

Organocatalysed additions
of ketones to diphenylmaleates

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I-2. Aminocatalysis

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Organocatalysis - Generalities

- Use of small organic molecules as catalytic species to accelerate chemical reaction
- Valuable alternative method to existing metal based methodologies
- Preparative advantages:
 - moisture and air stable
 - low cost and toxicity
 - availability



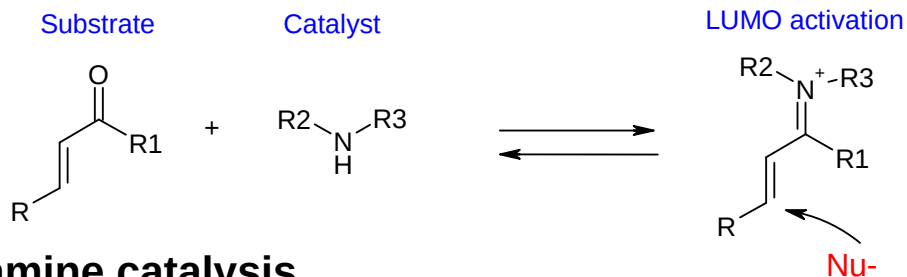
Direct benefit in the production of pharmaceutical intermediates

Aminocatalysis

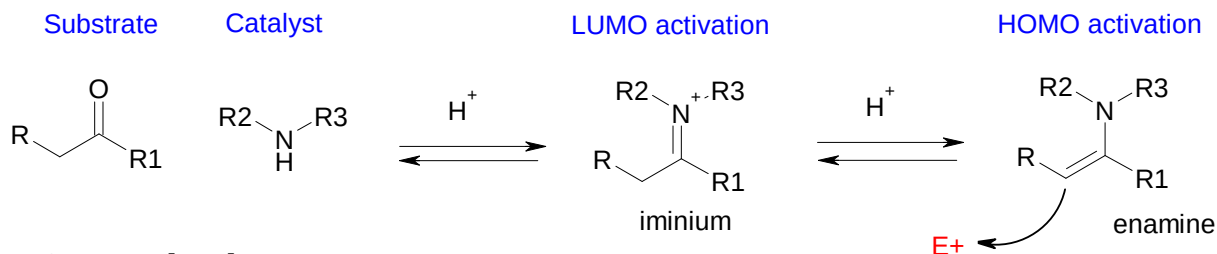
- Chiral secondary amine catalysis
- Method of choice for enantioselective functionalization of carbonyl compound
- Based on the aptitude of secondary amines to form activated enamine or iminium intermediate
- 3 different types of activation
 - enamine catalysis
 - iminium catalysis
 - SOMO catalysis

Aminocatalysis

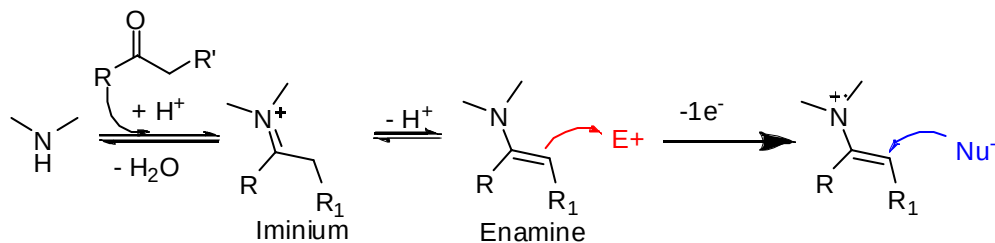
➤ Iminium catalysis



➤ Enamine catalysis



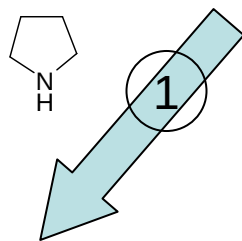
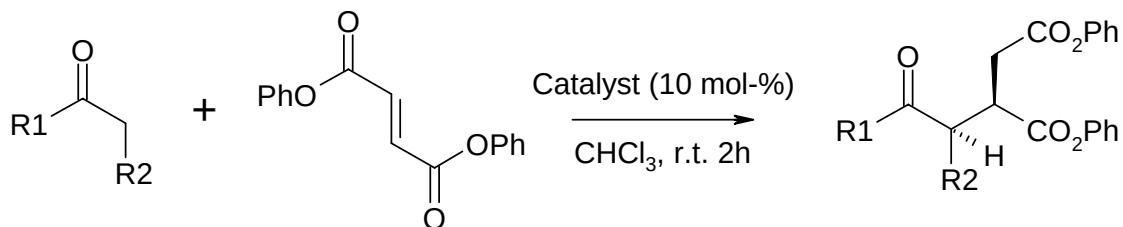
➤ SOMO catalysis



