Rhodium-Catalyzed Selective C(sp^2)-H Activation/Annulation of *tert*-butyl benzoyloxycarbamates with 1,3-Diynes: A one Step Access to Alkynylated isocoumarins and Bis-Isocoumarins

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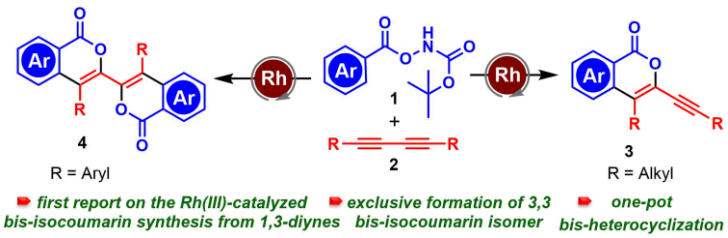
ABSTRACT: We report here a Rh(III) catalysed regio- and stereo-selective synthesis of alkynylated and bis-isocoumarin from 1,3-dialkyne. Exclusive one-pot formation of 3,3-bis-isocoumarin isomer has been achieved by eliminating several other possibilities. This is the first example of transition metal catalyzed synthesis of alkynylated and bis-isocoumarin scaffold. The protocol is compatible with a wide range of functional groups affording good to excellent yields. Several mechanistic investigations including deuterium labelling experiment and kinetic isotope effect study have been carried out.



Alkynylated and bis-isocoumarin belong to a distinct class of *O*-Containing heterocyclic units that are prevalent in numerous pharmaceuticals, natural products, and biologically active molecules.[1] Potent molecules such as gymnopalynes, corfin, tithoniamarin, salvcadorin, bireticulol, etc. contain the alkynylated and bis-isocoumarin as the core structural units (figure 1). These pharmacologically active molecules have been reported to have antimicrobial, anti-fungal, herbicidal, antibacterial, algicidal, antiviral, cytotoxic activities and so on[1].

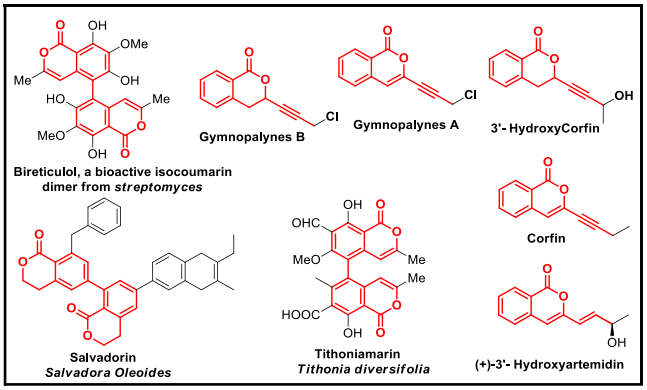
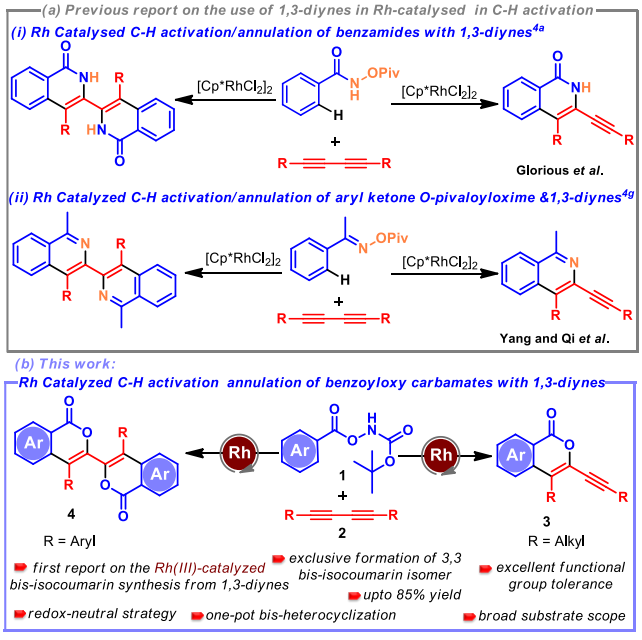


