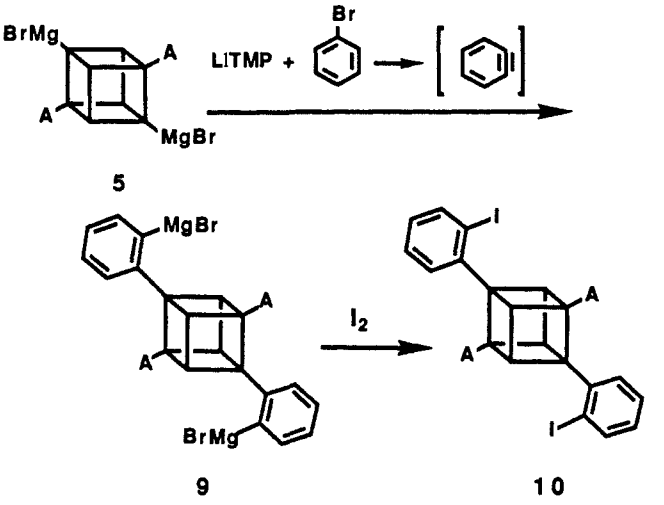
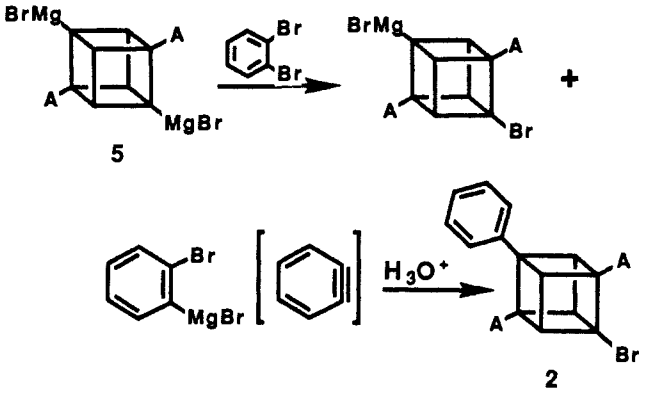
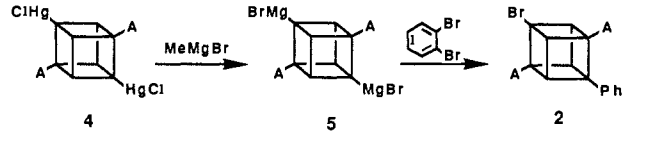
Scheme I



Scheme II



In a similar reaction cubane diGrignard **5** was prepared in situ from the reaction of cubane diamide dimercury chloride **4** and MeMgBr in THF at room temperature. Addition of dibromobenzene to this reaction mixture gave a 30% yield of bromophenylcubane diamide **2**, the first cubane derivative containing three different substituents. Here, it would appear that a benzyne



intermediate formed through metal halogen exchange subsequently reacts with the second Grignard function of the cubane to give **2**[9] (Scheme II).

We are now investigating the chemistry of phenylcubanes. The results of this investigation will be published in due course.

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Registry No. 1, 116531-75-0; **2**, 116531-76-1; **3**, 94161-36-1; **4**, 116531-77-2; **7**, 116564-45-5; **8**, 94138-19-9; **10**, 116531-78-3; LiTMP, 38227-87-1; $MgBr_2$, 7789-48-2; CH_3OD, 1455-13-6; MeMgBr, 75-16-1; $MgBr_2$·etherate, 29858-07-9; *o*-dibromobenzene, 583-53-9; bromobenzene, 108-86-1.

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Oxidative Ring Expansion of 1-(*tert*-Butylamino)indolines to 1,4-Dihydrocinnolines. Novel Neophyl Rearrangement of Hydrazyl Radicals

