A recyclable catalyst for asymmetric transfer hydrogenation with a formic acid–triethylamine mixture in ionic liquid†

Ikuo Kawasaki,[a] Kazuya Tsunoda,[a] Tomoko Tsuji,[a] Tomoko Yamaguchi,[a] Hiroki Shibuta,[a] Nozomi Uchida,[a] Masayuki Yamashita[ab] and Shunsaku Ohta*[ab]

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A novel task-specific ionic ligand with an imidazolium salt moiety was synthesized, and its catalytic ability and recyclability for asymmetric transfer hydrogenation of acetophenone derivatives with a formic acid–triethylamine azeotropic mixture in an ionic liquid [bmim][PF_6] was examined.

Recently, catalytic asymmetric transfer hydrogenation has become a useful tool to obtain optically active secondary alcohols from carbonyl compounds and is an interesting alternative to hydrogenation with molecular hydrogen. The hydrogen donors most commonly used for ketones are 2-propanol (generally used with a base) and formic acid (generally used as an azeotrope with triethylamine), and the latter is accompanied by evolution of CO_2 gas, rendering the reaction irreversible, and has attracted the interest of chemists.[1]

Imidazolium ionic liquids (ILs) such as [bmim][PF_6] **1** and [bmim][BF_4] **2** (Fig. 1) have been recognized as a new class of reaction solvent,[2] and we have been interested in ILs because we have investigated the chemistry of imidazolium and 1,2,4-triazolium compounds.[3] The most attractive properties of ILs, for us, are that they stabilize several transition metal catalysts and provide an excellent reaction medium for recycling of the catalyst,[4,5] and that the reaction system also can be applied to asymmetric hydrogenation of unsaturated bonds.[6] Schotten described microwave-assisted reduction in ILs under transfer hydrogenation conditions with an achiral palladium catalyst and formate salts.[7] Very recently, Dyson reported the asymmetric transfer hydrogenation of acetophenone with 2-propanol in IL, by use of a modified arene-Ru(II) complex with Noyori's chiral *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine (TsDPEN),[8] with catalyst recycling.[9] This catalyst afforded relatively good results with 2-propanol but somewhat poor results using formic acid. In this communication we would like to present the preparation of a novel task-specific chiral ionic ligand, with an attached imidazolium salt, and its use in the recyclable catalytic asymmetric transfer hydrogenation of ketones by an HCO_2H–Et_3N azeotrope in ILs.

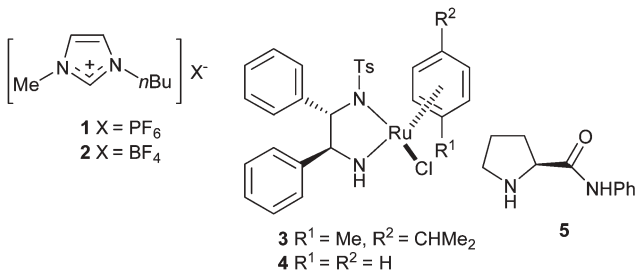


Fig. 1

Two types of chiral catalysts were selected for the recyclable asymmetric transfer hydrogenation of ketones with the azeotrope in ILs. One, the TsDPEN-coordinated Ru(II) complexes **3** and **4**, known as some of the most effective catalysts developed by Noyori, Ikariya and co-workers.[8,10] The other, a Ru(II) complex of the amino amide **5**, derived from proline in the presence of $[RuCl_2(cymene)]_2$ (**5**-*Ru*).[11] Results of the asymmetric transfer hydrogenation of **6** in the presence of **3**, **4** or **5**-*Ru* with the azeotrope in ILs **1** or **2** are summarized in Table 1. After several examinations, we found that the best combination was the chiral benzene-Ru complex **4** and the IL [bmim][PF_6] (entry 5). The present reaction system with **4** was also effective for asymmetric reduction of acetophenone derivatives **6b–e** (entries 7–10).

Then, we planned the synthesis of a new task-specific ionic chiral ligand based on attaching an imidazolium salt unit to TsDPEN, in order to prepare the corresponding benzene-Ru complex (*cf.* **4**) and to investigate its reactivity in the recyclable asymmetric transfer hydrogenation of ketones, using the azeotrope as a hydrogen source. The route to the designed ionic ligand **12** is shown in Scheme 2. Introduction of the imidazolium moiety to the chloroalkoxy TsDPEN derivative **10**, which was prepared starting from **8**, was achieved to give the quaternary salt **11**. Removal of

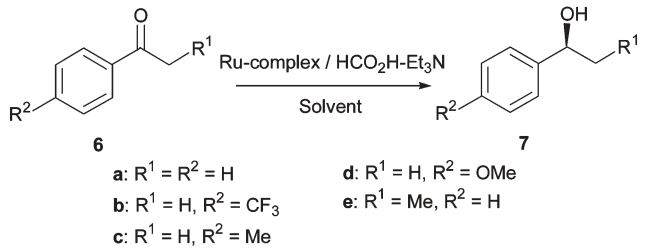
Table 1 Asymmetric transfer hydrogenation of ketones in ILs (Scheme 1)

