



## Na de hogyan?



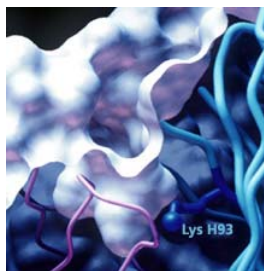
1. Aszimmetrikus bifunkcionális organokatalízis



2. Fluoros kémia - új fázisjelölés

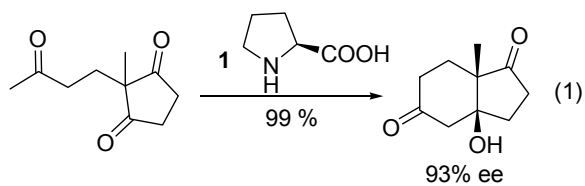
## Organokatalízis

- Új szintetikus megközelítés a szerves kémiában. Kisméretű szerves molekulák alkalmazása katalizátorokként. Környezetkímélő megközelítés.
- Egyensúly az aktivitás és szelektivitás között.



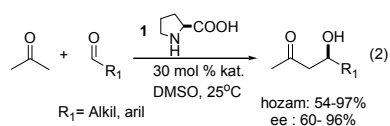
Néhány összefoglaló az organokatalízisről: a, Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*, Wiley-VCH: New York, **2005**. b, Dalkó, P. I.; Moissan L. *Angew. Chem. Int. Ed.* **2004**, *43*, 5138-5175. c, Gaunt, M. J.; Johnsson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**,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

## A kezdet

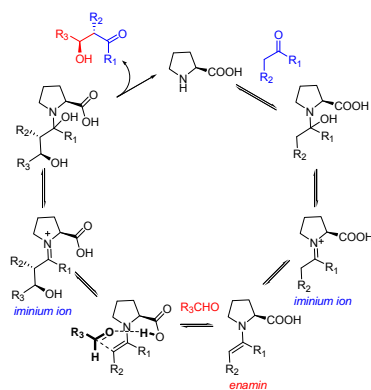


Hajós-Parrish-Eder-Sauer-Wichert  
1971

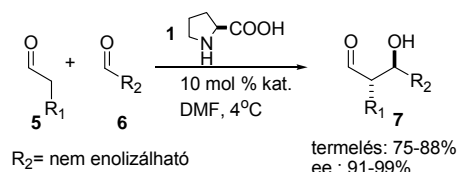
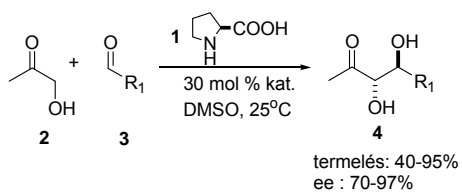
## A forradalom kezdete



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

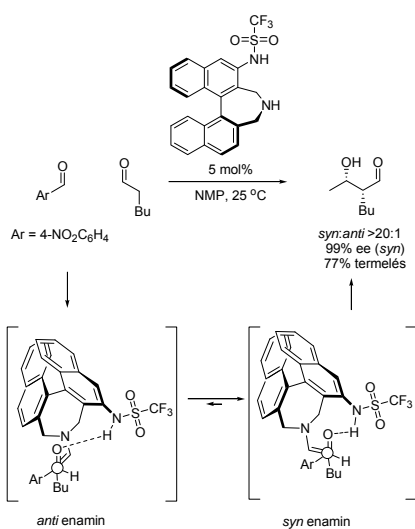


## Az prolin katalízis kiterjesztése



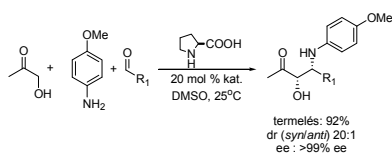
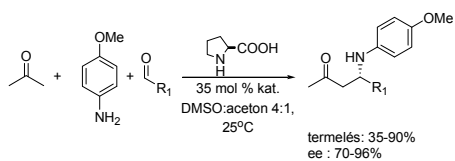
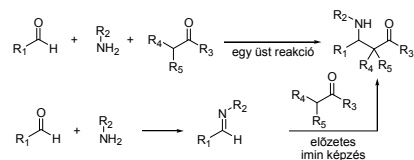
anti-aldol

