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Cp*Rh^{III}-Catalyzed Allyl–Aryl Coupling of Olefins and Arylboron Reagents Enabled by C(sp^3)–H Activation

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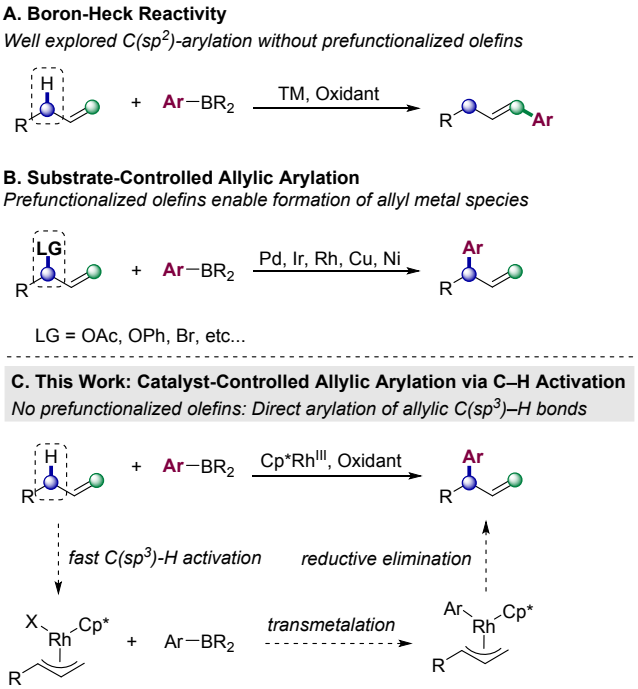
Supporting Information Placeholder

KEYWORDS C(sp^3)–H activation, rhodium, arylation, boroxines, allylic compounds

ABSTRACT: Herein, we present a mild Cp*Rh^{III}-catalyzed Suzuki-Miyaura-type allyl–aryl coupling of readily accessible arylboron reagents with a broad range of olefins. Allylic arylation was achieved without the need for prefunctionalized alkenes and the general Heck-type reactivity of olefins with arenes was not observed. Mechanistic studies indicate that the reaction was enabled through the fast generation of a Rh^{III}-allyl species via undirected C(sp^3)–H activation. Moreover, the developed protocol was applied to the highly concise synthesis of the anti-inflammatory drug flurbiprofen.

The Suzuki-Miyaura coupling is among the most commonly applied organic transformations for the construction of aryl–aryl bonds in organic synthesis. It has emerged as an indispensable workhorse in agro- and pharmaceutical chemistry since it utilizes bench stable, non-basic and broadly commercially available arylboron compounds as nucleophilic reagents that can be coupled reliably with a variety of electrophiles.[1] Beyond arene cross-coupling, organoboron compounds could be further applied to the arylation of olefins, also known as the boron Heck reaction (Scheme 1A).[2]

In contrast to the well explored C(sp^2)–C(sp^2) bond forming reactions, the Suzuki-Miyaura-type construction of C(sp^2)–C(sp^3) bonds has been rarely described due to the tendency of alkyl–metal species to undergo β-hydride elimination.[3] The arylation of allylic sp^3-hybridized carbon atoms is among those coupling reactions of particular interest since the alkyl metal complex is stabilized through the isomerization to an allyl metal species and allylic arylation generates a stereogenic sp^3-hybridized center while preserving the olefin moiety.[4] Thus, space for further functionalization remains. However, achieving allylic arylation is often difficult owing to the intrinsic Heck-type reactivity of olefins in transition metal catalysis.[2] Diverse approaches have been investigated to allow allylic arylation utilizing arylboron reagents. With the use of prefunctionalized olefins bearing suitable leaving groups (LGs), such as halides, ethers or acetates in the allylic position, the formation of metal–allyl species can be induced by the substrate (Scheme 1B).[5] Therefore, typical Heck-reactivity of olefins can be overridden and allylic arylation products can be obtained instead. In addition, Sigman and coworkers elegantly achieved the formation of products bearing arenes in the allylic position through palladium-catalyzed hydroarylation of 1,3-dienes using boronic esters.[6] However, the Suzuki-Miyaura-type construction of aryl–allyl bonds without the use of prefunctionalized olefins remains elusive.

