

F-2006

Devoted to Pr. I.L. Knunyants

June 5 to June 9, 2006 Moscow (Russia)

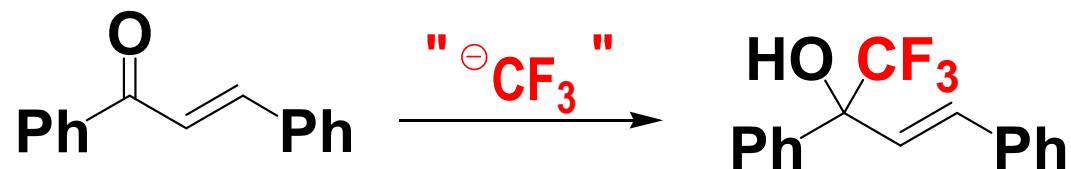
New Routes to Fluorinated Cycles and Bicycles.

**B.R. LANGLOIS,^a T. BILLARD,^a S. RADIX-LARGE,^a G. BLOND,^a
S. GILLE,^a A. FERRY,^a A. BARTHELEMY,^a C. CHRISTOPHE,^a
S. KUCHARSKI,^a S. HARTONG,^a G. HAUFE,^b J. LEUGER^b**

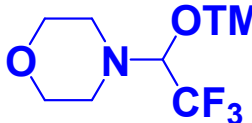
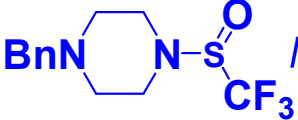
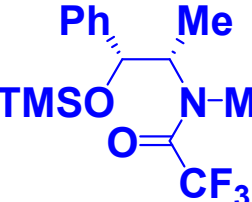
^a *Laboratoire SERCOF (UMR CNRS 5181)
Université Claude Bernard Lyon 1 (France).*

^b *Organisch-Chemisches Institut,
Westfälische Wilhelms-Universität Münster (Germany)*

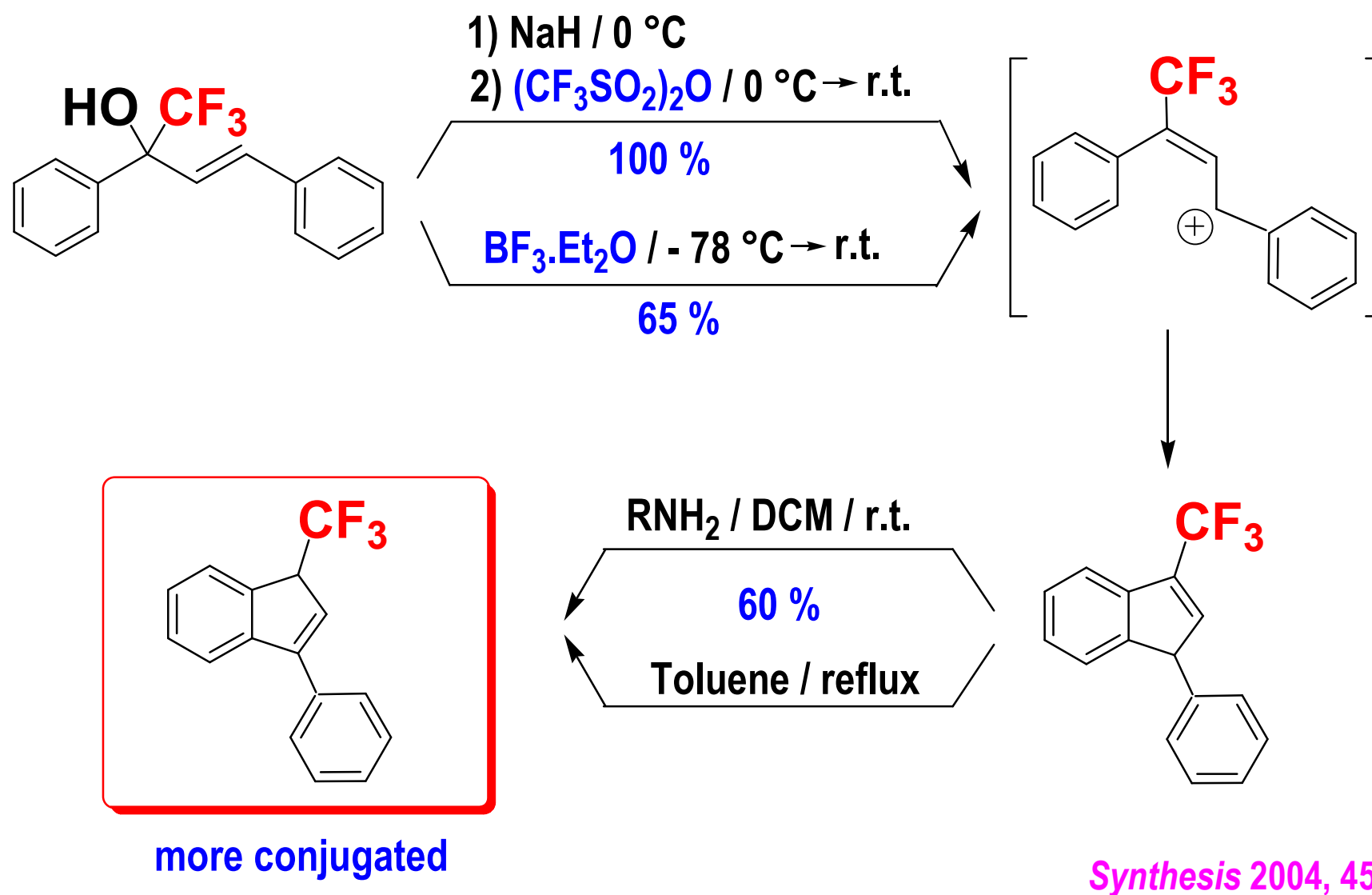
Indenes from Chalcones. 1st Step



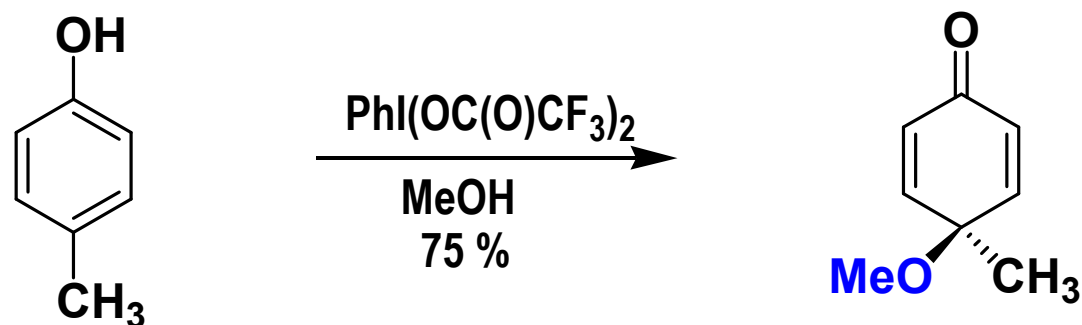
[1,2] addition exclusively

" CF_3^- "	$\text{CF}_3\text{TMS} / \text{BU}_4\text{NF} (0.1 \text{ eq}) / \text{THF} / 0^\circ\text{C}$	80 %	<i>Olah, Prakash et al.</i>
	$\text{HCF}_3 (\text{xs}) / \text{N}(\text{TMS})_3 (1.5 \text{ eq}) / \text{Me}_4\text{NF} (0.2 \text{ eq}) / \text{DMF} / -10^\circ\text{C}$	68 %	<i>J.O.C. 2000, 65, 8848</i>
	 $/ \text{CsF} (0.1 \text{ eq}) / \text{DME} / 80^\circ\text{C}$	70 %	<i>Synlett 2003, 233</i>
	 $/ t\text{-BuOK} (0.1 \text{ eq}) / \text{THF} / \text{r.t.}$	53 %	<i>Org. Lett. 2000, 2, 2101</i>
	 $/ \text{CsF} (0.1 \text{ eq}) / \text{DME} / \text{r.t.}$	68 %	<i>Angew. Chem. Int. Ed. 2003, 42, 3133</i>

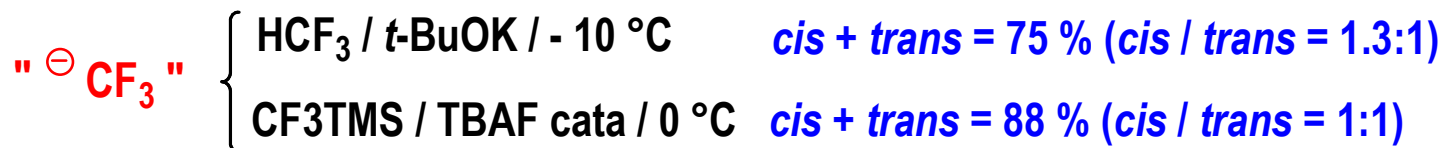
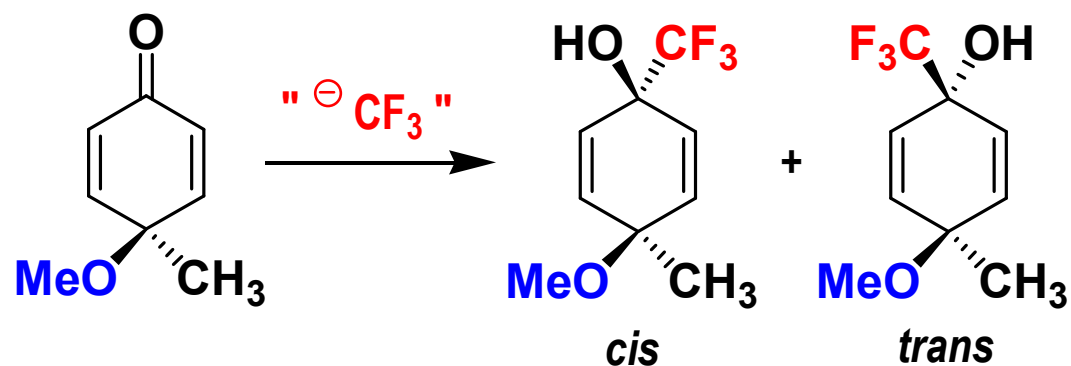
Indenes from Chalcones. 2nd Step



