



Application of Ionic Liquids in Michael Addition Reactions

by Haiying DU



Apr. 12, 2012

Contents

The definition and the advantage of ionic liquids



The use of ionic liquids as reactions medium



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The use of ionic liquids as reactions medium and catalyst



The definition of ionic liquids

An ionic liquid (IL) is a salt in the liquid state. In some contexts, the term has been restricted to salts whose melting point is below some arbitrary temperature, such as $100 \degree C (212 \degree F)$. While ordinary liquids such as water and gasoline are predominantly made of electrically neutral molecules, ILs are largely made of ions and short-lived ion pairs.

The advantage of ionic liquids

Greener solvents, suitable for a range of organic reactions

Meria Providing possibilities such as control of product distribution, enhanced rate and reactivity

Ease of product recovery, catalyst immobilization, and recycling

The important of Michael addition

The Michael addition reaction as a model reaction, which constitutes as one of the most important classes of new carbon–carbon bond-forming reactions for the preparation of organic target products in synthetic organic chemistry

So I choose the topic that

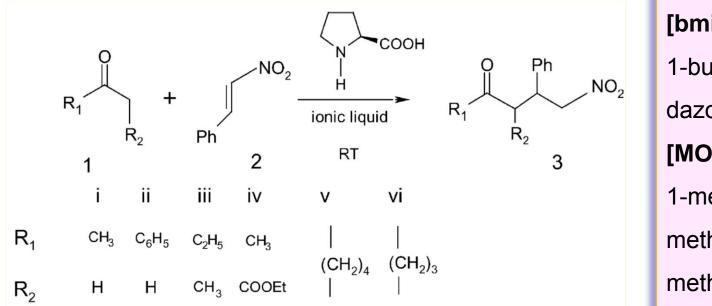
<Application of Ionic Liquids in Michael Addition Reactions>

<Application of Ionic Liquids in Michael Addition Reactions>

(a) Berner, O. M.; Tedeschi, L.; Enders, D. Eur. J. Org.Chem. 2002, 1877–1894
(b) Krause, N.; Hoffmann-Röder, A. Synthesis 2001,171–196
(c) Sibi, M. P.; Manyem, S. Tetrahedron 2000, 56, 8033–8061



L-proline catalysed Michael addition of ketones to nitrostyrene in iolic liquid



[bmim]Cl

1-butyl-3-methylimidazolium chloridel [MOEMIM]OMs 1-methoxyethyl-3methylimidazolium

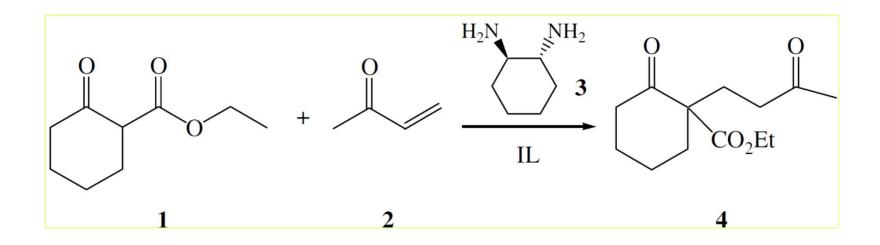
methanesulphonate

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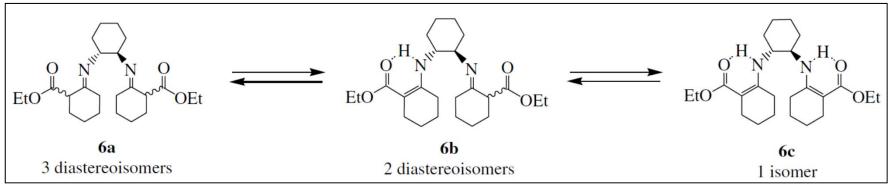
- 1. Ionic liquids can act as an efficient media for enhancing the selectivity of L-proline catalysed Micheal reaction
- 2. Catalyst recovery and solvent reusability
- 3. The catalytic activity was strongly dependent on the nature of the ionic liquid, which influenced the yield and selectivity of the reaction
- 4. The structure of ionic liquid can be well modulated to meet the needs of a sepcific process

The asymmetric Michael addition of ethyl cyclohexanone-2-carboxylate to methyl vinyl ketone In [bmim] BF_4 facilitated by (R,R)-trans-1,2-diaminocyclohexane



3 can facilitate the Michael addition of reaction through two different pathways. It can abstract the proton in the a position of the donor, thus, triggering a basic catalysis leading to a racemic mixture of the product. In alternative, the diamine can react with1 forming a composite mixture of isomers 6a–c in prototropic equilibrium.

Gallo V. et al. Journal of Organometallic chemistry 690(2005) 3535-3539

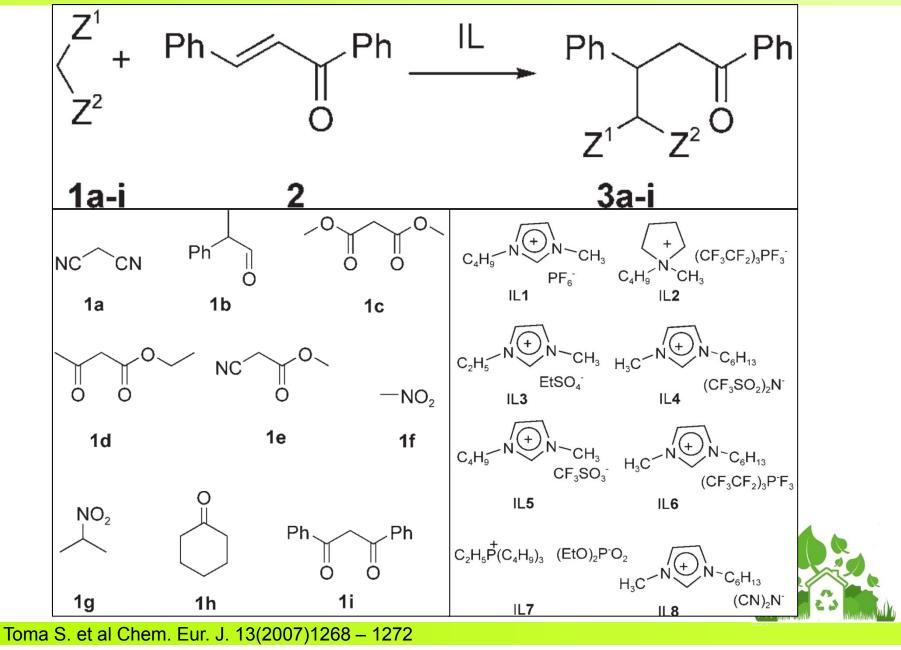


Prototropic equilibria involving the adducts between 1 and 3.

- In tetrafluoroborate based ionic liquids fair yields and enantimeric excesses up to 91%
- 2. Possibly recyclable, catalytic systems that exhibit higher activity than those obtainable with classic solvents



Gallo V. et al. Journal of Organometallic chemistry 690(2005) 3535-3539



In summary

The Michael addition of malononitrile and several other methylene active compounds proceeds successfully in pure ionic liquids, without any additional catalyst.

