.9 \text{ kcal/mol}$$

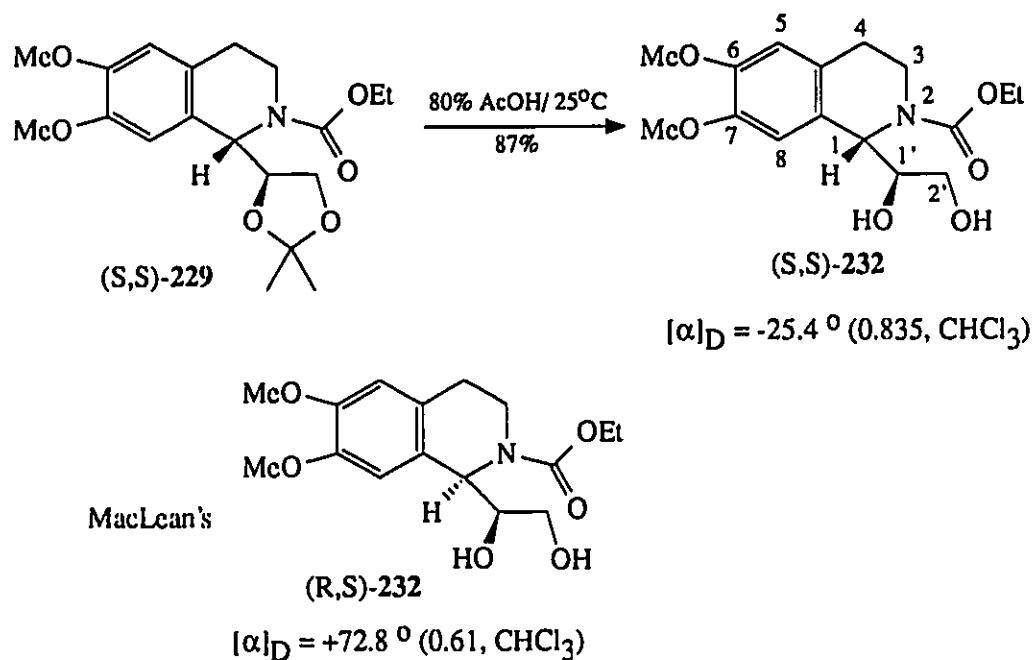
$$T_c = 19^\circ\text{C}$$

activation for the isomerization of carbamates 230¹⁵⁴ and 231¹⁵⁵ (Figure 6).

(154) Tanny, S.R.; Pickering, M.; Springer, C.S. *J. Am. Chem. Soc.* 1973, 95, 6227.

(155) Price, B.J.; Smallman, R.V.; Sutherland, I.G. *J. Chem. Soc., Chem. Commun.* 1966, 319.

Scheme 84



Removal of the acetonide functionality in carbamate $(S,S)\text{-229}$ with acetic acid gave the diol $(S,S)\text{-232}$ in 87% yield (Scheme 84).¹⁵⁶ The ^1H NMR data for this isoquinoline $(S,S)\text{-232}$ are clearly not the same as those published by MacLean for isoquinoline $(R,S)\text{-232}$ (Table 7). The optical rotation of the isoquinoline $(S,S)\text{-232}$, synthesized by the radical approach, was measured at two different concentrations and found to be -25.4° ($c=0.835$) and -25.6° ($c=0.242$) both in CHCl_3 . The optical rotation reported for the MacLean isoquinoline $(R,S)\text{-232}$, however, was $+72.8$ ($c=0.61$, CHCl_3). Clearly the relationship between these isoquinolines is that of diastereomers.

(156) Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G.S.; Yamanaka, E.; Hutchins, L.; Dipierro, M.; Cook, J.M. *J. Org. Chem.* **1979**, *44*, 535.

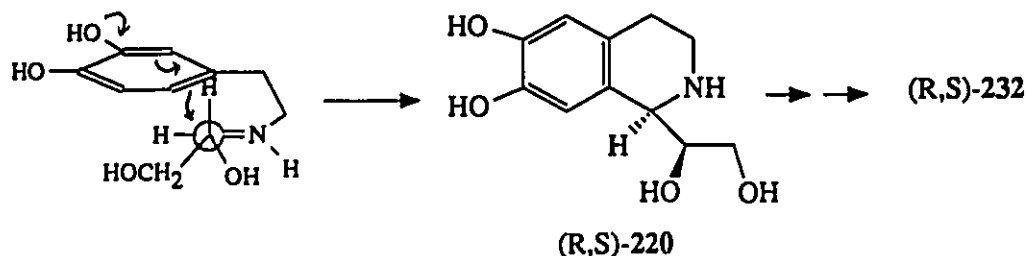
It is unclear from a comparison of the Darling models of isoquinoline (S,S)-232 and (R,S)-232 or from the corresponding transition states, why the pathway leading to the (S,S)-diastereomer 232 is favoured. The difference in activation energies in the two pathways is estimated to be only ca. 0.7 kcal/mol. Direct comparison may not be made between the radical based cyclization (Scheme 79) and MacLean's ionic cyclization (Scheme 78) since the starting materials are not identical. The stereochemical outcome of the Pictet-Spengler reaction was rationalized using Cram's rule (Scheme 85).¹⁵⁷

Table 7. ¹H NMR data for Isoquinolines (R,S)-232 and (S,S)-232

Compound	¹ H NMR (CDCl ₃ , TMS)
(R,S)-232	(90 MHz) δ 1.27 (t, J=8.0 Hz, CH ₂ -CH ₃), 2.80 (m, 2H, H-4), 3.60 (d, J=7.5 Hz, 2H, H-2'), 3.83 (s, 6H, OCH ₃), 3.97-4.37 (m, 7H, OCH ₂ -CH ₃ , 2H-3, H-1', 2OH), 5.18 (d, J=5.0 Hz, 1H, H-1), 6.62 (s, 1H, ArH), 6.76 (s, 1H, ArH).
(S,S)-232	(200 MHz) δ 1.30 (t, J=7.1 Hz, 3H, CH ₂ -CH ₃), 2.81 (t, J=6.3 Hz, 2H, H-4), 3.43-4.0 (m, 6H, 2H-3, 2OH, and 2H-2'), 3.88 (s, 6H, OCH ₃), 4.18 (q, J=7.1 Hz, 2H, OCH ₂ CH ₃), 4.92 (d, J=7.8 Hz, 1H, H-1), 6.66 (s, 1H, ArH), 6.90 (s, 1H, ArH).

(157) Eliel, E.L. In *Asymmetric Synthesis*; Morrison, J.D., Ed.; Academic Press: New York, Vol 2, 1983; Chapter 5.

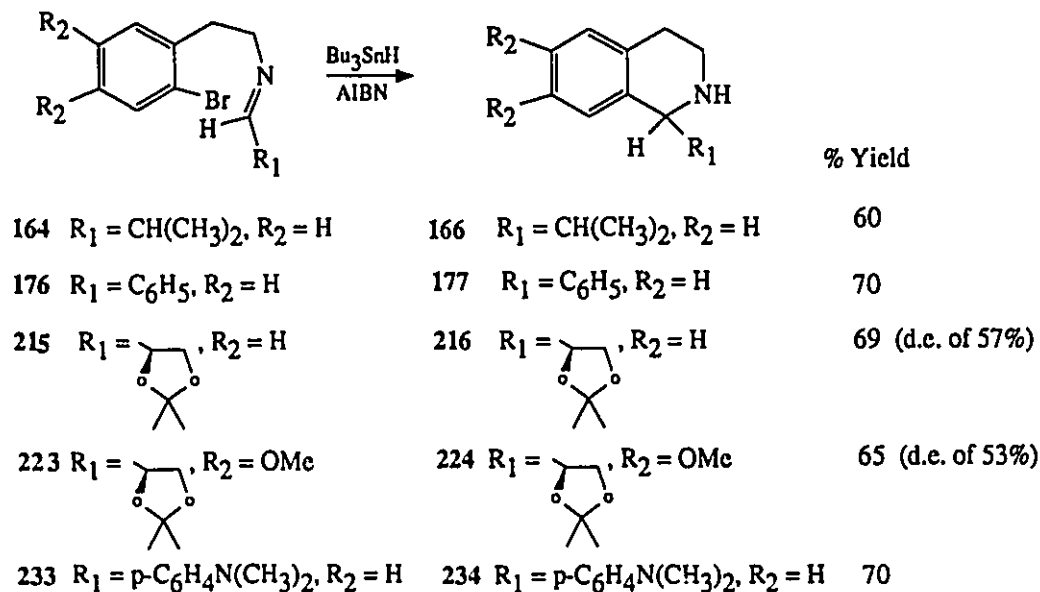
Scheme 85



Syntheses of Isoquinoline Derivatives - The Radical Approach

The synthesis of isoquinolines by the radical cyclization to the aldimino group is a novel and relatively efficient approach to constructing these heterocycles. In addition, the starting materials are straightforward to prepare. Aldimines that are prone to polymerization should not be isolated, but used directly in the radical cyclization reaction.

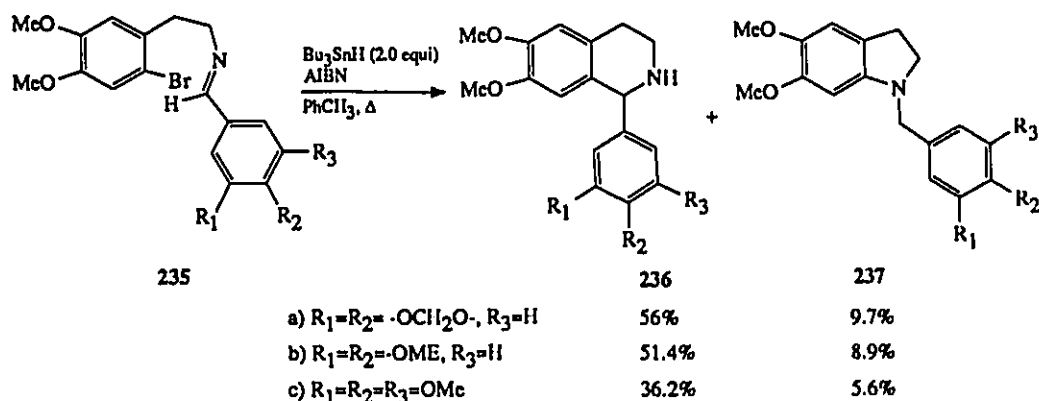
Scheme 86



Isolated yields of tetrahydroisoquinolines range from 60 to 70% (Scheme 86). Radical

cyclization to ketimines are likely to be less useful synthetically, due to the lower regioselectivity and rate constant in their closure. A report by Takano and co-workers,¹⁰⁰ that appeared while our work was in progress, examined the aryl radical cyclization to three related Schiff bases (Scheme 87). Takano's yields of tetrahydroisoquinolines ranged from 36 to 56% and are perhaps slightly lower than those reported by us due to the higher $[\text{Bu}_3\text{SnH}]$ used in their reactions. The full experimental details were not published.

Scheme 87

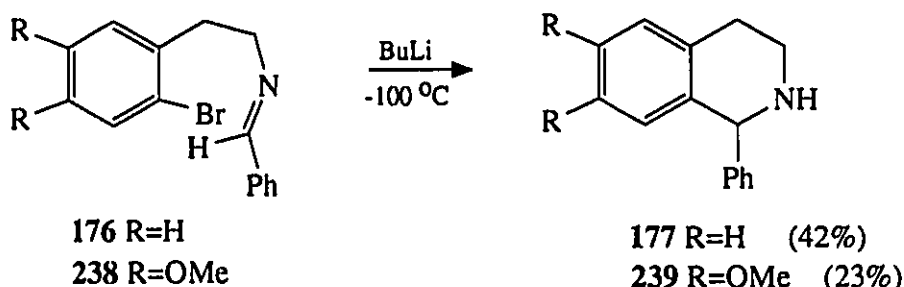


Isoquinoline Synthesis by Non-Radical Methods

The radical and the anionic based syntheses of tetrahydroisoquinoline **177** may be compared. Bradsher and Hunt,¹⁰¹ in 1981 found that treatment of benzaldimine **176** at -100°C with one equivalent of BuLi gave the isoquinoline **177** in 42% yield (Scheme 88). The anionic cyclization of the dimethoxy derivative **238** gave the corresponding isoquinoline **239** in 23% yield. Our radical based cyclization of the benzaldimine **176** gave the isoquinoline **177** in 70% yield. The radical approach, in addition to affording a

higher yield of the isoquinoline **177**, is potentially superior because of the high tolerance of free radicals for additional functionality.

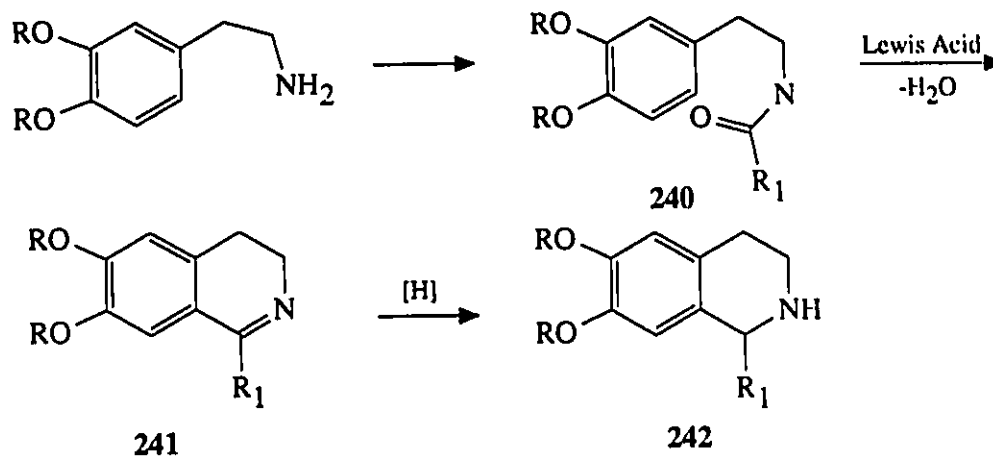
Scheme 88



The two most common non-radical approaches to the isoquinoline ring framework are the Bischler-Napieralski reaction and the Pictet-Spengler reaction.¹⁵⁸ An example of the Pictet-Spengler reaction is the anionic cyclization leading to isoquinoline **220** in Scheme 78. The most commonly employed dehydrating agent has been hydrochloric acid. This reaction is limited to meta substituents that are electron donating to aid in the electrophilic closure. Yields are generally very good.¹⁵⁸ The Bischler-Napieralski reaction involves the cyclization of the N-acyl derivative of β -phenethylamine **240** to 3,4-dihydroisoquinoline **241** in the presence of Lewis acids such as POCl_3 , P_2O_5 , or ZnCl_2 (Scheme 89). Reduction of the 3,4-dihydroisoquinoline **241** yields the 1,2,3,4-tetrahydroisoquinoline **242**. The Bischler-Napieralski reactions, however, are limited to the presence of an electron donating substituent in the meta position of the substrate.

(158) Kametani, T.; Fukumoto, K. In *Isoquinolines*; Grethe, G., Ed.; John Wiley: New York, Part 1, 1981: p139.

Scheme 89

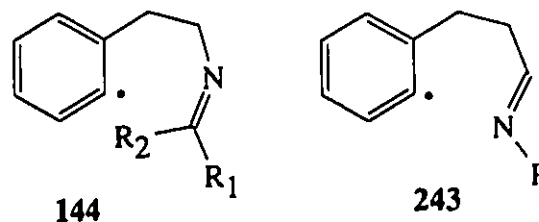


Reactions are carried out in refluxing solvents, PhH, PhCH₃, or CH₃CN and the yields range from good to excellent (60-98%).¹⁵⁸

Radical Cyclization to Aldimines with C-5/N-6

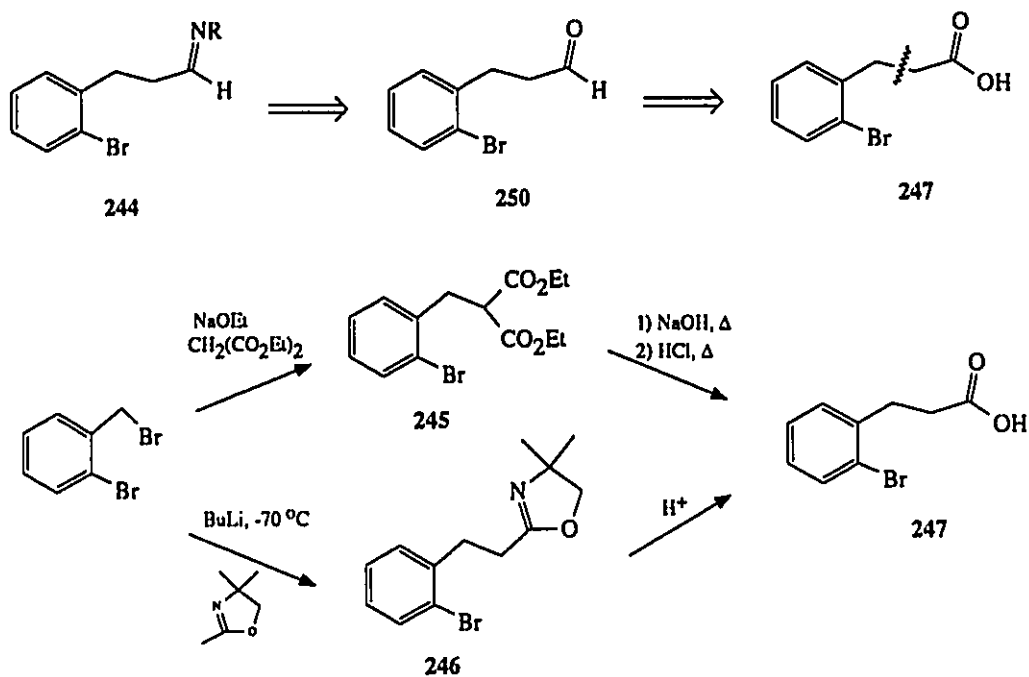
The interesting regiochemistry discovered in aryl radical cyclization to the imino group with the N-atom in the 5 position and the C-atom in the 6 position (144) led to the investigation of cyclization to the reverse imines in which the choice is between 5-exo cyclization to the C-atom and 6-endo cyclization to the N-atom (243).

A retrosynthetic analysis indicates that the aldimine 244 may be synthesized from an acetic acid derivative 247 (Scheme 90). Routes to the homologated acetic acids include



the classical malonic ester synthesis and Meyer's 2-oxazoline approach¹⁵⁹. Both of these methods were investigated (Scheme 90). The malonic ester synthesis gave 3-(o-

Scheme 90



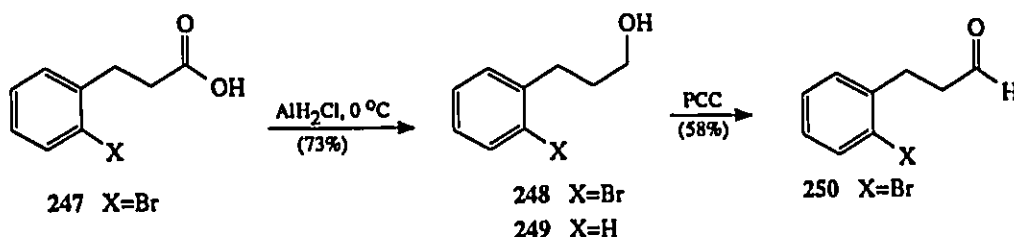
bromophenyl)-n-propionic acid (247) in 42% yield from o-bromobenzyl bromide.¹⁶⁰ The 2-oxazoline route, in contrast, formed the same product in 73% yield with considerably shorter reaction times.¹⁶¹

(159) Meyers, A.I.; Temple, D.L.; Nolen, R.L.; Mihelich, E.D. *J. Org. Chem.* 1974, 39, 2778.

(160) For a synthesis of 3-phenyl-n-propionic acid, see: Vogel, A. *Textbook of Practical Organic Chemistry* fourth edition: Longman Scientific and Technical: Essex, 1987; p.492.

(161) Beak, P.; Selling, G.W. *J. Org. Chem.* 1989, 54, 5574.

Scheme 91



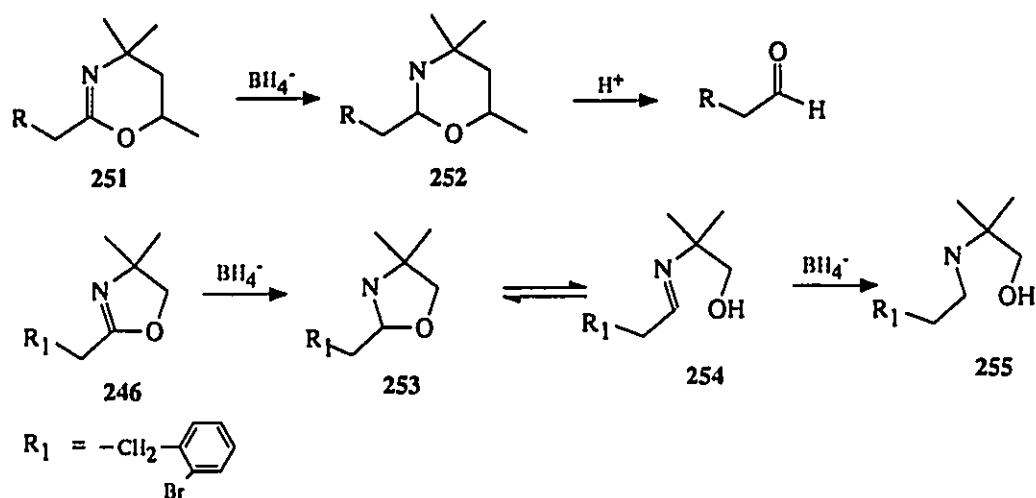
The desired aldehyde **250** was prepared in two steps from the propionic acid derivative **247** (Scheme 91). Reduction of the carboxylic acid **247** with the mixed anhydride, AlH_2Cl (1:1, $\text{LiAlH}_4:\text{AlCl}_3$), at 0°C gave the alcohol **248** in 73-77% yield.¹⁰⁷ Oxidation of the alcohol **248** with pyridinium chlorochromate in CH_2Cl_2 proceeded smoothly, furnishing the aldehyde **250** in 58% yield.¹⁶²

It is known that dihydro-1,3-oxazines **251** may be converted directly to the aldehyde in a good yield by reduction with NaBH_4 followed by hydrolysis (Scheme 92). Consequently, the analogous reaction was attempted with the oxazoline derivative **246**.¹⁶³ In the case of the 5-membered oxazoline, however, the same procedure resulted in a 1 to 1 mixture of the secondary amine **255** and starting material **246**. Apparently, the oxazolidine **253** is in equilibrium with the ring opened imine **254**, and the reduction of the imine gives the isolated amine **255**. Ring opening to the imine must be more prevalent in the 5-membered than in the 6-membered heterocycle, so that over reduction to the

(162) Corey, E.J.; Suggs, J.W. *Tetrahedron Lett.* 1975, 2647.

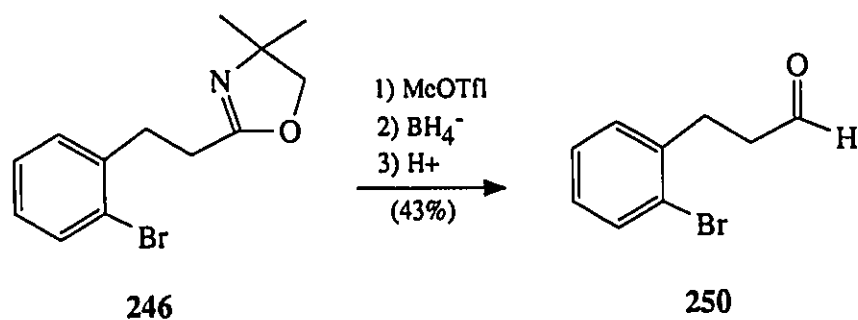
(163) Kovelesky, A.C.; Meyers, A.I. *Org. Procedures and Preparations* 1969, 1, 213.

Scheme 92



saturated amine alcohol cannot be circumvented.^{164,165} A one-step procedure from the oxazoline 246 to aldehyde 250, however, is possible by first quaternizing the N-atom of

Scheme 93



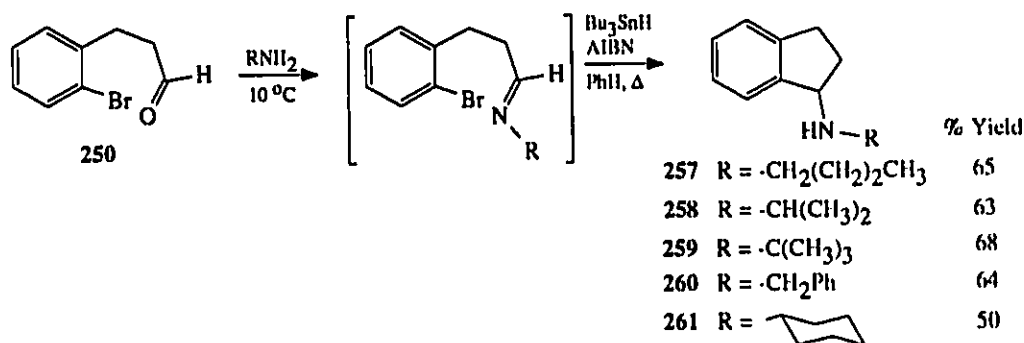
the oxazolino group (Scheme 93). Accordingly the methylation of the oxazoline 246

(164) Meyers, A.I.; Temple, D.L. *J. Am. Chem. Soc.* **1970**, *92*, 6644.

(165) Meyers, A.I.; Himmelsbach, R.J.; Reuman, M. *J. Org. Chem.* **1983**, *48*, 4053.

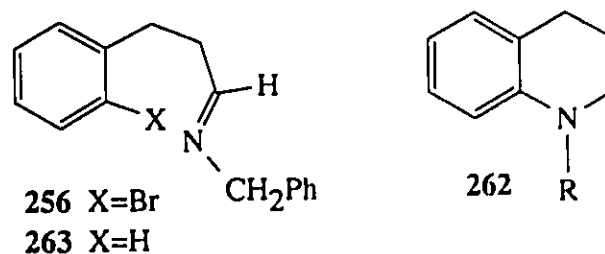
followed by reduction and hydrolyses afforded the desired aldehyde **250** in 43% yield.¹⁶⁶

Scheme 94



On account of the instability of primary aldimines, they were used in the cyclization reaction soon after preparation (Scheme 94). The condensation reactions were carried out in PhH at 6-10°C, with 4Å molecular sieves. Progress of these reactions was monitored by ¹H NMR spectroscopy which showed complete conversion to the aldimines. The filtered solutions were heated to reflux, at which point Bu₃SnH and AIBN were added. The only cyclized product detected were 1-indanamines from 5-exo closure to the C-atom. The products derived

from 6-endo cyclization, the tetrahydroquinolines **262**, have characteristic ¹H NMR spectra showing aromatic protons



(166) Meyers, A.I.; Luomski, K.A.; Laucher, D. *Tetrahedron* 1988, 44, 3107.

spanning the region 6.2 to 7.1ppm.¹⁶⁷ These were not evident. Isolated yields of indanamines ranged from 50 to 68%.

