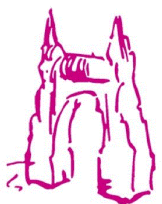


Desenvolupament de noves reaccions radicalàries per a la síntesi de productes farmacèutics

Seminari de Recerca, 04/04/2024



Ben Bradshaw



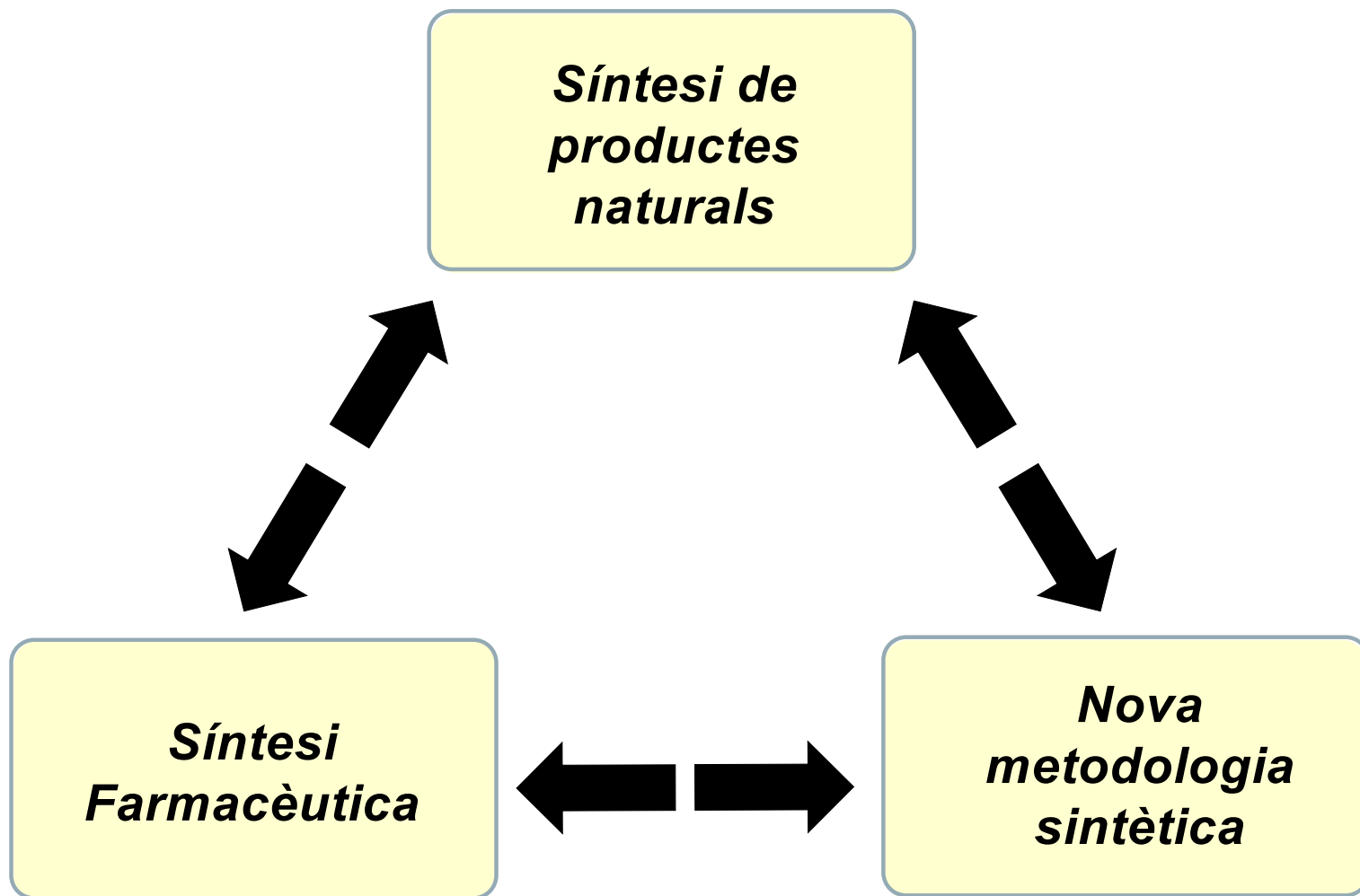
Facultat de
Farmàcia

FACULTAT DE FARMÀCIA I
CIÈNCIES DE L'ALIMENTACIÓ

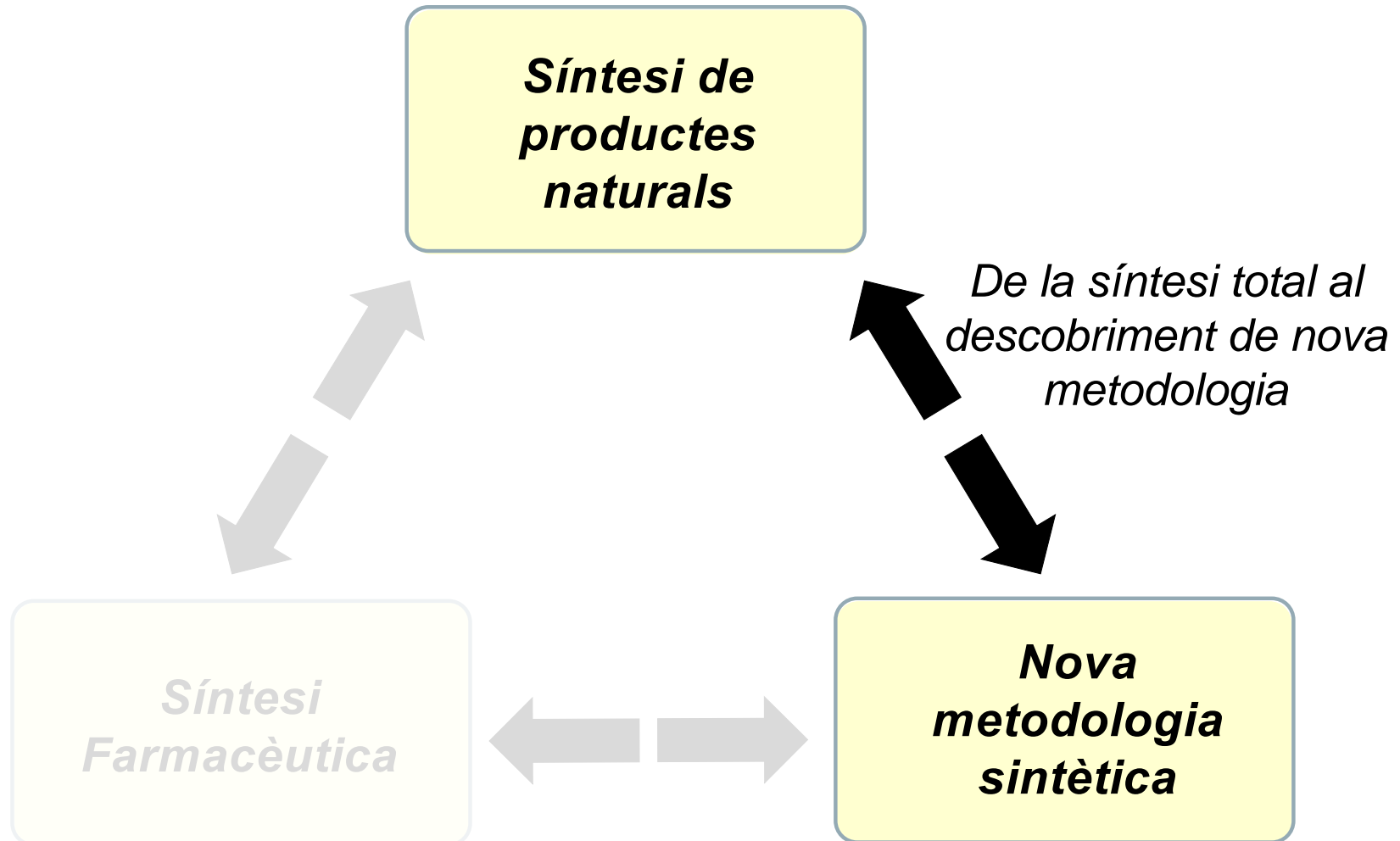


UNIVERSITAT DE
BARCELONA

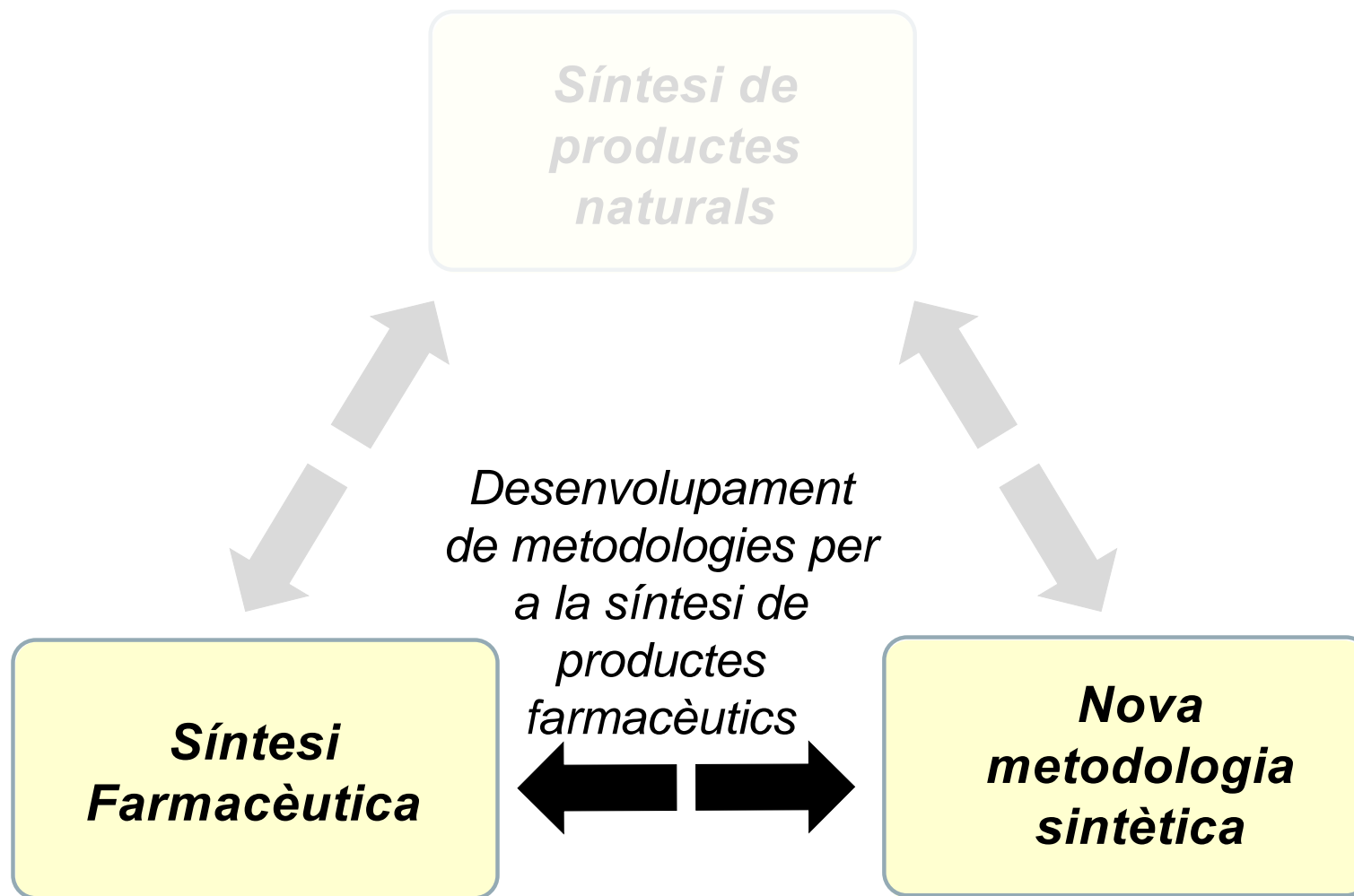
Focus de recerca



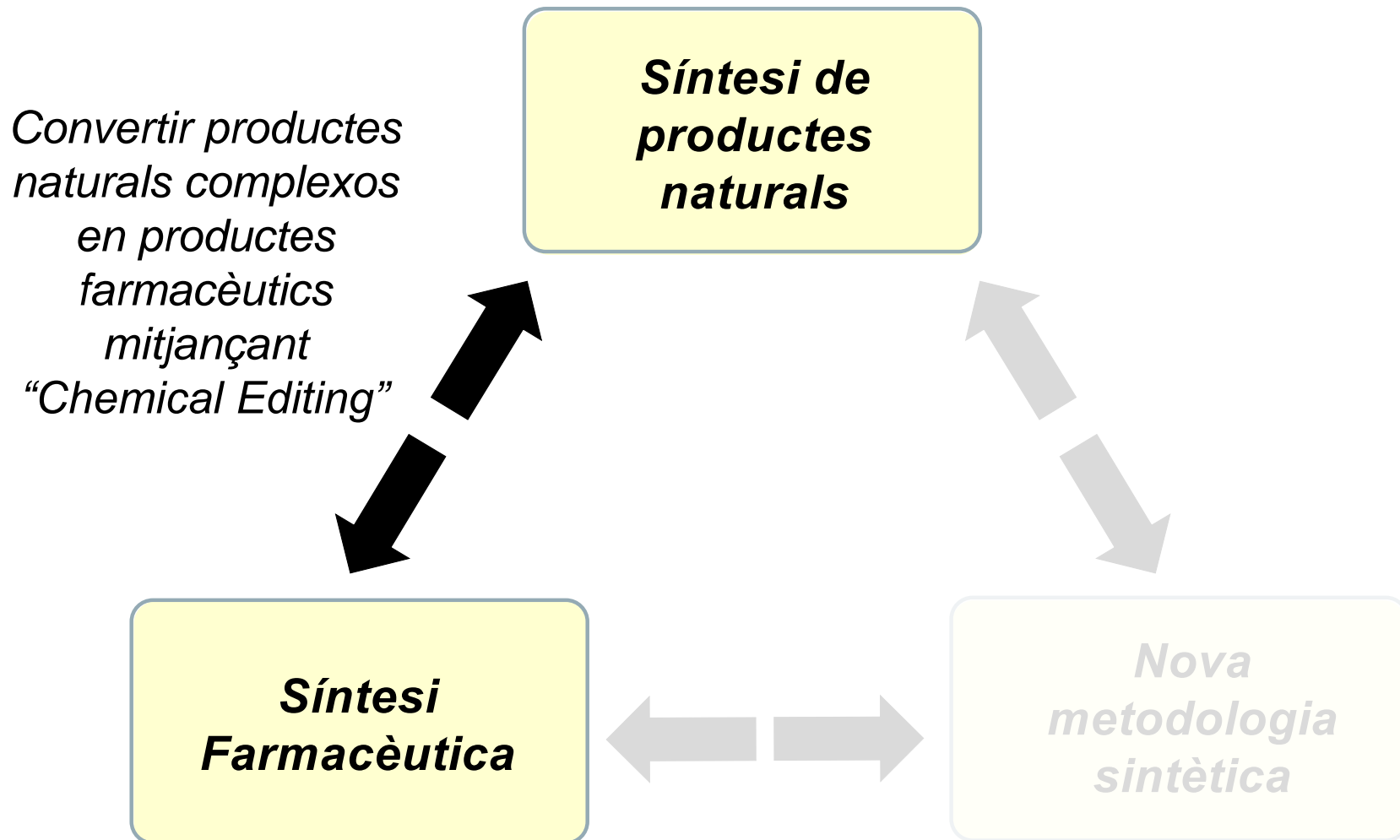
Presentació: Part 1



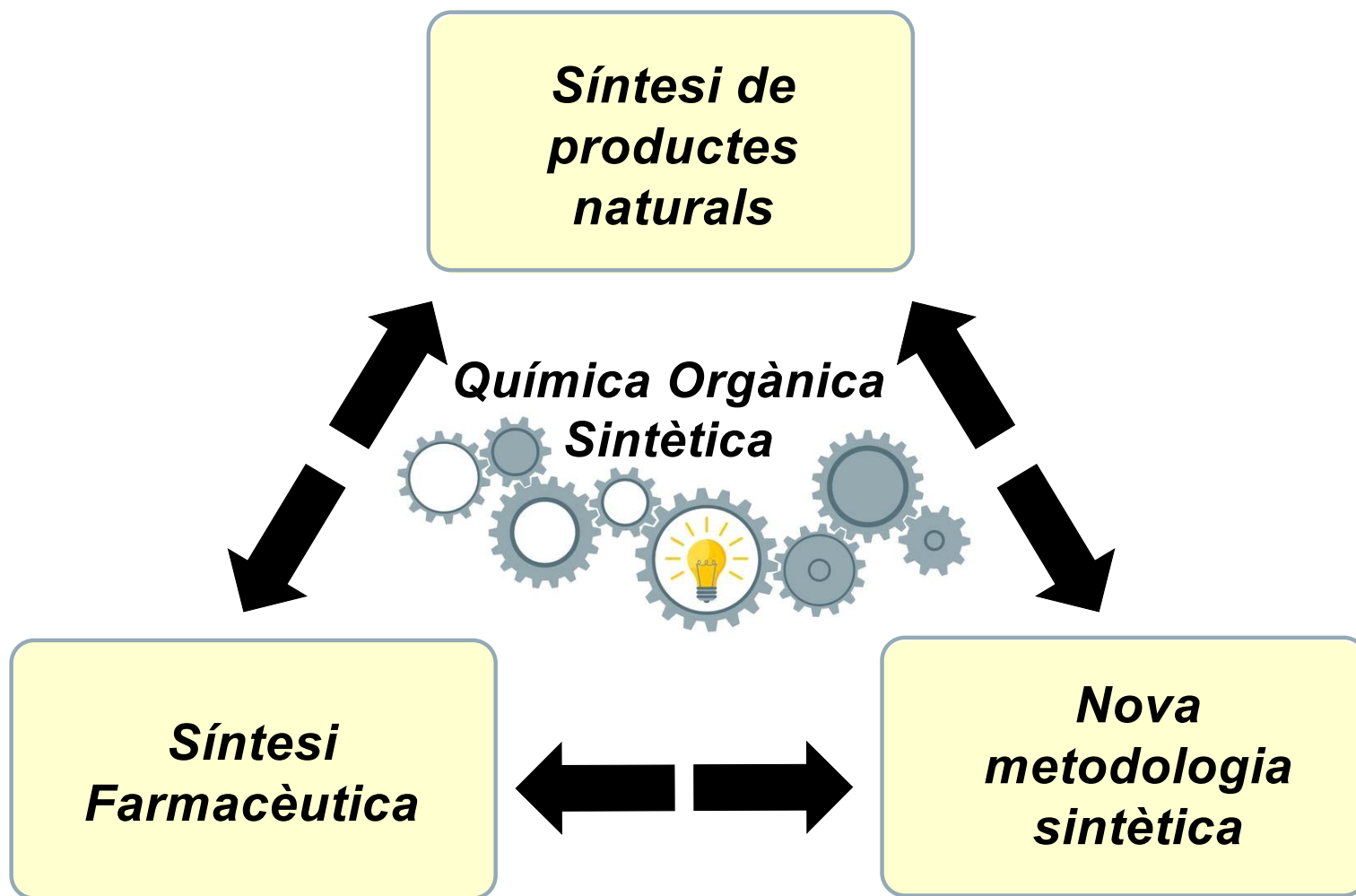
Presentació: Part 2



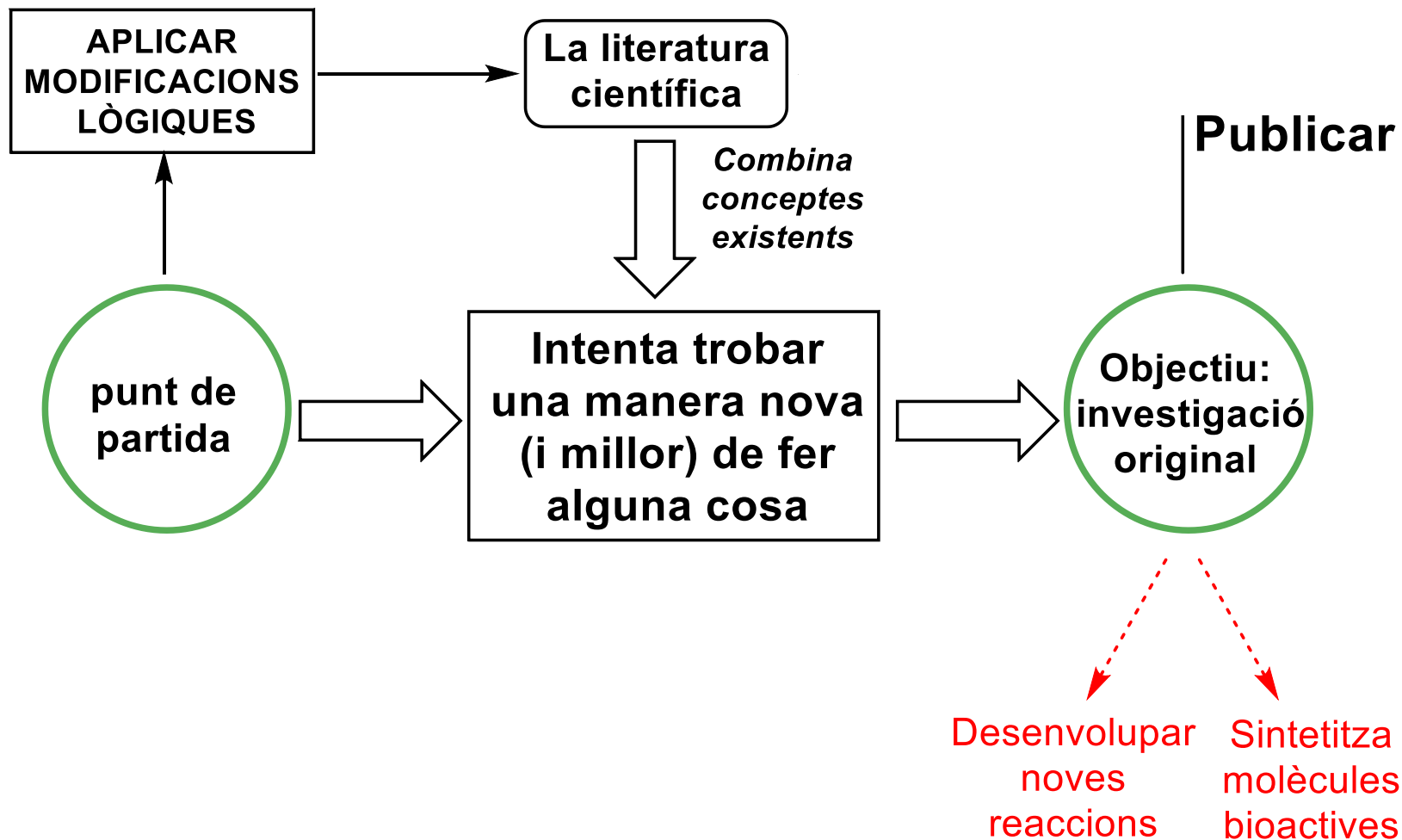
Presentació: Part 3



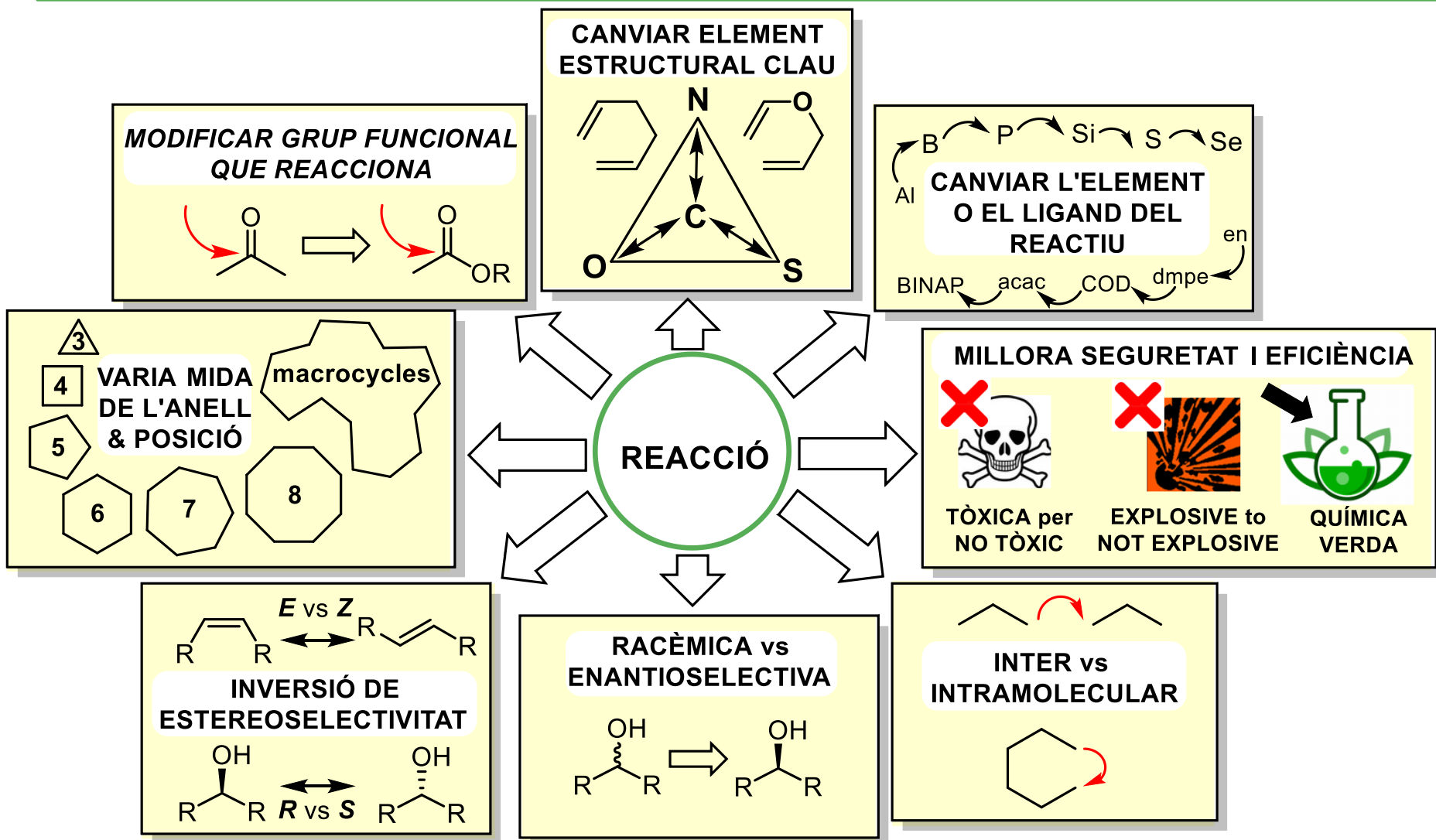
La química orgànica és el centre de tot



Desenvolupament de Projectes de Recerca



Modificadors de una reacció: 8 opcions possibles

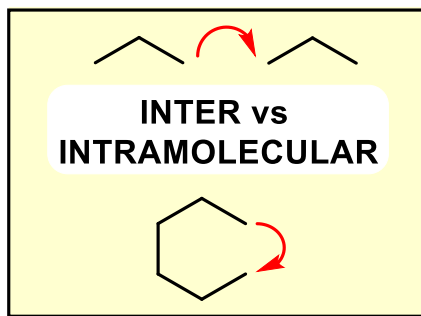
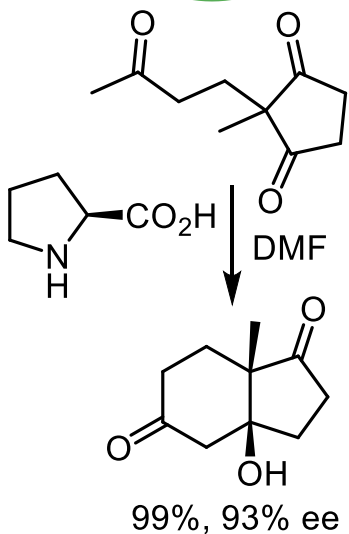


Un exemple: reacció de Hajos-Parrish → reacció aldòlica catalitzada amb prolina

discovered in 1970's

intramolecular

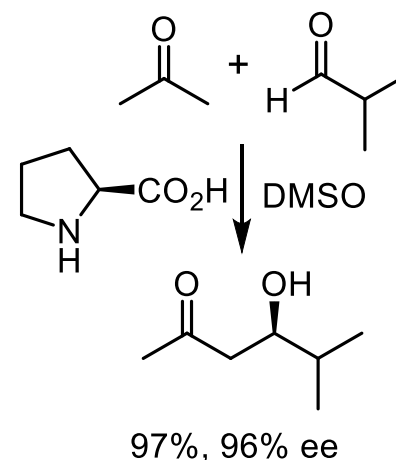
Hajos-Parrish
reaction
cat. by proline



discovered in 2000

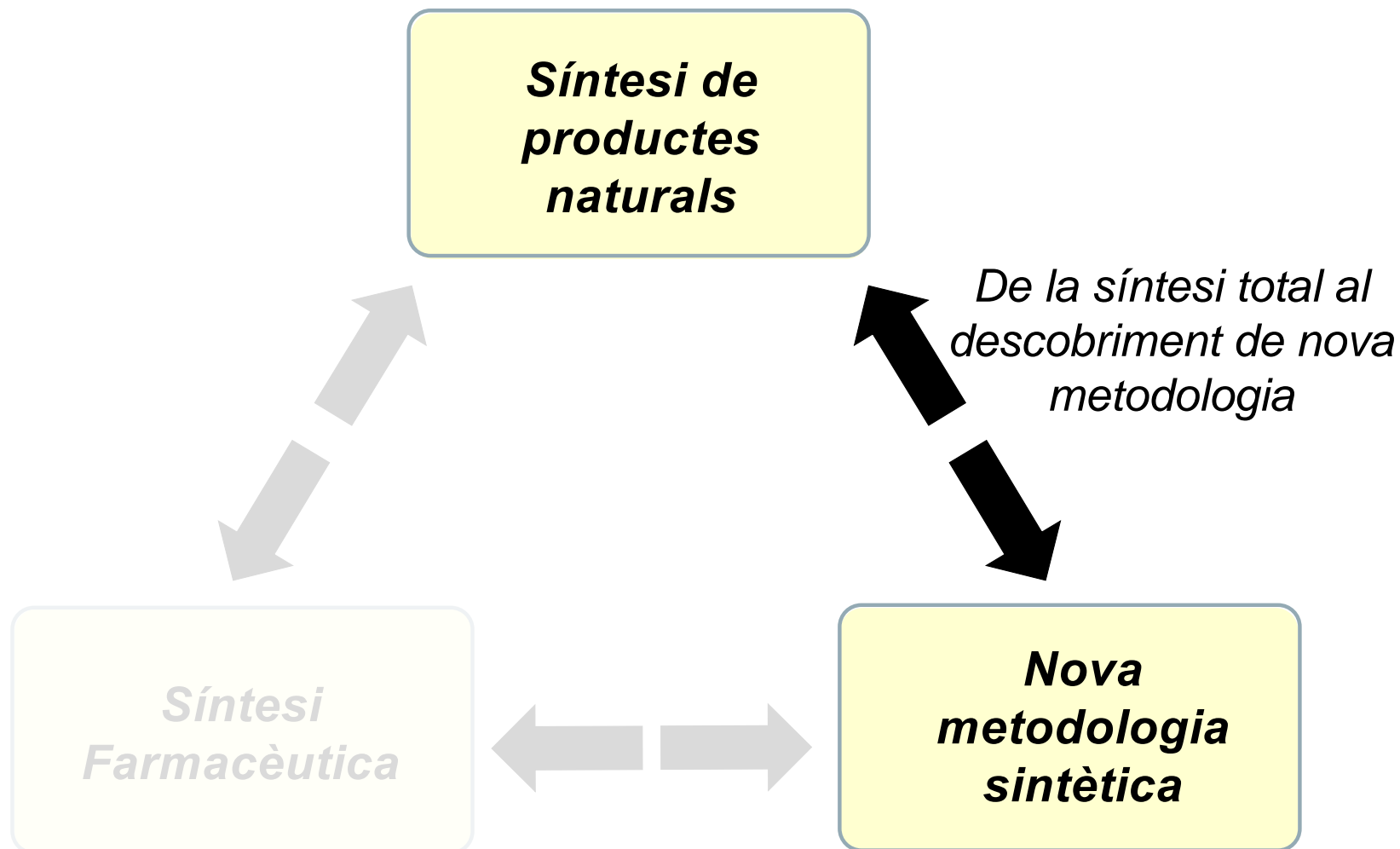