This observation can be explained by the different dissociation constants of

C-H acids in ionic liquids relative to classical solvents

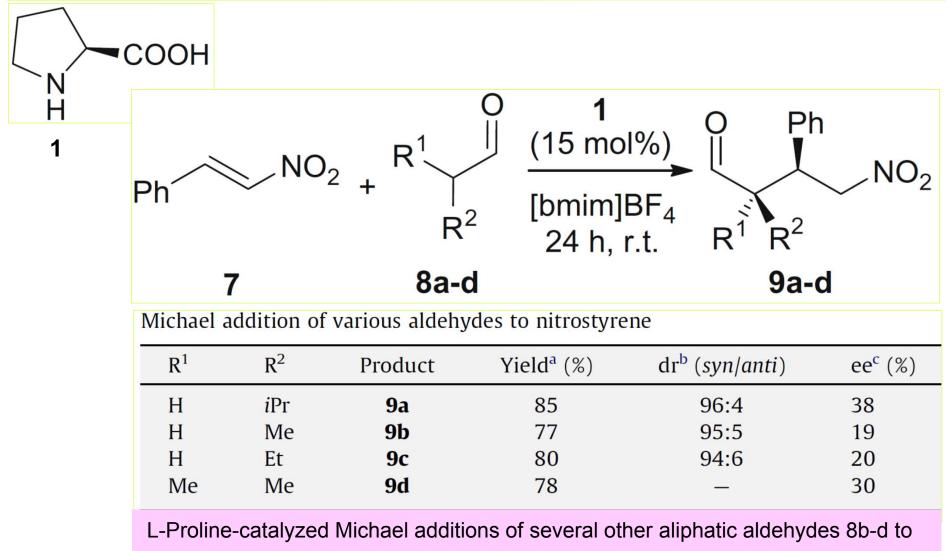
Observed that piperidine-catalysed (5 mol%) reactions in ionic liquids

proceed much faster than the same reactions in dichloromethane.



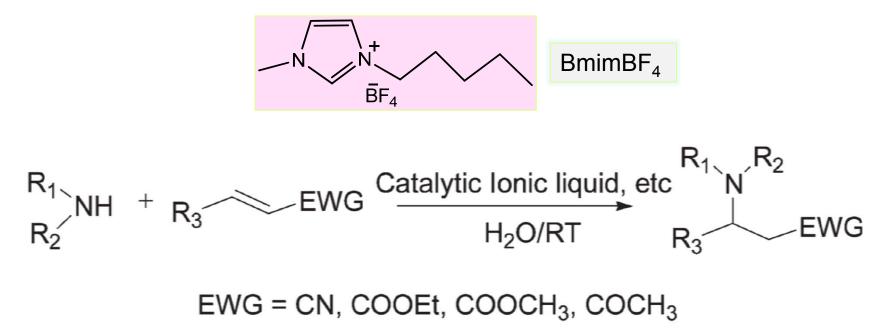


Toma S. et al Chem. Eur. J. 13(2007)1268 – 1272



 β -nitrostyrene 7 in [bmim]BF₄. Products 9b-d were isolated in high yields,excellent syn/anti ratio from 94:6 to 96:4 and moderate ee

Meciarova M. et al. Tetrahedron: Asymmetry 20(2009) 2403-2406



> Utilized a variety of aliphatic amines successfully with different α , β unsaturated compounds catalyzed by the simple hydrophilic ionic liquid,bmimBF₄. > Interestingly, all the aliphatic amines gave almost quantitative yields with α , β ethylenic compounds.



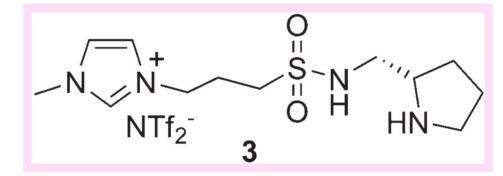


Table 2Michael addition reactions of aldehydes to trans-nitro-styrenes catalyzed by 3

Ar

$$NO_2$$
 + $H \xrightarrow{O}_{R_2} R_1$ $\underbrace{\text{catalyst } \mathbf{3} (20\%)}_{4^{\circ}C, Et_2O, 6d}$ $H \xrightarrow{O}_{R_1} NO_2$

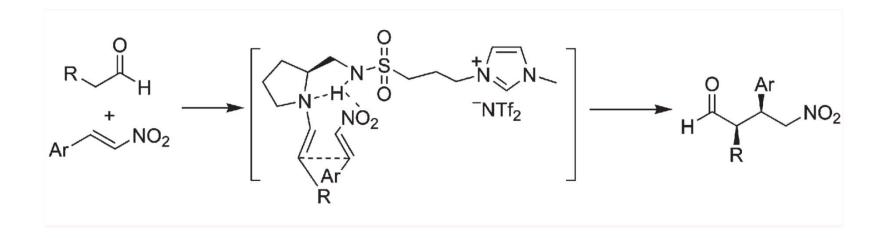
All aldehydes can undergo Michael reactions with different aryl-substituted nitrostyrenes.

March March Martin

Giving the corresponding Michael adducts in moderate yields(29-64%), good nantioselectivities (64-82%ee),and high diastereoselectivities.

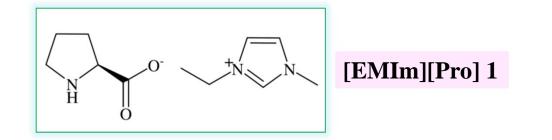
Headley A . D ., et al. Green chem., 9(2007) 737-739

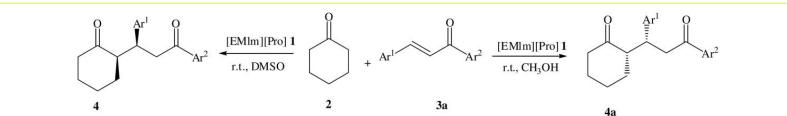
Mechanism for the Michael addition using catalyst 3



It is obvious that N-H acidic hydrogen plays an important role in the reaction by forming hydrogen bonds to the nitrostryene substrate in a manner that C-C bond formation would take place by the preferential enamine addition to the less hindered *Si* face of the nitrostyrene.







Entry	Ar ¹	Ar ²	Conditions ^d	<i>t</i> (h)	Yield ^a (%)	dr ^b	ee ^{b,c} (%)
1	Ph	Ph	А	4	98	20:80	86
2	4-MeC ₆ H ₄	Ph	Α	4	90	5:95	37
3	4-ClC ₆ H ₄	Ph	А	4	98	4:96	60
4	Ph	$4-ClC_6H_4$	А	4	97	15:85	23
5	$4-BrC_6H_4$	Ph	А	4	80	23:77	44
6	Ph	$4-NH_2C_6H_4$	Α	8	87	4:96	94
7	$2-ClC_6H_4$	4-MeC ₆ H ₄	А	4	99	1:99	29
8	Ph	Ph	В	4	95	12:88	-78
9	4-MeC ₆ H ₄	Ph	В	4	98	16:84	-72
10	$4-ClC_6H_4$	Ph	В	4	94	10:90	-65
11	Ph	$4-ClC_6H_4$	В	4	88	8:92	-72
12	$4-BrC_6H_4$	Ph	В	4	90	10:90	-39
13	Ph	$4-NH_2C_6H_4$	В	8	85	4:96	-91
14	$2-ClC_6H_4$	4-MeOC ₆ H ₄	В	4	99	4:96	-16

^a Isolated yields after column chromatography.

