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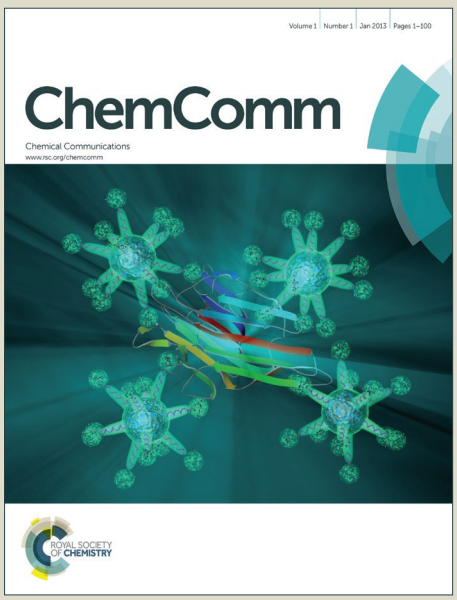

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Expedient Synthesis of New Cinnolinediones by Ru-Catalyzed Regioselective Unexpected Deoxygenation-Oxidative Annulation of Propargyl Alcohols with Phthalozinones and Pyridizinones

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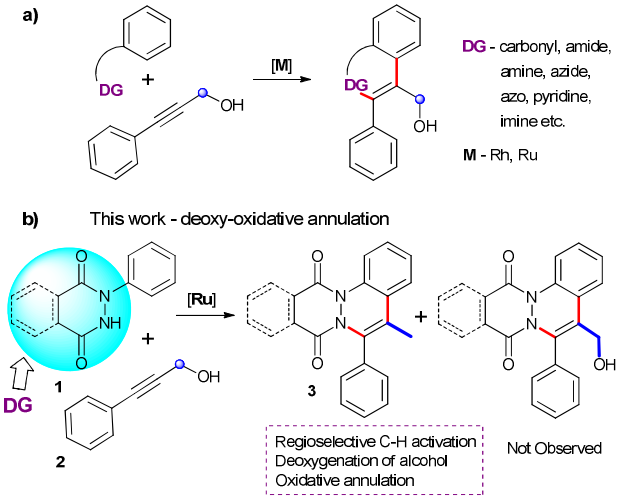
Ruthenium catalyzed simple, cascade and one-pot synthesis of cinnoline-fused diones has been synthesized by the C–H activation of phthalozinones/pyridizinones complied by the unusual deoxygenation of propargyl alcohols. The bound selectivity is accredited to the traceless directing nature of hydroxyl group of propargyl alcohol. A sequential C–H activation, insertion and deoxy-oxidative annulation has been proposed based on the preliminary mechanistic study.

Transition-metal-catalyzed direct C-H bond functionalization has taken a centre stage in modern organic synthesis as it could usher the chemists for rapid construction of complex compounds from easily accessible substrates.[1] Embracing this strategy, various fused polyheterocycles has been generated exhibiting step- and atom-economy, high selectivity and efficiency overcoming the traditional pre-functionalization route.[2] In addition, tethering the appropriate directing group (DG) in the substrate which can direct a metal catalyst to the reactive centre enables the diverse C-H bond functionalization.[3] In this regard, oxidative annulation reaction using alkynes are among the most acclaimed and well-studied approaches of C-C and C-N/C-O bond formation.[3d, 4] Specifically, syntheses of cinnolines and their derivatives are privileged polyheterocyclic scaffolds prevalent in natural products and are known for exhibiting interesting pharmaceutical[5] and optical properties.[6] Recently, Zhang, Cheng, You and Lee have disclosed the construction of cinnolines through Rh-catalyzed C-H activation/cyclization of azobenzene or N-aryl-1H-pyrazol-5(4H)-one with simple alkynes or Meldrum's acid by employing nitrogen as a directing group.[7] In addition, Ge and coworkers have developed intramolecular dehydrogenative cyclization of N-methyl-N-phenylhydrazones to yield 3-aryl-substituted cinnolines.[8] Simultaneously, Willis et al reported the copper-catalyzed annulation of a simple hydrazine diester with various 2-(2-bromoalkenyl)aryl bromides to give functionalized cinnolines.[9] Very recently, Subba Reddy and coworkers showed Pd-catalyzed synthesis of cinnoline derivatives involving sequential C-C and C-N bond formation using 1-arylhydrazine-1,2-dicarboxylate and aryl iodide as the precursors.[10]

