

Catalytic asymmetric arylation of olefins

Tamio Hayashi, Akihiko Kubo, and Fumiyuki Ozawa

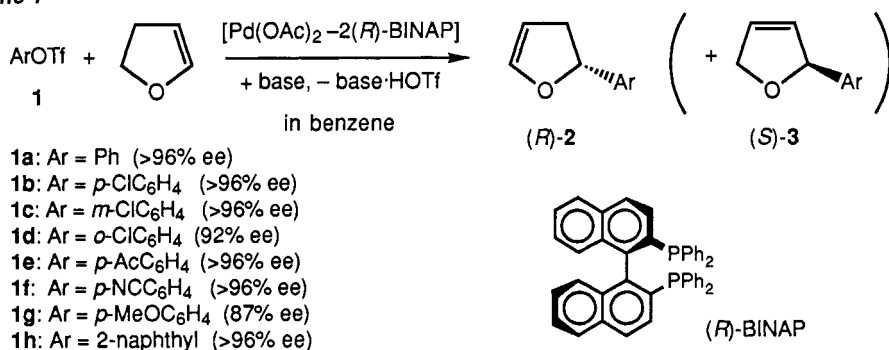
Catalysis Research Center and Graduate School of Pharmaceutical Science,
Hokkaido University, Sapporo 060, Japan

Abstract - Catalytic asymmetric arylation of 2,3-dihydrofuran with aryl triflate (**1**) in benzene at 40 °C in the presence of a base and a palladium catalyst, generated in situ from Pd(OAc)₂ and (*R*)-BINAP, gave optically active (*R*)-2-aryl-2,3-dihydrofuran (**2**) and a small amount of (*S*)-2-aryl-2,5-dihydrofuran (**3**). The relative ratio of **2** to **3** and the enantiomeric purities of the products were dependent upon the base employed. 1,8-Bis(dimethylamino)naphthalene (proton sponge) as a highly basic and sterically demanding amine gave major product (*R*)-**2** in extremely high enantioselectivity (>96–87% ee) for a variety of aryl triflates. The mechanism of this novel catalytic asymmetric reaction is discussed in detail.

INTRODUCTION

Asymmetric carbon–carbon bond forming reactions are of great significance for the synthesis of optically active compounds, and the use of chiral transition-metal catalysts for such reactions has recently attracted considerable attention owing to a number of advantages of catalytic asymmetric synthesis (ref. 1). We wish to report here the first example of intermolecular asymmetric Heck-type arylation of cyclic olefins catalyzed by chiral palladium complexes.

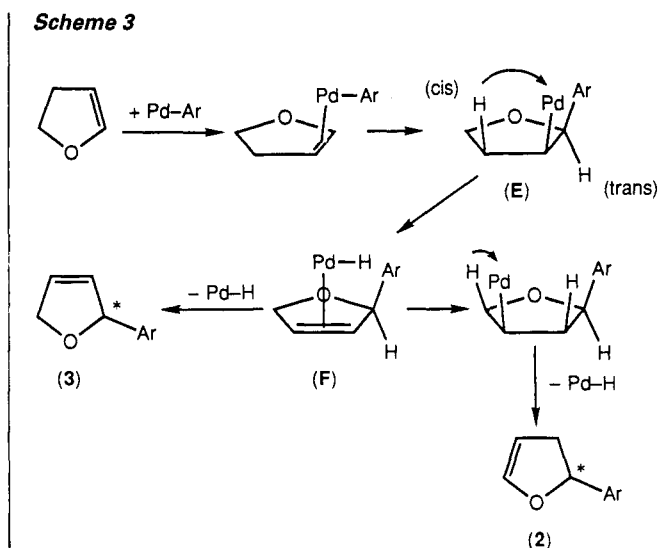
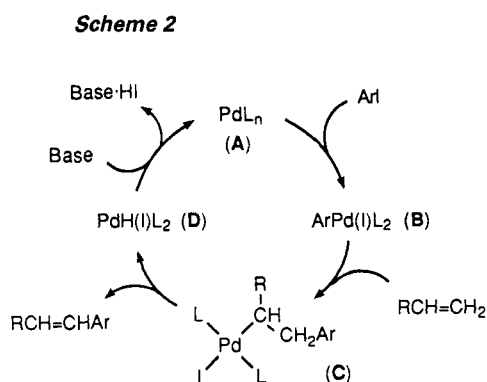
Scheme 1



