DIASTEREOSELECTIVE SYNTHESIS OF EXO-6-ARYL-3-AZA-BICYCLO[3.2.0]HEPTANE DERIVATIVES BY INTRAMOLECULAR [2+2] PHOTOCYCLOADDITIONS OF DIALLYLIC AMINES

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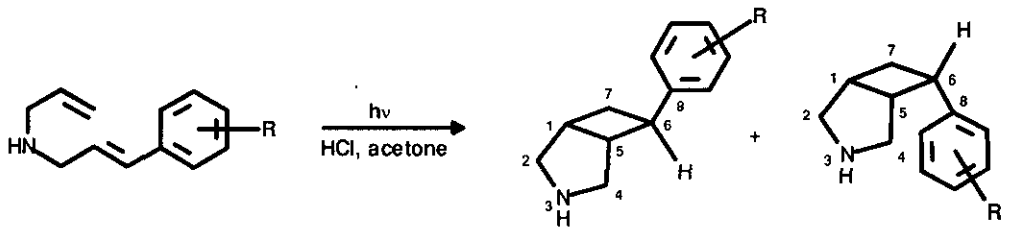
Abstract - *N*-Cinnamyl-*N*-allylamines (**1**) react upon irradiation with UV light *via* a photochemical [2+2] cycloaddition to give new exo-6-aryl-3-azabicyclo[3.2.0]heptanes (**2**) with high diastereoselectivity. A kinetic study as well as semiempirical quantum mechanical calculations support the proposed mechanism

An important structural element of central nervous system (CNS) active compounds is the basic side chain. In most cases, monocyclic amines, such as piperazine and piperidine, are used As part of a synthetic program for the development of new CNS active compounds it was our goal to substitute these conformationally flexible amino building blocks with bicyclic amines. With this in mind we focused our attention on finding a simple and straightforward synthesis of 3-azabicyclo-[3.2.0]heptanes (**2**).

To date, the photochemical [2+2] cycloaddition of allylamines has been studied relatively little,[1,2] whereas the corresponding allyl amides have been utilized more often.[1,3] The mechanism of the [2+2] photocycloaddition of conjugated enones with olefins, and in particular, the 1,4-diradical intermediates which are involved in the reactions have been closely studied.[1,4] In this paper we report the highly diastereoselective synthesis of new exo-aryl substituted 3-azabicyclo[3.2.0]-

heptanes (**2**) *via* intramolecular [2+2] photocycloaddition of substituted *trans*-*N*-cinnamyl-*N*-allyl-amines (**1**).[5]

Scheme 1



1 **2** **3**

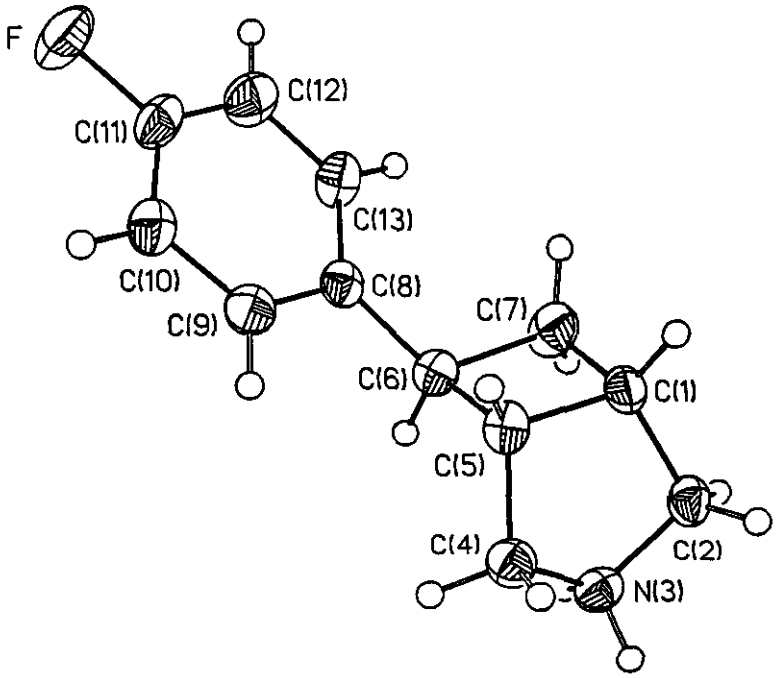
exo-racemate **endo-racemate**

	R	yield(%)	2 : 3 (%)
a	H	89	93 : 7
b	4-F	90	94 : 6
c	4-Cl	92	98 : 2
d	4-NO_2	89	99,5 : 0,5
e	3-Cl	91	96 : 4
f	2-F	90	97 : 3

