# Ligand-Free Copper-Catalyzed Arylation of Olefins by the Mizoroki–Heck Reaction

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Received 1 September 2010; revised 19 October 2010

**Abstract:** A novel ligand-free copper-catalyzed Mizoroki–Heck cross-coupling reaction of various aryl iodides with olefins has been developed. Both the solvent and the base were found to have a fundamental influence on the efficiency of the transformation in the presence of 10 mol%  $Cu_2O$ , with DMF and tetramethylammonium bromide (TMAB) being the optimal solvent and base, respectively. As a result, a set of the corresponding *E*-internal olefins were obtained selectively in moderate to good yields.

Key words: ligand-free, copper-catalyzed, Mizoroki–Heck reaction, cross-coupling, *E*-internal olefins

The Mizoroki–Heck cross-coupling reaction<sup>1</sup> is an important part of the synthetic chemist's toolbox, and has been applied to a huge variety of different substrates.<sup>2</sup> One of the benefits of the Mizoroki-Heck reaction is its outstanding trans-selectivity. Traditionally, palladium-catalyzed cross-coupling reactions have been proven to be extremely powerful synthetic tools and their scope continues to increase year after year.<sup>3</sup> Ligand-free palladium-catalyzed Mizoroki-Heck reaction has been studied for the past few years.<sup>4</sup> Later, significant efforts have been made in order to expand the scope of Heck-type coupling reaction by employing various transition metal catalysts.<sup>5</sup> However, it is a considerable drawback that an expensive metal catalyst (palladium, rhodium, iridium, ruthenium, etc.) is often lost at the end of the reaction. To achieve the recyclability of the metal catalyst, Xiao<sup>6</sup> and Wang<sup>7</sup> used room temperature ionic liquid immobilized catalysts as recyclable reaction system. Nevertheless, ionic liquids, especially imidazolium-based systems containing BF<sub>4</sub> anion, are toxic in nature because they liberate hazardous HF, and their high cost and disposability make their utility limited.<sup>8</sup> Recently, Yun and co-workers have also reviewed environmental fate and toxicity of ionic liquids.9 Moreover, the use of cheaper metal as a catalyst for the Heck-type reaction has been gaining attention more and more.<sup>10</sup> On the other hand, the operationally and economically more advantageous ligand-free Heck reaction catalyst systems remain extremely rare.

Recently, the use of copper salts as catalysts for the reaction has gained much prominence in organic synthesis due to their economic attractiveness, good functional group tolerance, and scalability in large-scale synthetic procedures.<sup>11</sup> To the best of our knowledge, a general and efficient ligand-free copper-catalyzed methodology for the arylation of olefins by the Mizoroki–Heck reaction has not been developed to date. We herein report that ligandfree copper-catalyzed arylation of olefins by the Mizoroki– Heck reaction selectively provide *E*-internal olefin derivatives with yields ranging from moderate to good.

The model coupling reaction between iodobenzene (1a) and *n*-butyl acrylate (2a) was conducted to screen the optimal reaction conditions, including bases, solvents, and catalysts and the results are listed in Table 1. Initially, considering that the catalyst always plays important roles in metal-catalyzed chemistry, the reaction conditions using CuI as the catalyst, Et<sub>3</sub>N as the base, and DMF as the solvent was adopted to study the synthesis of *n*-butyl (*E*)-cinnamate (**3aa**). It was observed that the desired product **3aa** was obtained in 19% yield (Table 1, entry 1). Encouraged by this promising result, the reaction conditions were further optimized including the effect of catalysts, bases, and solvents.

 
 Table 1
 Screening Conditions for Heck reaction Between Iodobenzene and *n*-Butyl Acrylate<sup>a</sup>

	+	catalyst Bu solvent, base		On-Bu
1a	2a		38	aa
Entry	Catalyst	Base	Solvent	Yield (%) <sup>t</sup>
1	CuI	Et <sub>3</sub> N	DMF	19
2	CuBr	Et <sub>3</sub> N	DMF	21
3	CuCl	Et <sub>3</sub> N	DMF	79
4	Cu <sub>2</sub> O	Et <sub>3</sub> N	DMF	85
5	CuBr <sub>2</sub>	Et <sub>3</sub> N	DMF	<5
6	Cu(OTf) <sub>2</sub>	Et <sub>3</sub> N	DMF	78
7	CuCl <sub>2</sub>	Et <sub>3</sub> N	DMF	53
8	Cu(OAc) <sub>2</sub>	Et <sub>3</sub> N	DMF	35
9	Cu <sub>2</sub> O	K <sub>2</sub> CO <sub>3</sub>	DMF	85
10	Cu <sub>2</sub> O	K <sub>2</sub> CO <sub>3</sub>	DMSO	NR

