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Asymmetric Heck-Type Reaction Utilizing Hypervalent Alkenyliodonium Salt

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Asymmetric Heck-type reaction of 1-cyclohexenylphenyliodonium salt with 2,3-dihydrofuran was investigated for the first time. The optically active (up to 78% ee) coupling product was obtained in low to moderate yield. The potential and associated problems of this asymmetric reaction are discussed.

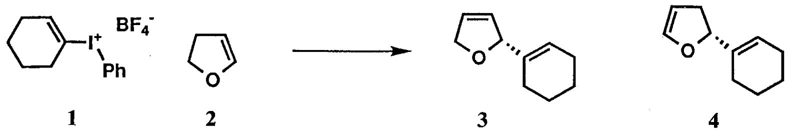
Keywords asymmetric Heck-type reaction; hypervalent iodonium salt; palladium; catalysis; asymmetric C–C bond formation

Since our first report on an asymmetric Heck reaction in 1989,[1] we have studied many asymmetric alkenylations using alkenyl iodides and alkenyl triflates.[2] This C–C bond-forming reaction is quite useful for catalytic asymmetric syntheses.[2,3] When alkenyl iodide is used as a substrate, silver salt is required to achieve high chemical and optical yield. In contrast, asymmetric Heck reactions using alkenyl triflate as a substrate afford good asymmetric induction even without silver salt. These findings suggest that efficient generation of square-planar cationic palladium intermediate is crucial in the asymmetric Heck reaction.

Recently, Moriarty *et al.* reported that hypervalent iodine could be used as a substrate for Heck-type olefination.[4] They showed that alkenylphenyliodonium salts coupled smoothly with olefins in *N*,*N*-dimethylformamide (DMF) in the presence of $NaHCO_3$ and 5 mol% of $Pd(OAc)_2$ at room temperature. This indicated that the hypervalent iodonium salt could be a good substrate for asymmetric Heck-type reaction. Here we would like to report preliminary results of the asymmetric Heck-type reaction using alkenylphenyliodonium salt.

To investigate the influence of chiral bidentate ligands in the reaction of hypervalent iodonium salts, we chose 1-cyclohexenylphenyliodonium salt **1**[5] and 2,3-dihydrofuran (**2**) as substrates. First, **1** was treated with $Pd(OAc)_2$ (5 mol%), (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl ((*R*)-BINAP)[6] (10 mol%), $NaHCO_3$ (2 eq), and **2** (5 eq) in DMF at room temperature. The coupling product **3** was obtained in only 13% chemical yield with 4% ee. After investigation of the effects of solvents and bases (Table I), reaction using Proton Sponge® [1,8-bis(dimethylamino)naphthalene] in CH_2Cl_2 was found to give a slightly better chemical (20%) and optical yield (21% ee). Benzene and toluene, which usually afford the best results in asymmetric Heck reaction of alkenyl tri-

TABLE I. Coupling Reaction of **1** with **2**



Entry[a]	$Pd(OAc)_2$ (mol%)	(*R*)-BINAP (mol%)	Solvent	Base	Temp.	Time (h)	Yield (%)	ee[c] (%)
1	5	10	DMF	$NaHCO_3$	rt	20	13	4
2	5	10	NMP	$NaHCO_3$	rt	20	9	6
3	5	10	DMSO	$NaHCO_3$	rt	20	22	1
4	5	10	THF	$NaHCO_3$	rt	20	5	37
5	5	10	THF	Proton Sponge®	rt	20	12	17
6	5	10	CH_2Cl_2	$NaHCO_3$	rt	20	7	22
7	5	10	CH_2Cl_2	Proton Sponge®	rt	20	20	21
8	5	10	Toluene	Proton Sponge®	rt	20	0	—
9	5	10	Toluene	Proton Sponge®	55 °C	20	14	14
10	5	10	Benzene	Proton Sponge®	55 °C	20	7	8
11	10	15	CH_2Cl_2	Proton Sponge®	rt	20	33	24
12[b]	10	15	CH_2Cl_2	Proton Sponge®	rt	20	26	22
13[b]	40	40	CH_2Cl_2	Proton Sponge®	rt	20	59	11
14[b]	40	60	CH_2Cl_2	Proton Sponge®	rt	20	22	78
15[b]	40	80	CH_2Cl_2	Proton Sponge®	rt	20	Trace	—
16	5	0	CH_2Cl_2	Proton Sponge®	rt	0.5	91	—
17	0	0	CH_2Cl_2	Proton Sponge®	rt	20	5	—

a) Molar ratio of **1**:**2**:base=1:5:2. *b*) $Pd(OAc)_2$, (*R*)-BINAP, Proton Sponge®, and **2** in CH_2Cl_2 were stirred at 40 °C for 24 h before the addition of **1**. *c*) Determined by ^{1}H-NMR using $Eu(hfc)_3$.

