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Synthesis of 1,3-Diarylpropenes through Palladium-Catalyzed Mizoroki–Heck and Allyl Cross-Coupling Reactions Using Hydrazones as Ligands

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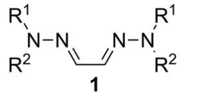
The palladium-catalyzed synthesis of unsymmetrical 1,3-diarylpropenes from allyl esters through a Mizoroki–Heck-type reaction with aryl iodides followed by allyl cross-coupling with a variety of arylboronic acids was developed; the products are obtained in moderate to good yields by using a hydrazone–$Pd(OAc)_2$ system.

Introduction

A 1,3-diarylpropene framework constitutes an important structural assembly in many molecules of biological importance.[1] The palladium-catalyzed allyl cross-coupling reaction of cinnamyl acetate with arylboronic acids provides a powerful tool for the synthesis of 1,3-diarylpropenes.[2] We previously reported the use of hydrazone ligands for the palladium-catalyzed allyl cross-coupling of cinnamyl acetate with boronic acids at room temperature.[3] Previously, the synthesis of cinnamyl acetate derivatives by the Mizoroki–Heck reaction of allyl acetate with aryl halides was studied by Jiao et al.[4] Recently, 1,3-diarylpropenes with the same aryl group were synthesized through the palladium-catalyzed diarylation of allylic esters with aryl iodides by using $Pd(OAc)_2$ (10 mol-%) at 120 °C by Li et al.[5] To the best of our knowledge, examples of the synthesis of 1,3-diarylpropenes with different aryl groups from allyl esters by diarylation have not been explored. We now report the synthesis of unsymmetrical 1,3-diarylpropenes by a palladium-catalyzed Mizoroki–Heck-type reaction of allyl esters with aryl iodides followed by allyl cross-coupling with a variety of arylboronic acids by using hydrazone **1**[6] as a ligand (Figure 1).



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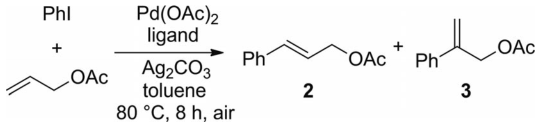
a: R^1, R^2 = $-(CH_2)_5-$
b: R^1 = Ph, R^2 = Me

Figure 1. Hydrazone ligands **1**.

Results and Discussion

Initially, we sought the optimal reaction conditions for the palladium-catalyzed Mizoroki–Heck-type reaction of allyl esters with aryl iodides by using hydrazone ligands. Allyl acetate and iodobenzene were chosen as model substrates with the Pd catalyst (5 mol-%) in toluene for 8 h under an atmosphere of air at 80 °C (Table 1). Under a modified version of Jiao's ligand-free conditions,[4a] the Mizoroki–Heck-type reaction gave a good yield of corresponding product **2** with a small amount of regioisomer **3** (Table 1, Entry 1). Using 5 mol-% of hydrazone **1a** as a ligand, we observed that the reaction proceeded to give desired product **2** in 56% yield (Table 1, Entry 2). We also tested hydrazone **1b** and found that it was an effective ligand for this reaction (Table 1, Entry 3).

Table 1. Optimization of the palladium-catalyzed Mizoroki–Heck-type reaction of allyl acetate with iodobenzene.[a]



Entry	Ligand	Yield of **2** [%][b]	Yield of **3** [%][b]
1	none	76	6
2	**1a**	56	5
3	**1b**	80	6

[a] Reaction conditions: Iodobenzene (0.5 mmol), allyl acetate (1.0 mmol), $Pd(OAc)_2$ (5 mol-%), ligand **1** (5 mol-%), Ag_2CO_3 (0.3 mmol), PhMe (3 mL) at 80 °C for 8 h in air. [b] Determined by ^1H NMR spectroscopy by using 2-methoxynaphthalene as an internal standard; E/Z ratio of **2** was >20:1.