Uv irradiation of acidified acetone solutions[6] of *trans*-**1** with a 700 W high pressure mercury lamp in a quartz reactor at room temperature produces bicyclic amines (**2**) in good yields (~ 90%) with a very high diastereoselectivity for the exo-aryl isomers (> 93% *via* gc, Scheme 1). The exo amines (**2**) were separated from the endo isomers (**3**) by crystallization with maleic acid. The structure of the free base (**2b**) was assigned from its ^{13}C-nmr spectrum. For comparison purposes, the endo isomer (**3b**) was isolated from the mother liquor by column chromatography and its structure assigned from the ^{13}C-nmr spectrum. The shielding ring current effect of the endo aryl group leads to an upfield shift of C-4 and C-5 signals in **3b** of 5.6 and 5.1 ppm, respectively, relative to **2b**. The bicyclic amines (**2**) and (**3**) form as a racemic mixture, the resolution of **2b** was achieved in the

classic way by chiral salt formation with (-)-2,3-di-*p*-toluoyl-L-tartaric acid to yield (+)-exo-**2b**, the absolute configuration of which was determined by X-ray crystallographic analysis of the HCl salt (Figure 1, Tables 2 and 3). Noteworthy is the essentially complete diastereoselection of the *p*-nitrophenyl substituted diallylamine (**1d**), whereas the unsubstituted cinnamylamine (**1a**) displays the lowest diastereoselectivity (Scheme 1).

Figure 1. Crystal structure of (+)-**2b** x HCl with absolute configurations: C1(S), C5(R) and C6(S).



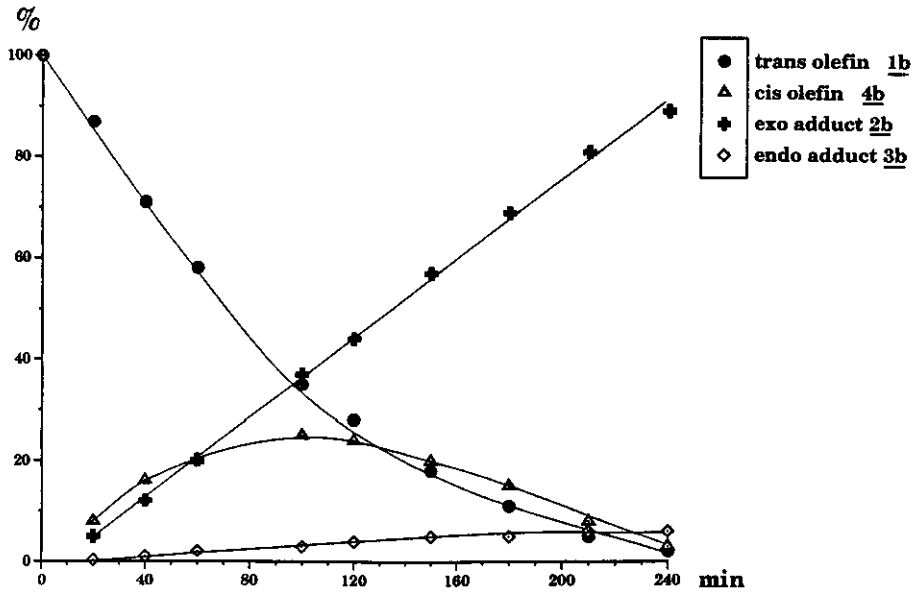
In following the reaction of **1b** *via* gc it was noted that parallel to the [2+2] photocycloaddition reaction a facile *cis/trans* isomerization of the benzylic double bond to **4b** occurs. The kinetics of the photocycloaddition reaction were followed via gc, where Table 1 and Figure 2 summarize the reaction of **1b** (439 mM) in acetone at 18 °C with a 700 W Hg-high pressure lamp. One sees that at *ca.* 50% conversion the remaining trans allylamine (**1b**) has photoisomerized to a ca. 1:1 cis/trans mixture of **1b**:**4b**, whereas the cycloadducts are present as a 90:10 diastereomeric mixture of exo-**2b**:endo-**3b**. During the remainder of the reaction the thermodynamically less

favorable ***cis*-4b** actually predominates ***trans*-1b** from the decay of the triplet biradicaloid intermediate (**5b**) to starting material, a phenomenon which is well known from stilbene photochemistry (Scheme 2).[7] A control experiment, where pure exo cycloadduct (**2b**) was irradiated under the usual reaction conditions, showed that there was no ring opening or exo/endo-isomerization