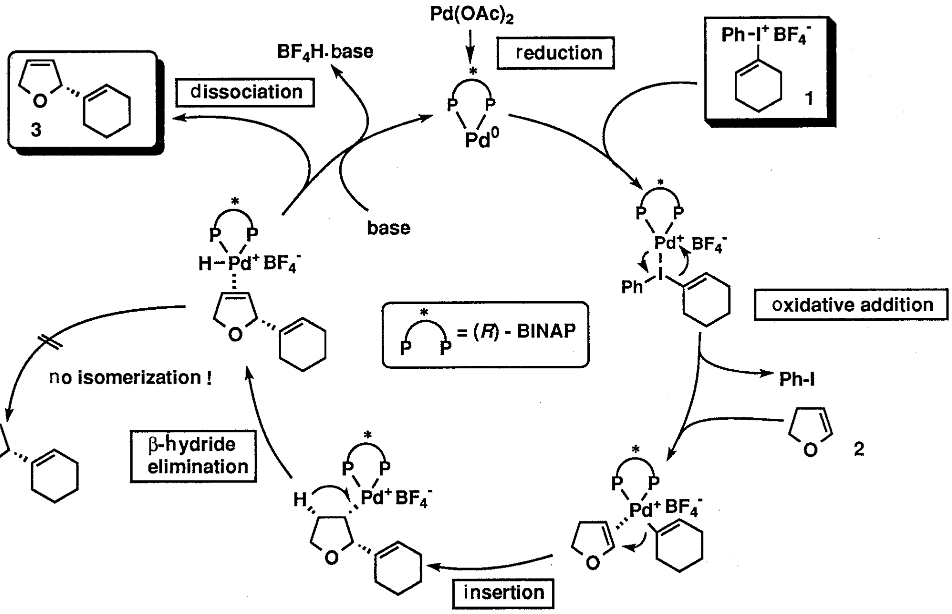


Chart 1. Possible Mechanism for Heck-Type Reaction of the Iodonium Salt

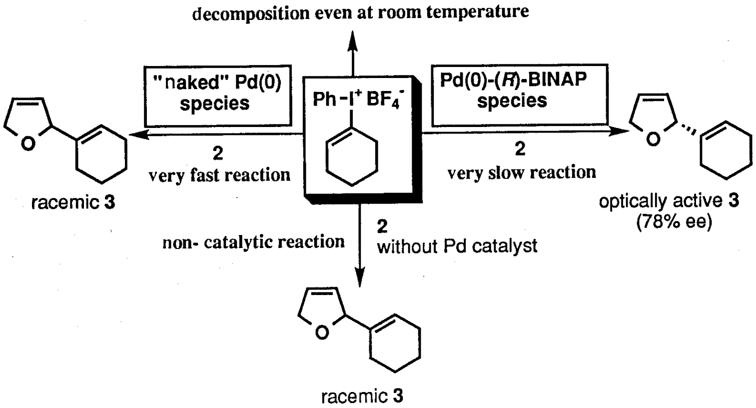


Chart 2. Competitive Pathways in the Heck-Type Reaction of Hypervalent Iodonium Salt

flates,[2,3] were found not to be good solvents in this case, probably because of the insolubility of **1** in these solvents. Although the asymmetric coupling reaction of cyclohexenyl triflate with dihydrofuran catalyzed by [(*R*)-binap]$_2$Pd in benzene was reported to give the isomerized product **4** as the major product,[3a] no isomerized product was detected in these reactions using hypervalent iodine and Pd(OAc)$_2$–(*R*)-BINAP. Ozawa *et al.* pointed out that nucleophilic acetate anion generated *in situ* from Pd(OAc)$_2$ enhanced dissociation of hydridopalladium cation from the coupling product and as a result prevented isomerization.[3h]

