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C–H Functionalization

Heteroatom-Guided, Palladium-Catalyzed, Site-Selective C–H Arylation of 4*H*-Chromenes: Diastereoselective Assembly of the Core Structure of Myristinin B through Dual C–H Functionalization

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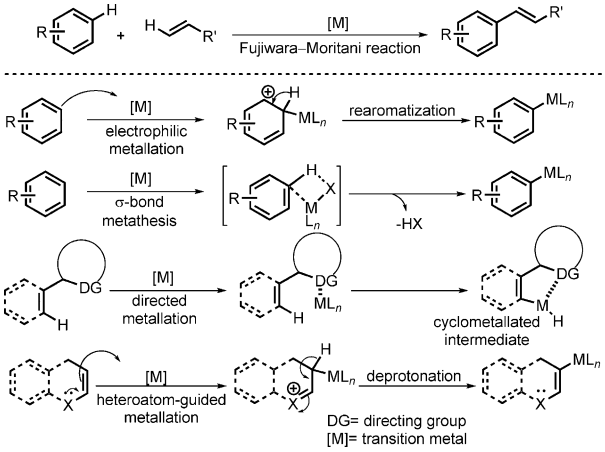
Abstract: A highly site-selective, heteroatom-guided, palladium-catalyzed direct arylation of 4*H*-chromenes is reported. The C–H functionalization is driven not only by the substituents and structure of the substrate but also by the coupling partner being used. The diastereoselective assembly of the core structure of Myristinin B has been achieved by using a dual C–H functionalization strategy for regioselective direct arylation.

Introduction

Over recent decades, carbon–carbon bond-formation reactions that take place through C–H functionalization have become one of the most popular research topics for synthetic chemists worldwide.[1] Transition-metal catalyzed and, in particular, palladium-mediate, C–H activation reactions offer a good alternative to organic transformations of unfunctionalized substrates without having to go through cumbersome prefunctionalization processes. In this regard, transformations proceeding through electrophilic palladation mechanisms have been employed in regioselective C–H functionalization of electron-rich arenes as well as many heterocyclic substrates.[2] This mode of C–H activation involves precoordination of the metal to the electron-rich π system, followed by formation of a Wheland-like intermediate or a σ complex, which then looses a proton to a bound nucleophilic ligand (Scheme 1).[3,4] The regioselectivity is usually determined by the most nucleophilic carbon center, and this is particularly true for electron-rich (hetero)arenes. Similarly, for alkenes over which a pair of electrons can be delocalized (electron-rich olefins), the oxidative-Heck reaction (also called the Fujiwara–Moritani reaction)[5] of arenes also follows a similar mechanism. This palladium-catalyzed transformation usually involves a Pd^{II}–Pd^{0} catalytic cycle in which C–H activation at the arene is often the first step.[6] After the first report by Hallberg and co-workers, several groups have succeeded in inverting the regioselectivity of migratory insertion for electron-rich olefins in the Mizoroki–Heck reaction, by using suitable heteroatom-based directing groups tethered to the olefin.[7] These transformations usually involve a Pd^{0}–Pd^{II} mechanism. There are a limited number of reports involving the Pd^{II}–Pd^{0} pathway in which the site-selectivity has been switched for such reactions.[8]



Scheme 1. Selected modes of C–H activation.

We have been interested in regioselective C–H functionalization reactions that proceed through electrophilic palladation mechanisms[9] in which it is possible to differentiate the electrophilic C–H activation of arenes from that of nonaromatic, electron-rich olefins with the term "heteroatom-guided C–H activation". This term has also been introduced to differentiate the "heteroatom-directed C–H activation" in which the Lewis-basicity of the heteroatom directing groups is utilized in "directing" the metal to a particular C–H bond.[2]

In the present study, we put forth our results on the direct arylation reactions of 4*H*-chromenes through C–H functionalizations and propose alternative mechanisms that explain our

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observations. These mechanisms differ from the regular carbopalladation mechanisms put forward to explain similar transformations.