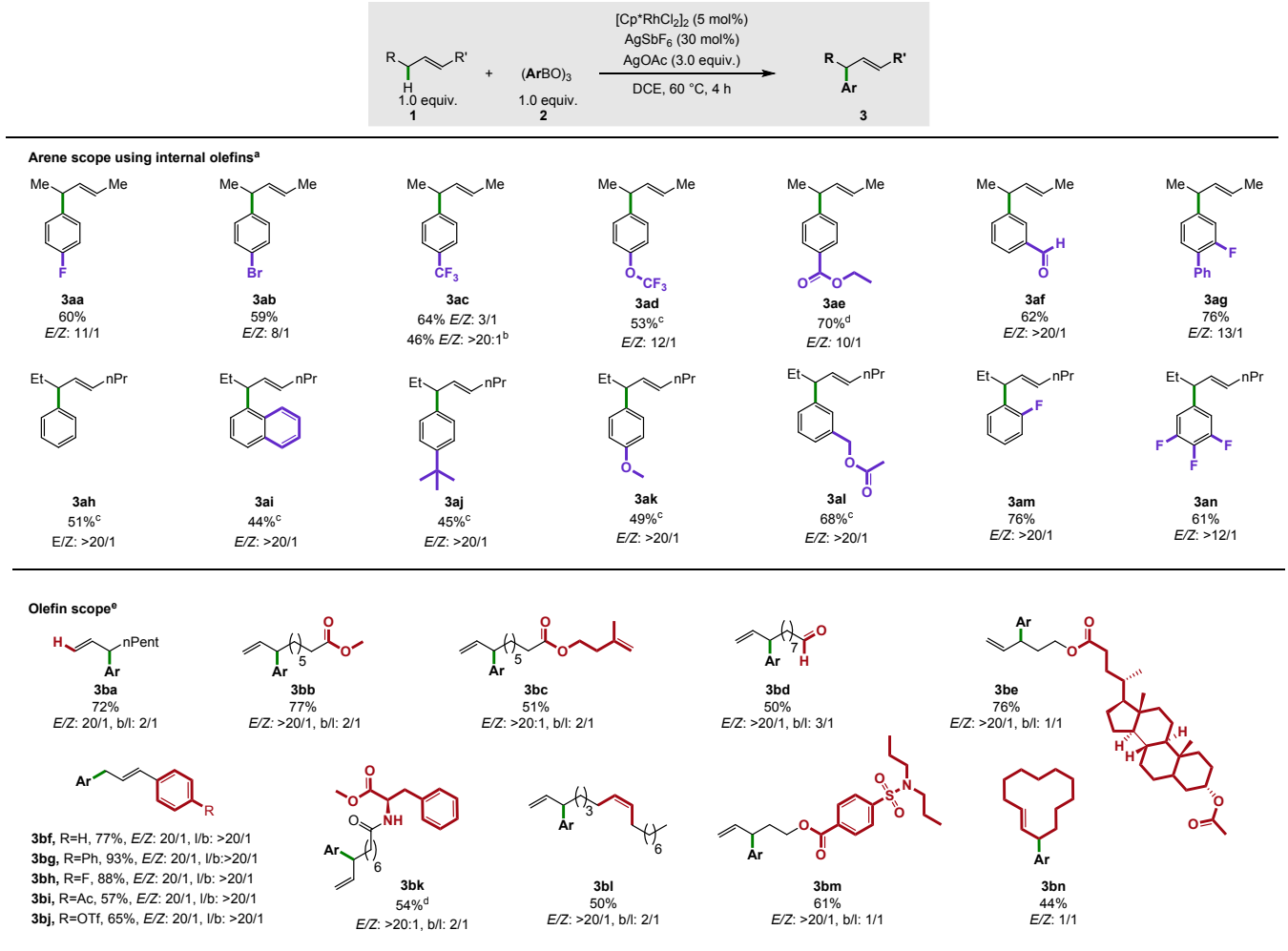


Scheme 1. Allylic vs. vinylic functionalization of olefins.

