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Pd(II)-catalyzed intermolecular enantioselective hydroamination of styrenes†

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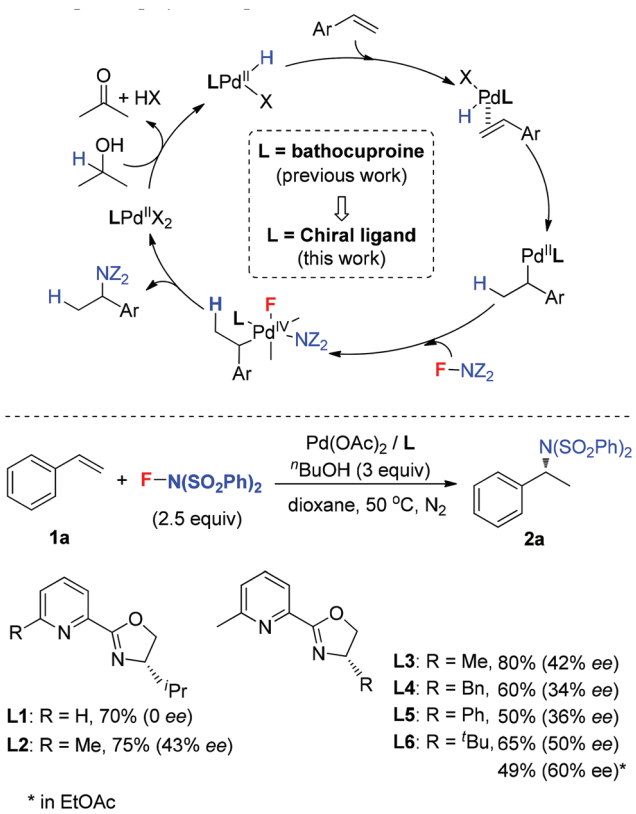
A Pd-catalyzed intermolecular asymmetric hydroamination of styrenes was developed to give various chiral benzyl amides exclusively, in which the oxidation-stable pyridine-oxazoline was used as the chiral ligand to provide moderate to good enantioselectivities.

Hydroamination presents one of the most efficient strategies to build up alkylamines, and has received much attention.[1] Among them, enantioselective hydroamination is much more attractive but challenging.[2] Compared to the significant progress in the intramolecular hydroamination of alkenes by rare-earth metals,[3] group 4 metals (Zr, Ti)[4] and main-group metal (Li, Mg) complexes,[5] the intermolecular enantioselective hydroamination reactions are less explored. For instance, Hartwig and coworkers developed a Pd-catalyzed intermolecular hydroamination of vinylarenes with arylamines in 2000, in which only two enantioselective examples were included using (*R*)-BINAP as the ligand.[6] Further enantioselective hydroamination with modified reaction conditions was reported by Takahashi and Lin.[7] Later, Shibata[8] and Hartwig[9] independently demonstrated that the enantioselective hydroamination of alkenes was achieved by using an Ir catalyst and chiral phosphine ligands. Very recently, the Buchwald[10a] and Miura[10b] groups found that a copper catalyst was used to catalyze the asymmetric hydroamination of alkenes to provide excellent enantioselectivities. Herein, we report our recent study on the Pd-catalyzed intermolecular asymmetric hydroamination of styrenes under oxidative reaction conditions, in which *N*-fluorobenzenesulfonimide (NFSI) was used as the nitrogen source as well as the oxidant, and pyridine-oxazoline (POX) type ligands were used as the chiral ligands to deliver good enatioselectivities.

In 2011, our group developed a palladium-catalyzed intermolecular hydroamination of styrenes.[11] As shown in Scheme 1 (top), this reaction was initiated by alcohol oxidation with a Pd(II) catalyst to provide palladium hydride species. After migratory insertion of styrene into the palladium hydride species, the formed benzyl–Pd intermediate was oxidized by NFSI to provide the final hydroamination product, in which a Pd(IV) was proposed as a key intermediate for the C–N bond formation. It is notable that the ligand bathocuproine plays an important role for the successful catalytic cycle. Based on these results, we investigated the enantioselective hydroamination reaction by employing chiral ligands. Compared to the chiral phosphine ligands used in the previous studies, nitro-



Scheme 1 Pd(II)-catalyzed asymmetric hydroamination of styrene.