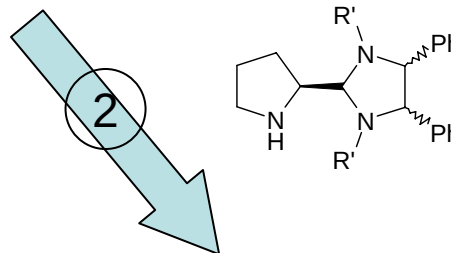
Enamine catalysis was employed for our work

Synthesis in the laboratory

➤ Organocatalysed additions of ketones to diphenylmaleates



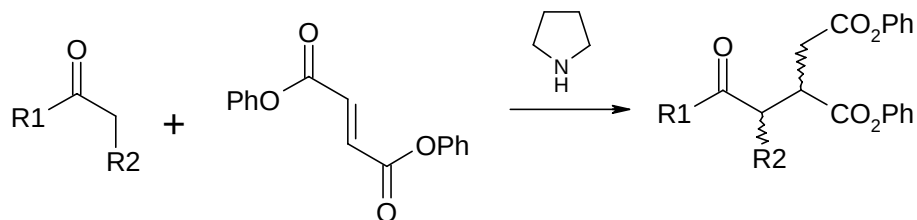
Non asymmetric studies



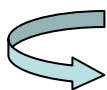
asymmetric studies

Synthesis 1st part

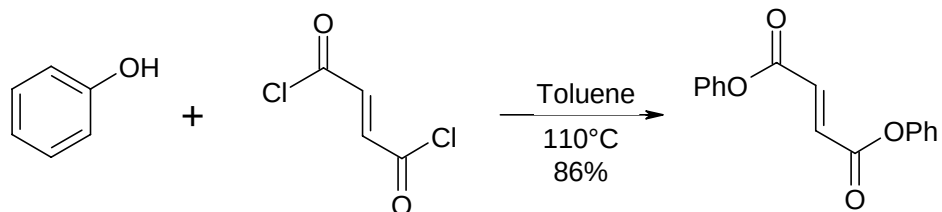
➤ Non asymmetric studies



- Reaction feasibility
- Allow obtention of racemate for asymmetric synthesis

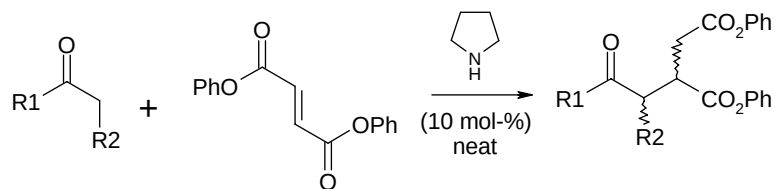


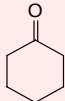
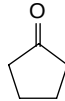
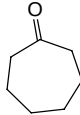
First step: Synthesis of starting material

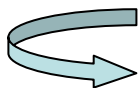


Synthesis 1st part

➤ Non asymmetric studies



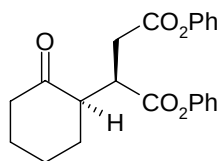
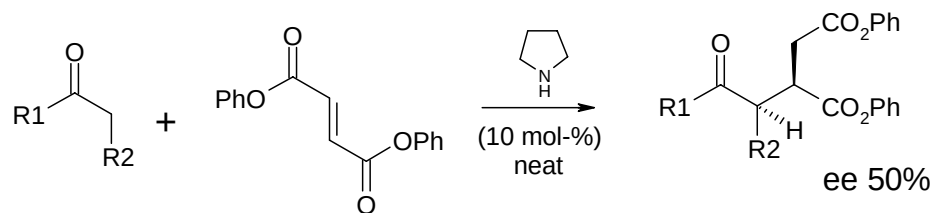
Entry	Substrate	Time	Yield
1		15 minutes	81%
2		15 minutes	63%
3		30 minutes	30%
4		30 minutes	36%
5		3 hours	12%



