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Divergent Reactivity of Rhodium (I) Carbenes Derived from Indole Annulation**

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Abstract

Rh(I)-carbenes were generated from propargylic alcohol derivatives as the result of a dehydrative indole annulation. Depending on the choice of the electron-withdrawing group on the aniline nitrogen nucleophile, either cyclopropanation product or dimerization product was obtained chemoselectively. Intramolecular hydroamidation occurred for the same type of propargylic alcohol derivatives when other transition metal catalysts were employed.

Keywords

carbene; cycloisomerization; rhodium; cyclopropane; indole

Metal carbenes are versatile intermediates for a variety of reactions.^[1] They were generally derived from diazo compounds or related derivatives.^[2] Fisher carbenes have been the primary precursors of Rh(I)-carbenes^[3] with a few exceptions.^[4] We^[5] and others^[6]

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discovered that Rh(I)-carbenes could be derived from 1,2-acyloxy migration of propargylic esters for cycloadditions.^[7] Recently, we also found that 3-hydroxy-1,4-enynes could serve as Rh(I)-carbene precursors and 5-carbon components in [5+1] cycloaddition reactions.^[8] In an effort to develop general carbene precursors for indole synthesis, we found that indole annulation of propargylic alcohol **1** could produce Rh(I)-carbene **2**, which underwent chemoselective cyclopropanation or dimerization to form products **3a** and **3b**, respectively, depending on the choice of the E-group (Scheme 1). Although a related Calcium-catalyzed tandem indole annulation and cyclopropanation involving multiple cationic species was developed by Niggemann, only intramolecular cyclopropanation was reported by tethering the alkene to the propargylic alcohol.^[9]

Indole is one of the most abundant bioactive heterocycles in natural products and pharmaceutical agents.^[10] Most previous indole synthesis focused on the construction of indole ring alone.^[11] It would be more efficient to couple indole annulation with other transformations in a cascade manner. Propargylic alcohol **1** has been used by Chan extensively for various Au- and Ag-catalyzed tandem indole annulation and nucleophilic additions (Scheme 2).^[12] We found that other catalysts, such as Pt-, Pd-, and Cu-based complexes could also mediate this process.^[13] Clearly, the Rh(I)-catalyst is unique in promoting the formation of carbene **2**, instead of hydroamidation product **4**, and subsequent divergent transformations.

Diazomethanes without an adjacent electron-withdrawing group are generally not very stable and those with an electron-rich aryl substituent are particularly difficult to prepare.^[14] Indeed, we were not able to prepare the indolyl substituted diazomethane precursor for carbene **2** using known methods,^[14] when we tried to explore alternative cyclopropanation methods.^[15] A tandem indole annulation of propargylic alcohol **1** followed by cyclopropanation allows the construction of both indole and cyclopropane, two of the most important rings in organic chemistry.^[10, 16]

We began our investigation by examining various transition metal catalysts that might mediate the cyclization of **6a**, in the presence of alkene **7a** (Table 1). Cationic Rh(I)-catalysts or neutral Rh(I)-catalysts without CO did not provide any desired product (entries 1-3, Table 1). High yield of product **8a** could be obtained by using [Rh(CO)₂Cl]₂ complex as the catalyst in the presence or absence of a CO balloon (entries 4 and 5). When the amount of alkene was reduced from 2 to 1.2 equivalent, slightly lower yield was observed (entry 6). No cyclopropanation products were formed when other metal complexes were employed (entries 7-10). In some cases, hydroamidation product **4** was observed, which was consistent with previous reports.^[12a-c, 13] The tosyl group of product **8a** can be removed as shown in the supporting information.

We then examined the scope of alkenes using propargylic alcohol **6a** as the carbene precursor. Various styrenes with a *para*-substituent participated in the cyclopropanation and yielded exclusively the *cis*-diastereoisomer (entries 1-4, Table 2). The reactivity of electron-poor styrene was lower than that of electron-rich styrene (entries 1 vs 5). Styrenes with multiple substituent or *ortho*-substituent could also be tolerated (entries 6 and 7). The structures of **8f** (CCDC 1042160) was unambiguously determined by X-ray analysis.

Trisubstituted cyclopropanes **8h-8j** were successfully prepared from 1,1-disubstituted alkenes (entries 8-10). Notably, free alcohols in **7i** and **7j** were tolerated under the standard conditions. Heterocycles such as indole could also be introduced to the diaryl cyclopropane products (entry 11). Unfortunately, 1,2-disubstituted alkene **7l** did not participate in the cyclopropanation. No cyclopropanation was observed by using alkenes with just an alkyl substituent including both electron-rich vinyl ethers and electron-poor enones.

We next explored the scope of the propargylic alcohols. The aryl sulfonyl group did not have obvious effect to the tandem annulation/cyclopropanation (entries 1-5, Table 3). The R¹ group could be a hydrogen or other alkyl groups (entries 6-8). Substituents could be introduced to the benzene ring of substrate **9i** (entry 9). Notably, aryl bromide in **9i** could be tolerated for Rh-catalyzed reactions.

