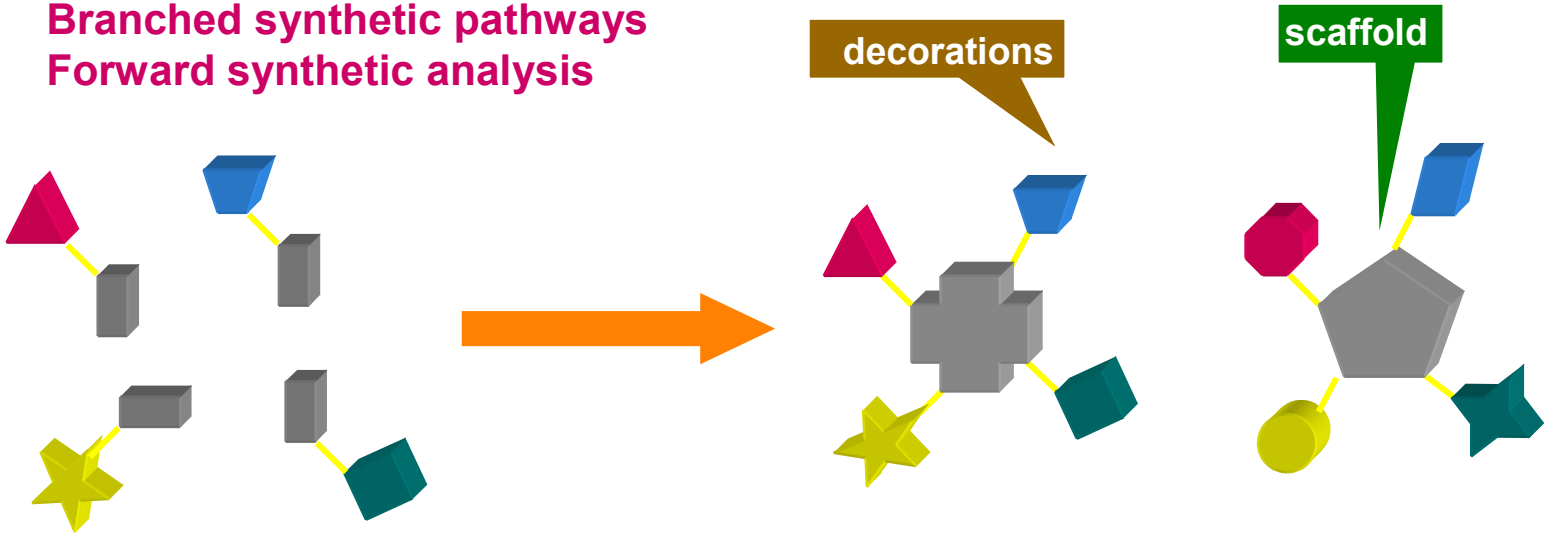
DIVERSITY ORIENTED SYNTHESIS

Scope: To develop synthetic protocols able to generate efficiently relatively complex molecules in few steps introducing at the same time various "diversity inputs"

Main features:

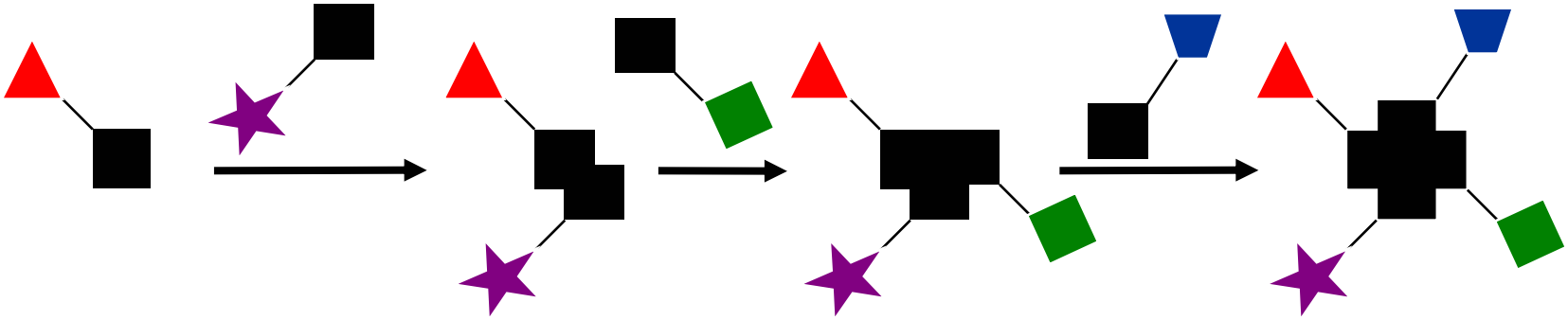
1) High rate of complexity increase *per* synthetic step (minimize the use of protecting groups)
2) Possibility of introducing diversity inputs (decoration diversity or scaffold diversity) without changing the general protocol
3) Branched synthetic pathways
4) Forward synthetic analysis



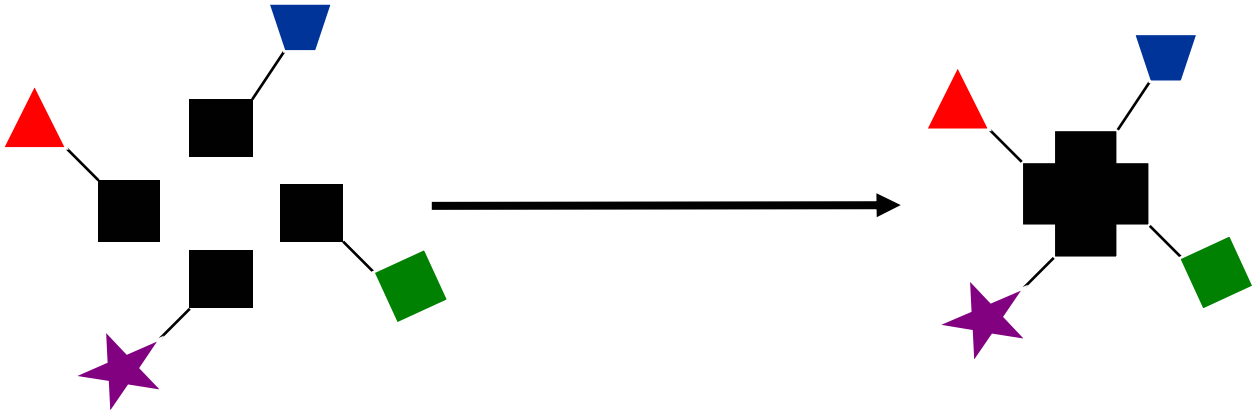
simple "building blocks" complex and diverse collections of products

MULTI DIVERSITY GENERATION REACTIONS (MDGR)

In a traditional combinatorial synthesis the various diversity inputs are added in a sequential way to build up a scaffold sorrounded by diverse “decorations”



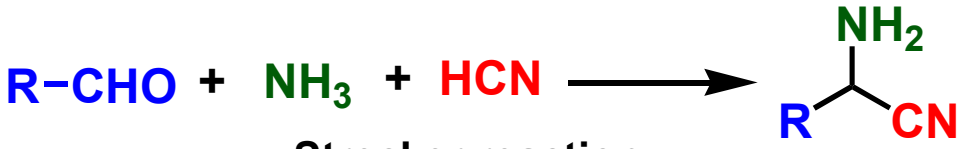
A multi diversity generation is a reaction that allows the simultaneous joining, in one synthetic step, of more than 2 diversity inputs



MULTICOMPONENT REACTIONS

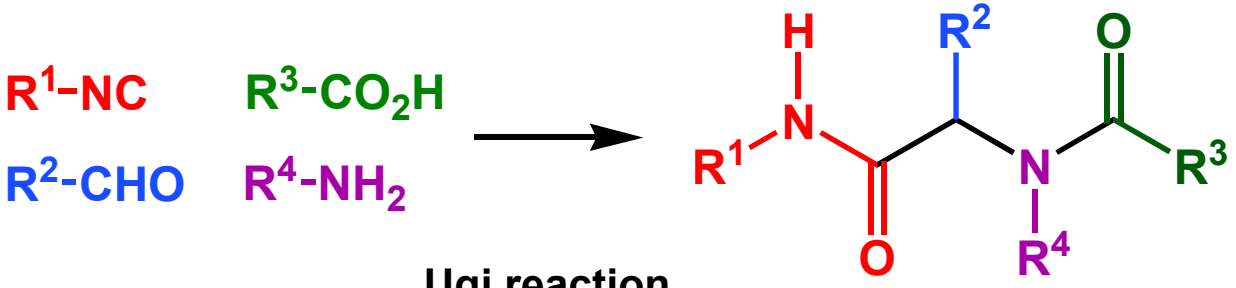
Reactions are defined as multicomponent when three or more substrates combine in just one step to give a product that contains essential parts of all components.

Multicomponent reactions are often, but not always, also multi diversity generation reactions (MDGRs).



Strecker reaction

The Strecker reaction is the oldest multicomponent reaction, but it is not a multi diversity generation reaction. Two components are "fixed".

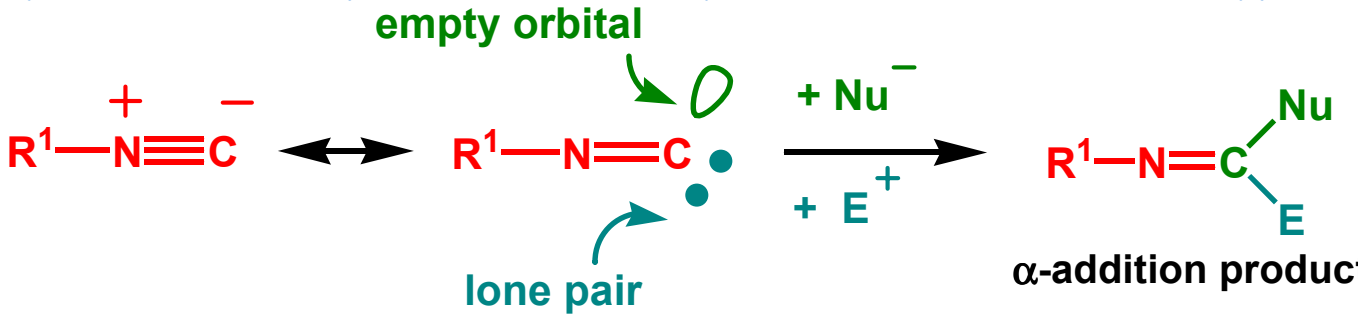


Ugi reaction

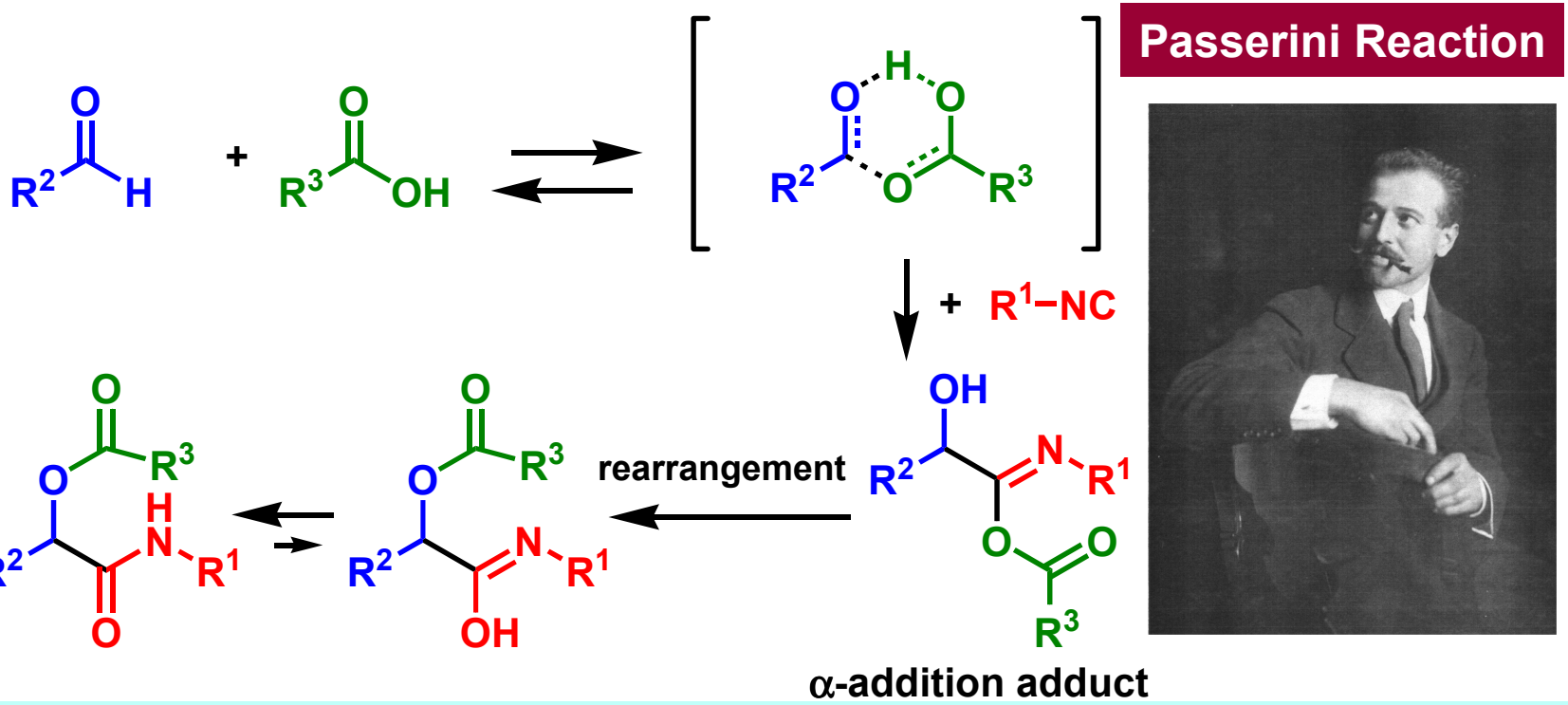
On the contrary, the Ugi reaction is a true MDGR, since it involves the introduction of 4 diversity inputs

