Presentation

-- previous research

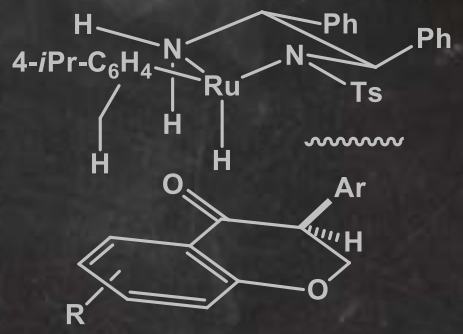
Tao Qin

- *Tianjin, China*
- *Nankai University*
- *Dresden, Germany*
- *TU Dresden*

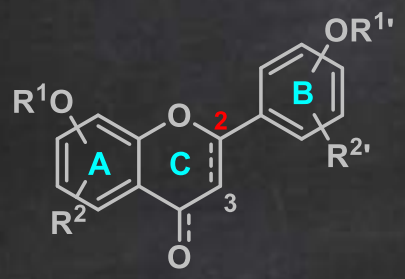
Contents

TECHNISCHE UNIVERSITÄT DRESDEN

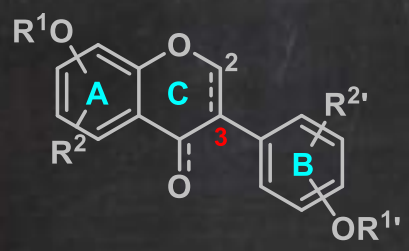
Enantioselective Synthesis of Isoflavonoids via Catalytic Dynamic Kinetic Resolution



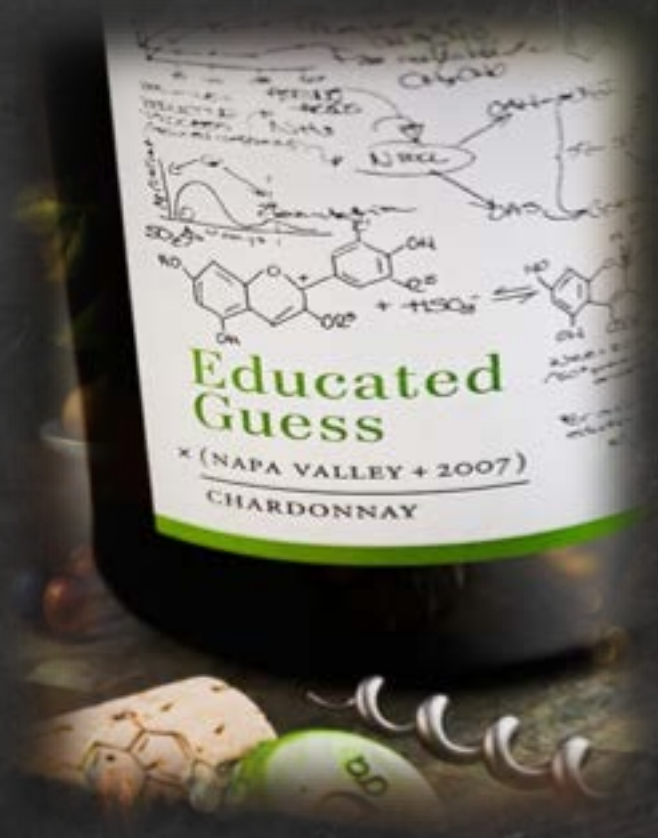
1.1 *Flavonoid Compounds* - Flavonoids & Isoflavonoids



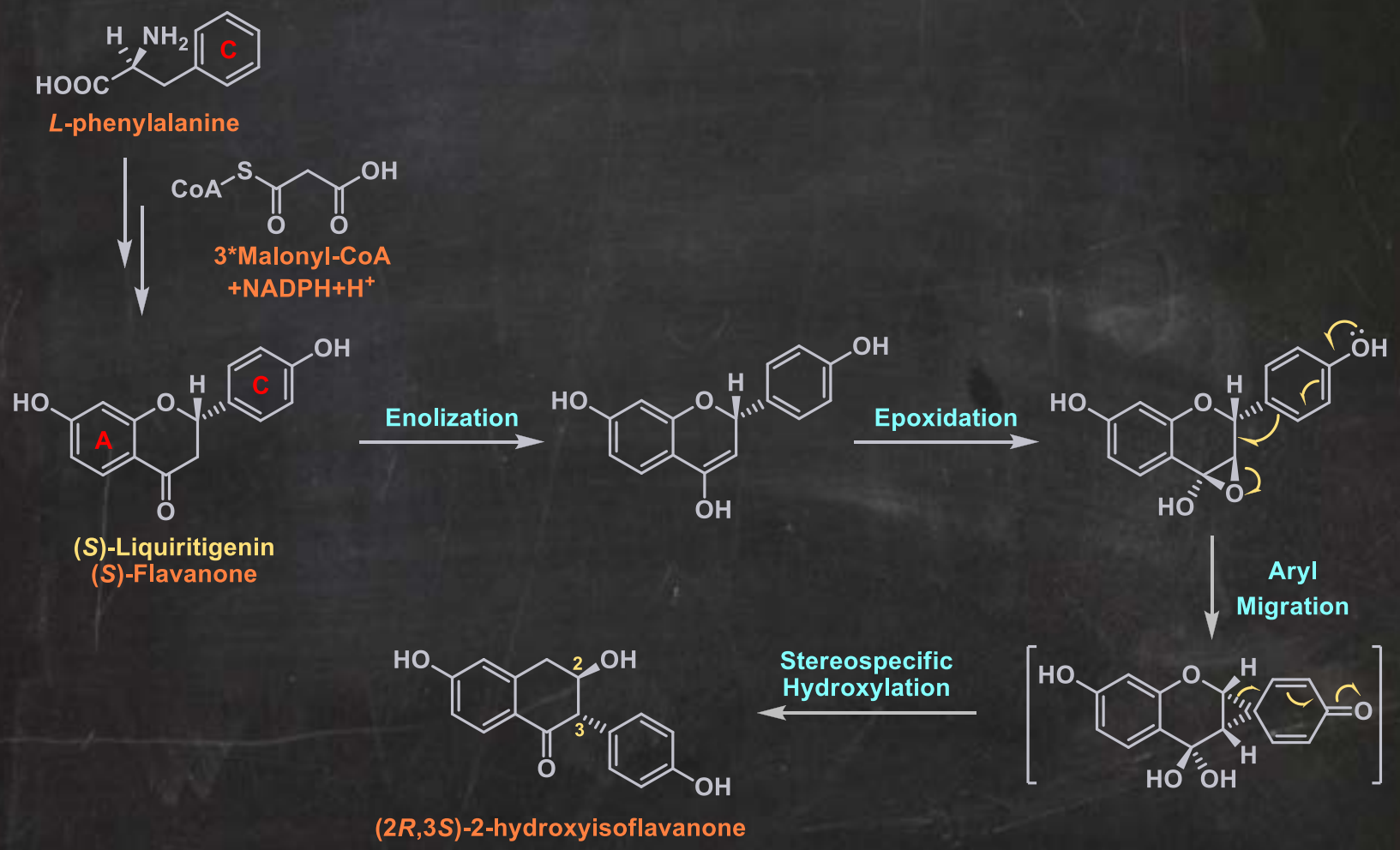
Flavonoids



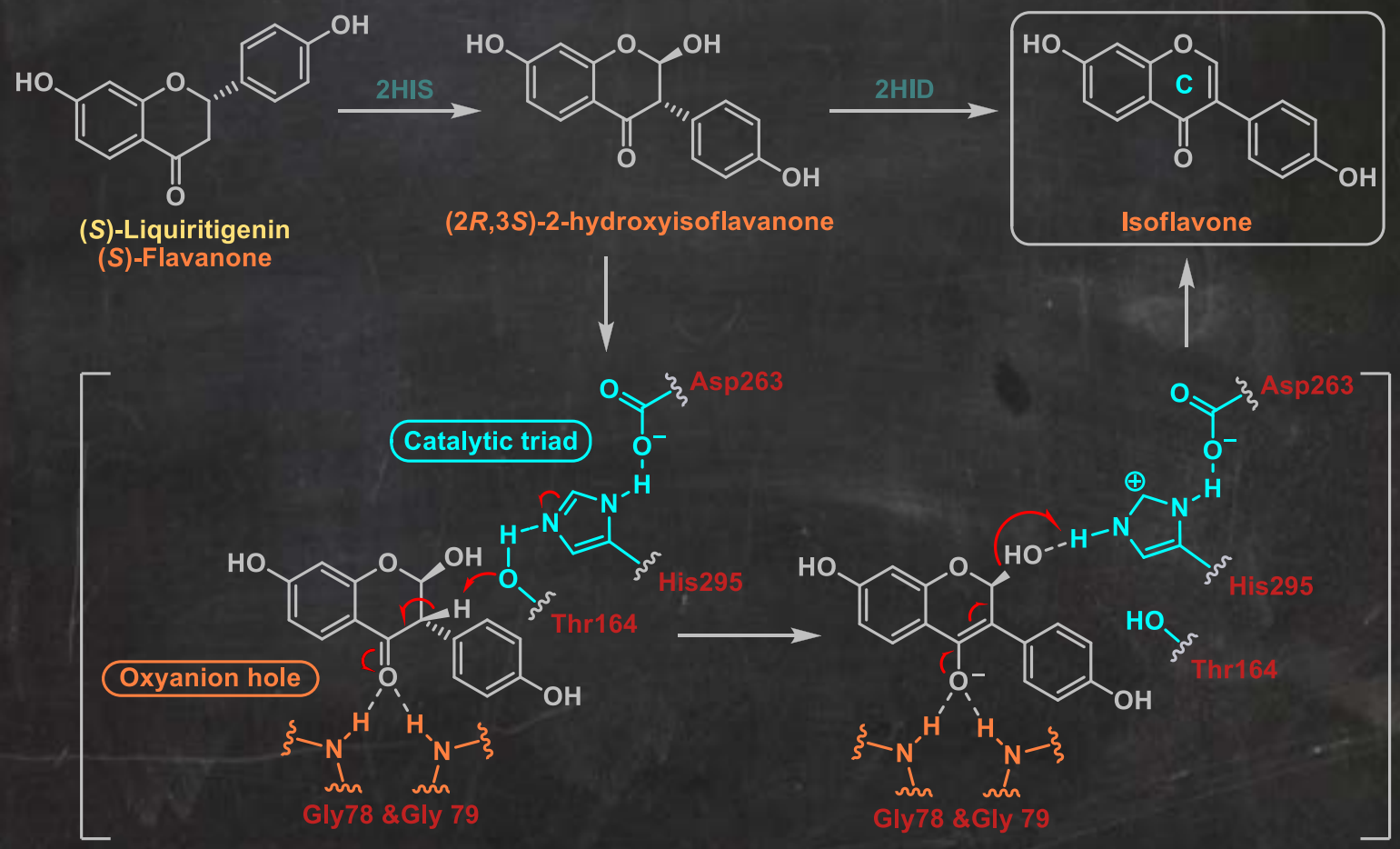
Isoflavonoids



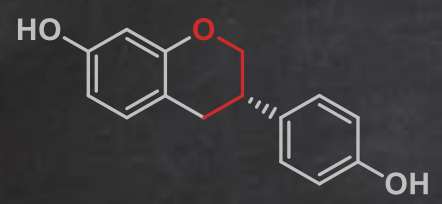
1.1 *Flavonoids & Isoflavonoids* – Biogenetic Relationships



