



Palladium-catalyzed conjugate addition of arylboronic acids to 2-substituted chromones in aqueous media

Anthony L. Gerten, Levi M. Stanley*

Iowa State University, Department of Chemistry, Ames, IA 50011, United States

ARTICLE INFO

Article history:

Received 30 August 2016

Revised 20 October 2016

Accepted 21 October 2016

Available online 24 October 2016

Keywords:

Conjugate addition

Palladium

Flavanones

Protodeboronation

Catalysis

ABSTRACT

Palladium-catalyzed conjugate additions of arylboronic acids to 2-alkylchromones are reported. The conjugate additions occur in aqueous media in the presence of a catalyst generated from palladium trifluoroacetate and 1,10-phenanthroline, and the flavanone derivatives containing a fully-substituted carbon center are formed in up to 90% yield.

© 2016 Elsevier Ltd. All rights reserved.

Introduction

Flavanone-containing scaffolds are present in an array of natural products, and the biological activity associated with many of these compounds renders them attractive synthetic targets [1a–f]. Conjugate additions of organometallic reagents to chromones have emerged as a powerful means to access these structures [1a]. In 2010, Huang and coworkers reported conjugate additions of arylboronic acids to chromones catalyzed by palladium complexes [2]. Since then, numerous reports of conjugate additions of arylboronic acids to chromones catalyzed by palladium [3a–c] and rhodium [4a–d] complexes have been disclosed (Scheme 1a).

However, there are currently no reports of conjugate additions of arylboronic acids to 2-substituted chromones. In fact, a report by the Stoltz group demonstrated that 2-methylchromone was unreactive under their conditions as a conjugate addition acceptor in palladium-catalyzed conjugate additions of arylboronic acids [3a].

Recent work from our laboratory showed that conjugate additions of arylboronic acids to sterically demanding β -aryl cycloalkenones catalyzed by a palladium(II) complex of 2,2'-bipyridine (2,2'-bpy) occur in high yields when carried out in aqueous sodium trifluoroacetate (NaTFA) [5]. This work built upon studies by Stoltz that demonstrate the presence of water in palladium-catalyzed

conjugate additions of arylboronic acids to β -substituted cyclic enones is important to protonate the palladium enolate intermediate and facilitate catalyst turnover [6]. We sought to leverage the increased reactivity toward challenging enone substrates when palladium-catalyzed conjugate additions of arylboronic acids are carried out in aqueous media. To this end, palladium-catalyzed conjugate additions of arylboronic acids to 2-substituted chromones are disclosed herein (Scheme 1b).

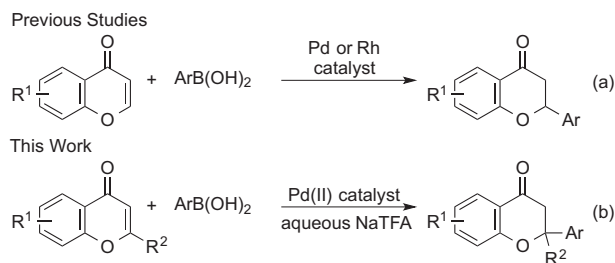
Results and discussion

We began our studies by evaluating the model conjugate addition of phenylboronic acid (**1a**) to 2-methylchromone (**2a**) to form 2-methyl-2-phenylchroman-4-one (**3a**) as the desired product (Scheme 2). The reaction conditions and catalyst identified for conjugate additions of arylboronic acids to β -aryl cycloalkenones were initially evaluated in the current model reaction [5]. The addition of **1a** (4 equiv) to **2a** catalyzed by a complex prepared from 2,2'-bipyridine and palladium trifluoroacetate (Pd(TFA)₂) occurs to form **3a** in low yield (29%) when the reaction is run at 100 °C in aqueous NaTFA. In addition to the desired product, we observed >90% protodeboronation of phenylboronic acid (**1a**) to form benzene and a small amount biphenyl from homocoupling of **1a**.

