

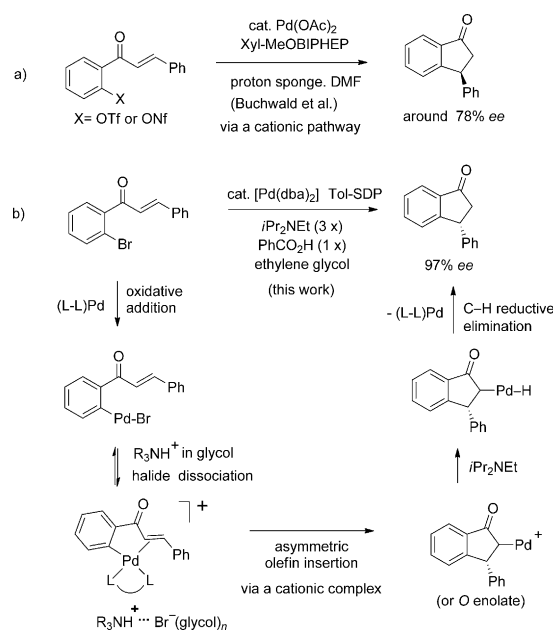
Palladium-Catalyzed Asymmetric Reductive Heck Reaction of Aryl Halides**

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Abstract: Asymmetric reductive Heck reaction of aryl halides is realized in high stereoselectivity. Hydrogen-bond donors, trialkylammonium salts in a glycol solvent, were used to promote halide dissociation from neutral arylpalladium complexes to access cationic, stereoselective pathways.

In the 1980s, Cacchi et al. reported that aryl halides reacted with enones and enals to form conjugate adducts in the presence of palladium catalysts.^[1] Alkyl amines and formates were the hydride source in the process.^[2] Typically, neutral or anionic aryl-Pd complexes were used and electron-poor olefins and styrene were preferred olefin substrates for insertion.^[3] As a common feature, the key aryl-Pd species were coordinatively saturated by ligands (phosphines, N-heterocyclic carbenes, halides, and acetates). This saturation successfully helps to out-compete undesirable β -hydride elimination processes.^[4] This reaction was used in racemic syntheses of drug candidates, and for many years an enantioselective version was unavailable.^[5] In comparison, metal-catalyzed conjugate additions using Cu,^[6] Rh,^[7] or Pd^[8] catalysts also afforded the same sets of conjugate adducts, but they needed to use organometallic reagents, the latter often being made from aryl halides.^[9]

Previously, Buchwald et al. initiated the study of asymmetric reductive Heck reactions using aryl triflates and nonaflates, and intramolecular insertion into enones gave moderate *ee* values in most examples (Scheme 1 a).^[10] Herein, we report reductive Heck reaction of aryl halides to provide 3-aryllindanones in high *ee* values (Scheme 1 b). These chiral compounds are used in the synthesis of indatraline (antidepressant), tefludazine (antipsychotic), and tolterodine for the treatment of urinary disorders.^[11] Today, a dozen asymmetric methods are available to access chiral indanones,^[12] but a general method to access 3-aryllindanones is still lacking.^[13]



Scheme 1. Comparison of two reductive Heck reactions. DMF = *N,N*-dimethylformamide, Tf = trifluoromethanesulfonyl.

Asymmetric 1,4-addition of organometallic reagents to indenone is often out-competed by 1,2-addition.^[14]

Initially, we used (*E*)-*o*-bromochalcone in a model study, and it was easily prepared from an aldol condensation of a methyl ketone and benzaldehyde (Table 1). After many trials, we found that spiro-di(1,1'-indanyl)bisphosphine (SDP) afforded excellent *ee* values (entries 1–3). The SDP ligands were pioneered by Qi-Lin Zhou and have found widespread applications in asymmetric metal catalysis.^[15] BINAP, DM-SEGPHOS, and Xyl-MeO-BIPHEP gave 35–77% *ee* (entries 4–9). Bisphosphine oxides and phosphine oxazolines (Pfaltz's PHOX) were found to be catalytically inactive (entries 10–12).

A 1:3 molar combination of benzoic acid and *i*Pr₂NEt were used to form an alkylammonium salt in situ during reaction. The latter was used to ionize the arylpalladium halide by hydrogen bonding, in a glycol solvent (Table 2). The excess alkylamine was needed for formation of palladium hydride and regeneration of the active catalyst. When benzoic acid was omitted, both the yield and *ee* value decreased significantly (Table 2, entry 1).

