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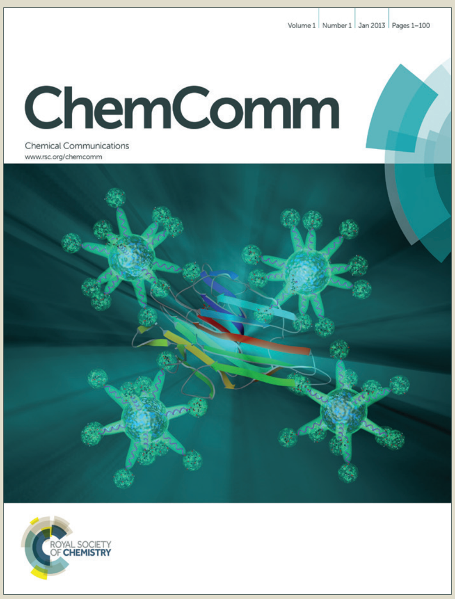

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Palladium-Catalyzed Asymmetric Intermolecular Mizoroki-Heck Reaction for Construction of Chiral Quaternary Carbon Center

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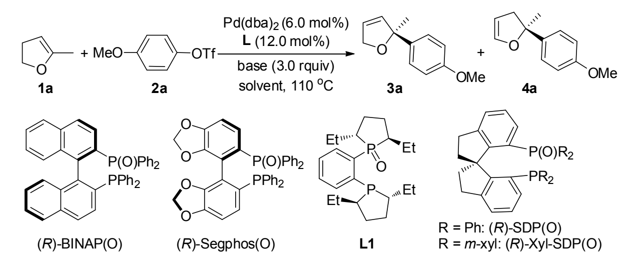
Qing-Song Zhang,[a] Shi-Li Wan,[a] Di Chen,[a] Chang-Hua Ding,*[a] and Xue-Long Hou*[a,b]

A palladium-catalyzed asymmetric intermolecular Mizoroki-Heck reaction for construction of a chiral quaternary carbon center is developed, affording 2,2-disubstituted 2,5-dihydrofurans in high yield with excellent enantioselectivity. The products are easily converted into the corresponding butenolides with retention of enantioselectivity.

The Pd-catalyzed intermolecular Mizoroki-Heck reaction between olefins and organic halides has become one of the most powerful tools for C-C bond formation and found wide application in the synthesis of natural products, pharmaceuticals, and functional materials since its discovery in more than 40 years ago.[1] Until twenty years later, the first intermolecular asymmetric variant was reported by Hayashi and co-workers.[2] This pioneering work has inspired many groups to devote considerable efforts to this area.[3] However, only a limited number of substrates were suitable for this Pd-catalyzed asymmetric intermolecular reaction for a long time, which hampered the applications of the reaction in organic synthesis severely. Only recently, some significant breakthroughs have been made by Jung, Zhou and Sigman.[3e,4–6] Aryl halides and benzylic electrophiles have been used successfully in Pd-catalyzed asymmetric intermolecular Mizoroki-Heck reaction, affording corresponding products in high enantioselectivities.[5] Even acyclic alkenes as well as trisubstituted alkenes have also been used in oxidative Heck or Heck-Matsada reaction to form chiral quaternary carbon center with excellent efficiency regarding the yield and enantioselectivity.[6f] These newly developed methodologies have also found their applications in organic synthesis.[5b,c,6c] In spite of the great progress has been achieved, successful examples are still limited with rather narrow substrate scope, especially the report concerning the use of trisubstituted alkenes and the methodology to form chiral quaternary carbon center, one of the key issues in asymmetric synthesis, is very few.[6f,7] Only one example of Pd-catalyzed asymmetric Heck reaction of 5-methyl-2,3-dihydrofuran with PhOTf was given by Tschoerner and Pregosin, affording the corresponding Heck product in 38% yield and 98% ee.[7a] Obviously, the development of Pd-catalyzed asymmetric intermolecular Mizoroki-Heck reaction, particularly, for the enantioselective construction of quaternary carbon is still a formidable challenge.

We have been involved in the program of Pd-catalyzed asymmetric intermolecular Mizoroki–Heck reaction and have realized a switch of regio- and enantio-selectivities in asymmetric Mizoroki–Heck reaction by tuning the electronic property of bisphosphines and benzylic substituents of ligands respectively.[8] These studies and recent progress in this area promoted us to explore the creation of chiral quaternary carbon center using this reaction. In this communication, we would like to disclose our preliminary results on the Pd-catalyzed asymmetric Heck reaction of 5-substituted-2,3-dihydrofurans with aryl triflates, affording the corresponding Heck products bearing a quaternary carbon center in high yields with excellent enantioselectivity.