TFMB from Phenols. 1st Step

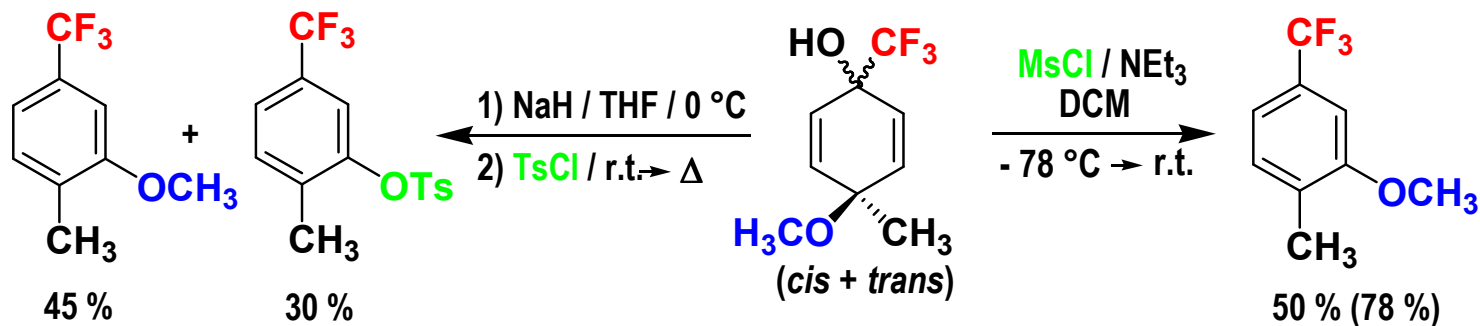


Mc Killop et al. *Perkin Trans.* 1994, 2047

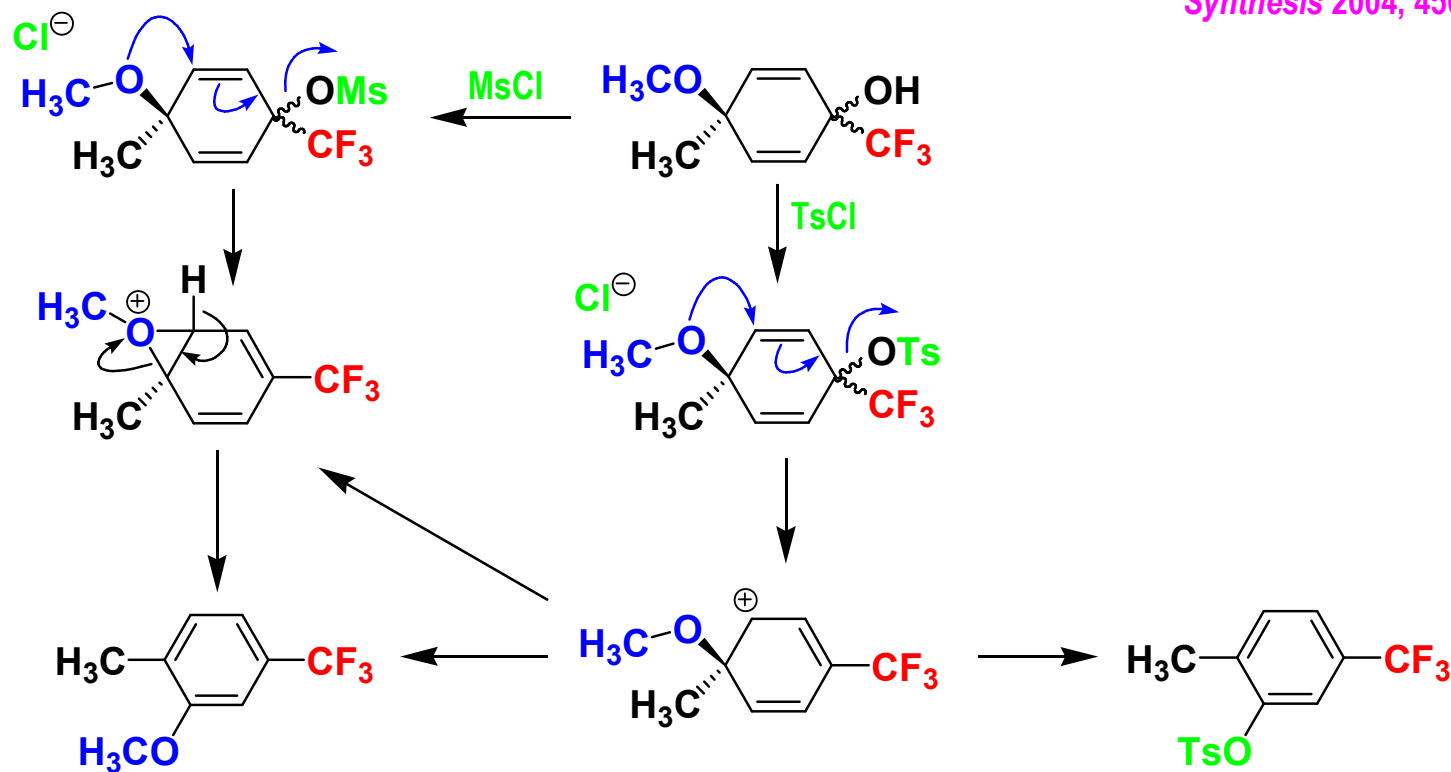


J. Org. Chem. 2000, 65, 8848

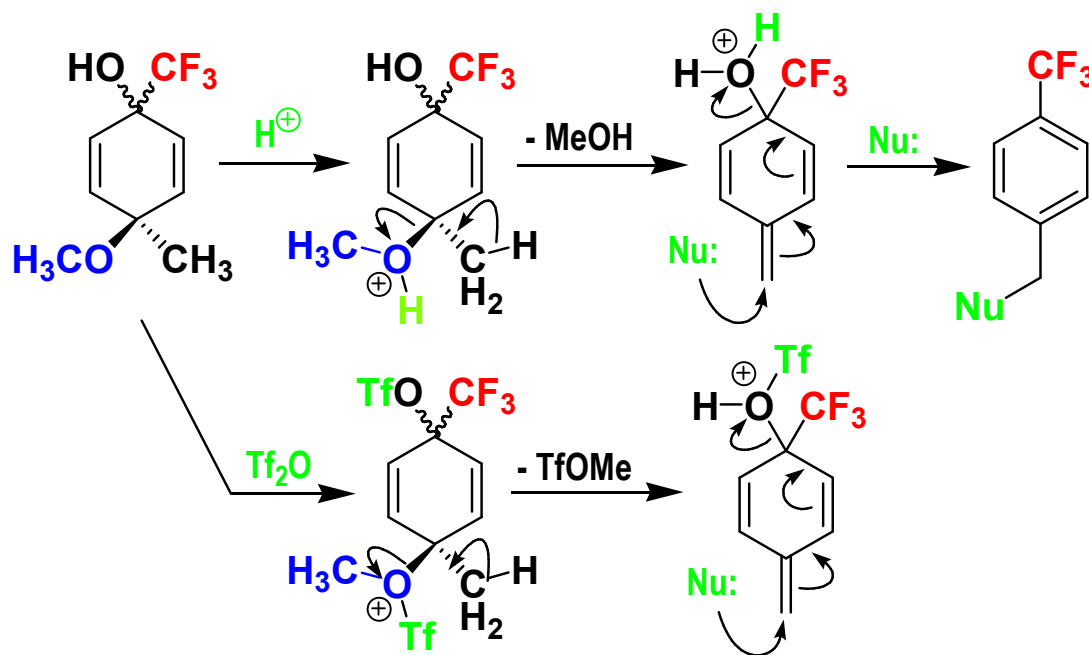
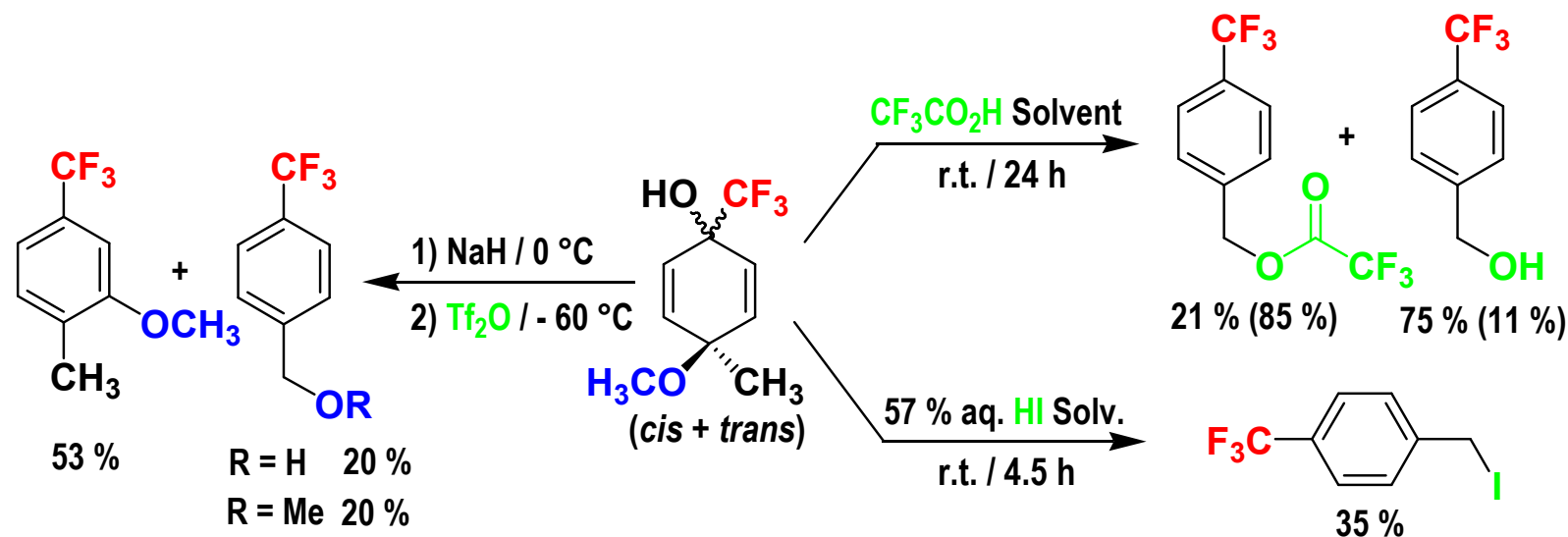
TFMB from Phenols. 2nd Step



Synthesis 2004, 456



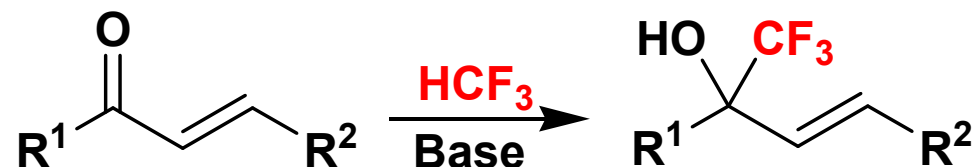
TFMB from Phenols. 2nd Step (cont'd)



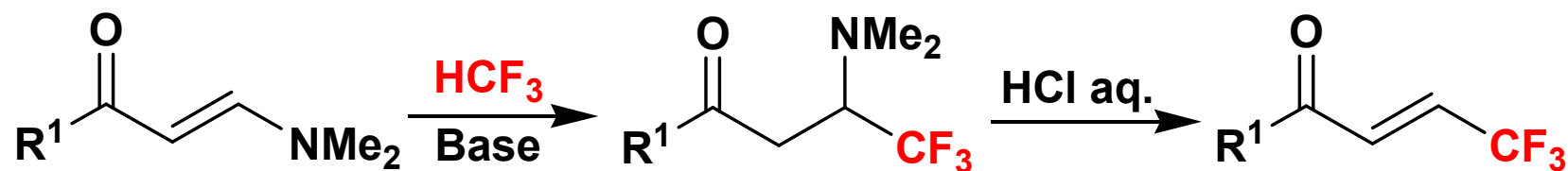
Synthesis 2004, 456

Synthesis of CF_3 -Enones. First Experiments

Usually :

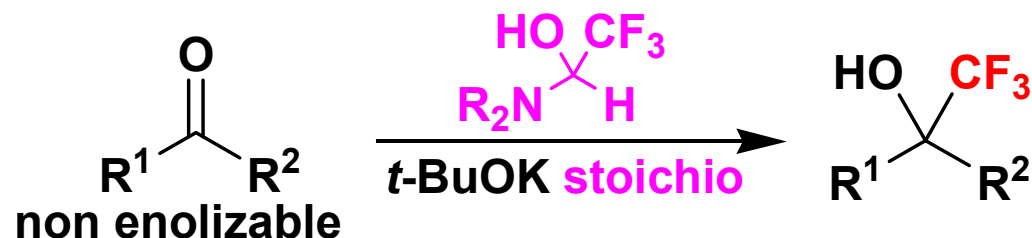


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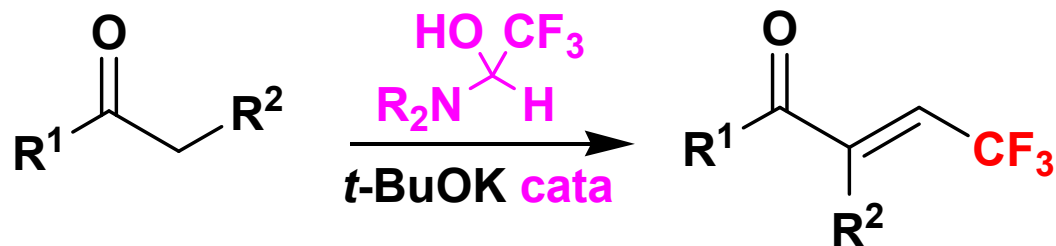


J. Org. Chem. 2000, 65, 8848

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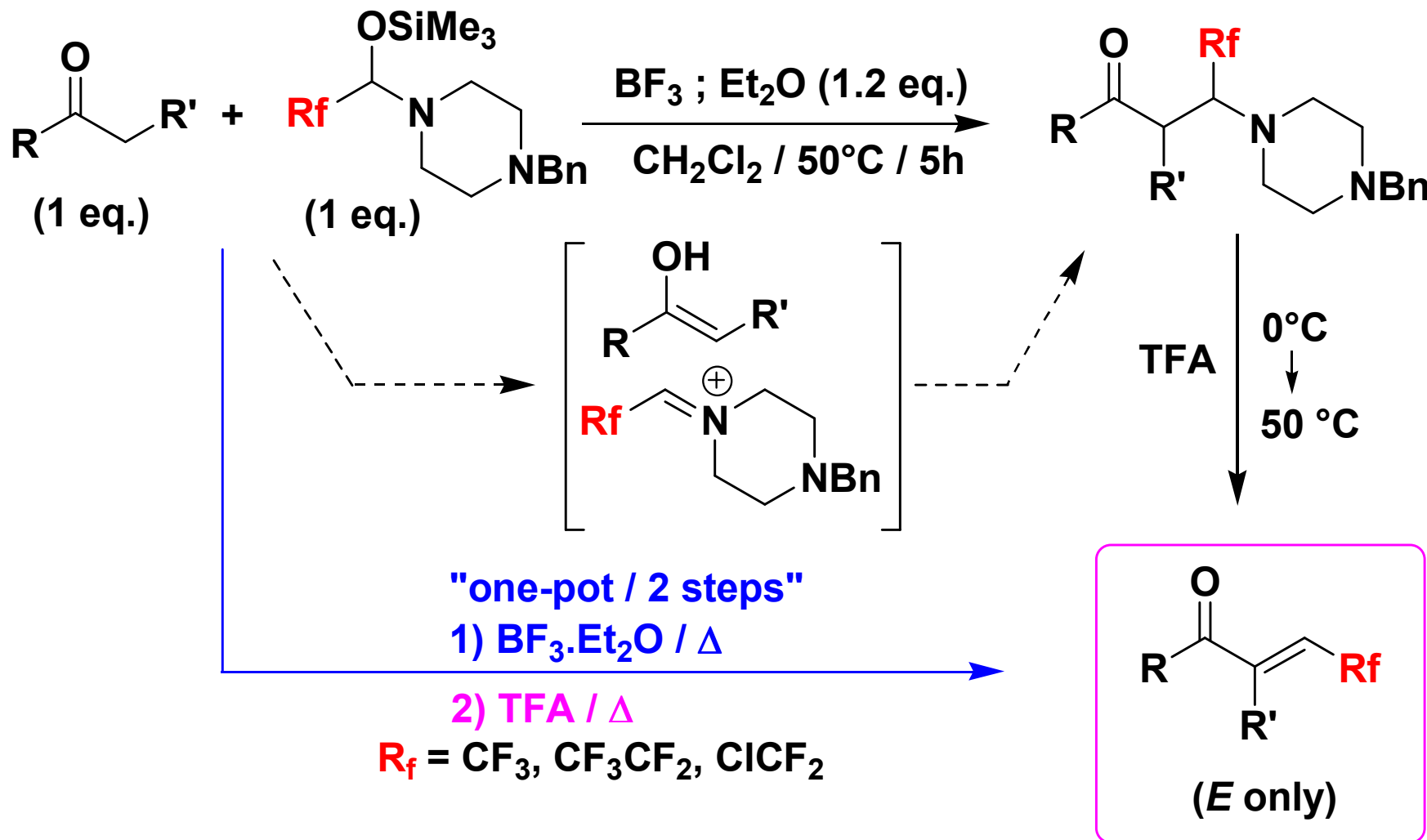


But :



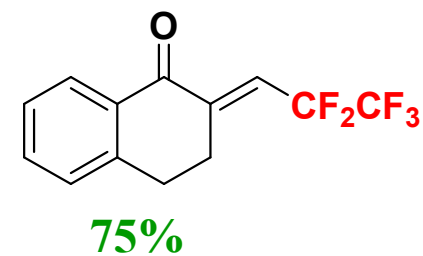
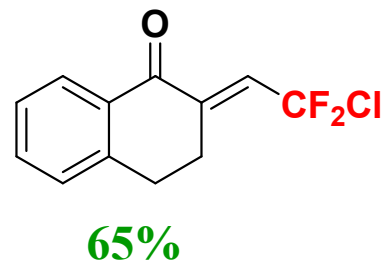
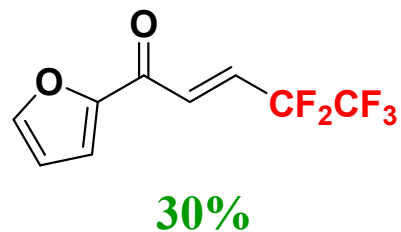
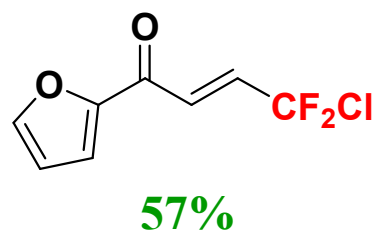
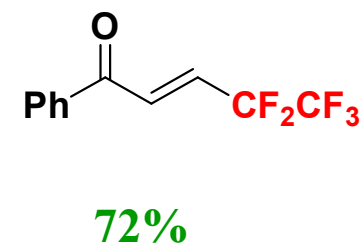
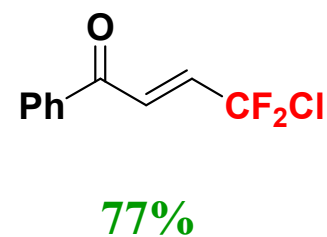
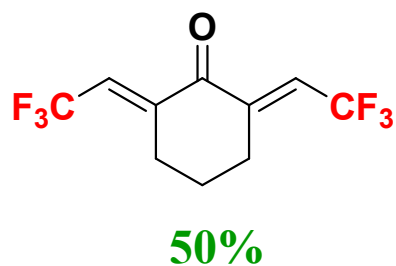
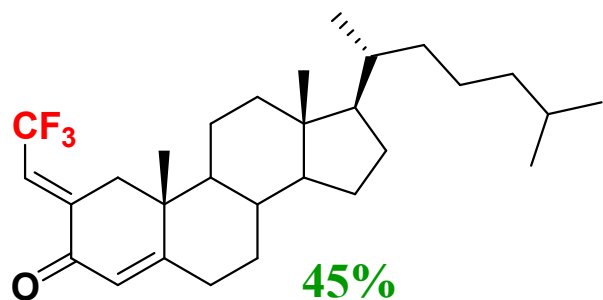
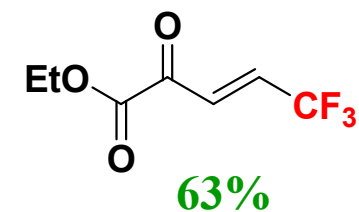
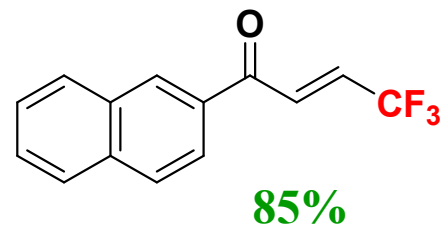
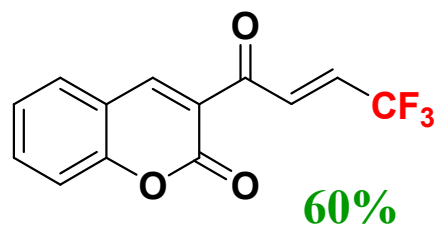
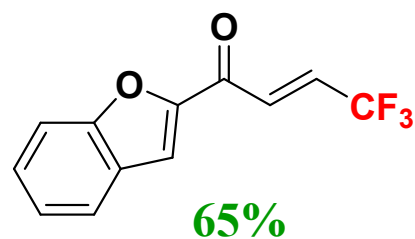
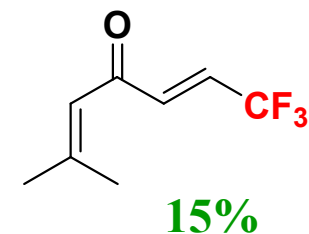
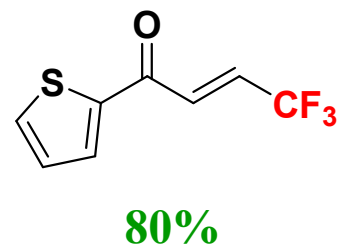
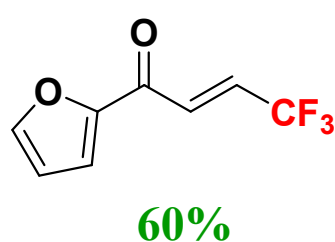
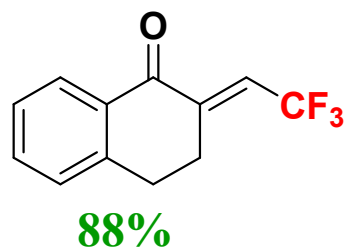
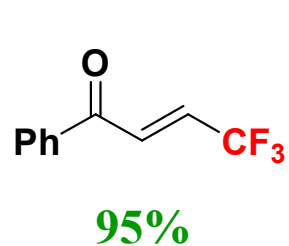
J. Org. Chem. 2001, 66, 4826

