



Palladium-catalyzed Mizoroki–Heck reaction of allyl aryl ethers with aryl iodides using phosphine-free hydrazone ligands

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ARTICLE INFO

Article history:

Received 8 June 2009

Revised 2 July 2009

Accepted 3 July 2009

Available online 15 July 2009

ABSTRACT

Palladium-catalyzed Mizoroki–Heck reaction of allyl aryl ethers with aryl iodides gave aryl cinnamyl ethers using a catalytic amount of Pd(OAc)₂ in DMF at 50 °C with phosphine-free hydrazone as a ligand in good yields.

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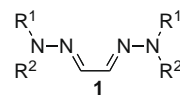
The Mizoroki–Heck reaction is one of the most widely used palladium-catalyzed methodologies in organic synthesis. The efficiency of several catalysts for the reaction of aryl halides with acrylates or styrene derivatives has been studied.¹ Although the synthesis of alkyl cinnamyl ethers using the Mizoroki–Heck-type reaction of allyl ethers has been reported by several groups,² the synthesis of aryl cinnamyl ethers using the Mizoroki–Heck-type reaction of allyl aryl ethers has attracted less attention.^{3,4} However an aryl cinnamyl ether framework constitutes an important structural assembly in many molecules of biological importance.^{4,5} The synthesis of aryl cinnamyl ethers using palladium-catalyzed etherification of cinnamyl alcohol,⁶ cinnamyl acetate,⁷ or cinnamyl carbonate⁸ by phenols via π -allylpalladium intermediate with phosphine ligands has been also reported. In these cases, it is necessary to prepare the corresponding cinnamyl alcohol derivatives.

We recently demonstrated an air-stable phosphine-free hydrazone as an effective ligand for palladium-catalyzed C–C bond formations such as the Suzuki–Miyaura reaction,⁹ the Mizoroki–Heck reaction of acrylates and styrene,¹⁰ the Sonogashira cross-coupling reaction,¹¹ the Hiyama cross-coupling reaction,¹¹ and the allyl cross-coupling reaction of allylic acetate with boronic acid.¹² We now report the use of phosphine-free hydrazone ligands **1a–d** (Fig. 1) for a palladium-catalyzed Mizoroki–Heck reaction of allyl aryl ethers with aryl halides for the synthesis of aryl cinnamyl ethers.

Initially, we tried to seek the optimal reaction conditions for the palladium-catalyzed Mizoroki–Heck reaction of allyl aryl ethers with aryl halides. Iodobenzene and allyl phenyl ether were chosen as model substrates with 3 mol % of Pd catalyst for 24 h under an argon atmosphere at 50 °C (Table 1). Using 3 mol % of hydrazone **1a** as a ligand, we observed that the Mizoroki–Heck reaction in

the presence of Pd(OAc)₂ with K₃PO₄ as a base in DMF as a solvent proceeded to give (*E*)-cinnamyl phenyl ether (**2a**) in 83% yield with a small amount of **3**¹³ and **4**^{3a} as by-products (Table 1, entry 1). We also tested other bishydrazone **1b–d**, and found that hydrazone **1b** was a very effective ligand for this reaction (entry 2 vs entries 1, 3 and 4). The effect of various palladium sources was investigated (entries 2, and 5–7). The use of Pd(OAc)₂ led to high yield for this reaction (entry 2). Several commonly used bases were tested (entries 2, and 8–11); K₃PO₄ was preferred this reaction (entry 2). The effect of various solvents was also investigated (entries 2, and 12–15). The use of DMF as a solvent led to high yield for this reaction (entry 2). We found the following optimized conditions; using the Pd(OAc)₂/hydrazone **1b** system, the reaction proceeded with 83% in DMF at 50 °C (entry 2).

Under optimized reaction conditions,¹⁴ the effect of various aryl iodides in the Mizoroki–Heck reaction was investigated using allyl phenyl ether (Table 2, entries 1–13). Using iodobenzene and 4-substituted aryl iodides led to good yields of the corresponding (*E*)-cinnamyl phenyl ether derivatives (entries 1–7). Moreover, 3-substituted, 2-substituted and multi-substituted aryl iodides also led to good yields (entries 8–12). Using 3-iodothiophene led to moderate yield of the corresponding product (entry 13). Based on the results of the Mizoroki–Heck reaction using allyl phenyl ether, we tested the reaction of various allyl aryl ethers (entries



