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Functionalized Cyclobutanes via Heck Cyclization

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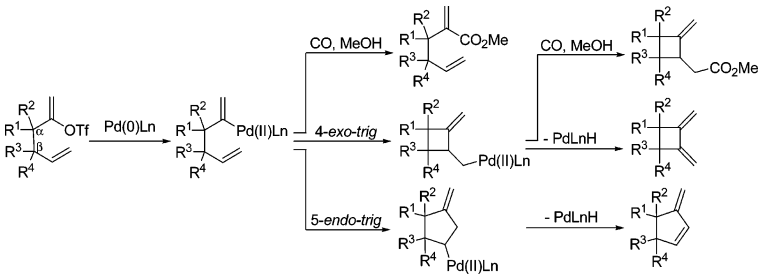
ABSTRACT



Heck-type 4-*exo-trig* cyclization of linear 2-enol triflate-1,5-hexadienes provides functionalized methylene cyclobutanes. Intramolecular palladium coordination can initiate *β*-hydride elimination leading to 1,2-dimethylene cyclobutane derivatives, which are obtained with high selectivity if substrates having a geminal diphenyl group at C_α are used. In parallel, formal 5-*endo-trig* cyclization and *β*-hydride elimination form 1-methylene cyclopent-2-en derivatives.

Intramolecular Heck reactions have become a powerful tool for the construction of cyclic natural products.[1] Thus, the cyclization of 2-halo-1,(*n*-1)-alkadienes and related compounds provides access to ring sizes from three to nine. However, the formation of cyclobutanes through intramolecular Heck reaction has been scarcely observed,[2−5] although the resulting functionalized cyclobutanes would be highly valuable key intermediates in total synthesis.[6] Herein we report novel Heck-type 4-*exo-trig* cyclizations of enol triflates which are accompanied by a variety of competing reactions, depending on the substitution pattern of the substrate and on the conditions applied (Scheme 1, Table 1).[7]

By using substrates with *gem*-disubstituted quaternary carbons, we hoped to increase the tendency toward ring formation according to the well-known Thorpe−Ingold effect. We assume that the reaction starts with an oxidative addition converting **1** into key intermediate **2**. From there, two competing processes **A** and **B** are possible: a 4-*exo-trig* cyclization to form **3** as well as direct carbonylation of **2** to ester **9** (Scheme 1). From cyclobutyl intermediate **3**, three routes can be envisioned: *syn*-palladium hydride

(1) Selected reviews include: (a) Sarlah, D.; Bulger, P. G.; Nicolaou, K. C. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 4442. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (c) Link, J. T. *Org. React.* **2002**, *60*, 157. (d) Bräse, S.; De Meijere, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons, Inc.: New York, 2002; Vol. 1, p 1223. (e) Liu, F.; Liou, S.; Ma, S.; Copéret, C.; Negishi, E. *Chem. Rev.* **1996**, *96*, 365.

(2) (a) Khan, F. A.; Czerwonka, R.; Reissig, H.-U. *Eur. J. Org. Chem.* **2000**, 3607. (b) Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2345. (c) Han, X.; Larock, R. C. *J. Org. Chem.* **1999**, *64*, 1875. (d) Bräse, S. *Synlett* **1999**, 1654. (e) Carpenter, N. E.; Kucera, D. L.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846. (f) Sukirthalingam, S.; Sridharan, V.; Grigg, R. *Tetrahedron Lett.* **1991**, *32*, 3855.

(3) (a) Ang, K. H.; Bräse, S.; Steinig, A. G.; Meyer, F.; Llebaria, A.; Voigt, K.; De Meijere, A. *Tetrahedron* **1996**, *52*, 11503. (b) Narula, C. K.; Mak, K. T.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 2792.

(4) Renaldo, A. F.; Overman, L. E. *J. Am. Chem. Soc.* **1990**, *112*, 3945.

(5) Gajewski, J. J.; Benner, C. W.; Stahly, B. N.; Hall, R. F.; Sato, R. I. *Tetrahedron* **1982**, *38*, 853.

(6) For natural products containing cyclobutanes, see, for example: (a) Wang, Y. H.; Hou, A. J.; Chen, D. F.; Weiller, M.; Wendel, A.; Staples, R. J. *Eur. J. Org. Chem.* **2006**, *15*, 3457. (b) Snider, B. B.; Lu, Q. *Synth. Commun.* **1997**, *27*, 1583. (c) Okauchi, T.; Kakiuchi, T.; Kitamura, N.; Utsunomiya, T.; Ichikawa, J.; Minami, T. *J. Org. Chem.* **1997**, *62*, 8419. (d) Jefferies, P. R.; Worth, G. K. *Tetrahedron* **1973**, *29*, 903.

