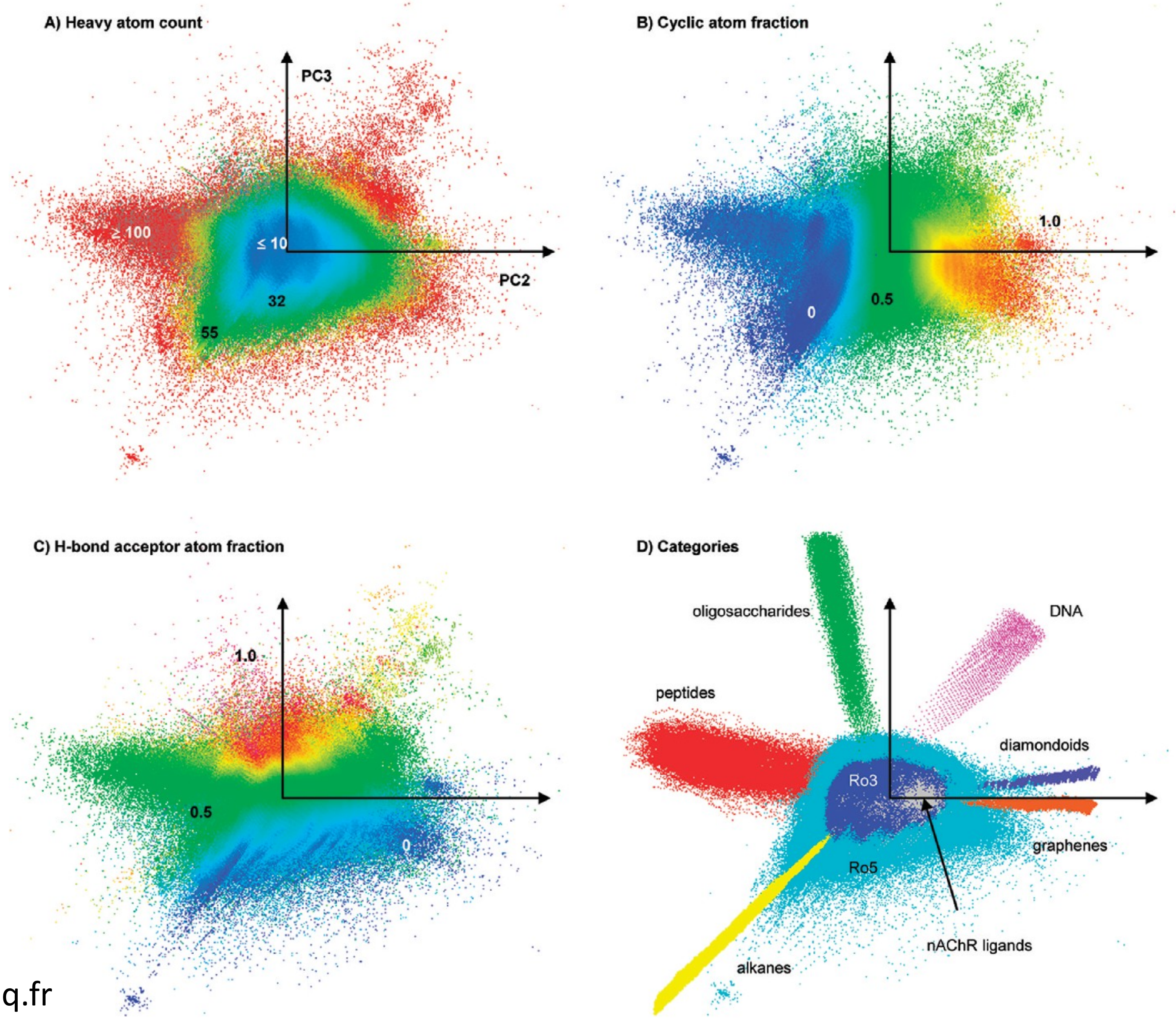
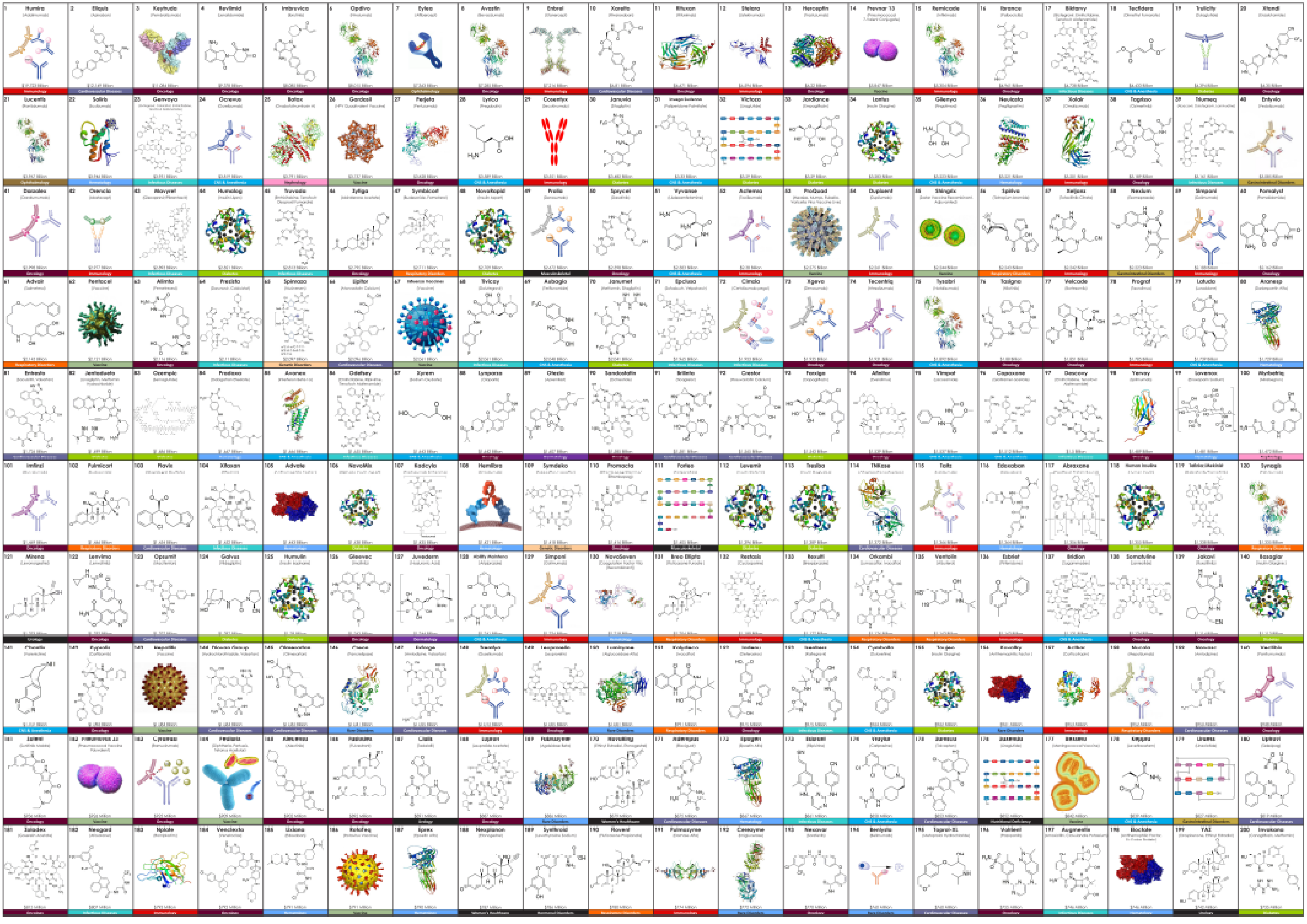
Synthèse pour la Diversité Moléculaire



Olivier DAVID
olivier.david@uvsq.fr

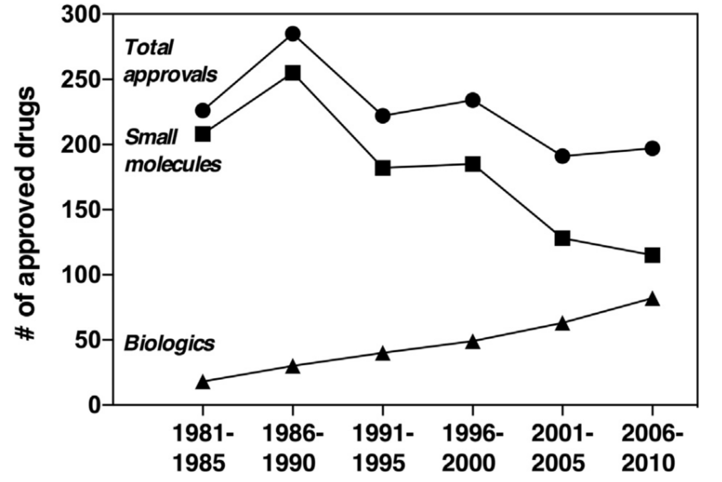
Pharmacie : Diversité Moléculaire ?

Top 200 Brand Name Drugs by Retail Sales in 2019



https://njardarson.lab.arizona.edu/content/top-pharmaceuticals-poster

Médicaments : Diversité Moléculaire ?



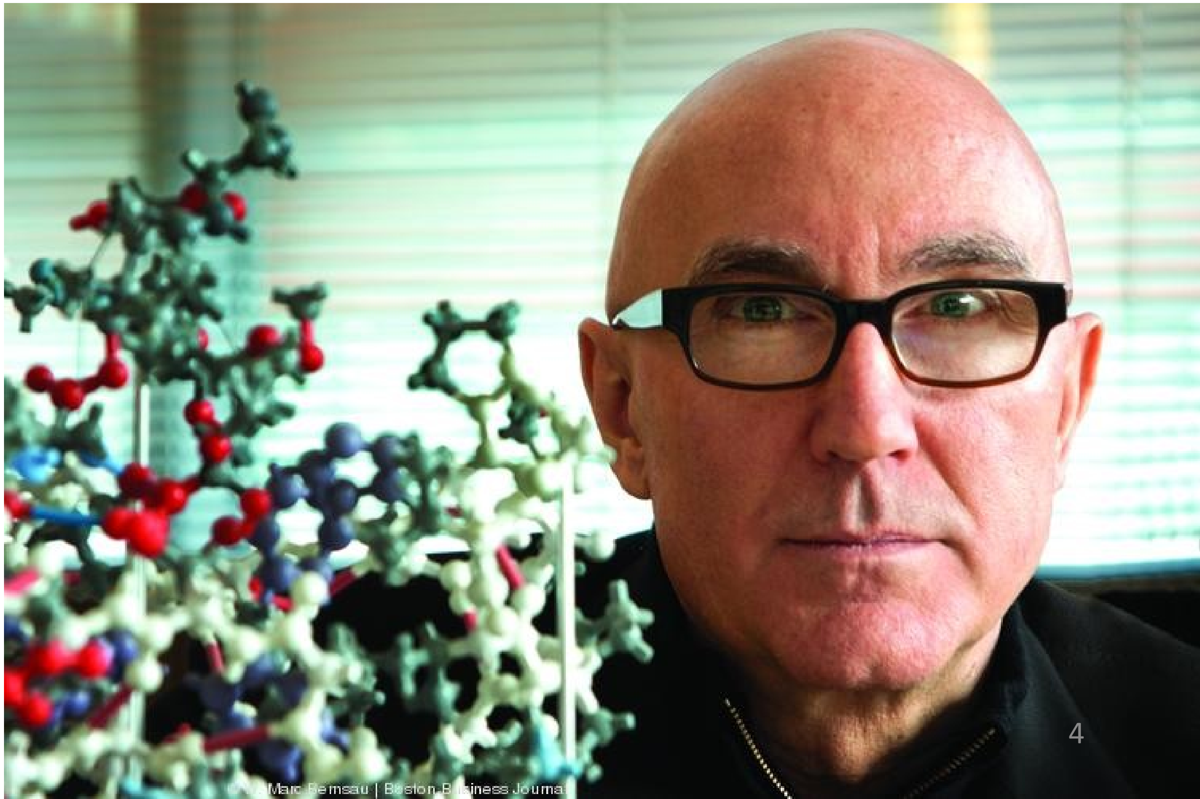
Moyenne	Produit naturel (49)	Hémisynthétique (277)	Synthétique Pharmacophore naturel (175)	Synthétique (515)
Masse molaire	626	634	386	343
Nombre N/O	4.1/9.3	4.4/8.3	3.0/4.1	2.4/2.6
Liaisons H D/A	6.4/10.3	5.0/9.2	2.5/5.2	1.3/4.2
Stéréocentres	8.2	6.7	1.9	0.8
Cycles	3.1	3.8	2.8	2.8
Aromatiques	0.8	1.3	1.9	1.9
Log P (OctOH/H_2O)	-2.2	-1.3	0.3	1.5

Cheminformatic comparison of approved drugs from natural product versus synthetic origins
Christopher F. Stratton, David J. Newman, Derek S. Tan
Bioorganic & Medicinal Chemistry Letters 25 (**2015**) 4802–4807

Synthèse pour la Diversité Moléculaire

Target-oriented and ***diversity-oriented organic synthesis*** *in drug discovery*

Stuart L. Schreiber *Science* **2000**, *287*, 1964– 1969



Synthèse pour la Diversité Moléculaire

Martin D. Burke

David R. Spring

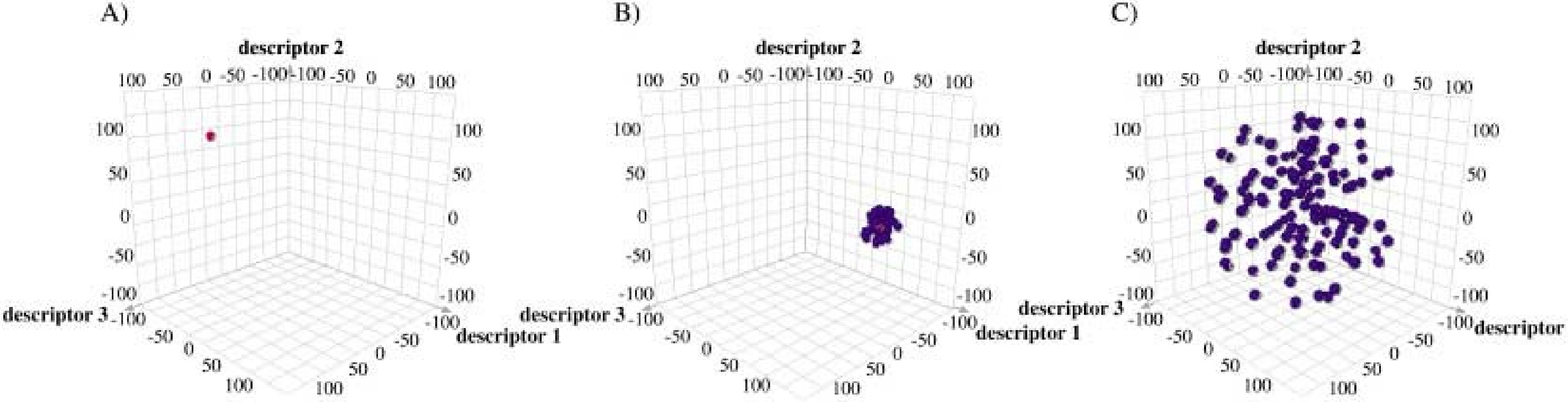
THE BASICS OF DIVERSITY-ORIENTED SYNTHESIS

Kieron M. G. O'Connell, Warren R. J. D. Galloway, and David R. Spring

Diversity-Oriented Synthesis: Basics and Applications in Organic Synthesis, Drug Discovery, and Chemical Biology, First Edition. Edited by Andrea Trabocchi.

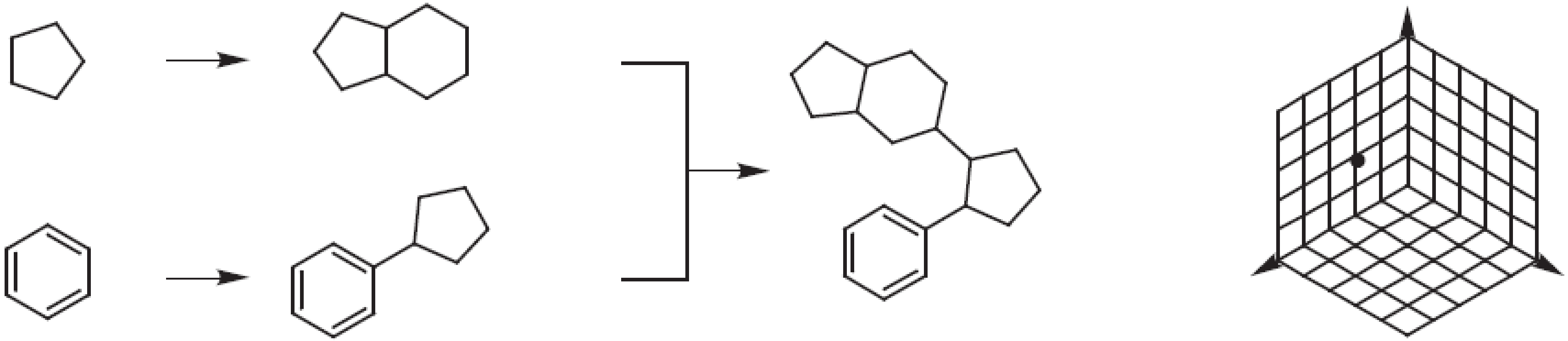
Espace Chimique

Si on considère au maximum **30** atomes C N O S,
on estime à **10^{60}** le nombre de molécules possibles



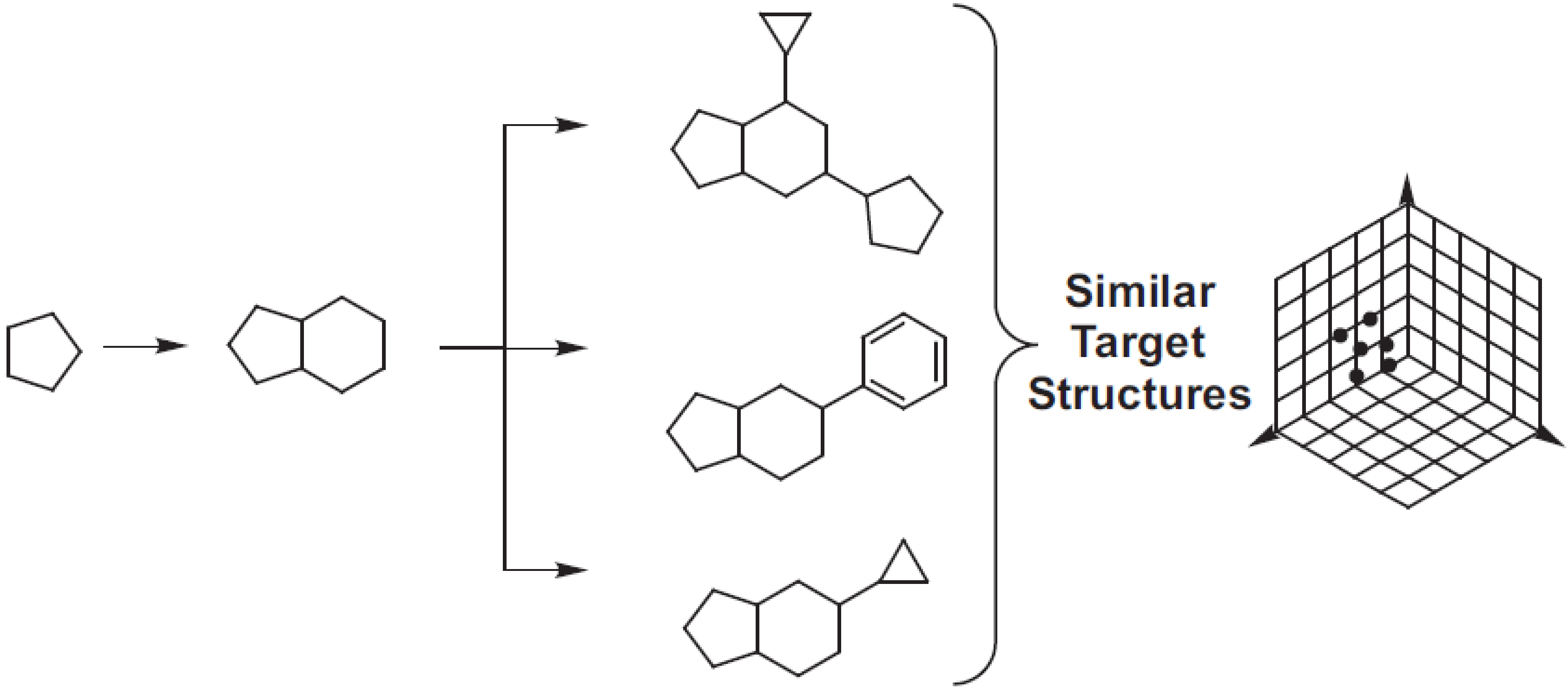
Synthèse pour la Diversité Moléculaire – Synthèse Ciblée

Target-Oriented Synthesis:

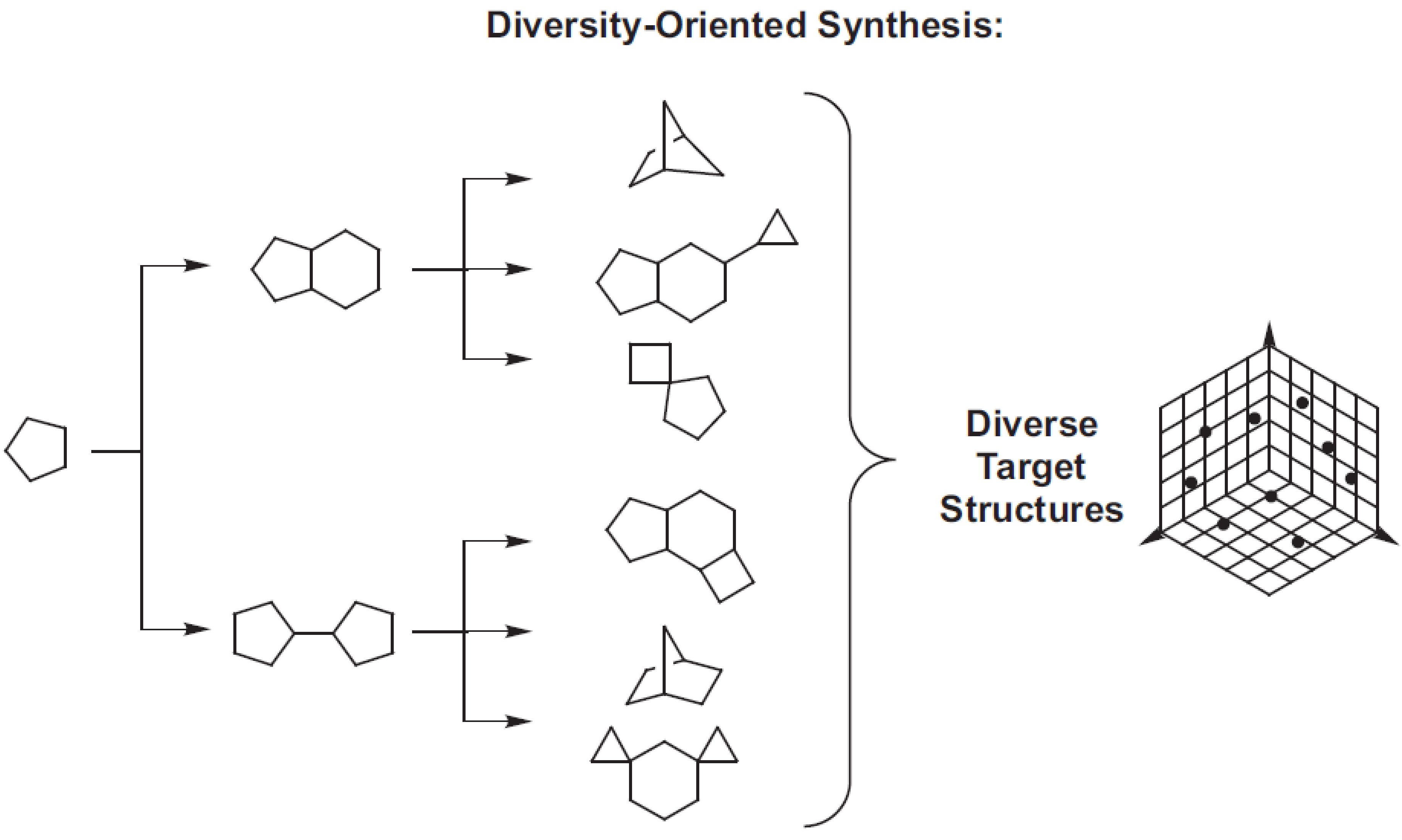


Synthèse pour la Diversité Moléculaire – Synthèse Combinatoire

Focused (Combinatorial) Library Synthesis:



Synthèse pour la Diversité Moléculaire



Moyens et Buts de la Chimie Médicinale Moderne

Le parcours vers un nouveau médicament

1. Identification de Hits : a. Sources Naturelles
   - Végétales (quinine, cocaine…)
   - Animales (Hormones)
   - Marines (toxines)
   - Champignons (Pénicilline)
   - Bactéries (gramicidine, peptides)

   b. Synthèse : Découverte des sulfamides antibiotiques en étudiant des colorants, et des sulfamides hypoglycémiants en cherchant un nouvel antibiotique.