With regard to the significant synthetic value of allyl groups and inspired by Nakamura's fundamental work on transition metal catalyzed allylic arylation[4a], we became motivated to develop a mild and broadly applicable strategy for the formation of allylic C(sp^2)–C(sp^3) bonds that obviates the need of prefunctionalized olefins which have to be prepared in multi-step procedures. Our design aimed to enable the allylic coupling of the vast number of commercially available arylboron reagents with the petrochemical feedstock of terminal and internal olefins by using catalyst-controlled allylic C–H activation instead of substrate-controlled formation of allyl-metal species (Scheme 1C).

Based on our experience, we envisaged that high valent Cp*Rh^{III}-catalysts (Cp*=$C_5Me_5^-$) might be capable to enable the direct arylation of allylic C–H bonds since they have not only shown their potential in allylic C–H activation reactions[7] but also in the arylation of C(sp^3)–H bonds utilizing organoboron reagents.[8]

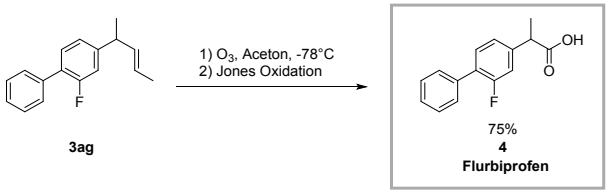
However, this transformation presents several intrinsic challenges: (i) The utilization of a transition metal (TM), a transmetalating reagent, an olefin and an oxidant typically results in the formation of Heck-type products.[2] Additionally, a variety of transformations has been described for the directing group assisted oxidative Heck reaction using Cp*Rh^{III}.[9,10] To achieve the desired reactivity the C(sp^3)–H activation/Rh^{III}–allyl formation must be favoured over arene transmetalation/migratory insertion (Scheme 1A); (ii) in order to avoid the formation of large quantities of arene homocoupling, the allylic arylation reaction must be faster than twofold arene transmetalation/C(sp^2)–C(sp^2) reductive elimination; (iii) the catalyst must distinguish between the formation of *syn*- and *anti*-π-allyl species to guarantee a high degree of diastereoselectivity.



Scheme *2*. Scope of the Rh^{III}-catalyzed allylic arylation. Reactions performed on a 0.3 mmol scale in 1.5 mL of 1,2-dichloroethane (DCE). Isolated yields are stated for isomeric mixtures unless otherwise noted. [a]Products were obtained as a single regioisomer using (*E*)-2-pentene and in a ~1.4:1 ratio using (*E*)-4-octene (see supporting information). [b]AgO_2C*n*pent was used instead of AgOAc. [c]20 mol% $AgSbF_6$ was used. [d]Yield determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as internal standard. [e]Ar = 2-fluorobenzene; AgO_2C*n*pent was used instead of AgOAc for all terminal olefins except allylarenes.

