Chiral Ionic Liquids (CILs) in Asymmetric Synthesis:

The story so far….

Literature Presentation
Aman Desai
06.16.06

1. *Angew. Chem. Int. Ed.* **2006**, *45*, 3689
2. *Angew. Chem. Int. Ed.* **2006**, *45*, 3093
3. *Tetrahedron: Asymmetry*, **2006**, *17*, 1032
4. *Tetrahedron: Asymmetry*, **2005**, *16*, 3921

Ionic liquids – what? & why?

"….are salts that are liquid at low temperatures (< 100 °C) – they are liquids which consist only of ions."

FEATURES:

- Form biphasic systems with organic product mixtures – easy isolation & recovery.
- Reusability.
- No vapor pressure – facilitates product separation by distillation.
- Tuneability - optimization for specific applications – referred to as *"designer solvents"*.
- Easy manipulation of melting points, thermal stability, density, viscosity & solubility characteristics.
- Green & clean.
- Chirality in either cation or anion.
- *Commercial availability & costs pose a problem.*

Angew. Chem. Int. Ed. **2000**, *39*, 3772

Chiral Ionic Liquids (CILs)

"*Pure imidazolium ionic liquid can be described as polymeric hydrogen-bonded supramolecules and in some cases when mixed with other molecules, they should better be regarded as nanostructured materials with polar and non polar regions rather than homogeneous solvent*"

– Dupont, J. *J. Braz. Chem. Soc.* **2004**, *43*, 4988

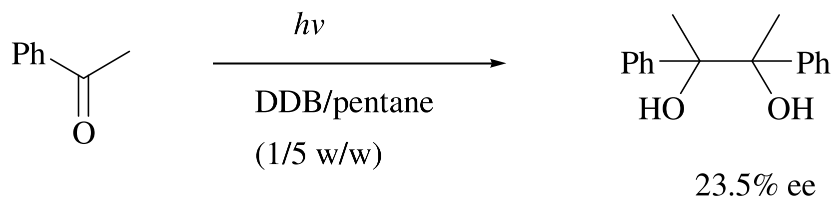
∴ With chiral ILs, solvent structuration – basis for molecular recognition – can be used to devise stereoselective reactions.

Applications of CILs:

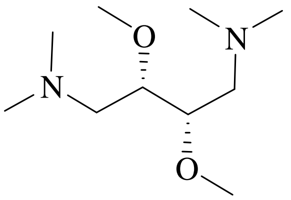
- Chiral solvents for stereoselective polymerisation
- Chiral phases for gas chromatography
- Chiral shift reagents in NMR
- Chiral crystals
- Chiral solvents for asymmetric synthesis

CILs in Asymmetric Synthesis up till 2006 – *only upto 44% ee*

First example of the use of a chiral solvent: Seebach, D. *Angew. Chem. Int. Ed.* **1975**, *87*, 629



23.5% ee

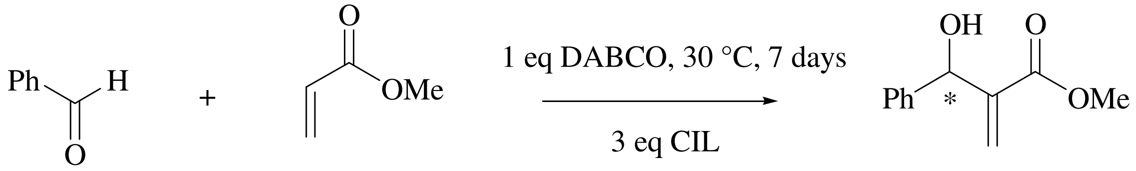


(S,S)-(+)-1,4-Bis (dimethylamino)-2,3-dimethoxybutane

DDB

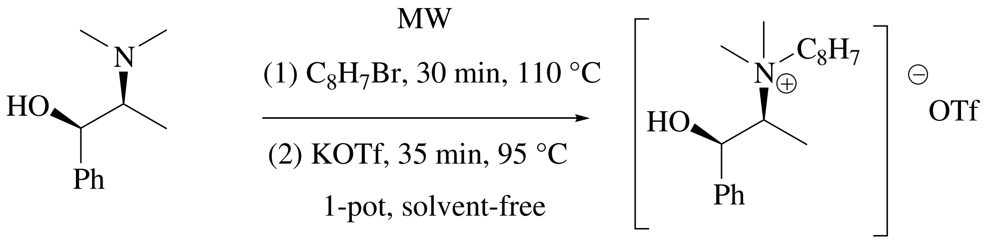
First significant asymmetric induction in use of a CIL as the sole source of chirality:

Vo-Thanh, *Tetrahedron Letters*, **2004**, *45*, 6425



60% yield

44% ee



(1R,2S) *N*-methyl ephedrine

CIL

91% yields

viscous liquid at RT

Workup: Simple extraction with ether - CIL (aq) recycled by dissolving in CH_2Cl_2 & washing with water & reused w/o loss of yield or ee

CILs in Asymmetric Synthesis in 2006

the light at the end of the tunnel?

1. Malhotra, S. *Tetrahedron: Asymmetry* **2006**, *17*, 1032

   → α-pinene based CILs in Cu-catalyzed enantioselective conjugate addition of diethyl zinc to α,β-unsaturated enones – *upto 76% ee*

2. Leitner, W. *Angew. Chem. Int. Ed.* **2006**, *45*, 3689

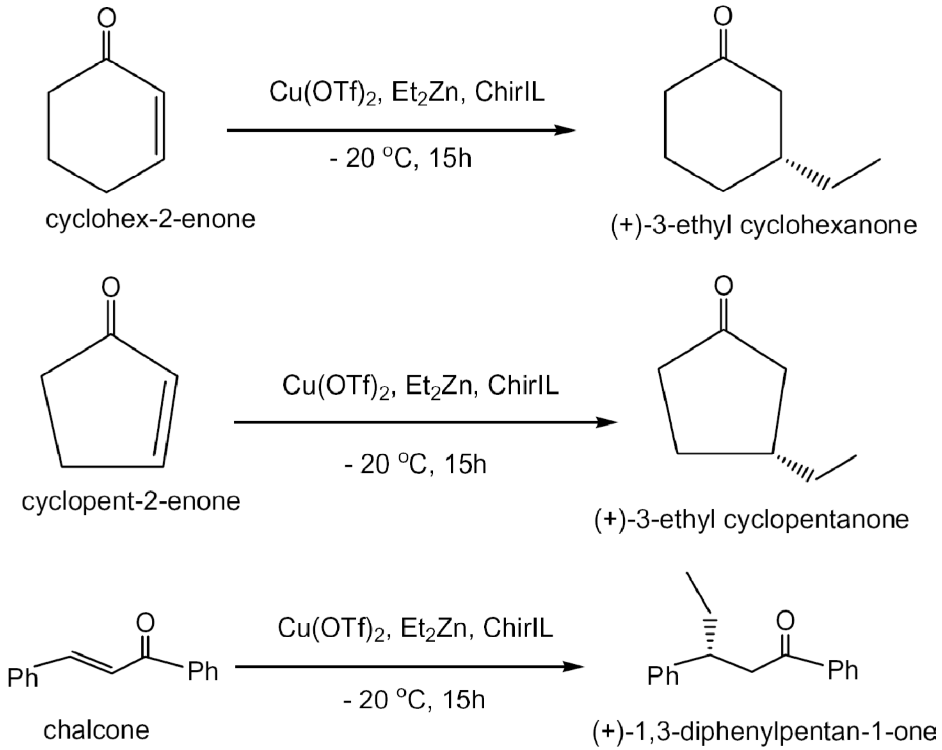
   → L-malic acid based CILs in enantioselective aza-Baylis-Hillman reaction – *upto 84% ee*

- LuO, S. and Cheng, J. P. *Angew. Chem. Int. Ed.* **2006**, *45*, 3093

  → L-proline based CILs as organocatalysts in enantioselective Michael addition to nitro-olefins – *upto 99% ee*

