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Rhodium-catalyzed selective [2 + 2 + 2] cyclizations of 1,6-diynes with monoynes leading to isoindolines and isobenzofurans

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Abstract

A highly efficient and selective [2 + 2 + 2] cyclization of diynes and monoalkynes was catalyzed by rhodium under room temperature in water/THF mixed solvent, affording isoindolines and isobenzofurans in good to excellent yields. The center atoms (N, O) in the diynes showed a significant effect for the cyclization.

Keywords: *N*,*N*-dipropargyl *p*-toluenesulfonamide; Dipropargyl ether; Cyclization; Rhodium complex; Diynes

Transition metal-catalyzed [2 + 2 + 2] cyclizations of three nonconjugated π-systems have been widely investigated as a valuable synthetic tool for the syntheses of aromatic and non-aromatic rings [1]. However, a limitation of the traditional Reppe-type cyclization is the difficulty in product control [2]. To address this issue, the intermolecular cycloaddition of diynes with monoalkynes, or the intramolecular cyclization of triynes has been developed as a promising tool to construct benzene derivatives [3]. But still dimerization of the diynes or trimerization of monoyne components is a serious drawback. Additionally, a large excess of the monoalkyne component and a high-dilution conditions are generally employed to suppress the competing side reactions [4]. The selectivity and yield of the cyclization highly depend on the substrates, catalysts and solvents, *etc*. Further efforts need to be made to broaden the scope and to overcome the limitations. Herein, we wish to report a highly efficient and selective rhodium-catalyzed [2 + 2 + 2] cycloaddition of diynes with monoalkynes at room temperature, with emphasis on the use of water/THF mixed solvent.

Previously, Eaton and co-workers showed that at 80 °C, a cobalt complex can catalyze [2 + 2 + 2] cyclization of alkynes in a mixture of water and toluene [5]. Kinoshita et al. reported a [2 + 2 + 2] cyclotrimerization of alkynes catalyzed by a water-soluble rhodium complex in a biphasic system [6]. Therein, water was used to accelerate the cycloaddition so as to compensate for the sacrificed efficiency due to high dilution. During our study of transition metal-catalyzed hydrosilylation of alkynes in aqueous media, we occasionally observed that oligomerization of alkynes to generate benzene derivatives as by-products could be suppressed by increasing the ratio of water. Subsequent investigations of bimolecular cyclization of some diynes with monoalkynes revealed that with the aid of water, the reaction could be realized at room temperature efficiently with no or minor side oligomerization products.

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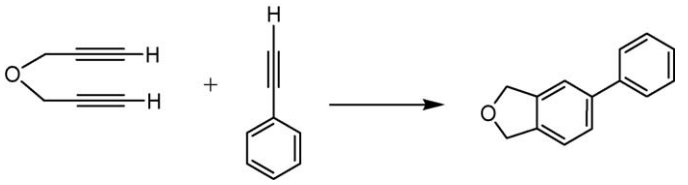
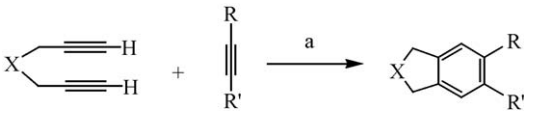


Scheme 1. (1) Reaction conditions. 1 mmol propargyl ether, 1 mmol phenylacetylene, in 4 mL H_2O/THF (1:1), at room temperature, 1 mol% catalyst, 1 h; (2) yields were determined by GC–MS using acetophenone as standard.



X= O, S, NTs, CH_2

Scheme 2. a 1%[Rh(cod)Cl]$_2$, H_2O/THF (1:1), r.t., 1 h.

