One-Carbon Oxidative Annulations of 1,3-Enynes by Catalytic C–H Functionalization and 1,4-Rhodium(III) Migration

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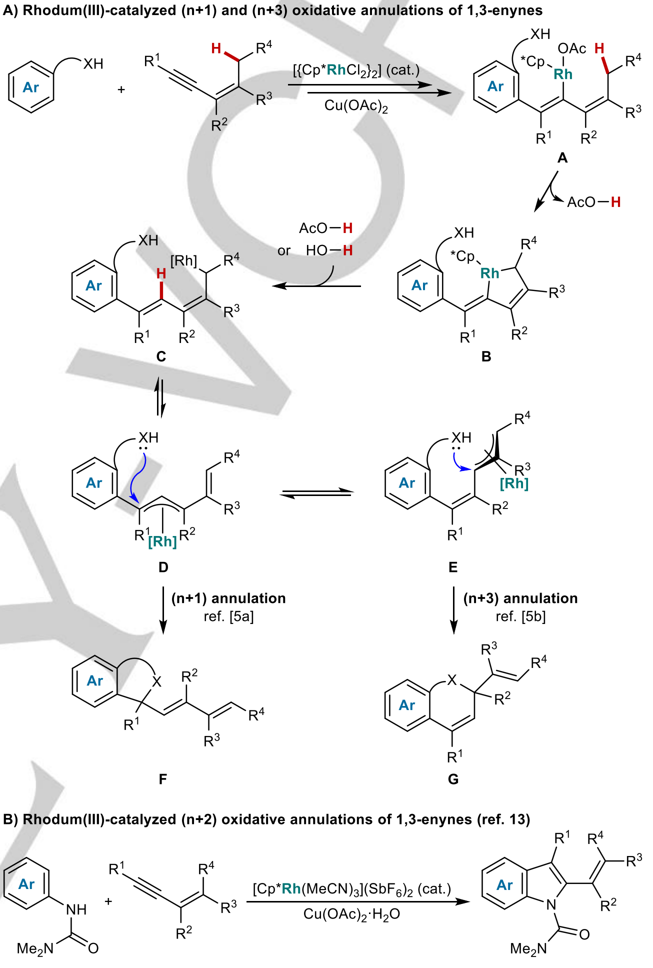
Abstract: Rhodium(III)-catalyzed C–H functionalization–oxidative annulations of aromatic substrates with 1,3-enynes that contain allylic hydrogen atoms *cis* to the alkyne are described. The key step in these reactions is an alkenyl-to-allyl 1,4-rhodium(III) migration to give electrophilic π-allylrhodium(III) species. Nucleophilic trapping of these species gives heterocycles such as benzopyrans, isobenzofuranones, and isoindolinones.

Introduction

1,4-Metal migration is a powerful process that enables the functionalization of remote C–H bonds by relaying reactivity from one site to another.[1] As such, this migration has been utilized in a diverse range of synthetic methods.[1–10] Key to the continued growth of this field is the discovery of new types of 1,4-metal migration that open up previously inaccessible modes of reactivity.

During the development of new oxidative annulations of alkynes by catalytic C–H functionalization,[11] we reported the first examples of alkenyl-to-allyl 1,4-rhodium(III) migration of 1,3-enynes that contain allylic hydrogen atoms *cis* to the alkyne (Scheme 1A).[5a,b] This process was used in the preparation of both heterocyclic[5a] and carbocyclic products.[5b] On the basis of deuterium transfer studies, the key 1,4-rhodium(III) migration step is proposed to occur by a concerted metalation–deprotonation of alkenylrhodium species **A** to give rhodacycle **B**, followed by protonolysis to give σ-allylrhodium(III) species **C**.[5a,b] Isomerization of **C** into electrophilic π-allylrhodium(III) species **D** or **E** (among other isomers) is followed by nucleophilic trapping with the XH directing group to give products of (n+1)[5a] or (n+3)[5b] annulation (products **F** and **G**, respectively).[12] This reactivity contrasts strongly with other rhodium(III)-catalyzed oxidative annulations of 1,3-enynes, in which the alkynyl moiety of the 1,3-enyne serves as a two-carbon annulation partner (Scheme 1B).[13,14] The utility of the (n+1) annulations was demonstrated principally with 2-aryl cyclic 1,3-dicarbonyl compounds, although five additional examples of other substrates with enol, phenol, carboxylic acid, or imide directing groups were also described.[5a] However, a more extensive investigation of these additional annulations was warranted to determine their scope and limitations. Herein, we describe a more thorough study of this process and demonstrate its applicability in the synthesis of a range of benzopyrans, isobenzofuranones, and isoindolinones.