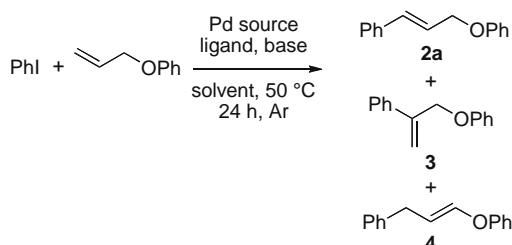
- 1**
a: R¹ = Ph, R² = Me
b: R¹, R² = -(CH₂)₆-
c: R¹, R² = -(CH₂)₅-
d: R¹, R² = -(CH₂)₂O(CH₂)₂-

Figure 1. Hydrazone ligands **1a–d**.

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Table 1

Optimization of reaction conditions on the palladium-catalyzed Mizoroki–Heck reaction of allyl phenyl ether with iodobenzene^a



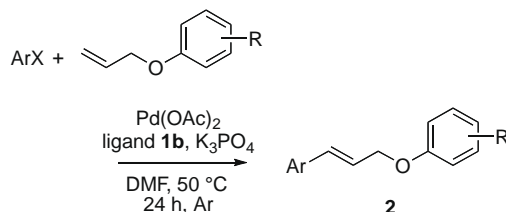
Entry	Ligand	Pd source	Base	Solvent	Yield ^b (%) 2a (E:Z)/ 3 / 4
1	1a	Pd(OAc) ₂	K ₃ PO ₄	DMF	76(34:1)/3/5
2	1b	Pd(OAc) ₂	K ₃ PO ₄	DMF	83(31:1)/4/5
3	1c	Pd(OAc) ₂	K ₃ PO ₄	DMF	79(32:1)/3/6
4	1d	Pd(OAc) ₂	K ₃ PO ₄	DMF	75(35:1)/3/5
5	1b	PdCl ₂	K ₃ PO ₄	DMF	55(45:1)/2/5
6	1b	Pd(OCOCF ₃) ₂	K ₃ PO ₄	DMF	66(39:1)/3/6
7	1b	Pd ₂ (dba) ₃	K ₃ PO ₄	DMF	53(45:1)/3/5
8	1b	Pd(OAc) ₂	K ₂ CO ₃	DMF	67(28:1)/3/6
9	1b	Pd(OAc) ₂	Cs ₂ CO ₃	DMF	2(-)/trace/trace
10	1b	Pd(OAc) ₂	KOAc	DMF	45(22:1)/2/5
11	1b	Pd(OAc) ₂	Na ₂ CO ₃	DMF	37(34:1)/2/3
12	1b	Pd(OAc) ₂	K ₃ PO ₄	NMP	80(31:1)/3/5
13	1b	Pd(OAc) ₂	K ₃ PO ₄	DMAc	78(42:1)/3/6
14	1b	Pd(OAc) ₂	K ₃ PO ₄	DMSO	19(14:1)/1/1
15	1b	Pd(OAc) ₂	K ₃ PO ₄	PhMe	4(72:1)/trace /1

^a Reaction conditions: PhI (0.5 mmol), allyl phenyl ether (0.7 mmol), ligand (3 mol %), Pd source (3 mol %), base (0.7 mmol), solvent (1 mL) at 50 °C for 24 h under Ar.

^b Determined by ¹H NMR using diphenylmethane as an internal standard.

Table 2

Palladium-catalyzed Mizoroki–Heck reaction of allyl aryl ethers with aryl halides^a



