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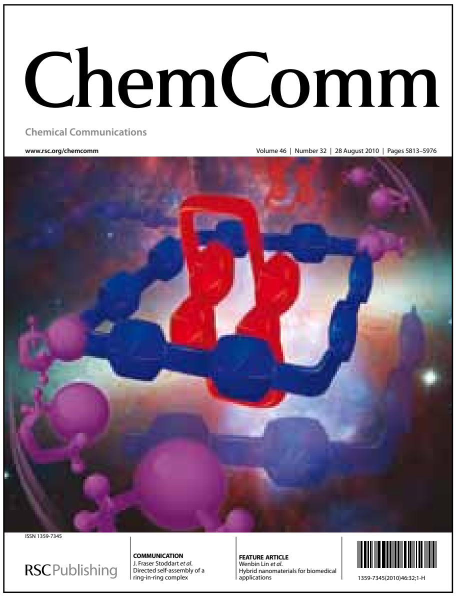

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ARTICLE TYPE

# Regioselective Heck Reaction of Aliphatic Olefins and Aryl Halides

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**A regioselective Heck reaction of aliphatic olefins and aryl bromides is realized at internal carbons of olefins. Methanol solvent promoted halide ionization from neutral arylpalladium halide complexes via hydrogen bonding, so as to create cationic aryl-Pd species for regioselective olefin insertion.**

Heck reaction of acrylates and styrenes introduced aryl groups very selectively at terminal positions. It has since been widely used in synthesis.[1] Aliphatic olefins that lack directing groups and electronic bias gave a mixture of Heck isomers.[2] Last year, we reported internally selective arylation between aliphatic olefins and aryl triflates using a bulky bisphosphine dnpf.[3] The method was a significant improvement of Carbri conditions that has been largely limited to electron-rich vinyl ethers through cationic pathways.[4] In Heck reaction of common aliphatic olefins, aryl halides are difficult to provide good regioselectivity, take Heck's example in Fig. 1a.[2a] Herein, we provide a solution to this longstanding problem with about 10:1 internal selectivity (Fig. 1b).

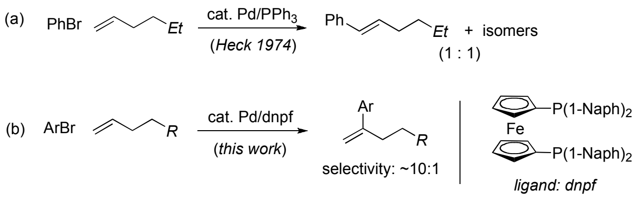


*Fig. 1* Heck reactions of aliphatic olefins.

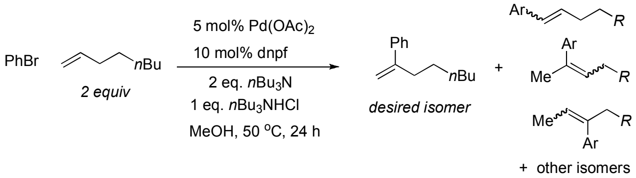
Initially, we attempted a model Heck reaction between PhBr and 1-octene, using silver salts as halide abstractors. Contrary to common belief, it led to very little Heck product and very poor selectivity under many conditions. We suspected that the $Ag^I$ salts may oxidize the $Pd^0$ catalysts.

Previously in Heck reaction of vinyl ethers and styrene, Xiao *et al* reported that ethylene glycol solvent or $i\mathrm{Pr_2NH{\cdot}HCl}$ additive can help chloride ionization from neutral Ar-Pd-X complexes via hydrogen bonding.[4b,5] Borrowing this idea, we found that the use of both methanol solvent and $n\mathrm{Bu_3N{\cdot}HCl}$ additive gave the desired Heck isomer in 83% yield and 11:1 selectivity (Table 1). The "s" ratio refers to the amount of the desired isomer versus *all other isomers*. After catalytic hydrogenation, the intrinsic regioselectivity was determined to be 16:1.

The bisphosphine dnpf formed the most active and selective catalyst. The high internal selectivity is consistent with our previous Heck reaction using ArOTf. The rigid dnpf ligand helps to prevent competing internal insertion via steric effect.[3] In comparison, dppf gave only very low yield and 6:1 selectivity; dippf was almost inactive. Other chelating bisphosphines such as dppe, dppp, dppb, Xantphos and BINAP were inactive, too. When 2 % Pd/dnpf catalyst was used, the conversion decreased.

