Merging Nucleophilic and Hydrogen Bonding Catalysis: An Anion Binding Approach to the Kinetic Resolution of Amines

Chandra Kanta De, Eric G. Klauber, and Daniel Seidel*

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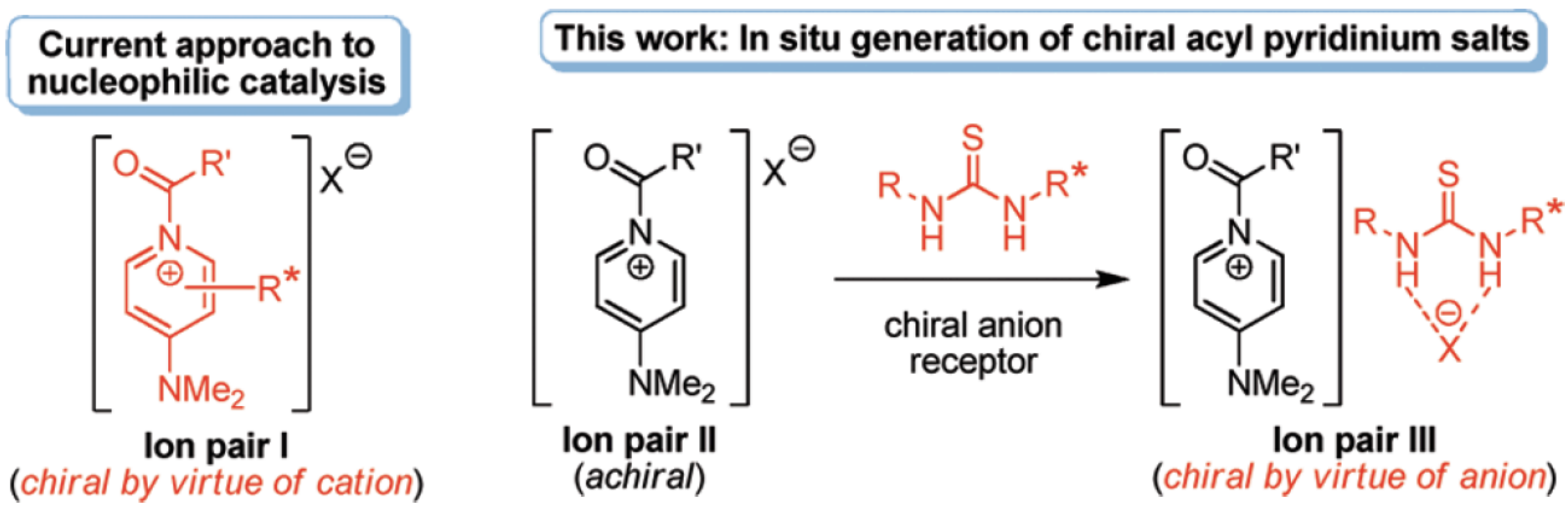
Enantioselective Acyl transfer Pathway



- used for kinetic resolution and desymmetrization processes
- enantioselective acyl transfer pathways

- **III could** be a better acylating agent than **II,**
- proper choice of X- and reaction medium : decrease solubility of **II over III**

new concept for asymmetric nucleophilic catalysis : kinetic resolution of primary amines.

