Immobilization of Grubbs Catalyst as Supported Ionic Liquid Catalyst (**Ru-SILC**)

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Abstract: Grubbs olefin metathesis catalyst was immobilized as a ruthenium-supported ionic liquid catalyst (Ru-SILC) in pores of amorphous alumina with the aid of ionic liquid [hmim]PF₆. This Ru-SILC was effective for various olefin metathesis reactions such as intra- or intermolecular macrocyclization and dimerization, and used up to six times after simple decantation.

Key words: heterogeneous catalysis, ionic liquids, methathesis, ruthenium, supported catalysis

Since the development of Ru and Mo metallocarbene complexes by Grubbs and Schrock (Figure 1), the olefin metathesis reaction has been extensively utilized for various synthetic transformations, and this innovated the concept of not only contemporary target-oriented synthesis but also various aspects of organic synthesis including polymer synthesis.¹ These metallocarbene complexes react only with olefins without affecting or being affected by other functional groups. In a substrate having two olefins in the same molecule, a cyclic compound is synthesize thus far. Therefore, the reaction has been utilized as a key process for syntheses of multifunctional compounds, especially complex natural products.²



Figure 1 Representative Grubbs olefin metathesis catalysts

However, these excellent catalysts have some drawbacks. Since the catalysts are homogeneous and easily deteriorate on workup, recycle use is difficult. Also, catalyst turnover number (TON) is not high. In addition, high price and large molecular weight circumvent a catalytic reaction in large scale. Another issue is ruthenium contamination of the product³ due to higher lipophilicity of

SYNLETT 2008, No. 12, pp 1813–1816 Advanced online publication: 02.07.2008 DOI: 10.1055/s-2008-1078570; Art ID: U03508ST © Georg Thieme Verlag Stuttgart · New York ruthenium carbene complexes even in nonpolar organic solvents such as *n*-hexane.

To solve these issues, immobilization of the Grubbs ruthenium catalyst has been investigated intensively not only on solid support but also on liquid support. Ionic liquid was used as a liquid support^{4,5} due to its nonlipophilicity, nonhydrophilicity and nonvolatility, although the higher solubility of Grubbs catalysts in organic solvents could not prevent loss of the catalyst from the ionic liquid layer during extraction of the product.⁶ Immobilization of the Grubbs ruthenium catalyst as a task-specific ionic liquid⁷ was successful to realize efficient recycle use by precipitation with a poor solvent. Additional efforts to immobicatalyst on organic supports include lize the immobilization on polymers,⁸ dendrimers,⁹ polyethylene glycol,¹⁰ and fluorous polymers,¹¹ and encapsulation in polymer beads.¹² On the other hand, immobilization on inorganic supports is rare except on silica,¹³ in which the Grubbs ruthenium catalyst was anchored with covalent bond on the silica surface. Toward this end, an easier and more economical protocol is desired to avoid tedious immobilization procedures.

In the present study, the Grubbs Ru catalyst in an ionic liquid was immobilized in pores of an inorganic support. The heterogeneous catalyst thus prepared [ruthenium-supported ionic liquid catalyst (Ru-SILC)] exhibited higher catalytic activity and a recyclable nature in olefin metathesis reactions (Figure 2).



Figure 2 Ru-SILC and metathesis reaction

The Ru-SILC was prepared according to the same procedure used for Pd-SILC.¹⁴ A suspension of amorphous inorganic solid in a solution of the Grubbs ruthenium catalyst and ionic liquid in tetrahydrofuran (THF) was stirred until pale blue, then the catalyst was transferred to a solid support. Subsequently, THF was evaporated to dryness to give pale blue powder. The free-flowing nature of Ru-SILC along with the amount of the ionic liquid used (10 wt% to support) suggest that the ionic liquid layer exists in the pores of amorphous solid in the same manner as Pd-SILC.^{14a}

Among various inorganic solid supports including hydroxyapatite, molecular sieves and their surface-modified support, normal-phase amorphous alumina powder enabled immobilization of Grubbs I catalyst (1) (Table 1). Immobilization of the Grubbs catalyst with reversed-phase silica or alumina was not successful (Table 1, entries 4, 6, and 7).^{3a} Grubbs II (2) and Hoveyda–Grubbs II (3) catalysts were also immobilized, although at slightly low loading (Table 1, entries 10 and 11). The loading of Grubbs I catalyst (1) was 0.03 mmol/g of the alumina at the maximum. Although amount of loading was evaluated roughly by weight gain, more than 99% of Grubbs I catalyst (1) was immobilized according to inductively coupled plasma atomic emission spectroscopy (ICP-AES) analysis of the ether rinse in entry 9.²⁰

Table 1 Investigation of Optimum Solid Support for Immobilization of 1 with the Aid of $[bmim]PF_6$

Entry	Support material	Loading of 1 (mmol/g)
1	hydroxyapatite	_
2	$3Al_2O_3 \cdot 2SiO_2$	_
3	MS 4 Å pellets	-
4	NDEAP- SiO ₂ ^b	_
5	SiO ₂	0.006
6	NDEAP-Al ₂ O ₃	0.0007
7	NAP-Al ₂ O ₃ ^c	0.009
8 ^d	Al_2O_3	0.0057
9	Al_2O_3	0.025–0.03
10 ^e	Al_2O_3	0.01
11 ^f	Al_2O_3	0.01
12 ^g	Al_2O_3	0.02

^a Obtained by weight gain.

