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Synthesis of Quaternary Carbon Centered Indolo[1,2-*a*]quinazolinones and Indazolo[1,2-*a*]indazolones via C-H Functionalization

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Kongkona Gogoi[†], Bidisha R. Bora[†], Geetika Borah[§], Bipul Sarma[‡], and Sanjib Gogoi[†,*]

An unprecedented Ru(II)-catalyzed Csp²-H bond activation and annulation reaction of phenylindazolones with diaryl substituted alkynes and dialkyl substituted alkynes provided efficient routes for the construction of all-carbon quaternary centered indolo[1,2-*a*]quinazolinones and quaternary carbon centered indazolo[1,2-*a*]indazolones, respectively. The indolo[1,2-*a*]quinazolinones were fomed via the Csp²-H activation, alkyne insertion and 1,2-phenyl shift pathways. The indazolo[1,2-*a*]indazolones were formed through a cascade reaction via the formation of exocyclic double bond containing indolo[1,2-*a*]quinazolinones.

Indoloquinazolinones are known to exhibit wide range of bioactivities such as anticancer, antibacterial, antifungal etc.[1] Among the indoloquinazolinones, the indolo[1,2-*a*]quinazolinones have attracted considerable attention recently, owing to their poly(ADP-ribose) polymerase-1 (PARP-1) and protein kinase CK2 inhibitory activities (Figure 1).[2] Therefore, development of novel practical methods to construct this heterocyclic scaffold is a thrust research area.[3] Again, recently, the indazole and indazolone ring fused heterocycles have emerged as pharmaceutically important compounds because of their remarkable biological activity.[4] Pyrazolo[1,2-*a*]indazolone and indazolo[1,2-*a*]indazolone are two such fused heterocyclic scaffolds which have got much attention very recently for their bioactivity and interesting laser activity.[4] However, method to construct the indazolo[1,2-*a*]indazolone skeleton is not considerably explored. Therefore, a direct method to synthesize this heterocyclic scaffold using simple and readily available starting material is highly desired. Last few decades have witnessed the significant evolution of metal-catalyzed C-H activation and alkyne annulation reactions for the step-economic construction of important heterocycles.[5] Very recently, Perumal and co-workers used phenylindazolones to perform Rh(III)-catalyzed activation of Csp²-H bond followed by direct alkyne annulation to synthesize indazolo[1,2-*a*]cinnolines (Scheme 1, eq 1).[5d] In our continuous

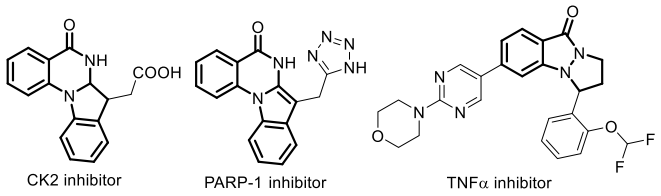
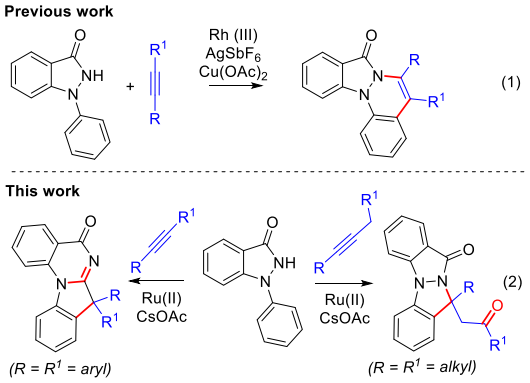


Figure 1. Examples of bioactive indolo[1,2-*a*]quinazolinones and pyrazolo[1,2-*a*]indazolone

effort to develop novel metal-catalyzed C-H bond functionalization reactions,[6] herein, we describe a novel Ru(II)-catalyzed Csp²-H activation and annulation reaction of phenylindazolones with aryl/heteroaryl substituted alkynes. This reaction proceeds through Csp²-H activation, alkyne insertion and 1,2-aryl shift to provide an efficient synthetic method for indolo[1,2-*a*]quinazolinones (Scheme 1, eq 2). We



Scheme 1. Metal-catalyzed annulation reactions of phenylindazolone and alkyne

also report an unprecedented Ru(II)-catalyzed cascade reaction of phenylindazolones with dialkyl substituted alkynes for the synthesis of indazolo[1,2-*a*]indazolones (Scheme 1, eq 2). Notably, these synthetic methods of indolo[1,2-