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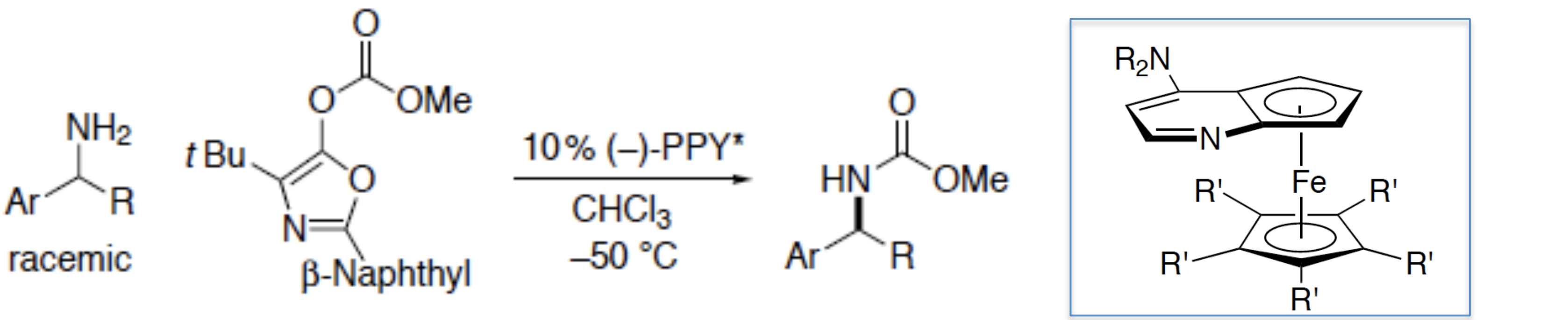
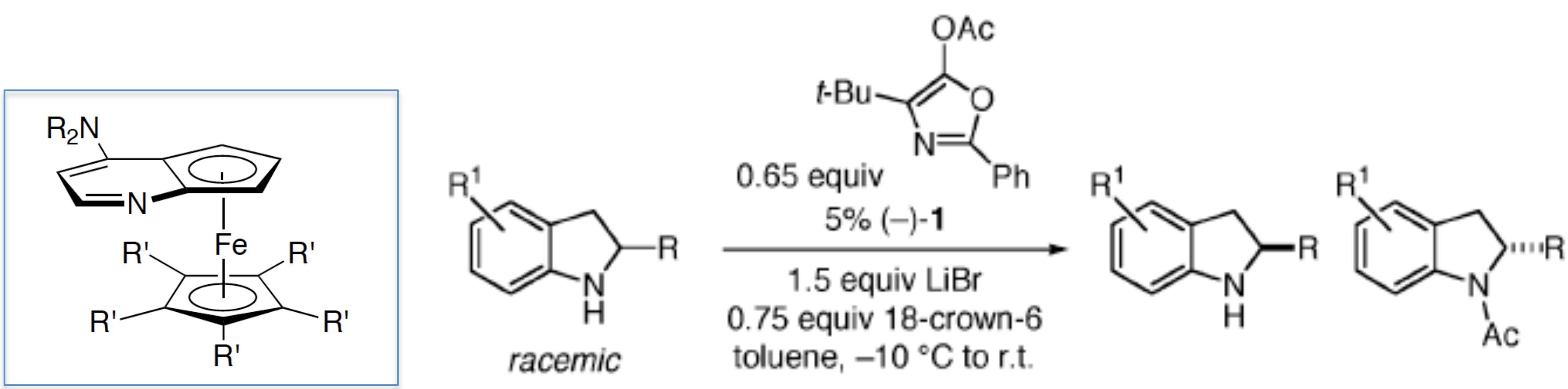
Kinetic Resolution of amine



NR$_2$ = pyrrolidino, R' = Me: (–)-PPY* (**1**)

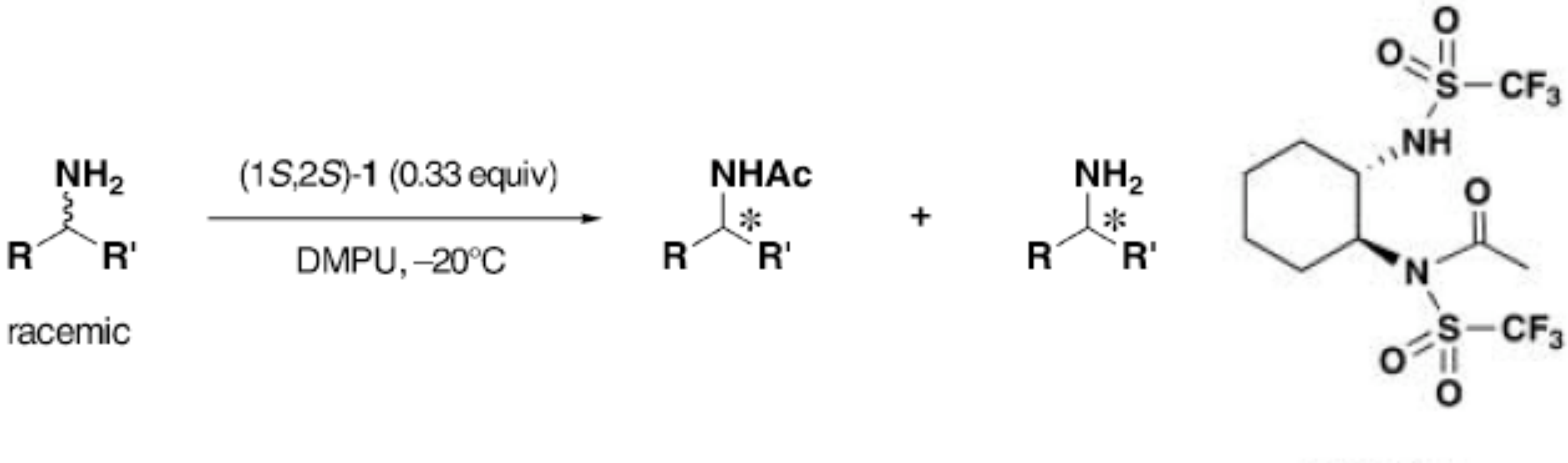
Fu, G. C.; Arai, S.; Bellemin-Laponnaz, S. *Angew. Chem. Int. Ed.* **2001**, *40,* 234-236.



