## A Magnetically Separable Heterogeneous Deallylation Catalyst: $[CpRu(\eta^3-C_3H_5)(2-pyridinecarboxylato)]PF_6$ Complex Supported on a Ferromagnetic Microsize Particle Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>

### Takuya Hirakawa,<sup>[a]</sup> Shinji Tanaka,<sup>[a]</sup> Naoki Usuki,<sup>[b]</sup> Hisao Kanzaki,<sup>[b]</sup> Mikio Kishimoto,<sup>[b]</sup> and Masato Kitamura<sup>\*[a]</sup>

Keywords: Sustainable chemistry / Supported catalysts / Ruthenium / Protecting groups / Magnetic particles / π-Allyl complexes

The highly reactive and chemoselective homogeneous deallylation catalyst  $CpRu(\eta^3-C_3H_5)(4$ -substituted-2-pyridinecarboxylato) was immobilized on microsize spherical Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub> particles. The resultant heterogeneous catalyst displays high saturation magnetization, weak coercive forces and high levels of dispersibility. The catalyst has increased the utility of deallylation by allowing the reaction to be conducted without extra additives. The only co-product of the

#### reaction is a volatile allyl ether compound. Here, we demonstrate the efficient deallylation and separation of highly polar multifunctional compounds as well as multiple rounds of catalyst recycling without significant loss of reactivity. The usefulness of this catalyst has been confirmed by the synthesis of a triribonucleotide 3–5 U.

(© Wiley-VCH Verlag GmbH & Co. KGaA, 69451 Weinheim, Germany, 2009)

#### Introduction

Over the past two decades there has been significant progress in the field of homogeneous catalysis.<sup>[1]</sup> As a result, many organic transformations are now achieved under catalytic conditions, realizing high efficiency in terms of atom economy, E factor, safety and operational simplicity.<sup>[2,3]</sup> Our deallylation and allylation catalyst,  $[CpRu(\eta^3-C_3H_5)(2$ quinolinecarboxylato)] $PF_6(1)$ , has also increased the utility of the allyl moiety as a suitable protecting group.<sup>[4]</sup> Removal of the allyl group from 2 proceeds in alcoholic solvents, typically in methanol, without the need of any extra nucleophiles such as amines, metal hydrides and enolates that are required for conventional Pd-based methods.<sup>[5]</sup> The only coproduct in the reaction is the volatile allyl ether, which can be easily removed by evaporation to afford the final product 3. However, separation of the catalyst from the product is still a major issue. Contamination of the product after the catalytic process reduces the efficiency of product isolation. Indeed, this problem is particularly serious for the synthesis of highly polar bio-related polymers such as peptides and oligonucleotides.<sup>[6]</sup> From an economic perspective, recycling

 [a] Research Center for Materials Science and Department of Chemistry, Nagoya University, Chikusa, Nagoya 464-8602, Japan Fax: +81-52-789-2958 E-mail: kitamura@os.rcms.nagoya-u.ac.jp

- [b] R&D Division, Hitachi Maxell, Ltd.,
- 1 Koizumi Ohyamazaki-cho, Otokuni-gun, Kyoto 618-8525, Japan
- Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

of the catalyst is highly desirable. One apparent solution to this problem is the immobilization of a homogeneous catalyst to an insoluble material. Indeed, a variety of suitable



Scheme 1.



## SHORT COMMUNICATION

organic and inorganic supports have already been reported.<sup>[7]</sup> This paper describes a new type of heterogeneous deallylation catalyst,  $[Fe_3O_4@SiO_2-L-CpRu(\eta^3-C_3H_5)]$  (4), which consists of ferromagnetic particles and a cationic  $CpRu(\eta^3-C_3H_5)$  complex immobilized through the 4-[5- $(C_2H_5O)_3Si(CH_2)_5NHCO]$ -2-pyridinecarboxylate monoanionic ligand 5 (Scheme 1).

