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REACTIVITY AND EFFICIENT RECYCLING OF A CHIRAL Pd-BINAP CATALYST FOR CATALYTIC ASYMMETRIC DIELS-ALDER REACTION IN IONIC LIQUID

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Abstract – Chiral cationic palladium-BINAP catalyst in ionic liquid showed an excellent asymmetric catalytic activity in the Diels-Alder reactions using several dienes and the catalyst was easily recycled 7 times with good chemical yield and excellent enantioselectivity (50-60%, 94-98% ee).

INTRODUCTION

Catalytic asymmetric reaction is, in practical perspective, one of the most attractive methods of obtaining a compound as a single enantiomer.[1] Recently, the recovery and reuse of catalysts has attracted growing interest to meet the need for environmentally friendly and cost-effective reaction processes.[2] Recently, ionic liquids (IL) have attracted extensive interest as excellent alternative to organic solvent, due to their favorable properties such as nonflammability, low toxicity, reusability, low cost, and high thermal stability.[3] Additionally, they provide good solubility for a wide range of organic, inorganic, and organometallic compounds.[4] However, the use of ionic liquids for catalytic asymmetric reactions has not yet been studied extensively. Furthermore, most of the reported studies have found that the efficient chemical yield of the reaction and the enantiomeric excess (ee) obtained in the usual organic solvents are difficult to reproduce in ILs, and that recycling of the catalyst is less satisfactory.[5]

The Diels-Alder (DA) reaction is one of the most efficient bond-forming reactions used widely in synthetic organic chemistry.[6] This reaction shows excellent “atom economy”[7] due to its simple method of

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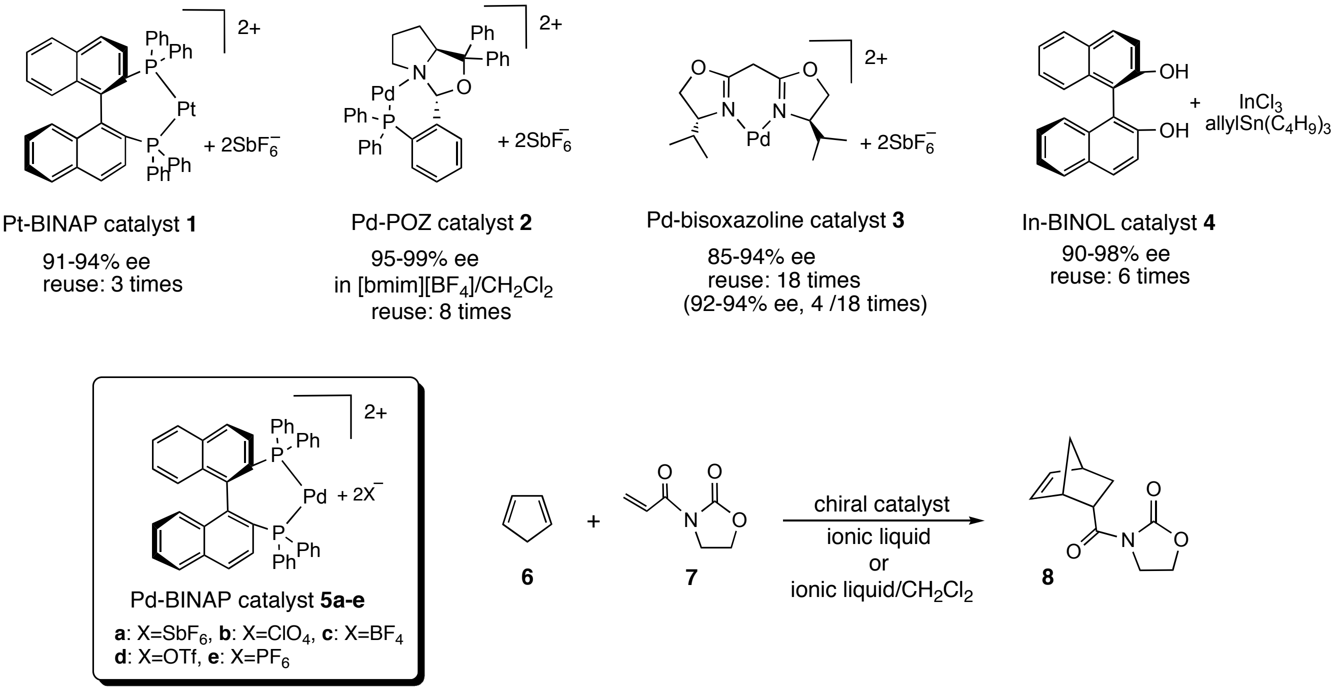
*Dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday cycloaddition using a diene and dienophile, and many research groups have reported an enantioselective version of the reaction that relies on a chiral catalyst. Therefore, it is significant to study the DA reaction in ionic liquid. However, successful results have been reported by only a few groups such as those of Doherty,[8] Kim,[9] Loh,[10] and ourselves[11]. Although, practical levels of chemical yield and ee have been obtained in these studies, satisfactory recycling has not yet been achieved. For example, Pt-BINAP catalyst **1** used by Doherty group was reused at only 3 times.[8] Pd-phosphinooxazolidine catalyst **2** used by our group has given excellent chemical yield and ee while being recycled 8 times in a mixed solvent of IL and CH_2Cl_2.[11] Furthermore, the bisoxazoline catalyst **3** used by Kim group has been recycled up to 18 times in an IL, though successful recycling has been achieved only 4 times with 92-94% ee.[9] Although the In-BINOL catalyst **4** used by Loh group afforded satisfactory results in the DA reaction using several dienes and gave 6 times recycling, the special bromoacrolein was only used as the dienophile and also need a large amount of allyltributylstannan as a co-catalyst.[10]



