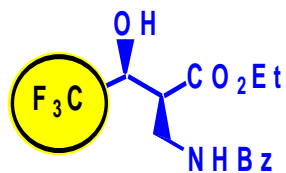
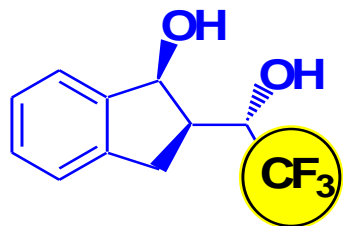
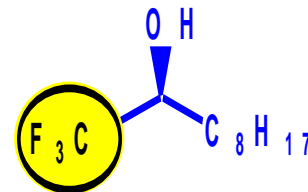
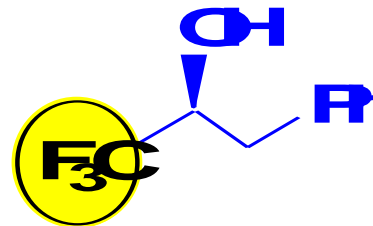
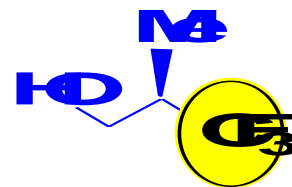
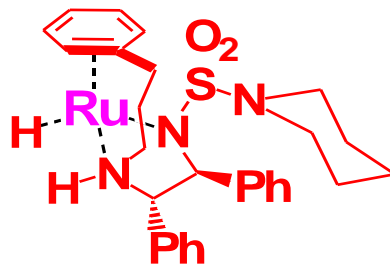


NOVA METODA ZA PRIPRAVO FLUORIRANIH KIRALNIH ALKOHOLOV



Naša nova oblika
kiralnega **Ru** katalizatorja



Levi ali Desni
enantiomer je
3D stereoizomer



KEMIJSKI INŠTITUT

Dr. Barbara MOHAR

Ljubljana, 16. oktober 2017



**NAŠ
SVET**



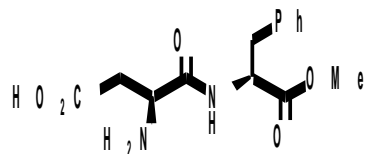
**NAMIŠLJEN ZRCALNI
SVET**

POSLEDICE KIRALNOSTI

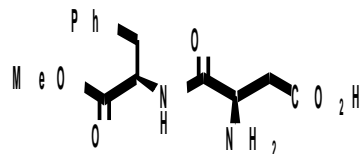
Zakaj sintetizirati določen stereoizomer ?

Različna bioaktivnost
stereoizomerov !

zrcalna ravnina



(S,S)-Aspartam
sladek okus



(R,R)-Aspartam
grenak okus



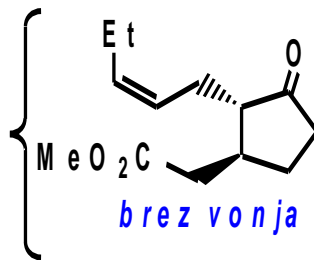
L-Dopa
anti-parkinsonik



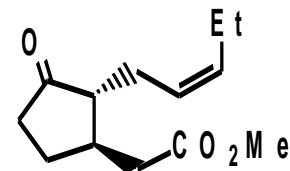
D-Dopa
zelo toksična

Metil jasmonati

trans-
par

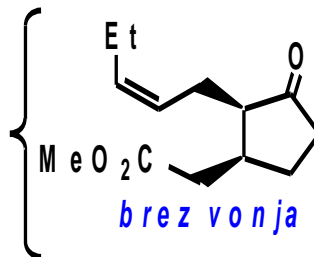


brez vonja

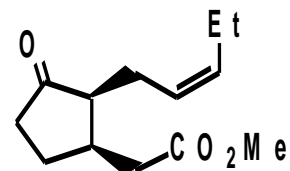


šibkejši,
prag vonja 0.24 ng/L

cis-
par



brez vonja

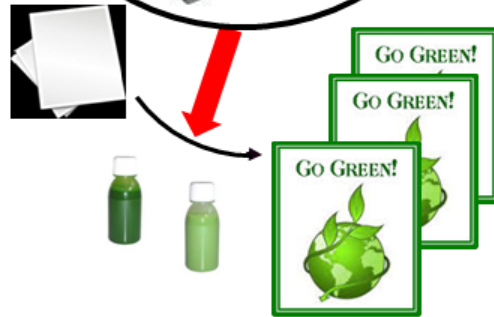


močan,
prag vonja 0.012 ng/L

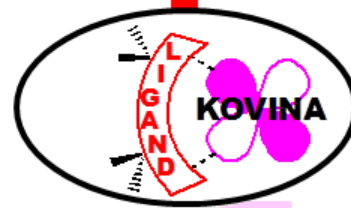
PowerPoint HOMOGENE ASIMETRIČNE KATALIZE



