Research Article

Ionic-Liquid-Mediated MacMillan's Catalyst for Diels-Alder Reaction

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Ionic liquids were used to enhance as well as recycle the MacMillan's catalyst **1** for the Diels-Alder reaction. Using our developed protocol, Diels-Alder adducts were obtained in good yields and selectivities along the 6 times recycling of MacMillan's imidazolidinone catalyst **1**. Synthesis of steroid **4** is the major outcome of our developed protocol.

1. Introduction

Over the past decade, the Diels-Alder reaction is found highly applicable as the most powerful organic reaction in area of chemical synthesis [1–5]. In recent times much interest has been developed for the synthesis of highly efficient organocatalysts for a variety of organic transformations [6–10]. MacMillan and coworkers have initially reported (5S)-2,2,3-trimethyl-5-phenylmethyl-4-imidazolidinone monohydrochloride catalyst (MacMillan's imidazolidinone catalyst **1**), as a promising organocatalyst for the Diels-Alder reaction *via* a LUMO-lowering activation reaction mechanism [8, 11, 12]. Although the MacMillan's imidazolidinone catalyst **1** was found highly active in terms of yield and selectivity but still this catalyst has suffered from various drawbacks like the need for high catalyst loading, requirement of polar solvents, catalyst recycling, and so forth [13–17]. To avoid such drawbacks and to make the MacMillan's imidazolidinone catalyst **1** more convenient for Diels-Alder reaction, various approaches have been reported from different groups to support this MacMillan's imidazolidinone catalyst **1** *via* ionic liquids [13], polymethylhydrosiloxane polymer [14], Montmorillonite [15], and so forth. The supported organocatalysts seem particularly attractive because they offer homogeneous/heterogeneous reactions medium, high selectivity, low catalyst loading, catalyst recycling, and so forth, but this supported system also carries various demerits

like requirement of costly starting materials, long preparation steps (3–4 steps), tedious work-up procedures, and lack of catalyst recycling.

In various reports, ionic liquids were also identified as an alternative solvent to immobilize not only to MacMillan's imidazolidinone catalyst **1** for the Diels Alder reaction [16, 17] but some organocatalysts too for various useful organic transformations. Recycling of catalytic, low catalyst loading and option to avoid the use of polar solvents are the major outcomes of ionic-liquid-mediated catalysis [17]. Considering the above facts and merits of ionic liquid immobilized organocatalysis, we initiated our work in the area of ionic liquid immobilized MacMillan's imidazolidinone catalyst **1** for Diels-Alder reaction.

2. Experimental Procedure

All the chemicals were purchased from Sigma Aldrich, Acros, or SD fine chemicals, and all the experiments were carried out under nitrogen unless noted. NMR spectra were recorded on standard Bruker300WB spectrometer with an Avance console at 300 and 75 MHz for ^1H and ^{13}C NMR, respectively. Enantiomeric excesses were determined by chiral-phase HPLC: Waters 600E System Controller and Waters 996 Photodiode Array Detector Column with Chiralcel AS-H, Chiralcel OD-H, and Chiralcel AD-H column from Daicel

TABLE 1: Screening of different ionic liquids for MacMillan's imidazolidinone catalyst **1** catalysed Diels-Alder reaction between cyclohexene **1** and acrolein **2**.

Entry	Ionic liquid	Ionic liquid amount (in mmol)	Yield ^a (%)	<i>endo</i> : <i>exo</i> ^b	ee (%) ^c
(1)	[bmim][Cl]	0.05	64	1.5 : 1	65
		0.10	63	1.6 : 1	67
(2)	[bmim][PF ₆]	0.05	68	1.8 : 1	71
		0.10	70	2.2 : 1	74
(3)	[bmim][NTf ₂]	0.01	65	3 : 1	71
		0.02	68	3.5 : 1	78
		0.05	84	4.2 : 1	88
		0.10	91	5.6 : 1	92
		0.5	94	19 : 1	95
		1	92	96 : 1	91
(4)	MeOH/H ₂ O	0.95 mL : 0.05 mL	8	2.3 : 1	87
(5)	CH ₃ CN/H ₂ O	0.95 mL : 0.05 mL	84	2.3 : 1	90

^aIsolated yield, ^b*endo* : *exo* ratio was determined by ¹H NMR, ^cee% was determined by HPLC, ^d1 mL MeOH/H₂O system.

SCHEME 1: Ionic-liquid-mediated Diels-Alder reaction.

Chemical Industries Ltd., eluting with *n*-hexane and 2-propanol.