					Product	
Entry	Ketone	Catalyst	Solvent	Time (h)	Conversion (%)[a]	ee (%)[a]
1	**6a**	**4**	none	5	60	96
2	**6a**	**4**	**2**	5	15	94
3	**6a**	**3**	**1**	5	10	97
4	**6a**	**4**	**1**	5	53	95
5	**6a**	**4**	**1**	24	96	93
6	**6a**	**5**-*Ru*[b]	**1**	24	75	72
7	**6b**	**4**	**1**	24	>99	88
8	**6c**	**4**	**1**	24	91	91
9	**6d**	**4**	**1**	44	78[c]	94
10	**6e**	**4**	**1**	24	85	89

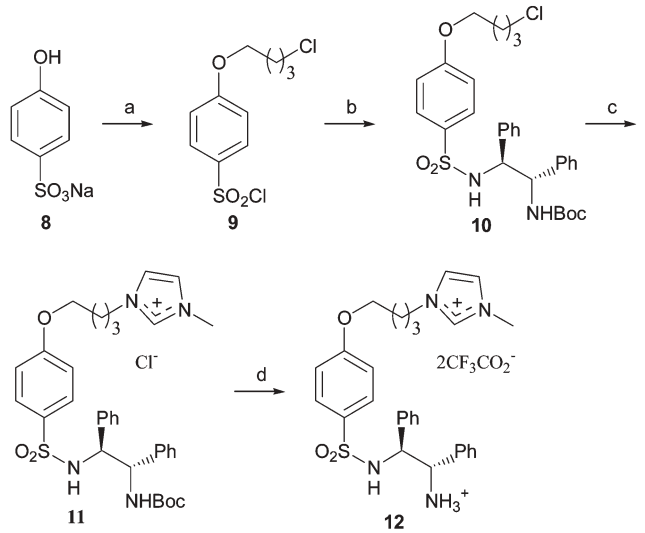
[a] Determined by capillary GLC analysis using a chiral Cyclodex-B column. [b] A mixture of **5** and $[RuCl_2(cymene)]_2$ was used. [c] Isolated yield after chromatographic separation (13% recovery of **6d**).

† Electronic supplementary information (ESI) available: experimental section. See http://www.rsc.org/suppdata/cc/b5/b500320b/

*sohta@mb.kyoto-phu.ac.jp



Scheme 1



Scheme 2 *Regents and conditions*: (a) (i) NaH, $Br(CH_2)_4Cl$, DMF, 100 °C (ii) $SOCl_2$, DMF, 90 °C, 54% (b) (i) (1*S*,2*S*)-1,2-diphenylethylenediamine, Et_3N, DCM, rt (ii) $(Boc)_2O$, Et_3N, DCM, rt, 70% (c) 1-methylimidazole, 80 °C, 95% (d) TFA, 0 °C, 97%.

the Boc group of **11** by treatment with TFA provided a novel ionic ligand **12** in 35% overall yield from **8**.

The recyclability of the asymmetric transfer hydrogenation of acetophenone **6a** was tested, both with **4** and with **12** in the presence of $[RuCl_2(benzene)]_2$ (**12**-*Ru*), in the IL **1** by using the azeotrope at room temperature in 24 hour cycles, and the results are listed in Table 2. We found that these catalysts, **4** and **12**-*Ru*, were fully soluble in the IL **1** under these reaction conditions and they were easily recovered after extraction of the produced 1-phenylethanol by addition of an organic solvent, and the residual IL phase was recycled and reused for the next reaction.‡

Table 2 Recycling of **4** and **12**-*Ru* in the asymmetric transfer hydrogenation of **6a** with the azeotrope in **1**[a]

	Catalyst **4**		Ligand **12**-*Ru*[b]	
Cycle	Conversion (%)[c]	ee (%)[c]	Conversion (%)[c]	ee (%)[c]
1	96	93	98	92
2	99	92	>99	93
3	95	92	99	93
4	88	92	92	93
5	63	93	75	90

[a] Reaction at rt for 24 h and S/C = 100. [b] A mixture of **12** and $[RuCl_2(benzene)]_2$ was used. [c] Determined by capillary GLC analysis using a chiral Cyclodex-B column.

The catalyst **4** showed good conversion and ee up to the third cycle, but its activity gradually decreased from the fourth cycle. The new ionic catalyst **12**-*Ru* showed somewhat better results than the catalyst **4**. This is probably due to immobilization of the imidazolium moiety in the IL phase. It is noteworthy that the enantioselectivity of **12**-*Ru* showed good values, which are comparable with those of **4**.[12]

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[a]*Department of Functional Molecular Chemistry, Kyoto Pharmaceutical University, Misasagi Yamashinaku, Kyoto 607-8414, Japan. E-mail: sohta@mb.kyoto-phu.ac.jp*
[b]*21st Century COE program*

Notes and references

‡ Typical recycling procedure: acetophenone (120 mg, 1.0 mmol) was added to a solution of the ionic ligand **12** (7.8 mg, 0.012 mmol) and $[RuCl_2(benzene)]_2$ (2.5 mg, 0.005 mmol) in the IL **1** (1.0 mL) with stirring under N_2, followed by addition of the formic acid–triethylamine azeotropic mixture[13] (bp 108 °C/29 mmHg, 0.5 mL). The reaction mixture was stirred at rt for 24 h. Then, *n*-hexane (3 × 5 ml) was added to the reaction mixture and the products were extracted by decantation of the upper layer, and the residual IL phase was dried *in vacuo* for 30 min. Acetophenone (120 mg, 1.0 mmol) and formic acid–triethylamine azeotropic mixture (0.5 mL) were added to the remaining IL solution, and the second cycle of the reaction was started.

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