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Selective arylation of 1,1-disubstituted olefins using a biphenyl-based phosphine in Heck coupling reactions

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ABSTRACT

The biphenyl-based phosphine, 2-diphenylphosphino-2′-methylbiphenyl is an effective ligand for palladium-catalyzed terminal arylation of 1,1-disubstituted olefins with aryl bromides in DMF and K_2CO_3 as base. The yields of products are independent of the electronic properties of the aryl bromides, however, the nature of the olefin has a major effect.

Palladium-catalyzed cross-coupling reactions are important methods for the construction of carbon–carbon bonds. An example is the Heck reaction, the Pd-catalyzed reaction of an olefin with an aryl derivative in the presence of a base, where formally a vinylic hydrogen is replaced by an aryl group.[1,2] The Heck coupling has been applied to a wide variety of monosubstituted olefins. However, only a few examples of the use of 1,1-disubstituted olefins have been reported to date.[3–9] Heck reaction of aryl halides with 1,1-disubstituted olefins affords bulky aryl olefins which display interesting pharmacological and physical properties.[10–13]

The arylation of 1,1-disubstituted olefins such as methacrylates, depending on the direction of β-hydride elimination, can give two possible isomers: (a) α-methylcinnamic acid esters **1** with an internal double bond, the stereochemistry of which can be *E* or *Z* and, (b) α-benzylacrylates **2** with a terminal double bond, which is susceptible to further arylation to give **3** (Scheme 1).

Generally, the combination of a palladium catalyst with various phosphine ligands results in excellent yields and high efficiency in the Heck reaction.[14–17] Inspired by the discovery that electron-rich and bulky phosphines are important ligands, several researchers have synthesized a number of Pd complexes associated with bulky and electron-rich phosphines. Among them, biphenyl-based phosphines are of significant interest in organic synthesis. Catalysts based on this class of ligands have not only displayed high stability, but have also shown increased reactivity in palladium-catalyzed carbon–carbon and carbon–heteroatom bond forming reactions.[18–22]

The stability of catalysts based on these phosphines is believed to be due to π-interactions between the non-phosphine-containing ring of the biphenyl ligand and the Pd(0) center. This π-interaction may stabilize any intermediate in the catalytic cycle thereby increasing the lifetime of the catalyst.[23–28]

We are interested in developing highly active palladium catalysts, and in this context we have focused on C–C coupling reactions.[29–32] Herein, we report that the sterically bulky biphenyl-based phosphine (**4**)–Pd complex is sufficiently active to promote Heck reactions of 1,1-disubstituted olefins with aryl bromides. We have reported that phosphine **4** can be successfully applied in the palladium-catalyzed Suzuki coupling of aryl halides as well as bromoarylphosphines and bromoarylphosphine oxides, with low catalyst loading and in good to excellent conversions.[31]

The biphenyl-based phosphine **4** was prepared in almost quantitative yield by Suzuki coupling of *o*-tolylboronic acid with either bromophenylphosphine or its corresponding oxide using $Pd(OAc)_2$ and various monophosphine ligands, as described earlier[30,31] (Scheme 2).

Based on our recent success with biphenyl-based phosphine **4** as a ligand in Heck coupling reactions of monosubstituted olefins with aryl bromides, we employed the same experimental protocol for the Heck reactions of 1,1-disubstituted olefins.[33] Thus, *N*,*N*-dimethylformamide (DMF) was chosen as the solvent and sodium carbonate (K_2CO_3) as the base for the reaction of aryl bromides with *n*-butyl methacrylate and α-methyl styrene at 135 °C using 0.025 mol% of $Pd(OAc)_2$.[34]

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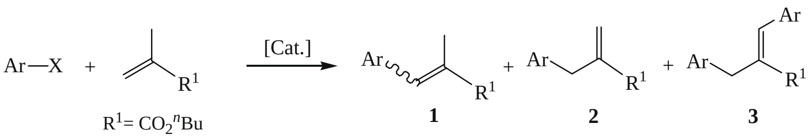
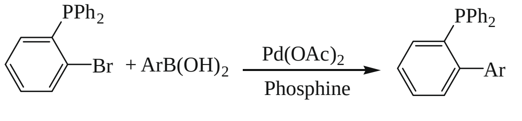


Scheme 1. Heck arylation of 1,1-disubstituted olefins.



