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Rhodium-Catalyzed Arylative and Alkenylative Cyclization of 1,5-Enynes Induced by Geminal Carbometalation of Alkynes

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Addition of carbon functionalities to unactivated alkenes and alkynes is a premier example of metal-mediated catalysis that enables otherwise difficult or infeasible bond construction with high degrees of selectivity.[1] In particular, this powerful chemistry allows efficient coupling between substrates possessing multiple π components and a range of carbon nucleophiles with concomitant cyclization (Scheme 1).[2] Despite considerable methodological advancements in this area that make use of various alkynyl substrates, the pivotal intermolecular coupling has invariably relied on 1,2-carbometalation, converting the alkyne to an *exo*-alkene upon ring closure. A 1,1-carbometalation pathway would offer an alternative reaction motif that gives rise to an *endo*-product but has remained unexplored.[3] We describe here a new addition−cyclization that occurs through a novel mechanism involving a metal vinylidene-mediated geminal carbometalation of alkynes. The reaction efficiently couples 1,5-enynes with a wide variety of aryl- and alkenylboronic acids to provide 1-substituted cyclopentene products.

Our approach to the addition−cyclization was based on the generation of an alkenyl rhodium species from the corresponding vinylidene complex.[4] We postulated that such reactivity, observed to date only in stoichiometric systems, might be catalytically viable to mediate the cyclization of enynes. Thus, the proposal was evaluated in the reaction of 1,5-enyne **1** with phenylboronic acid using a series of rhodium catalysts (Table 1). While the initial survey of phosphine ligands was disappointing,[5] the reaction with $[RhCl(COD)]_2$ in the absence of a phosphine formed **2** in 39% yield (entries 1−3). Interestingly, the analogous $[RhCl(C_2H_4)_2]_2$ complex proved to be ineffective but was rendered catalytically active in the presence of NBD, suggesting the crucial role played by COD as a ligand (entries 4 and 5).[6] Further screening revealed $[Rh(OH)(COD)]_2$/TEA/MeOH to be an optimal combination, which gave a 65% yield of **2** (entries 6−10).

Having established the effective conditions, we next examined the phenylative cyclization with a range of 1,5-enynes. As shown in Table 2, the reaction tolerated both acyclic and cyclic enones and substituents at the allylic and propargylic positions, furnishing 1-phenylcyclopentenes as the sole products. Notably, (*E*)- and (*Z*)-**15** participated well in the reaction notwithstanding the potential complication of a rhodium allenylidene formation.[7]

Experiments to probe the scope of organoboronic acids were next performed using enynes **1** and **5** (Table 3). As demonstrated in the formation of **17** and **18**, a wide range of arylboronic acids with electron-withdrawing or -donating groups at various positions, as well as a heteroarylboronic acid (cf. **18b**), were found to be good participants in the reaction. In addition, alkenylboronic acids also proved to be suitable components of the addition−cyclization process, incorporating the alkenyl unit with retention of geometry. While the reaction of (*E*)-styrylboronic acid with enyne **1** afforded **19** as a single product, (*E*)-1-octenyl and (*Z*)-propenyl boronic acids reacted with enyne **5** to give, respectively, cyclized 1,3-dienes **20a** and **21a** as the major products along with **20b** and **21b** arising from a simple 1,2-addition of the alkyne.[2b,8] It was noteworthy that these reactions with alkenylboronic acids were completed within minutes, in contrast to those employing arylboronic acids which typically required a reaction time frame of hours.

Scheme 1. Addition−Cyclization via Carbometalation of Alkynes

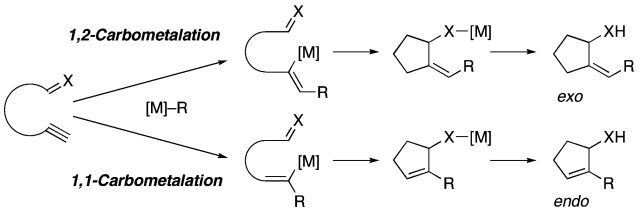
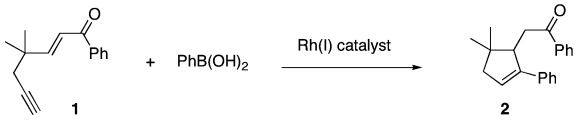


