Synthesis of Hydantoin, Benzodiazepine- and Piperazinedione-Fused Tricyclic Compound Library

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Wipf Group Research Topic Seminar

15 January 2011

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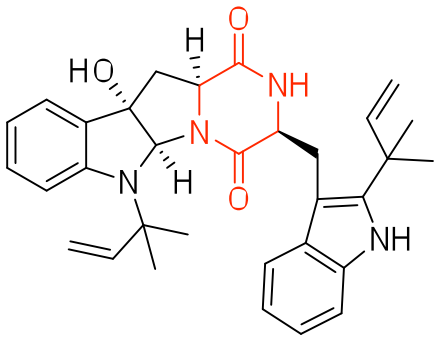
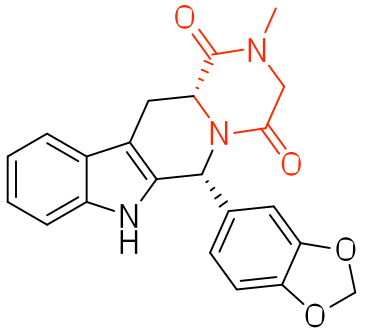
Hydantoin, Benzodiazepine- and Piperazinedione Biologically Active

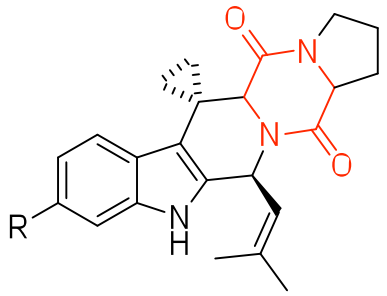


Okaramine C (1)
Insecticidal properties

Org. Biomol. Chem. **2004**, *2*, 2415



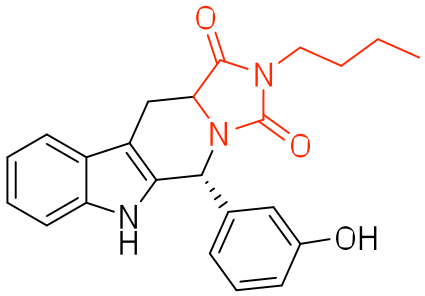
Tadalafil
Treatment of erectile dysfunction



R = OMe: Fumitremorgine C
R = H: Demethoxyfumitremorgine C

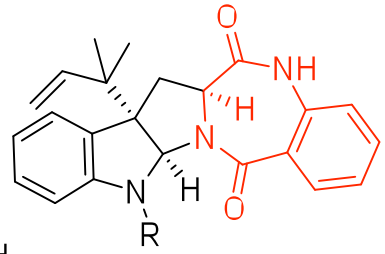
Cytotoxic against mammalian cancer

Eur. J. Org. Chem. **2005**, 610



HR22C16
Inhibtion of Eg5
(Kinesin spindle protein)

Angew. Chem. Int. Ed. **2003**, *42*, 2379



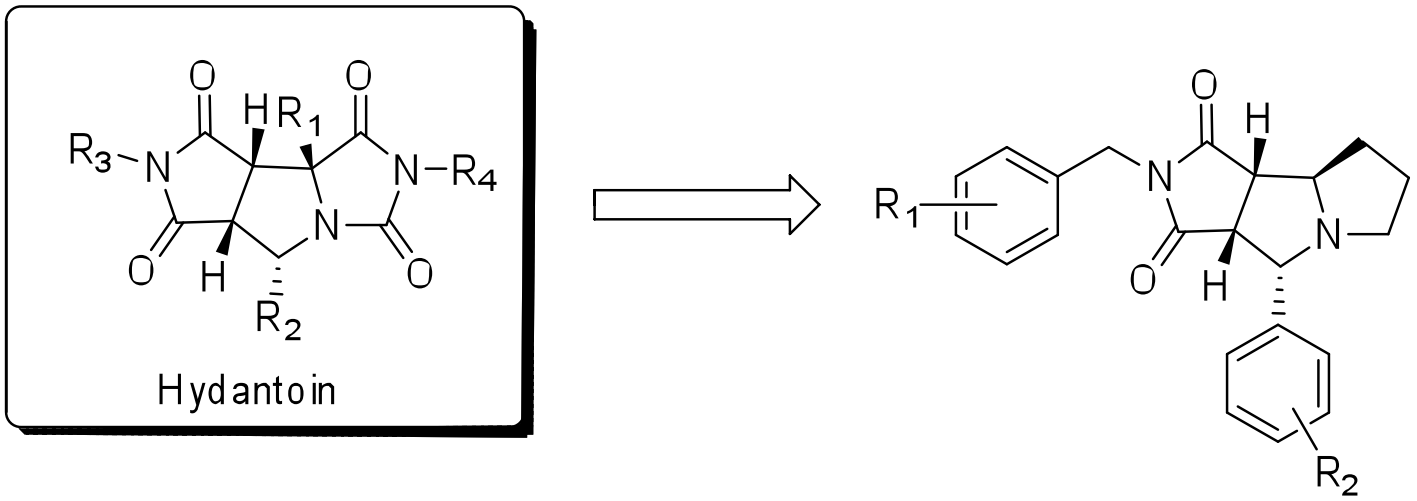
R = $COCH_3$
R = CHO
R = H

Aszonalenins
Psychoactive properties

Tetrahedron Lett. **2006**, *47*, 6099

Hydantoin, Benzodiazepine- and Piperazinedione Fused Tricyclic Compound Overview and Biological Importance

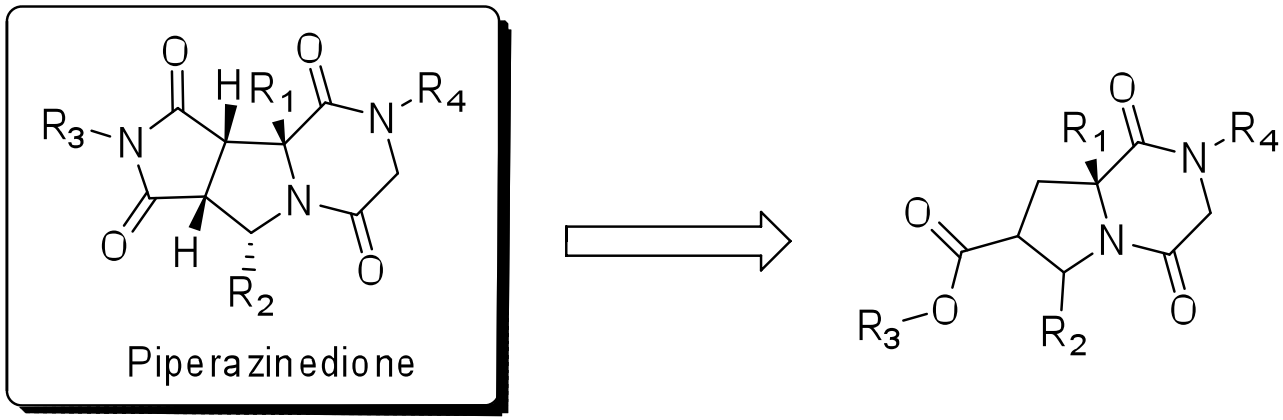
These heterocycles are present in a variety of biologically active compounds.



Skeleton similar to those of tricyclic thrombin inhibitors.

Org. Biomol. Chem., **2004**, *2*, 1339

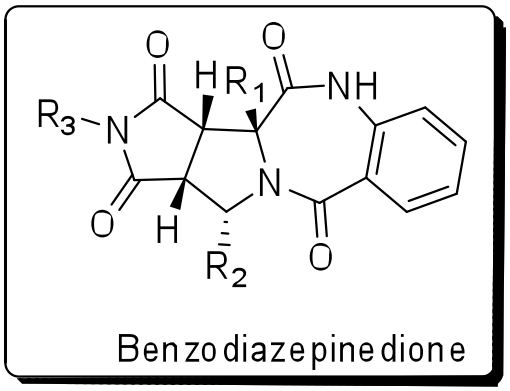
Hydantoin, Benzodiazepine- and Piperazinedione Scaffolds

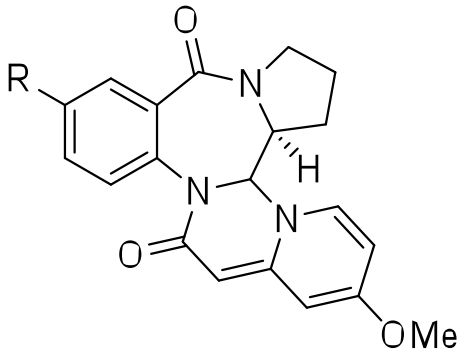


The structure of piperazinedione is partially related to diketopiperazine-based inhibitors of human hormone-sensitive lipase.

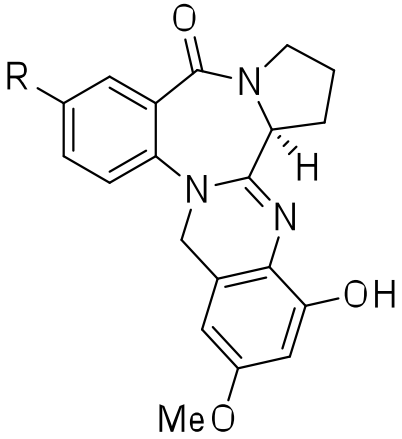
J. Med. Chem. **2003**, *46*, 1120

Hydantoin, Benzodiazepine- and Piperazinedione Scaffolds





R = OMe Circumdain A
R = H Circumdatin B

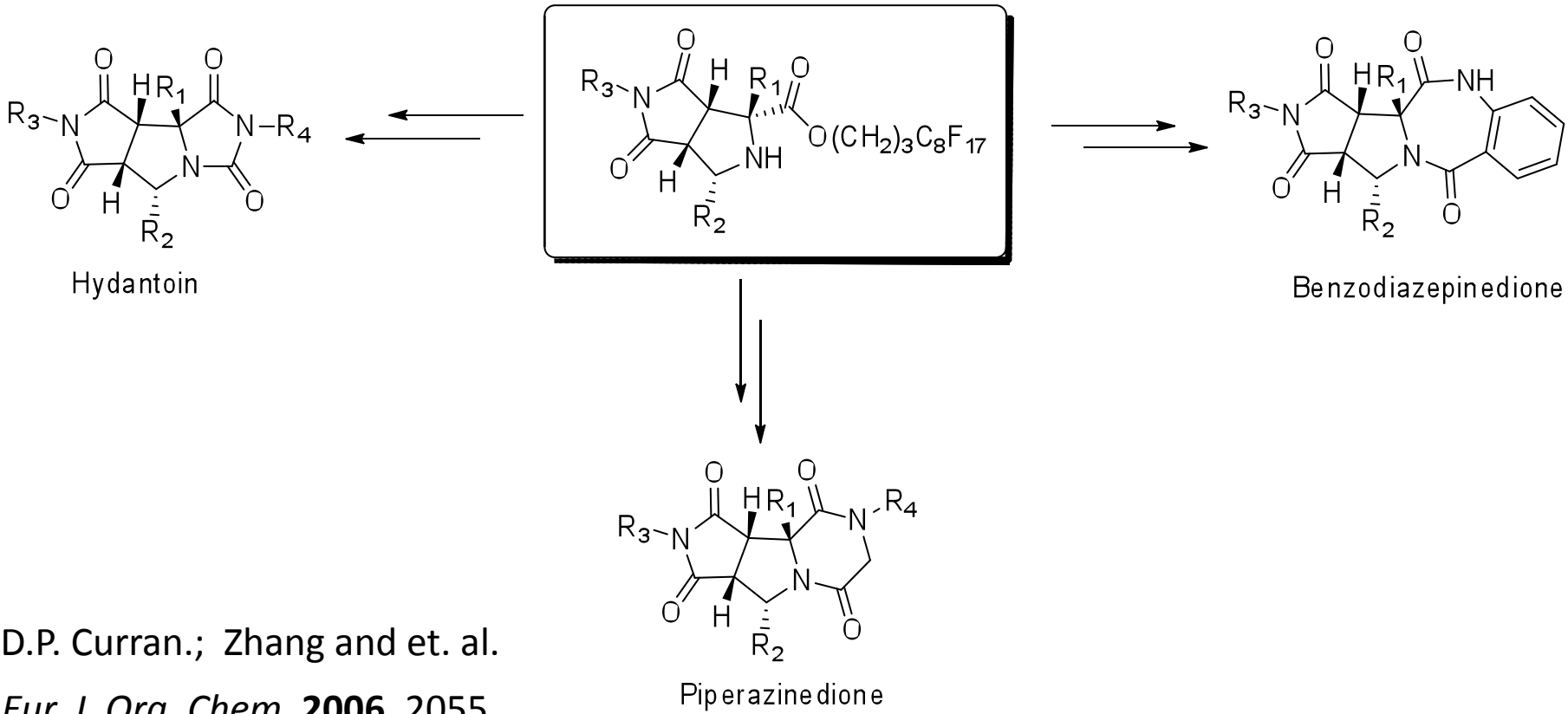


R = OMe Circumdain D
R = H Circumdatin E

Benzodiazepinedione contains a privileged benzodiazepine Moiety that has a wide range of pharmaceutical utilities.

Synthesis **2003**, 1707
Chem. Rev. **2003**, *103*, 893

Fluorous Diversity-Oriented Synthesis of Hydantoin, Benzodiazepine- and Piperazinedione Compound Library



D.P. Curran.; Zhang and et. al.

Eur. J. Org. Chem. **2006**, 2055
J. Comb. Chem. **2006**, *8*, 687
J. Comb. Chem. **2009**, *11*, 452

Fluorous Synthesis Advantages

Fluorous synthesis is highly efficient solution-phase synthesis technology. It employs perfluoroalkyl (RF) groups as "phase tags" to facilitate reaction mixture separation.

Characteristics:

1 This technology has been applied to parallel and mixture synthesis of small molecules, peptides, oligosaccharides, and others biomolecules.

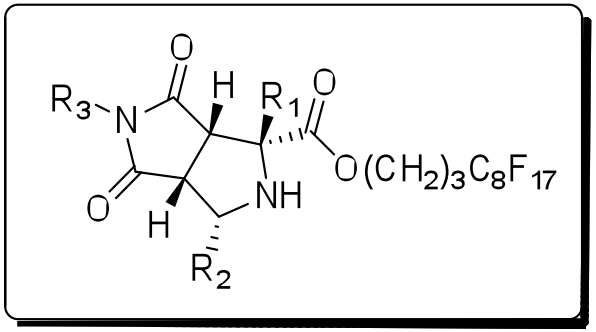
2 Fluorous molecules can be separated by the fluorous as well as conventional methods such as chromatography, distillation and recrystallization.

3 Can be monitored by conventional analytical methods such as TLC, HPLC, IR and NMR.

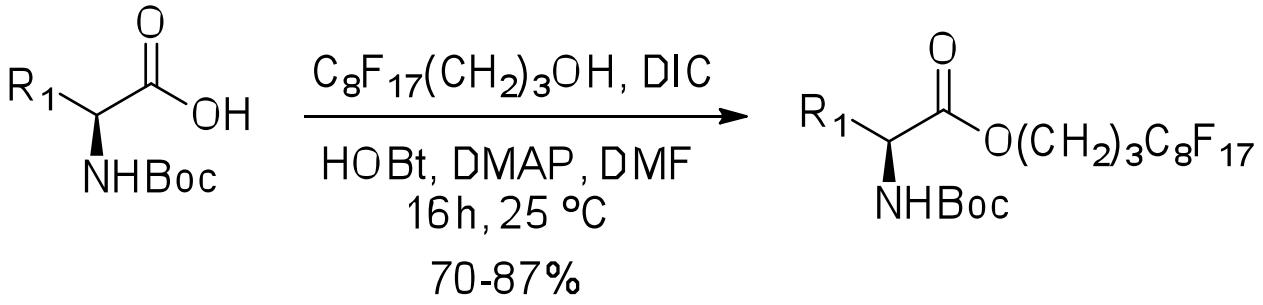
4 Good compatibility with other synthetic techniques such as microwave and multicomponent reactions.

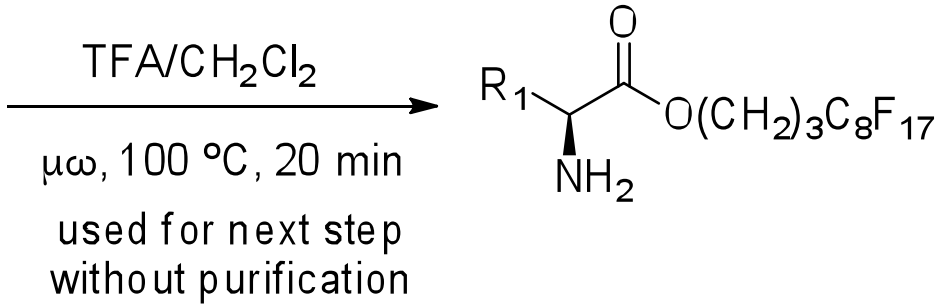
Chem. Rev. **2009**, *109*, 749
Chem. Rev. **2004**, *104*, 2531
Arkivoc **2004**, 101
Aldrichm. Acta **2006**, *39*, 3

Synthesis of the Bicycle Proline Intermediates



Preparation of fluorous amino esters.