2.1. General Methods for Ionic Liquid Mediated Diels-Alder Reaction. Ionic liquid (0.5 mmol) or MeOH (0.95 mL)/Water (0.05 mL) or CH₃CN (0.95 mL)/water (0.05 mL), MacMillan's imidazolidinone catalyst **1** (0.02 mmol), cyclohexadiene **1** (0.5 mmol), acrolein **2** (2.5 mmol), and CF₃COOH (5 mol%) were allowed to stir for 12 h at room temperature. The corresponding reaction product from the well-dried reaction mass (dried under high vacuum at 50 °C for 1 hour in order to remove all volatile impurities) was extracted with ether (5 × 2 mL). Combined organic layers were dried over high vacuum, and the reaction mixture was further purified by column chromatography.

2.2. Recycling of the Catalytic System. The recycling experiments were carried out using [bmim][NTf₂] (0.5 mmol) and MacMillan's imidazolidinone catalyst **1** (0.02 mmol) for the model Diels-Alder reaction between cyclohexadiene **1** (0.5 mmol), acrolein **2** (2.5 mmol), and CF₃COOH (5 mol%) at RT for 12 h. After completion of the first run, the reaction product was isolated with simple ether washing. The remaining reaction mass was allowed to dry under high vacuum at 50 °C for 1 hour in order to remove all the volatile impurities

from the reaction mass and then the reaction mass (mixture of [bmim][NTf₂]/(5*S*)-2,2,3-trimethyl-5-phenylmethyl-4-imidazolidinone monohydrochloride) subjected to Diels-Alder reaction.

2.3. Synthesis of Steroid 4. Ionic liquid (0.5 mmol), MacMillan's imidazolidinone catalyst **1** (0.02 mmol), 7-methoxy-4-vinyl-1,2-dihydronaphthalene **1** (0.5 mmol), 2-Bromo-propenal **2** (2.5 mmol), and CF₃COOH (5 mol%) were allowed to stir for 12 h at room temperature. The corresponding reaction product from the well-dried reaction mass (dried under high vacuum at 50 °C for 1 hour in order to remove all the volatile impurities) was extracted with hexane:ethylacetate (20% mixture) (5 × 2 mL). Combined organic layers were dried over high vacuum, and the reaction mixture was further purified by column chromatography.

3. Result and Discussion

As reported in Table 1, three different types of ionic liquid like [bmim][Cl], [bmim][PF₆], and [bmim][NTf₂] were tested as a reaction medium for MacMillan's imidazolidinone catalyst **1** to catalyzed our model Diels-Alder reaction between cyclohexadiene **1** and acrolein **2** (Scheme 1 and Table 1, Entry 1–3). As shown in Table 1 at room temperature our

TABLE 2: Screening of Acid cocatalysts for [bmim][NTf₂] mediated Diels-Alder reaction with MacMillan's imidazolidinone catalyst **1**.

Entry	Acid co-catalyst	Yield ^a (%)	<i>endo</i> : <i>exo</i> ^b	ee ^c (%)
(1)	CF ₃ COOH	98	19:1	97
(2)	CH ₃ COOH	90	19:1	95
(3)	TfOH	95	18:1	94
(4)	<i>p</i> -TSA	96	18:1	92
(5)	Cl ₃ COOH	20	17:1	87
(6)	HCl	75	17:1	92
(7)	Ph-COOH	76	17:1	89

^aIsolated yield, ^b*endo*:*exo* ratio was determined by ¹HNMR, ^cee% was determined by HPLC.

SCHEME 2: [bmim][NTf₂] mediated Diels-Alder reaction with MacMillan's imidazolidinone catalyst **1**.

model Diels-Alder reaction enjoyed a lot with [bmim][NTf₂] (0.5 mmol) mediated catalyst **1** and offered the desired product **3** with high yield (82% yield) and selectivity (24:1 *endo*:*exo*, 94% ee). Comparatively, lower yields and selectivities were obtained for the same model reaction (Table 1, Entry 1, 2) with both [bmim][Cl] and [bmim][PF₆], as the MacMillan's imidazolidinone catalyst **1** was almost insoluble in both [bmim][Cl] and [bmim][PF₆]. Instead of ionic liquids, MacMillan's imidazolidinone catalyst **1** was also treated with MeOH/H₂O solvent system for same model Diels-Alder reaction. The corresponding product **3** was obtained in an acceptable yield (68%) along with 2.3:1 *endo*:*exo* ratio and 72% ee.

Various acids were also tested to improve the yield and selectivity of Diels-Alder reaction (Table 2 and Scheme 2). The utilization of CF₃COOH, TfOH, CH₃COOH and *p*-TSA led to relatively good yields and selectivity for [bmim][NTf₂] mediated Diels-Alder reaction with MacMillan's imidazolidinone catalyst **1**. In contrast, relatively high yield (98%) and excellent enantioselectivity (97%) with good *endo*:*exo* ratio were obtained (>19:1) and produced when CF₃COOH, was selected. Thus, CF₃COOH was identified as the optimal acidic cocatalyst.