→ ***Besoin de cribler le plus grand nombre de candidats possible : DOS***

2. Optimisation : Améliorer les propriétés dans une indication précise
   LD_{50}, K_d, log P, $t_{1/2}$…

→ ***Besoin de préparer beaucoup d'analogues proches : Chimie Combinatoire (librairies)***

3. Développement : a. Production de grandes quantités pour les essais cliniques
   b. Aménagement de la synthèse pour la fabrication industrielle

→ ***Besoin d'une synthèse avec le maximum d'efficacité : Synthèse Ciblée***

DOS – Diversity Oriented Synthesis

Moyens

1. Réactif
2. Substrat

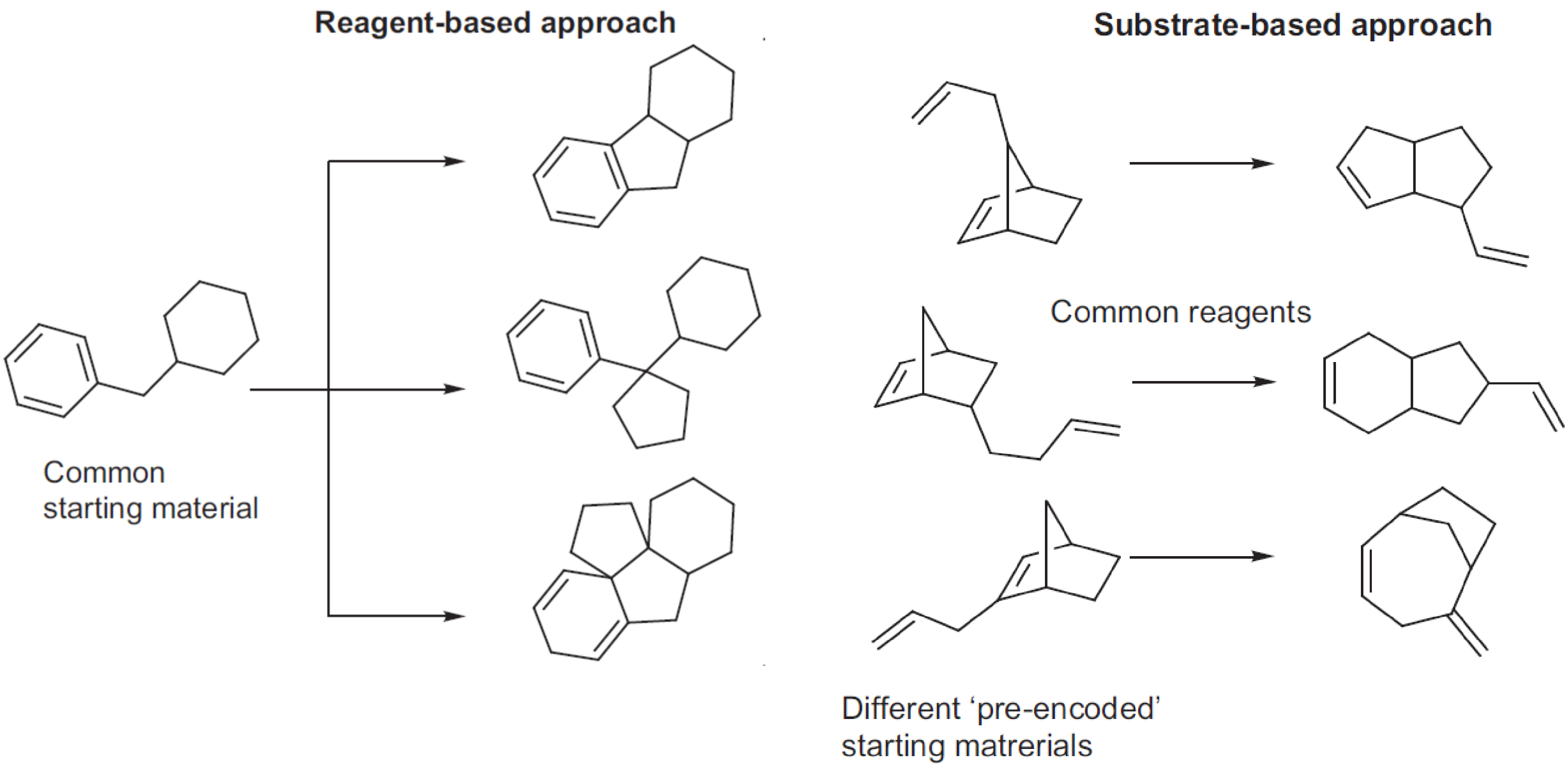
Types

1. Briques
2. Squelette
3. Stéréochimie

Phases

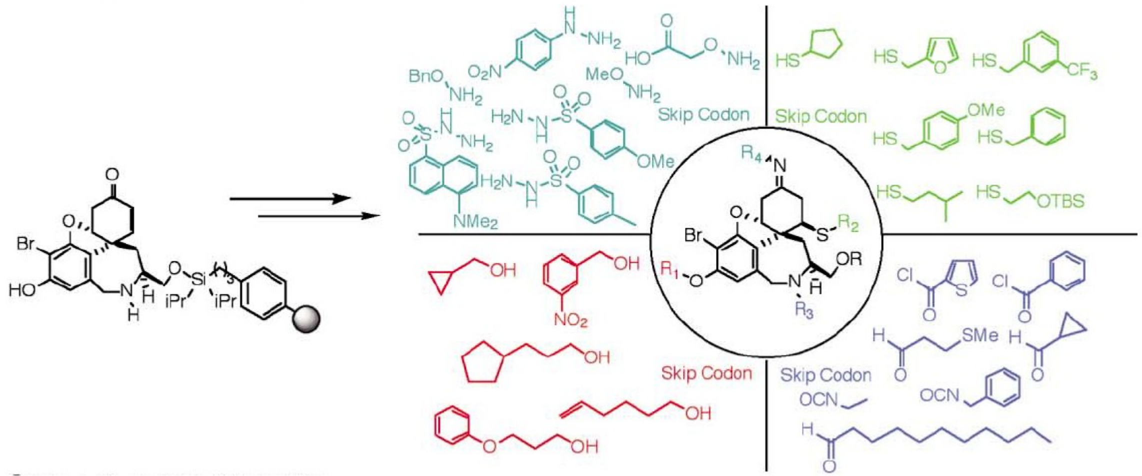
1. Construction
2. Couplage
3. Appariement

Moyens de Diversification : par les Réactifs/Substrats

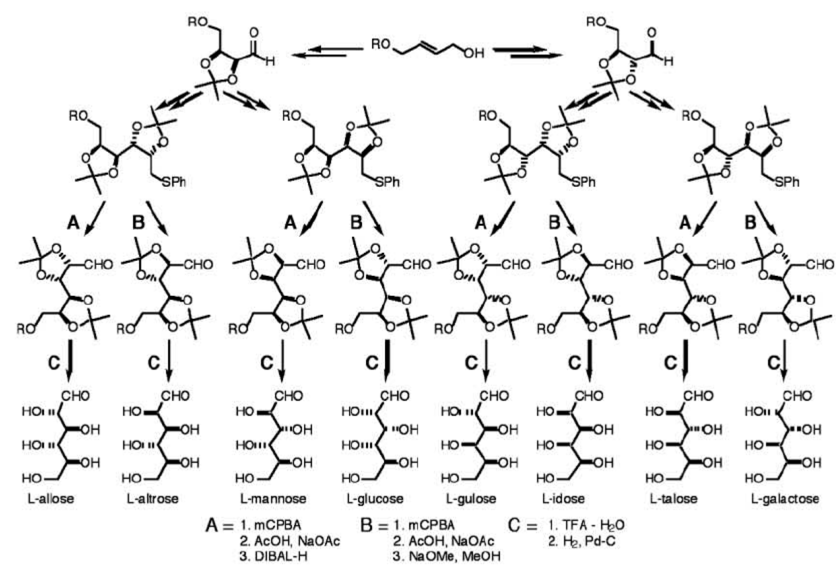


Les Trois Types de Diversités

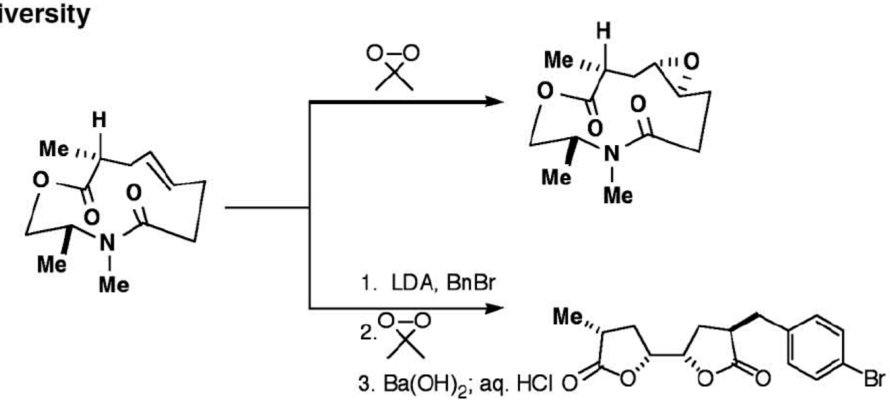
A Building-Block Diversity



B Stereochemical Diversity

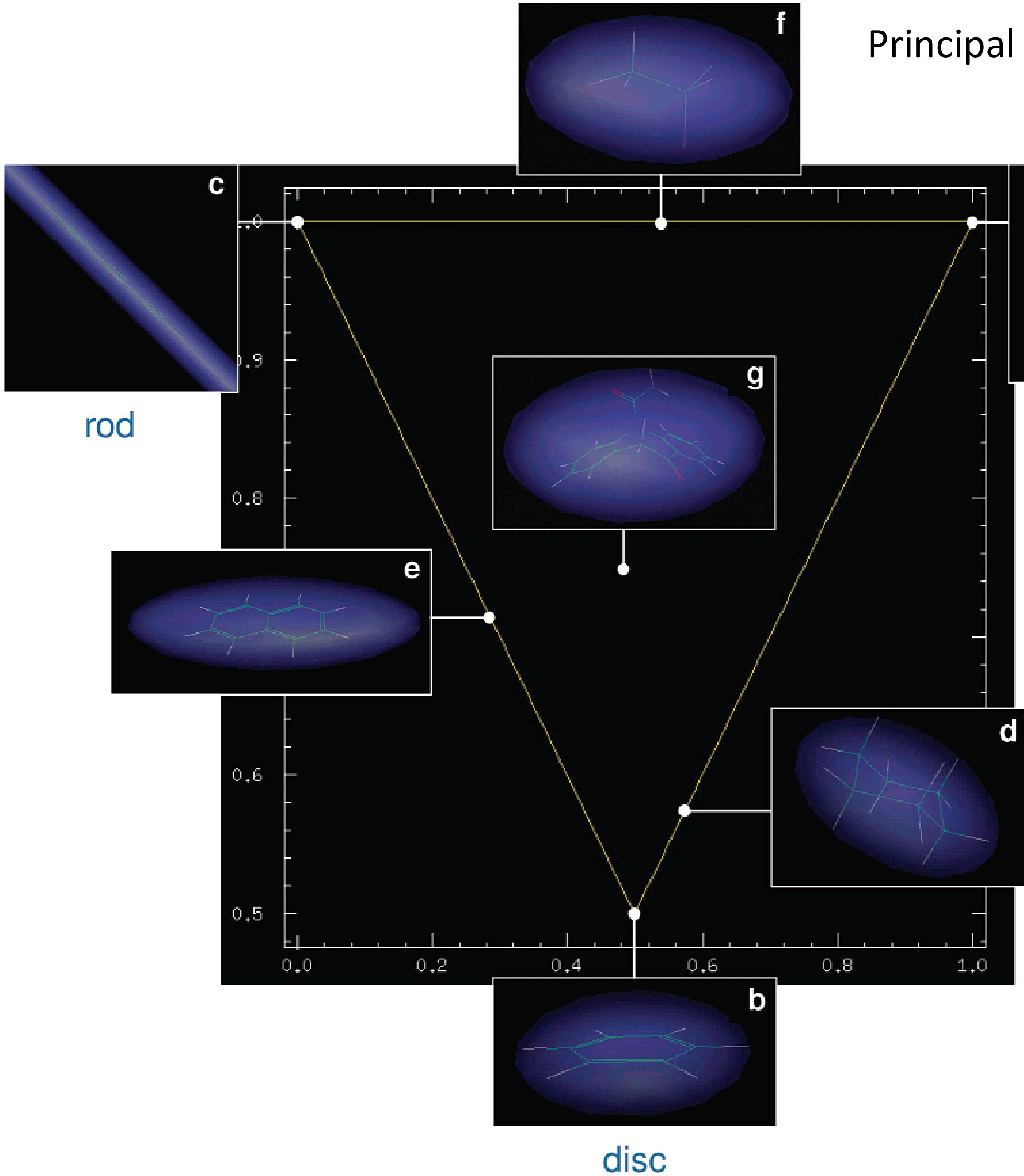


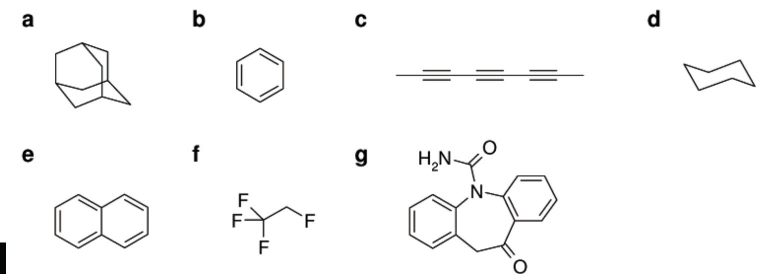
C Skeletal Diversity



Comment Quantifier la diversité ? Un exemple, le PMI

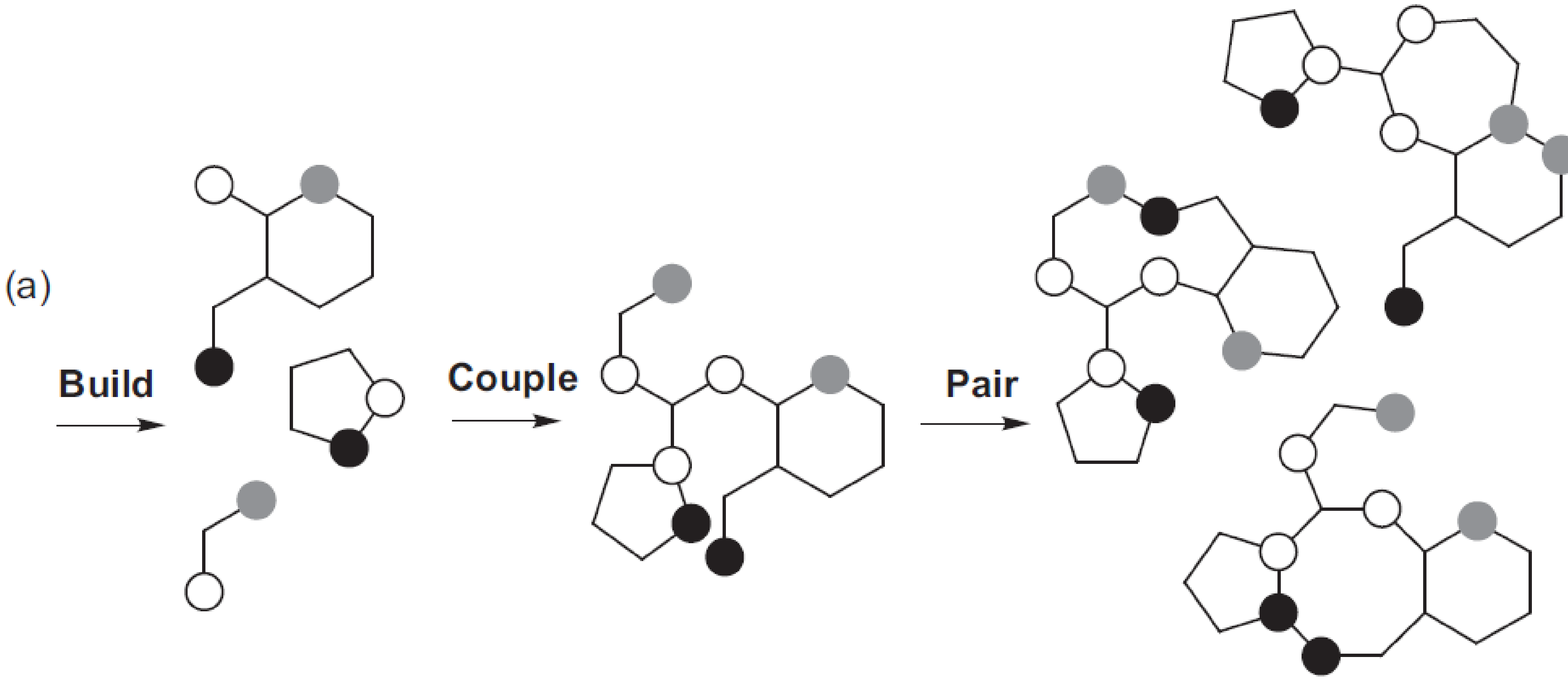
Principal Moments of Inertia (PMI)