In contrast to the rapid reaction without phosphine ligand (entry 16), reaction in the presence of (*R*)-BINAP was very slow, and an induction period of several hours was observed. Pretreatment of Pd(OAc)$_2$ with (*R*)-BINAP in the presence of **2** (40 °C, 24 h) shortened the induction period and improved the reproducibility of the reaction; however, no improvement in yield was observed. Increase of the catalyst amount to 40 mol% of Pd(OAc)$_2$ and 60 mol% of (*R*)-BINAP improved the optical yield considerably to 78% ee ($[\alpha]_D^{22}$ +154.6°, $c=0.22$, CHCl$_3$) (entry 14). This finding clearly indicates that the reaction catalyzed by the Pd species carrying BINAP ligand gives **3** with high ee, but proceeds very slowly. The BINAP/Pd ratio seems to be important in this reaction (entries 13—15). When the BINAP/Pd ratio is low, the ee of the product is substantially decreased, probably due to the participation of highly active Pd species without ligand. In contrast, when the BINAP/Pd ratio is high, the yield of the product is decreased, probably due to the formation of catalytically low-reactive bis-BINAP–Pd species. It is noteworthy that **1** is unstable and decomposed into black materials even at room temperature after several hours. Furthermore, even in the absence of the Pd-catalyst a small amount of **3** was formed (entry 17). This ultimately results in overall lower ee of the desired coupling product **3**. These findings suggest that fast asymmetric Heck-type reaction would be required to achieve both high chemical and optical yield (Chart 2).

In an attempt to overcome these problems, many reaction conditions (Pd catalyst, ligand,[7] syringe pump technique or additives[8]) were investigated. Unfortunately no further improvement of the chemical and optical yield

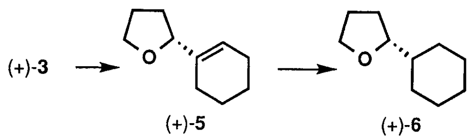


Chart 3. Determination of the Absolute Stereochemistry

of **3** could be achieved. The absolute stereochemistry of (+)-**3** was determined to be *R* by the conversion of (+)-**3** (76% ee) to (+)-**6** ($[\alpha]_D^{22}$ +5.3°)[3a,9] as shown in Chart 3.

In the course of the studies described above, we observed that the reaction catalyzed by 10 mol% of [(*R*)-binap]-$PdCl_2$ (2 eq of Proton Sponge®, CH_2Cl_2, room temperature) gave a different product. It was identified as the formal reduction product **5** (34% yield, 19% ee). Only a trace amount of the desired **3** was detected in this reaction. The hydride source for this reaction is unknown; one possible candidate may be 2,3-dihydrofuran (**2**).

In conclusion, asymmetric Heck-type reaction of hypervalent iodonium salt was investigated for the first time to afford the optically active coupling product **3** (up to 78% ee). Although these preliminary results are not satisfactory, the potential and associated problems of this asymmetric reaction, utilizing the hypervalent iodonium salt, have become evident. To resolve these problems and to clarify the mechanism of reductive coupling reaction, further investigation is in progress.

Experimental

Coupling Reaction of 1 with 2 Catalyzed by $Pd(OAc)_2$–(*R*)-BINAP A representative procedure is as follows. A solution of $Pd(OAc)_2$ (36.2 mg, 0.161 mmol), (*R*)-BINAP (150.8 mg, 0.242 mmol), and Proton Sponge® (173.0 mg, 0.807 mmol) in CH_2Cl_2 (0.5 ml) was degassed by three freeze–pump–thaw cycles. After addition of 2,3-dihydrofuran (**2**) (142.6 mg, 2.02 mmol) the whole mixture was stirred at 40 °C for 24 h. A solution of 1-cyclohexenylphenyliodonium tetrafluoroborate (150 mg, 0.404 mmol) in degassed CH_2Cl_2 was then added at room temperature, and the mixture was stirred at the same temperature for 20 h. After evaporation of the solvent, the dark red residue was purified by silica gel column chromatography (CH_2Cl_2) to give **3** (13.1 mg, 22%, 78% ee) as a colorless oil, $[\alpha]_D^{22}$ +154.6° (c=0.22, $CHCl_3$). IR (neat): 1666, 1618, 1135 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.51—1.69 (4H, m), 1.83—2.20 (4H, m), 4.60—4.83 (2H, m), 5.09—5.20 (1H, br s), 5.66—5.80 (2H, m), 5.89—6.00 (1H, m). ^{13}C-NMR ($CDCl_3$) δ: 22.5, 23.3, 25.0, 75.7, 90.6, 124.3, 127.1, 128.8, 138.0. MS m/z: 150 (M$^+$), 121, 109, 81 (bp). HR-MS: Calcd for $C_{10}H_{14}O$ 150.1045, Found: 150.1043.

