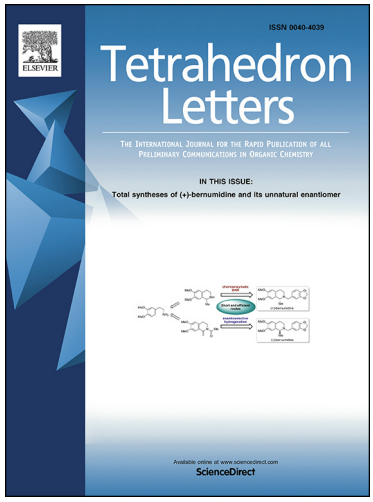

New spiro phosphinooxazolines for palladium-catalyzed asymmetric allylic amination

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New spiro phosphinooxazolines for palladium-catalyzed asymmetric allylic amination

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ABSTRACT

The new conformational rigid spiro phosphinooxazolines **1** were synthesized from 7-bromo-1-indanone. The asymmetric catalytic potential of them was demonstrated in the asymmetric palladium catalyzed allylic amination. High yields and enantioselectivities were obtained with alkylamines.

Introduction

Transition metal-catalyzed asymmetric allylic substitution has become a powerful method in the formation of carbon-carbon and carbon-heteroatom bond[1-3]. The enantioselective allylic amination is an important reaction for the synthesis of chiral allylamines which are ubiquitous in biologically active motifs and natural products[4-8]. Many efforts have been devoted to the design and synthesis of the chiral ligands. The rigid conformation of chiral ligand is an important factor for high enantioselectivity in asymmetric catalysis. The ligands with rigid backbone could reduce the conformation obscurity of catalyst and create an effective asymmetric environment around the central metal, which could lead to high enantioselectivities in asymmetric reactions[9]. However, there are only a few investigations on the catalyst's rigidity of backbones[10]. The phosphinooxazolines such as PHOX have proven to be efficient ligands in asymmetric allylic substitution[11-13]. Bidentate ligands with a more rigid linker between the two coordinating sites can form more rigid metallocycle with fewer available conformations and thus enhance the enantiofacial differentiation[14-15]. Herein, we report a new spiro phosphinooxazolines and their asymmetric catalytic potential in palladium catalyzed asymmetric allylic amination.

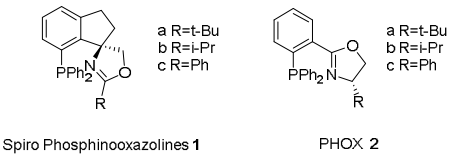
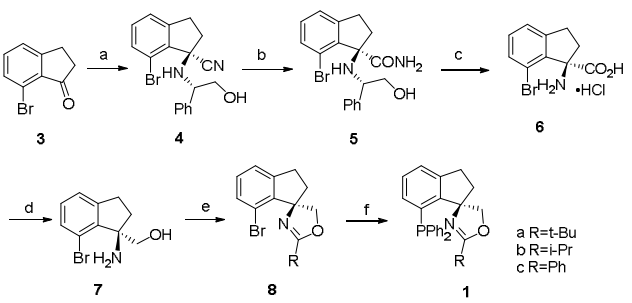


Figure 1. The phosphinooxazoline ligands.

Results and discussion

The synthetic route of the ligands was outlined in Scheme 1. The (R)-aminoacid **6** was synthesized by a modified Warmuth method[16]. Asymmetric Strecker reaction of 7-bromoindanone **3** with (*S*)-phenylglycinol and trimethylsilyl cyanide catalyzed by *p*-toluenesulfonic acid gave amino carbonitrile **4**, which was directly subjected to hydrolysis with sulfuric acid to afford (*R*)-aminocarboxamide **5** in 81% yield.



Scheme 1. Synthesis of spiro phosphinooxazolines

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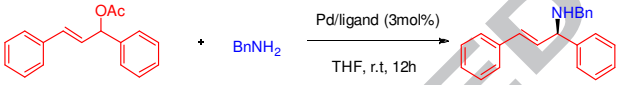
Reaction conditions: a. (i) TsOH, S-phenylglycinol, toluene, reflux (ii) TMSCN, DCM, 0℃; b. 90% H_2SO_4, -20 ℃; c. (i) $Pb(OAc)_4$, DCM/ MeOH, 0 ℃ (ii) 6M HCl, reflux; d. Borane dimethyl sulfide complex, THF, reflux; e (i) RCOCl, Et_3N, DCM, 0 ℃ (ii) MsCl, DIPEA, DCM, 0 ℃; f. n-BuLi, PPh2Cl, THF, -78 ℃

