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[20] a) Reaction of **5g** with $TsOH \cdot H_2O$ (10 mol%) as the catalyst in THF at 23 °C afforded **9** in 52% yield; b) cyclization to form an indole was also observed with **5f** ($Yb(OTf)_3$ catalyst). Details of this cyclization will be published elsewhere.
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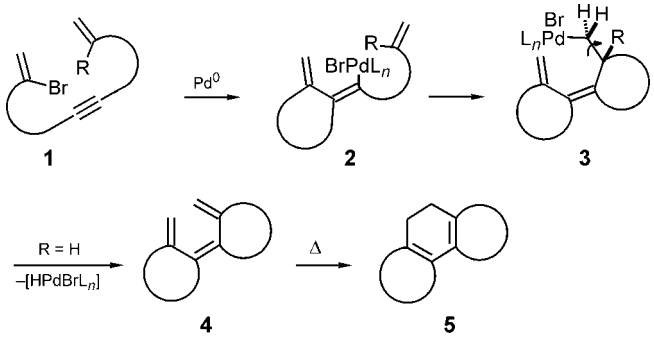
Two New Modes of Pd-Catalyzed Domino-Tetracyclization of Bromodienynes—5-*exo-trig* Cyclization Wins over β-Hydride Elimination**

Stefan Schweizer, Zhi-Zhong Song, Frank E. Meyer, Philip J. Parsons, and Armin de Meijere*

Dedicated to Professor Heinz Georg Wagner on the occasion of his 70th birthday

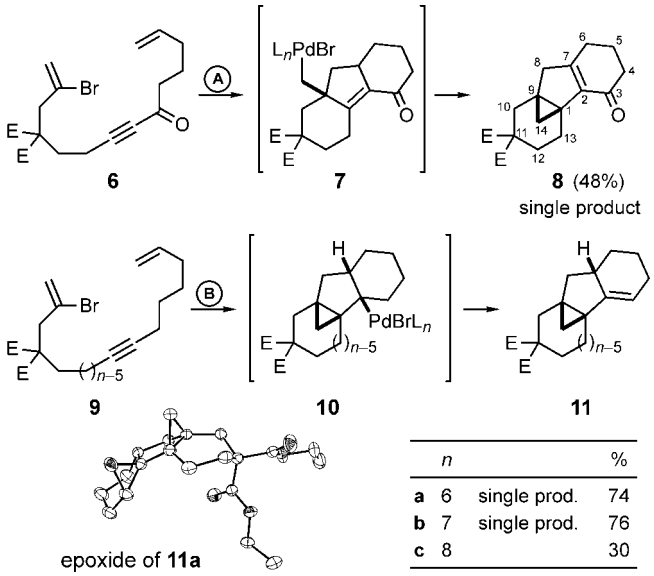
Multistep sequential transformations—domino[1] or cascade[2] reactions—which permit remarkable increases in molecular complexity in a single synthetic operation are gaining steadily increasing importance for the construction of complex organic molecules.[1–3] Among them, a variety of transition metal and in particular palladium-catalyzed multistep cascades are especially noteworthy in terms of atom economy, stereocontrol, and overall efficiency.[4, 5] As we have previously demonstrated, 2-bromododeca-1,11-diene-6-ynes and 2-bromotrideca-1,12-diene-7-ynes, under palladium catalysis, cleanly undergo overall tricyclizations in a sequence of two consecutive intramolecular Heck-type couplings and subsequent 6π electrocyclization (Scheme 1).[6, 7] Only when



Scheme 1.

the β-hydride elimination in the penultimate step is blocked by a substituent R ≠ H adjacent to the alkene terminus of the starting material **1**, does the intermediate **3** follow a different route to eventually yield a tetracyclic system with a bridging cyclopropane moiety between the A- and B-rings of its tricyclic skeleton.[6a, 8] We now report that 2-bromotetradeca-1,13-diene-7-ynes, which would have to give tricyclo[8.4.0.$0^{2,7}$]tetradeca-1(10),2(7)-dienes (1,2,3,4,5,6,7,8,9,10-decahydrophenanthrenes) by the usual Heck–Heck 6π-electrocyclization sequence, in reality undergo two types of tetracyclization depending on the pattern and the nature of substitution.

When the bromodieneynone **6**[9] was treated with palladium acetate, triphenylphosphane, and silver carbonate in acetonitrile at 80 °C, complete conversion was observed after three days, and the tetracyclo[7.4.1.$0^{1,9}$.$0^{2,7}$]tetradec-2(7)-en-3-one **8** was isolated in 45% yield.[10] Apparently, the alkylpalladium bromide intermediate of type **3** formed after two 6-*exo-trig* cyclizations undergoes a 5-*exo-trig* carbopalladation more rapidly than a β-hydride elimination, the neopentyl-type alkylpalladium bromide **7** then must continue to react by a 3-*exo-trig* carbopalladation before β-hydride elimination can occur (Scheme 2). The same type of tetracyclization occurred



	n		%
a	6	single prod.	74
b	7	single prod.	76
c	8		30

Scheme 2. A) Palladacycle[11] (5 mol%), K_2CO_3 (2.5 equiv), nBu_4NBr (0.5 equiv), LiCl (0.5 equiv), DMF, 110 °C, 2 d; B) $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Ag_2CO_3 (3 equiv), MeCN, 80 °C, 3 d. Below: Structure of the epoxide obtained from **11a** with dimethyldioxirane in the crystal.[13] E = CO_2Et.