Scheme 1. Catalytic oxidative annulations of 1,3-enynes.

Results and Discussion

Our studies began with the one-carbon oxidative annulations of 2-phenylphenol (**2a**) with 1,3-enynes **1a**–**1h** (1.1 equiv) that contain allylic hydrogen atoms *cis* to the alkyne (Table 1). From a brief evaluation of reaction variables (see the Supporting Information), the best results were obtained using $[\{Cp^*RhCl_2\}_2]$ (3.0 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (2.1 equiv) in dioxane at 120 °C. In addition, the inclusion of K_2CO_3 (3.0 equiv) was important for efficient reactivity, as extremely low conversions were observed in its absence. The reasons for this observation are not clear at the present time. Under these conditions, benzopyrans **3aa**–**3ac**

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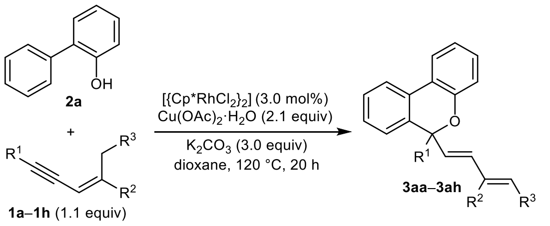
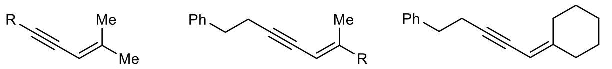
Table 1: Oxidative annulations of 2-phenylphenol with various 1,3-enynes.[a]



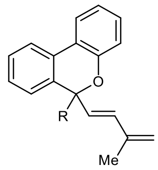
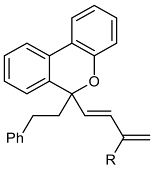
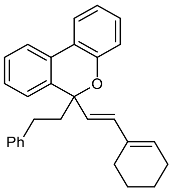
1,3-Enynes



1a R = CH_2CH_2Ph
1b R = *n*Bu
1c R = $(CH_2)_3OTBS$
1d R = $(CH_2)_3OH$
1e R = CH_2NMe_2

1f R = Ph
1g R = H

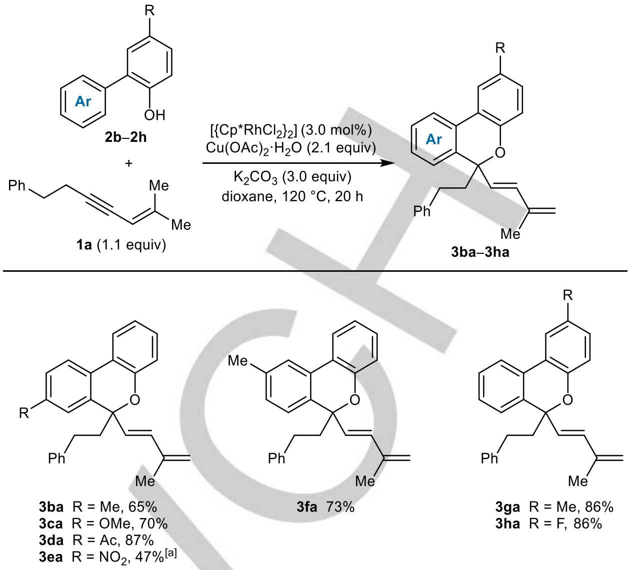
1h

Entry	1,3-Enyne	Product		Yield [%]
1	**1a**		**3aa** R = CH_2CH_2Ph	77
2[b]	**1b**		**3ab** R = *n*Bu	59
3[b]	**1c**		**3ac** R = $(CH_2)_3OTBS$	64
4	**1d**		**3ad** R = $(CH_2)_3OH$	<15[c]
5	**1e**		**3ae** R = CH_2NMe_2	<5[c]
6	**1f**		**3af** R = Ph	20
7	**1g**		**3ag** R = H	41
8[b]	**1h**		**3ah**	79

[a] Reactions were conducted with 0.50 mmol of **2a**. Yields are of isolated products unless otherwise noted. [b] Using 3.1 mol% of $[\{Cp^*RhCl_2\}_2]$. [c] Yields are based on ^1H NMR analysis of the crude reaction mixtures using 1,3,5-trimethoxybenzene as an internal standard.

and **3ae**–**3ah** were obtained in generally reasonable to good yields and with high *E*-selectivities with respect to the internal alkene.[15] 1,3-Enynes with aliphatic substituents at the alkyne, such as 2-phenylethyl (entries 1 and 6–8), *n*-butyl (entry 2), and 3-(*tert*-butyldimethylsilyloxy)propyl groups (entry 3) underwent successful oxidative annulations. However, 1,3-enynes **1d** and **1e**, which contain alcohol or amine moieties, respectively, gave very low conversions (entries 4 and 5). Variation of the group *trans* to the alkyne from methyl to phenyl (entry 6) or hydrogen (entry 7) was tolerated, but the yields were lower. The process is not limited to 1,3-enynes bearing a methyl group *cis* to the alkyne, as shown by the successful reaction of 1,3-enyne **1h** to give benzopyran **3ah** in 79% yield (entry 8).

