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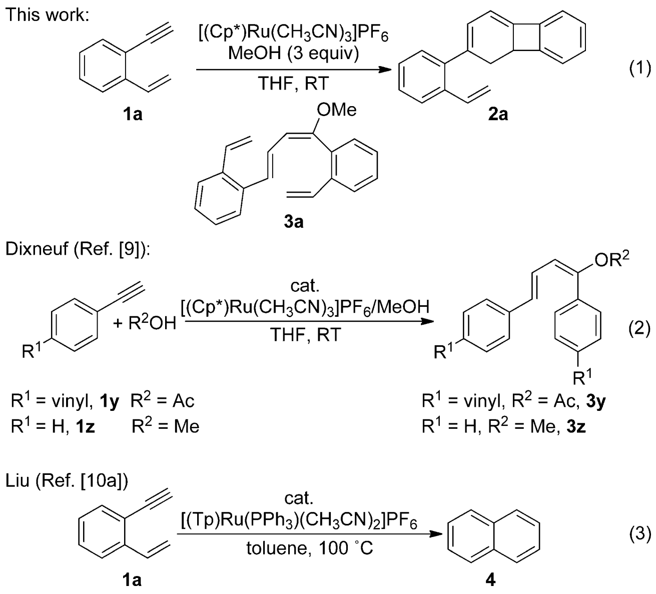
Biphenylenes

Dihydrobiphenylenes through Ruthenium-Catalyzed [2+2+2] Cycloadditions of *ortho*-Alkenylarylacetylenes with Alkynes**

Silvia García-Rubín, Carlos González-Rodríguez, Cristina García-Yebra, Jesús A. Varela, Miguel A. Esteruelas, and Carlos Saá**

Abstract: *A new synthetic route to dihydrobiphenylenes has been developed. The process involves a mild Ru^{II}-catalyzed [2+2+2] dimerization of ortho-alkenylarylacetylenes or its more versatile variant, the Ru-catalyzed [2+2+2] cycloaddition of ortho-ethynylstyrenes with alkynes. Mechanistic aspects of this [2+2+2] cycloaddition are discussed.*

Cyclobutane and benzannulated cyclobut(adi)ene derivatives, including biphenylene, are attractive molecules that can be used as starting materials for chemical synthesis and as spacers and building blocks for functionalized organic materials.[1] In the case of biphenylenes, synthetic methods that rely on ring-closure reactions, in which the cyclobutadiene ring is formed either by dimerization of benzynes[2] or by coupling reactions,[3] have been mainly exploited. However, Vollhardt's studies on the simultaneous formation of two rings by cobalt-catalyzed [2+2+2] cycloaddition of *ortho*-diethynylarenes with alkynes[4] has dominated this field because of the enormous synthetic potential towards [*N*]phenylenes,[5] molecules that contain biphenylene units with unique combinations of aromatic and antiaromatic properties.[6] Typically, most [(Cp)Co^{I}]-catalyzed cocyclizations of *ortho*-diethynylarenes require irradiation and/or heating at relatively elevated temperatures.[7]



Scheme 1. Ru-catalyzed [2+2+2] dimerization of *ortho*-ethynylstyrene (**1a**) to dihydrobiphenylene **2a**. Tp = tris(pyrazolyl)borate.

During our synthetic work towards the formation of 1,4-diaryldienes, required for the investigation of "formal" ruthenium-catalyzed [4+2+2] cycloadditions,[8] we discovered a new route to dihydrobiphenylene **2a** [Scheme 1, Eq. (1)]. This process involves the [2+2+2] dimerization of the starting *ortho*-ethynylstyrene (**1a**, a 1,5-enyne) instead of the expected Dixneuf product, the 1,4-diaryldiene **3a**, derived from head-to-head dimerization of arylacetylenes **1** with trapping of MeOH [Scheme 1, Eq. (2)].[9] Even more strikingly, aromatization to naphthalene (**4**) was not detected in this case, despite it being the thermodynamically favored product often observed on reacting 1,5-arenynes **1** in the presence of other Ru^{II} catalysts [Scheme 1, Eq. (3)].[10]

