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Full Research Paper

Asymmetric Glyoxylate-Ene Reactions Catalyzed by Chiral Pd(II) Complexes in the Ionic Liquid [bmim][PF_6]

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Abstract: The room temperature ionic liquid [bmim][PF_6] was employed as the reaction medium in the asymmetric glyoxylate-ene reaction of α-methyl styrene (**4a**) with ethyl glyoxylate using chiral palladium(II) complexes as the catalysts. [Pd(*S*-BINAP)(3,5-CF_3-$PhCN)_2$]($SbF_6)_2$ (**1b**) showed the highest catalytic activity. Under the reaction conditions of 40 ^oC, 0.5 h, and **1b**/**4a** molar ratio of 0.05, ethyl α-hydroxy-4-phenyl-4-pentenoate was obtained in excellent chemical yield (94 %) with high enantioselectivity (70 %). Other α-hydroxy esters can also be obtained in high chemical yields and enantioselectities through the glyoxylate-ene reactions of alkenes with glyoxylates catalyzed by **1b** in [bmim][PF_6]. Moreover, the ionic liquid [bmim][PF_6] which contained the palladium(II) complex could be recycled and reused several times without significant loss of the catalytic activity.

Keywords: Ionic liquid, glyoxylate-ene reaction, palladium, chiral, 1-*n*-butyl-3-methyl-imidazolium hexafluorophosphate

1. Introduction

Organic reactions catalyzed by chiral transition metal complexes are important tools in modern asymmetric synthesis. In most cases, chiral catalysts used in asymmetric catalytic reactions are expensive, so recovery and reuse of catalysts has attracted great interest to reduce the environmental and economic costs. Immobilization of chiral catalysts with solid supports or polymers is a

representative method to recover and reuse catalysts [1-3]. However, sometimes the catalytic activities of supported chiral catalysts will be lower than that under homogenous conditions and sometimes the enantioselectivity of products will decrease with each reuse of the catalysts. Room temperature ionic liquids are composed entirely of ions and have attracted extensive interest as excellent alternatives to conventional organic solvents due to their unique advantages of high thermal stability, non-flammability, low toxicity, negligible vapour pressure, high loading capacity, tunable polarity and interesting intrinsic physicochemical characteristics [4-11]. In addition, they possess the capacity to dissolve various organic, inorganic, and organometallic compounds. In ionic liquids, chiral transition metal complexes can be immobilized and organic products can be extracted with hexanes, toluene or ether. Thus, a new methodology of chiral catalysts separation and recycling is achieved. In fact, ionic liquids recently have been investigated as the reaction media for a variety of asymmetric catalytic reactions such as Diels-Alder, allylic amination, hydrogenation, Michael, fluorination, epoxidation and Aldol reactions [12-18]. In these reactions, the chiral catalysts used are recyclable at least several times.

The asymmetric glyoxylate-ene reaction, which affords optically active α-hydroxy esters of synthetic and biological importance, has been widely researched in recent years [19-20]. The reaction is generally catalyzed by chiral Lewis acidic catalysts, which are useful catalysts for carbon-carbon bond construction. Up to now, a number of chiral Lewis acidic catalysts have been used in the homogenous asymmetric glyoxylate-ene reaction, such as Ti complexes, Cu complexes, Ln complexes, Pt complexes, Pd complexes and Cr complexes, etc [21-35]. Previously, bis(oxazoline)-modified CuH zeoliteY and Cu(II) complex of insoluble polystyrene-bond bis(oxazoline) have been used to generate recyclable catalysts in the asymmetric glyoxylate-ene reaction [36,37]. However, to our knowledge the use of a palladium(II) complex-catalyzed glyoxylate-ene reaction in ionic liquids to recover and reuse of chiral catalysts has not been reported so far.

