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Rh(III)-Catalyzed Intramolecular Oxidative Annulation of Propargyl Amino Phenyl Benzamides to Access Pyrido/Isoquinolino Quinoxalinones

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Abstract: A rhodium catalyzed copper mediated double oxidative annulation of propargylamino phenyl benzamides is developed. A quick assembly of tri, tetra and penta cyclic pyrido/isoquinolo-quinoxilines are thus achieved from readily available linear substrates. The reaction is shown to be very general by accommodating a large variety of substrates in the transformation. A mechanism through an amide directed C–H bond activation followed by an intramolecular alkyne activation/annulation followed by an oxidation is postulated.

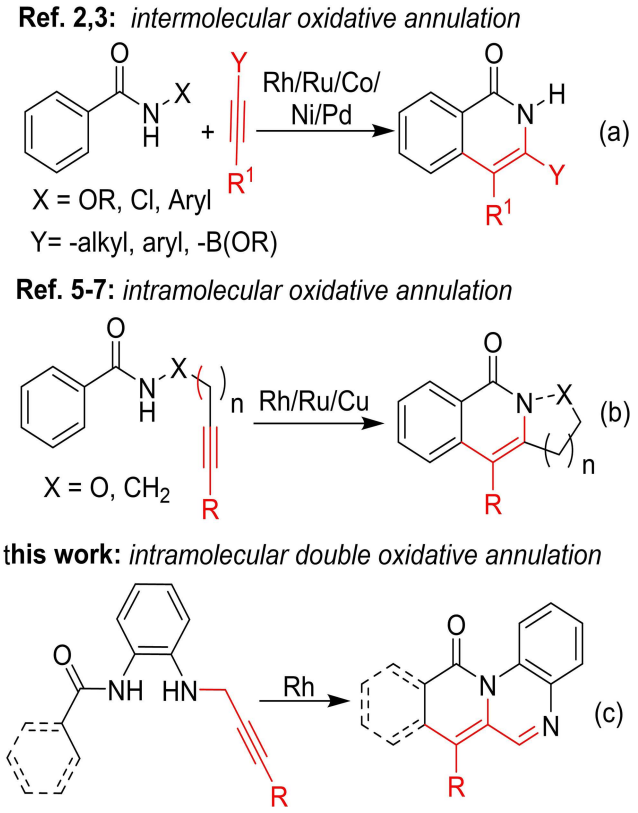
Keywords: Annulation; Rhodium; Oxidation; Benzamides; Quinoxalinones

Oxidative annulations of alkynes with unsaturated systems have grabbed an enormous attention in the recent past. With an appropriate choice of starting materials, it allowed synthesizing huge varieties of hetero and carbocycles.[1–7] Rhodium,[2] ruthenium,[3a–d] nickel,[3e] cobalt,[3f,g] palladium[3h,i] and even copper[3j] based catalysts which are capable of activating C–H bonds are found to execute such annulations. Having an alkyne as a tether in the basic unsaturated substrate itself at appropriate position enables an intramolecular annulation towards a quick assembly of multicyclic compounds.[4–7] In the light of difficulties associated with the systematic building of multicyclic compounds, which especially becomes a tedious job when huge libraries of such compounds are required to be built, these intramolecular annulations gain special attention.

On the other hand, isoquinolones and their fused analogues have gained substantial attention in both drug discovery and material chemistry.[8,9] Although a number of approaches for their construction are known, oxidative addition of alkynes with benzamides have drawn great attention as it does not require much prefunctionalization of the substrates while affording the multisubstituted adducts. Various groups[2,3] reported the annulations of both terminal and internal alkyens with benzamides with varied *N*-substitution (Scheme 1a).