MAIN ISOCYANIDE BASED MULTI COMPONENT REACTIONS

Isocyanides are simple bifunctional synthons, well suited for type 2 MCRs



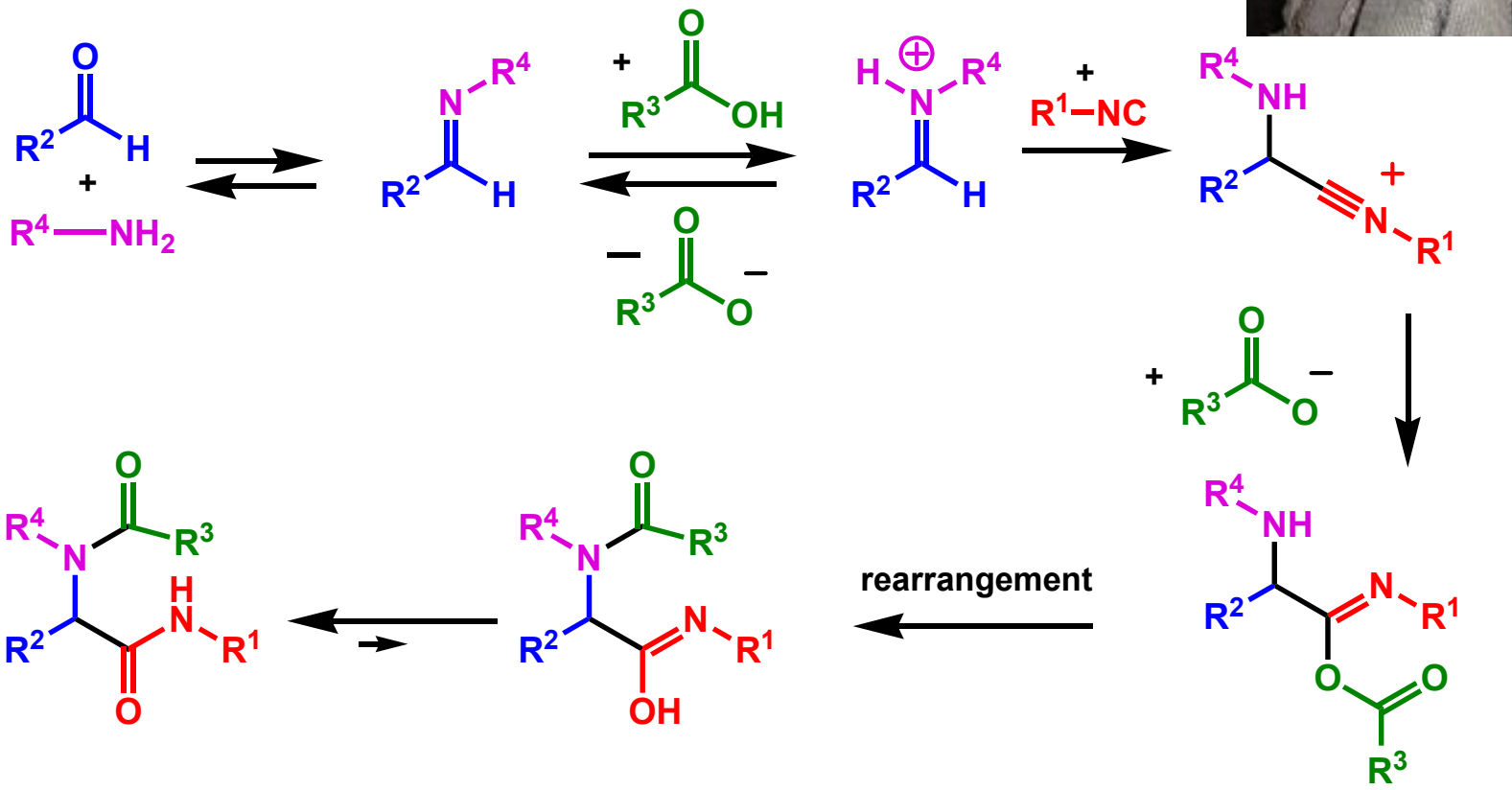
Passerini Reaction



MAIN ISOCYANIDE BASED MULTI COMPONENT REACTIONS

Ugi Reaction

The Ugi reaction represents a combination of imine formation and Passerini reaction

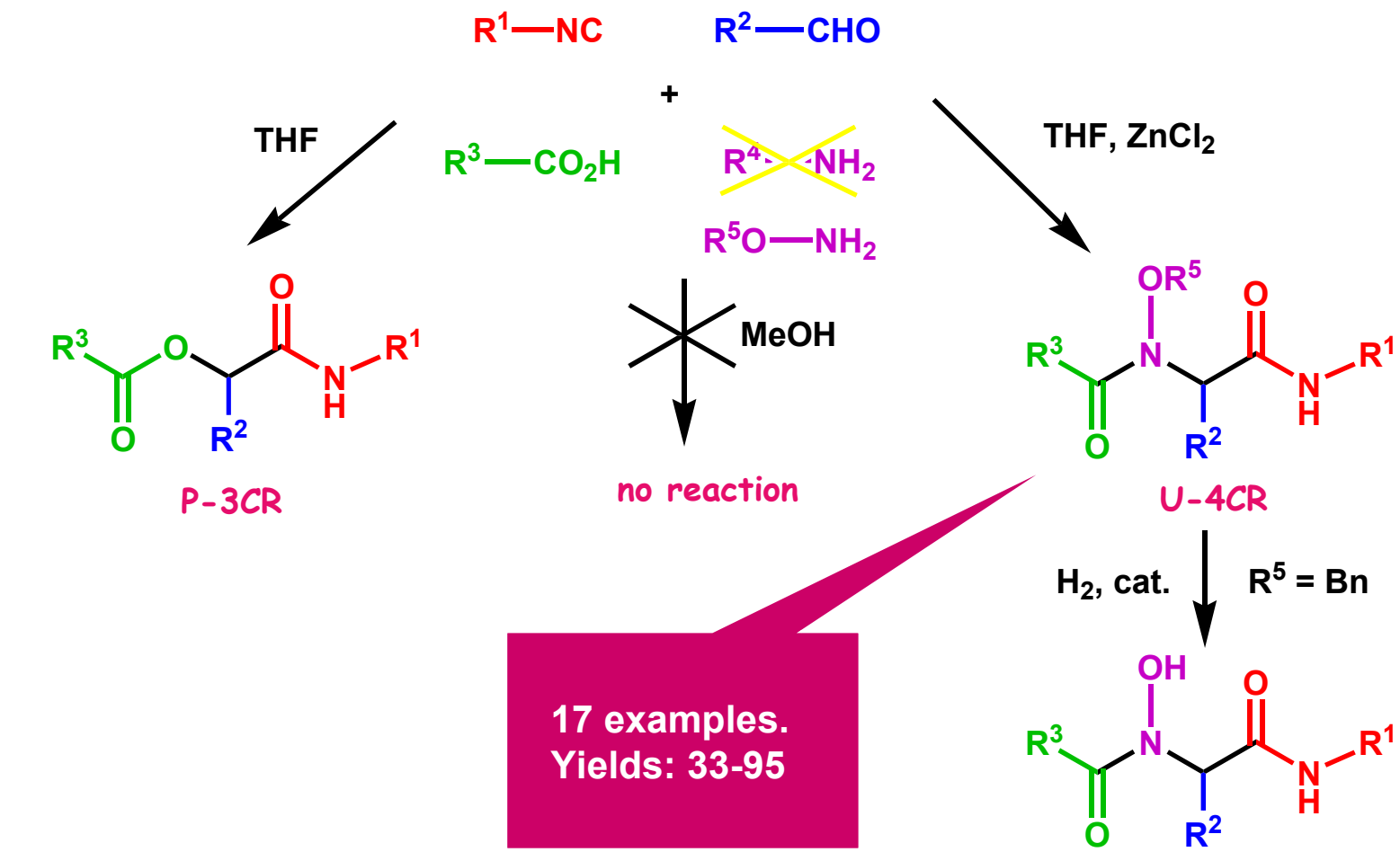


How to modify Passerini and Ugi reactions in order to obtain diverse scaffolds?

1. ***Intramolecular variants***
2. ***Substitution of one component with different reagents***
3. ***Post-condensation transformations***

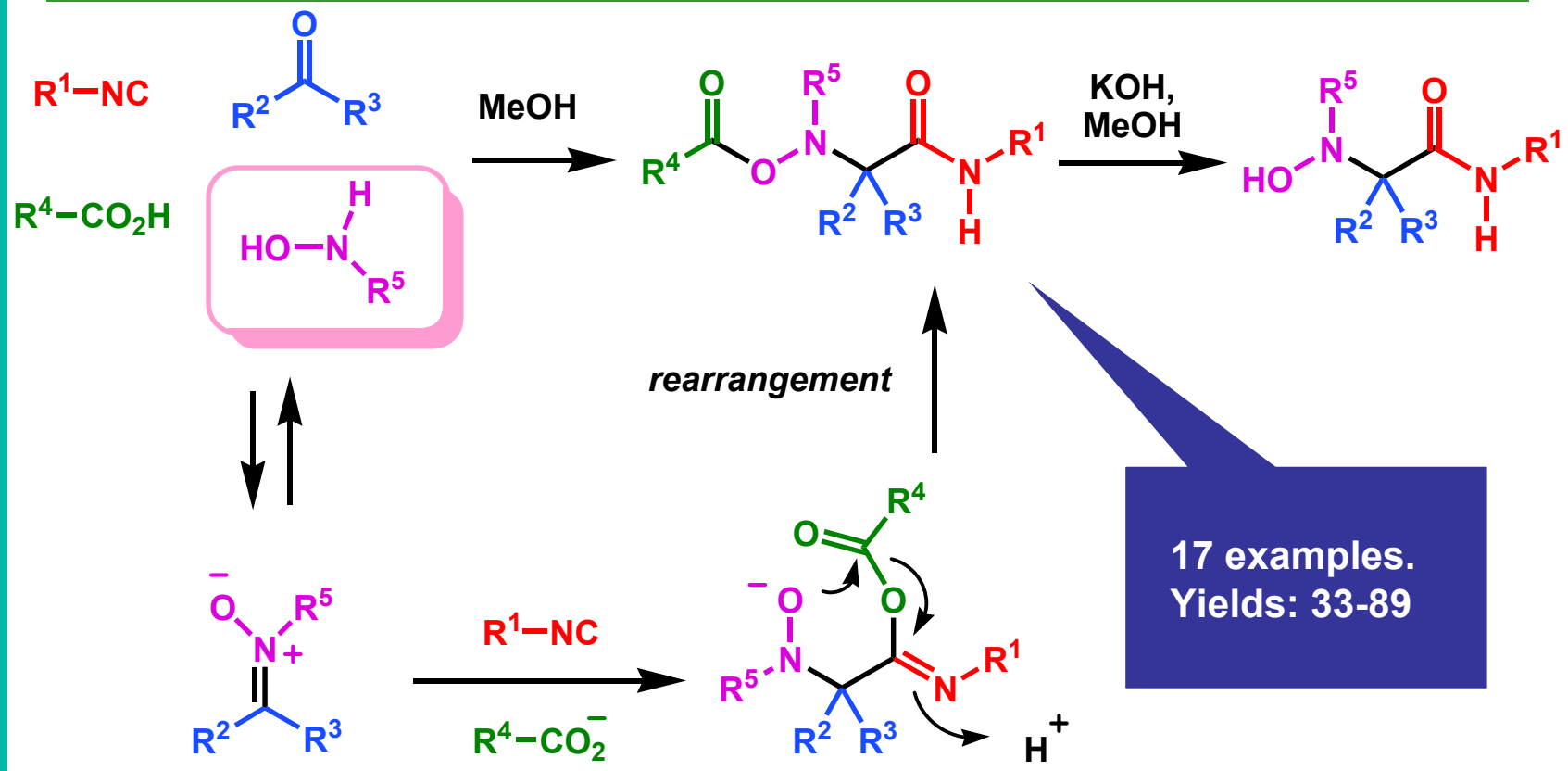
Through these modifications, a lot of new scaffolds, especially drug-like nitrogen heterocycles, have been obtained, most of them during the last 7-8 years

Strategy # 2: Substitution of a component



Basso, A.; Banfi, L.; Guanti, G.; Riva, R.; Riu, A. *Tetrahedron Lett.*, 2004, *45*, 6109

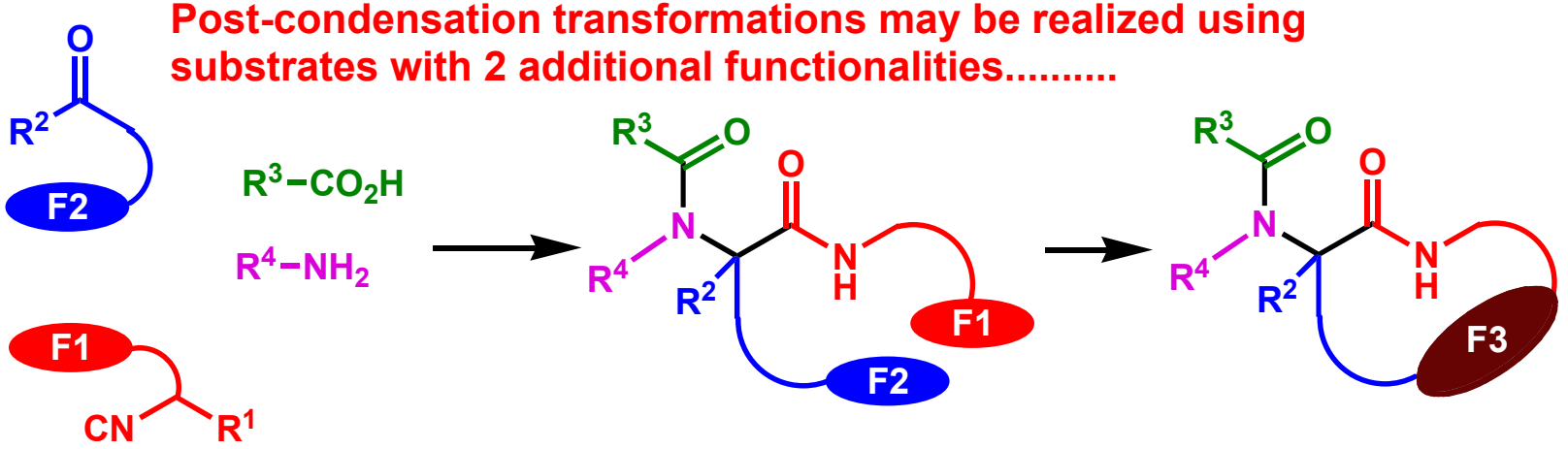
Strategy # 2: Substitution of a component



