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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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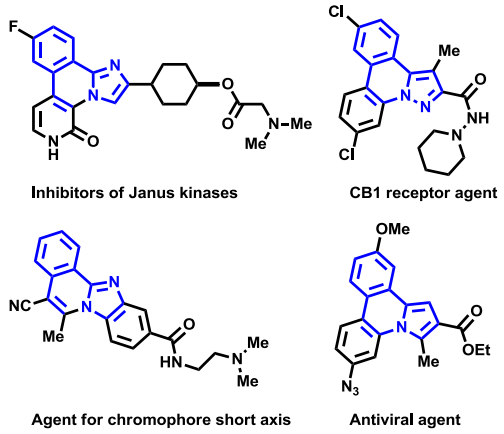
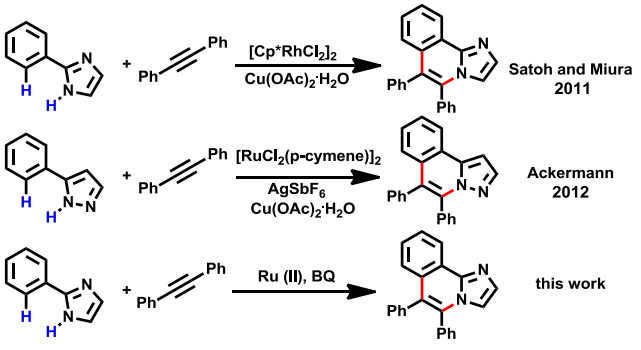


Scheme 1. Agents featuring core structure of isoquinoline.

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].

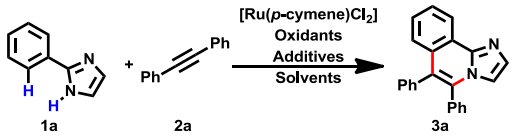


Table 1
Optimization conditions.[a]

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.