1,4-Rhodium(III) Migration

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All-Carbon [3+3] Oxidative Annulations of 1,3-Enynes by Rhodium(III)-Catalyzed C–H Functionalization and 1,4-Migration**

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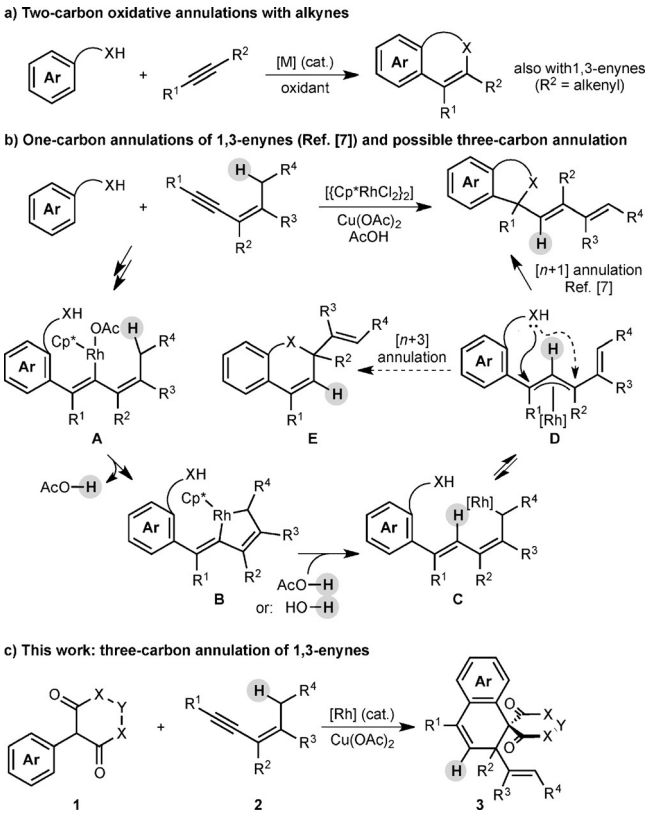
Abstract: *1,3-Enynes containing allylic hydrogens cis to the alkyne function as three-carbon components in rhodium(III)-catalyzed, all-carbon [3+3] oxidative annulations to produce spirodialins. The proposed mechanism of these reactions involves the alkenyl-to-allyl 1,4-rhodium(III) migration.*

Transition metal-catalyzed oxidative annulations of alkynes[1] that proceed by directing group-promoted C(sp^2)–H functionalization[1,2] are versatile methods for heterocycle[3] and carbocycle[4] synthesis. Alkynes, including 1,3-enynes,[5] serve as two-carbon components in these reactions (Scheme 1 a). However, analogous reactions that result in three-carbon annulation are currently underdeveloped,[6] and addressing this shortcoming would expand the range of products accessible using C–H functionalization/oxidative annulation chemistry.

Using rhodium(III) catalysis, we recently discovered a new mode of oxidative annulation of 1,3-enynes that contain allylic hydrogens *cis* to the alkyne, in which they act as one-carbon components (Scheme 1 b).[7] The proposed mechanism[7] involves the 1,4-rhodium(III) migration[8,9] of alkenylrhodium species **A** to give σ-allylrhodium(III) species **C** via rhodacycle **B**. Following isomerization of **C** into the electrophilic π-allylrhodium(III) species **D**, nucleophilic trapping by the directing group gives the product of [*n*+1] annulation. Given the isomerization of **C** into **D**, there exists the possibility for cyclization to occur at a different position of the extended π-system to give **E**, a product of [*n*+3] annulation (Scheme 1 b).[6]

Herein, we describe the realization of this possibility in rhodium(III)-catalyzed reactions of 2-aryl cyclic 1,3-dicarbonyls **1** with 1,3-enynes **2** to give spirodialins **3** (Scheme 1 c). The majority of the products obtained are spirocyclic barbiturates, which are of interest given the well-established medicinal importance of the barbiturate motif, and the biological activity of structurally related spirocycles (Figure 1).[10]



