



## Palladium-catalyzed arylation of methyl 2-(acetoxymethyl)acrylate: a convenient synthesis of rearranged Morita–Baylis–Hillman acetates

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### ABSTRACT

Palladium-catalyzed arylation of methyl 2-(acetoxymethyl)acrylate with aryl iodides afforded the primary acetates of Morita–Baylis–Hillman adducts in good yields with high stereoselectivity under mild conditions (50 °C).

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Very recently, a palladium-catalyzed chelation-assisted arylation of allyl acetate has been examined extensively to provide cinnamyl acetate via the selective  $\beta$ -H elimination process<sup>1,2</sup> instead of  $\beta$ -acetoxymethyl elimination.<sup>3</sup> As shown in Scheme 1, many research groups have reported the arylation of allyl acetate with various arene sources;<sup>1,2</sup> however, there is no precedent reports on the arylation of allyl acetate bearing an ester group at the 2-position via the selective  $\beta$ -H elimination process, to the best of our knowledge.<sup>3e–g</sup>

During the studies on the palladium-catalyzed oxidative arylation of alkenes with arenes,<sup>4</sup> we presumed that the primary acetate of Morita–Baylis–Hillman (MBH) adduct **2a** could be synthesized efficiently via a Pd-catalyzed chelation-assisted arylation of methyl 2-(acetoxymethyl)acrylate (**1a**),<sup>5,6</sup> as shown in Scheme 1. The primary acetate **2a** has been prepared most frequently via the rearrangement of an acetoxy group from the corresponding secondary MBH acetate,<sup>7</sup> and this compound has been widely used in organic synthesis.<sup>7i–k</sup>

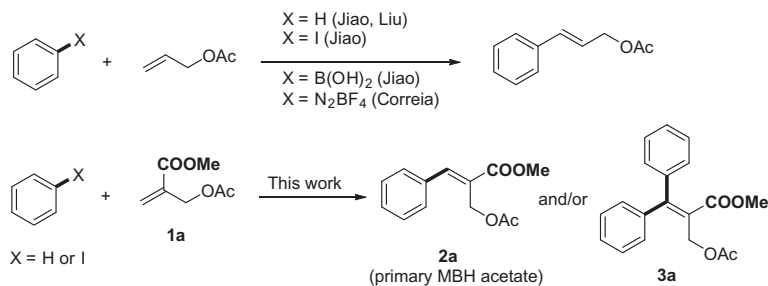
The starting material **1a** was prepared by the acetylation of the MBH adduct between formaldehyde and methyl acrylate as reported.<sup>5</sup> At the outset of our experiment, we examined the reaction of **1a** and benzene under the conditions of Jiao<sup>1b</sup> and Liu.<sup>1a</sup> However, the results of both conditions were disappointing. Compound **2a** was obtained in very low yields, 20% and 9% respectively, as shown in Table 1 (entries 1 and 2). Thus, we examined the reaction

of **1a** and benzene in the presence of Pd(TFA)<sub>2</sub>/AgOAc (2.5 equiv)/PivOH (entry 3).<sup>4a–e</sup> The yield of **2a** increased dramatically to 87%. Under the condition, a diphenyl compound **3a** was not formed even in the presence of an excess amount of AgOAc (6.0 equiv) after 48 h. Although compound **2a** was produced as an *E/Z* mixture (12:1), we examined the reaction with other arenes such as *p*-xylene, *o*-dichlorobenzene, *m*-dichlorobenzene, and *m*-xylene. The reaction of **1a** and *p*-xylene (entry 4) afforded **2b** in high yield (89%). However, a regioisomeric problem was observed when we used *o*-dichlorobenzene and *m*-dichlorobenzene (entries 5 and 6), although the combined yields of products were high (90–92%). When we used *m*-xylene (entry 7), an inseparable regioisomeric mixture was obtained in moderate yield (62%). The problematic regioselectivity in combination with unsatisfactory stereoselectivity reduced the synthetic applicability of this method.

Thus, we decided to examine the reaction of **1a** and iodobenzene, and the results of optimization of reaction conditions are summarized in Table 2. When we examined the conditions of Jiao employing an excess amount (2.0 equiv) of allyl acetate,<sup>2a</sup> compound **2a** was obtained in 80% (entry 1) with a similar stereoselectivity (*E/Z* = 10:1). However, compound **1a** is a valuable starting material as compared to simple allyl acetate, thus we examined the reaction with an equimolar amount of **1a** in the presence of 2.0 equiv of iodobenzene (entry 2). Then, the yield of **2a** decreased to 35%, and the results stated that both compound **1a** and allyl acetate might be destroyed to some extent under the reaction conditions. The yield of **2a** was not improved by using an excess amount of Ag<sub>2</sub>CO<sub>3</sub> (entry 3). In these respects, we have to consider other reaction conditions. Literature survey suggested that the condition

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**Table 1**  
Pd-catalyzed oxidative arylation of compound **1a**<sup>a</sup>

