
Asymmetric Intermolecular Heck Reaction of Aryl Halides by Pd-histidine Organocatalysts

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Abstract: Extensive studies of asymmetric intermolecular Heck reaction are described and provide a deeper insight into histidine-catalyzed. In particular, aspects of enantio- as well as diastereoselectivity of these reactions are discussed. As the first report, we synthesized five histidine-based organocatalysts including histidine as a well-defined and biodegradable natural structure alone and in combination with 2,4,6-trichloro-1,3,5-triazine, benzene-1,3-diamine, dimethyl malonate and dimeric structure applied in the asymmetric intermolecular Heck reaction of aryl halides; their efficiency was compared to each other's. These phosphine-free palladium catalysts were found as efficient catalytic system which provided the superior efficiency with excellent yields, regioselectivity and enantioselectivity. In these among, histidine with 2,4,6-trichloro-1,3,5-triazine which generate the star like molecule palladium catalyst gave the best activity in asymmetric intermolecular Heck reaction with excellent yields and good regio- and enantioselectivity under mild reaction conditions. The asymmetric intermolecular Heck reaction has been limited to aryl and vinyl triflates or aryl iodide in the rare reports of available Pd catalysts. Herein, we extend the reaction to aryl bromides. In addition, the scope of reaction was examined in two different techniques: conventional heating and microwave irradiation and compared. For the first time, microwave irradiation sintering is successfully used for this reaction. Comparison of catalytic activities of our catalyst (Pd/His) with literature examples confirmed our success.

Keywords: Heck, Asymmetric Reaction, Palladium, Organocatalyst, Histidine

1. Introduction

In recent years, asymmetric Heck reaction of aryl halides or aryl triflates with 2, 3-dihydrofuran have received considerable attention due to usages of some products in natural synthesis [1-2]. Up to now, numerous chiral catalytic systems for asymmetric Heck reaction of 2, 3-dihydrofuran with phenyl triflate were examined [3-5]; but, application of aryl halides, as more available substrates, in this coupling reaction is rare [6].

Amino acids are well-known as safe and green ligands for preparing asymmetric catalysts [7-10], such as proline/cyclobutane which used in asymmetric aldol additions, amino acid-containing peptide organocatalysts applying in asymmetric Michael addition [11], and conjugate addition reactions of aldehydes to maleimide [12-16].

However, to the best of our knowledge, asymmetric arylation of 2, 3-dihydrofuran employing histidine-based organocatalyst has never been reported.

The palladium catalyzed bond formation reaction between aryl halides and olefins bearing electron-withdrawing substituents (EWG, e.g. -COOR, -CN) was studied extensively [17, 18], the Heck coupling involving an olefin bearing a hydrogen atom in the allylic position has proved to be a more challenging substrate. Some developments have been made in palladium catalyzed regioselective intermolecular arylation of dihydrofuran (DHF). [19-22] Unfortunately, the most of these conventional methods were limited to using phosphine ligands. [23-33] As we know, a few reports are available in P-free conditions for this type of reactions that suffer from low selectivity.

As a further extension of our ongoing work; [34-37] Herein we describe efficient and facile methods for

intermolecular Heck reaction of aryl halides and 2, 3-dihydrofuran which catalyzed by several histidine base Pd-catalytic systems. The structure of organocatalyst's ligands were represented in Scheme 1. The ligand 1 was found as the most efficient compound for asymmetric coupling reaction

under thermal and microwave conditions with excellent regio- and stereoselectivities. As we know, this is the first report of using phosphorus-free palladium catalyst in regioselective intermolecular Heck reaction of aryl halides with 2, 3-dihydrofuran.

