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Ru(II)-Catalyzed C−H Activation and Annulation Reaction via Carbon−Carbon Triple Bond Cleavage

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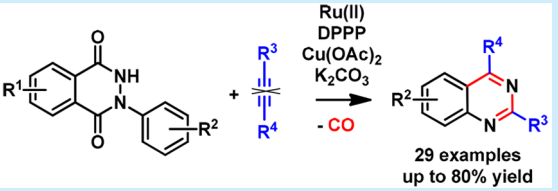
Supporting Information

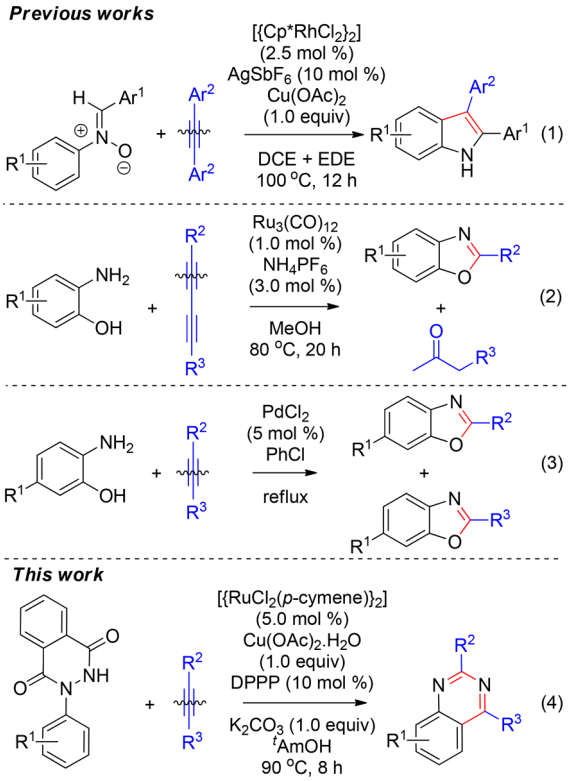
ABSTRACT: An unprecedented Ru(II)-catalyzed C−H activation and annulation reaction, which proceeds via C−C triple bond cleavage, is reported. This reaction of 2-phenyldihydrophthalazinediones with alkynes, which works most efficiently in the presence of bidented ligand 1,3-bis(diphenylphosphino)propane, affords good yields of substituted quinazolines.



In recent years, transition-metal-catalyzed cleavage of C−C single bonds and double bonds has emerged as one of the most challenging areas in organic reactions because of its utility in organic synthesis.[1] In contrast, metal-catalyzed C−C triple bond cleavage reactions are not well-studied, owing to the large bond dissociation energy of C−C triple bonds, and still remains one of the most challenging matters in organic chemistry. Traditionally, stoichiometric organometallic reactions and alkyne metathesis reactions are used for the C−C triple bond cleavage.[2] In the last two decades, only a few catalytic methods have been developed for the C−C triple bond cleavage using transition metal catalysts such as Pd,[3] Au,[4] Ru,[5] and Rh.[6] Concurrently, the transition-metal-catalyzed C−C triple bond reactions have also been used to perform a few annulation cleavage reactions for the efficient construction of some important heterocycles. For instance, Wan and co-workers reported a Rh(III)-catalyzed annulation reaction of nitrones with symmetrical diaryl alkynes for the synthesis of indoles, which proceeds via C−C triple bond cleavage (Scheme 1, eq 1).[6b] Similarly, Yamamoto and co-workers reported a Ru(0)-catalyzed simultaneous cleavage of C−C single and triple bonds of diynes to perform an annulation reaction with *o*-aminophenols (Scheme 1, eq 2).[5b] Recently, Pan and co-workers reported a Pd(II)-catalyzed annulation reaction of *o*-aminophenols with disubstituted alkynes which proceeds via C−C triple bond cleavage for the synthesis of benzoxazoles (Scheme 1, eq 3).[3c]

In the last two decades, transition-metal-catalyzed C−H activation and functionalization reactions have provided a new direction for the efficient syntheses of important heterocycles.[7] In particular, transition-metal-catalyzed C−H bond activation followed by annulation of alkynes has been frequently used for the efficient construction of a wide range of heterocycles.[7a] In continuation of our work on metal-catalyzed reactions,[8] here, we disclose an unprecedented Ru(II)-catalyzed C−H activation and annulation reaction, where the annulation occurs by cleavage of the triple bond of the alkyne. Notably, unlike the reported alkyne cleavage reactions, in the present reaction, both the fragments of the alkyne remain in the same product. This new annulation reaction provides an efficient method for the synthesis of quinazolines. Quinazolines are the main building block of a wide range of natural products, pharmaceutically active compounds, and pesticides (Figure 1).[9] The recent approval of a number of quinazoline-based drugs has made it essential to develop novel

