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# One-pot Relay Reduction-Isomerization of $\beta$ -Trifluoromethylated- $\alpha,\beta$ -Unsaturated Ketones to chiral $\beta$ -Trifluoromethylated Saturated Ketones Over Combined Catalysts in Aqueous Medium

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Despite great achievements obtained in tandem reactions, solution of the incompatible nature of bimetal complexes participated in a multi-step catalytic process is still an unmet challenge. Herein, we utilize an functionalized periodic mesoporous organosilica with well-defined single-site chiral organoruthenium active centers in its ordered dimensional-hexagonal mesopores as a heterogeneous catalyst, and combine it and  $[\text{RuCl}_2(\text{PPh}_3)_3]$  to enable an efficiently one-pot relay reduction-isomerization from achiral  $\beta$ -trifluoromethylated- $\alpha,\beta$ -unsaturated ketones to chiral  $\beta$ -trifluoromethylated saturated ketones in water with up to 97% *ee* and 100% enantiospecificity, supplying a gap of their incompatibility. Furthermore, the heterogeneous catalyst can be recovered conveniently and reused repeatedly for at least eight times without loss of reactivity in the enantioselective reduction of 4,4,4-trifluoro-1,3-diphenylbut-2-enone, showing particularly attractive in the practice of organic synthesis in an environmentally friendly manner.

## 1. Introduction

Tandem reactions as an important branch of green chemistry can reduce greatly pollution due to atom economy and minimum workup,<sup>[1]</sup> whilst microwave-assisted catalysis as a nontraditional methodology can accelerate significantly organic transformation from days or hours to minutes to enhance catalytic efficiency.<sup>[2]</sup> Together both, construction of optically pure molecules with  $\text{CF}_3$ -bearing chiral tertiary carbon center is particularly attractive because it acts as an motif of chiral trifluoromethyl family and can be converted into many types of biologically active compounds in fluorine chemistry.<sup>[3]</sup> So far, one-step enantioselective construction of these molecules from  $\beta$ - $\text{CF}_3$ -substituted  $\alpha,\beta$ -unsaturated carbonyl compounds have involved in different types of asymmetric reactions.<sup>[4]</sup> However, among these methods, high pressure of hydrogen in asymmetric hydrogenation,<sup>[4a]</sup> sensitive chiral diphosphine ligands in asymmetric conjugate reduction or addition,<sup>[4b,4c]</sup> and high catalytic amount in Friedel-Crafts alkylation<sup>[4d,4e]</sup> still limit their practical applications. Recently, an interesting two-step construction of chiral  $\beta$ - $\text{CF}_3$ -substituted saturated ketones through enantioselective reduction of  $\beta$ - $\text{CF}_3$ -substituted  $\alpha,\beta$ -unsaturated carbonyls followed by isomerization of a  $\text{C}=\text{C}$  bond of O-allylic substrates have been explored by Cahard groups.<sup>[5]</sup> Such an alternative strategy nicely complements the synthetic challenge in construction of these chiral  $\beta$ - $\text{CF}_3$ -substituted saturated ketones. However, in this catalytic

process, the incompatible nature of dual organoruthenium complexes compels to employ a two-pot catalytic reactions. Moreover, some inherent drawbacks, such as environmentally unfriendly solvent (toluene and  $\text{Et}_3\text{N}\cdot\text{HCOOH}$  as solvents), sensitive reaction system (strict isomerization condition), especially, inevitable transition-metal contamination and complicated product isolation, are still difficulty to meet the demand of green chemistry. Thus, based on environmental consideration, exploration of an immobilization strategy to realize expensive transition-metal recycling and development of one-pot reaction concomitant with microwave-assisted catalysis to overcome the limit of solvent and reaction system, are highly desirable both in fundamental research, as well as practical application.

Periodic mesoporous organosilica (PMO) as a support for immobilization of various organometallic complexes possesses attractive feature in asymmetric catalysis.<sup>[6]</sup> Besides general advantages, such large specific surface area/pore volume to enhance the loadings, the significant benefit of PMO materials has highly hydrophobic inner-surface derived from its intrinsic organosilicate inner wall<sup>[6a,6i]</sup> that are superior markedly to common Si-O-Si-linked mesoporous materials.<sup>[7]</sup> Such a feature can facilitate efficiently an aqueous asymmetric reaction, where fastly concentrating organic substrates from aqueous medium into active center can result in a highly catalytic efficiency for organic transformations.<sup>[6i]</sup>

In this contribution, we utilize the benefit of PMO materials in aqueous asymmetric reaction to construct an ethylene-bridged chiral organoruthenium-functionalized PMO as a heterogeneous catalyst,<sup>[8]</sup> and combine the advantage of one-pot reaction concomitant with microwave-assisted catalysis to explore one-pot relay reduction-isomerization in water. As presented in this study, combination of heterogeneous catalyst and  $[\text{RuCl}_2(\text{PPh}_3)_3]$

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realizes successfully an efficiently heterogeneous Ru-catalyzed enantioselective reduction from  $\beta$ -CF<sub>3</sub>-substituted  $\alpha,\beta$ -unsaturated carbonyls to  $\beta$ -CF<sub>3</sub>-substituted allylic alcohols followed by a homogeneous Ru-catalyzed isomerization under microwave irradiation from  $\beta$ -CF<sub>3</sub>-substituted allylic alcohols to enantioenriched  $\beta$ -CF<sub>3</sub>-substituted saturated ketones in one-pot relay manner, overcoming their incompatible drawbacks. Furthermore, the heterogeneous catalyst can be conveniently recovered and reused repeatedly for at least eight times without loss of reactivity in the enantioselective reduction of 4,4,4-trifluoro-1,3-diphenylbut-2-enone. As expected, this one-pot enantioselective reduction concomitant with microwave-assisted catalysis solves the limitation of Cahard's method, and realizes the recycling of chiral organoruthenium complex in first-step asymmetric transfer hydrogenation. This strategy offers an attractive method in the practical synthesis of valuable chiral  $\beta$ -CF<sub>3</sub>-substituted saturated ketones.