## A syn szelektív katalízis

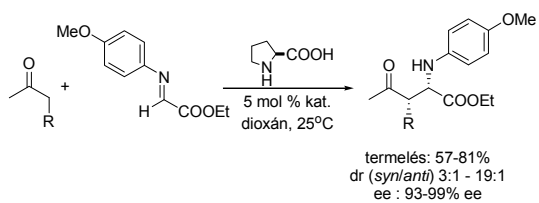


Maruoka

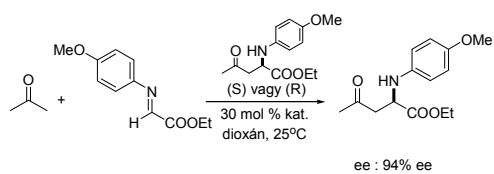
## Mannich reakciók



## Mannich reakciók

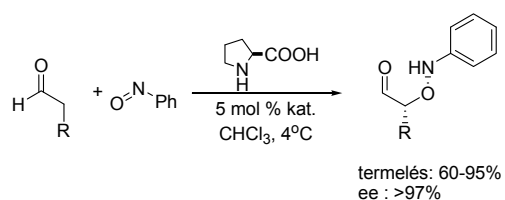
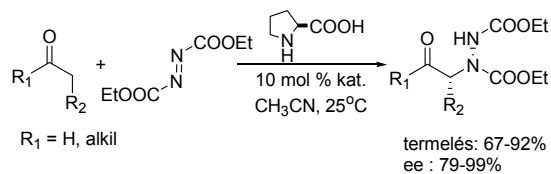


Barbas

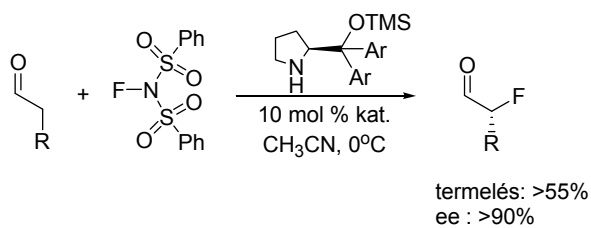
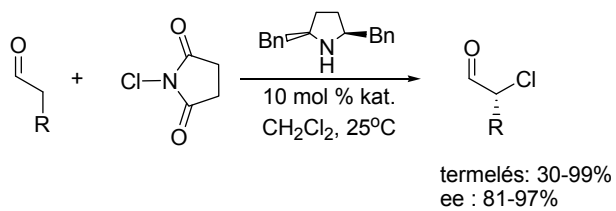


Tsogoeva

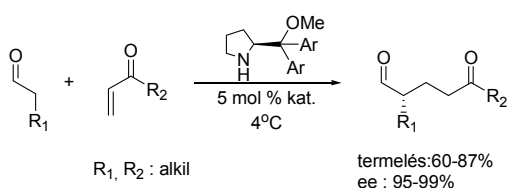
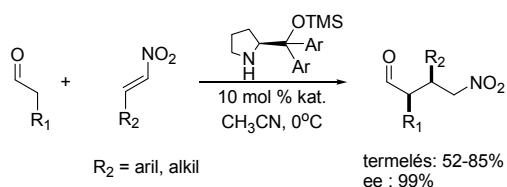
## Az énamin katalízis kiterjesztése



## Az énamin katalízis kiterjesztése

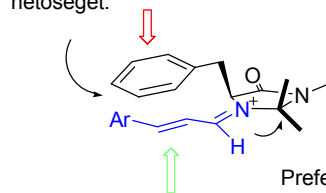


## Az énamin katalízis kiterjesztése



## McMillan kémiaja

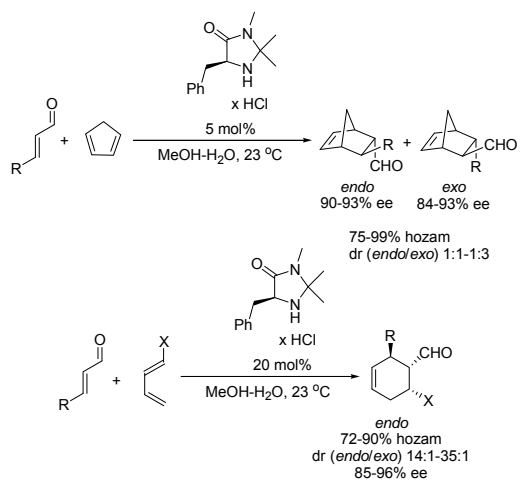
Feltételezhető  
 $\pi$ - $\pi$  kölcsönhatás,  
 amely korlátozza  
 az olefin megközelít-  
 hetőségét.



