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Development of a New Spiro-BOX Ligand and Its Application in Highly Enantioselective Palladium-Catalyzed Cyclization of 2-Iodoanilines with Allenes

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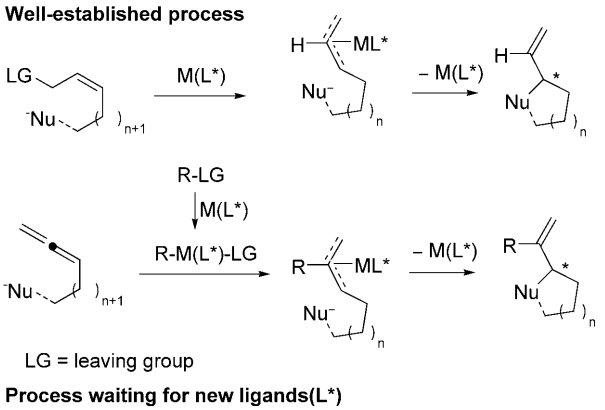
Abstract: In this communication, we report the synthesis of a new chiral spiro-bisoxazoline ligand, i.e., β-naphthylmethyl-substituted spiro-BOX [(R_a,*S*,*S*)-**L7**] and have successfully applied it to the palladium-catalyzed enantioselective cyclization reaction of simple allenes with *o*-aminoiodobenzenes, affording highly optically active 3-alkylideneindolines in good yields with excellent enantiomeric excesses.

Keywords: allenes; asymmetric catalysis; cyclization; indolines; palladium



Scheme 1. Two different protocols of enantioselective allylation.

Due to the potentials of compounds with chirality, asymmetric synthesis has always been a hot research area for organic chemists. In addition to the well-recognized asymmetric reactions of C=C bonds such as hydrogenation, epoxidation, etc., scientists are pursuing the efficient access to optically active compounds *via* catalytic enantioselective C–C and C–X bond formation processes. In this area, transition metal-catalyzed asymmetric allylic substitution, especially the Tsuji–Trost reaction, has been demonstrated to be one of the most powerful protocols to form these bonds with excellent enantioselectivity.[1] In principle, the carbometallation of allenes would usually provide *2-substituted π-allylic* metallic intermediates,[2] which provides a new pathway for asymmetric synthesis using allenes as the starting points (Scheme 1). However, the successful reports on the asymmetric allylic substitution with a *2-substituted π-allylic* palladium intermediate are still very limited,[3] thus, as expected, only a few examples on the asymmetric allylic substitution based on carbometallation of allenes *with low to moderate ee* have been reported.[4] Larock et al. reported the cyclization of 2-aminophenyl iodides with allenes catalyzed by Pd-(*R*)-Bn-BOX [(*R*)-**L1**] to afford a series of indolines in 80–82% *ee*;[5] This ligand has also been used by us to synthesize other heterocycles again with 80–84% *ee*.[6] We have tried many known ligands during the past ten years for this type of transformation with very limited success, thus, in order to make this type of transformation synthetically useful and practical, new effective ligands should be developed. In a case like this, there is really no substitute for the human labour required to identify new ligands. Thus, we pursued new bisoxazoline ligands from other commercially available amino acids. Herein, we wish to report the development of a new ligand, i.e., β-naphthylmethyl spiro-BOX (**L7**), which has been demonstrated for the enantioselective Pd-catalyzed cyclization of 2-iodoanilines with allenes, affording a wide range of 2*H*-indolines in good yields with 94–98% *ee* (Figure 1).