Scheme 1. Transition-Metal-Catalyzed Cleavage of Alkyne in Intermolecular Annulation Reactions



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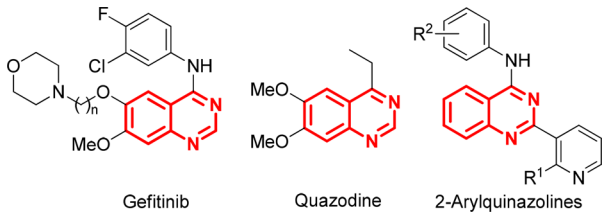
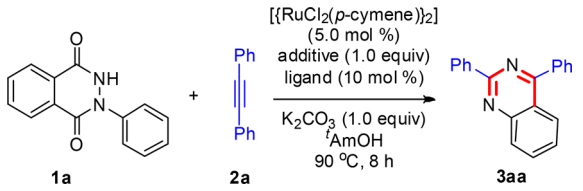


Figure 1. Examples of quinazoline drugs and bioactive compounds.

synthetic routes which can accommodate various substituents on the quinazoline ring. Initially, the Ru(II)-catalyzed annulation reaction was tested with 2-phenyldihydrophthalazinedione **1a** with alkyne **2a** for the synthesis of quinazoline **3aa** (Table 1 and

Table 1. Optimization of the Reaction Conditions for 3aa[a]

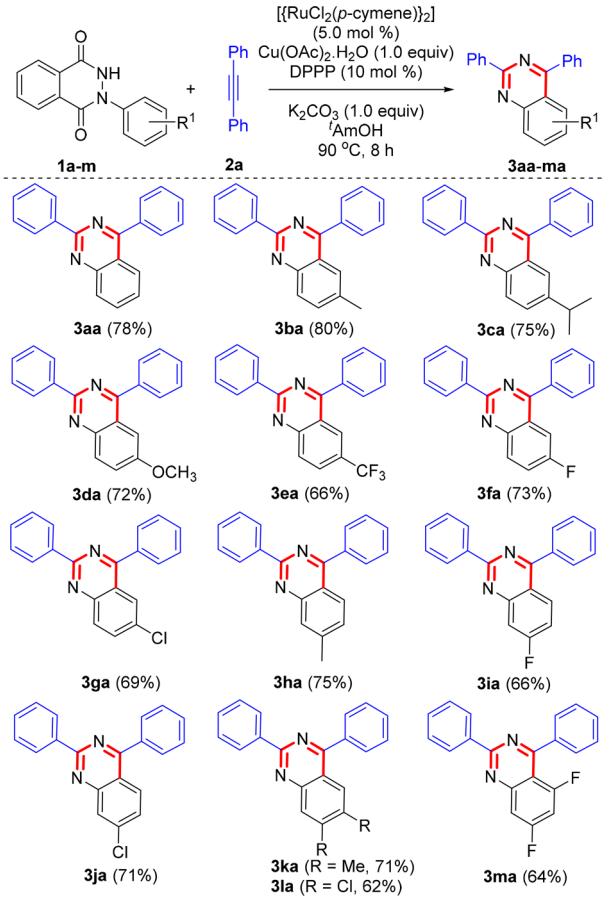


entry	catalyst	additive	ligand	3aa (%)[b]
1	$[RuCl_2(p\text{-cymene})_2]$	$Cu(OAc)_2{\cdot}H_2O$		37
2	$[RuCl_2(p\text{-cymene})_2]$	CsOAc		32
3	$[RuCl_2(p\text{-cymene})_2]$	$CuBr_2$		15
4	$[RuCl_2(p\text{-cymene})_2]$	AgOAc		28
5	$[RuCl_2(p\text{-cymene})_2]$	KOAc		16
6	$[RuCl_2(p\text{-cymene})_2]$	$Cu(OAc)_2{\cdot}H_2O$	PPh_3	43
7	$[RuCl_2(p\text{-cymene})_2]$	$Cu(OAc)_2{\cdot}H_2O$	dppe[c]	69
8	$[RuCl_2(p\text{-cymene})_2]$	$Cu(OAc)_2{\cdot}H_2O$	dppp[d]	78
9	$[RuCl_2(p\text{-cymene})_2]$	$Cu(OAc)_2{\cdot}H_2O$	Johnphos	52

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.25 mmol), catalyst (5.0 mol %), additive (0.25 mmol), ligand (10 mol %), and ^{t}AmOH (4.0 mL) at 90 °C under air for 8 h, unless otherwise mentioned. [b]Isolated yields. [c]1,2-Bis(diphenylphosphino)ethane. [d]1,3-Bis-(diphenylphosphino)propane.