[a.] [†]*Applied Organic Chemistry, Chemical Sciences & Technology Division, CSIR-North East Institute of Science and Technology, Jorhat-785006, AcSIR, Ghaziabad-201002, India,* [§]*Department of Chemistry, Dibrugarh University, Dibrugarh-786004, and* [‡]*Department of Chemical Sciences, Tezpur University, Tezpur-784028, India, Email: skgogoi1@gmail.com; sanjibgogoi@neist.res.in*

Electronic Supplementary Information (ESI) available: Experimental procedures, spectroscopic data and copies of ^{1}H NMR, ^{13}C NMR and HRMS spectrum of the synthesized compounds, See DOI:

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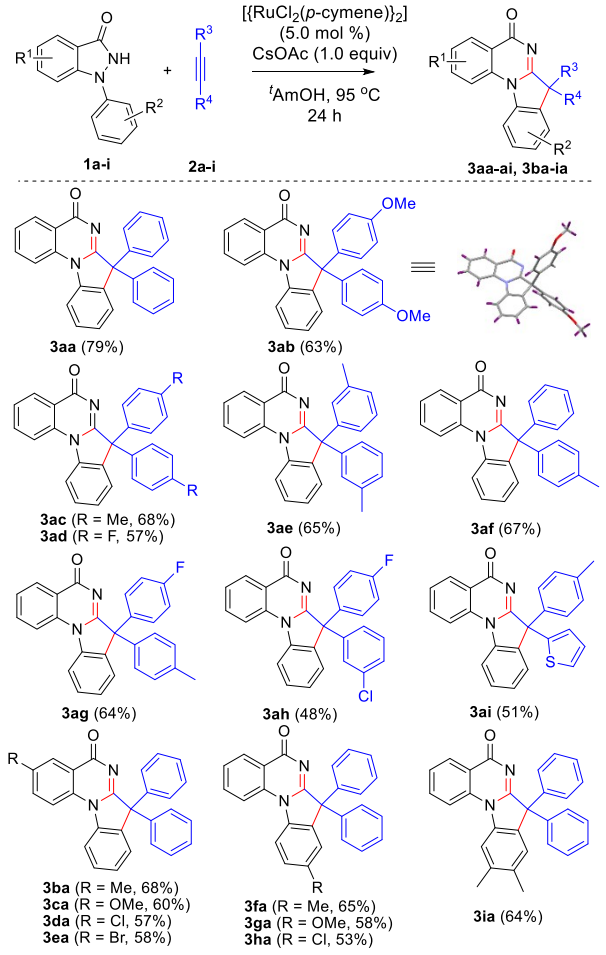
a]quinazolinones and indazolo[1,2-*a*]indazolones afford all-carbon quaternary carbon-centered and quaternary carbon-centered heterocycles. Again, the creation of a new method to construct a quaternary carbon stereo center, which is present in many bioactive molecules has itself been considered as a challenging task in organic synthesis.[7]

Initially, we tested the reaction of phenylindazolone **1a** with alkyne **2a** for the synthesis of indoloquinazolinone **3aa** (Table SI-1). Among various transition metal complexes tested, the [{$RuCl_2$(*p*-cymene)}$_2$] complex (5 mol %) together with the additive $Cu(OAc)_2.H_2O$ produced the highest yield of the product **3aa** in ^{t}AmOH (38%) (entry 2). Then, to further improve the yield of **3aa** some other additives were tested. Fortunately, the additive CsOAc provided the highest yield (79%) of the product **3aa** (entry 7). Further studies on solvents and catalyst loading could not improve the yield of **3aa** (entries 10-15). The highest yielding reaction conditions were then applied first to study the substrate scope of diaryl or aryl heteroaryl substituted alkynes **2a**-**i**. As shown in Table 1, the