Diene **11a** or **11b** participated in the cyclopropanation and afforded vinylcyclopropane **12**, which could undergo Cope rearrangement to yield cyclohepta[*b*]indole **14a** or **14b** (Scheme 3).^[17] Cyclohepta[*b*]indole is present in a number of natural products^[18] and bioactive pharmaceutical agents.^[19]

In addition to various arylsulfonyl groups in Table 3, we also explored the effect of other electron-withdrawing groups on the aniline nucleophile for the tandem annulation/cyclopropanation. Under the standard conditions in Table 3, no cyclopropanation product was observed for substrate **15a** (Table 4) in the presence of different styrenes. Instead, trace amount of dimeric indole **16a** was obtained in the presence or absence of styrenes. The yield of the dimeric indole was improved dramatically by simply attaching a CO balloon to the reaction flask (entry 1, Table 4). Under this condition, we previously did not observe any dimeric indole for substrate **6a** with a tosyl group on the nitrogen (entry 4, Table 1). No dimerization products were formed when other metal complexes were employed, such as those in entries 7-10 of Table 1.

Dimerization of carbenes is generally considered as a side reaction.^[20] Given the high yield of product **16a** and the potential utility of indole derivatives, we further examined the scope of the indole dimerization (Table 4). In addition to Boc-group, other alkoxy carbonyl groups (entry 2) or acyl group (entry 3) also facilitated the formation of dimer **16**. It is also interesting to note that the carbene intermediate cannot be trapped by an intramolecularly tethered alkene (entry 3). The R¹ substituent can be a hydrogen, ethyl, isopropyl, butyl, or phenyl group (entries 4-8). Dimeric indoles with a bromine substituent on the benzene ring could also be prepared (entry 9). The *E*- and *Z*-isomers were easily separated by column chromatography in several cases. The structures of the dimeric indoles were unambiguously determined by X-ray analysis of *E*-**16b** (CCDC 1042158) and *Z*-**16b** (CCDC 1042159).

The mechanism of the indole annulation/cyclopropanation or dimerization is proposed in Scheme 4. Coordination of the metal catalyst to alkyne in propargylic alcohol **1** will induce nucleophilic attack of the aniline nitrogen to form adduct **17**.^[12a-c] This process is promoted by electron withdrawing ligand such as CO on Rh^I complexes.^[7] Protonation to form the hydroamidation product **4** occurred for most π -acidic transition metals.^[12a-c] Elimination of water occurred to yield carbene intermediate **18**, which could undergo either

cyclopropanation or dimerization depending on the nature the E-group. We propose that the chemoselectivity may arise from the ability of the carbonyl group in **18b** to better coordinate to Rh^I-carbenes. The *cis*-selective cyclopropanation, based on X-ray structure of **8f** and NMR data, is presumably because both aryl substituents prefer to be away from the metal complex, which is consistent with gold-catalyzed 1,2-acyloxy migration of propargylic esters/intermolecular cyclopropanation.^[21]

In summary, various cyclopropanes with *cis*-1,2-diaryl substituents were prepared stereoselectively from propargylic alcohol derivatives *via* a tandem indole annulation and cyclopropanation. The enantioselective version of this cascade process is currently under investigation in our laboratory. Divergent reactivity was observed when the aniline nitrogen of the substrate is attached to different electron-withdrawing group. Computational studies are ongoing to elucidate the origin of the intriguing chemoselectivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Cyclopropanation or Dimerization

An indole annulation can be coupled together with stereoselective cyclopropanation or dimerization to form complex indole derivatives. The key intermediate is a putative Rh(I) carbene derived from cycloisomerization of ortho-aniline substituted propargylic alcohols.

Scheme 1.
Divergent Reactivity of Rh(I)-Carbenes Derived from Indole Annulation

(M = Au-, Ag-, Pt-, Pd-, and Cu-based complexes)

Scheme 2.
Metal-catalysts Mediated Hydroamidation

Scheme 3.

Sequential Indole Annulation, Cyclopropanation, and Cope Rearrangement

Scheme 4.

Proposed Mechanism for the Formation of Rh(I)-Carbenes and Their Divergent Reactivity

Table 1Screening Conditions for cyclopropanation^[a]

entry	conditions	Yield ^[b]
1	[Rh(COD) ₂]BF ₄ (5 mol%)	0
2	[Rh(PPh ₃) ₃]Cl (5 mol%)	0
3	[Rh(COD)Cl] ₂ (5 mol%)	0
4	[Rh(CO) ₂ Cl] ₂ (5 mol%), CO (1 atm)	82%
5	[Rh(CO) ₂ Cl] ₂ (5 mol%)	86%
6	[Rh(CO) ₂ Cl] ₂ (5 mol%)	77% ^[c]
7	[Ir(COD)Cl] ₂ (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), **6a** (1.0 equiv), **7a** (2.0 equiv), rt, 12-20 h, unless noted otherwise.

