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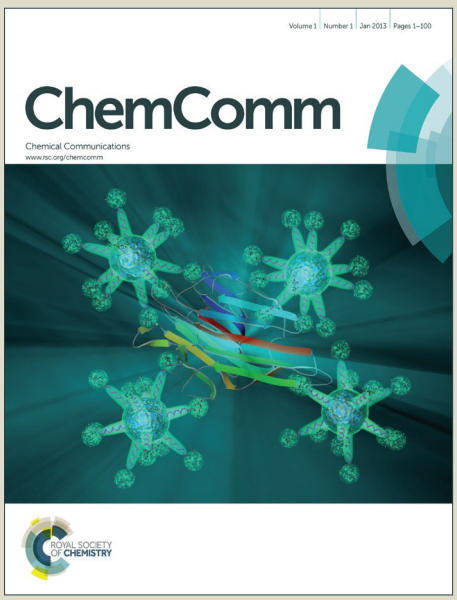

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ARTICLE TYPE

Isatins as the directing group and internal oxidant in Ru-catalyzed C-H activation and annulation reactions: Access to 8-amido isocoumarins

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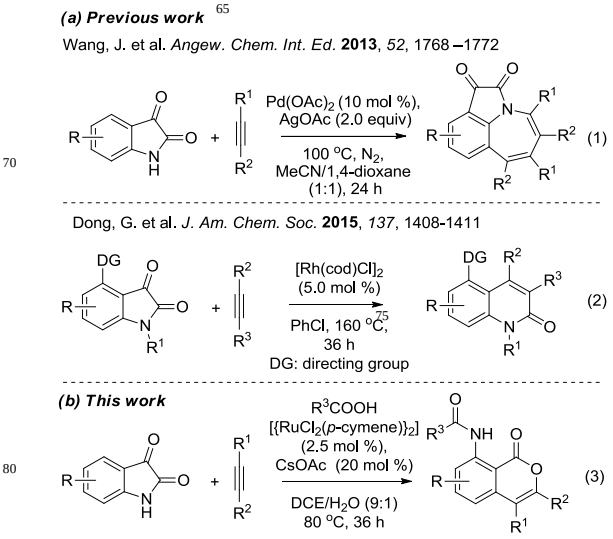
The N-O, N-N and O-O bonds are the frequently used internally oxidative directing groups used in various redox-neutral coupling reactions. The sole use of C-N bond as oxidizing directing group was reported recently by Li X. and co-workers for the Rh(III)-catalyzed C−H activation of phenacyl ammonium salts. Herein, we report the use of C-N amide bond of isatins as the oxidizing directing group for the Ru(II)-catalyzed redox-neutral C−H activation and annulation reactions with alkynes which afford 8-amido isocoumarins. The reaction also features excellent regioselectivity with alkyl aryl substituted alkynes.

In recent years, the transition-metal-catalyzed C-H activation and functionalization reactions have revolutionalized the way of construction of heterocycles owing to its sustainable and environmentally benign features.[1] The Pd, Ru and Rh-catalyzed annulation of alkynes by C-H/N-H bond activation strategies have proven particularly useful for the construction of nitrogen heterocycles using external oxidants.[2] In these reactions stoichiometric amount of external oxidants, typically metal salts such as copper(II) or silver(I) salts are often needed to turn over the valuable transition-metal catalysts. Very recently, air or molecular oxygen has also been used as the oxidant in the oxidative ruthenium-catalyzed C-H functionalization and alkyne annulation reactions.[3] The use of an oxidative functional group which serves as both directing group (DG) and internal oxidant has received significant attention in the development of redox-neutral C−H activation reactions.[4] The redox-neutral C−H activation reactions eliminate the use of stoichiometric amount of external oxidants which are typically toxic metal salts. Moreover, the presence of only internal oxidant can improve the yield, selectivity and substrate scope of the redox-neutral C−H activation reactions. Among the reported oxidative directing groups, the N-O, N-N and O-O bonds are the most prevalent, which have been used to turn over Rh, Pd, Ru metals in redox-neutral coupling reactions.[4] These internally oxidative N-O, N−N, O-O directing groups have been used effectively for the synthesis of various heterocycles using Ru and Rh catalysts. In contrast, oxidizing directing group that utilizes the C-N bond cleavage in C−H activation reactions is scarce. The only report of the use of C-N oxidizing directing group has been disclosed by Li X. and co-workers recently, for the Rh(III)-catalyzed C−H activation of phenacyl ammonium salts.[5] We envisioned that 4C-H activation and annulation of readily available isatins with alkynes would form a new redox-neutral reaction for various 8-amino isocoumarins, if the amide C-N bond of isatins could be used as a directing group and an internal oxidant. In continuation of our work on metal catalyzed C-H/C-C bond activation and functionalization reactions,[6] herein, we describe our efforts in developing Ru(II)-catalyzed new multi-component approach for selective 4C-H bond activation and annulation reactions of readily available isatins with alkynes, for the synthesis of diverse 8-amido isocoumarins utilizing C-N bond of isatins as the DG (eqn 3, Scheme 1). Notably, in one recent report, Wang et al. found that the reaction of same starting materials provided benzazepine heterocycles in the presence of Pd(II) catalyst (eqn 1, Scheme 1).[2a] Moreover, very recently, Dong, G. et al. disclosed directing group assisted annulation of isatins with alkynes in the presence of Rh(III) catalyst for the synthesis of quinilones (eqn 2, Scheme 1).[7]