Malhotra's Chemistry

α-pinene CILs in 1,4 additions of Et_2Zn to enones

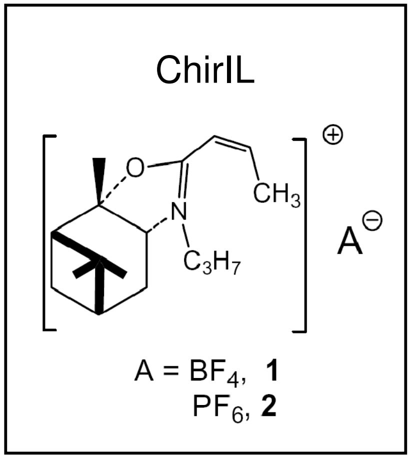


cyclohex-2-enone → (+)-3-ethyl cyclohexanone

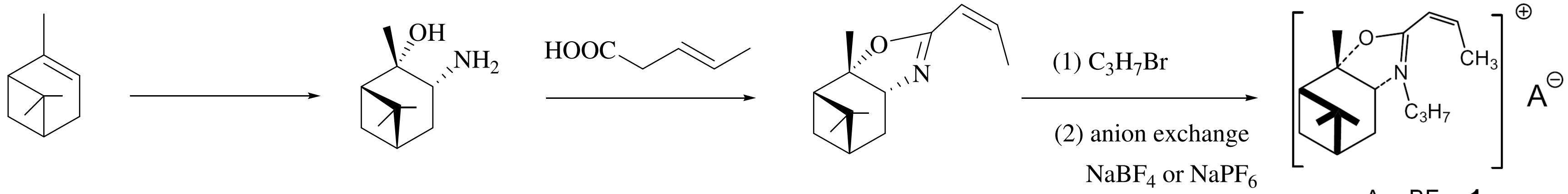
cyclopent-2-enone → (+)-3-ethyl cyclopentanone

chalcone → (+)-1,3-diphenylpentan-1-one

ChirIL



A = BF_4, **1**
PF_6, **2**



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Malhotra, S. *Tetrahedron: Asymmetry* **2006**, *17*, 1032

Malhotra’s Chemistry

Optimization of CIL concentration

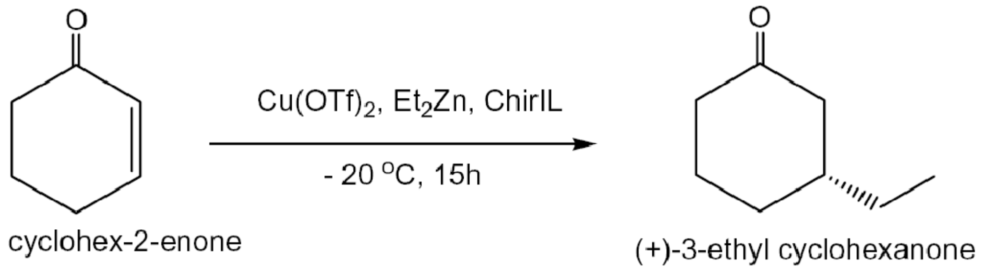


Table 1. Effect of ChirIL mol % on enatiomeric excess

Entry	ChirIL **1** (%)	% ee[a]
1	3	17
2	5	23
3	10	38
4	15	51
5	25	74
6	35	76

[a] ee measurements were confirmed by HPLC analysis with a Chiralpak WH column.

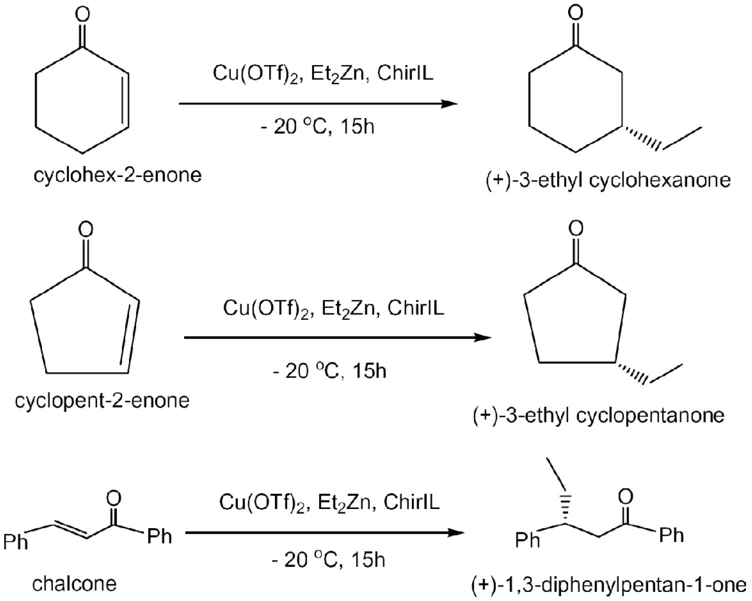
Malhotra, S. *Tetrahedron: Asymmetry* **2006**, *17*, 1032

Malhotra’s Chemistry

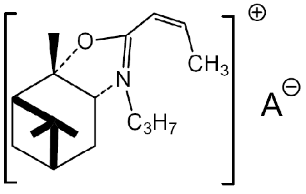
Results

Table 2. Results of the 1,4-addition of diethylzinc to enones in the presence of chiral ionic liquids

Entry	Enone	ChirIL[a]	Temperature (°C)	Product	
				Yield[b] (%)	ee[c] (%)
1	Cyclohexenone	**1**	−20	90	76
2	Cyclohexenone	**1**	0 (23)	93 (94)	68 (52)
3	Cyclohexenone	**2**	−20	87	35
4	Cyclohexenone	**2**	0 (23)	90 (91)	26 (24)
5	Cyclopentenone	**1**	−20	40	73
6	Cyclopentenone	**1**	0 (23)	39 (46)	55 (50)
7	Cyclopentenone	**2**	−20	48	20
8	Cyclopentenone	**2**	0 (23)	48 (52)	15 (12)
9	Chalcone	**1**	−20	52	61
10	Chalcone	**1**	0 (23)	55 (57)	48 (37)
11	Chalcone	**2**	−20	55	37
12	Chalcone	**2**	0 (23)	57 (58)	28 (23)



ChirIL



A = BF$_4$, **1**
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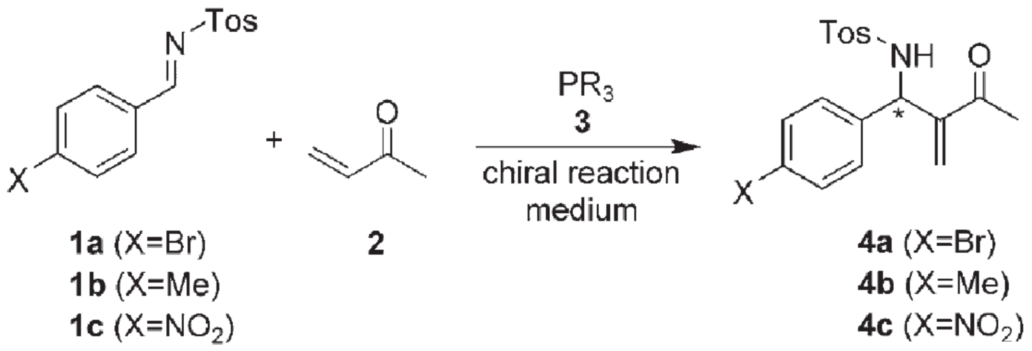
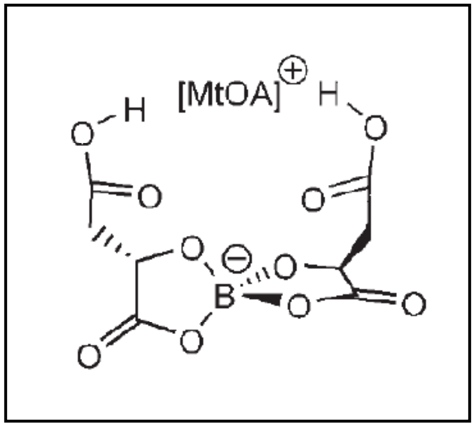
Malhotra, S. *Tetrahedron: Asymmetry* **2006**, *17*, 1032

