Water-Soluble Chiral Ruthenium(II) Phenyloxazoline Complex: Reusable and Highly Enantioselective Catalyst for Intramolecular Cyclopropanation Reactions

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Abstract: The intramolecular cyclopropanation of various *trans*-allylic diazoacetates and alkenyl diazoketones has been achieved with excellent enantio-selectivities of up to 98% *ee* and in quantitative yields by using a water-soluble ruthenium(II)/ hydroxymethyl(phenyl)oxazoline catalyst in a water/ether biphasic medium. The catalyst could be reused at least five times.

Keywords: asymmetric synthesis; biphasic medium; cyclopropanation; ruthenium; water-soluble catalyst

The intramolecular cyclopropanation reaction is one of the most useful synthetic methodologies for constructing bicyclic structures containing fused cyclopropane ring as natural product precursors.^[1] Since the first report in 1961 of the catalytic intramolecular cyclization with an unsaturated diazo ketone,^[2] different catalytic systems have been used for intramolecular cyclopropanations.^[3] Despite the high reactivity and enantioselectivity displayed by the previously reported catalysts, only a few catalytic reactions could be performed in aqueous media, which is desirable for green chemistry.^[4] Our research group has developed efficient water-soluble Ru(pybox) catalysts of **1** and **2** for asymmetric inter- and intramolecular cyclopropanation reactions.^[5] Although the Ru complex of **1** af-



forded excellent diastereo- and enantioselectivity (99:1 *trans/cis* and 97% *ee*, respectively) in the case of intermolecular cyclopropanation of terminal olefins with diazoacetate in a biphasic toluene/water system, only low enantioselectivity (52% *ee*) was obtained by using the Ru complex of **2** as a catalyst in the intra-molecular cyclopropanation of *trans*-cinnamyl diazo-acetate. The reusability of the water-soluble Ru complex of **1** suffered from a dramatic decrease in reactivity from 62% yield to 13% yield and in enantioselectivity from 97% *ee* to 42% *ee* in intermolecular cyclopropanation.

Very recently, we reported the efficient use of a novel macroporous polymer-supported chiral Ru(II)-Pheox catalyst in inter- and intramolecular cyclopropanation reactions.^[6] Despite the high reactivity, enantioselectivity and reusability of the macroporous catalyst, the challenge still remains to develop a robust, highly enantioselective and reusable catalyst, which has the ability to dissolve in water. Especially, water is a desirable solvent for catalysis with respect to environmental concerns, safety, and costs.^[7] During our ongoing research, we found that our novel Ru(II)-hydroxymethyl(phenyl)oxazoline [Ru(II)-hm-Pheox] complex 7 has ability to dissolve in water and is completely undissolved in diethyl ether. Interestingly, we found that the Ru(II)-hm-Pheox complex 7 could effectively catalyze the intramolecular cyclopropanation of trans-cinnamyl diazoacetate in a water/ ether biphasic system to furnish a 99% yield of cyclopropane-fused y-lactone system with 97% ee. Encouraged by this preliminary result, we prepared a variety of functionalized Ru(II)-Pheox complexes (3-6)^[8] and evaluated their catalytic activities in the intramolecular cyclopropanation of trans-cinnamyl diazoacetate as shown in Table 1. It was observed that catalysts 3 to 7 afforded very similar enantioselectivities, but

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N_a

C ₆ H ₅		cat. (5.0 mo H ₂ O/ether (1:1	^{DI%)} H v/v), r.t. C ₆ H₅	H, R C ₆ H ₅ H		
8a				9a		
Entry	cat.	Time/h	Yield [%] ^[b]	<i>ee</i> [%] ^[c]		
1	3	24	44	97		
2	4	24	67	96		
3	5	5	69	95		
4	6	24	72	97		
5	7	1.5	99	97		
6 ^[d]	7	3	97	97		

Tab	le 1. Intramole	ecular cyo	clopr	opanation	catalyzed	by	vari-
ous	Ru(II)-Pheox	catalysts	in a	biphasic 1	nedium. ^[a]		

^[a] Reaction conditions: to a solution of Ru(II)-Pheox complex (0.005 mmol, 5 mol%) in H₂O (3.0 mL) was added a solution of *trans*-cinnamyl diazoacetate in Et₂O (0.1 mmol in 3.0 mL, *ca*. 0.033 M) at room temperature and the absolute configuration was determined by comparison with the reported specific rotation values (ref.^[3i]).
^[b] Vield of isolated are dust.