Figure 1. Representative Examples of Natural Products and Drug Molecules bearing alkynylated and bis-isocoumarin Scaffold

Hence, designing of effective synthetic protocol to afford such molecules has gained considerable significance over the years. In this context, directing group aided transition metal catalysed C-H bond activation has surfaced as a powerful tool for step and atom economical synthesis of pharmacologically useful molecules. It can be attributed to its utility in streamlining organic synthesis by offering chemists with new retrosynthetic approaches involving the use of inert C-H bonds as latent functional groups.[2] In this context, the strategies involving the annulation of C-C π-components (alkenes, alkynes, allenes, and benzynes) by selective and sequential C-H bond activation/annulation is one of the most promising approaches to construct diverse carbo- and heterocycles.[3] Among the C-C π-components internal alkyne is one of the most commonly used coupling partners for the rapid construction of varied heterocycles.[3c,d,e,f] In contrary, the exploration of conjugated alkynes (1,3-diynes) for those analogous reactions is limited.[4] While the synthesis of isocoumarin scaffold by harnessing the directed C-H activation/annulation strategy has been well explored, strategies for accessing alkynylated and bis-isocoumarin by using a challenging conjugated 1,3-diyne system has not been explored.

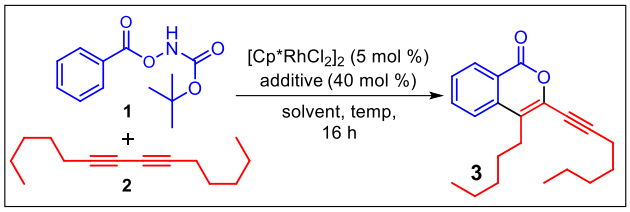
Scheme 1. Previous and Present Work



The 1,3-diynes are readily available synthetic moieties, and it finds its use in the synthesis of various natural products, heteroarenes, and arenes.[5] However, its use in the transition metal catalysed C-H bond activation/annulation for assembling alkynylated and bis-heterocycles is limited to only a handful of recent examples.[4] This is mainly due to the regio-and chemoselectivity challenges associated with the cyclometalated organometallic species during the migratory insertion with the 1,3-diyne unit.[4a] In addition, controlling the mono-functionalization over the di-functionalization is an added challenge .[4a] In this context, Glorius and co-workers in 2014 disclosed the first Rh(III)-catalysed synthesis of alkynylated and bis-isoquinolones by employing 1,3-diynes as reacting partners (scheme-1a-(i)).[4a] After this pioneering work of Glorius several other researchers have developed the transition metal catalysed bis-heterocycles synthesis by employing 1,3-diynes as coupling partner.[4] Yang and Qi group in 2017 described the Rh(III)-catalysed synthesis of alkynylated-isoquinolines and bis-isoquinolines from aryl ketone derived *O*-pivaloyloxime (scheme-1a-(ii)).[4b] Our group has also developed Ru and Pd catalysed synthesis of alkynylated isoquinolone and 1,3-enyne respectively by employing 1,3-diynes as reacting partner. [6a,b] Despite these reports, to the best of our knowledge rhodium-catalyzed regioselective C-H activation of benzoyloxycarbamate with 1,3-diynes for the synthesis of alkynylated and bis-isocoumarins is elusive. In pursuit of our continuous effort to develop new transformations on 1,3-dialkyne, herein, we disclose a Rh(III)-catalyzed C-H bond activation/annulation of benzoyloxycarbamates with 1,3-diynes for the one pot synthesis of alkynylated and bis-isocoumarins (scheme-1b).