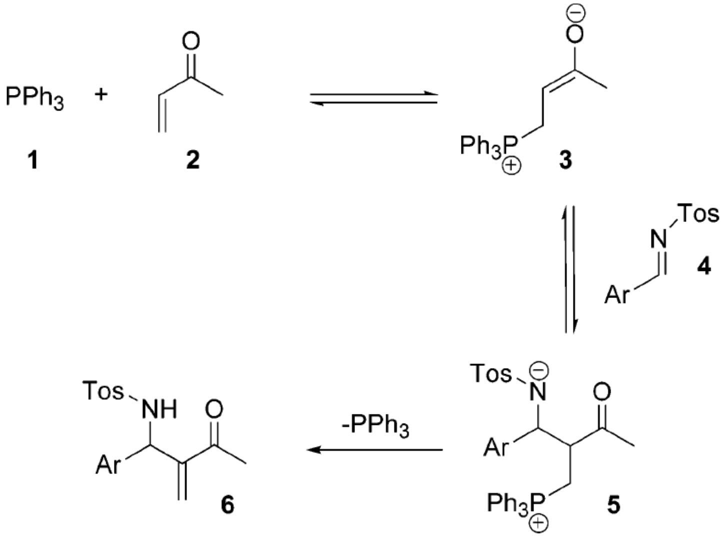
Leitner’s Chemistry

L-malic acid CILs in aza-Baylis Hillman (ABH) reactions

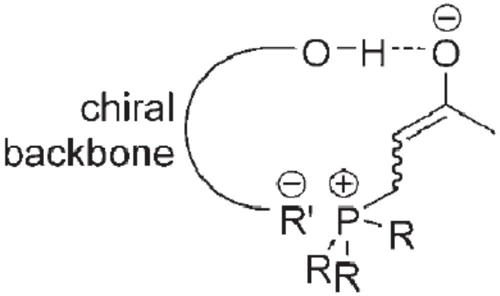




Scheme 1. Proposed Mechanism of the Aza-BH Reaction



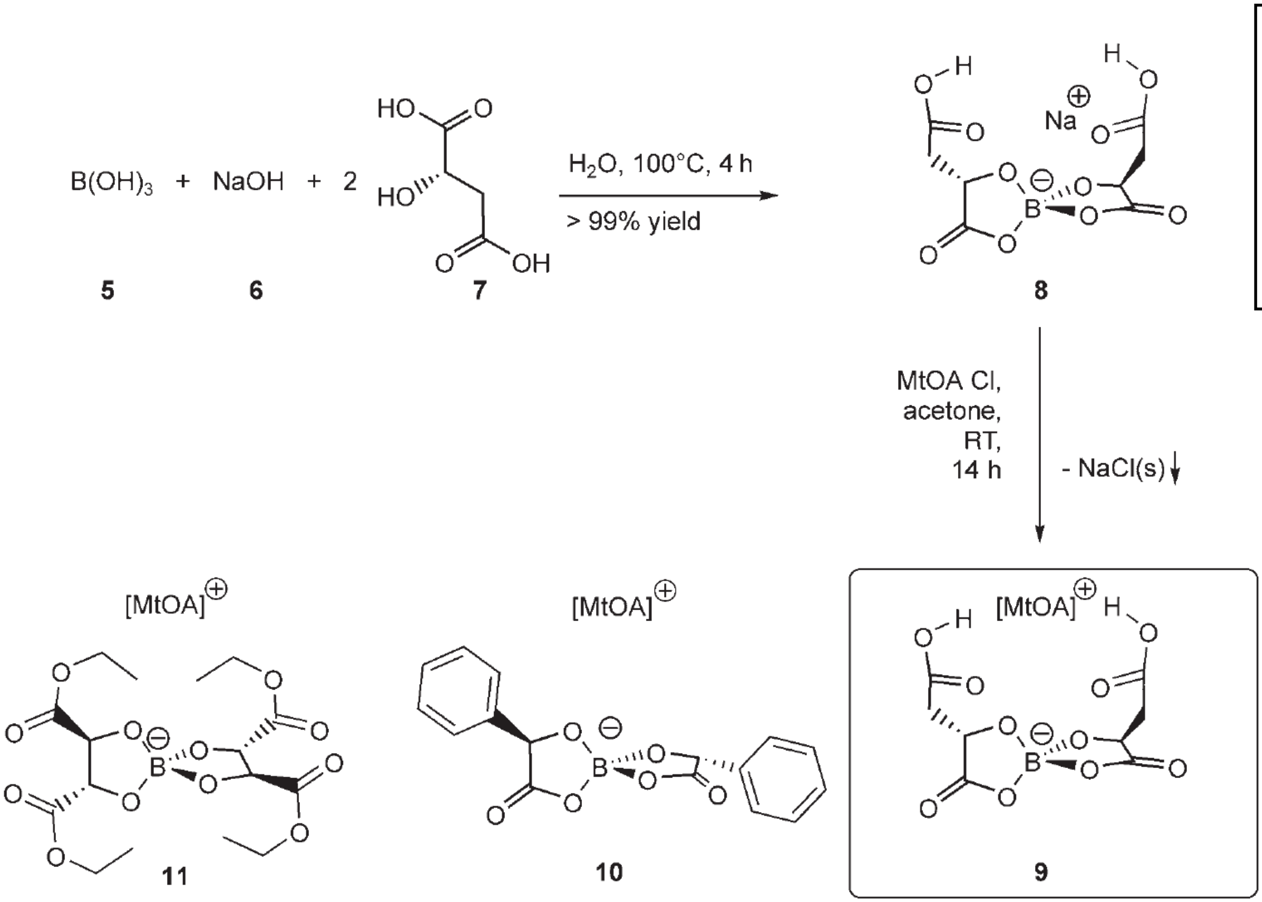
Possible bifunctional stabilization

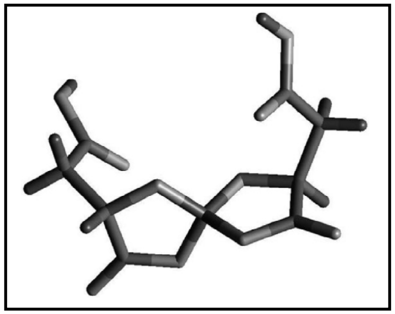


Leitner, W. *J.A.C.S.* **2005**, *127*, 16762
Leitner, W. *Angew. Chem. Int. Ed.* **2006**, *45*, 3689

Leitner's Chemistry

Synthesis of the CILs





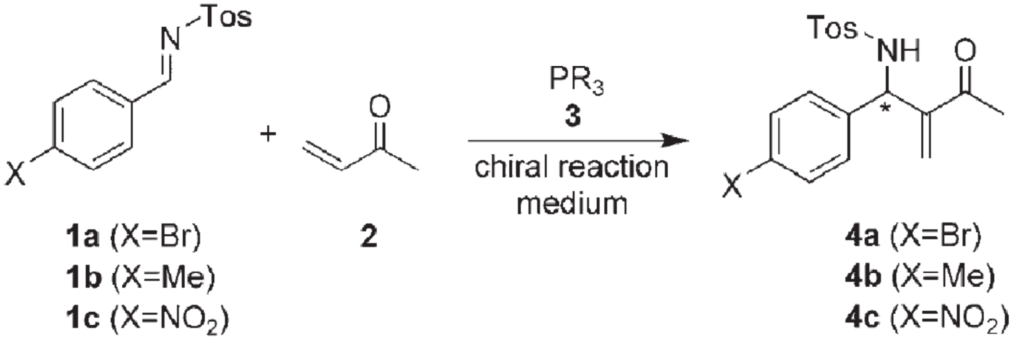
Scheme 2. Two-step synthesis of methyltrioctylammonium dimalatoborate (**9**). Only one of the two possible diastereoisomers is shown.