intermolecular

Aldol reaction
cat. by proline

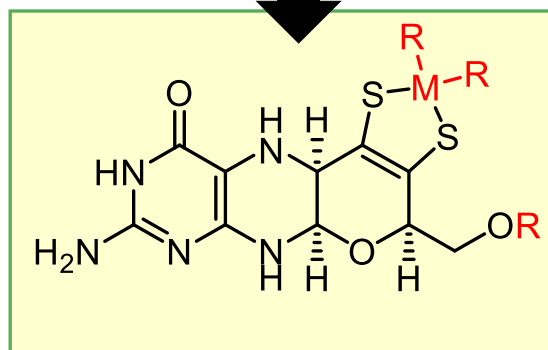
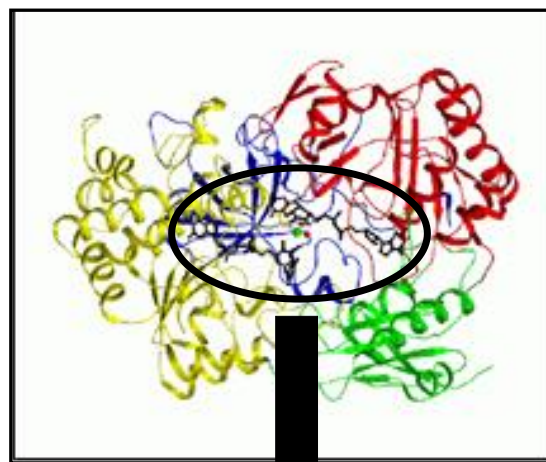


Benjamin List: Premi Nobel conjunt de Química 2021
per al descobriment de l'organocatàlisi

Part 1: Síntesi Total de Productes Naturals

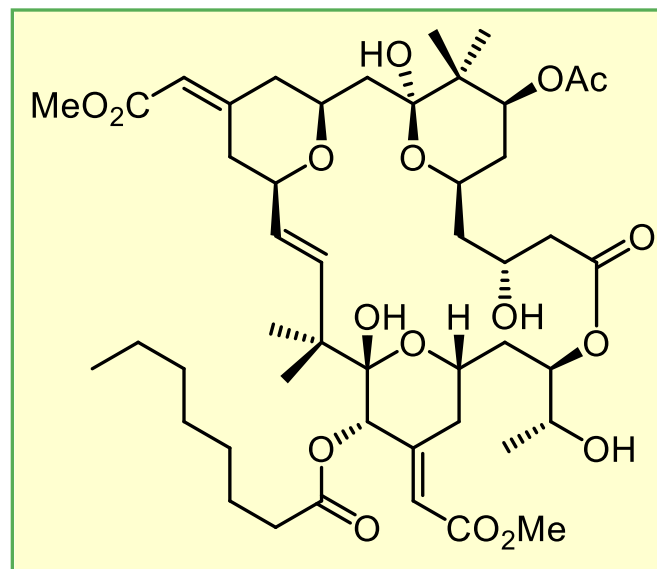


Experiència prèvia (Universitat de Manchester)



molybdopterin (MPT)

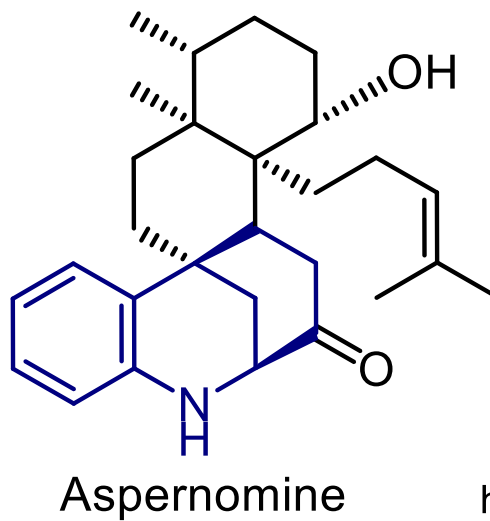
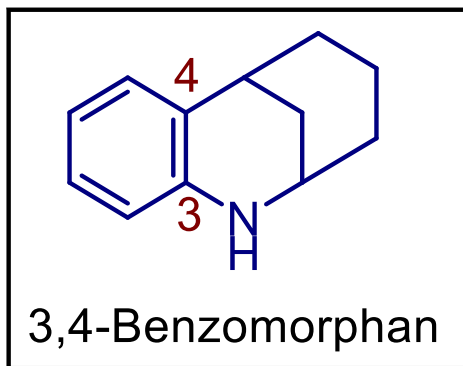
(Co-factor of
molydenum enzymes)



bryostatin 1

(from marine bryozoa)
anti-cancer activity

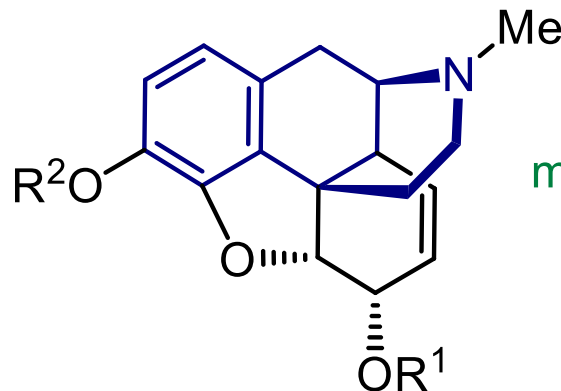
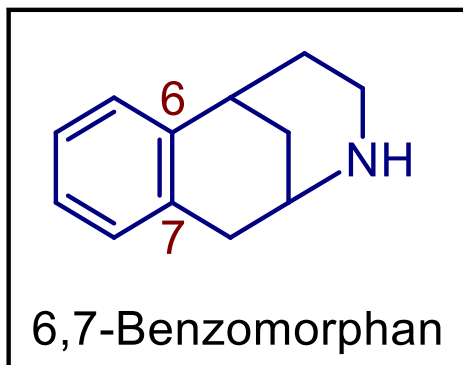
Punt de partida: Intentar la Síntesi Total d'Aspernomina



Isolated from *Aspergillus* species



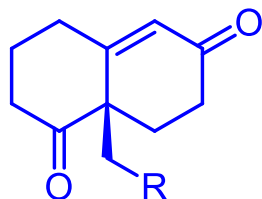
Active against three human tumor cell lines



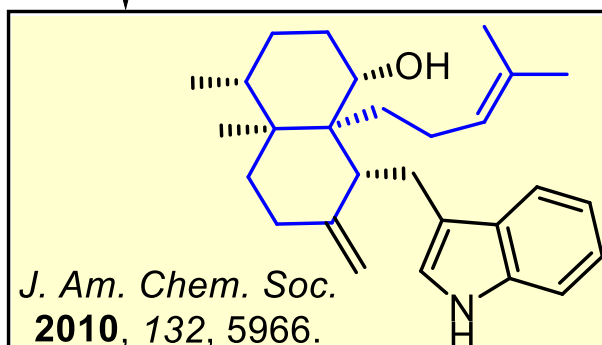
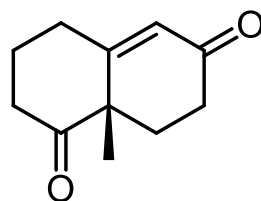
	R ¹	R ²
morphine:	H	H
heroin:	Ac	Ac
codeine:	H	Me

Objectius alternatius completats

anàleg de cetona de
Wieland- Miescher



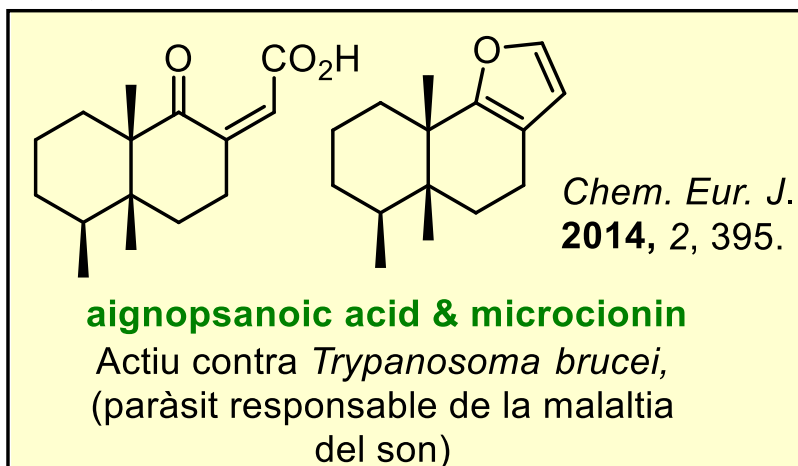
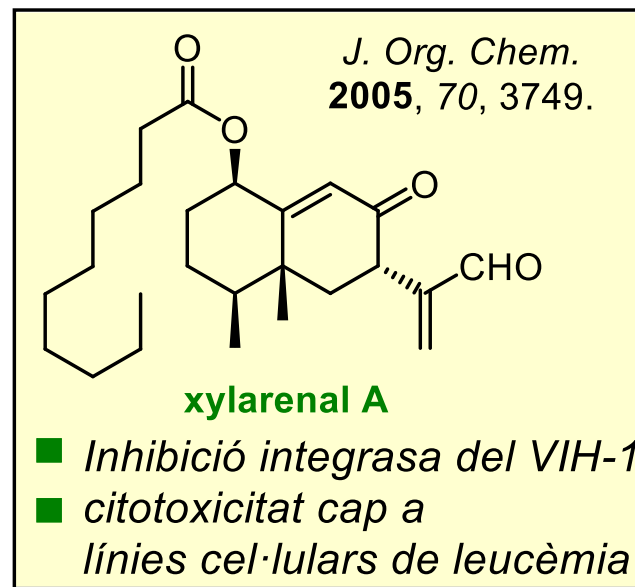
cetona
Wieland-Miescher