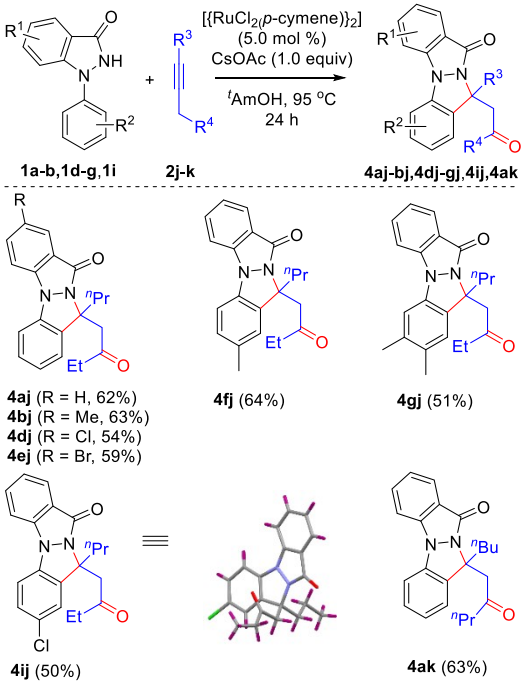
Table 1. Scope of alkynes (**2a**-**i**) and phenylindazolones (**1a**-**i**)



[a]**Reaction conditions**: **1a** (0.1 mmol), **2a** (0.1 mmol), catalyst (5 mol %), additive (0.1 mmol) and ^{t}AmOH (3.0 mL) at 95 °C under air for 24 h.

symmetrical alkynes possessing various electron-releasing or electron-withdrawing groups such as methyl, methoxy and fluoro on the phenyl ring of the alkyne (**2a**-**e**), endured the reaction conditions to afford 57-79% yields of indoloquinazolinones **3aa**-**ae**. Then, some of the representative unsymmetrical aryl group substituted alkynes **2f**-**h** were tested with **1a**, which afforded 48-67% yields of **3af**-**ah**. Similarly, the unsymmetrical alkyne substituted with an aryl and a heteroaryl group **2i** provided the desired product **3ai** in 51% yield. Next, the optimized reaction conditions were applied to study the substrate scope of some of the phenylindazolones **1b**-**i** with alkyne **2a**. As shown in Table 1, phenylindazolones substituted with electron-releasing or electron-withdrawing methyl, methoxy and chloro substituents at 5-position of the fused phenyl ring **1b**-**d** provided 57-68% yields of the desired compounds **3ba**-**da**. The sensitive bromo substituted phenylindazolone **1e** also tolerates the reaction conditions to afford **3ea** (58%). Then, some of the phenylindazolones possessing electron-releasing or electron-withdrawing substituents such as methyl, methoxy and chloro on the substituted phenyl ring of phenylindazolone **1f**-**i** were studied with alkyne **2a** to provide 53-65% yields of compounds **3fa**-**ia**. The annulation reaction of **1i** and **2a** was highly regioselective, which might be due to the steric effect of the substituted methyl group. Then, the optimized reaction conditions were tested for the annulation of dialkyl substituted alkyne **2j** with **1a** (Table 2). Notably, instead of providing the indolo[1,2-*a*]quinazolinone derivative, this reaction afforded indazolo[1,2-*a*]indazolone **4aj** in 62% yield. Because of the

Table 2. Scope of dialkyl alkynes (**2j**-**k**)



[a]**Reaction conditions:** **1a** (0.1 mmol), **2a** (0.1 mmol), catalyst (5 mol %), additive (0.1 mmol) and ^{t}AmOH (3.0 mL) at 95 °C under air for 24 h.

importance of indazolo[1,2-*a*]indazolone containing compounds, the scope of the reaction was further studied. The phenylindazolones possessing substituents either on the fused or substituted phenyl ring **1b**,**1d**-**g**,**1i** provided corresponding indazolo[1,2-*a*]indazolones **4bj**,**4dj**-**gj**,**4ij** with **2j**, albeit with