Scheme 1. Annulation reactions of isatins with alkynes

Isocoumarins are well-known heterocycles that form the structural scaffold of many pharmaceutical compounds, especially, amide substituted isocoumarins are known to exhibit a wide range of interesting biological properties and they are the key motif of many bioactive compounds.[8] Preparation of 8-amido

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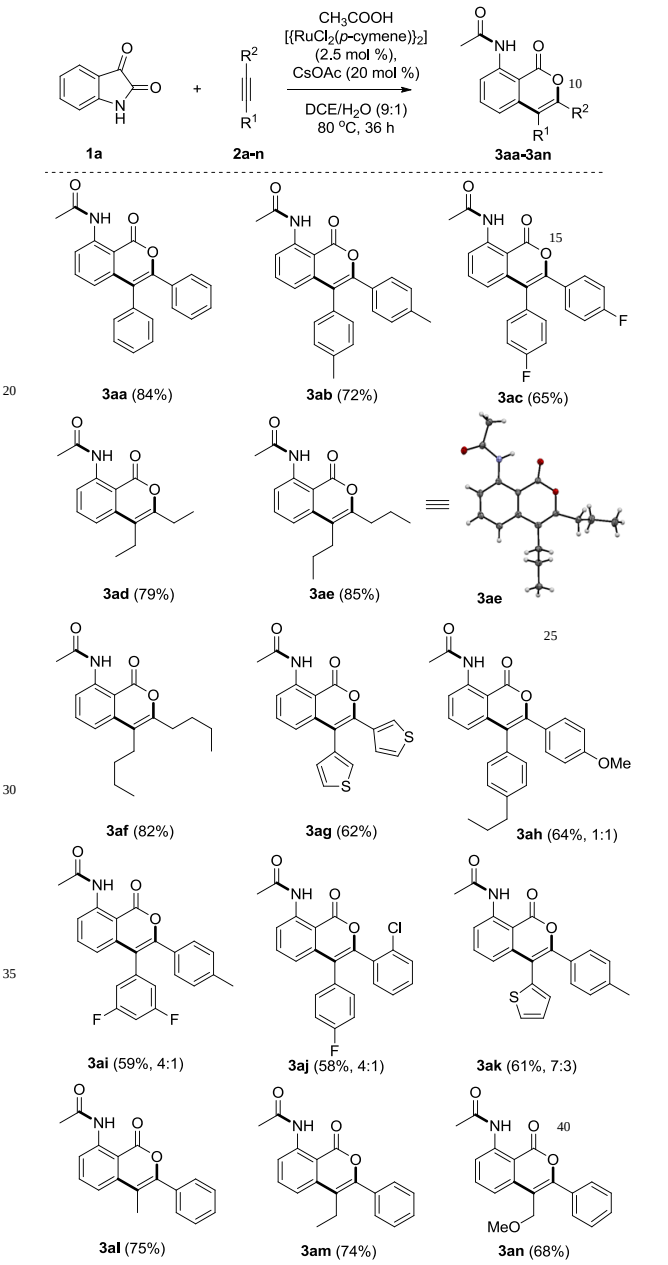
isocoumarins typically requires multiple synthetic steps as the starting materials are not readily available.[8g] Development of a direct method using simple and readily available starting materials would not only facilitate the construction of these scaffolds, but it would help the late stage modifications of the existing biologically active molecules.

