MULTICOMPONENT REACTIONS AND ORGANOCATALYSIS: A SUITABLE COMBINATION FOR STEREOSELECTIVE SYNTHESIS OF HIGHLY SUBSTITUTED BENZAZEPINES

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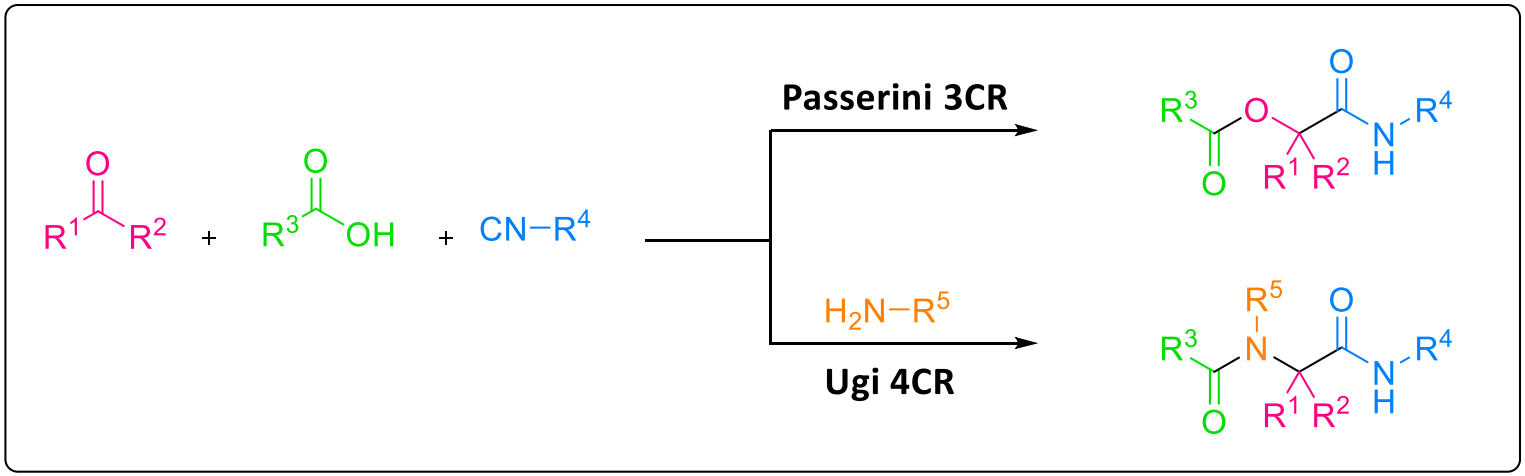
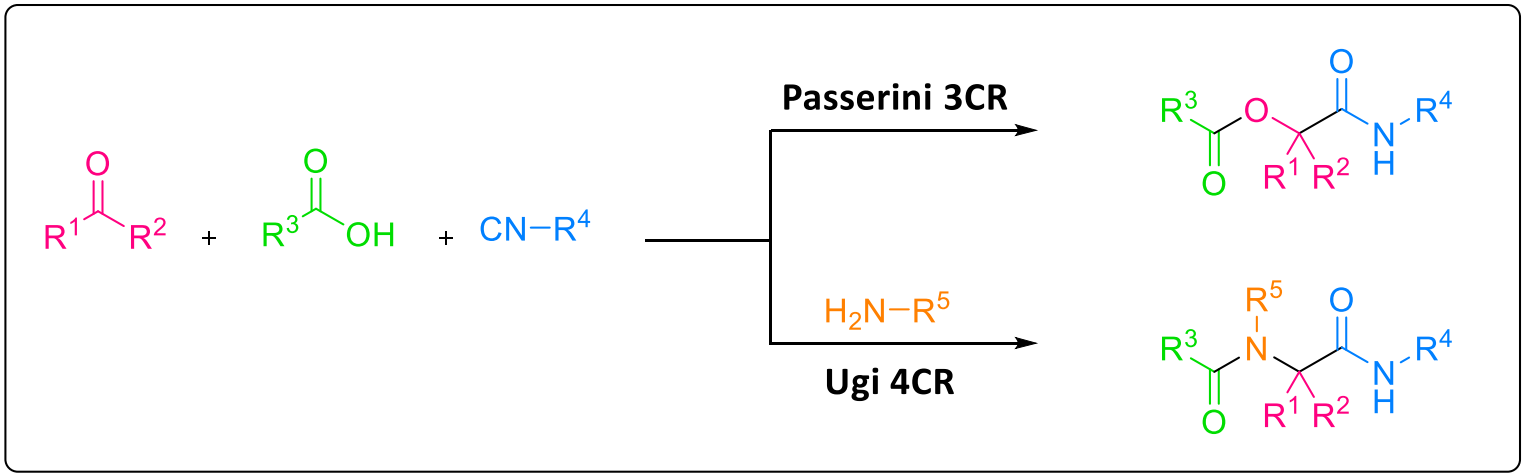
Main Isocyanide based multicomponent reactions



- ✓ Atom economy
- ✓ Step economy
- ✓ Decoration diversity

- X Scaffold diversity
- X Stereochemical issue

Main Isocyanide based multicomponent reactions



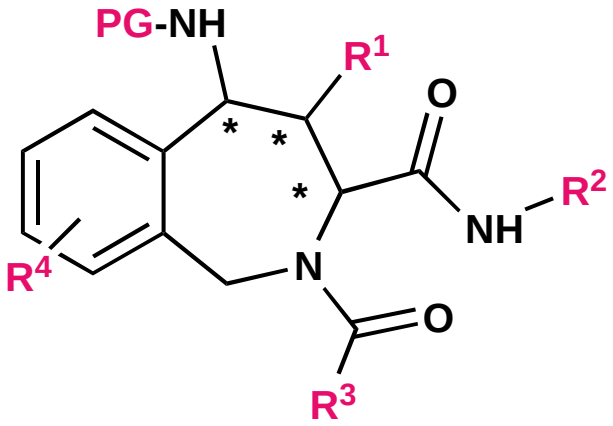
- ✓ Atom economy
- ✓ Step economy
- ✓ Decoration diversity

