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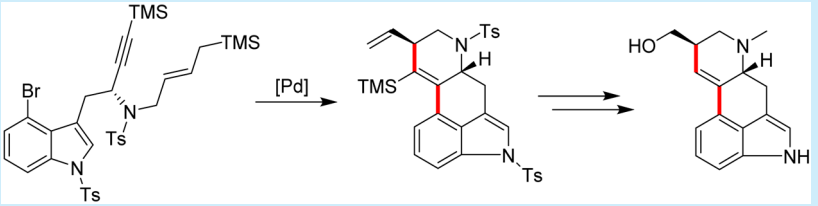
Enantioselective Total Synthesis of (+)-Lysergol: A Formal *anti*-Carbopalladation/Heck Cascade as the Key Step

Bastian Milde,[†] Martin Pawliczek,[†] Peter G. Jones,[‡] and Daniel B. Werz*[,†]

[†]Institut für Organische Chemie and [‡]Institut für Anorganische und Analytische Chemie, Technische Universität Braunschweig, Hagenring 30, 38106 Braunschweig, Germany

Supporting Information



ABSTRACT: The enantioselective synthesis of (+)-lysergol was completed in 12 steps and an overall yield of 13% starting from a known literature precursor. The key step relies on a domino reaction containing a formal *anti*-carbopalladation, which is terminated by a *β*-silyl-directed Heck reaction. During this transformation, the two six-membered rings of the ergot scaffold are formed in a completely stereospecific manner.

Three of the most famous indole alkaloids belonging to the ergot family are (+)-lysergol, **1**, (+)-isolysergol, **2**, and (+)-lysergic acid, **3**, the parent compound of LSD (Figure 1).

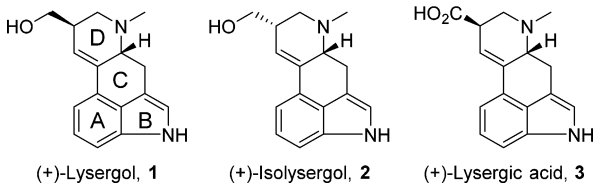
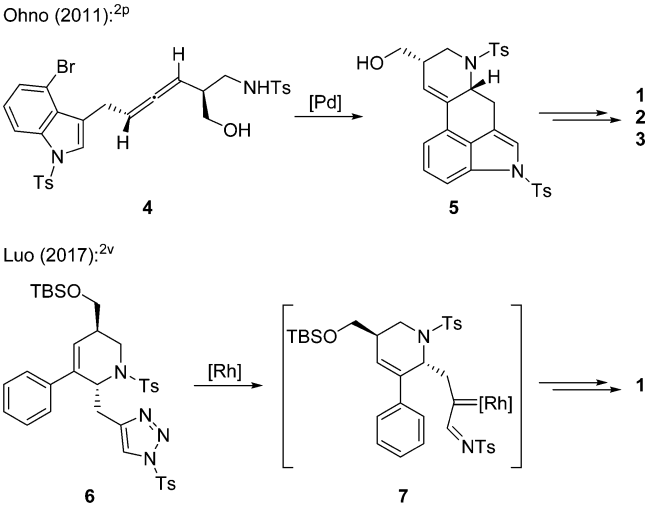


Figure 1. Indole alkaloids of the ergot family.

They have attracted much attention in the past few decades, especially because of their biological activity,[1] and therefore, numerous synthetic routes have been developed.[2] In 2011, the Ohno group presented a Pd-catalyzed domino cyclization starting from allene-substituted bromoindole **4** to access these prominent alkaloids (Scheme 1, top).[2p] This method allowed the assembly of the C and D rings in one step. In contrast, Luo et al. recently reported the construction of the ergot alkaloid scaffold using a Rh-catalyzed [3 + 2]-annulation, whereas the indole moiety was formed at a late stage (Scheme 1, bottom).[2v]

Latterly, we focused our research on the development of a novel type of a Pd-catalyzed domino reaction, in which an alkyne moiety is forced to undergo a formal *anti*-carbopalladation to obtain tetrasubstituted olefins.[3,4] A normal *syn*-carbopalladation usually proceeds via a *syn*-attack of an organometallic R-[Pd] species on the *π*-system of an alkyne, and therefore, the two residues [Pd] and R are located on the same side of the emerging double bond. Since such an intermediate is still a highly reactive species, additional transformations, such as further carbopalladations or a terminating cross-coupling reaction, are possible and

Scheme 1. Two Examples of the Synthesis of Indole Alkaloids of the Ergot Family



have been extensively used to build up complex scaffolds in only one step.[4,5] Under certain conditions (i.e., the absence of any *β*-hydrogen atoms at the alkyne terminus, monodentate phosphine ligands at the Pd center, and polar aprotic solvents), the system is forced to isomerize after the initial *syn*-attack in the coordination sphere of the metal. Residues [Pd] and R are now located in an *anti*-fashion across the emerging double bond. Since such a motif available via an *anti*-carbopalladation is also found in certain classes of natural products, we focused our efforts on a novel

