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Rh(III)-catalyzed regioselective C–H activation dialkenylation/annulation cascade for rapid access to 6*H*-isoindolo[2,1-*a*]indole†

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6*H*-isoindolo[2,1-*a*]indoles were accessed *via* a Rh(III)-catalyzed N–H free indole directed C–H activation dialkenylation/annulation cascade in moderate to excellent yields. This protocol also features: reaction procedures that are insensitive to air and moisture, excellent regioselectivity and good functional group tolerance.

The indole motif, which widely occurs in many natural products, pharmaceuticals and other functional molecules (Fig. 1), is evidently one of the most important skeletons.[1] Over the past few decades, people have developed numerous synthetic routes towards indole.[2] Among them, direct modification of indoles by transition-metal catalysis through a C–H activation strategy is quite interesting and is undoubtedly of great significance in consideration of atom economy and step simplicity, thus attracting much attention from both academia and industry.[2b,3,4]

Transition-metal catalyzed oxidative cross-coupling *via* a C–H activation pathway eliminating the need for preactivated reaction partners, has become one of the most powerful tools for molecule manipulation.[2c,5] Since the pioneering work of Murai,[6a] Fujiwara and Moritani,[6b,c] this research area has undergone rapid developments. Generally, in order to achieve good reactivity and controlled selectivity, a directing group is usually needed.[7] In this regard, various directing groups have been gradually designed and reported, including amides,[8a] amines,[8b] alcohols,[8c] carboxylic acids,[8d] esters,[8e] ketones,[8f] aldehydes,[8g] triazenes[8h] and N–H free indoles.[9]

Meanwhile, in contrast to the well-reported C–H arylation of indoles,[10] direct selective alkenylation of 2-position of N–H free indole is still limited and challenging due to the electrophilic nature of the C-2 position.[11] In 2005, Gaunt *et al.* reported Pd-catalyzed selective C-2 alkenylation of indoles,[11b] but the reaction efficiency is low and high catalyst loading is required (Scheme 1a). Another most effective strategy is pre-installing a directing group into the indole structure to control the selectivity (Scheme 1b).[12] For example, Miura *et al.* disclosed Pd-catalyzed C-2 alkenylation reaction using carboxylic acid as a blocking and directing group.[12a] Carretero and co-workers explored *N*-pyridylsulfonyl as a directing group to functionalize indole at the C-2 position employing excess of alkenes in the presence of Pd(II) catalyst.[12b]

In the above-mentioned examples, high catalyst loading[11b] (as much as 20 mol%, Scheme 2a) or pre-installed directing groups were generally required.[12] These directing groups, possessing functional groups containing a metal-binding heteroatom, remain part of the products after reaction. Such groups can rarely be conveniently removed under ambient conditions or undergo versatile cyclization reactions,[12c–f] which have greatly limited the structural diversity of the products and subsequent applications to complex molecule synthesis. Therefore, the need for exploration of traceless or easily removable directing groups that can address these drawbacks remains urgent. Recently, Huang *et al.* reported a N–H indole directed sequential cascade olefination/cyclization reaction (Scheme 1c).[13] However, the substrate scope of this transformation is limited, stepwise operation procedure is required, thus make this process tedious. Herein, we reported a Rh-catalyzed N–H free indole directed dialkenylation followed by an intramolecular cascade cyclization reaction leading to the efficient synthesis of 6*H*-isoindolo[2,1-*a*]indole.

Our initial study was carried out by examining 2-phenyl indole **1a** and ethyl acrylate **2a** in the presence of $[RhCp^*Cl_2]_2$ and $Cu(OAc)_2 \cdot H_2O$ in DMF under argon atmosphere (Table 1). To our delight, the dialkenylation product **3a′** was isolated in

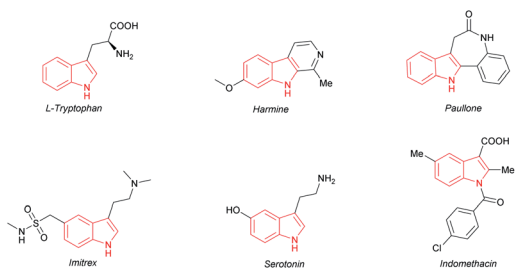

Fig. 1 Compounds containing indole motif.

