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Non-Directed Cross-Dehydrogenative (Hetero)arylation of Allylic C(sp^3)–H bonds enabled by C–H activation

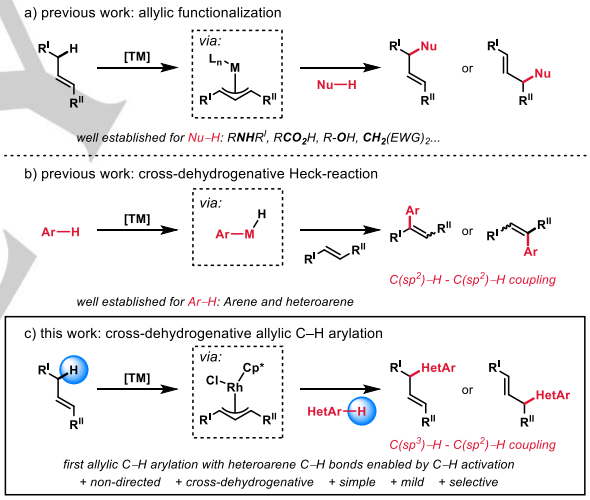
Andreas Lerchen, Tobias Knecht, Maximilian Koy, Johannes B. Ernst, Klaus Bergander, Constantin G. Daniliuc, and Frank Glorius*

Dedicated to Professor Helmut Schwarz on the occasion of his 75th birthday

Abstract: Herein, we report the selective, non-directed and cross-dehydrogenative coupling of allylic C(sp^3)–H bonds with C(sp^2)–H bonds of (hetero)arenes. The developed methodology employs the abundant chemical feedstocks of olefins and (hetero)arenes and could be applied in late-stage functionalization reactions of pharmaceuticals. Furthermore, the discovered system exclusively delivers the allylic C–C coupling products highlighting the preservation of the olefin substitution pattern for further derivatization.

The direct catalytic formation of C–C bonds through the selective activation of a specific C(sp^3)–H bond in organic molecules is an elementary goal of synthetic chemists in the pursuit of generating valuable and complex target molecules. To date, stoichiometric directing groups (DGs) have been used to enable such processes,[1] but the need to install and eliminate these DGs results in an overall tenuous atom-economy.[2] Significant improvements to this approach have been made by the groups of Yu and Ge, who independently reported the use of catalytic transient DGs.[3] However, the portfolio of reactions that avoid permanently installed or transient DGs remains underrepresented. Nevertheless, such challenging non-directed approaches are highly attractive in medicinal and materials chemistry because of their applicability in late-stage functionalization reactions.[4] Analogous to removing DGs to improve atom- and step-economy, the ideal (non-directed) coupling reaction should also not require wasteful pre-functionalization of the coupling partner and utilize only C–H bonds. However, there are other challenges associated with such a cross-dehydrogenative coupling (CDC) approach.[5] For example, the selectivity of a CDC reaction requires both the coupling partner and substrate to undergo either a catalyst- or substrate-controlled C–H activation event.[6] Furthermore, an inversion of catalyst reactivity is typically necessary after the first C–H activation event to prevent homo-coupling and to switch selectivity to the other coupling partner.[7]

Considering the above, we envisaged a combined non-directed CDC approach that solves two long-sought challenges. First, we wanted to investigate the selective non-directed coupling of a specific C(sp^3)–H bond with a C(sp^2)–H bond, that is enabled by a transition-metal catalyzed C–H activation approach. To the best of our knowledge this type of coupling is rarely explored in the literature.[8] However, the successful tackling of this desired approach could be realized by the coupling of allylic C(sp^3)–H bonds with C(sp^2)–H bonds of heteroarenes. Considering this reaction design, a second challenge needs to solved: While for instance the amination,[9] oxygenation[10] and alkylation[11] of allylic C(sp^3)–H bonds belong to established reactions in C–H activation approaches (Scheme 1a) the allylic C(sp^3)–H arylation is rarely explored and strongly limited in applicability.[12] So far only pre-functionalized (cyanoarenes/aryl-Grignards) or multifluorinated arenes can be employed. Given the lack of reports adressing these challenges by incorporating the selective coupling of abundant and unfunctionalized starting materials, clearly indicates the considerable need for research in this area.



Scheme 1: Dehydrogenative coupling reactions. Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl.