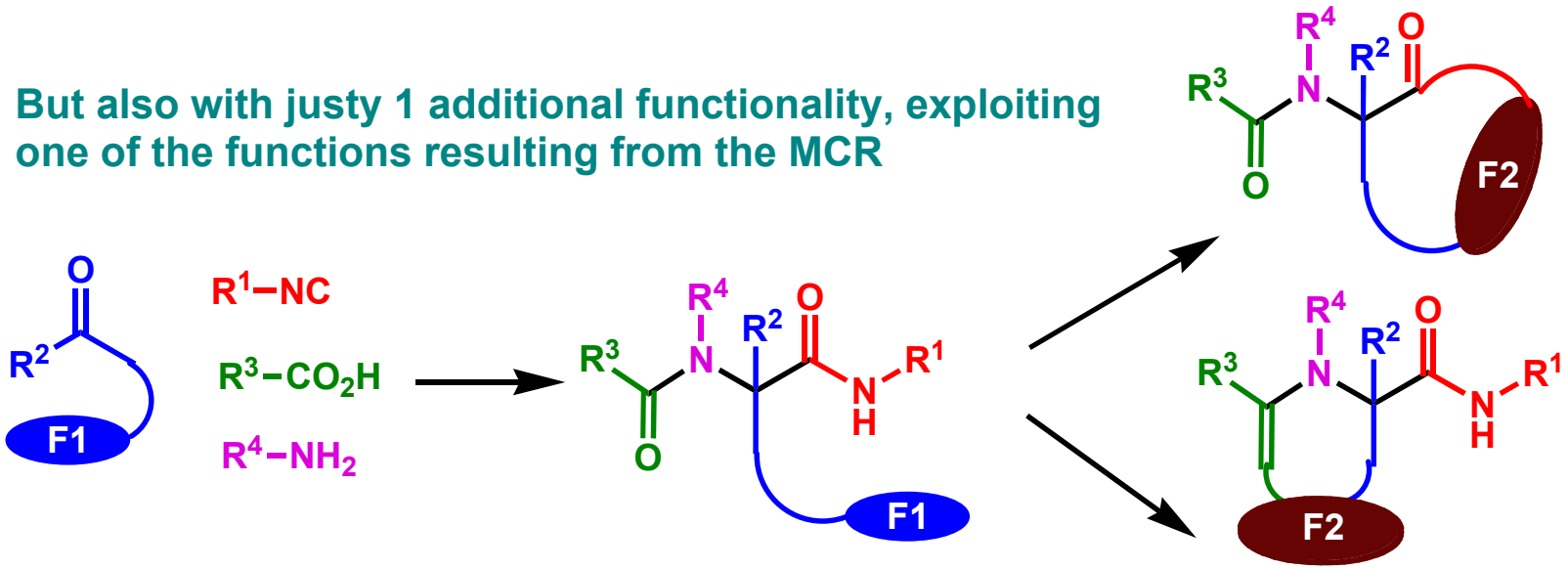
Basso, A.; Banfi, L.; Guanti, G.; Riva, R., *Tetrahedron Lett.*, 2005, *46*, 8003

Strategy # 3: Post-condensation transformations

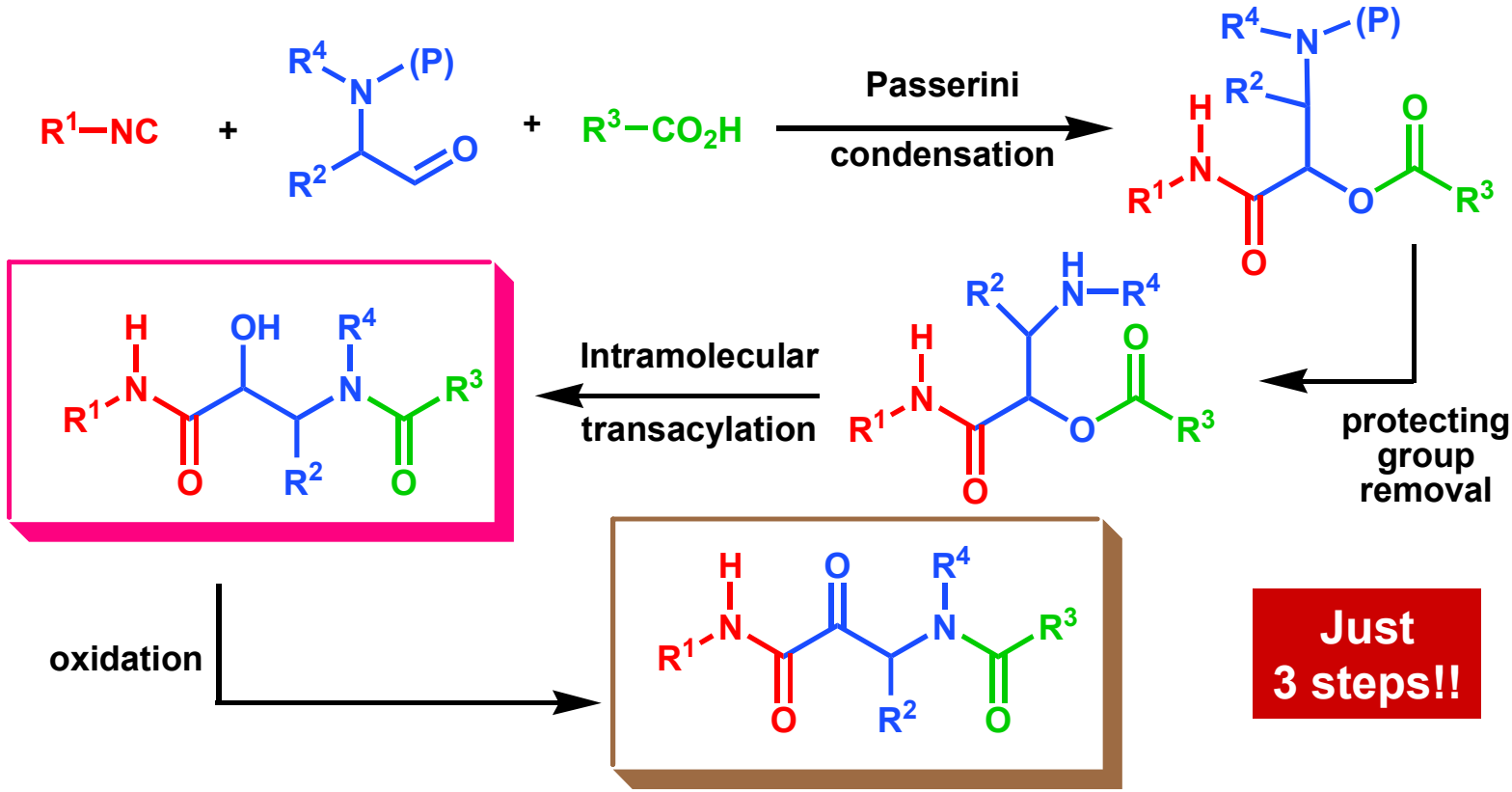
Post-condensation transformations may be realized using substrates with 2 additional functionalities.....



But also with justy 1 additional functionality, exploiting one of the functions resulting from the MCR



Post-condensation transformations: acyl transfer



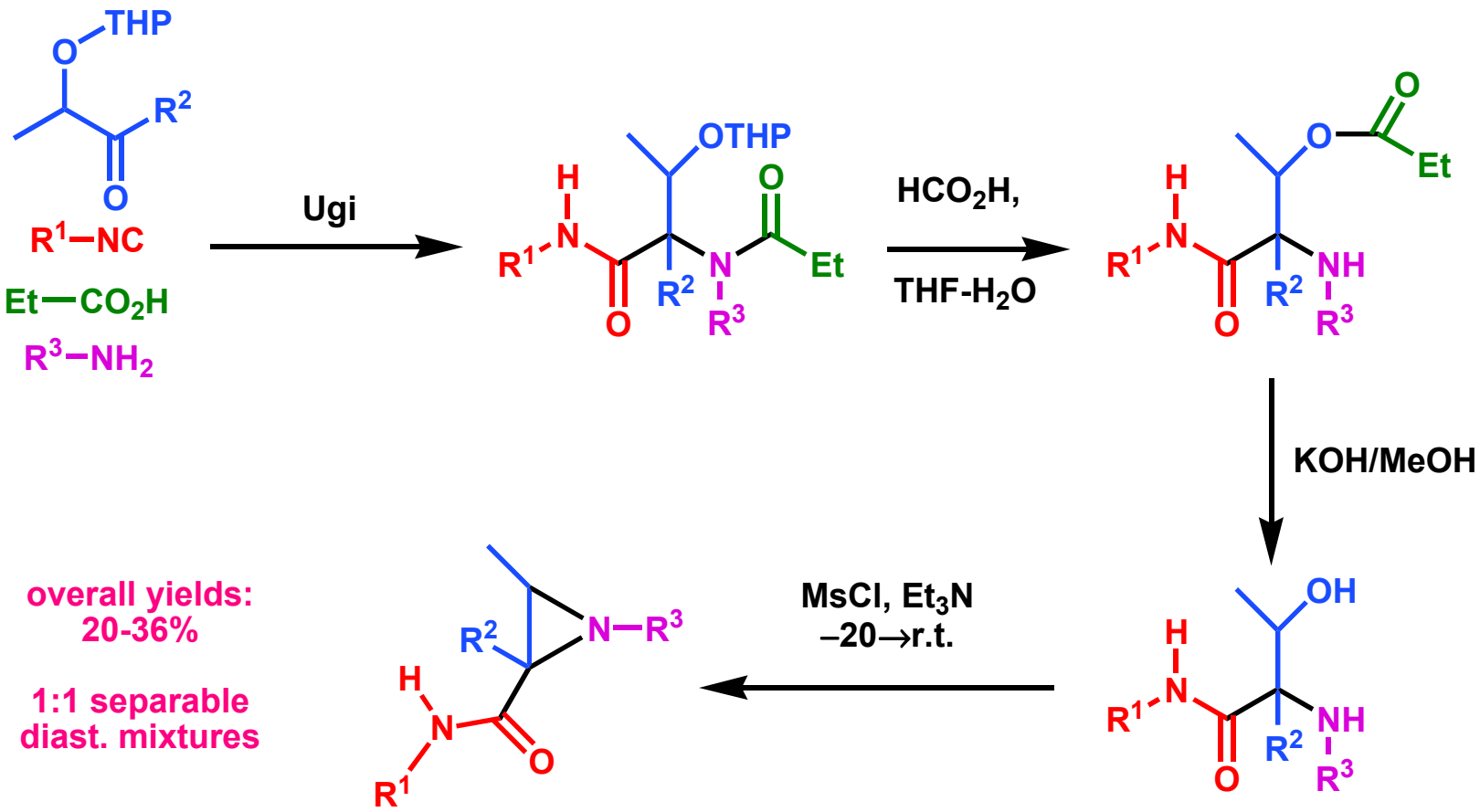
These structures are very important as protease inhibitors. Their previous syntheses required at least 7-8 steps!

Banfi, L.; Guanti, G.; Riva, R., *Chem. Commun.*, **2000**, 985-986. Banfi, L.; Guanti, G.; Riva, R.; Basso, A.; Calcagno, E., *Tetrahedron Lett.*, **2002**, 4067-4069

Solid phase synthesis: Banfi, L.; Basso, A.; Guanti, G.; Riva, R., *Molecular Diversity*, **2003**, 227-235. Basso, A., Banfi, L.; Riva, R.; Piaggio, P.; Guanti, G., *Tetrahedron Lett.*, **2003**, 2367-2370.

Post-condensation transformations: acyl transfer

New synthesis of densely substituted aziridines



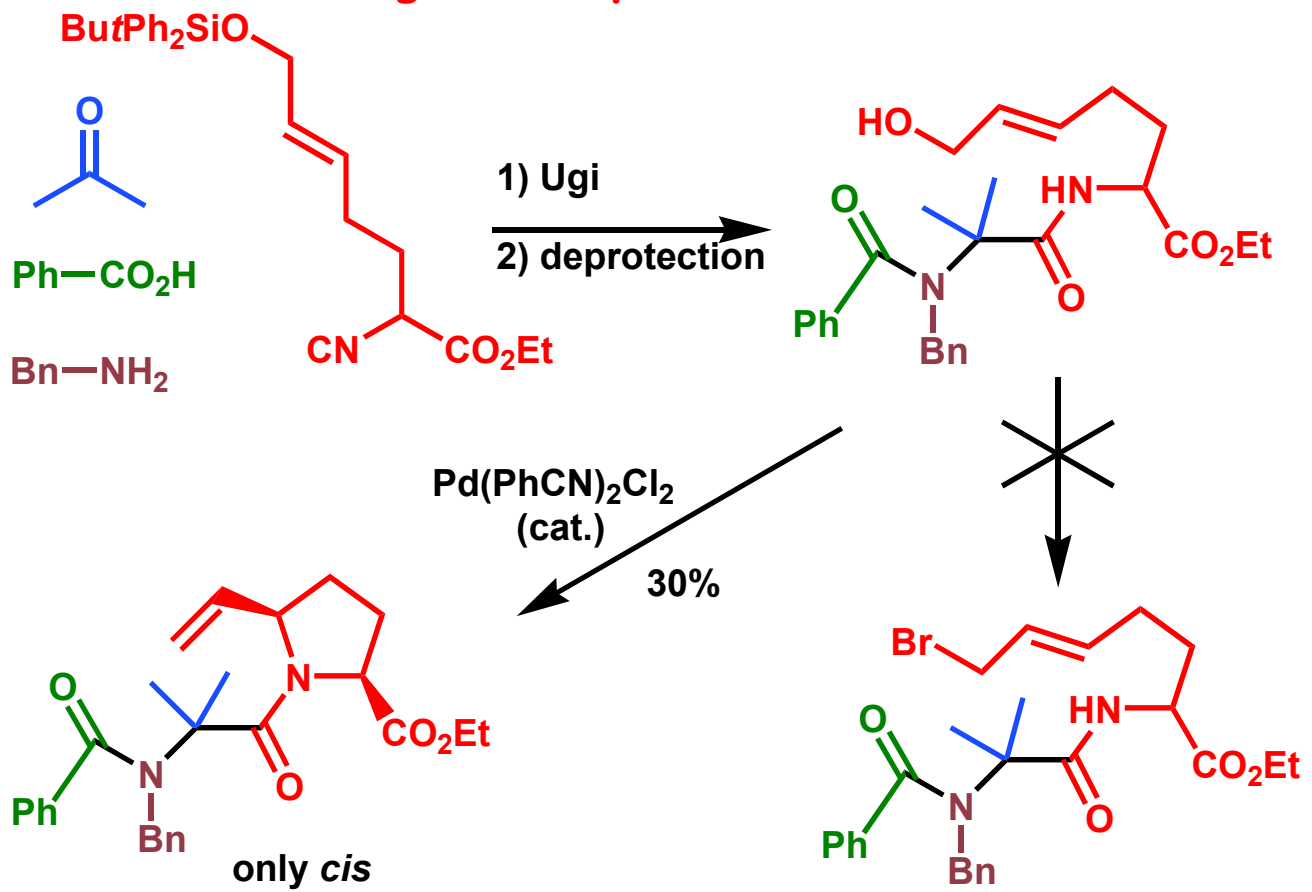
overall yields:
20-36%

1:1 separable
diast. mixtures

Banfi, L.; Basso, A.; Guanti, G.; Paravidino, M.; Riva, R., *QSAR & Comb. Sci.*, **2006**, 457-460

Post-condensation transformations: S_N2'