#### **Results and Discussion**

The  $Fe_3O_4(a)SiO_2-L-CpRu(\eta^3-C_3H_5)$  catalyst 4 has a microsize spherical shape and possesses characteristic ferromagnetic properties.<sup>[8]</sup> Each particle contains a few tens of Fe<sub>3</sub>O<sub>4</sub> beads (diameter of ca. 200 nm) with a catalyst supported on the silicate surface by covalent Si-O bonds, which significantly reduces leaching of the ligand moiety.<sup>[9]</sup> The >100 nm size of the Fe<sub>3</sub>O<sub>4</sub> particles increases the saturation magnetization. Furthermore, the spherical shape of the particles in the absence of magnetic anisotoropy weakens the coercive forces. Together, these factors avoid self-aggregation,<sup>[10]</sup> which is a serious problem associated with magnetic nanoparticles. The microsize of the particles maintains the appropriate dispersibility, although catalyst separation can be easily achieved by application of an external magnetic field. The particles are readily redispersed due to the relatively weak van der Waals force. This is also advantageous in comparison to nanoparticles, which are attracting considerable attention at the moment.<sup>[8,11]</sup> The Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub> particles were prepared according to the Hitachi method.<sup>[12]</sup> The ligand moiety 5 was synthesized in 71% yield by dehydrative condensation of 2-allyl hydrogen pyridine-2,4-dicarboxylate<sup>[13,14]</sup> with 5-(triethoxysilyl)pentan-1-amine.<sup>[15]</sup> Compound 5 was then immobilized on 50 mg of  $Fe_3O_4@SiO_2$  ([5] = 50 mM, toluene, reflux, 32 h), giving Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-L-CH<sub>2</sub>CH=CH<sub>2</sub>. Complexation of the pyridine region on Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-L-CH<sub>2</sub>CH=CH<sub>2</sub> with [CpRu(CH<sub>3</sub>CN)<sub>3</sub>]PF<sub>6</sub> (ca. 2.5 mol-equiv. for the pyridine moiety, 30 °C, 2 h) followed by magnetic separation afforded  $Fe_3O_4(a)SiO_2-L-CpRu(\eta^3-C_3H_5)$  (4). ICP-OES analysis of the solution phase before and after immobilization shows a diminution of Ru that corresponds to the amount of complex loaded onto the solid support (78-84 µmol/g).<sup>[14]</sup> An SEM image of uniform particles (diameter of ca.  $5 \,\mu\text{m}$ ) is given in Figure 1.



Figure 1. SEM image of Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-L-CpRu( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>) catalyst 4.

Table 1 lists the representative results of deprotection of alcohol 3 catalyzed by 4. AOC-protected 2-phenylethan-1ol (2a) was converted to 2-phenylethan-1-ol (3a) in >99%<sup>[16]</sup> within 1 h {Entry 1; [**2a**] = 100 mм, substrate/catalyst ratio (S/C) = 100, CH<sub>3</sub>OH, shaken at 30 °C}. Under these conditions the catalyst particles are well dispersed. Nevertheless, the catalyst can be quickly collected by application of a magnetic field. There was only a slight decrease in reactivity after 10 rounds of catalyst recycling (Entry 4).<sup>[14]</sup> During each cycle Ru leaching was below 0.2%. The reaction proceeds even with an S/C ratio of 10000 (Entry 6). Ethanol and 2-propanol were the solvents of choice (Entries 7, 8), but the reactivity was significantly reduced in tert-butyl alcohol (Entry 9). Water, DMF, THF, dichloromethane, and acetonitrile are usable as a co-solvent of methanol (Entries 10-14). Phenol as well as primary, secondary, and tertiary alcohols are efficiently deprotected from the AOC-protected forms 2a-d (Entries 1 and 15-17). Bn, Bz, MOM, and TBDPS groups in compounds 2e-h remain intact under all heterogeneous reaction conditions (Entries 18-21). Allyl carboxylate 2i as well as the less reactive allyl ether 2i are also suitable substrates (Entries 22, 23).

