



One-pot catalytic C–C double bond cleavage of α,β -enones aided by alkyl group-immobilized silica spheres

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This Letter is dedicated to the memory of the late Professor Chi Sun Han (1926–2009) of Yonsei University

ABSTRACT

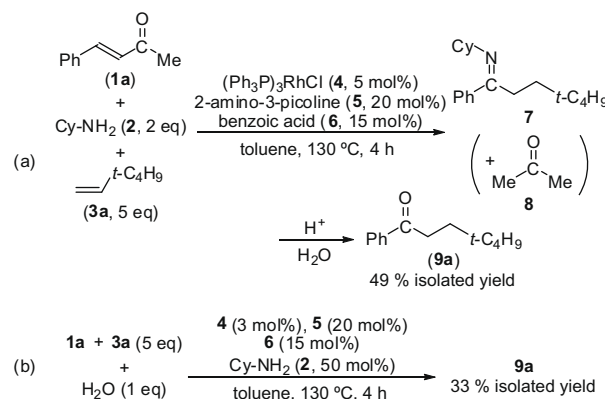
Catalytic C–C double bond cleavage of α,β -enones with a 1-alkene and H_2O was carried out in the presence of a $(\text{Ph}_3\text{P})_3\text{RhCl}$ catalyst, 2-amino-3-picoline, cyclohexylamine, benzoic acid, and alkyl group-immobilized silica spheres. Upon completion of the reaction, the corresponding ketones were obtained without needing a further hydrolysis step. In this reaction, alkyl group-immobilized silica spheres act as a water reservoir for hydrolysis of an intermediate ketimine and as a phase divider between the organic solution and H_2O .

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C–H bond activation by transition-metal catalysts is of current interest in organic synthesis in terms of atom economy.¹ We have successfully developed a Rh(I)-catalyzed C–H bond activation using 2-aminopyridine derivatives or benzylamine as a chelating auxiliary to induce facile cyclometallation.² In the course of our studies on chelation-assisted C–H bond activation, the Rh(I)-catalyzed hydroiminoacylation of an alkyne with an allylamine or an aldehyde, followed by retro-Mannich type fragmentation of the resulting α,β -unsaturated ketimine was found.^{3,4} We have also developed a C–C double bond cleavage of α,β -enone using amine and acid to produce ketones after hydrolysis step.⁵ For example, the reaction of 4-phenyl-but-3-en-2-one (**1a**), 3,3-dimethyl-1-butene (**3a**), and cyclohexylamine (**2**, 200 mol % based upon **1a**) was carried out at 130 °C for 4 h in the presence of the catalyst system of $(\text{Ph}_3\text{P})_3\text{RhCl}$ (**4**), 2-amino-3-picoline (**5**), and benzoic acid (**6**) to give acetone and ketimine **7**, which was hydrolyzed separately by acidic H_2O giving the corresponding ketone **9a** in a 49% isolated yield (Scheme 1a). This reaction requires greater than 100 mol % of cyclohexylamine based on the starting α,β -enone, and a further hydrolysis step for the resulting ketimine **7** to liberate ketone (**9a**). To decrease the amount of **2** used and to eliminate the separate hydrolysis step, H_2O can be added as a reactant to hydrolyze the in situ generated ketimine **7** resulting in the formation of **9a** directly (Scheme 1b). A proposed mechanism for this one-pot reaction is depicted in Scheme 2. Cyclohexylamine **2** undergoes conjugate addition to the α,β -enone **1a**, and the subsequent retro-Mannich type fragmentation of the resulting β -aminoketone **A** generates a mixture of aldimine **B** and ketone **8**. Since aldimine is not much susceptible for hydrolysis compared with ketimine,