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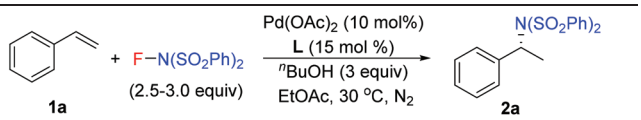
gen-based ligands, such as POX type ligands **L1–L6**, are more compatible with the oxidative reaction conditions, which have been widely used in the palladium-catalyzed oxidative transformations, including palladium-catalyzed intramolecular enantioselective oxidative amination of alkenes, asymmetric Heck reaction and others.[12] In order to assess the potential of asymmetric hydroamination, these ligands were used in the initial study. As shown in Scheme 1 (bottom), we were delighted to find that the POX type ligand was effective toward hydroamination. When simple POX ligand **L1** was used, the reaction did give the desired product **2a** in 70% yield, but unfortunately without enantioselectivity. Very interestingly, the sterically bulkier ligand **L2** bearing an *ortho*-methyl group on the pyridyl ring exhibited moderate enantioselectivity (43% ee) in good yield. Then a variety of POX ligands **L3–L6** with different groups at the oxazoline ring were screened and **L6** with the *tert*-butyl group provided the best result in 50% ee. After further optimization of the reaction conditions, the ee value of **2a** could be increased to 60% in EtOAc.

Our previous study revealed that the reductive elimination of the Pd(IV) intermediate undergoes an exclusive S_N2 type pathway.[13] Thus, the enantioselective migratory insertion step is responsible for the final ee value of the product. We reasoned that enlargement of the steric hindrance of ligands might be helpful to increase the enantioselectivity of migratory insertion. In order to test the above hypothesis, a series of POX ligands bearing different *ortho*-substituents on the pyridyl ring (**L7–L18**) were further synthesized and employed in the reaction (Fig. 1). As shown in Table 1, when **L7–L9** with Et, ^{n}Pr and ^{i}Pr groups were used to catalyze the reaction, slightly better enantioselectivities were obtained (entries 1–3). However, **L10** and **L11** with Ph and Bn groups exhibited poor reactivity (entries 4 and 5). Compared with the above ligands, **L12** with the ^{i}Bu group presented the best enantioselectivity to afford **2a** in 79% ee but with low yield (36%, entry 6). The reaction yield could be improved to 63% by increasing the catalyst loading to 10 mol% with a similar ee value (entry 7). Furthermore, the addition of triethyl orthoformate was beneficial to give a better reaction yield as well as enantioselectivity (entry 8). With these modified reaction conditions, extra ligands **L13–L18** were further screened. These ligands exhibited slightly poor selectivities compared to **L12** (entries 9–14). Finally, the best result

Table 1 Ligand screening[a]



Entry	Ligand	**2a** Yields (%)	ee (%)
1	**L7**	57	73
2	**L8**	46	77
3	**L9**	50	65
4	**L10**	Trace	—
5	**L11**	16	49
6	**L12**	36	79
7[b]	**L12**	63	82
8[b,c]	**L12**	72	86
9[b,c]	**L13**	40	71
10[b,c]	**L14**	75	80
11[b,c]	**L15**	45	59
12[b,c]	**L16**	40	75
13[b,c]	**L17**	52	79
14[b,c]	**L18**	50	75
15[b,c,d]	**L12**	75	87

[a] Conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), **L** (7.5 mol%), NFSI (2.5 equiv.) in EtOAc, at 30 °C. [b] $Pd(OAc)_2$ (10 mol%), ligand (15 mol%). [c] $HC(OEt)_3$ (1.5 equiv.). [d] NFSI (3.0 equiv.).

(87% ee and 75% yield) was obtained by increasing the amount of NFSI (3 equiv., entry 15). It should be noted here that the chiral amine **2a** was determined to have the (*S*)-configuration according to the X-ray structure (Fig. 2).