## 2. Experimental

### 2.1. Preparation of CymeneRuArDPEN-PMO (3)

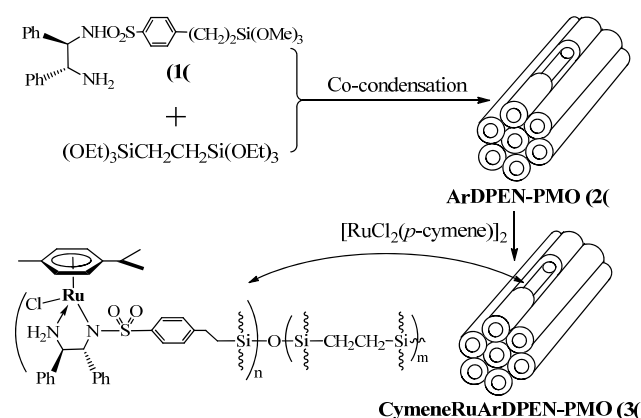
In a typical synthesis, [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (0.22 g, 0.40 mmol) were added to a suspension of **2** (1.00 g) in 20.0 mL of dry CH<sub>2</sub>Cl<sub>2</sub> at 20 °C, and the resulting mixture was stirred at 20 °C for 24 h. The mixture was filtered through filter paper and then rinsed with excess CH<sub>2</sub>Cl<sub>2</sub>. After Soxhlet extraction for 12 h in CH<sub>2</sub>Cl<sub>2</sub> to remove homogeneous and unreacted starting materials, the solid was dried at ambient temperature under vacuum overnight to afford catalyst **3** (1.09 g) as a light-yellow powder. ICP analysis showed that the Ru loading-amount was 10.42 mg (0.103 mmol) per gram catalyst. IR (KBr) cm<sup>-1</sup>: 3443.6 (s), 3066.2 (w), 2975.8 (w), 2912.9 (w), 1627.3 (m), 1501.5 (w), 1456.3 (w), 1413.1 (w), 1330.5 (w), 1267.6 (m), 1161.4 (s), 1098.5 (s), 1025.8 (s), 907.8 (m), 764.4 (m), 701.4 (m), 575.6 (m), 448.7 (m). <sup>13</sup>C CP/MAS NMR (161.9 MHz): 150.0, 137.5, 128.7 (C of Ph and Ar), 99.8, 87.7, 81.9 (C of MeC<sub>6</sub>H<sub>3</sub><sup>*i*</sup>Pr in *p*-cymene group), 76.3–69.6 (C of –NCHPh–), 58.8 (O–CH<sub>2</sub>CH<sub>3</sub>), 31.5 (C of –CH<sub>2</sub>Ar), 24.4 (C of CH<sub>3</sub>C<sub>6</sub>H<sub>3</sub>CH(CH<sub>3</sub>)<sub>2</sub> in *p*-cymene group), 23.4–13.2 (C of CH<sub>3</sub>C<sub>6</sub>H<sub>3</sub>CH(CH<sub>3</sub>)<sub>2</sub> in *p*-cymene group, and O–CH<sub>2</sub>CH<sub>3</sub>), 5.4 (C of –CH<sub>2</sub>Si) ppm. <sup>29</sup>Si MAS/NMR (79.4 MHz): T<sup>1</sup> (δ = –48.9 ppm), T<sup>2</sup> (δ = –57.4 ppm), T<sup>3</sup> (δ = –64.9 ppm).

### 2.2. Synthesis of the heterogeneous catalyst 3

Chiral CymeneRuArDPEN-functionality embedded within the PMO network, abbreviated as CymeneRuArDPEN-PMO (**3**), (CymeneRuArDPEN:<sup>[9]</sup> ((η<sup>6</sup>-cymene)RuCl[N-((1*R*,2*R*)-2-amino-1,2-diphenylethyl)-4-ethylbenzenesulfonamide], where ArDPEN = N-((1*R*,2*R*)-2-amino-1,2-diphenylethyl)-4-ethylbenzenesulfonamide) was prepared as outlined in Scheme 1. Firstly, key chiral ArDPEN-derived siloxane (**1**), (*R,R*)-4-(trimethoxysilyl)ethylphenylsulfonyl-1,2-diphenylethylenediamine, was synthesized according to the reported method.<sup>[8a]</sup> Co-condensation of **1** and 1,2-bis(triethoxysilyl)ethane did then afford chiral ligand-functionalized material ArDPEN-PMO (**2**) as a white powder. Finally, the heterogeneous catalyst **3** was obtained successfully by the direct complexation of [RuCl<sub>2</sub>(*p*-

cymene)]<sub>2</sub> and **2** followed by further Soxhlet extraction for clearness of its nanochannels as a light-yellow powder.