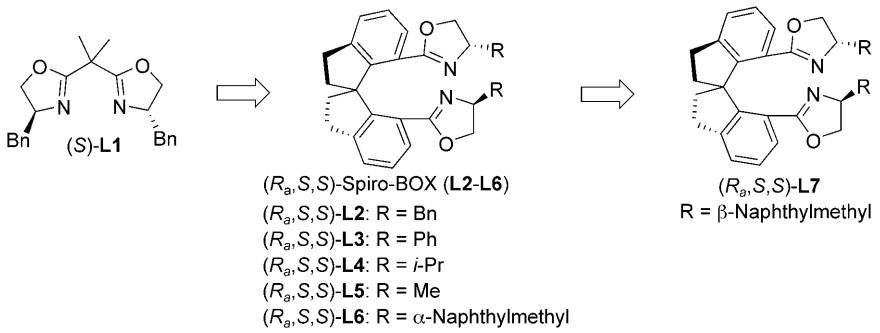
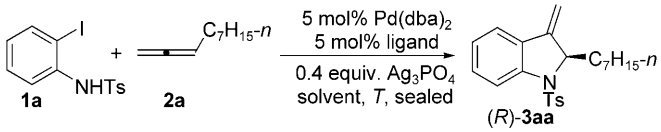


Figure 1. Evolution of the bisoxazoline ligands.

We started our investigation based on the reaction of **1a** with **2a** in DMF catalyzed by 5 mol% $Pd(dba)_2$ with 5 mol% (R_a,*S*,*S*)-**L2** having a chiral spiro-skeleton[7] as the ligand. To our disappointment, the desired product was obtained in 74% yield with 79% *ee* (Table 1, entry 1). Ligand (S_a,*S*,*S*)-**L2** led to the (*S*)-product in 70% *ee* (entry 2, Table 1). Further screening of the ligands revealed that the phenyl- and isopropyl-substituted spiro-BOX ligands [(R_a,*S*,*S*)-**L3** and **L4**] led to an almost racemic product (Table 1, entries 3 and 4). Interestingly, methyl-substituted spiro-BOX [(R_a,*S*,*S*)-**L5**] afforded **3aa** in 87% *ee* (Table 1, entry 5). When the α-naphthylmethyl group substituted spiro-BOX [(R_a,*S*,*S*)-**L6**] was introduced to this reaction, the same level of enantioselectivity (86%) was observed.[8] Luckily, to our surprise, we observed that when (R_a,*S*,*S*)-**L7** with a *β-naphthylmethyl substituent* was applied to the reaction under the same conditions, the *ee* value was improved to 90% (Table 1, entry 7). Quick screening on the solvent effect revealed that THF is the best (Table 1, entries 7–11). Increasing the reaction temperature can shorten the reaction time and surprisingly improve the yield without eroding the enantioselectivity (Table 1, entry 12). Further increasing the ratio of **1a**:**2a** to 1:4 led to a complete consumption of **1a** and **3aa** was obtained in 57% yield with 96% *ee* (Table 1, entry 14)! We then defined the reaction of 1 equivalent of **1a** and 4 equivalents of **2a** catalyzed by 5 mol% $Pd(dba)_2$ and 5 mol% (R_a,*S*,*S*)-**L7** with

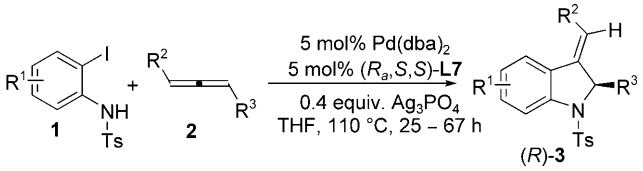
Table 1. Optimization of the reaction conditions for the Pd(0)-catalyzed enantioselective cyclization reaction of **1a** with **2a**.[a]

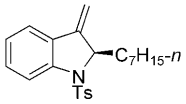
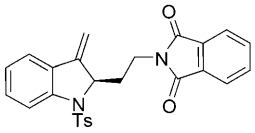
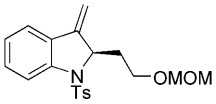
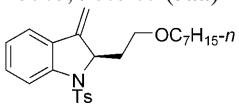
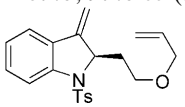
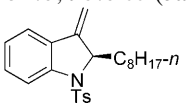
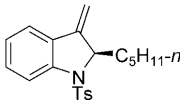
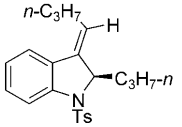
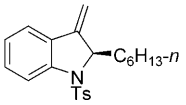
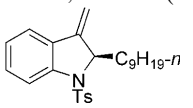
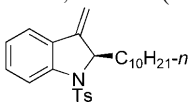
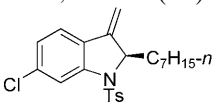
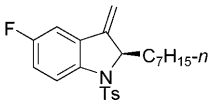
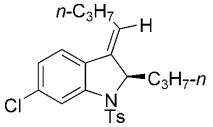
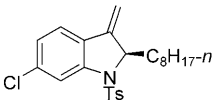