Table SI-1). Among the additives tested for the reactions, $Cu(OAc)_2{\cdot}H_2O$ provided the best yield of **3aa** in the presence of K_2CO_3 in ^{t}AmOH (entries 1−5). Screening of monodentate and bidentate phosphine ligands revealed DPPP [1,3-bis-(diphenylphosphino)propane] to be the best ligand to perform this annulation reaction (entries 6−9 and Table SI-1). These optimized reaction conditions were then tested for the annulation reaction of various 2-phenyldihydrophthalazine-diones **1a−m** with alkyne **2a** (Scheme 2). The 2-phenyldihydro-phthalazinediones substituted with electron-donating and electron-withdrawing substituents, such as Me, ^{i}Pr, OMe, CF_3, F, and Cl at the *para*-position of the 2-phenyl ring (**1b−g**), afforded good yields of quinazolines **3ba−ga**. Similarly, the reactions of 2-phenyldihydrophthalazinediones substituted with electron-donating and electron-withdrawing substituents, such as Me, F, and Cl at the *meta*-position of the 2-phenyl ring **1h−j**, were found to be highly regioselective to provide products **3ha−ja**. The dihydrophthalazinediones substituted with two sub-stituents on the 2-phenyl ring **1k−m** also turned out to be good substrates for this reaction to provide good yields of **3ka−ma**. Next, the scope of the alkynes **2b−o** was tested for this annulation reaction with **1a** (Scheme 3). All the tested diaryl-substituted symmetrical alkynes, substituted with electron-

Scheme 2. Scope of 2-Phenyl-2,3-dihydrophthalazine-1,4-diones 1a−m[a]



[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.25 mmol), catalyst (5.0 mol %), additive (0.25 mmol), ligand (10 mol %), and ^{t}AmOH (4.0 mL) at 90 °C under air for 8 h, unless otherwise mentioned.

donating and electron-withdrawing substituents, such as Me, OMe, and F on the phenyl rings of alkynes **2b−d**, afforded good yields of quinazolines **3ab−ad** with **1a**. The reactions of unsymmetrical diaryl-substituted alkynes **2e−i** with **1a** were found to be highly regioselective to afford compounds **3ae−ai**,**3af′**. Interestingly, the reaction of **2h** with **1a** under the standard reaction conditions, and in the absence of the ligand DPPP, was highly regioselective to provide the opposite isomer **3ah′**. However, the reaction of unsymmetrical alkynes **2g**, **2i**, and **2m** with **1a**, both in the presence of the ligand and in the absence of the ligand, afforded the same regioisomers. The sensitive Br-containing unsymmetrical alkyne **2j** and the aryl heteroaryl-substituted unsymmetrical alkyne **2l** were also found to be good substrates, affording **3aj** and **3al** regioselectively. The alkyne possessing biphenyl and phenyl substituent **2k** was tested, which provided highly regioselective product **3ak**. The alkylaryl-substituted alkynes **2m**,**n** were also found to be suitable starting materials for this annulation reaction to provide compounds **3am−an** regioselectively, albeit with poor yields. Nevertheless, the disubstituted alkyne **2o**, substituted with one phenyl and one ester group, turned out to be a very good substrate to perform this reaction, and it provided good yield of **3ao**. However, the dialkyl-substituted alkynes, terminal alkynes, silyl- and bromo-group-substituted alkynes were not found to be good substrates for this reaction. Previous studies on alkyne annulation reactions,

