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STEREOCHEMICAL ASPECTS OF PHOTO-SET INDUCED DIRADICAL CYCLIZATION REACTIONS AS PART OF ISOQUINOLINE ALKALOID SYNTHETIC STRATEGIES

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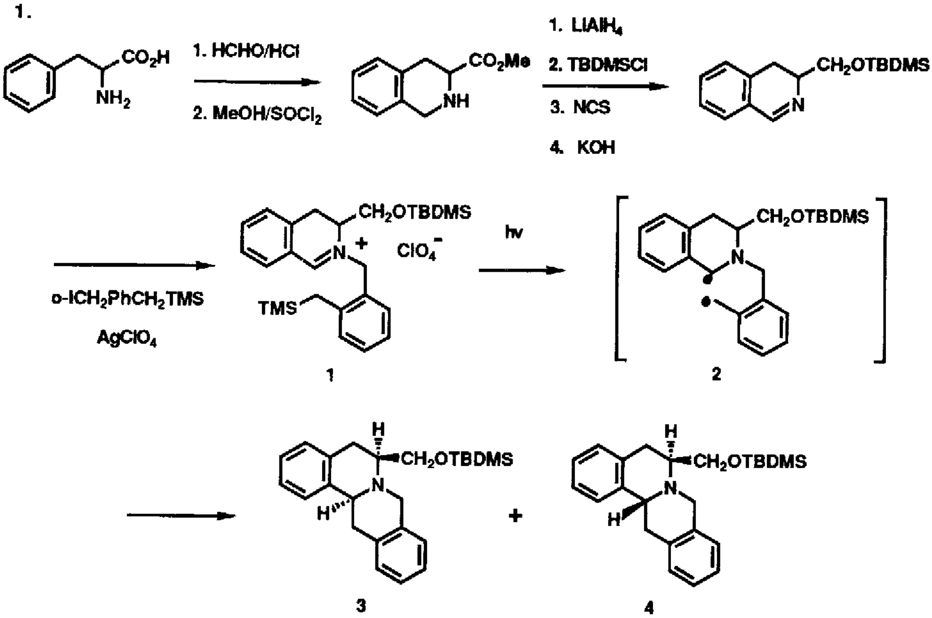
SUMMARY. Studies of the photo-SET induced cyclization reactions of an N-silylbenzyldihydroisoquinolinium salt have uncovered a potentially interesting feature governing stereoselectivities of diradical cyclization reactions.

The stereochemistry of radical pair combination and diradical cyclization processes has been investigated in the past as a method to probe reaction mechanisms[1] and medium effects on chain dynamics.[2] Little attention has been paid to the synthetic consequences of diradical cyclization stereochemistry. This is perhaps due in part to the limited number of efficient methods for generation of these intermediates and the low degrees of stereoselectivity anticipated for these cyclization. Recently, we have shown that synthetically interesting diradical cyclization reactions can be promoted by photoinduced electron transfer (SET) in silyl donor- iminium cation acceptor pairs.[3] These processes can be employed in the efficient construction of structurally complex N-heterocyclic and carbocyclic ring systems. Examples of this are found in approaches developed for harringtonine,[3a] erythrina[3b] and protoberberine[3c] alkaloid synthesis. Our continuing investigations in this area are aimed at developing an understanding of the factors which control the stereochemical course of these cyclization processes. Preliminary results gained thus far and reported below appear to show that multiplicity and stereoelectronic requirements for intersystem crossing contribute to the control of diradical cyclization stereoselectivites.

The dihydroisoquinolinium perchlorate **1**, selected for our initial studies in this area, was prepared by the sequence shown in Scheme 1.[4] This substance contains a remote chiral center external to the ring formed by cyclization of the diradical **2** which is generated by sequential SET-desilylation. This salt was transformed upon irradiation ($\lambda > 270$ nm) in MeCN to a separable mixture of the isomeric berbines, **3** and **4**,[5a] in an 82% yield and a **3**:**4** ratio of 1:2.4.[5b] Cyclization of **1** can be promoted by direct irradiation in a variety of solvents or by xanthone (triplet) sensitized irradiation. The **3**:**4** ratios for these processes are recorded in Table 1. In each case the trans-berbine **4** predominates and the **3**:**4** ratio appears to be relatively insensitive to temperature and to decrease for reaction in glassy solution. Importantly, the stereoselectivity is significantly enhanced in favor of **4** (*e.g.* 1:6.0 in CF_3CH_2OH) in triplet sensitized reactions.

By viewing the results summarized in Table 1 one can clearly see that the stereoselectivities are low for the direct irradiation photocyclization reactions. In contrast, the stereoselectivities are high and in the synthetically useful range for the sensitized processes. These observations appear to be understandable in terms of a photocyclization stereochemical control offered by factors such as multiplicity, intersystem crossing rates and bond rotation (chain dynamics) which govern the relative rates of diradical conformer interconversion and cyclization. We know[3c] that the direct irradiation process of 1 is initiated by SET from the benzylsilane moiety to the singlet excited dihydroisoquinolinium cation group. Since SET and ensuing cation diradical desilylation are fast processes,[6] the intermediate diradical **2** should be produced with singlet multiplicity in the direct irradiation reactions. Moreover, Scheme 1.



owing to a high exothermicity, singlet diradical cyclization should be fast relative to conformational equilibration.[7] As a result, the stereochemistry of the singlet reactions will reflect dihydroisoquinolinium salt conformer populations especially in highly viscous media.[8] Molecular mechanics calculations suggest a small energy differences between the two conformers **1c** and **1t** (Scheme 2) of the starting salt which serve as direct precursors of the respective diradical conformers **2c** and **2t**. The comparatively low stereoselectivity observed in glassy solution where bond rotation would be very slow relative to diradical coupling reflects this.