- X Scaffold diversity
- X Stereochemical issue

Use of chiral inputs

Organocatalysis

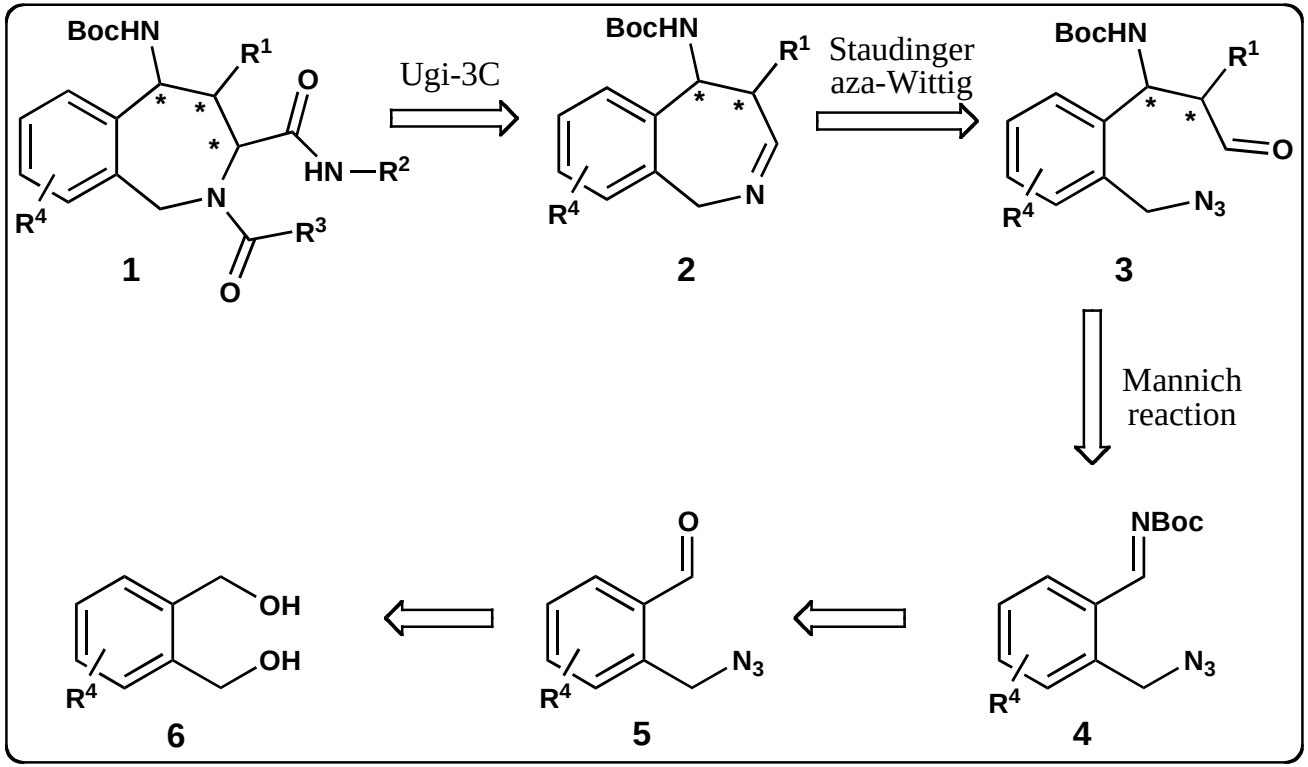
The target



- ✓ a new family of seven-membered heterocycles
- ✓ 3 new contigous stereogenic centers
- ✓ 4 possible points of diversity

Moni, L.; Basso, A.; Banfi, L.; Galatini, A.; Spallarossa, M.; Riva, R. *J. Org. Chem*. **2014**, *79*, 339−351

Retrosynthetic Analysis



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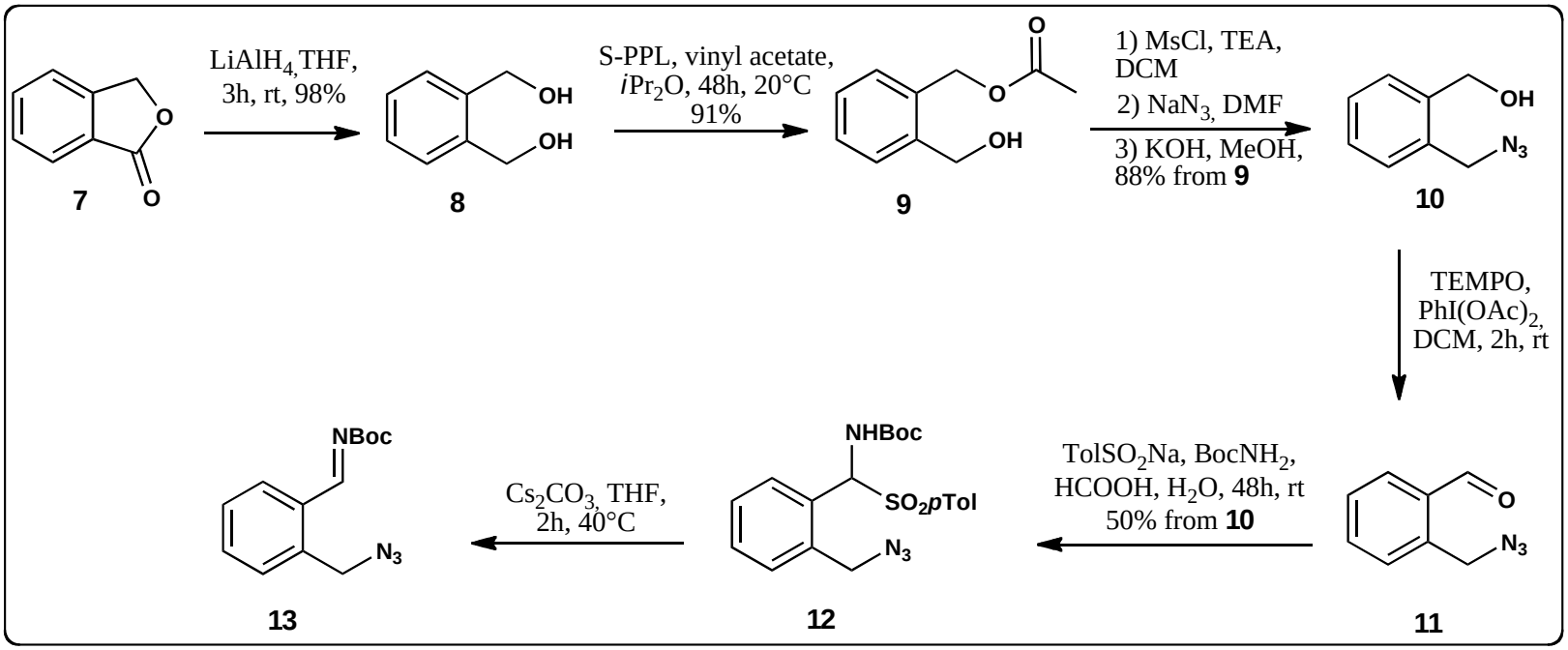
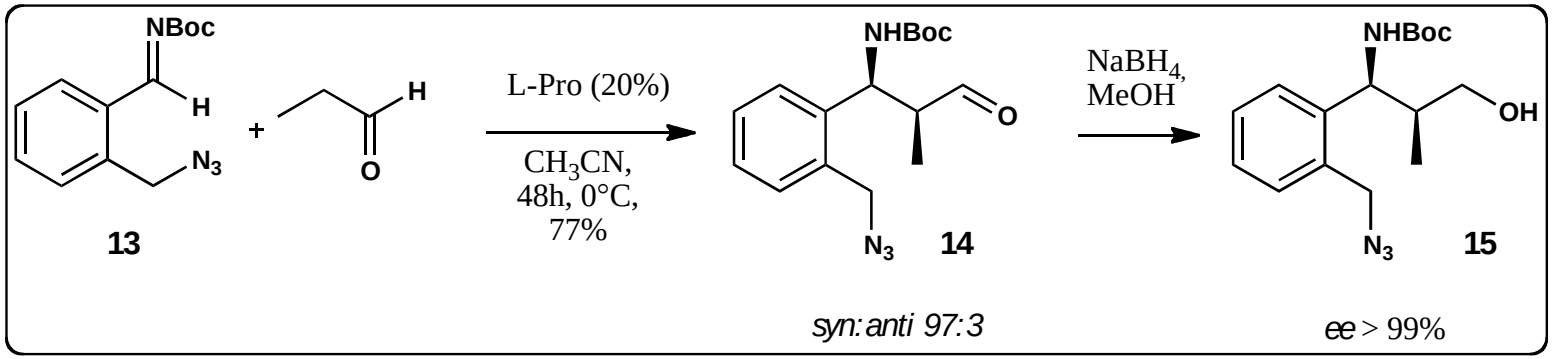
Synthesis of Boc-imine



