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Asymmetric Michael addition of aldehydes to maleimides in primary amine-based aqueous ionic liquid-supported recyclable catalytic system

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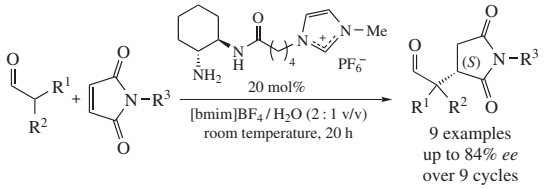
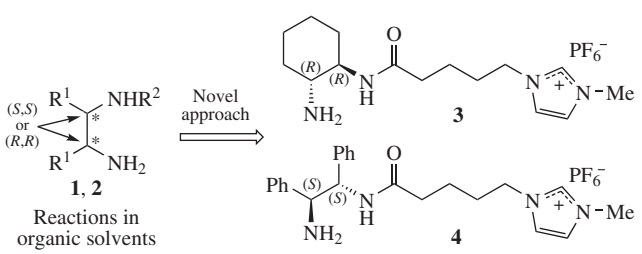
A primary amine-based aqueous ionic liquid-supported recyclable catalytic system for asymmetric Michael addition of aldehydes to maleimides has been developed. The best enantioselectivity (up to 84% *ee*) was attained at the [bmim]BF_4/water 2 : 1 (v/v) ratio.



Asymmetric organocatalysis is a mainstream of modern organic chemistry.[1] Many organocatalysts exhibit high level of stereoinduction and are tolerant to highly polar media, such as ionic liquids (ILs)[2] and water.[3] Usage of mixed IL/water solvent systems for catalytic reactions[4] is especially attractive as it allows one to significantly reduce IL consumption and, in some cases, enhance chemical yield and/or enantiomeric excess of products. Moreover, optimal combination of organocatalyst and aqueous IL may facilitate catalyst recovery and reuse in the same or similar catalytic reactions.[5]

Organocatalytic Michael reactions are extensively used for asymmetric synthesis of chiral bioactive compounds.[6] In particular, asymmetric addition of various nucleophiles to maleimides[7] in the presence of organocatalysts affords enantiomerically enriched succinimide scaffolds, which are incorporated into a number of natural compounds and pharmaceutical ingredients.[8] Furthermore, chiral succinimides are useful building blocks for asymmetric synthesis of other pharmaceutically relevant molecules bearing γ-lactam units,[9] which are applicable for treating of epilepsy,[10] HIV,[11] degenerative illnesses and depressions.[12]

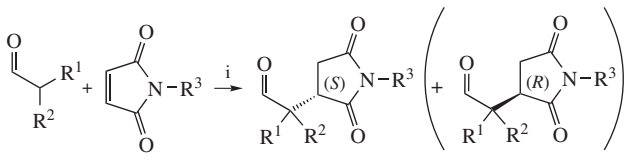
1,3-Dicarbonyl compounds,[13] 2-mercaptobenzaldehydes,[14] aza lactones,[15] and various carbonyl compounds[16] may serve as nucleophiles in these reactions. Asymmetric addition of aldehydes to maleimides is efficiently catalyzed by simple chiral *trans*-1,2-diamines **1**, **2** bearing primary amino group (Figure 1).[17] Recently, IL-supported analogues **3** and **4**[18] of these catalysts were prepared and used in asymmetric reactions of hydroxycoumarin with α,β-unsaturated ketones in an organic solvent. Herein, we report the first application of catalysts **3** and **4** for asymmetric additions of aldehydes to maleimides in IL/water solvent systems. This reaction has not been carried out in the presence of recyclable organocatalysts so far.



1a $R^1 + R^1 = (CH_2)_4$, R^2 = H
1b $R^1 + R^1 = (CH_2)_4$, R^2 = Boc
1c $R^1 + R^1 = (CH_2)_4$, R^2 = NHC(S)NHAr
2 R^1 = Ph, R^2 = H

Figure 1 Unsupported and IL-supported primary amine-derived organocatalysts.