We next tried to synthesize 1,3-diarylpropenes from allyl acetate through the Mizoroki–Heck-type reaction with iodobenzene in toluene at 80 °C for 8 h (Table 2, Reaction 1) followed by allyl cross-coupling with a phenylboronic acid in DMF/H_2O (3:1) at room temperature for 15 h

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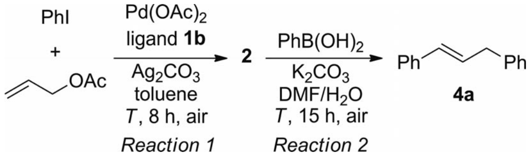
under an atmosphere of air (Table 2, Reaction 2). Although the reaction under ligand-free conditions gave intermediate product **2** without desired product **4a** (Table 2, Entry 1), with the use of ligand **1b** the reaction gave desired product **4a** in 37% yield, as determined by NMR spectroscopy (Table 2, Entry 2). When the reaction temperature of reaction 2 was increased to 50 °C, corresponding product **4a** was obtained in good yield (Table 2, Entry 3). After optimization of the reaction temperature, a Mizoroki–Heck-type reaction at 90 °C (reaction 1) followed by allyl cross-coupling at 50 °C led to 71% yield of corresponding product **4a** (Table 2, Entry 5). When allyl benzoate was used instead of allyl acetate, the corresponding product was obtained in high yield (85%, as determined by NMR spectroscopy; Table 2, Entry 7).

Table 2. Optimization of the palladium-catalyzed Mizoroki–Heck reaction and allyl cross-coupling reaction with iodobenzene.[a]

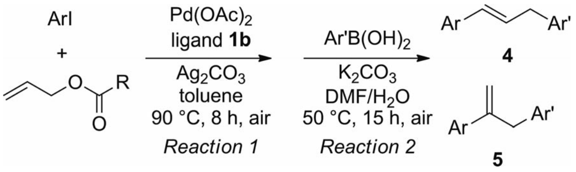


Entry	Temperature [°C] Reaction 1	Temperature [°C] Reaction 2	Yield of **4a** [%][b]
1[c]	80	r.t.	0(71)
2	80	r.t.	37(34)
3	80	50	68(0)
4	80	70	64(0)
5	90	50	71(0)
6	100	50	34(22)
7[d]	90	50	85(0)

[a] Reaction conditions: Reaction 1: Iodobenzene (0.5 mmol), allyl acetate (1.0 mmol), Pd(OAc)$_2$ (5 mol-%), ligand **1b** (5 mol-%), Ag$_2$CO$_3$ (0.3 mmol), PhMe (3 mL) for 8 h in air; Reaction 2: Phenylboronic acid (1.2 mmol), K$_2$CO$_3$ (2 mmol), DMF (1.5 mL), H$_2$O (0.5 mL) for 15 h in air. [b] Determined by ^{1}H NMR spectroscopy by using 2-methoxynaphthalene as an internal standard. NMR yield of **2** is shown in parentheses. [c] This reaction was carried out without the use of a ligand. [d] Allyl benzoate was used instead of allyl acetate.

Consequently, the scope of the aryl iodides and arylboronic acids was explored for 1,3-diarylpropenes under the optimized reaction conditions by using allyl benzoate or acetate. The use of iodobenzene with phenylboronic acid led to good yields of product **4a** with regioisomer **5a**[7] from intermediate **3** (**4a**/**5a** = 15:1; Table 3, Entry 1). The use of iodobenzene with 4-substituted arylboronic acids led to good yields of the corresponding unsymmetrical 1,3-diarylpropenes (Table 3, Entries 2–4). Moreover, 3,5-dimethylphenylboronic acid, 2-tolylboronic acid, and 1-naphthylboronic acid led to good yields (Table 3, Entries 5–7). We also tested the reaction of various aryl iodides with phenylboronic acid (Table 3, Entries 8–11). The corresponding unsymmetrical 1,3-diarylpropenes gave moderate to good yields by using 4-substituted and 3-substituted aryl iodides.

