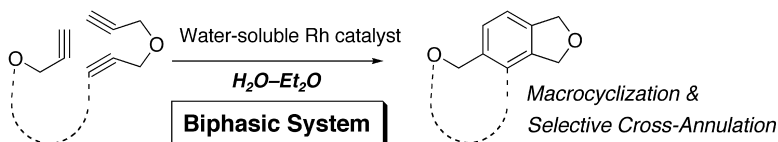


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Rhodium-Catalyzed [2 + 2 + 2] Cyclotrimerization in an Aqueous–Organic Biphasic System

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The synthesis of medium- and large-sized ring systems via intramolecular cyclization often requires highly diluted reaction conditions or the use of a slow addition technique to prevent intermolecular reactions.¹ However, the use of large quantities of solvent is uneconomical and inconvenient, and the process of slow addition requires a special apparatus and is a laborious operation. In addition, using highly diluted reaction conditions often retards the reaction rate and results in lower efficiency. It is highly desirable to develop a new tactic to circumvent these drawbacks.

We anticipated that a biphasic system could control the concentration of an organic hydrophobic substrate in the aqueous phase (Figure 1).^{2,3} Distribution of substrate would keep the concentration of substrate in the reaction phase low. If the reaction proceeds in the aqueous phase, the system would achieve diluted reaction conditions without the use of a large amount of solvents.

We examined a rhodium-catalyzed [2 + 2 + 2] cyclotrimerization of alkynes as a test case for our biphasic system.^{4,5} A Diels–Alder type mechanism involving the intermediacy of metallacyclopentadiene complexes has been postulated for the cyclotrimerization of alkynes (Scheme 1).⁶ Rate enhancement of the Diels–Alder reaction in aqueous media is well-recognized.⁷ We hoped that water might also accelerate this metal-mediated cycloaddition, compensating for the sacrificed efficiency due to high dilution.

A water-soluble rhodium catalyst was prepared in situ from [RhCl(cod)]₂ and the trisodium salt of tris(*m*-sulfonatophenyl)-phosphine (tppts) in water at 75 °C. The ability of this catalyst to promote cyclotrimerization in the biphasic system was examined with 4,9-dioxadodeca-1,6,11-triyn-1-ol **1a**. A solution of triyne **1a** in ether was introduced to the catalyst at room temperature, and tricyclic compound **2a** was obtained in good yield after stirring for 3 h (Scheme 2).

We then focused on the synthesis of medium and large rings in the water–ether biphasic system.⁸ The reaction of triynes with Wilkinson's catalyst generally induces polymerization of alkynes except in cases where 5–6–5 tricyclic systems are formed.⁹ To our delight, we found that medium and large rings can be obtained in excellent yields with only trace amounts of polymeric compounds. In addition, no dimerization products were detected in the reaction mixture.¹⁰ Table 1 summarizes the results of the cyclotrimerization of a series of triynes. It is noteworthy that 4,15-dioxaoctadeca-1,6,17-triyn-1-ol (**1h**) furnished 12-membered methacyclopentane **3h** in 32% yield along with the normal cyclized product **2h** (57%) (Scheme 3). Macrocyclization of **1i** to provide 12- and 13-membered ring systems was also successful.¹¹

We also examined the cross-annulation of dipropargyl ether with alkynols (Scheme 4). The [2 + 2 + 2] annulation between a 1,6-diyne and an alkyne often suffers from dimerization and trimerization of the diyne. In particular, dipropargyl ether is a highly reactive substrate and provides the dimerized product, propargyl ether **5**, and the trimerized product, benzyl ether **6**, very rapidly. Grigg has already reported that reacting a large excess (5 equiv)

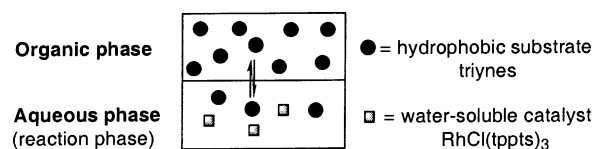
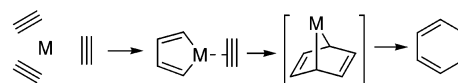


Figure 1. Control of concentration in the biphasic reaction system.

Scheme 1



Scheme 2

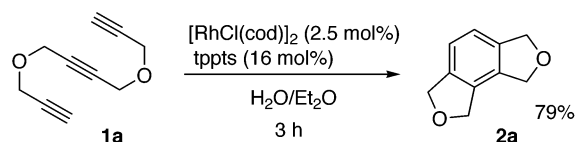


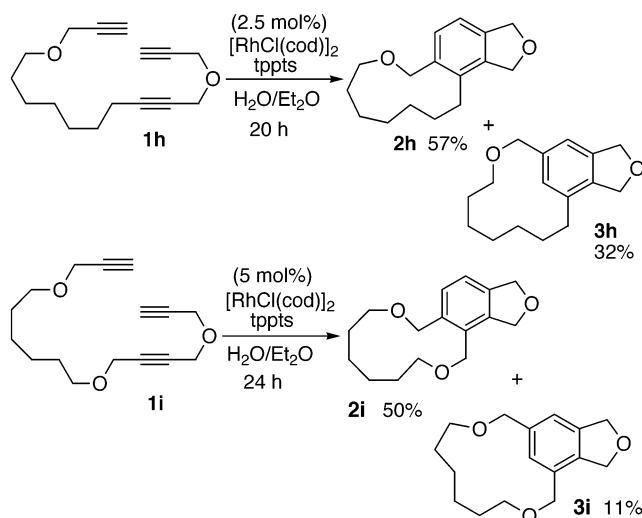
Table 1. Cyclization of Triynes in a H₂O–Et₂O Biphasic System^a