Table 8. Kinetic Data for Cyclization of N-Benzylaldimine **256** at 80 °C.

[SnH] ^a , M	Product Ratios ^b	Ratios of Rate Csts	Ratios to a Standard (TMS)	
			256/TMS	260+263/TMS
	260/263	k_2/k_{11}		
0.473	2.4	1.2	0.9	0.9
0.473	2.4	1.1	0.7	0.8
0.237	4.8	1.2	0.9	1.0
0.118	8.5	1.0	1.0	1.0
0.059	14	0.9	1.0	1.0
0.059	14	0.9	1.0	1.0

^a Bu₃SnH in 8.6 fold excess and concentration are averages based of a 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.

Kinetics of Ring Closure to Aldimines with C-5/N-6

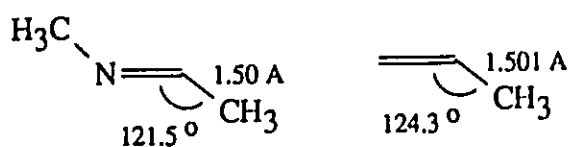
Table 8 provides a summary of product ratios and derived rate constants for the cyclization of the N-benzylaldimine (**256**). Reactions were conducted in NMR tubes containing excess Bu₃SnH (8.6 equivalents) and 7% AIBN in PhH and sealed under vacuum. Progress of the reactions was monitored by ¹H NMR spectroscopy. The heating of the reaction tubes was stopped soon after disappearance of starting material **256**.

(167) *The Aldrich Library of NMR spectra*; Pouchert, C.J.; Cambell, J.K., Ed.; Aldrich Company, 1972, Vol 5, p131B.

Reactions were found to proceed cleanly to the indanamine 260 and reduced starting material 263 as evident from the consistency of the ratio 256/TMS to 260+263/TMS. The value of 1.1 for the ratio k_2/k_{11} (M) indicates that the 5-exo closure of the aryl radical derived from 256 is efficient. Substituting the value⁵² for k_{11} of $5.0 \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ gives $k_{5\text{-exo}} = 5.3 \times 10^8 \text{ s}^{-1}$, at 80°C. The rate constant for 5-exo closure to the C-atom in 256 is the fastest rate constant for closure to the aldimino group that we found. It is some five times faster than the 6-endo closure in the isobutyraldimine 165 and 200 times the 5-exo rate constant for closure to the N-atom in 165. Assuming that 2% or less of the product (262 R=benzyl) arising from 6-endo closure to the N-atom would be detected by ¹H NMR (500 MHz) spectroscopy, the maximum rate constant for endocyclic ring closure is $1 \times 10^7 \text{ s}^{-1}$ at 80°C.

The regioselectivity and the values of rate constants for cyclization of the N-benzylaldimine 256 are, in fact, very similar to those for the o-butenylphenyl radical (41).

Figure 7. Bond lengths and bond angles for N-ethylidenemethanamine and propene.



The geometries at the transition state for these 5-exo closures must closely resemble each other, since the bond angles and bond lengths joining the radical site to the exocyclic position are similar (Figure 7).^{135, 168} Moreover, the higher coefficient of the LUMO at

(168) Geometry of N-ethylidenemethanamine from microwave spectroscopy, see: Meier, J.; Bauder, A.; Gunthard, H. *J. Chem. Phys.* 1972, 57, 1219.

the C-atom of the imino group would kinetically favour 5-exo attack (Figure 2). Jenkins and co-workers^{83a} working on the related oxime found closure in the 5-exo sense to the C-atom only (Scheme 34).

Novel Source of Tributylstannyl Radicals

Trialkylstannyl radicals are the most widely used chain-transfer agent in radical reactions.¹⁶⁹ Stannyl radicals can dehalogenate organic halides¹⁷⁰ and also add to unsaturated functional groups.¹⁷¹ The usual source of stannyl radicals is R_3SnH which, as a strong H-donor, unfortunately can reduce intermediate radicals before the desired addition or other reaction required by the synthesis.

Bis(trimethylstannyl)benzopinacolate (6) (TMBP) is formally a source of $Me_3Sn\cdot$ that is not derived from the tin hydride (Schemes 3 and 95).¹⁰ The high cost and toxicity of trimethyltin derivatives, however, have resulted in few applications.¹¹ Upon warming to 60°C, TMBP (6) is split reversibly into stannyl ketyls. The irreversible β -scission of the stannyl ketyls to distannane and benzophenone works best at temperatures over 100°C. It was hoped that the bulkier bis(tributylstannyl)benzopinacolate (265) (TBBP) would dissociate at lower temperatures and thereby make it a more useful reagent in synthesis. Moreover, the lower toxicity and cost of tributylstannyl derivatives would

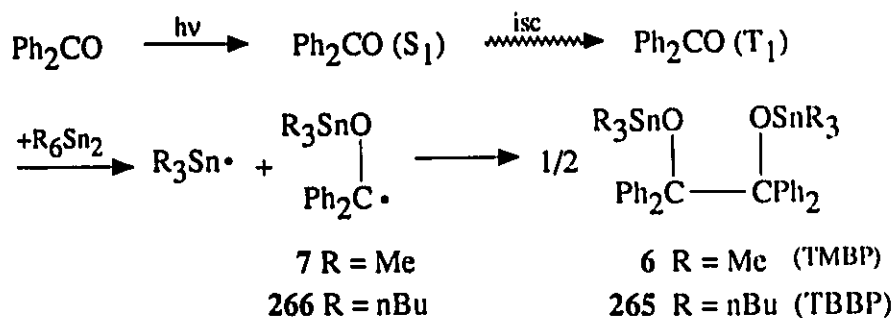
(169) Neumann, W.P. *Synthesis* 1987, 665.

(170) Kuivila, H.G. *Synthesis* 1970, 499.

(171) Enholm, E.J.; Prasad, G. *Tetrahedron Lett.* 1989, 30, 4939.

make this reagent more attractive.

Scheme 95

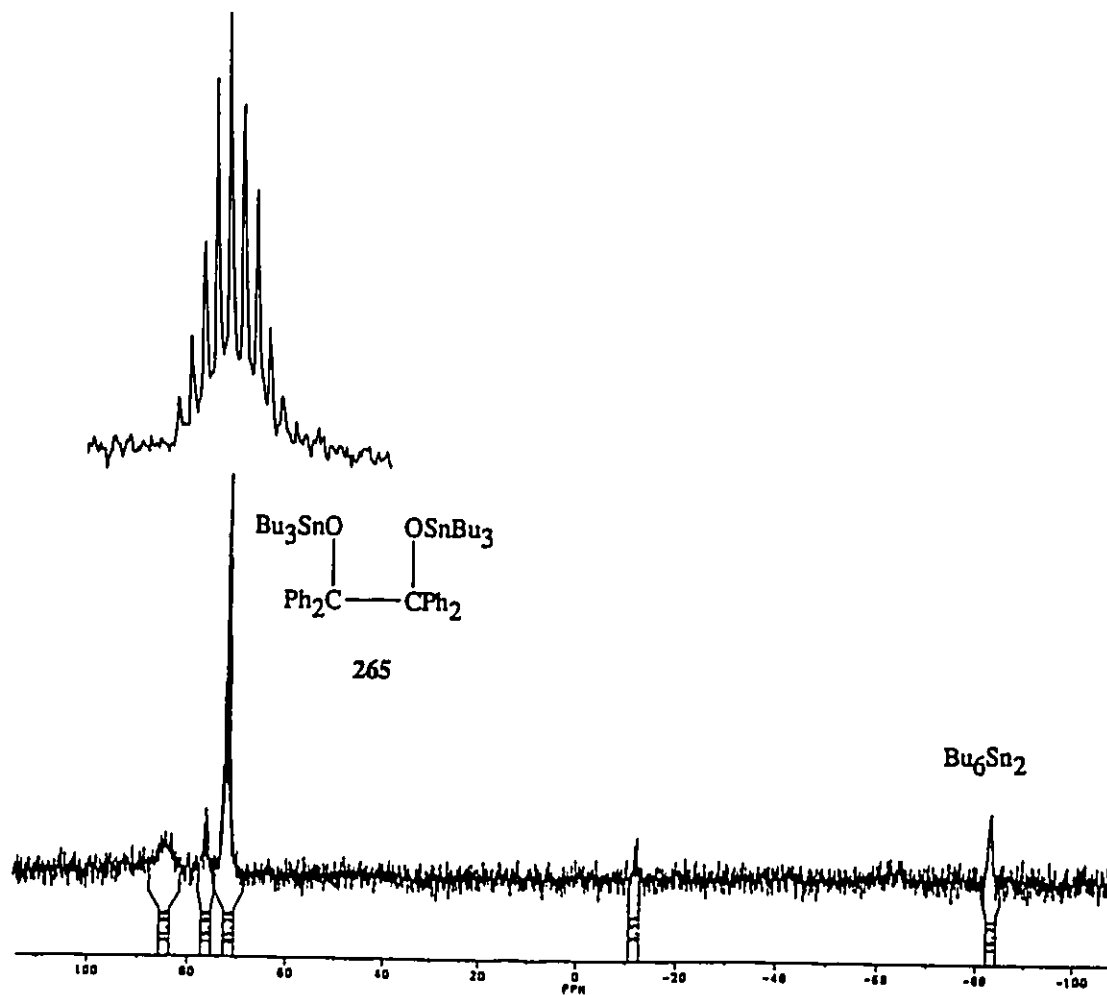


Bis(tributylstannyl)benzopinacolate (**265**) (TBBP) was prepared by photolysis of benzophenone and Bu_6Sn_2 (**264**)¹⁷² with 350 nm light at ca. 20°C in an oxygen free atmosphere for ca. 24 h (Figure 8, Scheme 95). After this time the ratio of TBBP (**265**) to Bu_6Sn_2 (**264**) was ca. 5.4 to 1. There were minor amounts of impurities present as well. Prolonged photolyses did not improve on the 5.4 to 1 ratio. By comparison, the photolysis of benzophenone and Me_6Sn_2 in only 7 h gave a ratio of TMBP (**6**) to Me_6Sn_2 of ca. 13 to 1.

The effect of solvent and temperature on the formation of TBBP (**265**) was investigated. Photolysis of benzophenone and Bu_6Sn_2 (**264**) in different solvents, namely, benzene, cyclohexane or t-butylbenzene, all gave similar ¹¹⁹Sn NMR spectra. A comparison of ¹¹⁹Sn NMR spectra of products of photolyses carried out at -45, 20 and 40°C showed no advantage to carrying out these photolyses at low temperatures.

(172) Boudjouk, P.; Han, B-H. *Tetrahedron Lett.* 1981, 22, 3813.

Figure 8. ^{119}Sn NMR (186.5 MHz, C_6D_6) spectrum showing bis(tributylstannyl)benzopinacolate (265) at +72 ppm.



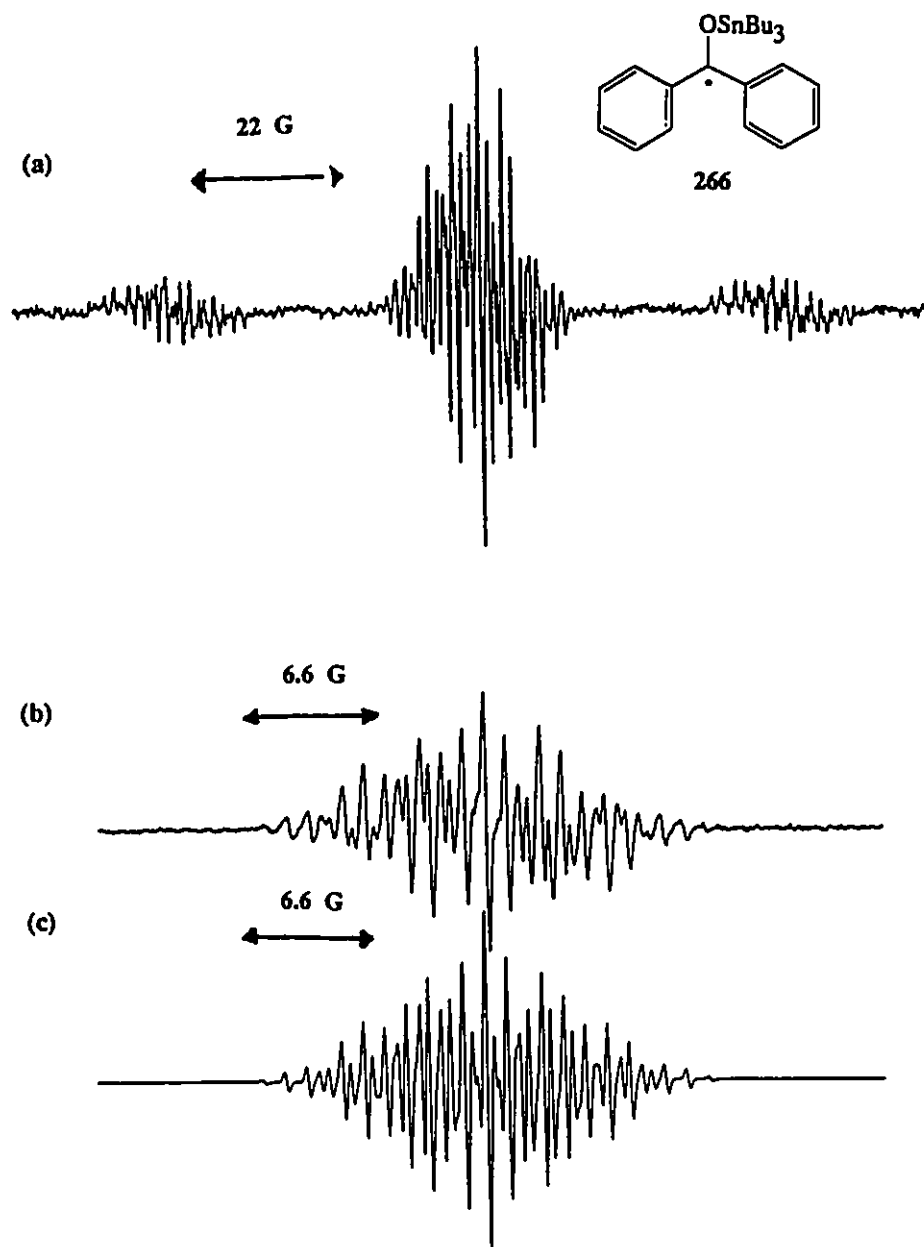
Photolysis at the higher temperature of 40°C, however, gave a ^{119}Sn NMR spectrum with more impurities.

Evidence to support the formation of TBBP (265) comes from ^{119}Sn NMR, ^{13}C NMR, MS, and ESR. Monitoring the progress of the reaction of Ph_2CO and Bu_6Sn_2 (264) by ^{119}Sn NMR clearly shows the depletion of Bu_6Sn_2 (264), characterized by the signal at -83 ppm, and the formation of a new compound with a signal at +72 ppm (Figure 8). This new signal is in the region reported for tributyltin ethers. For example, the chemical shift of $\text{Bu}_3\text{SnOCH}(\text{Me})_2$ is at 76 ppm relative to SnMe_4 .¹³⁷ The 2-D Sn-H heterocorrelated spectrum of TBBP (265) shows that ^{119}Sn couples to the α - and β -methylene protons ($^2J_{\text{Sn-H}}$ and $^3J_{\text{Sn-H}}$). The ^{13}C NMR spectrum shows a signal at 88 ppm which is reasonable for the benzylic carbon of TBBP (265). Finally, the mass spectrometric analysis indicates an ion at $1/2 M^+$ of 3% intensity which is similar to that reported^{10b} for TMBP (6), $1/2 M^+$ of 5% intensity.

Warming a solution of TBBP (265) to 65°C in an oxygen free atmosphere forms a salmon red colour, which is characteristic of stannyl ketyl radicals.^{10b} This colour soon fades upon removal from heat. The ESR spectrum of the stannyl ketyl radical 266 is shown in Figure 9a. The hyperfine coupling to ^{117}Sn and ^{119}Sn are evident on either side of the main signal. The simulated spectrum (Figure 9c), based on the hyperfine coupling constants reported¹⁷³ for the methyl analogue 7, shows a very close resemblance to the

(173) Neumann, W.P.; Schroeder, B.; Ziebarth, M. *Liebigs Ann. Chem.* 1975, 2279.

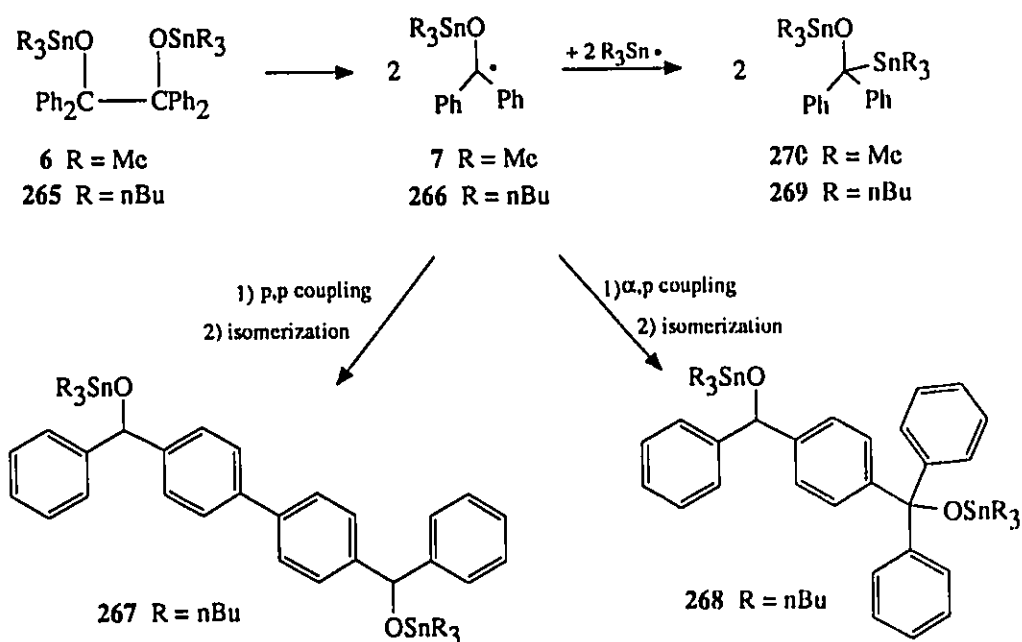
Figure 9. (a) ESR spectrum of tributylstannyl ketyl radical 266 in cyclohexane at 71 °C. (b) Partial ESR spectrum of 266 and (c) a simulated spectrum. The simulated spectrum was generated using the hyperfine coupling constants of the trimethylstannyl ketyl radical 7.



ESR spectrum of 266 (Figure 9b). The calculated g-factor for the tributylstannyl ketyl 266 is 2.0025 ± 0.004 at 56°C which is close to the value reported¹⁷³ for the trimethylstannyl ketyl 7, 2.0024 at 31°C . These are slightly larger than the g-factor of 2.00223 for the free electron.¹⁷⁴

From ^{119}Sn and ^{13}C NMR spectra it is evident that the thermolysis of TBBP (265) at 85° for ca. 30 min regenerates in part Bu_6Sn_2 (264) and benzophenone. Other possible products that are formed on thermolysis are the p,p coupling product 267, α ,p coupling product 268 and the cross coupling product 269 (Scheme 96). The adduct 270

Scheme 96



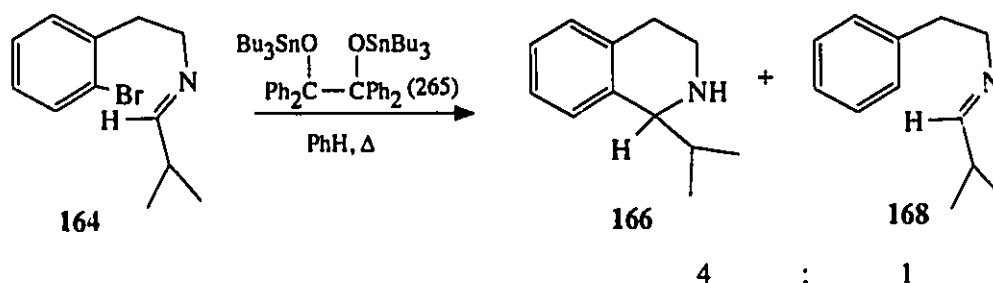
was detected in the thermolysis of the trimethyl tin compound 6.

(174) Fischer, H. In *Free Radicals*; Kochi, J.K., Ed.; Wiley: New York, Vol. 2, 1973; p451.

Application of TBBP to Synthesis

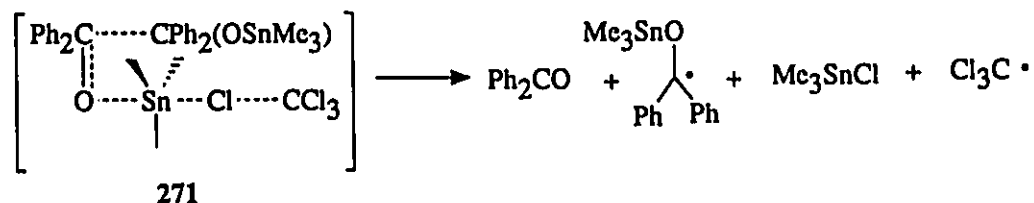
Radical cyclization reactions may be carried out with TBBP (265) acting as a canned source of $\text{Bu}_3\text{Sn}^\bullet$. Thermolysis of TBBP (265) in the presence of isobutyraldimine 164 resulted in a 4 to 1 ratio of isoquinoline 166 to dehalogenated aldimine 168 (^1H NMR) (Scheme 97). This product ratio is comparable to that which may be achieved by the tin hydride method at high dilution, or via slow addition of Bu_3SnH . These latter approaches, however, would not be practical on a large scale. The temperature necessary to carry out a reaction with TBBP (265), however, was not as low as was hoped. At 70°C the reaction time is ca. 14 h but at 100°C it is less than 3 h.

Scheme 97



The mechanism by which bis(tributylstannyl)benzopinacolate (265) reacts with isobutyraldimine 164 is not known. Neumann^{10b} found that the reaction of TMBP (6) with substrates such as O_2 , I_2 , some alkyl halides, carbonyls, and azo compounds, are much too fast to be the result of homolysis of TMBP (6). Neumann, therefore, proposed a mechanism of molecule assisted homolysis in which there are no free stannyl radicals (Scheme 98).

Scheme 98

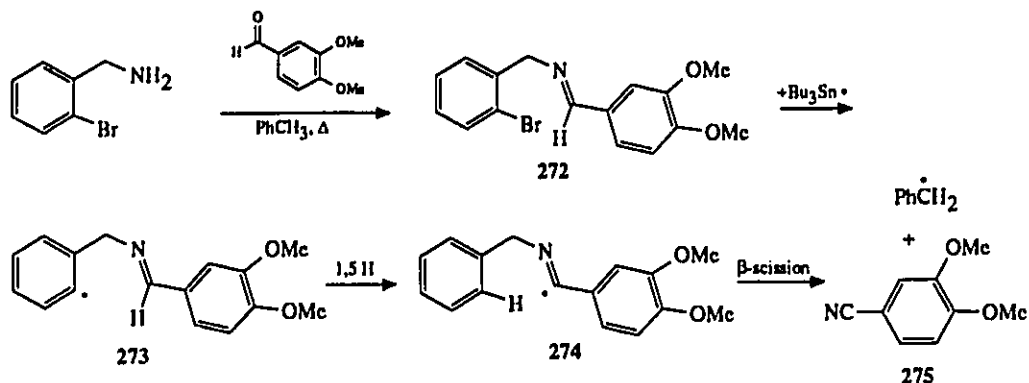


Radical Cyclization to Imines with N-4/C-5

Radical cyclization to an imine in which the only feasible closure would be to the 5-endo C-atom was also investigated. The Schiff base 272 was prepared in 68% yield by condensation of 2-bromobenzylamine with 3,4-dimethoxybenzaldehyde. Thermolysis of Schiff base 272 with syringe-pump addition of Bu_3SnH and catalytic amounts of AIBN gave 3,4-dimethoxybenzoxonitrile (275) and toluene but none of the cyclized product (Scheme 99). By shortening the chain separating the radical site and the imino group the chemistry has dramatically changed. A reasonable mechanism is the following; after loss of the Br-atom to $\text{Bu}_3\text{Sn}^\bullet$, the aryl radical 273 abstracts the azomethine H-atom forming the imidoyl radical 274 which subsequently fragments to 3,4-dimethoxybenzoxonitrile 275 and the benzyl radical.

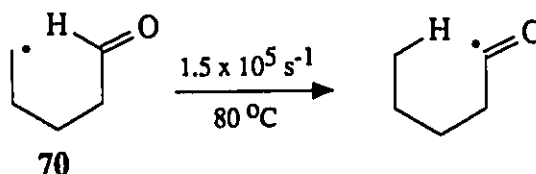
Although no literature examples of intramolecular 1,5 H-atom transfers in imines could be found, the 1,5 H-atom transfer is well known with aldehydes. The rate constant for the 1,5 H-atom transfer in 4-formylbutyl radical (70) is $1.5 \times 10^5 \text{ s}^{-1}$, at 80°C (Scheme 100).⁷³ The intermolecular abstraction of the azomethine proton, however, is well

Scheme 99



known.^{175, 176, 177} The imidoyl radical has also been generated from the selenoimidate 276 on reaction with $\text{Bu}_3\text{Sn}^\bullet$ (Scheme 101).¹⁷⁸

Scheme 100



There are literature precedents for fragmentation of imidoyl radicals affording

(175) Danen, W.C.; West, C.T. *J. Am. Chem. Soc.* **1973**, *95*, 6872.