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

During our studies of metal-catalyzed oxidative annulations of alkynes,[4a,b,e,7] the reaction of 5-arylbarbituric acid **1a** with 1,3-enyne **2a** was performed using [{Cp^*RhCl_2}$_2$] (2.5 mol%) and $Cu(OAc)_2 \cdot H_2O$ (2.1 equiv) in dioxane/H_2O

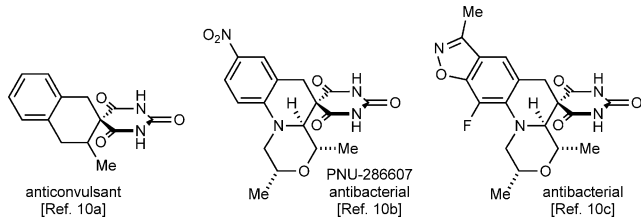


Figure 1. Biologically active spirocyclic barbiturates.

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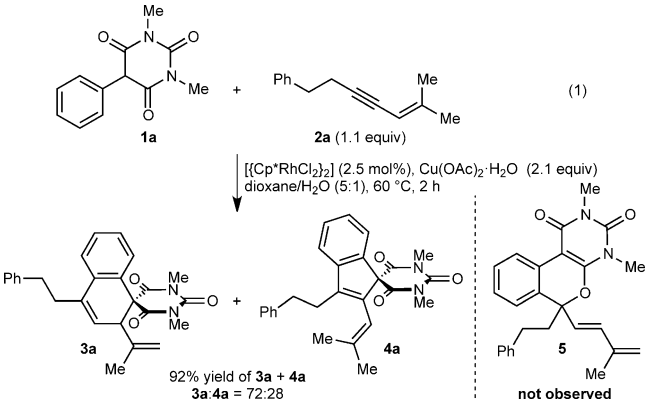
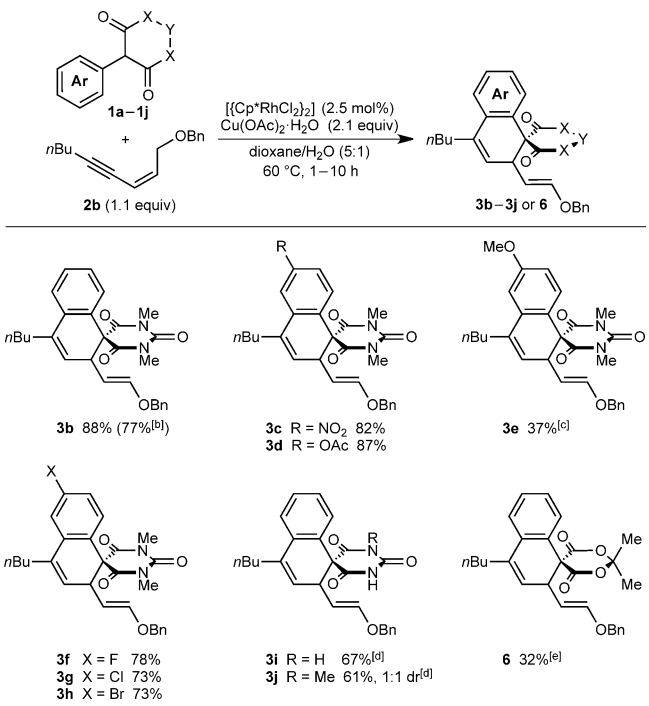
(5:1) at 60 °C [Eq. (1)]. As well as providing the spiroindene **4a** through a standard two-carbon annulation,[4a,b,e] a [3+3] annulation occurred to give spirodialin **3a** as the major product. No one-carbon annulation product **5**[7] was detected. Chromatographic purification gave a 72:28 mixture of **3a** and **4a** in 92 % yield. Without H_2O, more side products were formed and the ratio of **3a**:**4a** decreased to ca. 50:50. No reaction occurred without $Cu(OAc)_2{\cdot}H_2O$.[11]