4: Ar = *o*-tolyl

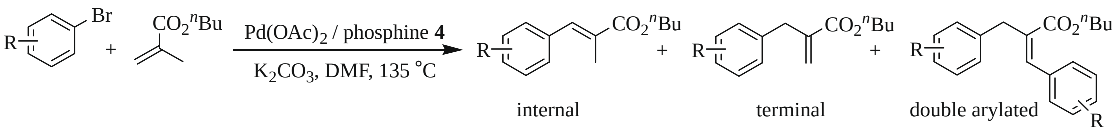
Scheme 2. Synthesis of biphenyl-based phosphine **4**.

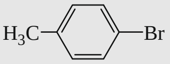
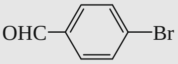
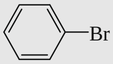
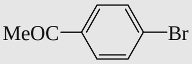
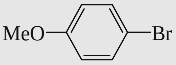
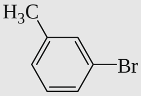
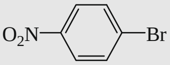
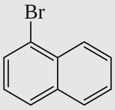
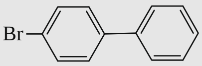
We observed that *n*-butyl methacrylate in the presence of K_2CO_3 as base, gave terminal olefins as the major coupling products in all cases ($K_{TI} \gg 99/1$), and only a small amount of the double arylated product was formed ($K_{MD} \gg 99/1$) (Table 1).

Using a phosphinito Pd complex in DMF at 180 °C, Jensen observed that in the Heck arylation of olefins in the presence of both inorganic and organic bases, the internal olefin was obtained as the major product.[3] In contrast, Beller found that in the Heck arylation of olefins, catalyzed by Herrmann's palladacycle, the nature of the base had a significant effect on the regioselectivity. Inorganic bases such as sodium acetate gave a mixture of the two regioisomers with the terminal olefin as the major product, whereas the internal olefin was favored by organic bases such

Table 1

Heck reaction of *n*-butyl methacrylate with aryl bromides[a]



Entry	Aryl bromide	Terminal[b] (%)	K_{TI}[c]	K_{MD}[d]	TON
1		80	>99/1	>99/1	3200
2		73	14.6	>99/1	2920
3		95	>99/1	>99/1	3800
4		17 (45)	1.7 (>99/1)	2.7 (>99/1)	1840 (1800)
5		49 (50)	16 (5.5)	>99/1 (6.5)	2040 (2720)
6		90	>99/1	>99/1	3600
7		5 (42)	>99/1 (8.4)	>99/1 (6.71)	200 (2160)
8		40	>99/1	>99/1	1600
9		20	>99/1	>99/1	800

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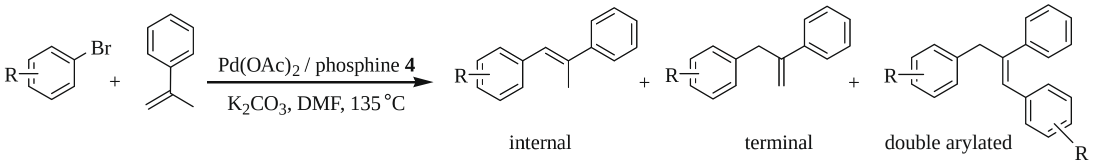
[a] Reaction conditions: aryl bromide (4 mmol), *n*-butyl methacrylate (4 mmol), K_2CO_3 (4 mmol), $Pd(OAc)_2$ (0.025 mol %), phosphine **4** (0.05 mol %), DMF (3 mL), 135 °C, 1 h, N_2.

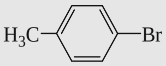
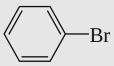
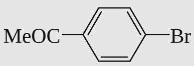
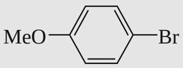
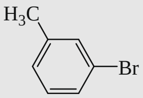
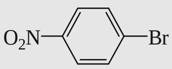
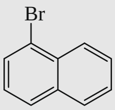
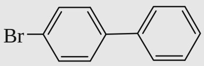
[b] GC yield. The numbers in parentheses are from 24 h reactions.

