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# Ring Strain Effects in Enyne-Allene Thermolysis: Switch from the Myers-Saito Reaction to the $C^2$-$C^6$ Biradical Cyclization [1]

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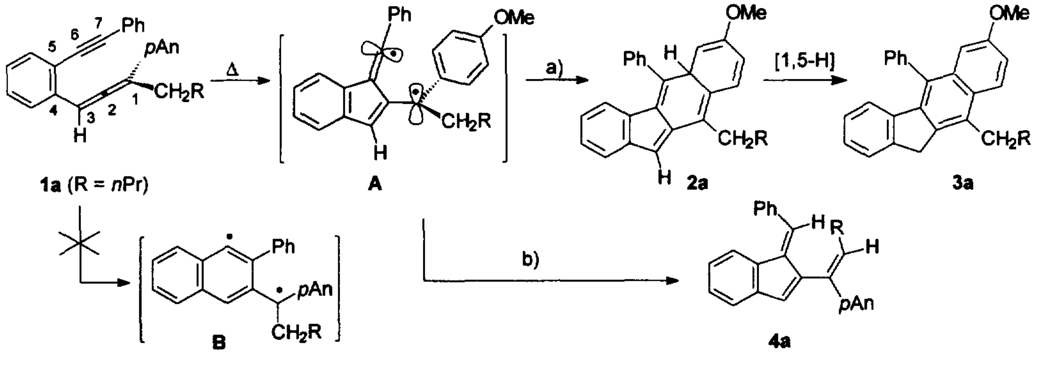
**Abstract :** The mode of the thermal cyclization of enyne-allenes **1** depends on ring strain effects: when the ene functionality is part of a benzene, cyclohexene or cycloheptene ring the novel $C^2$-$C^6$ biradical cyclization is observed, while when it is part of a cyclopentene ring the Myers-Saito cycloaromatization is registered.

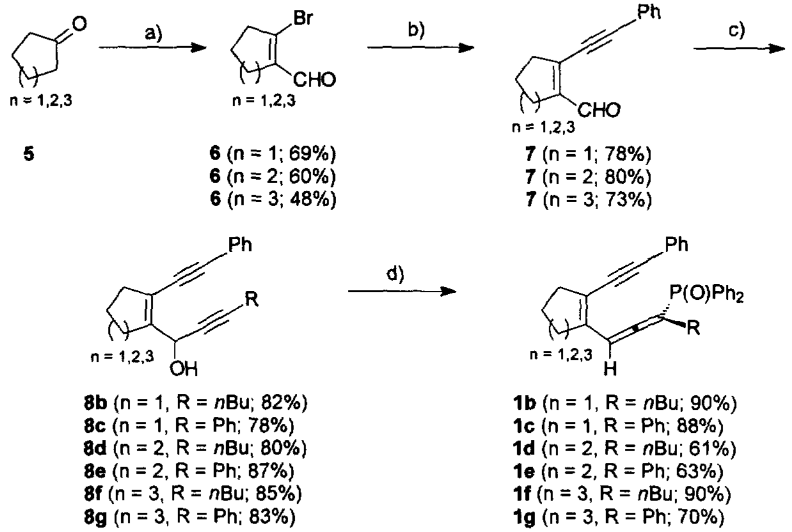
Recent results from our laboratory[2,3] and later from two other groups[4,5] have unambiguously established that the well-known Myers-Saito cycloaromatization[6,7] of enyne-allenes via biradical **B** can be completely replaced by a novel $C^2$-$C^6$ cyclization as soon as aryl groups or sterically demanding substituents are affixed to the acetylene terminus. Mechanistic investigations[8] and DFT calculations[9] indicate that the novel cyclization proceeds via intermediate biradical **A** the vinyl radical center of which is stabilized by the attached phenyl group.[3b] After rapid intramolecular follow-up reactions **A** gives rise to either formal Diels-Alder or ene products. For example, after heating enyne-allene **1a** afforded both $C^2$-$C^6$ cyclization products **3a** and **4a**, with no Myers-Saito cycloaromatization compounds formed via **B**.[10]



