

## Heck Reaction

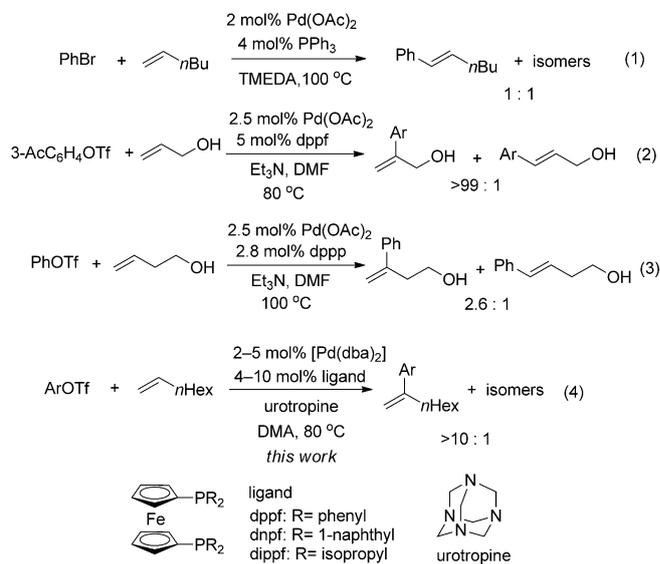
## Intermolecular Mizoroki–Heck Reaction of Aliphatic Olefins with High Selectivity for Substitution at the Internal Position\*\*

Liena Qin, Xinfeng Ren, Yunpeng Lu, Yongxin Li, and Jianrong (Steve) Zhou\*

The Mizoroki–Heck reaction generally refers to Pd-catalyzed C–C bond formation between organic (pseudo)halides and olefins. Today, it has become a powerful tool to prepare substituted olefins.<sup>[1]</sup> A key issue in intermolecular Heck reactions is the control of the site where aryl groups insert into olefins. High regioselectivity can be easily achieved for olefins carrying substituents with a significant electronic difference at the two olefinic sites,<sup>[2]</sup> such as acrylates<sup>[3]</sup> and vinyl ethers.<sup>[4]</sup>

Aliphatic olefins, however, generally lack intrinsic electronic differentiation between two olefinic positions and it has been challenging to achieve good regiocontrol [Eq. (1), Scheme 1].<sup>[5,6]</sup> To induce terminal insertion, coordinating groups are often present on olefins to serve as chelates.<sup>[7]</sup> The chelation strategy was also used in oxidative<sup>[8]</sup> and decarboxylative<sup>[9]</sup> Heck reactions to achieve regioselectivity. Recently, Sigman and Werner reported high terminal selectivity even for olefins without chelating groups.<sup>[10]</sup> For aliphatic olefins, high internal selectivity also proved very difficult to achieve, except a few special cases.<sup>[11]</sup> For example, Cabri et al. reported that olefin insertion into cationic aryl–Pd intermediates can be biased toward the internal position, but the selectivity was too low to be synthetically useful.<sup>[12]</sup> As a special case, allylic alcohol gave excellent internal selectivity, because owing to the inductive effect of its hydroxy group the electronic density on the internal carbon atom is decreased [Eq. (2), Scheme 1]. The inductive effect quickly diminishes over several bonds. Thus, for homoallylic alcohol the selectivity dropped drastically [Eq. (3), Scheme 1]. Herein, we report a general method for Heck reactions of aliphatic olefins in high internal selectivity, by using a set of ferrocene-based bisphosphine ligands [Eq. (4), Scheme 1].

The Heck products,  $\alpha$ -alkylstyrenes can be readily converted to various chiral building blocks by asymmetric catalytic processes.<sup>[13]</sup> They are also intermediates in the synthesis of bioactive natural products<sup>[14]</sup> and drug candidates.<sup>[15]</sup> The  $\alpha$ -alkylstyrenes used to be prepared by cross-couplings of 2-alkenyl electrophiles or 2-alkenyl metallic



**Scheme 1.** Intermolecular Heck reactions of aliphatic olefins. TMEDA = *N,N,N',N'*-tetramethylethylenediamine, Tf = trifluoromethanesulfonyl, dppf = 1,3-bis(diphenylphosphino)propan, dba = dibenzylideneacetone, DMA = dimethylacetamide.

reagents. Our new method directly uses simple olefins and does not require preactivation of olefin substrates.