The desired Heck process only proceeded efficiently in methanol (Table 1). In other less polar alcohols, the catalytic activity dropped dramatically. For instance, in *t*-BuOH, no desired product was detected. In water and all other organic solvents, no Heck reaction was seen.

***Table 1.*** Effect of solvents on the model reaction (PhBr conversion, yield and selectivity determined by GC).



| Entry | Solvent | Conv (%) | Yield (%) | Selectivity |
|---|---|---|---|---|
| 1 | **MeOH** | **99** | **83** | **11** |
| 2 | EtOH | 55 | 38 | 10 |
| 3 | *n*BuOH | 46 | 32 | 11 |
| 4 | *i*PrOH | 20 | 7 | 11 |
| 5 | *t*BuOH | 15 | 0 | -- |
| 6 | Ethylene glycol | 39 | 13 | 4 |

When $n\mathrm{Bu_3N{\cdot}HCl}$ additive was not included, only about 40% yield and 5:1 selectivity resulted (Table 2). $n\mathrm{Bu_3N{\cdot}HOTf}$ had little effect. With $n\mathrm{Bu_4NCl}$ or $n\mathrm{Bu_4NBr}$ was added, the yield was only 60%. A combination of $n\mathrm{Et_3N{\cdot}HCl}$ and $n\mathrm{Et_3N}$ only afforded poor conversion and low selectivity.

***Table 2.*** Effect of additives on model Heck reaction (PhBr conversion, yield of the desired isomer and internal selectivity determined by GC).

| Entry | Additive | Conv (%) | Yield (%) | Selectivity |
|---|---|---|---|---|
| 1 | **None** | **64** | **41** | **5** |
| 2 | $\mathbf{\mathit{n}Bu_3N{\cdot}HCl}$ | **99** | **83** | **11** |
| 3 | $n\mathrm{Bu_3N{\cdot}HOTf}$ | 60 | 45 | 6 |
| 4 | $n\mathrm{Bu_4NCl}$ | 80 | 65 | 7 |
| 5 | $n\mathrm{Bu_4NBr}$ | 71 | 57 | 11 |

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| | | | | |
|---|---|---|---|---|
| 6 | $Et_3N{\cdot}HCl$; $Et_3N$ | 16 | 13 | 5 |

Next, we examined various terminal olefins in reactions with *p-t*-butylphenyl bromide (Fig. 2). Polar groups such as nitriles, esters, phthalimides and free alcohols can be present on oleins..[4a-c] Allylbenzene, which is prone to undergo palladium hydride-catalyzed olefin isomerization, coupled well.[6] Selective insertion into internal positions was also seen with vinylcyclohexane, but with *t*-butylethylene, insertion occurred predominantly at terminal positions.

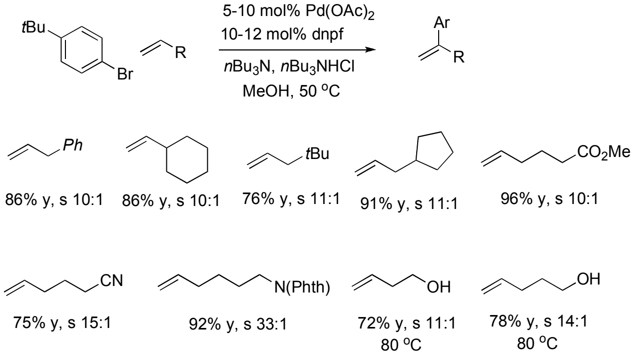

***Fig. 2*** Examples of aliphatic olefins.

Various aryl bromides and some heteroaryl bormides can couple selectively (Fig. 3). One example of alkenyl bromide was also included. For *o*-tolyl and *o*-anisyl bromides, <10:1 selectivity was seen and in some cases moderate yield resulted, due to reduction of aryl bromides to arenes. Some alkylamines can donate hydrides to arylpalladium species and lead to reduction.[7]

