Rh(1)-catalyzed formal [2+2+2] cycloadditions of 1,6-diynes with potassium (Z)-(2-bromovinyl)trifluoroborate: a new strategy and a facile entry to polysubstituented benzene derivatives[†]

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A new strategy for Rh(1)-catalyzed [2+2+2] cycloadditions of 1,6-diynes with potassium (Z)-(2-bromovinyl)trifluoroborate as the third two-atom unit has been realized, which provides a facile entry to polysubstituented benzene derivatives.

Transition metal catalyzed trimerization of alkynes has been recognized as one of the most powerful and straightforward synthetic methods for polysubstituted benzene derivatives.¹ Particularly, the cycloaddition between 1,6-diyne 1 and monoalkynes has attracted increasing attention² and has been widely used³ in the field of materials science, fine chemical synthesis and natural product synthesis. In this context, rhodium catalysis has shown great potential, with the considerable successes of high degrees of chemo-, regio- and even enantioselectivity, as evident from recent reports, which mainly result from, under mechanistic consideration, the putative rhodacyclopentadiene Rh(III) intermediate A (part A, Scheme 1).⁴ Although these great successes have already been achieved, new mechanistic strategies for cycloaddition still remain as an important goal to demonstrate the potentials of rhodium chemistry. Herein, we report a novel Rh(1)catalyzed [2+2+2] cycloaddition of 1,6-divne 1 with potassium (Z)-(2-bromovinyl)trifluoroborate 2, in which substrate 2 could be viewed as a novel third two-atom unit (eqn (1) in Scheme 1). This strategy might provide a complementary protocol to classical Rh(1)-catalyzed synthesis of polysubstituented benzene derivatives (part B, Scheme 1).

In the presence of a proper rhodium catalyst, potassium (Z)-(2-bromovinyl)trifluoroborate 2 is thought to be transformed to the corresponding vinyl-Rh(i) intermediate \mathbf{B} ,⁵ which will undergo insertion of the alkyne of 1,6-diyne 1 to generate intermediate \mathbf{C} , followed by the formation of intermediate \mathbf{D} via a second insertion of an alkyne (path a, Scheme 1). Then, intramolecular oxidative addition⁶ of Rh(I) to vinylbromine occurs to produce intermediate \mathbf{F} , which can also be generated via path b, consisting of oxidative addition of Rh(I) to vinylbromine in intermediate \mathbf{C} and insertion of alkyne in \mathbf{E} (path b, Scheme 1). In the end, the reductive elimination of \mathbf{F} would release the Rh(I)-catalyst and deliver polysubstituented benzene derivatives 3, furnishing a formal [2+2+2] cycloaddition.

Several issues have to be addressed to make this new strategy work. First, the large-scale synthesis of potassium (2-bromovinyl)trifluoroborate **2** needs to be readily available⁷ and (*Z*)-configuration of alkene in **2** is mandatory for the oxidative addition step. Second, necessary manipulations should be conducted to avoid potential competition of cyclometallation⁸ between Rh(1)-complex and 1,6-diyne.

In the first attempt to test our new strategy, the reaction between **1a** and **2a** (1.5 equiv.) was examined in the presence of 10 mol% Rh(OH)(cod) with the mixture of dioxane and water (20:1) as solvent (Table 1, entry 1). To our delight, the desired [2+2+2] cycloaddition product could be obtained although the yield was only 7% (Table 1, entry 1). The ligand had a positive effect on reaction yield (entries 2 and 3), PPh₃ seemed to be better than BINAP (entry 7). Addition of caesium fluoride also played an important role, increasing the yield to 57% (entry 4). Other Rh(1)-catalyst precursors, such as Rh(CO)₂(acac), [Rh(cod)₂]BF₄, RhCl(PPh₃)₃ and RhCl(cod), were workable but with slightly less efficiency (Table 1, entries 9–12). Further screening has identified that the optimum conditions were 10 mol% Rh(OH)(cod), 20 mol% PPh₃, and 3.0 equivalents of substrate **2a** and CsF (Table 1, entry 6).



part B: new strategy for Rh(I)-catalyzed [2+2+2] cycloaddition of 1,6-diyne



Scheme 1 New scenario for Rh(i)-catalyzed [2+2+2] cycloaddition of 1,6-diyne.

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Table 1 Optimization for cycloaddition of 1a with 2a^a



6 CsF (3.0) 76 Rh(OH)(cod) PPh₃ 3.0 7' Rh(OH)(cod) BINAP 3.0 CsF (3.0) 62 84 Rh(OH)(cod) PPh₃ 3.0 CsF (3.0) 69 9 $Rh(CO)_2(acac)$ PPh₃ 3.0 CsF (3.0) 53 CsF (3.0) 10 PPh₃ 50 [Rh(cod)₂]BF₄ 3.0 11 RhCl(PPh₃)₃ 3.0 CsF (3.0) 61 12 RhCl(cod) PPh₃ 3.0 CsF (3.0) 63

^{*a*} Reaction conditions: the mixture of dioxane and water (3 mL, 20:1) was injected into **1a** (0.3 mmol), **2a**, ligand, Rh(1) and additive in reaction vessel (10 mL). The resulting mixture was stirred at 100 °C for 24 h. ^{*b*} Without ligand. ^{*c*} 10 mol% ligand was used. ^{*d*} 5 mol% Rh(1) and 10 mol% PPh₃ were used. ^{*e*} Isolated yield.

