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Studies on palladium-catalyzed enantioselective cyclization of 3,4-allenylic hydrazines with organic halides

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ABSTRACT

A convenient route to optically active pyrazolidine derivatives from Pd(0)/(*R*,*R*)-Bn-BOX-catalyzed enantioselective cyclization of 3,4-allenylic hydrazines in the presence of organic halides has been developed, the ee value is 75–84%. The absolute configuration of the products was determined by the conversion of one of the products to a known product prepared in this group. The reaction may proceed via the oxidative addition, intermolecular carbometallation of the allene moiety forming a π-allylic palladium intermediate, and the intramolecular enantioselective allylation.

1. Introduction

Pyrazolidine, an important heterocyclic unit existed in many natural and bioactive products,[1] has attracted more and more attention of both bio- and synthetic chemists. Although the pyrazolidine structural unit is usually available from [3+2] cycloaddition[2,3] and hetero-Diels–Alder cycloaddition of 1,3-cyclopentadiene with diethyl azodicarboxylate,[4] these existing methods often suffer from the complexity of starting materials. Since enantiomers often exhibit significant variance in biological activities,[5] the development of asymmetric synthetic methodologies has been of prime importance to organic chemists. However, the catalytic asymmetric synthesis of pyrazolidine derivatives has been much less explored.[6]

Transition metal-catalyzed coupling–cyclization reactions involving functionalized allenes have been demonstrated to be one of the most powerful protocols to construct carbo- and heterocycles.[7] We and others have developed transition metal-catalyzed coupling–cyclization reactions of functionalized allenes with organic halides.[8] Meanwhile, the palladium-catalyzed asymmetric allylic substitution reaction has been shown to be a useful means for forming new carbon–carbon,[9] carbon–nitrogen,[10] carbon–oxygen,[11] and carbon–sulfur[12] bonds in an enantioselective manner. Most work in this area has been focused on the development of improved chiral ligands for intermolecular nucleophilic substitution of the allylic systems.[13] In contrast, relatively little work has been done with more complicated intramolecular systems.[14] Larock et al. reported a palladium-catalyzed asymmetric hetero- and carboannulation of allenes using aryl and vinylic iodides bearing a nucleophilic functionality to construct various cyclic products in moderate to good ee.[15] In 2004, our group reported an efficient method for the synthesis of pyrazolidine derivatives through Cu- and Pd-catalyzed asymmetric one-pot tandem addition–cyclization reaction of 2-(2′,3′-alkadienyl)-3-ketoesters and dibenzyl azodicarboxylate in the presence of organic halides in high ee (up to 99%) but moderate diastereoselectivity (cis/trans=33:77 to 45:55).[16] Recently, a highly diastereoselective palladium-catalyzed cyclization of optically active 3,4-allenylic hydrazines with organic halides was also realized in our group by using $Pd(OAc)_2$ and (*R*,*R*)-Bn-BOX as the ligand.[17] However, the high enantiopurities of the products in the above mentioned two methods came partially from the preintroduced chiral information in the substrates. Herein, we wish to report a catalytic enantioselective synthesis of pyrazolidine derivatives by cyclization of 3,4-allenylic hydrazines in the presence of organic halides.

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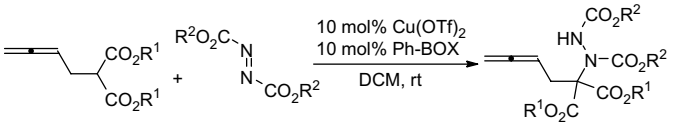
2. Results and discussion

2.1. Synthesis of starting 3,4-allenylic hydrazines

The starting 3,4-allenylic hydrazines were synthesized via Cu-catalyzed Michael addition of 2-(2′,3′-butadienyl)malonate with azodicarboxylate (Scheme 1).



1a: R^1 = Me, R^2 = Bn, 88%
1b: R^1 = Bn, R^2 = Bn, 77%
1c: R^1 = Et, R^2 = Et, 85%
1d: R^1 = Et, R^2 = Bn, 54%

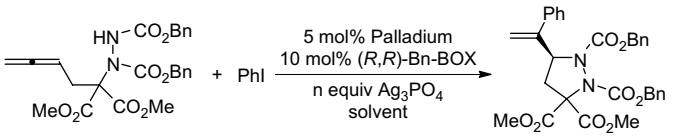
Scheme 1. Synthesis of 3,4-allenylic hydrazines **1a**–**1d**.

2.2. Pd(0)-catalyzed enantioselective cyclization of 3,4-allenylic hydrazines with organic halides

Our initial efforts were focused on the cyclization of 3,4-allenylic hydrazine **1a** with iodobenzene. The effect of solvents and the amount of silver salt were screened with Ag_3PO_4 being used as the base (Table 1). THF was found to be the best solvent in terms of the enantioselectivity (compare entries 1–5, Table 1). No remarkable change of ee of the product was observed by increasing the amount of Ag_3PO_4 from 0.4 to 0.5 equiv, although the use of 0.45 equiv of Ag_3PO_4 afforded the product **3aa** in the highest yield (entries 5–7, Table 1). Lowering the reaction temperature to 70 °C further improved the yield and the enantioselectivity (compare entries 7 and 8, Table 1).

