Organic LETTERS

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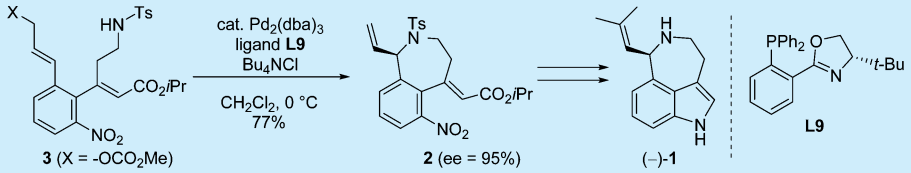
Asymmetric Synthesis of (−)-Aurantioclavine via Palladium-Catalyzed Intramolecular Allylic Amination

Satoshi Suetsugu, Hiromi Nishiguchi, Chihiro Tsukano, and Yoshiji Takemoto*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

Supporting Information



ABSTRACT: The total synthesis of (−)-aurantioclavine (**1**) was accomplished based on an intramolecular asymmetric amination of allyl carbonate **3** containing a *p*-tosylamide group. The reaction using tris(dibenzylideneacetone)dipalladium(0), *t*Bu-phosphinooxazoline, and Bu_4NCl in CH_2Cl_2 gave azepane **2** in 77% yield with 95% enantiomeric excess. The obtained azepane **2** was also converted to a substructure of communesin F.

(−)-Aurantioclavine (**1**), originally isolated from *Penicillium aurantiovirens* in 1981 by Kozlovskii et al., is a tricyclic alkaloid (Figure 1).[1] The structure of **1** consists of an azepane skeleton

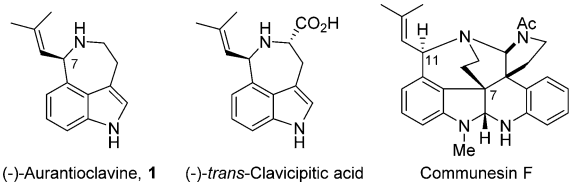


Figure 1. Aurantioclavine and related alkaloids.

fused with an indole ring. This molecule and a related alkaloid, clavicipitic acid, are thought to be biosynthetic intermediates of the polycyclic alkaloids communesins.[2] These molecules have therefore attracted much interest as synthetic targets,[3,4] and several racemic[5] and three enantiomeric syntheses of (−)-**1**[6−8] have been achieved to date. The absolute stereochemistry was established as 7*R* by Stoltz et al., based on their total synthesis.[6] Although these enantioselective syntheses were concise, introduction of the chiral center using kinetic optical resolution,[6] a chiral auxiliary,[7] and a chiral starting material[8] was needed before construction of the azepane ring. However, catalytic enantioselective formation of the azepane ring has not yet been reported. We therefore focused on an intramolecular asymmetric allylic amination using a metal catalyst.

The intramolecular asymmetric amination of allylic alcohol derivatives with an amine, amide, or carbamate is a powerful transformation for the construction of nitrogen heterocycles, and many methods have been developed using metal catalysts, including palladium, iridium, ruthenium, gold, and copper.[9] In these methods, the enantioselective formation of pyrrolidines and piperidines is often focused on. However, to the best of our knowledge, there have been few reports of enantioselective cyclizations of seven-membered rings.[10−15] Trost reported an intramolecular palladium-catalyzed amination of an allyl acetate to give an azepane ring in good yield and with high enantiomeric excess (ee), but achiral allyl acetates were not suitable for this reaction.[10] Helmchen, You, and Feringa described intramolecular asymmetric allylic aminations using a catalytic amount of $[Ir(COD)Cl]_2$ and a chiral phosphoramidite ligand to give azepanes with high enantioselectivities.[11−13] Unfortunately, the scope of these cyclizations to azepanes under these conditions was limited. Additionally, specific substrates were often required to improve the enantioselectivity and avoid undesired diene formation.[14,15]

