Reuse of chiral cationic Pd–phosphinooxazolidine catalysts in ionic liquids: highly efficient catalytic asymmetric Diels–Alder reactions†

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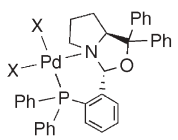
Chiral cationic palladium–phosphinooxazolidine catalysts in ionic liquid afforded excellent enantioselectivity in Diels–Alder reactions and the catalyst was easily recycled eight times without any significant decrease in chemical yields or enantioselectivity (89–99%, 88–99% ee).

Recently, the recovery and reuse of catalysts in a catalytic reaction has attracted growing interest to meet the need for environmentally friendly and cost-effective reaction processes. Many methodologies have been attempted to achieve recovery and reuse;[1] among them, the use of immobilized chiral catalysts on soluble or insoluble polymers in an asymmetric synthesis is representative.[1a–c] However, these approaches require ligand or catalyst modification for immobilization to the polymer and this modification tends to be complicated. In addition, it is sometimes difficult to reproduce the reaction efficiency obtained under homogeneous conditions using a monomer catalyst. Ionic liquids have attracted extensive interest as excellent alternatives to organic solvents, due to their favorable properties such as non-flammability, low toxicity, reusability, low cost and high thermal stability.[2] Additionally, they provide good solubility for a wide range of organic, inorganic and organometallic compounds.[3] To date, several reactions have been demonstrated in ionic liquid (IL). However, the use of a catalytic asymmetric reaction 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 usual organic solvents were difficult to reproduce in ionic liquid, and that recycling of the catalyst was less satisfactory.[4] To our knowledge, only three groups[5] have reported a successful study which afforded satisfactory ee and recycling in catalytic asymmetric reactions. The Diels–Alder (DA) reaction is one of the most efficient bond-forming reactions used widely in synthetic organic chemistry.[6] Therefore, many research groups have reported an enantioselective version of the reaction that relies on a chiral catalyst.[7] Nevertheless, to the best of our knowledge, only four examples of asymmetric DA reactions in IL have been reported; these reactions used Cu–bisoxazoline,[8] Pt–BINAP,[9] Pt–NUPHOS[9] catalysts and MacMillan's organocatalyst.[10] Although these reactions afforded moderate to excellent chemical yields (65–100%) and good enantioselectivity (89–93% ee), they were unable to achieve an excellent practical level of ee (over 95%) and catalysts were successfully reused only 3 times in the experiment with the best result. Given this background, our present aim was to explore efficient catalytic asymmetric DA reactions using IL as a solvent, and with particular attention to reactions in which the catalyst can be recovered and reused.

We here report a successful catalytic asymmetric DA reaction using cationic Pd–phosphinooxazolidine (POZ) catalyst[11] in IL. In a reaction of cyclopentadiene **2** with acryloyl-1,3-oxazolidin-2-one **3a**, we found that the catalyst could be reused 8 times without any significant decrease in chemical yields or enantioselectivity (89–99%, 88–99% ee). To the best of our knowledge, this is the first time that a catalytic asymmetric DA reaction has been performed repeatedly with a high level of enantioselectivity in IL.

In order to compare the present results of the reaction in IL, we first examined the DA reactions of **2** with **3a** using cationic Pd–POZ catalysts **1a–e** (Fig. 1: new catalyst **1b**[11c] and our previously reported catalysts **1a, c–e**[11a,b]) in CH_2Cl_2 as a usual organic solvent (Table 1), finding that the hexafluoroantimonate catalyst **1c** was the most effective for obtaining the highest chemical yield and enantioselectivity (entry 4).

