C–H Functionalization

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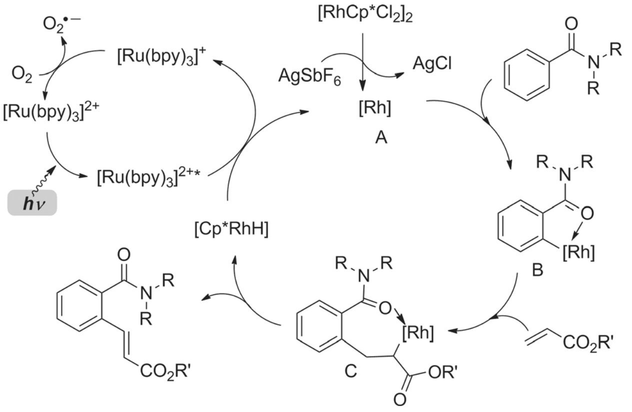
Combining Rhodium and Photoredox Catalysis for C–H Functionalizations of Arenes: Oxidative Heck Reactions with Visible Light**

*David C. Fabry, Jochen Zoller, Sadiya Raja, and Magnus Rueping**

Abstract: *Direct, oxidative metal-catalyzed C–H functionalizations of arenes are important in synthetic organic chemistry. Often, (over-)stoichoimetric amounts of organic or inorganic oxidants have to be used in these reactions. The combination of rhodium and photoredox catalysis with visible light allows the direct C–H olefination of arenes. Small amounts (1 mol %) of a photoredox catalyst resulted in the efficient C–H functionalization of a broad range of substrates under mild conditions.*

The concept of C–H activation and functionalization has proven to be a powerful tool in organic chemistry in recent years.[1] Metal-catalyzed C–H functionalization has also been established as a reliable method for the construction of complex natural products.[2] In this important field of C–H functionalization, it is the oxidative Heck reaction that has gained prominent attention, since a variety of metals, such as palladium, rhodium, and ruthenium, allow the introduction of synthetically useful building blocks.[3] In this context, Miura and co-workers reported the first Rh-catalyzed *ortho*-mono- and bisolefination of phenylpyrazoles with alkenes.[1a,o,p,4,5] The use of $Cu(OAc)_2$ led to regeneration of the rhodium catalyst. Glorius and co-workers described a rhodium-catalyzed olefination and vinylation of arenes by using a directing acetamide motif and $Cu(OAc)_2$ as the oxidant.[6,7] Liu and co-workers,[7a] as well as Feng and Loh,[7b] showed that this catalyst system can also be transferred to phenyl carbamates by using overstoichiometric amounts of $Cu(OAc)_2$. As independently shown by several research groups, the oxidative Heck reaction can also be conducted with other substrate classes by using Rh[6a,7c,d] or Ru catalysts[8,9] in combination with different amounts of $Cu(OAc)_2$.

Nevertheless, the necessity of directing groups and relatively harsh reaction conditions still limit the sustainability of this method, and the dependency on stoichiometric amounts of an external oxidant, in particular, poses a major drawback of these olefination reactions. In these procedures, the intermediary metal–hydride complex that is formed through β-H elimination is reoxidized by an oxidant. Even though improved procedures using internal oxidants have been reported in the last few years, they are still dependent upon specific functional-directing moieties which limit the general applicability to the synthesis of complex substrate classes.[10] On the basis of our studies on photoredox catalysis[11] we questioned to what extent the recyclization of the metal catalyst in the oxidative olefination reaction can be successfully accomplished by a photoredox-based process (Scheme 1).[12,13]



Scheme 1. Working hypothesis for the combined rhodium- and photoredox-catalyzed C–H functionalization. $Cp^* = C_5Me_5$.

Herein, we report the first combination of photoredox and rhodium catalysis for the direct, oxidative C–H olefination of aryl amides using visible light.

Initial studies using the photoredox catalyst $[Ru(bpy)_3](PF_6)_2$ in the rhodium-catalyzed C–H functionalization of amide **1a** with acceptor **2a** showed a significant yield (65 %) of the olefinated product **3a** after 16 h (Table 1, entry 7).[14,15] It must be highlighted that not only is 1 mol% photoredox catalyst sufficient for the described reaction, but the usual high reaction temperatures could also be lowered from 120 °C to a moderate 80 °C. A subsequent solvent screening revealed that chlorinated solvents led to conversion, and that chlorobenzene was the best solvent, affording the product in 89 % yield (Table 1, entry 8).