Table 1. Scope of alkynes

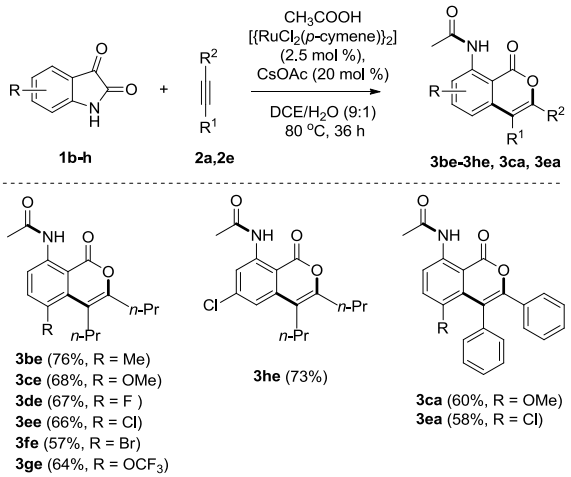


Reaction conditions: Isatin (0.5 mmol), alkyne (0.5 mmol) and Ru-catalyst (2.5 mol %), CsOAc (20 mol %) and acetic acid (0.5 mmol) in DCE/H_2O (5.0 mL, 9:1) was heated at 80 °C for 36 h under air.

In preliminary experiments, the performance of the [$RuCl_2$(*p*-cymene)]$_2$ catalyst for the oxidative annulation reaction of isatin **1a** with diphenylacetylene **2a** was studied in the presence of various additives and solvents (entries 1-16, Table S1, SI).[4m-n] The best yield of 8-amido isocoumarin **3aa** (84%) was obtained using CsOAc as the additive in DCE/H_2O (9:1, entry 13, Table S1). Further screening of Ru-catalysts could not provide better yield of **3aa** (entries 17-19, Table S1). Subsequently, the optimized reaction conditions were first tested for the annulation reaction of isatin **1a** with various functionalized alkynes (**2a-n**, Table 1). Internal alkynes substituted with electron-rich aryl, electron-poor aryl, alkyl and heteroaryl substituents were found to be good substrates for this annulation reaction (**3aa-3ag**). Similarly, the unsymmetrical internal alkynes substituted with various aryl, heteroaryl and alkyl groups also worked well to provide isocoumarins **3ah-3an**. Notably, the annulation reactions of **1a** with unsymmetrical alkynes **2l-n** were highly regioselective to provide **3al-3an**. The annulation pattern is similar to the reported Rh,[9a-b] Ni,[9c] Co[9d] and Ru[9e-f]-catalyzed annulation reactions, where the more sterically hindered or the electron rich substituents occupy the 3-position of the isocoumarin scaffold. The structure of the compound **3ae** was unambiguously confirmed by the single X-ray crystallography studies.[10] The regioselectivity of the products were proved by their NOE spectra. The terminal alkynes were not found to be suitable substrates for this reaction. Next, the scope of commercially available isatins **1b-h** was examined for this annulation reaction. As shown in Table 2, isatins substituted with various useful electron-donating, electron-withdrawing substituents such as methyl, methoxy, halogens (F, Cl and Br) and trifluoromethoxy at C-5 position showed good reactivity with alkynes **2a**, **2e** affording corresponding isocoumarins in good yields (**3be-3ge**). Some of these functional groups could be used for further synthetic transformations. Similarly, isatin substitued at C-6 position also afforded higher yield of isocoumarin **3he**.

The scope of acid as coupling partner was also examined in this redox-neutral C-H bond activation reaction. Besides acetic acid, aliphatic acids such as propanoic acid, butanoic acid, 2-methoxyacetic acid, 2-phenylacetic acid, 2-(4-methoxyphenyl)acetic acid and 3-(4-methoxyphenyl)propanoic acid also turned out to be feasible substrates for this multi-component reaction affording corresponding 8-amido isocoumarins **5ab-5ag** in moderate to good yields (Table 3).