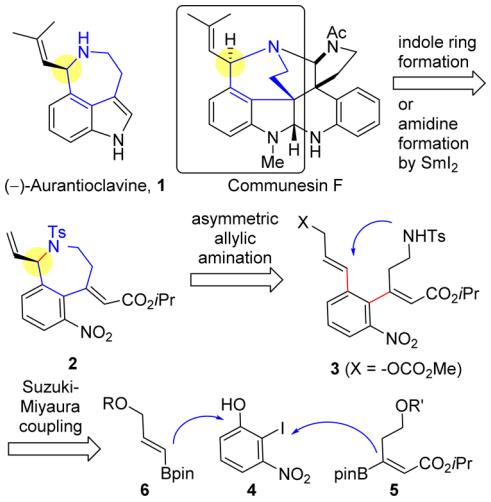
Based on the above points, compound **2** was designed as an intermediate that could be converted to (−)-aurantioclavine (**1**) by formation of an indole ring (Scheme 1). The intermediate **2** could also be used in the synthesis of a substructure of communesin F, based on the SmI_2-mediated amidine formation developed by us.[16] The seven-membered ring of **2** could be constructed by the intramolecular asymmetric amination of the achiral allyl carbamate **3** containing a *p*-tosylamide (TsNHR) group,[17] synthesized by Suzuki−Miyaura coupling of the known compound **4** with vinylboranes **5** and **6**. It was necessary to develop suitable conditions for formation of the azepane ring. In this paper, we describe the enantioselective total synthesis of (−)-aurantioclavine (**1**) and synthesis of the substructure of communesin F, by catalytic asymmetric allylic amination, for the construction of azepane **2**, using a palladium catalyst.

For investigation of the key asymmetric amination, allyl carbamate **3** was first prepared from 2-iodo-3-nitrophenol (**4**).[18] The protection of **4** with a 2-(trimethylsilyl)ethoxymethyl group, followed by Suzuki−Miyaura coupling with vinylborane **5**, which was prepared from 3-butyn-1-ol in three

Received: December 23, 2013

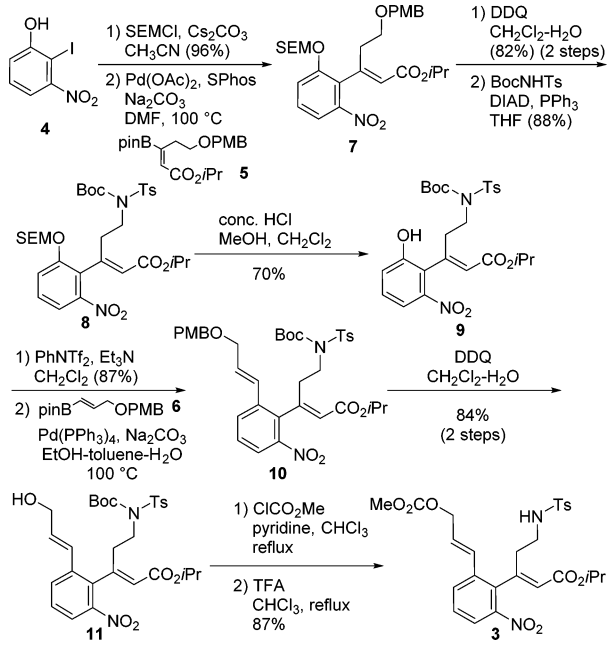
   dx.doi.org/10.1021/ol4037314 | *Org. Lett.* XXXX, XXX, XXX−XXX

Scheme 1. Retrosynthesis of (−)-Aurantioclavine (1) and Communesin F



steps, gave the coupling product **7** (Scheme 2). After removal of the PMB group by treatment with DDQ, a Mitsunobu

Scheme 2. Synthesis of Cyclization Precursor 3[a]

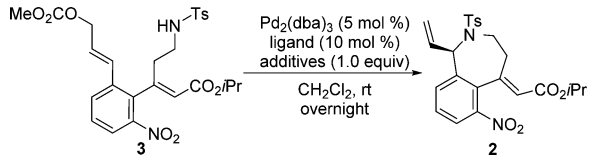


[a]SPhos: 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, pin: pinacolato, DIAD: diisopropyl azodicarboxylate. See Supporting Information for further details.

reaction of the resultant alcohol with *N*-(*tert*-butoxycarbonyl)-*p*-toluenesulfonamide (BocNHTs) under the standard conditions gave compound **8** in good yield. The 2-(trimethylsilyl)-ethoxymethyl group was removed by treatment with concentrated HCl to give phenol **9**. Triflation of **9** followed by Suzuki−Miyaura coupling with vinylborane **6** gave compound **10**. After removal of the PMB group, the resultant allyl alcohol **11** was converted to the cyclization precursor **3** by carbonate formation and removal of the Boc group.