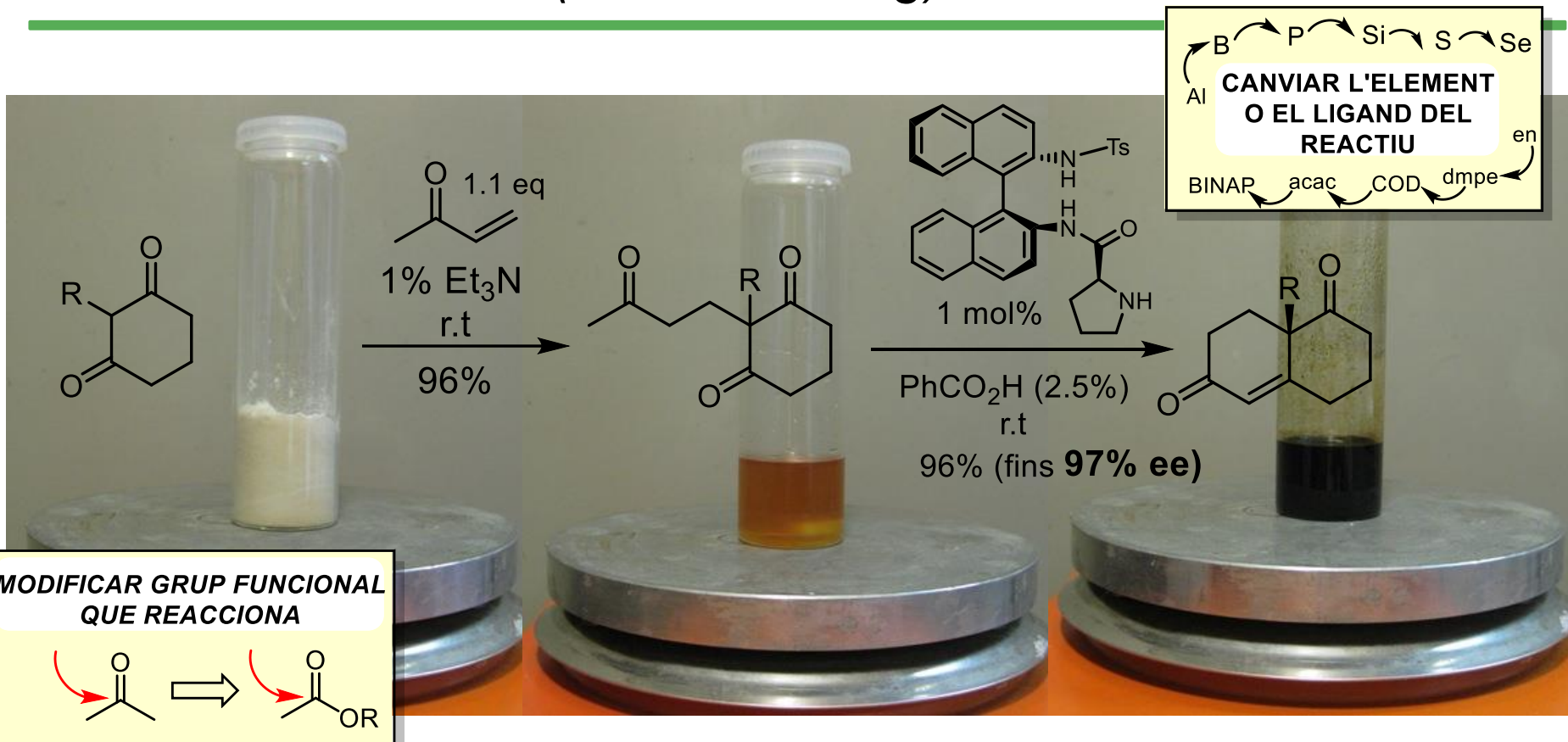
J. Am. Chem. Soc.
2010, 132, 5966.

anominine

Aspergillus nomius
(metabolit fúngic amb
 propietats contra insectes)



Un protocol senzill per a la síntesi d'anàlegs WMK (escala de 15 g)



Adv. Synth. Catal. **2009**, 351, 2482–2490.

Organic Syntheses, **2011**, 88, 317-329.

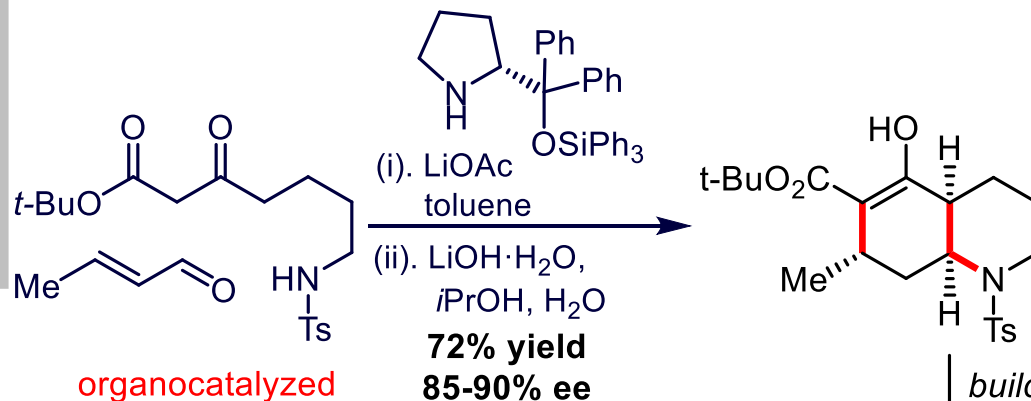
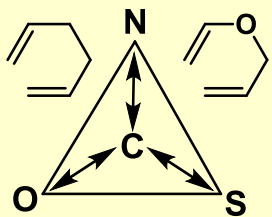
Organic Syntheses, **2011**, 88, 330-341.

Review: *Synlett*, 23, 337-356.

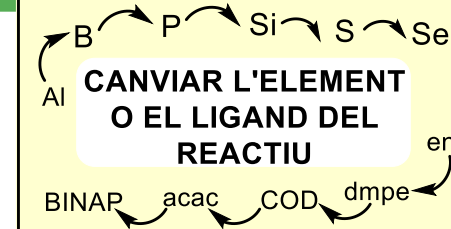
ChemCatChem, **2019**, 11, 4064– 4071.

cis-Decahidroquinolines mitjançant organocatàlisi asimètrica: aplicació a la síntesi total dels alcaloides flegmarins

CANVIAR ELEMENT
ESTRUCTURAL CLAU

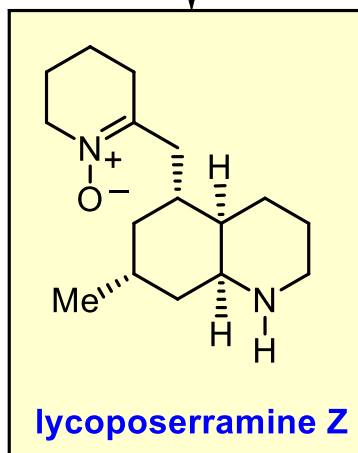


organocatalyzed
Robinson/aza-Michael

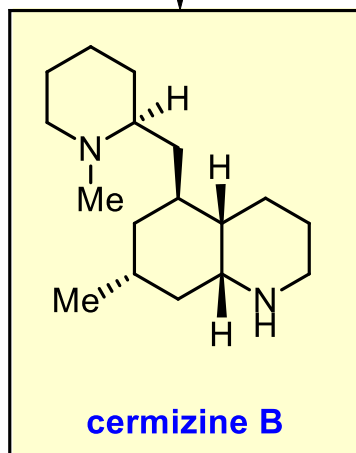


**decahydroquinoline
ring system**

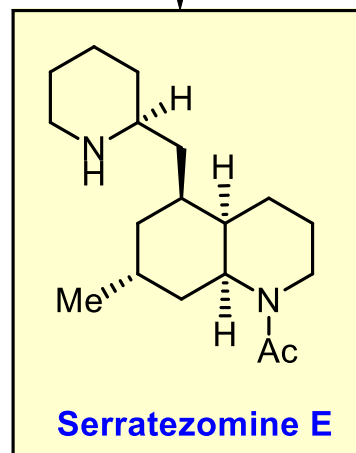
building block for multiple
total syntheses



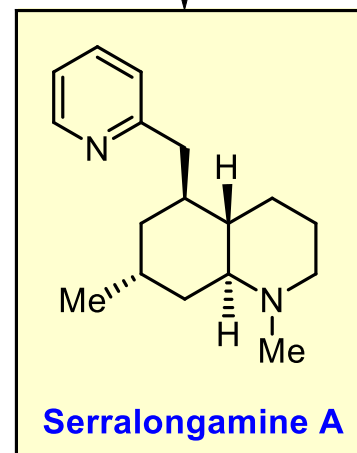
Org. Lett.
2013, 15, 326.



Chem Comm.
2014, 50, 7099.

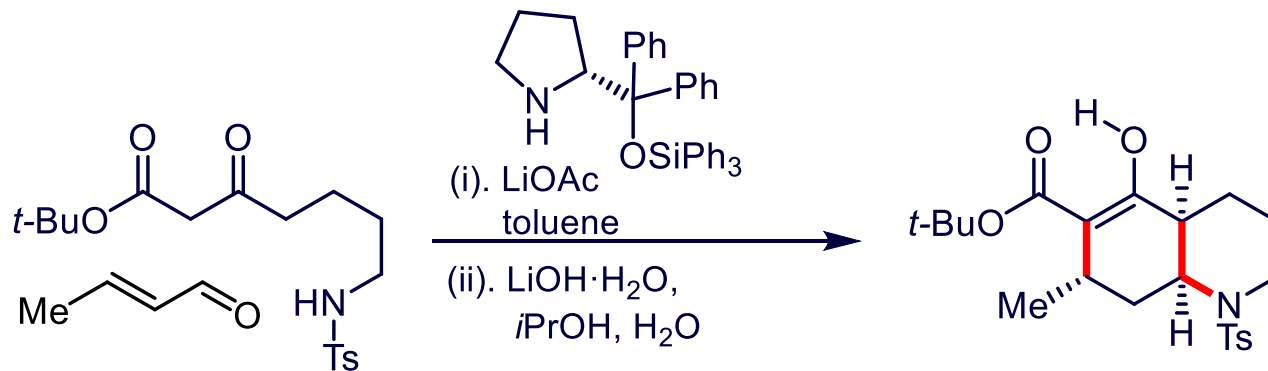


Org. Lett.
2015, 17, 5084.

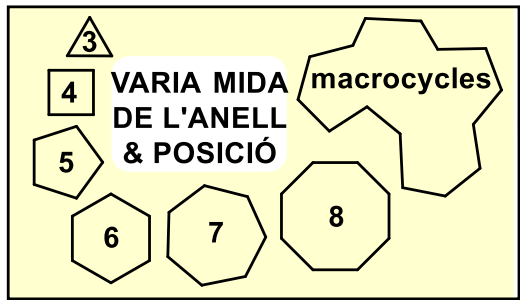
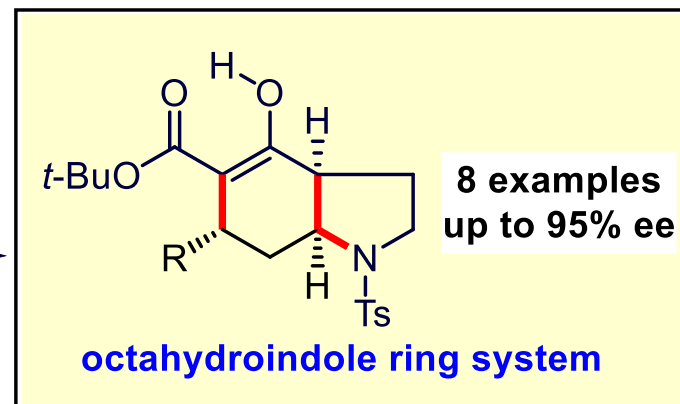
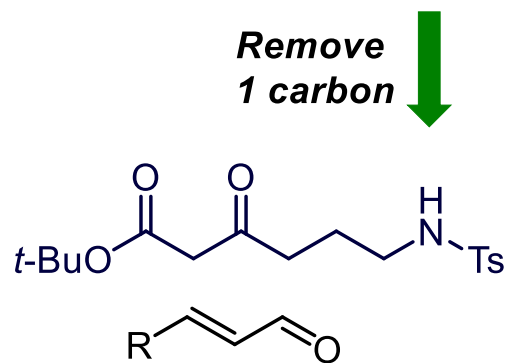


J. Org Chem
2016, 81, 2629

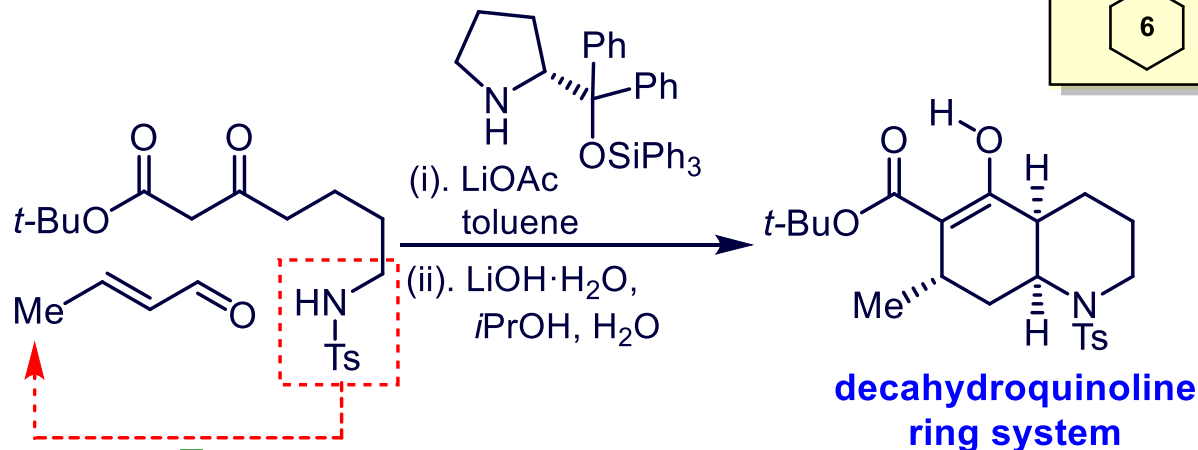
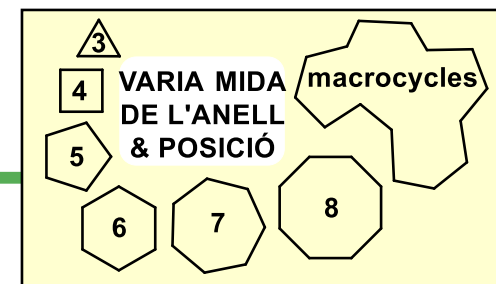
Síntesi d'octahidroindols



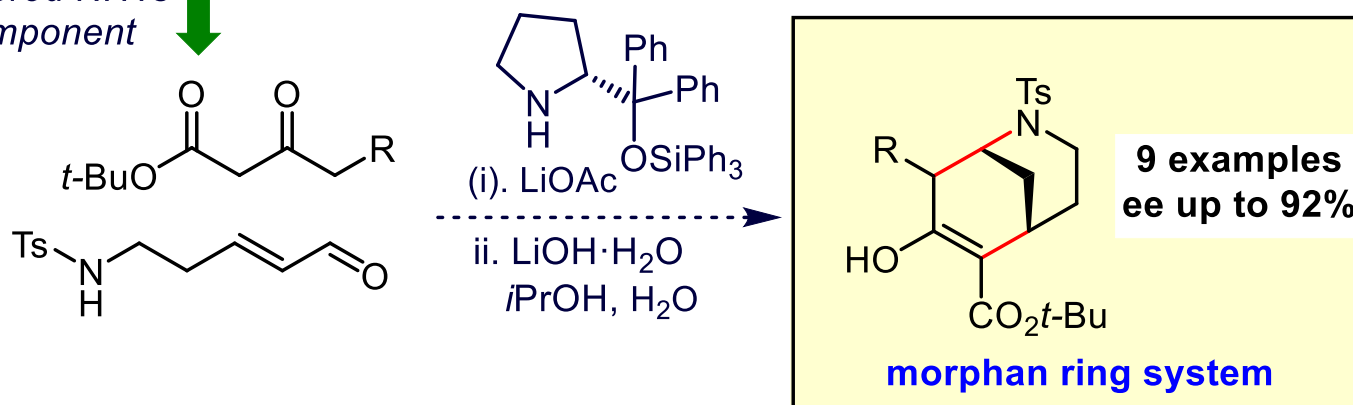
decahydroquinoline ring system



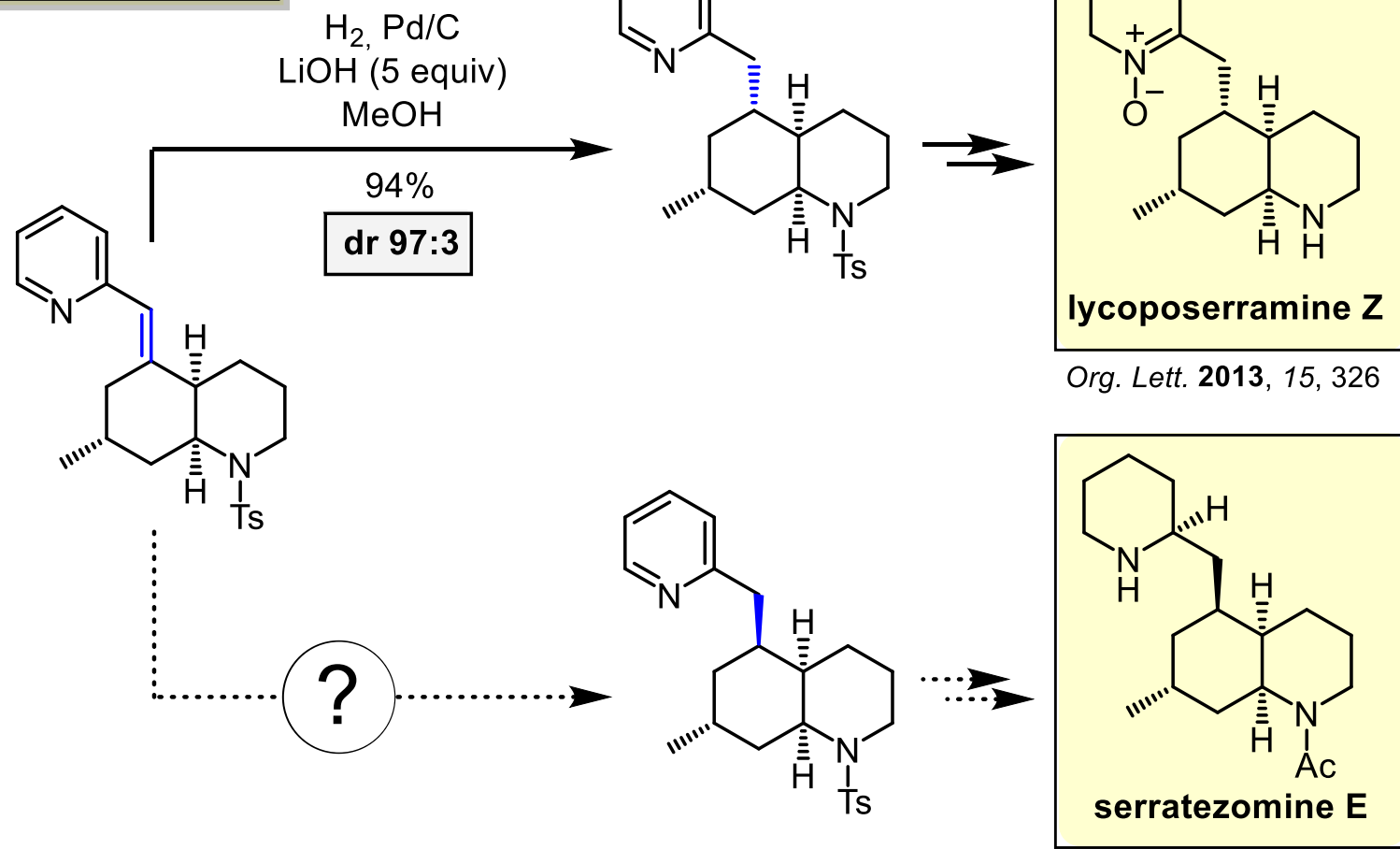
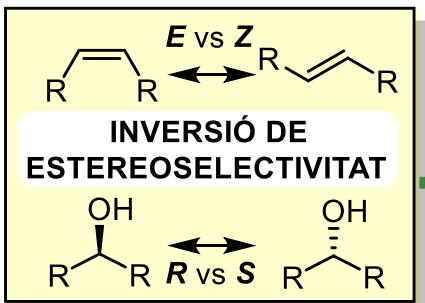
Síntesi asimètrica organocatalitzada de morfans



