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Regioselective Pd-catalyzed alkylative lactonizations of 4-hydroxy-2-alkynecarboxylates with organoboronic acids

Chang Ho Oh,* Su Jin Park, Jin Hyang Ryu and Arun Kumar Gupta

Department of Chemistry, Hanyang University, Haengdang-17, Sungdong-Gu, Seoul 133-791, Korea

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Abstract—The palladium-catalyzed addition of aryl- and alkenylboronic acids to 4-hydroxy-2-alkynecarboxylates and in situ lactonization would constitute a novel methodology for the synthesis of various butenolides with an excellent stereoselectivity and a high control of regioselectivity.

Many butenolides exist in nature and some of them exhibit interesting biological activities (Fig. 1).[1] Because of the enormous importance in chemical as well as pharmaceutical research, a number of synthetic methods for substituted butenolides have been reported.[2] Among them, ruthenium-catalyzed carbonylative cyclization of allenols,[3] palladium-catalyzed cyclization of allenecarboxylic acids,[4] and enyne metathesis[5] are the most valuable synthetic methodologies. There is still a continuing need for simple and versatile synthetic methods for substituted butenolides. Palladium-catalyzed reactions involving nucleophilic attack on π-alkene-, π-alkyne-, and π-allyl-metal complexes provide convenient and powerful tools for organic synthesis and also a large number of selective organic transformations have been reported.[6,7]

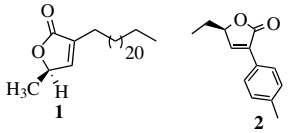
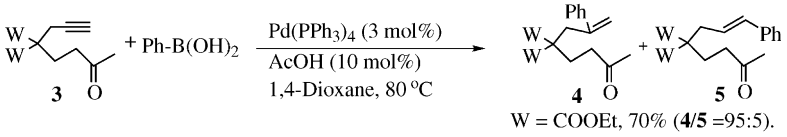


Figure 1.

Recently, we reported the hydroarylation and hydroalkenylation of alkynes[8] and allenes[9] with a variety of organoboronic acids. During our studies, we found that incorporation of a specific functional group such as a keto (Eq. 1), –OH (Eq. 2), or nitrogen of 2-pyridyl (Eq. 3) could play a role in controlling the site of addition. Mechanistically, we anticipated that oxygen or nitrogen atoms present in the alkyne substrate would bind the Lewis acidic $RB(OH)_2$ and thereby direct the addition site.[10,11] On the other hand, bulky substituents might block addition to one end of the alkyne. The regioselectivity can also be controlled by employing a various types of ligands.[12]



(1)

It is worthy to explore the possibility of combining arylation/alkenylation with lactonization in a one step; thus the compounds **12a**–**g** bearing both a –OH group and a –COOEt group were prepared for Pd-catalyzed

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* Corresponding author. Tel.: +82 2 2290 0932; fax: +82 2 2299 0762; e-mail: changho@hanyang.ac.kr

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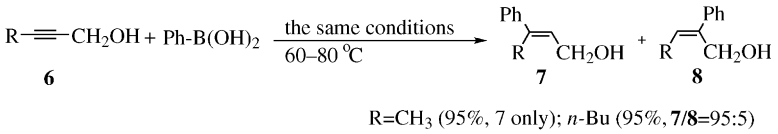
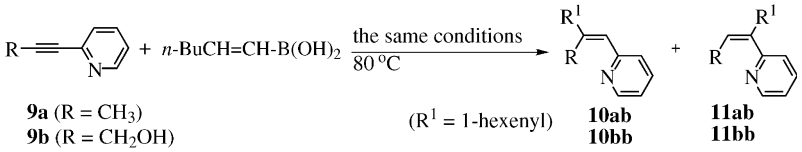


(2)

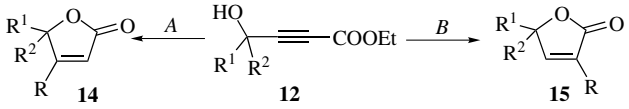
R=CH_3 (95%, 7 only); *n*-Bu (95%, **7**/**8**=95:5)



(3)

hydroarylations and alkenylations.[13] When **12a** was treated with 3 mol% of palladium acetate, 3 mol% of dppe as a ligand, and 10 mol% of acetic acid in the presence of 1.2 equiv of 1-hexenylboronic acid **13a**, addition of 1-hexenyl group and then subsequent in situ lactonization occurred to give a 7:1 mixture of the corresponding butenolides **14aa** and **15aa** in combined 87% yield. To the best of our knowledge, there was no literature report on this type of reaction. Hence, here we wish to report a new Pd-catalyzed arylative- and alkenylative lactonizations of 4-hydroxy-2-alkynecarboxylates with a high control of regioselectivity and *syn*-stereo selectivity (Eq. 4). We have attempted investigation of this protocol for **12a**–**g** with **13a**–**b** (Scheme 1) under two conditions.