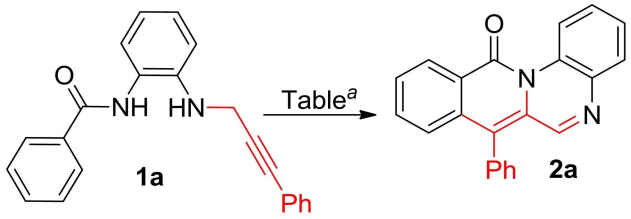
The group of Glorius[2b] successfully annulated even the alkynyl boronic acids with similar benzamides to get regioselectivly borylated isoquinolones. Park's and Guli'as groups independently reported the intramolecular capture of the alkyne with the benzamide tether to synthesize isoquinolone fused tricyclic compounds (Scheme 1b).[5] Very recently, Eycken et al reported an elegant synthesis of indolizinone and quinolizinone based natural products rosettacin and oxypalmatime through such intramolecular cyclizations.[6] A major advantage of intramolecular cyclization is the defined regioselectivity and the ability to quickly construct multicyclic frameworks from linear compounds, which thus demands huge search for novel such transformations. In continuation of our interest in discovery of novel reactions via activation of alkynes,[10] we herein report the synthesis of pyridoquinoxaline fused tri-, tetra-, and pentacyclic compounds through intramolecular double oxidative annulations of propargyl aminophenyl benzamides (Scheme 1c).

We chose **1a** to optimize the reaction conditions. Use of CuCl[7a] following Han's work did not produce



Scheme 1. Oxidative annulation of alkynes with benzamides.

Table 1. Optimization studies.[a]



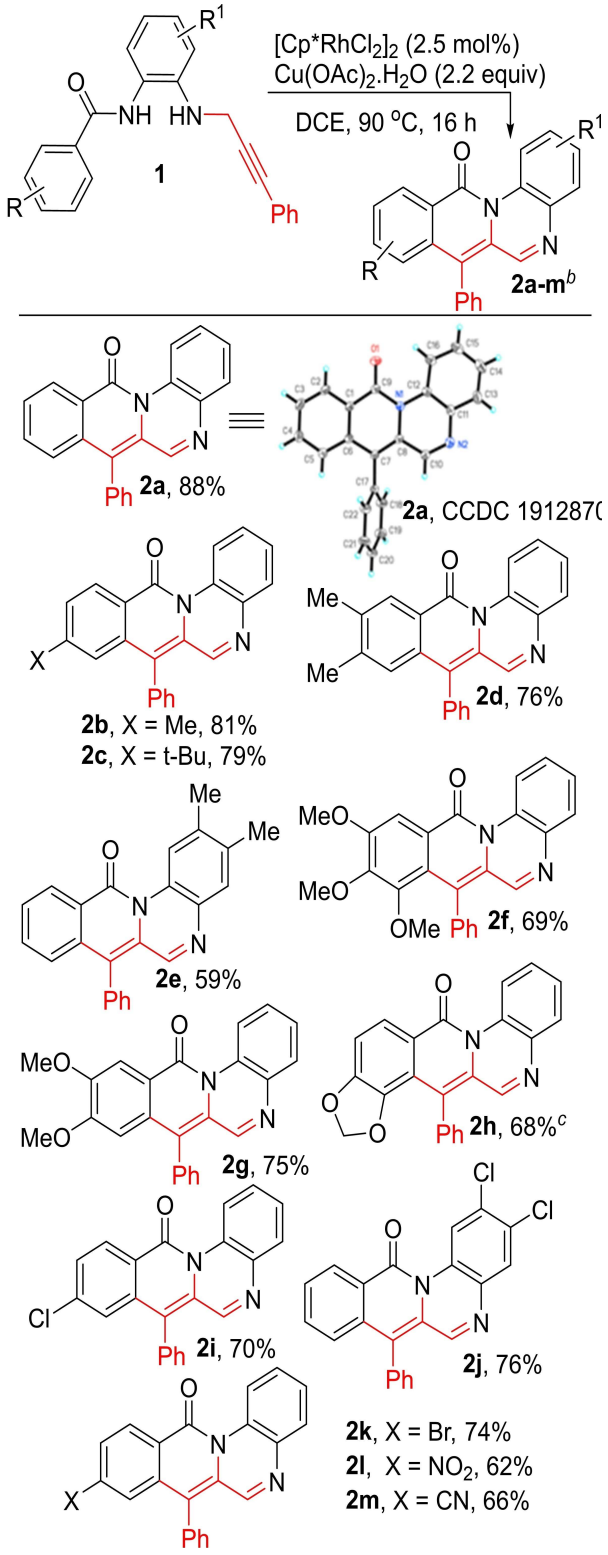
S.No.	catalyst	Additive	Solvent	Yield[b]
1	CuCl	–	DCE	n.r
2	$Pd(OAc)_2$	CsOAc	DCE	n.r
3	$Ni(acac)_2$	CsOAc	DCE	n.r
4	$Co(acac)_2$	CsOAc	DCE	n.r
5	$[Cp^*RhCl_2]_2$	CsOAc	DCE	69
6	$[Cp^*RhCl_2]_2$	KOAc	DCE	55
7	$[Cp^*RhCl_2]_2$	NaOAc	DCE	50
8	$[Cp^*RhCl_2]_2$	AcOH	DCE	trace
9	$[Cp^*RhCl_2]_2$	NaOTf	DCE	n.r
10	$[Cp^*RhCl_2]_2$	O_2 (balloon)	DCE	52
11	**$[Cp^*RhCl_2]_2$**	**$Cu(OAc)_2 \cdot H_2O$**	**DCE**	**88**
12	$[Ru(p\text{-cymene})Cl_2]$	$Cu(OAc)_2 \cdot H_2O$	DCE	76
13	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2 \cdot H_2O$	^{t}AmOH	79
14	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2 \cdot H_2O$	Dioxane	56
15	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2 \cdot H_2O$	Toluene	65
16	$[Cp^*RhCl_2]_2$	$Cu(OAc)_2 \cdot H_2O$	THF	40

