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Synthesis of new chiral benzylically substituted *P*,*N*-ligands and their applications in the asymmetric Heck reaction

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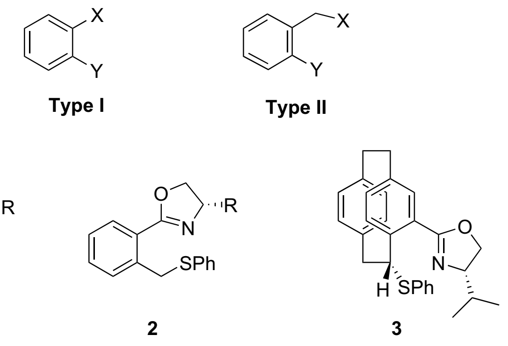
Abstract—A series of new chiral *P*,*N*-ligands with substituents at the benzylic position has been prepared. Their high catalytic activity is shown in the Pd-catalyzed asymmetric Heck reaction and allylic substitution reaction.

Chiral ligands play a crucial role in asymmetric catalysis with a variety of ligands with different structural features being synthesized and used in asymmetric catalysis.[1] Among them, the ligands with a type I structure, which have both substituents at benzene ring-positions, are common; one of the representatives is PHOX, which allows effective asymmetric induction in a variety of metal-catalyzed reactions (Scheme 1).[2,3] However, only a few reports on the synthesis and application of ligands with type II, which have one of the substituent at the benzylic position, have appeared although the structure of type II ligands seems simple.[4] During the course of design, synthesis and application of chiral ligands in asymmetric catalysis,[5] we found that ligands **2** and **3**, which have a substituent at the benzylic position, show higher catalytic activity.[6] Based upon these findings, other ligands with a substituent at the benzylic position have been synthesized and used in asymmetric catalysis to confirm if this phenomenon is general. Herein we report the synthesis of *P*,*N*-ligands having the substituent at the benzylic position and their higher catalytic activity in asymmetric Heck reaction.



Scheme 1.

The synthetic route to ligand **8** with an oxazoline ring as the substituent at the benzylic position is depicted in Scheme 2. Lithiation of *o*-bromotoluene **4** with BuLi followed by quenching with PPh_2Cl afforded phosphine **5**. Acid **6** was prepared by direct benzylic-lithiation of phosphine **5** and then quenching with CO_2. Esterification of acid **6** followed by treatment with amino alcohol salts derived from the reaction with BuLi and ring-closure gave rise to ligands **8a**–**c**.

With the ligands in hand, the Pd-catalyzed asymmetric Heck reaction was used to test their efficiency.[7] The reaction of 2,3-dihydrofuran and PhOTf proceeded at 60 °C in THF using 1.5 mol % of $[Pd_2(dba_3)dba]$ and 6 mol % ligand with the results summarized in Table 1. It can be seen that all the reactions were complete in 20 h to give the products in high regioselectivity; 4–5 days are usually needed for completion when using PHOX as ligands. The highest enantioselectivity (94% ee) with the ratio of 70:1 for **9** and **10** was obtained using ligand (*S*)-**8b** (entry 2), which was close to that using PHOX as the ligand (97% ee).[8] The ligands also proved suitable when ArOTf was used as the reagent (entries 4 and 5).

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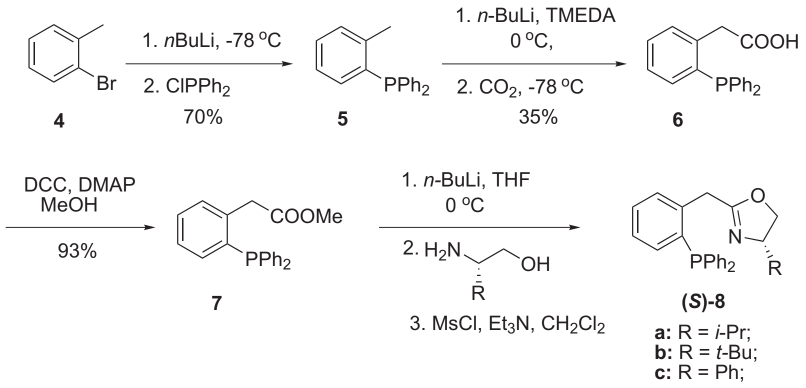
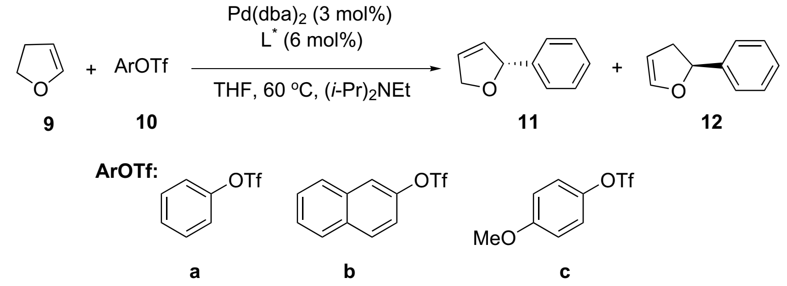


