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# The Oxidative Annulation of Tertiary Benzyl Alcohols with Internal Alkynes using an (Electron-Deficient $\eta^5$-Cyclopentadienyl)Rhodium(III) Catalyst under Ambient Conditions

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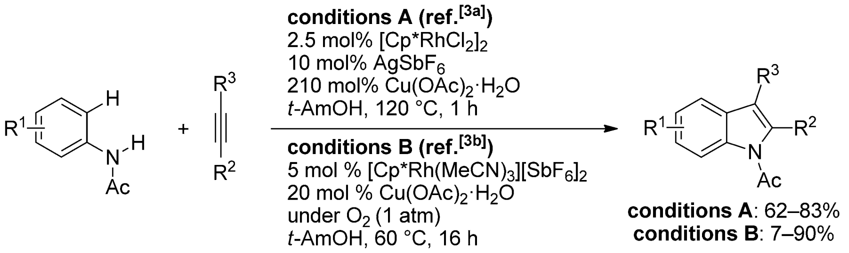
**Abstract:** It has been established that a dinuclear (electron-deficient $\eta^5$-cyclopentadienyl)rhodium(III) complex catalyzes the oxidative annulation of tertiary benzyl alcohols with internal alkynes *via* $sp^2$ C−H/O−H functionalization under ambient conditions (at room temperature under air) to give substituted isochromenes in good yields. The preference for annulation across electron-rich substrates over electron-deficient substrates was observed using this electron-deficient rhodium(III) complex.

**Keywords:** alkynes; annulation; benzyl alcohols; C−H bond functionalization; rhodium

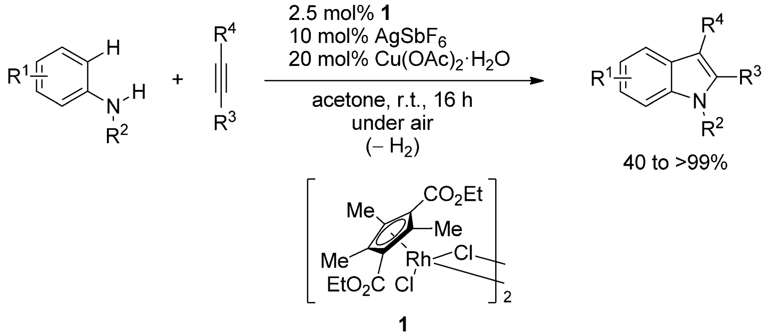
## Introduction

Dicationic rhodium(III)/Cp* complexes,[1] derived from $[Cp^*RhCl_2]_2$, are highly active catalysts for numbers of C−H bond functionalization reactions.[2] For example, Fagnou and co-workers reported the oxidative annulation of acetanilides with internal alkynes using dicationic rhodium(III)/Cp* complexes as catalysts.[3,4] In their initial communication, the reactions of acetanilides with internal alkynes were conducted at high temperature (120 °C) using an *in situ* generated dicationic rhodium(III)/Cp* complex, derived from $[Cp^*RhCl_2]_2$, as a catalyst and a stoichiometric amount of $Cu(OAc)_2$ as an oxidant to give the corresponding indoles in good yields (conditions A, Scheme 1).[3a] In their subsequent article, the same reactions proceeded at lower temperature (60 °C) in higher yields by using an isolated dicationic rhodium(III)/Cp* complex, $[Cp^*Rh(MeCN)_3][SbF_6]_2$, as a catalyst, with $O_2$ and a catalytic amount of $Cu(OAc)_2$ as oxidants (conditions B, Scheme 1).[3b]