To gain further insight into the role of the photoredox catalyst, the standard reaction was performed in the absence of either the photoredox catalyst or light (Table 1, entries 11 and 12). In the absence of light, only traces of product could be detected, whereas no conversion could be observed if no photoredox catalyst was present during the reaction. The photocatalytic step, is therefore, indispensable for the whole process to occur.

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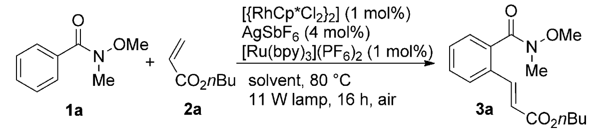
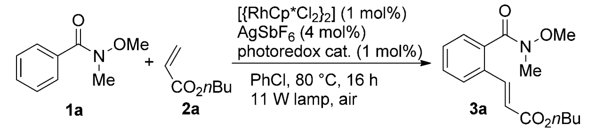
Table 1: Optimization of reaction conditions and control experiments[a]

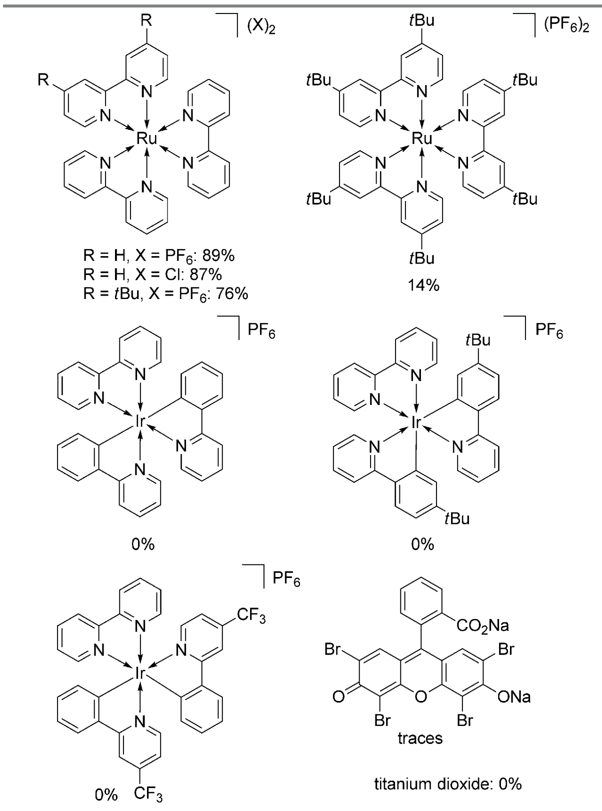


Entry	Solvent	Yield [%][b]
1	PhMe	0
2	MeCN	0
3	DMF	0
4	DMSO	0
5	EtOH	0
6	*t*BuOH	< 5
7	dichloroethane	65
8	PhCl	89
9	PhCl, 8 h	79
10	PhCl, 4 h	54
11	PhCl, no photocatalyst, 16 h	0
12	PhCl, no light, 16 h	< 3
13	PhCl, inert atmosphere, 16 h, photocatalyst (1 mol%)	< 3
14	PhCl, inert atmosphere, 16 h, photocatalyst (1 equiv)	48
15	[D$_5$]PhCl, 16 h	81
16	[D$_5$]PhCl, 8 h	72
17	[D$_5$]PhCl, 4 h	58

[a] Reaction conditions: 0.1 mmol aryl amide **1a**, 2 equiv acrylate **2a**, 1 mL solvent, irradiation at a distance of 3 cm; reaction vessels were wrapped with aluminum for reactions in the dark. [b] Yield after purification by column chromatography.

Table 2: Optimization of the catalyst system.[a]





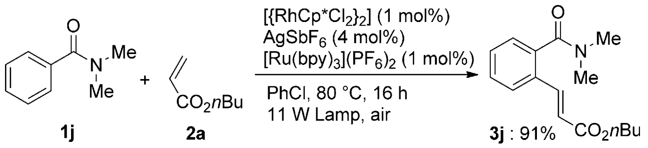
[a] Reaction conditions: 0.1 mmol aryl amide **1a**, 2 equiv acrylate **2a**, 1 mL chlorobenzene, irradiation at a distance of 3 cm. Yield after purification by column chromatography.

