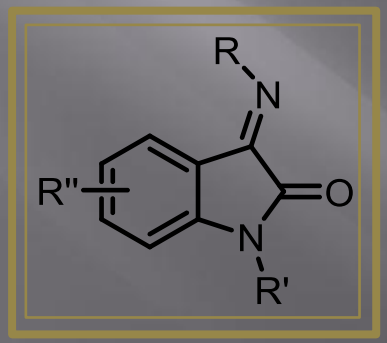
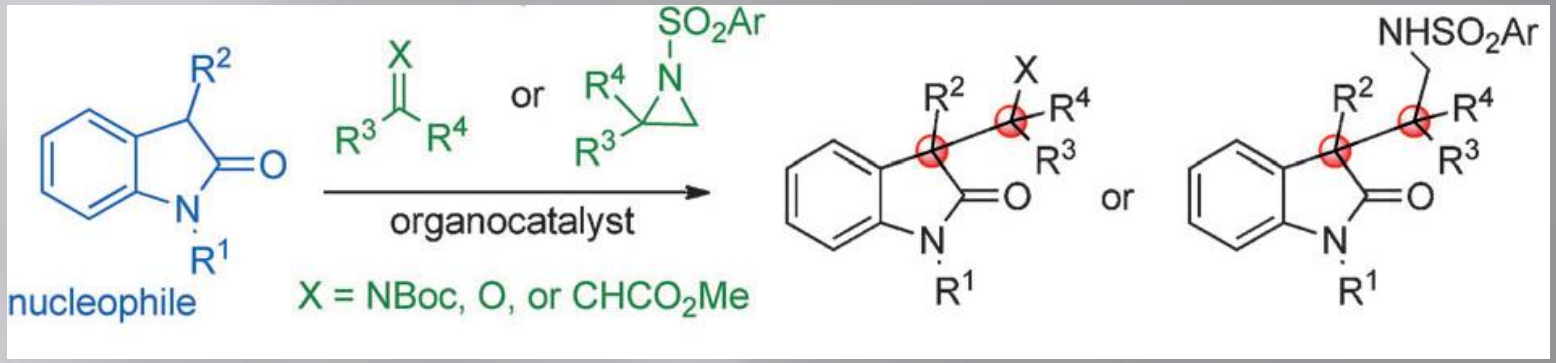
Stereoselective Organocatalytic synthesis of Oxindoles with adjacent tetrasubstituted stereocenters



Oliver D. Engl, Sven P. Fritz and Helma Wennemers
Angew. Chem. Int. Ed. **2015, *54*, 1 - 6**

