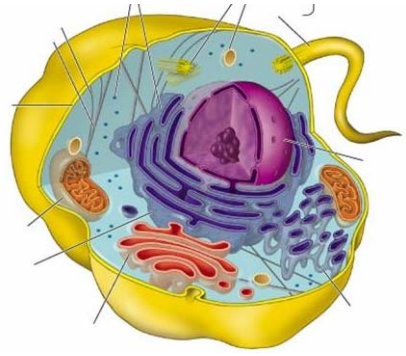
Chemical Research Center
of the Hungarian Academy of Sciences

Paradigmaváltás az aszimmetrikus kémia területén: Organokatalízis

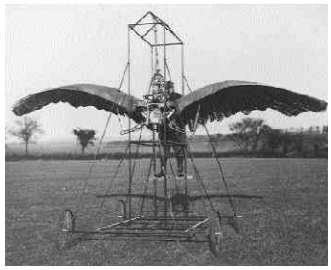
Soós Tibor

A biomimetikus megközelítés alkalmazása szintetikus módszerek fejlesztésben



1. Katalízis
2. Fázisjelölés

Na de hogyan?



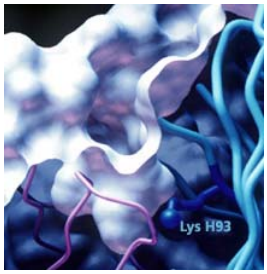
1. Aszimmetrikus bifunkcionális organokatalízis

2. Fluoros kémia – új fázisjelölés

Organokatalízis

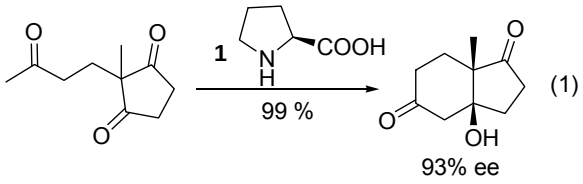
- Új szintetikus megközelítés a szerves kémiában. Kisméretű szerves molekulák alkalmazása katalizátorokként. Környezetkímélő megközelítés.

- Egyensúly az aktivitás és szelektivitás között.



Néhány összefoglaló az organokatalízisről: a, Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*, Wiley-VCH: New York, **2005**. b, Dalkó, P. I.; Moissan L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138-5175. c, Gaunt, M. J.; Johnsson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8-27. d, *Enantioselective Organocatalysis*, (Ed. Dalkó, P. I.), Wiley-VCH, **2007**.

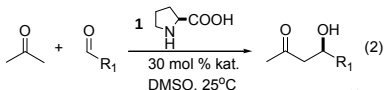
A kezdet



(1)

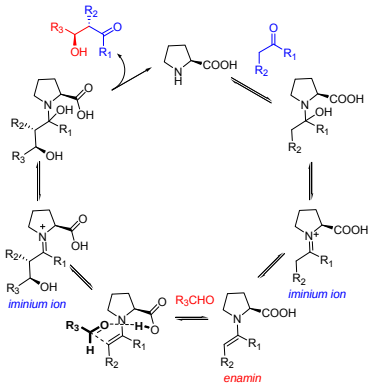
Hajós-Parrish-Eder-Sauer-Wichert
1971

A forradalom kezdete

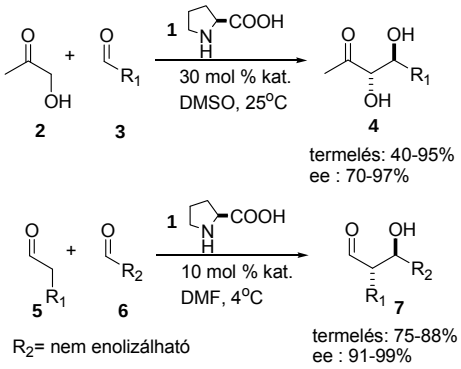


(2)

List, B.; Lerner, R. A.; Barbas III, C. F. *J. Am. Chem. Soc.* **2000**, *122*, 2395-2396.



