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Rhodium-Catalyzed Tandem Annulation and (5 + 1) Cycloaddition: 3-Hydroxy-1,4-enyne as the 5-Carbon Component

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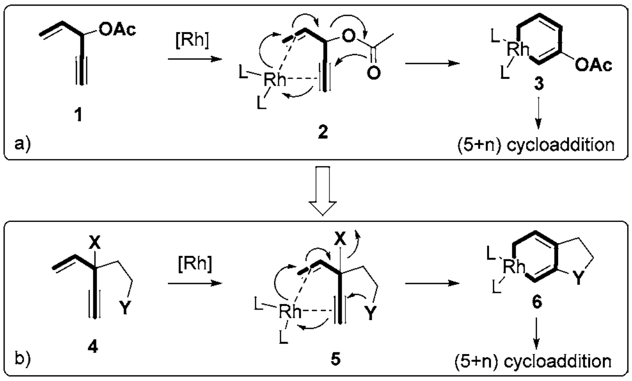
Ⓢ *Supporting Information*

ABSTRACT: A Rh-catalyzed tandem annulation and (5 + 1) cycloaddition was realized. 3-Hydroxy-1,4-enyne served as the new 5-carbon component for the (5 + 1) cycloaddition. Substituted carbazoles, dibenzofurans, and tricyclic compounds containing a cyclohexadienone moiety could be prepared efficiently. The identification of a byproduct suggests that metal carbene and ketene intermediates may be involved in the (5 + 1) cycloaddition.

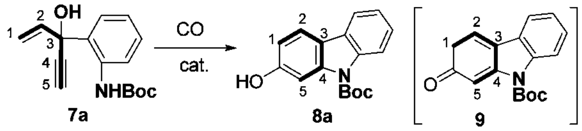
Transition-metal-catalyzed cycloaddition represents one of the most efficient ways to access highly functionalized carbo- and heterocycles.[1] These cycloadditions usually involve the formation of a metallacycle by oxidative cyclization; insertion of CO, alkene, or alkyne to a carbon−metal bond; and reductive elimination. The development of new methods to generate novel metallacycles can then lead to a series of new cycloadditions. For example, we and others have developed (5 + 1)[2] and (5 + 2)[3] cycloadditions involving metallacyclohexadiene intermediate **3** (Scheme 1a).[4] Based on DFT calculations, a rhodium-mediated concerted oxidative cyclization accompanied by 1,2-acyloxy migration was proposed for the formation of metallacycle **3** from ester **1**.[5] We envisioned that a completely new type of bicyclic metallacycle **6** might be generated for cycloadditions if the ester group in enyne **1** could be replaced by a leaving group X and a nucleophile Y in 1,4-enyne **4** (Scheme 1b). We herein report the application of this concept to a tandem annulation and (5 + 1) cycloaddition by forming three bonds and two rings in one reaction. This new transformation has led to the preparation of various substituted carbazloles, an important class of heterocycles with diverse ranges of pharmacological activities.[6]

Scheme 1. Design of New 5-Carbon Building Blocks for Rhodium-Catalyzed Cycloadditions



Vinylcyclopropane and its related derivatives have been the primary 5-carbon components for transition-metal-mediated (5 + 1) cycloadditions. A stoichiometric amount of metals and photoirradiation were required in early studies.[7] Only recently, (5 + 1) cycloadditions of vinylcyclopropane and CO were reported to be promoted by metal catalysts under thermal conditions.[8] Related allenylcyclopropanes[9] and cyclopropenes[10] were used in (5 + 1) cycloadditions for the synthesis of highly unsaturated six-membered carbocycles. More complex cycloadditions involving (5 + 1) cycloaddition of vinylcyclopropane and CO as the basic step were also developed.[11] Inspired by the formation of metallacycle **3** from propargylic ester **1** via 1,2-acyloxy migration, we designed generic structure **4** as a new versatile 5-carbon building block for cycloadditions.