The benzopyran (or chromane) framework is present in several natural products of biological importance such as flavonoids, and many of these exhibit unique pharmacological activities. Myristinins,[10] sarcandrones,[11] ephedrannin,[12] and procyanidins[13] are a few of the notable examples in which the chromane has a 2,4-diaryl substitution (Figure 1). Myristinins

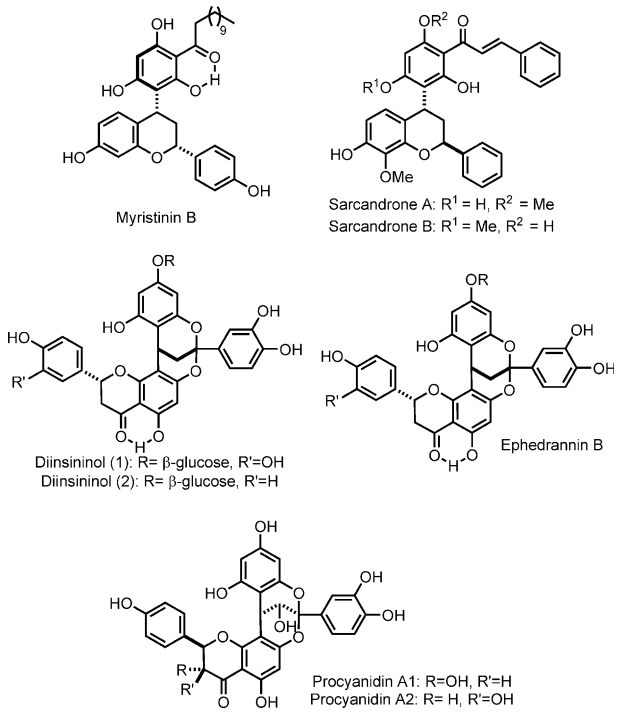


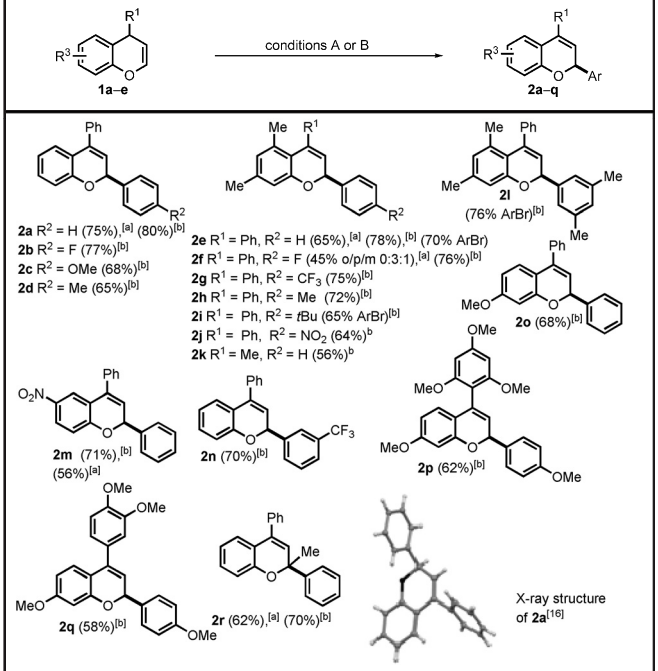
Figure 1. 2,4-Diarylchromane-containing natural products.

A–F have been isolated from a variety of natural sources and some of them possess very impressive biological activities such as being DNA damaging agents and DNA polymerase β-inhibitors.[10]

Results and Discussion

To derive a general approach towards the synthesis of these natural products, which incorporate a 2,4-diaryl chromane framework, we were required to devise a strategy for the installation of both aryl groups through C–H functionalization. To our knowledge, such an approach has not been reported for this class of compounds. Whereas most reports of arylations of chromenes with aryl halides usually follow a Pd^0–Pd^{II} pathway, we were more interested in developing a Pd^{II}–Pd^0 pathway.[8a,14] In this context, we first took up the direct arylation reactions of 4*H*-chromenes monosubstituted at the C4-position. The substrate scope of the reaction with arenes, as well as aryl halides worked out quite well under different optimized conditions, as depicted in Table 1.[15] In all cases, the regioselectivity was the same; the C2-arylated compounds **2a**–**r** were

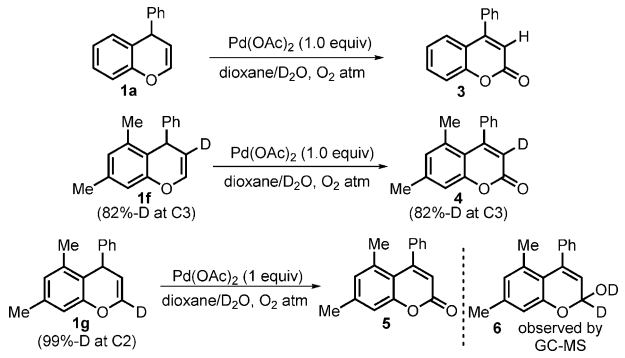
Table 1. Substrate scope of the reaction with arenes and aryl halides and monosubstituted chromenes.[16]