Treatment of **5** with lead tetraacetate, followed by hydrolysis with hydrochloric acid afforded **6**. Reduction of **6** by borane dimethyl sulfide complex afforded enantiopure (*R*)-amino alcohol **7** in 90% yield. Oxazoline **8** was synthesized by adapting literature methods[17]. N-acylation of **7** with acyl chloride in the presence of diisopropylethylamine, followed by addition of mesyl chloride furnished the ring cyclization in 79-91% yields. Lithiation of **8** with n-butyllithium followed by addition of diphenylphosphine chloride afforded the desired spiro phosphinooxazolines **1**. The total yields were 80%, 75%, and 87% for **1a**, **1b**, and **1c** respectively.

With the spiro phosphinooxazolines in hand, we investigated the asymmetric allylic amination reaction using *E*-1,3-diphenylallyl actate and benzylamine. The initial reactions were performed with the combination of spiro phosphinooxazoline **1a** with various palladium sources in tetrahydrofuran at room temperature. The results are summarized in Table 1. Reactions using $PdCl_2(dppf)_2$ and $Pd(Ph_3P)_4$ lead to moderate yields and low enantioselectivities (Entry 1-2). The enantioselectivities were improved significantly when $Pd(OAc)_2$, $Pd_2(dba)_3$, and $[Pd(C_3H_5)Cl]_2$ were used (Entry 3-5). We found that the best result was achieved using $[Pd(C_3H_5)Cl]_2$ as palladium source. The enantioselectivity reached 95.5% ee (Entry 5). The other ligands **1b** and **1c** showed slightly lower enantioselectivities compared to **1a** (Entry 6-7). Compared with the classical PHOX ligand **2a**, spiro phosphinooxazolines **1** showed better enantioselectivity (Entry 8).

Table 1. Asymmetric allylic amination[a]



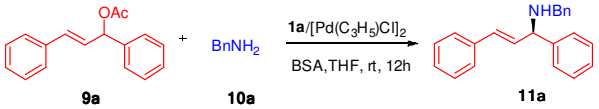
9a **10a** **11a**

Entry	Ligand	Metal Salt	yield[b] [%]	ee[c, d] [%]
1	1a	$PdCl_2(dppf)_2$	36	0.7
2	1a	$Pd(Ph_3P)_4$	41	33.7
3	1a	$Pd(OAc)_2$	36	92.9
4	1a	$Pd_2(dba)_3$	24	95.9
5	1a	$[Pd(C_3H_5)Cl]_2$	33	95.5
6	1b	$[Pd(C_3H_5)Cl]_2$	34	93.6
7	1c	$[Pd(C_3H_5)Cl]_2$	41	93.7
8	2a	$[Pd(C_3H_5)Cl]_2$	39	88.1

[a]Reaction conditions: *E*-1,3-diphenylallyl acetate **9a** (0.6 mmol), benzylamine **10a** (1.80 mmol), ligand (0.021 mmol), palladium compound (0.018 mmol), THF (2mL). [b]Isolated yield. [c]Determined by HPLC analysis. [d]The absolute configurations were assigned as R by comparison with literature data [18].

We then explored the optimum reaction condition. The results were showed in Table 2. The reaction yields were greatly influenced by the amount of N,O-Bis(trimethylsilyl)acetamide (BSA), reaction temperature, catalyst loading, and solvents, while the enantioselectivities were little affected. The reaction yields increased as the equivalent of BSA and catalyst added. When 3 equivalents of BSA and 0.04 equivalent of catalyst loading were added, the yield was reached 63.1% (Entry 1-6). Optimization of the temperature showed that the yield improved significantly when the reaction was warmed to 40℃ (Entry 7). Examination of different solvents and reaction time disclosed that dichloromethane was the best solvent of choice and the best reaction time was 6 hours (Entry 9-13).