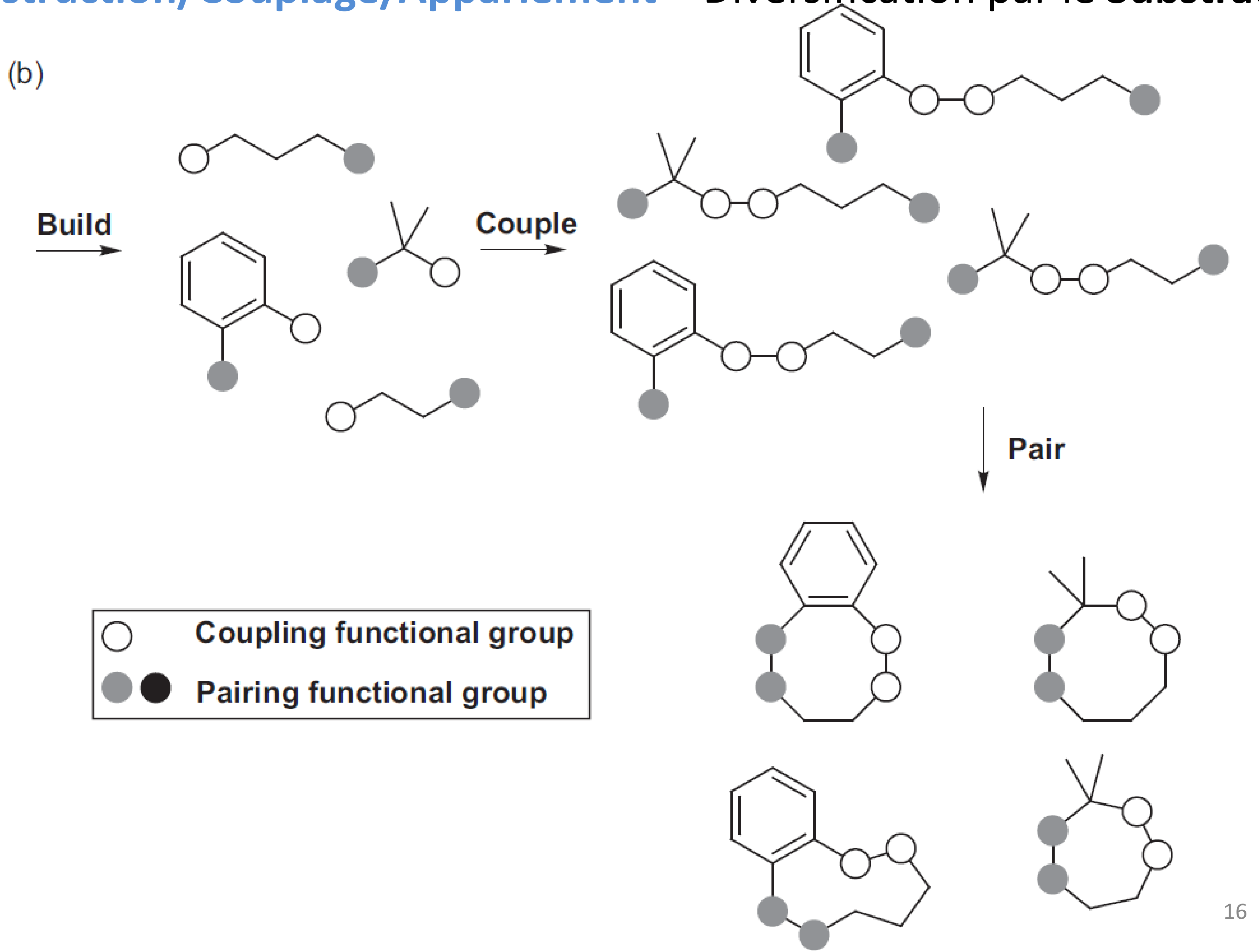
Les Phases de diversification

Construction/Couplage/Appariement – Diversification par le **Réactif**



Les Phases de diversification

Construction/Couplage/Appariement – Diversification par le **Substrat**



Synthèse pour la Diversité Moléculaire

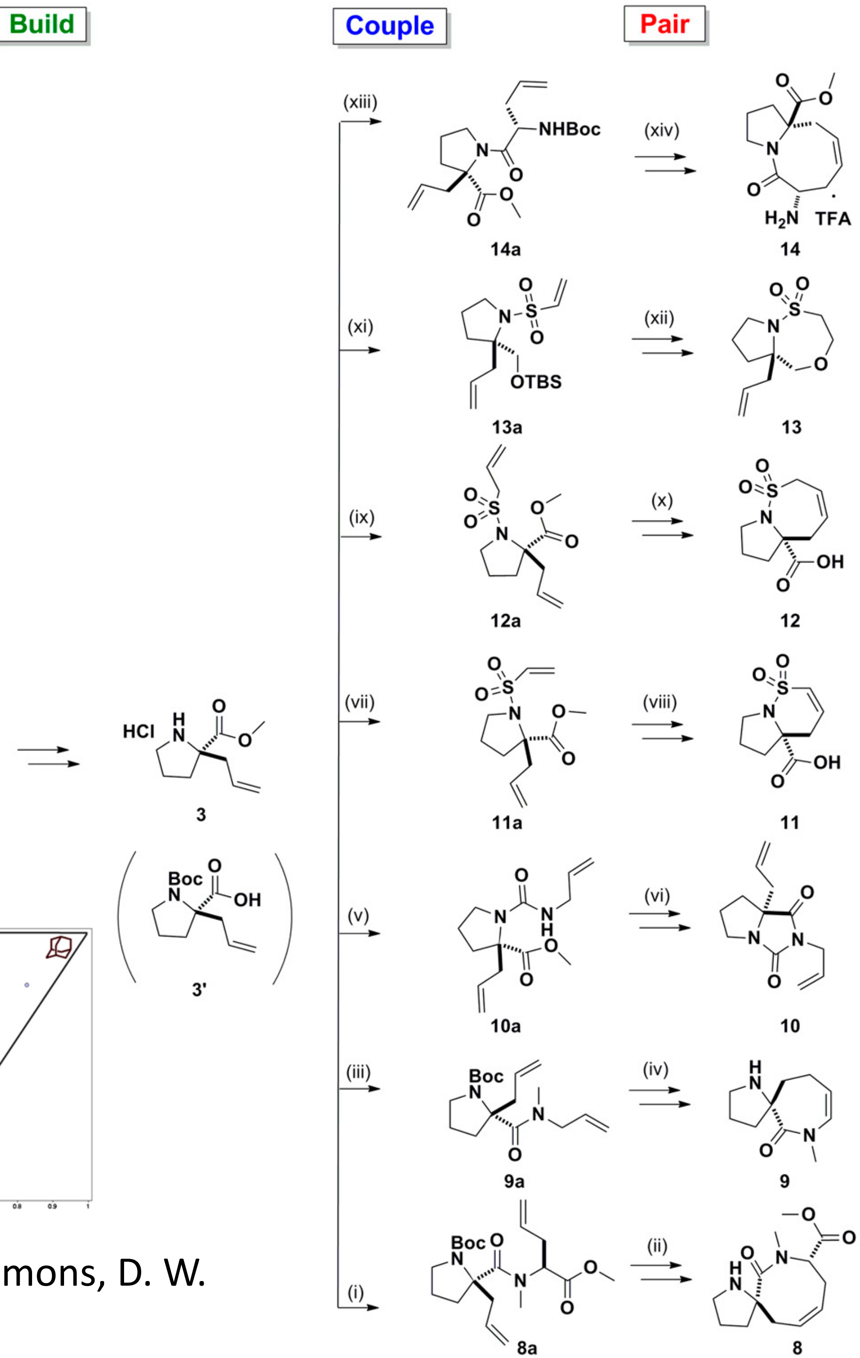
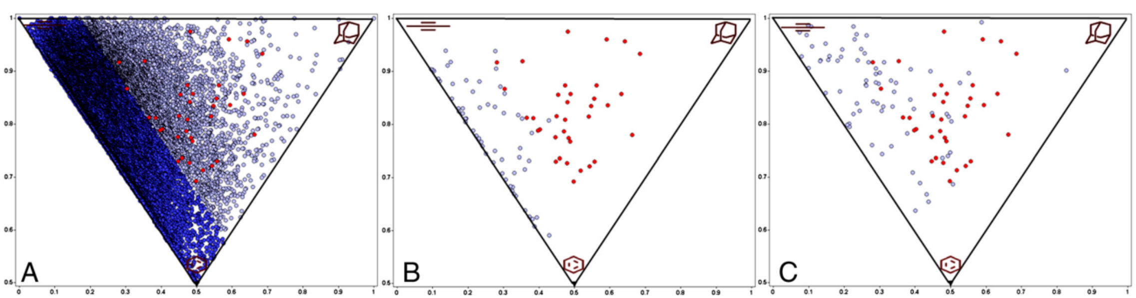
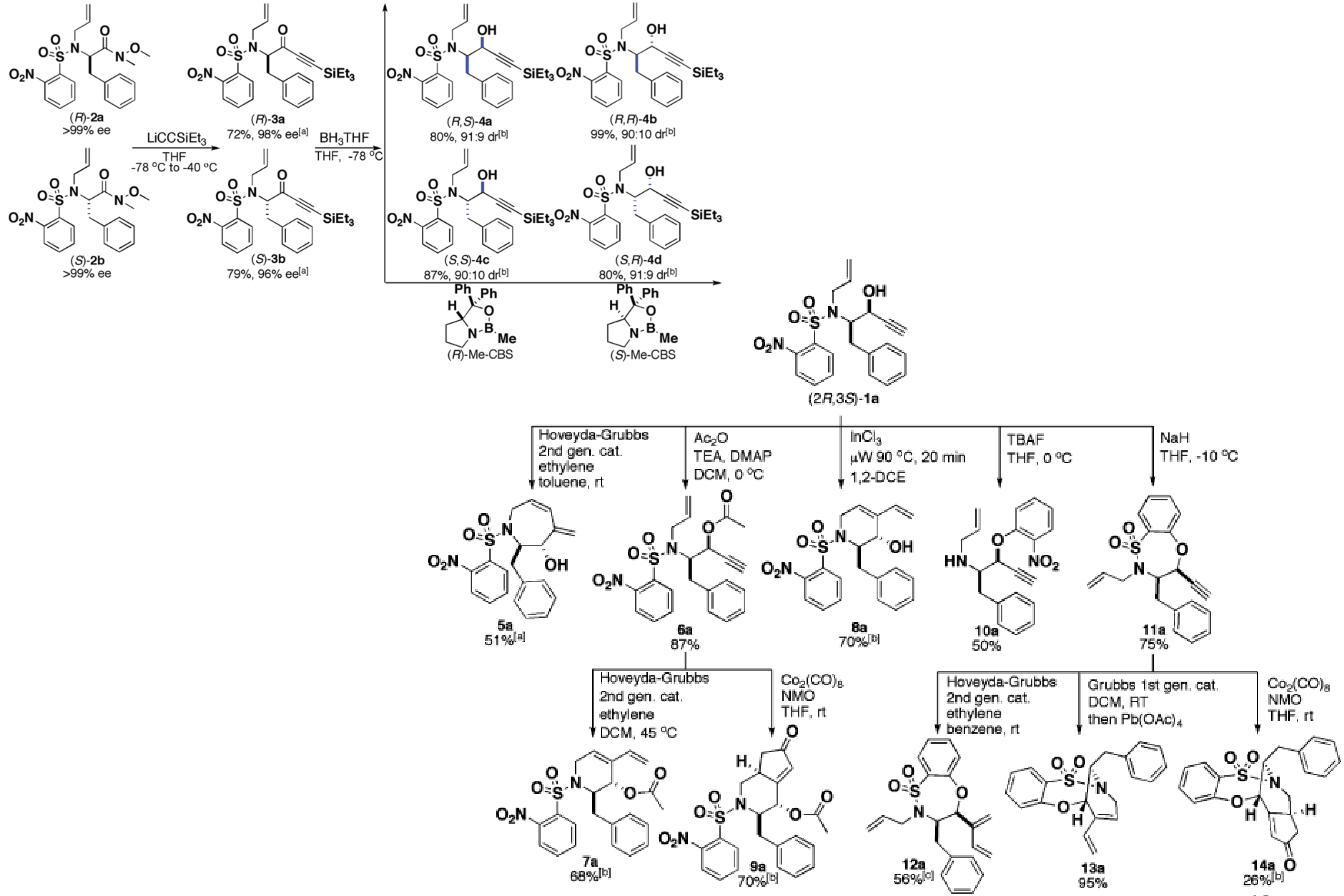


Fig. 3. Application of a B/C/P approach starting from proline **3**/**3′** to give compounds **8–14**. From **3′**, (*i*) (*S*)-allylglycine methyl ester, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDCI), Oxyma, Et_3N, CH_2Cl_2, 89%; NaH, MeI, DMF, 89%; (*ii*) Grubbs II, CH_2Cl_2, reflux, 34%; TFA; (*iii*) allylamine, EDCI, Oxyma, Et_3N, CH_2Cl_2, 91%; NaH, MeI, dimethylformamide (DMF), 72%; (*iv*) Grubbs II, toluene, 60%; TFA. From **3**, (*v*) allyl isocyanate, Et_3N, CH_2Cl_2, 70%; (*vi*) NaH, DMF, 93%; (*vii*) 2-chlorosulfonyl chloride, Et_3N, CH_2Cl_2, 62%; (*viii*) Grubbs II, CH_2Cl_2, reflux, 92%; LiOH, THF, 53%; (*ix*) prop-2-ene-1-sulfonyl chloride, Et_3N, CH_2Cl_2, 44%; (*x*) Grubbs II, CH_2Cl_2, reflux, 96%; LiOH, THF, 71%; (*xi*) $LiAlH_4$, THF; *tert*-butyldimethylsilylchloride, Et_3N, CH_2Cl_2 (24% over two steps); 2-chlorosulfonyl chloride, Et_3N, CH_2Cl_2, 33%; (*xii*) tetrabutylammonium fluoride, THF, 45%; (*xiii*) (*S*)-*N*-Boc-allylglycine, EDCI, Oxyma, Et_3N, CH_2Cl_2, 48%; (*xiv*) Grubbs II, CH_2Cl_2, reflux, 41%; TFA.



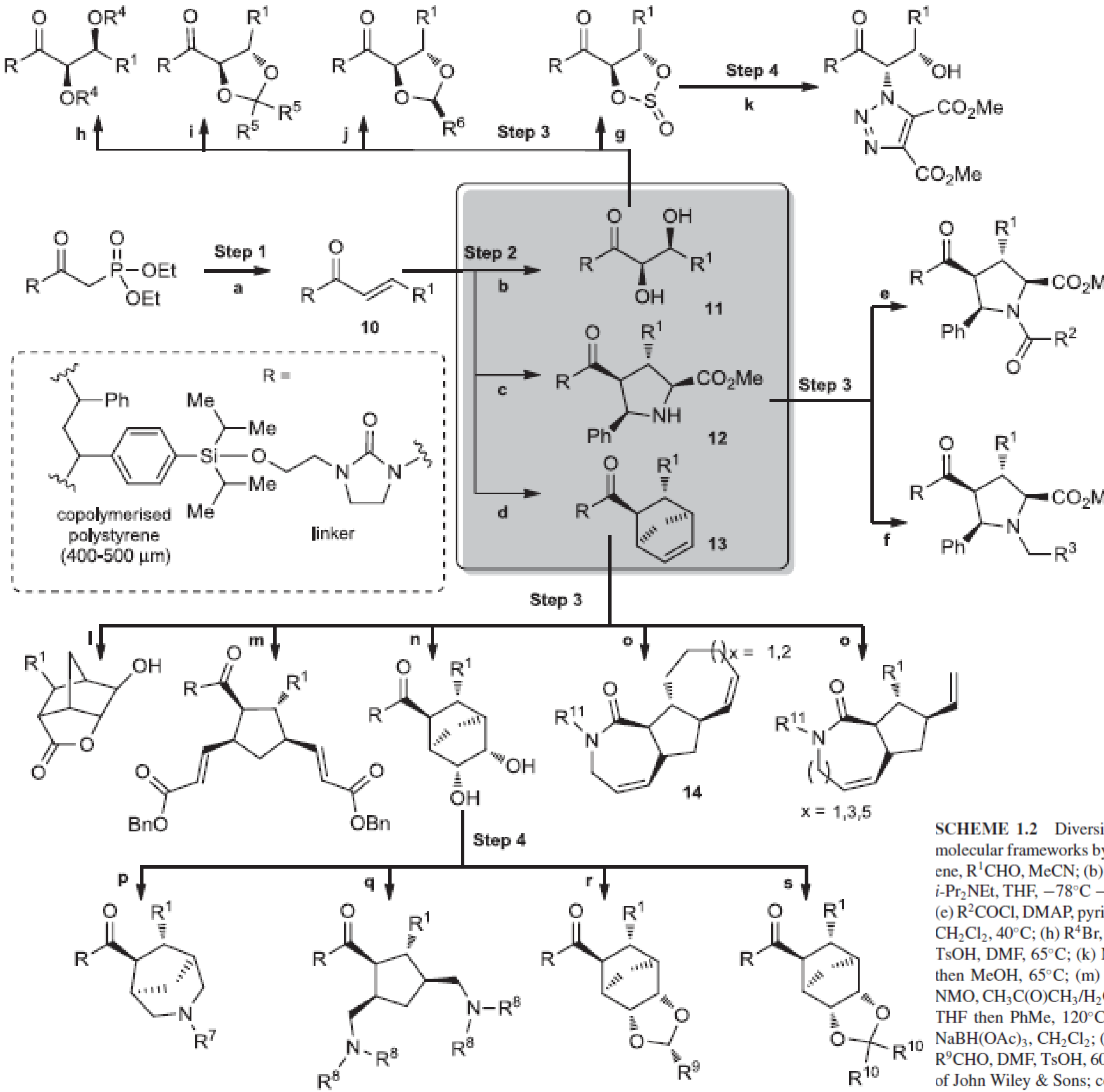
A. W. Hung, A. Ramek, Y. Wang, T. Kaya, J. A. Wilson, P. A. Clemons, D. W. Young, *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 6799–6804

Synthèse pour la Diversité Moléculaire



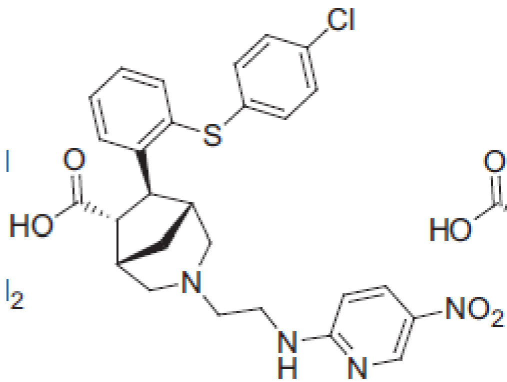
D. Pizzirani, T. Kaya, P. A. Clemons, S. L. Schreiber, *Org. Lett.* **2010**, *12*, 2822–2825

Synthèse pour la Diversité Moléculaire

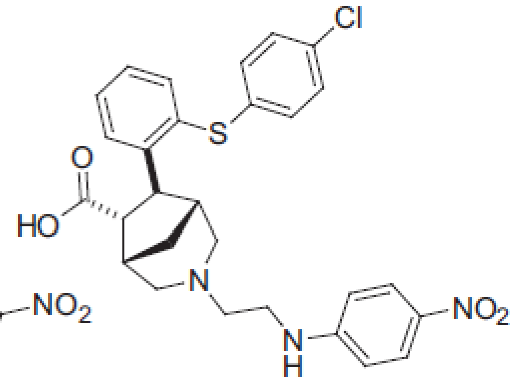


SCHEME 1.2 Diversity-oriented synthesis of 242 compounds based around 18 discrete molecular frameworks by Thomas et al. Conditions: (a) LiBr, 1,8-diazabicyclo[5.4.0]undec-7-ene, R^1CHO, MeCN; (b); AD-mix, (DHQD)PHAL, THF/H_2O (1:1); c) (*R*)-QUINAP, AgOAc, *i*-Pr_2NEt, THF, −78°C → 25°C; (d) chiral bis(oxazoline), $Cu(OTf)_2$, 3 Å MS, CH_2Cl_2, C_5H_6; (e) R^2COCl, DMAP, pyridine, CH_2Cl_2; (f) R^3CHO, BH_3·pyridine, MeOH; (g) $SOCl_2$, pyridine, CH_2Cl_2, 40°C; (h) R^4Br, Ag_2O, CH_2Cl_2, 40°C; (i) $R^5C(O)R^5$, TsOH, DMF, 65°C; (j) R^6CHO, TsOH, DMF, 65°C; (k) NaN_3, DMF, 100°C then DMAD, PhMe, 65°C; (l) *m*CPBA, CH_2Cl_2 then MeOH, 65°C; (m) $CH_2{=}CHCO_2Bn$, PhMe, 120°C, Grubbs II, $CH_2{=}CH_2$; (n) OsO_4, NMO, $CH_3C(O)CH_3/H_2O$ (10 : 1); (o) RNH_2, Me_2AlCl, PhMe, 120°C, then NaH, $R^{11}X$, DMF, THF then PhMe, 120°C, Grubbs II, $CH_2{=}CH_2$; (p) $NaIO_4$, THF/H_2O (1 : 1) then R^7NH_2, $NaBH(OAc)_3$, CH_2Cl_2; (q) $NaIO_4$, THF/H_2O (1:1) then R^8NHR^8, $NaBH(OAc)_3$, CH_2Cl_2; (r) R^9CHO, DMF, TsOH, 60°C; (s) $R^{10}C(O)R^{10}$, DMF, TsOH, 60°C. (From [47], with permission of John Wiley & Sons; copyright (© 2008 John Wiley & Sons.)

Synthèse pour la Diversité Moléculaire



gemmacin



gemmacin-B

TABLE 1.1 The Comparable Effects of Emmacin, the Enantiomers of Gemmacin, Gemmacin B, Erythromycin, and Oxacillin on Three Strains of *Staphylococcus aureus*

	MIC_{50} (μg/mL)		
	MSSA	EMRSA-15	EMRSA-16
Emmacin	2	9	9
(±)-Gemmacin B	Not determined	8	8
(±)-Gemmacin	2	16	32
Erythromycin	0.5	>64	>64
Oxacillin	0.5	>32	>32

G. L. Thomas, R. J. Spandl, F. G. Glansdorp, M. Welch, A. Bender, J. Cockfield, J. A. Lindsay, C. Bryant, D. F. Brown, O. Loiseleur, H. Rudyk, M. Ladlow, D. R. Spring, *Angew. Chem. Int. Ed.* ***2008**, 47*, 2808–2812

Chimie Combinatoire

TANULMÁNY, GYÓGYÁSZATILAG HASZNOSITHATÓ PEPTIDEK SZISZTEMATIKUS FELKUTATÁSÁNAK LEHETŐSÉGEIRŐL

Készitette Dr. Furka Árpád egyetemi tanár, Budapest, 1982 május 29.

Többek között az eddig felfedezett peptidhormonok példája is tanusitja, hogy a hosszabb-rövidebb peptidek az élő szervezetben számos fontos funkciót láthatnak el. Feltehető, hogy ezeknek a biológiailag aktiv, és potenciális terápiás hatással biró peptideknek eddig csak egy kis töredékét ismerjük. Ez indokolja, hogy ezen a területen világszerte és hazánkban is, intenziv kutatómunka folyik.

Az ujfajta biológiai hatással rendelkező peptidek felkutatására kétféle elvi lehetőség kinálkozik:

1. A peptidek izolálása az élő szervezetből, előzetesen felismert biológiai hatásuk alapján.

2. A peptidek szintetikus előállitása és biológiai hatásaik utólagos felderitése.

Eddig az izolálásos módszer bizonyult járhatóbbnak annak ellenére, hogy ez is igen munkaigényes. Ennek az a magyarázata, hogy az adott tagszámu peptidek lehetséges száma olyan gyorsan nő a tagszámmal, hogy már a tetrapeptidek teljes számban /160 ezer/ történő előállitása is a gyakorlatban megoldhatatlan feladatnak tünik. Ha a 20 féle fehérjealkotó aminosavat vesszük alapul, a lehetséges peptidek számát /N_n/ a következő egyenlet fejezi ki a tagszám /n/ függvényében:

$$N_n = 20^n$$

Ha a peptideket lépésenként és egymástól függetlenül állitjuk elő, az n tagu peptidek esetében az ehhez szük-

- 14 -

<u>A módszer kiterjesztése más vegyülettipusokra</u>

Az előzőekben kifejtett módszer nemcsak aktiv peptidek szisztematikus felkutatására alkalmas. Ugyanaz az elv minden más szekvenciális felépitésü vegyülettipusra érvényes, vagyis amikor a vegyülettipushoz tartozó vegyületek az egymáshoz sorban kapcsolódó épitőelemek minőségében és sorrendjében különböznek egymástól. Ezek között lehetnek természetes vegyületek mint például az oligoszacharidok, vagy oligonukleotidok, de elképzelhetők mesterséges vegyületek is. Ez utóbbiak esetében szekvenciális kopolimer tipusu vegyületek jöhetnek széba, vagy szekvenciális polikondenzátumok.

Furka Árpád
Dr. Furka Árpád
egyetemi tanár

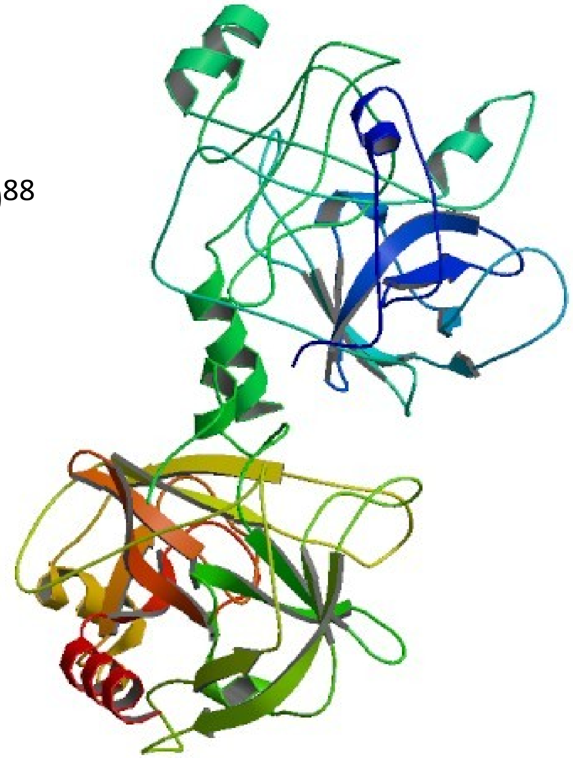
36237/1982. ügyszám

Tanusitom, hogy ezt a 14.azaz Tizennégy oldalból álló összefüzött okiratot dr. Furka Árpád egyetemi tanár Budapest VII., Csengery utca 23. III.2.szám alatti lakos előttem sajátkezüleg irta alá. -
Budapest, 1982. Ezerkilencszáznyolcvankettő évi junius hó 15. /Tizenötödik/ napján. -

Dr. [illegible]ókai Judit
[illegible] közjegyző

Concept introduit en mai 1982

Árpád Furka



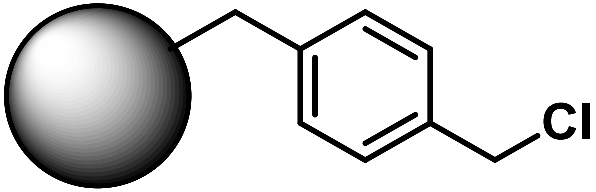
Chymotrypsinogène : 245 AA

$20^{245} = 5.65 \times 10^{318}$ séquences, nb de particules dans l'univers : ~10^{88}

Table 1.1. The number of possible peptide sequences.

Number of residues	Name	Number of sequences
2	Dipeptides	400
3	Tripeptides	8,000
4	Tetrapeptides	160,000
5	Pentapeptides	3,200,000
6	Hexapeptides	64,000,000
7	Heptapeptides	1,280,000,000

Synthèse sur Support Solide

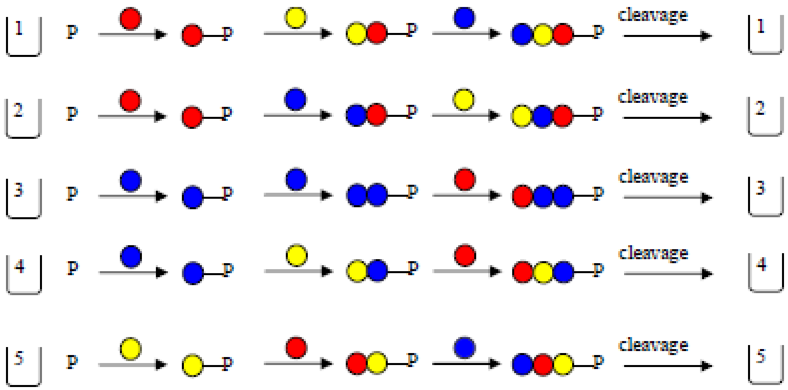


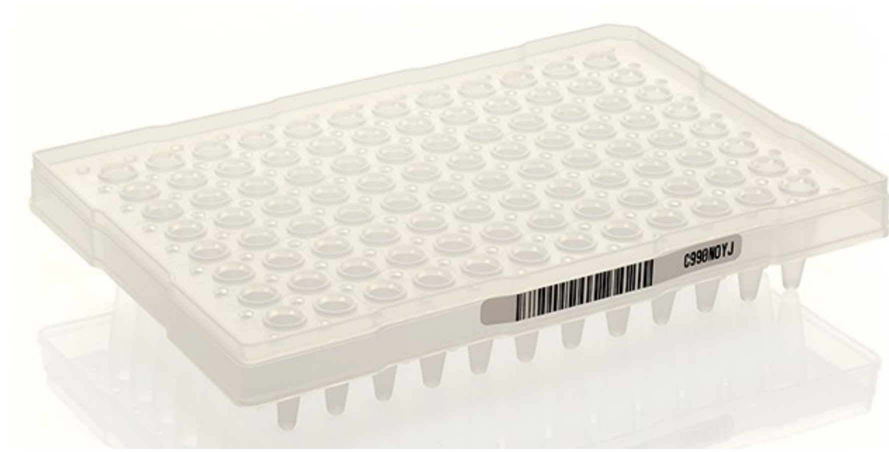
1963, synthèse sur des billes de polystyrène fonctionnalisé

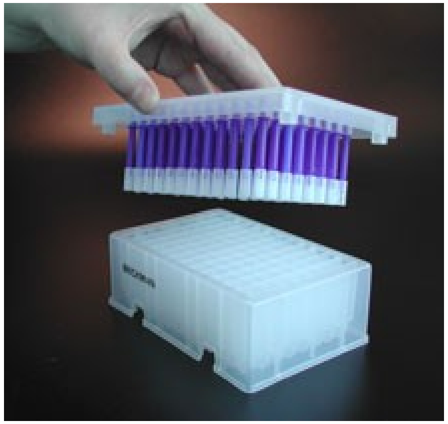
Bruce Merrifield , Nobel 1984

John Stewart (left) and Bruce Merrifield (right) with the first automatic peptide synthesizer

Synthèse Parallèle







Méthode d'Houghten « tea bag synthesis »

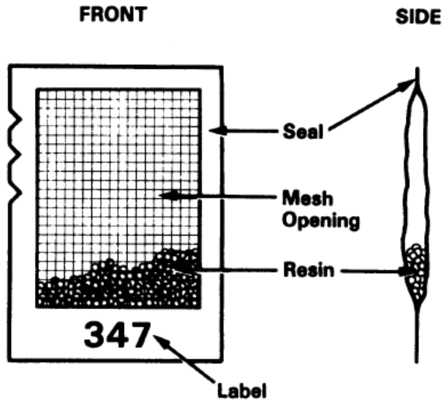
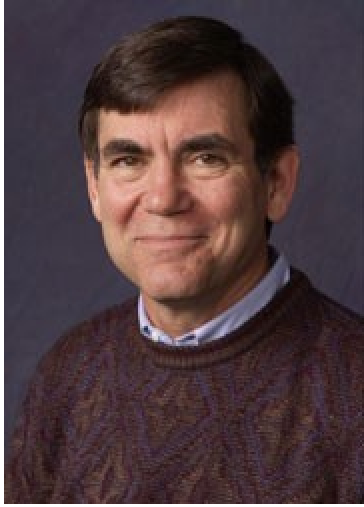


FIG. 1. Illustration of a mesh packet containing resin.



