

Rhodium(III)-Catalyzed [3+2] Annulation of 5-Aryl-2,3-dihydro-1H-pyrroles with Internal Alkynes through C(sp²)-H/Alkene Functionalization**

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Abstract: This study describes a new rhodium(III)-catalyzed [3+2] annulation of 5-aryl-2,3-dihydro-1H-pyrroles with internal alkynes using a Cu(OAc)₂ oxidant for building a spirocyclic ring system, which includes the functionalization of an aryl C(sp²)-H bond and addition/protonolysis of an alkene C=C bond. This method is applicable to a wide range of 5-aryl-2,3-dihydro-1H-pyrroles and internal alkynes, and results in the assembly of the spiro[indene-1,2'-pyrrolidine] architectures in good yields with excellent regioselectivities.

The 1-azaspiro[4.4]nonanes, including spiro[indene-1,2'-pyrrolidines], are used in many bioactive natural products, pharmaceuticals, and pesticides, as they have important pharmacological and pesticidal properties,^[1] including inhibition of the hepatitis C virus (HCV),^[1a] inhibition of β -secretase (BACE-1),^[1b] agonism of the nicotinic acetylcholine receptors (mAChR),^[1c-d] as well as herbicidal activity^[1e] and anticancer activity^[1f-k] (Figure 1). The routes most commonly used to build the 1-azaspiro[4.4]nonane ring system are the formation of a cyclopentane ring onto a pre-existing pyrrolidine ring and the formation of a pyrrolidine ring onto a pre-existing cyclopentane ring.^[2-3] However, these transformations often require multiple synthetic steps, thus limiting the functional group choice. Therefore, a new strategy for the facile one-pot assembly and derivatization of the 1-azaspiro[4.4]nonane ring system is highly desirable.

Transition-metal-catalyzed cycloaddition reactions have emerged as powerful and step-economic methodologies for the construction of complex cyclic compounds in organic synthesis.^[4-8] The transition-metal-catalyzed cycloaddition of aromatic compounds with 2 π components (e.g., alkenes, allenes, and alkynes) involving the functionalization of the C(sp²)-H bonds is promising, as it exhibits a high efficiency and provides opportunities to discover new reactions.^[5-7]

However, annulation methods^[6,7] using this C(sp²)-H functionalization strategy for the construction of five-membered carbocycles, particularly the annulation methods in the presence of oxidants,^[6] are uncommon. These transformations are focused on aryl carbonyl compounds and their derivatives, including benzaldehydes, arylketones, benzamides, and aryl imines, and their reaction with alkynes (Scheme 1a).^[6,7] However, approaches involving the cleavage of the C-C π bond of alkenes for the annulation of 2 π components remain an unexploited area.^[8] We report a new, highly selective rhodium(III)-catalyzed [3+2] annulation of 5-aryl-2,3-dihydro-1H-pyrroles with internal alkynes for the selective synthesis of spiro[indene-1,2'-pyrrolidines] (Scheme 1b). This method achieves C(sp²)-H functionalization, the insertion of an alkyne, the addition of a C-C double bond, and a protonolysis.

We began our investigations by optimizing the reaction conditions for the annulation of 3,5-diphenyl-1-tosyl-2,3-dihydro-1H-pyrrole (**1a**) with 1,2-diphenylethyne (**2a**) (Table 1). Extensive screening of various reaction parameters revealed that 5 mol % [[Cp*RhCl₂]₂], 20 mol % AgSbF₆,

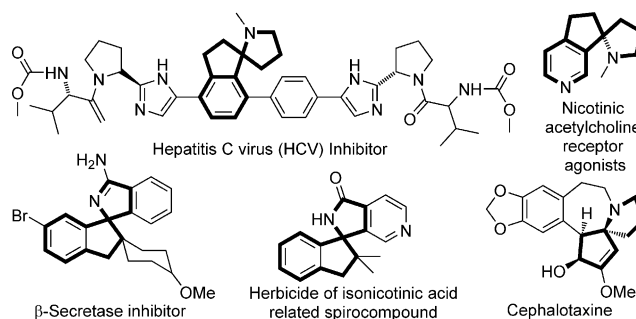


Figure 1. Examples of important 1-azaspiro[4.4]nonanes.

