ARTICLE

Site-selective Ru-catalyzed C-H bond alkenylation with biologically relevant isoindolinones: a case of catalyst performance controlled by subtle stereo-electronic effects of the weak directing group

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The first use of biologically relevant isoindolinones as weak directing groups in transition metal-catalyzed carbon-carbon bond formation via C-H bond functionalization is presented. Notably, besides the presence of two aromatic C-H sites available for functionalization, selective mono-alkenylation in the *ortho*-position with respect to the nitrogen atom were achieved with a readily available ruthenium catalyst. The scalability, versatility and high functional group tolerance of the catalysis enabled the late-stage functionalization of biologically relevant indoprofen and further derivatizations. Preliminary mechanistic studies indicate (1) the ease of the C-H bond activation step, (2) the key role of the carbonyl group as a weak directing group throughout the catalytic cycle and (3) the unexpected subtle differences associated between cyclic amides and imides as weak directing groups in ruthenium-catalyzed C-H bond alkenylation reactions. The isolation and role of an unprecedented off-cycle ruthenium complex is discussed as well.

Introduction

Transition metal-catalyzed C-H bond functionalization using weak directing groups (WDG) has emerged in the last decade as a powerful approach in chemical synthesis.[1] Indeed, it allows an efficient and sustainable entry in the late-stage functionalization of molecules relevant for many fields, which is appealing from an industrial and academic point of view.[2] Carbonyl-containing moieties represent arguably the most important class of WDG and their use in bond forming reactions via transition metal-catalyzed C-H bond functionalizations is well established, especially when it is part of an acyclic WDG.[3] When this carbonyl group is part of a cyclic WDG a limited number of examples exist, most of them based on a six-membered ring.[4]

On the other hand, the use of carbonyl-containing WDG based on a five-membered ring is synthetically appealing because these heterocycles are ubiquitous in multiple biologically relevant scaffolds.[5] Regarding the formation of carbon-carbon bonds via C-H bond functionalization, they have been exploited in a number of C-H bond arylation, methylation and acylation reactions using expensive and scarce Pd, Rh and Ir catalysts (Fig. 1A).[6] For C-H bond alkenylation reactions, Frost and Ackermann, independently, reported on oxazolidinone, pyrrolidinone, thiazolidinone, hydantoin, succinimide and pyrazolone as WDG using bench-stable ruthenium catalysts and electron deficient olefins such as acrylates (Fig. 1B).[7] It is relevant to note that these previous carbon-carbon bond forming reactions using five-membered ring weak directing groups operate via carbonyl coordination to the metal catalyst and that they present only one aromatic C-H bond available for functionalization, thus limiting selectivity issues.[6,7] As such, the design of selective carbon-carbon and carbon-heteroatom bond forming reactions via transition metal-catalyzed C-H bond functionalization strategies using heterocyclic carbonyl-containing WDG is highly attractive.[8]

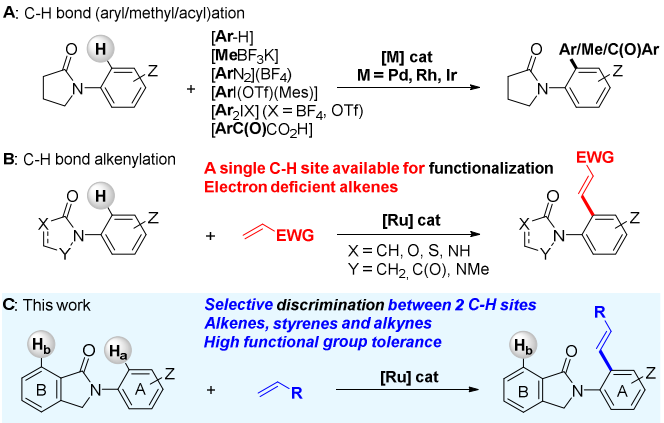

Fig. 1 State-of-the-art for carbon-carbon bond forming reactions via transition metal catalyzed C-H bond functionalizations with five-membered ring weak directing groups.