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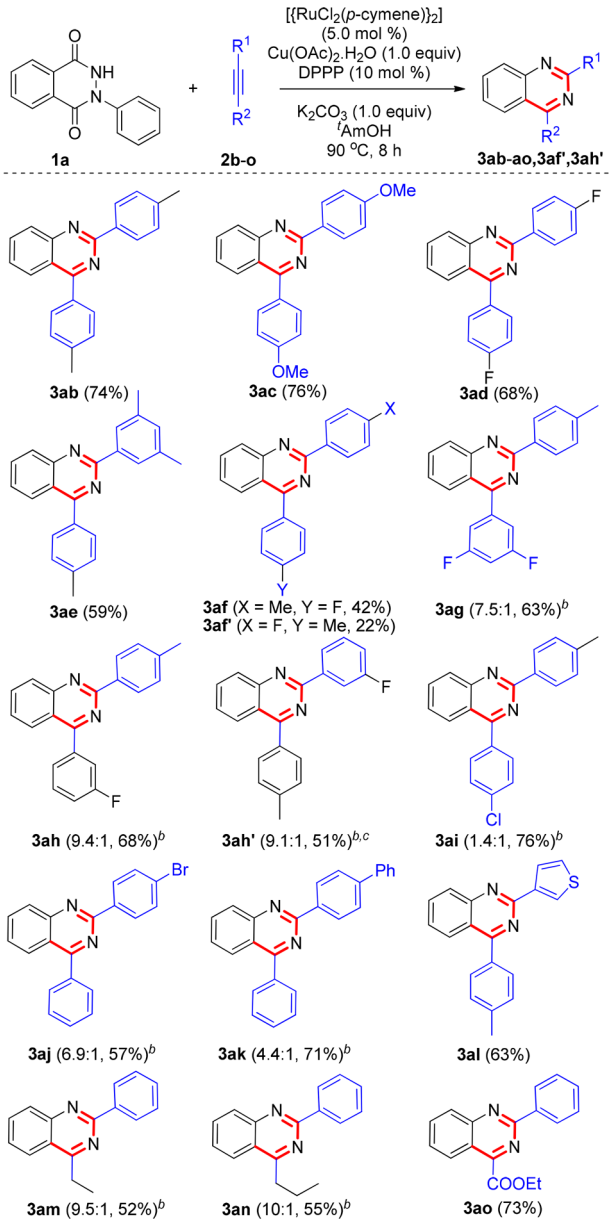
Scheme 3. Scope of Alkynes[a]

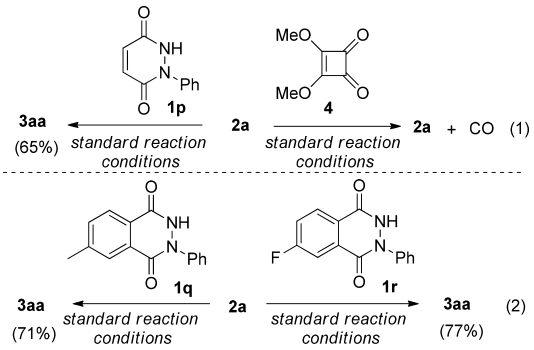


[a]Reaction conditions: **1a** (0.25 mmol), **2** (0.25 mmol), Ru catalyst (5.0 mol %), $Cu(OAc)_2 \cdot H_2O$ (0.25 mmol), DPPP (10 mol %), and K_2CO_3 (0.25 mmol) in ^{t}AmOH (4.0 mL) was heated at 90 °C for 8 h under air. [b]Major isomer is depicted. [c]DPPP was not used.

catalyzed by transition metal catalysts, demonstrated that the insertion of alkyne was controlled by electronic effect rather than the steric effect.[10] In the present reaction, the annulation pattern of diaryl-, arylalkyl-, and arylester-substituted unsymmetrical alkynes is similar to the previously reported transition-metal-catalyzed annulation reactions.[10] In these annulation reactions of unsymmetrical alkynes, the insertion of the alkynes occurs in such a way that the electron-rich center of the alkyne binds with the metal, thus providing regioselectivity into the final annulated products. The structures of the products were determined by spectroscopic studies and the spectral data compared to that of the reported compounds.[9]

The reaction of alkyne **2a** with phenyldihydropyridazinedione **1p** under the standard reaction conditions provided **3aa** in 65% yield (Scheme 4, eq 1). This result indicates a similar role of the leaving moieties in the starting materials **1a** and **1p**. In another

