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Ruthenium(II)-catalyzed amide directed spiroannulation with naphthoquinones: access to spiro-isoindolinone frameworks

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A mild ruthenium(II)-catalyzed spiroannulation between benzamides and naphthoquinones is developed for succinct synthesis of biologically relevant spiro-isoindolinone scaffolds. A base promoted transannulation of spirocyclic products *en route* to valuable benzo[*b*]phenanthridinetriones in good yields has also been accomplished.

Spirocyclic frameworks are synthetically attractive targets owing to their unique structural and chemical features.[1] Especially, molecules embedded with azaspirocycles are valuable as they are prevalent structural backbone in copious natural products and synthetic bioactive molecules (Figure 1).[2]

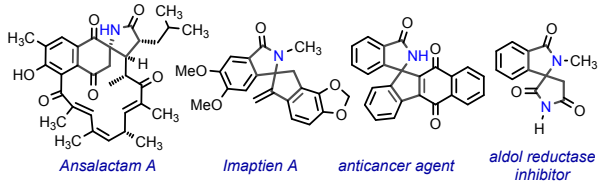
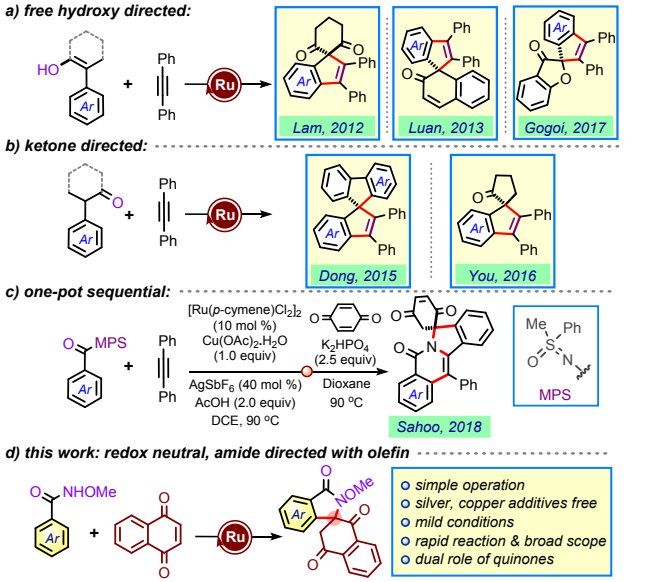


Figure 1. Biologically important spiroisoindolinone derivatives.

Further, the innate strain on the quaternary carbon center in a spirocycle can be exploited, enabling them as pivotal synthetic intermediates for the construction of various important heterocyclic architectures.[2a,b,k] Thus, engineering modular strategies for systematic tailoring of these scaffolds is a highly coveted area of research.

Over the past decades, site-selective inert C–H bond activaion/functionalization reactions have burgeoned as a utopian maneuver to inflate molecular complexity of simple organic molecules.[3,4] In this vein, Ru(II)-catalysts have attracted significant attention owing to its inexpensive nature and unique reactivity particularly under the assistance of weak coordination.[4,5] Construction of spirocycles has also been accomplished under Ru(II)-catalysis, however, such transformations are rather limited and mostly confined to internal alkynes as coupling partners.[6] One of the earliest examples was reported by Lam group, where spiroindenes were prepared by coupling of aryl-substituted 1,3-dicarbonyl compounds with internal alkynes (Scheme 1a).[6a] Later, Luan and Gogoi groups independently disclosed strategies for the synthesis of spiroindenes by exploiting phenolic -OH functionality as the directing group (Scheme 1a).[6b,c] Strategic designing of weakly coordinating carbonyl directed C–H activation/annulation cascade for the construction of spiro-carbocycles has also been demonstrated by the groups of Dong and You (Scheme 1b).[6d,e] Recently, Sahoo group illustrated a useful one-pot sequential two-fold C–H activation/annulation strategy to make spiro-isoquinolones (Scheme 1c).[6f] Despite these progresses, the synthesis of aza-spirocycles utilizing simple amide as a directing group under Ru(II)-catalysis is still obscure.



Scheme 1. Ru(II)-Catalyzed C–H activation/spiroannulation reactions.