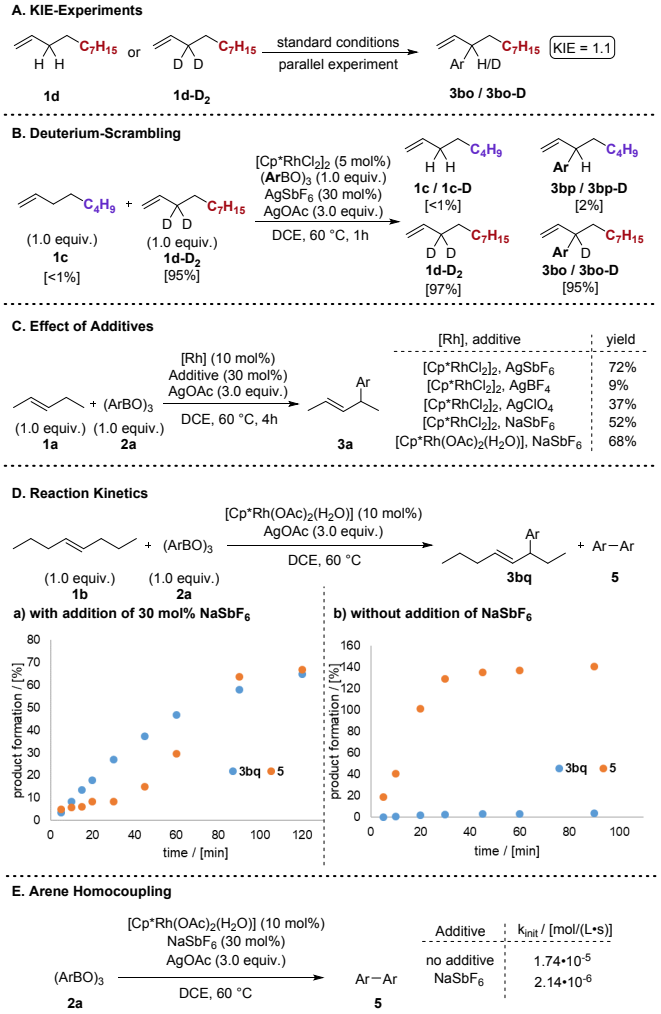
We began our studies using (*E*)-2-pentene as the substrate. The catalyst would have to distinguish between the activation of the internal versus the terminal C–H bonds. Additionally we were aware of the formation of *syn*- and an *anti*-Rh^{III}–allyl species possibly leading to (*E*)- or (*Z*)-isomers, respectively. 4-Fluorophenylboronic acid was chosen to be the coupling partner and the reaction was carried out with $[Cp^*RhCl_2]_2$ (5.0 mol%), $AgSbF_6$ (20 mol%) and AgOAc (2.0 equiv.) in DCE (0.2 M) at 60 °C (see Table S1, supporting information). Unfortunately, only traces of homo-coupled arene and no desired product formation (**3aa**) were observed. Upon switching from the boronic acid to its anhydride the tris(4-fluorophenyl)boroxine, we were delighted to obtain product **3aa** in 59% GC-yield. By a slight increase of the oxidant to 3.0 equivalents and $AgSbF_6$ to 30 mol% we obtained the arylated product in 72% GC- and 60% isolated yield, noting the volatility of the product. The diastereoselectivity was determined to be 11:1. Interestingly, with the use of the slightly more sterically demanding Cp^{iPr}-ligand (Cp^{iPr}=isopropyl-tetramethyl-cyclopentadienyl) we could obtain **3aa** in 60% yield and excellent diastereoselectivity (>20:1) (see supporting information). With the optimized reaction conditions in hand, we began to investigate the scope using triarylboroxines, internal olefins as coupling partners and the commercially available $[Cp^*RhCl_2]_2$ as the catalyst (Scheme 2). The *para* substituted bromophenyl boroxine **2b** reacted smoothly to provide **3ab** in 59% yield. A strongly electron-withdrawing trifluoromethyl substituent gave a 64% yield of **3ac** with a poor diastereomeric ractio of 3:1. Intriguingly, by a simple switch of the Ag-carboxylate from acetate to *n*-hexanoate we could