**Scheme 1.** a) Formal Diels-Alder reaction via biradical **A**; b) formal ene reaction via biradical **A**.

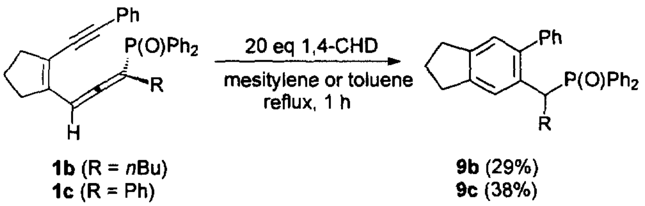
Since the thermal Myers-Saito biradical cyclization has been invoked in a large amount of enyne-allenes with pharmacological activity[6a,7,11] it is of considerable importance to clarify which structural motifs will direct the thermal reaction to either of the two cyclization modes. Herein, we now describe that the switch from the Myers-Saito to the novel $C^2$-$C^6$ cyclization can be brought about solely by *ring strain effects with all other substituents kept identical* as demonstrated by the thermolysis results of the novel enyne-allenes **1b-g**.

After formation of the 1-(2-bromo-1-cycloalkenyl)carboxaldehydes **6** from the corresponding cyclic ketones **5**,[12] subsequent Pd-catalyzed cross coupling of **6** with phenylacetylene furnished aldehydes **7**. Alcohols **8b,c** were prepared by addition of BrMg-C≡C-R to **7**, while alcohols **8d-g** could be afforded after reaction of aldehyde **7** with the appropriate sodium diethyldialkynylaluminates (SDAA).[13] Finally the rearrangement of propargylalcohols **8** with chlorodiphenylphosphine produced enyne-allenes **1b-g** that were isolated and fully characterized.[14]



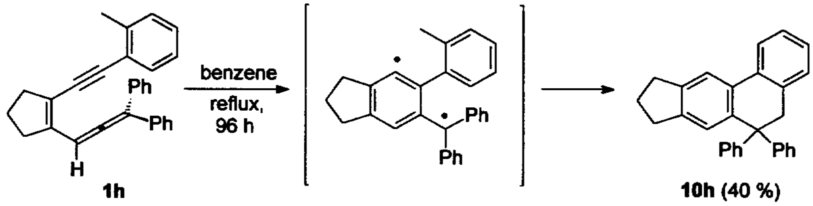
**Scheme 2.** Synthesis of enyne-allenes **1b-g**. a) $PBr_3$, DMF, $CHCl_3$; b) Ph-C≡CH, $Pd(PPh_3)_4$, CuI, $NEt_3$, DMF / $Cl_2Pd(PPh_3)_2$, CuI, $NEt_3$; c) BrMg-C≡C-R, $Et_2O$ / SDAA, toluene; d) $PClPh_2$, $NEt_3$, THF, -80 °C.

After heating in presence of 1,4-cyclohexadiene (1,4-CHD) enyne-allenes **1b,c** furnished the Myers-Saito cyclization products in 29% (**9b**; mesitylene) and 38% (**9c**; toluene) yield despite the presence of a phenyl substituent at the alkyne terminus (*cf.* scheme 1) that was expected to favor biradical **A** over **B**.[3b]



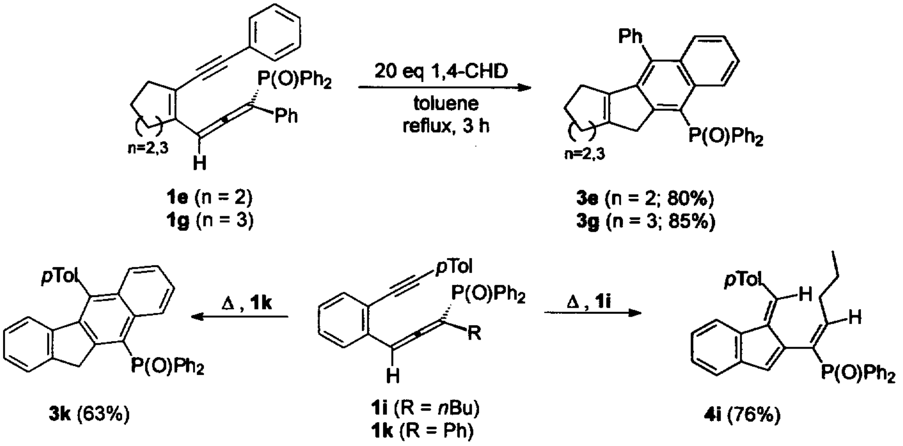
**Scheme 3.** Thermolysis of enyne-allenes **1b,c**.