With the optimized reaction conditions in hand, the scope of styrene was subsequently examined. As shown in Table 2, the styrenes with halides at the *para* position afforded the corresponding chiral amides **2b–2e** in good ee values and yields. For the product **2e**, **L6** with small steric hindrance provided better yield and poor enantioselectivity than that of **L12**. Compared to the electron-deficient halide group, the electron-rich styrenes gave slightly lower ee values to generate products **2f–2h**. For the *meta*-substituted styrenes, good enantioselectivity was also obtained to generate products **2i–2k** but with poor yields, especially for the cases of substrates with a *meta*-halide. However, these substrates reacted smoothly under the reaction conditions with **L6** as the ligand to afford the desired products **2j–2l** in good yields and ee values. Further-

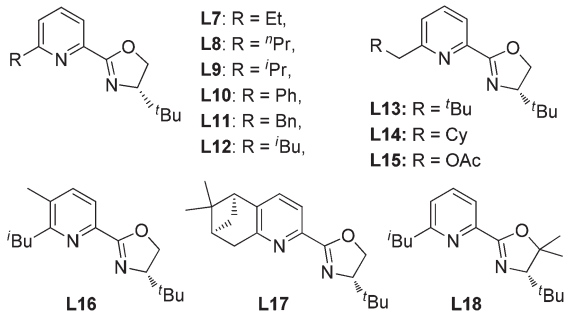


Fig. 1 The structure of POX ligands.

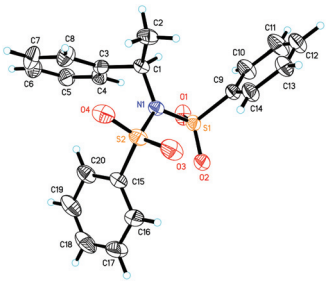


Fig. 2 The X-ray structure of **2a**.

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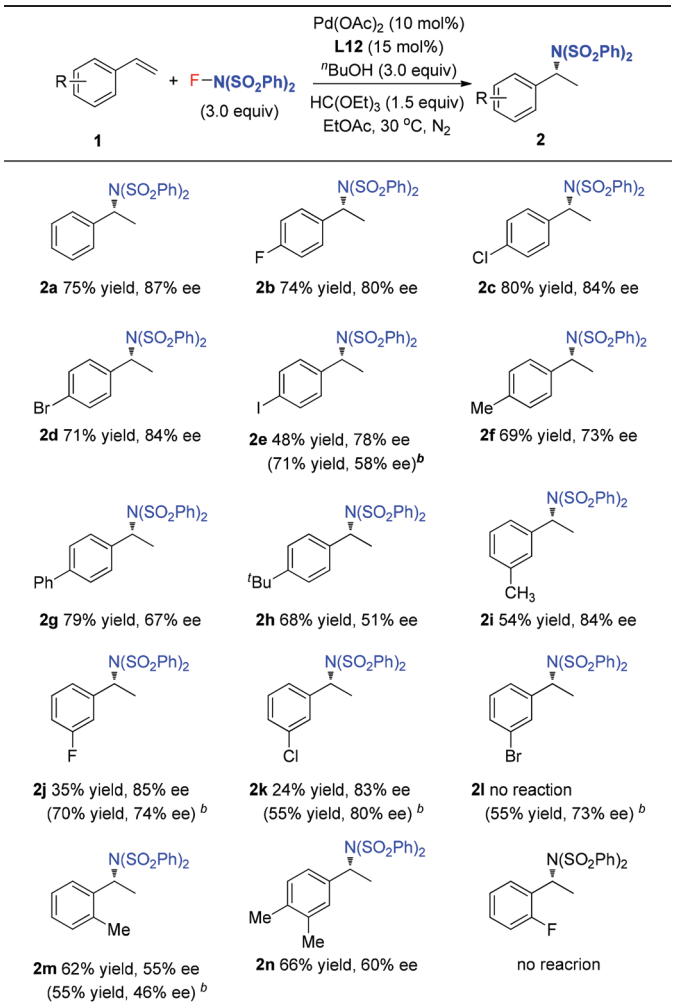
Table 2 Scope of styrenes[a]