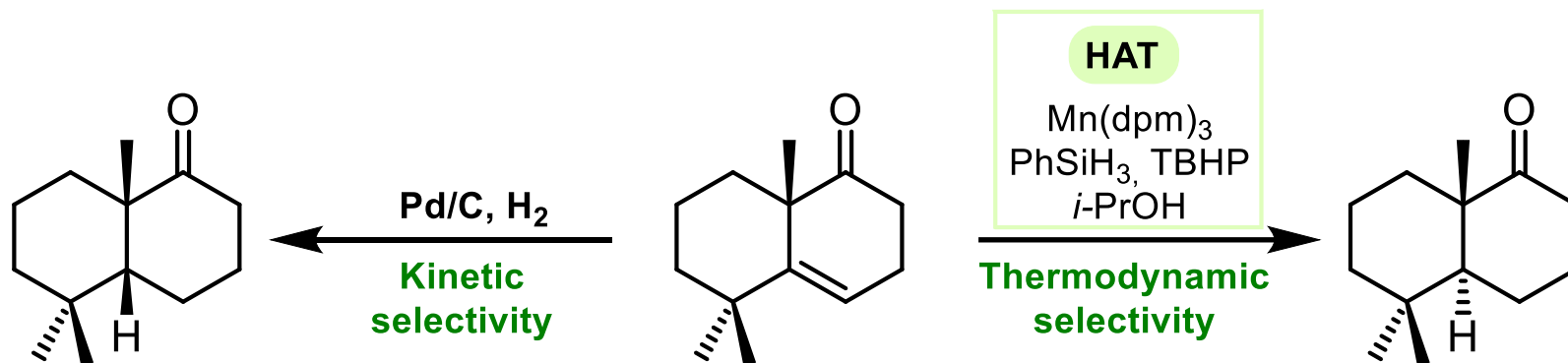
move tethered NHTs
to enal component



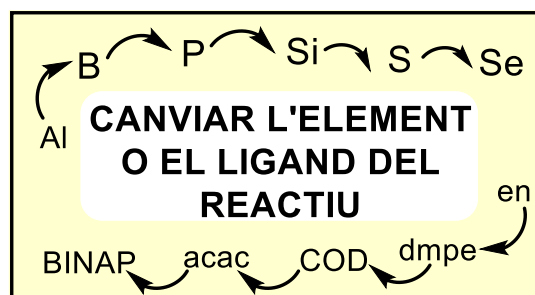
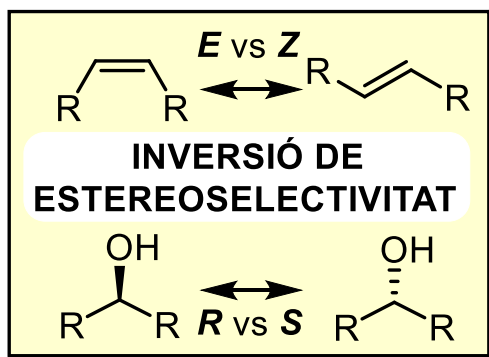
Estratègia de reducció divergent



Estratègia de reducció divergent amb MHAT a la literatura



Shenvi *et al.* *J. Am. Chem. Soc.* **2014**, 136, 1300



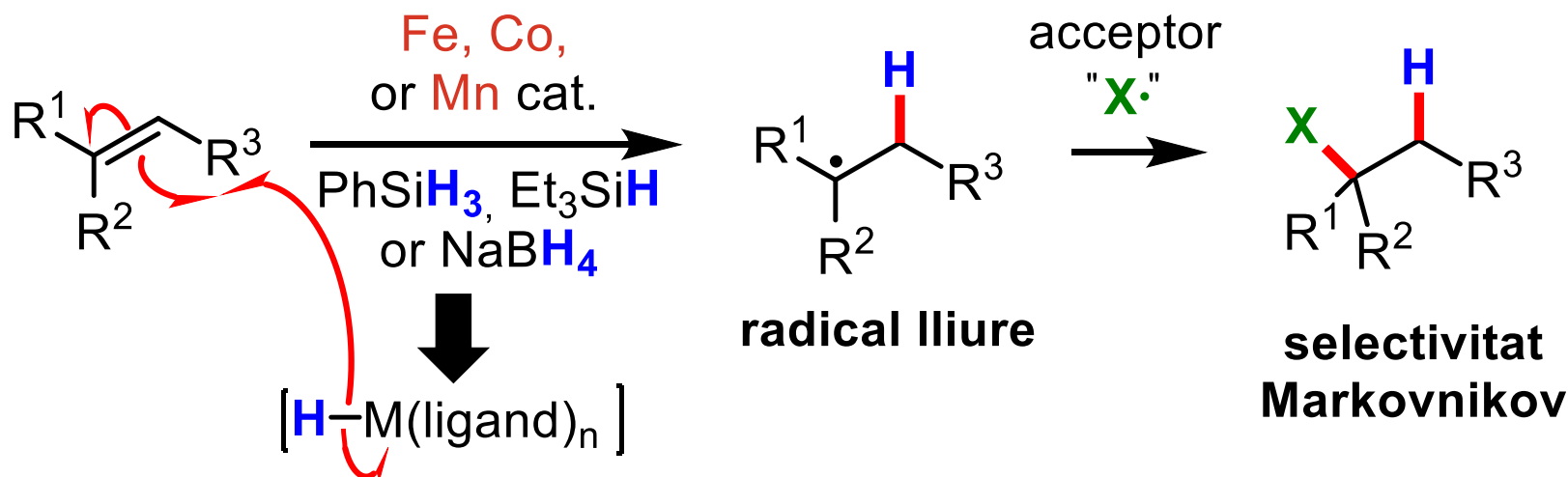
MILLORA SEGURETAT I EFICIÈNCIA

~~☠~~ **TÒXICA per NO TÒXIC**

~~💣~~ **EXPLOSIVE to NOT EXPLOSIVE**

➔ **QUÍMICA VERDA**

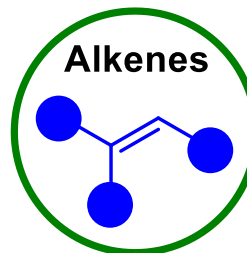
Què és la transferència d'àtoms d'hidrogen catalitzat per metalls (MHAT)?



MHAT
reactions

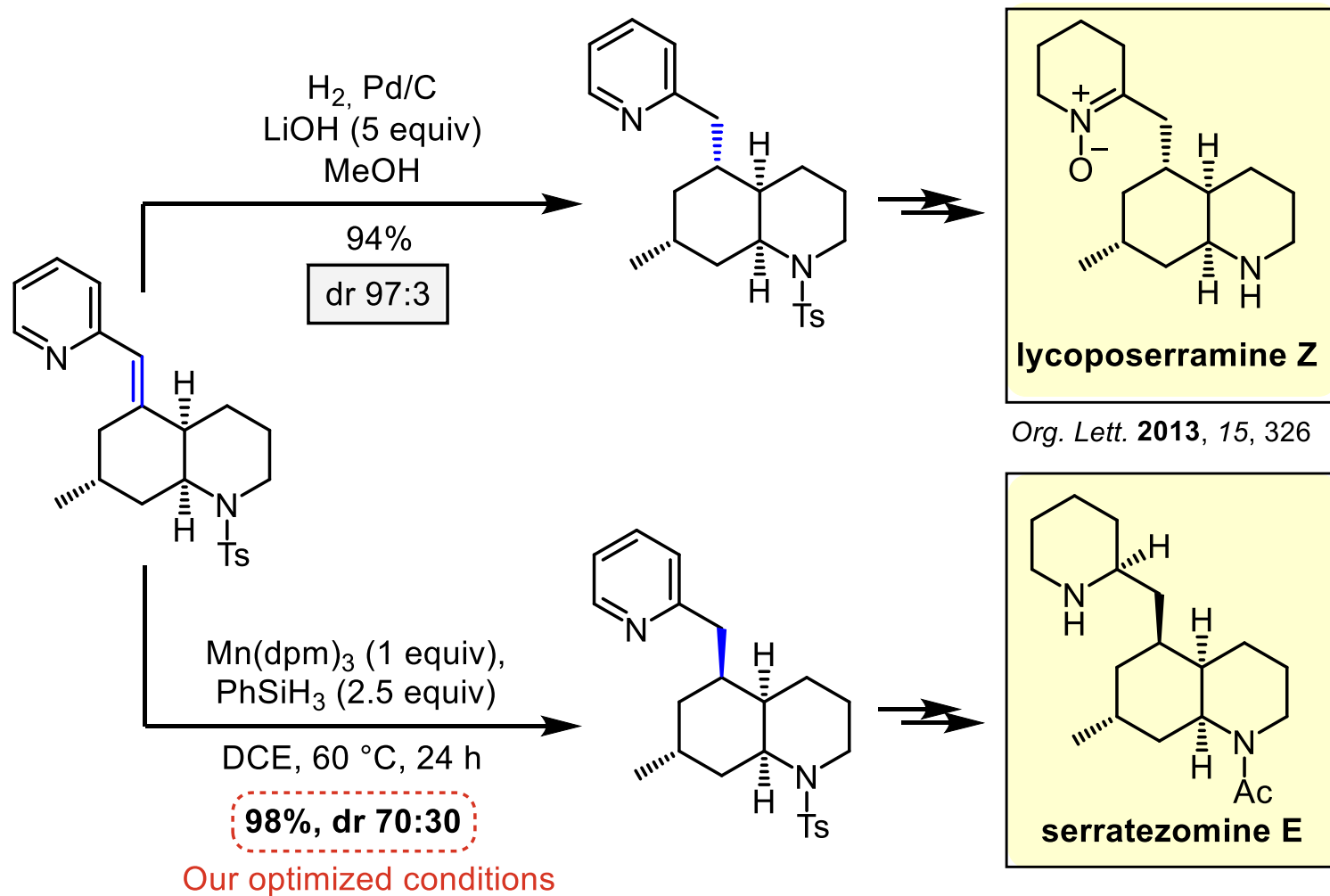
- *Condicions de reacció suaus i reactius no tòxics*
- *Potencials nous enfocaments de desconnexió per a la formació d'enllaços C-C*

Alkenes

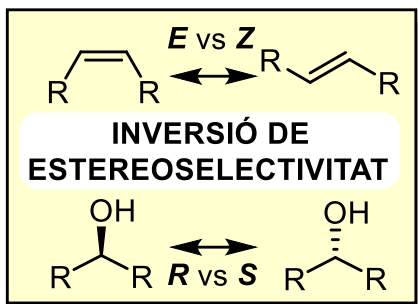


- *De baix cost*
- *Fàcilment disponibles*

Intent de reducció divergent utilitzant condicions MHAT

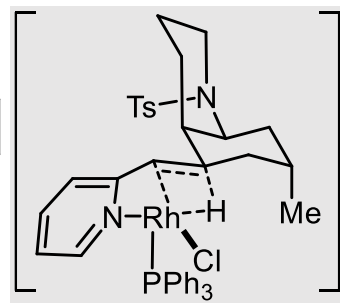


Inversió completa de l'estereoselectivitat mitjançant el catalitzador de Wilkinson



