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Citation:

Polyene Cyclization by a Double Intramolecular Heck Reaction. A DFT Study
David Balcells, Feliu Maseras, Brian A. Keay, and Tom Ziegler
pp 2784 – 2796.

Abstract:

A density functional theory (DFT) model study has been carried out on the cyclization of aryl polyene triflate catalyzed by a Pd(II)-BINAP complex in a Heck type reaction. In the model study, the catalyst was represented by Pd(PH₂(CH)₄PH₂), whereas the aryl polyene triflate substrate was simplified by replacing the dimethoxy naphthalene fragment with hydrogens. Formally, this cyclization reaction consists of an intramolecular Heck reaction with two olefin insertions, also known as a double or cascade Heck reaction. The postulated cationic pathway for aryl triflate substrates has been explored as the reaction mechanism. The study has mainly focused on the two migratory insertion steps, where the identity of the final reaction products is decided. At both steps two distinct insertions may occur: exo, or 1,2-insertion, and endo, or 2,1-insertion. The computation of the possible intermediates and transition states demonstrated that the first insertion is exo-selective, with an energy barrier of only 4.1 kcal/mol, while the second insertion is endo-selective, involving a much higher energy barrier of 22.8 kcal/mol. The calculated subsequent preference for exo and endo selectivity is in good agreement with qualitative experimental observation. According to our results, the main factor controlling the exo/endo selectivity, at both the thermodynamic and the kinetic levels, is the relative stability of the cyclic system resulting from the migratory insertion. Furthermore, a furan ring present in the substrate can play an important role by forming a stable and inert σ -complex that is able to suppress subsequent migratory insertion steps. On the other hand, taking into account the solvent effects using a continuum model, we found that the exo/endo selectivity of the first insertion step is solvent-dependent. As the polarity of the solvent increases, the relative stability of the endo intermediate also increases, in good agreement with the available experimental data. The β -elimination steps affording the final reaction products were also investigated. The results show that the β -elimination on the endo intermediates is thermodynamically favored over the β -elimination on the exo intermediates. On the other hand, the results for the β -elimination on the endo intermediates show that this reaction is highly reversible.

Figures:

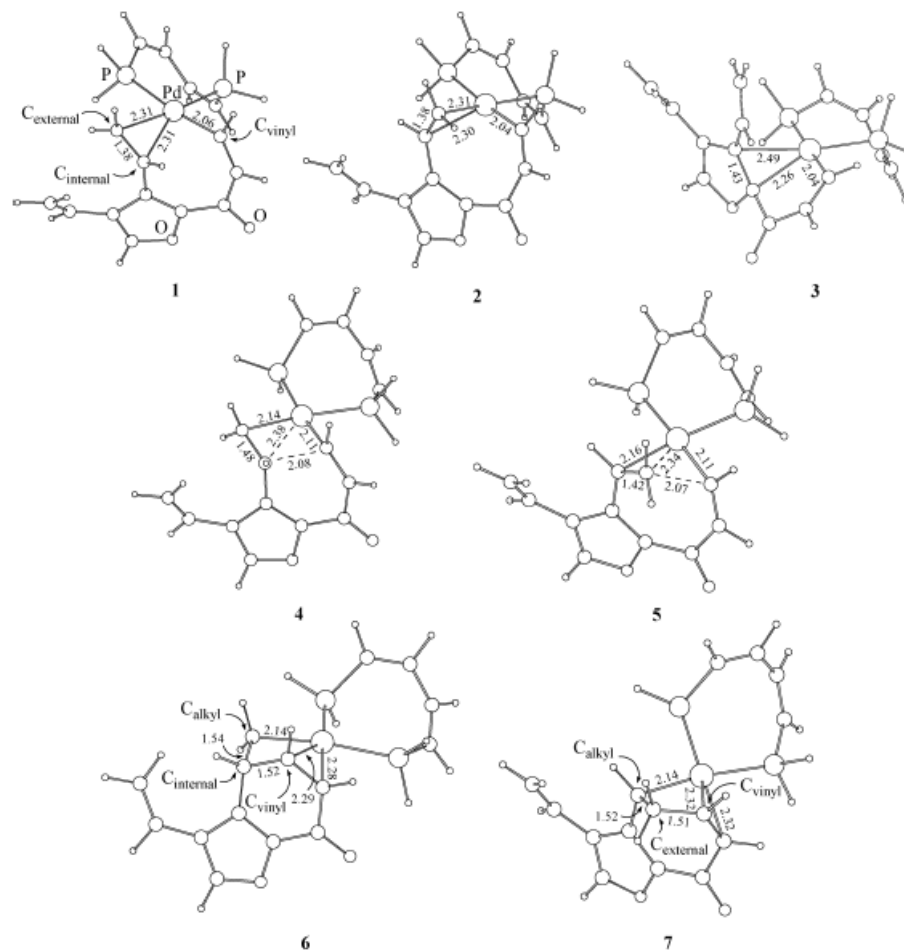


Figure 1. Stationary points located along the first migratory insertion pathway. All the interatomic distances are in Å. The heteroatoms are indicated in complex 1.

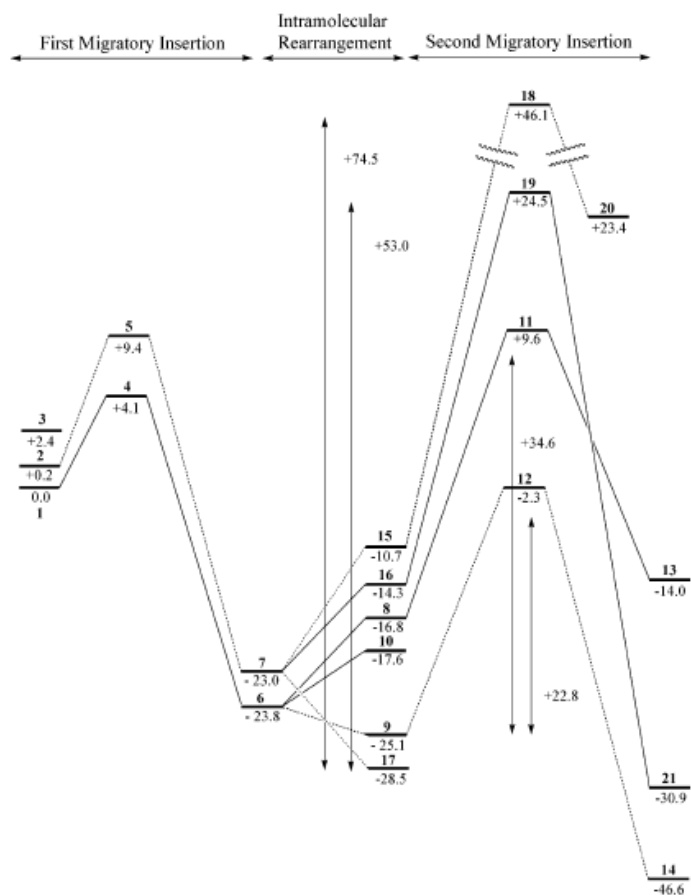


Figure 2. Relative energy profiles for the two sequential olefin insertions. The solid line is for the exo route, while the dotted line is for the endo. All the energies are in kcal/mol.

