ENSTA ParisTech location in Paris
before our transfer to Palaiseau in 2012

Searching for new reactions:

A selection from our experience with isocyanides and multicomponent reactions

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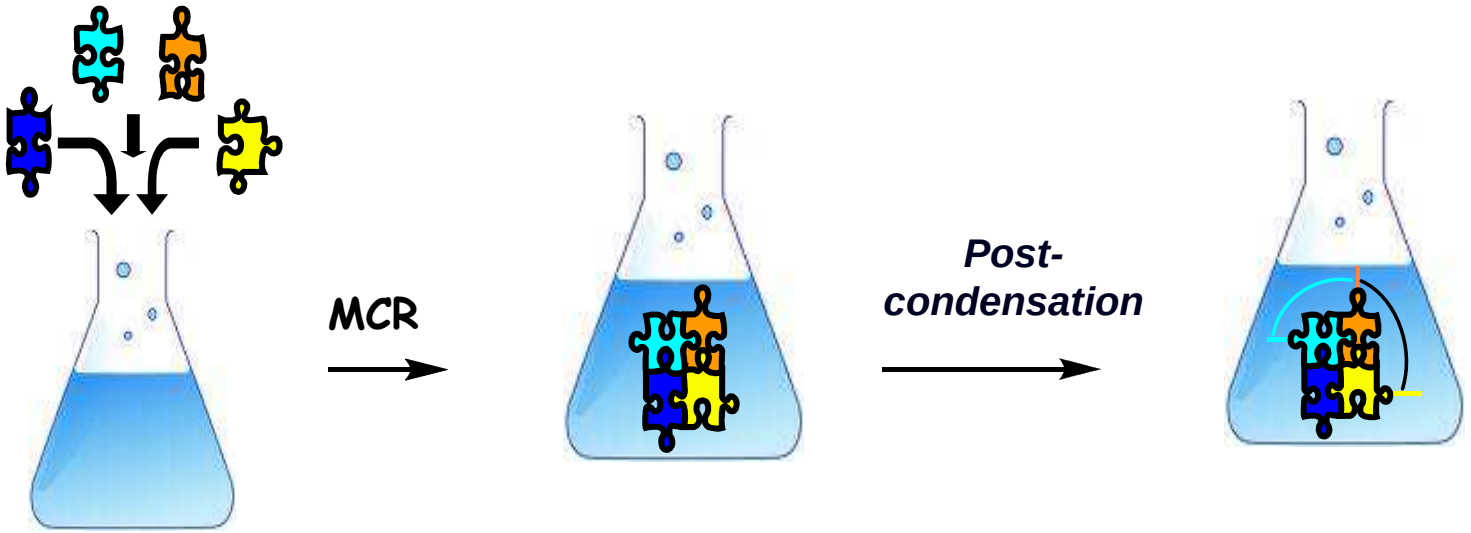
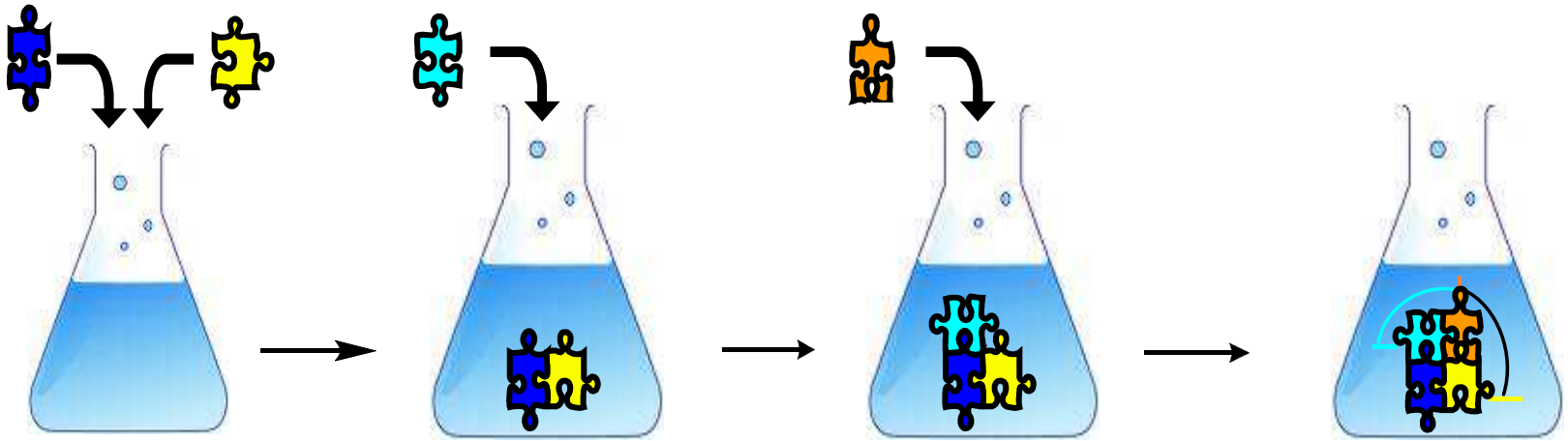
Ecole Nationale Supérieure des Techniques Avancées
Palaiseau, 91120, France.

Multicomponent reactions (MCRs)

Multicomponent approach in synthesis:

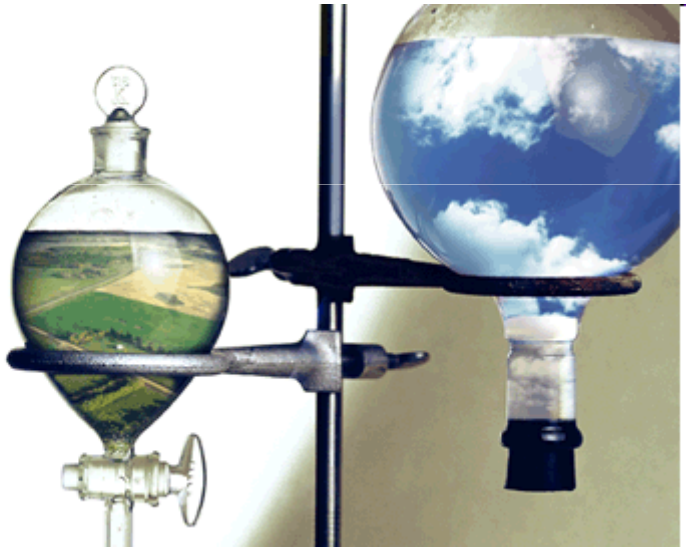


Sequential additions are not real MCRs:



Multicomponent reactions

Environmental concern
in chemistry

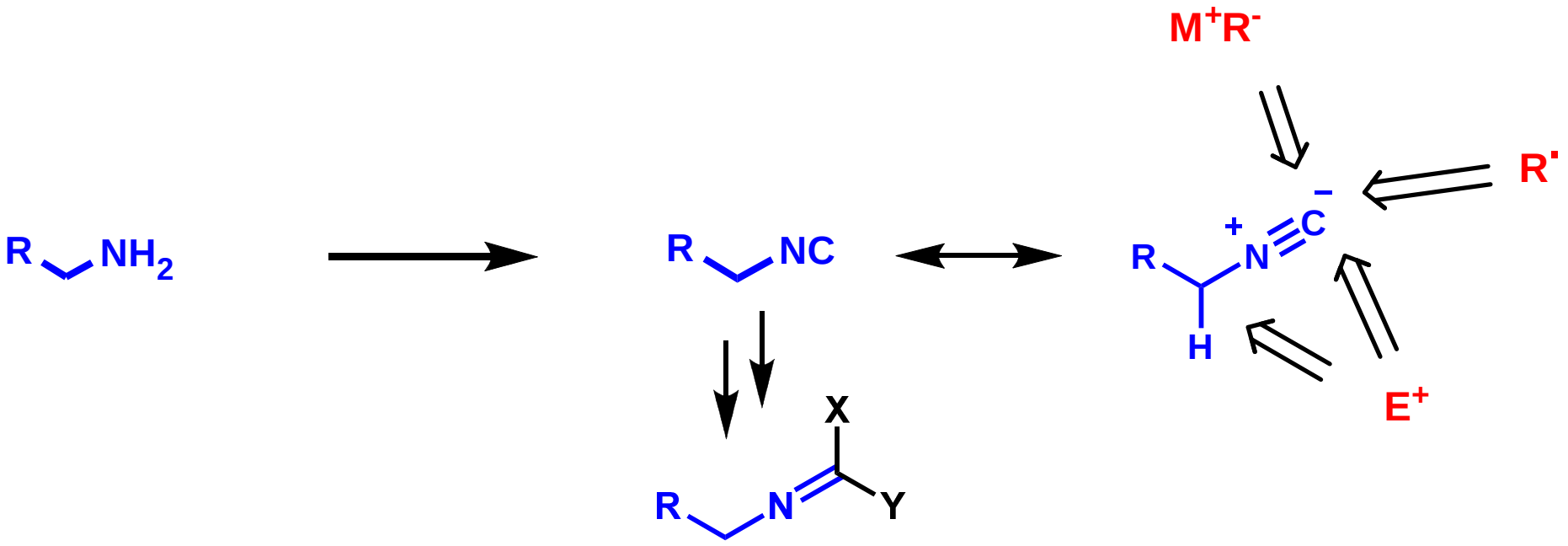


- ✓*Atom and step economy*
- ✓*Catalytical processes*
- ✓*New modes of activation*
- ✓*Solvent free reactions or in water*
- ✓*Cascades and domino reactions*
- ✓*Multicomponent reactions*

MCRs giving fast access to highly complex products are strongly associated with step economy

Isocyanide based MCRS combine step and atom economy

Isocyanides and multicomponent reactions

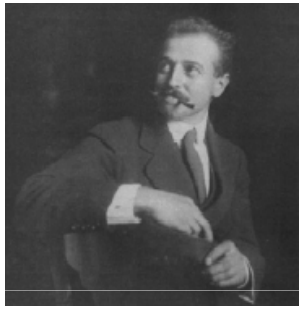


Many potential new bonds but isocyanides are relatively stable carbenes and poor nucleophiles

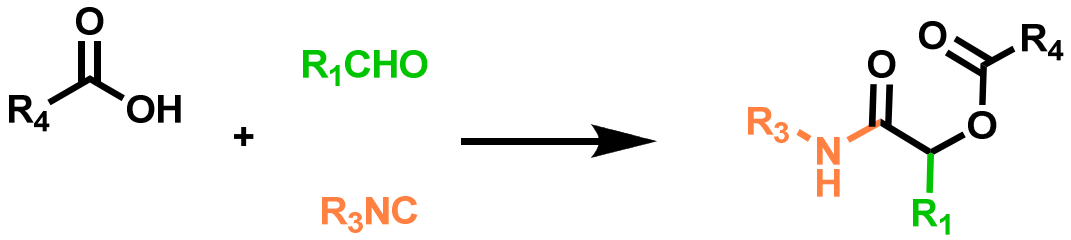
No reaction with aldehydes or imines without electrophilic activation

Isocyanides and multicomponent reactions

Passerini reaction:



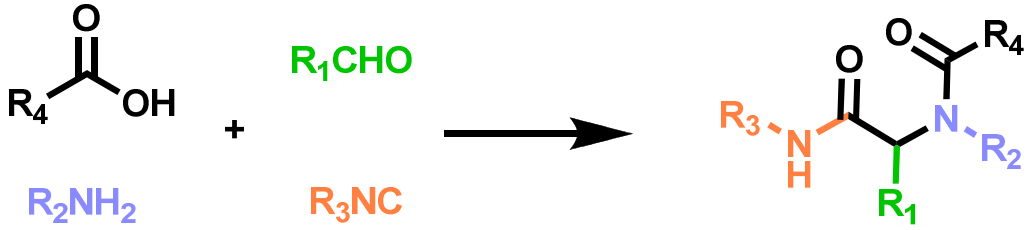
M. Passerini:1891-1962



revue: L. Banfi, *Org. React.* **2005**, *65*, 1

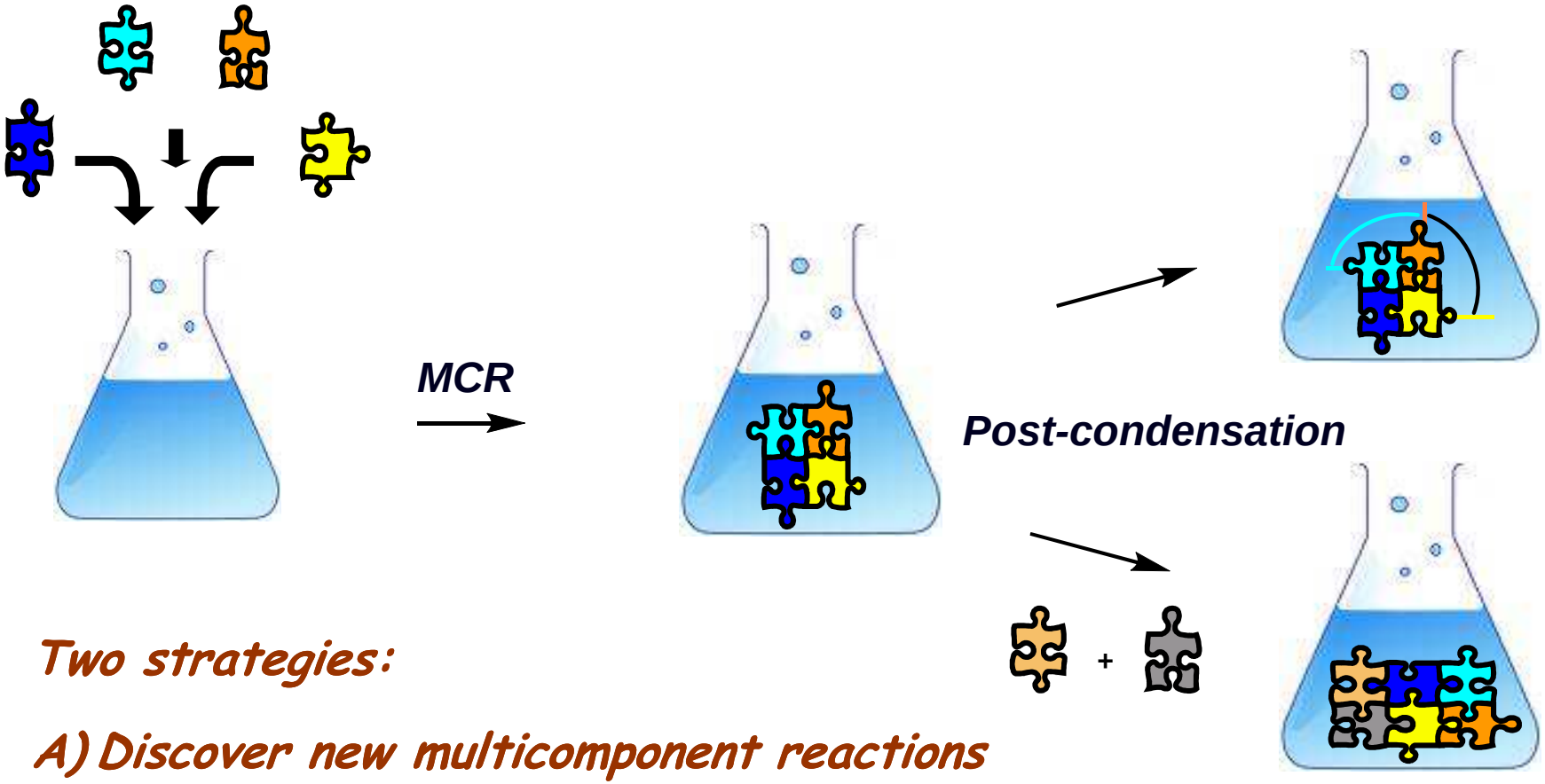
Ugi reaction :