Previously Xiao et al. reported that alkylammonium salts or a glycol solvent facilitated halide dissociation in regioselective Heck reactions.^[16] We found that both R₃NH⁺ salts and glycol were needed in our study of the asymmetric Heck

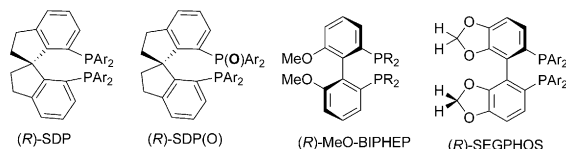
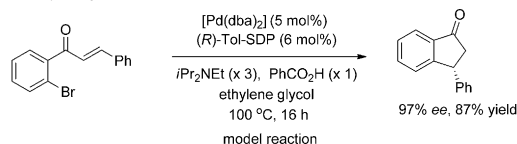
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Table 1: The effect of chiral bisphosphines (GC conversion and calibrated GC yield).



Entry	Chiral ligands	Conv. [%] ^[a]	Yield [%] ^[a]	ee [%] ^[b]
1	(R)-SDP	100	93	97
2	(R)-Tol-SDP	100	87	97
3	(R)-Xyl-SDP	100	43	69
4	(R)-BINAP	50	35	−60
5	(R)-DM-Segphos	75	68	−54
6	(R)-DTBM-Segphos	0	0	−
7	(R)-MeO-BIPHEP	25	20	−71
8	(R)-iPr-MeO-BIPHEP	100	78	−81
9	(R)-Xyl-MeO-BIPHEP	65	61	−77
10	(R)-BINAP(O)	0	0	−
11	(R)-Xyl-SDP(O)	0	0	−
12	(R)-iPr-PHOX	0	0	−

[a] Determined by GC. [b] Determined by HPLC on a chiral stationary phase. dba = dibenzylideneacetone.

Table 2: Optimization of reaction conditions for the model reductive Heck reaction.

Entry	Change of conditions	Conv. [%] ^[a]	Yield [%] ^[a]	ee [%] ^[b]
1	no BzOH	100	36	55
2	AcOH instead of BzOH	100	80	91
3	CF ₃ CO ₂ H	100	91	97
4	AgOTf instead of BzOH	100	45	58
5	Ag ₂ CO ₃	90	38	74
6	ZnCl ₂	100	55	76
7	ZnBr ₂	100	51	80
8	proton sponge as base	100	93	96
9	Et ₃ N	100	94	95
10	DABCO	100	88	93
11	NaOAc	100	73	96

[a] Determined by GC. [b] Determined by HPLC on a chiral stationary phase. DABCO = 1,4-diazabicyclo[2.2.2]octane.

reaction of aryl halides.^[17] In our DFT studies, hydrogen bonding of trialkylammonium NH and alcoholic ROH with a halide ion not only lowered the barrier, but also stabilized the ionized products.^[18] Silver salts were commonly believed to remove halide ions from neutral aryl palladium halides with ease in Heck reactions.^[19] However, AgOTf and Ag₂CO₃ led to poor results (Table 2, entries 4 and 5). They probably caused oxidation of phosphines. In comparison, redox-inactive zinc salts gave around 80% ee (entries 6 and 7). In entries 1–7 where there was a problem of material balance, and a complex mixture of unidentifiable byproducts were seen in the GC analysis. The simple byproduct from reduction

Table 3: Effect of solvents on the model reductive Heck reaction.

Entry	Solvent	Dielectric constant	Conv. [%] ^[a]	Yield [%] ^[a]	ee [%] ^[b]	Cationic pathway
1	ethylene glycol	37	100	87	97	yes
2	EtOH	25	35	30	99	yes
3	iPrOH	18	55	38	95	yes
4	THF	8	100	72	0	no
5	acetone	21	70	54	11	no
6	DMA	38	100	76	5	no
7	DMF	37	100	78	86	mainly

[a] Determined by GC. [b] Determined by HPLC on a chiral stationary phase. DMA = dimethylacetamide, THF = tetrahydrofuran.

