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Biphasic Synthesis

Synthesis of Medium- and Large-Sized Lactones in an Aqueous–Organic Biphasic System**

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Numerous natural products and biologically active compounds have various types of ring moieties.[1] Cyclization reactions have been investigated extensively, and the devel-

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opment of efficient methods to construct cyclic structures has been a central field in organic synthesis.

The formation of medium-sized ring compounds is still problematic even today. The reaction forming the medium-sized ring often proceeds sluggishly, due to the unfavorable transannular interaction and negative activation entropy for the cyclization.[2] In addition, the preparation of macrocycles is not always trivial, since the two reaction sites in a molecule cannot interact with each other efficiently in some cases. In these cases, intermolecular reactions compete with the desired intramolecular reaction. To retard the intermolecular process, high-dilution conditions with large amounts of solvent combined with a slow-addition technique have been adopted in the construction of medium- and large-sized ring compounds. However, the use of large quantities of solvent is uneconomical and inconvenient, and the process of slow addition is a laborious operation. Recently, we have proposed the use of an aqueous–organic biphasic system to circumvent such drawbacks.[3] The biphasic system controls the concentration of the organic hydrophobic substrate in the aqueous phase (Figure 1). The distribution of the substrate retains the high-dilution conditions in the aqueous reaction phase. The applicability of the system has been demonstrated in rhodium-catalyzed [2+2+2] annulation reactions of triynes.

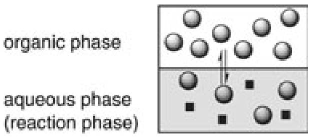
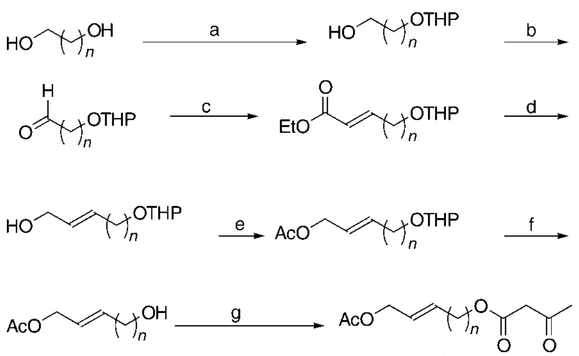


Figure 1. Concept of biphasic control of the concentrations in an aqueous phase. Circles: hydrophobic substrate, squares: water-soluble catalyst.

The formation of medium-sized lactones is still a challenging cyclization. There are few examples of effective medium-sized-lactone formation.[4,5] Herein we wish to report the preparation of a series of medium- and large-sized lactones by an intramolecular Tsuji–Trost reaction without high-dilution conditions.

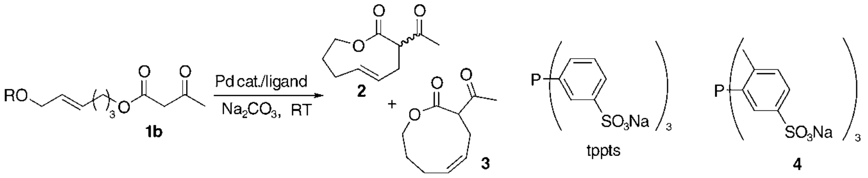
We investigated the aqueous Tsuji–Trost reaction for the synthesis of medium-sized lactones in the biphasic system for the following reasons: 1) A conformational change of the substrate, which would facilitate ring formation, is expected due to the hydrophobic effect in water. 2) π-Allylpalladium species can be readily formed from allylic esters in aqueous media.[6] 3) Macrocyclization by the Tsuji–Trost reaction has served as a pivotal step in a number of total syntheses of natural products,[7] and it is therefore highly desirable to develop a related efficient procedure without high dilution. The starting materials were synthesized as shown in Scheme 1.



