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Sequential Rhodium-Catalyzed Stereo- and Regioselective Addition of Organoboron Derivatives to the Alkyl 4-Hydroxy-2-Alkynoates/Lactonizaction Reaction

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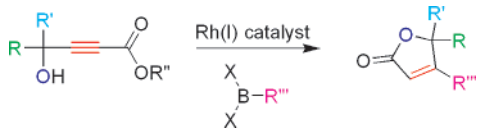

The sequential rhodium-catalyzed addition/lactonization reaction of organoboron derivatives to alkyl 4-hydroxy-2-alkynoates would constitute a novel methodology for the synthesis of 4-aryl/heteroaryl/vinyl-2(5*H*)-furanones with an excellent control of the regio- and chemoselectivity. The role played by rhodium precatalyst, ligands, reaction medium, and the feature of organoboron derivatives has been explored.

Introduction

Compounds containing the 2(5*H*)-furanone moiety are important synthetic targets[1] due to their presence as a subunit in many natural products[2] and, more precisely, they may play a significant role in the discovery of new therapeutic agents. A series of 3-aryl-5-substituted-2(5*H*)-furanones related to incrustoporine, a natural compound isolated from the extract of fermentation of the basidiomycete *Incrustoporia carneola*, are especially valuable as wide-spectrum antifungal agents.[3] 4-Substituted 2(5*H*)-furanone is a subunit in Rubrolides B, a family of biologically active marine ascidian (tunicate) metabolites that have been isolated from *Ritterella Rubra*, and *Synoicum bolchmanni*, which are potent antibiotics and show selective inhibition of protein phosphatases 1 and 2A, significant cytotoxicity against P-388 suspension cultures of mouse lymphoid neoplasm and monolayer cultures of human lung carcinoma (A-549), human colon carcinoma (HT-29), and human melanoma (Mel-28).[4] Compounds containing the 2(5*H*)-furanone scaffold have also been evaluated as insecticides, herbicides, seed plant regulators, allergy inhibitors, cyclooxygenase inhibitors, and phospholipase A_2 inhibitors.[5] 4-(1-Alkynyl)-2(5*H*)-furanones were found to exhibit potent cytotoxicity.[6] As valuable synthetic intermediates, 2(5*H*)-furanones are frequently utilized as key intermediates to construct complex molecules[7] and also appear as a substructure in peptide analogues and HIV-1 protease

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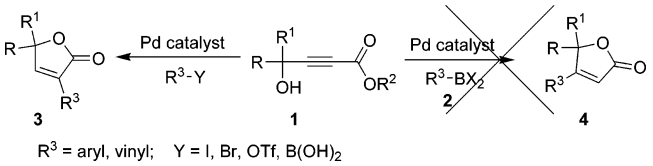
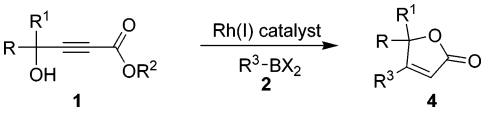
inhibitors.[8] Because of their importance in both chemical and pharmaceutical research, a number of syntheses of 2(5*H*)-furanones have been reported[9] and many of them rely upon transition metal-catalyzed methodologies. Among them, ruthenium-catalyzed carbonylative cyclization of allenols[10] and enyne methatesis[11] resulted as valuable synthetic procedures. Cross-coupling reaction such as Sonogashira,[12] Stille,[6,13] and Suzuki−Miyaura[14] reactions have been studied. Cyclization of allenic acid derivatives and (*Z*)-enynols provides the title compounds by means of the catalysis of Ag(I),[15] Au (III),[16] and Pd(II).[17] Access to the 2(5*H*)-furanone skeleton can be accomplished through palladium-mediated cyclization−carbonylation[18] or coupling−cyclization[19] reactions of propargylic esters. Palladium-catalyzed reaction of unsaturated triflates and halides with methyl-4-hydroxy-2-butenoate and its tetrahydropyranyl derivative afforded 4-aryl- and 4-vinyl-2(5*H*)-furanones through an in situ vinylic substitution/annulation sequence.[20] As part of an ongoing program, devoted to the use of transition metal catalyzed reactions of alkynes bearing proximate suitable functionalities to obtain cyclic derivatives,[21] some of us have been involved in the development of a regioselective synthesis of 3-aryl- and 3-vinylfuran-2(5*H*)-ones **3** through sequential palladium-catalyzed hydroarylation and hydrovinylation/lactonization reactions of alkyl 4-hydoxy-2-alkynoates **1** with aryl/vinyl halides/triflates.[22] Subsequently, this methodology has been extended by Oh and co-workers[23] for the use of organoboronic acids for palladium-catalyzed arylative lactonizations of **1**. Organoboron reagents offer significant advantages. They are easily accessed by a variety of routes and the inorganic byproducts of the reaction with boron derivatives are nontoxic and can be removed by simple workup procedures. However, the regioselectivity control of the reaction resulted in a dramatic influence by the reaction conditions, features of the substrates and the catalytic system. Moreover, conversely to the easy accomplishment of the synthesis of 3-substituted-2(5*H*)-furanones **3**, the regioselective control required to generate 4-substituted-2(5*H*)-furanones **4** as an exclusive regioisomer through the sequential palladium-catalyzed addition of organoboron derivatives **2** to alkyl 4-hydroxy-2-alkynoates **1**/lactonization reactions has not been accomplished (Scheme 1).