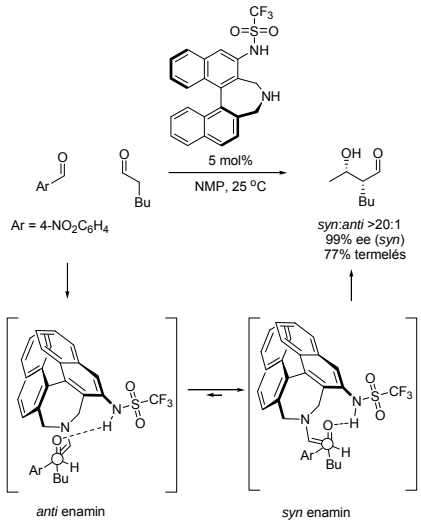
Az prolin katalízis kiterjesztése



R_2= nem enolizálható

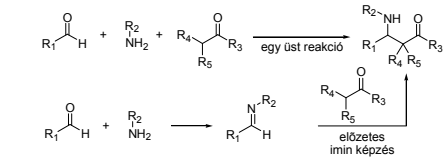
anti-aldol

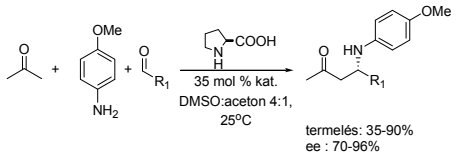
A syn szelektív katalízis



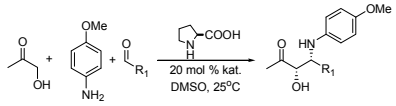
Maruoka

Mannich reakciók



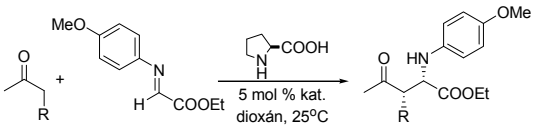


termelés: 35-90%
ee : 70-96%



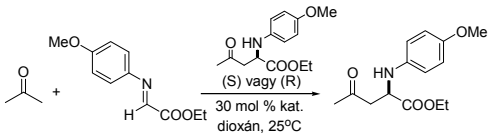
termelés: 92%
dr (*syn*/*anti*) 20:1
ee : >99% ee

Mannich reakciók



termelés: 57-81%
dr (*syn*/*anti*) 3:1 - 19:1
ee : 93-99% ee

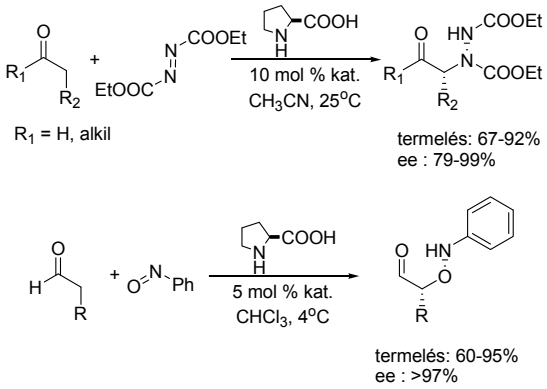
Barbas



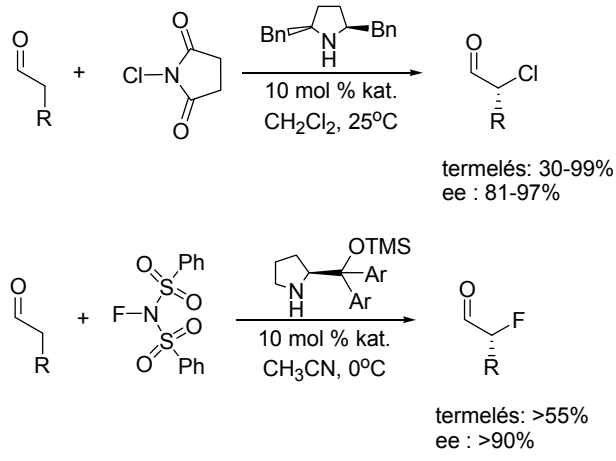
ee : 94% ee

Tsogoeva

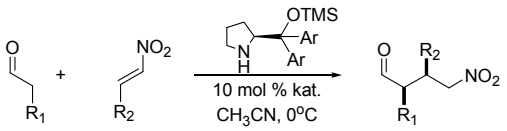
Az énamin katalízis kiterjesztése



Az énamin katalízis kiterjesztése

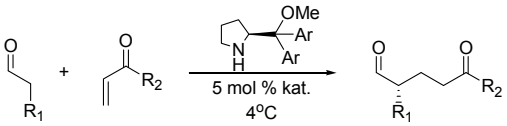


Az énamin katalízis kiterjesztése



R_2 = aril, alkil

termelés: 52-85%
ee : 99%

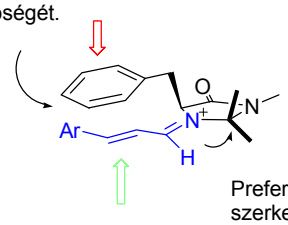


R_1, R_2 : alkil

termelés:60-87%
ee : 95-99%

McMillan kémiája

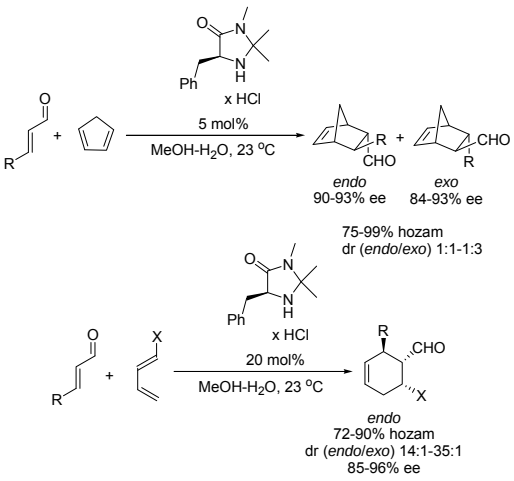
Feltételezhetõ
π-π kölcsönhatás,
amely korlátozza
az olefin megközelít-
hetõségét.