To achieve such a challenging reaction, the competing cross-dehydrogenative Heck-type coupling of the arene C(sp^2)–H bond and the olefin C(sp^2)–H bond that is also known as Fujiwara-Moritani reaction needs to be overcome (Scheme 1b).[13] Therefore, an effective catalyst-controlled differentiation in between the activation of the allylic C(sp^3)–H bond, the heteroarene C(sp^2)–H bond and the olefinic C(sp^2)–H bond is necessary. This means for our desired scenario that a catalyst is needed which selectively activates the allylic C(sp^3)–H bond first (Scheme 1c). Then, a selective activation of the heteroarene C(sp^2)–H bond needs to be guaranteed at the electronically activated site and therefore a dichotomous behavior of the catalyst needs to be ensured. This means, that the activation of the heteroarene is less favored by the initial catalyst, whereby a high affinity is needed of the rhodium-allyl intermediate for the heteroarene activation. In this way, complementary reactivity to

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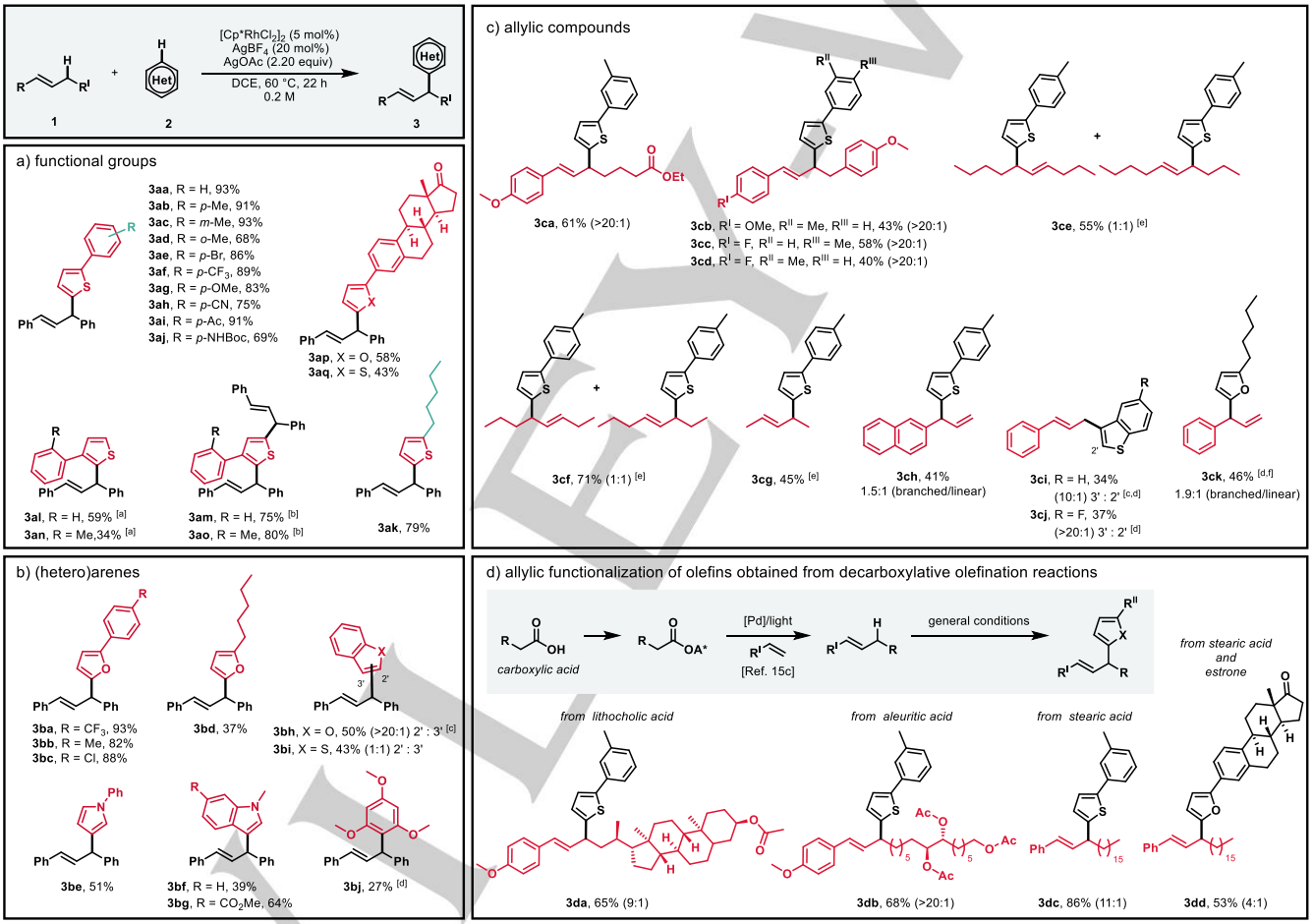
previously reported dehydrogenative Heck-type reactions can be achieved.

