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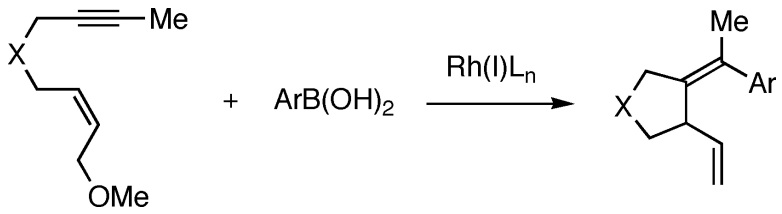

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Rhodium-Catalyzed Cyclization of 1,6-Enynes Triggered by Addition of Arylboronic Acids

Tomoya Miura, Masahiko Shimada, and Masahiro Murakami*

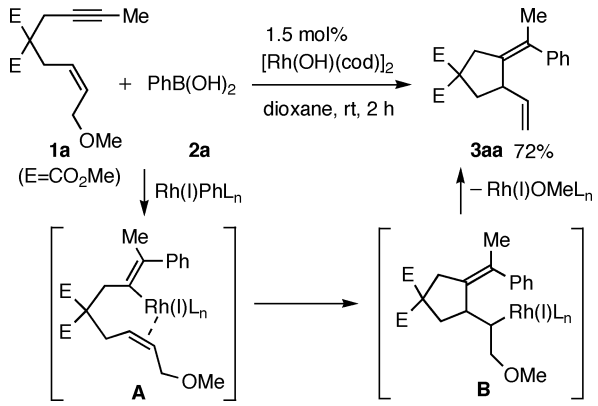
Department of Synthetic Chemistry and Biological Chemistry, Kyoto University, Katsura, Kyoto 615-8510, Japan

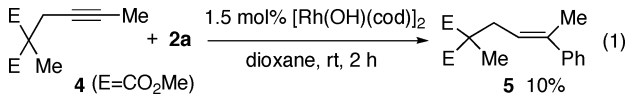
Received October 27, 2004; E-mail: murakami@sbchem.kyoto-u.ac.jp

The rhodium(I)-catalyzed addition of arylboronic acids to alkenes or alkynes has recently emerged as a useful synthetic protocol for the formation of carbon−carbon bonds in organic chemistry.[1] Unlike most palladium-catalyzed carbon−carbon bond-forming reactions, which involve a Pd(II)/Pd(0) redox process,[2] the formal oxidation state of rhodium remains 1+ through the reaction. In the course of the addition reaction, the intermediate organorhodium(I) species is easily protodemetalated by a proton source (HX) that is present as a cosolvent or additive, regenerating the catalytically active Rh(I)−X species to promote the next catalytic cycle.[3] The intermediate complexes are rarely used for further carbon−carbon bond formation despite their potential usefulness. Recently a few reports on cyclization reactions involving the second carbon−carbon bond-forming process have appeared, wherein a catalytic rhodium(I) species was also regenerated by protodemetalation.[4] We then envisaged that the ensuing carbon−carbon bond formation would be feasible in a catalytic sense if an allylic ether were placed at an appropriate position in the molecule. The intermediate organorhodium complex formed by the intramolecular addition to the allylic carbon−carbon double bond may undergo a facile β-alkoxy elimination.[5] The resulting alkoxyrhodium(I) would be suitable to participate in the next catalytic cycle through transmetalation with an arylboronic acid.[6] In this report, we describe the intramolecular cyclization reaction of 1,6-enynes that is triggered by the rhodium-catalyzed addition of arylboronic acids to the carbon−carbon triple bond.[7,8]