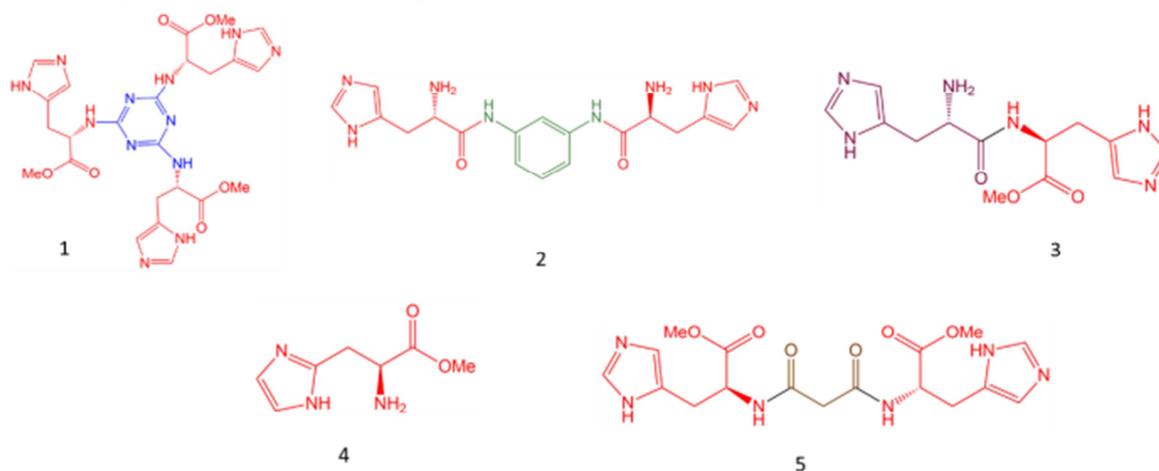


Figure 1. The structure of used histidine ligands.

2. Results and Discussion

Firstly, their catalytic efficiency in intermolecular Heck reaction of aryl halides with dihydrofuran were explored. To obtain the optimum experimental conditions, the Heck cross-coupling of 4-methoxyiodobenzene with 2, 3-dihydrofuran was chosen as a model reaction and various reaction conditions was explored. The results are summarized in Table 1. At first, the reaction was done applying different Pd/His

catalysts, as can be seen, ligand 1 gave the best results. In continues, various reactions conditions in presented of this ligand were optimized. Different solvents such as acetonitrile, ethanol, dimethyl sulfoxide and tetrahydrofuran were examined. The last one (THF) was found as the most effective solvent in reaction conversion, selectivity and enantioselectivity. After optimization of reaction temperature, 40°C was selected as sufficient heat. Among various base, K₂CO₃ was found as the most effected. The reaction was performed in THF with K₂CO₃ at 40 °C for 6 h.

Table 1. Optimization conditions of the Heck reaction of iodobenzene with 2, 3-dihydrofuran.^a

Entry	Base	Solvent	T (°C)	Ligand ^b	Conv.% ^c (3+4)	Selectivity ^c 3/4 (%)	ee ^d (%)
1	K ₂ CO ₃	THF	40	1	87	93	96
2	K ₂ CO ₃	THF	40	2	69	80	67
3	K ₂ CO ₃	THF	40	3	68	91	84
4	K ₂ CO ₃	THF	40	4	43	n. d. ^e	n. d.
5	K ₂ CO ₃	THF	40	5	24	n. d.	n. d.
6	K ₂ CO ₃	CH ₃ CN	40	1	12	89	90
7	K ₂ CO ₃	EtOH	40	1	38	81	83
8	K ₂ CO ₃	DMSO	40	1	59	70	86
9	K ₂ CO ₃	THF	25	1	54	82	89
10	K ₂ CO ₃	THF	60	1	88	93	89
11	KOH	THF	40	1	90	85	93
12	NaOH	THF	40	1	69	80	69
13	Li ₂ CO ₃	THF	40	1	77	87	86

^aIodobenzene (0.5 mmol), 2, 3-dihydrofuran (1 mmol), solvent (3 mL) and base (2 mmol), 6 h; ^bwith 0.04 mol% PdCl₂; ^cConversion percentages and selectivity was determined by GC [29]; ^dThe enantioselectivity was measured by GC equipped with chiral column; ^e Due to low conversion, regio-and enantio-selectivity were not detected.

As shown herein, Pd/His exhibits good catalytic activity and enantioselectivity, which is obtained in the mildest reaction conditions (low temperature and relatively shorter reaction times).

Using microwave irradiation, the reaction times was decreased remarkably. So, to further optimize the reaction conditions, the temperature and the MW power were also optimized and the best results were obtained using K_2CO_3 , THF at 400 W. The optimum temperature was found as 40 °C. No increase in yield was observed at higher temperatures, while lowering the temperature below 40°C reduced the reaction rate. In continuous, the generality and versatility of this asymmetric palladium catalyst in regioselectivity arylation reaction of 2, 3-dihydrofuran cross-coupling of aryl halides was examined in two different techniques: conventional heating (method A) and MW irradiation (method B), were compared. As shown in Table 2, the microwave-assisted reactions were superior to those using conventional heating. It was observed that in both technics, some varieties of aryl halides with either electron-rich or electron-deficient substitutes reacted efficiently with 2, 3-dihydrofuran and gave the corresponding products in moderate to good yields, regio- and enantioselectivity. In general, high yields (80–99%), good regioselectivity and excellent enantioselectivity are observed for aryl iodides and

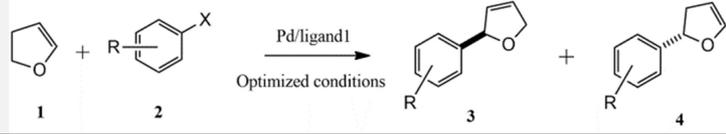
bromide substrates bearing either electron donating or electron-withdrawing substituents (entries 1–9). Actually, founding active substrates is one of the major limitations of this reaction; so, these results can be introduced as a success.

