Rhodium-catalyzed cycloaddition of 1,6-enynes with 2-bromophenylboronic acids: synthesis of a multi-substituted dihydronaphthalene scaffold†

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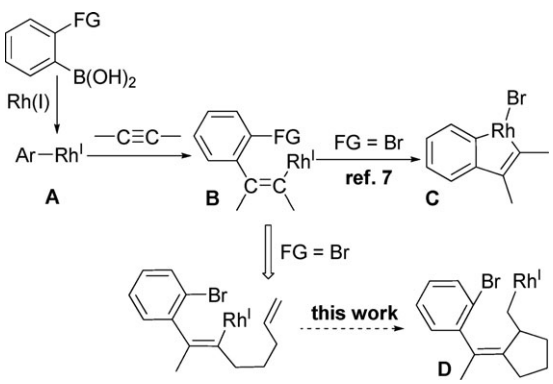
A formal [2 + 2 + 2] cycloaddition of a 1,6-enyne with 2-bromophenylboronic acid has been realized to construct a multi-substituted dihydronaphthalene scaffold, in which the direct reductive elimination mechanism of aryl-Rh(III)-C_{sp^3} species has been established to form an aryl-C_{sp^3} bond.

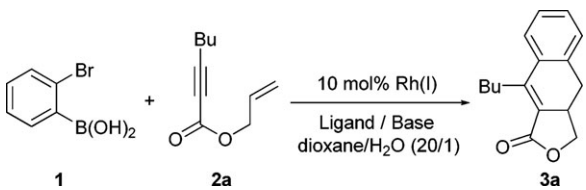
As powerful and efficient methods for multiple C–C bond formation, transition metal-catalyzed tandem reactions have been widely developed.[1] The advantages of these reactions are the formation of several bonds in a one-pot procedure using a single catalyst without either isolation of intermediates or a change in reaction conditions, high efficiency and favorable environmental considerations. Recently, the Rh(I)-catalyzed tandem reactions of alkynes with *ortho*-functionalized arylboronic acids, which lead to structurally complex molecules from relatively ready-available substrates, have been extensively studied.[2] As shown in Scheme 1, the reaction is initiated by the insertion of the alkyne into the aryl–rhodium(I) bond of species **A**, which is generated *via* the transmetalation of a Rh(I) complex with *ortho*-functionalized arylboronic acids, to give vinylrhodium(I) intermediate **B**. The flexibility of **B** has been demonstrated through its reaction with different functional groups (FG), such as aldehydes and ketones,[3] electron-deficient olefins,[4] $-CH_2Cl$,[5] nitriles,[6] and so on. With respect to arylbromides as FGs, intermediate **B** would undergo the oxidative addition of the C–Br bond to the vinyl–Rh(I) bond to form **C**, which has been proposed as a key intermediate by Chatani *et al.*[7] Inspired by their work, we envisioned that the insertion of olefins would occur prior to the oxidative addition step if one C=C double bond was introduced into **B** in an intramolecular way. As a result, intermediate **D** would be formed. Apparently, 1,6-enyne substrates[8] would be a suitable platform to fulfil this strategy. In this Communication, we report a new Rh(I)-catalyzed reaction of 1,6-enynes with 2-bromophenylboronic acid that provides a facile pathway to multi-substituted 1,2-dihydronaphthalene derivatives.[9]



Scheme 1 Strategies for the Rh(I)-catalyzed reactions of alkynes with 2-bromophenylboronic acids.

To test our hypothesis, initial experiments were performed on the reaction between 2-bromophenylboronic acid (**1**) and 1,6-enyne **2a** in the presence of 10 mol% of Rh(I) (Table 1). Fortunately, product **3a** was isolated under the reaction conditions of $Rh(CO)_2(acac)$ (10 mol%) and K_2CO_3 (1.2 equiv.), although the yield was as low as 21% (Table 1, entry 1). The ligands PPh_3 and BINAP obviously had a positive effect on the yield, and the best results were obtained when the ratio of PPh_3 to Rh(I) was 2 : 1 (Table 1, entries 2–4). The nature of the base also had an important impact on the

Table 1 Optimization of the Rh(I)-catalyzed reaction of **2a** with **1**[a]



1 2a 3a

Entry	Rh(I)	Ligand	Base	Yield (%)[c]
1	$Rh(CO)_2(acac)$	—	K_2CO_3	21
2	$Rh(CO)_2(acac)$	PPh_3[b]	K_2CO_3	64
3	$Rh(CO)_2(acac)$	PPh_3	K_2CO_3	73
4	$Rh(CO)_2(acac)$	BINAP[b]	K_2CO_3	40
5	$Rh(CO)_2(acac)$	PPh_3	Na_2CO_3	50
6	$Rh(CO)_2(acac)$	PPh_3	KOH	Trace
7	RhCl(COD)	—	K_2CO_3	17
8	RhCl(COD)	BINAP[b]	K_2CO_3	<10
9	$RhCl(PPh)_3$	—	K_2CO_3	Trace
10	RhOH(COD)	—	K_2CO_3	25
11	RhOH(COD)	PPh_3	K_2CO_3	56

[a] Reaction conditions: **2a** (0.3 mmol), **1** (0.45 mmol), Rh(I) (0.03 mmol), ligand (0.06 mmol), base (0.36 mmol) in dioxane/H_2O (20 : 1, 3 mL) at 100 °C for 5 h. [b] 10 mol% of ligand was added. [c] Isolated yield.