Synthesis of β -fluoroalkylenones

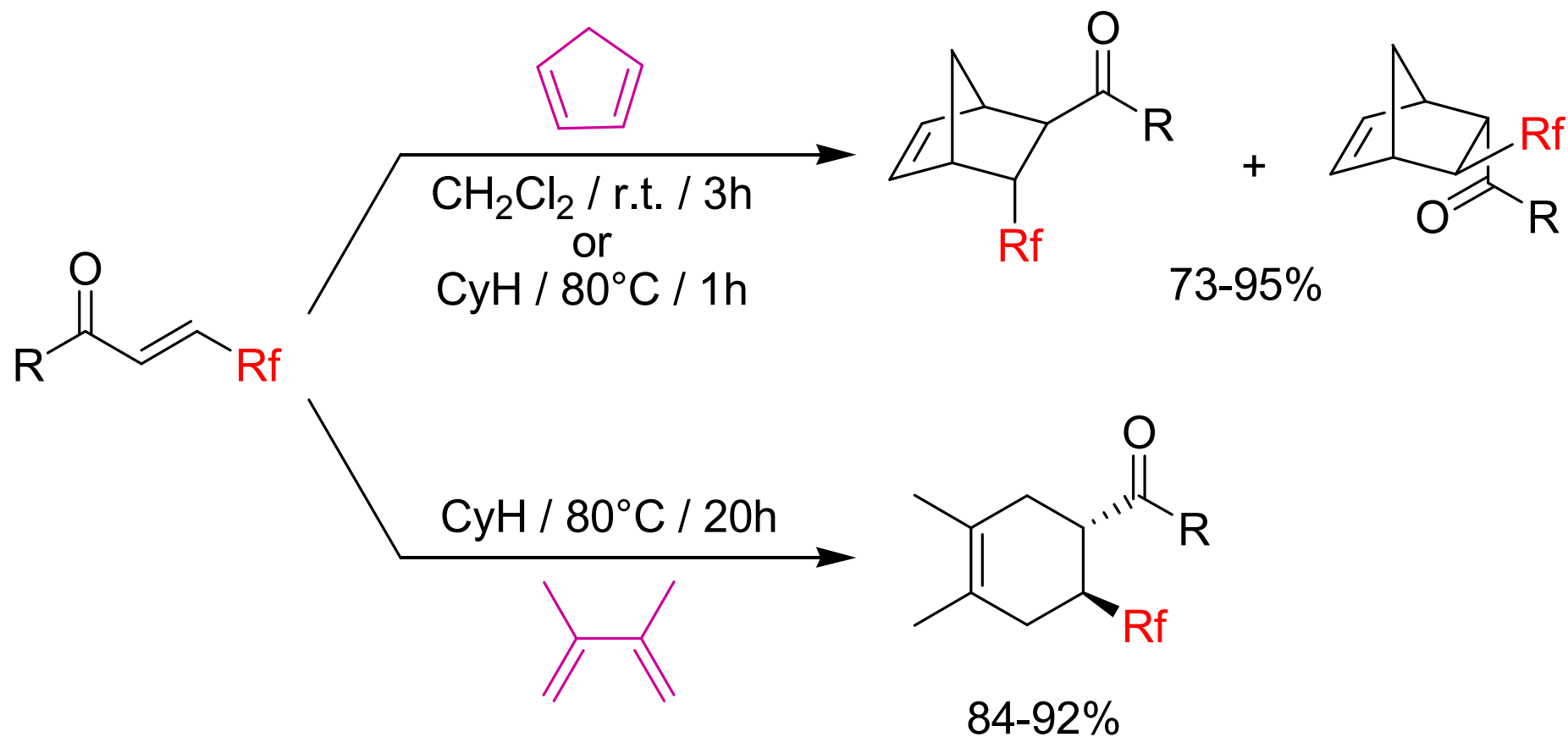


Simplest and shortest route to CF_3 -enones

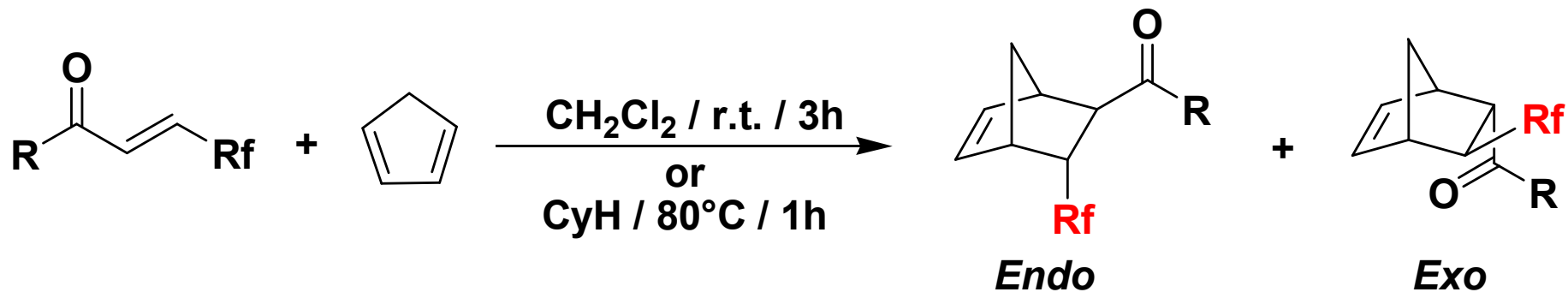
Synthesis of β -Fluoroalkyl Enones



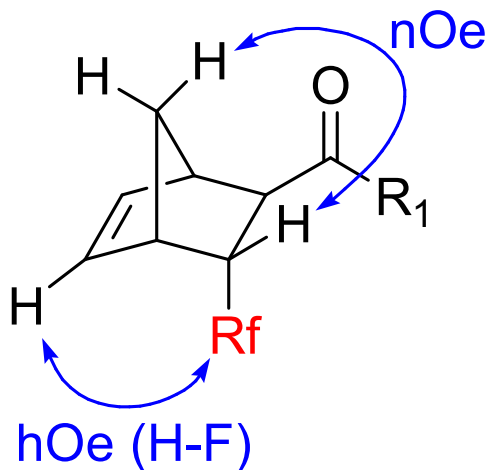
Diels-Alder Cycloadditions



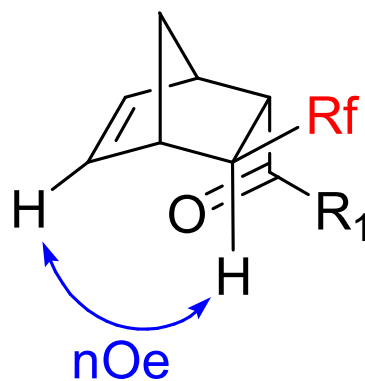
Diels-Alder Stereoselectivity : Role of R_f



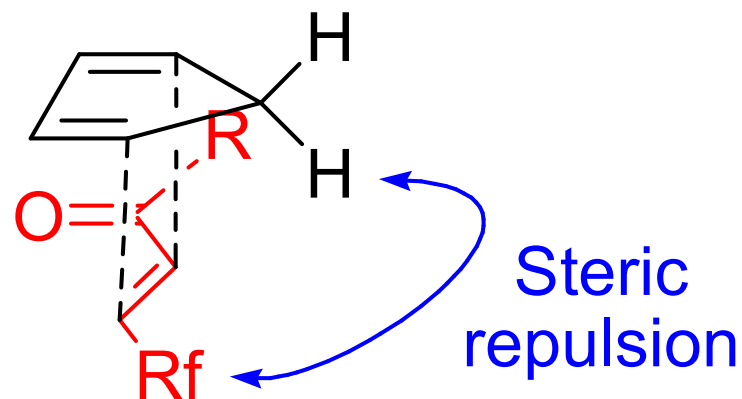
Endo / Exo : 75 / 25



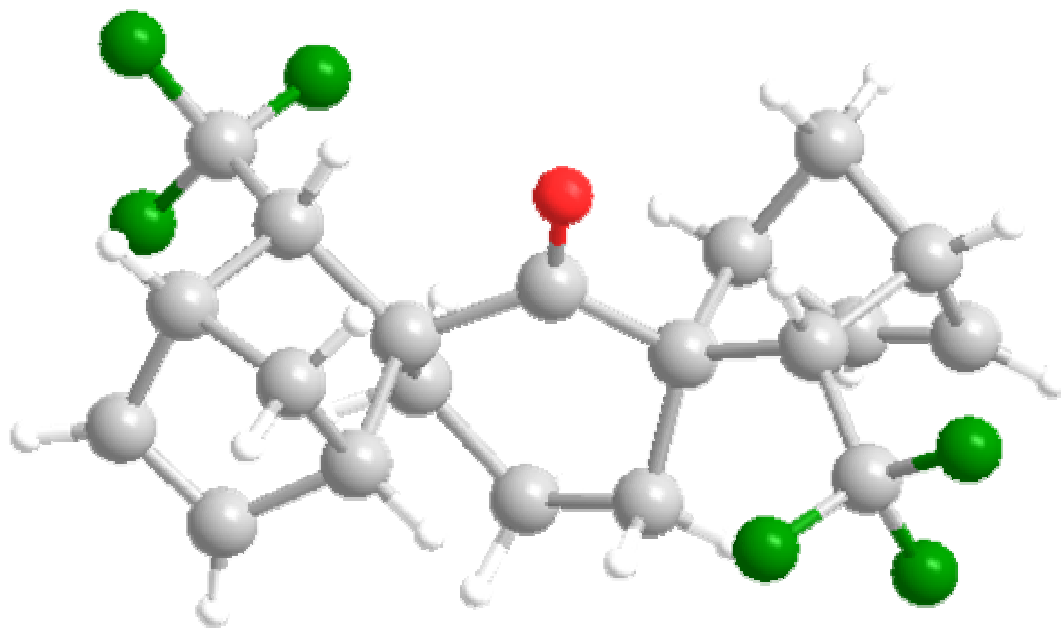
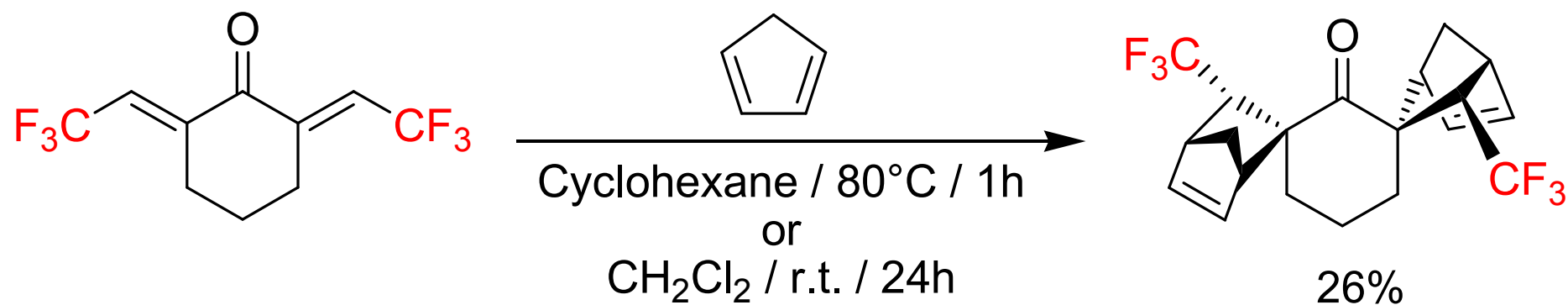
Endo



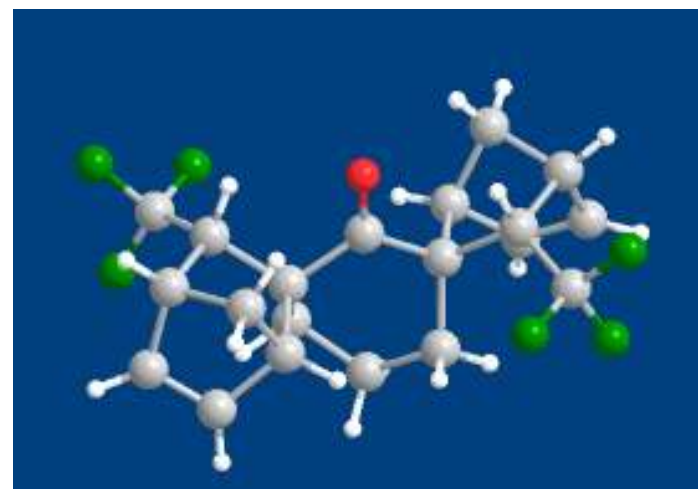
Exo



Diels-Alder Cycloadditions

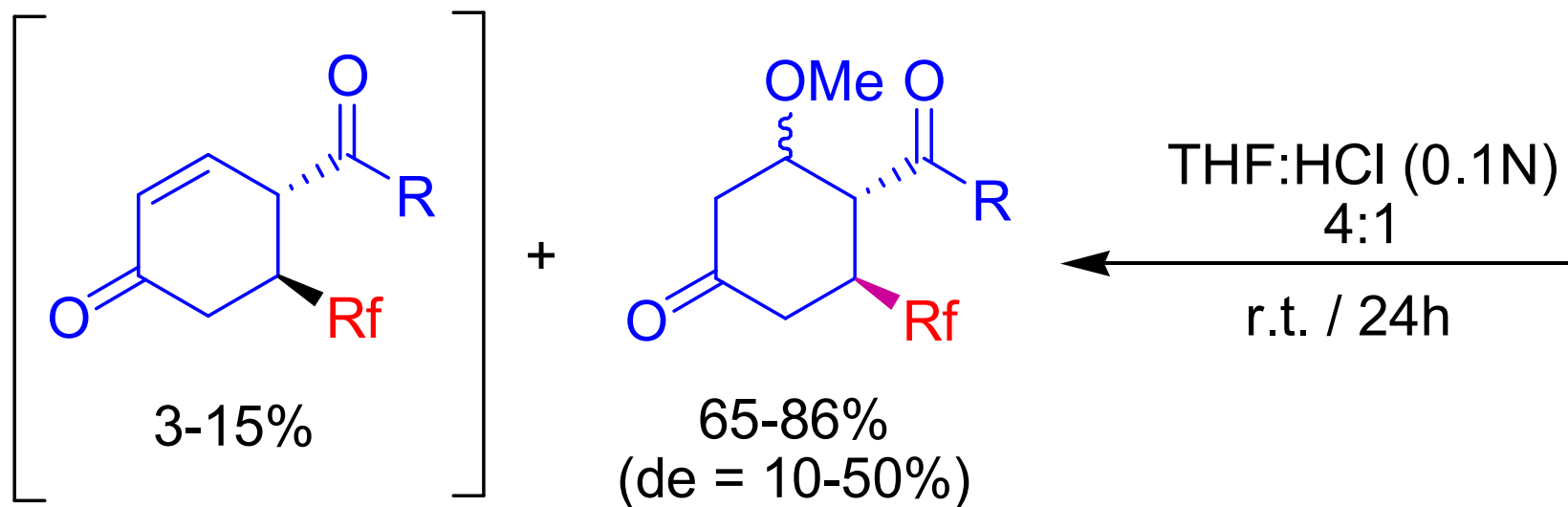
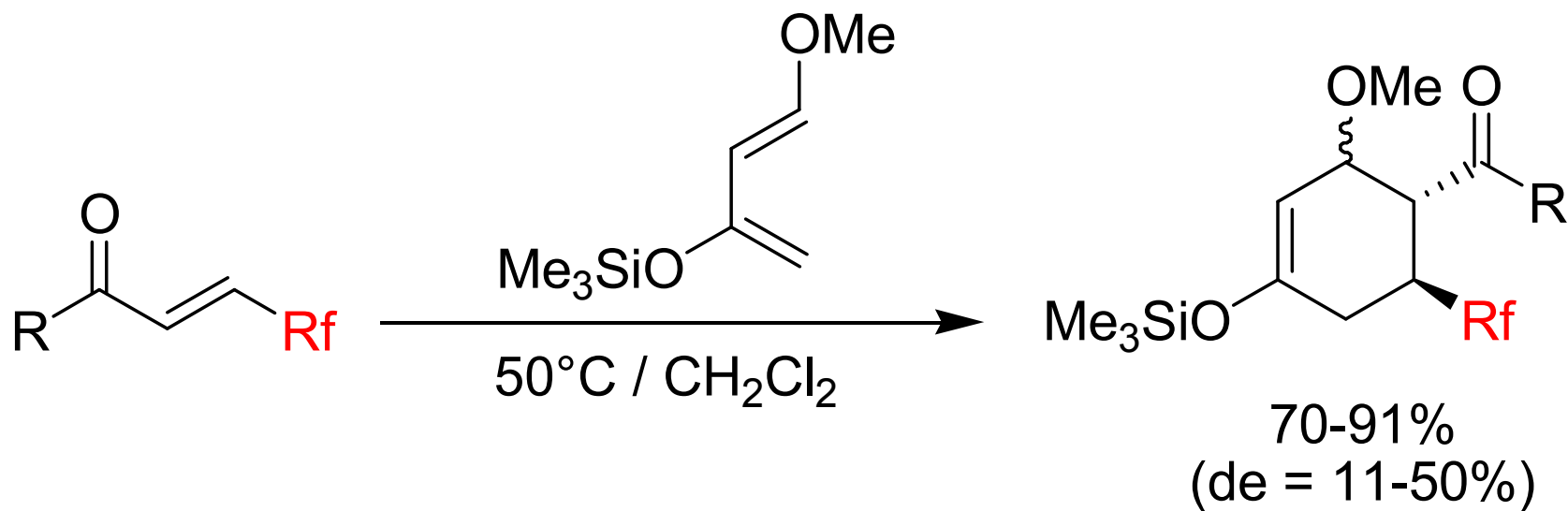