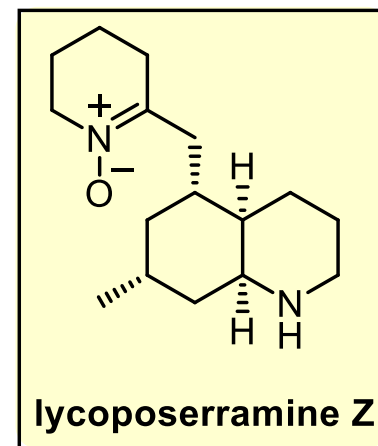
H_2 , Pd/C
LiOH (5 equiv)
MeOH

94%
dr 97:3

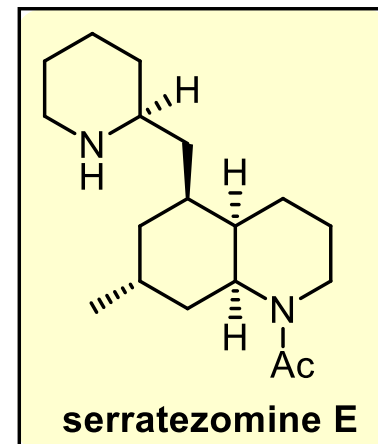


H_2 , RhCl(PPh₃)₃ (2 mol%)
MeOH

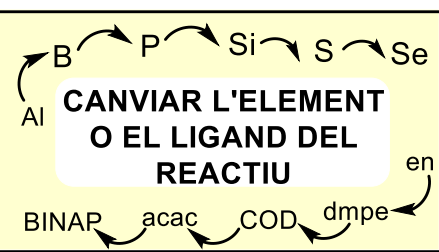
quantitative
dr 96:4



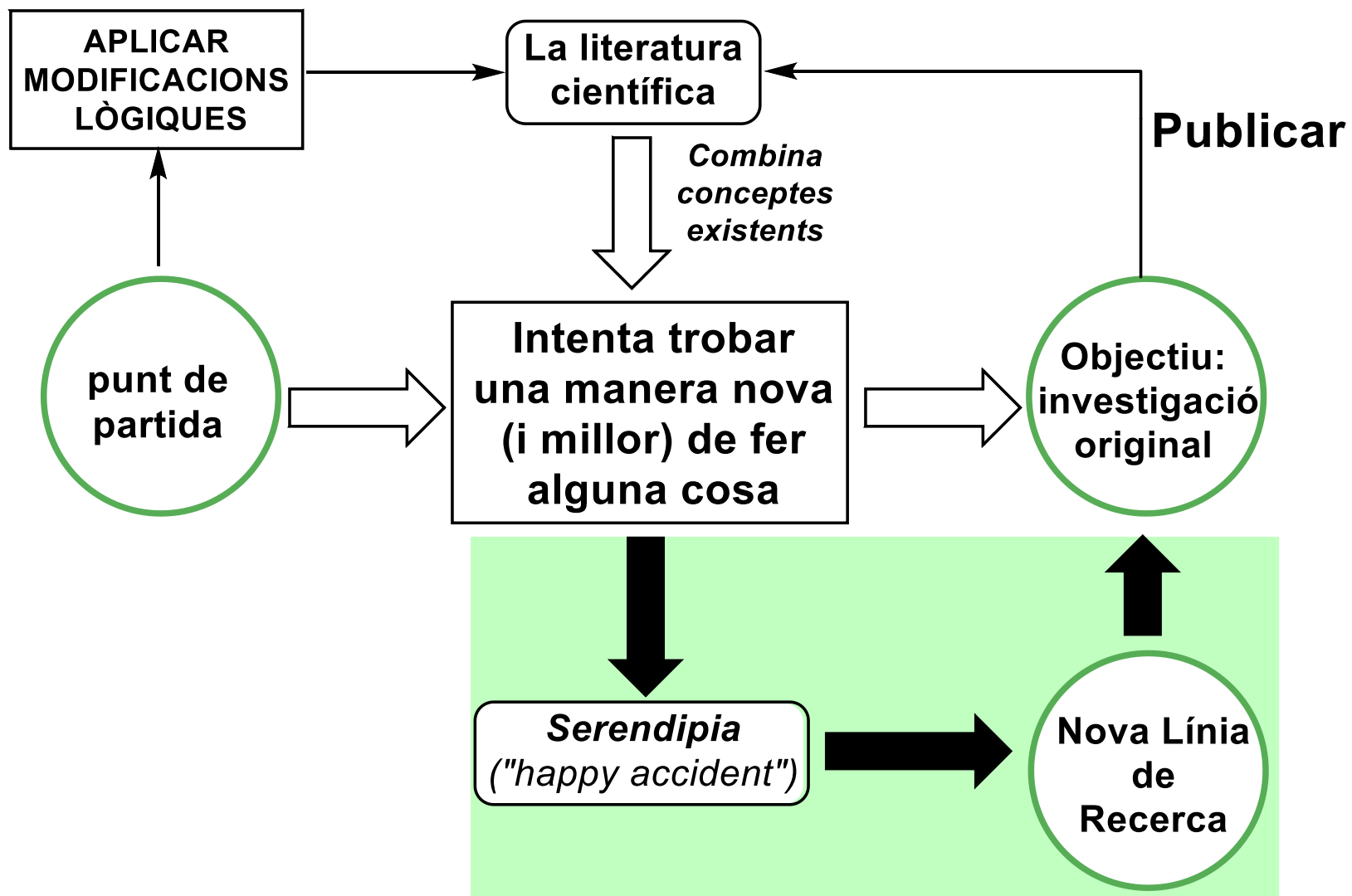
Org. Lett. 2013, 15, 326



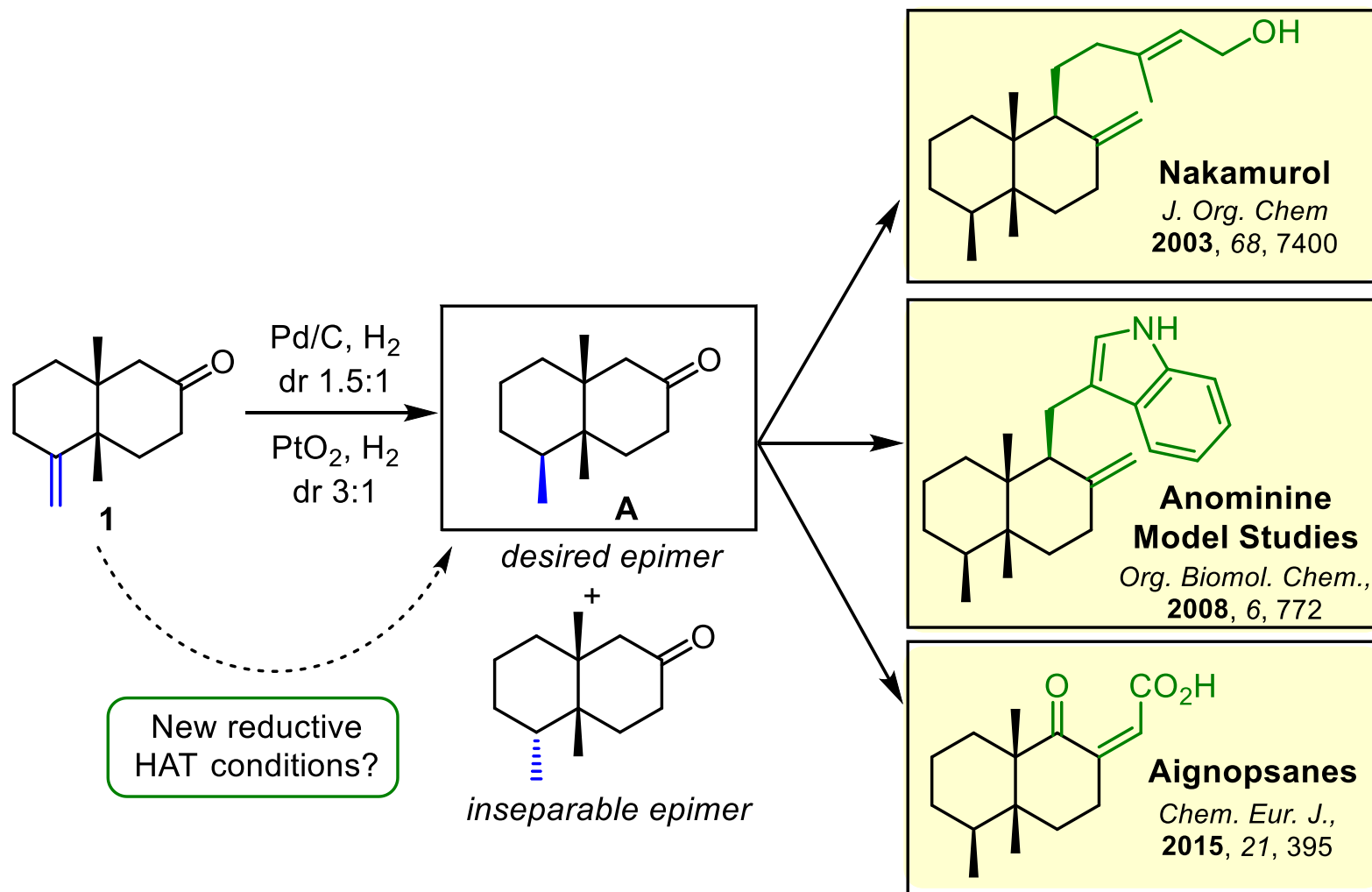
Org. Lett. 2015, 17, 5084



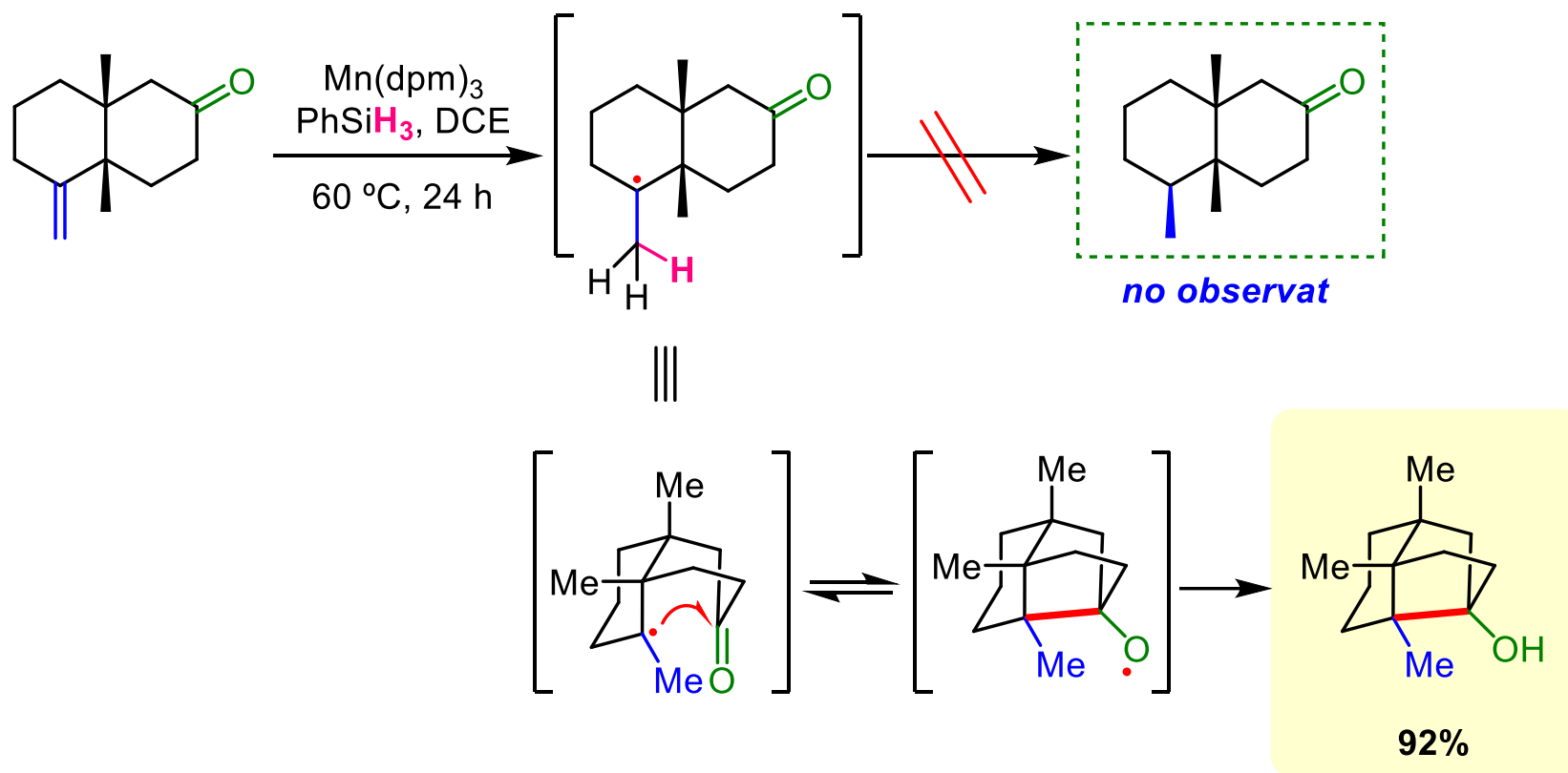
Desenvolupament de Projectes de Recerca



Aplicació de condicions de reducció de MHAT per a la síntesi total

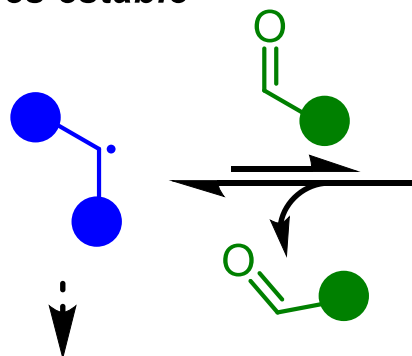


Una ciclització MHAT inesperada



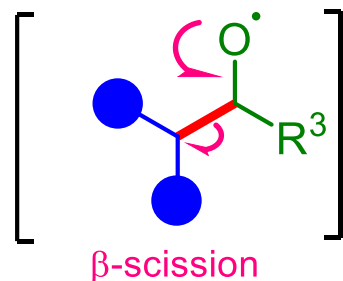
Els carbonils no actuen normalment com a acceptors de radicals a causa de la reversibilitat de la reacció

més estable



reducció

menys estable

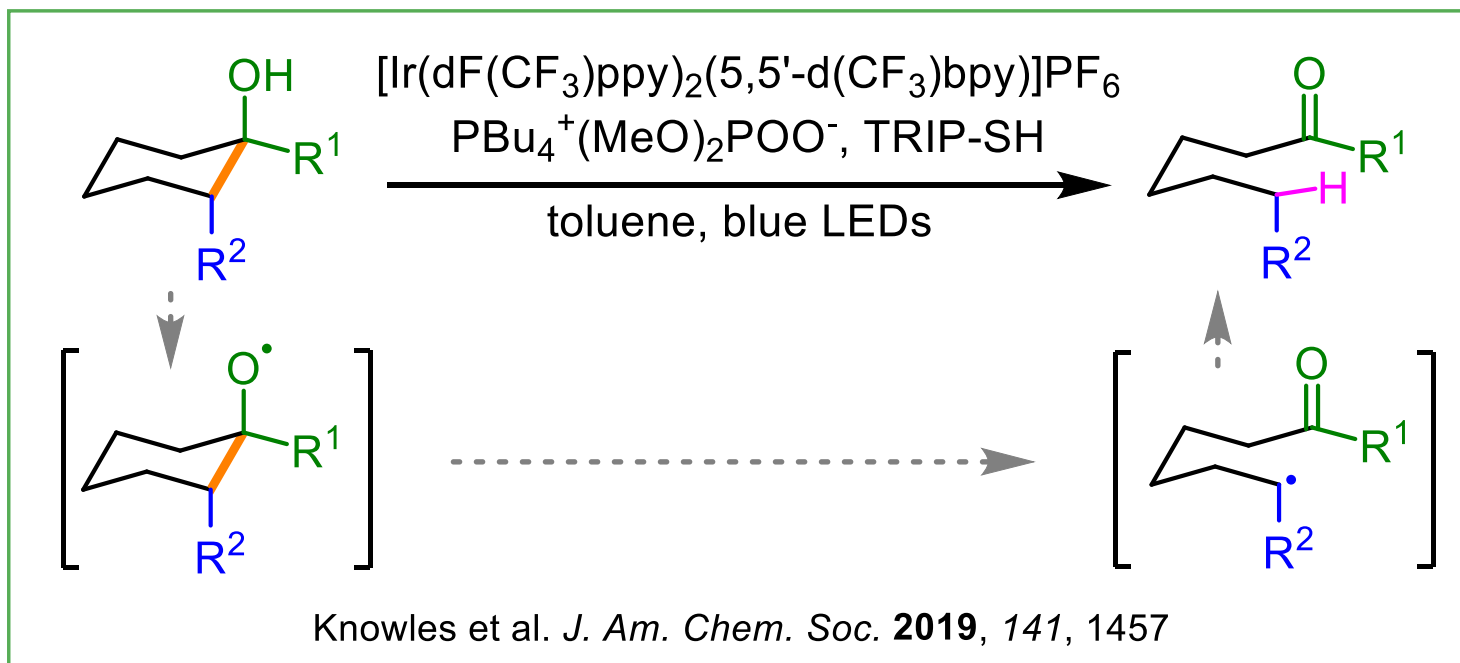


atrapar el radical

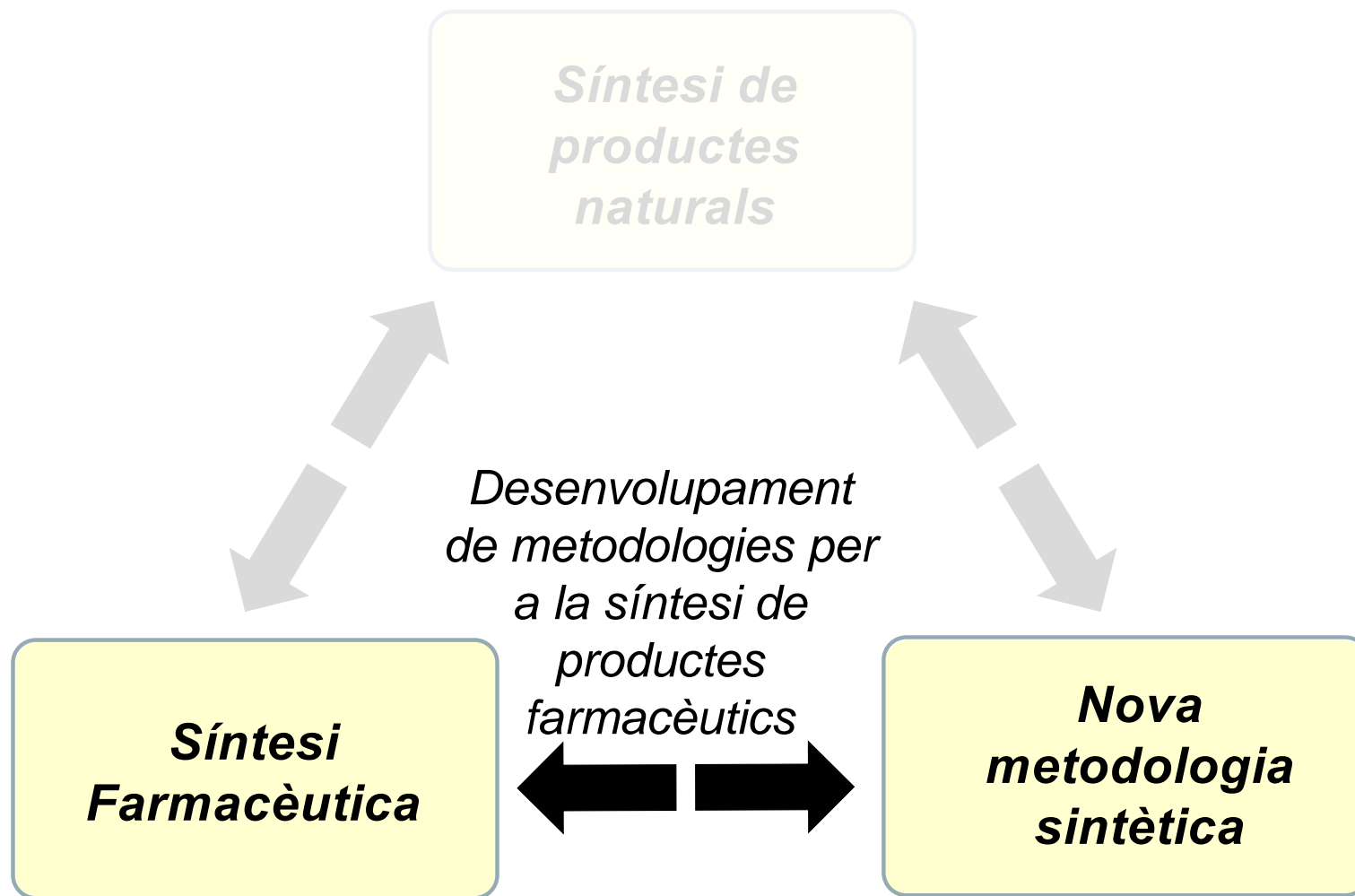
generar el radical



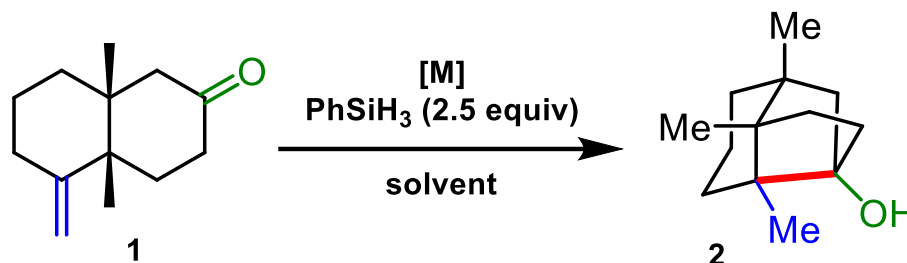
e.g.
photocatalysis



Part 2: Desenvolupament de metodologia sintètica

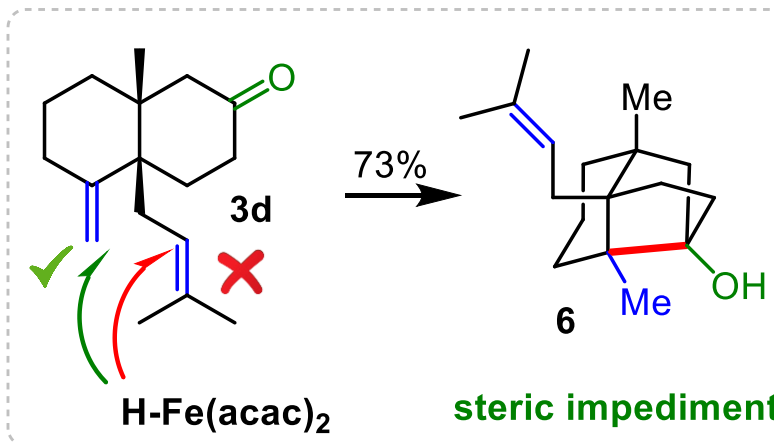
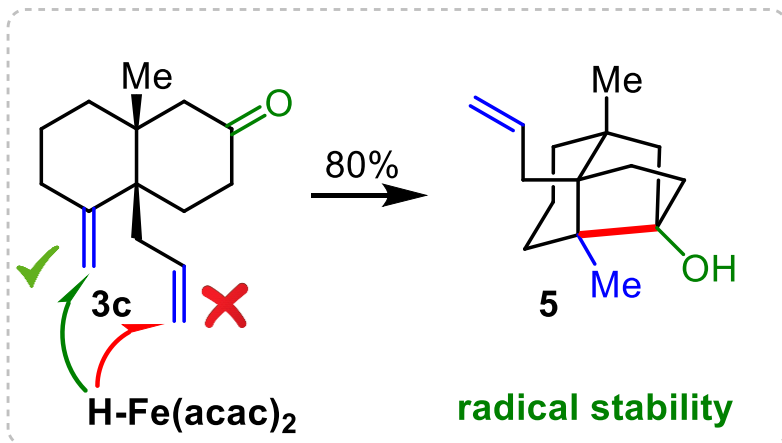
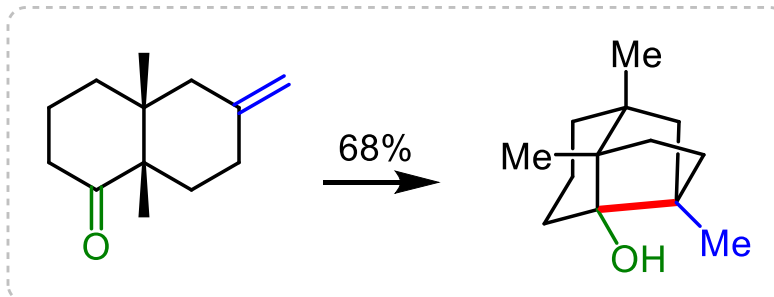
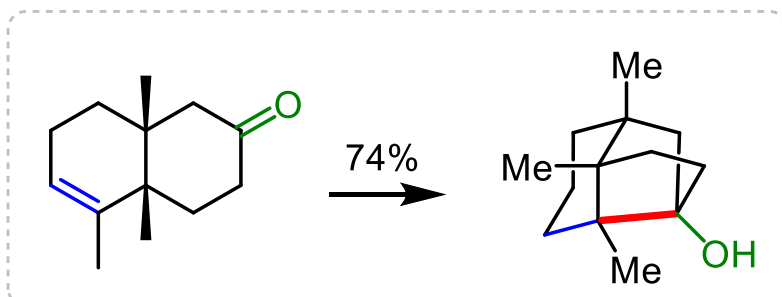
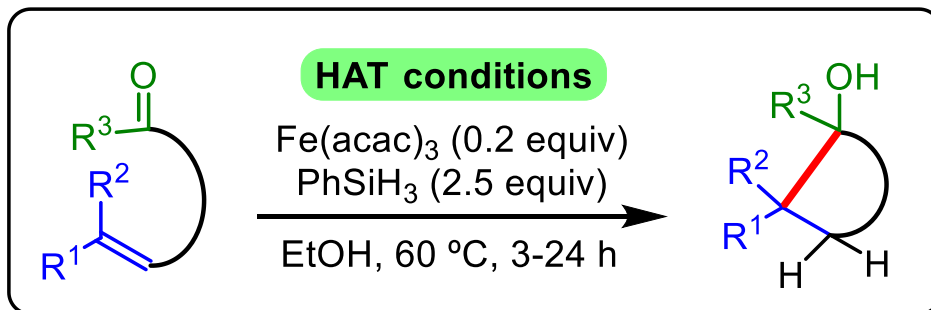


Metodologia Part 1: Optimització de la reacció

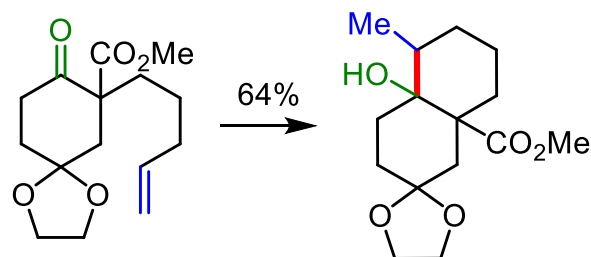
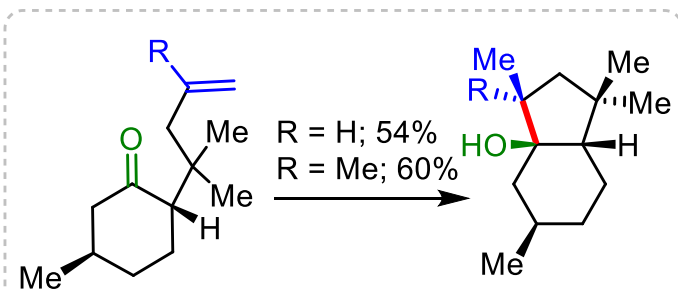


Entry	Metal (equiv)	Solvent	T (°C)	Time (h)	Yield
1	Mn(dpm) ₃ (1)	DCE	60	24	92%
2	Mn(dpm) ₃ (1)	EtOH	60	24	86%
3	Mn(dpm) ₃ (0.2)	DCE	60	24	79%
4	Fe(acac) ₃ (0.2)	DCE	60	24	30%
5	Fe(acac) ₃ (0.2)	EtOH	60	24	95%
6	Fe(acac) ₃ (0.2)	EtOH	60	3	92%
7	Fe(acac) ₃ (0.2)	EtOH	25	24	95%
8	Fe(acac) ₃ (0.2)	EtOH	25	3	59%

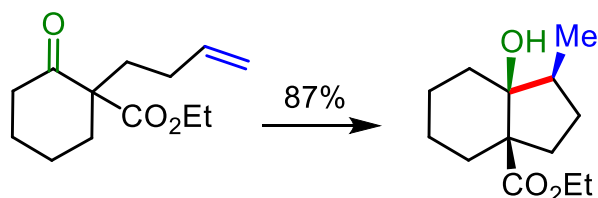
Metodologia Part 2: Determinar el "Substrate Scope"



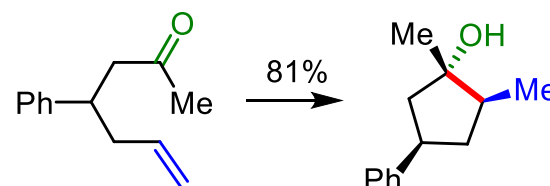
“Substrate Scope”