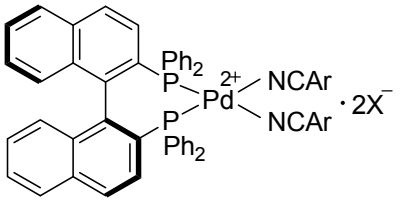
As a part of our interest in performing glyoxylate-ene and other organic reactions in ionic liquids [38,39], we report herein a mild and effective procedure for the asymmetric glyoxylate-ene reaction catalyzed by chiral palladium(II) catalysts using the ionic liquid [bmim][PF_6] as the reaction medium. Furthermore, we demonstrate that the catalytic system can be recycled and reused for several runs without any significant loss of catalytic activity.

2. Results and Discussion

2.1. Effect of solvents and palladium(II) complexes

Palladium(II) complexes (Scheme 1) derived from (*S*)-BINAP, (*S*)-MeO-Biphep [40], and (*S*)-C3-TunePhos [41] were used as the chiral catalysts in the glyoxylate-ene reaction of α-methyl styrene (**4a**) with ethyl glyoxylate (**5a**). The reaction (0.5 mmol of **4a**, 1.5 mmol of **5a**, 0.025 mmol of catalyst) was performed in different organic solvents and two ionic liquids (Scheme 2), and the results were listed in Table 1. The reaction of **4a** with **5a** using (S)-BINAP-coordinated palladium complexes ([Pd(*S*-BINAP)$(PhCN)_2$]$(BF_4)_2$ **1a**, [Pd(*S*-BINAP)$(PhCN)_2$]$(SbF_6)_2$ **1b**, [Pd(*S*-BINAP)(3,5-CF_3-$PhCN)_2$]$(BF_4)_2$ **1c** and [Pd(*S*-BINAP)(3,5-CF_3-$PhCN)_2$]$(SbF_6))_2$ **1d**) as the catalysts in 1,2-dichloroethane proceeded at 40 ^oC to give ethyl α-hydroxy-4-phenyl-4-pentenoate ((*R*)-**6aa**) in excellent chemical yields (entries1-4).

Scheme 1. Structures of palladium(II) complexes.

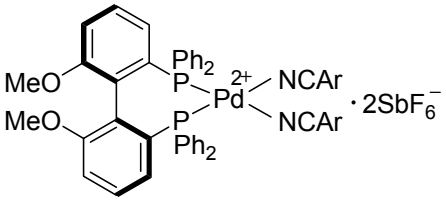


1a: Ar = C_6H_5, X = BF_4^-; [Pd(*S*-BINAP)(PhCN)$_2$](BF_4)$_2$

1b: Ar = C_6H_5, X = SbF_6^-; [Pd(*S*-BINAP)(PhCN)$_2$](SbF_6)$_2$

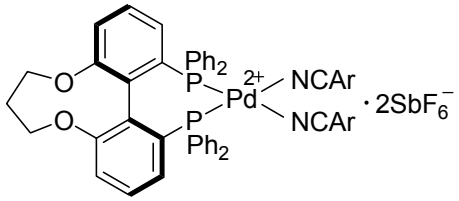
1c: Ar = 3,5-CF_3-C_6H_5, X = BF_4^-; [Pd(*S*-BINAP)(3,5-CF_3-PhCN)$_2$](BF_4)$_2$

1d: Ar = 3,5-CF_3-C_6H_5, X = SbF_6^-; [Pd(*S*-BINAP)(3,5-CF_3-PhCN)$_2$](SbF_6)$_2$



2: Ar = 3,5-CF_3-C_6H_5

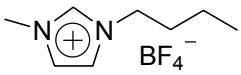
[Pd(*S*-MeO-Biphep)(3,5-CF_3-PhCN)$_2$](SbF_6)$_2$



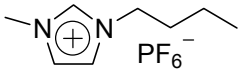
3: Ar = 3,5-CF_3-C_6H_5

[Pd(*S*-C3-TunePhos)(3,5-CF_3-PhCN)$_2$](SbF_6)$_2$

Scheme 2. Structures of ionic liquids.