Herein we report an amide assisted *ortho*-C–H bond activation/spiroannulation cascade of arenes with naphthoquinones, offering a range of biologically relevant

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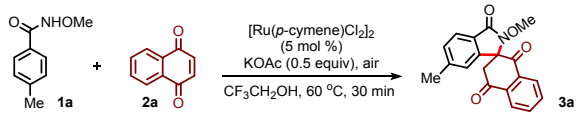
spiro-isoindolinone analogues in high yields (Scheme 1d). The strategy enables a rapid spirocyclization under mild, silver-additive free conditions, and possesses ample scope tolerating various common organic functionalities.

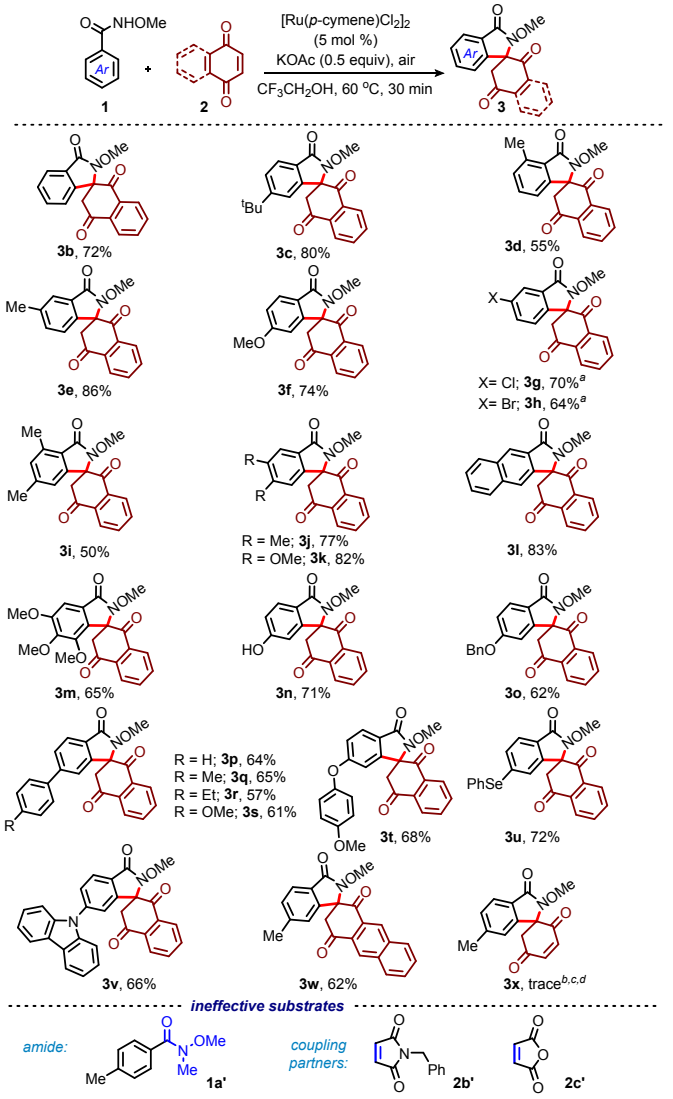
Table 1. Optimization of spiroannulation reaction[a]



entry	deviation from standard conditions	**3a** (%)
1	none	84
2	DMF, DCE, or THF instead of TFE	NP
3	MeOH, HFIP, or TCE instead of TFE	<10/66/29
4	H_2O or AcOH instead of TFE	NR
5	NaOAc, K_2CO_3, or K_3PO_4 instead of KOAc	73/<5/<5
6	at room temperature or 80 °C	38[b]/35
7	without $[Ru(p\text{-cymene})Cl_2]_2$ or KOAc	trace
8	$[Ru(p\text{-cymene})(OAc)_2]$ instead of $[Ru(p\text{-cymene})Cl_2]_2$	52[c]
9	$Pd(OAc)_2$ or $[Cp^*IrCl_2]_2$ instead of $[Ru(p\text{-cymene})Cl_2]_2$	trace
10	reaction in 1.5 mmol scale	76[d]

[a]Reaction conditions: **1a** (0.15 mmol, 1.0 equiv), **2a** (1.2 equiv), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %), KOAc (0.5 equiv), TFE (0.3 mL), air at 60 °C for 30 min. [b]Reaction was performed for 24 h. [c]10 mol % of catalyst was used. [d]Reaction time was 1 h. TFE: trifluoroethanol; DCE: 1,2-dichloroethane; HFIP: hexafluoroisopropanol; TCE: 2,2,2-trichloroethanol; NP: complex reaction mixture with no product formation; NR: no reaction with recovery of starting materials.