When 1,6-enyne **1a** was treated with phenylboronic acid (**2a**, 2.0 equiv) in the presence of $[Rh(OH)(cod)]_2$ (0.03 equiv of Rh, cod = cycloocta-1,5-diene)[3a] in dioxane at room temperature under a nitrogen atmosphere for 2 h (*COD conditions*), (*Z*)-1-(1-phenylethylidene)-2-vinylcyclopentane **3aa** was obtained as a single isomer in 72% isolated yield (Scheme 1). The *Z* configuration of the exo double bond was confirmed by a difference NOE study. The reaction is initiated by regioselective addition of a phenylrhodium(I) species, generated in situ by the transmetalation of rhodium(I) with phenylboronic acid (**2a**), onto the alkyne, giving the alkenylrhodium(I) intermediate **A**. Intramolecular carborhodation to the pendent allylic double bond then occurs in a 5-exo mode, leading to the formation of the alkylrhodium(I) intermediate **B**. Finally, β-elimination of methoxy group affords the (*Z*)-1-(1-phenylethylidene)-2-vinylcyclopentane **3aa** with generation of a catalytically active rhodium(I) methoxide. It is noteworthy that the phenylrhodium species formed by transmetalation underwent highly regioselective 1,2-addition across the carbon−carbon triple bond flanked by methyl and primary alkyl substituents.[9] When the dppb was used as an additional ligand [0.03 equiv of $[Rh(OH)(cod)]_2$/dppb, 2 equiv of $PhB(OH)_2$, dioxane, room temperature (*DPPB conditions*)], 1,6-enyne **1a** gave **3aa** in moderate yield (49%) in 2 h with 32% of **1a** unreacted. For comparison, an analogous reaction was carried out using substrate **4** lacking an olefinic moiety. The addition reaction proceeded sluggishly and in 2 h formed the 1,2-adduct **5** only in 10% yield under the COD conditions (eq 1). Almost no reaction occurred under the DPPB conditions (vide supra). These contrasting results indicated that the olefinic moiety of **1a** intramolecularly coordinates to rhodium to facilitate the initial 1,2-addition.[10] It is also conceivable that the stronger π-acidic character of the cod ligand facilitates intramolecular olefin coordination with **A**.

Scheme 1





The results obtained with a variety of arylboronic acids and 1,6-enynes are summarized in Table 1. The catalytic process worked well with a sterically and electronically diverse array of arylboronic acids to give the corresponding products **3ab**−**3ah** in good yield. Cyclization successfully occurred with substrates having a free hydroxyl group or a silyl ether at the allylic position. The reaction of the allylic acetate was slower and required a larger amount of the rhodium catalyst (6 mol %). A slightly better yield was obtained with **1e**, having an ethyl-substituted alkyne, than with **1a**. The reaction of phenyl-substituted alkyne **1f** suffered from a lower regioselectivity of the initial 1,2-addition to give the product **3fa** only in 25% yield. Enyne **1g**, having an *E*-olefin, was also converted to the product **3aa** in good yield. Even substrate **1h**, equipped with trisubstituted olefin, reacted to give the product **3ha**, bearing a quaternary carbon center. Substrate **1i**, having a dimethyl acetal at the allylic position, gave the aldehyde **3ia** in 70% yield after acidic hydrolysis. The reaction tolerated the presence of a variety of functional groups, including ether **1j** and sulfone **1k**. The reaction of aza-1,6-enyne **1l**, bearing a sulfonamide group in the backbone, gave the product **3la** in only 27% yield due to the low regioselectivity of 1,2-addition of a phenylrhodium(I) species to alkyne.

Next, we examined the asymmetric version of this process using a chiral phosphine ligand instead of the cod ligand.[3a,11] A high level of asymmetric induction (97% ee) was observed with the product

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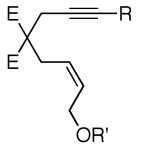
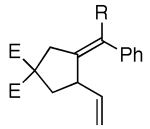
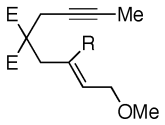
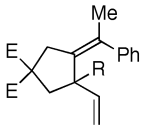
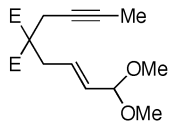
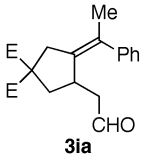
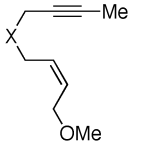
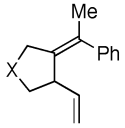
Table 1. Rhodium-Catalyzed Cyclization of 1,6-Enynes **1** with Arylboronic Acids **2**[a]

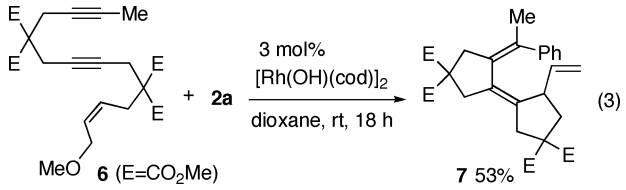
substrate[b]		$ArB(OH)_2$		product	time (h)	yield (%)[c]
						
