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Asymmetric Intermolecular Heck Reaction of Aryl Halides

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Supporting Information

ABSTRACT: The asymmetric intermolecular Heck reaction has been limited to aryl and vinyl triflates. Herein, we extend the reaction to aryl and vinyl bromides. Various cyclic olefins coupled with high enantioselectivity. Only bisphosphine oxides on a spiro backbone formed highly stereoselective Pd catalysts. The use of alcoholic solvents and alkylammonium salts were essential to promote halide dissociation from neutral arylpalladium complexes.

The asymmetric intermolecular Heck reaction of aryl triflates was first reported by Hayashi et al. in 1991.[1] Since then, the reaction has served as a common testing ground for chiral phosphorus ligands.[2,3] Although an excellent *ee* was obtained with simple cyclic olefins such as cyclopentene and 2,3-dihydrofuran, carbon electrophiles were mostly restricted to aryl or vinyl triflates, which limited the synthetic value of the intermolecular coupling. Recently, Sigman et al. realized the asymmetric arylation of acyclic internal olefins in good *ee*, using either aryldiazonium salts or arylboronic acids as arylating agents.[4]

Previously, Overman[5] and Shibasaki[6] reported asymmetric intramolecular Heck reactions using vinyl and aryl halides (Figure 1). Some Heck products were used in natural product synthesis, but the scope of the reaction remained rather limited. To date, an asymmetric intermolecular Heck reaction of aryl halides was never reported. It is difficult to displace a halide ligand with a neutral olefin on Pd centers.

Initially we chose a model reaction of *p*-tolyl bromide and 2,3-dihydrofuran and tried to find a suitable catalyst. After extensive experimentation, we were gratified to find a suitable catalytic system (Figure 2). When the Pd/Xyl-SDP(O) catalyst was used, the model reaction gave 96% *ee* and the selectivity "s" between two olefinic isomers was 11:1 after 6 h at 80 °C.

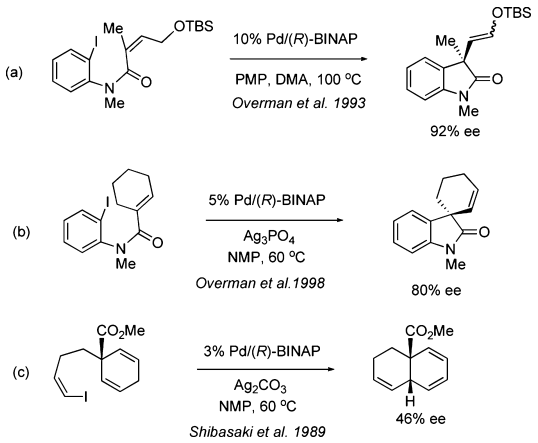

Figure 1. Intramolecular Heck reaction of aryl and vinyl halides.

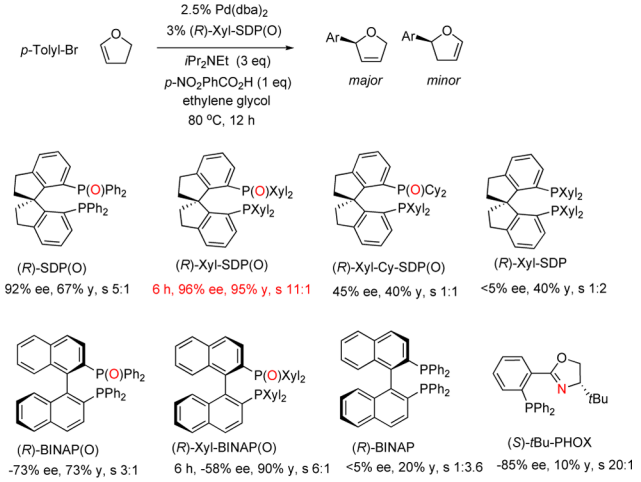

Figure 2. Ligand screening in the model Heck reaction.