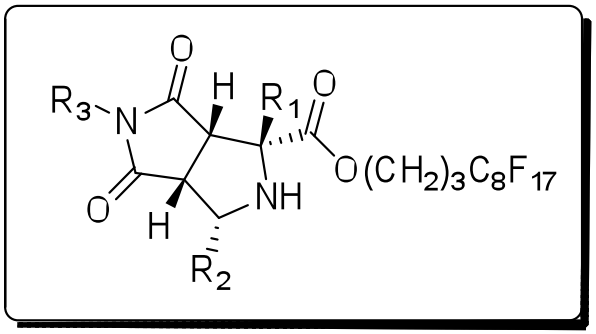


Eur. J. Org. Chem. **2006**, 2055
J. Comb. Chem. **2006**, *8*, 687
J. Comb. Chem. **2009**, *11*, 452

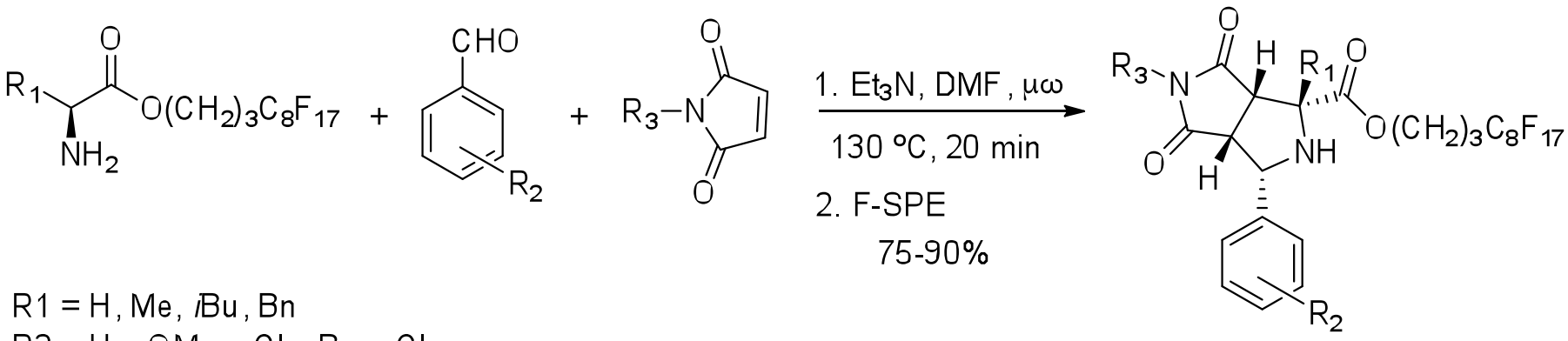
Chem. Rev. **2005**, *105*, 2765

8

Synthesis of the Bicycle Proline Intermediates



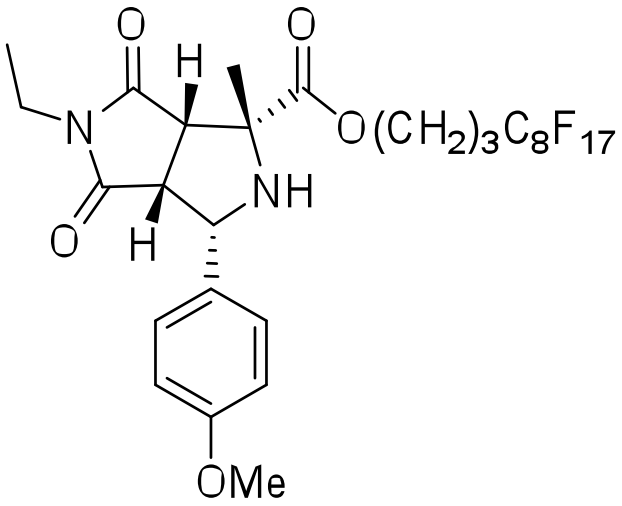
Synthesis of fluorous proline by one-pot three component [3+2] cycloaddition reaction.

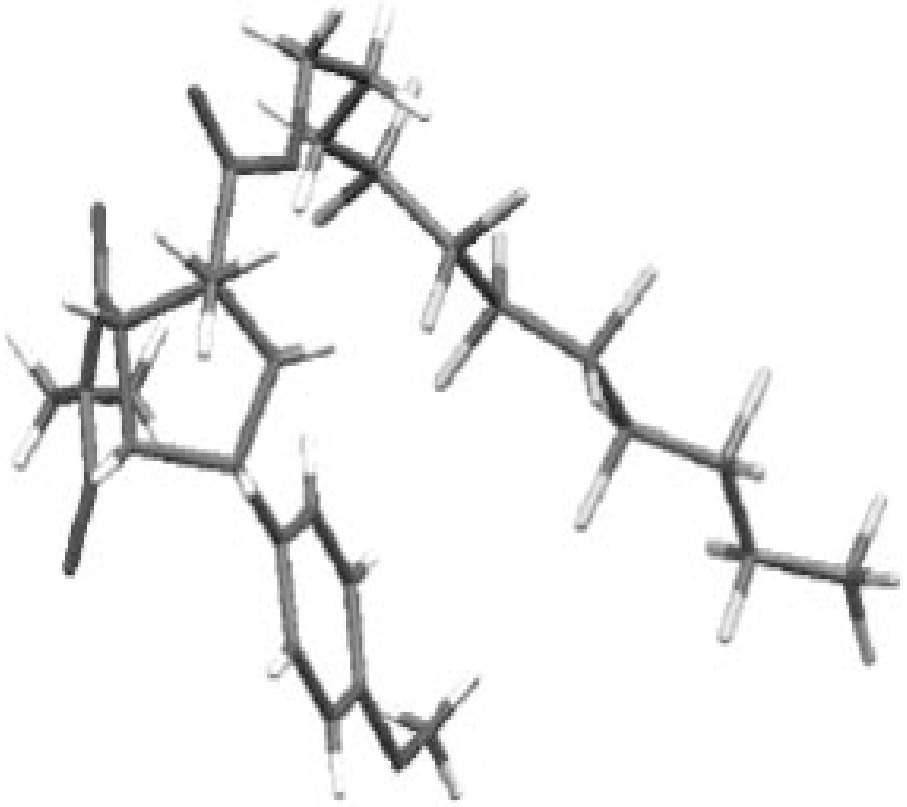


R1 = H, Me, *i*Bu, Bn
R2 = H, *p*OMe, *p*Cl, *p*Br, *m*Cl
R3 = Me, Et, *t*Bu, Bn, cC_6H_{11}

Eur. J. Org. Chem. **2006**, 2055

Stereochemistry of Bicycle Proline Intermediate
Single-Crystal X-ray Diffraction

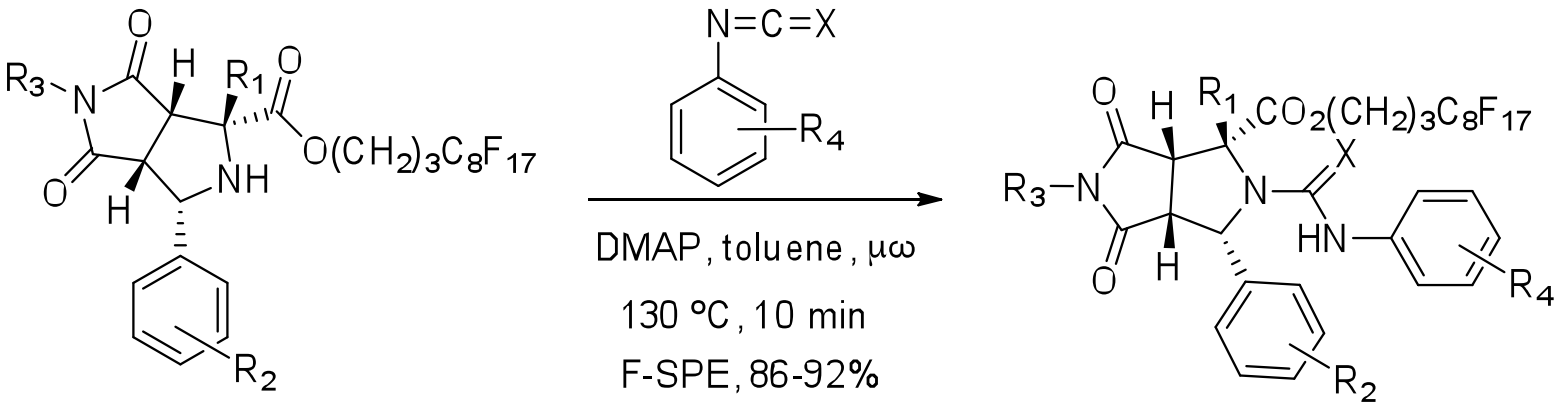




Eur. J. Org. Chem. **2006**, 2055

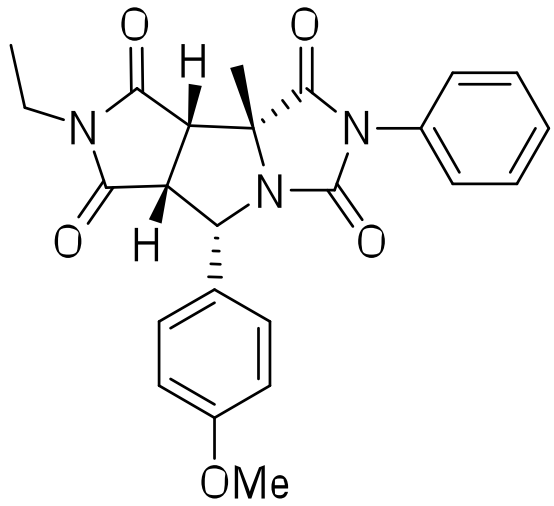
Org. Lett. **2001**, *3*, 3491

Fluorous Synthesis of Hydantoin

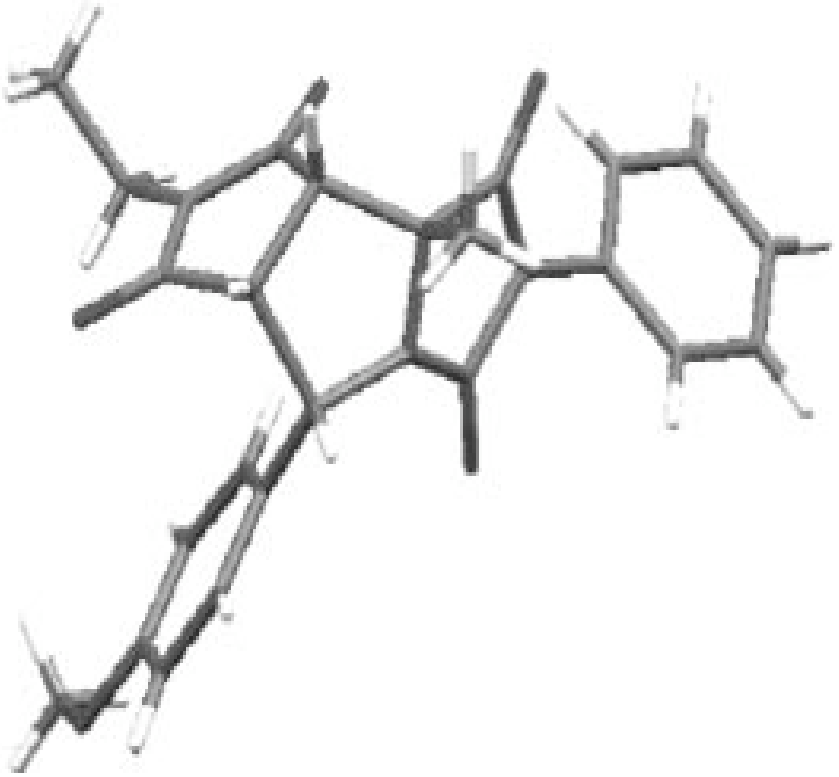


R1	R2	R3	R4	X	Yield
Me	*p*OMe	Et	H	O	85%
Me	*p*OMe	Et	H	S	79%
*i*Bu	*p*Br	*t*Bu	*m*Cl	O	75%
Bn	*p*Cl	cC_6H_{11}	*m*Br	O	81%

Stereochemistry of Hydantoin – Single-Crystal X-ray Diffraction

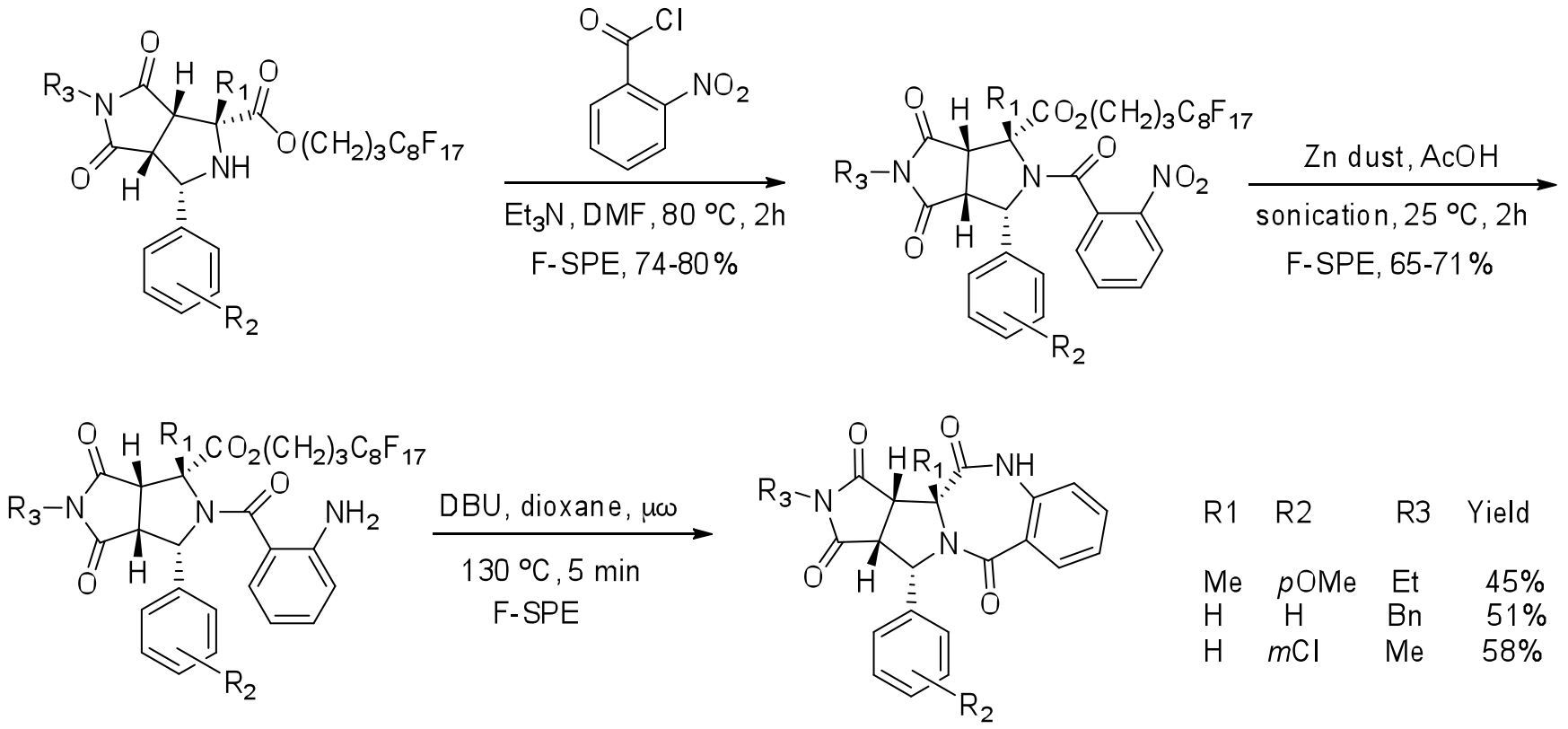


Hydantoin



Eur. J. Org. Chem. **2006**, 2055

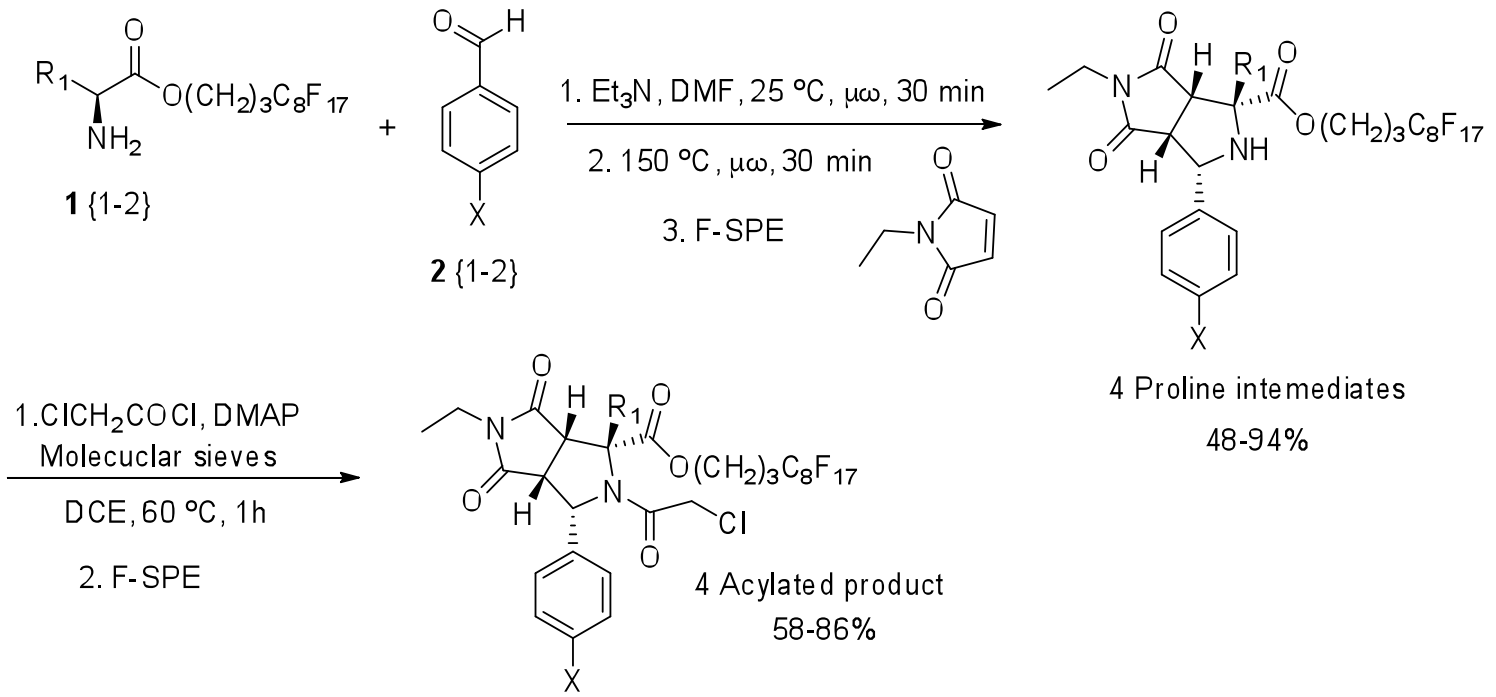
Fluorous Synthesis of Benzodiazepinedione

