

# Catalyse organométallique pour une chimie verte et durable

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Organométalliques: Matériaux et Catalyse

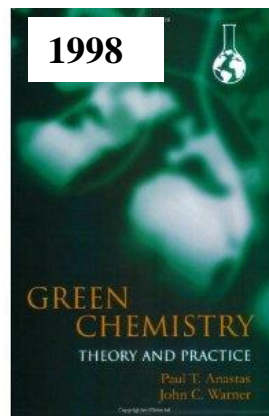
UMR 6226 : CNRS – Université de Rennes 1

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Rennes, France

# Green Chemistry: Definitions

*Green Chemistry is the **design of chemical products and processes that reduces or eliminates the use or generation of hazardous substances.***



Dr. Anastas began his career as a staff chemist at EPA, where he rose to the positions of chief of the Industrial Chemistry Branch, and director of the U.S. Green Chemistry Program. It was during his work at EPA that Dr. P. Anastas coined the term "**green chemistry.**"

From 1999 to 2004 he worked at the White House Office of Science and Technology Policy, concluding his service there as the assistant director for the environment. During the period 2009-2012, he was Assistant Administrator & Science Advisor for the US Environmental Protection Agency's Office of Research and Development and became a Science Advisor to the Agency.

He is director of the Center for Green Chemistry and Green Engineering at Yale.

Dr. Warner is President, Chief Technology Officer, and Chairman of the Board of the Warner Babcock Institute for Green Chemistry, which he founded with Jim Babcock in 2007. Dr. Warner received his B.S. in Chemistry from the University of Massachusetts-Boston and his M.S. and Ph.D. from Princeton in Organic Chemistry.

<http://www.warnerbabcock.com/>

# Les 12 principes de la chimie verte

Source: Paul T. Anastas et John C. Warner,  
*Green Chemistry: Theory and Practice*, Oxford University Press, New York, 1998.

## 1. Prévention

Mieux vaut éviter de produire des déchets que d'avoir ensuite à les traiter ou s'en débarrasser.

## 2. Économie d'atomes

Mise en œuvre de méthodes de synthèse qui incorporent dans le produit final tous les matériaux entrant dans le processus.

## 3. Conception de méthodes de synthèse moins dangereuses

Dans la mesure du possible, les méthodes de synthèse doivent utiliser et produire des substances peu ou pas toxiques pour l'homme et l'environnement.

## 4. Conception de produits chimiques plus sûrs

Mise au point de produits chimiques atteignant les propriétés recherchées tout en étant les moins toxiques possible.

## 5. Solvants et auxiliaires moins polluants

Renoncer à utiliser des auxiliaires de synthèse (solvants, agents de séparation, etc.) ou choisir des auxiliaires inoffensifs lorsqu'ils sont nécessaires.

## 6. Recherche du rendement énergétique

La dépense énergétique nécessaire aux réactions chimiques doit être examinée sous l'angle de son incidence sur l'environnement et l'économie, et être réduite au minimum. Dans la mesure du possible, les opérations de synthèse doivent s'effectuer dans les conditions de température et de pression ambiantes.

## 7. Utilisation de ressources renouvelables

Utiliser une ressource naturelle ou une matière première renouvelable plutôt que des produits fossiles, dans la mesure où la technique et l'économie le permettent.

## 8. Réduction du nombre de dérivés

Éviter, si possible, la multiplication inutile des dérivés en minimisant l'utilisation de radicaux bloquants (protecteurs/déprotecteurs ou de modification temporaire des processus physiques ou chimiques) car ils demandent un surplus d'agents réactifs et peuvent produire des déchets.

## 9. Catalyse

L'utilisation d'agents catalytiques (aussi sélectifs que possible) est préférable à celle de procédés stœchiométriques.

## 10. Conception de produits en vue de leur dégradation

Les produits chimiques doivent être conçus de telle sorte qu'en fin d'utilisation ils se décomposent en déchets inoffensifs biodégradables.

## 11. Observation en temps réel en vue de prévenir la pollution

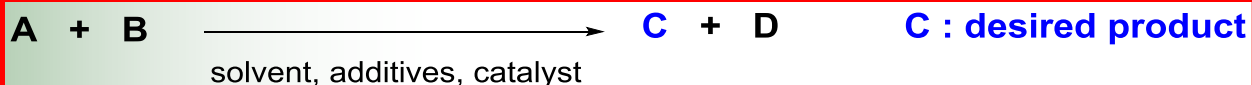
Les méthodes d'observation doivent être perfectionnées afin de permettre la surveillance et le contrôle en temps réel des opérations en cours et leur suivi avant toute formation de substances dangereuses.

## 12. Une chimie fondamentalement plus fiable

Les substances entrant dans un processus chimique, ainsi que leur état physique, doivent être choisis de façon à prévenir les accidents tels qu'émanations dangereuses, explosions et incendies.

## 1. E factor, PMI, EYM (the environmental factors)

1) **Prevention:** It is better to **prevent waste** than to treat or clean up waste after it has been created



- **Environmental factor (E-factor):** Measure waste generated (optimal  $E = 0$ )

$$\text{E-factor} = \frac{\text{Mass of waste}}{\text{Mass of desired product C}}$$

**Waste :** product **D** + unreacted **A** and **B** + additives + solvent losses + fuel

R. A. Sheldon, *Chem. Ind.* **1992**, 903; R. A. Sheldon, *ChemTech* **1994**, 24, 38; R. A. Sheldon, *Green Chem.* **2007**, 9, 1273.

- **Process Mass Intensity (PMI or MI):** Measure the use of raw materials (optimal  $PMI = 1$ )

$$\text{MI} = \frac{\text{Mass of material used}}{\text{Mass of desired product C}} = \text{E-factor} + 1$$

A. D. Curzons, D. J. C. Constable, *et al.*, *Green Chem.* **2001**, 3, 1-6. & 7-9.

C. Jimenez-Gonzalez, C. S. Ponder, Q.B. Broxterman, J. B. Manley, *Org. Process. Res. Dev.* **2011**, 15, 912.

- **Effective Mass Yield (EMY) :** =  $1/\text{MI} \times 100$  (optimal  $EMY = 100\%$ )

T. Hudlicky, D. A. Frey, L. Koroniak, C. D. Claeboe, L. E. Brammer, *Green Chem.* **1999**, 1, 57-59.

## 1. E factor (environmental factor)

1) **Prevention:** It is better to prevent waste than to treat or clean up waste after it has been created.

$$\text{E-factor} = \text{kg of waste} / \text{kg product}$$

The ideal or target E value is 0.

	Product (t)	E-factor
Petrochemical Industries	$10^6 - 10^8$	0.1
Basic chemicals	$10^4 - 10^6$	1 - 5
Fine Chemistry	$10^2 - 10^4$	5 - 50
Pharmaceuticals	$10^1 - 10^3$	25 - >100

R. A. Sheldon, *Chem. Ind. (London)* **1992**, 903.

### 2) Atom Economy

Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.



$$\text{Atom Economy (\%)} = \frac{\text{Mass of the desired product } C}{\text{Mass of all products } (C + D)} \times 100 \quad (\text{optimum AE} = 100\%)$$

B.M. Trost, *Science*, **1991**, 254, 1471

C. J. Li, B. M. Trost, *PNAS*, **2008**, 105, 13197

B. M. Trost, *Angew. Chem. Int. Ed.* **1995**, 34, 259

## 2) Atom Economy

### Some atom economic reactions

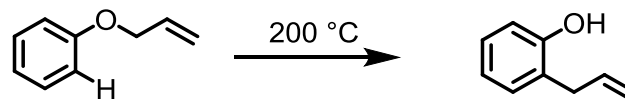
Addition reactions

Carbonylation

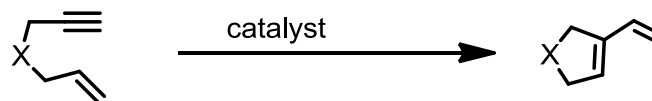
Hydrogenation

Dimerization

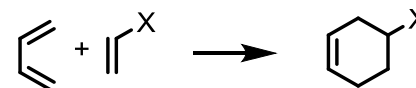
Rearrangement reactions



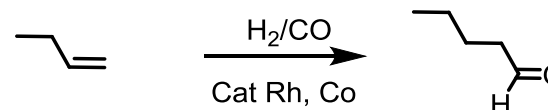
Enyne metathesis



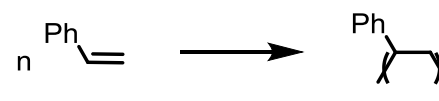
Diels-Alder addition and other cycloadditions and  
concerted reactions



Hydroformylation



Polymerisation





## 2. Atom Economy

### and some atom non-economic reactions

Substitution reactions

Aromatic substitution reactions

(nitration, halogenation,  
diazotation, Friedel-Crafts...)

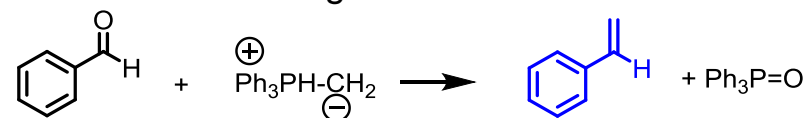
Elimination reactions

Reactions with Grignards reagents

Asymmetric Aminohydroxylation

Classical oxidation and reduction

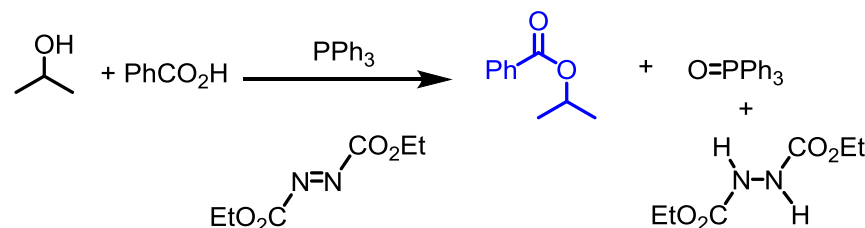
### Wittig reactions



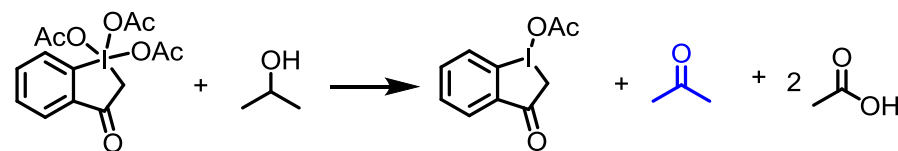
### Friedel-Crafts



### Mitsunobu reactions



### Oxidation



### Why do we need solvents....what are the advantages ?

- Get molecules into an homogeneous phase by dissolving solid reagents
- Lower viscosity and facilitate mixing
- Regulate temperature of reactions by heating at reflux
- Facilitate thermal exchanges in particular for exothermic reactions
- Facilitate purifications : Filtration, extraction, crystallisation.....

### but solvents may also be

- (Highly) toxic for humans, nature, environment
- Hazardous : Fire, explosion
- Costly

and solvents are usually the chemicals used in the largest amount in a chemical transformation

## Solvent Selection Guides - Pfizer

Preferred	Usable	Undesirable
Water	Cyclohexane	Pentane
Acetone	Heptane	Hexane(s)
Ethanol	Toluene	Di-isopropyl ether
2-Propanol	Methylcyclohexane	Diethyl ether
1-Propanol	Methyl t-butyl ether	Dichloromethane
Ethyl acetate	Isooctane	Dichloroethane
Isopropyl acetate	Acetonitrile	Chloroform
Methanol	2-Methyl THF	Dimethylformamide
Methyl ethyl ketone	Tetrahydrofuran	N-methylpyrrolidinone
1-Butanol	Xylenes	Pyridine
t-Butanol	Dimethyl sulfoxide	Dimethylacetamide
	Acetic acid	Dioxane
	Ethylene glycol	Dimethoxyethane
		Benzene
		Carbon tetrachloride

“The guide and replacement table seem almost ridiculously simple but when used by our enthusiastic site teams they led to amazing results, including a 50% reduction in chlorinated solvent use across the whole of our research division (more than 1600 lab based synthetic organic chemists, and four scale-up facilities) during the time period 2004–2006. Even sites that had an increase in the number of chemists during that period were able to report a 50% reduction in chlorinated solvent use. In addition, we were able to reduce the use of an undesirable ether by 97% over the same two year period and substantially promote the use of heptane compared with hexane (more toxic) and pentane (much more flammable).”