The palladium complex-catalyzed arylation and alkenylation of olefins, which were first discovered in the 1970's by Heck (ref. 2), are one of the most useful synthetic means for making a carbon–carbon bond. These reactions have been extensively applied in organic synthesis during the past two decades (ref. 3). However, "asymmetric Heck reaction" where the carbon–carbon formation proceeds with high enantioselectivity did not appear until very recently. Shibasaki and his co-workers reported an asymmetric intramolecular cyclization of alkenyl iodides to give *cis*-decalin derivatives of 80–91% ee, where a combination of a (*R*)-BINAP-coordinated palladium complex and a silver salt was employed for generating an efficient chiral catalyst (refs. 4 and 5). Overman et al. reported an intramolecular cyclization of alkenyl triflate, giving a chiral quaternary carbon center of 45% ee (ref. 6). Our search for asymmetric Heck reaction was started with more simple reaction systems with hope to gain an insight into this novel catalytic asymmetric reaction (ref. 7).

SEARCH FOR THE EFFICIENT CATALYTIC SYSTEM

Scheme 2 shows the generally accepted mechanism for the catalytic arylation of olefins with aryl iodides in the presence of a tertiary phosphine-coordinated palladium catalyst and a base (ref. 3a). Oxidative addition of aryl iodide (ArI) to a Pd(0) species (A), which is generated most commonly from palladium diacetate and tertiary phosphine ligand, forms an arylpalladium iodide complex (B). Coordination of olefin on B followed by insertion of the coordinated olefin into the Pd–Ar bond forms a σ -alkylpalladium species (C), which undergoes β -hydrogen elimination reaction to give the arylation product and a hydridopalladium complex (D). Interaction of D with a base regenerates the Pd(0) species (A) as a carrier of further catalytic cycle.

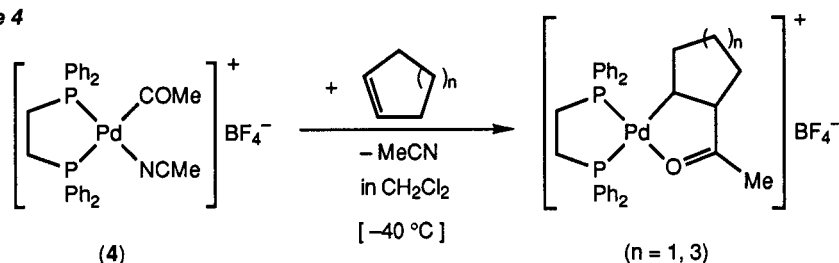


Generally, Heck reaction is not applied to asymmetric synthesis because the chiral carbon center formed by the olefin-insertion is lost at the subsequent β -hydrogen elimination step. When a cyclic olefin such as 2,3-dihydrofuran is used, however, the chiral carbon center will remain in the arylation product as illustrated in Scheme 3. The reaction of 2,3-dihydrofuran with an arylpalladium species via the common cis insertion process forms alkylpalladium intermediate E. In this intermediate, the hydrogen bound to the arylated carbon, that is trans to the palladium, can not participate in the β -hydrogen elimination. Alternatively, the cis β -hydrogen at another β -carbon must be abstracted by palladium. Dissociation of the coordinated olefin from the resulting hydrido-olefin complex F gives 2-aryl-2,5-dihydrofuran (3), whereas insertion of the olefin into the Pd–H bond in F followed by β -hydrogen elimination forms thermodynamically more stable 2-aryl-2,3-dihydrofuran (2), in which the arylated carbon center remains chiral.