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**Scheme 1.** Immobilization of CymeneRuArDPEN-functionality within the PMO silicate network.

### 2.3. Characterization

Ru loading amounts in catalysts were analyzed using an inductively coupled plasma optical emission spectrometer (ICP, Varian VISTA-MPX). Fourier transform infrared (FT-IR) spectra were collected on a Nicolet Magna 550 spectrometer using KBr method. Transmission electron microscopy (TEM) images were performed on a JEOL JEM2010 electron microscope at an acceleration voltage of 220 kV. X-ray photoelectron spectroscopy (XPS) measurements were performed on a Perkin-Elmer PHI 5000C ESCA system. A 200 μm diameter spot size was scanned using a monochromatized Aluminum K $\alpha$  X-ray source (1486.6 eV) at 40 W and 15 kV with 58.7 eV pass energies. All the binding energies were calibrated by using the contaminant carbon (C<sub>1s</sub> = 284.6 eV) as a reference. Nitrogen adsorption isotherms were measured at 77 K with a Quantachrome Nova 4000 analyzer. The samples were measured after being outgassed at 423 K overnight. Pore size distributions were calculated by using the BJH model. The specific surface areas (SBET) of samples were determined from the linear parts of BET plots (*p/p*<sub>0</sub> = 0.05–1.00). Solid state NMR experiments were explored on a Bruker AVANCE spectrometer at a magnetic field strength of 9.4 T with <sup>1</sup>H frequency of 400.1 MHz, <sup>13</sup>C frequency of 100.5 MHz and <sup>29</sup>Si frequency of 79.4 MHz with 4 mm rotor at two spinning frequency of 5.5 kHz and 8.0 kHz, TPPM decoupling is applied in the during acquisition period. <sup>1</sup>H cross polarization in all solid state NMR experiments was employed using a contact time of 2 ms and the pulse lengths of 4 μs.

### 2.4. General procedure for the one-pot enantioselective reduction-isomerization of $\beta$ -trifluoromethylated- $\alpha,\beta$ -unsaturated ketones

A typical procedure was as follows: The catalyst **3** (29.1 mg, 3.0 μmol of Ru, based on ICP analysis),  $\beta$ -trifluoromethylated- $\alpha,\beta$ -unsaturated ketones (0.15 mmol), HCO<sub>2</sub>Na (204.0 mg, 3.0 mmol), and 2.0 mL of water were added sequentially to a 5.0 mL thick walled Pyrex tube. The mixture was then stirred at room temperature (20 °C) for 17h. During this period, the reaction was monitored constantly by TLC. When the reaction was completed,

the tube was added  $[\text{RuCl}_2(\text{PPh}_3)_3]$  (2.77 mg, 3.0  $\mu\text{mol}$ ) and positioned in a circular single-mode cavity CEM Microwave reactor with optional cooling using nitrogen gas from CEM Corporation (USA), adjusting the reaction temperature at 70  $^\circ\text{C}$  and producing continuous irradiation at 2.45 GHz, and the mixture was irradiated with 170 W for 15 minutes. After completion of the reaction, catalyst was separated by centrifugation (10,000 rpm) for the recycling experiment. The aqueous solution was extracted with ethyl ether ( $3 \times 3.0 \text{ mL}$ ). The combined ethyl ether extracts were washed with  $\text{NaHCO}_3$  and brine, and then dehydrated with  $\text{Na}_2\text{SO}_4$ . After evaporation of ethyl ether, the residue was purified by silica gel flash column chromatography to afford the desired product. The yields were determined by  $^1\text{H-NMR}$ , and the *ee* values were determined by a HPLC analysis using a UV-Vis detector and a Daicel chiralcel column ( $\Phi 0.46 \times 25 \text{ cm}$ ).

### 3. Results and discussion

#### 3.1. Characterization of the heterogeneous catalyst 3

FT-IR spectra of **2** and catalyst **3** (see SI in Figure S1). Showed that both **2** and **3** exhibited the characteristic bands of the organosilicate materials around 3443, 1627 and 1098  $\text{cm}^{-1}$  for  $\nu(\text{O-H})$ ,  $\delta(\text{O-H})$  and  $\nu(\text{Si-O})$ , respectively.<sup>[10]</sup> The relatively weak bands between 3100–2800  $\text{cm}^{-1}$  were assigned to the asymmetric and symmetric stretching vibrations of the C–H bonds. The peaks indicative of  $\nu(\text{Si-C})$  should appear at 1100  $\text{cm}^{-1}$ , however, they were difficult to be distinguished due to the overlapping absorbance peaks from  $\nu(\text{Si-O})$ .<sup>[11]</sup> The bands between 1510–1450  $\text{cm}^{-1}$  were attributed to the breathing vibrations of the C=C bonds in the aromatic ring.<sup>[10]</sup> The intensity of these peaks in catalyst **3** increased consistently relative to those in **2**, implying the coordination of  $[\text{RuCl}_2(p\text{-cymene})]_2$  occurs. These observations suggested the incorporation of the chiral CymeneRuArDPEN moiety within its organosilicate network.

