



An efficient synthesis of 4-substituted coumarin derivatives via a palladium-catalyzed Suzuki cross-coupling reaction



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ABSTRACT

An efficient Pd-catalyzed Suzuki cross-coupling reaction of sterically crowded 4-chlorocoumarin derivatives with air- and moisture-stable potassium organotrifluoroborates is developed. This methodology has been used to generate a series of novel alkyl, aryl, and vinyl substituted coumarin derivatives in good to excellent yields. The twisted conformation of the vinyl groups in the X-ray crystal structures of (2-oxo-4-vinyl-2H-chromen-3-yl)methyl acetate (**2**) and (2-oxo-4-vinyl-2H-chromen-3-yl)methyl 2,2,2-trichloroacetimidate (**3**), along with the atropisomerism of 3-(hydroxymethyl)-4-(2-methoxyphenyl)-2H-chromen-2-one (**1d**), are evidence of the steric crowding in these adducts.

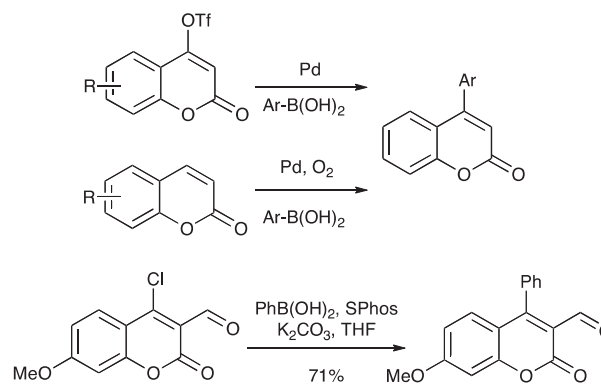
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Introduction

The coumarin ring system is present in a variety of natural products and biologically active compounds.¹ These important heterocycles are known for their diverse physiological activities such as antibacterial, anticoagulant, antioxidant, and anti-inflammatory.² The 4-aryl coumarin skeleton forms the major structural component of neoflavones, a type of neoflavonoids.³

A number of methods are known in the literature to access coumarin scaffolds.⁴ Among these, direct substitution at C-4 of the preformed coumarin ring is reported as an efficient strategy.⁵ Finet and co-workers have reported the synthesis of polyoxygenated 4-heteroaryl substituted coumarins by the Suzuki–Miyaura cross-coupling utilizing heteroaryl boronic acids and 4-trifluoromethylsulfonyloxycoumarins.⁶ Very recently Duan et al.^{7a} reported Pd-catalyzed oxidative Heck coupling to access 4-aryl coumarins using coumarins and arylboronic acids. Glass and co-workers^{7b} reported a fluorescent chemosensor for studying neurotransmitters for which a key synthetic step was a Suzuki coupling of phenylboronic acid to a chlorocoumarin (Scheme 1).

As part of our continuing interest in pseudopericyclic 3,5-sigmatropic rearrangements⁸ we sought a convenient synthesis of 3,4-disubstituted coumarin **1a**. We expected that **1a** could be readily converted into acetate **2** and isoelectronic trichloro-



Scheme 1. Prior examples of Suzuki and Heck couplings of coumarins.

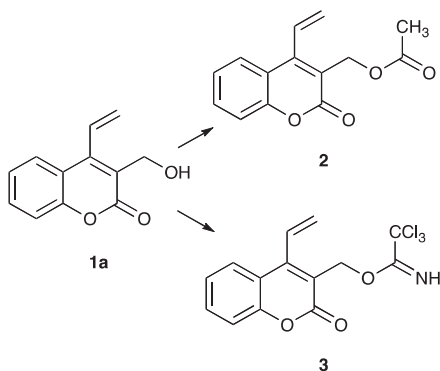
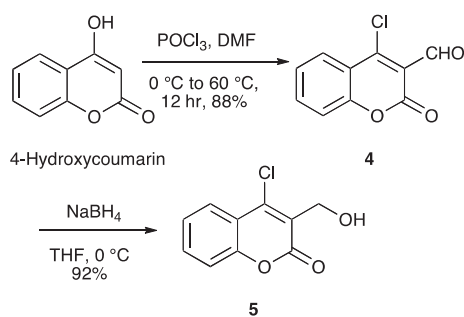
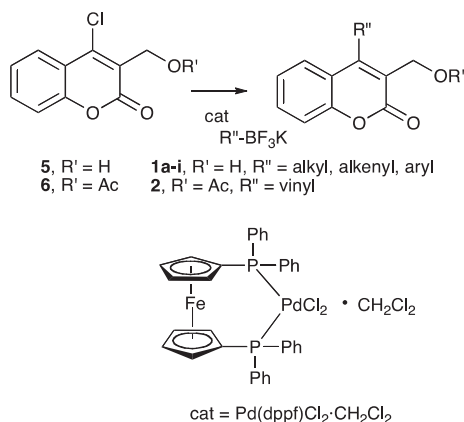
roacetimidate **3** (Scheme 2). The acetate **2** contains a pentadienyl ester, a bonding pattern which we have previously shown can undergo a 3,5-sigmatropic rearrangement, in preference to a 3,3-rearrangement.⁸

