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Rhodium(III)-Catalyzed Direct Oxidative Cross Coupling at the C5 Position of Chromones with Alkenes

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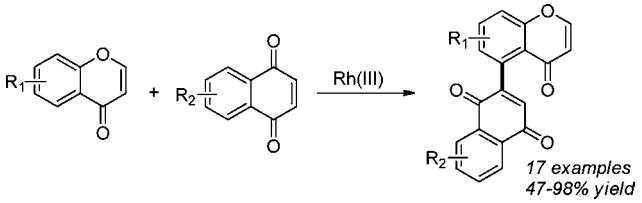
ABSTRACT



An atom-economical, Rh(III)-catalyzed, direct oxidative cross-coupling at the C5 position of chromones and flavones with a broad range of alkenes was developed. The products were formed in a highly regioselective manner in good to excellent yields. The developed method was applied in the cross-coupling of natural products for the synthesis of hybrid molecules.

Transition-metal-catalyzed carbon−carbon or carbon−heteroatom bond-forming transformations via C−H bond functionalization reactions have gained significant attention from the entire chemical community due to their extensive application in straightforward formation of complex molecular structures.[1] Over the past decades, varieties of processes were developed for the coupling of prefunctionalized building blocks in high yields and with predictable regioselectivity. However, direct methods for coupling of nonprefunctionalized partners can avoid the preparation of activated coupling partners, and make the synthetic strategy more atom-economic.[2] Cross-dehydrogenative coupling (CDC) often requires a directing group containing substrate, a coupling partner with a transition metal, and a terminal oxidant to furnish the desired regioselectivity and catalytic turnover.[2b] Among CDC reactions, oxidative arene olefination[3] catalyzed by transition metals,[4] especially rhodium,[5,6] have been intensively studied in recent times. Unfortunately, the choice of olefins in these transformations is typically limited to styrenes and

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acrylates. This fact has also been highlighted in the recent review by Glorius et al.[5f] and others.[5a−e]

Recently Hong et al. developed a direct cross-coupling between chromones and electron-deficient olefins at the most electron-rich C3 position of chromone using $Pd(OAc)_2$ as catalyst,[7] and Jeganmohan et al. showed that the C5 position of chromone can be alkenylated using a chelation-assisted ruthenium-catalyzed transformation (Figure 1).[8] However, these two methodologies also suffer from limitations in terms of the scope of olefins that can be efficiently used.

In the wake of these reports and their associated limitations and as part of our studies on the direct functionalization of unactivated C−H bonds,[9] we planned to establish a relatively general methodology for the direct regioselective functionalization of chromone derivatives at the C5 position with a variety of olefins using the keto group of chromone as directing group.

Moreover, regioselective introduction of chemically versatile alkene moieties to chromone, having multiple reactive sites, is of immense importance as chromones are present in many biologically active scaffolds.[10] We also thought that the coupling of chromones, if possible, with quinone derivatives[11] which themself are present in many bioactive scaffolds could provide ready access to a new class of so-called "hybrid molecules".[12] Hybrid molecules can be defined as chemical entities with two or more structural domains having different biological functions.[12b] The hybrid approach is a promising direction for medicinal drugs that can effectively target multifactorial diseases. Herein, we report a Rh(III)-catalyzed highly regioselective dehydrogenative cross coupling of a large variety of chromone derivatives with a broad range of olefins.

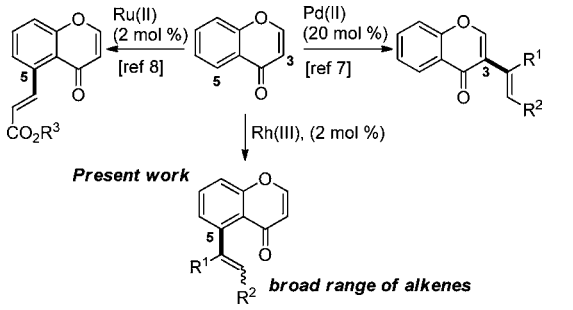

Figure 1. Dehydrogenative cross-coupling with chromones.