(*R*)-Xyl-SDP(O), a bisphophsine oxide having a spirobisindane skeleton, was highly active for the model reaction of ArBr.[7] The parent bisphosphine (*R*)-Xyl-SDP gave almost racemic products. In comparison, both (*R*)-BINAP(O) and its *P*-*m*-Xylyl derivative exhibited moderate stereoselectivity, 73% *ee* and 58% *ee*, respectively.[8] The parent bisphosphine (*R*)-BINAP showed poor reactivity and gave <5% *ee*. (*R*)-BINAP dioxide was inactive as a ligand. Pfaltz's ligand, *t*Bu-PHOX, was also tested, but it showed very low activity with 85% *ee*.

Other reaction parameters, a benzoic acid additive (1 equiv), iPr$_2$NEt base (3 equiv), and ethylene glycol solvent were also critical to this difficult transformation (Table 1). *p*-NO_2PhCO_2H reacted with iPr$_2$NEt to form an ammonium salt $R_3NH^+ArCO_2^-$, which was very efficient in promoting halide ionization from the neutral arylpalladium bromide (entry 1). Other aromatic carboxylic acids led to lower yields, while acetic acid gave a much slower reaction (entries 2−6). When ammonium salt iPr$_2$NEt·HCl was used, the Heck reaction gave a good result, but when the HOTf salt was used, the olefinic ratio was only 3:1 (entries 7−8). In comparison, the model reaction gave a 56% yield, 3:1 s ratio, and 94% *ee* in the absence

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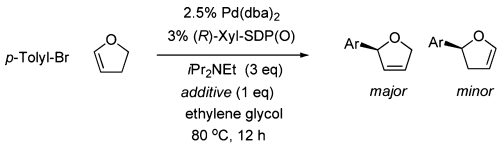
Table 1. Effect of Additives



entry	additive	conv (%)	yield (%)	s ratio	ee (%)
1	p-NO_2PhCO_2H (6 h)	100	95	11	96
2	p-NO_2PhCO_2H (12 h)	100	93	7	95
3	$PhCO_2H$	88	73	7	94
4	p-tBuPhCO_2H	86	67	9	90
5	$PhCH_2CO_2H$	80	64	8	94
6	$MeCO_2H$	60	20	37	96
7	iPr$_2$NEt·HCl	80	73	8	96
8	iPr$_2$NEt·HOTf	90	67	3	95
9	None	80	56	3	94
10	AgOTf	100	80	9	97
11	AgOBz	95	84	24	96
12	Ag_2CO_3	90	78	13	97

of the acid additive (entry 9). The use of expensive silver salts as halide abstractors also worked to give the desired product in good selectivity (entries 10−12). Notably, the use of silver salts in common solvents, e.g., toluene, ether, and 1,4-dioxane, led to poor results.

In methanol, the model Heck reaction was slower, while, in THF or dioxane, no Heck reaction took place. Previously, Xiao reported that alcohols or alkylammonium salts promoted the regioselective Heck reaction of vinyl ethers and styrene, by assisting halide dissociation from Pd complexes via hydrogen bonding.[9] Recently, we also reported a similar regioselective Heck reaction of aliphatic olefins and styrene.[10] Based on DFT calculations, we proposed a concerted substitution on the Pd center, which was accelerated by hydrogen bonding between incoming methanol and a leaving bromide anion.

The Pd/Xyl−SDP(O) catalyst was successfully applied to the Heck reaction of various aryl bromides with 2,3-dihydrofuran and cyclopentene (Figures 3−4). In most cases, >90% *ee* was observed and the ratio of olefinic isomers was >10:1. In reactions of cyclopentene, methanol was a better solvent than ethylene glycol. *Ortho* substituents and electronic perturbation