increase the diastereoselectivity to >20:1 (see supporting information). Other electron-withdrawing groups such as trifluoromethoxy (**2d**), ester (**2e**) or formyl (**2f**) substituents in the *para* or *meta* positions delivered the desired products in good yields and moderate to excellent diastereoselectivies. We observed that *E*/*Z* selectivities are dependent on the electronics of the arylboron reagent and speculate that electron-rich arylboroxines tend to undergo transmetalation faster than electron-poor arylboroxines, thus leading to higher *E*/*Z* selectivities since the Rh-allyl species has less time to isomerize. Notably, by switching from (*E*)-2-pentene to (*E*)-4-octene the Rh^{III} catalyst can hardly distinguish between the reductive elimination in the 3- or 4- positions delivering a roughly 1.4:1 regioisomeric ratio (see supporting information). Triphenylboroxine (**3ah**) gave 51% product formation and >20:1 diastereoselectivity using (*E*)-4-octene (**1b**) as the coupling partner. Sterically more demanding tris(1-naphthyl)-boroxine (**2i**) resulted in 44% product formation. Electron-donating substituents such as *tert*-butyl (**2j**) or methoxy (**2k**) led to moderate yields and excellent *E*/*Z* ratios. An *ortho*-fluoro substituted arene (**2m**) led to 76% product formation. Multi-substituted arenes could be also utilized and delivered **3ag** and **3an** in high yields. We proceeded to evaluate the scope of the reaction using different unactivated terminal olefins. Interestingly, even though we only observed the internal arylation product using (*E*)-2-pentene we were likewise able to functionalize a variety of terminal olefins. 1-Octene could be arylated in 73% yield, excellent diastereoselectivity and a 2:1 regiosiomeric ratio favouring the branched product. The regioisomeric ratio could be inversed to 1:2 when a sterically less demanding tetramethylcyclopentadienyl ligand was used (see supporting information). An olefin attached to a methyl ester gave a similar result as 1-octene (**3bb**) and an aliphatic aldehyde resulted in 50% product formation (**3bd**). A lithocholic acid derivate delivered 76% of the corresponding product (**3be**). Furthermore, a variety of allylarenes could be functionalized. To our delight, exclusively linear products were obtained with perfect diastereoselectivites and good to excellent yields (**3bf**–**3bj**). We assume that the formation of linear products is favoured owing to conjugation of the double bond. Product **3bm**, bearing the Probenecid drug scaffold, was obtained in 61% yield. Additionally, we were able to obtain the arylated product derived from phenylalanine (**3bk**) in 54% yield. Interestingly, cyclic olefins could be used as substrates. Cyclododecene was converted to **3bn** in a moderate yield and a roughly 1:1 *E*/*Z* mixture. Selective functionalization at the terminal olefin was obtained even when the molecules contained a terminal-branched (**3bc**) or a *cis* double bond (**3bl**).



Scheme 3. Concise synthesis of flurbiprofen.

2-Arylpropionic acids are a highly important class of nonsteroidal anti-inflammatory drugs, however, the synthesis of α-arylated carboxylic acids is still synthetically challenging. By applying our developed reaction protocol we were able to prepare flurbiprofen in a highly concise synthetic sequence.[11] Starting from the cheap and commercially available boronic acid we prepared the boroxine **2g** quantitatively by refluxing under Dean-Stark conditions and coupled it with *E*-2-pentene by our standard protocol. The allylically arylated product **3ag** was further converted by ozonolysis and subsequent oxidative workup to yield 75% of flurbiprofen in overall 3 straightforward steps (Scheme 3).[12]



Scheme 4. Mechanism studies. Yields determined by GC-FID. Deuterium incorporation indicated in square brackets; Ar = 4-fluorophenyl. Structures of major isomers given.

We were intrigued by the reaction mechanism and started its investigation by kinetic isotope effect (KIE) studies. In a parallel experiment with deuterated and undeuterated 1-undecene (**1d**, **1d-D_2**) no significant KIE was observed, suggesting that the C–H activation is unlikely to be occurring during the rate limiting step (Scheme 4A, for further details see supporting information).[13] Subsequently deuterium scrambling experiments were conducted, in which deuterated **1d-D_2** and undeuterated **1c** were submitted to the standard reaction conditions for just 1 h to prevent full conversion of the olefins (Scheme 4B). Neither in the remaining starting materials (**1c**, **1d-D_2**) nor in the corresponding products (**3bp**, **3bo-D**) were significant amounts of deuterium/hydrogen exchange detected. This is indicating that presumably either the nature of the C–H activation step or the olefin coordination to the metal center is irreversible under the reaction conditions. Low coordinating silver salts are typically added in Rh^{III}-catalyzed C–H activation protocols to guarantee fast halogen abstraction from the $[Cp^*RhCl_2]_2$ pre-catalyst rendering it more reactive. During the reaction optimization we found that an increased $AgSbF_6$ loading from 20% to 30% led to higher yields even though 20% $AgSbF_6$ should be sufficient to abstract all halogen ions. Subsequently, we probed this effect by the addition of different additives (Scheme