Richard A. Houghten

"By using these packets, 260 individual peptides were synthesized with a total of >3380 coupling steps in a period of 4 weeks. Each peptide was obtained in 10-to 20-mg quantities "

Proc. Natl. Acad. Sci. USA
Vol. 82, pp. 5131–5135, August 1985
Immunology

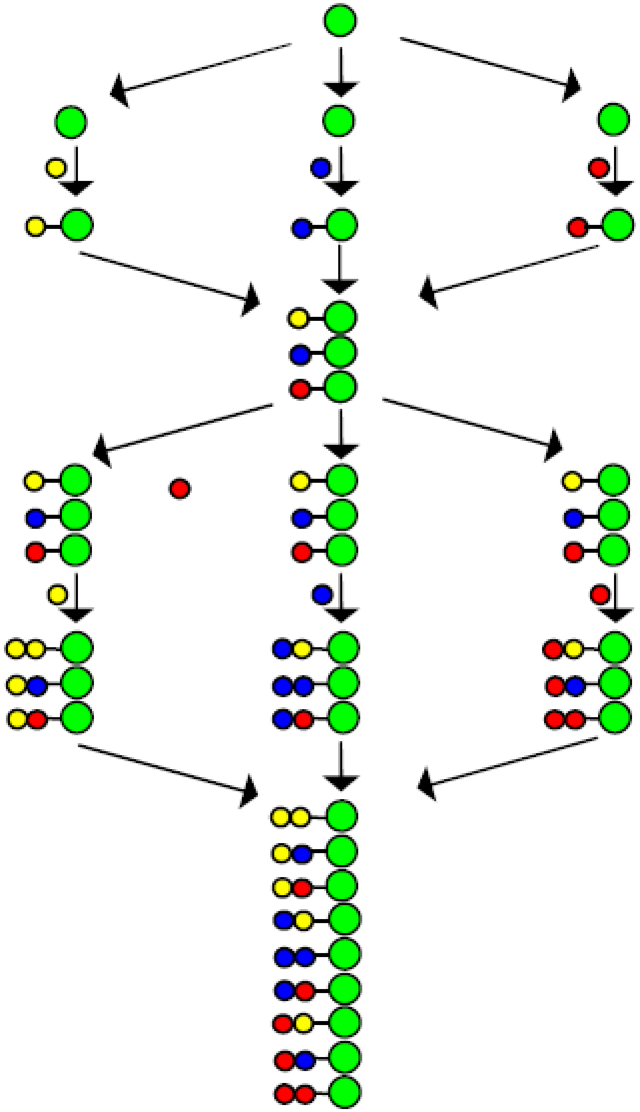
General method for the rapid solid-phase synthesis of large numbers of peptides: Specificity of antigen–antibody interaction at the level of individual amino acids

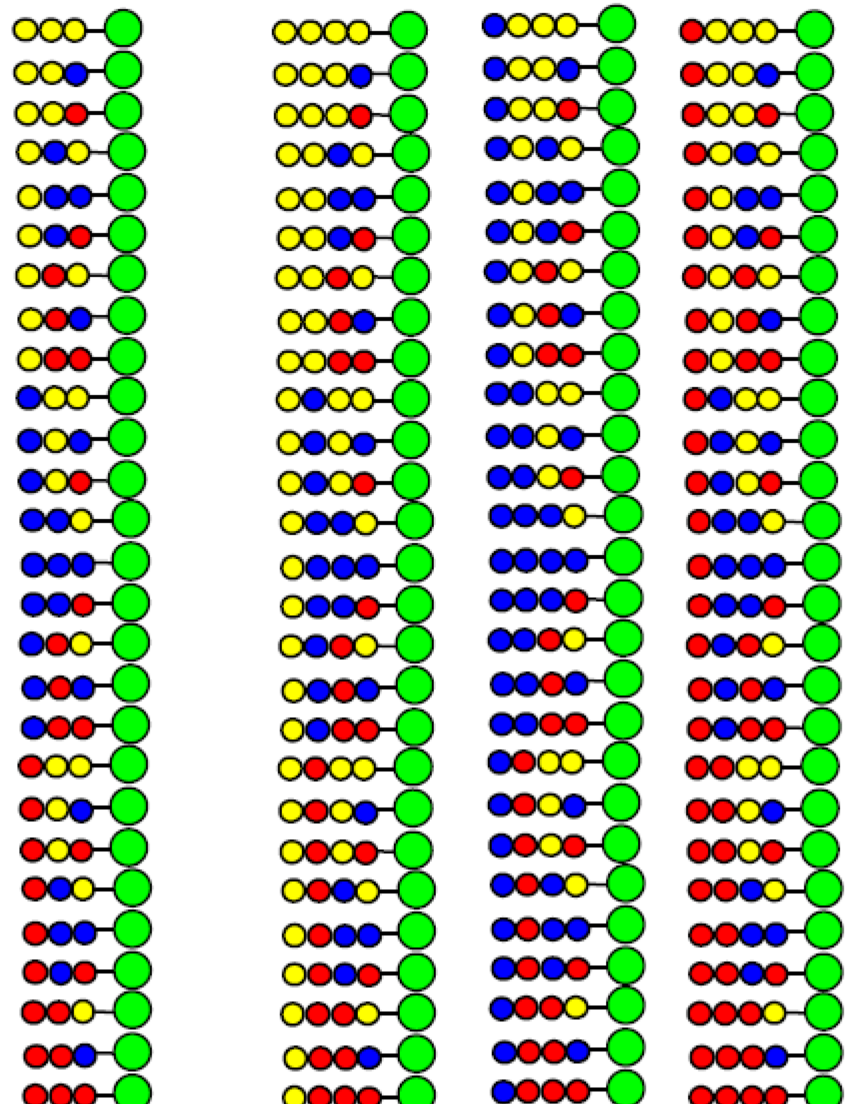
(simultaneous multiple-peptide synthesis)

RICHARD A. HOUGHTEN

Department of Molecular Biology, Scripps Clinic and Research Foundation, 10666 North Torrey Pines Road, La Jolla, CA 92037

Générer de la Diversité – Mix & Split



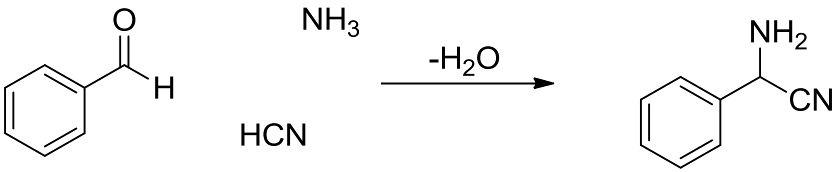


1. Á. Furka, F. Sebestyén, M. Asgedom, G. Dibó, In *Highlights of Modern Biochemistry*, Proceedings of the 14th International Congress of Biochemistry, VSP. Utrecht, The Netherlands, **1988**, Vol. 5, p 47.
2. Á. Furka, F. Sebestyén, M. Asgedom, G. Dibó *Proceedings of the 10th International Symposium of Medicinal Chemistry,* Budapest, Hungary, **1988**, p 288, Abstract P-168.
3. Á. Furka, F. Sebestyén, M. Asgedom, G. Dibó *Int. J. Peptide Protein Res.* **1991,** 37, 487.

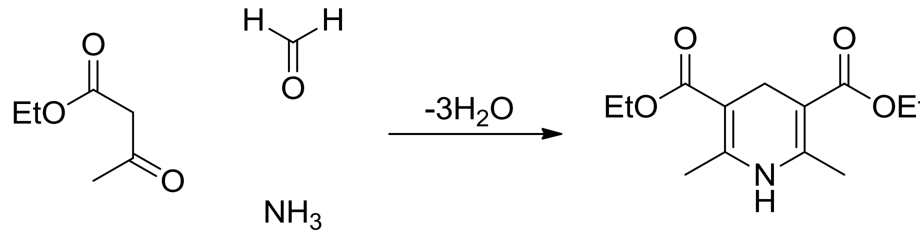
Réactions Multicomposants – Définition, Historique

“Multicomponent reactions (MCRs) are generally defined as reactions where more than two starting materials react to form a product, incorporating essentially all of the atoms of the educts"

Alexander Dömling *Chem. Rev.* **2006**, *106*, 17-89



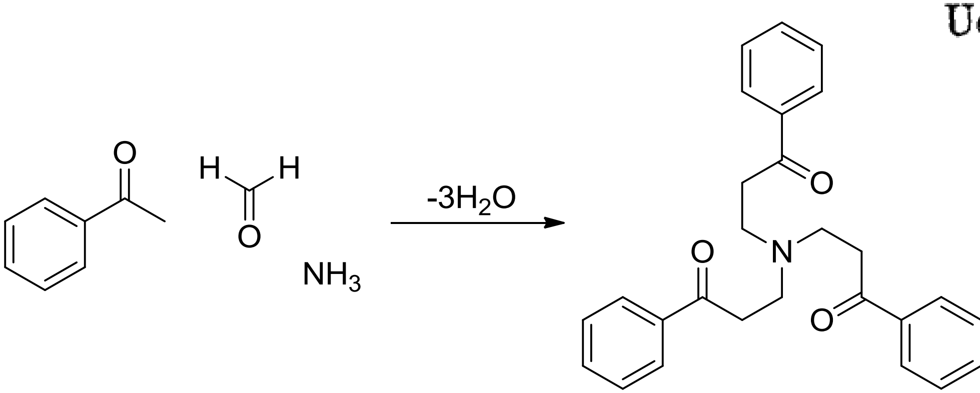
A. Strecker, *Liebigs Ann. Chem.* **1850**, *75*, 27.



A. Hantzsch, *Justus Liebigs Ann. Chem.* **1882**, *215*, 1.

Ueber die Synthese pyridinartiger Verbindungen aus Acetessigäther und Aldehydammoniak;

von Dr. *Arthur Hantzsch* *).

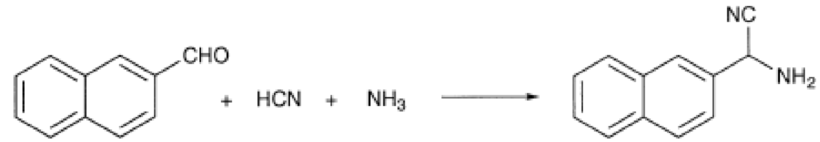
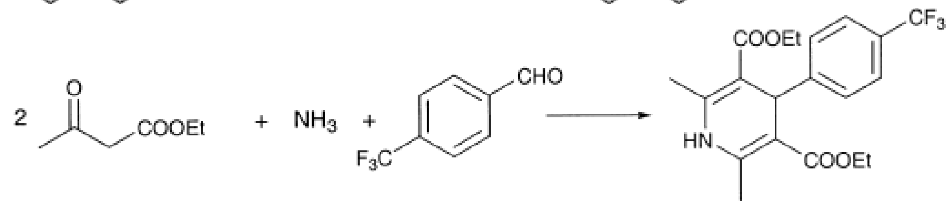
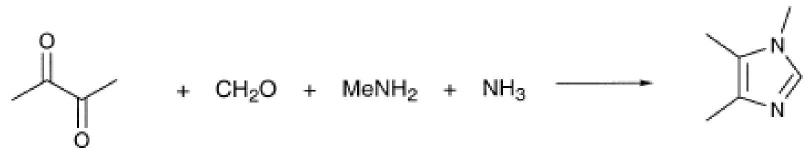
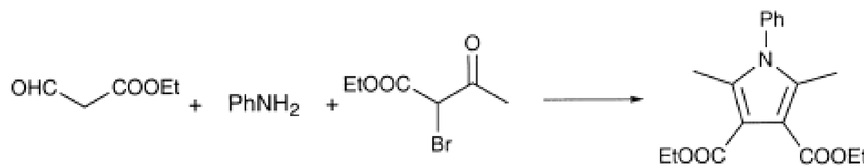
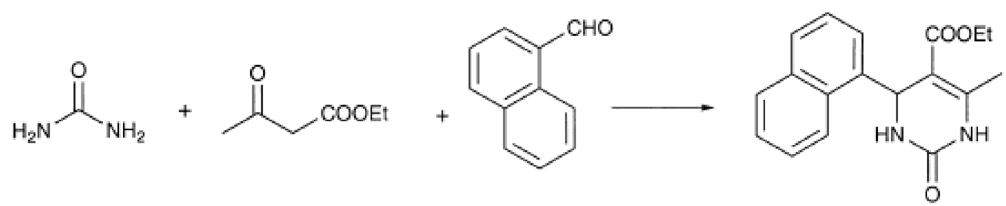
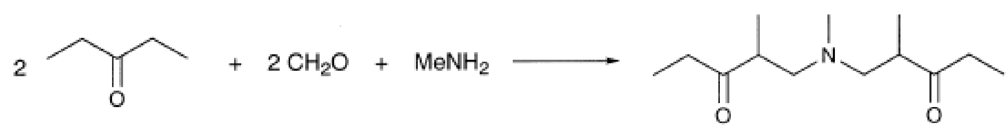
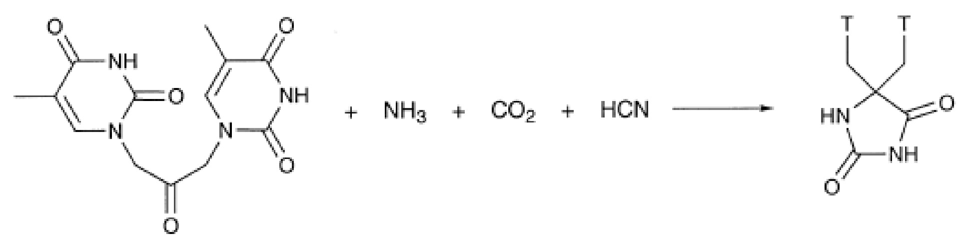


343. H. Schäfer und B. Tollens: Ueber die Bildung von Basen aus Acetophenon, Formaldehyd und Chlorammonium[1]).

[Mitgetheilt von B. Tollens.]

(Eingegangen am 7. Juni 1906.)

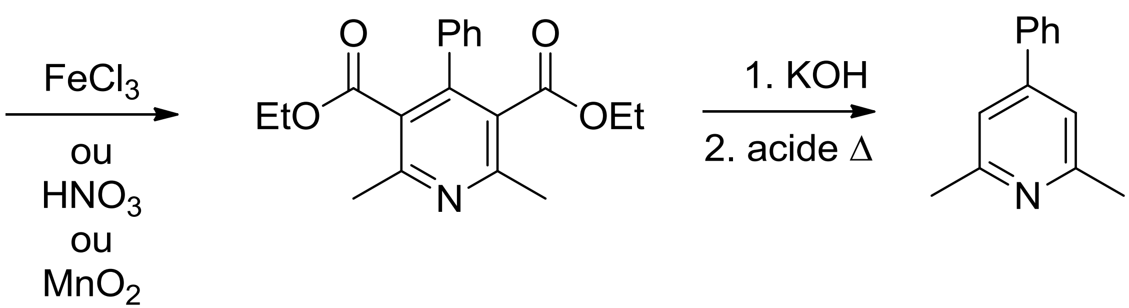
Réactions Multicomposants – Carbonyle/Imine

Name of the reaction	Year of discovery	Example[a]
Strecker synthesis[10]	(1838) 1850	
Hantzsch dihydropyridine synthesis[15]	1882	
Radziszewski imidazole synthesis[21]	1882	
Hantzsch pyrrole synthesis[22]	1890	
Biginelli reaction[23, 24]	1891	
Mannich reaction[25]	1912	
Bucherer – Bergs hydantoin synthesis[20, 26]	1941	

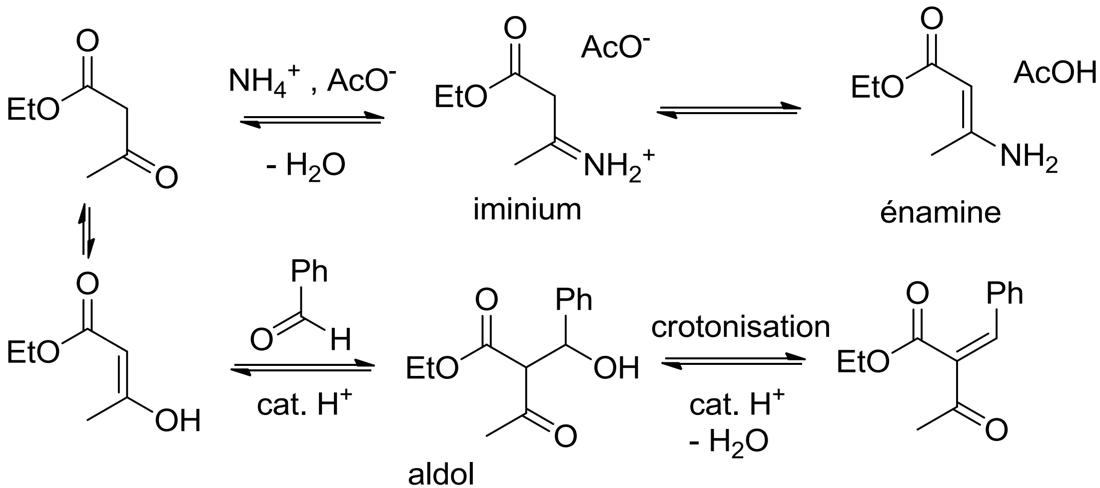
Réactions Multicomposants – Hantzsch (1882)

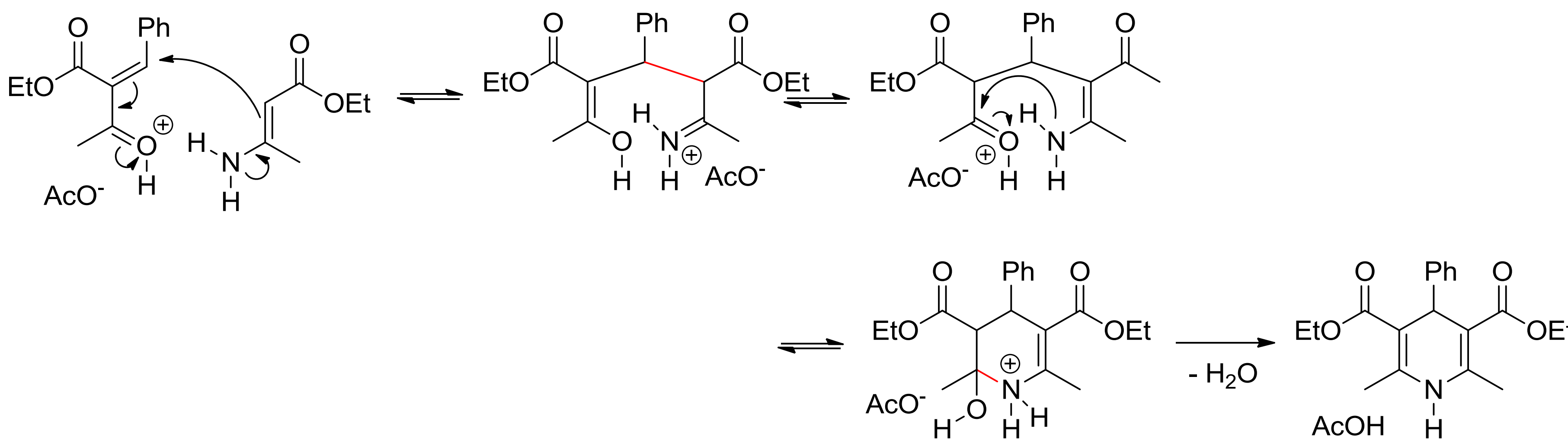
1,4-dihydropyridines

Arthur Rudolf Hantzsch
7 mars 1857 – 14 mars 1935

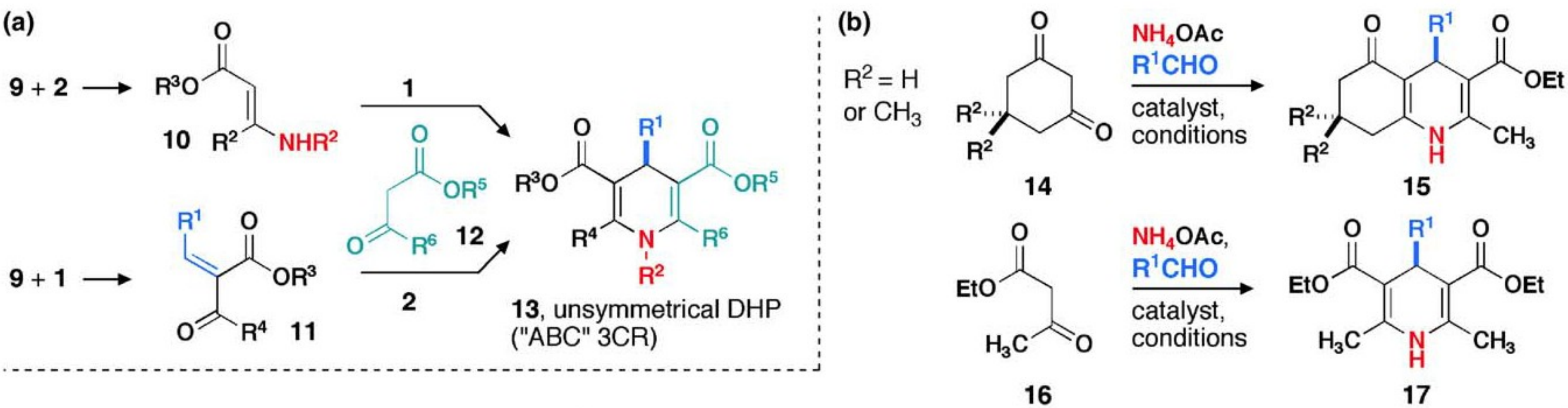


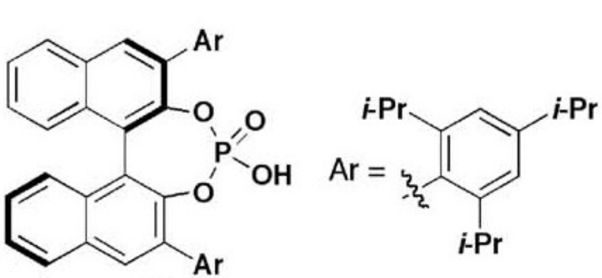
Hantzsch - mécanisme





Réactions Multicomposants – Hantzsch

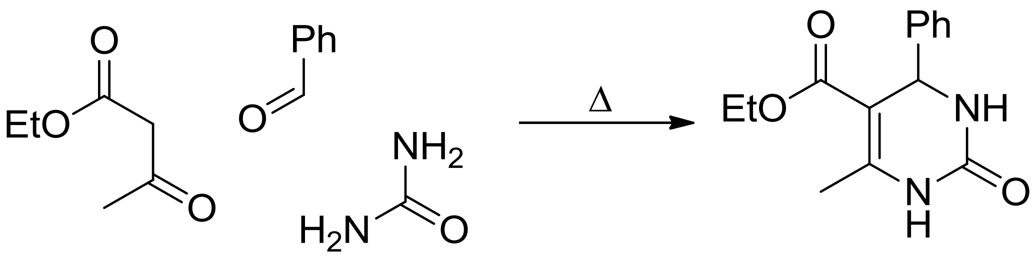




18

catalyst	$Yb(OTf)_3$	CAN	L-Pro	**18**	$PhB(OH)_2$	$CeCl_3 \cdot 7H_2O$
product	**15**	**15**	**15**	**15**	**17**	**17**
loading (mol%)	5	5	10	10	10	5
yield (%)	85-95	85-98	83-96	69-94	81-95	61-92
solvent	EtOH	EtOH	(none)	CH_3CN	EtOH	CH_3CN
time (h)	2-8	0.5-4	0.5	5	4-5	3-6
temperature	25 °C	25 °C	25 °C	25 °C	80 °C	25 °C
# of examples	17	16	14	15	13	15
ee	-	-	-	87-99%	-	-

Réactions Multicomposants – Biginelli (1891)



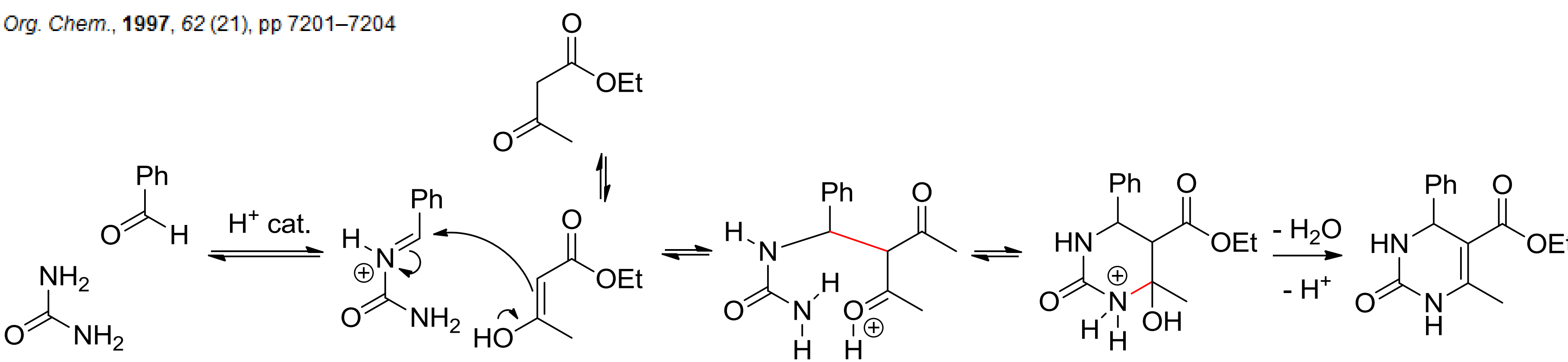
3,4-dihydropyrimidin-2(1*H*)-ones

Pietro Biginelli
25 juillet 1860 – 15 janvier 1937

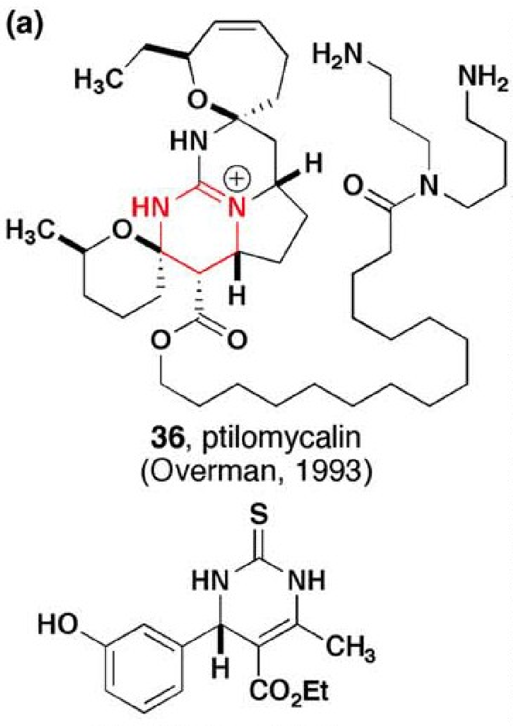
A Reexamination of the Mechanism of the Biginelli Dihydropyrimidine Synthesis. Support for an *N*-Acyliminium Ion Intermediate[1]

