Organocatalysts wrapped around by poly(ethylene glycol)s (PEGs): a unique host–guest system for asymmetric Michael addition reactions†

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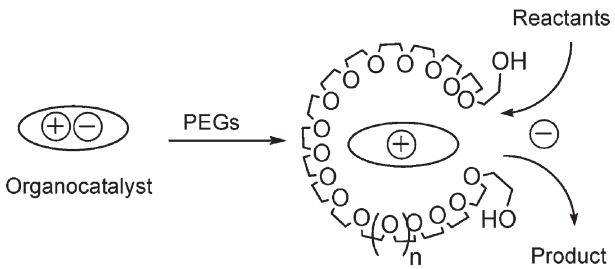
Asymmetric Michael addition reactions of unmodified ketones to nitroalkenes were performed in PEGs catalyzed by novel pyrrolidinyl-thioimidazolium salts to give products in up to 97% yield and 99% enantioselectivity; ESI mass spectrometric detection for the first time gave evidence of the presence of the PEG–organocatalyst host–guest complex.

Recently, a significant advantage of organocatalysis in mimicking enzyme function in organic synthesis has been exhibited.[1] In particular, proline-based compounds have become attractively powerful catalysts for asymmetric Michael addition of carbonyl compounds to nitroalkenes, which have been studied extensively due to their broad application.[2] In this process the configuration of the final Michael adducts is generally controlled by steric hindrance or by hydrogen-bond donors of the substituent α to the pyrrolidine nitrogen.[3] On the other hand, it is also important to recognize the functions and potential advantages associated with the stereoelectronic effect of the solvent, which can provide a reaction circumstance in favor of desired enamine configurations and transition state stabilities. Therefore, development of a strategy to improve organocatalytic performance in a favorable solvent system is desirable. In this communication, we wish to present a unique catalytic system for the Michael addition reaction using chiral ionic organocatalysts in poly(ethylene glycol) (PEG) media.

Liquid PEGs, as novel green solvents, have been attracting increasing interest. Moreover, PEGs have especially been used as phase-transfer catalysts for catalytic reactions since the "crown-like" poly(ethylene oxide) chains can form complexes with metal cations.[4,5] Based on the metal cation coordination ability of PEGs, we anticipated that an appropriate combination of PEGs and organocatalysts, whose catalytic reactive unit have a positively-charged group, might make it possible to form a unique host–guest complex of PEG–organocatalyst and thus to develop an alternative catalytic system for asymmetric organocatalysis (Scheme 1).

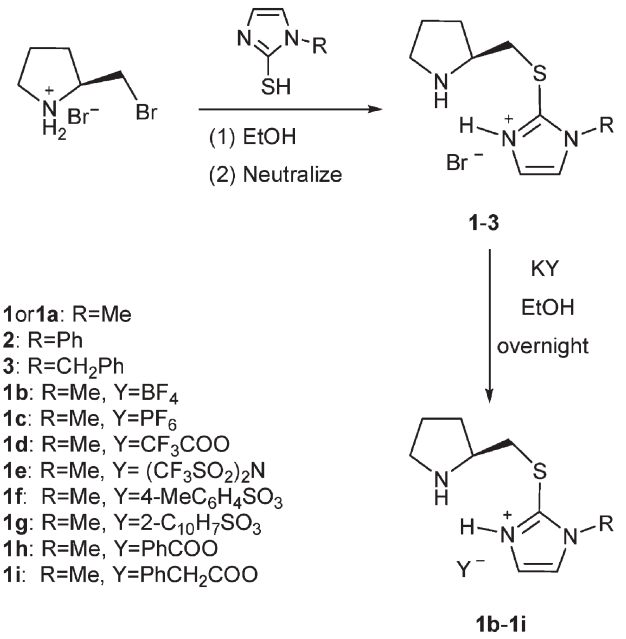
The organocatalysts investigated herein were novel pyrrolidinyl-thioimidazolium salts **1**–**3**, which were designed and readily synthesized by treating 2-mercapto-1-methylimidazole or analogs with (*S*)-(+)-2-bromomethylpyrrolidine hydrobromide. Anion metathesis of **1a** with KY afforded **1b**–**1i** (Scheme 2). The key



Scheme 1 Proposed catalytic system.

precursor (*S*)-(+)-2-bromomethylpyrrolidine hydrobromide was synthesized from commercially available L-proline according to our previous work.[6] NMR, IR, HRMS and X-ray diffraction analysis results confirmed their molecular structures (ESI‡).

The Michael addition of cyclohexanone **4** to β-nitrostyrene **5** was selected as a model reaction (Table 1). As expected, to our delight, apparent higher enantioselectivities were achieved using **1**–**3** in PEGs than in DMSO and other conventional organic solvents (entries 2–14). Moreover, PEG-800 led to a considerable rate acceleration with yields reaching 58–84% after 2–3 days (entries 12–14), while it took 6 days to reach 78–97% yields in DMSO, 77% in DMF, 91% in MeOH, 66% in THF and even less



Scheme 2 Synthesis of organocatalysts **1**–**3**.