We therefore studied asymmetric arylation of 2,3-dihydrofuran. In our initial attempts, we applied chiral diphosphine ligands to a common arylation system using phenyl iodide as the arylating reagent (ref. 8), but no or little asymmetric induction has been observed. For example, the reaction of 2,3-dihydrofuran with phenyl iodide in THF in the presence of triethylamine and 3 mol% of a palladium catalyst, prepared in situ from Pd(OAc)₂ and (*R*)-BINAP, at 40 °C for 44 h gave racemic 2-phenyl-2,3-dihydrofuran (2a) and 2-phenyl-2,5-dihydrofuran (3a) in 23% and 2% yields, respectively. This reaction must involve [PdPh(I)(BINAP)] intermediate formed by oxidative addition of phenyl iodide to a [Pd(0)(BINAP)] species generated in the system. Recent mechanistic studies on olefin-insertion into the related tertiary phosphine-coordinated acylpalladium halide complexes [Pd(COR)(X)L₂] revealed that the insertion process involves displacement of one of the phosphine ligands with olefin to give [Pd(COR)(olefin)X(L)] type intermediate (refs. 9 and 10). Therefore, we reasoned that the absence of asymmetric induction in the arylation system with phenyl iodide is attributable to partial dissociation of BINAP ligand during the olefin-insertion process.

On the other hand, we recently found that a cationic acetyl-palladium complex coordinated with 1,2-bis(diphenylphosphino)ethane (dppe) as a potent bidentate ligand [Pd(COMe)(NCMe)(dppe)]⁺BF₄⁻ (4) possesses extremely high reactivity toward olefin-insertion (Scheme 4) (ref. 11). Complex 4 reacted with cyclic olefins including cyclopentene and cycloheptene under very mild conditions (–40 °C) to give the olefin-inserted complexes.

Scheme 4



Cationic complex 4 has the coordination site that is weakly coordinated with acetonitrile and easily accessible for coordination of olefins. The presence of bidentate ligand allows the acetyl group and the coordinated olefin to come to the adjacent sites (cis) convenient for the subsequent olefin-insertion. The overall situation results in the facile olefin-insertion without involving the partial dissociation of phosphine ligand.

Taking the above mechanistic information into account, we sought the catalytic asymmetric arylation system that involves a cationic arylpalladium intermediate. First, we examined the reaction of 2,3-dihydrofuran with phenyl iodide and Et₃N in the presence of AgClO₄ and a palladium catalyst bearing (*R*)-BINAP ligand. The silver salt employed may react with the [PdPh(I)(BINAP)] intermediate to generate a desirable cationic phenylpalladium species. The reaction carried out in THF at 40 °C for 44 h actually gave optically active (*R*)-2-phenyl-2,3-dihydrofuran (**2a**) of 61% ee (50% yield) together with a small amount of its regioisomer (**3a**). Secondly, we tried to employ arylpalladium triflate intermediate [Pd(Ar)(OTf)(BINAP)] (**5**) which may be generated in the catalytic system by oxidative addition of aryl triflate to a Pd(0) species (ref. 7). Complex **5** having triflate ligand as a good leaving group was expected to form a cationic olefin-coordinated species [Pd(Ar)(olefin)(BINAP)]⁺OTf⁻ (**6**) with retention of the chelate coordination of BINAP ligand, leading to the highly enantioselective Heck Reaction.