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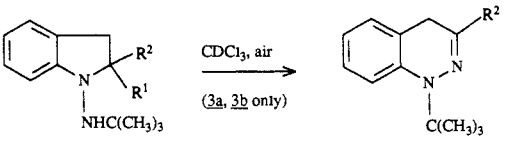
Free-radical rearrangements that convert one 2-aryl radical (**1**) to another (**2**) (eq 1) are called "neophyl" rearrangements and

$$\underset{\mathbf{1}}{\text{Ar–X–Y}} \rightarrow \underset{\mathbf{2}}{\text{Ar–Y–}\dot{\text{X}}} \qquad (1)$$

have received much attention.[1] Examples in which X and Y of **1** are both carbon-centered are common and include the parent system (Ar = C_6H_5, X = $C(CH_3)_2$, Y = CH_2·) that gives the class of rearrangements its name.[1] Examples of non-carbon moieties (X and/or Y of **1**) are less common but include the cases X = O, Y = C-centered[3] and X = C-centered, Y = O.[4] There are still no examples, apparently, of aryl migration from C to N or from N to C,[5] nor are rearrangements known in which both X and Y are unsaturated sites, as in 2-arylvinyl[6] or in aryldiazenyl radicals.[7] Other examples of eq 1 in which both X and Y are heteroatoms or heteroatom-centered, as in peroxyls, aminoxyls, oxaminyls, and hydrazyls, appear to be unknown also. We were therefore surprised to find the clean oxidative rearrangements of 1-aminoindolines (**3**) to 1,4-dihydrocinnolines (**4**) that appear to require neophyl rearrangement of hydrazyls as a key step, eq 2.



(2)

3a, $R^1 = R^2 = H$
3b, $R^1 = H$; $R^2 = CH_3$
3c, $R^1 = R^2 = CH_3$

4a, $R^2 = H$
4b, $R^2 = CH_3$

Compounds **3** were synthesized from azo precursors (**5**)[8] by free-radical chemistry reported previously,[9] Scheme I, and they were separated from the other cyclic coproducts **6** by careful chromatography on silica gel under N_2.

Degassed solutions of **3a–c** in $CDCl_3$, in sealed NMR tubes, were stable indefinitely at room temperature. However, when the tubes were opened and capped with plastic caps, **3a** and **3b** disappeared in 2–3 days with clean formation of **4a** and **4b**, respectively. The fact that air starts the reaction and that the products are oxidized as well as structurally rearranged, with respect to starting materials, suggests a free-radical mechanism, Scheme II. Oxidation of **3** to hydrazyl **7**, followed by neophyl rearrangement[1] through diaziridine intermediate (**8**) to isomeric

† Visiting scholar from Xian Modern Chemistry Research Institute, 1986–1988.

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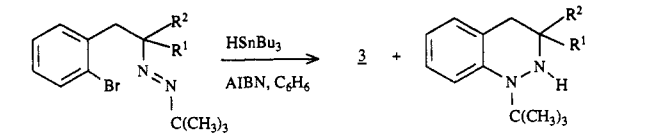
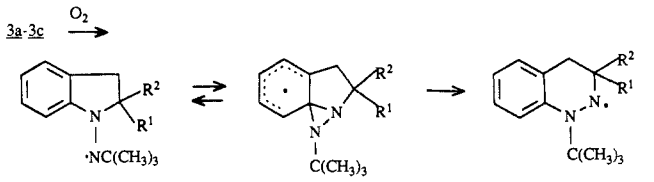
Scheme I



5a, $R^1 = R^2 = H$
5b, $R^1 = H$, $R^2 = CH_3$
5c, $R^1 = R^2 = CH_3$

6a, $R^1 = R^2 = H$
6b, $R^1 = H$, $R^2 = CH_3$
6c, $R^1 = R^2 = CH_3$

Scheme II



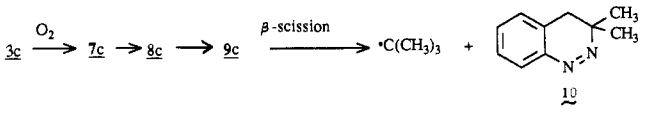
7a, $R^1 = R^2 = H$
7b, $R^1 = H$; $R^2 = CH_3$
7c, $R^1 = R^2 = CH_3$

8a, $R^1 = R^2 = H$
8b, $R^1 = H$; $R^2 = CH_3$
8c, $R^1 = R^2 = CH_3$

9a, $R^1 = R^2 = H$
9b, $R^1 = H$; $R^2 = CH_3$
9c, $R^2 = R^2 = CH_3$

9a, 9b $\xrightarrow{O_2}$ **4a, 4b**

Scheme III



hydrazyl (**9**) readily accounts for the observations.