To begin our studies towards this goal, we selected $[Cp^*RhCl_2]_2$ as catalyst of choice as this catalyst has already shown reactivity in all of the above activation scenarios.[14] Next, after brief optimization studies (see the Supporting Information) we selected to use (*E*)-prop-1-ene-1,3-diyldibenzene as a substrate for allylic C(sp^3)–H bond activation to obviate selectivity and potential homo-coupling issues and arylated thiophenes were chosen as coupling partners. Then, we investigated the scope (Scheme 2a), which revealed that several 2-aryl substituted thiophenes could be tolerated and did not influence the selectivity (**3aa**–**3ad**). Additionally, compound **3ac** was unambiguously confirmed by X-ray crystallographic analysis (see the Supporting Information). Thiophenes bearing electron-withdrawing (**3ae**, **3af**, **3ah**, **3ai**) or electron-donating substituents (**3ag**, **3aj**) were then examined, which all afforded reliably the desired products in good to excellent yield, demonstrating a broad functional group tolerance. Moreover, a C2-alkylated thiophene was also well tolerated under the reaction conditions (**3ak**). For thiophenes bearing an aryl substituent at the C3-position we were able to promote either mono-substitution at the C2-position (**3al**, **3an**) or di-substitution at both the C2- and C5-position (**3am**, **3ao**). Additionally, the furan and the thiophene bearing an estrone moiety at the C2-position, reacted with the standard substrate in moderate yield (**3ap**, **3aq**). Next, other heteroarenes were investigated (Scheme 2b). Arylated and alkylated furans all delivered the corresponding products in moderate to high yield (**3ba**–**3bd**). Pleasingly, aza-heterocycles could also be readily functionalized under the reaction conditions (**3be**–**3bg**). Whilst, benzofuran was primarily functionalized in the C2-position (**3bh**), benzothiophene afforded the corresponding product with a 1:1 selectivity for the C2:C3 positions (**3bi**). Finally, 1,3,5-trimethoxybenzene could also be reacted to afford the corresponding product (**3bj**).



Scheme 2: Substrate scope of the cross-dehydrogenative (hetero)arylation of allylic C(sp^3)–H bonds. General conditions: **2** (0.2 mmol), **1** (1.50 equiv), $[Cp^*RhCl_2]_2$ (5 mol%), $AgBF_4$ (20 mol%), AgOAc (2.20 equiv) in 1,2-dichloroethane (1.0 mL) were used. [a] **1** (0.2 mmol) and **2** (4.00 equiv) were used. [b] **1** (4.00 equiv), **2** (0.2 mmol) and AgOAc (4.40 equiv) were used. [c] Reaction was stirred for 48 hours. [d] **1** (2.00 equiv) were used. [e] **1** (4.00 equiv) were used. [f] Reaction was run at room temperature. DCE = 1,2-dichloroethane, Boc = *tert*-butyloxycarbonyl, Ac = Acetyl.

Furthermore, a variety of internal olefins were tested under the optimized conditions (Scheme 2c). *Trans*-β-alkyl styrenes, all underwent selective heteroarylation at the allylic C(sp^3)–H bond and the styrenyl-moiety remained untouched (**3ca**–**3cd**). Then, the internal olefins 4-octene and 5-decene were tested, which both delivered the corresponding heteroarylation products as 1:1 regioisomers (**3ce**, **3cf**). However, the unsymmetrical internal olefin 2-pentene delivered the desired product as a single regioisomer (**3cg**), indicating that the catalyst favors the formation of an internal rhodium-allyl species versus the terminal.

