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Asymmetric Total Syntheses of (−)-Angustureine and (−)-Cuspareine via Rhodium-Catalyzed Hydroamination

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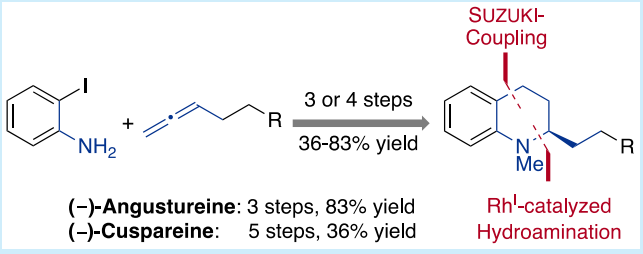
Supporting Information

ABSTRACT: Concise syntheses of the Hancock alkaloids (−)-angustureine and (−)-cuspareine are presented, applying and refining a recently developed rhodium-catalyzed hydroamination for the stereoselective construction of the chiral secondary amine. Furthermore, the syntheses include an allene synthesis via boron−magnesium exchange as well as the construction of the tetrahydroquinoline motive via a hydroboration/Suzuki−Miyaura coupling sequence.



Alkaloids bearing tetrahydroquinoline motifs are occurring widely in plants, and many of them exhibit interesting biological activities.[1,2] Prominent examples include the members of the family of Hancock alkaloids, e.g., (−)-angustureine, (−)-cuspareine, (−)-galipeine, and (−)-galipinine (Figure 1). All of these natural products were isolated by

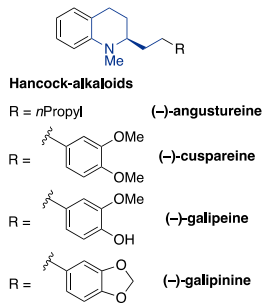


Figure 1. Examples of naturally occurring tetrahydroquinoline alkaloids.

Jacquemond-Collet from the bark of *Galipea officinalis* Hancock, which comprises 20 different species found in northern South America.[1b] In light of their biological activity profiles, extracts from these plants have been used in folk medicine for the treatment of dysentery and fever.[3a] More recently, extracts of the bark of *Galipea officinalis* also have been shown to possess antiplasmodial and cytotoxic activities.[3b]

Encouraged by these interesting biological properties, many chemists contributed to the development of asymmetric synthesis of these tetrahydroquinoline motifs. Bearing in mind that the main challenge is the asymmetric generation of the secondary amine, a variety of reactions have been utilized as key steps,[4−10] with most syntheses relying on asymmetric catalytic hydrogenation of quinolines.[11] Another general approach for the construction of the chiral secondary amine by allylic substitution was developed by Helmchen using an Ir/phosphoramidite-based catalyst system.[12,13]

In the recent past, our research group has developed a rhodium-catalyzed asymmetric hydroamination of allenes with anilines, a method which could be seen as an atom-efficient alternative to allylic substitution.[14] Herein, we report a novel and concise total synthesis of (−)-angustureine and (−)-cuspareine in the absence of protecting groups, enabled by a highly enantioselective hydroamination strategy.

In the beginning, the two required allenes **1** and **2** were synthesized in two short and efficient ways. *n*-Hexyl allene **1** was prepared through propargylic substitution employing propargyl bromide and the Grignard reagent derived from *n*-hexyl bromide in the presence of a copper catalyst on a 200 mmol scale reaction in 69% yield. The aryl functionalized allene **2** was obtained in a two-step sequence starting from 2,3-dimethoxystyrene employing an iridium-catalyzed linear selective hydroboration and subsequent boron−magnesium exchange.[15] The obtained Grignard reagent was then trapped in an analogous manner with propargyl bromide under copper catalysis to give allene **2** in 60% yield over both steps (Scheme 1).

Building on our previously reported hydroamination results provided by a Rh/Josiphos **J003-2** based catalyst system, we tested these previous standard conditions for 2-iodo aniline (**7**) and *n*-hexyl allene (**1**). Surprisingly, we obtained the desired product **8** either with EtOH as a cosolvent or with PPTS as an additive in low optical purities (Table 1, entries 1 and 2). Furthermore, EtOH enabled a dehalogenation by transfer hydrogenation leading to dehalogenated allylic aniline **9**. To overcome the problem of low enantioselectivity, we tested the sterically more demanding ligand **J009-2** (entry 3). However, in the reaction in the presence of PPTS, the desired product **8** was obtained in low yield and enantioselectivity. To exclude