SYNTHESIS 2011, No. 2, pp 0213–0216 Advanced online publication: 26.11.2010 DOI: 10.1055/s-0030-1258338; Art ID: F16010SS © Georg Thieme Verlag Stuttgart · New York

zene and n-Butyl Acrylate<sup>a</sup> (continued)

catalvst On-Bu solvent, base ∩*n-*Ru 2a 3aa 1a Solvent Yield (%)<sup>b</sup> Entry Catalyst Base 11 Cu<sub>2</sub>O K<sub>2</sub>CO<sub>3</sub> toluene 68 12 NR  $Cu_2O$  $K_2CO_3$ xylene 13  $Cu_2O$ K<sub>2</sub>CO<sub>3</sub> **EtOH** NR<sup>c</sup> 14 K<sub>2</sub>CO<sub>3</sub> MeCN NR<sup>c</sup>  $Cu_2O$ 15  $Cu_2O$ K<sub>2</sub>CO<sub>3</sub> 1,4-dioxane 39 16 Cu<sub>2</sub>O K<sub>2</sub>CO<sub>3</sub> sulfolane 19 17  $Cu_2O$ K<sub>2</sub>CO<sub>3</sub> HMPA 15 18 Cu<sub>2</sub>O K<sub>2</sub>CO<sub>3</sub> PEG-400 42 19 Cs<sub>2</sub>CO<sub>3</sub> DMF <5  $Cu_2O$ 20 NaOAc  $Cu_2O$ DMF 60 21 LiOH 40  $Cu_2O$ DMF 22  $Cu_2O$ LiF DMF 37 **TMAB**<sup>d</sup> 23 DMF 87  $Cu_2O$ 24  $Cu_2O$ TMAB DMF 87<sup>e</sup> 25 Cu<sub>2</sub>O TMAB DMF 72<sup>f</sup>

<sup>a</sup> All reactions were run with iodobenzene (**1a**; 0.30 mmol), *n*-butyl acrylate (2a; 0.45 mmol), catalyst (10 mol%), base (0.60 mmol) and 4 Å MS (100 mg) in anhyd solvent (2 mL) at 120 °C for 30 h under N<sub>2</sub> atmosphere.

<sup>b</sup> Isolated yield. NR = no reaction.

<sup>c</sup> Under reflux.

<sup>d</sup> TMAB: tetramethylammonium bromide.

<sup>e</sup> With 20 mol% Cu<sub>2</sub>O.

<sup>f</sup> With 5 mol% Cu<sub>2</sub>O.

First, a series of copper salts such as CuBr, CuCl, Cu<sub>2</sub>O,  $CuBr_2$ ,  $Cu(OTf)_2$ ,  $CuCl_2$ , and  $Cu(OAc)_2$  were examined (Table 1, entries 2–8). To our delight, the coupling reaction proceeded smoothly and generated the desired product *n*-butyl (E)-cinnamate (3aa) in 85% yield, representing one of the best results when 10 mol% of Cu<sub>2</sub>O was used as catalyst with ligand-free than other copper salts tested in DMF under nitrogen atmosphere (Table 1, entry 4). Next, both base and solvent were tested. Among all the bases screened, TMAB was superior to some others such as Et<sub>3</sub>N, K<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, NaOAc, LiOH, LiF, and TMAB (Table 1, entries 1, 9, 19-23). The choice of solvent was also vital to the success of the catalytic reaction. DMF appeared to be the best choice among the common solvents such as DMSO, toluene, xylene, ethanol, acetonitrile, 1,4-dioxane, sulfolane, HMPA, and PEG-400 (Table 1, entries 9-18). In addition, the influence of the amount of catalyst on the yields was also stud-

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With optimal conditions in hand, the scope of coppercatalyzed coupling of various aryl iodides with different olefins was investigated and the results are summarized in Table 2.

mol% Cu<sub>2</sub>O was used in the system (Table 1, entry 25).