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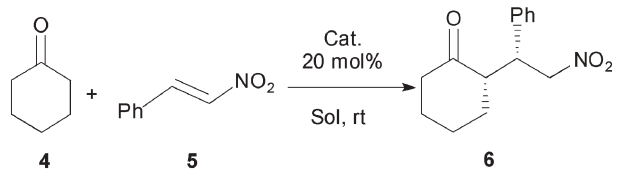
Table 1 Catalytic asymmetric Michael addition of cyclohexanone **4** to β-nitrostyrene **5** in conventional organic solvents and PEGs[a]



4 **5** **6**

Entry	Catalyst	Solvent	Time/h	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (%) (*syn*)
1	L-Proline	DMSO	10	93	91/9	32
2	**1**	DMSO	144	97	94/6	78
3	**2**	DMSO	144	84	92/8	75
4	**3**	DMSO	144	78	93/7	78
5	**1**	DMF	144	77	93/7	76
6	**1**	MeOH	144	91	90/10	73
7	**1**	THF	144	66	95/5	81
8	**1**	CH_2Cl_2	144	<10	N. D.[f]	N. D.
9	**1**	PEG-200	144	59	90/10	91
10	**1**	PEG-400	144	63	89/11	90
11	**1**	PEG-600	144	54	92/8	88
12	**1**	PEG-800	48	84	92/8	87
13	**2**	PEG-800	72	79	96/4	80
14	**3**	PEG-800	72	58	96/4	89
15	L-Proline	PEG-800	24	95	90/10	36
16	**1b**	PEG-800	48	65	97/3	96
17	**1c**	PEG-800	48	68	95/5	98
18	**1d**	PEG-800	24	90	95/5	87
19	**1e**	PEG-800	24	92	97/3	93
20	**1f**	PEG-800	36	81	96/4	91
21	**1g**[e]	PEG-800	36	80	93/7	92
22	**1h**	**PEG-800**	**12**	**95**	**97/3**	**97**
23	**1h**	DMSO	36	89	92/8	88
24	**1i**	PEG-800	36	78	91/9	92

[a] All reactions were conducted in solvent (2 mL) using **4** (1 mmol) and **5** (0.5 mmol) in the presence of 20 mol% of the catalyst at room temperature (25 °C). [b] Isolated yield. [c] Determined by GC-MS. [d] Determined by chiral HPLC analysis with CD detector (Daicel Chiralpak AS-H). [e] Anion of **1g** was β-naphthalenesulfonate. [f] N. D. = not determined.

than 10% in CH_2Cl_2 respectively (entries 2–8). In the case of the non-ionic-organocatalyst L-proline, the reaction was almost not improved in PEG-800 (entries 1 and 15). The influence effect of the anion of the catalyst on the catalytic performance in PEG-800 was also investigated. In contrast to Br^- anion, most anions screened displayed positive effects on the activity and enantioselectivity except anions BF_4^- and PF_6^-, which showed negative effects on the activity (entries 16–17). The greatest enhancement was recorded from the choice of $PhCO_2^-$ anion (**1h**), which afforded 95% yield and 97% ee after 12 h (entry 22). The present improvement of ionic organocatalyst in PEG-800 unambiguously indicated the synergistic effect of an appropriate PEG, which could provide a favorable microenvironment for the catalysis.

Electrospray ionization (ESI) mass spectrometric detection gave direct evidence supporting the presence of the presumed PEG–organocatalyst complex, from which the synergistic action of PEGs resulted.[7] As shown in Fig. 1, signals in Fig. 1(a) could be assigned to $[PEG + Na]^+$ inclusions, whereas signals in the high mass region of Fig. 1(b) (*m*/*z* 900–1400) were observed to be the result of ~175 Da shift from signals in Fig. 1(a) (*m*/*z* 720–1200) respectively. For example, ~175 Da shift from the signal at *m*/*z* 878.2 in Fig. 1(a) gave rise to the signal at *m*/*z* 1052.9 in Fig. 1(b).

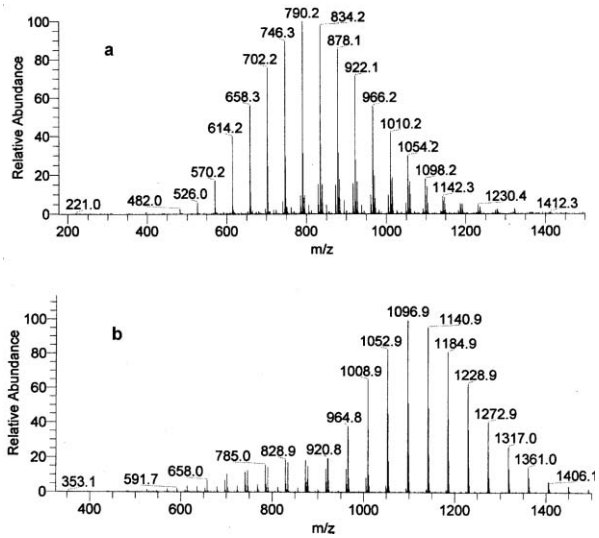


Fig. 1 ESI mass spectra: (a) PEG-800; (b) **1h**–PEG-800.