Table 2. Scope of isatins



Reaction conditions: Isatin (0.5 mmol), alkyne (0.5 mmol) and Ru-catalyst (2.5 mol %), CsOAc (20 mol %) and acetic acid (0.5 mmol) in DCE/H_2O (5.0 mL, 9:1) was heated at 80 °C for 36 h under air.

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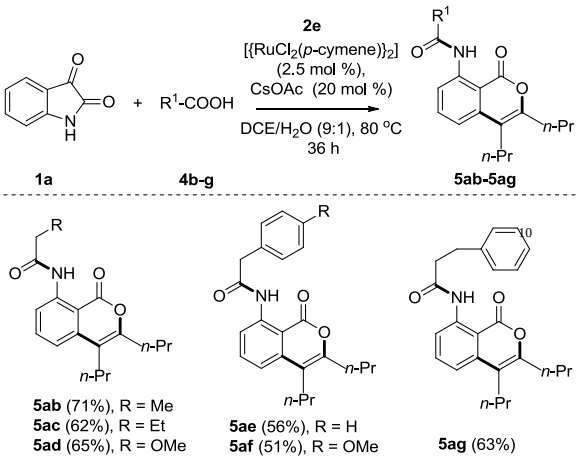
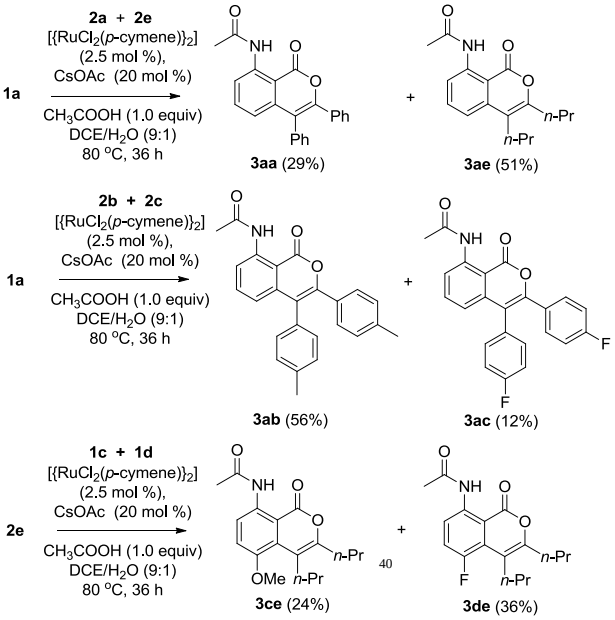
However, aromatic acids were not found to be suitable substrates for this reaction.

Table 3. Scope of acids



Reaction conditions: Isatin (0.5 mmol), alkyne (0.5 mmol), acid (0.5 mmol), Ru-catalyst (2.5 mol %) and CsOAc (20 mol %) in DCE/H_2O (5.0 mL, 9:1) was heated at 80 °C for 36 h under air.

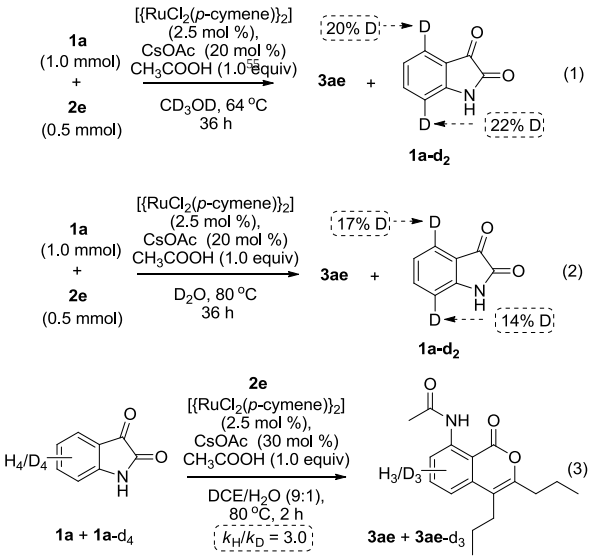
To gain more insights about the mechanism of the reaction, a series of experiments were performed. The intermolecular competition experiments revealed preferential conversion of electron-rich alkynes to their corresponding isocoumarin derivatives **3ae** and **3ab** (Scheme 2). In contrast, competition