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† CCDC 1895843 (**2g**), 1895844 (**2h**), 1895845 (**2l**), 1895846 (**2t**), and 1895847 (**2v**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

Electronic Supplementary Information (ESI) available: Experimental details, characterization and NMR spectra. See DOI: 10.1039/x0xx00000x

Consequently, and considering the growing interest to develop transition metal-catalyzed C-H bond functionalizations applicable also to biologically appealing WDG, we turned our attention to isoindolinones.[9] The isoindolinone motif neighboring an *ortho*-substituted carbon-containing fragment is prevalent in pharmacologically relevant structures.[10-12] For instance, **A** behaves as a liver X receptor modulator,[10] **B** is a IGF-1R (type-1 insulin-like growth factor receptor) inhibitor[11] and **C** is a microsomal triglyceride transfer protein inhibitor (Fig. 2).[12] Herein, we report on selective ruthenium-catalyzed C-H bond alkenylations of *N*-arylisoindolinones with a large scope of alkenes (beyond acrylates) and a high functional group tolerance (Fig. 1C). Notably, despite the presence of two potentially reactive aromatic C-H sites (Ha and Hb), the C-H bond alkenylation reaction selectively occurred in the phenyl ring attached to the nitrogen atom (Fig. 1C). The synthetic potential of the isoindolinone motif as WDG is demonstrated in several post-functionalization reactions including the late-stage derivatization of the biologically relevant indoprofen. Preliminary mechanistic studies indicate the ease of the C-H bond activation step for this type of substrates and the identification of an unprecedented off-cycle ruthenium complex. Comparison of reactivity with related weak directing groups such as cyclic imides have been carried revealing unexpected differences of reactivity associated to subtle stereo-electronic effects.

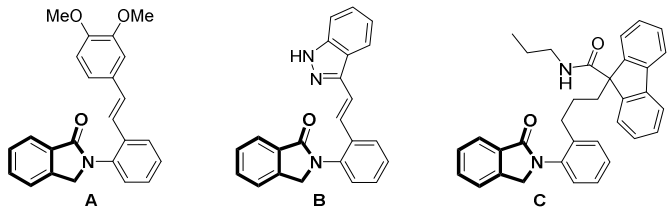
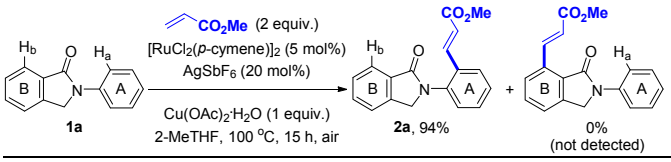


Fig. 2 Selected biologically relevant molecules featuring the isoindolinone core with alkene and alkane substituents in the *ortho*-position of the *N*-phenyl ring.

Results and discussion

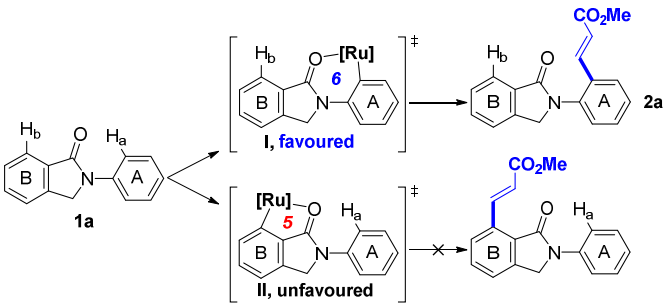
Initially, exhaustive reaction conditions were screened (Table 1) and we found that previously reported reaction conditions were also compatible for the C-H bond alkenylation of isoindolinone **1a**.[7] It consisted of $[RuCl_2(p\text{-cymene})]_2$ (5 mol%) as pre-catalyst, $AgSbF_6$ (20 mol%) as chloride scavenger and $Cu(OAc)_2 \bullet H_2O$ (1 equiv.) as oxidant in 2-MeTHF as solvent under air at 100 °C for 15 hours in the presence of 2 equivalents of methyl acrylate. Under these reaction conditions, *N*-phenyl-substituted **1a** fully reacted with methyl acrylate leading to **2a** in 94% isolated yield (Table 1, entry 1). The resulting 1,2-disubstituted alkene double bond in **2a** displayed *E*-configuration according to the high $J_{H,H}$ coupling constant (*ca.* 16 Hz) observed for the alkene protons by NMR spectroscopy studies. Control experiments indicated the need of all reagents and variations of temperature, reaction time, solvent, stoichiometries, as well as reagents and solvents did not improve the efficiency of the catalysis (Table 1, entries 2-15). Notably, the reaction was regio- and site-selective as no C-H bond alkenylation was observed in the fused benzene ring (Hb). This is consistent with the isoindolinone core accommodating a plausible six-membered ruthenacycle intermediate **I** with the C-H bond activation occurring in the phenyl ring A rather than a five-membered one **II** with the C-H bond activation taking place in benzene ring B (Scheme 1).