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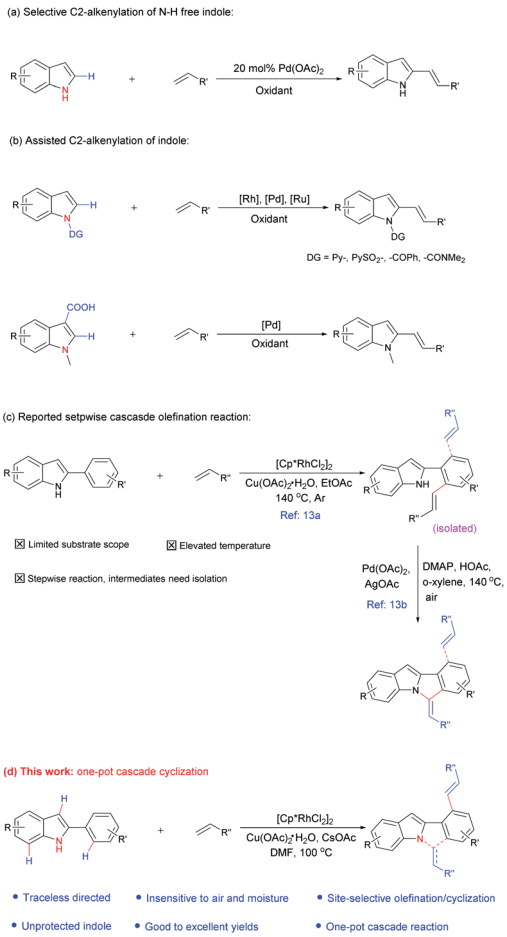
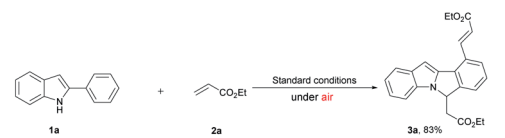


Scheme 1 Transition-metal catalyzed C-2 alkenylation of indole.

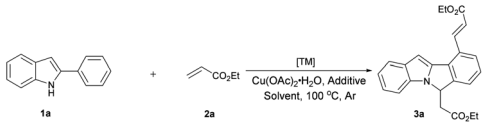


Scheme 2 Reaction under air.

54% yield (entry 2). When base was added, fortunately, the desired cyclization product **3a** was obtained in 55% yield (entry 4). In addition, the yield could be further improved to 86% when 2.5 equiv. ethyl acrylate **2a** was employed (entry 13). Other solvents and bases failed to improve this result (entries 1, 3, 5 and 6). Catalysts proved to be critical to this transformation. Among the catalysts optimized, $[RhCp^*Cl_2]_2$ appeared to be the best (entries 4, 10 and 11). The reaction was shut down in the absence of Rh catalyst or stoichiometric amounts of copper oxidant (entries 7–9). Finally, the optimized conditions were eventually identified as: 2-phenyl indole **1a** (1.0 equiv.), ethyl acrylate **2a** (2.5 equiv.), $[RhCp^*Cl_2]_2$ (5 mol%), CsOAc (2.0 equiv.), and $Cu(OAc)_2 \cdot H_2O$ (2.0 equiv.) in DMF under argon at 100 °C.

With the optimized conditions in hand, we next tend to investigate the scope of this transformation (Table 2). First, various activated olefins were tested. Good to excellent yields

Table 1 Conditions optimization[a]



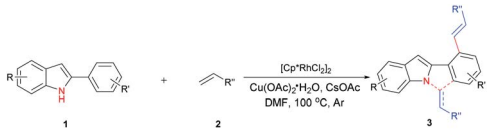
Entry	Solvent	Catalyst	Additive	Yield
1	*o*-xylene	$[Cp^*RhCl_2]_2$	Na_2CO_3	10%
2	DMF	$[Cp^*RhCl_2]_2$	—	54%
3[b]	*t*-AmylOH	$[Cp^*RhCl_2]_2$	$AgSbF_6$	Trace
4	DMF	$[Cp^*RhCl_2]_2$	CsOAc	55%
5	DMF	$[Cp^*RhCl_2]_2$	$K_3PO_4 \cdot 3H_2O$	23%
6	DMF	$[Cp^*RhCl_2]_2$	*t*-BuOK	—
7[c]	DMF	$[Cp^*RhCl_2]_2$	CsOAc	Trace
8[d]	DMF	$[Cp^*RhCl_2]_2$	CsOAc	Trace
9[e]	DMF	—	CsOAc	—
10	DMF	$[RuCl_2(p\text{-cymene})]_2$	CsOAc	Trace
11	DMF	$RhCl(PPh_3)_3$	CsOAc	Trace
12	DMF	$[Cp^*RhCl_2]_2$	$Cu(acac)_2$	Trace
13[f]	DMF	$[Cp^*RhCl_2]_2$	CsOAc	86%