Pt-BINAP catalyst **1**
91-94% ee
reuse: 3 times

Pd-POZ catalyst **2**
95-99% ee
in $[bmim][BF_4]/CH_2Cl_2$
reuse: 8 times

Pd-bisoxazoline catalyst **3**
85-94% ee
reuse: 18 times
(92-94% ee, 4 /18 times)

In-BINOL catalyst **4**
90-98% ee
reuse: 6 times

Pd-BINAP catalyst **5a-e**
a: $X=SbF_6$, **b**: $X=ClO_4$, **c**: $X=BF_4$
d: X=OTf, **e**: $X=PF_6$

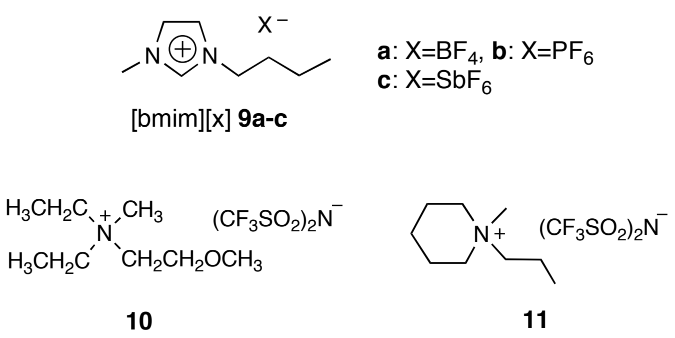
Scheme 1. Chiral catalysts **1-5** for asymmetric Diels-Alder reaction in ionic liquid

Given this background, our present aim was to explore efficient catalytic asymmetric DA reactions using an IL as a solvent, with particular attention being paid to reactions in which the catalyst can be prepared easily, afford a practical ee and can also be recovered and reused.

We here report a successful catalytic asymmetric DA reaction using cationic Pd-BINAP catalyst **5** in IL. Although Pd-BINAP complex acts as a superior catalyst in several catalytic asymmetric reactions,[12] its use in IL has never been reported. We found that the catalyst shows superior asymmetric catalytic activity in DA reactions such as the reaction of cyclopentadiene **6** with acryloyl-1,3-oxazolidin-2-one **7** to afford the corresponding DA adduct **8** with good chemical yield and excellent ee, and that it can be reused 7 times with good chemical yield (50-66%) and without any significant decrease in enantioselectivity (94-98% ee). To the best of our knowledge, this is the best result that has been reported for which recycling has been performed repeatedly with a practical level of ee over 90% in a catalytic asymmetric DA reaction using only IL.

