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Direct asymmetric aza Diels–Alder reaction catalyzed by chiral 2-pyrrolidinecarboxylic acid ionic liquid

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ABSTRACT

The utility of [EMIm][Pro] as an efficient catalyst for the one-pot direct asymmetric aza Diels–Alder reaction has been developed. A set of cyclic α,β-unsaturated ketones have been explored in up to 93% yield with up to >99/1 dr and >99% ee. Moreover, the catalytic system can be recycled and reused for six times without any significant loss of catalytic activity.

1. Introduction

The synthesis of enantiomerically enriched nitrogen-containing heterocylic compounds is of significantly important in organic synthesis and in the chemical industry. The asymmetric aza Diels–Alder reaction has emerged as a valuable synthetic methodology to construct six-membered nitrogen-containing rings for complex molecules such as alkaloids, azasugars and piperidine derivatives [1,2]. Over the past decades, Lewis acids [3–5], Brønsted acids [6,7] and rare metal salts [8,9] have been investigated as the catalysts for aza Diels–Alder reaction. Only a few examples have been reported concerning the direct asymmetric aza Diels–Alder reaction catalyzed by organocatalysts [10,11].

In recent years, a growing number of chiral ionic liquids have been considered as intensively promising green reaction media [12–17], not only due to their favorable properties including reusability, nonvolatile nature and high thermal stability but also due to their unique selectivity and reactivity. Furthermore, ionic liquids have currently been widely employed either as catalysts or solvents for a vast majority of examples [12–20], especially the Diels–Alder reactions [20–30]. Recently, Giang Vo-Thanh and coworkers reported that a novel chiral ammonium and imidazolium-based ionic liquid could catalyze the aza Diels–Alder reaction [27–29]. However, there is no report that ionic liquid catalysts accompanying chiral anion as a stereocontrolling moiety for the direct asymmetric aza Diels–Alder reaction. In view of a myriad of examples employing proline and its derivatives as the successful organocatalysts [31,32] and an increasing number of reactions catalyzed by ionic liquids, we proposed the combination of proline as an effective anion module with ionic liquids in promoting enantioselective aza Diels–Alder reaction. Previously, we have reported that [EMIm][Pro] (**1**) ionic liquid using (S)-proline as anion (1-ethyl-3-methylimidazolium-(S)-2-pyrrolidinecarboxylic acid salt) could facilitate the asymmetric Michael addition reaction via enamine mechanism [33]. This chiral ionic liquid is readily available from simple and inexpensive starting materials and we routinely prepare it on large scale.

In light of these facts, here we report the application of [EMIm][Pro] (**1**) as an effective catalyst for the direct asymmetric aza Diels–Alder reaction. This direct asymmetric aza Diels–Alder reaction induced by the chiral anion ionic liquid that may greatly enlarge the extension of design and application of chiral ionic liquids in organic synthesis.

2. Experimental

2.1. General

^{1}H and ^{13}C NMR spectra were measured on either a Bruker-DPX 400 or AV-400 spectrometer with tetramethylsilane (TMS) as the internal standard. HPLC analysis was performed on Shimadzu CTO-10AS by using a Chiralpak AD-H or OD-H column purchased from Daicel Chemical Industries. All yields refer to isolated products after purification. All chemicals (AR grade), unless otherwise stated, were commercially available and used without further purification.

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2.2. Preparation of amino acid ionic liquid [EMIm][Pro] **1**

[EMIm][Pro] could be easily synthesized from commercially available chemicals in 80% overall yield according to the reference (Scheme 1) [34]. ^{1}H NMR (300 MHz, DMSO-d_6) δ (ppm): 9.67 (s, 1H), 7.87 (s, 1H), 7.79 (s, 1H), 4.25 (q, J = 10.17 Hz, 2H), 3.90 (s, 3H), 3.32 (broad, 1H), 2.97–3.05 (m, 1H), 2.72 (broad, 1H), 1.83–1.90 (m, 1H), 1.69–1.74 (m, 1H), 1.53–1.59 (m, 2H), 1.42 (t, J = 7.30, 7.30 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ (ppm): 176.0, 136.9, 123.5, 121.9, 61.8, 46.4, 44.0, 35.5, 30.6, 25.3, 15.1. ESI-MS: m/z $C_6H_{11}N_2^+$ (M^+) Calc. 111.09. Found: 111.21; $C_5H_8NO_2^-$ (M^-), Calc. 114.06, Found: 114.21. $[\alpha]_D^{25}$ = +51.0 (c1, MeOH).

2.3. Typical procedure for one-pot asymmetric Diels–Alder reaction

A 25 mL round-bottomed flask was charged with *p*-anisidine (0.3 mmol), aqueous formaldehyde (0.1 mmol, 36 vol.% aqueous solution), **1** (30 mol%) and CH_2Cl_2 (0.5 mL). After being stirred vigorously at room temperature until the imine was formed as monitored by TLC, 2-cyclohexen-1-one (0.5 mmol) was added to the mixture. When the reaction was finished, the reaction mixture was worked up by addition of saturated ammonium chloride, and extracted with AcOEt. The organic layers were washed with water, dried over Na_2SO_4, filtered, concentrated under vacuum and purified by flash column chromatography to afford the desired aza Diels–Alder product.