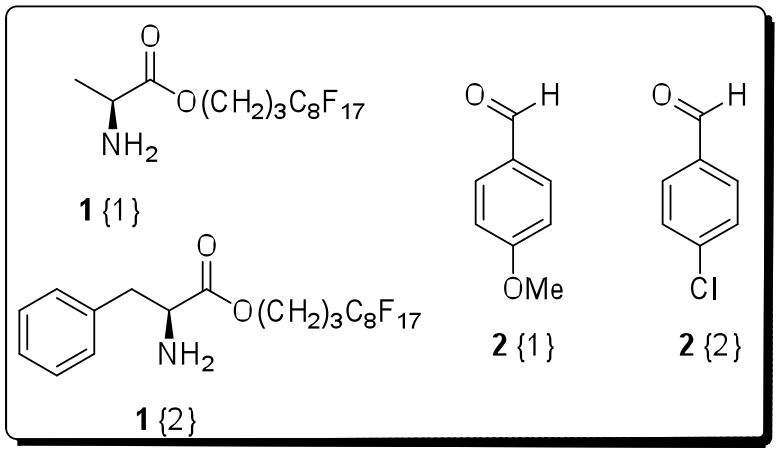


R1	R2	R3	Yield
Me	*p*OMe	Et	45%
H	H	Bn	51%
H	*m*Cl	Me	58%

Eur. J. Org. Chem. **2006**, 2055

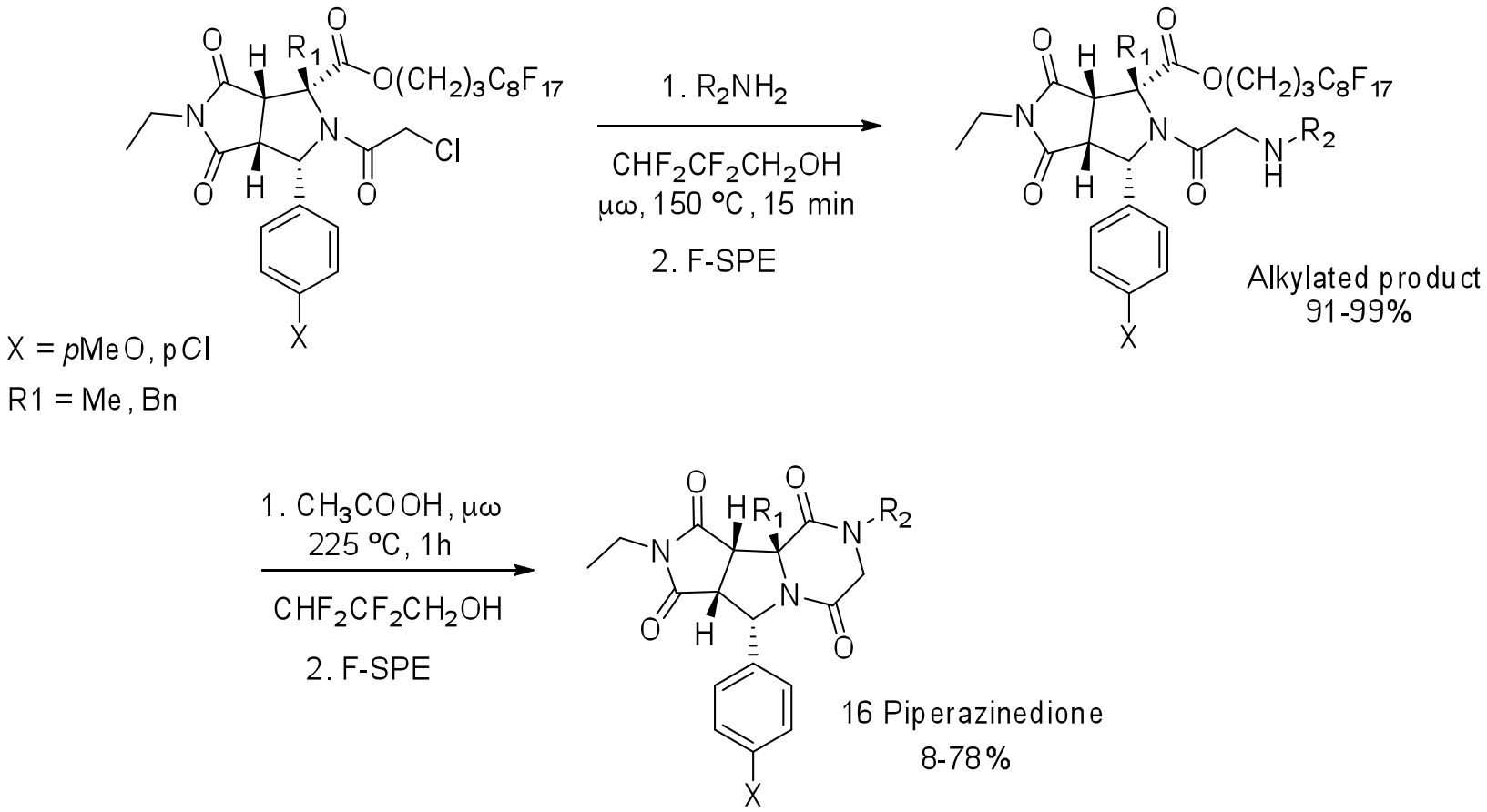
Fluorous Synthesis of Piperazinedione

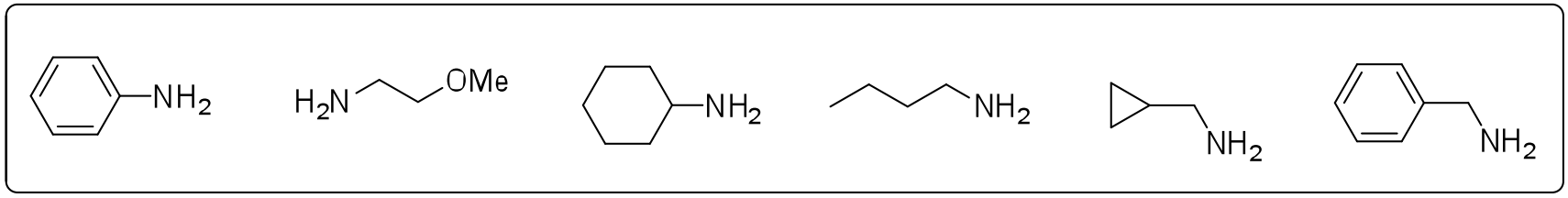




D.P. Curran.; Zhang and et. al.

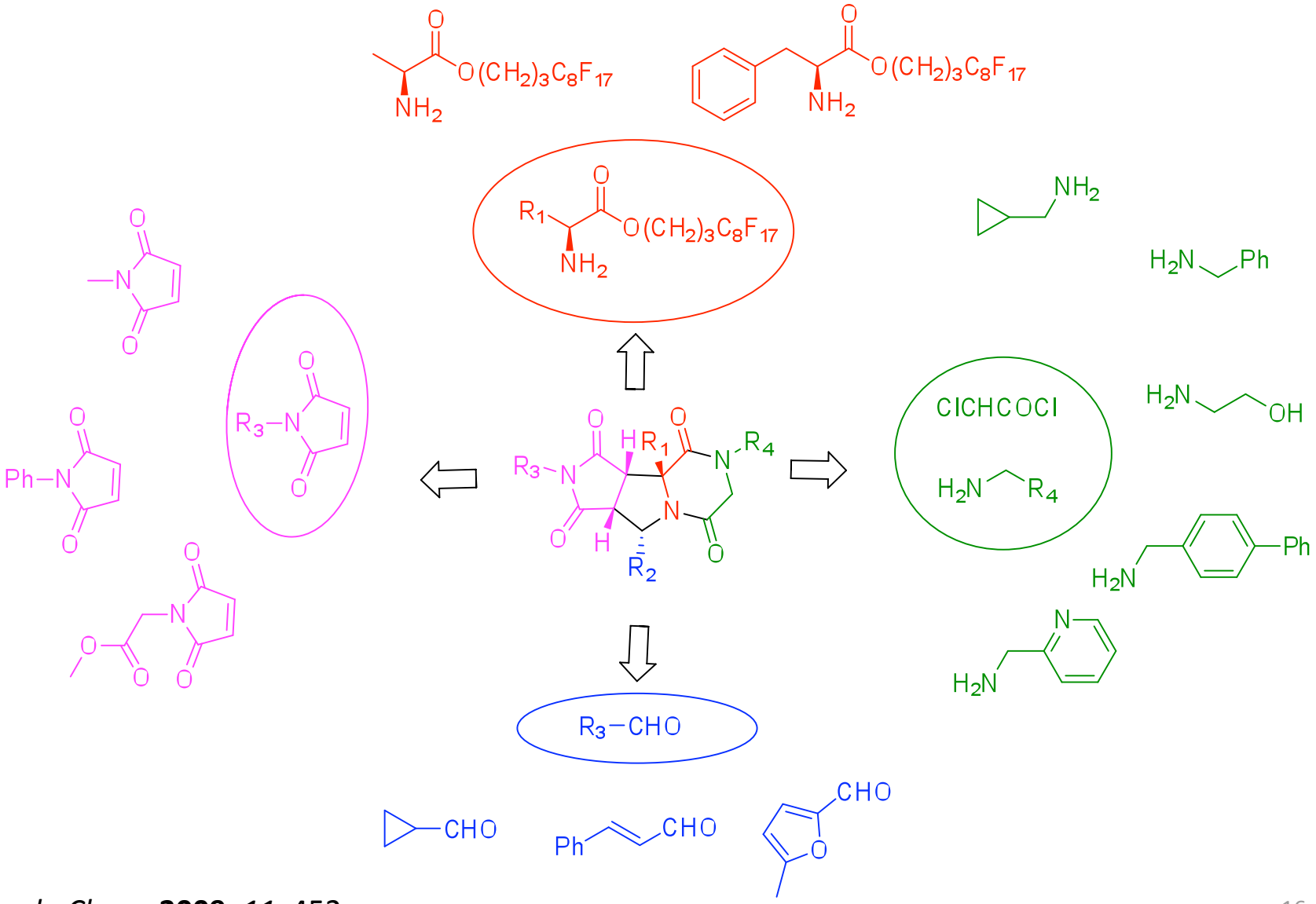
J. Comb. Chem. **2009**, *11*, 452





J. Comb. Chem. **2009**, *11*, 452

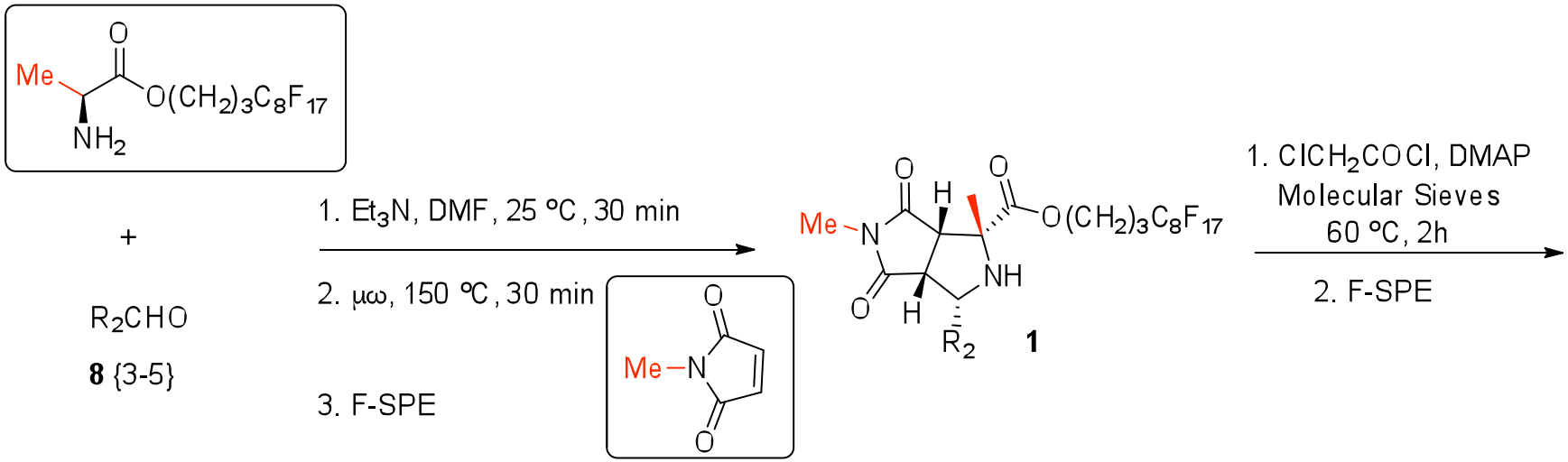
Fluorous Synthesis of 90- Compound Library of Piperazinedione



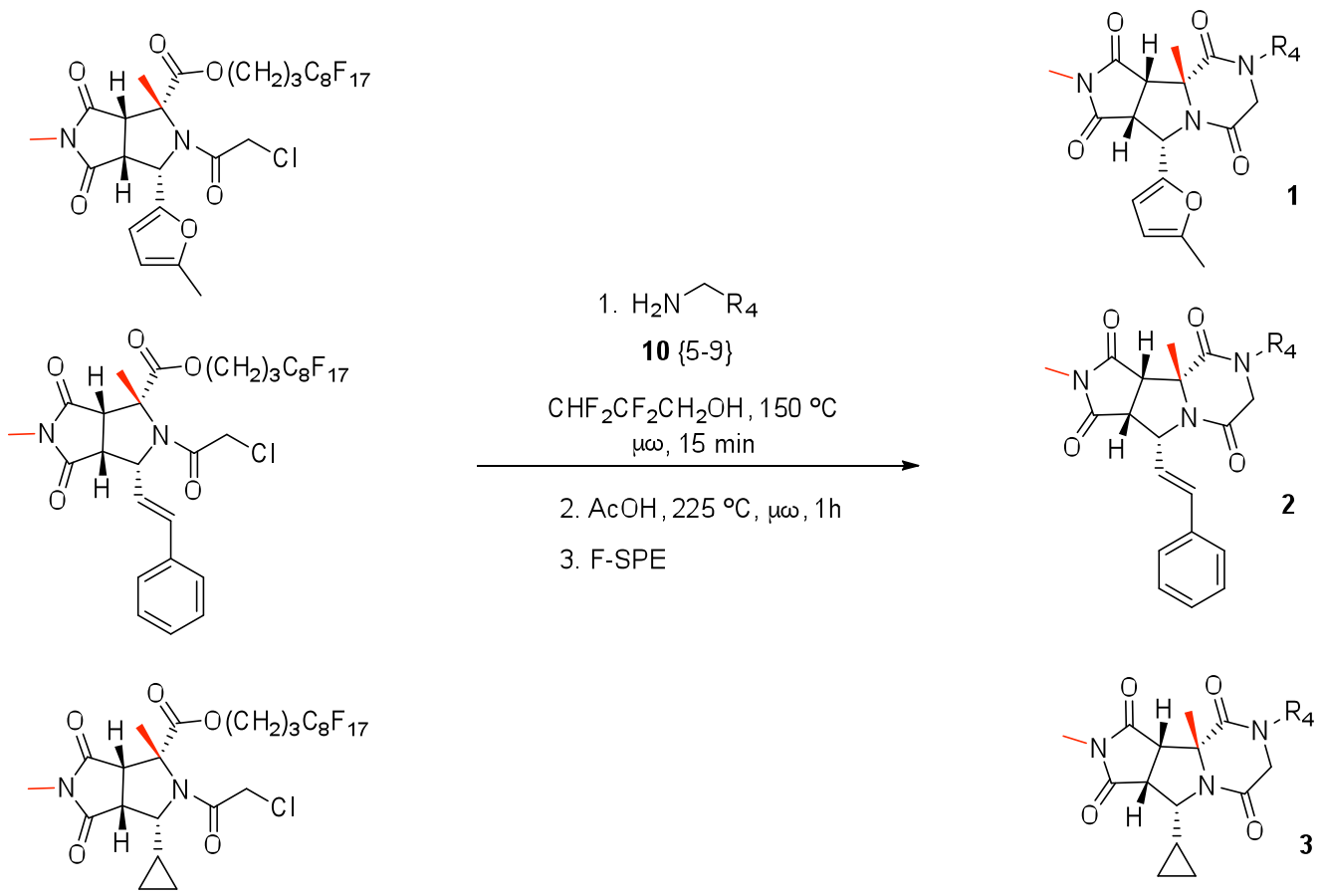
J. Comb. Chem. **2009**, *11*, 452

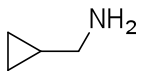
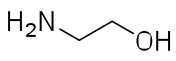
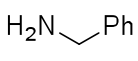
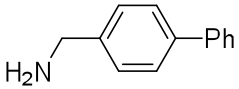
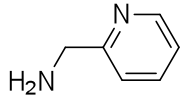
Synthesis of Fluorous Proline Intermediates

Methyl – Methyl Series



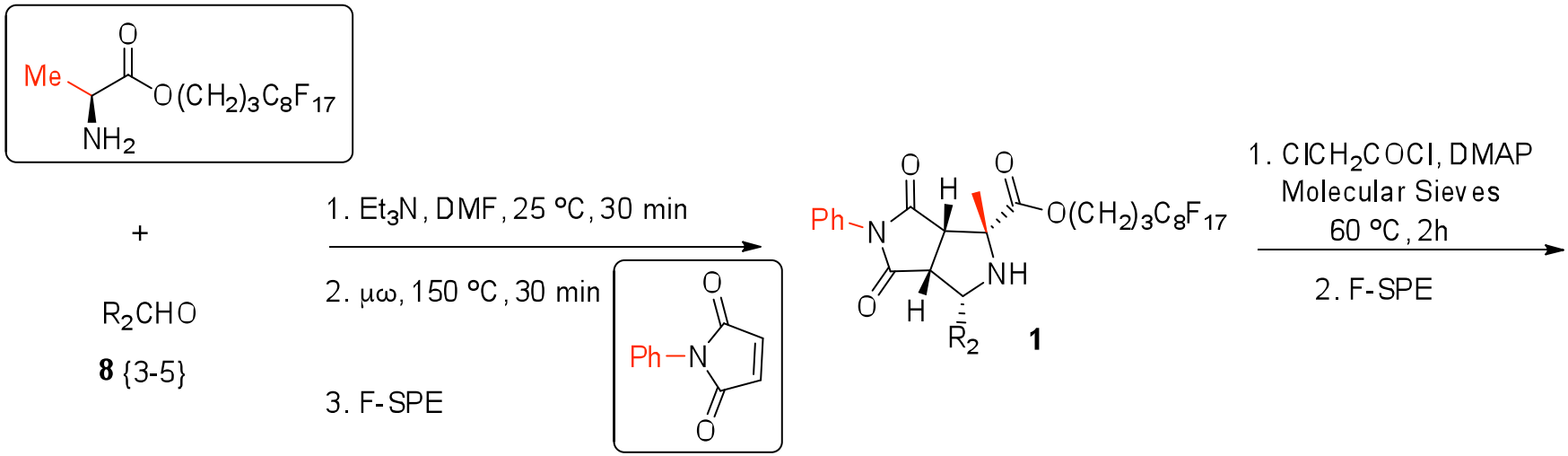
1	81%	85%	75%
2	62%	73%	43%



	 **10** {5}	 **10** {7}	 **10** {6}	 **10** {8}	 **10** {9}
1	59%	46%	12%	51%	30%
2	56%	55%	35%	58%	57%
3	59%	64%	Failed	68%	Failed