Scheme 1. Preparation of the starting materials. a) 3,4-Dihydro-2*H*-pyran, TsOH (cat.), THF; b) Swern oxidation, c) $(EtO)_2P(O)CH_2C(O)OEt$, NaH, THF, 0°C→RT; d) DIBAL-H (2 equiv), hexane, 0°C→RT; e) Ac_2O, pyridine; f) TsOH (cat.), CH_3OH; g) diketene, THF, AcONa, reflux. DIBAL-H = diisobutylaluminum hydride, THP = tetrahydropyranyl, Ts = toluene-4-sulfonyl.

The macrocyclization of **1b** ($n = 3$, 0.5 mmol) to the nine-membered lactone with a water-soluble palladium complex prepared from $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (2.5 mmol%) and the trisodium salt of tris(*m*-sulfonatophenyl)phosphine (tppts; 22 mol%) in water (5 mL) at room temperature for 24 h led to the desired lactone in only 1% yield. After several trials, we found that an efficient macrocyclization reaction was accomplished in a water–ethyl acetate biphasic system. The results are shown in Table 1. In the biphasic system, an isomeric mixture of lactones **2** and **3** (2:1) was obtained in 63% combined yield after 12 h (entry 2). Lactone **2** consists of two diastereomers as a consequence of the planar chirality of its *trans* olefinic linkage. With a methoxycarbonate group instead of the acetate group as the leaving group, the yield was slightly improved but the selectivity was decreased (entry 3).[8] The amount of water and ethyl acetate is crucial:

Table 1: Optimization of the reaction conditions for the synthesis of nine-membered lactones.[a]

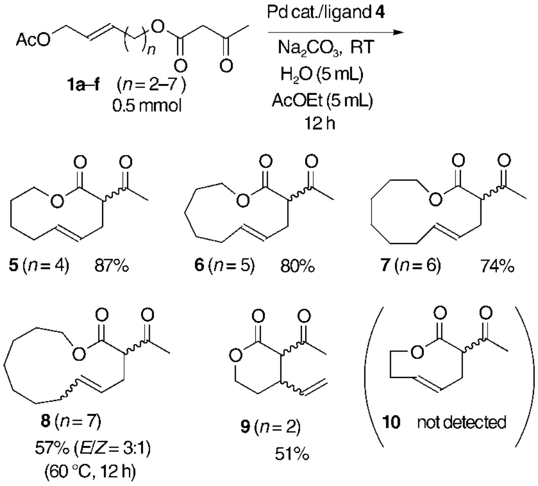


Entry	RO	Ligand	System	*t* [h]	Yield [%][b]	Ratio **2**:**3**[c]
1	AcO	tppts	H_2O[d]	24	trace	
2	AcO	tppts	H_2O/AcOEt	12	63	2:1
3	ZO[e]	tppts	H_2O/AcOEt	24	66	1:1
4	AcO	tppts	H_2O/AcOEt[f]	24	n.r.[g]	
5	HO	tppts	H_2O/AcOEt	24	trace	
6	AcO	**4**	H_2O/AcOEt	12	74	13:1
7	AcO	PPh_3	THF[h]	12	36	1:1

[a] If not otherwise stated, $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (2.5 mol%), water-soluble ligand (22 mol%), Na_2CO_3 (1.2 mmol), **1b** (0.5 mmol), H_2O (5 mL), and AcOEt (5 mL) were employed. [b] Yield of isolated product. [c] Determined by NMR spectroscopy. [d] H_2O (5 mL) was employed. [e] Z: methoxycarbonyl. [f] H_2O (50 mL)/AcOEt (10 mL). [g] Not recorded. [h] THF (10 mL, 0.05 M) was employed.

