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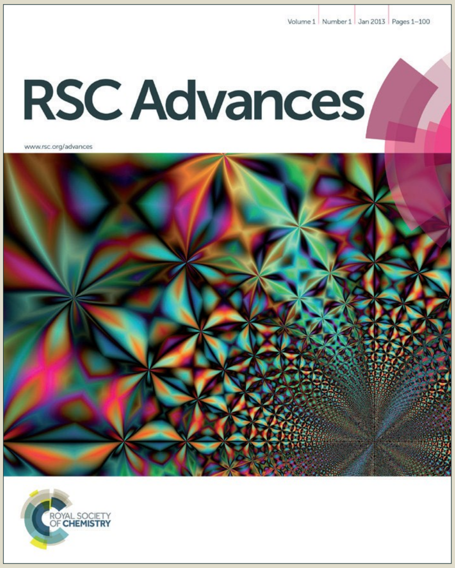

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Kinetic Resolution of 2-Substituted-2,3-dihydrofurans by Palladium-Catalyzed Asymmetric Heck Reaction

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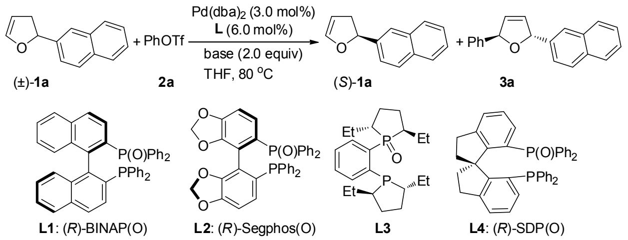
Hao Li,[a,b] Shi-Li Wan,[b] Chang-Hua Ding,*[,b] Bin Xu*[,a] and Xue-Long Hou[b]

The kinetic resolution of 2-substituted-dihydrofurans via palladium-catalyzed asymmetric Heck reaction was realized, providing optically active 2-substituted-dihydrofurans and *trans*-2,5-disubstituted-dihydrofurans in high yield and good enantioselectivities with the *S* factor up to 70.

Catalytic Kinetic resolution is a powerful tool for accessing optically active compounds in organic synthesis.[1] One of the advantages of the kinetic resolution is providing a simple approach for preparing both products and recovered starting materials with high enantioselectivity and yield. Classical kinetic resolution usually does not create new stereogenic center in products. Recently some protocols of catalytic kinetic resolution appeared that involves formation of one, even multiple new chiral centers in products.[2] It remains a undeveloped field, however, the development of new reaction for such kind of kinetic resolution is highly valuable.

On the other hand, the Mizoroki–Heck reaction is widely used in synthesis of natural products, drugs, and functional materials.[3] The early Pd-catalyzed asymmetric intermolecular Heck reaction usually needs the use of cyclic olefins as substrates to avoid an undesired β-H elimination reaction.[4] Recently, Zhou's group realized the use of aryl halides and benzylic esters, two challenging electrophiles, in Pd-catalyzed asymmetric intermolecular Mizoroki-Heck reaction.[5] Jung and Sigman groups reported oxidative Heck or Heck-Matsada reaction using acyclic alkenes as well as trisubstituted alkenes as substrates.[6] In spite of these significant progresses, the asymmetric intermolecular Heck reaction usually forms a single stereocenter for a long time. This situation was changed with the coming of Liu and Zhou's report that two stereocenters were established in high enantioselectivity by desymmetrization of cyclic olefins via asymmetric Heck reaction.[5c] In continuation of our program of Pd-catalyzed asymmetric Heck reaction,[7] herein, we report kinetic resolution of 2-substituted-2,3-dihydrofurans by palladium-catalyzed asymmetric Heck reaction. To our knowledge, this constitutes the first example of kinetic resolution by Heck reaction and provides a new approach to form two stereocenters by Pd-catalyzed asymmetric Heck reaction.