Substrate **7a** was prepared by sequential addition of vinyl and alkynyl Grignard reagents to the corresponding amide (eq 1).[12]



(1)

The OH and aniline nitrogen in substrate **7a** are the leaving group and nucleophile, respectively. A new method for the synthesis of carbazole **8a** through cyclohexadienone intermediate **9** can be realized if a tandem indole annulation[13] and (5 + 1) cycloaddition reaction occurs. The 3-hydroxy-1,4-enyne moiety in **7a** will become a novel 5-carbon component for the (5 + 1) cycloaddition.

We first explored different Rh(I) catalysts for the proposed tandem reaction (Table 1, entries 1−5). The cationic Rh(I) catalyst led to the formation of a complex mixture, and no desired product was detected (entry 1). Only a trace amount of product **8a** was observed by using the Wilkinson catalyst (entry 2). We were pleased to find that product **8a** was produced in good yields in the presence of $[Rh(COD)Cl]_2$ or $[Rh(CO)_2Cl]_2$ catalyst and CO (1 atm) (entries 3 and 4). A lower yield was obtained at a lower or higher CO pressure (entry 5). Other metal catalysts based on Ir, Pd, Pt, and Au led

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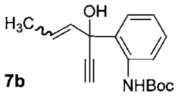
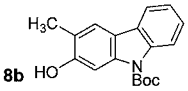
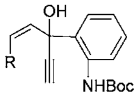
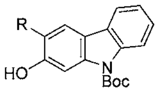
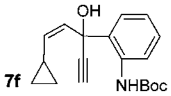
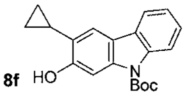
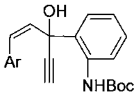
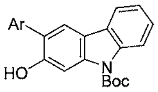
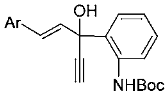
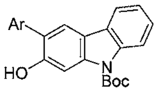
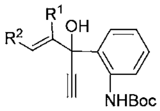
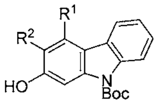
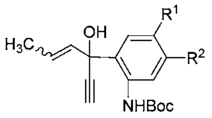
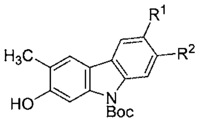
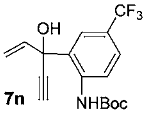
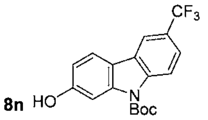
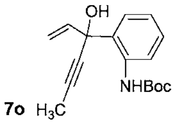
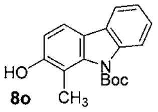
Table 1. Screening of Conditions for Substrate 7a[a]

entry	conditions	yield of **8a**[b]
1	$[Rh(COD)_2]BF_4$ (5 mol %)	0
2	$[Rh(PPh_3)_3Cl]$ (5 mol %)	trace
3	$[Rh(COD)Cl]_2$ (5 mol %)	81%
4	$[Rh(CO)_2Cl]_2$ (5 mol %)	88% (82%)[c]
5	$[Rh(CO)_2Cl]_2$ (5 mol %)	51%[d] or 78%[e]
6	$[Ir(COD)Cl]_2$ (5 mol %)	0
7	$[Ir(CO)(PPh_3)_2Cl]$ (5 mol %)	0
8	$Pd(OAc)_2$ (5 mol %)	0
9	$PtCl_2$ (5 mol %)	0
10	$Au(PPh_3)Cl$ (5 mol %)	0

[a] Conditions: dichloroethane (DCE), CO (1 atm), 60 °C, 10 h, unless noted otherwise. [b] The yield was determined by ^1H NMR of crude product using internal standard. [c] Isolated yield of **8a**. [d] CO (0.1 atm). [e] CO (24 atm).

