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Total synthesis of (+)-azimine via diastereoselective aminopalladation

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ABSTRACT

The aminopalladation of amino allylic alcohol using $Cl_2Pd(MeCN)_2$ in CH_2Cl_2 gave the 2,6-disubstituted piperidine with excellent diastereoselectivity. This compound was successfully converted into (+)-azimine (**1**) using cross-metathesis and Shiina macrolactonization.

1. Introduction

Among a lot of numbers of biologically active natural compounds, the alkaloids are most paid attention due to their significant biological activities and unique structures.[1,2] Most of piperidine alkaloids possess a chiral center at C2 and/or C6 position, thus stereoselective construction is very important. For example, excellent diastereoselective syntheses have been achieved as follows. Stereoselective synthesis of *trans*-2,6-disubstituted piperidine alkaloids using Pd(0) catalyzed N-alkylation has been achieved by Tadano in 1993.[3] In 2000, Hirai reported Pd(II) catalyzed cyclization of amino allylic alcohol to afford 2-substituted piperidine with excellent diastereoselectivity.[4]

While most of alkaloids generally exist as monomers, (+)-azimine (**1**) is macrocyclic dilactone, which was isolated from *Azima tetracantha* L.[5,6] Structurally, azimine (**1**) is a dimer of (+)-azimic acid (**2**), which has 2-methyl-3-piperidinol skeleton with a carboxyl group at terminal position. This compound is presumed biosynthetic and synthetic precursor of (+)-azimine (**1**) (Fig. 1). The syntheses of (+)-azimic acid (**2**) were reported by many researchers,[7] however, there is only one example of asymmetric total synthesis of (+)-azimine (**1**) by Kibayashi and co-workers using stereoselective intramolecular hetero-Diels–Alder reaction of an acylnitroso compound.[8]

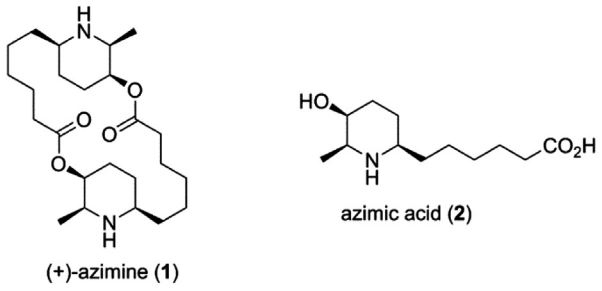

Fig. 1. The structures of (+)-azimine (**1**) and (+)-azimic acid (**2**).

In our previous report, we accomplished an asymmetric total synthesis of (−)-cassine using diastereoselective aminopalladation, however, the yield of this reaction was not high enough.[9] Therefore, we have investigated to improve the yield and found that the effect of solvent was useful for diastereoselective aminopalladation. Here we wish to report improved diastereoselective Pd(II)-catalyzed cyclization and its application to the total synthesis of azimine (**1**).

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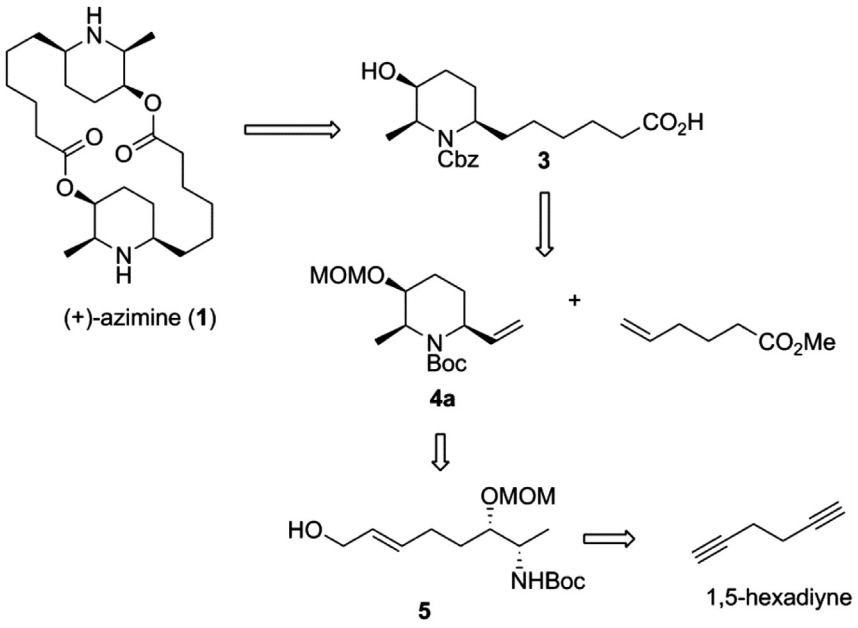
2. Results and discussion