NR$_2$ = pyrrolidino, R = 3,5-dimethylphenyl

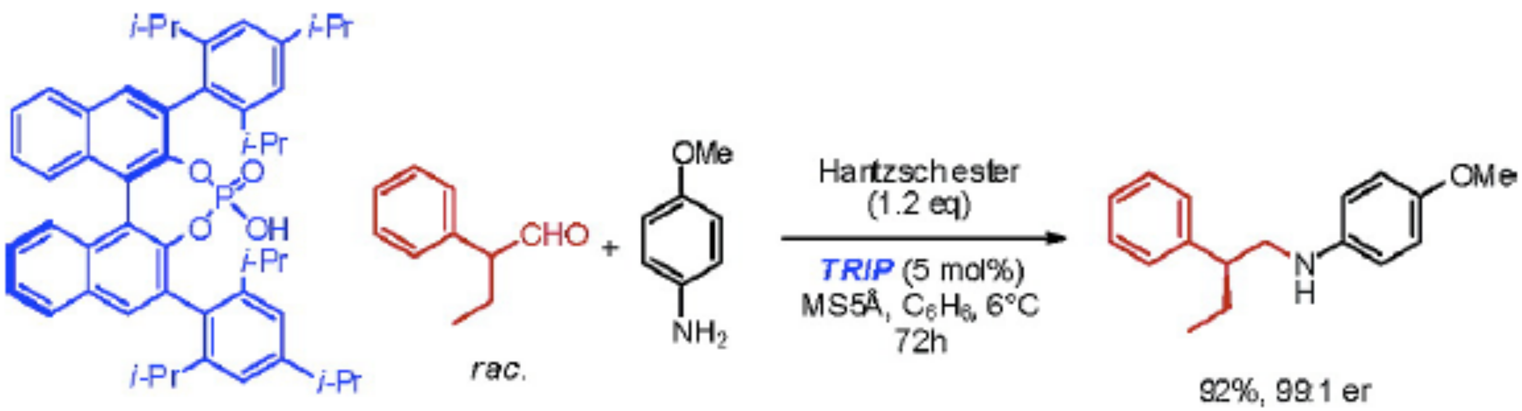
Fu, G. C.; Arp, F. O. *J. Am. Chem. Soc* **2006,** *128*, 14264-14265.

Kinetic Resolution of amine/imine



(1S,2S)-1

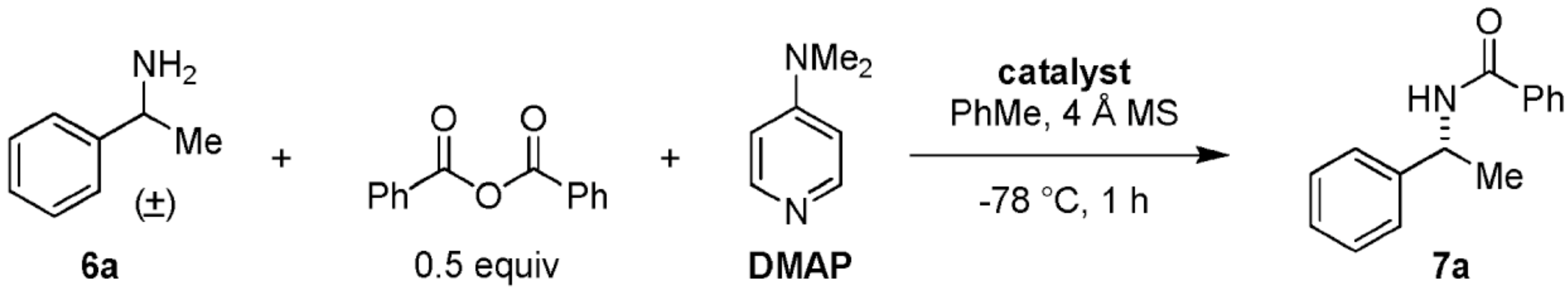
Mioskowski, C.; Srseniyadis, S.; Valleix, A.; Wagner, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 3314-3317.