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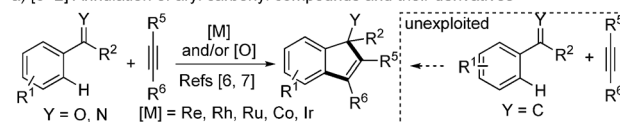
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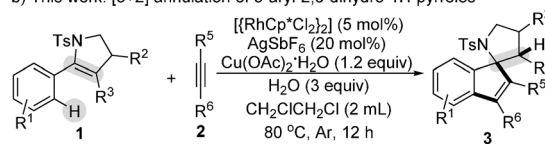
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a) [3+2] Annulation of aryl carbonyl compounds and their derivatives



b) This work: [3+2] annulation of 5-aryl-2,3-dihydro-1H-pyrroles



Scheme 1. [3+2] annulation routes to carbocycles. Cp* = C₅Me₅, Ts = 4-toluenesulfonyl.

Table 1: Screening for optimal reaction conditions.^[a]

Entry	Variation from the standard conditions	Yield [%]
1	none	82
2	at 60 °C	70
3	at 100 °C	67
4	[[Cp*RhCl2]2] (2 mol %)	71
5	[[Cp*RhCl2]2] (10 mol %)	81
6	without [[RhCpCl2]2]	0
7	AgSbF6 (30 mol %)	80
8	AgSbF6 (10 mol %)	52
9	without AgSbF6	0
10	AgOAc, Ag2CO3, or AgOTf instead of AgSbF6	trace
11	Cu(OAc)2·H2O (2 equiv)	82
12	Cu(OAc)2·H2O (0.6 equiv)	66
13	without Cu(OAc)2·H2O	16
14	MeOH instead of CH2ClCH2Cl	trace
15	tAmOH instead of CH2ClCH2Cl	36
16	H2O (6 equiv)	75
17	without H2O for 24 h	78
18 ^[b]	none	80

[a] Reaction conditions: **1a** (0.15 mmol), **2a** (0.18 mmol), [[Cp*RhCl2]2] (5 mol %), AgSbF6 (20 mol %), Cu(OAc)2·H2O (1.2 equiv), H2O (3 equiv), and CH2ClCH2Cl (2 mL) at 80 °C under Ar for 12 h. The d.r. value is 1.1:1 as determined by ¹H NMR analysis. [b] **1a** (1 g) for 48 h.

1.2 equivalents Cu(OAc)2, and 3 equivalents H2O in CH2ClCH2Cl at 80 °C for 12 hours was the best set of conditions for the annulation of **1a** with **2a**, thus providing the desired spiro[indene-1,2'-pyrrolidine] **3aa** in 82 % yield (entry 1). The reaction temperatures were found to affect the reaction, as the yield of **3aa** decreased from 82 % at 80 °C to 70 % at 60 °C (entry 2) and to 67 % at 100 °C (entry 3). For the amounts of [[Cp*RhCl2]2] and AgSbF6 used, we found that 5 mol % [[Cp*RhCl2]2] and 20 mol % AgSbF6 were preferred for the annulation reaction (entry 1 versus entries 4, 5, 7, and 8). Notably, a rhodium catalyst was necessary for successful annulation, as its absence resulted in no detectable amount of **3aa** (entry 6). In addition, the reaction did not proceed without silver salts (entry 9) because the formation of an active cationic rhodium species requires a silver salt to trap the Cl anions from the rhodium catalyst.^[6] The use of other silver salts, including AgOAc, Ag2CO3, and AgOTf, showed relatively lower reactivity (entry 10). Subsequently, the amount of Cu(OAc)2 was examined (entries 11–13). The reaction yield when using 2 equivalents Cu(OAc)2 was identical to that of 1.2 equivalents Cu(OAc)2, whereas the yield decreased from 82 to 52 % when using 0.6 equivalents Cu(OAc)2 (entry 1 versus entries 11 and 12). It should be noted that the reaction can take place without Cu(OAc)2, albeit with a lower yield (entry 13). The screening of solvents revealed that MeOH and tAmOH, two reported efficient solvents for the rhodium-catalyzed annulation,^[5–7] were less efficient than CH2ClCH2Cl for the annulation of **1a** (entries 14 and 15). Notably, the presence of H2O accelerated the reaction (entries 1, 16, and 17). In the presence of additional H2O **1a** was consumed completely within 12 hours