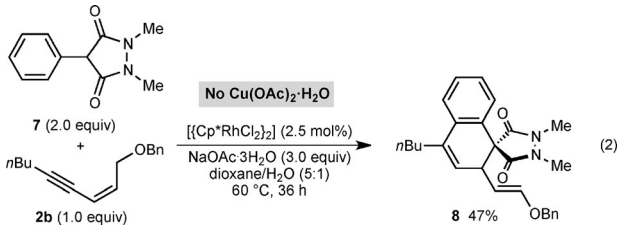
(1)

Further studies revealed the benzyloxy-containing 1,3-enyne **2b** to be superior to **2a**; the reaction of **2b** with **1a** gave spirodialin **3b** only, in 88 % yield as the *E*-isomer (Scheme 2). Reaction of **2b** with various 5-arylbarbituric acids[12] demonstrated compatibility with nitro (**3c**), acetoxy (**3d**), and halogen substituents (**3f**–**3h**) on the aryl group.[13] Spirodialin **3e** was not formed under the standard conditions,[14] but replacing dioxane/H_2O with undried DMF enabled productive [3+3] annulation and isolation of **3e** in 37 % yield, along with several side products.[14] Free N–H groups on the barbituric acids were also tolerated (**3i** and **3j**). In the latter case, **3j** was formed as a 1:1 inseparable mixture of diastereomers. The reaction of 2-phenyl Meldrum's acid also gave [3+3] annulation, but the yield of **6** was only 32 % due to decomposition of the starting material and product under the acidic conditions.[15] Decreasing the loading of $[\{Cp^*RhCl_2\}_2]$ to 0.5 mol % in the reaction of **1a** with **2b** was well-tolerated and provided **3b** in 77 % yield.



Scheme 2. [a] Conducted with 0.50 mmol of **1a**–**1j**. [b] Yield of isolated products. [b] Conducted with 0.5 mol % of $[\{Cp^*RhCl_2\}_2]$. [c] Conducted in undried DMF. Side products were also obtained; see Ref. [14]. [d] Conducted at 120 °C. [e] Conducted with 5 mol % of $[\{Cp^*RhCl_2\}_2]$.

Interestingly, $Cu(OAc)_2{\cdot}H_2O$ rapidly decomposed cyclic hydrazide **7**, precluding its use as the oxidant in the reaction with 1,3-enyne **2b** [Eq. (2)]. However, reaction of **7** (2.0 equiv) with **2b** without $Cu(OAc)_2{\cdot}H_2O$ but with inclusion of $NaOAc{\cdot}3H_2O$ (3.0 equiv) gave spirodialin **8** in 47 % yield, along with **2b** (30 % recovery). We speculate that the N–N bond of **7** could be serving as an oxidant to regenerate the catalyst,[16] but we were unable to isolate the reduced form of **7** to confirm this hypothesis.



(2)

Table 1 presents the results of oxidative annulations of 5-arylbarbituric acids with various 1,3-enynes. No spiroindenes or benzopyrans from two- or one-carbon annulations, respectively, were detected. 1,3-Enynes **2c** and **2d**, containing protected or unprotected 2-hydroxyethyl groups on the alkyne were tolerated (entries 1 and 2). Use of a methoxy group in the 1,3-enyne in place of a benzyloxy group was also possible (entry 3). With a 5-(4-nitrophenyl)-substituted barbituric acid, oxidative annulations with 1,3-enynes **2a**, **2f**, and **2g** containing various groups *trans* to the alkyne proceeded efficiently to give spirodialins **3n**–**3p** in 72–95 % yield (entries 4–6). As with the corresponding one-carbon annulations,[7] the 4-nitrophenyl group favors 1,4-rhodium(III) migration over the formation of spiroindenes [compare with Eq. (1)]. 1,3-Enynes **2h** and **2i** containing cyclic groups were also competent substrates (entries 7 and 8), and spirodialin **3r** was isolated in 57 % yield, despite containing a potentially acid-sensitive enol acetal.

