EurJOC
European Journal of Organic Chemistry

Communications
doi.org/10.1002/ejoc.202100832

Chemistry Europe
European Chemical Societies Publishing

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Synthesis of (−)-(*R*)-Sitagliptin by Rh^{I}-Catalyzed Asymmetric Hydroamination

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In memory of Klaus Hafner

We report of a concise synthesis of (*R*)-sitagliptin monophosphate – a drug predominantly applied in the treatment of type 2 diabetes. Utilizing our recently developed Rh^{I}-catalyzed hydroamination of allenes for the stereoselective construction of the inherent chiral amino function, a new approach to (*R*)-sitagliptin monophosphate on a 3.5 mmol scale was established.

Type 2 diabetes mellitus (T2DM) is a major and rapidly growing disease, which affects millions of people worldwide every year.[1] In this context the treatment by drugs, e.g. (*R*)-sitagliptin (**1**) – an orally active, safe and selective DPP-IV inhibitor – is of ever growing interest. **1**, originally discovered by Merck, Sharp & Dohme (MSD) in 2005, inhibits the proteolytic activity of dipeptidyl peptidase-4, an enzyme that breaks down the incretins, which play a key role in glucoregulation by increasing insulin secretion and suppressing glucagon release.[2] The significance of sitagliptin as the active pharmaceutical ingredient in commercial drugs such as Januvia® and Janumet® is best illustrated by the fact, that it is present in the top 200 best-selling drugs since its first approval by the FDA in 2006.[3]

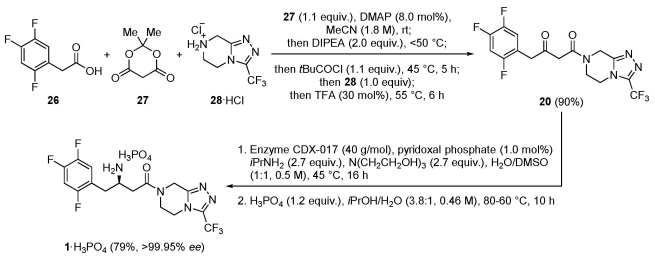
For this reason the synthesis of (*R*)-sitagliptin (**1**) has been established as a benchmark target for chiral amine synthesis and therefore, attracted the attention of many different research groups and pharmaceutical companies reporting of extensive efforts on its asymmetric synthesis. The key methods employed to install the chiral primary amine include auxiliary controlled alkylation of amides followed by Arndt-Eistert homologation,[2,4] intramolecular Pd-catalyzed [2,3]-sigmatropic rearrangement,[5] asymmetric *aza*-Michael addition,[6] auxiliary controlled amination of enolates,[7] auxiliary controlled reduction or (transfer-)hydrogenation,[8] asymmetric (transfer-) hydrogenation[9] and enantioselective or auxiliary controlled Mannich reaction[10] (Figure 1).

However, the best and most elegant synthesis until today was developed by Merck, Sharp & Dohme (DSM) itself in cooperation with Codexis, providing **1** by a biocatalytic route utilizing an engineered transaminase enzyme.[9d] The latter enabled a tandem amination/asymmetric hydroamination process as a one-pot procedure avoiding hazardous and expensive hydrogenation conditions (Scheme 1).

Although especially the synthetic routes containing the construction of the chiral amine by asymmetric hydrogenation, transamination and Michael addition are straightforward and efficient, there is still interest in convenient, atom efficient and synthetically applicable alternatives to the mentioned methodologies.

In the recent past our research group developed a broad variety of inter- and intramolecular hydroamination reactions of allenes and alkynes employing different *N*-nucleophiles such as *N*-heterocycles, sulfonylamines and anilines. These methodologies can be seen as an atom economic alternative to allylic substitution.[12] Among the above mentioned methods for asymmetric preparation is a Rh^{I}/Josiphos J003-catalyzed hydroamination of benzophenone imine of allenes of further interest since this procedure provides an efficient access towards free or protected chiral primary allylic amines in a highly enantioselective fashion.[12g]

Herein, we report such an alternate approach exploiting our above mentioned methodology to accomplish the asymmetric installation of the chiral amine. We initiated our synthetic study by preparing fluorinated allene **30** via a Cu^{I}-catalyzed Grignard addition of benzylic bromide **29** to propargylic bromide. This reaction, carried out on a 75 mmol scale, provided allene **31** in 74% yield. Next, we were able to optimize the original



Scheme 1. Industrial process for the synthesis of (*R*)-(−)-Sitagliptin (**1**) developed by DSM and Codexis.