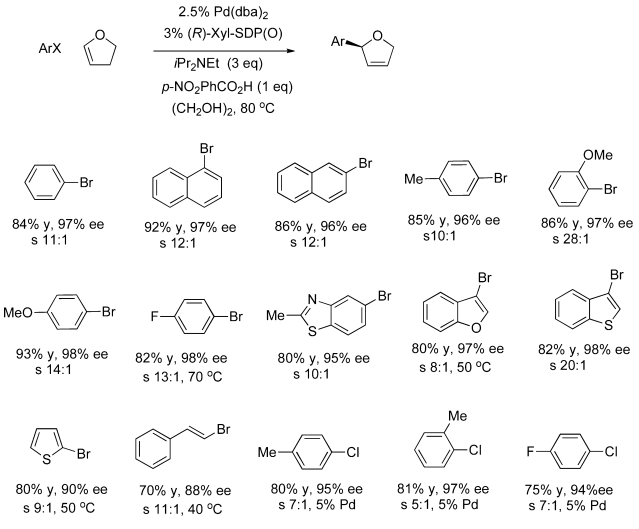


Figure 3. Asymmetric Heck reaction of 2,3-dihydrofuran.

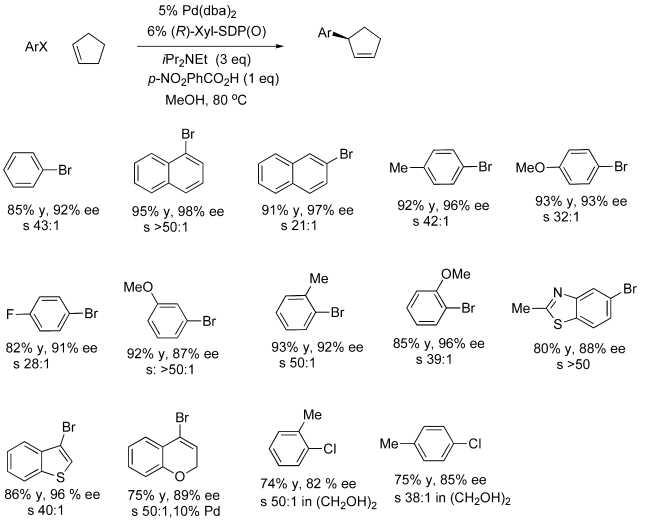


Figure 4. Asymmetric Heck reaction of cyclopentene.

on aryl rings were well tolerated. Some vinyl and heteroaryl bromides also coupled well. *m*-Anisyl bromide and cyclopentene coupled to give 87% *ee*. The Heck product can be used in the asymmetric synthesis of Preclamor,[7a] a promising antipsychotic agent for the treatment of schizophrenia.[11] A few examples of ArCl were included with an acceptable level of *ee*.

N-Boc-2,3-dihydropyrrole, cycloheptene, and cyclooctene can also couple well (Figure 5). For example, *p*-fluorophenyl

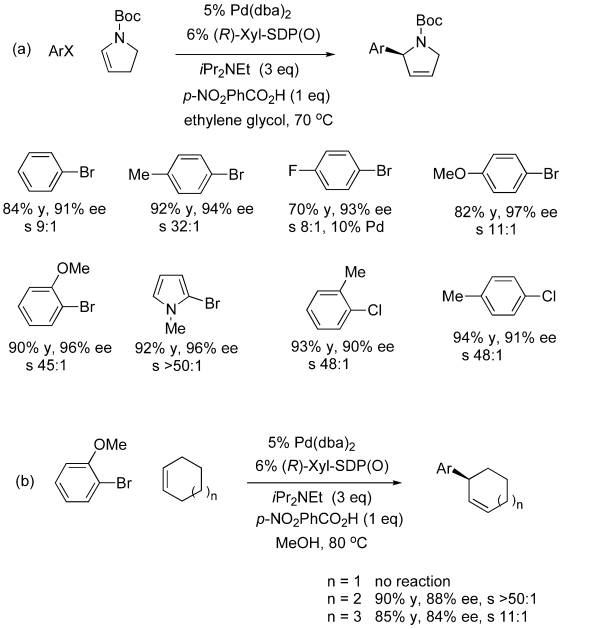


Figure 5. Asymmetric Heck reaction of *N*-Boc-2,3-dihydropyrrole, cycloheptene, and cyclooctene.

bromide coupled with *N*-Boc-2,3-dihydropyrrole in 93% ee. The resulting azacycle can be used to prepare BMS-394136,[7a] which was developed for the treatment of cardiac arrhythmia.[12] Cyclohexene, however, did not react. Its half-chair conformation prevented olefin binding and insertion on the Pd center.