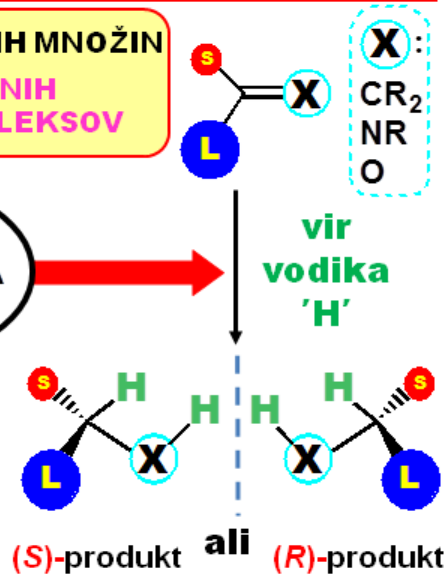
UČINKOVITO OBLIKOVANJE KIRALNIH LIGANDOV & KATALIZATORJEV
za pripravo produktov z visoko stereoizomerno čistostjo: *aminokisljine, kisline, alkoholi, amini...*



Uporaba KATALITSKIH MNOŽIN
TOPNIH KIRALNIH
KOVINSKIH KOMPLEKSOV



Fe	Co	Ni	Cu
Ru	Rh	Pd	Ag
Os	Ir	Pt	Au

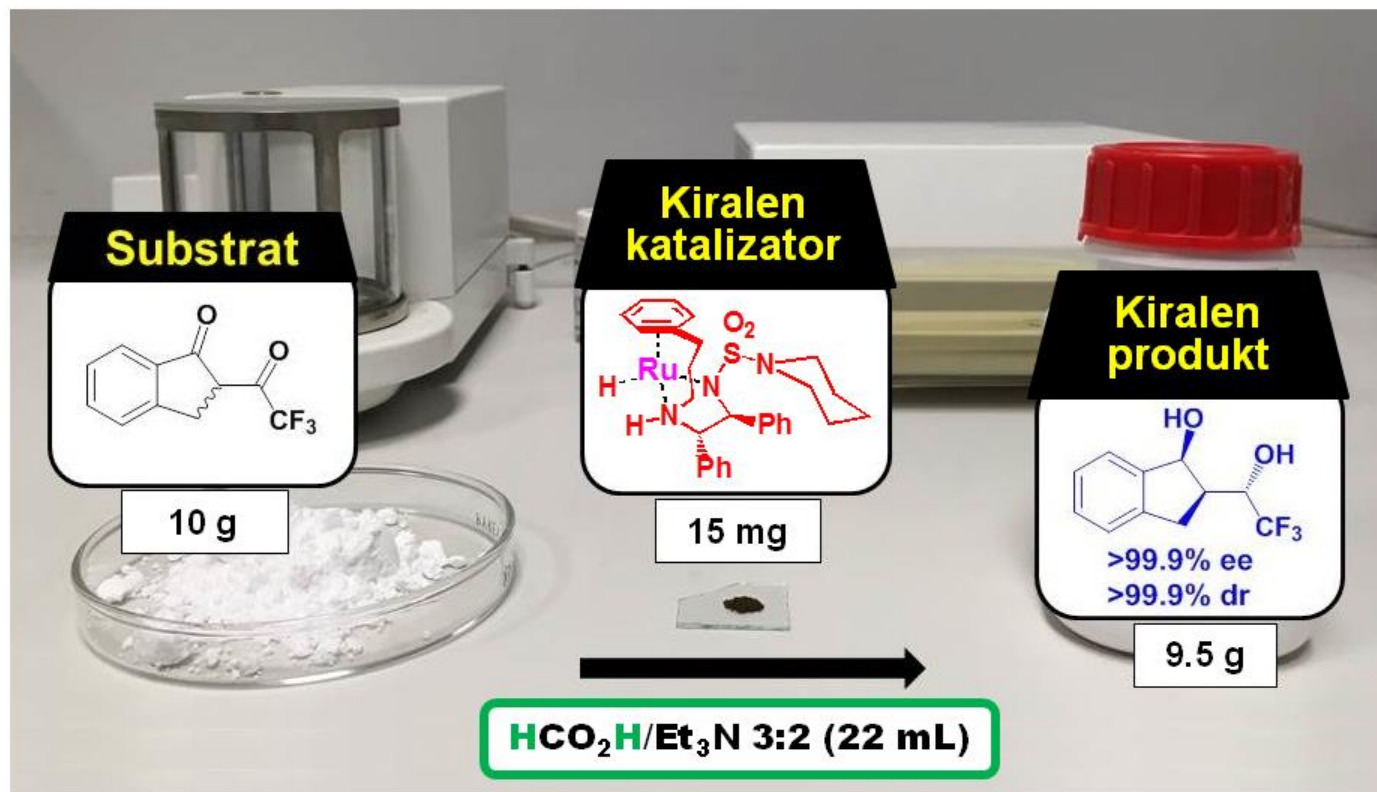


**Kiralnost
katalizatorja odloči!**

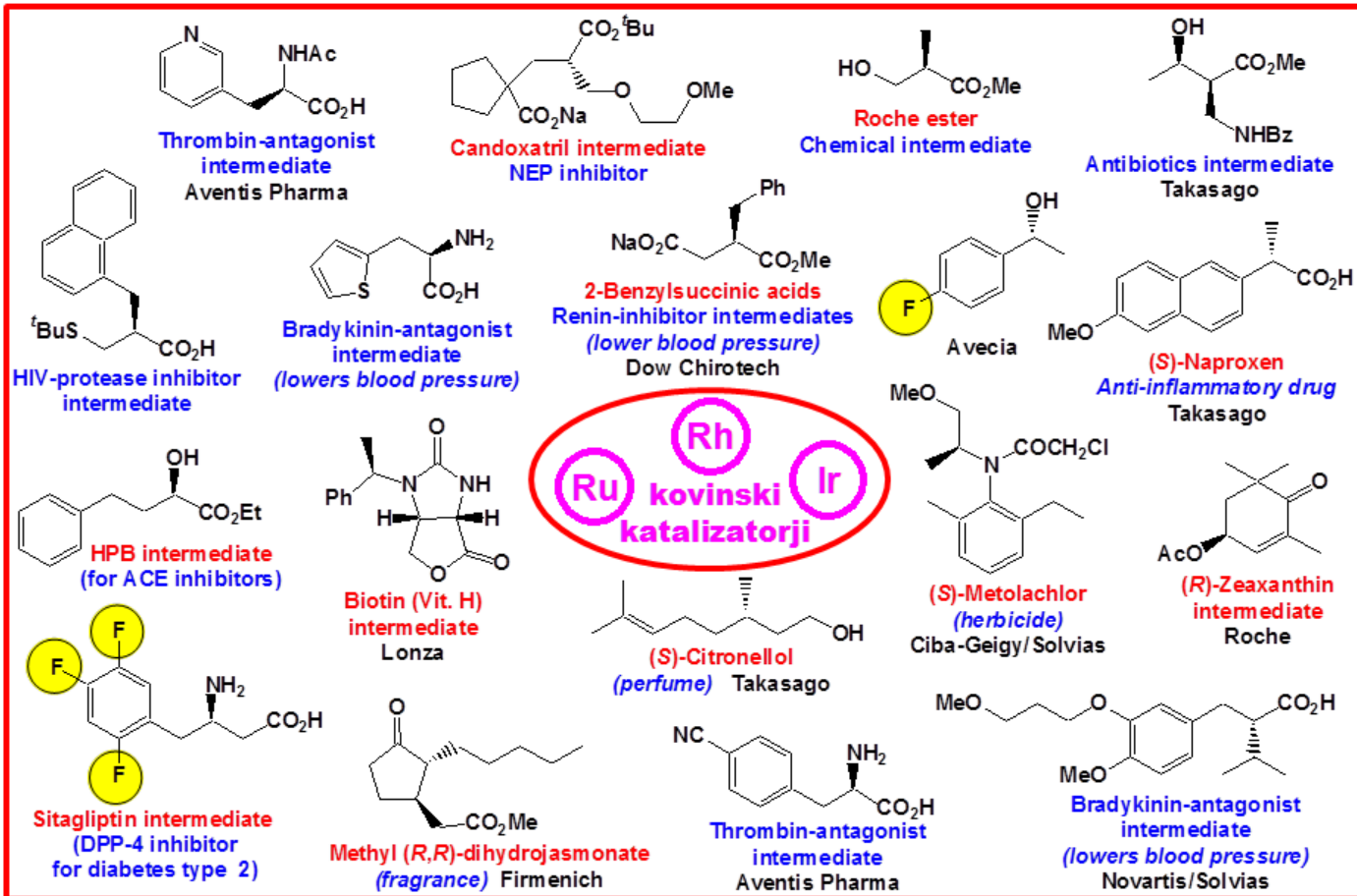
Klasična sinteza vodi do
zmesi **2** stereoizomerov