[a] Reaction conditions: 2.5 mol% catalyst, 2.2 equiv. additive at 90 °C for 16 h under air.
[b] Isolated yield.

any desired product **2a** in our case (Table 1, entry 1). $Pd(OAc)_2$, well known for C–H activation, also totally failed to deliver even a trace amount of the expected product (entry 2). Similarly, no product was observed when $Ni(acac)_2$ or $Co(acac)_2$ were employed as catalysts in presence of CsOAc as additive (entry 3,4). Pleasingly, employing $[Cp^*RhCl_2]_2$ as catalyst along with CsOAc in DCE at 90 °C (under air) produced the desired product **2a** in 69% yield (entry 5). Employing other additives like KOAc, NaOAc, AcOH or NaOTf was found to be less effective or totally ineffective (entry 6–9). A control experiment without any additive, but in presence of O_2, indeed gave the product but in 52% yield (entry 10). Use of $Cu(OAc)_2.H_2O$ as an additive/oxidant (along with air) cleanly produced the annulated adduct in 88% yield (entry 11). Use of less expensive $[Ru(p\text{-cymene})Cl_2]$ in similar conditions indeed produced **2a** cleanly, but in relatively lower yield (entry 12). The other solvents like *t*-AmOH, dioxane, toluene or THF with Rh-catalyst were not as good as DCE (entry 12–16). The structure of **2a** was determined by its X-ray diffraction.[11]