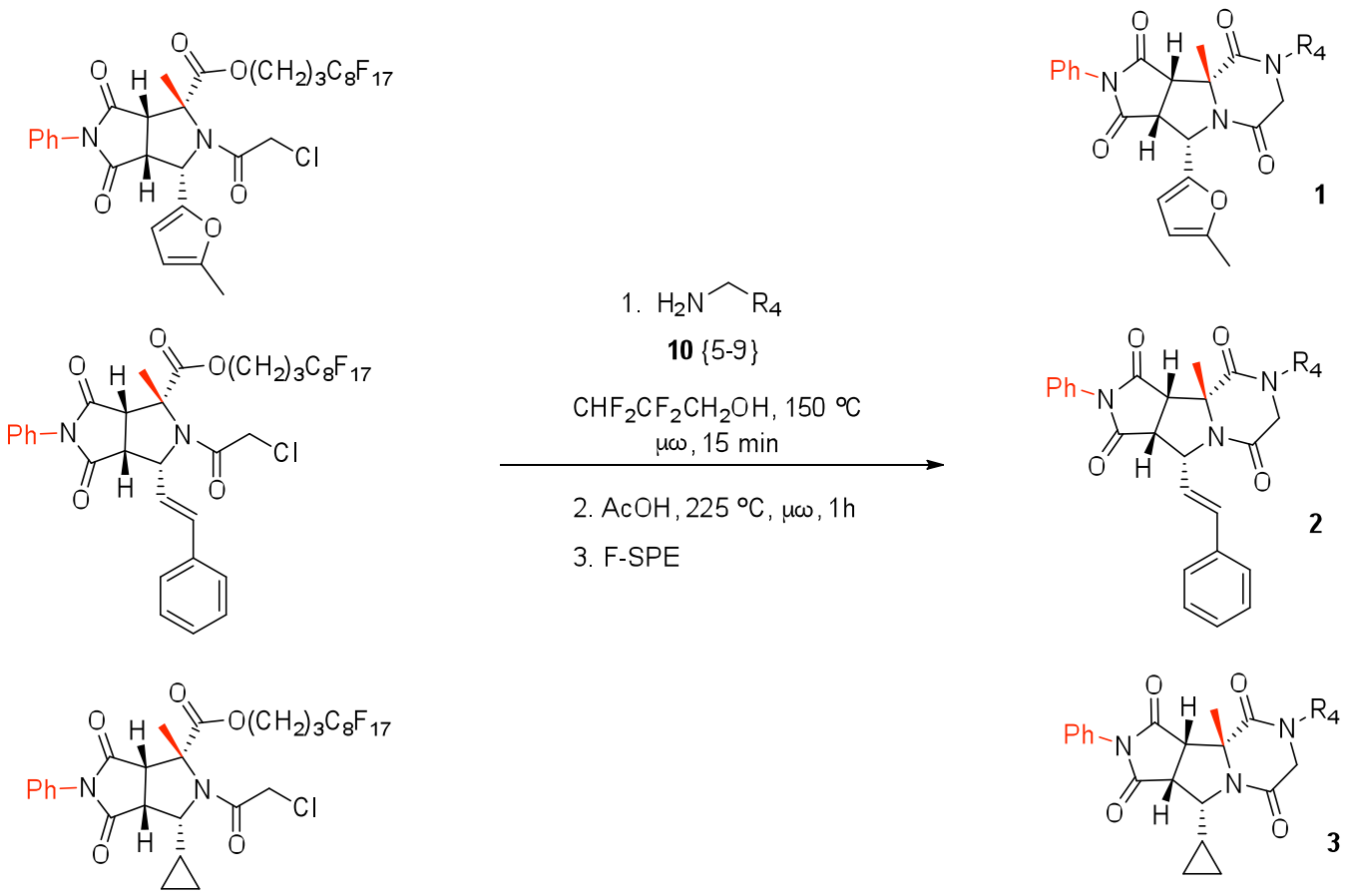
Synthesis of Fluorous Proline Intermediates

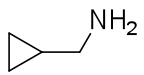
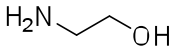
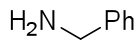
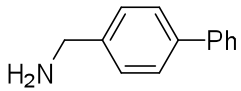
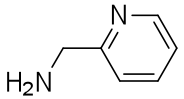
Methyl – Phenyl Series



	8 {5}	8 {4}	8 {3}
1	81%	42%	42%
2	75%	80%	76%

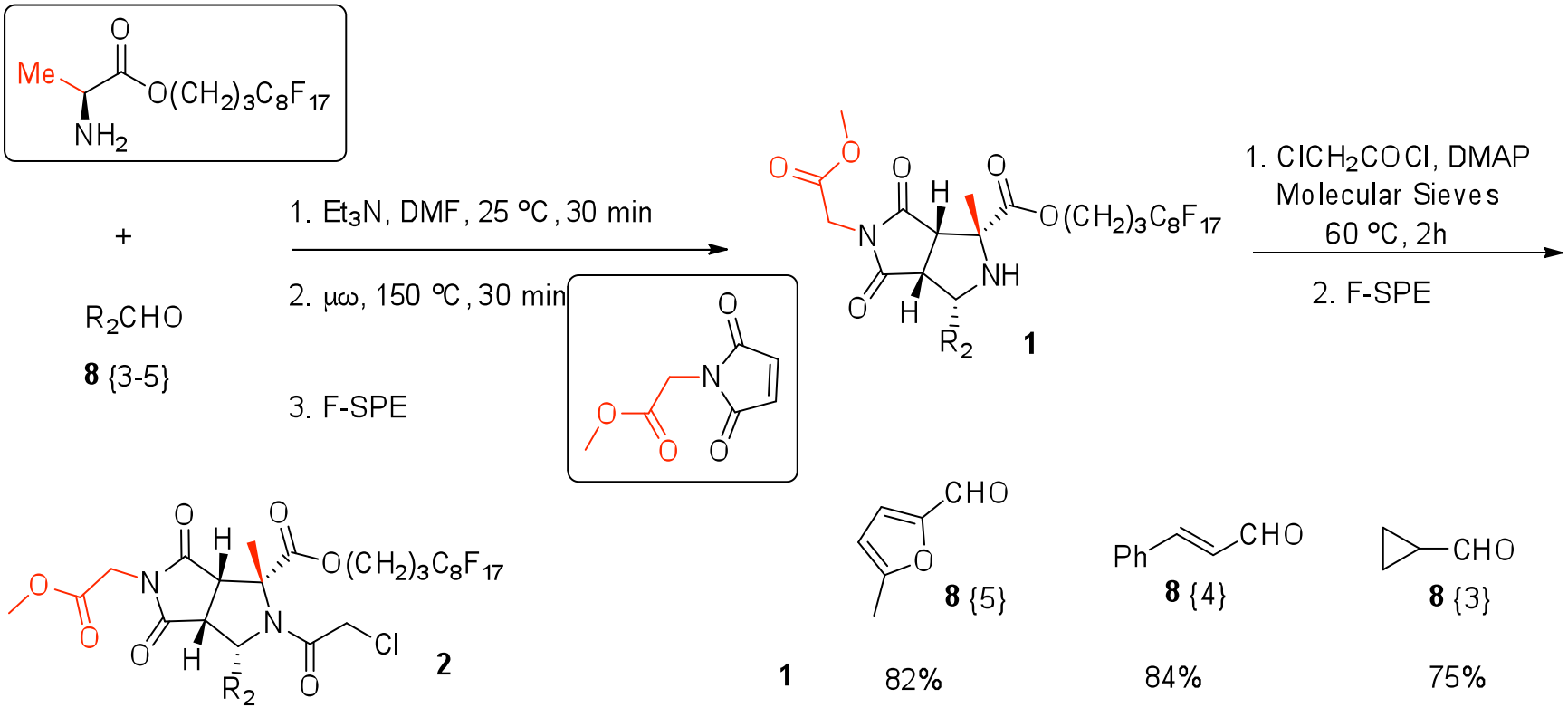
J. Comb. Chem. **2009**, *11*, 452



	 **10** {5}	 **10** {7}	 **10** {6}	 **10** {8}	 **10** {9}
1	94%	42%	40%	42%	21%
2	24%	45%	39%	33%	19%
3	69%	60%	62%	Failed	96%

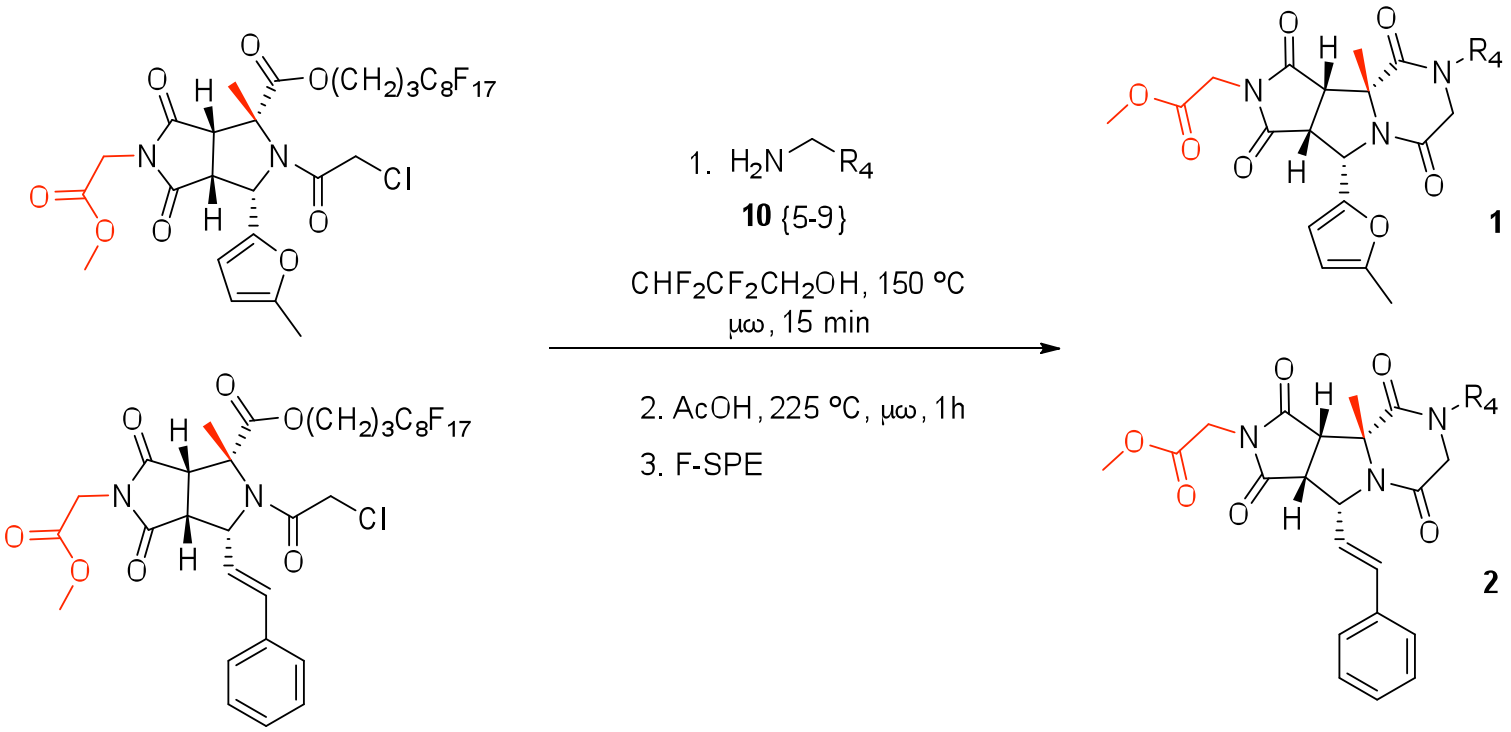
Synthesis of Fluorous Proline Intermediates

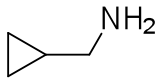
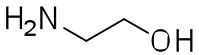
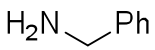
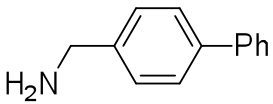
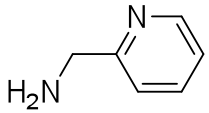
Methyl – Ester Series



	8 {5}	8 {4}	8 {3}
1	82%	84%	75%
2	61%	85%	No reaction

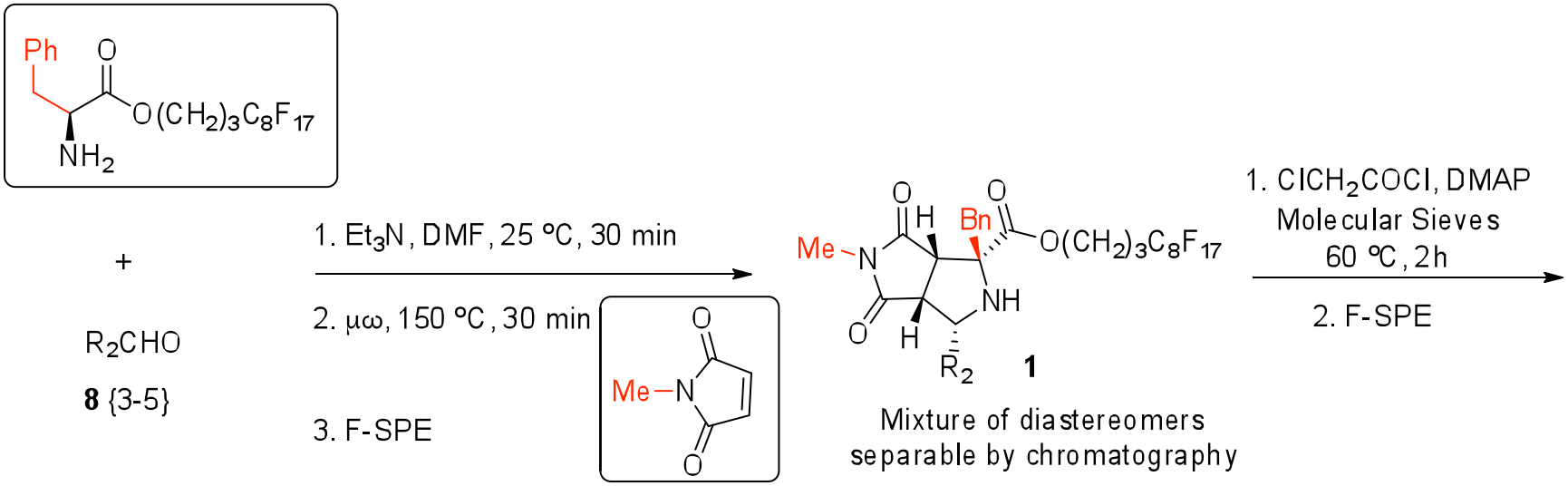
J. Comb. Chem. **2009**, *11*, 452



	 **10** {5}	 **10** {7}	 **10** {6}	 **10** {8}	 **10** {9}
1	18%	29%	18%	25%	23%
2	40%	54%	39%	23%	26%

Synthesis of Fluorous Proline Intermediates

Phenyl – Methyl Series



	8 {5}	8 {4}	8 {3}
1	50%	30%	78%
2	80%	88%	80%

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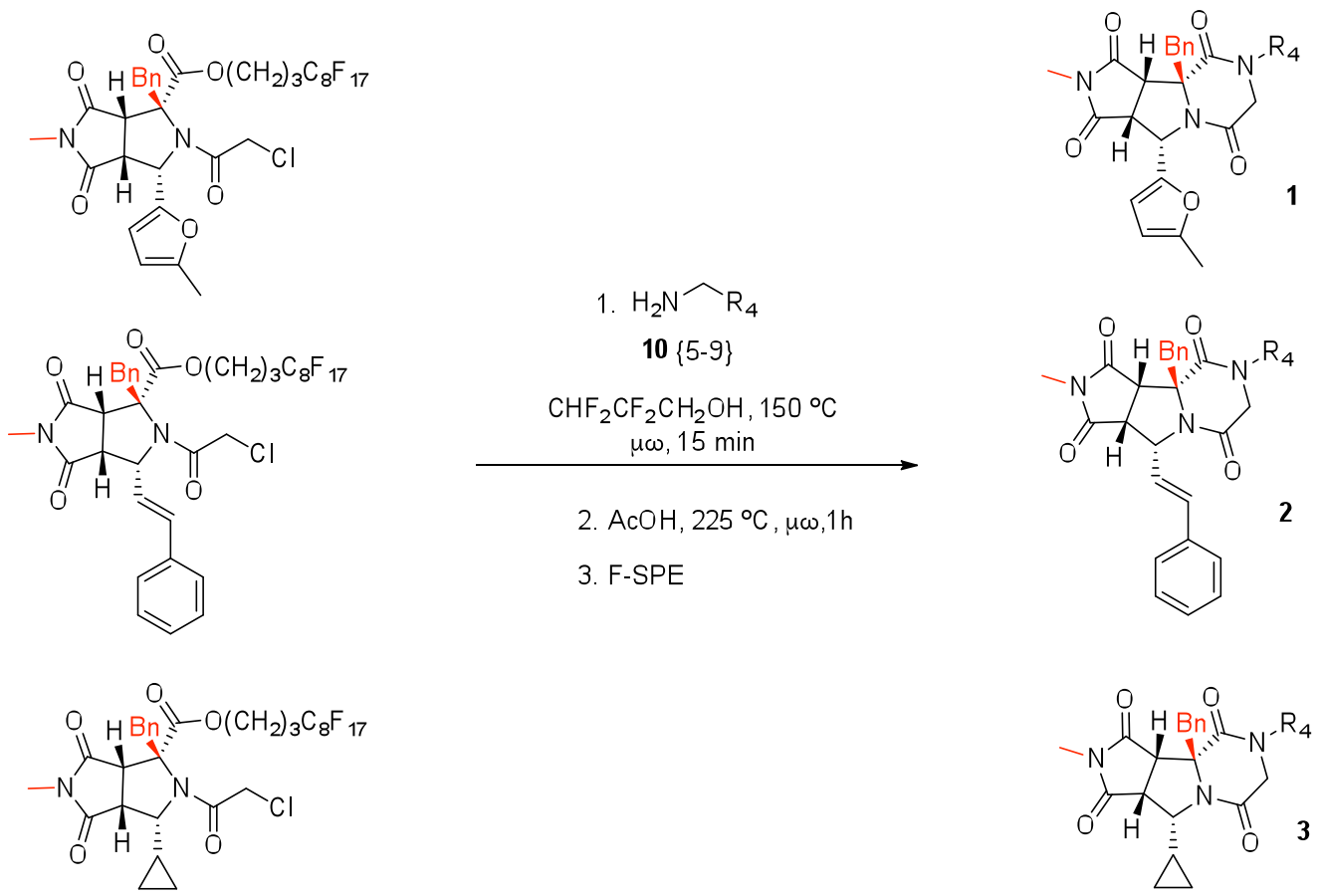
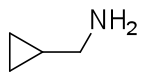
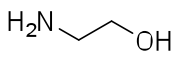
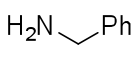
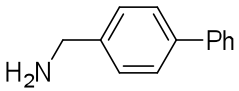
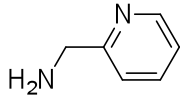
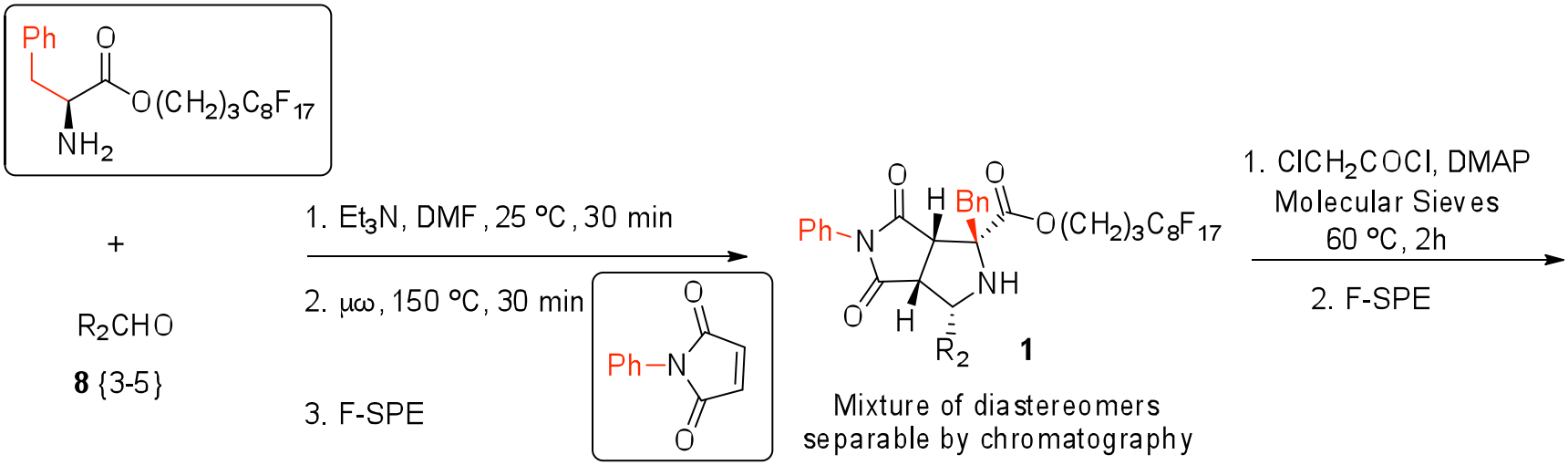
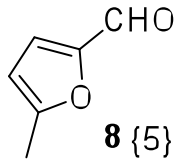
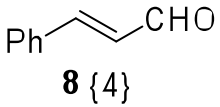
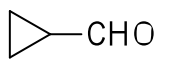