## Green(er) Solvents

**Low (eco)toxicity, hazards, risks**

*CMR, LD, LC, flash point, explosion limits, peroxides...*

**Easy recyclability**

**Easy separation from products/reagents/catalyst**

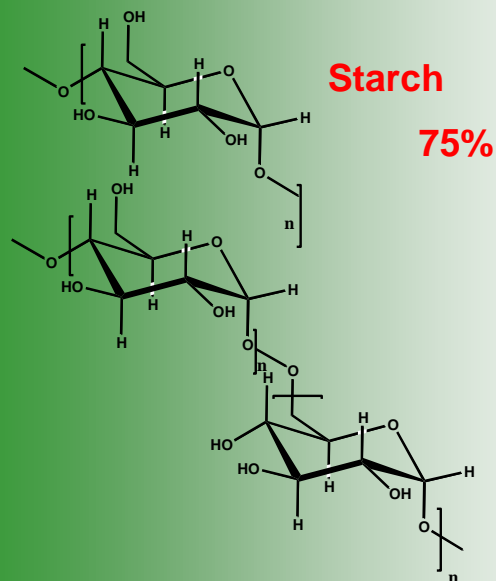
**Biodegradable**

**Green synthesis of the solvent**

1. Water
2. Ionic Liquids (ILs)
3. Super Critical fluids (ScCO<sub>2</sub>)
4. Perfluoroalkanes

170 billion ton/year of available biomass

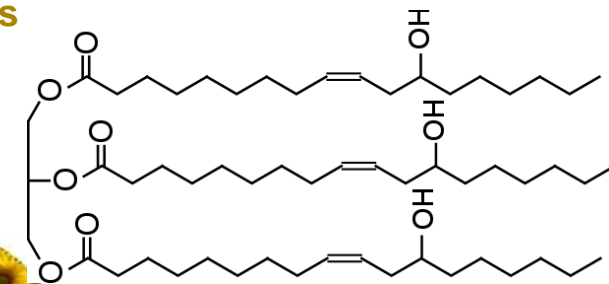
Utilization: Less than 3 %



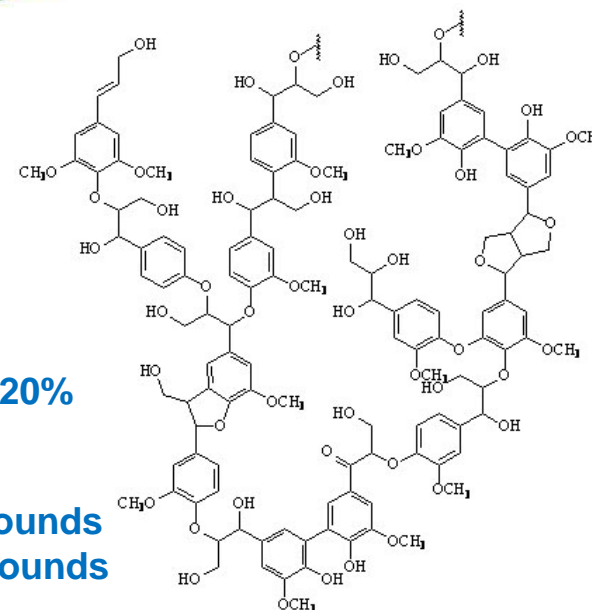
**Lignocellulose**  
*Hemicellulose, cellulose, lignin*

**Fats and oils**

5%



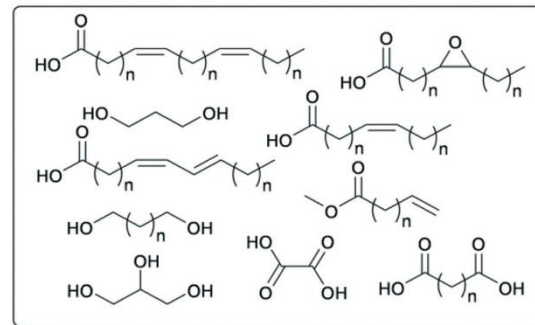
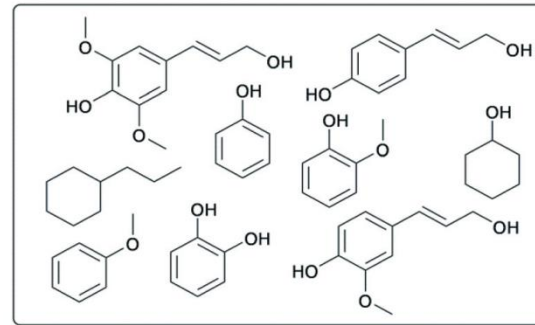
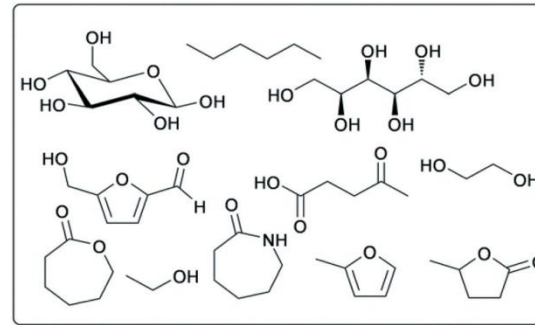
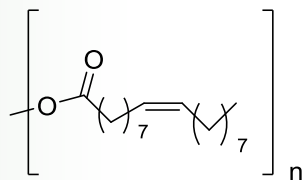
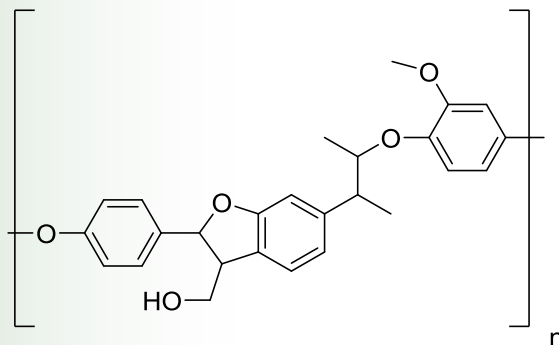
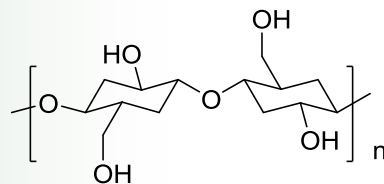
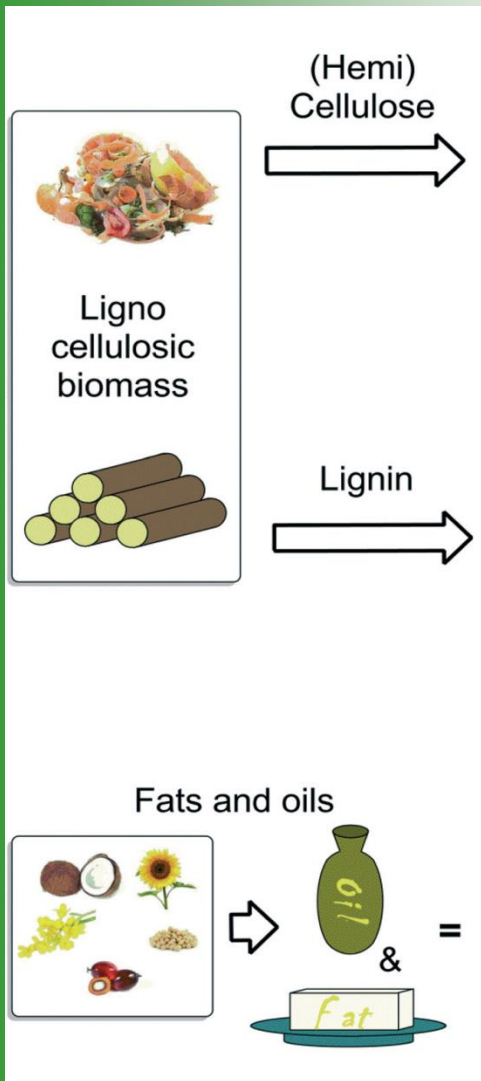
**Long chain aliphatic  
compounds**



**Oxygenated compounds**

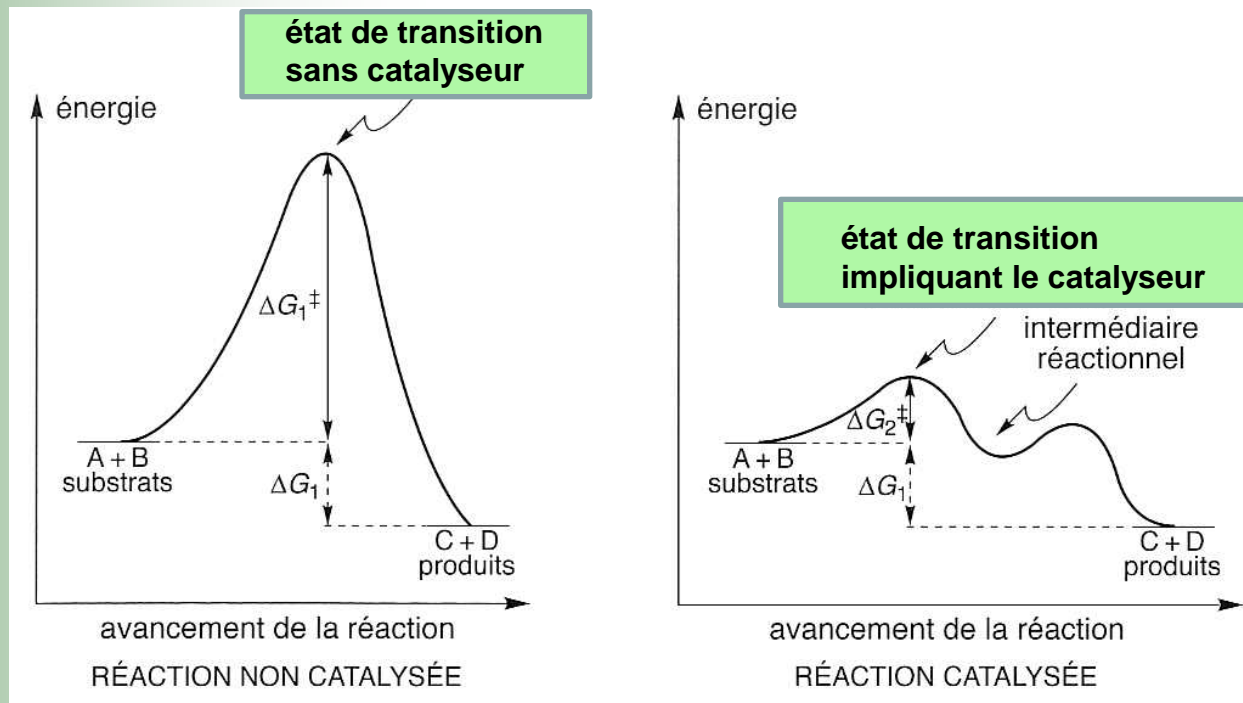
**Phenolic compounds  
Aromatic compounds**

**Biomass transformations to chemicals**



## 9. Catalysis

Energy economy / selectivity / new transformations made possible



The energy levels of the starting substrates on one hand and reaction products on the other hand are the same with or without catalyst ( $\Delta G_1$  constant), but the activation energy  $\Delta G^\ddagger$  is much lower when the reaction is catalyzed ( $\Delta G_{1^\ddagger} \gg \Delta G_{2^\ddagger}$ ).

A catalyzed reaction can eventually involve one or several reaction intermediates (for instance, one intermediate in the right figure above).



## 9. Catalysis

### Different types of catalysis:

**Homogeneous catalysis**

**Heterogeneous catalysis**

**Enzymatic catalysis**

**Acid and base catalysis**

**Organocatalysis**

**Photo-catalysis**

**Redox catalysis**

**Supported catalysis**

**Metallo-dendritic catalysis**

**Biphasic catalysis**

*Source:*

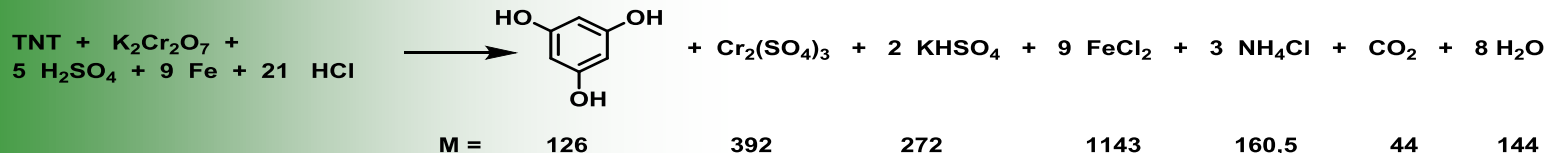
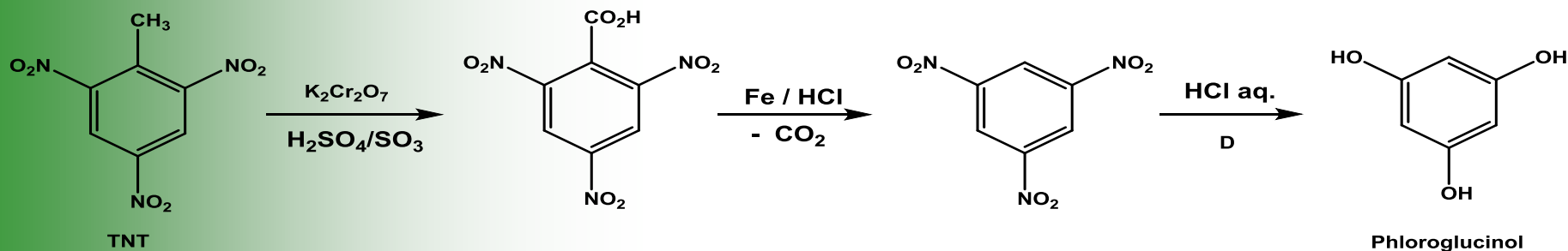
*Organometallic Chemistry and Catalysis*

*D. Astruc*

*Grenoble Sciences, 2013*



## The synthesis of phloroglucinol : Chemistry from the past ?



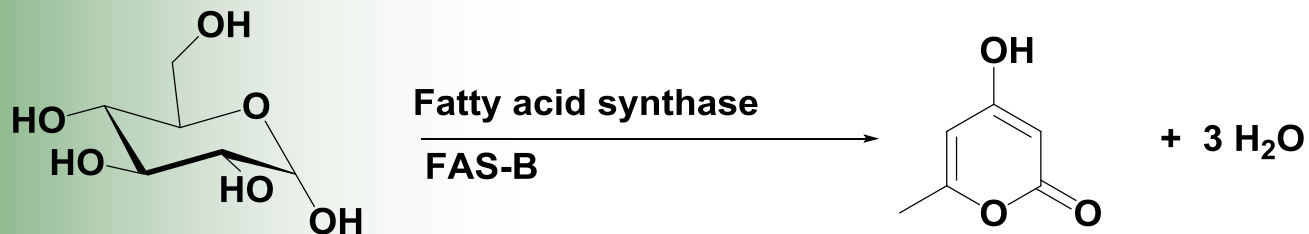
$$\% \text{ Atom Efficiency} = 100 \times 126 / (126 + 392 + 272 + 1143 + 160.5 + 44 + 144) = 126 / 2281.5 = \mathbf{5.5\%}$$

$$E = (392 + 272 + 1143 + 160.5 + 44 + 144) / 126 = 2155.5 / 126 = \mathbf{17}$$
 ( in reality, around 40 !!)

