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Communication

Ruthenium catalyzed oxidative annulation with alkynes via cascade C–H/N–H bond functionalizations

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ABSTRACT

Ruthenium(II) complexes catalyzed tandem C–H/N–H bonds functionalizations of 2-phenyl imidazole and its derivatives with alkynes were realized. This transformations allowed for rapid synthesis of isoquinoline derivatives under open-flask condition.

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1. Introduction

Isoquinoline, a heterocyclic aromatic compound, is actually a structural isomer of quinoline. Firstly isolated in 1885, isoquinolines have more than four hundred members till now. Isoquinoline alkaloids display an extensive range of biological activities such as anti-malarial, anti-HIV, insect growth retarding anti-tumor, antimicrobial, anti-leukemic, anti-bacterial, and treatment of Parkinson's disease *etc.* [1] Considering its structural extensiveness and biological activities, synthetic effort toward these transformation is of great importance. As depicted in Scheme 1, considerable medical/natural molecules (*i.e.* Janus kinases inhibitor) possess the isoquinoline skeleton, which the core framework is the complex hetero-aromatic part.

Although isoquinolines exist in numerous natural and medical compounds, a long multi-step synthesis is required in classic methods [2]. These methods included classic strategies: (i) Bischler–Napieralski reaction; (ii) Pictet–Gams reaction; (iii) Pictet–Spengler reaction; (iv) Pomeranz–Fritsch reaction and most recently, the novel pathways such as formations of C_3–C_4 and N_2–C_3 and/or ring expansion of other ring systems. Another interesting case is the C–H activation. It directly affords the corresponding adducts, in sharp contrast to its pre-functionalized precursor synthesis, which is more efficient. C–H functionalization has emerged as a versatile tools for the construction of complex molecules. This strategy is considerable valuable in view of atom-economy and resource-sustainability over the past several decades [3].

Among this, transition metals catalyzed C–H bonds functionalizations via oxidative annulations reactions have attracted significant research interest, not only because these methods avoid the multiple steps synthesis of the pre-activated precursors, but also allow for an overall state-of-the-art molecules constructions, which make them more valuable in modern organic synthesis. Pioneering work disclosed by the research groups of Murai and Satoh (Scheme 2, top) [4], Fagnou [5], and Jones [6] revealed that rhodium catalysts enabled effective dehydrogenated annulation reactions of alkynes through chelation assistance [7,8]. This have set the stage for recently accomplishment of the rhodium catalyzed isoquinoline synthesis [2f,9]. Notably, the use of inexpensive ruthenium [3a,10] catalysts for oxidative annulations through cleavages of C–H bonds have also been reported by Ackermann et al. (Scheme 2, middle). Recently, the same research group disclosed unprecedented ruthenium-catalyzed direct annulations of alkynes through the chemo- and regio-selective functionalizations of both C–H and N–H bonds [11].

However, imidazole as an effective directing group and a useful coupling partner in the tandem C–H/N–H bonds functionalizations via oxidative annulations to construct isoquinoline derivatives which broadly existing in natural and medical

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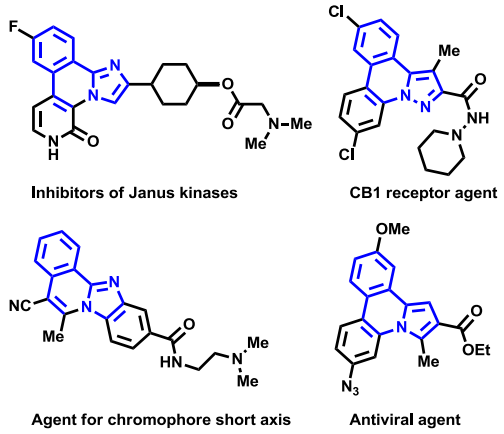
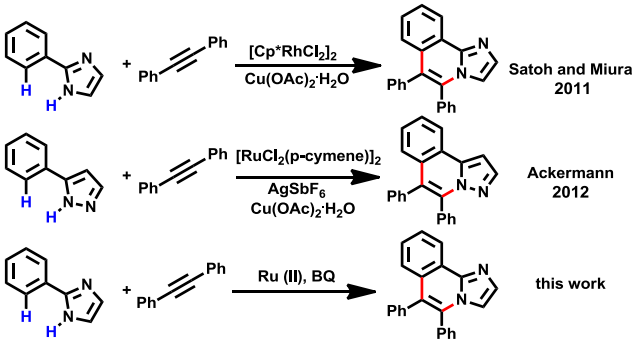