With these results in hand, we next examined the DA reaction of **2** with dienophile **3a** in the presence of 5 mol% of superior antimonate catalyst **1c** in seven different ILs (Fig. 2), [bmim][X] **5a–f** and [bmmim][BF_4] **5g** at room temperature for 48 h. Ether was selected for separation, and ILs **5a–g** formed a bilayer with the ether. The desired DA adduct was isolated from the ether layer after the purification by preparative TLC; the results are summarized in Table 2. Moderate to good chemical yields (52–89%) and good to excellent enantioselectivities (76–96% ee) were obtained in the examined reactions (Table 2, entries 1–7) and both reactivity and enantioselectivity were strongly influenced by the nature of the anions X. Using [bmim][BF_4] **5a** as IL, the desired DA adduct **4** was obtained in 89% yield and 96% ee (Table 2, entry 1). This result was better than those obtained in a usual organic solvent (CH_2Cl_2) under the same reaction conditions (Table 1, entry 3), and it also showed almost the same degrees as those obtained in CH_2Cl_2 at −50 °C (Table 1, entry 4). Contrary to our expectations, [bmim][SbF_6] **5c** did not give a satisfactory result (Table 2, entry 3), unlike the results obtained in CH_2Cl_2 (Table 1, entry 4). The reason for these results was clarified by attempting reactions in **5a** or **5c** in the absence of catalyst **1c**



1a : X = BF_4
1b : X = PF_6
1c : X = SbF_6
1d : X = TfO
1e : X = ClO_4

cationic Pd-POZ catalysts **1a-e**

Fig. 1 Pd–phosphinooxazoline complexes.

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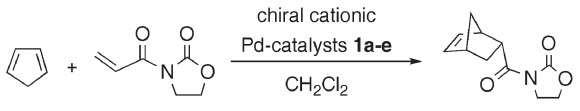
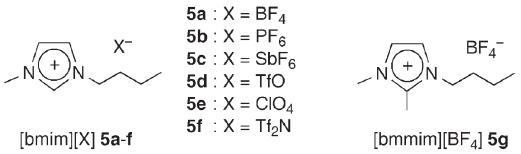
Table 1 Pd–POZ catalyzed asymmetric DA reaction of cyclopentadiene **2** with dienophile **3a** in CH_2Cl_2



2 **3a** (2*R*)-**4**

Entry	Catalyst (mol%)	Temp. (°C)	Time (h)	Yield[a] (%)	*endo*/*exo*[b]	ee[c] (%)
1	**1a**:BF_4 (5)	−30	48	41	91 : 9	93
2	**1b**:PF_6 (5)	−45	48	74	98 : 2	98
3	**1c**:SbF_6 (5)	rt	6	75	87 : 13	88
4[d]	**1c**:SbF_6 (5)	−50	22	94	97 : 3	97
5[d]	**1d**:TfO (10)	−45	45	52	86 : 14	74
6[d]	**1e**:ClO_4 (10)	−45	20	97	94 : 6	93

[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 (0.5 mL min^{-1}, hexane : 2-propanol = 90 : 10). [d] See references.[11a,b]



[bmim][X] **5a-f** [bmmim][BF_4] **5g**

Fig. 2 Ionic liquids.

Table 2 Pd–POZ **1c** catalyzed asymmetric DA reaction of cyclopentadiene **2** with dienophile **3a** in ILs **5a–g**

Entry	Ionic liquid	Yield[a] (%)	*endo*/*exo*[b]	ee[c] (%)
1	**5a**:BF_4	89	96 : 4	96
2	**5b**:PF_6	61	92 : 8	85
3	**5c**:SbF_6	80	95 : 5	81
4	**5d**:TfO	52	91 : 9	76
5	**5e**:ClO_4	55	92 : 8	80
6	**5f**:Tf_2N	77	92 : 8	83
7	**5g**:BF_4	55	92 : 8	89
8[d]	**5a**:BF_4	20	92 : 8	—
9[d]	**5c**:SbF_6	61	90 : 10	—

[a] Isolated yields. [b] The *endo*/*exo* ratio was determined by HPLC. [c] The ee of the *endo* isomer was determined by chiral HPLC. [d] No Pd–POZ catalyst.

(Table 2, entries 8 and 9). Thus, ILs **5a** and **5c** afforded the DA adduct in 20% and 61% yields, respectively. We assume that ILs **5c** catalyzed the reactions, with **5c** showing higher catalytic activity than **5a**. This characteristic might have brought about a decrease in enantioselectivity. Although these results prompted us to try the reaction at a low temperature, this was not possible due to the viscosity of the IL.