Figure 1 Previous works - oxidative annulation



Herein, we wish to report a less expensive Ru-catalyzed oxidative annulation reaction of easily accessible phthalazinone/pyridizinone with propargyl alcohol to afford cinnoline-fused diones in moderate to excellent yields. Besides, we witnessed unprecedented deoxygenation of propargyl alcohol which is considered as a poor leaving group (Figure 1a).[11] It is quite well-known that deoxygenation of alcohols to alkanes is very attractive process as it holds good scope in converting the natural products to biofuels. However, the removal of a hydroxyl group to form corresponding alkanes is very challenging, and it is achieved by classical Barton-McCombie reaction or by other multistep processes.[12] Initially, 2-phenyl-2,3-dihydrophthalazine-1,4-dione **1a** was treated with 3-phenylprop-2-yn-1-ol **2a** in the presence of $[RuCl_2(p\text{-cymene})]_2$) (5 mol %), and NaOAc (30 mol %) in methanol at 80 °C for 22 h. To our surprise, we observed the cascade reaction involving facile deoxy-oxidative annulation reaction resulting in the formation of **3aa**, but in poor yield. However, it is a noteworthy transformation signifies the concomitant regioselectivity and deoxygenation process (Figure 1b).

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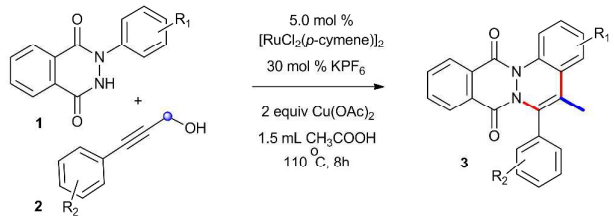
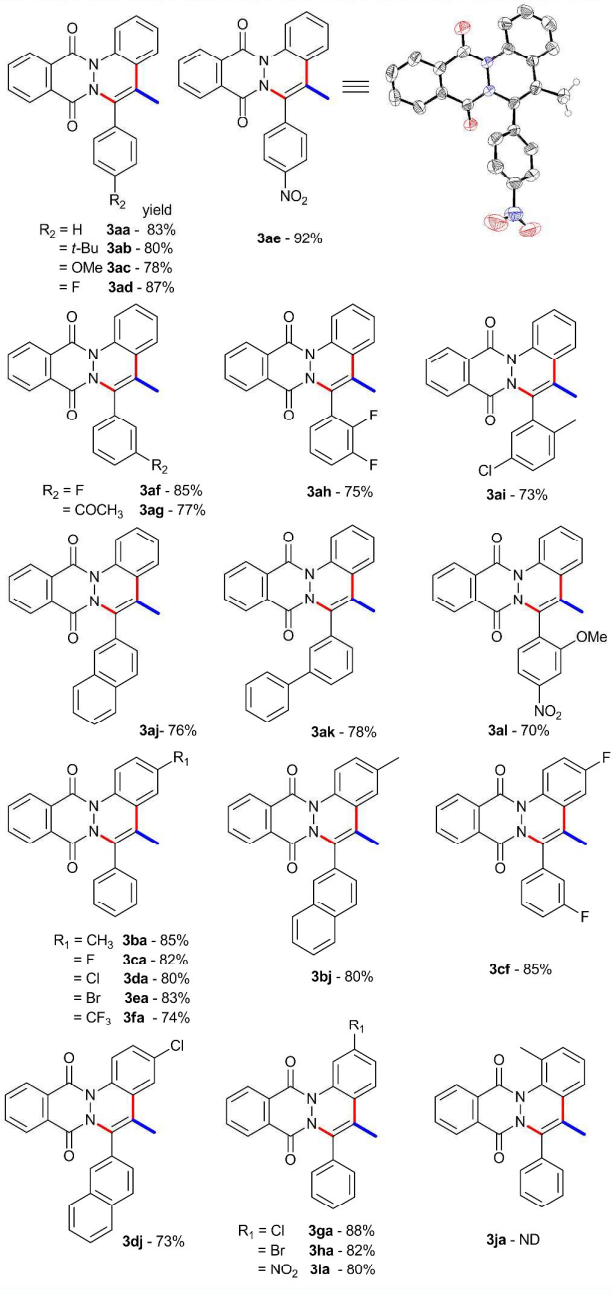
Scheme 1 Scope of phthalazinone with various primary propargyl alcohol