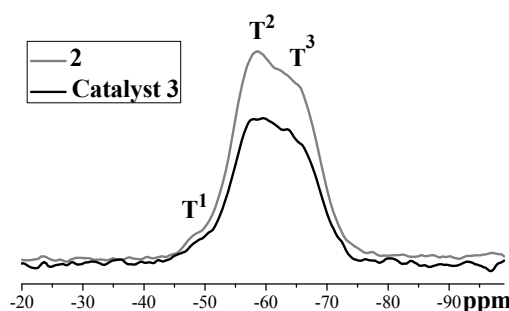


Figure 1. Solid-state  $^{29}\text{Si}$  CP/MAS NMR spectra of **2** and **3**.

As shown in Figure 1, the  $^{29}\text{Si}$  magic angle spinning (MAS) NMR spectra disclosed that both **2** and catalyst **3** presented one group of exclusive T signals that were derived from organosilica, suggesting that all Si species were covalently attached to carbon

atoms.<sup>[8a]</sup> As compared with those typical isomer shift values in the literature<sup>[12]</sup> (–48.5/–58.5/–67.5 ppm for  $\{\text{[R(HO)}_2\text{SiOSi]/[R(HO)Si(OSi)}_2\text{]/[RSi(OSi)}_3\text{]}\}$ ), two strong T signals at –57.4 and –64.9 ppm were corresponding to  $\text{T}^2$   $[\text{R-Si(OSi)}_2\text{(OH)}]$  and  $\text{T}^3$   $[\text{R-Si(OSi)}_3]$  ( $\text{R} = \text{CymeneRuArDPEN-functionalized alkyl-linked group or ethylene-bridged group}$ ), which were strongly similar to those reported literatures.<sup>[13]</sup> Both typical T signals demonstrated that **2** and catalyst **3** possessed the organosilicate networks with  $\text{R-Si(OSi)}_2\text{(OH)}$  and  $[\text{R-Si(OSi)}_3]$  species as their main organosilicate walls. Furthermore, the absence of signals for Q-series from –90 to –120 ppm indicated that no cleavage of carbon–silicon bond occurred during co-condensation process.

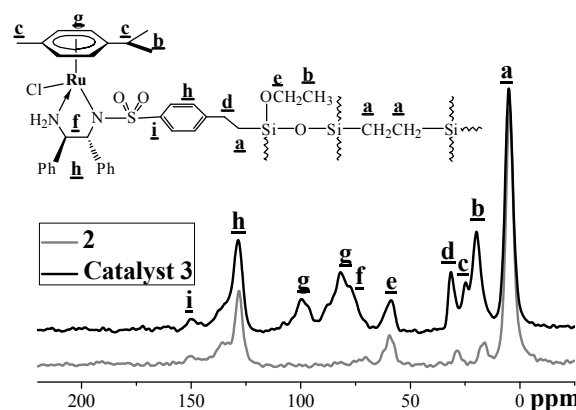


Figure 2. Solid-state  $^{13}\text{C}$  CP/MAS NMR spectra of **2** and **3**.

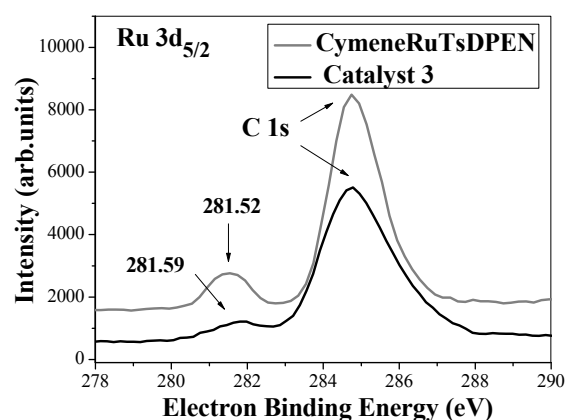


Figure 3. XPS spectra of the homogeneous CymeneRuArDPEN and **3**.

Incorporation of well-defined single-site active CymeneRuArDPEN center within its organosilicate network of **3** could be proven by solid-state  $^{13}\text{C}$  cross-polarization (CP)/magic angle spinning (MAS) NMR spectroscopy. As shown in Figure 2, both **2** and catalyst **3** produced strongly characteristic carbon signals of  $-\text{SiCH}_2$  groups at  $\sim 5 \text{ ppm}$  that were ascribed their ethylene-bridged silica embedded within their organosilicate networks. The carbon signals at  $\sim 70 \text{ ppm}$  and  $\sim 129 \text{ ppm}$  were corresponded to carbon atoms of the  $-\text{NCHPh}$  groups and of the



–C<sub>6</sub>H<sub>5</sub> groups in ArDPEN moiety, respectively. Peaks between 100 and 75 ppm in the spectrum of **3** were assigned to the carbon atoms of the aromatic ring in *p*-cymene moiety, and peaks at ~24 and ~20 ppm in the spectrum of **3** are attributed to the carbon atom of the  $\text{CH}_3$  and  $\text{CH}$  groups attached to the aromatic ring in *p*-cymene moiety. These peaks were absent in the spectrum of **2**, suggesting the formation of the CymeneRuArDPEN functionality as single-site center in catalyst **3**. These chemical shifts of catalyst **3** were similar to those of its homogeneous counterpart CymeneRuTsDPEN,<sup>[9a]</sup> confirming that they had the same well-defined single-site active species. The XPS investigation (Figure 3) further testified both had similar electronic environments, where catalyst **3** and its counterpart showed the similar Ru 3d<sub>5/2</sub> electron binding energy (281.52 eV for its homogeneous counterpart versus 281.59 eV for catalyst **3**) that were obviously different from that of their parent [RuCl<sub>2</sub>(*p*-cymene)]<sub>2</sub> (see SI in Figure S2). In addition, the peaks around 16 and 58 ppm should be attributed to the nonhydrolyzed ethoxy groups ( $\text{CH}_3\text{CH}_2\text{O}$ ) that often appeared in the CP MAS spectra.<sup>[14]</sup>