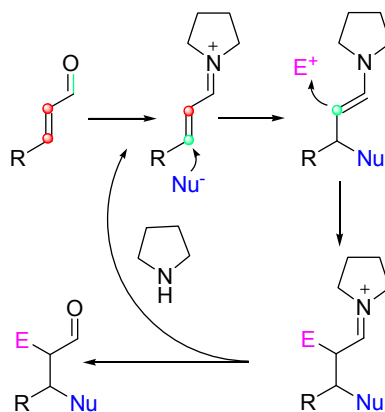
Az olefin kötés  
 megközelíthetőségének  
 iránya

Preferált iminium ion  
 szerkezet, minimális  
 Van der Waals  
 kölcsönhatás

## McMillan kémiaja

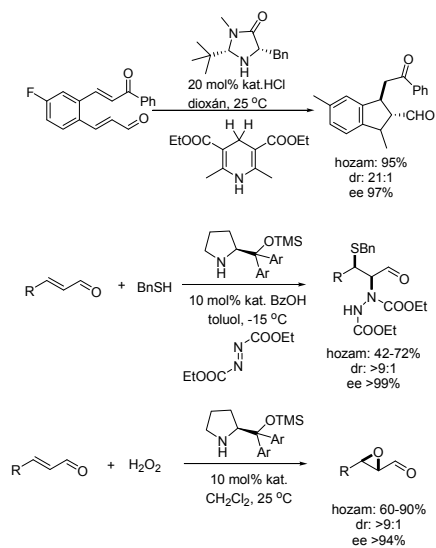


## Iminium-énamin tandem katalízis

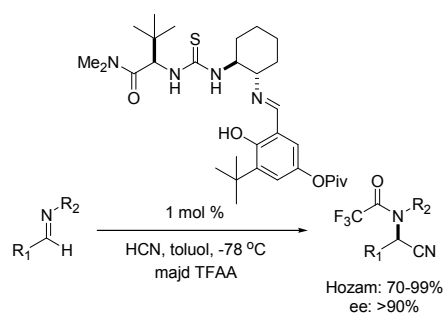




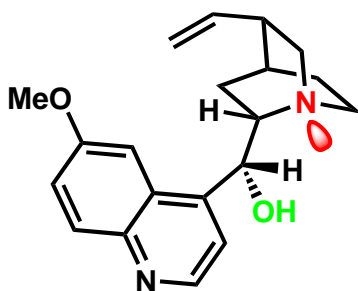
## Iminium-énamin tandem katalízis



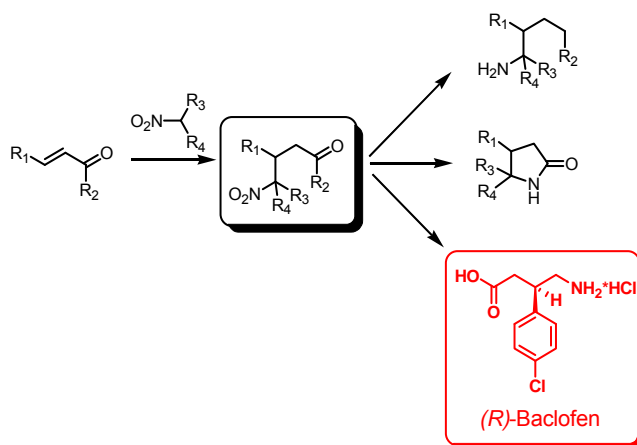
## Királis H-híd donor katalízis



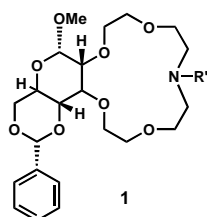
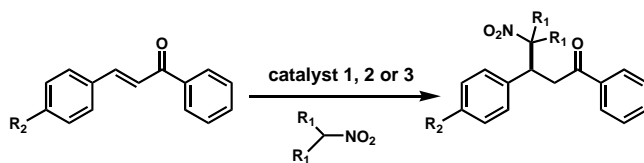
## Királis bifunkcionális H-hidas organokatalizátorok



## Nitroalkánok konjugált addíciója



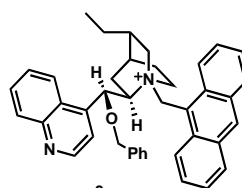
## A model reakció



$R_1 = \text{Me}$ ,  $R_2 = \text{H}$ , NaOtBu,  
33 mol% cat., ee=10-60%  
Bakó, P.; Szöllösy, A.; Bombicz, P.;  
Tóke, L. *Synlett*, 1997, 291

LaK<sub>3</sub>tris((R)-binaphthoxide

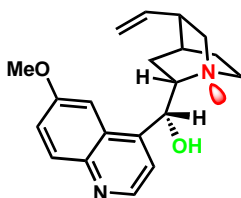
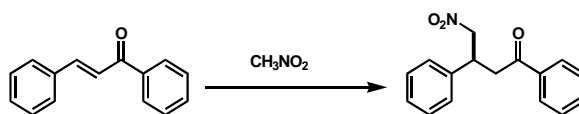
2



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

$R_1 = \text{H}$ ,  $R_2 = \text{H, Cl}$   
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