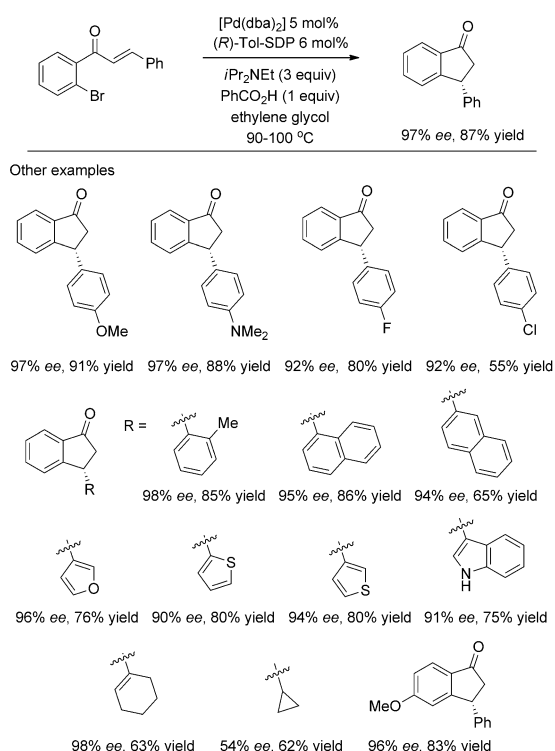
of the aryl–Br bond was not significant. Trialkylamines were the hydride source (entries 8–10), as previously reported by others.^[10a,20] When NaOAc was used as the base, the glycol was the plausible hydride source (entry 11).^[21]

The glycol solvent was also important to stabilize the bromide anion (Table 3, entry 1).^[22] The reaction became much slower in both ethanol and isopropanol (entries 2 and 3). In THF, toluene, and acetone, almost 0% ee was observed. Thus, in these solvents, olefin insertion into the neutral palladium complex took place, and was non-stereoselective. A dramatic disparity was found between DMF (86% ee) and DMA (5% ee; entries 6 and 7).^[23] The difference cannot be explained by high solvent polarity^[24] or strong solvation of metal cations. The formyl hydrogen atom of DMF was reported to participate in hydrogen bonding between DMF molecules.^[25] Thus, DMF may serve as the hydrogen-bond donor in this case, while DMA cannot.^[26]

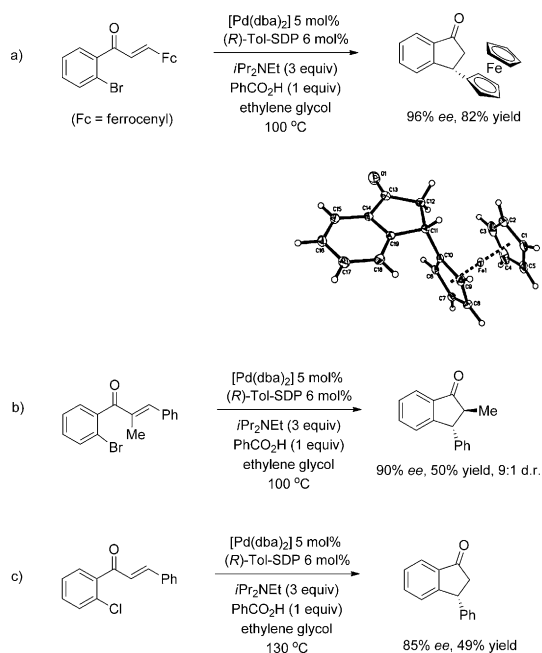
In examination of the scope of the asymmetric cyclization (Scheme 2), we chose to use Tol-SDP because it performed better than the parent SDP in cyclization of most substrates. Both electron-donating and electron-withdrawing groups can be present on β-aryl rings of chalcones. Thiophene, furan, and indole were compatible with the palladium catalysis. A β-cyclohexyl group can also be present. A β-cyclopropyl group led to 54% ee while other alkyl groups led to even lower selectivity.

Single-crystal X-ray diffraction of a product containing ferrocene unequivocally established the 3S configuration (Scheme 3a). For a chalcone carrying an α-methyl group, asymmetric cyclization gave the *trans* isomer as the major product, which is both the kinetically and thermodynamically favored product (Scheme 3b). When *ortho*-chlorochalcone was tested, the reaction did not proceed at 100 °C because of the difficult oxidative addition. At 130 °C, 85% ee was observed (Scheme 3c).