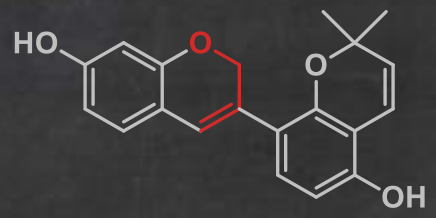
1.1 *Flavonoids & Isoflavonoids* – Biogenetic Relationships



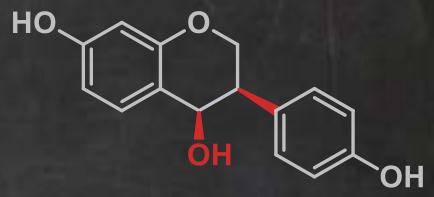
1.1 *Flavonoids & Isoflavonoids* – Structural Diversity



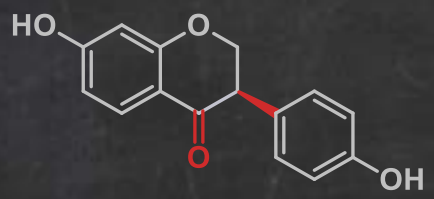
Equol
Isoflavan



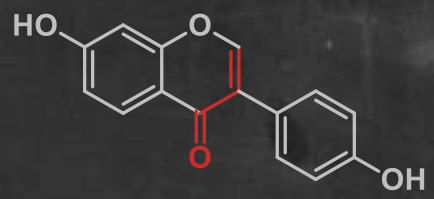
Glabrene
Isoflavene



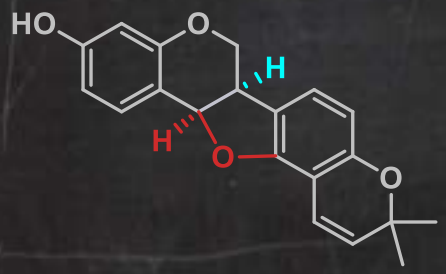
Tetrahydrodaidzein
Isoflavanol



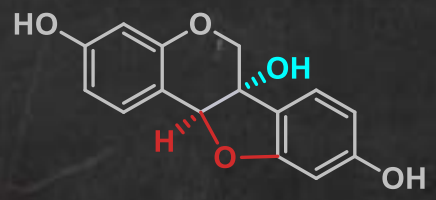
Dihydrodaidzein
Isoflavanone



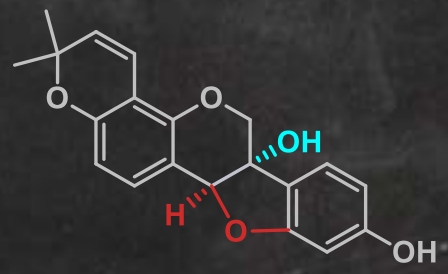
Daidzein
Isoflavone



Phaseolin
Pterocarpan

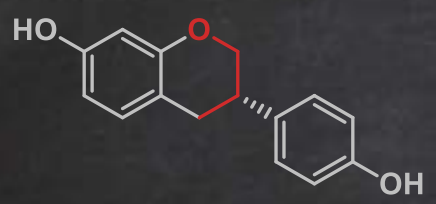


Glycinol
Pterocarpan

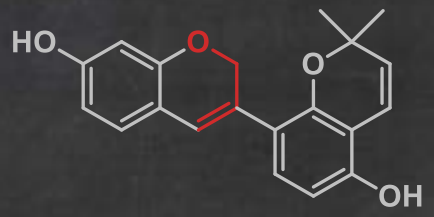


Glyceollin I
Pterocarpan

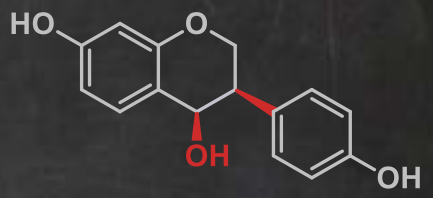
1.1 *Flavonoids & Isoflavonoids* – Structural Diversity



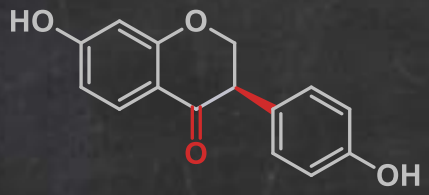
Equol
Isoflavan



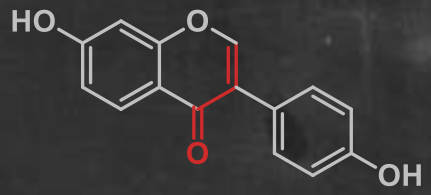
Glabrene
Isoflavene



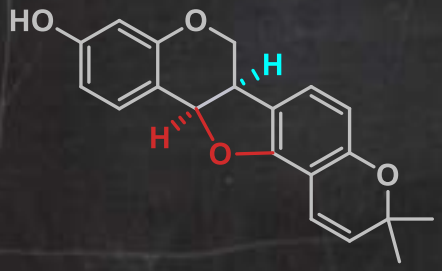
Tetrahydrodaidzein
Isoflavanol



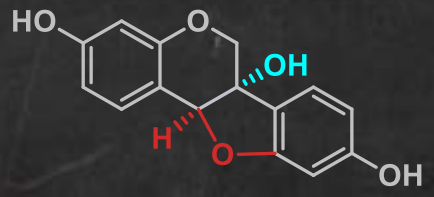
Dihydrodaidzein
Isoflavanone



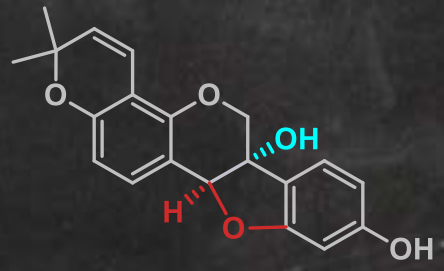
Daidzein
Isoflavone



Phaseolin
Pterocarpan



Glycinol
Pterocarpan

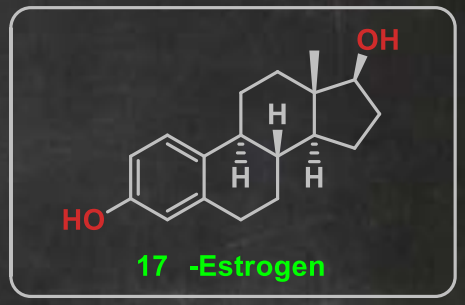


Glyceollin I
Pterocarpan

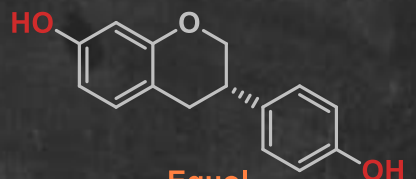
1.2 *Bioactivities* – Hormonal Activities as Phytoestrogen

Phytoestrogen:

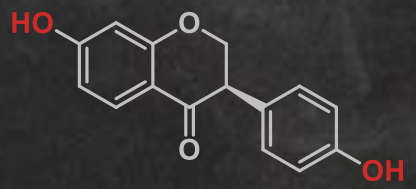
- ✓ *-OH with proper configeration*
- ✓ *A critical space of 1.2 nm*



- ***Agonism**: stimulating the estrogenic action*
- ***Antagonism**: blocking the estrogenic action*
- ***Selective Estrogen Receptor Modulators** (SERMs)*



Equol

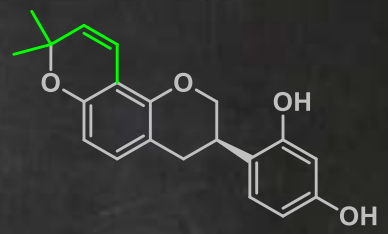


Dihydrodaidzein

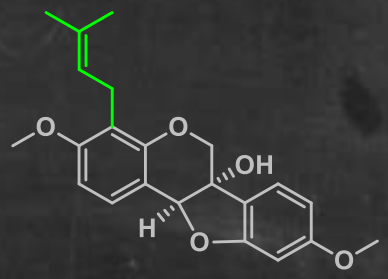
1.2 *Bioactivities* – Hormonal Activities as Phytoestrogen

Prenylation of isoflavonoids

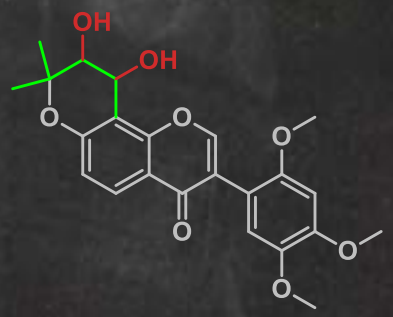
- *position*
- *modification*
- *multi-prenylation*