X-Ray Structure

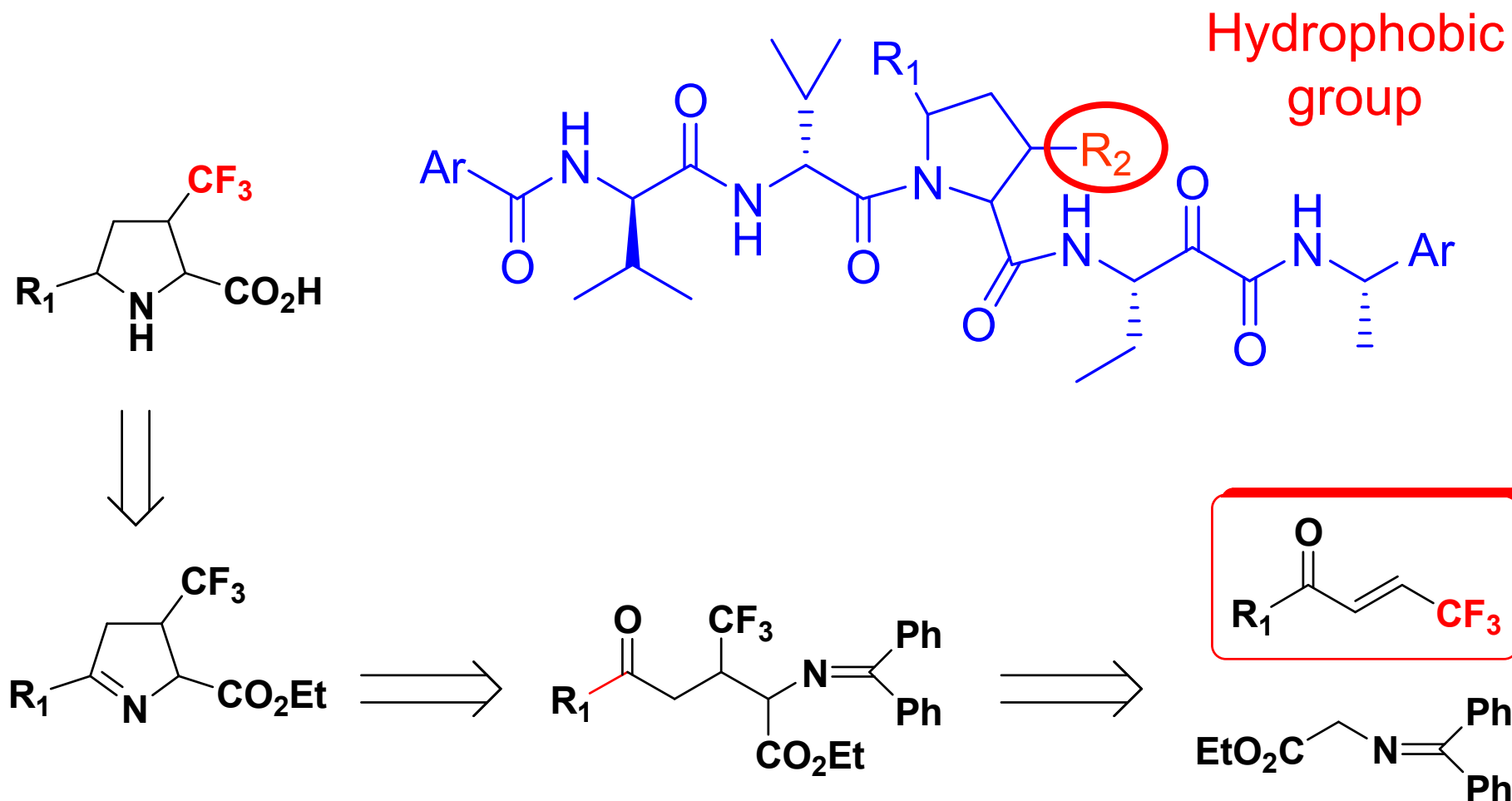


J. Org. Chem. 2006, 71, 2735.

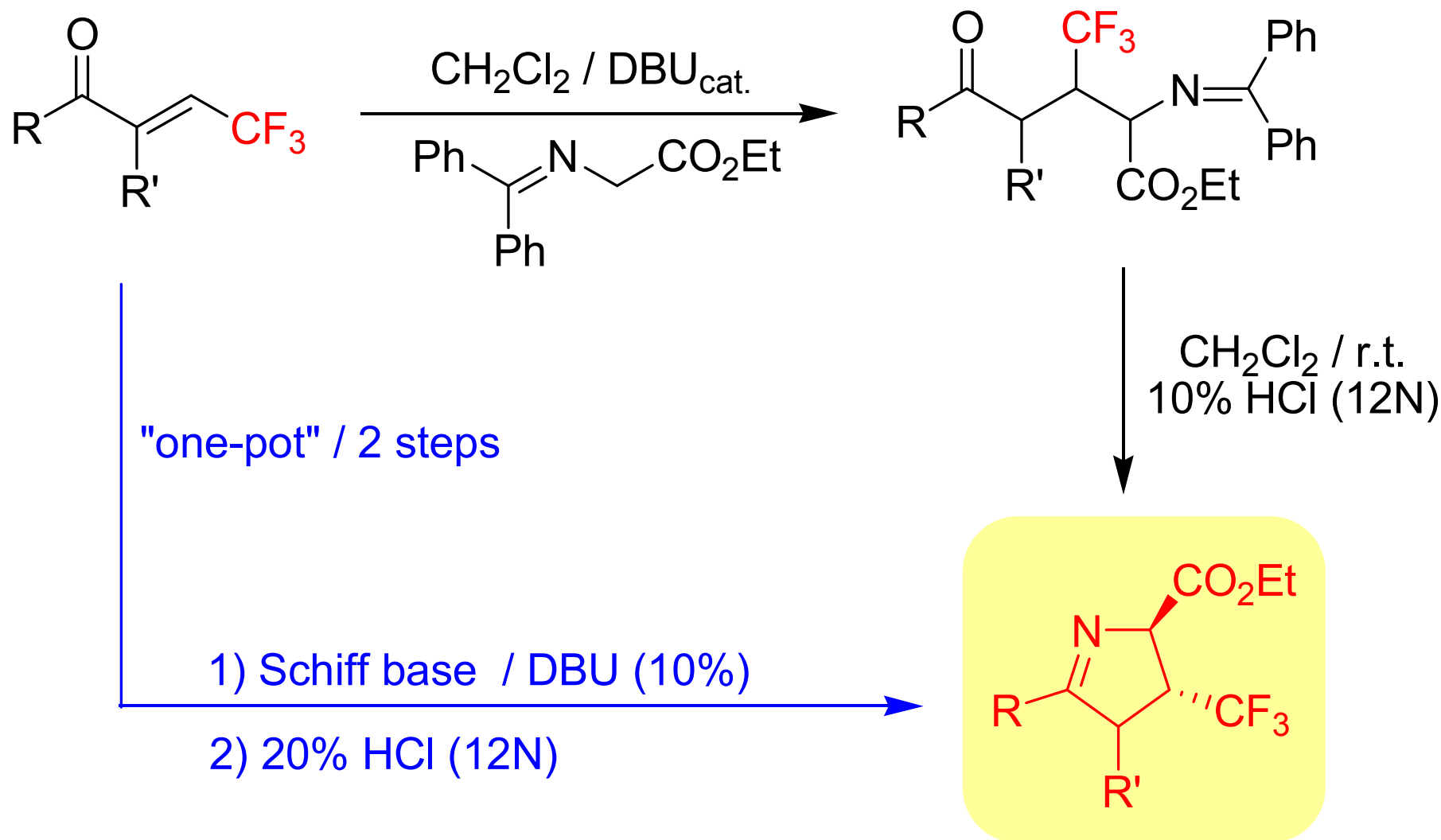
Diels-Alder Cycloadditions



Synthetic application : Inhibitors of Hepatitis C Virus NS3-4A Protease.

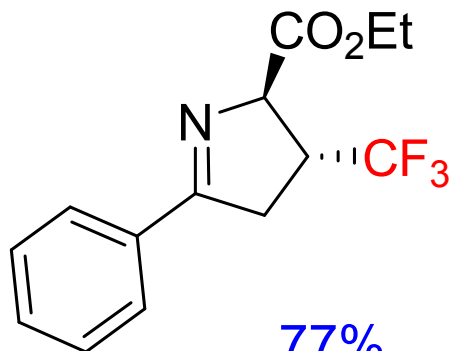


Synthesis of Proline Derivatives

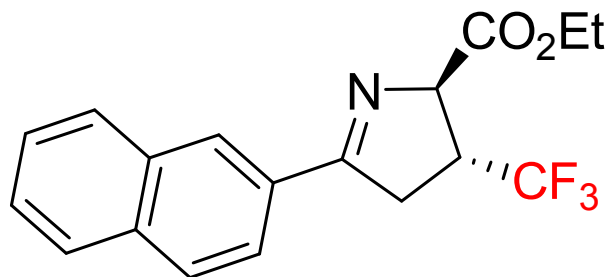


Unpublished

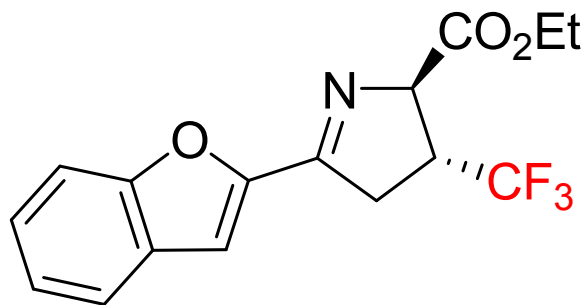
Synthesis of Proline Derivatives



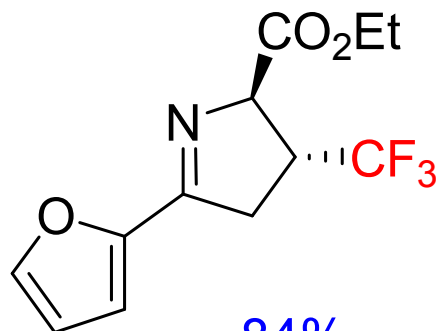
77%
(de = 77%)



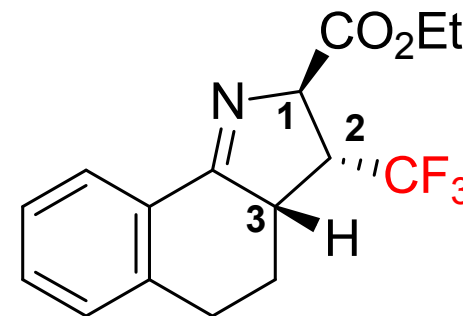
87%
(de = 74%)



71%
(de = 75%)



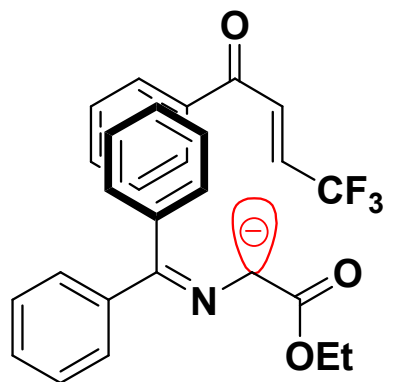
84%
(de = 80%)



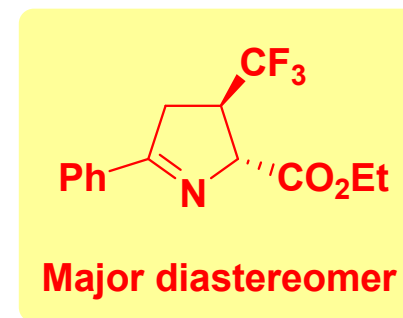
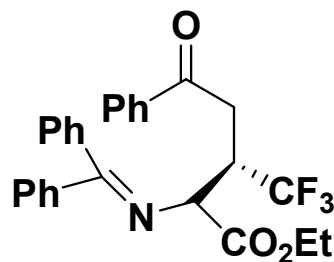
83%
(de [1-2] > 95%)
(de [2-3] = 47%)

Unpublished

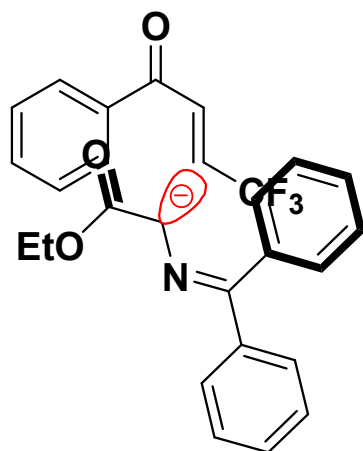
Synthesis of Proline Derivatives



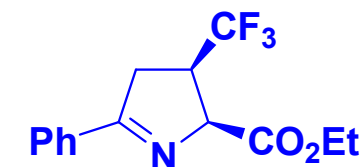
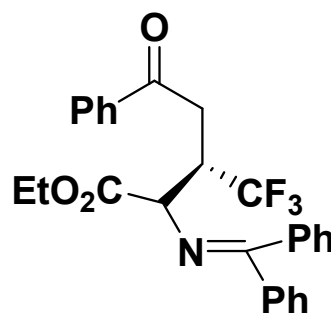
Favored
(π -stacking interaction)



Major diastereomer



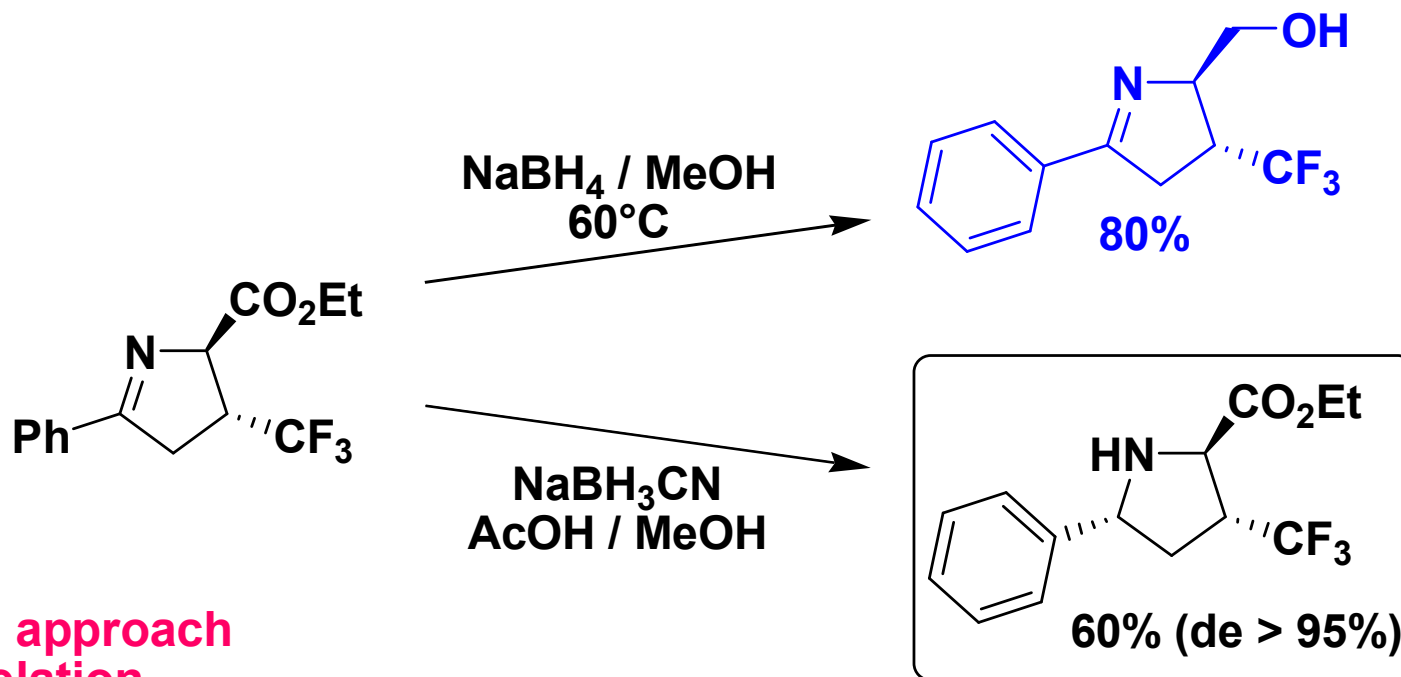
Unfavored



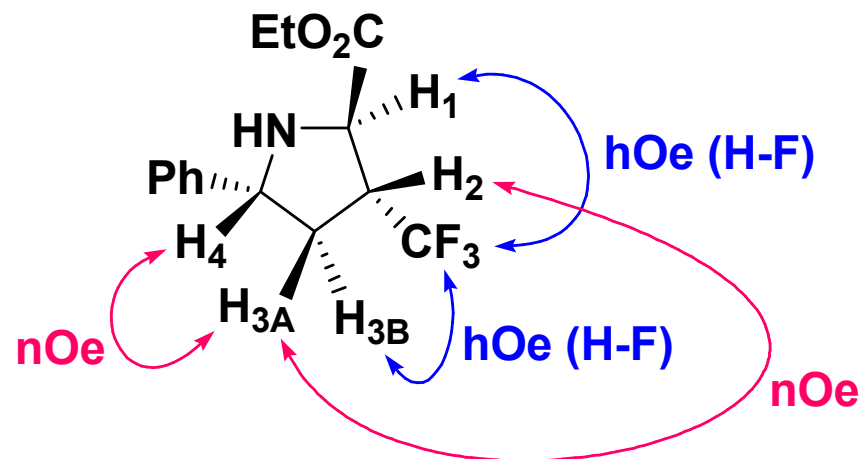
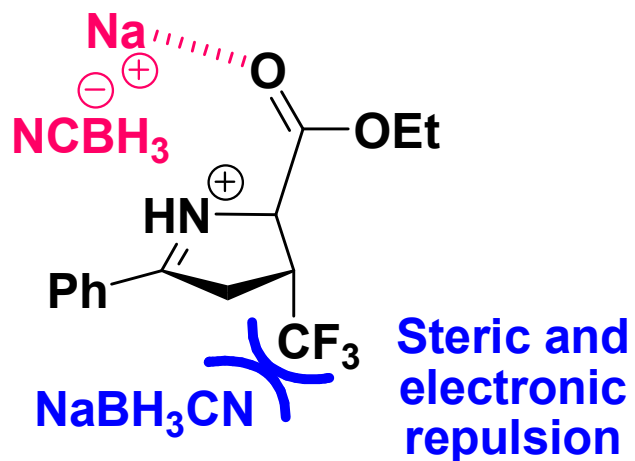
Minor diastereomer