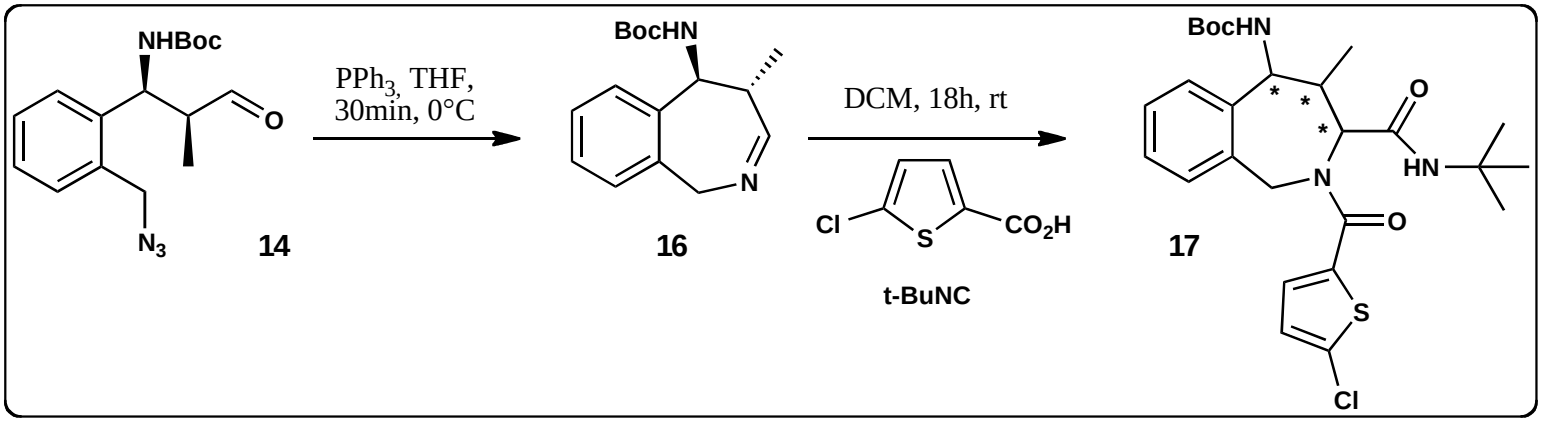
Qing, Z.; Takacs, J. M. *Org. Lett.* **2008**, *10*, 545.
Banfi, L.; Guanti, G.; Riva, R. *Tetrahedron: Asymmetry* **1995**, *6*, 1345.
Yang, J. W.; Stadler, M.; List, *B Angew. Chem. Int. Ed.* ***2007***, *46*, 609.

Organocatalytic Mannich Reaction



Yang, J. W.; Pan, S. C.; List, B. *Org. Synth*, **2009**, *86*, 11.
Yang, J. W.; Stadler, M.; List, B *Angew. Chem. Int. Ed*. **2007**, *46*, 609.