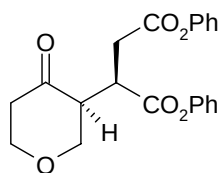
Synthesis of cyclohexanone derivatives

Synthesis 1st part

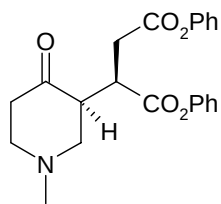
➤ Non asymmetric studies



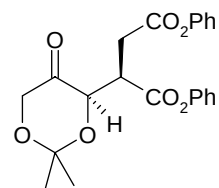
15 min, 81%



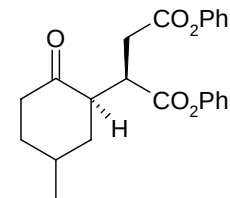
40 min, 76%



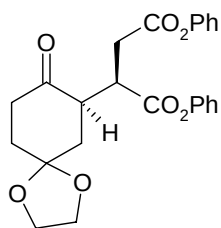
1h, 58%



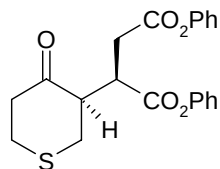
3.5h, 54%



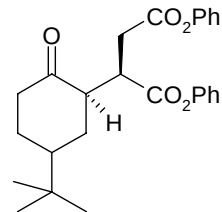
20 min, 60%



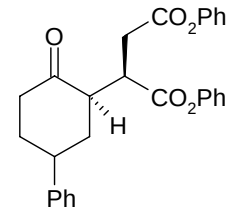
4h, 49%



1h, 84%



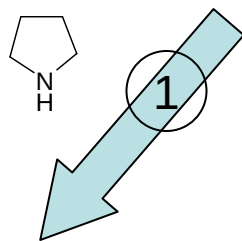
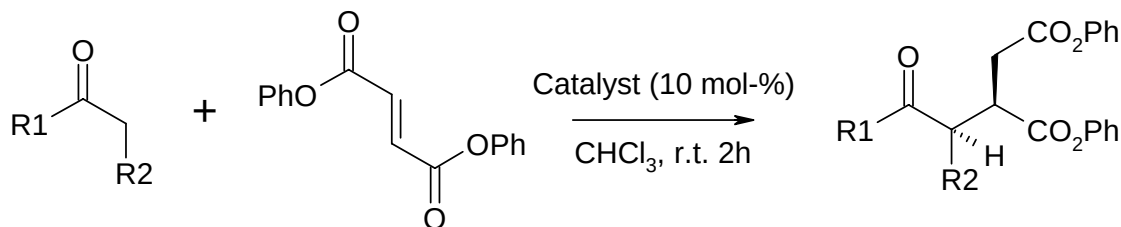
48h, 26%



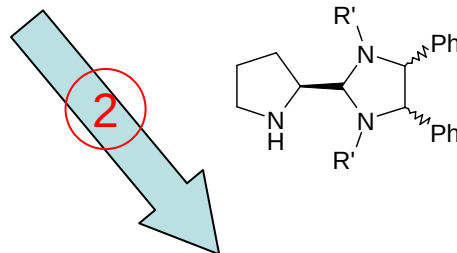
24h, 32%

Synthesis in the laboratory

➤ Organocatalysed additions of ketones to diphenylmaleates



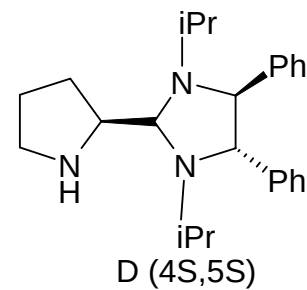
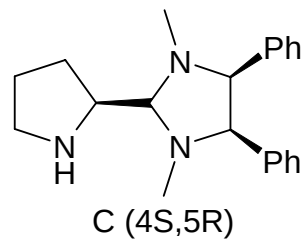
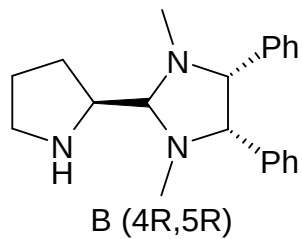
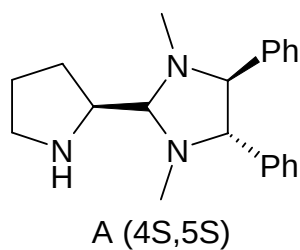
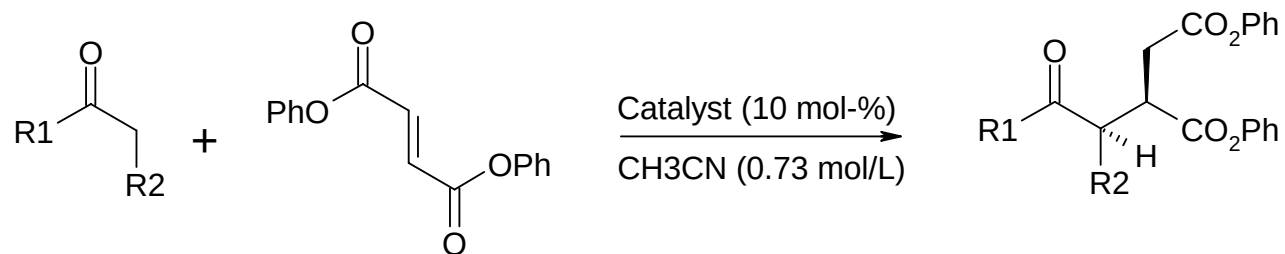
Non asymmetric studies