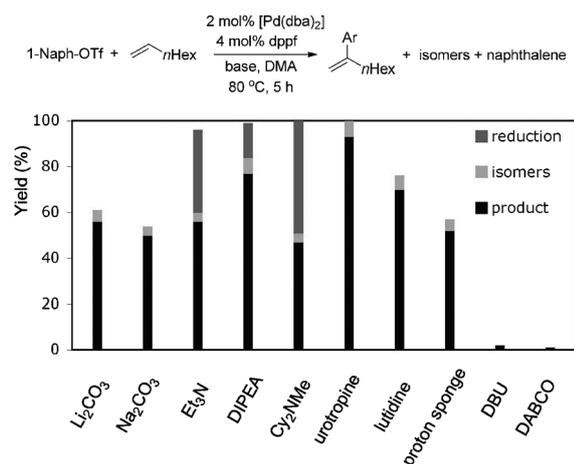
Initially, we used a model reaction of 1-naphthyl triflate and 1-octene and dppf as supporting ligand for the palladium catalyst (Figure 1). To our surprise, a dramatic effect of bases was observed (Figure 1). In particular, when trialkylamines, such as triethylamine and Hünig's base, were used, significant reduction of aryl triflate was observed, and the corresponding reduction product was obtained in up to 50% yield.<sup>[16]</sup> In contrast, when urotropine was used, no reduction byproduct was detected and Heck products were formed in almost quantitative yield. The ratio of the desired isomer, 2-aryl-1-octene versus all other isomers was 13:1, determined by GC.<sup>[17]</sup> It is worth pointing out that this ratio is not equivalent to regioselectivity. Urotropine is a relatively weak Lewis base,<sup>[18]</sup> and it does not compete strongly for the vacant site on a cationic (dppf)Pd(Ar) intermediate. Furthermore, its  $\beta$ -hydrogen atom cannot eliminate to donate a hydride to palladium, according to Bredt's rule. In comparison, when the more basic and donating bases DBU and DABCO were used, only small amounts of Heck products were formed. Other bases such as 2,6-lutidine, proton sponge, and Li<sub>2</sub>CO<sub>3</sub> gave much lower yields than urotropine.

In the model reaction of 1-naphthyl triflate and 1-octene, we have screened many bisphosphine ligands to improve the

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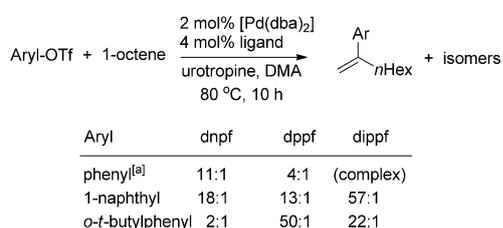
[\*\*] We thank Singapore National Research Foundation (NRF-RF2008-10) and Nanyang Technological University for financial support and Johnson-Matthey for a gift of palladium.

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**Figure 1.** Effect of bases on the formation of different products of the model reaction. In addition to the formation of the Heck product (black bars) and isomers (light gray), reduction of the aryl triflate (dark gray) was also observed. DIPEA = diisopropylethylamine, Cy = cyclohexyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DABCO = 1,4-diazabicyclo[2.2.2]octane.

