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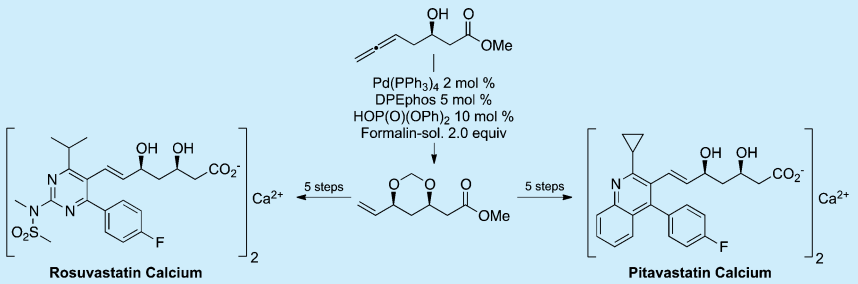
Palladium-Catalyzed Stereoselective Cyclization of *in Situ* Formed Allenyl Hemiacetals: Synthesis of Rosuvastatin and Pitavastatin

Pierre A. Spreider and Bernhard Breit*

Institut für Organische Chemie, Albert-Ludwigs-Universität Freiburg, Albertstrasse 21, 79104 Freiburg im Breisgau, Germany

Supporting Information



ABSTRACT: A diastereoselective palladium-catalyzed cyclization of allenyl hemiacetals is described. It permits the selective synthesis of 1,3-dioxane derivatives, precursors for *syn*-configured 1,3-diols which make an appearance in all of the statin representatives. The reaction allows the total synthesis of Rosuvastatin and Pitavastatin in a straightforward fashion.

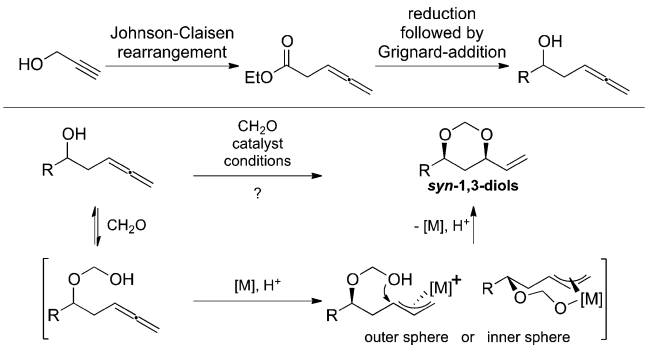
Statins represent a class of biologically active compounds and are the most commonly prescribed drugs worldwide for the treatment of lipid disorders. They have been found to reduce cardiovascular diseases by competitively inhibiting HMG-CoA reductase.[1] A *syn*-configured 1,3-diol function appears as a common element in all of the statins, e.g. in Fluvastatin, Pitavastatin, or Rosuvastatin. They can also be found in many polyketide derived natural products.[2] The synthesis of both Rosuvastatin and Pitavastatin has been tackled numerous times in the past,[3] and the development of a new synthetic tool for their stereoselective catalytic access is herein investigated.

As an evolution of the transition-metal-catalyzed allylic oxidation[4] and substitution,[5] our group described several atom-economical methodologies for the addition[6] of pronucleophiles to allenes[7] and alkynes[8] yielding branched allylic products.

Having recently developed C−O bond forming reactions[9] and an 1,3-aminoalcohol yielding cyclization reaction,[6p] we speculated whether it would be possible to construct the important *syn*-1,3-diol motif by the intramolecular cyclization of *in situ* generated hemiacetals from the corresponding homoallenyl alcohols (Scheme 1). We reasoned that both an outer or inner sphere mechanism via the corresponding π-allyl complex, generated from the allene through the action of a metal and Brønsted acid catalyst, should deliver the desired thermodynamically more stable *syn*-1,3-diol motif.[10]