To shed light on the role of the photoredox catalyst, various catalysts with different properties were examined. First, the coordination ability of the counterion was varied. Changing from weakly coordinating PF$_6$ to the more strongly coordinating Cl anions did not have a significant impact on the yield, whereas the electronic character of the ligands had a substantial influence on the reaction (Table 2, row 1). Increasing the electron density through sequential introduction of *t*Bu groups on the bipyridine backbone led to a drop in the yields from 89 to only 14%. Changing rhodium to iridium also led to complete suppression of the conversion,[16] irrespective of whether electron-rich or -poor ligands were used (Table 2, rows 2 and 3 (left)). This finding indicated that no radical oxo species[17] are directly involved in the rhodium–hydride oxidation, since both [Ru(bpy)$_3$]$^{2+}$ and the corresponding iridium complex are known to generate reactive oxygen intermediates.

This observation suggested that the reduction potential of the photoredox catalyst may be the crucial parameter in guaranteeing a successful recycling. Furthermore, no conversion was observed when stoichiometric amounts of either eosin Y or titanium dioxide were applied as the photoredox catalysts (Table 2, row 3 (right)). However, the following experiments were of greater importance: When the reaction was carried out using 1 mol% photoredox catalyst in an inert atmosphere, a negligible yield of 3% was obtained, which indicates no catalyst turnover occurs. In contrast, conducting the same reaction with stoichiometric amounts of photoredox catalyst led to a 48% yield of the product **3a**, thus demonstrating that the photoredox catalyst is able to recycle the Rh catalyst (Table 1, entries 13 and 14).

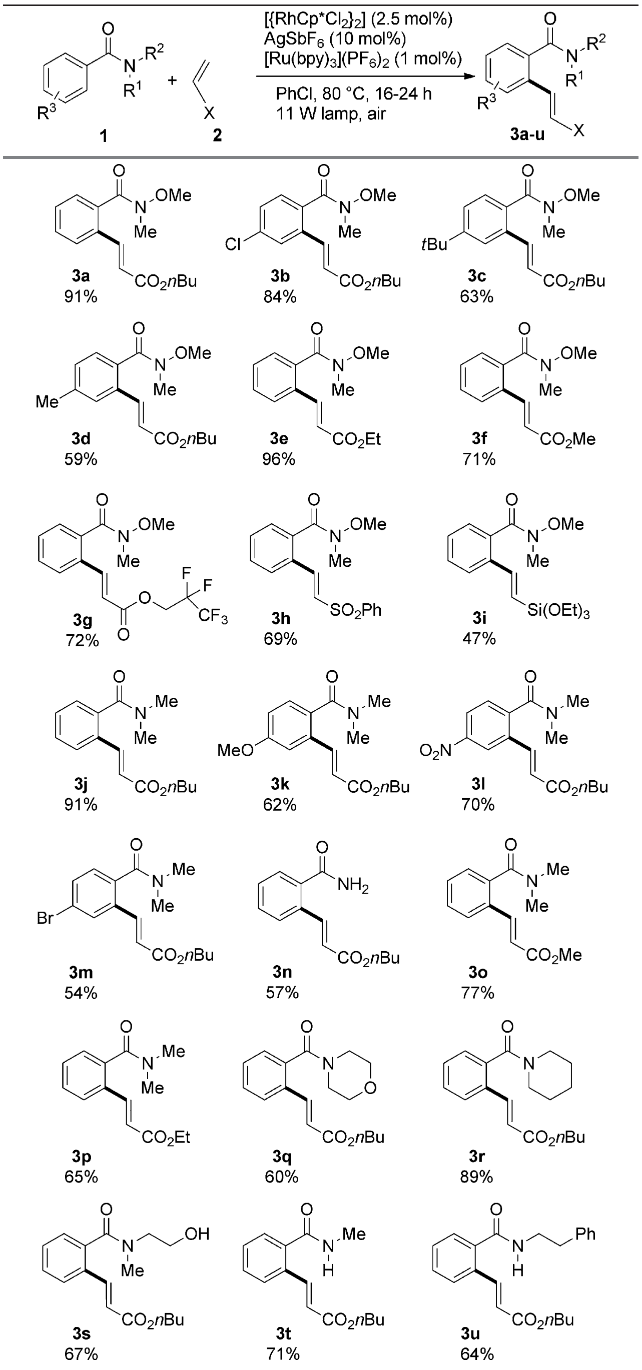
These findings reveal that the reduction potential of the photoredox catalyst is the crucial parameter in the recycling of the active rhodium catalyst. However, this also means that oxygen participates in the recycling of the rhodium catalyst if the reaction is performed with 1 mol% photoredox catalyst, with hydrogen peroxide generated as a by-product.