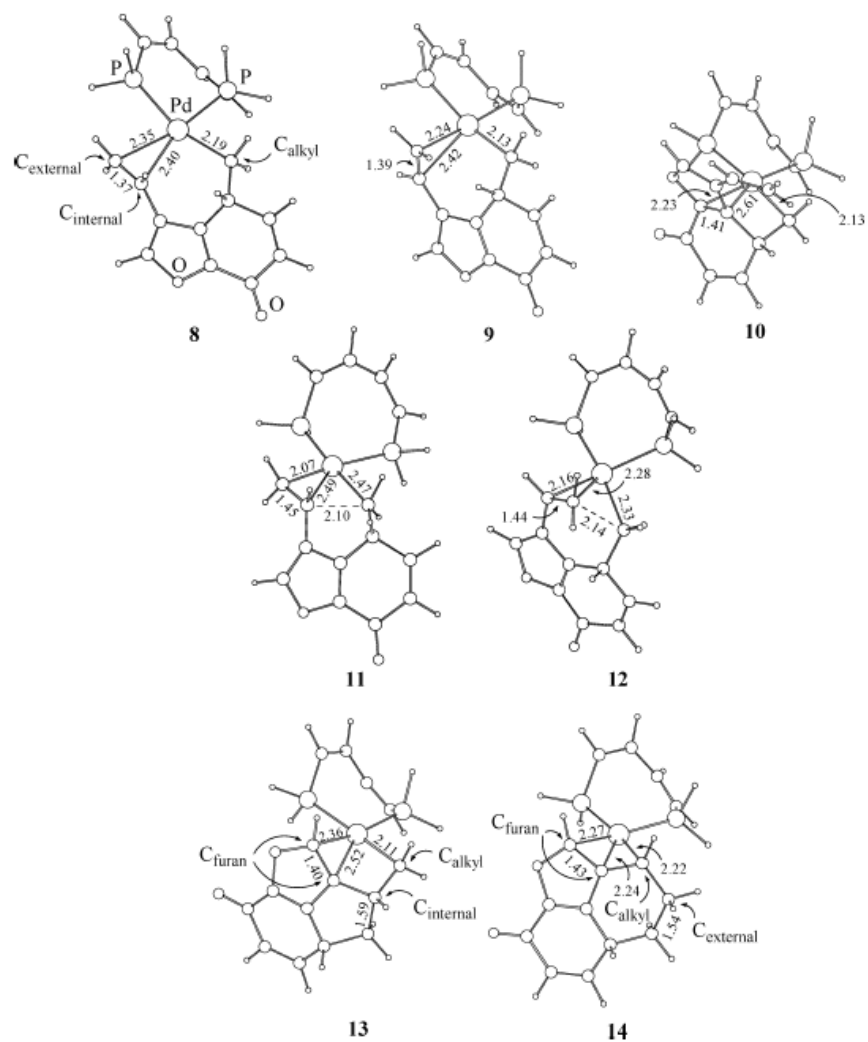


Figure 3. Stationary points involved in the second migratory pathway in the 6-exo intermediate. All the interatomic distances are in Å. The heteroatoms are indicated in complex **8**.