CATALYTIC ASYMMETRIC ARYLATION OF OLEFINS

Reaction of 2,3-dihydrofuran with aryl triflate in benzene in the presence of a base and a palladium catalyst, generated in situ from Pd(OAc)₂ and 2 equivalents of (*R*)-BINAP, gave (*R*)-2-aryl-2,3-dihydrofuran (**2**) and a small amount of the regioisomer (*S*)-2-aryl-2,3-dihydrofuran (**3**) (Scheme 1) (refs. 7 and 12). Table 1 demonstrates that the arylation reaction proceeds in high enantioselectivity over 87% ee with a variety of aryl triflates. Particularly, almost optically pure (*R*)-**2** was obtained with 2-naphthyl triflate and phenyl triflates bearing an electron-withdrawing substituent at the para or meta position.

TABLE 1. Catalytic asymmetric arylation of 2,3-dihydrofuran with aryl triflates (**1**) promoted by Pd(OAc)₂-(*R*)-BINAP catalyst.^a

Run	ArOTf (1)		% ee ^b			yield (%) ^c	
			(<i>R</i>)- 2	(<i>S</i>)- 3	2/3 ^d	(<i>R</i>)- 2	(<i>S</i>)- 3
1	Ph	(a)	>96	17	71/29	46	24
2	<i>p</i> -ClC ₆ H ₄	(b)	>96	6	70/30	54	21
3	<i>m</i> -ClC ₆ H ₄	(c)	>96	39	72/28	66	22
4	<i>o</i> -ClC ₆ H ₄	(d)	92	53	73/27	53	21
5	<i>p</i> -AcC ₆ H ₄	(e)	>96	7	e)	50	24
6	<i>p</i> -NCC ₆ H ₄	(f)	>96	4 (<i>R</i>)	66/34	52	26
7 ^f	<i>p</i> -MeOC ₆ H ₄	(g)	87	11 (<i>R</i>)	63/37	42	25
8	2-naphthyl	(h)	>96	10	69/31	52	26

a) The reaction was carried out in benzene at 40 °C under a nitrogen atmosphere in the presence of 1,8-bis(dimethylamino)naphthalene (proton sponge) as the base for 2–9 days unless otherwise noted. Initial conditions: ArOTf/2,3-dihydrofuran/base/Pd(OAc)₂/BINAP = 1/5/3/0.03/0.06. b) Determined by ¹H NMR analysis using an optically active shift reagent Eu(hfc)₃. c) Isolated yield by silica gel column chromatography at 100% conversion of aryl triflate. d) Product ratio in the catalytic solution as determined by GLC. e) Not measured. f) The reaction was carried out at 50 °C.

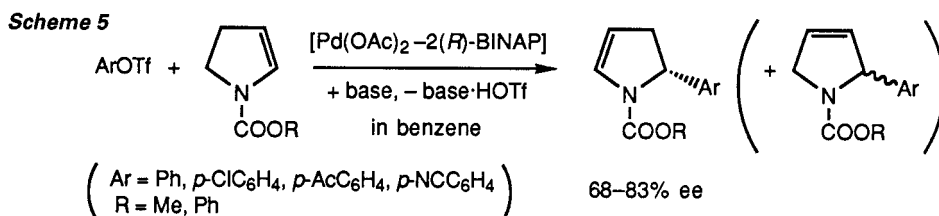
TABLE 2. Effect of base on the catalytic asymmetric arylation of 2,3-dihydrofuran with phenyl triflate (1a) promoted by Pd(OAc)₂-(*R*)-BINAP catalyst.^{a)}

Run	Base ^{b)}	Reaction time	Conversion ^{c)} of 1a (%)	2/3 ^{c)}	% ee ^{d)}	
					(<i>R</i>)-2a	(<i>S</i>)-3a
1	Et ₃ N	26 h	100	98/2	75	9
2	<i>i</i> -Pr ₂ NEt	24 h	100	92/8	82	60
3	Cy ₂ NH	17 h	100	86/14	82	43
4		9 d	100	71/29	>96	17
5		9 d	38	100/0	69	—
6		5 d	88	100/0	77	—
7 ^{e)}	MeCOONa	2 d	87	96/4	71	3 (<i>R</i>)
8 ^{e)}	Na ₂ CO ₃	1 d	100	97/3	75	93 (<i>R</i>)