HOMOGENA ASIMETRIČNA KATALIZA

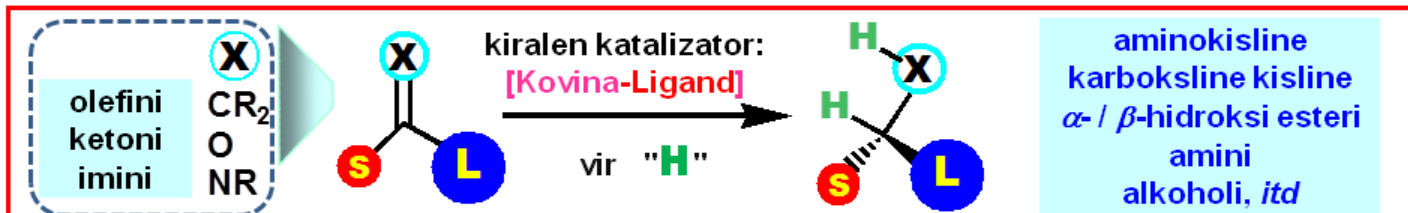
Primer učinkovitosti: **Substrat / Katalizator = 2000**



KIRALNA ZDRAVILA, AGRO & FARMA INTERMEDIATI & API-ji PRIPRAVLJENI preko ASIMETRIČNEGA (TRANSFER) HIDROGENIRANJA



KATALIZIRANE ASIMETRIČNE REDUKCIJE S TOPNIMI KOVINSKIMI KOMPLEKSI



HIDROGENIRANJE

z uporabo plina H_2 (1–100 atm)

TRANSFER HIDROGENIRANJE

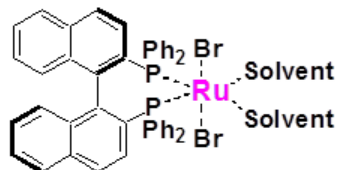
z uporabo Me_2CHOH , $\text{HCO}_2\text{H}/\text{Et}_3\text{N}$, itd

R. Noyori
Takasago, JP

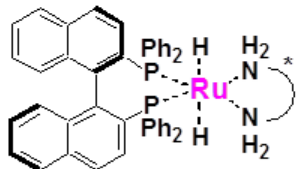
**Nobelova
2001**

W. Knowles
Monsanto, ZDA

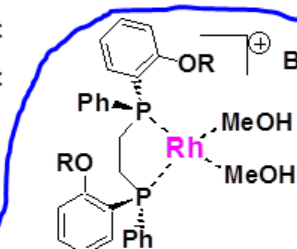
R = Me: Rh-(DiPAMP)



Ru-BINAP



Ru-BINAP-diamin

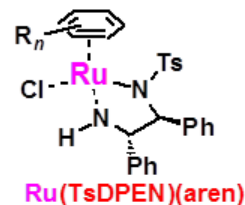


R = ^tBu: Rh-(^tBu-SMS-Phos)

Inovacija našega
laboratorija

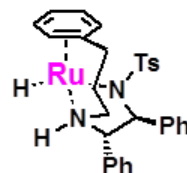
(predstavljen v e-EROS)

R. Noyori
Takasago, JP



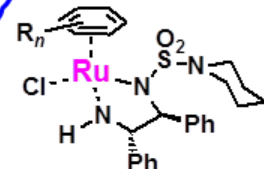
Ru(TsDPEN)(aren)

M. Wills
Johnson-Matthey, UK

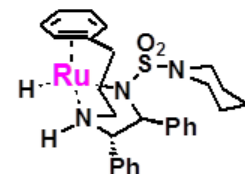


nC-[Teth-TsDPEN-RuCl]

Inovacija našega
laboratorija



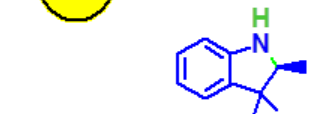
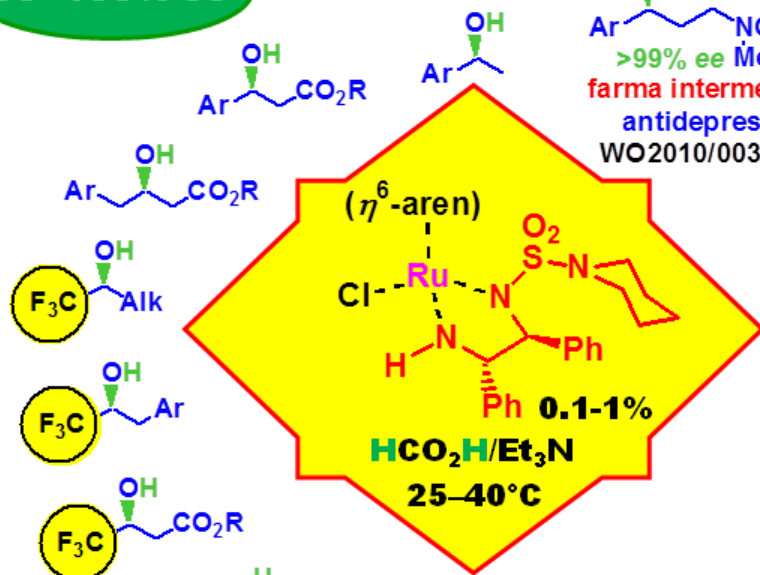
Ru(PipSO₂DPEN)(aren)



ansa-Ru(PipSO₂DPEN)(benzen)