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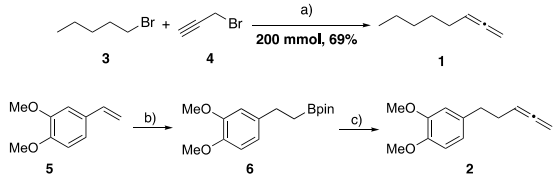
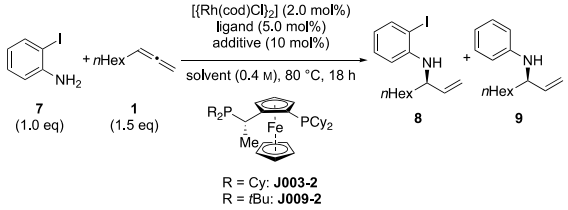
Scheme 1. Preparation of Allenes 1 and 2[a]



[a]Reaction conditions: (a) (1) **3** (1.0 equiv), Mg (1.2 equiv), THF (0.1 M), rt−70 °C, 2 h; (2) **4** (1.2 equiv), CuBr (10 mol %), THF (0.6 M), 0 °C−rt, 12 h, 69%; (b) HBpin (1.2 equiv), [{Ir(cod)Cl}$_2$] (1.0 mol %), dppp (2.0 mol %), toluene (1.0 M), rt, 18 h, 83%; (c) (1) ClMg(CH$_2$)$_4$MgCl (2.0 equiv), toluene/THF (1:1, 0.3 M), 0 °C−rt, 2 h; (2) propargyl bromide (**4**) (1.2 equiv), CuBr (10 mol %), THF (0.5 M), 0 °C−rt, 12 h, 72%.

Table 1. Optimization of the Hydroamination of 2-Iodo Aniline (7) and *n*-Hexyl Allene (1)



entry	ligand	additive	yield of **8**[c] (%)	ee of **8**[d] (%)	yield of **9**[c] (%)	ee of **9**[d] (%)
1[a]	**J003-2**		49	75	42	74
2[b]	**J003-2**	PPTS	97	79		
3	**J009-2**	PPTS	77	35		
4	**J009-2**		89	95		

[a]Reaction conditions: 2-iodo aniline (**7**) (1.0 mmol) and *n*-hexyl allene (**1**) (1.5 mmol) in DCE/EtOH (7:1, 2.5 mL) at 80 °C, 18 h. [b]Reaction conditions: 2-iodo aniline (**7**) (1.0 mmol), *n*-hexyl allene (**1**) (1.0 mmol), and PPTS (10 mol %) in DCE (2.5 mL) at 80 °C, 18 h. [c]Yield of isolated product. [d]Determined by chiral HPLC analysis. cod = 1,5-cyclooctadiene, PPTS = pyridinium *p*-toluenesulfonate.

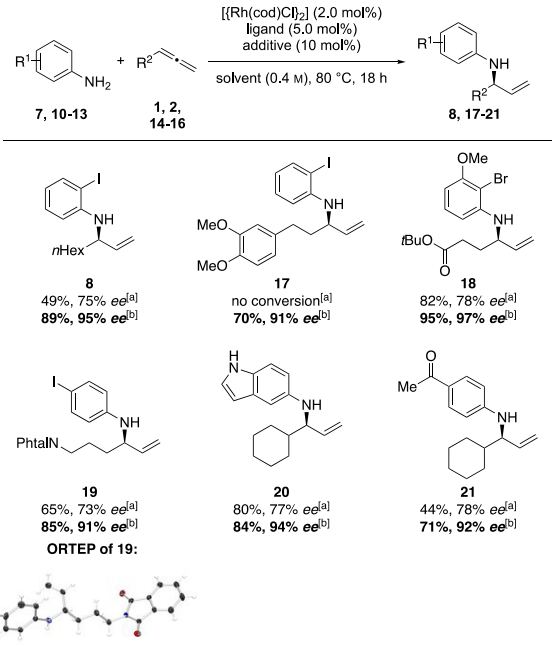
the possibility that the PPTS had a negative effect as an additive, the reaction was performed in the absence of it (entry 4). To our delight, **9** was obtained in high yield and excellent enantioselectivity, providing new optimized conditions for the hydroamination of allenes.[16]

With these optimized conditions in hand, we sought to examine a small scope of substrates, which did not perform satisfactorily under the previously reported conditions.[14] In all tested substrate combinations, the desired secondary anilines were obtained in better yields and higher enantioselectivities by the new catalyst system (Scheme 2).

Furthermore, product **19** allowed us to determine the absolute configuration, which was found to be the same as that obtained for the previous, **J003-2** based method.