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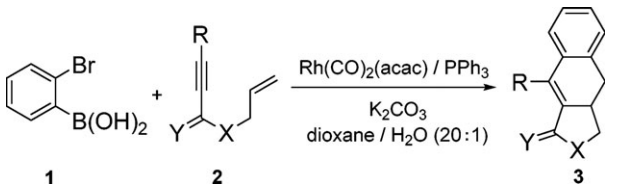
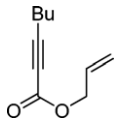
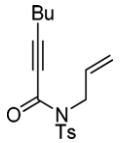
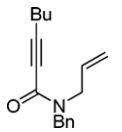
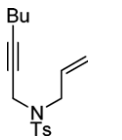
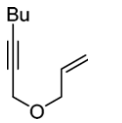
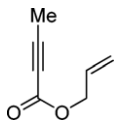
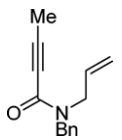
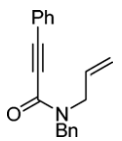
Table 2 The Rh(I)-catalyzed cycloaddition of **1** and **2**[a]



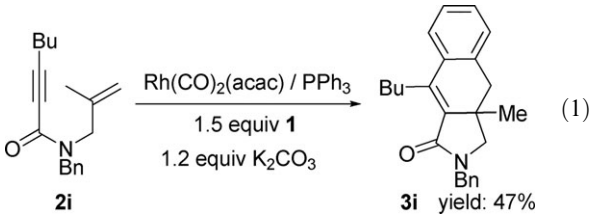
1 **2** **3**

Entry	1,6-Enyne	Product	Time/h	Yield (%)[c]
1	**2a**		5	**3a** 73
2	**2b**		4	**3b** 64
3	**2c**		4	**3c** 69
4	**2d**		8	**3d** 62
5	**2e**		4	**3e** 46
6	**2f**		3	**3f** 70
7	**2g**		3	**3g** 75
8	**2h**		7	**3h** 32
9[b]			3	**3h** 55

[a] Reaction conditions: 1,6-enyne (0.3 mmol), **1** (0.45 mmol), $Rh(CO)_2(acac)$ (0.03 mmol), PPh_3 (0.06 mmol), K_2CO_3 (0.36 mmol) in dioxane/H_2O (20 : 1, 3 mL) at 100 °C. [b] RhOH(COD) (0.03 mmol) was used. [c] Isolated yield.

reaction result. Other bases, such as Na_2CO_3 and KOH, were much less efficient than K_2CO_3 (Table 1, entries 5 and 6). With regard to the rhodium source, RhCl(COD) and $RhCl(PPh_3)_3$ were found to be inert in this transformation (Table 1, entries 8 and 9). However, RhOH(COD), with or without PPh_3, was found to be slightly less effective than $Rh(CO)_2(acac)$ (Table 1, entries 10 and 11).

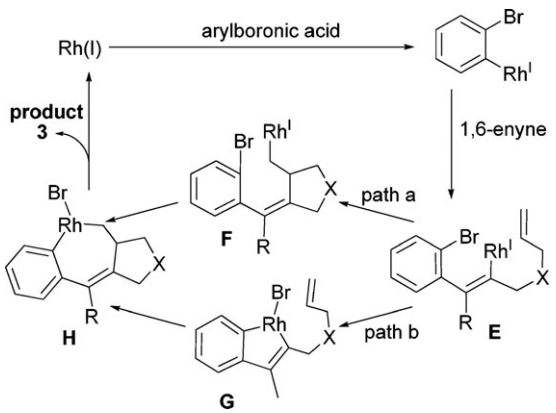
With the optimized conditions in hand, we further examined the scope of this new [2 + 2 + 2] cycloaddition by using a variety of 1,6-enynes (Table 2). In general, 1,6-enynes with an electron-deficient alkyne presented better results than those with an electron-rich alkyne. Both nitrogen- and oxygen-linked 1,6-enynes could be employed with similar performance. Primary alkyl groups, as well as the phenyl group, can be used as substituents on the alkyne, but the latter had a negative effect on the reaction, probably due to its steric bulk (Table 2, entry 8). The complex RhOH(COD) catalyst was found to be more efficient for 1,6-enynes with a phenyl substituent on the alkyne (Table 2, entry 9). It is worth noting that a quaternary carbon atom in product **3i** can be easily established from substrate **2i** under the same conditions (eqn (1)).