To gain further insight into the mechanism, the reaction was conducted in chlorobenzene and in deuterated chlorobenzene, since the solubility and reactivity of any potentially involved singlet oxygen $^1O_2$ should have an impact.[18] The yields in both cases were almost identical (Table 1, entries 8–10 and 15–17), which indicates that singlet oxygen does not have a direct impact on the reaction outcome. Glorius and coworkers reported the use of halogenated arenes as stoichiometric oxidants.[19] Thus, we employed deuterated chlorobenzene in the reaction. However, no formation of pentadeuterium benzene was detected, which led to the conclusion that chlorobenzene does not act as an oxidant. Moreover, no incorporation of deuterium into product **3a** could be observed.



Scheme 2. Control reactions to exclude internal oxidants.

Table 3: Substrate scope of the aryl amide.[a]



[a] Reaction conditions: 0.2 mmol aryl amide **1**, 2 equiv acrylate **2**, 1 mL chlorobenzene, irradiation at a distance of 3 cm. Yield after purification by column chromatography.

To exclude the possibility that the *N*-methoxy group of the Weinreb amide acts as internal oxidant,[10b] dialkylamide **1j** was applied in the dual catalysis (Scheme 2). Product **3j** was obtained in a yield of 91%, thus demonstrating that an internal oxidant can be excluded and the rhodium catalyst regeneration can be exclusively attributed to the photoredox catalyst. This also shows that the carbonyl oxygen atom or the amide nitrogen atom acts as a directing group to stabilize the Rh complex and to enable C−H insertion.

With the optimized reaction conditions and a general understanding of the mechanism in hand, the substrate scope of the reaction was investigated. Electron-poor aryl amides could be successfully converted in very good yields (Table 3, **3b** 84%). Good yields could also be obtained with electron-poor arenes (Table 3, **3c** 63%, **3d** 59%). To further prove the synthetic utility of the dual catalysis, different terminal olefins were tested, which revealed that the reaction is neither limited to different acrylates (**3e–g**) nor to vinyl sulfones (**3h**) and silanes (**3i**) as the electrophile.

As described above (Scheme 2), it was shown that alkyl amides can be converted in this reaction. Thus, this substrate class was also examined in terms of their electronic and steric effects. Similar to the case with Weinreb amides, the reaction showed a broad acceptance of electron-rich and -poor arenes (**3k–m**). Additionally, cyclic amides (**3q**,**r**) and hydroxyalkyl amides (**3s**) could be transformed in good yields. The latter also reveals the tolerance of the reaction towards unprotected hydroxy groups and thereby the attractiveness of the method for the synthesis of complex compounds. As previously mentioned for the Weinreb amides, variations of the acrylate did not have a significant impact on the reaction. Furthermore, the substrate scope could also be extended to secondary (**3t**,**u**) and primary alkyl amides (**3n**). The products were obtained in moderate to good yield, which highlights the general applicability of the method for the *ortho* olefination of different amides.

In summary, a dual catalysis concept for the *ortho* olefination of aryl amides has been developed and its applicability to a broad range of substrates was highlighted. The previously often used (over)stoichiometric amounts of oxidants can be readily substituted with a photoredox catalyst, which makes this system both attractive and a more environmentally sound alternative. Further attempts to apply this new type of combined catalysis to other substrate classes and metal catalysts are currently underway.

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Keywords: C−H activation · olefination · oxidative Heck reaction · photoredox catalysis · rhodium catalysis

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Communications

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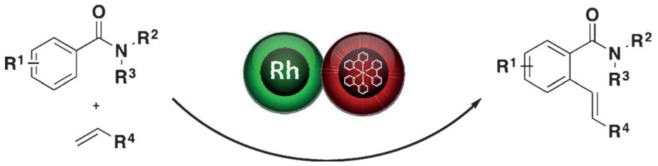

Much milder and environmentally friendly reaction conditions can be used for oxidative Heck reactions through the combined use of rhodium and redox catalysis. This allows the rhodium complex to be catalytically regenerated. A broad range of substrates was tolerated in the reaction and afforded different amides in good to very good yields.