[a] Conditions A: Ar-H, $Pd(OAc)_2$ (10 mol%), AgOAc (2.0 equiv), PivOH (3.0 equiv), 80–100 °C (yield of isolated product); [b] Conditions B: Ar-I (2.0 equiv), $Pd(OAc)_2$ (10 mol%), AgOAc (2.0 equiv), dioxane (0.2 M), 80 °C. Yields given refer to isolated products.

formed, which were characterized by a double bond in a position that differed from that of substrates **1a**–**e**. Product **2r** was obtained from 2,4-disubstituted 4*H*-chromene.

In both cases (arenes as well the aryl halides), one could postulate a simple Heck-type carbopalladation mechanism on the monosubstituted chromene, and *syn* β-hydrogen elimination to generate the C3–C4 endocyclic olefin. However, this pathway seems quite unlikely when aryl halides are employed because the Pd^{II} catalyst would not undergo a favorable oxidative insertion with the ArX so as to generate a Pd^{IV} species, which then would have to undergo a migratory insertion with the chromene. Such migratory insertions involving Pd^{IV} are rather difficult and uncommon.[17] Furthermore, reductive elimination from Pd^{IV} is expected to be faster than carbopalladation. Another argument that could be put forth is the generation of Pd^0 by sacrificing some of the chromene through the mechanism reported by Heck.[18] This could then undergo an oxidative insertion to generate ArPdX and the further catalytic cycle would follow. During the optimization of the reaction conditions, reactions with Pd^0 catalysts and phosphine ligands resulted in quite sluggish conversions.[15] Given that we were not convinced that the regular carbopalladation pathway was being followed in this transformation, we attempted to carry out a deuterodemetalation on the substrate **1a** (Scheme 2). No deuterodemetalation was observed when the reaction was carried out in D_2O. In case of substrate **1a**, the major product obtained under a dioxane/D_2O mixture was undeuterated



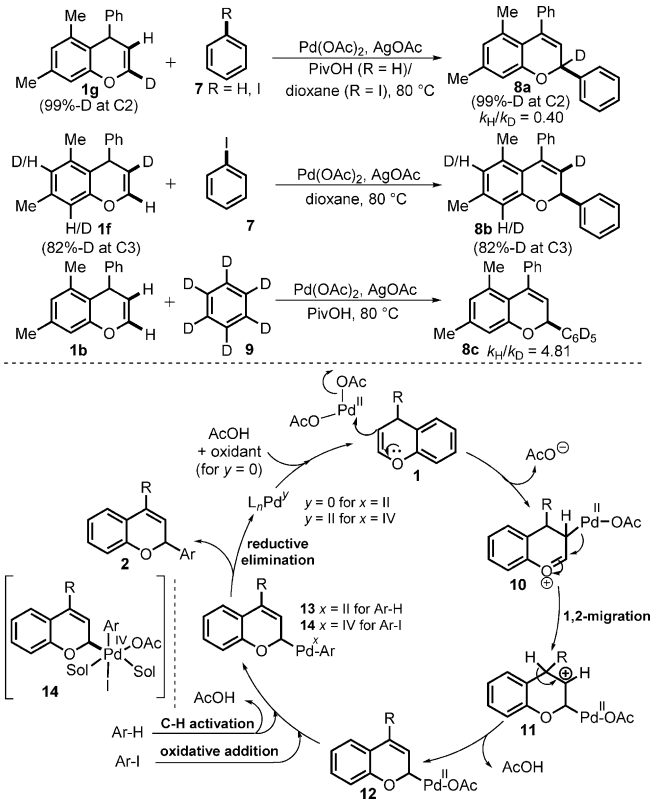
Scheme 2. Attempts at deuterodemetalation.

coumarin **6a**. The reaction resulted in the same products even without the oxygen atmosphere.

