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Efficient planar chiral 2′-substituted 1,1′-P,N-ferrocene ligands for the asymmetric Heck reaction: control of enantioselectivity and configuration by planar chiral substituent

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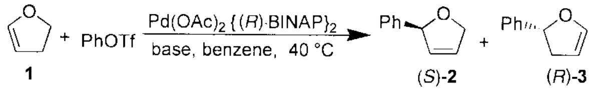
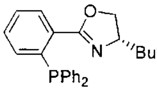
Planar chiral 1,1′P,N-2′-substituted 2′ substituted 1,1′-P,N-ferrocene derivatives were efficient ligands for the Pd-catalyzed asymmetric Heck reaction, in which 79–85% yields with high enantioselectivity (80–92%) were obtained within several hours; the enantioselectivity and the absolute configuration were controllable by changing the size of the planar chiral group and/or configuration of planar chirality.

Among palladium-catalyzed C–C bond-forming reactions, the Heck reaction enjoys considerable current popularity because of its versatility and tolerance of functionality.[1] It has only recently been exploited in the key steps of many total syntheses[2] although the first intramolecular asymmetric Heck reactions were reported, independently, by Shibasaki[3] and Overman[4] in 1989. Two years later, the intermolecular asymmetric version of the Heck reaction was reported by Hayashi,[5] with BINAP as ligand. The reaction was carried out with dihydrofuran **1** and phenyltriflate and afforded a mixture of regioisomers **2** and **3** in a 29 : 71 ratio, with the major product **3** obtained in high ee (96%) (Scheme 1).

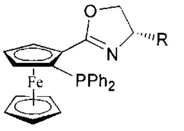


Scheme 1

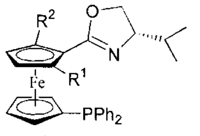
In an important extension to this work, Pfalz[6] described the application of the diphenylphosphinooxazoline **4** (PHOX) ligand to arylation and alkenylation of substrate **1**. In contrast to the regioisomer problem observed by Hayashi, the phenylation of dihydrofuran **1** produced the 2,5-dihydrofuran derivative **2** in high yield (85%) and with so far the best enantioselectivity (97% ee). Although impressive results have been achieved in asymmetric inter- and intra-molecular Heck reactions with several kinds of ligands,[6–8] there are still problems for the practical use of this asymmetric reaction, such as low reaction rates (usually several days) and high catalyst loading. Therefore, it is important and challenging to develop novel highly efficient ligands.



PHOX 4



(S,S_p)-**5a**, R = *i*-Pr
(S,S_p)-**5b**, R = *t*-Bu



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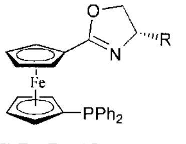
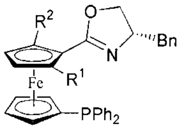
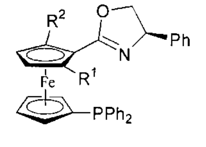


(*S*)-**7a**, R = *i*-Pr
(*S*)-**7b**, R = Bn
(*S*)-**7c**, R = *t*-Bu
(*R*)-**7d**, R = Ph



(S,S_p)-**8a**, R^1 = TMS, R^2 = H
(S,S_p)-**8b**, R^1 = H, R^2 = Me
(S,R_p)-**8c**, R^1 = H, R^2 = TMS



(R,R_p)-**9a**, R^1 = H, R^2 = TMS
(R,R_p)-**9b**, R^1 = Me, R^2 = H

Ferrocene-based planar chiral ligands have been proven to be effective and highly reactive in many kinds of asymmetric catalytic reaction.[9] However, to the best of our knowledge, there is so far no report on their use in the asymmetric Heck reaction, except for the result of Guriy[8] that excellent enantioselectivity was observed with very low catalytic activity (14 days for a complete conversion) by using ferrocene-type ligands **5** in the phenylation of 2,2-dimethyl-2,3-dihydrofuran. Quite recently, as a part of the program aimed at the design and application of chiral ligands to asymmetric synthesis,[10] we synthesized a new kind of planar chiral 1,1′-P,N-ferrocene ligand **6**, which showed that the planar chirality is decisive in exerting control over both absolute configuration and enantiomeric excess in Pd-catalyzed allylic substitution reactions.[11] These encouraging results prompted us to extend the scope of these new structural-framework ligands to the asymmetric Heck reaction. Herein we report our initial findings on the phenylation of 2,3-dihydrofuran **1** by using palladium complexes derived from new ligands **7**, **8** and **9**, which were synthesized by our group.[11,12]