Table 3. Palladium-catalyzed Mizoroki–Heck reaction and allyl cross-coupling reaction.[a]



Entry	Ar	R	Ar′	Yield **4** + **5** [%][b]	Ratio **4**/**5**[c]
1	Ph	Ph	Ph	92	15 (**4a**):1
2	Ph	Me	4-MeC$_6$H$_4$	67	13 (**4b**):1
3[d]	Ph	Ph	4-MeOC$_6$H$_4$	58	9 (**4c**):1
4	Ph	Ph	4-ClC$_6$H$_4$	67	10 (**4d**):1
5[e]	Ph	Ph	3,5-Me$_2$C$_6$H$_3$	69	10 (**4e**):1
6	Ph	Ph	2-MeC$_6$H$_4$	67	10 (**4f**):1
7[f]	Ph	Ph	1-naph	68	17 (**4g**):1
8	4-MeC$_6$H$_4$	Me	Ph	70	14 (**4h**):1
9[g]	4-MeOC$_6$H$_4$	Ph	Ph	64	7 (**4i**):1
10	4-ClC$_6$H$_4$	Ph	Ph	51	12 (**4j**):1
11	3-MeC$_6$H$_4$	Me	Ph	85	13 (**4k**):1

[a] Reaction conditions: Reaction 1: Aryl iodide (0.5 mmol), allyl ester (1.0 mmol), Pd(OAc)$_2$ (5 mol-%), ligand **1b** (5 mol-%), Ag$_2$CO$_3$ (0.3 mmol), PhMe (3 mL) at 90 °C for 8 h in air; Reaction 2: Arylboronic acid (1.2 mmol), K$_2$CO$_3$ (2 mmol), DMF (1.5 mL), H$_2$O (0.5 mL) at 50 °C for 15 h in air. [b] Isolated yield. [c] Determined by ^{1}H NMR spectroscopy; *E*/*Z* ratio of **4** was >40:1. [d] Reaction 1 was carried out for 6 h. [e] Reaction 1 was carried out for 6 h and Reaction 2 was carried out for 24 h at 70 °C. [f] Reaction 2 was carried out at 70 °C. [g] Reaction 1 was carried out for 6 h and reaction 2 was carried out for 24 h.

Conclusions

In conclusion, we found that a hydrazone–Pd(OAc)$_2$-catalyzed Mizoroki–Heck-type reaction of allyl esters with aryl iodides in toluene followed by allyl cross-coupling with a variety of arylboronic acids in DMF/H$_2$O (3:1), all in air, provides unsymmetrical 1,3-diarylpropenes in moderate to good yields.

Experimental Section

General Procedure for the Palladium-Catalyzed Mizoroki–Heck and Allyl Cross-Coupling Reactions: To a mixture of aryl iodide (0.5 mmol), Ag$_2$CO$_3$ (0.3 mmol), Pd(OAc)$_2$ (25 µmol), and ligand **1b** (25 µmol) in PhMe (3.0 mL) was added allyl ester (1.0 mmol) at room temperature under an atmosphere of air. The mixture was stirred at 90 °C. After 8 h, the reaction mixture was filtered though Celite. The filtrate was concentrated under reduced pressure. To a mixture of arylboronic acid (1.2 mmol) and K$_2$CO$_3$ (2.0 mmol) in DMF (1.5 mL) and H$_2$O (0.5 mL) was added the residue at room temperature under an atmosphere of air. The mixture was stirred at 50 °C. After 15 h, the mixture was diluted with ethyl acetate and water. The organic layer was washed with brine, dried with MgSO$_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (hexane or hexane/ethyl acetate, 20:1).

Supporting Information (see footnote on the first page of this article): Characterization data and copies of the NMR spectra of the products.

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