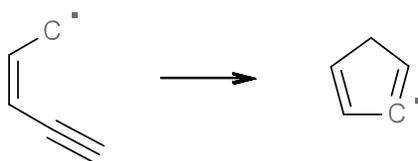


## Engineering a more Energetically Favorable 5-Endo-Dig Radical Cyclization Reaction

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**Figure 1.** An example of the 5-endo-dig cyclization. 5 refers to the number of heavy atoms in the cyclic product. Dig, short for diagonal, describes cyclizations involving additions to triple bonds. Endo specifies the orientation of the double or triple bond relative to the molecule. In the case of dig cyclizations, since the triple bond must be linear relative to its nearest connected bond, these cyclizations are all considered endo.

The 5-endo-dig radical cyclization reactions have been suggested as key reactions in synthesizing heterocyclic molecules as well as in the reaction cascade towards polymerizing enediynes, potent anti-cancer drugs. Using steric effects and aromaticity, we present various engineered reactions intended to increase the favorability of formation of 5-endo-dig radical cyclized products through the lowering of the activation energy barrier and reaction energy of the general 5-endo-dig radical cyclization reaction. Through substitution of the first terminal carbon with various elements, including sulfur, nitrogen and oxygen, we can design an aromatic 5-carbon product and increase stability, thus decreasing both activation and reaction energies. In addition to substitution, simple benzannulation also increases the overall stability of the radical product due to conjugation with the newly added benzene ring. Lastly, we apply para-substitution to the benzene rings to force steric repulsion on the 5-endo-dig reactants. This allows the reactants to look more geometrically similar to their respective transition states effectively lowering the corresponding energy barriers. We have found that combining all of these effects allows us to tune the thermodynamic and kinetic feasibility of the 5-endo-dig radical cyclization. This reaction involves sulfur substitution on the terminal carbon, benzannulation and para-substitution with extremely steric adamantyl groups. Further calculations with these effects applied to the enediyne reactions will be presented.