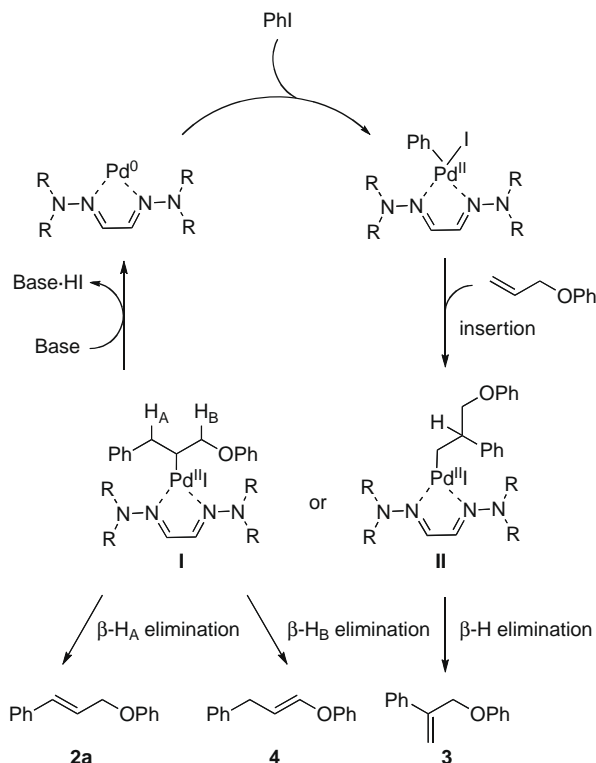
Entry	ArX	R	Product	Yield ^b (%)
1	PhI	H	2a	76
2	4-MeC ₆ H ₄ I	H	2b	74
3	4- ⁱ PrC ₆ H ₄ I	H	2c	64
4	4-CF ₃ C ₆ H ₄ I	H	2d	70
5	4-MeOC ₆ H ₄ I	H	2e	64
6 ^c	4-AcC ₆ H ₄ I	H	2f	43
7	4-BrC ₆ H ₄ I	H	2g	77
8	3-MeC ₆ H ₄ I	H	2h	68
9	3-CF ₃ C ₆ H ₄ I	H	2i	74
10	3,5-Me ₂ C ₆ H ₃ I	H	2j	74
11	3,4-Me ₂ C ₆ H ₃ I	H	2k	73
12	2-MeC ₆ H ₄ I	H	2l	60
13	3-Iodothiophene	H	2m	51
14	4-MeC ₆ H ₄ I	4-Me	2n	71
15	4-MeC ₆ H ₄ I	4-MeO	2o	71
16 ^d	PhI	4-Cl	2p	62
17	PhBr	H	2a	17

^a Reaction conditions: Aryl halide (0.5 mmol), allyl aryl ether (0.7 mmol), ligand (3 mol %), Pd(OAc)₂ (3 mol %), K₃PO₄ (0.7 mmol), DMF (1 mL) at 50 °C for 24 h under Ar.

^b Yields refer to isolated yields with >98% purity as determined by GC–MS or ¹H NMR.

^c This reaction was carried out for 3 h.

^d This reaction was carried out for 48 h.



Scheme 1. A plausible mechanism for Mizoroki–Heck reaction of allyl phenyl ether with iodobenzene.

14–16). Using allyl 4-methylphenyl ether and allyl 4-methoxyphenyl ether led to good yields of the Mizoroki–Heck reaction products (entries 14 and 15). The reaction of allyl 4-chlorophenyl ether with iodobenzene was necessary to extend the reaction times, such as to 48 h (entry 16). We also investigated the reaction of bromobenzene instead of that of iodobenzene. Unfortunately, the reaction using bromobenzene with allyl phenyl ether gave (*E*)-cinnamyl phenyl ether with low yield (entry 17).

A plausible mechanism for Mizoroki–Heck reaction of allyl phenyl ether with iodobenzene is illustrated in Scheme 1. The first step is the oxidative addition of iodobenzene to Pd(0)–hydrazone complex. Subsequently, the insertion reaction of Pd complex with allyl phenyl ether followed by β -hydride elimination of H_A gives cinnamyl phenyl ether **2a**. On the other hand, enol ether **4** is obtained from Pd complex **I** by β -hydride elimination of H_B instead of H_A. When Pd complex **II** is formed instead of Pd complex **I**, branched allyl ether **3** is obtained. After reductive elimination of HI by base, the Pd(0) complex is regenerated and the catalytic cycle is completed.

In summary, we found that the palladium-catalyzed Mizoroki–Heck reaction of allyl aryl ethers with various aryl iodides gave aryl cinnamyl ethers using a catalytic amount of Pd(OAc)₂ in DMF at 50 °C with phosphine-free hydrazone as a ligand in good yields.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.046.

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14. *General procedure of palladium-catalyzed Mizoroki–Heck reaction of allyl aryl ethers with aryl halides:* To a mixture of aryl halide (0.5 mmol), K_3PO_4 (148.5 mg, 0.7 mmol), $Pd(OAc)_2$ (3.37 mg, 15 μ mol) and ligand **1b** (3.75 mg, 15 μ mol) in DMF (1.0 mL) was added allyl aryl ether (0.7 mmol) at room temperature under an atmosphere of argon. The mixture was stirred at 50 °C. After 24 h, the mixture was diluted with ethyl acetate and water. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane/ $CHCl_3$ = 80–6/1).