- ^b N,N-Diethylaminopropylated silica.
- ^c Aminopropylated silica.

^d Immobilization in aluminum pellet without ionic liquid.

^e Grubbs II catalyst (2) was immobilized.

^f Hoveyda–Grubbs II catalyst (3) was immobilized.

^g Immobilization in aluminum powder without ionic liquid.



Equation 1 RCM reaction of diethyl diallylmalonate (4)

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Employing the ring-closing metathesis (RCM) reaction of diethyl diallylmalonate (4) as a probe to tune reaction parameters (Equation 1), various Ru-SILC based on normalphase alumina were prepared by changing ionic liquid support, and then their catalytic activities were evaluated. Among them, Ru-SILC immobilized with [bmim]PF₆ or [hmim]PF₆ provided the best result in the RCM reaction (Table 2, entries 4 and 5). Employing the catalyst (Table 1, entry 12) prepared without an ionic liquid, a large amount of starting material was recovered in entry 6. This result suggests that the ionic liquid layer of SILC plays an important role to provide medium for the RCM reaction, as illustrated in Figure 2.

Table 2Investigation of Optimum Ionic Liquid for Support inRCM Reaction of 4

Entry ^a	Ionic liquid	Time (h)	Yield (%) ^b
1	[bmim]Br	4	_c
2	[bmim]NTf ₂	4	
3	[bmim]CF ₂ H(CF ₂) ₃ CH ₂ OSO ₃	18	58
4	[bmim]PF ₆	2.5	77
5	[hmim]PF ₆	1	79
6 ^d	-	2	4

^a Reaction was catalyzed by 0.1 equiv of Grubbs I Ru-SILC (1) in refluxing toluene.

^b Isolated pure product.

^c Starting material was recovered.

^d Reaction was carried out in refluxing benzene with 0.05 equiv of Ru-SILC.

Then, the effect of solvents was investigated, in which aromatic hydrocarbon solvents provided better results (Table 3, entries 6–8). It is worthy of note that the leaching of Ru from Ru-SILC was 0 ppm by ICP-AES analysis.

Table 3 Effect of Solvents on RCM Reaction of 4

Entry ^a	Solvent	Conditions	Yield (%) ^b
1	perfluoropolyether	r.t. to 120 °C, 10 h	_c
2	tert-butylmethyl ether	reflux, 10 h	_c
3	CH ₂ Cl ₂	reflux, 10 h	_c
4	EtOH	reflux, 4 h	_c
5	H ₂ O	r.t., 10 h	_c
6	benzene	reflux, 1 h	82
7 ^d	benzene	reflux, 18 h	77
8	toluene	reflux, 2.5 h	76

^a Reaction was catalyzed by 0.1 equiv of Grubbs I Ru-SILC (1) immobilized on normal-phase alumina with the aid of [hmim]PF₆. ^b Isolated pure product.

^c Starting material was recovered.

^d Grubbs I Ru-SILC (0.005 equiv) was used. TON was calculated to be 154.

This result means that the RCM reaction proceeds inside of the Ru-SILC. A TON of 154 is reasonable (Table 3, entry 7) compared with literature precedents.¹³

By employing the optimized reaction conditions (Table 3, entry 6), Ru-SILC was successfully recycled in the RCM reaction of diethyl diallylmalonate (4) employing 0.05 equivalents of Ru-SILC in refluxing benzene up to five times in 78% average yield (Table 4). During recycle experiments, the decrease in catalytic activity was moderate.

 Table 4
 Recycle Use of Ru-SILC in RCM Reaction of 4²¹

Entry ^a	Time (h)	Yield (%) ^b
1	1	82
2	1	81
3	1	76
4	2	81
5	2	78
6	2	70

^a Reaction was carried out in refluxing benzene catalyzed by 0.05 equiv of Grubbs I Ru-SILC (1) immobilized on alumina with the aid of [hmim]PF₆.

^b Isolated pure product.

The present RCM reaction conditions catalyzed by Ru-SILC were successful in closing 7-, 14- and 15-membered rings (Scheme 1, equations 4, 5, and 6). Unfortunately, dimeric compounds were obtained even in very dilute solutions due to inherent difficulty in cyclizing 9- and 11membered carbocycles (Scheme 1, equations 7 and 8). In equations 5, 7–9 (Scheme 1), single stereoisomers were obtained. By employing Ru-SILC, which immobilized Hoveyda–Grubbs II catalyst (**3**), trisubstituted olefin **7** was synthesized (Scheme 1, equation 2).