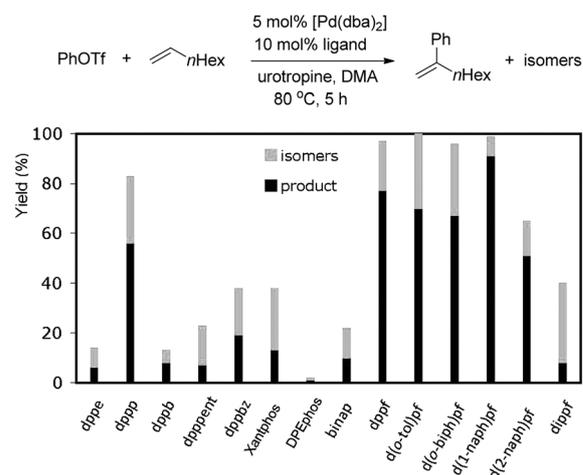
selectivity. To our delight, ferrocene-derived 1,1'-bisphosphine ligands were particularly selective in delivering the branched product (Figure 2). For example, when the ligand dppf was used, the selectivity was improved to 57:1 in the presence of 2 mol% palladium catalyst (for details, see the Supporting Information).



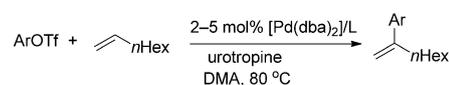
**Figure 2.** Interplay between ligands and aryl triflates on selectivity. The ratios of the branched Heck product to all other isomers are shown. [a] 5 mol% [Pd(dba)<sub>2</sub>] and 10 mol% ligand were used.

Later, we found that the selectivity was highly dependent on the aryl electrophiles. For example, if the aryl triflate contained a large *ortho-tert*-butyl group, the ligand dppf was very selective and gave a selectivity of 50:1 (Figure 2). In general, we found it very difficult to achieve high selectivity for aryl triflates without an *ortho* group. In model reactions with phenyl triflate, the ligand dppf only afforded 4:1 selectivity, and the ligand dippf gave a complex mixture of product isomers. After examination of a dozen of bisphosphine ligands, we found that the new ligand 1,1'-bis[di(1-naphthyl)phosphino]ferrocene (dnpf) can give a good selectivity of 11:1 (Figure 3; dnpf = d(1-naph)pf in Figure 3).<sup>[19]</sup>

After establishing suitable conditions for each subclass of aryl triflates, we examined the scope of aryl triflates with 1-octene as model olefin (Scheme 2). Some observations are noteworthy. a) For aryl electrophiles without *ortho* groups,

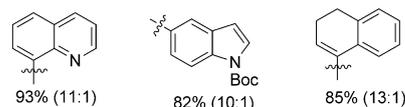


**Figure 3.** Effect of ligands in the Heck reaction of phenyl triflate. dppe, dppb, dppp, and dppent are typical bisphosphine ligands.<sup>[19]</sup>



**a) Aryl without *ortho* substituent, L = dnpf**

Ar = phenyl	93% (11:1)	
2-naphthyl	92% (13:1)	
<i>m</i> -xylyl	93% (11:1)	
		Y = <i>t</i> Bu 93% (16:1)
		CO <sub>2</sub> Et 91% (9:1)
		<i>t</i> Bu 92% (15:1)
		OMe 74% (7:1)



**b) Aryl with small *ortho* substituent L = dippf**

Ar = 1-naphthyl	74% (>100:1)
2,5-dimethylphenyl	68% (70:1)

Y = Me	71% (60:1)
Cl	77% (>100:1)
CN	74% (60:1), 10 mol% Pd
OMe	94% (10:1), L = dnpf

**c) Aryl with large *ortho* substituent L = dppf**

Ar = 2-mesityl	87% (27:1), 100 °C
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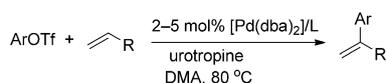
Y = NO <sub>2</sub>	83% (11:1)
CO <sub>2</sub> Me	81% (10:1)
NMe <sub>2</sub>	81% (23:1)
<i>t</i> Bu	86% (50:1)

**Scheme 2.** Scope of organic triflates in the Heck reaction of 1-octene. The ratios of the Heck product shown in the scheme to all other isomers are given in brackets.