RESULTS AND DISCUSSION

Initially, to find out an optimal medium for the reaction, we screened a set of ILs composed of [bmim][X], varying the anionic counterpart: BF_4^-, PF_6^-, and SbF_6^-. The DA reactions of diene **6** with dienophile **7** in the presence of 10 mol% of Pd-BINAP catalysts 5**a-e** in five different ionic liquids (Scheme 2), [1-butyl-3-methylimidazolium: bmim][X] **9a-c** (**9a:** X=BF_4^-, **9b:** X=PF_6^-, **9c:** X=SbF_6^-), *N,N*-diethyl-*N*-methyl-*N*-(2-methoxyethyl)ammonium bis(trifluoromethanesulfonyl)imide **10**, and *N*-methyl-*N*-propylpiperidinium bis(trifluoromethanesulfonyl)imide **11** were carried out at room temperature for 24 h. The results of the DA reactions of **6** with **7** in ILs **9a-c, 10, 11** are summarized in Table 1. Ether was used for the separation of DA adduct **8**, because the ILs **9a-c, 10, 11** form a bilayer with ether. The desired **8** was isolated from the ether layer after purification by preparative thin layer chromatography (TLC). The reactions of cationic catalysts having counter anions **5a-d** in [bmim][BF_4] **9a** afforded moderate to good chemical yields (48-66%) and fairly good enantioselectivities (93% ee, entries 1-4). However, the reaction using PF_6-catalyst **5e** afforded only a low chemical yield and ee (27%, 58% ee, entry 5). Next, the reactions using catalysts **5a-e** in [bmim][PF_6] **9b** were examined under the same reaction conditions as those used for **9a**. The best ee with good chemical yield was obtained by using antimonate catalyst **5a** (60%, 98% ee, entry 6). In contrast, the catalytic activities of **5b-e** were quite low (10-36%), although the reactions gave satisfactory enantioselectivities (93->99% ee, entries 7-10). Unfortunately, the catalytic loading from 10 mol% to 5 mol% of catalyst **5a** brought about a remarkable decline in the chemical yield (entry 18). In contrast, the reactions in [bmim][SbF_6] **9c** afforded the DA adduct **8** with only low chemical yields (29-47%, entries 11-15), but the ee was fairly good (80-94% ee). On the other hands, the uses of **10** or **11** afforded the DA adduct **8** with poor enantioselectivities (entries 16,17), although chemical yields were better than those obtained results in ILs **9a,b**. Based on these results, it can be concluded that the combination of antimonate Pd-BINAP catalyst **5a** and [bmim][PF_6] **9b** is the most effective combination for this reaction to give the DA adduct **8** in good chemical yield with excellent enantioselectivity. Furthermore, this result is almost the same as those obtained in the usual organic solvent (CH_2C1_2) at -78 °C as reported by Ghosh group (87%, 96% ee, Table 1, entry 1).[12b]



Scheme 2. Ionic liquids

Table 1. Pd-BINAP **5a-e** catalyzed asymmetric DA reactions of diene **6** with dienophile **7** in ionic liquids **9a-c, 10, 11**

$$\mathbf{6} + \mathbf{7} \xrightarrow[\text{ionic liquids } \mathbf{9a\text{-}c}, \mathbf{10}, \mathbf{11}; \text{ rt, 24h}]{\text{Pd-BINAP catalysts } \mathbf{5a\text{-}e}} (2S)\text{-}\mathbf{8}^d$$

