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COMMUNICATION

Palladium-catalyzed formal aryacylation of allenes employing acid chlorides and arylboronic acids

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Palladium-catalyzed formal aryacylation of allenes using acid chlorides and arylboronic acids has been achieved. The reaction afforded the corresponding α,β -unsaturated ketones regio- and stereoselectively.

The addition of carbonyl compounds to carbon–carbon unsaturated bonds is an efficient method to functionalize unsaturated compounds.¹ To date, the addition of aldehydes (hydroacylation),² formamides (hydrocarbamoxylation),³ formates (hydroesterification),⁴ and acid chlorides (chloroacylation)⁵ to carbon–carbon unsaturated bonds have been reported. The addition of ketone, namely carboacylation, is also an efficient method to synthesize highly functionalized ketones. However, the activation of acyl–carbon bonds of ketones has been difficult. To achieve carboacylation, directing groups⁶ or strained structures^{7,8} were required. Therefore, formal carboacylation using a carbon nucleophile and a carbonyl electrophile as a ketone equivalent is desirable as an alternative method. The reactions of organometallic reagents with carbon–carbon unsaturated bonds followed by trapping with acid chlorides as the electrophile have been investigated.⁹ However, highly reactive organometallic reagents such as organomagnesium or organozinc reagents or the presence of directing groups in unsaturated compounds were indispensable to control the reactivity and regioselectivity. There is only one precedent to data on acylmetalation strategy; Miura et al. reported the Rh-catalyzed carboacylation of norbornene using acid anhydrides and organoboron reagents.^{10,11}

Allenes are valuable substrates in transition-metal-catalyzed reactions.¹² In particular, allenes can be easily inserted to Pd–C bonds to form the corresponding π -allyl Pd species.^{12a} Cheng and co-workers reported the acylmetalation of allenes using acid chlorides with diborane, disilane, and distannane.¹³ Recently, we reported the formal hydroacylation of allenes using acid chlorides and hydrosilanes.¹⁴ We envisioned that the use of carbon nucleophiles in place of hydrosilanes would achieve the formal carboacylation of allenes. In this paper, we describe the palladium-catalyzed formal aryacylation of allenes using acid

Table 1. Optimization of reaction conditions.^a

Entry	Changes	Total yield of 4a (%) ^b	(<i>E</i>)- 4a : other isomers ^c	5 (mmol) ^f
1	standard condition	86 (80) ^d	96:4	0.034
2	without Pd ₂ (dba) ₃	0	-	0
3	addition of PPh ₃ ^e	0	-	0.22
4	in toluene as a solvent	62	88:12	0.027
5	in MeCN as a solvent	0	-	0
6	without CuCl	31	96:4	0.014
7	without H ₂ O	6	88:12	0.005
8	H ₂ O (8.0 equiv)	66	96:4	0.040
9	PhB(pin) ^f	0	-	0
10	PhBF ₃ K	0	-	0.001

^a Reaction conditions: 3-phenylpropionyl chloride (**1a**, 0.40 mmol), cyclohexylallene (**2a**, 0.20 mmol, yield and equiv are based on this amount), PhB(OH)₂ (**3a**, 0.30 mmol), Pd₂(dba)₃·CHCl₃ (0.010 mmol, 5.0 mol %), CuCl (0.020 mmol, 10 mol %), K₃PO₄ (0.40 mmol), H₂O (4.0 equiv, 0.80 mmol) in toluene/MeCN = 9/1 (v/v, 4.0 mL), at 50 °C, for 3 h. ^b Yield by the GC internal standard method. ^c Determined by GC. ^d Isolated yield of pure (*E*)-**4a**. ^e P/Pd = 2. ^f pin = pinacolato

chlorides and arylboronic acids. Notably, no directing groups were required in the present reaction and various α,β -unsaturated ketones are obtained regio- and stereoselectively.