(entries 1 and 16). However, without additional H2O a longer reaction time was required (approximately 24 h) to complete the reaction (entry 17). Gratifyingly, a reaction on a one gram scale of **1a** was successfully performed in good yield (entry 18).

After determining the optimal reaction conditions, the scope of this rhodium(III)-catalyzed annulation protocol with respect to the 5-aryl-1-tosyl-2,3-dihydro-1H-pyrroles **1** and alkynes **2** was investigated (Table 2 and Table 3).^[9] As shown in Table 2, we first applied these optimal reaction conditions

Table 2: Variation of internal alkynes (**2**).^[a]

R = Me, 3ab , 76% (1.3:1)	R = OMe, 3ac , 69% (1.1:2)	R = Cl, 3ad , 77% (1.4:1)
R = OMe, 3ae , 72% (1:1)	R = Br, 3af , 81% (1.4:1)	
		3ag , 74% (1.3:1)
		3ah , 71% (1.4:1)
		R = H, 3ai , 76% (2:1)
		R = OMe, 3aj , 71% (2:1)
R = Me, 3ak , 74% (1.4:1)	R = Ac, 3al , 70% (1.4:1)	
		3am , 72% (2:1)
		R ⁵ = nC7H15, 3an , 0% ^[b]
		R ⁵ = H, 3ao , 0% ^[b]

[a] Reaction conditions: **1a** (0.15 mmol), **2** (0.18 mmol), [[Cp*RhCl2]2] (5 mol %), AgSbF6 (20 mol %), Cu(OAc)2·H2O (1.2 equiv), H2O (3 equiv), and CH2ClCH2Cl (2 mL) at 80 °C under Ar 12 h. The d.r. value is given within parentheses. [b] 4-Methyl-N-(4-oxo-2,4-diphenylbutyl)benzenesulfonamide (**4a**), a ring-opening product from **1a** and H2O, was isolated in about 60 % yield.^[9]

to the annulation of **1a** with a variety of symmetrical or unsymmetrical internal alkynes (**2b–m**), thus affording a broad array of spiro[indene-1,2'-pyrrolidines] (**3ab–am**) in good yield. In the presence of **1a**, [[Cp*RhCl2]2], AgSbF6, Cu(OAc)2, and H2O, the 1,2-diarylethynes **2b–g**, bearing Me, MeO, Cl, and Br groups on the aromatic rings, afforded the products **3ab–ag** in 69–81 % yield. Importantly, halogen substituents were well-tolerated under the optimal reaction conditions, thereby making the [3+2] annulation protocol more useful in organic synthesis because of the potential to further modify at the halogenated positions (**3ad** and **3af**). The annulation of the unsymmetrical internal alkynes **2h–m**

also afforded **3ah–am** in good yields with excellent levels of regiocontrol. Several substituents, including OMe, OAc, and Cl, were compatible with the optimal reaction conditions. The reaction of 1-phenylpropyne (**2h**) with **1a** regiospecifically delivered **3ah** in 71 % yield.^[10] We were pleased to find that the alkynes **2k–m**, containing OMe, OAc, and Cl groups, respectively, on the alkyl moiety also had high reactivity and afforded **3ak–am** in 70–74 % yield. However, the aliphatic internal alkyne **2n** and the aliphatic terminal alkyne **2o** were not viable substrates in the construction of the spiro[indene-1,2'-pyrrolidines] **3an** and **3ao**, respectively.