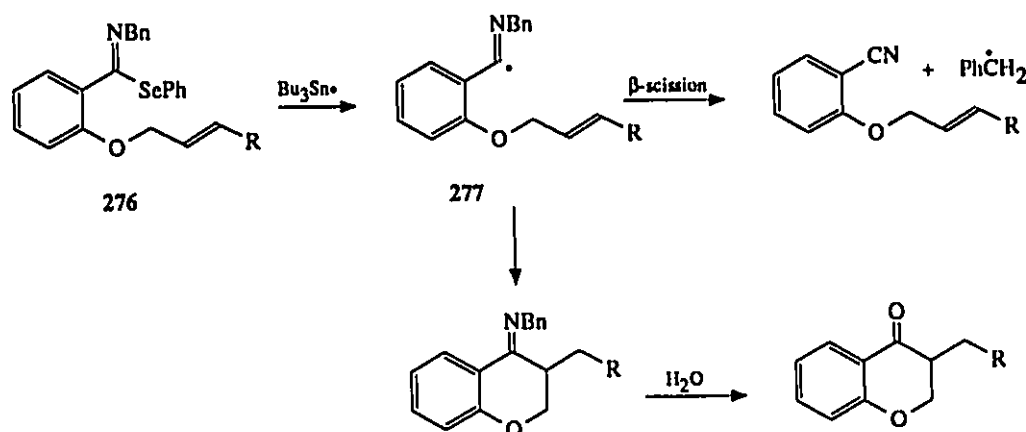
(176) (a) Leardini, R.; Nanni, D.; Tundo, A.; Zanardi, G. *J. Chem. Soc., Chem. Commun.* **1989**, 757. (b) Leardini, R.; Nanni, D.; Tundo, A.; Zanardi, G. *Gazz. Chim. Ital.* **1989**, *119*, 637. (c) Leardini, R.; Tundo, A.; Zanardi, G. *Synthesis* **1985**, 107.

(177) Ohta, H.; Tokumaru, K. *Chem. Ind. (London)* **1971**, 1301.

(178) Bachi, M.D.; Denenmark, D. *J. Am. Chem. Soc.* **1989**, *111*, 1886.

nitriles.^{178, 179} For example, Bachi and Denenmark¹⁷⁸ found that the imidoyl radical **277** underwent β -scission to form the benzyl radical in competition with cyclization of the imidoyl radical (Scheme 101). When the benzyl group was replaced by the p-tolyl group, cyclization was the only pathway.

Scheme 101

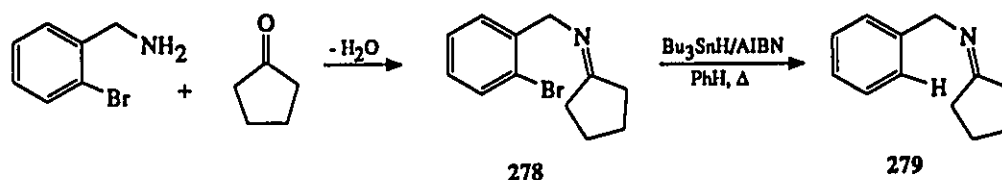


As the 1,5 H-atom transfer was determined to be faster than 5-endo cyclization to the C-atom in Schiff base **273**, cyclization in ketimine **278** was investigated next (Scheme 102). The ketimine **278**, prepared from cyclopentanone and 2-bromobenzylamine, was treated with a small excess of dilute Bu_3SnH (0.07 M) and AIBN in PhH. Product analysis showed that the bromo ketimine **278** was cleanly converted to the dehalogenated ketimine **279** and none of ring cyclized product was detected (^1H NMR). Even with syringe-pump addition of Bu_3SnH and AIBN none of the product from 5-endo closure could be detected. The ^1H NMR and GC spectra of the product were

(179) Singer, L.A.; Kim, S.S. *Tetrahedron Lett.* 1974, 10, 861.

identical to those of authentic **279**.

Scheme 102



From Beckwith's second guideline, it is known that the rate constant for radical cyclization is greatly retarded by substituents at the site of radical attack.^{7, 19} Based on the assumption that 4% or less would not be detected by ¹H NMR spectroscopy, the ratio k_6/k_{11} is ≤ 0.0016 M, assuming a mean stannane concentration of 0.039M at 80°C. Substituting the value of $5.0 \times 10^8 \text{ M}^{-1}\text{s}^{-1}$ for k_{11} ,⁵² gives an upper limit for the rate constant $k_{5\text{-endo}}$ of $7.8 \times 10^5 \text{ s}^{-1}$ at 80°C. The 5-endo cyclization of the *o*-propenyloxyphenyl radical (43) is equally poor and the ratio k_5/k_{11} is < 0.01 M at 130°C.⁵⁷ The low yields of cyclic products, afforded from 5-endo cyclization to the imino or olefinic group, is a reflection of the difficulty for these lower homologues to attain the preferred transition state in which the orbitals containing the three electrons involved in the redistribution process lie in the one plane.⁵⁷

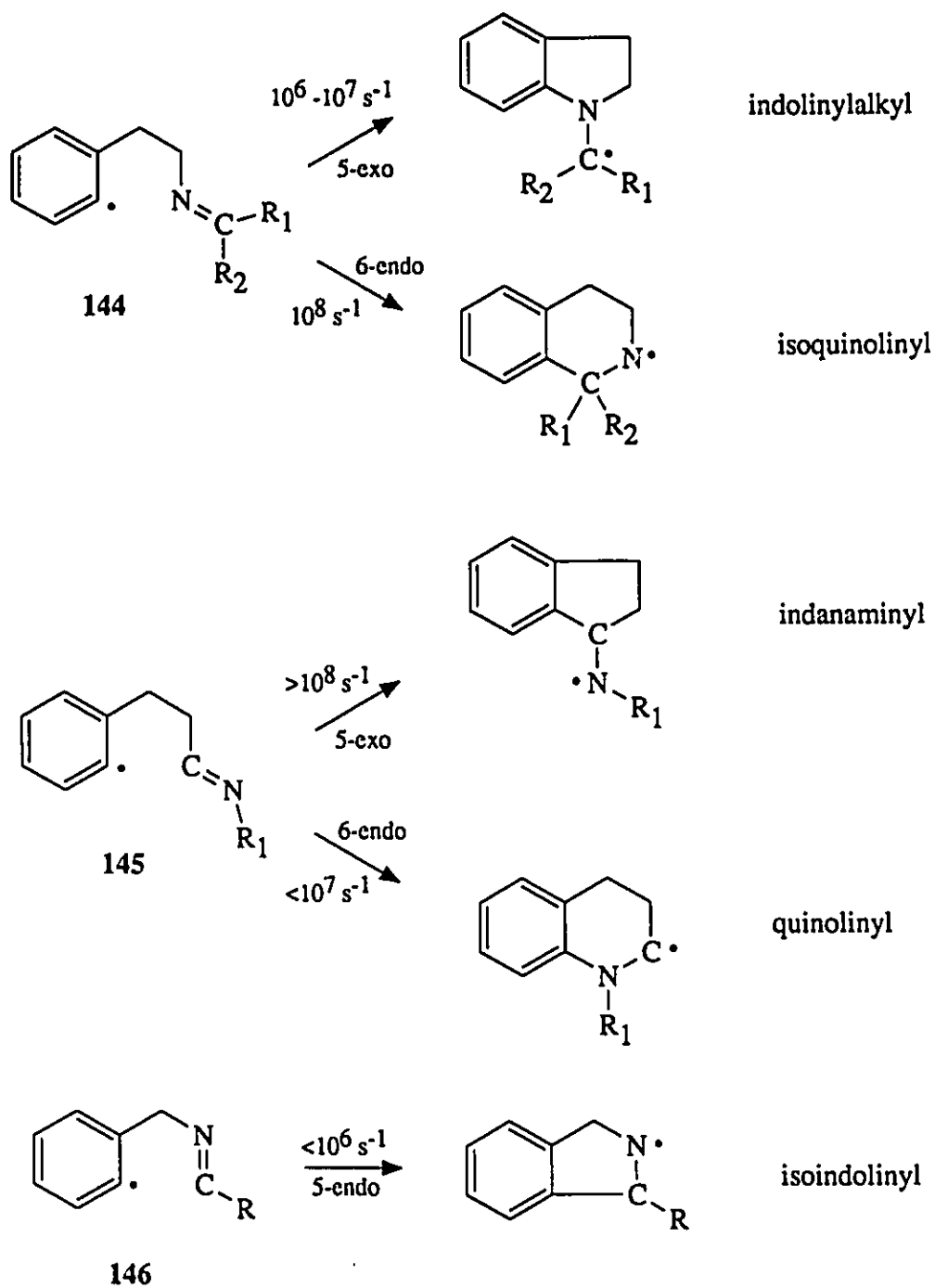
Conclusion

Ortho-substituted aryl radicals **144** ($R_1=H$, $R_2=\text{alkyl, aryl}$) cyclize to the imino functional group with a large 6-endo preference because k_6 is greatly enhanced and k_5 is

somewhat reduced, both relative to corresponding rate constants for cyclization to C=C (Scheme 103). The utility of the 6-endo closure was demonstrated with the synthesis of chiral and achiral tetrahydroisoquinolines. Aryl radical cyclization to the C=N of a ketimine 144 ($R_1=R_2$ = alkyl) is likely to be less synthetically interesting because of low regioselectivity. The rate constants for 5-exo closure to the N-atom and 6-endo to the C-atom in 144 ($R_1=R_2$ =Et) are very similar, ca. $2 \times 10^6 \text{ s}^{-1}$ at 80 °C. The isomeric aryl radicals 145, in turn, cyclize regiospecifically in the 5-exo sense. The rate constant for 5-exo closure in this system is $5.3 \times 10^8 \text{ s}^{-1}$ at 80 °C and it is close to that reported for the *o*-butenylphenyl radical (41).⁴⁵ The regioselectivity of aryl radical cyclization to a 5,6 situated imino group was explained using an argument based on bond energies, geometries and π^* orbital coefficients.

In the lower homologue 146, wherein the choice was 5-endo to the C-atom and 4-exo to the N-atom, the products resulting from ring closure were not found. The upper limit for the rate constant for 5-endo closure to the C-atom in 146 (ketimine of 3-pentanone) is estimated to be $7.8 \times 10^5 \text{ s}^{-1}$ at 80 °C.

Scheme 103



CHAPTER THREE

EXPERIMENTAL

General Notes:

- i) Melting points (mp) were determined on a Thomas-Hoover 6406-H melting point apparatus and are corrected.
- ii) Infrared spectra were recorded on a Perkin Elmer 283 spectrophotometer as a liquid film on NaCl plates, as chloroform solution in NaCl solution cells, or as a KBr disc.
- iii) Proton nuclear magnetic resonance (^1H NMR) spectra were obtained on a Bruker AM500 (500 MHz), a Bruker AC200 (200 MHz), or a Varian EM-390 (90 MHz) spectrometer. Tetramethylsilane (TMS) served as the internal standard. Chemical shifts, quoted as δ values (ppm) were measured relative to TMS. The symbols, s, singlet, d, doublet, t, triplet, q, quartet, br, broad and m, multiplet were used in reporting the spectra.
- iv) Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were determined on either the Bruker AM500 (125.8 MHz) or AC200 (50.3 MHz) spectrometer at ambient temperature. The chloroform-d signal at 77.0 ppm was used as the internal reference. ^{13}C multiplicity was determined from a J-modulated spin sort pulse sequence.
- v) Deuterium nuclear magnetic resonance (^2H NMR) spectra were recorded on the Bruker AM500 (76.8 MHz) at ambient temperature without field frequency

locking. Sample tubes were 10 mm in diameter. The data were collected in a series of blocks, each containing the same number of scans. The free induction decays (FIDs) of block sets were averaged, Fourier-transformed, multiplied by a window function, phase-corrected and baseline corrected. These spectra were then combined with the program NMRstat, written in Pascal for the Aspect computer, to form an average spectrum and a standard deviation spectrum.^{126, 127}

vi) Tin nuclear magnetic resonance (^{119}Sn NMR) spectra were determined on a Bruker AM500 (186.5 MHz) or a WM250 (93.28 MHz) spectrometer. The external reference was SnMe_4 set to 0 ppm.

vii) Electron spin resonance (ESR) spectra were obtained on a Bruker ER 100D spectrometer. The solvent used was cyclohexane and the solutions were degassed and flame sealed. The temperature range investigated was 21 to 71 °C. The decay traces of the ESR signal were collected and manipulated on an IBM PC.¹⁸⁰ The g factor was calculated using the equation: $g = (h\nu)/BH$. The microwave frequency, ν , and magnetic field, H, were measured.

viii) Mass spectra (MS) EI and CI (NH_3) were obtained with a VG Analytical ZAB-E mass spectrometer. Elemental composition determinations were made at a resolution of 5000.

ix) Gas liquid chromatography (GC) was carried out on a Hewlett-Packard 5890 gas chromatograph with a HP 3396a integrator. The column employed was either

(180) Morse, P.D. *Biophys. J.* 1987, 51, 4409.

a DB-1 (15 meters) or a DB-17 (15 and 30 meters) megabore column (1 μm film thickness). A thermal conductivity detector was used and helium (6.6 mL/min) was the carrier gas.

- x) Syringe pump additions were done with a Harvard Apparatus Syringe Infusion Pump 22.
- xi) Photolyses were carried out in a Rayonet photochemical reactor with external irradiation. Lamps were low pressure mercury lamps emitting 300 or 350 nm light.
- xii) Optical rotations were determined on the Perkin Elmer 241 MC polarimeter, using the sodium D line. A 10 cm long solution cell holder with an internal volume of ca. 1 mL was used. The polarimeter was zeroed with pure solvent in the solution cells.
- xiii) The enantiomeric purity of isoquinoline **224** was determined from the ^1H NMR (500 MHz) spectra of CDCl_3 solutions ca. 0.2 M in (R)-**226** (CSA) and 0.07 M in isoquinoline **224**. Lowering the ratio of CSA to isoquinoline lessens the nonequivalence.
- xiv) Thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} or Merck aluminum oxide 60 F_{254} neutral, precoated aluminium or plastic backed sheets with layer thickness of 0.2 mm. Chromatograms were visualized by exposure to ultraviolet light followed by iodine vapors or spraying with a solution⁽¹⁸¹⁾ of 5%

(181) Harwood, L.M.; Moody, C.J. In *Experimental Organic Chemistry*; Blackwell: London, 1989; p522.

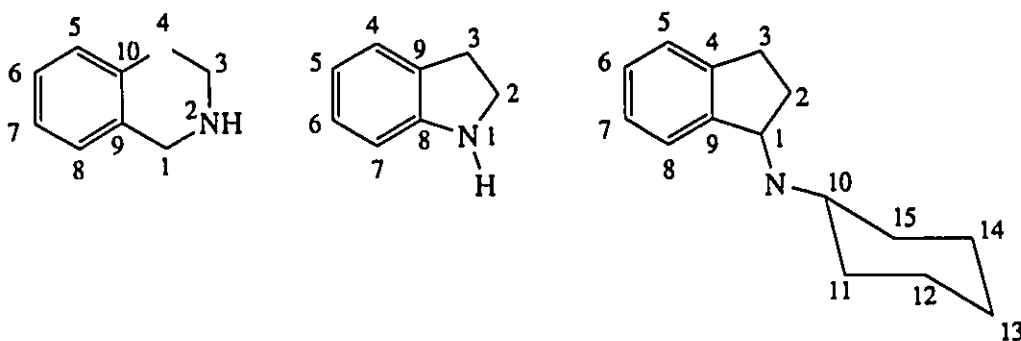
$(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}$ and 0.2% $\text{Ce}(\text{SO}_4)_2$ in 5% H_2SO_4 and heating to 150 °C.

xv) Column chromatography was carried out according to Still¹⁸² using Merck silica gel 60 (200-400 mesh ASTM).

xvi) Centrifugal chromatography was performed on a Harrison Research Chromatotron model 7924T. Glass plates (etched) were coated (1, 2 or 4 mm thickness) with Merck silica gel PF₂₅₄ or Merck aluminium oxide 60 PF₂₅₄ neutral with added CaSO_4 .

xvii) Anhydrous diethyl ether and tetrahydrofuran (THF) were freshly distilled from sodium and benzophenone. Dry methylene chloride was obtained by distillation from P_2O_5 . Chloroform was stored over Al_2O_3 and filtered prior to use in chromatography. Benzene, DMSO, acetonitrile, di-n-butylether and DMF were purified according to published procedures.¹⁸³ Tributyltin hydride (Aldrich) was stored in a freezer under nitrogen.

In reporting the ^{13}C NMR data the following numbering of C-atoms was used:



(182) Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* 1978, 43, 2923.

(183) Vogel, A. In *Vogel's Textbook of Practical Organic Chemistry*; 4th ed.; Longman: New York, 1978; p264-278.

2-Bromophenylacetonitrile (153)

Following the procedure of Smiley and Arnold,¹⁰⁹ to a 3-neck round bottom flask fitted with a condenser, mechanical stirrer, and dropping funnel was added a solution of NaCN (14.12 g, 0.28 mol) (dried overnight at 110 °C) in dry DMSO (150 mL). The mixture was heated on a steam bath and stirred vigorously. After 30 min, the mechanical stirrer was replaced by a thermometer and a stir bar. o-Bromobenzylbromide (152) (60 g, 0.24 mol) was added to the reaction mixture at a rate sufficient to keep the pot temperature in the range 100 to 115 °C (25 min). The mixture was heated on the steam bath for an additional 30 min and then allowed to cool. The orange coloured precipitate was dissolved by adding 140 mL of H₂O. The aqueous phase was extracted with diethyl ether (2 x 150 mL), and the combined ether extracts were washed with brine (2 x 150 ml) and dried over MgSO₄. The residue after concentration under reduced pressure was purified by vacuum distillation to give 2-bromophenylacetonitrile (153) (33.86 g, 72%) as a colourless oil: bp 103 °C at 0.85 mm, lit.¹⁸⁴ bp 140-141 °C at 13 mm; IR (film): 3060, 2260, 1565, 1475, 1020, 740 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 3.80 (s, 2H, CH₂), 7.18 (triplet of doublets, ³J=7.8 Hz, ⁴J=1.7 Hz, 1H, ArH-4 or ArH-5), 7.33 (triplet of doublets, ³J=7.8 Hz, ⁴J=1.7 Hz, 1H, ArH-4 or ArH-5), 7.49 (dd, ³J=7.8 Hz, ⁴J=1.7 Hz, ArH-6), 7.57 (dd, ³J=7.8 Hz, ⁴J=1.7 Hz, ArH-3); ¹³C NMR (50.3 MHz, CDCl₃) δ 24.6 (CH₂), 116.7 (CN), 123.3 (aryl, C-2), 127.9 (aryl, CH-5), 129.5 (aryl, CH-4 or CH-6), 129.6 (aryl, CH-4 or CH-6), 129.7 (aryl, C-1), 132.8 (aryl, CH-3); MS (EI) m/z (%):

(184) *Aldrich Chemical Catalogue: 1992-1993*, 205.

197 (MH⁺, 34), 195 (MH⁺, 35), 171 (8), 169 (9), 116 (100), 89 (36).

2-Bromophenethylamine (154)

Following the procedure of Miller and Klinman,¹⁰⁷ to a 1 L three-neck flask equipped with a mechanical stirrer, reflux condenser, and dropping funnel was added LAH (4 g, 0.1 mol) in 130 mL of dry ethyl ether under N₂. An ethereal solution of AlCl₃ (13.3 g, 0.1 mol in 100 mL) was run in quickly with rapid stirring. After stirring for 10 min, an ethereal solution of 2-bromophenylacetonitrile (153) (15 g, 0.076 mol) was added dropwise over 15 min, and the mixture was stirred vigorously at room temperature. After 35 min, TLC (SiO₂, 1:2:3 benzene:ethyl acetate:methanol) showed only one spot (R_f=0.3) corresponding to the product. While the solution was being cooled with ice/water, the excess LAH was quenched by the dropwise addition of water (75 mL) followed by acidification with 6N H₂SO₄ (75 mL). An additional 150 mL of H₂O dissolved the aluminum salts completely. After separation, the aqueous layer was washed with ether (130 mL), taken to pH > 11 with KOH pellets, and extracted with ether (3x200 mL). The ether was dried over MgSO₄, filtered and evaporated in vacuo to give an oil. Distillation under vacuum gave **154** as a colourless oil (12.5 g, 82%): bp 85 °C at 0.4 mm; IR (film): 3375, 3050, 2920, 1520, 1465, 1430, 1010, 740 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 1.09 (br s, 2H, NH), 2.91 (m, 4H, CH₂CH₂), 7.04 (m, 1H, ArH), 7.23 (m, 2H, ArH), 7.52 (d, J=7.7 Hz, 1H, ArH-3); ¹³C NMR (50.3 MHz, CDCl₃) δ 40.2 (CH₂), 41.9 (CH₂), 124.4 (aryl, C-Br), 127.2 (aryl, CH-4 or CH-5), 127.7 (aryl, CH-4 or CH-5), 130.6 (aryl, CH-6),

132.6 (aryl, CH-3), 138.9 (aryl, C-CH₂); MS (CI) m/z (%): 202 (MH⁺, 100), 200 (MH⁺, 98), 120 (14).

N-Isobutyrylimidazole (158)

Following the procedure of Staab and Rohr,¹¹⁵ to a solution of imidazole (6.4 g, 0.094 mol) in THF (30 mL) was added isobutyryl chloride (5 g, 0.047 mol) over 2 min under nitrogen. The mixture was stirred at ambient temperature for 3.5 h. The reaction mixture was then filtered through a bed of Celite/MgSO₄ (1:1 ratio) and the filtrate was concentrated under reduced pressure. The residue was distilled affording **158** as a colourless oil (4.65 g, 72%): bp 40 °C at 1 mm, lit.¹⁸⁵ bp 92 °C at 18 mm; IR (CHCl₃): 3130, 2970, 1735, 1700, 1460, 1390, 1050, 940 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 1.34 (d, J=6.8 Hz, 6H, CH₃), 3.24 (sept, J=6.8 Hz, 1H, CH(CH₃)₂), 7.10 (s, 1H, ArH), 7.51 (s, 1H, ArH), 8.21 (s, 1H, ArH); ¹³C NMR (50.3 MHz, CDCl₃) δ 18.82 (CH₃), 33.7 (CH(CH₃)₂), 116 (aryl, CH-3), 130.7 (aryl, CH-2), 135.9 (aryl, CH-1), 173.4 (C=O); MS (EI) m/z (%): 138 (M⁺, 48), 110 (12), 95 (8), 71 (100), 69 (95), 68 (90).

Preparation of Isobutyraldehyde-1-d (159)

Following the procedure of Staab and Braunling,¹¹³ to a solution of imidazolidine **158** (1.5 g, 11 mmol) in dry ether (40 mL) cooled to -20 °C (CCl₄/CO₂ (s)) was added LiAlD₄ (0.116 g, 2.71 mmol) in 30 mL of dry ether over 15 min under N₂.

(185) Staab, H.A. *Chem. Ber.* **9156**, 89, 2088.

The reaction mixture was stirred for an additional 90 min at -20 °C and then quenched with H₂O (5 mL), and 5% H₂SO₄ (20 mL). The aqueous suspension was extracted with ether (4 x 20 mL) and the combined extracts were dried with MgSO₄ and used immediately in the condensation reaction.

Preparation of Benzaldehyde-1-d (162)

Following the procedure of Schowen and co-workers,¹¹⁶ to a solution of benzil (21 g, 0.1 mol, recrystallized from CCl₄) in dry 1,4-dioxane (50 mL) was added 30 mL of D₂O with stirring under N₂. To the resulting suspension were added with rapid stirring, at 2-min intervals, eight 1.5 g portions of KCN (total of 12 g, 0.18 mol). The reaction mixture was stirred for an additional 10 min and then the mixture was diluted with 100 mL of water and extracted with ether (2x100 mL). The combined ether extracts were washed with 5% Na₂CO₃ (100 mL), water (200 mL), and brine (100 mL). Traces of water were removed with MgSO₄, and the solvent was evaporated in vacuo to give an orange-yellow oil. Distillation under vacuum gave **162** as a colourless oil (6.6 g, 62%): bp 35-37 °C at 1.3 mm, lit.¹¹⁶ bp 84-86 °C at 30 mm; IR (film): 3030, 2100, 1690, 1600, 1450 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 7.57 (m, 3H, 2xArH-3 and ArH-4), 7.87 (m, 2H, 2xArH-2); MS (CI) m/z (%): 125 (M⁺+18, 100), 107 (MH⁺, 21), 105 (61).

General Procedure A for the Condensation of Low Boiling Carbonyl Compounds:

Preparation of 2-Bromo-N-(2-methylpropylidene) benzeneethanamine (164)

To a solution of isobutyraldehyde (1.51 g, 20 mmol) over 4Å molecular sieves (9 g) in 30 mL of dry diethyl ether was added a solution of 2-bromophenethylamine (**154**) (2 g, 10 mmol) in 20 mL of dry ether over 5 min. The reaction flask was fitted with a CaCl₂ drying tube and the mixture was stirred for 2.5 h at room temperature. The reaction mixture was filtered through Celite, and the filtrate was evaporated under vacuum. Kugelrohr distillation (75 °C at 0.6 mm) of the residue gave 1.96 g of **164** as a colourless oil (77%): IR (CHCl₃): 2965, 2870, 1670, 1470, 1440, 1025 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 1.00 (d, J=6.8 Hz, 6H, CH₃), 2.36 (distorted octet, J=6.8, 5.0 Hz, 1H, CH(CH₃)₂), 3.03 (t, 7.2 Hz, 2H, CH₂-Ar), 3.60 (t, J=7.2 Hz, 2H, CH₂-N), 7.01-7.07 (m, 1H, ArH), 7.13-7.22 (m, 2H, ArH), 7.31 (d, J=5.0 Hz, 1H, HC=N), 7.50 (d, J=8.2 Hz, 1H, ArH); ¹³C NMR (50.3 MHz, CDCl₃) δ 19.0 (CH₃), 33.7 (CH(CH₃)₂), 37.3 (CH₂-Ar), 60.2 (CH₂-N), 124.4 (aryl, C-Br), 127.0, 127.6, 131.4, and 132.5 (aryl, 4 x CH), 138.9 (aryl, C-CH₂), 170.5 (C=N); MS (CI) m/z (%): 256 (MH⁺, 100), 254 (MH⁺, 98), 174 (15), 84 (16).

Preparation of 2-Bromo-N-(2-methylpropylidene-d) benzeneethanamine (**165**)

Following the general procedure A, a solution of isobutyraldehyde-1-d (11 mmol) and the amine **154** (1 g, 5 mmol) was stirred for 4 h at room temperature. Kugelrohr distillation of the residue (ca. 80 °C at 0.6 mm) gave 0.8 g of **165** as a colourless oil (67%): IR (CHCl₃): 2960, 2935, 1655, 1470, 1020, 900 cm⁻¹; ¹H NMR (200

MHz, CDCl₃) δ 1.01 (d, J=6.9 Hz, 6H, CH₃), 2.36 (septet, J=6.9 Hz, 1H, CH(CH₃)₂), 3.03 (t, J=7.2 Hz, 2H, CH₂-Ar), 3.61 (t, J=7.2 Hz, 2H, CH₂-N), 7.00-7.12 (m, 1H, ArH), 7.14-7.26 (m, 2H, ArH), 7.50-7.56 (m, 1H, ArH); ¹³C NMR (50.3 MHz, CDCl₃) δ 19.2 (CH₃), 33.8 (CH(CH₃)₂), 37.4 (CH₂-Ar), 60.4 (CH₂-N), 124.6 (aryl, C-Br), 127.1, 127.8, 131.5, and 132.7 (aryl, 4 x CH), 139.1 (aryl, C-CH₂), 170.4 (t, C=N); MS (CI) m/z (%): 257 (MH⁺, 98), 255 (MH⁺, 100), 175 (22), 85 (16).