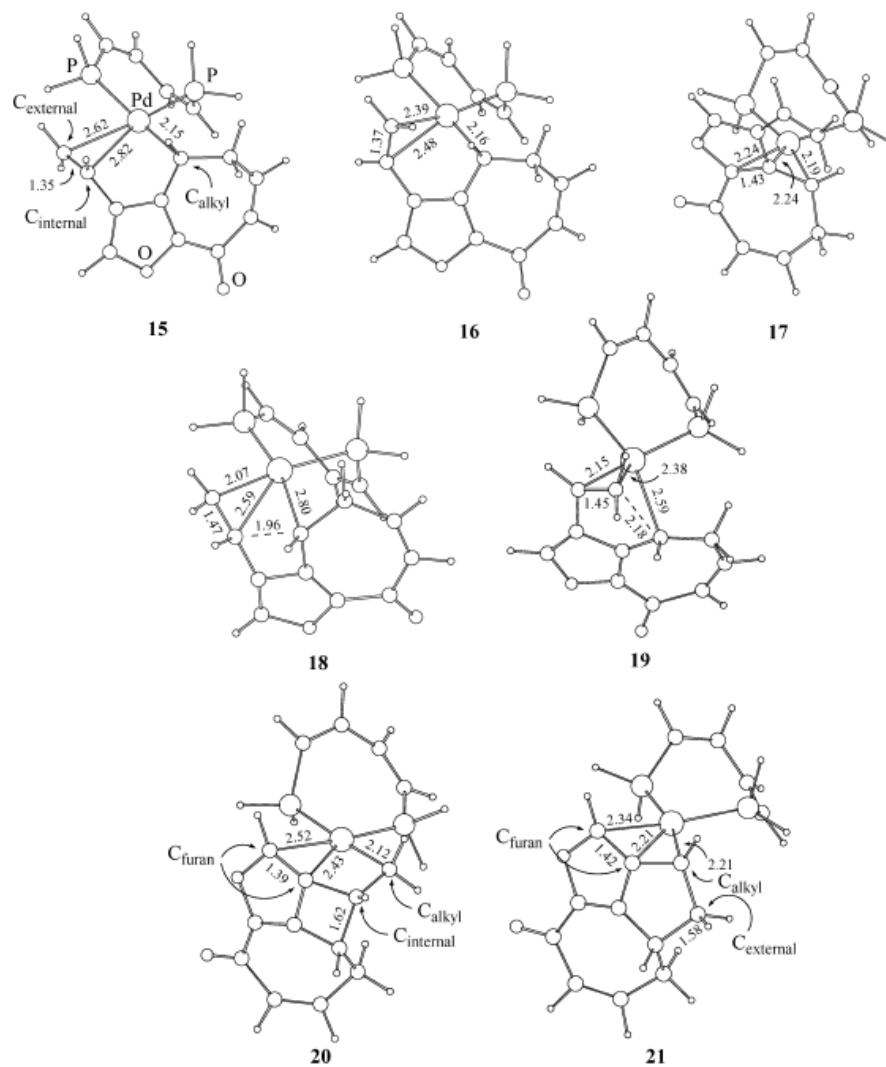


Figure 4. Stationary points involved in the second migratory pathway in the 7-endo intermediate. All the interatomic distances are in Å. The heteroatoms are indicated in complex 15.

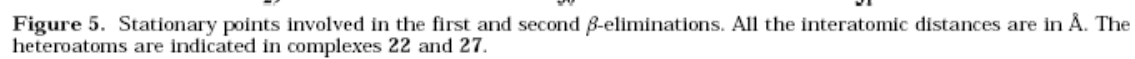


Figure 5. Stationary points involved in the first and second β -eliminations. All the interatomic distances are in Å. The heteroatoms are indicated in complexes **22** and **27**.

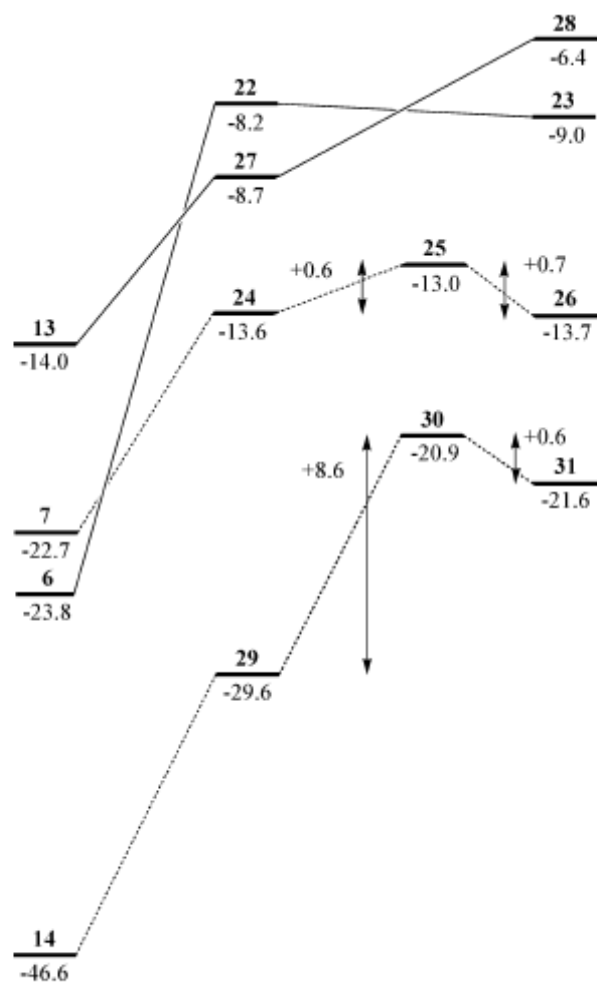


Figure 6. Relative energy profiles for the β -eliminations. The solid line is for the exo route, while the dotted line is for the endo. All the energies are in kcal/mol.