Notably, the formation of a highly sterically hindered spirodialin **3s** containing contiguous all-carbon sp^3 quaternary centers from 1,3-enyne **2j** occurred efficiently [Eq. (3)]. The reaction of **1b** with 1,3-enyne **9**, which does not contain any *cis*-allylic hydrogens, led only to the formation of spiroindene **4b** in 82 % yield, thus highlighting the importance of this structural feature for [3+3] annulation [Eq. (4)].

Scheme 3 depicts a possible catalytic cycle for these reactions, using representative substrates **1a** and **2a**. This cycle is similar to that proposed for the one-carbon annulations we described previously.[7] Cyclorhodation of **1a** with rhodium diacetate **10** would give rhodacycle **11**. Migratory

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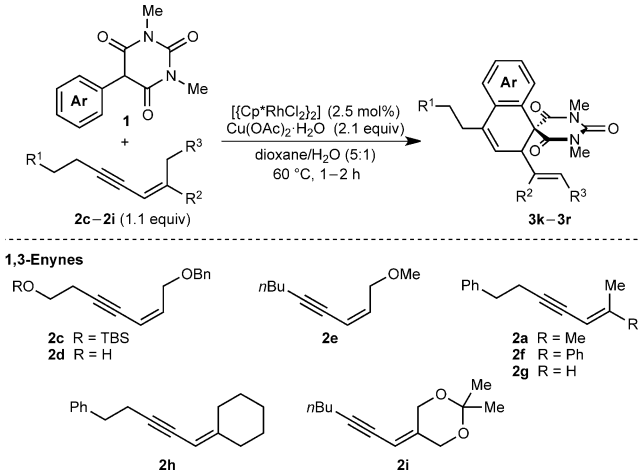
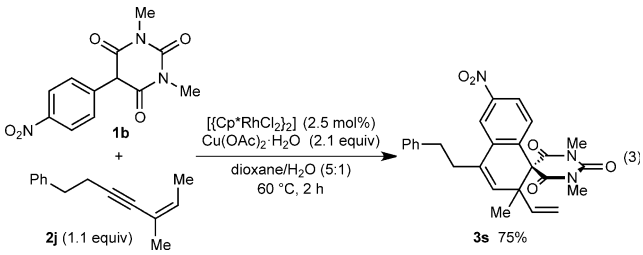
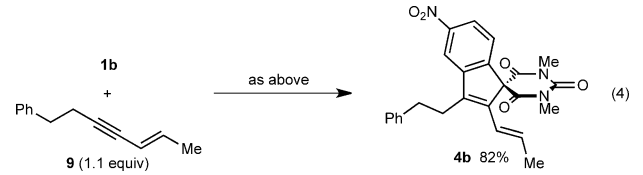
Table 1: [3+3] Oxidative annulations of various 1,3-enynes.[a]

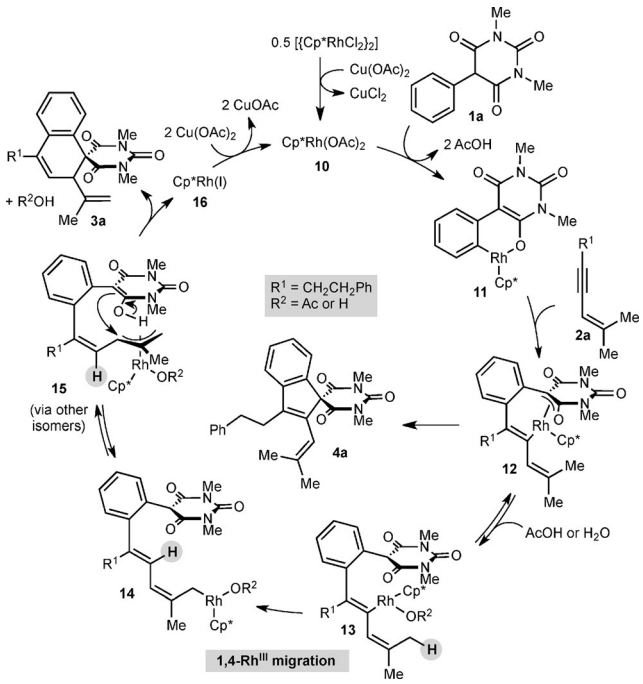


Entry	1,3-Enyne	Product	Yield [%][b]
1	**2c**	**3k** R = TBS	60
2	**2d**	**3l** R = H	64
3	**2e**	**3m**	80
4	**2a**	**3n** R = Me	95
5	**2f**	**3o** R = Ph	78
6	**2g**	**3p** R = H	72
7	**2h**	**3q**	86
8	**2i**	**3r**	57