^[b] The yield was determined by ¹H NMR of crude product using CH₂Br₂ as the internal standard.

^[c] **7a** (1.2 equiv).

Table 2Scope of Alkenes for the Tandem Indole Annulation/Cyclopropanation with **6a**^[a]

entry	substrate 7	product 8 (dr) ^[b]	Yield ^[c]
1	7a , R = MeO	8a (20:1)	80%
2	7b , R = H	8b (20:1)	48%
3	7c , R = Me	8c (20:1)	68%
4	7d , R = <i>i</i> Bu	8d (20:1)	70%
5	7e , R = CF ₃	8e	20% ^[b]
6	 7f ,	 8f , (20:1)	78%
7	 7g ,	 8g , (20:1)	70%
8	7h , R ¹ = Me, R ² = H	8h , (20:1)	63%
9	7i , R ¹ = CH ₂ OH, R ² = H	8i , (20:1)	52%
10	7j , R ¹ = CH ₂ OH, R ² = MeO	8j , (20:1)	87%
11 ^[d]	 7k	 8k (20:1)	60%
12	 7l (E/Z = 1:1)	-	0%

^[a] Conditions: [Rh(CO)₂Cl]₂ (5 mol%), DCE, **6a** (1.0 equiv), **7** (2.0 equiv), rt, 12-20 h, unless noted otherwise.^[b] Determined by ¹H NMR of crude product.^[c] Isolated yield.^[d] Substrate **9f** (Table 3) was employed in this case.

Table 3Scope of Propargylic Alcohols for the Tandem Indole Annulation/Cyclopropanation^[a]

entry	substrate 9	product 10 (dr) ^b	yield ^c
1	9a , R ¹ = Me, R ² = H, Ar = Ph	10a (20:1)	72%
2	9b , R ¹ = Me, R ² = H, Ar = 4-FC ₆ H ₄	10b (20:1)	77%
3	9c , R ¹ = Me, R ² = H, Ar = 4- <i>t</i> BuC ₆ H ₄	10c (20:1)	72%
4	9d , R ¹ = Me, R ² = H, Ar = 4-MeOC ₆ H ₄	10d (20:1)	73%
5	9e , R ¹ = Me, R ² = H, Ar = 1-naphthyl	10e (20:1)	75%
6	9f , R ¹ = R ² = H, Ar = 4-MeC ₆ H ₄	10f (20:1)	66%
7	9g , R ¹ = Et, R ² = H, Ar = 4-MeC ₆ H ₄	10g (5:1)	81%
8	9h , R ¹ = <i>n</i> Bu, R ² = H, Ar = 4-MeC ₆ H ₄	10h (5:1)	77%
9	9i , R ¹ = Me, R ² = Br, Ar = 4-MeC ₆ H ₄	10i (20:1)	71%

^[a] Conditions: [Rh(CO)₂Cl]₂ (5 mol%), DCE, **9** (1.0 equiv), **7a** (2.0 equiv), rt, 12–20 h, unless noted otherwise.

^[b] Determined by ¹H NMR of crude product.

^[c] Isolated yield.

Table 4

Scope of Indole Dimerization^[a]

entry	substrate 15	product 16 (<i>E/Z</i>) ^b	yield ^c
1	15a , R ¹ = Me, R ² = H, R ³ = <i>t</i> BuO	16a (1.4:1)	81%
2	15b , R ¹ = Me, R ² = H, R ³ = MeO	16b (1.2:1)	81%
3	15c , R ¹ = Me, R ² = H, R ³ = CH ₂ =CHCH ₂ CH ₂	16c (1.4:1)	82%
4	15d , R ¹ = R ² = H, R ³ = <i>t</i> BuO	16d (1.2:1)	88%
5	15e , R ¹ = Et, R ² = H, R ³ = <i>t</i> BuO	16e (1.3:1)	47% ^d 35% ^e
6	15f , R ¹ = <i>i</i> Pr, R ² = H, R ³ = <i>t</i> BuO	16f (1.3:1)	74%
7	15g , R ¹ = <i>n</i> Bu, R ² = H, R ³ = <i>t</i> BuO	16g (1.5:1)	46% ^d 34% ^e
8	15h , R ¹ = Ph, R ² = H, R ³ = <i>t</i> BuO	16h (1.1:1)	33% ^d 27% ^e
9	15i , R ¹ = Me, R ² = Br, R ³ = <i>t</i> BuO	16i (1.3:1)	92%

^[a] Conditions: [Rh(CO)₂Cl]₂ (5 mol%), CO (1 atm), DCE, **15a**, 60 °C, 10 h, unless noted otherwise.

^[b] Determined by ¹H NMR of crude product.

^[c] Isolated yield of two isomers.

^[d] Isolated yield of *E*-isomer.

^[e] Isolated yield of *Z*-isomer.