Coupling Reaction of 1 with 2 Catalyzed by [(*R*)-binap]$PdCl_2$ A solution of [(*R*)-binap]$PdCl_2$ (37.1 mg, 0.04 mmol), and Proton Sponge® (173.0 mg, 0.807 mmol) in CH_2Cl_2 (0.5 ml) was degassed by three freeze–pump–thaw cycles. After addition of **2** (142.6 mg, 2.02 mmol), the whole mixture was stirred at 40 °C for 24 h. A solution of 1-cyclohexenylphenyliodonium tetrafluoroborate (150 mg, 0.404 mmol) in degassed CH_2Cl_2 was then added at room temperature, and the mixture was stirred at the same temperature for 20 h. After evaporation of the solvent, the dark yellow residue was purified by silica gel column chromatography (CH_2Cl_2) to give **5** (20.6 mg, 34%, 19% ee) as a colorless oil, $[\alpha]_D^{22}$ +0.87° (c=1.03, $CHCl_3$). IR (neat): 1668, 1136 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.50—1.70 (5H, m), 1.71—2.00 (7H, m), 3.77 (1H, ddd, J=10.6, 7.2, 2.0 Hz), 4.16 (1H, dd, J=7.3, 6.6 Hz), 5.67 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 23.1, 24.4, 25.4, 26.6, 30.6, 68.7, 83.4, 122.8, 138.4. MS m/z: 152 (M$^+$), 150, 123, 121, 81 (bp). HR-MS: Calcd for $C_{10}H_{16}O$: 152.1201, Found: 152.1212.

Hydrogenation of (+)-3 A solution of (+)-**3** (15.4 mg, 0.103 mmol, 76% ee) and $RhCl(PPh_3)_2$ (9.4 mg, 0.0102 mmol) in degassed benzene (0.5 ml) was stirred under a hydrogen atmosphere at room temperature for 2 h. The mixture was concentrated and purified by silica gel column chromatography (CH_2Cl_2) to give **5** (6.4 mg, 41%, 75% ee, determined by ^{1}H-NMR using tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) ($Eu(hfc)_3$) as a colorless oil, $[\alpha]_D^{22}$ +6.7° (c=0.31, $CHCl_3$). A suspension of PtO_2 (2 mg) and (+)-**5** (5.4 mg, 0.036 mmol) in methanol (0.3 ml) was stirred under a hydrogen atmosphere at room temperature for 4 h. After removal of the catalyst by filtration, the filtrate was concentrated and purified by silica gel column chromatography (CH_2Cl_2) to afford the known compound[3a] (+)-**6** (3.1 mg, 57%) as a colorless oil, $[\alpha]_D^{22}$ +5.3° (c=0.31, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.91—1.10 (2H, m), 1.20—1.39 (4H, m), 1.46—1.93 (9H, m), 3.4—3.5 (1H, m), 3.6—3.7 (1H, m), 3.7—3.8 (1H, m). IR (neat): 1379, 1151 cm^{-1}.

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7) (*S*)-(*R*)-BPPFOAc ((*S*)-1-[(*R*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethyl acetate), (*S*)-(*R*)-BPPFOH ((*S*)-1-[(*R*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethanol), (−)-DIOP ((4*R*-*trans*)-[(2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(diphenylphoshine)), and 2,2′-methylenebis[4(*S*)-4,5-dihydro-4-isobutyloxazole] were also investigated as ligands. No improved results were obtained.

8) Molecular sieves 4A, Ag_3PO_4, Ag_2CO_3, Ag-zeolite.

9) (*R*)-**6** derived from (*R*)-2-phenyl-2,3-dihydrofuran shows (+)-optical rotation. We would like to thank Prof. F. Ozawa for this information.[3a]