We initiated our investigation following the bench-mark reaction between benzamide **1a** and 1,4-naphthoquinone **2a** (Table 1). We considered hydroxamic acid ester as the suitable choice of benzamide, contemplating its aptitude of performing C–H activation under mild conditions and innate electronic feature of acting as an internal oxidant.[7] When **1a** was treated with **2a** in the presence of KOAc (0.5 equiv) base in 2,2,2-trifluoroethanol (TFE) solvent at 60 °C, we observed the selective formation of spirocyclic isoindolinone **3a** in 84% yield within 30 minutes (Table 1, entry 1). Solvent played a decisive role in this catalytic reaction. Aprotic solvent such as DMF, DCE, and THF generated a complex mixture without any product formation (entry 2). The acidity of protic solvents has a tangible impact; methanol could only provide <10% of **3a**, while comparatively more acidic HFIP and TCE rendered 66% and 29% yields of product, respectively (entry 3). However, reaction was unsuccessful in water and acetic acid (entry 4). The change of base from KOAc to NaOAc, K_2CO_3, or K_3PO_4 gave inferior results (entry 5). The reaction was sluggish at room temperature and **3a** was formed in reduced yield even after prolonging the reaction time (entry 6). At higher temperature, addition of solvent to the naphthoquinone **2a** was predominant, albeit **3a** was formed in 35% yield (entry 6). Control experiments revealed that the presence of Ru(II)-catalyst and KOAc base were necessary for the product formation (entry 7). Of note, $[Ru(p\text{-cymene})(OAc)_2]$ catalyst can also catalyzed the reaction, however, product **3a** was isolated in reduced yield (entry 8). Other transition-metal catalysts such as $Pd(OAc)_2$ and $[Cp^*IrCl_2]_2$ did not showcase fruitful results (entry 9). Satisfyingly, the reaction was scaled up to 1.5 mmol and the desired spiroisoindolinone **3a** was isolated in 76% yield (entry 10).

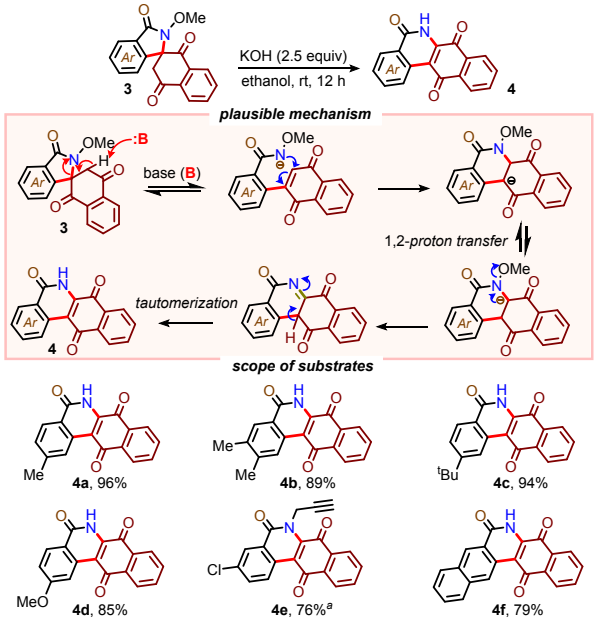


Reaction conditions: **1** (0.15 mmol, 1.0 equiv), **2** (1.2 equiv), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol %), KOAc (0.5 equiv), TFE (0.3 mL), air, at 60 °C. [a]Reaction time was 3 h. [b]the reaction was performed under air for 6 h. [c]Additional 50 mol % $Cu(OAc)_2.H_2O$ was added and reaction was continued for 6 h. [d]The reaction was performed under oxygen atmosphere for 6 h.

Scheme 2. Scope of the Ru(II)-catalyzed spirocyclization reaction.

Having acquired the reaction conditions in hand, we next focused to examine the substrate compatibility with various benzamides (Scheme 2). The protocol was found quite general with a series of hydroxamic acid esters consisting of diverse common organic functional groups. Unsubstituted benzamide along with its alkyl or methoxy group substituted variants furnished good to high yields of corresponding spiroisoindolinones (**3b**–**f**). Synthetically modifiable halogen substituents remained untouched during spirocycle formation, providing **3g** and **3h** in 70% and 64% yields, respectively. Disubstituted benzamides along with 2-naphthoic acid derived