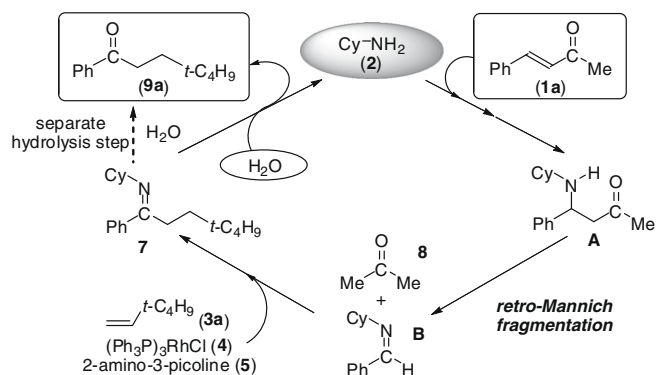
the aldimine survives even in the presence of H_2O during the reaction. Therefore, the aldimine **B** undergoes hydroiminoacylation with 1-alkene (**3a**) mediated by the cocatalyst system of $(\text{Ph}_3\text{P})_3\text{RhCl}$ (**4**) and 2-amino-3-picoline (**5**) to afford ketimine **7**. This type of transimination/hydroiminoacylation protocol has been utilized in the efficient conversion of aldimine to ketimine.⁶ Now the ketimine **7** is readily hydrolyzed by additional H_2O giving ketone **9a** with regeneration of cyclohexylamine (**2**), which can be involved in the catalytic cycle. Based on this it can be said that without additional H_2O no catalytic reaction takes place since cyclohexylamine cannot be regenerated.

However, addition of H_2O afforded a very low yield of **9a** (33% isolated yield, Scheme 1b) from the reaction of **1a** with **3a** and



Scheme 1. (a) Retro-Mannich fragmentation and subsequent hydroacylation of **1a** with **3a**, and 2 equiv of **2** in the presence of **4–6**. (b) Reactions of **1a** with **3a**, a catalytic amount of **2**, and H_2O in the presence of **4–6**.

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Scheme 2. Proposed mechanism for retro-Mannich fragmentation and subsequent hydroacylation of **1a** with **3a** and H₂O in the presence of **2**, **4**–**6**.

H₂O (100 mol %) in the presence of **2** (50 mol %), **4** (3 mol %), **5** (20 mol %), and **6** (15 mol %).⁷ To overcome this problem, it is necessary to separate the H₂O and organic solution phase (Fig. 1). Herein, we wish to report the efficient one-pot amine-assisted C–C double bond cleavage of α,β-enones aided by alkyl group-immobilized silica spheres. Since the alkyl group-immobilized silica spheres act as both a phase separator and a reservoir for water, the activity of the transition-metal catalyst is maintained even in the presence of water, and a separate hydrolysis step is avoided.

Recently, some organometallic catalytic reactions in aqueous phase have been studied based on the heterogeneous system.⁸ We have developed a new method for the surface-fabrication of the high density long chain alkyl group-grafted silica, which can be used as a divider between the organic reaction media and H₂O absorbed on the silica.⁹ Using this protocol, octadecyl group-functionalized silica spheres **11a** (loading rate of octadecyl group = 0.40 mmol g^{−1})¹⁰ were prepared by the reaction of silanol group on the surface of silica ball (10 μm in diameter, 11.67 nm pore size, purchased from Kromasil) with octadecyltrimethylsilylsilane (**10a**) in the presence of a Sc(OTf)₃ catalyst (OTf = trifluoromethylsulfonate) at room temperature (Scheme 3a). To prove the effect of **11a**, the catalytic reaction of **1a**, **3a**, and H₂O (100 mol %) with the catalyst system of (Ph₃P)₃RhCl (**4**), 2-amino-3-picoline (**5**), cyclohexylamine (**2**), and benzoic acid (**6**) was carried out in the presence of **11a** for 4 h to give the corresponding ketone **9a** in a 92% isolated yield without any further hydrolysis step.¹¹

For comparison, other alkyl group-immobilized silica spheres with different alkyl group loading rates were applied to this reaction under the identical reaction conditions: reaction of **1a** with **3a** at 130 °C for 4 h affording **9a** (Table 1). Among these modified silica additives, **11a** (loading rate of 0.45 mmol g^{−1}) exhibited better reactivity than **11b** (0.71 mmol g^{−1}), and **11c** (1.06 mmol g^{−1}), prepared from octadecylmethyl-dimethylsilylsilane (**10b**) and octadecyldimethylmethallyl-silane (**10c**), respectively (entries 2 and 3). Interestingly, when the reaction of **1a** with **3a** was conducted