Table 1 Reaction optimization for the ruthenium-catalyzed site-selective C-H bond alkenylation of **1a**.[a]



Entry	Deviation from above conditions	Yield **2a** (%)[b]
1	none	97 (94)
2	3 equiv. of methyl acrylate	96
3	1.5 equiv. of methyl acrylate	69
4	80 °C	50
5	120 °C	77
6	without $Cu(OAc)_2 \cdot 2H_2O$	traces
7	without $AgSbF_6$	29
8	without $[RuCl_2(p\text{-cymene})]_2$	0
9	1 mol% $[RuCl_2(p\text{-cymene})]_2$	46
10	argon instead of air	93
11	THF instead of 2-MeTHF	96
12	1,4-dioxane instead of 2-MeTHF	90
13	1,2-dichloroethane instead of 2-MeTHF	90
12	H_2O instead of 2-MeTHF	0
13	γ-valerolactone instead of 2-MeTHF	41
14	diethylcarbonate instead of 2-MeTHF	48
15	1-pentanol instead of 2-MeTHF	39

[a]Reaction conditions: **1a** (0.1 mmol), methyl acrylate (0.2 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $AgSbF_6$ (20 mol%), $Cu(OAc)_2 \cdot H_2O$ (0.1 mmol), 2-MeTHF (0.5 mL), 100 °C, 15 h, air. [b]Determined by ^1H NMR spectroscopy against dibromomethane (internal standard). Isolated yield is shown in parentheses.