Staudinger Aza Wittig/Ugi-Joullié



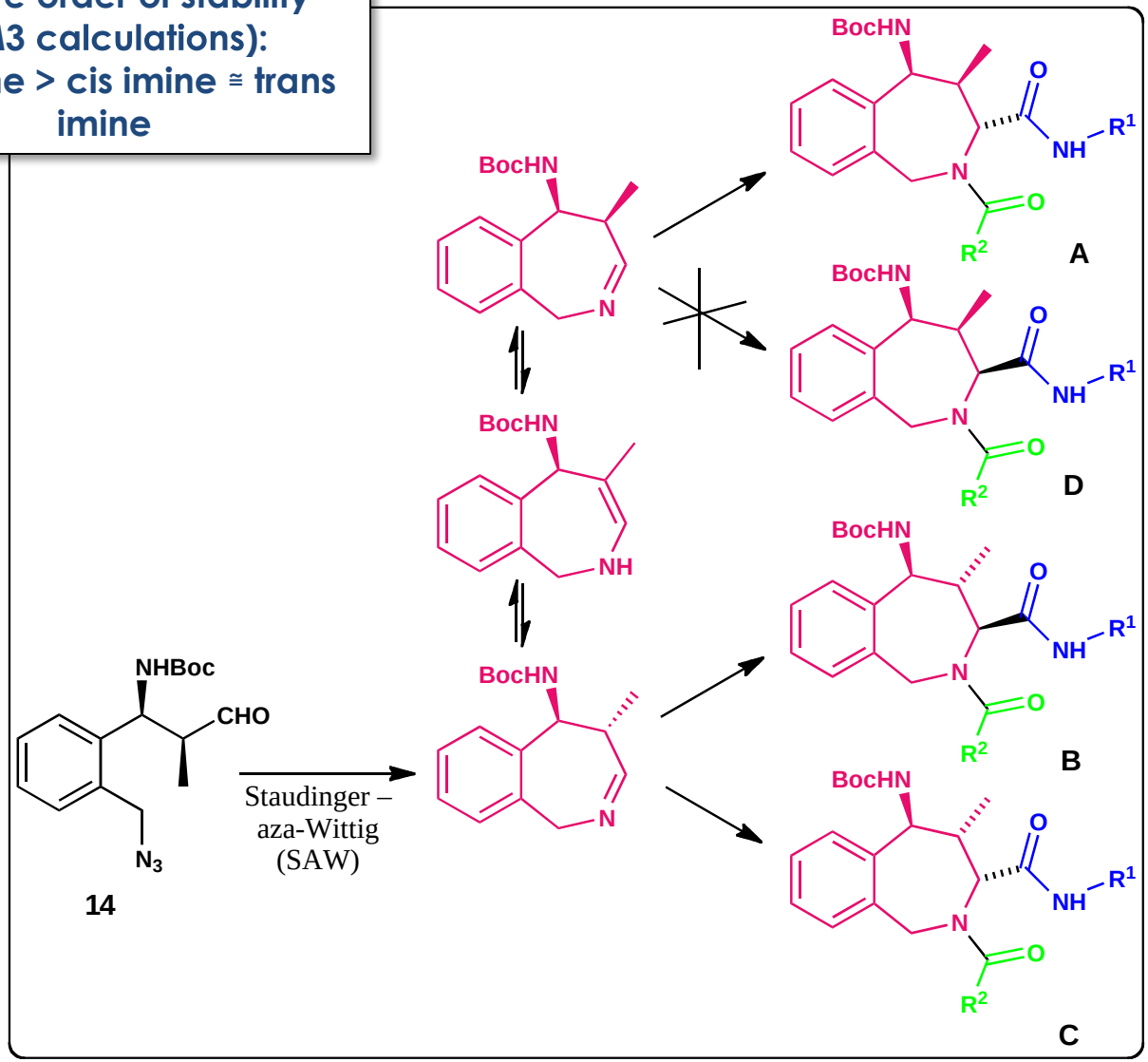
entry	PR_3	temp. (SAW)	solvent (Ugi)	*dr* (17a: 17b:17c)	yield % (4 steps)
1	PPh_3	rt	MeOH	51.5 : 28.4 : 20.1	19
2	PPh_3	rt	DCM	58.4 : 27.1 : 14.4	18
3	PPh_3	rt	TFE	48.1 : 26.4: 25.4	13
4	PPh_3	rt	Toluene	53.4 : 30.2 : 16.4	14
5	PPh_3	0°C	DCM	64.0 : 22.4 : 13.6	58
6	PMe_3	0°C	DCM	37.3 : 42.0 : 20.7	26
7	PBu_3	0°C	DCM	43.3 : 37.2 : 19.5	8
8	PPh_3	0°C	DCM	68.6 : 19.9 : 11.5	54

Yield: 58% (4 steps)

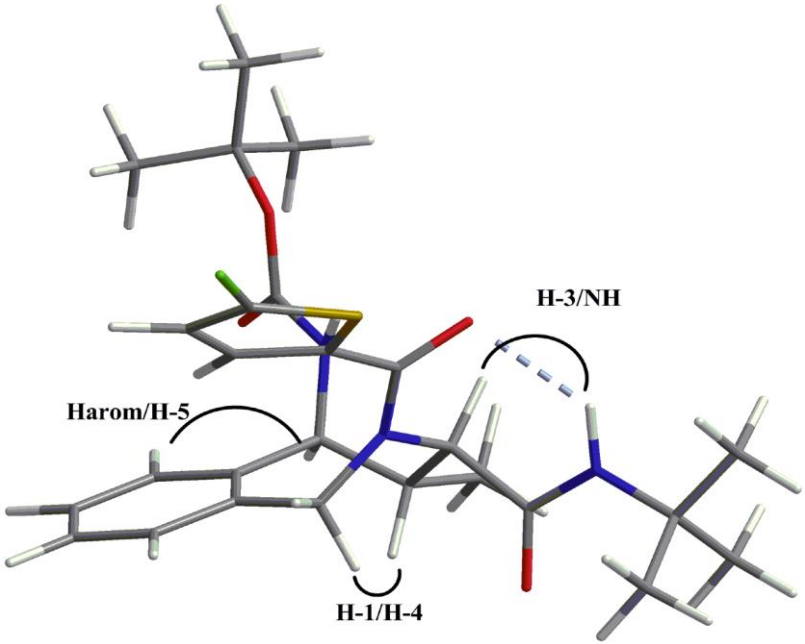
3 diastereomers 64:22:14

relative order of stability (PM3 calculations): enamine > cis imine ≅ trans imine

