Ruthenium Carbene Mediated [2+2+2] Cyclotrimerizations

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Dedicated to Prof. José Barluenga on the occasion of his 70th birthday

Abstract: Second-generation Grubbs' catalyst and Hoveyda–Grubbs' catalyst are able to catalyze both crossed [2+2+2] cyclotrimerization of diynes with alkynes and di- or trimerizations of diynes. Selection of the reaction conditions allows us to favor one particular process. The process is selective when applied to unsymmetric diynes.

Key words: cyclization, ruthenium, carbenes, alkynes, arenes

Multisubstituted benzenes and pyridines have traditionally been synthesized by aromatic electrophilic substitution. As an elegant alternative, the [2+2+2]-cycloaddition reaction of alkynes is remarkable because it is atom efficient and group tolerant and involves the formation of several C–C bonds in a single step.[1] Cyclotrimerization of acetylenes is catalyzed by a variety of transition-metal catalyst, being $CpCo(CO)_2$ one of the most commonly utilized.[2]

Other extensively used catalysts are $[IrCl(cod)]_2$, $Ni(cod)_2$, and much commonly rhodium complexes such as Wilkinson's catalyst, $[RhCl(PPh_3)_3]$, or other RhL_n complexes which are becoming the catalyst of choice in many recent applications. Ruthenium catalyst such as [Cp*RuCl(cod)] are able to catalyze trimerization of alkynes,[3] and are useful in the [2+2+2] cycloaddition of 1,6-diynes with nitriles, isocyanates, and isothiocyanates to afford pyridines, bicyclic pyridones, and thiopyridones in good yields.[4]

There are a few precedents in using Grubbs' first-generation catalyst **[Ru]-I** to mediate in cyclotrimerization [2+2+2] reactions. Blechert et al. reported for the first time that **[Ru]-I** is an efficient catalyst for the intramolecular cyclotrimerization of alkynes. A cascade metathetic mechanism is postulated in these examples where vinyl carbene complexes would be the reactive intermediates.[5] Roy and Das prepared a carbohydrate derivative by a **[Ru]-I**-catalyzed cyclotrimerization of a terminal alkyne.[6] Certain 1,6-diynes were crossed cyclotrimerized with alkynes with **[Ru]-I**,[7] and this catalyst has been used in solid supported cyclotrimerizations[8] and in the synthesis of indacenes from triynes.[9]

On the other hand, second-generation Grubbs catalysts **[Ru]-II**, and reusable Hoveyda–Grubbs complex **[Ru]-III**, have not been used for these cyclotrimerizations.

We present here the synthesis of functionalized polycycles through an easy experimental procedure based on **[Ru]-III** and **[Ru]-I** catalysts.

In order to optimize the reaction, dipropargyl ether **1a** was reacted with phenylacetylene under a variety of reaction conditions (Table 1). The first tests were carried out in toluene with 2 mol% of catalyst **[Ru]-III** and 3 equivalents of phenylacetylene. They showed the need for heating up to 60 °C to reach moderate yields of product **2a** (entries 1 and 2, Table 1). The reaction was complete after 16 hours (TLC). Increasing the concentration of diyne up to 1.25 M allowed a better yield while the amount of dimerization product **3a** was only slightly higher (entries 2–5). A reaction in a sealed tube (entry 6) at 95 °C showed no improvement in yield. The need to use an excess of alkyne was verified under conditions of entry 7, where a reaction with one equivalent of phenylacetylene provided a low yield of **2a**, with **3a** being the major product in this case. Increasing to 5 equivalents of alkyne did not lead to a significant improvement (entry 8). The next study was the selection of the best solvent (entries 9–14). Polar solvents revealed a better performance, with acetone providing the best yield of **2a** (88%) and selectivity as neither starting material nor product **3a** were detected in the crude mixture (entry 10). Reaction time could be reduced to 30 minutes without significant decrease in yields (entry 15), although further reduction to 5 minutes resulted in a 77% yield of **2a** and the presence of the starting diyne in the crude mixture (entry 16). Using a lower catalyst loading (1 mol%) in acetone led to an important decrease in yields (entry 17). Finally, for comparison reasons, we used our best conditions (1.25 M of diyne, 3 equiv of alkyne, in acetone at 60 °C, reaction time 30 min), with Grubbs catalysts **[Ru]-I** and **[Ru]-II** (entries 18 and 19), showing poor performance of these catalysts in terms of both yield and selectivity.