The fact that the double bond rearranged to the benzylic position indicated that the product did not arise from a simple hydration of the benzopyran and subsequent oxidation of the lactol. The C3-deuterated substrate **1f**, when reacted under the same conditions, resulted in coumarin **4**, in which the deuterium remained. In the case of C2-deuterated chromene **1g**, intermediate lactol **6** was clearly detected by GC–MS analysis.

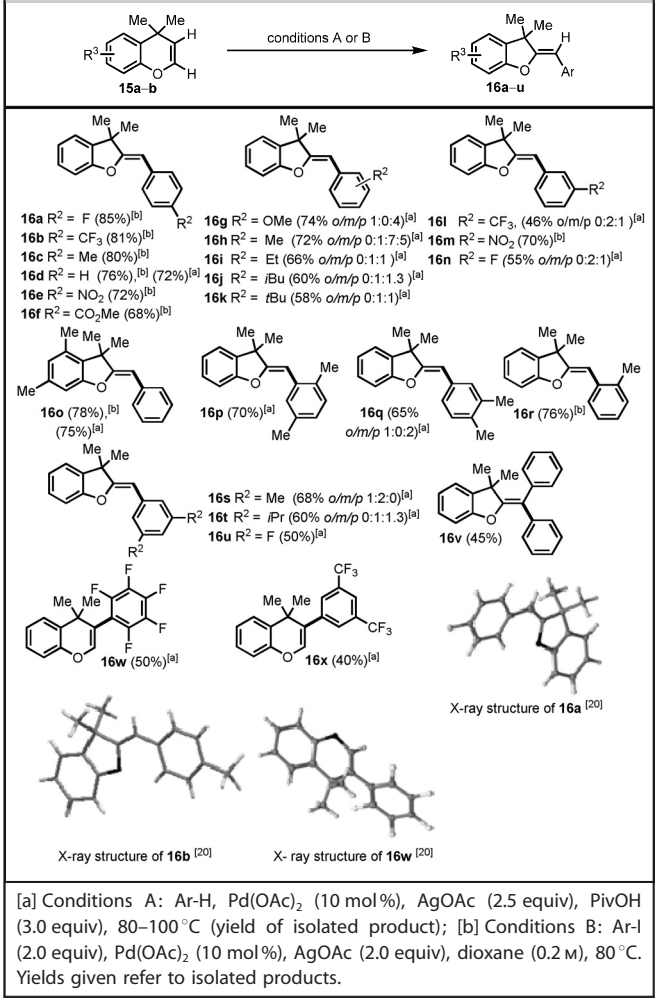
In our opinion, this result gives a strong indication of the first palladation occurring at C3. In another observation, the arylation reactions with C2- or C3-deuterated substrates resulted in products in which the deuterium label remained intact (Scheme 3), with almost no loss of deuterium content. Interestingly, substrate **1g**, showed a secondary kinetic isotope effect (k_H/k_D) of 0.4. The reaction of **1b** with deuterated benzene showed a primary kinetic isotope effect of 4.81, which indicated that C–H activation through a concerted metalation–deprotonation (CMD) process[4] on the arene occurred either before or during the rate-limiting step. Based on these observations, a mechanism was proposed (Scheme 3) in which the initially formed C3-palladated species could then undergo a 1,2-migration so as to generate the C2-palladated species, with the C3–C4 olefin being generated by removal of the C4 hydrogen. Such 1,2-migrations of palladium have been documented earlier.[19] The pathway depicted in Scheme 3 would also necessitate the involvement of Pd^{IV} species of type **14** being generated in the case of oxidative addition with aryl halides.

The C2-palladated species would undergo a C–H activation with the arene (Ar–H) followed by reductive elimination to yield the observed C2-arylated chromene. Given that the deuterium labeling studies showed that neither C2-H nor C3-H are lost in the reaction, a CMD-type metalation on the chromene can be ruled out. These studies however, do not yet rule out the possibility of a Heck-type pathway in this substrate.



Scheme 3. Studies with the deuterated substrates and postulated mechanism involving 1,2-palladium migration.