SCHEME 1



SCHEME 2



Regioselective hydroarylation/hydrovinylation of β-(2-aminophenyl)-α,β-ynones with arylboronic acids or potassium aryl and vinyl trifluoroborates in the presence of Rh(acac)(C_2H_2)/dppf as catalyst, followed by heterocyclization accomplished the synthesis of functionalized 4-aryl and 4-vinylquinolines.[24] Consequently, it was thought that Rh(I)-catalyzed addition of organoboron derivatives **2** to alkyl 4-hydoxy-2-alkynoates **1** (Scheme 2) would allow the regioselective formation of 4-substituted-2(5*H*)-furanones **4**.

The Rh(I)-catalyzed reaction of alkyl 4-hydoxy-2-alkynoates **1** with organoboron derivatives **2** was then investigated. The detailed report of the results obtained follows.

Results and Discussion

Since Miyaura et al.[25] demonstrated in 1997 that arylboronic acid may be add efficiently to Michael acceptors in the presence

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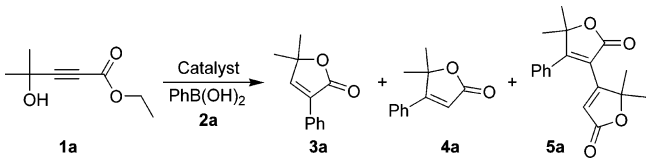
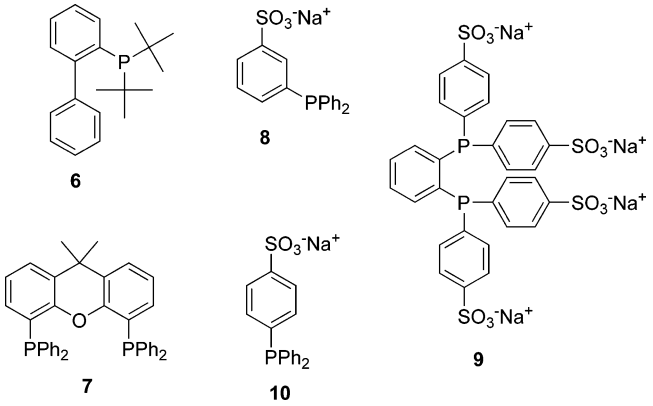
TABLE 1. Optimization Studies