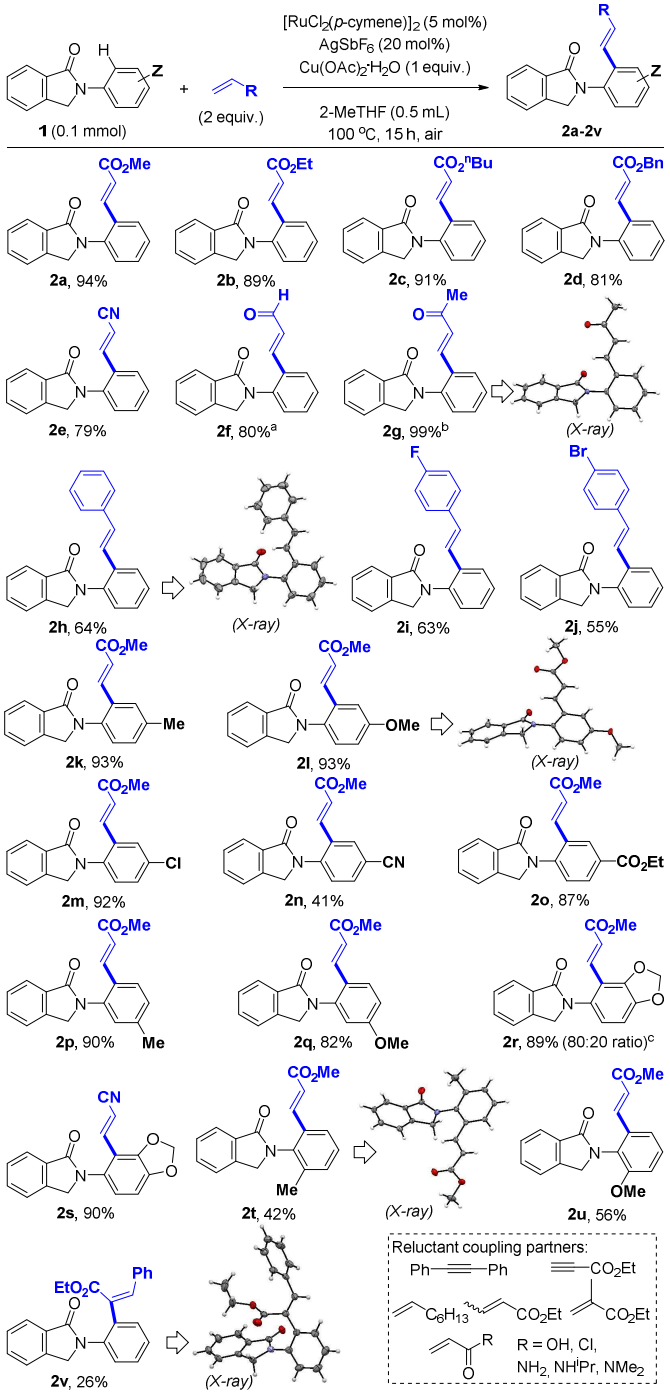


Scheme 1 Plausible intermediates controlling the site-selectivity for the C-H bond alkenylation of **1a**.

Next, the scope of the reaction was evaluated and the catalysis was found efficient with other alkyl acrylates, such as ethyl, butyl and benzyl, leading to the corresponding products **2b**-**2d** in 81-91% yield (Table 2). Interestingly, other electron

deficient terminal alkenes containing synthetically useful functional groups such as nitrile, aldehyde and ketone efficiently reacted with **1a** leading to **2e**-**2g** in high yields as well. In the case of **2f** and **2g**, small amounts of alkylated product were detected. Unexpectedly, the reaction was efficient with less electron deficient alkenes such as styrene derivatives leading to **2h**-**2j** in a decent 55-64% yield. It is important to emphasize that the alkene coupling partners leading to products **2e**-**2j** have been scarcely used in transition metal-catalyzed C-H bond alkenylation reactions,[13] despite their obvious synthetic potential. The catalysis also tolerated different *para*-substitution patterns in the *N*-phenyl side of **1** leading to **2k**-**2m** in >90% yields. The reaction was equally efficient at large scale starting from 3 mmol of isoindolinone **1k**. Notably, although nitrile and ester groups are known to behave as weak directing groups in similar ruthenium-catalyzed C-H bond alkenylation reactions,[14] under our reaction conditions, the isoindolinone core exclusively dictates the selectivity of the reaction leading to **2n** and **2o** in 41 and 87% isolated yields, respectively, with no other regoisomers detected in the reaction mixture. *meta*-Substitution in the phenyl ring of **1** with electronically different methyl and methoxy substituents led to the same, less hindered regioisomers **2p** and **2q** in 90 and 82% isolated yields, respectively. This indicates that the most sterically accessible C-H bond is preferentially functionalized for these substrates. In contrast, dioxolane-containing isoindolinone reacted with methyl acrylate leading selectively to the most sterically hindered regioisomer (80:20 ratio) in 89% isolated yield (**2r**). When using acrylonitrile as coupling partner, a single regioisomer (**2s**) was selectively obtained in 90% isolated yield. The heterocyclic dioxolane group seems to behave as an additional WDG to some extent for ruthenium-catalyzed C-H bond alkenylations as it was reported before.[15] The *ortho*-substitution pattern in the phenyl ring slightly decreased the efficiency of the catalysis as shown in the formation of **2t** and **2u** in 42 and 56% isolated yields, respectively. Ethyl phenylpropiolate as internal alkyne was reacted with **1a**, under our standard reaction conditions, leading to **2v** in 26% isolated yield. Additionally, the molecular structures of **2g**, **2h**, **2l**, **2t** and **2v** were unambiguously established by single crystal X-ray diffraction studies, which further supported the regio-, site- and stereo-selectivity of the alkenylation reaction (Table 2). Unfortunately, very challenging alkynes, acrylamides, acrylic acid, aliphatic olefins (e.g. 1-octene) and sterically hindered alkenes were not reactive under these conditions (Table 2).