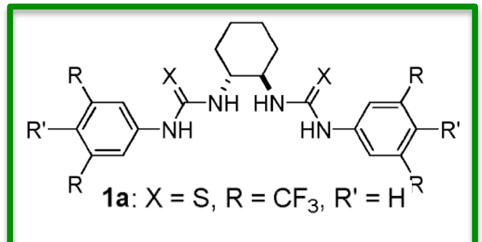
TRIP

List, B.; Hoffmann, S.; Nicoletti, M. *J. Am. Chem. Soc* **2006,** *128*, 13074-13075.

Evaluation of Reaction Parameters



entry	catalyst (mol %)	DMAP (mol %)	concn [M]	conversion (%)	*s*-factor
1	**1a** (20)	50	0.06	47	5.5
2	**1a** (20)	50	0.03	47	7.0
3	**1a** (20)	50	0.02	47	8.6
4	**1a** (20)	50	0.01	45	9.5
5	**1a** (20)	50	0.005	44	9.4
6	**1a** (20)	40	0.01	47	9.4
7	**1a** (20)	30	0.01	47	10
8	**1a** (20)	20	0.01	45	10
9	**1a** (20)	10	0.01	43	8.5
10	**1a** (20)	5	0.01	44	7.7
11	**1a** (15)	15	0.01	46	9.0
12	**1a** (10)	10	0.01	46	9.0
13	**1a** (5)	5	0.01	44	8.5



0.01 M concentration providing the best *s-factor*

20 mol % of DMAP improving *s-factor* to 10

Lowering of both catalysts:
s-factors slightly reduced

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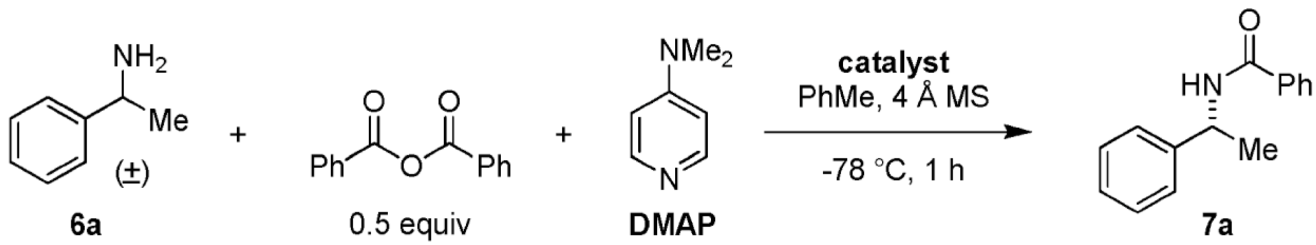
Evaluation of Reaction Parameters