the ligand dnpf gave a selectivity above 10:1 for most substrates. For aryl triflates substituted with either electron-donating or electron-withdrawing groups at the *para* position, the selectivity dropped slightly. Some heteroaryl triflates, derived from indole and quinoline, worked well. One example of a vinyl electrophile is also included. b) For aryl electrophiles carrying small *ortho* substituents, the dippf ligand afforded 2-aryl-1-octenes almost exclusively in most cases. Both aromatic chloride and nitrile were tolerated under the catalytic condition. For *o*-anisyl triflate, the ligand dnpf was found to be more selective than dippf. c) For aryl electrophiles carrying large *ortho* groups, the dppf ligand gave good to excellent selectivity. Even sterically demanding 2-mesityl triflate can give high selectivity at 100 °C. Some polar *ortho*

substituents such as nitro, ester, and dimethylamino substituents did not interfere with the catalytic cycle.

Next, we studied the scope of terminal olefins with each subclass of aryl triflates (Scheme 3). Many polar groups on olefins are compatible, such as ester, nitrile, phthalimide,



**a) Ar = *p*-*t*-butylphenyl, L = dnpf**

R = isobutyl	94% (10:1)		96% (10:1)		1.20 g, 92% (12:1)
neopentyl	78% (13:1)				
benzyl	93% (15:1)				
			95% (12:1)		Y = OAc 98% (15:1) N(Phth) 91% (38:1)

**b) Ar = *o*-tolyl, L = dppf**

R = isobutyl	71% (85:1)		Y = OH 89% (66:1)		86% (100:0)
<i>c</i> -hexyl	74% (29:1), 10 mol% Pd		OBn 72% (79:1), 10 mol% Pd		
benzyl	86% (87:1)				
<i>t</i> -butyl	68% (9:1)		Y = CO <sub>2</sub> Me 87% (28:1)		85% (69:1)
	10 mol% Pd, L = dppf		CN 78% (70:1)		

**c) Ar = *o*-*t*-butylphenyl, L = dppf**

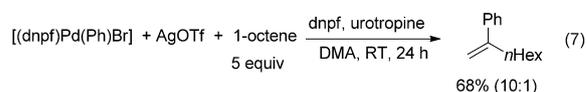
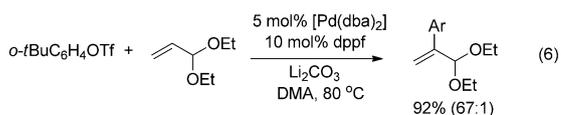
R = <i>c</i> -hexyl	91% (>100:1)		71% (100:0)		96% (29:1)		94% (23:1)
isobutyl	94% (45:1)						
neopentyl	93% (48:1)						
benzyl	94% (93:1)		92% (100:0)		94% (21:1), 100 °C		78% (39:1)

**Scheme 3.** Scope of olefins in Heck reactions of model aryl triflates. The ratios of the Heck product shown in the scheme to all other isomers are given in brackets. Phth = phthaloyl, Ts = *p*-toluenesulfonyl.

sulfonamide, and even alcohol groups. Most reactions provided good internal selectivity. For example, homoallylic and bishomoallylic alcohols coupled with aryl triflates carrying no *ortho* substituents in more than 10:1 selectivity, which is unprecedented.<sup>[12]</sup> Some very hindered olefins can also be used. In a reaction of *tert*-butylethylene, the aryl group added preferentially to the more hindered internal position in 9:1 selectivity, in the presence of the dppf ligand. Furthermore, allylbenzene reacted smoothly, although it is prone to undergo facile olefin isomerization catalyzed by palladium hydride.<sup>[20]</sup> One example, with 5-hydroxy-1-pentene as olefin substrate, was scaled up to produce 1.2 g of the Heck product without loss of selectivity (12:1). The desired isomer can be separated from other isomers by flash chromatography.

