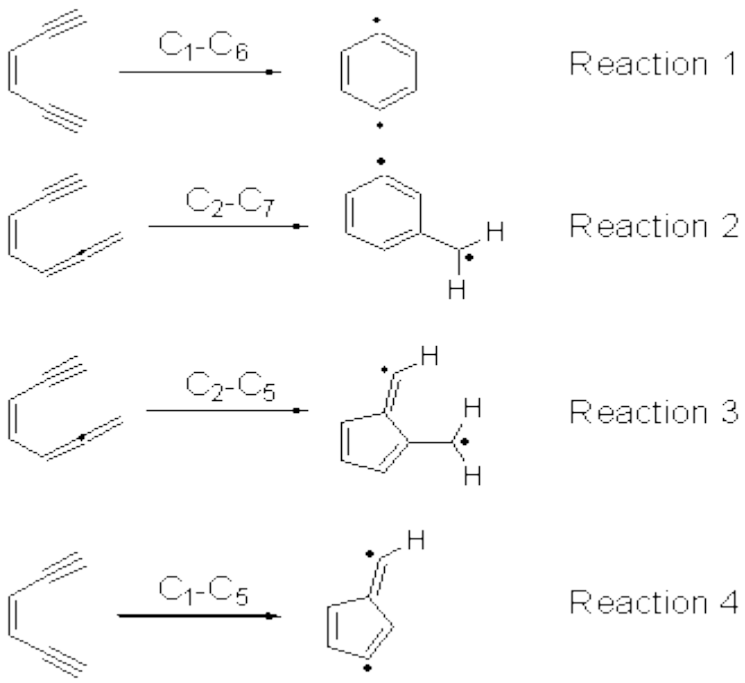
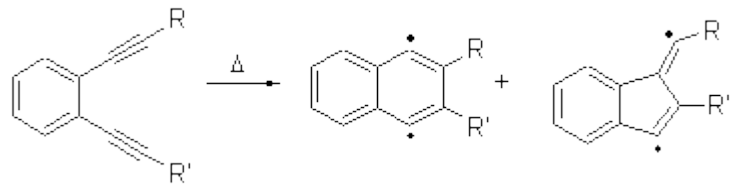
C1-C5 CYCLIZATION OF ENEDIYNES – ALTERNATIVE TO THE BERGMAN REACTION

Cyclization of enediynes is thoroughly discussed in Chapter 3.3 of my book. The reaction that started all the excitement is the C_1-C_6 cyclization (the Bergman cyclization, Reaction 1). Meyers and Saito then proposed the alternative C_2-C_7 cyclization (Reaction 2), and a variant on this, the Schmittel cyclization (Reaction 3) followed soon thereafter. Now, Pascal completes the theme with a report on the C_1-C_5 cyclization (Reaction 4).[1]



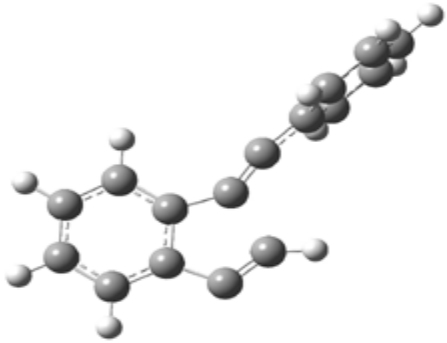
Pascal begins with the assumption that terminal aryl substitution on the enediyne will both (a) inhibit the C_1-C_6 cyclization due to steric interactions and (b) the C_1-C_5 cyclization should be enhanced due to stabilization of the radical by the neighboring aryl group. He computed the activation energies of a series of analogues, some of which are listed in Table 1. The transition state structures are shown in Figure 1 for **1b** and **1c**. Phenyl substitution does accomplish both suggestions: the activation barrier for the Bergman cyclization increases by 4 kcal mol^{-1}, while the barrier for the C_1-C_5 cyclization is lowered by nearly 6 kcal mol^{-1}. Further substitution of the phenyl ring by either chloro or methyl groups brings the barriers into near degeneracy.