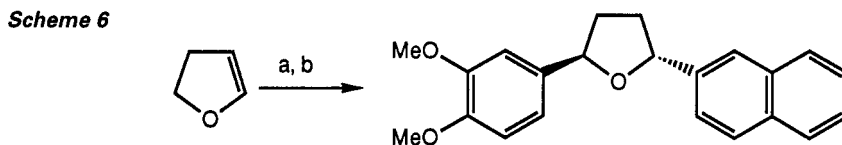
a) The reaction was carried out in benzene under a nitrogen atmosphere at 40 °C unless otherwise noted. Initial conditions: 1a/2,3-dihydrofuran/base/Pd(OAc)₂/BINAP = 1/5/3/0.03/0.06. b) Cy₂NH = dicyclohexylamine. c) Determined by GLC. d) Determined by ¹H NMR analysis using an optically active shift reagent Eu(hfc)₃. e) The reaction was carried out at 60 °C.

The regioselectivity and the enantiomeric purities of the arylation products are strongly affected by the base employed (ref. 12). Table 2 lists the results of catalytic reactions of 2,3-dihydrofuran with phenyl triflate in the presence of a variety of bases. Extremely high enantioselectivity for (*R*)-2a over 96% ee was obtained with highly basic and sterically demanding 1,8-bis(dimethylamino)naphthalene (proton sponge) (run 4). On the other hand, the optical purity of (*R*)-2a lowers in the reactions using more compact aliphatic amines and less basic amines including pyridine derivatives (runs 1–3, 5 and 6). Inorganic bases such as sodium acetate and sodium carbonate also gave lower enantioselectivity (runs 7 and 8). It is interesting to note that increasing product ratio of minor product (*S*)-3a tends to increase the optical purity of major product (*R*)-2a.

Under similar reaction conditions, *N*-substituted pyrrolines were arylated in 68–83% ee (Scheme 5) (ref. 13).



The asymmetric arylation of 2,3-dihydrofuran was applied to the enantioselective synthesis of an antagonist of platelet activating factor (PAF), *trans*-(*R,R*)-2-naphthyl-5-(3,4-dimethoxyphenyl)tetrahydrofuran (Scheme 6) (refs. 12 and 14).

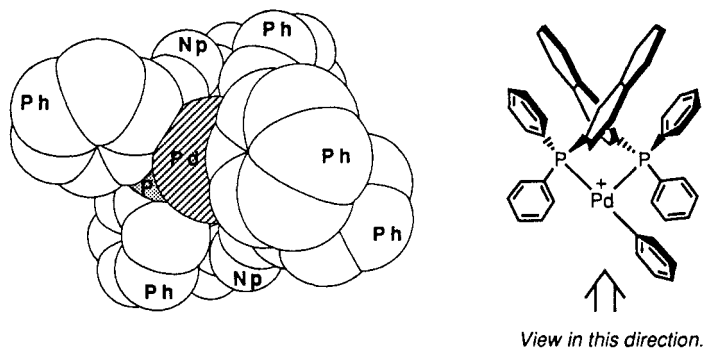


(a) 3 mol% Pd(OAc)₂/6 mol% (*R*)-BINAP/proton sponge/benzene/2-naphthyl triflate (40 °C), then 3,4-dimethoxyphenyl triflate (80 °C) (36%); (b) PtO₂/H₂/AcOEt (room temp.) (100%).