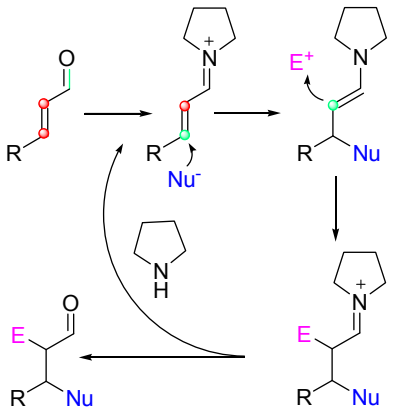
Az olefin kötés
megközelíthetõségének
iránya

Preferált iminium ion
szerkezet, minimális
Van der Waals
kölcsönhatás

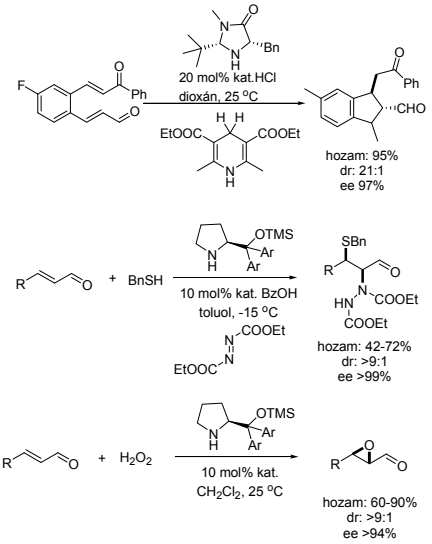
McMillan kémiája



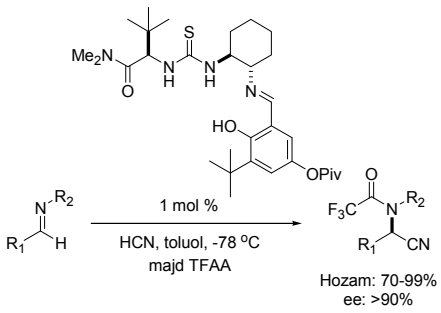
Iminium-énamin tandem katalízis



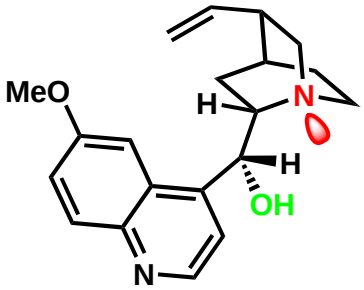
Iminium-énamin tandem katalízis



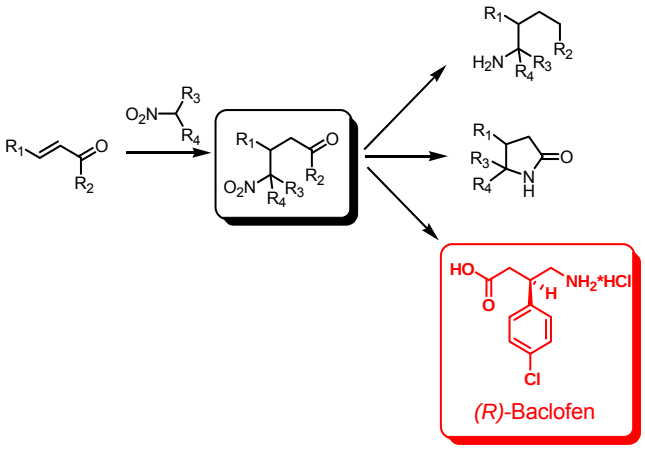
Királis H-híd donor katalízis



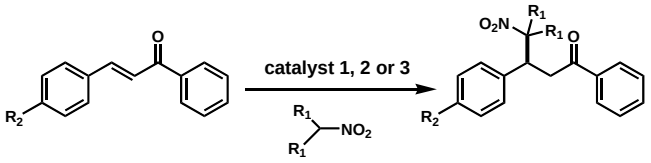
Királis bifunkcionális H-hídas organokatalizátorok

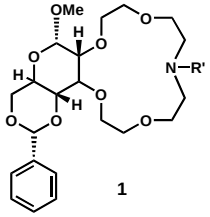


Nitroalkánok konjugált addíciója



A model reakció

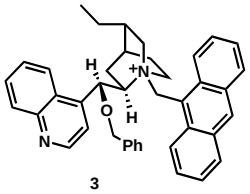




1

LaK_3tris((*R*))-binapthoxide

2



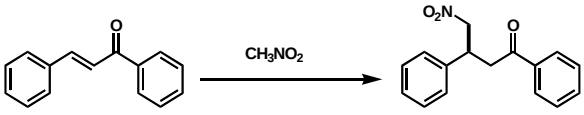
3

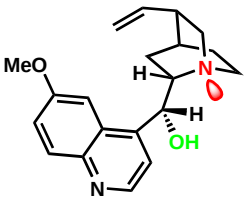
R_1=Me, R_2=H, NaOtBu, 33 mol% cat., ee=10-60%
Bakó, P.; Szöllősy, A.; Bombicz, P.; Tőke, L. *Synlett*, **1997**, 291

R_1=H, R_2=H,Cl 20 mol% cat., -20 °C, ee=88-97%
Funabashi, K.; Saida, Y.; Kanai, M.; Arai, T.; Sasai, H.; Shibasaki, M. *Tetrahedron Lett.* **1998**, *39*, 7557

R_1=H, R_2=Cl, CsF, 10 mol% cat., -40 °C, ee=70%
E. J. Corey; F.-Y. Zhang, *Org. Lett.* **2000**, *26*, 42.

Lehetséges-e a katalízis szervetlen sók nélkül?