1a	R=Me R'=Me	**2b**	4-F-C_6H_4	**3ab**	2	77
1a		**2c**	4-NO_2-C_6H_4	**3ac**	6	82
1a		**2d**	4-Me-C_6H_4	**3ad**	10	68
1a		**2e**	3-MeO-C_6H_4	**3ae**	2	77
1a		**2f**	3-Cl-C_6H_4	**3af**	2	77
1a		**2g**	2-Me-C_6H_4	**3ag**	8	80[d]
1a		**2h**	1-naphthyl	**3ah**	13	81[d]
1b	R=Me R'=H	**2a**	Ph	**3aa**	2	63
1c	R=Me R'=TBS	**2a**	Ph	**3aa**	2	78
1d	R=Me R'=Ac	**2a**	Ph	**3aa**	24	52[e,f]
1e	R=Et R'=Me	**2a**	Ph	**3ea**	2	80
1f	R=Ph R'=Me	**2a**	Ph	**3fa**	2	25[g]
						
1g	R=H	**2a**	Ph	**3aa**	2	75
1h[h]	R=Me	**2a**	Ph	**3ha**	23	61
						
1i		**2a**	Ph	**3ia**	2	70
						
1j	X=C(CH_2OMe)$_2$	**2a**	Ph	**3ja**	2	81
1k	X=C(SO_2Ph)$_2$	**2a**	Ph	**3ka**	16	70[e]
1l	X=NTs	**2a**	Ph	**3la**	12	27[e]

[a] The reaction was carried out with **1** (0.2 mmol) and **2** (0.4 mmol) in dioxane (2 mL) in the presence of $[Rh(OH)(cod)]_2$ (0.03 equiv of Rh) at room temperature, unless otherwise noted. [b] E = CO_2Me. [c] Isolated yields. [d] Mixture of atropisomers (52:48 for **3ag**, 62:38 for **3ah**). [e] **2** (4 equiv) and $[Rh(OH)(cod)]_2$ (0.06 equiv of Rh) were used. [f] The starting material remained. [g] 50 °C. [h] (*E*):(*Z*) = 9:1.

3aa, whereas the chemical yield was moderate owing to a low regioselectivity that was peculiar to the use of phosphine ligands (eq 2).[12] We assume that the less sterically demanding character of the cod ligand compared with (*R*)-BINAP contributes to the high regioselectivity observed under the COD conditions.

$$\mathbf{1a} + \mathbf{2a} \xrightarrow[\text{dioxane, rt, 14 h}]{\text{2.5 mol \% } [Rh(OH)((R)\text{-BINAP})]_2} \underset{\text{60\%, 97\% ee}}{\mathbf{3aa}} \qquad (2)$$

Thus, the intermediate organorhodium(I) species was successively utilized in the second carbon−carbon bond formation as part of the catalytic cycle. Finally, we examined a domino cyclization process using enediyne **6**.[13] When **6** was treated with phenylboronic acid (**2a**) in the presence of $[Rh(OH)(cod)]_2$ (0.06 equiv of Rh) for 18 h, the bicyclic triene derivative **7** was obtained in 53% yield as a single isomer through successive carborhodation processes (eq 3).



In summary, we have developed new cyclization reactions of 1,6-enynes triggered by the rhodium-catalyzed regioselective addition of an arylrhodium(I) species to alkynes. The results obtained demonstrated that multiple carbon−carbon bond-forming processes can operate with a single catalytic system using only rhodium(I).

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Supporting Information Available: Experimental details and selected spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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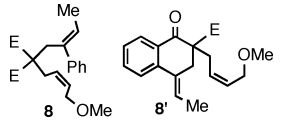
(12) Byproducts **8** and **8′** were formed in ∼20% yield by addition of a phenylrhodium species with the opposite regiochemistry. The compound **8′** was formed through 1,4-shift of rhodium and acylation with the ester group. The ratio **3aa**:(**8** + **8′**) in the reaction shown in Scheme 1 (COD conditions) was >95:5.



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