Entry	Catalyst (mol%)	Ionic liquid	Yield[a] (%)	*Endo*/*exo*[b]	E.e.[c] (%)
1	**5a** : X = SbF_6 (10)	**9a**	66	95:5	93
2	**5b** : X = ClO_4 (10)	**9a**	48	98:2	93
3	**5c** : X = BF_4 (10)	**9a**	59	96:4	93
4	**5d** : X = OTf (10)	**9a**	48	96:4	93
5	**5e** : X = PF_6 (10)	**9a**	27	92:8	58
6	**5a** : X = SbF_6 (10)	**9b**	60	95:5	98
7	**5b** : X = ClO_4 (10)	**9b**	16	95:5	>99
8	**5c** : X = BF_4 (10)	**9b**	27	97:3	95
9	**5d** : X = OTf (10)	**9b**	10	95:5	>99
10	**5e** : X = PF_6 (10)	**9b**	36	95:5	93
11	**5a** : X = SbF_6 (10)	**9c**	38	93:7	86
12	**5b** : X = ClO_4 (10)	**9c**	34	94:6	91
13	**5c** : X = BF_4 (10)	**9c**	47	94:6	94
14	**5d** : X = OTf (10)	**9c**	34	93:7	80
15	**5e** : X = PF_6 (10)	**9c**	29	94:6	93
16	**5a** : X = SbF_6 (10)	**10**	56	94:6	42
17	**5a** : X = SbF_6 (10)	**11**	76	95:5	21
18	**5a** : X = SbF_6 (5)	**9b**	54	96:4	94

a) Isolated yields. b) The *endo/exo* ratio was determined by HPLC. c) The ee of the *endo* isomer was determined by chiral HPLC using a Daicel OD-H column (1mL/min, Hexane:2-propanol=90:10). d) (*S*)-Configuration based on the specific rotation with liturature data.[11c]

We examined the reuse of superior catalyst **5a** in [bmim][BF_4] **9a** or [bmim][PF_6] **9b**, as shown in Table 2. As the first attempts, the reaction of **6** with **7** in [bmim][BF_4] was examined. After the first run afforded a good chemical yield and ee (66%, 93% ee), the same amounts of starting materials were again added to the separated ionic liquid [bmim][BF_4] layer. The desired DA adduct **8** was isolated from the ether layer after purification by preparative TLC. Good chemical yields and fairly good enantioselectivities were also obtained in the second and third runs (2nd: 60%, 94% ee, 3rd: 63%, 92% ee). Unfortunately, the enantioselectivity decreased greatly (67% ee) in the fourth run due to the generation of palladium black. Effective recycling was carried out 3 times. Next, the reuse in [bmim][PF_6] was examined. The first run was afforded good chemical yield and excellent ee (60%, 98% ee). After the first run, good chemical yield and excellent ee (60%, 95% ee) were also obtained in the second run. The catalyst was successfully recycled 7 times without any significant decrease in the good chemical yield and excellent ee (50-60%, 98-94% ee). In the eighth run, however, the chemical yield decreased to 30%, although the ee was kept at 94%. Effective recycling was carried out 7 times, which corresponds to the best frequency obtained in the recycling experiment of the DA reaction in IL that was kept over 90% ee.

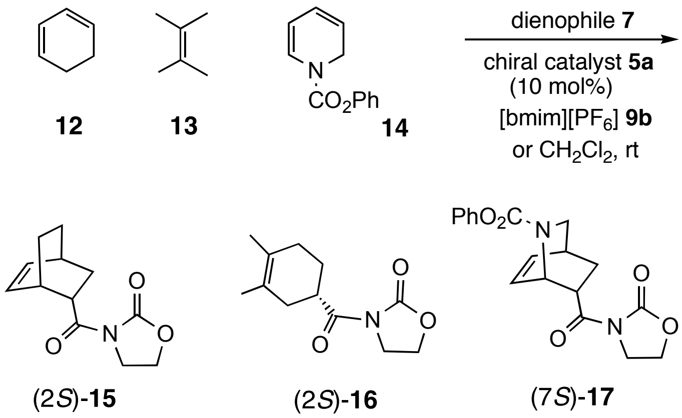
Table 2. Reuse of Pd-BINAP catalyst **5a** for asymmetric DA reactions of **6** with **7** in ionic liquids **9a,b**

Cycle	Ionic liquid	Reaction time (h)	Yield[a] (%)	*Endo*/ *exo*[b]	E.e.[c] (%)
1	**9a**	24	66	95:5	93
2	**9a**	48	60	94:6	94
3	**9a**	72	63	88:12	92
4	**9a**	72	68	92:8	67
1	**9b**	24	60	95:5	98
2	**9b**	48	60	94:6	95
3	**9b**	72	55	96:4	94
4	**9b**	72	55	97:3	94
5	**9b**	72	56	95:5	94
6	**9b**	72	55	96:4	94
7	**9b**	72	50	94:6	94
8	**9b**	72	30	95:5	94

a) Isolated yields. b) The *endo*/*exo* ratio was determined by HPLC. c) The ee of the *endo* isomer was determined by Chiral HPLC using a Daicel OD-H column.