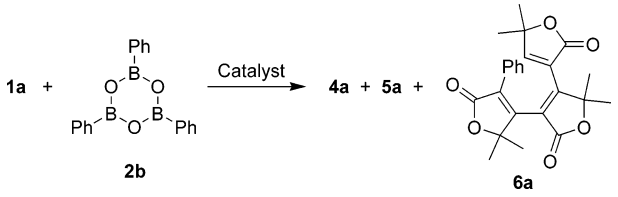
entry	solvent[a]	T (°C)/t (h)	catalyst	ligand	**3a** (% yield)[b]	**4a** (% yield)[b]	**5a** (% yield)[b]
1	dioxane/H_2O 10/1	100/3	[Rh(cod)OH]$_2$ (3 mol %)	dppf (6 mol %)	10	69	20
2	dioxane/H_2O 10/1	100/6	[Rh(cod)Cl]$_2$ (3 mol %)	dppf (6 mol %)	4	42	28
3	dioxane/H_2O 10/1	100/3	Rh(acac)(C_2H_4)$_2$ (3 mol %)	dppf (6.6 mol %)		44	
4	dioxane/H_2O 10/1	100/1	[Rh(cod)OH]$_2$ (3 mol %)		7	50	27
5	dioxane/H_2O 10/1	100/0.5	[Rh(cod)OH]$_2$ (3 mol %)	PPh_3 (6 mol %)	18	26	52
6	dioxane/H_2O[c] 10/1	100/0.5	[Rh(cod)OH]$_2$ (3 mol %)	PPh_3 (6 mol %)		11	35
7	dioxane/H_2O 10/1	100/23	[Rh(cod)OH]$_2$ (3 mol %)	**6** (6 mol %)	5	55	34
8	dioxane/H_2O 10/1	100/0.5	[Rh(cod)OH]$_2$ (3 mol %)	**7** (6 mol %)			
9	dioxane/H_2O 10/1	100/1	[Rh(cod)OH]$_2$ (3 mol %)	dppe (6 mol %)	5	31	53
10	dioxane/H_2O 10/1	100/0.5	[Rh(cod)OH]$_2$ (3 mol %)	dppp (6 mol %)	7	41	40
11	dioxane/H_2O 10/1	100/0.5	[Rh(cod)OH]$_2$ (3 mol %)	dppb (6 mol %)		88	9
12	dioxane/H_2O[d] 10/1	100/1.0	[Rh(cod)OH]$_2$ (3 mol %)	dppb (6 mol %)		90	9
13	dioxane/H_2O[e] 10/1	40/24	[Rh(cod)OH]$_2$ (3 mol %)	dppb (6 mol %)		63	
14	dioxane/H_2O[d,f] 10/1	40/24	[Rh(cod)OH]$_2$ (3 mol %)	dppb (6 mol %)			
15	EtOH	100	[Rh(cod)OH]$_2$ (3 mol %)	dppb (6 mol %)	9	40	30
16	EtOH	100	Rh(acac)(C_2H_4)$_2$ (3 mol %)	dppf (6.6 mol %)		42	15
17	H_2O	100/6.5	[Rh(cod)OH]$_2$ (1.5 mol %)	**8** (6 mol %)		23	
18	H_2O[g]	40/1.5	[Rh(cod)OH]$_2$ (3 mol %)	**9** (6 mol %)		16	
19	H_2O[h]	rt/3.5	[Rh(cod)OH]$_2$ (3 mol %)	**10** (6 mol %)		22	
20	toluene/H_2O 1/1	100/1.0	[Rh(cod)OH]$_2$ (1.5 mol %)	**10** (6 mol %)	10	18	

[a] All reactions were carried out with 5 equiv of **2a**/1 equiv of **1a**, unless otherwise indicated. [b] Yields are based on products isolated by column chromatography. [c] **2a**/**1a** = 2.5. [d] **2a**/**1a** = 2.0. [e] **2a** was recovered in a 15% yield. [f] **1a** and **2a** were recovered in a 82% and 61% yield, respectively. [g] **2a** was recovered in a 71% yield. [h] **2a** was recovered in a 50% yield.

CHART 1



SCHEME 3



of rhodium(I) catalysts, growing attention has been devoted to the development of new reactions by using a combination of rhodium catalyst and organoboron reagents. The rhodium catalysis allowed the addition of arylboronic acids and their analogues to the carbon−carbon and carbon−heteroatom multiple bonds.[26] The rhodium-catalyzed addition of organoboron derivatives to alkynes[27] has definite advantages over other methods due to high regioselectivity and high stereoselectivity, which may obtain feasible sequential addition−cyclization reactions of alkynes bearing proximate suitable functionalities.[28]

The reaction of 4-hydroxy-4-methyl-pent-2-ynoic acid ethyl ester **1a** and PhB(OH)$_2$ **2a** has been chosen as a model system with the aim of optimizing conditions for the rhodium-catalyzed synthesis of 4-substituted-2(5*H*)-furanones **4** (Table 1). The 5,5-dimethyl-4-phenyl-5*H*-furan-2-one **4a** was isolated in a 69% yield together with the regioisomer **3a** (10% yield) by reacting, in dioxane/water 10/1 (v/v), 1 equiv of **1a** with 5 equiv of **2a**, using [Rh(cod)(OH)]$_2$/1,1′-bis(diphenylphosphino)ferrocene (dppf) as catalyst; the formation of **5a** (20% yield) as byproduct was also observed (Table 1, entry 1).[24,27d] The use of [Rh(cod)OH]$_2$/dppf resulted in a more active catalytic system with respect to [Rh(cod)Cl]$_2$/dppf and Rh(acac)(C_2H_4)$_2$/dppf (Table 1, entries 1−3), even if the latter combination was highly selective.[29]

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TABLE 2.

entry	catalytic system	time (h)/*T* (°C)	**4a** (% yield)	**5a** (% yield)	**6a** (% yield)[a,b]
1	$[Rh(cod)OH]_2$/dppb (3 mol %)/(6 mol %)	28/40[c]	10		
2	$[Rh(cod)OH]_2$/dppb (3 mol %)/(6 mol %)	2/100[c]	42	45	
3	$[Rh(cod)OH]_2$/dppe (3 mol %)/(6 mol %)	1/100[d]	31	64	
4	$[Rh(cod)OH]_2$/dppe[d] (3 mol %)/(6 mol %)	1.5/100[e]	14	31	27
5	$[Rh(cod)OH]_2$/dppe[f] (3 mol %)/(6 mol %)	1.0/100[d]	25	11	40

[a] Yields are based on products isolated by column chromatography. [b] Reactions carried out in dioxane/water (10/1). [c] **1a**:**2b** = 1:1. [d] **1a**:**2b** = 2:1. [e] **1a**:**2b** = 3:1. [f] The reaction was carried out in dry 1,4-dioxane.