Table 2 Ligand-Free Copper-Catalyzed Mizoroki-Heck Reaction<sup>a</sup> Cu<sub>2</sub>O (10 mol%)

Arl	+ =	ТМА	B . DMF	Ar			
1	R <sup>2</sup> 2		_ ,	3	К' 3		
Entry	Aryl iodide 1	Olefin	2	Product	Yield (%) <sup>b</sup>		
	Ar	$\mathbb{R}^1$	$\mathbb{R}^2$				
1	Ph (1a)	Н	CO <sub>2</sub> <i>n</i> -Bu ( <b>2a</b> )	3aa	87		
2	$2\text{-MeOC}_{6}\text{H}_{4}\left(\mathbf{1b}\right)$	Н	2a	3ba	82		
3	$4\text{-}\text{MeOC}_{6}\text{H}_{4}\left(\mathbf{1c}\right)$	Н	2a	3ca	86		
4	$4\text{-HOC}_{6}\text{H}_{4}\left(\mathbf{1d}\right)$	Н	2a	3da	83		
5	$2\text{-HOC}_{6}\text{H}_{4}\left(\mathbf{1e}\right)$	Н	2a	3ea	77		
6	$2 - O_2 NC_6 H_4 (1f)$	Н	2a	3fa	79		
7	$3-O_{2}NC_{6}H_{4}(1g)$	Н	2a	3ga	86		
8	$4-O_{2}NC_{6}H_{4}(1\mathbf{h})$	Н	2a	3ha	92		
9	$4-BrC_{6}H_{4}(1i)$	Н	2a	3ia	77		
10	$4\text{-MeC}_{6}\text{H}_{4}\left(\mathbf{1j}\right)$	Н	2a	3ja	86		
11	$2-H_2NC_6H_4(1\mathbf{k})$	Н	2a	3ka	71		
12	2,4,6-Me <sub>3</sub> C <sub>6</sub> H <sub>2</sub> (11)	Н	2a	3la	65		
13	1b	Me	$CO_2Me(\mathbf{2b})$	3bb	80		
14	1c	Me	2b	3cb	87		
15	1f	Me	2b	3fb	79		
16	1a	Н	$CO_2Me(2c)$	3ac	84		
17	1c	Н	2c	3cc	83		
18	1f	Н	2c	3fc	83		
19	1h	Н	2c	3hc	90		
20	1a	Н	$CO_2Et(2d)$	3ad	89		
21	1h	Н	2d	3hd	91		
22	1j	Н	2d	3jd	82		
23	1a	Н	Ph (2e)	3ae	65		
24	1c	Н	2e	3ce	76		
25	1j	Н	2e	3je	71		
<sup>a</sup> All reactions were run with aryl iodide <b>1</b> (0.30 mmol), olefin <b>2</b> (0.45 mmol), Cu <sub>3</sub> O (10 mol%), TMAB (0.60 mmol), and 4Å MS (100 mg)							

in anhyd DMF (2 mL) at 120 °C for 30 h under N2 atmosphere.

<sup>b</sup> Isolated yield.

 $R^2$ 

As shown in Table 2, aryl iodides bearing either electrondonating or electron-withdrawing groups on the aromatic ring were investigated under the optimal conditions. In general, the substitution groups on the aromatic ring have no obvious effect on the yields. It is worth mentioning that 4-nitroiodobenzene (1h) reacted smoothly with 2a, 2c, 2d to afford **3ha**, **3hc** and **3hd** in 92%, 90%, and 91% yield, respectively (Table 2, entries 8, 19 and 21). Next, the chemoselective reaction in the presence of unprotected reactive functional groups, such as OH, NH<sub>2</sub> also proved to be successful. The corresponding products of 3da, 3ea, and 3ka were obtained in good yields (Table 2, entries 4, 5, and 11). Furthermore, the bromo group was left untouched in the coupling reaction of the substrate 1-bromo-4-iodobenzene (1i) with 2a to give the product 3ia (Table 2, entry 9).

This method was also successful with various olefins to afford the corresponding *E*-internal olefins **3** in moderate to good yields under standard conditions. Compared to acrylate 2a-d, styrene (2e) reacted with 1a, 1c, and 1j sluggishly compared to the olefins containing electron-withdrawing groups and gave comparatively lower yields (Table 2, entries 23–25).

The steric effect in our system was then examined. A monosubstitution on the *ortho-*, *meta-* and *para-*position of aryl iodides (Table 2, entries 2–8) had some effects on the yields of the reaction. For example, **2a** reacted with aryl iodides, such as 2-nitroiodobenzene (**1f**), 3-nitroiodobenzene (**1g**), and 4-nitroiodobenzene (**1h**) efficiently and afforded **3fa**, **3ga**, and **3ha** in 79%, 86%, and 92% yield, respectively (Table 2, entries 6–8). Interestingly, using the present protocol, the larger sterically hindered aryl iodide such as 2,4,6-trimethyliodobenzene (**1l**) also reacted with **2a**, providing **3la** in 65% yield (Table 2, entry 12).