Table 1. Catalytic cleavage of allyl esters and ethers by using  $Fe_3O_4$ -@SiO\_2-L-CpRu( $\eta^3$ -C\_3H\_5) catalyst 4.<sup>[a]</sup>

Entry	Substrate	Solvent	Conversion (%) <sup>[b]</sup>
1	2a	CH <sub>3</sub> OH	>99
2	2a	CH <sub>3</sub> OH	>99 <sup>[c]</sup>
3	2a	CH <sub>3</sub> OH	>99 <sup>[d]</sup>
4	2a	CH <sub>3</sub> OH	>99 <sup>[e]</sup>
5	2a	CH <sub>3</sub> OH	>99 <sup>[f]</sup>
6	2a	CH <sub>3</sub> OH	>99 <sup>[g]</sup>
7	2a	C <sub>2</sub> H <sub>5</sub> OH	>99 <sup>[h]</sup>
8	2a	<i>i</i> -C <sub>3</sub> H <sub>7</sub> OH	>99 <sup>[i]</sup>
9	2a	t-C <sub>4</sub> H <sub>9</sub> OH	>99 <sup>[j]</sup>
10	2a	CH <sub>3</sub> OH/H <sub>2</sub> O (1:1)	>99
11	2a	CH <sub>3</sub> OH/DMF (1:1)	>99
12	2a	$CH_3OH/THF$ (1:1)	>99
13	2a	$CH_3OH/CH_2Cl_2$ (1:1)	>99
14	2a	CH <sub>3</sub> OH/CH <sub>3</sub> CN (1:1)	>99
15	2b	CH <sub>3</sub> OH	99
16	2c	CH <sub>3</sub> OH	>99 <sup>[k]</sup>
17	2d	CH <sub>3</sub> OH	>99
18	2e	CH <sub>3</sub> OH	>99
19	2f	CH <sub>3</sub> OH	>99
20	2g	CH <sub>3</sub> OH	>99
21	2h	CH <sub>3</sub> OH	>99
22	2i	CH <sub>3</sub> OH	>99
23	2j	CH <sub>3</sub> OH	98 <sup>[1]</sup>

[a] All reactions were carried out under the following conditions, unless otherwise specified: [2] = 100 mM; 50–90 µmol scale; 10 mg of 4 (0.52–0.85 µmol depending on the catalyst loading on Fe<sub>3</sub>O<sub>4</sub>-@SiO<sub>2</sub>); S/C = 100; 30 °C; 1 h. [b] Determined by <sup>1</sup>H NMR spectroscopy.<sup>[14,16]</sup> [c] Isolated yield in a reaction of 177 mg of 2a.<sup>[14]</sup> [d] Use of 4 after 4 recycles. [e] Use of 4 after 9 recycles. Reaction time: 2 h. [f] [2a] = 500 mM; S/C = 1000; 11 h. [g] [2a] = 500 mM; S/C = 10000; 50 °C; 15 d. [h] 2 h. [i] 6 h. [j] 3 d. [k] 2 h. [i] 8 h.

A dipeptide Fmoc-Phe-Asp(allyl)-OtBu (6) was quantitatively converted into the corresponding Fmoc-Phe-Asp-OtBu (7) without affecting the *t*Bu ester and Fmoc groups under standard reaction conditions. The existence of a po-



lar peptide linkage exerts little influence on the reactivity. A triuridine 3–5 U derivative **8**, which is fully protected by allyl groups at C(2') and phosphoric acid, was successfully deprotected and isolated as the diethylammonium salt **10**. The acid form of 3–5 U (**9**) is unstable. Therefore, deprotection at 30 °C for <1 h followed by diethylamine treatment is required. High loading of catalyst (8 mol-% per allyl group) can realize quantitative deprotection by using [CpRu( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>)(2-quinolinecarboxylato)]PF<sub>6</sub> in a homo-



Figure 2. <sup>1</sup>H and <sup>31</sup>P NMR spectra of 3–5 U (9) and the diethylammonium salt 10 obtained by the reactions using homogeneous [CpRu( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>)(2-quinolinecarboxylato)]PF<sub>6</sub> (1) complex (a) and heterogeneous Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-L-CpRu( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>) (4) (b and c) at 30 °C for 40 min in CD<sub>3</sub>OD. (a) Reaction mixture; blue: 1, green: CD<sub>3</sub>OCH<sub>2</sub>CH=CH<sub>2</sub>. (b) Reaction mixture after magnetic separation of 4. (c) Deallylation followed by (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>NH addition and magnetic separation of 4. The supernatant was concentrated and dissolved in D<sub>2</sub>O at 25 °C.



