

RESEARCH ARTICLE

View Article Online

View Journal | View Issue



Cite this: *Org. Chem. Front.*, 2015, **2**, 819

Received 25th March 2015,
Accepted 7th May 2015

DOI: 10.1039/c5qo00096c

rsc.li/frontiers-organic

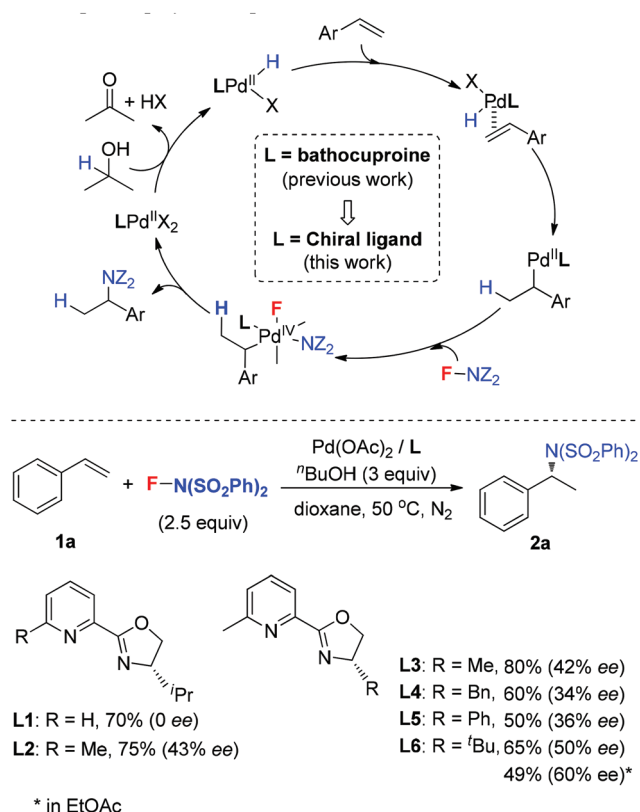
Pd(II)-catalyzed intermolecular enantioselective hydroamination of styrenes†

Feng Yu, Pinhong Chen* and Guosheng Liu*

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, Shibata⁸ and Hartwig⁹ 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 enantioselectivities.

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



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

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-

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, 345 Lingling Road, Shanghai, China. E-mail: pinhongchen@sioc.ac.cn, gliu@mail.sioc.ac.cn; Fax: +86-21-64166128; Tel: +86-21-54925346

† Electronic supplementary information (ESI) available. CCDC 1055926. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5qo00096c

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, ⁿPr and ⁱPr 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 ⁱBu 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-

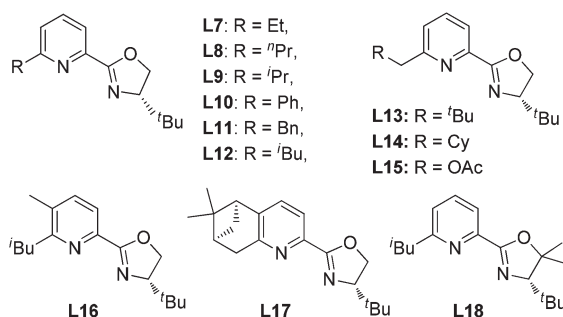
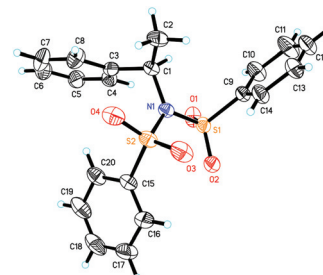


Fig. 1 The structure of POX ligands.

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

21421091, and 21472217), and the Science Technology Commission of the Shanghai Municipality (12ZR1453400). P.H.C. also thanks the Key Laboratory of Functional Small Organic Molecules, Ministry of Education, Jiangxi Normal University (no. KLFS-KF-201402), for the financial support.