REACTION MECHANISM

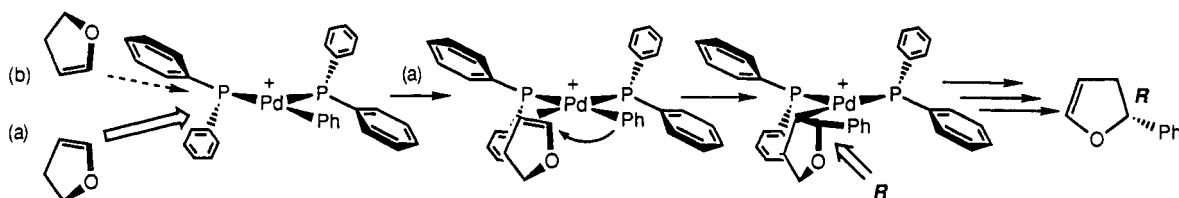
Scheme 7 depicts a molecular view of $[\text{PdPh}\{(R)\text{-BINAP}\}]^+$ species which was drawn with *Chem 3D*TM computer program using the partial X-ray structure of $[\text{PdCl}_2\{(R)\text{-BINAP}\}]$. It is seen that the lower part of the empty coordination site widely opens whereas the upper part is blocked by one of the phenyl groups of the BINAP ligand.

Scheme 7 Molecular model of $[\text{PdPh}\{(R)\text{-BINAP}\}]^+$ species.



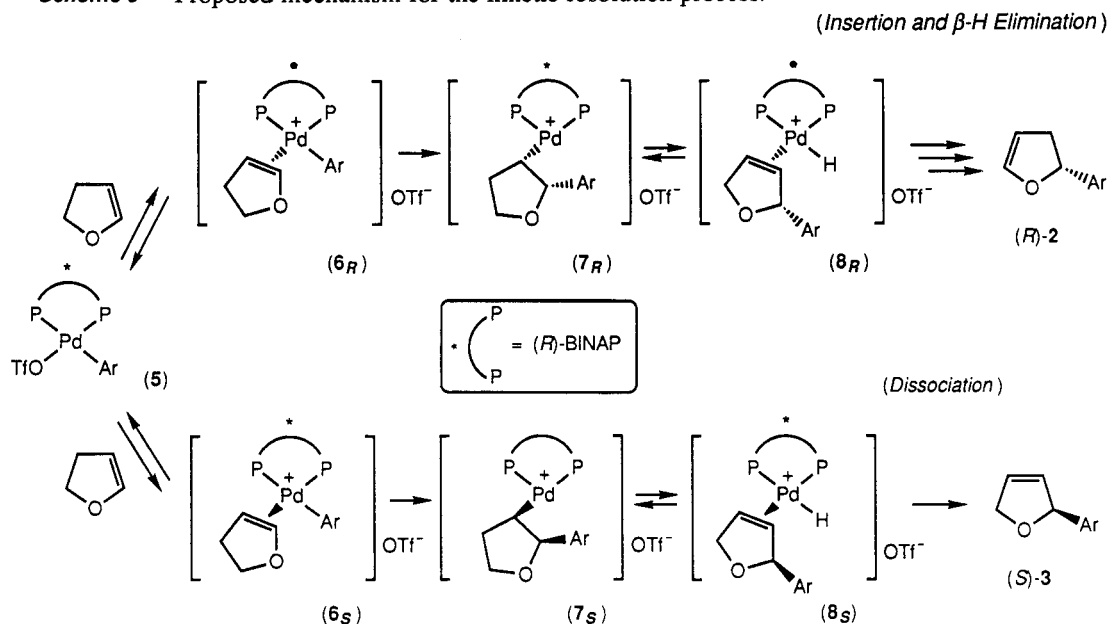
Scheme 8 shows the two possible modes for coordination of 2,3-dihydrofuran to the $[\text{PdPh}\{(R)\text{-BINAP}\}]^+$ species. As suggested from the molecular model in Scheme 7, dihydrofuran may coordinate to the palladium center more easily in mode (a) than (b). The olefin-coordination in mode (a) followed by olefin-insertion and β -hydrogen elimination reactions forms the phenylation product having (*R*)-configuration, that is the observed configuration in major regioisomer **2** in the actual catalytic reactions.