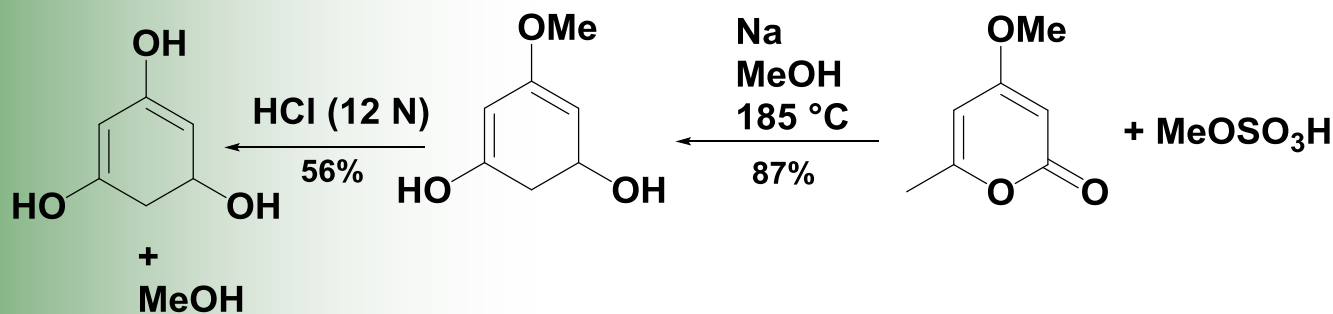
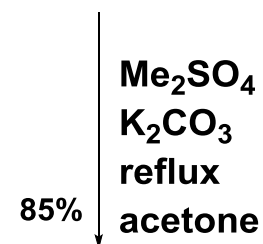
Production of around 40 kg of solid wastes ( $\text{Cr}_2(\text{SO}_4)_3$ ,  $\text{NH}_4\text{Cl}$ ,  $\text{FeCl}_2$ ,  $\text{KHSO}_4$ ) per kg of Phloroglucinol

$$MI = 41$$

T. Iwata, H. Miki, Y. Fujita, in *Ullmann's Encyclopedia of Industrial Chemistry*, **1991**, vol. A19, p. 347.



H. Zhao *et al.* *J. Am. Chem. Soc.* **2004**, *126*, 4534.

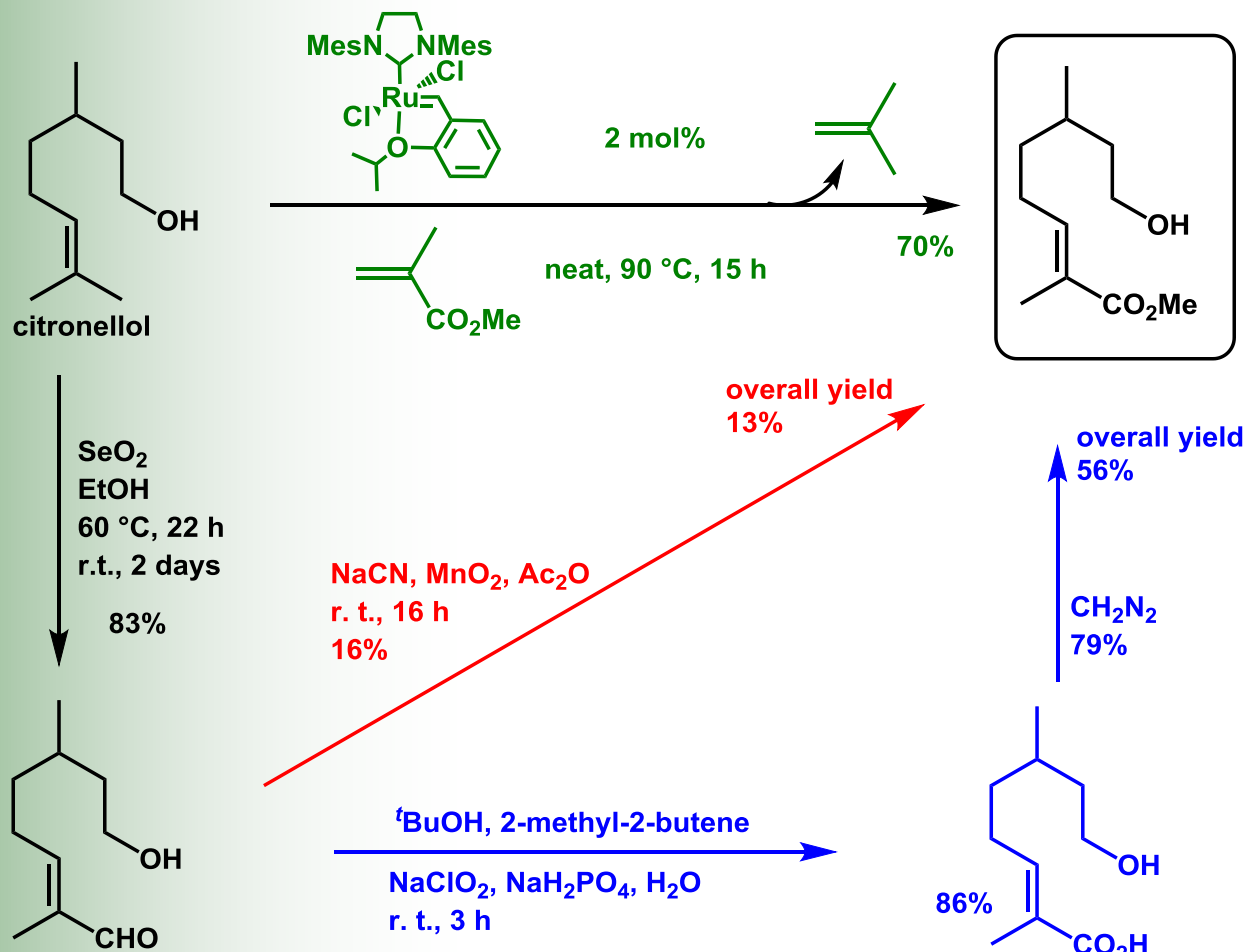


J.W. Frost, C. A. Hansen, *J. Am. Chem. Soc.* **2002**, *124*, 5926.

**% Atom Efficiency** =  $100 \times 126 / (126 + 48 + 112 + 32) = 100 \times 126 / 318 = 40\%$

**E-factor** :  $(126 + 48 + 112 + 32) / 126 = 2.5$

## Olefin cross metathesis : one step, good yield, green conditions



R. T. Brown, S. P. Mayalarp, J. Watts, *J. Chem. Soc., Perkin Trans.* **1997**, 1, 1633

T. Tsuji & al., *Biosci. Biotechnol. Biochem.* **1999**, 63, 731

H. Bilel, H. Naceur, F. Zagrouba, C. Fischmeister, C. Bruneau, *Green Chem.* **2011**, 13, 1448

## APPLICATION OF OLEFIN METATHESIS

### ACCESS TO HIGH ADDED VALUE CHEMICALS



## 1) Polyamide precursors from FAMES

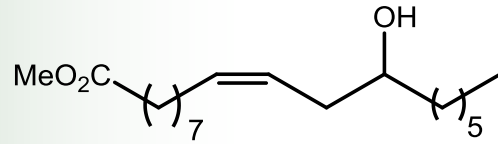
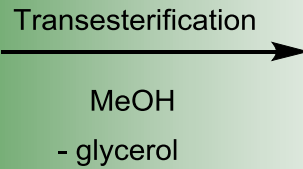


Cooperation with

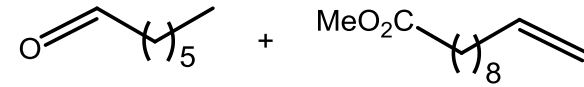
**ARKEMA**  
INNOVATIVE CHEMISTRY

# Polyamide precursors from FAMES

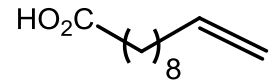
Castor oil  
(Ricin oil)



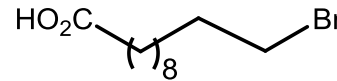
Pyrolysis



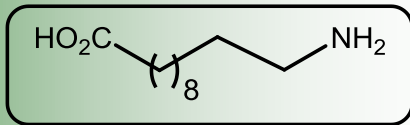
Hydrolysis



Hydrobromation



Amination  
NH<sub>3</sub>



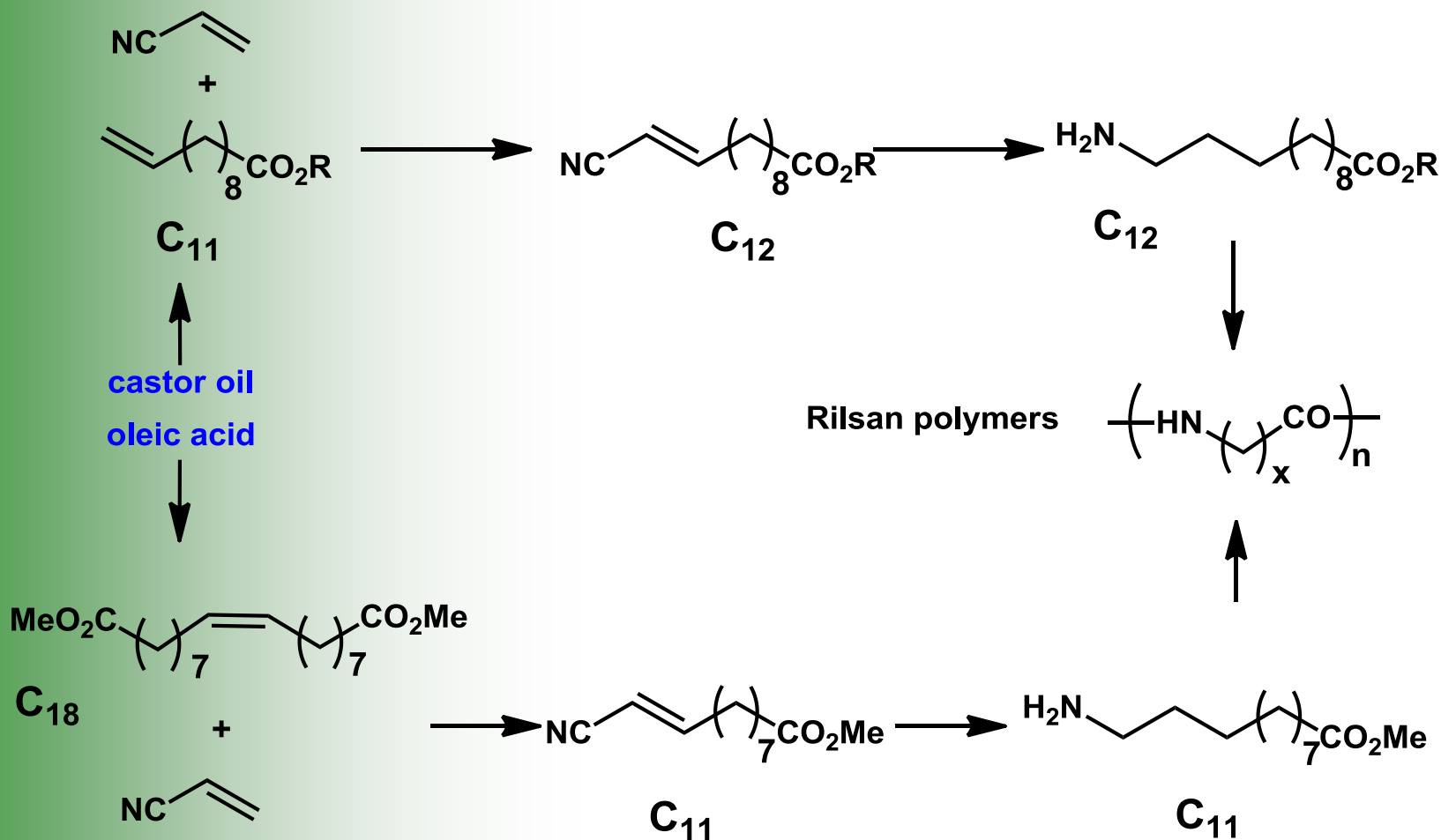
C11  
Polyamide  
(Rilsan)



Can linear aminoacids (esters),

the precursors of polyamides, be obtained from plant oils ?

Would cross-metathesis with acrylonitrile of unsaturated esters be a possible solution ?



## Problems to face

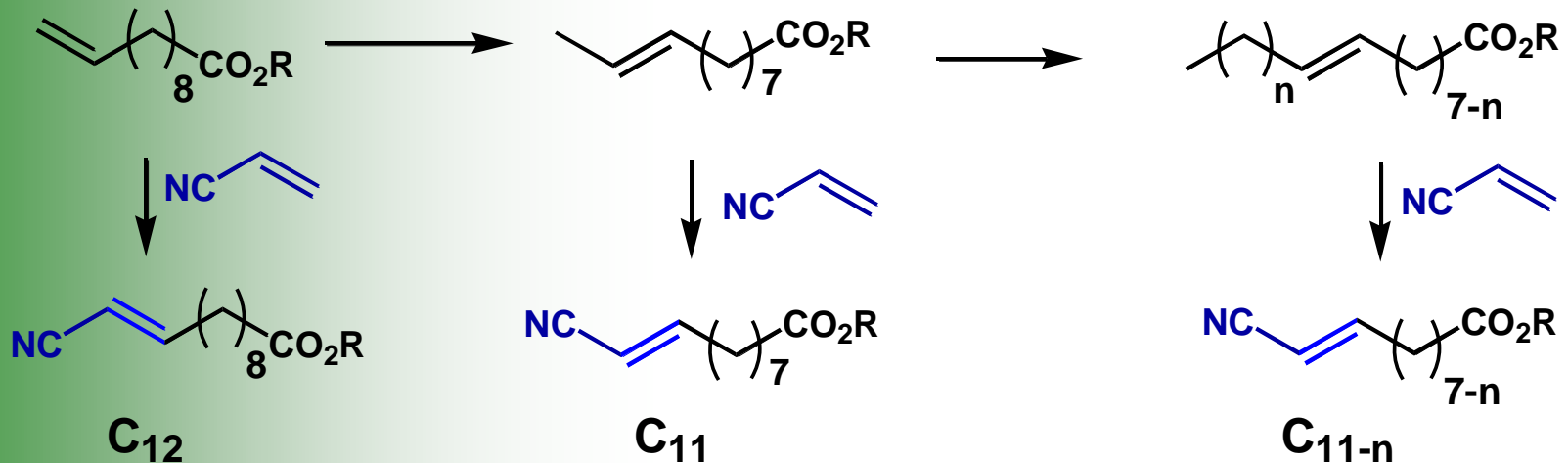
### Catalyst tolerance to acrylonitrile functionality

*Eur. J. Lipid Sci. Technol.* **2010**, *121*, 3.