C. Oliver Kappe *
Institute of Organic Chemistry, Karl-Franzens-University Graz, A-8010 Graz, Austria

J. Org. Chem., **1997**, *62* (21), pp 7201–7204

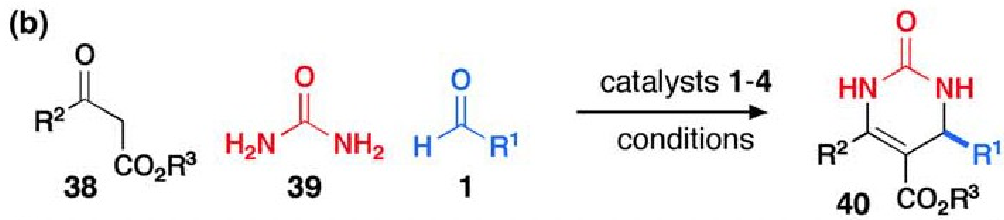


Réactions Multicomposants – Biginelli

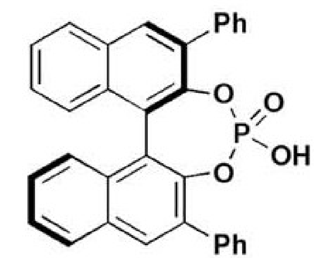


36, ptilomycalin (Overman, 1993)

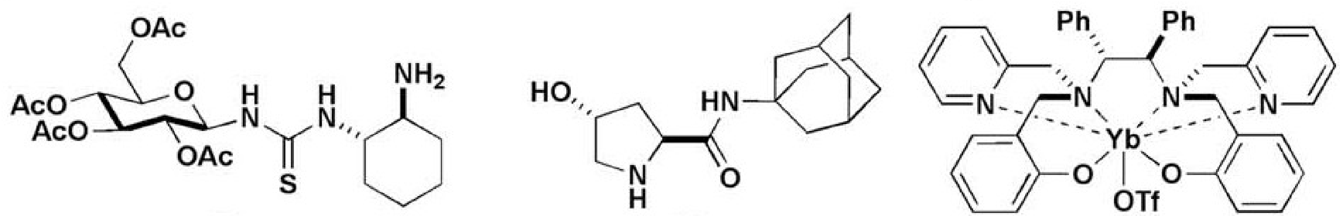
37, (*S*)-monastrol (Mitchison, 1999)



	41	42	43	44
loading (mol%)	10	5	5	10
ee (%)	88-97	15-99	70-98%	88-99
yield (%)	40-94	51-93	34-73%	73-94%
solvent	CH_2Cl_2	CH_2Cl_2	dioxane/THF (1:4)	THF
time (h)	96	72	36-156	20-30
temperature	25 °C	25 °C	25 °C	25 °C
# of examples	24	13	15	14



41



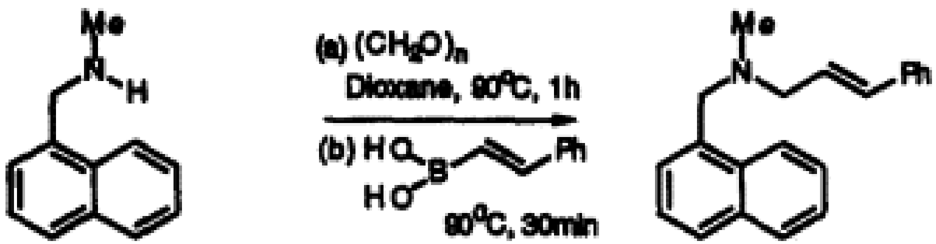
42 43 44

Réactions Multicomposants – Petasis (1993)

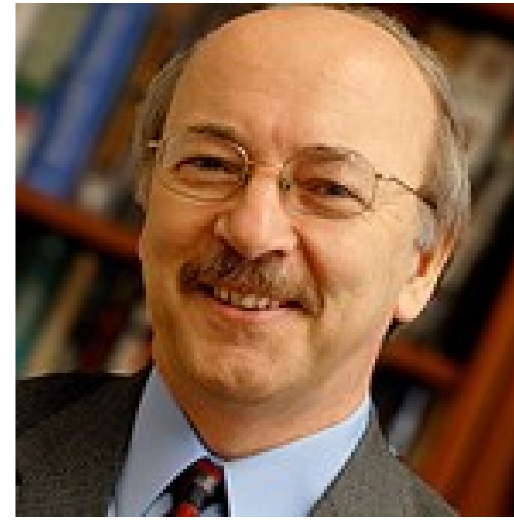
Tetrahedron Letters
Volume 34, Issue 4, 22 January 1993, Pages 583–586
The International Journal for the Rapid Publication of Preliminary

The boronic acid mannich reaction: A new method for the synthesis of geometrically pure allylamines

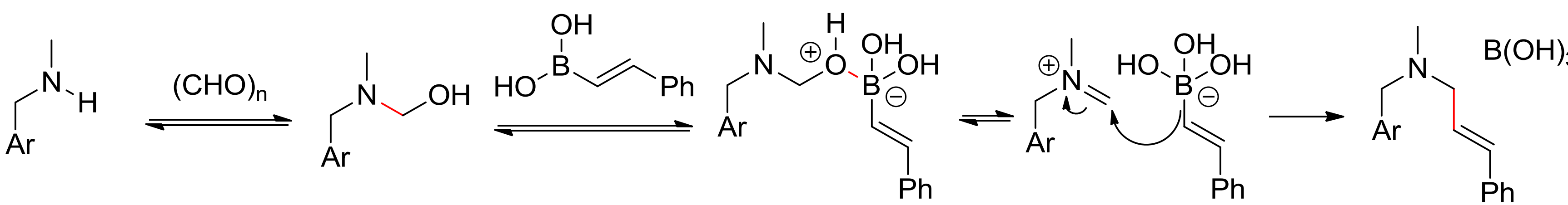
Nicos A. Petasis, Irini Akritopoulou



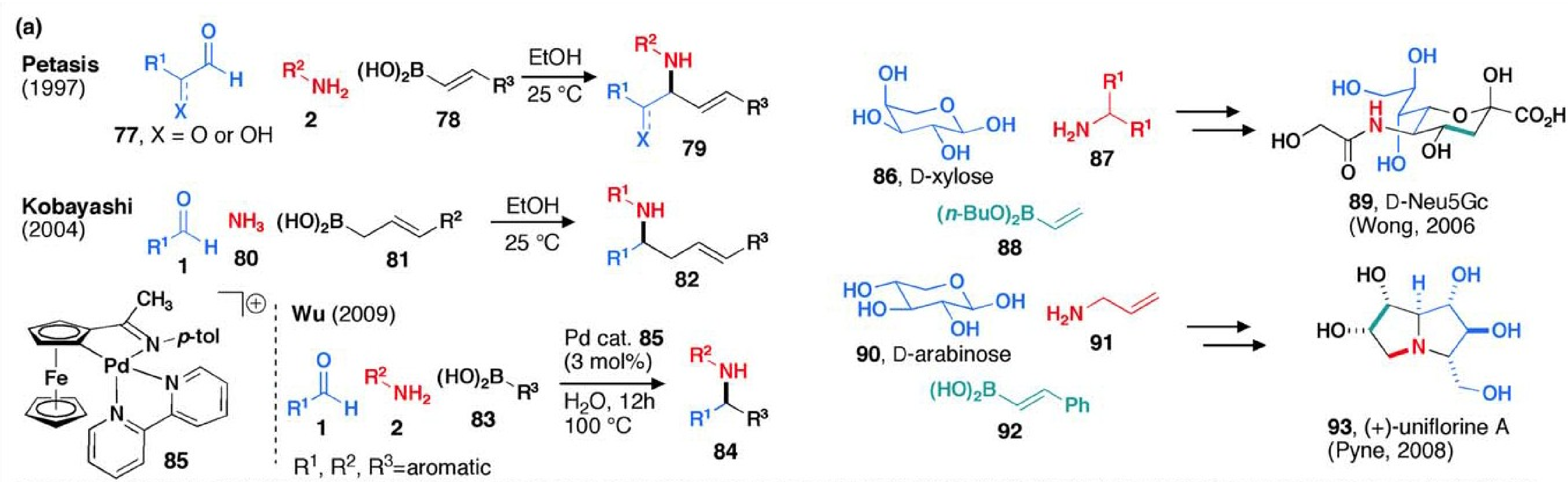
Naftifine (82%)



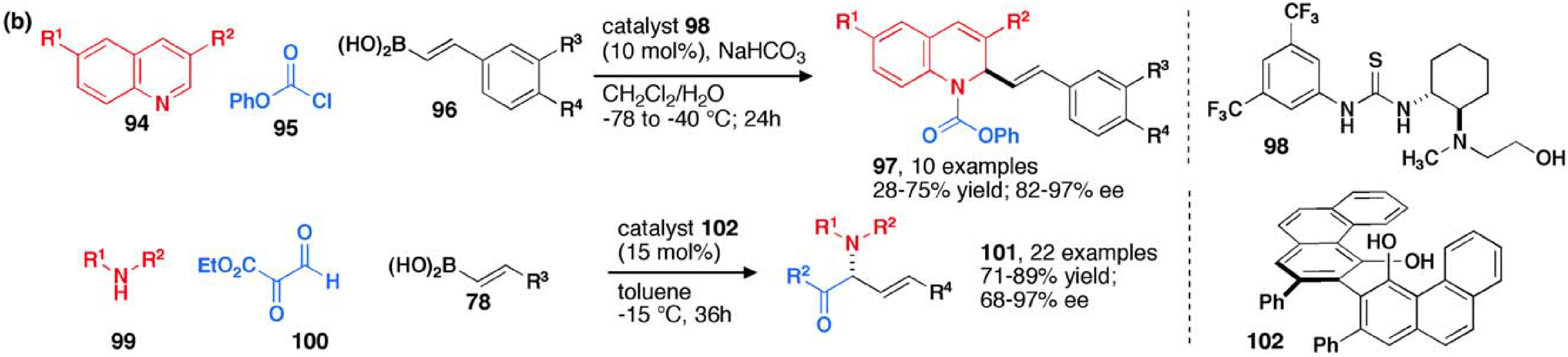
Nicos A. Petasis

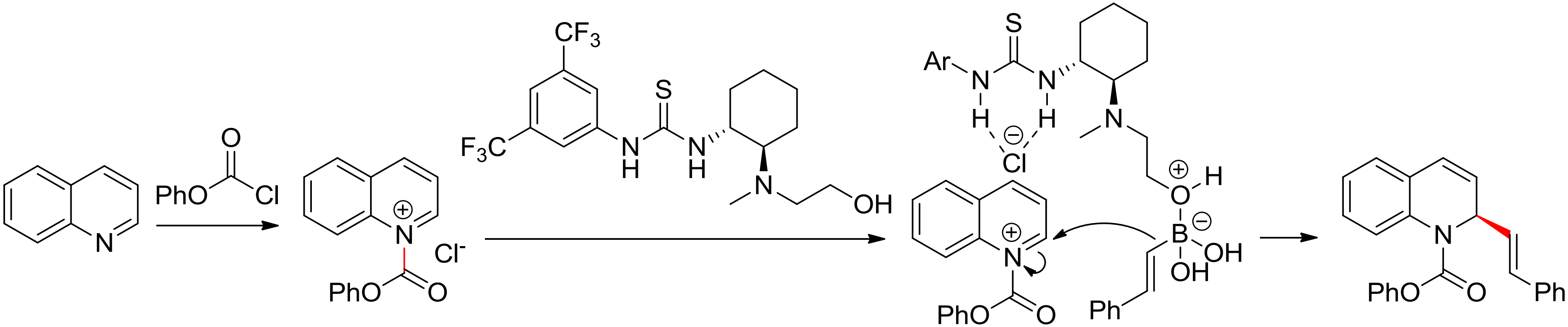


Réactions Multicomposants – Petasis

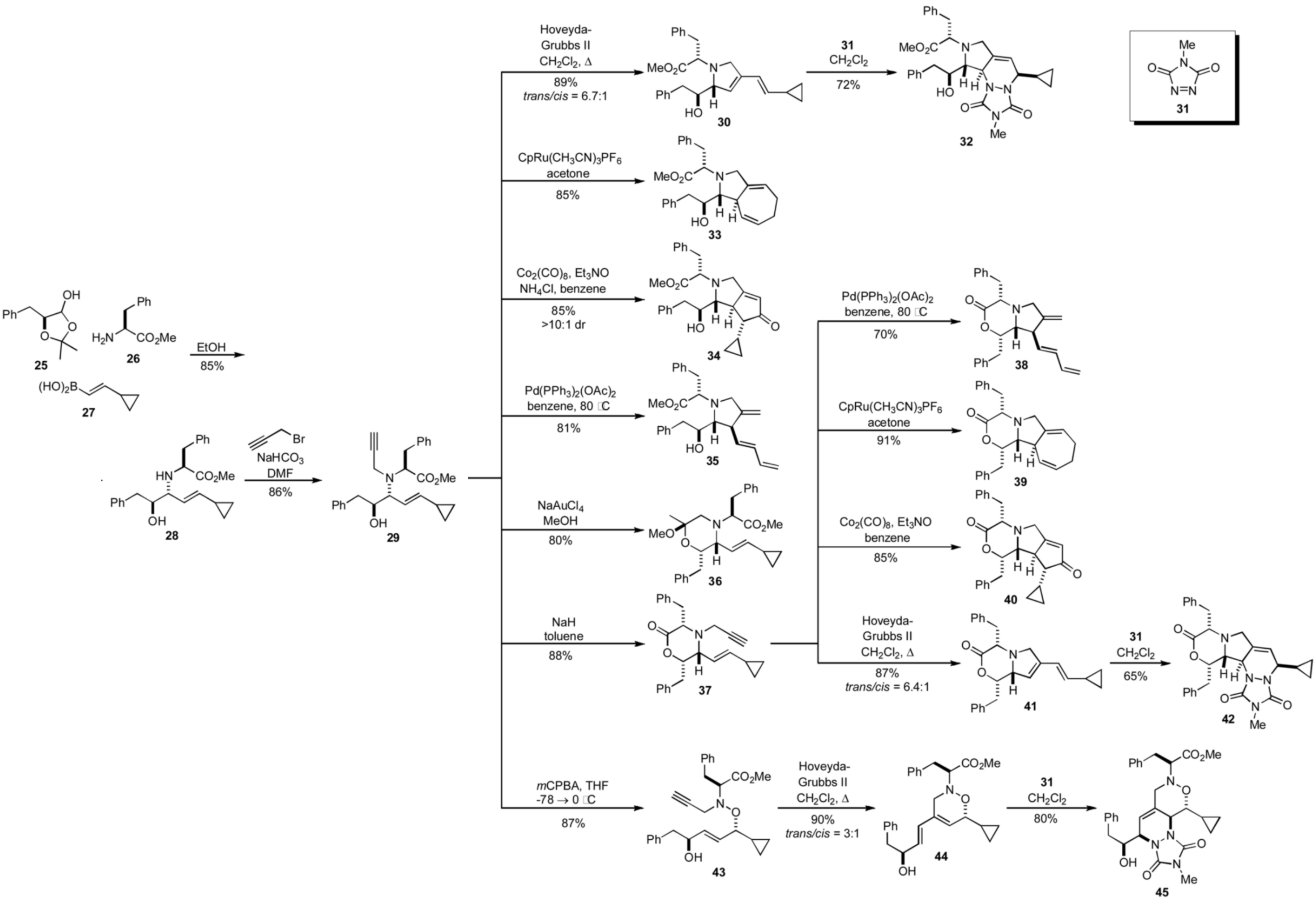


Réactions Multicomposants – Petasis

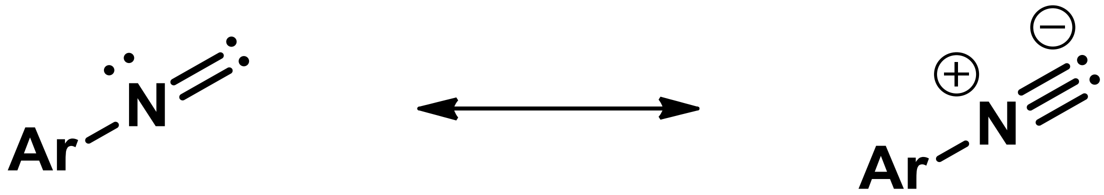


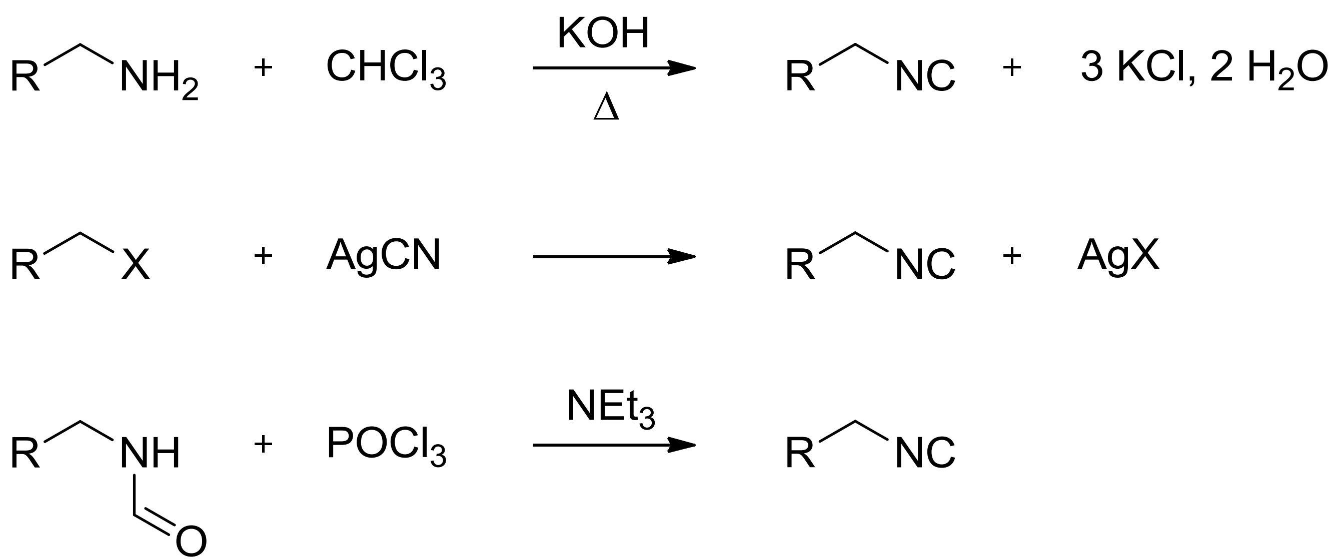


Réactions Multicomposants – Petasis pour la DOS



Réactions Multicomposants – Isonitriles



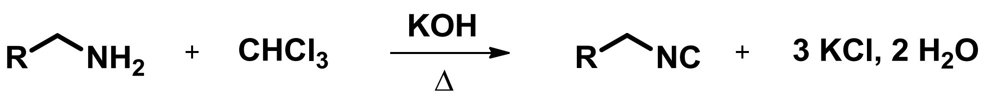


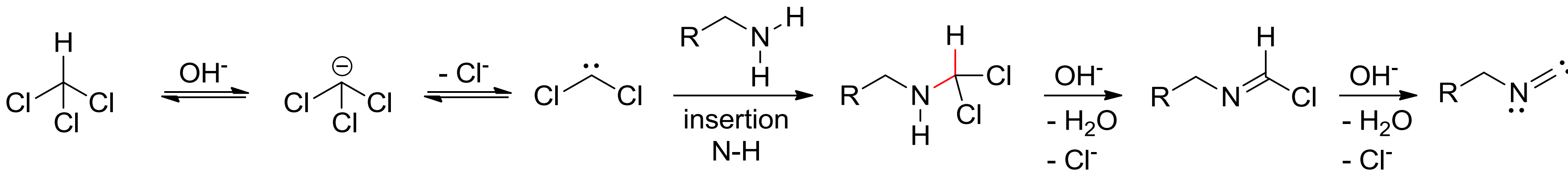
Ueber die Einwirkung des Chlorwasserstoffs u. a. auf das Aethyl- und Methylcyanür;

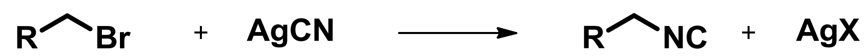
1867. von *A. Gautier* *).

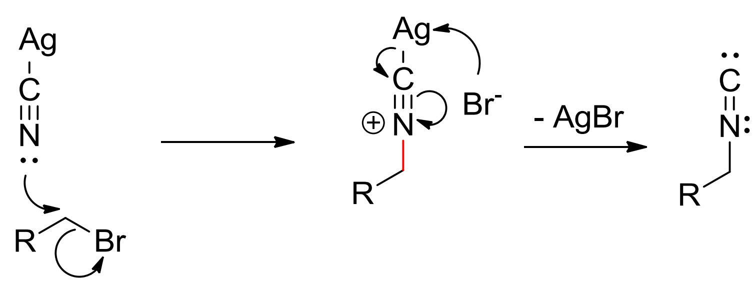
Einwirkung der Wasserstoffsäuren. — **Läfst man einen Strom getrockneten Chlorwasserstoffgases durch reines Aethyl-**

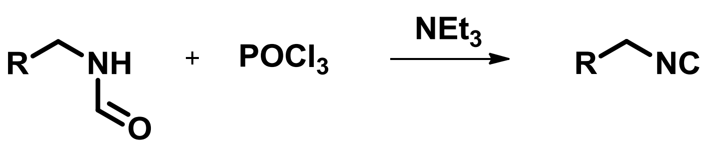
Réactions Multicomposants – Isonitriles

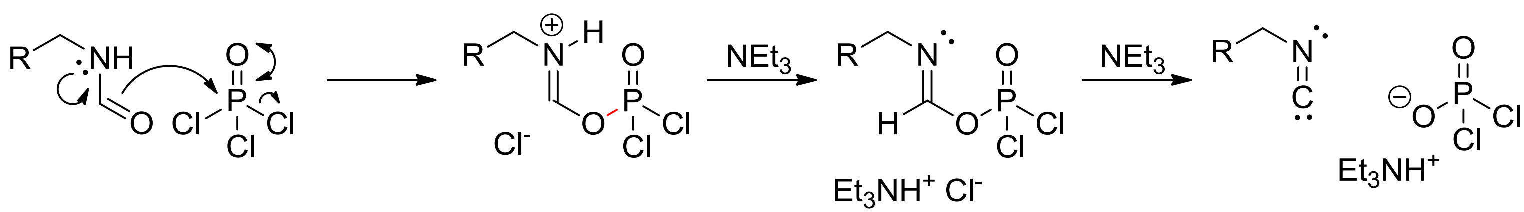




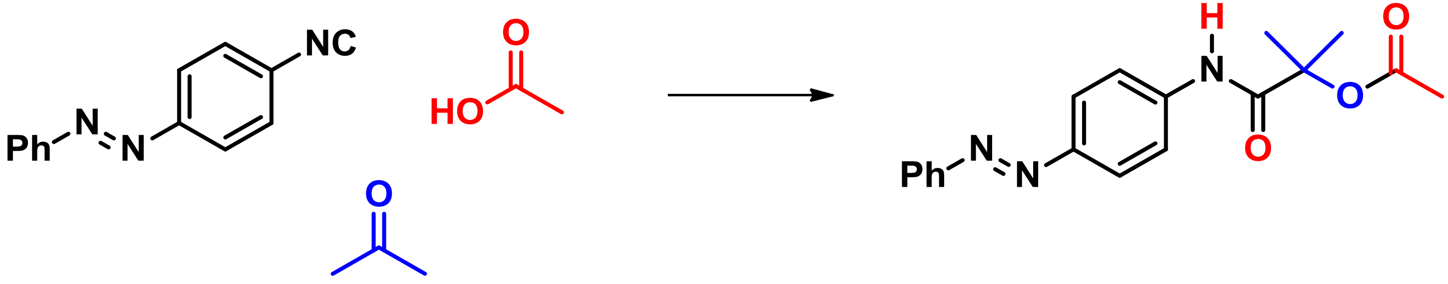




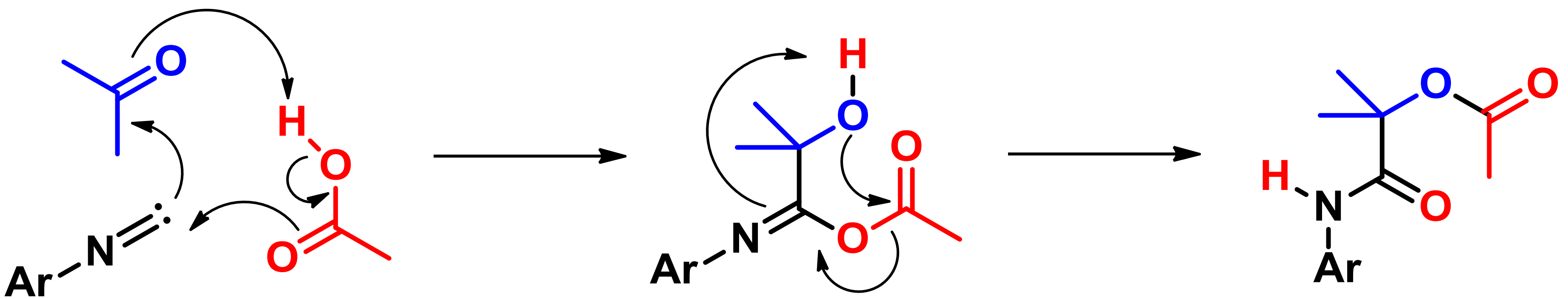




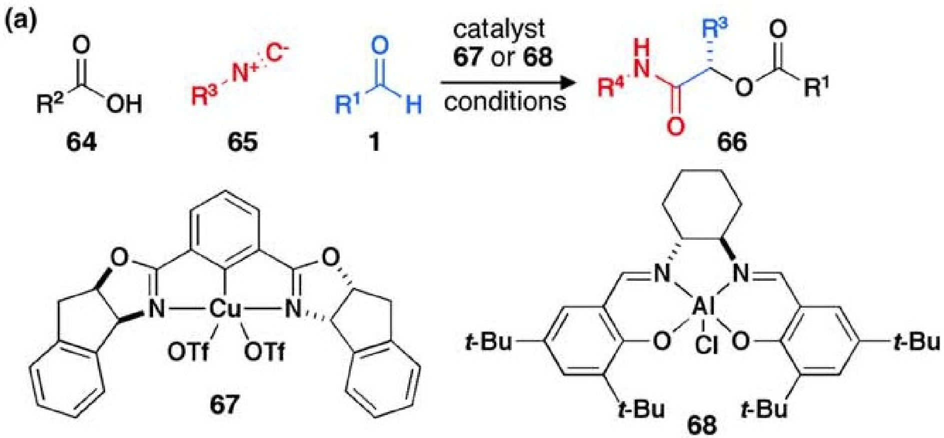
Réactions Multicomposants – Passerini (1921)