Table 2. Substrate scope of the reaction with arenes and aryl halides and 4,4-disubstituted chromenes.[20]

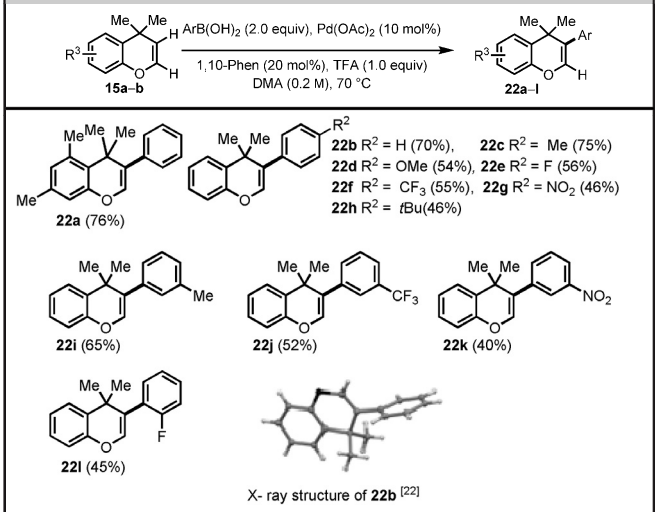


[a] Conditions A: Ar-H, $Pd(OAc)_2$ (10 mol%), AgOAc (2.5 equiv), PivOH (3.0 equiv), 80–100 °C (yield of isolated product); [b] Conditions B: Ar-I (2.0 equiv), $Pd(OAc)_2$ (10 mol%), AgOAc (2.0 equiv), dioxane (0.2 M), 80 °C. Yields given refer to isolated products.

To probe the above conclusions further, we envisaged that preventing β-hydrogen elimination would give further insights into the mechanism. For this purpose, 4,4-dimethylchromenes were chosen as substrate. The arylation reactions were performed under the same conditions as that for chromene **1a**–**e**. As expected, the results were different. The reactions with arenes and aryl iodides resulted exclusively in ring contraction and concomitant arylation (Table 2).[15] The products obtained were deduced to possess *Z* stereochemistry. In the case of the reaction with arenes, traces of C3-arylation products were obtained in which the ring contraction had not taken place. Notably, benzofuran substrates **16a**–**u** were excellent starting materials for the synthesis of chroman spiroketals, and this method constitutes a unique approach to this class of compounds.[21] Initially, it seemed that the ring may have opened up so as to generate an alkyne species. However, the formation of the products with *Z* stereochemistry negated this possibility of a 5-*exo*-dig type cyclization.

As shown in Scheme 4, the product of C2-deuterated starting material **15d** was found to be missing the deuterium, whereas the deuterium was present in the product arising from the C3-deuterated starting material **15c**. Here too, a primary kinetic isotope effect of 5.0 was observed with deuterated benzene. This led us to propose a different mechanism in which we postulated a migration of the C3–C4 carbon–carbon bond to explain the ring contraction (Scheme 4). This mechanism probably also explains why the products are exclusively formed with *Z* stereochemistry; the relative orientation of the groups on the carbocation is such that the palladium is away from the gem-dimethyl groups.

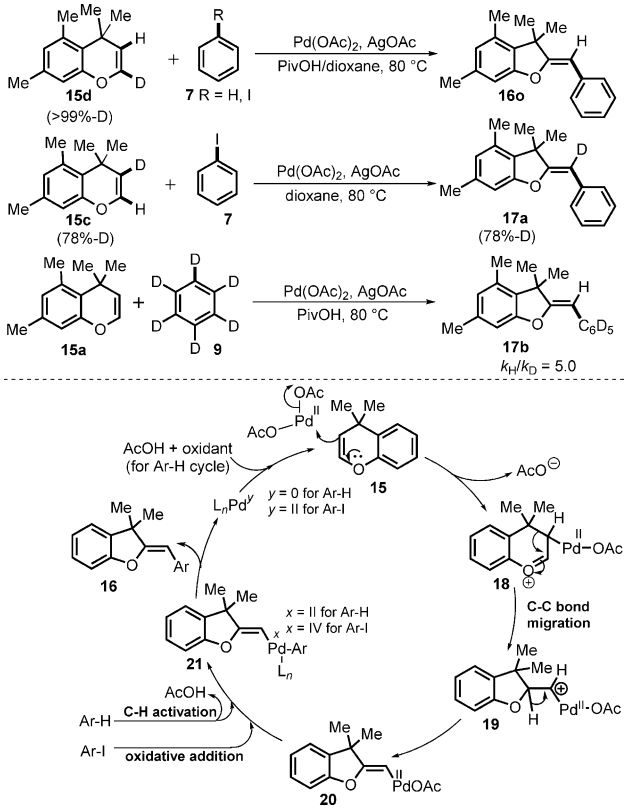
Table 3. Substrate scope of the reaction with 4,4-disubstituted chromenes and arylboronic acids.[a,22]