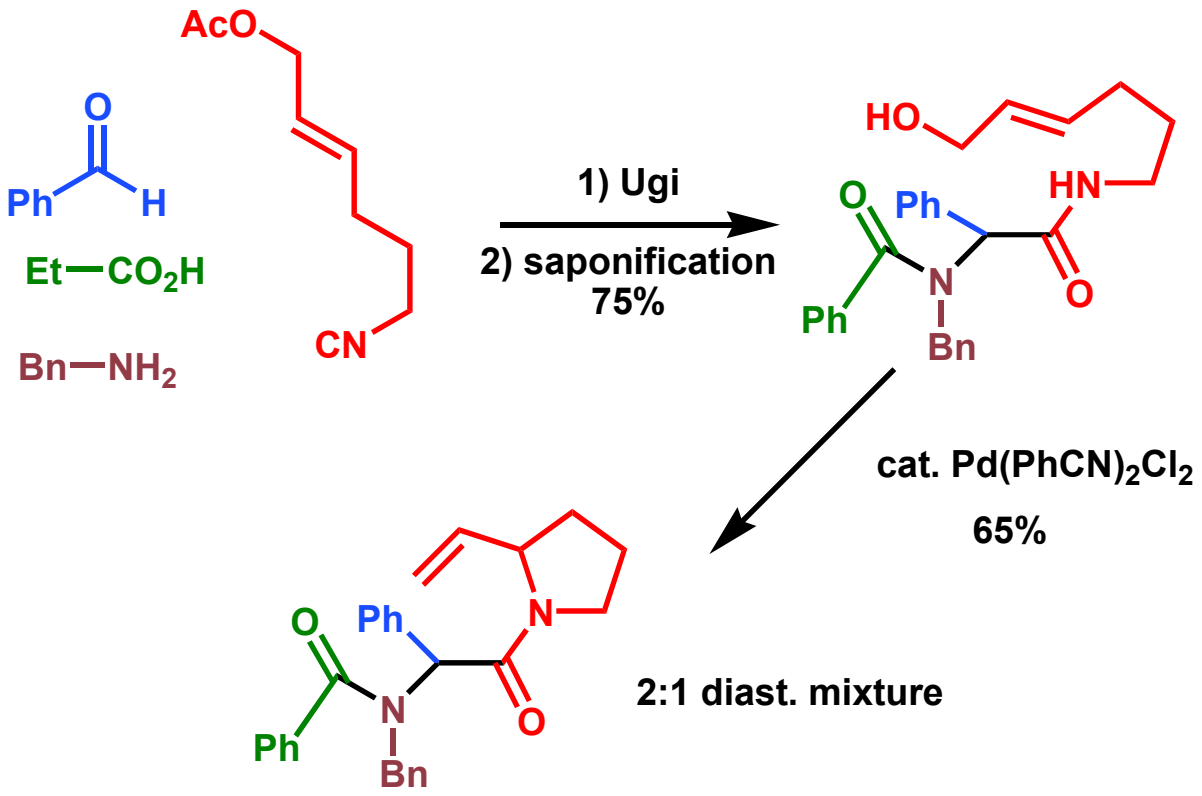
Use of the isocyanide-derived secondary amide for cyclization through nucleophilic substitution



Banfi, L.; Basso, A.; Guanti, G.; Riva, R., preliminary results

Post-condensation transformations: S_N2'

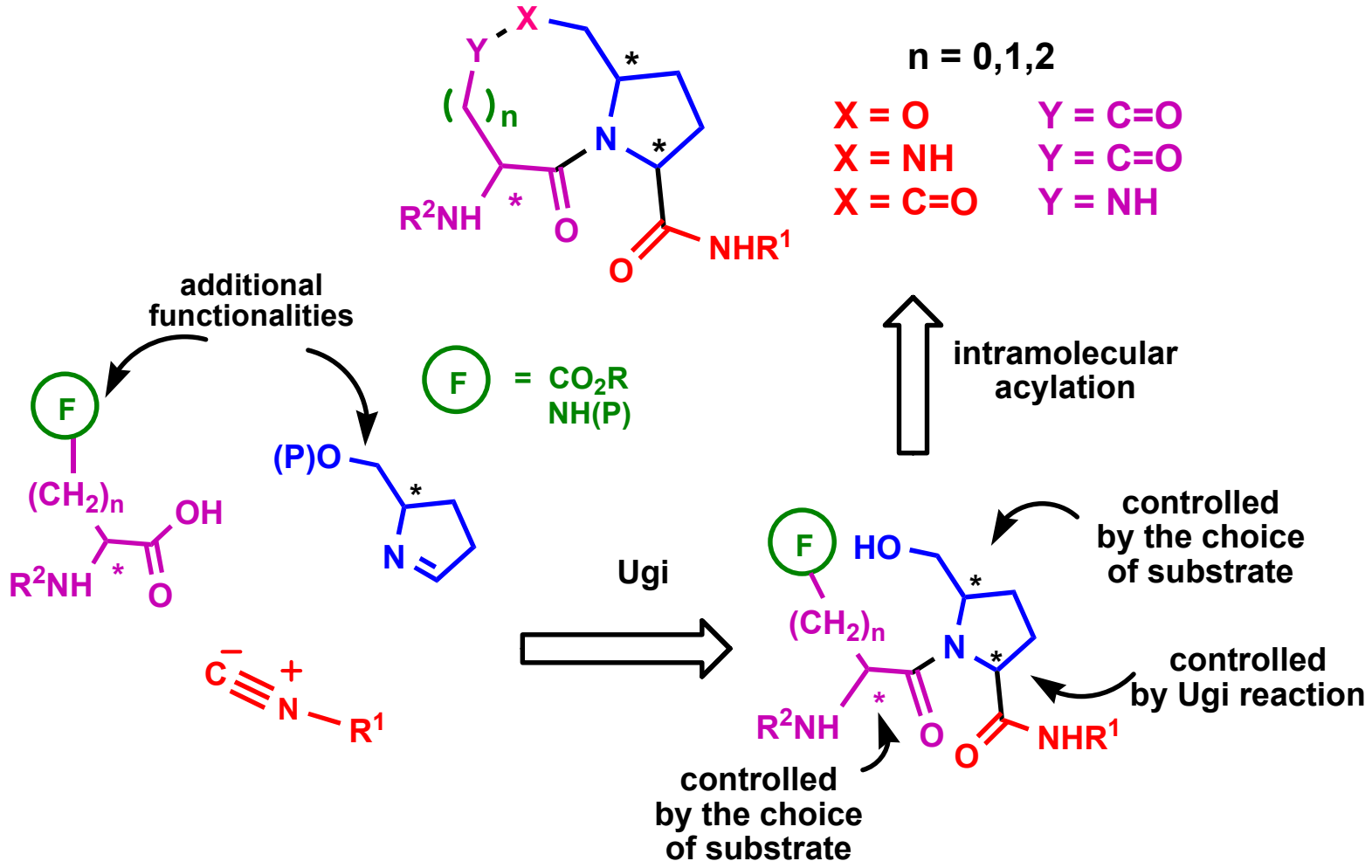
Use of the isocyanide-derived secondary amide for cyclization through nucleophilic substitution



Banfi, L.; Basso, A.; Guanti, G.; Riva, R., preliminary results.
See Hirai, Y. et al., *Org. Lett.,* **2000**, 2427

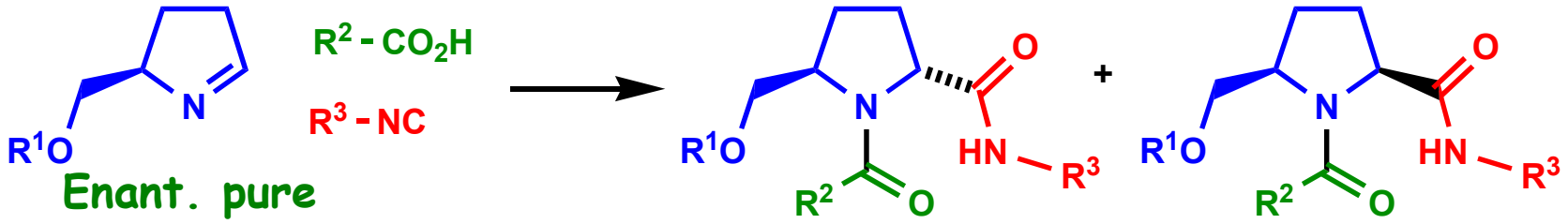
Post-condensation transformations: acylation

The post-condensation transformation may be a simple intramolecular acylation



Synthesis of functionalised pyrrolidines through an intramolecular Ugi reaction

Use of Aminoaldehydes (cyclic imines) as components

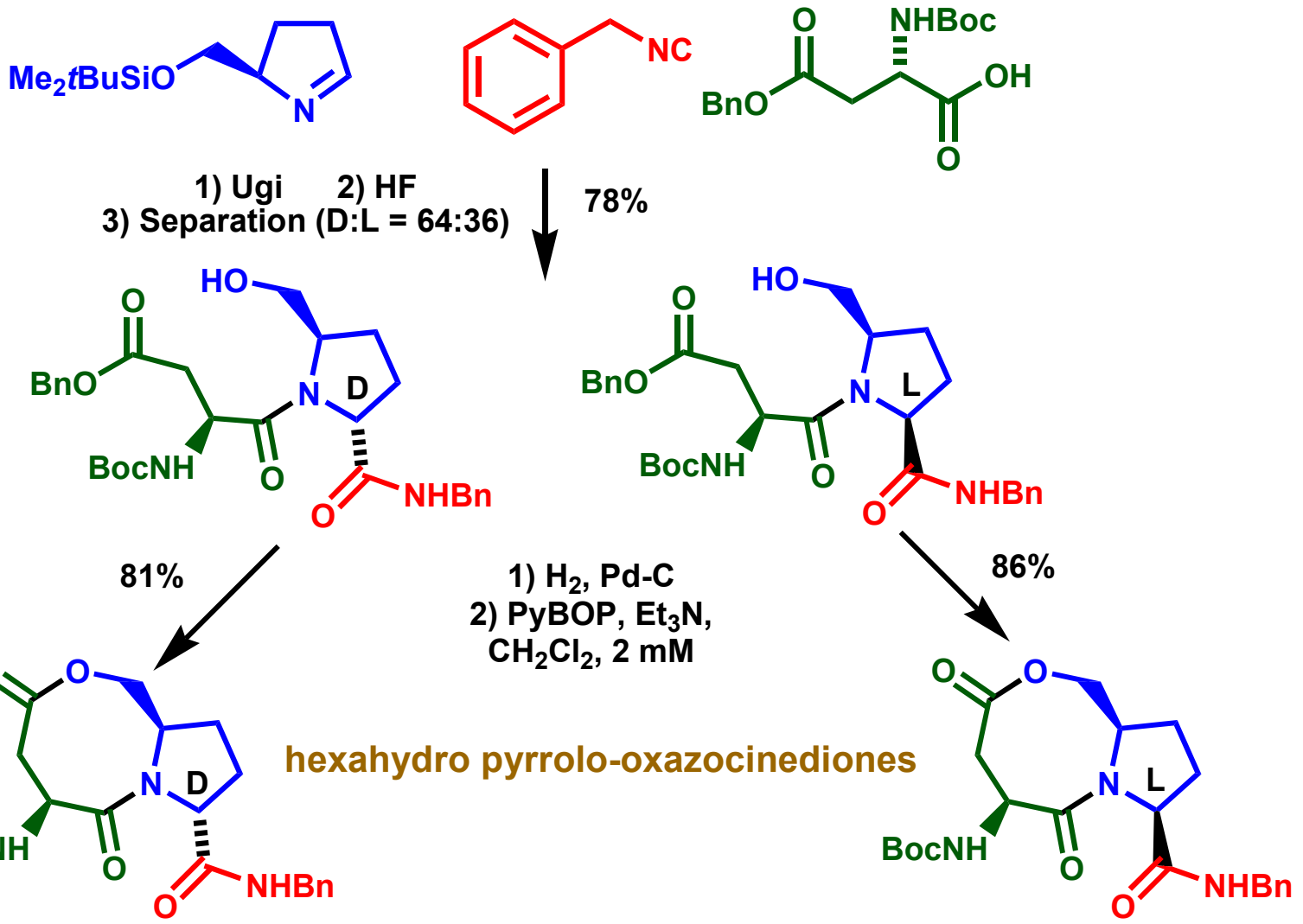


Entry[a]	R^1	R^2	R^3	Yield	D. r.
1	$SiMe_2tBu$	nC_3H_7	Bn	45%	68 : 32[b]
2	Tr	nC_3H_7	Bn	70%	53 : 47[c]
3	$SiMe_2tBu$	Ph	CH_2CO_2tBu	62%[d]	53 : 47[e,f]
4	$SiMe_2tBu$	Ph	nC_4H_9	44% [d]	64 : 36[b]
5	$SiMe_2tBu$	Ph	tBu	46% [d]	63 : 37[b]
6	$SiMe_2tBu$	$CH_2=CH(CH_2)_2$	Bn	60%	68 : 32[e]
7	$SiMe_2tBu$	Fmoc-L-Ala	Bn	80%	64 : 36[e]
8	$SiMe_2tBu$	Fmoc-D-Ala	Bn	69%	65 : 35[e]
9	$SiMe_2tBu$	Boc-L-Asp(OBn)	Bn	85%	64 : 36[e]

Note: [a] all the reactions were carried out in MeOH (0.30 M) at r.t. for 1-2 h; [b] by GC-MS; [c] by weight; [d] yield from azidoaldehyde; [e] by HPLC; [f] Determined after $SiMe_2tBu$ removal (HF/CH_3CN or nBu_4NF).

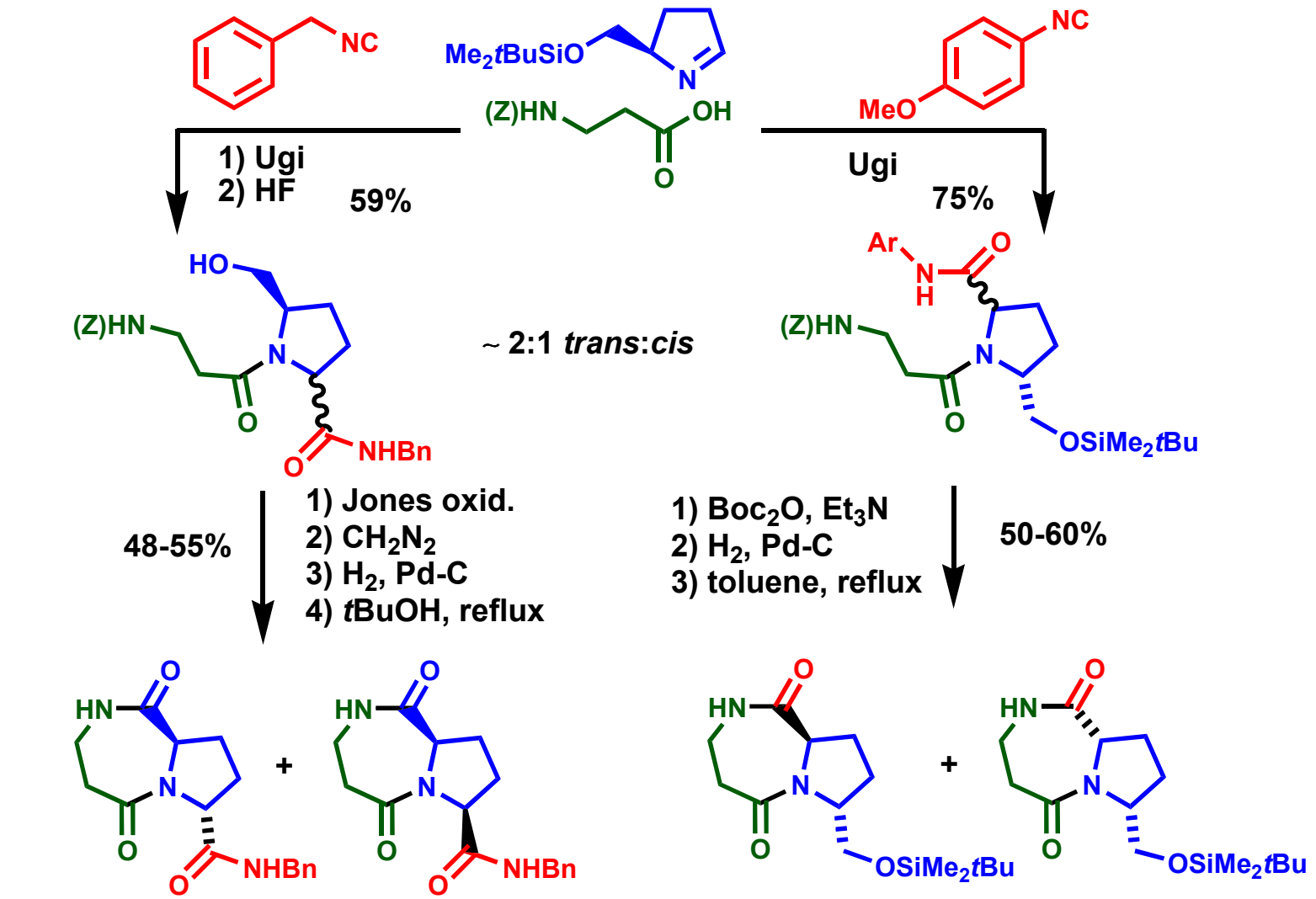
Banfi, L.; Basso, A.; Riva, R.; Guanti, G., *Tetrahedron Lett.*, **2004**, *45*, 6637-6640.