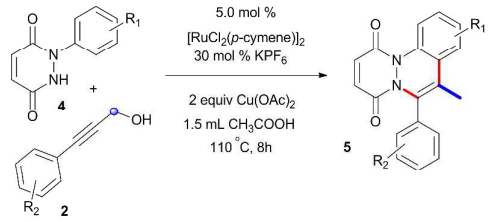


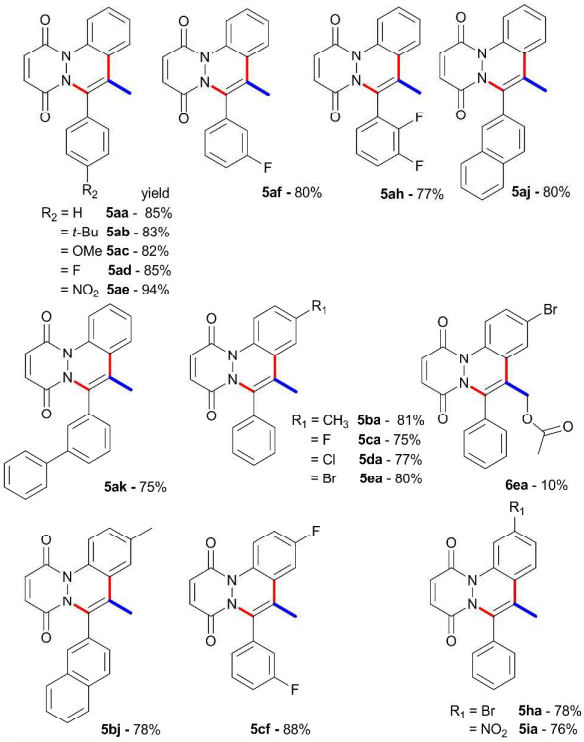


1 (0.2 mmol), **2** (0.22 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $Cu(OAc)_2$ (2 equiv), KPF_6 (30 mol %), Acetic acid, 110 °C, 8 h. [a] Isolated yield

After we surprisingly observed the product **3aa,** our next task is to improve its yield, we chose certain variable like solvents, additives, oxidants and Ru salts (see Supplementary Information).

Scheme 2 Scope of pyridizinone with various primary propargyl alcohol



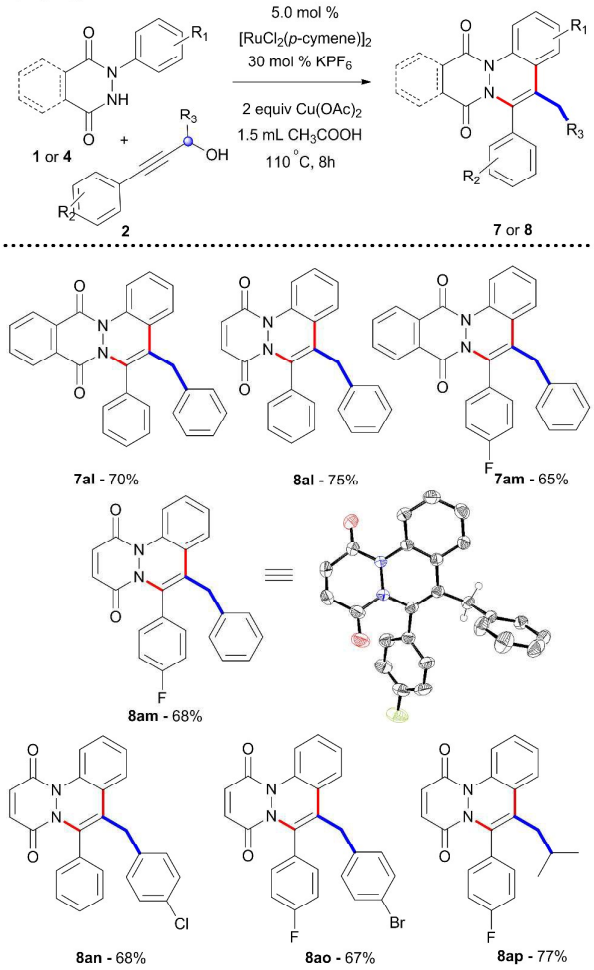


4 (0.2 mmol), **2** (0.22 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $Cu(OAc)_2$ (2 equiv), KPF_6 (30 mol %), Acetic acid, 110 °C, 8 h. [a] Isolated yield.

Predictably, the annulation reaction did not proceed in the absence of ruthenium catalyst. Screening the solvents ensued that acetic acid is the best among toluene, dioxane, 1,2-dichloroethane and water. Further, good increment in the product formation was observed by introducing $Cu(OAc)_2$ as external oxidant. Pleasingly, combination of oxidant $Cu(OAc)_2$ with co-catalyst KPF_6 proved to be efficient in annulation reaction compared to other additives like KOAc, $AgSbF_6$, AgOAc, and CsOAc. Oxidant loading seems to be critical, **3aa** yield decreases when its amount is reduced. When $[RuCl_2(p\text{-cymene})]_2$ was replaced with $RuCl_3.XH_2O$ and $Ru(DMSO)_4Cl_2$), regrettably, no product was formed. However, $RuCl_2(PPh_3)_3$ and $[Ru(COD)Cl_2]_n$ generated trace amount of **3aa**.