Notably, all of these experiments could be performed under air without affecting the reaction results.



Having established the optimized reaction conditions, we setout to explore the scope of this transformation (Table 2). In general, the Rh(I)-catalyzed [2+2+2] cycloadditions can be smoothly achieved to provide benzene derivatives 3 in moderate to good yields irrespective of whether the 1,6-divnes are nitrogen, oxygen or carbon linked. When terminal diyne 1b is used, the yield would dramatically drop, probably due to its reactivity⁹ towards the Rh(1)-complex (entry 2, Table 2). The oxo-substituented diynes can be employed to offer 1,4-phenylenedimethanol derivatives 3fa and 3ga with lower vields (entries 6 and 7). It is noted that some unidentified side products are detected in all cases, which are thought to be the reason for lower yields of 3. With respect to the third 2-atom unit, trifluoroborate 2b, with a butyl group at 2-position, can be also employed and exhibits similar reactivity (entries 8-10, Table 2). However, asymmetric diyne 1h, with an electron-deficient alkyne, presents worse results and generates two isomers with low regeoselectivity (2:1) (eqn (2)). Similar performance also happens to diyne 1i, providing a mixture of 3i-1 and 3i-2 (2.5:1) which could be readily reduced to offer phenylenedimethanol derivative 4^{10} (Scheme 2).

To shed the light on the mechanism, two control experiments were designed and performed with compounds **1j-1** and **1j-2** as the substrates (Scheme 3). Interestingly, these two different



Scheme 2 Synthesis of phenylenedimethanol derivative 4.

Table 2 The scope of [2+2+2] cycloaddition between 1 and 2^a



Entry	$1 (R^{1}, X)$	2 (R ²)	t/h	Yield $(\%)^{b}$
1	1a (Ph, NTs)	2a (Ph)	24	76 (3aa)
2	1b (H, NTs)	2a (Ph)	12	20 (3ba)
3	1c (Ph, O)	2a (Ph)	5	75 (3ca)
4^c	1d (Ph, Y)	2a (Ph)	3	83 (3da)
5	1e (Bu, NTs)	2a (Ph)	2	88 (3ea)
6	1f (CH ₂ OMe, NTs)	2a (Ph)	1	60 (3fa)
7	1g (CH ₂ OAc, NTs)	2a (Ph)	2	40 (3ga)
8^c	1d (Ph, Y)	2b (Bu)	3	85 (3db)
9	1a (Ph, NTs)	2b (Bu)	5	75 (3ab)
10	1c (Ph, O)	2b (Bu)	5	70 (3cb)
				. /

^{*a*} Reaction conditions: the solvent of dioxane and water (3 mL, 20:1) was injected into the mixture of **1** (0.3 mmol), **2** (0.9 mmol), PPh₃ (15.7 mg, 0.06 mmol), Rh(OH)(cod) (6.8 mg, 0.03 mmol) and CsF (136.8 mg, 0.9 mmol) in reaction vessel. The resulting mixture was stirred at 100 °C. ^{*b*} Isolated yield. ^{*c*} Y = C(CO₂Et)₂.

substrates exhibited almost the same reactivity under the standard conditions, in which two corresponding "normal" products **3ja-1** and **3ja-2** could be isolated in a yield of 56% and 50%, respectively; meanwhile a common "abnormal" product, compound **5**, could be obtained in a yield of 11% and 10%, respectively.

On the basis of these results, the detailed mechanism is outlined in Scheme 4 and we conclude that the reaction pathway should involve intermediate **D-2** which corresponds to the formation of compound 5. At present, we do not have convincing evidence to distinguish these two different mechanisms (Schemes 1 and 4), but the outcome in Scheme 3 tempts us to conclude that our new strategy for Rh(1)-catalyzed [2+2+2] cycloaddition is really operating *via* path a.



Scheme 3 Two control experiments



Scheme 4 Explanation for the formation of compounds 3ja and 5.

In summary, we have realized a novel Rh(i)-catalyzed formal [2+2+2] cycloaddition between 1,6-diyne **1** and potassium (*Z*)-(2-bromovinyl)trifluoroborate **2**, which provides a facile access to highly substituted benzene derivatives. In this transformation, compound **2**¹¹ is thought to be crucial to fulfil this new strategy for Rh(i)-catalyzed [2+2+2] cycloaddition due to its dual structural functions with nucleophilic vinyl borate and electrophilic vinylbromine. Further studies on the mechanism and synthetic utility are underway in our laboratory and will be reported in due course.

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