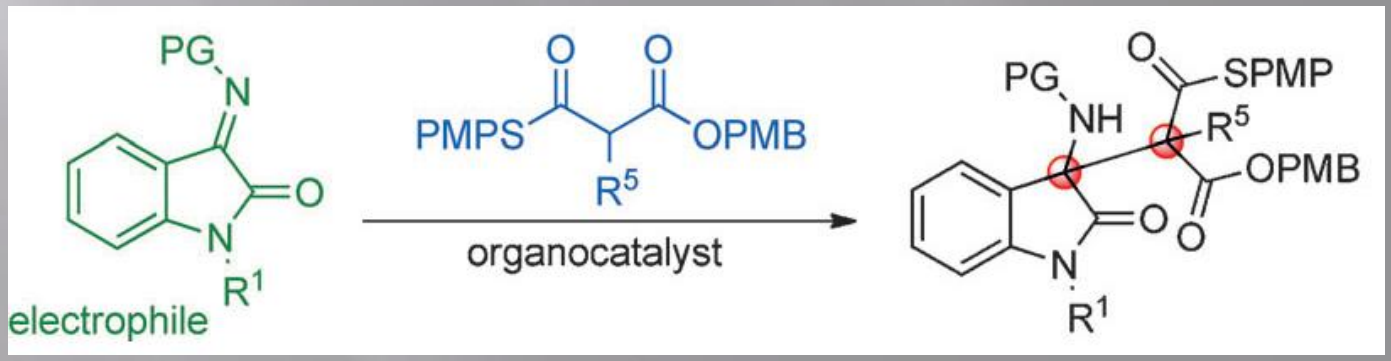
Previous work

- **Nucleophilic Oxindol:[1] enolate pathway**



This work

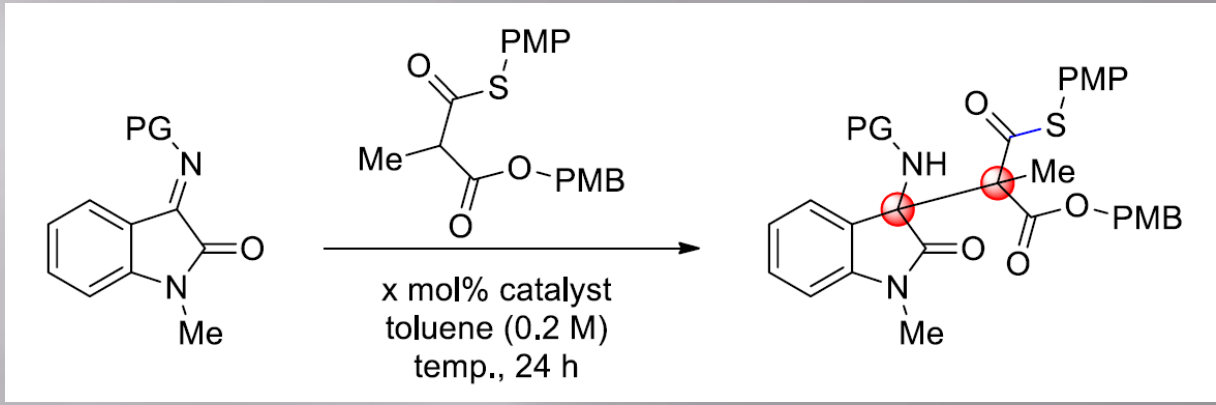
- **Electrophilic Oxindol:[2] conjugate addition**

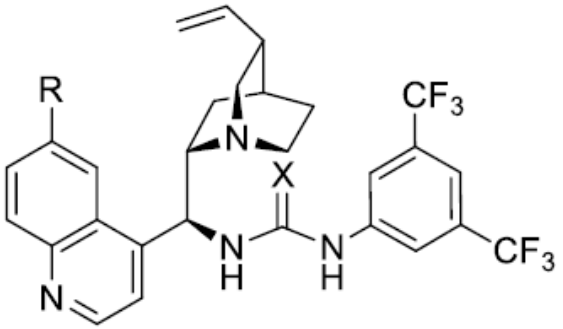


[1] a) K. Ohmatsu, Y. Ando, T. Ooi, *J. Am. Chem. Soc*. **2013**, *135*, 18706 – 18709 ; b) B. Tan, N. R. Candeias, C. F. Barbas, *Nat.Chem.* **2011**, *3*, 473 – 477.

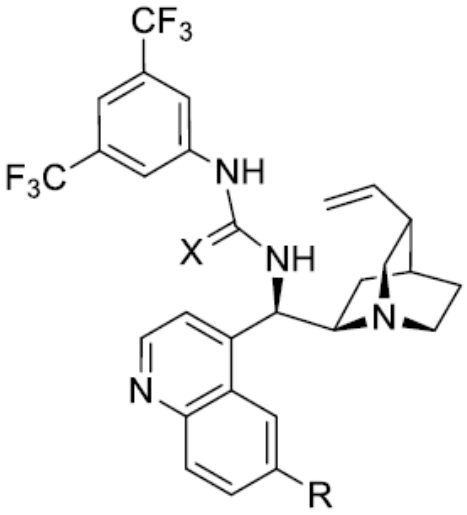
[2] L. Tian-Ze, W. Xi-Bo, S. Feng, W. Xin-Yan, *J. Org. Chem.* **2014**, *79*, 4332-4339

Optimization of the reaction

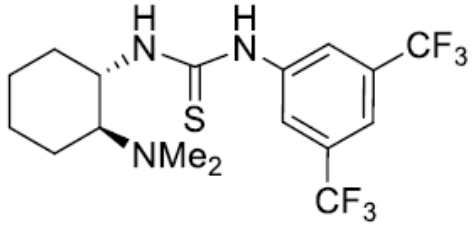




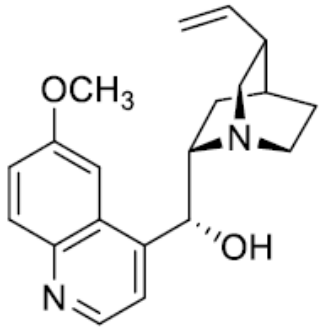
E, epiQNTU: X=S, R=OMe
D, epiCDTU: X=S, R=H
C, epiQNU: X=O, R=OMe
A, epiCDU: X=O, R=H