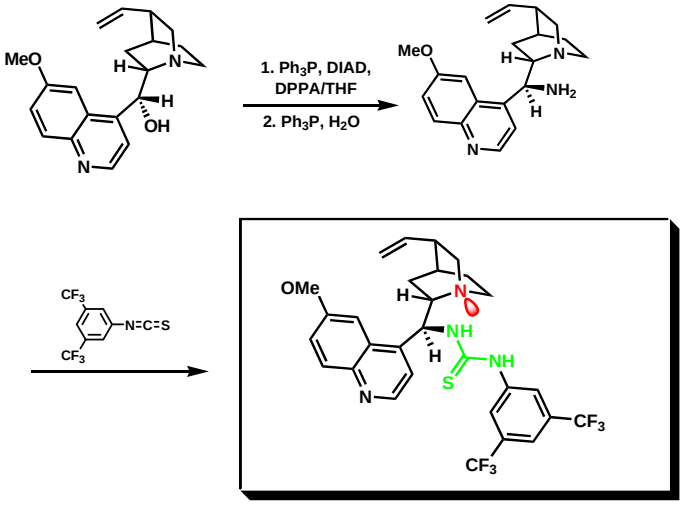


Hans Wynberg

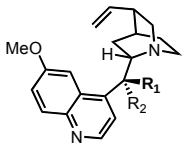
Yamada et.al. *J. Org. Chem.* **1988**, *53*, 1157.

400 MPa

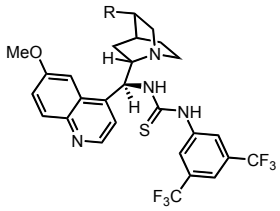
A katalizátor szintézise



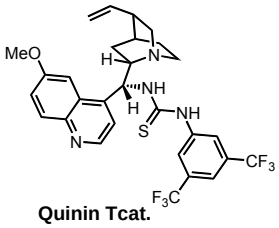
Organokatalizátor jelöltek



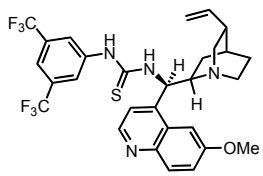
R_1 = H, R_2 =OH, **Quinine**
R_1 = OH, R_2 = H, **EpiQuinine**



R = $CH{=}CH_2$, **EpiQuinine Tcat.**
R = CH_2CH_3, **DIHYDRO EpiQuinine Tcat.**

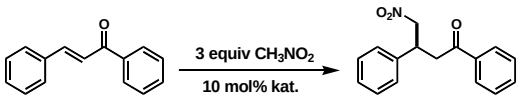


Quinin Tcat.

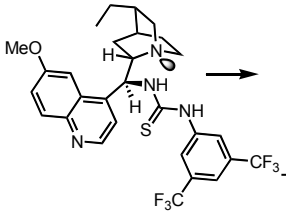


EpiQuinidine TCat.

A katalizátorok vizsgálata

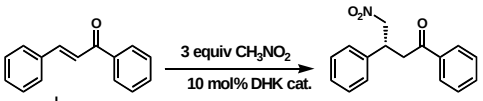


katalizátor	time [h]	% yield	% ee
Kinin	99	4	42 (S)
Epikinin	99	0	-
Epikinin Tkat.	99	71	95 (R)
Dihidro Epikinin Tcat.	**99**	**93**	**96 (R)**
Kinin Tcat.	99	0	-
Epikinidine Tcat.	99	59	86 (S)



DHK kat.

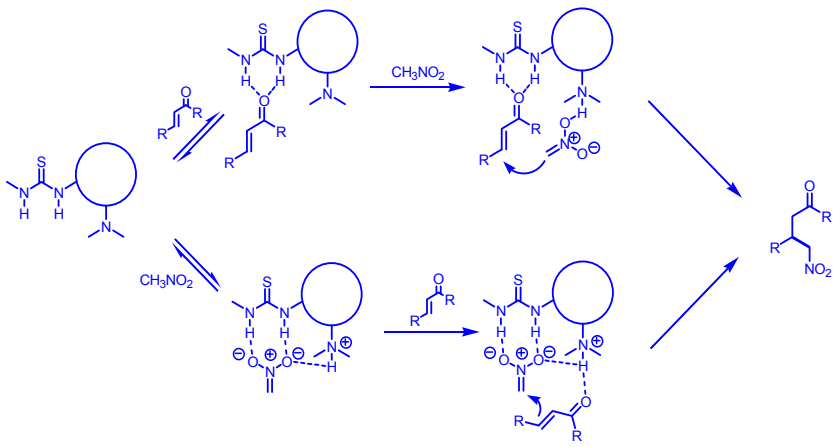
Kísérleti körülmények hatása



Solvent	T [°C]	Cat. [mol %]	t [h]	% Yield	% ee
Toluene	25	10	110	94	96
CH_2Cl_2	25	10	110	84	93
THF	25	10	110	38	95
MeOH	25	10	110	31	67
-	25	10	48	95	94
-	50	5	19	97	91
-	50	3	27	95	91
-	50	2	45	94	92
-	50	1	91	94	93
-	**50**	**0.5**	**171**	**82**	**94**
-	75	5	10	94	90
-	100	5	5	68	85