Post-condensation transformations: acylation



Banfi, L.; Basso, A.; Riva, R.; Guanti, G., *Tetrahedron Lett.*, **2004**, *45*, 6637-6640.

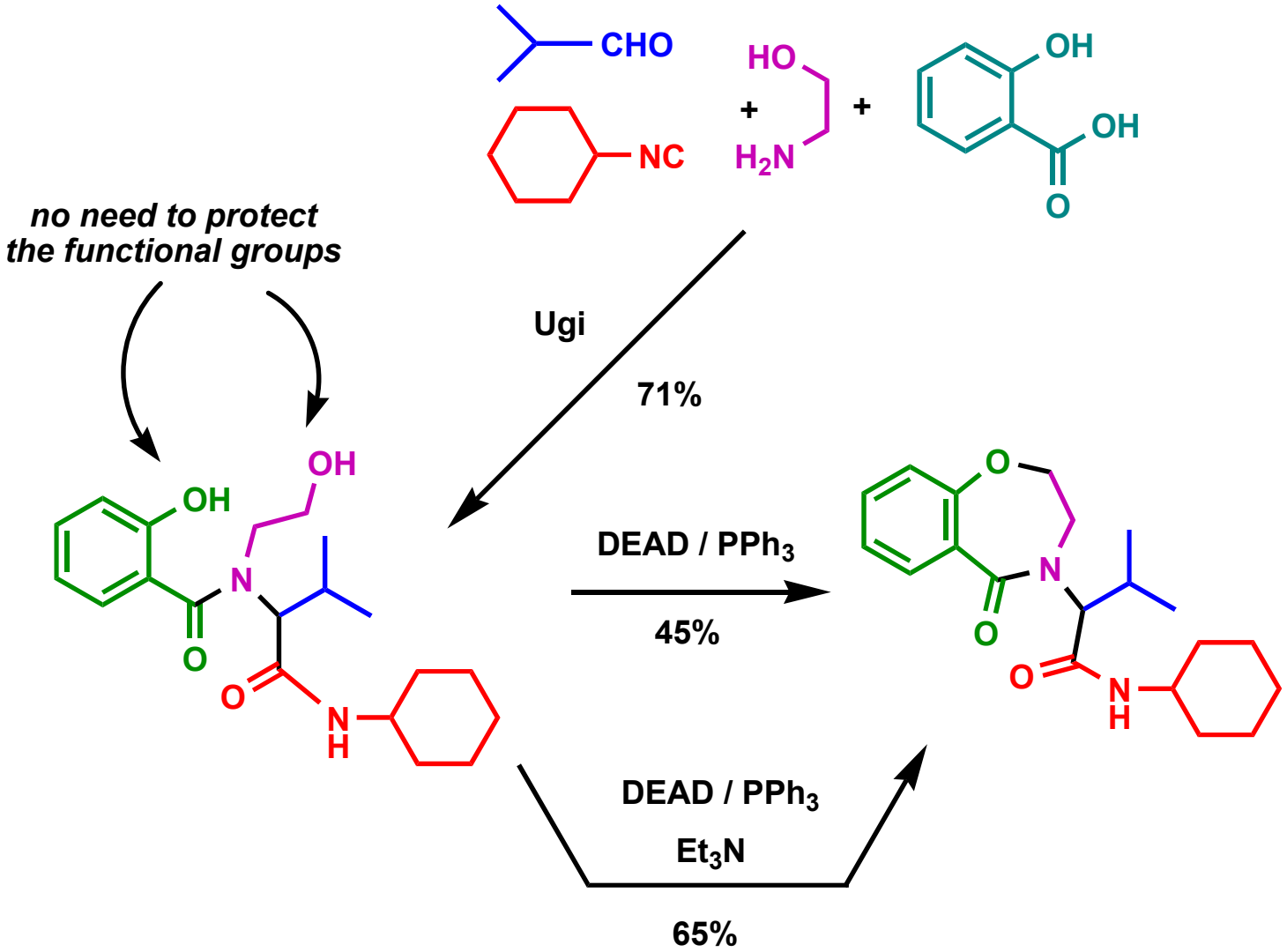
Post-condensation transformations: acylation



Banfi, L.; Basso, A.; Riva, R.; Guanti, G., *unpublished*

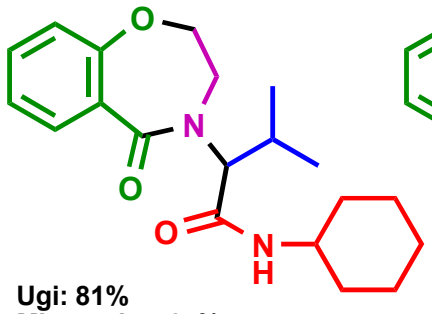
hexahydro-pyrrolodiazepinediones

Short synthesis of benzoxazepinones

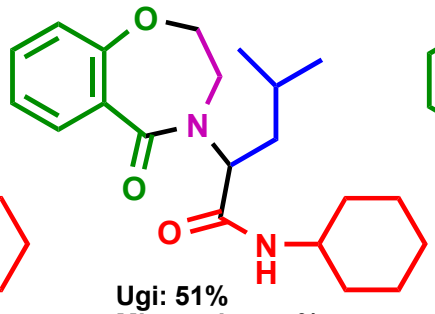


Banfi, L.; Basso, A.; Lecinska, P.; Guanti, G.; Riva, R., *Org. Biomol. Chem.*, in press

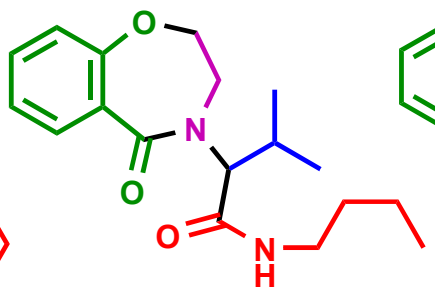
A collection of diverse benzoxazepinones has been prepared



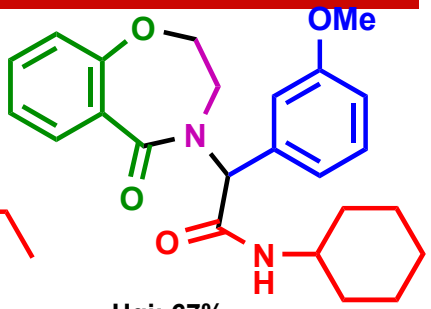
Ugi: 81%
Mitsunobu: 65%



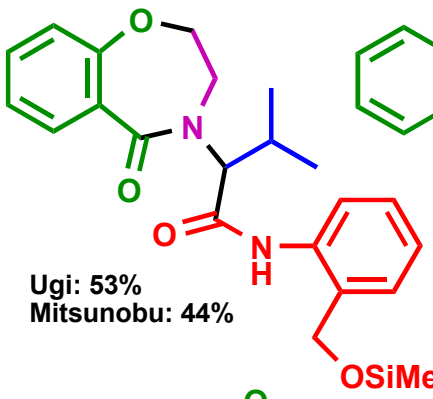
Ugi: 51%
Mitsunobu: 57%



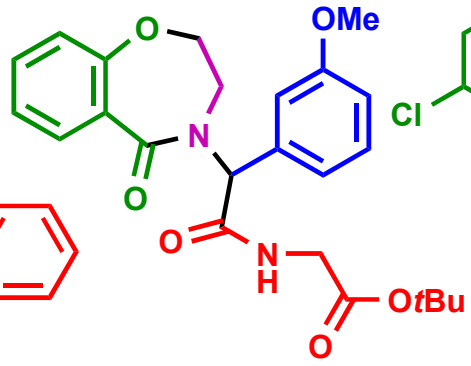
Ugi: 74%
Mitsunobu: 34%



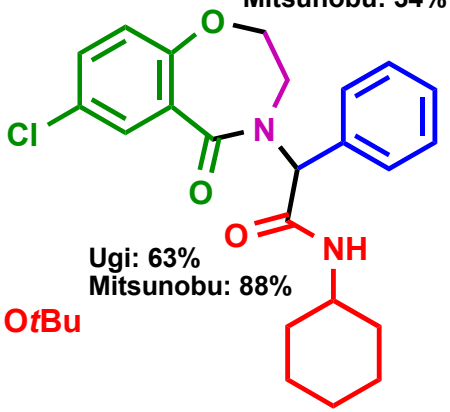
Ugi: 67%
Mitsunobu: 84%



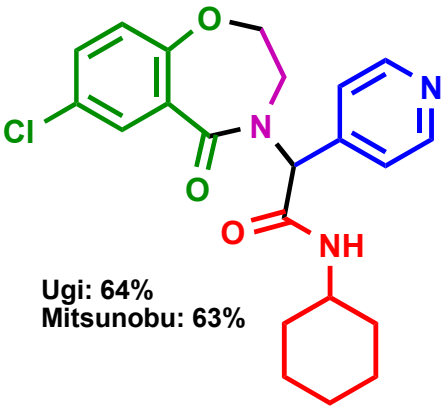
Ugi: 53%
Mitsunobu: 44%



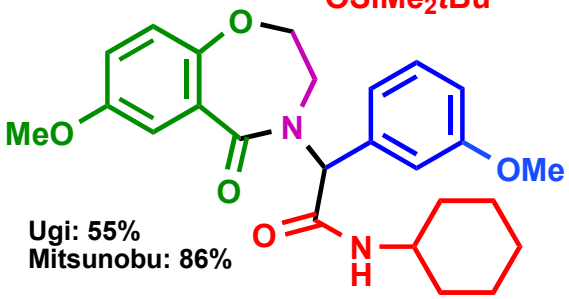
Ugi: 66%
Mitsunobu: 79%



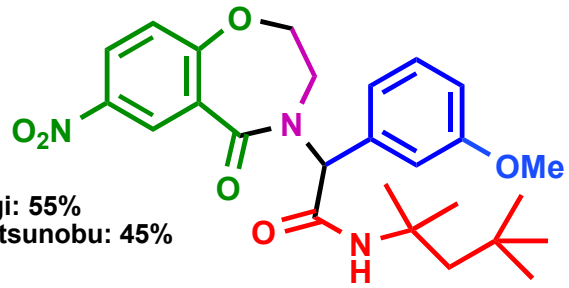
Ugi: 63%
Mitsunobu: 88%



Ugi: 64%
Mitsunobu: 63%



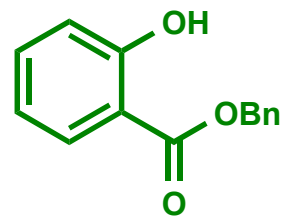
Ugi: 55%
Mitsunobu: 86%



Ugi: 55%
Mitsunobu: 45%

Banfi, L.; Basso, A.; Lecinska, P.; Guanti, G.; Riva, R., *Org. Biomol. Chem.*, in press

Alternative access to the same compounds

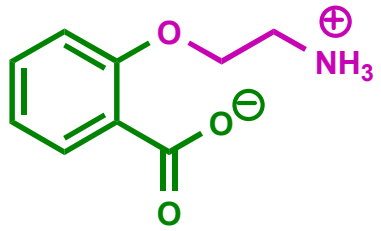


+

1) Mitsunobu

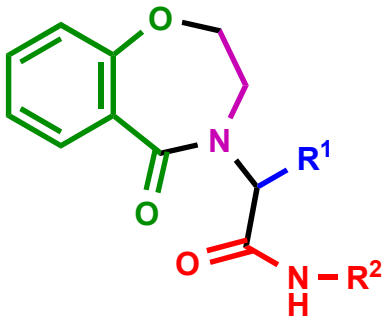
2) H_2, Pd-C

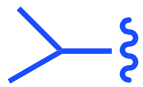
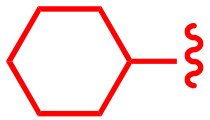
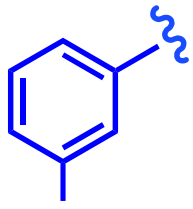
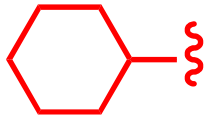
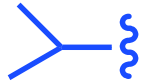
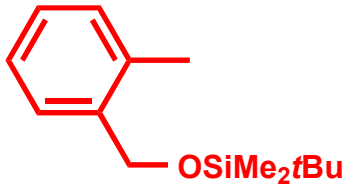
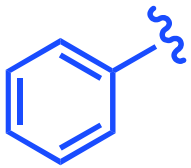
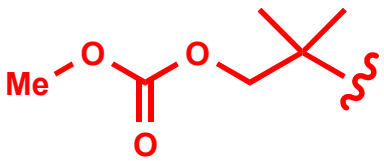
69%