^b Determined by HPLC analysis on a chiral AD-H column.

^c An inverse configuration determined by HPLC analysis on a chiral AD-H column.

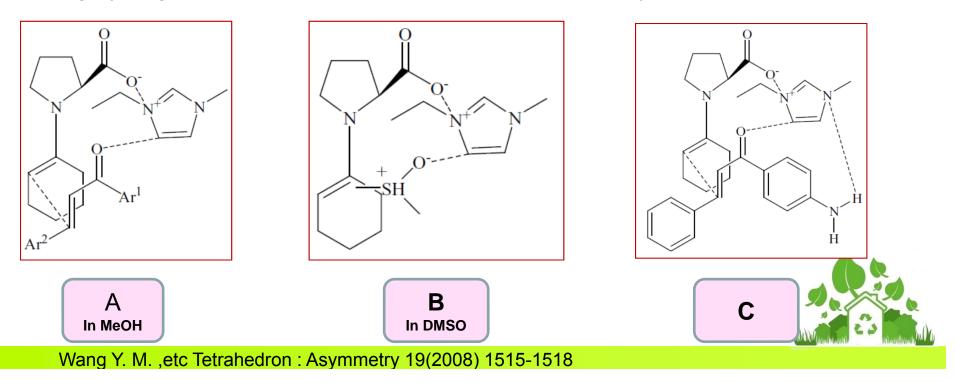
^d Conditons A: reaction performed in CH₃OH; conditions B: reaction performed in DMSO.

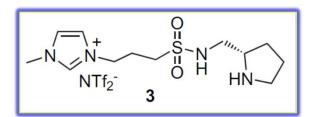


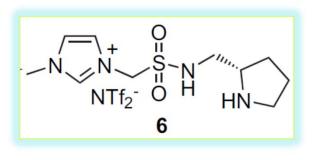
Catalytic asymmetric Michael addition of cyclohexanone 2 with chalcone 3

Notably, the solvent-dependent inversion of the enantioselectivity took place in all reactions. Products obtained from DMSO mostly displayed a higher ee value than those obtained from CH_3OH .

C: assumed that between catalyst 1 and the amine group there was probably a strong hydrogen-bond to anchor the substrate in a firm way.







Ph NO ₂ +	$H \xrightarrow{O} \underline{cat}$	alyst 6 (20 solvent	^{0%)} ► H	O Ph NC (R)-7a) ₂
Solvent	Additive	Т	<i>t</i> (d)	Yield ^a (%)	ee ^b (%)
CH ₃ CN	—	rt	6	<5	С
MeOH	—	rt	6	86	79
<i>i</i> -PrOH	—	rt	6	84	79
DCM/MeOH	—	rt	6	80	81
MeOH	5% TFA	rt	3	90	84
MOU		100	C	-10	С
MeOH	5% TFA	4 °C	6	<10	
меОН МеОН	5% TFA 10% TFA	rt	6	<10 81	79
	Solvent CH ₃ CN MeOH <i>i</i> -PrOH DCM/MeOH MeOH	SolventAdditiveCH_3CNMeOH i -PrOHDCM/MeOHMeOH5% TFA	SolventAdditiveT CH_3CN rt $MeOH$ rt i -PrOHrt $DCM/MeOH$ rt $MeOH$ 5% TFArt	NO_2 H $Catalyst 6 (20\%)$ solvent H SolventAdditive T $t (d)$ CH_3CN $ rt$ 6 $MeOH$ $ rt$ 6 i -PrOH $ rt$ 6 $DCM/MeOH$ $ rt$ 6 MeOH $ rt$ 6 MeOH $ rt$ 6 MeOH $ rt$ 6 MeOH $ rt$ 6	catalyst 6 (20%) solventNO2Hcatalyst 6 (20%) solventHNO2SolventAdditiveTt (d)Yield ^a (%)CH3CNrt6<5MeOHrt686i-PrOHrt684DCM/MeOHrt680MeOH5% TFArt390

Noteworthy, catalyst 6 exhibited superior enantiocontrol, compared to catalyst 3 in MeOH and i-PrOH. The introduction of the electron-withdrawing imidazolium cation in close proximity to the NH in catalyst 6 increases the strength of hydrogen bond interaction in the transition state, which results in enhanced stereochemical control.

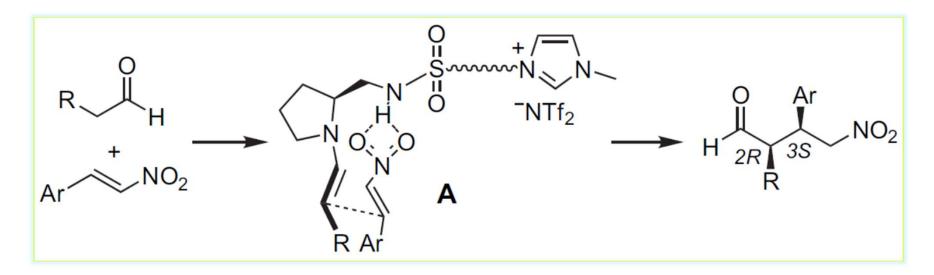
Interestingly, the addition of a catalytic amount of the organic acid, TFA, dramatically increased the reaction rate, along with an improvement in the ee of 84% with MeOH. The observation indicates that acidic additives in the reaction accelerate the formation of the enamine intermediate and promote the catalytic cycle.

Zhang Q, et al. Tetrahedron 64(2008) 5091-5097

3

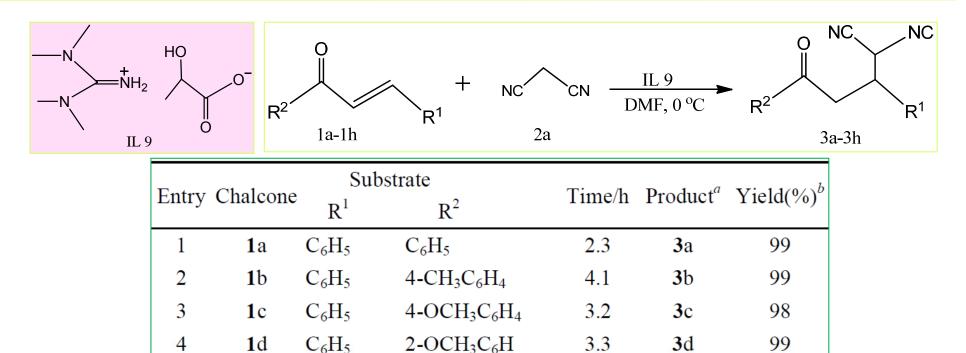
6 7

Mechanism for the Michael addition using catalysts 3 and 6



It is obvious that the N-H acidic hydrogen plays an important role in the reaction by forming hydrogen bonds to the nitrostyrene substrate in a manner that the C-C bond formation would take place by the preferential enamine addition to the less hindered Si-face of the nitrostyrene generating 2R,3S configuration of products.

