Recycling Chiral Imidazolidin-4-one Catalyst for Asymmetric Diels–Alder Reactions: Screening of Various Ionic Liquids

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Abstract: Various imidazolium ionic liquids such as [Bmim]PF_6, [Bmim]SbF_6, [Bmim]OTf and [Bmim]BF_4 were screened for recycling an organic catalyst [(5*S*)-5-benzyl-2,2,3-trimethylimidazolidin-4-one (**1**)] for asymmetric Diels–Alder reactions. Good yields and enantioselectivies (up to 85% yield and 93% ee) were obtained from reactions in [Bmim]PF_6 or [Bmim]SbF_6. However, reactions in [Bmim]OTf or [Bmim]BF_4 gave racemic products in low yields. Isolation of the products by simple extraction using diethyl ether allowed recycling of the ionic liquid containing the immobilized catalyst in subsequent reactions without significant decrease of yields and enantioselectivities.

Keywords: asymmetric catalysis; Diels–Alder reaction; ionic liquid; organic catalyst; recycling

The development of new catalytic asymmetric processes using metal-free organic molecules has received keen attention from organic chemists during the last few years.[1] In many cases, reactions employing these small organic compounds proceed with high enantioselectivities and in excellent yields. That the reactions can usually be performed in wet solvents under an aerobic atmosphere offers a practical advantage. Recently Macmillan[2] reported highly efficient, enantioselective Diels–Alder (D-A) reactions catalyzed by an amine salt **1**. Efforts to immobilize the organic catalyst were reported by Cozzi[3] and Pihko[4], independently, where chiral imidazolidin-4-one derivatives were attached to solid supports. The immobilized catalysts were recycled up to four times in the D-A reactions with some loss of yields and enantioselectivity. We envisioned that, based on the ionic nature of the catalyst **1**, it could be contained in a polar medium such as an ionic liquid. This would then enable one to recycle the catalyst by simply extracting the ionic liquid with a relatively non-polar organic solvent after reaction.

Room temperature ionic liquids have been successfully applied as alternative solvents in many organic transformations.[5] In processes involving ionic liquids, recycling of the ionic liquids by simple decantation or distillation of lighter solvents has been common. Although there have been many examples of immobilizing transition metal catalysts into the ionic liquids, organic catalysts free of metal have rarely been examined in ionic liquid solvents.[6] Herein we report our results on the use of ionic liquids in asymmetric D-A reactions catalyzed by **1**.[7]

We investigated a set of ionic liquids derived from the imidazole core by varying the anionic counterpart, namely [Bmim]PF_6, [Bmim]SbF_6, [Bmim]BF_4 and [Bmim]OTf.[8] The former two are known as hydrophobic solvents and the latter two hydrophilic.[9] As a test reaction, the D-A reaction between cyclohexadiene and acrolein was chosen. Reactions were run with 5 mol % of the catalyst **1** in a 95 : 5 v/v mixture of ionic liquid and water as shown in Scheme 1. The results of the D-A reactions are summarized in Table 1. After the catalyst **1** was dissolved in an ionic liquid completely in 5 minutes, acrolein and cyclohexadiene were added successively. When the reaction was complete (normally within 18 h) diethyl ether was added to the mixture and D-A adducts were obtained by simple decantation of the ether layer followed by evaporation and silica gel column chromatography. When [Bmim]PF_6 was used, a 17 : 1 *endo/exo* mixture of the adduct was obtained in 76% yield after purification and the major *endo*-diastereomer exhibited 93% ee (entry 1), which is comparable to the value obtained in acetonitrile (94% ee, entry 7). The ionic liquid was recycled after allowing the remaining diethyl ether to evaporate under atmospheric pressure and in the 2nd run a 72% yield of a 17 : 1 diastereomeric mixture was obtained with the *endo*-isomer exhibiting 91% ee (entry 2). In the 3rd recycling experiment, the *endo*-product of 87% ee in 17 : 1 diastereoselectivity was obtained in 70% yield (entry 3). Reactions employing [Bmim]SbF_6 gave similar results yielding the *endo*-product of 92% ee with 17 : 1 diastereoselectivity in 74% yields (entry 4). However in [Bmim]OTf and in [Bmim]BF_4, the products were isolated in very low yields, i.e., 7% and 5%, respectively (entries 5 and 6) and no enantiomeric enrichment for the *endo*-isomer was observed.[10] In these reactions water appears to play a