Once the best conditions for the crossed cyclotrimerization of diynes with alkynes were selected, we studied the scope of the process reacting different diynes with alkynes (Table 2).[11] Dipropargyl ether **1a** reacted smoothly with terminal alkynes such as propargyl alcohol. Although this reagent gave a better yield when protected as silyl ether (entry 1), the presence of the free hydroxy group did not prevent the reaction from taking place (entry 2). Hex-1-

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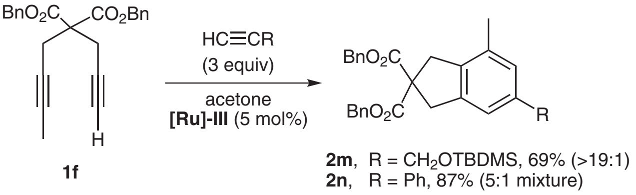
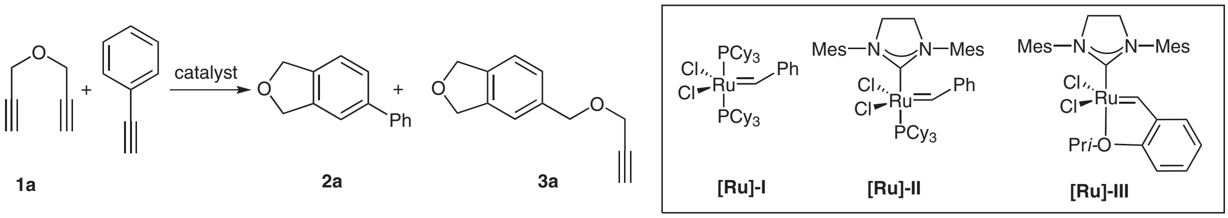
yne gave a good yield of the corresponding arene **2d**. On the other hand, internal alkynes such as hex-3-yne and electron-poor alkynes like ethyl propiolate reacted poorly, giving low yields of the desired arenes **2e** and **2f**, respectively (entries 4 and 5). Then we studied the behavior of other diynes. Dibenzyloxycarbonylhepta-1,6-diyne (**1b**) gave the best results of the whole study and a possible explanation for this is the presence of a favorable Thorpe–Ingold effect (entries 7–9). Thus, we obtained excellent yields of **2g** and **2h** whereas the reaction with 3-hexyne gave a much lower yield of **2i** although better than with dipropargyl ether (compare entries 4 and 9). Protected amino diynes **1c** and **1d**[10] gave moderate yields of the corresponding arenes **2j–k** with a better performance of the 2,4-dimethoxybenzyl (DMB)-protected compound. No dimeric product was detected in these reactions (entries 10 and 11). Finally the procedure was tested with a nonterminal diyne **1e**, which gave an excellent yield of **2l** in the reaction with phenylacetylene (entry 12).

Next, we addressed the problem of regioselectivity. Thus diyne **1f** was reacted with two different alkynes under the



Scheme 1 Synthesis of arenes **2m** and **2n**

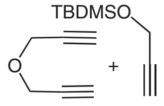
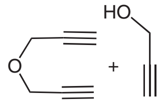
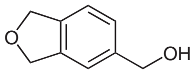
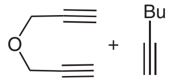
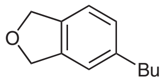
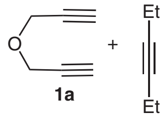
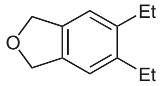
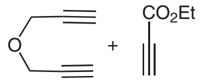
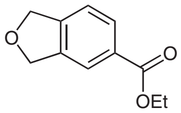
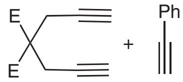
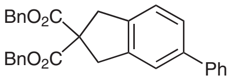
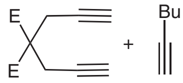
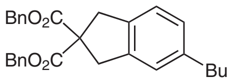
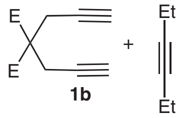
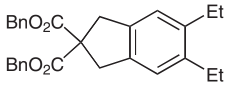
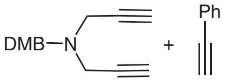
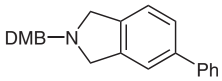
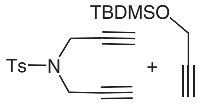
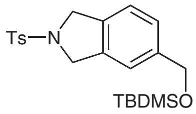
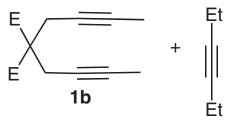
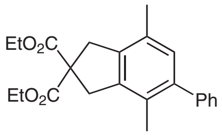
Table 1 Selection of Reaction Conditions for the Crossed Cyclotrimerization Reaction of **1a** with Phenylacetylene