Herein we present our novel and mild procedure to obtain dihydrobiphenylenes **2** by simple Ru-catalyzed [2+2+2] dimerization of *ortho*-alkenylarylacetylenes **1** (1,5-enynes) in MeOH at room temperature [Scheme 1, Eq. (1) and Table 2] and dihydrobiphenylenes **6** by [2+2+2] cocyclization of **1** with different alkynes **5** (Table 3).[11]

The ruthenium-catalyzed dimerization of **1a** was optimized by systematically changing the reaction parameters (Table 1). On changing the solvent polarity, the catalytic activity changed dramatically (lower reaction yields, longer reaction times, and recovery of the starting material, entries 2 and 3 vs entry 1, Table 1). Removal of MeOH as an additive was also detrimental for the catalytic activity with either THF, acetone, or acetic acid as solvents (entries 4–6, Table 1).[9a,b]

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[*] Dr. S. García-Rubín,[+] Dr. C. González-Rodríguez,[+] Dr. J. A. Varela, Prof. C. Saá
Departamento de Química Orgánica y Centro Singular de Investigación en Química Biológica y Materiales Moleculares (CIQUS)
Universidad de Santiago de Compostela
15782 Santiago de Compostela (Spain)
E-mail: carlos.saa@usc.es
Homepage: http://www.usc.es/gi1603/saa
Dr. C. García-Yebra, Prof. M. A. Esteruelas
Departamento de Química Inorgánica
Instituto de Síntesis Química y Catálisis Homogénea (ISQCH)
Universidad de Zaragoza-CSIC
50009 Zaragoza (Spain)
E-mail: maester@unizar.es

[+] These authors contributed equally to this work.

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Table 1: Optimization of Ru-catalyzed [2+2+2] dimerization of *ortho*-ethynylstyrene (**1a**) to dihydrobiphenylene **2a**.[a]

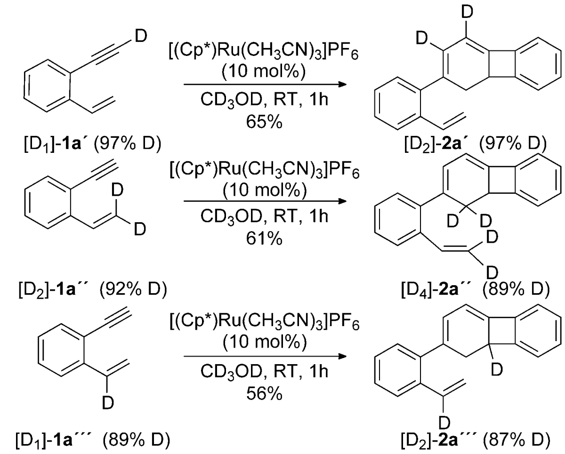
Entry	Catalyst	Solvent	t [h]	Yield [%][b]
1	$[(Cp^*)RuL_3]PF_6$	THF/MeOH (3 equiv)	3	65
2	$[(Cp^*)RuL_3]PF_6$	Acetone/MeOH (3 equiv)	48	36[c]
3	$[(Cp^*)RuL_3]PF_6$	DMF/MeOH (3 equiv)	48	32[c]
4	$[(Cp^*)RuL_3]PF_6$	THF	48	19[c]
5	$[(Cp^*)RuL_3]PF_6$	Acetone	48	14[c]
6	$[(Cp^*)RuL_3]PF_6$	AcOH	48	18[c]
7	$[(Cp^*)RuL_3]PF_6$	MeOH	1	72 (63)[d]
8	$[(Cp^*)RuL_3]PF_6$	EtOH	12	50
9	$[(Cp^*)RuL_3]PF_6$	*i*PrOH	24	38[c]
10	$[(Cp)RuL_3]PF_6$	MeOH	48	21[e]
11	$[(Cp^*)RuCl(cod)]$	MeOH	48	50
12[f]	$[Au(PPh_3)Cl]/AgSbF_6$	MeOH	48	–[g]

[a] Typical reaction conditions: catalyst (10 mol%), RT, [**1a**] = 0.3 M. [b] Yields of isolated products. [c] Minor amounts of **1a** were recovered. [d] Reaction was performed with 1.2 mmol of **1a**. [e] 100 °C. [f] 3 mol% of catalyst was used. [g] 1-(2-Vinylphenyl)ethanone was isolated in 70% yield. L = CH_3CN. cod = 1,5-cyclooctadiene, Cp = cyclopentadienyl, Cp* = pentamethylcyclopentadienyl.

