Design of novel asymmetric organocatalysts

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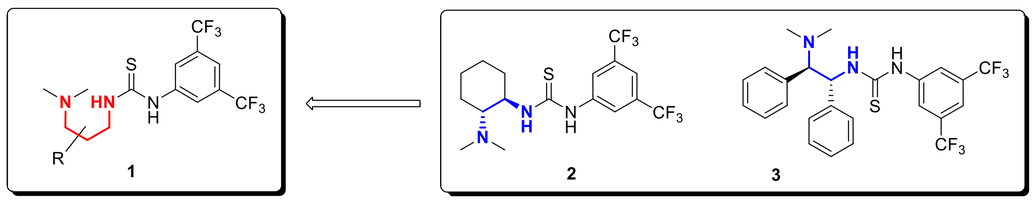
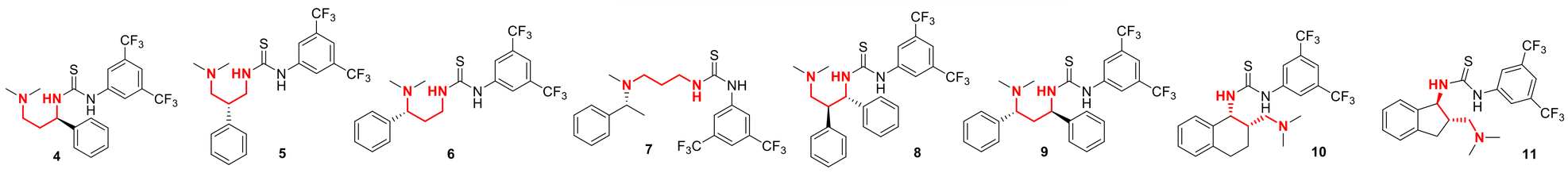
Goals

1. Development of asymmetric organocatalysts based on 1,3-propylenediamine scaffold

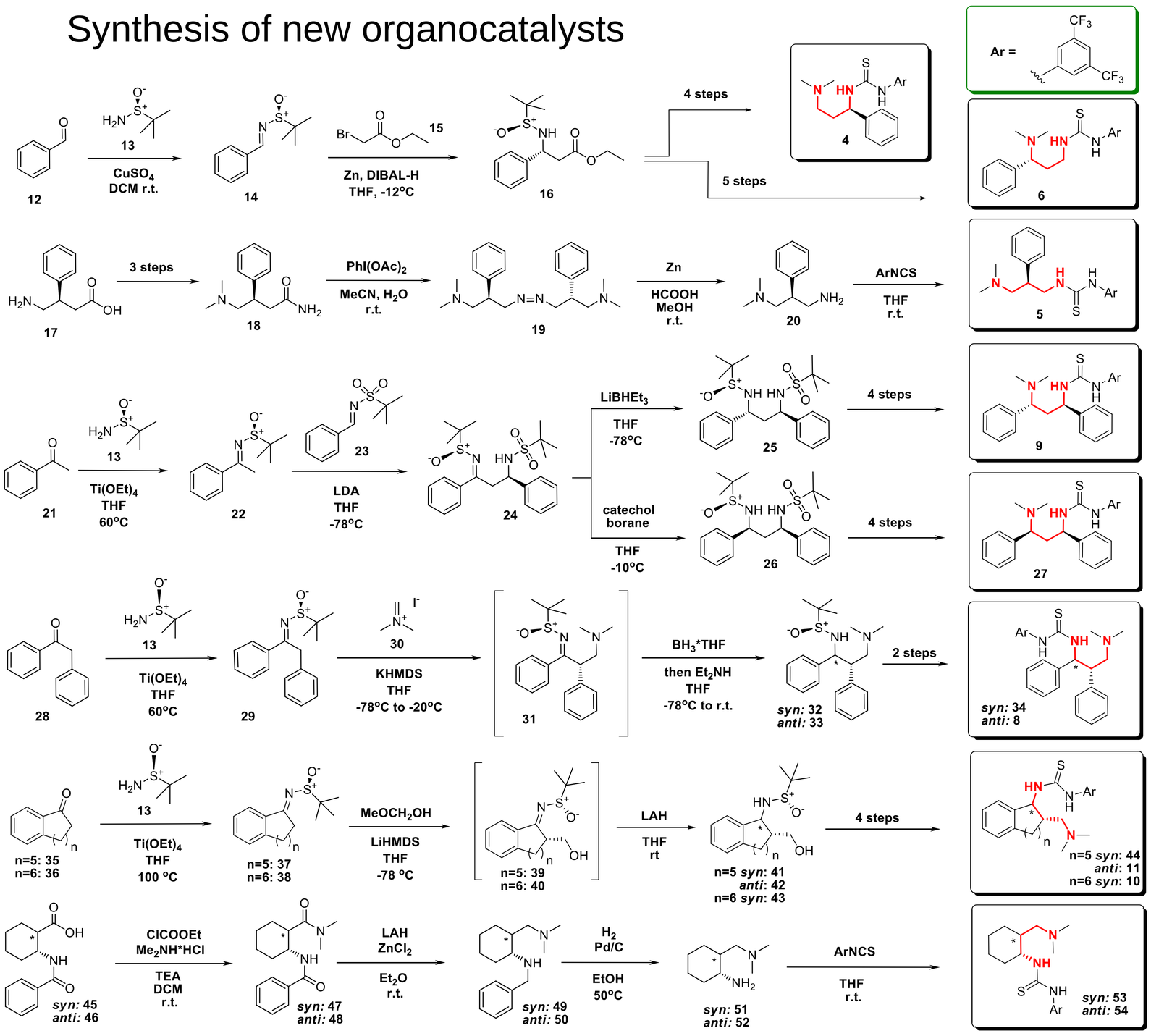
2. Identification of the optimal position for the chiral center in the 1,3-propylenediamine moiety