*Green Chem.* **2011**, *13*, 2258.

### Ru-catalyzed double bond migration

mono unsaturated C<sub>11</sub> isomers

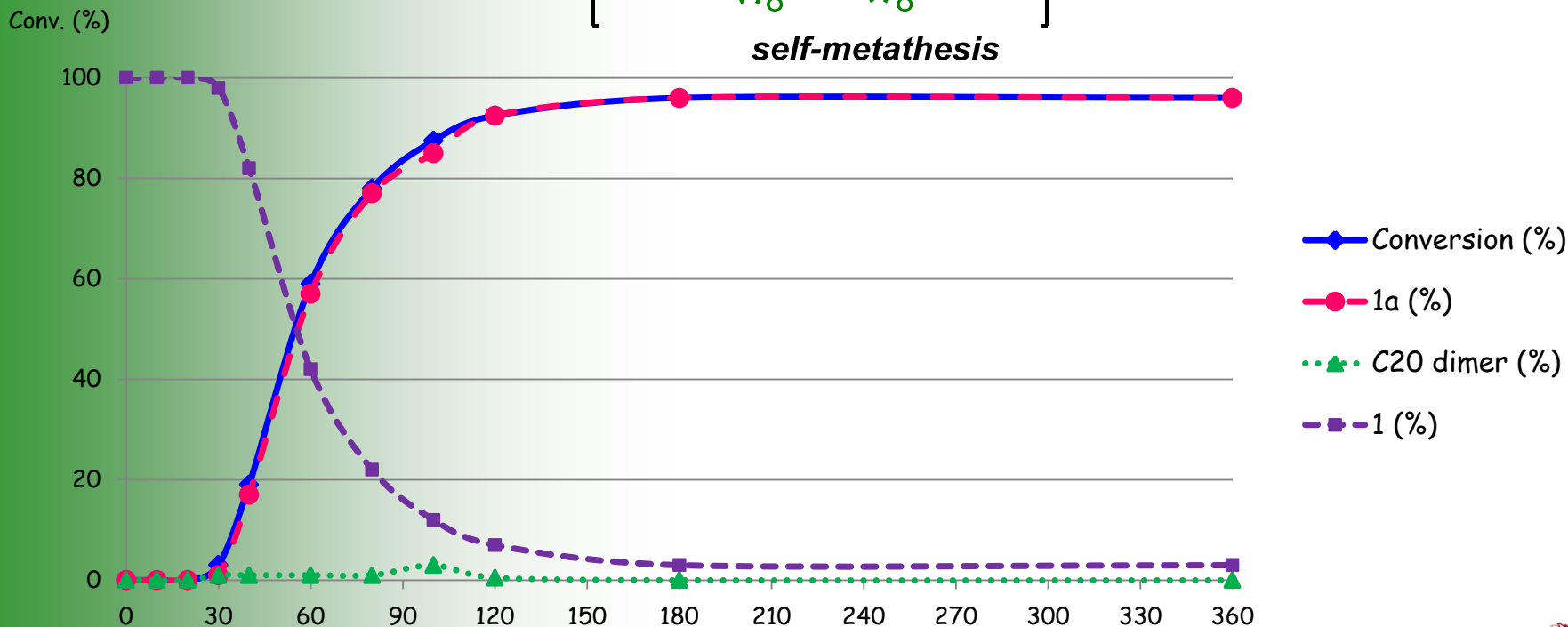
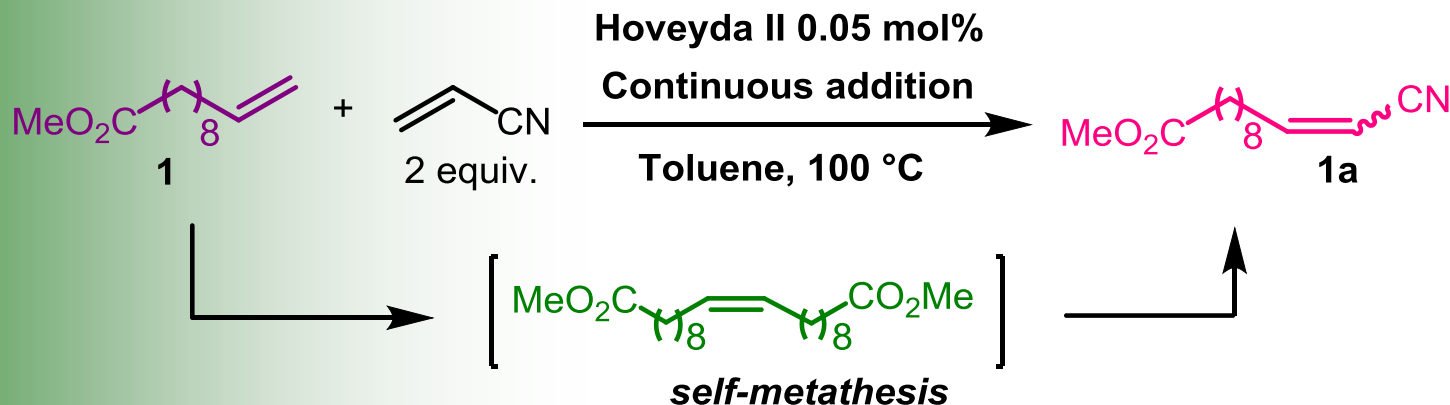


### Competing self-metathesis of the fatty olefin

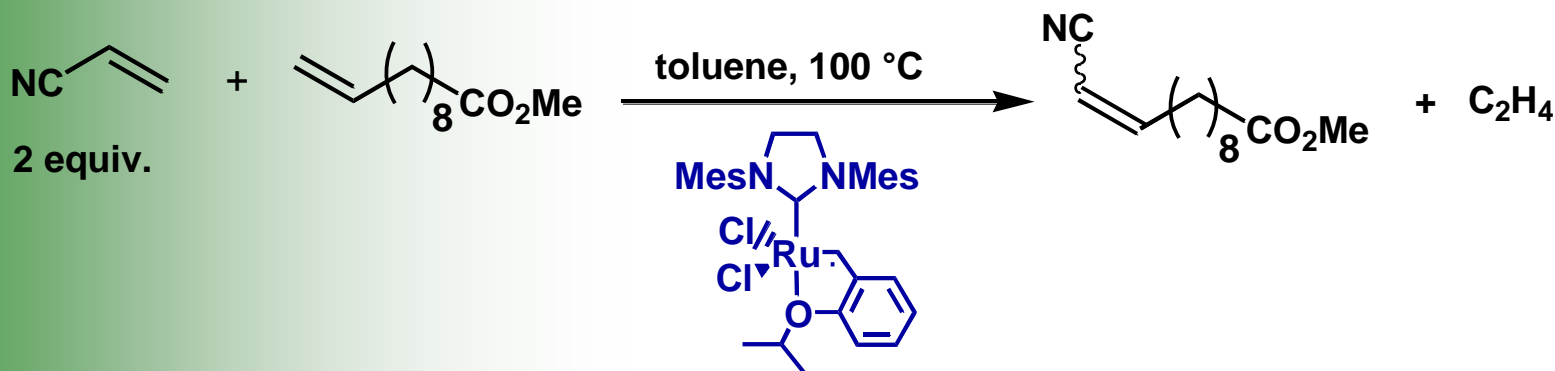




## Cross-metathesis with acrylonitrile

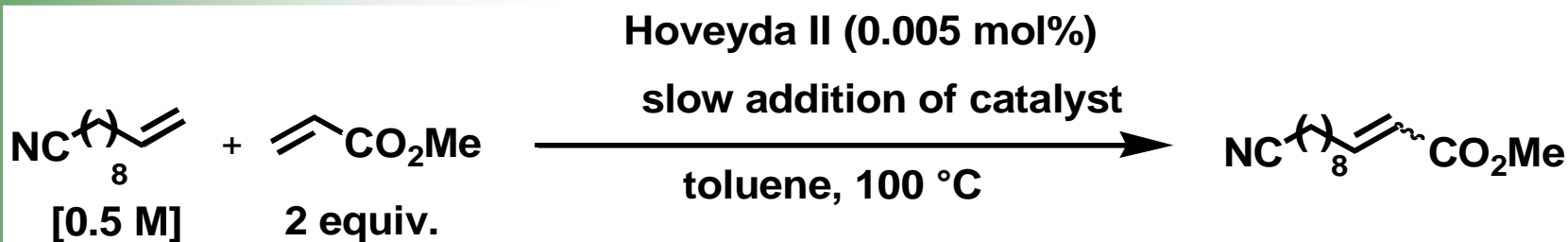


# Cross metathesis of fatty acid derivatives (derived from castor oil) with electron deficient olefins



0.025 mol% of catalyst added over 2 h 40 (5 h reaction time)  
Continuous addition of acrylonitrile (1 equiv. + 1 equiv.) } Conv.: 75% TON 3000

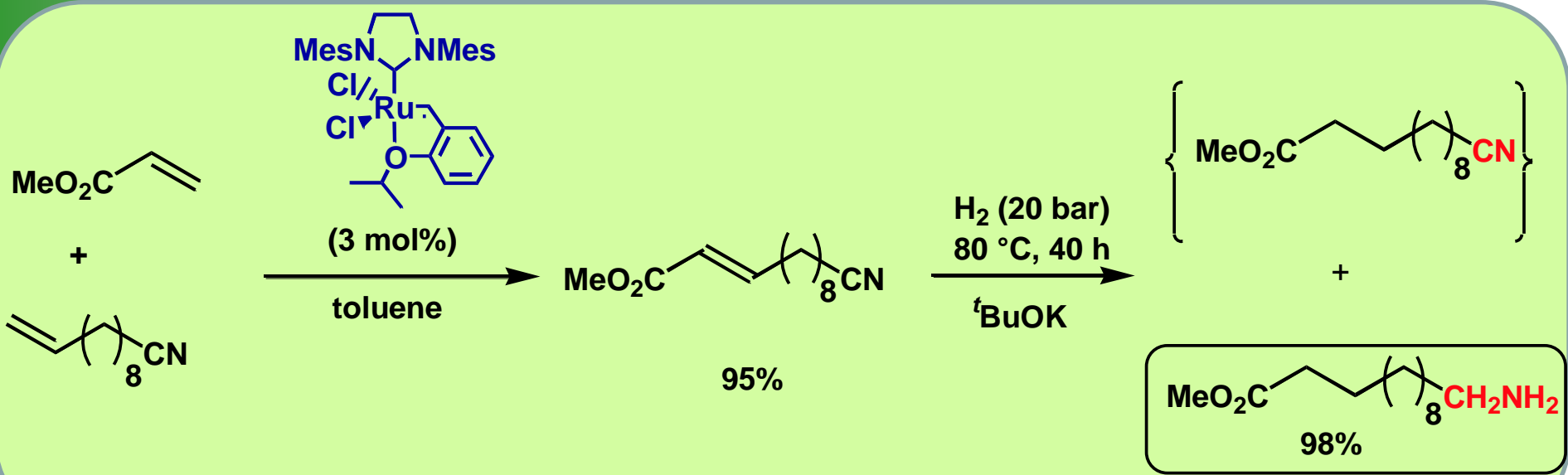
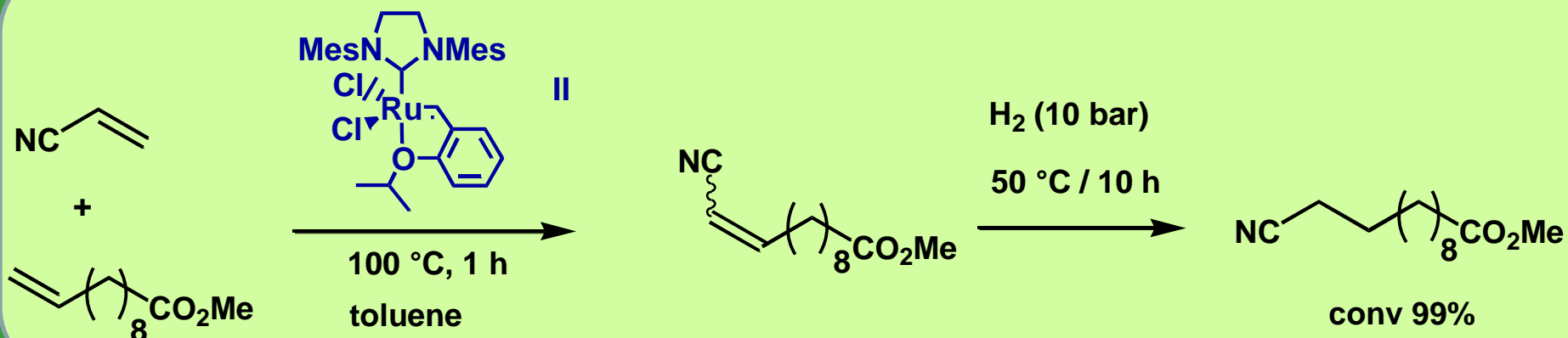
*Green Chem.*, 2011, 13, 2258