Table 2. Scope of the Tandem Reaction[a]

entry	substrate **7**	Product **8**	yield[b]
1	 **7b**	 **8b**	80%
			
2	**7c**, R = *n*Pr	**8c**, R = *n*Pr	78%
3	**7d**, R = CH_2OTBS	**8d**, R = CH_2OTBS	80%
4	**7e**, R = CH_2OH	**8e**, R = CH_2OH	68%
5	 **7f**	 **8f**	82%
			
6	**7g**, Ar = Ph	**8g**, Ar = Ph	81%
7	**7h**, Ar = $4\text{-}MeOC_6H_4$	**8h**, Ar = $4\text{-}MeOC_6H_4$	72%
			
8	**7g'**, Ar = Ph	**8g**, Ar = Ph	70%
9	**7h'**, Ar = $4\text{-}MeOC_6H_4$	**8h**, Ar = $4\text{-}MeOC_6H_4$	53%
10	**7i'**, Ar = $4\text{-}FC_6H_4$	**8i**, Ar = $4\text{-}FC_6H_4$	70%
			
11	**7j**, $R^1 = CH_3$, $R^2 = H$	**8j**, $R^1 = CH_3$, $R^2 = H$	52%
12	**7k**, $R^1 = R^2 = CH_3$	**8k**, $R^1 = R^2 = CH_3$	50%
			
13	**7l**, $R^1 = Br$, $R^2 = H$	**8l**, $R^1 = Br$, $R^2 = H$	79%
14	**7m**, $R^1 = R^2 = OMe$	**8m**, $R^1 = R^2 = OMe$	74%
15	 **7n**	 **8n**	71%
16	 **7o**	 **8o**	36%

[a] Conditions: $[Rh(CO)_2Cl]_2$ (5 mol %), DCE, CO (1 atm), 60 °C, 8–12 h. [b] Isolated yield of **8**.

to complex mixtures, and no desired product **8a** was observed (entries 6–10). DCE afforded higher yields than other solvents we screened including THF, dioxane, toluene, and DCM. We also tried (5 + 2) cycloadditions by replacing CO with propargylic alcohol or its methyl ether, no desired product was observed using catalysts employed for the (5 + 1) cycloaddition.

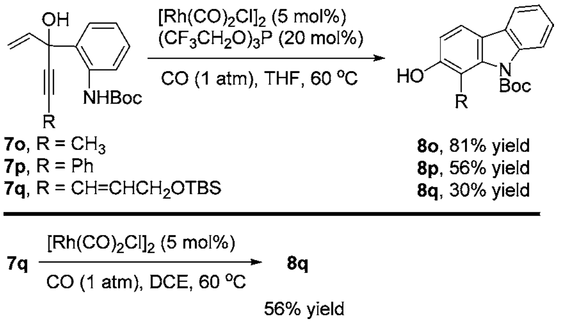
We then investigated the scope of the tandem annulation and (5 + 1) cycloaddition for the synthesis of various substituted carbazoles. Enyne **7b** was prepared as a mixture of *E*/*Z* alkenes in a 2:1 ratio by sequential addition of propenyl and ethynyl Grignard reagents (Table 2, entry 1). The high yield obtained for product **8b** suggested that both isomers participated in the cycloaddition and the methyl substituent had no effect on the yield of the carbazoles. Enynes **7c**–**7h** were prepared as the pure *Z*-isomer by reduction of the corresponding alkyne. Various substituents including alkyl, cyclopropyl, and aryl groups could be tolerated on the alkene termini (entries 2–7). Some of these substituents were difficult to be introduced to carbazoles by existing methods.[6] A slightly lower yield was obtained when a free alcohol was present in the substrate (entry 4). Enynes containing an *E*-arylalkene (**7g'**–**7i'**) were synthesized by aldol condensation between a methyl arylketone and an aryl aldehyde followed by the addition of an ethynyl Grignard reagent. Interestingly, yields of products **8g** and **8h** obtained from *E*-alkenes were lower than those from *Z*-alkenes (entries 6 and 7 vs entries 8 and 9). Electron-poor styrene **7i'** afforded a higher yield than electron-rich styrene **7h'** (entries 9 and 10). When the substituent was introduced to the internal position of the alkene in **7j**, the desired product was isolated in a 52% yield (entry 11). A similar yield of product **8k** was obtained from enyne **7k** with a trisubstituted alkene.