Table 2. Optimization of the reaction conditions[a]

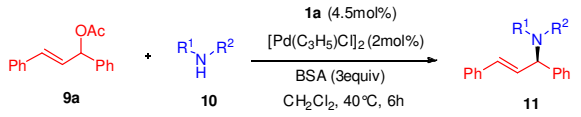


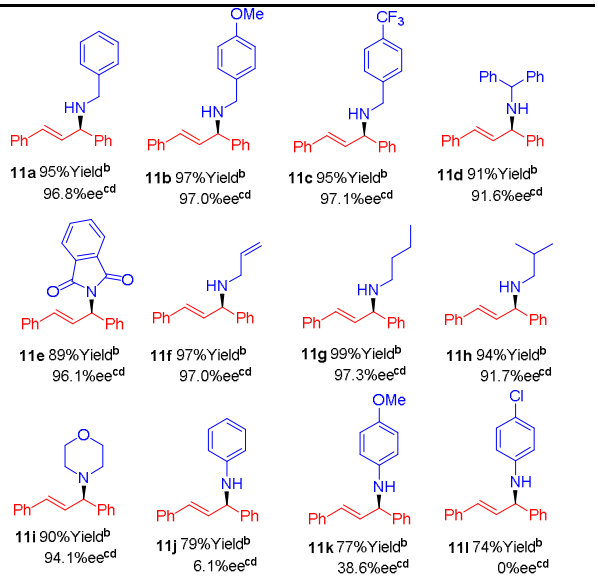
9a **10a** **11a**

Entry	BSA (equiv)	Catalyst (equiv)	Temp. (℃)	Time (h)	Solvent	Yield[b] [%]	ee[cd] [%]
1	1.0	0.03	rt	12	THF	44	95.3
2	2.0	0.03	rt	12	THF	49	95.5
3	3.0	0.03	rt	12	THF	51	95.4
4	4.0	0.03	rt	12	THF	51	94.8
5	3.0	0.04	rt	12	THF	63	95.8
6	3.0	0.05	rt	12	THF	63	95.7
7	3.0	0.04	40	12	THF	89	96.2
8	3.0	0.04	60	12	THF	90	96.1
9	3.0	0.04	40	2	THF	84	96.8
10	3.0	0.04	40	6	THF	89	96.5
11	3.0	0.04	40	12	THF	89	96.2
12	3.0	0.04	40	6	DCM	95	96.4
13	3.0	0.04	40	6	Toluene	85	96.3

[a]Reaction conditions: *E*-1,3-diphenylallyl acetate **9a** (0.6 mmol), benzylamine **10a** (1.80 mmol), Solvent (2mL). [b]Isolated yield. [c]Determined by HPLC analysis. [d]The absolute configurations were assigned as R by comparison with literature data [18].

Table 3. Scope of nucleophiles in asymmetric allylic amination[a]



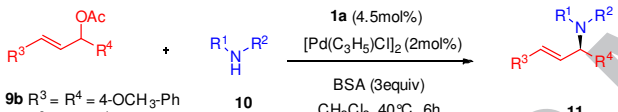


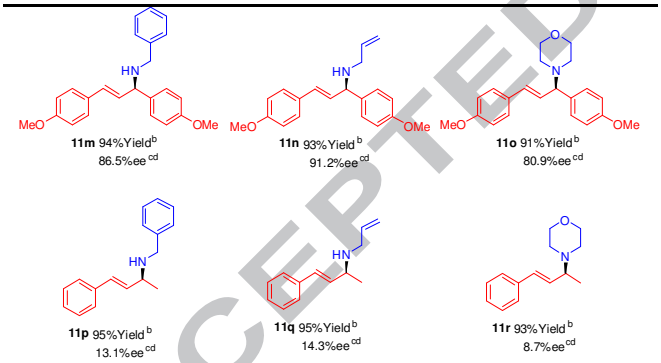
[a]Reaction conditions: *E*-1,3-diphenylallyl actate **9a** (0.6 mmol), benzylamine **10a** (1.8 mmol), ligand (0.027 mmol), palladium compound (0.012 mmol), BSA (1.8mmol), DCM (2mL). [b]Isolated yield. [c]Determined by HPLC analysis. [d]The absolute configurations were assigned as R by comparison with literature data[18].

Next, the scope of the nucleophiles was studied using spiro phosphinooxazoline **1a** under optimum reaction condition. The results were shown in Table 3. For alkylamines, the desired products **11a-11j** were obtained in excellent yields and enatioselectivities both for primary and secondary amines. Benzylamine and substituted benzylamines gave the products in high yields and enatioselectivities (**11a-11c**). The electron property of the aromatic ring of benzylamine has no effect on the yields and enatioselectivities. The steric hindrance has some effect on the enantioselectivity. The excellent yields and enantioselectivities were obtained for n-butylamine (**11g**), whilst slightly lower ee value when isobutylamine was used (**11h**). Compared with the PHOX ligand, spiro phosphinooxazolines **7** had better enatioselectivities with benzylamine as the nucleophile (**11a**, 96.8% ee *vs*. 89% ee)[12]. The aromatic amines were not as good nucleophiles as the alkylamines in terms of yields and enatioselectivities. The substituents on the rings of aromatic amines influenced the reaction significantly. The reactions proceeded in good yields with anilines, but the enantioselectivities were inferior to alkylamines (**11j-11l**).

