Synthesis of a new spiro-BOX ligand and its application in enantioselective allylic cyclization based on carbopalladation of allenyl hydrazines†

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In this paper, we developed a new bisoxazoline ligand with a spiro skeleton and a α-naphthylmethyl substituent, *i.e.* (R_a,*S*,*S*)-L3, which has been successfully applied to the highly enantioselective cyclic allylation based on the carbopalladation of 3,4-allenyl hydrazines with ee values ranging from 92–95%.

Transition metal-catalyzed asymmetric allylic substitution of allylic acetate or carbonates is a well-established process for the highly enantioselective formation of carbon–carbon or heteroatom bonds.[1–5] As we know, the carbometallation of allenes would usually provide 2-substituted π-allylic metallic intermediates.[6,7] However, the success on the asymmetric allylation with 2-substituted allylic metallic species is very limited.[1c,8] Several examples on the enantioselective allylation based on the carbopalladation of allenes have been reported, but only moderate enantiomeric excesses have been achieved except in a few rare cases: Hiroi *et al.* reported two examples of reaction of 1-phenyl-1,2-butadiene with sodium malonate using bppfOAc[9a] and intramolecular cyclization of 2-(*N*-allenyl)-aminophenyl iodides with modified BINAP[9b] as the ligands in 96 and 88% ee, respectively; (*R*)-Bn-BOX ((*R*)-**L1**) has been used first by Larock[9c,d] followed by us[10] to study the enantioselective intramolecular allylations based on carbopalladation of allenes with moderate ee (<84%). According to our own unpublished results in this area, most of the known ligands do not work well for the allene-based enantioselective allylation, probably due to the *syn*/*anti*-complexity caused by the introduction of the substitutent at the 2-position of the π-allylic moiety. Thus, it is of high interest to develop new catalyst systems for the highly enantioselective allylation based on carbometallation of allenes. On the other hand, Zhou *et al.* has demonstrated that bidentate P–P ligands with a spiro skeleton are privileged ligands in asymmetric synthesis.[11] In addition, Zhou *et al.* has successfully applied spiro-BOX in copper-catalyzed highly enantioselective insertion of carbenoids into O–H and N–H bonds.[12] We envisioned that this type of bisoxazoline with a spiro-skeleton may be useful for the Pd-catalyzed enantioselective allene-based allylation reactions. Herein, we wish to report the synthesis of a new spirobisoxazoline ligand with a α-naphthylmethyl substituent, *i.e.*, (R_a,*S*,*S*)-**L3** (Fig. 1), which is a fairly good ligand for the enantioselective cyclization of 3,4-allenyl hydrazines with organic halides, affording the optically active 3-substituted pyrazolidines in good yields with 92–95% ee.

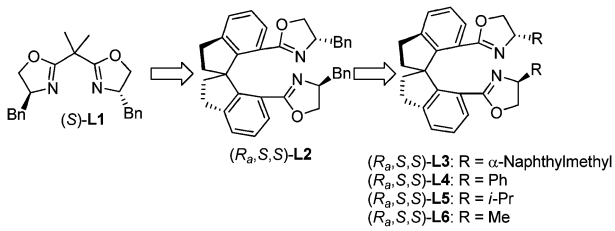

Fig. 1 Evolution of the bisoxazoline ligands.