(7) Enol triflates were prepared in a five- (compounds **1a**−**1g**) or six-step (compounds **1h** and **1i**) sequence using standard chemical methods. Details on the experimental procedures are given in the Supporting Information.

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Scheme 1. Selected Pathways for Palladium-Mediated Formation of Cyclobutanes in the Presence of Carbon Monoxide

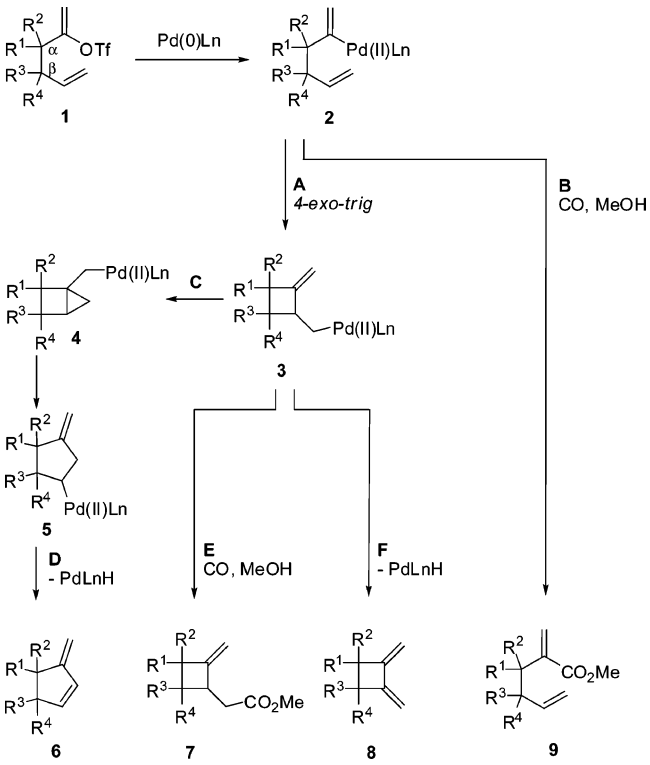
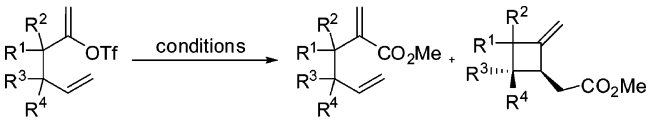


Table 1. Product Distribution for Enol Triflates **1a**−**1e**



1a-e **9a-e** **7a-e**

substrate		condn[a]	products[b]	
1a	R^1, R^2, R^3 = Me, R^4 = H	I	**9a** (60%)	**7a** (5%)
		II	**9a** (9%)	**7a** (56%)
		III	**9a** (3%)	**7a** (65%)
1b	R^1, R^2 = Me, R^3 = Et, R^4 = H	III	-	**7b** (60%)
1c	R^1, R^2 = Me, R^3 = *i*-Pr, R^4 = H	III	-	**7c** (65%)
1d	R^1 = OBn, R^2 = H, R^3, R^4 = Me	III	**9d** (75%)	-
1e	R^1, R^3, R^4 = Me, R^2 = H	III	**9e** (70%)	-

[a] Conditions I: 1 equiv of substrate in a 0.06 M solution, MeOH/DMF (2:1), 0.1 equiv of $Pd(PPh_3)_2Cl_2$, 3.2 equiv of NEt_3, CO atmosphere, 50 °C, 18 h. II: 1 equiv of substrate in a 0.06 M solution, MeOH/DMF (2:1), 0.1 equiv of $Pd(PPh_3)_2Cl_2$, 0.2 equiv of PPh_3, 3.2 equiv of NEt_3, CO atmosphere, 50 °C, 18 h. III: 1 equiv of substrate in a 0.06 M solution, MeOH/DMF (2:1), 0.1 equiv of $Pd(PPh_3)_4$, 3.2 equiv of NEt_3, CO atmosphere, 50 °C, 2−18 h. [b] Percentage refers to yield of isolated product.

elimination (pathway **F**) to produce 1,2-dimethylene cyclobutane (**8**) or, alternatively carbonylation to generate cyclobutane ester **7** (pathway **E**). Cyclopropane formation followed by homoallyl rearrangement[8] can provide the formal 5-*endo-trig* product[9] (pathway **C/D**). Alternatively, a direct conversion of **2** into **5** cannot be excluded.