## Lehetséges-e a katalízis szervesen sók nélkül?

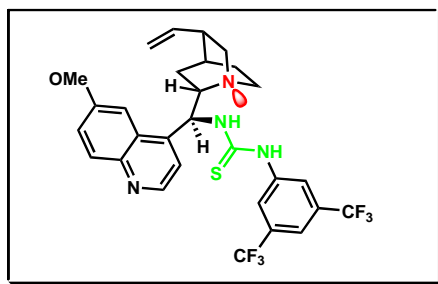
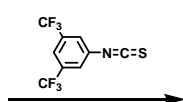
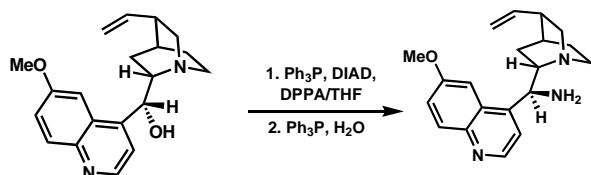


Hans Wynberg

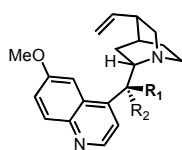
Yamada et.al. *J. Org. Chem.* 1988, 53, 1157.

400 MPa

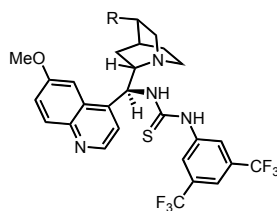
## A katalizátor szintézise



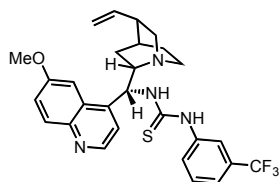
## Organokatalizátor jelöltek



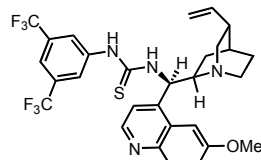
$\text{R}_1 = \text{H}$ ,  $\text{R}_2 = \text{OH}$ , **Quinine**  
 $\text{R}_1 = \text{OH}$ ,  $\text{R}_2 = \text{H}$ , **EpiQuinine**



$\text{R} = \text{CH}=\text{CH}_2$ , **EpiQuinine Tcat.**  
 $\text{R} = \text{CH}_2\text{CH}_3$ , **DIHYDRO EpiQuinine Tcat.**

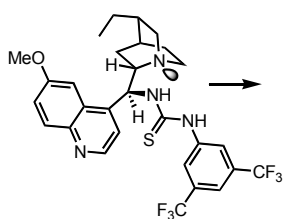
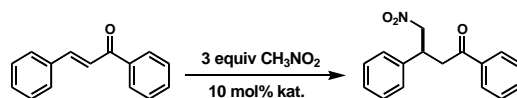


**Quinin Tcat.**



**EpiQuinidine Tcat.**

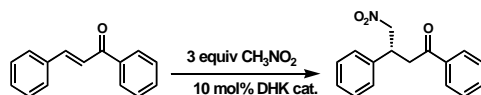
## A katalizátorok vizsgálata



DHK kat.

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

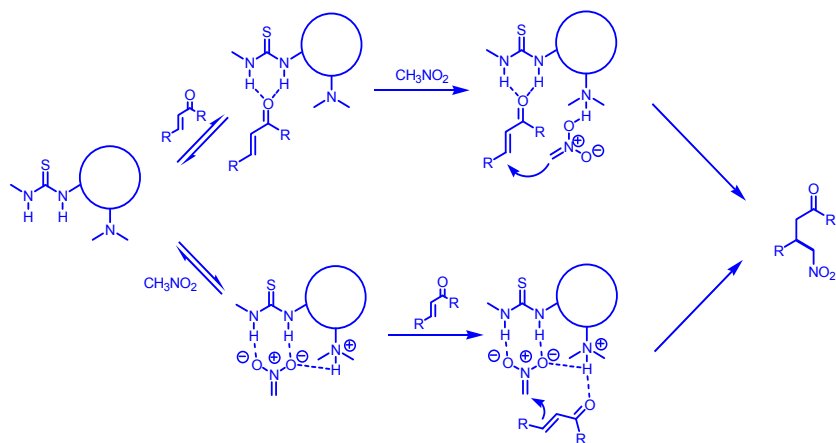
## Kísérleti körülmények hatása



Solvent	T [°C]	Cat. [mol %]	t [h]	% Yield	% ee
Toluene	25	10	110	94	96
CH <sub>2</sub> Cl <sub>2</sub>	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
-	<b>50</b>	<b>0.5</b>	<b>171</b>	<b>82</b>	<b>94</b>
-	75	5	10	94	90
-	100	5	5	68	85