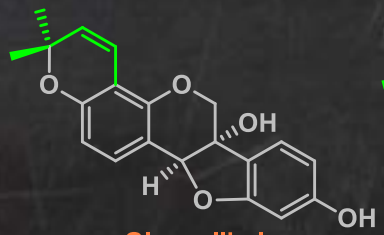


Glabridin

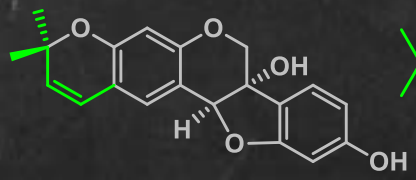


Bitucarpin A

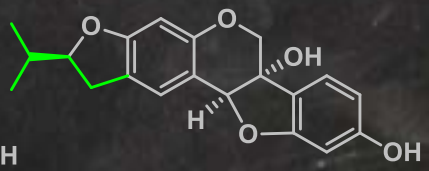




Glyceollin I



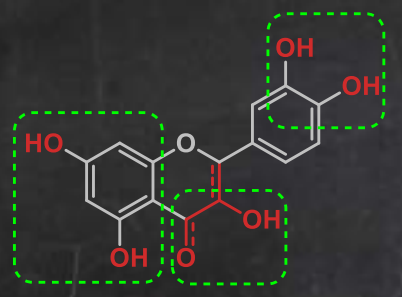
Glyceollin II



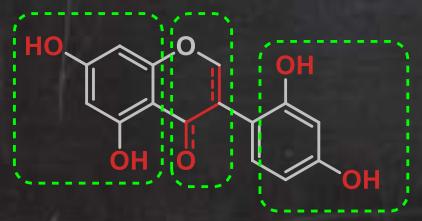
Glyceollin III

1.2 *Bioactivities* – Non-Hormonal Activities as Antioxidant

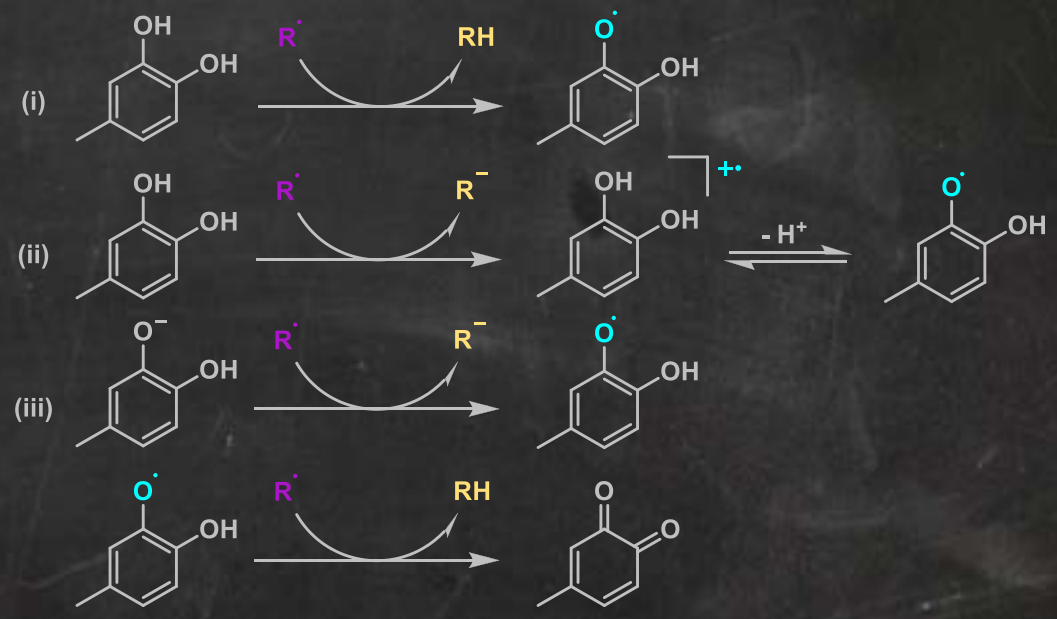
- *Reactive Oxygen Species (ROS)*
- *ROS scavenging by polyphenolic compounds*