Next, the scope of the 2-arylphenol was examined in reactions with 1,3-enyne **1a** (Scheme 2). Changing the *para*-substituent of the 2-aryl ring to electron-donating (**3ba** and **3ca**) or electron-withdrawing groups (**3da** and **3ea**) is generally well-tolerated. Benzopyran **3ea** was obtained as a 7.6:1 mixture of *E*:*Z* isomers in 47% yield.[15] 2-(3-Methylphenyl)phenol led to C–H functionalization at the sterically more accessible site to give benzopyran **3fa** in 73% yield. Methyl or fluoride groups *para*- to the hydroxyl moiety of the phenol are also accommodated (**3ga** and **3ha**).



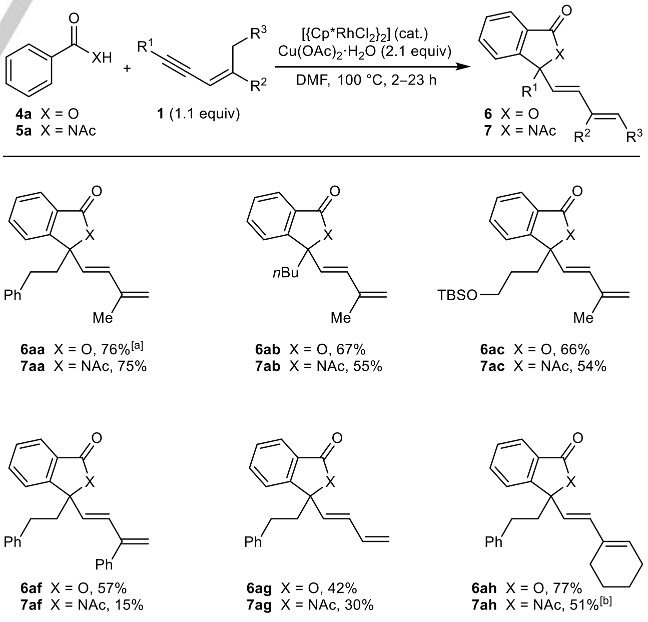
3ba R = Me, 65%
3ca R = OMe, 70%
3da R = Ac, 87%
3ea R = NO_2, 47%[a]

3fa 73%

3ga R = Me, 86%
3ha R = F, 86%

Scheme 2. Reactions of various 2-arylphenols with 1,3-enyne **2a**. Reactions were conducted with 0.50 mmol of **2b**–**2h**. Yields are of isolated products. [a] Isolated as a 7.6:1 mixture of *E*:*Z* isomers.

Next, benzoic acid (**4a**) and *N*-acetylbenzamide (**5a**) were evaluated in reactions with a range of 1,3-enynes (Scheme 3). In these reactions, DMF is superior to dioxane, K_2CO_3 is unnecessary, and the temperature can be decreased to 100 °C. Furthermore, the loading of $[\{Cp^*RhCl_2\}_2]$ was reduced to 1.0 mol% and 1.5 mol% for **4a** and **5a**, respectively, and satisfactory results were maintained. Pleasingly, benzoic acid reacted smoothly with a range of 1,3-enynes to give isobenzofuranones



6aa X = O, 76%[a]
7aa X = NAc, 75%

6ab X = O, 67%
7ab X = NAc, 55%

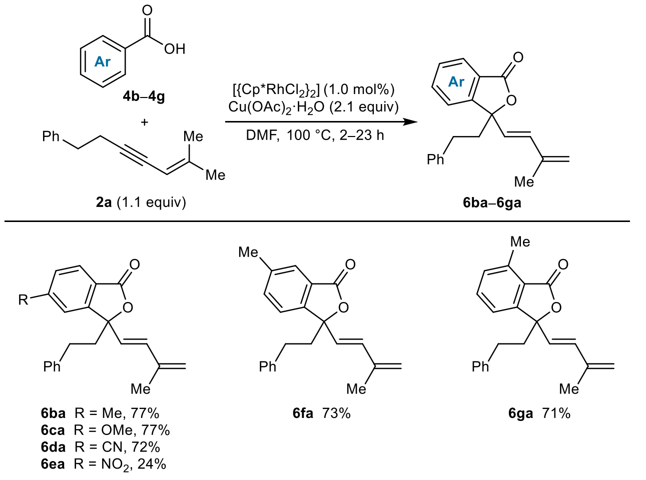
6ac X = O, 66%
7ac X = NAc, 54%

6af X = O, 57%
7af X = NAc, 15%

6ag X = O, 42%
7ag X = NAc, 30%

6ah X = O, 77%
7ah X = NAc, 51%[b]