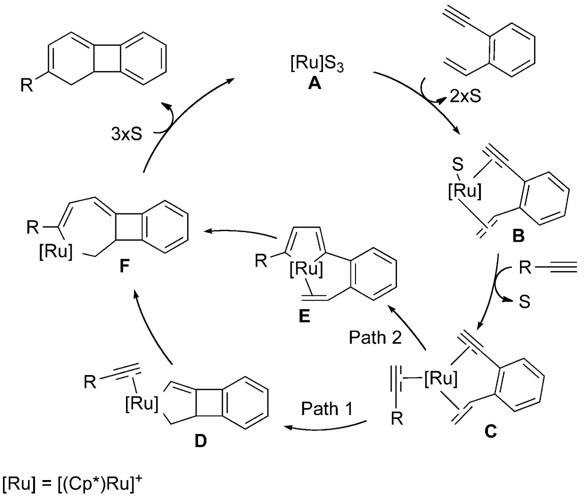
Interestingly, dihydrobiphenylene **2a** was obtained in a fairly good yield (72 %) in just one hour at room temperature when MeOH was used as solvent (entry 7, Table 1).[12] Other alcohols, such as ethanol or *iso*-propanol, were less effective and required longer reaction times to give lower yields (entries 8 and 9, Table 1). Modification of the electronic nature of the catalyst by using the cationic ruthenium catalyst $[(Cp)Ru(CH_3CN)_3]PF_6$ (entry 10) or the neutral ruthenium catalyst $[(Cp^*)RuCl(cod)]$ (entry 11, Table 1) was not beneficial. On the other hand, the use of Au^I and Pt^{II} catalysts under the same conditions did not lead to dimerization, but to alkyne activation of **1a** (ketone, dimethylketal), with the alkene unit remaining untouched (entry 12, Table 1).[13]

Having identified the optimized reaction conditions (entry 7, Table 1), we proceeded to investigate the substrate scope of the dimerization (Table 2). The (*ortho*-alkenyl)phenylacetylenes **1b** and **1c** afforded the corresponding dihydrobiphenylenes **2b** and **2c**, respectively, with moderate to good yields (entries 1 and 2, Table 2).[14] However, internal alkyne 1-(hex-1-yn-1-yl)-2-vinylbenzene (**1d**) failed to react, and the starting material was completely recovered. The electronic nature of the phenyl ring did not appear to have an influence on the course of the reaction, irrespective of the location and electron-richness of the substituents, since the bromo-, methyl-, and methoxy-substituted derivatives **1e–1g** afforded the corresponding dihydrobiphenylenes **2e–g** in rather good yields (entries 3–5, Table 2). Fused aliphatic rings on the *ortho*-ethynylstyrene, that is, **1h** and **1i**, or aromatic rings, such as in naphthyl derivative **1j**, also afforded the corresponding dihydrobiphenylenes **2h–j** in fairly good yields (entries 6–8, Table 2).[15] Notably, the phenyl ring present in **1a** is crucial, because the analogous cyclohexene derivative **7** gave the tetrahydronaphthalene (**8**) in a low yield of 30 % (entry 9, Table 2).[10c] To our surprise, *ortho*-allylphenylacetylene (**9**) also dimerized to give the corresponding dihydrofluorene **10**, albeit in a lower yield despite the decrease in ring strain caused by the formation of the five-membered ring (entry 10, Table 2).