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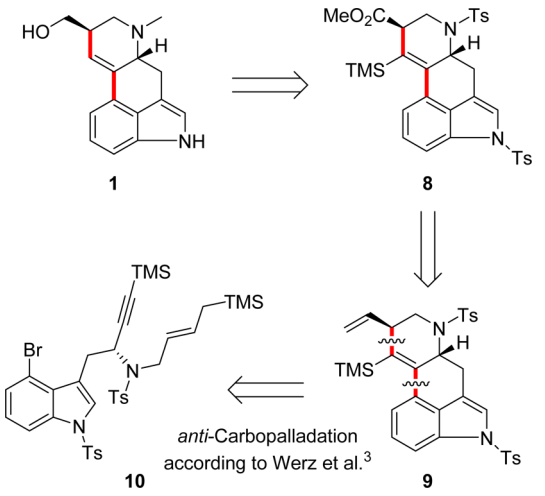
approach to synthesize (+)-lysergol, **1**. Our retrosynthetic analysis revealed that the alkaloid scaffold can be traced back to the TMS-substituted tetrasubstituted double bond in tosyl-protected amine **8** (Scheme 2). Previous studies showed that the

Scheme 2. Retrosynthetic Analysis



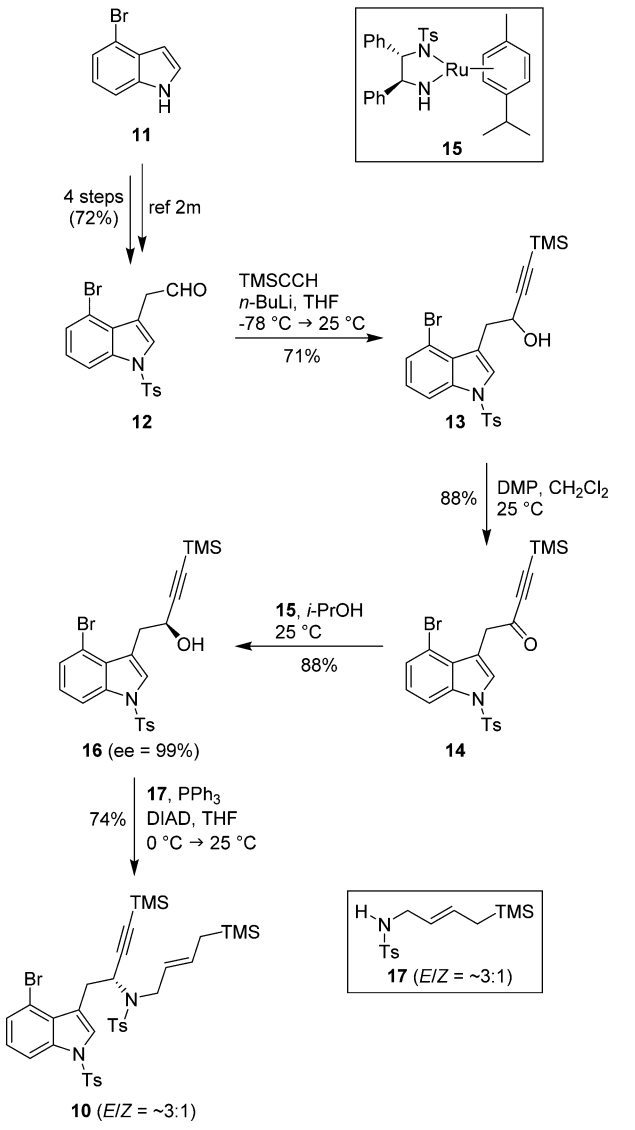
silyl group can be easily removed either under acidic conditions or in the presence of a fluoride source.[3d] The ester moiety in **8** arises from an oxidation sequence of the exocyclic double bond in **9**. As a key step, a cascade involving a formal *anti*-carbopalladation reaction and a terminating β-silyl-directed Heck reaction is envisioned. The allylic TMS group at the side chain of the domino precursor **10** seems to be crucial because we expect a fully conjugated system to be formed in its absence.