Unpublished

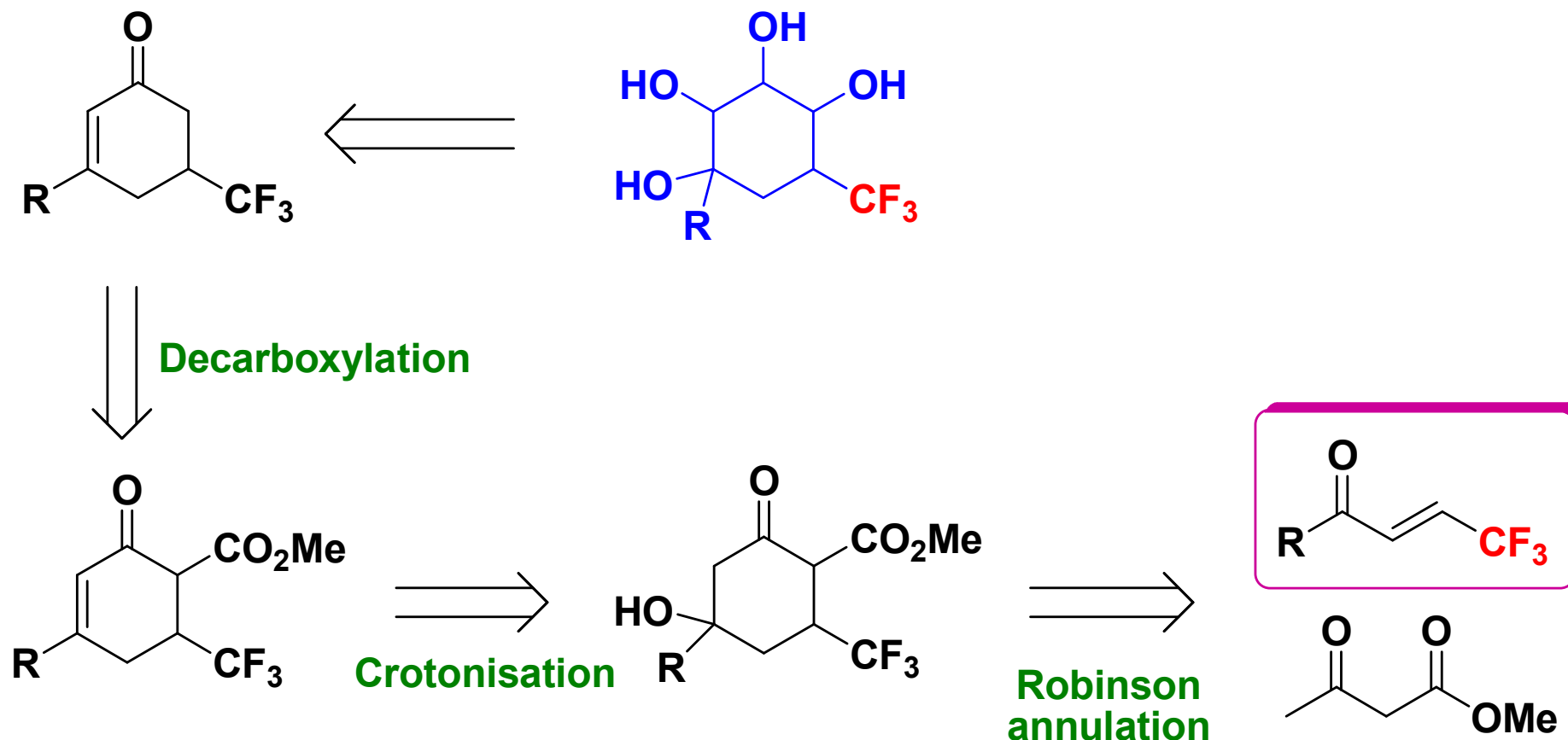
Synthesis of Proline Derivatives



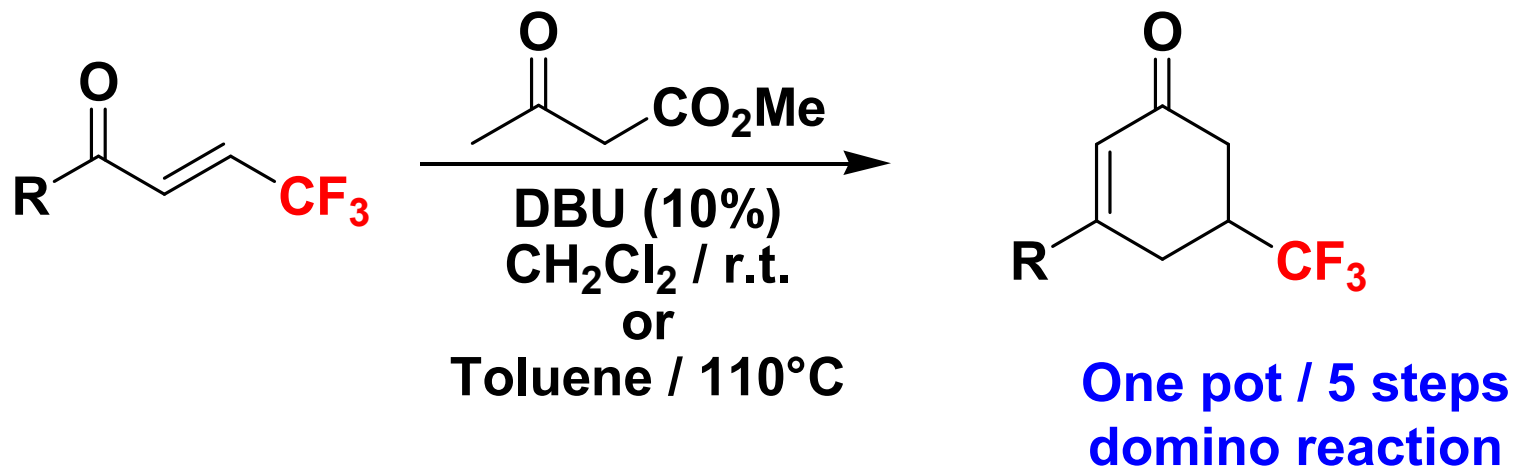
Favorised approach
by chelation



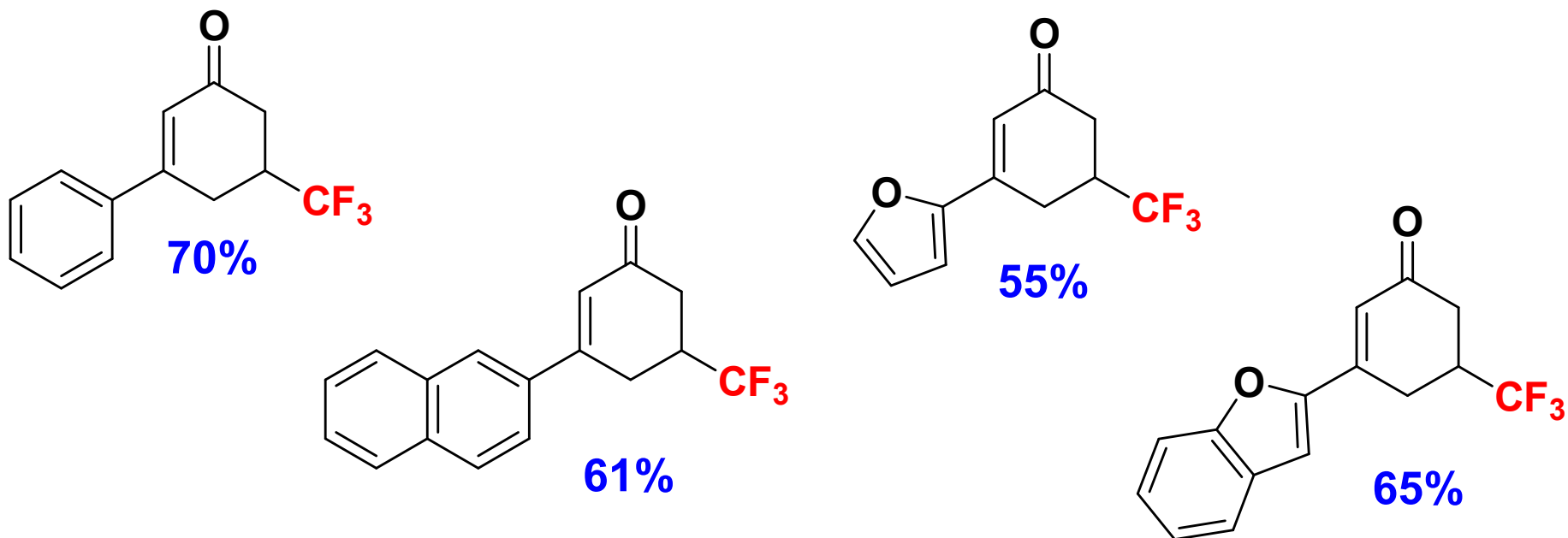
Synthetic application : Synthesis of Trifluoromethylated Cyclitols.



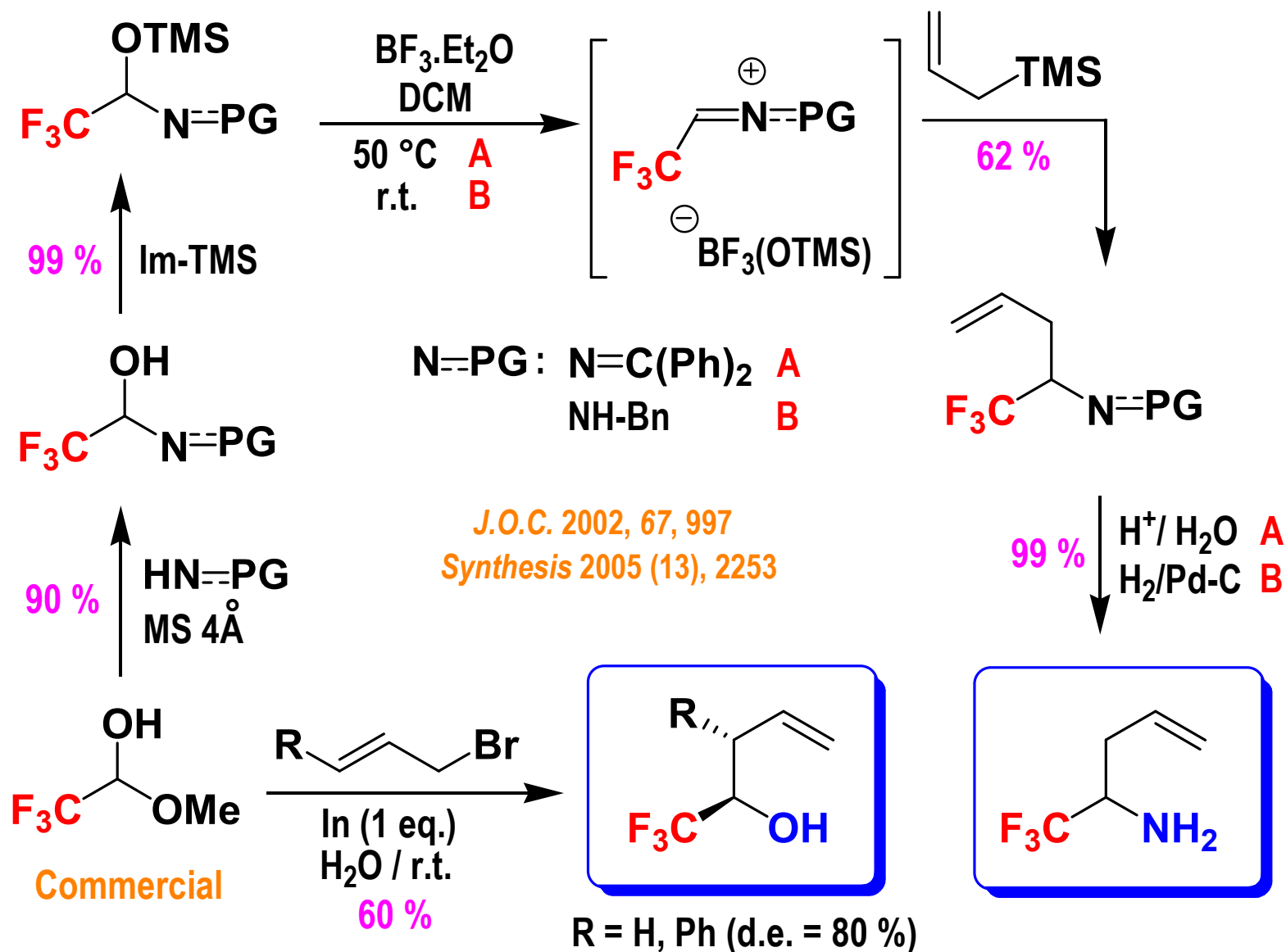
Synthesis of Cyclohexenones



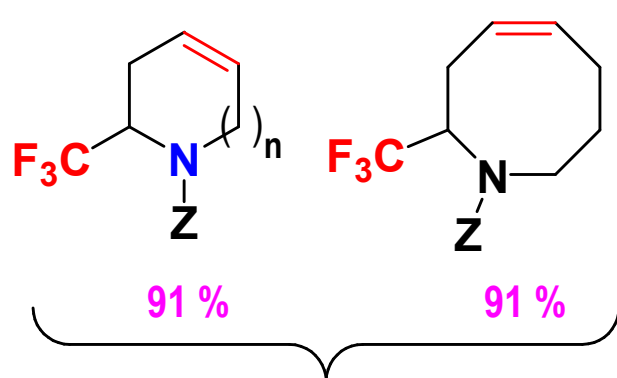
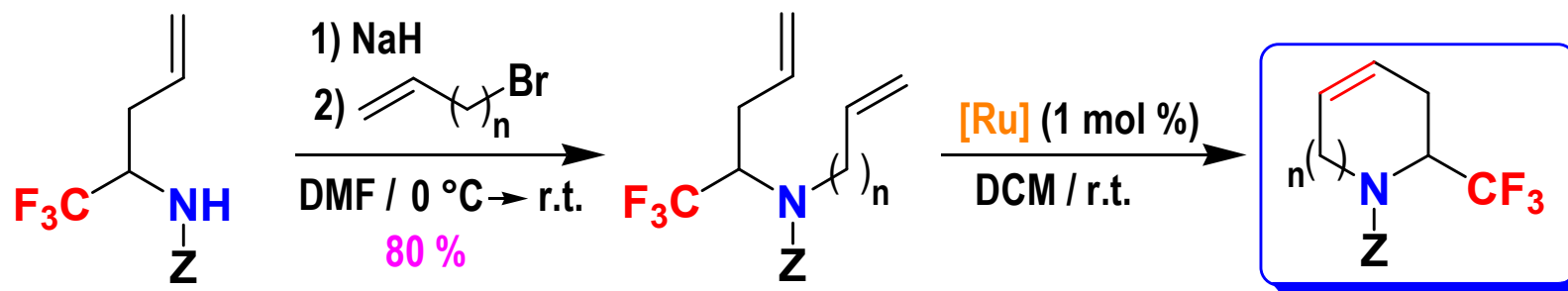
Eur. J. Org. Chem. 2005, 3745



α -CF₃-Allylamine and allyl alcohol

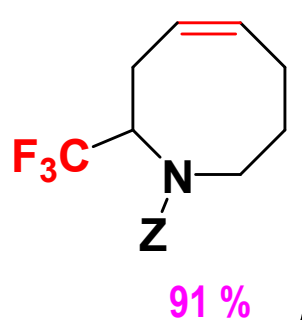


RCM from α -CF₃-Allylamine Derivatives (1)