^[b] Yield of isolated product.

- ^[c] Determined by GLC using chiral β -Dex 225.
- ^[d] Performed with 1.0 mmol of *trans*-cinnamyl diazoacetate in 30 mL of Et₂O (*ca.* 0.033 M).



with different yields and in different times. The Ru(II)-hm-Pheox catalyst 7 was found to be the most effective (Table 1, entry 5) and we can attribute this to its ability to form strong hydrogen bonding with water, which makes it easily soluble and highly effective. Indeed, the solubility is very important in this case, since only the soluble molecules will migrate to the interface and react with the carbene source (allylic diazoacetate). To test the practicality of the current catalytic system, the reaction on a 1-mmol scale of trans-cinnamyl diazoacetate in 30 mL of Et₂O was carried out and we found that the cyclopropanation reaction was able to afford bicylic product 9a with little effect on the yield and reaction time (Table 1, entry 6). Additionally, the catalyst could be recovered in 83% in this scale by extaction with CH₃CN.

The difference in the solubility is the main reason for the variations of the yields. For example, Ru(II)-Pheox catalyst **3** was slightly soluble in water and afforded only a 44% yield of the product in one day (Table 1, entry 1).



Ether +

allylic

diazoacetate

and **7** in water is shown in Figure 1. Notably, when we replaced the hydroxymethyl group by the methoxy group, a 69% yield was obtained in 5 h (Table 1, entry 3). However, the use of other polar groups like chloromethyl or chloro as substituent could not increase the yield to more than 72% (Table 1, entries 2 and 4). Thus, an Ru(II)-Pheox catalyst functionalized with polar protic groups is the best choice for the efficient intramolecular cyclopropanation of *trans*-allylic diazoacetates in a water/ether biphasic medium. The effect of the functional group on the solubility and the reactivity of the ruthenium catalysts can easily be understand from the proposed mechanism shown in Scheme 1.



Scheme 1. Plausible mechanism for the intramolecular cyclopropanation of *trans*-cinnamyl diazoacetate catalyzed by **7** in a water/ether medium.

Ether +

allylic

diazoacetate

The effect of the catalyst 7 loading on the intramolecular cyclopropanation of trans-cinnamyl diazoacetate in water/ether biphasic medium was also investigated. It was possible to reduce the catalyst loading from 5 to 1 mol% without detrimental effects on the yield and enantioselectivity, but a longer reaction time was required (from 1.5 h to 4 h). By using ruthenium catalyst 7 and under the optimized reaction conditions, a broad palette of trans-allylic diazoacetates 8a-8g, which were derived from the corresponding allylic alcohols using the Fukuyama method,^[9] were investigated as shown in Table 2 (entries 1-15). Excellent reactivities and enantioselectivities were obtained in all of the cases. Interestingly, the water-soluble catalvst 7 could effectively promote the intramolecular cyclopropanation of both substituted and non-substituted trans-cinnamyl diazoacetates (Table 2, entries 1-7) and alkyl trans-allylic diazoacetates with short (Table 2, entries 8, 14) and long (Table 2, entries 11, 13) chains. Furthermore, the reusability of the watersoluble catalyst 7 was checked by separating the ether-phase and washing the aqueous-phase with ether until no product remains adherent to the aqueous-phase. A new amount of trans-allylic diazoacetate dissolved in ether was added and vigorously stirred for $1 \sim 3$ h. It is noteworthy that catalyst 7 could be reused at least five times without any significant decrease in reactivity or enantioselectivity in the intramolecular cyclopropanation of trans-cinnamyl diazoacetate as shown in Table 2 entries 1-5. Additionally, catalyst 7 had the ability to be reused from two to three times with the other substrates (Table 2, entries 8–10, 11 and 12, and 14 and 15).