To test our notion, we started with 4-bromoindole (**11**); aldehyde **12** was obtained in 72% yield using a known four-step protocol (Scheme 3).[2m] The procedure consists of a C3-selective allylation followed by *N*-protection and finally the oxidation of the double bond to the corresponding aldehyde using an OsO_4/$NaIO_4$-mediated cleavage. In the next step, the alkyne moiety was installed using trimethylsilylacetylene, and secondary alcohol **13** was obtained in 71% yield as a racemic mixture. To generate the desired enantiomer, a redox manipulation was applied using Dess-Martin periodinane to oxidize the alcohol. The resulting ketone **14** was reduced enantioselectively by employing Noyori's catalyst **15**.[6] After the formation of Mosher's ester, an enantiomeric excess of ~99% was observed using ^{19}F NMR integration. The synthesis of the domino precursor was finalized in 74% yield by applying a Mitsunobu reaction with sulfonamide **17**. The latter compound was easily prepared in 68% yield using the second generation Hoveyda–Grubbs catalyst and the corresponding terminal olefins.

To elucidate the stereochemistry of chiral alcohol **16**, X-ray crystallography seemed to be the method of choice. Unfortunately, the secondary alcohol did not yield any single crystals. Therefore, ester **18**, bearing a camphanoyl moiety, was synthesized.[7] The bicyclic scaffold facilitates crystallization, and suitable single crystals were obtained. After X-ray analysis, the absolute configuration was unequivocally established (Figure 2).

With domino precursor **10** in hand, we next investigated its transformation to the desired ergot scaffold **9**, containing a terminal double bond arising from a β-silyl-directed Heck reaction. Based on our previous results, we first chose a catalytic system consisting of $[PdCl_2(PhCN)_2]$, Fu's salt,[9] to liberate the highly sterically encumbered tris(*t*-butyl)phosphine as the ligand

Scheme 3. Synthesis of the Domino Precursor



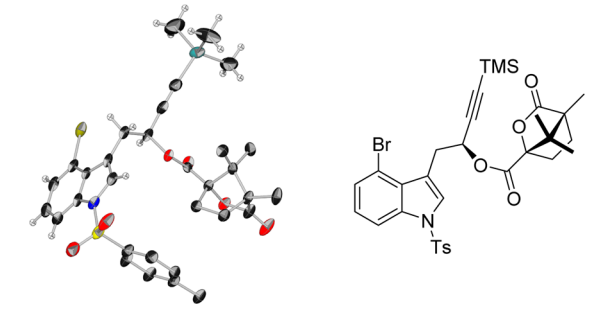


Figure 2. Molecular structure (50% ellipsoid probability) of **18** in the solid state. Oxygen atoms are shown in red, sulfur atom in yellow, bromine atom in dull yellow, nitrogen atom in blue, and silicon atom in turquoise. Some hydrogen atoms are omitted for clarity.[8]

and Et_3N in DMF at 70 °C (Table 1, entry 1). After 15.5 h, a mixture of the desired product **9** and the silyl-containing side product **19**, which is formed by β-hydrogen elimination, was obtained in a ratio of almost 1:1. The ratio slightly increased by heating the reaction to 100 °C, but a major improvement was first effected by switching to XPhos[10] instead of tris(*t*-butyl)-

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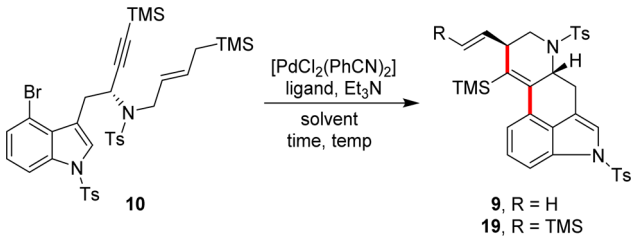
Table 1. Optimization of the Domino Reaction[a]