We initially used (R_a,*S*,*S*)-**L2** with a spiro-skeleton[12] to replace (*S*)-**L1** (83% ee) for this palladium-catalyzed enantioselective cyclization of allenyl hydrazine **1a** with phenyl iodide. It is interesting to observe that when the reaction was performed in THF at 70 °C (very slow!) or 100 °C with the catalyst generated *in situ* from mixing 5 mol% of $Pd(dba)_2$ and 6 mol% of (R_a,*S*,*S*)-**L2**, the cyclization product (*R*)-**3aa** was obtained in 91% ee (entries 1 and 3, Table 1). Comparison of the two diastereomers of ligand **L2** clearly revealed that the (R_a,*S*,*S*)-**L2** has a matched combination of chiralities in terms of enantioselectivity (compare entries 1 and 2, Table 1). Considering the steric bulkiness of the α-naphthylmethyl substituent, a new ligand (R_a,*S*,*S*)-**L3** was prepared according to the known procedure.[12] We are happy to observe that when (R_a,*S*,*S*)-**L3** was applied to this reaction in THF at 100 °C, the pyrazolidine (*R*)-**3aa** was obtained in 69% yield with 94% enantioselectivity (entry 4, Table 1)! Unfortunately, the product was contaminated with an inseparable impurity. We tried to carry out this reaction in different solvents, such as DME and anisole (entries 5 and 6, Table 1), but the problem remained unsolved. To our delight, when the reaction was conducted at a lower temperature (80 °C), it proceeded smoothly to afford (*R*)-**3aa** cleanly in 85% yield and 93–94% ee (entry 7, Table 1). However, phenyl and isopropyl substituted spirobisoxazoline ligands (R_a,*S*,*S*)-**L4** and (R_a,*S*,*S*)-**L5** only led to a complicated mixture (entries 8 and 9, Table 1). Methyl substituted spirobisoxazoline ligand (R_a,*S*,*S*)-**L6** induced the reaction in 91% yield and 88% ee (entry 10, Table 1). All these data indicated that both the spiro-skeleton and the bulkiness of the α-naphthylmethyl group are responsible for the high enantioselectivity of this reaction.

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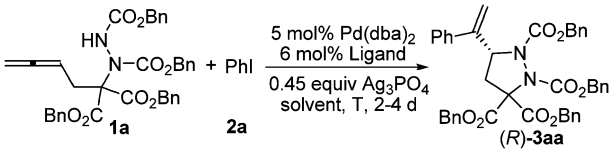
Table 1 Optimization of the reaction conditions for the Pd(0)-catalyzed enantioselective cyclization of **1a** with PhI[a]



Entry	Ligand	Solvent	T/°C	Yield[b] (%)	ee[c] (%)
1	(R_a,*S*,*S*)-**L2**	THF	70	70[d]	91
2	(S_a,*S*,*S*)-**L2**	THF	70	47[e]	−29
3	(R_a,*S*,*S*)-**L2**	THF	100	89	91
4	(R_a,*S*,*S*)-**L3**	THF	100	(69)	94
5	(R_a,*S*,*S*)-**L3**	DME	100	(36)	nd[f]
6	(R_a,*S*,*S*)-**L3**	Anisole	100	(48)	nd[f]
7	(R_a,*S*,*S*)-**L3**	THF	80	85	93–94
8	(R_a,*S*,*S*)-**L4**	THF	100	Trace[g]	nd[f]
9	(R_a,*S*,*S*)-**L5**	THF	100	Trace[g]	nd[f]
10	(R_a,*S*,*S*)-**L6**	THF	100	91	88

[a] The reaction was carried out by using 0.1 mmol of **1a**, 0.12 mmol of PhI, 0.045 mmol of Ag_3PO_4, 5 mol% of $Pd(dba)_2$, and 6 mol% of ligand in 2 mL of THF in a Schlenk tube with a screw cap. [b] Isolated yields unless otherwise stated, the yields in parentheses are NMR yields using mesitylene as the internal standard. [c] The ee values were determined by chiral HPLC analysis. [d] 53% of **1a** was recovered, and the yield was calculated based on the converted **1a**. [e] 46% of **1a** was recovered, and the yield was calculated based on the converted **1a**. [f] nd = not determined. [g] The starting material **1a** was completely consumed.

Encouraged by these promising results obtained in the cyclization of 3,4-allenyl hydrazine **1a** with iodobenzene **2a** catalyzed by spirobisoxazoline (R_a,*S*,*S*)-**L3** in THF at 80 °C, we tested a variety of organic halides and 3,4-allenyl hydrazines under the standard conditions. The results are listed in Table 2. Various aryl iodides with electron-withdrawing and electron-donating groups proceeded smoothly to afford the corresponding pyrazolidine derivatives in good yields and high enantioselective excesses (entries 1–9, Table 2). Poly-substituted aryl iodides are compatible in this reaction (entries 10–12, Table 2). There is an excellent selectivity of the C–I bond over the C–Br bond (entries 4, 9, and 14, Table 2). A heteroaryl iodide is also a suitable substrate for this process (entry 15, Table 2). The corresponding reaction of **1b** and **1c** also proceeded smoothly to afford (*R*)-**3be** and (*R*)-**3cd** in 93–95% ee with good yields (entries 13 and 14, Table 2). The absolute configuration of the products is confirmed to be *R* by comparison of the chiral HPLC report and the specific rotation of **3cd** prepared in this study with the known product (*S*)-**3cd**.[10b]