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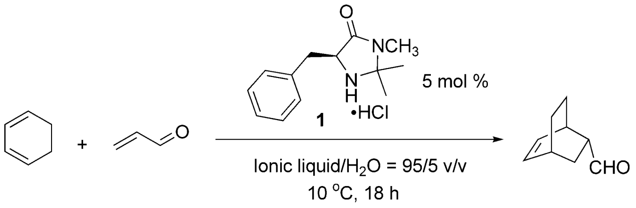


Scheme 1.

Table 1. Results of organic catalyst (**1**) catalyzed Diels–Alder reaction in various ionic liquids.

Entry	Ionic liquid or organic solvent	*Endo* ee [%][a]	*Endo*:*exo*[a]	Yield [%][b]
1	[Bmim]PF$_6$	93	17:1	76
2[c]	[Bmim]PF$_6$	91	17:1	72
3[d]	[Bmim]PF$_6$	87	17:1	70
4	[Bmim]SbF$_6$	92	17:1	74
5	[Bmim]OTf	0	17:1	7
6	[Bmim]BF$_4$	0	17:1	5
7[e]	CH_3CN	94	14:1	82

[a] ee values and *endo/exo* ratios were determined though GLC analysis using a Chiraldex G-TA column. GC conditions: HP 6890; constant pressure 10 psi; oven temp. 70 °C; major peak at 87.4 min, minor at 92.3 min.
[b] Yields after silica gel column chromatography.
[c] 2nd run.
[d] 3rd run.
[e] Results reported by Macmillan et al.[2a]

critical role in facilitating the iminium ion hydrolysis in the catalytic cycle.[2] The anomalous results in entries 5 and 6 might be due to the inherent hydrophilic nature of the ionic liquids, which form a stronger hydrogen bond with water than the other two ionic liquids used in entries 1 and 4.

To check the influence of water on the reactivity and enantioselectivity, reactions were performed in [Bmim]OTf containing varying amounts of water and the results are shown in Table 2. When the water content in the reaction medium was increased from 5% to 10%, no dramatic change was observed (entry 2). However, when the water content was 20%, a noticeable increase of the yield (22%) was observed and the reaction proceeded with a considerable degree of enantioselectivity (*endo* product of 54% ee) (entry 3). Based upon this result, it is presumed that at least 20% of water by volume in polar ionic liquids is required for the hydrolysis of the transient iminium ion thus enabling the catalytic cycle to turn over.

To evaluate the influence of the ionic liquid on the rate of the D-A reaction, the rates in acetonitrile and [Bmim]PF$_6$ were compared. As shown in Figure 1, the reaction was significantly faster in [Bmim]PF$_6$ than in acetonitrile.

Table 2. Influence of water on the yield and enantioselectivity in reactions employing [Bmim]OTf.

Entry	Water [%][a]	*Endo* ee [%]	*Endo*:*exo*	Yield [%][b]
1	5	0	17:1	7
2	10	1	17:1	7
3	20	54	18:1	22

[a] % Volume of water in the mixture.
[b] Yields after silica gel column chromatography.

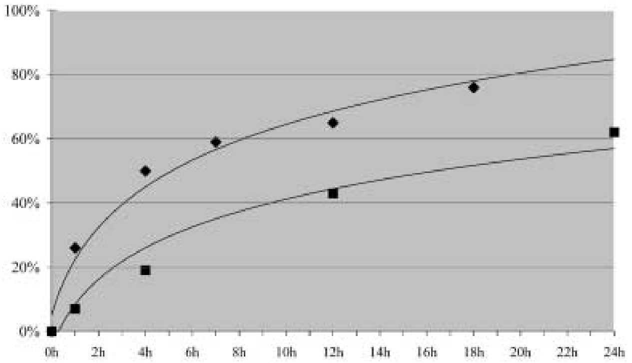


Figure 1. Comparison of the D-A reaction rates in CH_3CN (■) and [Bmin]PF$_6$ (◆) at 10 °C.