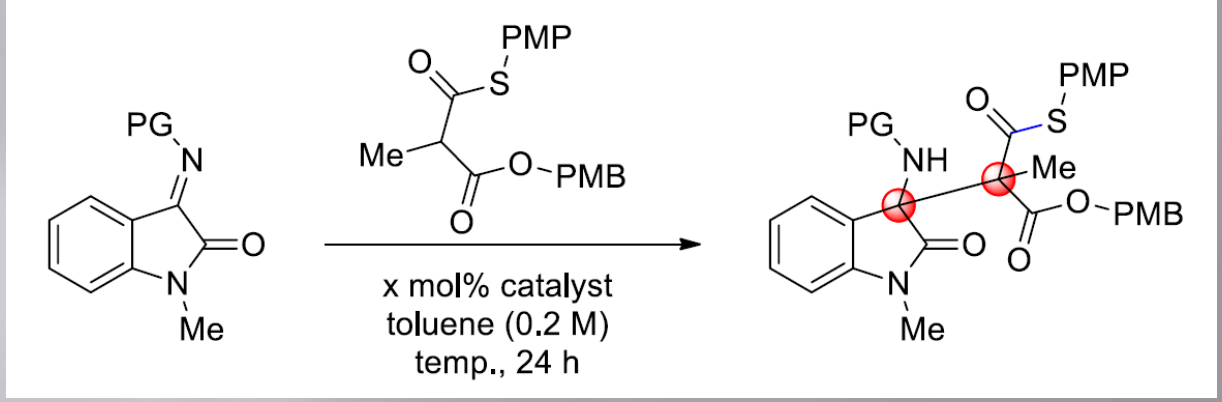
F, epiQDTU: X=S, R=OMe
G, epiCNTU: X=S, R=H
H, epiQDU: X=O, R=OMe
I, epiCNU: X=O, R=H



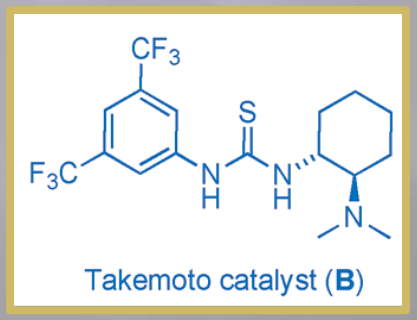
B, Takemoto's catalyst

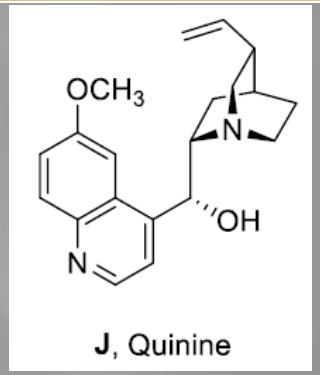


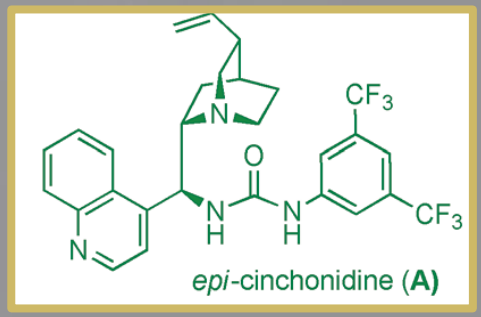
J, Quinine



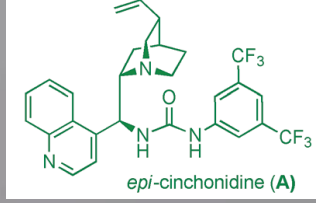
PG	Temperature	Cat.	Cat. Loading	Conversion[a]	dr[b]	ee[c]
Boc	RT	E	10 mol%	50%	2:1	73%
Cbz	RT	E	5 mol%	90%	20:1	99%
Cbz	-15	F	5 mol%	70%	3:1	96%[d]
Cbz	-15	G	5 mol%	85%	6:1	98%[d]
Cbz	-15	H	5 mol%	25%	2:1	95%[d]
Cbz	-15	I	5 mol%	90%	9:1	98%[d]
Cbz	**-15**	**B**	**5 mol%**	**>95%**	**>20:1**	**>99%[d]**
Cbz	-15	J	5 mol%	80%	1:18	5%
Cbz	**-15**	**A**	**2 mol%**	**95%**	**>20:1**	**>99%**