Therefore, signals in the high mass region of Fig. 1(b) could be assigned to ions of $[PEG + \mathbf{1h} - PhCO_2^-]^+$, which demonstrated that the pyrrolidinyl-thioimidazolium cation could be completely wrapped by PEG-800. In addition, it formed a 1 : 1 (molar ratio) inclusion of PEG–catalyst-cation, as no other signals were observed in a higher mass region than *m*/*z* 1400 of Fig. (1b). The obtained facts also implied that PEGs with molecular weight lower than 720 should be difficult to form stable complexes with these ionic-organocatalysts due to their shorter poly(ethylene oxide) chains, which coincided with the investigation result that such apparent peak shifting was not found for lower molecular weight PEGs such as PEG-200, PEG-400 and PEG-600.

The general utility of the novel PEG–organocatalyst system for the asymmetric transformation was examined. The results are summarized in Table 2. Various aryl nitroalkenes reacted smoothly with **4** to afford high enantioselectivities (88–99%) in the catalytic system **1h**–PEG-800 (entries 1–10). Tetrahydropyran-4-one and tetrahydrothiopyran-4-one were also suitable substrates as Michael donors (entries 11–12).

One of the noteworthy features of the present catalytic system is its reusability. As shown in Table 3, the stable unsupported **1h**–PEG-800 system could be directly reused after adduct **6** had been extracted with hexane–ether (6 : 1). Though the reaction time was prolonged gradually, the desired **6** was obtained with steady good yield, excellent enantioselectivity (94–97%) and diastereoselectivity (≥93/7) even after seven recycles.

In conclusion, we have developed novel pyrrolidinyl-thioimidazolium salts as chiral organocatalysts and described the unique host–guest complex of PEG–ionic-pyrrolidine as a highly efficient and reusable system for the direct enantioselective Michael addition of ketones to nitroalkenes. Mass spectrometry analysis results showed apparent evidence for PEGs' coordination ability to the ionic organocatalyst. The obtained facts may open new opportunities and alternatives of the PEG-mediated construction of chiral suprastructures and their intriguing prospects for asymmetric organocatalysis.

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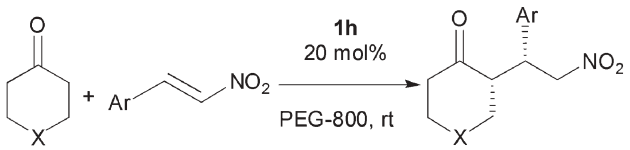
Table 2 Catalytic asymmetric Michael addition of ketones to nitroalkenes in **1h**–PEG-800 system[a]



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Entry	Adduct	X	Ar	Time/h	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee[d] (%) (*syn*)
1	**7**	C	*o*-MeO–C_6H_4	12	97	93/7	94
2	**8**	C	*m*-MeO–C_6H_4	12	90	96/4	93
3	**9**	C	*p*-MeO–C_6H_4	12	79	97/3	99
4	**10**	C	*p*-Me–C_6H_4	24	87	93/7	99
5	**11**	C	*p*-Cl–C_6H_4	12	94	93/7	98
6	**12**	C	*p*-CF_3–C_6H_4	48	90	94/6	99
7	**13**	C	*o*-NO_2–C_6H_4	48	78	96/4	88
8	**14**	C	2-Furanyl	12	96	90/10	94
9	**15**	C	2-Thioanyl	12	75	94/6	92
10	**16**	C	2-Naphthyl	12	88	90/10	96
11	**17**	O	Ph	12	87	95/5	99
12	**18**	S	Ph	12	70	96/4	90

[a] All reactions were conducted in PEG-800 (2 mL) using ketone (1 mmol) and nitroalkene (0.5 mmol) in the presence of 20 mol% **1h**. [b] Isolated yield. [c] Determined by GC-MS. [d] Determined by chiral HPLC analysis with CD detector (Daicel Chiralpak AS-H).

Table 3 Reusability of the catalytic system **1h**–PEG-800

Recycle	Time/h	Conversion (%)	Yield (%)	dr (*syn*/*anti*)	ee (%) (*syn*)
	12	100	95	97/3	97
1	12	100	95	96/4	97
2	12	99	93	96/4	97
3	18	95	90	93/7	96
4	18	90	88	94/6	97
5	24	89	83	96/4	94
6	24	85	76	98/2	96
7	24	82	75	96/4	96

Notes and references

‡ Crystal structure of **1f**'s hydrobromide salt: CCDC 639780. For crystallographic data in CIF format see DOI: 10.1039/b708525g

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7 The detected samples were mixtures of **1h** (0.025 mmol) and/or PEG-800 (20 mg) in 1 mL ethyl acetate–methanol (3 : 1).