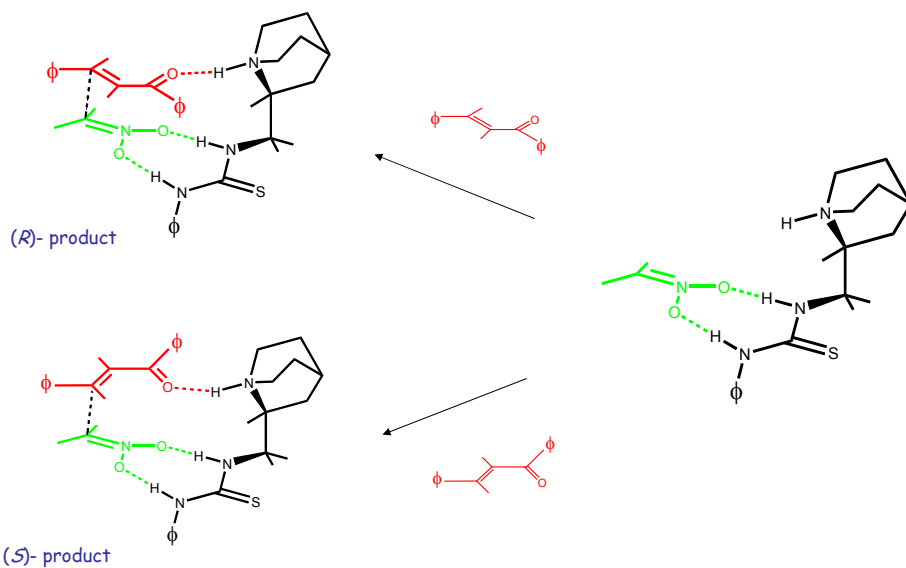
B. Vakulya, Sz. Varga, A. Csámpai, T. Soós *Org. Lett.* **2005**, 7, 1967.

## Mechanizmus javaslat

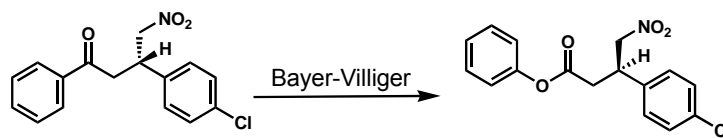


$$v = k[\text{katalizátor}][\text{kalkon}][\text{nitrometán}]$$

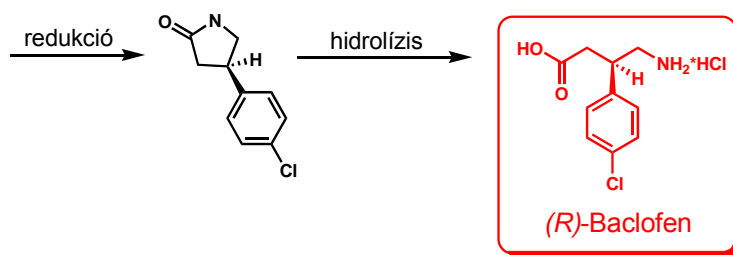
## Az enantioszelektivitás értelmezése



## Alkalmazás



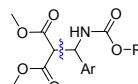
E. G. Corey: ee = 70 %  
Soós - Vakulya: ee = 95 %



## További alkalmazások



Melchiorre, Chem. Comm., 2007, 722



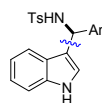
Dixon, Chem. Comm., 2006, 1191.



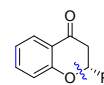
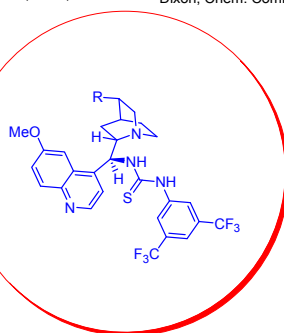
Scheidt, JACS, 2006, 4933.



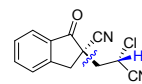
Deng, JACS, 2007, 6364.



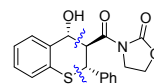
Deng, JACS, 2006, 8157.



Scheidt, JACS, 2007, 3831.

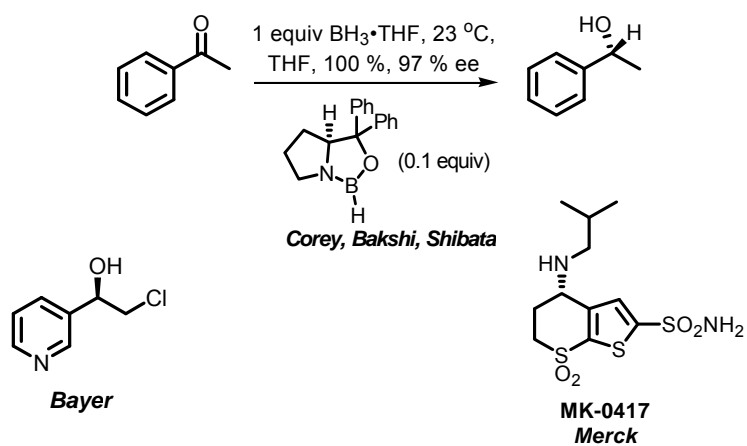


Deng, JACS, 2007, 768.