First, the reaction of 3-phenylpropionyl chloride (**1a**), cyclohexylallene (**2a**) and phenylboronic acid (**3a**) was carried out in the presence of a catalytic amount of Pd₂(dba)₃ (dba = dibenzylideneacetone) and CuCl with K₃PO₄ and H₂O in toluene/MeCN (9/1, v/v) at 50 °C (Table 1). Under the standard reaction conditions (entry 1), (*E*)-**4a** was obtained with high regio- and stereoselectivity (96/4). As a side product, a small amount of ketone **5**, which was formed by the Suzuki–Miyaura coupling of **1a** with **3a**,¹⁵ was detected. Notably, styrene formation via the decarbonylation of **1a** followed by β -hydrogen

elimination was not observed. With a column chromatography, pure (*E*)-**4a** was isolated in 80% yield. Without Pd₂(dba)₃, the reaction did not proceed at all (entry 2). In this reaction, the addition of auxiliary ligands such as PPh₃ inhibited the formation of **4a** and only **5** was obtained in 73% yield (0.22 mmol) based on **3a** (entry 3). When MeCN was removed from the reaction system (only toluene was used as the solvent), both the yield and selectivity decreased considerably (entry 4). In contrast, the use of MeCN as the solvent did not afford **4a** at all (entry 5). In the Suzuki-Miyaura coupling, it was known that the addition of a Cu salt promotes the coupling reaction.^{15d,16} Thus, without CuCl, the yield of **4a** decreased to 31% (entry 6). The addition of H₂O was also found to be important in this reaction; the yield of **4a** was very low in the absence of H₂O (entry 7). In contrast, when the amount of H₂O was increased to 8.0 equiv (1.6 mmol), the yield of **4a** decreased and that of **5** increased (entry 8; cf. entry 1). The use of PhB(pin) or PhBF₃K instead of PhB(OH)₂ did not afford **4a** at all (entries 9 and 10).

Various acid chlorides reacted with **2a** and **3a** (Table 2). The reactions of aliphatic acid chlorides (**1b–g**) gave the corresponding products (**4b–g**) in good to high yields (entries 1–6). Ether (entry 3) and ester (entry 4) functional groups were tolerated in the reaction. In the case of cyclohexanecarbonyl chloride (**1f**), the desired product was obtained in a moderate yield in the presence of 8.0 equiv of H₂O (entry 5). In general, less reactive acid chlorides **1** tend to require comparatively more amount of H₂O to ensure good yields. The reaction with pivaloyl

Table 2. Scope of acid chlorides.^a

Entry	Acid chloride 1	Product (<i>E</i>)- 4	H ₂ O (equiv)	Yield (%) ^b
1			6.0	80
2			4.0	80
3			4.0	84
4			4.0	69
5			8.0	60
6			6.0	57 ^c
7			6.0	73
8			8.0	66
9			6.0	72

^a Reaction conditions: acid chloride (**1**, 0.40 mmol), **2a**, (0.20 mmol, yield and equiv are based on this amount), **3a** (0.30 mmol), Pd₂(dba)₃·CHCl₃ (0.010 mmol, 5.0 mol %), CuCl (0.020 mmol, 10 mol %), K₃PO₄ (0.40 mmol), H₂O (x equiv) in toluene/MeCN = 9/1 (v/v, 4.0 mL), at 50 °C, for 3 h. ^b Isolated yield of (*E*)-**4b–j**. ^c Mixture of isomers (*E/Z* = 87/13).

Table 3. Scope of allenes.^a

Entry	Allene 2	Product (<i>E</i>)- 4	H ₂ O (equiv)	Yield (%) ^b
1 ^c			3.5	60
2			6.0	79
3			8.0	90
4			5.0	38
5			5.0	81
6			5.0	91

^a Reaction conditions: **1a** (0.40 mmol), allene (**2**, 0.20 mmol, yield and equiv are based on this amount), **3a** (0.30 mmol), Pd₂(dba)₃·CHCl₃ (0.010 mmol, 5.0 mol %), CuCl (0.020 mmol, 10 mol %), K₃PO₄ (0.40 mmol), H₂O (x equiv) in toluene/MeCN = 9/1 (v/v, 4.0 mL), at 50 °C, for 3 h. ^b Isolated yield of (*E*)-**4k–p**. ^c **3a** (0.40 mmol).

chloride afforded the *E/Z* mixture of the products in moderate yield with a ratio of *E/Z* = 87/13 (entry 6). Benzoyl chloride derivatives (**1h–j**) with electron-donating (**1i**) and electron-withdrawing substituents (**1j**) afforded the corresponding products in good yields (entries 7–9).