We started our optimization using the simple natural products chromone[13] (**1a**) and 1,4-naphthoquinone[14] (**2a**) for Rh(III)-catalyzed CDC. Our initial attempt based on reported conditions[6i,s] using stoichiometric amounts of anhydrous copper acetate as oxidant, 2 mol % of bis-(pentamethylcyclopentadienylrhodium dichloride) and 8 mol % of $AgSbF_6$ as an additive in *tert*-amyl alcohol at 100 °C led to selective formation of the desired product (**3a**) with an impressive 70% yield (Table 1, entry 1). *It is remarkable; there are six C−H bonds (two C−H bonds in chromone and four in 1,4-naphthoquinone) that can be activated by transition metal and lead to different regioisomeric and dimerized products. Nevertheless, selective formation of only one product was observed.* Further screening of various solvents resulted in the improved isolated yield of **3a** (77%) in 1,4-dioxane (Table 1, entries 1−6). Application of copper(II) triflate as oxidant was not able to provide the desired product in detectable amount (Table 1, entry 8). Among other oxidants tested, Ag_2O provided the best yield with 73% in 17 h (Table 1, entry 10). Unfortunately, the attempt to use air as an oxidant in the presence of substoichiometric amounts of anhydrous copper acetate was not successful (Table 1, entry 7). In further control experiments, it was revealed that in the absence of Rh(III) catalyst or additive ($AgSbF_6$) the reaction did not provide the desired product **3a** (Table 1, entries 13 and 14). In further optimization, it was found that the decrease of the amount of copper acetate to 1.2 equiv or **2a** to 1.5 equiv still provided the desired product in comparable isolated yield (77−79%) after 22 h (Table 1, entry 15 and 16) at 120 °C. However, a decrease of both substances to 1.2 and 1.5 equiv led to decreased yields of product (68%) (Table 1, entry 17). It is important to note that the use of $[RuCl_2(p\text{-cymene})]_2$ as

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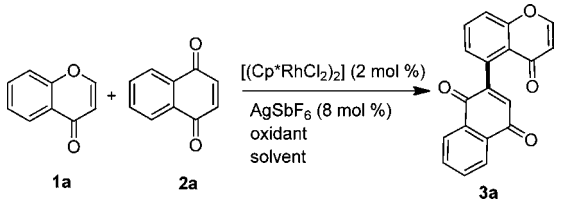
catalyst, which is known as the cheaper alternative for this kind of coupling, under reported optimized conditions provided only poor yields of the desired product **3a** (Table 1, entries 18 and 19).[8] This clearly proves Rh catalyst to be a more suitable choice for this important transformation. Finally, we decided to use 2 mol % of Rh(III) catalyst along with 8 mol % of $AgSbF_6$ and 1.2 equiv of $Cu(OAc)_2$ as oxidant in 1,4-dioxane at 120 °C as the optimized reaction conditions. Notably, the use of only 1.2 equiv of $Cu(OAc)_2$ as oxidant represents an advancement as usually at least 2 equiv of oxidant is needed in Rh(III)-catalyzed reactions.[5f]

Table 1. Screening of Reaction Conditions[a]



entry	oxidant (equiv)	solvent	time (h)	temp (°C)	yield[b] (%)
1	$Cu(OAc)_2$ (2.2)	*t*-AmOH	12	100	70
2	$Cu(OAc)_2$ (2.2)	1,2-DCE	12	100	72
3	$Cu(OAc)_2$ (2.2)	1,4-dioxane	12	100	77
4	$Cu(OAc)_2$ (2.2)	1,2-DME	12	100	69
5	$Cu(OAc)_2$ (2.2)	toluene	12	100	traces
6	$Cu(OAc)_2$ (2.2)	DMF	12	100	n.d.
7	$Cu(OAc)_2$ (0.25)	1,4-dioxane	45	120	17
8	$Cu(OTf)_2$ (2.2)	1,4-dioxane	17	120	n.d.
9	AgOAc (2.2)	1,4-dioxane	17	120	41
10	Ag_2O (2.2)	1,4-dioxane	17	120	73
11	$AgOCOCF_3$ (2.2)	1,4-dioxane	17	120	n.d.
12	Ag_2CO_3 (2.2)	1,4-dioxane	17	120	49
13[c]	$Cu(OAc)_2$ (2.2)	1,4-dioxane	17	120	traces
14[d]	$Cu(OAc)_2$ (2.2)	1,4-dioxane	17	120	n.d.
15[e]	$Cu(OAc)_2$ (2.2)	1,4-dioxane	22	120	77
16	**$Cu(OAc)_2$ (1.2)**	**1,4-dioxane**	**22**	**120**	**79**
17[e]	$Cu(OAc)_2$ (1.2)	1,4-dioxane	19	120	68
18[f]	$Cu(OAc)_2$ (1.2)	1,4-dioxane	22	120	12
19[f,g]	$Cu(OAc)_2$ (0.25)	1,2-DCE	24	110	20