[a] Conditions: **1a** (0.2 mmol), $Pd(OAc)_2$ (10 mol%), **L12** (15 mol%), NFSI (3.0 equiv.), ^{n}BuOH (3.0 equiv.), $HC(OEt)_3$ (50 μL) in EtOAc at 30 °C for 36 h, isolated yield. [b] **L6** (15 mol%) was used instead of **L12**.

more, the current reaction conditions were also compatible for the *ortho*-methyl styrene and dimethyl styrene to give products **2m–2n** in moderate yields and ee values. However, *ortho*-halide substituted styrenes were ineffective. It is notable that, unfortunately, styrenes with a strong electron-withdrawing group, such as ester, nitro, and ketone, were ineffective for the transformation.

The above observations revealed that, compared to **L6**, the large steric hindrance of ligand **L12** exhibited a negative impact on the reactivity but a positive impact on the enantioselectivity. Originally, we reasoned that ligand **L12** bearing two substituents in both oxazoline and pyridine might act as a pseudo *C*2-symmetric ligand to coordinate with palladium(II) in the reaction system (Fig. 3A), which is helpful to control the stereochemistry of hydropalladation. Surprisingly, the X-ray of complex (**L12**)$PdCl_2$ showed the two substituents in the same face (Fig. 3B). In addition, the X-ray structure indicated that

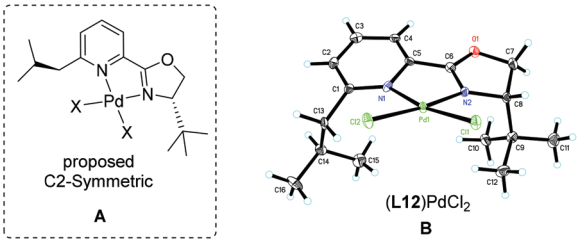
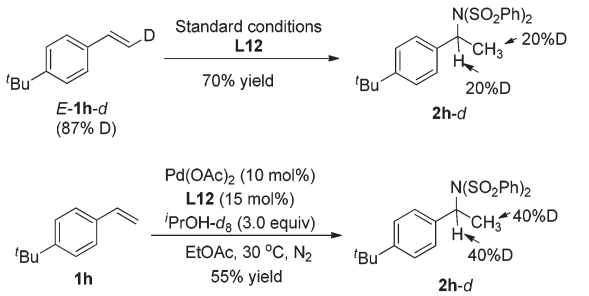


Fig. 3 The X-ray structure of complex (**L12**)$PdCl_2$.

there are two (**L12**)$PdCl_2$ in a unit lattice, and a weak interaction between the two palladium centers is observed (Pd(1)–Pd(2) = 3.854 Å), and the two ligands are aligned parallel, which forces the two substituents in the same face to lower the lattice energy, due to the flexible ^{i}Bu group (see ESI†). These observations reveal that the rotation of the ^{i}Pr group of the (**L12**)$PdCl_2$ complex should be easier than our expectation.

Furthermore, deuterium labeled styrene *E*-**1h**-*d* was subjected to the standard conditions, and the hydroamination product **2h**-*d* was obtained as a mixture of isomers with the deuterium incorporation on both α and β carbon (eqn (1)). In addition, when substrate **1h** was treated under the standard conditions with ^{i}PrOH-d_8, the same product **2h**-*d* was obtained (eqn (2)). These observations indicated that a quick reversible migratory insertion of styrene into the palladium hydride species was involved in the reaction, which is possible to ruin the enantioselectivity to some degree.



In conclusion, we have described a Pd-catalyzed intermolecular enantioselective hydroamination of styrenes, which afforded various chiral branched amides with excellent regio- and good enantioselectivity, in which the modified pyridine-oxazoline ligand was used under oxidation conditions. Preliminary mechanistic understanding reveals that the modified ligand presented a good enantioselective control on the migratory insertion step. However, the ligand structure still needs to be improved to act as a pseudo *C*2-symmetric ligand in future study. In addition, we hope this new type of ligand could also improve the sequential process of benzyl C–Pd(II) oxidation to C–Pd(IV) and the following reductive elimination, which could reduce the β-H elimination of the benzyl C–Pd(II). The related investigation is in progress in our laboratory.

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