Further study was undertaken to improve the reaction by varying a series of parameters (ligand, Rh/ligand ratio, solvent, temperature, **1a**/**2a** ratio) with $[Rh(cod)OH]_2$ as a precatalyst. The use of $[Rh(cod)OH]_2$ without the addition of phosphine ligands also resulted in efficiently promoting the reaction, however, with no improvements in terms of selectivity (Table 1, entry 4). The combination of $[Rh(cod)OH]_2$ with PPh_3 has proven to be unsuitable and generally resulted in low selectivity (Table 1, entries 5 and 6). The choice of the bulky, electron-rich 2-(di-*tert*-butylphosphino)biphenyl **6** as ligand (Chart 1), which was reported to have beneficial effects on the rhodium-catalyzed addition of alkynes to 1,2-diketones, 1,2-ketoesters, and aldehydes,[30] failed in reaching high selectivity (Table 1, entry 7). Chelating bisphosphine ligands gave discrepant results. The features of the bisphosphine ligands played a pivotal role in determining the outcome of the reaction. Even if it has been postulated that excellent catalytic activities could arise from diphosphine ligands based on the xantene backbone,[31] our experiments obtained a complex reaction mixture (Table 1, entry 8) from the catalytic system $[Rh(cod)OH]_2$/9,9-dimethyl-4,5-bis(diphenylphosphino)xantene (Chart 1, xantphos **7**) under normal reaction conditions. Whereas **5a** (53% yield) formation prevailed with 1,2-bis(diphenylphosphino)ethane (dppe) (Table 1, entry 9), improvement of the target **4a** yield was observed by increasing the distance between the two phosphorus atoms in the series dppe, 1,3-bis(diphenylphosphino)propane (dppp), and 1,4-bis(diphenylphosphino)butane (dppb) (Table 1, entries 10 and 11). Among the examined bisphosphine ligands, dppb was significantly effective (Table 1, entry 10). Other improvements were attempted in order to completely reverse the selectivity toward **5a**. Surprisingly, the use of a smaller amount of boronic acid (2 equiv) essentially provided a similar high chemical yield as 5 equiv of **2a** (Table 1, entry 12). At a temperature as low as 40 °C, it was found to exclusively obtain **4a** in a 63% yield (Table 1, entry 13); however, at said temperature, the ratio **2a**/**1a** resulted in a determining factor for the resulting arylative lactonization process (Table 1, entry 14).

After screening the solvent, it was found that the use of ethanol instead of 1,4-dioxane was detrimental to the selectivity of the reaction (Table 1, entries 15 and 16). The reaction was also carried out in neat water[32] and in a biphasic water/toluene system[27a,b] by associating the $[Rh(cod)OH]_2$ with water-soluble ligands **8**−**9** (Chart 1). Surprisingly enough, even if disappointing results were observed from a synthetic point of view (Table 1, entries 17−19), the reaction in water led to the formation of **4a** as a single regioisomer. Conversely, in the biphasic water/toluene system, we observed a lack of regioselectivity (Table 1, entry 20). One common feature may be extrapolated from these examples. It seems that the reaction selectivity may be strongly influenced by the reaction medium, temperature, and precatalyst feature. It is worth noting that the formation of **5a** has been observed by using $[Rh(cod)OH]_2$ as a precatalyst even under reaction conditions where an excess of arylboronic acid is used in the presence of a large excess of water. It may be ruled out that the formation of **5a** is caused by the entropy-driven association because its formation has not been observed in water.[27a,b] On the basis of previous results reported by Hayashi and co-workers,[27d] the role played by the phenylboroxine **2b** in the reaction outcome was explored (Scheme 3; Table 2).