Next, various allenes were reacted with **1a** and **3a** in the presence of suitable amounts of H₂O (Table 3). Although the reaction of **2b** with a primary alkyl group gave the product (**4k**) in moderate yield (entry 1), those of **2c** and **2d** bearing a secondary and a tertiary alkyl group afforded the corresponding products (**4l** and **4m**) in high yields (entries 2 and 3). The reaction of phenylallene (**2e**) gave **4n** in a low yield (entry 4). 1,1-Disubstituted (**2f**) and 1,3-disubstituted (**2g**) allenes successfully gave the corresponding products (**4o** and **4p**) in high yields (entries 5 and 6).

Various arylboronic acids (**3**) afforded the corresponding α,β -unsaturated ketones (**4**) in high yields (Table 4). In the case of a reactive arylboronic acid bearing the electron-donating substituent (**3b**), the corresponding product was obtained in 82% yield in the presence of a smaller amount (2.0 equiv) of H₂O (entry 1). On the other hand, more H₂O (5–9 equiv) was beneficial to realize high yields with less reactive **3c–g** bearing electron-withdrawing substituents (entries 2–6). Under the reaction conditions, chloro (**3d**), bromo (**3e**), cyano (**3f**), and methoxycarbonyl (**3g**) functionalities on the phenyl rings remained intact (entries 3–6). The reaction of 1-naphthylboronic acid (**3h**) also afforded the product in 89% yield (entry 7). More reactive (*E*)-styrylboronic acid (**3i**) gave the corresponding product (**4x**) in a moderate yield, even without the addition of CuCl to the catalyst system.

A plausible catalytic cycle is shown in Scheme 1. First, the oxidative addition of an acid chloride (**1**) to Pd(0) species **A**

Table 4. Scope of Boronic acids^a.

entry	boronic acid 3	product (<i>E</i>)- 4	H ₂ O (equiv)	yield (%) ^b
1			2.0	82
2	3b : R = MeO	4q		
3	3c : R = F	4r	7.0	87
4	3d : R = Cl	4s	5.0	90
5	3e : R = Br	4t	7.0	84
6	3f : R = CN	4u	7.0	73
6	3g : R = COOMe	4v	9.0	79
7			7.0	89
8 ^c			6.0	62
	3i	4x		

^a Reaction conditions: **1a** (0.40 mmol), **2a** (0.20 mmol, yield and equiv are based on this amount), boronic acid (**3**, 0.30 mmol), Pd₂(dba)₃·CHCl₃ (0.010 mmol, 5.0 mol %), CuCl (0.020 mmol, 10 mol %), K₃PO₄ (0.40 mmol), H₂O (x equiv) in toluene/MeCN = 9/1 (v/v, 4.0 mL), at 50 °C, for 3 h. ^b Isolated yield of (*E*)-**4q-x**. ^c Two equiv of **3i** was used without CuCl.

affords an acylpalladium species **B** (step a). Next, the fast insertion of an allene (**2**) to **B** instead of the transmetalation with **3** (step b') or decarbonylation (step b'') gives a π -allylpalladium intermediate **C** (step b). The transmetalation of aryl boronic acid (**3**) with **C** in presence of a base and CuCl affords an arylpalladium species **D** (step c). Finally, the reductive elimination of **D** provides the α,β -unsaturated ketone (**4**) and regenerates the palladium(0) species **A** (step d). Water must play an important role to activate boronic acid and/or Pd catalyst species.^{15c,17} In the present formal arylacylation, the adducts can be efficiently and selectively obtained by simply adjusting the amount of H₂O depending on reactivity of substrates.

Notes and references

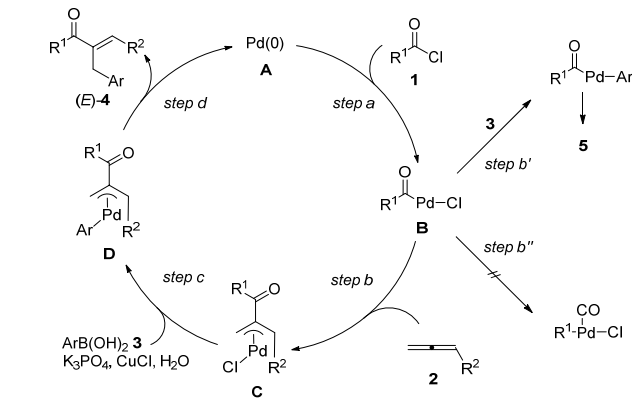
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Scheme 1. Plausible mechanism.



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