Notes and references

- For some reviews on the hydroamination: (a) T. E. Müller and M. Beller, *Chem. Rev.*, 1998, **98**, 675; (b) M. Norbis and B. D. Hölscher, *Angew. Chem., Int. Ed.*, 2001, **40**, 3983; (c) N. Nishina and Y. Yamamoto, *Top. Organomet. Chem.*, 2013, **43**, 115; (d) E. Chong, P. Garcia and L. L. Schafer, *Synthesis*, 2014, 2884; (e) A. L. Reznichenko, A. J. Nawara-Hultzsich and K. C. Hultzsich, *Top. Curr. Chem.*, 2014, **343**, 191; (f) L. Huang, M. Arndt, K. Gooßen, H. Heydt and L. J. Gooßen, *Chem. Rev.*, 2015, **115**, 2596.
- For the reviews on the asymmetric hydroamination, see: (a) K. C. Hultzsich, *Adv. Synth. Catal.*, 2005, **347**, 367; (b) H. Jerome and S. Emmanuelle, *Chem. – Eur. J.*, 2013, **19**, 4972; (c) G. Zi, *J. Organomet. Chem.*, 2010, **696**, 68; (d) K. D. Hesp, *Angew. Chem., Int. Ed.*, 2014, **53**, 2034; (e) P. W. Roesky and T. E. Mueller, *Angew. Chem., Int. Ed.*, 2003, **42**, 2708.
- (a) M. R. Gagne, L. Brard, V. P. Conticello, M. A. Giardello, C. L. Stern and T. J. Marks, *Organometallics*, 1992, **11**, 2003; (b) S. Hong, A. M. Kawaoka and T. J. Marks, *J. Am. Chem. Soc.*, 2003, **125**, 15878; (c) Y. Chapurina, J. Hannedouche, J. Collin, R. Guillot, E. Schulz and A. Trifonov, *Chem. Commun.*, 2010, **46**, 6918; (d) Y. Zhang, W. Yao, H. Li and Y. Mu, *Organometallics*, 2012, **31**, 4670; (e) A. L. Reznichenko, H. N. Nguyen and K. C. Hultzsich, *Angew. Chem., Int. Ed.*, 2010, **49**, 8984.
- (a) D. A. Watson, M. Chiu and R. G. Bergman, *Organometallics*, 2006, **25**, 4731; (b) A. L. Gott, A. J. Clarke, G. J. Clarkson and P. Scott, *Organometallics*, 2007, **26**, 1729; (c) M. C. Wood, D. C. Leitch, C. S. Yeung, J. A. Kozak and L. L. Schafer, *Angew. Chem., Int. Ed.*, 2006, **46**, 354; (d) K. Manna, S. Xu and A. D. Sadow, *Angew. Chem., Int. Ed.*, 2011, **50**, 1865.
- (a) P. Horrillo Martínez, K. C. Hultzsich and F. Hampel, *Chem. Commun.*, 2006, 2221; (b) J. Deschamp, C. Olier, E. Schulz, R. Guillot, J. Hannedouche and J. Collin, *Adv. Synth. Catal.*, 2010, **352**, 2171; (c) X. Zhang, T. J. Emge and K. C. Hultzsich, *Angew. Chem., Int. Ed.*, 2012, **51**, 394.
- (a) M. Kawatsura and J. F. Hartwig, *J. Am. Chem. Soc.*, 2000, **122**, 9546; (b) U. Nettekoven and J. F. Hartwig, *J. Am. Chem. Soc.*, 2002, **124**, 1166; (c) M. Utsunomiya and J. F. Hartwig, *J. Am. Chem. Soc.*, 2003, **125**, 14286.
- A. Hu, M. Ogasawara, T. Sakamoto, A. Okada, K. Nakajima, T. Takahashi and W. Lin, *Adv. Synth. Catal.*, 2006, **348**, 2051.
- S. Pan, K. Endo and T. Shibata, *Org. Lett.*, 2012, **14**, 780.
- (a) C. S. Sevov, J. Zhou and J. F. Hartwig, *J. Am. Chem. Soc.*, 2012, **134**, 11960; (b) C. S. Sevov, J. Zhou and J. F. Hartwig, *J. Am. Chem. Soc.*, 2014, **136**, 3200.
- (a) S. Zhu, N. Niljianskul and S. L. Buchwald, *J. Am. Chem. Soc.*, 2013, **135**, 15746; (b) Y. Miki, K. Hirano, T. Satoh and M. Miura, *Angew. Chem., Int. Ed.*, 2013, **52**, 10830.
- T. Xu, S. Qiu and G. Liu, *J. Organomet. Chem.*, 2011, **696**, 46.
- For some recent examples, see: (a) A. B. Weinstein and S. S. Stahl, *Angew. Chem., Int. Ed.*, 2012, **51**, 11505; (b) G. Yang, C. Shen and W. Zhang, *Angew. Chem., Int. Ed.*, 2012, **51**, 9141; (c) J. C. Holder, L. Zou, A. N. Marziale, P. Liu, Y. Lan, M. Gatti, K. Kikushima, K. N. Houk and B. M. Stoltz, *J. Am. Chem. Soc.*, 2013, **135**, 14996; (d) T.-S. Mei, E. W. Werner, A. J. Burckle and M. S. Sigman, *J. Am. Chem. Soc.*, 2013, **135**, 6830; (e) Y. Zhang and M. S. Sigman, *J. Am. Chem. Soc.*, 2007, **129**, 3076; (f) E. L. Ingalls, P. A. Sibbald, W. Kaminsky and F. E. Michael, *J. Am. Chem. Soc.*, 2013, **135**, 8854; (g) W. He, K.-T. Yip, N.-Y. Zhu and D. Yang, *Org. Lett.*, 2009, **11**, 5626.
- H. Peng, Z. Yuan, H.-Y. Wang, Y.-L. Guo and G. Liu, *Chem. Sci.*, 2013, **4**, 317.