Table 1 Optimization of Reaction Parameters for Kinetic Resolution of 2,3-dihydrofuran **2a**[a]



entry	L	base	1a yield (%)[b]	1a ee (%)[c]	3a yield (%)[b]	3a ee (%)[c]	*S*[g]
1	*rac*-BINAP	^{i}Pr$_2$NEt	59	–	16	–	–
2	**L1**	^{i}Pr$_2$NEt	61	43	30	93	42
3	**L1**	Cy$_2$NMe	59	50	39	93	45
4	**L1**	K_2CO_3	79	8	15	64	5
5	**L1**	NaOAc	73	9	19	43	3
6	**L1**	LiOH	71	2	5	83	11
7	**L1**	Li_2CO_3	51	64	37	92	46
8	**L1**	LiOAc	42	78	43	90	45
9	**L2**	LiOAc	56	43	36	84	18
10	**L3**	LiOAc	80	6	11	54	4
11	**L4**	LiOAc	42	-80	44	-96	121
12[d]	**L1**	LiOAc	81	-3	4	52	3
13[e]	**L1**	LiOAc	55	61	37	87	27
14[f]	**L1**	LiOAc	39	58	43	93	50

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[a] Department of Chemistry, Innovative Drug Research Center, Shanghai University, Shanghai, 200444, China
[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China.
† E-mail: dingch@sioc.ac.cn; xubin@shu.edu.cn; Tel: +86 21 5492 5146

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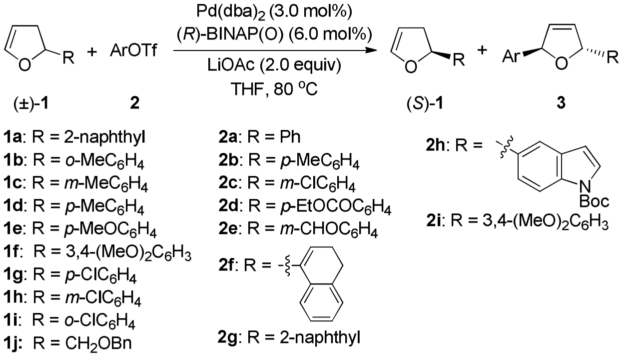
[a] Conditions: molar ratio of **1a**/**2a**/Pd(dba)$_2$/**L**/base = 100:50:3:6:200. [b] Isolated yield. [c] Determined by chiral HPLC; a minus symbol means the opposite sign of optical rotation of the product. [d] Reaction was performed at 60 °C. [e] molar ratio of **1a**/**2a**/Pd(dba)$_2$/**L1** = 100:50:2.5:3. [f] molar ratio of **1a**/**2a**/Pd(dba)$_2$/**L1** = 100:50:5:6. [g] Calculated by the method describe by Kagan.[1a] S = ln[(1-C)(1-ee)]/ln[(1-C)(1+ee)] [C = ee/(ee+ee`), ee = enantiomeric excess of **1a**, ee`= enantiomeric excess of **3a**].