With the optimized condition in hand, we first tested substrate scope (Scheme 1) of 2-phenyl-2,3-dihydrophthalazine-1,4-dione **1a** with substituted/ring fused 3-phenylprop-2-yn-1-ol **2b**-**2l** bearing various valuable electron-donating and electron-withdrawing groups in the phenyl ring were well tolerated to provide regioselective deoxy-oxidative annulated cinnoline-fused diones **3ab**-**3al**. Formation of regioselective deoxy-oxidative annulated product was ascertained by NOESY and single crystal X-ray diffraction study.

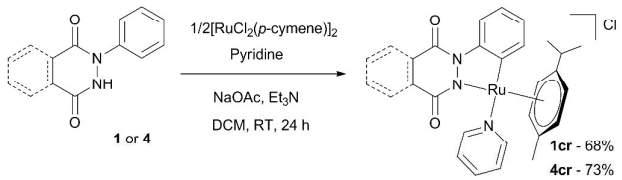
Scheme 3 Scope of phthalazinone/pyridizinone with various secondary propargyl alcohol



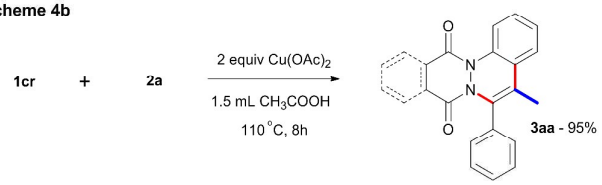
1 or **4** (0.2 mmol), **2** (0.22 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), $Cu(OAc)_2$ (2 equiv), KPF_6 (30 mol %), Acetic acid, 110 °C, 8 h. [a] Isolated yield

Meta- **3af**, **3ag**, *ortho*/*meta*- **3ah**, **3ai**, *ortho*/*para*- **3al** substituted 3-phenylprop-2yn-1-ol, 3-(naphthalen-2-yl)prop-2-yn-1-ol **3aj** and 3-([1,1′-biphenyl]-3-yl)prop-2-yn-1-ol **3ak** also proved to be good substrate for the regioselective deoxy-oxidative annulation. Scope of the reaction was further extended by varying the electron-donating and electron-withdrawing groups on 2-phenyl-2,3-dihydrophthalazine-1,4-dione derivatives **1b**-**1j**. Meta substituted 2-phenyl-2,3-dihydrophthalazine-1,4-dione (*m*-Cl, *m*-Br, *m*-NO_2) also smoothly reacted to give the corresponding product **3ga**, **3ha**, and **3ia** with exclusive selectivity. However, reaction of *ortho*-methyl substituted 2-phenyl-2,3-dihydrophthalazine-1,4-dione does not occur **3ja** due to sterics. The deoxy-oxidative annulation was successfully tested with 1-phenyl-1,2-dihydropyridazine-3,6-dione derivatives **4** and **2** as shown in the Scheme 2 to give **5aa**-**5ia**. Steadfastly, substrate **4** reactivity seems to be very similar to its higher congener **1**. Interestingly, **6ea** (10% Yield), an ester counterpart of **5ea**, is a lone example of this kind which was isolated and characterised. This indicates that, some amount of ester is intact in the catalytic reaction and bypasses the deoxygenation step.