Colorless viscous liquid
MP -32 ℃

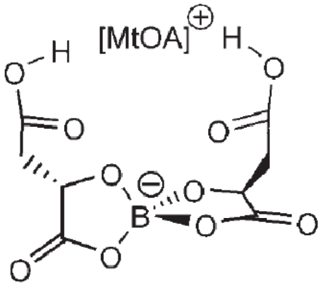
Leitner, W. *Angew. Chem. Int. Ed.* **2006**, *45*, 3689

Leitner's Chemistry

Results



No	Imine	Nucleophilic catalyst	CIL	product	conversion %	%ee
1-4	**1a**	PPh_3	**9**	**4a**	34-39	71-84
5	**1a**	PPh_3	**10**	**4a**	15	racemic
6	**1a**	PPh_3	**11**	**4a**	14	racemic
7	**1a**	P(*o*-tolyl)$_3$	**9**	**4a**	35	74
8	**1a**	$(C_6F_5)PPh_2$	**9**	**4a**	9	71
9	**1b**	PPh_3	**9**	**4b**	39	64
10	**1c**	PPh_3	**9**	**4c**	-	10



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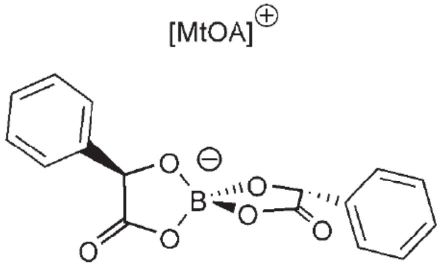

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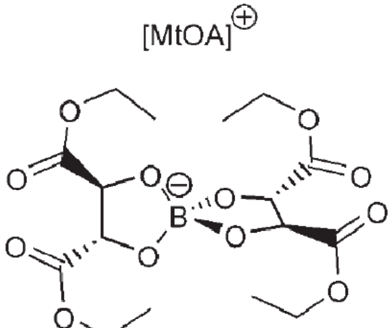

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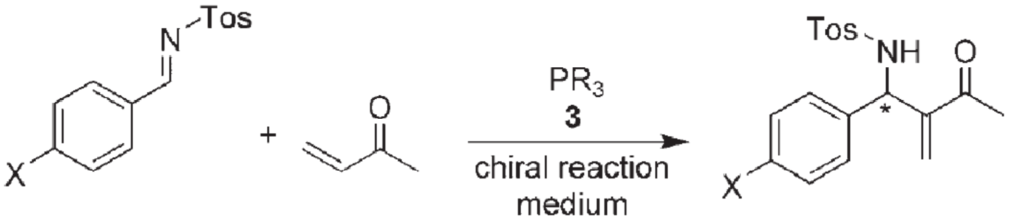
Leitner, W. *Angew. Chem. Int. Ed.* **2006**, *45*, 3689

Leitner’s Chemistry

Results



1a (X=Br)
1b (X=Me)
1c (X=NO$_2$)

2

4a (X=Br)
4b (X=Me)
4c (X=NO$_2$)

No	Imine	Nucleophilic catalyst	CIL	product	conversion %	%ee
1-4	**1a**	PPh$_3$	**9**	**4a**	34-39	71-84
5	**1a**	PPh$_3$	**10**	**4a**	15	racemic
6	**1a**	PPh$_3$	**11**	**4a**	14	racemic
7	**1a**	P(*o*-tolyl)	**9**	**4a**	35	74
8	**1a**	(C$_6$F$_5$)PPh$_2$	**9**	**4a**	9	71
9	**1b**	PPh$_3$	**9**	**4b**	39	64
10	**1c**	PPh$_3$	**9**	**4c**	-	10

Comparable with the best catalysts in conventional solvents for ABH reactions

→ 94% ee

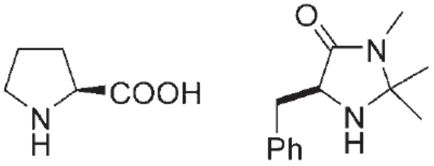
JACS, **2005**, *127*, 3680

Leitner, W. *Angew. Chem. Int. Ed.* **2006**, *45*, 3689

Luo & Cheng's Chemistry

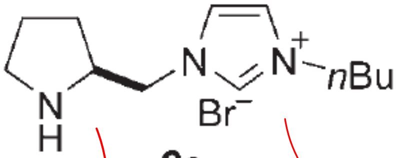
L-proline CILs in Michael Addition to Nitroolefins

The inspiration:



Scheme 1. Privileged organic catalysts.

Design for functionalized CILs



2a

Ionic liquid moiety

Phase-tag & chiral-induction group

Chiral pyrrolidine unit

Catalytic Site

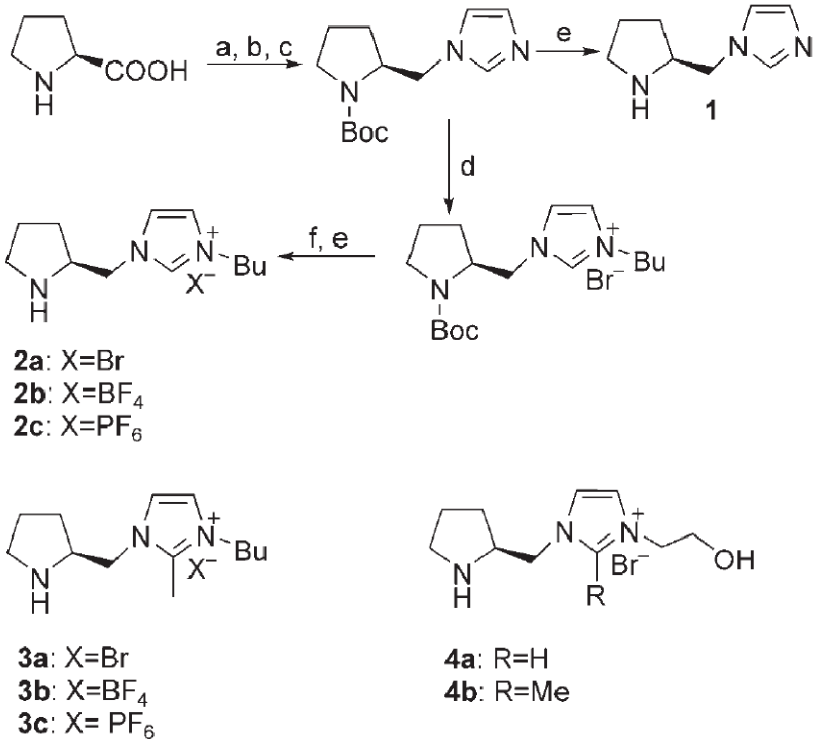
(1) Bulky & planar organic cation imparts space shielding to reaction intermediate

(2) Proximity of ionic-liquid unit to active site creates reaction friendly environment

LuO, S. and Cheng, J. P. *Angew. Chem. Int. Ed.* **2006**, *45*, 3093

Luo & Cheng’s Chemistry

Synthesis of CILs



Scheme 2. Synthesis of functionalized chiral ionic liquids. Conditions a) $LiAlH_4$, THF, 75%; b) 1. Boc_2O, NaOH; 2. TosCl, pyridine, 90% for 2 steps; c) NaH, imidazole, 83%; d) *n*BuBr, toluene, 70°C, 93%; e) HCl/EtOH; then sat. $NaHCO_3$, 90%; f) NaX, acetone/acetonitrile, room temperature. Boc = *tert*-butoxycarbonyl, THF = tetrahydrofuran, Tos = toluene-4-sulfonyl.

45% total yield

Straightforward synthesis

All CILs – viscous liquids at RT

Soluble in moderately polar solvents & insoluble in less polar solvents

Hence, suffice for practical applications!!