	 **10** {5}	 **10** {7}	 **10** {6}	 **10** {8}	 **10** {9}
1	21%	25%	11%	39%	17%
2	54%	25%	33%	30%	35%
3	Failed	Failed	19%	57%	24%

Synthesis of Fluorous Proline Intermediates

Phenyl – Phenyl Series



	 8 {5}	 8 {4}	 8 {3}
1	50%	19%	64%
2	10%	44%	72%

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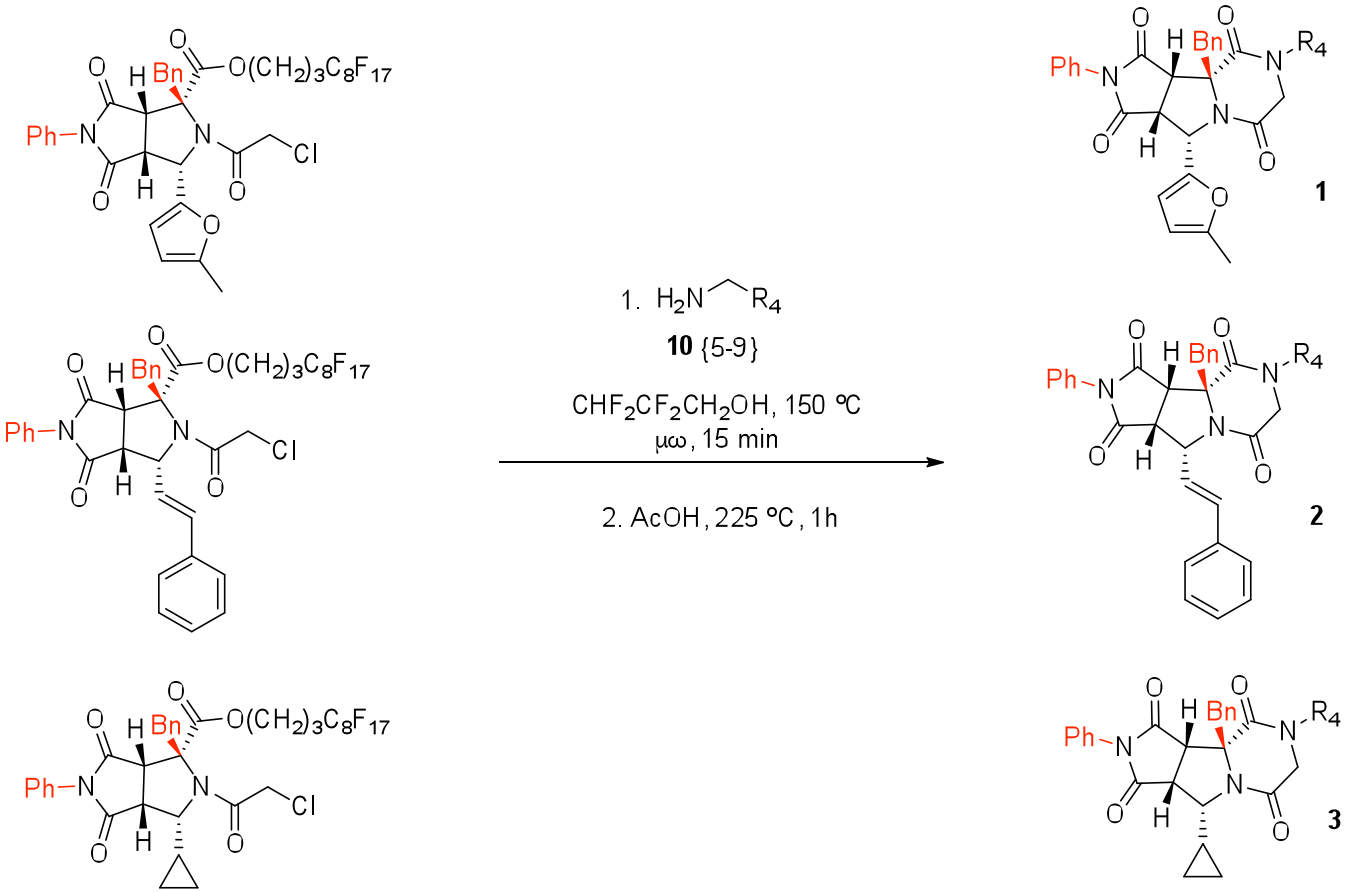
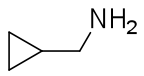
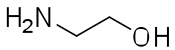
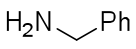
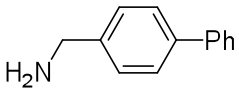
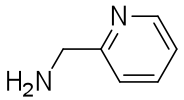
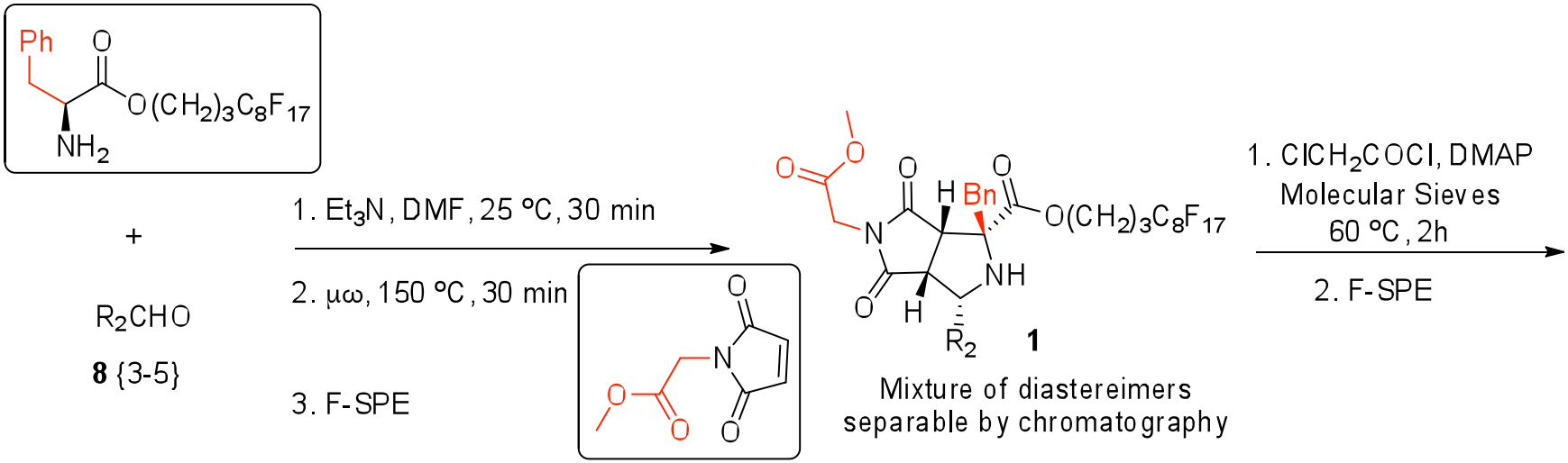


	 **10** {5}	 **10** {7}	 **10** {6}	 **10** {8}	 **10** {9}
1	20%	89%	9%	78%	23%
2	34%	Failed	26%	88%	20%
3	23%	Failed	24%	6%	24%

Synthesis of Fluorous Proline Intermediates

Phenyl – Ester Series



	8 {5}	8 {4}	8 {3}
1	80%	27%	35%
2	74%	74%	77%

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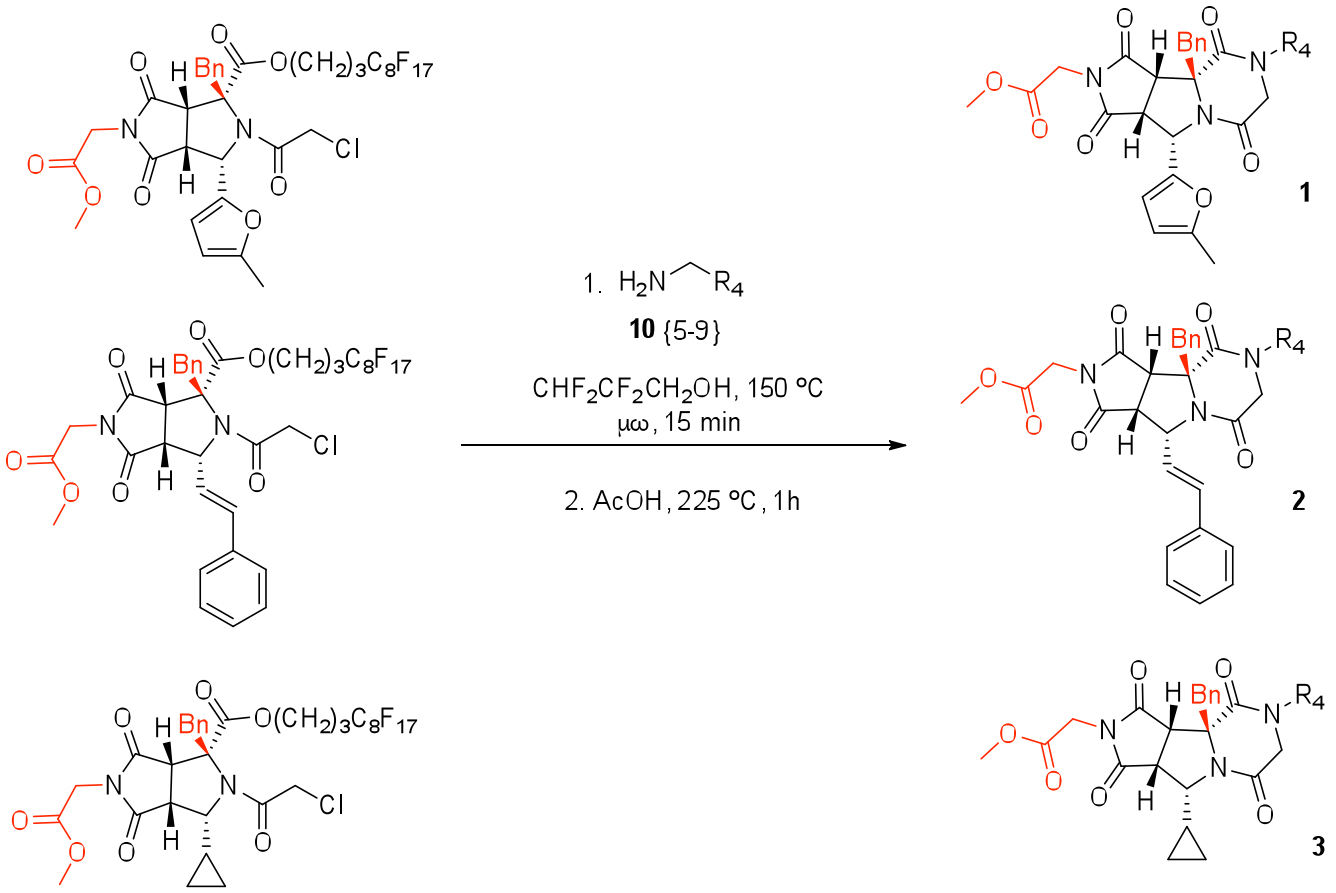
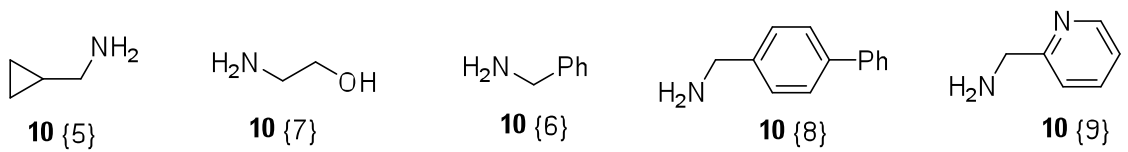




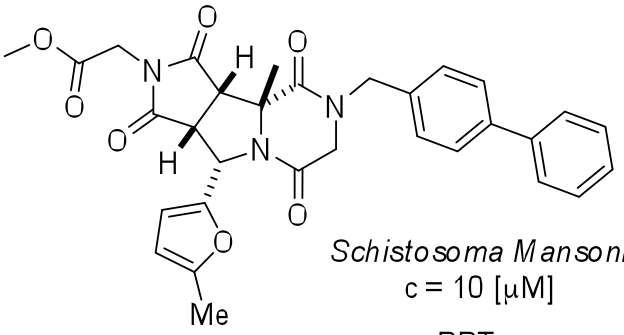
1	21%	30%	12%	Failed	17%
2	16%	20%	16%	32%	25%
3	Failed	Failed	20%	62%	24%

Piperazinedione - Biological Activities

- 63 compounds have been submitted to the NIH repository and evaluated in several high-throughput screening progams.
- 6 compounds showed activities against *Schistosoma Mansoni*.
- 2 compound showed inhibitors of *Bacillus subtilis* Sfp phosphopantetheinyl transferase (PPTase).
- 1 compound showed active against Parkinson's disease (5'UTR protein).

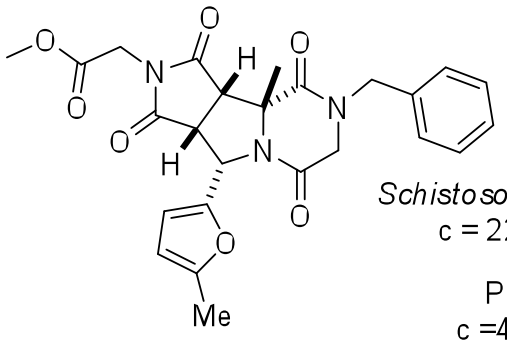
http://pubchem.ncbi.nlm.nih.gov/

Piperazinedione - Biological Activities



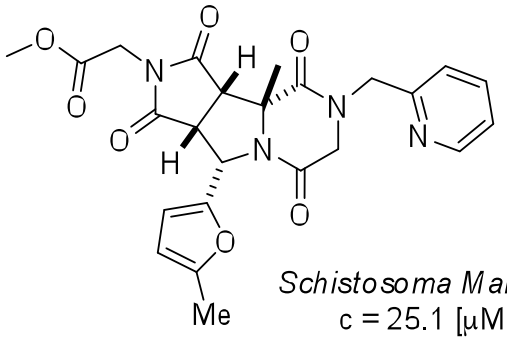
Schistosoma Mansoni
c = 10 [μM]

PPTase
c = 12.5 [μM]

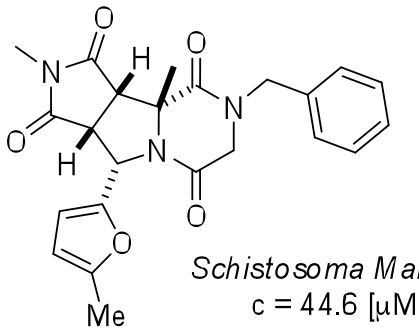


Schistosoma Mansoni
c = 22.3 [μM]

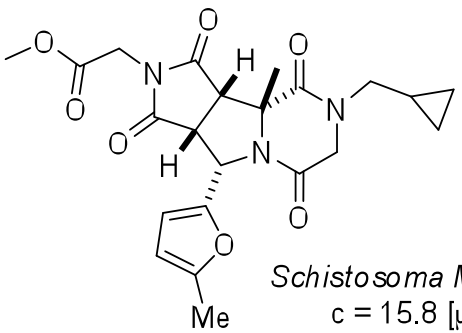
PPTase
c =44.6 [μM]



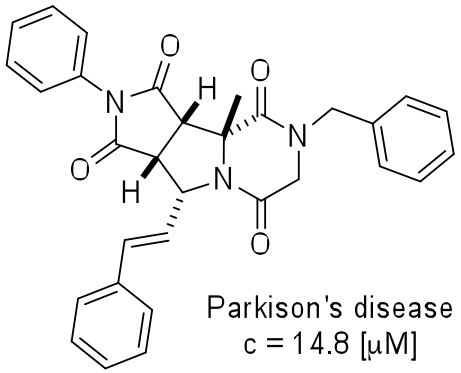
Schistosoma Mansoni
c = 25.1 [μM]



Schistosoma Mansoni
c = 44.6 [μM]