[a] Conditions: Chromone **1a** (0.2 mmol, 1 equiv), **2a** (0.6 mmol, 3 equiv), oxidant, solvent (0.2 M). [b] Isolated yields after column chromatography. [c] No $AgSbF_6$ used. [d] No Rh(III) catalyst used. [e] 1.5 equiv of **2a** used. [f] 2 mol % of $[RuCl_2(p\text{-cymene})]_2$ used. [g] 10 mol % of $AgSbF_6$ used, and the reaction was performed in 0.33 M concentration on a 1 mmol scale.

Having the optimized reaction conditions in hand, we started to explore the generality of the reaction. Initially, the effect of substituents at the different positions of chromone for the cross-coupling with the highly electron-deficient 1,4-naphthoquinone was studied. Electron-donating and electron-withdrawing groups in positions C6 and C7 of chromone were tolerated (Figure 2, products **3b** and **3c**).

2-Substituted chromones such as flavone (vitamin P) and α-naphthoflavone were also coupled with naphthoquinone with good yields under the optimized reaction conditions (Figure 2, products **3e** and **3d**). When we tested the transformation on flavones having substituents with different electronic properties, the products were formed with good yields (Figure 2, products **3f**–**h**). Notably, 3-arylchromone (isoflavone) can be regioselectively functionalized at the C5 position of chromone, although there was a possibility that the keto group of the chromone can direct the olefin to the aryl ring at its C3 position (Figure 2, product **3i**). Further, alkenylation of chromone at the C5 position is also possible with methylbenzoquinone but with poor yield (26% in 2:1 regioisomeric mixture, see the Supporting Information).

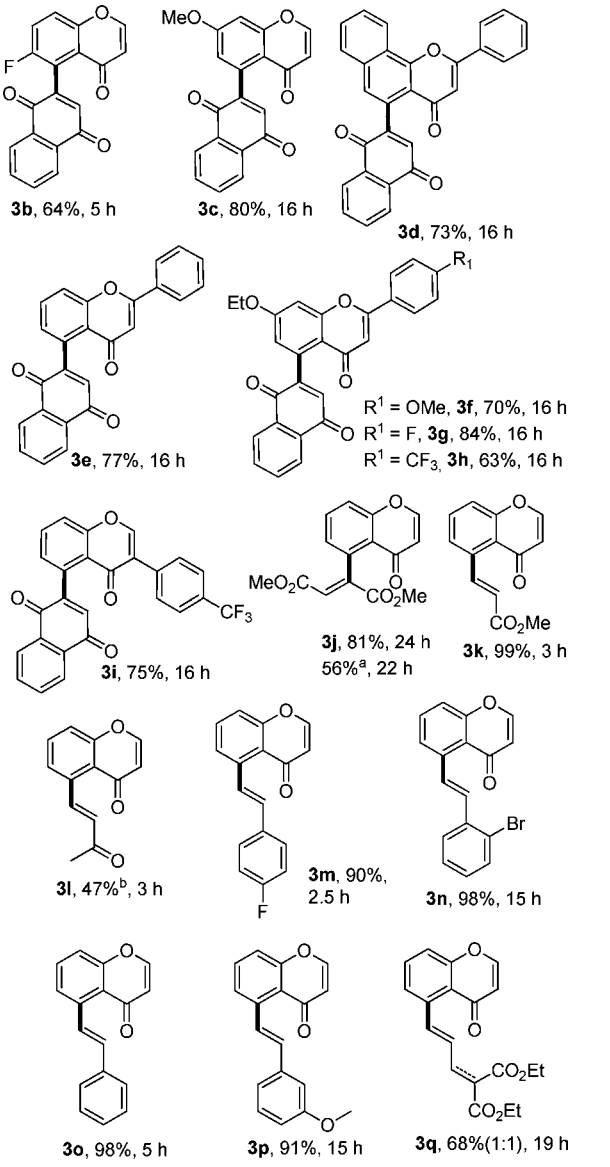


Figure 2. Scope of the reaction. Reaction conditions: chromone **1a** (0.2 mmol, 1 equiv), alkene (0.6 mmol, 3 equiv), $[(Cp^*Rh(III)Cl_2)_2]$ 2 mol %, $AgSbF_6$ (8 mol %), anhydrous $Cu(OAc)_2$ (0.24 mmol, 1.2 equiv), 1,4 dioxane (0.2 M). [a]Dimethyl maleate was used as alkene. [b]Reaction conditions: $[(Cp^*Rh(III)Cl_2)_2]$ 5 mol %, $AgSbF_6$ (20 mol %), anhydrous $Cu(OAc)_2$ (0.44 mmol, 2.2 equiv), 1,4 dioxane (0.2 M).