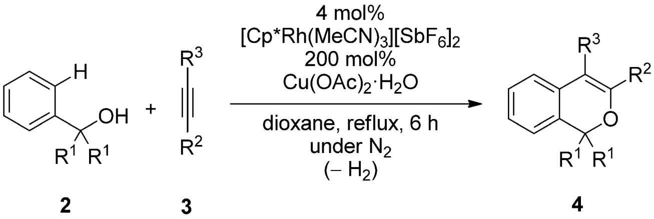
On the other hand, our research group recently reported the synthesis of an (ethoxycarbonyl-substituted cyclopentadienyl)rhodium(III) complex [$Cp^ERhX_2$ (**1**), Scheme 2] *via* the rhodium(I)-catalyzed cross-[2+2+1] cyclotrimerization of silylacetylenes and two alkynyl esters, leading to substituted silylfulvenes, followed by reductive complexation with $RhCl_3$ in ethanol.[5] It was anticipated that an in situ generated electron-deficient dicationic rhodium(III)/$Cp^E$ complex,[6] derived from **1**, would show higher catalytic activity than the dicationic rhodium(III)/Cp* complexes in the C−H bond functionalization of electron-rich sub-



**Scheme 1.** Fagnou's oxidative annulation of acetanilides with internal alkynes using dicationic rhodium(III)/Cp* catalysts.[3]



**Scheme 2.** Our research group's oxidative annulation of acetanilides with internal alkynes using a dicationic rhodium(III)/Cp$^E$ catalyst.[7]



**Scheme 3.** Oxidative annulation of tertiary benzyl alcohols with internal alkynes using the dicationic rhodium(III)/Cp* catalyst.[9]

strates. Indeed, this new electron-deficient rhodium(III) complex catalyzed the oxidative annulation of acetanilides with internal alkynes at room temperature under air (Scheme 2).[7,8] On the contrary, the electron-deficient rhodium(III) complex **1** was not a suitable precatalyst for the C–H bond functionalization of electron-deficient substrates, such as benzamides.[7]

The above successful application of the electron-deficient rhodium(III) complex **1** to the C–H bond functionalization prompted our investigation into the C–H bond functionalization of another electron-rich substrate. Satoh and Miura recently reported the oxidative annulation of tertiary benzyl alcohols **2** with internal alkynes **3**, leading to isochromenes **4**, *via* $sp^2$ C–H/O–H functionalization by using the isolated dicationic rhodium(III)/Cp* complex, $[Cp^*Rh(MeCN)_3][SbF_6]_2$, as a catalyst and an excess amount of $Cu(OAc)_2$ as an oxidant at high temperature (Scheme 3).[9–11] We anticipated that the electron-deficient rhodium(III) complex **1** would be a highly active precatalyst for this oxidative annulation reaction and promote this reaction under ambient conditions (at room temperature under air).

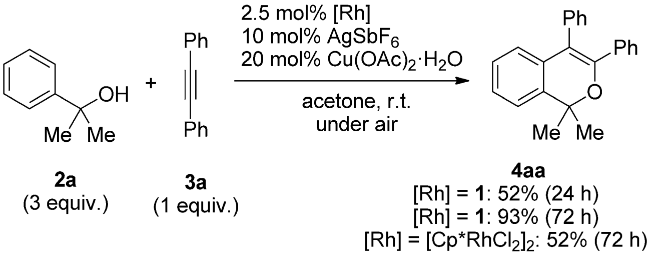
In this paper, we wish to present the oxidative annulation of tertiary benzyl alcohols with internal alkynes *via* $sp^2$ C–H/O–H functionalization by using the (electron-deficient $\eta^5$-cyclopentadienyl)rhodium(III) catalyst under ambient conditions.[12]