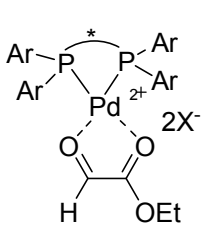


[bmim][BF_4]



[bmim][PF_6]

However, **1b** and **1d**, which contained SbF_6^-, were found to give higher enantioselectivity (59 and 63 % ee, respectively) than **1a** and **1c** which contained BF_4^- (35 and 28 % ee). The good catalytic activities of **1b** and **1d** were partially due to the higher group electronegativity of SbF_6^- compared with that of BF_4^-. In addition, the less coordinating ability of SbF_6^- towards palladium(II) was beneficial to the stability of the bidentate intermediate **7** which was formed through the complexation of the carbonyl groups of **5a** with palladium(II) complex and could react with **4a** to form (*R*)-**6aa**. When the anion was BF_4^-, intermediate **7** probably had more chance to convert to intermediate **8,** which resulted in the observed decrease in product enantioselectivity [26,42].



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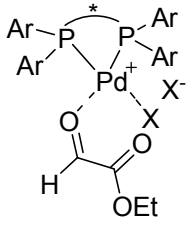

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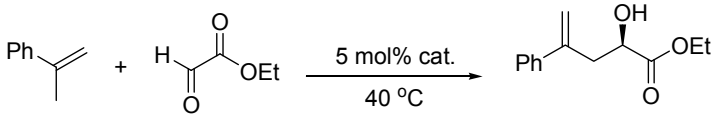
Table 1. Effect of reaction media and palladium(II) complexes on glyoxylate-ene reaction [a].



4a **5a** (*R*)-**6aa**

Entry	Solvent	Catalyst	Time (h)	Yield (%)[b]	ee (%)[c]
1	1,2-dichloroethane	**1a**	2	94	35
2	1,2-dichloroethane	**1b**	2	91	59
3	1,2-dichloroethane	**1c**	2	93	28
4	1,2-dichloroethane	**1d**	2	93	63
5	1,2-dichloroethane	**2**	2	95	61
6	1,2-dichloroethane	**3**	2	94	56
7	chlorobenzene	**1d**	2	92	65
8	1,2-dichloroethane/toluene (1/1)	**1d**	2	92	66
9	toluene	**1d**	2	93	70
10	[bmim][BF_4]	**1d**	2	75	45
11	[bmim][PF_6]	**1d**	0.5	94	70
12	[bmim][PF_6]	**1a**	3.5	92	60
13	[bmim][PF_6]	**1b**	5.5	94	64
14	[bmim][PF_6]	**1c**	1.5	92	65
15	[bmim][PF_6]	**2**	1.5	93	68
16	[bmim][PF_6]	**3**	1.5	93	66

[a] Reaction conditions: **4a** (0.5 mmol), **5a** (1.5 mmol), catalyst (0.025 mmol), 5 ml organic solvent or 1.5 g ionic liquid, 40 °C.

[b] Isolated yield.

[c] Determined by HPLC using Chialpak AD-H, 5 % *i*-PrOH in hexane (v/v).

The coordinated nitrile ligands of palladium(II) dication also showed some effect on enantioselectivity of the products, but the effect was slight. Considering that **1d** showed the highest catalytic activity in 1,2-dichloroethane, we synthesized the similar catalysts [Pd(*S*-MeO-Biphep)(3,5-CF_3-PhCN)$_2$](SbF_6)$_2$ (**2**) and [Pd(*S*-C3-TunePhos)(3,5-CF_3-PhCN)$_2$](SbF_6)$_2$ (**3**), in which chiral diphosphine ligands (*S*)-MeO-Biphep and (*S*)-C3-TunePhos replaced the (*S*)-BINAP in **1d**. The results were not satisfying when catalysts **2** and **3** were used in the reaction of **4a** with **5a**, and ee values of the product were 61 and 56 %, respectively (entries 5, 6).