Entry	Alkyne (equiv)	Concn of diyne (M)	Solvent	Temp (°C)[a]	Time (h)	Cat. (mol%)	Yield of **2a** (%)	Yield of **3a** (%)
1	3	1	toluene	0	16	2	20	6
2	3	0.1	toluene	60	16	2	42	<5
3	3	0.25	toluene	60	16	2	58	5
4	3	0.75	toluene	60	16	2	55	8
5	3	1.25	toluene	60	16	2	61	12
6[a]	3	0.25	toluene	95	16	2	59	23
7	1	1.25	toluene	60	16	2	11	48
8	5	1.25	toluene	60	16	2	62	11
9	3	1.25	benzene	60	16	2	60	22
10	3	1.25	acetone	60	16	2	88	n.d.
11	3	1.25	dioxane	60	16	2	64	23
12	3	1.25	DCE	60	16	2	79	15
13	3	1.25	DMF	60	16	2	70	17
14	as solvent	1.25	–	60	16	2	77	6
15	3	1.25	acetone	60	0.5	2	86	<5
16	3	1.25	acetone	60	5 min	2	77	<5
17	3	1.25	acetone	60	16	1	57	35
19[b]	3	1.25	acetone	60	0.5	2	55	7
20[c]	3	1.25	acetone	60	0.5	2	60	22

[a] Reaction was conducted in a sealed tube.
[b] With **[Ru]-I** as catalyst.
[c] With **[Ru]-II** as catalyst.

Table 2 Scope of the Crossed Cyclotrimerization Reaction

Entry	Reagents	Product	Yield of **2** (%)[a]	Yield of **3** (%)[a]
1	 **1a**		**2b** 80	**3a** 17
2	 **1a**		**2c** 55	**3a** 16
3	 **1a**		**2d** 78	**3a** 5
4	 **1a**		**2e** 19	**3a** <5
5	 **1a**		**2f** 5	–
7	 **1b**		**2g** 83	–
8	 **1b**		**2h** 86	–
9	 **1b**		**2i** 28	**3b** 11
10	 **1c**		**2j** 61	<5
11	 **1d**		**2k** 47	–
12	 **1b**		**2l** 98	–

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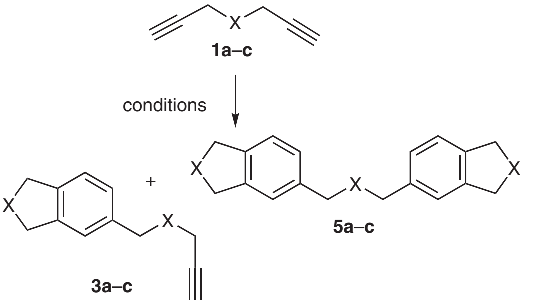
[a] Yield (%) of pure product.

optimized reaction conditions (Scheme 1). Both reactions gave the desired arenes **2m**,**n** in excellent yields. While the crossed cyclotrimerization of **1f** with protected propargyl alcohol produced only the *meta* product **2m**, the parent reaction with phenylacetylene gave a 5:1 mixture of *meta*/*ortho* regioisomers. Major compound **2n** was separated and characterized.[11] This *meta* selectivity is in agreement with previous studies[5,7] with **[Ru]-I**, where a metathetic cascade is claimed as the mechanism and thus the less hindered *meta* isomer is favored.