APLIKACIJA NAŠE 1. GENERACIJE Ru(II) KATALIZATORJEV V ASIMETRIČNEM TRANSFER HIDROGENIRANJU

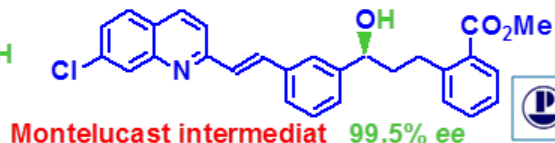
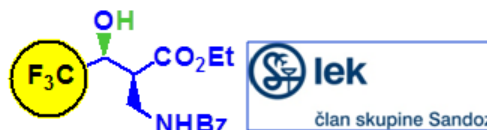
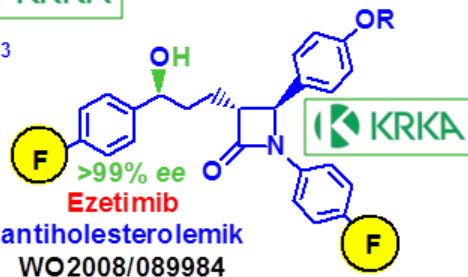
90–100% ee



Stephan & Mohar et al:

- *Tetrahedron: Asymm.* 2002, 13, 2605
- *Org. Lett.* 2006, 8, 5935
- *Tetrahedron* 2010, 66, 4144

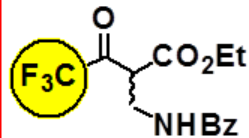
▪ našeti patenti: Krka, Lek, Pliva



APLIKACIJA NAŠE 1. GENERACIJE Ru(II) KATALIZATORJEV V ASIMETRIČNEM TRANSFER HIDROGENIRANJU

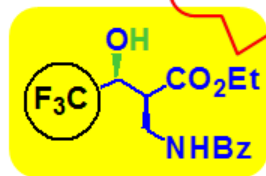
Primer fluoriranega alkohola z dvema sosednjima kiralnima centroma

racemna zmes

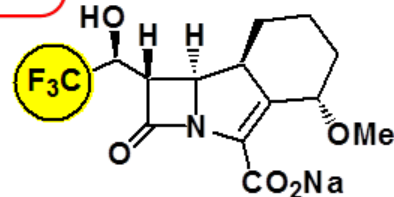


DKR / ATH

kiralen
katalizator

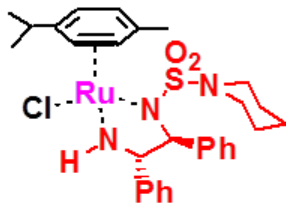


Klasična sinteza:
zmes $2^2 = 4$
stereoizomerov



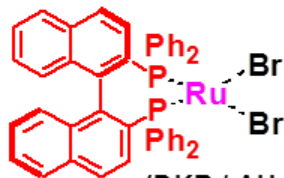
fluoriran trinem
potencialen nov antibiotik

Mohar,
Stephan



$dr = 94:6$ $>99\%$ ee

Noyori



$dr = 94:6$ 22% ee

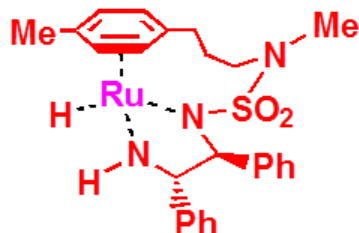
(DKR / AH: 80 bar H₂)



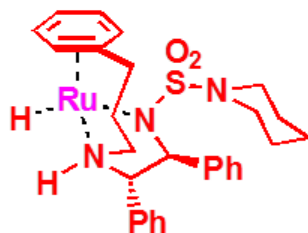
WO2009/153297
Plantan, Preželj, Urleb,
Mohar, Stephan

APLIKACIJA NAŠE 2. in 3. GENERACIJE Ru(II) katalizatorjev v ATH za pripravo kiralnih fluoriranih alkoholov

2. GEN. (2013)



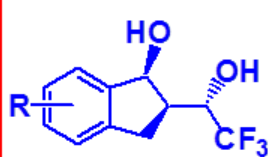
3. GEN. (2015)