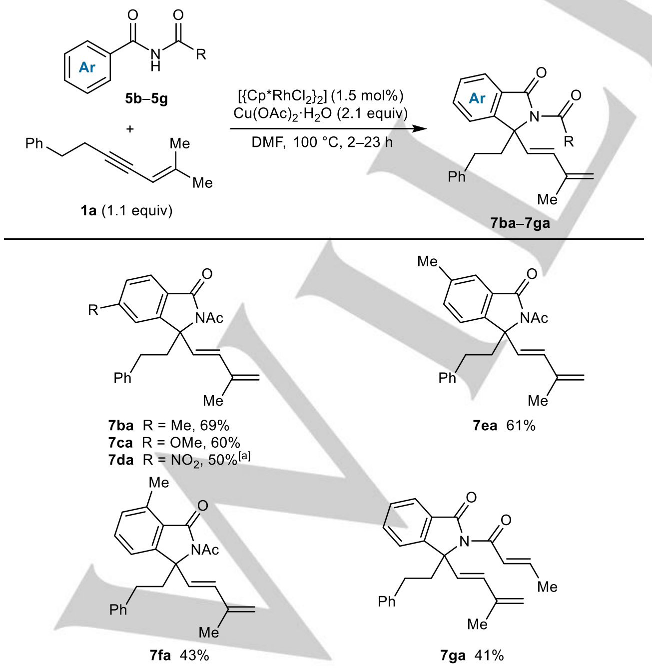
Scheme 3. Reactions of benzoic acid (**4a**) or *N*-acetylbenzamide (**5a**) with various 1,3-enynes. Reactions with **4a** were conducted using 1.0 mol% of $[\{Cp^*RhCl_2\}_2]$, whereas 1.5 mol% of $[\{Cp^*RhCl_2\}_2]$ was used in the reactions of **5a**. [a] An isochromenone **8**, resulting from two-carbon oxidative annulation, was also isolated in 13% yield (see the Supporting Information for the structure of **8**). [b] Isolated as a 7:1 mixture of *E*:*Z* isomers.



Scheme 4. Reactions of various benzoic acids with 1,3-enyne **2a**. Reactions were conducted with 0.50 mmol of **4b–4g**.

6aa–**6ac** and **6af**–**6ah** in 42–77% yield. These reactions also gave small quantities of other products which could not be readily identified. However, in the reaction with 1,3-enyne **1a**, isochromenone **8**, resulting from two-carbon oxidative annulation, was isolated in 13% yield (see the Supporting Information). *N*-Acetylbenzamide (**5a**) reacted with the same 1,3-enynes to give isoindolinones **7aa**–**7ac** and **7af**–**7ah**, although the yields were often appreciably lower than those of the corresponding reactions of benzoic acids. In the lower-yielding reactions, ^{1}H NMR analysis of the crude mixtures showed that in addition to the annulation products, residual 1,3-enyne and other unidentified products were present. Isoindolinone **7ah** was isolated as a 7:1 mixture of *E*:*Z* isomers.

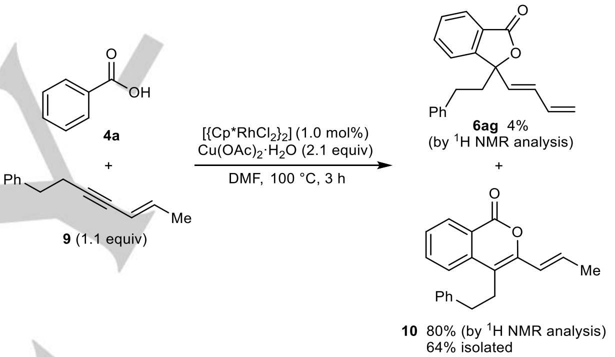
The scope of the process with respect to various benzoic acids was then investigated using 1,3-enyne **2a** (Scheme 4). Electron-donating substituents such as methyl (**6ba**) or methoxy groups (**6ca**) at the *para*-position of the benzoic acid are tolerated, as is an electron-withdrawing nitrile group (**6da**). However, 4-nitrobenzoic acid is poorly effective and gave **6ea** in only 24% yield, along with unreacted starting materials. Benzoic acids with a methyl group at the *meta*- or *ortho*-position are competent substrates (**6fa** and **6ga**), with C–H functionalization occurring at the sterically less-hindered site in the case of **6fa**.