Table 1

time min	conversion (%) **2b** + **3b**	**2b** : **3b** (%)	**1b** : **4b** (%)
0	0	-	100 : -
20	5	5 : 0.3	87 : 8
40	13	12 : 1	71 : 16
60	22	20 : 2	58 : 20
100	40	37 : 3	35 : 25
120	48	44 : 4	28 : 24
150	62	57 : 5	18 : 20
180	74	69 : 5	11 : 15
210	87	81 : 6	5 : 8
240	95	89 : 6	2 : 3
300	~ 100	94 : 6	0.2 : 0.2

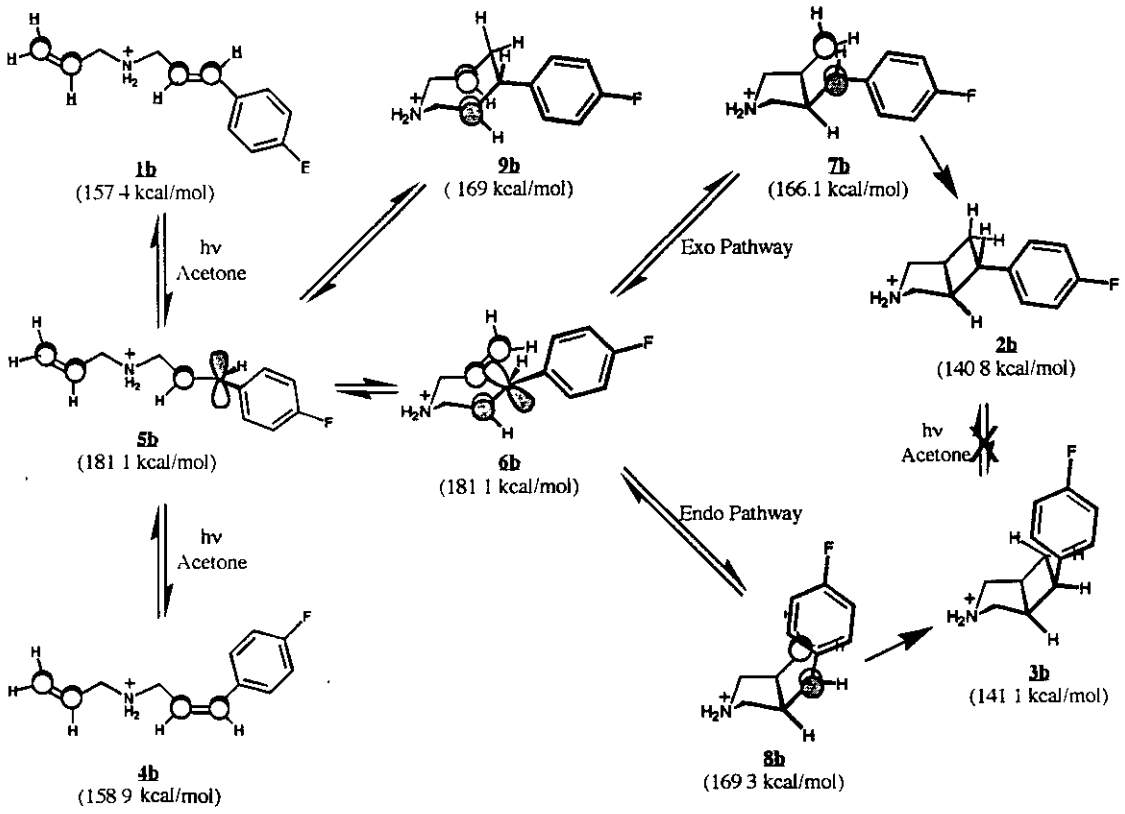
Figure 2



The current experimental facts are consistent with the mechanism shown in Scheme 2, which is analogous to that proposed originally by Corey,[1,8] and is further supported by semiempirical quantum mechanical calculations with the program MOPAC 6.0.[9] All excited state intermediates are assumed to be triplets in the calculations since acetone is an effective triplet sensitizer (E_t = 78 kcal/mol) and the MOPAC results for the first triplet and singlet excited states show that the triplet state is *ca.* 52 kcal/mol lower in energy than the corresponding singlet. Irradiation of **1b** leads to the first excited triplet which has the perpendicular structure (**5b**) which, upon decay to starting material, accounts for the cis/trans isomerization depending on the direction of rotation of the benzylic group. Upon conformational change from **5b** the triplet exciplex (**6b**) undergoes a reversible cyclization reaction to 1,4-biradicaloid triplet species (**7b**) and (**8b**) which go on to close the second ring σ-bond forming exo-**2b** and endo-**3b** respectively. An alternate cyclization of **6b** to the cycloheptyl biradicaloid species (**9b**) has been shown not to occur in conjugated enones.[10] The minimized triplet (**9b**), although comparable in energy to **6b**, does not have the orbitals of the radical centers aligned such that further ring closure reaction to **2b** can occur. The high preference for the exo pathway is a result of unfavorable steric interactions of the aryl group with the terminal methylene of the biradicaloid triplet intermediate (**8b**). This results in favoring the exo pathway by 3.2 kcal/mole. The *cis/trans* equilibration of **1b** to **4b** via **5b** is faster than the irreversible ring closure of **7b** (**8b**) to **2b** (**3b**).

The transition states for the two cyclization steps were also located, optimized and characterized. The transition states for the second cyclization step (**7b** → **2b** and **8b** → **3b**) were found to have an energy difference of 2.85 kcal/mol in favor of the exo pathway. The final product distribution arises from the energy difference between the transition states of the endo and exo pahtways of the final irreversible ring closure step. Assuming that the entropy of the endo and exo transition states are comparable