Tandem Olefin Migration–Aldol Condensation in Water with an Amphiphilic Resin-Supported Ruthenium Complex

in water

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Abstract: A catalytic tandem olefin migration–aldol condensation process with allylic carbinols and aryl aldehydes was performed with 0.5 mol% of an amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG) resin supported phosphine–ruthenium complex in water as a single reaction medium under heterogeneous conditions to give the corresponding aldols with *syn* selectivity. Inverse stereoselectivity (*anti* selectivity) was observed when the reaction was carried out in the presence of K₂CO₃.

Key words: tandem reaction, aldol condensation, aqueous media, polymer support, ruthenium catalyst

Aqueous and heterogeneous switching of a given organic transformation has been rapidly gaining in importance for its ability to provide safe and green-chemical processes.^{2,3} In 1997, we published our first report on the development of heterogeneous aquacatalytic reactions by the use of amphiphilic polystyrene-poly(ethylene glycol) (PS-PEG)^{4,5} resin supports, in which we described very early examples of catalytic organic transformations in water without any organic media with immobilized heterogeneous palladium complexes. Since then we have developed a variety of PS-PEG resin supported transition-metal catalysts to achieve various catalytic transformations in water under heterogeneous conditions. As part of our continuing effort to demonstrate the wide utility of this heterogeneous aquacatalytic system, we have now developed PS-PEG resin supported ruthenium complexes^{6,7} which were found to promote the Kharasch reaction efficiently in water without any radical initiator (Scheme 1). Li's recent finding that a ruthenium complex catalyzes the formation of aldol products from allyl alcohols via the tandem olefin migration-aldol condensation under aqueous conditions (Scheme 2),^{8,9} prompted us to examine the tandem aldol formation process in water under heterogeneous conditions using the PS-PEG resin supported CpRu(phosphine) complex. Herein we wish to report our preliminary results on the catalytic tandem olefin migration-aldol condensation process, which is promoted by the ruthenium complex anchored onto the amphiphilic PS-PEG resin supported triarylphosphine in water under heterogeneous conditions to give the corresponding aldol products.

SYNLETT 2011, No. 6, pp 0787–0790 Advanced online publication: 25.02.2011 DOI: 10.1055/s-0030-1259689; Art ID: D32210ST © Georg Thieme Verlag Stuttgart · New York



Scheme 1 Amphiphilic polymeric Ru-catalyzed Kharasch reaction

S/C = 2,000, in H_2O ; TOF = 1445 h^{-1} (at initial 15 min)



Scheme 2 Ru-catalyzed tandem olefin migration-aldol condensation

First, the reaction of benzaldehyde (3) and 3-buten-2-ol (2) was carried out in neat water in the presence of various PS-PEG resin supported transition-metal complexes, where PS-PEG-phosphine-RuCl₂Cp* (1) was found to catalyze the tandem olefin migration-aldol condensation process smoothly at 45 °C (Scheme 3). Thus, a mixture of 2 (2.0-3.0 equiv), 3, and 0.5 mol% Ru of PS-PEG-phosphine-RuCl₂Cp* (1) was agitated in water at 45 °C for 2 hours. The reaction mixture was filtered, and the resin beads were rinsed with a small portion of hot water, and the combined aqueous filtrates were freeze-dried in vacuo. The diastereomeric (syn/anti) ratio of the resulting aldol 4 was determined by ¹H NMR spectroscopic analysis of the crude material to be 82:18, and the chemical yield was determined via chromatographic isolation of the syn/ anti mixture of 4 to be 74%. The tandem aldol formation with PS-PEG-phosphine-RuCl₂(p-cymene) (5), PS-PEGphosphine-RhCl(CO)₂ (6), or PS-PEG-phosphine- $PdCl(\eta^3-C_3H_5)$ (7) afforded <3% of 4 even at 100 °C (in



Scheme 3

refluxing water) under otherwise similar conditions (Scheme 3).