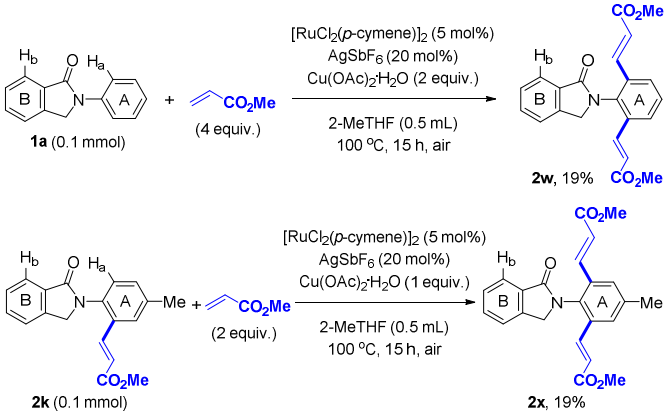
Table 2 Scope for the ruthenium-catalyzed C-H bond alkenylation reaction using the isoindolinone motif as a weak directing group.



[a]It contained 6% of alkylated product. [b]It contained 23% of alkylated product. [c]The major regioisomer is presented.

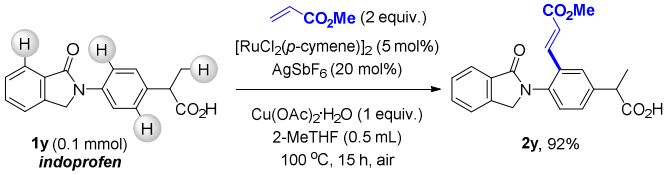
In some cases, trace amounts (<5%) of bis-functionalization was observed by NMR and GC-MS. In order to obtain some useful quantities of bis-functionalized product, the amounts of copper oxidant and methyl acrylate in the catalysis were doubled. Under these conditions, bis-alkenylated **2w** was obtained in 19% isolated yield besides major formation of mono-alkenylated **2a** (Scheme 2, top). Similarly, submitting the

mono-alkenylated **2k** to the standard reaction conditions afforded bis-alkenylated **2x** in 19% isolated yield (Scheme 2, bottom). This confirms that the bis-alkenylation is difficult for this type of substrates, although feasible to some extent, in contrast to other weak directing groups were no bis-alkenylation was observed at all.[7] Moreover, the site-selectivity of the reaction was remarkable because even under these reactions conditions (Scheme 2) no functionalization was observed in the benzene ring B.



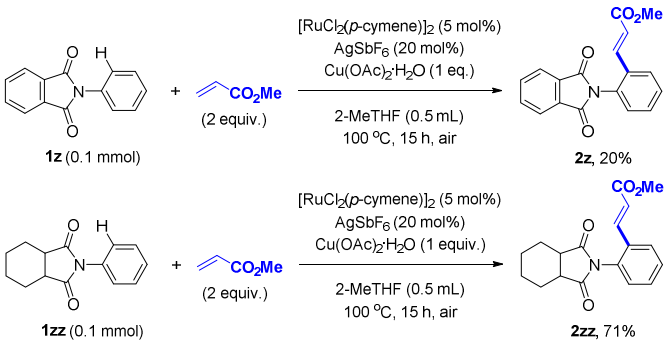
Scheme 2 Twofold ruthenium-catalyzed site-selective C-H bond alkenylation with the isoindolinone core as a weak directing group.

To further demonstrate the practical utility of the methodology, we aimed at performing the late-stage functionalization of a biologically relevant compound. Indoprofen (**1y**) was selected as it displays anti-inflammatory activity (Scheme 3).[16] Interestingly, the ruthenium-catalyzed C-H bond alkenylation reaction exclusively led to the product **2y** as confirmed by multinuclear NMR studies in an excellent 92% isolated yield under our standard reaction conditions (Scheme 3). Importantly, despite the presence in the molecule of a carboxylic acid that could eventually act as a WDG as well for this transformation,[18] the isoindolinone core, again, dictates the regio- and site-selectivity of the catalysis even for this challenging substrate. In short, one out of four possible C-H bonds is selectively alkenylated. Overall, this methodology is compatible with a large number of functional groups including alkyl, benzyl, phenyl, halide (F, Cl, Br), ester, nitrile, ketone, aldehyde, carboxylic acid and (a)cyclic ether (Table 1 and Schemes 2-3).