the expected product distribution (K_{eq}) can be estimated from the difference of the calculated heats of formation of the transition state structures from the formula: $\Delta H = RT\ln(K_{eq})$. For an exo/endo energy difference of 2.85 kcal at a reaction temperature of 291 K the expected product distribution is ca. 99 : 1 (exo endo) and is in qualitative agreement with the experimental ratio of 94 : 6 (exo : endo) in that it predicts a high degree of diastereoselectivity for this reaction.

Scheme 2



A caveat to note is that the calculations were carried out in vacuo and do not take into account the important solvent/solute interactions which play an important role in the stabilization of charged structures. The dependence of the reaction rate on the addition of triplet sensitizer as well as the influence of the para phenyl substituents on the diastereoselectivity are currently under investigation.

Experimental

Melting points were determined with a Büchi melting point apparatus and are uncorrected. The ^{13}C-nmr spectra were recorded on a Bruker AC 400 spectrometer at 100 MHz using $CDCl_3$ as the solvent and TMS as the reference. Column chromatography was carried out on neutral silica gel (micon, 70-200 µm). The gc analyses were performed using a Hewlett Packard 5890 with a 10 m OV 1701 column (Macheray-Nagel).

exo- and endo-6-(*p*-Fluorophenyl)-3-azabicyclo[3.2.0]heptanes (2b) and (3b). 365 ml (1.05 mol) of 10 % hydrochloric acid were added to 102.5 g (0.450 mol) of *N*-allyl-*N*-[3-(4-fluorophenyl)allyl]amine (**1b**) x HCl in 1450 ml of acetone The mixture was irradiated under nitrogen with a 700 watt high pressure mercury lamp in a quartz glass apparatus at room temperature for 8 h. The mixture was then made alkaline with 50 % sodium hydroxide solution under cooling with ice and extracted twice with methyl *t*-butyl ether. The combined organic phases were dried over sodium sulfate and evaporated to yield 84.3 g (98 %) of crude **2b** + **3b**.

The crude product mixture was dissolved in 340 ml of isopropanol and a solution of 52.2 g (0.450 mol) of maleic acid in 490 ml of isopropanol was slowly added under stirring. After stirring at room temperature for 18 h the crystals which separated upon cooling were filtered off with suction and washed with isopropanol followed by methyl *t*-butyl ether. A suspension of the crystals in water was prepared and after adjusting to pH 10 with aqueous 50 % sodium hydroxide, the aqueous phase was extracted twice with methyl *t*-butyl ether. The combined organic phases were dried over sodium sulfate and concentrated to yield 70 6 g (82 %) of exo-cycloadduct (**2b**), mp 165-166 °C (maleate).