Asymmetric addition of isobutyraldehyde **5a** to *N*-phenylmaleimide **6a** was chosen as model reaction (Scheme 1). In the presence of catalyst **3** (20 mol%), this reaction affords adduct **7a** in nearly quantitative yield with moderate enantioselectivity (60–72% *ee*) both in traditional organic solvents ($CHCl_3$ or DMF) and in IL, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) (Table 1, entries 1–3). Unlike a majority of molecular organic solvents, the IL does not leach into organic solution (Et_2O) during workup allowing convenient recycling of the catalytic system to be accomplished. Compound **4** appeared significantly less active and stereoselective catalyst under comparable conditions (entry 4). Interestingly, changing of solvent resulted in enantioselectivity switching: the product (*S*)-**7a** was



5a $R^1 = R^2$ = Me
5b R^1 = H, R^2 = Me
5c R^1 = H, $R^2 = n$-C_5H_{11}
5d R^1 = H, $R^2 = n$-C_6H_{13}
5e R^1 = H, R^2 = Bn
5f R^1 = H, R^2 = 4-$MeOC_6H_4CH_2$
5g R^1 = H, $R^2 = Pr^i$

6a R^3 = Ph
6b R^3 = Bn
6c R^3 = Cy

7a $R^1 = R^2$ = Me, R^3 = Ph
7b $R^1 = R^2$ = Me, R^3 = Bn
7c $R^1 = R^2$ = Me, R^3 = Cy
7d R^1 = H, R^2 = Me, R^3 = Bn
7e R^1 = H, $R^2 = n$-C_5H_{11}, R^3 = Bn
7f R^1 = H, $R^2 = n$-C_6H_{13}, R^3 = Bn
7g R^1 = H, R^2 = Bn, R^3 = Bn
7h R^1 = H, R^2 = 4-$MeOC_6H_4CH_2$, R^3 = Bn
7i R^1 = H, $R^2 = Pr^i$, R^3 = Bn

Scheme 1 *Reagents and conditions*: i, catalyst **3** or **4**, solvent, 20 °C, 20 h.

Table 1 Optimization of model reaction between compounds **5a** and **6a**.[a]

Entry	Catalyst (mol%)	Solvent	Conversion (%)[b]	*ee* of **7a**[a] (%) (absolute configuration)
1	**3** (20)	$CHCl_3$	99	68 (*R*)
2	**3** (20)	DMF	99	72 (*S*)
3	**3** (20)	[bmim]BF_4	99	60 (*S*)
4	**4** (20)	DMF	34	28 (*R*)
5	**3** (20)	DMF / H_2O (2 : 1)	99	76 (*S*)
6	**3** (20)	[bmim]BF_4/H_2O (95 : 5 v/v)	99	76 (*S*)
7	**3** (20)	[bmim]BF_4/H_2O (80 : 20 v/v)	99	78 (*S*)
8	**3** (20)	[bmim]BF_4/H_2O (67 : 33 v/v)	99	84 (*S*)
9	**3** (20)	[bmim]BF_4/H_2O (50 : 50 v/v)	99	80 (*S*)
10	**3** (20)	[bmim]BF_4/H_2O (33 : 67 v/v)	99	75 (*S*)
11	**3** (20)	[bmim]BF_4/H_2O (20 : 80 v/v)	99	64 (*S*)
12	**3** (20)	H_2O	99	25 (S)
13[d]	**3** (20)	[bmim]BF_4	12	60 (*S*)
14[d]	**3** (20)	[bmim]BF_4/H_2O (95 : 5 v/v)	28	75 (*S*)
15[d]	**3** (20)	[bmim]BF_4/H_2O (80 : 20 v/v)	46	78 (*S*)
16[d]	**3** (20)	[bmim]BF_4/H_2O (67 : 33 v/v)	68	84 (*S*)
17	**3** (15)	[bmim]BF_4/H_2O (67 : 33 v/v)	99	80 (*S*)
18	**3** (10)	[bmim]BF_4/H_2O (67 : 33 v/v)	99	82 (*S*)
19	**3** (5)	[bmim]BF_4/H_2O (67 : 33 v/v)	20	80 (*S*)

[a]The reactions were carried out with isobutyraldehyde **5a** (354 μmol), *N*-phenylmaleimide **6a** (118 μmol) and organocatalyst **3** or **4** in the specified solvent (300 μl) at room temperature for 20 h. [b]Determined by ^{1}H NMR spectroscopic analysis of the crude product. [c]Determined by HPLC (Chiralpak OD-H). [d]The reactions were carried out for 6 h.

formed in DMF or [bmim]BF_4 whereas (*R*)-**7a** was generated in $CHCl_3$ (similar stereoswitching was reported[17(a)] for catalyst **1b**).