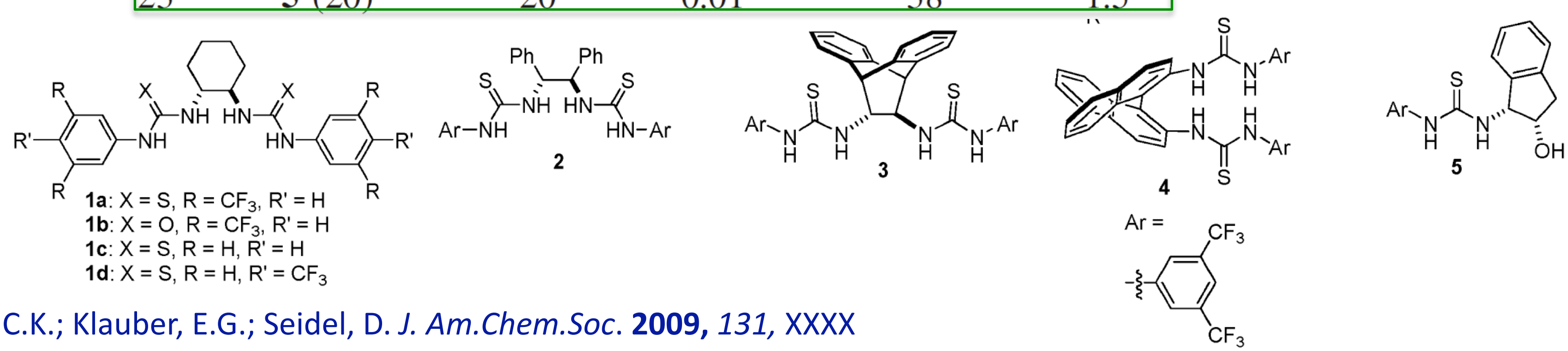


entry	catalyst (mol %)	DMAP (mol %)	concn [M]	conversion (%)	*s*-factor
14	none	none	0.01	<1	N/A
15	none	20	0.01	<2	N/A
16	**1a** (20)	none	0.01	40	1.4
17	**1b** (20)	20	0.01	40	8.6
18	**1c** (20)	20	0.01	43	4.5
19	**1d** (20)	20	0.01	21	4.1
20	**2** (20)	20	0.01	44	7.2
21	**3** (20)	20	0.01	42	3.7
22	**4** (20)	20	0.01	30	1.2
23	**5** (20)	20	0.01	38	1.5

Only DMAP:No effect on reaction rate

no DMAP : significant amounts of enantioenriched product

Other HB catalysts:inferior results



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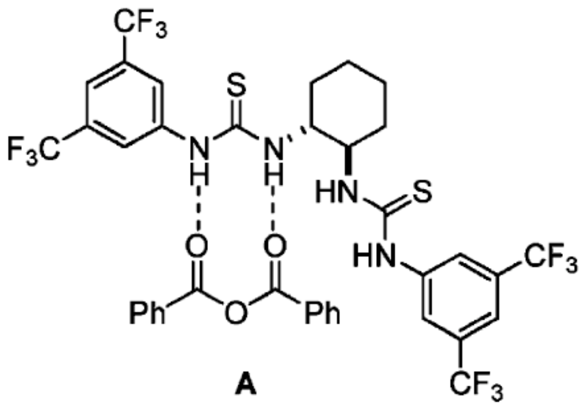
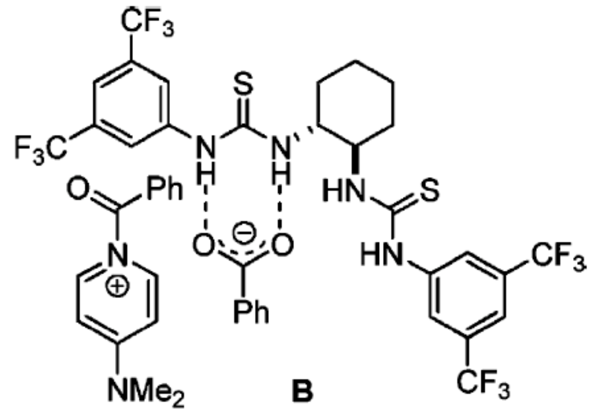
Proposed Chiral Ion Pair Intermediate