Entry	Conditions	Product <sup>b</sup> (%)
1	Pd(OAc) <sub>2</sub> (5 mol%), Ag <sub>2</sub> CO <sub>3</sub> (0.6 equiv), CH <sub>3</sub> (CH <sub>2</sub> ) <sub>3</sub> COOH (16 equiv) BQ (2.0 equiv), benzene (100 equiv), reflux, 36 h	<b>2a</b> (20)
2	Pd(OAc) <sub>2</sub> (10 mol %), AgOAc (2.0 equiv), DMSO (3.0 equiv) benzene (60 equiv), reflux, 12 h	<b>2a</b> (9)
3	Pd(TFA) <sub>2</sub> (5 mol %), AgOAc (2.5 equiv), PivOH (6.0 equiv) benzene (60 equiv), reflux, 12 h	<b>2a</b> (87) <sup>c</sup>
4	Pd(TFA) <sub>2</sub> (5 mol %), AgOAc (2.5 equiv), PivOH (6.0 equiv) <i>p</i> -xylene (60 equiv), 110 °C, 12 h	<b>2b</b> (89) <sup>d</sup>
5	Pd(TFA) <sub>2</sub> (5 mol %), AgOAc (2.5 equiv), PivOH (6.0 equiv) <i>o</i> -dichlorobenzene (60 equiv), 110 °C, 12 h	<b>2c-meta</b> (52) <sup>e</sup> <b>2c-ortho</b> (40) <sup>e</sup>
6	Pd(TFA) <sub>2</sub> (5 mol %), AgOAc (2.5 equiv), PivOH (6.0 equiv) <i>m</i> -dichlorobenzene (60 equiv), 110 °C, 12 h	<b>2d-meta</b> (73) <sup>e</sup> <b>2d-ortho</b> (17) <sup>e</sup>
7	Pd(TFA) <sub>2</sub> (5 mol %), AgOAc (2.5 equiv), PivOH (6.0 equiv) <i>m</i> -xylene (60 equiv), 110 °C, 12 h	<b>2e-meta</b> <sup>e,f</sup> <b>2e-ortho</b> <sup>e,f</sup>

<sup>a</sup> Substrate **1a** (0.5 mmol).

<sup>b</sup> Isolated yield.

<sup>c</sup> *E/Z* ratio = 12:1.

<sup>d</sup> *E/Z* ratio = 11:1.

<sup>e</sup> Variable amount of *Z* isomer (ca. 5–10%) was contaminated.

<sup>f</sup> An inseparable mixture of **2e-meta** and **2e-ortho** (1:1) was obtained in 62% yield.

**Table 2**  
Optimization of Pd-catalyzed arylation of **1a** with iodobenzene

Entry	Conditions	Product (%)
1	<b>1a</b> (2.0 equiv), PhI (1.0 equiv), Pd(OAc) <sub>2</sub> (5 mol %) Ag <sub>2</sub> CO <sub>3</sub> (0.6 equiv), benzene, O <sub>2</sub> balloon, reflux, 10 h	<b>2a</b> (80) + <b>3a</b> (0)
2	<b>1a</b> (1.0 equiv), PhI (2.0 equiv), Pd(OAc) <sub>2</sub> (5 mol %) Ag <sub>2</sub> CO <sub>3</sub> (0.6 equiv), benzene, O <sub>2</sub> balloon, reflux, 12 h	<b>2a</b> (35) + <b>3a</b> (0)
3	<b>1a</b> (1.0 equiv), PhI (2.0 equiv), Pd(OAc) <sub>2</sub> (5 mol %) Ag <sub>2</sub> CO <sub>3</sub> (3.0 equiv), benzene, O <sub>2</sub> balloon, reflux, 12 h	<b>2a</b> (23) + <b>3a</b> (20)
4	<b>1a</b> (1.0 equiv), PhI (1.1 equiv), Pd(OAc) <sub>2</sub> (5 mol %) AgOAc (1.1 equiv), AcOH (50 equiv), reflux, 1 h	<b>2a</b> (82) <sup>d</sup> + <b>3a</b> (9)
5 <sup>b</sup>	<b>1a</b> (1.0 equiv), PhI (2.1 equiv), Pd(OAc) <sub>2</sub> (5 mol %) AgOAc (3.0 equiv), AcOH (50 equiv), reflux, 3 h	<b>2a</b> (<5) + <b>3a</b> (81)
6 <sup>c</sup>	<b>1a</b> (1.0 equiv), PhI (1.1 equiv), Pd(OAc) <sub>2</sub> (5 mol %) AgOAc (1.1 equiv), AcOH (50 equiv), 50 °C, 5 h	<b>2a</b> (86) <sup>d</sup> + <b>3a</b> (0)
7	<b>1a</b> (1.0 equiv), PhI (1.1 equiv), Pd(OAc) <sub>2</sub> (5 mol %) AgOAc (1.1 equiv), AcOH (50 equiv), 25 °C, 6 h	<b>2a</b> (68) <sup>d</sup> + <b>3a</b> (0)

<sup>a</sup> *E/Z* = 13:1 (based on <sup>1</sup>H NMR spectrum).

<sup>b</sup> Selected as condition B.

<sup>c</sup> Selected as condition A.

<sup>d</sup> *E/Z* >32:1 (based on <sup>1</sup>H NMR spectrum).

of Chen could be a choice.<sup>8,4a</sup> According to Chen's condition, the reaction of **1a** and iodobenzene was examined in the presence of Pd(OAc)<sub>2</sub>/AgOAc/AcOH (entry 4), and compound **2a** was obtained in good yield (82%). It is interesting to note that diaryl compound

**3a** could be synthesized in high yield (81%) by increasing the amount of iodobenzene and AgOAc (entry 5).<sup>9,10</sup> However, the moderate stereoselectivity (*E/Z* = 13:1) was still a problem, although we could increase the yield of **2a** up to 82% (entry 4).

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