Flavonoid

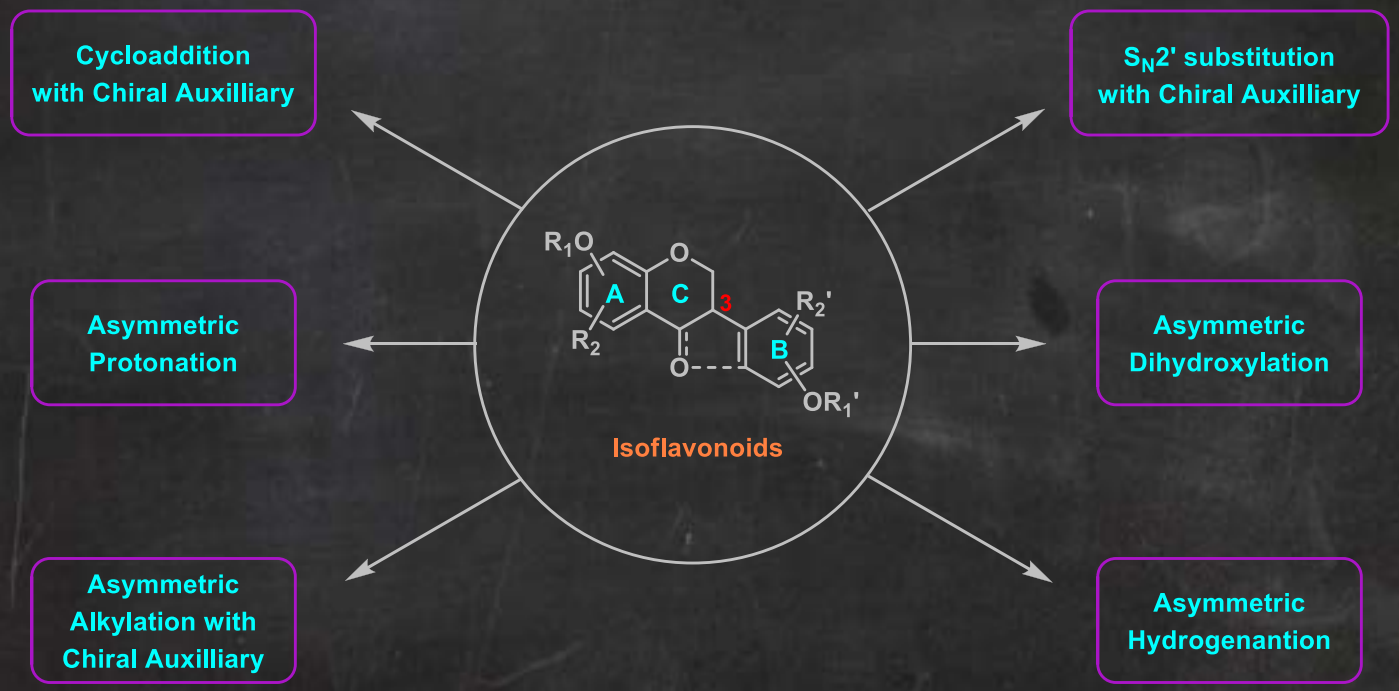


Isoflavonoid



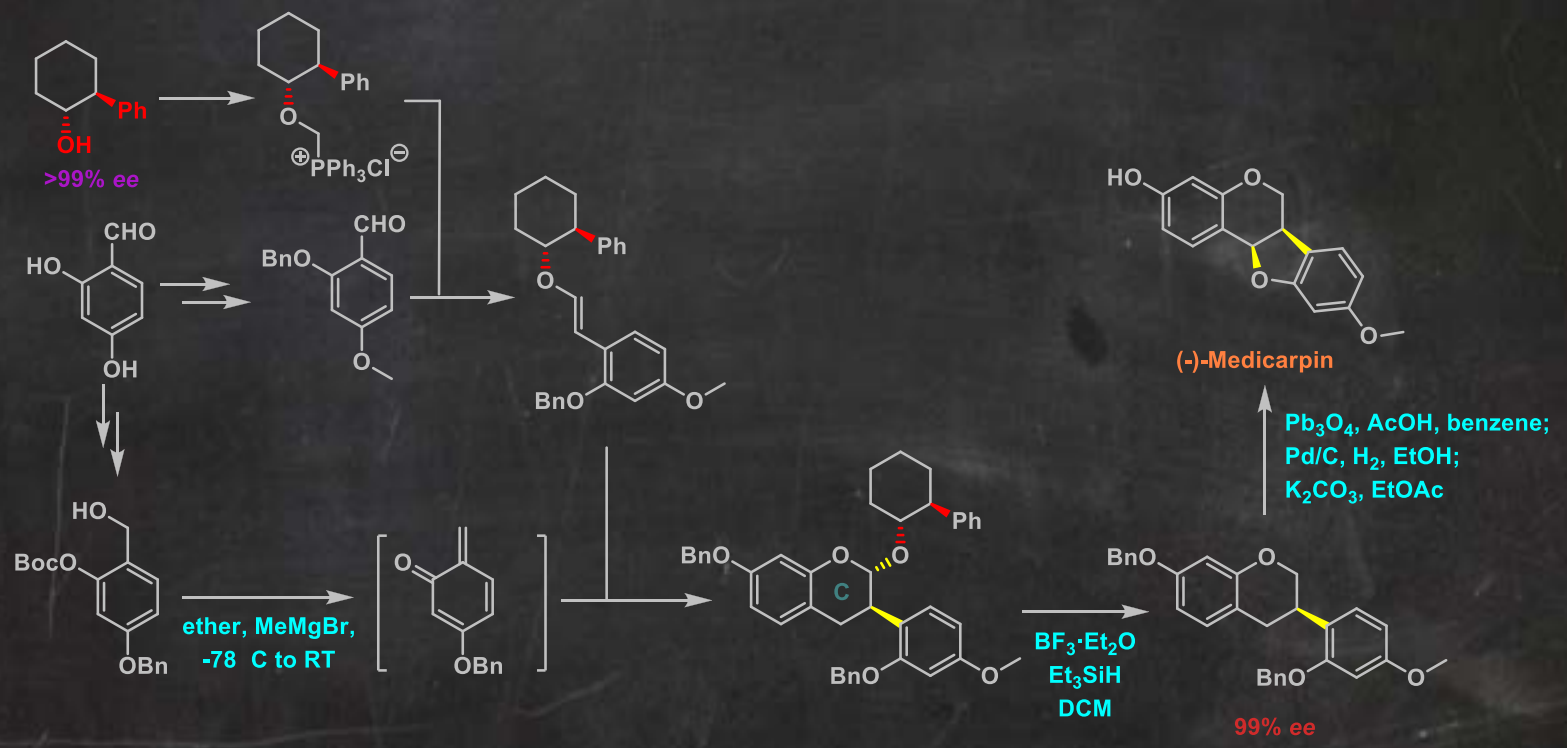
1.3 *Synthetic Strategies*

- **Enantioselective methodologies for introduction of C-3 chirality:**



1.3 *Synthetic Strategies* – Pettus *et al.*'s strategy

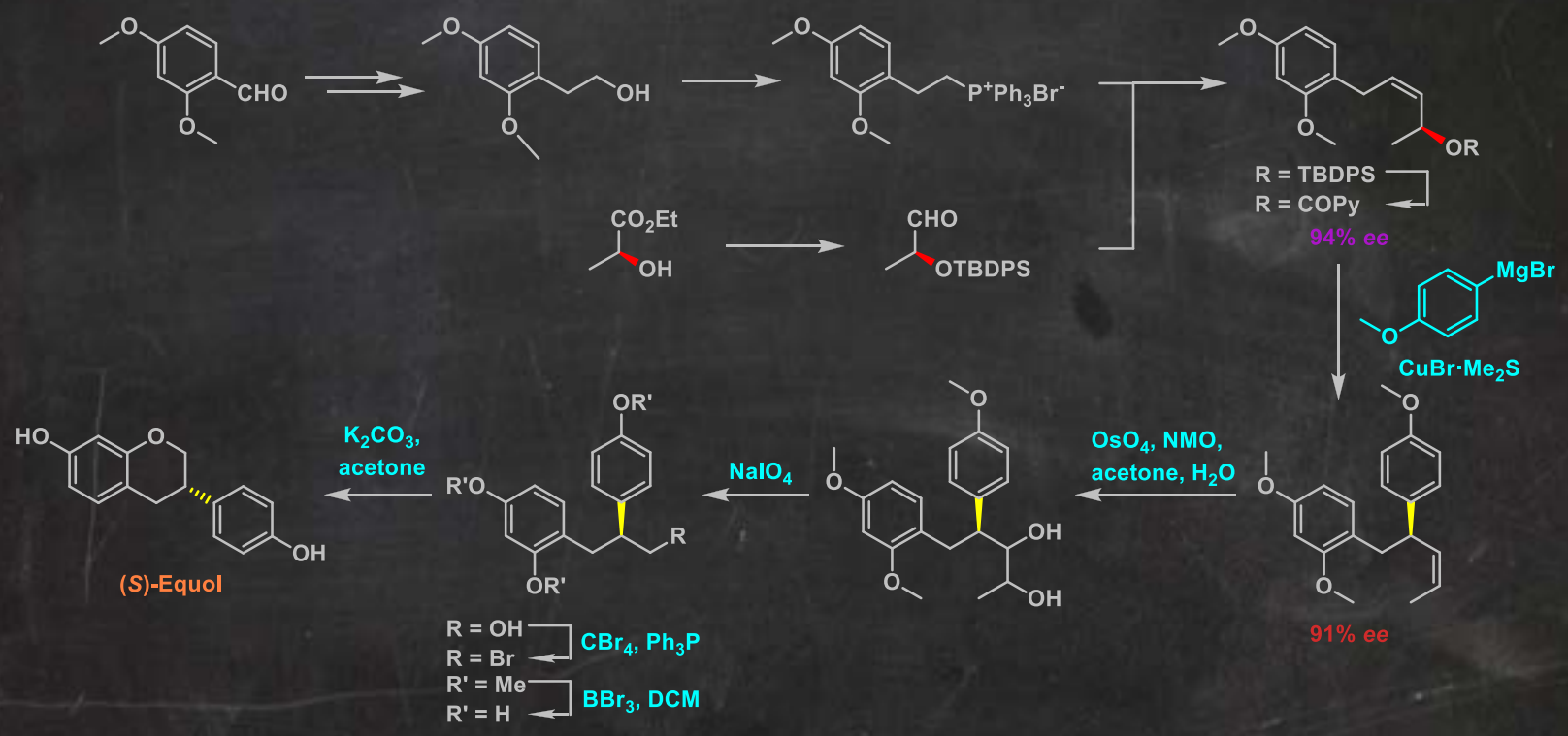
Cycloaddition with Chiral Auxilliary



Z. G. Feng, W. J. Bai, T. R. R. Pettus, *Angew. Chem. Int. Ed.*, **2015**, *127*, 1884-1887.

1.3 *Synthetic Strategies* – Takashima *et al.*'s strategy

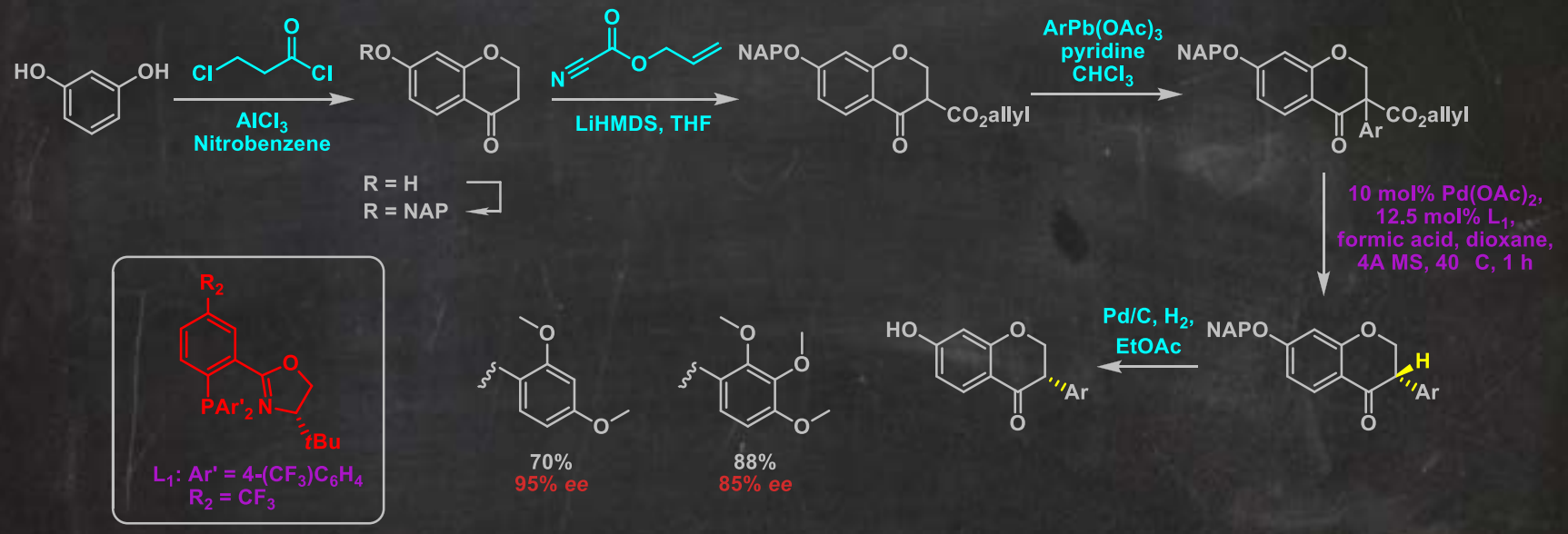
S_N2' substitution with Chiral Auxilliary



Y. Takashima, Y. Kaneko, Y. Kobayashi, *Tetrahedron*, **2010**, *66*, 197.
Y. Takashima, Y. Kobayashi, *Tetrahedron Lett.*, **2008**, *49*, 5156.

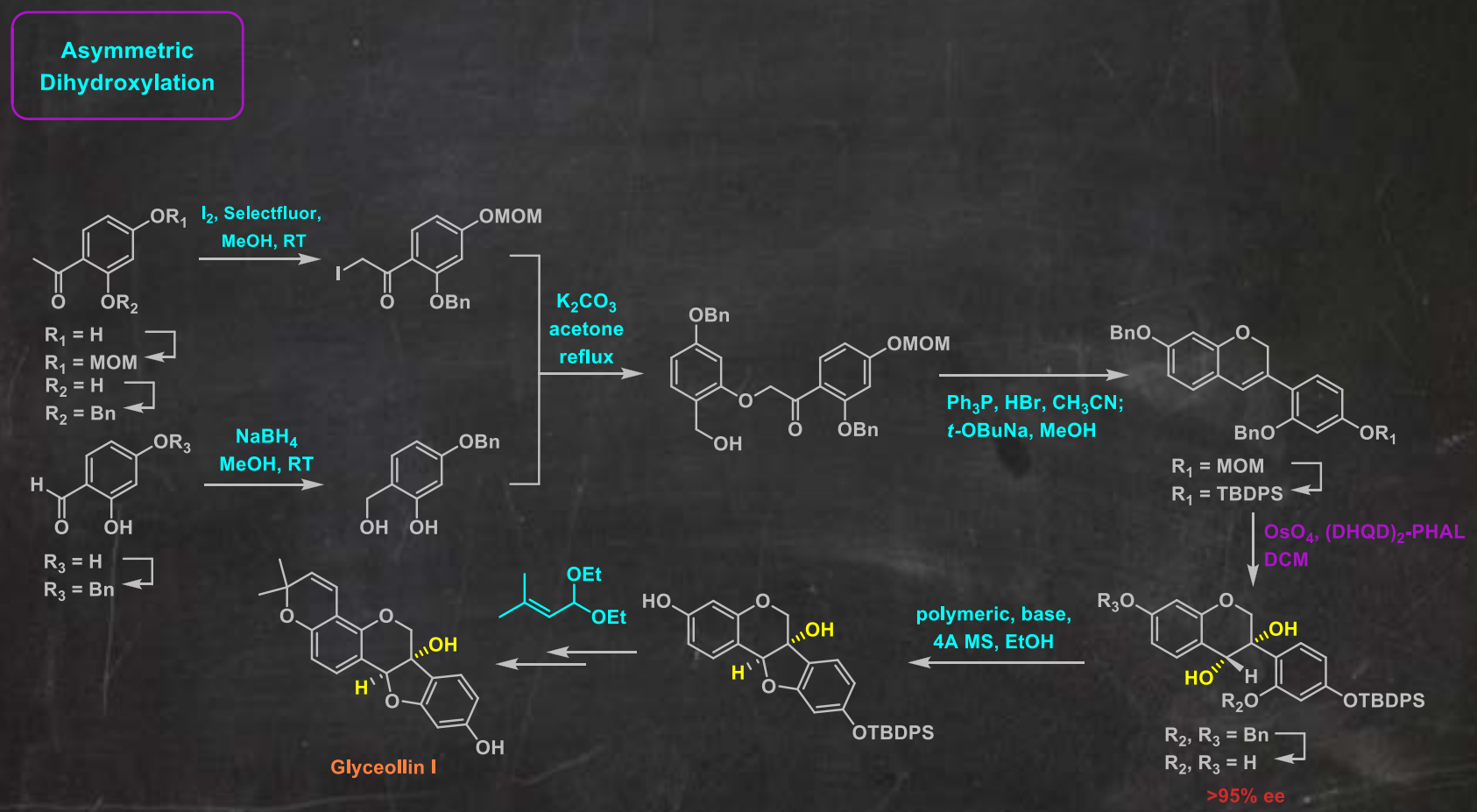
1.3 *Synthetic Strategies* – Guiry *et al.*'s strategy

Asymmetric Protonation



M. P. Carroll, H. Mueller-Bunz, P. J. Guiry, *Chem. Commun.*, **2012**, *48*, 11142-11144.
R. Doran, M. P. Carroll, R. Akula, B. F. Hogan, M. Martins, S. Fanning, P. J. Guiry, *Chem. Eur. J.*, **2014**, *20*, 15354-15359.