To expand the scope of the application of this catalyst-ionic liquid system, we examined the DA reaction of several dienes **12-14** with dienophile **7** in the superior combination of [bmim][PF_6] **9b** as a solvent and antimonate catalyst **5a**. The results are summarized in Table 3. The reaction of inactive cyclohexadiene **12** with **7** afforded a moderate chemical yield and a fairy good enantioselectivity (55%, 92% ee, entry 1). When 2,3-dimethyl-1,3-butadiene **13** was used as an acyclic diene, the reaction with dienophile **7** remarkably increased the value of ee (76%, 96% ee, entry 2) compared with the results obtained in the usual organic solvent (66%, 79% ee, entry 3). The reactions using 1,2-dihydropyridine as diene were also found to afford the DA adducts (isoquinuclidines), which are useful synthetic intermediates for oseltamivir (Tamiflu),[13] ibogain,[14] and so on. The reaction of 1-phenoxycarbonyl-1,2-dihydropyridine **14**[15] with dienophile **7** gave the DA adduct **17** in good chemical yield and fairly good ee (83%, 93% ee, entry 4). The ee in this result was also superior to that obtained in the usual organic solvent (CH_2Cl_2)(80%, 77% ee, entry 6). The change in the catalytic loading from 2.5 mol% to 5 mol% slightly decreased the ee (83%, 90% ee, entry 5).

Table 3. Pd-BINAP **5a** catalyzed asymmetric DA reaction using several dienes **12-14** with dienophile **7** in [bmim][PF_6] **9b**



Entry	Diene (eq.)	Solvent	Time (h)	DA adduct	Yield[a] (%)	*Endo*/ *exo*[b]	E.e.[c] (%)
1	**12** (2.5)	**9b**	72	**15**[d]	55	95:5	92
2	**13** (2.5)	**9b**	72	**16**[d]	74	---	96
3	**13** (2.5)	CH_2Cl_2	96	**16**	66	---	79
4	**14** (2.5)	**9b**	96	**17**[d]	83	---	93
5	**14** (5)	**9b**	96	**17**	83	---	90
6	**14** (2.5)	CH_2Cl_2	96	**17**	80	---	77

a) Isolated yields. b) The *endo/exo* ratio was determined by HPLC. c) The ee of the *endo* isomer was determined by chiral HPLC using a Daicel Chiralpak AD-H or Chiralpak AS column. d) (*S*)-Configuration based on the specific rotation with liturature data.[11c,14]

In conclusion, we have developed an efficient asymmetric DA reaction using cationic Pd-BINAP catalyst in IL. Thus, the combination of antimonate catalyst **5a** and [bmim][PF_6] **9b** as an IL afforded a good chemical yield and good to excellent enantioselectivities in the reactions of several dienes with 2-acryloyl-1,3-oxazolidine **7**. Furthermore, the catalyst **5a** was easily recycled and showed excellent asymmetric catalytic activity in the DA reaction of **6** with **7** using ionic liquid **9b**. Thus, catalyst was successfully reused 7 times without any significant decrease in chemical yield and enantioselectivity (50-60%, 94-98% ee). The asymmetric DA reactions using Pd-BINAP catalyst in IL have been shown to provide a possibility towards practical application from both an economical and environmental perspective. Further studies to examine the scope and limitations of our Pd-BINAP catalyst in the asymmetric DA reaction in ionic liquids are now in progress.