Plenty of methods for the stereoselective synthesis of 1,3-diols have been developed: Allylation of β-hydroxyaldehydes,[11] catalytic aldol reactions,[12] stereoselective reduction,[13] stereoselective hydrogenation,[14] catalytic olefin carbonylation,[15] biocatalytic methods,[16] cyclization of homoallylic carbonates,[17] Michael addition,[18] tandem hemiacetal formation/Tsuji−Trost reation,[19] catalytic oxy-alkenylation of homoallylic alcohols,[20]

Scheme 1. Concept of Allenyl Hemiacetal Cyclization towards *syn*-1,3-Diols



or catalytic dehydrative allylation[21] just to mention a few. We herein report a diastereoselective palladium-catalyzed intramolecular cyclization of *in situ* formed allenyl hemiacetals in order to access *syn*-configured methylene acetal protected 1,3-diols selectively.

Primary reactivity examinations were conducted by using a phenyl substituted allenyl alcohol in the presence of [Rh(COD)Cl]$_2$ (2.0 mol %), DPEphos (5.0 mol %), diphenyl phosphate (10.0 mol %), and aq. formalin-sol. (37 wt % in H_2O) in DCE at 80 °C. The *syn*-configured product could be obtained in a promising yield of 40% and an excellent dr of >95:5 (Table 1, entry 1). Altering the catalytic system had significant effects on the yield without degrading the dr, especially with the use of [Pd(PPh$_3$)$_4$] increasing the yield to

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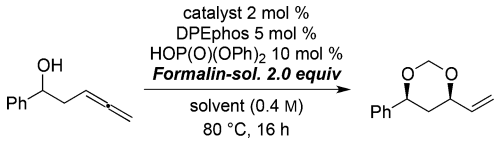
Table 1. Transition-Metal-Catalyzed Diastereoselective Addition of Hemiacetals to Terminal Allenes[a]



entry	catalyst	solvent	yield [%][b]	syn/anti[c]
1	$[Rh(COD)Cl]_2$	DCE	40	>95:5
2	$[Pd_2(dba)_3]$	DCE	77	>95:5
3	$[PdCl(allyl)]_2$	DCE	20	>95:5
4	$[Pd(PPh_3)_4]$	DCE	91	90:10
5[d]	$[Pd(PPh_3)_4]$	DCE	–	–
6[e]	$[Pd(PPh_3)_4]$	DCE	20	95:5
7	$[Pd(PPh_3)_4]$	toluene	94	92:8
8[f]	**$[Pd(PPh_3)_4]$**	**toluene**	**92**	**91:9**

[a]Formalin-Sol. 37 wt % in H_2O [b]Combined yield of *syn*- and *anti*-configured product. [c]Diastereoselectivity determined by ^1H NMR analysis of the crude reaction mixture. [d]Reaction was performed without $HOP(O)(OPh)_2$. [e]Reaction was performed without DPEphos. [f]Reaction was performed with 1 mol % $[Pd(PPh_3)_4]$, 2 mol % DPEphos, and 5 mol % $HOP(O)(OPh)_2$.