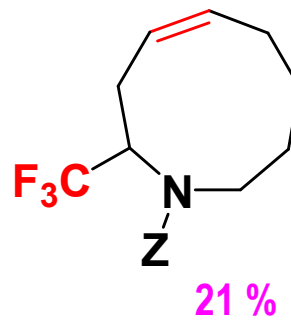
91 %

Grubbs I

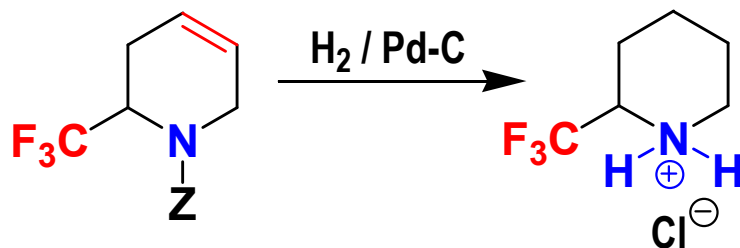
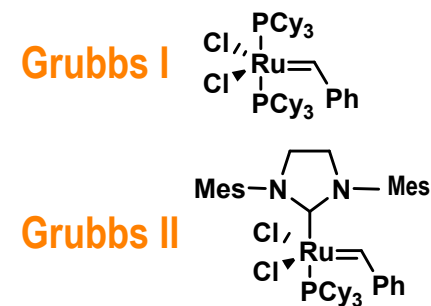


91 %

Grubbs II



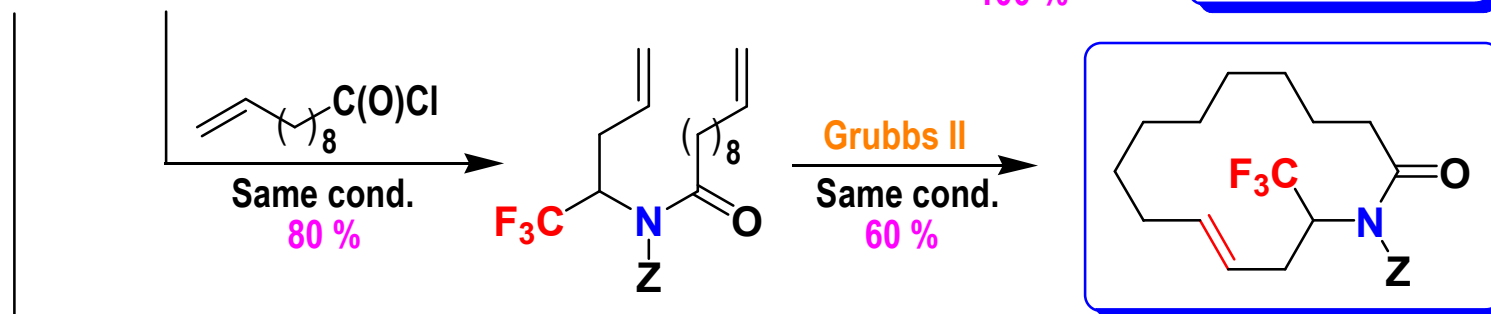
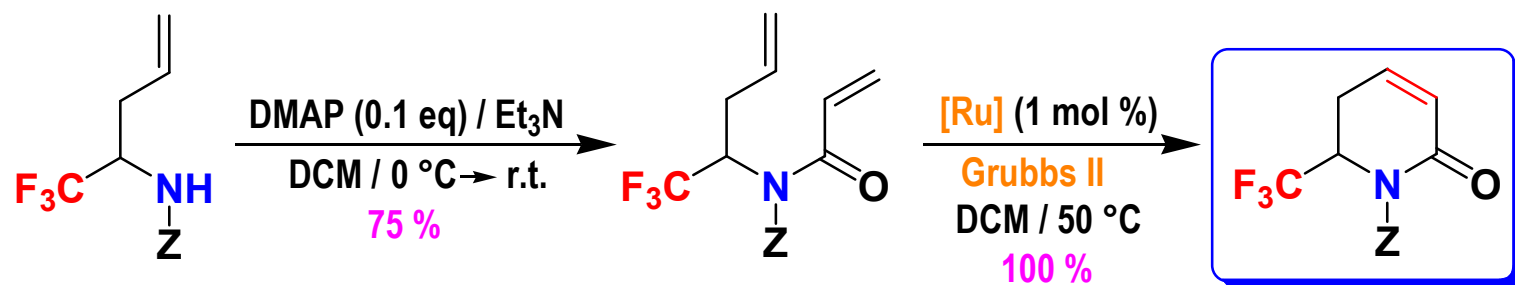
21 %



Pipecoline analog
(neurology, obesity)

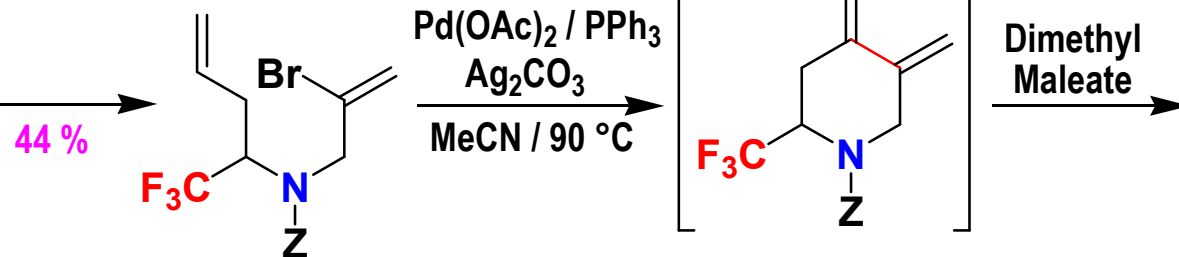
J.O.C. 2003, 68, 8932

RCM from α -CF₃-Allylamine Derivatives (2)

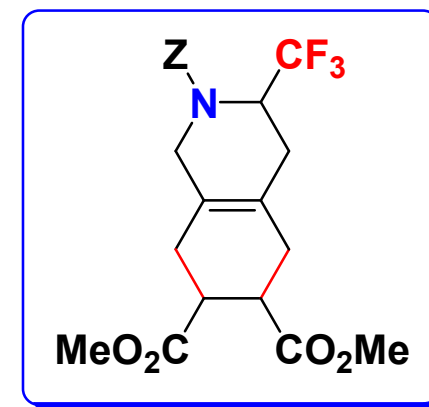


J.O.C. 2003, 68, 8932

- 1) NaH/ DMF/ 0 °C
- 2) Bu₄Ni cat./ r.t.
- 3) CH₂=C(Br)CH₂Br
90 °C

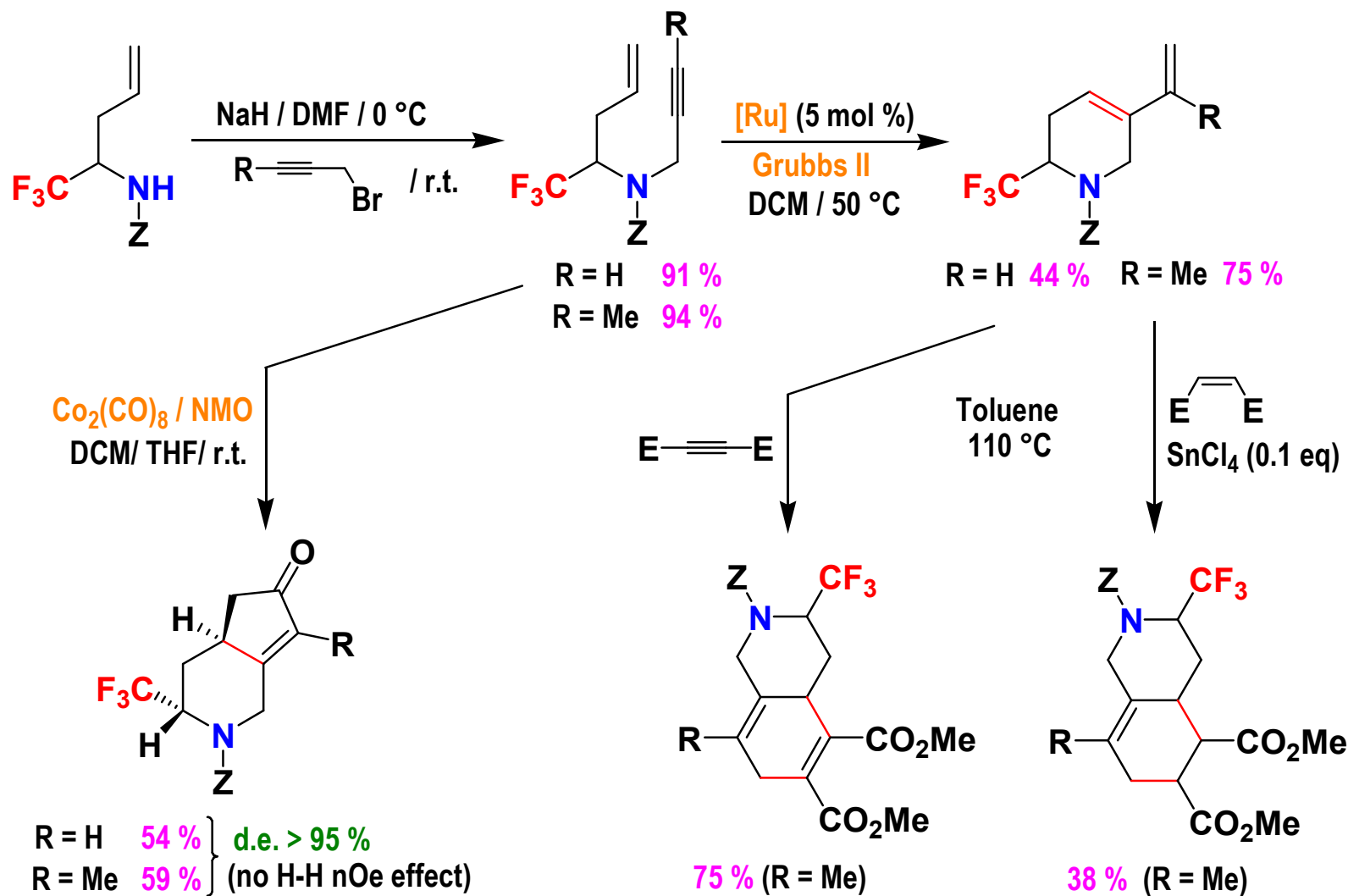


Synlett 2005, 1027

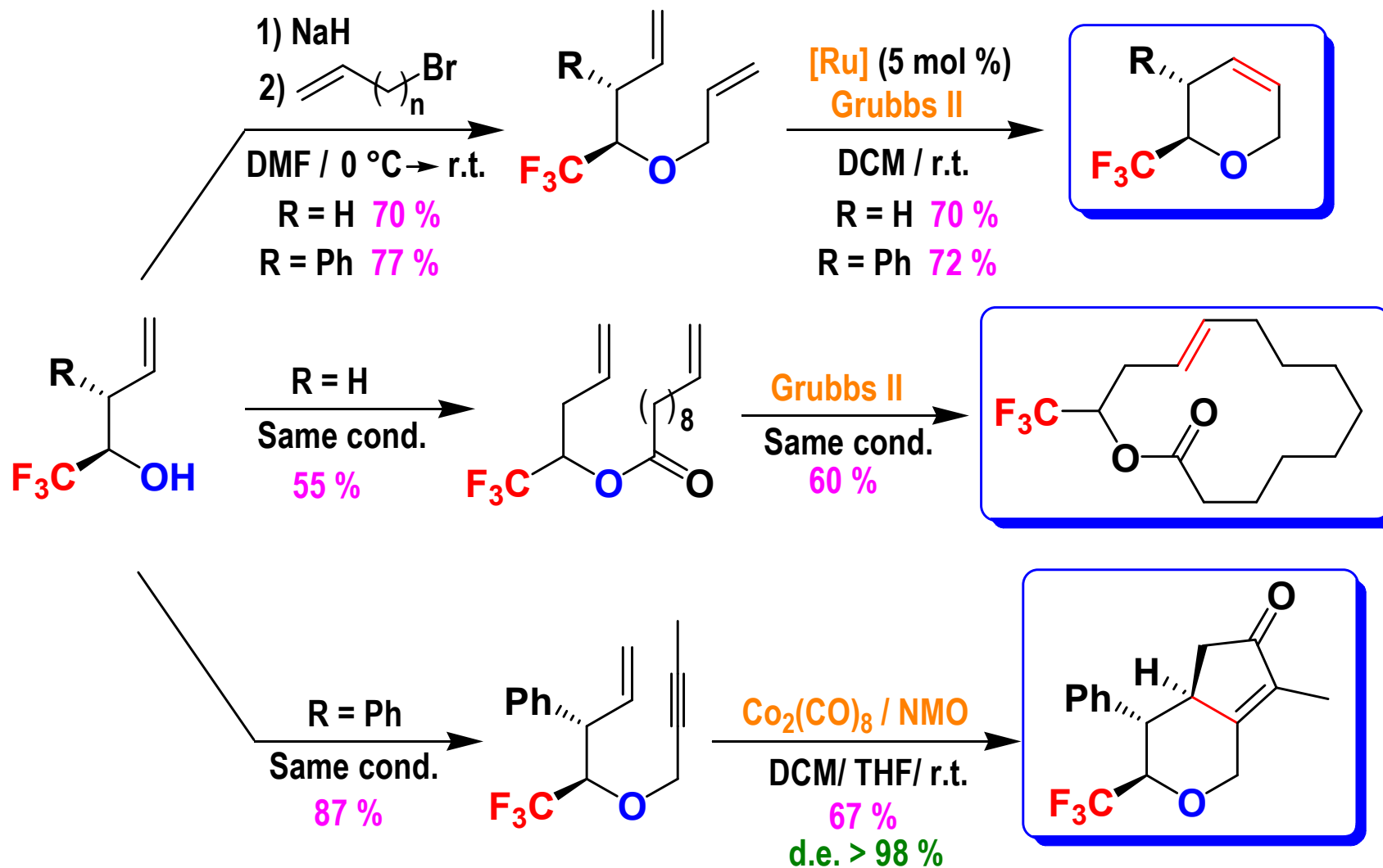


global yield : 27 %

RCM from α -CF₃-Allylamine Derivatives (3)