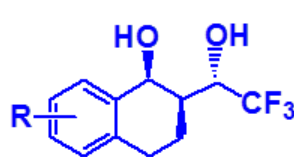
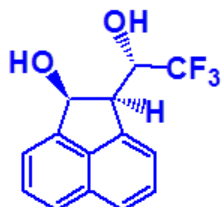
PREDNOSTI NOVIH OBLIK
***ansa*-Ru(II) KOMPLEKSOV**

- ✓ Bolj obstojni zaradi sidranja η^6 -arena
- ✓ Povečana aktivnost

Primeri fluoriranih alkoholov s trema sosednjimi kiralnimi centri

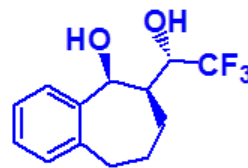
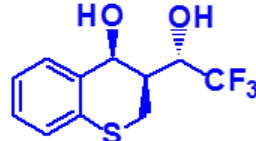
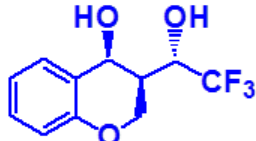
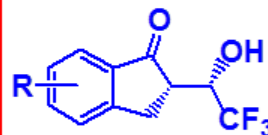


R
H
5-Br
6-OH
7-OH
7-NHAc



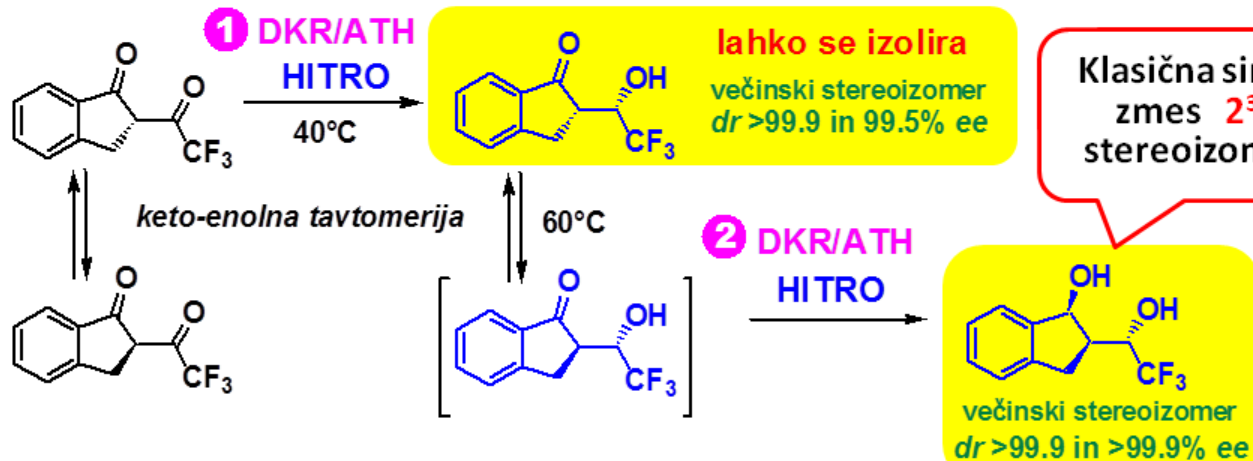
R
H
6-OMe
7-OMe

Izolirani v
>99% *de*
>99% *ee*

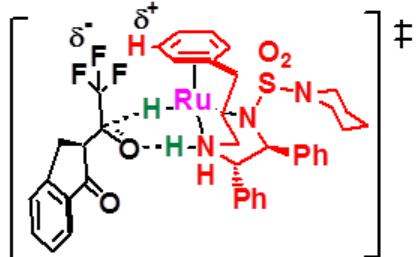


ZAKAJ TAKO VISOKA STEREOSELEKTIVNOST ?
Dve zaporedni DKR/ATH: PRVI PRIMER V LITERATURI

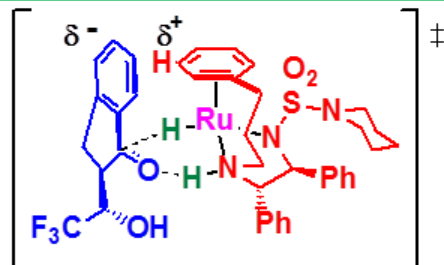
**Katalizator
 izbere prednostno**



1 CH...F privlačna
 elektrostatska interakcija

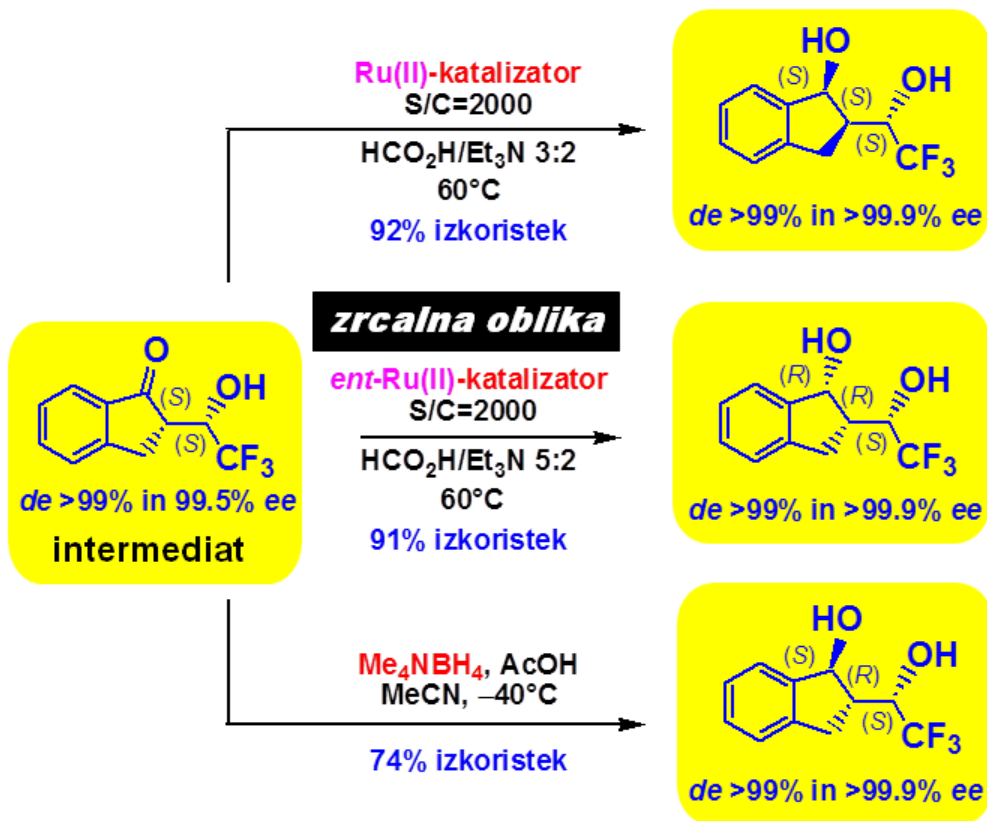


2 CH... π privlačna
 elektrostatska interakcija