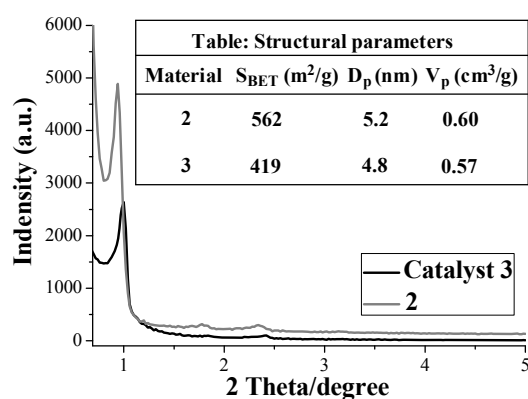


Figure 4. Small-angle powder XRD patterns of **2** and **3**.

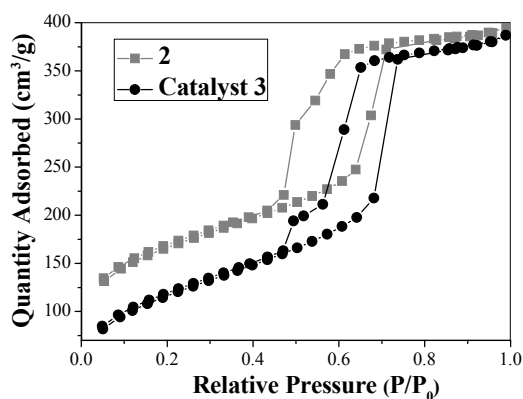


Figure 5. Nitrogen adsorption-desorption isotherms of **2** and **3**.

Their orderly mesostructures and well-defined pore arrangements were also investigated using X-ray diffraction (XRD), transmission electron microscopy (TEM), and nitrogen adsorption-desorption technique. As shown in Figure 4, the small-angle XRD patterns revealed that both **2** and catalyst **3** presented one similar intense  $d_{100}$  diffraction peak along with two similar weak diffraction peaks ( $d_{110}$ ,  $d_{200}$ ), suggesting that the

dimensional-hexagonal pore structure ( $p6mm$ ) observed in ArDPEN-PMO (**2**) could be retained.<sup>[8a]</sup> Similarly, both the nitrogen adsorption-desorption isotherms (Figure 5) also exhibited the typical IV type isotherms with H<sub>1</sub> hysteresis loop and a visible step at  $P/P_0 = 0.50$ – $0.90$ , corresponding to capillary condensation of nitrogen in mesopores. Their structural parameters were listed in Table that were inserted in Figure 4. The TEM morphology (see SI in Figure S3) further confirmed that catalyst **3** possessed the ordered mesostructure with the dimensional-hexagonal arrangements.

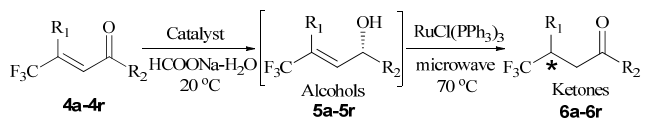
## 3.2. Catalytic performance of the heterogeneous catalyst