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-		-03	0,1 02011200113			
6	1 f	C_6H_5	$4-ClC_6H_4$	2.5	3 f	97
7	1 g	$4-C1C_6H_4$	$4-C1C_6H_4$	1.6	3 g	99
8	1 h	$4-C1C_6H_4$	$4-OCH_3C_6H_4$	2.5	3 h	98
	a The prod	lucts are obt	tained by direct filtra	ation b is	plated vield	S

45

3e

99

UNAN USAL KILISIN

3 4-O2CH2C6H2

a. The products are obtained by direct initiation, b. isolated yields.

1. All products could be obtained in high purity by simple filtration and wash with water.

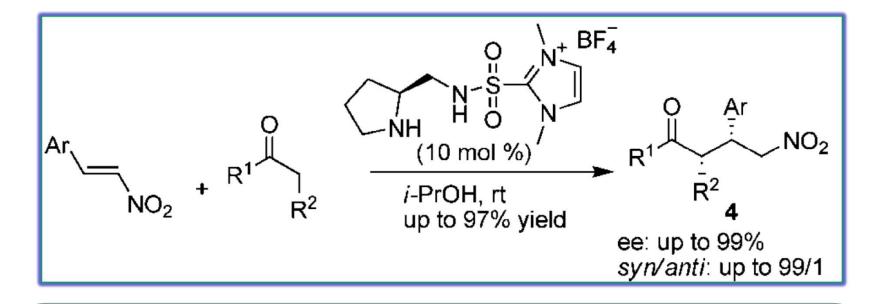
2. Simple procedure , very mild conditions , and quantitative yields

Jie L. Y. et al. Chem. Res. Chinese universities 25(2009) 169-173

C_cH₅

1e

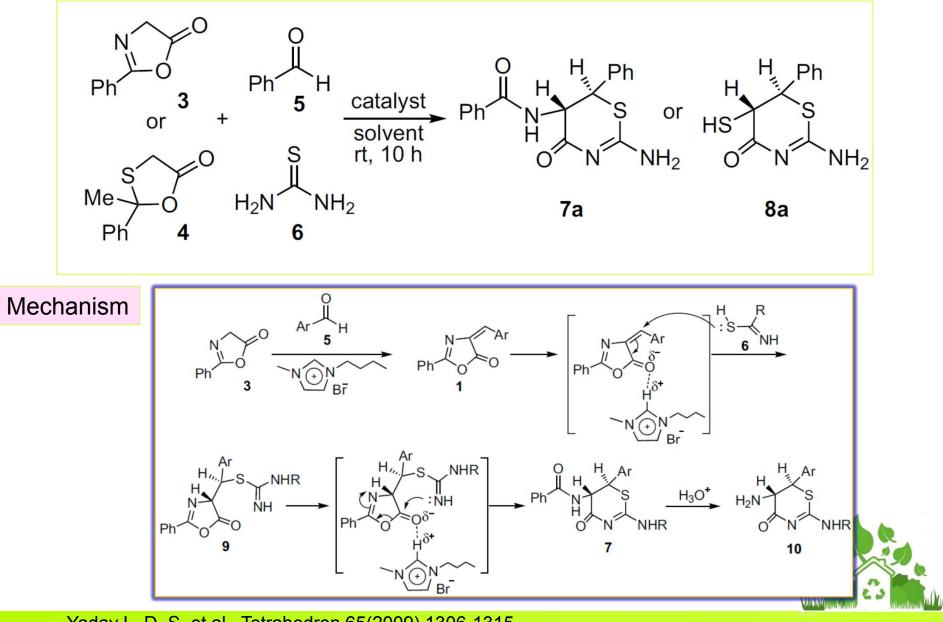
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1. All 6-membered ring ketones can efficiently undergo Michael reactions with different aryl-substituted nitroolefins

2. Highly efficient ,asymmetric Michael addition reactions of ketones and aldehyde to nitroolefins

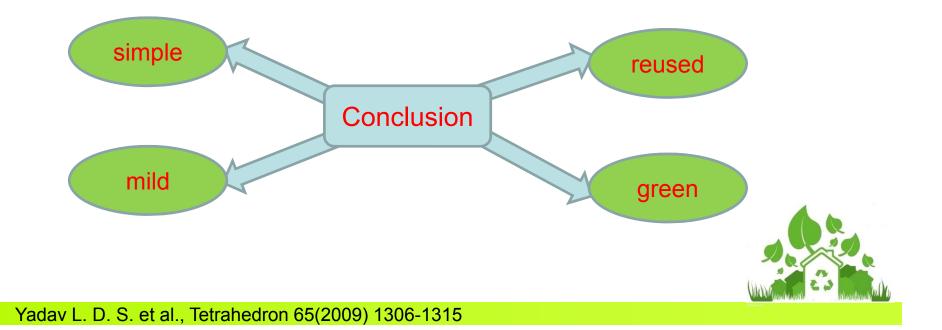
3. The catalyst is readily recovered and reused for at least five times without significant loss of catalytic activity and stereoslectivity

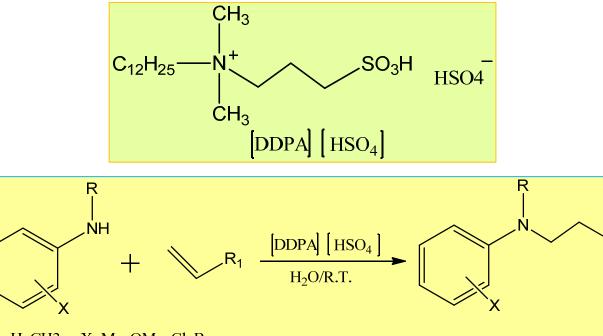


Yadav L. D. S. et al., Tetrahedron 65(2009) 1306-1315

In summary

- 1. The first ionic liquid-promoted one-pot diastereoselective synthesis of 2,5 diamino-
- /2-amino -5-mercapto-1,3-thiazin-4-ones using masked amino/mercapto acids
- 2. The one-pot diastereoselective synthesis is operationally simple, high yielding , and performed at r.t.
- 3. Using the ionic liquid [Bmim]Br as an environmentally benign catalyst