Table 1 Optimization of Reaction Conditions for Pd-catalyzed Heck Reaction of 5-Methyl-2,3-dihydrofuran (**1a**) and Triflate **2a**[a]



entry	L	base	solvent	3a/4a[b]	yield (3a,%)[c]	ee (%)[d]
1[f]	(R)-BINAP	$^{i}Pr_2NEt$	THF	1/2.3	15	–83
2[e]	(R)-BINAP(O)	$^{i}Pr_2NEt$	1,4-dioxane	>99/1	26	–88
3	(R)-BINAP(O)	$^{i}Pr_2NEt$	1,4-dioxane	>99/1	64	–87

[a.] State Key Laboratory of Organometallic Chemistry,
[b.] Shanghai–Hong Kong Joint Laboratory in Chemical Synthesis,
Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China.
† E-mail: dingch@sioc.ac.cn; xlhou@sioc.ac.cn; Tel: +86 21 5492 5144
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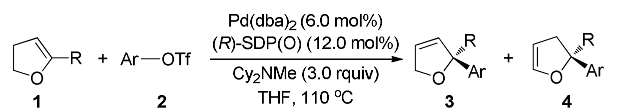
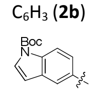
4[f]	(*R*)-BINAP(O)	$^{i}Pr_2NEt$	1,4-dioxane	5/1	25	–79
5[g]	(*R*)-BINAP(O)	$^{i}Pr_2NEt$	1,4-dioxane	ND[k]	trace	–[j]
6[h]	(*R*)-BINAP(O)	$^{i}Pr_2NEt$	1,4-dioxane	>99/1	50	–88
7	(*R*)-Seg-phos(O)	$^{i}Pr_2NEt$	1,4-dioxane	ND[k]	34	–85
8	**L1**	$^{i}Pr_2NEt$	1,4-dioxane	ND[k]	trace	ND[k]
9[i]	(*R*)-BINAP(O)	$^{i}Pr_2NEt$	THF	21/1	76	–87
10[i]	(*R*)-BINAP(O)	Cy_2NMe	THF	65/1	83	–87
11[i]	(*R*)-SDP(O)	Cy_2NMe	THF	17/1	84	95
12[i]	(*R*)-xyl-SDP(O)	Cy_2NMe	THF	5/1	53	95
13[i,j]	(*R*)-SDP(O)	Cy_2NMe	THF	18/1	48	92

[a] Conditions: molar ratio of **1a**/**2a**/Pd(dba)$_2$/**L**/base = 500:100:6:12:300. [b] Determined by GC. [c] Isolated yield. [d] Determined by chiral HPLC; A minus sign means that the product has the opposite configuration. [e] **1a**/**2a**/Pd(dba)$_2$/**L** = 500:100:6:6.6. [f] Pd(OAc)$_2$ used as palladium source. [g] [Pd(η^3-C_3H_5)Cl]$_2$ used as palladium source. [h] Reaction temperature: 90 °C. [i] Performed in sealed tube due to low boiling point of THF and high reaction temperature. [j] **1a**/**2a**/Pd(dba)$_2$/**L** = 500:100:3:6. [k] ND = not determined.