Addition of water improved enantioselectivity, this effect was more pronounced in aqueous IL medium (entries 5, 6 *vs.* 2, 3). Moreover, the plot *ee vs.* water content (Figure 2) has a maximum (84% *ee*), which corresponds to IL/H_2O ratio of 2 : 1 (v/v) (see Table 1, entries 7–12). Further increasing of water amount led to a less efficient stereoinduction (25% *ee* in 'pure' water), which testifies to synergistic action of the solvent system ingredients in the corresponding transition state. Water content affected the reaction rate as well: the conversion over 6 h was only 12% in anhydrous IL, whereas in the IL/H_2O (2 : 1) solvent system it reached 68% for the same period (Table 1, entries 13–16). A reduction of catalyst **3** loading resulted in a somewhat lower enantioselectivity and/or a reduced conversion (entries 17–19).

It is known that even a small amount of water may dramatically influence the liquid properties of ILs such as diffusion coefficient, viscosity, polarity, and surface tension and this may have an effect on reaction rates (see ref. 4 and papers cited therein). Moreover, the formation of invisible-to-the-naked-eye self-organized microstructures and nanostructures of water molecules (the diameters of channels varied from hundreds of nanometers to 5–10 mm) in unrestrictedly miscible with water [bmim]BF_4 were recently detected by means of transmission electron microscopy (TEM).[20] Most likely, the extreme character of the plot *ee vs.* water content may be attributed to favorable localization and self-organization of ambiphilic catalyst **3** within these micro-domains or on their surface in the transition state.

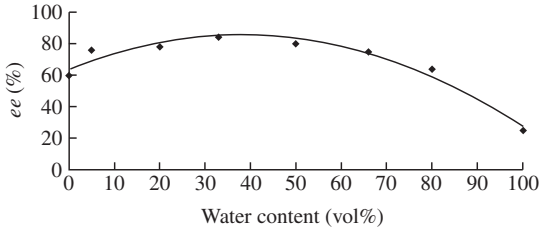


Figure 2 The plot *ee vs.* water content for the reaction between compounds **5a** and **6a** in aqueous [bmim]BF_4.

Under the optimal conditions, isobutyraldehyde **5a** reacted with maleimides **6a–c** bearing various groups at the imide nitrogen atom to afford the corresponding Michael adducts **7a–c** with enantioselectivity 80–84% *ee* (Scheme 1, Table 2, entries 1–3).† A variability of the aldehyde component was demonstrated by asymmetric reactions of **6b** with linear (**5b–f**) and β-branched (**5g**) aldehydes. In these cases, mixtures of diastereomeric compounds **7d–i** were generated with enantiomeric enrichment 70–77% *ee* for major isomer (entries 4–9). Absolute (*S*)-configuration was assigned to compounds **7a** and **7b** based on comparison of their specific optical rotations $[\alpha]_D^{20}$ = –4.1 (*c* 0.6, CH_2Cl_2) for **7a** and $[\alpha]_D^{20}$ = +4.2 (*c* 0.6, $CHCl_3$) for **7b** with reported data[19(a)] subject to different enantiomeric enrichment of compared samples. Configurations of adducts **7c–i** were assigned analogously.

Unlike reported catalysts **1** and **2**, the **3**/[bmim]BF_4/H_2O (2 : 1 v/v) catalytic system appeared recoverable and multiply reusable in asymmetric Michael reaction [see also ref. 17(*i*)]. Once a complete conversion was attained (20 h), product **7a** was extracted with Et_2O, and fresh portions of reactants **5a** and **6a** were added to the remaining **3**/aqueous [bmim]BF_4 mixture

Table 2 Enantioselective addition of aldehydes **5** to maleimides **6** under optimized conditions.[a]