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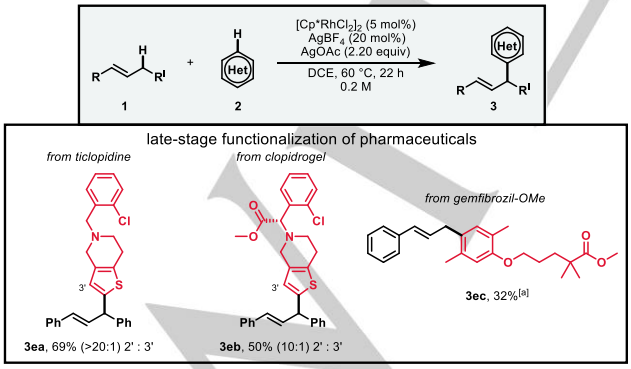
Afterwards, allylbenzene was employed as an example for terminal alkenes and coupled with each, benzothiophene as well as 5-fluorobenzothiophene to afford the corresponding linear functionalized products in moderate yield (**3ci**, **3cj**). Next, allylbenzene was reacted with 2-pentylfuran and the coupling product **3ck** was isolated in 46% yield. However, in this reaction a regioisomeric mixture of 1.9:1 was obtained while the branched functionalization was favored over the linear. A similar result was observed when 2-(*p*-tolyl)thiophene and 2-allylnaphthalene were reacted. Under the optimized conditions the corresponding product **3ch** was isolated in 41% as a mixture of regioisomers (1.5:1 branched/linear).

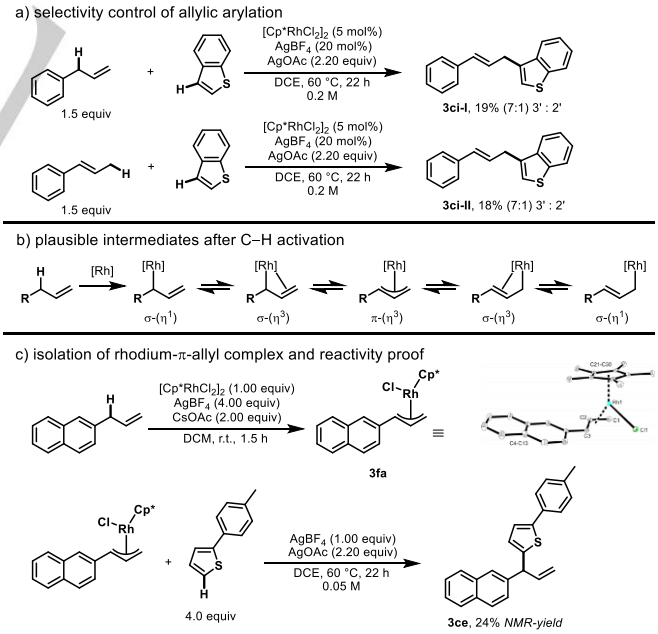
Recently, the use of naturally occurring carboxylic acids in decarboxylative olefination reactions has received significant attention from the chemical community.[15] The highly functionalized products resulting from those reactions generally bear an allylic C(sp^3)–H bond adjacent to the olefin. Therefore, we wanted to investigate whether our developed methodology could be employed for further functionalization of those motifs (Scheme 2d). Indeed, acetyl-protected lithocholic acid could be coupled with 4-methoxystyrene and the resulting olefin could be derivatized with 2-(*m*-tolyl)thiophene at the allylic C(sp^3)–H position in 65% (**3da**). In a similar manner, acetyl-protected aleuritic acid could be employed and the corresponding product **3db** was isolated in 68% yield. Finally, stearic acid was coupled first with styrene and further derivatization with 2-(*m*-tolyl)thiophene delivered **3dc** in high yield. Moreover, the furan substituted at the C2-position with an estrone unit could also be reacted with an olefin arising from stearic acid and the desired product was obtained in 53% yield (**3dd**).

To further establish the broad applicability of this protocol and considering its potential applications in late-stage modification, we sought to apply our methodology to pharmaceuticals (Scheme 3). Ticlopidine, an antiplatelet drug, reacted with (*E*)-prop-1-ene-1,3-diyldibenzene to form the desired product (**3ea**) in 69% yield and with >20:1 selectivity (C2:C3). Similar reactivity was also obtained when using clopidrogel as substrate (**3eb**). To our delight, the methyl-protected drug gemfibrozil bearing an electron-rich arene scaffold also reacted in combination with allylbenzene to afford the product (**3ec**) in modest yield.



Scheme 3: Late-stage functionalization of pharmaceuticals. General conditions: **2** (0.2 mmol) and **1** (1.50 equiv) were used. [a] **1** (2.00 equiv) were used.