The obtain results was compared to various reported chiral catalysts for the asymmetric intramolecular Heck reaction arylation of 2, 3-dihydrofuran (Table 3). Almost of reported methods applied palladium catalyst with complex phosphine chiral ligands and in long reaction times.

Phenyl triflates were used as substrates in the typical process of the Heck arylation of 2, 3-dihydrofuran, the main disadvantage of triflate is easily hydrolysis. To the best of our knowledge, a few reports about stereoselective Heck coupling of 2, 3-dihydrofuran with aryl hides are available. Aryl hides are cheaper, more stable and more easily available substrates compared with triflates. Therefore, present procedure can be a valuable for the homochiral catalysts in asymmetric synthesis of derivatives of 2, 5-dihydro-2-phenylfuran.

One of the trends of the catalysis industry and green chemistry in environmental and economical point of view is scale-up synthesis. To gain insight into this issue, the Heck reaction of iodobenzene with 2, 3-dihydrofuran was selected and the scale of the reaction was increased to 10.0 mmol, keeping the reaction stoichiometry intact.

Table 2. Heck reactions of aryl halides with 2, 3-dihydrofuran.^a



Entry	R / X	Method A			Method B		
		Conv. ^b (%)	Selectivity ^b 3/4 (%)	Ee ^c (%)	Conv. ^b (%)	Selectivity ^b 3/4 (%)	Ee ^c (%)
1	H / I	87	93	93	89	92	93
2	4-Cl / I	83	91	94	86	92	90
3	4-OMe / I	85	88	91	84	86	92
4	4-NO ₂ / I	92	94	89	89	90	91
5	H / Br	79	89	93	81	86	89
6	4-OMe / Br	76	95	95	80	91	93
7	4-NO ₂ / Br	80	92	92	90	93	89
8	4-Cl / Br	81	90	89	87	89	94
9	2-Bromonaphthalene	90	92	94	93	91	92
10	H / Cl	-	-	-	-	-	-

^aIodobenzene (0.5 mmol), 2, 3-dihydrofuran (1 mmol), THF (3 mL) and K_2CO_3 (2 mmol), 6 h in method A and 20 min in method B; ^bIsolated yield; ^cSelectivity was determined by GC.[25] ^dThe enantioselectivity was measured by chiral column GC.

3. Conclusion

This is the first report of applying oxidant- and phosphine-free catalyst in asymmetric Heck reaction of aryl halides with 2, 3-dihydrofuran. The reaction was found to proceed successfully, the corresponding product was obtained in good

yields, high regio- and enantioselectivity at mild reaction conditions without inert atmosphere and phase transfer agents. In this work, we developed a novel palladium catalyst using palladium chloride salt and nitrogen rich histidin-based ligands (Pd/His) with cleaner reaction profiles and simple operation.

Table 3. Comparison of catalytic activities of our catalyst (Pd/His) with literature examples.

Entry [ref]	X	Catalytic system	Reaction conditions	Conv. (%)	Selectivity	ee (%)
1 [34]	I	Pd (OAc) ₂ (1 mol%), Chiral IL, PhI	DMF, K ₂ CO ₃ , 70°C, 2 h	100.0	70: 30	4.2
2 [30]	-OTf	Pd (OAc) ₂ (1 mol%), P, O-ligands	THF, (i-Pr) ₂ NEt, 60°C, 3days	68	20: 80	49.8
3 [31]	-OTf	Pd (OAc) ₂ (3 mol%), 3, 3-Disubstituted xylBINAP	DIPEA, benzene, 40°C, 24 h	32	10: 90	57
4 [35]	-OTf	Pd (dba) ₂ (3 mol%), P, O-ligands	THF, 60°C, (i-Pr) ₂ NEt, 20 h	75	94: 6	77.1
5 [29]	-OTf	Pd (dba) ₂ , ferrocenyl ligands	Toluene, 60°C, iPr ₂ NEt, 36 h.	99	97: 3	80
6 [4]	Br	Pd (dba) ₂ (2 mol%), branched P-ligand	MeOH, 24°C, KOAc, 2h	66	87: 13	-
7 [34]	Br	Pd ₂ (dba) (2.5 mol%), Xyl-SDP(O)	(CH ₂ OH) ₂ , 80°C, (iPr) ₂ NEt, 12 h	84	91: 9	91
8 [8]	I	Pd/DNA@MWCNTs	THF, 50°C, Li ₂ CO ₃ , 48 h	92	87: 13	-
9 [this work]	I, Br	Pd/His	THF, 40°C, K ₂ CO ₃ , 6 h	87	93: 7	93

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