We initiated our study for finding the suitable reaction conditions for the rhodium catalyzed selective C(sp^2)-H activation/annulation of tert-butyl benzoyloxycarbamate with 1,3-diynes. Subsequently, tert-butyl benzoyloxycarbamate **1a** and tetradeca-6,8-diyne **2b** were chosen as the model substrate and coupling partner in the presence of 5 mol % of $[Cp^*RhCl_2]_2$ catalyst. Initially, various solvents were screened with Ag_2O as an additive at 60 °C (Table 1, entries 1-5). With HFIP as solvent we failed to get desired annulated product. However, with MeOH, and EtOH as solvent we were delighted to observe 8% and 10% yield of the desired annulated product respectively (Table 1, entries 2,3). The use of DCE as solvent failed to improve the yield further. Since, with the alcoholic solvents we observed the desired product formation, we next, screened fluorinated alcoholic solvent TFE. We were pleased to observe a significant improvement (38%) in the product yield (Table 1, entry 5). Since, we observed better yield with TFE among the solvents used, we stuck to TFE and varied various silver additives for further enhancement of the product yield (Table 1, entries 6-9). The silver additives such as AgOTf, and $AgBF_4$ failed to produce the desired annulated product **3ab**. Gratifyingly, the other silver additives such as Ag_2CO_3, and AgOAc helped significantly to enhance the product yield (Table 1, entries 6 and 9). It is worth mentioning here that AgOAc was found to be most effective among them, affording 82% yields of **3ab**. Intrigued by these results, we next explored the effect of various acetate additives (KOAc, NaOAc, CsOAc, and NaOPiv) on the outcome of the reaction (Table 1, entries 10-12 & 14). However, the yield of **3ab** further did not improve with the acetate additives used. Since, CsOAc gave a moderate yield of 48%, we sought to explore the effect of Cs_2CO_3 on the reaction outcome (Table 1, entries 13). However, the use of Cs_2CO_3 also failed to further enhance the product yield (46%). Next, the attempts to carry out the reaction at higher (80 °C) and lower temperatures (40 °C & rt) resulted in loss of the product yield, affording the desired product in 52%, 55%, and 17% yield respectively (Table 1, entries 15-17). Attempts to replace the catalyst $[Cp^*RhCl_2]_2$ by $[Cp^*CoCOI_2]$ had a deleterious effect on the reaction failing to produce the desired product (Table 1, entry 18). To check the influence of additive (AgOAc) and catalyst $[Cp^*RhCl_2]_2$ we performed two control experiments.

Table 1. Optimization of Reaction Conditions[a]