## Results and Discussion

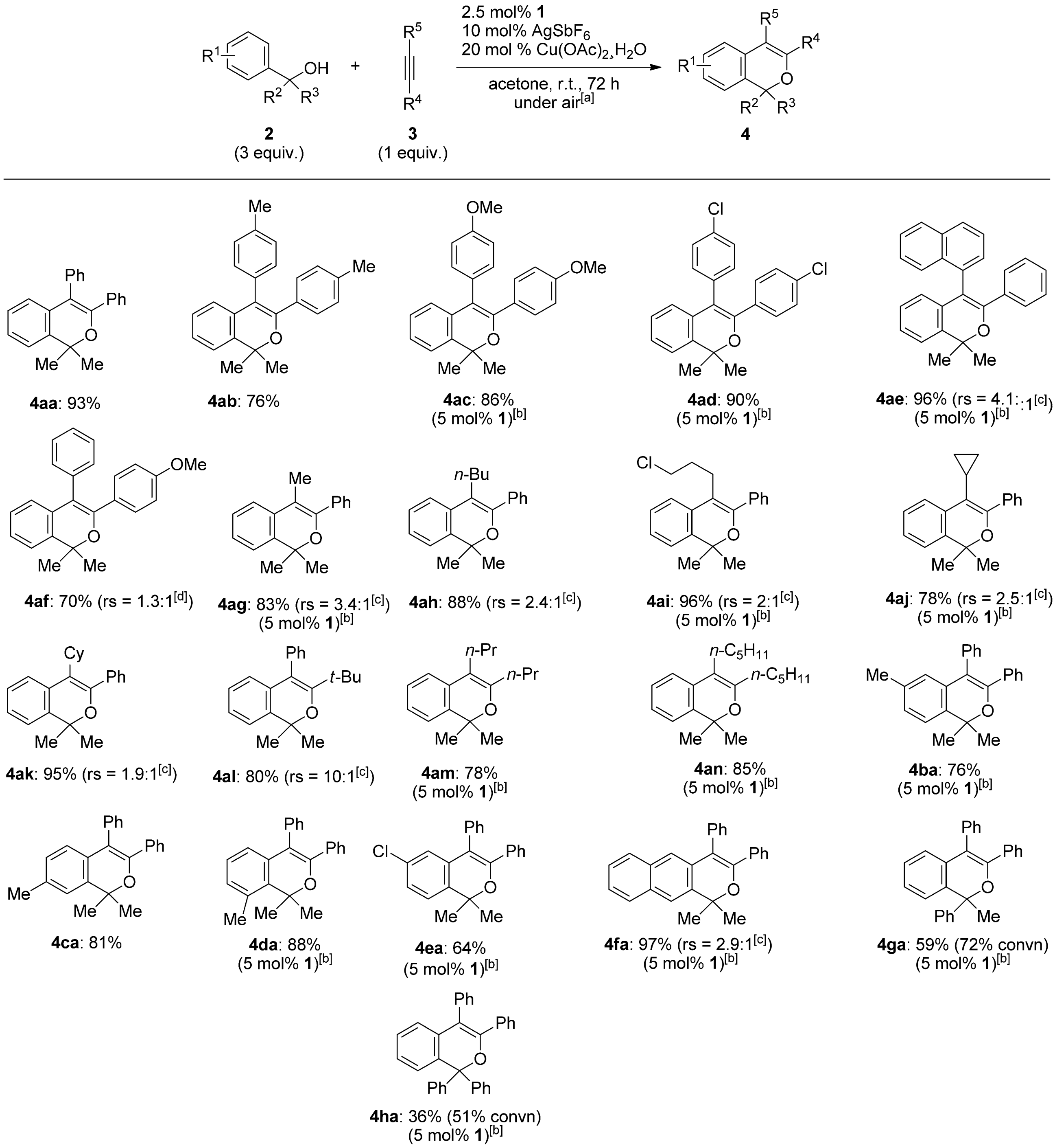
We first examined the reaction of 2-phenyl-2-propanol (**2a**) with diphenylacetylene (**3a**) using an *in situ* generated electron-deficient dicationic rhodium(III)/Cp$^E$ complex, derived from **1** (2.5 mol%), as a catalyst, with air and a catalytic amount of $Cu(OAc)_2$ as oxidants at room temperature for 24 h. Pleasingly, the desired oxidative annulation reaction proceeded to give the corresponding isochromene in moderate yield (**4aa**, Scheme 4). Prolonged reaction time (72 h) increased the yield of **4aa** (Scheme 4). The catalytic activities of the rhodium(III)/Cp$^E$ and Cp* complexes were compared under the same reaction conditions. As shown in Scheme 4, the activity of the rhodium(III)/Cp$^E$ complex was significantly higher than that of the rhodium(III)/Cp* complex.