I. Ugi:1930-2005



A. Dömling, *Chem. Rev.* **2006**, *106*, 1

Strategies in multicomponent reactions



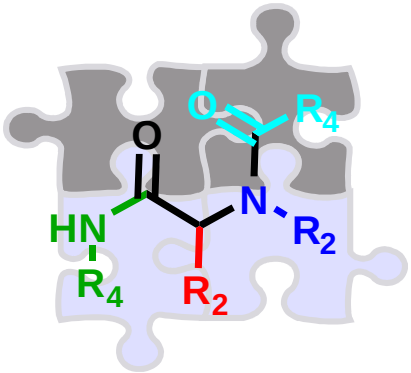
Two strategies:

A) Discover new multicomponent reactions

B) Work on MCR adducts of efficient MCRs: post-condensation approach

Some Ugi post-condensations from our colleagues

Ionic chemistry



- **-Knoevenagel:** **Pyrrole** (Marcaccini 1994,1999), **pyridones** (Marccacini 1997), **pyridazines** (Torroba 2003), **quinolinones** (Torroba 2004)
- **-UDC:** **γ- Lactames** (Hulme 2000), **imidazoline** (Hulme 1999), **benzimidazoles, ketopiperazines** (Hulme 1998), **quinoxalines** (Hulme 2002)
- **-S_NAr :** **Indazolinones,benzodiazepines** (Tempest 2001), **macrolactames** (Zhu 2001) **Benzoxazepines** (Dai 2006)
- **-Davidson Cycl. :** **Imidazoles** (Zhang 1996, Sung 2002)
- **-Wittig:** **Pyrrolinones** (Dömling 2004)

Cycloadditions

- **-[4+2]:** **Lactames** (Paulvannan 1999), **isoindolines** (Wright 2002, Chen 2005)
- **-[3+2]:** **Pyrroles** (Armstrong 1995,1996), **isoxazoles** (Akritopoulou-Zanze 2004)
- **-[2+2] :** **Lactames** (Akritopoulou-Zanze 2007)

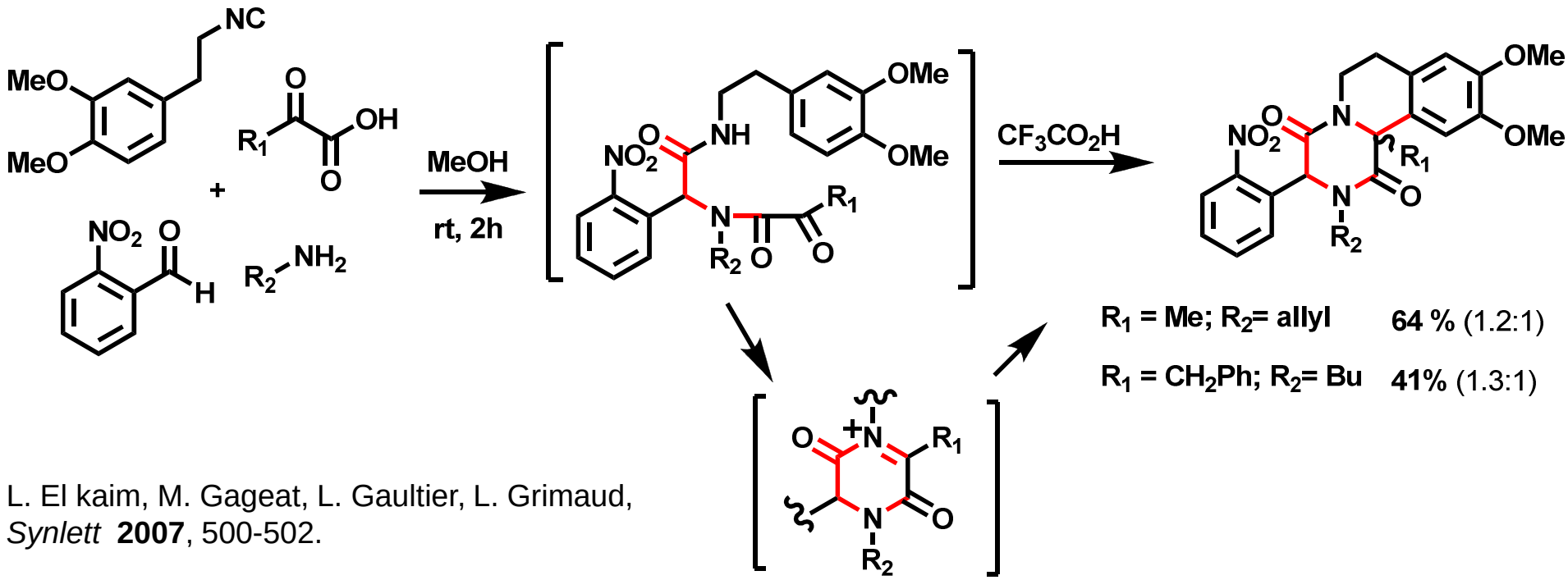
Organometallic couplings

- **-Heck:** **Lactames** (Gracias, 2004), **indoles** (Umkehrer, 2006), **isoquinoline** (Chen, 2004)
- **-RCM:** **Azepines** (Piscopio, 1999), **lactames** (Schreiber 2000, Banfi 2003, Westermann 2004), **macrolactones** (Dömling 2003)
- **-Buchwald:** **Oxindoles** (Zhu 2006)

Ugi-postcondensations at ENSTA

Our philosophy: due to the large number of post-condensations already disclosed, new studies must bring the highest structural complexity

Ex: first Ugi/Pictet-Spengler cascade:



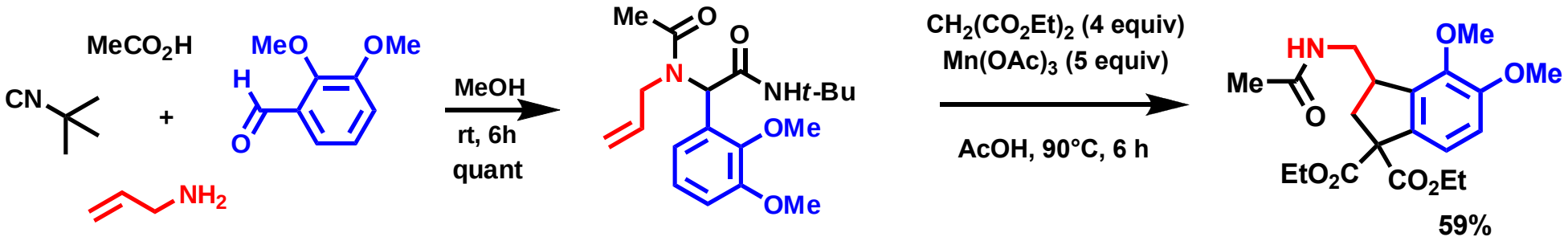
R_1 = Me; R_2= allyl **64 %** (1.2:1)

R_1 = CH_2Ph; R_2= Bu **41%** (1.3:1)

L. El kaim, M. Gageat, L. Gaultier, L. Grimaud, *Synlett* **2007**, 500-502.

Ugi-postcondensations at ENSTA

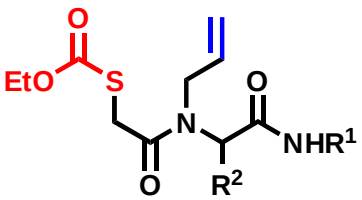
Ex: Radical reactions and Ugi adducts



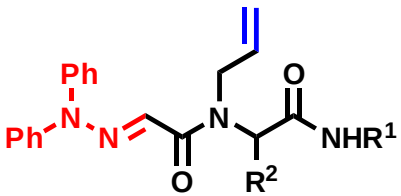
L. El Kaim, L. Grimaud, E. Vieu, *Org. Lett.*, **2007**, 4171.

Other radical projects:

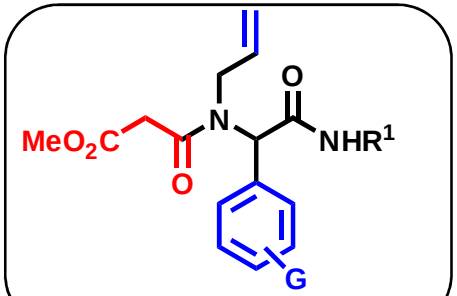
Xanthate transfer



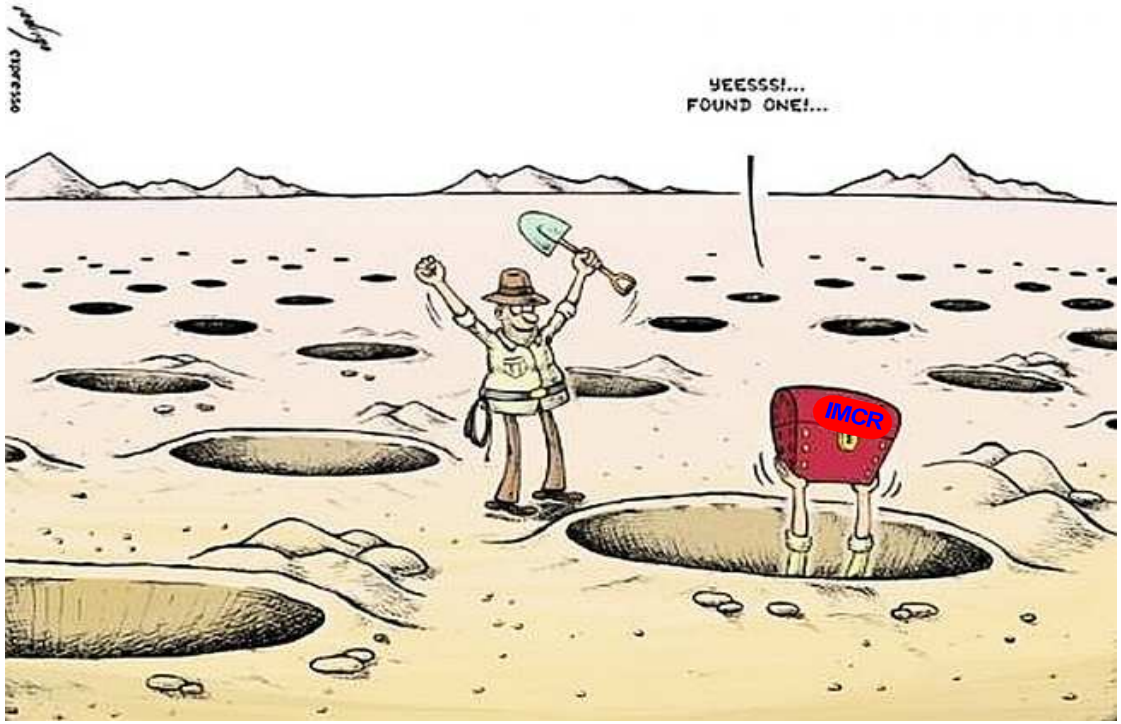
Hydrazone cyclization



Mn(III) chemistry

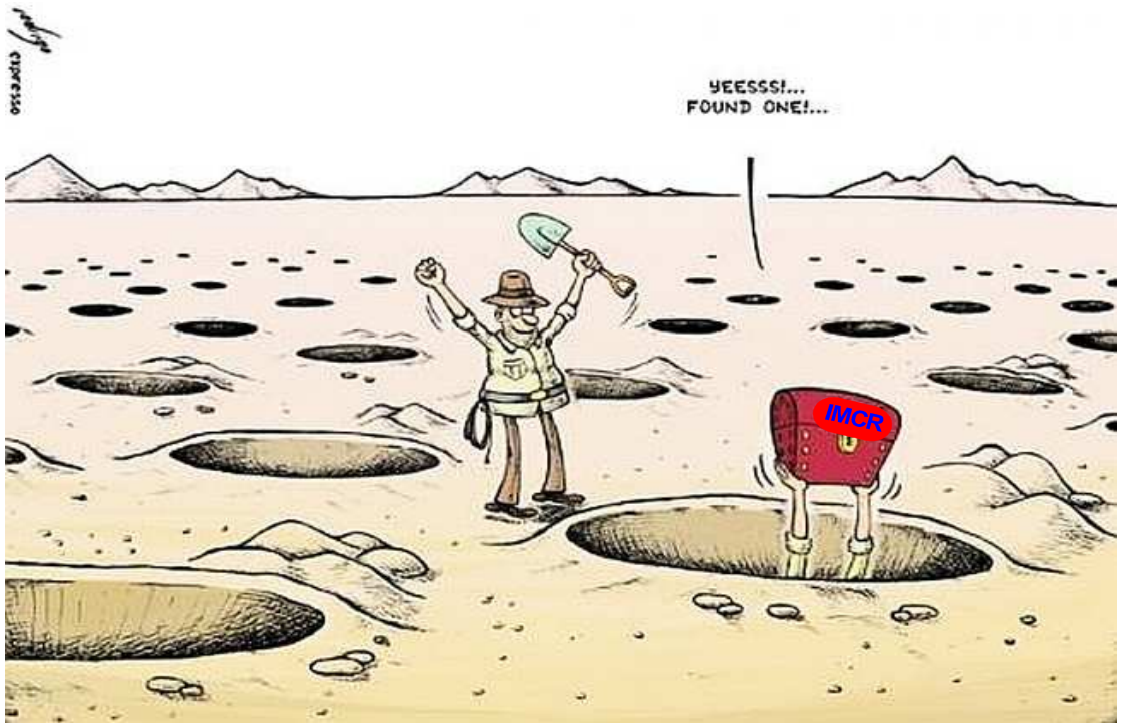


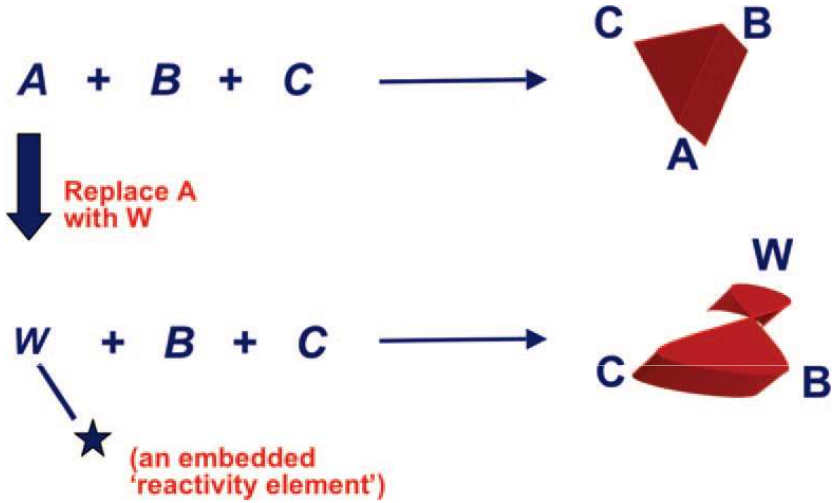
Finding new IMCRs ?