Scheme 5. Reactions of various *N*-acylbenzamides with 1,3-enyne **2a**. Reactions were conducted with 0.50 mmol of **5ba–5ga**. [a] Isolated as a 6.5:1 mixture of *E*:*Z* isomers.

The reactions of 1,3-enyne **2a** with a range of *N*-acylbenzamides gave results similar to those with the benzoic acids (Scheme 5, compare with Scheme 4). However, *N*-acetyl-4-nitrobenzamide is superior to 4-nitrobenzoic acid, as shown by the formation of isoindolinone **7da** in 50% yield (albeit as a 6.5:1 mixture of *E*:*Z* isomers). A substrate with an *N*-crotonoyl substituent reacted successfully to give isoindolinone **7ga** in 41% yield.

To confirm the structural requirements in the 1,3-enyne for efficient one-carbon annulation to occur, representative substrate **4a** was reacted with 1,3-enyne **9**, which lacks allylic hydrogen atoms *cis* to the alkyne [Eq. (1)]. ^{1}H NMR analysis of the crude mixture using an internal standard showed the formation of two-carbon annulation product **10** in 80% yield,[16] and isobenzofuranone **6ag** in 4% yield. Purification of the mixture led to isolation of **10** in 64% yield. This experiment demonstrates that allylic hydrogen atoms *cis* to the alkyne in the 1,3-enyne are important for efficient one-carbon annulation, which in turn provides further support for 1,4-rhodium(III) migration occurring through the intermediacy of rhodacycle **B** (Scheme 1A). The reasons for the formation of small quantities of one-carbon annulation product **6ag** are not clear at this time, but may result from some type of *E*/*Z* isomerization occurring during the reaction.[17]



(1)

Conclusions

We have reported rhodium(III)-catalyzed oxidative annulations of 2-arylphenols, benzoic acids, and *N*-acylbenzamides with 1,3-enynes that contain allylic hydrogen atoms *cis* to the alkyne to give benzopyrans, isobenzofuranones, and isoindolinones, respectively. The key step in these reactions is the 1,4-rhodium(III) migration from an alkenyl position to an allyl position, an allylic C–H activation that constitutes an underexplored method to access electrophilic π-allylrhodium(III) species.[5a,b] This reactivity enables these 1,3-enynes to serve as one-carbon annulation partners rather than two-carbon annulation partners as might otherwise have been expected on the basis of literature precedent.[13] These studies further demonstrate the utility of alkenyl-to-allyl 1,4-rhodium migration as a platform for novel reaction discovery.[3j,k,5a,b] Additional investigations in this area will be reported in due course.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: catalysis · C–H functionalization · enyne · isomerization · rhodium

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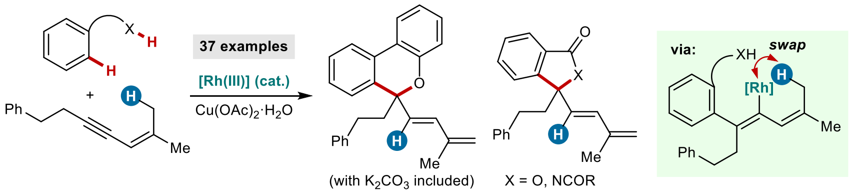
[17] Performing the experiment shown in [Eq. (1)] but omitting benzoic acid (**4a**) led to the recovery of 1,3-enyne **9** with no evidence of *E*/*Z* isomerization into 1,3-enyne **1g** (see the Supporting Information). This observation suggests that if *E*/*Z* isomerization of **9** into **1g** occurs in the experiment shown in [Eq. (1)], benzoic acid is important in generating the species that promotes this isomerization.



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One-Carbon Oxidative Annulations of 1,3-Enynes by Catalytic C–H Functionalization and 1,4-Rhodium(III) Migration

Can’t wait to migrate: Rhodium(III)-catalyzed C–H functionalization–oxidative annulations of aromatic substrates with 1,3-enynes that contain allylic hydrogen atoms *cis* to the alkyne are described. The key step in these reactions is an alkenyl-to-allyl 1,4-rhodium(III) migration to give electrophilic π-allylrhodium(III) species, which are trapped to give benzopyrans, isobenzofuranones, and isoindolinones.