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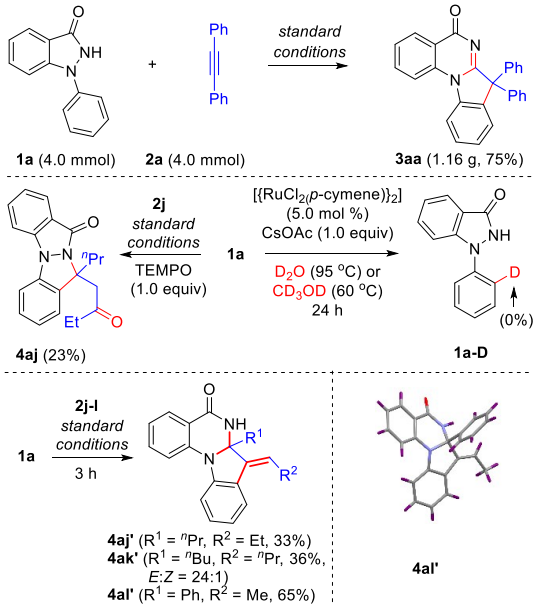
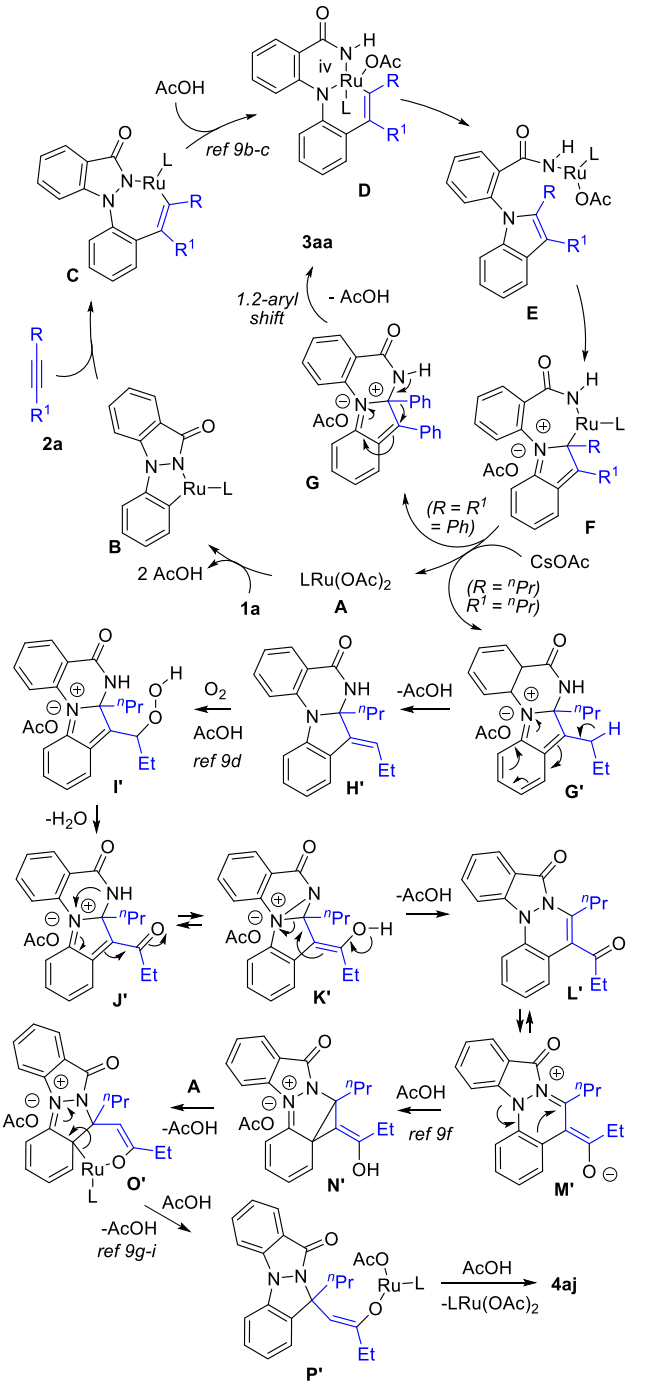
low yields (50-63%). Similarly, another dialkyl substituted alkyne **2k** tested for this reaction provided 63% yield of **4ak**. The structure of synthesized compounds was determined with the help of NMR spectroscopy and single X-ray crystallographic studies of compounds **3ab** and **4ij**.[8] The phenyl acetylene, trimethyl(phenylethynyl)silane, methyl 3-phenylpropiolate, 1,2-di-o-tolylethyne, 1,2-bis(2-chlorophenyl)ethyne and 1-octene could not provide corresponding annulated indolo[1,2-*a*]quinazolinone derivatives. The practical utility of this annulation reaction was established by accomplishing a gram-scale reaction between **1a** and **2a** which provided 75% yield of **3aa** (Scheme 2). Next, to determine the mechanism of this reaction, some of the control experiments were performed. The reaction of **1a** with **2j** in the presence of one equivalent of TEMPO furnished only 23% yield of **4aj**, indicating the involvement of free radical in the formation of **4aj**. Again, when the reactions between **1a** and **2j/2k** were stopped in three hours, without allowing total consumption of the starting materials, the indolo[1,2-*a*]quinazolinones **4aj'** (*E* isomer) and **4ak'** (*E*:*Z* = 24:1) were formed in 33-36% yields. These intermediates disappeared once the reactions were