Scheme 1. Agents featuring core structure of isoquinoline.

compounds has been investigated rarely (Scheme 2, bottom) [12]. Herein, we wish to reveal our preliminary results in this research area. That is, ruthenium catalyst mediated oxidative annulations of 2-phenyl imidazole with acetylene, which is depicted in Scheme 2.

In all these cases, 2-phenyl imidazole are coupled with various alkynes, and the corresponding oxidative annulation adducts were obtained in moderate to good yield. This one pot synthesis of isoquinoline derivatives is absolutely valuable, not only because the rapid construction of complex molecules via atom-economic strategy, but also the structure-diversity achievement in the process. From the fundamental perspective of modern organic chemistry, the reduced waste-generation transformations are of high importance. A more straightforward synthetic strategy is highly appreciated, instead of tedious procedures requiring pre-functionalized precursors such as classic halogen or boronic derivatives.

Ruthenium catalyst have recently gained interest in organic community, which is largely due to its relative low price compared with rhodium complex. Notably, ruthenium catalyzed cascade C–H/N–H bonds functionalizations have been investigated by Ackermann et al. in the past decades [3a,11]. To date, the directing groups (DGs) are required in most of these reactions. Consequently, the corresponding partners are generated at the ortho-position of the DGs, with the assistance of transition metals (*i.e.*, Pd, Rh and Cu) to fulfill this transformation process [8]. Pd or Rh catalyzed transformations either require harsh reaction conditions and/or use of a high cost of metal [8a–f,h,i]. Interestingly, ruthenium catalyzed C–H bond activation has emerged as an comprehensive strategy to



Scheme 2. TMs catalyzed cascade C–H/N–H bonds activations.

accomplish such transformations [3a]. This may be due to several reasons, which can be summarized as follows: first, ruthenium is less expensive than rhodium; second, ruthenium complexes are air stable in an open flask; third, with low loading the catalyst, the transformation can be efficiently accomplished under relatively mild conditions. With these advantages of ruthenium in mind, we aim to develop an useful protocol to realize a valuable transformation for the construction of natural products and/or medically interesting molecules.

2. Experimental section

Considering the advantages of a ruthenium complex, and the widely existence of isoquinoline derivatives in natural and medical molecules, we chose 2-phenyl imidazole (**1a**) as one part and diphenylacetylene (**2a**) as corresponding coupling partner in the transformation of a tandem C–H/N–H bond activation reaction.

As depicted in Table 1, we first investigated different oxidants (entries 1–6). Copper acetate monohydrate (2.0 equivalent) afforded **3a** in 90% conversion and 84% yield (entry 1). A trace amount of acetylene was not completely consumed. Silver oxide (2.0 equivalent) combined with silver hexafluoroantimonate (30 mol%) increased the conversion, but only led to 78% isolated yield (entry 2). Interestingly, when the loading in this reaction with *p*-benzoquinone (2.0 equivalent), we observed the best result, which is obtained in quantitative conversion and 88% isolated yield (entry 3). Other oxidants such as ^{t}BuOOBz and DDQ did not provide promising results (entries 4 and 5). To take into account the solvent effects, suitable solvents were also screened. For example, when DMF was replaced by methanol, only 60% conversion of this process was detected (entry 6). In addition to solvents and oxidants screening, we also tried to add suitable bases (CsOAc and NaOAc). However, all these investigations led to negative results (entries 7 and 8). Notably, in control experiment, when the reaction was conducted without loading of any oxidant, we still observed 60% conversion (entry 9), which clearly demonstrated the importance of the oxidant in the transformation. Reaction without addition of ruthenium complex led to failure [13].