Scheme 8 A schematic process for the enantioselective insertion of 2,3-dihydrofuran into the Pd–Ph bond in $[\text{PdPh}\{(R)\text{-BINAP}\}]^+$ species, showing the two possible modes (a) and (b) for olefin-coordination. The binaphthyl group of (*R*)-BINAP ligand is omitted for clarity.

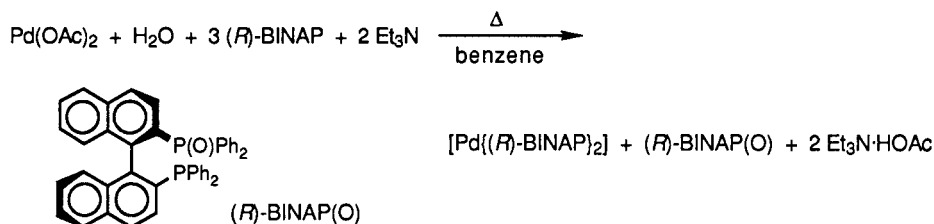


An interesting feature of this asymmetric reaction is that the arylation products **2** and **3** have the opposite configurations to each other, indicating that a kinetic resolution process enhances the enantiomeric purity of major product (*R*)-**2** by selective elimination of (*S*)-isomer as minor product **3** from the catalytic cycle (Scheme 9). Coordination of dihydrofuran on arylpalladium intermediate **5** forms two types of olefin-coordinated complexes **6_R** and **6_S**, depending on the selection of enantiofaces of olefin. Complexes **6_R** and **6_S** thus formed undergo the subsequent olefin-insertion and β -hydrogen elimination reactions to give a pair of diastereomers of hydrido-olefin complexes having (*R*)-2-aryl-2,5-dihydrofuran and (*S*)-2-aryl-2,5-dihydrofuran ligands, **8_R** and **8_S**, respectively. Molecular inspection using CPK models has suggested that **8_R** has a preferable structure for further olefin-insertion and β -hydrogen elimination reactions to give major product (*R*)-**2**. On the other hand, the diastereomer **8_S** suffers considerable steric repulsion between the coordinated olefin and one of the phenyl groups in BINAP ligand. Consequently, **8_S** is prone to release the coordinated olefin (*S*)-**3**. The overall process gives rise to the enhancement in the optical purity of major product (*R*)-**2**. For example, based on the product ratio of (*R*)-**2a** to (*S*)-**3a** and the optical purities of both compounds, the relative ratio of **8_R** to **8_S** in run 1 in Table 1 may be calculated as 81 : 19. Therefore, if both diastereomers gave the same regioisomer **2a**, the catalytic reaction should give (*R*)-**2a** of 62% ee; the value being much lower than that observed in the actual catalytic system (>96% ee).

The initial step of the catalytic cycle is oxidative addition of aryl triflate to a BINAP-coordinated Pd(0) species. Since, in the actual catalytic system, $\text{Pd}(\text{OAc})_2$ and (*R*)-BINAP are used as the precursors of the

Scheme 9 Proposed mechanism for the kinetic resolution process.

Pd(0) species, reduction of Pd(OAc)₂ into the BINAP-coordinated Pd(0) species should be operative prior to the catalytic reaction. Although Pd(OAc)₂ is the most commonly used precursor of a Pd(0) species in many palladium-catalyzed organic reactions, no direct information has been reported so far on its reduction process. In this study, we confirmed for the first time that the reduction proceeds according to the process involving a combination of tertiary phosphine (BINAP) and water as the reducing reagent (Scheme 10) (ref. 15). Treatment of a benzene solution of Pd(OAc)₂ and 3 equivalents of (*R*)-BINAP with an excess amount of Et₃N resulted in change in the color of the solution from yellow to red. ³¹P{¹H} NMR study of the resulting solution revealed the formation of [Pd{(R)-BINAP}₂] and BINAP monoxide (BINAP(O)) in a 1 : 1 ratio. Labeling experiments showed the participation of 1 equivalent of residual water in the reduction system. Thus, the reaction carried out in solution saturated with ¹⁸OH₂ gave ¹⁸O-labeled BINAP(¹⁸O).