As shown in Scheme 5, this rhodium-catalyzed oxidative annulation under the above mild reaction conditions showed a wide scope with respect to both tertiary benzyl alcohols **2** and internal alkynes **3**, although higher catalyst loadings (5 mol% of **1**) were required in some cases.

The scope of internal alkynes was first examined. A variety of diarylacetylenes **3a–3f** reacted with **2a** to give the corresponding isochromenes **4aa–4af** in good to high yields. In terms of regioselectivity, the use of arylacetylene **3e** possessing sterically different aryl groups showed good regioselectivity and the sterically demanding naphthyl group is mainly located in the 4-



**Scheme 4.** Oxidative annulation of **2a** with **3a** using **1** *vs.* $[Cp^*RhCl_2]_2$.



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[a] **1** (0.0050 mmol), $AgSbF_6$ (0.020 mmol), $Cu(OAc)_2\cdot H_2O$ (0.040 mmol), **2** (0.60 mmol), **3** (0.20 mmol), and acetone (1.0 mL) were used. The cited yields are of the isolated products.

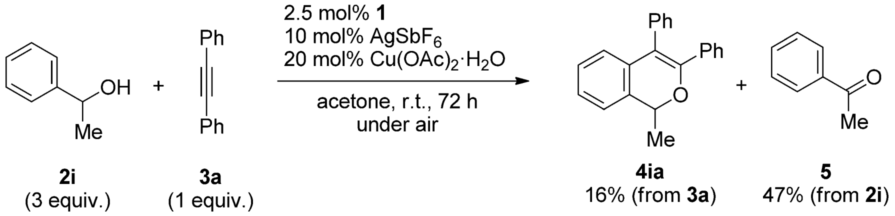
[b] **1** (0.010 mmol), $AgSbF_6$ (0.040 mmol), $Cu(OAc)_2\cdot H_2O$ (0.080 mmol), **2** (0.60 mmol), **3** (0.20 mmol), and acetone (1.0 mL) were used.

[c] Ratios of regioisomers. Major regioisomers are shown.

[d] Ratios of regioisomers. A major regioisomer could not be determined.

**Scheme 5.** Oxidative annulation of tertiary benzyl alcohols **2a–2h** with internal alkynes **3a–3n** using rhodium(III) complex **1** under ambient conditions.

position of the product isochromene **4ae**. Unfortunately, poor regioselectivity was observed using unsymmetrical diarylacetylene **3f**, possessing electronically different aryl groups. Not only diaryl- but also

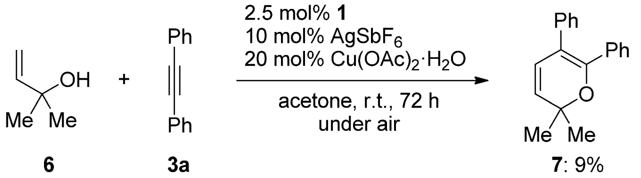


**Scheme 6.** Oxidative annulation of secondary benzyl alcohol **2i** with **3a**.

aryl-alkylacetylenes **3g–3l** reacted with **2a** to give the corresponding isochromenes **4ag–4al** in high yields with moderate to high regioselectivities. In the reactions of aryl-alkylacetylenes **3g–3k**, the aryl groups are mainly located in the 3-position of the product isochromenes **4ag–4ak**. On the contrary, in the reaction of the highly sterically demanding *tert*-butyl-substituted internal alkyne **3l**, the aryl group is located in the 4 position of the product isochromene **4al**. It is worthy of note that unstable cyclopropyl-substituted alkyne **3j** could be employed for this reaction. Importantly, dialkylacetylene **3m** showed very low reactivity in the Cp*Rh(III) complex-catalyzed isochromene synthesis,[13] on the contrary, dialkylacetylenes **3m** and **3n** reacted with **2a** in the presence of the $Cp^ERh(III)$ catalyst to give the corresponding isochromenes **4am** and **4an**, respectively, in high yields.