In summary, we have developed a new chiral spirobisoxazoline ligand (R_a,*S*,*S*)-**L3**, which has been applied to the enantioselective cyclization of allenyl hydrazines with aromatic iodides successfully, affording optically active pyrazolidine derivatives in high yields and high enantiomeric excesses. Based on the control experiment, it is believed that both the unique spiro skeleton and the α-naphthylmethyl group are important for the high enantioselectivity observed. This type of new bisoxazoline ligands may be useful in other related asymmetric reactions. Further study in this area is ongoing in our laboratory and will be reported in due course.

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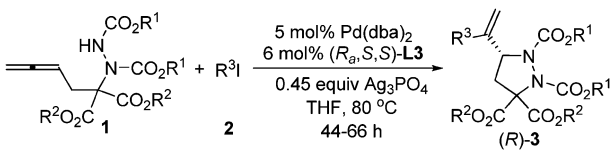
Table 2 Substrate scope of the palladium-catalyzed enantioselective cyclization of **1** with **2**[a]



Entry	**1** R[1]	**1** R[2]	**2** R[3]	Yield of (*R*)-**3** (%)[b]	ee (%)[c]
1	Bn	Bn (**1a**)	C_6H_5 (**2a**)	85 ((*R*)-**3aa**)	93–94
2	Bn	Bn (**1a**)	4-MeC_6H_4 (**2b**)	71 ((*R*)-**3ab**)	93
3	Bn	Bn (**1a**)	3-MeC_6H_4 (**2c**)	90 ((*R*)-**3ac**)	92
4[d]	Bn	Bn (**1a**)	4-BrC_6H_4 (**2d**)	83 ((*R*)-**3ad**)	93
5	Bn	Bn (**1a**)	4-$MeOCC_6H_4$ (**2e**)	75 ((*R*)-**3ae**)	95
6	Bn	Bn (**1a**)	4-$MeO_2CC_6H_4$ (**2f**)	76 ((*R*)-**3af**)	93
7	Bn	Bn (**1a**)	4-NCC_6H_4 (**2g**)	78 ((*R*)-**3ag**)	94
8	Bn	Bn (**1a**)	4-PhC_6H_4 (**2h**)	88 ((*R*)-**3ah**)	92
9	Bn	Bn (**1a**)	4-(4′-BrC_6H_4)C_6H_4 (**2i**)	71 ((*R*)-**3ai**)	92
10	Bn	Bn (**1a**)	3,4-$Me_2C_6H_3$ (**2j**)	76 ((*R*)-**3aj**)	95
11	Bn	Bn (**1a**)	3,5-$Me_2C_6H_3$ (**2k**)	83 ((*R*)-**3ak**)	93
12	Bn	Bn (**1a**)	3,4-$(OCH_2)_2C_6H_3$ (**2l**)	74 ((*R*)-**3al**)	93
13	Et	Et (**1b**)	4-$MeOCC_6H_4$ (**2e**)	83 ((*R*)-**3be**)	93
14[d]	Bn	Et (**1c**)	4-BrC_6H_4 (**2d**)	86 ((*R*)-**3cd**)	95
15	Bn	Bn (**1a**)	3-thienyl (**2m**)	85 ((*R*)-**3am**)	92

[a] The reaction was carried out by using 0.1 mmol of **1**, 1.2 equiv. of **2**, 0.45 equiv. of Ag_3PO_4, 5 mol% of $Pd(dba)_2$ and 6 mol% of (R_a,*S*,*S*)-**L3** in 2 mL of THF in a Schlenk tube with a screw cap. [b] Isolated yields. [c] The ee values were determined by chiral HPLC analysis. [d] 10 mol% of $Pd(dba)_2$ and 12 mol% of (R_a,*S*,*S*)-**L3** were used.

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