Afterward, we turned our attention to acyclic electron-deficient alkenes. Dimethyl fumarate provided excellent yields from the cross-coupling with chromone (Figure 2, product **3j**). When dimethyl maleate was used as coupling partner, the product turned out to be the same as with dimethyl fumarate (**3j**) due to thermal isomerization of the *cis*-double bond into the more stable *trans*-bond. In further continuation, chromone was coupled with methyl acrylate in excellent yield (Figure 2, product **3k**). However, coupling with methyl vinyl ketone required increased loading of Rh(III) catalyst to provide moderate yield (Figure 2, product **3l**). Notably, electron-deficient as well as electron-rich styrenes performed comparably well as coupling partners with excellent yield in each case (Figure 2, products **3m**−**p**). As an important result, the inactivated double bond of diethyl 2-allylmalonate underwent oxidative coupling with chromone smoothly in a regioselective manner. However, the formed product was further oxidized to give the inseparable 1:1 mixture of the desired product with the corresponding conjugated diene (Figure 2, product **3q**). The over-oxidation of the immediate product can be rationalized due to its high tendency to undergo oxidation because the resulting product **3q** is highly conjugated.

Mechanistically, we assume that this kind of metal-catalyzed directing-group assisted dehydrogenative Heck coupling started via C−H bond activation (Scheme 1). The catalytic cycle was initiated by the removal of chloride ligands from the $[(Rh(III)Cp^*Cl_2)_2]$ by $AgSbF_6$ to generate a more active rhodium complex. More likely, this active rhodium species contains ligands like acetate or solvent in addition to pentamethylcyclopentadienyl (Cp*) ligands. Coordination of this active rhodium(III) species with the keto group of **1a** and subsequent *ortho* C−H bond activation via the concerted metalation/deprotonation (CMD process) offered the five-membered rhodacycle intermediate **A**. Insertion of alkene to the rhodium−carbon bond of **A** led to the formation of the seven membered rhodacycle **B**. β-H elimination from intermediate **B** offered the desired product **3** with the reduced inactive $[Rh^ICp^*]$ complex. Thus, the essential task of copper acetate is to reoxidise the $[Rh^ICp^*]$ complex to the $[Rh^{III}Cp^*]$ species to carry on the catalytic cycle. Moreover, copper acetate could be the source of acetate ligand for the active rhodium species.[15]

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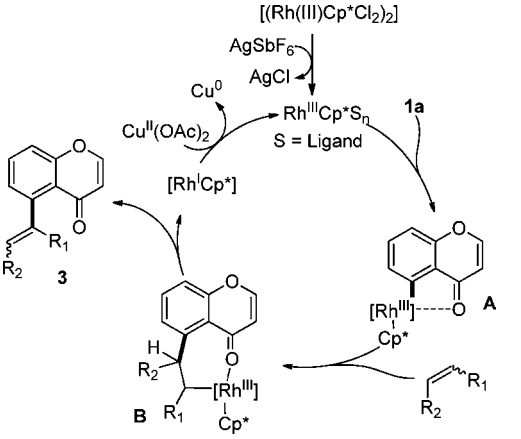
Scheme 1. Proposed Mechanism of the Cross Coupling



In conclusion, we have developed a Rh(III)-catalyzed, highly efficient, atom-economical, oxidative cross-coupling of chromones and flavones with a variety of olefins having variable electronic character. The desired products were formed in a highly regioselective manner. This methodology works efficiently with one of the broadest known ranges of olefins reported for similar transformations. This method also provides a practical way to couple structurally different natural product scaffolds such as chromone, flavones, and 1,4-naphthoquinone in a single-step transformation.

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Supporting Information Available. Experimental procedures, full characterization of new compounds, and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.