Entry	Ligand	Solvent	*T* [°C]	*t* [h]	Yield of **3aa** [%][b]	*ee* [%][c]
1	(R_a,*S*,*S*)-**L2**	DMF	90	24	74	79
2	(S_a,*S*,*S*)-**L2**	DMF	90	10	66 (17)	−70
3	(R_a,*S*,*S*)-**L3**	DMF	90	37	60 (21)	16
4	(R_a,*S*,*S*)-**L4**	DMF	90	18	75	9
5	(R_a,*S*,*S*)-**L5**	DMF	90	32	76	87
6	(R_a,*S*,*S*)-**L6**	DMF	90	24	59 (15)	87
7	(R_a,*S*,*S*)-**L7**	DMF	90	22	67 (15)	90
8	(R_a,*S*,*S*)-**L7**	toluene	90	36	68 (17)	82
9	(R_a,*S*,*S*)-**L7**	DCE	90	36	42 (39)	68
10	(R_a,*S*,*S*)-**L7**	THF	90	86	34 (43)	97
11	(R_a,*S*,*S*)-**L7**	dioxane	90	65	31 (40)	95
12	(R_a,*S*,*S*)-**L7**	THF	110	48	36 (40)	95
13[d]	(R_a,*S*,*S*)-**L7**	THF	110	48	46 (16)	95
14[e]	(R_a,*S*,*S*)-**L7**	THF	110	48	57	96

[a] The reaction was carried out by using 0.2 mmol of **1a**, 0.4 mmol of **2a**, 0.08 mmol of Ag_3PO_4, 5 mol% of $Pd(dba)_2$, and 5 mol% of ligand in 2 mL of indicated solvent in a Schlenk tube with a screw cap unless otherwise stated.
[b] Isolated yields, the yields in parentheses are the recoveries of **1a**.
[c] The *ee* values were determined by chiral HPLC analysis.
[d] 0.6 mmol of **2a** were used.
[e] 0.8 mmol of **2a** were used.

Table 2. Substrate scope of the Pd(0)-catalyzed enantioselective cyclization of various **1** with allenes **2**.[a]



		
57%, 96% *ee* (**3aa**)	87%, 97% *ee* (**3ab**)	52%, 96% *ee* (**3ac**)
		
76%, 95% *ee* (**3ad**)	69%, 95% *ee* (**3ae**)	79%, 96% *ee* (**3af**)
		
67%, 95% *ee* (**3ag**)	53%, 98% *ee* (***E*-3ah**)	63%, 95% *ee* (**3ai**)
		
63%, 95% *ee* (**3aj**)	69%, 95% *ee* (**3ak**)	78%, 95% *ee* (**3ba**)
		
69%, 94% *ee* (**3ca**)	56%, 94% *ee* (***E*-3bh**)	76%, 95% *ee* (**3bf**)

[a] The reaction was carried out by using 0.2 mmol of **1**, 0.8 mmol of **2**, 0.08 mmol of Ag_3PO_4, 5 mol% of $Pd(dba)_2$, and 5 mol% of (R_a,*S*,*S*)-**L7** in 2 mL of THF in a Schlenk tube with a screw cap. The yields given are isolated yields. The *ee* values were determined by chiral HPLC analysis.

0.4 equivalents of Ag_3PO_4 as base in THF at 110 °C as the standard conditions for further study.