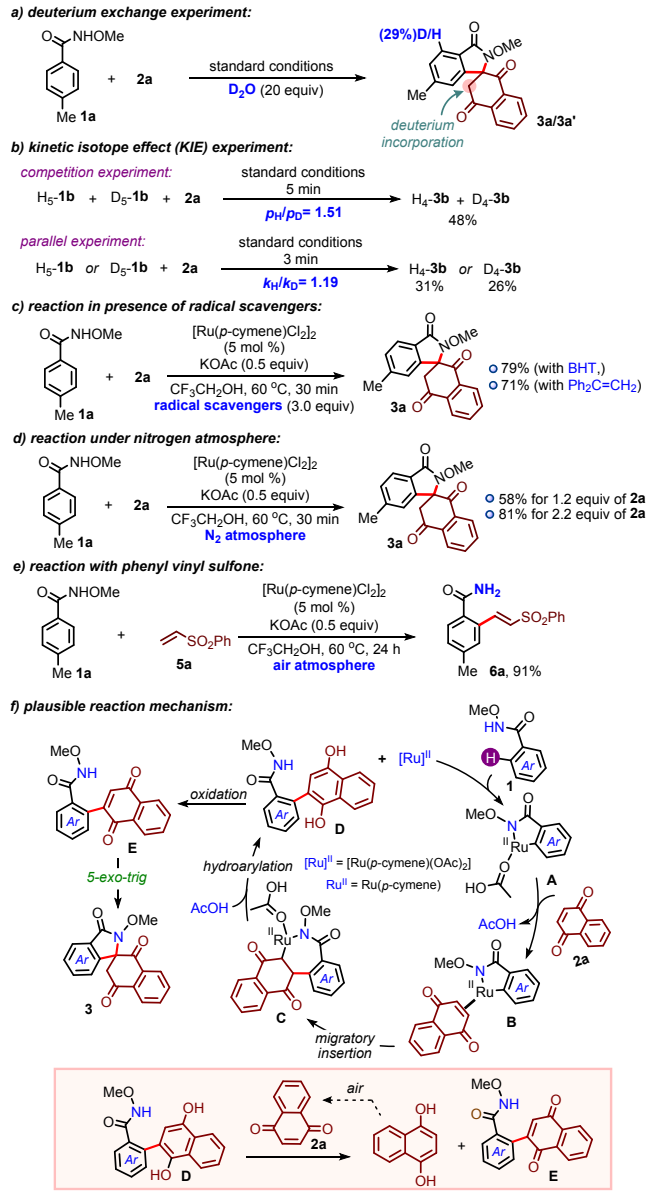
amide were also equally compatible to give **3i**–**l** in high yields. Sterically hindered 3,4,5-trimethoxybenzoic acid derived amide also effectively participated in the reaction, delivering 65% yield of **3m**. Delightfully, the reaction conditions tolerated free hydroxy group in the aromatic ring to offer **3n** in 71% yield. Common protecting group such as benzyl group (**3o**) also remained intact under the reaction conditions. The synthetic method was also fruitful with a range of biphenyl-derived benzamides, offering desired spiroisoindolinones **3p**–**s** in good yields. Aryl ether, aryl selenoether, and heterocyclic carbazole substituted benzamides could be effectively converted to spirocycles **3t–v** in high yields (66–72%). Noticeably, the protocol can also exert 1,4-anthraquinone as a coupling partner to fabricate polyaromatic variant of spirocycle **3w** in 62% yield. However, spirocyclization with parent 1,4-benzoquinone turned out unsuccessful under the standard reaction conditions. The presence of additional amount of copper acetate or molecular oxygen also did not improve the reaction outcome. The reaction was not effective with Weinreb amide (**1a'**), signifying the importance of free N–H bond in this reaction. Further, employment of maleimide (**2b'**) and maleic anhydride (**2c'**) as coupling partners did not lead to any product formation and we have recovered unreacted starting materials for both cases (Scheme 2).



Reaction conditions: **3** (0.2 mmol), KOH (2.5 equiv), ethanol (1.0 mL), rt, 12 h, air. [a]Isolated and characterized after *N*-propargylation owing to solubility issue.

Scheme 3. Synthesis of benzo[*b*]phenanthridine-5,7,12(*6H*)-triones.