Entry	Reactants		Product							
	5	**6**	**7**	R^1	R^2	R^3	Conversion (%)[b,c]	*dr*[b]	*ee* (major) / *ee* (minor) (%)[d]
1	**5a**	**6a**	**7a**	Me	Me	Ph	99 (90)	–	84
2	**5a**	**6b**	**7b**	Me	Me	Bn	63	–	82
3	**5a**	**6c**	**7c**	Me	Me	Cy	73	–	80
4	**5b**	**6b**	**7d**	H	Me	Bn	99	55 : 45	72/65
5	**5c**	**6b**	**7e**	H	*n*-C_5H_{11}	Bn	99 (90)	40 : 60	75/68
6	**5d**	**6b**	**7f**	H	*n*-C_6H_{13}	Bn	99 (92)	44 : 56	77/65
7	**5e**	**6b**	**7g**	H	Bn	Bn	99 (92)	60 : 40	70/60
8	**5f**	**6b**	**7h**	H	4-MeO-$C_6H_4CH_2$	Bn	99 (93)	65 : 35	74/55
9	**5g**	**6b**	**7i**	H	Pr^i	Bn	29 (21)	30 : 70	58/70

[a] The reactions were carried out with organocatalyst **3** (10 mg, 24 μmol), aldehyde **5** (354 μmol) and maleimide **6** (118 μmol) in [bmim]BF_4 (200 μl)/water (100 μl) solvent system at ambient temperature for 20 h. [b] Calculated from ^{1}H NMR spectra of the crude material. [c] Isolated yields (flash chromatography) are given in parentheses. [d] From chiral HPLC.

† *Succinimides* **7** *(general procedure)*. A mixture of aldehyde **5** (354 μmol), maleimide **6** (118 μmol), catalyst **3** (10 mg, 24 μmol), [bmim]BF_4 (200 μl) and water (100 μl) was stirred at ambient temperature for 20 h. Product **7** was extracted with Et_2O (5×3 ml), the combined organic extracts were filtered through a silica gel pad (1 g) and evaporated under reduced pressure (15 Torr). Reactant **6** conversions and *dr* values of product **7** were derived from ^{1}H NMR spectroscopy data. Values *ee* of **7** were determined by HPLC [chiral phases: Chiralcel OD–H or Chiralpak AD–H, hexane–propan-2-ol (75 : 25), 1.0 ml min^{-1}, 220 nm]. NMR data for succinimides **7a–c** are available in the literature.[19]

2-(1-Benzyl-2,5-dioxopyrrolidin-3-yl)propanal **7d**. Light yellow oil, yield 26 mg (90%), R_f = 0.26 (light petroleum–EtOAc, 2:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.13*/1.31 (d, 3H, *J* 7.5 Hz), 2.35–2.55 (m, 1H), 2.73–3.25 (m, 3H), 4.60–4.80 (m, 2H), 7.22–7.51 (m, 5H), 9.60/9.70* (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 9.25/11.24*, 31.10/31.72*, 39.43/40.76*, 42.56/42.60*, 46.13/46.57*, 127.88, 128.03, 128.61, 128.70, 135.69, 175.73, 178.11*/178.26, 201.13*/201.47. HRMS (ESI), *m/z*: 245.1059 $[M]^+$ (calc. for $C_{14}H_{15}NO_3$, *m/z*: 245.1052). HPLC analysis: major diastereomer: t_R (major) 12.8 min, t_R (minor) 31.8 min; minor diastereomer: t_R (major) 14.4 min, t_R (minor) 17.3 min.

For characteristics of compounds **7e–i**, see Online Supplementary Materials.

Table 3 Recycling of the catalystic system **3**/[bmim]BF_4/H_2O (2 : 1 v/v) in the reaction between compounds **5a** and **6a**.

Cycle	Conversion of **6a** (%)	*ee* of **7a** (%)	Cycle	Conversion of **6a** (%)	*ee* of **7a** (%)
1	99	84	6	99	78
2	99	82	7	99	76
3	99	82	8	99	72
4	99	81	9	99	70
5	99	81	10[a]	99	80

[a] Fresh portion of water (100 μl) was added.

(Table 3). A slight reduction of enantioselectivity in each next cycle may be attributed to gradual leaching of water from the IL to Et_2O during workup. Indeed, addition of water (100 μl) to the nine-fold recycled catalytic system significantly improved enantioselectivity of the catalytic reaction (Table 3, cycle 10).

In summary, a simple and readily recyclable chiral primary amine-based aqueous ionic liquid-supported catalytic system has been designed and successfully applied to asymmetric addition of aldehydes to maleimides. A significant impact of the IL/H_2O ratio on stereoselectivity of the catalytic reaction has been revealed.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2017.09.014.

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