It is presumed that phenylboronic acid **2a** is in equilibrium with arylboroxine **2b** and water under reaction conditions. This equilibrium should influence the reaction stoichiometry with no bearing on the coupling process. By contrast, results clearly point out the drastic effect of the triphenylboroxine **2b** besides the **1a**/**2b** ratio, ligand, and temperature of the resulting reaction.[33] Indeed the reaction of an equimolecular amount of **1a** with phenylboroxine **2b**, in the presence of a rhodium-dppe catalytic system in 1,4-dioxane/H_2O at 100 °C for 2 h, gave a 45% yield of the dibutenolide derivative **5a** together with the derivative **4a (**Table 2, entry 2). The formation of **5a** in a better yield was observed by reacting the boroxine **2b** with excess alkyne **1a (**Table 2, entry 3). A different reactivity of boroxines[33] compared to the corresponding boronic acid derivatives can be suggested. Similarly, a drastic effect of the boron reagent has also been reported in the nickel-catalyzed 1,2-addition of arylboroxines to aromatic aldehydes.[34] The formation of the tributenolide derivative **6a** was observed when the **1a** excess was increased (Table 2, entry 4) or in dry solvent, using 1,4-dioxane (dried with molecular sieves). The results of Table 2 highlight the importance of the temperature, the boroxine/alkyne ratio, and the amount of water in determining the rhodium coming back to the catalytic cycle after it effects the dimerization and trimerization of alkyne **1a** resulting in **5a** and **6a**.

(28) (a) Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 217−224. (b) Harada, Y.; Nakanishi, J.; Fujihara, H.; Tobisu, M.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2007**, *129*, 5766−5761. (c) Miura, T.; Shimada, M.; Murakami, M. *Tetrahedron* **2007**, *63*, 6131−6140. (d) Chen, Y.; Lee, C. *J. Am. Chem. Soc.* **2006**, *128*, 15598−15599. (e) Shintani, R.; Yamagami, T.; Hayashi, T. *Org. Lett.* **2006**, *8*, 4799−4801. (f) Kinder, R. E.; Windenhoefer, R. A. *Org. Lett.* **2006**, *8*, 1967−1969. (g) Miura, T.; Shimada, M.; Murakami, M. *Synlett* **2005**, 667−669. (h) Miura, T.; Murakami, M. *Org. Lett.* **2005**, *7*, 3339−3341. (i) Shitani, R.; Okamoto, K.; Hayashi, T. *Chem. Lett.* **2005**, *34*, 1294−1295. (j) Matsuda, T.; Makino, M.; Murakami, M. *Chem. Lett.* **2005**, *34*, 1416−1417. (k) Miura, T.; Sasaki, T.; Nakazawa, H.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 1390−1391. (l) Miura, T.; Shimada, M.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 1094−1095. (m) Shintani, R.; Okamoto, K.; Otomaru, Y.; Ueyama, K.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 54−55.

(29) NMR and GC-MS analysis showed that its regioisomeric purity is higher than 96%.

(30) Dhondi, P. K.; Chisholm, J. D. *Org. Lett.* **2006**, *8*, 67−69.

(31) (a) Bruss, A. J.; Gelesky, M. A.; Machado, G.; Dupont, J. *J. Mol. Catal. A*: *Chem.* **2006**, *252*, 212−218. (b) Bronger, R. P. J.; Bermon, J. P.; Herwig, J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Adv. Synth. Catal.* **2004**, *346*, 789−799.

(32) Wu, W.; Li, C.-J. *Chem. Commun.* **2003**, 1668−1669.

(33) Miura, T.; Takahashi, Y.; Muratami, M. *Chem. Commun.* **2007**, 595−597.

(34) Arao, T.; Kondo, K.; Aoyama, T. *Tetrahedron Lett.* **2007**, *48*, 4115−4117.

TABLE 3.