LuO, S. and Cheng, J. P. *Angew. Chem. Int. Ed.* **2006**, *45*, 3093

Luo & Cheng's Chemistry

Trying out the different toys…

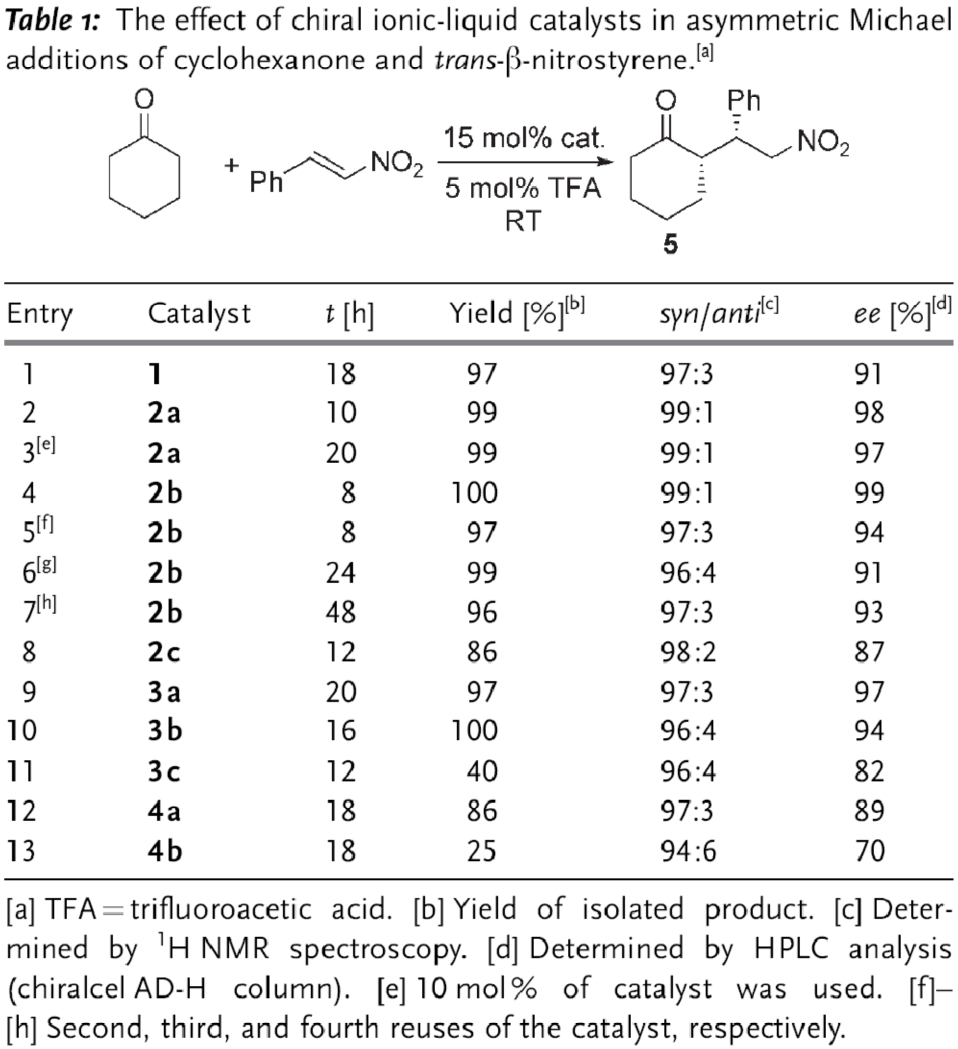
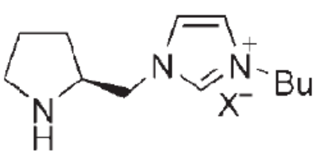


Table 1: The effect of chiral ionic-liquid catalysts in asymmetric Michael additions of cyclohexanone and *trans*-β-nitrostyrene.[a]

Entry	Catalyst	*t* [h]	Yield [%][b]	*syn/anti*[c]	*ee* [%][d]
1	**1**	18	97	97:3	91
2	**2a**	10	99	99:1	98
3[e]	**2a**	20	99	99:1	97
4	**2b**	8	100	99:1	99
5[f]	**2b**	8	97	97:3	94
6[g]	**2b**	24	99	96:4	91
7[h]	**2b**	48	96	97:3	93
8	**2c**	12	86	98:2	87
9	**3a**	20	97	97:3	97
10	**3b**	16	100	96:4	94
11	**3c**	12	40	96:4	82
12	**4a**	18	86	97:3	89
13	**4b**	18	25	94:6	70

[a] TFA = trifluoroacetic acid. [b] Yield of isolated product. [c] Determined by ^{1}H NMR spectroscopy. [d] Determined by HPLC analysis (chiralcel AD-H column). [e] 10 mol% of catalyst was used. [f]–[h] Second, third, and fourth reuses of the catalyst, respectively.



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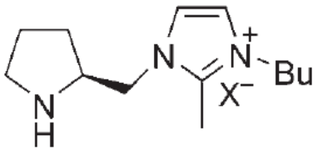
2c: X=PF$_6$



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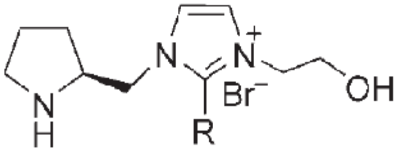
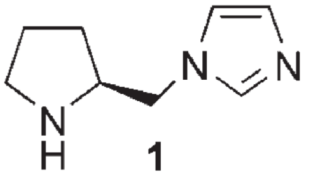


4a: R=H
4b: R=Me



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LuO, S. and Cheng, J. P. *Angew. Chem. Int. Ed.* **2006**, *45*, 3093

Luo & Cheng's Chemistry

Trying out the different toys…

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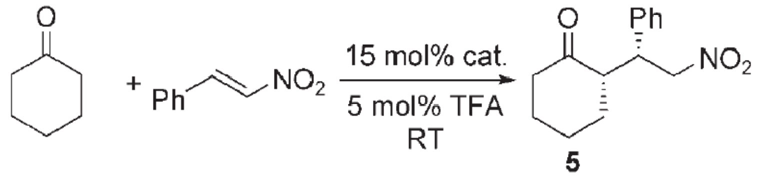

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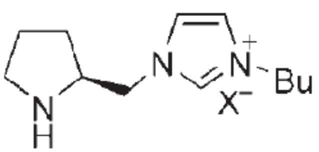

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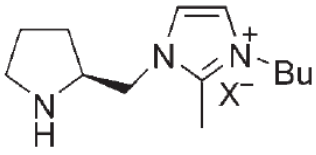

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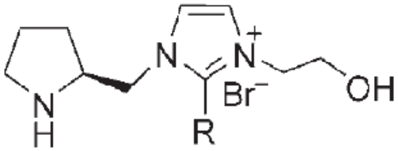

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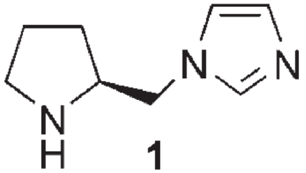

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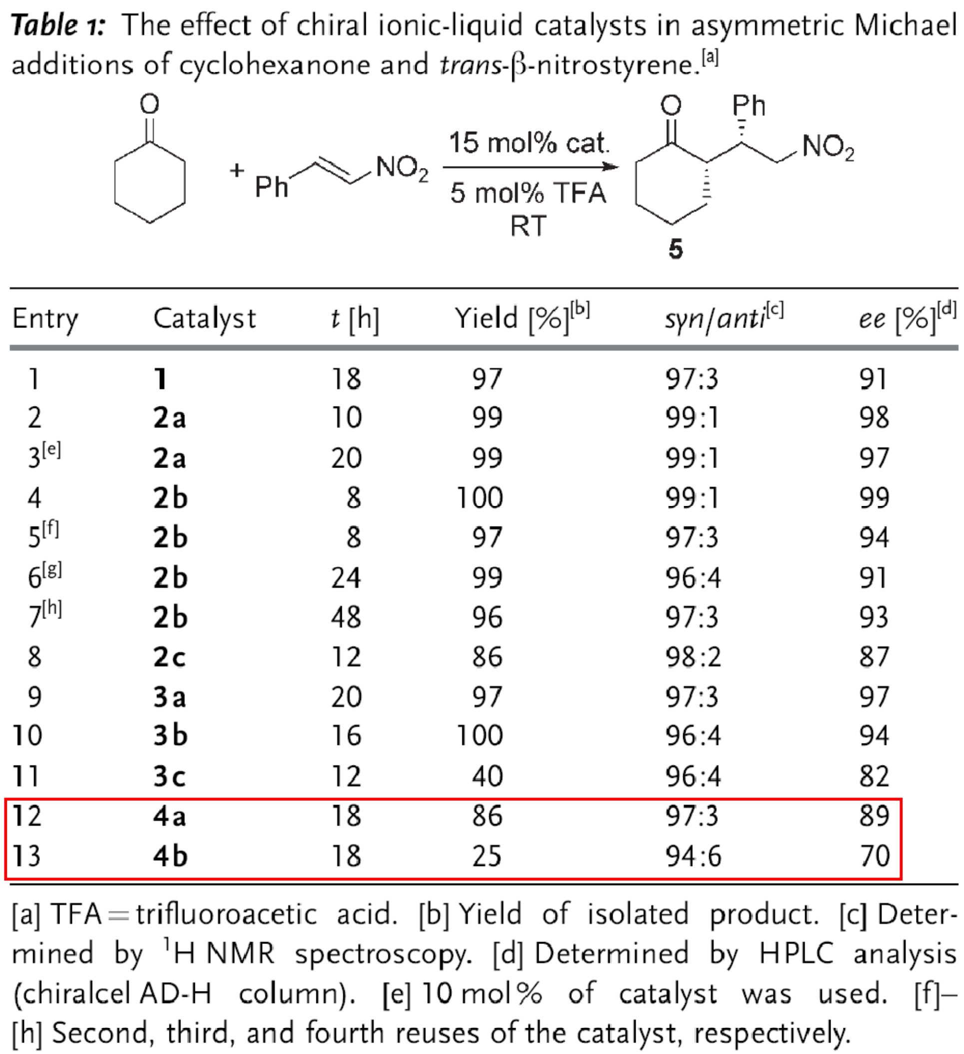
LuO, S. and Cheng, J. P. *Angew. Chem. Int. Ed.* **2006**, *45*, 3093