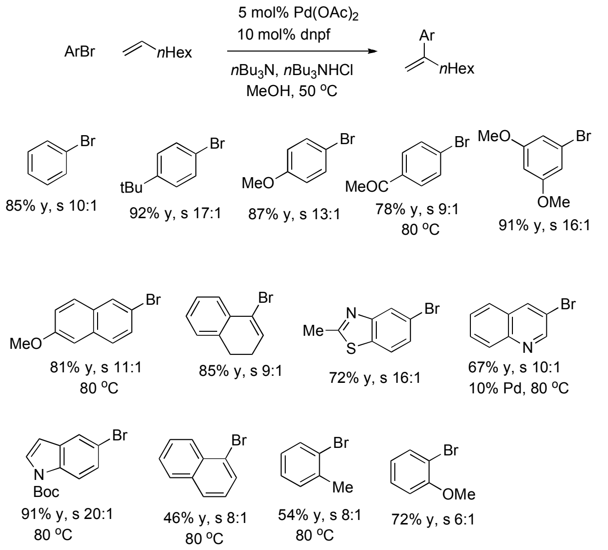

***Fig. 3*** Examples of aryl and vinyl bromides.

When we replaced *n*-tributylamine with DABCO, the reduction was minimized to <5% (Fig. 4s). In DABCO, hydrogens $\alpha$ to nitrogens are slow to eliminate to give a bridgehead iminium species, according to Bredt's rule.[8] Also in the modified procedure, the $n\mathrm{Bu_3N{\cdot}HCl}$ was unnecessary. We found in some cases the less hindered dppf performed better than dnpf. The new procedure can also be applied to electron-poor aryl chlorides. Electron-neutral and electron–rich aryl chlorides did not react due to slow oxidative addition. Aryl iodides gave poor selectivity (3:1). The new method can be used to make olefin **A** directly from homoallylic alcohol (Fig. 4b). **A** was previously prepared via Suzuki coupling of aryl-B(pin) and vinyl iodide in Padwa's synthesis of minfiensine.[9]

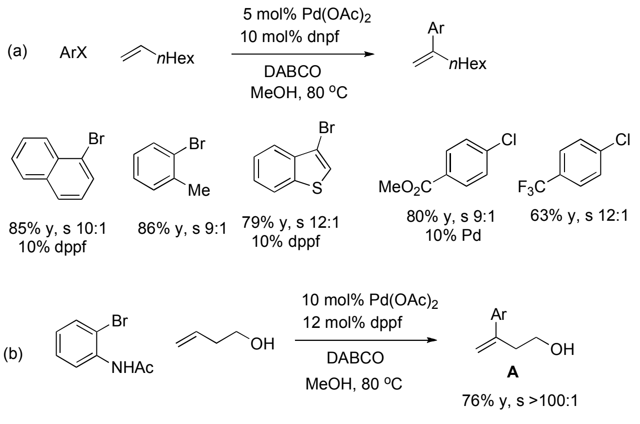

***Fig. 4*** Examples of aryl bromides and chlorides without using acidic additives.

Our Heck procedure can be applied to substituted styrens to give 1,1'-diarylethenes (Fig. 5). 1,1–Diarylethylenes are core structures in anticancer agents bexarotene[10] and isocombretastatins A.[11] Under most Heck conditions, selective internal arylation of styrene was difficult to achieve.[12]

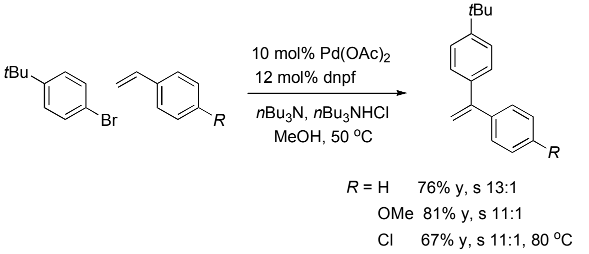

***Fig.5*** Examples of aromatic olefins.

We then performed DFT calculations on the step of halide ionization from (dnpf)Pd(phenyl)(Br) (Fig. 6). No significant effect of hydrogen bonding was seen during oxidative addition of PhBr. In a dissociative pathway (a), no energetic minimum could be located for the cationic aryl-Pd species with a vacant site. In associative pathway (b), no stabilized pentacoordinate Pd species can be located.[13] Instead, a new pathway (c), *hydrogen-bonding-assisted concerted substitution is energetically more favorable.* The displacement of the bromide by one methanol on the Pd center was concerted and stabilized by internal hydrogen bonding between the two. Thus, the barrier was reduced to +13 kcal/mol and the whole process became endergonic by +4 kcal/mol. The barrier and energy of the ionized products can be further reduced by incorporation of a second hydrogen bond donor, e.g., a second MeOH or one $Me_3NH$ cation (d and e).