Scheme 3 Late-stage C-H bond site-selective alkenylation of biologically relevant indoprofen highlighting the four C-H bonds that could a priori be functionalized.

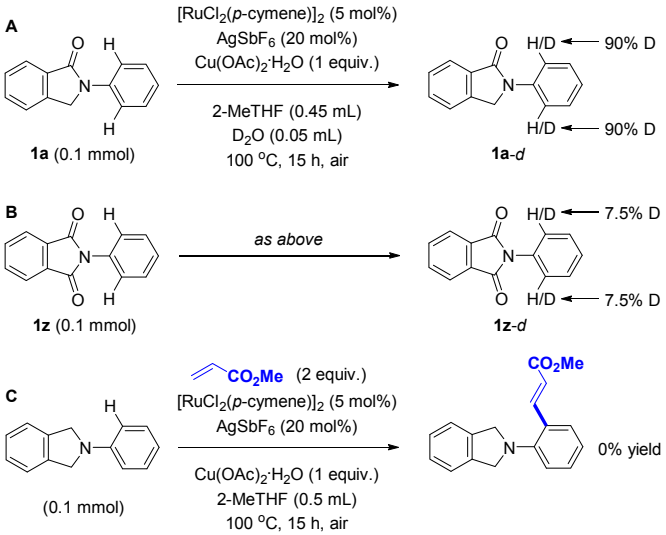
For comparison purposes, the catalysis was performed with phthalimide as WDG (**1z**), which is structurally related to isoindolinone but contains one additional carbonyl group (Scheme 4, top). Unexpectedly, the mono-alkenylated product **2z** was obtained in a poor 20% isolated yield with >70% of unreacted phthalimide starting material **1z** and formation of dienes derived from acrylate homocoupling as side products (Scheme 4, top).[18] Similar observations were made with other WDG containing two carbonyl groups such as succinimides, although the yields were slightly higher in those cases (ca. 50%).[7b] Intrigued by the difference of reactivity encountered between isoindolinones and phthalimides, we decided to attempt a C-H bond alkenylation with substrate **1zz** (Scheme 4, bottom). This substrate is related to phthalimides but contains a fully hydrogenated benzene ring, which forces the carbonyl groups to be out of plane with respect to the *N*-phenyl ring. Under our standard reaction conditions, an interesting 71% yield of the alkenylated product **2zz** was obtained (Scheme 4, bottom). This clearly highlights that a certain degree of flexibility within the WDG is key to achieve decent levels of reactivity in ruthenium-catalyzed C-H bond alkenylations. Nevertheless, the same regio- and site-selectivity as for isoindolinone as WDG was observed for **1z** and **1zz** (Scheme 4).



Scheme 4 Ruthenium-catalyzed site-selective C-H bond alkenylation of cyclic imides **1z** and **1zz**.

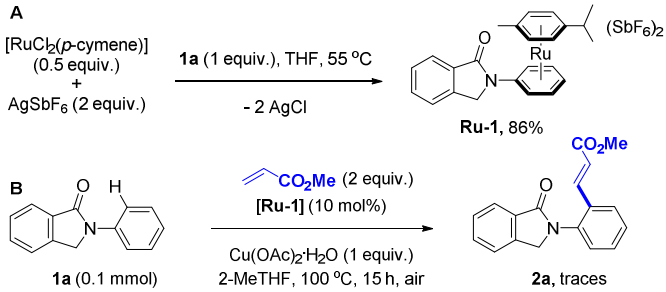
The high reactivity of the isoindolinone fragment versus the phthalimide one as WDG for ruthenium-catalyzed C-H bond alkenylation reactions was evidenced in deuteration experiments as well. With isoindolinone as WDG (**1a**), 90% deuterium incorporation was reached in the C-H bonds that can undergo alkenylation (Scheme 5A). This shows the selectivity, ease and reversibility of the C-H bond activation step for *N*-arylisoindolinones. On the other hand, only 7.5% deuterium was incorporated in the case of phthalimide **1z** as WDG (Scheme 5B). It appears that, under the reactions conditions required for alkenylation, (i) the phthalimide fragment is too rigid to accommodate the ruthenacycle intermediate that enables the C-H activation step to occur and/or (ii) significant catalyst deactivation by substrate and/or product inhibition takes place. This contrasts with the ruthenium-catalyzed C-H bond hydroxylation of phthalimides and isoindolinones as WDG, where both substrates reacted in a very similar manner.[19] The catalysis performed with isoindoline, a substrate lacking both carbonyl groups, did not