Luo & Cheng's Chemistry

Trying out the different toys…



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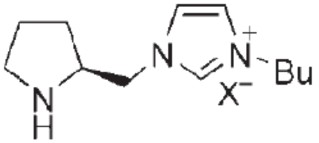

2a: X=Br
2b: $X=BF_4$
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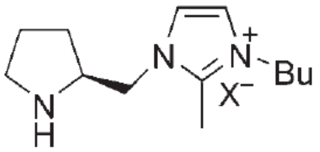

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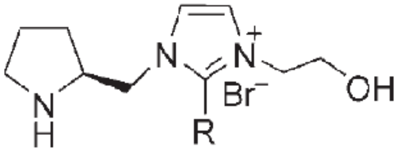

4a: R=H
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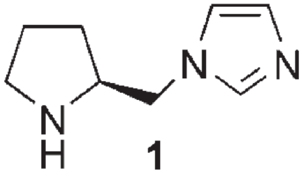

1

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Trying out the different toys…

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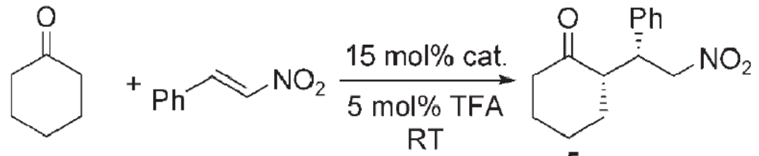

5

Entry	Catalyst	*t* [h]	Yield [%][b]	*syn/anti*[c]	*ee* [%][d]
1	**1**	18	97	97:3	91
2	**2a**	10	99	99:1	98
3[e]	**2a**	20	99	99:1	97
4	**2b**	8	100	99:1	99
5[f]	**2b**	8	97	97:3	94
6[g]	**2b**	24	99	96:4	91
7[h]	**2b**	48	96	97:3	93
8	**2c**	12	86	98:2	87
9	**3a**	20	97	97:3	97
10	**3b**	16	100	96:4	94
11	**3c**	12	40	96:4	82
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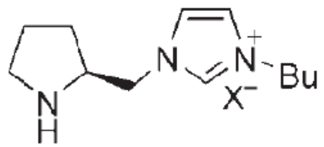

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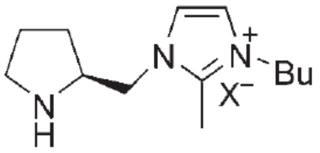

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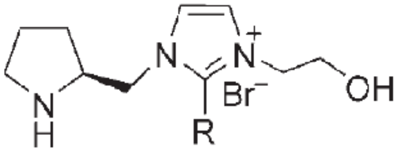

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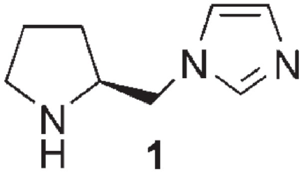

1

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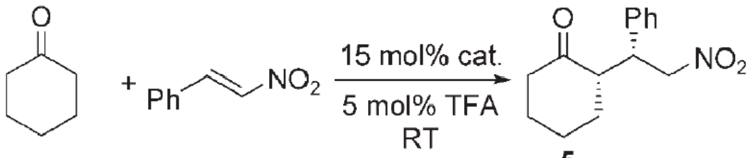

5

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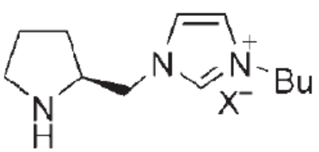

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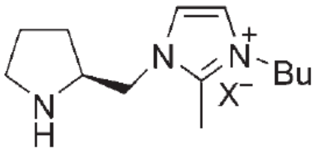

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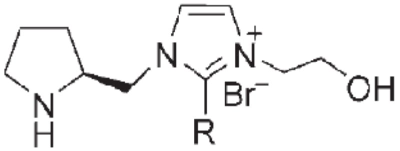

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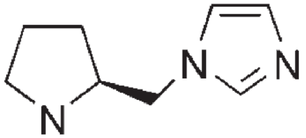

1

But wait a minute!! Why ionic liquids right?

Well, recoverability & reusability!!

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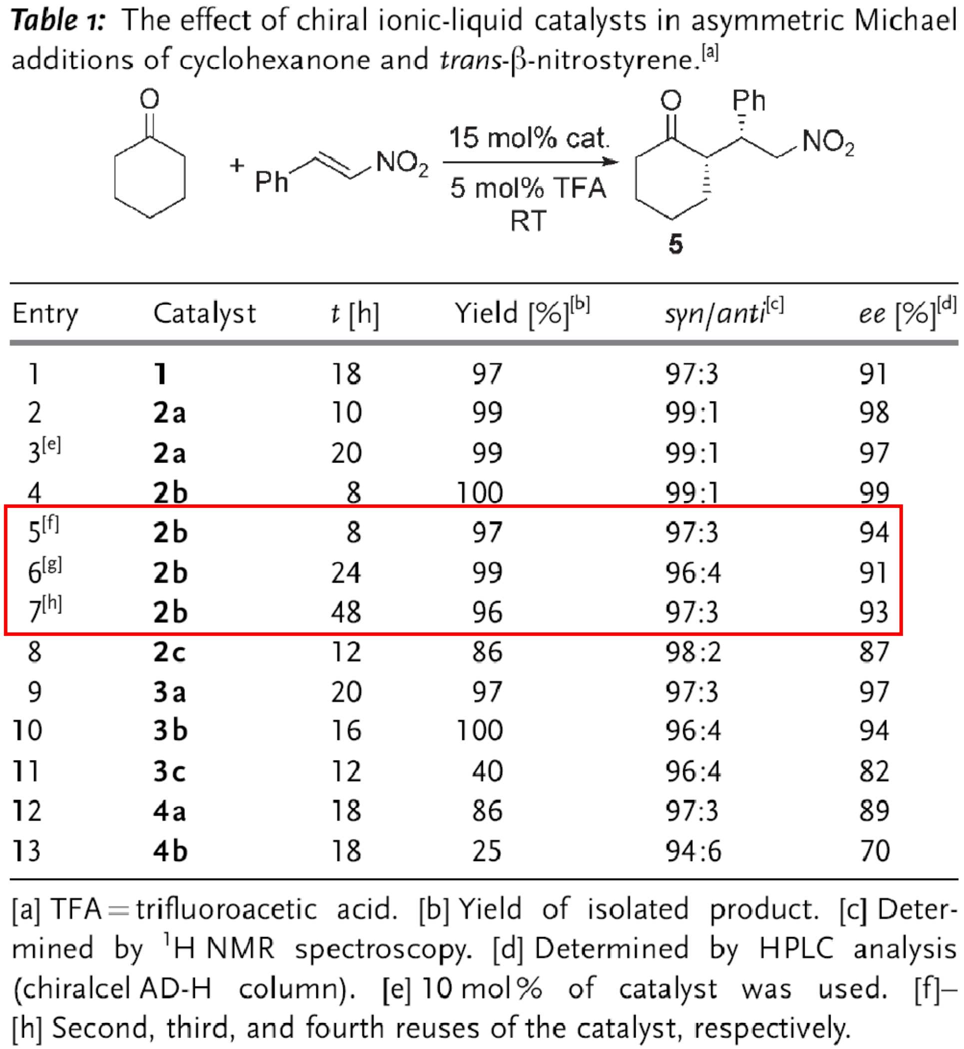
Trying out the different toys…