entry	triyne	<i>n</i>	R	time (h)	product	yield (%)
1	1b	1	H	10	2b	93
2	1c	2	H	19	2c	84
3	1d	3	H	19	2d	88
4	1e	4	H	19	2e	91
5	1f	5	H	22	2f	89
6	1g	2	CH ₃	19	2g	85

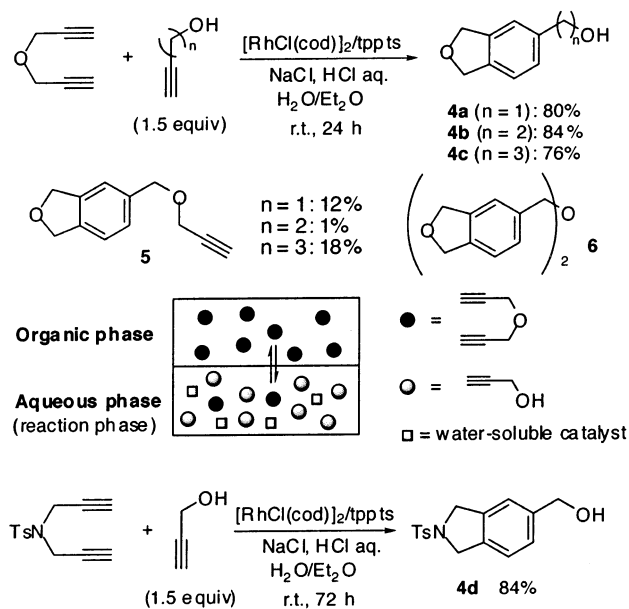
^a Reaction conditions: [RhCl(cod)]₂ (0.0125 mmol), tppts (0.08 mmol), triyne (0.5 mmol), H₂O (50 mL), ether (10 mL), room temperature.

of propargyl alcohol with dipropargyl ether yields the desired product **4a** in 44% yield along with **5** and **6**.¹² We anticipated that the formation of dimer **5** and trimer **6** would be suppressed in a biphasic system due to the limited concentration of the hydrophobic diyne in the aqueous phase. Propargyl, homopropargyl, and bishomopropargyl alcohol, which are completely soluble in water, were selected as hydrophilic alkyne partners.¹³ We were pleased to find that the reaction in the biphasic system cleanly provided the desired cross-annulation products **4** in good yields even with 1.5 equiv of alkynols. The use of hydrochloric acid and sodium chloride improved selectivity and conversion of the reaction, although the reason is not yet clear at this stage. In addition, the cross-annulation of *N*-tosyl-*N,N*-dipropargylamine with propargyl alcohol furnished isoindoline **4d** in 84% yield. Diethyl 2,2-dipropargylmalonate, which is completely insoluble in water, yielded none of the annulation product. This result indicates that,

Scheme 3



Scheme 4



for the reaction to proceed, some of the diyne partner must be present in the aqueous phase.

To date, transition metal catalysis in biphasic systems has been developed mainly for the purpose of easy separation and for the efficient recycling of catalysts. Here, we expand the utility of the biphasic system by demonstrating its ability to control substrate concentration.¹⁴ A rhodium-catalyzed [2 + 2 + 2] cyclotrimerization of triynes in a water–organic biphasic system has been explored. The biphasic system offers diluted reaction conditions for macrocyclization reactions. Selective cross-annulation between hydrophobic diynes and hydrophilic alkynes has also been achieved.

Further research on the water–organic biphasic system is currently underway in our laboratory.

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Supporting Information Available: General procedures and spectral data for compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (8) Ruthenium-catalyzed cyclization of **1b** and **1c** in high dilution conditions has been recently reported at the 49th Symposium on Organometallic Chemistry, Japan, 2002. Yamamoto, Y.; Arakawa, T.; Itoh, K. *Abstracts of the 49th Symposium on Organometallic Chemistry*; Japan, 2002; p 246.
- (9) The reaction of **1c** (0.5 mmol) with $\text{RhCl}(\text{PPh}_3)_3$ (5 mol %) in ethanol (50 mL) at room temperature resulted in formation of **2c** in only 20% yield along with unidentified oligomeric products.
- (10) The reaction without the ether phase resulted in extensive formation of polymeric products.
- (11) The existence of oxygen at the 9-position is crucial: the reaction of 4,10-dioxanonadeca-1,6,18-triyne afforded 12-membered cyclized product in 16% yield along with 13-membered methacyclophane in 14% yield.
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- (13) We could not detect any of the tri(hydroxymethyl)benzenes. A rhodium-catalyzed cyclotrimerization of monoalkyne is generally slow.
- (14) The concentration of **1c** in the aqueous phase was roughly measured to be 1.3×10^{-4} mol/L.

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