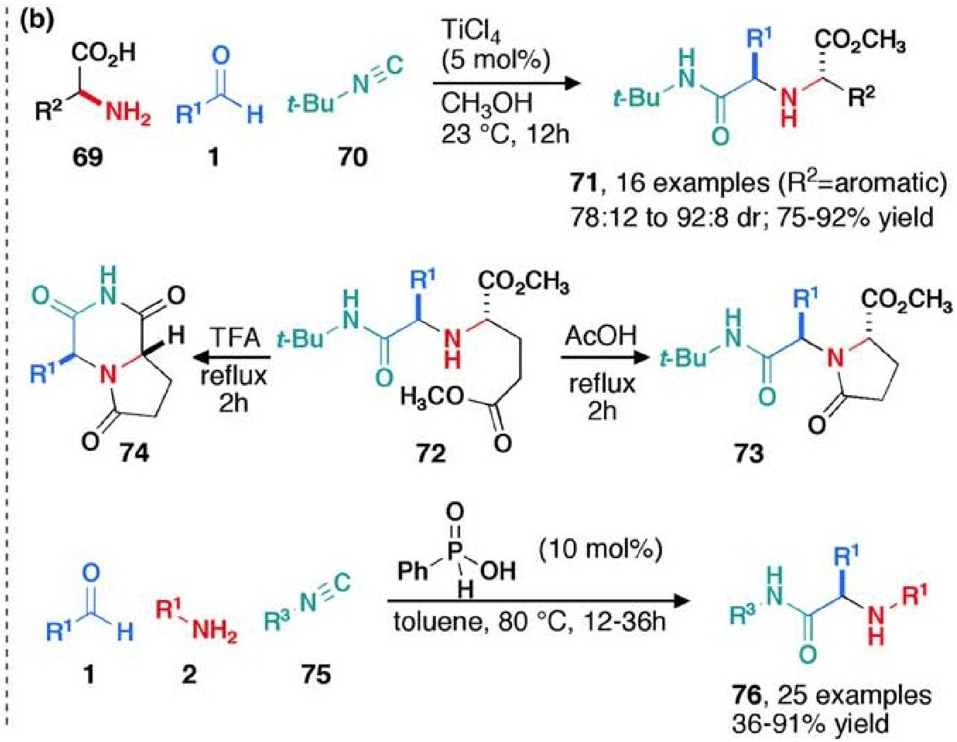
Mario (Torquato) Passerini
(1891–1962)

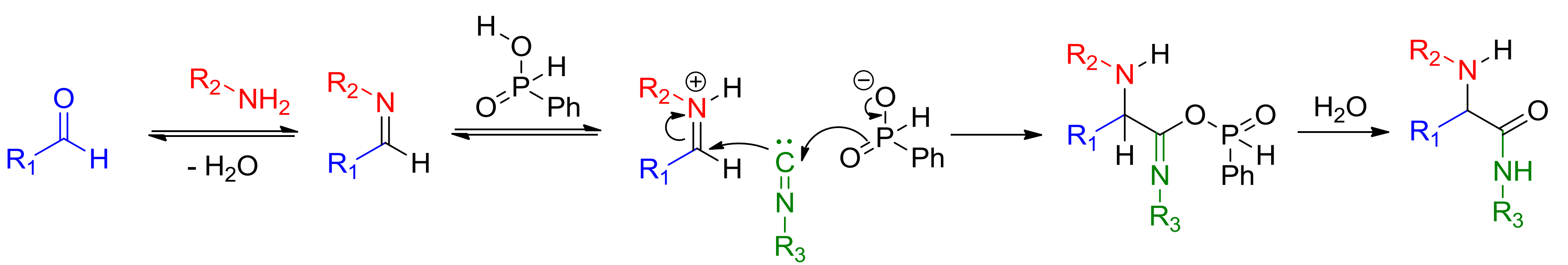


Réactions Multicomposants – Passerini



catalyst	67	68
loading (mol%)	20	10
ee (%)	62-98	63-99
yield (%)	75-98	51-70
solvent	CH_2Cl_2	toluene
time (h)	12-24	48
temperature	0 °C	-40 °C
# of examples	16	16





Réactions Multicomposants – Ugi (1962)

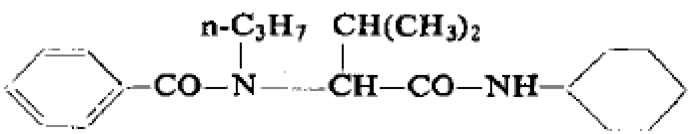
Novel Methods of Preparative Organic Chemistry IV

The α-Addition of Immonium Ions and Anions to Isonitriles Accompanied by Secondary Reactions

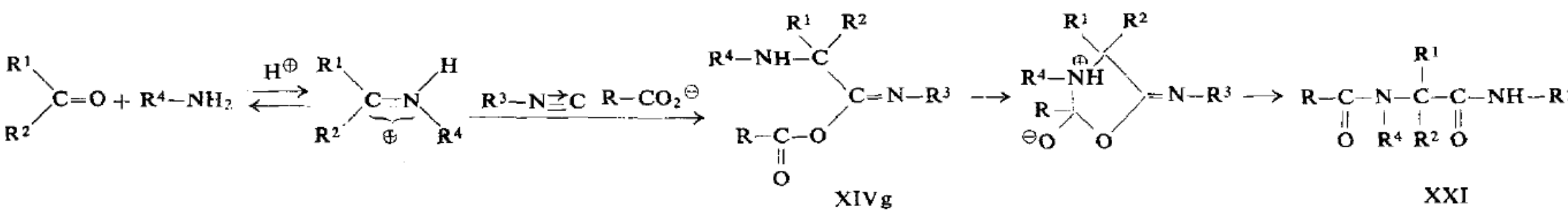
BY DOZ. DR. IVAR UGI [1]
INSTITUT FÜR ORGANISCHE CHEMIE DER UNIVERSITÄT MÜNCHEN

Angew. Chem. internat. Edit. | Vol. 1 (1962) | No. 1

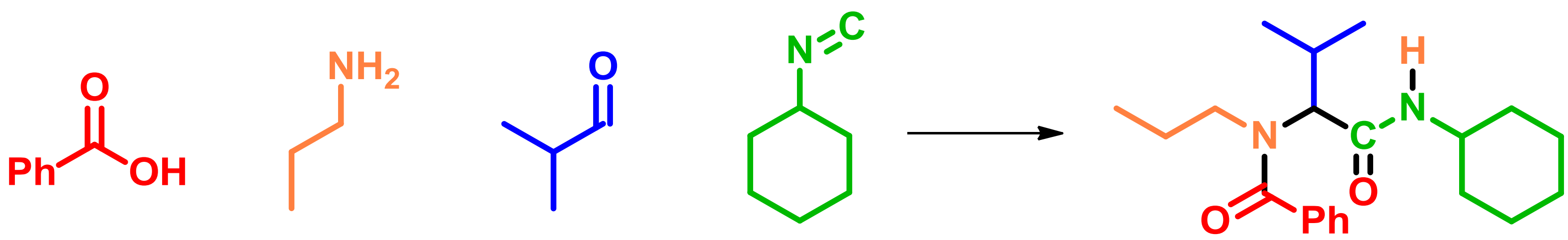
Ivar Karl Ugi
9 sept. 1930 - 29 sept. 2005

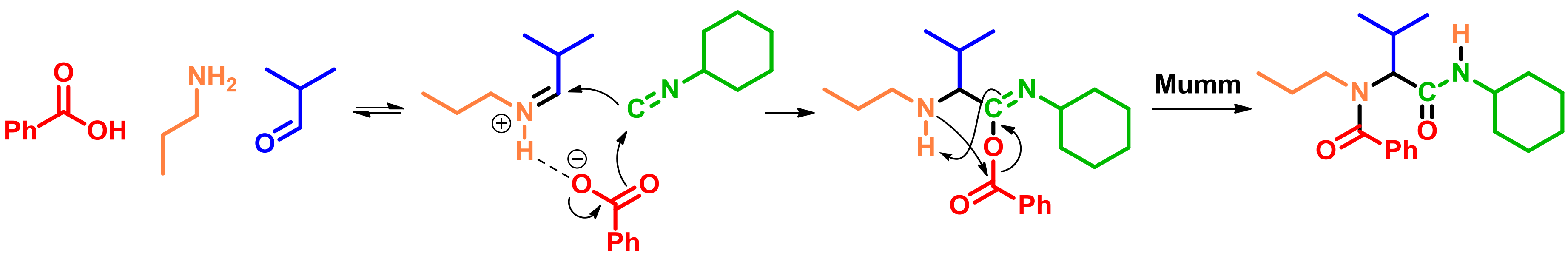


XXIm (80 %)

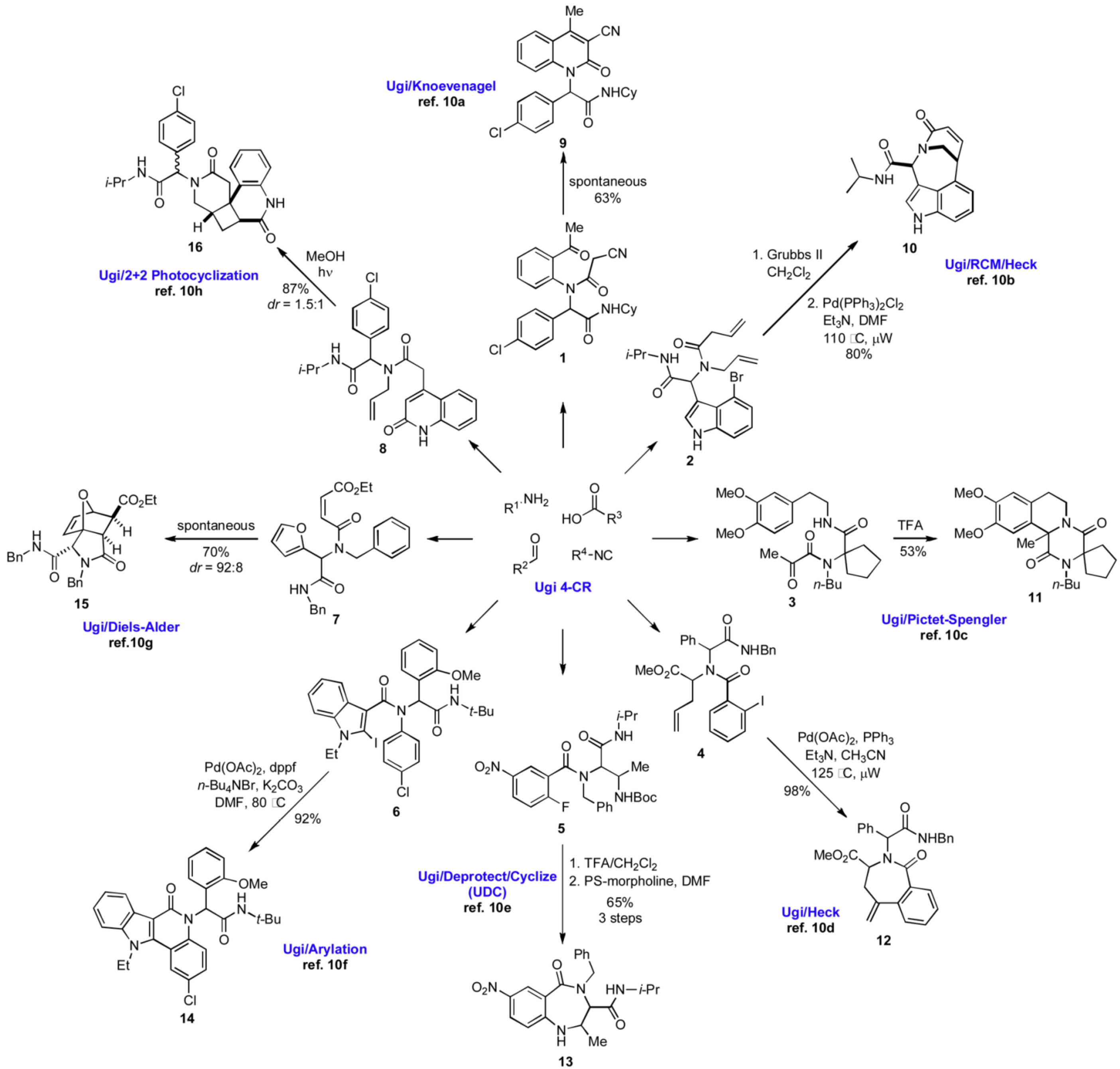


Mécanisme de la réaction de Ugi





Ugi pour la DOS



MCR Le Record

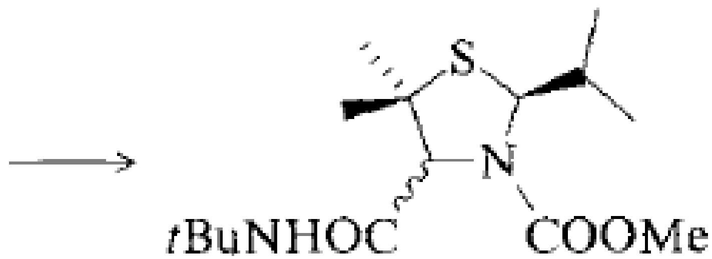
The Seven-Component Reaction**

By *Alexander Dömling* and *Ivar Ugi**

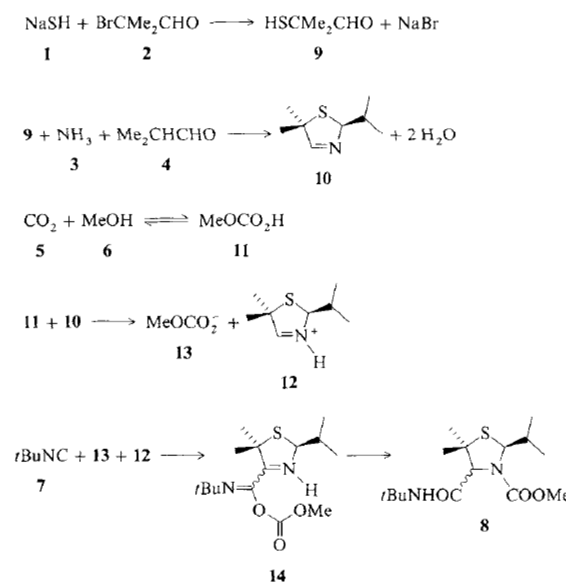
[*] Prof. Dr. I. Ugi, Dipl.-Chem. A. Dömling
Organisch-chemisches Institut I der Technischen Universität München
Lichtenbergstrasse 4, D-W-8046 Garching (FRG)

Angew. Chem. Int. Ed. Engl. **1993**, *32, No. 4*

$$\underset{\mathbf{1}}{NaSH} + \underset{\mathbf{2}}{BrCMe_2CHO} + \underset{\mathbf{3}}{NH_3} + \underset{\mathbf{4}}{Me_2CHCHO} + \underset{\mathbf{5}}{CO_2} + \underset{\mathbf{6}}{MeOH} + \underset{\mathbf{7}}{tBuNC}$$

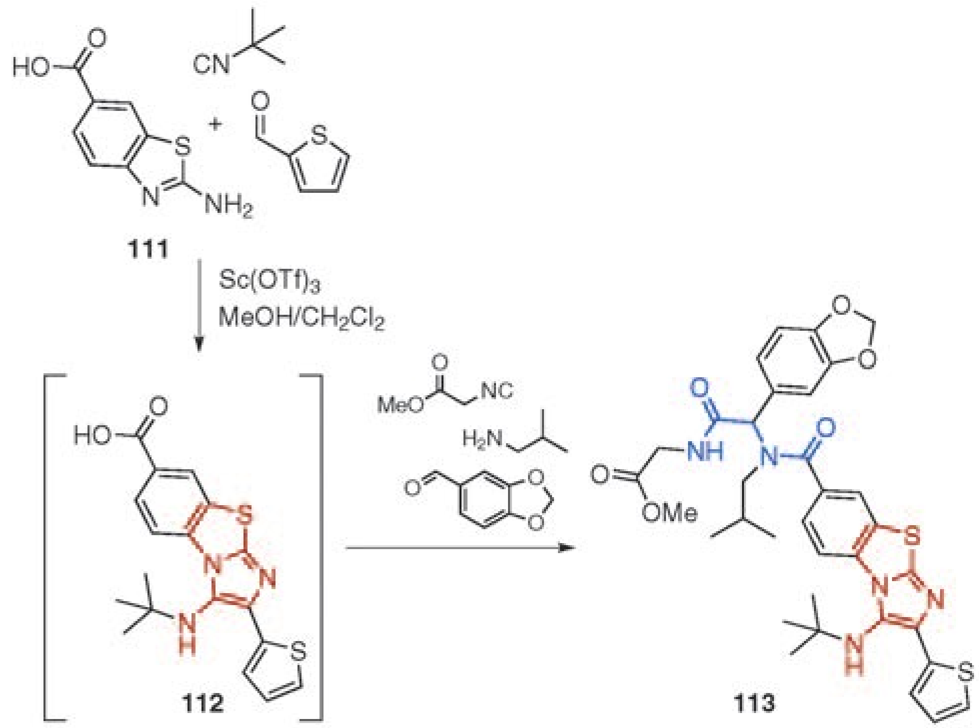


$+ 2\,H_2O + NaBr$



Scheme 2. Mechanism of the 7CC.

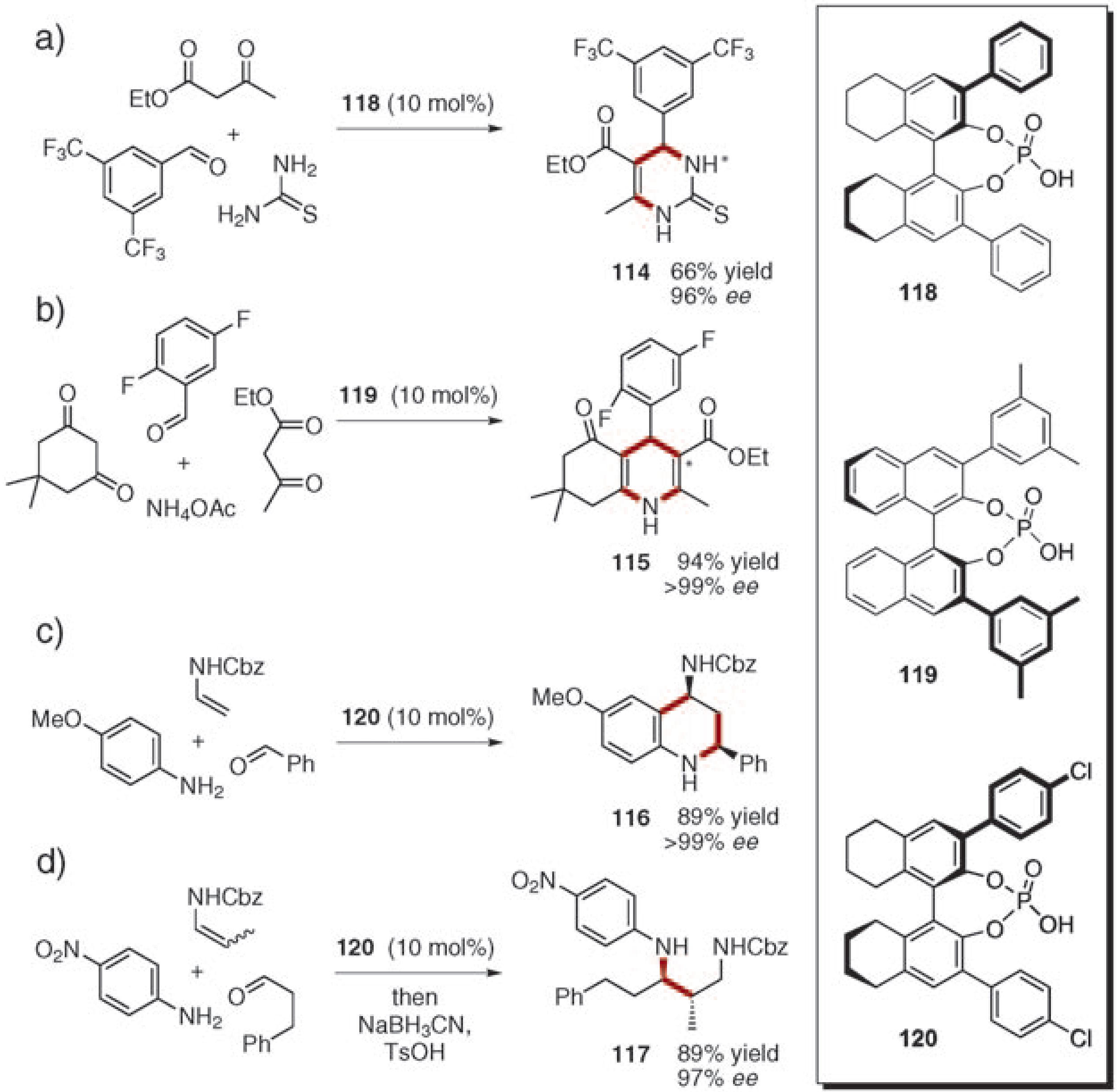
Exercices



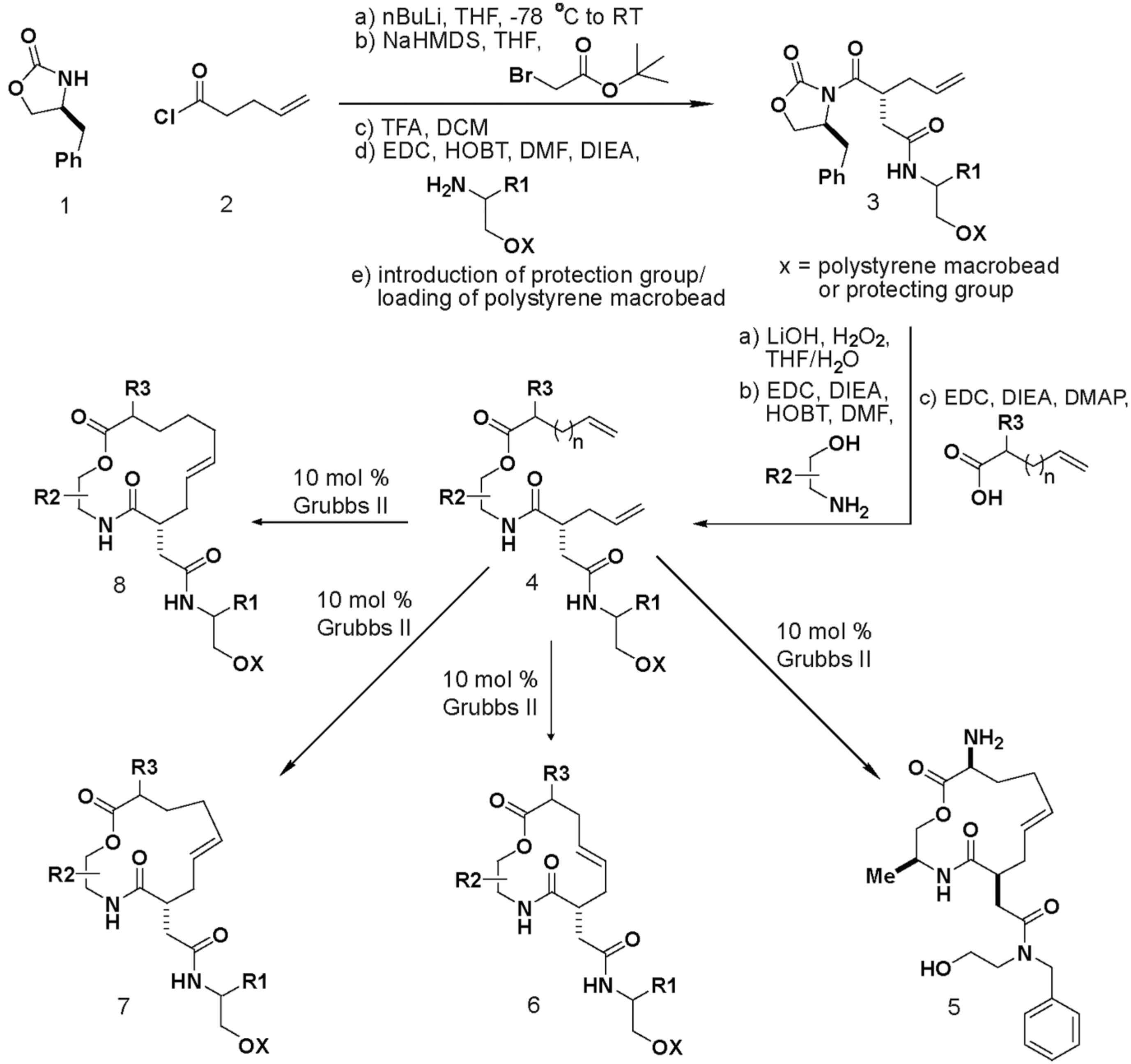
Combination of Groebke–Bienaym–Blackburn 3CR and Ugi 4CR. The primary MCR scaffold structures are shown in red and the secondary scaffolds in blue.