geneous state. However, isolation yield of the final product as the ammonium salt is generally less than 95%. Use of Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>-L-CpRu( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>) complex **4** solved this problem because of the easy separation of the product from the catalyst and an excess amount of diethylamine by simply applying an external magnetic field. <sup>1</sup>H NMR spectra of **9** obtained by homogeneous and heterogeneous catalysis and of the final ammonium salt **10** are shown in Figure 2.

#### Conclusions

We have developed a heterogeneous deallylation catalyst by immobilization on microsized spherical  $SiO_2$  particles containing  $Fe_3O_4$ . The resultant catalyst displays high saturation magnetization, weak coercive forces and high dispersibility. The catalyst can be removed from the reaction mixture by simple magnetic separation and is recyclable. Furthermore, the catalyst can operate in alcoholic solvents in the absence of any extra additives. The heterogeneous version of the catalyst should further enhance the utility of the CpRu-catalyzed deallylation in protecting group chemistry and in organic synthesis.

#### **Experimental Section**

General Procedure for the Catalytic Removal of the Allyl Group in 2 by Using 4: Fe<sub>3</sub>O<sub>4</sub>@SiO<sub>2</sub>–L–CpRu( $\eta^3$ -C<sub>3</sub>H<sub>5</sub>) particles (4; 10.6 mg, 78.5 µmol/g, 0.832 µmol) were placed in a dry and argon-filled 5mL tube equipped with a Young's tap. Into this vessel a 100 mM solution of allyl 2-phenylethyl carbonate (2a) in methanol (0.832 mL, 0.0832 mmol), degassed three times by freeze-thaw cycles, was added through an inlet capped by a septum rubber under an argon stream. After the rubber was replaced with a Young's tap, the suspension was shaken at 30 °C for 1 h. The particles were magnetically separated, and the liquid phase was concentrated under reduced pressure (100 Torr) to give a crude product. The conversion and purity were determined to be >99% by <sup>1</sup>H NMR analysis.<sup>[14,16]</sup>

**Supporting Information** (see footnote on the first page of this article): The details of catalyst preparation and general procedures for the deallylation.

#### Acknowledgments

This work was supported by the Ministry of Education, Culture, Sports, Science and Technology, Japan through a Grant-in-Aid for Scientific Research on Priority Areas (No. 19028024, "Chemistry of Concerto Catalysis").

a) Applied Homogeneous Catalysis with Organometallic Compounds (Eds: B. Cornils, W. A. Herrmann), Wiley-VCH, Weinheim, 2002, vol. 1–3; b) P. W. N. M. van Leeuwen, in Homogeneous Catalysis, Understanding the Art, Kluwer Academic Publishers, Dordrecht, 2004; c) M. Kitamura, in Kagaku Binran Kisokagakuhen, 5th ed. (Ed.: Y. Iwasawa), Maruzen, Tokyo, 2004.

<sup>[2]</sup> Definition of the *E* factor: R. A. Sheldon, *Chem. Ind.* 1992, 903–906.