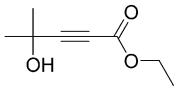
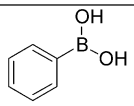
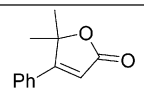
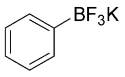
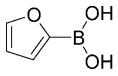
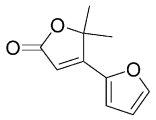
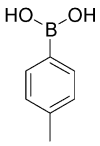
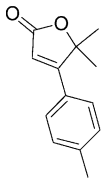
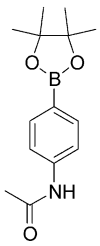
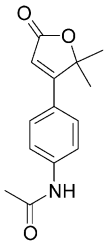
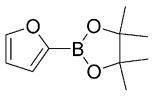
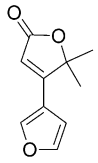
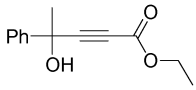
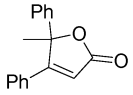
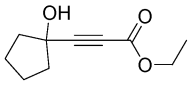
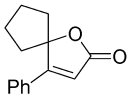
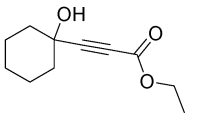
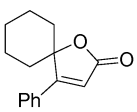
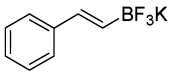
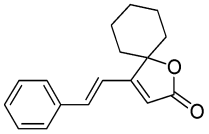
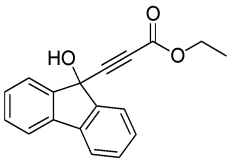
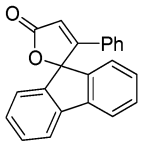
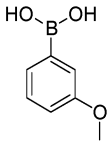
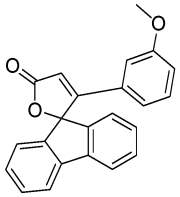
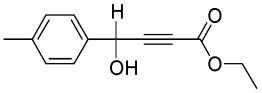
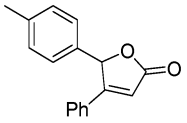
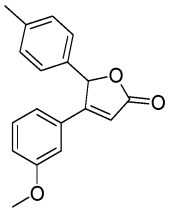
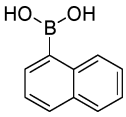
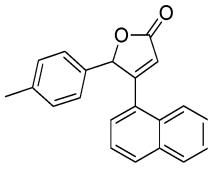
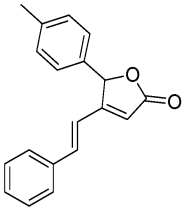
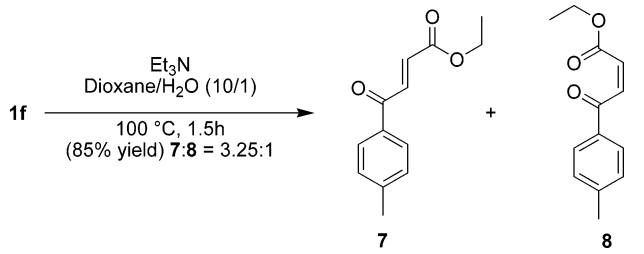
entry	Alkyl 4-Hydroxy-2-Alkynoate **1**	Organoboron Derivative **2**	Procedure	Time (h)	4-Substituted-5(H)-Furanone **4** (% yield)[a]
1	 **1a**	 **2a**	A[b]	3	 **4a** (90)[c]
2	**1a**	 **2c**	B[d]	3	**4a** (55)
3	**1a**	 **2d**	B	2	 **4b** (67)
4	**1a**	 **2e**	B	5	 **4c** (64)
5	**1a**	 **2f**	A	2	 **4d** (39)
6	**1a**	 **2g**	A	2	 **4e** (36)
7	 **1b**	**2a**	A		 **4f** (70)
8	 **1c**	**2a**	A	1	 **4g** (77)[e]
9	**1c**	**2a**	B	3	**4g** (80)
10	**1c**	**2a**	C[f]	1	**4g** (90)[g]
11	 **1d**	**2a**	A	1	 **4h** (79)[h]

Table 3 (Continued)

entry	Alkyl 4-Hydroxy-2-Alkynoate **1**	Organoboron Derivative **2**	Procedure	Time (h)	4-Substituted-5(H)-Furanone **4** (% yield)[a]
12	**1d**	**2a**	B	2	**4h** (77)
13	**1d**	 **2h**	B	2	 **4i** (79)
14	 **1e**	**2a**	A	2	 **4j** (61)
15	**1e**	 **2i**	B	3	 **4k** (67)
16	 **1f**	**2a**	A	1	 **4l** (70)
17	**1f**	**2i**	B	1.5	 **4m** (80)
18	**1f**	 **2j**	B	2	 **4n** (58)
19	**1f**	**2e**	B	2	 **4o** (69)

[a] Yields are based on products isolated by column chromatography. [b] Procedure A: The reaction was carried out at 100 °C in dioxane/water (10/1), using the following molar ratios: **1**:**2**:[Rh(cod)OH]$_2$:dppb= 1:2:0.03:0.06. [c] **5a** was isolated in a 9% yield. [d] Procedure B: The reaction was carried at 100 °C in dioxane/water (10/1), using the following molar ratios: **1**:**2**:Rh(acac)(C_2H_4)$_2$:dppf= 1:5:0.03:0.066. [e] **5g** was isolated in a 19% yield. [f] Procedure C: The reaction was carried out at 100 °C in dioxane/water (10/1), using the following molar ratios: **1**:**2**:[Rh(cod)OH]$_2$:dppb= 1:5:0.03:0.06. [g] **5g** was isolated in a 9% yield. [h] **5h** was isolated in a 16% yield.

