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

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Dedication((optional))

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 new [2+2+2] cycloaddition are discussed.

Cyclobutane and benzannulated cyclobut(adi)ene derivatives, including biphenylene, are intrinsically 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 benzyne^[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 due to the enormous synthetic potential towards *N*-phenylenes,^[5] molecules that contain biphenylene units with unique combinations

of aromatic and antiaromatic properties.^[6] Typically, most CpCo(I)-catalyzed cocyclizations of *ortho*-diethynylarenes require irradiation and/or heating at relatively elevated temperatures.^[7]

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 totally unexpected but successful result that provides 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]

Scheme 1. Ru-catalyzed [2+2+2] dimerization of *ortho*-ethynylstyrene **1a** to dihydrobiphenylene **2a**.

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, *i.e.* protic to aprotic, the catalytic

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activity changed dramatically (lower reaction yields, longer reaction times and recovery of the starting material, entries 2–3, 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).^[9a,b] Interestingly, dihydrobiphenylene **2a** was obtained in fairly good yield (72%) in just one hour at room temperature when MeOH was used as solvent (entry 7).^[12] Other alcohols, such as ethanol or *iso*-propanol, were less effective and required longer reaction times to give lower yields (entries 8–9). Modification of the electronic nature of the catalyst by using the cationic ruthenium catalyst [Cp*Ru(CH₃CN)₃]PF₆ (entry 10) or the neutral ruthenium catalyst [Cp*RuCl(COD)] (entry 11) was not beneficial. On the other hand, Au(I) and Pt(II) catalysts, under the same conditions, did not lead to dimerization but gave alkyne activation products of **1a** (ketone, dimethylketal), with the alkene unit remaining untouched (entry 12).^[13]

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

Entry	Catalyst	Solvent	Time	Yield (%) ^[b]
1	[Cp*RuL ₃]PF ₆	THF/MeOH (3 equiv)	3 h	65
2	[Cp*RuL ₃]PF ₆	Acetone/MeOH (3 equiv)	48 h	36 ^[c]
3	[Cp*RuL ₃]PF ₆	DMF/MeOH (3 equiv)	"	32 ^[c]
4	[Cp*RuL ₃]PF ₆	THF	"	19 ^[c]
5	[Cp*RuL ₃]PF ₆	Acetone	"	14 ^[c]
6	[Cp*RuL ₃]PF ₆	AcOH	"	18 ^[c]
7	[Cp*RuL ₃]PF ₆	MeOH	1 h	72 (63) ^[d]
8	[Cp*RuL ₃]PF ₆	EtOH	12 h	50
9	[Cp*RuL ₃]PF ₆	<i>i</i> -PrOH	24 h	38 ^[c]
10	[CpRuL ₃]PF ₆	MeOH	48 h	21 ^[e]
11	[Cp*RuCl(COD)]	MeOH	"	50
12 ^[f]	AuPPh ₃ Cl/AgSbF ₆	MeOH	"	– ^[g]

[a] Typical reaction conditions: [Cp*Ru(CH₃CN)₃]PF₆ (10 mol %), rt, [**1a**] = 0.3 M.

[b] Yields of the isolated products. [c] Minor amounts of **1a** were recovered. [d] Reaction performed with 1.2 mmol of **1a**. [e] 100 °C. [f] 3 mol% of catalyst. [g] 1-(2-Vinylphenyl)ethanone was isolated in 70% yield. L = CH₃CN

Having identified the optimized reaction conditions (entry 7), we proceeded to investigate the substrate scope of the dimerization (Table 2). We observed that terminal *cis*- and internal methyl mono-substituted (*ortho*-alkenyl)phenylacetylenes **1b** and **1c** afforded the corresponding dihydrobiphenylenes **2b** and **2c**, respectively, with moderate to good yields (entries 1 and 2).^[14] However, internal alkyne 1-(hex-1-yn-1-yl)-2-vinylbenzene (**1d**) failed to react with total recovery of starting material. 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 richness of the substituents, since the bromo-, methyl- and methoxy- derivatives **1e–1g** afforded the corresponding dihydrobiphenylenes **2e–g** in rather good yields (entries 3–5). Fused aliphatic rings on the *ortho*-ethynylstyrene, *i.e.* **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).^[15] Notably, the importance of the phenyl ring present in **1a** is crucial since the analogous cyclohexene derivative **7** gave the tetrahydronaphthalene **8** in a low 30% (entry 9).^[10c] To our initial surprise, *ortho*-allylphenylacetylene **9** also dimerized to give the corresponding dihydrofluorene **10**, albeit in lower yield in spite of the decrease in ring strain caused by the formation of the five-membered ring (entry 10).