Preparation of N-(2-Methylpropylidene) benzeneethanamine (168)

A solution of phenethylethanamine (1.55 g, 12.8 mmol) and isobutyraldehyde (1.11 g, 15.4 mmol) in PhCH₃ (35 mL) was heated to reflux for 17.5 h. Kugelrohr distillation (ca. 70 °C at 0.7 mm) of the residue gave 1.97 g of 168 as a colourless oil (88%): IR (CHCl₃): 2960, 2840, 1670, 1605, 1450, 1370 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 0.99 (d, J=6.9 Hz, 6H, CH₃), 2.36 (distorted octet, J=6.9, 5.1 Hz, 1H, CH(CH₃)₂), 2.89 (t, J=7.3 Hz, 2H, CH₂-Ar), 3.59 (t, J=7.3 Hz, 2H, CH₂-N), 7.11-7.35 (m, 6H, HC=N and ArH); ¹³C NMR (50.3 MHz, CDCl₃) δ 19.1 (CH₃), 33.7 (CH(CH₃)₂), 37.1 (CH₂-Ar), 62.5 (CH₂-N), 125.8, 128.0, and 128.9 (aryl, 3 x CH), 139.7 (aryl, C-CH₂), 170.2 (C=N); MS (EI) m/z (%): 175 (M⁺, 6), 132 (12), 105 (75), 91 (38), 84 (100), 77 (30), 65 (16).

Preparation of N-(2-Methylpropylidene-d) benzeneethanamine (169)

To an ethereal (40 mL) solution of isobutyraldehyde-1-d (0.2 g, 3 mmol)

containing 4Å molecular sieves (6 g) and cooled to 0 °C was added phenethylamine (0.36 g, 3.0 mmol) in 5 mL of dry ether over 7 min. The reaction was stirred for 2 h and then filtered through Celite. The filtrate was concentrated under vacuum and the residue was purified by Kugelrohr distillation (ca. 70 °C at 0.7 mm) giving 0.43 g of **169** as a colourless oil (69%): IR (CHCl₃): 2960, 2870, 2110, 1655, 1600, 1495, 1450, 1365 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) 0.98 (d, J=6.9 Hz, 6H, CH₃), 2.36 (septet, J=6.9 Hz, 1H, CH(CH₃)₂), 2.90 (t, J=7.2 Hz, 2H, CH₂-Ar), 3.60 (t, J=7.2 Hz, 2H, CH₂-N), 7.12-7.34 (m, 5H, ArH); ¹³C NMR (50.3 MHz, CDCl₃) δ 19.1 (CH₃), 33.6 (CH(CH₃)₂), 37.1 (CH₂-Ar), 62.4 (CH₂-N), 125.9, 128.1, and 129.0 (aryl, 3 x CH), 140 (aryl, C-CH₂), 170 (t, C=N); MS (EI) m/z (%): 176 (M⁺, 6), 133 (10), 105 (100), 91 (39), 77 (16), 65 (11).

General Procedure B for the alkylation of Indoline at the N-atom: Preparation of N-(2-methylpropyl)indoline (**170**).

Following the procedure of Belsky and co-workers,¹²⁴ indoline (0.86 g, 7.2 mmol) was added to NaHCO₃ (0.76 g, 9 mmol) in 5 mL of water and the mixture was stirred with heating to 95 °C. Isobutyryl bromide (0.99 g, 7.2 mmol) was added dropwise during 1.5 h, and heating was continued for an additional 4.5 h. After cooling the layers were separated, and the aqueous layer was extracted with ether (2 x 15 mL). The solvent was removed in vacuo and the residue was purified by Chromatotron chromatography (4 mm, SiO₂, 100% hexane) to yield **170** (0.77 g, 60%): IR (CHCl₃): 2960, 2930, 2870, 1610, 1490, 1470, 1385, 1250-1190, 1040 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 0.96 (d,

$J=6.6$ Hz, 6H, CH_3), 1.92 (nine lines, $J=6.6$ Hz, 1H, $\text{CH}_2\text{-CH}(\text{CH}_3)_2$), 2.79 (d, $J=7.2$ Hz, 2H, NCH_2CH), 2.96 (t, $J=8.4$ Hz, 2H, $\text{NCH}_2\text{CH}_2\text{Ar}$), 3.34 (t, $J=8.4$ Hz, 2H, $\text{NCH}_2\text{CH}_2\text{Ar}$), 6.42 (d, $J=8.1$ Hz, 1H, ArH-7), 6.60 (t, $J=7.3$ Hz, 1H, ArH-5), 7.04 (m, 2H, ArH-4 and H-6); ^{13}C NMR (50.3 MHz, CDCl_3) δ 20.6 (2 x CH_3), 27.7 ($\text{CH}(\text{CH}_3)_2$), 28.6 ($\text{CH}_2\text{-Ar}$), 53.9($\text{CH}_2\text{CH}_2\text{N}$), 58.0 ($\text{HC-CH}_2\text{-N}$), 106.4 (aryl, CH-7), 116.9 (aryl, CH-5), 124.3 (aryl, CH-6), 127.3 (aryl, CH-4), 129.5 (aryl, C-9), 153.3 (aryl, C-8); MS (EI) m/z (%): 175 (M^+ , 29), 132 (100), 117 (8).

Kinetic Study of the Cyclization of Isobutyraldimine (164) using ^1H NMR Spectroscopy (Table 1).

A 2-mL volumetric flask was filled to the mark with a C_6D_6 solution containing the bromide 164 (36 mg, 0.138 mmol), Bu_3SnH (413.1 mg, 1.42 mmol) and AIBN (3 mg, 0.018 mmol) (Solution I, $[\text{Bu}_3\text{SnH}]_0 = 0.71$ M). A 57- μL aliquot of Solution I was diluted with 0.50 mL of C_6D_6 (Solution II, $[\text{Bu}_3\text{SnH}]_0 = 0.073$ M). A 29- μL aliquot of Solution I was withdrawn and placed in a 1-mL volumetric flask and filled to the mark with C_6D_6 (Solution III, $[\text{Bu}_3\text{SnH}]_0 = 0.021$ M). A 175- μL aliquot of solution III was combined with 0.50 mL of C_6D_6 (Solution IV, $[\text{Bu}_3\text{SnH}]_0 = 0.005$ M). Approximately 0.4 mL of Solutions I, II, and IV were placed into separate 5-mm nmr tubes with ground glass joints. The solutions were degassed by four freeze/pump/thaw cycles and the tubes were sealed under vacuum. The nmr tubes were heated in a constant temperature bath set at 80.0 ± 0.2 °C for 135 min. Product ratios were determined from the integrals in the ^1H

NMR (500 MHz) spectra. The indoline 170 was detected in the reaction mixture from solution II (ratio of 166 to 170 was ca. 60, ^1H NMR). The spectral width was set at 5000 Hz, the pulse width at 5 μs and the relaxation delay at 2 s.

General Procedure C for the Kinetic Study of the Cyclization of Isobutyraldimine-d 165 using ^2H NMR Spectroscopy (Table 2).

A 10-mL volumetric flask was filled to the mark with a solution of the deuterated imine 165 (0.2180 g, 0.8543 mmol), Bu_3SnH (2.3360 g, 8.026 mmol) and AIBN (0.0071 g, 0.043 mmol) in PhH (solution I, $[\text{Bu}_3\text{SnH}]_0 = 0.803 \text{ M}$). A 5-mL aliquot of solution I was placed in a separate 10-mL volumetric, and filled to the mark with PhH (solution II, $[\text{Bu}_3\text{SnH}]_0 = 0.402 \text{ M}$). A 5-mL aliquot of solution II was then placed in a separate 10-mL volumetric flask and filled to the mark with PhH (solution III, $[\text{Bu}_3\text{SnH}]_0 = 0.202 \text{ M}$). In a similar manner, solution IV $[\text{Bu}_3\text{SnH}]_0 = 0.101 \text{ M}$, and solution V $[\text{Bu}_3\text{SnH}]_0 = 0.0504$ were prepared. Aliquots (2 mL) of solution I through V were transferred into separate 10-mm nmr tubes. Aliquots (0.4 mL) of solution III and V were also transferred to 5-mm nmr tubes. The solutions in the nmr tubes were deoxygenated by three freeze/pump/thaw cycles and the tubes were sealed under vacuum. The nmr tubes were heated in a constant-temperature bath set at $80.0 \pm 0.2 \text{ }^\circ\text{C}$. The reactions were monitored by ^1H NMR (90 MHz) spectroscopy using the 5-mm sample tubes. The heating times were as follows: solution I, 25 min; solution II, 40 min; solution III, 40 min; solution IV, 2 h, and solution V, 4.5 h. The reaction mixtures were cooled, opened, and

pumped (ca. 1 mm) for several minutes to remove the bulk of the PhH. The residue was dissolved in dry CH_2Cl_2 and immediately analyzed by ^2H NMR spectroscopy. A delay of 1.5 s between pulses was applied to ensure full relaxation of spins. A 90° pulse width of 14 μs was used. The spectral width was 729.9 Hz and the digital resolution was 0.36 Hz/pt. A line broadening (LB) factor of 3 Hz was applied. The data were collected in blocks, ranging from 7 to 60, with 128 scans in each block. The concentration of deuterium in the sample determined the number of blocks collected. Product ratios were determined from the peak heights: tetrahydroisoquinoline **167** δ 3.87 ppm (Ar-CD-N), benzaldimine-d **169** δ 7.41 ppm (N=CD), relative to natural abundance deuterium in the solvent, CH_2Cl_2 , set at 5.32 ppm. A gravimetric calibration of the peak heights was done. Three solutions with known quantities of isoquinoline **167** and aldimine **169** were prepared. The product ratios, **167/169** (6H/RH), as determined from the measurement of the peak height in the ^2H NMR spectrum were multiplied by 1.7.

General Procedure D for the Cyclization of Isobutyraldimine **164** with Syringe-pump Addition of Bu_3SnH : Preparation of 1,2,3,4-Tetrahydro-1-(1-methylethyl) isoquinoline (**166**).

A solution of isobutyraldimine **164** (0.599 g, 2.36 mmol) in PhH (50 mL) was thoroughly degassed with nitrogen and heated to reflux. A degassed solution of Bu_3SnH (0.988 g, 3.39 mmol), and AIBN (0.085 g, 0.5 mmol) in 18 mL of PhH was introduced by means of a syringe-pump addition over 13 h to the heated substrate solution. The

solution was heated at reflux for an additional 4 h. GC analysis (DB-17, 30 m, 130 °C for 3 min, 10 °C/min to 240 °C) of the reaction mixture showed the formation of 4 new products, in the ratio 166:168:170:172 = 55:11:1.0:3.4. Authentic samples of indoline 170 and aldimine 168 were prepared for comparison. The solvent was removed in vacuo and the residual oil was dried under high vacuum (0.05 mm). The oil was added to an ice cold ethereal solution saturated with HCl (g) (15 mL) in a Schlenk tube filled with nitrogen. The mixture was agitated and diluted with 7 mL of dry ether giving pale-yellow crystals. The crystals were separated by filtration under nitrogen, washed with dry ether (3 x 7 mL), and dissolved in 2M NaOH (40 mL). The aqueous solution was extracted with CH₂Cl₂ (3 x 35 mL) and the combined organic extracts were dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by Chromatotron chromatography (2mm, SiO₂). Initial elution with 2% CH₃OH/CHCl₃ (150 mL) gave a small amount of indoline 170 (spectral data for 170 given above) contaminated with organotins. Elution with 2.5% CH₃OH/CHCl₃ afforded ca. 25 mg of 172: ¹H NMR (200 MHz, CDCl₃) δ 1.24 (d, J=6.8 Hz, 6H, CH₃), 2.69 (t, J=7.3 Hz, 2H, CH₂-Ar), 3.31 (septet, J=6.8 Hz, 1H, CH(CH₃)₂), 3.70 (t, J=7.3 Hz, 2H, CH₂-N), 7.15-7.42 (m, 3H, ArH), 7.54 (d, J=9H, 1H, ArH). Further elution with 5% CH₃OH/CHCl₃ afforded the isoquinoline 166 (0.246 g, 60%): IR (CHCl₃): 3350, 2960, 2930, 2880, 1600, 1490, 1460, 1385, 1365, 1090 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 0.74 (d, J=6.8 Hz, 3H, CH₃), 1.12 (d, J=6.8 Hz, 3H, CH₃), 1.78 (br s, 1H, NH), 2.27-2.43 (m, 1H, CH(CH₃)₂), 2.60-3.03 (m, 3H, CH₂CH₂), 3.23-3.35 (m, 1H, CH₂), 3.95 (d, J=3.8 Hz, 1H, Ar-CH-N), 7.03-7.21 (m, 4H, ArH); ¹³C

NMR (50.3 MHz, CDCl₃) δ 15.7 , 20.2 (2 x CH₃), 30.4 (CH₂-Ar), 32.2 (CH(CH₃)₂), 42.5 (CH₂N), 60.9 (Ar-CH-N), 125.6, 125.7, and 125.9 (aryl, 3 x CH), 129.1 (aryl, CH-5), 136.2 (aryl, C-9), 138.7 (aryl, C-10); MS (DCI) m/z (%): 176 (MH⁺, 100), 132 (25); HRMS calcd for C₁₂H₁₇N - C₃H₇ or C₉H₁₀N 132.0813 found 132.0819.

Thermolysis of 1,2,3,4-Tetrahydro-1-(1-methylethyl) isoquinoline (166) with AIBN.

A solution of isoquinoline 166 (4 mg, 0.02 mmol) and AIBN (7 mg, 0.04 mmol) in C₆D₆ (0.4 mL) was transferred to a 5-mm nmr tube fitted with a ground glass joint and it was subjected to three cycles of freeze/pump/thaw degassing at 10⁻¹ mm before the tube was sealed. The solution was heated in a constant-temperature bath set at 80 °C for 6 h. ¹H NMR (200 MHz, C₆D₆) analysis of the reaction mixture showed one new product, corresponding to 3,4-dihydroisoquinoline 172 (15%, the remainder was 166): The ¹H NMR data for 172 were given previously.

Syring-Pump Addition of Bu₃SnH to Isobutyraldimine 165: Preparation of 1,2,3,4-Tetrahydro-1-(1-methylethyl) isoquinoline-1d (167).

Following the standard high-dilution procedure D, the imine 165 (0.52 g, 2.0 mmol) in PhH (50 mL) was treated with Bu₃SnH (0.82 g, 2.8 mmol) and AIBN (81 mg, 0.49 mmol) in PhH (20 mL). GC analysis (DB-17, 30 m, 130 °C for 3 min, 10 °C/min to 240 °C) of the reaction mixture showed the formation of four new compounds, in the ratio of 167:169:171:172 = 57:10:1.0:2.1. The reaction was worked up according to the

standard procedure D. The crude residue isolated was purified by Chromatotron chromatography (SiO₂, 2% MeOH/CHCl₃ increasing to 5% MeOH/CHCl₃) to give 163 mg (48%) of isoquinoline 167 as a clear oil: IR (CHCl₃): 3005, 2960, 2930, 1600, 1490, 1440, 1380, 1090 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 0.75 (d, J=6.8 Hz, 3H, CH₃), 1.12 (d, J=6.8 Hz, 3H, CH₃), 1.72 (br s, 1H, NH), 2.34 (sept, J=6.8 Hz, 1H, CH(CH₃)₂), 2.50-3.02 (m, 3H, CH₂CH₂), 3.12-3.49 (m, 1H, CH₂), 7.03-7.26 (m, 4H, ArH); ¹³C NMR (50.3 MHz, CDCl₃) δ 15.8 and 20.2 (2 x CH₃), 30.4 (CH₂-Ar), 32.2 (CH(CH₃)₂), 42.5 (CH₂-N), 60.9 (t, Ar-CD-N), 125.6, 125.7, and 125.9 (aryl, 3 x CH), 129.1 (aryl, CH-5), 136.2 (aryl, C-9), 138.7 (aryl, C-10); MS (CI) m/z (%): 177 (MH⁺, 100), 133 (86).

General Procedure E for the Condensation of High Boiling Carbonyl Comounds:

Preparation of 2-Bromo-N-(1-benzylidene) benzeneethanamine (176).

A solution of 2-bromophenethylamine 154 (1.52 g, 7.6 mmol) and benzaldehyde (0.81 g, 7.6 mmol) in PhCH₃ (35 mL) was heated to reflux for 3 h in a Dean-Stark apparatus. The solvent was removed under vacuum and the residue was distilled in a Kugelrohr apparatus (105 °C at 0.6 mm) to give 1.7 g of 176 as a clear oil that solidified on standing (78%): mp 38-39 °C; IR (CHCl₃): 2950, 2845, 1645, 1580, 1450, 1035 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 3.12 (t, J=7.4 Hz, 2H, CH₂-Ar), 3.83 (t, J=7.4 Hz, 2H, CH₂-N), 6.99-7.70 (m, 9H, ArH), 8.13 (s, 1H, HC=N); ¹³C NMR (50.3 MHz, CDCl₃) δ 37.5 (CH₂-Ar), 60.9 (CH₂-N), 124.5 (aryl, C-Br), 127.2, 127.8, 127.9, 128.4, 130.4, 131.2, and 132.6 (aryl, 7 x CH), 136.0 (aryl, C-C=N), 139.0 (aryl, C-CH₂),

161.5 (C=N); MS (CI) m/z (%): 290 (MH⁺, 100), 288 (MH⁺, 98), 118 (28), 103 (15), 91 (9). The ¹H NMR and IR data for 176 match well with those reported by Bradsher and Hunt.¹⁰¹

Preparation of N-benzylindoline (178).

Following general procedure B, indoline (2.0 g, 17 mmol) was alkylated with benzyl bromide (2.8 g, 17 mmol) in aqueous NaHCO₃ (2.1 g, 25 mmol in 6 mL). The residue was purified by Chromatotron chromatography (SiO₂, 4 mm). Elution with 2% ethyl acetate/hexane, afforded 0.82 g (23%) of 178 as a yellow oil: IR (CHCl₃): 3000, 2960, 2920, 2825, 1610, 1485, 1450, 1355, 1260-1140, 900 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 2.97 (t, J=8.2 Hz, 2H, NCH₂CH₂Ar), 3.30 (t, J=8.2 Hz, 2H, NCH₂CH₂Ar), 4.25 (s, 2H, PhCH₂N), 6.52 (d, J=7.8 Hz, 1H, ArH-7), 6.68 (t, J=6.9 Hz, 1H, ArH-5), 7.08 (m, 2H, ArH-4 and H-6), 7.33 (m, 5H, ArH); ¹³C NMR (125.8 MHz, CDCl₃) δ 28.5 (CH₂-Ar), 53.50 (Ph-CH₂-N), 53.59 (CH₂-CH₂-N), 107.0 (aryl, CH-7), 117.6 (aryl, CH-5), 124.4, 127.0, 127.2, 127.8, and 128.4 (aryl, 5 x CH), 129.9 (aryl, C-9), 138.4 (aryl, C-CH₂-N), 152.5 (aryl, C-8); MS (EI) m/z (%): 209 (M⁺, 100), 132 (20), 118 (16), 91 (48).

Preparation of N-(1-Benzylidene) benzeneethanamine (179).

Following general procedure E, a solution of benzaldehyde (4.38 g, 41 mmol) and phenethylamine (5 g, 41 mmol) in PhCH₃ (35 mL) was heated to reflux for 4 h. Kugelrohr distillation (ca. 150 °C at 0.3 mm) of the residue gave 6.68 g of 179 as an oil

that solidified on cooling (white solid) (78%): mp 38-39 °C; IR (CHCl₃): 2945, 2850, 1640, 1605, 1490, 1450 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 3.01 (t, J=7.4 Hz, 2H, CH₂-Ar), 3.87 (t, J=7.4 Hz, 2H, CH₂-N), 7.15-7.47 (m, 8H, ArH), 7.67-7.75 (m, 2H, ArH), 8.15 (s, 1H, HC=N); ¹³C NMR (50.3 MHz, CDCl₃) δ 37.5 (CH₂-Ar), 63.1 (CH₂-N), 126.0, 128.0, 128.3, 128.5, 129.0, and 130.5 (aryl, 6 x CH), 136.1 (aryl, C=C=N), 139.8 (aryl, C-CH₂), 161.5 (C=N); MS (EI) m/z (%): 209 (M⁺, 3), 132 (5), 118 (100), 91 (83), 77 (12).

General Procedure F for the Cyclization of Benzaldimine 176 with the Syringe-Pump Addition of Bu₃SnH: Synthesis of 1,2,3,4-Tetrahydro-1-phenyl isoquinoline (177).

A solution of imine 176 (0.59 g, 2.05 mmol) in PhH (50 mL) was thoroughly degassed with N₂ and was heated to reflux under N₂. A degassed solution of Bu₃SnH (0.88 g, 3.0 mmol) and AIBN (0.12 g, 0.73 mmol) in PhH (20 mL) was introduced by means of a syringe-pump addition over 16 h to the heated substrate. ¹H NMR (200 MHz, CDCl₃) analysis of the reaction mixture showed a 177/178 (6H/5H) product ratio of 11. The solvent was removed in vacuo to give pale-yellow oil that partially solidified on standing. This product mixture was filtered and the white crystals were washed with hexane (15 mL). The mother liquor was concentrated under vacuum to a volume of 5 mL and stored in the freezer overnight. The resulting white crystals were collected and washed with hexane. Two more crops of crystals were obtained from the mother liquor. The combined solid was recrystallized from ether giving 0.30 g of 177 as white crystals

(70%): mp 96-97 °C (lit.¹⁸⁶ mp 97-98 °C): IR (CHCl₃): 3340, 3000, 2960, 2930, 2835, 1605, 1490, 1455, 1190 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 2.10 (br s, 1H, NH), 2.73-2.92 (m, 1H, CH₂), 2.93-3.15 (m, 2H, CH₂CH₂), 3.16-3.32 (m, 1H, CH₂), 5.09 (s, 1H, Ph-CH-N), 6.74 (d, J=7.6 Hz, 1H, ArH), 6.96-7.36 (m, 8H, ArH); ¹³C NMR (50.3 MHz, CDCl₃) δ 29.7 (CH₂-Ar), 42.2 (CH₂-N), 62.1 (Ar-CH-N) 125.6, 126.2, 127.4, 128.1, 128.4, and 129.0 (aryl, 6 signals for 7 x CH), 135.4, 138.2, and 144.8 (aryl, 3 x C); MS (CI) m/z (%): 210 (MH⁺, 100), 132 (14). Spectral data for 177 match those reported in the literature.^{186, 101}

Photolysis of Me₆Sn₂ with Benzaldimine 176.

A solution of benzaldimine 176 (29.7 mg, 0.103 mmol), Me₆Sn₂ (27.8 mg, 0.085 mmol), and cumene (15.3 mg, 0.127 mmol) in C₆D₆ (0.4 mL) was transferred to a 5-mm nmr tube fitted with a ground glass joint. The solution was deoxygenated by three freeze/pump/thaw cycles and the tube was sealed under vacuum. The solution was irradiated in the Rayonet photochemical reactor with 300 nm lamps for 24 h at ca. 25 °C. The product ratios were determined from the peak heights in the ¹H NMR spectra: 177/178 (6H/5H) = 20 (25% conversion). Spectral data for 177 and 178 were given previously.

(186) Seebach, D.; Lohmann, J.-J.; Syfrig, M.A.; Yoshifuji, M. *Tetrahedron* 1983, 39, 1963.

Reaction of Benzaldimine 176 with (Me₃Si)₃SiH (Table 5).

Following general procedure C, solutions containing the imine 176, 9.7 equivalents of (Me₃Si)₃SiH and 11% AIBN (relative to the imine) in C₆D₆ were prepared. The initial concentrations of (Me₃Si)₃SiH were: 0.628 M (solution I), 0.126 M (solution II) and 0.063M (solution III). The solutions were deoxygenated by three freeze/pump/thaw cycles and the nmr tubes were sealed under vacuum. The tubes were heated in a constant-temperature bath set at 80 ± 0.2 °C for 19.5 h. The product ratios were determined from the ¹H NMR spectra (200 MHz, C₆D₆): solution I, 177:178:179 (6H:5H:RH) = 23:7:16, 46% conversion; solution II, 6H:5H:RH = 21:4:10, 35% conversion; solution III, 6H:5H:RH = 18:2.5:10.5, 31% conversion. The spectral data for 177, 178, and 179 were given previously.

Preparation of 2-Bromo-N-[(4-methylphenyl)methylene] benzeneethanamine (181).

Following the general procedure E, a solution of p-tolualdehyde (11.17 g, 93 mmol) and 2-bromophenethyamine 154 (18.2 g, 93 mmol) in PhCH₃ (32 mL) was heated to reflux for 5 h. Short-path distillation of the residue gave 18.4 g of 181 as an oil that solidified on standing (white crystals) (66%): mp 48-49 °C; bp 170-175 °C at 0.4 mm; IR (CHCl₃): 2950, 2845, 1645, 1610, 1470, 1435, 1035, 900 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 2.38 (s, 3H, CH₃), 3.14 (t, J=7.4 Hz, 2H, CH₂-Ar), 3.85 (t, J=7.4 Hz, 2H, CH₂-N), 7.01-7.63 (m, 8H, ArH), 8.14 (s, 1H, HC=N); ¹³C NMR (50.3 MHz, CDCl₃) δ 21.5 (CH₃), 37.7 (CH₂-Ar), 61.0 (CH₂-N), 124.6 (aryl. C Br), 127.2, 127.8, 128.0, 129.2, 131.3,

and 132.7 (aryl, 6 x CH), 133.5 (aryl, $\underline{\text{C}}\text{-C=N}$), 139.1 (aryl, $\underline{\text{C}}\text{-CH}_2$ or aryl, $\underline{\text{C}}\text{-CH}_3$), 140.8 (aryl, $\underline{\text{C}}\text{-CH}_2$ or aryl, $\underline{\text{C}}\text{-CH}_3$), 161.6 (C=N); MS (CI) m/z (%): 304 (MH⁺, 100), 302 (MH⁺, 98), 222 (11), 132 (14).