0.005 mol% of catalyst added over 2 h 40 (5 h reaction time) Conv.: 86% TON 17200

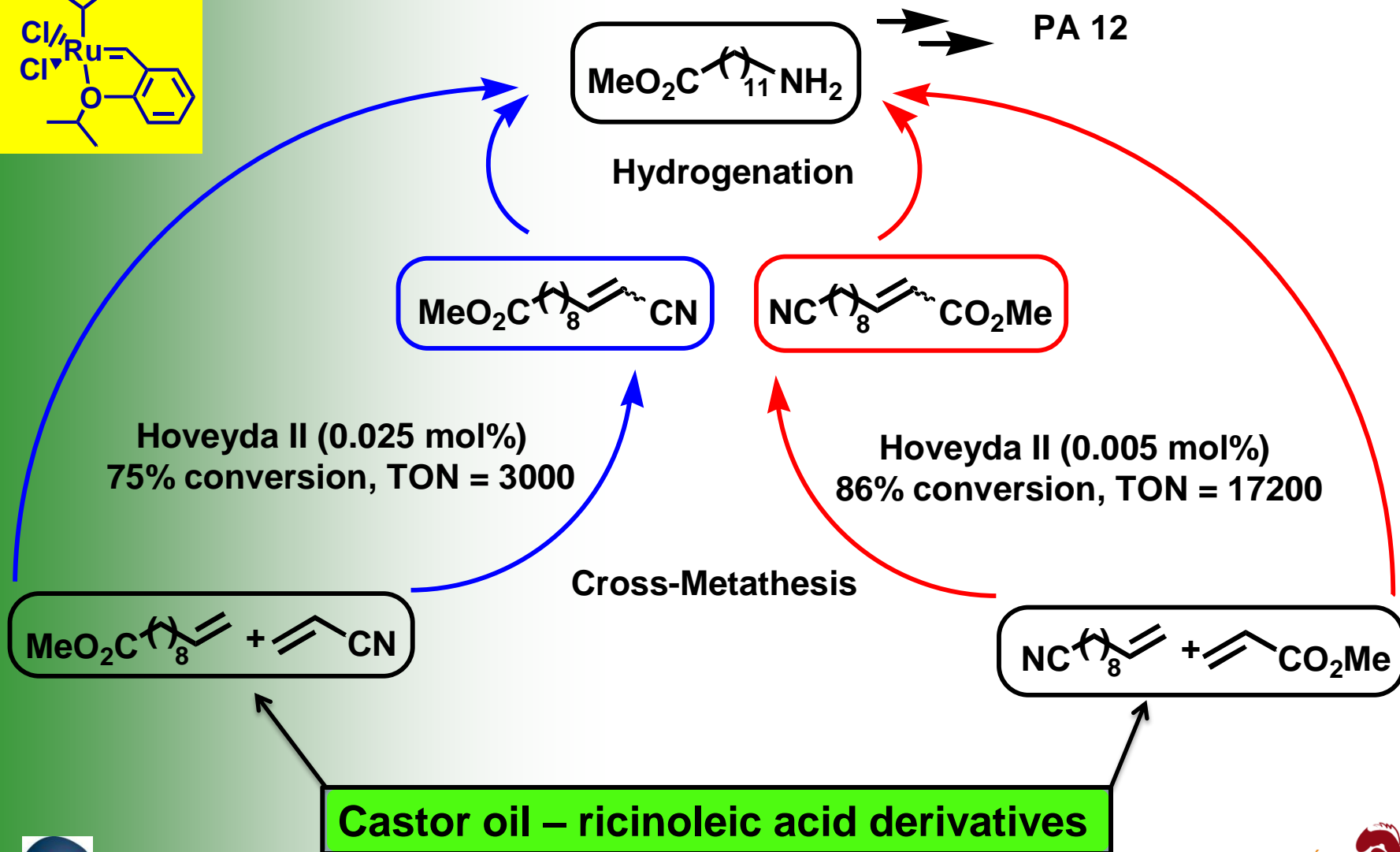
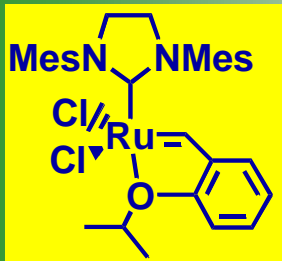
*Green Chem.* 2012, 14, 2179

# Hydrogenation of unsaturated nitriles



*ChemSusChem* 2012, 5, 1410-1414. *ChemCatChem* 2012, 4, 1911-1916.

# Precursor of polyamide 12 from two different FAME sources



**Procédé de préparation d'amino-acides ou esters saturés comprenant une étape de métathèse**

J.-L. COUTURIER, J.-L. DUBOIS, X. MIAO, C. FISCHMEISTER, C. BRUNEAU, P. DIXNEUF  
FR 10 53595 (07/05/2010)

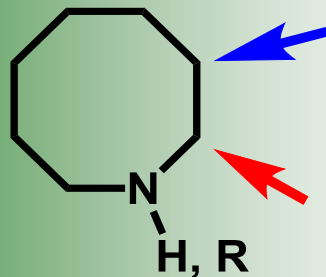
**Process for preparation of amino acids or saturated esters including a metathesis step**

From Fr. Demande (2011), FR 2959742 A1 20111111; From PCT Int. Appl. (2011), WO 2011138051 A1 20111110.

**ARKEMA**  
INNOVATIVE CHEMISTRY

# Selective functionalization of aliphatic cyclic amines based on ruthenium- and iridium-catalyzed hydrogen transfers

$sp^3C(3)$ -H functionalization via enamine intermediates



**C3-functionalization via C-C bond formation**

**C2-functionalization via C-C bond formation**

**Problems to create C-C bond at  $\beta$ -position:**

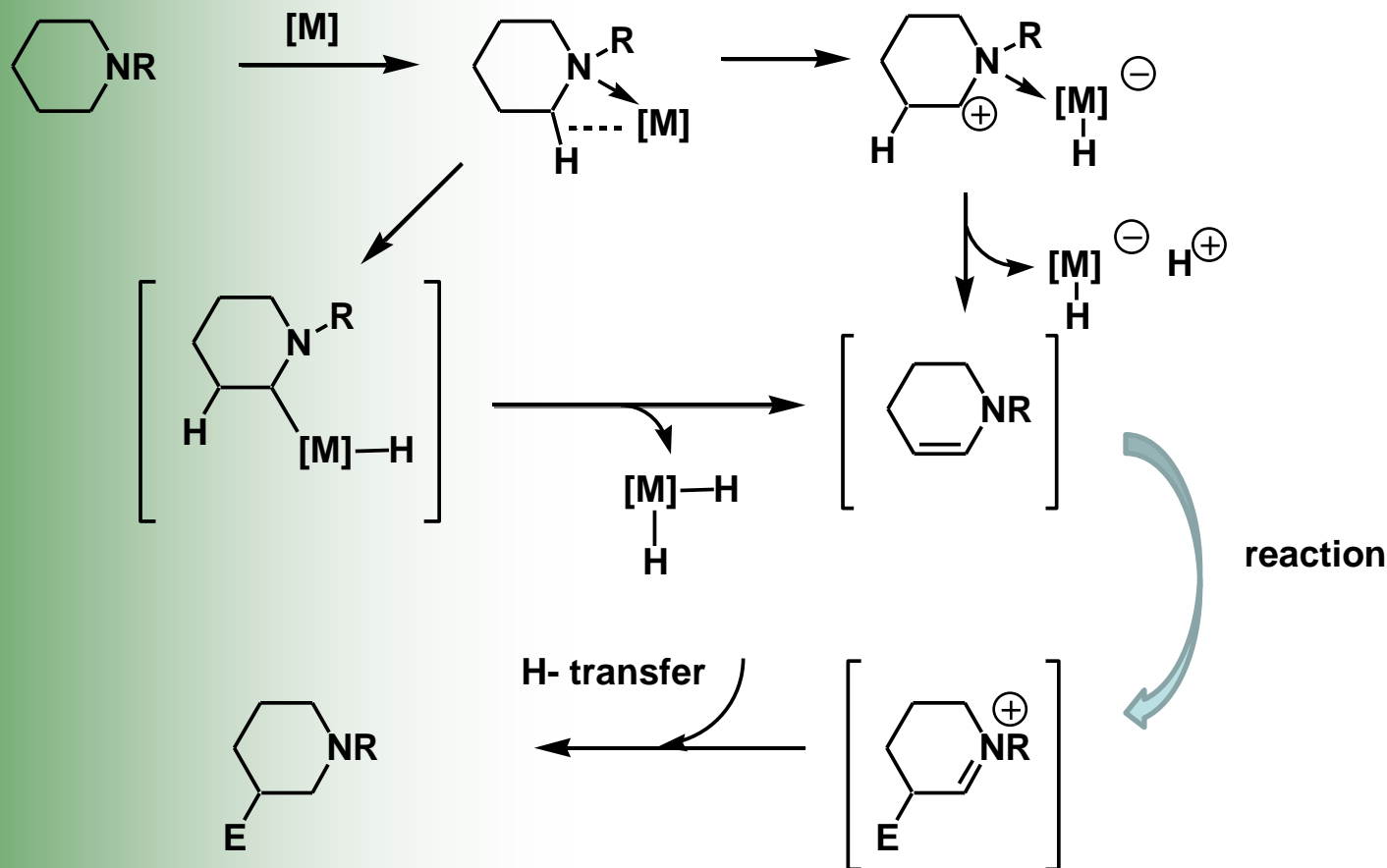
**$sp^3$ C-H activation**

**No directing group for directed coordination**

**No strong electronic effect**

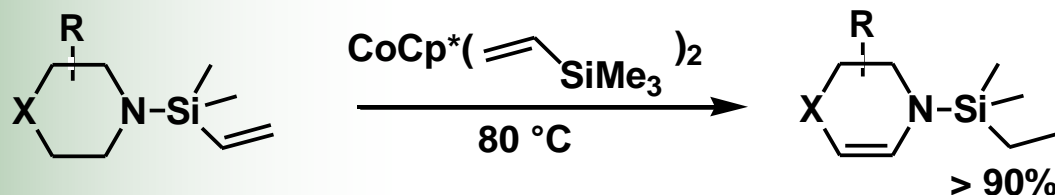
**Need to create a reactive centre : regioselectivity driven by reactivity**

## Possible mechanisms for enamine formation



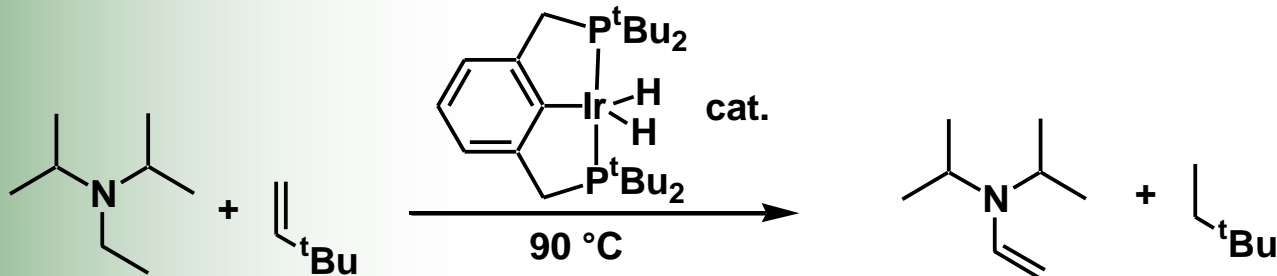


## Enamines from cyclic saturated amines



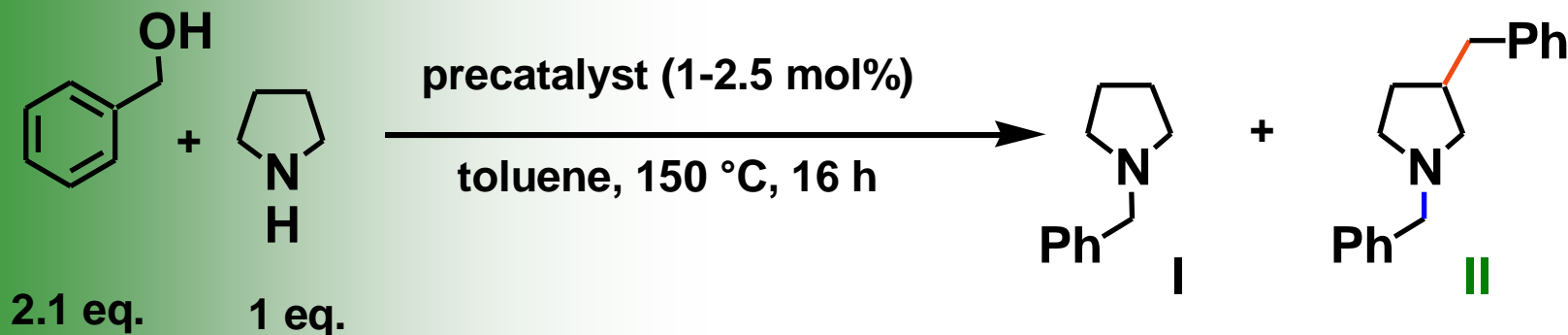
A.D. Bolig, M. Brookhart, *J. Am. Chem. Soc.*, **2007**, 129, 14544

## Enamines from linear tertiary saturated amines



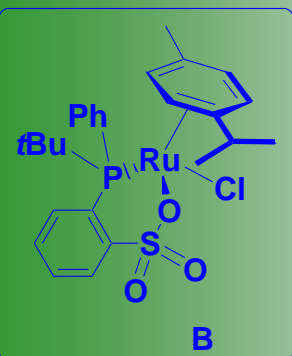
A. S. Goldman *et al.*, *Chem Commun.*, **2003**, 2060