# SHORT COMMUNICATION

- [3] a) P. T. Anastas, M. M. Kirchhoff, Acc. Chem. Res. 2002, 35, 686–694; b) Handbook of Green Chemistry & Technology (Eds: J. Clark, D. Macquarrie), Blackwell Publishing, Richmond, 2002; c) Green Chemistry (Eds: M. Misono, S. Murahashi), Ko-dansha Scientific, Tokyo, 2001.
- [4] a) S. Tanaka, H. Saburi, M. Kitamura, Adv. Synth. Catal. 2006, 348, 375–378; b) H. Saburi, S. Tanaka, M. Kitamura, Angew. Chem. Int. Ed. 2005, 44, 1730–1732; c) S. Tanaka, H. Saburi, Y. Ishibashi, M. Kitamura, Org. Lett. 2004, 6, 1873–1875.
- [5] a) F. Guibé, *Tetrahedron* 1997, *53*, 13509–13556; b) F. Guibé, *Tetrahedron* 1998, *54*, 2967–3042.
- [6] a) Y. Hayakawa, H. Kato, M. Uchiyama, H. Kajino, R. Noyori, J. Org. Chem. 1986, 51, 2400–2402; b) X. Zhang, B. L. Gaffney, R. A. Jones, Nucleic Acids Res. 1997, 25, 3980–3983.
- [7] a) Multiphase Catalysis, Green Solvents and Immobilization in Adv. Synth. Catal. 2006, 348, 1317–1771 (special issue); liquid/ liquid two-phase system: b) Handbook of Fluorous Chemistry (Eds: J. A. Gladysz, D. P. Curran I. T. Horváth), Wiley-VCH, Weinheim, 2004; c) Fluorous Chemistry (Ed.: J. Otera), CMC Publishing, Tokyo, 2005; d) Ionic Liquids in Synthesis (Eds: P. Wasserscheid, T. Welton), Wiley-VCH, Weinheim, 2007; e) Immobilized Catalysts: Solid Phases, Immobilization and Applications (Ed.: A. Kirsching), Springer-Verlag, Berlin, 2004, vol. 242.
- [8] For recent reports on magnetically separable catalysts, see: a) T.-J. Yoon, J. I. Kim, J.-K. Lee, *Inorg. Chim. Acta* 2003, 345, 228–234; b) A. Hu, G. T. Yee, W. Lin, *J. Am. Chem. Soc.* 2005, 127, 12486–12487; c) L. Bromberg, T. A. Hatton, *Ind. Eng.*

*Chem. Res.* **2005**, *44*, 7991–7998; d) Y. Zheng, C. Duanmu, Y. Gao, *Org. Lett.* **2006**, *8*, 3215–3217; e) R. Abu-Reziq, H. Alper, D. Wang, M. L. Post, *J. Am. Chem. Soc.* **2006**, *128*, 5279–5282; f) D. Lee, J. Lee, H. Lee, S. Jin, T. Hyeon, B. M. Kim, *Adv. Synth. Catal.* **2006**, *348*, 41–46; g) N. T. S. Phan, C. S. Gill, J. V. Nguyen, Z. J. Zhang, C. W. Jones, *Angew. Chem. Int. Ed.* **2006**, *45*, 2209–2212; h) M. Kawamura, K. Sato, *Chem. Commun.* **2007**, 3404–3405; i) C. Ó. Dálaigh, S. A. Corr, Y. Gun'ko, S. J. Connon, *Angew. Chem. Int. Ed.* **2007**, *46*, 4329–4332.

- [9] C. Merckle, J. Blümel, Chem. Mater. 2001, 13, 3617-3623.
- [10] Review: F. J. Himpsel, J. E. Ortega, G. J. Mankey, R. F. Willis, *Adv. Phys.* **1998**, 47, 511–597; see also: C. Baker, S. I. Shah, S. K. Hasanain, *J. Magn. Magn. Mater.* **2004**, 208, 412–418.
- [11] For difficulties in the dispersion of magnetic nanoparticles, see:
  a) H. Kamiya, M. Mitsui, H. Takano, S. Miyazawa, J. Am. Ceram. Soc. 2000, 83, 287–293; b) H. Kamiya, Chem. Eng. 2006, 51, 115–118.
- [12] Y. Nishiya, M. Kishimoto, Jpn. Patent 102473, 2003.
- [13] X.-B. Wang, J. E. Dacres, X. Yang, K. M. Broadus, L. Lis, L.-S. Wang, S. R. Kass, J. Am. Chem. Soc. 2003, 125, 296–304.
- [14] For details, see Supporting Information.
- [15] B. P. Pichon, M. W. C. Man, C. Bied, J. J. E. Moreau, J. Organomet. Chem. 2006, 691, 1126–1130.
- [16] The crude products consist of only the desired compound, and the conversion corresponds approximately to the yield.

Received: November 25, 2008

Published Online: January 12, 2009