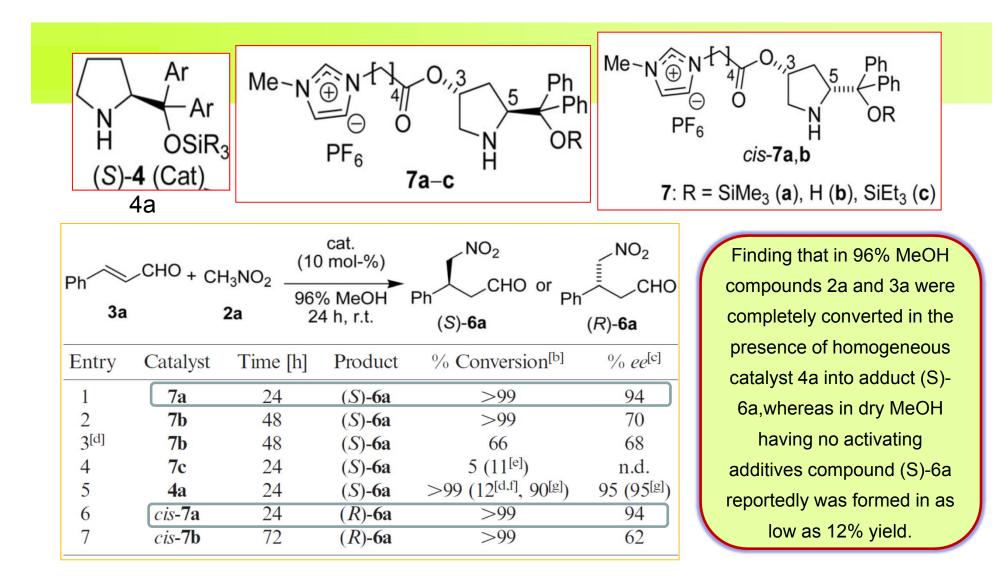


R=H, CH3 X=Me, OMe, Cl, Br R₁=COMe, CN, CO₂Me

 \sum Aromatic amines with α , β -unsaturated compounds catalyzed by

[DDPA][HSO₄] to produce β -amino compounds.

 \gg High yields of the products , short reaction times , mild reaction conditions and simple procedure.



From the table, we can obtein that enantiomer (R)-6a was the major product of the reactions between compounds 2a and 3a in the presence of catalysts cis-7a and cis-7b. Moreover, conversions and enantioselectives in these reaction were similar to those in the reactions catalyzed by transisomers 7a and 7b, where opposite enantiomer (S)-6a was formed.

Uhha

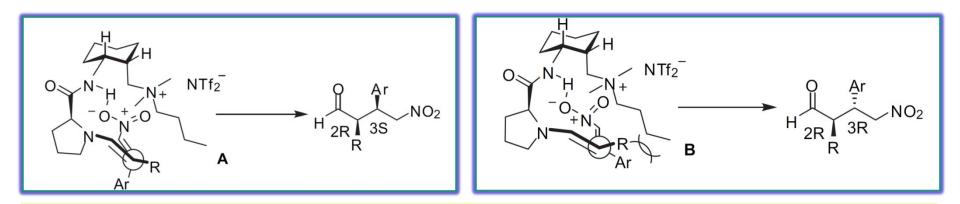
Zlotin S. G., et al. Eur. J. Org. Chem. (2010) 2927-2933

	Michael addition of aldehydes to <i>trans</i> -β-nitrostyrene ^a							
	ł	O R	+	Ph_	NO ₂ 5	CIL mol% TFA	$H \xrightarrow{O Ph} NO_2$	
	Entry	R	CIL	T(h)	Yield ^b (%)	dr ^c (syn/anti)	ee ^d (%) <i>syn</i> (anti)	Pr.
~ 0	1	Me	1a	12	95	68/32	84 (81)	8a
	2		1b	12	95	77/23	88 (89)	
$\begin{array}{c c} & HN \\ H $	2 3 4	Et	1a	12	96	82/18	76 (75)	8b
$\begin{array}{c} \mathbf{H} \\ $	4		1b	12	99	89/11	87 (82)	
	5	n-Pr	1a	24	96	80/20	75 (71)	<mark>8c</mark>
	6		1b	24	98	87/13	81 (78)	
NTf ₂	7	i-Pr	1a	60	37	97/3	77	8d
	8		1b	60	84	99/1	82	
	9	n-Bu	1a	36	97	73/27	72 (73)	8e
	10		1b	36	99	90/10	80 (77)	
	^a The reaction was conducted with β-nitrostyrene (0.1 mmol), ald (0.6 mmol), and CIL 1a (20 mol %) in 1 mL of THF or CIL 1b (15 mol %) in 1 mL of the function of the							
							f DCM	
	at rt.							
	^b Isola	ted yiel	d.					

- 1. Excellent yields (95-99%) ,moderate to high diastereoselectivitues
- 2. Enantioselectivities(72-88%) the enantioselectivity decreased slightly with the

increase of carbon chain length of aldehydes, for either CIL 1a or 1b was used

Hirose T. et al, Tetrahedron 66(2010)4970-4976



The bulky IL group and the hydrogen bonding between the amide NH and the nitro group of nitroolefin are considered to be important to the high catalyticactivity and the stereoselectivity. The possible ionic attraction between ammonium cation and nitro group of the substrate should also contribute to stabilization of the intermediate. The enaminetends to attack from the less hindered Si face of the nitroolefin. (2R, 3S)configuration of the corresponding adduct is generated preferentially(Fig. A).

The flexible butyl side chain of ammonium group may cause moderate repulsive interaction with anaryl group of nitroolefin (Fig. B).

> The moderate diastereoselectivity of the reaction could be rationalized by considering this weak interaction.

Quininium bromide 1

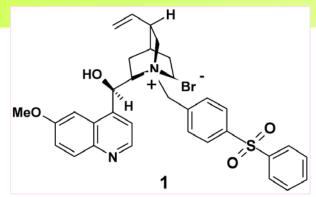
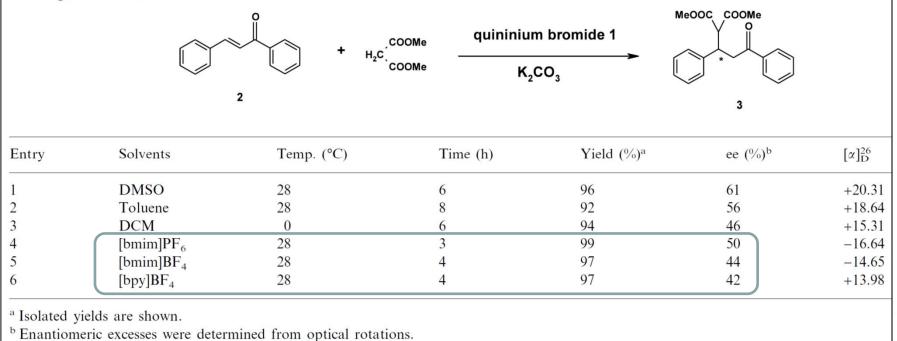
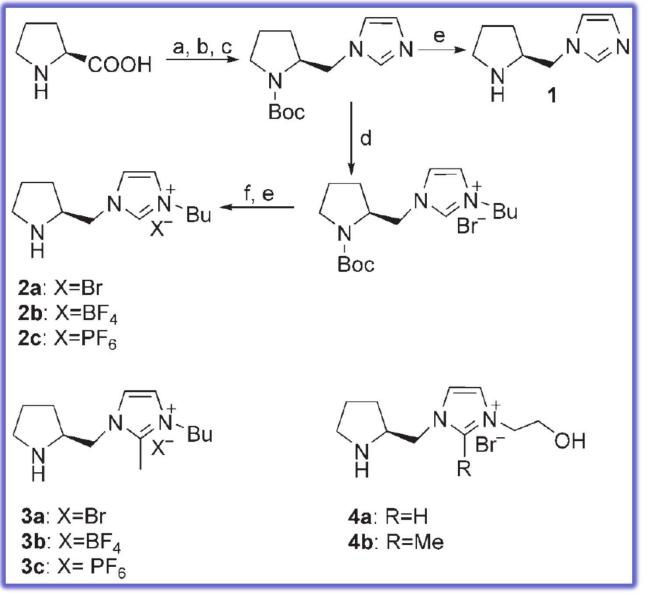