### 3.2.1. Catalytic properties

Based on the idea of one-pot relay enantioselective reduction-isomerization of  $\beta$ -trifluoromethylated- $\alpha,\beta$ -unsaturated ketones, two single-step model reactions, the enantioselective reduction of 4,4,4-trifluoro-1,3-diphenylbut-2-enone to (*R*)-4,4,4-trifluoro-1,3-diphenylbut-2-enol catalyzed by **3** and the isomerization of (*R*)-4,4,4-trifluoro-1,3-diphenylbut-2-enol to (*R*)-4,4,4-trifluoro-1,3-diphenylbutan-1-one catalyzed by [RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>], were investigated separately. In the case of first-step enantioselective reduction, the asymmetric reaction catalyzed by **3** was screened through the use of HCOONa as a hydrogen resource and H<sub>2</sub>O as a solvent that was inspired by the works of Xiao and Deng on asymmetric transfer hydrogenation.<sup>[15]</sup> The result showed that the enantioselective reduction of 4,4,4-trifluoro-1,3-diphenylbut-2-enone gave (*R*)-4,4,4-trifluoro-1,3-diphenylbut-2-enol with 96% yield and 97% *ee*. Such an *ee* value was comparable to that of its homogeneous counterpart, even that obtained with HCO<sub>2</sub>H-NEt<sub>3</sub> azeotropic mixture as a hydrogen source and solvent.<sup>[5, 8f]</sup> Notably, water as a solvent is greener than that obtained in HCO<sub>2</sub>H-NEt<sub>3</sub> reaction system. In the case of second-step isomerization using H<sub>2</sub>O as a solvent, however, the single-step isomerization catalyzed by [RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>] did not occur from (*R*)-4,4,4-trifluoro-1,3-diphenylbut-2-enol to (*R*)-4,4,4-trifluoro-1,3-diphenylbutan-1-one although various traditional reaction conditions had been screened. To our delight, under a nontraditional microwave irradiation, this single-step isomerization could be completed rapidly within 15 minute, in which the quantitative yield and the retaining *ee* value of (*R*)-4,4,4-trifluoro-1,3-diphenylbutan-1-one could be obtained. Such a high catalytic efficiency indicated the benefit of microwave-assisted catalysis, which could boost greatly the reaction rate from 2 hours to 15 minutes.<sup>[5]</sup> More importantly, by combining both into one-pot relay process, the **3**-catalyzed enantioselective reduction followed by the [RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>]-catalyzed isomerization, still retained the same results as two single-step process (Entry 1 versus Entry 1 in brackets, Table 1).<sup>[5]</sup> It was worth mentioning that this one-pot relay enantioselective reduction-isomerization of 4,4,4-trifluoro-1,3-diphenylbut-2-enone to (*R*)-4,4,4-trifluoro-1,3-diphenylbutan-1-one was significantly better than that obtained with the mixed homogeneous CymeneRuTsDPEN plus [RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>] because the mixed dual catalysts afforded a mixture of the intermediate of (*R*)-4,4,4-trifluoro-1,3-diphenylbut-2-enol (90% *ee*) and the target product of (*R*)-4,4,4-trifluoro-1,3-diphenylbutan-1-one (75% *ee*) (the mole ratio of 59 to 41) (Entry 2, Table 1). This comparison demonstrated that the

designed dual catalyst in relay reaction could overcome efficiently the incompatible nature of dual organoruthenium complexes.

**Table 1.** One-pot enantioselective reduction-isomerization of  $\beta$ -trifluoromethylated- $\alpha,\beta$ -unsaturated ketones.<sup>a</sup>



Ent ry	Compound (R <sub>1</sub> , R <sub>2</sub> )	Alcohol (5a-5r)	Ketone (6a-6r)		%es
		%ee <sup>b</sup>	%Yield <sup>b</sup>	%ee <sup>b</sup>	
1	<b>4a</b> (Ph, Ph)	97(97) <sup>c</sup>	96 (92)	97(97) <sup>c</sup>	100
2 <sup>d</sup>	<b>4a</b> (Ph, Ph)	90	41 (29)	75	83
3 <sup>e</sup>	<b>4a</b> (Ph, Ph)	93	88 (76)	92	99
4	<b>4b</b> ( <i>p</i> -FPh, Ph)	94	96 (89)	92	98
5	<b>4c</b> ( <i>p</i> -ClPh, Ph)	95	97 (91)	95	100
6	<b>4d</b> ( <i>p</i> -BrPh, Ph)	96	95 (90)	94	98
7	<b>4e</b> ( <i>m</i> -BrPh, Ph)	95	94 (88)	95	100
8	<b>4f</b> ( <i>p</i> -CF <sub>3</sub> Ph, Ph)	95	97 (91)	93	98
9	<b>4g</b> ( <i>p</i> -MePh, Ph)	94	96 (91)	93	99
10	<b>4h</b> ( <i>p</i> -MeOPh, Ph)	95	92 (85)	93	98
11	<b>4i</b> (Me, Ph)	90	97 (92)	88	98
12	<b>4j</b> (Ph, <i>p</i> -ClPh)	91	96 (91)	88	97
13	<b>4k</b> (Ph, <i>p</i> -BrPh)	94	95 (89)	94	100
14	<b>4l</b> (Ph, <i>p</i> -MePh)	95	95 (87)	90	95
15	<b>4m</b> (Ph, <i>p</i> -MeOPh)	90	92 (89)	90	100
16	<b>4n</b> (Ph, <i>m</i> -ClPh)	94	95 (91)	93	99
17	<b>4o</b> (Ph, <i>m</i> -BrPh)	93	96 (92)	93	100
18	<b>4p</b> (Ph, <i>o</i> -MeOPh)	92	95 (90)	92	100
19	<b>4q</b> ( <i>p</i> -FPh, <i>p</i> -BrPh)	91	95 (91)	91	100
20	<b>4r</b> ( <i>p</i> -BrPh, <i>p</i> -BrPh)	93	94 (89)	90	97

<sup>a</sup> Reaction conditions: catalyst **3** (29.1 mg, 3.0  $\mu\text{mol}$  of Ru, based on ICP analysis) or CymeneRuTsDPEN (1.91 mg, 3.0  $\mu\text{mol}$ ),  $\beta$ -trifluoromethylated- $\alpha,\beta$ -unsaturated ketones (0.15 mmol), 2.0 mL of water were added sequentially to a 5.0 mL of thick walled Pyrex tube. The mixture was then stirred at room temperature ( $20^\circ\text{C}$ ) for 17h. After that,  $[\text{RuCl}_2(\text{PPh}_3)_3]$  (2.77 mg, 3.0  $\mu\text{mol}$ ) was added and the mixture was irradiated with 170 W for 15 minutes. <sup>b</sup>Yields were determined by <sup>1</sup>H-NMR (data in bracket is isolated yield) and *ee* values were determined by chiral HPLC analysis (see SI in Figures S4-5, S7). <sup>c</sup> Data were obtained in