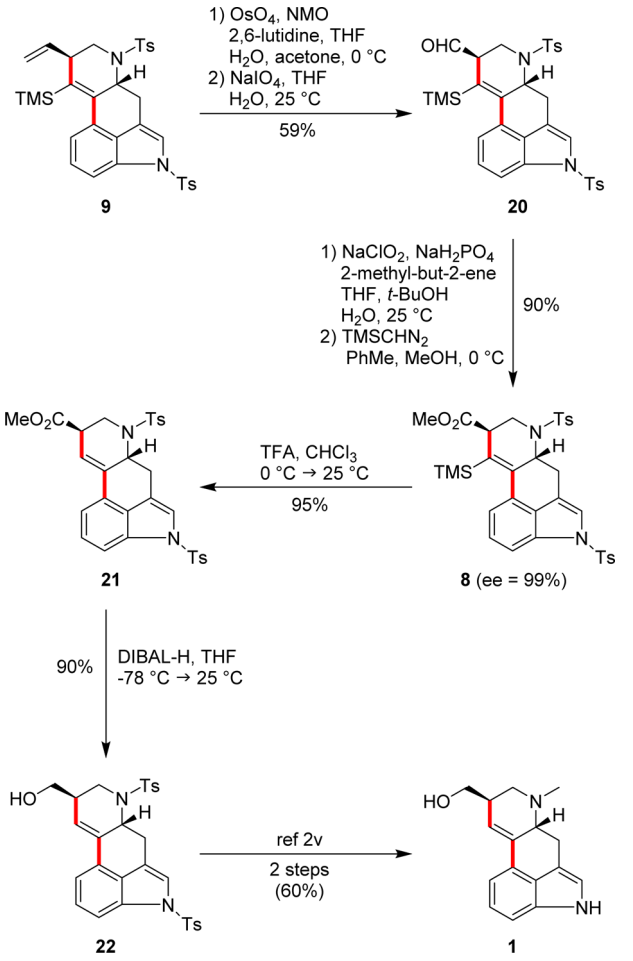
entry	ligand	solvent	temp (°C)	time (h)	yields (%)
1	[*t*-Bu$_3$PH][BF$_4$]	DMF	70	15.5	**9**, 29
					19, 37
2	[*t*-Bu$_3$PH][BF$_4$]	DMF	100	1.5	**9**, 41
					19, 34
3	XPhos	DMF	100	2.5	**9**, 59
					19, 13
4	BrettPhos	DMF	100	7.5	**9**, 56
					19, 13
5	XPhos	DMF	120	2.0	**9**, 68
					19, 17
6	XPhos	DMA	120	2.0	**9**, 80
					19, 17
7[b]	XPhos	DMF	120	decomposition	
8[c]	XPhos	DMF	120	many side reactions	
9	XPhos	DMA	140	2.0	**9**, 72
					19, 12

[a]Reaction conditions: **10** (1.0 equiv), [PdCl$_2$(PhCN)$_2$] (10 mol %), ligand (20 mol %), Et$_3$N (5.0 equiv), solvent (25 mM), temp, time. [b]*n*-Bu$_4$NOAc (5.0 equiv) was used instead of Et$_3$N. [c][Pd(OAc)$_2$] (10 mol %) was used instead of [PdCl$_2$(PhCN)$_2$].

phosphine as the ligand (Table 1, entries 2 and 3). Using a more polar ligand, namely, BrettPhos,[10] did not further increase the yield, but when the reaction was carried out at 120 °C, the desired product was obtained in 68% yield (Table 1, entries 4 and 5). As much as 80% of the desired domino product **9** was formed when the solvent was changed to DMA, representing the best conditions (Table 1, entry 6). Further attempts to optimize this reaction by using *n*-Bu$_4$NOAc, [Pd(OAc)$_2$], or the use of even higher temperatures were not successful (entries 7−9). It is noteworthy that the cyclization cascade proceeds in a completely stereoselective manner: only one diastereoisomer was formed, and the enantiomeric excess remains at 99%, as analyzed by chiral HPLC.

With optimized conditions in hand, we proceeded to finish the total synthesis of (+)-lysergol, **1** (Scheme 4). Again, an OsO$_4$/NaIO$_4$-mediated oxidative cleavage of the exocyclic double bond was applied to obtain the corresponding aldehyde **20**. Attempts to achieve the desired cleavage by ozonolysis proved to be unsuccessful and led to decomposition of the complete skeleton. Next, the generated aldehyde **20** was reduced to the corresponding alcohol, but unfortunately, all attempts to cleave the TMS group at this stage either under acidic conditions or by using a fluoride source have been in vain. Therefore, the aldehyde was converted into methyl ester **8** in 90% yield via a two-step protocol comprising Pinnick oxidation and subsequent esterification using trimethylsilyldiazomethane. The enantiomeric excess remains at 99% as determined by chiral HPLC. The trisubstituted olefin in **21** was now obtained by silyl deprotection using TFA. Finally, DIBAL-H was used to reduce the ester to the known primary alcohol **22**. A following two-step sequence,

Scheme 4. Finalization of the (+)-Lysergol Synthesis



containing tosyl deprotection and selective *N*-methylation, would yield (+)-lysergol in 60% yield.

In summary, we have shown that the formal *anti*-carbopalladation reaction developed in our lab is a powerful and reliable synthetic tool for constructing tetrasubstituted olefins, even in more complex scaffolds. A novel enantioselective route to access the ergot alkaloid (+)-lysergol was achieved in 12 steps and an overall yield of 13% starting from the known racemic alcohol **13**. During the key step, the formal *anti*-carbopalladation which is terminated by a silyl-directed Heck reaction, two rings are formed in a completely stereospecific way.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00675.

Detailed experimental procedures, analytical data for all new compounds (PDF)

Crystal data for **18** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: d.werz@tu-braunschweig.de.

ORCID

Daniel B. Werz: 0000-0002-3973-2212

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Notes

The authors declare no competing financial interest.

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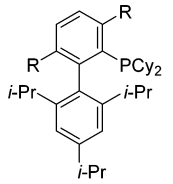

XPhos, R = H
BrettPhos, R = OMe

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