The low yield of conjugate addition product **3a** and the undesired protodeboronation and homocoupling pathways prompted us to follow the reaction over time. After two hours, we observed 28% yield of **3a** with 69% protodeboronation. The yield of **3a** did not increase after approximately two hours, while

* Corresponding author.

E-mail address: lstanley@iastate.edu (L.M. Stanley).

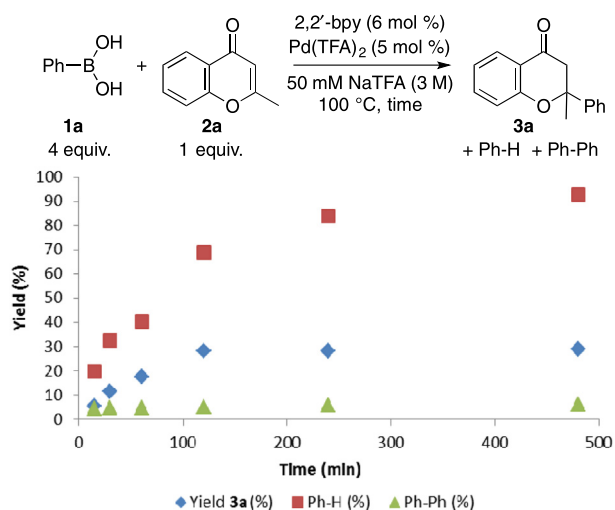


Scheme 1. Synthesis of flavanone derivatives by conjugate additions of arylboronic acids to chromones.

protodeboronation continued to occur. After 8 h, the phenylboronic acid was completely consumed, and 93% protodeboronation was observed. Initial efforts to mitigate the undesired protodeboronation reaction, including evaluation of a variety of arylboron nucleophiles, reaction temperatures, and reaction concentrations were largely unproductive (see ESI for details) [7].

After our early efforts to reduce protodeboronation did not lead to an acceptable solution, we next examined the issue of biphenyl formation in our reactions. The generally accepted mechanism for palladium-catalyzed conjugate additions of arylboronic acids to enones is a non-redox process involving Pd(II) intermediates [6]. The observed homocoupling of phenylboronic acid led us to believe that this undesired side reaction was removing the requisite Pd(II) from the catalytic cycle by reductive elimination from a PdAr₂ species to form a Pd(0) species [8]. Greatly diminished yields of **3a** under rigorously oxygen-free conditions lent even greater evidence to the formation of an off-cycle Pd(0) species (see ESI for details). The inclusion of oxygen is necessary to reoxidize Pd(0) species to Pd(II) species to ensure that the desired conjugate addition pathway remains operative.

The observation that the yield of product **3a** does not increase after two hours led us to hypothesize that once the concentration of 2-methylchromone (**2a**) was low relative to the concentration of phenylboronic acid (**1a**), the desired conjugate addition reaction ceases and protodeboronation becomes the dominant reaction pathway for phenylboronic acid (**1a**). With this hypothesis in mind and further inspired by a report from Minaard [9], we examined the impact of increasing the concentration of chromone **2a** relative



Scheme 2. Reaction profile for conjugate addition of phenylboronic acid (**1a**) to 2-methylchromone (**2a**). Reaction conditions: **1a** (2.00 mmol), **2a** (0.500 mmol), Pd(TFA)₂ (0.025 mmol), 2,2'-bpy (0.030 mmol), 50 mM aq. NaTFA (0.167 mL), 100 °C, 8 h. Yields are determined by GC using tridecane as an internal standard.

to phenylboronic acid (**1a**) in an attempt to minimize protodeboronation.