provide any alkenylated product (Scheme 5C). These observations highlight the key role of the coordination of the carbonyl group belonging to the isoindolinone motif to ruthenium as a WDG throughout the catalytic cycle.



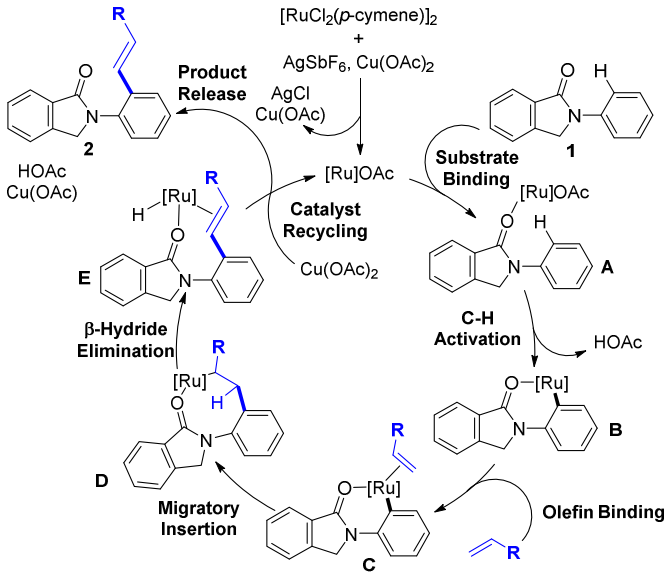
Scheme 5 Mechanistic considerations. Deuteration experiments with isoindolinone **1a** (A) and phthalimide **1z** (B), and attempt of ruthenium-catalyzed C-H bond alkenylation of isoindoline (C).

Unfortunately, attempts to isolate ruthenium species belonging to the catalytic cycle failed so far. Interestingly, we managed to isolate in 86% yield the **Ru-1** complex in which the ruthenium(II) center is η^6-coordinated both to the *para*-cymene ligand and to the phenyl ring of **1a** (Scheme 6A). The molecular structure of **Ru-1** was established by NMR and HRMS.[20] This ruthenium sandwich complex was used in catalytic amounts for the alkenylation of **1a**. In this case, only trace amounts of product **2a** were detected (Scheme 6B). Consequently, **Ru-1** complex might be regarded as an off-cycle intermediate that leads to catalyst deactivation by substrate inhibition. Similar η^6-coordinated ruthenium species reported by Hartwig and Zhao were unreactive for ruthenium-catalyzed decarboxylative alkyne hydroarylation reactions.[21]



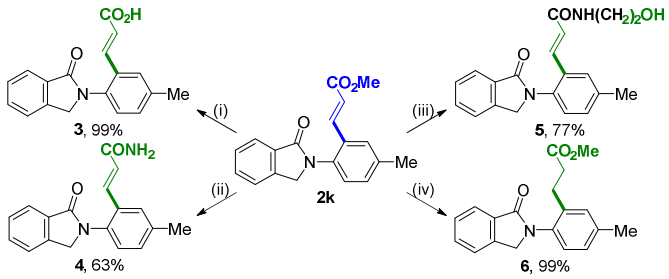
Scheme 6 Synthesis of **Ru-1** (A), and attempt of ruthenium-catalyzed C-H bond alkenylation of **1a** with **Ru-1** as the pre-catalyst (B).