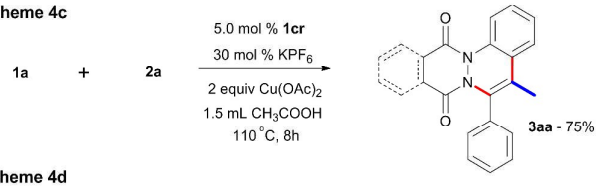
Scheme 4a



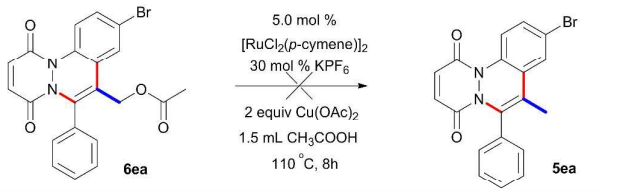
Scheme 4b



Scheme 4c



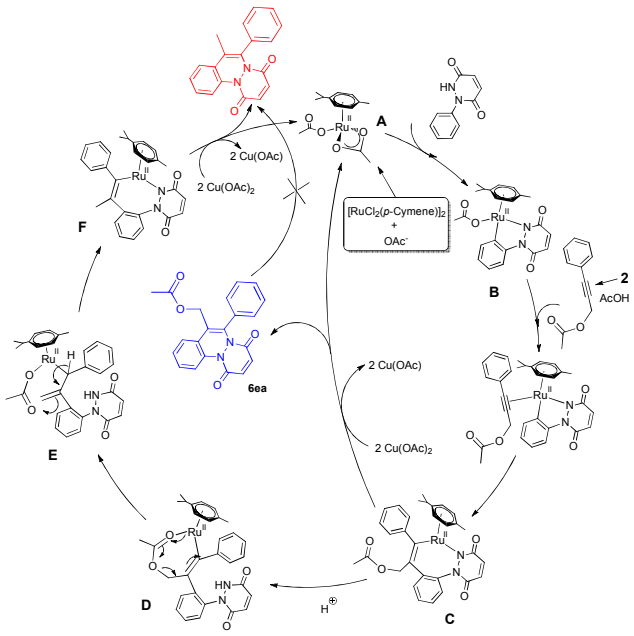
Scheme 4d



Having established regioselective deoxy-oxidative annulation of primary propargyl alcohol with phthalazinone/pyridizinone, we set to investigate the feasibility of such annulation reaction with secondary propargyl alcohol. The reaction of **1a**/**4a** with various secondary propargyl alcohols **2l**-**2p** afforded regioselective deoxy-oxidative product with satisfactory yield **7al**-**8ap** (Scheme 3). Thus the regioselectivity was consistent with secondary propargyl alcohol as well. However, attempts to make tertiary propargyl alcohol to participate for oxidative annulation proved futile as it always ended up with unidentified products.

In an effort to gain insight into the reaction mechanism, we performed a series of experiment. Firstly, the cycloruthenated complex **1cr** was prepared by the direct reaction of **1a** with stoichiometric amount of $[RuCl_2(p\text{-cymene})]_2$ and pyridine in dichloromethane at room temperature in the presence of NaOAc and Et_3N for 24 h (Yield 68%).[13] The isolated **1cr** was reacted with **2a** at room temperature for 24 h resulted in deoxy-oxidative annulated product **3aa** in low yield, however, increase in temperature afforded quantitative yield (95%). Furthermore, the reaction of **1a** and **2a** in the catalytic amount of **1cr** (5 mol %) gave a yield (75%) of **3aa.** These outcomes support a sequential C–H activation, insertion and deoxy-oxidative annulation. Moreover, sequence of the deoxygenation step (whether this processes is occurring before or after annulation reaction) could be understood from scheme 4d. When **6ea** was subjected to the optimized catalytic reaction, surprisingly, no deoxygenation processes was observed and this implies that before oxidative annulation, the deoxygenation was taking place. Presumably, the propargylic ester is the alkyne source in the deoxy-oxidative annulation as it was formed by the reaction between propagylic alcohol and acetic acid.

Scheme 5 Proposed mechanism for deoxy-oxidative annulation



To further corroborate this process, in a separate reaction propargylic ester was chosen as the alkyne source and it was found out that it undergoes deoxy-oxidative annulation at ease (see Supplementary Information). Based on the above-mentioned experimental results, a plausible mechanism was outlined in Scheme 5. Initially Ru(II)-catalyzed C-H activation takes place to give ruthenacycle **B**, which is followed by the regioselective insertion of alkyne (in situ formed propargylic ester) gives seven member Ru(II) species **C**, which upon isomerise to generate another intermediate **D**, in the presence of acidic condition. Further, **D** was rearranged to new Ru(II) species **E** - a γ-deoxygenation step.[12d, 14] In the penultimate step, again seven membered Ru(II) species **F** is formed with the removal of -OAc and eventually oxidative annulated product was generated.

In summary, we have developed a convenient synthesis of new cinnoline fused-diones by Ru(II)-catalyzed regioselective deoxygenation-oxidative annulation of propargyl alcohols with phthalozinones and pyridizinones. This cascade reaction proceeds with the generation of -OAc as the sole by-product. Broad substrate scope and excellent functional group tolerance are highlight of this work. Resultant deoxygenated products could be impetus to study the detailed mechanism of this process and above all it opens up new strategy to generate new heterocycles possessing potential biological and photochemical applications.

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