Komplementarna stereodivergentna sinteza
stereoizomerov 2-CF₃-CH(OH)-1-INDANOLA

S spreminjanjem pogojev
lahko ločeno pripravimo
6 stereoizomerov



A Journal of the Gesellschaft Deutscher Chemiker
Angewandte
International Edition **Chemie**
www.angewandte.org

Cotman, Cahard, Mohar
2016, 55, 5294

Key words

transfer
hydrogenation
ruthenium catalysis
asymmetric
reduction

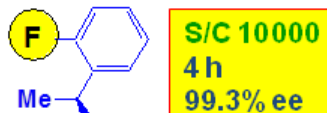
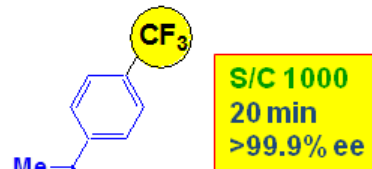
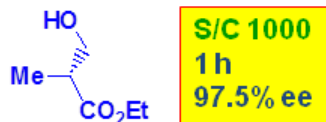
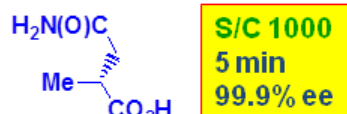
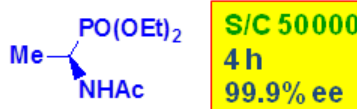
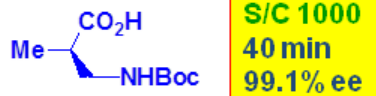
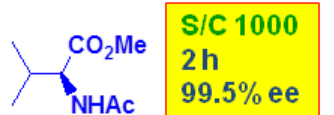
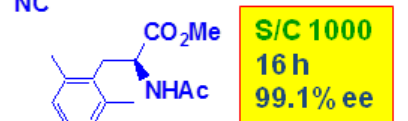
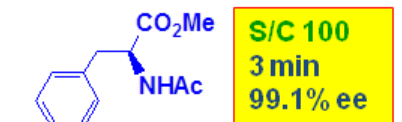
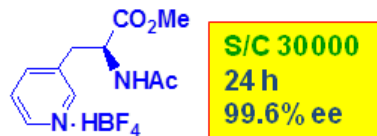
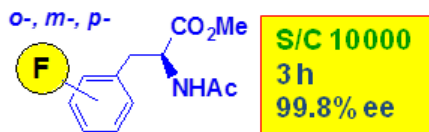
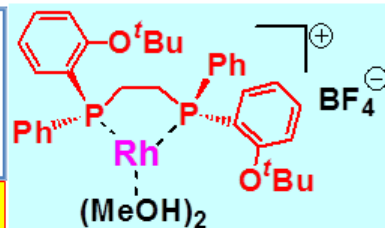
Synfact
of the month