Scheme 10

On the basis of the well-defined information on the catalytic system, our attention was directed toward further details of the kinetic resolution process. Thus, the catalytic reaction was examined with isolated [Pd{(R)-BINAP}₂] catalyst and *i*-Pr₂N⁺Et as the base (Table 3). Surprisingly, (*R*)-2 was exclusively formed in the catalytic reaction using the [Pd{(R)-BINAP}₂] catalyst (run 1), indicating that no kinetic resolution takes place (run 1). Addition of BINAP(O) did not cause the kinetic resolution (run 2). In contrast, the kinetic resolution occurred in the presence of added acetic acid (runs 3 and 4). The larger amount of acetic acid gave rise to the higher ratio of (*S*)-3 and the higher optical purity of (*R*)-2. In the presence of 5 equiv./Pd of acetic acid, almost optically pure (*R*)-2a was obtained.

Since the catalytic system contains an excess amount of amine, acetic acid added to the system forms the ammonium acetate salt, which is also formed in the catalytic system starting with Pd(OAc)₂ as the catalyst precursor during the conversion of Pd(OAc)₂ into a Pd(0) species (Scheme 10). The results described above demonstrate that the acetate anion thus formed serves as the promoter of the kinetic resolution process. Since the hydrido-olefin complex **8_S** in Scheme 9 has a 16e square planar structure, dissociation of the coordinated olefin should proceed via an associative mechanism involving an 18e transition state formed by nucleophilic attack of an incoming ligand to the palladium center. The acetate anion may possess the high nucleophilicity toward the cationic palladium center in **8_S** to cause the dissociation of the olefin.

TABLE 3. Catalytic asymmetric arylation of 2,3-dihydrofuran with phenyl triflate (**1a**) promoted by [Pd(*R*)-BINAP]₂ catalyst.^{a)}

Run	Additive (equiv./Pd)	2/3 ^{c)}	% ee ^{b)}	
			(<i>R</i>)-2a	(<i>S</i>)-3a
1	—	100/0	77	—
2	BINAP(O) (1)	100/0	76	—
3	AcOH (2)	89/11	83	64
4	AcOH (5)	84/16	>96	60

a) The reaction was carried out in benzene at 40 °C under a nitrogen atmosphere in the presence of *i*-Pr₂NEt as the base for 1–2 days. Initial conditions: **1a**/2,3-dihydrofuran/*i*-Pr₂NEt/catalyst = 1/5/3/0.03. b) Determined by ¹H NMR analysis using an optically active shift reagent Eu(hfc)₃. c) Product ratio in the catalytic solution as determined by GLC.

The nucleophilicity of acetate anion should be defined by the counter cation particularly in nonpolar media such as benzene. The marked difference in effect of bases in the kinetic resolution process is attributable to the difference in the nucleophilicity of acetate anion that is controlled by the ammonium cation. Proton sponge as one of the most strong bases for trapping proton in organic solvents may generate the highly reactive acetate anion that promotes the efficient kinetic resolution giving (*R*)-2 of extremely high optical purity.

CONCLUSION

We confirmed that the catalytic system using aryl triflates as arylating reagents is efficient in the asymmetric arylation of 2,3-dihydrofuran to give 2-aryl-2,3-dihydrofuran derivatives of extremely high enantiomeric purity. A catalytic cycle involving a novel kinetic resolution process has been suggested, which is promoted by acetate anion and enhances the optical purity of major regioisomer. A similar catalytic mechanism involving a kinetic resolution process may be operative in related catalytic asymmetric Heck reactions of cyclic olefins.

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