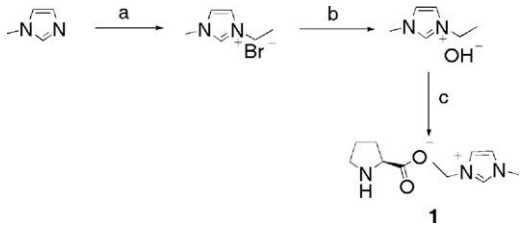
2.4. Reusability of the catalyst

A catalytic amount of **1** (30 mol%) was added to a solution of *p*-anisidine (0.3 mmol), aqueous formaldehyde (0.1 mmol, 36 vol.% aqueous solution) at room temperature. The progress of the reactions was monitored by TLC. After the imine was formed, Ketone **2b** was added to the mixture. In the end, the reaction was recovered directly for the next cycle after full extraction of the product three times with 5 mL ethyl ether per extraction and drying *in vacuo*.

3. Results and discussion

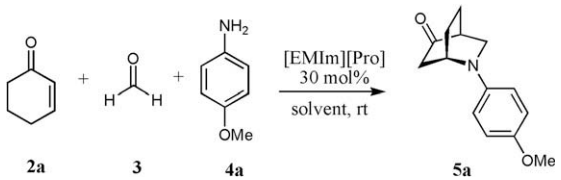
The initial investigation was carried out among 2-cyclohexen-1-one (**2a**), aqueous formaldehyde (**3**) and *p*-anisidine (**4a**) in DMSO at room temperature in the presence of 30 mol% **1**. To our delight, the reaction proceeded readily, favoring the *endo* product **5a** with 78% ee and 67/33 dr (Table 1, entry 3). In order to increase the yield and enantiomeric excess, we screened a variety of solvents. When the reaction was conducted in CH_2Cl_2, the desired product **5a** was isolated in higher yield (67%) with 94% ee and 70/30 dr than its counterparts (Table 1, entry 1).

To optimize the reaction condition, the proportion of reactants was examined. When the ratio of **2a**/**3**/**4** was 5:1:3, the highest yield (75%) were obtained (Table 2, entry 3). This constitutes a significant improvement of yields as compared to proline-catalyzed direct aza Diels–Alder reaction [10] (30% yield). Lowering the catalyst loading to 20 mol% and 10 mol% respectively resulted in sharply decreasing dr and ee values (Table 2, entries 8–9).



Scheme 1. Conditions: (a) CH_3CH_2Br, $CH_3CO_2C_2H_5$, △, 80%; (b) 201 × 7 styrene-DVB; (c) proline, 80%.

Table 1
Solvent screen for the direct asymmetric aza Diels–Alder reaction.[a]



2a 3 4a 5a

Entry	Solvent	Yield[b] (%)	dr (endo/exo) [c]	ee (%)[d]
1	CH_2Cl_2	67	70/30	94
2	CH_3CN	45	51/49	51
3	DMSO	57	67/33	78
4	THF	47	55/45	53
5	NMP	58	57/43	85
6	Dixone	40	68/32	42
7	DMF	60	52/48	68
8	[BMIm][BF_4]	56	56/43	63
9	$CHCl_3$	54	66/34	74
10	$ClCH_2CH_2Cl$	51	53/47	11
11	Toluene	52	62/38	24
12	MeOH	30	55/45	24
13	*t*-BuOH	46	61/39	51

[a] The reaction was performed using 2-cyclohexen-1-one (0.5 mmol), aqueous formaldehyde (0.1 mmol, 36 vol.% aqueous solution), *p*-anisidine (0.2 mmol) and catalyst (30 mol%) in a solvent (0.5 mL) for 15 h.
[b] Yield of product isolated by column chromatography.
[c] Determined by ^{1}H NMR analysis.
[d] The ee of the endo isomer was determined by chiral-phase HPLC using a Daicel Chiralpak OD-H column.

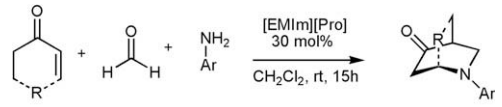
Table 2
Optimization of the effect of the ratio of reactants for the direct asymmetric aza Diels–Alder reaction.

Entry	2a/3/4a	Yield[a] (%)	dr (endo/exo)[b]	ee (%)[c]
1	5:1:2	67	70/30	94
2	5:1:2.5	68	71/29	91
3	5:1:3	75	84/16	98
4	2:1:3	40	68/32	62
5	3:1:3	48	68/32	63
6	4:1:3	50	81/19	81
7	6:1:3	48	82/18	76
8[d]	5:1:3	70	66/34	52
9[e]	5:1:3	66	58/42	28

[a] Yield of product isolated by column chromatography.
[b] Determined by ^{1}H NMR analysis.
[c] The ee of the endo isomer was determined by chiral-phase HPLC using a Daicel Chiralpak OD-H column.
[d] 20% catalyst.
[e] 10% catalyst.