major stereoisomer ee > 99%



Relative configuration of the isomers



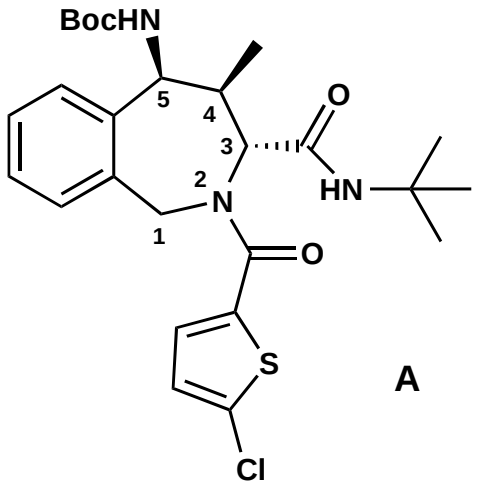
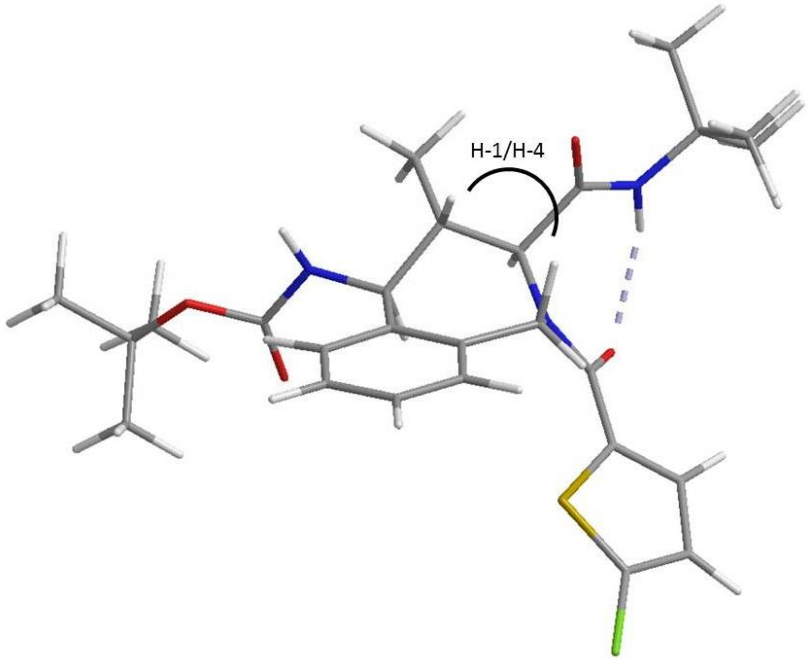
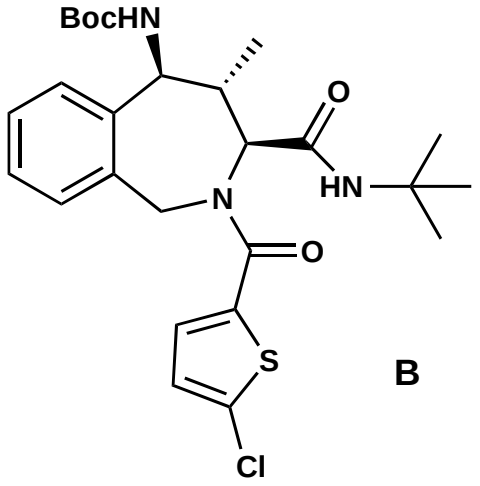


Table S3: Experimental coupling constants.

Stereoisomer	J_{3-4}	J_{4-5}
a	6.6 Hz	0 Hz
b	6.9 Hz	8.7 Hz
c	6.0 Hz	7.2 Hz

Relative configuration of the isomers



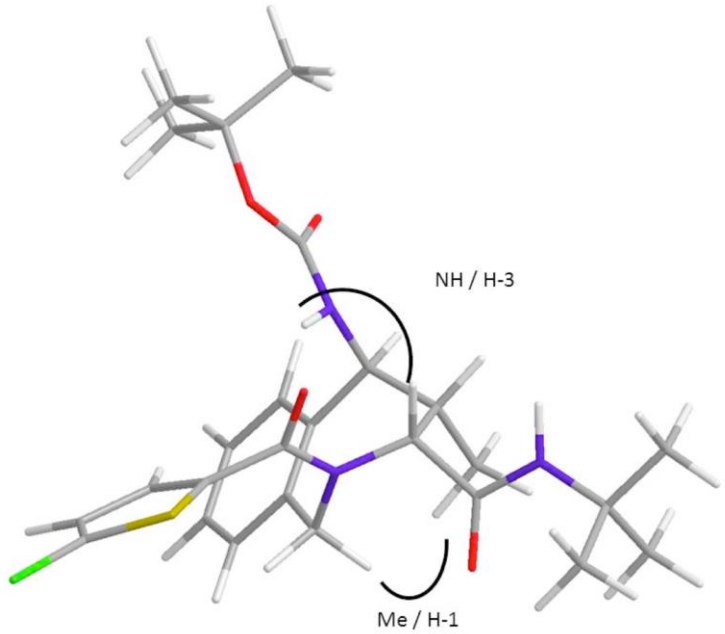


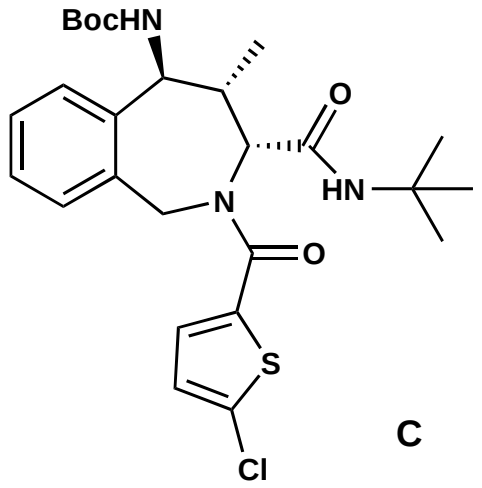
B

Table S3: Experimental coupling constants.

Stereoisomer	J_{3-4}	J_{4-5}
a	6.6 Hz	0 Hz
b	6.9 Hz	8.7 Hz
c	6.0 Hz	7.2 Hz

Relative configuration of the isomers



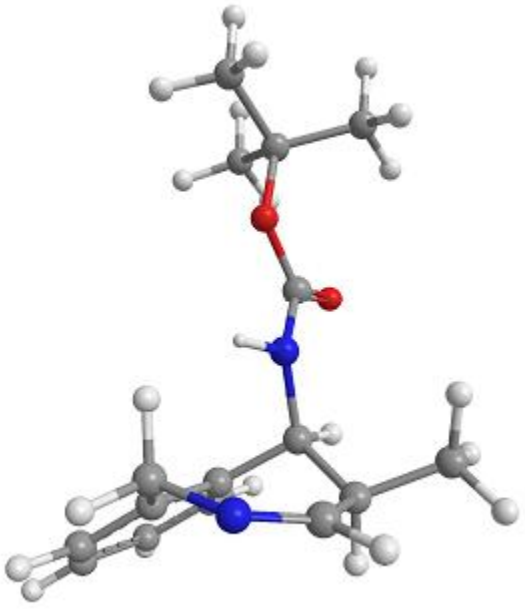


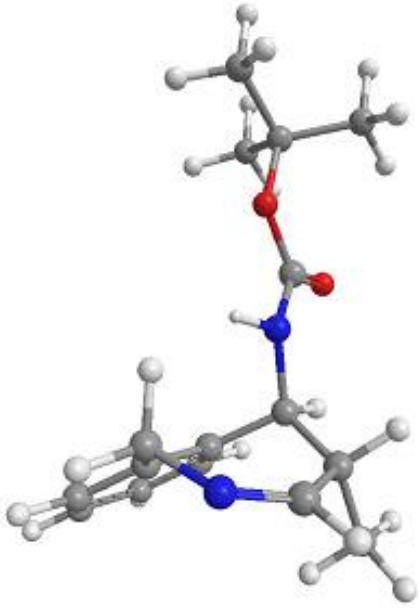
C

Table S3: Experimental coupling constants.