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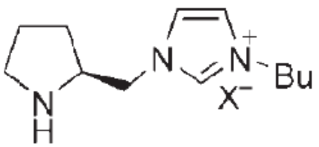

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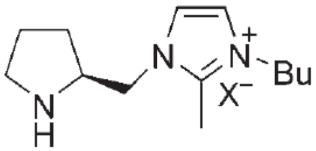

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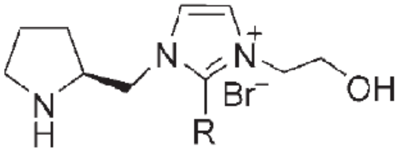

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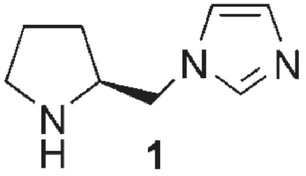

1

Experimental: Mix, stir, dilute with ether, separate – product to column and catalst used directly for next run

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Luo & Cheng's Chemistry

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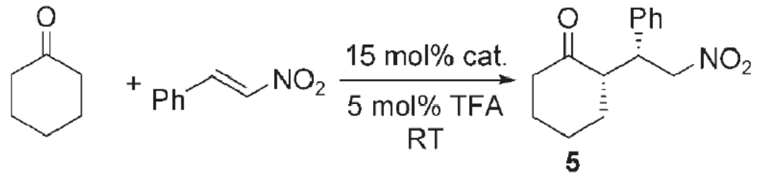

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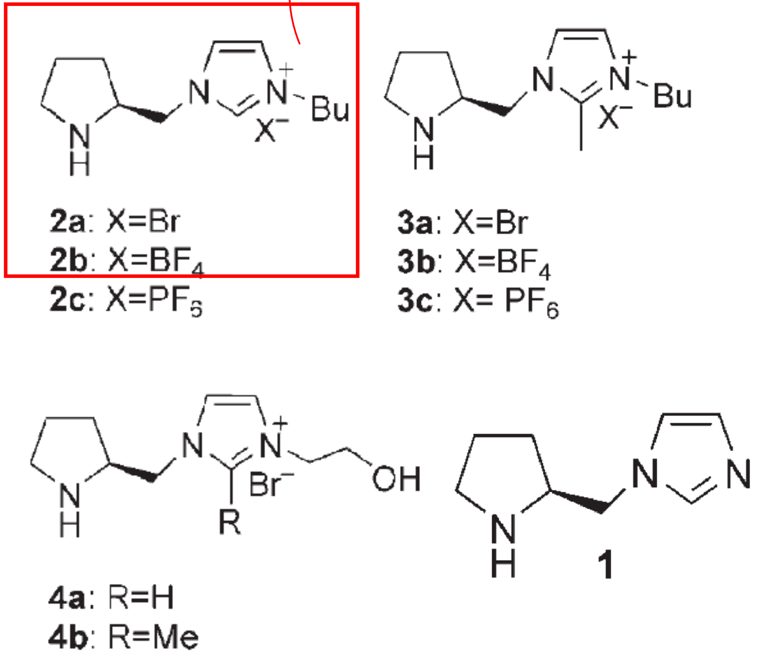

optimal catalysts

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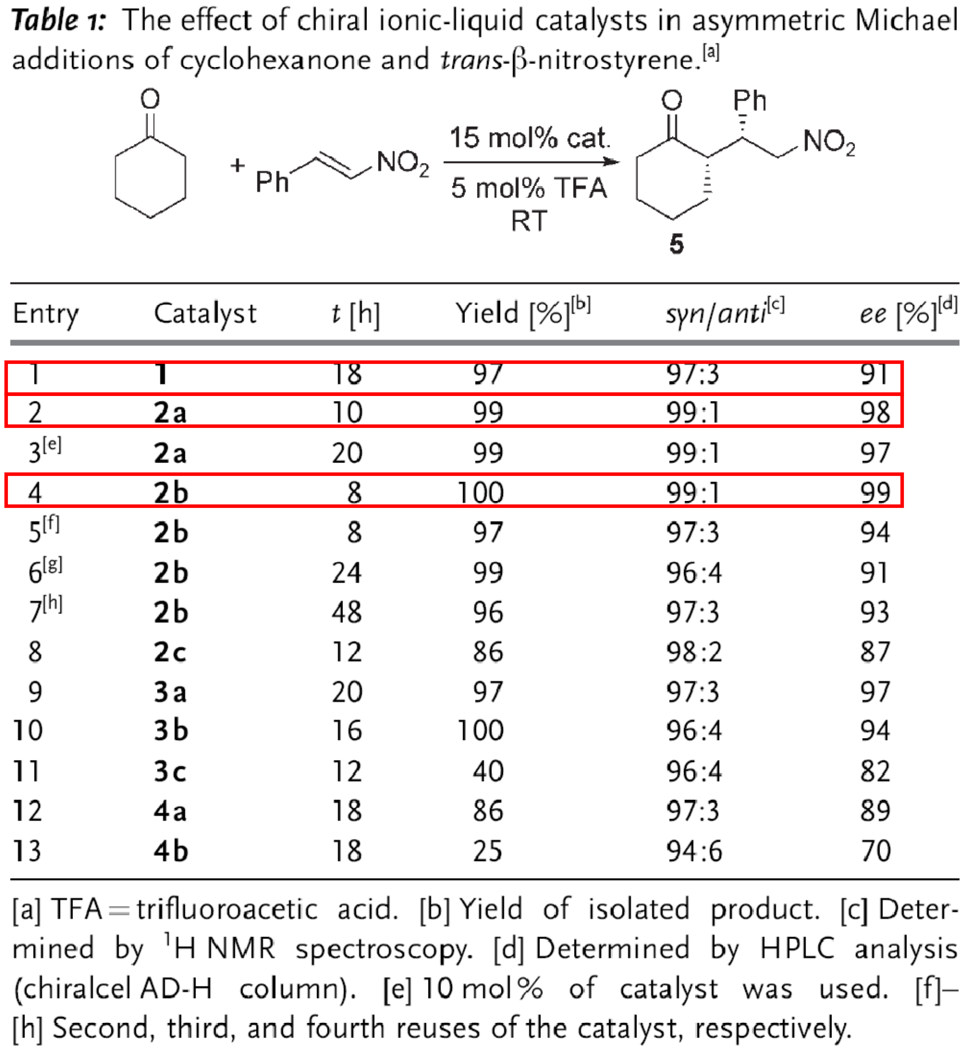

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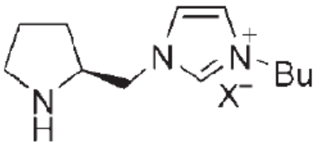

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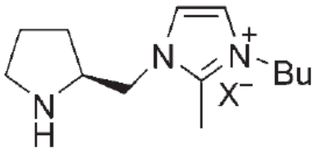

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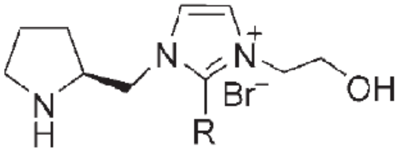

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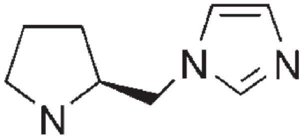

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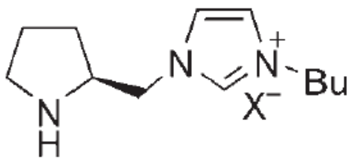
How general is this?