Having the optimized reaction condition for Diels-Alder reaction by utilizing MacMillan's imidazolidinone catalyst **1** and [bmim][NTf₂] as the reaction solvent, we subsequently applied the optimized reaction condition to various substrates to explore the generality of the reaction system. As summarized in Table 3, entry 1–10, The Diels-Alder reaction involving various α,β -unsaturated aldehydes and different cyclic dienes proceeded efficiently in the presence of MacMillan's imidazolidinone catalyst **1** in [bmim][NTf₂],

loading the corresponding products in good yield with excellent enantioselectivities. The comparable ee's were obtained in contrast to the use of imidazolidinone as a reaction catalyst which was previously reported by MacMillan and coworkers. For example, when *trans*-cinnamaldehyde was used as substrate, the utilization of MacMillan's imidazolidinone catalyst **1** affords the desired product in 93% ee. Likewise, by employing [bmim][NTf₂] reaction solvent for MacMillan's imidazolidinone catalyst **1** in the Diels-Alder reaction almost similar results were achieved as well (Table 3, entry 10) [11].

With the success of the above reactions, we embark to test our modified protocol for the synthesis of steroids *via* Diels-Alder reaction, using complex open-chain diene and 7-methoxy-4-vinyl-1,2-dihydronaphthalene (Scheme 3) [18]. The cycloadduct **4** was obtained with a good enantiomeric excess (80%) and chemical yield (70%).

Next, we continued our study by exploring the recycling of MacMillan's imidazolidinone catalyst **1** for our model Diels-Alder reaction using [bmim][NTf₂] as solvent (Scheme 4); after completion, the reaction product was extracted with ether. The MacMillan's imidazolidinone catalyst **1**/[bmim][NTf₂] residue was dried under high vacuum at 50°C for 1 hour to facilitate the removal of volatile remnants prior to subsequent addition of the cyclohexadiene and acrolein in the next cycle (Scheme 4). The results are shown in Table 4.

It was noteworthy that the MacMillan's imidazolidinone catalyst **1** can be recycled for seven successive runs with comparable enantioselectivities and yields without loss of catalytic activity. Moreover, the extraction process was operationally simple, which offers easy product separation.

TABLE 3: [bmim][NTf₂] mediated MacMillan's imidazolidinone catalyst **1** catalysed, Diels-Alder reaction of various dienes with dienophiles.

Entry	Diene	Dienophiles	Yield ^a (%)	<i>endo:exo</i> ^b	ee (%) ^c
(1)			98	19 : 1	97
(2)			90	1.5 : 1	92
(3)		n-Pr	97	3 : 1	96
(4)		Ph	85	1.5 : 1	97
(5)			95	49 : 1	98
(6)		Br	98	99 : 1	95
(7)		Br	99	1.1 : 1	78
(8)		Cl	88	1.1 : 1	88
(9)		n-Bu	90	1 : 1	89
(10)			99	1.2 : 1	92

^aIsolated yield, ^b*endo:exo* ratio was determined by ¹H NMR crude reaction product, ^cee% or was determined by HPLC or GC analysis.

SCHEME 3: Synthesis of steroids using the developed methodology.

SCHEME 4: Recycling experiment for MacMillan's imidazolidinone catalyst **1**.

TABLE 4: Recyclability of MacMillan's imidazolidinone catalyst **1**/[bmim][NTf₂] system.

No. of cycles	Yield (%) ^a	<i>endo</i> : <i>exo</i> ^b	ee (%) ^c
(1)	98	19 : 1	97
(2)	97	19 : 1	97
(3)	94	19 : 1	97
(4)	92	19 : 1	96
(5)	90	17 : 1	97
(6)	92	17 : 1	95

^aIsolated yield, ^b*endo* : *exo* ratio was determined by ¹HNMR crude reaction product, ^cee% or was determined by HPLC.

4. Conclusion

In conclusion, we developed a modified and improved protocol for MacMillan's imidazolidinone catalyst **1** Diels-Alder reaction using ionic liquid as the reaction media and we successfully obtained enantiomerically enriched Diels-Alder adducts with high yields and selectivities. The main features of this reaction are as follows: (1) the procedure is operationally simple; (2) the cycloaddition adducts were obtained in good yield and selectivities for variety various dienes with dienophiles resulted in good yields and high selectivity. (3) We obtained the cycloaddition adduct with low catalyst loading (0.02 mmol instead of 0.036 mmol); (4) the catalyst can be recycled up to six cycles with comparable yields and selectivities. (5) Our modified protocol was found active in the synthesis of a tedious steroid **4** molecule.

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