Experimentally, we tested the validity that methanol promotes halide dissociation from a neutral complex (dnpf)Pd(phenyl)(Br). When it was treated with 1-octene *in methanol*, Heck products were produced in excellent internal selectivity (Fig. 7). The high internal selectivity is characteristic of insertion into cationic aryl-Pd(dnpf) species, as we reported previously.[3] Notably, the

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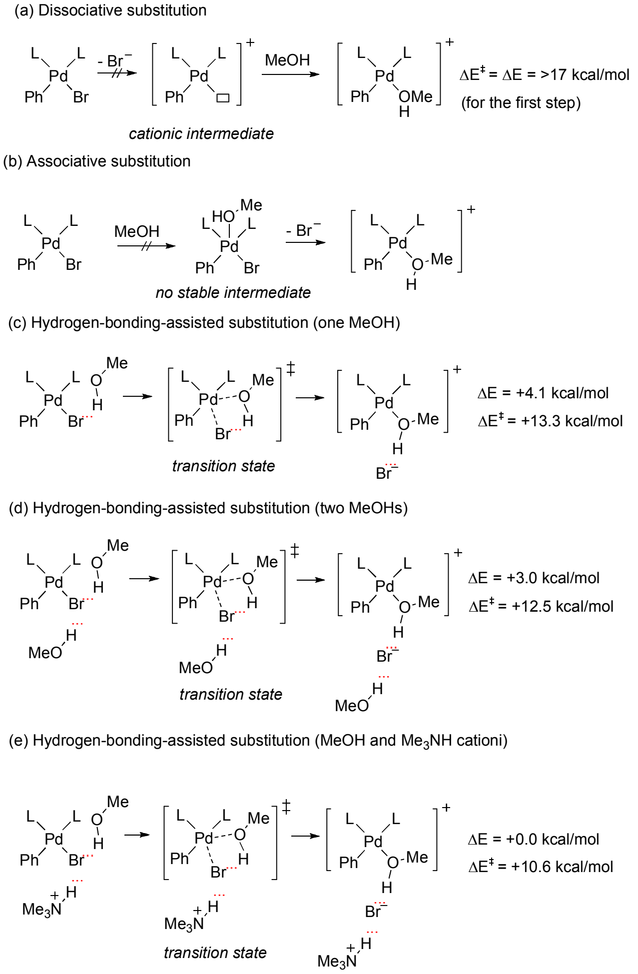
selectivity decreased progressively over time, due to in situ product isomerization. In 1,4-dioxane or DMA, no such Heck reaction occurred. The neutral complex is barely soluble in methanol. When (dnpf)Pd(phenyl)(Br) was dissolved in 1:1 $MeOH/CH_2Cl_2$, no cationic complex can be detected at RT by $^{31}P$ NMR spectroscopy. Thus, we gained indirect evidence suggesting that methanol solvent promoted ionization of the neutral bromide complex.


(a) Dissociative substitution

(b) Associative substitution

(c) Hydrogen-bonding-assisted substitution (one MeOH)

(d) Hydrogen-bonding-assisted substitution (two MeOHs)

(e) Hydrogen-bonding-assisted substitution (MeOH and $Me_3NH$ cationi)

***Figure 6.*** Pathways for halide ionization in methanol solventThe B3LYP DFT functional was used in conjunction with the Lanl2dz ECP basis set for Fe and Pd. The solvent effect in methanol was taken into account by IEFPCM.

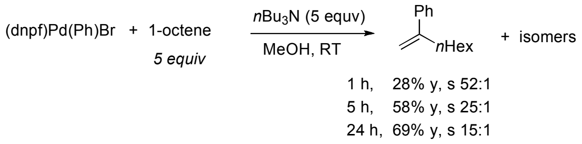


***Figure 7.*** Stoichiometric reaction of olefin insertion in methanol.

In conclusion, Heck reaction of aliphatic alkenes and aryl bromides can now be performed selectively at internal sites.[14] Methanol solvent promoted efficient halide ionization to produce cationic aryl-Pd species, critical for olefin insertion.

## Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures and characterization of isolated compounds. See DOI: 10.1039/b000000x/

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14 When PhBr was replaced by PhOTf in the model reaction described in Table 1 (50 ºC, 24 h), the desired Heck isomer was produced in 84% yield and 11:1 selectivity.

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Heck reaction of aryl bromides and aliphatic olefins gives selective arylation at internal positions of olefins. Methanol solvent promotes halide dissociation from neutral arylpalladium halides.