To further explore the scope of the reaction, the palladium catalyzed allylic aminations were examined using symmetrical and unsymmetrical allylacetates under optimum conditions. As seen in Table 4, for the symmetrical allylacetate **9b**, the catalyst showed high yields and good enatioselectivities (**11m-11o**). For the unsymmetrical allylacetate **9c**, the catalyst showed high yields and regioselectivities, but the enatioselectivities was decreased greatly (**11p-11r**).

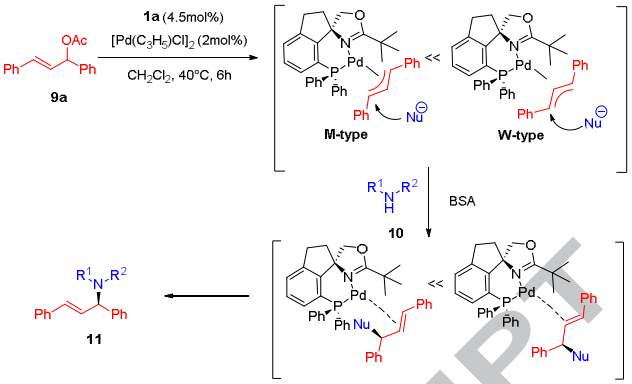
Table 4. Substrate scope of asymmetric allylic amination[a]





[a]Reaction conditions: allyl actates **9** (0.6 mmol), amines **10** (1.8 mmol), ligand (0.027 mmol), palladium compound (0.012 mmol), BSA(1.8 mmol), DCM (2mL). [b]Isolated yield. [c]Determined by HPLC analysis. [d]The absolute configurations of **11m-11o** were assigned as R by comparison with literature data[18]. The absolute configurations of **11p-11r** were assigned as S by comparison with literature data[19, 20].

A plausible mechanism was proposed to account for the observed stereochemistry of the products. As is shown in Scheme 2, the W-type allyl transition state of Pd-η^3-allyl intermediate formed preferentially over its M-type counterpart, due to the steric interaction between the two phenyl rings of the phosphine and those of *(E)*-1,3-diphenylallyl acetate. Thus, the N-nucleophiles would attack trans to the P atom to afford the corresponding products.



Scheme 2.The plausible reaction mechanism

Conclusions

In summary, the new conformationally rigid phosphinooxazolines were developed and synthesized. The asymmetric catalytic potential of them were demonstrated in the asymmetric palladium catalyzed allylic aminations, affording the corresponding chiral allylamines in high yields and enatioselectivities. Further investigations of these new spiro phosphinooxazolines in asymmetric catalysis are underway and will be reported in due course.

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at doi:

Graphical Abstract

New spiro phosphinooxazolines for palladium-catalyzed asymmetric allylic amination

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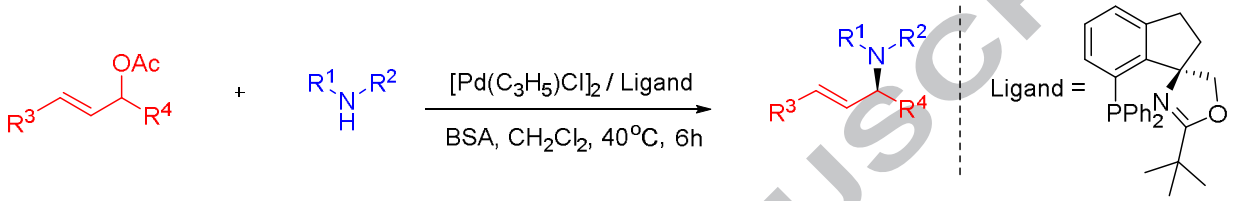

The new conformationally rigid spiro phosphinooxazolines ligands were synthesized from 7-bromo-1-indanone. The asymmetric catalytic potential of them was demonstrated in the asymmetric palladium catalyzed allylic amination. High yields and enantioselectivities were obtained with alkylamines.

The new rigid spiro phosphinooxazolines ligands were synthesized.

New spiro ligands for palladium-catalyzed asymmetric allylic amination were detected.

High yields and enantioselectivities were obtained with alkylamine.