Tables:

Table 1. Relative Energies, in kcal/mol, of the Stationary Points Involved in the First Olefin Insertion

	gas phase	toluene	NMP
1	0.0	0.00	0.0
2	+1.2	+0.2	+0.0
3	+2.7	+2.4	+2.7
4	+4.7	+4.1	+4.5
5	+9.4	+9.4	+10.0
6	-23.2	-23.8	-23.0
7	-22.7	-22.7	-22.4

Table 2. Energies Relative to 1, in kcal/mol, of the Stationary Points Involved in the Second Olefin Insertion

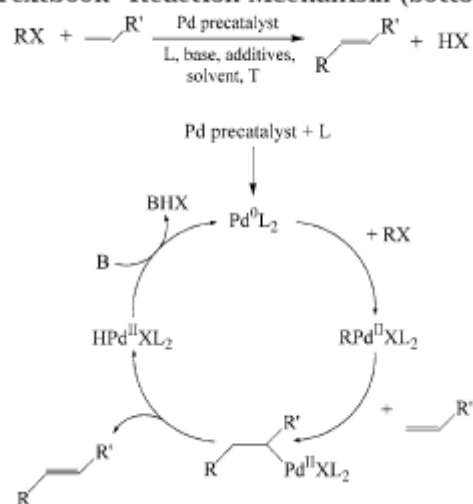
	gas phase	toluene
8	-12.7	-16.8
9	-22.0	-25.1
10	-19.0	-17.6
11	+12.4	+9.6
12	-0.0	-2.3
13	-14.7	-14.0
14	-46.2	-46.6
15	-8.9	-10.7
16	-12.0	-14.3
17	-29.3	-28.5
18	+47.4	+46.1
19	+25.4	+24.5
20	+23.4	+23.4
21	-30.9	-30.9

Table 3. Energies Relative to 1, in kcal/mol, of the Stationary Points Involved in the First and Second β -Eliminations

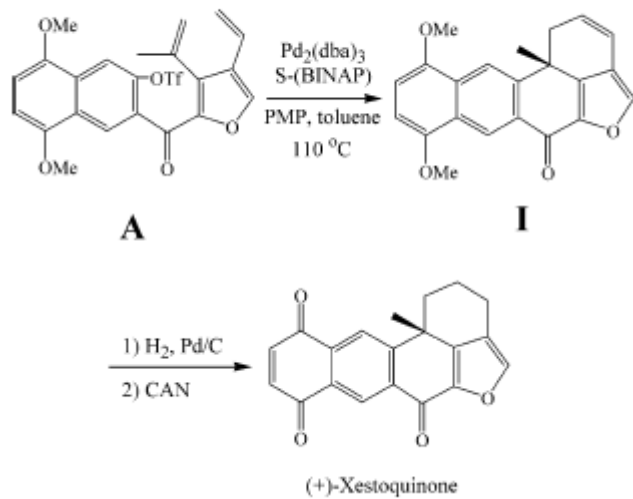
	gas phase	toluene
22	-5.5	-8.2
23	-6.6	-9.0
24	-13.0	-13.6
25	-12.0	-13.0
26	-13.1	-13.7
27	-6.0	-8.7
28	-4.1	-6.4
29	-26.7	-29.6
30	-17.5	-20.9
31	-19.2	-21.6

Schemes:

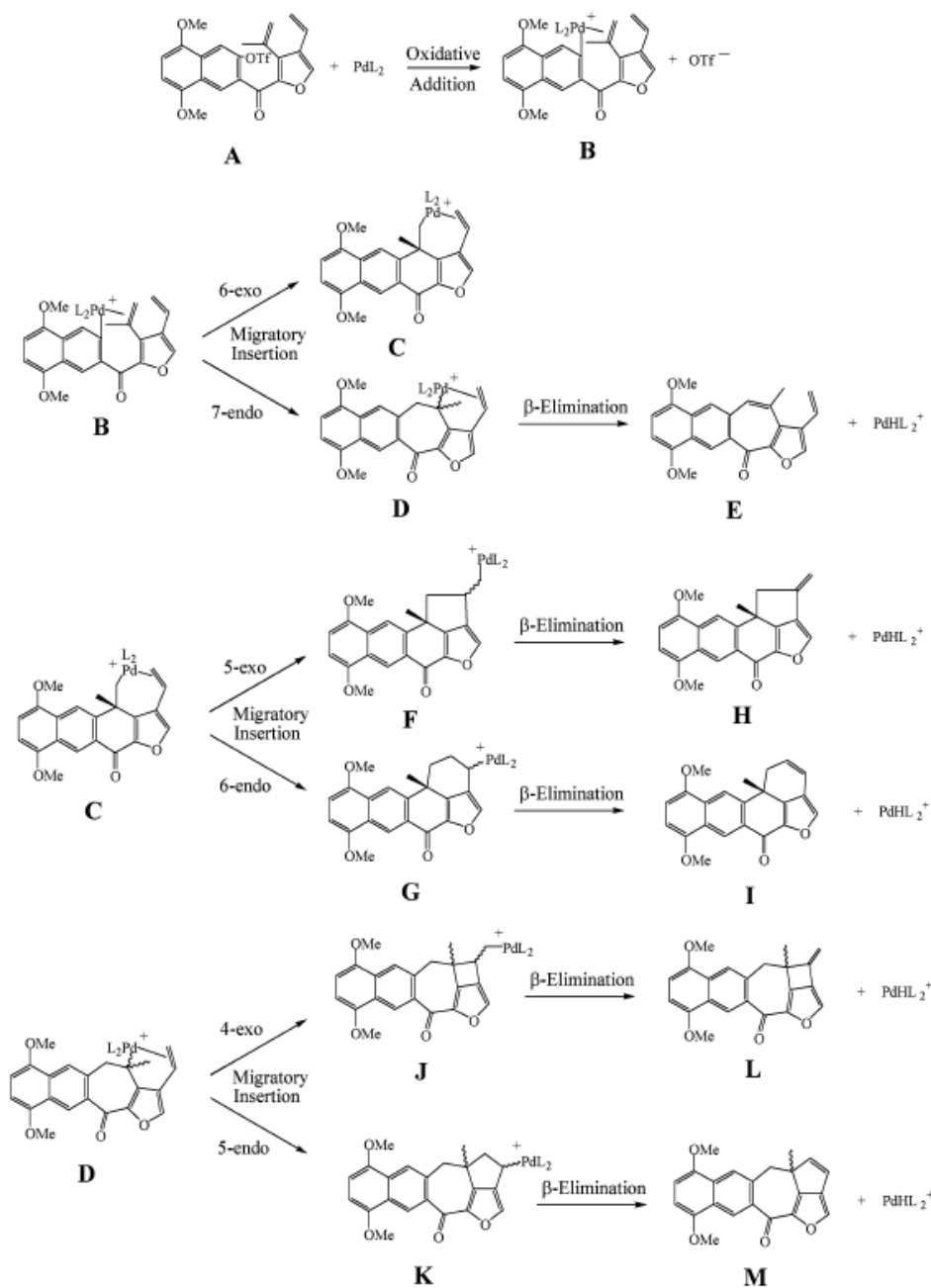
Scheme 1. Heck Reaction (top) and Its "Textbook" Reaction Mechanism (bottom)



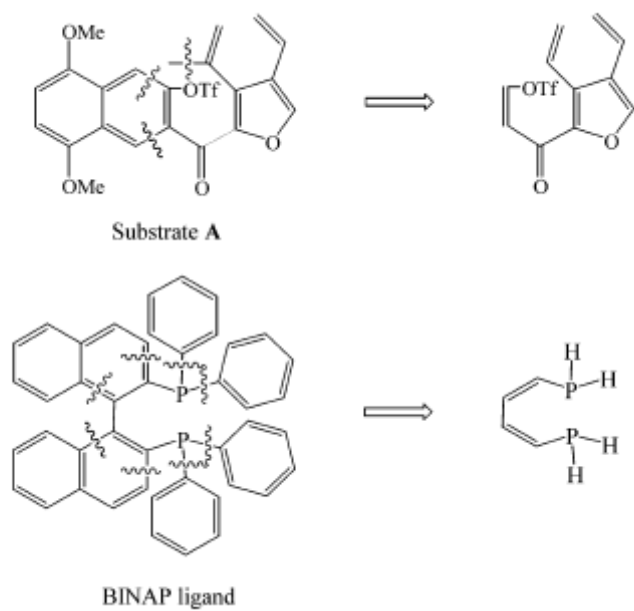
Scheme 2. Last Steps of the Total Synthesis of (+)-Xestoquinone



Scheme 3. Possible Reaction Pathways in the Cationic Double-Insertion Mechanism



Scheme 4. Modelization of the Catalytic System



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