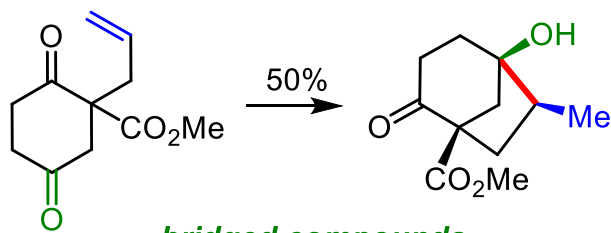
6-membered ring compounds



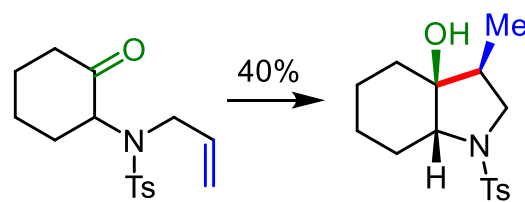
cis-hydrindane compounds



acyclic compounds

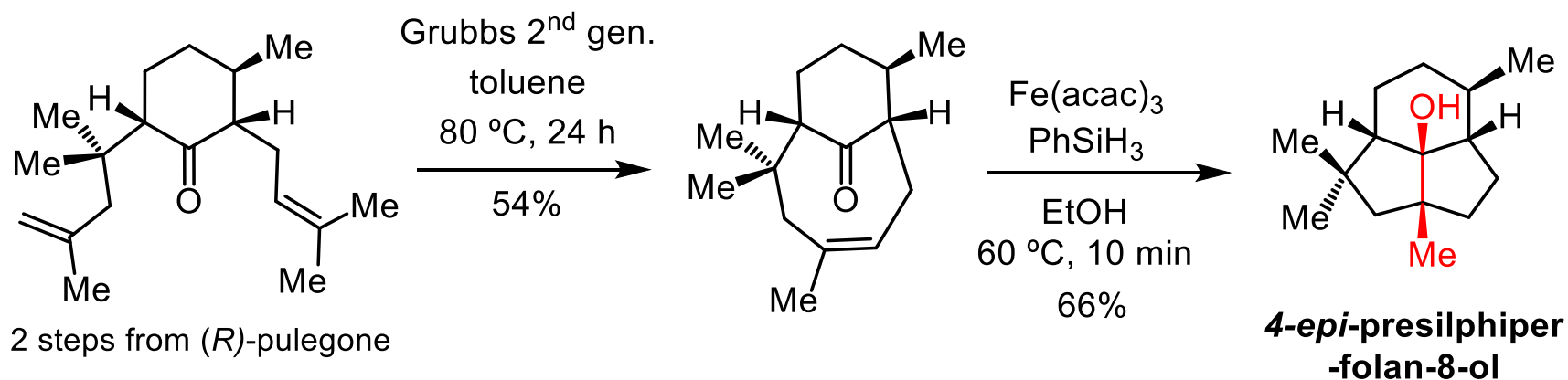
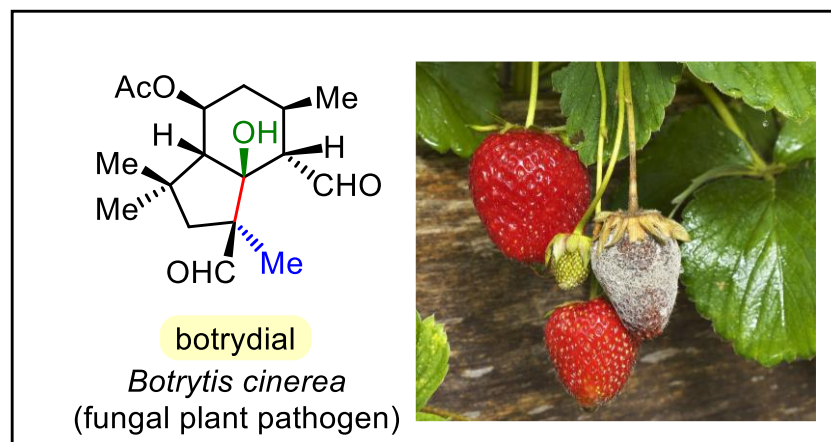
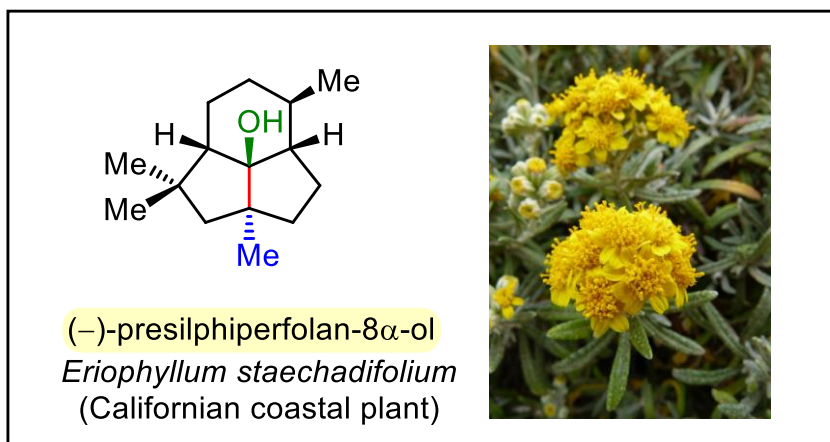


bridged compounds

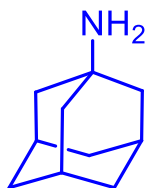
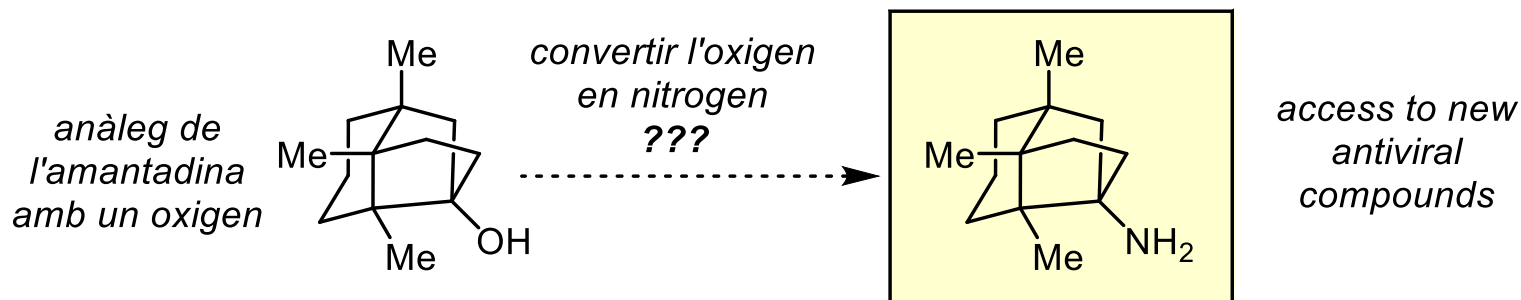


heterocyclic compounds

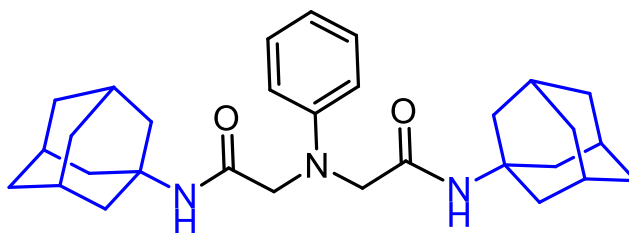
Aplicació a la síntesi de productes naturals



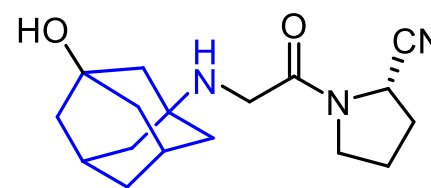
α -Amines terciàries



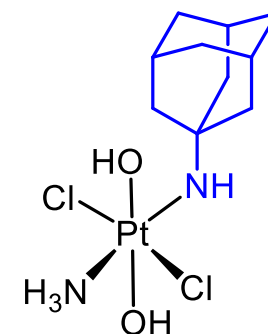
amantadine
*Parkinsons and
type A influenza virus*



Anti-HSV agent
Herpes simplex virus



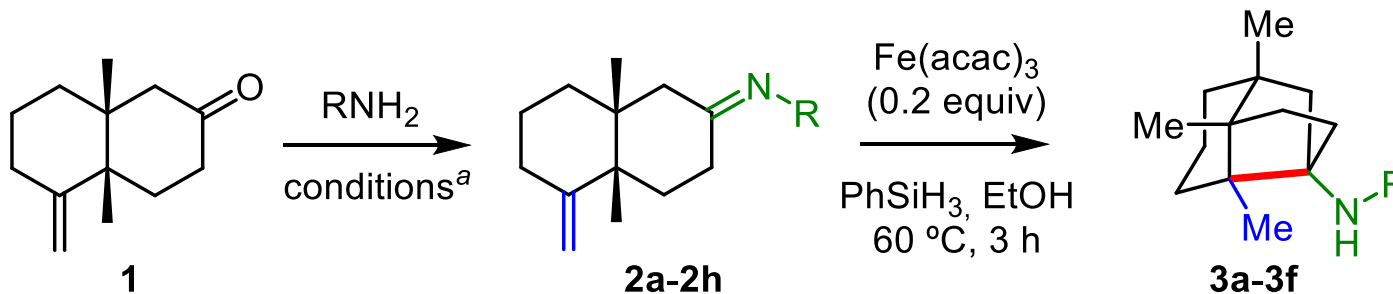
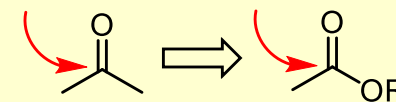
Vildagliptin®
Type 2 diabetes



Cisplatin analogue
Anti-cancer agent

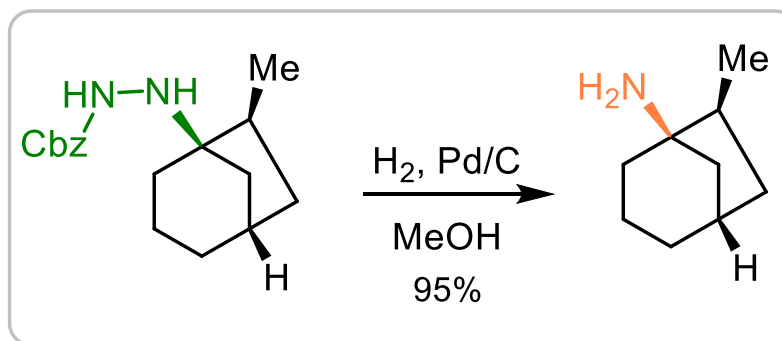
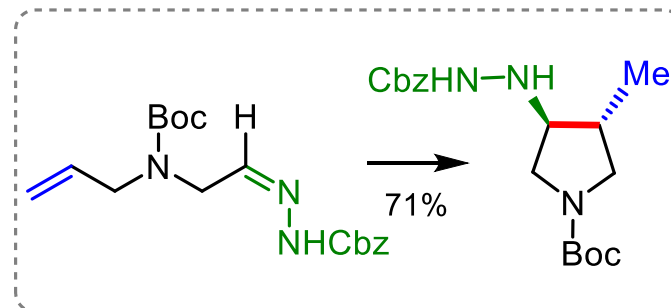
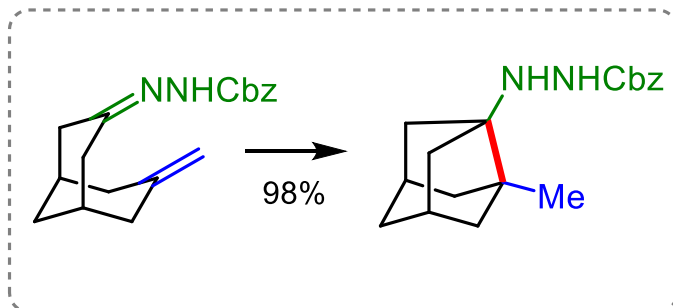
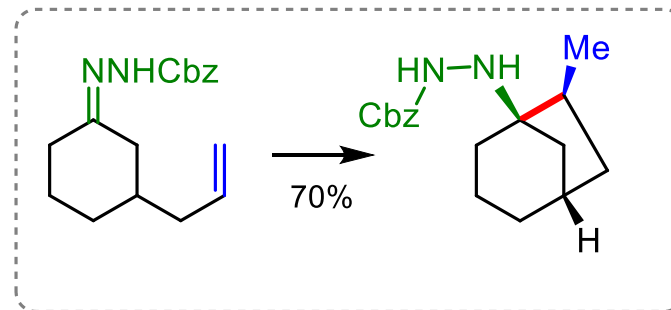
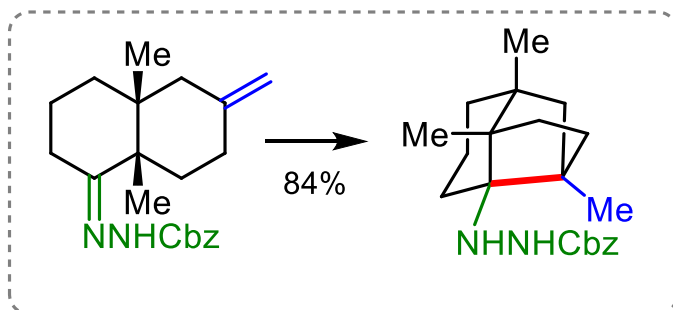
Acoblament MHAT amb C=N

MODIFICAR GRUP FUNCIONAL
QUE REACCIONA

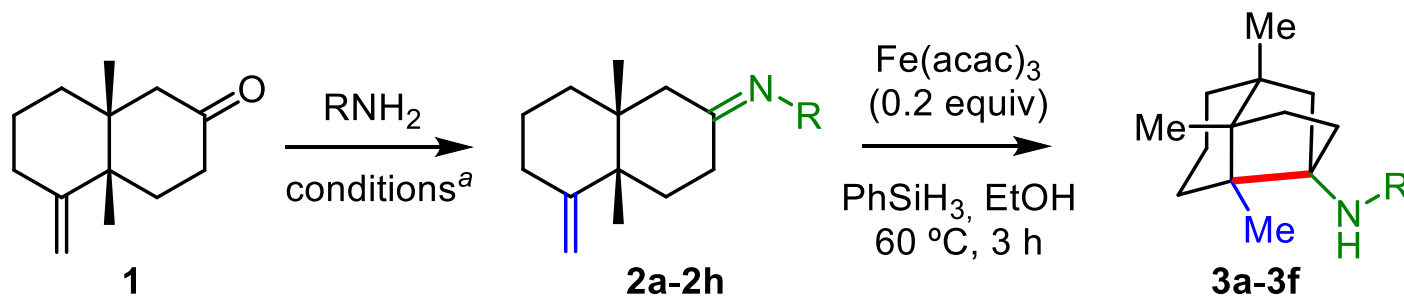


entry	R	yield [%]	yield [%]
1	NHCbz	2a (97)	3a (98)
2	NHBoc	2b (82)	3b (90)
3	OMe	2c (98)	3c (87)
4	NHPh	2d (98)	3d (19)
5	NMe ₂	2e (98)	3e (8)
6	NHTs	2f (98)	3f (18)
7	NH ₂	2g (50)	nd
8	Bn	2h (55)	nd

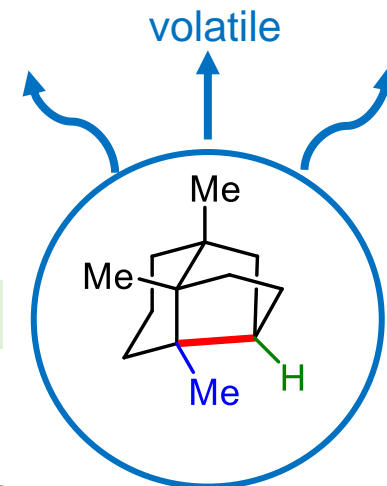
Exemples seleccionats



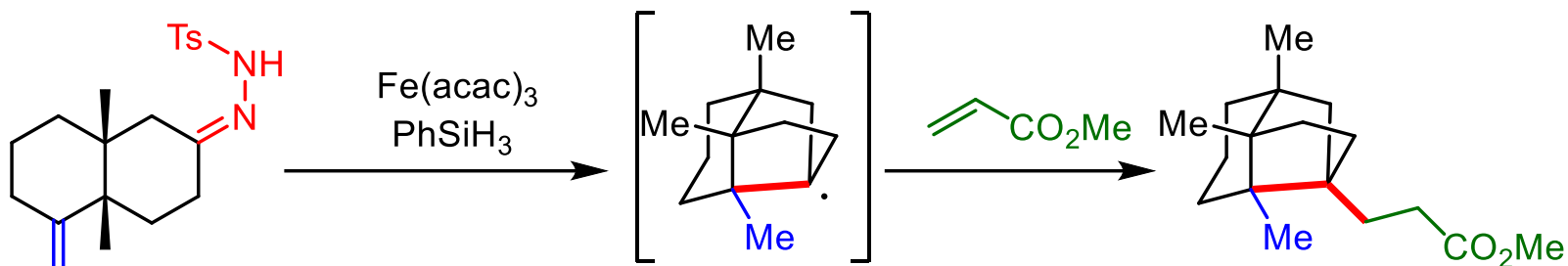
Estudi previ: Observació d'una reacció secundària



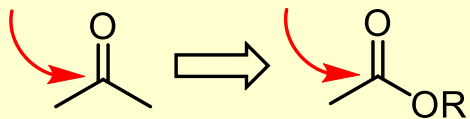
entry	R	yield [%]	yield [%]
1	NHCbz	2a (97)	3a (98)
2	NHBoc	2b (82)	3b (90)
3	OMe	2c (98)	3c (87)
4	NHPh	2d (98)	3d (19)
5	NMe ₂	2e (98)	3e (8)
6	NHTs	2f (98)	3f (18)
7	NH ₂	2g (50)	nd
8	Bn	2h (55)	nd



MHAT per generar Adamantanes substituïts



MODIFICAR GRUP FUNCIONAL QUE REACCIONA



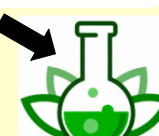
MILLORA SEGURETAT I EFICIÈNCIA



TÒXICA per
NO TÒXIC

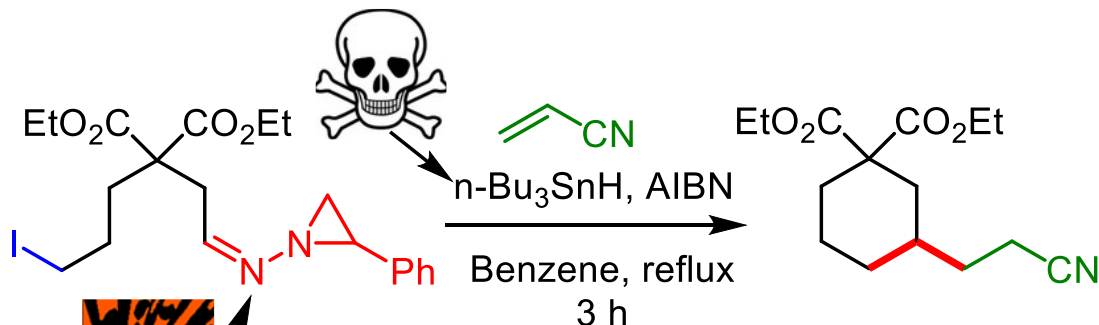


EXPLOSIVE to
NOT EXPLOSIVE

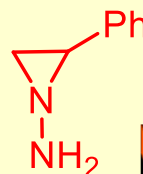


QUÍMICA
VERDA

Reaction Precedent: Kim, Lee et al. *J. Am. Chem. Soc.*, 1991, 113, 9882.