➡ strategies needed

Finding new IMCRs ?





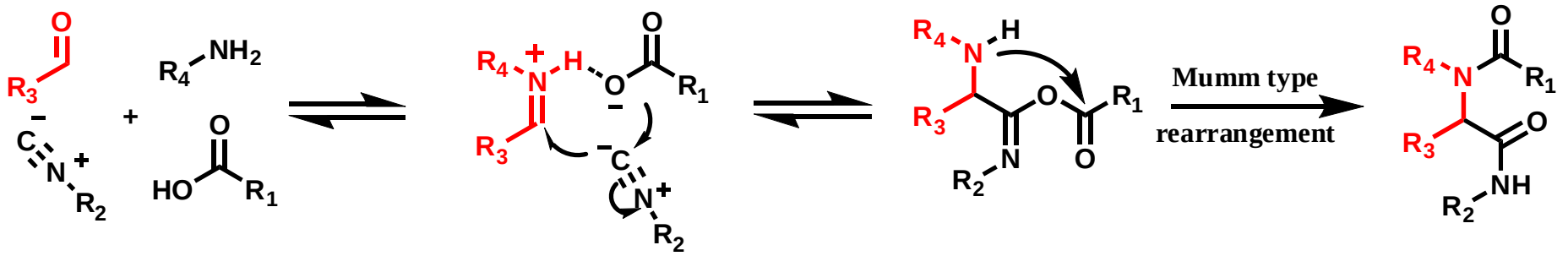
The Single Reactant Replacement approach to finding new MCRs.

strategies needed

In « Strategies for Innovation in Multicomponent Reaction Design »
Bruce GANEM, ACR, 2009

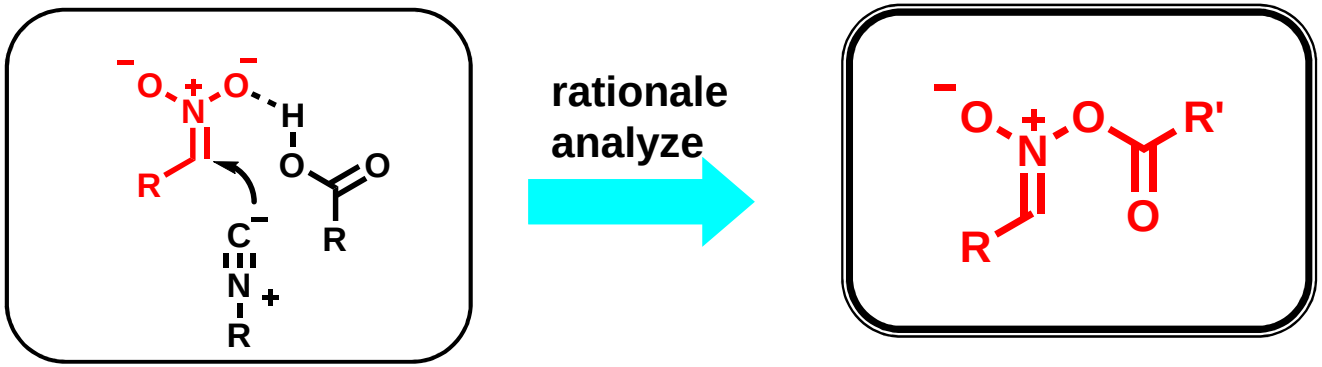
Replacement approach with Ugi reactions

Always come back to the mechanism of the reaction you want to modify:



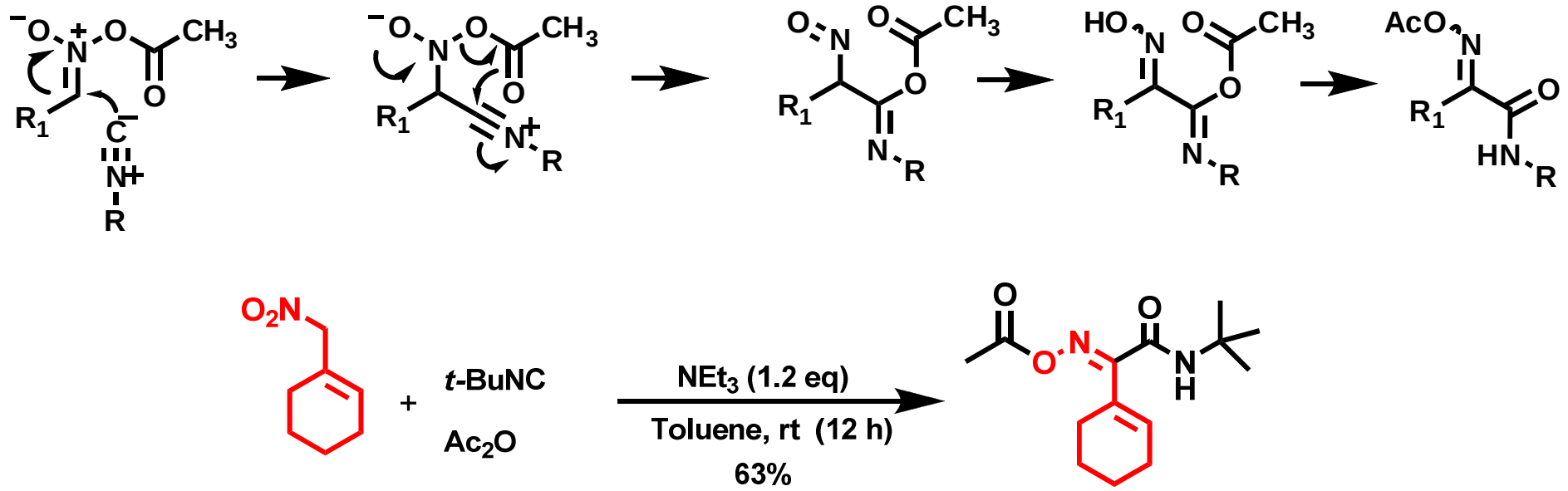
Can we replace the iminium in Ugi couplings by more exotic C=N bonds?

Nitronates ?



Replacement approach with Ugi reactions

Mechanism and product:

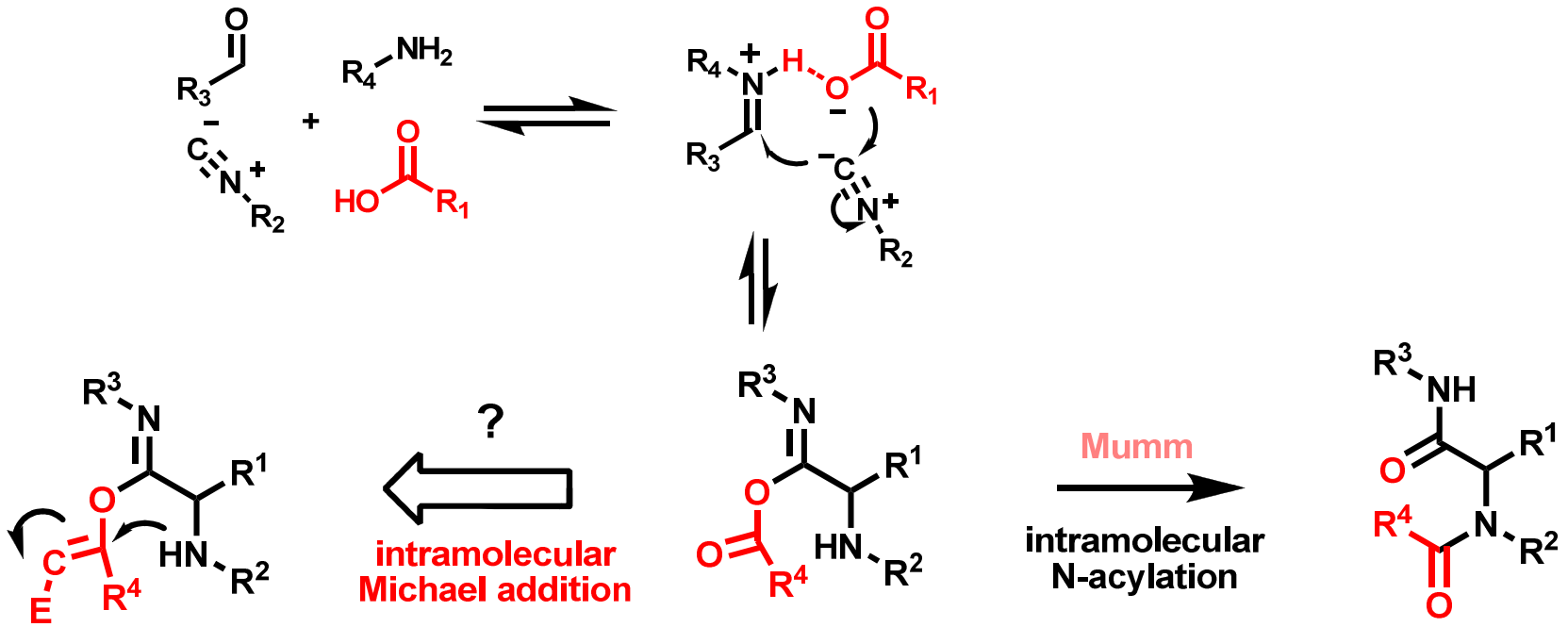


P. Dumestre, L. El Kaim, A. Gregoire, *Chem. Comm.*, **1999**, 775.

A new reaction with a nice mechanism but a low potential in MCRs (the acyloximes being easily hydrolysed, the 3CC goes to a 2CC)

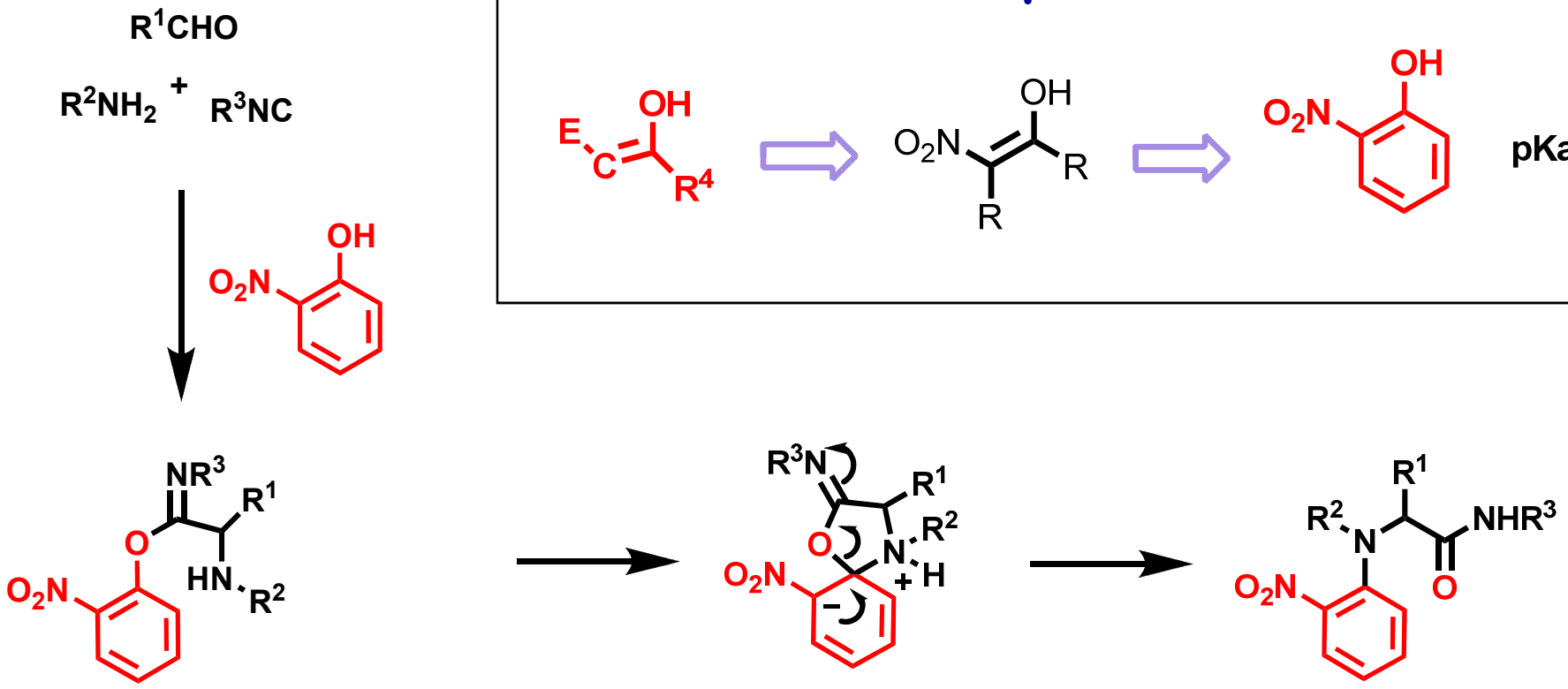
Ugi-Smiles couplings

Phenols as carboxylic acid surrogates in Ugi reactions



Underlying idea: replace the acyl transfer of the Ugi/Mumm by a Michael addition leading to a vinyl shift

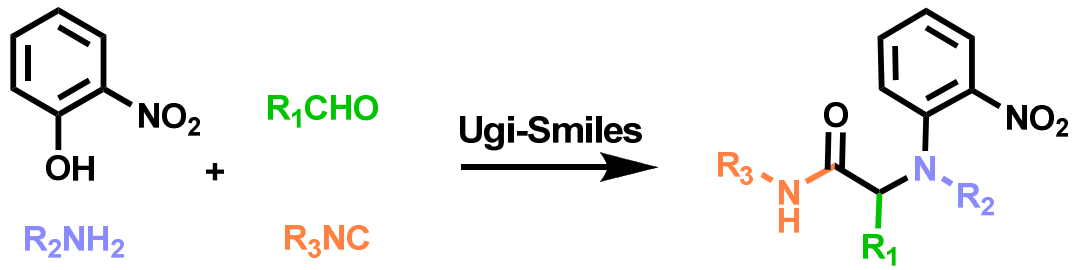
Ugi-Smiles Couplings

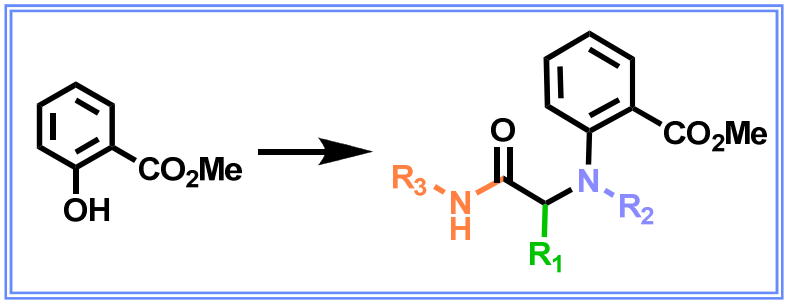


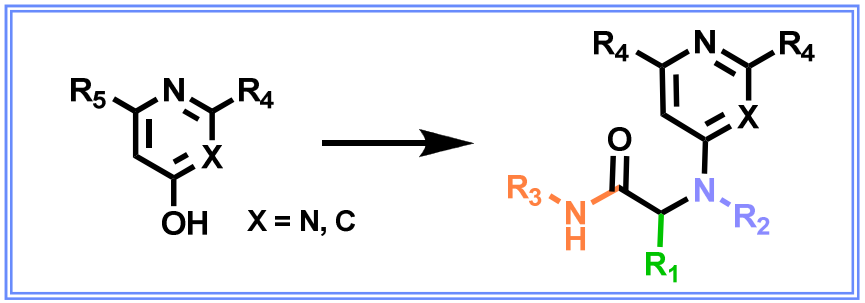
Best Michael acceptors are nitrolefines!