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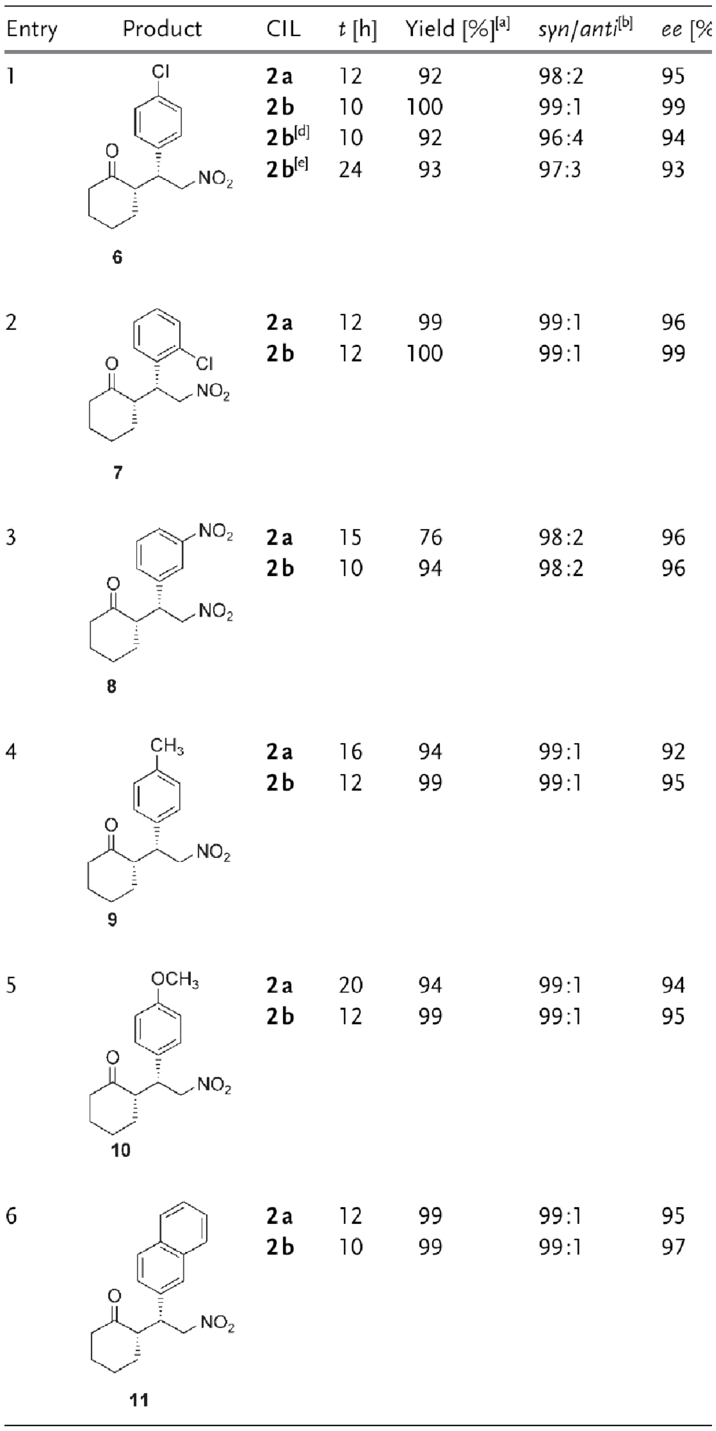

Entry	Product	CIL	*t* [h]	Yield [%][a]	*syn/anti*[b]	*ee* [%
1	**6**	**2a**	12	92	98:2	95
		2b	10	100	99:1	99
		2b[d]	10	92	96:4	94
		2b[e]	24	93	97:3	93
2	**7**	**2a**	12	99	99:1	96
		2b	12	100	99:1	99
3	**8**	**2a**	15	76	98:2	96
		2b	10	94	98:2	96
4	**9**	**2a**	16	94	99:1	92
		2b	12	99	99:1	95
5	**10**	**2a**	20	94	99:1	94
		2b	12	99	99:1	95
6	**11**	**2a**	12	99	99:1	95
		2b	10	99	99:1	97

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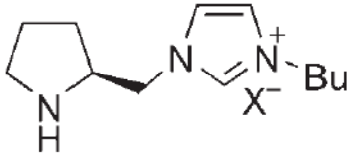

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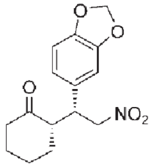
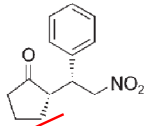
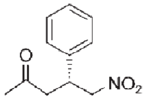
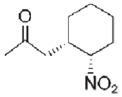
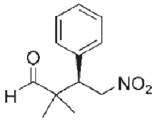
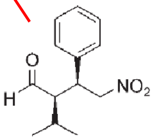
Entry	Product	CIL	*t* [h]	Yield [%][a]	*syn*/*anti*[b]	*ee* [%][c]
7	 **12**	**2a** **2b**	42 24	99 99	98:2 99:1	94 97
8	 **13**	**2a** **2b**	80 60	61 87	75:25 63:37	83/80 79/82
9	 **14**	**2a** **2b**	12 12	77 83	– –	45 43
10	 **15**	**2a** **2b**	24 24	57 92	83:17 85:15	79/81 76/80
11	 **16**	**2a** **2b**	96 96	51 70	– –	89 86
12	 **17**	**2a** **2b**	60 60	73 100	90:10 90:10	77 72

opp. facial induction???

LuO, S. and Cheng, J. P. *Angew. Chem. Int. Ed.* **2006**, *45*, 3093

Luo & Cheng’s Chemistry

Model for observed diastereo- & enantio-selectivity

Acyclic synclinical model

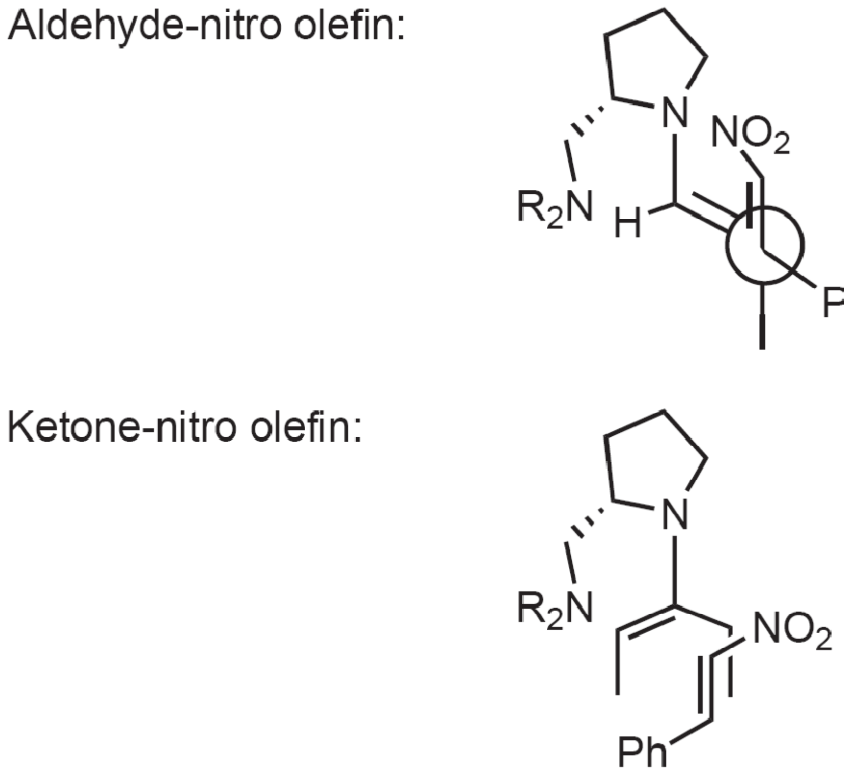


Figure 1 Potential transition states

Betancourt, J. M. *Synthesis*, **2004**, *9*, 1509

Conclusions

- A series of tables containing all the CILs described to date and their physical properties.

  Tetrahedron: Asymmetry, **2005**, *16*, 3921

- Owing to their unique features, CILs are lot better than conventional solvents from a practical standpoint

- Recoverable & reusable repeatedly with almost equivalent results.

- Green & clean.

- Easy manipulation to suit needs.

- If developed, it might be a powerful lab as well as industrial scale tool.

- Recent applications have shown excellent results – comparable with results from conventional systems – could be the start of an exciting field…

or with just a few good papers out there, does it really have a future?