Stereoisomer	J_{3-4}	J_{4-5}
a	6.6 Hz	0 Hz
b	6.9 Hz	8.7 Hz
c	6.0 Hz	7.2 Hz

Configuration of the two epimeric imines

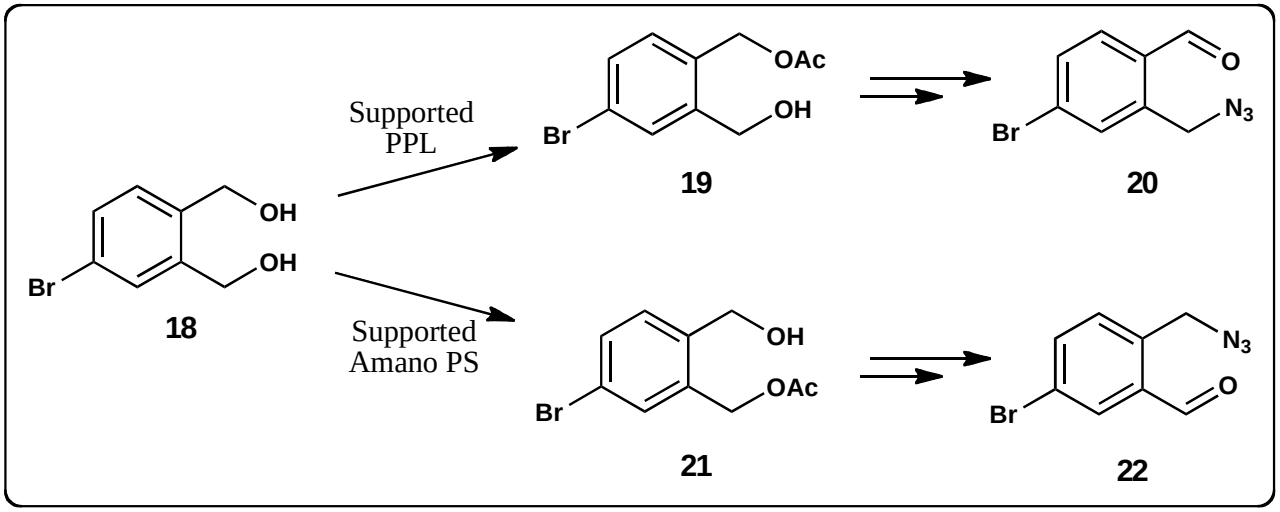




A careful observation of the preferred conformation of cis imine suggests that the bottom face is relatively free and therefore a high diastereoselectivity favouring the product A is expected.

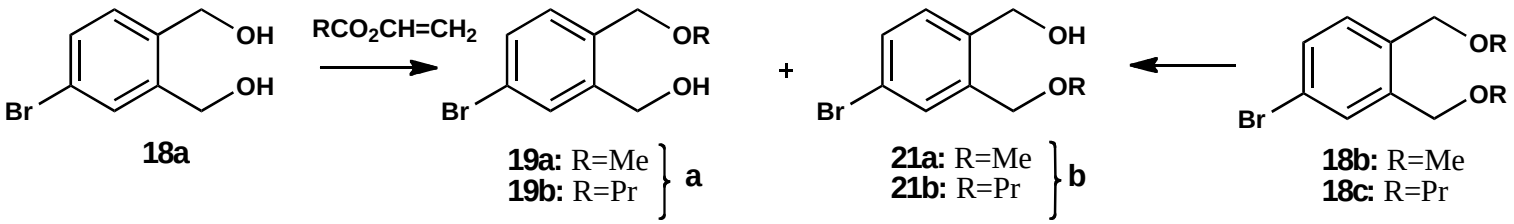
On the other hand, in the preferred conformation of trans imine, the upper face is encoumbered by the axial NH(Boc) group, but the lower face is also encoumbered, this time by the axial methyl group. Therefore the Ugi-Joullié reaction is expected to be less diastereoselective and slower.

Study of the scope



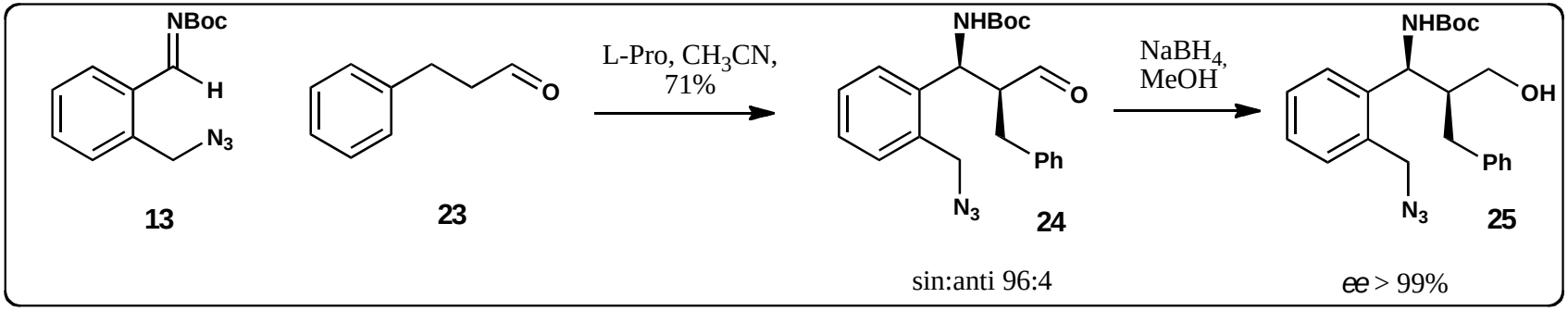
regioselectivity problem ⟹ enzyme catalysis