# N- and C(3)-dialkylation of cyclic amines by benzyl alcohol involving hydrogen transfer



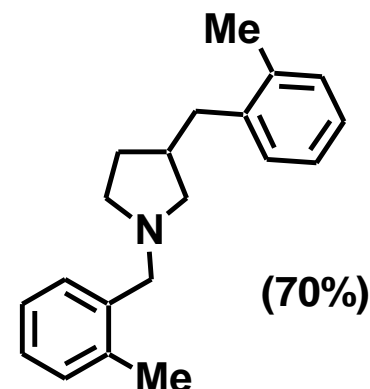
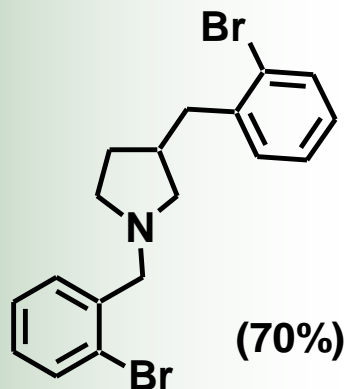
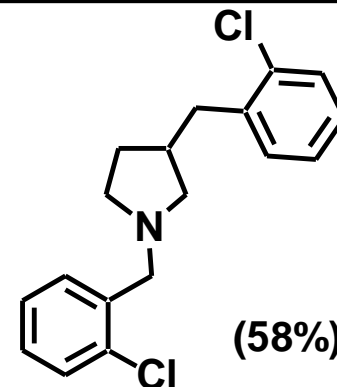
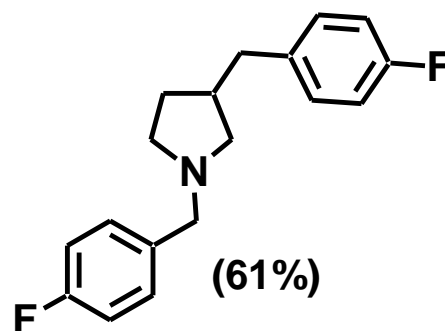
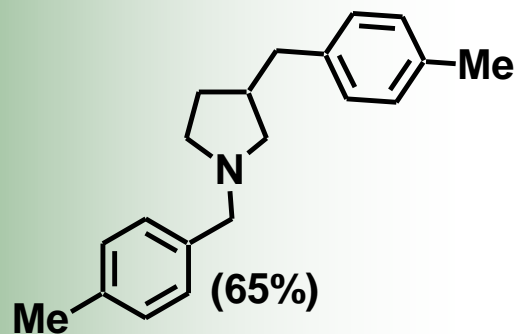
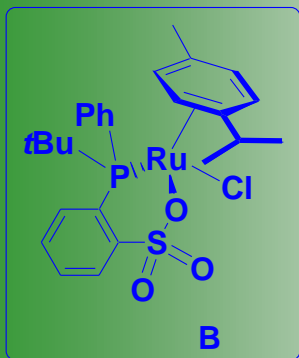
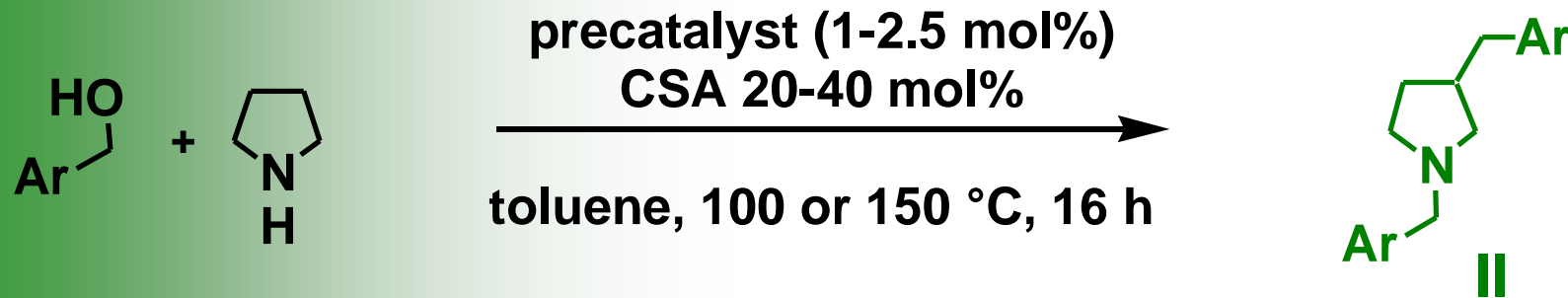
catalyst	Additive (mol%)	solvent	I/II	GC conversion
<b>B</b>	no	toluene	93/7	80%
<b>B</b>	CSA(10)	toluene	40/60	99%
<b>B</b>	CSA(15)	toluene	37/63	99%
<b>B</b>	CSA(20)	toluene	31/69	99%
<b>B</b>	CSA(30)	toluene	25/75	99%
<b>B</b>	<b>CSA(40)</b>	<b>toluene</b>	<b>12/88</b>	<b>99%(80)</b>
<b>B</b>	CSA(100)	toluene	25/32	15%

CSA = Camphor Sulfonic Acid

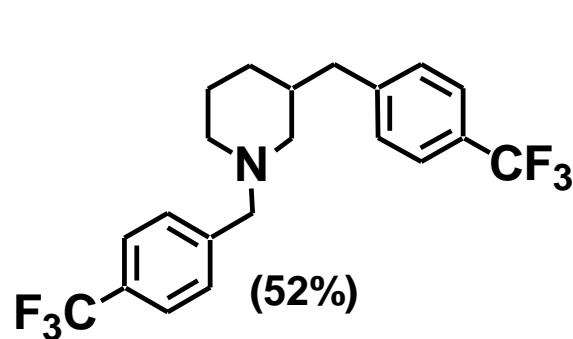
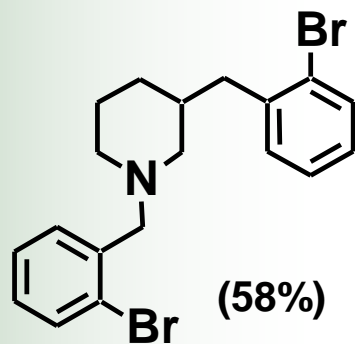
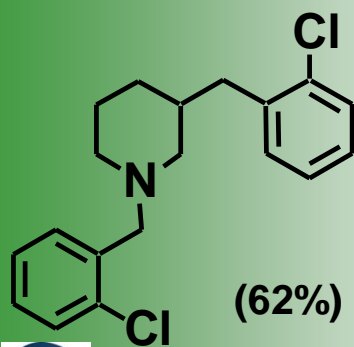
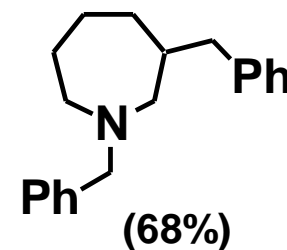
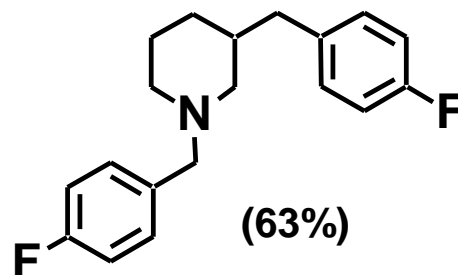
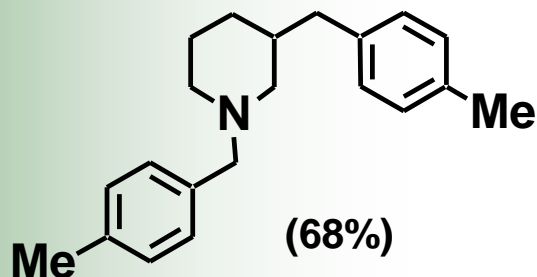
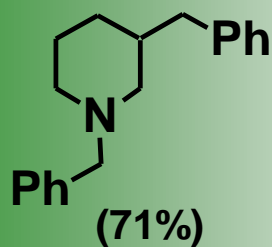
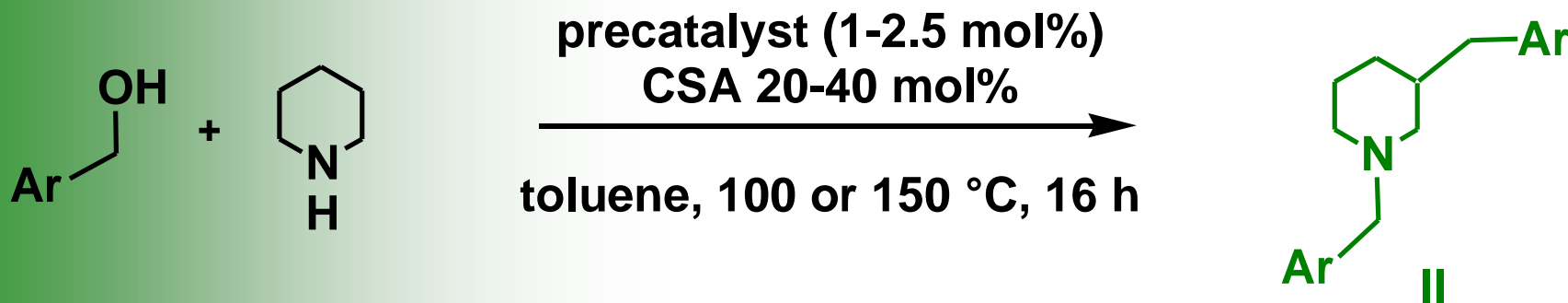


## Regioselective C(3)-alkylation

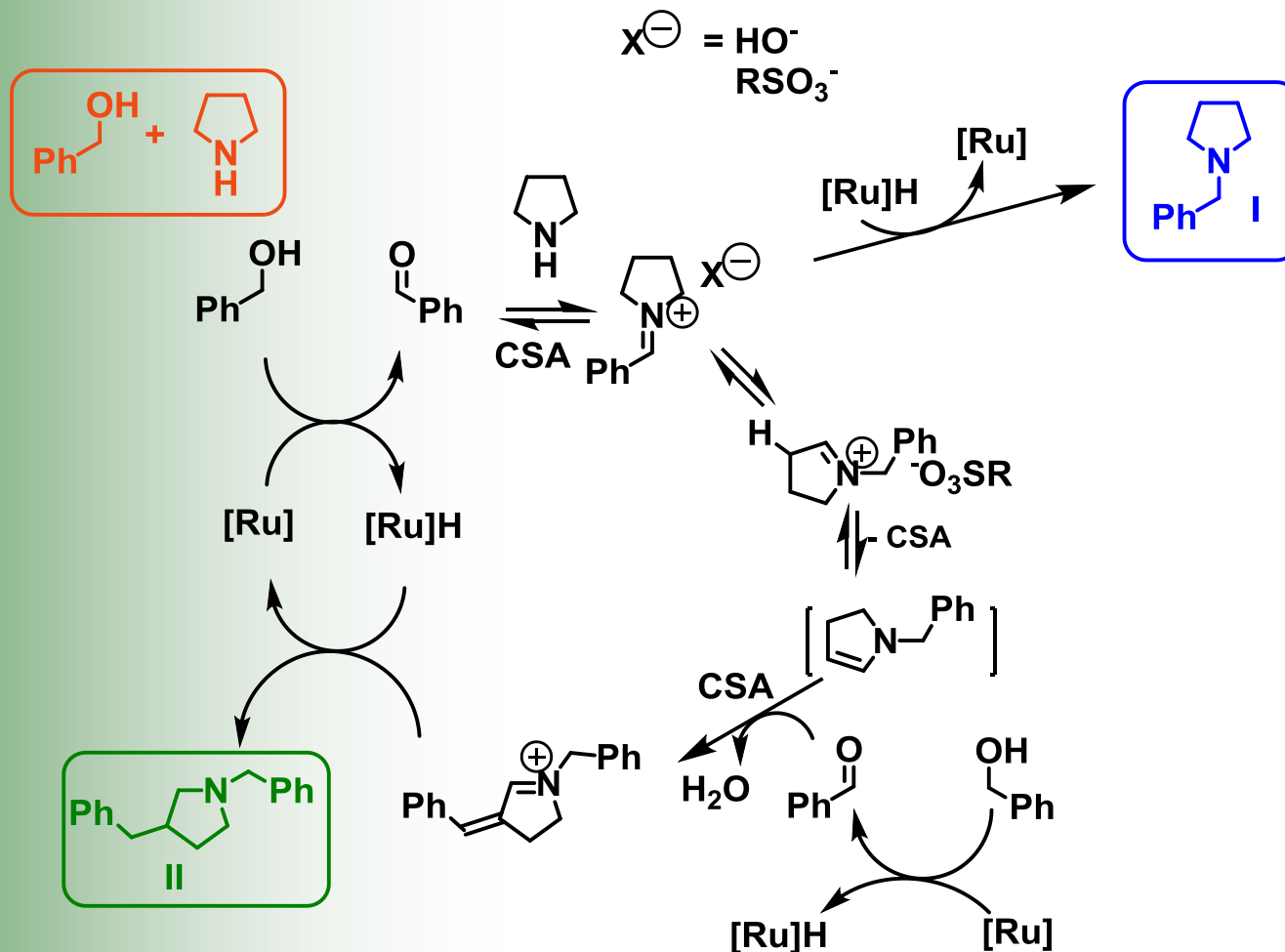
# N- and C(3)-dialkylation of pyrrolidine by benzylic alcohol