Next, we investigated the asymmetric allylic amination of allyl carbonate **3**, by screening metal catalysts and chiral ligands (Table 1). We first attempted the reactions of **3** with $[Pd(allyl)Cl]_2$[10] and $[Ir(COD)Cl]_2$[11−13,19] as catalysts, based

Table 1. Intramolecular Asymmetric Allylic Amination of 3



entry	ligand	additives	yield[a]	ee
1	**L1**	none	NR[b]	NA[c]
2	**L1**	Bu_4NCl	quant	22%
3[d]	**L1**	Bu_4NCl	73%	12%
4	**L2**	Bu_4NCl	NR	NA
5	**L3**	Bu_4NCl	NR	NA
6	**L4**	Bu_4NCl	84%	47%
7	**L4**	none	84%	48%
8	**L5**	none	quant	78%
9	**L6**	none	81%	17%
10	**L7**	none	72%	74%
11	**L8**	none	quant	87%
12	**L9**	Bu_4NCl[e]	88%	92%
13[f]	**L9**	Bu_4NCl	77%	95%
14[g]	**L9**	Bu_4NBr	89%	92%

[a]Isolated yield. [b]NR = no reaction. [c]NA = not applicable. [d]DMF was used as a solvent instead of CH_2Cl_2. [e]0.01 equiv of Bu_4NCl was used. [f]The reaction was performed using $Pd_2(dba)_3$ (15 mol %), **L9** (45 mol %), and Bu_4NCl (0.30 equiv) in CH_2Cl_2 at 0 °C for 72 h. [g]The reaction was performed using $Pd_2(dba)_3$ (2.5 mol %), **L9** (7.5 mol %), and Bu_4NBr (0.10 equiv) in CH_2Cl_2 at rt for 4 h.

on Trost's and Helmchen's procedures, respectively. Only a trace amount of the product **2** or no desired product was obtained (not shown).[20] Although use of tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$), **L1** (Figure 2), in

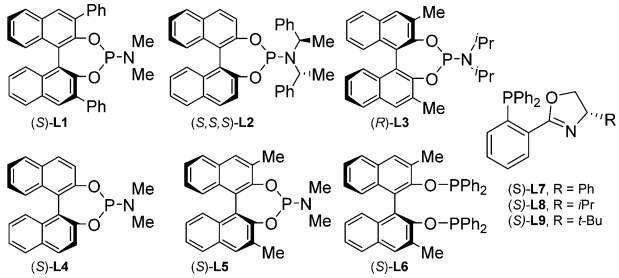


Figure 2. Chiral ligands for asymmetric allylic amination.

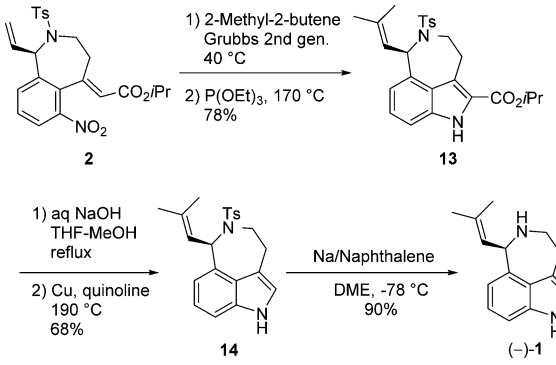
CH_2Cl_2[15,21] resulted in no reaction, the reaction proceeded to give product **2** by the addition of Bu_4NCl, which is effective for allylic substitution,[22] albeit with 22% ee (Table 1, entries 1, 2). The use of DMF instead of CH_2Cl_2 gave a lower ee (entry 3). It has been reported that a bulky amine unit in the phosphoramidite improved the ee,[15] so ligands **L2** and **L3** were examined. These ligands, however, were not effective with allyl carbonate **3** (entries 4, 5). In contrast, **L4** and **L5**, which have no substituents and a methyl group on the naphthyl ring, improved the enantioselectivities to 48% ee and 78% ee, respectively (entries 6−8). Interestingly, it was found that the reactions with **L4** and **L5** proceeded in the absence of Bu_4NCl, and the phosphoramidite ligand **L5** was suitable for this reaction (entries 7, 8). Because the obtained ee values were not