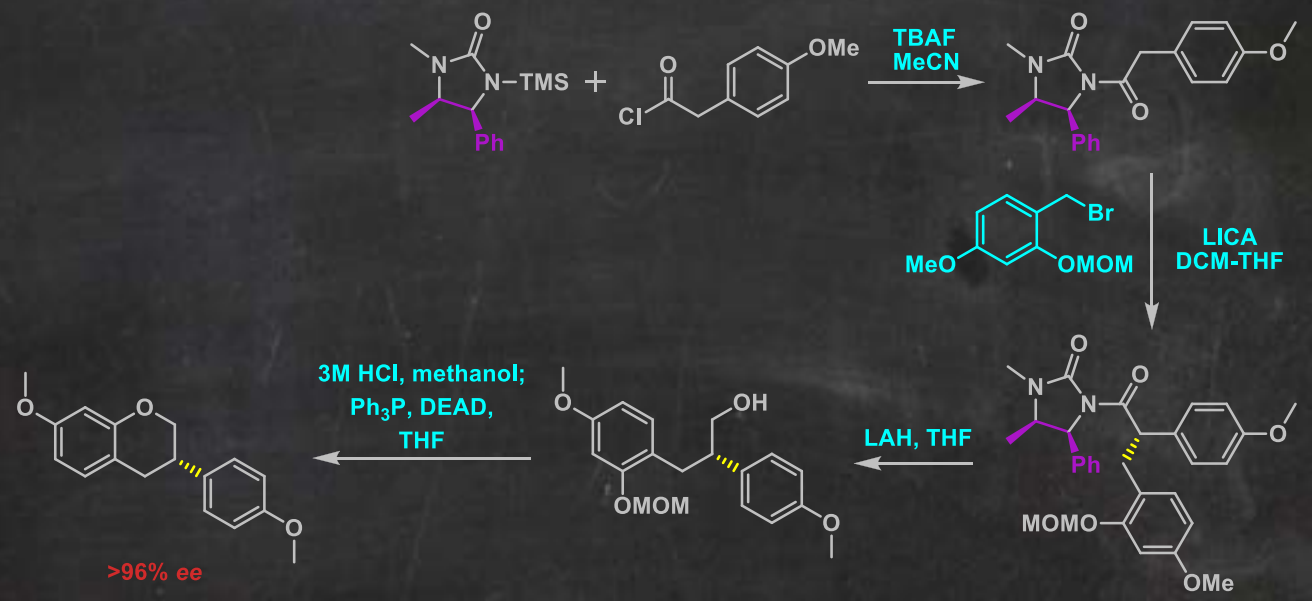
1.3 *Synthetic Strategies* – Erhardt *et al.*'s strategy



R. S. Khupse, P. W. Erhardt, *Org. Lett.*, **2008**, *10*, 5007.
A. Luniwal, R. S. Khupse, M. Reese, L. Fang, P. W.Erhardt, *J. Nat. Prod.* **2009**, *72*, 2072-2075.

1.3 *Synthetic Strategies* – Versteeg *et al.*'s strategy

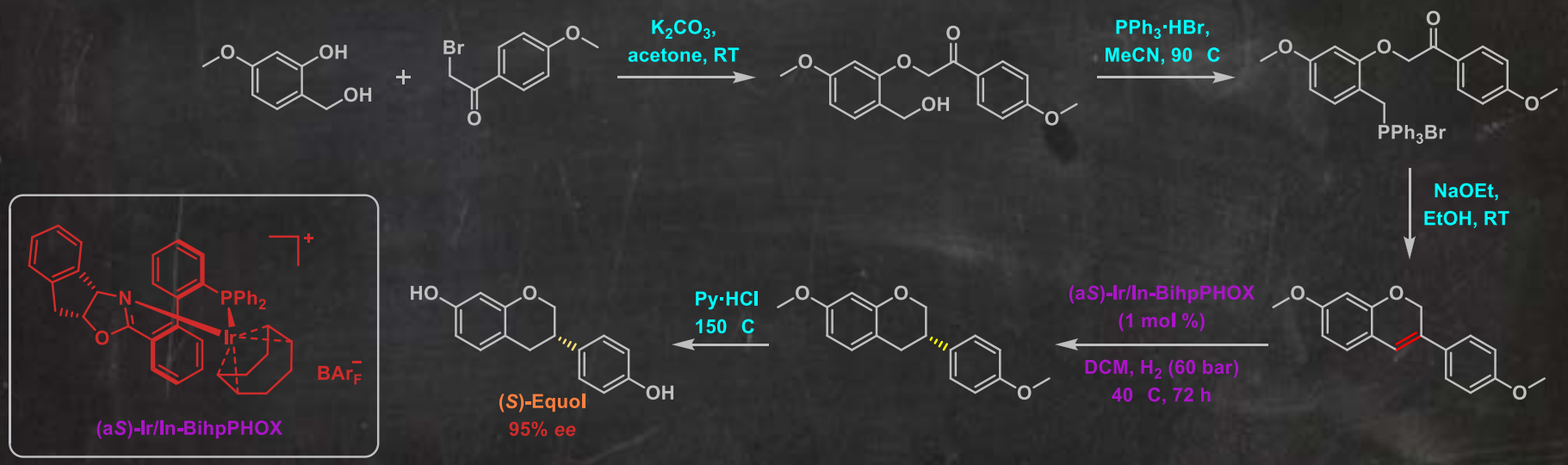
Asymmetric Alkylation with Chiral Auxilliary



M.Versteeg, B. C. B. Bezuidenhoudt, D. Ferreira, K. J. Swartb, *J. Chem. Soc., Chem. Commun.*, **1995**, 1317.
M.Versteeg, B. C. B. Bezuidenhoudt, D. Ferreira, *Tetrahedron*, **1999**, *55*, 3365.

1.3 *Synthetic Strategies* – Yang & Zhang *et al.*'s strategy

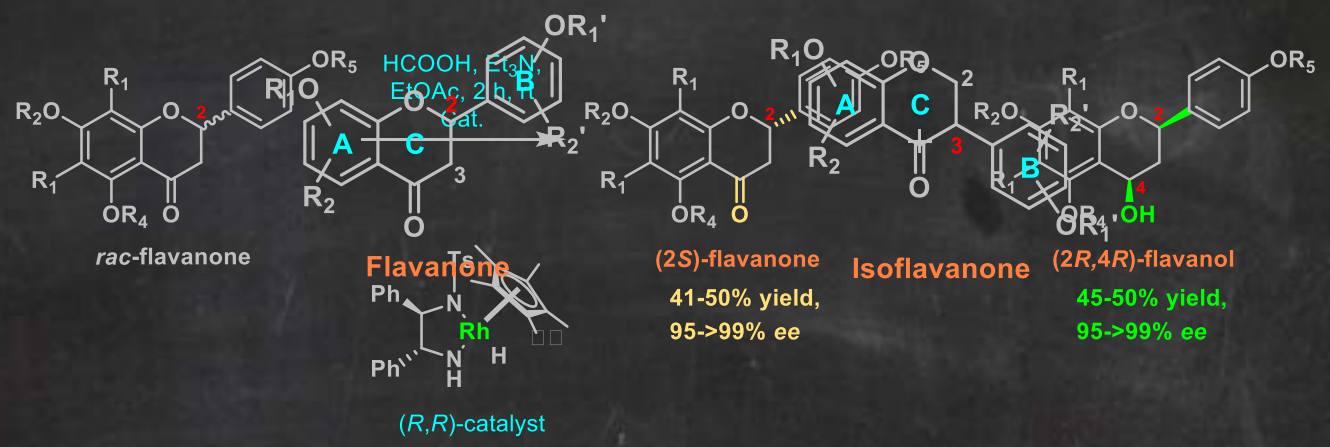
Asymmetric Hydrogenantion



Z. Ding, J. Yang, T. Wang, Z. Shen, Y. Zhang, *Chem. Commun.*, **2009**, 571-573

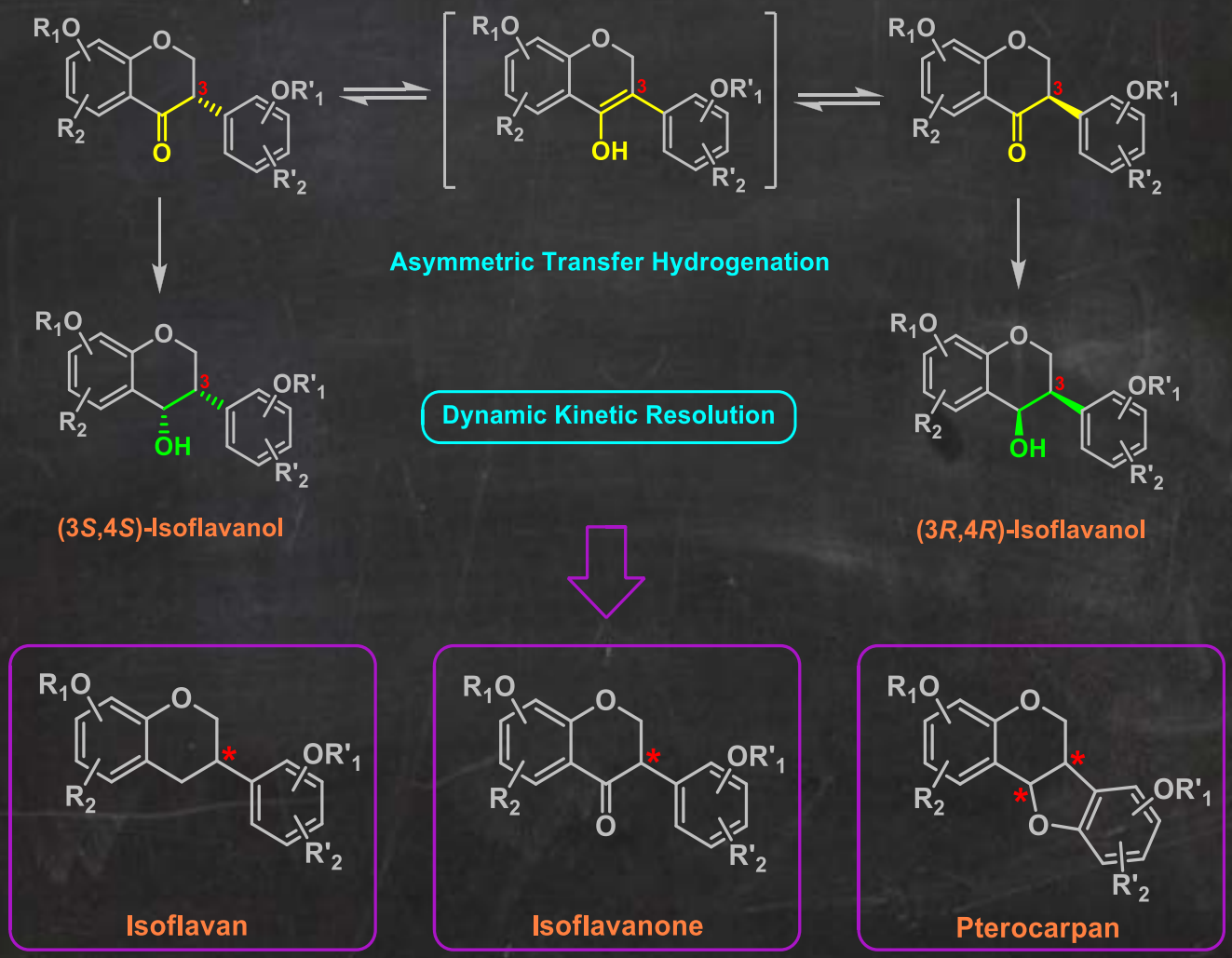
1.3 *Synthetic Strategies* – Kinetic Resolution of Flavanones (Metz Group in 2013)