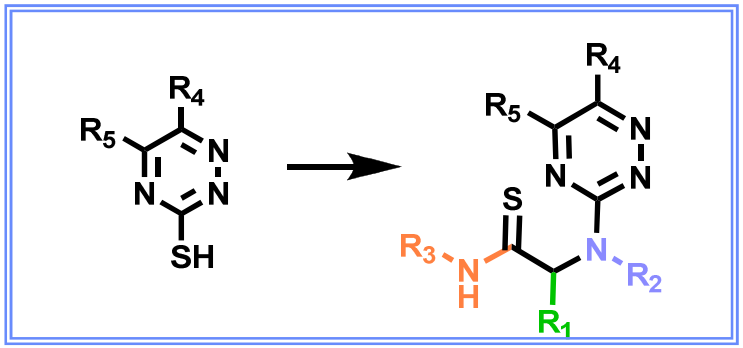
pKa : 7.2

Ugi-Smiles Couplings







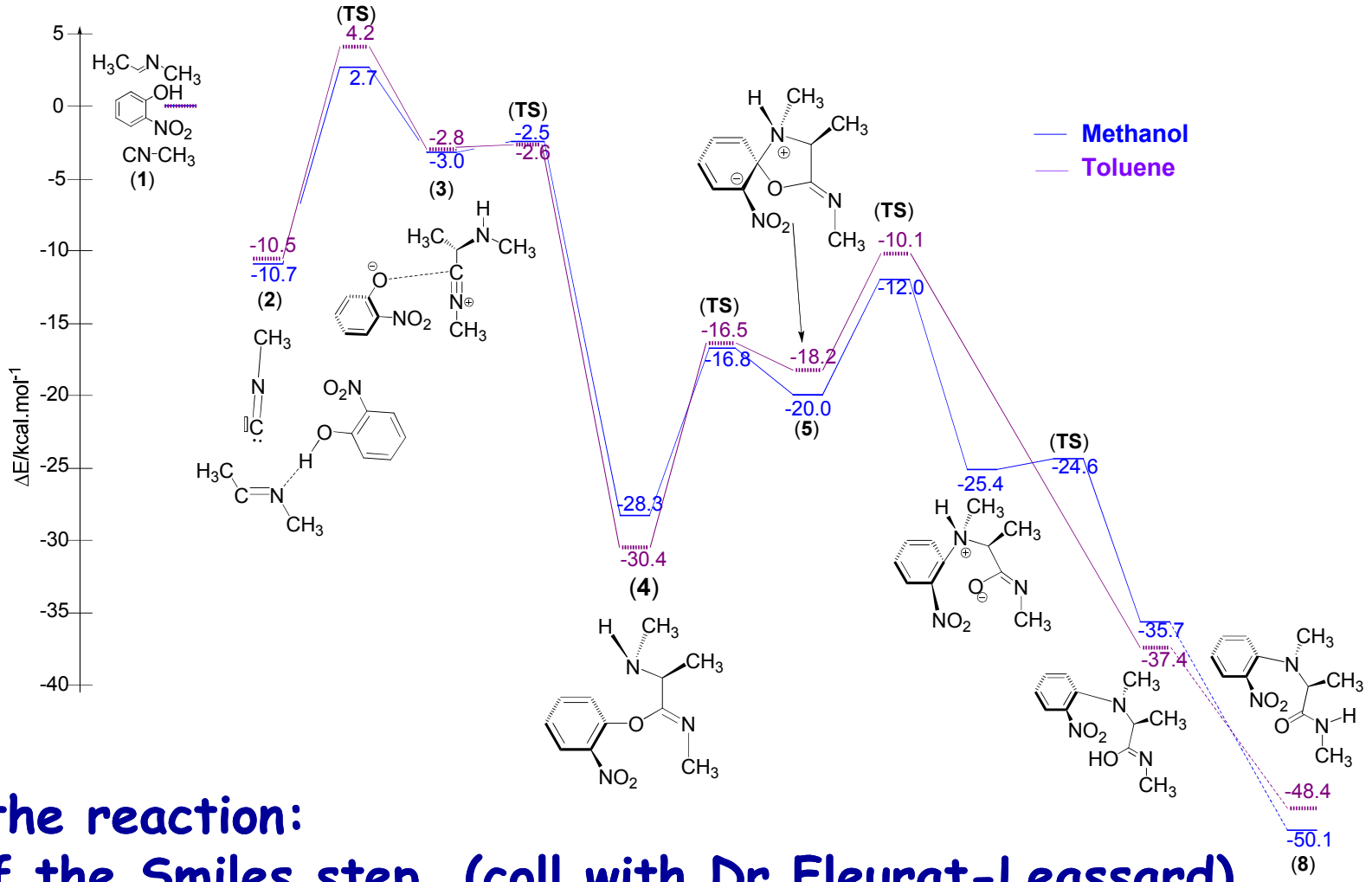


El Kaim, Grimaud, Oble *Angew.Chem. Int. Ed* **2005**, 7961

El Kaim, Gizolme, Grimaud, Oble *Org. Lett.***2006**, *8*, 4019

El Kaïm, Gizolme, Grimaud, Oble *J. Org. Chem.* **2007**, *72*, 4169

Ugi-Smiles Couplings

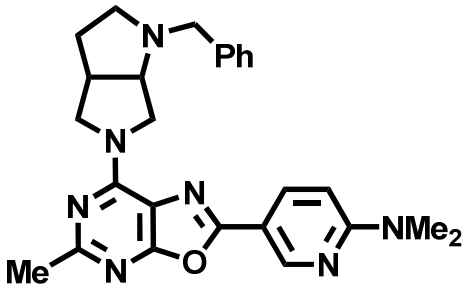


DFT study of the reaction:
importance of the Smiles step (coll with Dr Fleurat-Leassard)

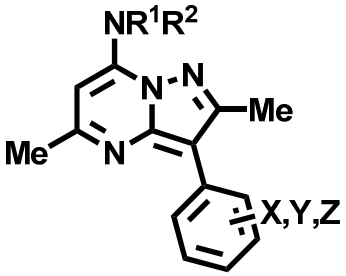
Ugi

Smiles rearrangement

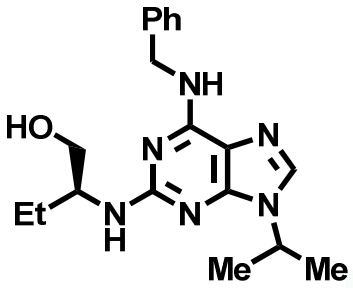
Biological interest of pyrimidine derivatives



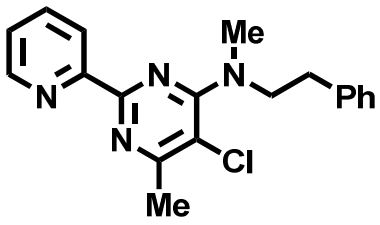
Adénosine kinase inhibitor
(Bayer Heath Care, 2004)



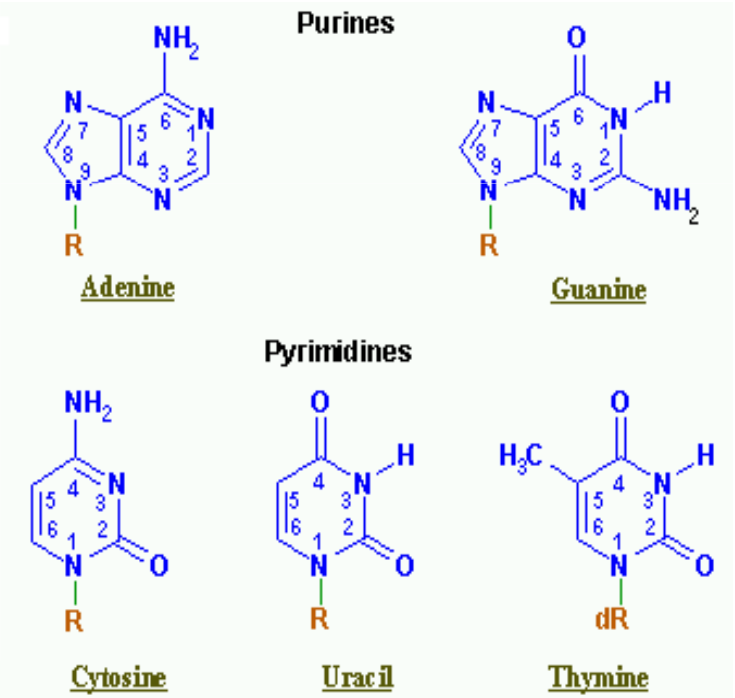
*h*CRF$_1$ inhibitor
(anxiolytique, DuPont, 2000)[d]



Roscovitine, CDK Inhibitor de
(breast cancer, 2008, clinical
phase II)

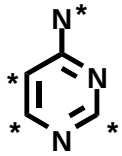


Human méthionine aminopeptidase inhibitor
(John Hopkins University, antitumoral, 2006)

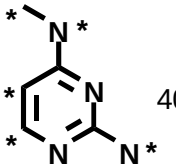


Ugi

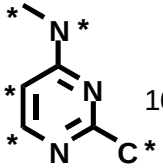
Smiles rearrangement



114 250 compounds with biol. activities in Reaxis



40927



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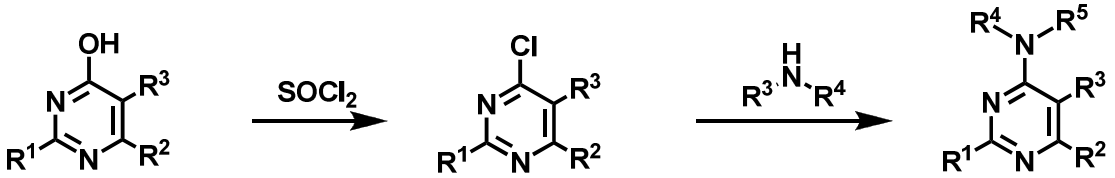
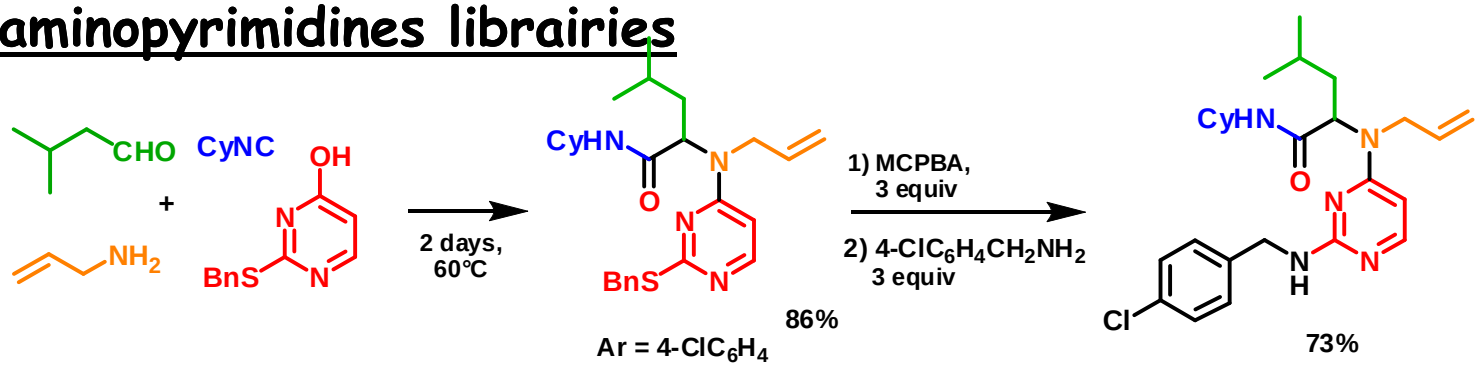
Traditional preparation of amino-pyrimidines