The isopropanol filtrate was concentrated and the residue was partitioned, after adjusting to pH 10 with aqueous 50 % sodium hydroxide, between methyl *t*-butyl ether and water. The organic phase was dried over sodium sulfate and evaporated to yield 11.5 g of further product mixture. This mixture was separated by column chromatography (silica gel, methylene chloride + 20 % methanol) to yield 6.5 g (7.6 %) of endo-cycloadduct (**3b**) with mp 196-198 °C (tosylate) and further 0.70 g (0.8 %) of exo-cycloadduct (**2b**).

(2b): ^{13}C-Nmr δ 31.9 (C-7), 34.8 (C-1), 41.3 (C-5), 47.2 (C-6), 53.8 (C-4, C-2), 115.1 (C-10, C-12, J_{C-F} = 20.9 Hz), 127.8 (C-9, C-13, J_{C-F} = 7.7 Hz), 142.4 (C-8, J_{C-F} = 3.0 Hz), 161.2 (C-11, J_{C-F} = 243 Hz). *Anal.* Calcd for $C_{12}H_{14}NF$ x $C_4H_4O_4$ (maleate): C, 62.53; H, 5.90; N, 4.56; F, 6.18. Found: C, 62.6; H, 6.1; N, 4.7, F, 6.2.

(3b): ^{13}C-Nmr δ 28.1 (C-7), 35.3 (C-1), 36.3 (C-5), 43 6 (C-6), 48.2 (C-4), 53.5 (C-2), 115.0 (C-10, C-12, J_{C-F} = 21.2 Hz), 128.8 (C-9, C-13, J_{C-F} = 7.7 Hz), 137.1 (C-8; J_{C-F} = 3.0 Hz), 161.1 (C-11, J_{C-F} = 244 Hz). *Anal.* Calcd for $C_{12}H_{14}NF$ x $C_7H_8O_3S$ (tosylate): C, 62.79; H, 6.10; N, 3.85; S, 8.82; F, 5.23. Found: C, 62.6; H, 6.0; N, 3.9; S, 8.7; F, 5.2.

(+)-exo-6-(*p*-Fluorophenyl)-3-azabicyclo[3.2.0]heptane (+) - (2b). The (+)-enantiomer was obtained by adding 52.0 g (0.272 mol) of the exo racemate (**2b**) dissolved in 150 ml of ethanol to a solution of 126.8 g (0 314 mol) of (-)-2,3-di-*p*-toluoyl-L-tartaric acid x H_2O in 1250 ml of boiling ethanol. The crystals (42.0 g) which separated after stirring at boiling temperature for 0.5 h were filtered off with suction, washed with ethanol and recrystallized from 600 ml of n-propanol with the addition of 330 ml of water. Liberation of the free base provided 15.4 g (30 %) of (+)-**2b** with $[\alpha]_D$ = + 97.8° (c = 1.082, EtOH), abs configuration in Fig. 1.

Suitable crystals of (+)-**2b** x HCl ($C_{12}H_{15}NFCl$, formular weight: 227 7) have been obtained from acetone. A specimen of 0.73 x 0.17 x 0 08 mm has been used to determine the cell parameters on a Siemens R3m diffractometer with graphite-monochromatized Cu K_α radiation (1.5418 Å). a: 6.852(1), b: 7.221(1), c: 11.666(2) Å, β = 94.07(1)^0, monoclinic space group $P2_1$, V: 575.8(2) Å^3, ρ = 1.313 Mg/m^3, μ = 2.779 mm^{-1}, Z = 2. Data were recorded at 203 K between Θ 3.5 and 56.1^0 in Θ/2Θ-scan resulting in 1246 observations. Three standard reflections monitored at regular intervals showed no significant variation in intensity during data collection. After correction for Lorentz-, polarization, and background effects and empirical absorption correction (minimal transmission 0.59, ψ-scan, 73 reflections and DIFABS[11]) the averaging of symmetry equivalent refections (R_{int} = 0.033) resulted in 968 unique reflections. The strucutre was solved using direct methods as implemented in SHELXS86.[12] An initial model of the structure could be obtained which finally converged at R_{F^2} = 0.0344, R_{wF^2} = 0.0909 (all data included) using a full-matrix least-squares refinement with SHELXL92.[13] All non-hydrogen atoms were refined using anisotropic atomic displacement parameters. The positions of all hydrogen atoms were found in

subsequent difference Fourier maps and refined in a riding model using isotropic displacement parameters. The largest peaks in the final difference Fourier map were heights of 0.277 and -0.206 eÅ^{-3}. The atomic scattering factors were those stored in SHELXL92. The absolute configuration has been determined according to Flack's absolute structure parameter x (x=0.0006±0.023).[14] The fractional atomic coordinates and equivalent isotropic displacement parameters are given in Tab. 2. Selected molecular dimensions are listed in Tab. 3. In Figure 1, the molecular structure is shown together with ellipsoids scaled to the 50 % probability level. Listings of the fractional coordinates of all atoms, of the atomic displacement parameters and of the observed and calculated structure factors are available as supplementary material.