RCM from α -CF₃-Allyl alcohol Derivatives



Acknowledgements



Pr Günter HAUFE



Dr Thierry BILLARD



**Julia
LEUGER**

**Sékolène
GILLE**

**Aurélien
FERRY**



**Carole
CHRISTOPHE**

**Audrey
BARTHELEMY**

**Stéphanie
KUCHARSKI**

**Steven
HARTONG**

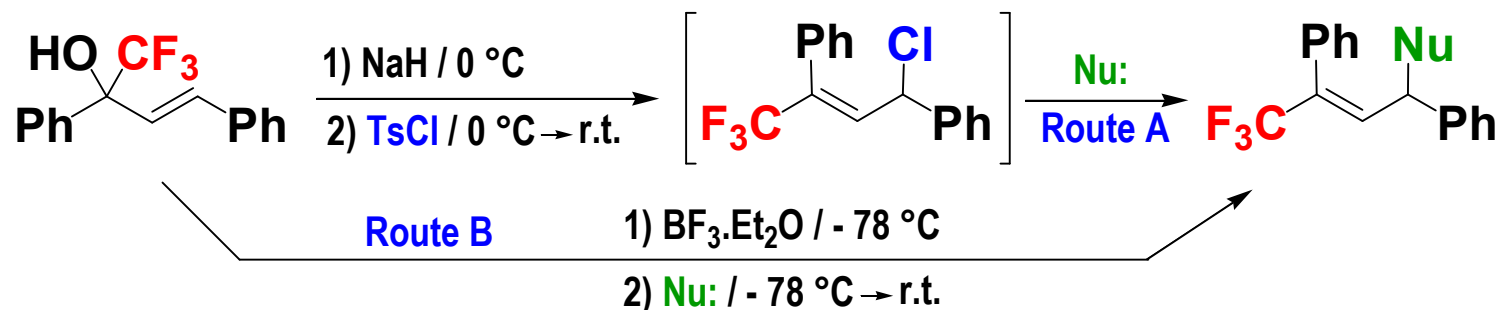


**Dr Gaëlle
BLOND**

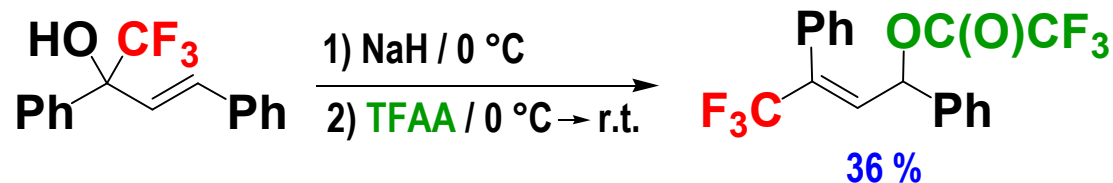


**Dr Sylvie
RADIX-LARGE**

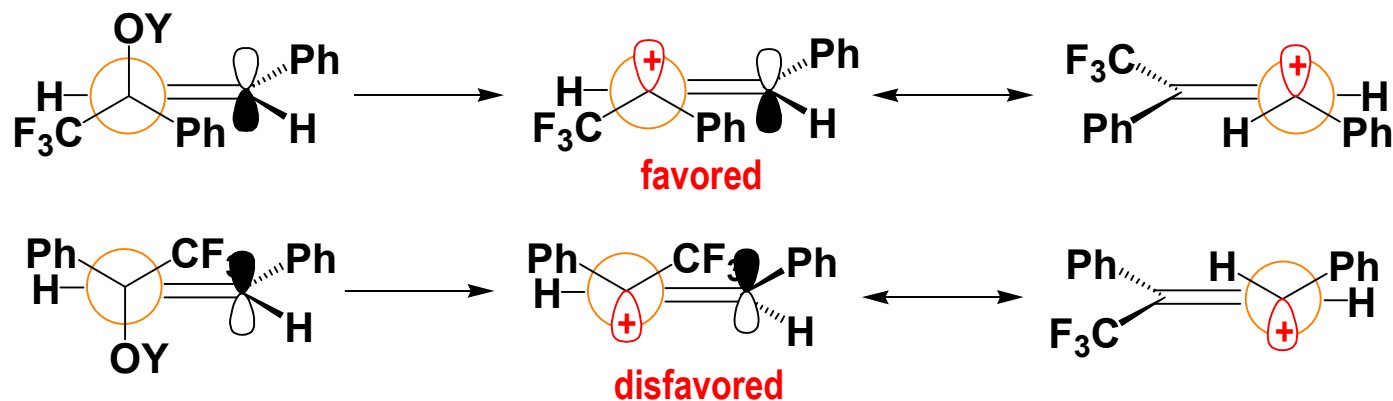
Indenes from Chalcones. 2nd Step



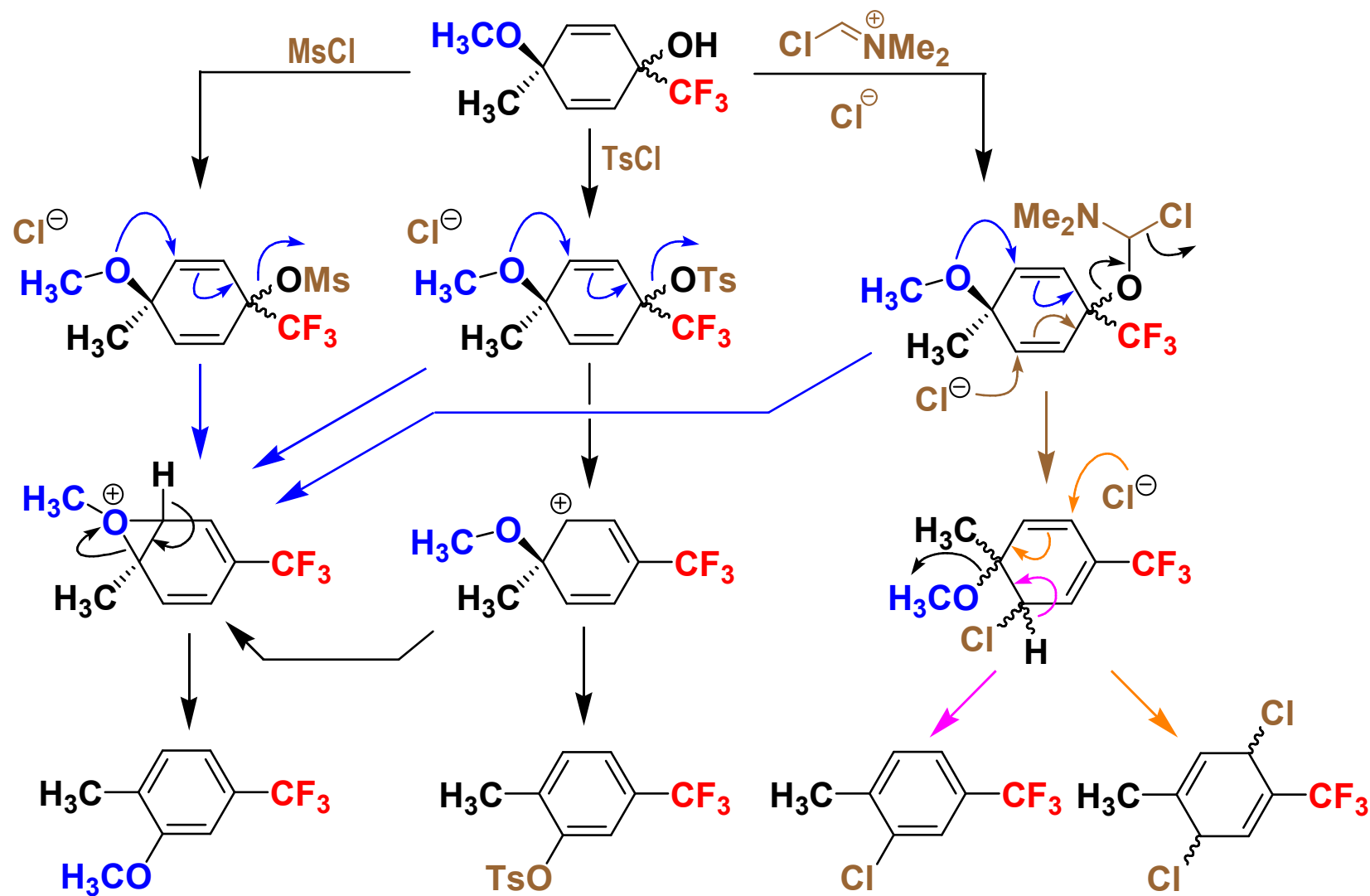
Nu: = $\text{C}_8\text{H}_{17}\text{SH}$ (A: 61 %, B: 100 %), PhCH_2OH (A: 40 %), NaN_3 (B: 22 %)



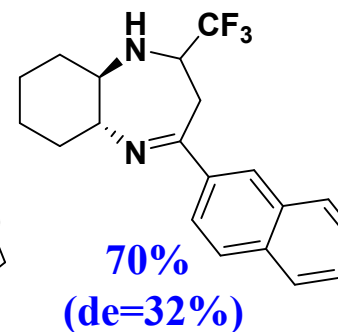
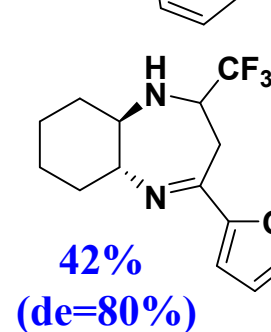
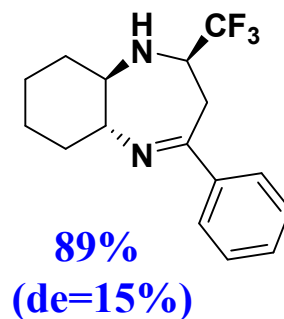
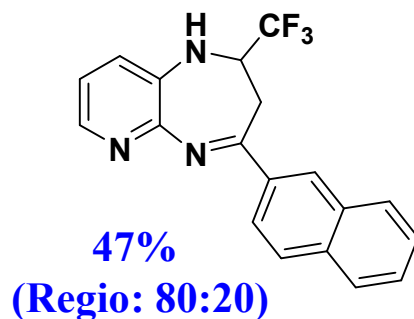
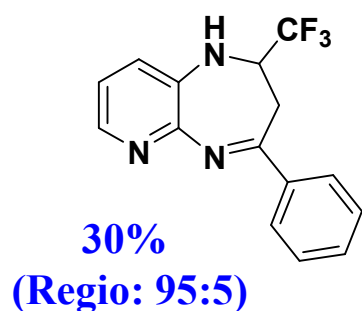
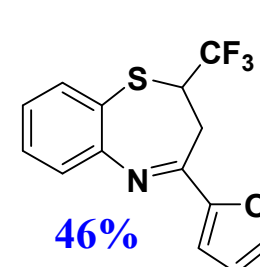
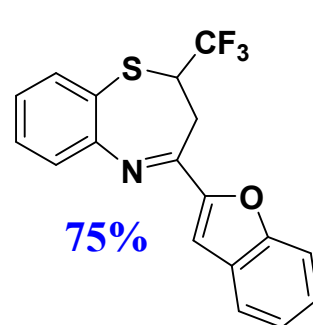
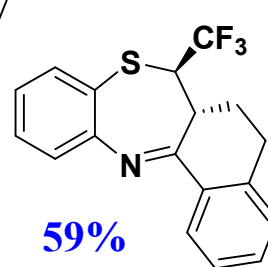
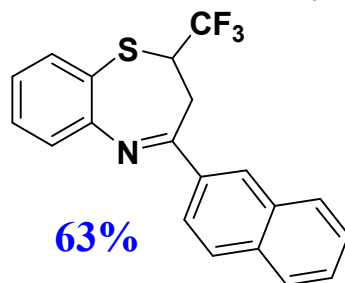
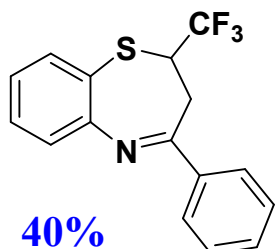
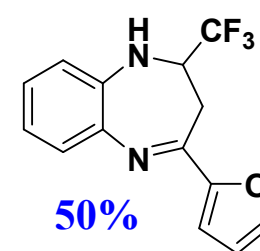
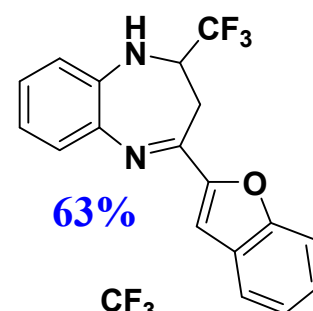
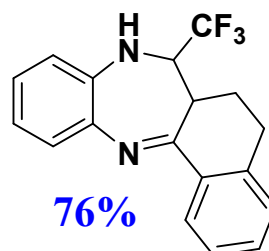
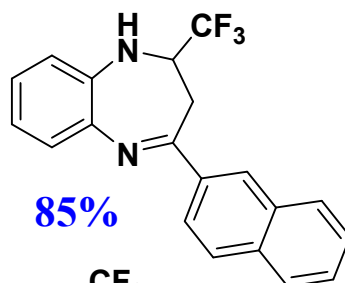
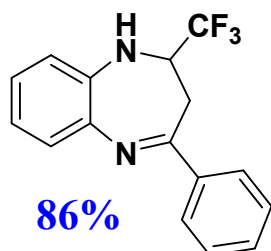
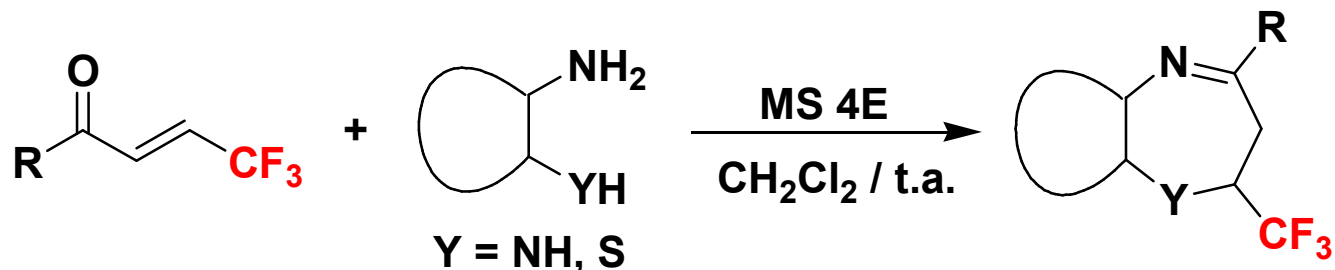
Synthesis 2004, 456



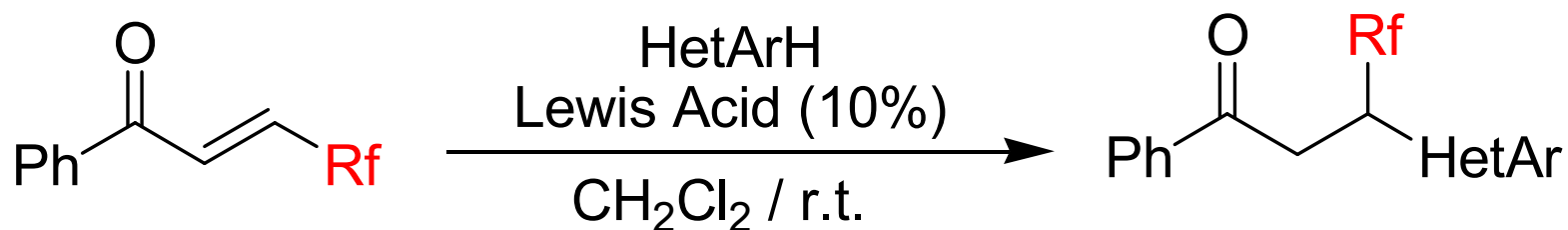
TFMB from Phenols. 2nd Step (cont'd)



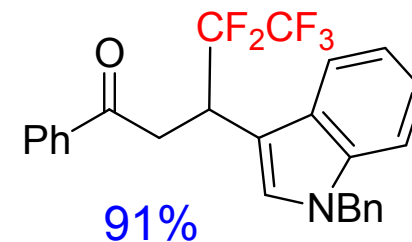
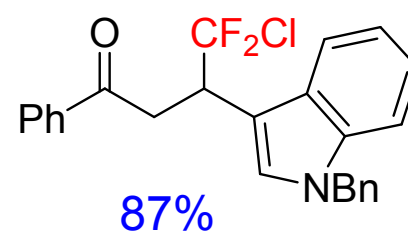
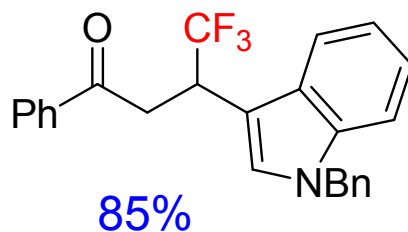
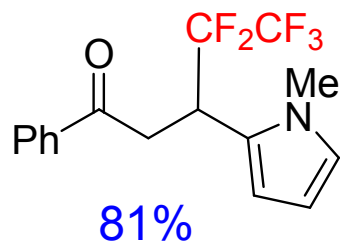
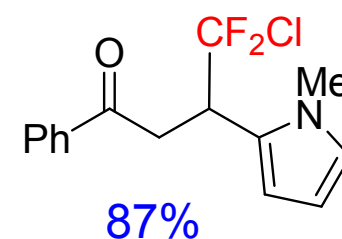
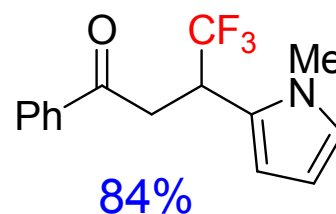
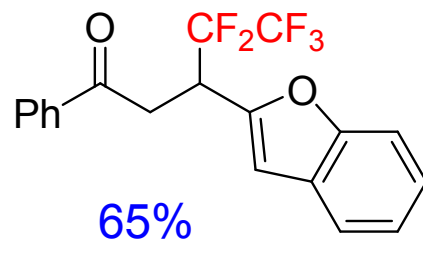
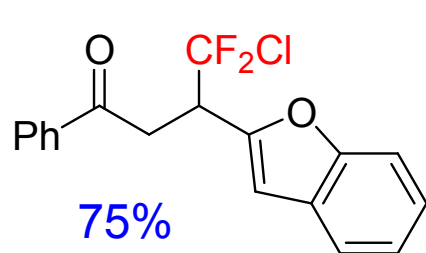
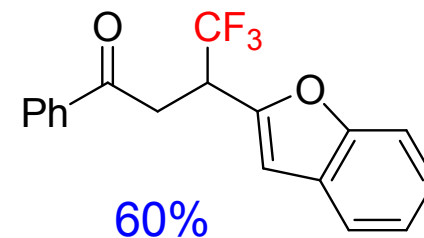
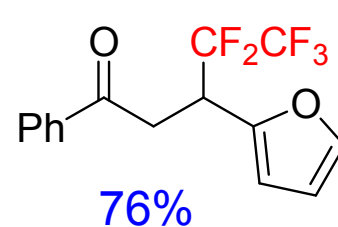
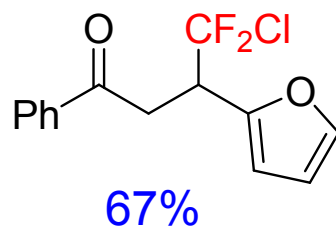
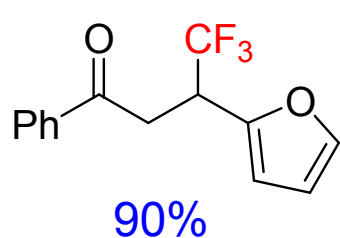
Benzo-diazepines or Benzothiazepines