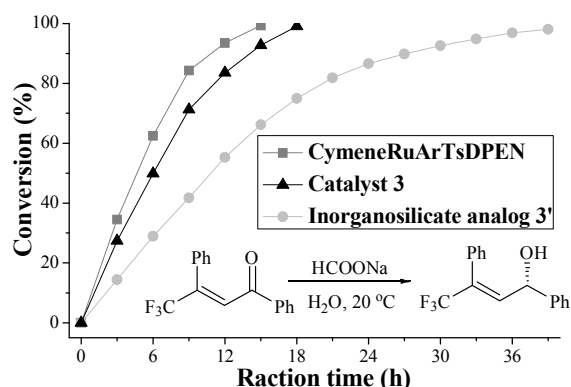
two single-step reactions. <sup>d</sup> Data were obtained using the mixed homogeneous CymeneRuTsDPEN plus  $[\text{RuCl}_2(\text{PPh}_3)_3]$  as catalysts. <sup>e</sup> Data were obtained using a parallel CymeneRuArDPEN-SBA-15 (**3'**) plus  $[\text{RuCl}_2(\text{PPh}_3)_3]$  as catalysts within 40 h plus 15 minute reaction time.

Having established an efficiently one-pot relay enantioselective reduction-isomerization, we further investigated the general applicability with a series of substituted substrates. As shown in Table 1, in general, high yields and enantioselectivities of chiral  $\beta$ -CF<sub>3</sub>-substituted saturated ketones could be obtained steadily. In particular, relative to the single-step enantioselective reduction of 4,4,4-trifluoro-1,3-diphenylbut-2-enone to chiral intermediate (*R*)-4,4,4-trifluoro-1,3-diphenylbut-2-enol catalyzed by catalyst **3** that were also performed and listed in the column 3 of Table 1, these chiral  $\beta$ -CF<sub>3</sub>-substituted saturated ketones had very high enantiospecificities (%es) [%es = 100 (product *ee*)/(chiral intermediate *ee*)], ranging from 95 to 100%,<sup>[5,16]</sup> confirming the advantage of microwave-assisted catalysis. Furthermore, it was found that the structures and electronic properties of substituents on the aromatic rings at R<sub>1</sub> or R<sub>2</sub> did not affect the enantiospecificity. Taking the reactions with substrates bearing phenyl groups at R<sub>2</sub> as examples, we found that the asymmetric reactions with various electron-withdrawing and -donating substituents on the aryl moiety at R<sub>1</sub> were equally efficient (Entries 4–10). Moreover, the reactions with both substrates bearing aromatic rings at R<sub>1</sub> and R<sub>2</sub> were enantioselective toward the target products, in which two representative examples with high enantiospecificities could be obtained (Entries 19-20, Table 1).

### 3.2.2. Investigation of factors affecting catalytic performance

Besides the markedly enhanced reaction rate in the second microwave-assisted  $[\text{RuCl}_2(\text{PPh}_3)_3]$ -catalyzed isomerization-step of the relay reaction, it was found that the first enantioselective reduction-step catalyzed by **3** had also a relatively high catalytic efficiency. In order to demonstrate the role of catalyst **3** in the first-step enantioselective reduction of the relay reaction, the single-step reaction from 4,4,4-trifluoro-1,3-diphenylbut-2-enone to (*R*)-4,4,4-trifluoro-1,3-diphenylbut-2-enol catalyzed by **3** was further investigated. It was found that the asymmetric reaction could be completed within 17 h, which was slightly longer than that obtained with homogeneous counterpart (15 h). This phenomenon is rare in a generally heterogeneous catalytic system since a heterogeneous catalysis often needs an obviously longer reaction time than its corresponding homogeneous counterpart due to slow diffusion of reactants and products. Thus, such a near reaction time indicated that a positive hydrophobic effect dominated its catalytic performance that was possibly attributed to the hydrophobic nature of the PMO-type organosilicate network in catalyst **3**. In order to confirm this judgment, two comparable analogs with the similar ordered mesostructures and dimensional-hexagonal arrangements, SBA-15-supported ArDPEN-functionalized material (ArDPEN-SBA-15 (**2'**)) and CymeneRuArDPEN-functionalized material (CymeneRuArDPEN-SBA-15 (**3'**)), were prepared through the use of the similar synthetic process.<sup>[8g]</sup> Differed from ethylene-bridged units as their main networks of **2-3**, the parallel analogs **2'-3'** had Si-O-Si-linked units as their main networks. In this case, we performed a parallel adsorption experiment to investigate their

hydrophobic differences through the analyses of changes of substrate's concentrations, where the tested substrate of 4,4,4-trifluoro-1,3-diphenylbut-2-enone, and equivalent **2** or **2'** were suspended 2.0 mL of water respectively. After stirring for 5.0 hours and filtrating, it was found that the mole ratio of 4,4,4-trifluoro-1,3-diphenylbut-2-enone for **2'**-to-**2** in solution was 1.6 : 1, suggesting that **2** had a high hydrophobicity due to the high concentration of 4,4,4-trifluoro-1,3-diphenylbut-2-enone in solid-state relative to **2'**. This observation demonstrated that the organosilicate network of **2** had a stronger ability than the Si-O-Si-linked silicate network of **2'** to draw 4,4,4-trifluoro-1,3-diphenylbut-2-enone into the catalytically activity center from aqueous system, thereby accelerating reaction rates.<sup>[8a-c]</sup>