R^1 – CHO

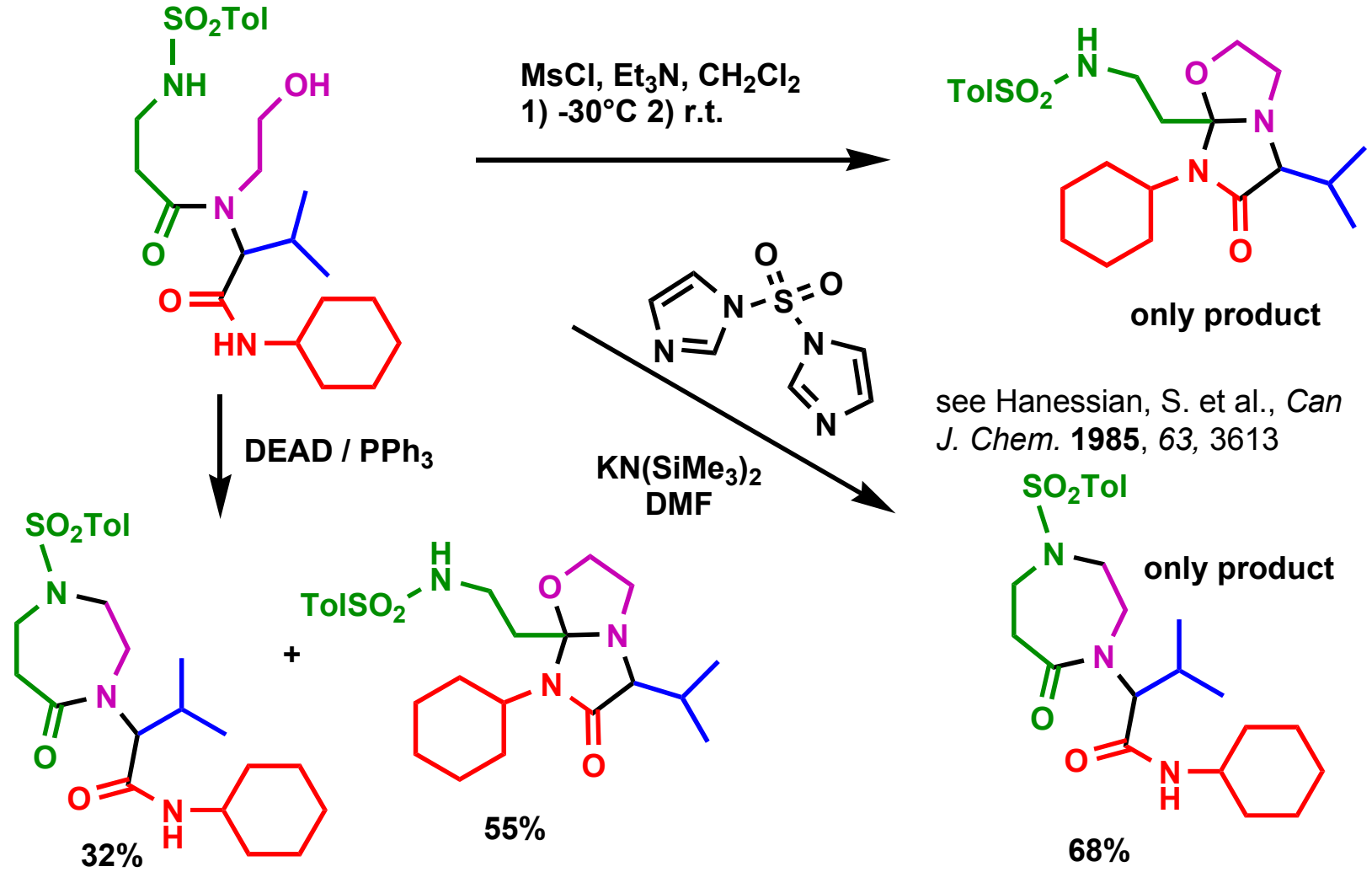
R^2 – NC



R^1	R^2	Yield
		61%
		45%
		81%
		77%

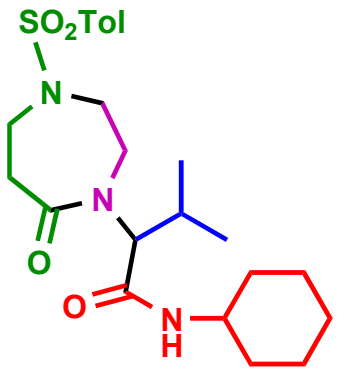
Banfi, L.; Basso, A.; Lecinska, P.; Guanti, G.; Riva, R., *Org. Biomol. Chem.*, in press

A solution was eventually found

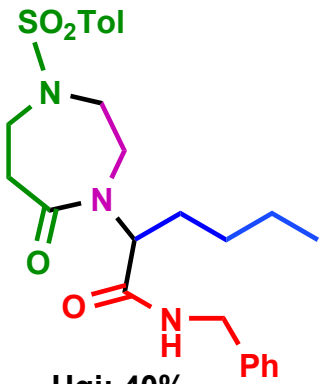


Banfi, L.; Basso, A.; Guanti, G.; Riva, R., *Tetrahedron Lett.*, submitted

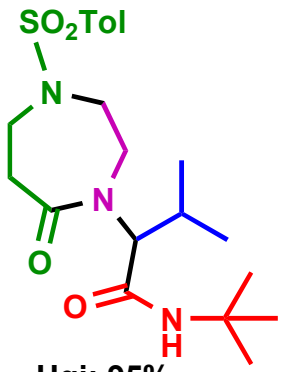
Preparation of diverse sulfonyl diazepanones



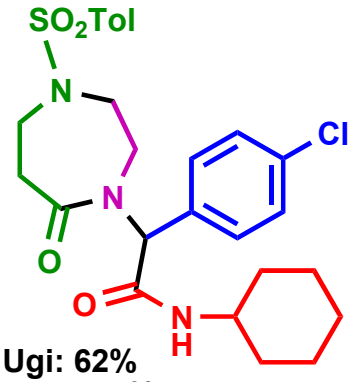
Ugi: 67%
cycl.: 68%



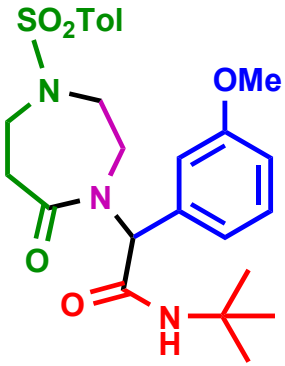
Ugi: 40%
cycl.: 46%



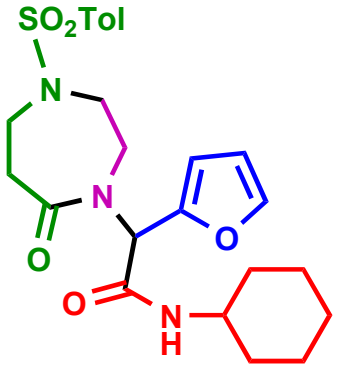
Ugi: 95%
cycl.: 62%



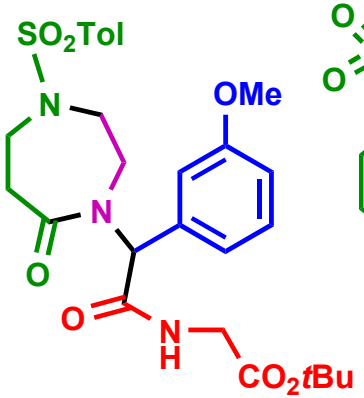
Ugi: 62%
cycl.: 52%



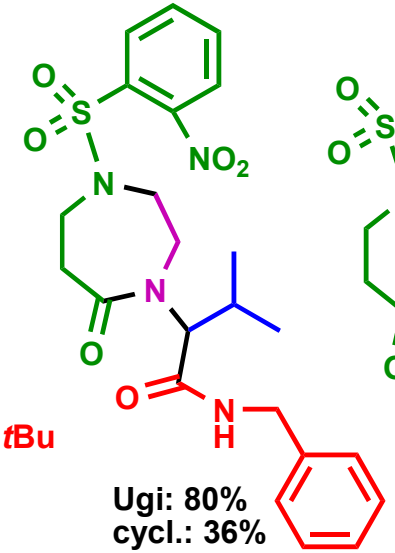
Ugi: 70%
cycl.: 60%



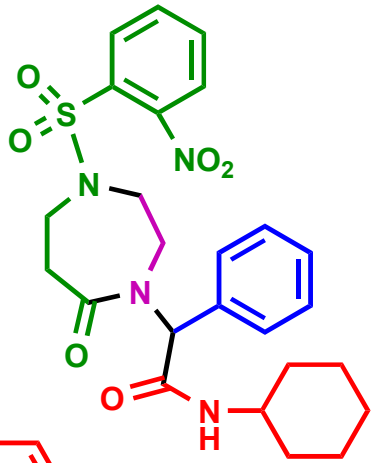
Ugi: 77%
cycl.: 27%



Ugi: 90%
cycl.: 30%



Ugi: 80%
cycl.: 36%

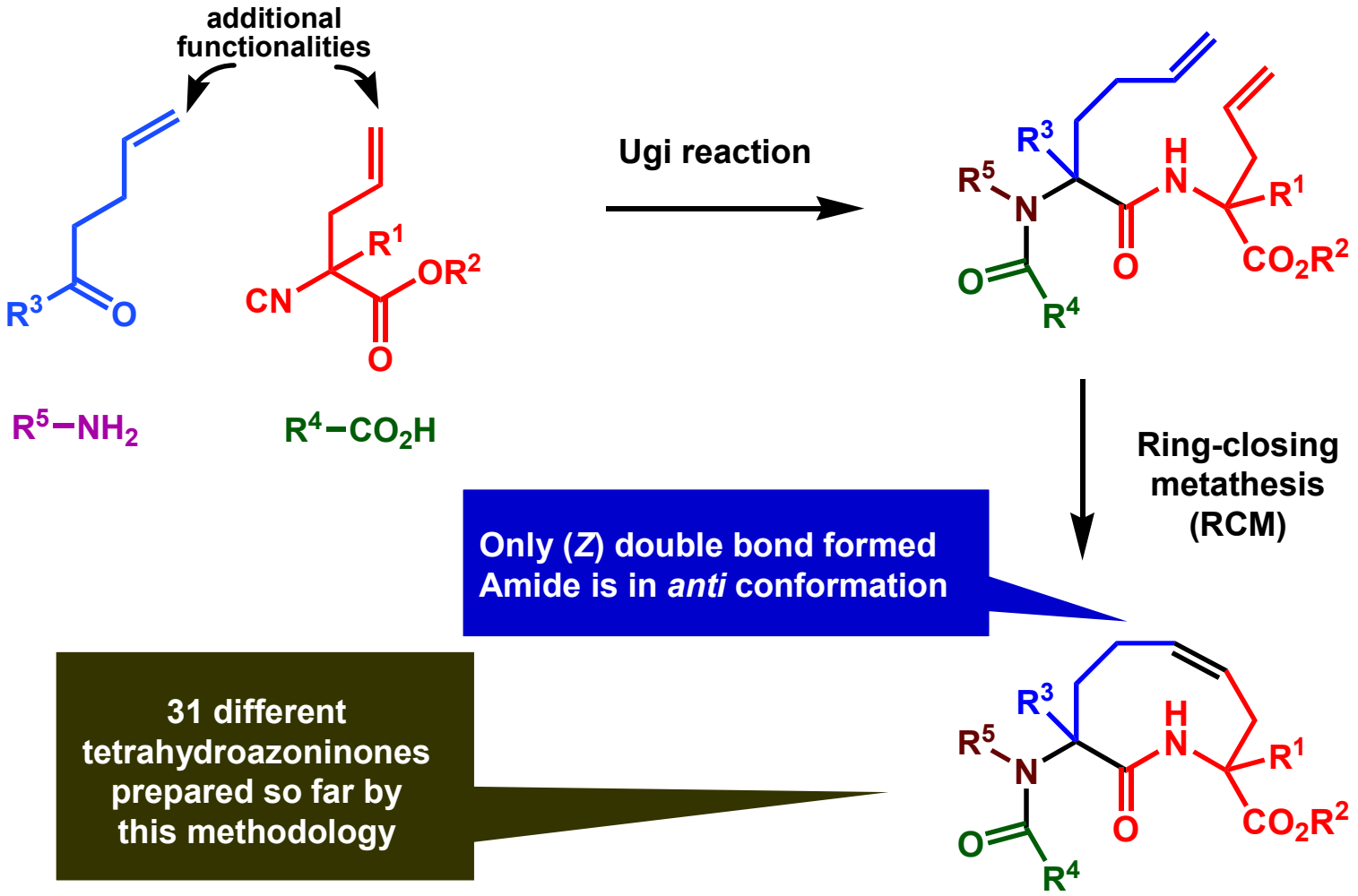


Ugi: 79%
cycl.: 41%

Banfi, L.; Basso, A.; Guanti, G.; Riva, R., *Tetrahedron Lett.*, submitted

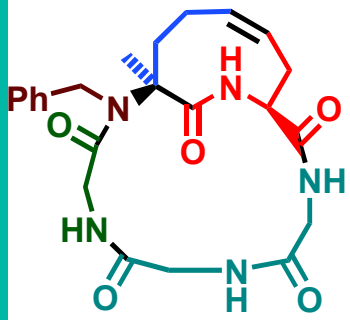
Post-condensation transformations: metathesis

2-step synthesis of tetrahydroazoninones through Ugi followed by RCM

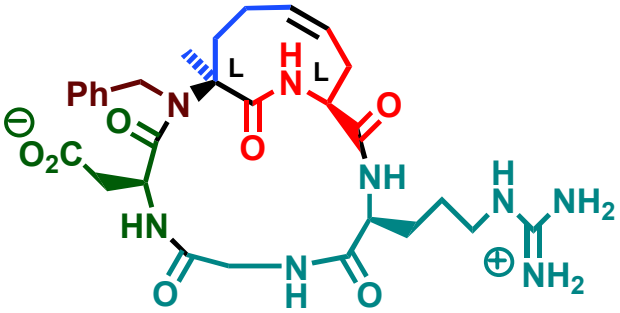


Banfi, L.; Basso, A.; Guanti, G., Riva, R., *Tetrahedron Lett.*, **2003**, *44*, 7655-7658.