We next examined substrates with substituents on the aromatic ring (entries 13–15). Bromine, methoxy, and trifluoromethyl groups could all be tolerated. The bromine substituent in product **8l** allows further derivatizations by cross-coupling reactions. The efficiency of the tandem annulation (5 + 1) cycloaddition appeared to be irrelevant to the electronic nature of the substituent on the benzene ring of anilines (entry 14 vs 15). Under the conditions optimized for substrate **7a**, only a 36% yield of product **8o** was obtained from substrate **7o**, which had an internal alkyne (entry 16).

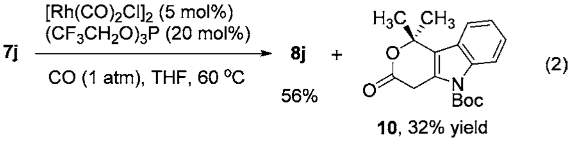
Previously, we found that electron-poor ligands were often beneficial for the Rh-catalyzed cycloadditions involving acyloxy migration of propargylic esters by increasing the acidity of Rh.[3] We then examined different ligands for substrate **7o** including $(p\text{-}CF_3C_6H_4)_3P$, $(3,5\text{-}(CF_3)_2C_6H_3)_3P$, $(C_6F_5)_3P$, $(CF_3CH_2O)_3P$, and $[(CF_3)_2CHO]_3P$. Gratifyingly, a 70% yield was obtained by using the $(CF_3CH_2O)_3P$ ligand in

DCE. Switching the solvent to THF further improved the yield of product **8o** to 81% (Scheme 2). A 56% yield was obtained for substrate **7p** with a phenyl substituted internal alkyne. For substrate **7q**, however, a better yield was observed in the absence of ligand (Scheme 2).

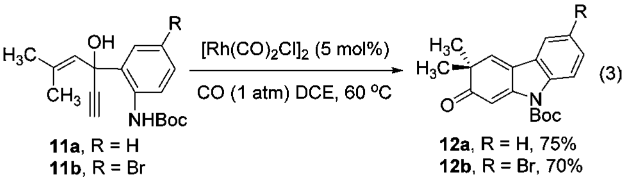
Scheme 2. Tandem Annulation and (5 + 1) Cycloaddition for Substrates with an Internal Alkyne



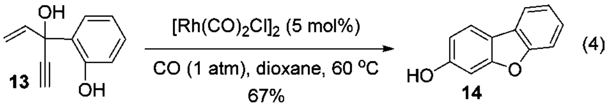
We also re-examined substrates **7j** and **7k** in the presence of the $(CF_3CH_2O)_3P$ ligand. Desired cycloaddition product **8j** was isolated in a slightly better yield together with byproduct **10**, which was not observed previously (eq 2 vs entry 11 in Table 2). For substrate **7k**, no significant improvement was observed after the addition of the phosphite ligand.

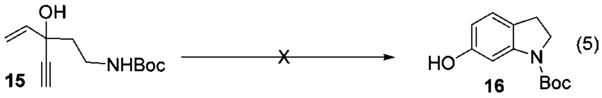


Cyclohexadienones **12a** and **12b** could be prepared efficiently in 75% and 70% yields, respectively (eq 3). This demonstrated that the (5 + 1) cycloaddition also allowed the preparation of nonbenzoid structural motifs.



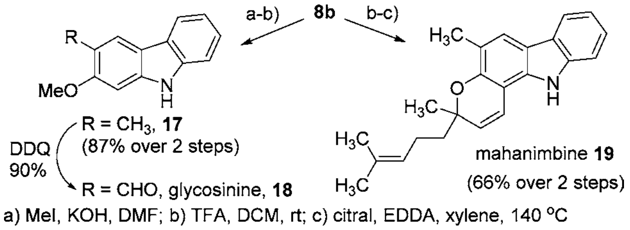
Phenol can be employed as the nucleophile for this tandem annulation and (5 + 1) cycloaddition to afford dibenzofuran **14** (eq 4). Carbamate **15**, however, did not yield any desired product under previously employed conditions (eq 5).