Scheme 2.



(1)

Table 1. Pd-catalyzed asymmetric Heck reaction using ligand **8**

Entry	Ligand	ArOTf	Time (h)	Yield %[a]	Ee% of **11**[b,c]	Ratio of **11** and **12**[d]
1	(*S*)-**8a**	**10a**	20	75	77.1 (*R*)	15:1
2	(*S*)-**8b**	**10a**	20	82	93.6 (*R*)	70:1
3	(*S*)-**8c**	**10a**	20	65	57.6 (*R*)	65:1
4	(*S*)-**8b**	**10b**	20	85	89.5[e]	
5	(*S*)-**8b**	**10c**	20	66	59.2	

[a] Isolated yield.

[b] Determined by chiral GC.[5l]

[c] The absolute configuration of the product was determined through comparison of the sign of specific rotations with literature data.[8a]

[d] Determined by GC.[5l]

[e] Determined by chiral HPLC.[5l]

Table 2. The influence of the amount of catalyst on the reaction of Eq. 1 using ligand (*S*)-**8b**

Entry	Pd(dba)$_2$ (mol%)[a]	Time (h)	Yield %[b]	Ee% of **11**[c]	Ratio of **11** and **12**[d]
1	3	20	82	93.6 (*R*)	70:1
2	1.5	20	83	93.3 (*R*)	80:1
3	0.5	40	54	92.6 (*R*)	25:1

[a] Pd(dba)$_2$:ligand = 1:2.

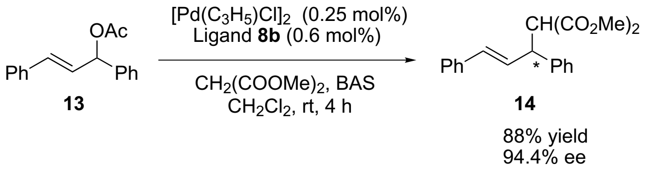
[b] Isolated yield.

[c] Determined by chiral GC.[5l]

[d] Determined by GC.[5l]

When the amount of Pd(dba)$_2$ was varied from 3 to 1.5 mol%, there was little change in ee values and yield (Table 2, entry 1 vs entry 2). Even when the amount of Pd(dba)$_2$ was decreased to 0.5 mol%, high ee was still obtained (Table 2, entry 3), although the yield was slightly lower (54%) with 40 h needed for completion (Table 2, entry 3). This result provides an example of using less than 1 mol% catalyst in the asymmetric Heck reaction. The high catalytic efficiency of the ligand was also shown in the Pd-catalyzed allylic substitution reaction (Eq. 2).[9] Reaction product **14** was provided in 96.6% ee and 86% yield when the reaction proceeded in 2 h and 2.5 mol% of $[Pd(C_3H_5)Cl]_2$ and 6 mol% of ligand **8b** were used as catalyst, while 94.4% ee and 88% yield were also obtained for **14** when the amount of $[Pd(C_3H_5)Cl]_2$ and **8b** was decreased to 0.25 and

0.6 mol%, respectively, with the reaction being complete in 4 h (95% ee and 94% yield were provided using 2 mol% of PHOX with *tert*-butyl as substituent on oxazoline ring as ligand).[3b] These results and our previous studies[6] clearly show that the ligands with the substituent at the benzylic position are more effective in catalytic efficiency.



(2)

In summary, several novel *P*,*N*-ligands with the substituent at the benzylic position have been prepared with the high catalytic efficiency of them being shown in the Pd-catalyzed asymmetric Heck reaction and allylic substitution reaction. Further studies regarding their applications in asymmetric catalysis and the reason why the ligands give such high catalytic efficiency are in progress.

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