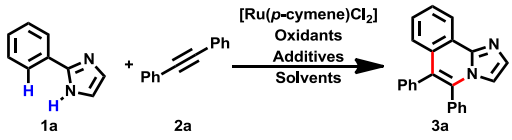
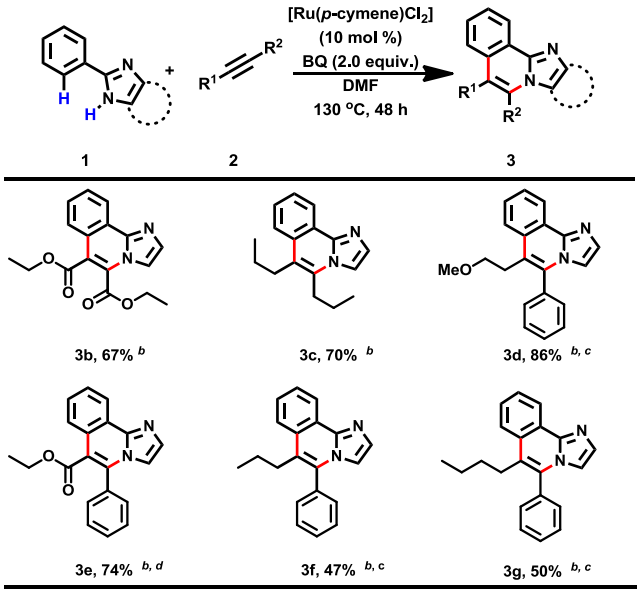


Table 1
Optimization conditions.[a]

Entry	Oxidants and additives	Conversion (%)[b]	Yield (%)[c]
1	$Cu(OAc)_2·H_2O$ (2.0 equiv.)	90	84
2	Ag_2O (2.0 equiv.), $AgSbF_6$ (30 mol%)	100	78
3	**BQ (2.0 equiv.)**	**100**	**88**[d]
4	^{t}BuOOBz (2.0 equiv.)	100	20
5	DDQ (2.0 equiv.)	100	<5
6	$Cu(OAc)_2·H_2O$ (2.0 equiv.), MeOH	60	49
7	$Cu(OAc)_2·H_2O$ (2.0 equiv.), CsOAc (2.0 equiv.)	60	31
8	$Cu(OAc)_2·H_2O$ (2.0 equiv.), NaOAc (2.0 equiv.)	80	42
9	None oxidant	60	53

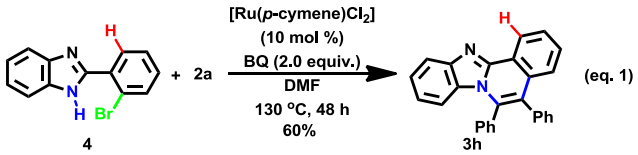
[a] Conditions: 2-phenyl imidazoles **1a** (0.2 mmol), alkynes **2a** (0.3 mmol), [Ru(*p*-cymene)Cl_2] (10 mol%), oxidants (2.0 equiv.), DMF (2.0 mL), 130 °C, 48 h.
[b] Conversion based on isolated products.
[c] Yields based on isolated yields.
[d] Isolated yield.



Scheme 3. Substrates scopes.[a] [a]Conditions: imidazoles 1 (0.2 mmol), alkynes 2 (0.3 mmol), [Ru(*p*-cymene)Cl_2] (10 mol%), BQ (2.0 equiv.), DMF (2.0 mL), 130 °C, 48 h. [b] Isolated yield. [c] Based on NOESY experiments. [d] No direct evidence was detected base on NOESY experiment, see supporting information.