EXPERIMENTAL

All reactions were carried out under argon in oven-dried glassware with magnetic stirring. Ionic liquids **9a-c** were purchased from Tokyo Kasei. Pd-(*R*)-BINAP complex was prepared according to a literature procedure.[1,2] Commercial grade solvents and reagents were used without further purification with the following exceptions: Dichloromethane (CH_2Cl_2) was prepared from calcium hydride. Cyclohexadiene and 2,3-dimethyl-1,3-butadiene were purchased from Aldrich or Tokyo Kasei. Cyclopentadiene was prepared by cracking dicyclopentadiene over calcium hydride. *N*-Phenoxycarbonyl-1,2-dihydropyridine was prepared according to a literature procedure.[15]

General procedure for the asymmetric DA reactions using cationic catalysts 5a-e in ionic liquids 9a-c, 10, 11. $PdCl_2$-BINAP complex (0.023 mmol)[12c] and AgX (X = PF_6, BF_4, SbF_6, 0.046 mmol) were dissolved in CH_2Cl_2 (3.0 mL), and the mixture was stirred for 1 h at rt under Ar to produce a yellow solution with a white AgCl precipitate, respectively. The mixture was filtered in air through filter paper. To the resulting cationic catalyst solution, was added ionic liquids **9a-c, 10, 11** (0.3 mL) and dienophile **7** (30 mg, 0.21 mmol). After the mixture was stirred for a few minutes, CH_2Cl_2 was removed completely under reduced pressure and then diene **6** (35 mg, 0.53 mmol) was added. The reaction mixture was stirred at rt under Ar. After 24 h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted twice with Et_2O. The combined organic layer was washed with brine, dried with anhydrous $MgSO_4$, and concentrated. The crude product was purified by preparative TLC on silica gel (hexane:AcOEt 1:1) to give the DA adduct **8**. HPLC analysis (Daicel Chiralcel OD-H) indicated the *endo*/*exo* ratio and the enantiomeric excess of the product (Table 1).[11a,b] (*S*)-Configuration of **8** were based on the specific rotation with literature data.[11c]

Reuse of cationic catalyst 5a in [bmim][BF_4] 9a or [bmim][PF_6] 9b for the asymmetric DA reaction. The cationic catalyst **5a** was prepared according to the above procedure. To a solution of catalyst **5a** (0.023 mmol) in [bmim][BF_4] **9a** or **9b** (0.3 mL), was added dienophile **7** (30 mg, 0.21 mmol) and diene **6** (35 mg, 0.53 mmol). The reaction mixture was stirred at rt for 48-76 h. The mixture was washed with Et_2O (1.0 mL×10). The resulting ionic liquid was dried under reduced pressure for 2 h and charged with dienophile **7** (30 mg, 0.21 mmol) and diene **6** (35 mg, 0.53 mmol), then continued to the next cycle. The combined Et_2O layer was purified according to the above procedure, giving the DA adduct **8** (Table 2). Spectral data matched literature values.[11b]

General procedure for the asymmetric DA reactions of dienes 12-14 with dienophile 7 using cationic catalyst 5a in [bmim][PF_6] 9b. $PdCl_2$-BINAP complex (0.023 mmol) and AgX (X = PF_6, BF_4, SbF_6, 0.046 mmol) were dissolved in CH_2Cl_2 (3.0 mL), and the mixture was stirred for 1 h at rt under Ar to produce a yellow solution with a white AgCl precipitate. The mixture was filtered in air through filter paper. To the resulting cationic catalyst solution, was added ionic liquid **9b** (0.3 mL) and dienophile **7** (30 mg, 0.21 mmol). After the mixture was stirred for a few minutes, CH_2Cl_2 was removed completely under reduced pressure and then dienes **12-14** (0.53 mmol) was added. The reaction mixture was stirred at rt under Ar. After 72-96 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution and extracted twice with Et_2O. The combined organic layer was washed with brine, dried with anhydrous $MgSO_4$, and concentrated. The crude product was purified by preparative TLC on silica gel (hexane:AcOEt 1:1) to give the DA adduct **15-17**, respectively. HPLC analysis (**15**: Chiralpak AD-H, **16**: ChiralPak AS, **17**: Chiralpak AD-H) indicated the *endo*/*exo* ratio and the enantiomeric excess of the product (Table 3). (*S*)-configurations of **15-17** were based on the specific rotations with literature data.[11c,14a,b]

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