In the presence of **1d**, the reaction of **4a** with **5a** in chlorobenzene and 1,2-dichloroethane/toluene (v/v, 1/1) proceeded smoothly and similar enantioselectivity was obtained (ca. 65 % ee, entries 7, 8). Toluene was found as an excellent organic solvent for the reaction of **4a** with **5a**, and the highest ee value (70 %) was achieved (entry 9). However, the recycle and reuse of **1d** was difficult when toluene was used as the reaction solvent. Thus, the ionic liquids 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) and 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ([bmim][PF_6]), which have often been used in transition metal-catalyzed reactions for recycling and reusing catalysts, were used as the reaction media in this reaction. The ionic liquid [bmim][PF_6] was shown to be a good

reaction medium which afforded the product in 94 % chemical yield and 70 % ee, whereas [bmim][BF_4] afforded the product 75 % chemical yield and 45 % ee (entries 10, 11). The catalytic activities of **1a**, **1b**, **1c**, **2** and **3** in [bmim][PF_6] were also investigated, and ee values were found to be improved compared with those obtained in 1,2-dichloroethane (entries 12-16). Especially for **1a** and **1c**, ee values increased from 35 to 60 % and 28 to 65 %, respectively. A longer reaction time was needed for complete conversion of **4a** using **1b** as the catalyst due to its low solubility in [bmim][PF_6]. These experimental results suggested that ionic liquid [bmim][PF_6] could act as an appropriate medium in the palladium(II) complexes-catalyzed glyoxylate-ene reaction of **4a** with **5a** to produce (*R*)-**6aa**.

2.2. Effect of reaction temperature

Table 2 shows the effect of reaction temperature on the glyoxylate-ene reaction of **4a** with **5a**. At 0 ^oC, the conversion of **4a** was 62 % after 24 h. The chemical yield and ee value of the product were 58 and 70 %, respectively.

Table 2. Effect of reaction temperature on glyoxylate-ene reaction of **4a** with **5a** [a].

Entry	Temperature (^oC)	Time (h)	Conversion (%)	Yield (%)[b]	ee (%)[c]
1	0	24	62	58	70
2	20	6	100	93	70
3	40	0.5	100	94	70
4	50	0.3	100	87	70

[a] Reaction conditions: **4a** (0.5 mmol), **5a** (1.5 mmol), **1d** (0.025 mmol), 1.5 g [bmim][PF_6].

[b] Isolated yield.

[c] Determined by HPLC using Chialpak AD-H, 5 % *i*-PrOH in hexane (v/v).

Obviously, when the reaction temperature increased from 0 to 50 ^oC, the reaction rate increased. The optimum reaction temperature was 40 ^oC, at which 94 % chemical yield and 70 % ee of the product were obtained only after 0.5 h. At a reaction temperature of 50 ^oC, the reaction was complete in 0.3 h, but the chemical yield decreased to 87 % because of more side reactions, such as acid-catalyzed dimerization of **4a**, *etc*. It was noteworthy that the ee value of the product was always 70 % regardless of any variation of the reaction temperature. These results indicated that the enantioselectivity of (*R*)-**6aa** in the reaction of **4a** with **5a** catalyzed by **1d** using [bmim][PF_6] as the reaction medium was independent of the reaction temperature.

*2.3. Effect of the molar ratio of **1b**/**4a***

The effect of the molar ratio of **1b**/**4a** on the glyoxylate-ene reaction of **4a** with **5a** was examined using [bmim]PF_6 as the reaction medium at 40 ^oC, and the results are listed in Table 3.

Table 3. Effect of the molar ratio of **1b**/**4a** on glyoxylate-ene reaction of **4a** with **5a** [a].

Entry	**1b**/**4a** (mol/mol)	Time (h)	Conversion (%)	Yield (%)[b]	ee (%)[c]
1	0.01	6	100	89	69
2	0.02	2.5	100	92	70
3	0.05	0.5	100	94	70
4	0.07	0.5	100	93	70

[a] Reaction conditions: **4a** (0.5 mmol), **5a** (1.5 mmol), 1.5 g [bmim][PF_6], 40 ^oC.