Initially, *rac*-2,3-dihydrofuran **1a** was adopted as substrate to react with aryl triflate **2a** in the presence of 3 mol% Pd(OAc)$_2$ and 6 mol% *Rac*-BINAP in THF at 80 °C (entry 1, Table 1). Heck reaction product **3a** was obtained in 14% yield with recovered **1a** in 59% yield. A byproduct derived from ring-opening of 2,3-dihydrofuran ring was observed.[8] Screening various palladium sources, bases and solvents did not improve the reaction and could not inhibit the formation of the byproduct. Inspired by Oestreich's[9] and Zhou's[5] research using bisphosphine monoxides as ligand for intermolecular Heck reaction, (*R*)-BINAP(O) **L1** was tested as a ligand (entry 2, Table 1). Pleasingly, the formation of byproduct was completely prevented. The Heck product **3a** was afforded in 30% yield with 93% ee while **1a** was recovered in 61% yield with 43% ee (entry 2, table 1). We next examined the effect of other reaction parameters including bases, solvents, ligands, and reaction temperature on the kinetic resolution. Various bases were tested (entries 3-8, Table 1), revealing comparably weak inorganic base Li$_2$CO$_3$ and LiOAc improved the kinetic resolution substantially (entries 7 and 8, Table 1). The reaction using LiOAc as base gave the **3a** in 43% yield with 90% ee and the recovered **1a** in 42% yield with 78% ee (entry 8, Table 1). Then, the effect of solvent on the reaction was investigated, indicating other solvents such as 2-MeTHF, toluene, DMF, 1,4-dioxane gave inferior results.[8] The investigation using other chiral bisphosphine oxide ligands showed that ligand **L2** gave unsatisfactory enantioselectivity (entry 9, Table 1) while ligand **L3** demonstrated low catalytic reactivity in this Heck reaction (entry 10, Table 1). The enantioselectivity was improved by using a bisphosphine oxide (*R*)-SDP(O) **L4**, a ligand based on spiro backbone, providing **3a** with 96% ee and **1a** with 80% ee (entry 11, Table 1). Decreasing the reaction temperature to 60 °C resulted in a low conversion of the **1a** (entry 12, Table 1). Reducing the catalyst loading or changing the ratio of Pd/**L1** from 1/2 to 1/1.2 had a detrimental effect on the kinetic resolution (entry 6 vs entries 13 and 14).

On the basis of the above optimal conditions and in view of the more ready availability of (*R*)-BINAP(O) than (*R*)-SDP(O), we chose (*R*)-BINAP(O) as the ligand to examine the substrate scope of the kinetic resolution of 2-substituted-2,3-dihydrofurans **1** with triflates **2** (Table 2). Generally, the reactions provided Heck products **3** with *trans*-stereoselectivity in 32–50% yields and 87–94% ee accompanied with 35–57% yields of recovered starting materials **1** in 28–95% ee. The *S*-factor was between 25 and 70. The electron-donating and -withdrawing substituents at the *ortho-, meta-* or *para-* position of the 2-aryl group on the 2,3-dihydrofurans **1** had limited effect on the enantioselectivity of Heck products **3**, as its enantioselectivity was consistently excellent (entries 2-9). In contrast, the enantioselectivity of the recovered 2,3-dihydrofurans **1** was greatly affected by the electronic effect of the 2-substituents; the reaction with electron-rich aryl group gave higher enantioselectivity than that with electron-deficient aryl group (entries 2–6 vs entries 7–9). Notably, alkyl substituted substrate, such as 2-((benzyloxy)methyl)-2,3-dihydrofuran **1k** was suitable substrate to produce the corresponding product **3j** in 40% yield and with 91% ee (entry 10). Then 2,3-dihydrofuran **1e** was reacted with a wide array of aryl triflates; the Heck products **3** were also obtained with over 87% enantioselectivity and both electronic perturbation and *ortho-, meta-* or *para*-substituents was well tolerated (entries 11–19). The kinetic resolution can tolerate polar groups such as ester and aldehyde (entries 13 and 14). The reaction of 2,3-dihydrofuran **1e** with an alkenyl triflate **2f** afforded the product **3q** with 90% ee (entry 15). A heteroaryl triflate **2h** based on indoles also reacted efficiently in good ee (entry 17). The absolute configuration of the recovered 2,3-dihydrofuran **1a** was determined to be *S* by comparing its sign of the optical rotation with that reported in literature.[10] The *trans* configuration of the product **3a** was supported by its NOE spectrum. Thus, the absolute configuration of Heck product **3a** is (2*R*,5*R*). The absolution configuration of the product **3r** was also determined to be (2*R*,5*R*) by comparing its sign of the optical rotation with that reported in literature.[10]