Table 3 Reuse of Pd–POZ catalyst **1c** catalyst for asymmetric DA reaction of **2** with **3a** in IL **5a**[a]

Cycle	1	2	3	4
Yield (%)[b]	89	89	90	69
endo/*exo*[c]	96 : 4	97 : 3	92 : 8	92 : 8
ee (%)[d]	96	93	85	65

[a] DA reaction was performed in presence of catalyst **1c** (5 mol%) at room temperature for 48 h in [bmim][BF_4]. [b] Isolated yields. [c] The *endo*/*exo* ratio was determined by HPLC. [d] The ee of the *endo* isomer was determined by chiral HPLC.

We next challenged the reuse of superior catalyst **1c** under optimized conditions, as shown in Table 3. The same amounts of starting materials were again added to the separated IL layer. The reaction produced DA adduct **4** in an 89% yield and with 93% ee at the second run. However, enantioselectivity decreased to 85% ee at the third run, although the chemical yield remained constant at a 90% yield. Both the chemical yield and the enantioselectivity decreased greatly to 69% and 65% ee, respectively, at the fourth run. Recycling was thus carried out effectively 3 times.

In order to improve the recycling efficiency of catalyst **1c**, we planned to use a mixture of [bmim][BF_4] **5a** and CH_2Cl_2 as a solvent because IL **5a** showed high viscosity at −40 °C. We again tried to reuse catalyst **1c** in [bmim][BF_4]–CH_2Cl_2 (1 : 2) solvent; the results are summarized in Table 4. Consistent with our expectations, this attempt brought about a great increase in chemical yield with excellent enantioselectivity (99%, 95% ee, cycle 1). After the first run, CH_2Cl_2 was removed under reduced pressure. Ether was selected for separation and [bmim][BF_4] **5a** formed a bilayer with the ether. The desired DA adduct was isolated from the ether layer after purification by preparative TLC. This result prompted us to attempt the reuse of catalyst **1c**. Thus, CH_2Cl_2 solvent and the same amounts of starting materials were again added to the separated IL layer. Excellent chemical yield and enantioselectivity (99%, 99% ee) were obtained at the second run. The catalyst was successfully recycled 7 times without any significant decrease in the excellent enantioselectivity (94–99% ee), although the chemical yield decreased slightly to 89%. Furthermore, the reaction afforded fairly good results (89%, 88% ee) at the ninth run as well. The effective number of recycling times was 8, and this was also the best result obtained in the recycling experiment of the DA reaction in IL.

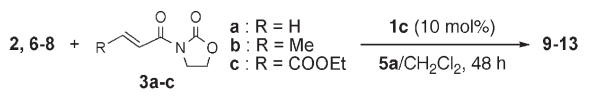
Finally, we examined the DA reaction using several dienes (**2**, cyclohexadiene **6**, furan **7** or 1-phenoxycarbonyl-1,2-dihydropyridine **8**) and dienophiles (**3a–c**) in a superior combination of [bmim][BF_4] and CH_2Cl_2 as a solvent and superior catalyst **1c** at room temperature and at −40 °C slowly increased to room temperature. The results are summarized in Table 5. Unfortunately, the reactions of **2** with **3b** or **3c** and of cyclohexadiene **6** with **3a** did not afford results as satisfactory as

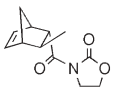
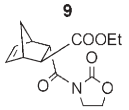
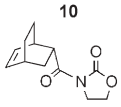
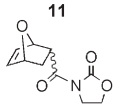
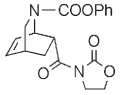
Table 4 Reuse of Pd–POZ catalyst **1c** for asymmetric DA reaction of **2** with **3a** in IL **5a**–CH_2Cl_2[a]

Cycle	1	2	3	4	5	6	7	8	9	10
Time (h)	48	48	48	48	72	72	72	72	96	96
Yield (%)[b]	99	99	96	94	99	98	91	89	89	57
endo/*exo*[c]	97 : 3	97 : 3	98 : 2	99 : 1	98 : 2	98 : 2	97 : 3	97 : 3	96 : 4	95 : 5
ee (%)[d]	95	99	96	99	94	95	95	95	88	75

[a] DA reaction was performed in presence of catalyst **1c** (10 mol%) at −40 °C to room temperature for 48–96 h in [bmim][BF_4]–CH_2Cl_2 = 1 : 2. [b] Isolated yields. [c] The *endo*/*exo* ratio was determined by HPLC. [d] The ee of the *endo* isomer was determined by chiral HPLC.