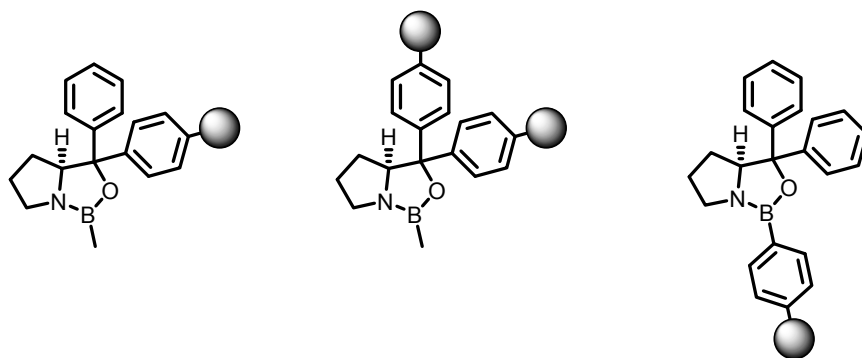


Wang, JACS, 2007, 1036

## A CBS redukció

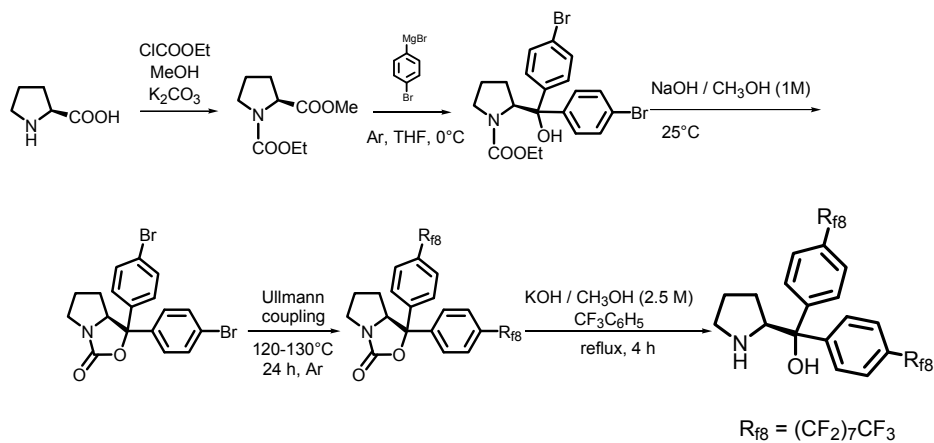


## Visszaforgatható CBS katalizátorok





## Az első generációs fluoros prolinol szintézise



## A fluoros kémia kihívásai

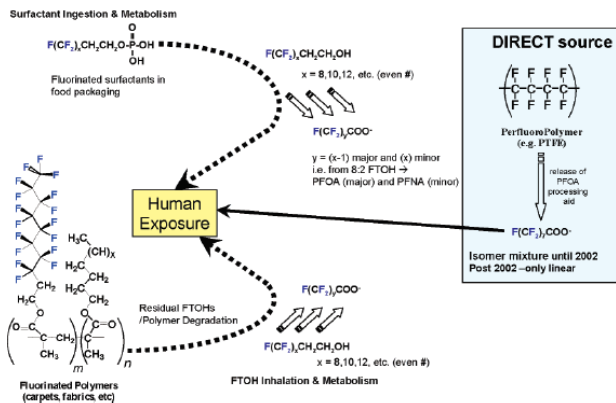
Of every 20 children tested,



19 had blood contaminated with PFOA.

# A fluoros kémia kihívásai

## INDIRECT sources of PFCAs (linear)



**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 residuals, 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 PFCAs (major product) and odd PFCAs (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 (75).

# A fluoros kémia kihívásai

(pp 144/-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 active ingredients in these products.

**Environmental News**

**Leftovers may explain perfluorinated compound puzzle**

**C**hemicals left over from the manufacturing of stain inhibitors and other products could be a major source of the perfluorinated compounds present in people used in the environment, according to a new study published in this issue of *ES&T*.

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 active ingredients in these consumer and industrial products. The residuals are found in the commercial and industrial products because the processes used to synthesize the surfactants and polymers do not always incorporate all of the fluorinated alcohols. However, these unbound residuals remain associated with the active ingredients.

PFOA (perfluorooctanoic acid) and PFOS (perfluorooctanesulfonic acid) are the most common perfluorinated chemicals, but have been detected at low levels in human blood samples worldwide. These chemicals are even found in the remote Arctic, far from any possible sources. This is a puzzle for environmental scientists and government regulators. As a percentage of total annual production, the concentrations of residual fluorinated alcohols reported in this new paper study (7) would add several thousand additional emissions at atmospheric concentrations that have been measured, the authors say.