Next, the Heck reaction of aryl bromides with *n*-butyl acrylate was also examined (Scheme 1). Unfortunately, the present catalytic system was less effective when aryl bromides were used. The treatment of activated aryl bromides **1n**–**p** with *n*-butyl acrylate afforded the corresponding products in lower yields. Attempt to couple 1-bromo-4-methylbenzene with *n*-butyl acrylate failed.

Finally, the Heck reaction in a 2.2:1:0.01 molar ratio of *n*butyl acrylate to 4,4'-diiodobiphenyl (**1m**) to  $Cu_2O$  in DMF was investigated (Scheme 2). As expected, the reaction proceeded using the present protocol and the desired product **3ma** was obtained in moderate yield.

In summary, a ligand-free copper-catalyzed Mizoroki– Heck reaction has been developed for the selective synthesis of *E*-internal olefins in moderate to good yields in the presence of TMAB in DMF under nitrogen atmosphere. Although the reactivity of  $Cu_2O$  under these conditions is limited only to the coupling of aryl iodides and olefins, this limitation is more than offset by the benefit of using a ligand-free as well as inexpensive catalyst. Work to probe the detailed mechanism and apply the reaction in organic synthesis is currently underway.

All chemicals were either purchased or purified by standard techniques without special mention. The molecular sieve (4Å) powder has to be activated before using. IR spectra were recorded on a Bruker EQUINOX55 spectrometer. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra were recorded on a Bruker 300 spectrometer or Bruker 500 spectrometer using CDCl<sub>3</sub> as the solvent with TMS as an internal standard at r.t. Mass spectrometric analysis was performed by GC/MS analysis (Shimadzu GC/MS-QP2010). Elemental analyses were determined on a Carlo-Erba 1108 instrument. All reactions were conducted using standard Schlenk techniques. Column chromatography was performed using EM Silica gel 60 (300–400 mesh).







Scheme 2 Heck reaction of 4,4'-diiodobiphenyl with *n*-butyl acrylate

#### **E-Internal Olefins 3; General Procedure**

A mixture of aryl iodide **1** (0.30 mmol), olefin **2** (0.45 mmol),  $Me_4NBr$  (0.6 mmol),  $Cu_2O$  (10 mol%), and activated 4 Å MS powder (100 mg) in anhyd DMF (2 mL) was placed in a Schlenk tube. After stirring for 0.5 h at r.t., the solution was heated to 120 °C for 30 h under  $N_2$  atmosphere. After completion of the reaction (monitored by TLC), the reaction mixture was then allowed to cool to r.t. and added to  $H_2O$  (20 mL) and extracted with  $CH_2Cl_2$  (3 × 20 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel with EtOAc-petroleum ether (bp 60–90 °C) to give the desired product **3** (Table 2).

## Methyl (E)-2-Methyl-3-(2-nitrophenyl)acrylate (3fb)

Yield: 79%; yellow oil.

IR (KBr): 2984, 1737, 1528, 1373, 1237, 1118, 1045, 939, 846, 789, 712  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 8.12-8.15 (m, 1 H, ArH), 7.90 (s, 1 H, C=CH), 7.63-7.68 (m, 1 H, ArH), 7.48-7.53 (m, 1 H, ArH), 7.35-7.37 (m, 1 H, ArH), 3.84 (s, 3 H, OCH<sub>3</sub>), 1.90 (s, 3 H, CH<sub>3</sub>).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 168.1 (C=O), 147.8 (ArNO<sub>2</sub>), 135.6 (C=CH), 133.2, 131.8, 131.3, 130.2, 129.0, 124.9, 52.2 (OCH<sub>3</sub>), 14.0.

MS (EI, 70 eV): m/z (%) = 221 (0.19, [M<sup>+</sup>]), 144 (25), 120 (100), 115 (32), 92 (52), 77 (28), 65 (21).

Anal. Calcd for  $C_{20}H_{21}NO_2$ : C, 59.73; H, 5.01. Found: C, 59.79; H, 4.96.

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

## Acknowledgment

We are grateful for financial support from the National Key Technology R & D Program (No. 2007BAI34B00), the National Natural Science Foundation of China (No. 21072153), the Natural Science Foundation of Zhejiang Province (No. Y4080107), and the Wenzhou Science & Technology Bureau Program (No. G20090076).

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