 Table 1. Catalytic enantioselective Michael addition of dimethyl malonate to 1,3-diphenylprop-2-en-1-one in ionic liquids and organic solvents



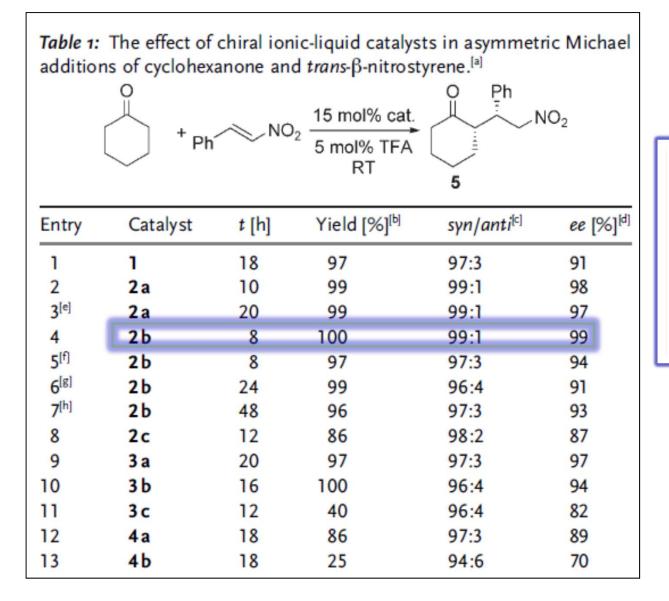
63







Angew. Chem. Int. Ed. 2006, 45, 3093–3097

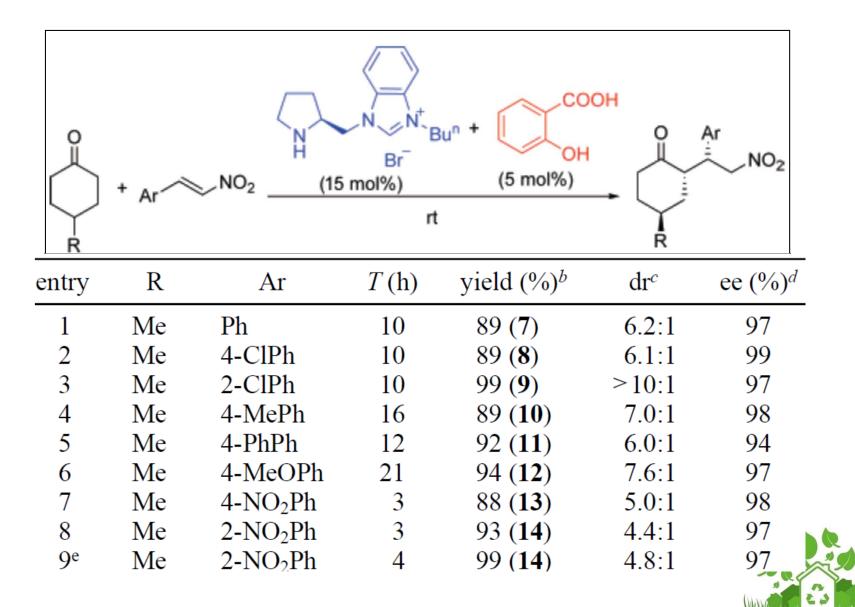


$$\sum_{\substack{N\\H}} N \swarrow_{X^{-}}^{N} Bu$$

2a: X=Br
2b: X=BF₄
2c: X=PF₆

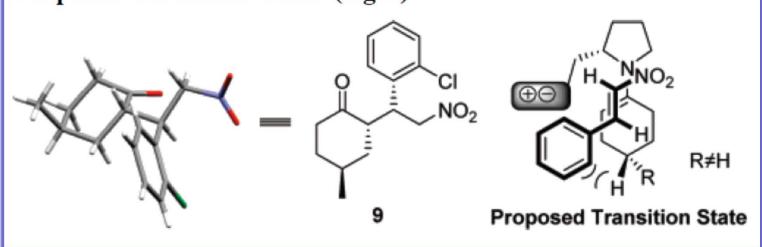


Angew. Chem. Int. Ed. 2006, 45, 3093 – 3097

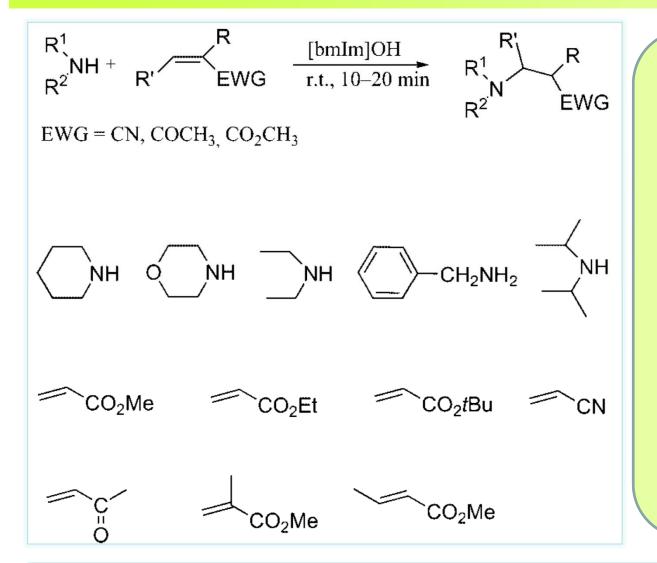


J. Org. Chem. 2007, 72, 9350-9352

SCHEME 2. X-ray Crystal Structure of 9 (left) and the Proposed Transition State (right)



Functionalized chiral ionic liquids were found to be highly effective and reusable organocatalysts for asymmetric Michael additions of 4-substituted cyclohexanones. The desymmetrization reaction afforded the desired Michael adducts bearing three carbon stereocenters with up to 99% ee.