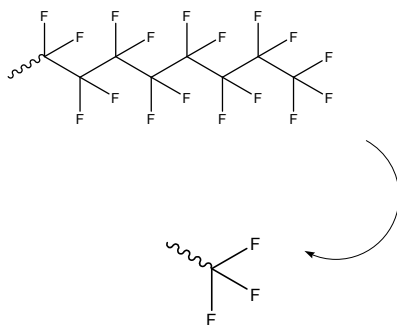
"These PFOS, PFOA, and similar compounds are not allowed to be used as commercial or industrial products, the question has always been, 'Where do they come from?'" explains Dinglasan-Panlilio. "This is the first systematic study that clearly identifies a point source for the fluorinated chemicals that we believe are present in our blood," she adds.

Mabury, Ford Hesse Co. chemist Tim Wallington, and their colleagues had previously identified that these volatile alcohols were the precursors to chemicals such as PFOS and PFOA. However, until now there were only data on the chemical residues of fluorinated alcohols. The new analysis was the first in the peer-reviewed literature to indicate that production wastes, not just manufacturing or application processes, are sources.

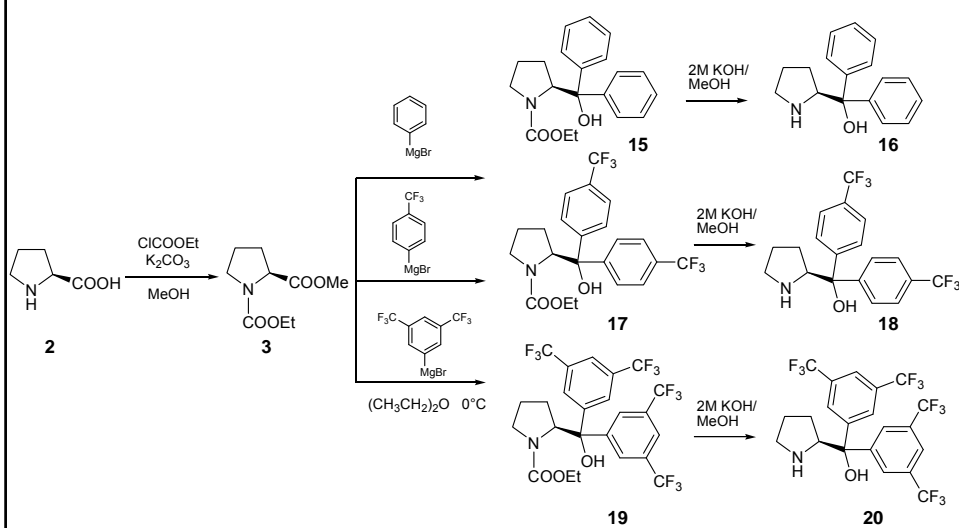
"We call perfluorinated chemicals 'dark matter' because we think that there are many sources in the home, although they have not been

Product	Percentage
Paint	~100
Carpet	~100
Washer fluid	~100
Polish	~100
Stain inhibitor	~100
Other	~100