We commenced our study with the reaction of 5-methyl-2,3-dihydrofuran (**1a**) and 4-methoxyphenyl trifluoromethanesulfonate (**2a**) under the catalysis of Pd(OAc)$_2$ and a commercially available ligand, (*R*)-BINAP (entry 1, Table 1). The reaction afforded Heck products **3a** and **4a** in 15% yield (83% ee) and 34% yield (72% ee) respectively. Although these results are promising, further optimization of reaction conditions, such as screening the base, increasing or lowering the reaction temperature, did not improve the reaction (not shown in Table). The reaction always suffered from a low selectivity of **3a**/**4a**. Another severe problem is the formation of side-products derived from ring-opeing of furan ring (see supporting information). These concerns promoted us to use other kind of ligands. Oestreich's[9a,b] and Zhou's[5] success of using chiral bisphosphine monoxides for intermolecular Heck reaction inspired us to replace (*R*)-BINAP with (*R*)-BINAP(O) as the ligand (entry 2, Table 1). Gratifyingly, the reaction was improved significantly, affording the corresponding Heck product **3a** with a chiral quaternary carbon with 88% ee and >99:1 regioselectivity, but the yield was only 26% with some recovered triflate **2a**. Further experiments revealed that the problem was tackled by adding an additional equivalent of (*R*)-BINAP(O) and the product **3a** was isolated in 64% yield with 87% ee (entry 3, Table 1). These promising results encouraged us to investigate the impact of the reaction parameters on the reaction. The palladium precursor plays a critical role in the reaction. When Pd(OAc)$_2$ was used in place of Pd(dba)$_2$, a significant drop of the yield to 25% for **3a** with only 79% ee was observed (entry 4, Table 1) while the use of [Pd(η^3-C_3H_5)Cl]$_2$ heavily retarded the reaction, forming trace amount of **3a** (entry 5, Table 1). The temperature was found to influence the reaction very much. Lowering the reaction temperature from 110 °C to 90 °C resulted in a lower conversion of triflate **2a** (entry 6 vs entry 3, Table 1). The examination of several other chiral bisphosphine monoxides showed that the reaction with (*R*)-Segphos(O) gave the product **3a** in high enantioselectivity but very low yield (entry 7, Table 1). A commercially available duphos monoxide **L1** demonstrated no catalytic activity (entry 8, Table 1). The investigation of the solvent effect on the reaction revealed that the use of THF afforded 76% yield of **3a** in 87% ee (entry 9 vs entry 3, Table 1) and the yield of **3a** was further increased to 83% by using Cy_2NMe instead of $^{i}Pr_2NEt$ as the base (entry 10, Table 1); (for details of the investigation of solvent and base effect on the reaction, please see supporting information). Further screening of chiral bisphosphine monoxide ligand revealed that the product **3a** in 84% yield with 95% ee and 17:1 regioselectivity was obtained when (*R*)-SDP(O) was used as the ligand (entry 11 vs entry 10, Table 1). A more bulky ligand (*R*)-xyl-SDP(O) proved to be less active and gave inferior olefin selectivity than (*R*)-SDP(O) (entry 12 vs entry 11, Table 1). The yield of the product **3a** dropped significantly when the catalyst loading decreased, and the triflate **2a** was not fully consumed also (entry 13 vs entry 11, Table 1). Several other commercially available ligands, such as (*S*)-*tert*-BuPHOX, Josiphos, and (*R,R*)-DACH-phenyl Trost' ligand were examined, nevertheless, no desired product was acquired (not shown in Table).

Table 2 Substrate Scope for the Pd-catalyzed Heck Reaction of 5-Substituted-2,3-dihydrofurans **1** and Triflates **2**[a]



entry	R (**1**)	Ar (**2**)	**3**/**4**[b]	yield (**3**,%)[c]	ee (%)[d]
1	Me (**1a**)	4-MeO-C_6H_4 (**2a**)	17/1	84 (**3a**)	95
2	**1a**	3,4-(MeO)$_2$-C_6H_3 (**2b**)	32/1	96 (**3b**)	94
3	**1a**	 (**2c**)	21/1	74 (**3c**)	92
4	**1a**	2-naphthyl (**2d**)	17/1	57 (**3d**)	84
5	**1a**	Ph (**2e**)	25/1	63 (**3e**)	94
6	**1a**	3-Me-C_6H_4 (**2f**)	69/1	78[f] (**3f**)	–90[f]
7	**1a**	2-Me-C_6H_4 (**2g**)	17/1	45[f] (**3g**)	–96[f]
8	**1a**	4-F-C_6H_4 (**2h**)	46/1	64 (**3h**)	95
9	**1a**	3-F-C_6H_4 (**2i**)	22/1	31 (**3i**)	90
10	**1a**	2-F-C_6H_4 (**2j**)	10/1	21 (**3j**)	90
11	*n*-Pr (**1b**)	**2a**	8/1	57 (**3k**)	95
12	**1b**	**2c**	–[e]	78 (**3l**)	94
13	BnO(CH$_2$)$_3$ (**1c**)	**2a**	59/1	83 (**3m**)	97

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14	**1c**	**2c**	–[e]	85 (**3n**)	96
15	**1c**	**2e**	10/1	55 (**3o**)	93
16	**1c**	**2f**	9/1	63 (**3p**)	95
17	**1c**	4-CO_2Et-C_6H_4 (**2k**)	3.3/1	30 (**3q**)	70
18	$SiMe_3$ (**1d**)	**2e**	4/1	46 (**3r**)	93

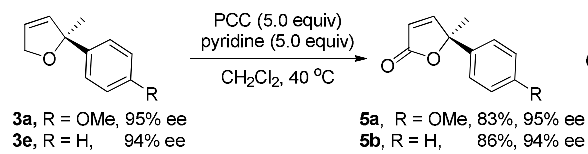
[a] Conditions: molar ratio of **1**/**2**/Pd(dba)$_2$/(*R*)-SDP(O)/Cy_2NMe = 500:100:6:12:300. [b] Determined by GC. [c] Isolated yield. [d] Determined by chiral HPLC. [e] Not determined. [f] (*R*)-BINAP(O) was the ligand; A minus symbol means the opposite sign of optical rotation of the product.