To gain crucial mechanistic understanding of the developed transformation, several experiments were conducted (Scheme 4). First, we performed two independent reactions to investigate the activation mechanism of the allylic moiety (Scheme 4a). For this reason, either allylbenzene or *trans*-β-methylstyrene were reacted together with benzothiophene under the general reaction conditions and both reactions delivered exactly the same products with identical selectivity (**3ci-l**, **3ci-ll**). Based on these results two crucial hypotheses can be postulated: first, a Heck-type carbometalation pathway can be excluded[12b] and therefore second, the generation of either a η^3-π-allyl, a η^3-σ-allyl or a η^1-σ-allyl species can be proposed in the reaction medium (Scheme 4b).[16] Although it is known that these species can undergo a σ-π-σ-isomerization[16,17] we then attempted to isolate one of these proposed intermediates. Pleasingly, we were indeed successful in isolating a Rh-π-allyl complex (**3fa**) from C–H activation conditions when 2-allylnaphthalene was employed (Scheme 4c). The solid-state structure of the complex was confirmed by X-Ray crystallography showing that a η^3-π-allyl-complex was obtained.[18] Then, the reactivity of this rhodium-η^3-π-allyl complex (**3fa**) was investigated in a stoichiometric experiment. The branched product of the arylated allylnaphthalene (**3ce**), that is supposed to be the major isomer in its corresponding catalytic reaction, was exclusively observed by NMR-spectroscopy, suggesting that a rhodium-π-allyl complex is an active intermediate in this transformation. However, the formation of the linear isomer was not observed. It could be reasoned that the η^3-π-allyl-intermediate is not the most reactive species that is generated in the catalytic medium. Even though a η^3-σ-allyl or a η^1-σ-allyl species could be more reactive, we were already able to demonstrate that the allylic moiety can be isomerized by the catalyst (Scheme 4a). Considering a η^3-π-allyl-species is very likely to be an intermediate in this σ-π-σ-isomerization process, we can therefore conclude that this species is indeed present in the catalytic cycle.[17b]



Scheme 4: Mechanistic investigations.

Finally, we investigated the substrate-activation and the subsequent coupling-selectivity of the Cp*Rh(III)-catalyst for the heteroarenes, since the homo-coupling reactivity has already been observed for this catalyst.[7c] When only benzofuran or 2(*o*-tolyl)thiophene were employed under the standard conditions,

the homo-coupling products (**4a**, **4b**) were not observed (see the Supporting Information). This result indicates that the homo-coupling of the heteroarenes is less favored by the Cp*Rh(III)-catalyst than the functionalization of the allylic moiety. Further mechanistic investigations and the development of either racemic or enantioselective Cp*Rh(III)-catalyzed allylic functionalization reactions are on-going in our laboratory.

In summary, a new concept of methodology is developed for the non-directed, selective and predictable cross-dehydrogenative coupling of allylic C(sp^3)–H bonds and (hetero)arene C(sp^2)–H bonds. This C–H activation methodology employs the abundant chemical feedstocks of olefins and (hetero)arenes without the need for pre-functionalization of both, substrate and coupling partner. Moreover, the discovered system exclusively delivers the allylic C–C coupling products preserving the substitution pattern of the olefin. Additionally, we demonstrated the excellent functional group tolerance of this mild reaction protocol and its application in late-stage functionalization.

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Keywords: rhodium • cross-dehydrogenative coupling • CDC • allylic arylation • heteroarenes

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[18] Crystallographic data for (**3ac**) and (**3fa**) are available free of charge from the Cambridge Crystallographic Data Centre under CCDC-1839138 and CCDC-1839139.

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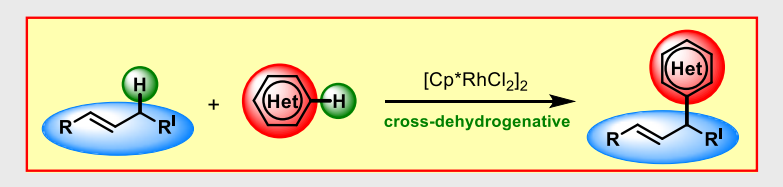

*Andreas Lerchen, Tobias Knecht, Maximilian Koy, Johannes B. Ernst, Klaus Bergander, Constantin G. Daniliuc, and Frank Glorius**

Page No. – Page No.

Non-Directed Cross-Dehydrogenative (Hetero)arylation of Allylic C(sp^3)–H bonds enabled by C–H activation

Catch Desired Couplings: The non-directed cross-dehydrogenative coupling of allylic C(sp^3)–H bonds with (hetero)arene C(sp^2)–H bonds is developed. This desired approach is enabled by C–H activation and employs the abundant chemical feedstocks of olefins and (hetero)arenes. A particular highlight of this mild reaction protocol is the applicability in late-stage functionalization reactions. Moreover, the discovered system exclusively delivers the allylic C–C coupling products preserving the substitution pattern of the olefin.