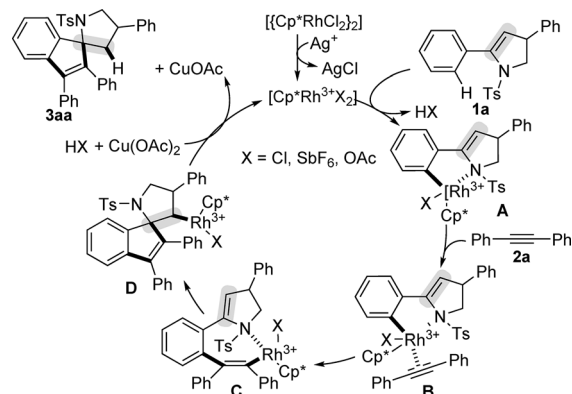
We next turned our attention to applying the optimal redaction conditions to the annulation of various 5-aryl-2,3-dihydro-1H-pyrroles (**1**) with either **2a**, **2g**, or **2h** (Table 3). The pyrroles **1b–g**, which contain several substituted aryl groups, including 4-MeC₆H₄, 4-ClC₆H₄, 4-BrC₆H₄, 4-NO₂C₆H₄, 3-ClC₆H₄, and naphthalen-1-yl, were compatible with the optimal reaction conditions, and gave **3ba–ga**, **3cg**, **3ch**, **3dh**, and **3fh** in good yields. Moreover, the electronic properties of the substituted aryl groups had no distinct effect on the reaction. While the 4-MeC₆H₄-substituted pyrrole **1b** delivered **3ba** in 77 % yield, **1e**, containing an electron-withdrawing NO₂ group, afforded **3ea** in 72 % yield. The chloro-substituted pyrroles **1c** and **1f** were also successfully reacted with the alkynes **2a**, **2g** or **2h**, providing **3cg**, **3ch**, **3fa** and **3fh** in good yields and excellent regioselectivities. The pyrrole **1h**, containing two substituents—a 3-phenyl group and a 4-methyl group—provided **3ha** in 66 % yield.^[9] 2-Phenyl-3a,4,5,6,7,7a-hexahydro-1H-indole (**1i**) was also a viable substrate, thus giving **3ia** in 68 % yield. Several substituents on the pyrrole nitrogen atom (Ts, PhCO, Boc, and H) were examined (**3ja–ma** and **3jh**), and only the N-tosyl-substituted substrate **1j** smoothly delivered the spiro[indene-1,2'-pyrrolidine] ring system (**3ja** and **3jh**). The substrates **1n** and **1o** were unsuitable for the annulation reaction (**3na** and **3oa**). Notably, the optimal reaction conditions were applicable to the pyrroles **1p–s**, which bore a Me, Cl, or Br group on the aromatic ring of the 5-phenyl moiety (**3pa–sa**). When using **1p** to react with **2a**, [(Cp**Rh*Cl₂)₂], AgSbF₆, Cu(OAc)₂, and H₂O, the reaction afforded **3pa** in 75 % yield. Interestingly, the chloro- (**1q**) and bromo-substituted pyrroles (**1r**) were well-tolerated and provided the corresponding **3qa** and **3ra** in 74 and 72 % yield, respectively. The more sterically hindered 3,5-dimethyl-substituted pyrrole **1s** was annulated with **2a** smoothly to deliver **3sa** in 78 % yield. Notably, the annulation was applicable to the assembly of the polycyclic aromatic spirocyclic ring **3ta** in good yield using the naphthalen-1-yl-substituted pyrrole **1t**.