Table 5 Pd–POZ **1c** catalyzed asymmetric DA reaction of dienes **2**, **6–8** with dienophiles **3a–c** in [bmim][BF_4] **5a**–CH_2Cl_2[a]



Entry	Diene/ dienophile	Product	Temp. (°C)	Yield[b] (%)	*endo*/ *exo*[c]	ee[d] (%)
1	**2/3b**	 **9**	rt	47	90 : 10	81
			−40 to rt	59	90 : 10	98
2	**2/3c**	 **10**	rt	99	85 : 15	79[e]
			−40 to rt	92	85 : 15	87[e]
3	**6/3a**	 **11**	rt	70	97 : 3	74
			−40 to rt	77	98 : 2	86
4[f]	**7/3a**	 **12a**(*endo*),**12b**(*exo*)	−30	46	41 : 59	**12a**: 85 **12b**: 98
5	**8/3a**	 **13**	rt	19	—	23
			rt	80	—	96[g]

[a] DA reaction was performed in [bmim][BF_4]–CH_2Cl_2 = 1 : 2. [b] Isolated yields. [c] The *endo*/*exo* ratio was determined by HPLC or ^{1}H NMR. [d] The ee of the *endo* isomer was determined by chiral HPLC using a Daicel OD-H column or AD-H column. [e] The ee was determined by comparison with the known optical rotation after iodolactonization. [f] DA reaction was performed in [bmim][BF_4]–CH_2Cl_2 = 1 : 10. [g] DA reaction was performed in [bmim][BF_4].

those obtained under usual conditions previously reported by our group[11a,b] (entries 1–3), although the enantioselectivities increased to 98, 87, and 86% ee, respectively, when the reactions were carried out at −40 °C to room temperature. Reactions using furan **7** or 1,2-dihydropyridine **8** as dienes were also examined (entries 4 and 5). The obtained DA adducts **12** and **13** are valuable intermediates in pharmacologically important compounds.[12,13] When the reaction of furan **7** with **3a** was carried out at −30 °C, DA adduct **12** was obtained as a 41 : 59 mixture of *endo*-**12a**/*exo*-**12b** isomers in a 46% yield. Although the reaction afforded the DA adducts as an isomer mixture, high enantioselectivities were obtained for both the *endo*-**12a** and *exo*-**12b** isomers; indeed, the ee of *exo*-**12b** was almost complete (98% ee). The reaction of 1,2-dihydropyridine **8** with dienophile **3a** at room temperature was unsuccessful due to the generation of palladium black, although the reason is not clear. The effectiveness of IL was demonstrated when IL was used alone as a solvent, which produced DA adduct **13** in a good chemical yield and with excellent enantioselectivity (80%, 96% ee).

In summary, we have developed a highly efficient asymmetric DA reaction using cationic Pd–POZ catalyst in IL. The combination of cationic Pd–POZ catalyst **1c** with SF_6 counter ion and [bmim][BF_4] **5a** as an IL was found to be effective in the reaction of **2** with **3a**, affording the corresponding DA adduct **4**. Additionally, the chemical and optical yields were high using a mixture of [bmim][BF_4] **5a** and CH_2Cl_2 as a solvent. In the reaction, catalyst **1c** was successfully reused 8 times giving 89–99% yield and 88–99% ee. Moreover, this system was also effective in reactions using furan **7** or 1,2-dihydropyridine **8** as dienes, affording the corresponding DA adducts (**12** and **13**) at excellent enantioselectivities. Our asymmetric DA reactions in IL have thus been shown to be practical from both economic and environmental points of view. Further studies to examine the scope and limitations of our catalytic version of the asymmetric DA reaction in IL are now in progress.

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