With the optimized reaction conditions in hand, we next expanded the substrates scope as shown in Scheme 3. First, symmetric alkynes provided desired product in moderate isolated yields. That is, diphenylacetylene (**3a**), dimethyl acetylenedicarboxylate (**3b**) and dipropylacetylene (**3c**), all of these alkynes, whether aryl alkyne (**3a**) or alkyl alkynes (**3b**, **3c**), proceeded successfully under standard conditions to afford the corresponding dehydro-coupling products in moderate to good yields. Generally, electron-withdrawing groups such as phenyl acetylene (**3a**) provided better yield than electron-donating group (*i.e.*, **3c**). Second, asymmetric acetylenes afforded complicated results (**3d**, **3e**, **3f** and **3g**). The dehydrogenative coupling product (**3d**) can be obtained in 86% isolated yield. The regioselectivity was confirmed by corresponding NOESY NMR spectral evidence. Not surprisingly, ethyl phenyl acetylenecarboxylate afforded coupled product (**3e**) with similar regioselectivity, but only in 74% isolated yield. However, the assignment of regiochemistry by the NOESY experiment was not obvious, thus the stereochemistry was postulated as shown in Scheme 3. Phenyl propylacetylene only provided the corresponding isoquinoline (**3f**) in 47% yield. The NOESY spectrum directly indicated that there were several kinds of cross-peaks from NOE interactions between the protons of alkyl group and the protons in the benzene group of the 2-phenyl imidazole. Phenyl butylacetylene gave the corresponding isoquinoline (**3g**) in 50% yield, a similar NOESY experiment confirmed the stereochemistry.

Interestingly, one intelligible case was also investigated (Eq. (1)). The cascade reaction was realized via catalytic ruthenium complex under standard reaction conditions. The estimated bond dissociation energies of $C_{(aryl)}$–H bond and $C_{(aryl)}$–Br bond are 472 kJ/mol and 336 kJ/mol, respectively. This intuitively indicates that the cleavage of $C_{(aryl)}$–Br bond is expected. Actually, upon completion of the reaction, we examined the crude product via LC-MS, surprisingly, no characteristic bromo-containing compound was detected. That is, the competition between the hydrogen and bromo is dominated by the strong bond. After purification, the dominant process afforded coupling product **3h** in 60% isolated yield. This case straightforward indicated that the direct C–H/N–H



bonds activations are more preferred comparing with tedious pre-activated strategy. In view of the sustainability chemistry, this one is valuable, although the later one can be easily realized under similar reaction condition.

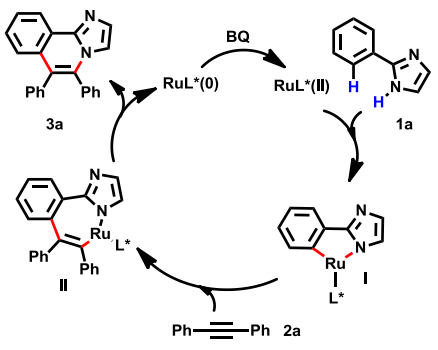
3. Results and discussion

Based upon the preceding results and known transition metal-catalyzed C–H bond activation/annulation reactions that have been achieved [14], a plausible mechanism to account for the current catalytic process was postulated (Scheme 4).

Ackermann et al. disclosed the pioneering mechanistic studies. In view of these facts, we assumed a catalytic cycle. The ruthenium catalyzed oxidative annulation to proceed via C–H/N–H bonds ruthenation to provide the five-member ring intermediate **I**, alkyne insertion to generate **II**, and subsequent reductive elimination to afford the isoquinoline **3a**. The corresponding Ru(**0**), is then oxidized by benzoquinone to Ru(**II**) to complete this transformation (Scheme 4).

4. Conclusion

In conclusion, we have developed the ruthenium catalyzed oxidative annulation reactions of alkynes with 2-phenyl imidazole, which provided efficient access to various isoquinolines. The valuable of this inexpensive catalytic process is represented by its remarkably high chemo- and regioselectivity. Based on relevant mechanistic studies on this C–H/N–H bonds functionalizations process, the current transformations afford evidence for a rate-limiting C–H bond metalation, a striking difference to known rhodium catalyzed isoquinoline syntheses [8a–f]. Furthermore, it is noteworthy that the ruthenium catalyst converts electron-deficient alkynes with increased efficacy and leads to improved isoquinoline yields. Further applications of ruthenium catalyzed oxidative C–H bond functionalizations are ongoing in our laboratories, and will be reported in due course.



Scheme 4. Plausible mechanism pathway.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jorganchem.2014.02.014.

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