In our effort to synthesize compound **1a**, we have developed an efficient protocol to access new analogs of 4-substituted coumarins that potentially have biological activity. Coumarin **5** was prepared in high yield in two steps starting from commercially available 4-hydroxycoumarin. Following a literature procedure,⁹ 4-hydroxycoumarin underwent a Vilsmeier–Haack reaction using POCl₃/DMF to yield 4-chlorocoumarin aldehyde **4**. Selective reduction of the aldehyde **4** under typical NaBH₄ reduction condition led to

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Scheme 2. Proposed derivatizations of **1a**.Scheme 3. Synthesis of 4-chlorocoumarin **5**.Scheme 4. Suzuki couplings of 4-chlorocoumarins **5** and **6**.

the formation of **5** (Scheme 3). Compound **5** serves as a key intermediate as we envisioned that it could be functionalized into a variety of potentially useful coumarin derivatives.

The key step in the synthesis is the Suzuki cross-coupling reaction of 3-substituted 4-chlorocoumarins (**5** and **6**) with potassium alkyl/alkenyl/aryl trifluoroborates (Scheme 4). Our optimized conditions employed Pd(dppf)Cl₂·CH₂Cl₂ (5–10 mol %) as catalyst. We also report the application of this chemistry for the synthesis of a small library of novel and sterically crowded 4-alkyl/alkenyl/aryl substituted coumarin derivatives (**1a–i** and **2**) in good to excellent yields.

Results and discussion

The 4-substituted coumarin derivatives discussed in the current work are challenging substrates to synthesize particularly with steric crowding of the biaryl linkages. The Suzuki coupling is a powerful method for forming C–C bonds, but in the case of **5**, the reduced reactivity of chlorides as compared to their bromide, iodide, or triflate counterparts suggests that the reaction might be more difficult.¹⁰ Molander et al. have reported numerous examples employing potassium organotrifluoroborates as mild, air, and moisture stable alternatives to boronic acids or esters in Suzuki cross-coupling reactions, but generally with more reactive leaving groups and less congested products.¹¹

We first explored the cross-coupling of 4-chloro-3-(hydroxymethyl)coumarin **5** with potassium vinyltrifluoroborate. Initial investigations for Suzuki reaction conditions were disappointing as no product formation was observed using Pd(OAc)₂ as catalyst. Pd(dppf)Cl₂·CH₂Cl₂ has been successfully employed as catalyst in many cross-coupling reactions involving potassium aryltrifluoroborates as coupling partners.¹² Gratifyingly, 4-chlorocoumarin **5** underwent coupling with potassium vinyltrifluoroborate when Pd(dppf)Cl₂·CH₂Cl₂ (10 mol %) was used as catalyst. Several combinations of base, solvent, and reaction time were explored, as summarized in Table 1. Consistent with the literature precedents,¹² addition of water as co-solvent or use of a protic solvent was

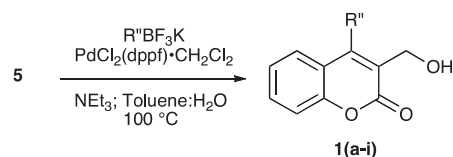
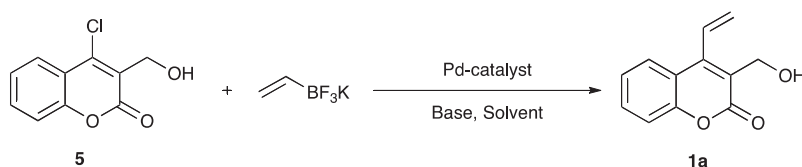
Scheme 5. Optimized conditions for the Suzuki coupling of **5**.

Table 1
Optimization of reaction conditions for Suzuki coupling of **5** with potassium vinyltrifluoroborate



Pd-catalyst (mol %)	Base (equiv)	Solvent	Reaction temp (°C)/time (h)	% Yield ^a
Pd(OAc) ₂ (5 mol %)	K ₂ CO ₃ (3 equiv)	Methanol	Reflux/2	n.r.
Pd(dppf)Cl ₂ ·CH ₂ Cl ₂ (9 mol %)	Cs ₂ CO ₃ (3 equiv)	THF–H ₂ O (10:1)	80/5	60
Pd(dppf)Cl ₂ ·CH ₂ Cl ₂ (5 mol %)	Et ₃ N (1.5 equiv)	<i>i</i> PrOH	Reflux/3	70
Pd(dppf)Cl ₂ ·CH ₂ Cl ₂ (5 mol %)	Et ₃ N (3 equiv)	Toluene (dry)	100/24	n.r.
Pd(dppf)Cl ₂ ·CH ₂ Cl ₂ (2 mol %)	Et ₃ N (1.5 equiv)	Toluene–H ₂ O (10:1)	100/24	20
Pd(dppf)Cl ₂ ·CH ₂ Cl ₂ (10 mol %)	Et ₃ N (3 equiv)	Toluene–H ₂ O (10:1)	100/1	90
Pd(dppf)Cl ₂ ·CH ₂ Cl ₂ (5 mol %)	Et ₃ N (1.5 equiv)	Toluene–H ₂ O (10:1)	100/3	92

^a Isolated yield (n.r. = no reaction).

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