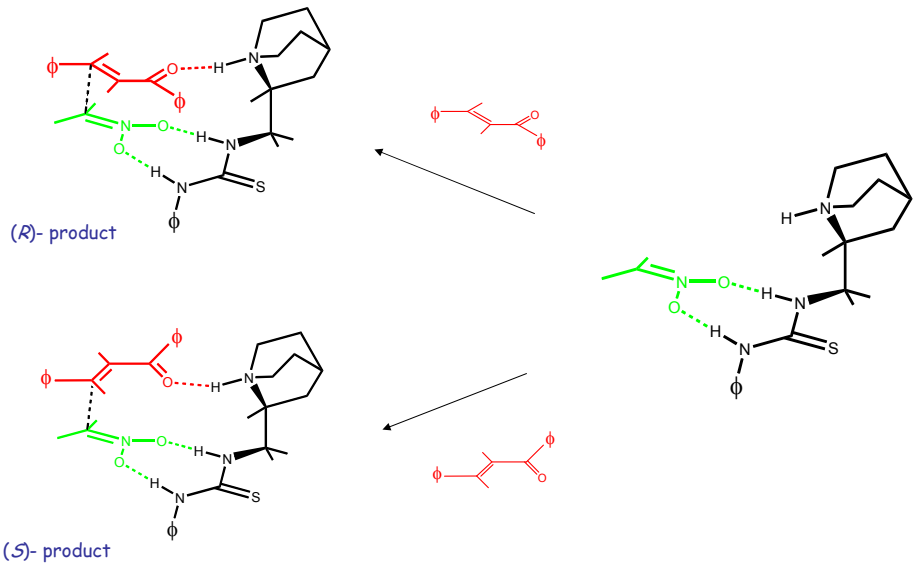
B. Vakulya, Sz. Varga, A. Csámpai, T. Soós *Org. Lett.* **2005**, *7*, 1967.

Mechanizmus javaslat



$v = k$[katalizátor][kalkon][nitrometán]

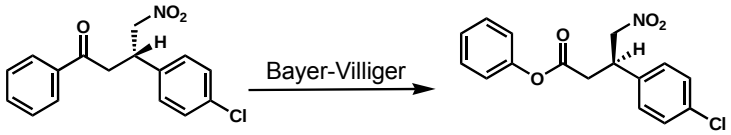
Az enantioszelektivitás értelmezése



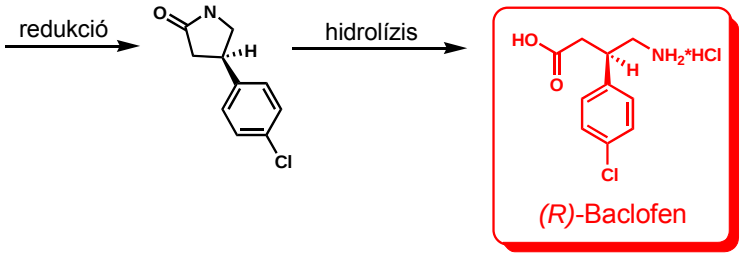
(*R*)- product

(*S*)- product

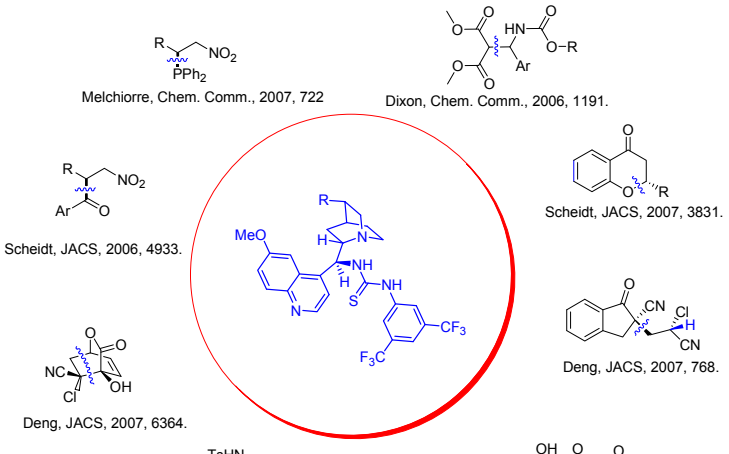
Alkalmazás



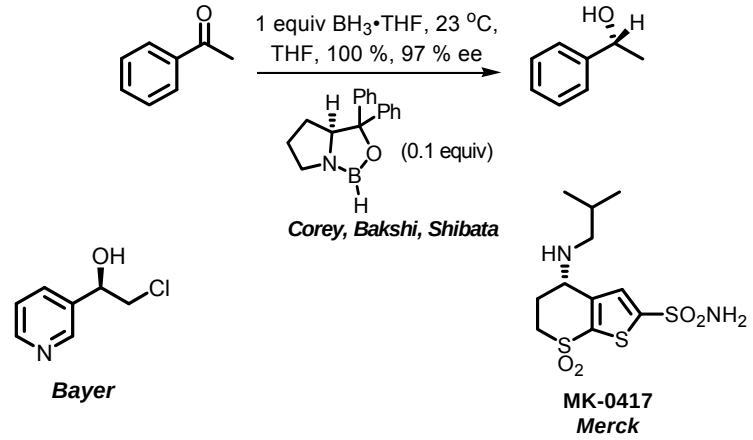
E. G. Corey: *ee* = 70 %
Soós - Vakulya: *ee* = 95 %