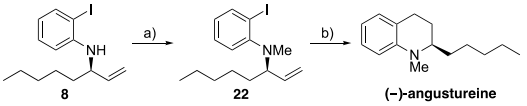
As we were now capable of synthesizing catalysis products **8** and **17** in high yield and enantioselectivity, the synthesis of (−)-angustureine and (−)-cuspareine was envisioned next. In contrast to the synthesis of Helmchen,[12a] the methylation of the secondary aniline was performed first for both natural products, as we assumed that the free amine could complicate the intramolecular Suzuki coupling by promoting unwanted side reactions.[17] In both cases, the amine methylation proceeded smoothly through reductive amination in good yields (Schemes 3 and 4). However, for the hydroboration of

Scheme 2. Comparison of Previous and New Hydroamination Conditions[a]



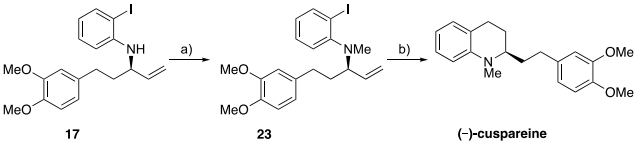
[a][a] Reaction conditions: aniline (1.0 mmol), allene (1.5 mmol), [{Rh(cod)Cl}$_2$] (2.0 mol %), and **J003-2** (5.0 mol %) in DCE/EtOH (7:1, 2.5 mL) at 80 °C, 18 h. [b] Reaction conditions: aniline (1.0 mmol), allene (1.5 mmol), [{Rh(cod)Cl}$_2$] (2.0 mol %), and **J009-2** (5.0 mol %) in DCE (2.5 mL) at 80 °C, 18 h.

Scheme 3. Synthesis of (−)-Angustureine[a]



[a]Reaction conditions: (a) Formaline sol. (40 wt %, 15 equiv), NaCNBH$_3$ (1.5 equiv), AcOH (10 equiv), MeCN (0.1 M), rt, 18 h, 99%; (b) 9-BBN (1.05 equiv), THF (0.5 M), 0 °C−rt; then [Pd(dppf)Cl$_2$] (1.5 mol %), NaOH$_{aq}$ (3.0 M, 3.0 equiv), 80 °C, 18 h, 94%.

Scheme 4. Synthesis of (−)-Cuspareine[a]



[a]Reaction conditions: (a) (CH$_2$O)$_n$ (15 equiv), NaCNBH$_3$ (10 equiv), AcOH (10 equiv), MeCN (0.1 M), rt, 18 h, 94%; (b) 9-BBN (2.5 equiv), THF (0.8 M), 70 °C, 20 min; then [Pd(dppf)Cl$_2$] (5.0 mol %), Cs$_2$CO$_3$ (2.0 equiv), DMF/H$_2$O (15:1, 0.4 M), 80 °C, 24 h, 63%.

the allylic double bond and the subsequent intramolecular Suzuki coupling, slightly different conditions had to be applied. Transformation of allylic aniline toward (−)-angustureine occurred under mild conditions, employing only 1 equiv of 9-BBN at rt, furnishing quantitively the desired hydroboration product. Its subsequent treatment with [Pd(dppf)Cl$_2$] and an

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aqueous NaOH solution at 80 °C furnished (−)-angustureine in 94 and 83% yield over three steps starting from allene **1**.

The synthesis of (−)-cuspareine starting from allylic amine **17**, however, did not succeed satisfactorily employing the same reaction conditions. Conversely, more forceful reaction conditions had to be chosen in order to guarantee complete hydroboration. Furthermore, the previously used conditions for the Suzuki coupling resulted in low yields. Finally, after being freed from the solvent (THF), the hydroboration intermediate was reacted in the presence of $[Pd(dppf)Cl_2]$ and Cs_2CO_3 in a solvent mixture of DMF/H_2O. These reaction conditions provided (−)-cuspareine in 63% yield and 25% overall yield in four steps starting with commercially available 4-vinyl veratrole (**5**).

In conclusion, we have developed concise, enantioselective, and protecting-group-free syntheses of (−)-angustureine and (−)-cuspareine. In this context, we improved the catalyst system of our previously developed hydroamination of allenes with anilines now reaching higher yields and enantioselectivities. This allylic addition can be seen as an atom efficient alternative to the conventionally applied allylic substitution.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04334.

All synthetic procedures for new compounds as well as their analytical data, involving ^{1}H NMR and ^{13}C NMR spectra and scanned HPLC chromatograms for chiral compounds (PDF)

Accession Codes

CCDC 1885897 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.

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Notes

The authors declare no competing financial interest.

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(16) Concerning the higher yield and enantiomeric purities of the products obtained with Josiphos ligand J009, we assume that the higher steric hindrance of J009 in comparison with J003 increases the energy difference between the favored and disfavored transition states as well as the stability of the Rh−Josiphos complex towards oxidation, as it has been observed in preliminary experiments. The latter one prevents the catalyst from decomposition during the reaction.
(17) Unfortunately, the yields in the reaction sequence indicated by Helmchen were not reproducible in our hands. Furthermore, our sequence enabled the possibility to circumvent the addition of toxic triphenylarsine in the Suzuki coupling due to its order.

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