The results presented in Table 1, entries 1–3 demonstrate that the relative rate of protodeboronation versus conjugate addition is highly dependent on the concentration of **2a**. The model reaction catalyzed by complex **C1**, prepared in situ from Pd(TFA)₂ and 2,2'-bpy, occurred to form product **3a** in 38% yield when the reaction was run at 60 °C with a 1:4 ratio of **2a:1a** (entry 1). However, we still observed 70% protodeboronation under these reaction conditions. When the reaction was run with a 1:1 ratio of **2a:1a**, we observed 27% yield of product **3a**, 35% protodeboronation, and 21% biphenyl formation (entry 2). Encouraged by the lower relative rate of protodeboronation versus desired conjugate addition observed under these conditions, we ran the reaction with a 2:1 ratio of **2a:1a**. This reaction delivered product **3a** in 56% yield and decreased protodeboronation and biphenyl formation to 19% and 12%, respectively (entry 3).

To further improve upon our reaction conditions, we examined the impact of electronically distinct bipyridine ligands on the activity of the palladium catalyst (entries 3–5). A more electron-rich palladium center led to a higher relative rate of protodeboronation (compare entry 4 with entry 3). The outcome of the reaction conducted in the presence of the electron-poor catalyst complex **C3** (R = CF₃) was essentially unchanged from that observed with complex **C1** (compare entry 5 with entry 3).

Notably, the complex derived from 1,10-phenanthroline (**C4**) led to higher yield of product **3a** relative to the palladium complexes of bipyridine ligands. Complex **C4** catalyzed the addition of **1a** to **2a** to form **3a** in 68% yield with 16% protodeboronation and 13% biphenyl formation (entry 6). We hypothesize that the palladium complex of 1,10-phenanthroline eliminates the potential for rollover C–H activation of 2,2'-bipyridine ligands that may remove palladium from the catalytic cycle [10].

Encouraged by the results of reactions catalyzed by complex **C4**, we sought to identify reaction conditions to further increase the yield of **3a** and limit protodeboronation. Increasing the temperature of the reaction to 80 or 100 °C led to a decrease in the yield of **3a** and an increase in protodeboronation (entries 7 and 8). Increasing the concentration of the reaction to 4.5 M based on phenylboronic acid led to the formation of **3a** in 76% isolated yield (entry 9). Protodeboronation and biphenyl formation could be further suppressed by conducting the reaction with a 3:1 ratio of **2a:1a** (entry 10), and 2-methyl-2-phenylchroman-4-one (**3a**) was isolated in 87% yield.

With a practical catalyst system identified, we proceeded to evaluate conjugate additions of a variety of arylboronic acids to 2-methylchromone (**2a**). These results are summarized in Scheme 3. Additions of arylboronic acids containing electron-donating and electron-neutral groups at the *para*-position to **2a** formed the corresponding 2-methyl-2-arylchroman-4-ones **3b–3e** in 68–83% yield. Moderately electron-deficient *p*-fluorophenyl and *p*-chlorophenylboronic acids reacted with **2a** to generate 2-methyl-2-arylchroman-4-ones **3f** and **3g** in 51% and 57% yield, respectively. However, the additions of *p*-bromophenylboronic acid and electron-poor *p*-trifluoromethylphenylboronic acid to **2a** formed **3h** and **3i** in low yields. Additions of *m*-methoxy- and *m*-methylphenylboronic acid generated **3j** and **3k** in good yields (68–69%), while a *m*-halogenated arylboronic acid led to low yields of the corresponding 2-methyl-2-arylchroman-4-one **3l**. Additions of electron-rich 3,4- and 3,5-disubstituted arylboronic acids to **2a** formed 2-methyl-2-arylchroman-4-ones **3m–3o** in good-to-excellent yields (60–90%).

Notably, *o*-substituted arylboronic acids displayed decreased reactivity in conjugate additions to **2a**. The addition of *o*-fluorophenylboronic acid to **2a** formed **3p** in <5% yield. *o*-Methoxyphenylboronic acid displayed increased reactivity

Download English Version:

<https://daneshyari.com/en/article/5258243>

Download Persian Version:

<https://daneshyari.com/article/5258243>

[Daneshyari.com](https://daneshyari.com)