Kinetic Study of the Cyclization of p-Tolylaldimine 181 using ¹H NMR Spectroscopy (Table 3).

Following general procedure C, solutions containing the imine 181, 10 equivalents of Bu₃SnH and 5% AIBN (relative to the imine) in C₆D₆ were prepared. The initial concentrations of Bu₃SnH were: 1.50, 0.939, 0.564, 0.303, 0.076, 0.045, and 0.015 M. Reactions were heated at 80 ± 0.2 °C for 8 h. Product ratios were determined from the integrals in the ¹H NMR (500 MHz, C₆D₆; TMS ref.) spectra: tetrahydroisoquinoline 182 δ 4.85 ppm (s, 1H, Ar-CH-N); indoline 183 δ 3.97 ppm (s, 2H, N-CH₂-Ph); amine 185 δ 2.65 (m, 4H, Ph-CH₂-CH₂-N), 3.55 (s, 2H, N-CH₂-Ph); imine 184 δ 7.88 ppm (s, 1H, N=CH). Spectral data for 183 and 184 were identical to those of authentic materials prepared by other routes. The isoquinoline was isolated from the mixture in the kinetic experiments by chromatography (SiO₂, 2 mm, 3% MeOH/CHCl₃): spectral data for 1,2,3,4-Tetrahydro-1-(4-methylphenyl) isoquinoline (182): ¹H NMR (500 MHz, C₆D₆) δ 1.26 (br s, 1H, NH), 2.13 (s, 3H, CH₃), 2.50-2.57 (m, 1H, CH₂), 2.71-2.78 (m, 1H, CH₂), 2.88-2.98 (m, 2H, CH₂CH₂), 4.87 (s, 1H, Ar-CH-N), 6.82 (d, J=7.8 Hz, 1H, ArH-8), 6.92 (t, J=7.4 Hz, 1H, ArH-6), 6.97-7.25 (m, 6H, ArH); MS (CI) m/z (%): 224 (MH⁺, 100), 132 (9).

Preparation of N-(p-xylyl)indoline (183).

Following general procedure B, indoline (1.16 g, 9.73 mmol) was alkylated with 4-methylbenzyl bromide (1.8 g, 9.7 mmol) in aqueous NaHCO₃ (1.5 g, 18 mmol in 5 mL). Work up afforded 1.4 g (65%) of indoline 183 of high purity: IR (CHCl₃): 3000, 2960, 2930, 1610, 1470, 1460, 1190 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 2.34 (s, 3H, ArCH₃), 2.95 (t, J=8.3 Hz, 2H, NCH₂CH₂Ar), 3.28 (t, J=8.3 Hz, 2H, NCH₂CH₂Ar), 4.20 (s, 2H, Ar-CH₂-N), 6.51 (d, J=7.8 Hz, 1H, ArH-7), 6.65 (t, J=7.3 Hz, 1H, ArH-5), 7.00-7.34 (m, 6H, ArH); ¹³C NMR (50.3 MHz, CDCl₃) δ 21.5 (CH₃-Ar), 28.5 (CH₂-Ar), 53.4 (Ar-CH₂-N or CH₂-CH₂-N), 53.5 (Ar-CH₂-N or CH₂-CH₂-N), 107.0 (aryl, CH-7), 117.6 (aryl, CH-5), 124.4, 127.3, 127.9, and 129.1 (aryl, 4 x CH), 130.5 (aryl, C-9), 135.5 (aryl, C-CH₃), 137.0 (aryl, C-CH₂-N), 153.5 (aryl, C-8); MS (EI) m/z (%): 223 (M⁺, 84), 132 (8), 118 (13), 105 (100).

Preparation of N-[(4-Methylphenyl)methylene] benzeneethanamine (184).

Following general procedure E, a solution of p-tolualdehyde (2.98 g, 24.8 mmol) and phenethylamine (3.0 g, 25 mmol) in PhCH₃ (25 mL) was heated to reflux for 4 h. Short-path distillation (ca. 145 °C at 0.5 mm) of the residue gave 3.6 g of 184 as an oil that solidified on standing (white crystals) (65%): mp 42 °C; IR (CHCl₃): 2940, 2840, 1645, 1610, 1490, 1450, 1025 cm⁻¹; ¹H NMR (200MHz, CDCl₃) δ 2.38 (s, 3H, CH₃), 3.00 (t, J=7.5 Hz, 2H, CH₂-Ar), 3.84 (t, J=7.5 Hz, 2H, CH₂-N), 7.18-7.65 (m, 9H, ArH), 8.13 (s, 1H, HC=N); ¹³C NMR (50.3 MHz, CDCl₃) δ 21.5 (CH₃-Ar), 37.5 (CH₂-Ar), 63.2 (CH₂-

N), 126.0, 128.0, 128.3, 129.0, and 129.3 (aryl, 5 x CH), 133.5 (aryl, $\underline{\text{C}}\text{-C=N}$), 139.9 (aryl, $\underline{\text{C}}\text{-CH}_2$ or $\underline{\text{C}}\text{-CH}_3$), 140.8 (aryl, $\underline{\text{C}}\text{-CH}_2$ or $\underline{\text{C}}\text{-CH}_3$), 161.4 (C=N); MS (EI) m/z (%): 223 (M^+ , 8), 132 (100), 105 (52).

Preparation of 2-Bromo-N-(1-benzylidene-d) benzeneethanamine (186).

Following the general procedure E, a solution of benzaldehyde-1-d (162) (2.0 g, 18.7 mmol) and 2-bromophenethylamine (154) (3.74 g, 18.7 mmol) in PhCH_3 (25 mL) was heated to reflux in a Dean-Stark apparatus for 2 h. Kugelrohr distillation (115 °C at ca. 1 mm) of the residue gave 4.8 g of 186 as an oil that solidified on standing (white crystals) (89%): mp 38.5-39.0 °C; IR (KBr): 3065, 2940, 2840, 2130, 1635, 1580, 1490, 1440, 1025 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3) δ 3.12 (t, $J=7.4$ Hz, 2H, $\text{CH}_2\text{-Ar}$), 3.83 (t, $J=7.4$ Hz, 2H, $\text{CH}_2\text{-N}$), 6.95-7.76(m, 9H, ArH); ^{13}C NMR (50.3 MHz, CDCl_3) δ 37.6 ($\text{CH}_2\text{-Ar}$), 60.9 ($\text{CH}_2\text{-N}$), 124.6 (aryl, C-Br), 127.3, 127.9, 128.0, 128.5, 130.6, 131.3, and 132.7 (aryl, 7 x CH), 136.0 (aryl, $\underline{\text{C}}\text{-C=N}$), 139.1 (aryl, $\underline{\text{C}}\text{-CH}_2$), 161.0 (t, C=N); MS (CI) m/z (%): 291 (MH^+ , 98), 289 (MH^+ , 100), 209 (20), 119 (41), 91 (15), 77 (3), 65 (2).

Thermolysis of Benzaldimine-d 186 at two different concentrations of Bu_3SnH and the formation of the Amine 190.

A solution of benzaldimine-d 186 (20 mg, 0.10 mmol; 0.051 M), Bu_3SnH (36 mg, 0.12 mmol; 0.061 M) and AIBN (1.5 mg, 0.009 mmol) in PhH (2mL) was transferred to a 10-mm nmr tube fitted with a ground glass joint and it was subjected to three cycles

of freeze/pump/thaw degassing before the tube was sealed (solution I). In a similar manner a second 10-mm nmr tube containing a solution of benzaldimine-d 186 (0.051 M), Bu_3SnH (0.52 M) and AIBN (9%) in PhH (2 mL) was prepared (solution II). The sealed tubes were heated in a constant-temperature bath set at 80 ± 0.2 °C for 18 h. Product ratios were determined from the integrals in the ^2H NMR spectra: solution I, 187:188:189 (no amine 190 could be detected, <2%) = 74:12:14; solution II, 187:188:189:190 = 37:10:46:7. ^2H NMR (76.8 MHz, PhH at 7.26 ppm) chemical shift data: amine 190 δ 3.62 (N-CHD-Ph), indoline 188 δ 4.01 (N-CHD-Ph), isoquinoline 187 δ 4.89 (N-CD-Ph), and Schiff base 189 δ 7.94 (N=CD).

Preparation of N-benzylphenethylamine 180.

Following the procedure of Billman and Diesing,¹³⁶ to a solution of benzaldimine 179 (1.5 g, 7.2 mmol) in MeOH (20 mL) was added NaBH_4 (0.28 g, 7.2 mmol) over 5 min. The reaction mixture was then heated to reflux for 15 min. The bulk of the solvent was removed under reduced pressure and the residue was combined with 2M NaOH (30 mL). The aqueous mixture was extracted with CH_2Cl_2 (2 x 30 mL) and the combined organic extracts were washed with brine and dried over Na_2SO_4 . The solvent was removed under reduced pressure giving pure 180 as a clear oil (1.41 g, 93%). ^1H NMR (200 MHz, C_6D_6) δ 2.65 (m, 4H, Ph- CH_2 - CH_2 -N), 3.55 (s, 2H, N- CH_2 -Ph), 7.0-7.4 (m, 10H, ArH); MS (CI, NH_3) m/z (%): 212 (MH^+ , 100), 120 (19), 91 (12); GC (DB-17, 30 m, 190 °C for 2 min, 10 °C/min to 240 °C): t_R , 6.7 min.

Thermolysis of Benzaldimine-d 189 with Bu₃SnH: Formation of the Amine 190.

The Schiff base 189 (30.3 mg, 0.144 mmol, 0.13 M), Bu₃SnH (420 mg, 1.44 mmol, 1.3 M) and AIBN (5%) were taken up in PhH (1.1 mL). The solution was deoxygenated by three freeze/pump/thaw cycles and the glass tube was sealed under vacuum. The sample was heated at 80 °C for 15 h. The reaction mixture was analyzed by ²H NMR, ¹H NMR spectroscopy, and GC: ²H NMR (76.7 MHz, PhH, referenced to the solvent signal at 7.26 ppm) analysis of the reaction mixtures showed a 1.9 to 1 ratio of starting material 189 (δ 7.93 ppm, N=CD) to the amine 190 (δ 3.60 ppm, N-CHD-Ph) (by integration); partial ¹H NMR (200 MHz, C₆D₆) spectral data for the amine 190: δ 2.62 (Ph-CH₂-CH₂-N), 3.55 (N-CHD-Ph); GC (DB-17, 30 m, 190 °C for 2 min, 10 °C/min to 240 °C) t_R = 6.7 min for amine 190 and 7.8 min for the starting material 189.

Preparation of Diethylaminotributylstannane 193.

Following the procedure of Jones and Lappert,¹⁴¹ to a solution of n-BuLi (2.45 M solution in hexane; 11.45 mL, 28 mmol) cooled to -78 °C was added diethylamine (2.10 g, 30.8 mmol) in dry ether (15 mL) under N₂. The reaction mixture was allowed to warm up to room temperature (ca. 20 min) and a solution of tributylchlorostannane (9.11 g, 28 mmol) in ether (20 mL) was added. The resulting mixture was heated to reflux for 3 h and was cooled to room temperature. The solution was filtered through Celite and the filtrate was concentrated under vacuum. The residue was purified by Kugelrohr distillation

(ca. 80 °C at 0.27 mm, lit.¹⁸⁷ bp 124-134°C at 8 mm) to give 8.2 g (82%) of **193** as a colourless oil. The sample was stored under N₂; IR (film) 2960, 2930, 1460, 1375, 765 cm⁻¹; ¹H NMR (200 MHz, C₆D₆) δ 0.83-1.68 (m, 27H, 3 x CH₂-CH₂-CH₂-CH₃) 1.10 (t, J=7.0 Hz, 6H, N-CH₂-CH₃), 3.04 (q, 4H, J=7.0 Hz, N-CH₂).

Reaction of Diethylaminotributylstannane **193** with Bu₃SnH.

A solution of Bu₃SnNEt₂ (**193**) (30.5 mg, 0.084 mmol) and Bu₃SnH (30.8 mg, 0.106 mmol) in C₆D₆ (0.4 mL) was transferred to a 5-mm nmr tube, and the tube was capped. A ¹H NMR (90 MHz, C₆D₆/TMS) spectrum taken 30 min after mixing the tin hydride with aminostannane showed 60% conversion to diethylamine.

Preparation of Benzyl-α-d₁ alcohol **195**.

The procedure of Gannon and House¹⁴³ was modified. To a suspension of LAH (0.39 g, 10 mmol) in dry ether with mechanical stirring was added dropwise a solution of benzaldehyde-1-d (**162**) (2.0 g, 19 mmol) in dry ether (4 mL) over 15 min. The reaction mixture was heated to reflux for 1.5 h. After the mixture cooled to ambient temperature, water (2 mL) and 10% H₂SO₄ (35 mL) were added. The solution was extracted with ether (3 x 20 mL), and the combined extracts were washed with water (10 mL), brine (10 mL) and were dried (Mg₂SO₄). The solvent was removed under reduced pressure to give 1.8 g (88%) of **195** as a colourless oil of high purity: ¹H NMR (90 MHz,

(187) Sisido, K.; Kozima, S. *J. Org. Chem.* **1962**, *27*, 4051.

CDCl_3) δ 2.33 (br s, 1H, OH), 4.57 (br s, 1H, CHD), 7.32 (s, 5H, ArH) [lit.¹⁸⁸ ^1H NMR (CDCl_3) δ 3.65 (br s, 1H, OH), 4.55 (br s, 1H, CHD), 7.35 (s, 5H, ArH).

Preparation of Benzyl- α -d, Chloride 196.

Following the procedure of Kwart and Brechbiel,¹⁴² pyridine (2.35 mL, 30 mmol) was added dropwise to a solution of the crude alcohol 195 (1.8 g, maximum 17 mmol) in dry PhH (10 mL). The reaction flask was cooled to 0 °C and thionyl chloride (2.2 mL, 30 mmol) was then added over 5 min with stirring. The mixture was heated to reflux for 12 h. After cooling, the mixture was diluted with water (20 mL) and extracted with ether (3 x 20 mL). The combined ether extracts were washed with 10% NaOH (30 mL), 6N HCl (30 mL), and finally distilled water to neutrality (6 x 30 mL). The ethereal solution was dried under MgSO_4 , and the solvent was removed under vacuum to give 0.35 g (20%) of 196 as a pale-yellow oil of high purity: ^1H NMR (90 MHz, CDCl_3) δ 4.54 (br s, 1H, CHD), 7.40 (s, 5H, ArH) [lit.¹⁸⁸ ^1H NMR (CDCl_3) δ 4.55 (br s, 1H, CHD), 7.45 (s, 5H, ArH).

Preparation of N-benzylindoline-d (188)

Following general procedure B, indoline (0.34 g, 2.9 mmol) was alkylated with benzyl- α -d, chloride (196) (0.37 g, 2.9 mmol) in aqueous NaHCO_3 (0.36 g, 4.3 mmol in 5 mL). The residue was purified by Chromatotron chromatography (SiO_2 , 2 mm).

(188) Kwart, H.; Gaffney, A. *J. Org. Chem.* 1983, 48, 4502.

Elution with 1.5% ethyl acetate/hexane afforded 0.31 g (52%) of **188** as an oil: IR (CHCl₃): 3000, 2960, 2920, 2840, 1605, 1480, 1260-1180, 900 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 2.96 (t, J=8.0 Hz, 2H, NCH₂CH₂Ar), 3.30 (t, J=8.0 Hz, 2H, NCH₂CH₂Ar), 4.23 (t, J=2 Hz, 1H, Ph-CHD-N), 6.50 (d, J=7.8 Hz, 1H, ArH-7), 6.67 (t, J=7.0 Hz, 1H, ArH-5), 7.07 (m, 2H, ArH-4 and H-6), 7.33 (m, 5H, ArH); ¹³C NMR (50.3 MHz, CDCl₃), 28.5 (CH₂-Ar), 53.3 (t, Ph-CHD-N), 53.5 (CH₂-CH₂-N), 107.0 (aryl, CH-7), 117.6 (aryl, CH-5), 124.5, 127.1, 127.3, 127.9, and 128.4 (aryl, 5 x CH), 129.9 (aryl, C-9), 138.4 (aryl, C-CH₂-N), 152.5 (aryl, C-8); MS (EI) m/z (%): 210 (M⁺, 50), 133 (28), 118 (31), 92 (100), 77 (7), 65 (20).

Kinetics of the Cyclization of Benzaldimine-d **186** using ²Li NMR Spectroscopy (Table 4).

Following general procedure C, solutions containing benzaldimine-d **186**, Bu₃SnH (9.8 equiv) and AIBN (6% of imine) in PhH were prepared. The initial concentration of Bu₃SnH, and the heating time at 80 ± 0.2 °C were: 0.702 M, 26 min; 0.351 M, 66 min; 0.176 M, 66 min; 0.088 M, 4.5 h; 0.044 M, 4.5 h; 0.022 M, 4.5 h. ²H NMR spectra were run in PhH. The inversion-recovery sequence gave the T₁ values (s): **187** (0.21), **188** (0.30) and **189** (0.27). The pulse delay was therefore set at 1.5 s, or 5 x T₁. A 90° pulse width of 14.2 μs was used. The spectral width was 996 Hz, and the digital resolution was 0.49 Hz/pt. A line broadening factor of 3 Hz was applied. The data were collected in blocks, ranging from 10 to 45, with 128 scans in each block. The

number of blocks collected depended on the concentration of deuterium in the sample. Product ratios and standard deviations were determined from the peak heights in the ^2H NMR spectra (76.8 MHz, PhH, referenced to the solvent signal at 7.24 ppm): indoline **188** δ 3.98; isoquinoline **187** δ 4.85; imine **189** δ 7.90 ppm. A gravimetric calibration of the peak heights was done. Three solutions containing known quantities of isoquinoline **187**, indoline **188** and aldimine **189** were prepared. The product ratios, **187/188** (6H/5H), **187/189** (5H/RH) and **188/189** (6H/RH), as determined from measuring the peak heights in the ^1H NMR spectra, were multiplied by 0.95, 1.17, and 1.11, respectively. MS (DCI/ NH_3) m/z (%) for product mixtures with initial Bu_3SnH concentrations of 0.044 and 0.022 M: 419 (MH^+ , 5%); corresponding to **202**.

Reaction of Benzaldimine-d **186** with dilute Bu_3SnH : A Change in the ratio **187/188**.

A solution of benzaldimine-d **186** (0.75 g, 2.59 mmol) in PhH (50 mL) was thoroughly degassed with nitrogen and heated under reflux. A degassed solution of Bu_3SnH (1.14 g, 3.74 mmol) and AIBN (0.15g, 0.91 mmol) in PhH (20 mL) was introduced by means of a syringe-pump addition over 18 h to the heated substrate solution. After 18 h, GC analysis indicated ca. 50% conversion of starting imine. AIBN (0.02 g, 0.12 mmol) was added to the solution which was heated at reflux for an additional 6 h. GC analysis indicated ca. 75% conversion. AIBN (0.05 g) was added and the mixture was heated for an additional 2 h. After this time, no starting imine was detected (GC). The product ratios determined by GC (DB-17, 15 m, 170 °C for 5 min,

10 °C/min to 240 °C) were: **187:188:189** (6H:5H:RH) = 18:1.0:1.7. The product ratios from peak heights in the ²H NMR spectra (76.8 MHz, PhH) (following general procedure C) were: **187:188:189** (6H:5H:RH) = 18:1.1:1.0 (corrected). Tetrahydroisoquinoline **187** was isolated by following general procedure F (white crystals): mp 97-98 °C; IR (KBr): 3260, 3060, 2900, 2780, 1600, 1485, 1440, 730-710 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 1.70 (br s, 1H, NH), 2.70-2.93 (m, 1H, CH₂), 2.94-3.17 (m, 2H, CH₂CH₂), 3.18-3.33 (m, 1H, CH₂), 6.75 (d, J=7.8 Hz, 2H, ArH), 6.98-7.38 (m, 8H, ArH); ¹³C NMR (50.3 MHz, CDCl₃) δ 29.7 (CH₂-Ar), 42.1 (CH₂-N), 62.1 (t, Ar-CD-N), 125.6, 126.2, 127.3, 128.1, 128.4, 128.90, and 128.98 (aryl, 7 x CH), 135.4, 138.2 and 144.8 (aryl, 3 x C); MS (DCI) m/z (%): 211 (MH⁺, 100), 133 (8); HRMS calcd for C₁₂H₁₄ND 210.1267 found 210.1271. Spectral data for **188** and **189** are given elsewhere.

Preparation of N-(1-Benzylidene-d) benzeneethanamine (**189**).

Following general procedure E, a solution of benzaldehyde-1-d (**162**) (0.15 g, 1.4 mmol) and phenethylamine (0.17 g, 1.4 mmol) in PhCH₃ (15 mL) was heated to reflux for 2 h. Kugelrohr distillation (ca. 150 °C at 0.3 mm) gave 0.20 g of **189** as a colourless oil that solidified on cooling (white solid) (68%): mp 39 °C; IR (KBr): 3040, 2930, 2840, 2135, 1635, 1580, 1490, 1450, 1025 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 3.01 (t, J=7.4 Hz, 2H, CH₂-Ar), 3.84 (t, J=7.4 Hz, 2H, CH₂-N), 7.15-7.42 (m, 8H, ArH), 7.65-7.73 (m, 2H, ArH); ¹³C NMR (50.3 MHz, CDCl₃) δ 37.5 (CH₂-Ar), 63.1 (CH₂-N), 126.1, 128.0, 128.3, 128.5, 129.0, and 130.6 (aryl, 6 x CH), 136.1 (aryl, C-C=N), 140.0

(aryl, $\underline{\text{C}}\text{-CH}_2$), 160.8 (t, C=N); MS (EI) m/z (%): 210 (M^+ , 3), 133 (6), 119 (100), 91 (83), 77 (13), 65 (11).

Preparation of 2-Bromo-N-(1-ethylpropylidene) benzeneethanamine (208).

Following the general procedure E, a solution of 3-pentanone (0.86 g, 10 mmol) and amine 154 (1g, 5.0 mmol) in PhH (35 mL) was heated to reflux for 18 h. Kugelrohr distillation (90 °C at 0.4 mm) of the residue gave 1.28 g of 208 as a colourless oil (95%): IR (film): 2965, 2930, 1670, 1475, 1025, 745 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 0.96 (t, J=7.6 Hz, 3H, CH_3), 1.08 (t, J=7.6 Hz, 3H, CH_3), 2.13 (q, J=7.6 Hz, 2H, $\underline{\text{CH}}_2\text{CH}_3$), 2.25 (q, J=7.6 Hz, 2H, $\underline{\text{CH}}_2\text{CH}_3$), 3.05 (t, J=7.7 Hz, 2H, $\text{CH}_2\text{-Ar}$), 3.57 (t, J=7.7 Hz, 2H, $\text{CH}_2\text{-N}$), 7.02-7.57 (m, 4H, ArH); ^{13}C NMR (125.8 MHz, CDCl_3) δ 10.6 (CH_3), 10.8 (CH_3), 23.6 (syn $\underline{\text{C}}\text{H}_2\text{-CH}_3$), 32.3 (anti $\underline{\text{C}}\text{H}_2\text{-CH}_3$), 37.6 ($\text{CH}_2\text{-Ar}$), 50.1 ($\text{CH}_2\text{-N}$), 124.4 (aryl, C-Br), 127.0, 127.5, 131.1, and 132.4 (aryl, 4 x CH), 139.6 (aryl, $\underline{\text{C}}\text{-CH}_2$), 175.6 (C=N); MS (EI) m/z (%): 270 (MH^+ , 2), 268 (M^+ , 3), 240 (2), 238 (2), 188 (46), 98 (100), 70 (36).

Kinetics of Cyclization of Ketimine 208 with Bu_3SnH (Table 6).

Following general procedure C, solutions containing ketimine 208, Bu_3SnH (1.9 equiv) and AIBN (5% of imine) in PhH were prepared. The initial concentrations of Bu_3SnH were: 0.078, 0.056, 0.045, 0.022, and 0.011 M. The solutions were deoxygenated by three freeze/pump/thaw cycles and the nmr tubes were sealed. The tubes were heated

in a constant-temperature bath set at 80 ± 0.2 °C for 48 h. The reaction mixtures were analyzed by ^1H NMR spectroscopy, and the product ratios are summarized in Table 6. Partial ^1H NMR (500 MHz, C_6D_6) spectral data for isoquinoline **209**: δ 2.54 (t, $J=5.8$ Hz, 2H, $\text{CH}_2\text{-N}$), 2.84 (t, $J=5.8$ Hz, $\text{CH}_2\text{-Ar}$). The ^1H NMR (200 MHz, C_6D_6) chemical shifts for the model compound 1,2,3,4-tetrahydroisoquinoline are: δ 2.49 (t, $J=5.8$ Hz, 2H, $\text{CH}_2\text{-N}$), 2.75 (t, $J=5.8$ Hz, 2H, $\text{CH}_2\text{-Ar}$). The indoline was isolated by purification using Chromatotron chromatography (SiO_2 , 2 mm; 100% petroleum ether ($R_f = 0.61$ with 100% petroleum ether)). Spectroscopic data for indoline **210**: IR (CHCl_3) 2970, 2940, 2880, 1610, 1490, 1460, 1360-1280 cm^{-1} ; ^1H NMR (500 MHz, C_6D_6) δ 0.82 (t, $J=7.4$ Hz, 6H, CH_3), 1.30 (m, 4H, CH_2CH_3), 2.67 (t, $J=8.6$ Hz, 2H, $\text{NCH}_2\text{CH}_2\text{Ar}$), 2.99 (t, $J=8.6$ Hz, 2H, $\text{NCH}_2\text{CH}_2\text{Ar}$), 3.09 (m, 1H, N-CH), 6.35 (d, $J=7.8$ Hz, ArH-7), 6.66 (t, $J=7.2$ Hz, ArH-5), 7.02 (d, $J=7.5$ Hz, ArH-4), 7.10 (t, $J=7.3$ Hz, ArH-6); ^{13}C NMR (50.3 MHz, CDCl_3) δ 11.7 (2 x CH_3), 24.4 ($\text{CH}_2\text{-CH}_3$), 28.6 ($\text{CH}_2\text{-Ar}$), 45.2 ($\text{CH}_2\text{-N}$), 58.0 (CH-N), 105.6 (aryl, CH-7), 115.6 (aryl, CH-5), 124.3 (aryl, CH-6), 127.2 (aryl, CH-4), 129.5 (aryl, C-9), 153.5 (aryl, C-8); MS (EI) m/z (%): 189 (M^+ , 18), 160 (100), 145 (11), 130 (6), 118 (10), 91 (8). Partial ^1H NMR (500 MHz, C_6D_6) spectrum for the dehalogenated Schiff base **211**: δ 3.00 (t, $J=7.5$ Hz, 2H, $\text{CH}_2\text{-Ar}$), 3.48 (t, $J=7.5$ Hz, 2H, $\text{CH}_2\text{-N}$).