T. H. Al-Tel, R. A. Al-Qawasmeh, W. Voelter, *Eur. J. Org. Chem.* **2010**, 5586

Exercices

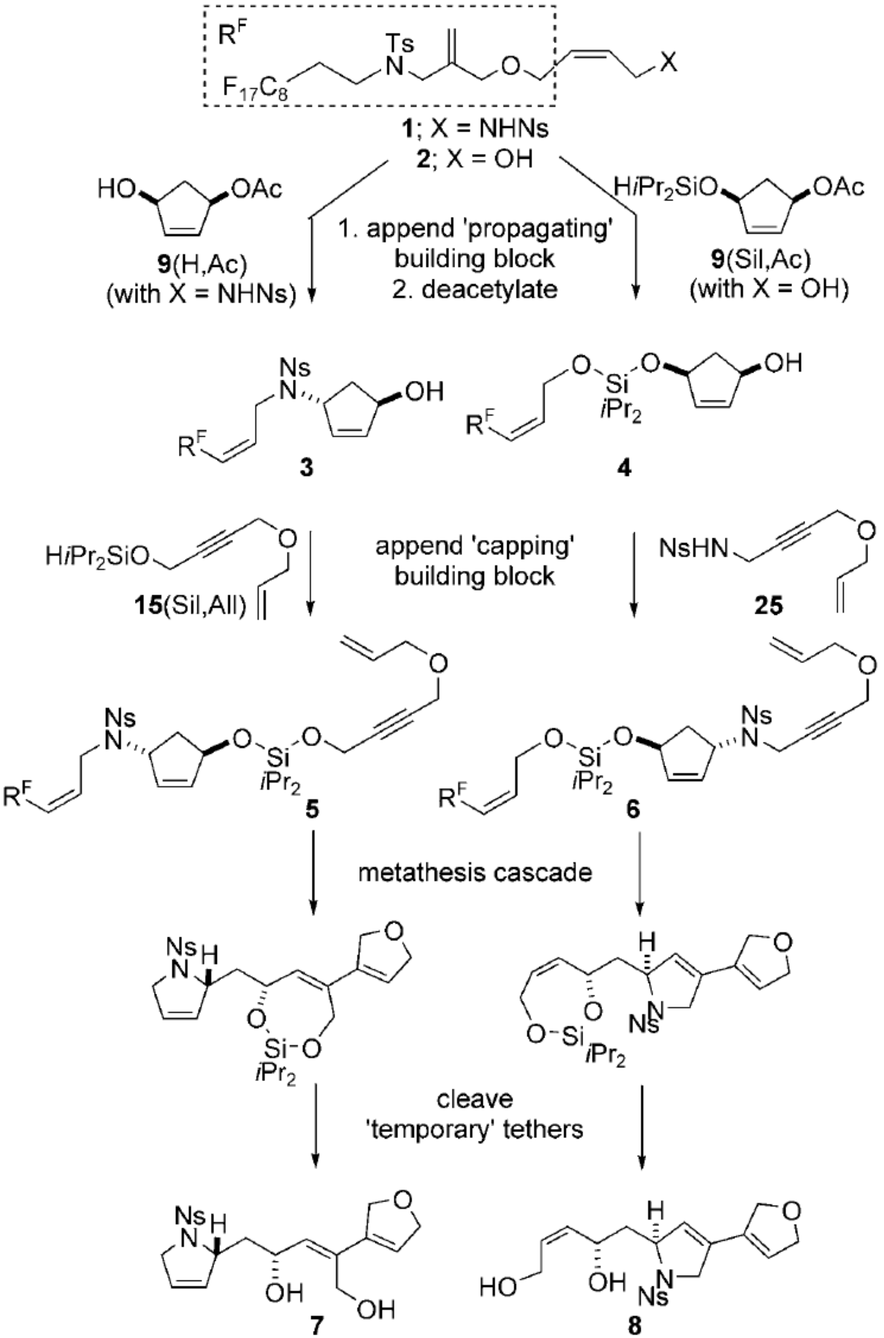


Organocatalytic asymmetric Biginelli 3CR using chiral phosphoric acid 118.[93] b) Organocatalytic asymmetric Hantzsch 4CR using chiral phosphoric acid 119.[92] c) Organocatalytic asymmetric Povarov 3CR using chiral phosphoric acid 120.[94] d) Organocatalytic asymmetric Mannich 3CR using chiral phosphoric acid 120.[95] Ref : [92] C. G. Evans, J. E. Gestwicki, Org. Lett. 2009, 11, 2957. [93] L.-Z. Gong, X.-H. Chen, X.-Y. Xu, Chem. Eur. J. 2007, 13, 8920. [94] H. Liu, G. Dagousset, G. Masson, P. Retailleau, J. Zhu, J. Am. Chem. Soc. 2009, 131, 4598. [95] G. Dagousset, F. Drouet, G. Masson, J. Zhu, Org. Lett. 2009, 11, 5546.

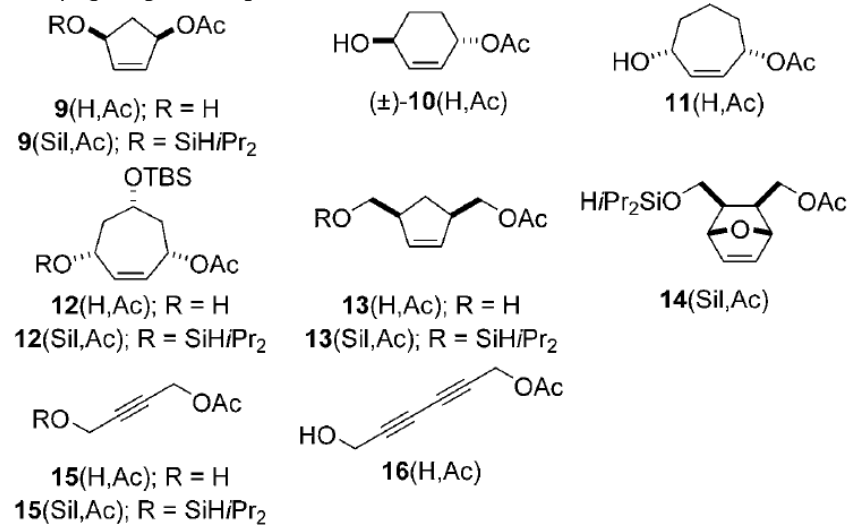


a) nBuLi, THF, -78 °C to RT
b) NaHMDS, THF,
c) TFA, DCM
d) EDC, HOBT, DMF, DIEA,
e) introduction of protection group/ loading of polystyrene macrobead
x = polystyrene macrobead or protecting group
a) LiOH, H2O2, THF/H2O
b) EDC, DIEA, HOBT, DMF,
c) EDC, DIEA, DMAP,
10 mol % Grubbs II
1
2
3
4
5
6
7
8

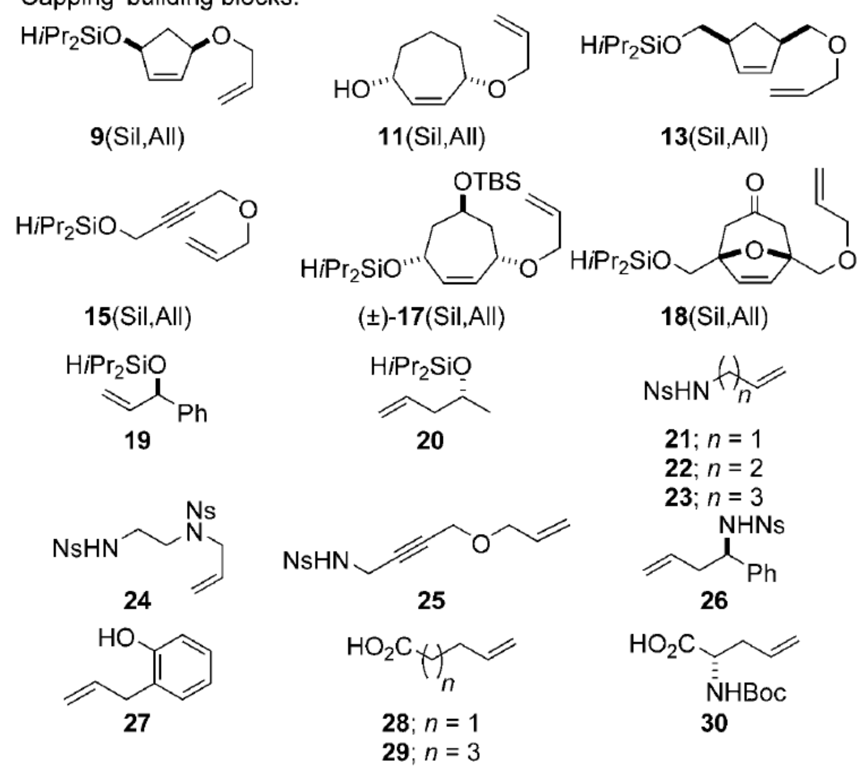
Exercices

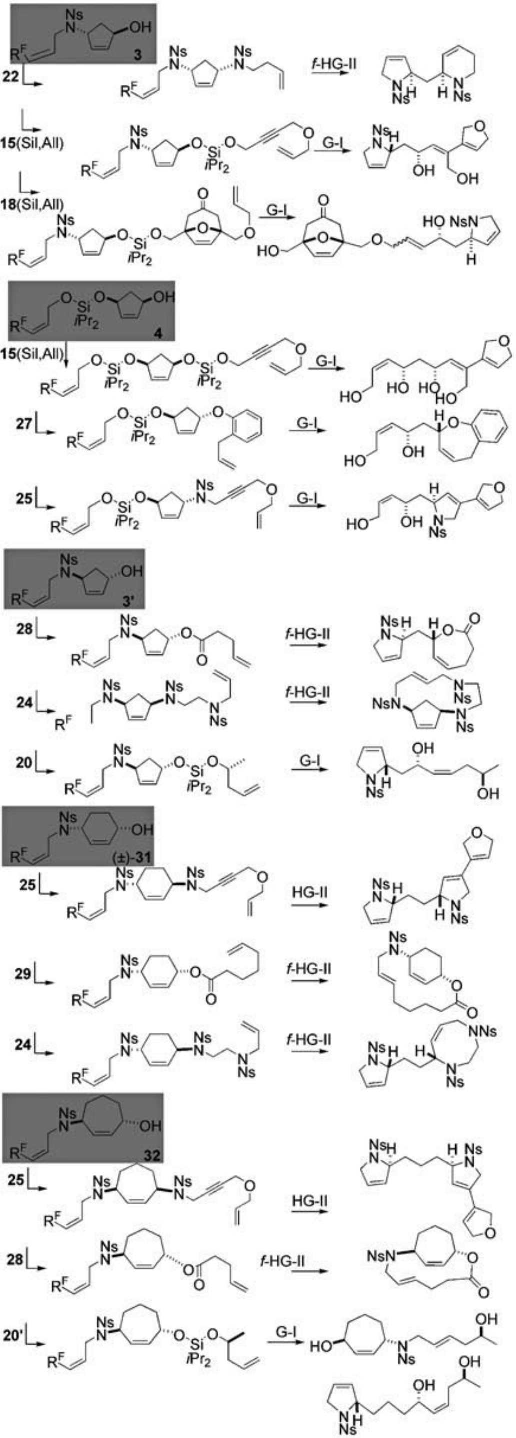


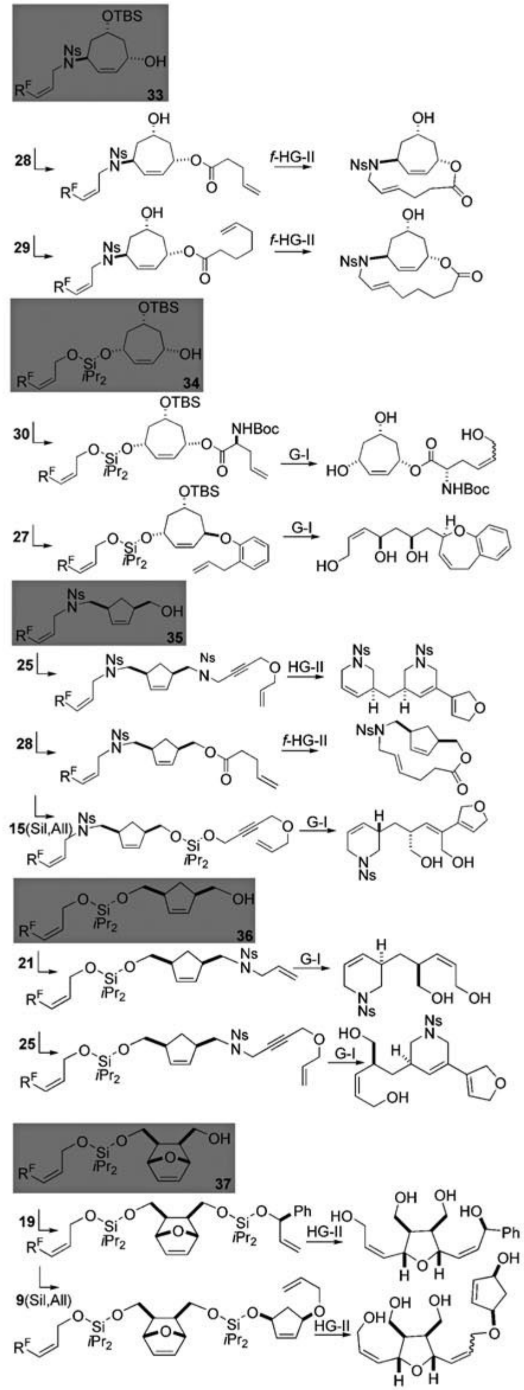
'Propagating' building blocks:

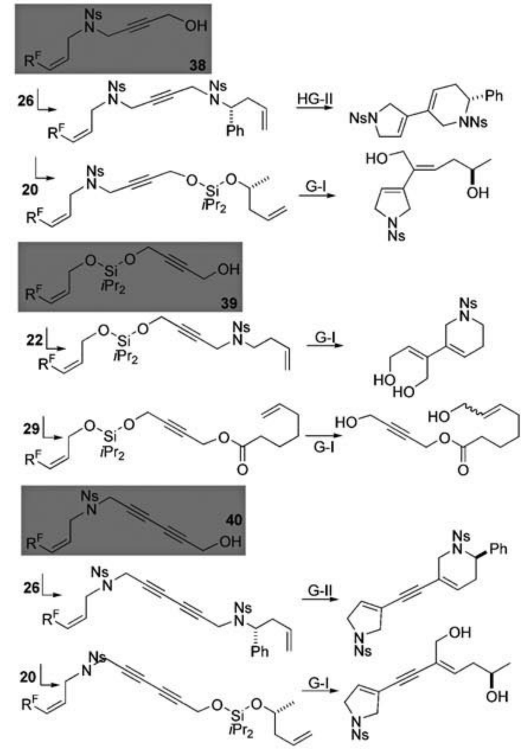


'Capping' building blocks:









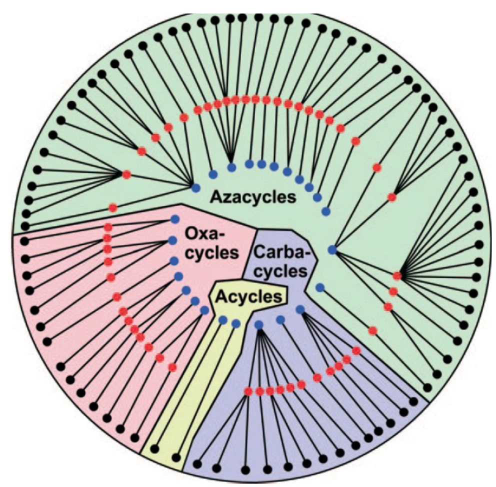
VIP Scaffold Diversity

DOI: 10.1002/anie.200804486

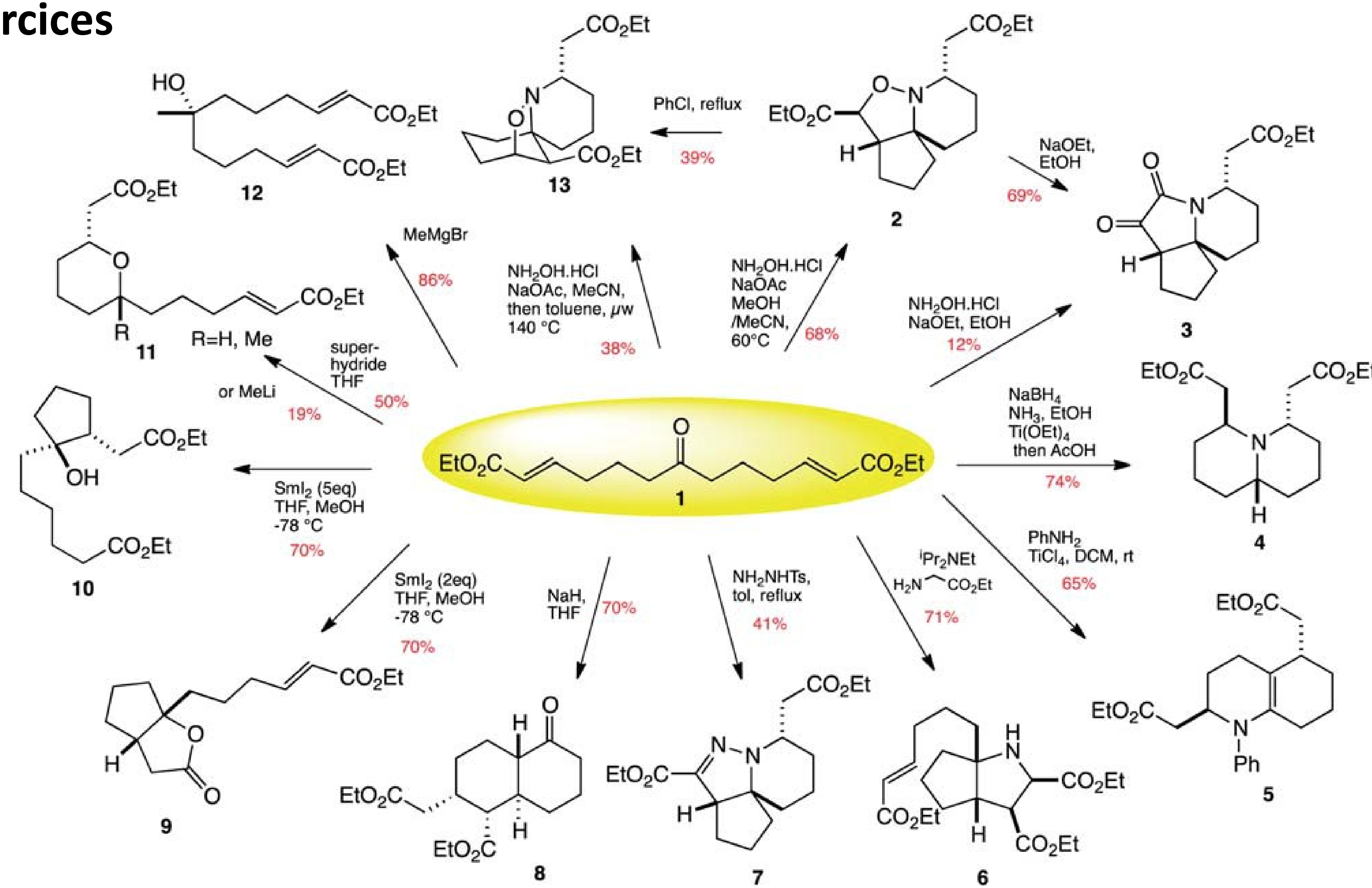
Synthesis of Natural-Product-Like Molecules with Over Eighty Distinct Scaffolds**

*Daniel Morton, Stuart Leach, Christopher Cordier, Stuart Warriner, and Adam Nelson**

Angew. Chem. Int. Ed. **2009**, *48*, 104–109



Exercices



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www.rsc.org/chemicalscience

EDGE ARTICLE

Synthesis of natural-product-like scaffolds in unprecedented efficiency *via* a 12-fold branching pathway†‡

Diane Robbins,[a] Annabella F. Newton,[a] Camille Gignoux,[a] Jean-Christophe Legeay,[a] Alex Sinclair,[b] Martin Rejzek,[b] Carly A. Laxon,[b] Sai K. Yalamanchili,[b] William Lewis,[a] Maria A. O'Connell*[b] and Robert A. Stockman*[a]

Exercices

Synthesis of analogues 14-21

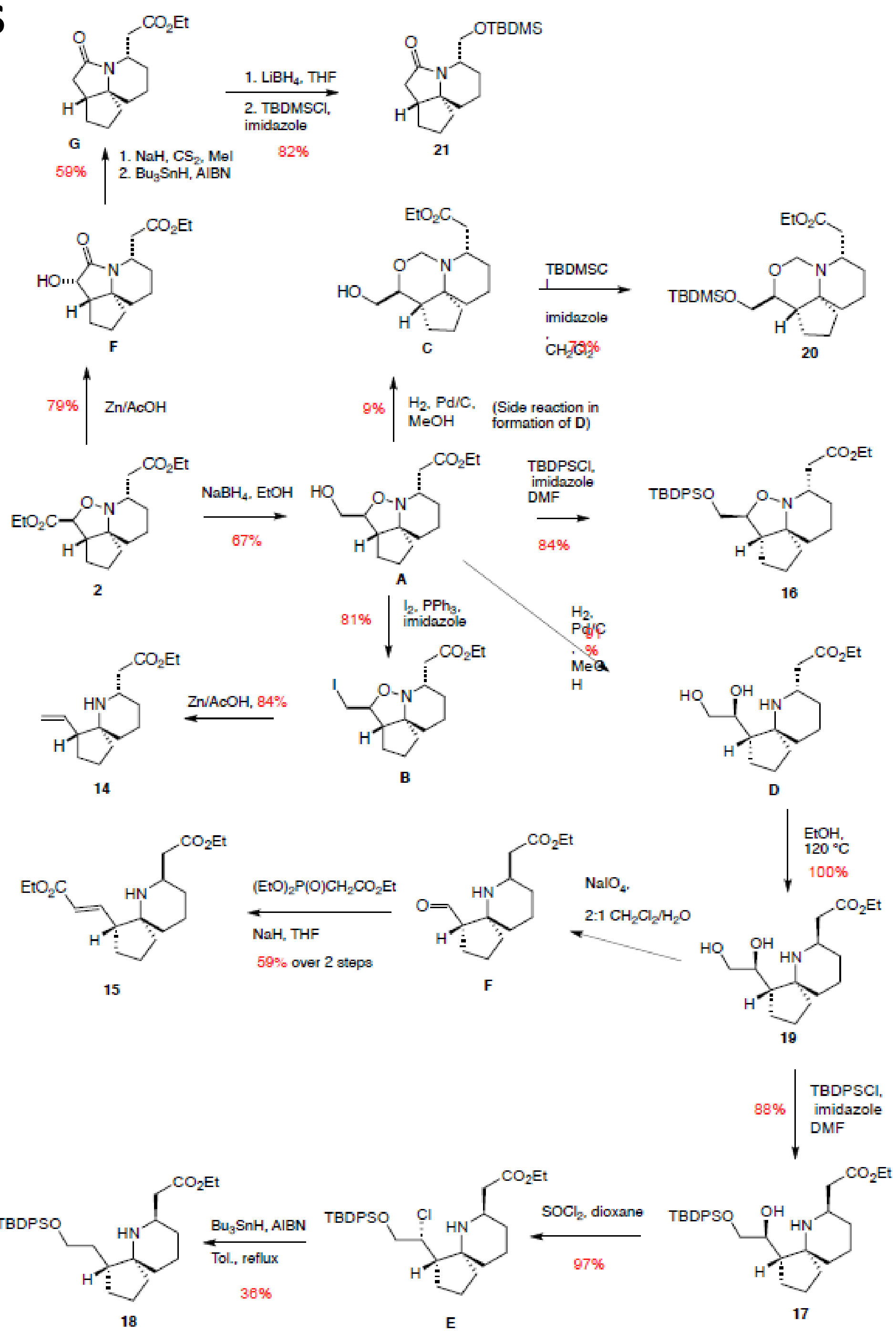
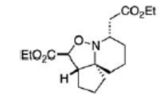
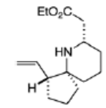
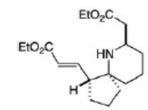
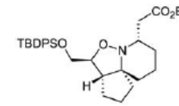
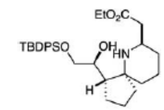
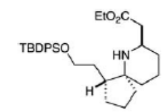
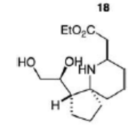
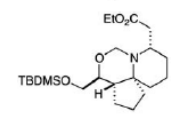
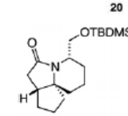
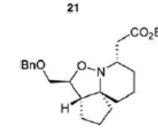