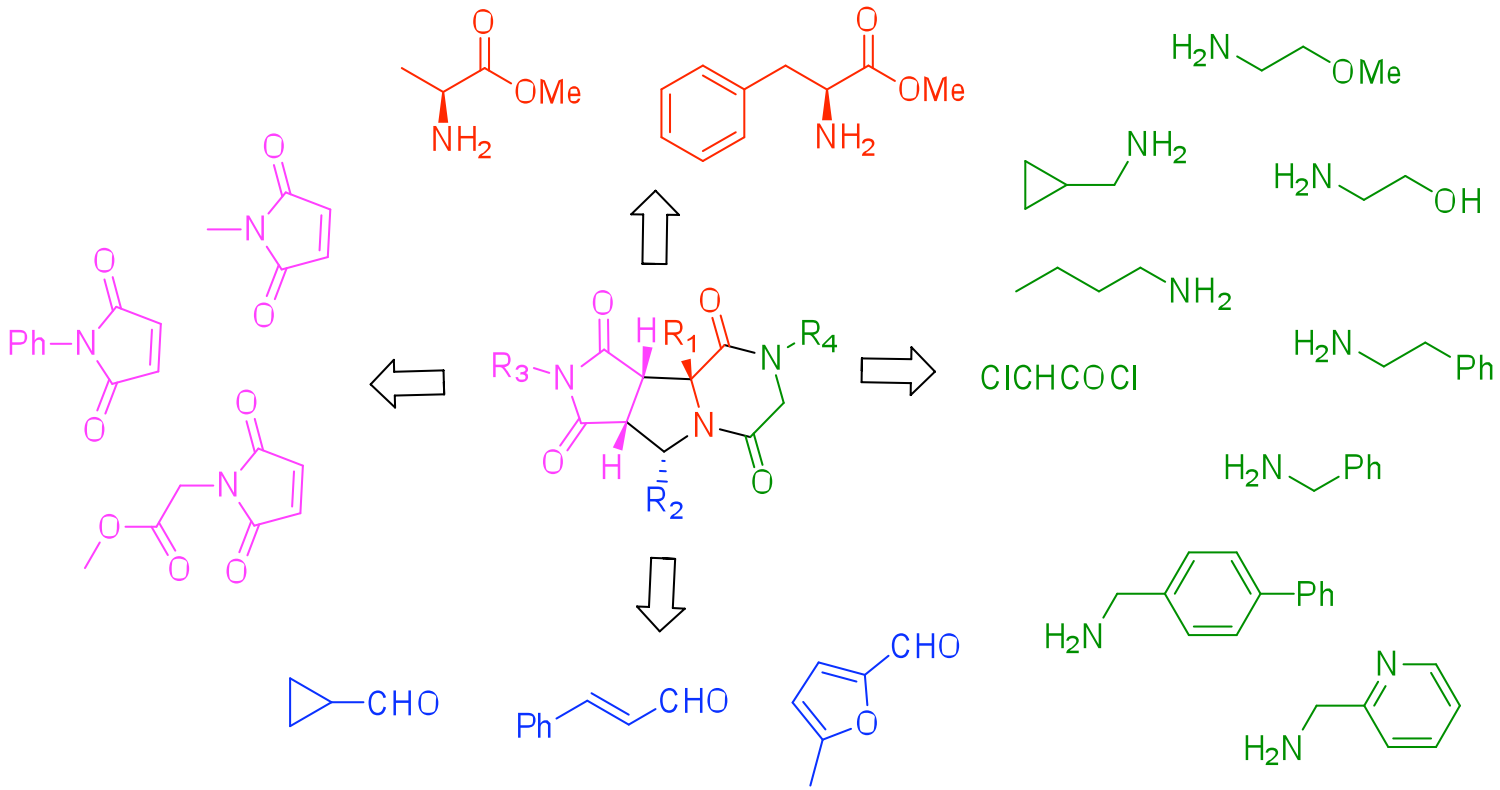
Schistosoma Mansoni
c = 15.8 [μM]



Parkison's disease
c = 14.8 [μM]

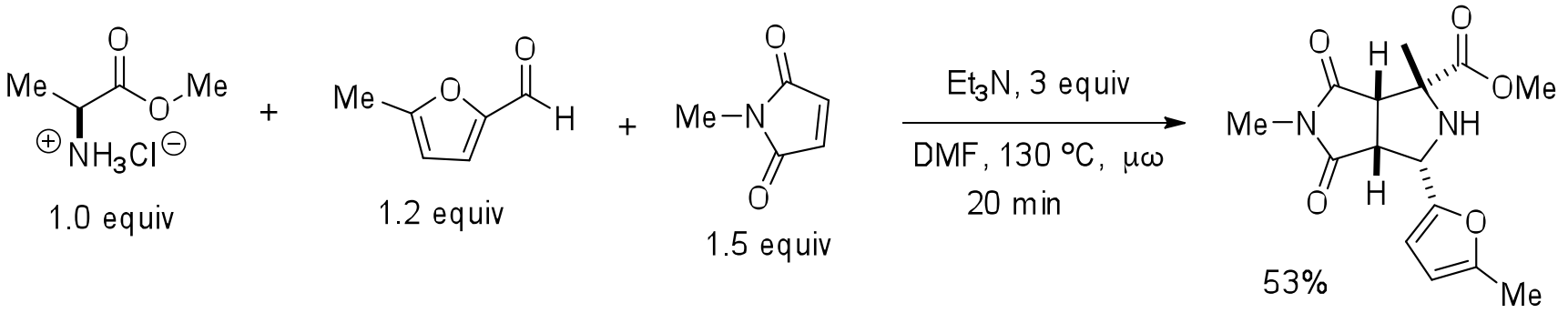
Current Strategy and Objectives

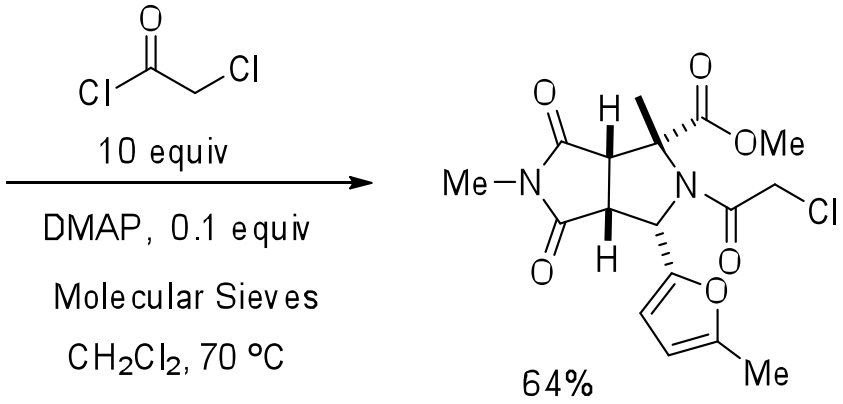
- Synthesized of a piperazinedione – compound library
- To store the collection of compounds UPCMLD
- Future biological assay



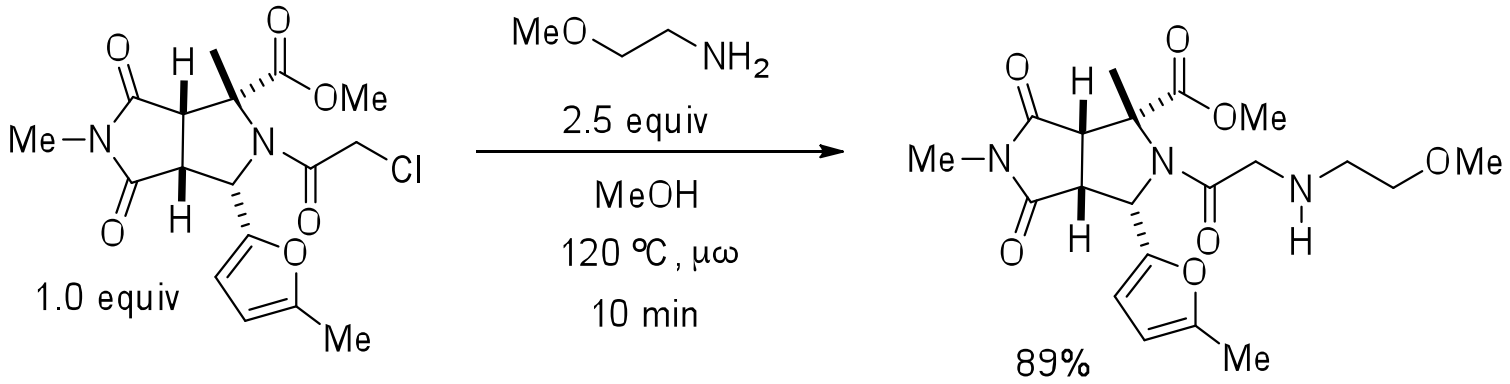
Current Work

Preparation of the bicycle proline derivative – Furyl series





Current Work



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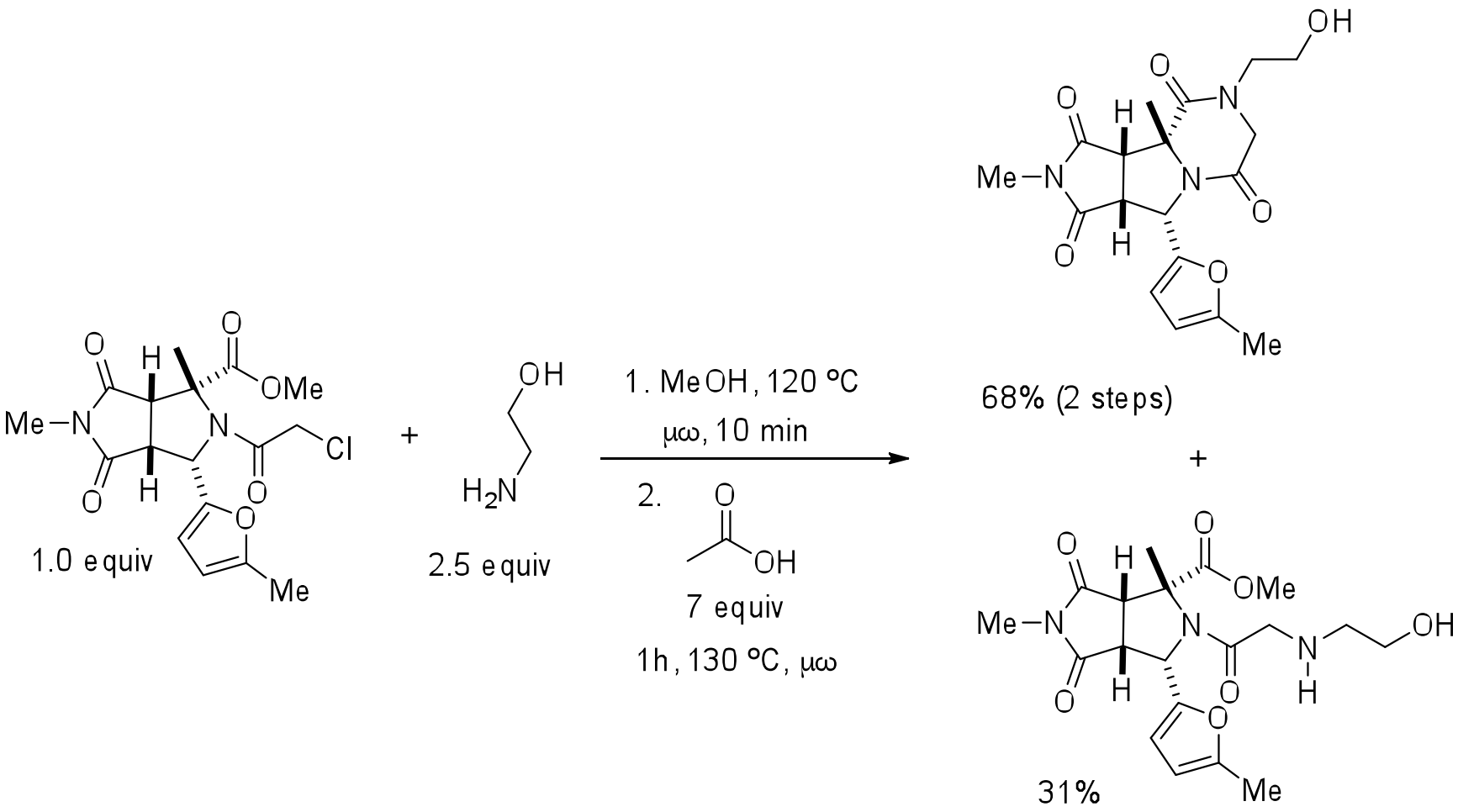

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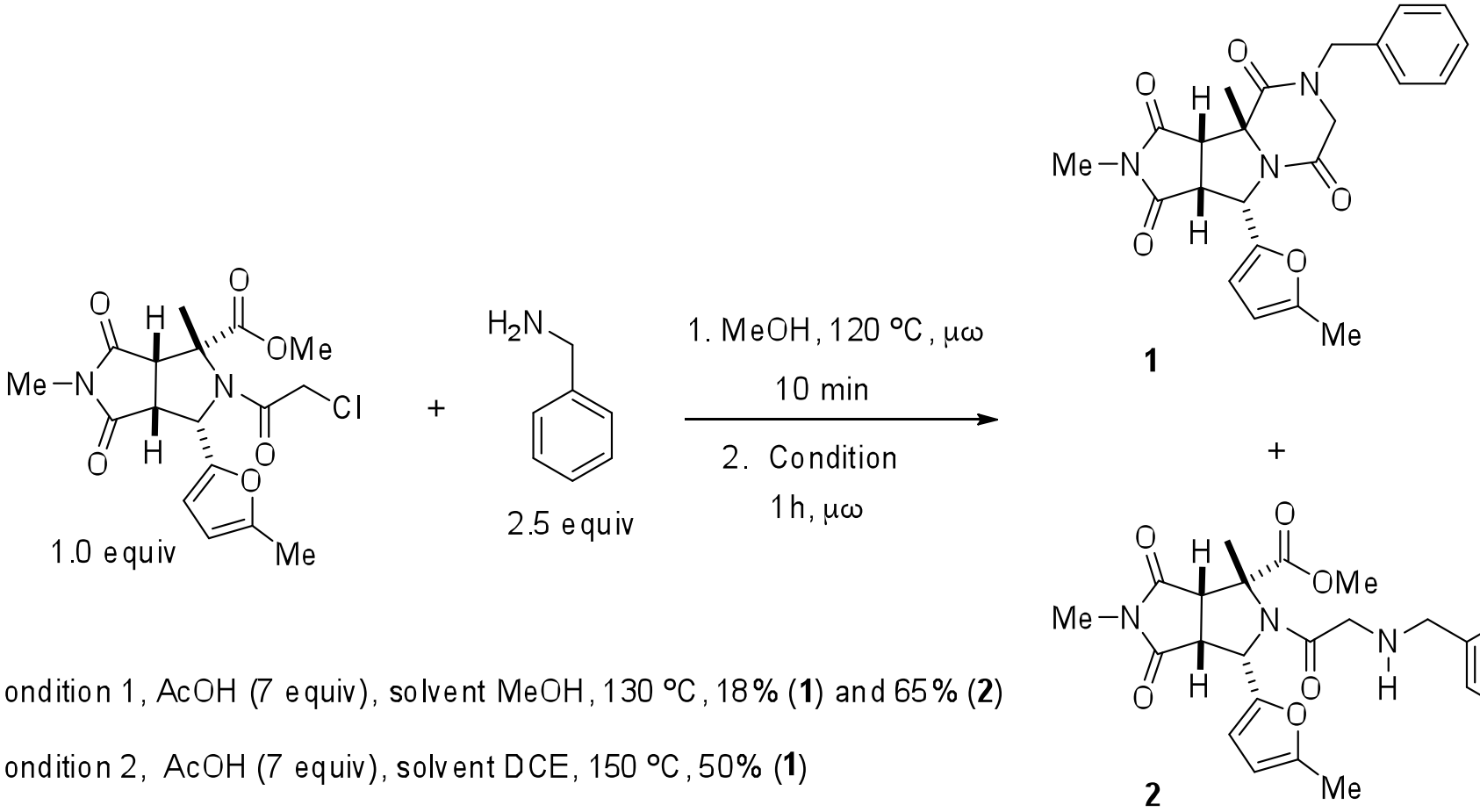
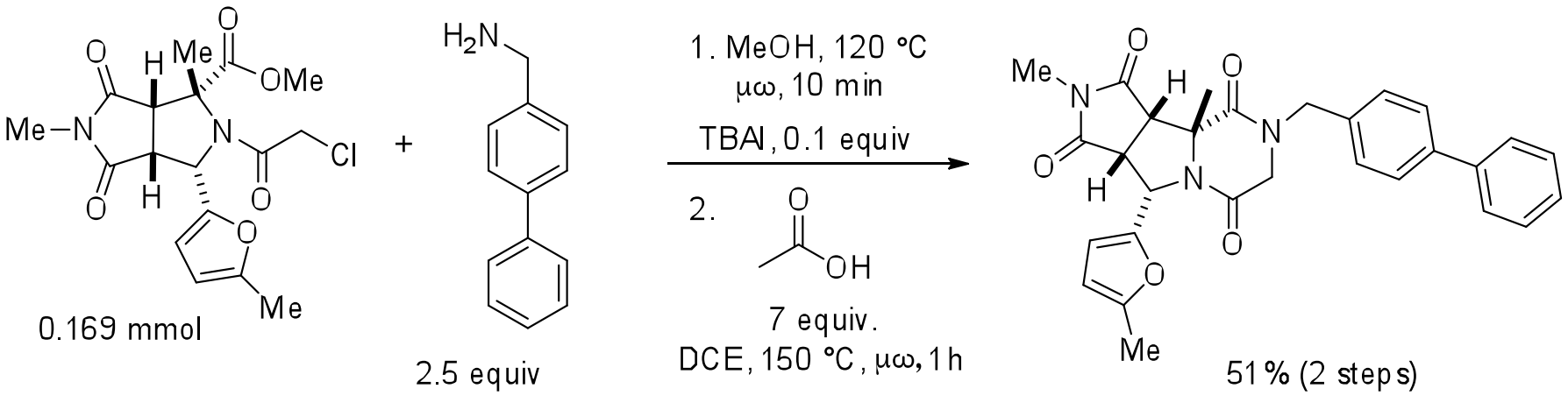
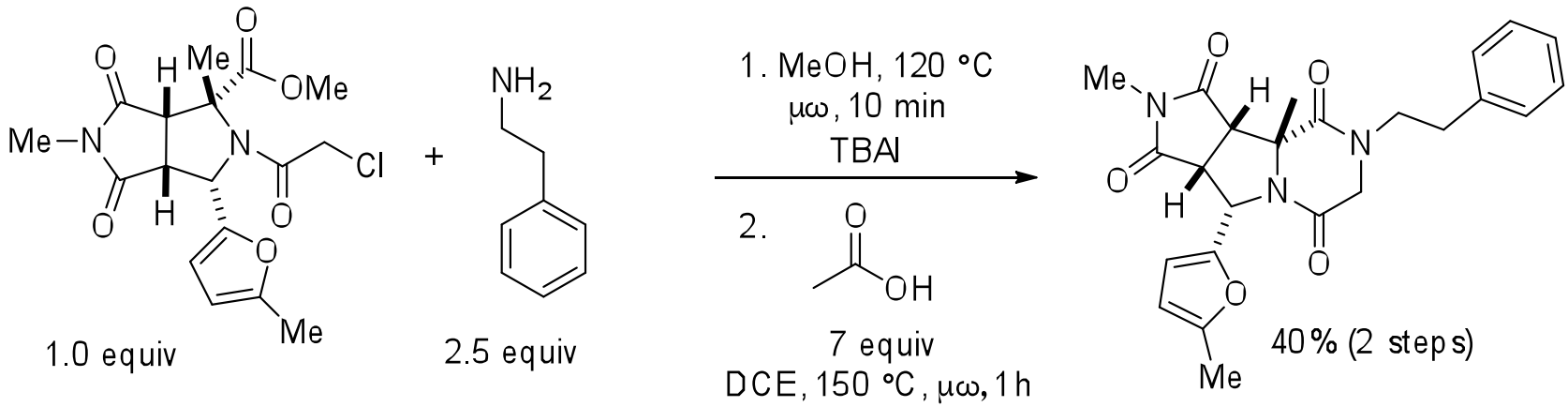