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Supporting information for this article is available on the WWW under https://doi.org/10.1002/ejoc.202100832

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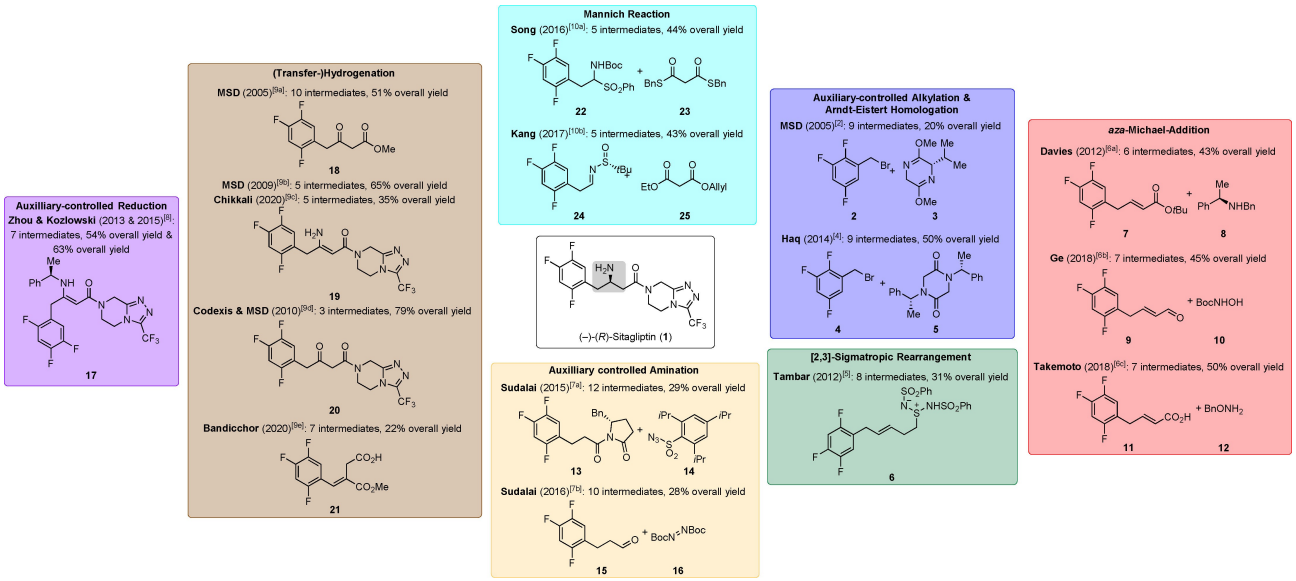
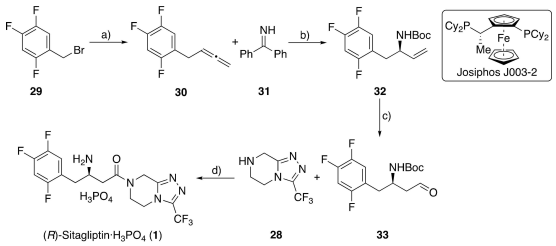


Figure 1. Retrosynthetic overview on key intermediates for the asymmetric synthesis of (−)-(*R*)-Sitagliptin (**1**) based on the synthetic strategies.[11]

conditions for asymmetric benzophenone imine addition to allenes[12g] in terms of lowering the catalyst loading by simultaneously obtaining a satisfying yield.[13] The reaction sequence involved a Rh^{I}/Josiphos-catalyzed hydroamination with benzophenone imine as an ammonia surrogate, cleaving of the imine and BOC-protection. The desired BOC-protected allylic amide **32** was thus obtained in one sequence on a 7.5 mmol scale in 78% yield and excellent enantioselectivity (99.2% *ee*). Applying reaction conditions for *anti*-Markovnikov selective Wacker oxidation developed by Feringa the corresponding aldehyde **33** was obtained in 83% yield and good linear/branched ratio.[14] Next, aldehyde **33** was then converted in a three step sequence via Pinnick oxidation and EDC-mediated amide coupling in (*R*)-Sitagliptin (**1**), which was isolated after the third step as the phosphate salt in 72% yield. A total of more than 1.4 g (3.5 mmol) of the phosphate salt of **1** was obtained in an overall yield of 47% over three isolated intermediates avoiding stereochemical enrichment, such as recrystallization, to obtain enantiomerically pure (*R*)-Sitagliptin (**1**), as it is the case in many previously reported syntheses (Scheme 2).

