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PALLADIUM-CATALYZED MIZOROKI-HECK TYPE REACTION WITH ARYLIODINE DIACETATES USING HYDRAZONE LIGAND

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Abstract – We developed a palladium-catalyzed Mizoroki-Heck type reaction of olefins with such hypervalent iodine reagents as iodobenzene diacetate in good to high yields using 2 mol% of a heterocyclic hydrazone (**1b**)-$Pd(OAc)_2$ system in NMP under air at 90 °C.

INTRODUCTION

The arylation of olefins, also known as 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] Recently, palladium-catalyzed Mizoroki-Heck type reactions of olefins with aryliodine diacetates as hypervalent iodine reagents instead of aryl halides were reported.[2] For example, Mao and co-workers reported a palladium-catalyzed Mizoroki-Heck type reaction with aryliodine diacetates with 4 mol% of $Pd(OAc)_2$.[3] But PEG-400 had to be used as a solvent because such commonly used organic solvents as DMF and THF were not effective under these conditions. Magedov and co-workers also reported a reaction with aryliodine diacetates.[4] In this case, binary catalysts such as $Pd(OAc)_2$ (3-5 mol%)-Ag_2CO_3 (50 mol%) systems with TEMPO (50 mol%) as an additive in MeCN are needed to efficiently obtain the products. On the other hand, we recently demonstrated hydrazone as an effective ligand for such palladium-catalyzed C-C bond formation as the Suzuki-Miyaura reaction,[5] the Mizoroki-Heck reaction,[6]

the Sonogashira cross-coupling reaction,[7] the Hiyama cross-coupling reaction,[7a] and the allyl cross-coupling reaction of allylic acetate[8] and ether[9] with boronic acid. We also reported a palladium-catalyzed Mizoroki-Heck type reaction with aryl trimethoxysilanes.[10] We now report the use of hydrazone ligands (**1a**-**e**) and (**2**) (Figure 1) for a palladium-catalyzed Mizoroki-Heck type reaction of olefins with iodobenzene diacetates instead of aryl halides.

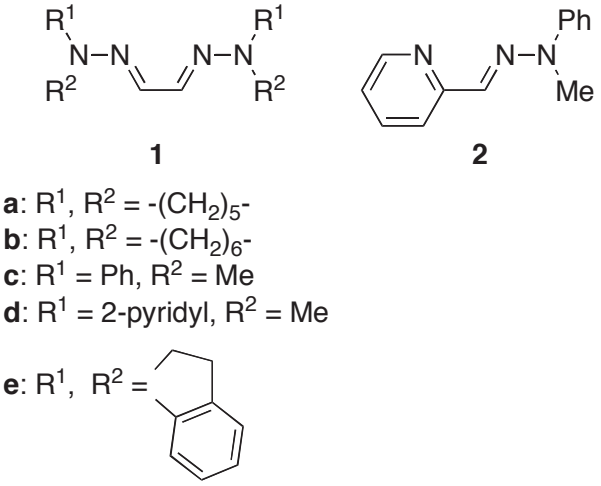
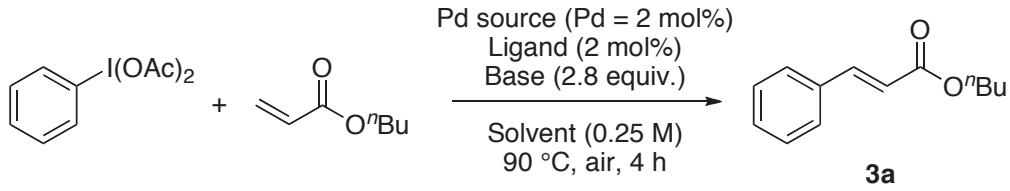