Table 1. RBLYP/6-31G(d) Activation energies (kcal mol^{-1}) for competing cyclization reactions of substituted enediynes.[1]

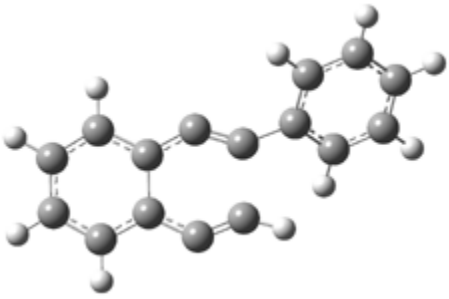


R	R’	$E_a(C_1$-$C_6)$	$E_a(C_1$-$C_5)$
H (**1a)**	H	24.6	37.2
Phenyl (**1b**)	H	28.7	31.4

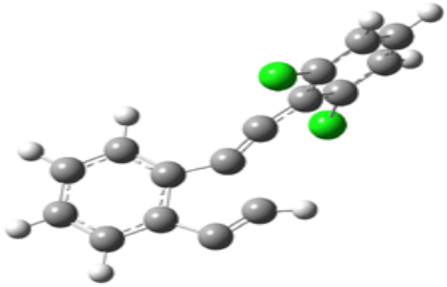
2,6-dichlorophenyl (**1c**)	H	30.8	31.6
2,6-dimethylphenyl (**1d**)	H	30.5	30.9
Phenyl (**2a**)	Phenyl	38.5 (32.9)[a]	36.3 (35.1)[a]
2,4,6-trichlorophenyl (**2b**)	2,4,6-trichlorophenyl	43.2	38.7
[a]Computed at BCCD(T)/cc-pVDZ//-BLYP/6-31G(d).			



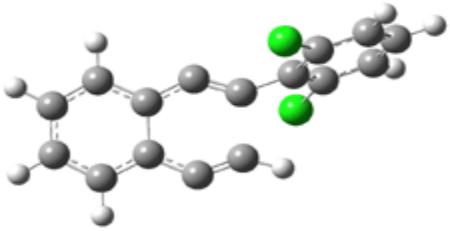
C_1-C_5 TS of **1b**



C_1-C_6 TS of **1b**



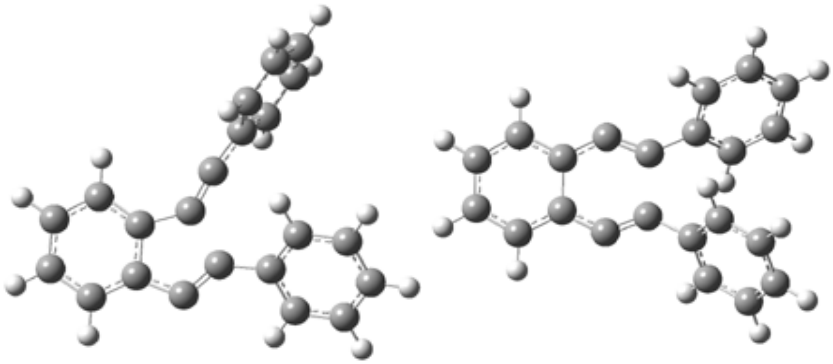
C_1-C_5 TS of **1c**



C_1-C_6 TS of **1c**

Figure 1. RBLYP/6-31G(d) optimized geometries of the C_1-C_5 and C_1-C_6 transition states for **1b**and **1c**.[1]

The di-substituted enediynes were examined next. The C_1-C_5 and C_1-C_6 transition states for the phenyl (**2a**) analogue are shown in Figure 2, and the activation energies for it and the 2,4,6-trichlorophenyl (**2b**) analogue are listed in Table 1. With BLYP, the C_1-C_5 cyclization is favored by a significant amount over the Bergman cyclization. This may be an overestimation as the BCCD(T)/cc-pVDZ//-BLYP/6-31G(d) computations predict the opposite energy ordering.



C_1-C_5 TS of **2a** C_1-C_2 TS of **2a**

Figure 1. RBLYP/6-31G(d) optimized geometries of the C_1-C_5 and C_1-C_6 transition states for **2a**.[1]

Pascal synthesized **2b** and subjected it to thermolysis. Only indenes were obtained, indicative of the C_1-C_5 cyclization occurring in total preference over the C_1-C_6 pathway. The presence of 1,4-cyclohexadiene does improve the yields, suggestive that the transfer hydrogenation mechanism may be operative.

However, when the reaction is done in the absence of 1,4-cyclohexadiene and at lower temperature (180 °C), the C_1-C_5 cyclization is still observed and no Bergman cyclization is seen. It appears that C_1-C_5 cyclization of enediynes is a viable reaction.

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