[b] Isolated yield.

[c] Determined by HPLC using Chialpak AD-H, 5 % *i*-PrOH in hexane (v/v)

With a molar ratio of 0.01 between **1b** and **4a**, the latter was completely converted in 6 h, and the chemical yield and ee value were 89 and 69 %, respectively. Increasing the molar ratio of **1b**/**4a** from 0.01 to 0.05, the reaction time was shortened to 0.5 h, and the chemical yield slightly increased to 94 %. When the molar ratio of **1b**/**4a** further increased to 0.07, the reaction result did not obtain significant improvement. Thus, the molar ratio of **1b**/**4a** should not be more than 0.05 from practical opinion.

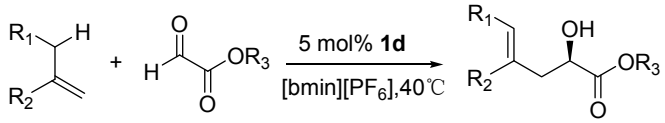
2.4. Glyoxylate-ene reactions between different substrates

Glyoxylate-ene reactions between alkenes and glyoxylates catalyzed by **1d** in [bmim][PF_6] were carried out at 40 ^oC and the results are summarized in Table 4. In all cases, the reactions proceeded smoothly to give the corresponding desired α-hydroxy esters in good chemical yields and enantioselectivities. The electron-withdrawing substituent group on the phenyl ring had an obvious influence on the reactivity of α-methyl styrenes. When 4-chloro-α-methyl styrene (**4b**) reacted with **5a** or methyl glyoxylate (**5b**), reaction time of 2 h was needed which was longer than that of **4a** reacted with **5a** or **5b**, though the ee values of α-hydroxy esters in these four reactions were very close (69-70%, entries 1-4). The highest ee value of α-hydroxy ester (82 %) was obtained in the glyoxylate-ene reaction of methylenecyclohexane (**4c**) with **5a**. When **5a** was replaced by **5b** in the glyoxylate-ene reaction of **4c**, the ee value of α-hydroxy ester decreased to 76 %.

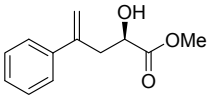
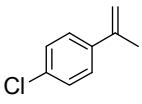
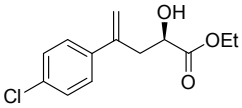
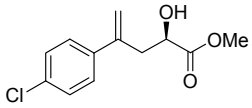
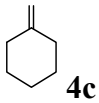
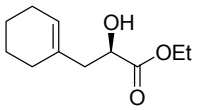
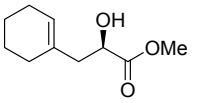
2.5. Reuse of the catalytic systems

One of the main aims of using [bmim][PF_6] as the reaction medium in the glyoxylate-ene reaction was to study the possibility of recycling and reuse of catalytic systems. In the glyoxylate-ene reaction of **4a** with **5a**，the products could be separated by extracted with ether and the ionic liquid phase containing palladium(II) complexes could be reused several times. The results were listed in Table 5. Although the chemical yield of the product slightly decreased to 90 % in run 5 in the **1d**-catalyzed glyoxylate-ene reaction of **4a** with **5a**, the ee value was maintained at 70 %. The slight decrease of chemical yield might be due to slight leaching of **1d**. Similarly, palladium(II) complex **3** provided unchanged enantioselectivity in [bmim][PF_6] during three consecutive catalytic cycles.

Table 4. Glyoxylate-ene reactions between different substrates catalyzed by **1b** in [bmim][PF_6] [a].