Condition 1, AcOH (7 equiv), solvent MeOH, 130 °C, 18% (**1**) and 65% (**2**)

Condition 2, AcOH (7 equiv), solvent DCE, 150 °C, 50% (**1**)

Current Work





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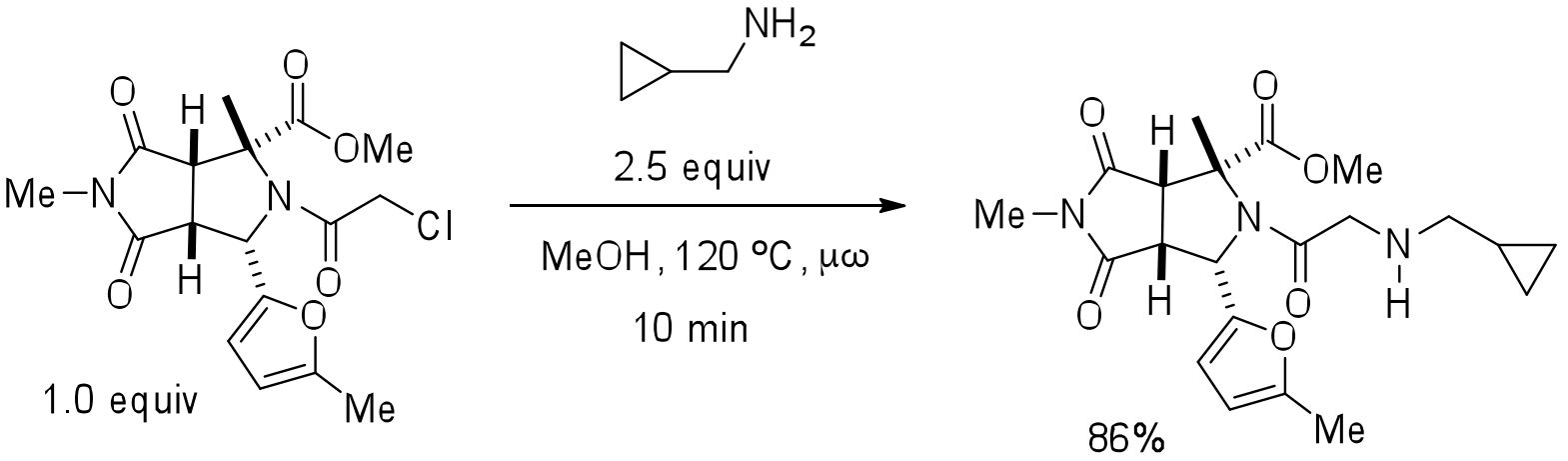

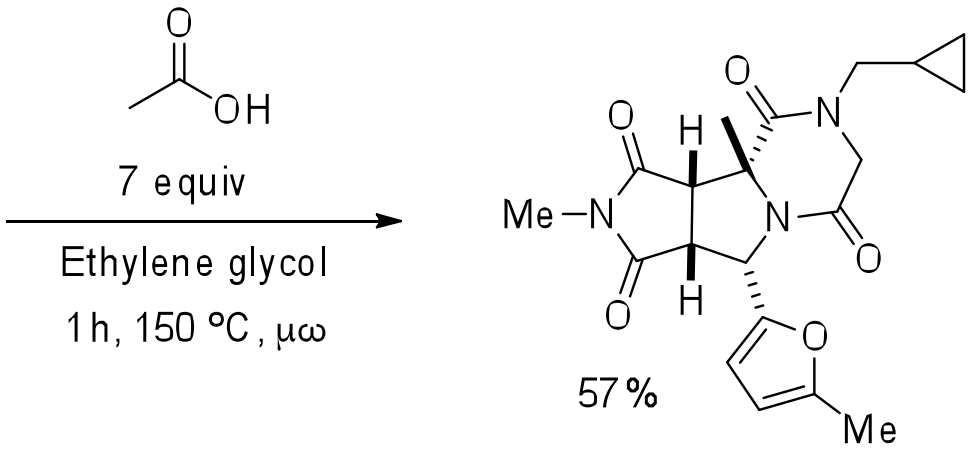

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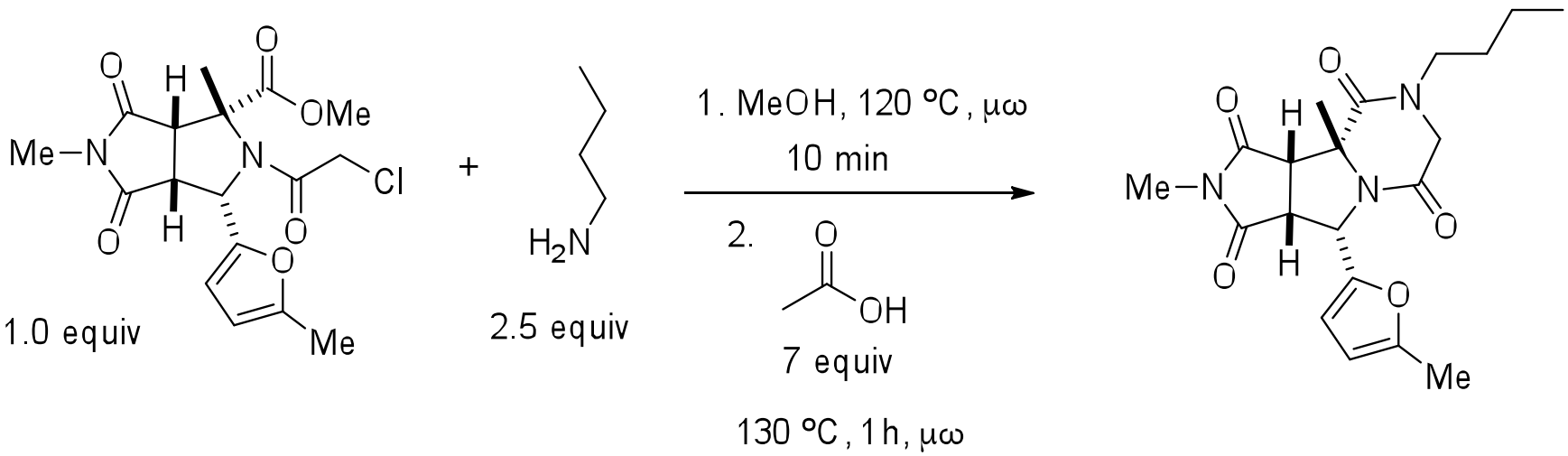
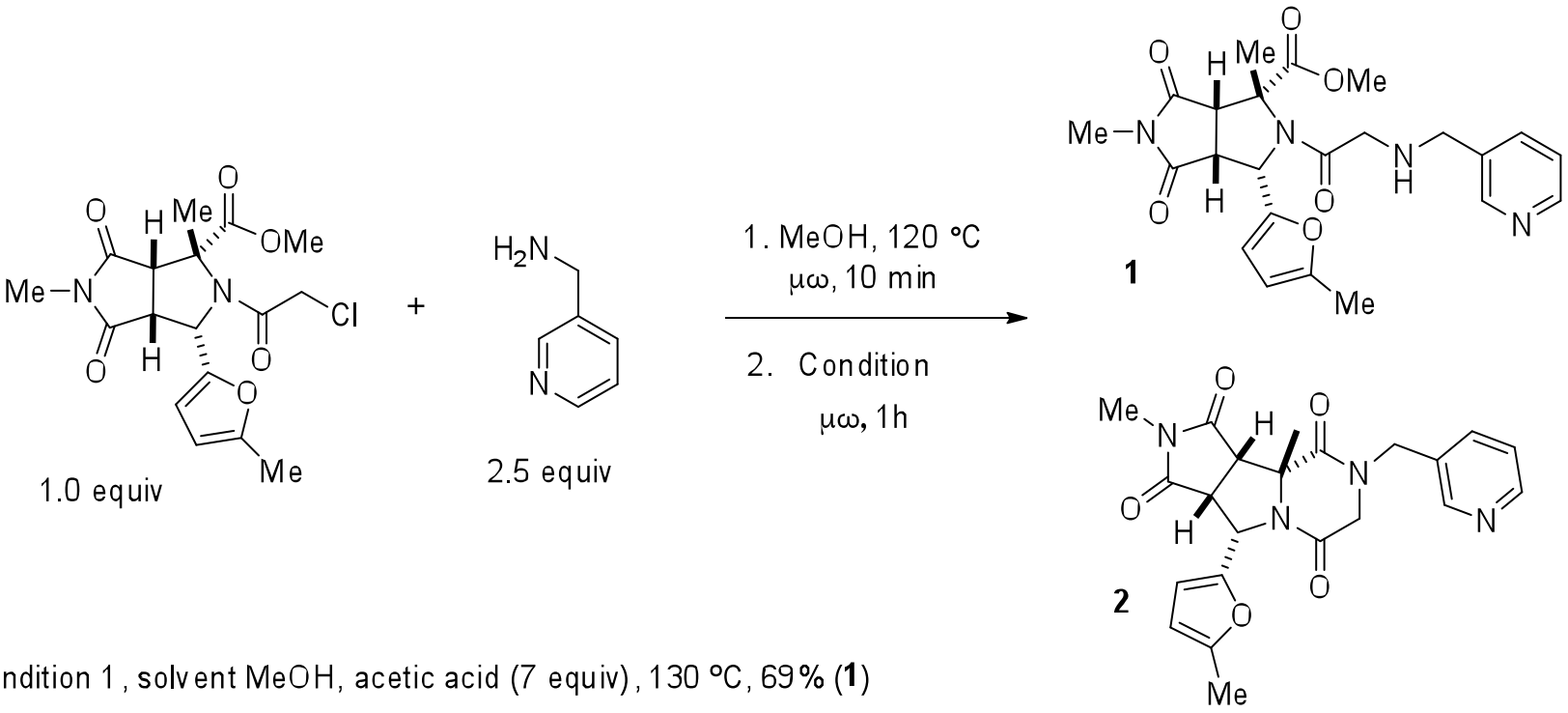


Condition 1, solvent MeOH, 130 °C, 54%

Condition 2, solvent ethylene glycol, 150 °C, 64%

38

Current Work



Condition 1, solvent MeOH, acetic acid (7 equiv), 130 °C, 69% (**1**)

Condition 2, solvent DCE, acetic acid (7 equiv), 150 °C, decompose

Condition 3, TBAI, solvent ethylene glycol, acetic acid (7 equiv), 150 °C, 13% (**2**)

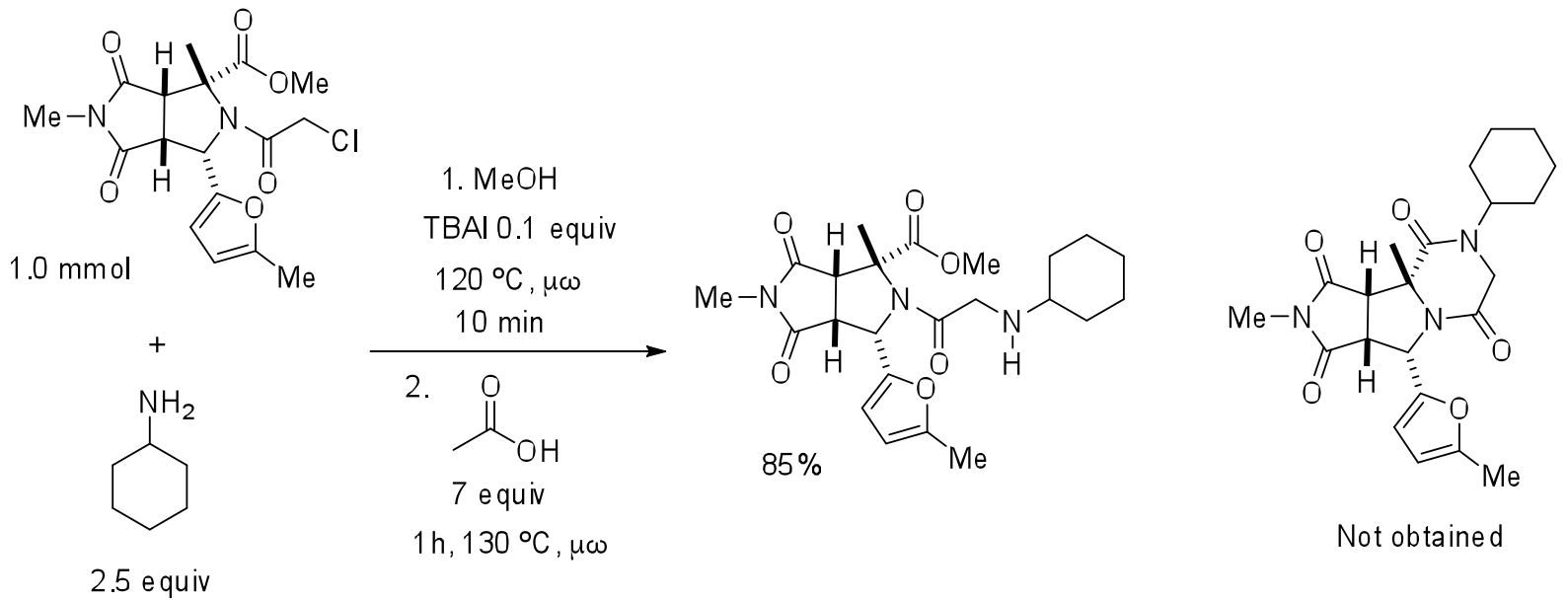
Condition 4, TBAI, DBU (2 equiv), solvent MeOH/Dioxane, 130 °C, Decompose

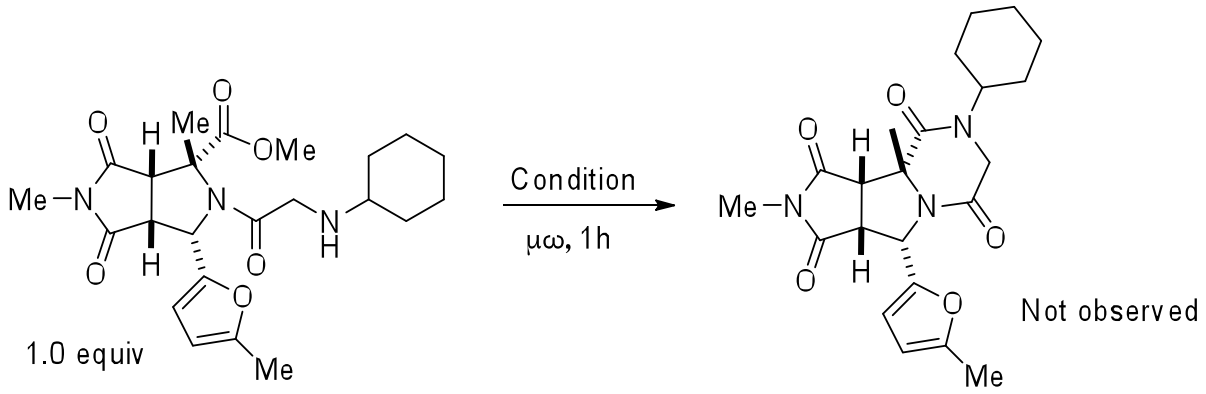
Condition 5, TBAI, solvent DCE, Trifluoroethanol 10 equiv, 150 °C, Decompose

Condition 6, TBAI, solvent NMP, H_2O 10 equiv, 150 °C, Decompose

Condition 7: TBAI, PPTS, solvent Trifluoroethanol, 150 °C, 70% (**1**)

Current Work



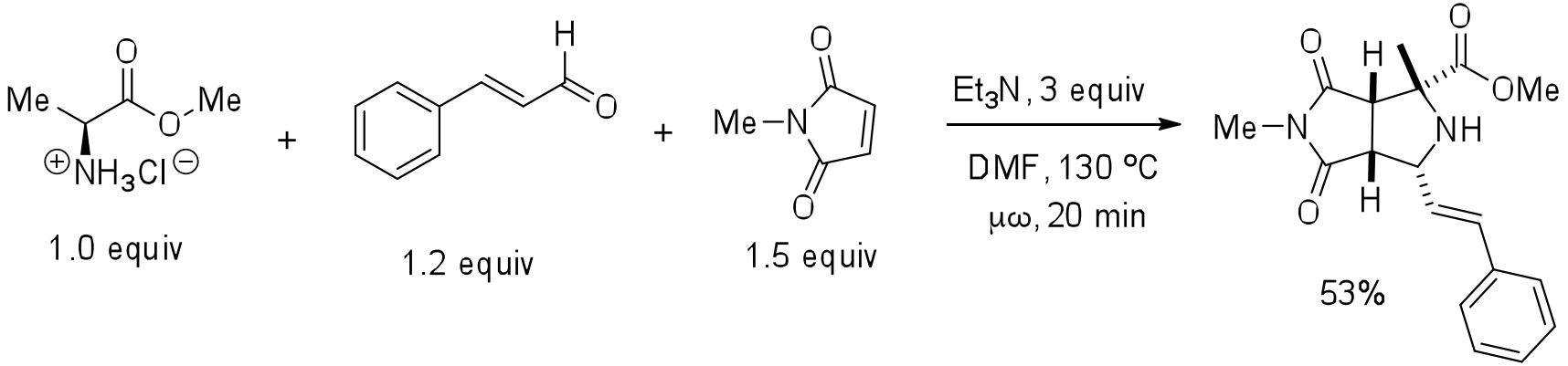


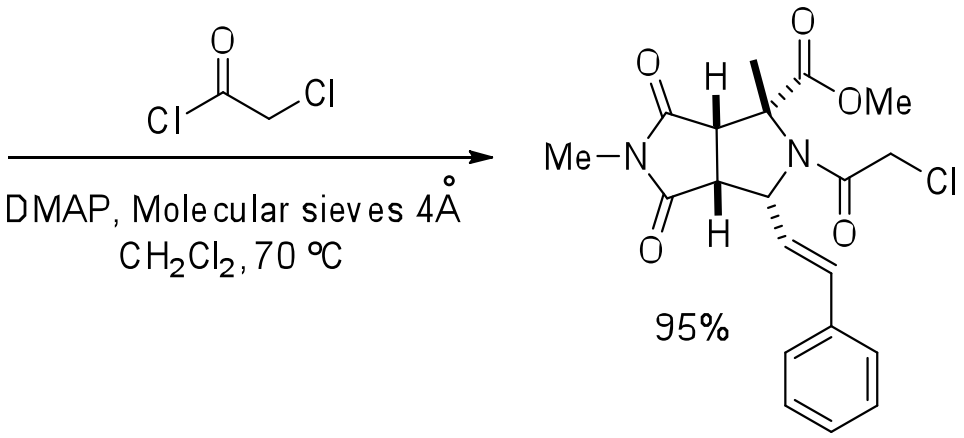
Condition 1, solvent DCE, Trifluoroethanol (10 equiv), 150 °C, 83% SM