SCHEME 4

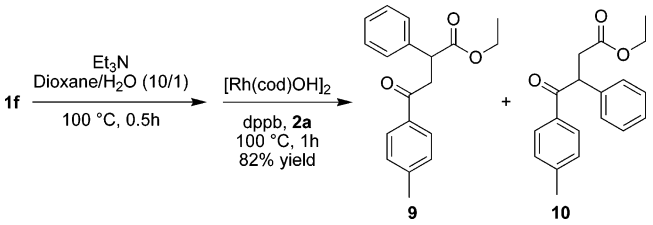


A subsequent investigation was carried out to study the scope of the rhodium-catalyzed alkylative lactonization; results are summarized in Table 3.

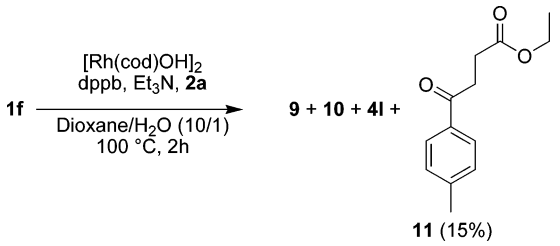
The reactivity of various alkyl 4-hydroxy-2-alkynoates **1** bearing dialkyl, arylalkyl, diaryl- and aryl groups at the propargyl position was studied. Interestingly, the rhodium-catalyzed reaction of the tertiary propargylic alcohol derivatives resulted in reversal of the regioselectivities compared to those observed in their palladium-catalyzed process.[23] Moreover, by contrast with the results obtained in the palladium-catalyzed alkylative lactonization of **1** with organoboronic acids, the bulkiness of groups near the triple bond did not affect the regioselectivity of the rhodium-catalyzed reaction, which was directed by the ester group. Further studies[35] have been described since Pellicciari's[36] first report regarding the rhodium-catalyzed isomerization of propargyl alcohols directly attached to an ester. Under the reaction conditions used, the γ-hydroxy-α,β-alkynoate **1f** selectively underwent the sequential rhodium-catalyzed alkylative lactonization rather than the isomerization to the corresponding γ-oxo-α,β-alkenoate/coupling reaction. To shed light on this point, isomerization of **1f** was attempted under basic conditions (Scheme 4).

The base-promoted isomerization of electron-deficient propargylic alcohols to the corresponding enones and its mechanism has been previously explored.[37] The prevailing *E*-selectivity in the isomerization reaction of **1f** is presumably due to the equilibration of (*Z*)-**8** to (*E*)-**7** in dioxane at 100 °C in the presence of triethylamine (Et_3N) as suggested in the literature.[38] Subsequently, **1f** afforded the formation in a 82% yield of the two regioisomer derivatives **9**−**10** (**9**:**10** = 1:1) through a one-flask two-step process involving Et_3N-promoted isomerization of **1f** to the corresponding enone derivatives **7** and **8**, followed by rhodium-catalyzed conjugate addition of the aryl boronic acid **2a** (Scheme 5). Most likely the reaction temperature is responsible for the lack of regioselectivity control of the rhodium-catalyzed conjugate addition step. It was previously reported that the treatment of ethyl 4-aryl/heteroaryl-4-hydroxy-2-butynoate with (*S*)-alanine and other (*S*)-amino acid benzyl esters at rt in ethanol in the presence of Et_3N may provide a general, regioselective entry into *N*-(3-aryl/heteroaryl-1-ethoxycarbonyl-3-oxopropyl) (*S*)-amino acid esters through sequential base-catalyzed isomerization/conjugate addition.[39]

SCHEME 5



SCHEME 6



Interestingly enough, the rhodium-catalyzed reaction of **1f** with **2a** in the presence of Et_3N in domino conditions allowed the isolation of the 4-oxo-4-tolylbutyric acid ethyl ester **11** (15% yield) together with the furanone ***4l*** (27% yield) and **9**−**10** (7% yield) derivatives (Scheme 6).