 Amines exhibited higher nucleophilicity in ionic liquids than in organic solvents

 The hydroxide anion of the ionic liquid [bmim]OH might assist in the formation of nucleophilic anions generated from amines, which should increase the nucleophilicity of amines

Michael additions between amines and α , β -unsaturated carbonyl compounds



Lin X. F. et al. Eur. J. Org. Chem. (2007) 1798-1802

N N N N N N N N N N N N N N N N N N N			IL-supportec cyclohexano	-		asymmetric ostyrene ^b	Michael
2	0 8	+ Ph	< <u>∕</u> NO₂ 9	15 mc r.t	\rightarrow	O Ph	, NO₂
	Entry	Solvent	Additive	Time (h)	Yield ^c (%)	dr ^d (<i>syn/anti</i>)	ee ^e (%)
IL-supported catalyst retained, good activity and high selectivity.	$ \begin{array}{c} 1 \\ 2 \\ 3 \\ 4 \\ 5 \\ 6 \\ 7 \\ 8 \\ 9^{f} \\ 0^{g} \\ 11 \\ 12 \\ \end{array} $	DMSO CHCl ₃ H ₂ O — DMSO CHCl ₃ H ₂ O — — —	— — TFA ^a TFA TFA TFA TFA TFA TFA TFA TFA	72 72 72 72 72 48 48 48 48 48 48 48 48 72 72 72 72 72	41 34 29 47 90 95 94 97 89 90 73 60	n.d. ^a n.d. n.d. n.d. 94:6 96:4 93:7 97:3 96:4 96:4 96:4 96:4 95:5	n.d. n.d. n.d. n.d. 88 92 90 94 94 94 93 93 83

L.-Y. Wu et al. / Tetrahedron: Asymmetry 18 (2007) 2086–2090

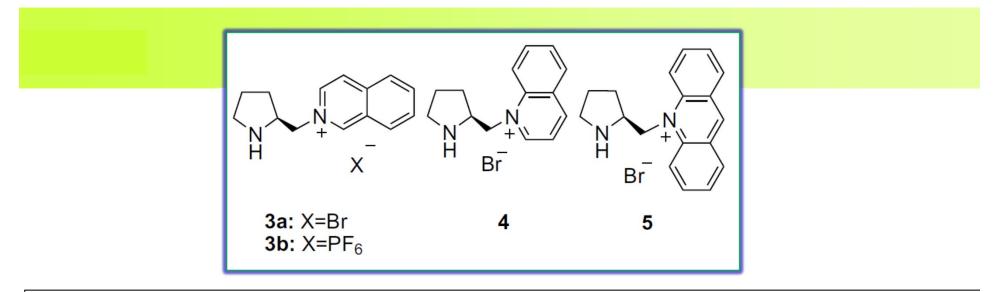
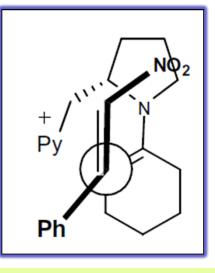
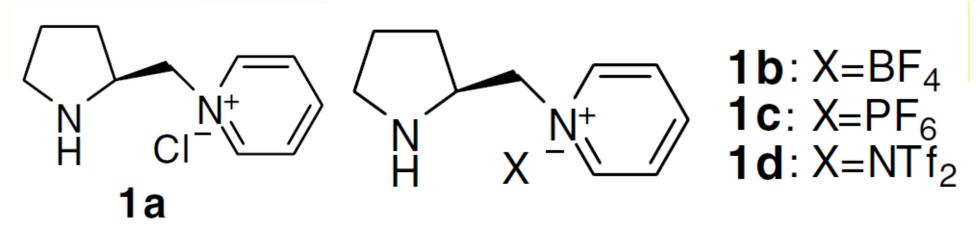


Table 1. Orga	nocatalyzed direct	Michael addition of cyclo	hexanone 6 to <i>trans</i> - β -	nitrostyrene 7a in ILs ^a						
$ \begin{array}{c} $										
		6	7a	8a						
Entry	Cat.	IL	Time (h)	Yield ^b (%)	dr ^c (syn/anti)	ee ^d (%)				
1	1	BMImPF ₆	48	93	91/9	28				
2	2	BMImPF ₆	48	19	91/9	7				
3	3a	BMImPF ₆	48	88	96/4	95				
4	3b	BMImPF ₆	48	90	90/10	41				
5	4	BMImPF ₆	48	74	91/9	8				
6	5	BMImPF ₆	48	8	91/9	23				
7	1	BMImBF ₄	24	94	90/10	68				
8	2	BMImBF ₄	48	80	91/9	4				
9	3a	BMImBF ₄	20	95	93/7	99				
10	3b	BMImBF ₄	20	95	96/4	93				
11	4	BMImBF ₄	24	92	91/9	17				
12	5	$BMImBF_4$	48	92	91/9	52				
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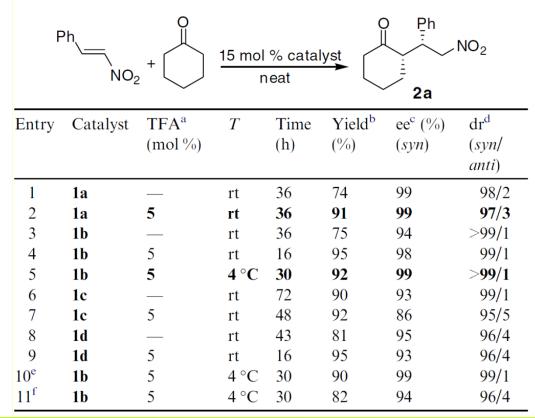
D.-Q. Xu et al. / Tetrahedron: Asymmetry 18 (2007) 1788–1794



 Pyrrolidine-pyridinium conjugates must catalyze a Re-face attack on 6 via an enamine transition state, in which the Si-face was shielded by the pyridinium moiety on the catalyst as outlined.
 The ionic liquid BMImBF4 might play a key role in stabilizing the formed iminium-ion transition state, owned a greater charge density than the initial reaction molecules, by operating favorable electrostatic interactions, which led to the enhancement of the overall reaction efficiency.