4 **5** (*R*)-**6**

Entry	Alkene	Glyoxylate	Product	Time (h)	Yield(%)[b]	ee(%)[c]
1	**4a**	**5a**	(*R*)-**6aa**	0.5	94	70
2	**4a**	methyl glyoxylate **5b**	 (*R*)-**6ab**	0.5	92	69
3	 **4b**	**5a**	 (*R*)-**6ba**	2	93	70
4	**4b**	**5b**	 (*R*)-**6bb**	2	92	69
5	 **4c**	**5a**	 (*R*)-**6ca**	4	91	82[d]
6	**4c**	**5b**	 (*R*)-**6cb**	4	90	76[d]

[a] Reaction conditions: **4** (0.5 mmol), **5** (1.5 mmol), **1d** (0.025 mmol), 1.5 g [bmim][PF_6], 40 °C.

[b] Isolated yield.

[c] Determined by HPLC using Chialpak AD-H, 5% *i*-PrOH in hexane (v/v).

[d] Determined by GC using BETA DEX™ 325.

Table 5. Recycling and reuse of catalystic systems in the glyoxylate-ene reaction of **4a** with **5a** using [bmim][PF_6] as the reaction medium [a].

Entry	Catalysts	Run	Time (h)	Yield (%)[b]	ee (%)
1	**1d**	1	0.5	94	70
2	**1d**	2	0.5	94	70
3	**1d**	3	0.5	93	70
4	**1d**	4	0.5	91	70
5	**1d**	5	0.5	90	70
6	**3**	1	1.5	93	66
7	**3**	2	1.5	92	66
8	**3**	3	1.5	92	66

[a] Reaction conditions: **4a** (0.5 mmol), **5a** (1.5 mmol), catalyst (0.025 mmol),1.5 g [bmim][PF_6], 40 °C.

[b] Isolated yield.

[c] Determined by HPLC using Chialpak AD-H, 5% *i*-PrOH in hexane (v/v).

In conclusion, we have demonstrated that **1b** is an effective chiral palladium catalyst to catalyze the asymmetric glyoxylate-ene reaction in the ionic liquid [bmim][PF_6]. Under the reaction conditions of 40 °C, 0.5 h, and **1b**/**4a** molar ratio of 0.05, the glyoxylate-ene reaction of **4a** with **5a** afforded the

product in 94 % chemical yield with 70 % ee. Other α-hydroxy esters can also be obtained in high chemical yields and enantioselectivities through the glyoxylate-ene reactions of alkenes with glyoxylates catalyzed by **1b** in [bmim][PF_6]. In addition, the catalytic systems could be recycled and reused.

3. Experimental Section

3.1. General methods

All reactions were carried out under a nitrogen atmosphere by using standard Schlenk line techniques in dried glassware. Solvents were treated prior to use according to the standard methods. The ionic liquids [bmim][PF_6] and [bmim][BF_4] were synthesized according to the literature procedures [43]. Palladium(II) complexes **1a-1d**, **2** and **3** were also prepared according to the procedures described in the literature [44]. The glyoxylate-ene reaction was monitored by HPLC (Varian Prostar) equipped with a C_{18} column or GC (9790) equipped with a FFAP capillary column. The ee value was determined by HPLC (Agilent 1100) analysis on a Chialpak AD-H column with isopropanol/hexane as eluent or by GC (9790) using BETA DEX^{TM} 325 column. The products obtained were purified and identified by ^{1}H NMR spectroscopy (Varian PLUS-400) and GC-MS (Finnigan Trace GC Ultrar- Finnigan Trace DSQ).

3.2. General procedure

To a stirred solution of a palladium(II) complex (0.025 mmol) in a reaction medium (organic solvent 5 ml or [bmim][PF_6] 1.5 g) under a nitrogen atmosphere was added glyoxylate (1.5 mmol) and alkene (0.5 mmol). When the reaction was complete, the mixture was extracted with ether. After ether was evaporated *in vacuo*, the product was further purified by column chromatography and identified by GC-MS and ^{1}H-NMR. The MS and ^{1}H-NMR data of the α-hydroxy esters are in good agreement with literature data [24,25,37]. The ionic liquid phase containing palladium(II) complexes could be directly used in the next run without further treatment.

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