However, because it is quite difficult to prepare pure **1a**, allenylic hydrazine with dibenzyl malonate moiety **1b** was used instead to screen the ligands for the reaction (Table 2). As shown in Table 2, the reaction in THF at 70 °C with 0.45 equiv of Ag_3PO_4 as the base afforded the desired product **3ba** in good enantiomeric excess (83%) when bisoxazoline (*R*,*R*)-**L1** and $Pd(dba)_2$ were used as the catalysts (entry 1, Table 2). Notably, the trioxazoline ligands **L4** and

Table 1
The effect of solvent and base on the Pd-catalyzed enantioselective coupling–cyclization of **1a** with PhI[a]

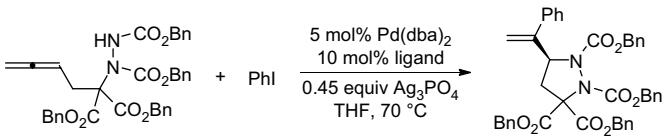


1a **3aa**

Entry	Solvent	*n* equiv Ag_3PO_4	Temperature (°C)	Yield of **3aa**[b] (%)	ee[c] (%)
1	DMF	0.4	80	72	63
2	1,4-Dioxane	0.4	80	69	71
3	Toluene	0.4	80	68	62
4	THF/DMF[d]	0.4	80	57	77
5	THF	0.4	80	54	81
6	THF	0.45	80	67	82
7	THF	0.5	80	61	82
8[e]	THF	0.45	70	75	84

[a] The reaction was carried out using 0.2 mmol of **1a**, 0.24 mmol of PhI, 0.2×*n* mmol of Ag_3PO_4, 5 mol % of $Pd(OAc)_2$, and 10 mol % of (*R*,*R*)-Bn-BOX in 2 mL of solvent in a Schlenk tube with a screw cap unless otherwise stated.
[b] Isolated yields.
[c] The ee values were determined by chiral HPLC analysis.
[d] THF/DMF=1:1.
[e] $Pd(dba)_2$ (5 mol %) and (*R*,*R*)-Bn-BOX (10 mol %) were used.

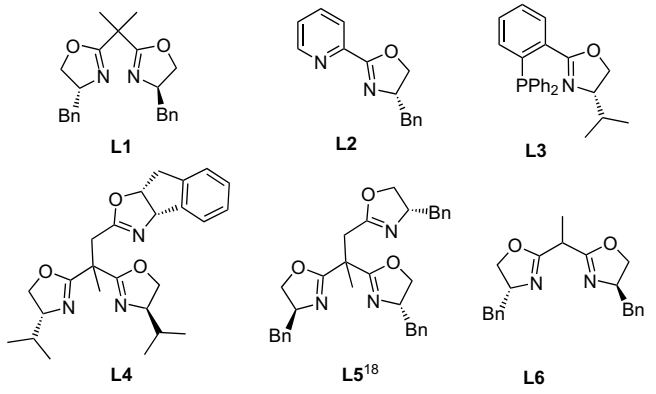
Table 2
Ligand effect on the Pd-catalyzed enantioselective coupling–cyclization of **1b** with PhI[a]



1b **2a** **3ba**

Entry	Ligand	Yield of **3aa** (%)[b]	ee[c] (%)
1	**L1**	75	83
2	**L2**	Complex	—
3	**L3**	NR[d]	—
4	**L4**	75	80
5	**L5**	69	83
6	**L6**	NR[d]	—

[a] The reaction was carried out using 0.1 mmol of **1b**, 0.12 mmol of PhI, 0.045 mmol of Ag_3PO_4, 5 mol % of $Pd(dba)_2$, and 10 mol % of ligand in 2 mL of THF at 70 °C in a Schlenk tube with a screw cap.
[b] Isolated yields.
[c] The ee values were determined by chiral HPLC analysis.
[d] NR=No reaction.



L5[18] also catalyzed the reaction to afford the product in 80% ee and 83% ee, respectively (entries 4 and 5, Table 2). However, ligands **L2**, **L3**, and **L6** were ineffective (entries 2, 3, and 6, Table 2). On the basis of these results, we defined 1.0 equiv of **1b**, 1.2 equiv of **2a**, 0.45 equiv of Ag_3PO_4, 5 mol % of $Pd(dba)_2$, and 10 mol % of (*R*,*R*)-Bn-BOX(**L1**) in THF at 70 °C as the standard reaction conditions.

With the optimized reaction conditions in hand, we studied the scope of this catalytic stereoselective cyclization reaction with respect to organic halides and allenylic hydrazines (Table 3). As shown in Table 3, pyrazolidines were obtained in good yields with good enantiopurity (>80%) in most cases. Not only aryl halides with electron-donating and -withdrawing groups could be used in this reaction (entries 2–9, Table 3), heteroaryl and 1-alkenyl iodides are also suitable substrates (entries 10–13, Table 3). Moreover, (*S*,*S*)-Bn-BOX can also catalyze the reaction to form the opposite enantiomer in comparable yield and ee value (entry 14, Table 3).

Since all the pyrazolidines obtained above are viscous oils, we tried to vary R^1 and R^2 groups on the substrate, intending to prepare a solid product to elucidate the absolute configuration of the products (entries 15 and 16, Table 3), but all efforts proved to be fruitless. Thus, tentative assignment on the configuration in the products was made based on the previous results in our group.[16,17] By using (*R*,*R*)-Bn-BOX as the ligand, the reaction of (*R*), (*S*), or racemic 2-(*N*,*N*-bis-(benzyloxycarbonyl)hydrazino)-2-(2′,3′-butadienyl)-3-oxobutyric acid ethyl ester with phenyl iodide all afforded the 5*S*-isomers as the major products. In consideration of the similarity of these two systems, the absolute configuration of