Scheme 4. Controlled Experiments



experiment of diketo compound **4** with alkyne **2a**, performed under standard conditions, we observed the elimination of carbon monoxide gas from the reaction mixture (Scheme 4, eq 1). However, we could not isolate any product from the reaction mixture other than isolating the starting alkyne **2a**. Interestingly, in the absence of the alkyne **2a**, the diketo compound **4** could not react under standard conditions to produce carbon monoxide, and **4** was recovered after 8 h. The dihydrophthalazinediones **1q** and **1r**, which have fused electron-rich and electron-poor aryl rings, did not show significant difference in their reactivity with alkyne **2a** under standard conditions (Scheme 4, eq 2). The parallel or intermolecular competition experiments conducted between electron-rich and electron-poor alkynes **2b** and **2d** with **1a** revealed preferential conversion of **2d** to **3ad** (Scheme SI-2). Again, in another competition experiment of dihydrophthalazinediones **1b** and **1f** possessing electron-rich and electron-poor 2-phenyl substituents with **2a** revealed preferential conversion of **1b** to **3ba** (Scheme SI-3). The reaction of **1a** alone or in the presence of alkyne **2a**, under the standard condition in CD_3OD, could not afford the deuterium exchanged product **1a-D**, indicating the irreversible initial C−Ru bond formation (Scheme SI-4). The competitive intermolecular experiment between **1a** and **1a-D$_5$** with **2c** provided $k_H/k_D = 1.2$ (Scheme SI-6), whereas the competitive parallel experiments between **1a** and **1a-D$_5$** with **2c** provided $k_H/k_D = 1.1$ (Scheme SI-7). Thus, the Ru−C bond formation step might not be the rate-determining step of this annulation reaction.

Based on our results and the literature reports, a possible mechanism is proposed in Scheme 5 for the formation of quinazoline derivative **3aa**.[7a,11] First, the active Ru(II) catalyst **A**, generated from $[RuCl_2(p\text{-cymene})_2]$ and $Cu(OAc)_2$, irreversibly reacts with **1a** to generate Ru complex **B** via activation of the C−H bond. Insertion of alkyne into the C−Ru bond produces seven-membered Ru(II) complex **C**, which on further oxidation by cleavage of the N−N bond generates Ru(IV) complex **D**.[11] Subsequently, reductive elimination of the Ru metal generates indole derivative **E**. Activation at C-2 of the indole moiety of **E** leads to the formation of Ru complex **F**, which on subsequent reductive elimination, in the presence of $Cu(OAc)_2$, affords a seven-membered amide **G**, and it regenerates the active catalyst **A**. Next, intramolecular cyclization of **G** might generate diazacyclopropane azulene **H**, which on intramolecular rearrangement and elimination reaction produces the quinazoline derivative **3aa** and diketo compound **I**. However, our attempt to isolate **I** from the reaction mixture failed. Nevertheless, the

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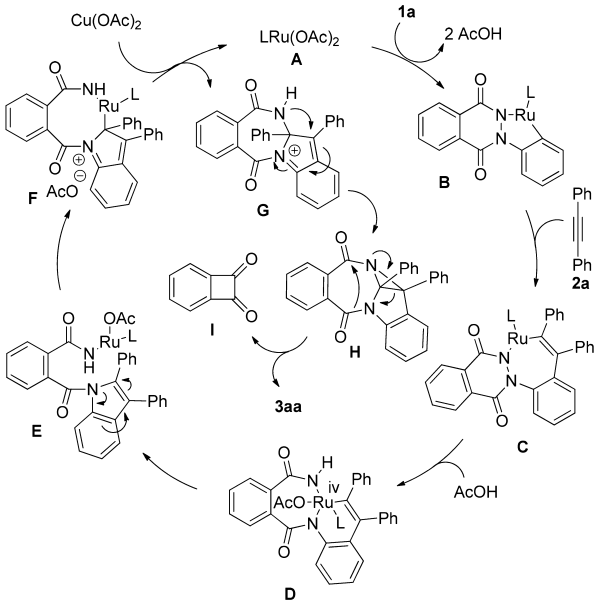
Scheme 5. Proposed Mechanism



phosphomolibdic acid−$PdCl_2$ test performed in the synthesis of **3aa** from the reaction of **1a** and **2a** indicated the elimination of CO from the reaction mixture (Figure SI-1).[8a,12] Probably, under the standard reaction conditions, diketo compound **I** decomposes to eliminate carbon monoxide, similar to the control experiment mentioned in Scheme 4 (eq 1).

In summary, we have developed a novel Ru(II)-catalyzed C−H activation and annulation reaction, in which the annulation proceeds via cleavage of the triple bond of the alkyne. This new reaction of *N*-arylpyrazol-5-ones and diaryl/arylalkyl-substituted alkynes provided an easy synthetic route for the biologically important substituted quinazolines by accommodating both the fragments of the alkyne in the same product.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00643.

Experimental procedures, spectroscopic data and copies of ^{1}H NMR, ^{13}C NMR and HRMS spectrum of synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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