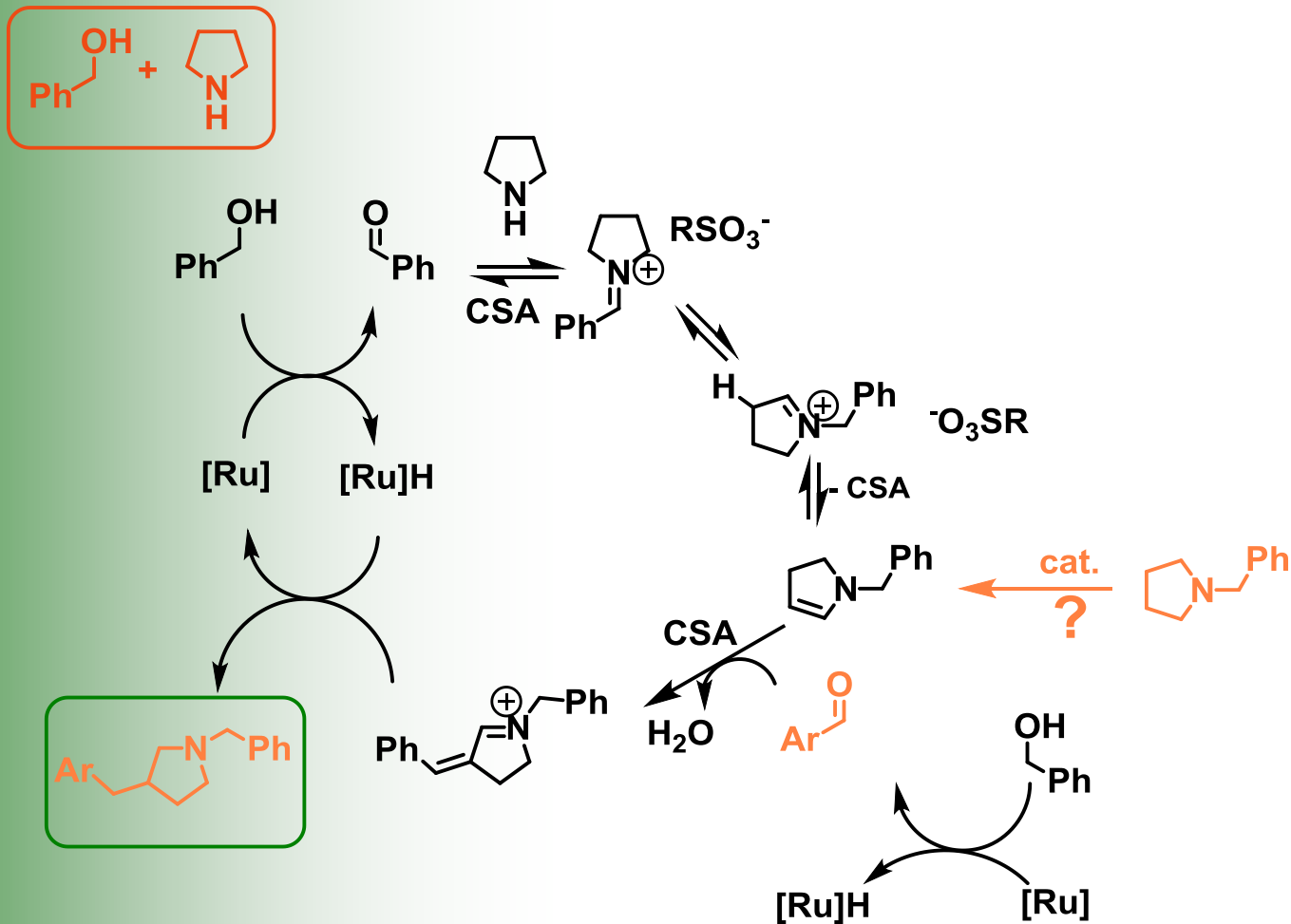
# N- and C(3)-dialkylation of piperidine by benzylic alcohol



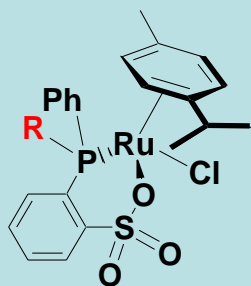
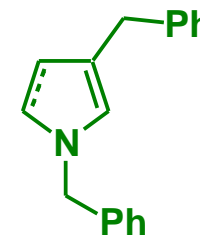
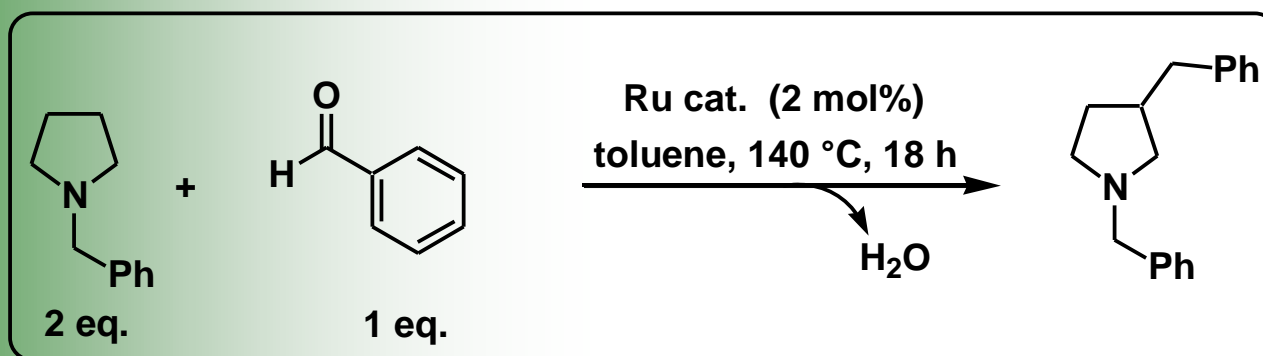
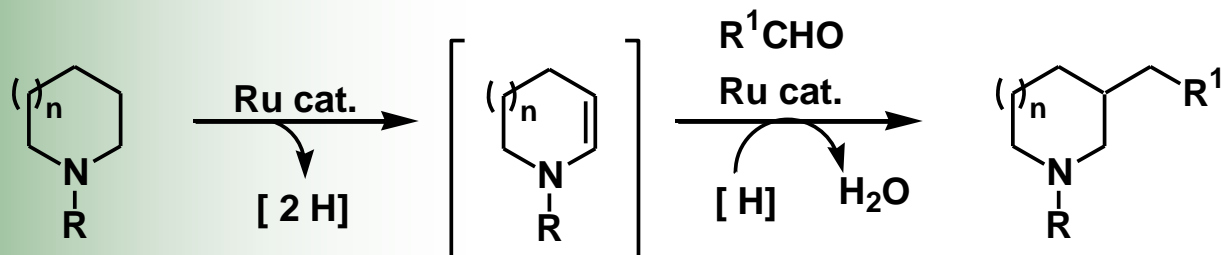
# Proposed catalytic cycle



# Another option



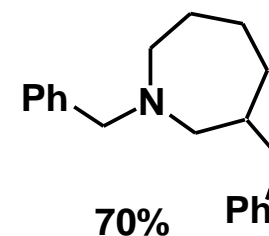
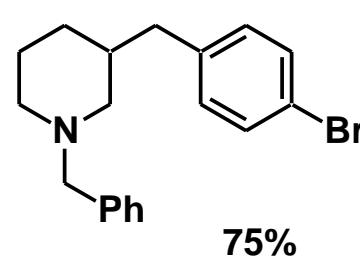
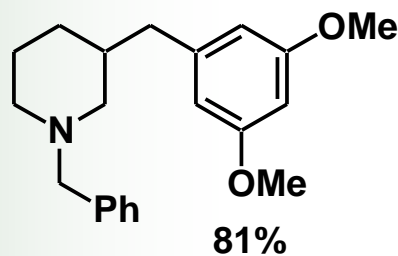
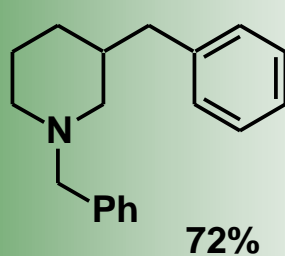
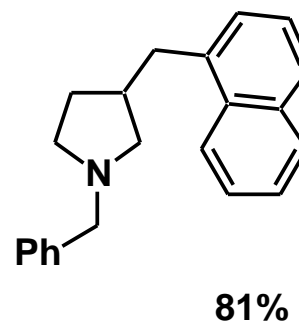
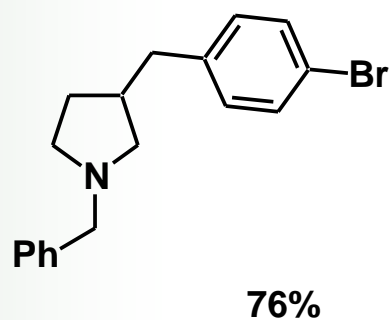
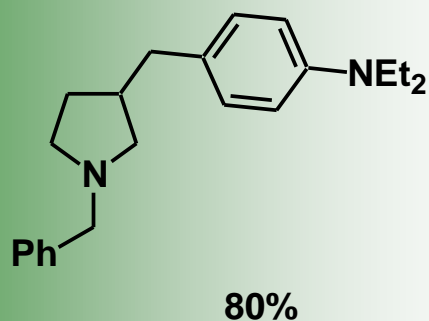
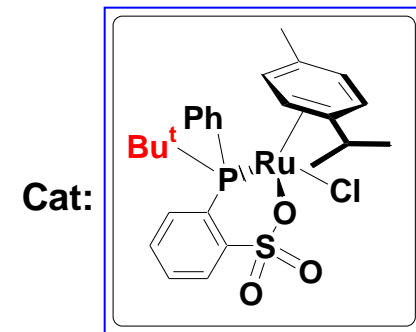
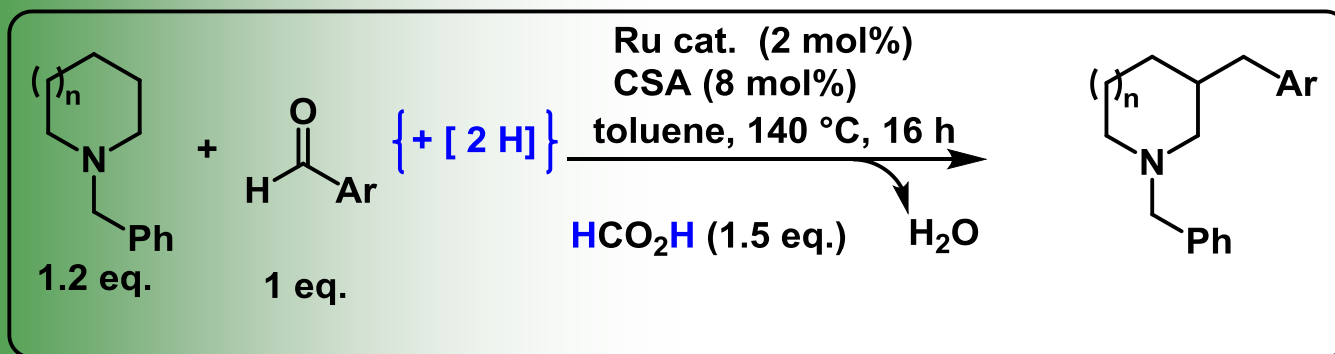
# Metal-mediated hydrogen transfer towards C(3)-alkylation



A: R = Ph  
B: R = *t*-Bu

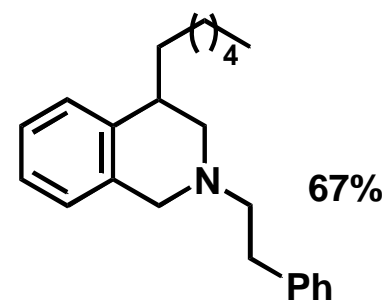
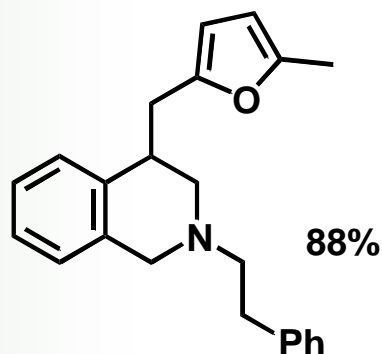
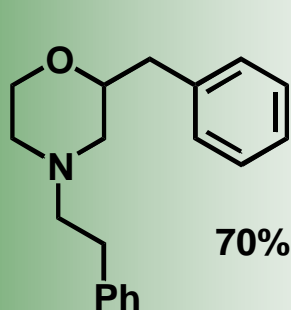
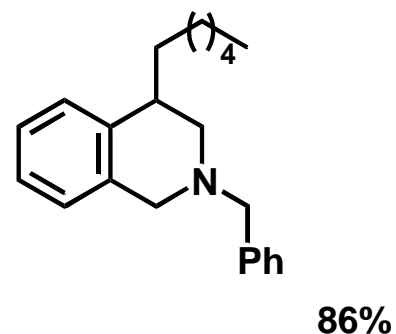
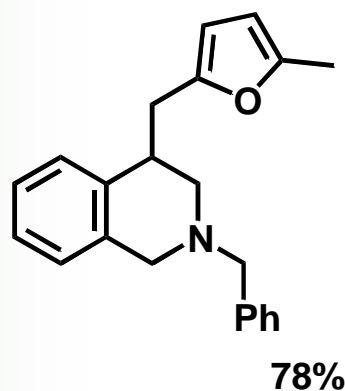
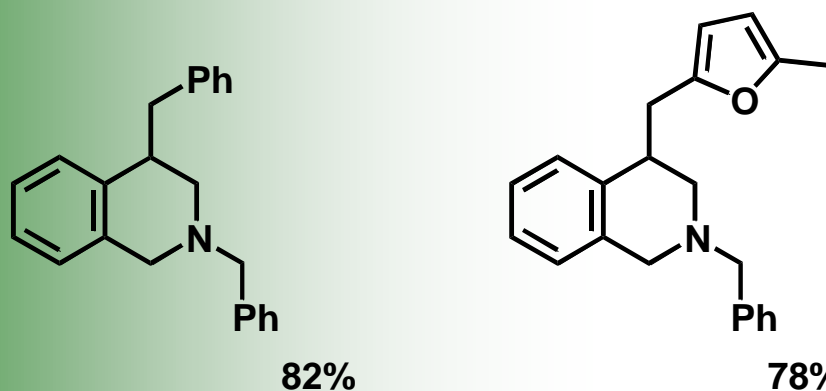
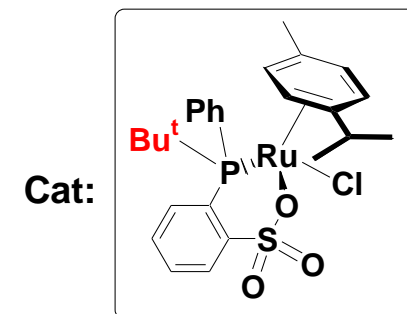
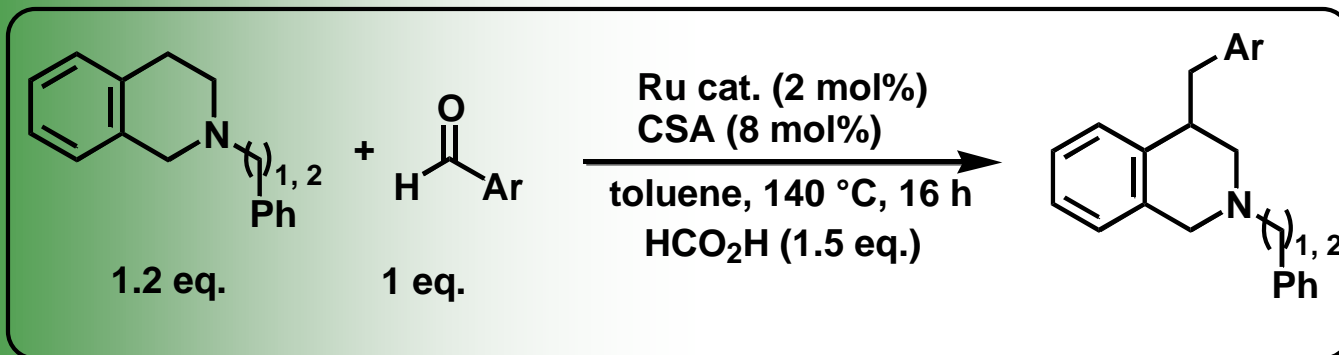
Catalyst	aldehyde conv.	Selectivity
$[RuCl_2(p\text{-cymene})]_2$	53%	67/32
$[RuCl_2(p\text{-cymene})]_2$ + CSA (10 mol%)	86%	71/29
Cat A. + CSA (10 mol%)	99%	89/11
<b>Cat B. + CSA (6 mol%)</b>	<b>99%</b>	<b>91/9 (82% isolated)</b>