With the optimized reaction conditions in hand, we turned to examine the substrate scope of this process. The results are listed in Table 2. Various terminal allenes are proper substrates for this process, affording corresponding (*R*)-2-alkylideneindolines[9] in moderate to good yields with 94–98% *ee*. Notably, many functional groups, such as ether, amide, and MOM, were easily tolerated in this reaction. 1,3-Disubstituted allenes are also compatible in this asymmetric cyclization, giving the *E*-products **3ah** and **3bh** highly stereoselectively in moderate yields with very high *ee*.

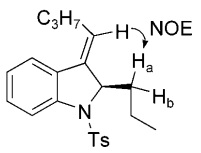


Figure 2. NOE study of (*R*)-*E*-**3ah**.

The configuration of the double bond is confirmed by an nOe study of **3ah** (Figure 2). Besides *N*-(2-iodophenyl)-4-methylbenzenesulfonamide, 4-F or 5-Cl substitution on the phenyl ring is also suitable in this reaction, leaving further opportunity for elaboration.

In summary, we have developed a new spiro-BOX ligand, i.e., (R_a,*S*,*S*)-**L7**, and demonstrated its successful application in the Pd-catalyzed asymmetric allylic annulation of readily available 2-iodoanilines with allenes[10] affording the potentially useful 3-alkylideneindolines[11,12] in good yields with high to excellent enantiomeric excesses (94–98% *ee*). This type of ligand may show potential in highly enantioselective constructions of a variety of cyclic compounds with potentials based on carbometalation of allenes and other bisoxazoline ligand-promoted asymmetric reactions. Further investigations in this area, especially the scope of different organic halides/nucleophiles (Scheme 1) and application in other classic reactions, are ongoing in our laboratory.

Experimental Section

Typical Procedure for the Preparation of (*R*)-3

To a Schlenk tube with a screw cap were added $Pd(dba)_2$ (6 mg, 0.011 mmol), (R_a,*S*,*S*)-**L7** (7 mg, 0.011 mmol), and 1 mL of THF. The resulting mixture was stirred for 2 h at room temperature, which was followed by sequential introduction of Ag_3PO_4 (34 mg, 0.081 mmol), **1a** (75 mg, 0.20 mmol), **2a** (112 mg, 0.81 mmol), and 1 mL of THF at room temperature. The resulting solution was stirred at 110 °C. When the reaction was completed as monitored by TLC, the solvent was evaporated under vacuum, and the residue was purified by chromatography on silica gel (eluent: petroleum ether:ethyl acetate = 70:1) to afford (*R*)-**3aa** as an oil; yield: 44 mg (57%); 96% *ee* determined by HPLC analysis [Chiralcel AD-H, hexane/*i*-PrOH = 85/15, 0.7 mL min^{-1}, 230 nm)]: tR = 4.8 min (minor), 6.6 min (major); $[\alpha]_D^{20}$: +9.4 (*c* 0.50, EtOAc); ^{1}H NMR (400 MHz, acetone-d_6): δ = 7.72 (d, *J* = 8.4 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.44 (dd, *J* = 7.6, 0.4 Hz, 1H), 7.36–7.30 (m, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.11–7.05 (m, 1H), 5.48 (d, *J* = 2.0 Hz, 1H), 4.99 (d, *J* = 2.0 Hz, 1H), 4.80–4.75 (m, 1H), 2.31 (s, 3H), 2.12–2.04 (m, 1H), 1.86–1.76 (m, 1H), 1.47–1.21 (m, 10H), 0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100.5 MHz, acetone-d_6): δ = 146.1, 145.1, 144.9, 135.4, 131.3, 130.8, 130.4, 128.1, 125.3, 121.9, 117.4, 103.5, 67.3, 37.9, 32.5, 30.4, 29.9, 23.5, 23.2, 21.3, 14.3; MS (EI): *m/z* (%) = 384 (M^++1, 10.27), 383 (M^+, 38.49), 144 (100); IR (neat): ν = 2954, 2926, 2856, 1599, 1494, 1454, 1372, 1306, 1292, 1229, 1187, 1172, 1153, 1120, 1093, 1021 cm^{-1}; HR-MS: *m/z* = 383.1918, calcd. for $C_{23}H_{29}NO_2S$ (M^+): 383.1919.

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