The competition between pathways **A** and **B** was studied first (Table 1). Thus, when subjecting **1a** to conditions I, the acyclic ester **9a** is the main product. Only negligible amounts of the cyclization product **7a** are found. Addition of PPh_3 (conditions II) strongly increases the product ratio in favor of **7a**. These phosphine ligands obviously promote the intramolecular Heck reaction, and in fact, when using $Pd(PPh_3)_4$ as the only catalyst (conditions III), cyclobutane ester **7a** is formed in 65% yield with d.e. > 98%.[10] Apparently, these are the best conditions determined for the tandem Heck cyclization carbonylation pathway **A/E**.[11] It is noteworthy that this is the first example providing methylenecyclobutylacetates through such a cascade. Interestingly, no products formed from the reverse order of transformations, i.e., first carbonyl insertion then cyclization, were observed.[9b] Performing the reaction of **1a** in the absence of CO leads to an inseparable mixture of compounds **6a** and **8a** (1:1) via β-hydride elimination from intermediates **3a** and **4a**, respectively (pathways **C/D** and **F**). For enol triflate **1a**, bidentate ligands such as diphenylphosphinoferrocene (dppf) and 1,2-bis(diphenylphosphino)ethane (dppe) were also tried. Dppf did not react at all, and for dppe the results were the same as those for PPh_3, with or without the addition of CO.

Under conditions III, **1b** and **1c** are smoothly converted into **7b**,**c** (d.e. > 98%). No acyclic esters **9b**,**c** are formed. Both **1b** and **1c** have an alkyl substituent at C_β and two geminal methyl groups at C_α. The position of the methyl groups is crucial for the cyclization, which obviously fails if there is only one substituent at C_α. Thus, **1d** and **1e**, which carry two methyl groups at C_β and only one substituent at C_α, furnish acyclic esters **9d** and **9e** exclusively. A possible rationalization lies in the conformational effect exerted by the bulky palladium substituent. For **1d**,**e**, the corresponding organopalladium intermediate **2d**,**e** will adopt conformation **10** to avoid steric interference with substituent R^4. Hence, Pd addition to the second olefin is inhibited, and ester **9** is formed. For **1b**,**c**, conformer **11** should be favored to avoid

(8) For related formation of formal 6-*endo* products see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (b) Owczarczyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E. *J. Am. Chem. Soc.* **1992**, *114*, 10091.

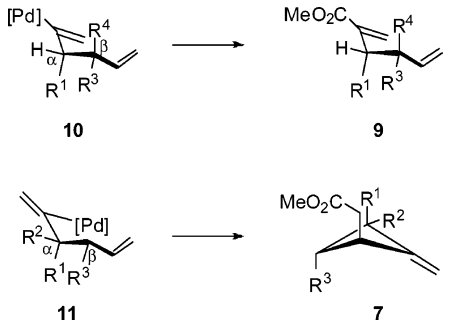
(9) For other examples of formal 5-*endo trig* Heck cyclizations, see: (a) Vital, P.; Norrby, P. O.; Tanner, D. *Synlett* **2006**, 3140. (b) Sakoda, K.; Mihara, J.; Ichikawa, J. *Chem. Commun.* **2005**, 4684. (c) Ackermann, L.; Kaspar, L. T.; Geschrei, C. J. *Chem. Commun.* **2004**, 2824. (d) Watanabe, T.; Arai, S.; Nishida, A. *Synlett* **2004**, 907. (e) Chen, C.; Lieberman, D. R.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 2676. (f) O'Connor, B.; Zhang, Y.; Negishi, E. *Tetrahedron Lett.* **1988**, *29*, 3903.

(10) Stereochemical assignment was confirmed by NOESY experiments. See Supporting Information.

(11) For tandem carbopalladation of alkenes terminated by carbonylation, see: (a) Copéret, C.; Negishi, E. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons, Inc.: New York, 2002; Vol. 1, p 1431 and references therein. (b) Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65.

Pd−R^2 repulsions. This facilitates Pd addition to the double bond and therefore results in the formation of **7** (Scheme 2).

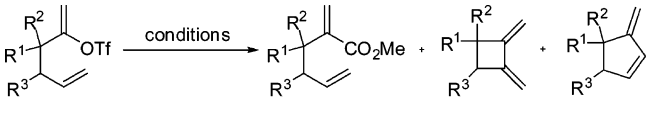
Scheme 2. Conformation of the Acyclic Pd Intermediates Optimal for Heck Cyclization and Premature Trapping with CO, Respectively