To start our research, cross-coupling between dipropargyl ether and phenylacetylene was used as a model reaction (Scheme 1) and several commercially available catalysts were examined for the cyclization. Because all the catalysts screened are insoluble and always results in a solid ball in water, pure water is not a good choice as the reaction media. Otherwise the reaction is difficult to be carried out completely. Therefore, a water/THF (1:1) mixed solvent was employed as the reaction media for a balanced solubility and reactivity. The use of [Ir(cod)Cl]$_2$ or [Ir(coe)$_2$Cl]$_2$ led to either low yield or no desired reaction product, respectively, while as it was reported that the reaction can occur in the presence of specific ligand (like DPPE) [7]. The use of rhodium-based catalyst such as Rh(acac)(C_2H_4)$_2$ and [Rh(cod)Cl]$_2$ provide the cyclization product smoothly in 65% and 72% isolated yield respectively. Other metal complexes such as RuCHPhCl$_2$[P(C_6H_{12})$_3$]$_2$, Ru(CO)(H_2)(PPh_3)$_3$, (CH_2=$CHCH_2PdCl$)$_2$, $Pd_2(dba)_3$, $PdCl_2(PPh_3)_2$, as well as $Re(CO)_5Cl$ were virtually inactive under the same reaction conditions.

Subsequently, various diynes and alkynes including both terminal alkynes and internal alkynes were employed under our standard condition (Scheme 2). The results with [Rh(cod)Cl]$_2$ catalyst are listed in Table 1. In each case, when *N*,*N*-dipropargyl *p*-toluenesulfonamide was used as the diyne (Table 1, entries 1–7) essentially no by-product (such as due to oligomerizations) was observed when reacting with a terminal alkyne to yield the corresponding cyclization product in high yields. However, the use of internal alkynes decreased the reactivity, possibly due to steric reasons.

Recently, Yus and co-workers reported synthesis of 4-phenylphthalan via cyclization of dipropargyl ether with phenyl acetylene, by use of Wilkinson's catalyst in toluene [8]. The reaction gave only a moderate yield (50%). In our cases, good yields can still be observed for most reactions when dipropargyl ether was used as the diyne (Table 1, entries 8–16). In addition, when an internal alkyne with electron-withdrawal groups was employed as the monoalkyne, the reaction gave a rather low yield (entry 17, 34%). It is worthy to note that the yields (71–84%) for dipropargyl ether reactions were roughly lower than those for *N*,*N*-dipropargyl *p*-toluenesulfonamide reactions. Obviously the center atom (N or O) played a crucial role for this cyclization. To further test this center atom effect of the diynes, 1,6-heptadiyne (Table 1, entry 18), 2,2-dipropargyl-1,3-cyclohexadione(Table 1, entry 19) and dipropargylthioether (Table 1, entry 20), in which the center atom is either C or S, were used as diynes for the cyclization. Interestingly, very low yields of the cyclization products were observed. These reactions showed a significant drop in reaction rate and resulted in complicated mixture of products.

To the best of our knowledge, although a variety of diynes with either electron-donating or electron-withdrawing groups were investigated as substrates for the cyclization [9], there is no comment on the role of center atom. It is more reasonable that coordination between the metal and the center atom played an important role for certain kind of diyne substrates, than something related to its electronic effects. To verify such a hypothesis (see Table 2), *N*,*N*-dipropargyl *p*-toluenesulfonamide was reacted with 1,6-heptadiene under the same reaction condition, again virtually a single cyclization product was obtained, with an excellent yield (98%). The reaction of dipropargyl ether with 1,6-heptadiyne lead to the cross-cyclization product as major product (yield 67%), together with some oligomerization products. No

Table 1
Reaction of various diynes with monoalkynes at room temperature.