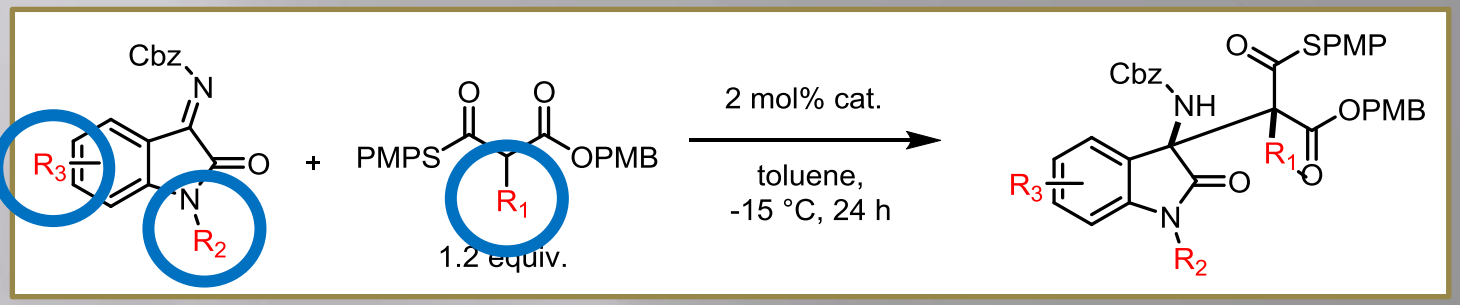


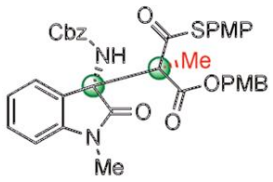




Reaction scope

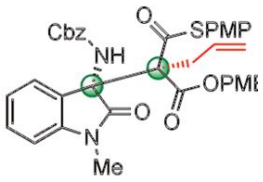




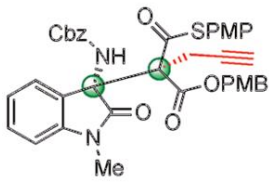


3a, 94% yield
>20:1 d.r., >99% *ee*

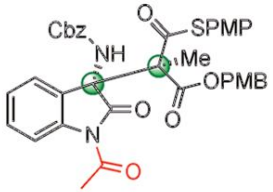
3b, 93% yield
>20:1 d.r., >99% *ee*



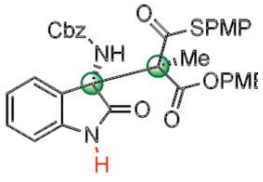
3c, 95% yield
15:1 d.r., 99% *ee*



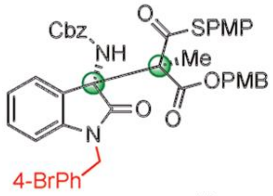
3d, 91% yield
15:1 d.r., >99% *ee*



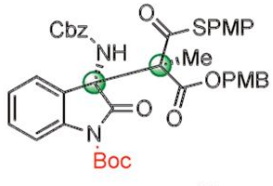
3e, 95% yield
>20:1 d.r., >99% *ee*



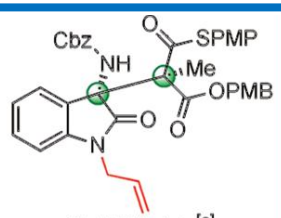
3f, 52% yield