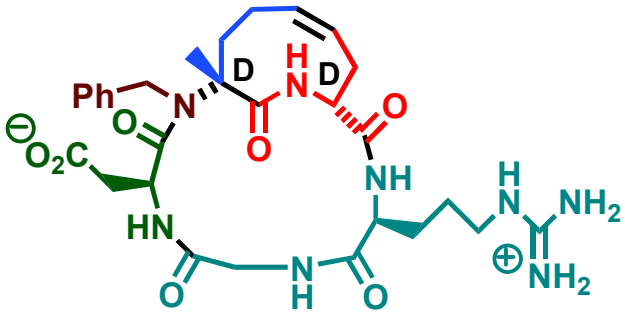
Synthesis of cyclopeptides grafted onto tetrahydroazoninones



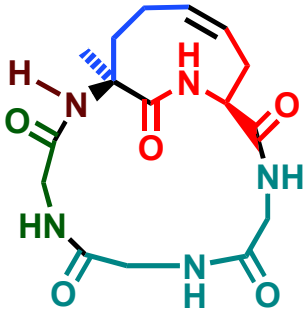
GGG



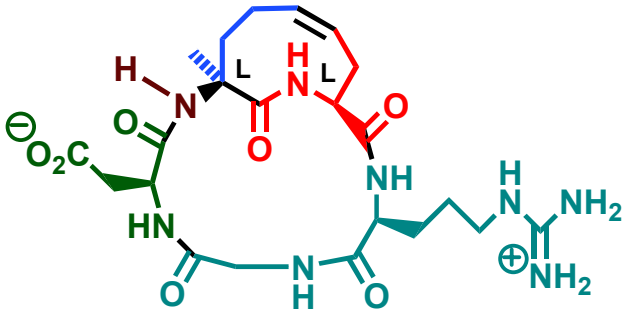
RGD



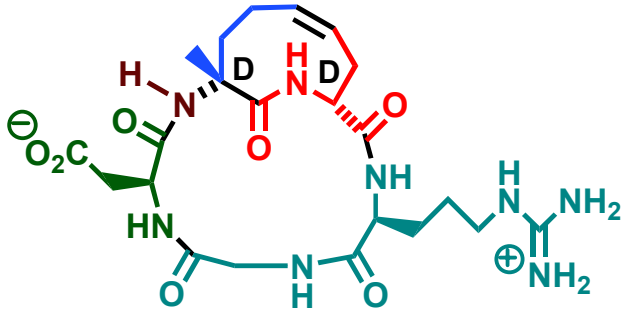
RGD



GGG



RGD



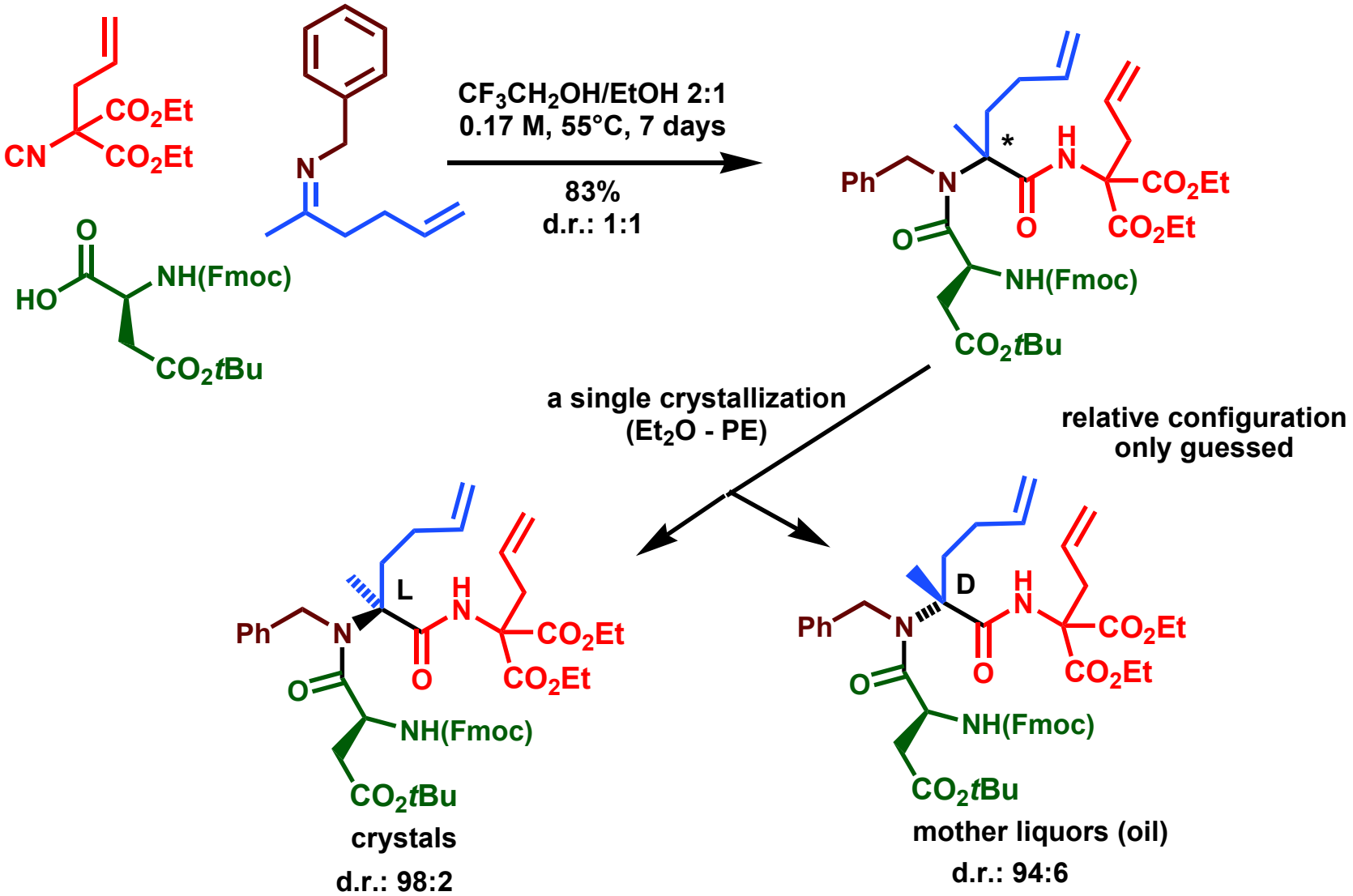
RGD

RGD cyclic peptide based on tetrahydroazoninones proved to be selective ligands for Integrin $\alpha_V\beta_3$

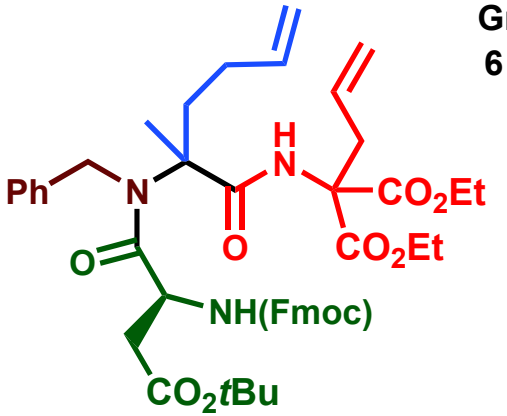
Anthoine-Dietrich, S.; Banfi, L.; Basso, A.; Damonte, G.; Guanti, G., Riva, R., *Org. Biomol. Chem.*, **2005**, *3*, 97-106.
Banfi, L.; Basso, A.; Damonte, G.; De Pellegrini, F.; Guanti, G.; Monfardini, I.; Riva, R.; Scapolla, C., *submitted*

Banfi, L.; Basso, A.; Damonte, G.; Guanti, G.; Monfardini, I.; Riva, R.; Scapolla, C., *to be published*

Enantioselective synthesis of tetrahydroazoninones



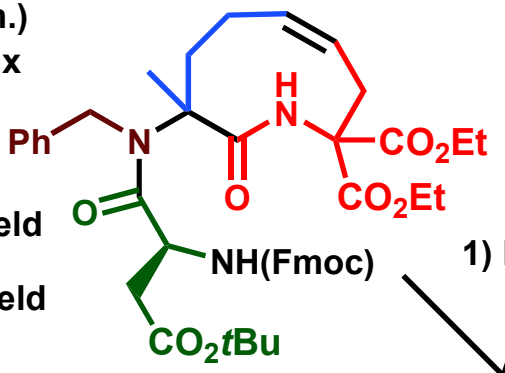
Enantioselective synthesis of tetrahydroazoninones



Grubbs cat. (1st gen.)
6 mM, CH_2Cl_2, reflux
4 days

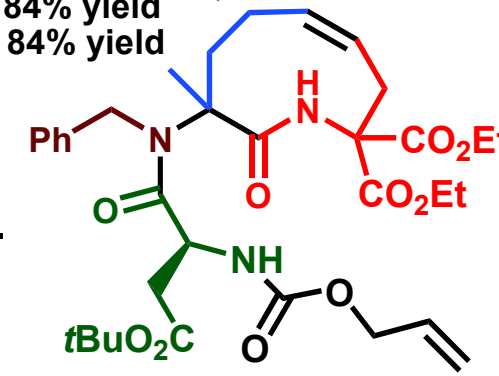
L : 89 (95) % yield

D : 85 (94) % yield

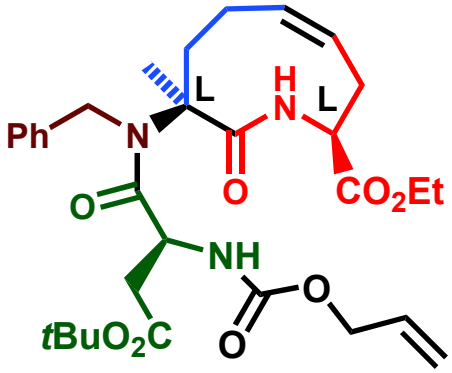


1) Et_2NH, CH_2Cl_2
2) Alloc-Cl, $NaHCO_3$,
dioxane-water

L : 84% yield
D : 84% yield

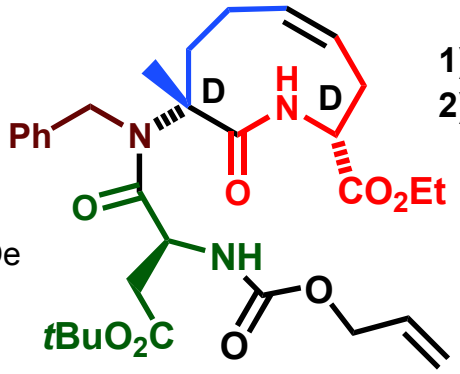


L:
77% yield.
Cis : *trans*: 7:3



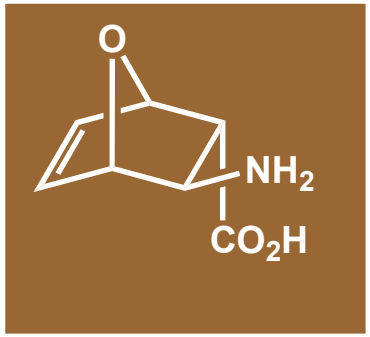
1) NaOH, EtOH
2) H^+, Δ

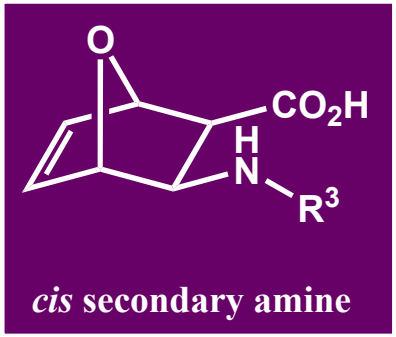
D:
78% yield.
Cis : *trans*: 66:34



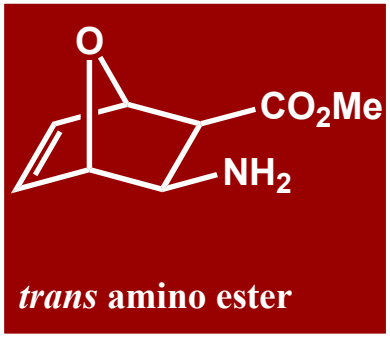
Banfi, L.; Basso, A.; Damonte, G.; De Pellegrini, F.; Guanti, G.; Riva, R.; Scapolla, C., *submitted*