asymmetric studies

Synthesis 2nd part

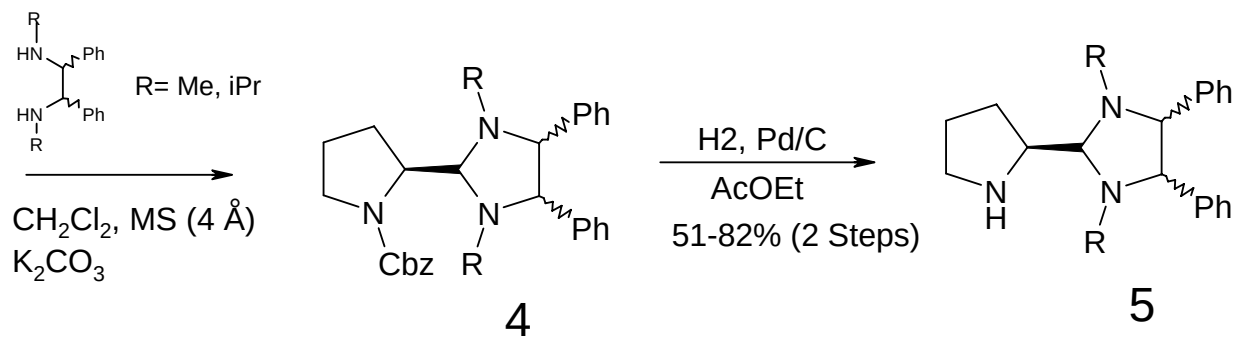
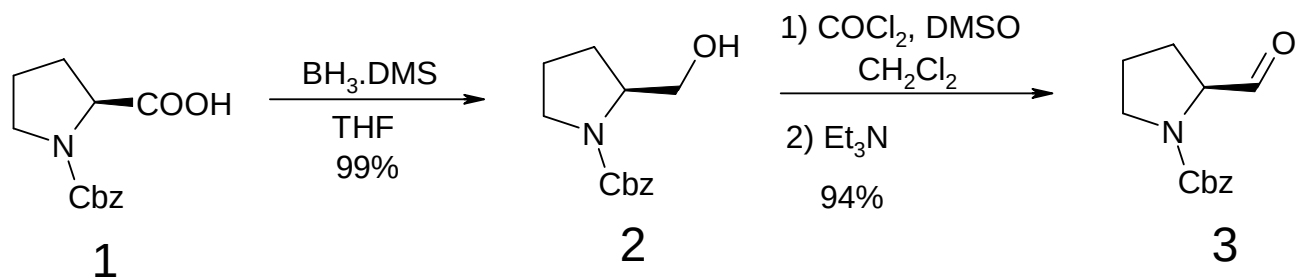
➤ Asymmetric studies