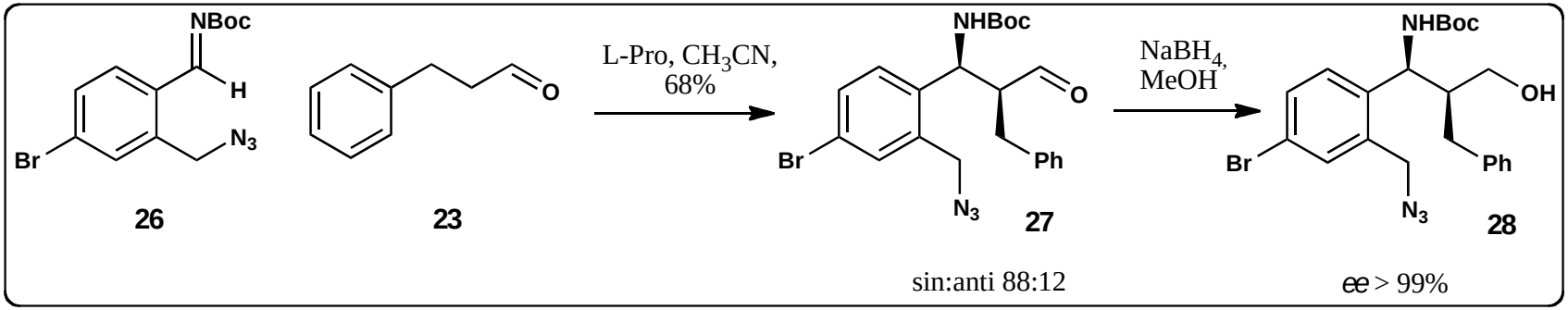
Study of the scope



entry	subs	products	lipase	solvent	lipase/substrate (mg/mmol)	temp	time	**a** : **b**	yield (**a** + **b**)	conv
1	**18a**	**19a, 21a**	S-Amano PS	vinil acetate	22	10 °C	2 h	37:63	77%	60%
2	**18a**	**19a, 21a**	S-PPL	vinil acetate	65	20 °C	2 h	75:25	76%	50%
3	**18a**	**19b, 21b**	Amano AK	vinil butyrate	22	0 °C	6 h	0:100	40%	80%
4	**18a**	**19b, 21b**	S-PPL	vinil butyrate	44	10 °C	24 h	100:0	66%	67%
5	**18a**	**19b, 21b**	CAL	vinil butyrate	22	10 °C	6 h	68:32	76%	62%
6	**18b**	**19a, 21a**	CAL	buffer/iPr$_2$O[d]	29	20 °C	15 h	21:79	20%	85%
7	**18c**	**19b, 21b**	CAL	buffer/iPr$_2$O[d]	29	10 °C	19 h	12:88	25%	33%

Study of the scope





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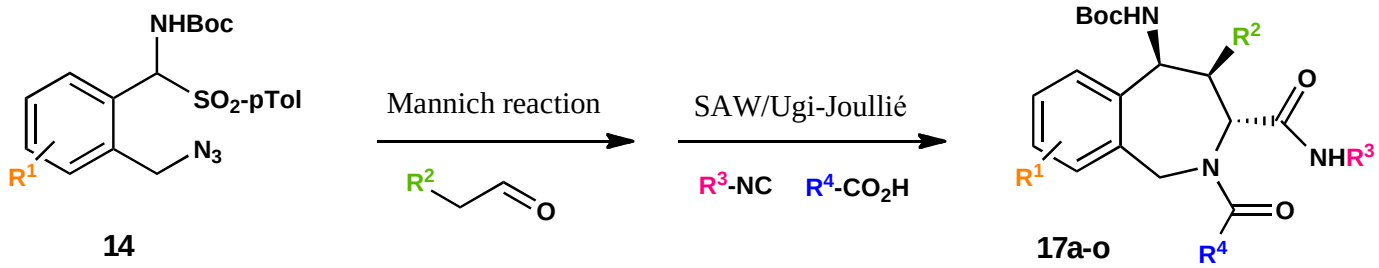


17a
R^1 = H
R^2 = Me
R^3 = *t* -Bu
R^4 = 5-Cl-2-thienyl
Y (A): 53%
Y (A + B + C): 83%

17b
R^1 = H
R^2 = Me
R^3 = *n* -Bu
R^4 = 3-Br-C_6H_4
Y (A): 48%
Y (A + B + C): 76%

17c
R^1 = H
R^2 = Me
R^3 = *n* -Bu
R^4 = Ph
Y (A): 60%
Y (A + B + C): 86%

17d
R^1 = H
R^2 = Me
R^3 = 2,6 -(Me_2)-C_6H_3
R^4 = Et
Y (A): 55%
Y (A + B + C): 84%

17e
R^1 = H
R^2 = Me
R^3 = CH_2CO_2Et
R^4 = Et
Y (A): 53%
Y (A + B + C): 83%

17f
R^1 = H
R^2 = Me
R^3 = cyclohexyl
R^4 = S -BnCHNHFmoc
Y (A): 48%
Y (A + B + C): 68%

17g
R^1 = H
R^2 = Me
R^3 = nC_5H_{11}
R^4 = S -*i*PrCHNHCbz
Y (A): 55%
Y (A + B + C): 78%

17h
R^1 = H
R^2 = Me
R^3 = Bn
R^4 = $MeOCH_2$
Y (A): 55%
Y (A + B + C): 73%

17i
R^1 = H
R^2 = Bn
R^3 = *t* -Bu
R^4 = 5-Cl-2-thienyl
Y (A): 42%
Y (A + B + C): 69%

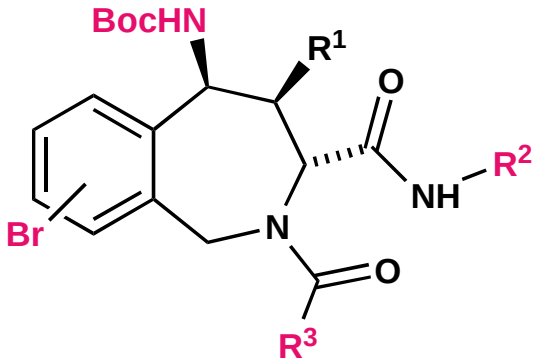
17l
R^1 = H
R^2 = Bn
R^3 = Me
R^4 = 3-OMe-C_6H_4
Y (A): 47%
Y (A + B + C): 70%