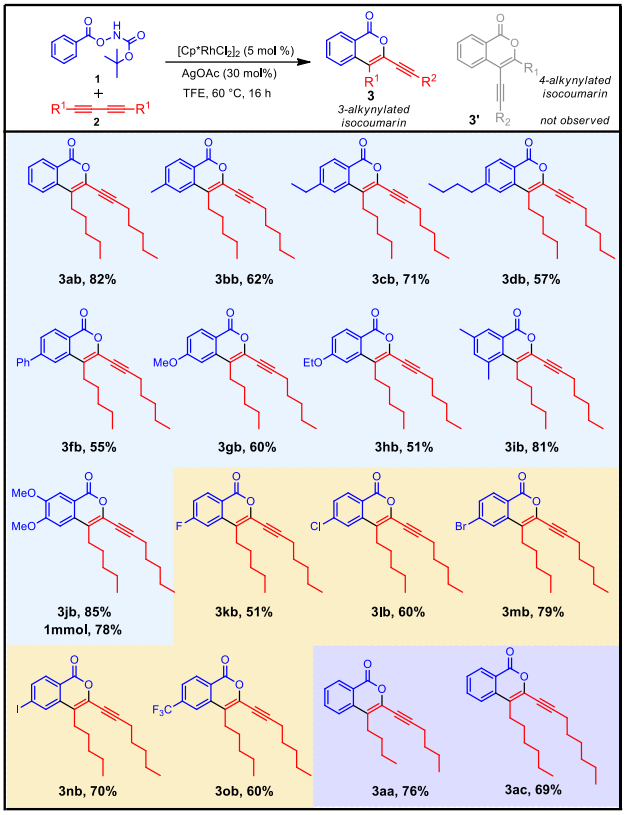
entry	solvent (0.1 M)	catalyst	additive	yield of **3a** (%)[b]
1	HFIP	$[Cp^*RhCl_2]_2$	Ag_2O	nd[c]
2	MeOH	$[Cp^*RhCl_2]_2$	Ag_2O	8
3	EtOH	$[Cp^*RhCl_2]_2$	Ag_2O	10
4	DCE	$[Cp^*RhCl_2]_2$	Ag_2O	<5
5	TFE	$[Cp^*RhCl_2]_2$	Ag_2O	38
6	TFE	$[Cp^*RhCl_2]_2$	Ag_2CO_3	40
7	TFE	$[Cp^*RhCl_2]_2$	AgOTf	nd[c]
8	TFE	$[Cp^*RhCl_2]_2$	$AgBF_4$	nd[c]
9	**TFE**	**$[Cp^*RhCl_2]_2$**	**AgOAc**	**82(85)**
10	TFE	$[Cp^*RhCl_2]_2$	KOAc	14
11	TFE	$[Cp^*RhCl_2]_2$	NaOAc	18
12	TFE	$[Cp^*RhCl_2]_2$	CsOAc	48
13	TFE	$[Cp^*RhCl_2]_2$	Cs_2CO_3	46
14	TFE	$[Cp^*RhCl_2]_2$	NaOPiv	26
15[d]	TFE	$[Cp^*RhCl_2]_2$	AgOAc	52[d]
16[e]	TFE	$[Cp^*RhCl_2]_2$	AgOAc	55[e]
17[f]	TFE	$[Cp^*RhCl_2]_2$	AgOAc	17[f]
18	TFE	$[Cp^*CoCOI_2]$	AgOAc	nd[c]
19	TFE	$[Cp^*RhCl_2]_2$	--	04
20	TFE	--	AgOAc	nd[c]

[a]Unless otherwise specified, all reactions were carried out using catalyst (5 mol %), additive (0.4 equiv), **1a** (0.15 mmol, 1.5 equiv), **2b** (0.10 mmol, 1.0 equiv) in a solvent (0.10 M) for 16 h. [b]Yields determined by NMR, using 1,3,5-trimethoxy benzene as internal reference. [c]nd = not detected. [d]Reaction was carried out at 80 °C. [e]Reaction was carried out at 40 °C. [f]Reaction was carried out at rt.

In the absence of AgOAc, 4% of **3ab** was obtained while without $[Cp^*RhCl_2]_2$ catalyst we did not observe any product

formation. (Table 1, entries 19-20). Hence, the use of 5 mol % of $[Cp^*RhCl_2]_2$ along with 40 mol % of AgOAc in TFE (0.1 M) at 60 °C gave the best yield of **3ab** (Table 1, entry 9). With the optimal reaction conditions in hand, we next moved to examine the scope and generality of this highly selective annulation protocol. To demonstrate the versatility of this developed protocol, an array of substituted *tert*-butyl benzoyloxycarbamates **1** and aryl-, alkyl-substituted 1,3-diynes **2** were subjected to the optimized reaction conditions (Table **2,** and **3**). Delightfully, benzoyloxycarbamates bearing electron donating substituents worked efficiently to give 51-85% yield of their respective annulated adducts **3ab**-**3jb**. Likewise, the reaction was also viable with the benzoyloxycarbamates bearing electron withdrawing substituents (halo, and trifluoromethyl) affording their corresponding annulated compounds **3kb**-**3ob**.