Condition 2, solvent DCE, acetic acid (7 equiv) 150 °C, 41% SM

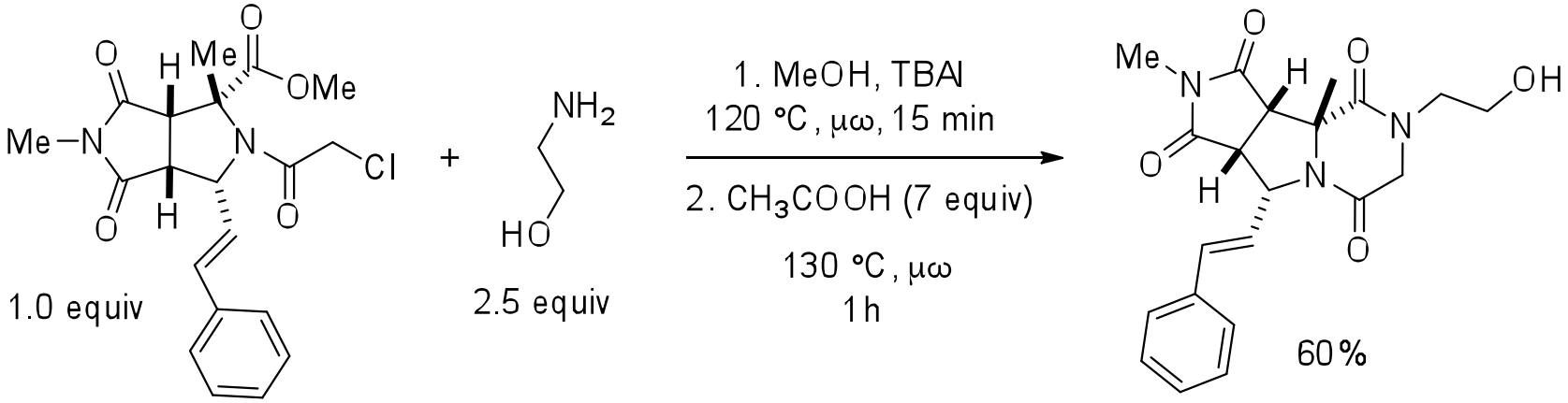
Current Work

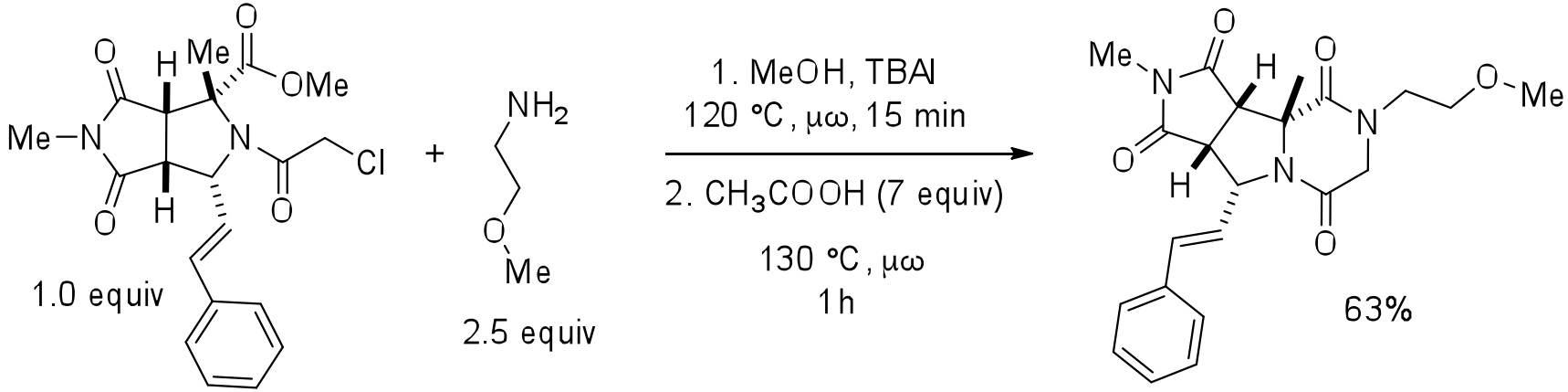
Preparation of the bicycle proline derivative – Cinnamyl series





Current Work





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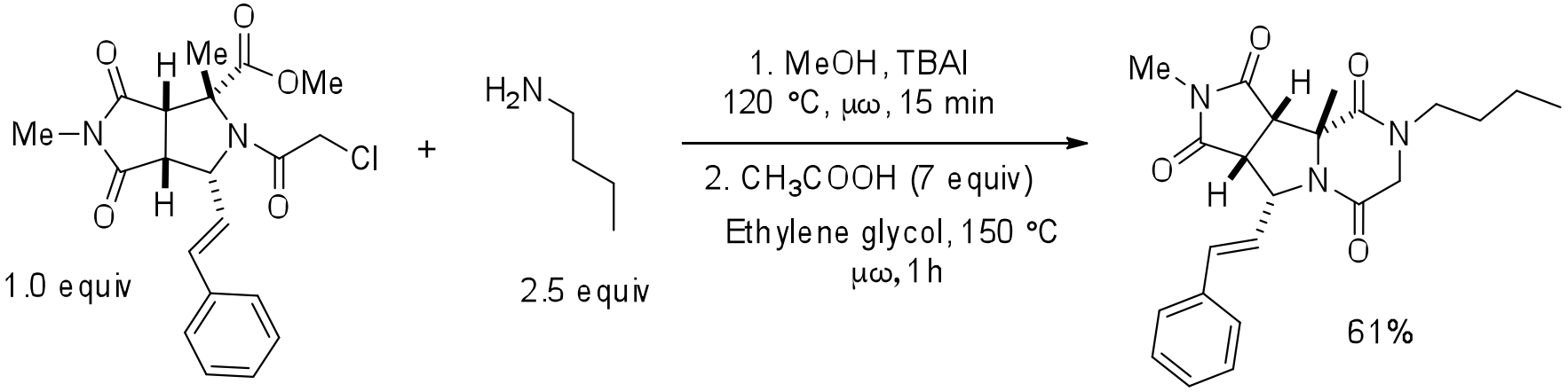

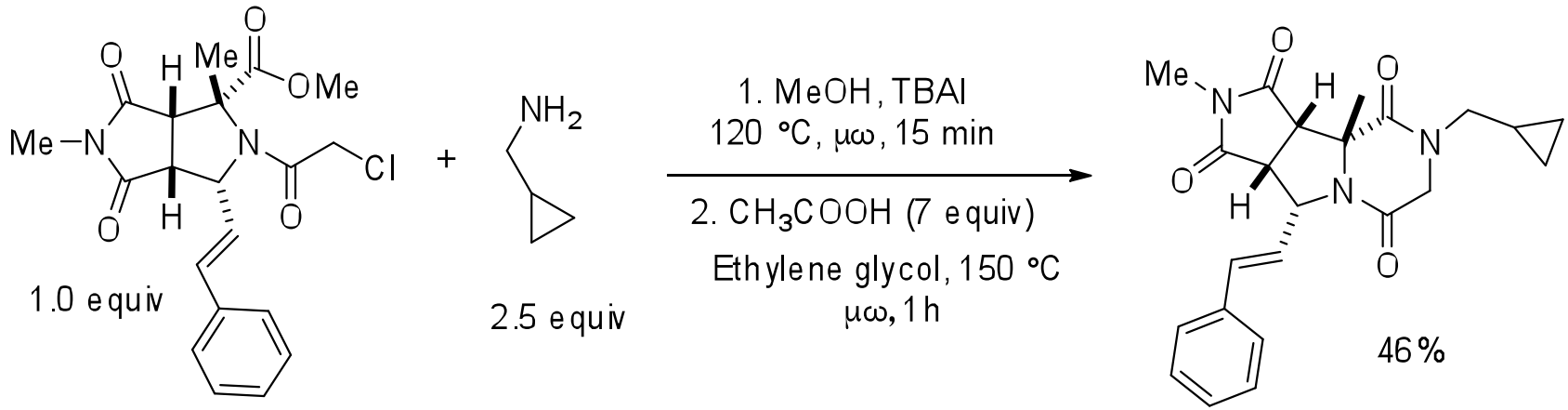

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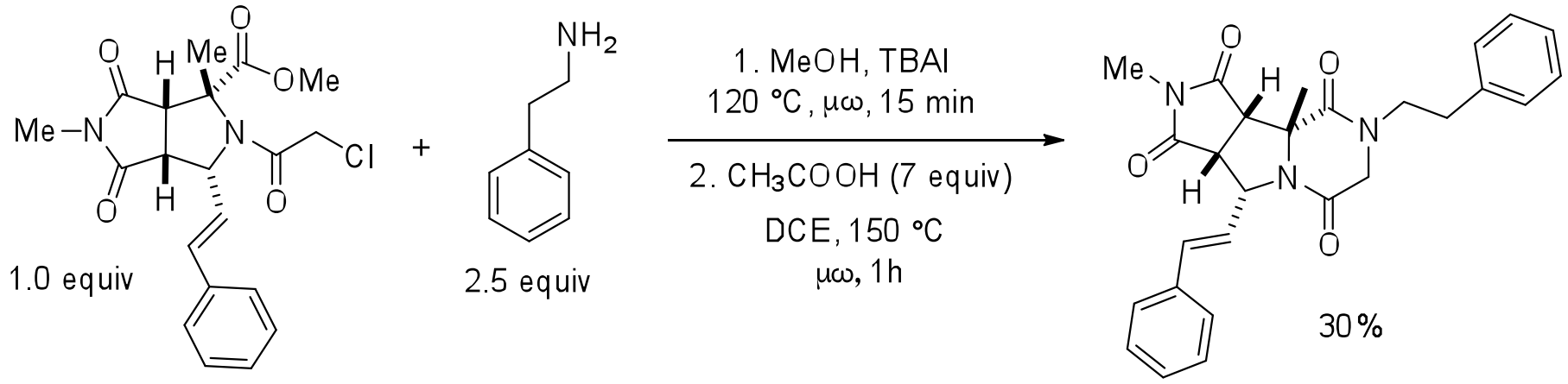

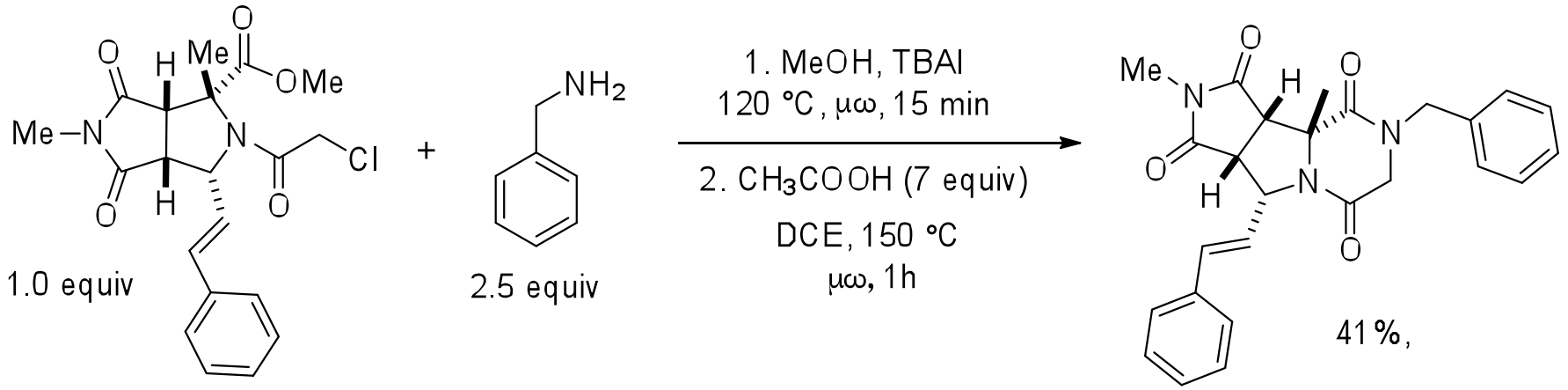

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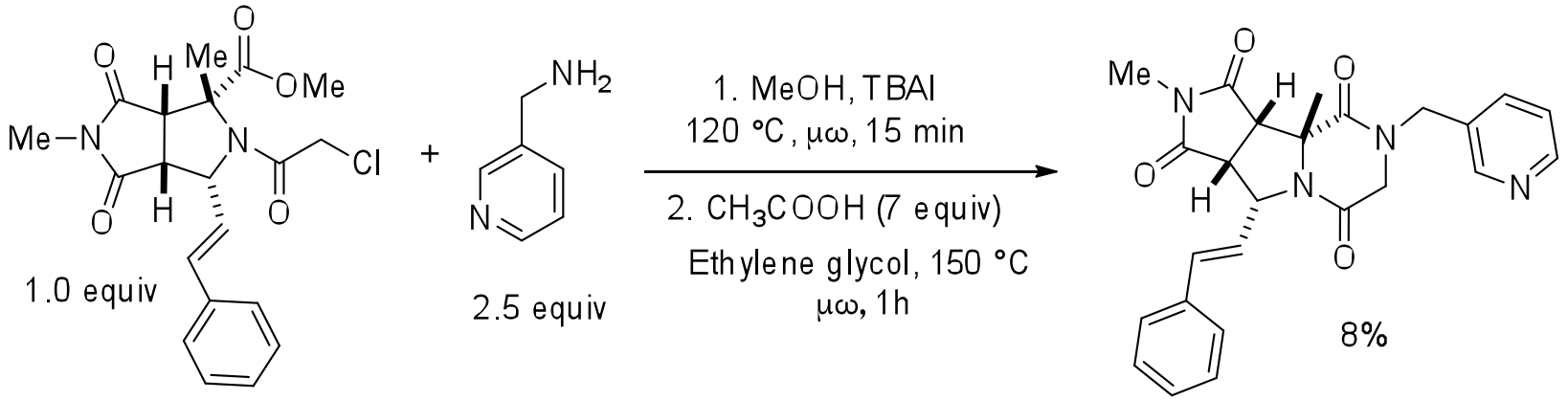

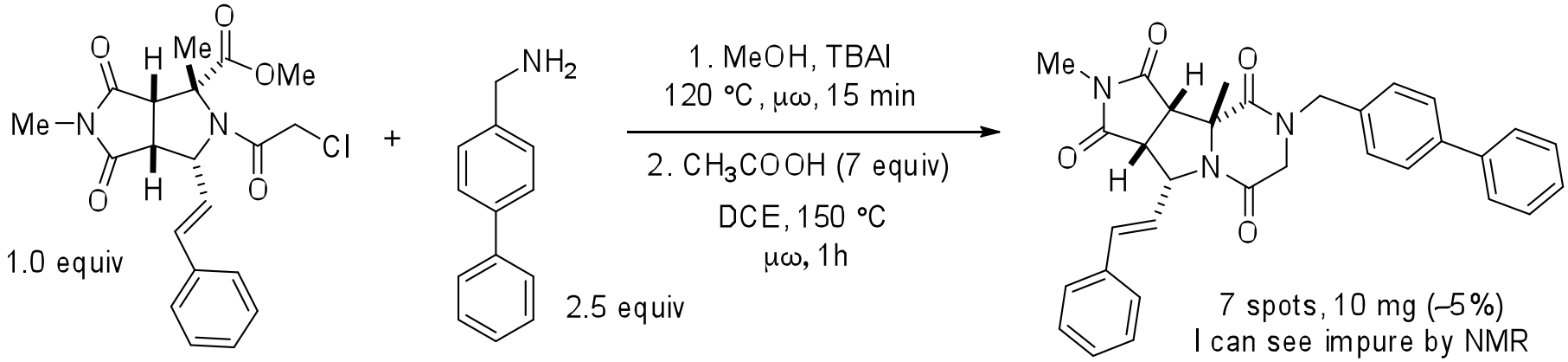

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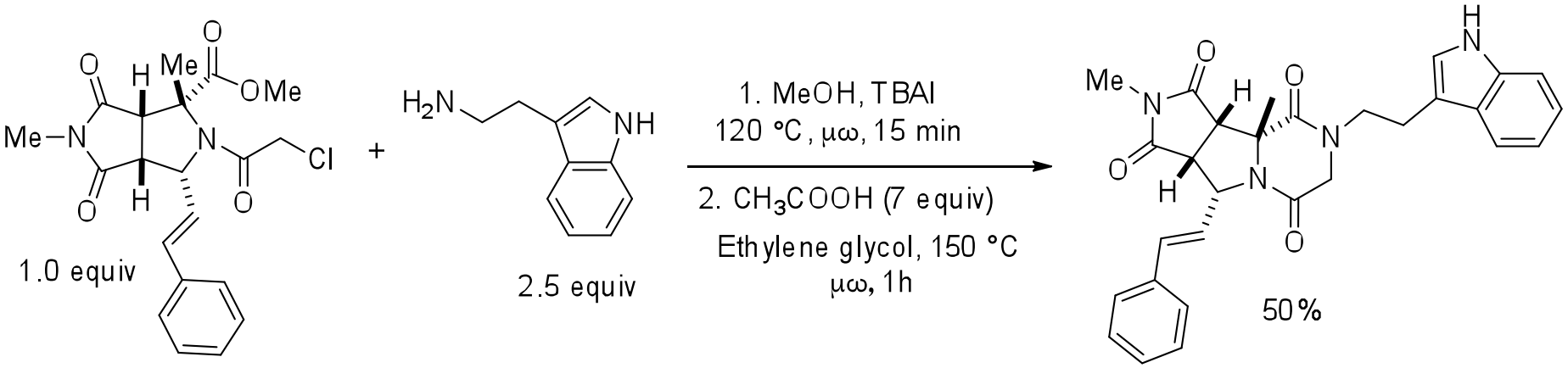

Acknowledgements

- Dr. Wipf
- Wipf group members
- University of Pittsburgh and CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico) for Fellowship