Figure 1. Hydrazones **1** and **2**

RESULTS AND DISCUSSION

Initially, we examined the reaction of iodobenzene diacetate and *n*-butyl acrylate as model substrates with 2 mol% of Pd catalyst for 4 h under an air atmosphere at 90 °C (Table 1). Using 2 mol% of $PdCl_2(MeCN)_2$ and hydrazone (**1a**) as a ligand, we observed that the reaction in the presence of Cs_2CO_3 as a base in NMP as a solvent gave corresponding product (**3a**) in a 62% yield (Table 1, Entry 1). We tested other hydrazones (**1b-e**) and (**2**) (Entries 2-6) and found that heterocyclic hydrazone (**1b**) was an effective ligand for this reaction (Entry 2). Several palladium sources were also tested (Entries 2, and 7–12). Palladium acetate was the most effective palladium source in this reaction (Entry 7). Next, the effects of various bases and solvents were investigated (Entries 7, and 13-22). Using Cs_2CO_3 in NMP led to a 96% yield for this reaction (Entry 7). Although the Mizoroki-Heck type reaction proceeded in MeCN under Magedov's conditions,[4] MeCN was not an effective solvent in the hydrazone (**1b**)-$Pd(OAc)_2$ system (Entry 22).

Table 1. Optimization of Palladium-Catalyzed Mizoroki-Heck Type Reaction with Iodobenzene Diacetate Using Hydrazone Ligand[a]



3a

Entry	Pd source	Ligand	Base	Solvent	Yield of **3a** (%)[b]
1	$PdCl_2(MeCN)_2$	**1a**	Cs_2CO_3	NMP	62
2	$PdCl_2(MeCN)_2$	**1b**	Cs_2CO_3	NMP	78
3	$PdCl_2(MeCN)_2$	**1c**	Cs_2CO_3	NMP	69
4	$PdCl_2(MeCN)_2$	**1d**	Cs_2CO_3	NMP	21
5	$PdCl_2(MeCN)_2$	**1e**	Cs_2CO_3	NMP	74
6	$PdCl_2(MeCN)_2$	**2**	Cs_2CO_3	NMP	42
7	***$Pd(OAc)_2$***	***1b***	***Cs_2CO_3***	***NMP***	***96***
8	$Pd(acac)_2$	**1b**	Cs_2CO_3	NMP	87
9	$[Pd(\eta^3\text{-allyl})Cl]_2$	**1b**	Cs_2CO_3	NMP	87
10	$PdCl_2$	**1b**	Cs_2CO_3	NMP	83
11	$Pd(tfa)_2$	**1b**	Cs_2CO_3	NMP	79
12	$Pd_2(dba)_3$	**1b**	Cs_2CO_3	NMP	87
13	$Pd(OAc)_2$	**1b**	K_2CO_3	NMP	36
14	$Pd(OAc)_2$	**1b**	K_3PO_4	NMP	54
15	$Pd(OAc)_2$	**1b**	$Ca(OH)_2$	NMP	11
16	$Pd(OAc)_2$	**1b**	NaOAc	NMP	16
17	$Pd(OAc)_2$	**1b**	Et_3N	NMP	49
18	$Pd(OAc)_2$	**1b**	Cs_2CO_3	DMA	76
19	$Pd(OAc)_2$	**1b**	Cs_2CO_3	DMSO	66
20	$Pd(OAc)_2$	**1b**	Cs_2CO_3	DMF	43
21	$Pd(OAc)_2$	**1b**	Cs_2CO_3	PhMe	42
22	$Pd(OAc)_2$	**1b**	Cs_2CO_3	MeCN	4

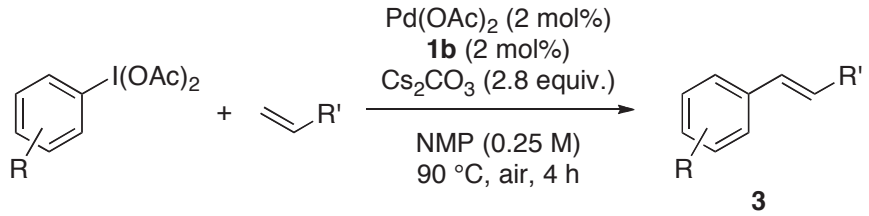
[a] Reaction conditions: Iodobenzene diacetate (0.5 mmol), *n*-butyl acrylate (3.0 mmol), Pd source (Pd = 2 mol%), ligand (2 mol%), base (1.4 mmol), solvent (2 mL) at 90 °C for 4 h under air.

[b] Isolated yields.