In summary, Grubbs ruthenium catalysts were immobilized as Ru-SILC in alumina pores with the aid of the ionic liquid [hmim]PF₆.¹⁵ Immobilization was simple and cost effective, since there was no need to synthesize a polymer or to employ a large amount of ionic liquid. The present protocol offers an effective and simple method of immobilizing sophisticated but unstable homogeneous organometallic catalysts with the aid of ionic liquid in pores of amorphous inorganic supports.

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^d Hovevda–Grubbs II Ru-SILC **3** (0.1 equiv) was used.

^e Grubbs I Ru-SILC **1** (0.1 equiv) was used.

^f Inseparable mixture of *cis/trans* (1:2.3) isomers.

^g Separable mixture of *cis/trans* (1:2:3) isomers.

^h A single isomer was obtained.

Scheme 1 Catalytic activity of Ru-SILC^{16–19,22–25}

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- (20) Preparation of Ru-SILC
 - To activated Al_2O_3 (powder for column chromatography purchased from Wako Chemical Co., 300 mesh, 1.545 g) and Grubbs I catalyst (1, 38 mg, 0.046 mmol, 0.03 mmol/g of Al_2O_3) was added a solution of [hmim]PF₆ (150 mg, 10 wt%) in THF. The resulting slurry was stirred at r.t. for 4 h, when the pale blue color of THF solution was transferred to Al_2O_3 . After evaporation of THF in vacuo, the powder was rinsed with anhyd Et₂O twice. Evacuation in vacuo provided Ru-SILC (1.732 g) as a pale blue powder. Since leaching of Ru into the ether rinse was 0.05 ppm (0.105% as the catalyst 1) by ICP-AES analysis, more than 99% of Grubbs I catalyst(1) was immobilized on Al_2O_3 .
- (21) RCM Reaction of Diethyl Diallylmalonate 4
 A stirred suspension of diethyl 2,2-diprop-2-enylpropane1,3-dioate (4, 31 mg, 0.13 mmol) and Ru-SILC [308 mg,
 0.0065 mmol of Grubbs I catalyst(1)] in benzene (1.5 mL)
 was heated under reflux for 1 h. The organic layer was
 separated by filtration, and the flask was rinsed with Et₂O.
 The combined organic layer was evaporated to dryness in
 vacuo. The residue was purified by medium pressure LC
 (eluent: *n*-hexane–EtOAc = 9:1) to give ethyl 1-(ethoxy-carbonyl)cyclopent-3-enecarboxylate (5, 23 mg, 82%).
 Recovered Ru-SILC was used intact for further recycle
 experiments.
- (23) Compound **17**: ¹H NMR (270 MHz, CDCl₃): $\delta = 1.21-1.28$ (m, 20 H), 1.84–2.00 (m, 16 H), 4.14–4.22 (m, 8 H), 5.39– 5.42 (m, 4 H). ¹³C NMR (67.5 MHz, CDCl₃): $\delta = 171.7$, 130.1, 61.1, 57.0, 32.1, 30.2, 23.5, 14.2. MS: *m/z* (%) = 536 (7) [M⁺], 491 (13), 444 (8), 399 (15), 336 (19), 279 (8), 265 (16), 251 (12), 173 (100). IR: 1719, 1463, 1445, 1369, 1299, 1254, 1095, 1028 cm⁻¹. HRMS: *m/z* calcd for C₂₈H₄₃O₇ [M – OCH₂CH₃]⁺: 491.3009; found: 491.3017.
- (24) Compound **19**: ¹H NMR (500 MHz, CDCl₃): $\delta = 1.21-1.34$ (m, 14 H), 1.55–1.67 (m, 4 H), 1.73–2.05 (m, 12 H), 2.43– 2.60 (m, 4 H), 3.39–3.45 (m, 2 H), 4.14–4.19 (m, 4 H), 5.34– 5.42 (m, 4 H). ¹³C NMR (67.5 MHz, CDCl₃): $\delta = 205.1$, 169.7, 130.3, 129.5, 61.2, 58.3, 41.4, 32.3, 31.8, 28.9, 27.9, 27.4, 23.0, 14.2. MS: *m/z* (%) = 476 (3) [M⁺], 431 (7), 412 (16), 402 (4), 384 (15), 366 (11), 175 (19), 108 (45), 91 (51), 79 (73), 67 (95), 55 (100). IR: 1738, 1710, 1445, 1370, 1268, 1188, 909 cm⁻¹. HRMS: *m/z* calcd for C₂₆H₃₉O₅ [M – OCH₂CH₃]⁺: 431.2797; found: 431.2802.

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