15:1 d.r., 97% *ee*



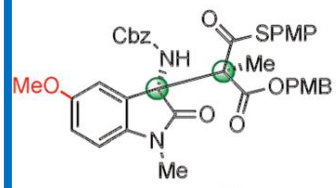
3g, 57% yield[a]
18:1 d.r., 99% *ee*



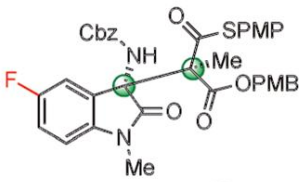
3h, 51% yield[a]
5:1 d.r., 73% *ee*



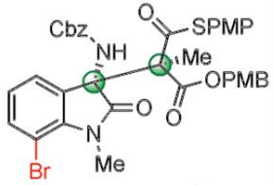
3i, 95% yield[a]
4:1 d.r., 91% *ee*



3j, 58% yield[a]
>20:1 d.r., >99% *ee*

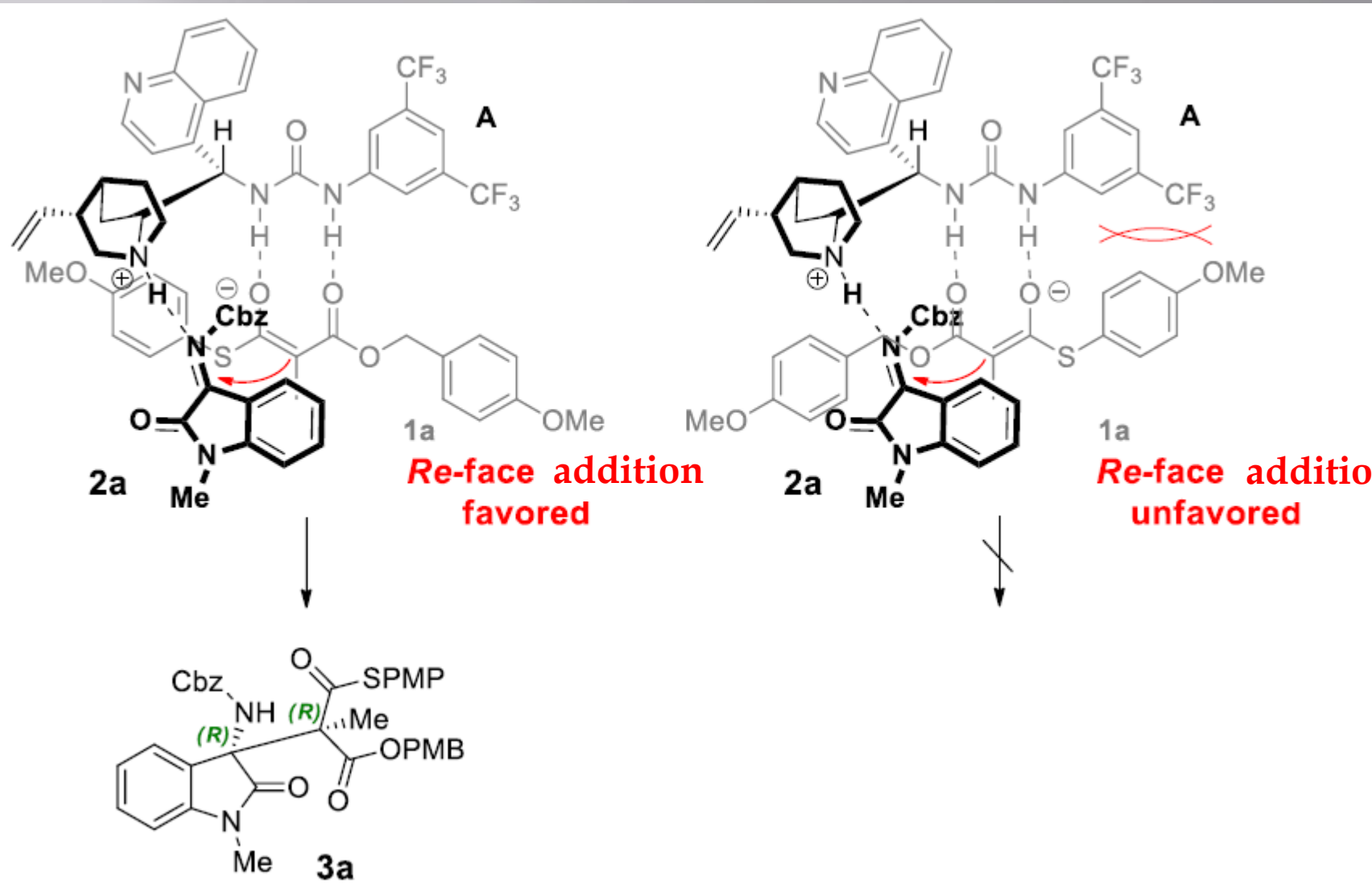


3k, 57% yield[a]
>20:1 d.r., 99% *ee*



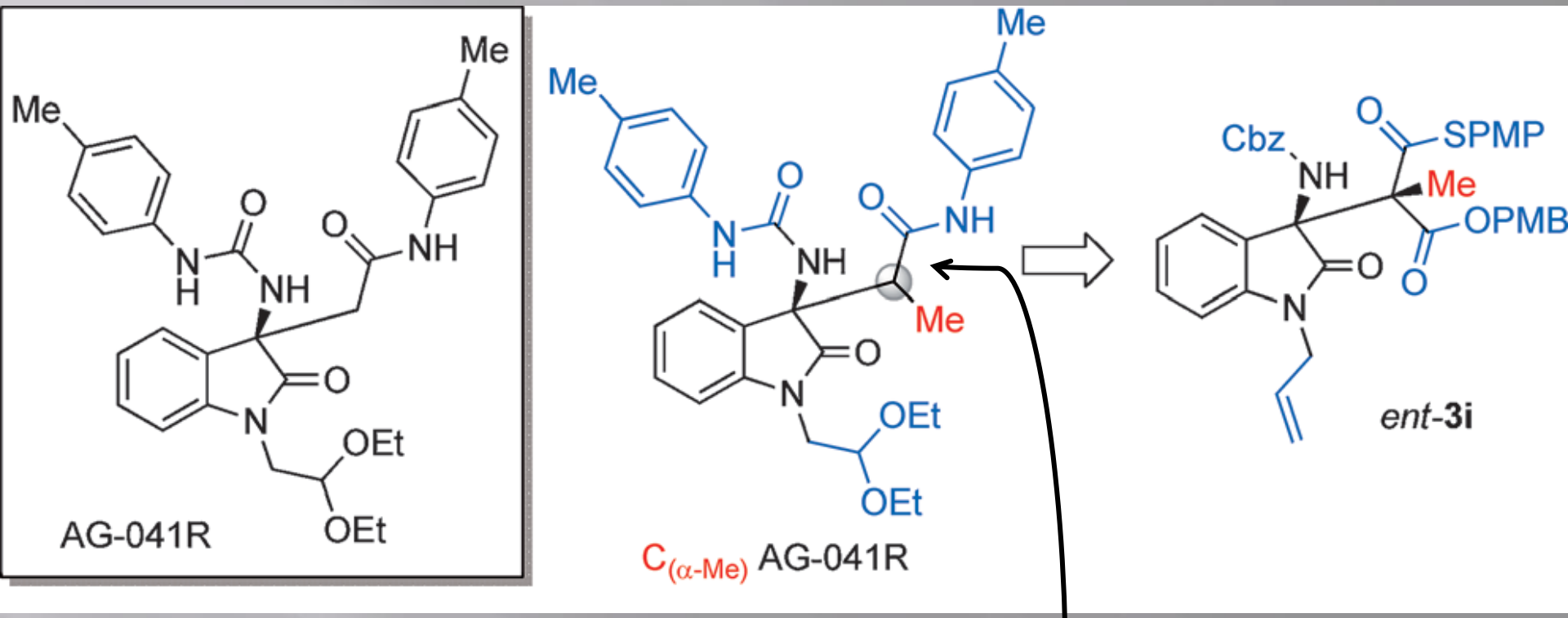
3l, 61% yield[a]
>20:1 d.r., 96% *ee*

Plausible transition-state model for the conjugate addition[3]



