

Functionalized Cyclobutanes via Heck
Cyclization

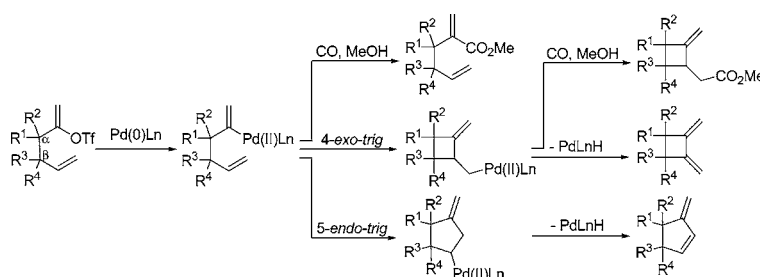
Anna Innitzer, Lothar Brecker, and Johann Mulzer*

Institut für Organische Chemie der Universität Wien, Währingerstrasse 38,
1090 Wien, Austria

johann.mulzer@univie.ac.at

Received July 18, 2007

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 $_{\alpha}$ 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.

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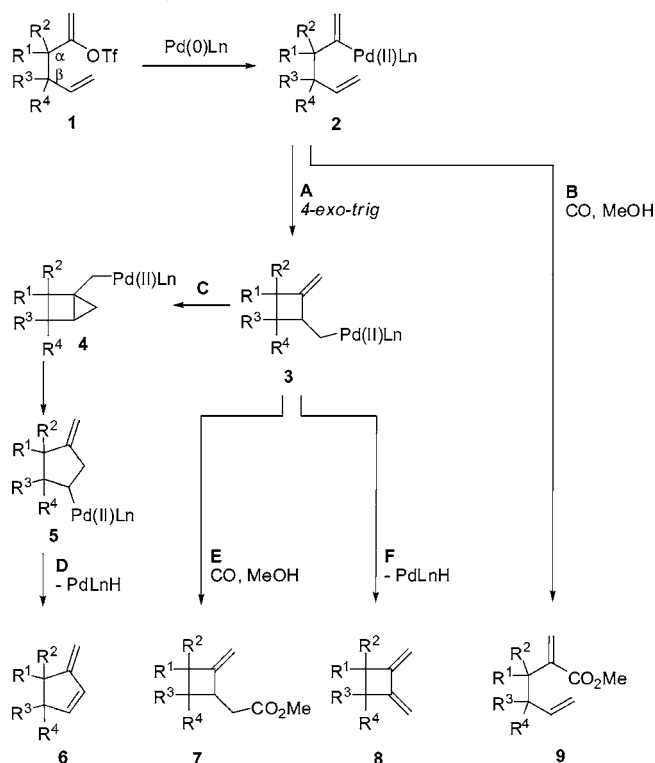
(4) Renaldo, A. F.; Overman, L. E. *J. Am. Chem. Soc.* **1990**, *112*, 3945.

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(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.

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



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 rearrangement⁸ can provide the formal 5-*endo-trig* product⁹ (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 PPh₃ (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(PPh₃)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 methyl-enecyclobutylacetates through such a cascade. Interestingly,

(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.

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

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

^a Conditions I: 1 equiv of substrate in a 0.06 M solution, MeOH/DMF (2:1), 0.1 equiv of Pd(PPh₃)₂Cl₂, 3.2 equiv of NEt₃, 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(PPh₃)₂Cl₂, 0.2 equiv of PPh₃, 3.2 equiv of NEt₃, 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(PPh₃)₄, 3.2 equiv of NEt₃, CO atmosphere, 50 °C, 2–18 h. ^b Percentage refers to yield of isolated product.

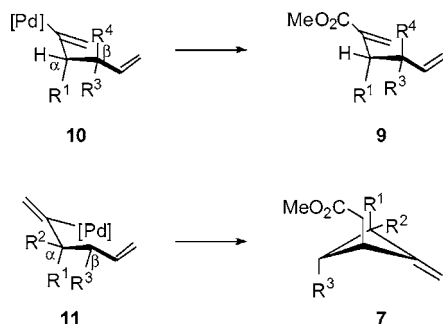
no products formed from the reverse order of transformations, i.e., first carbonyl insertion then cyclization, were observed.^{9b} Performing the reaction of **1a** in the absence of CO leads to an inseparable mixture of compounds **6a** and **8a** (1:1) via β -hydride elimination from intermediates **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 PPh₃, 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 R⁴. Hence, Pd addition to the second olefin is inhibited, and ester **9** is formed. For **1b,c**, conformer **11** should be favored to avoid

(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–R² 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**)

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

substrate		condn ^a	products ^b		
1f–i			9f–i	8f–i	6f–i
1f	R ¹ , R ³ = Me, R ² = OPMB	III	9f (22%)	8f (15%)	6f (25%)
		IV	–	8f (25%)	6f (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>i</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(PPh₃)₄, 3.2 equiv of NEt₃, argon atmosphere, 50 °C, 2–18 h. ^b Unless stated otherwise, percentage refers to yield of isolated product. ^c Yield determined by ¹H NMR.

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

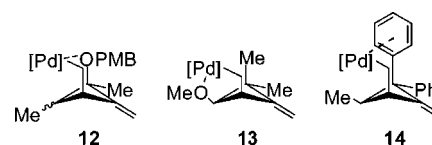
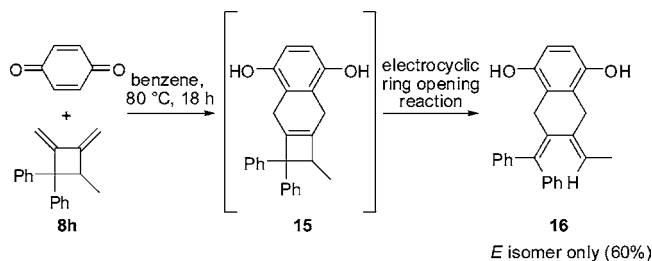


Figure 1. Intramolecular palladium coordinations of (a) **1f**, (b) **1g**, and (c) **1h** leading to β-elimination and formation of 1,2-dimethylene cyclobutanes.

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.

The 1,2-dimethylene cyclobutanes **8** are suitable substrates for Diels–Alder reactions. As an example, compound **8h** was treated with benzoquinone as a dienophile (Scheme 3).

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.

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(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.

Acknowledgment. The authors thank Susanne Felsinger (University of Vienna) for NMR. Robert Saf (TU Graz) is thanked for mass spectrometry.

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>.

OL701697R