Synthesis 2nd part

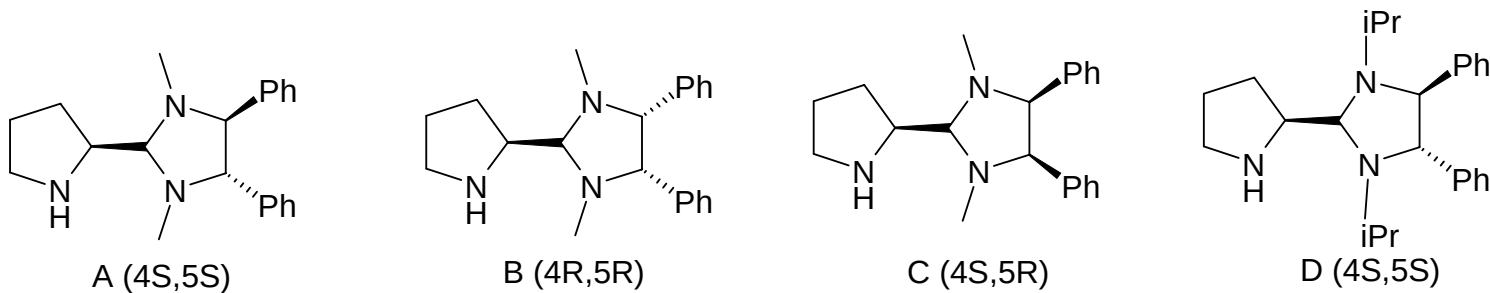
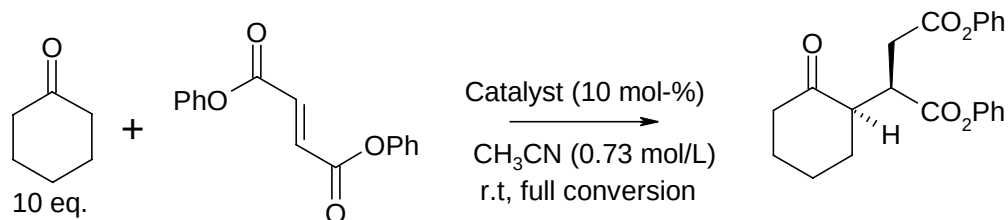
➤ Asymmetric studies

Catalyst B synthesis



Synthesis 2nd part

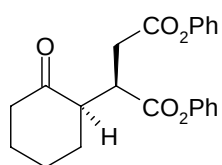
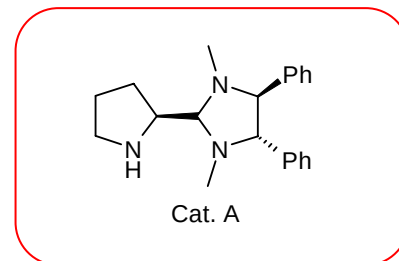
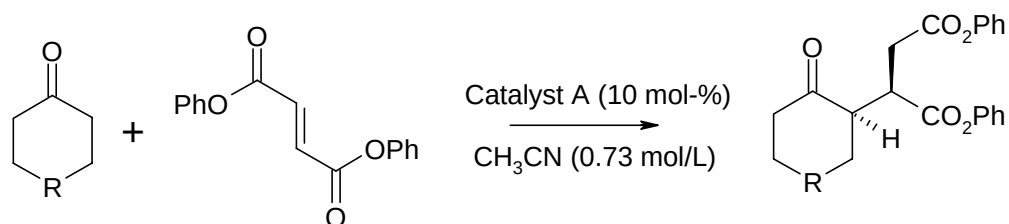
➤ Asymmetric studies



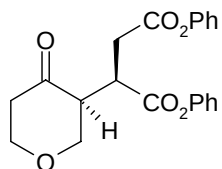
Entry	Cat.	t (h)	dr (syn/anti)	ee (syn) %
1	A	15	75:25	79
2	B	19	66:34	49
3	C	18	78:22	57
4	D	21	71:29	76

Synthesis 2nd part

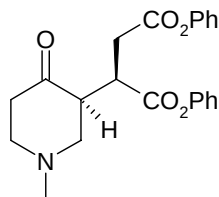
➤ Asymmetric studies



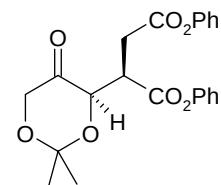
Yield: 82%, 79% ee
dr (syn/anti): 75/25



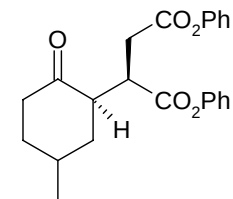
Yield: 85%, 72% ee
dr (syn/anti): 80/20



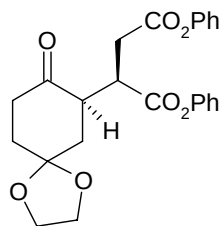
Yield: 66%, 65% ee
dr (syn/anti): 66/34



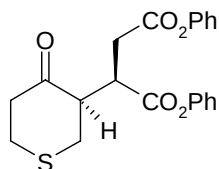
Yield: 52%, 63% ee
dr (syn/anti): 70/30



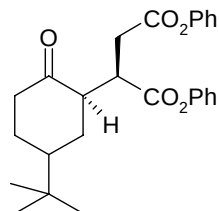
Yield: 70%, 68% ee
dr (syn/anti): 72/28



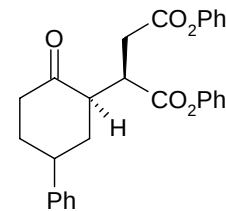
N.R.