2016, 6, 589

Aplikacija našega kiralnega **Rh(I)-^tBu-SMS-Phos** katalizatorja v hidrogeniranju

Priprava različnih funkcionaliziranih kiralnih spojin

Pogoji: 1-10 bar H₂ / RT / MeOH



Synfacts

Highlights in Chemical Synthesis

Key words

chiral phosphines

asymmetric
hydrogenation

alkenes

rhodium

2010, 6, 676

e-EROS

ENCYCLOPEDIA OF
REAGENTS FOR
ORGANIC
SYNTHESIS



2014

Most Requested Patent Families 1Q07-Chemistry and Related Science

Listed below are the chemistry and related science patent families which researchers have most frequently requested while using CAS products. (SciFinder, SciFinder Scholar, STN, and CA on CD).

Title	Author/Affiliation	Source
1. Pyrrolo[2,3-b]pyridine derivatives as protein kinase inhibitors and their preparation, pharmaceutical compositions and use in the treatment of diseases [details]	Ibrahim, Prahbha N.; Artis, Dean R.; et al. Plexxikon, Inc., USA	PCT Int. Appl. WO2007002325
2. Cosmetic and pharmaceutical foam [details]	Tamarkin, Dov; Friedman, Doron; et al. Foamix Ltd., Israel	PCT Int. Appl. WO2004037225
3. Dosage form containing modified- and immediated-release portions [details]	Vaya, Navin; Karan, Rajesh Singh; et al. Torrent Pharmaceuticals Limited, India; Guota Vinod, Kumar	PCT Int. Appl. WO2004012700
4. Asymmetric Michael and aldol addition using bifunctional Cinchona alkaloid based catalysts [details]	Deng, Li; Li, Hongming Brandeis University, USA	PCT Int. Appl. WO2005121137
5. Copper-catalyzed formation of carbon-heteroatom and carbon-carbon bonds by arylation and vinylation of amines, amides, hydrazides, heterocycles, alcohols, enolates, and malonates, using aryl, heteroaryl, and vinyl halides and analogs [details]	Buchwald, Stephen L.; Klapars, Artis; et al. Massachusetts Institute of Technology, USA	PCT Int. Appl. WO2002085838
6. Methods and compositions for increasing the efficacy of biologically-active ingredients such as antitumor agents [details]	Windsor, J. Brian; Roux, Stan J.; et al. Board of Regents, the University of Texas System, USA	PCT Int. Appl. WO2005014777
7. Preparation of new P-chiral ortho-functionalized arylphosphines, their borane complexes and transition metal catalysts for asymmetric addition and substitution reactions [details]	Stephan, Michel (F); Mohar, Barbara (SLO) PhosPhoenix; National Institute of Chem.	Fr. Demande FR2887253
8. Phenyl-substituted oxazolidinone derivatives and their preparation, pharmaceutical compositions, and use as antimicrobials [details]	Das, Biswajit; Ahmed, Shahadat; et al. Ranbaxy Laboratories Limited, India	PCT Int. Appl. WO2006038100
9. Preparation of amino acid prodrugs [details]	Chandran, V. Ravi Signature Pharmaceuticals, LLC, USA	PCT Int. Appl. WO2005046575
10. Clickphosphines for transition metal-catalyzed reactions [details]	Zhang, Xumu, The Penn State Research Foundation, USA	PCT Int. Appl. WO2006130842

RAZISKOVALCI, KI SO PRISPEVALI K PREDSTAVLJENI KEMIJI

obdobje 2000 - 2017

Študenti

Andrej E. COTMAN



Marko JERAN



Nekdanji študenti

Dr. Andrea KIŠIČ



Dr. Slavko RAST



Dr. Borut ZUPANČIČ



član skupine Sandoz

Dr. Damjan ŠTERK



član skupine Sandoz

Raziskovalci

Dr. Michel STEPHAN



&



Dr. Dominique CAHARD



Doc.dr. Barbara MODEC
(za kristalne strukture)



Podpora:

ARRS (P1-0242; Proteus)

Lek, Krka, Pliva

Prof. dr. Janez PLAVEC