A simplified reaction mechanism also based on previous observations from the literature is proposed (Scheme 7).[7,13] The in situ generated chloride-free ruthenium(II) species coordinates to the substrate **1** via the oxygen lone pair of the carbonyl group to form the intermediate **A**, which, after the C-H bond activation generates the six-membered ruthenacycle **B**. Coordination of the alkene coupling partner to the ruthenium center via the C=C double bond leads to **C**, which, forms **D** after migratory insertion. Isomerization followed by β-hydride elimination forms **E** that leads to product **2** and regeneration of the ruthenium(II) catalyst by the copper salt oxidant.



Scheme 7 Proposed reaction mechanism.

Finally, the potential of the presented methodology was further studied by performing derivatization reactions from compound **2k**. The ester group in **2k** was transformed into carboxylic acid (**3**) in quantitative yield, into primary amide (**4**) in 63% isolated yield and secondary amide (**5**) in 77% isolated yield, respectively (Scheme 8). These transformations overcome the few issues encountered in the lack of reactivity of acrylic acid and acrylamides as coupling partners, respectively, in the ruthenium-catalyzed site-selective C-H bond alkenylation (Table 2). Moreover, the alkene double bond of **2k** was subsequently hydrogenated in the presence of catalytic amounts of Pd/C under 1 bar of H_2 affording the alkylated product **6** in quantitative yield (Scheme 8). Clearly, the C-H bond functionalization/hydrogenation sequence is a useful approach when direct C-H bond alkylations are not trivial as it is the case here for WDG.[22]



Scheme 8 Derivatizations of **2k**. Reaction conditions: (i) KOH (1.1 equiv.), MeOH:H_2O, 50 °C, 16 h, then HCl; (ii) NH_3 (10 equiv.), $CaCl_2$ (2 equiv.), MeOH, 80 °C, 24 h; (iii) Ethanolamine (5 equiv.), Na_2CO_3 (1 equiv.), MeOH, reflux, 16 h; (iv) Pd/C, H_2 (1 atm), MeOH, 20 °C, 16 h.

Conclusions

In summary, we have shown the first use of biologically appealing isoindolinones as WDG in transition metal-catalyzed carbon-carbon bond forming reactions via C-H bond functionalizations. This was disclosed for alkenylation reactions in the presence of a readily affordable ruthenium catalyst. The catalysis is efficient, selective and compatible with a broad scope of alkenes as coupling partners as well as with a large number of synthetically useful functional groups. Post-functionalizations and late-stage derivatization of a biologically relevant compound (indoprofen) account for the potential of this methodology. Although the **Ru-1** complex is not involved as intermediate in the reaction mechanism of this catalysis, its application in other C-H bond functionalization reactions remains to be addressed. Unexpectedly, an important difference in reactivity was observed between cyclic amides and cyclic imides as weak directing groups, when comparing isoindolinones and phthalimides in ruthenium-catalyzed C-H bond alkenylation reactions. These observations highlight the difficulty in predicting the catalytic outcome even for structurally similar weak directing groups, where small variations on torsion angles and electronic effects are at play.

Experimental

General procedure for ruthenium-catalyzed site-selective C-H bond alkenylation: In an oven dried Schlenk tube, to a solution of isoindolinone **1** (0.1 mmol, 1 equiv.) and the corresponding alkene (0.2 mmol, 2 equiv.) in 2-MeTHF (0.5 mL) was added the combined solids: $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $AgSbF_6$ (20 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (0.1 mmol, 1 equiv.). The Schlenk tube was sealed with a Teflon cap leaving the tap open to air and it was heated to 100 °C for 15 h. The reaction mixture was diluted in EtOAc and filtered using a silica plug eluting with EtOAc. The solvent was removed in vacuo and the crude mixture was purified by column chromatography (*n*-heptane/EtOAc, 4/1 to 1/1, *v*/*v*) to give the pure alkenylated product **2**.

Conflicts of interest

There are no conflicts to declare.

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TOC

A general regio- and site-selective ruthenium-catalyzed C-H bond alkenylation with the biologically relevant isoindolinone fragment serving as a weak directing group is presented. Isoindolinones turned out to be better weak directing groups than their doubly-carbonyl containing analogues, phthalimides.