Table 1 Screen of scaffold **2** and analogues against three cancer cell lines

Compound	IC_{50} values/µM		
	HL-60	THP-1	A549
 **2**	—	>100	—
 **14**	22.4	27.5	41.3
 **15**	>100	>100	>100
 **16**	24	33	29
 **17**	4.7	2.1	22.4
 **18**	11.0	3.5	>100
 **19**	48.8	>100	>100
 **20**	34	44	44
 **21**	42	36	43
 **22**	18.6	>100	—

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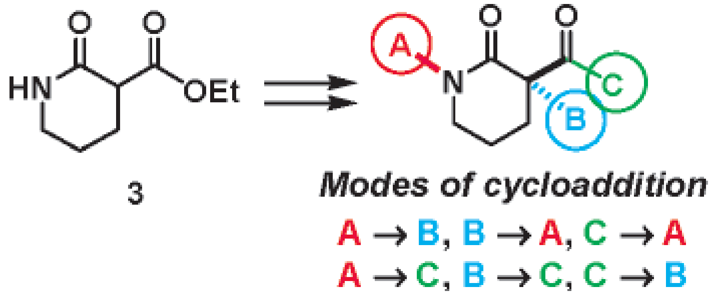
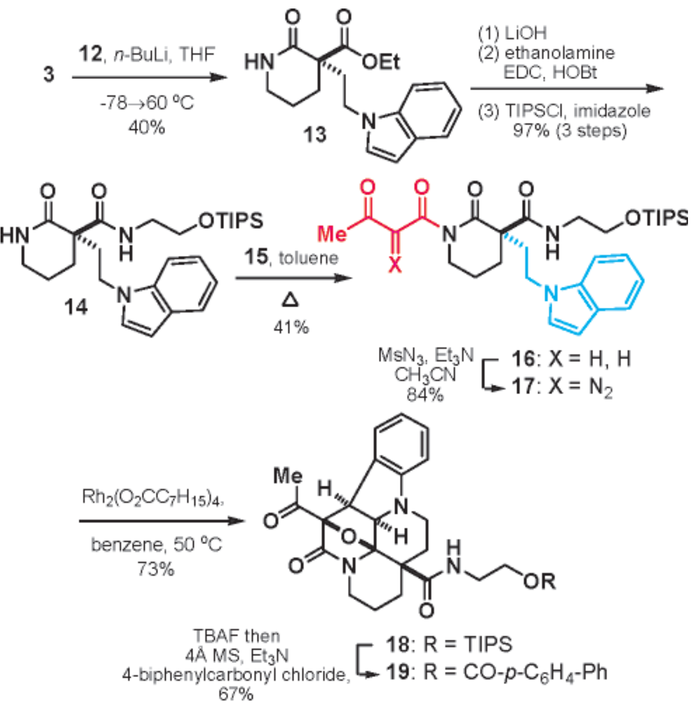
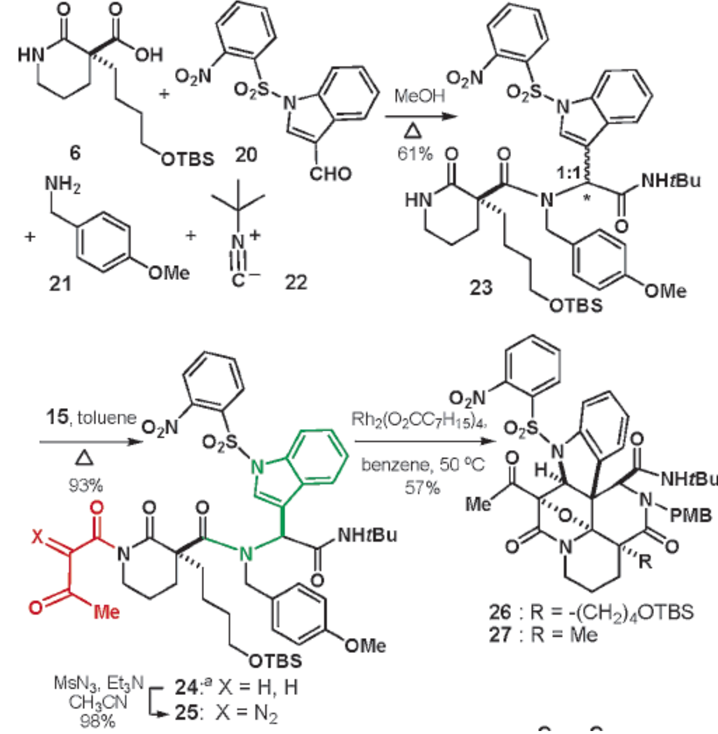
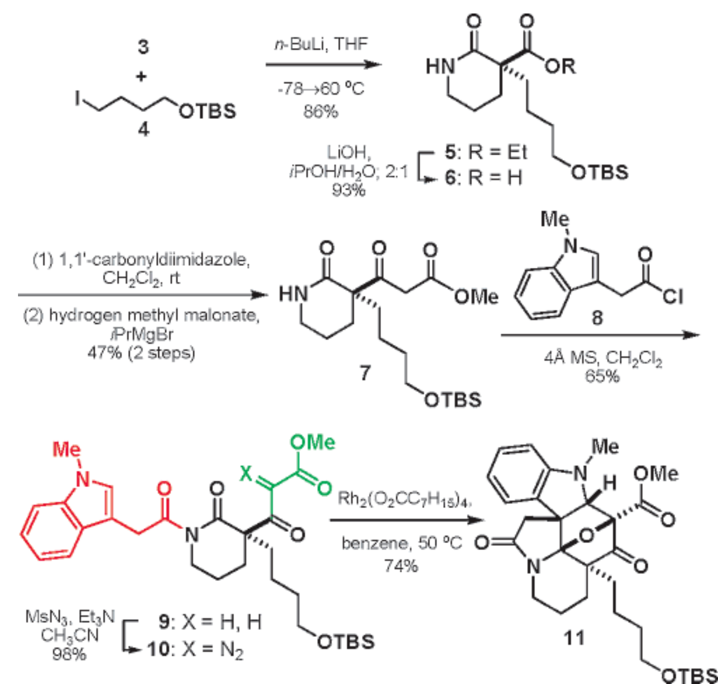






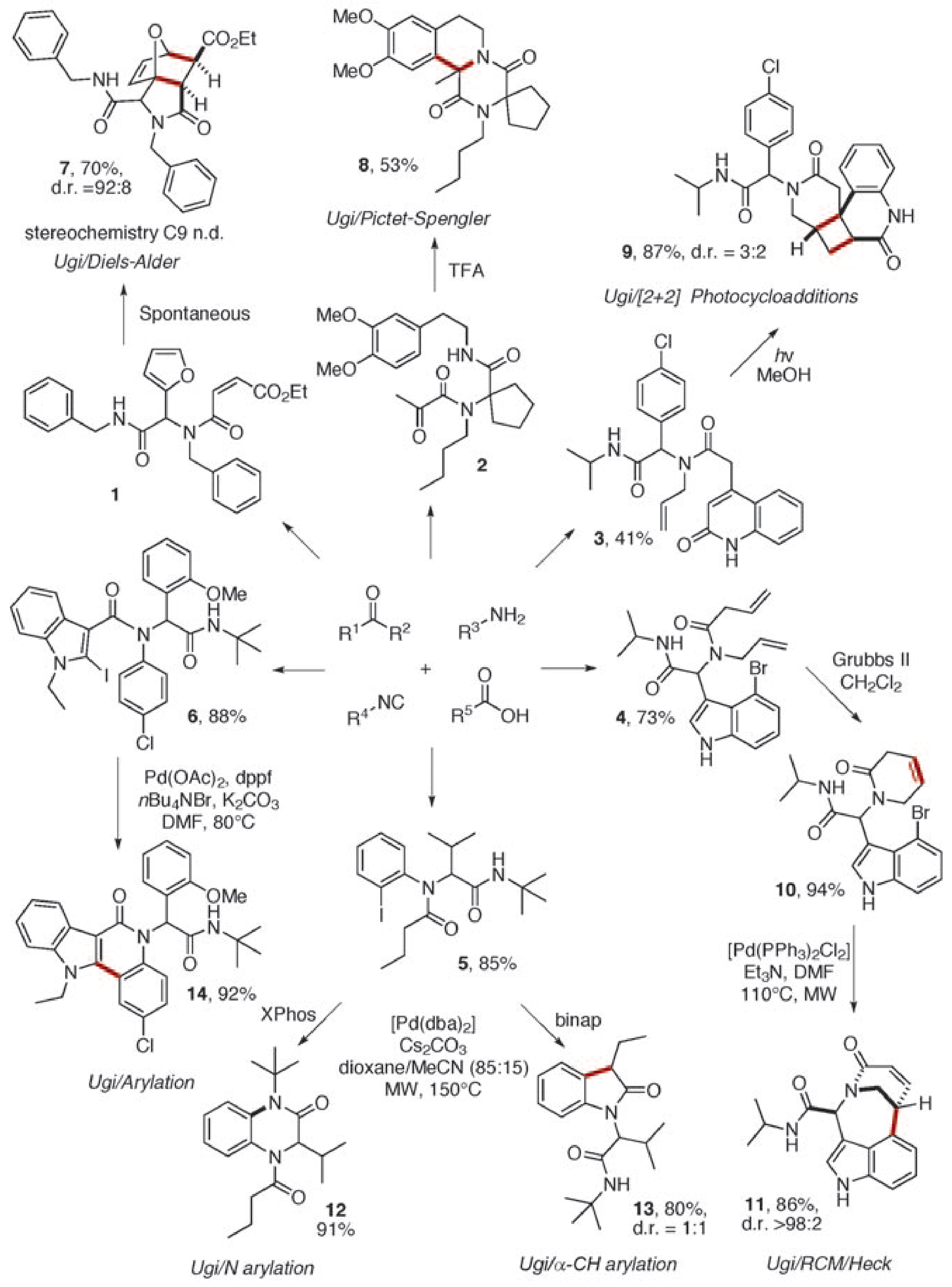


Skeletal Diversity via a Folding Pathway: Synthesis of Indole Alkaloid-Like Skeletons

Hiroki Oguri and Stuart L. Schreiber*

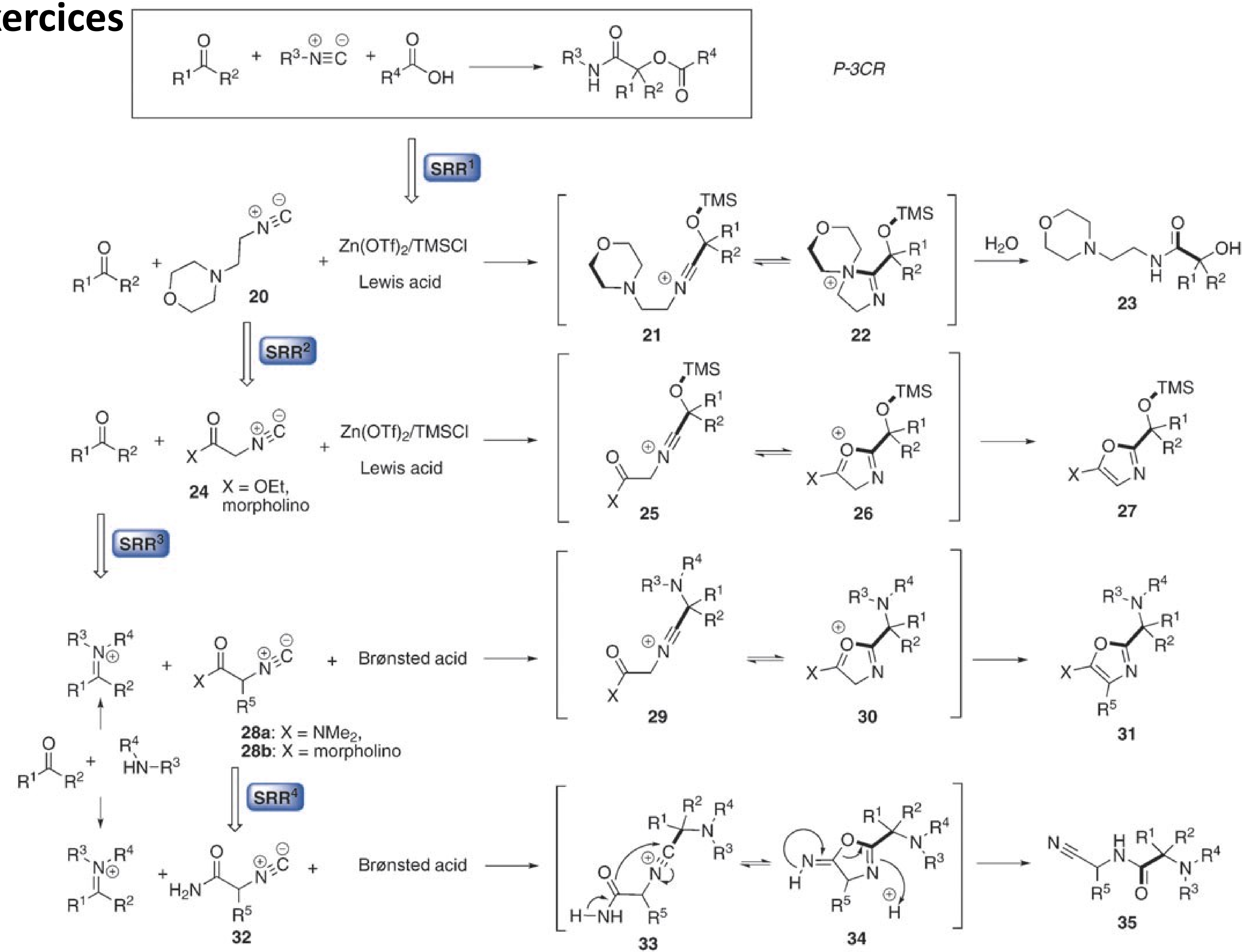
ORGANIC LETTERS
2005
Vol. 7, No. 1
47−50

Exercices



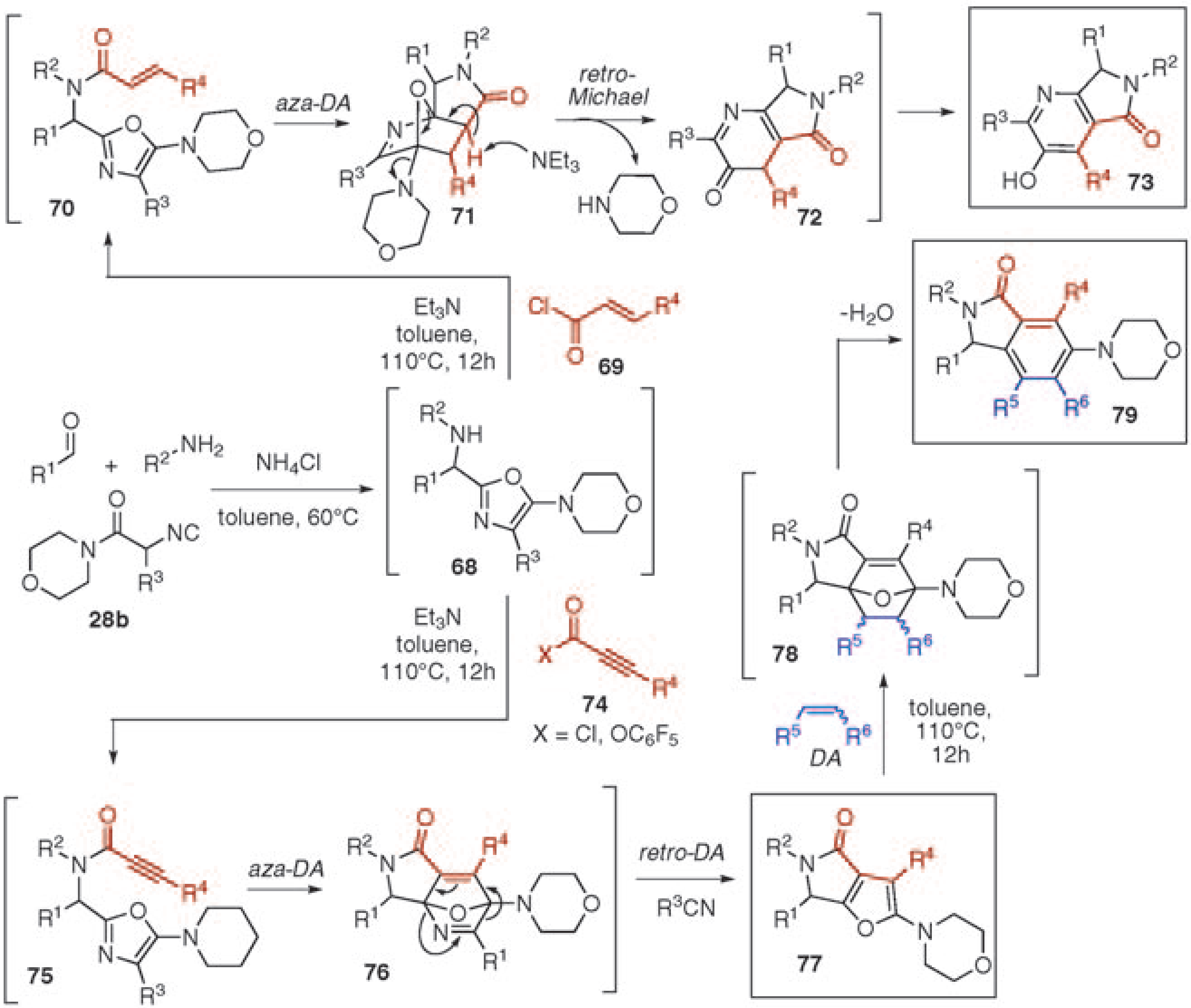
7, 70%, d.r. =92:8
stereochemistry C9 n.d.
Ugi/Diels-Alder
Spontaneous
1
8, 53%
Ugi/Pictet-Spengler
TFA
2
9, 87%, d.r. = 3:2
Ugi/[2+2] Photocycloadditions
hν MeOH
3, 41%
6, 88%
4, 73%
Grubbs II CH2Cl2
10, 94%
Pd(OAc)2, dppf nBu4NBr, K2CO3 DMF, 80°C
14, 92%
Ugi/Arylation
5, 85%
[Pd(PPh3)2Cl2] Et3N, DMF 110°C, MW
XPhos
[Pd(dba)2] Cs2CO3 dioxane/MeCN (85:15) MW, 150°C
binap
12 91%
Ugi/N arylation
13, 80%, d.r. = 1:1
Ugi/α-CH arylation
11, 86%, d.r. >98:2
Ugi/RCM/Heck

Exercices



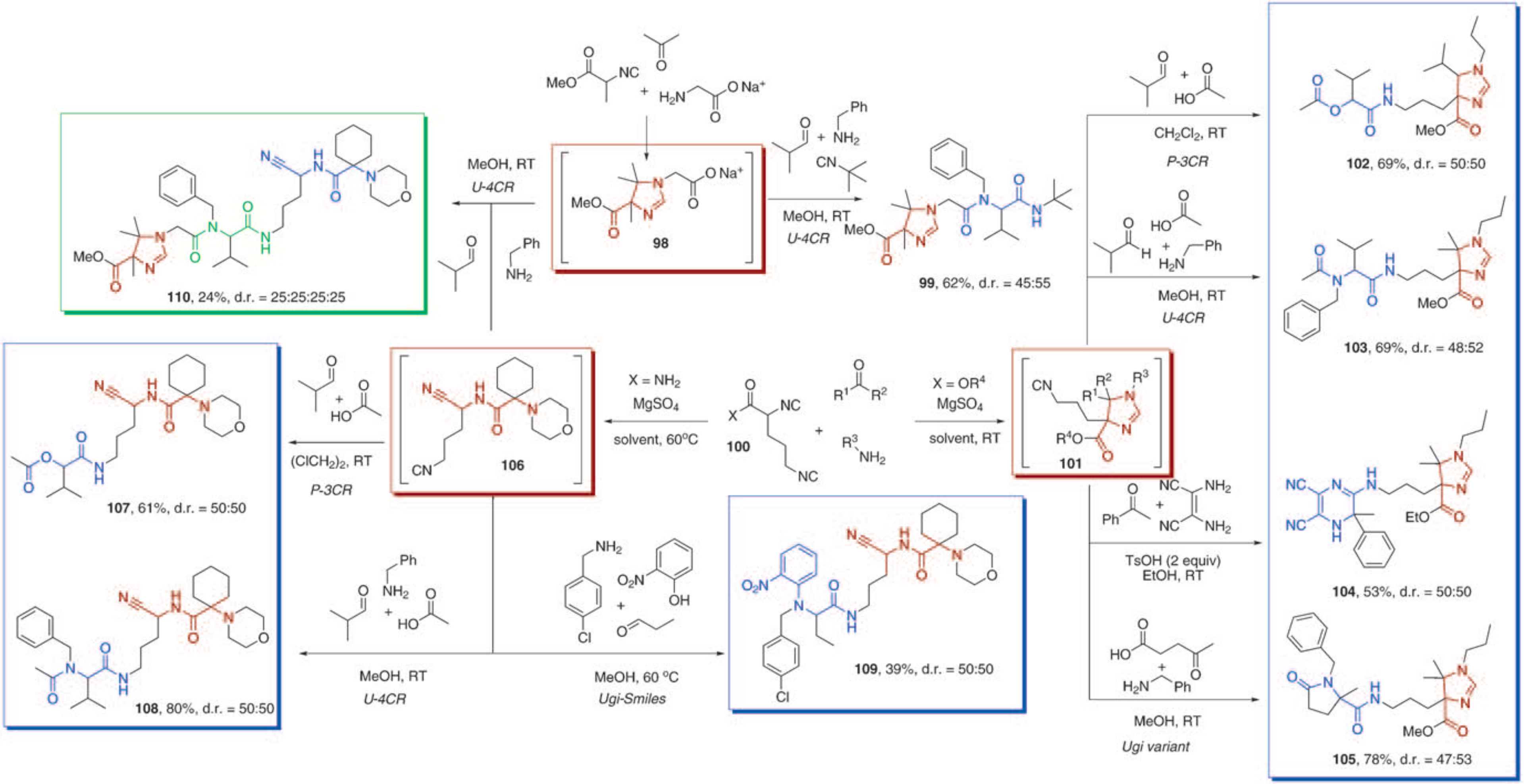
P-3CR
SRR1
Zn(OTf)2/TMSCl
Lewis acid
H2O
20
21
22
23
SRR2
24
X = OEt, morpholino
25
26
27
SRR3
Brønsted acid
28a: X = NMe2,
28b: X = morpholino
29
30
31
SRR4
32
33
34
35

Exercices



aza-DA
retro-Michael
NEt3
HN
70
71
72
73
Et3N
toluene,
110°C, 12h
69
-H2O
79
NH4Cl
toluene, 60°C
28b
68
78
74
X = Cl, OC6F5
DA
toluene,
110°C,
12h
75
76
retro-DA
R3CN
77

Exercices


MeOH, RT
U-4CR
98
MeOH, RT
U-4CR
99, 62%, d.r. = 45:55
110, 24%, d.r. = 25:25:25:25
CH2Cl2, RT
P-3CR
102, 69%, d.r. = 50:50
MeOH, RT
U-4CR
103, 69%, d.r. = 48:52
X = NH2
MgSO4
solvent, 60°C
100
X = OR4
MgSO4
solvent, RT
101
106
(ClCH2)2, RT
P-3CR
107, 61%, d.r. = 50:50
TsOH (2 equiv)
EtOH, RT
104, 53%, d.r. = 50:50
MeOH, RT
U-4CR
MeOH, 60 °C
Ugi-Smiles
109, 39%, d.r. = 50:50
108, 80%, d.r. = 50:50
MeOH, RT
Ugi variant
105, 78%, d.r. = 47:53