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

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6H-isoinindolo[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 consider-
ation of atom economy and step simplicity, thus attracting much
attention from both academia and industry.3–5

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.6–8 Since the pioneering work of Murai,6a Fujiwara
and Moritani,6b this research area has undergone rapid develop-
ments. 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 re-
ported, including amides,7a amines,7b alcohols,7c carboxylic acids,7d
esters,7e ketones,7f aldehydes,7g triazines7h and N–H free indoles.7i

Meanwhile, in contrast to the well-reported C–H arylation of
indoles,7j 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.8 In 2005, Gaunt et al. reported Pd-
catalyzed selective C-2 alkenylation of indoles,8a 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).8b For example, Miura et al. disclosed Pd-
catalyzed C-2 alkenylation reaction using carboxylic acid as a
blocking and directing group.8b 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.8c

In the above-mentioned examples, high catalyst loading8d (as
much as 20 mol%, Scheme 2a) or pre-installed directing groups
were generally required.8e 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,8f–g 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).8i 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 effi-
cient synthesis of 6H-isoinindolo[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*Cl2],
and Cu(OAc)2·H2O in DMF under argon atmosphere (Table 1).
To our delight, the dialkenylation product 3a’ was isolated in

Fig. 1 Compounds containing indole motif.
eventually identified as: 2-phenyl indole – 9). Finally, the optimized conditions were used 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 6H-isodindole[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 CF₃-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, 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 1  Conditions optimization

| Entry | Solvent | Catalyst | Additive | Yield |
|-------|---------|----------|----------|-------|
| 1     | o-xylene | [Cp*RhCl₂]₂ | Na₂CO₃ | 10%   |
| 2     | DMF     | [Cp*RhCl₂]₂ | —       | 54%   |
| 3     | t-amyLOH| [Cp*RhCl₂]₂ | AgSbF₅ | Trace |
| 4     | DMF     | [Cp*RhCl₂]₂ | CsOAc   | 55%   |
| 5     | DMF     | [Cp*RhCl₂]₂ | K₂PO₄·3H₂O | 23% |
| 6     | DMF     | [Cp*RhCl₂]₂ | t-BuOK  | —     |
| 7     | DMF     | [Cp*RhCl₂]₂ | CsOAc   | Trace |
| 8     | DMF     | [Cp*RhCl₂]₂ | —       | CsOAc |
| 9     | DMF     | —         | —       | CsOAc |
| 10    | DMF     | [RuCl₂(p-cymene)]₂ | CsOAc | Trace |
| 11    | DMF     | RhCl₂(PPh₃)₃ | CsOAc | Trace |
| 12    | DMF     | [Cp*RhCl₂]₂ | Cu(acac)₂ | Trace |
| 13    | DMF     | [Cp*RhCl₂]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·H₂O (2.0 equiv.), [TM] (3 mol%), solvent (1.5 mL), under N₂, 21 h, isolated yield. *b* Additive (0.15 equiv.). *c* Without oxidant. *d* 10 mol% [Cu] under O₂. *e* Without [Rh]. *f* Using 2a (2.5 equiv.), [Rh] (5 mol%), 41 h.

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*Cl₂]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*Cl₂]₂ (5 mol%), CsOAc (2.0 equiv.), and Cu(OAc)₂·H₂O (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 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 6H-isodindole[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 CF₃-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, 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.
Next, we try to investigate the regioselectivity of this reaction. As it is showed in Scheme 3, N-(2-phenyl-1H-indol-5-yl)pivalamide 1q can smoothly undergo this conversion and only afforded the desired 6H-isooindolo[2,1-a]indole product 3v and no amide group directed C–H alkenylation product was detected, 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).

**Table 2** Substrates scope

| Substrates | Isolated yield (%) |
|------------|-------------------|
| 3a         | 86%               |
| 3b         | 77%               |
| 3c         | 78%               |
| 3d         | 73%               |
| 3e         | 57%               |
| 3f         | 62%               |
| 3g         | 88%               |
| 3h         | 80%               |
| 3i         | 90%               |
| 3j         | 57%               |
| 3k         | 55%               |
| 3l         | 43%               |
| 3m         | 45%               |
| 3n         | 36%               |
| 3o         | 53%               |
| 3p         | 90%               |
| 3q         | 85%               |
| 3r         | 58%               |
| 3s         | 76%               |
| 3t         | 54%               |
| 3u         | 56%               |

*a* Isolated yield. *b* As a mixture (1 : 1.7). *c* Mono/di = 1 : 2.4.
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. First, $[\text{Cp}^*\text{RhCl}_2]_2$ dissociates and generates the active catalyst species $[\text{Cp}^*\text{Rh(OAc)}_2]$ in the presence of cesium acetate. C–H activation of 2-phenyl indole 1a by Rh(II) A produces rhodacyclic complex B, followed by olefin insertion and reductive elimination to afford 3a". One more this process gave rise to 3a' which can be further oxidized into Rh(III) by copper acetate and fulfilled the catalytic cycle. 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 6H-isoxindolo[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
This work was supported by the “Fundamental Research Funds for the Central Universities” (21620318, 2019QNGG22). C. Wang also thanks the Jinan University (start-up fund) for additional support.

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