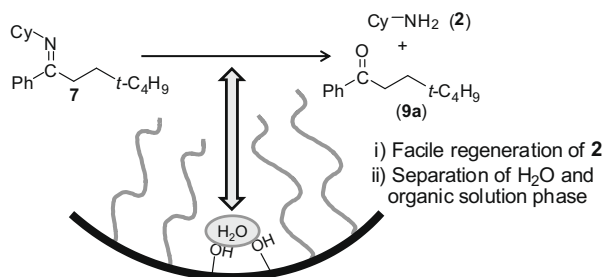
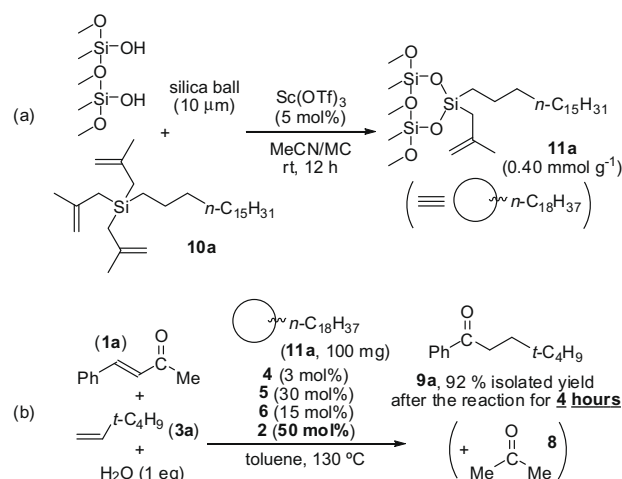


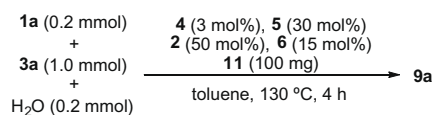
Figure 1. Hydrolysis of ketimine on the alkyl group-immobilized silica spheres.



Scheme 3. (a) Preparation of **11a** through the immobilization reaction of **10a** onto silica spheres under Sc(OTf)₃ catalysis. (b) Representative reaction of **1a** with **3a** and H₂O in the presence of **2**, **4**–**6**, and **11a**.

Table 1

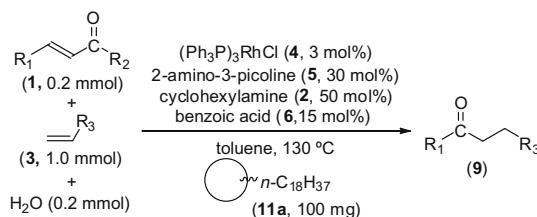
The effect of **2** on the catalytic C–C double bond cleavage of α,β-enone (**1**) and subsequent hydroacylation with **3**



Entry	Octadecyl group-immobilized silica (11)	Isolated yield of 9a (%)
1	(11a , 0.45 mmol g ^{−1})	92
2	(11b , 0.71 mmol g ^{−1})	49
3	(11c , 1.06 mmol g ^{−1})	28
4	(11a-SiMe₃) ^a	20
5	silica sphere (TMS-coated, 1.3 mmol g ^{−1}) ^a	30
6	Silica sphere (bare)	49

^a **11a-SiMe₃** and TMS-coated silica spheres were prepared by the reaction of **11a** or untreated silica spheres with 1,1,1,3,3,3-hexamethyldisilazane, respectively.

using **11a-SiMe₃**, in which the residual silanol groups on **11a** were fully capped with trimethylsilyl groups by treatment of **11a** with 1,1,1,3,3,3-hexamethyldisilazane,¹² compound **9a** was obtained in a low isolated yield (20%) (entry 4), which suggests that the residual silanol groups on **11a** are essential for the in situ hydrolysis

Table 2Catalytic C–C double bond cleavage of α,β -enone (**1**) and subsequent hydroacylation with **3**

Entry	α,β -Unsaturated ketone (1) (R_1, R_2)	Olefin (3) (R_3)	Rxn time	Yield of 9 ^a (%)	Yield of 9 without using 11a ^a (%)
1	Ph, Me (1a)	<i>n</i> -C ₄ H ₉ (3b)	4 h	89(98) (9b)	41(51)
2		<i>n</i> -C ₆ H ₁₃ (3c)		85(98) (9c)	47(56)
3		<i>c</i> -C ₆ H ₁₂ (3d)		77(80) (9d)	25(33)
4		C ₆ H ₅ (3e)		83(95) (9e)	54(58)
5		SiMe ₃ (3f)		89(99) (9f)	30(45)
6		SiEt ₃ (3g)		88(97) (9g)	17(33)
7	Me, Me (1b)	3a	45 min	(82) (9h)	(44)
8	Ph, Ph (1c)	3a	14 h	85(89) (9a)	51(61)

^a Isolated yield. The yields in parentheses are determined by GC.