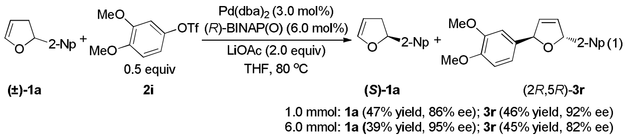
Table 2 Substrate Scope for the Kinetic Resolution of 2-Substituted-2,3-dihydrofuran



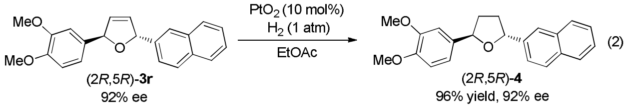
Entry	1	2	1		3		S[d]
			Yield (%)[b]	ee (%)[c]	Yield (%)[b]	ee (%)[c]	
1	**1a**	**2a**	**1a**, 42	78	**3a**, 43	90	45
2	**1b**	**2a**	**1b**, 51	60	**3b**, 38	90	35
3	**1c**	**2a**	**1c**, 43	53	**3c**, 40	93	47
4	**1d**	**2a**	**1d**, 44	58	**3d**, 40	92	43
5	**1e**	**2a**	**1e**, 42	65	**3e**, 36	92	47
6	**1f**	**2a**	**1f**, 48	69	**3f**, 42	91	44
7	**1g**	**2a**	**1g**, 47	39	**3g**, 39	93	40
8	**1h**	**2a**	**1h**, 57	42	**3h**, 37	93	42
9	**1i**	**2a**	**1i**, 48	28	**3i**, 37	90	25
10	**1j**	**2a**	**1j**, 44	55	**3j**, 40	91	37
11	**1e**	**2b**	**1e**, 44	30	**3k**, 38	94	43
12	**1e**	**2c**	**1e**, 45	82	**3l**, 41	91	54
13	**1e**	**2d**	**1e**, 42	67	**3m**, 48	87	29
14	**1e**	**2e**	**1e**, 39	75	**3n**, 42	93	62
15	**1e**	**2f**	**1e**, 35	95	**3o**, 42	90	70
16	**1e**	**2g**	**1e**, 41	88	**3p**, 41	87	42

17	**1e**	**2h**	**1e**, 41	83	**3q**, 48	88	41
18	**1a**	**2i**	**1a**, 49	83	**3r**, 50	92	62
19	**1f**	**2i**	**1f**, 46	85	**3s**, 42	92	65

[a] Molar ratio of **1**/**2**/Pd(dba)$_2$/(R)-BINAP(O)/LiOAc = 100:50:3:6:200. [b] Isolated yield. [c] Determined by chiral HPLC. [d] Calculated by the method describe by Kagan.[1a] S = ln[(1-C)(1-ee)]/ln[(1-C)(1+ee)] [C = ee/(ee+ee\`), ee = enantiomeric excess of recovered substrate **1**, ee\` = enantiomeric excess of product **3**].



This kinetic resolution proceeded smoothly on gram-scale. Treatment of 1.18 g of **1a** with 0.86 g of **2i** under the above reaction conditions afforded 45% yield of (2*R*,5*R*)-**3r** with 82% ee and 39% yield of **1a** with 95% ee (eq 1).



This product **3r** was subjected to hydrogenation under the effect of PtO$_2$ according to the procedure reported by Hayashi group,[10] providing tetrahydrofuran (2*R*,5*R*)-**4** in 96% yield with retention of the enantioselectivity (eq 2). *trans*-2,5-Diaryl tetrahydrofuran has a good anti-platelet activating factor (PAF) activity. PAF are related a variety of biological, such as smooth muscle contraction, platelet aggregation, heart, kidneys, and stomach and intestinal disorders.[11]

In conclusion, we have realized the kinetic resolution of 2-substituted-2,3-dihydrofurans via palladium-catalyzed asymmetric Heck reaction, affording Heck products and recovered substrates in high yield and enantioselectivity. Studies on the extension of the protocol to other kind of alkenes and applications of the procedure in organic synthesis are in progress.

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