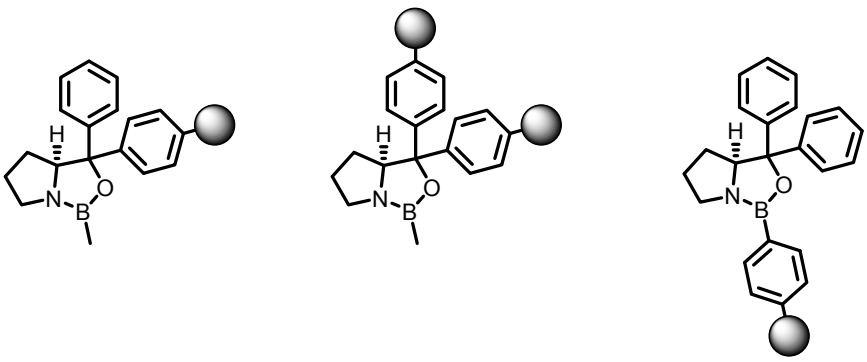
További alkalmazások



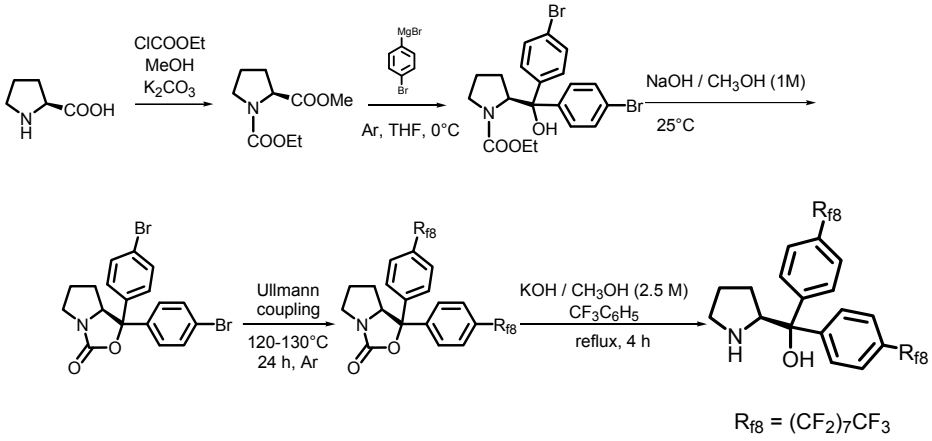
A CBS redukció



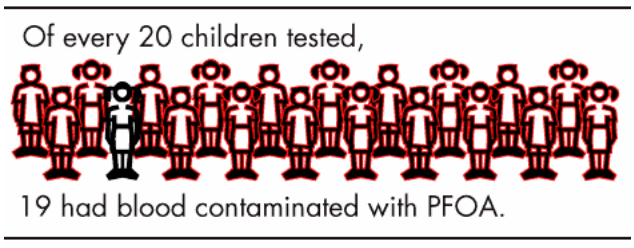
Visszaforgatható CBS katalizátorok



Az első generációs fluoros prolinol szintézise



A fluoros kémia kihívásai



A fluoros kémia kihívásai

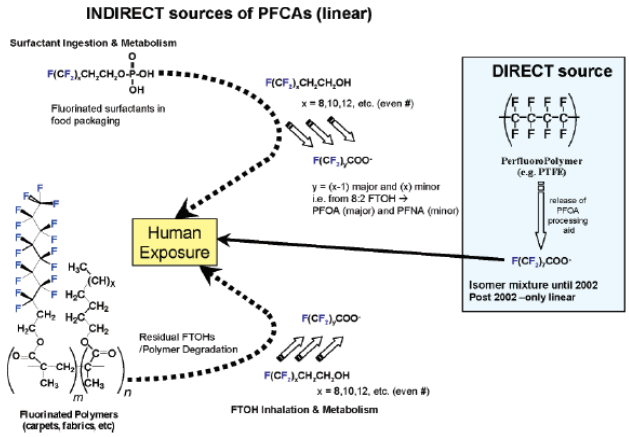


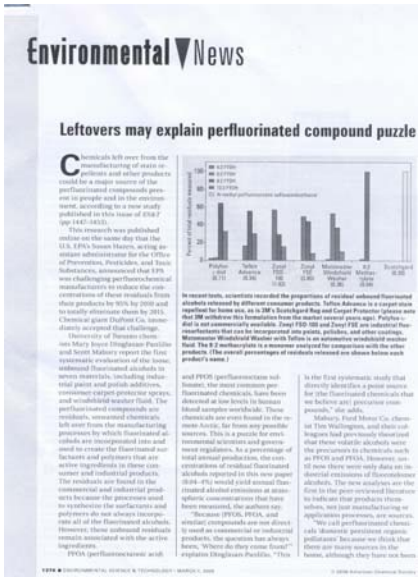
FIGURE 3. Potential indirect and direct sources of PFCAs in humans. Indirect sources may include fluorotelomer phosphates and volatile fluorotelomer precursors (such as FTOHs). Fluorotelomer phosphate surfactants, used in food packaging treatments, may be ingested and undergo hydrolysis or via enzymes produce FTOHs. Fluorinated polymers may yield FTOHs, arising from residual content or polymer degradation, which would be inhaled (46). Subsequent FTOH metabolism leads to even PFCA (major product) and odd PFCA (minor product). All of these are expected to be linear. Direct sources of PFCAs (PFOA and PFNA) are those used as a processing aid in polymers such as PTFE and PVDF. ECF PFOA, a source of branched isomers was employed until 2002 for this purpose. Post 2002 linear telomer PFOA was used. Telomer PFNA has also been manufactured and employed for polymer treatment (15).