In conclusion, the synthesis of (*R*)-Sitagliptin (**1**) demonstrates an attractive application of our recently developed hydroamination reaction, a method, which can be seen not only as an atom economic alternative to allylic substitution, but also as an approach for the synthesis of chiral amines comparable to the asymmetric *aza*-Michael addition, stereoselective reduction and Mannich reaction. Applying this methodology, **1** was synthesized over three isolated intermediates on a scalable and concise route highlighting the potential of hydroamination of allenes. Its scope will be further extended towards the asymmetric addition of unactivated *N*-nucleophiles, such as aliphatic amines and amino acids to allenes and will be reported in due course.



Scheme 2. Synthesis of (*R*)-Sitagliptin (**1**) employing a Rh^{I}/Josiphos J003-catalyzed hydroamination of allenes. Reaction conditions: a) 1. Mg (1.2 equiv.), Et_2O (1.0 M), rt – 45 °C, 4 h; 2. propargylic bromide (1.2 equiv.), CuI (10 mol%), Et_2O (1.0 M), 0 °C – rt, 3 h, 74%; b) 1. **30** (1.0 equiv.), **31** (1.0 equiv.), [{Rh(cod)Cl}$_2$] (0.50 mol%), Josiphos J003-2 (1.1 mol%), PPTS (2.5 mol%), DCE (0.4 M), 80 °C, 36 h; 2. HCl_{aq} (2.0 M, 5.0 mL/mmol), Et_2O (5.0 mL/mmol), rt, 12 h; 3. Boc_2O (1.5 equiv.), NEt_3 (4.0 equiv.), CH_2Cl_2 (0.2 M), rt, 12 h, 78%, 99.2% *ee*; c) [Pd(MeCN)Cl$_2$] (5.0 mol%), benzoquinone (1.1 equiv.), *t*BuOH (0.25 M), rt, 18 h, 83%, linear/branched = 91:9; d) 1. $NaOCl_2$ (1.5 equiv.), NaH_2PO_4 (3.0 equiv.), THF/H_2O/2-methyl-2-butene/*t*BuOH (10:6:3:3, 0.05 M), rt, 4 h; 2. **28** (1.2 equiv.), *N*-Me-morpholine (1.0 equiv.), EDC·HCl (1.5 equiv.), MeCN (0.3 M), 0 °C, 2 h; 3. H_3PO_4 (1.0 equiv.), *i*PrOH (0.1 M), rt, 12 h, 72%.

Acknowledgements

D.B. is grateful for a Feodor-Lynen Fellowship from the Alexander von Humboldt Foundation. Furthermore, D.B. and Prof. Willem van Otterlo thank Prof. Reinhard Brückner for admission to his research group at short notice. We thank the analytical department, especially Dr. Manfred Keller for NMR analysis and Joshua Emmerich for ee determinations via HPLC. Open Access funding enabled and organized by Projekt DEAL.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Allenes · Catalysis · Hydroamination · Rhodium · Sitagliptin

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Manuscript received: June 13, 2021
Revised manuscript received: August 31, 2021
Accepted manuscript online: September 3, 2021

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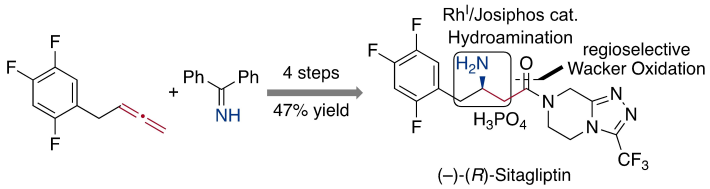

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A concise, asymmetric synthesis of (−)-(*R*)-Sitagliptin is presented utilizing a Rh^{I}/Josiphos-based hydroamination strategy as a key step beside allene preparation and amide coupling. The unusual β-amino function was accomplished by an *anti*-Markovnikov selective Wacker oxidation and subsequent Pinnick oxidation. The synthesis of (−)-(*R*)-Sitagliptin proceeded over three isolated intermediates providing 3.5 mmol in an overall yield of 47 %.