Development of a new chiral auxiliary for the Ugi reaction

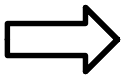




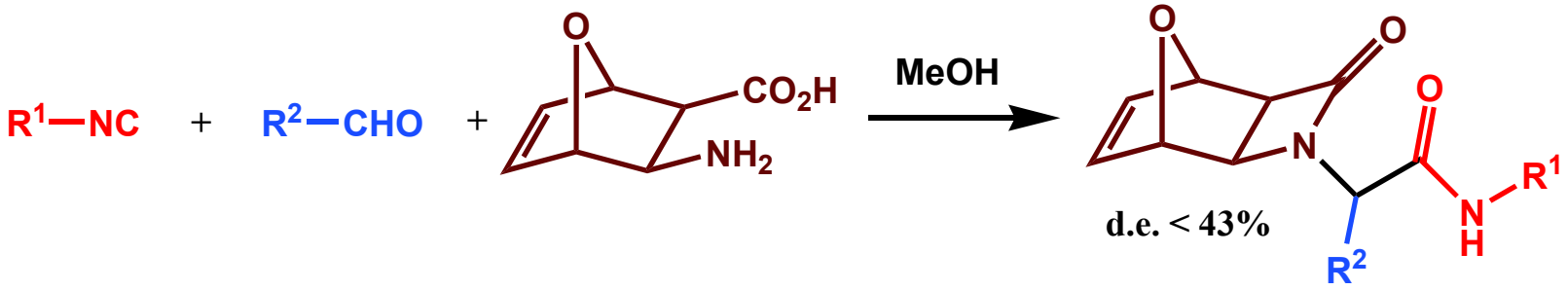
cis secondary amine

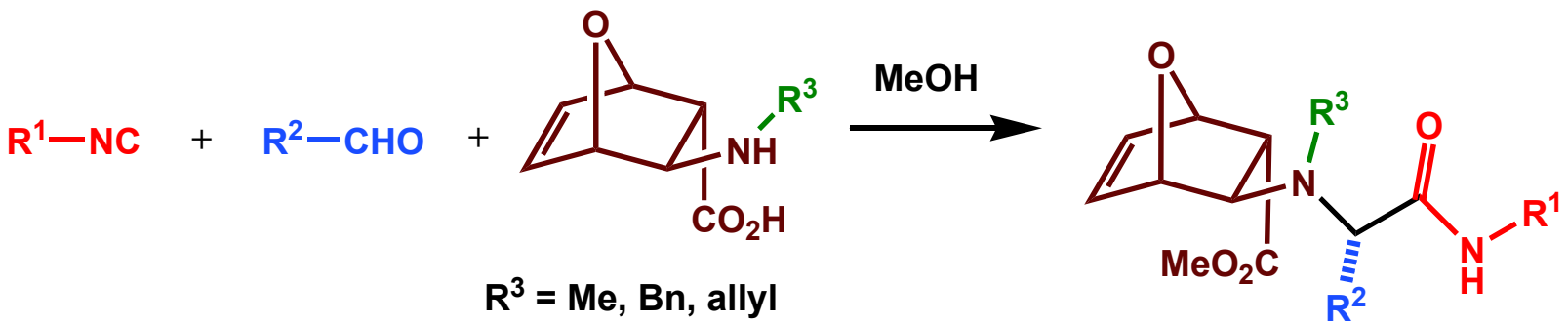


trans amino ester



unsatisfactory results



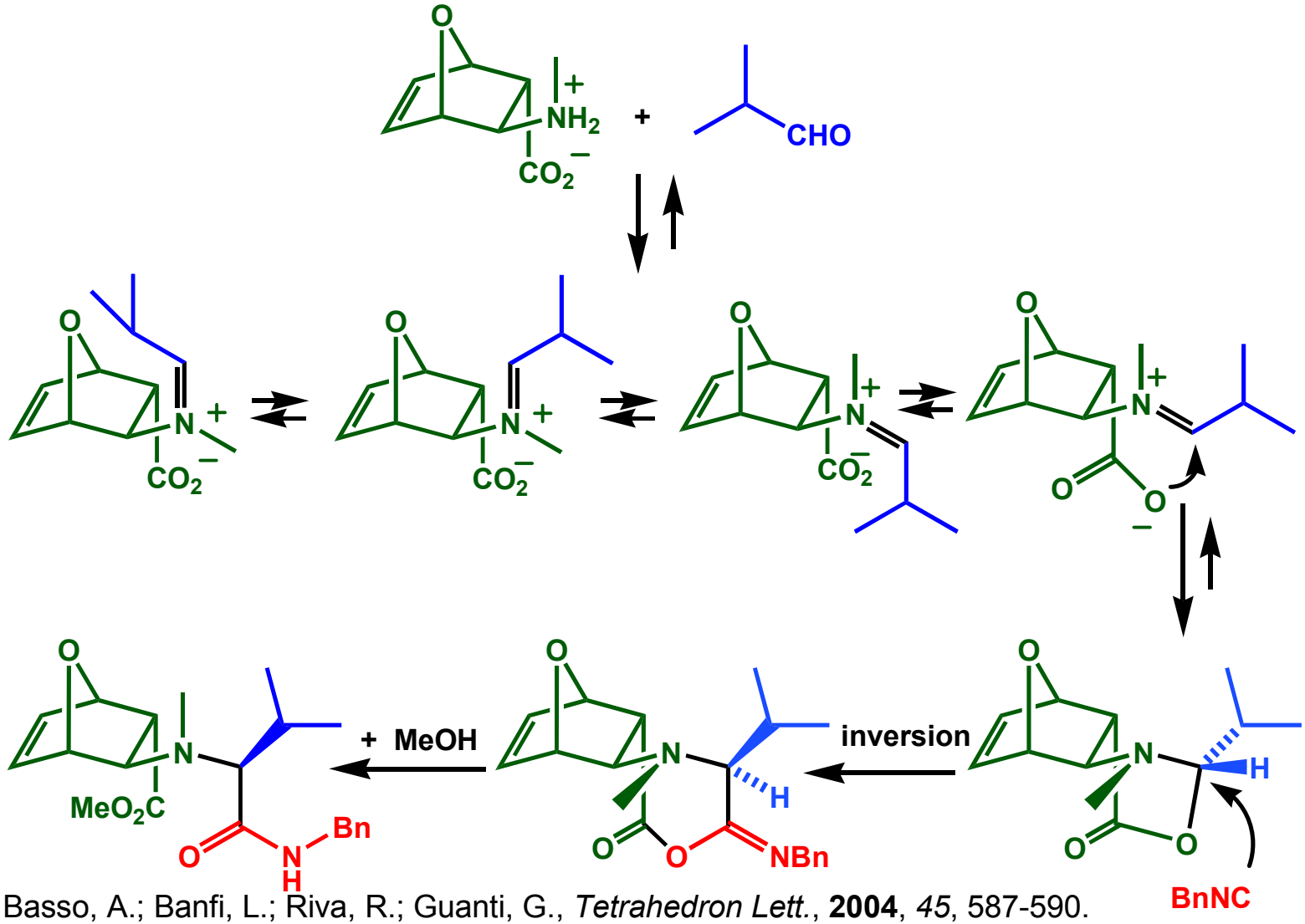


R^3 = Me, Bn, allyl

22 examples, d.e. always > 90%

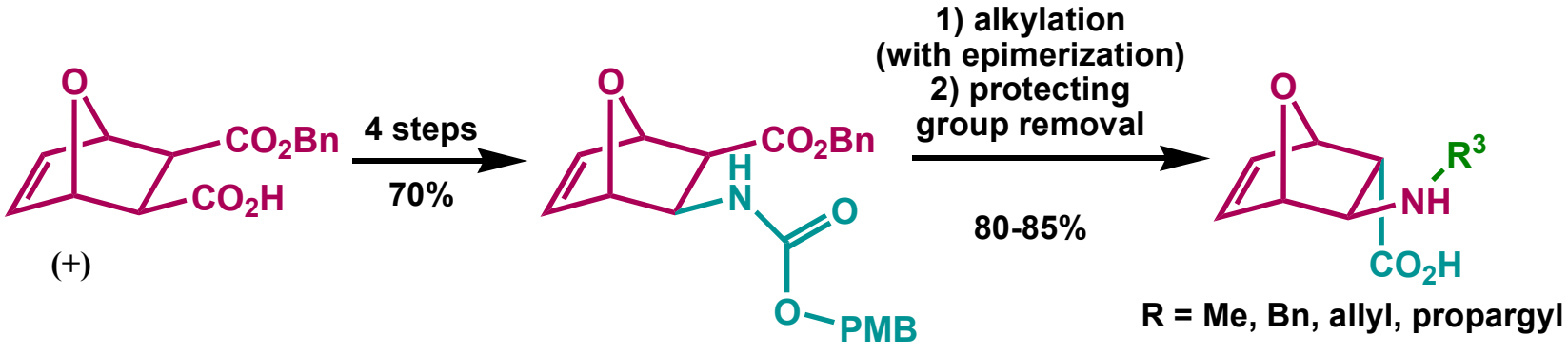
Basso, A.; Banfi, L.; Riva, R.; Guanti, G., *Tetrahedron Lett.*, **2004**, *45*, 587-590.

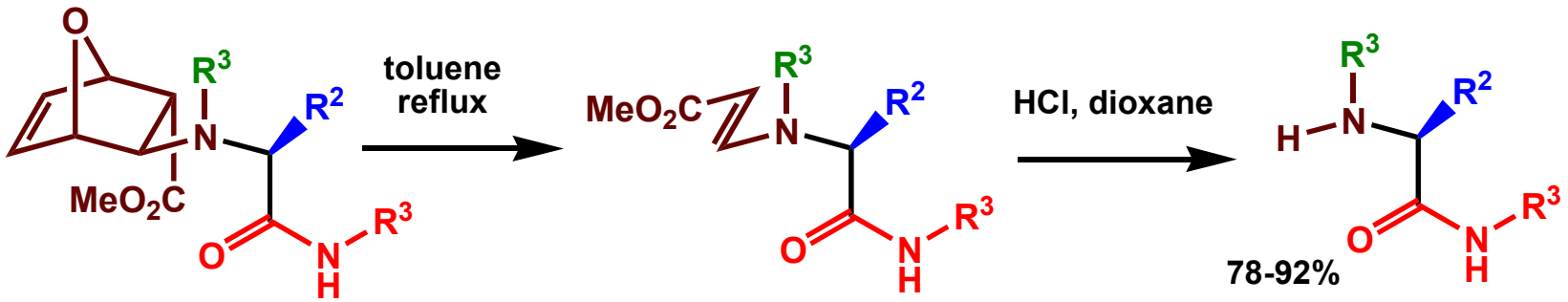
Development of a new chiral auxiliary for the Ugi reaction



Basso, A.; Banfi, L.; Riva, R.; Guanti, G., *Tetrahedron Lett.*, **2004**, *45*, 587-590.

Development of a new chiral auxiliary for the Ugi reaction

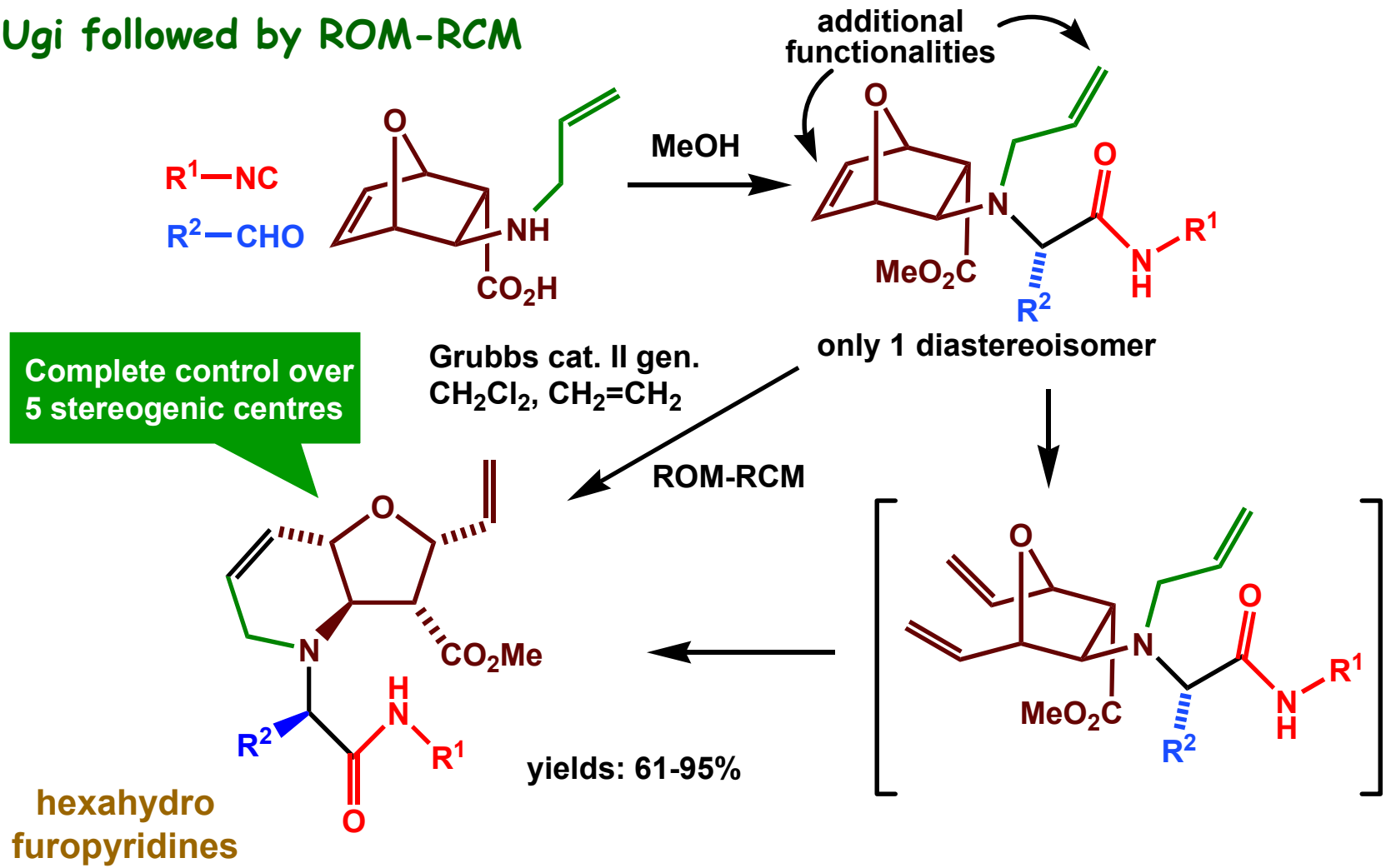




Basso, A.; Banfi, L.; Riva, R.; Guanti, G., *J. Org. Chem.*, **2005**, *70*, 575-579.

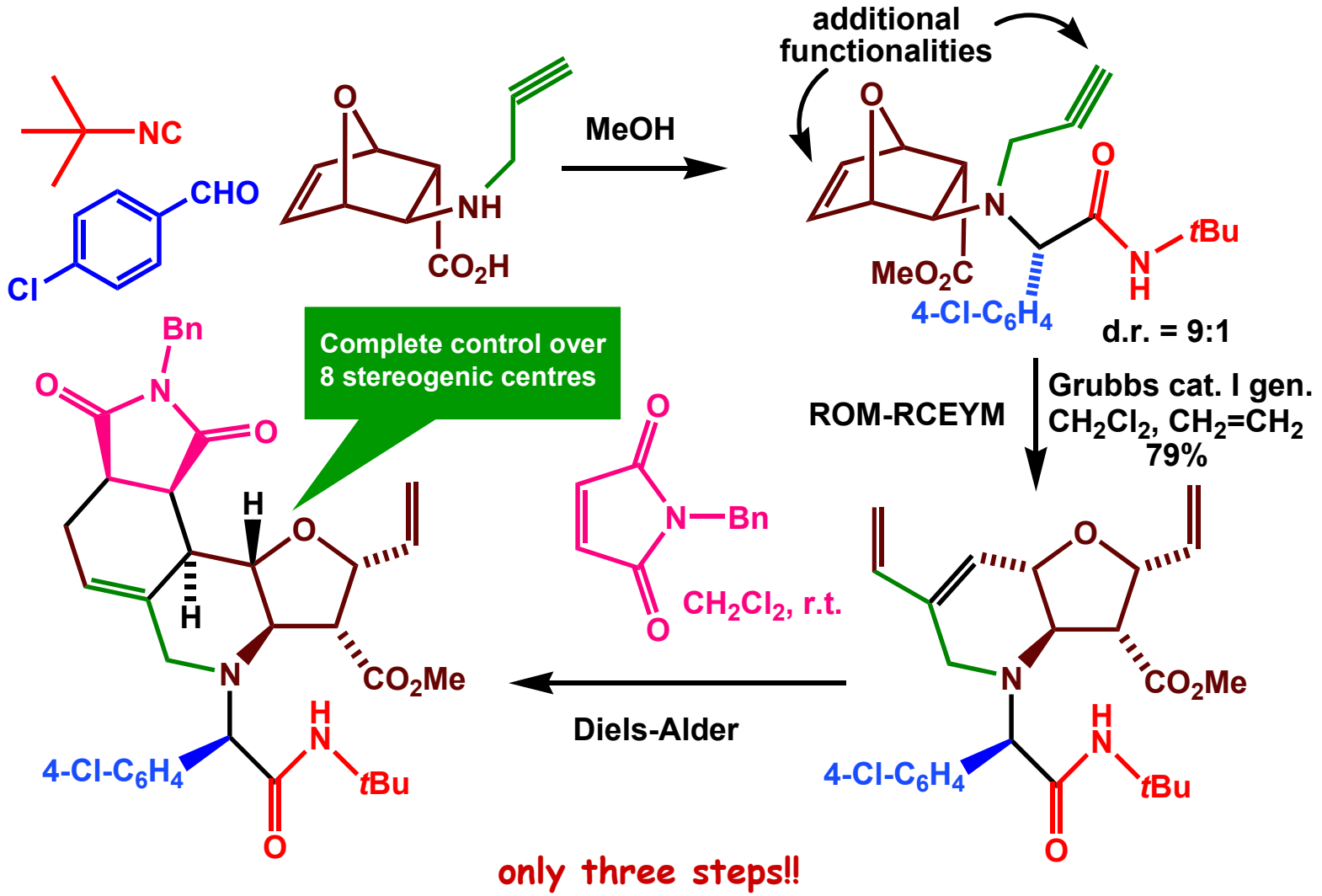
Post-condensation transformations: metathesis

Ugi followed by ROM-RCM



Basso, A.; Banfi, L.; Riva, R.; Guanti, G., *Tetrahedron*, 8830 (2006)

Multiple post-condensation transformations: metathesis - Diels-Alder



Basso, A.; Banfi, L.; Riva, R.; Guanti, G., *Tetrahedron*, 8830 (2006)