Asymmetric Transfer Hydrogenation (ATH):

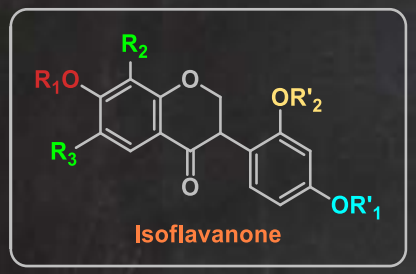


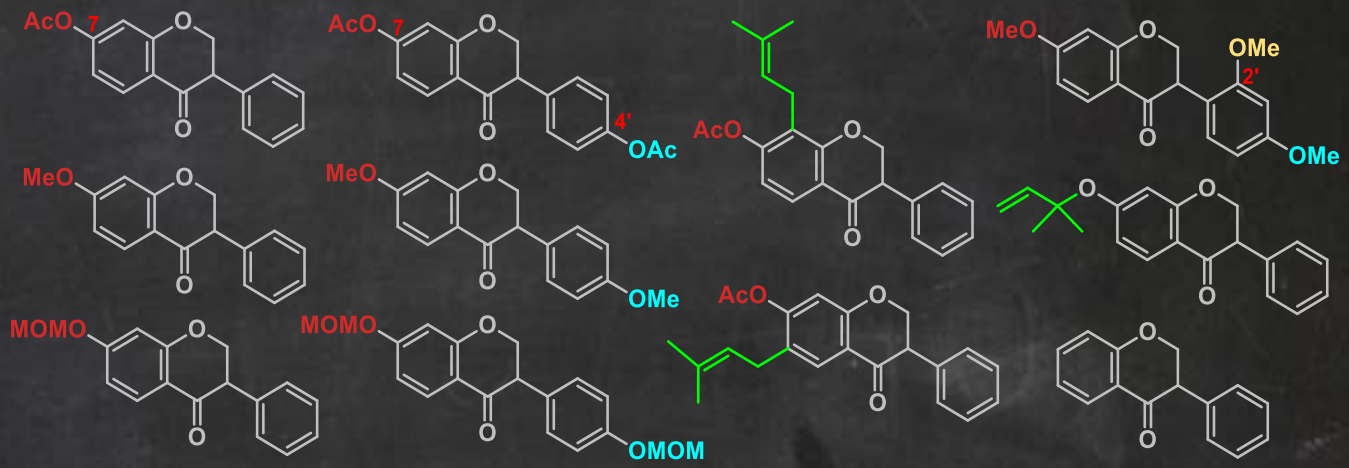
M.-K. Lemke, P. Schwab, P. Fischer, S. Tischer, M. Witt, L. Noehringer, V. Rogachev, A. Jäger, O. Kataeva, R. Fröhlich, P. Metz, *Angew. Chem.*, **2013**, *125*, 11865-11869.

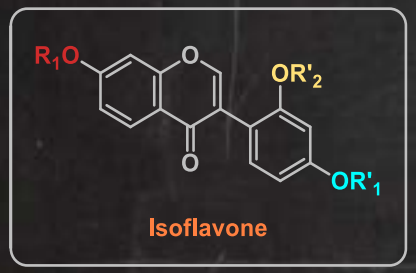
1.3 *Our Strategy* – The Proposal of Dynamic Kinetic Resolution for Isoflavonoids

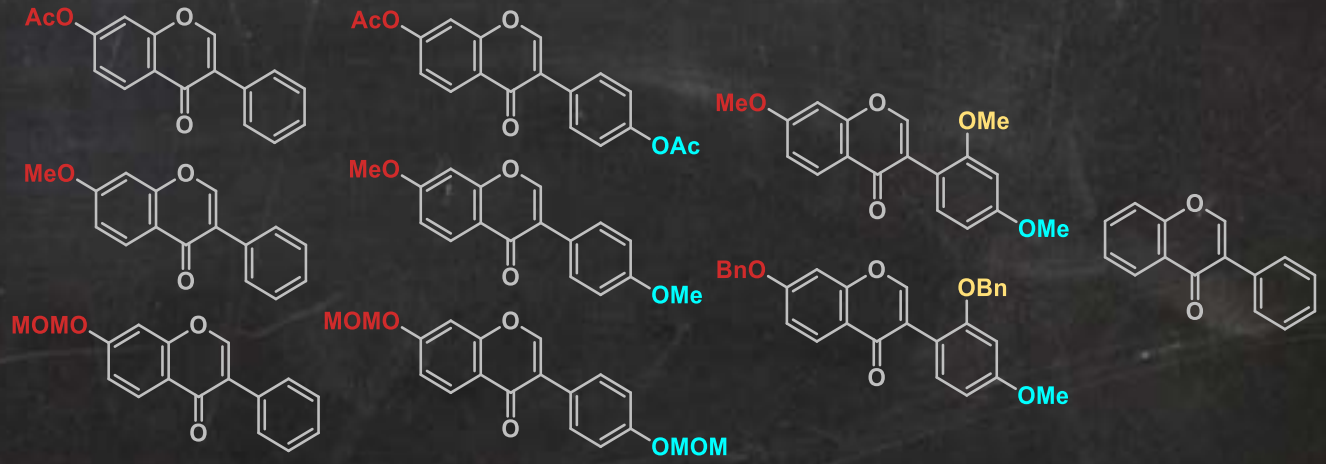


2. *Enantioselective Synthesis of Isoflavonoids*



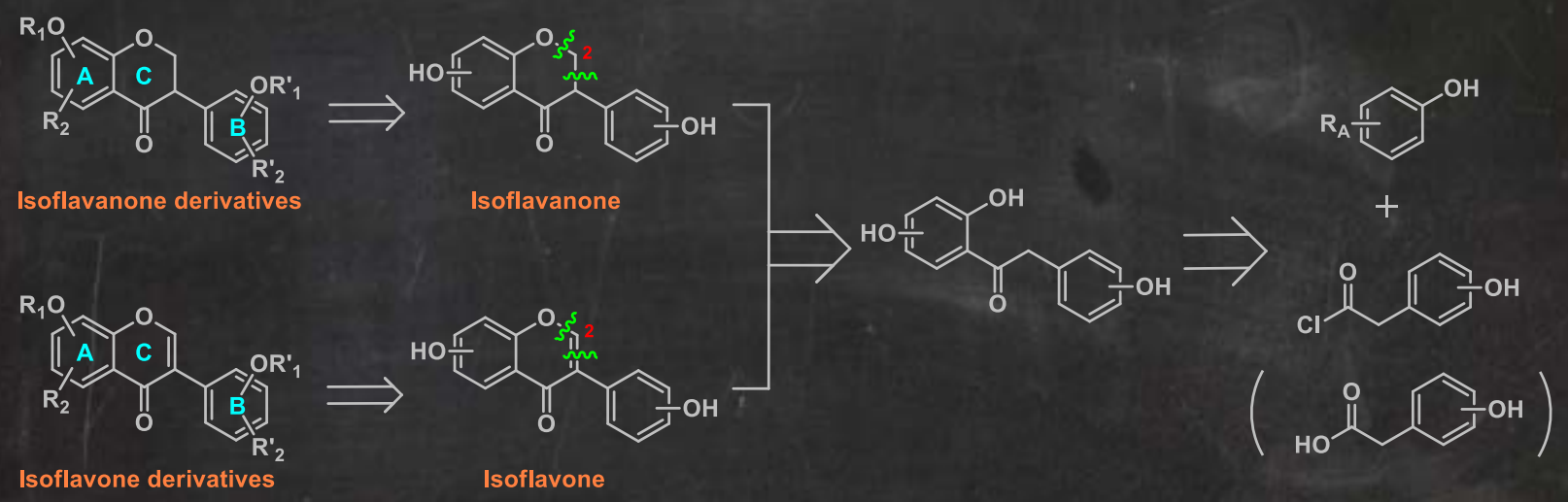






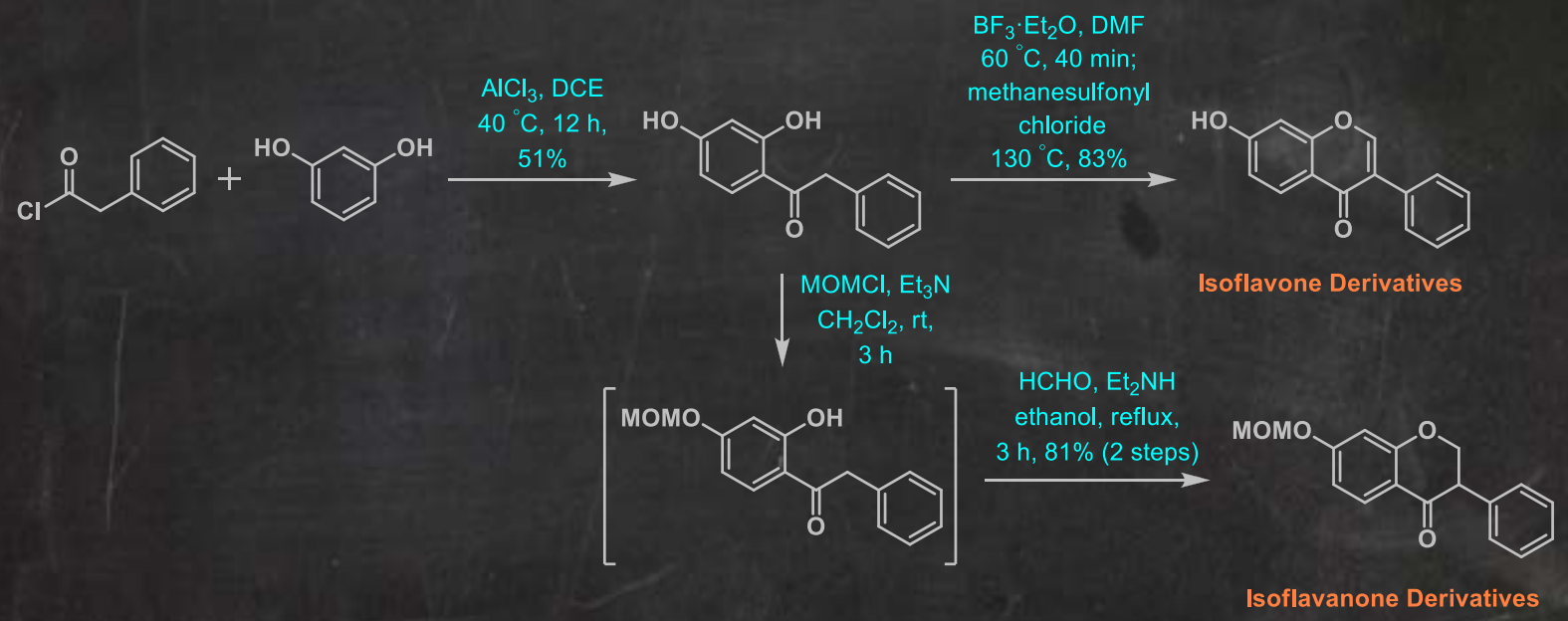
2.1 *Synthesis of rac-Isoflavonoids*

Route A:



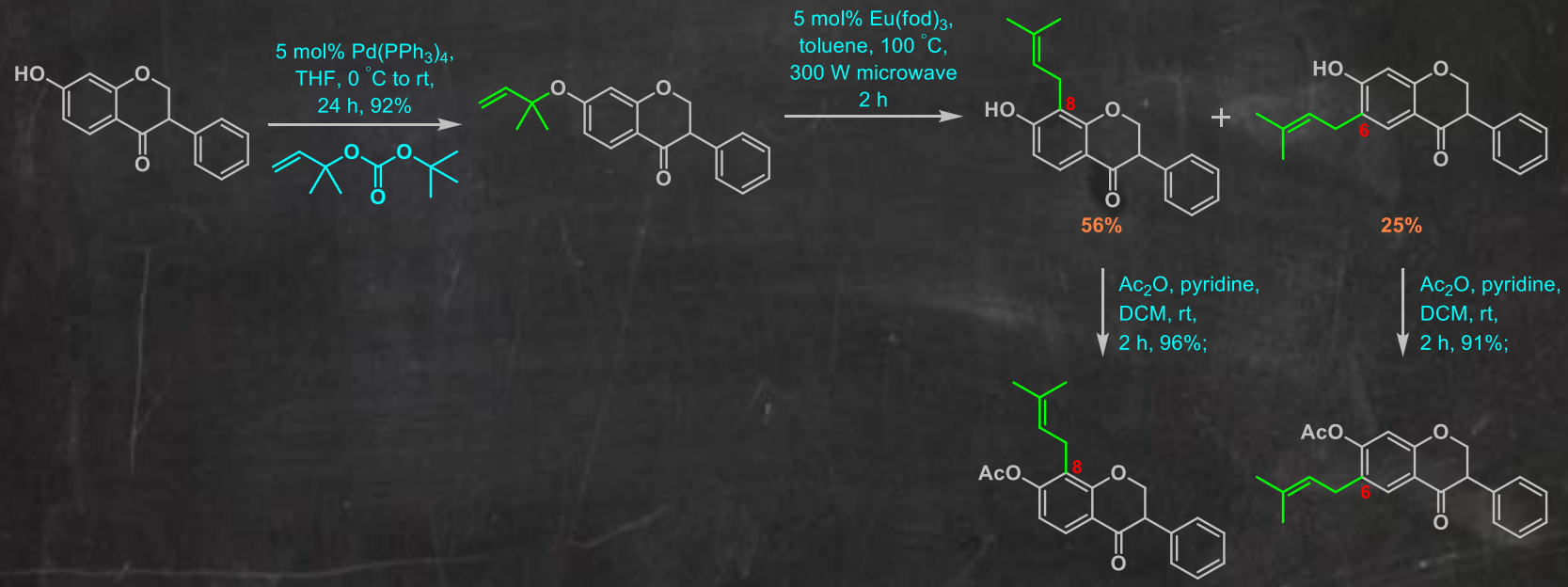
2.1 *Synthesis of rac-Isoflavonoids*

Route A: Synthetic Example - *Single-substituted derivatives*



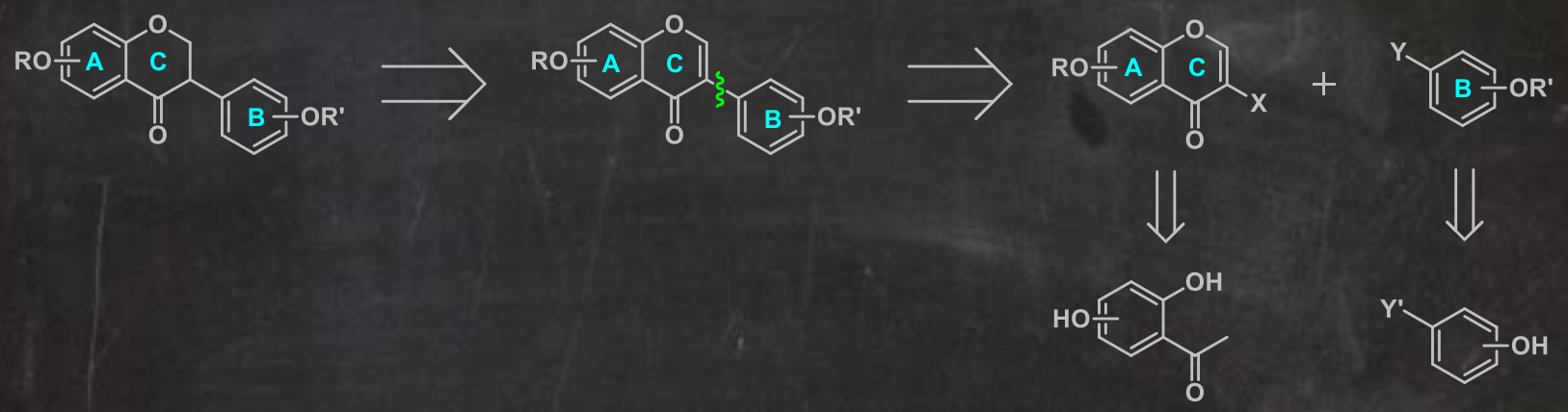
2.1 *Synthesis of rac-Isoflavonoids*

Route A: Prenylation



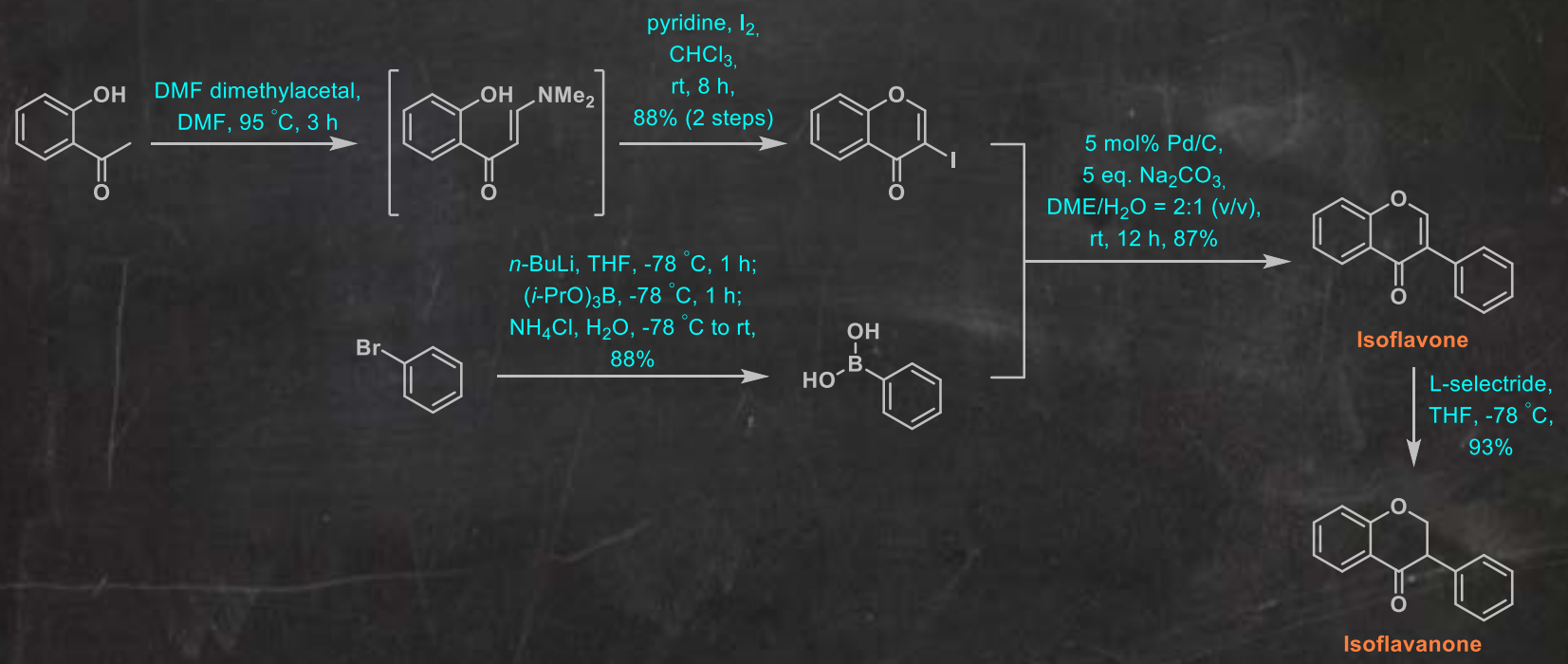
2.1 *Synthesis of rac-Isoflavonoids*

Route B:



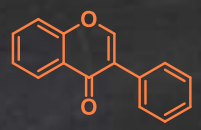
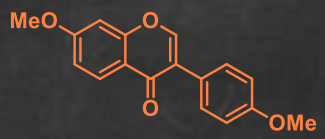
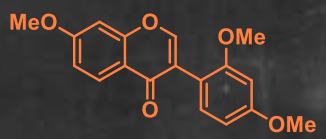
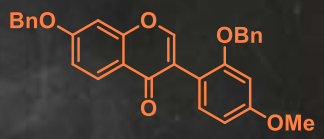
2.1 *Synthesis of rac-Isoflavonoids*