[*] Prof. Dr. A. de Meijere, Dipl.-Chem. S. Schweizer, Dr. Z.-Z. Song, Dr. F. E. Meyer
Institut für Organische Chemie der Universität
Tammannstrasse 2, D-37077 Göttingen (Germany)
Fax: (+49) 551-39-9475
E-mail: ameijer1@uni-goettingen.de
Prof. Dr. P. J. Parsons
Department of Chemistry, University of Sussex
Falmer, Brighton, BN1 2QJ (UK)

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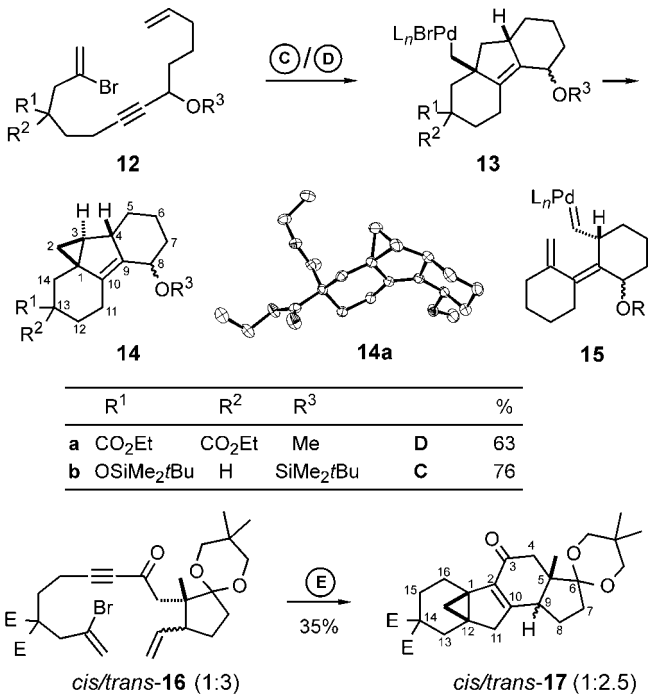
with the bromodieneyne **9a** as well as its homologues **9b** and **9c**,[10] except that final β-hydride elimination in the intermediates **10a–c** removed one of the methylene hydrogen atoms in the six-membered C-ring rather than the angular hydrogen atom between the B- and C-ring in the corresponding intermediate leading to **8**. The yields of isolated **11a** and even **11b**, in which a seven-membered ring is formed in the initial Heck-type coupling, were around 75%, and **11a** and **11b** were the only products. The tetracyclic enone **8** was also formed as a single product just as **11a**, **b**, but partial decomposition of **8** may have occurred upon silica gel chromatography due to its electrophilic enone moiety. The relative configuration of **11a** as depicted was proved by an X-ray crystal structure analysis of the epoxide formed from **11a** with dimethyldioxirane.[13] It is particularly remarkable that even **9c**, in which an eight-membered ring is formed in the first step,[12] underwent the same type of tetracyclization, not as cleanly though as **9a**,**b**, and thus the yield of isolated product was only 30%.

Even more surprising is the fact that bromodieneyne **12a** which differs from **9a** only by the methoxy group in the 9-position, gave the completely different tetracyclo-[8.4.0.0^{1,3}.0^{4,9}]tetradec-9-ene derivative **14a** as a separable mixture of two diastereomers (1.2:1.0) in good yield (63%). The structure of the major diastereomer was proved by X-ray crystal structure analysis[13] to be that of the 8-*exo*-methoxy derivative *exo*-**14a**, while ^{1}H and ^{13}C NMR spectra corroborated the minor product to be the 8-*endo* diastereomer *endo*-**14a** (Scheme 3). The 4,9-disilyloxy-2-bromotetradeca-1,13-diene-7-yne (**12b**) (1:1 mixture of two diastereomers) gave the tetracycle **14b** as a separable mixture of four diastereomers (ratio 1.2:1.0:1.7:2.0) in even better yield (76%).



	R^1	R^2	R^3		%
a	CO_2Et	CO_2Et	Me	**D**	63
b	$OSiMe_2tBu$	H	$SiMe_2tBu$	**C**	76

Scheme 3. C) Same as B) in Scheme 2, but 2 d; D) $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), Ag_2CO_3 (1.5 equiv), $(iPr)_2NH$ (3 equiv), MeCN, 120°C, 18 h; E) Same as D), but 2 d. In the center: Structure of **14a** in the crystal.[13]

There is no experimental evidence as to how the skeleton of **14** evolves, but it might form via an alkylpalladium intermediate **13** which is analogous to the intermediate **7** en route to the other tetracyclic skeleton. An unprecedented γ-hydride elimination in **13** would then lead to **14**.[14] Alternatively, an alkylpalladium intermediate of type **3** might undergo α-dehydrobromination (α with respect to the metal atom) to yield a palladium carbene complex **15**[15] that would certainly intramolecularly cyclopropanate the opposite exomethylene group. It is not obvious, though, why and how the 9-oxy substituents in **12a**, **b** would cause the corresponding intermediates of type **3** or **13** to undergo α-dehydrobromination or γ-hydride elimination, respectively.