Preparation of 1,2:5,6-Diisopropylidene-D-mannitol **213**.

Following the procedure of Schmid and co-workers,¹⁴⁵ to a flask equipped with overhead mechanical stirrer and reflux condenser was added D-mannitol (75 g, 0.41

mol), glyme (180 mL, freshly distilled), and 2,2-dimethoxypropane (120 mL, 0.98 mol). To this stirred mixture was added SnCl_2 (0.081 g, 0.4 mmol) and the mixture was heated to reflux for 100 min. The reaction mixture was cooled to ambient temperature, and pyridine (0.09 mL, 1.14 mmol) was added. The solvents were removed in vacuo (contents heated to approximately 80 °C), and the last traces of solvents were removed under a high vacuum (0.05 mm). The crude material was stirred in dry CH_2Cl_2 (530 mL) at ambient temperature for 1 h and then filtered. The filtrate was concentrated in vacuo and the contents were recrystallized twice (n-butyl ether, 3 mL/g) to give 52 g of **213** (48 %) as a white powder: TLC $R_f = 0.75$ ($\text{CH}_3\text{OH} : \text{CHCl}_3$, 1:4); mp 117-118 °C (lit.¹⁴⁵ 121.8-123.4 °C); $[\alpha]_D^{23} = +1.6^\circ$ (c = 2.13, CH_3OH) (lit.¹⁴⁵ $[\alpha]_D = +1.9^\circ$ (c = 1.74, CH_3OH)); IR (KBr): 3420-3360, 2980, 2925, 2890, 1380, 1370, 1260, 1205, 1060, 1000, 850 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.36 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 2.74 (br s, 2H, OH), 3.74 (d, J=6.6 Hz, 2H, $\text{CH}_2\text{-O}$), 3.98 (dd, J=8.5, 5.5 Hz, 2H, $\text{CH}_2\text{-O}$), 4.11 (dd, J=8.5, 6.4 Hz, 2H, HC-OH), 4.18 (q, J=6.4 Hz, 2H, HC-O-C); ^{13}C NMR (50.3 MHz, CDCl_3) δ 25.2 and 26.7 (2 x CH_3), 66.7 ($\text{CH}_2\text{-O}$), 71.1 (CH-O), 76.1 (CH-O), 109.3 (O-C-O); MS (DCI) m/z (%): 280 ((M + NH_4) $^+$, 100), 263 (MH^+ , 93), 247 (41), 189 (16), 101 (17). Spectroscopic data are in agreement with those reported by Schmid.¹⁴⁵

Preparation of (R)-2,3-O-(Isopropylidene)-D-glyceraldehyde ((R)-214).

Following the procedure of Schmid and co-workers,¹⁴⁵ to a flask equipped with mechanical stirrer and thermometer was added diacetonide **213** (8.03 g, 0.031 mmol)

in CH_2Cl_2 (80 mL). Saturated aqueous NaHCO_3 (2.9 mL) was then added to the flask, maintaining the temperature at or below 25 °C. NaIO_4 (12.8 g) was then added portionwise over a 20 min period with vigorous stirring and the reaction was allowed to proceed for 2 h while the temperature was maintained below 25 °C. The solids were removed by filtration and the filtrate was distilled at atmospheric pressure to a temperature of 45 °C. Kugelrohr distillation of the residue gave 6.38 g (50-60 °C/10 mm Hg) of (R)-214 as a colourless oil (80 %): $[\alpha]_D = 66.9^\circ$ (c = 1.32, PhH) [lit.¹⁴⁵ $[\alpha]_D = +80.1^\circ$ (c = 1.534, C_6H_6), lit.¹⁸⁹ $[\alpha]_D = +63.3^\circ$ (c = 1.25, C_6H_6)]; IR (film): 3440, 2985, 1740, 1380, 1375, 1255, 1210, 1070, 840 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3) δ 1.42 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 4.06-4.23 (m, 2H, $\text{CH}_2\text{-O}$), 4.35-4.42 (m, 1H, CH-O), 9.71 (d, J=1.8 Hz, HC=O); ^{13}C NMR (50.3 MHz, CDCl_3) δ 25.0 and 26.1 (2 x CH_3), 65.4 ($\text{CH}_2\text{-O}$), 79.7 (CH-O), 111.1 (O-C-O), 201.6 (C=O); MS (DCI) m/z (%): 148 ((M + NH_4)⁺, 12), 131 (MH^+ , 100), 115 (16), 101 (45). Spectroscopic data are in agreement with those reported by Schmid.¹⁴⁵

Preparation of 2,3-O-(Isopropylidene)-DL-glyceraldehyde 214.

Racemic glyceraldehyde 214 was prepared from D-sorbitol according to the procedure used to prepare (R)-214 from D-mannose (212). To a solution of D-sorbitol (10 g, 55 mmol) and 2,2-dimethoxypropane (16 mL) in glyme (24 mL) were added SnCl_2 (10 mg) and later pyridine (10 mg, 0.13 mmol). An oil was isolated and it was used directly

(189) Jackson, D. *Synth. Commun.* 1988, 18, 337.

in the oxidation reaction without further purification. To a solution of the crude oil in CH_2Cl_2 (38 mL) and a saturated aqueous solution of NaHCO_3 (1.4 mL) was added NaIO_4 (6.5 g, 30 mmol). Distillation of the residue gave 0.45 g of **214** as an oil (11%): IR (film): 3440, 2990, 2940, 1735, 1455, 1380, 1370, 1255, 1210, 1070, 840 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3) δ 1.43 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 4.05-4.22 (m, 2H, $\text{CH}_2\text{-O}$), 4.35-4.42 (m, 1H, CH-O), 9.72 (d, $J=1.8$ Hz, HC=O); ^{13}C NMR (50.3 MHz, CDCl_3) δ 25.0 and 26.1 (2 x CH_3), 65.4 ($\text{CH}_2\text{-O}$), 79.7 (CH-O), 111.2 (O-C-O), 201.8 (C=O); MS (DCI) m/z (%): 148 ($(\text{M} + \text{NH}_4)^+$, 26), 131 (MH^+ , 100), 115 (15), 101 (36); HRMS calcd for $\text{C}_6\text{H}_{11}\text{O}_3$ (MH^+) 131.0708 found 131.0705.

Preparation of (S)-2-Bromo-N-[(2,2-dimethyl-1,3-dioxolan-4-yl)methylene]benzeneethanamine ((S)-**215**).

To a solution of glyceraldehyde (R)-**214** (0.74 g, 5.7 mmol) and 4Å molecular sieves (4 g) in dry CH_2Cl_2 (30 mL) was added 2-bromophenethylamine **154** (1.14 g, 5.7 mmol). The reaction flask was fitted with a CaCl_2 drying tube and the mixture was stirred gently for 135 min. The reaction mixture was filtered through a mixture of Celite: Na_2SO_4 1:1 and the solvent was removed in vacuo to give (S)-**215** (1.7 g, 95%) as pale yellow oil of high purity. The sample was used immediately in the next reaction. Distillation of the sample was accompanied by considerable decomposition: IR (CHCl_3): 2990, 2440, 2875, 1660, 1470, 1440, 1380, 1370, 1240, 1150, 1055 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3) δ 1.38 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 3.05 (t, $J=7.3$ Hz, 2H, $\text{CH}_2\text{-Ar}$), 3.58-3.85 (m, 3H,

2H from CH₂-N and 1H from CH₂-O), 4.15 (dd, 8.4, 6.8 Hz, 1H, CH₂-O), 4.53 (q, J=6.5 Hz, CH-O), 7.01-7.3 (m, 3H, ArH), 7.45-7.56 (m, 2H, ArH and HC=N); ¹³C NMR (50.3 MHz, CDCl₃) δ 25.4 and 26.4 (2 x CH₃), 37.1 (CH₂-Ar), 60.2 (CH₂-N), 67.2 (CH₂-O), 76.8 (CH-O), 110.1 (O-C-O), 124.5 (aryl, C-Br), 127.2 (aryl, CH-4 or CH-5), 128.0 (aryl, CH-4 or CH-5), 131.3 (aryl, CH-3 or CH-6), 132.8 (aryl, CH-3 or CH-6), 138.6 (aryl, C-1), 163.9 (C=N); MS (DCI) m/z (%): 314 (MH⁺, 97), 312 (MH⁺, 100), 232, (20), 174 (14), 132(8); HRMS calcd for C₁₄H₁₉NO₂Br (MH⁺) 312.0599, found 312.0600.

Cyclization of (S)-2-Bromo-N-[(2,2-dimethyl-1,3-dioxolan-4-yl)methylene]benzeneethanamine ((S)-215).

A solution of imine (S)-215 (0.51 g, 1.6 mmol) in PhH (31 mL) was thoroughly degassed with nitrogen and was heated to reflux under nitrogen. A degassed solution of Bu₃SnH (0.595 g, 2.0 mmol) and AIBN (60 mg, 0.36 mmol) in PhH (9 mL) was introduced to the heated substrate solution over 9 h. The solution was heated at reflux for an additional 2 h. ¹H NMR (200 MHz, CDCl₃) and GC analysis (DB-17, 15 m, 150 °C for 3 min, 10 °C/min to 240 °C) of the reaction mixture showed four new products: (S,S)-216:(R,S)-216:(S)-217:(S)-218 = 37:9.8: ca 1.0:5.7. The solvent was removed under reduced pressure and one-half of the residue was purified by flash chromatography. The organotin and a trace of the indoline (S)-217 were first eluted with 100% CHCl₃ and then 1% MeOH/CHCl₃ was used to elute the major isoquinoline (S,S)-216 (103 mg) followed by minor isoquinoline (R,S)-216 (26 mg). The combined yield of diastereomeric

isoquinolines was 69%. Data for major diastereomer (S,S)-**216**; $[\alpha]_D^{22} = +51^\circ$ (c 3.45, CH₃OH); IR (CHCl₃) 3350, 2980, 2920, 2810, 1600, 1450, 1380, 1370, 1260-1180, 1150, 1035, 900, 850 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 1.39 and 1.51 (s, 3H, 2 x CH₃), 2.06 (br s, 1H, NH), 2.55-2.74 (m, 1H, ArCH₂CH₂N), 2.80-3.1 (m, 2H, ArCH₂CH₂), 3.2-3.3 (m, 1H, ArCH₂CH₂N), 3.7-3.9 (m, 2H, CH₂-O), 4.32 (d, J=4.5 Hz, Ar-CH-N), 4.69 (q, J=4.6 Hz, CH-O), 7.05-7.30 (m, 4H, ArH); ¹³C NMR (50.3 MHz, CDCl₃) δ 24.9 and 26.3 (2 x CH₃), 41.9 (CH₂-N), 56.2 (Ar-CH-N), 65.5 (CH₂-O), 78.7 (CH-O), 109.2 (O-C-O), 125.67, 125.72, 126.3, 129.4 (aryl, 4 x CH), 135.1 (aryl, C-9 or C-10), 136.1 (aryl, C-9 or C-10); MS (DCI) m/z (%): 234 (MH⁺, 100), 176 (6), 132 (30).

Minor isoquinoline (R,S)-**216**: IR (CHCl₃) 3350, 2990, 2940, 1605, 1455, 1380, 1370, 1260-1180, 1155, 1060, 905, 850 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 1.37 and 1.46 (s, 3H, CH₃), 2.09 (br s, 1H, NH), 2.82 (t, J=5.9 Hz, 2H, CH₂-Ar), 2.93-3.07 (m, 1H, CH₂-N), 3.23-3.38 (m, 1H, CH₂-N), 3.93-4.12 (m, 3H, CH₂-O and Ar-CH-N), 4.45 (q, J=6.2 Hz, CH-O), 7.03-7.22 (m, 4H, ArH); ¹³C NMR (50.3 MHz, CDCl₃) δ 25.4 and 26.6 (2 x CH₃), 29.8 (CH₂-Ar), 40.4 (CH₂-N), 57.4 (Ar-CH-N), 67.3 (CH₂-O), 77.7 (CH-O), 109.0 (O-C-O), 125.8, 126.3, 126.7, 129.5 (aryl, 4 x CH), 135.0 (aryl, C-9 or C-10), 136.1 (aryl, C-9 or C-10); MS (DCI) m/z (%): 234 (MH⁺, 100), 132 (27).

Indoline (S)-**217**: ¹H NMR (200 MHz, CDCl₃) δ 1.38 (s, 3H, CH₃), 1.46 (s, 3H, CH₃), 2.9 (t, J=8.4 Hz, 2H, CH₂-Ar), 3.20 (d, J=6.3 Hz, 2H, H-1'), 3.44 (t, J=8.4 Hz, 2H, CH₂-N), 3.76 (dd, J=6.3, 8.2 Hz, 1H, H-3'), 4.12 (dd, J=6.3, 8.2 Hz, 1H, H-3'), 4.37 (q, J=6.3 Hz, 1H, H-2'), 6.48 (d, J=7.7 Hz, 1H, ArH-7), 6.66 (t, J=7.7 Hz, ArH-5), 7.06 (overlapping

d, $J=7.2$ Hz, 2H, ArH-4 and ArH-6).

Cyclization of (S)-2-Bromo-N-[(2,2-dimethyl-1,3-dioxolan-4-yl)methylene]benzeneethanamine (S)-215 with Bu_3SnH at 56 °C.

A solution of aldimine (S)-215 (50 mg, 0.16 mmol), Bu_3SnH (70 mg, 0.23 mmol) and AIBN (47 mg, 286 μmol) in C_6D_6 (0.4 mL) was transferred to a 5-mm nmr tube fitted with a ground glass joint. The solution was deoxygenated by three freeze/pump/thaw cycles and the tube was sealed under vacuum. The mixture was heated in a constant-temperature bath set at 80 ± 0.2 °C for 1.5 h. GC analysis (DB-17, 15 m, 10 °C for 3 min, 10 °C/min to 240 °C) of the reaction mixture showed the product ratio (S,S)-216:(R,S)-216:(S)-218 = 4.65:1.00:8.32 (d.e. of 65%). Spectral data for the diastereomers were given previously.

Preparation of 2-Bromo-4,5-dimethoxyphenethylamine 222.

Following the procedure of Harley-Mason,¹⁴⁸ to a 3-neck flask fitted with a dropping funnel, reflux condenser and mechanical stirrer was added 3,4-dimethoxyphenethylamine 221 (9.06 g, 0.05 mol) in glacial acetic acid (33 mL). The mixture was cooled with ice/water. To this mixture was added a solution of Br_2 (2.6 mL, 0.05 mol) in glacial acetic acid (25 mL) over a 30 min-period with stirring. The mixture was allowed to warm up to ambient temperature and then was stirred for an additional 2 h. Filtration and recrystallization (40 mL of 95% ethanol) gave 11.40 g of white crystals

of the HBr salt of **222** (67%): mp 203-203.5 °C (lit.¹⁴⁸ mp 202-204 °C). The free base **222** was extracted from a solution of the HBr salt in 2M KOH with CH₂Cl₂. The combined organic extracts were dried over K₂CO₃ and concentrated in vacuo to give **222** as a colourless oil (64%): IR (CHCl₃): 3300-3140, 2930, 2840, 1600, 1550, 1490, 1460, 1435, 1375, 1250-1180, 1155, 900, 840 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 1.38 (br s, 2H, NH₂), 2.8-2.9 (m, 2H, CH₂-Ar), 2.9-3.05 (m, 2H, CH₂-N), 3.85 (s, 3H, OCH₃), 3.86 (s, 3H, OCH₃), 6.74 (s, 1H, ArH), 7.01 (s, 1H, ArH); ¹³C NMR (50.3 MHz, CDCl₃) δ 39.8 (CH₂), 42.3 (CH₂), 56.1 (2 x OCH₃), 113.4 (aryl, CH-3 or CH-6), 114.3 (aryl, C-Br), 115.6 (aryl, CH-3 or CH-6), 131.0 (aryl, C-1), 148.0 (aryl, C-4 or C-5), 148.3 (aryl, C-4 or C-5); MS (DCI) m/z (%): 262 (MH⁺, 98), 260 (MH⁺, 100), 182 (20), 180 (14).

Preparation of (S)-2-Bromo-6,7-dimethoxy-N-[(2,2-dimethyl-1,3-dioxolan-4-yl)methylene]benzeneethanamine ((S)-223).

A solution of amine **222** (1.3 g, 5 mmol) containing 4Å molecular sieves (2.5 g) in dry ether (30 mL) was cooled to 5 °C and protected by a CaCl₂ drying tube. To the stirring mixture was added by means of a syringe-pump a solution of glyceraldehyde (R)-**214** (0.72 g, 5.5 mmol) in 10 mL ether over a period of 1 h. The mixture was stirred at 5 °C for an additional 1 h. The reaction mixture was filtered, and the filtrate was concentrated at reduced pressure to give 1.6 g (86%) of (S)-**223** as a pale-yellow oil of high purity. The sample was used immediately in the cyclization reaction with Bu₃SnH. Distillation even at reduced pressures was accompanied by decomposition: IR (CHCl₃):

2930, 2840, 1670, 1600, 1495, 1455, 1370, 1210, 1155, 1025, 900 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.38 (s, 3H, CCH_3), 1.40 (s, 3H, CCH_3), 2.92-3.03 (m, 2H, $\text{CH}_2\text{-Ar}$), 3.60-3.72 (m, 2H, $\text{CH}_2\text{-N}$), 3.85 (s, 6H, 2 x OCH_3), 3.8-3.9 (obscured signal, 1H, $\text{CH}_2\text{-O}$), 4.16 (dd, $J=8.3, 6.8$ Hz, 1H, $\text{CH}_2\text{-O}$), 4.54 (q, $J=6.2$ Hz, 1H, CH-O), 6.69 (s, 1H, ArH), 7.03 (s, 1H, ArH), 7.52 (d, $J=4.9$ Hz, 1H, HC=N); ^{13}C NMR (50.3 MHz, CDCl_3) δ 25.4 and 26.4 ($\text{C}(\text{CH}_3)_2$), 36.8 ($\text{CH}_2\text{-Ar}$), 56.0 and 56.1 (2 x OCH_3), 60.6 ($\text{CH}_2\text{-O}$), 67.3 ($\text{CH}_2\text{-O}$), 76.9 (CH-O), 110.2 (O-C-O), 113.9 (aryl, CH-3 or CH-6), 114.2 (aryl, C-Br), 115.5 (aryl, CH-3 or CH-6), 130.6 (aryl, C-1), 148.1 (aryl, C-4 and C-5), 163.9 (C=N); MS (DCI) m/z (%): 374 (MH^+ , 100), 372 (MH^+ , 100), 294 (18), 260 (19), 192 (18), 130 (9), 84 (5).

Preparation of (R and S)-2-Bromo-6,7-dimethoxy-N-[(2,2-dimethyl-1,3-dioxolan-4-yl)methylene] benzeneethanamine ((R+S)-223).

Following the procedure used to prepare (S)-223, to a solution of amine (0.94 g, 3.6 mmol) and 4Å molecular sieves (1.9 g) cooled to 5 °C was added glyceraldehyde (R+S)-214 (0.64 g, 4.9 mmol). The solvent was removed in vacuo to give 1.3 g of (R+S)-223 of sufficient purity (ca. 80% pure, ^1H NMR) to proceed to the next step: IR (CHCl_3): 3000, 2940, 1675, 1600, 1500, 1465, 1380, 1250-1180, 1160, 1055 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 1.38 (s, 3H, CCH_3), 1.40 (s, 3H, CCH_3), 2.98 (m, 2H, $\text{CH}_2\text{-Ar}$), 3.66 (m, 2H, $\text{CH}_2\text{-N}$), 3.84 (s, 6H, 2 x OCH_3), 3.84 (obscured t, 1H, $\text{CH}_2\text{-O}$), 4.16 (t, $J=6.9$ Hz, 1H, $\text{CH}_2\text{-O}$), 4.54 (q, $J=5.3$ Hz, 1H, CH-O), 6.69 (s, 1H, ArH), 7.00 (s, 1H, ArH), 7.52 (d,

$J=5.0$ Hz, 1H, HC=N); ^{13}C NMR (50.3 MHz, CDCl_3) δ 25.4 ($\underline{\text{C}}\text{-CH}_3$), 26.4 ($\underline{\text{C}}\text{-CH}_3$), 36.8 ($\text{CH}_2\text{-Ar}$), 55.9 ($\text{CH}_3\text{-O}$), 56.1 ($\text{CH}_3\text{-O}$), 60.5 ($\text{CH}_2\text{-N}$), 67.3 ($\text{CH}_2\text{-O}$), 76.9 ($\text{CH}_2\text{-}\underline{\text{C}}\text{H-O}$), 110.2 ($\underline{\text{C}}(\text{CH}_3)_2$), 113.9 (aryl, CH), 114.2 (aryl, C-Br) 115.5 (aryl, CH), 130.5 (aryl, $\underline{\text{C}}\text{-CH}_2$), 148.1 (aryl, 2 x $\underline{\text{C}}\text{-OCH}_3$), 163.9 (C=N); MS (DCI) m/z (%): 374 (MH^+ , 98), 372 (MH^+ , 100), 294 (19), 292 (15), 260 (15), 234 (15), 192 (12) 84 (11); HRMS calcd for $\text{C}_{16}\text{H}_{22}\text{NO}_4\text{Br}$ 371.0732 found 371.0714.

Cyclization of (S)-2-Bromo-6,7-dimethoxy-N-[(2,2-dimethyl-1,3-dioxolan-4-yl)methylene] benzeneethanamine ((S)-223) with Bu_3SnH .

A solution of imine (S)-223 (1.53 g, 4.11 mmol; ca. 95% pure) in PhH (50 mL) was thoroughly degassed with N_2 and was heated to reflux under N_2 . A degassed solution of Bu_3SnH (1.66 g, 5.70 mmol) and AIBN (0.23 g, 1.4 mmol) in PhH (18 mL) was introduced by means of a syringe-pump addition over 12 h to the heated substrate. The solution was heated at reflux for an additional 5 h. The yellow solution was cooled to ambient temperature and the solvent was removed in vacuo. ^1H NMR (500 MHz, CDCl_3) and GC analysis (DB-17, 30 m, 230 °C for 3 min, 10 °C/min to 250 °C) of the reaction mixture showed the ratio (S,S)-224:(R,S)-224:(S)-225 = 3.3:1.0:0.82 (t_{R} for (S,S)- and (R,S)-224 were 7.7 and 8.0 min, respectively). The residual oil was treated with dry acetonitrile (55 mL) and the organotins were extracted with hexane (5 x 25 mL). The acetonitrile layer was then concentrated under reduced pressure to give an orange-red oil which was purified by Chromatotron chromatography (SiO_2 , 4 mm). The residual

organotins were first eluted with 100% CHCl_3 and then 1% $\text{MeOH}/\text{CHCl}_3$ was used to elute the major isoquinoline (S,S)-**224** (0.502 g) followed by the minor isoquinoline (R,S)-**224** (0.239 g). The combined yield of isoquinoline diastereomers (S,S)- and (R,S)-**224** was 62% from the amine **222** or ca. 65% from the imine (S)-**223**. Data for the major isoquinoline diastereomer (S,S)-**224**, a yellow oil: $[\alpha]_D^{22} = +54.2^\circ$ ($c=1.71$, CHCl_3); IR (CHCl_3): 3360, 2930, 2830, 1610, 1505, 1455, 1380, 1370, 1250-1180, 1040, 900 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3) δ 1.39 (s, 3H, CCH_3), 1.51 (s, 3H, CCH_3), 2.05 (br s, 1H, NH), 2.52-2.69 (m, 1H, $\text{ArCH}_2\text{CH}_2\text{N}$), 2.80-3.06 (m, 2H, $\text{ArCH}_2\text{CH}_2\text{N}$), 3.19-3.31 (m, 1H, $\text{ArCH}_2\text{CH}_2\text{N}$), 3.85 (s, 6H, OCH_3), 3.78-3.98 (obscured, 2H, $\text{CH}_2\text{-O}$), 4.21 (d, $J=4.8$ Hz, 1H, Ar-CH-N), 4.58 (q, $J=6.1$ Hz, 1H, CH-O), 6.59 (s, 1H, ArH), 6.76 (s, 1H, ArH); ^{13}C NMR (50.3 MHz, CDCl_3) δ 25.0 and 26.4 ($\text{C}(\text{CH}_3)_2$), 29.6 ($\text{CH}_2\text{-Ar}$), 41.9 ($\text{CH}_2\text{-N}$), 55.7 (Ar-CH-N), 56.0 (2 x OCH_3), 65.9 ($\text{CH}_2\text{-O}$), 78.8 (CH-O), 109.2 (O-C-O), 109.3 (aryl, CH-5 or CH-8), 111.9 (aryl, CH-5 or CH-8), 127.0 (aryl, C-9 or C-10), 128.4 (aryl, C-9 or C-10), 146.9 (aryl, C-6 or C-7), 147.4 (aryl, C-6 or C-7); MS (DCI) m/z (%): 294 (MH^+ , 100), 236 (2), 192 (20); HRMS calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_4$ (MH^+) 294.1705 found 294.1715.

Spectroscopic data for the minor isoquinoline diastereomer (R,S)-**224**, a yellow solid: mp 81.5-83 $^\circ\text{C}$; $[\alpha]_D^{23} = -5.9^\circ$ ($c=1.07$, CHCl_3); IR (CHCl_3): 3340, 2930, 2830, 1610, 1505, 1450, 1370, 1260-1180, 1110, 1050, 900 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3) δ 1.37 (s, 3H, CCH_3), 1.46 (s, 3H, CCH_3), 2.22 (br s, 1H, NH), 2.73 (t, $J=5.8$ Hz, $\text{CH}_2\text{-Ar}$), 2.90-3.06 (m, 1H, $\text{CH}_2\text{-N}$), 3.17-3.33 (m, 1H, $\text{CH}_2\text{-N}$), 3.85 (s, 6H, OCH_3), 3.8-4.12 (m, 3H, $\text{CH}_2\text{-O}$

and Ar-CH-N), 4.43 (q, J=6.5 Hz, CH-O), 6.60 (s, 1H, ArH), 6.63 (s, 1H, ArH); ^{13}C NMR (50.3 MHz, CDCl_3) δ 25.4 and 26.7 ($\text{C}(\text{CH}_3)_2$), 29.3 ($\text{CH}_2\text{-Ar}$), 40.5 ($\text{CH}_2\text{-N}$), 55.8 (OCH_3), 56.0 (OCH_3), 56.8 (Ar-CH-N), 67.1 ($\text{CH}_2\text{-O}$), 78.1 (CH-O), 108.9 (O-C-O), 109.6 (aryl, CH-5 or CH-8), 112.0 (aryl, CH-5 or CH-8), 126.7 (aryl, C-9 or C-10), 128.4 (aryl, C-9 or C-10), 147.0 (aryl, C-6 or C-7), 147.8 (aryl, C-6 or C-7); MS (DCI) m/z (%): 294 (MH^+ , 100), 192 (24); HRMS calcd for $\text{C}_{16}\text{H}_{24}\text{NO}_4$ (MH^+) 294.1705 found 294.1718.