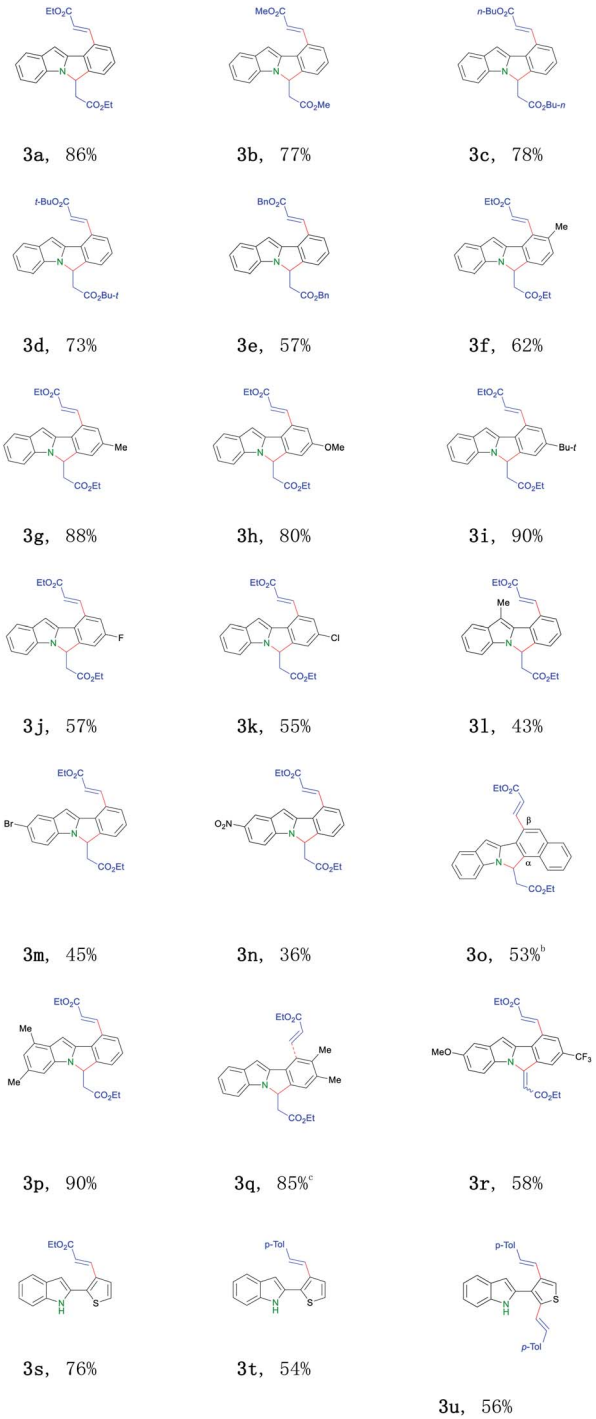
[a] Reaction on a 0.2 mmol scale, using **1a** (1.0 equiv.), **2a** (1.5 equiv.), additive (2.0 equiv.), $Cu(OAc)_2 \cdot H_2O$ (2.0 equiv.), [TM] (3 mol%), solvent (1.5 mL), under N_2, 21 h, isolated yield. [b] Additive (0.15 equiv.). [c] Without oxidant. [d] 10 mol% [Cu] under O_2. [e] Without [Rh]. [f] Using **2a** (2.5 equiv.), [Rh] (5 mol%), 41 h.

were obtained for different substituted acrylates (**3a–e**). Interestingly, when 2-thienyl substituted indole was employed, only mono-alkenylation product was got (**3s**). Significantly, unactivated 4-methyl styrene **2f** also proceeded regularly in this transformation (**3t–3u**), further broadening the practical scope of this conversion. Next, different indole substrates were explored. The reaction proceeded smoothly for electron-rich substituted indoles with good yields (**3f–i**, **3l**, **3p** and **3q**). Various 2-aryl indoles **1b–m** with a broad substitution pattern and of different electronic nature at the *ortho*-, *meta*-, and *para*-positions on the phenyl ring can be well applied, thus smoothly affording the related 6*H*-isoindolo[2,1-*a*]indole products (**3f–3q**) in middle to good yields. Halogens did not interfere with this transition-metal catalyzed process and were well tolerated (**3j–3k**, **3m**), thus provided possibilities for further modifications. Surprisingly, for CF_3-substituted substrate, related cyclization olefination product was got (**3r**). Substrates bearing two methyl groups (**3p** and **3q**), a substitution pattern widely found in indole motifs,[14] also smoothly participated in this reaction. Currently, no electron-biased alkenes (for example: 1-octene) failed to afford the desired products for some unknown reasons.

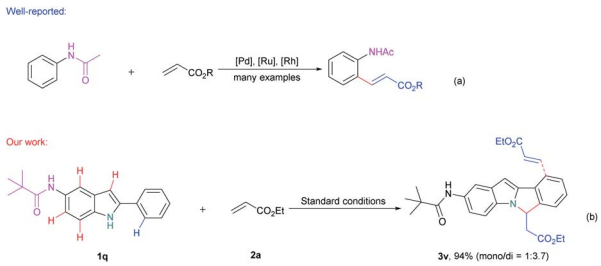
The robustness of this Rh-catalyzed indole derivatization method was further examined under air instead of argon. Similar synthetic efficiency was got, thus further proving the practicality of this transformation (Scheme 2). It is worth dating that this dual C–H activation/annulation process is also insensitive to moisture. Commercially available solvent and reagents were directly used as received and were well-compatible in this reaction without any further purifications, which additionally expands the practical application of this conversion.