Ugi-Smiles: an efficient access to librairies of pyrimidines

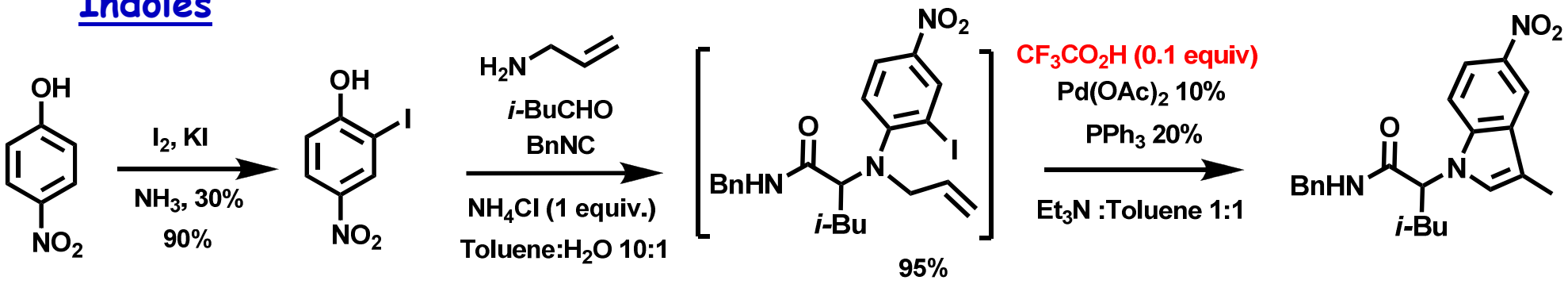
Ex: New diaminopyrimidines librairies



M. Ait Sidhoum, L. El Kaïm, L. Grimaud, Synlett, **2012**,

Ugi-Smiles couplings towards biologically relevant scaffolds

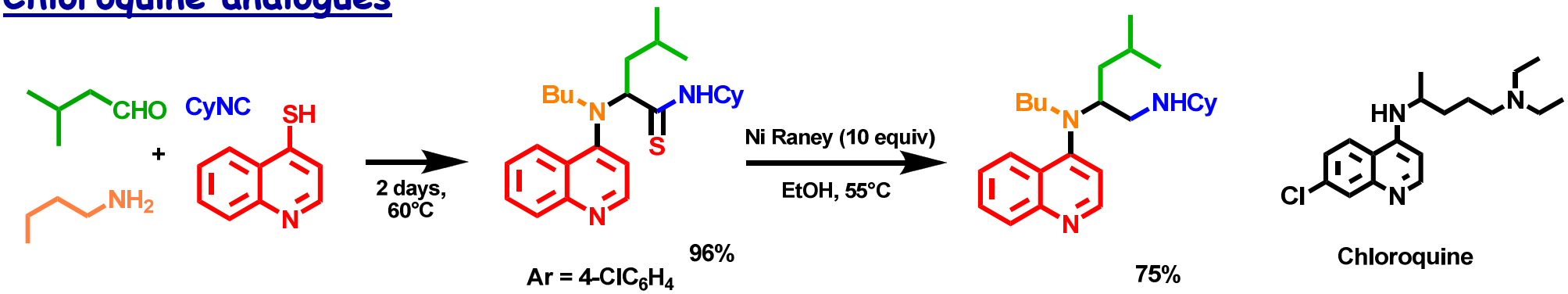
Indoles



One-pot indole synthesis 72%

L. El kaim, M. Gizzi, L. Grimaud *Org. Lett.* **2008**, *10*, 3419

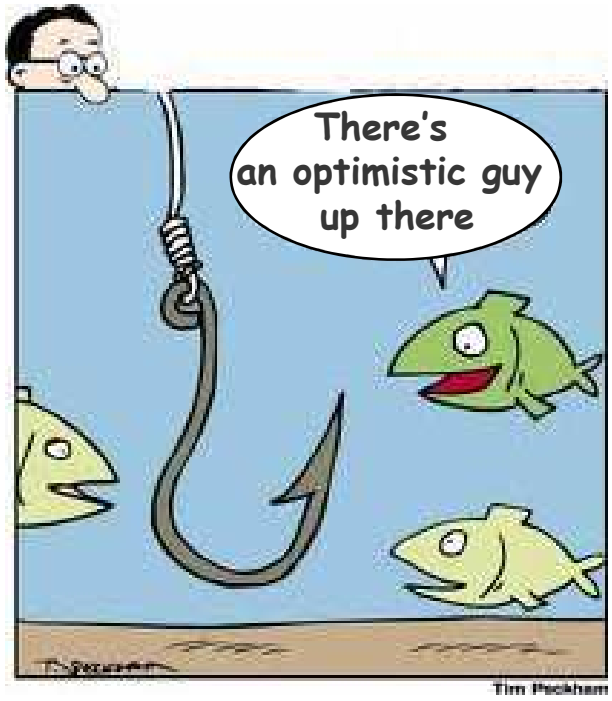
Chloroquine analogues



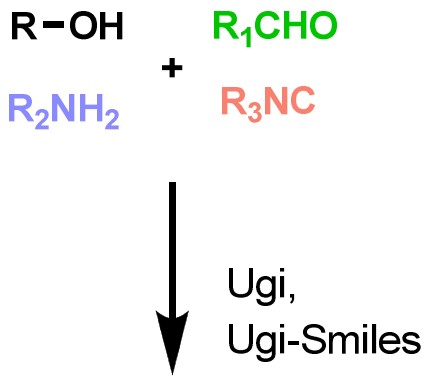
El Kaim, Grimaud, Pravin *Org. Lett.* **2011**, 7961

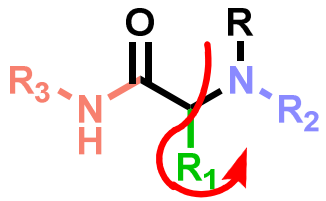
Our philosophy with Ugi-type reactions: MCRs as tools for reactivity study

Ugi and Ugi Smiles adducts are formed in one step and are highly decorated, they are ideal substrates to test and discover new reactions.

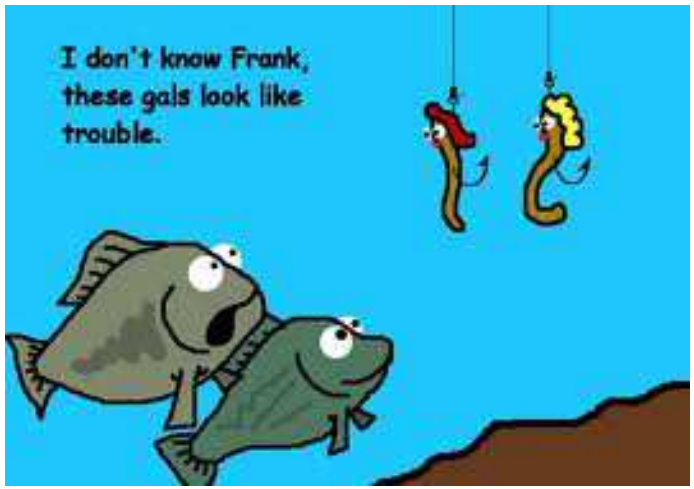


Catching big fishes with MCRs

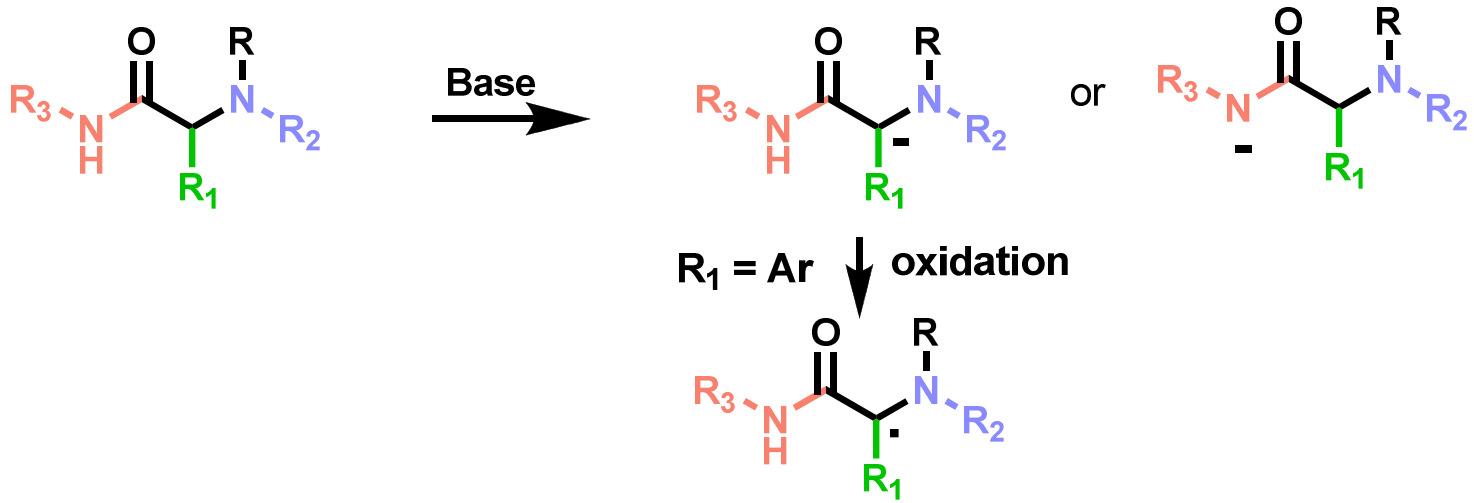




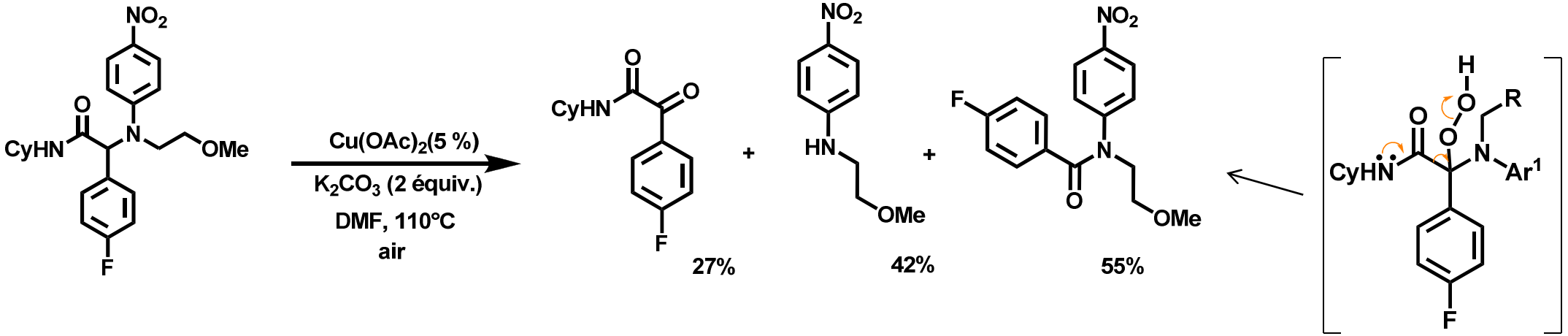
MCR for reactivity and cyclization studies



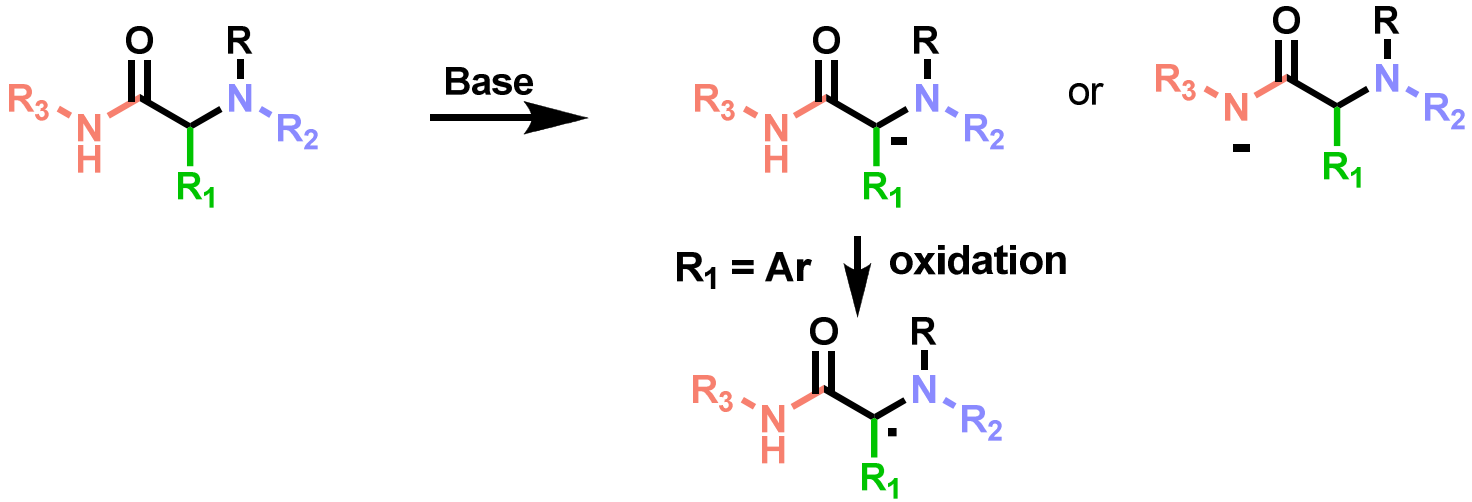
Ugi adducts: reactivity of the "peptidyl" position



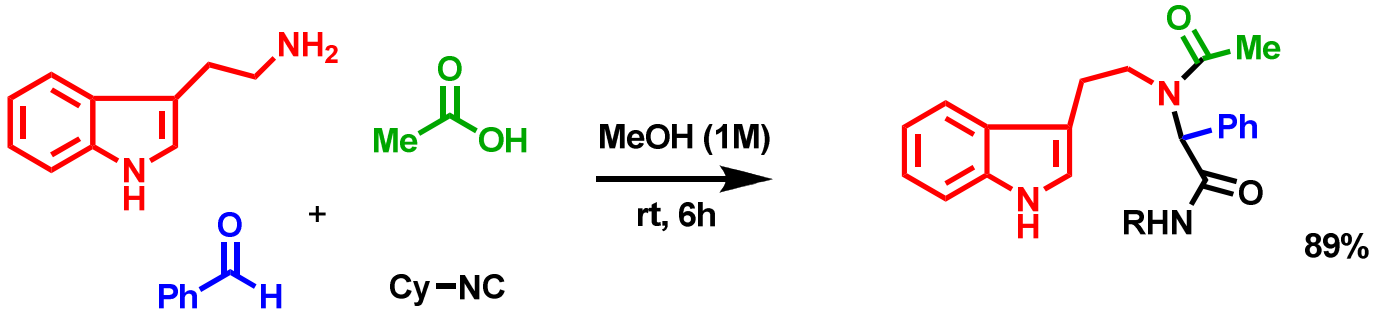
The stabilized peptidyl radical is easily oxidyzed leading to fragmentations of low synthetic interest.



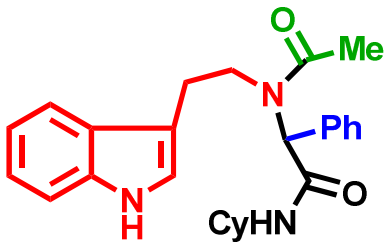
Ugi adducts: reactivity of the "peptidyl" position



To avoid oxydation, the radical must be trapped to a fast radical trapping agent. Choice of indole scaffolds:



Ugi adducts: reactivity of the "peptidyl" position

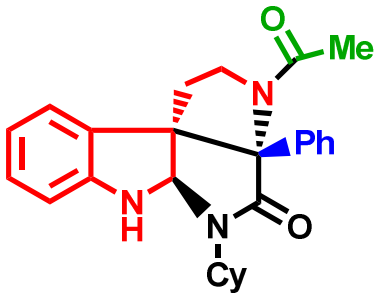


$Cu(OAc)_2$ x equiv

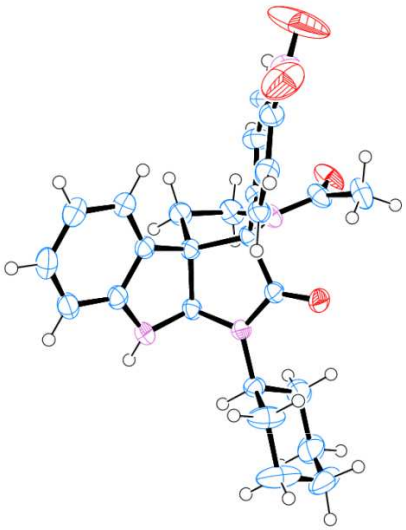
DBU 1 equiv

solvent, reflux

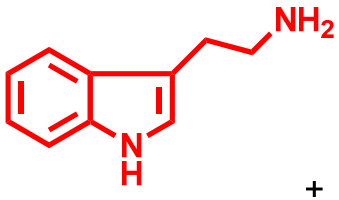
air



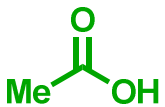
MeCN, Cu(II): 1equiv 10%
MeOH, Cu(II): 1 equiv 25%
THF, Cu(II): 1 equiv 77%
THF, Cu(II): 0.5 equiv 60%

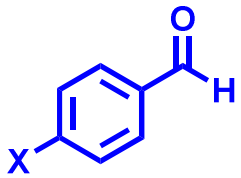


The power of Ugi MCR approach: one-pot preparation of complex spiroindolines without any protection and from commercially available materials:



+

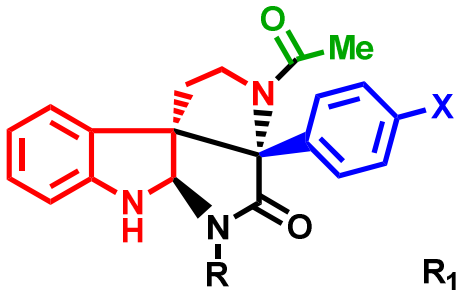




R−NC

1) MeOH (5M)
rt, 2h

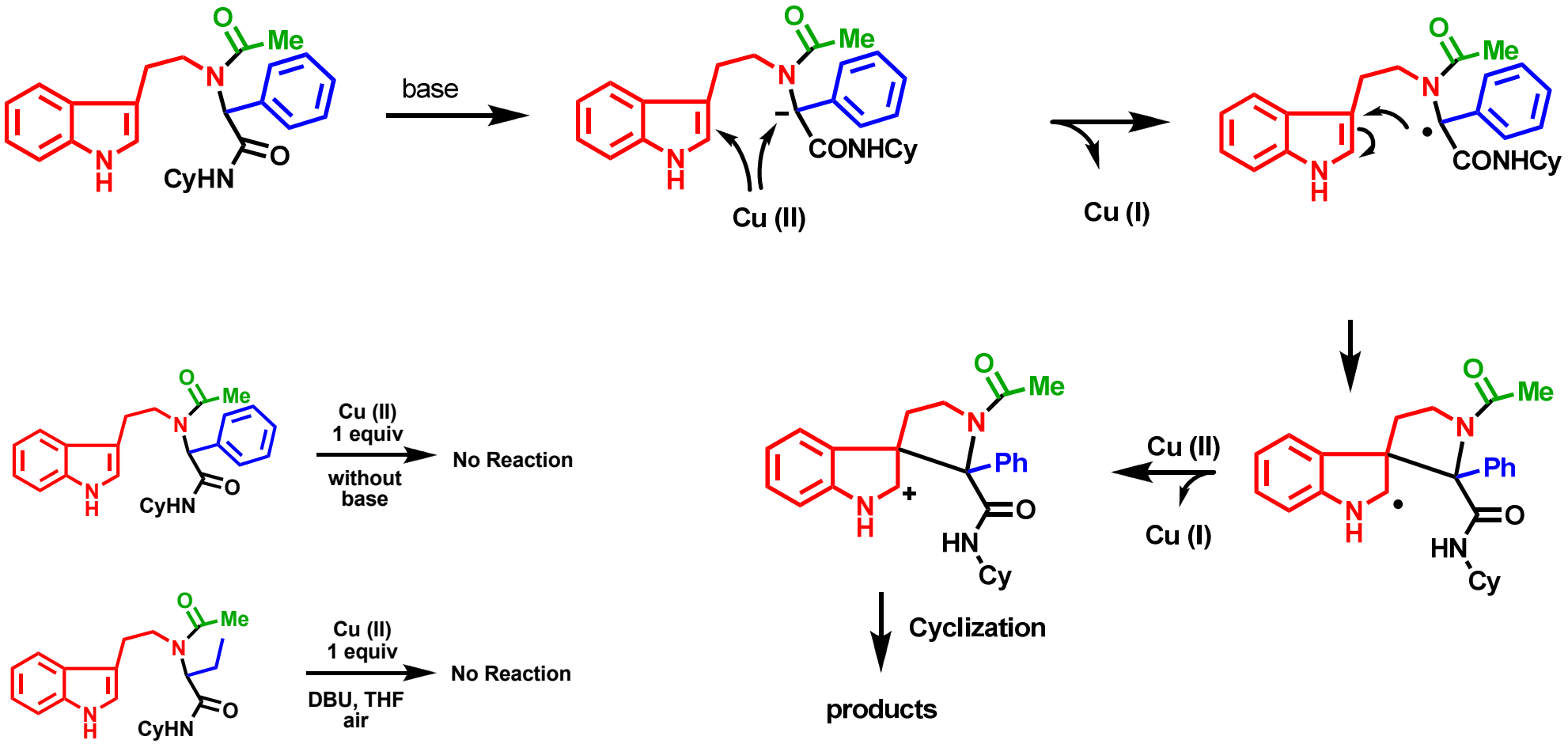
2) THF (0.2 M), DBU,
$Cu(OAc)_2$, air



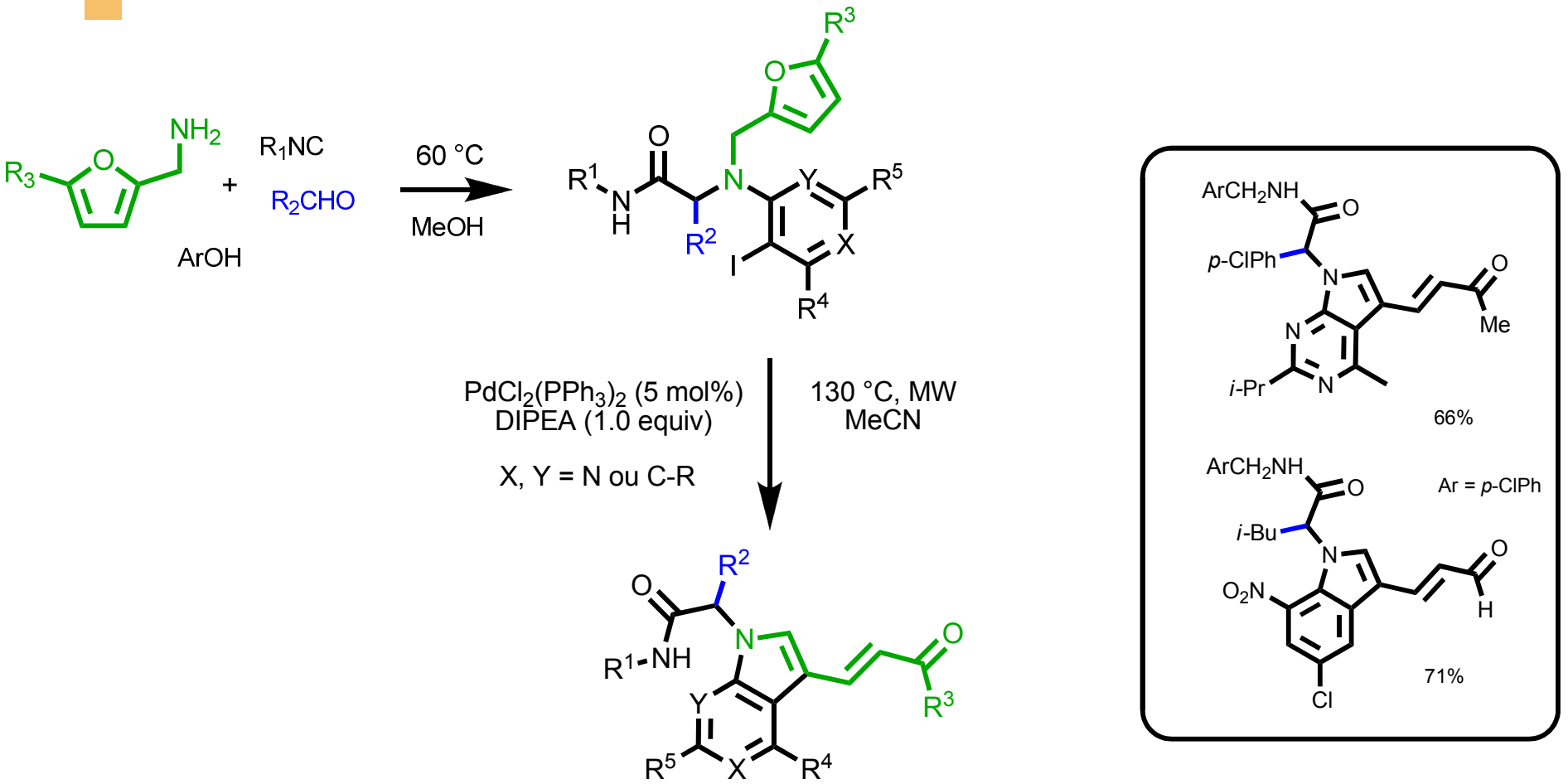
R_1 = Cy, R_2=Me, X=H, 65%
R_1 = *t*-Bu, R_2=Me, X=Cl 76%
R_1 = *t*-Bu, R_2=Ph, X=NO_2 63%

L. El kaim, L. Grimaud, X. Legoff, M. M. Azarte, L. Miranda, *Chem. Commun.* **2011**, 8145-8147

Ugi adducts: reactivity of the "peptidyl" position



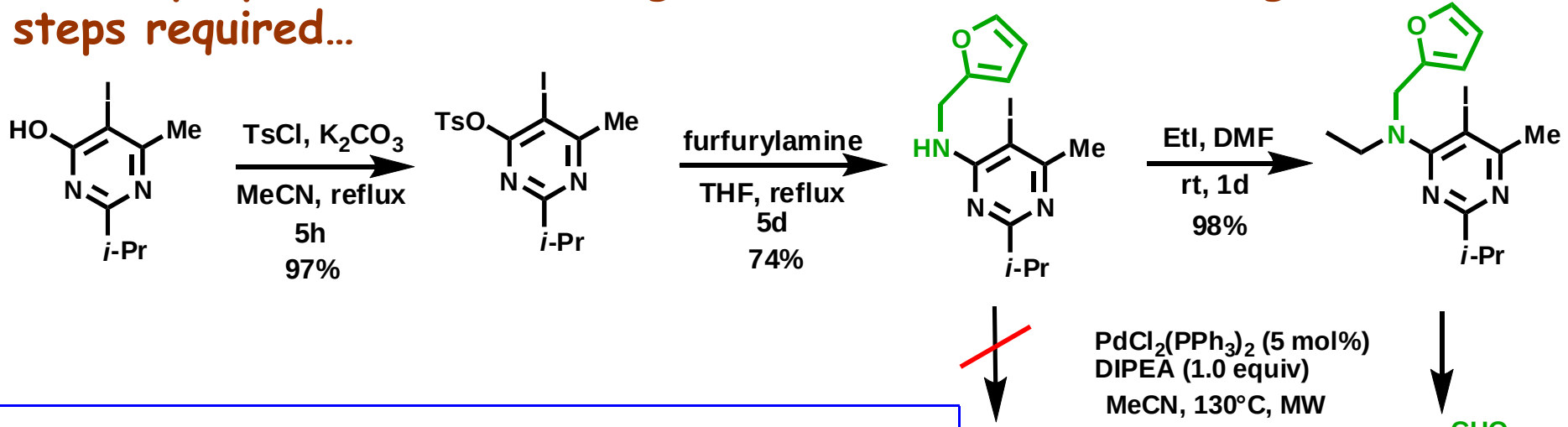
MCRs for new Palladium catalyzed ring-opening



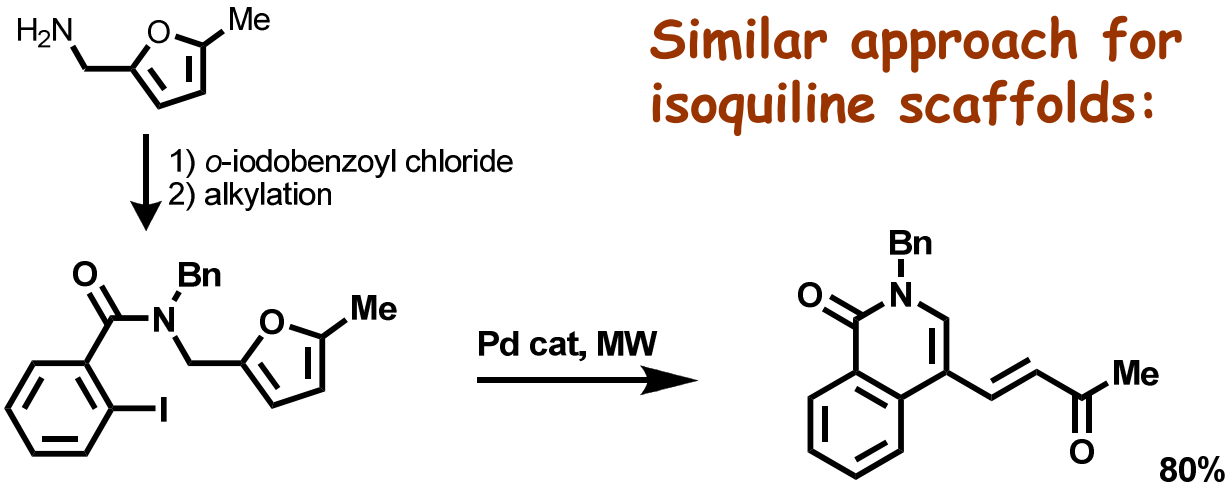
L. El Kaïm, L. Grimaud, S. Wagschal *Chem. Comm.* **2011**, 47, 1887-1889

MCRs for new Palladium catalyzed ring-opening

Conventionnal preparation of starting materials for this new fragmentation: Three steps required…

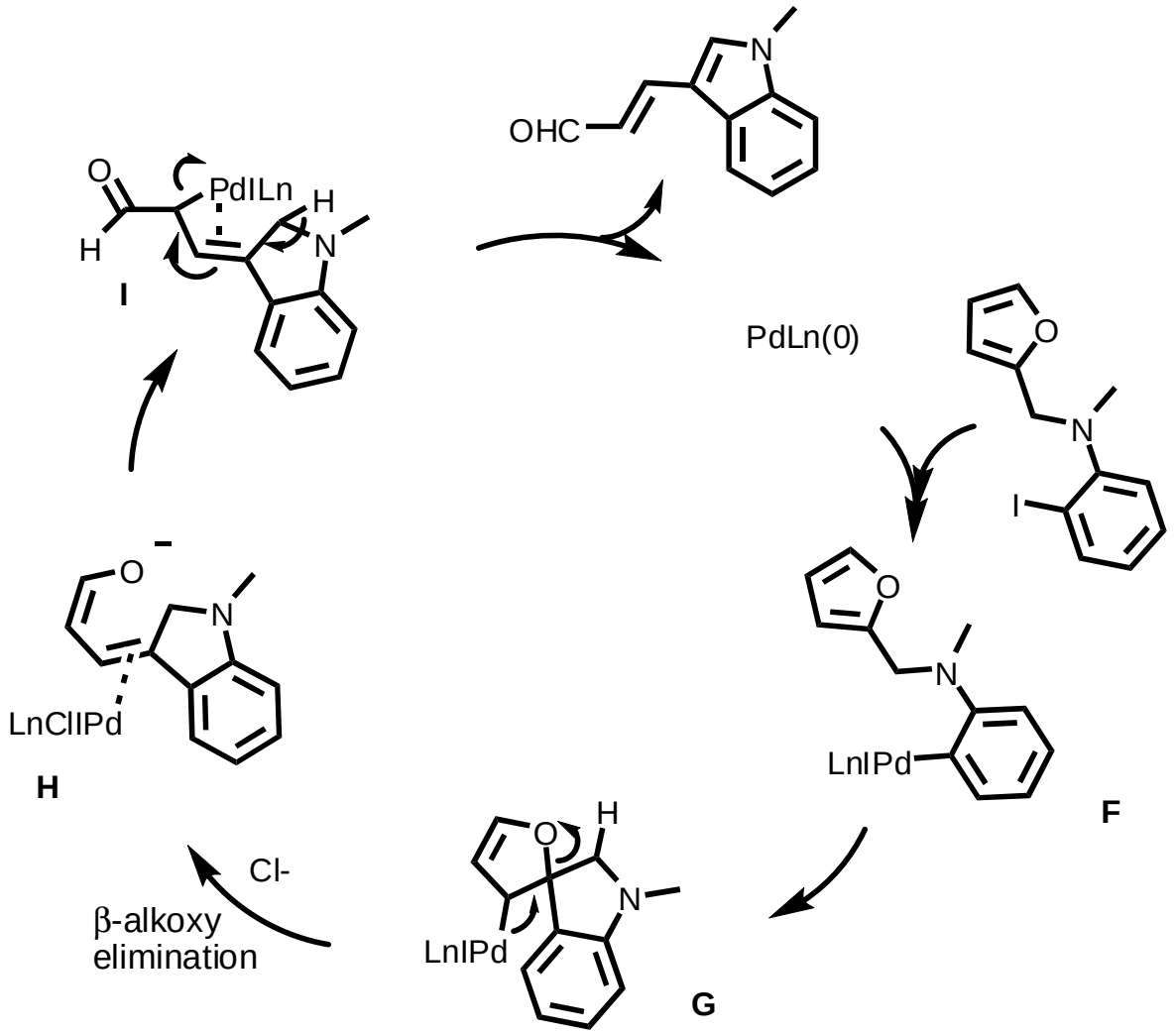


Similar approach for isoquiline scaffolds:



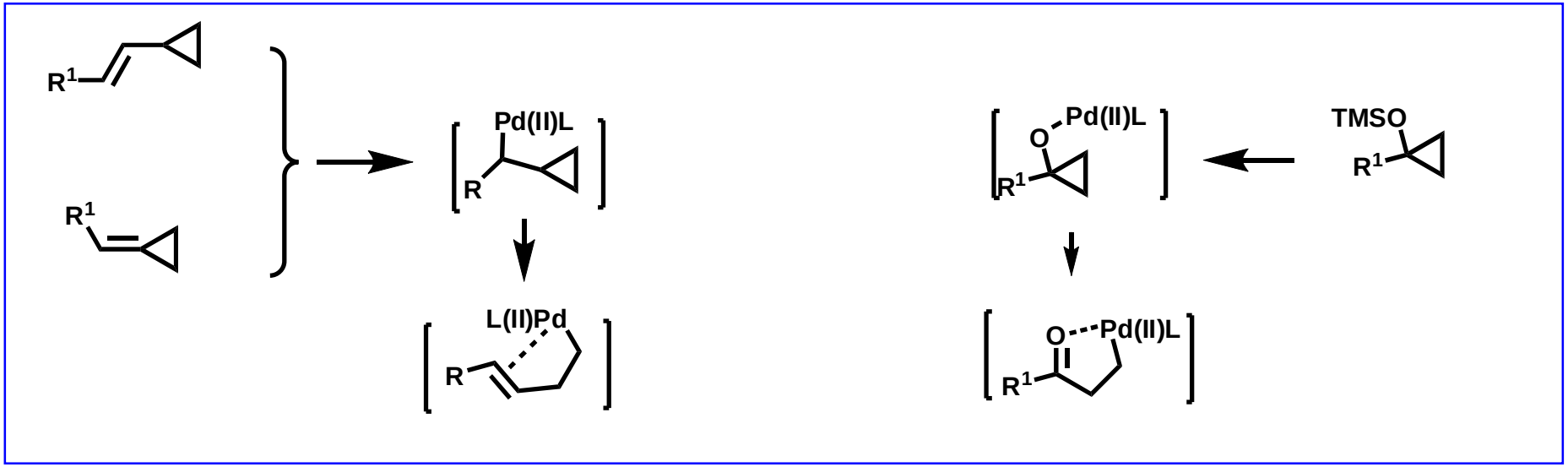
MCRs for new Palladium catalyzed ring-opening

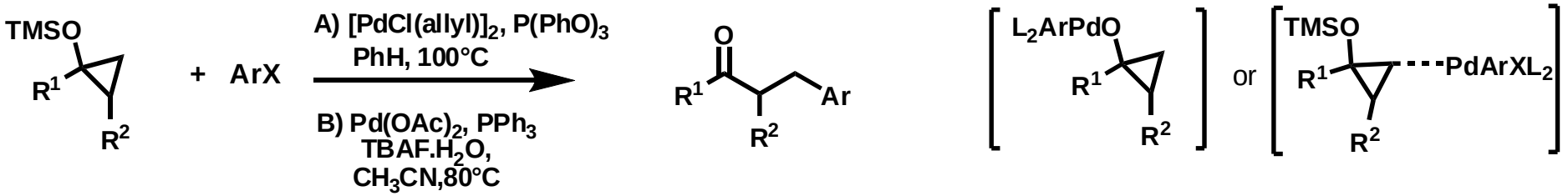
Carbopalladation Mechanism:



MCRs for new Palladium catalyzed ring-opening

Classical ring-openings of cyclopropanes triggered by palladium:

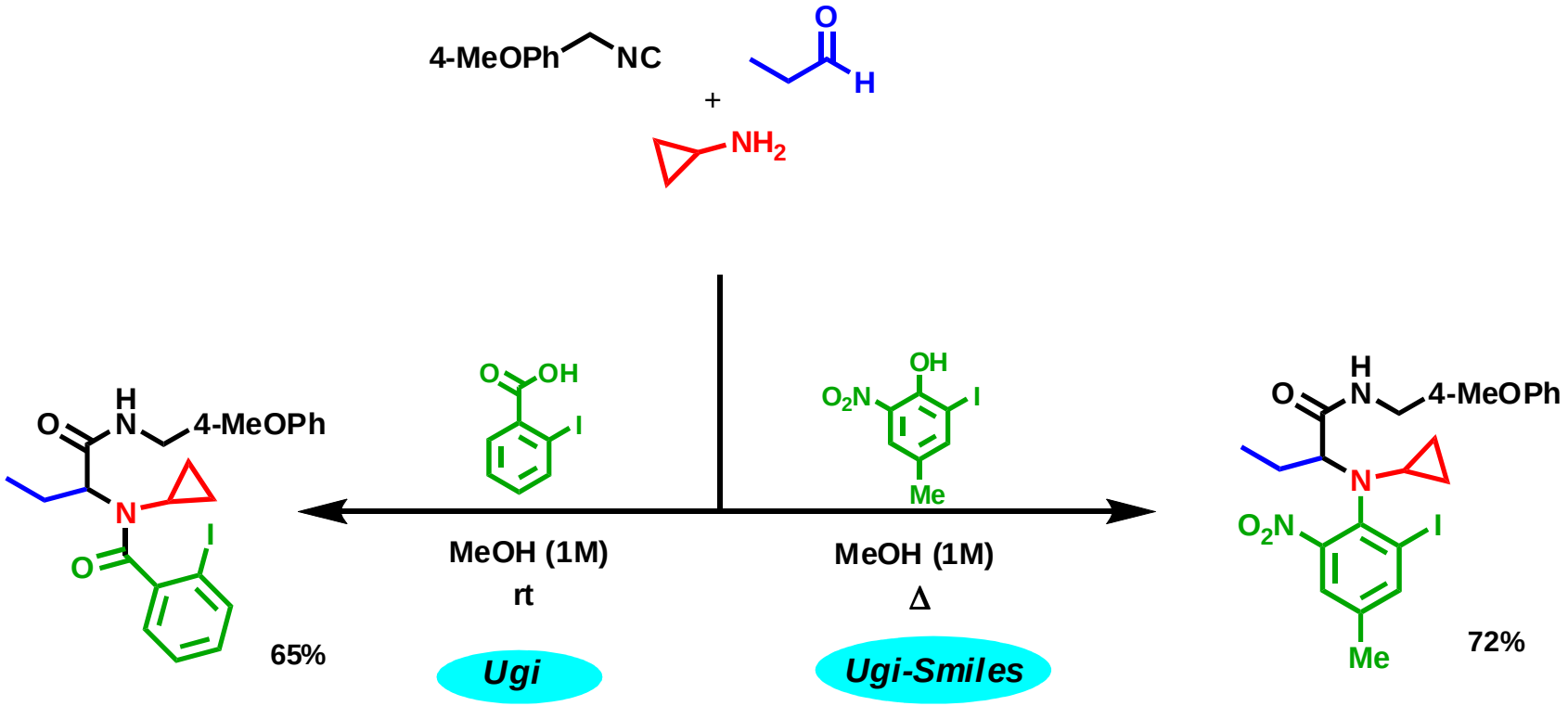




A. E. Nakamura, I. Kuwajima, *J. Am. Chem. Soc*. **1977**, *99*, 7360.
B. D. Rosa, A. Orellana, *Org. Lett.* **2011**, *13*, 110-113.

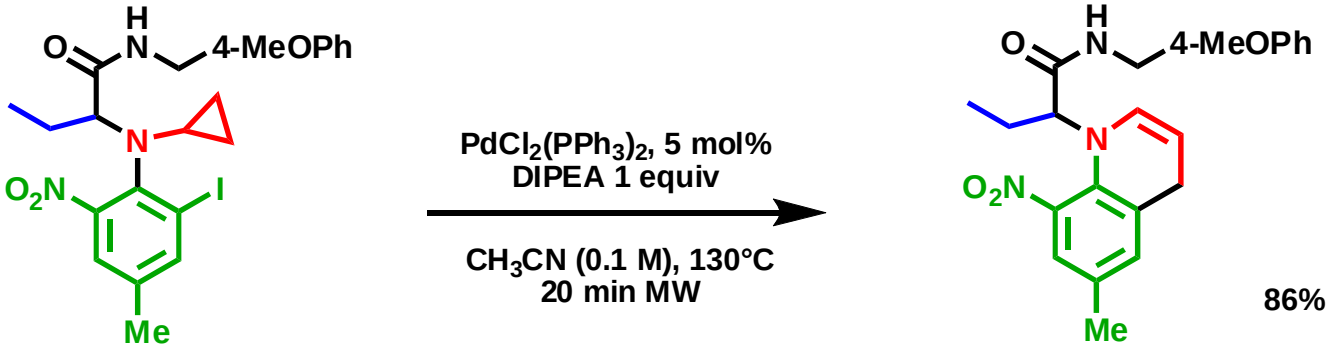
MCRs for new Palladium catalyzed ring-opening

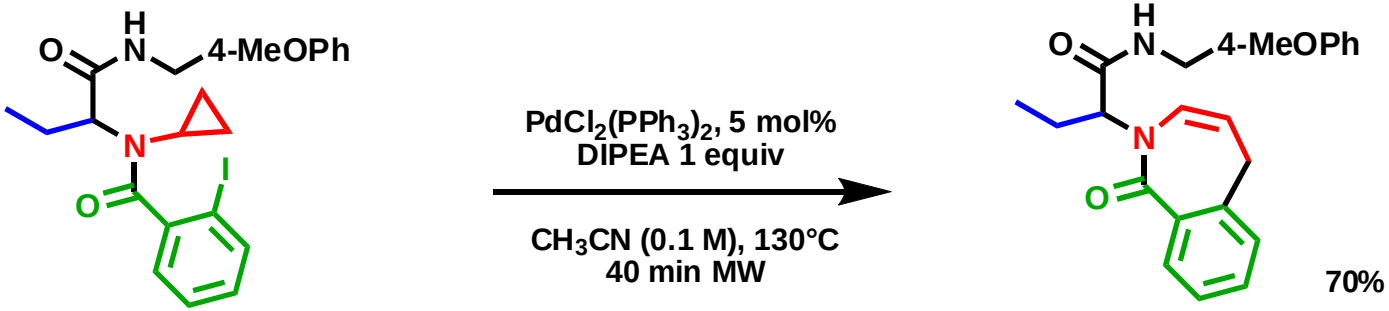
Cyclopropylamine in Ugi couplings:



MCRs for new Palladium catalyzed ring-opening

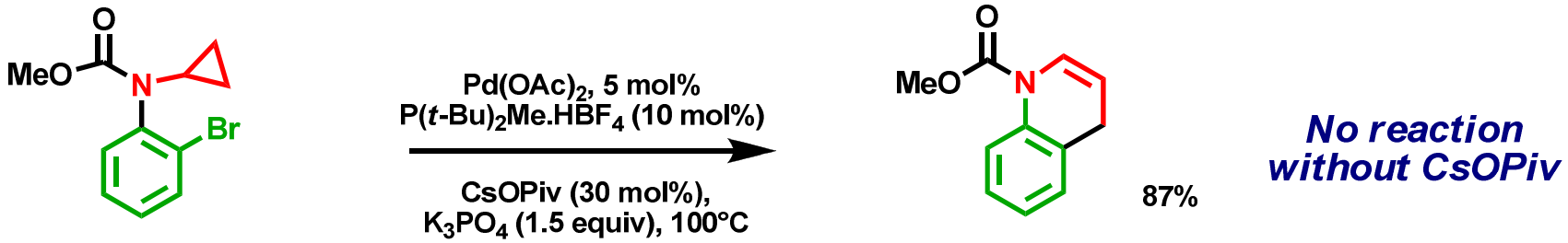
Fragmentation of Ugi adducts :





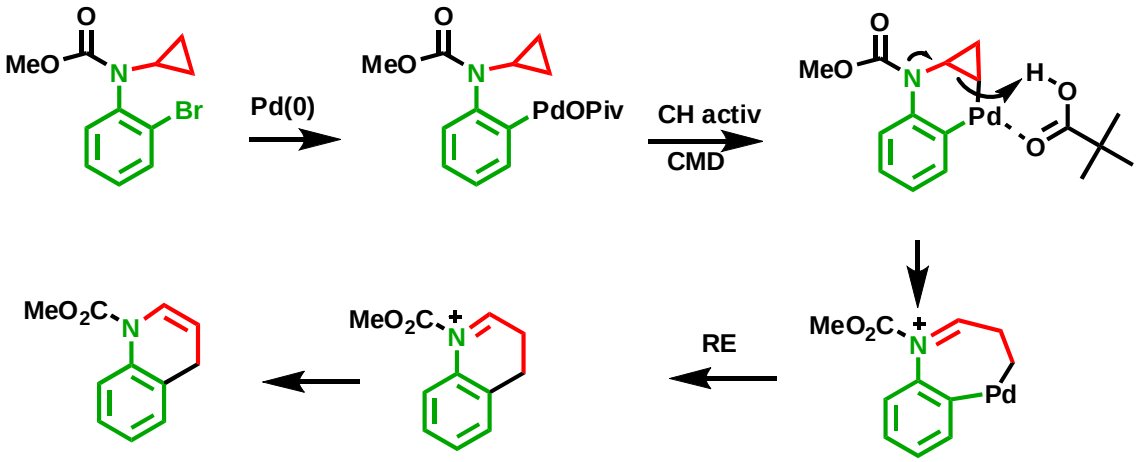
MCRs for new Palladium catalyzed ring-opening

Publication by S. Rousseaux et al, apparently the same reaction (published just a couple of months before our study…)



No reaction without CsOPiv

Their mechanistic proposition via a CMD due the role of CsOPiv:

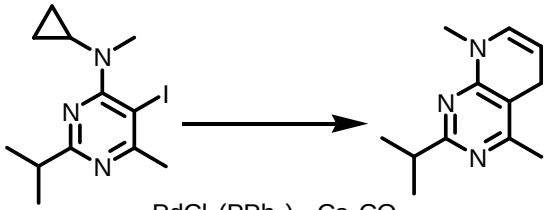


Our simple catalytical system ($PdCl_2(PPh_3)_2$ indicates a different mechanism.