Based on the above results,^[9] as well as previous studies,^[5–8] the mechanism outlined in Scheme 2 is proposed. Initially, [(Cp**Rh*Cl₂)₂] is easily converted into the active [Cp**Rh*³⁺X₂] species (X = Cl, SbF₆, OAc) by a Ag⁺ species.^[5,6] Subsequently, the C(sp²)–H bond of **1a** is cleaved by the [Cp**Rh*³⁺X₂] species to form the rhodium intermediate **A**. The complexation of **A** with alkyne **2a** produces the intermediate **B**, and subsequent insertion of **2a** into the aryl C(sp²)–Rh bond of **B** gives the intermediate **C**. Within intermediate **C**, the addition of the vinyl C(sp²)–Rh bond to the C–C double bond of the pyrrole moiety leads to the

Table 3: Variation of 5-Aryl-2,3-dihydro-1H-pyrroles (**1**).^[a]

 R = Me, 3ba , 77% (1:1:1) R = Cl, 3ca , 76% (1:1:1) R = Br, 3da , 73% (1:3:1) R = NO ₂ , 3ea , 72% (1:1:1)	 3cg , 78% (1:4:1)	 R = Cl, 3ch , 73% (2:1) R = Br, 3dh , 68% (2:1)
 R ⁶ = Ph, 3fa , 81% (1:1:1) R ⁶ = Me, 3fh , 72% (1:4:1)	 3ga , 68% (1:1:1)	 3ha , 66% (3:1)
 3ia , 68% (4:1)	 R ⁴ = Ts, 3ja , 76% R ⁴ = PhCO, 3ka , trace ^[b] R ⁴ = Boc, 3la , trace ^[c] R ⁴ = H, 3ma , 0% ^[d]	 3jh , 66% R ³ = Ph, 3na , 0% ^[e] R ³ = Me, 3oa , 0% ^[f]
 R = Me, 3pa , 75% (1:1) R = Cl, 3qa , 74% (1:3:4) R = Br, 3ra , 72% (1:3:4)	 3sa , 78% (1:7:1)	 3ta , 77% (2:1)

[a] Reaction conditions: **1** (0.15 mmol), **2** (0.18 mmol), [(Cp**Rh*Cl₂)₂] (5 mol %), AgSbF₆ (20 mol %), Cu(OAc)₂·H₂O (1.2 equiv), H₂O (3 equiv), and CH₂ClCH₂Cl (2 mL) at 80 °C under Ar for 12 h. The d.r. value is given within parentheses. [b] *N*-(4-Oxo-4-phenylbutyl)benzamide (**4k**) was isolated in 61 % yield. [c] *tert*-Butyl 4-oxo-4-phenylbutylcarbamate (**4l**) was obtained in 66 % yield. [d] 5-Phenyl-3,4-dihydro-2H-pyrrole (**5m**) was obtained in 72 % yield. [e] 1,2-Diphenylethanone (**6n**; 43 % yield) and benzil (**7n**; 22 % yield) from **1n** were isolated. [f] Greater than 89 % of **1o** was recovered. Boc = *tert*-butoxycarbonyl.



Scheme 2. Possible mechanism.

intermediate **D** (cis addition is major according the diastereoselectivity^[10] as a result of the complex of the Rh species with the nitrogen atom). Finally, cleavage of the C–Rh bond of **D** through protonolysis produces **3aa** and regenerates the active [Cp*Rh³⁺X₂] species with the aid of Cu(OAc)₂.

In summary, we have developed the first rhodium(III)-catalyzed [3+2] annulation of 5-aryl-2,3-dihydro-1H-pyrroles with internal alkynes through aryl C(sp²)–H/alkene functionalization. This new method is general for the construction of the spiro[indene-1,2'-pyrrolidine] ring system with excellent functional-group tolerance and good control of selectivity. Moreover, DFT calculations were carried out to better understand the exclusive regioselectivity observed.^[9] Studies on the detailed mechanism and applications of this annulation method are currently underway in our laboratory.

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- [9] Detailed data, including the deuterium-labelling experiments and an intermolecular kinetic isotope effect experiment (see Scheme S1 in the Supporting Information), the DFT calculations, the crystallographic data of **3ah**, 2D NMR spectra of the two isomers of **3ah**, and 2D NMR spectra of **3ha**, are summarized in the Supporting Information.
- [10] CCDC 971156 (**3ah**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.