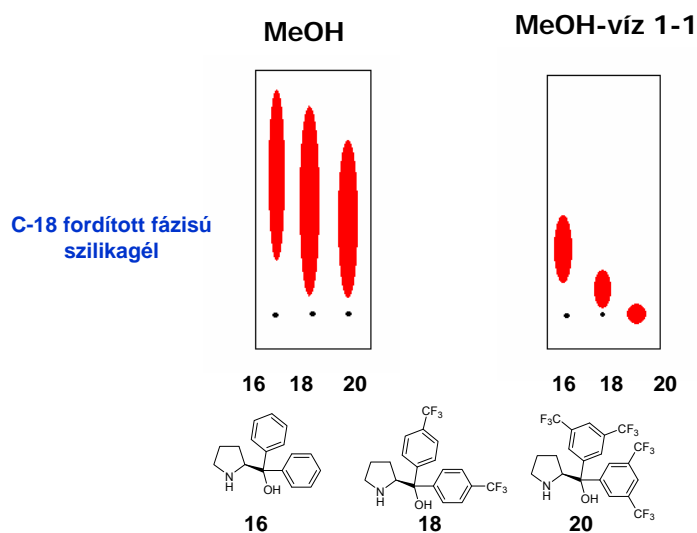
## Egy radikális megközelítés



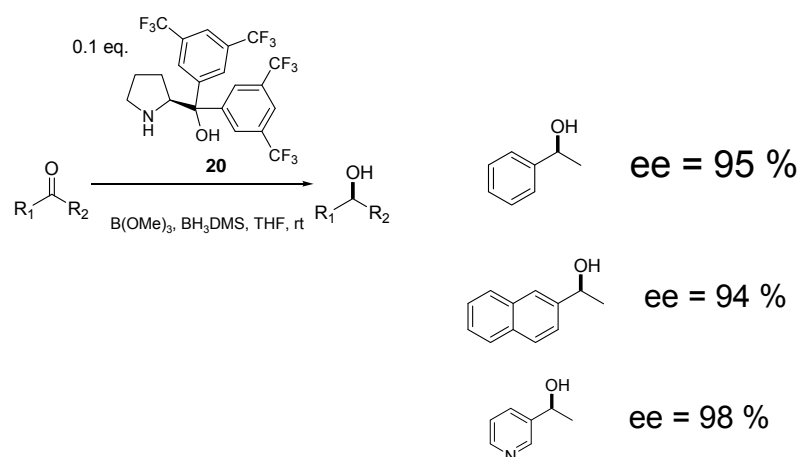
## Prolinok szintézise



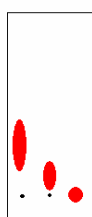
## Alkalmazható a CF<sub>3</sub> csoport fázisjelölésre?



## A CF<sub>3</sub> jelölt CBS katalizátor alkalmazása

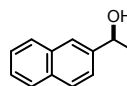


## Szilárd fázisú extrakciók



MeOH-víz 1-1

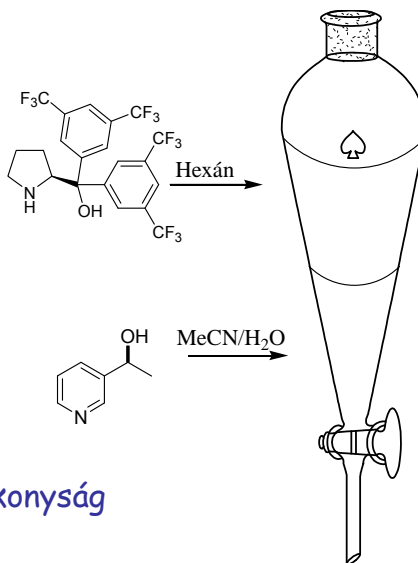
Adsorbens



$\gamma$ - $\text{Al}_2\text{O}_3$ /FSPE	85.2 %	-	-
$\gamma$ - $\text{Al}_2\text{O}_3$ /DSC18	96.2 %	-	-
$\alpha$ - $\text{Al}_2\text{O}_3$ /DSC18	96.9 %	>99.9 %	>99.9 %
$\alpha$ - $\text{Al}_2\text{O}_3$ / $\alpha$ - $\text{Al}_2\text{O}_3$	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**

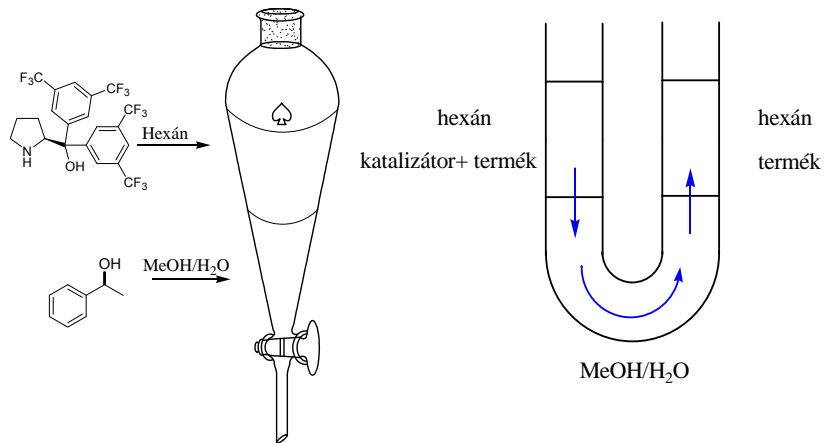
## Folyadék fázisú extrakció



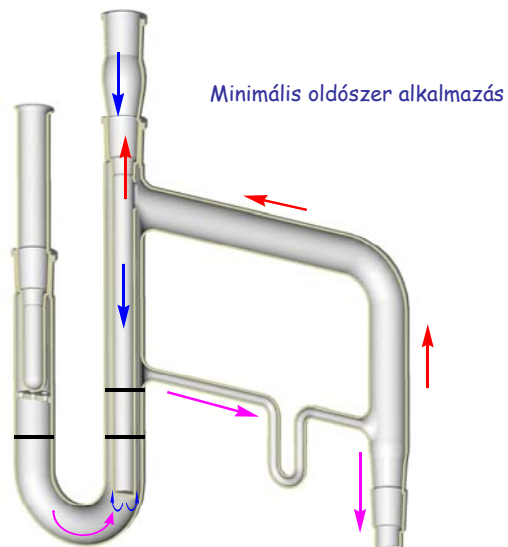
1315 mg katalizátor

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  $\text{CF}_3$  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

Pápai Imre

Schubert Gábor

COMGENEX

UBICHEM Kft.

MediChem 2