In an approach to a steroidal skeleton, the cyclopentanone derivative **16** (1:3 mixture of *cis*- and *trans*-diastereomers) resembling the acyclic tetradecadieneynone **6**, was assembled[9] and subjected to typical Heck coupling conditions. This did indeed react in complete analogy to **6** and led to the pentacyclic compounds *cis*-/*trans*-**17** (ratio 1:2.5) which resemble a steroidal skeleton with a five-membered B-ring. While the major diastereomer was isolated as an oil, the minor one gave good crystals and was proved by X-ray structure analysis to have a *cis* C/D-ring junction with the angular methyl group on the same side as the bridging cyclopropane ring (Figure 1).[13] By comparison of the ^{1}H and ^{13}C NMR spectra, the major isomer could thus be assigned the *trans*-configurated structure *trans*-**17**. Although the yield was only

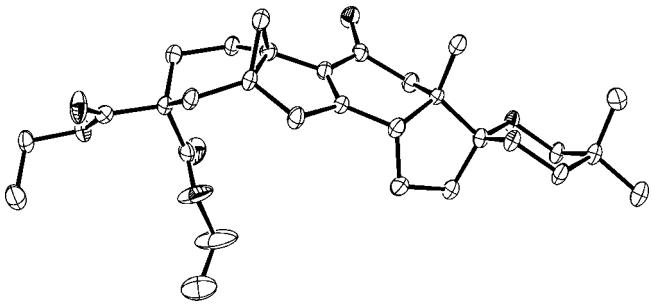


Figure 1. Structure of compound *cis*-**17** in the crystal.[13]

moderate (35%), this new domino cyclization offers an access to interesting steroid analogues. Pure *cis*-**16** under the same conditions gave *cis*-**17** in 40% yield. It remains to be seen whether changes in the type and pattern of substituents will alter the mode of cyclization.

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Palladium-Catalyzed Synthesis of Substituted Hydantoins—A New Carbonylation Reaction for the Synthesis of Amino Acid Derivatives**

Matthias Beller,* Markus Eckert, Wahed A. Moradi, and Helfried Neumann

Amino acids and their derivatives are unequivocally one of the most important classes of organic compounds. In addition to biochemical applications, amino acid derivatives are used as chemical feedstocks for industrial fine chemical synthesis.[1] Despite the well known "classical methods" such as the Strecker synthesis[2] and the highly selective procedures developed in the research groups of Schöllkopf,[3] Seebach,[4] Evans,[5] Williams[6] as well as recent developments,[7] a need for new, more efficient protocols for the preparation of amino acid derivatives remains. In the past, researchers focused exclusively on the asymmetric synthesis of amino acid derivatives, and successful procedures were judged accordingly. However, other important factors also need to be addressed. For example, the procedures need to be improved in terms of their atom economy.[8] This also applies to the asymmetric hydrogenation of acetamidoacrylates and acetamidocinnamates,[9] since the hydrogenation precursors are often expensive and difficult to prepare.[10]

Racemic imidazolidine-2,4-diones, generally called hydantoins,[11] are important building blocks for enantioselective amino acid synthesis because enantiomerically pure amino acids can be prepared from these by dynamic kinetic racemic resolution.[12] The practicability of this method was demonstrated on an industrial scale by Ajinomoto[13] and Kanegafuchi[14] for the production of D-*p*-hydroxyphenylglycine. Substituted hydantoins are also of pharmacological interest and are used, for example, for the treatment of epilepsy.[15] Since only atom economic procedures for the production of N-unsubstituted hydantoins are known (Bucherer – Bergs reaction,[16] amidoalkylation[17]), we set out to examine to what extent substituted hydantoins can be made directly from simple, inexpensive starting materials. We describe here a new one-pot synthesis of 5-, 3,5-, and 1,3,5-substituted hydantoins that is based on the carbonylation of aldehydes in the presence of urea derivatives.

In the context of our work on the carbonylation of aldehydes with amides (amidocarbonylation)[18] in the presence of a palladium catalyst,[19] we examined to what extent sulfonamide, urethanes and urea derivatives can be used as amide components. The conversion of cyclohexanecarbalde-

[*] Prof. Dr. M. Beller, Dipl.-Chem. M. Eckert,
Dipl.-Chem. W. A. Moradi, Dr. H. Neumann
Institut für Organische Katalyseforschung (IfOK) an der Universität Rostock e.V.
Buchbinderstrasse 5 – 6, D-18055 Rostock (Germany)
Fax: (+49) 381-466-9324
E-mail: matthias.beller@ifok.uni-rostock.de

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