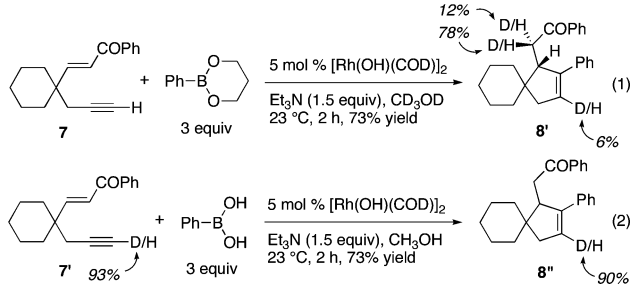
Table 1. Rhodium-Catalyzed Addition−Cyclization of Enyne **1**[a]



entry	[Rh]	ligand	solvent[b]	base	time (h)	yield[c] (%)
1	$RhCl(PPh_3)_3$		dioxane		24	0
2	$[RhCl(C_2H_4)_2]_2$	BINAP	MeOH/H_2O	KOH	24	0
3	$[RhCl(COD)]_2$		dioxane/H_2O	KOH	12	39
4	$[RhCl(C_2H_4)_2]_2$		MeOH/H_2O	KOH	24	0
5	$[RhCl(C_2H_4)_2]_2$	NBD[d]	MeOH/H_2O	KOH	24	35
6	$[Rh(OH)(COD)]_2$		dioxane/H_2O	KOH	24	42
7	$[Rh(OH)(COD)]_2$		MeOH/H_2O	KOH	5	46
8	$[Rh(OH)(COD)]_2$		MeOH	KOH	1	47
9	$[Rh(OH)(COD)]_2$		MeOH		4	52
10	$[Rh(OH)(COD)]_2$		MeOH	TEA	1	65

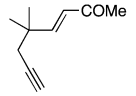
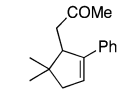
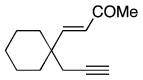
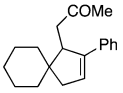
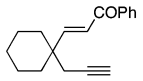
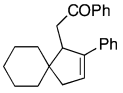
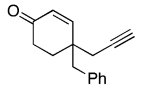
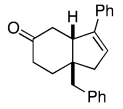
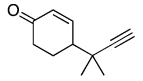
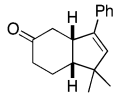
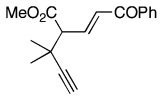
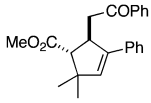
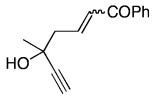
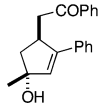
[a] All reactions were performed with 0.05 mmol of enyne **1**, 0.15 mmol of $PhB(OH)_2$, 10 mol % of [Rh], 10 mol % of ligand, and 0.015 mmol of KOH (or 0.075 mmol of TEA) in 1.0 mL of solvent at 23 °C. [b] MeOH:H_2O = 1,4-dioxane:H_2O = 10:1. [c] Isolated yield. [d] Norbornadiene.

In order to further explore the mechanism of the reaction, a set of labeling studies was carried out. In an experiment employing CD_3OD as the solvent, the reaction of **7** with 2-phenyl-1,3-dioxa-2-borinane[9] produced **8′** with 6% deuterium incorporation at the olefin and 90% at the α-carbonyl position, in which the label was diastereotopically distributed in a 6.5:1 ratio (eq 1).[10] When deuterated enyne **7′** was subjected to the same conditions with phenylboronic acid, the alkynyl deuterium migrated cleanly to the adjacent carbon upon formation of **8″**, suggesting the involvement of a metal vinylidene mechanism in the reaction (eq 2).[11]