Scheme 2. Intermolecular competition reactions

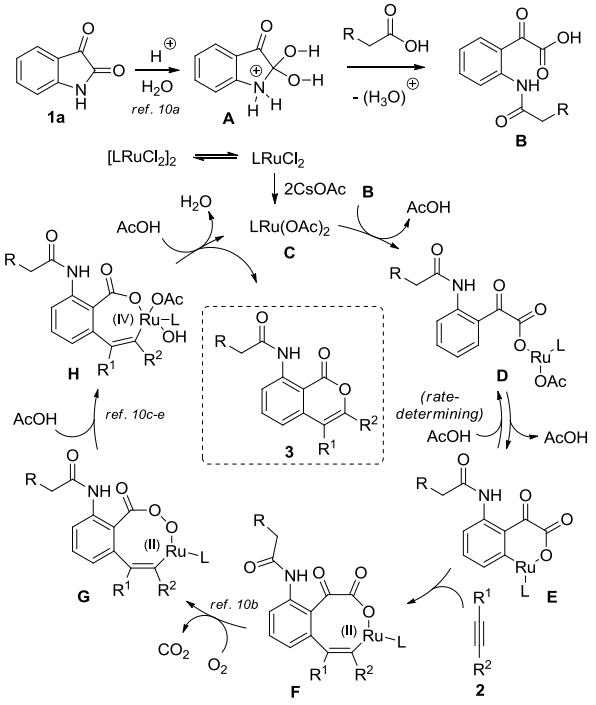
experiments performed with differently substituted isatins indicated electron-withdrawing substituent on the isatin moiety to be beneficial (**3de**, Scheme 2). The reaction between isatin (**1a**) and alkyne **2e** in CD_3OD and D_2O under standard conditions, using excess of **1a** resulted in a significant D/H exchange in the fourth and seventh aromatic protons of the recovered starting compound **1a-d$_2$** (eqns 1-2, Scheme 3). These results indicate the reversible C-H bond ruthenation step in this annulation reaction.

Furthermore, the intermolecular kinetic isotope effect experiment



Scheme 3. Isotopically Labelled Experiments

performed between **1a**+**1a**-d_4 (1:1) and **2e**, exhibited a significant kinetic isotope effect (k_H/k_D = 3.0, eqn 3), which indicated that C-H bond cleavage might be involved in the rate-limiting step. The reaction of **1a** and acetic acid in absence of the alkyne, provided an inseparable mixture of 2-(2-acetamidophenyl)-2-oxoacetic acid and 2-acetamidobenzoic acid (~1:1) at 12 hours under the standard conditions (52%). This mixture of acids on treatment with 4-octyne under the standard conditions provided isocoumarin **3ae** (91%). On the basis of our findings and literature precedence,[11] a catalytic cycle is proposed for this



Scheme 4. Plausible Reaction Mechanism

reaction which is depicted in Scheme 4. In the presence of acid, isatin forms 2-amido α-oxo phenylacetic acid **B** *via* intermediate

A.[11a] The active Ru(II) acetate **C** reacts with acid **B** to form α-oxo phenyl carboxylate- Ru complex **D** irreversibly. This is supported by the preferential formation of **3de** in the competition reaction between **1c**, **1d** and **2e** (Scheme 2), as the initial formation of complex **D** might be easier for more acidic substrate **1d**. This complex **D** on reversible cycloruthenation forms the six-membered metalacycle **E**, which on coodinative alkyne insertion reaction generates intermediate **F**.[11b] In the presence of O_2 of air, **F** forms intermediate **G** by releasing CO_2 (detected by IR spectroscopy), which on further oxidation provides Ru(IV) species **H** by the cleavage of the cyclic O−O bond.[11b-d] Finally, reductive elimination generates the product **3** and regenerates the Ru(II) catalyst.

In summary, we have designed isatins as novel but readily available substrates for external oxidant free C-H activation and annulation reaction with alkynes to prepare 8-amido isocoumarins. In this Ru(II)-catalyzed reaction, the amide C-N bond of isatin acts as an oxidizing directing group to facilitate 4C-H activation of isatin. Considering the valuable structure of the products, the broad substrate scope, less catalyst loading, simple experimental procedure, high regioselectivity with some unsymmetrical alkynes and good functionality tolerance, this reaction should be of synthetic utility.

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† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra of synthesized compounds. See DOI:

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