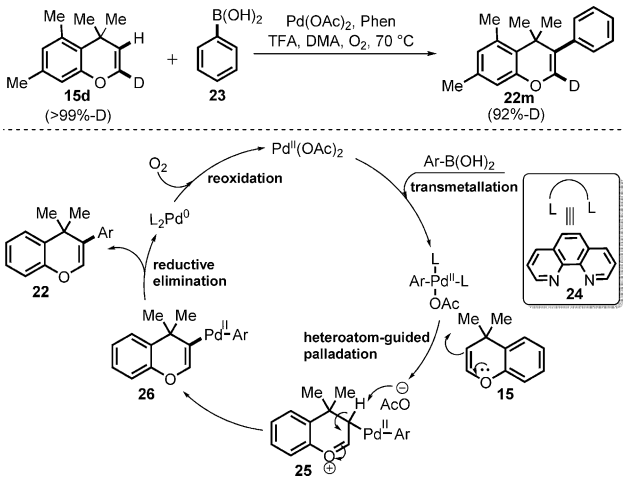
[a] Yields given refer to isolated products.

In the direct arylation with pentafluorobenzene and 1,3-bis(trifluoromethyl)benzene, the C3 aryl products were obtained (**16w**, **16x**), without any ring contraction (Table 2). This observation gives a strong indication that the palladation would occur on the C3-position and that the mechanism may not follow a simple Heck-type pathway. After the arylations using arenes and aryl iodides, we then attempted the reaction with boronic acids.[15] The reactions proceeded very well and gave, as expected, the C3-arylated product without any trace of the ring contraction product (Table 3). The substrate scope was very good and the site-selectivity was excellent. In fact, to our knowledge, direct C3 arylation of 4*H*-chromenes has not been reported.

The reaction with C2-deuterated substrate resulted in the deuterium remaining in the product (Scheme 5). The C3 deute-



Scheme 4. Studies with deuterated substrates and postulated pathway involving C–C bond migration.



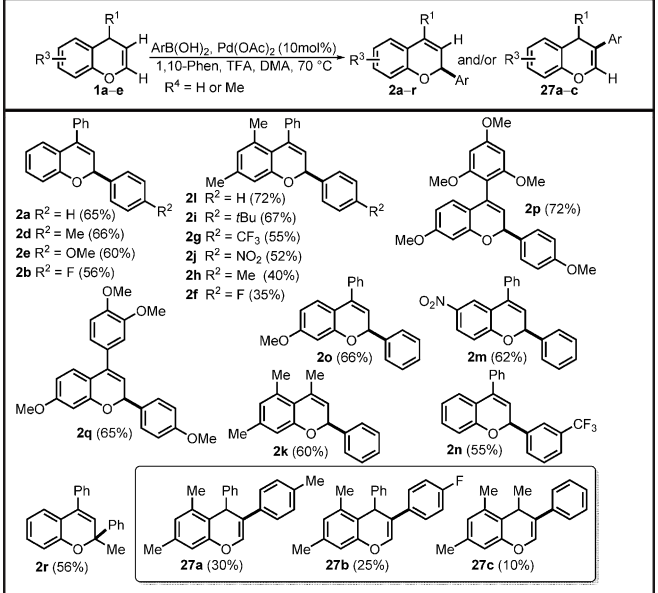
Scheme 5. Plausible pathway for the direct C3 arylation with arylboronic acids.

rium did not survive the reaction conditions because, under protic conditions, the deuterium at C3 is very labile and exchanges very fast. The pathway seems to follow an electrophilic palladation route that is heteroatom-guided at C3 (Scheme 5). In the case of arylboronic acids, it may also be possible that the transmetalation is the first step followed by a heteroatom-guided C–H activation at C3. A fast reductive elimination is proposed so as to negate the possibility of a competing ring contraction process.

It is quite possible that the formation of **16w** and **16x** (both electron-deficient arenes with more acidic C–H than normal arenes), may follow a pathway similar to that shown in Scheme 5, with the C–H activation through CMD being the first step.