Table 2 Substrates scope[a]

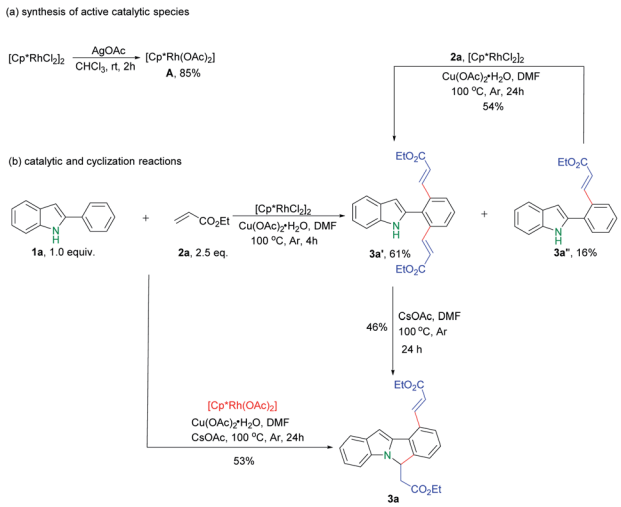




[a] Isolated yield. [b] As a mixture (1 : 1.7). [c] Mono/di = 1 : 2.4.



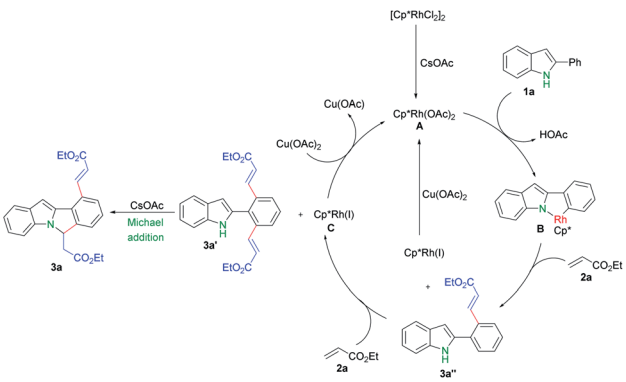
Scheme 3 Regioselectivity of different directing groups.



Scheme 4 Mechanism study.

Next, we try to investigate the regioselectivity of this reaction. As it is showed in Scheme 3, *N*-(2-phenyl-1*H*-indol-5-yl) pivalamide **1q** can smoothly undergo this conversion and only afforded the desired 6*H*-isoindolo[2,1-*a*]indole product **3v** and no amide group directed C–H alkenylation product was detected,[15] thus indicating the excellent selectivity of the C–H activation/annulation process.

In order to shed lights on the mechanism of this transformation, a series of experiments were carried out. First, possible active rhodium catalytic species **A** was synthesized according to previous reports (Scheme 4a).[13] Next, catalytic



Scheme 5 Proposed mechanism.

reaction of rhodium complex **A** with ethyl acrylate **2a** under standard reaction conditions gave rise to desired product **3a** in 53% yield (Scheme 4b), which indicate complex **A** possibly involves in this reaction. Thirdly, only mono- and di- alkenylation products were obtained in the absence of base while the cyclization product **3a** produced by further extra addition of CsOAc (Scheme 4b). Moreover, the mono-alkenylation product **3a″** can also be smoothly converted into the dialkenylation product **3a′** upon further treatments (Scheme 4b).

Finally, we proposed a mechanism for this transformation based on above experiments and reported literatures.[9,13,16,17] First, [{Cp*RhCl$_2$}$_2$] dissociates and generates the active catalyst species [Cp*Rh(OAc)$_2$] in the presence of cesium acetate.[9d,16] C–H activation of 2-phenyl indole **1a** by Rh(III) **A** produces rhodacyclic complex **B**,[9] followed by olefin insertion and reductive elimination to afford **3a″**. One more this process gave rise to **3a′** and generated Rh(I), which can be further oxidized into Rh(III) by copper acetate and fulfilled the catalytic cycle.[9,17] A base promoted intramolecular aza-Michael addition of **3a′** finally produced the cascade cyclization product **3a** (Scheme 5)

In summary, we have reported a Rh-catalyzed N–H free indole directed C–H activation dialkenylation and cascade cyclization reaction. This strategy provides a general functionalization route of simple 2-aryl indole leading to the efficient synthesis of 6*H*-isoindolo[2,1-*a*]indoles. Excellent regioselectivity was obtained with substrates containing amide directing group. Further exploration of the synthetic utility of this chemistry is currently underway in our laboratory and will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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