To our delight, not only [2+2+2] dimerizations of *ortho*-alkenylarylacetylenes **1**, but also [2+2+2] cocyclizations with different terminal alkynes **5** were possible to obtain substituted dihydrobiphenylenes **6** in fairly good yields (Table 3). Typically, under optimized conditions (5.0 equivalents of alkynes **5**), parent and electron-rich phenyl-, naphthyl-, and thiophenylacetylenes (**5a–c**, **5e**, and **5f**, respectively) could be cocyclized with *ortho*-ethynylstyrene (**1a**) to give their corresponding dihydrobiphenylenes (**6a–c**, **6e**, and **6f**, respectively) in fairly good yields (entries 1–6, Table 3). On the other hand, electron-rich *ortho*-alkenylarylacetylene **1h** and naphthylenyne **1j** also participated as partners in [2+2+2] cycloadditions with **5a** to afford the corresponding dihydrobiphenylenes **6h** and **6j**, respectively, in quite good yields (entries 7 and 8, Table 3). Interestingly, not only arylacetylenes act as cycloaddition partners; conjugated enyne **5k** smoothly gave dihydrobiphenylene **6k** in an excellent yield (entry 9, Table 3) and even cyclohexylacetylene **5l** (a

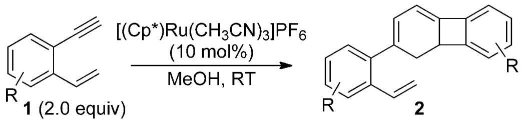


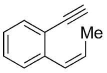
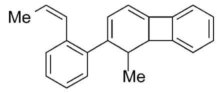
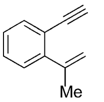
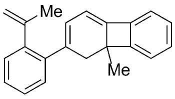
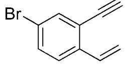
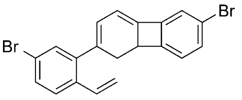
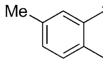
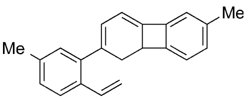
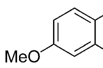
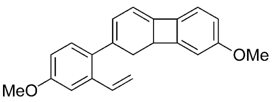
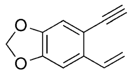
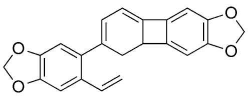
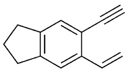
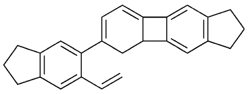
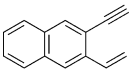
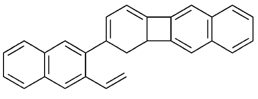
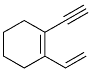
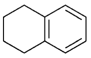
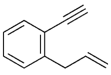
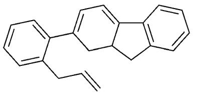
Scheme 2. Deuterium-labeling experiments.



Scheme 3. Catalytic cycle for the Ru-catalyzed [2+2+2] dimerization/cycloaddition of *ortho*-alkenylarylacetylenes with alkynes.

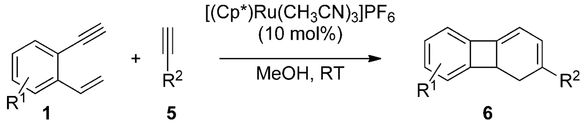
Table 2: Ru-catalyzed [2+2+2] dimerization of *ortho*-alkenylarylacetylenes **1** to dihydrobiphenylenes **2**.[a]

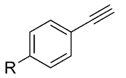
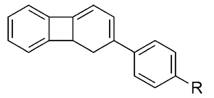
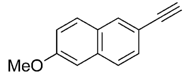
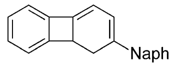
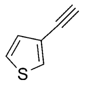
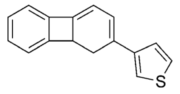
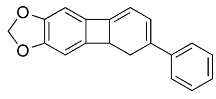
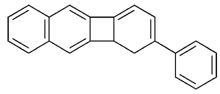
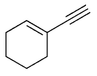
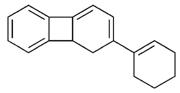
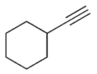
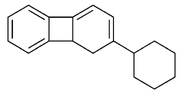


Entry	Substrate		Product		Yield [%][b]
1	**1b**		**2b**		55
2	**1c**		**2c**		63
3	**1e**		**2e**		65
4	**1f**		**2f**		70
5	**1g**		**2g**		64
6	**1h**		**2h**		70
7	**1i**		**2i**		68
8	**1j**		**2j**		82
9	**7**		**8**		30
10	**9**		**10**		33

[a] Typical reaction conditions: [(Cp*)Ru(CH$_3$CN)$_3$]PF$_6$ (10 mol%), RT, 1–2 h. MeOH. [b] Yields of the isolated products.