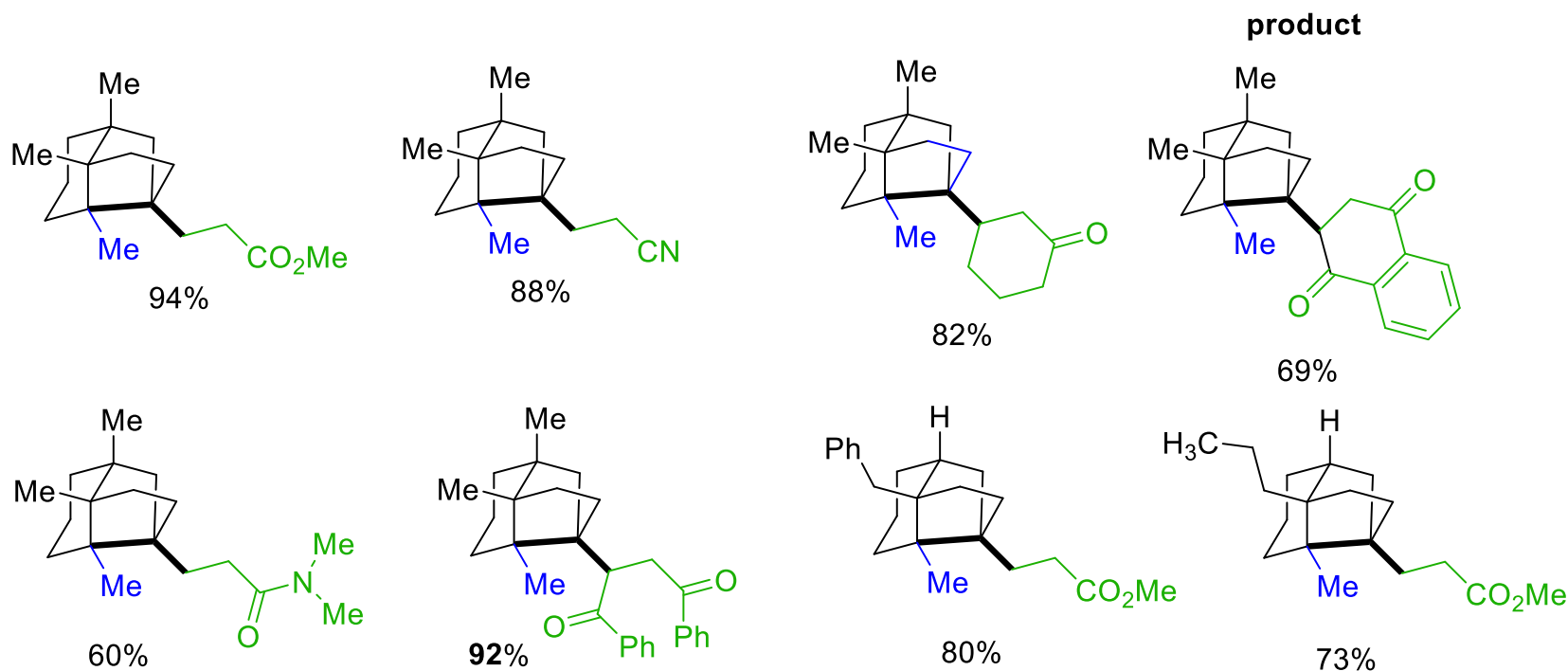
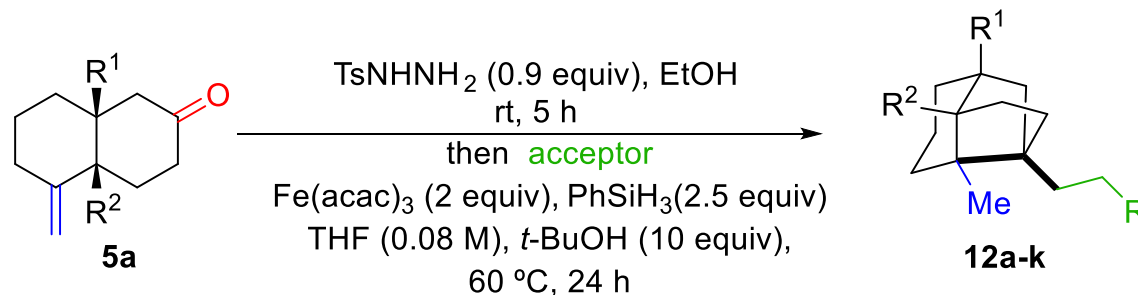


reagent used

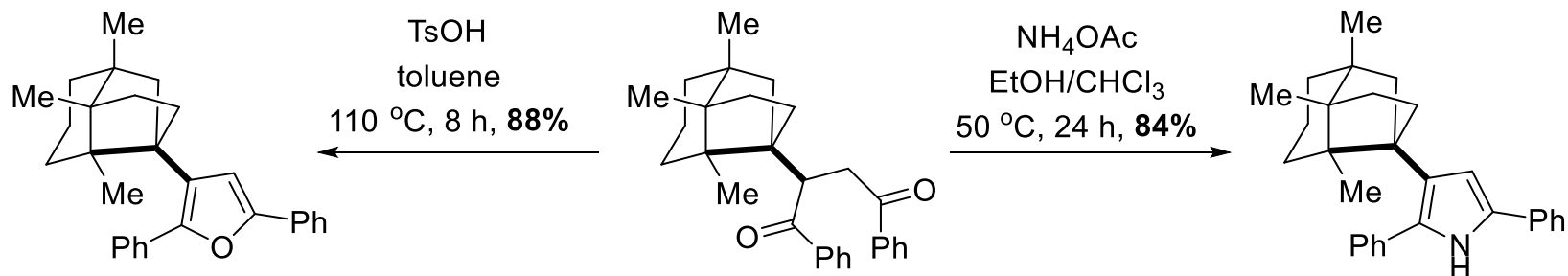


potentially explosive!!
keep in solution <5°C

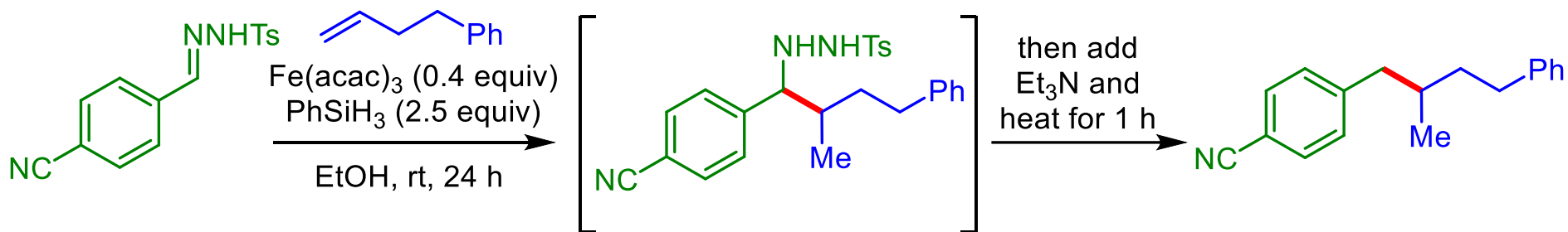
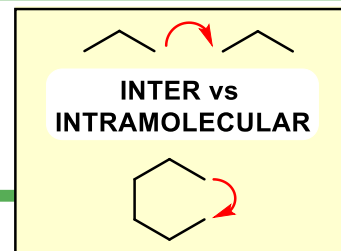
Síntesi de compostos semblants a l'adamantà substituïts mitjançant una reacció tàndem MHAT



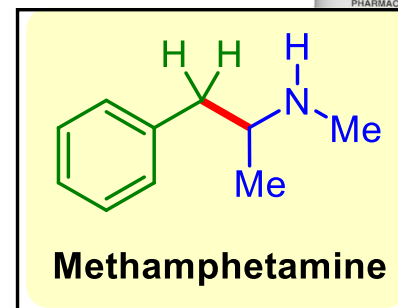
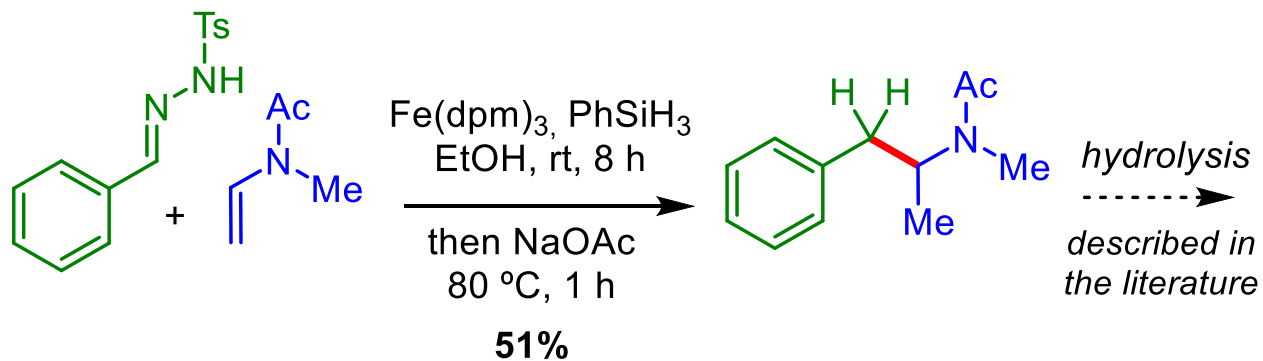
Síntesi d'heterocicles que incorporen un bloc de construcció d'amantadina



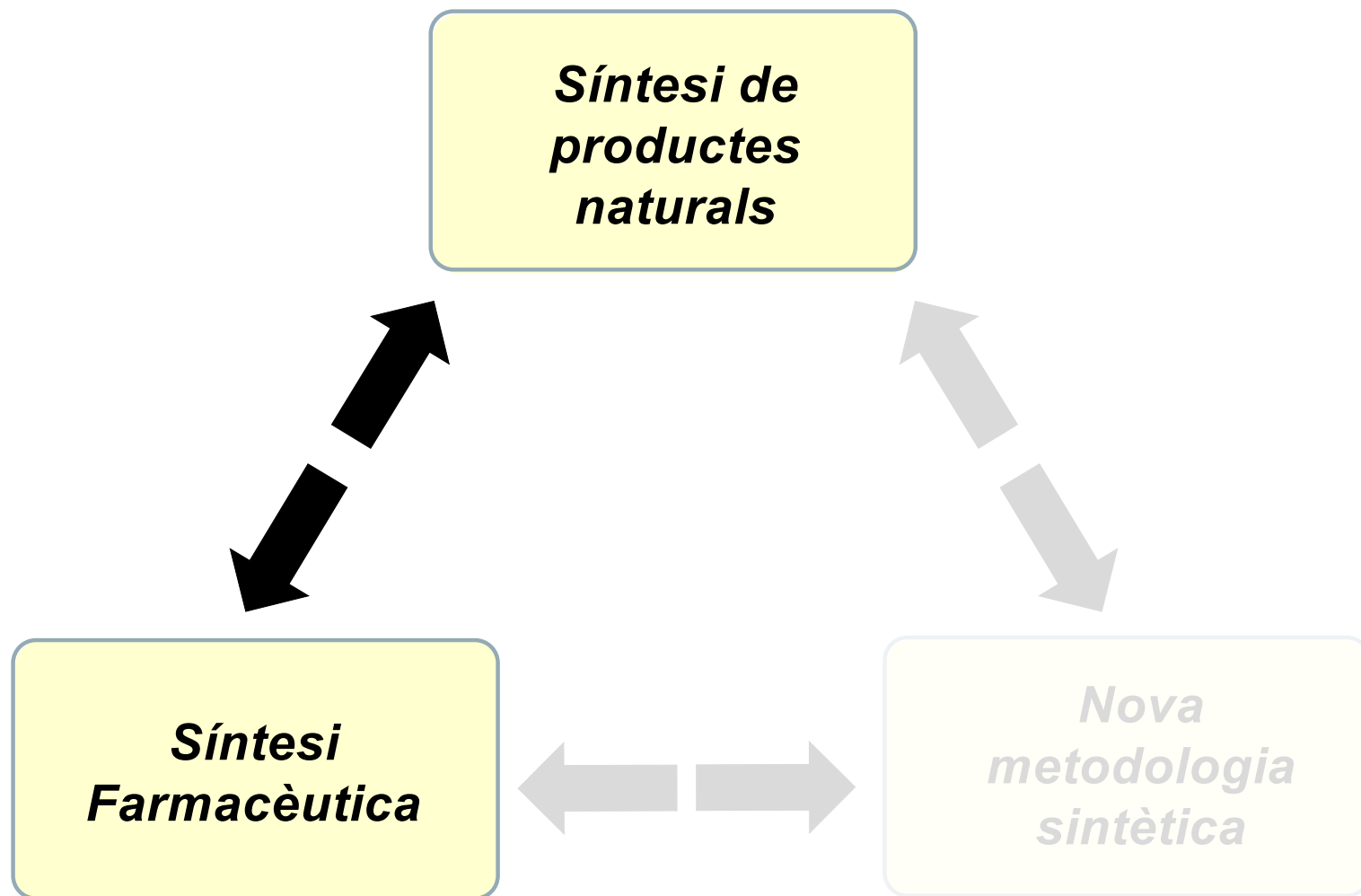
Acoblament MHAT intermolecular de tosilhidrazones



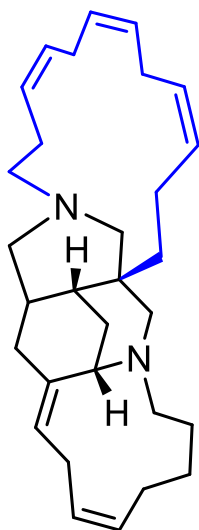
Application of the reaction. Formal Synthesis of Methamphetamine



Part 3: Convertir productes naturals complexos en productes farmacèutics



Reducció de la complexitat

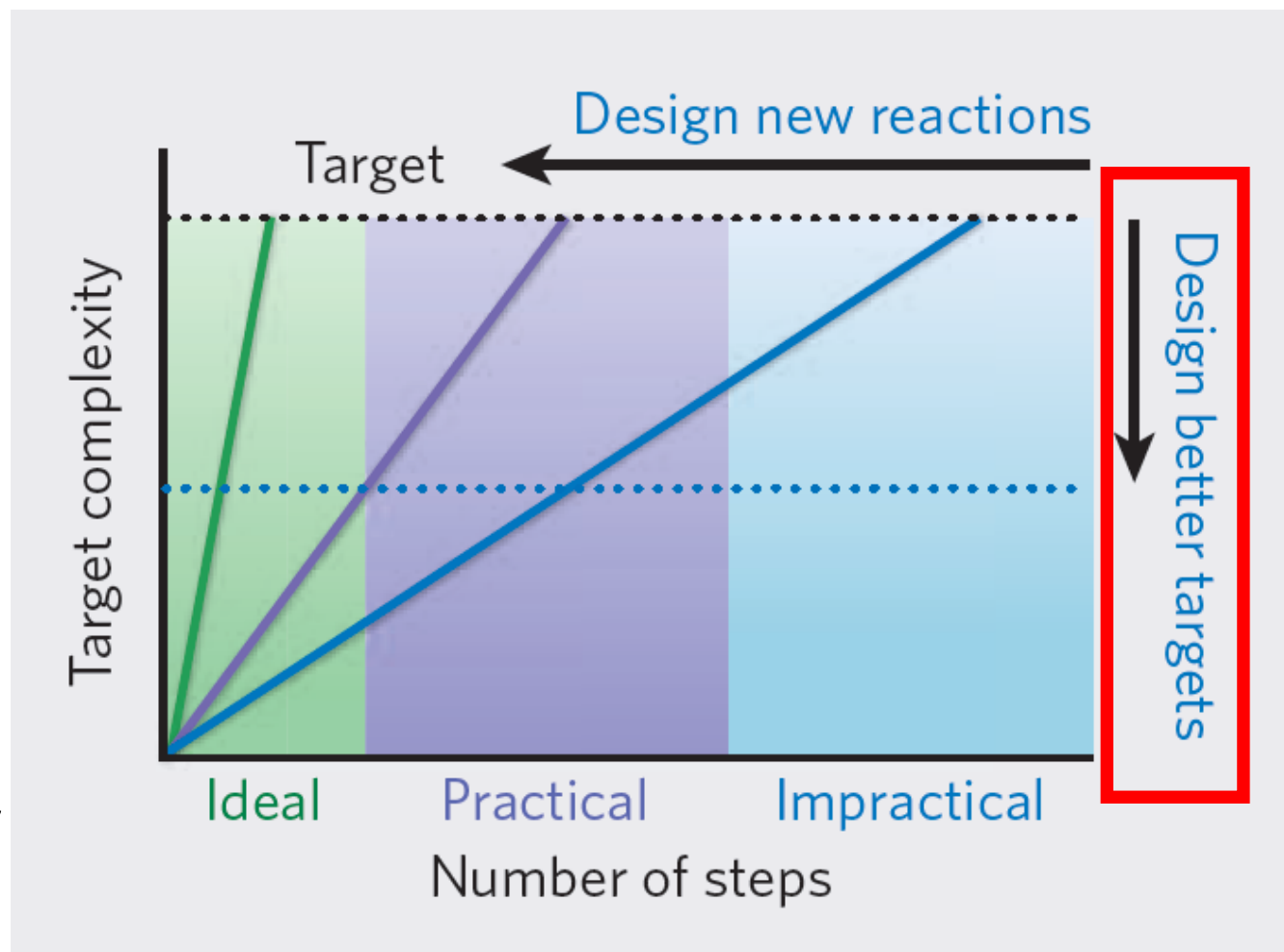


Madangamine A

(Activitat contra el càncer)

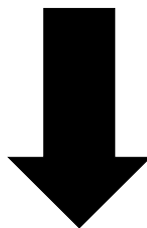
baixa biodisponibilitat

Massa complex per sintetitzar
amb quantitat

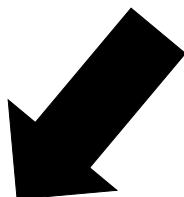


Eliminar la funcionalitat pot simplificar molt la síntesi

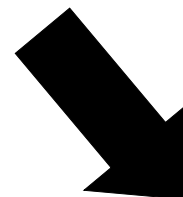
**Una part important d'un producte natural
pot ser innecessari per a la seva activitat biològica.**



Elimina les funcionalitats innecessàries



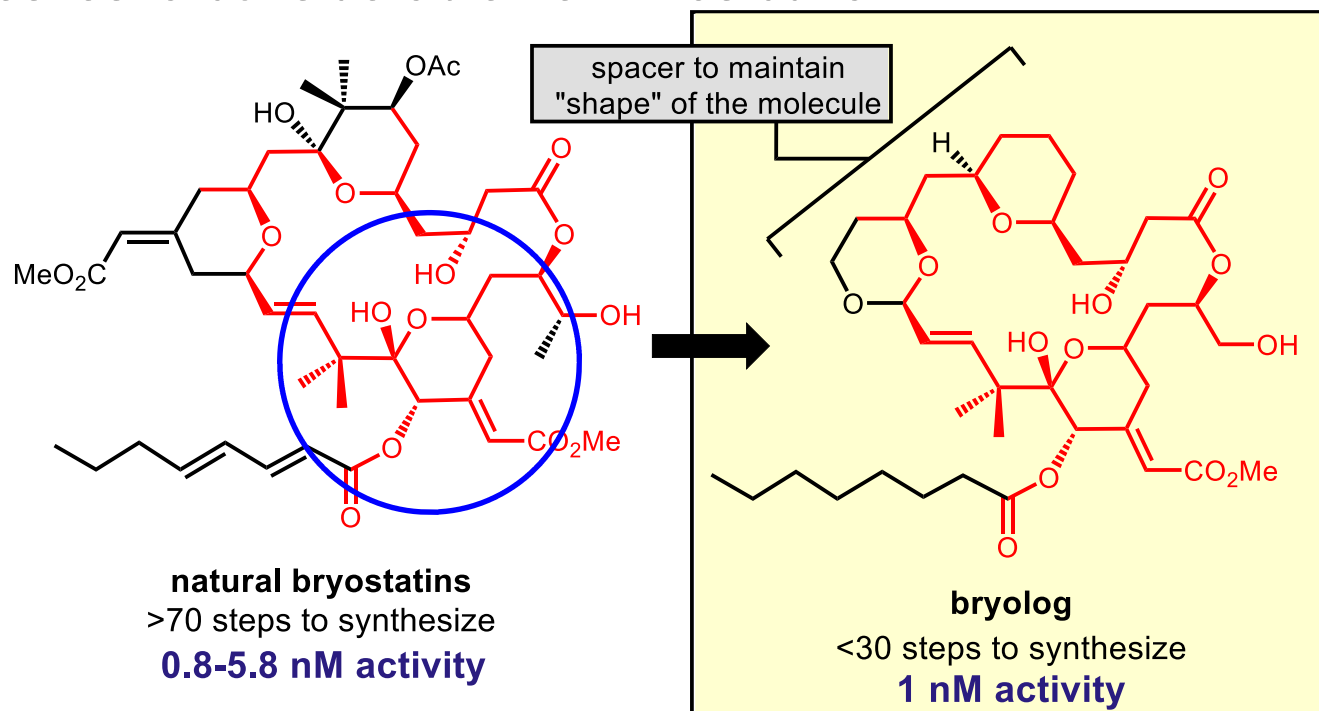
síntesi simplificada



Anàlegs més actius?