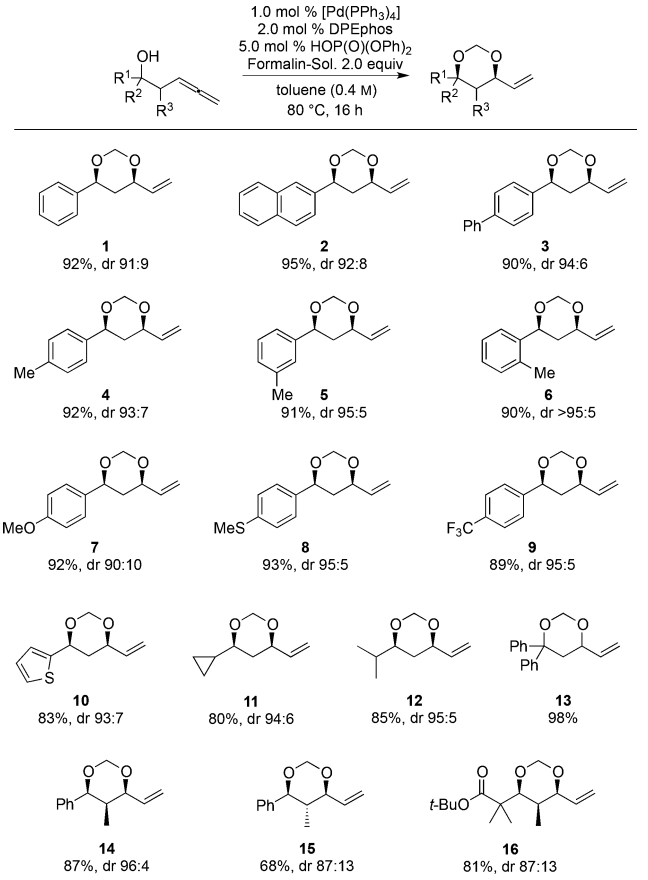
91% (entry 4). Running the reaction without diphenyl phosphate completely shut down the reaction, showing that the acidic additive is indispensable to the catalysis (entry 5). Altering the solvent to less toxic toluene slightly increased yield and dr (entry 7). Finally, lowering the loading of the catalytic system to 1 mol % of $[Pd(PPh_3)_4]$, 2 mol % DPEphos, and 5 mol % of diphenyl phosphate provided optimized conditions, with which the scope of this reaction was studied (Scheme 2).

Various functional groups were tolerated in the catalysis and yielded the corresponding 1,3-dioxanes in good to excellent yields. Several aromatic moieties with different electronic properties (**1**–**3**) were suitable in this catalysis. The reaction is sterically rather tolerant as shown by the clean reaction of *ortho*-, *meta*-, and *para*-tolyl substituted derivatives (**4**–**6**). Functional groups attached to the aromatic moiety such as ethers, thioethers, or a trifluoromethyl group were also well tolerated to afford the desired products (**7**–**9**) in good to excellent yields and dr (up to 95% and up to >95:5). Starting material bearing a thiophene moeity also behaved well in terms of yield and diastereoselectivity (**10**), as well as aliphatic substituents such as cyclopropyl or isopropyl (**11**, **12**). Bulky diphenyl substituted tertiary allenyl alcohol delivered an excellent yield (**13**). Installing a methyl group in the 5-position of the 1,3-dioxane slightly decreased the yield and dr, nevertheless showing that a herein reported catalytic reaction can be performed with a substituent situated directly next to the reactive center (**14**, **15**, **16**). The relative configurations of the *syn*-configured products were determined by NOE experiments.[10]

To gain insight into the origin of the stereoselectivity of this catalysis some preliminary experiments were performed (Scheme 3). When a mixture of *syn*- and *anti*-configured 1,3-dioxane **1** was subjected to the catalytic reaction conditions, a shift of the diastereomeric ratio in favor of the *syn* product was observed. Based on these experimental data, the reaction is most likely to be reversible, thus yielding the thermodynamically more stable *syn*-configured 1,3-dioxane.

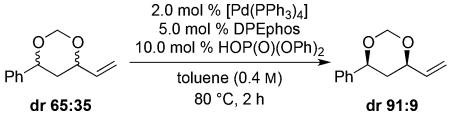
Assorted product transformations of **1** were elaborated to highlight the synthetic utility of this catalytic reaction. The

Scheme 2. Scope of the Catalytic Diastereoselective Cyclization of *in Situ* Formed Allenyl Hemiacetals towards *syn*-Configured Compounds[a–c]



[a]Combined yield. [b]Selectivities determined by ^1H NMR analysis of the crude reaction mixture. [c]Formalin-Sol. 37 wt % in H_2O.