step. Although the reason for this result is not clear, but we speculate that H₂O bound on the surface of silanol groups readily interacts with ketimine **7** to be hydrolyzed in organic solution as shown in Figure 1. However, if silanol group on the silica surface is completely covered with hydrophobic SiMe₃ or octadecylmethylsilyl groups, there is no room for H₂O on the silica surface, and H₂O may smear into the interior of the silica network. This fact was also confirmed by the use of exclusive TMS-coated silica spheres (loading rate: 1.3 mmol g^{−1}), prepared by treatment of silica spheres with 1,1,1,3,3,3-hexamethyldisilazane. With this TMS-coated silica spheres, only a 30% yield of **9a** was isolated (entry 5). When silica spheres untreated with alkylating reagents were used, only a 49% isolated yield of **9a** was obtained (entry 6). It is known that transition-metal phosphine complexes can react with silanol groups on the silica surface to generate inactive metal catalysts due to the formation of P(V) species of the ligand phosphine.¹³

The reactions of various α,β -enones (**1**) with olefins (**3**) are summarized in Table 2. The reaction of 4-phenyl-but-3-en-2-one (**1a**), 1-hexene (**3b**), and H₂O was carried out at 130 °C for 4 h in the presence of **4** (3 mol %), **5** (30 mol %), **2** (50 mol %), and **6** (15 mol %) using the octadecyl group-immobilized silica spheres (**11a**) to afford 1-phenylheptan-1-one (**9b**) in an 89% isolated yield. Under identical reaction conditions without **11a**, the reaction of **1a** and **3b** produced a 41% isolated yield of **9b** (Table 2, entry 1). Similar results were observed in the reactions of other 1-alkenes (**3c–g**), as fairly good yields of the corresponding isolated ketones (**9c–g**) were obtained with **11a** (Table 2, entries 2–6); only low yields of the products were obtained in the absence of C₁₈-immobilized silica **11a**. When other substituted α,β -enones (**1b** and **1c**) were applied to the reaction with **3a**, different reactivities were observed depending on the substrate (Table 2, entries 7 and 8). The reaction of 3-penten-2-one (**1b**) with **3a** proceeded to give an 82% GC yield of **9h** after 45 min using the identical catalytic system; however, the reaction of *trans*-chalcone (**1c**) with **3a** was sluggish, requiring 14 h to get a similar GC yield (89%) of corresponding ketone **9a**. These results about different reactivity based on the substituent of substrate imply that the rate-determining step is probably the cleavage of double bond which proceeds by the addition of cyclohexylamine followed by retro-Mannich type fragmentation.

In conclusion, we have demonstrated the one-pot catalytic C–C double bond cleavage of α,β -enone using alkyl group-immobilized silica spheres and a catalyst system consisting of Rh(I) complex, 2-amino-3-picoline, cyclohexylamine, and benzoic acid. In this

reaction alkyl group-immobilized silica spheres act as a water reservoir for hydrolysis of the ketimine and a phase divider for the organic solution and H₂O on the silica. This one-pot catalytic reaction system is simple and efficient, and practical. Further applications of this one-pot catalytic system with functional group-immobilized silica are currently being investigated.

Acknowledgments

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10. Loading rate was determined based on the C value of an elemental analysis. Calculation of loading rate of **11a** (C (%) 10.5841) = $(10.5841 \times 10^{-2} \text{ g of C/1 g of sample } \mathbf{11a}) \times (10^3 \text{ mmol of C/12 g of C}) \times (1 \text{ mmol of C in octadecylmethoxysilyl group/22 mmol of C}) = 0.40 \text{ mmol octadecyl group/1 g of } \mathbf{11a}$.
11. General procedure (Scheme 3b): A screw-capped pressure vial (1 ml) equipped with a magnetic stirring bar was charged with 4-phenylbut-3-en-2-one (**1a**, 29.2 mg, 0.2 mmol), 3,3-dimethyl-1-butene (**3a**, 84.0 mg, 1.0 mmol), water (3.6 mg, 0.2 mmol), $(\text{Ph}_3\text{P})_3\text{RhCl}$ (**4**, 5.5 mg, 0.006 mmol), 2-amino-3-picoline (**5**, 6.5 mg, 0.06 mmol), cyclohexylamine (**2**, 9.9 mg, 0.1 mmol), and **11a** (100 mg) dissolved in 400 mg of toluene, then the reaction mixture was stirred at 130 °C for 4 h. After the reaction, a crude mixture was purified by column chromatography (SiO_2 , *n*-hexane/ethyl acetate = 20:1) to give 43.7 mg (92% yield based on **1a**) of 4,4-dimethyl-1-phenylpentan-1-one (**9a**).
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