The scope of tertiary benzyl alcohols was next examined. The 2-, 3-, and 4-methyl-substituted benzyl alcohols **2b–2d** reacted with **3a** to give the corresponding isochromenes **4ba–4da** in high yields. It is worthy of note that the reaction of 3-methyl-substituted benzyl alcohol **2c** proceeded with perfect regioselectivity and that of sterically demanding 3-methyl-substituted benzyl alcohol **2c** proceeded in high yield. Not only electron-rich methyl-substituted benzyl alcohols but also electron-deficient 4-chloro-substituted benzyl alcohol **2e** reacted with **3a** to give the corresponding isochromene **4ea** in good yield. Not only benzene derivatives but also 2-(2-naphthyl)-2-propanol (**2f**), which showed poor reactivity towards **3a** in the Cp*Rh(III) complex-catalyzed isochromene synthesis,[14] reacted with **3a** to give the corresponding isochromene **4fa** in high yield, although **4fa** was obtained as a mixture of regioisomers. Finally, the reactions of 1,1-diphenylethanol (**2g**) and triphenylmethanol (**2h**) with **3a** were examined. Although these reactions were sluggish, the desired isochromenes **4ga** and **4ha** were obtained in moderate yields.

The reaction of secondary benzyl alcohol **2i** with **3a** was also examined. Unfortunately, dehydrogenation, rather than the oxidative annulation, of **2i** proceeded predominantly to give acetophenone (**5**) as a major product and isochromene **4ia** as a minor product (Scheme 6).