Inspired by the results above, the intramolecular cyclopropanations of alkenyl diazo ketone **8h** and *trans*allylic diazoacetamides **8i–8j** were also investigated under the same reaction conditions (Table 2, entries 16–18). Although the catalytic system was not suitable for the cyclization of *trans*-allylic diazoacetamides, the reaction of alkenyl diazo ketone proceeded smoothly to afford the corresponding cyclopropane ring fused ketone product **9h** in high yield with excellent enantioselectivity (98% *ee*).

To explore further insights, the intermolecular cyclopropanation of styrene with EDA catalyzed by **7** in a water/ether biphasic medium was also checked. Although high *trans*-selectivity (97% *ee*) was obtained, only 30% yield of the cyclopropanation product was isolated. The reason for this low yield may came from the partial solubility of EDA in the water-phase and the possibility of the O–H insertion reaction.^[10]

In conclusion, we have developed an efficient water-soluble Ru(II)-*hm*-Pheox catalyst **7**. The water-soluble catalyst **7** delivered excellent reactivities with up to 99% yield and enantioselectivitis up to 98% *ee* in the intramolecular cyclopropanation of *trans*-allylic diazoacetates and alkenyl diazo ketone in a water/

Table 2. Asymmetric intramolecular cyclopropanation of various *trans*-allylic diazo compounds catalyzed by **7**.^[a]



 ^[a] Reaction conditions: to a solution of Ru(II)-hm-Pheox complex 7 (0.005 mmol, 5 mol%) in H₂O (3.0 mL) was added a solution of *trans*-allylic diazo compound in Et₂O (0.1 mmol in 3.0 mL, *ca*. 0.033 M) at room temperature and the mixture stirred for 1–3 h.

^[c] Determined by GLC or HPLC, see the Supporting Information.

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^[b] Yield of isolated product.

ether biphasic medium. The functionality of the ruthenium catalyst with a polar protic group is important to furnish high yields. The easy separation of the ether phase, which contains the cyclopropane product, allows the simple reuse of the catalyst in the water phase at least five times without significant decrease in reactivity or enantioselectivity. To the best of our knowledge, this is the first report of a reusable watersoluble catalyst in the intramolecular cyclopropanation reaction. We are currently applying this catalyst for other carbon-carbon bond forming reactions in aqueous medium.

Experimental Section

General Remarks

All reactions were performed under the normal air atmosphere. CH_2Cl_2 dehydrated was purchased from Kanto Chemical Co., Inc. Et_2O dehydrated was purchased from Wako Pure Chemical Industries Co., Ltd. Reactions were monitored by TLC, glass plates pre-coated with silica gel – Merck 60 F_{254} , layer thickness 0.2 mm. All the starting materials (*trans*-allylic diazoacetates) were prepared using the Fukuyama method.^[8] Flash column chromatography was performed over Merck silica gel (Art. No. 7734).

Typical Procedure for Intramolecular Cyclopropanation Catalyzed by Ru(II)-*hm*-Pheox Complex 7

To a solution of Ru(II)-*hm*-Pheox complex **7** (0.005 mmol, 5.0 mol%) in H₂O (3.0 mL) was added a solution of *trans*-allylic diazo compound in Et₂O (0.1 mmol in 3.0 mL, *ca*. 0.033 M) at room temperature. The biphasic medium was stirred vigorously for 1–3 h. After the starting material had completely reacted, the product was collected by separation of the ether phase. The water phase, which contains the catalyst, was washed three times with ether (3×5.0 mL). The collected product in the ether-phase was dried over anhydrous Na₂SO₄ and condensed under reduced pressure. The crude product was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 10:1) to afford the corresponding bicyclic product. The remaining water-soluble catalyst was reused for the next cycle. The enantiomeric excesses of products were determined by HPLC or GC analysis.

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