It is noteworthy that the catalytic performance of the polymeric complex PS-PEG-phosphine-RuCl₂Cp* (1) in water was much higher than that reported for $RuCl_2(PPh_3)_3$ in aqueous reaction media. Thus, 0.5 mol% Ru of the polymeric catalyst 1 promoted the tandem olefin migration-aldol condensation in water at 45 °C within 2 hours, whereas the reaction with 3 mol% of RuCl₂(PPh₃)₃ required 110 °C (5–10 h) under aqueous conditions (e.g., H_2O -toluene = 4:1). The inefficiency of the aqueous reaction system using RuCl₂(PPh₃)₃ is presumably attributable to the heterogeneity of the reaction mixture. In the present reaction system using PS-PEG-phosphine-RuCl₂Cp* (1) in water, the organic substrates 2 and 3 should automatically diffuse into the PS-PEG matrix, because of their hydrophobicity, to afford highly self-concentrated conditions, where the condensation reaction would proceed efficiently to decrease the molar concentration of the reaction matrix.

Table 1 summarizes the representative results of the tandem olefin migration-aldol condensation process with various allylic alcohols and benzaldehydes catalyzed by PS-PEG-phosphine-RuCl₂Cp* (1) in water under heterogeneous conditions, where the structures of the major diastereomeric isomer are depicted. Pentyl vinyl carbinol (2b) reacted with benzaldehyde (3) to give a 45% yield of the aldol 8 (syn/anti = 74:26). Reactions of 2a with benzaldehydes bearing methyl, methoxy, chloro, and bromo substituents at their 4-positions 3B-E afforded the corresponding aldols 9-12 in 67%, 61%, 52%, and 64% yield,



 Table 1
 Catalytic Tandem Olefin Migration–Aldol Condensation
 in Water with PS-PEG-phosphine-RuCl₂Cp* (1)^a



^a All reactions were carried out in H₂O at 45 °C for 2 h with 0.5 mol% Ru of 1. The ratio of 2 (mol)/3 (mol)/Ru (mol)/H₂O (L) = 2.0:1.0:0.005:1.0.

^b The structure of the major diastereomer is depicted. ^c Isolated yield.

^d Determined by ¹H NMR.

respectively, where the syn isomers were obtained with 75-81% selectivity.

During the screening of the catalytic conditions, inversion of diastereoselectivity was observed when the reaction was carried out in the presence of potassium carbonate (Table 2). Thus, when the reaction of benzaldehyde (3)and 3-buten-2-ol (2) was carried out in the presence of 20 mol% of K₂CO₃ under otherwise similar conditions, the aldol product 4 was obtained in 79% yield with a syn/anti diastereoselectivity of 26:74 (Table 2, entry 1).

A similar anti-selective trend was observed in the reactions with combinations of the substrates 2b/3A, 2a/3B, 2a/3C, 2a/3D, and 2a/3E where the corresponding aldols 8-12 were obtained in 48-98% yield with 67-81% anti-

OH R ¹ 2a,b a: R ¹ =	+ H	$ \begin{array}{c} $	R ¹ 4, ;	DH 3-12 R ² = Br
b : $R^1 =$ Entry	2/3	B : $R^2 = Me$ D : $R^2 = Cl$ Product ^b		Yield (%) ^c
1	2a/3A	O OH	4	(<i>syn/anti</i>) ^a 79 (26:74)
2	2b/3A ^e	n-C ₅ H ₁₁	8	75 (19:81)
3	2a/3B	O OH	9	78 (26:74)
4	without I	Ru complex 1	9	no reaction
5	Na ₂ CO ₃ was used		9	69 (23:77)
6	K ₃ PO ₄ was used		9	52 (30:70)
7	2a/3C	O OH OMe	10	48 (27:73)
8	2a/3D	O OH	11	98 (33:67)
9	2a/3E	O OH 	12	92 (33:67)
10 ^f	recycle experiment		12	81 (37:63)
11 ^f	recycle experiment		12	38 (32:68)

Table 2Catalytic Tandem Olefin Migration–Aldol Condensationin Aqueous K_2CO_3 with PS-PEG-phosphine-RuCl₂Cp* (1)^a

^a All reactions were carried out in H₂O at 45–55 °C for 2 h with 0.5 mol% Ru of **1**. The ratio of **2** (mol)/**3** (mol)/Ru (mol)/K₂CO₃ (mol)/ H₂O (L) = 2.0:1.0:0.005:0.2:5.0, unless otherwise noted.

^b The structure of the major diastereomer is depicted.

^c Isolated yield.

^d Determined by ¹H NMR.

^e Ratio of **2b/3A** = 1.5:1.0.