Under optimized reaction conditions (Table 1, Entry 7), we explored the scope and limitation of both aryliodine diacetates and olefins (Table 2). The reaction of iodobenzene diacetate with *n*-butyl acrylate for 2 h also gave product (**3a**) with high yield instead of 4 h (Table 2, Entry 1 vs. Table 1, Entry 7). When the reaction was carried out without using ligand (**1b**), the yield of **3a** was decreased (Entry 1 vs. Entry 2). Using iodobenzene diacetate with *tert*-butyl acrylate and ethyl acrylate for 4 h led to good yields of

corresponding products (**3b**) and (**3c**) (Entries 3 and 4). The reaction of methyl acrylate also gave corresponding product (**3d**) in 81% for 18 h (Entry 5). Moreover, methyl vinyl ketone and styrene led to good yields of products (**3e**) and (**3f**) (Entries 6 and 7). We also found that the reaction of iodomesitylene diacetate and *m*-(diacetoxyiodo)anisole with various acrylates gave corresponding products (**3g**-**l**) with moderate to good yields (Entries 8-13). Although true mechanism was not revealed, we thought the aryliodine was generated *in situ* from aryliodine diacetate and then the related Mizoroki-Heck type reaction occurred.[3,4]

Table 2. Scope and Limitations of Palladium-Catalyzed Mizoroki-Heck Type Reaction of Olefins with Aryliodine Diacetates[a]



3

Entry	R	R'	yield of **3** (%)[b]
1[c]	H	$CO_2{}^n$Bu	96(**3a**)
2[c,d]	H	$CO_2{}^n$Bu	85(**3a**)
3	H	$CO_2{}^t$Bu	71(**3b**)
4	H	CO_2Et	88(**3c**)
5[e]	H	CO_2Me	81(**3d**)
6[f]	H	COMe	58(**3e**)
7[e]	H	Ph	79(**3f**)
8	2,4,6-triMe	$CO_2{}^n$Bu	79(**3g**)
9[g]	2,4,6-triMe	$CO_2{}^t$Bu	39(**3h**)
10[e]	2,4,6-triMe	CO_2Et	58(**3i**)
11	3-MeO	$CO_2{}^n$Bu	93(**3j**)
12[g]	3-MeO	$CO_2{}^t$Bu	59(**3k**)
13[e]	3-MeO	CO_2Et	91(**3l**)

[a] Reaction conditions: Aryliodine diacetate (0.5 mmol), olefin (3.0 mmol), $Pd(OAc)_2$ (2 mol%), **1b** (2 mol%), Cs_2CO_3 (1.4 mmol), NMP (2 mL) at 90 °C for 4 h under air.

[b] Isolated yields.

[c] This reaction was carried out for 2 h.

[d] This reaction was carried out without using ligand **1b**.

[e] This reaction was carried out for 18 h.

[f] This reaction was carried out for 8 h.

[g] This reaction was carried out for 24 h.

In summary, we found that a palladium-catalyzed Mizoroki-Heck type reaction of olefins with aryliodine diacetates in NMP gave corresponding products in good to high yields using 2 mol% of heterocyclic hydrazone (**1b**)-$Pd(OAc)_2$ system under air at 90 °C for 2-24 h.

EXPERIMENTAL

General

Melting points were measured on a Asone micromelting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX-300 spectrometer. Chemical shifts are reported in δ ppm referenced to an internal $SiMe_4$ standard. Infrared (IR) spectra were obtained using a JASCO FT/IR 230 spectrophotometer. Mass spectra were recorded on a GCMS-QP5050. HRMS was recorded on a Thermo Fisher Scientific Exactive using ESI.

General Procedure for Palladium-Catalyzed Mizoroki-Heck Type Reaction with Aryliodine Diacetates.

To a mixture of aryliodine diacetate (0.5 mmol), Cs_2CO_3 (1.4 mmol), $Pd(OAc)_2$ (10 μmol), and **1b** (10 μmol) in NMP (2 mL) was added olefin (3.0 mmol) at room temperature under an air atmosphere. The mixture was stirred at 90 °C. After 2-24 h, the mixture was diluted with EtOAc 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:EtOAc = 20-10:1 or $CHCl_3$:EtOAc = 10:1).