As pointed out in the preceding section, the spirocyclic products are high-value intermediates for valuable synthetic transformations. Indeed, when product **3a** was exposed to ethanolic KOH solution at room temperature, a base promoted transannulation cascade involving spirocyclic ring opening, 6-*endo-trig* cyclization, N–O bond cleavage, and subsequent tautomerization was observed, producing the benzo[*b*]phenanthridine-5,7,12(*6H*)-trione **4a** in almost quantitative yield (Scheme 3). Notably, benzo[*b*]phenanthridine-5,7,12(*6H*)-triones have recently introduced as a novel small molecule ROS-generators, in vitro study of which displayed effective functioning against methicillin-resistant Staphylococcus aureus (MRSA) strains.[8] Further, functionalized quinones offer the necessary redox-active set up for various redox-processes in biological system.[9] This transannulation strategy was amenable to electron-donating alkyl, alkoxy, and electron-withdrawing chloro variants of isoindolinones, affording products **4b**–**e** in excellent yields (Scheme 2). The strategy was also effective to fabricate a polyaromatic dibenzo[*b,j*]phenanthridinetrione **4f** in 79% yield from naphthoic acid derived spirocycle (Scheme 3).



Scheme 4. Mechanistic studies and reaction mechanism.

To gain mechanistic insights of the catalytic process, we have performed a set of control experiments. Deuterium exchange experiment displayed 29% deuterium incorporation in **3a**, implying a reversible C–H metalation process (Scheme 4a). Both competition KIE experiment (p_H/p_D~1.51) and parallel KIE experiment (k_H/k_D~1.19) suggested that the C–H bond cleavage is possibly not the rate limiting step (Scheme 4b). In presence of

radical scavengers, product **3a** was also formed in significant amount, which refutes the involvement of a single electron transfer (SET) process (Scheme 4c). When we studied the reaction strictly under nitrogen atmosphere using 1.2 equivalents of **2a**, the yield of **3a** was reduced to 58% and a higher yield of 81% was obtained when 2.2 equivalents of **2a** was employed (Scheme 4d). In similar to Scheme 2, we did not observe the cleavage of labile N–O bond in both cases. In contrast, when vinyl sulfone **5a** was considered as reaction partner, we found exclusive *Heck*-type olefination product **6a** with N–O bond cleavage (Scheme 4e). These observations demonstrate that this catalytic spirocyclization is unique where the oxidation state of the Ru(II)-catalyst remains unchanged.

Based on the results of the control experiments a plausible reaction mechanism is elucidated in Scheme 4. Benzamide (**1**) can undergo *ortho*-C–H metalation to form metallacycle **A**, which experiences migratory insertion with naphthoquinones to give key intermediate **C** (Scheme 4f). At this stage, hydroarylation at quinone double bond leads to intermediate **D**, which then could spontaneously oxidize to quinone analogue **E** under aerobic conditions.[10] Michael addition onto activated quinone double bond in *5-exo-trig* fashion can produce a spirocyclic isoindolinone **3**. Notably, both quinone and air are playing crucial roles in this process to drive the high yields of products. Most likely, the intermediate **D** is oxidized to intermediate **E** with naphthoquinone **2a** and reduced 1,4-naphthalenediol is reoxidized to **2a** by air (Scheme 4f).[10]

In conclusion, we have disclosed a Ru(II)-catalyzed oxidative annulation reaction between easily accessible hydroxamic acid esters and naphthoquinones to construct diverse spiro-isoindolinones. The protocol is operationally simple, proceeds under mild conditions, and offers products in high yields. Preliminary mechanistic studies revealed a reversible metalation process to be involved, where C–H bond cleavage is possibly not the rate limiting step and naphthoquinone plays a dual role of reagent as well as oxidant. The spirocyclic products, upon exposure to ethanolic KOH, smoothly transformed to benzo[*b*]phenanthridine-5,7,12(6H)-triones, a novel class of redox-active small molecule ROS-generators. Further explorations on C–H activation/annulation cascades to fabricate heteroatom-bearing spirocycles are ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

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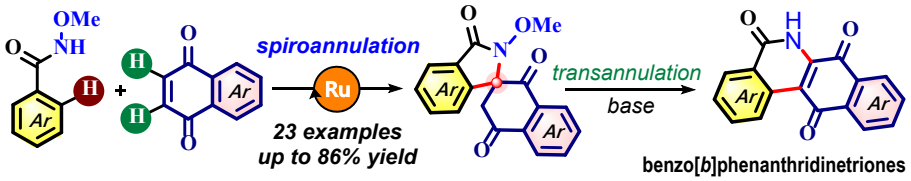

rapid reaction with broad scope *simple operation and silver additive free* *dual role of quinones*