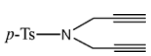
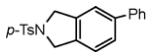
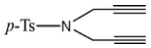
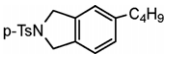
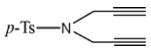
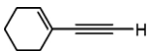
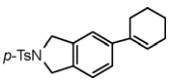
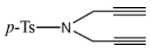
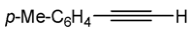
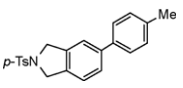
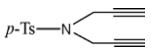
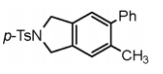
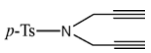
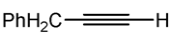
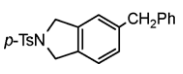
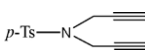
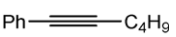
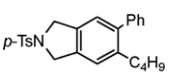
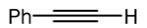
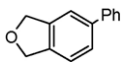
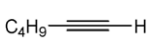
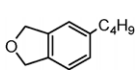
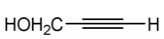
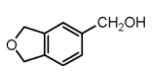
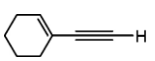
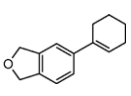
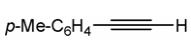
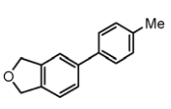
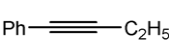
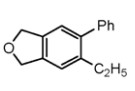
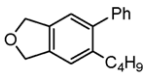
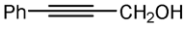
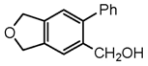
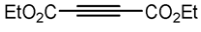
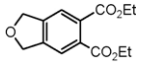
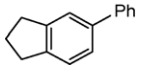
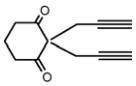
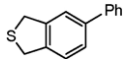
Entry	Diyne	Alkyne	Product	Yield (%)[a]
1				97
2				92
3				90
4				95
5				76
6				92
7				64
8				82
9				77
10				64
11				84
12				84
13				80
14				71

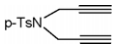
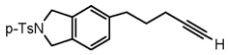
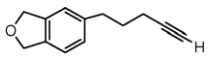
Table 1 (*Continued*)

Entry	Diyne	Alkyne	Product	Yield (%)[a]
15				87
16				74
17				34
18				16[b]
19			No reaction	
20				10[b]

[a] Isolated yields after column chromatography.

[b] Determined by GC–MS. All reactions were carried out with 1 mmol of diyne, 2 mmol of alkyne, and 1% $[Rh(cod)Cl]_2$ as catalyst for 1 h at room temperature.

Table 2
Cyclization between two diynes.

Entry	Diyne (A)	Diyne (B)	Product	Yield (%)
1				94
2				67

cyclization product was found in which 1,6-heptadiyne reacted as a diyne for the cyclization. This suggested that ''N'' coordinated stronger than ''O'' onto rhodium.

In conclusion, a highly efficient and selective [2 + 2 + 2] cross-cyclization of diynes with monoalkynes was discovered at room temperature in water/THF mixed solvent via rhodium catalysis. The high efficiency and high regioselectivity together with the convenient reaction conditions make it readily applicable for the syntheses of isoindolines and isobenzofurans. Further studies on the scope, mechanism, and synthetic application of the reaction are currently under investigation.

Typical procedure: A mixture of dipropargyl ether (94 mg, 1 mmol), 3-phenyl-2-propyn-1-ol (264 mg, 2 mmol) and chloro(1,5-cyclooctadiene)rhodium(I) dimer (5 mg, 0.01 mmol) in 4 mL of water/THF (1:1) was capped and stirred at r.t. for 1 h. Then the reaction mixture was extracted with methylene chloride (3 × 5 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent:hexane/ethyl actate = 4:1) to give the desired product (167 mg, 74% yield). IR (neat) 3406, 3058, 2869, 1625, 1446, 1356, 1267, 1046, 1007, 880, 770, 702. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.11 (m, 7H), 5.10 (s, 4H), 4.57 (s, 2H), 2.15 (b, 1H). ^{13}C NMR (100 M, $CDCl_3$): δ 140.9, 140.8, 138.8, 138.6, 137.9, 129.4, 128.5, 127.6, 122.7, 121.0, 73.7, 73.6, 63.1, MS: 51, 84, 152, 167, 178, 197, 226(M^+). EA calcd. (%) for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.41; H, 6.33.

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