Both the acidic additive and alcoholic solvent were crucial to halide ionization from neutral Pd complexes. We prepared a neutral arylpalladium complex **A** from $Pd(dba)_2$, *p*-F-phenyl

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bromide, and (*R*)-Xyl-SDP(O) (Figure 6). When complex **A** was treated with cyclopentene (5 equiv) in the presence of

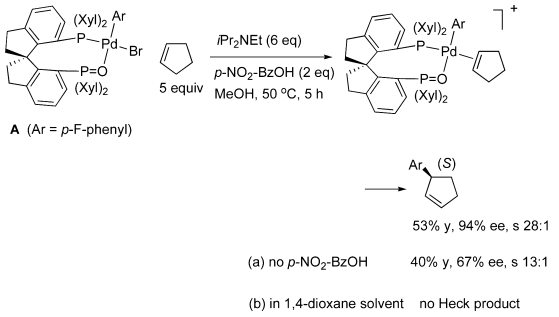

Figure 6. Stoichiometric olefin insertion of neutral Pd complex **A**.

iPr_2NEt and *p*-NO_2PhCO_2H in methanol solvent, olefin insertion occurred at 50 °C and gave Heck products in 94% ee and 28:1 olefinic selectivity. When *p*-NO_2PhCO_2H was omitted, only 67% *ee* was obtained due to a competing neutral pathway without halide ionization. If the solvent was switched to 1,4-dioxane, no insertion occurred at 50 °C.

The (*S*)-configuration of Heck products and high *ee* in general herein were similar to our previous results in asymmetric Heck reactions of aryl triflates using the same chiral ligand.[7a] The similarity suggested that in reactions of aryl halides, aryl insertion proceeded via a common cationic (L)Pd(aryl)(olefin) species, after halide dissociation in alcohols. In our X-ray diffractional study of an arylpalladium halide support by (*R*)-Xyl-SDP(O), *P,O*-chelation was observed.[7a,b] In our previous DFT calculations on olefin insertion in cationic arylpalladium(II) complexes, *P,O*-chelation was crucial to the creation of a chiral environment for the highly asymmetric olefin insertion.[7a] The calculated pathway was consistent with the high *ee* and (*S*)-configuration of major Heck isomers.

Bisphosphine oxides may also bind to Pd(0) centers via a monodendate mode or *P,C*-chelation involving an arene−Pd interaction, as observed by Grushin et al. in $(BINAP)_2Pd(0)$.[13] These alternative bonding modes afforded much less stable aryl−Pd(II) complexes, as compared with *P,O*-chelation in our calculations. Thus, they were discounted in our study.[7a]

In summary, we report the asymmetric Heck reaction of common aryl bromides and chlorides and various cyclic olefins.[14] Most cases gave a high *ee* and good olefinic ratio. Both alkylammonium salts and alcohol solvents were crucial to creating cationic aryl−Pd species for enantioselective olefin insertion. In future, we plan to examine the asymmetric intramolecular Heck reaction of aryl halides and expand its scope using the cationic pathway.[5,6]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures for Heck reaction and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) PhI generally gave rather unsatisfactory results after >90% conversion of each olefin. Reaction of cyclopentene (80 °C, 16 h): 20% yield, s 50:1, and 90% *ee*. Reaction of 2,3-dihydrofuran (80 °C, 6 h): 50% yield, s 1:2, and 80% *ee*. Reaction of *N*-Boc-2,3-dihydropyrrole (70 °C, 40 h): 67% yield, s 21:1, and 66% *ee*.