Yield: 92%, 80% ee
dr (syn/anti): 85/15



N.R.



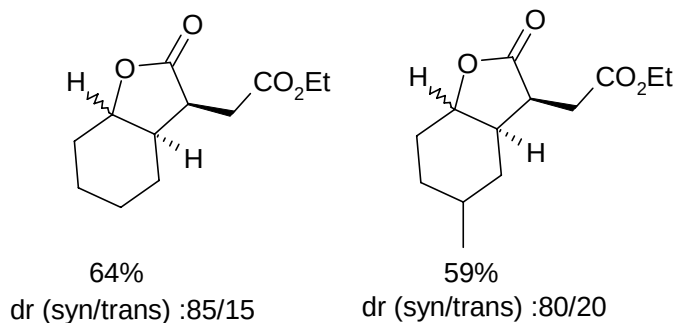
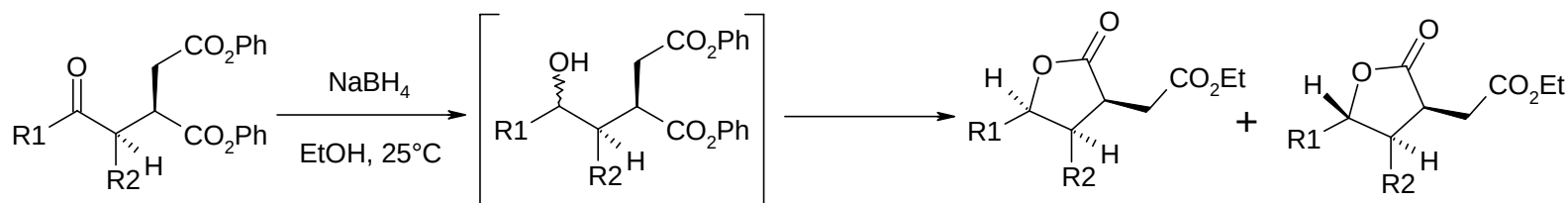
N.R.

Application

- Presence of the lactone ring in many natural product and in pharmaceutical active compounds.

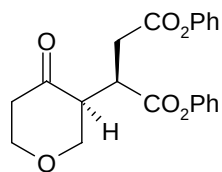
➤ Synthesis of bicyclic γ -lactone

- S. Drioli *et al.*, J. Chem. Soc., Perkin Trans. 1, **2000**, 2839–2842

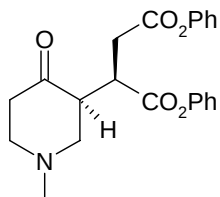


Conclusion and perspectives

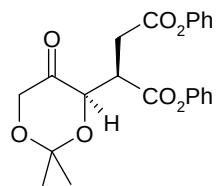
➤ Final molecules performed



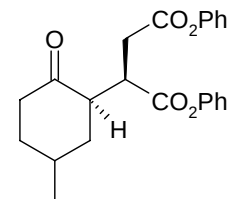
Yield: 85%, 72% ee
dr (syn/anti): 80/20



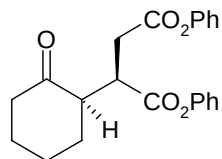
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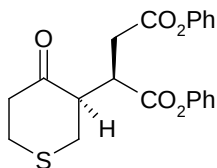
Yield: 52%, 63% ee
dr (syn/anti): 70/30



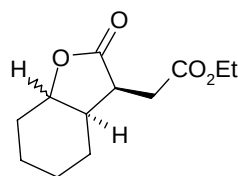
Yield: 70%, 68% ee
dr (syn/anti): 72/28



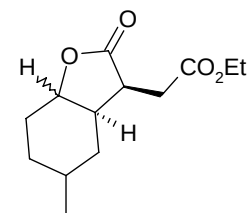
Yield: 82%, 79% ee
dr (syn/anti): 75/25



Yield: 92%, 80% ee
dr (syn/anti): 85/15



64%,
dr (syn/trans): 85/15



59%,
dr (syn/trans): 80/20

➤ Reactions planned

- Cyclisation of all cyclohexanone derivatives