In Heck reactions of  $\alpha,\beta$ -unsaturated carbonyl compounds, there is a strong bias for aryl groups to insert at the electron-poor  $\beta$  position.<sup>[21]</sup> Thus, to introduce aryl groups at the  $\alpha$  position, cross-couplings of  $\alpha$ -halogenated or  $\alpha$ -metalated acrylates are often employed.<sup>[22]</sup> Interestingly, our Heck condition can be applied to perform selective  $\alpha$  arylation of acrolein diethyl acetal [Eqs. (5)–(6), Scheme 4].<sup>[23]</sup>

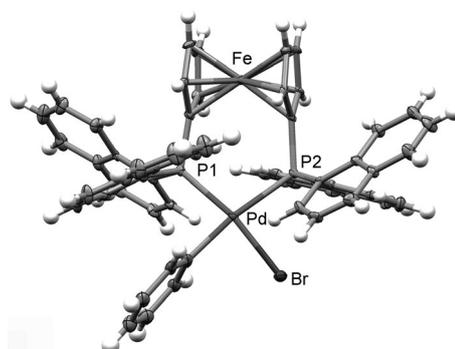
To determine the origin of high selectivity from the dnpf ligand, we have prepared its oxidative addition complex with PhBr. Treatment of [(dnpf)Pd(Ph)Br] with 1-octene in the



**Scheme 4.**  $\alpha$  Arylation of acrolein diethyl acetal [Eqs. (5) and (6)] and treatment of the [(dnpf)Pd(Ph)Br] complex with 1-octene [Eq. (7)].

presence of AgOTf gave the Heck product in 68% yield and 10:1 selectivity [Eq. (7), Scheme 4].<sup>[24]</sup> The selectivity is very similar to that observed under catalytic conditions. Single-crystal X-ray diffraction analysis of the complex showed some unusual structural features.<sup>[25]</sup> First, the backbone of dnpf adopts an almost eclipsed ferrocene conformation, unlike staggered ones in related dppf complexes.<sup>[26]</sup> Edge-to-edge interactions between two neighboring *P*-naphthyl groups were identified to enforce this unusual conformation. Second, the coordination geometry is significantly distorted from square planarity. For example, the bond angles  $\angle$ P2-Pd-C(phenyl) and  $\angle$ P1-Pd-Br are deviated from linearity by more than 10 degrees (Figure 4). Furthermore, both the *Pd*-phenyl group and bromine atom are forced substantially out of the plane defined by P1-Pd-P2; this kind of distorted geometry is absent in dppf complexes.<sup>[26]</sup> The distortion is caused by steric repulsion with neighboring *P*-naphthyl groups of the ligand. In the terminal insertion mode, the olefinic substituent will experience severe steric repulsion with the ligand. Thus, terminal insertion is greatly disfavored.

We have also conducted DFT calculations (PBE1PBE) on the insertion step using propene as model olefin. The purpose is to understand the effect of both ligands and *ortho* groups on *Pd*-phenyl groups on regioselectivity. Assuming fast equilibrium among olefin conformers of each complex, regioselectivity will be dictated by relative energy ( $\Delta E$ ) of transition



**Figure 4.** ORTEP representation of the [(dnpf)Pd(Ph)Br] complex with 50% thermal ellipsoid probability. Important bond angles:  $\angle$ Br-Pd-C(phenyl) = 84°;  $\angle$ P1-Pd-P2 = 103°;  $\angle$ P2-Pd-C(phenyl) = 168°;  $\angle$ P1-Pd-Br = 166°.



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## Communications

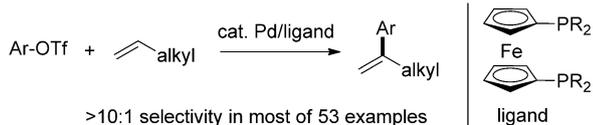


### Heck Reaction

L. Qin, X. Ren, Y. Lu, Y. Li,  
J. Zhou\*



Intermolecular Mizoroki–Heck Reaction of Aliphatic Olefins with High Selectivity for Substitution at the Internal Position



**New ligand for old reaction:** The title reaction of aryltriflates with aliphatic olefins leads to substitution at the internal position with high selectivity. The ratio of the desired isomer (shown in the scheme) to the sum of all other isomers

is generally above 10:1. The key to success is the use of a ferrocene bisphosphine ligand (R = 1-naphthyl). The reaction can be easily scaled up, and minor isomers can be separated by chromatography.