# Metal-mediated hydrogen transfer towards C(3)-alkylation

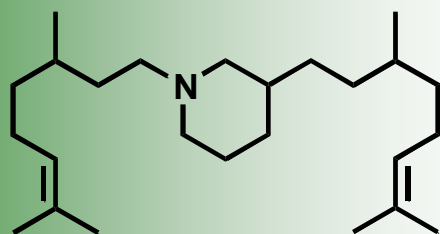
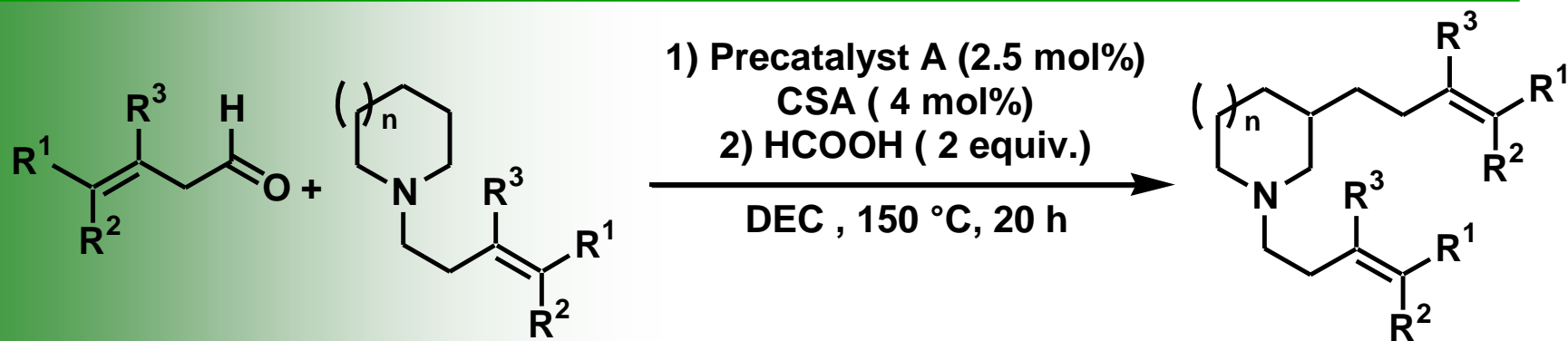




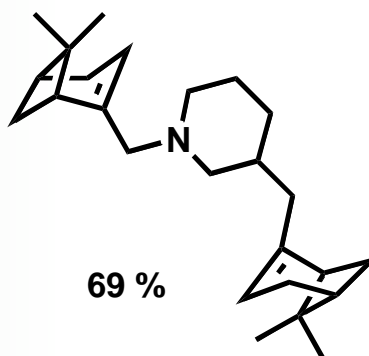
# Metal-mediated hydrogen transfer towards C(3)-alkylation



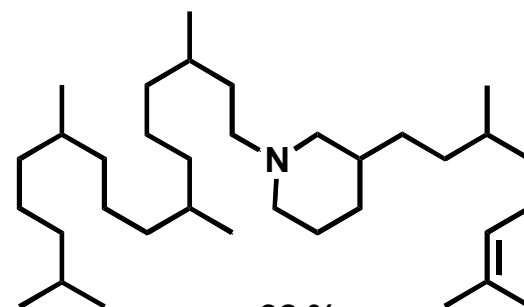
# Preparation of C(3),N-alkylated amines derived from terpenes



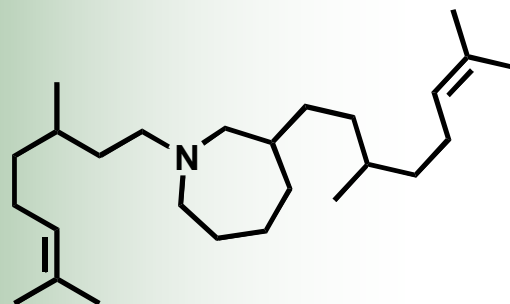
99 (62%)



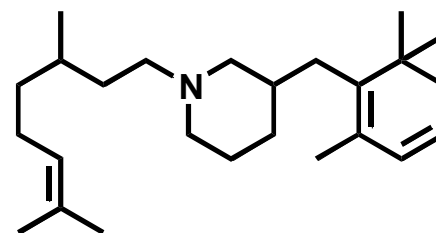
69 %



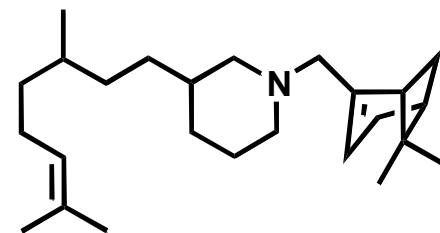
98 %



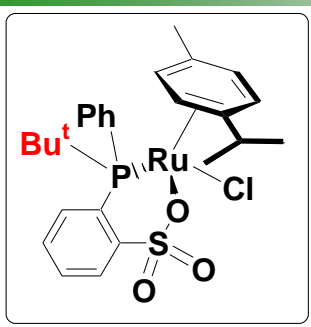
85 %

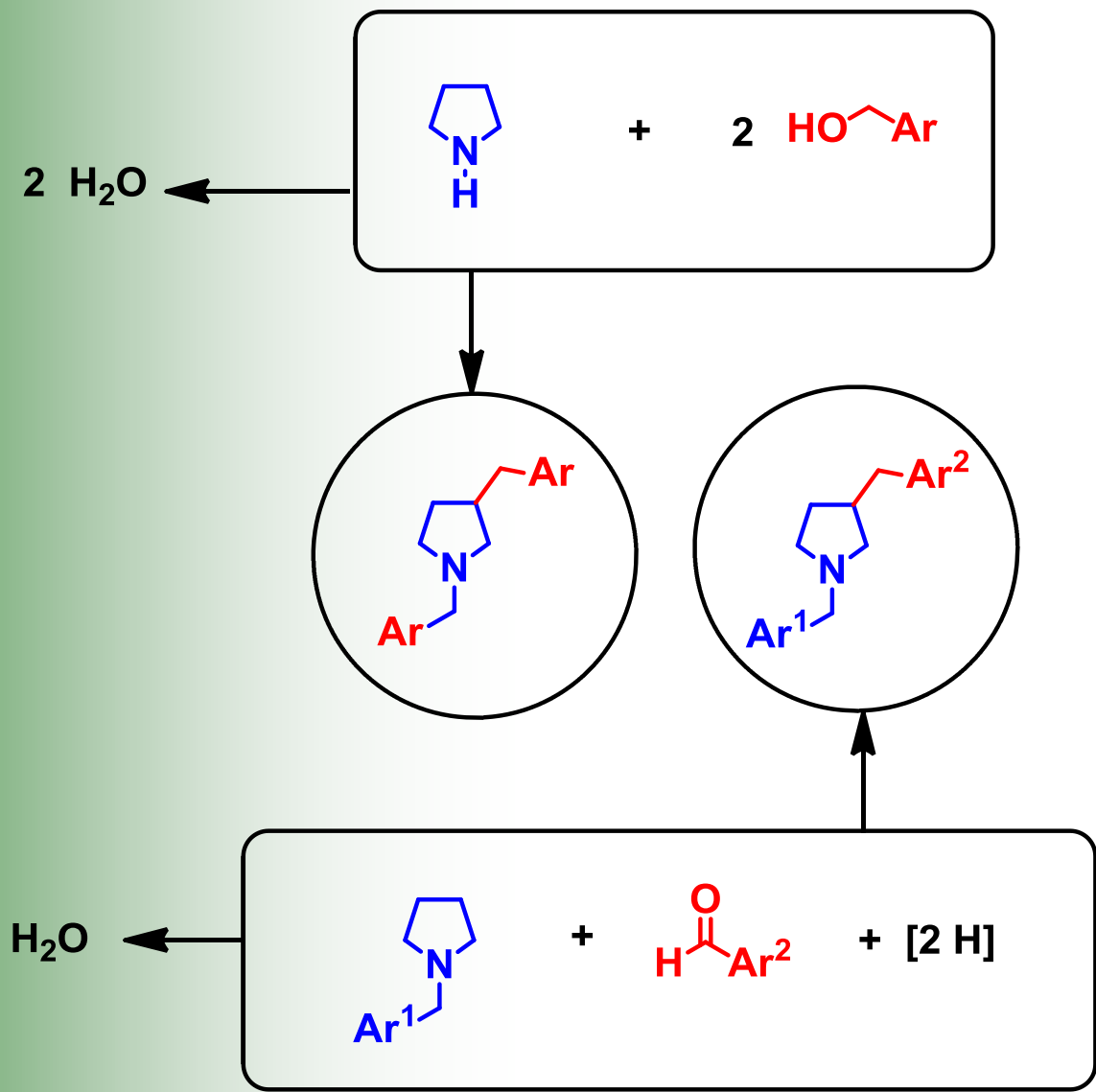


70 %

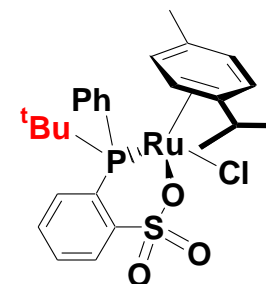


83 (51 %)





Catalyst



# ACKNOWLEDGEMENTS

**CNRS, MENR,  
Université de Rennes 1 / Région Bretagne  
French ANR, ADEME**

**CNRS:  
PICS (France - Russia)  
GDRI (France - Russia - Italy) / French Embassy in Russia**

**French Embassy in China**

**Bilateral cooperations:  
PHC programmes with Brazil, Germany, Tunisia, Turkey, Spain,  
CEFIPRA (Indo-French projects)**

**European networks :  
Activation of Small Molecules , IDECAT, SYNFLOW  
RTN projects  
COST Actions**

**Industry : Oril, SNPE, Arkema, SEAC, Firmenich**



# ACKNOWLEDGEMENTS

## *External collaborators*

S. Lécolier (SNPE)  
J.-C. Souvie (Oril)  
P. Langlois (Oril)  
J.-P. Lecouvé (Oril)  
J.-L. Dubois (Arkema)  
J.-L. Couturier (Arkema)  
H. Olivier-Bourbigou (IFPEn)

A. Jutand (ENS Paris)  
M. Beller (LIKAT Rostock)  
W. Leitner (RTWH Aachen)  
S. Osipov (INEOS Moscow)  
Z. Xi (Pekin Univ.)  
G.V.M. Sharma (IICT Hyderabad)  
I. Özdemir (Univ. Malatya)  
N. Hamdi (Tunis)  
E. Dos Santos (Belo Horizonte)  
D. Mandelli (Sao Paulo)

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J.-M. Joumier  
H. Doucet  
B. Seiller  
C. Darcel  
P. Le Gendre  
M. Picquet  
P. Dupau  
D. Sémeril  
J. Le Nôtre  
R. Aoun

T. Jerphagnon  
C. Thurier  
B. Liégault  
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S. Masoud  
Y. Yuan

P. Dixneuf  
C. Fischmeister  
J.-L. Renaud  
M. Achard  
B. Demerseman  
H. Doucet  
S. Dérien  
D. Touchard  
R. Gramage-Doria

L. Toupet  
T. Roisnel  
V. Dorcet

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