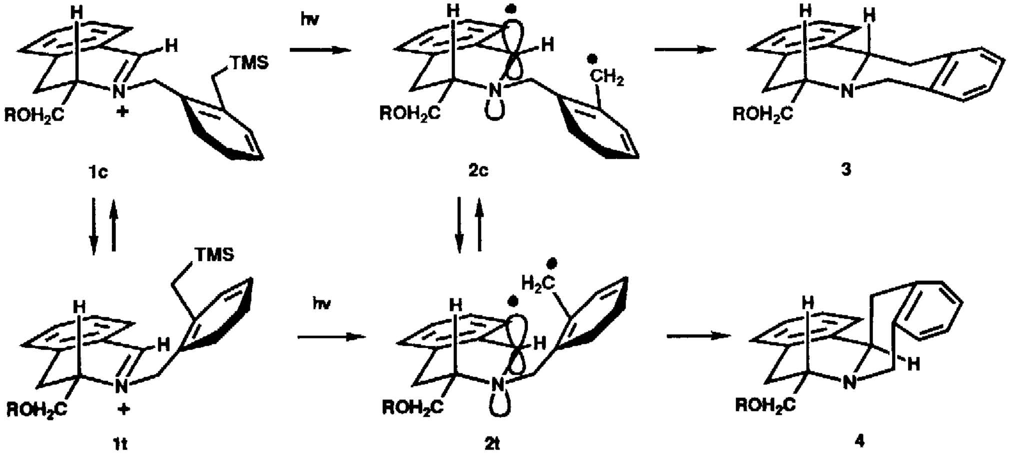
Table 1. Stereochemistry of Photocyclization of Dihydroisoquinolinium Perchlorate **1**.

Solvent	Irradiation Conditions Method/Temperature/State	Berbine Stereoisomer Ratio (**3**:**4**)
CH_3CN	Direct/20°C/Solution	1:2.4
CH_3CN	Direct/-50°C/Glass	1:1.3
25%CH_2Cl_2-CH_3CN	Direct/-50°C/Solution	1:2.3
CH_3CN	Sensitized/20°C/ Solution	1:4.0
CH_2Cl_2	Direct/20°C/Solution	1:2.5
CH_3OH	Direct/20°C/ Solution	1:1.8
CH_3OH	Direct/-50°C/Solution	1:1.9
CF_3CH_2OH	Direct/20°C/ Solution	1:1.7
CF_3CH_2OH	Sensitized/20°C/ Solution	1:6.0

In contrast, diradical **2** delivered as a triplet in the xanthone sensitized process[9a] can undergo conformer equilibration (**2c**$\rightleftarrows$**2t**) since intersystem crossing is required prior to cyclization. This factor alone can not be responsible for the higher stereoselectivities of the sensitized reactions since it is difficult to see why there would be a greater preference for pre-trans conformer **2t** in the triplet diradical as compared to for **1t** in the starting salt.[9b] However, the enhanced selectivities of the triplet processes might be due to a novel stereoelectronic control of intersystem crossing (ISC) rates. This view finds its origins in the combined results of Scaiano[10a] and Doubleday[10b] which suggest that ISC occurring by the spin orbital coupling mechanism[11] and transforming triplet to singlet diradicals has a rate which is inversely dependent upon the distance between the odd electron centers.[12] In addition, these workers suggest that singlet diradicals produced by ISC undergo bonding faster than conformational relaxation. Model inspection suggests that interaction between the radical centers in triplet diradical conformer **2t** can be greater since the orbital orientation (pseudo axial) required better preserves benzylic and amine stabilization of the α-amino radical center and is consistent with the steric requirements of the side chain benzylic radical. Thus, the preference for formation of **4** in the sensitized reactions might arise from a larger rate for ISC associated with pseudo-axial approach to the tetrahydroisoquinolinyl center in the triplet diradical and rapid bond formation in the singlet diradical thus formed.

Clearly, this proposal requires extensive testing before it can be accepted and used as a predictive method. In any event, it is clear that SET-induced photocyclization reactions which proceed via the intermediacy of diradicals can display useful degrees of stereoselectivity depending upon the multiplicity of the reacting excited state and corresponding diradical intermediates.

Scheme 2.



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(4) (a) Complete synthetic details and spectroscopic characteristics of the substances reported will be given in a full paper on the subject; (b) Racemic phenylalanine, used as starting material in this sequence was coverted to the known tetrahydroisoquinoline ester by the reported method (ref 4c); (c) Dean R. T.; Rapoport, H. *J. Org. Chem.*, **1978**, *43*, 2115.

(5) (a) Stereochemical assignments to **3** and **4** are based upon characteristic ^{1}H- and ^{13}C-NMR spectroscopic data; (b) Isomer **3**:**4** ratios were determined by ^{1}H NMR integration and isolation.

(6) Intramolecular SET in the singlet excited state of **1** should be $\geq$ *ca.* 1 X 10^{10}s^{-1} (ref. 3c) and benzylsilane desilylation rates in MeCN have been estimated to be $\geq$ 5 X 10^{9} s^{-1}(unpublished results).

(7) While to our knowledge no information is available on the rates of singlet diradical cyclization, indirect evidence (ref. 8 and 10) suggests that this process is faster than conformational changes.

(8) Jaffe, A.B; Skinner, K.J.; McBride, J.M., *J. Am. Chem. Soc.*, **1972**, *94*, 8510.

(9) (a)This proposal is based upon the assumption that desilylation is faster than ISC in the intermediate triplet cation diradical; (b) The greater selectivities for the triplet reactions can also be rationalized on the basis of conformational equilibration in the triplet diradical and a large preference for the pre-trans conformer in diradical **2** as compared to in the starting salt **1**.

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