3-Arylindanones can be transformed into many chiral compounds (Scheme 4), which are not straightforward to make from other reactions: hydrogenolysis over Pd/C, reduction to a *cis*-alcohol with NaBH₄, Baeyer–Villiger oxidation oxidized to a lactone, and palladium-catalyzed α-arylation with good *trans* selectivity.^[27] No ee erosion was observed on biarylmethine centers. Furthermore, *cis*-3-phenyl-1-indanol was readily substituted with either a thiophene ring^[28] or an allyl group by *trans* addition to an indanyl cation.

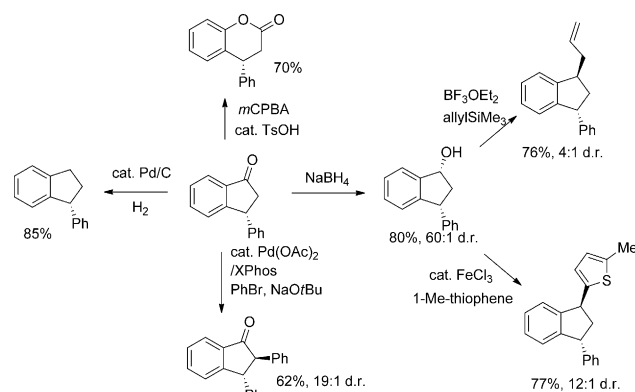


Scheme 2. Reductive Heck reaction of *ortho*-bromochalcones. Yields are those of isolated products (0.5 mmol scale).



Scheme 3. Reductive Heck reaction of other chalcone derivatives (yields of isolated products) and ORTEP of (*S*)-3-ferrocenyl-1-indanone with 50% probability of thermal ellipsoids.^[34]

We then conducted DFT calculations on the stereo-determining step of aryl insertion using a cationic complex [(*R*)-Tol-SDP](*o*-chalconyl)palladium(II) (Figure 1). Several



Scheme 4. Transformation of chiral 3-phenylindane without loss in the *ee* values.

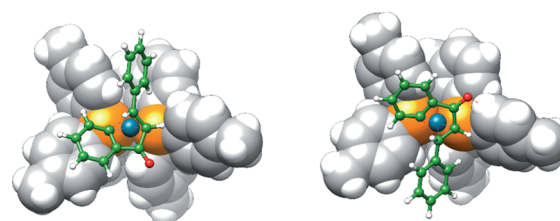


Figure 1. Transition structure TS-R (left) and lower-energy transition structure TS-S (right) for aryl insertion in cationic [(*R*)-Tol-SDP](*o*-chalconyl)palladium(II). The ligand Tol-SDP is in space-filling model and other atoms of the complex are shown as ball-and-stick model. Pd blue, P orange, O red, and C (of chalcone) green.

conclusions were drawn: a) The energy gap of two transition states was calculated to be 4.6 kcal mol^{−1}, which is consistent with observed 97% *ee* at 90–100 °C. b) The main pathway that proceeds via TS-S gives the major *S*-configured product and its insertion barrier is around 17 kcal mol^{−1}. c) No severe van der Waals contact was identified in either of the two TSs, so a simple model of steric repulsion seems implausible. d) A close examination of TS-S revealed that the ketone oxygen atom (highlighted in red) was close to a hydrogen atom of a *P*-tolyl ring. The C–H...O distance is 2.2 Å and the bond angle of C–H–O is 152°. They fall into the prescribed range for C–H...O weak hydrogen bonds,^[29] and provides stabilization of around 0.5–4 kcal mol^{−1}.^[30] This kind of attractive interaction was absent in TS-R. Recently, the use of aryl CH...O hydrogen bonding and other weak attractive forces have emerged in asymmetric metal catalysis.^[31]

In summary, we report a reductive Heck reaction process which uses aryl halides directly to afford 3-arylindanones in high *ee* values. As a key reaction design, alkylammonium salts and glycol were used as hydrogen-bond donors to help halide dissociation under mild reaction conditions. Alkylammonium salts are routinely formed from alkylamines in asymmetric Heck reactions^[32] and they may act as halide abstractors in polar solvents in, for example, Overman's Heck cyclizations.^[33]

Keywords: asymmetric catalysis · hydrogen bonding · olefins · palladium · synthetic methods

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