[a] Conducted with 0.50 mmol of **1**. [b] Yield of isolated products.







Scheme 3. Possible catalytic cycle.

insertion of 1,3-enyne **2a** then provides rhodacycle **12**, which upon reductive elimination would give spiroindene **4a**. However, reversible protonolysis of **12** forms alkenyrhodium species **13**, which can then undergo 1,4-rhodium(III) migration to form σ-allylrhodium(III) species **14**. This intermediate can lead to π-allylrhodium(III) species **15** by a series of σ–π–σ interconversions and *E*/*Z* isomerization. Outer sphere nucleophilic attack of the π-allylrhodium(III) moiety[17,18] of **15** by C5 of the barbituric acid then gives spirodialin **3a** and rhodium(I) species **16**, which undergoes $Cu(OAc)_2$-promoted oxidation to regenerate **10**. The preference of 5-monosubstituted barbituric acids for *C*-allylation over *O*-allylation has been observed previously in Pd-catalyzed asymmetric allylic alkylations.[19] However, an alternative pathway involving an inner-sphere reductive elimination cannot be excluded.

The reaction of **1a** with 1,3-enyne **2k** gave spiroindene **4c** only (Scheme 4), a result that differs from the formation of spirodialins **3b** (Scheme 2) and **3m** (Table 1, entry 3) from 1,3-enynes **2b** and **2e**, respectively. A possible explanation for

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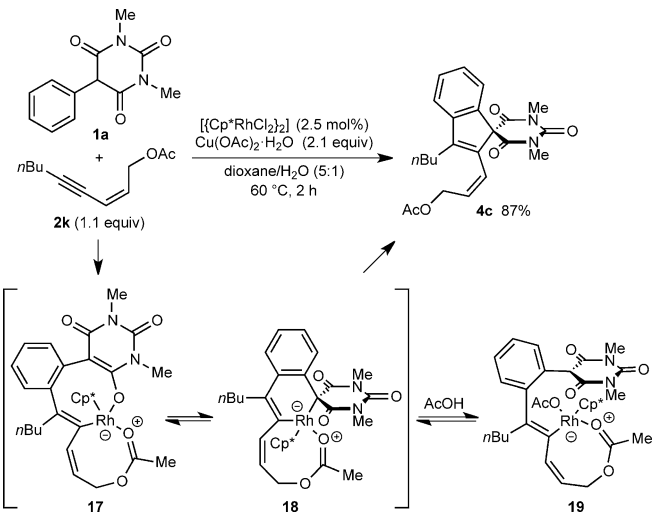
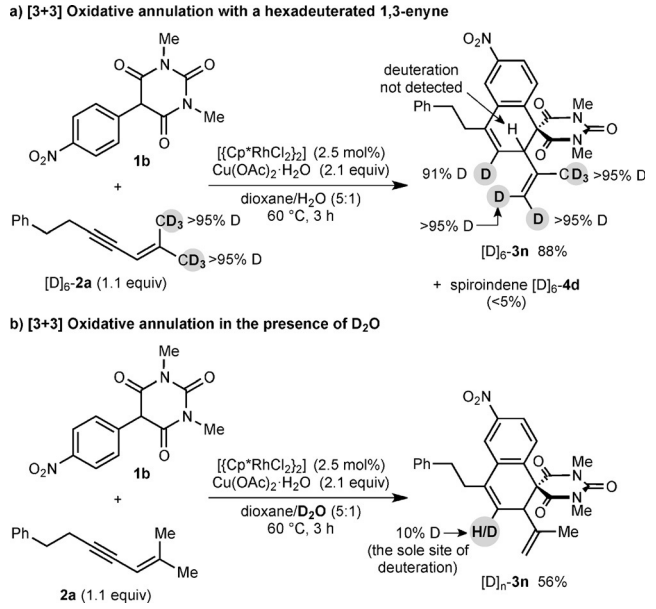