[c] K_{TI} = terminal/internal.

[d] K_{MD} = mono arylated/double arylated, mono arylated = sum of terminal and internal isomers.

Table 2
Heck reaction of α-methylstyrene with aryl bromides[a]



Entry	Aryl bromide	Terminal[b] (%)	K_{TI}[c]	K_{MD}[d]	TON
1		78	9.75	>99/1	3440
2		95	19	>99/1	4000
3		10 (40)	2 (>99/1)	>99/1	600 (600)
4		40	>99/1	>99/1	1600
5		82	9.1	>99/1	3640
6		35	3.9	4.9	2120
7		40	>99/1	>99/1	1600
8		15	>99/1	>99/1	600

[a] Reaction conditions: aryl bromide (4 mmol), α-methylstyrene (4 mmol), K_2CO_3 (4 mmol), $Pd(OAc)_2$ (0.025 mol %), phosphine **4** (0.05 mol %), DMF (3 mL), 135 °C, 1 h, N_2.

[b] NMR yield. The numbers in parentheses are from 24 h reactions.

[c] K_{TI} = terminal/internal.

[d] K_{MD} = mono arylated/double arylated, mono arylated = sum of terminal and internal isomers.

as Bu_3N and diisopropylethylamine (DIPEA).[4] Sun and co-workers[5] reported that during the arylation of 1,1-disubstituted olefins catalyzed by Co hollow nanospheres, only internal olefins were obtained, in contrast to the palladium nanoparticle-catalyzed reaction reported by Caló et al. in which isomerized products (terminal isomer) were generated.[6]

We considered α-methylstyrene a suitable candidate for further evaluation of the influence of biphenyl-based phosphine **4** on the Heck reactions with 1,1-disubstituted olefins because it has excellent NMR monitorable protons. Analogous to the reactions with *n*-butyl methacrylate, high selectivity was observed for the terminal olefin albeit with slower reaction rates (Table 2). In addition, selectivity toward the mono-arylated product was better than that with *n*-butyl methacrylate and no double-arylated products were observed apart from the case of 1-bromo-4-nitrobenzene in which a small amount of the double arylated product was formed (Table 2, entry 6). It would seem that the existence of a strong electron-withdrawing NO_2 group on the aryl bromide makes it more susceptible to further oxidative addition to the Pd species.

If in the Heck coupling reaction oxidative addition of the aryl halide to the Pd(0) species is the rate-determining step, electron-withdrawing groups on the aryl halide should lead to improved rates, whereas electron-donating groups should decrease reaction rates. As shown in Tables 1 and 2 aryl bromides with both electron-withdrawing and electron-donating groups showed no obvious difference in reactivity. In addition, reasonable yields were observed with electron-donating Me and OMe substituents on the bromobenzene. On the other hand, the nature of the olefin has a dominating effect on the yield and selectivity of the reaction. These results lead to some doubts about the effect of the aryl bromide on the rate-determining step and infer a greater contribution of the coordination and/or insertion of the olefin in the rate-determining step.

In summary, the use of biphenyl-based phosphine **4** as a ligand and K_2CO_3 as a base in Heck reactions, leads to the terminal isomers of 1,1-disubstituted olefins, selectively, and in reasonable yields in most cases regardless of the nature of the substituents on the arylbromides.

Acknowledgments

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34. *Typical experimental procedure for the Heck arylation*: A reaction tube was charged with bromobenzene (4 mmol), α-methylstyrene (4 mmol), and K_2CO_3 (4 mmol) under a dry nitrogen atmosphere. A solution of palladium acetate (0.025 mol % in 1 mL of DMF) followed by a solution of phosphine **4** (0.05 mol % in 2 mL of DMF) was added through a rubber septum and the resulting mixture was heated at 135 °C for 1 h. The reaction mixture was then cooled to room temperature. After extraction with CH_2Cl_2 (3 × 20 mL), the combined organic layer was dried over $MgSO_4$. The solvent was evaporated and the crude product was characterized by ^{1}H NMR spectroscopy.