Scheme 1 outlines our synthetic strategy. (+)-Azimine (**1**) would be derived from **3** via macrolactonization. Hydroxy carboxylic acid **3** would be prepared via several steps from **4a** and methyl 5-hexenate including Grubbs cross-metathesis. Piperidine **4a** would be synthesized using similar procedure from **5** as we reported previously (Scheme 1).[9]

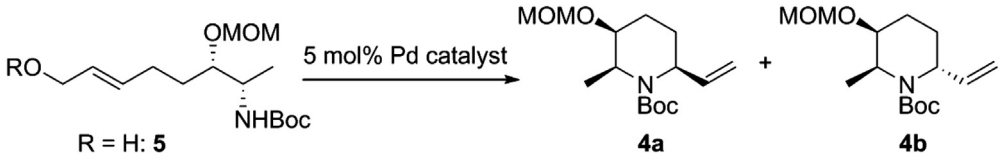


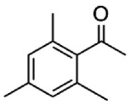
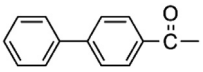
Scheme 1. Synthetic strategy of (+)-azimine (**1**).

The cyclization precursor **5** was synthesized from 1,5-hexadiyne as we reported earlier.[9] The results of diastereoselective aminopalladation of **5** and its derivatives are summarized in Table 1. At first we used the reaction condition as we have reported before to give **4a** in a moderate yield.[9] Using Pd(II) catalysts with phosphine ligands such as PPh_3 and dppf did not afford cyclized product. We also examined allylic ester such as pivaloyl, mesityl, and biphenyl esters because Hirai reported Pd(II) catalyzed cyclization of amino allylic pivaloyl ester afforded 3,4,5,6-substituted piperidine with excellent diastereoselectivity in 36% yield.[4] However, the yield of cyclized product was very low in our cases. We found that using allylic ester was difficult to construct 2,6-piperidine ring. Finally, we switched the solvent from THF to CH_2Cl_2 to afford **4a** in good yield.

Because we have optimized the reaction condition for stereoselective aminopalladation to prepare **4a**, we began total synthesis

Table 1
Stereoselective aminopalladation of **5** and its derivatives



Entry	R	Catalyst	Solvent	Time (h)	Yield % (**4a**/**4b**)	**4a**/**4b**[a]
1	H	$PdCl_2$	THF	12	61	>49:1
2	H	$Cl_2Pd(MeCN)_2$	THF	12	39	>49:1
3	H	$Cl_2Pd(PPh_3)_2$	THF	24	0	—
4	H	Cl_2Pd(dppf)	THF	24	0	—
5		$Cl_2Pd(MeCN)_2$	THF	24	Trace	—
6		$Cl_2Pd(MeCN)_2$	THF	24	0	—
7		$Cl_2Pd(MeCN)_2$	THF	24	0	—
8	H	$Cl_2Pd(MeCN)_2$	CH_2Cl_2	20	82	>49:1

[a] The relative stereochemistry of **4a** was determined by 2D-NOESY experiment.[9]