in the absence of DMAP : HB activation of the anhydride

In the presence of DMAP: **B dominates**

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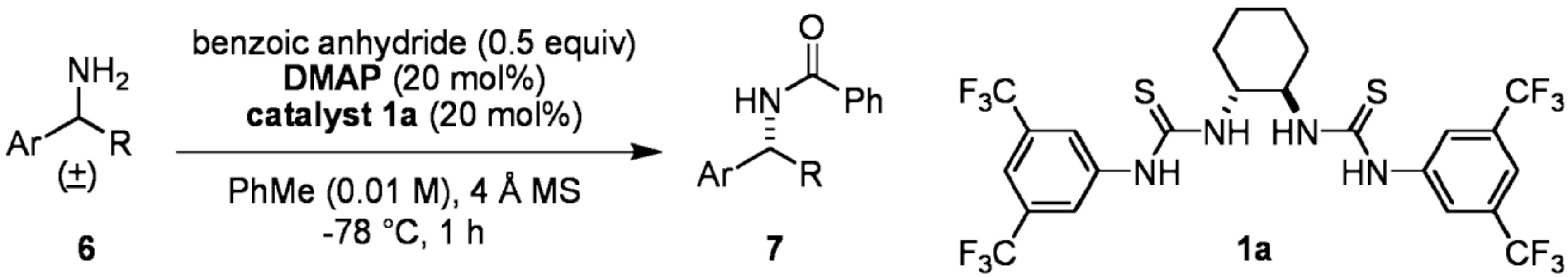
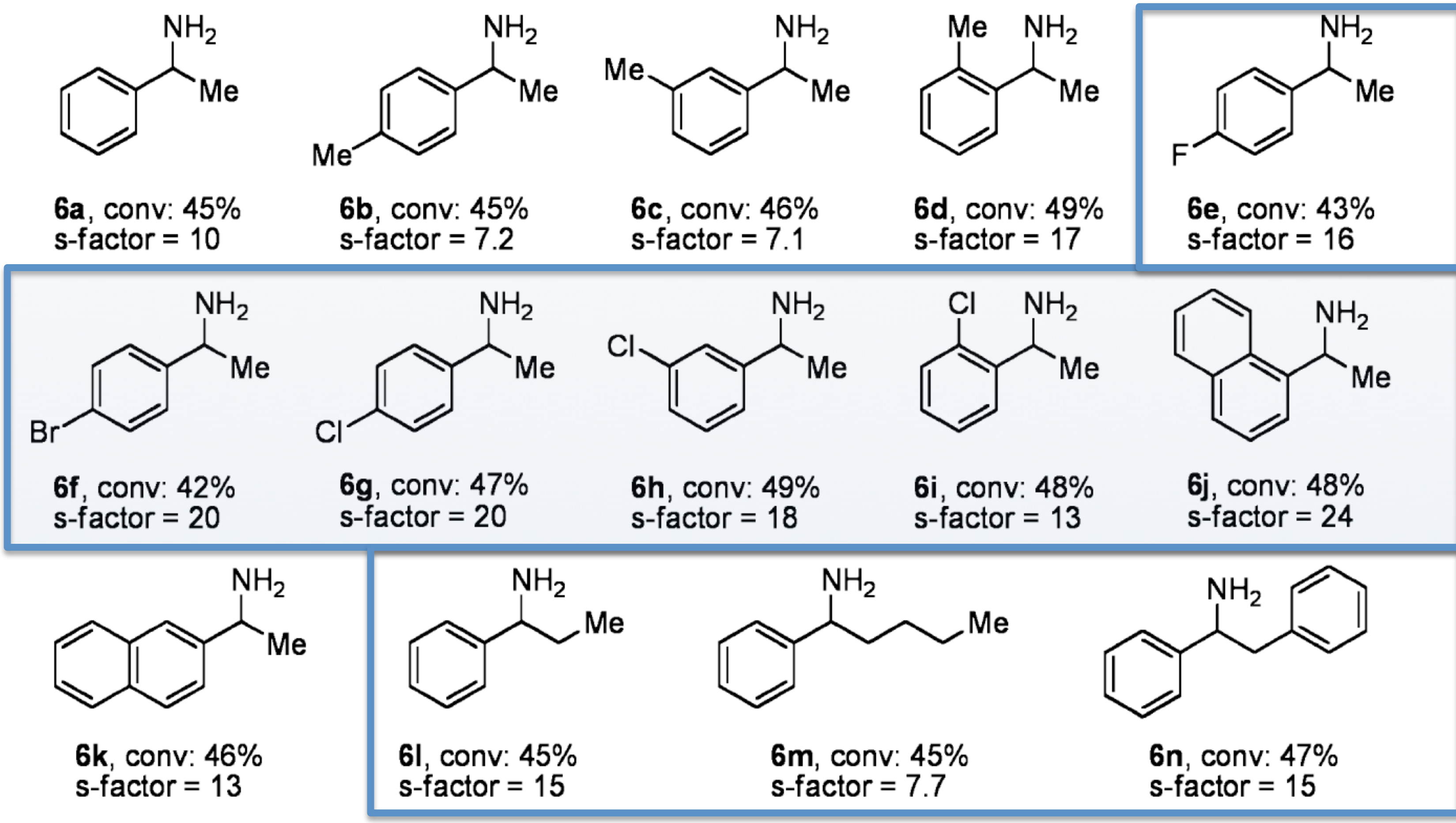
Scope of the Reaction





e poor :better
s-factor