^f Entries 10 and 11 were performed with catalyst beads recovered from entries 9 and 10, respectively.

selectivity (Table 2, entries 2, 3, 7–9). The aldol reaction did not occur without the polymeric Ru complex 1 even in the presence of K_2CO_3 (Table 2, entry 4). The reactions with Na₂CO₃ and K_3PO_4 instead of K_2CO_3 provided the

anti-4 as the major isomer with 77% and 70% diastereoselectivity, respectively (Table 2, entries 5 and 6), though the isolated chemical yield of 4 was slightly lower. A recycling experiment was examined for the reaction of 2a with 4-bromobenzaldehyde (3E). Thus, after the 1st catalytic use of the PS-PEG resin-supported Ru complex 1 (12; 78% yield, *syn/anti* = 33:67; entry 9), the catalyst beads were collected by simple filtration, rinsed with water and EtOAc, dried in vacuo, and subjected to the second catalytic use (entry 10). The reaction of 2a and 3E with the recycled catalyst beads gave 81% isolated yield of 12 with 63% of the anti selectivity under similar conditions. Though loss of the catalytic activity was observed in the subsequent recycle experiment affording 38% yield of 12 (entry 11), the anti selectivity was retained almost intact (syn/anti = 32:68). When the aldol 9 (syn/anti = 70:30)was exposed to the anti-selective catalytic conditions (Table 2, footnote a), 9% of retro-aldol product 3B was obtained but no significant epimerization giving anti-9 was observed. The aldol condensation of 2-butanone and **3B** did not take place under the catalytic conditions (Scheme 4). Thus, neither α -carbonyl epimerization nor a retro-aldol-aldol sequence could explain the anti-selective aldol formation. Though the reaction mechanism is as yet unclear, inversion of the diastereoselectivity by the simple additive should enhance its practical utility.



Scheme 4

In summary, the catalytic tandem olefin migration–aldol condensation of allylic alcohols and aldehydes has been achieved in water with an amphiphilic polymer-supported ruthenium complex to give the corresponding aldol products. The polymeric complex exhibited high catalytic performance even at 45 °C with 0.5 mol% of ruthenium. A detailed mechanistic study and further catalytic applications of **1** are currently under investigation in our lab and will be reported in due course.

Experimental: PS-PEG Resin Supported Ruthenium Complex (1)

A reactor was charged with PS-PEG-PPh₂ (340 mg), $Cp*RuCl_2$ (35 mg), and CH_2Cl_2 (10 mL). The reaction mixture was shaken on a wrist action shaker at 25 °C for 5 h. The solvent was removed by fil-

Synlett 2011, No. 6, 787-790 © Thieme Stuttgart · New York

tration, and the collected beads were washed with CH_2Cl_2 (5 × 5 mL) and dried under reduced pressure overnight to give PS-PEG-PPh₂-Cp*RuCl₂ (1) as reddish beads (0.23 mmol Ru/g, 0.24 mmol P/g).

General Procedure for Isomerization–Aldol Condensation Reaction of Benzaldehyde and 3-Buten-2-ol with the Polymeric 1 in Water

A typical procedure is given for the reaction with benzaldehyde (**3A**) and 3-buten-2-ol (**2a**) in H₂O (Table 1, entry 1). A mixture of PS-PEG-PPh₂-Cp*RuCl₂ (**1**, 11 mg, 0.0025 mmol Ru), 3-buten-2-ol (**2a**, 72 mg, 1.0 mmol), benzaldehyde (**3A**, 53 mg, 0.5 mmol), and H₂O (2.5 mL) was shaken at 45 °C for 2 h under nitrogen atmosphere. The reaction mixture was filtered, and the resin was rinsed three times with 5 mL of hot H₂O or supercritical CO₂ (flow extraction system). The crude product was purified by silica gel column chromatography to give a diastereomeric (*syn/anti* = 82:18) mixture of **4** (66 mg, 74% yield). The ratio of the diastereomers was determined by ¹H NMR analysis.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We thank Ms. Aya Tazawa for her technical assistance. This work was supported by the CREST program, which is sponsored by the JST. We also acknowledge the JSPS (Grant-in-Aid for Scientific Research #20655035; Grant-in-Aid for Scientific Research on Innovative Area #2105) for partial financial support of this work.

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