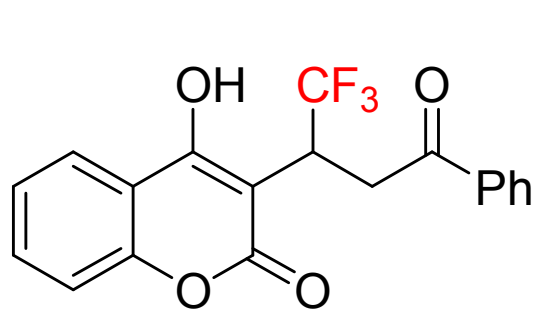
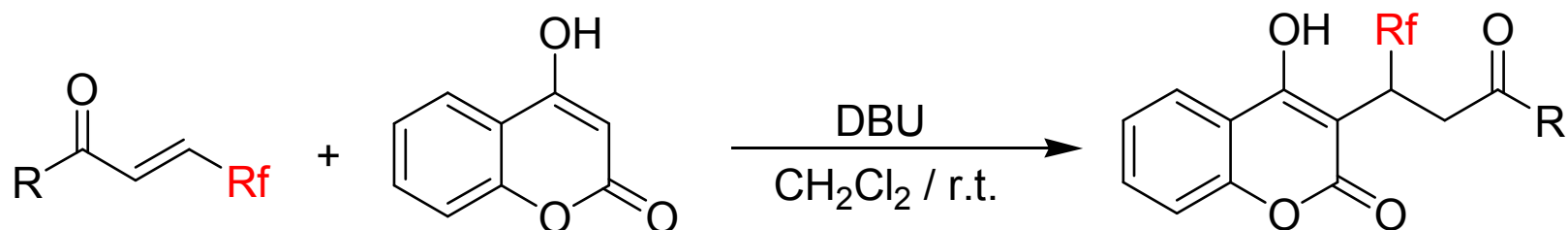
Friedel-Crafts Like (or Michael) Reactions



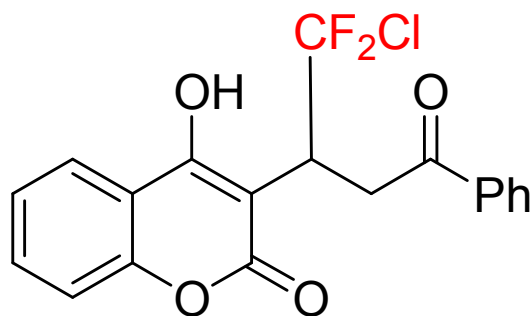
Lewis Acid: $\text{BF}_3 \cdot \text{Et}_2\text{O}$ / TiCl_4 / SnCl_4 / $\text{Cu}(\text{OTf})_2$ / $\text{In}(\text{OTf})_3$



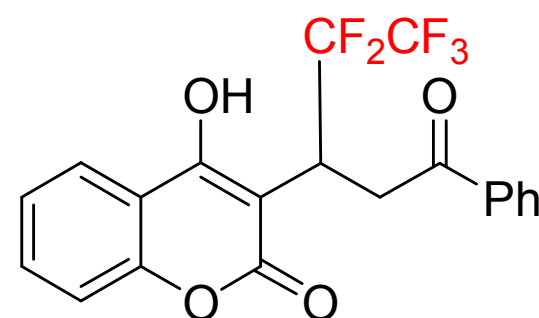
Synthesis of Warfarin Analogs



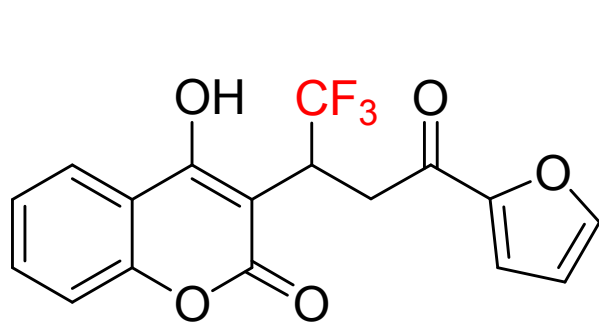
83%



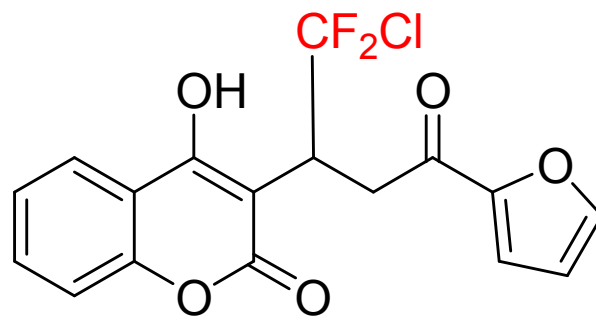
35%



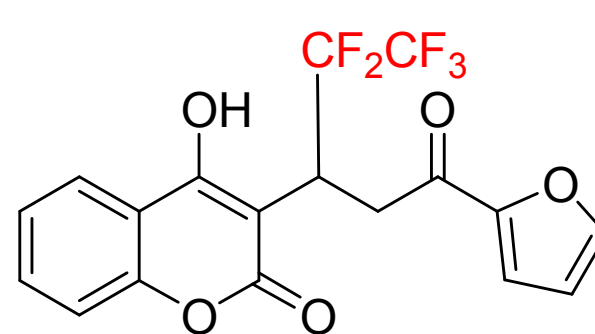
93%



74%

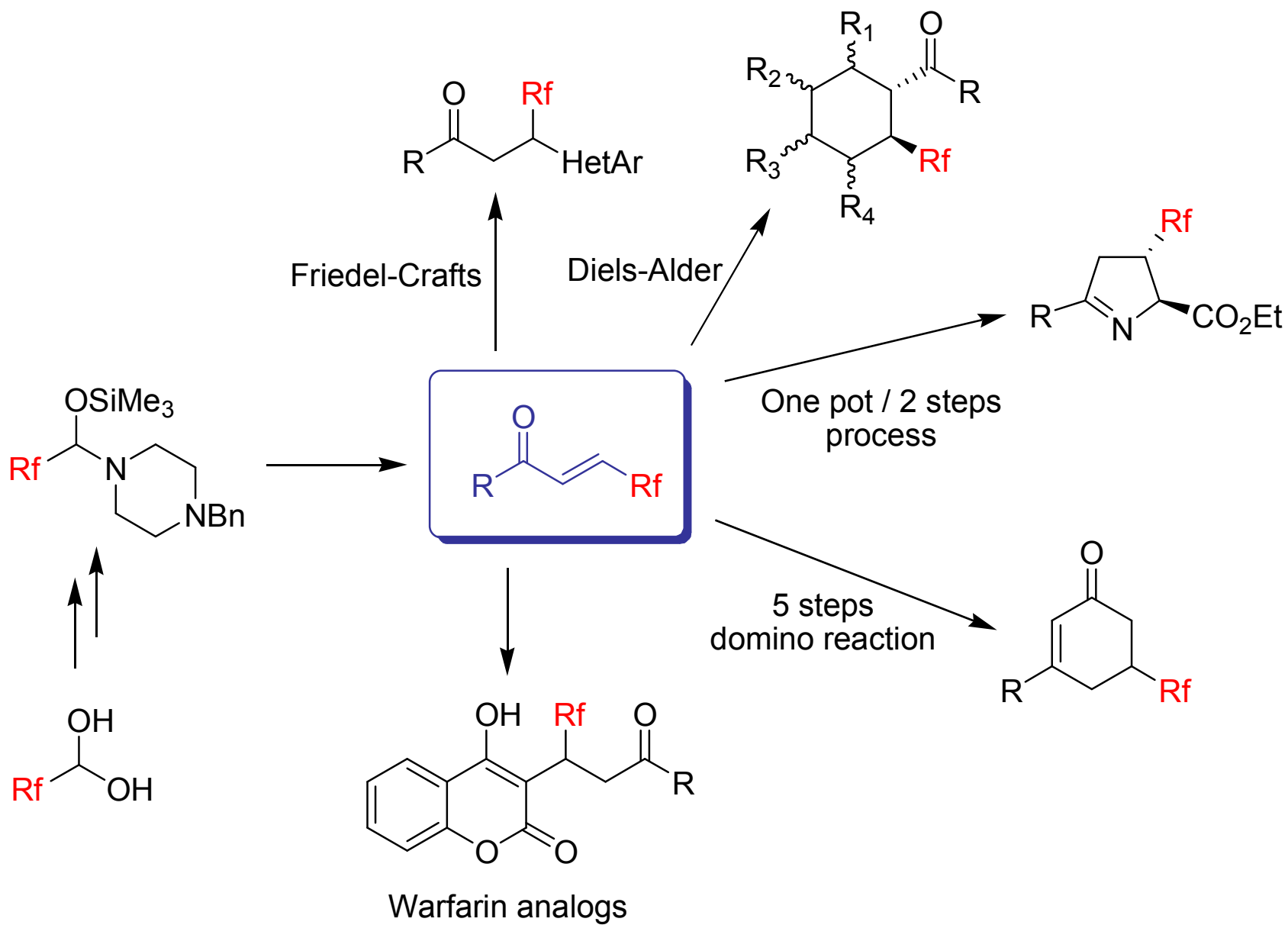


89%

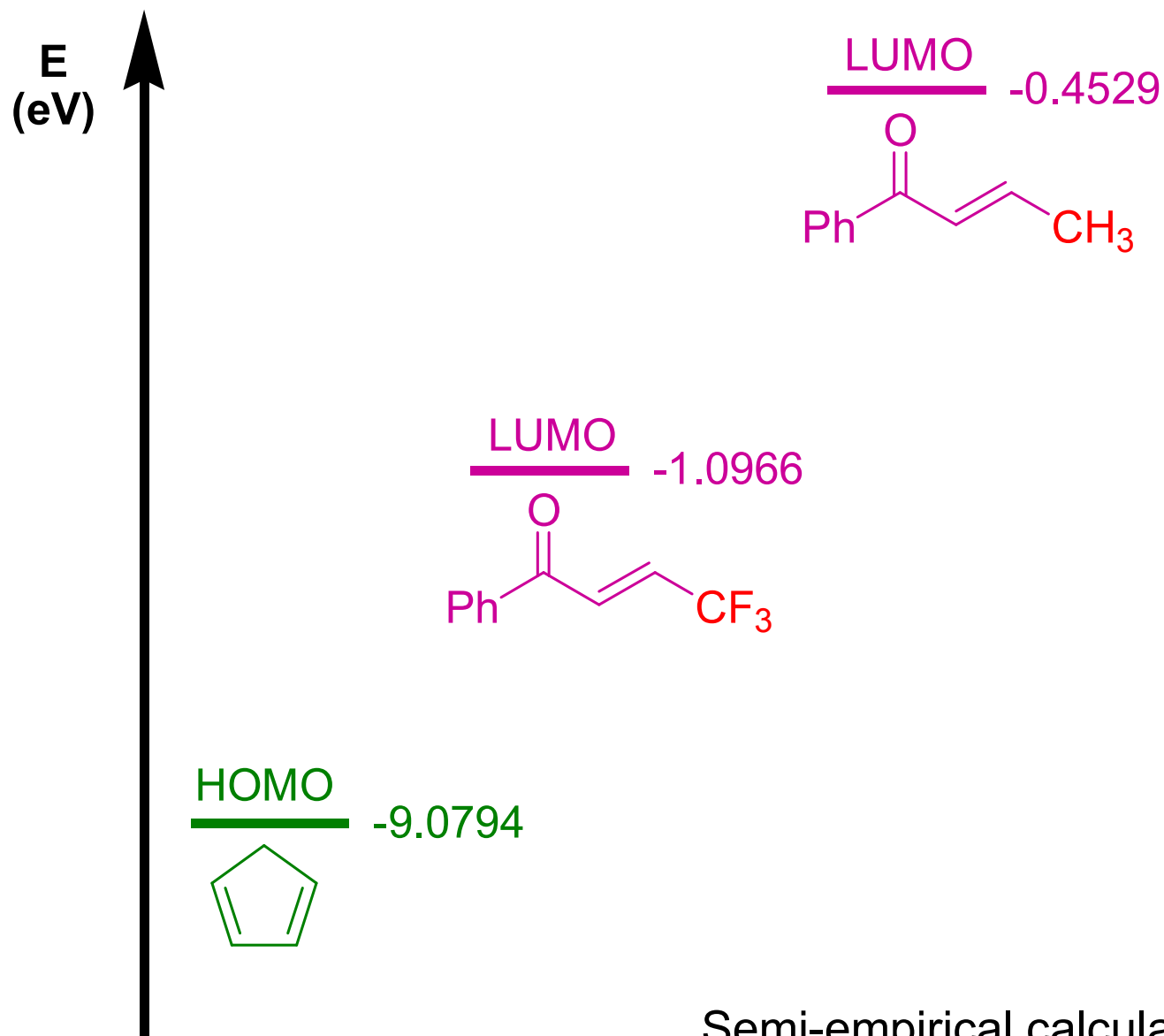


71%

Conclusion

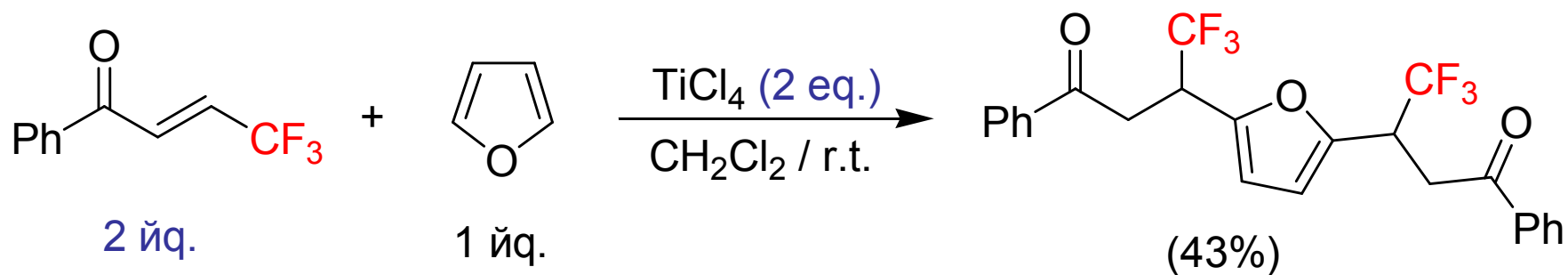
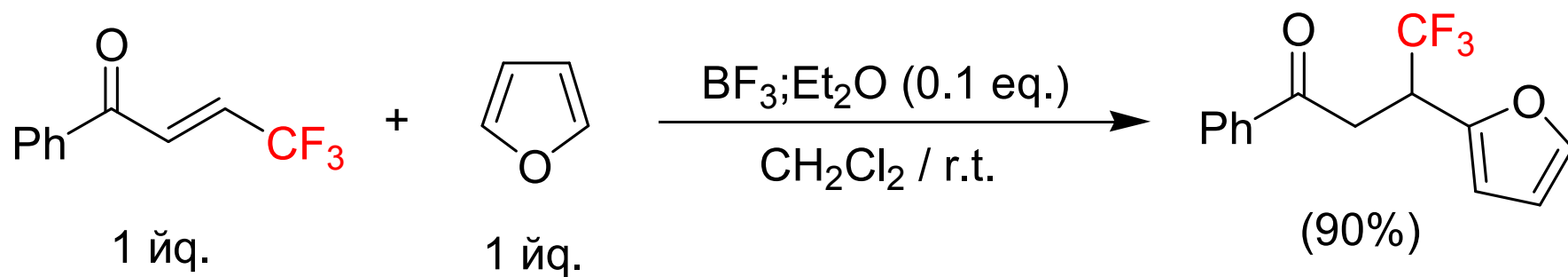


HOMO / LUMO Energy Level

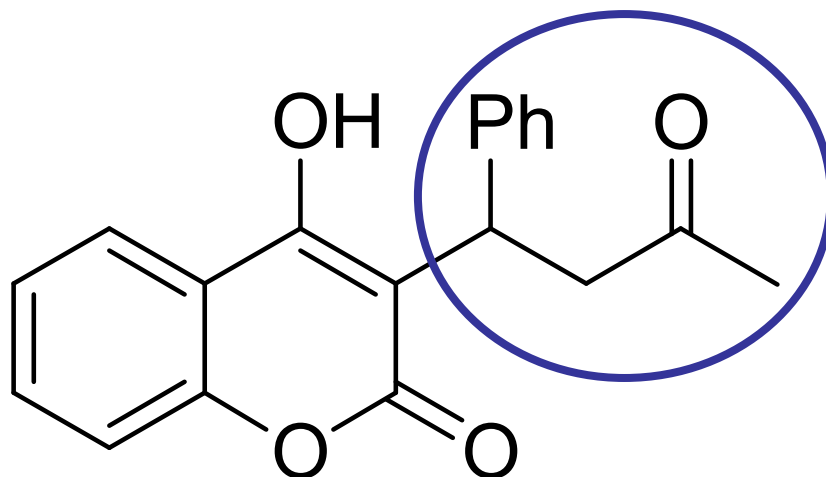


Semi-empirical calculations (AM1)

Double Process



Synthetic application : Synthesis of Fluorinated analogs of Warfarin.



Warfarin (Coumadin™)
Anticoagulants