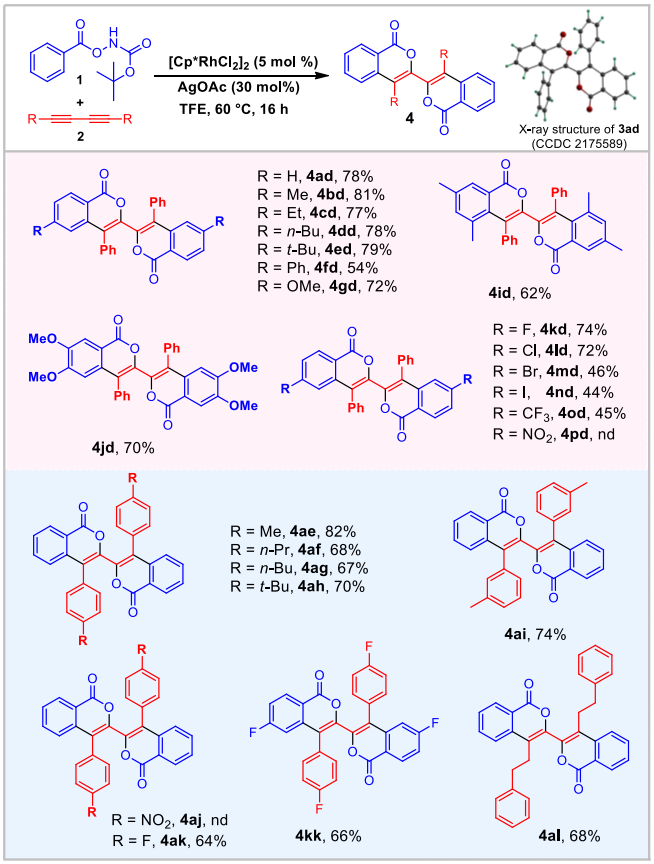
Table 2. Scope of benzoyloxycarbamates and 1,3-Diynes for Regioselective mono-Annulation[a]



[a]Unless otherwise specified, all reactions were carried out using $[Cp^*RhCl_2]_2$ (5 mol %), AgOAc (40 mol %), **1** (0.15 mmol), **2** (0.10 mmol) in TFE (0.10 M) at 60 °C for 16 h. Isolated yields are mentioned.

It should be emphasised that all the halo-substituted (F, Cl, Br, and I) benzoyloxycarbamates delivered their respective annulated adducts **3kb**-**3nb** in 51-79%. It is worth noting that unsymmetrical benzoyloxycarbamates **1j** underwent annulation in a highly regioselective fashion furnishing the desired annulated product in high yield. These results show that the annulation strategy developed is robust for both electronically rich as well as electronically poor benzoyloxycarbamates. To showcase the workability of the developed annulation strategy a 1 mmol scale synthesis of **3ab** (78%) was carried out. After evaluating the scope with electronically diverse benzoyloxycarbamates, we next moved to explore the scope with different aliphatic 1,3-diynes. Gratifyingly, other alkyl 1,3-diynes such as **2a** and **2c** reacted smoothly to afford their annulated products **3aa**-**3ac**. We next focused on the double C-H bond activation/annulation for the synthesis of bis-isocoumarins. The sequential synthesis is a suitable method for generating bis-heterocycles. However, the easiest approach is the one-pot way. There are only a few reports available on the transition metal catalysed one-pot approach for such bis-heterocycles synthesis. Hence, we executed a one-pot synthetic approach in the presence of 1,4-diphenylbuta-1,3-diyne as coupling partner under the standard reaction conditions. We were delighted to observe the formation of symmetrical bis-isocoumarin (3,3-isomer) molecules. The scope of the bis-isocoumarin synthesis was extended to electronically and functionally diverse benzoyloxycarbamates and 1,3-diynes. The benzoyloxycarbamates bearing electron donating substituents worked efficiently to give 54-81% yield of their respective bis-annulated adducts **4ad**-**4jd**.