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

Entry	Substrate	Product	Yield (%) ^[b]
1			55
2			63
3			65
4			70
5			64
6			70
7			68
8			82
9			30
10			33

[a] Typical reaction conditions: [Cp*Ru(CH₃CN)₃]PF₆ (10 mol %), rt, 1–2 h. MeOH. [b] Yields of the isolated products.

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 performed to obtain substituted dihydrobiphenylenes **6** in fairly good yields (Table 3). Typically, under optimized conditions (5.0 equiv of alkynes **5**), parent and electron-rich phenyl-, naphthyl- and thiophenylacetylenes **5a–c,e–f**,

respectively, could be cocyclized with *ortho*-ethynylstyrene **1a** to give fairly good yields of their corresponding dihydrobiphenylenes **6a–c**, **e–f** (Table 3, entries 1–3). On the other hand, electron-rich and naphthylenes **1h** and **1j** also participated as partners in [2+2+2] cycloadditions with **5a** to afford the corresponding dihydrobiphenylenes **6h** and **6j** in quite good yields (entries 4–5). Interestingly, not only arylacetylenes act as cycloaddition partners since conjugated enyne **5k** smoothly gave an excellent yield of the dihydrobiphenylene **6k** (entry 6) and even cyclohexylacetylene **5l** (a secondary alkyl-substituted alkyne) gave the corresponding dihydrobiphenylene **6l** in moderate yield (entry 7).

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 5b , R = Me 5c , R = OMe 5d , R = CF ₃	6a , R = H 6b , R = Me 6c , R = OMe 6d , R = CF ₃	65 (6a) ^[d] 70 (6b) ^[e] 88 (6c) 26 (6d)
2	1a	5e	6e Naph = 6-methoxy-2-naphthyl	90
3	1a	5f	6f	55
4	1h	5a	6h	57
5	1j	5a	6j	67
6	1a	5k	6k	85
7	1a	5l	6l	35

[a] Typical reaction conditions: [Cp*Ru(CH₃CN)₃]PF₆ (10 mol %), enyne **1** (0.3 mmol), alkyne **5** (1.5 mmol), MeOH (1.5 mL), rt, 1–24 h. [b] Yields of the isolated products. [c] Low amounts of the 1,4-diaryldienes **3** (< 5% respect to **5**) were also isolated in most cases (up to 20% when toluene **5b** was used). [d]

Same yield obtained using 1.2 mmol of **1a**. [e] Yield calculated with trimethoxybenzene as internal standard, 59% isolated yield.

In an effort to gain further insights into the reaction mechanism for this dimerization/cycloaddition process, a series of deuterium labelling experiments were conducted. When the ruthenium catalyzed dimerization of deuterated *ortho*-ethynylstyrenes **1a'**-d₁, **1a''**-d₂ and **1a'''**-d₁ was carried out in CD₃OD, 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).

Scheme 2. Deuterium labelling experiments.

According to these labelling 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 **I** by the substrate should lead to the key intermediate **III** via **II**.^[19] Subsequently, complex **III** would evolve by intramolecular alkyne-olefin oxidative coupling to give **IV** (path A) or, alternatively, by intermolecular alkyne-alkyne oxidative coupling to afford **V** (path B).^[16] Insertion of the coordinated C-C triple bond (path A) or C-C double bond (path B) into the Ru-C bond should yield complex **VI**. Finally, reductive coupling would release the dihydrobiphenylenes with concomitant regeneration of the catalytic species.^[20]

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

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 labelling 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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Biphenylenes

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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 new [2+2+2] cycloaddition are discussed.