Scheme 2. Gram-scale synthesis and control experiments

allowed to run for longer time. In case of aryl alkyl group containing alkyne **2l**, the intermediate **4al'** (*E* isomer) did not disappear after 24 hours also.[8] An experiment performed under standard conditions using **1a** alone and CD_3OD (or D_2O) as solvent could not provide the H/D exchanged compound **1a-D** (Scheme 2). This reaction indicates a non-reversible formation of acyclic ruthenium complex as an intermediate.

Based on the literature reports and our findings, a possible mechanism for the formation of compounds **3aa** and **4aj** is proposed (Scheme 3).[9] The active Ru(II) catalyst **A** first activates C-H bond of **1a** irreversibly to form a Ru(II) complex **B**. Then, alkyne metal coordination, followed by insertion of alkyne in between C-Ru bond affords Ru complex **C**. Insertion of the metal in between the weak N-N bond affords a six-membered Ru(IV) complex **D**, which on reductive elimination of the metal and subsequent C-2 activation generates a seven membered Ru complex **F**. The reductive elimination of the metal from **F** might have generated **G** and **G'**, using alkynes **2a** and **2j** respectively. Then, elimination of a molecule of acetic acid from **G** and concomitant 1,2-phenyl group migration



Scheme 3. Probable mechanism

affords the final compound **3aa**. In the presence of alkyl substituents, elimination of a proton from alkyl side chain of **G'** is faster than the elimination of a proton from amide N-H which results in the formation of **H'** (**4aj'**). Addition of a molecule of oxygen in the exocyclic double bond of **H'** (**4aj'**), followed by elimination of a molecule of water, subsequent N-N bond formation and rearrangement affords **L'**. Probably, the

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intermediate **J'** might exist in equilibrium with the intermediate **K'**. Because of the presence of the attached conjugated electron withdrawing keto functionality in **J'**, the quaternary nitrogen is more electrophilic and as a result intramolecular cyclization occurs leading to the formation of N-N bond. The tautomer **M'** of **L'** might generate the tricyclic intermediate **N'** on intramolecular cyclization. Then hydroxy group directed oxidative addition of the metal in the C-C bond of cyclopropane ring closer to the C=N bond, might afford a six membered Ru complex **O'**, which in the presence of acetic acid generates **4aj** via intermediate **P'**.

In conclusion, we have developed novel routes for the synthesis of quaternary carbon centered indolo[1,2-*a*]quinazolinones and indazolo[1,2-*a*]indazolones using the Ru(II)-catalyzed Csp^2-H activation and annulation reaction of readily available phenylindazolones with internal alkynes. Because of the rapid assemblage of complex skeletons and simplicity in operation, these methods might be useful for the synthesis of related heterocyclic scaffolds.

Conflicts of interest

"There are no conflicts to declare".

Acknowledgment

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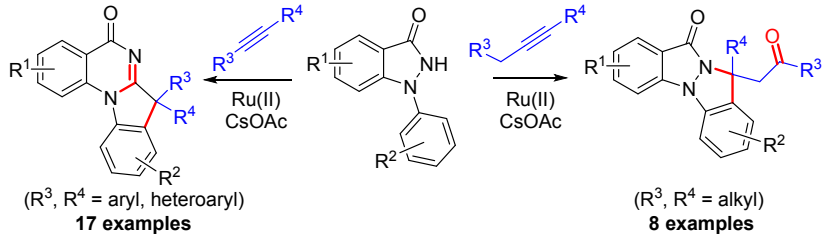
A cascade, Ru(II)-catalyzed annulative transformation of phenylindazolones and alkynes into indolo[1,2-*a*]quinazolinones and indazolo[1,2-*a*]indazolones is reported.



(R^3, R^4 = aryl, heteroaryl)
17 examples

(R^3, R^4 = alkyl)
8 examples

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