A fluoros kémia kihívásai

(pp 1447–1453).

This research was published online on the same day that the U.S. EPA's Susan Hazen, acting assistant administrator for the Office of Prevention, Pesticides, and Toxic Substances, announced that EPA was challenging perfluorochemical manufacturers to reduce the concentrations of these residuals from their products by 95% by 2010 and to totally eliminate them by 2015. Chemical giant DuPont Co. immediately accepted that challenge.

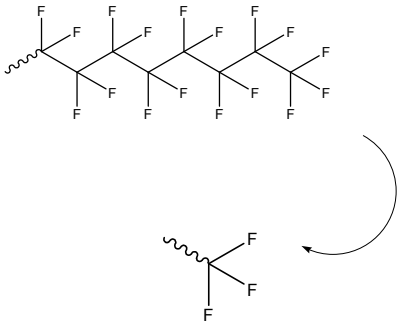
University of Toronto chemists Mary Joyce Dinglasan-Panlilio and Scott Mabury report the first systematic evaluation of the loose, unbound fluorinated alcohols in seven materials, including industrial paint and polish additives, consumer carpet-protector sprays, and windshield washer fluid. The perfluorinated compounds are residuals, unwanted chemicals left over from the manufacturing processes by which fluorinated alcohols are incorporated into and used to create the fluorinated surfactants and polymers that are



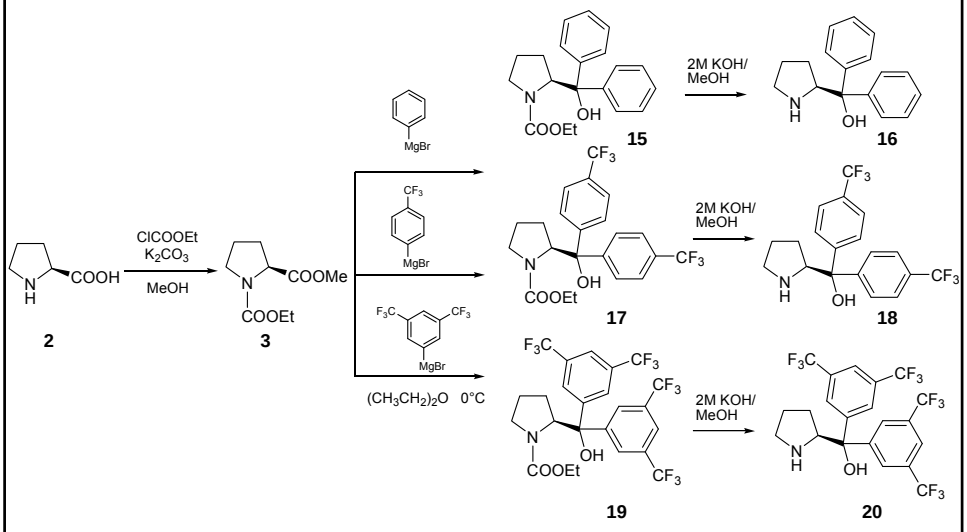
Environmental News

Leftovers may explain perfluorinated compound puzzle

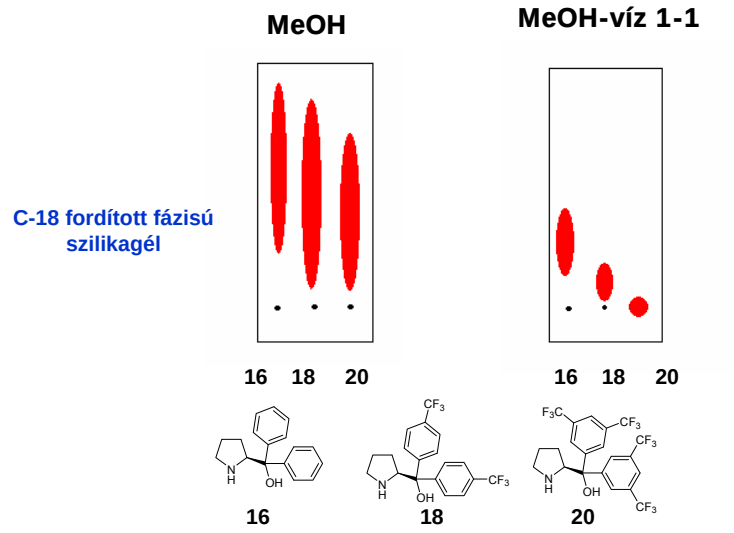
Egy radikális megközelítés



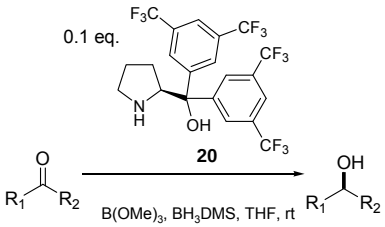
Prolinolok szintézise

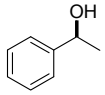


Alkalmazható a CF_3 csoport fázisjelölésre?