Table 3. Scope of benzoyloxycarbamates and 1,3-Diynes for Regioselective di-annulation[a]

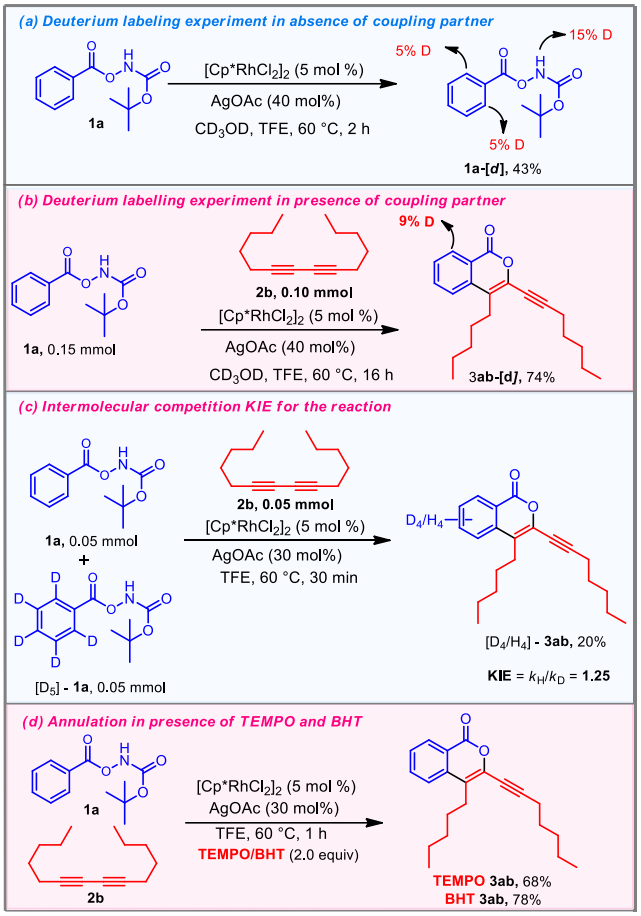


[a]Unless otherwise specified, all reactions were carried out using $[Cp^*RhCl_2]_2$ (5 mol %), AgOAc (40 mol %), **1** (0.15 mmol), **2** (0.10 mmol) in TFE (0.10 M) at 60 °C for 16 h. Isolated yields are mentioned.

Likewise, the reaction was also viable with the benzoyloxycarbamates bearing electron withdrawing substituents (halo, and trifluoromethyl) affording their corresponding bis-annulated compounds **4kd**-**4od**. After evaluating the scope with electronically diverse benzoyloxycarbamates, we next moved to explore the scope with different 1,3-diynes. Gratifyingly,

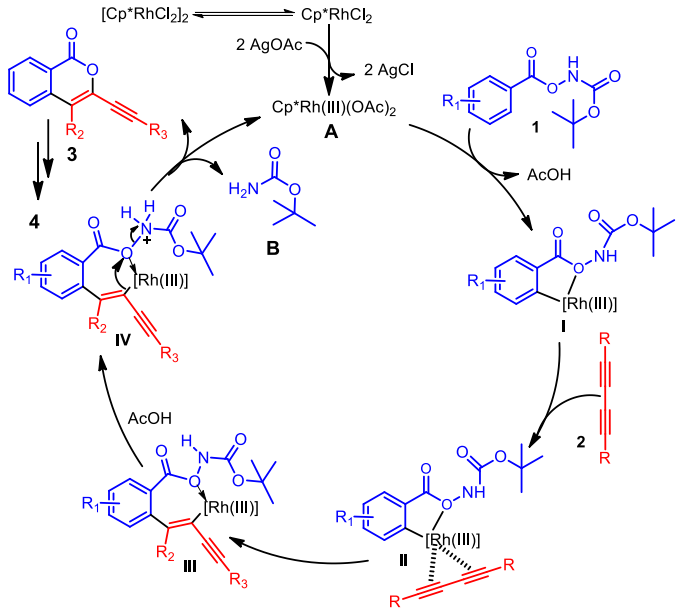
both electronically rich and poor aryl, and alkyl 1,3-diynes reacted smoothly to afford their annulated products **4ae-4al**. Interestingly, a tetra-floro substituted molecule **4kk** could be obtained by using fluorinated substrate **1k** and fluorinated diyne **2k**. The regio-and stereoselectivity of the bis-annulated molecule **3ad** was confirmed unambiguously by single crystal X-ray analysis.