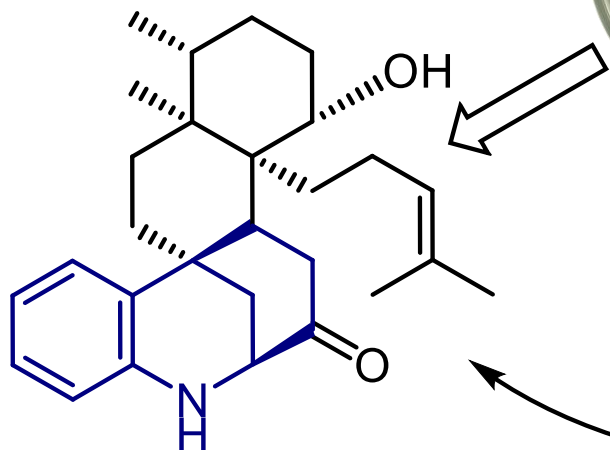
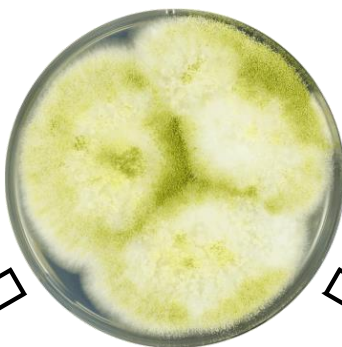
Exemple: de briostatina a "briolog"

- En el compost anticancerígen briostatina només el fragment sud interacciona amb la diana.
- En eliminar la funcionalitat innecessària del fragment nord de la síntesi es fa considerablement més curta



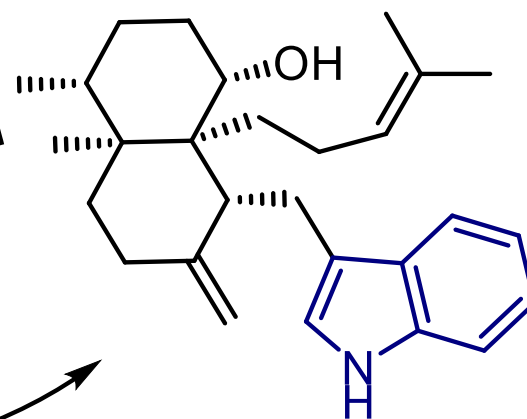
Tornant a la síntesi de l'aspernomina

*Isolated from
Aspergillus species*



aspernomina

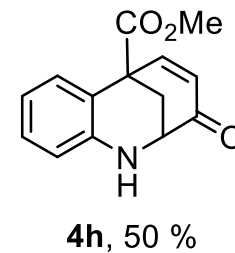
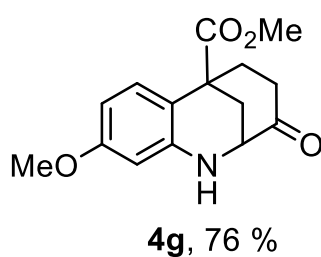
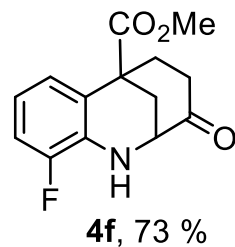
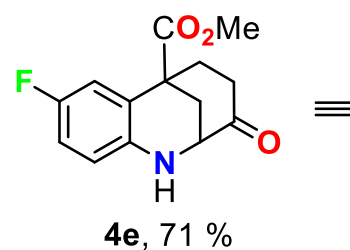
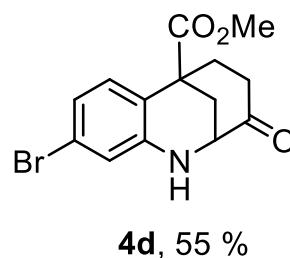
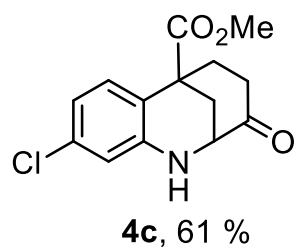
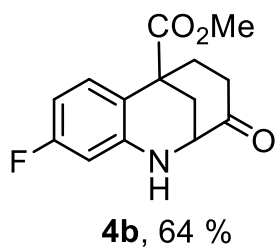
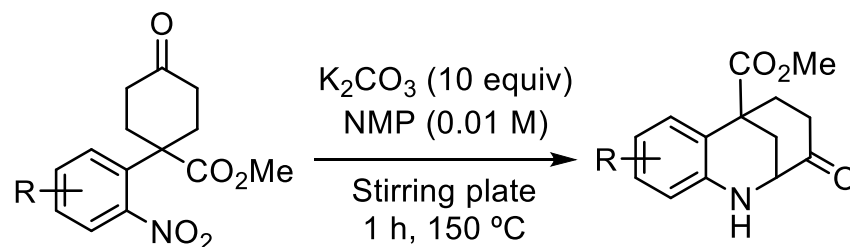
Activitat contra diverses
línies de cèl·lules tumorals
humanes



anominina

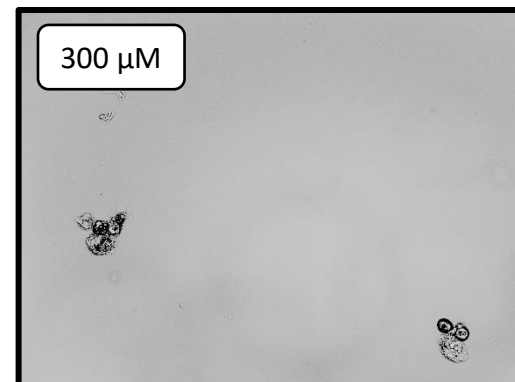
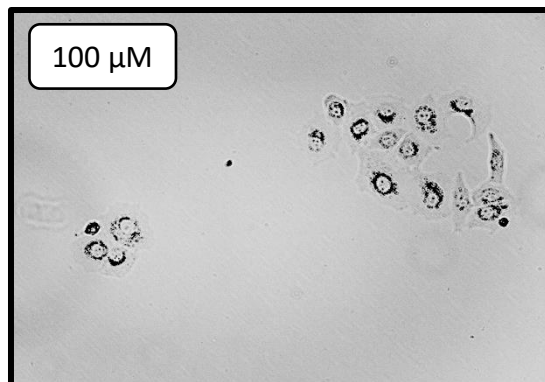
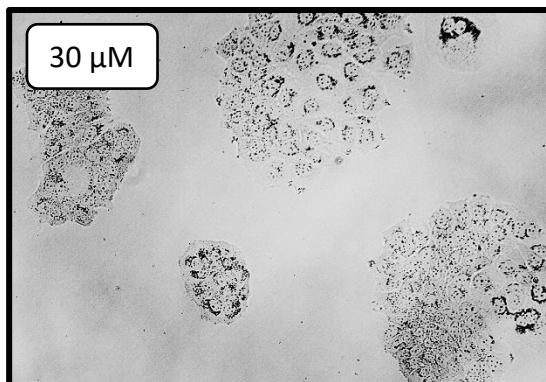
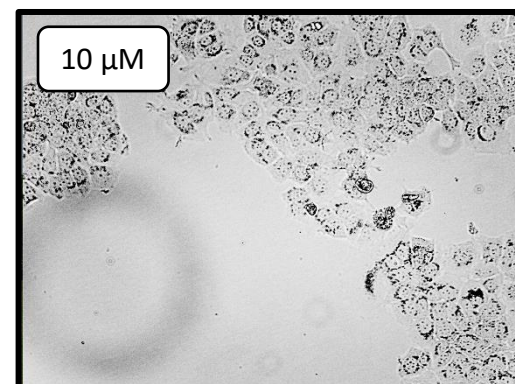
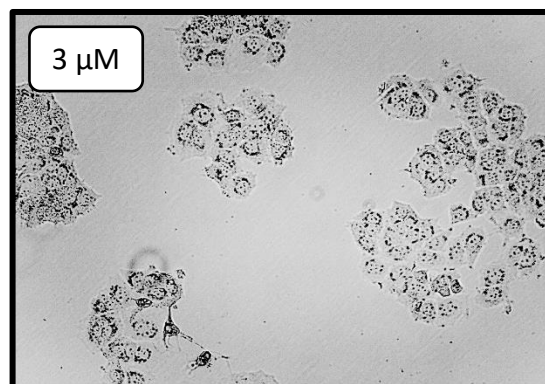
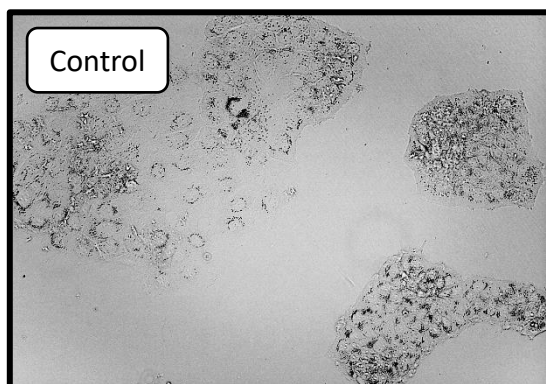
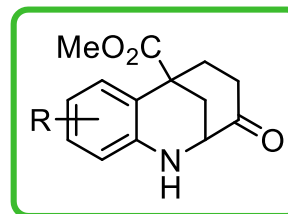
Propietats insecticides
Sense activitat contra el càncer

Síntesi del nucli aromàtic de l'aspernomina

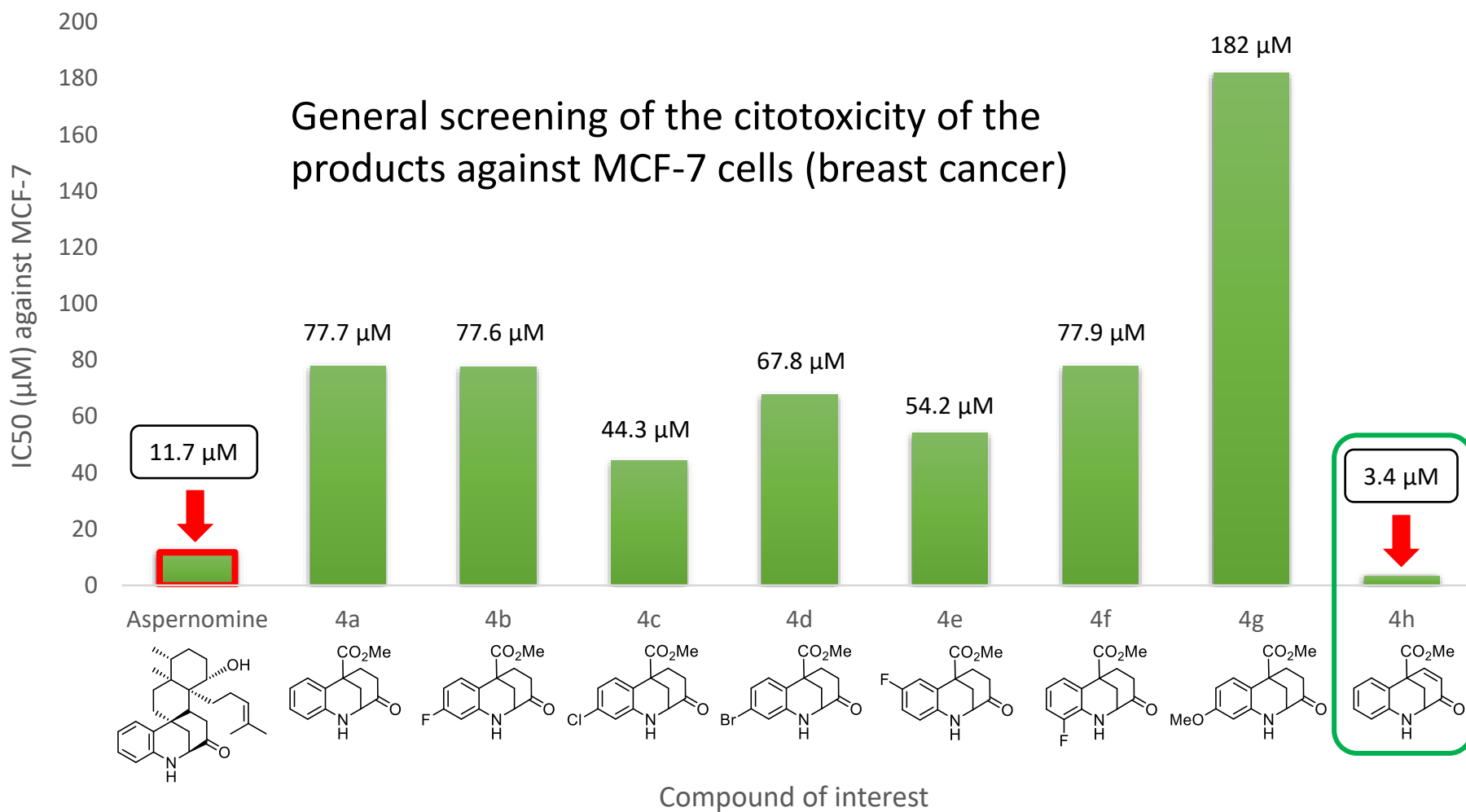


Avaluació de les propietats biològiques

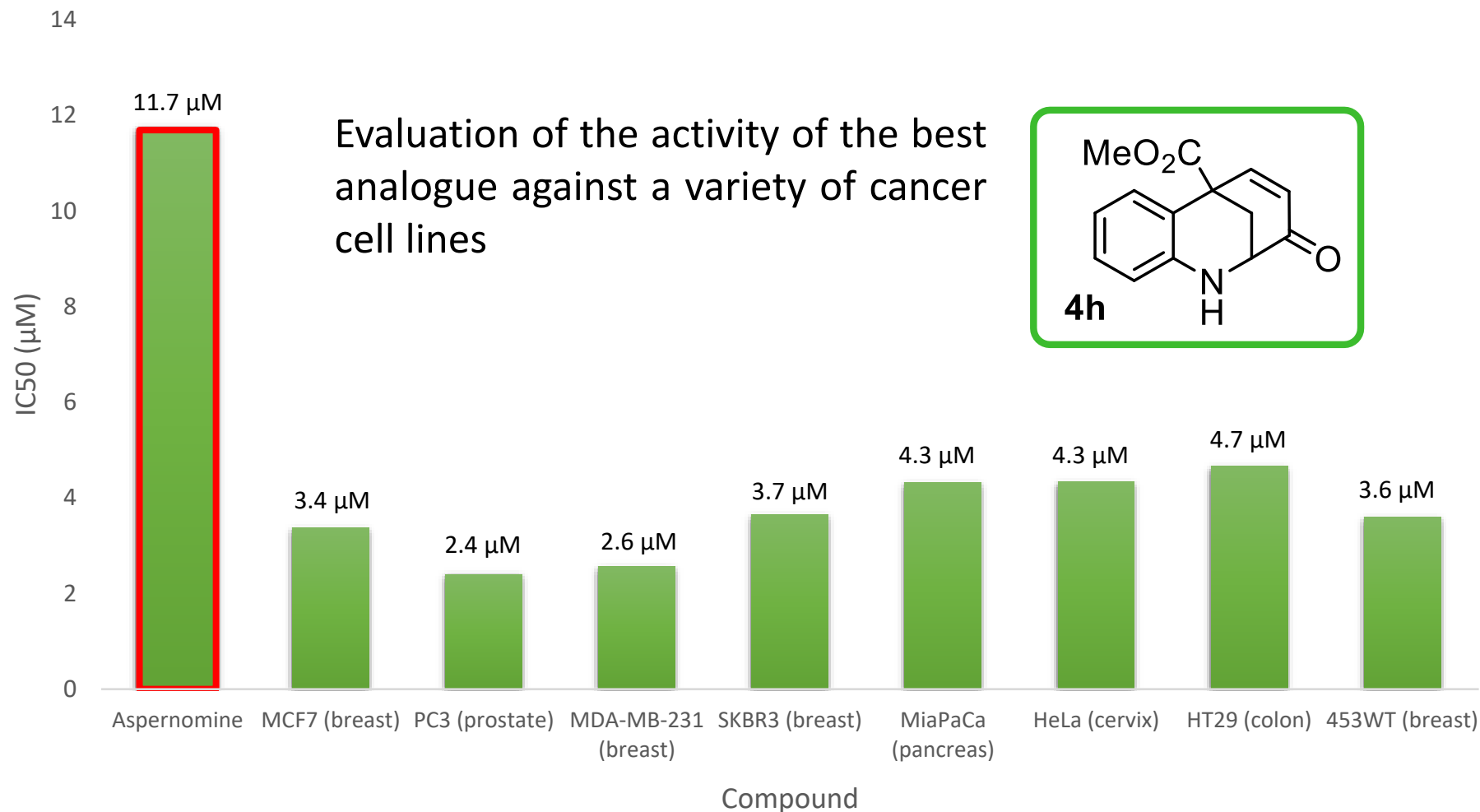
“Screening” general de la citotoxicitat dels productes contra cèl·lules MCF-7 (càncer de mama)



Avaluació de les propietats biològiques

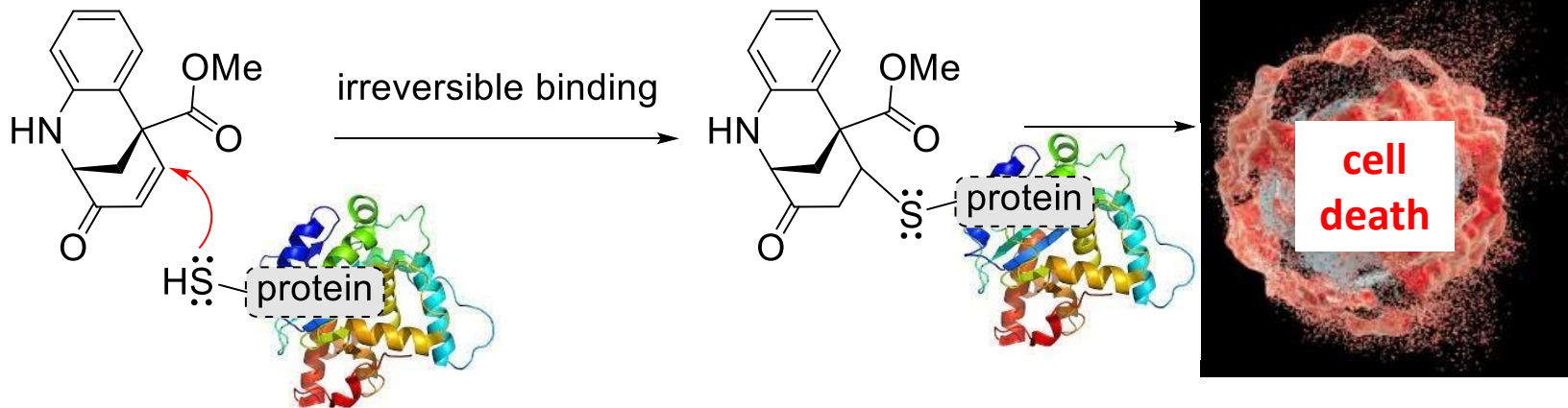


Avaluació de les propietats biològiques



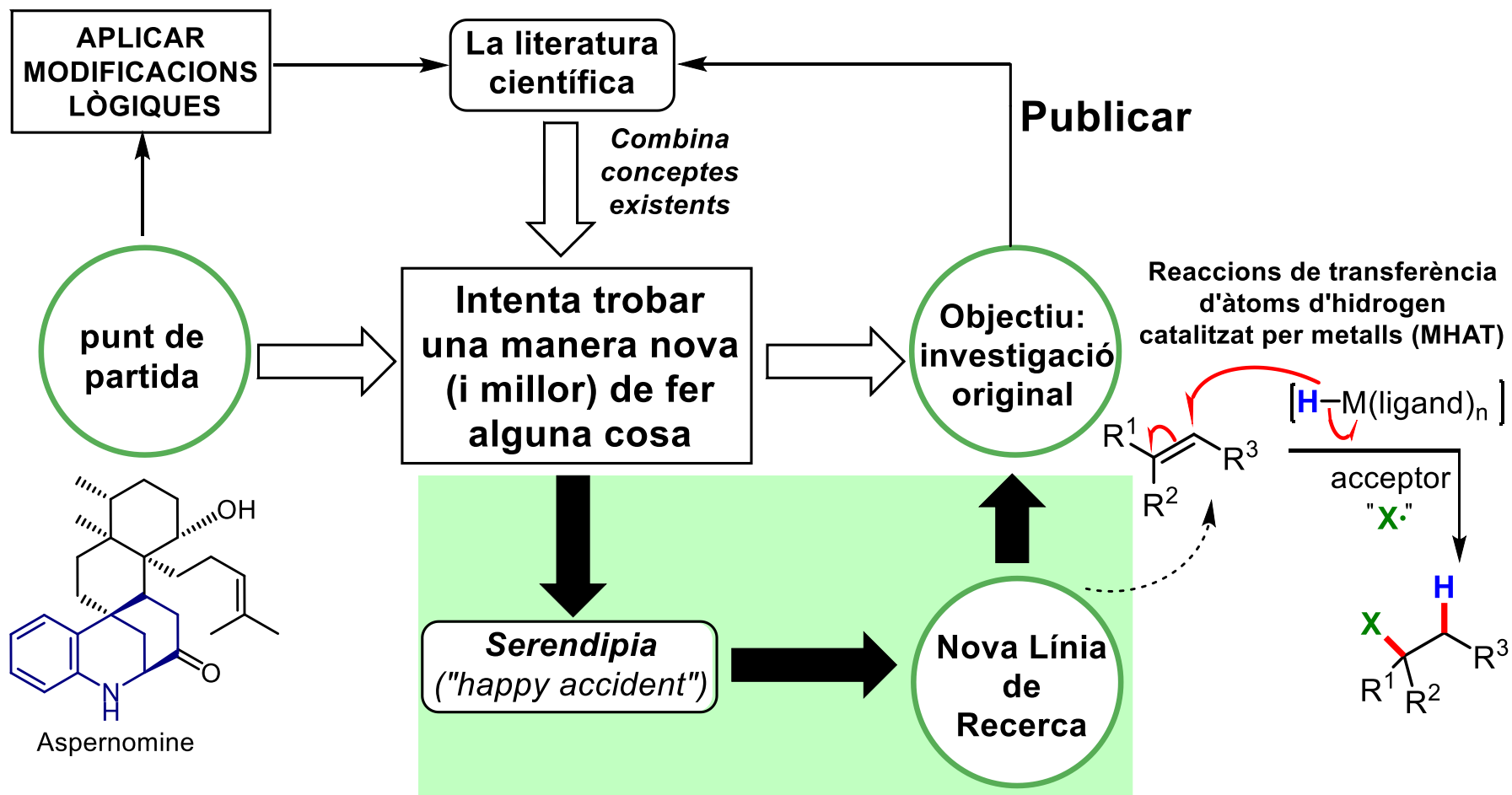
Rodríguez, L. G; Delgado, A.; Ciudad, C. J.; Noé, V.; Bonjoch, J; Bradshaw, B.
J. Org. Chem., **2022**, *87*, 15693.

Mecanisme d'actuació proposat



Conclusions

Una visió general del desenvolupament de projectes de recerca



Agraïments

- Prof. Josep Bonjoch

Grant number: PID2022-139257NB-I00

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- Jordi Puig (MHAT)
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- Mar Saladrigas (MHAT)
- Claudio Parra (Organocatalysis)
- Caroline Bosch (Total Synthesis)
- Gisela Saborit (Total Synthesis)
- Carlos Luque Corredera (Organocatalysis & Total Synthesis)
- Gorka Exterbarria (Organocatalysis & Total Synthesis)

Estudiants de Màster

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- Xavier Bravo (Functionalization of Heterocycles)
- Wilson Perugachi (MHAT)
- Guillhem Loren (MHAT)



Proves biològiques

- Ana Delgado
- Carlos J. Ciudad
- Véronique Noé