The condition A is composed of a catalytic system of 3 mol% $Pd(OAc)_2$ and 3 mol% dppe, while the condition B is composed of a catalytic system of 3 mol% $Pd(OAc)_2$ and 6 mol% tri(*tert*-butyl)phosphine. The results, obtained under both condition A and B, are summarized in Table 1. It should be noted that both the ester group and the hydroxyl group induced more β-addition



R^1, R^2 =	-H, -H	**12a**	R = *n*-BuCH=CH-	**13a**
	-H, $-CH_3$	**12b**	= 4-$CH_3OC_6H_4$-	**13b**
	-H, $-CH_2CH_2CH_3$	**12c**	= 4-$CH_3C_6H_4$-	**13c**
	-H, $-CH(CH_3)_2$	**12d**		
	-H, $-C(CH_3)_3$	**12e**		
	-H, -Ph	**12f**		
	$-CH_3$, $-CH_3$	**12g**		

cond A: $RB(OH)_2$ (**13**), 3 mol% $Pd(OAc)_2$, 3 mol% dppe, 10 mol% AcOH
cond B: $RB(OH)_2$ (**13**), 3 mol% $Pd(OAc)_2$, 6 mol% $(t\text{-Bu})_3P$, 10 mol% AcOH

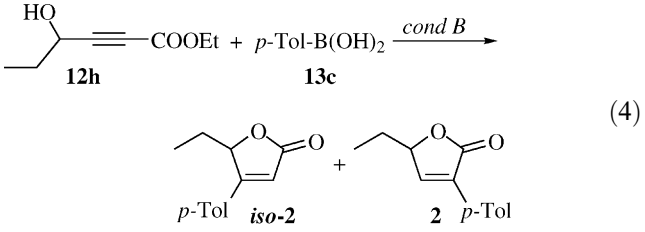
Scheme 1. Reagents and conditions: (A) $RB(OH)_2$ (**13**), 3 mol% $Pd(OAc)_2$, 3 mol% dppe, 10 mol% AcOH; (B) $RB(OH)_2$ (**13**), 3 mol% $Pd(OAc)_2$, 6 mol% $(t\text{-Bu})_3P$, 10 mol% AcOH.

of organoboronic acids under the condition A, implying that the OH group did not show a good directing effect compared to the primary –OH group in the substrate **12a**. Since the ester group might have stronger directing effect over hydroxyl group, the products from **13a** and **13b** gave a 7:1 mixture of **14aa** and **15aa** in 87% yield and a 11:1 mixture of **14ab** and **15ab** in 74% yield, respectively. The size of alkyl group in 4-hydroxy-2-alkynecarboxylates has showed a dramatic effect on regioselectivity. Even in case of ethyl 4-hydroxy-2-butynecarboxylate **12b** under condition A with both **13a** and **13b** gave only a 3:1 mixture of **14ba** and **15ba** and a 6:1 mixture of **14bb** and **15bb**, respectively. Similarly, the substrate **12c** contained *n*-butyl group under the same condition with both **13a** and **13b** afforded a 3:1 mixture of **14ca** and **15ca** and a 4:1 mixture of **14cb** and **15cb**, respectively. When we introduced an isopropyl group at the propargylic position (**12d**), a little improvement in regioselectivity with both **13a** and **13b** was observed to give a 6:1 mixture of **14da** and **15da** and a 7:1 mixture of **14db** and **15db**, respectively. Not surprisingly with the substrate **12e** bearing a *tert*-butyl group at the propargylic position, the regioselectivities with both **13a** and **13b** were dramatically diminished to give a 1:2 mixture of **14ea** and **15ea** and a 2:1 mixture of **14eb** and **15eb**, respectively. The more pronounced effect was observed with *tert*-alcohol **12g** with both **13a** and **13b** resulted in reversal of regioselectivities, giving a 1:2 mixture of **14ga** and **15ga** and a 1:3 mixture of **14gb** and **15gb**, respectively. But **12f** bearing a phenyl group gave a 4:1 mixture of **14fa** and **15fa** and a 10:1 mixture of **14fb** and **15fb**, respectively. Interestingly, when the substrate **12a** was applied to condition B gave almost a 1:1 mixture of **14aa** and **15aa**, implying that the substrate **12a** has competitive effect by the primary OH group and the ester group. The alkyl group size has also showed the dramatic effect in regioselectivity in these reactions. Ethyl-4-hydroxy-2-pentynecarboxylate **12b** with both **13a** and **13b** gave a 1:10 mixture of **14ba** and **15ba** and almost **15bb**, respectively. Similarly, the substrate **12c** with **13a** gave a 1:12 mixture of **14ca** and **15ca**, while **13b** gave exclusively **15cb**. The **12d** bearing an isopropyl group at the propargylic position under condition B with **13a** afforded a 1:16 mixture of **14da**