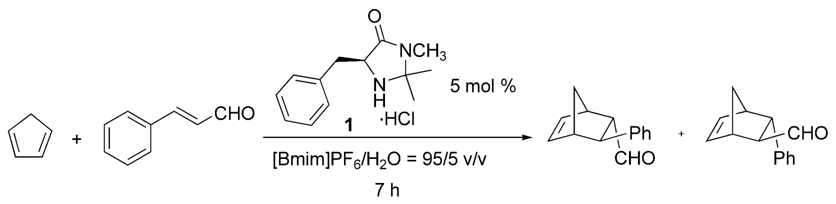
Table 3. Influence of catalyst loading on the reaction yield and enantioselectivity in [Bmim]PF$_6$ according to Scheme 1.[a]

Entry	Catalyst [mol%]	ee [%]	*Endo*:*exo*	Yield [%][b]
1	5	93	17:1	85
2	2.5	88	13:1	70
3	1	86	13:1	43
4	0	–	17:1	8

[a] Reactions were carried out at r.t. for 20 h.
[b] Yields after silica gel column chromatography.

The influence of the catalyst amount in [Bmim]PF$_6$ towards the D-A reaction was also examined and the results are shown in Table 3. As the amount of the catalyst was decreased, the diastereoselectivity and the enantioselectivity of the Diels–Alder reactions deteriorated slightly and a more significant drop in yield was observed (entries 2 and 3). In the absence of the organic catalyst **1**, an 8% yield of the D-A products was obtained in 17:1 diastereoselectivity (entry 4).

Another set of substrates was examined to investigate the scope of the D-A reactions in ionic liquids. When cyclopentadiene and cinnamaldehyde were employed under the same reaction conditions, the enantioselectivity and *endo*/*exo* diastereoselectivity (*endo* 82% ee, *exo* 76% ee, *endo:exo* = 1:1.1) were somewhat lower than the values obtained in non-ionic solvents (*endo* 93% ee, *exo* 93% ee, *endo:exo* = 1:1.3)[2a] (Table 4, entry 1). When the organic catalyst **1** was recycled, in the 4th



Scheme 2.

Table 4. Results of imidazolidin-4-one (**1**) catalyzed D-A reactions between cyclopentadiene and cinnamaldehyde in [Bmim]PF_6.

Entry	ee (*endo*, *exo*) [%][a]	*Endo*:*exo*[a]	Yield [%][b]
1	82, 76	1:1.1	99
2[c]	86, 80	1:1.1	98
3[d]	78, 77	1:1.3	91
4[e]	57, 56	1:1.1	77

[a] ee values and *endo/exo* ratios were determined though GLC using a J & W cyclodex β column. GC Conditions: HP 6890; constant rate 1.5 mL/min, oven temp. 60 °C to 150 °C by 1 °C/min and 30 min at 150 °C, *exo* 101.7 min, 104.6 min; *endo* 103.7 min, 105.6 min.

[b] Yields after silica gel column chromatography.

repetition the enantioselectivity and yield dropped to a considerable degree.

In conclusion, we have investigated imidazolidin-4-one (**1**) catalyzed asymmetric D-A reactions in ionic liquids, and found that reactions in hydrophobic ionic liquids such as [Bmim]PF_6 and [Bmim]SbF_6 proceeded at a faster rate than in acetonitrile. Hydrophilic ionic liquids were found to be poor solvents for the D-A reactions, however, addition of more water enhanced the yields and enantioselectivity. The ionic liquid ([Bmim]PF_6) containing the organic catalyst was recycled in subsequent reactions without significant decrease in yields and enantioselectivities of the Diels–Alder reactions. Further studies on the optimization and the extension of this methodology to other asymmetric reactions are currently in progress.

Experimental Section

General Procedure for Amine-Catalyzed D-A Reaction in Ionic Liquid

To a solution of catalyst 1 (14 mg, 0.053 mmol) in ionic liquid (1.0 mL) containing H_2O (52 μL) was added acrolein (210 μL, 3.15 mmol). After the mixture had been stirred for 3 min, cyclohexadiene (100 μL, 1.05 mmol) was added in one portion. When the reaction was complete, the product was extracted with Et_2O, concentrated under reduced pressure, and purified on a chromatographic column (silica gel), and the ionic liquid was reused for the next reaction.

Acknowledgements

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