With the optimized conditions in hand, the substrate scope of the reaction was examined and the results are compiled in Table 2. It can be seen that a wide range of dihydrofurans **1** with different substituents, including methyl, propyl, even bulkier trimethylsilyl, are suitable substrates, affording the corresponding 2,2-disubstituted 2,5-dihydrofurans **3** with a chiral quaternary carbon center in high yield with high regio- and enantioselectivities (entries 1, 11, 13, and 18, Table 2). It is noteworthy that 5-(γ-benzyloxy propyl)-2,3-dihydrofurans **1c** is also a suitable substrate (entries 13-17, Table 2). The removal of benzyloxy group will provide an additional functional group in the product, which makes it more useful in organic synthesis.

Reaction of different aryl trifluoromethanesulfonates **2** with electron-donating group at *m*- and *p*-position, provided the corresponding products in excellent results regarding the yields, regio-, and enantioselectivities (entries 1, 2, 6, 11, 13 and 16, Table 2). Noticeably, heteroaromatic triflate **2c** is also viable substrate to afford desired products in 74-85% yield along with >92% ee (entry 3, 12, and 14, Table 2). In contrast, the Heck products were obtained in low yield for the aryl triflates **2** that contain an electron-deficient aromatic ring (entries 9-10, and 17, Table 2). In these cases, the reduction product of triflates was observed. However, the reaction of 4-fluoro phenyl triflate (**2h**) afforded rather good results (entry 8, Table 2). It was found that dihydrofuran **3d** in 57% yield with 85% ee was obtained by the reaction of **2d** with a bulkier naphthyl group (entry 4, Table 2) while the reaction of 2-substituted-aryl triflates **2** afforded lower yields of the corresponding products, also due to the reduction of the triflates (entries 7 and 10, Table 2). Better yields were obtained in the reaction of **1a** with **2f** and **2g** by using (*R*)-BINAP(O) in place of (*R*)-SDP(O) as ligand (entries 6 and 7, Table 2). Some other alkene substrates, such as 5-phenyl-2,3-dihydrofuran, 6-methyl-3,4-dihydro-2*H*-pyran, and *tert*-butyl 5-methyl-2,3-dihydro-1*H*-pyrrole-1-carboxylate were examined, but the corresponding Heck reaction product was not observed (not shown in Table 2).

This Heck reaction can be scaled up to 2.0 mmol scale. Treatment of 512 mg of the triflate **2a** with 672 mg of 5-methyl-2,3-dihydrofuran (**1a**) under the optimized reaction conditions provided 334 mg of the product **3a** in 88% yield with 95% ee. The absolute configuration of the product **3e** was determined to be *S* by comparing its sign of optical rotation with that reported by the literature.[10a]

These chiral quaternary carbon-containing Heck reaction products were transformed into other important building blocks easily according to the known methods.[10] Allylic oxidation of the Heck reaction products **3a** and **3e** using PCC in CH_2Cl_2 in the presence of pyridine, a procedure reported by Hong goup,[10a] afforded butenolides **5a** and **5b**[10a,14] with chiral quaternary carbon center respectively without the loss of optical activity (eq 1), which is an important structural motif presented in many natural products and biologically active compounds such as rugulovasine A[11] and (+)-pinnatolide.[12] This approach provides an simple and efficient way to these optically active γ-disubstituted α,β-unsaturated butenolides and represents one of few catalytic examples for their synthesis.[13] The absolute configuration of the product **3e** was determined as *S* by comparing the sign of optical rotation of the butenolides **5b** with that reported in literature.[14] It should be noted that partial racemization occurred in the allylic oxidation of the compopunds **3a** and **3e** if chromium trioxide was used as oxidant according to the procedure of Marco group,[10b,c]



(1)

To have more understanding on the beneficial effect of an additional ligand on the reaction, some controlled experiments were performed with (*R*)-BINAP(O) as an example due to its more ready availability than (*R*)-SDP(O). Using 6 mol% of Pd(dba)$_2$ and (*R*)-BINAP(O) in the presence of an external achiral 1,2-bis(diphenylphosphino)ethane monoxide [DPPE(O)] as catalyst, product **3a** in 64% yield with 86% ee was afforded. It can also be noted that the product **3a** in 88% ee was obtained if the catalyst with 1:1 ratio of Pd/(*R*)-BINAP(O) was used (entry 2, Table 1), which means that the additional ligand did not improve the enantioselectivity and it was not involved in the enantioselectivity-determine step of the reaction. All of these facts means that the additional ligand plays a role to stabilize the Pd(0) species so that to improve the yield of the reaction.

In conclusion, we have realized a palladium-catalyzed asymmetric intermolecular Mizoroki-Heck reaction for the construction of chiral quaternary stereocenter, affording 2,2-disubstituted 2,5-dihydrofurans in high yields with excellent enantioselectivity. The importance of the presence of additional ligand in the reaction has been found, and its role has also been studied.

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