**Figure 6.** Comparison of the enantioselective reduction of 4,4,4-trifluoro-1,3-diphenylbut-2-enone catalyzed by **3**, its silicate analog **3'**, and the

**Table 2.** Reusability of catalyst **3** for enantioselective reduction of 4,4,4-trifluoro-1,3-diphenylbut-2-enone to (*R*)-4,4,4-trifluoro-1,3-diphenylbut-2-enol.<sup>a,b</sup>

Run time	1	2	3	4	5	6	7	8
Yield [%]	96	96	96	96	96	95	93	91
ee [%]	97	96	97	97	96	94	92	90

<sup>a</sup> Reaction conditions: catalyst **3** (291.0 mg, 0.030 mmol of Ru based on ICP analysis), 4,4,4-trifluoro-1,3-diphenylbut-2-enone (1.50 mmol), HCO<sub>2</sub>Na (2.04 g, 30.0 mmol), 20.0 mL of water, reaction time (17 h). <sup>b</sup> Determined by chiral HPLC analysis (see SI in Figure S6).

## Conclusions

In conclusions, we develop an ethylene-bridged PMO-supported chiral ruthenium-functionalized heterogeneous catalyst **3**. By combining it and [RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub>] as dual catalysts, we realize successfully an efficiently one-pot relay reduction-isomerization of β-trifluoromethylated-α,β-unsaturated ketones to chiral β-CF<sub>3</sub>-substituted saturated ketones in water. As presented in this study, the hydrophobic nature of the heterogeneous catalyst **3** and the benefit of microwave-assisted catalysis further promote the catalytic performance. Furthermore, the heterogeneous catalyst **3** could be recovered easily and reused repeatedly eight times without obvious effect on its reactivity in the enantioselective reduction of 4,4,4-trifluoro-1,3-diphenylbut-2-enone to (*R*)-4,4,4-trifluoro-1,3-diphenylbut-2-enol. The outcomes from the study afford a practical approach for realization of one-pot reaction by

homogeneous CymeneRuTsDPEN. Reactions were carried out at substrate-to-catalyst mole ratio of 100. DOI: 10.1039/C5GC00479A

A further direct evidence to support this judgment came from a kinetic investigation in the enantioselective reduction of 4,4,4-trifluoro-1,3-diphenylbut-2-enone catalyzed by catalyst **3**, its silicate analog **3'**, and its homogeneous counterpart as shown in Figure 6. It was found that the enantioselective reduction of 4,4,4-trifluoro-1,3-diphenylbut-2-enone catalyzed by catalyst **3** resulted in an initial activity obviously higher than that achieved with its silicate analog **3'** (the initial TOFs were 9.1 versus 4.7 molmol<sup>-1</sup>h<sup>-1</sup>), and slightly lower than that obtained with its homogeneous counterpart (the initial TOFs were 9.1 versus 10.5 molmol<sup>-1</sup>h<sup>-1</sup>). Notably, the highly hydrophobic nature of PMO-type catalyst **3** relative to that of SBA-15-type silicate analog **3'** was responsible for its fast reaction rate in the **3**-catalyzed enantioselective reduction.

### 3.2.3. Catalyst's stability and recyclability

In addition to the realization of one-pot relay enantioselective reduction-isomerization, another aim in the design of the heterogeneous catalyst **3** is the ease of separation and ability of the catalyst to retain its reactivity and enantioselectivity after multiple recycling. As observed, the heterogeneous catalyst **3** is easy to recover from the reaction system by simple centrifugation. As shown in Table 2, in eight consecutive reactions, the heterogeneous catalyst **3** still produced (*R*)-4,4,4-trifluoro-1,3-diphenylbut-2-enol with 91% yield and 90% ee in the enantioselective reduction of 4,4,4-trifluoro-1,3-diphenylbut-2-enone to (*R*)-4,4,4-trifluoro-1,3-diphenylbut-2-enol.

overcoming incompatible nature of bimetal complexes participated in one-pot process, which are an attractive in the practical preparation of valuable chiral β-CF<sub>3</sub>-substituted saturated ketones in an environmentally friendly manner.

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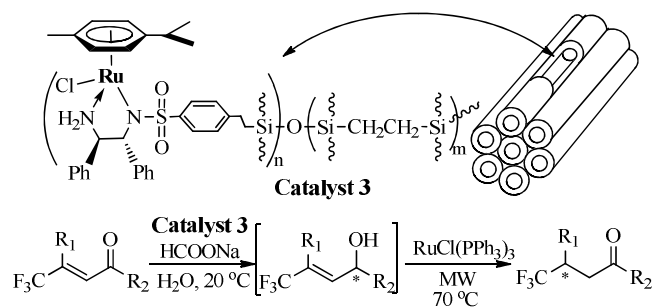
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## A table of contents entry.



Combined ruthenium-functionalized organosilica and tris(triphenylphosphine)ruthenium as dual catalysts enable one-pot relay reduction-isomerizations of  $\beta$ -CF<sub>3</sub>-substituted- $\alpha,\beta$ -unsaturated ketones to chiral  $\beta$ -CF<sub>3</sub>-substituted saturated ketones.