Importantly, in both thermolyses no $C^2$-$C^6$ cyclization products could be detected, a result reminescent of the thermolysis of another five-membered ring enyne-allene reported by Wang (**10h**).[15]



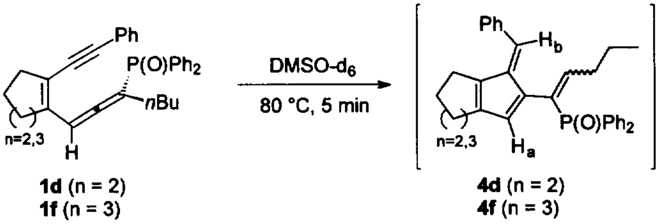
**Scheme 4.** Thermolysis of enyne-allene **1h**.

On the contrary, the thermolysis of the cyclohexene and cycloheptene derived enyne-allenes **1e,g** (3 h, toluene) resulted in the formation of the formal Diels-Alder products in 80% (**3e**) and 85% (**3g**) yield, respectively, in line with earlier results on the thermal rearrangement of benzene derived enyne-allene **1k**.[3a]



**Scheme 5.** Thermolysis of enyne-allenes **1e,g,i,k**.

In analogy, we expected the $C^2$-$C^6$ cyclization of **1d,f** to result in net ene products as such a reaction has been observed for **1a** and **1i**. However, thermolysis of **1d,f** under various conditions (different temperatures, flash pyrolysis) always afforded complex mixtures of products that could not been identified. We hypothesized that vinyl fulvenes **4d,f** are thermally unstable in line with results on simple fulvenes[16] and 1-vinylfulvenes,[17] and consequently followed their reaction by $^1$H-NMR. Indeed, after 5 min (80 °C) signals could be observed indicative of **4d,f** as judged by the known signals of **4i**.[3b] After prolonged heating **4d,f** finally decomposed.

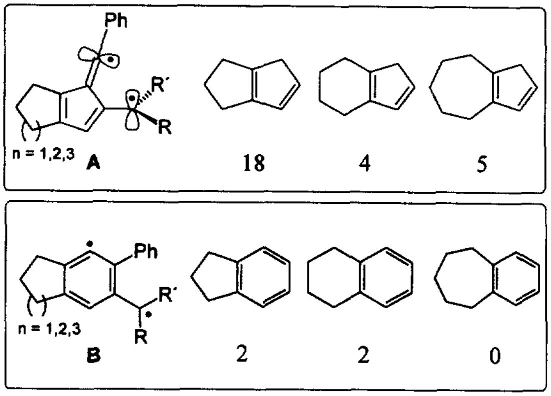


| n | $\delta(H_a)^*$ | $\delta(H_b)$ |
|---|---|---|
| 2 | 5.53 | 6.48 |
| 3 | 5.68 | 6.62 |

*(d, $J_{H\text{-}P}$ = 3.5 Hz)

**Scheme 6.** $C^2$-$C^6$ cyclization of enyne-allenes **1d,f**. Selected $^1$H NMR data of **4d,f** (in ppm).

The present thermolysis results demonstrate that a switch from the Myers-Saito to the novel $C^2$-$C^6$ cyclization can be brought about solely by ring strain effects. When comparing the ring strain in the annulated biradicals **A** and **B** as approximated by simple model compounds, it becomes obvious that the Myers-Saito cyclization is not affected by ring strain energies, while the $C^2$-$C^6$ cyclization is strongly impeded in case of n = 1.



**Scheme 7.** (right) Ring strain energies of simple models of biradicals **A** and **B** (in kcal•mol$^{-1}$).[18]

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