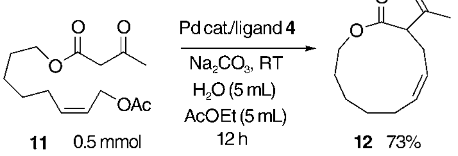
in a biphasic system with 50 mL of water and 10 mL of ethyl acetate, the lactone was not obtained even after a prolonged reaction period (24 h, entry 4). Using the water-soluble ligand **4**,[9] prepared by sulfonation of tri(*o*-tolyl)phosphine with oleum, instead of tppts greatly enhanced the yield and selectivity (**2**:**3**, entry 6). Obviously, ligand **4** can suppress the isomerization of the π-allylpalladium intermediate, an isomerization that results in the formation of the more stable *cis*-configured nine-membered ring structure **3**. The reaction in THF also provided lactones **2** and **3**, but yield and selectivity were far less than those observed in the biphasic system (entry 7).[10] Since we have recently reported that π-allylpalladium species can be prepared from allylic alcohols in an aqueous system,[11] we attempted the direct use of an allylic alcohol as the substrate. Disappointingly, the desired lactone was not obtained (entry 5).[12]

Under the optimized reaction conditions, we conducted the synthesis of medium- and large-sized lactones with the substrates that have longer methylene chains, **1c**–**f** (Scheme 2). These substrates afforded the desired lactones in high yields without any byproducts, as in the case with **1b**, R = OAc. In contrast, the reaction of **1e** in *N,N*-dimethylformamide (DMF, 0.05 M) provided the 12-membered lactone **7** in only 28 % yield. Formation of the 13-membered lactone from **1f** proceeded slowly to provide the product **8** in 17 % yield (with 51 % recovered starting material) under the biphasic conditions at room temperature for 12 h. However, the yield of **8** was improved to 57 % when an elevated reaction temperature was used (60 °C for 12 h), although the stereoselectivity was decreased (*E*/*Z* = 3:1). Substrate **1a** afforded only **9** in 51 % yield by 6-*exo* cyclization. The eight-membered lactone **10** was not detected.



Scheme 2. Synthesis of medium- and large-sized lactones in the biphasic system. The product formed by **1b** (*n* = 3) is shown in Table 1.

To elucidate the configuration of the olefin moiety in the lactones, we conducted methanolysis of the products. The configuration of the double bond was assigned as *E* in all cases on the basis of ^{1}H NMR spectroscopy analysis and comparison with authentic samples. Interestingly, the configuration of the substrates is retained in the products under the aqueous biphasic conditions with ligand **4**. As shown in Scheme 3, the substrate **11** that has a *Z* olefin moiety afforded the *Z*-configured lactone **12** in excellent yield and with high selectivity.



Scheme 3. Cyclization of a *cis* isomer in the biphasic system.

In conclusion, we have succeeded in synthesizing medium- and large-sized lactones in high yields in an aqueous–ethyl acetate biphasic system without the use of large amounts of solvent. These lactones retain the original configuration of the olefin moiety in their rings. We propose that the biphasic cyclization protocol is a useful tool for the preparation of medium- and large-sized ring compounds.

Experimental Section

Representative standard procedure: $[\mathrm{PdCl}(\eta^3\text{-}C_3H_5)]_2$ (4.6 mg, 0.0125 mmol) and **4** (67.5 mg, 0.11 mmol) were placed in a 20-mL flask under an argon atmosphere. Degassed water (5 mL) was introduced, and the mixture was stirred vigorously at 75 °C for 15 min. Na_2CO_3 (127.2 mg, 1.2 mmol) and ethyl acetate (3 mL) were added to the homogeneous clear yellow solution at room temperature. A solution of **1c** (128.1 mg, 0.5 mmol) in ethyl acetate (2 mL) was added to the ethyl acetate phase. After stirring for 12 h, the mixture was extracted with ethyl acetate. The organic extracts were dried and concentrated. Purification of the residual oil afforded 3-acetyl-3,4,7,8,9,10-hexahydrooxecin-2-one (**5**, 85.7 mg, 0.44 mmol) in 87 % yield.

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[12] This allylic alcohol is quite soluble in water. We confirmed that more than 70 % of it existed in the water phase. We suppose that the β-dicarbonyl moiety of the substrate affects the activity of the water-soluble palladium catalyst. On the other hand, the concentration of **1c** ($n = 4$) in the aqueous phase was measured to be roughly 1.7×10^{-3} mol L^{-1}. This value equals 1.7 % of the introduced substrate.