Cyclization of (R and S)-2-Bromo-6,7-dimethoxy-N-[(2,2-dimethyl-1,3-dioxolan-4-yl)methylene] benzeneethanamine ((R+S)-223) with Bu_3SnH .

Following the procedure used for the cyclization of (S)-223, the imine (R+S)-223 (1.2 g, 3.3 mmol; ca. 80% pure) in 60 mL of PhH was treated with Bu_3SnH (1.3 g, 4.6 mmol) and AIBN (0.19 g, 1.1 mmol). ^1H NMR (500 MHz, CDCl_3) analysis of the reaction mixture showed the ratio (S,S)+(R,R)-224:(R,S)+(S,R)-224 = 3.3:1.0. The work up was identical to that used for (S)-223. Chromatotron chromatography gave 0.32 g of (S,S)+(R,R)-224 and 0.17 g of (R,S)+(S,R)-224. The isolated yield of the 4 stereoisomeric isoquinolines 224 was 63% based on 80% purity of the starting imine (R)+(S)-223. The spectroscopic data for (S,S)+(R,R)-224: IR (CHCl_3): 3350, 2995, 2940, 2840, 1605, 1510, 1460, 1380, 1370, 1260-1190, 900 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3) δ 1.40 (s, 3H, C- CH_3), 1.51 (s, 3H, C- CH_3), 2.41 (br s, 1H, NH), 2.50-3.33 (m, 4H, $\text{ArCH}_2\text{CH}_2\text{N}$), 3.85 (s, 6H, OCH_3), 3.8-3.95 (obscured triplet, 2H, $\text{CH}_2\text{-O}$), 4.22 (d, J=5.0 Hz, 1H, Ar-CH-N), 4.60 (q, J=6.3 Hz, 1H, CH-O), 6.59 (s, 1H, ArH), 6.76 (s, 1H, ArH); ^{13}C NMR (50.3

MHz, CDCl₃) δ 24.9 and 26.3 (2 x C-CH₃), 29.4 (CH₂-Ar), 41.7 (CH₂-N), 55.6 (Ar-CH-N), 55.8 (2 x OCH₃), 65.7 (O-CH-CH₂-O), 78.6 (O-CH-CH₂-O), 109.1 (aryl, CH-5 or CH-8), 109.2 (O-C-O), 111.7 (aryl, CH-5 or CH-8), 126.7 (aryl, C-9 or C-10), 128.2 (aryl, C-9 or C-10), 146.9 (aryl, CH-6 or CH-7), 147.4 (aryl, CH-6 or CH-7); MS (DCI) m/z (%): 294 (MH⁺, 100), 236 (4), 192 (40); HRMS calcd for C₁₆H₂₄NO₄ (MH⁺) 294.1705 found 294.1702.

The spectroscopic data for (R,S)+(S,R)-224: IR (CHCl₃): 3350, 2990, 2940, 2840, 1610, 1465, 1380, 1370, 1260-1190, 1045, 900 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 1.37 (s, 3H, C-CH₃), 1.46 (s, 3H, C-CH₃), 2.22 (br s, 1H, NH), 2.73 (t, J=5.8 Hz, 2H, ArCH₂CH₂N), 3.01 (m, 1H, ArCH₂CH₂N), 3.23 (m, 1H, ArCH₂CH₂N), 3.85 (s, 6H, O-CH₃), 3.9-4.1 (m, 3H, OCH₂ and Ar-CH-N), 4.42 (q, J=6.1 Hz, 1H, OCH), 6.59 (s, 1H, ArH), 6.63 (s, 1H, ArH); ¹³C NMR (50.3 MHz, CDCl₃) δ 25.4 and 26.7 (2 x C-CH₃), 29.3 (CH₂-Ar), 40.5 (CH₂-N), 55.6 and 55.8 (2 x OCH₃), 56.6 (Ar-CH-N), 67.1 (O-CH-CH₂-O), 78.1 (O-CH-CH₂-O), 108.9 (O-C-O), 109.3 (aryl, CH-5 or CH-8), 111.8 (aryl, CH-5 or CH-8), 126.7 (aryl, C-9 or C-10), 128.4 (aryl, C-9 or C-10), 147.0 (aryl, CH-6 or CH-7), 147.8 (aryl, CH-6 or CH-7); MS (DCI) m/z (%): 294 (MH⁺, 82), 192 (100); HRMS calcd for C₁₆H₂₄NO₄ (MH⁺) 294.1705 found 294.1710.

Preparation of the Carbamate (S,S)-229.

Following the procedure of MacLean and co-workers,¹⁴⁷ a solution of isoquinoline (S,S)-224 (0.261 g, 0.89 mmol) and 1% aqueous NaOH (35 mL) in CH₂Cl₂

(35 mL) was cooled to 5 °C. The mixture was stirred vigorously while ethyl chloroformate (1.75 mL) was added dropwise over 1 h. Several drops of 10% NaOH were added to keep the reaction mixture alkaline (pH ~ 10) and stirring was continued for an additional 30 min at 5 °C. TLC analysis of the reaction mixture showed only one spot, $R_f=0.52$ (2% CH₃OH/CHCl₃). The organic layer was then separated and washed with brine (2 x 30 mL). The solution was dried over MgSO₄ and concentrated in vacuo. The residue was purified by Chromatotron chromatography (SiO₂, 2 mm) using 1% CH₃OH/CHCl₃ to give 0.325 g of the carbamate (S,S)-229 as a yellow-orange oil (100%); $[\alpha]_D^{23} = -82.5^\circ$ (c=1.62, CHCl₃); IR (CHCl₃): 2930, 2840, 1685, 1605, 1505, 1450, 1380, 1370, 1260-1180, 900 cm⁻¹; (Restricted rotation about N-CO bond) ¹H NMR (500 MHz, CDCl₃) δ 1.20-1.52 (m, 9H, C(CH₃)₂ and OCH₂CH₃), 2.65-2.96 (series of m, 2H, CH₂-Ar), 3.18-3.27 (m, 1/2H, CH-O), 3.36-3.42 (m, 1/2H, CH-O), 3.85 (s, 6H, OCH₃), 3.97-4.32 (series of m, 6H, OCH₂CH₃, CH₂-O, and CH₂-N), 4.97 (d, J=8.0 Hz, 1/2H, Ar-CH-N), 5.09 (d, J=8.0 Hz, 1/2H, Ar-CH-N), 6.61 (s, 1H, ArH-5), 6.90 (s, 1/2H, ArH-8), 6.92 (s, 1/2H, ArH-8); ¹³C NMR (50.3 MHz, CDCl₃) δ 14.7 (CH₂CH₃), 25.5 and 25.6 (2 signals for 1 CH₃ of C(CH₃)₂), 26.5 and 26.7 (2 signals for 1 CH₃ of C(CH₃)₂), 29.7 (CH₂-Ar), 39.0 and 39.9 (2 signals for CH₂-N), 55.8 (OCH₃), 56.4 (Ar-CH-N), 61.7 (CH₂CH₃), 67.5 (CH₂-O), 78.0 and 78.2 (2 signals for CH-O), 109.9 (O-C-O), 110.9 and 111.2 (aryl, 2 signals for 1 CH, CH-5 or CH-8), 112.0 and 112.1 (aryl, 2 signals for 1 CH, CH-5 or CH-8), 126.0 and 126.2 (aryl, C-9 or C-10), 126.6 and 126.7 (aryl, C-9 or C-10), 146.8 (aryl, C-6 or C-7), 148.1 (aryl, C-6 or C-7), 155.5 and 156.2 (2 signals for C=); MS (DCI) m/z (%):

366 (MH⁺, 100), 350 (2), 308 (54), 290 (8), 264 (56), 192 (18); HRMS calcd for C₁₉H₂₈NO₆ (MH⁺) 366.1916 found 366.1907.

Preparation of the Diol (S,S)-232.

The procedure of Cook and co-workers¹⁵⁶ was modified. The carbamate (S,S)-229 (325 mg, 0.89 mmol) was dissolved in 80% acetic acid (25 mL) and the solution was stirred for 13.5 h at room temperature. TLC analysis (6% CH₃OH/CHCl₃) of the reaction mixture showed one new spot, R_f=0.29. The solvent was removed under reduced pressure and the residue was dissolved in CH₂Cl₂ (75 mL). The solution was washed with 2M KOH (10 mL), brine (40 mL) and was dried over K₂CO₃. The solvent was removed in vacuo to give a light yellow oil. This material was purified by Chromatotron chromatography (SiO₂, 1.5% CH₃OH/CHCl₃) to yield 247 mg of (S,S)-232 as a white oil that foamed under high vacuum (87%): [α]_D²³ = -25.4° (c=0.835, CHCl₃), [α]_D²³ = -25.6° (c=0.242, CHCl₃); IR (CHCl₃): 3550, 3420, 2930, 2830, 1665, 1610, 1505, 1460-1410, 1340, 1260-1180, 1120, 1110, 900 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 1.30 (t, J=7.1 Hz, 3H, OCH₂CH₃), 2.81 (t, J=6.3 Hz, 2H, CH₂-Ar), 3.43-3.81 (m, 4H, CH₂-N and CH₂-OH), 3.87 (s, 3H, OCH₃), 3.88 (s, 3H, OCH₃), 4.18 (q, J=7.1 Hz, 2H, OCH₂CH₃), 4.92 (d, J=7.8 Hz, 1H, Ar-CH-N), 6.66 (s, 1H, ArH), 6.90 (s, 1H, ArH); ¹³C NMR (50.3 MHz, CDCl₃) δ 14.6 (CH₂CH₃), 27.7 (CH₂-Ar), 41.2 (CH₂-N), 56.0 (OCH₃), 56.1 (Ar-CH-N), 62.2 (CH₂CH₃), 62.7 (CH₂-O), 74.0 (CH-O), 111.0 (aryl, CH-5 or CH-8), 112.2 (aryl, CH-5 or CH-8), 126.5 (aryl, C-9 and C-10), 147.2 (aryl, C-6 or C-7), 148.2 (aryl, C-6 or C-7),

157.8 (C=O); MS (DCI) m/z (%): 326 (MH^+ , 100), 264 (63), 192 (15); HRMS calcd for $C_{16}H_{24}NO_6$ (MH^+) 326.1604 found 326.1603.

Preparation of 2-Bromo-N-[(4-N,N-dimethylaminophenyl)methylene] benzeneethanamine (233).

Following the general procedure E, a solution of 4-N,N-dimethylamino benzaldehyde (2.0 g 13.4 mmol) and 2-bromophenethylamine 154 (2.5 g, 13.4 mmol) in $PhCH_3$ (25 mL) was heated to reflux for 6 h. GC analysis of the reaction mixture showed 87% conversion after 2 h, 93% after 4 h, and 96% after 5 h. Kugelrohr distillation (150-160 °C at 0.3 mm) gave 3.88 of 233 as a bright-yellow oil (87%): IR ($CHCl_3$): 2940, 2850, 1640, 1610, 1360 cm^{-1} ; 1H NMR (200 MHz, $CDCl_3$) δ 3.00 (s, 6H, CH_3), 3.11 (t, $J=7.2$ Hz, 2H, CH_2 -Ar), 3.81 (t, $J=7.2$ Hz, 2H, CH_2 -N), 6.63-7.62 (m, 8H, ArH), 8.05 (s, 1H, HC=N); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 38.0 (CH_2 -Ar), 40.2 (CH_3), 61.0 (CH_2 -N), 124.3 (aryl, C-Br or aryl, CH), 124.6 (aryl, C-Br or aryl, CH), 127.3, 127.8, 129.5, 131.4, and 132.7 (aryl, 6 x CH), 139.4 (aryl, \underline{C} - CH_2), 152.0 (aryl, C-N), 161.7 (C=N); MS (DCI) m/z (%): 333 (MH^+), 331 (MH^+ , 100), 253 (3), 161 (21).

Cyclization of 2-Bromo-N-[(4-N,N-dimethylaminophenyl)methylene] benzeneethanamine (233) with Bu_3SnH : The synthesis of 1,2,3,4-tetrahydro-1-(4-N,N-dimethylaminophenyl) isoquinoline (234).

Following the general procedure F, to a solution of the Schiff base 233 (0.587

g, 1.77 mmol) in PhH (35 mL) was added a solution of Bu_3SnH (0.743 g, 2.48 mmol) and AIBN ((0.1 g, 0.6 mmol) in PhH (10 mL) by means of a syringe-pump addition over 14 h. The reaction mixture was heated at reflux for an additional 6 h. The work up was as outlined in the general procedure F. The product was recrystallized from hexane and ether to give 0.31 g (70%) of light-brown crystals: mp 126.5-127.3 °C; IR (CHCl_3): 2980, 2930, 1615, 1520, 1355, 1190, 900 cm^{-1} . ^1H NMR (200 MHz, CDCl_3) δ 1.83 (br s, 1H, NH), 2.71-3.35 (m, 4H, CH_2CH_2), 2.93 (s, 6H, $\text{N}(\text{CH}_3)_2$), 5.02 (s, 1H, Ar-CH-N), 6.68 (d, $J=7.6$ Hz, 2H, ArH-2'), 6.79 (d, $J=7.5$ Hz, 1H, ArH-8), 6.95-7.17 (m, 5H, ArH); ^{13}C NMR (50.3 MHz, CDCl_3) δ 25.4 (CH_2 -Ar), 39.4 (CH_2 -N), 40.2 (Ar- $\text{N}(\text{CH}_3)_2$), 59.4 (Ar-CH-N), 112.0 (aryl, CH-3'), 122.8 (aryl, C-1'), 126.9, 128.0, 128.2, 128.8, and 131.5 (aryl, 5 x CH), 131.7, 132.1 (aryl, C-9 or C-10), 150 (aryl, $\underline{\text{C}}\text{-N}(\text{CH}_3)_2$); MS (CI) m/z (%): 253 (MH^+ , 100), 132 (5), 122 (8).

Preparation of 2-((o-Bromophenyl)ethyl)-4,4-dimethyl-2-oxazoline (246) and 3-(o-bromophenyl)-n-propionic acid (247) from 2-oxazoline.

Following the general procedure of Beak and Selling,¹⁶¹ to 2,4,4-trimethyl-2-oxazoline (5.94 g, 52 mmol) in 150 mL of THF at -78°C was added n-butyllithium (23 mL, 57 mmol; 2.48 M) producing a yellow solution. After stirring for 45 min at this temperature, o-bromobenzyl bromide (13.13 g, 52 mmol) in 25 mL of THF was added. The solution darkened on addition. The solution was then allowed to warm to ambient temperature (ca. 1 h). After 1 h at room temperature, TLC (9:1 hexane : ethyl acetate)

showed no more *o*-bromobenzyl bromide (reaction mixture A).

To isolate the oxazoline derivative **246**: Reaction mixture A was poured slowly onto ice water (100 g) and then acidified to pH 2-3 with 9N HCl (ca. 10 mL). The mixture was extracted with pentane (2 x 30 mL). While cooling with ice, the aqueous layer was neutralized with 40% NaOH. The mixture was extracted three times with ether (60 mL). The combined extract were dried with MgSO₄, and the solvent was removed. Kugelrohr distillation (60-75°C at 0.4 mm Hg) gave 13.1 g of **246** as a colourless oil (89% yield). Spectroscopic data for the oxazoline **246**: IR (film): 3025, 2960, 2920, 2880, 1670, 1470-1430, 1360, 1140, 1020, 980, 745 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 1.23 (s, 6H, C(CH₃)₂), 2.56 (t, J=7 Hz, 2H, CH₂-C=N), 3.06 (t, J=7 Hz, 2H, CH₂-Ar), 3.88 (s, 2H, CH₂-O), 6.97- 7.00 (m, 1H, ArH), 7.03-7.38 (m, 2H, ArH), 7.50 (dd, J=7.7, 1.0 Hz, 1H, ArH-3); MS (CI) m/z (%): 284 (MH⁺, 98), 282 (MH⁺, 100), 202 (19), 112 (14).

Hydrolysis of the reaction mixture A to the acid **247**: Reaction mixture A was quenched with 3 mL of H₂O and the solvent was removed in vacuo. Ether (60 mL) was added and the mixture was extracted with 10% HCl (5 x 60 mL). The combined aqueous extract was basified with 40% NaOH. The mixture was extracted with ether (5 x 150 mL). The ether was removed in vacuo to give an oil. The oil was then dissolved in 10% HCl (150 mL) and the mixture was heated at reflux for 30 min. After cooling, the mixture was extracted with ether (5 x 100 mL). The organic layer was then extracted with 10% NaOH (5 x 150 mL). The aqueous layer was acidified with 20% HCl and extracted with ether (5 x 100 mL). The organic layer was dried over MgSO₄ and concentrated in vacuo

to give 8.5 g (71%) of **247** as a white crystalline solid. Spectroscopic data for 3-(*o*-bromophenyl)-*n*-propionic acid (**247**): IR (CHCl₃) 3400-2400, 1710, 1435, 1025 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 2.71 (t, J=7.4 Hz, CH₂-Ar), 3.07 (t, J=7.4 Hz, CH₂-COOH), 7.02-7.30 (m, 3H, ArH), 7.55 (d, J=8.1 Hz, 1H, ArH-3), 11.5 (s, 1H, COOH); ¹³C NMR (50.3 MHz, CDCl₃) δ 31.1 (CH₂), 33.8 (CH₂), 124.3 (aryl, C-Br), 127.6 (aryl, CH-4 or CH-5), 128.2 (aryl, CH-4 or CH-5), 130.4 (aryl, CH-6), 132.9 (aryl, CH-3), 139.4 (aryl, C-CH₂), 178.8 (COOH); MS (EI) m/z (%): 230 (MH⁺, 2), 228 (MH⁺, 2), 171 (20), 169 (18), 149 (100), 107 (30), 77 (34), 51 (24).

The Malonic Ester Synthesis of 3-(*o*-bromophenyl)-*n*-propionic acid (**247**).

Following the procedure of Vogel,¹⁶⁰ a dry 3-neck flask was fitted with a dropping funnel, a mechanical stirrer and a condenser with a CaCl₂ drying tube. To sodium metal (0.94 g, 41 mmol) was added cautiously dry ethanol (30 mL). After 10 min, diethyl malonate (6.4 g, 40 mmol) was added dropwise. Five minutes after the addition, *o*-bromobenzyl bromide (10 g, 40 mmol) was added dropwise. The mixture was then heated at reflux for 3 h. The mixture was quenched with water (17 mL), and the mixture was extracted with ether (3 x 30 mL). The organic phase was dried over MgSO₄, and the solvent was evaporated in vacuo to give 11.8 g of diethyl(*o*-bromophenylmethyl)malonate **245** as an oil of sufficient purity to proceed to the next step: ¹H NMR (90 MHz, CDCl₃) δ 2.22 (t, J=7.2 Hz, 6H, CH₃), 3.33 (d, J=7.5 Hz, 2H, CH₂-Ar), 3.84 (t, J=7.5 Hz, CH(CO₂Et)₂), 4.17 (q, J=7.2 Hz, 4H, CH₂-CH₃), 6.9-7.7 (m, 4H, ArH).

In a flask, fitted with a mechanical stirrer, condenser and dropping funnel, was placed a hot solution of KOH (5 g) in water (5 mL). The solution was stirred and malonate **245** (11.8 g) was added dropwise over 15 min. The mixture was heated to reflux for 5 h and then was stirred at room temperature for an additional 16 h. Water (30 mL) was added, and the solvent was evaporated under vacuum near to dryness. To the residue was added 5M H₂SO₄ (40 mL), and the mixture was heated to reflux for 3.5 h. After cooling, the aqueous layer was decanted from the oily residue and extracted with ether (4 x 30 mL). The ether extracts were combined with the oily residue and the mixture was extracted with brine (50 mL). The organic layer was dried, concentrated in vacuo, and distilled to give 3.83 g of **247** (42% from o-bromobenzyl bromide) as white crystalline solid. The spectral data for **247** matched those of previously synthesized material: bp ca. 160 °C at 1.8 mm.

Preparation of 3-(o-Bromophenyl)-1-propanol (**248**) from the acid **247**.

Following the procedure of Miller and Klinman,¹⁰⁷ LAH (0.21 g, 5.5 mmol) was dissolved in ether (6 mL) under N₂ in a dry 50-mL three-neck flask equipped with a mechanical stirrer, dropping funnel and condenser. An ethereal solution of AlCl₃ (0.75 g, 5.6 mmol) was run in quickly with stirring. The reaction flask was cooled with ice/water. An ethereal solution of 3-(o-bromophenyl)-n-propionic acid **247** (1.07 g, 4.67 mmol in 20 mL) was then added dropwise via syringe-pump over 20 min and the reaction was stirred vigorously for 2 h at 0 °C. The excess LAH was quenched by cautious

dropwise addition of water (ca. 5 mL) followed by acidification with 20% HCl (20 mL). After separation, the aqueous layer was washed with ether (3 x 30 mL). The ether extracts were combined, washed with a saturated solution of NaHCO₃ (10 mL), and then dried over MgSO₄. The solvent was removed under vacuum giving 0.72 g (73%) of **248** as a clear oil of high purity: IR (CHCl₃) 3615, 3450, 2930, 2870, 1515, 1470, 1015, 900 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 1.75-1.95 (m, 2H, CH₂-CH₂-CH₂), 2.79 (distorted t, J=6.3 Hz, 2H, CH₂-Ar), 3.17 (br s, 1H, OH), 3.65 (t, J=6.3 Hz, 2H, CH₂-O), 6.92-7.10 (m, 1H, ArH), 7.11-7.24 (m, 2H, ArH), 7.50 (d, J=7.6 Hz, ArH-3); ¹³C NMR (50.3 MHz, CDCl₃) δ 32.2 (CH₂-Ar or CH₂-CH₂-CH₂), 32.4 (CH₂-Ar or CH₂-CH₂-CH₂), 62.5 (CH₂-OH), 124.2 (aryl, C-Br), 127.2 (aryl, CH-5 or CH-4), 127.4 (aryl, CH-5 or CH-4), 130.1 (aryl, CH-6), 132.5 (aryl, CH-3), 140.7 (aryl, C-CH₂); MS (EI) m/z (%): 216 (M⁺, 7), 214 (M⁺, 7), 198 (20), 196 (22), 135 (22), 117 (100), 91 (68), 77 (39), 63 (15), 51 (20).

Preparation of 3-(Bromophenyl)propanal (**250**) from the Alcohol **248**.

Following the procedure of Corey and Suggs,¹⁶² pyridinium chlorochromate (8.6 g, 40 mmol) was suspended in dry CH₂Cl₂ (50 mL) and the alcohol **248** (5.7 g, 26 mmol in 100 mL) was rapidly added at room temperature. TLC analysis (R_f of alcohol and aldehyde are 0.57 and 0.79, respectively: SiO₂, 1:1 ethyl acetate:hexane) after stirring the mixture for 2 h showed no starting alcohol. The mixture was diluted with dry ether (35 mL) and the supernatant liquid was decanted from the black gum. The black residue was washed with 3 x 25 mL portions of warm ether. All of the organic layers were

combined and filtered through a pad of Florisil. The solvent was removed under vacuum and the residue was purified by Kugelrohr distillation (50-55 °C at 0.3 mm) to give 3.27 g (58%) of the aldehyde **250** as a colourless oil: IR (CHCl₃) 2820, 2720, 1725, 1435, 1015 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 2.79 (t, J=7.6 Hz, 2H, CH₂-C=O), 3.05 (t, J=7.6 Hz, 2H, CH₂-Ar), 7.02-7.14 (m, 1H, ArH), 7.15-7.30 (m, 2H, ArH), 7.52 (d, J=7.9 Hz, 1H, ArH-3), 9.81 (s, 1H, CHO); ¹³C NMR (50.3 MHz, CDCl₃) δ 28.6 (CH₂-Ar), 43.6 (CH₂-CHO), 124.2 (aryl, C-Br), 127.5 (aryl, CH-4 or CH-5), 127.7 (aryl, CH-4 or CH-5), 130.4 (aryl, CH-6), 132.9 (aryl, CH-3), 141.1 (aryl, C-CH₂), 201.5 (CHO); MS (EI) m/z (%): 214 (M⁺, 2), 212 (M⁺, 2), 171 (17), 169 (19), 133 (100), 105 (31), 91 (33), 77 (41).

Preparation of 3-(o-Bromophenyl)-n-propanal (**250**) from the oxazoline **246**.

Following the procedure of Meyers and co-workers,¹⁶⁶ a solution of the oxazoline **246** (6.5 g, 23 mmol) in CH₂Cl₂ (80 mL) was treated dropwise (over 15 min) with methyl trifluoromethylsulfonate (2.87 mL, 25.3 mmol) at room temperature. The mixture was stirred for 1 h. A solution of NaBH₄ (0.96 g, 25 mmol) in ethanol (80 mL) was slowly added to the CH₂Cl₂ solution, and the mixture was stirred for 6.5 h at room temperature. The mixture was poured into 220 mL of 0.2 M KOH and extracted with ether (3 x 100 mL). The combined ether extracts were concentrated to a residue which was dissolved in THF (90 mL) and 2M HCl (90 mL). This solution was stirred for 16 h at room temperature and then extracted (3 x 100 mL) with ether. The ethereal extract was washed with water (100 mL) and brine (100 mL) and dried (MgSO₄). Concentration gave

an oil which was purified by Chromatotron chromatography (SiO₂, 4 mm) using 2.5% ethyl acetate in hexane. The fractions were monitored using TLC (uv light and I₂ stain). Chromatography afforded 2 g (43%) of aldehyde **250** as a colourless oil; spectral data for **250** were given previously.

General Procedure G for the Preparation of N-(n-Butyl)-1-indanamine (257).