The one-pot isomerization/hydrogenation reaction of 4-aryl-4-hydroxy-2-alkynoates, under basic conditions, has been previously reported to occur by means of the in situ generated palladium hydride.[37d] β-Aryl[40]/alkyl elimination reactions on an alkoxorhodium[41] intermediate derived from tertiary propargyl alcohol have not been observed. The formation of allenic and propargylic arenes previously reported to occur in the palladium-catalyzed reaction of propargylic alcohol derivatives with arylboronic acids may also be ruled out in all examined cases.[42] Finally, it is worth noting that the addition of organorhodium intermediates onto the ester moiety of **1** was never observed under the present reaction conditions. Both rhodium-catalyzed intramolecular[28k] and intermolecular[26b] arylation on the carbonyl carbon of esters have been reported. As far as organoboron derivatives are concerned, the process tolerates aryl-/heteroaryl boronic acids, their corresponding pinacol esters, and aryl-/vinyltrifluoroborate salts. The latter derivatives have emerged as promising new compounds that can overcome certain limitations of other organoboron derivatives.[43] According to the literature,[44] the yield of 4-aryl/heteroaryl/2(5*H*)-furanones starting from pinacol ester derivatives **2f**,**g** was lower than that observed starting from boronic acids. According to the results observed with the model system, the use of $[RhOH(cod)]_2$/dppb as the catalytic system (procedure A) accomplished the formation of the target 4-substituted-2(5*H*)-furanones **4** still in good yield with excellent regioselectivity by reducing the quantity of orgaboron reagent from 5 to 2 equiv. Multiple addition derivatives were detected as byproducts. The best selectivity was observed by using $Rh(acac)(C_2H_4)_2$/dppf (procedure B). Nonetheless, to achieve satisfactory results from a synthetic

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point of view the quantity of organoboron derivative must be increased to 5 equiv.

Conclusion

In conclusion, a new approach to the synthesis of 4-aryl/heteroaryl/vinyl-2(5*H*)-furanones through a sequential regioselective rhodium-catalyzed addition/lactonization reaction of alkyl 4-hydroxy-2-alkynoates with organoboron derivatives was developed. The rhodium-catalyzed reaction of alkyl 4-hydroxy-2-alkynoates bearing a tertiary propargylic alcohol group resulted in reversal of the regioselectivity compared to that observed in the palladium-catalyzed process. In addition, the regioselective outcome of the rhodium-catalyzed reaction of alkyl 4-hydroxy-2-alkynoates bearing a secondary propargylic alcohol is not affected by the bulkiness of groups close to the C−C triple bond. Moreover, the reaction is carried out under neutral conditions. $[RhOH(cod)]_2$/dppb was the more effective catalytic system, but multiple addition derivatives may be observed as side products. The organoboron derivative feature also plays a pivotal role in determining the formation of the multiple addition byproducts. When $Rh(acac)(C_2H_4)_2$/dppf was used as a catalytic system an excellent selectivity was achieved.

Experimental Section

General Procedure A. Typical procedure A is given for the reaction of ethyl 4-hydroxy-4-methyl-2-pentynoate **1a** with phenylboronic acid **2a** giving 5,5-dimethyl-4-phenyl-5*H*-furan-2-one **4a** (entry 1, Table 3). To a mixture of $[Rh(cod)OH]_2$ (7.4 mg, 16.0 μmol), 1,4-bis(diphenylphosphino)butane (dppb) (14 mg, 33.0 μmol), and phenylboronic acid (133 mg, 1.1 mmol; **2a**) was added ethyl 4-hydroxy-4-methyl-2-pentynoate (85 mg, 0.55 mmol; **1a**), 1,4-dioxane (2.0 mL), and water (0.2 mL). The mixture was stirred at 100 °C for 1 h. Subsequently, the solvent was removed by evaporation. The residue was purified by chromatography on silica gel (230−400 mesh), eluting with *n*-hexane/ethyl acetate 80:20 mixture to afford 5,5-dimethyl-4-phenyl-5*H*-furan-2-one **4a** (92 mg, 90% yield).

General Procedure B. Typical procedure B is given for the reaction of 4-hydroxy-4-*p*-tolylbute-2-ynoic acid ethyl ester **1f** with 3-metoxybenzeneboronic acid **2i** giving 4-(3-methoxyphenyl)-5-*p*-tolyl-5*H*-furan-2-one **4m** (entry 15, Table 3). To a mixture of $Rh(acac)(C_2H_4)_2$ (5 mg, 19.0 μmol), 1,1′-bis(diphenylphosphino)-ferrocene (dppf) (23 mg, 41.0 μmol), and 3-metoxybenzeneboronic acid (478 mg, 3.15 mmol; **2i**) was added 4-hydroxy-4-*p*-tolylbute-2-ynoic acid ethyl ester (137 mg, 0.63 mmol; **1f)**, 1,4-dioxane (3.0 mL), and water (0.3 mL), and the mixture was stirred at 100 °C for 1.5 h. Subsequently, the solvent was removed by evaporation. The residue was purified by chromatography on silica gel (230−400 mesh), eluting with *n*-hexane/ethyl acetate 90:10 mixture, to afford 4-(3-methoxyphenyl)-5-*p*-tolyl-5*H*-furan-2-one **4m** (113 mg, 80% yield).

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Supporting Information Available: Experimental information including characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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