To extend the lifetime of intermediate **3**, we decided to examine substrates in which electron-donating substituents might stabilize the palladium species via complexation and, hence, retard or inhibit the insertion of CO. In fact, the presence of an ether group at C_α or C_β (Table 2, **1f** and **1g**) leads to a competition among pathways **B**, **C/D**, and **F**. Under conditions III, the acyclic esters (**9f** and **9g**) are obtained in substantial amounts; however, no CO insertion occurs at the stage of intermediate **4**. Instead, the 1,2-dimethylene cyclobutanes **8f** (1:1 diastereomeric mixture) and **8g** are generated via β-hydride elimination. In the absence of CO (conditions IV), the dimethylene cyclobutanes (**8f**−**i**) are the main products. Remarkably, under conditions III and IV, **1f** and **1g** also form the formal 5-*endo* cyclization products **6f** and **6g** in appreciable amounts. However, despite the quaternary center at C_α, no 1,2-migration of the alkenyl palladium intermediate **2** was observed.[12]

Possibly, in these cases, palladium intermediate **3** does not coordinate with CO, which may be rationalized by an intramolecular coordination of the oxygen atom to palladium.[13] Thus Pd species such as **12** or **13** may be formed, in which complexation of CO to the metal center is disfavored (Figure 1). Enol triflates (**1h** and **1i**) with two geminal phenyl groups at C_α exclusively react to 1,2-dimethylene-cyclobutanes **8h** and **8i** (Table 2), in the presence or absence of CO. A presumptive intermediate is **14** in which, as in **12** and **13**, palladium coordination to one of the phenyl groups prevents CO complexation.

Table 2. Product Distribution for Enol Triflates **1f**−**1i**



substrate		condn[a]	products[b]		
1f	R^1, R^3 = Me, R^2 = OPMB	III	**9f**[c] (22%)	**8f**[c] (15%)	**6f**[c] (25%)
		IV	–	**8f**[c] (25%)	**6f**[c] (35%)
1g	R^1, R^2 = Me, R^3 = OMe	III	**9g**[c] (22%)	**8g**[c] (20%)	**6g**[c] (17%)
		IV	–	**8g** (30%)	**6g** (30%)
1h	R^1, R^2 = Ph, R^3 = Me	III		**8h** (70%)	
		IV	–	**8h** (87%)	
1i	R^1, R^2 = Ph, R^3 = *i*-Pr	IV	–	**8i** (75%)	

[a] Conditions III: see Table 1. Conditions IV: 1 equiv of substrate in a 0.06 M solution, MeOH/DMF (2:1), 0.1 equiv of $Pd(PPh_3)_4$, 3.2 equiv of NEt_3, argon atmosphere, 50 °C, 2−18 h. [b] Unless stated otherwise, percentage refers to yield of isolated product. [c] Yield determined by ^1H NMR.

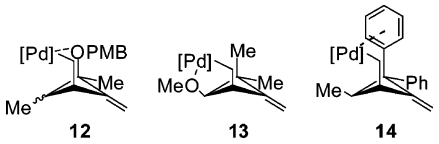
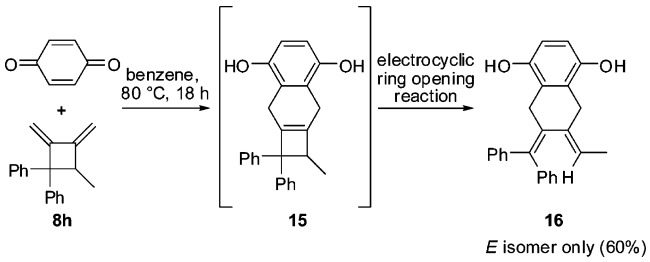


Figure 1. Intramolecular palladium coordinations of (a) **1f**, (b) **1g**, and (c) **1h** leading to β-elimination and formation of 1,2-dimethylene cyclobutanes.

Scheme 3. Cycloaddition−Electrocyclic Ring-Opening Cascade



A cascade reaction occurred to produce **16** as the only product. Obviously, the primary Diels−Alder adduct **15** has undergone an electrocyclic ring opening.

(12) (a) Ebran, J. P.; Hansen, A. L.; Gøgsig, T. M.; Skrydstrup, T. *J. Am. Chem. Soc.* **2007**, *129*, 6391. (b) Hansen, A. L.; Ebran, J. P.; Ahlquist, M.; Norrby, P.-O.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3349.

(13) Review: (a) Oestreich, M. *Eur. J. Org. Chem* **2005**, 783. (b) Jeong, S.; Chen, X.; Harran, P. G. *J. Org. Chem.* **1998**, *63*, 8640.

In conclusion, we have explored the vinyl triflate **1**/Heck-type reaction manifold. All the reactions suggested in Scheme 1 have been detected, and in some cases there is considerable selectivity in favor of one pathway. Specifically, the formation of cyclobutane esters **7** and 1,2-dimethylene cyclobutanes **8** may be of particular synthetic value. To explain the different reaction pathways for individual substrates, detailed mechanistic investigations are currently being undertaken and will be reported in due course.

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Supporting Information Available: Experimental procedures and NMR spectra for all new compounds provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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