Finally, a more convincing indication of C3 palladation was obtained when arylboronic acids were used in the direct arylation of C4-monosubstituted 4*H*-chromenes (Table 4). In some

Table 4. Substrate scope of the reaction with arylboronic acids and 4-monosubstituted 4*H*-chromenes.[a]

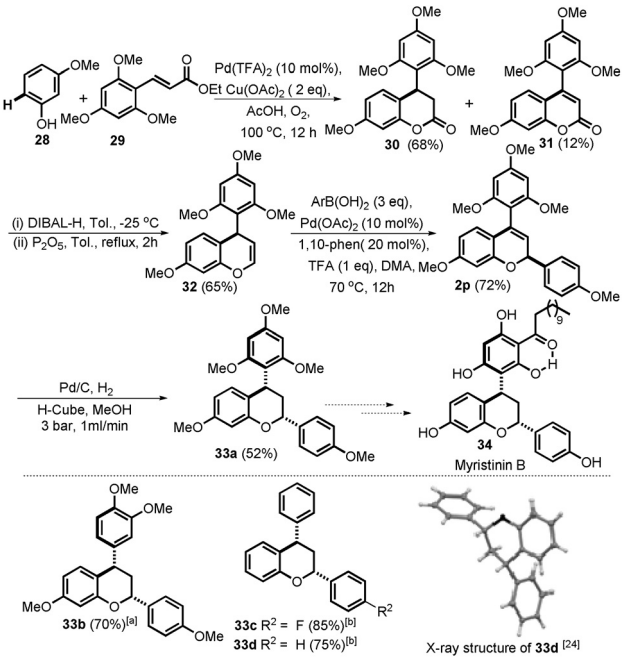


[a] Yields given refer to isolated products.

cases, we were able to isolate a good amount of C3-arylated products (**27a–c**), without rearrangement of the double bond. The products were obtained together with the corresponding C2-arylated substrates (**2h**, **2f**, and **2l**, respectively). This result also gives an indication that, unlike the case of arenes or aryl iodides, the pathway proposed in Scheme 5 for arylboronic acids may involve the generation of arylpalladium species in the first step, followed by palladation at C3.

Furthermore, to devise a general strategy for the synthesis of natural products possessing the 2,4-diarylbenzopyran core, we attempted the synthesis of the racemic form of the core structure of Myristinin B (Scheme 6).

Starting with phenol **28**, the annulation reaction through an oxidative-Heck reaction using the substituted ethyl cinnamate



Scheme 6. Synthesis of the core structure of Myristinin B.[24] [a] Prepared from $ArB(OH)_2$. [b] Prepared from ArH; yield is for the hydrogenation step.

29, worked well.[23] The reaction was carried out in acidic medium, which meant that the protodemetalation was a faster process than β-hydride elimination and resulted in the formation of lactone **30** as the major product. Coumarin **31** was obtained as a minor product and was easily converted into **30** by simple hydrogenation. Diisobutylaluminum hydride (DIBAL-H)-mediated reduction of the lactone and subsequent dehydration of the resulting lactol provided dihydropyran **32** for the arylation reaction. As depicted in Table 4, this reaction proceeded reasonably with aryl boronic acid to result in **2p**. The hydrogenation of the endocyclic olefin proceeded in a highly diastereoselective fashion to give **33a**. Thus, the diastereoselective synthesis of the core structure for Myristinin B was achieved by using a dual C–H functionalization strategy. Substrates **33b–d** were also achieved in a similar fashion, and the relative stereochemistry was easily established based on the crystal structure of **33d**.

Conclusion

We have presented herein, the site-selective direct arylation of 4*H*-chromenes, in which we propose a heteroatom-guided or electrophilic metalation followed by a migration of the metal to the neighboring carbon, so as to explain the regioselectivity of the arylation. In the case of the 4,4-disubstituted chromenes, we propose a C–C bond migration to explain the formation of the observed benzopyrans. In both cases, we feel the reaction may not proceed through the usually postulated Heck-type carbopalladation pathway of the chromene with the arylpalladium species; rather, it is quite possible that electrophilic metalation may be the predominant pathway. We have also demonstrated a rare direct C3 arylation of chromenes. The

reactions depicted herein proceed with high regioselectivity and with good to moderate yields. We also feel that the method is general and shall be of good synthetic utility. The utility of this arylation methodology has been demonstrated in the diastereoselective synthesis of the core structure of Myristinin B.

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Keywords: arylation · C–H activation · chromenes · diastereoselectivity · oxygen heterocycles · palladium

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