(*E*)-*n*-Butyl cinnamate (3a):[10] 96% as a colorless oil; IR (neat, cm^{-1}): 1713 (C=O); ^1H NMR ($CDCl_3$) δ: 0.97 (t, *J* = 7.3 Hz, 3H), 1.38-1.50 (m, 2H), 1.65-1.72 (m, 2H), 4.21 (t, *J* = 6.7 Hz, 2H), 6.45 (d, *J* = 16.0 Hz, 1H), 7.38-7.40 (m, 3H), 7.52-7.55 (m, 2H), 7.69 (d, *J* = 16.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 13.7, 19.2, 30.7, 64.4, 118.2, 128.0, 128.9, 130.2, 134.4, 144.5, 167.1; EI-MS *m*/*z* (rel intensity) 204 (M^+, 23).

(*E*)-*t*-Butyl cinnamate (3b):[10] 71% as a colorless oil; IR (neat, cm^{-1}): 1708 (C=O); ^1H NMR ($CDCl_3$) δ: 1.54 (s, 9H), 6.37 (d, *J* = 16.0 Hz, 1H), 7.36-7.38 (m, 3H), 7.50-7.53 (m, 2H), 7.59 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 28.2, 80.5, 120.1, 127.9, 128.8, 129.9, 134.6, 143.5, 166.3; EI-MS *m*/*z* (rel intensity) 204 (M^+, 10).

(*E*)-Ethyl cinnamate (3c):[10] 88% as a colorless oil; IR (neat, cm^{-1}): 1708 (C=O); ^1H NMR ($CDCl_3$) δ: 1.34 (t, *J* = 7.1 Hz, 3H), 4.27 (q, *J* = 7.1 Hz, 2H), 6.44 (d, *J* = 16.0 Hz, 1H), 7.38-7.40 (m, 3H), 7.52-7.55 (m, 2H), 7.69 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.3, 60.5, 118.2, 128.0, 128.8, 130.2, 134.4, 144.5, 167.0; EI-MS *m*/*z* (rel intensity) 176 (M^+, 40).

(*E*)-Methyl cinnamate (3d):[10] 81% as a white solid; mp 33-34 ºC; IR (KBr, cm^{-1}): 1718 (C=O); ^1H NMR ($CDCl_3$) δ: 3.81 (s, 3H), 6.45 (d, *J* = 16.0 Hz, 1H), 7.37-7.40 (m, 3H), 7.51-7.55 (m, 2H), 7.70 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 51.7, 117.7, 128.0, 128.9, 130.3, 134.3, 144.9, 167.4; EI-MS *m*/*z* (rel intensity) 162 (M^+, 53).

(*E*)-4-Phenylbut-3-en-2-one (3e):[10] 58% as a yellow oil; IR (neat, cm^{-1}): 1668 (C=O); ^1H NMR ($CDCl_3$) δ: 2.39 (s, 3H), 6.72 (d, *J* = 16.3 Hz, 1H), 7.39-7.41 (m, 3H), 7.49-7.57 (m, 3H); ^{13}C NMR ($CDCl_3$) δ: 27.5, 127.1, 128.2 128.9, 130.5, 134.4, 143.4, 198.4; EI-MS *m/z* (rel intensity) 146 (M^+, 65).

***trans*-Stilben (3f):**[10] 79% as a white solid; mp 124-125 ºC; ^1H NMR ($CDCl_3$) δ: 7.11 (s, 2H), 7.24-7.28 (m, 2H), 7.36 (t, *J* = 7.5 Hz, 4H), 7.52 (d, *J* = 7.3 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ: 126.5, 127.6, 128.7, 137.3; EI-MS *m/z* (rel intensity) 180 (M^+, 100).

(*E*)-*n*-Butyl 3-mesitylacrylate (3g).[11] 79% as a white solid; mp 30-31 ºC; IR (KBr, cm^{-1}): 1709 (C=O); ^1H NMR ($CDCl_3$) δ: 0.97 (t, *J* = 7.4 Hz, 3H), 1.38-1.50 (m, 2H), 1.65-1.74 (m, 2H), 2.28 (s, 3H), 2.33 (s, 6H), 4.21 (t, *J* = 6.7 Hz, 2H), 6.06 (d, *J* = 16.4 Hz, 2H), 6.89 (s, 2H), 7.84 (d, *J* = 16.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 13.8, 19.2, 21.0, 21.1, 30.7, 64.4, 123.1, 129.1, 130.1, 136.8, 138.3, 143.1, 167.1; EI-MS *m/z* (rel intensity) 246 (M^+, 24).