Having achieved the optimized reaction conditions, we extended the scope of [EMIm][Pro] catalyzed direct asymmetric aza Diels–Alder reaction on a series of olefine ketones and the results are summarized in Table 3. In most cases, the reactions proceeded efficiently to provide exclusively the *endo* products **5** in modest to good yields (40–93%) with high enantioselectivities (92–>99%) and diastereoselectivities range from 84/16 to >99/1. However, only trace amounts of the corresponding product **5l** was observed in the reaction (Table 3, entry 12). It should be noted that the aza Diels–Alder reactions with aniline and anilines bearing an electron-donating substituent at the *para* position formed the *endo*-isomers in higher yields in comparison to the halogenated anilines. Surprisingly, when the direct enantioselective aza Diels–Alder reaction was treated with preformed imines under the same

Table 3
One-pot asymmetric aza Diels–Alder reactions catalyzed by [EMIm][Pro].[a]



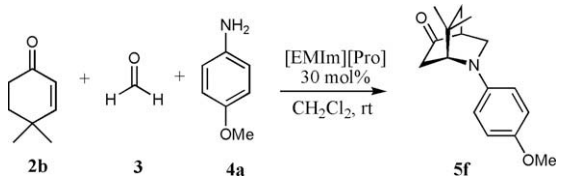
2 3 4 5

Entry	Ketone	Ar	Product	Yield[b] (%)	dr (endo/exo)[c]	ee (%)[d]
1	2a	PMP	5a	75	84/16	98
2	2a	Ph	5b	65	94/6	96
3	2a	4-FC_6H_4	5c	51	>99/1	99
4	2a	4-BrC_6H_4	5d	40	>99/1	94
5	2a	4-ClC_6H_4	5e	57	>99/1	98
6	2b	PMP	5f	72	>99/1	>99
7	2b	Ph	5g	89	>99/1	98
8	2b	4-FC_6H_4	5h	58	>99/1	99
9	2b	4-ClC_6H_4	5i	90	>99/1	92
10	2c	PMP	5j	85	99/1	98
11	2c	Ph	5k	93	98:2	99
12	2d	PMP	5l	<5%	n.d.	n.d.

[a] Conditions: see typical procedure.
[b] Yield of product isolated by column chromatography.
[c] Determined by ^1H NMR analysis and HPLC.
[d] The ee of the endo isomer was determined by chiral-phase HPLC using a Daicel Chiralpak OD-H column.

conditions, no expected product was observed after seven days. After added the equivalent amount of water, the reaction could occur smoothly. However, the addition of excess water to the reaction was deleterious to both the diastereo- and the enantioselectivities of the Diels–Alder products. Thus, the amount of water of aqueous formaldehyde proved to be favorable for enhancing the reaction rate.

Table 4
Recycling of the catalytic system for asymmetric Diels–Alder reaction.[a]



2b 3 4a 5f

Run	Yield (%)[b]	dr (endo/exo)[c]	ee (%)[d]
1	72	>99/1	>99
2	71	>99/1	>99
3	71	>99/1	>99
4	70	99/1	98
5	71	98/2	97
6	70	98/2	95

[a] The reaction was performed using ketone **2b** (0.5 mmol), aqueous formaldehyde (0.1 mmol, 36 vol.% aqueous solution), *p*-anisidine (0.3 mmol) and catalyst (30 mol%) in CH_2Cl_2 (0.5 mL) for 15 h.
[b] Yield of product isolated by column chromatography.
[c] Determined by ^1H NMR analysis and HPLC.
[d] The ee of the endo isomer was determined by chiral-phase HPLC using a Daicel Chiralpak OD-H column.

The absolute configurations of the aza Diels–Alder products have been determined by chiral-phase HPLC analysis and by comparison with the literature [10]. Next, we continued to explore the recyclability of **1** which is important from the viewpoint of environment friendly and cost-effectiveness. We carried out the model study by using ketone **2b** and *p*-anisidine in the presence of 30 mol% **1** (Table 4). After the reaction was completed, the mixture was easily extracted to afford the adduct, avoiding the need to recourse to stringent anhydrous conditions. It can be reused for six successive cycles with comparable enantioselectivities and yields without significant loss of catalytic activity.

4. Conclusion

In summary, we have demonstrated the first direct asymmetric aza Diels–Alder reaction catalyzed by [EMIm][Pro] **1** ionic liquid. The method has proved to be practical and convenient, furnishing the resulting products in modest to good yields with excellent enantioselectivities and diastereomeric ratios. Additionally, this catalyst is easily prepared from rather inexpensive starting materials. The catalyst can be recovered and reused up to six times through a simple extraction protocol. Further research and application of this catalyst to other reactions is underway.

Acknowledgments

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