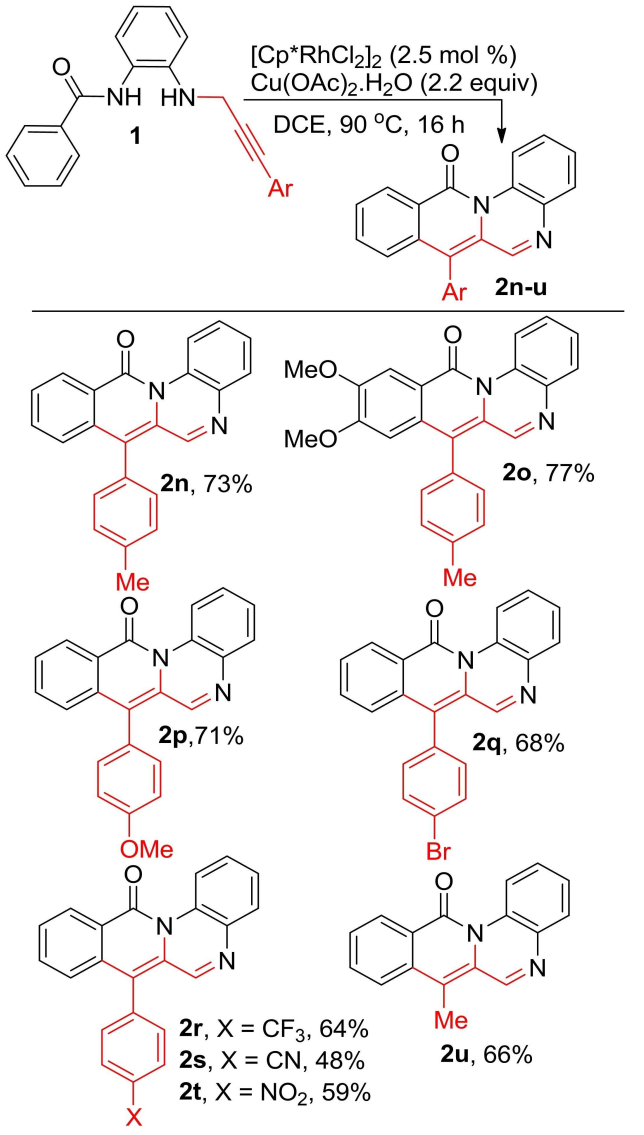
With the optimal reaction conditions in hand, diversified alkyne-amides were investigated to examine the scope of this double oxidative annulation (Table 2). The influence of substituents on amide unit was initially studied. Substrates with *p*-methyl or *p*-^{t}butyl benzamides **1b–c** reacted as good as **1a** to produce the expected products **2b–c** in 79–81% yields. We were next curious about dimethyl amide **1d** which has two different sites to react and may produce two regioisomers. Surprisingly, only **2d** was obtained as single regioisomer in 76% yield. We reason that the rhodium complexation, after C–H activation, adjacent to methyl group suffers some steric discomfort and hence it only occurred at less hindered other position. Alkyl substation even on 1,2-diaminobenzene core (**1e**) was also equally tolerated (**2e**). Next, Trimethoxy amides **1f** could be smoothly transformed to the corresponding adduct **2f** in similar high yield. Dimethoxy amide **1g** also gave a single regioisomer (**2g** in 75% yield), despite having the second but sterically congested site, as in case of **1d**. But similar substrate **2h** with methylene dioxy substitution (than dimethoxy) gave a mixture of isomers. Compared to **1d** and **1g**, it obviously exerts less steric hindrance difference between the available two sites and thus it led to form a mixture of two regioisomers. Halogenated substrates **1i–k** also consistently showed normal reactivity to deliver the desired products (**2i–k**) in excellent yields (70–76%). Electron deficient cyano and nitro substituted substrates **1l–m** were found to be less productive

Table 2. Scope of benzamides.[a]



[a] Reaction conditions: 2.5 mol% catalyst, 2.2 equiv. additive, DCE (2 mL) at 90 °C for 16 h under air.
[b] Isolated yield.
[c] Ratio of 3,4-Methylene dioxy- and 4,5-Methylene dioxy is 8.2:1.8.

Table 3. Scope of alkynes.