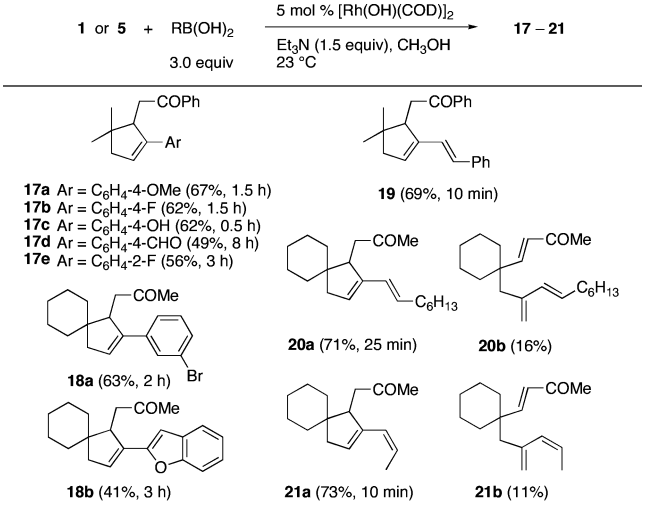
10.1021/ja067125+ CCC: $33.50

Table 2. Rhodium-Catalyzed Phenylative Cyclization of 1,5-Enynes[a]

entry	enyne		product		time	yield[b]
1		**3**		**4**	3	66
2		**5**		**6**	6	74
3		**7**		**8**	2	73
4		**9**		**10**	6	48
5		**11**		**12**	24	60
6		**13**		**14**	16	46
7		*E*-**15** *Z*-**15**		**16**	7 5	84[c] 70[d]

[a] All reactions were performed with 0.05 mmol of enyne, 0.15 mmol of $PhB(OH)_2$, 5 mol % of $[Rh(OH)(COD)]_2$, and 0.075 mmol of TEA in 1.0 mL of MeOH at 23 °C. Products were obtained as single diastereomers in entries 4−6. [b] Isolated yield. [c] Diastereomeric ratio = 3:1 [from (*E*)-**15**]. [d] Diastereomeric ratio = 1:1 [from (*Z*)-**15**].

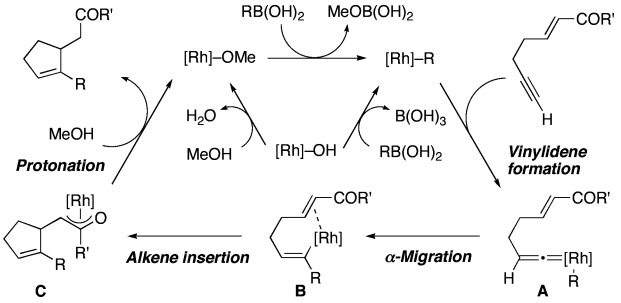
Table 3. Rh(I)-Catalyzed Addition−Cyclization of Enynes **1** and **5**: Scope of Aryl- and Alkenylboronic Acids[a]



[a] Isolated yields and reaction times.

On the basis of these observations, we propose a mechanism as outlined in Scheme 2, in which the catalytic cycle is initiated by transmetalation of the rhodium precatalyst (OH or OMe complex) with an organoboronic acid to generate a [Rh]−R complex.[12] Following the formation of rhodium vinylidene **A**, α-migration of the R group from the Rh center to the vinylidene ligand provides alkenylrhodium **B**, which then undergoes addition to the pendent enone to give rhodium enolate **C**. Finally, protonation of **C** regenerates the [Rh]−OMe complex and accomplishes a net R,H-addition across the enyne π system.

Scheme 2. Proposed Mechanism for the Rh-Catalyzed Addition−Cyclization of 1,5-Enynes with Aryl- and Alkenylboronic Acids



In summary, we have developed a rhodium-catalyzed addition−cyclization of 1,5-enynes with aryl- and alkenylboronic acids that occurs under mild conditions in an unprecedented modality. Exploration of the full potential of the metal vinylidene-mediated 1,1-carbofunctionalization process, including the development of asymmetric variants, is an ongoing subject of our studies, the result of which will be reported in due course.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) No reaction occurred at 23 °C, while extensive decomposition of enyne **1** was observed at 60 °C.

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(9) The 2-phenyl-1,3-dioxa-2-borinane was chosen instead of phenylboronic acid to avoid proton scrambling.

(10) The isotopic composition remained constant upon resubjection of **8′** to the same reaction conditions for 2 h. In a separate control experiment employing unlabeled **8**, no deuterium incorporation was observed.

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