We initially tested the effectiveness of the structurally novel 1,1′-disubstituted P,N-ferrocene ligands **7**. At the same time, 1,2-disubstituted P,N-ferrocene ligands **5** were also used for this reaction in order to compare the catalytic activity of **5** and **7**. The results are summarized in Table 1.

With 3 mol% of catalyst, prepared *in situ* from Pd(dba)$_2$ and 1.5 equiv. of ligands **7a–d**, the corresponding 2,5-dihydrofurans **2** were formed as sole products (as shown by TLC), similar to the results Pfalz obtained.[6] The best enantioselectivity (76.5%) and also the highest catalyst activity (affording 80% of yield in 8 h) was observed with ligand **7b** (Table 1). Ligand **7d** showed the same catalytic activity as ligand **7b**, however, gave the lowest enantioselectivity (42.4%). It is noteworthy that 1,2-disubstituted P,N-ferrocene ligands **5a–b** had almost no catalytic activity in this reaction even with the reaction time prolonged to 24 h.[8] Usually, 1.5 equiv. of ligand were used in this reaction. However, when 1.0 or 2.0 equiv. of the ligand were used the resulting ee values and yields of reaction product were slightly lower. Next, a variety of solvents and bases were investigated and the results showed that the ee value was independent of the base used, which is in consistent with Pfaltz's results. However, the enantioselectivity with benzene as solvent was inferior to that with THF. For ligands **7b** and **7d**, the yields in asymmetric Heck reactions are good with higher reaction rates (several hours) using 3 mol% of catalyst compared with literature results[6] (2 to 3 days for a high conversion).

Considering the high reactivity of ligands **7b** and **7d**, we envisaged that the enantioselectivity and/or the configuration of the reaction product might be improved and/or inverted by introducing planar chirality into these two ligands according to our previous experience on the role of planar chirality in Pd-catalyzed allylic alkylation reactions.[11] Consequently, planar chiral ligands (S,S_p)-**8a**, (S,S_p)-**8b** and (S,R_p)-**8c**, (R,R_p)-**9a** and (R,R_p)-**9b**, containing a newly introduced Me or TMS group on the same Cp ring with oxazoline moiety, were synthesized and

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Table 1 Enantioselective Heck reaction of **1** and phenyltriflate with ligands **5** and **7**[a]

Entry	Ligand	Solvent	Base	Time	Yield (%)[b]	ee (%)[c] (config.)[d]
1	**7a**	THF	*i*-Pr$_2$NEt	8 h	46	68.1 (*R*)
2	**7b**	THF	*i*-Pr$_2$NEt	8 h	80	**76.5 (R)**
3	**7c**	THF	*i*-Pr$_2$NEt	8 h	25	64.0 (*R*)
4	**7d**	THF	*i*-Pr$_2$NEt	8 h	79	42.4 (*S*)
5	**5a**	THF	*i*-Pr$_2$NEt	24 h	Trace	n.d.
6	**5b**	THF	*i*-Pr$_2$NEt	24 h	Trace	n.d.
7[e]	**7b**	THF	*i*-Pr$_2$NEt	8 h	72	75.7
8[f]	**7b**	THF	*i*-Pr$_2$NEt	8 h	77	75.4
9	**7b**	THF	Proton sponge	8 h	82	76.0
10[e]	**7b**	THF	Et$_3$N	8 h	85	76.0
11	**7b**	Benzene	Proton sponge	8 h	71	71.0
12	**7b**	Benzene	*i*-Pr$_2$NEt	8 h	77	69.9

[a] The reaction was carried out under an argon atmosphere. Pd : PhOTf : **1** : base = 0.03 : 1.0 : 5.0 : 2.0. Reaction temperature: 60 °C. Pd : **L*** = 1 : 1.5 unless otherwise stated. [b] Isolated yields based on phenyltriflate. [c] Determined by chiral GC. [d] Determined by comparing the sign of optical rotation with literature data. [e] Pd : **L*** = 1 : 1. [f] Pd : **L*** = 1 : 2.