The mechanism of Scheme II is supported strongly by the behavior of **3c**, which afforded 3,4-dihydrocinnoline (**10**), Scheme III. Hydrazyl **9c** would be expected to lose the *tert*-butyl radical, rather than the CH_3 radical, by β-scission. There is precedent for facile loss of *tert*-butyl from a hydrazyl[10] except in cases of fixed and unfavorable geometry.[11]

It was possible to observe hydrazyl **7c** by irradiation of a solution of **3c** at −40 °C in a mixed solvent consisting of di-*tert*-butyl peroxide and CH_2Cl_2 (1:1 by volume), in the cavity of an EPR spectrometer. Although the initial spectrum was complex, probably because of an impurity present, continued irradiation led quickly to a steady five-line spectrum (intensity ratios within 20% of 1:2:3:2:1 at $g = 2.0038$). The g value is close to those of typical hydrazyls,[12] and the observation of five-lines as described implies that $a_{N(1)} \simeq a_{N(2)} \simeq 11.8$ G. In most hydrazyls,[12] $a_{N(1)} > a_{N(2)}$ but the reverse is known,[13] and it is therefore not surprising that $a_{N(1)} \simeq a_{N(2)}$ should be encountered, as is the case for **7c**. The signal faded rapidly when the light was turned off.

Increasing the temperature did not lead to a change in the spectrum, indicating either that neophyl rearrangement is slow or that the rearranged radical **9c** loses the *tert*-butyl group very rapidly. A strong indication that the latter is true came from attempts to prepare **9c** directly from **6c**, by the method described above for the generation of **7c** from **3c**. No signal at all was observable. Since it is highly unlikely that *tert*-butoxyl radicals abstract efficiently from **3c** but not from **6c**, the conclusion is that loss of *tert*-butyl from **9c** is very much faster than the neophyl rearrangement of **7c** to **9c**.

The sequence of reactions of **3**, induced by oxygen, represents the first examples of neophyl rearrangements of hydrazyls to isomeric hydrazyls. Rearrangement of radicals **7** is surprising because hydrazyls are normally stabilized by three-electron π-bonding. Recent results, that add to an extensive body of literature on the subject of bonding in hydrazyls, include the observation that the NH_2 hydrogens of 1-phenylhydrazyl are nonequivalent[14] and calculations of torsional and inversion barriers for hydrazyl itself.[15] In the case of radicals **7**, hydrazyl resonance is probably less important because it requires the *tert*-butyl group to be held, with entropic cost, in or near the molecular plane, where it must interact sterically with either the CR^1R^2 moiety or with the "peri" hydrogen at C-7. Although radicals **9** also have a "peri" interaction of the type mentioned above, hydrazyl resonance comes at lower entropic cost because both N atoms are in a ring. Rearrangement of **7** to **9** can therefore be expected to be exothermic and effectively irreversible.

Neophyl rearrangement could conceivably be involved during the synthesis of **3** and **6** (Scheme I). Beckwith and co-workers[16] have found that 5-exo cyclizations of alkenylaryl and (alkenyloxy)aryl radicals are followed by neophyl rearrangements that can compete with H-abstraction from $HSnBu_3$. In the present cases, the ratios (**3**:**6**) were independent of the initial concentration of $HSnBu_3$ in the range 0.20–1.15 M. That result suggests that the neophyl rearrangements of **7** are relatively slow, as expected,[17] for it is unlikely that the neopentyl-like **7** abstracts from $HSnBu_3$ with rate constants much larger than those of the Beckwith[16] radicals.

The oxidative rearrangements of **3a** and **3b** reported here may represent an attractive route to 1-alkyl-1,4-dihydrocinnolines, such as **4a** and **4b**, from 1-(alkylamino)indolines.

Registry No. 3a, 116302-23-9; **3b**, 109638-02-0; **3c**, 109637-95-8; **4a**, 116302-24-0; **4b**, 116302-25-1; **7c**, 116302-26-2; **10**, 116302-27-3.

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Control of Enzyme Enantioselectivity by the Reaction Medium

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Stereoselectivity is one of the hallmarks of enzymatic catalysis.[1,2] In principle, enzyme stereoselectivity could be altered by protein engineering[3] which would be of profound significance for both enzyme-catalyzed preparative synthesis[4] and mechanistic biochemistry. Recently, we have observed that upon a transition from water to organic solvents as the reaction medium the enantioselectivity of the protease subtilisin Carlsberg in the reaction of peptide synthesis dramatically relaxes.[5] If general, this phe-

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