Table 3: Ru-catalyzed [2+2+2] cocyclization of *ortho*-alkenylarylacetylenes **1** with alkynes **5**.[a]



Entry	Enyne	Alkyne	Dihydrobiphenylene	Yield [%][b,c]
				
1	**1a**	**5a** R=H	**6a** R=H	65[d]
2	**1a**	**5b** R=Me	**6b** R=Me	70[e]
3	**1a**	**5c** R=OMe	**6c** R=OMe	88
4	**1a**	**5d** R=CF$_3$	**6d** R=CF$_3$	26
5	**1a**	**5e** 	**6e** 	90
6	**1a**	**5f** 	**6f** 	55
7	**1h**	**5a**	**6h** 	57
8	**1j**	**5a**	**6j** 	67
9	**1a**	**5k** 	**6k** 	85
10	**1a**	**5l** 	**6l** 	35

[a] Typical reaction conditions: [(Cp*)Ru(CH$_3$CN)$_3$]PF$_6$ (10 mol%), enyne **1** (0.3 mmol), alkyne **5** (1.5 mmol), MeOH (1.5 mL), RT, 1–24 h. [b] Yields of isolated products. [c] Low amounts of the 1,4-diaryldienes **3** (< 5% with respect to **5**) were also isolated in most cases (up to 20% when toluene **5b** was used). [d] The same yield was obtained using 1.2 mmol of **1a**. [e] Yield calculated with trimethoxybenzene as internal standard, 59% yield of isolated product. Naph = 6-methoxy-2-naphthyl.

secondary alkyl-substituted alkyne) gave the corresponding dihydrobiphenylene **6l** in moderate yield (entry 10).

In an effort to gain further insights into the reaction mechanism for this dimerization/cycloaddition process, a series of deuterium-labeling experiments were conducted. When the ruthenium-catalyzed dimerizations of deuterated *ortho*-ethynylstyrenes [D$_1$]-**1a**′, [D$_2$]-**1a**″, and [D$_1$]-**1a**‴ were carried out in CD$_3$OD, deuterium scrambling in dihydrobiphenylenes **2a**′, **2a**″, and **2a**‴ was not observed, with all deuterium atoms located in the same positions as in the corresponding starting materials (Scheme 2).

According to these labeling experiments (Scheme 2), formation of a ruthenium–hydride species followed by sequential insertion of the triple and double bonds can be ruled out.[16] These results can be rationalized according to the catalytic cycle shown in Scheme 3, in which, notably, a less common cationic Ru^{II} catalyst[17] is employed in the [2+2+2] cycloaddition between alkynes and alkenes.[18] Displacement of the solvent molecules from the metal center of **A** by the substrate should lead to the key intermediate **C** via **B**.[19] Subsequently, complex **C** would evolve by intramolecular alkyne–olefin oxidative coupling to give **D** (path 1) or, alternatively, by intermolecular alkyne–alkyne oxidative coupling to afford **E** (path 2).[16] Insertion of the coordinated C≡C bond (path 1) or C=C bond (path 2) into the Ru−C bond should give complex **F**. Finally, reductive coupling would release the dihydrobiphenylenes with concomitant regeneration of the catalytic species.[20]

In summary, we have developed a new and efficient process to access dihydrobiphenylenes. This route involves a mild Ru^{II}-catalyzed [2+2+2] cycloaddition of *ortho*-alkenylarylacetylenes with alkynes. Deuterium-labeling experiments clearly support a catalytic cycle being involved in the

Ru^{II}-catalyzed [2+2+2] cycloaddition of two alkynes with one alkene. More detailed mechanistic studies and further applications are currently being explored.

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[20] As a tentative hypothesis, we believe that MeOH helps to recover the active Ru cationic species by decomplexation of an initial coordinated η^4-diene of dihydrobiphenylene **2**.