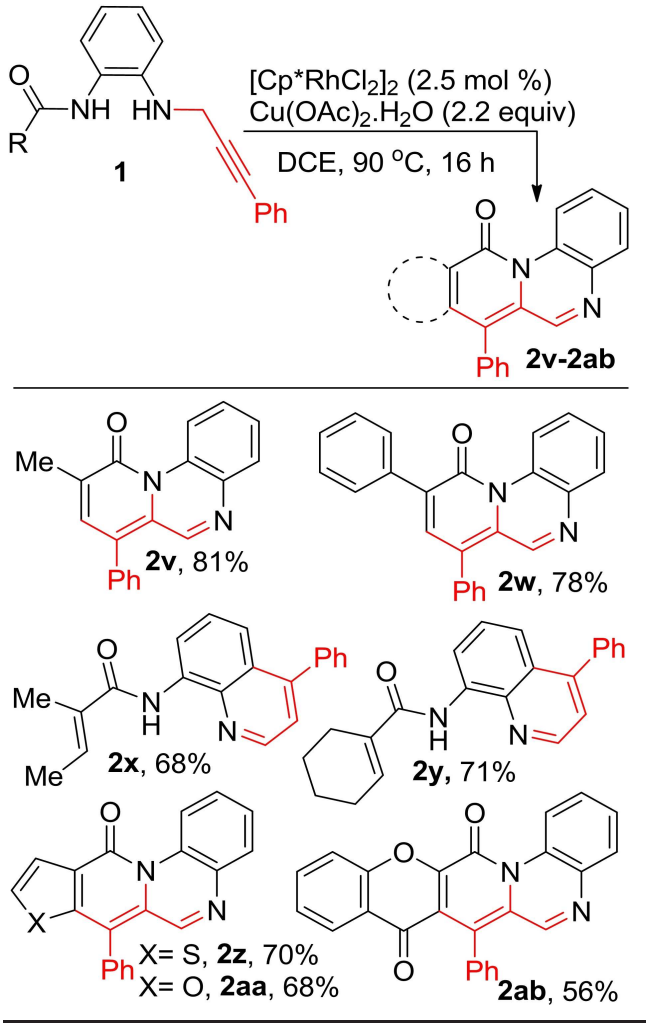
compared to their electron rich and neutral substrates and thus produced **2l–m** in 62–66% yields.

We next moved to evaluate the scope of varied aryl substitution on alkyne terminus (Table 3). Methyl and methoxy phenyl substrates **1n–o** reacted generally and gave the corresponding products **2n–o** in 71–77% yields. Bromo and trifluoromethyl phenyl substrate gave slightly lower yields of the corresponding adducts **2q–r**. Like in earlier set of examples **1l–m**, electron deficient materials **1s–t** with nitro and cyano groups led to a fair reduction in the product yields (**2s**, **t** in 48–59%). Expanding the scope this oxidative annulation, the aliphatic substitution on alkyne terminus (**1u**) cleanly fit in the reaction to afford the adduct **2u** in 66% yield.

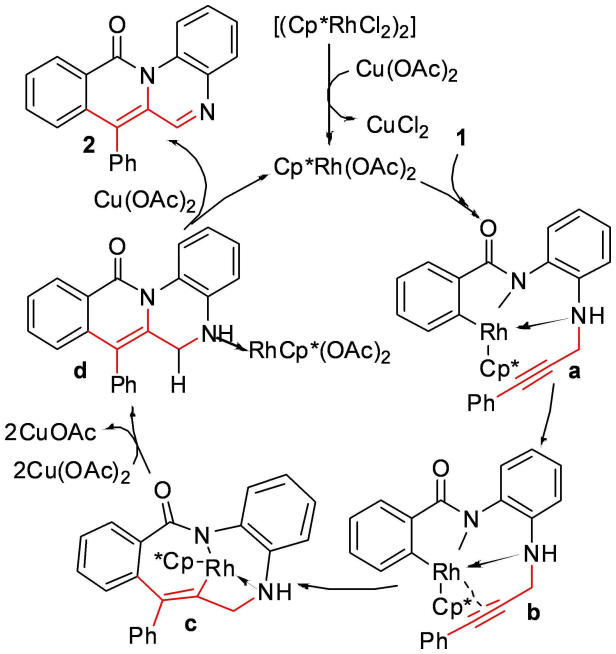
We next became curious to see the fate of substrates with amide tethers other than benzamides under the