(*E*)-*t*-Butyl 3-mesitylacrylate (3h): 39% as a white solid; mp 62-63 ºC; IR (KBr, cm^{-1}): 1711 (C=O); ^1H NMR ($CDCl_3$) δ: 1.54 (s, 9H), 2.28 (s, 3H), 2.33 (s, 6H), 5.98 (d, *J* = 16.3 Hz, 1H), 6.88 (s, 2H), 7.75 (d, *J* = 16.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 21.0, 21.1, 28.2, 80.4, 124.8, 129.1, 131.1, 136.8, 138.0, 138.1, 142.0; EI-MS *m/z* (rel intensity) 246 (M^+, 28); HRMS (ESI-MS) *m/z* calcd for $C_{16}H_{22}O_2$+Na 269.1512, found 269.1510.

(*E*)-Ethyl 3-mesitylacrylate (3i):[12] 58% as a white solid; mp 36-37 ºC; IR (KBr, cm^{-1}): 1701 (C=O); ^1H NMR ($CDCl_3$) δ: 1.35 (t, *J* = 7.1 Hz, 3H), 2.28 (s, 3H), 2.33 (s, 6H), 4.27 (q, *J* = 7.1 Hz, 2H), 6.06 (d, *J* = 16.3 Hz, 1H), 6.90 (s, 2H), 7.84 (d, *J* = 16.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.3, 21.0, 21.1, 60.5, 123.1, 129.1, 130.9, 136.8, 138.3, 143.1, 167.0; EI-MS *m/z* (rel intensity) 218 (M^+, 40).

(*E*)-*n*-Butyl 3-(3-methoxyphenyl)acrylate (3j):[13] 93% as a colorless oil; IR (neat, cm^{-1}): 1713 (C=O); ^1H NMR ($CDCl_3$) δ: 0.97 (t, *J* = 7.3 Hz, 3H), 1.38-1.50 (m, 2H), 1.65-1.74 (m, 2H), 3.84 (s, 3H), 4.21 (t, *J* = 6.7 Hz, 2H), 6.43 (d, *J* =15.9 Hz, 1H), 6.93 (dd, *J* = 8.2 and 1.8 Hz, 1H), 7.05 (t, *J* = 2.0 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 7.30 (t, *J* = 7.9 Hz, 1H), 7.65 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 13.7, 19.2, 30.7, 55.2, 64.4, 112.8, 116.1, 118.5, 120.7, 129.8, 135.8, 144.4, 159.8, 167.0; EI-MS *m/z* (rel intensity) 234 (M^+, 40).

(*E*)-*t*-Butyl 3-(3-methoxyphenyl)acrylate (3k):[14] 59% as a yellow oil; IR (neat, cm^{-1}): 1706 (C=O); ^1H NMR ($CDCl_3$) δ: 1.54 (s, 9H), 3.83 (s, 3H), 6.36 (d, *J* = 16.0, 1H), 6.91 (dd, *J* = 8.2 and 2.5 Hz, 1H), 7.03 (t, *J* = 1.9 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 1H), 7.55 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 28.2, 55.2, 80.5, 112.7, 115.8, 120.4, 120.7, 129.8, 136.0, 143.4, 159.8, 166.3; EI-MS *m/z* (rel intensity) 234 (M^+, 28).

(*E*)-Ethyl 3-(3-methoxyphenyl)acrylate (3l):[15] 91% as a colorless oil; IR (neat, cm^{-1}): 1712 (C=O); ^1H NMR ($CDCl_3$) δ: 1.34 (t, *J* = 7.1 Hz, 3H), 3.83 (s, 3H), 4.27 (q, *J* = 7.1 Hz, 2H), 6.43 (d, *J* = 16.0 Hz, 1H), 6.93 (dd, J = 8.2 and 1.9 Hz, 1H), 7.04 (t, *J* = 1.9 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.9 Hz,

1H) 7.65 (d, J = 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.3, 55.3, 60.5, 112.8, 116.1, 118.5, 120.7, 129.8, 135.8, 144.5, 159.8, 166.9; EI-MS *m/z* (rel intensity) 206 (M^+, 67).

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