Scheme 3. Control Experiment Regarding Reversibility of the Catalytic Reaction



olefin moiety has been functionalized in different manners in order to obtain different polyol sequences (Scheme 4). On the one hand the double bond was functionalized by hydroformylation using our self-assembly ligand 6-diphenylphosphinopyridone (6-DPPon).[22] On the other hand hydroboration furnished the terminal alcohol **19** in excellent yields (98%), which could smoothly be transformed in the corresponding aldehyde **21** by Swern oxidation. Ozonolysis of the allylic moiety delivered the C_1-shortened terminal alcohol **18**, which was converted into the primary bromide **20**. At last, the 1,3-dioxane was cleaved to the unprotected 1,3-diol **22** in 90% yield using relatively mild conditions.[23]

Inspired by these synthetic possibilities, this new catalytic reaction was applied to the synthesis of the Rosuvastatin lactone **32** and the Pitavastatin lactone **33**. Therefore, enantiomeric pure allenyl alcohol **26** was prepared according to the method of Perlmutter and co-workers.[24] Literature known aldehyde **24**[6p] was subjected to the borylenolate derived from the acetylsultam **23** to furnish by column chromatography

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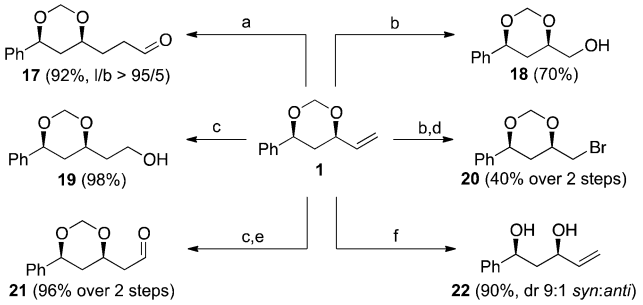
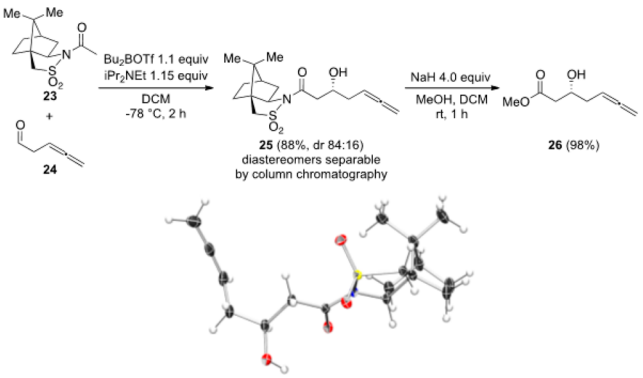
Scheme 4. Follow-up Chemistry of the 1,3-Dioxane[a]



[a](a) $[Rh(CO)_2acac]$ (0.5 mol %), 6-DPPon (10 mol %), CO/H_2 (1:1, 10 bar), toluene, 80 °C, 18 h, 92% (*l*/*b* > 95:5). (b) (i) O_3, MeOH, −78 °C, 1 h (ii) $NaBH_4$, MeOH, −78 °C, 1 h, 70%). (c) 9-BBN, NaOH, H_2O_2, THF, 0 °C, 98%. (d) PPh_3, CBr_4, MeCN, 0 °C, 52%. (e) $C_2Cl_2O_2$, DMSO, NEt_3, DCM, −78 °C, 1 h, 98%. (f) TFAA, AcOH, DCM, rt, 2 h, 90%, (dr 9:1 *syn*/*anti*).

a separable mixture of two aldol products (**25**) in 88% yield (dr 84:16). The relative configuration was confirmed by X-ray diffraction analysis.[10] Cleavage of the amid moiety delivered the ester **26** in an excellent yield of 98%, while recycling Oppolzer-sultam quantitatively in order to refurnish acetylsultam **23** in one step (Scheme 5).