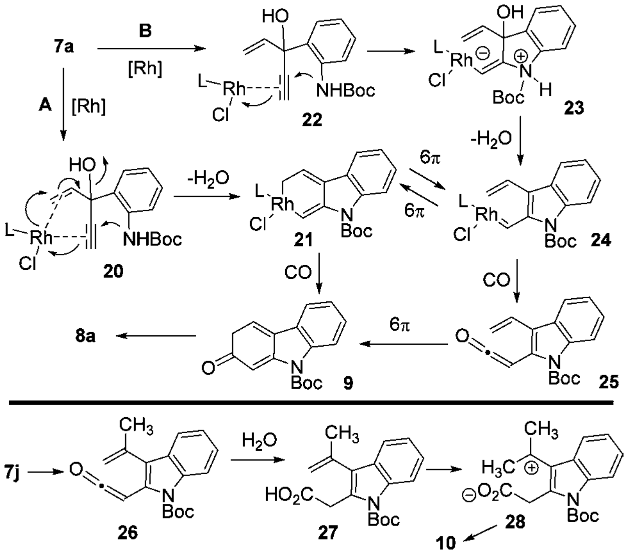
2-Oxygenated carbazole is one of the most common naturally occurring carbazole alkaloids.[6] The tandem annulation (5 + 1) cycloaddition method can be easily applied to the synthesis of natural products **17** to **19** (Scheme 3).[14] Methylation of **8b** followed by removing the Boc group afforded 2-methoxy-3-methylcarbazole **17**,[15] which represents a formal synthesis of glycosinine **18** (or *O*-methylmukonal),[15a,b,16] a compound with significant anti-HIV-1 activity.[17] Removal of the Boc group in **8b** by TFA followed by annulation with citral in the presence of ethylenediammonium diacetate (EDDA)[18] yielded natural product mahanimbine **19**,[19] which showed antihyperglycemic and antilipidemic effects in diabetic rats.[20] Although the last annulation step had been reported for the synthesis of **19**,[19] the yield was only 35%.

Scheme 3. Synthesis of Carbazole Natural Products



Two pathways are proposed for the Rh-catalyzed tandem annulation and (5 + 1) cycloaddition as shown in Scheme 4. In pathway **A**, a concerted annulation and oxidative cyclization is proposed for the formation of metallacycle **21**. Insertion of CO followed by reductive elimination may yield (5 + 1) cycloaddition product **9**, which undergoes aromatization to afford carbazole **8a**. For substrates **11a** and **11b**, aromatization to carbazole does not occur after the (5 + 1) cycloaddition. The reaction stops at the stage of cyclohexadienone to yield products **12a** and **12b**, respectively.

Scheme 4. Proposed Mechanism



Previously, we[21] and others[22] have used a methoxy group as the leaving group to generate metal carbenes from propargylic ethers. An alternative mechanism involving the formation of Rh(I) carbene **24** by eliminating water from intermediate **23** can also be proposed. This dienyl metal carbene may undergo 6π electrocyclization to form metallacycle **21** and eventually final product **8a**. Alternatively, insertion of CO to metal carbene **24** can produce ketene **25**, which may undergo 6π electrocyclization to yield cyclohexadienone **9**. The formation of byproduct **10** from substrate **7j** may be explained by the formation of ketene **26**, which can produce carboxylic acid **27** upon hydrolysis. A relatively stable tertiary carbocation **28** may be generated from acid **27**. Trapping this carbocation by a carboxylate will lead to the formation of lactone byproduct **10**. The addition of external water resulted in lower yields of both **8j** and **10**. Since the conversion from metallacycle **21** to carbene **24** is also possible through a 6π electrocyclic ring-opening reaction, the isolation of byproduct **10** does not rule out the possibility of pathway **A**.

In summary, we have developed a new 5-carbon component, 3-hydroxy-1,4-enyne, in the context of a tandem annulation and (5 + 1) cycloaddition reaction for the synthesis of substituted carbazoles, dibenzofurans, and tricyclic compounds with a cyclohexadienone motif. In this transformation, one C−Y (Y = N or O) bond and two C−C bonds are formed, while classical cycloadditions generally involve the construction of just two bonds. The strategy of combining the annulation event with cycloadditions may have broad implications in the synthesis of polycyclic compounds.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization data, and spectra (IR, ^{1}H, ^{13}C NMR and HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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