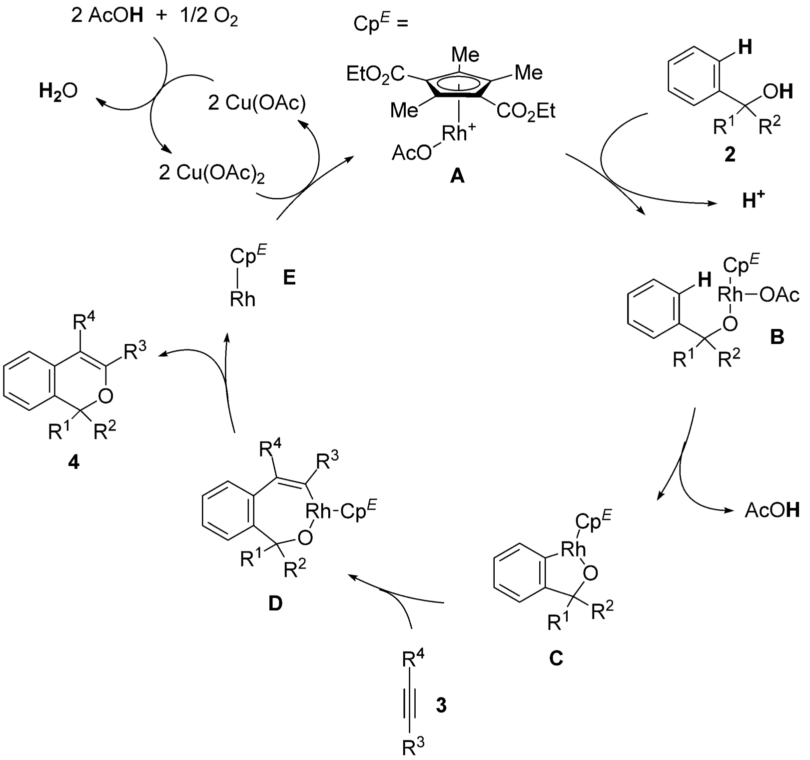


**Scheme 7.** Oxidative annulation of tertiary allyl alcohol **6** with **3a**.

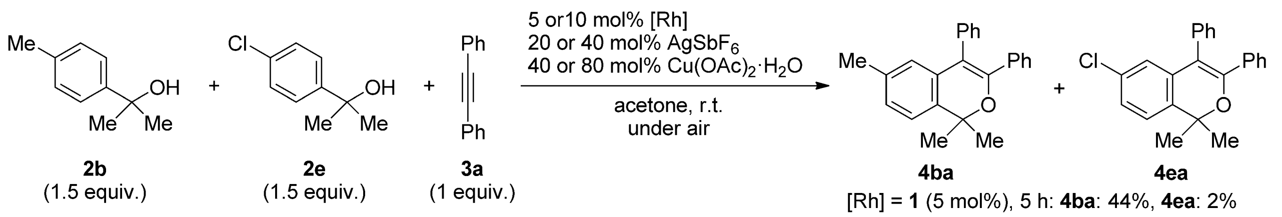
In the previous report by Satoh and Miura, tertiary allyl alcohol **6** also underwent the oxidative annulation with **3a** using the $[Cp^*Rh(MeCN)_3][SbF_6]_2$ catalyst in refluxing dioxane to give the corresponding 2*H*-pyran **7** in moderate yield.[9] Unfortunately, the present ambient reaction conditions using **1** as the precatalyst were not effective for the above transformation (Scheme 7).

A plausible mechanism for the rhodium(III)-catalyzed isochromene synthesis is shown in Scheme 8.[9] Rhodium(III) complex **A** reacts with tertiary benzyl alcohol **2** to generate rhodium(III) alkoxide **B**. Intramolecular C–H bond cleavage proceeds to produce the five-membered oxarhodacycle **C**. Coordination followed by migratory insertion of internal alkyne **3** occurs to afford the seven-membered oxarhodacycle **D**. Then, C–O bond reductive elimination affords the desired isochromene **4** along with rhodium(I) complex **E**. This rhodium(I) complex **E** is then oxidized back to the active rhodium(III) complex **A** with copper(II) acetate and the resulting copper(I) acetate is then reoxidized by molecular oxygen.

It was expected that electron-deficient rhodium(III) complex **A** would facilitate the C–H bond cleavage of electron-rich substrates over electron-deficient substrates. Indeed, in the previous report, we have demonstrated that the intermolecular competition experiment between electron-deficient and electron-rich anilides with diphenylacetylene using **1** as a precatalyst reveals the preference for annulation across the electron-rich anilide over the electron-deficient anilide.[7] Additionally, we have demonstrated that the intermolecular competition experiment between electron-deficient diarylacetylene and electron-rich dialkylacetylene with anilide using **1** as a precatalyst reveals the preference for migratory insertion across dialkylacetylene over diarylacetylene.[7]



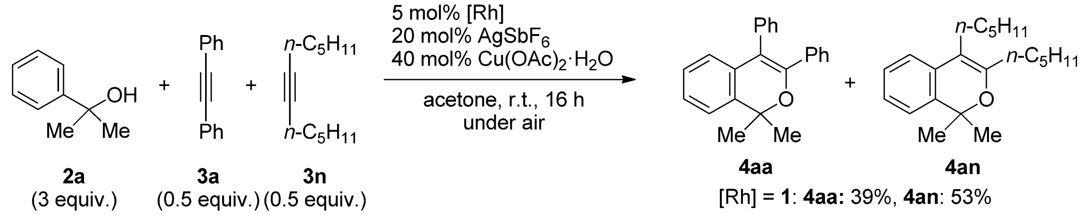
Scheme 8. Plausible mechanism for the formation of isochromene **4**.



[Rh] = **1** (5 mol%), 5 h: **4ba**: 44%, **4ea**: 2%
(**4ba**/**4ea** = 22:1)
[Rh] = $[Cp^*RhCl_2]_2$ (10 mol%), 27 h: **4ba**: 23%, **4ea**: 3%
(**4ba**/**4ea** = 8:1)

**Scheme 9.** Competition experiments between electron-deficient and electron-rich benzyl alcohols **2b** and **2e** using **1** *vs.* $[Cp^*RhCl_2]_2$.