4C). By employing $AgSbF_6$ **3a** was obtained in 72% yield whereas only 9% product was formed when $AgBF_4$ was used and 37% of **3a** was observed by applying $AgClO_4$. We would expect the anion to exhibit minor or no effects if the role of the salt is limited to halogen abstraction. Spurred by this observation we opted to determine if the Ag^+-ion is indispensable for the reaction outcome. To our surprise, with the addition of $NaSbF_6$ we could obtain **3a** in 52% yield (Scheme 4C). When compared to our standard catalytic system, the combination of a Cp^*Rh^{III} acetate pre-catalyst and $NaSbF_6$ led to an almost identical amount of product (68%). Therefore, it is likely that $AgSbF_6$ is playing a bifunctional role, guaranteeing a fast halogen abstraction owing to the weakly coordinated Ag^+ and additionally facilitating the reaction. The addition of non-coordinating anions can lead to ion pair partitioning and thus forming a more cationic catalyst as it has been described for palladium catalysed allylic substitution.[14] We decided to record reaction kinetics using $[Cp^*Rh(OAc)_2(H_2O)]$ as the pre-catalyst and $NaSbF_6$ as the additive to exclude influences of the halogen abstraction (Scheme 4d, for a full reaction profile see supporting information S3). With the addition of $NaSbF_6$ (Scheme 4D-a) product formation is initially faster than arene homocoupling. With a decreasing olefin concentration (**1b**) homocoupling (**5**) begins to override cross-coupling (**3bq**) and similar amounts of both products are formed after 2 h reaction time. In contrast, without the addition of $NaSbF_6$ only traces of cross-coupled product **3bq** were formed and homocoupling proceeded until triarylboroxine **2a** was consumed. The SbF_6–anion is presumably either decreasing the transmetalation rate, allowing the formation of Rh-allyl species that can further react to the corresponding arylated products, or accelerating the allylic C–H activation. Investigation of the initial rates of the arene homocoupling revealed that the addition of $NaSbF_6$ tremendously slows down the reaction (Scheme 4E). Similar results were obtained with $[Cp^*RhCl_2]_2$ in combination with $AgBF_4/AgSbF_6$ (see supporting information). Thus, we assume that allylic arylation is enabled when C–H activation is maintained faster than transmetalation.

In conclusion we have developed the first Suzuki-Miyaura-type allylic coupling of unactivated terminal and internal olefins with both electron-rich and -deficient arylboroxines. Further, the reaction could be applied to the efficient synthesis of the anti-inflammatory drug flurbiprofen. Mechanistic investigations were conducted to give insights into the reaction mechanism and an unexpected role of the SbF_6^- counter-ion was observed.

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Author Contributions

‡These authors contributed equally.

Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org website at DOI:

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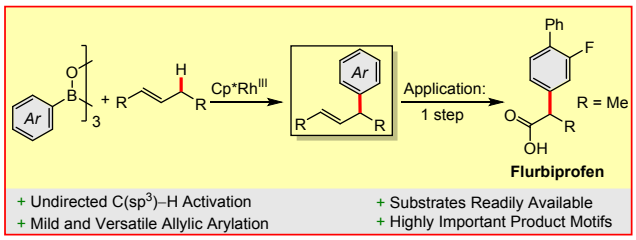
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Application:
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Flurbiprofen
+ Undirected C(sp3)–H Activation
+ Mild and Versatile Allylic Arylation
+ Substrates Readily Available
+ Highly Important Product Motifs