Finally, as the synthesis of dimeric products such as **3a** could be interesting, the reaction conditions were tuned to allow the synthesis of these compounds. Thus, diyne **1a** was reacted under different reaction conditions (Table 3). The concentration and reaction temperature were critical to drive the competition between the formation of dimer **3a** and trimer **5a**. The concentration of substrate was fixed at 1 M as higher concentrations produced large amounts of a polymeric material, thereby decreasing the yields (entries 1–4). The temperature that optimized yields in **3a** was 10 °C (entry 5).[12] A reaction with **Ru-II** was carried out for comparative reasons, and gave poorer results and an increase in the amount of **5a** (entry 7). In addition, in view of the good results obtained in the synthesis of highly substituted aromatic rings with **[Ru]-I** we envisioned the possibility of obtaining **5a** as the major product if this latter catalyst is used. Indeed, the reaction of **1a** with **[Ru]-I** gave a 52% yield of **5a** and only a 23% of **3a** (entry 8). The two best conditions for the synthesis of both products were used with diynes **1b**,**c**. However, **1b** gave only a moderate yield of dimer **3b** (38%, entry 9), under **[Ru]-III** catalysis at 10 °C with formation of 22% of **5b**, whereas with **[Ru]-I** we achieved a low yield of the latter compound (32%, entry 10). Raising the reaction temperature to 60 °C allowed the formation of **5b** in 60% yield, along with only 7% yield of **3b** (entry 11). Finally, diyne **1c** gave the corresponding dimer **3c** in 51% yield along with 16% of trimer **5c** under **[Ru]-III** catalysis at 60 °C (entry 12). The reaction with **[Ru]-I** at this temperature gave a 14% yield of **3c** but only 23% of **5c** (entry 13).

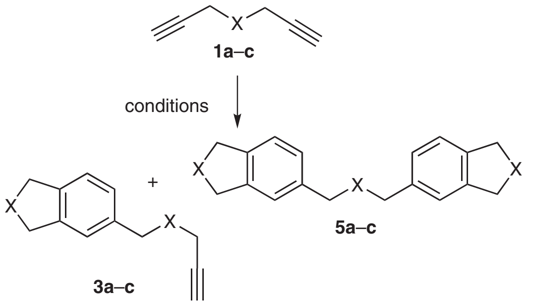
Table 3 Dimerization and Trimerization of Compounds **1**[a]



Entry	Catalyst[a]	X	Concn (M)	Temp (°C)	3a–c[b]	5a–c[b]
1	**[Ru]-III**	O	1	–10	20	2
2	**[Ru]-III**	O	2	–10	37	2
3	**[Ru]-III**	O	2	0	3	n.d.
4	**[Ru]-III**	O	4	0	11	3
5	**[Ru]-III**	O	1	10	55	6
6	**[Ru]-III**	O	1	20	32	5
7	**[Ru]-II**	O	1	10	40	16
8	**[Ru]-I**	O	1	10	23	52
9	**[Ru]-III**	$(BnO_2)_2C$	1	10	38	22
10	**[Ru]-I**	$(BnO_2)_2C$	1	10	11	32
11	**[Ru]-I**	$(BnO_2)_2C$	1	60	7	60
12	**[Ru]-III**	NDMB	1	60	51	16
13	**[Ru]-I**	NDMB	1	60	14	23

[a] For all reactions: reaction time: 16 h; 5 mol% cat. loading, toluene.
[b] Yield (%) of pure product.

Table 3 Dimerization and Trimerization of Compounds **1**[a]



In conclusion, we have achieved a new protocol for crossed diyne–alkyne cyclotrimerizations mediated by Hoveyda–Grubbs complex **[Ru]-III**. This catalytic protocol offers an efficient access to substituted arenes. For highly substituted arenes, complex **[Ru]-I** gives better results. In addition, we have optimized conditions for the synthesis of diyne dimers and trimers using alternatively the two Grubbs complexes.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(10) Diynes **1b**, **1d**, and **1e** were prepared by known procedures. Compound **1b**: (a) Shibata, T.; Yamashita, K.; Katayama, E.; Takagi, K. *Tetrahedron* **2002**, *58*, 8661. Compound **1d**: (b) Kang, S.-K.; Baik, T.-G.; Nulak, A. N.; Ha, Y.-H.; Lim, Y.; Park, J. *J. Am. Chem. Soc.* **2000**, *122*, 11529. Compound **1e**: (c) Sylvester, K. T.; Chirik, P. K. *J. Am. Chem. Soc.* **2009**, *131*, 8772. (d) For details on the preparation of **1c** and **1f**, see Supporting Information.

(11) Ratio of isomers calculated by integration of well resolved signals in the ^{1}H NMR spectrum of the reaction crude

(12) The work up of this reaction (entry 5, Table 3) allowed the recovery of 50% of the catalyst used.