Scheme 2. Mechanistic Studies with Labeled Substrates



After successfully carrying out the scope of varied benzoyloxycarbamates and 1,3-diynes we performed several mechanistic experiments to understand the catalytic cycle (Scheme **2**). Initially, we conducted the deuterium labelling experiment in the absence and presence of coupling partner and kinetic isotope effect study. The deuterium labelling experiment of benzoyloxycarbamates **1** with CD_3OD under the optimized reaction conditions in the absence coupling partner showed 5% deuterium incorporation at the *ortho*-position of benzoyloxycarbamates **1a-[*d*]** in 43% yield, while the deuterium incorporation was found to be 9% at the ortho position of **3ab-[*d*]** in the presence of coupling partner **2b**. These results, indicate reversibility of the C-H metalation step. In addition, an intermolecular kinetic isotope effect study was carried out with **1a/[D_5]-1a** with **2a.** The KIE value (1.25) obtained reveals that the C-H activation may not be the rate limiting step (Scheme 2c). Moreover, for further mechanistic insights we carried out two reactions in the presence of radical scavengers such as 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) and 2,6-di-tert-butyl-4-methyl-phenol (BHT) to probe the involvement of radical intermediate in the reaction (Scheme 2d). The yields of 68, and 78% in the presence of TEMPO and BHT respectively rules out the possibility of the involvement of radical intermediate in the reaction.

Scheme 4. Proposed Catalytic Cycle



Based on the above mechanistic findings and literature precedents[7], a plausible catalytic cycle is depicted in the scheme-**4**. The active Rh(III)-species **A** is generated from Rh(III)-dimer in presence of AgOAc. The benzoyloxycarbamate **1** undergoes cyclometallation with the active catalyst species **A** to form the rhodacyclic intermediate **I**. The intermediate **II** is generated by the coordination of 1,3-diyne **2** with the rhodacycle **I**. Subsequently, the 1,2-insertion of the coordinated 1,3-diyne in the intermediate **II** leads to the generation of seven-membered rhodacycle intermediate **III**. An intramolecular nucleophilic substitution via intermediate **IV** triggered by acetic acid leads to the formation of C-O bond, cleavage of the N-O bond to furnish *tert*-butyl carbamate **B**, active Rh(III) species **A**, and the alkynylated product **3**. The alkynylated product **3** undergoes another annulation sequence to generate the desired bis-isocoumarin molecule **4**.

In conclusion, we have demonstrated a Rh(III)-catalysed selective redox-neutral double C-H bond activation/annulation strategy of the benzoyloxycarbamate with 1,3-diynes to access an array of biologically active bis-isocoumarin derivatives. This work is the first report on the transition metal catalysed synthesis of alkynylated-isocoumarins and bis-isocoumarins from 1,3-diynes. Moreover, the developed annulation strategy is mild and efficient tolerating a wide range of functionality. Moreover, the mechanistic findings with the deuterated substrates revealed the non-involvement of the C-H bond activation in the rate limiting step of the reaction. The mechanistic findings with radical scavengers revealed the non-involvement of the radical intermediate in the annulation protocol.

ASSOCIATED CONTENT

Supporting Information

Additional experimental procedures, X-ray crystallographic analysis, and spectroscopic data for the synthesized compounds (PDF).

FAIR Data is available as supporting information for publication and includes NMR FID files for compounds **1a**-**1p**, **3aa**-**3ac**, **3ab**-**3ob**, **4ad**-**4gd**, **4id**, **4jd**, **4kd**-**4od**, **4ae**-**4ah**, **4ai**, **4ak**, **4kk**, **4al.**

The Supporting Information is available free of charge on the ACS Publications website. http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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