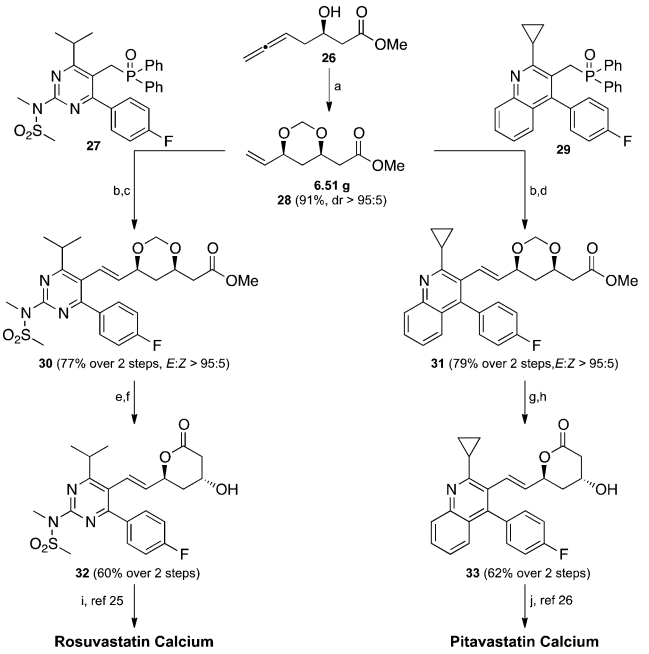
Scheme 5. Synthesis of Enantiomeric Pure Allenyl Alcohol 26 including ORTEP of 25



Next, the enantiomerically enriched starting material **26** was subjected to a multigram scale catalysis to yield 6.51 g of 1,3-dioxane **28** in 91% yield and an excellent dr of >95:5 (Scheme 6). The obtained catalysis product is the starting point for the potential divergent synthesis of different statins. In the following, the exemplary synthesis of two statin representatives is demonstrated. Ozonolysis of the allylic double bond furnished the corresponding aldehyde, which was subsequently treated with either diphenyl phosphoryl compound **27** or **29** to yield the associated olefins **30** and **31** in respectively good yields and excellent *E*/*Z* selectivities. At this point, the enantiomeric purity was in each case confirmed by chiral HPLC analysis.[10] Finally, basic ester hydrolysis followed by acidic cleavage of the 1,3-dioxane moiety to the unprotected 1,3-diols delivered both precursors **32** and **33** as lactones due to spontaneous lactonization of formed intermediates. The latter can easily be converted into the calcium salts according to reported procedures.[25,26]

In summary, we have accomplished a highly diastereoselective method to synthesize 1,3-dioxanes respectively 1,3-diols

Scheme 6. Total Synthesis of Both Rosuvastatin Lactone 32 and Pitavastatin Lactone 33[a]



[a](a) $[Pd(PPh_3)_4]$ (2 mol %), DPEphos (5 mol %), $HOP(O)(OPh)_2$ (10 mol %), toluene, 80 °C, 16 h, 91% (dr >95:5). (b) O_3; Me_2S, MeOH, −78 °C, 98%. (c) 27, NaHMDS, THF, −78 °C, 3 h, 79%. (d) 29, NaHMDS, THF, −78 °C, 3 h, 81%. (e) NaOH, EtOH, 80 °C, 16 h, 98%. (f) HCl, toluene, rt, 8 h, 61%. (g) NaOH, EtOH, 80 °C, 16 h, 98%. (h) HCl, toluene, rt, 8 h, 63%. (i) NaOH, $Ca(OAc)_2$, THF, rt, 3 h, 83%. (j) NaOH, $CaCl_2$, H_2O, rt, 4 h, 95%.

using a palladium/DPEphos system. A variety of functional groups are tolerated in this reaction. Synthetic possibilities for derivatization of the allylic function have been explored, especially in the synthesis of both Rosuvastatin and Pitavastatin lactone. This pathway highlights the synthetic utility of this catalytic reaction and could potentially be applied in further statin syntheses. Investigations on implied syntheses and other suitable target oriented syntheses are currently being pursued in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01156.

Experimental procedures and analytical data for the synthesized compounds, including ^1H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1573385 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: bernhard.breit@chemie.uni-freiburg.de.

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ORCID

Bernhard Breit: 0000-0002-2514-3898

Notes

The authors declare no competing financial interest.

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