Takemoto *et al., J. Am. Chem. Soc.*, **2005**, *127*, 119



Synthesis of new organocatalysts



(*S*)-*tert*-Butylsulfinyl group was employed as a chiral auxiliary in diastereomeric synthesis of **4**, **6**, **8**, **9**, **10, 11**, **27**, **34** and **44.**

Key step in the synthesis of organocatalysts **4** and **6** is highly diastereoselective Reformatsky reaction of chiral imine **14**.

Organocatalyst **5** was prepared from commercially available **17**. Hofmann rearrangement of amide **18** afforded unexpected product - dimer **19**.

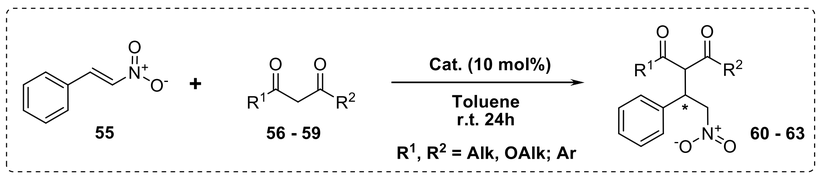
Organocatalysts **8, 9, 27** and **34** were prepared in a higly diastereoselective Mannich reaction / reduction sequence.

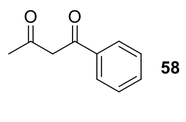
Organocatalysts **10, 11** and **44** were prepared in a higly diastereoselective hidroxymethylation / reduction sequence.

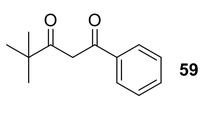
Catalysts **8** and **34** were seperated using RP column chromatography.

Organocatalysts **53** and **54** were prepared as described by Hirose *et al*. (*Tetrahedron: Asymmetry*, **2010**, *21*, 2925).

Catalyst efficiency in Michael reaction







Cat.	Yield, %	ee, %
2*	80	86
3*	55	29
4	85	18
5	56	15
6	52	4
7	58	2
8	35	0
9	71	4
27	74	14
34	23	8
53*	32	7
54*	71	8
9	29	1
10	71	30
44	26	3

Cat.	Yield, %	ee, %	dr
2*	97	+87	1:1.3
3*	94	-79/-45	1:1.8/1:5.8
4	99	+16	1:1.9
5	99	+9	1:1.3
6	88	+12	1:1.7
7	99	+6	1:1.6
8	99	+47	1:1.6
9	99	-36	1:1.5
27	99	+5	1:1.7
34	94	-68	1:1.5
53*	85	-68/-46	1:1.2/1:1.2
54*	99	-14	1:1.7
10	97	+24	1:1.6
11	99	-59	1:1.5
44	99	+51	1:1.6

Cat.	Yield, %	ee, %	dr
2*	97	+75	1:1.4
3*	99	-66	1:1.6
4	99	+9	1:1.7
5	99	+20	1:1.6
6	99	+23	1:1.3
7	84	-2	1:1.6
8	99	+36	1:1.4
9	99	-25	1:1.5
27	81	-21	1:1.5
34	61	-50	1:1.5
53*	97	-18	1:1.6
54*	99	21	1:1.5
10	99	+16	1:1.6
11	97	-55	1:1.3
44	99	+50	1:1.5

Cat.	Yield, %	ee, %	dr
2*	60	+62	1:3.5
3*	80	+28/+47	1:7.2 / 1:4.6
4	80	+8	1:4.3
5	77	-2/+10	1:4.0 / 1:4.0
6	94	0	1:4.4
7	71	-3	1:4.6
8	80	-3	1:4.8
9	80	-4	1:4.2
27	86	+2	1:3.4
34	26	+6	1:3.2
53*	71	+3	1:4.2
54*	86	-1	1:7.5
10	80	-1	1:5.0
11	97	-60	1:4.8
44	74	-5	1:5.0

*Known organocatalysts

1.Chemical yields of 1,3-propylenediamine derivative-catalysed reactions were comparable to those catalysed by 1,2-ethylenediamine analogues. However, stereoselectivities in most cases were lower.

2. Stereoselectivity in the Michael reaction using 1,3-propylenediamine moiety-containing organocatalysts is very sensitive to steric and / or electronic properties of dicarbonyl substrates.

3. Organocatalysts **5** – **9** are too weak bases to deprotonate substrate **56**. Possibly, this is responsible for low reaction yields.

4. Highest enantioselectivities were obtianed with vicinally substituted catalysts **8**, **34** and indane derivatives **11** and **44**.