To a solution of n-butylamine (86 mg, 1.17 mmol) in PhH (1 mL) was added molecular sieves (4Å, 1 g) and the mixture was cooled to 8-10 °C (ice in water). The aldehyde **250** (255 mg, 1.17 mmol) was added dropwise over 3 min and the reaction mixture was stirred gently for 2 h. The sieves were separated from the mixture by filtration. An aliquot of the reaction mixture was checked by ¹H NMR and showed no starting aldehyde and a high conversion to the aldimine: ¹H NMR (200 MHz, PhH and C₆D₆/TMS) δ 0.86 (t, J=7.1 Hz, 3H, CH₃), 1.10-1.68 (m, 4H, CH₂-CH₂-CH₃), 2.43 (m, 2H, CH₂-C=N), 2.95 (t, J=7.1 Hz, CH₂-Ar), 3.39 (triplet of doublets, J=7.0 and 1 Hz, CH₂-N), the aromatic and the azomethine signals were obscured by PhH, the solvent.

The above solution of the aldimine (max 1.17 mmol) in PhH (9 mL) was heated to reflux under N₂. After 30 min, the solution was checked for hydrolysis/decomposition of the aldimine by ¹H NMR spectroscopy, but none was found. A solution of Bu₃SnH (440 mg, 1.5 mmol) and AIBN (10 mg, 0.06 mmol) in PhH (1 mL) was added. After one and two hours, more AIBN (10 mg each time, 0.06 mmol) was added. After a total of 6 h, the reaction mixture was allowed to cool to ambient

temperature. The mixture was diluted with hexane (60 mL) and extracted with 2M HCl (3 x 50 mL). The combined aqueous extracts were cooled with ice/water and the solution was made basic with the addition of 40% NaOH. The aqueous mixture was extracted with CH_2Cl_2 (3 x 55 mL) and the combined extracts were washed with brine and dried over K_2CO_3 . The solvent was removed under reduced pressure and the residue was purified by Chromatotron chromatography (100% CHCl_3) to give 144 mg (65% from aldehyde **250**) of the **257** as a pale-yellow oil: IR (CDCl_3) 3200, 2920, 2860, 1450, 1320, 1120, 1090 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3) δ 0.92 (t, $J=7.1$ Hz, 3H, CH_3), 1.21-1.60 (m, 5H, CH_3 - CH_2 - CH_2 + NH), 1.75-1.95 (m, 1H, CH_2 -CH), 2.32-2.50 (m, 1H, CH_2 -CH), 2.71 (t, $J=7.1$ Hz, CH_2 -N), 2.7-2.90 (obscured m, 1H, CH_2 -Ar), 2.92-3.10 (m, 1H, CH_2 -Ar), 4.23 (t, $J=6.6$ Hz, 1H, CH-N), 7.10-7.28 (m, 3H, ArH), 7.28-7.40 (m, 1H, ArH); ^{13}C NMR (50.3 MHz, CDCl_3) δ 14.0 (CH_3), 20.5 (CH_2 - CH_3), 30.3 (CH_2 -CH), 32.6 (N- CH_2 - CH_2 or CH_2 -Ar), 33.6 (N- CH_2 - CH_2 or CH_2 -Ar), 47.1 (CH_2 -N), 63.3 (N-CH-Ar), 124.0, 124.7, 126.1, 127.2 (aryl, 4 x CH), 143.6 (aryl, C-4), 145.4 (aryl, C-9); MS (CI) m/z (%): 190 (MH^+ , 100), 146 (3), 132 (2), 117 (3), 74 (10); HRMS calcd for $\text{C}_{13}\text{H}_{19}\text{N}$ 189.1518 found 189.1522.

Preparation of N-Isopropyl-1-indanamine (258).

Following the standard procedure G, the mixture of isopropyl amine (0.117g, 1.98 mmol) over molecular sieves (1g) in PhH (1.5 mL) was treated with the aldehyde **250** (421 mg, 1.98 mmol) at 8-10 °C. After 2.5 h, a ^1H NMR spectrum (200 MHz)

indicated complete conversion to the aldimine.

The aldimine (max 1.98 mmol) was treated with Bu_3SnH (760 mg, 2.6 mmol) and AIBN (20 mg, 0.12 mmol) in 20 mL of PhH. The mixture was heated to reflux. An additional 20 mg of AIBN was added after 2 and 4 h. The mixture was refluxed for a total of 7.5 h. Work up and purification according to the conditions used in procedure G gave indanamine **258** (0.218 g, 63% from aldehyde **250**) as a yellow oil: IR (CDCl_3) 3400-3100, 2930, 2850, 1455, 1370, 1335, 1160 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3) δ 1.12 (dd, $J=7.2, 1.1$ Hz, 6H, 2 x CH_3), 1.30 (br s, 1H, NH), 1.68-1.99 (m, 1H, $\text{CH}_2\text{-CH}_2\text{-CH}$), 2.33-2.51 (m, 1H, $\text{CH}_2\text{-CH}_2\text{-CH}$), 2.70-2.89 (m, 1H, $\text{CH}_2\text{-Ar}$), 2.90-3.10 (obscured m, 1H, $\text{CH}_2\text{-Ar}$), 3.08 (septet, $J=6.2$ Hz, 1H, $\text{N-CH}(\text{CH}_3)_2$), 4.29 (t, $J=6.7$ Hz, 1H, $\text{Ar-CH}_2\text{-N}$), 7.11-7.28 (m, 3H, ArH), 7.31-7.40 (m, 1H, ArH); ^{13}C NMR (50.3 MHz, CDCl_3) δ 22.9 (CH_3), 23.8 (CH_3), 30.2 ($\text{CH}_2\text{-CH}_2\text{-CH}$), 34.6 ($\text{CH}_2\text{-Ar}$), 46.4 ($\text{N-CH}(\text{CH}_3)_2$), 60.5 (N-CH-Ar), 123.9, 124.6, 126.2, 127.2 (aryl, 4 x CH), 143.3 (aryl, C-4), 146.1 (aryl, C-9); MS (CI) m/z (%): 176 (MH^+ , 100), 160 (4), 117 (4); HRMS calcd for $\text{C}_{12}\text{H}_{17}\text{N}$ 175.1361 found 175.1368.

Preparation of N-(t-Butyl)-1-indanamine (259).

Following the standard procedure G, the mixture of t-butyl amine (0.126g, 1.73 mmol) over molecular sieves (1g) in PhH (1.5 mL) was treated with the aldehyde **250** (367 mg, 1.73 mmol) at 8-10 °C. After 2.5 h, a ^1H NMR spectrum (200 MHz) indicated complete conversion to the aldimine.

The aldimine (max 1.73 mmol) was treated with Bu_3SnH (660 mg, 2.3 mmol) and AIBN (20 mg, 0.12 mmol) in 20 mL of PhH. The mixture was heated to reflux. An additional 20mg of AIBN was added after 2 and 4 h. The mixture was refluxed for a total of 7.5 h. The purification conditions outlined in procedure G gave 0.224 g of indanamine 259 (68% from aldehyde 250) as a yellow oil: IR (CDCl_3) 3500-3100, 1662, 1600, 1455, 1360 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3) δ 1.1 (br s, 1H, NH), 1.20 (s, 9H, CH_3), 1.61-1.80 (m, 1H, $\text{CH}_2\text{-CH}$), 2.37-2.54 (m, 1H, $\text{CH}_2\text{-CH}$), 2.68-2.87 (m, 1H, $\text{CH}_2\text{-Ar}$), 2.89-3.06 (m, 1H, $\text{CH}_2\text{-Ar}$), 4.26 (t, $J=7.3$ Hz, 1H, CH-N), 7.08-7.35 (m, 4H, ArH); ^{13}C NMR (50.3 MHz, CDCl_3) δ 30.6 (CH_3), 30.7 ($\text{CH}_2\text{-CH}$), 38.7 ($\text{CH}_2\text{-Ar}$), 51.0 (N-C-(CH_3)₃), 58.1 (N-CH-Ar), 123.9, 124.6, 127.5, 127.1 (aryl, 4 x CH), 143.1 (aryl, C-4), 147.5 (aryl, C-9); MS (CI) m/z (%): 190 (MH^+ , 100), 174 (8), 117 (5), 74 (26); HRMS calcd for $\text{C}_{13}\text{H}_{19}\text{N}$ 189.1518 found 189.1524.

Preparation of N-Benzyl-1-indanamine (260).

Following the standard procedure G, a mixture of benzylamine (0.191 g, 1.78 mmol) and molecular sieves (1g) in PhH (1.5 mL) was treated with the aldehyde 250 (372 mg, 1.75 mmol) at 8-10 °C. A ^1H NMR spectrum (200 MHz) taken after 75 min indicated complete conversion to the aldimine 256.

The aldimine 256 (max 1.75 mmol) was treated with Bu_3SnH (670 mg, 2.3 mmol) and AIBN (15 mg, 0.091 mmol) in 30 mL of PhH. The mixture was heated to reflux. An additional 15mg of AIBN was added after 1 and 2 h. The mixture was refluxed

for a total of 7 h. The purification outlined in procedure G gave 0.248 g (64% from the aldehyde 250) of indanamine 260 as a pale-yellow oil: IR (CDCl₃) 3320, 2940, 2850, 1600, 1450 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 1.54 (br s, 1H, NH), 1.79-1.99 (m, 1H, CH₂-CH), 2.32-2.51 (m, 1H, CH₂-CH), 2.71-2.90 (m, 1H, CH₂-CH₂-CH), 2.91-3.11 (m, 1H, CH₂-CH₂-CH), 3.90 (distorted dd, 2H, N-CH₂-Ar), 4.29 (t, J=6.6 Hz, 1H, CH-N), 7.11-7.43 (m, 9H, ArH); ¹³C NMR (50.3 MHz, CDCl₃) δ 30.4 (CH₂-CH₂-CH), 33.6 (CH₂-Ar), 51.4 (N-CH₂-Ph), 62.7 (N-CH-Ar), 124.1, 124.7, 126.2, 126.8, 127.3, 128.1, 128.3 (aryl, 7 x CH), 140.68 (aryl, C-11), 143.58 (aryl, C-4), 145.3 (aryl, C-9); MS (CI) m/z (%): 224 (MH⁺, 100), 132 (4), 108 (6); HRMS calcd for C₁₆H₁₇N 223.1361 found 223.1370.

Preparation of N-Cyclohexyl-1-indanamine (261).

Following the standard procedure G, a mixture of cyclohexylamine (177 mg, 1.78 mmol) over molecular sieves (1g) in PhH (2 mL) was treated with the aldehyde 250 (366 mg, 1.72 mmol) at 8-10 °C. After 30 min, a ¹H NMR spectrum (200 MHz) indicated complete conversion to the aldimine.

To a solution of aldimine (max 1.72 mmol) in PhH (30 mL) heated to reflux under N₂ was added a solution of Bu₃SnH (0.65 g, 2.2 mmol) and AIBN (0.1026 g, 0.625 mmol) in 3 mL over a period of 9 h (syringe-pump). The resulting solution was stirred at 80 °C for an another 6 h. The solvent was removed in vacuo, and the residue was purified by extraction and chromatography as described in the standard procedure G.

Indanamine **261** (184 mg, 50% from aldehyde **250**) was isolated as a pale-yellow oil: IR (CDCl₃) 3400-3100, 2920, 2850, 1450, 1110, 885 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 1.05-2.08 (m, 12H, 5 x CH₂ from cyclohexyl + 1H from CH₂-CH₂-Ar + NH), 2.35-2.51 (m, 1H, CH₂-CH₂-Ar), 2.62-2.90 (m, 2H, N-CH₂-(CH₂)₂- + CH₂-Ar), 2.91-3.10 (m, 1H, CH₂-Ar), 4.35 (t, J=6.7 Hz, Ar-CH-N), 7.10-7.30 (m, 3H, ArH), 7.30-7.39 (m, 1H, ArH); ¹³C NMR (50.3 MHz, CDCl₃) δ 25.0 (CH₂-12 or CH₂-14), 25.1 (CH₂-12 or CH₂-14), 26.1 (CH₂-13), 34.4 (CH₂-11 or CH₂-15), 34.7 (CH₂-11 or CH₂-15), 123.9, 124.6, 126.1, 127.1 (aryl, 4 x CH), 143.3 (aryl, C-4), 145.1 (aryl, C-9); MS (CI) m/z (%): 215 (MH⁺, 100), 172 (4), 112 (6), 100 (22); HRMS calcd for C₁₅H₂₁N 215.1674 found 215.1688.

Kinetic Study of the Cyclization of N-benzylaldimine (256) (Table 8).

To a solution of benzylamine (31.3 mg, 0.29 mmol) in C₆D₆ (0.5 mL) was added molecular sieves (4Å, 0.15 g) and the mixture was cooled to 8-10 °C (ice in water). The aldehyde **250** (61.9 mg, 0.29 mmol) was added dropwise over 3 min and the reaction mixture was stirred gently for 30 min. The sieves were separated from the mixture by filtration. The ¹H NMR spectrum indicated no starting aldehyde and complete conversion to the aldimine **256**: ¹H NMR (200 MHz, C₆D₆) δ 2.35-2.48 (m, 2H, CH₂-C=N), 2.95 (t, J=7.7 Hz, 2H, CH₂-CH₂-Ar), 4.39 (s, 2H, CH₂-Ph), 6.59-7.40 (m, 10H, 9 x ArH and HC=N).

Following general procedure C, solutions containing aldimine **256** (max 0.29 mmol), Bu₃SnH (8.6 equiv), TMS (3 μL), and AIBN (7% of imine) in C₆D₆ were

prepared. The initial concentrations of Bu_3SnH were: 0.5024, 0.2512, 0.1256, and 0.0628 M. The solutions were deoxygenated by three freeze/pump/thaw cycles and the nmr tubes were sealed. The tubes were heated in a constant-temperature bath set at 80 ± 0.2 °C. The 0.5024 M and 0.1256 M solutions were heated for 80 min and the others for 100 min. The reaction mixtures were analyzed by ^1H NMR spectroscopy (500 and 200 MHz) and the product ratios are summarized in Table 8. The spectral data for N-benzylindanamine (260) were given previously.

Preparation of Hexabutylditin (264).

Following the procedure of Boudjouk and Han¹⁷², a solution of Bu_3SnCl (19.6 g, 60 mmol) containing Li wire (0.45 g, 65 mmol) in dry THF (35 mL) was placed in an ultrasound bath for 11 h. The milky mixture was filtered through Celite and the filtrate was concentrated under vacuum. The residue was filtered through Celite for a second time and the resulting solution was distilled (fractionating column containing steel wool) to give 12.43 g (71%) of 264 as a colourless oil: bp 180-185 °C at 0.2-0.4 mm; IR (film): 2960, 2930, 1460, 1375, 765 cm^{-1} ; ^{119}Sn NMR (93.3 MHz, PhH) δ -83.18, [lit.¹⁹⁰ ^{119}Sn NMR (CDCl_3) δ -83.2 ppm].

Preparation of Bis(tributylstannyl)benzopinacolate (TBBP) (265).

A solution of benzophenone (75.7 mg, 0.415 mmol) and hexabutylditin (264)

(190) Mitchell, T.N.; Walter, G. J. *Chem. Soc. , Perkin Trans. II* 1977, 1842.

(120.8 mg, 0.208 mmol) in C_6D_6 (0.4 mL) was transferred to a 5-mm tube fitted with a ground glass joint. The solution was deoxygenated by three freeze/pump/thaw cycles and the tube was sealed under vacuum. The sample was immersed in water in a water cooled quartz dewar. The solution was photolysed in a Rayonet reactor fitted with 350 nm lamps for 24 h at 20 °C. The colour of the resulting solution was yellow. The presence of TBBP was ascertained by ^{119}Sn NMR, ^{13}C NMR spectroscopy and MS. ^{119}Sn NMR (186.5 MHz, C_6D_6 , ext. ref. $SnMe_4$ at 0.0 ppm) δ +71.9 ppm (TBBP), -83.6 (Bu_6Sn_2). The ratio of TBBP to Bu_6Sn_2 was ca. 5.4; ^{13}C NMR (62.9 MHz, in C_6H_{12} , referenced to 26.4 ppm) δ 87.9 ppm (benzylic carbon of 265); MS (CI, NH_3) m/z (%): 473 (1/2 M^+ , 3%); Partial 1H NMR (500 MHz, C_6D_6) δ 0.59-1.08 (m, 30 H, 6 x $Sn-CH_2$ and 6 x CH_3), 1.08-1.35 (m, 12H, 6 x $Sn-CH_2-CH_2-CH_2$), 1.35-1.71 (m, 12H, 6 x $Sn-CH_2-CH_2$).

Preparation of Bis(trimethylstannyl)benzopinacolate (TMBP) (6).

The procedure of Neumann and co-workers^{10b} was simplified. A solution of benzophenone (147 mg, 0.807 mmol) and hexamethylditin (132 mg, 0.404 mmol) in PhH (0.4 mL) was transferred to a 5-mm nmr tube fitted with a ground glass joint. The solution was deoxygenated by three freeze/pump/thaw cycles and the tube was sealed under vacuum. The sample was immersed into water in a water cooled quartz dewar. The solution was photolysed in a Rayonet reactor fitted with 350 nm lamps for 7 h at 20 °C to give a pale yellow solution. The ratio of TMBP to Me_6Sn_2 was ca. 13:1: Partial 1H NMR (90 MHz, PhH) data for TMBP (6): δ 0.04 (s, $J(^{117}Sn) = 54$ Hz, $J(^{119}Sn) = 56$ Hz;

CH₃) [lit.^{10b} ¹H NMR (CH₂Cl₂) δ 0.08 (s, J(¹¹⁷Sn) = 56 Hz, J(¹¹⁹Sn) = 58.6 Hz; CH₃).

Reaction of Bis(tributylstannyl)benzopinacolate (265) with Isobutyraldimine 164.

A glass apparatus in the shape of the letter "h" was prepared. The legs of this apparatus consisted of two 5-mm nmr tubes joined by glass tubing and onto the top of one of the nmr tubes was attached a ground glass joint. A solution of Bu₃Sn₂ (138 mg, 0.237 mmol) and Ph₂CO (84 mg, 0.461 mmol) in 0.5 mL of C₆D₆ in a syringe was transferred into one of the nmr tubes. In a similar manner, a solution of isobutyraldimine **164** (27 mg, 0.108 mmol) in 0.5 mL of C₆D₆ was transferred into the other nmr tube. The entire apparatus was connected to a vacuum line and the solutions were deoxygenated by three freeze/pump/thaw cycles and the apparatus was sealed at the neck under vacuum. The tube containing the aldimine **164** was wrapped in aluminum foil and the entire apparatus was placed in a water cooled quartz dewar. The solution was photolysed in the Rayonet reactor with 350 nm lamps for 24 h at 21 °C. The solutions in the two nmr tubes were thoroughly mixed and then frozen in liquid N₂. The two nmr tubes were flame sealed. The tubes were heated in separate constant-temperature baths, one set at 70 °C and the other at 100 °C. At 70 °C the reaction mixture was complete after 14 h. Approximately 80% of product mixture was assignable to the isoquinoline **166** (the ratio **166:168** (6H:RH) was ca. 4). At 100 °C, on the other hand, the reaction was complete after only 3h, and it showed the same product composition.

Preparation of 2-Bromo-N-[(3,4-dimethoxyphenyl)methylene] benzenemethanamine (272).

Following general procedure E, a solution of 3,4-dimethoxybenzaldehyde (1.08 g, 6.5 mmol), and 2-bromobenzylamine (1.22 g, 6.5 mmol) in PhCH₃ (45 mL) was heated in a Dean-Stark apparatus for 17 h. The solvent was removed under vacuum, and the residue was distilled in a Kugelrohr apparatus (105 °C at ca 0.3 mm) giving 1.62 g (68%) of 272 as an oil that solidified on standing (white solid): mp 75-76 °C; IR (CHCl₃): 2940, 2840, 1645-1420, 1370-1290, 1235, 1015, 900 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ 3.90 (s, 3H, OMe), 3.93 (s, 3H, OMe), 4.84 (s, 2H, CH₂), 6.87 (d, J=8.2 Hz, 1H, ArH), 7.05-7.60 (m, 6H, ArH), 8.29 (s, 1H, HC=N); ¹³C NMR (50.3 MHz, CDCl₃) δ 55.7 (OCH₃), 63.9 (CH₂), 108.5 (aryl, CH-10 or CH-13), 110.2 (aryl, CH-10 or CH-13), 123.3 (aryl, C-Br), 129.1 (aryl, C=C=N), 123.1, 127.2, 128.2, 129.5, 132.2 (aryl, 5 x CH), 138.6 (aryl, C-CH₂), 149.1 (aryl, C-OMe), 151.3 (aryl, C-OMe), 162.2 (C=N); MS (CI, NH₃) m/z (%): 336 (MH⁺, 95), 334 (MH⁺, 100); HRMS calcd for C₁₆H₁₆NO₂Br 333.0364 found 333.0362.

Thermolysis of 2-Bromo-N-[(3,4-dimethoxyphenyl)methylene] benzenemethanamine (272) with Bu₃SnH.

A solution of Schiff base 272 (0.521 g, 1.56 mmol) in PhH (25 mL) was thoroughly degassed with nitrogen and was heated to reflux under N₂. A degassed solution of Bu₃SnH (0.58 g, 2.0 mmol) and AIBN (90 mg, 0.55 mmol) in PhH (10 mL) was

introduced by means of a syringe-pump addition over 16 h to the heated substrate solution. GC analysis (DB-17, 30 m column; 150 °C for 3 min, 10 °C/min to 240 °C) of the reaction mixture showed two new products corresponding to Bu_3SnBr and 3,4-dimethoxybenzotrile (**275**). The solution was concentrated under vacuum to afford a pale-yellow solid. The solid was washed with hexane (30 mL) and then recrystallized from water giving 0.18 g (72%) of benzonitrile **275**: mp 67-68 °C; ^1H NMR (200 MHz, CDCl_3) δ 3.91 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.90 (d, $J=8.4$ Hz, 1H, ArH), 7.08 (d, $J=1.6$ Hz, ArH), 7.28 (dd, $J=8.4$ and 1.6 Hz, 1h, ArH). The ^1H NMR spectrum of **275** was identical to that reported in the literature.¹⁹¹

Preparation of Ketimine 278.

Cyclopentanone (0.428 g, 5.09 mmol) was added to a solution of 2-bromobenzylamine (0.933 g, 4.93 mmol) in PhH (13 mL) containing molecular sieves (4Å, 2 g). The mixture was stirred gently for 16 h at room temperature. The mixture was filtered and the filtrate was shown to be of high purity (ca. 95%) by ^1H NMR (200 MHz). The spectral data for ketimine **278**: IR (CHCl_3): 2940, 2875, 1675, 1435, 1015 cm^{-1} ; ^1H NMR (200 MHz, PhH and $\text{C}_6\text{D}_6/\text{TMS}$) δ 1.36 (m, 4H, CH_2 -10 and CH_2 -11), 1.72 (distorted t, 2H, CH_2 -9 or CH_2 -12), 2.26 (distorted t, 2H, CH_2 -9 or CH_2 -12), 4.43 (s, 2H, Ar- CH_2 -N), 6.7-7.6 (obscured ArH, 4H); ^{13}C NMR (50.3 MHz, CDCl_3) δ 24.3 (CH_2 -10

(191) *The Aldrich Library of NMR Spectra*; Pouchert, C.J.; Campbell, J.K., Ed.; Aldrich Company; 1974, Volume 7, p133A.

or CH₂-11), 29.6 (syn, CH₂-12), 36.6 (anti, CH₂-9), 57.3 (Ar-CH₂-N), 123.5 (aryl, C-Br), 127.4, 128.3, 129.6, 132.4 (aryl, 4 x CH), 139.4 (aryl, C-CH₂), 182.4 (C=N); MS (CI, NH₃) m/z (%): 254 (MH⁺, 98), 252 (MH⁺, 100), 188 (32), 186 (34), 154 (10), 112 (100).

Preparation of Ketimine 279.

The procedure used to prepare the halogenated ketimine 278 was followed. A solution of benzylamine (0.4 g, 3.7 mmol) over molecular sieves (4Å, 2g) in PhH (5 mL) was treated with 3-pentanone. The mixture was stirred for 16 h at room temperature. GC analysis (DB-17, 30 m, 150 °C for 3 min, 10 °C/min to 245 °C) of the reaction mixture showed only one new product, corresponding to the ketimine 279: $t_R = 8.3$ min. Vacuum distillation of the filtered solution resulted in decomposition and hence the spectral data for ketimine 279 were acquired on the crude solution: IR (CHCl₃): 2940, 2875, 1675, 1450, 900 cm⁻¹; ¹H NMR (200 MHz, PhH and C₆D₆/TMS): δ 1.25-1.50 (m, 4H, CH₂-10 and CH₂-11), 1.73 (distorted t, 2H, CH₂-9 or CH₂-12), 2.28 (distorted t, 2H, CH₂-9 or CH₂-12), 4.34 (s, 2H, Ar-CH₂-N), 7.0-7.6 (obscured Ar-H, 5H); ¹³C NMR (50.3 MHz, CDCl₃) δ 24.1 (CH₂-8 or CH₂-9), 24.7 (CH₂-8 or CH₂-9), 29.1 (syn, CH₂-10), 36.4 (anti, CH₂-7), 57.4 (Ar-CH₂-N), 126.3 (aryl, CH-4), 127.6, 128.1 (aryl, CH-2 and CH-3), 140.1 (aryl, C-CH₂), 181.1 (C=N); MS (EI) m/z (%): 173 (M⁺, 19), 91 (100), 65 (11).

Thermolysis of Ketimine 278 with Bu₃SnH.

(i) All at once addition of Bu₃SnH.

To a solution of ketimine **278** (2 mmol) in PhH (25 mL) heated to 80 °C under nitrogen was added a solution of Bu₃SnH (0.70 g, 2.4 mmol) and AIBN (17 mg, 0.10 mmol) in PhH (5 mL). The resulting solution was stirred at 80 °C. After 4 h, ¹H NMR analysis indicated 50% conversion. AIBN (17 mg, 0.10 mmol) was added and the reaction mixture was heated at 80 °C for an additional 2 h. ¹H NMR analysis (200 MHz, PhH + C₆D₆/TMS) of the reaction mixture showed 90% conversion to the dehalogenated ketimine **279**. The spectral data for **279** from **278** were identical to those reported for authentic **279**. GC analysis (DB-17, 30 m, 150 °C for 3 min, 10 °C/min to 245 °C) of the product mixture showed only two new products, t_r = 7.6 and 8.3 min, corresponding to Bu₃SnBr and the ketimine **279**, respectively.

(ii) Syringe-pump addition of Bu₃SnH.

To a solution of ketimine **278** (2 mmol) in PhH (30 mL) heated to 80 °C under nitrogen was added a solution of Bu₃SnH (0.76 g, 2.6 mmol) and AIBN (0.11 g, 0.67 mmol) in 5 mL of PhH over 14 h. GC and ¹H NMR analysis of the product mixture indicated complete conversion to the ketimine **279**.