Thus, similar intermolecular competition experiments were conducted between electron-deficient and electron-rich benzyl alcohols **2b** and **2e**, and electron-deficient diarylacetylene **3a** and electron-rich dialkylacetylene **3n** as shown in Scheme 9 and Scheme 10. The use of electron-deficient complex **1** revealed the



[Rh] = **1**: **4aa:** 39%, **4an**: 53%
(**4aa**/**4an** = 1:1.4)
[Rh] = $[Cp^*RhCl_2]_2$: **4aa:** 27%, **4an**: 21%
(**4aa**/**4an** = 1.3:1)

**Scheme 10.** Competition experiments between diaryl- and dialkylacetylenes **3a** and **3n** using **1** *vs.* $[Cp^*RhCl_2]_2$.

preference for the annulation across electron-rich benzyl alcohol **2b** over electron-deficient benzyl alcohol **2e** and the same preference was also revealed in the case of using electron-rich $[\mathrm{Cp^*RhCl_2}]_2$ (Scheme 9). The use of **1** revealed the slight preference for the migratory insertion across dialkylacetylene **3n** over diarylacetylene **3a** (Scheme 10); on the contrary, the use of $[\mathrm{Cp^*RhCl_2}]_2$ revealed the slight preference for the migratory insertion across **3a** over **3n** (Scheme 10).

## Conclusions

In conclusion, it has been established that a dinuclear (electron-deficient $\eta^5$-cyclopentadienyl)rhodium(III) complex is a highly active precatalyst for the oxidative annulation of tertiary benzyl alcohols with internal alkynes, leading to isochromenes, under ambient conditions (at room temperature under air). The present catalysis could be conducted using air and a catalytic amount of $\mathrm{Cu(OAc)_2}$ as oxidants in acetone at room temperature, therefore, this new protocol is operationally more convenient than the previously reported protocol [employing excess $\mathrm{Cu(OAc)_2}$ as an oxidant in refluxing dioxane]. This study revealed that our new $\mathrm{Cp^ERhX_2}$ precatalyst (**1**) is more active for the directed C–H bond functionalization of electron-rich arenes, including not only anilides[7] but also benzyl alcohols, than the conventional $\mathrm{Cp^*RhX_2}$ precatalyst. The preference for annulation across electron-rich substrates over electron-deficient substrates, which is similar to the previously studied indole synthesis,[7] was observed in the electron-deficient dicationic rhodium(III)/$\mathrm{Cp^E}$ complex-catalyzed isochromene synthesis.

## Experimental Section

### Typical Procedure for Rhodium(III)-Catalyzed Oxidative Annulation of Tertiary Benzyl Alcohols with Internal Alkynes under Ambient Conditions (4aa, Scheme 4 and Scheme 5)

To a 13.5-mL screw-cap vial bottle was added $\mathrm{AgSbF_6}$ (6.9 mg, 0.020 mmol), **1** (4.3 mg, 0.0050 mmol), $\mathrm{Cu(OAc)_2 \cdot H_2O}$ (8.0 mg, 0.040 mmol), 2-phenylpropan-2-ol (**2a**, 81.7 mg, 0.600 mmol), diphenylacetylene (**3a**, 35.6 mg, 0.200 mmol), and acetone (1.0 mL) under air in this order. The vessel was sealed and the mixture stirred at room temperature under air for 72 h. The resulting mixture was diluted with ether, filtered through a silica gel pad, and washed with EtOAc. The solvent was concentrated under reduced pressure and the residue was purified by a preparative TLC (hexane/EtOAc/toluene/$\mathrm{CH_2Cl_2}$ = 40:1:5:5) to give **4aa**; yield: 57.8 mg (0.185 mmol, 93%).

**1,1-Dimethyl-3,4-diphenyl-1*H*-isochromene (4aa):**[9]:Colorless solid. $^1$H NMR ($\mathrm{CDCl_3}$, 500 MHz): $\delta = 7.41–7.11$ (m, 13H), 6.96–6.90 (m, 1H), 1.84 (s, 6H); $^{13}$C NMR ($\mathrm{CDCl_3}$, 125 MHz): $\delta = 148.2$, 137.2, 136.4, 136.2, 132.1, 131.8, 128.9, 128.7, 127.9, 127.6, 127.4, 127.1, 127.0, 123.7, 122.3, 115.8, 77.8, 27.2; HR-MS (APCI): *m/z* = 313.1597, calcd. for $\mathrm{C_{23}H_{21}O}$ $[\mathrm{M+H}]^+$: 313.1587.

## Acknowledgements

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[14] In ref.[9] isochromene **4fa** was obtained in 43% yield.