Table 1. Reactions of 4-hydroxy-2-alkynecarboxylate **12** with organoboronic acids **13a**–**b** under conditions A and B

Entry	12	13	Conditions	Temperature (°C)/time (h)	Products	%Yield (ratio)
1	**12a**	**13a**	A, $CHCl_3$	50/5	**14aa**, **15aa**	87 (7:1)
2			B, THF	60/4		97 (1:1.4)
3	**12a**	**13b**	A, $CHCl_3$	50/5	**14ab**, **15ab**	74 (11:1)
4			B, THF	60/4		98 (1:1.5)
5	**12b**	**13a**	A, $CHCl_3$	60/20	**14ba**, **15ba**	74 (3:1)
6			B, THF	60/4		97 (1:10)
7	**12b**	**13b**	A, $CHCl_3$	60/24	**14bb**, **15bb**	75 (6:1)
8			B, 1,4-dioxane	60/4		94 (**15bb** only)
9	**12c**	**13a**	A, $CHCl_3$	50/24	**14ca**, **15ca**	67 (3:1)
10			B, THF	60/4		95 (1:12)
11	**12c**	**13b**	A, $CHCl_3$	50/12	**14cb**, **15cb**	76 (4:1)
12			B, 1,4-dioxane	60/4		96 (**15cb** only)
13	**12d**	**13a**	A, $CHCl_3$	50/12	**14da**, **15da**	85 (6:1)
14			B, THF	60/6		98 (1:16)
15	**12d**	**13b**	A, $CHCl_3$	50/12	**14db**, **15db**	73 (7:1)
16			B, 1,4-dioxane	60/4		96 (**15db** only)
17	**12e**	**13a**	A, 1,4-dioxane	100/24	**14ea**, **15ea**	89 (1:2)
18			B, 1,4-dioxane	100/24		96 (1:11)
19	**12e**	**13b**	A, 1,4-dioxane	80/24	**14eb**, **15eb**	80 (2:1)
20			B, THF	70/10		98 (**15eb** only)
21	**12f**	**13a**	A, $CHCl_3$	60/12	**14fa**, **15fa**	73 (4:1)
22			B, THF	60/8		96 (1:10)
23	**12f**	**13b**	A, $CHCl_3$	60/12	**14fb**, **15fb**	75 (10:1)
24			B, THF	60/4		96 (**15fb** only)
25	**12g**	**13a**	A, 1,4-dioxane	80/48	**14ga**, **15ga**	77 (1:2)
26			B, THF	60/4		97 (**15ga** only)
27	**12g**	**13b**	A, 1,4-dioxane	80/48	**14gb**, **15gb**	79 (1:3)
28			B, THF	60/4		98 (**15gb** only)

and **15da**, but surprisingly that with **13b** gave **15db** as a sole product. The similar trend was observed in case of **12e** bearing a *tert*-butyl, **12f** bearing a phenyl group with both **13a** and **13b**. An excellent regioselectivity was obtained with **12g**. It is implying that the bulkiness of the alkyl group near the triple bond affects the regioselectivity. In general, the regioselectivities raised from the use of the bulky ligand under condition B were much higher than those obtained under condition A. In order to prove the application of this methodology, we synthesized a racemic version of **2** (Eq. 4). When the condition B was applied to a mixture of **12h** and *p*-toluneboronic acid (**13c**) at 60 °C for 2 h in THF, a 1:11 mixture of *iso*-**2** and **2** were synthesized in combined 98% yield.



(4)

The phenomena of in situ lactonization are the convincing evidence of *syn*-addition of the organic group from organoboronic acids to alkynecarboxylates. In precise, we have demonstrated the Pd-catalyzed addition of aryl and alkenylboronic acids to 4-hydroxy-2-alkynecarboxylates and in situ lactonization with an excellent stereoselectivity and a high control of regioselectivity. No doubt that this investigation would constitute a novel methodology for the synthesis of various butenolides, which are interest of natural and pharmaceutical research. We are currently pursuing the application of this methodology to the combinatorial synthesis of a butenolid library.

Acknowledgements

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