17m
R^1 = 8 -Br
R^2 = Bn
R^3 = CH_2CO_2Et
R^4 = Ph
Y (A): 33%
Y (A + B + C): 46%

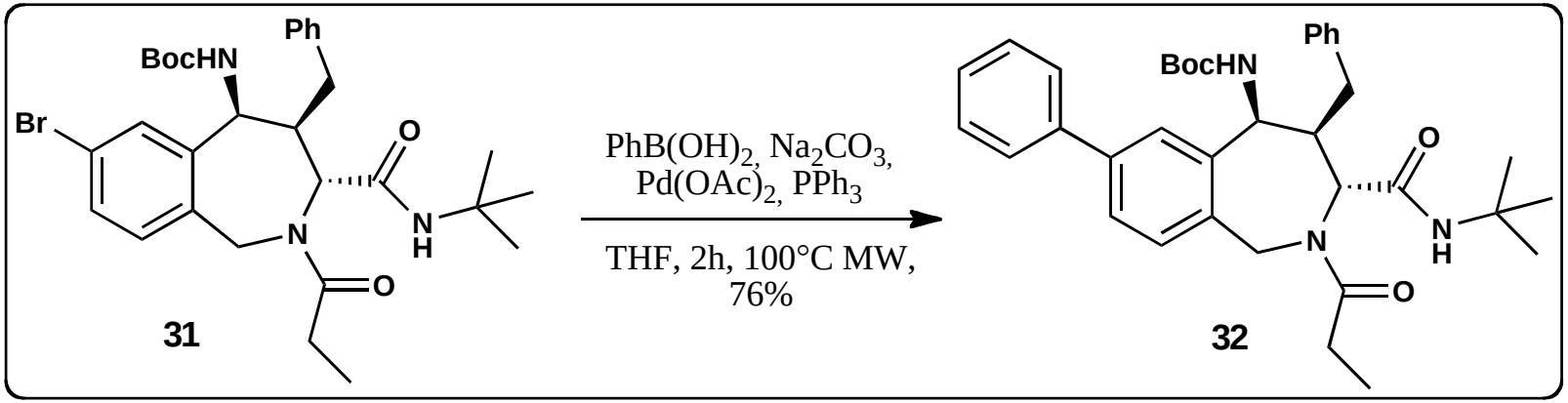
17n
R^1 = 8 -Br
R^2 = Bn
R^3 = Bn
R^4 = $CH_2NHFmoc$
Y (A): 47%
Y (A + B + C): 57%

17o
R^1 = 7 -Br
R^2 = Bn
R^3 = *t* -Bu
R^4 = Et
Y (A): 30%
Y (A + B + C): 41%

Secondary transformations



Suzuki reaction



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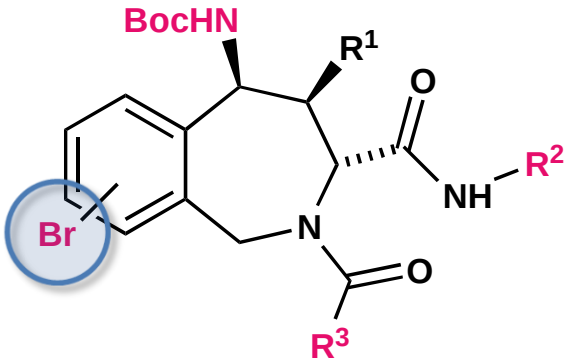

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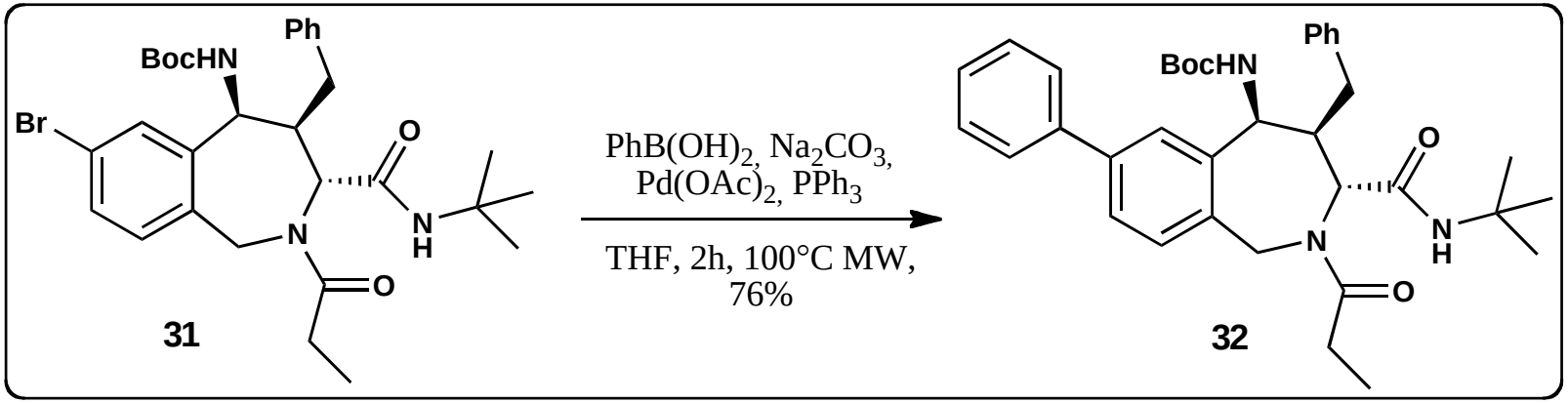

Conclusion

✓ New method for fast assembly of a new family of seven-membered heterocycles.

✓ Possibility of synthesizing, in high enantiomeric excess, unknown azido aldehydes by an organocatalytic procedure.

✓ Isolation in good overall yield of a single stereoisomer (out of eight) of a new heterocyclic structure endowed with three contiguous stereogenic centers.

✓ The final products can be further derivatized.


obrigado
Dank U
Merci
mahalo
Köszi
спасибо
Grazie
Thank you
mauruuru
Takk
Gracias
Dziękuję
Děkuju
danke
Kiitos