optimized conditions. Pleasingly, methacrylamide **1v** and phenyl acrylamide **1w** cleanly reacted in the standard conditions and afforded the corresponding tricyclic adduct **2v–w** in 81% and 78% yields respectively (Table 4). But in case of β-alkyl substituted acrylamides **1x** and **1y**, the cyclization occurred on aniline aryl itself to give amidated quinolines apparently through a competitive electrophilic cyclization. Gratifyingly, thiophenamide **1z** and furanamide **1aa** participated well in the reaction and produced the desired tetracyclic products **2z–aa** in 68% and 70% yields respectively. Expanding the scope further, 2-chromonamide **1ab** also could be transformed to the expected pentacyclic product **2ab** albeit in 56% yield.

Table 4. Scope of acrylic/hetrocyclic amides.



With the assistance of some literature precedence[5a,b,6c] we propose a plausible reaction mechanism as depicted in Scheme 2. An active $Cp^*Rh(OAc)_2$ was generated by a ligand exchange with $Cu(OAc)_2.H_2O$. Amide directed C–H bond activation led to the intermediate **a** where Rh could also coordinate to alkyne moiety (**b**). Cyclization with the N–Rh bond intact formed **c** and subsequent reductive elimination gave the semi-saturated tetracyclic intermediate **d**. Oxidation of **d** afforded the desired adduct **2**. Reoxidation of reduced Rh or the oxidation of **d** or part of both were done with the assistance of aireal oxygen as the demand of $Cu(OAc)_2.H_2O$ was only in two equivalents.



Scheme 2. proposed mechanisum.

In conclusion, we have developed an expeditious synthesis of quinoxaline fused tri, tetra and penta cyclic compounds through a double oxidative annulation of propargylamino phenyl benzamides. The reaction, catalyzed by Rh(III) and directed by stoichiometric copper(II) acetate, is assumed to go through an amide directed C–H bond activation followed by an intramolecular alkyne activation/annulation prior to the oxidation. A detailed investigation is done on the scope of the reaction to show the generality, and a variety of fused hetero pyrido quinoxalinones are thus achieved.

Experimental Section

General procedure for synthesis starting material 1 from N-propargyl 1,2-diaimo benzene (II) taking Synthesis of 1a as an Example: In a 50 ml round bottom flask N-propargyl 1,2-diaimo benzene[12] (222 mg, 1 mmol, 1 equiv.) in DMF (6 mL) was added HATU (384 mg, 1 mmol, 1 equiv.), DIPEA (0.69 ml, 4 mmol, 4 equiv.) and Benzoic acid (122 mg, 1 mmol, 1 equiv.), at 0 °C under N_2 atmosphere and the reaction mixture was stirred at RT for 30 min. upon completion, reaction mixture was diluted with ice water and extracted with ethyl acetate. The combined extracts were dried over Na_2SO_4 concentrated under

reduced pressure. The crude material was purified on silica gel using 20% EtOAc/hexane to get **1** (293 mg 90%) as white solid.

General procedure for synthesis compound 2 from 1 taking Synthesis of 2 a as an Example: In a 50 ml round bottom flask **1 a** (65 mg, 0.2 mmol, 1 eq), $[Cp^*RhCl_2]_2$ (3 mg, 0.005 mmol, 2.5 mol%) and $Cu(OAc)_2.H_2O$ (87 mg, 0.4 mmol, 2.2 equiv.) in DCE (2 mL). the reaction mixture was stirred at 90 °C under air until complete conversion of starting materials (16 h). upon completion, the reaction continents were concentrated under reduced pressure. The reaction mixture was diluted with water and extracted with EtOAc (2 × 10 mL). Combined extracts were washed with brine (10 mL) and dried over Na_2SO_4 and concentrated under reduced pressure. The crude material was purified on silica gel using 30% EtOAc/hexane to get **2 a** (56 mg, 88%) light yellow color solid.

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[11] CCDC 1912870 (**2 a**) contains the supplementary crystallographic data. These data can be obtained from The Cambridge Crystallographic Data Centre.

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