dx.doi.org/10.1021/ol4037314 | Org. Lett. XXXX, XXX, XXX−XXX

satisfactory, other ligands were also examined. The use of a bidentate ligand **L6** decreased the ee significantly (entry 9). In sharp contrast, the reaction with phosphinooxazoline (PHOX) ligands **L7**–**L9**, which are effective ligands for intermolecular asymmetric allylic aminations,[23] gave product **2** in good yield with high enantioselectivities (entries 10–12). The bulkiness of the substituents on the oxazoline affected the enantioselectivity, and a high ee was observed in the case of ligand **L9**. Finally, the ee was improved to 95% ee by performing the reaction with **L9** at 0 °C for 72 h (entry 13). Additionally, use of Bu_4NBr was effective for reducing the reaction time (entry 14).[20,22] Although the newly generated stereochemistry was not determined at this stage, we assumed that it was *R*, based on Pfaltz and Helmchen's report.[23] These conditions could also be used with substrate **12**, which has a nosyl (Ns) group instead of a Ts group, and the asymmetric allylic amination gave the corresponding product in 40% yield and 90% ee (not shown).[24] It is worth noting that PHOX ligands **L7**–**L9** have been used in intramolecular asymmetric allylic aminations.[25]

With the optically active compound **2** in hand, we investigated further transformations toward (−)-aurantioclavine (**1**). Introduction of a propenyl group by cross-metathesis using Grubbs' second-generation catalyst[26] and 2-methyl-2-butene was followed by formation of the indole ring by treatment with $P(OEt)_3$ at 170 °C (Scheme 3).[27] Hydrolysis of compound **13**,

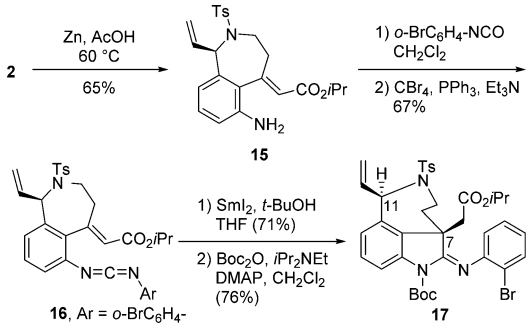
Scheme 3. Total Synthesis of (−)-Aurantioclavine (1)



followed by decarboxylation using copper powder in quinoline, gave the protected aurantioclavine **14**.[28] Finally, removal of the Ts group using sodium naphthalenide completed the total synthesis of (−)-aurantioclavine (**1**). The spectroscopic data, i.e., NMR, IR, and high-resolution MS, of the synthetic sample were identical to the reported data. Additionally, the optical rotation of the synthetic sample was −29.3°, which indicated that the stereochemistry at the C7 position was *R*, i.e., the natural enantiomer.[1,2]

We then turned our attention to the synthesis of the tricyclic core with a quaternary carbon center that is a substructure of communesin F. Reduction of the nitro group of **2**, followed by formation of urea and dehydration, gave carbodiimide **16** in 44% overall yield from **2** (Scheme 4). The key cyclization of carbodiimide **16** using SmI_2 and *t*BuOH proceeded smoothly to give an amidine, which was immediately converted to the Boc-protected amidine **17** in good yield.[16] The newly generated stereochemistry was determined by NMR experiments, including NOESY, and it was found that the quaternary carbon center at the C7 position had the *R* configuration.[29,30] We successfully constructed the tricyclic compound **17** with a

Scheme 4. Synthesis of Substructure of Communesin F



quaternary carbon center and an amidine moiety, although epimerization at the C11 position was required.

In summary, the catalytic enantioselective total synthesis of (−)-aurantioclavine was achieved, in a total of 16 steps, from 3-nitro-2-iodophenol. The key intramolecular asymmetric amination of allyl carbonate **3**, which has a TsNHR group, using $Pd_2(dba)_3$, *t*Bu-PHOX (**L9**), and Bu_4NCl in CH_2Cl_2, proceeded smoothly, with high enantioselectivity, to give compound **2** in good yield (77%, 95% ee). This asymmetric allylic amination was therefore a powerful tool for construction of the enantiomeric azepinoindole skeleton. Additionally, the synthetic intermediate **2** could be used for the synthesis of the substructure of communesin F. We are now investigating further applications of this reaction to communesins.

■ ASSOCIATED CONTENT

Supporting Information

Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: takemoto@pharm.kyoto-u.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported in part by a Grant-in-Aid for Scientific Research (B) (Y.T.) and "Platform for Drug Discovery, Informatics, and Structural Life Science" from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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(25) To our knowledge, there is one example of intramolecular asymmetric amination using the PHOX ligand via a π-allylpalladium intermediate, although the ee was moderate (50% ee); see: Zenner, J. M.; Larock, R. C. *J. Org. Chem.* **1999**, *64*, 7312.
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(29) Numbering for communesins was used.
(30) See Supporting Information.

dx.doi.org/10.1021/ol4037314 | *Org. Lett.* XXXX, XXX, XXX−XXX