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [Å^2 x 10^3] for (+)-**2b** x HCl. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Cl	-1855(1)	2237(3)	6011(1)	32(1)
F	3044(3)	1848(5)	-2913(2)	55(1)
C(1)	3860(5)	2912(6)	3344(3)	30(1)
C(2)	3243(5)	2443(8)	4528(3)	31(1)
N(3)	1344(4)	1429(2)	4318(2)	31(1)
C(4)	337(4)	2236(9)	3260(3)	35(1)
C(5)	1986(5)	2734(5)	2509(3)	28(1)
C(6)	2944(5)	1099(6)	1880(3)	28(1)
C(7)	4845(5)	1394(8)	2663(3)	41(1)
C(8)	3020(5)	1311(6)	598(3)	27(1)
C(9)	1319(5)	1761(6)	-70(3)	36(1)
C(10)	1307(5)	1928(7)	-1253(3)	38(1)
C(11)	3033(5)	1678(6)	-1747(3)	35(1)
C(12)	4743(5)	1254(7)	-1135(3)	41(1)
C(13)	4728(5)	1054(7)	45(3)	34(1)

Table 3. Selected molecular dimensions in (+)-**2b** x HCl, bond lengths [Å] and angles [deg]

C(1)-C(7)	1 537(6)	C(2)-C(1)-C(7)	118 3(4)
C(5)-C(6)	1.559(5)	C(4)-C(5)-C(6)	116.5(4)
C(6)-C(7)	1 552(4)	C(2)-C(1)-C(5)	106 3(3)
C(1)-C(2)	1 511(5)	C(4)-C(5)-C(1)	105.8(3)
C(4)-C(5)	1 521(5)	C(7)-C(1)-C(5)	89 5(3)
C(1)-C(5)	1 562(4)	C(7)-C(6)-C(5)	89 0(3)
C(2)-N(3)	1 498(5)	C(1)-C(7)-C(6)	91 2(3)
C(4)-N(3)	1.489(5)		
C(6)-C(8)	1 508(5)		
F-C(11)	1 366(4)		
C(1)-C(5)-C(6)-C(7)	-3.77(0.28)		
C(7)-C(1)-C(5)-C(6)	3 81(0.29)		
C(5)-C(1)-C(7)-C(6)	-3 83(0.29)		
C(5)-C(6)-C(7)-C(1)	3 83(0 29)		
C(5)-C(1)-C(2)-N(3)	18 34(0 42)		
C(1)-C(2)-N(3)-C(4)	-32 95(0 45)		
C(2)-N(3)-C(4)-C(5)	34 20(0 48)		
N(3)-C(4)-C(5)-C(1)	-21 75(0 47)		
C(4)-C(5)-C(1)-C(2)	2 04(0 43)		
C(5)-C(6)-C(8)-C(9)	-51 22(0 46)		

Computational Methodology: Input files for MOPAC 6 0[9] were generated as internal coordinates in the Z-matrix format. All calculations were carried out on an Indigo R-4000 workstation from Silicon Graphics Visualization of results was done with the Program QUANTA from Molecular Simulations, Inc.[15] All structures were optimized with the key words PRECISE, CHARGE=1 and NODIIS using the AM1 Hamiltonian.[16] Excited states were optimized with the additional keywords TRIPLET and UHF. Transition state structures were localized via a reaction path calculation where the energy maxima were optimized with the eigenvector following routine of baker (keyword TS).[17] The optimized transition state structures were characterized by a FORCE calculation where the Hessian matrix displayed a single negative eigenvalue, which is indicative of a saddle point. The vibration corresponding to the negative eigenvalue was viewed graphically to visually confirm that it corresponds to the bond closure vibration. As a final test of the transition states they were perturbed minutely in the direction of reactants and products of the individual steps in the proposed mechanism and the geometry optimized. Each perturbed structure minimized to its expected reactant or product structure

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* Dedicated to Prof. Rolf Huisgen on the occasion of his 75th birthday

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