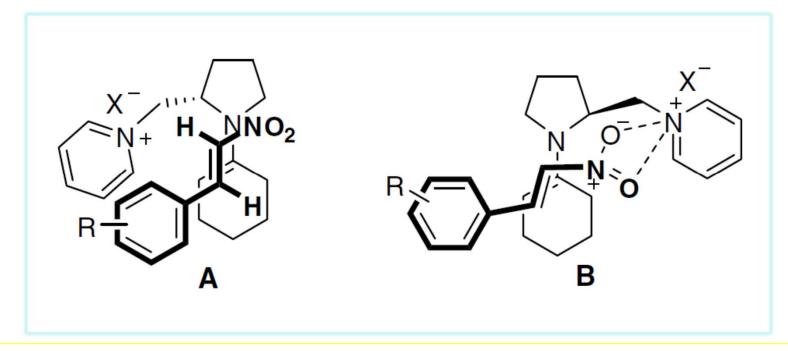


The effect of catalyst in the Michael reaction of cyclohexanone and nitrostyrene





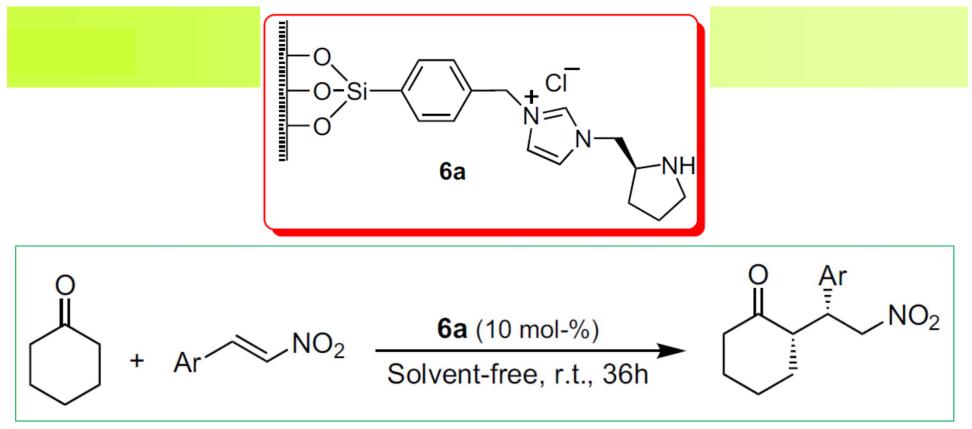
B. Ni et al. / Tetrahedron Letters 49 (2008) 1249–1252



1. The high diastereo- and enantioselectivities may be explained by an acyclic synclinal transition **state A**, in which the pyridinium ring plays an important role in shielding the si-face of enamine double bond.

2. The possible ionic attraction between pyridinium cation and nitro group of the substrate (transition **state B**) should also contribute to the enantioselectivity observed.

B. Ni et al. / Tetrahedron Letters 49 (2008) 1249–1252



Synthesis of silica gel supported pyrrolidine-based chiral ionic liquid and its application in asymmetric Michael addition to nitrostyrenes.



P. Li et al. / Tetrahedron 64 (2008) 7633-7638

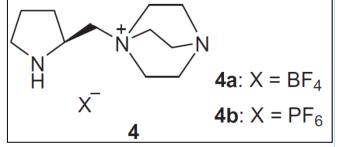
In summary

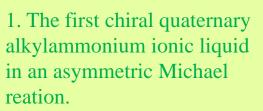
1.Developed a novel silica gel supported pyrrolidine-based chiral ionic liquids, which are capable of catalyzing Michael addition reaction of ketones with nitrostyrenes in good yields, excellent enantioselectivities and high diastereoselectivities.

2. The method is operationally simple, the catalyst can be easily recycled, and reused six times without a significant loss of catalytic activity and stereoselectivity.



Recycling studies of ionic liquid [Pro-dabco][BF₄] catalyzed Michael addition of cyclohexanone to trans-b-nitrostyrenea

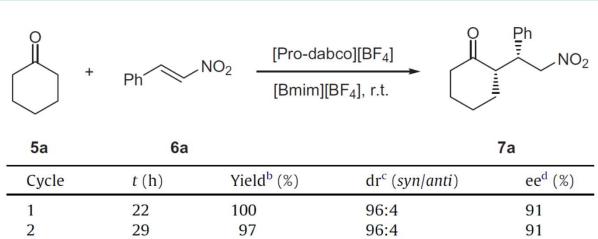




2. The chiral ionic liquid were easily prepared from L-prolinol

3. Highly enantioselective and diastereoselective

4. The solvent were readily recovered and reused at five times without a significant loss of catalytic activity.



^a All reactions were conducted in [Bmim][BF₄] (0.5 mL) using **5a** (0.1 mL, 1.0 mmol) and **6a** (15 mg, 0.1 mmol) in the presence of 20 mol % of the catalyst.

93:7

95:5

96:4

95:5

^b Isolated yield.

35

41

43

62

^c Determined by ¹H NMR spectroscopy.

^d Determined by HPLC analysis (chiralcel AD-H column).

95

88

93

90

shown in Table 2, catalyst **4a** could be recycled and reused at least five more times without any loss of stereoselectivity (ee >90%; *syn/anti* >93:7) but a slight decrease in activity was observed in cycles 2–6.



90

92

91

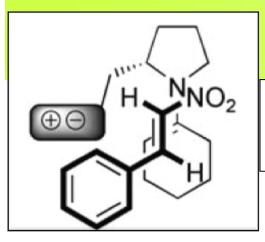
91

3

4

5

6



the ionic-liquid moiety would effectively shield the Si face of the enamine double bond in the ketone donor and the reaction would occur through a Re-Re approach

The pyrrolidine-ionic-liquid conjugates have several noteworthy features:

 they can very efficiently catalyze the Michael additions for a broad range of Michael donors (both ketones and aldehydes) and Michael acceptors (nitroolefins) with high yields (up to 100%), excellent enantioselectivity (up to 99% ee), and very good diastereoselectivity (syn/anti up to 99:1);
 the ionic-liquid moiety can not only act as a phase tag to facilitate recycling and reuse of the catalyst but can also function as an efficient chiral-induction group

to ensure high selectivity;

3) the modular and tuneable features of ionic liquids promise further developments.

Conclusion



Ionic liquids as environmental-friendly solvents and catalysts with high activity and selectivity and easily recovered materials were used to replace solvent and catalysts.



Using the traditional solvent generally suffered from disadvantages such as waste production, corrosion and environmental problems.



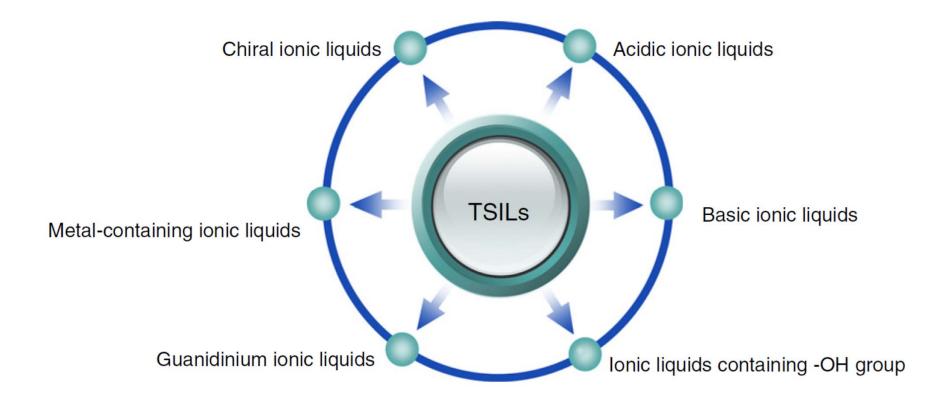
Ionic liquids offering a new possibility for developing environmentally friendly catalysts .They are flexible, nonvolatile, noncorrosive, and immiscible with many organic solvents.



Ionic liquids have been used in catalyzed processes in Michael addition, especially task-specific Ionic liquids.



Task-Specific Ionic liquids





Thank you for your attention!