Rousseaux, S., Liégault, B., Fagnou, K. *Chem. Sci.* **2012**, *3*, 244-248

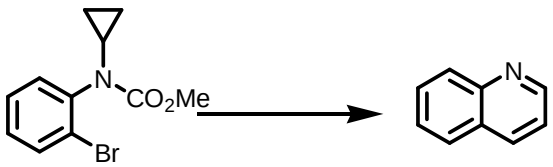
MCRs for new Palladium catalyzed ring-opening

Iodo and bromoarenes show a different behavior under treatment with the two catalytical systems:



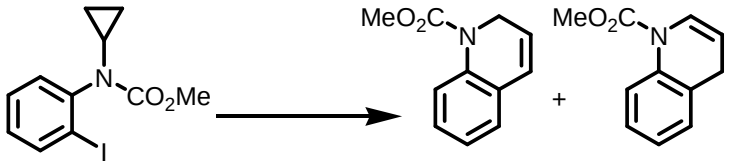
$PdCl_2(PPh_3)_2$, Cs_2CO_3
CH_3CN, 130°C, MW — **61 %**

$Pd(OAc)_2$ $PBu_2Me.HBF_4$
K_3PO_4, CsOPiv,
120°C, Mesitylene — **0 %**



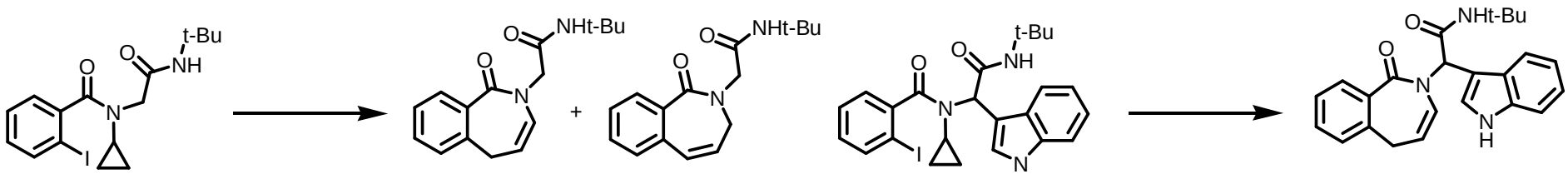
$PdCl_2(PPh_3)_2$, Cs_2CO_3
CH_3CN, 130°C, MW — **0%**

1) $Pd(OAc)_2$ $PBu_2Me.HBF_4$
K_3PO_4, CsOPiv, 120°C, Mesitylene
2) DDQ, THF — **87 %**



$PdCl_2(PPh_3)_2$, Cs_2CO_3
CH_3CN, 130°C, MW — **48 %** — **5%**

$Pd(OAc)_2$ $PBu_2Me.HBF_4$
K_3PO_4, CsOPiv,
120°C, Mesitylene — **45 %** — **0 %**



$PdCl_2(PPh_3)_2$, Cs_2CO_3
CH_3CN, 130°C, MW — **47 %** — **17 %**

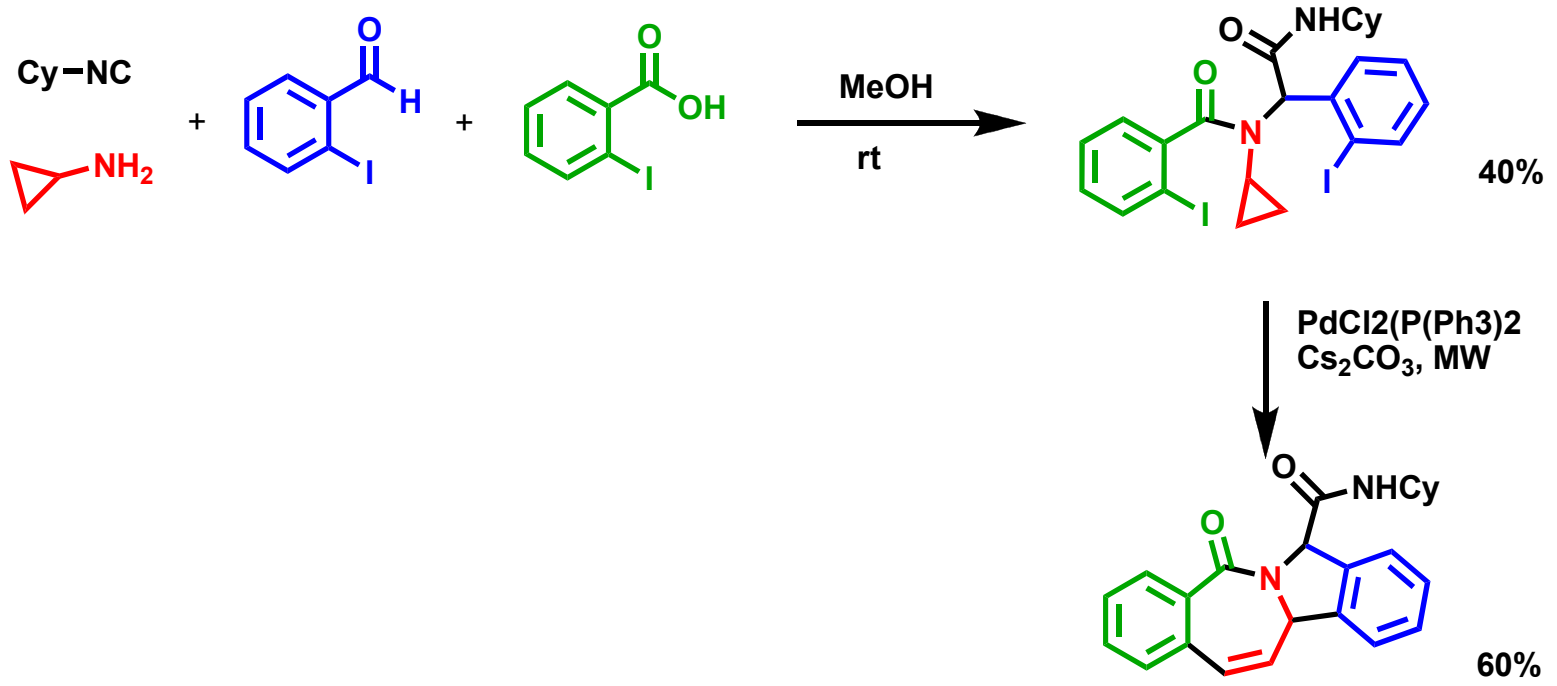
$Pd(OAc)_2$ $PBu_2Me.HBF_4$
K_3PO_4, CsOPiv,
120°C, Mesitylene — **17 %** — **37 %**

$PdCl_2(PPh_3)_2$, Cs_2CO_3
CH_3CN, 130°C, MW — **69 %**

$Pd(OAc)_2$ $PBu_2Me.HBF_4$
K_3PO_4, CsOPiv,
120°C, Mesitylene — **0%**

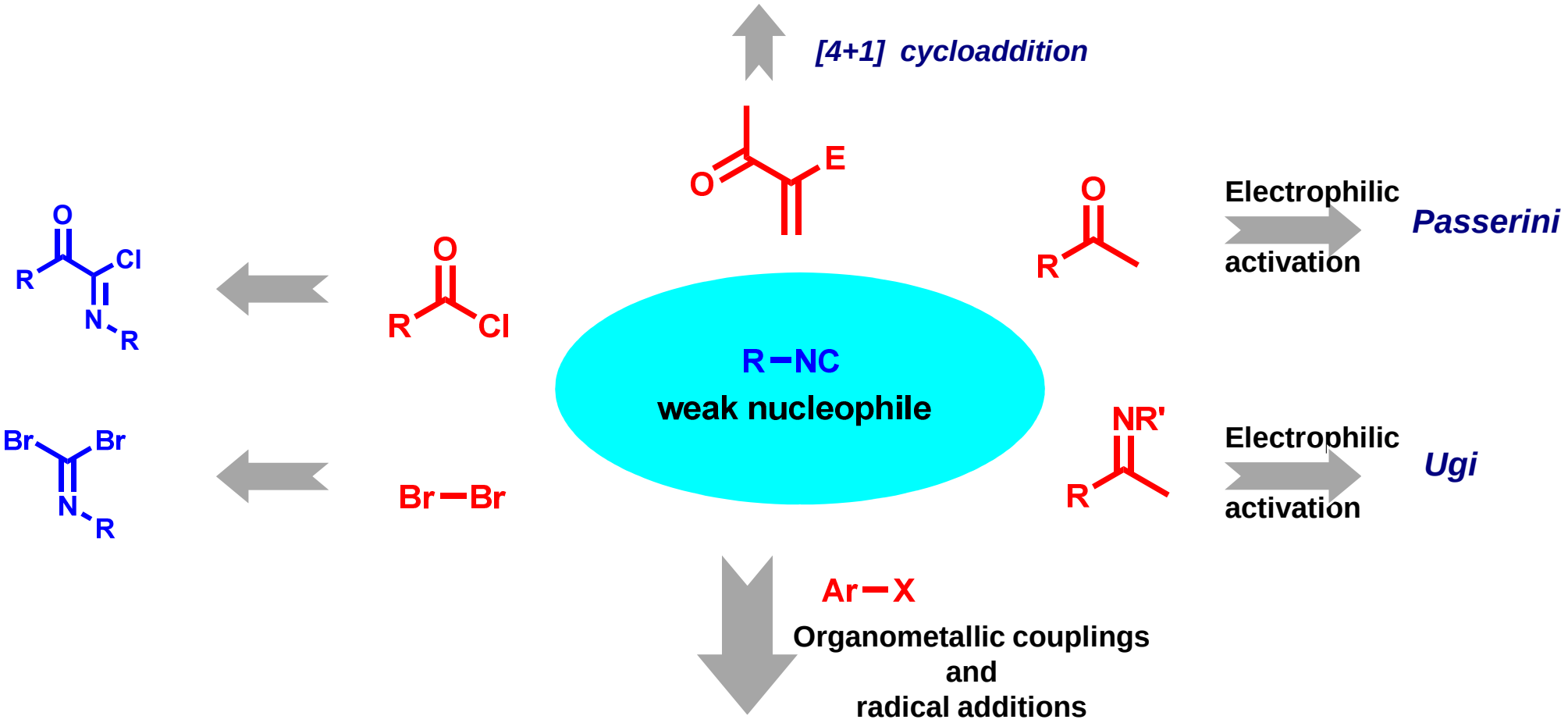
MCRs for new Palladium catalyzed ring-opening

The power of MCRs for a palladium triggered cyclization cascade:

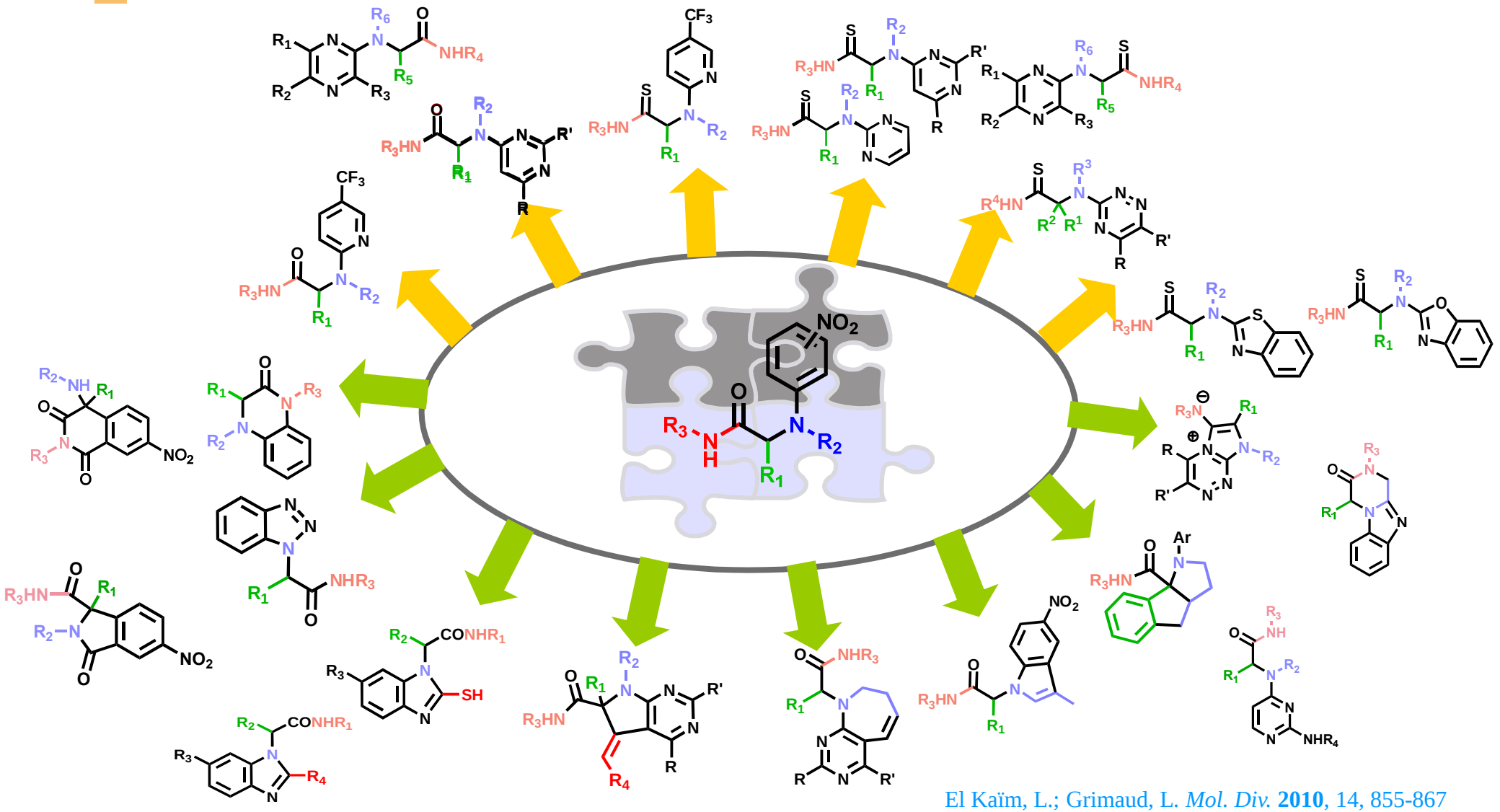


A. Dos Santos, L. El kaim, L. Grimaud, R. Ramozzi. *Synlett.* **2012**, *23*, 438.

Other interest for isocyanide based MCRs at ENSTA



Ugi-Smiles scaffolds prepared at ENSTA (up to 2010)



El Kaïm, L.; Grimaud, L. *Mol. Div.* **2010**, 14, 855-867

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Dr Martha Menez
Dr Pravin Patil
Romain Ramozzi

Diazonium chemisttry
Murali Basavanag
Aurélie Dos Santos

Collaboration:

Pr R. G. Montano (Guanajuato
Dr L. Miranda (UNAM-Mexico)
Dr Paul Fleurat-Lessard

CNRS,
ANR
DGA,
ENSTA,
Polytechnique

ENSTA From Paris
To Palaiseau (08/2012)