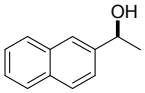


A CF_3 jelölt CBS katalizátor alkalmazása





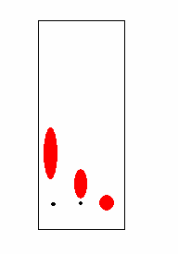
ee = 95 %



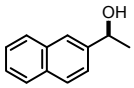
ee = 94 %

ee = 98 %

Szilárd fázisú extrakciók

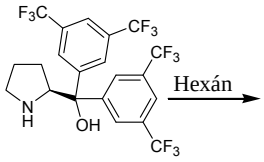


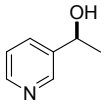
MeOH-víz 1-1

Adszorbens			
γ- Al_2O_3/FSPE	85.2 %	-	-
γ- Al_2O_3/DSC18	96.2 %	-	-
α- Al_2O_3/DSC18	96.9 %	>99.9 %	>99.9 %
α- Al_2O_3/ α- Al_2O_3	94.6 %	99.9 %	97.3 %

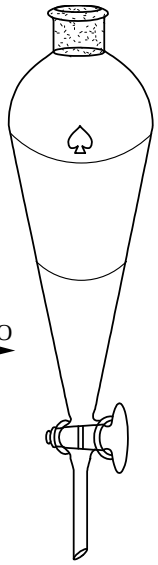
- 1. Fluoros fordított fázisú szilikagél 22$/g
- 2. C-18 fordított fázisú szilikagél 3$/g
- 3. Korrund, **1 $/kg**

Folyadék fázisú extrakció





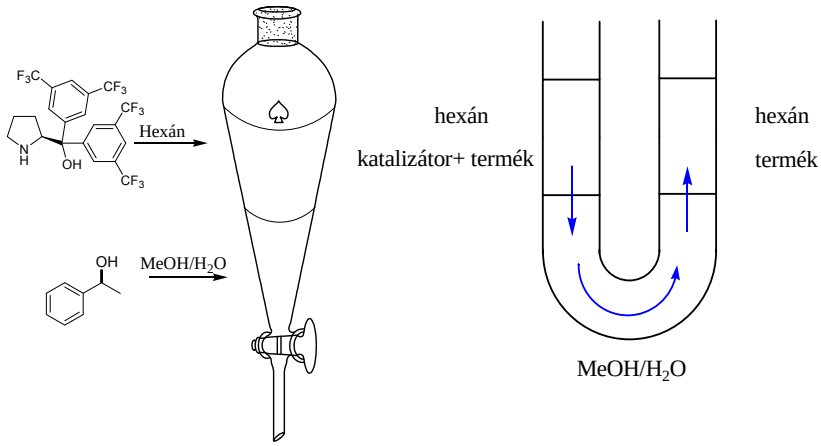
$MeCN/H_2O$



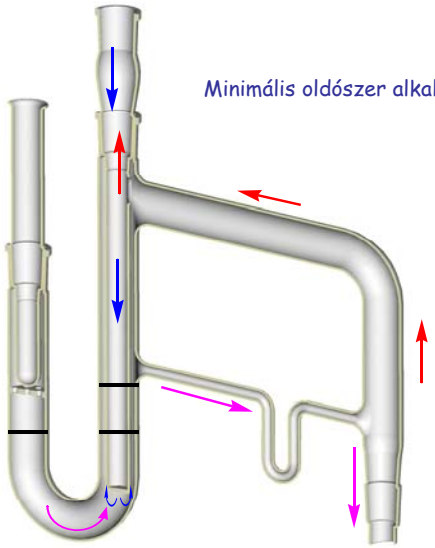
1315 mg katalizátor

1308 mg, 99.5 % hatékonyság

Folyadék fázisú extrakció

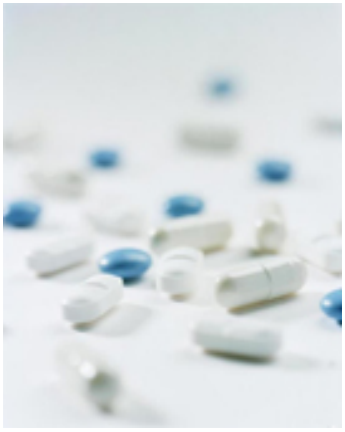


Folyamatos folyadék membrános extraktor



Összefoglalás

1. Cinkona alkaloidokból bifunkcionális tiokarbamid organokatalizátorok szintézisét valósítottuk meg, majd Michael addíciós reakciókban alkalmaztuk sikerrel.
2. Egy új fluoros módszert dolgoztunk ki, amely a CF_3 fázisjelölő csoportok felhasználására épül. Továbbá egy folyamatos üzemű folyadék fázisú extraktort fejlesztettünk ki.



Köszönetnyilvánítás

Vakulya Benedek (organokatalízis)

Dalicsek Zoltán (fluoros CBS módszer)

Varga Szilárd (organokatalízis)

Köszönetnyilvánítás

Csámpai Antal

Pollreisz Ferenc

Gömöry Ágnes

Payer Károly

PápaiImre

Schubert Gábor

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