Scheme 4. Formation of spiroindene **4c** from 1,3-enyne **2k**.

this contrasting behavior might be coordination of the acetoxy group to rhodium, resulting in stabilization of 18-electron intermediates such as rhodacycles **17** and **18** (analogous to **12** in Scheme 3, but the σ-haptomers) or alkenylrhodium species **19**. This stabilization likely disfavors 1,4-rhodium(III) migration and leads instead to reductive elimination from **18** to give **4c**.

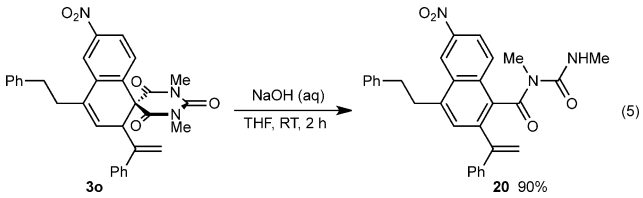
The reaction of **1b** with the hexadeuterated 1,3-enyne $[D]_6$-**2a** gave traces of a spiroindene $[D]_6$-**4d** (< 5%), and spirodialin $[D]_6$-**3n** in 88% yield (Scheme 5a), in which incomplete deuterium transfer (91% D) from the *cis*-allylic position of $[D]_6$-**2a** to the alkenyl position of the dialin ring of $[D]_6$-**3n** was observed. Furthermore, the reaction of **1b** with **2a** in 5:1 dioxane/D_2O led to 10% deuteration at the same position of $[D]_n$-**3n**, with no spiroindene detected (Scheme 5b). These results are similar to the corresponding



Scheme 5. Oxidative annulation with a hexadeuterated 1,3-enyne.

experiments with $[D]_6$-**2a** in the one-carbon annulations reported previously,[7] and are consistent with 1,4-rhodium(III) migration occurring by a concerted metalation-deprotonation/reprotonation sequence (similar to **A** to **C** in Scheme 1b).[7]

Although the spirocyclic barbiturates prepared in this study are themselves of interest, they can be transformed into other compounds. For example, treatment of **3o** with aqueous NaOH in THF gave the highly functionalized naphthalene **20** in 90% yield [Eq. (5)].



(5)

In conclusion, we have reported rhodium(III)-catalyzed, all-carbon [3+3] oxidative annulations of 5-arylbarbituric acids and related compounds with 1,3-enynes containing allylic hydrogens *cis* to the alkyne. This new mode of oxidative annulation further demonstrates the power of alkenyl-to-allyl 1,4-rhodium(III) migration in generating electrophilic allylrhodium species for the construction of polycyclic systems. Other applications of this method of allylmetal generation will be reported in due course.

Keywords: allylation · C—H activation · enynes · homogeneous catalysis · rhodium

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[12] Many of the 5-arylbarbituric acids were prepared by the rhodium(II)-catalyzed direct arylation of 5-diazobarbituric acids, see: D. Best, D. J. Burns, H. W. Lam, *Angew. Chem. Int. Ed.* **2015**, *127*, 7518–7521; *Angew. Chem.* **2015**, *54*, 7410–7413.

[13] The structure of **3h** was confirmed by X-ray crystallography. CCDC 1057433 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[14] Under the standard conditions, an oxidative dimer of 5-(4-methoxyphenyl)-1,3-dimethylbarbituric acid was the sole product. In 5:1 DMF/H_2O, spirodialin **3e** was accompanied by this oxidative dimer and the spiroindene resulting from two-carbon annulation. See the Supporting Information for further details.

[15] Basic additives such as K_2CO_3 (see Ref. [4a]) were detrimental.

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