[3] Bahlinger, A.; Fritz, S. P.; Wennemers, H. *Angew. Chem. Int. Ed.* **2014**, *53*, 8779-8783. *(b)* Arakawa, Y.; Fritz, S. P.; Wennemers, H. *J. Org. Chem.* **2014**, 79, 3937-3945. *(c)* Schreiner, R. R.; Wittkopp, A. *Org. Lett.* ***2002***, *4*, 217-220.

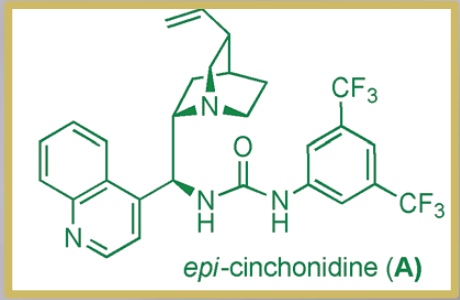
Access to a therapeutic product



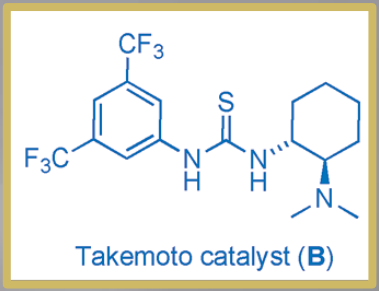
This methodologies permit a fonctionnalization in $C_{(\alpha)}$ position

Conclusion

- ✓ Using mild conditions and low catalytic amouth
- ✓ Excellent dia and enantioselectivity for both "*syn*" enantiomers



and



- ✓ Access to tetrasubstituted stereogenic centers with orthogonal protecting groups