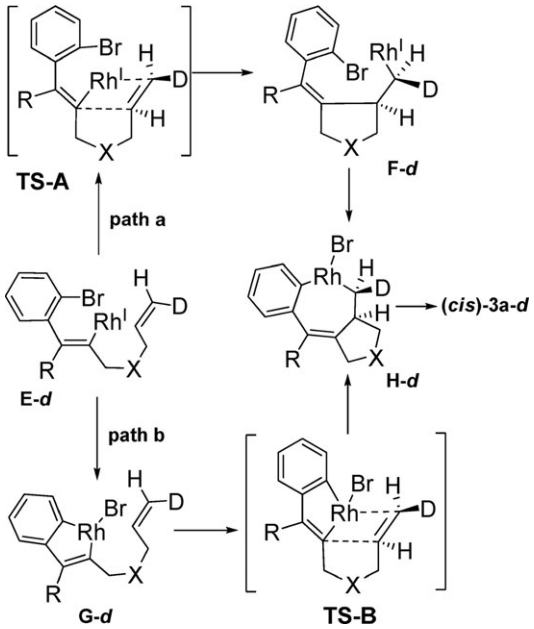
(1)

The proposed mechanism for this [2 + 2 + 2] cycloaddition is believed to follow the path shown in Scheme 2. Transmetalation firstly occurs between the Rh(I) complex and **1** to give an arylrhodium complex.[10] Next, insertion of the alkyne of the 1,6-enyne substrate into the aryl–rhodium bond produces vinylrhodium(I) intermediate **E**, which is expected to undergo the intramolecular insertion of olefins to give **F** (path a). Oxidative addition of the C–Br bond to the Rh(I) center leads to the formation of seven-membered ring Rh(III) species **H**.[11] Another possibility for the formation of **H** *via* intermediate **G** must also be considered (path b).[12] In the end, the reductive elimination of **H** releases product **3** and regenerates the Rh(I) catalyst.

To further investigate the proposed mechanism, deuterium-labelled substrate ***(Z)*-2a-*d*** was synthesized and subjected to the same conditions (eqn (2)). Compound ***(cis)*-3a-*d*** was isolated and its stereochemistry was assigned

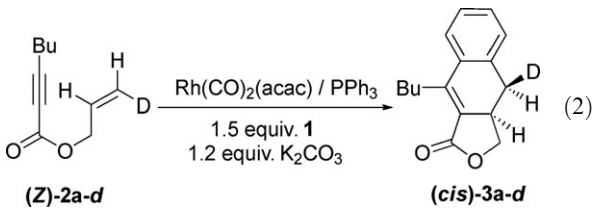


Scheme 2 The proposed catalytic cycle for the rhodium-catalyzed [2 + 2 + 2] reaction.



Scheme 3 A proposal for the outcome of eqn (2).

as the *cis*-configuration on the basis of ^{1}H NMR analysis (see the ESI†).



(2)

The outcome of eqn (2) is explained by the proposal outlined in Scheme 3. In the case of path a, the insertion of the olefin in **E-*d*** proceeds stereospecifically *via* **TS-A** to generate alkyl-Rh(I) intermediate **F-*d***, which is oxidized by C–Br to produce Rh(III)-intermediate **H-*d***. With regard to path b, similar chemistry also leads to the formation of **H-d** *via* **TS-B**. Finally, reductive elimination takes place with retention of stereochemistry to yield product **(*cis*)-3a-*d***. This means that the information about the C_{sp^2} stereochemistry can be completely transferred to the corresponding C_{sp^3} center.[13] We believe that this conclusion will be helpful for enantioselective reactions. This result also provides strong evidence that the formation of the aryl–C_{sp^3} bond from the aryl-Rh(III)-C_{sp^3} species proceeds *via* a direct reductive elimination mechanism.[14]

In summary, we have realized a new rhodium-catalyzed [2 + 2 + 2] cycloaddition of a 1,6-enyne with 2-bromophenylboronic acid, which was viewed as one two-component partner. The reaction involves the Rh-catalyzed regioselective insertion of an alkyne into an arylrhodium(I) species and the oxidative addition of C–Br bonds in the adjacent phenyl ring to the resulting vinylrhodium(I) species as key steps. More importantly, the outcome of the deuterium labelling experiment disclosed that a direct reductive elimination mechanism dominates over the formation of aryl–C_{sp^3} bonds from aryl-Rh(III)-C_{sp^3} species. Further studies on the application of the products and the reaction mechanism are ongoing in our laboratories, and will be reported in due course.

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