Table 2 Enantioselective Heck reaction of **1** and phenyltriflate with ligands **8** and **9**[a]

Entry	Ligand	Time	Ratio (2 : 3)[b]	Yield (%)[c]	ee (%)[d] (config.)[e]
1	(*S*)-**7b**	8 h	n.d.	80	76.5 (*R*)
2	(S,S_p)-**8a**	8 h	n.d.	72	83.5 (*S*)
3	(S,S_p)-**8b**	8 h	64 : 1	79 (82)[b]	88.5 (*R*)
4	(S,R_p)-**8c**	8 h	n.d.	75	**92.1 (*R*)**
5	(*R*)-**7d**	8 h	n.d.	79	42.4 (*S*)
6	(R,R_p)-**9a**	8 h	n.d.	75	80.2 (*R*)
7	(R,R_p)-**9b**	8 h	32 : 1	85 (91)[b]	88.4 (*S*)

[a] The reaction was carried out in THF in the presence of diisopropylethylamine under an argon atmosphere. PhOTf : **1** : *i*-Pr$_2$NEt : Pd(dba)$_2$: ligands = 1.0 : 5.0 : 2.0 : 0.03 : 0.06. Reaction temperature: 60 °C. [b] Determined by GC. [c] The isolated yields based on phenyltriflate. [d] Determined by chiral GC. [e] Configurations were assigned by comparison of the signs of optical rotation.

tested for this reaction. The results are summarized in Table 2.

A dramatic change in the enantioselectivity of the reaction was observed with (S,S_p)-**8a** containing a (S_p)-TMS planar chiral group. The enantiomeric excess of reaction product **2** changed from 76.5% with *R* configuration by using ligand **7b** to 83.5% with *S* configuration (entry 2 *vs.* entry 1 of Table 2). This exciting result encouraged us to probe the effect of the newly introduced group with opposite planar chirality, which might increase the ee value and with the same configuration of product **2** from that by using ligand **7b**. Therefore, (S,S_p)-**8b** containing a (S_p)-Me planar chiral group was synthesized and subjected to the same reaction. Just as expected, a remarkable improvement in the ee value (88.5%, *R* configuration) was observed. The same phenomenon was observed by using ligands (R,R_p)-**9a** and (R,R_p)-**9b** (compare entries 6 and 7 with entry 5). These results indicate that the effect of planar chirality on the stereochemical outcome is significant in this Heck reaction, which is inconsistent with our previous results with Pd-catalyzed asymmetric allylic alkylation.[11] Maybe the planar chirality has the same role in two different reaction systems, *i.e.* the planar chirality controls and tunes the ee value and absolute configuration of the reaction product by changing the ratio of rotamers of the axial chirality on coordinating with metal Pd due to its steric repulsion on the coordinating center.[12] If this is true, then increasing the steric bulkiness of the newly introduced planar chiral group may improve the ee value of product **2**. In fact, the ee value actually increased to 92% when ligand (S,R_p)-**8c** containing a bulky TMS group was used in this reaction. Thus, the ee value and absolute configuration of product **2** are controllable and tunable just by changing the configuration and/or size of the planar chiral group. In addition, a very small amount of regioisomer **3** (entries 3 and 7) in the reaction product was detected by GC but not observed by preparative TLC.

In conclusion, the above mentioned new kind of ligand is effective and attractive in the asymmetric Heck reaction not only because of the high reactivity and enantioselectivity but also because the absolute configuration of the reaction product can be controlled just by changing the configuration and/or size of the planar chiral group of these ligands. Further studies on the improvement of enantioselectivity *via* modifying these ligands and their application to other substrates are in progress.

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