Route* B: Synthetic Example - *Non-substituted derivatives



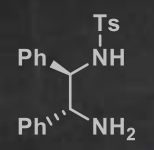
2.1 *Synthesis of rac-Isoflavonoids*

Route B: *Suzuki-Miyaura* Coupling

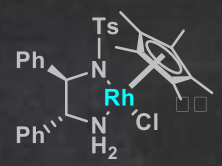
Suzuki-Miyaura Coupling				
5 mol% Pd/C, 5 eq. Na_2CO_3, DME/H_2O = 2:1, rt, 12 h	89%	trace	No reaction	No reaction
5 mol% Pd/C, 5 eq. Na_2CO_3, DME/H_2O = 2:1, 45 °C, 24 h			No reaction	No reaction
10 mol% $Pd(PPh_3)_4$, 5 eq. Na_2CO_3, Benzene, reflux, 24 h			trace	trace
10 mol% $Pd(OAc)_2$, 20 mol% P(*o*-tol)$_3$, 5 eq. K_2CO_3, DME/H_2O = 2:1 50 °C, 24 h		42%	26%	trace
10 mol% $Pd(OAc)_2$, 20 mol% P(*o*-tol)$_3$, 10 eq. K_2CO_3, DME/H_2O = 2:1 50 °C, 24 h,		81%	47%	40%

2.2 *Asymmetric Transfer Hydrogenation of Isoflavanones*

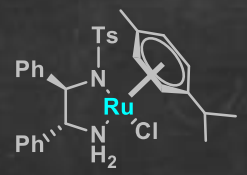
pre*-Catalysts with *different transition metal & ligands



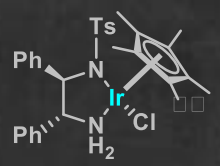
(*R*,*R*) - Ligand A



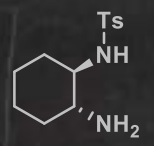
I



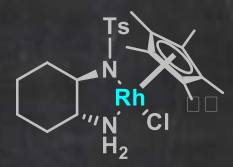
II



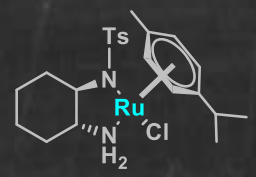
III



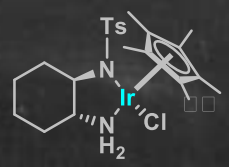
(*R*,*R*) - Ligand B



IV



V

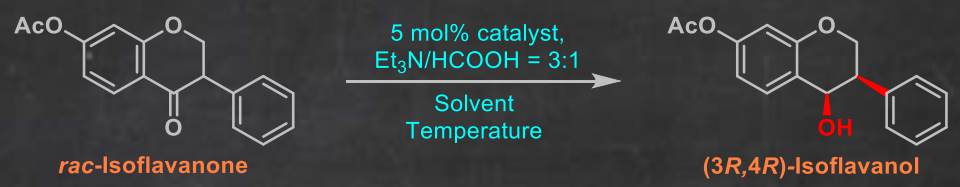


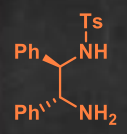
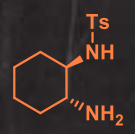
VI

Chiral metal-diamine complexes I - VI. Ts=tosyl=*p*-toluenesulfonyl.

- *6 catalysts*
- *Temperature*
- *Solvent*
- *Different H Source*
- *Lower Load of catalyst*

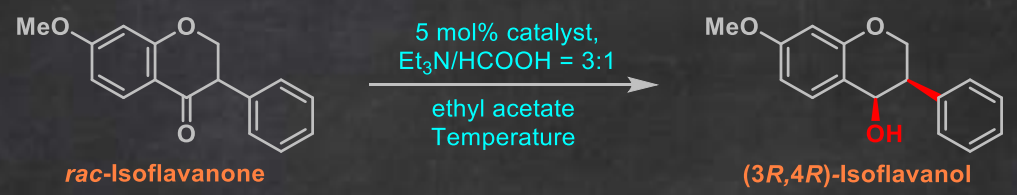
2.2 *Asymmetric Transfer Hydrogenation of Isoflavanones*

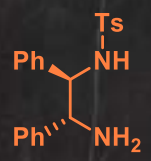


(*R*,*R*) - catalysts Ligand	complex Metal	Temperature	Solvent	Time [hours]	*ee*[b] of (3*R*,4*R*)-Isoflavanol[c]	Yield[a] of (3*R*,4*R*)-Isoflavanol[c]
	Rh complex (I)	0 °C	DCM	120	>99%	82%
	Ru complex (II)		DCM	120	>99%	66%
	Ir complex (III)		DCM	144	93%	90%
Ligand A	Rh complex (I)	RT	DCM	144	93%	30%
	Ru complex (II)		DCM	24	>99%	92%
	Ir complex (III)		DCM	48	>99%	39%
	Rh complex (IV)	0 °C	DCM	120	39%	6%
	Ru complex (V)		DCM	144	>99%	40%
	Ir complex (VI)		DCM	144	93%	10%
Ligand B	Rh complex (IV)	RT	DCM	144	22%	12%
	Ru complex (V)		DCM	48	>99%	76%
	Ir complex (VI)		DCM	120	-	-
Ligand A	Ru complex (II)	45 °C	EtOAc	3	>99%	94%

[a] Yield of isolated product. [b] Determined by HPLC on a chiral stationary phase. [c] After oxidation to give *(R)*-isoflavanone determined by optical rotation.

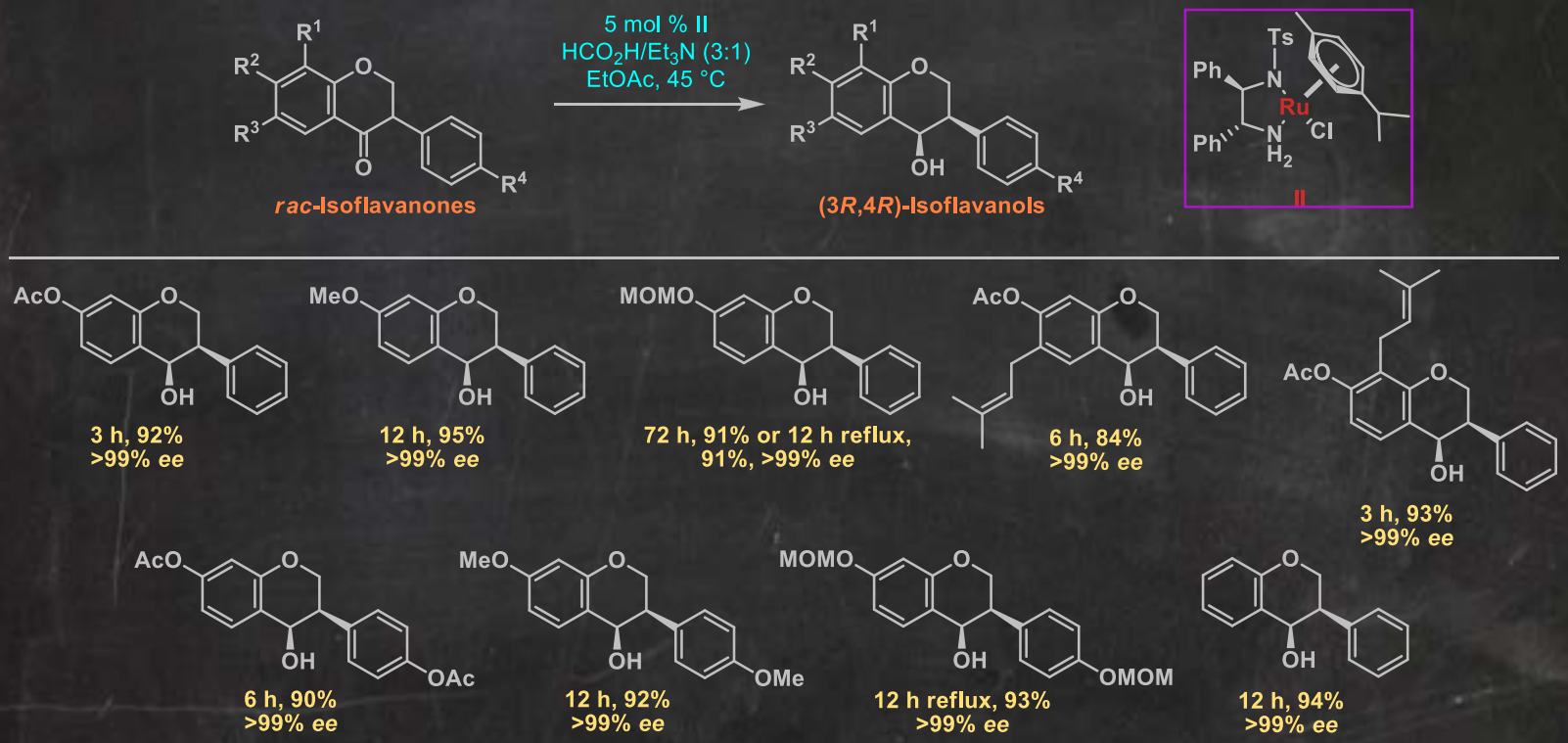
2.2 *Asymmetric Transfer Hydrogenation of Isoflavanones*



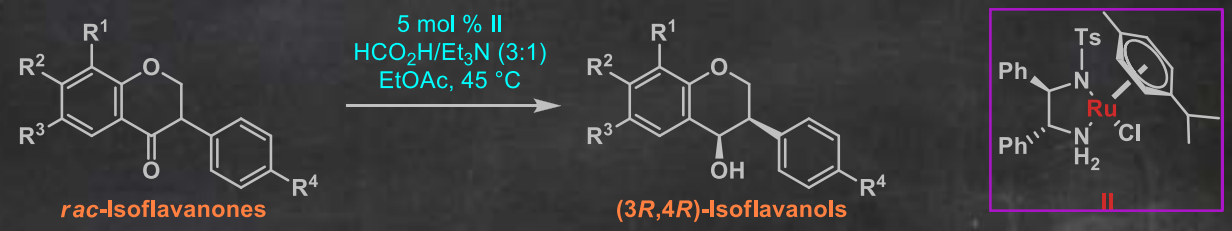
(*R*,*R*) – catalysts Ligand	Metal complex	Temperature	Solvent	Time [hours]	ee[b] of (3*R*,4*R*)-Isoflavanols[c]	Yield[a] of (3*R*,4*R*)-Isoflavanols[c]
 Ligand A	**Rh** complex (I)	RT	EtOAc	96	>99%	17%
	Ru complex (II)		EtOAc	96	>99%	98%
	Ir complex (III)		EtOAc	96	>99%	36%
	Rh complex (I)	45 °C	EtOAc	12	>99%	14%
	Ru complex (II)		EtOAc	12	>99%	96%
	Ru complex (II)[d]		EtOAc	9.5	>99%	97%
	Ir complex (III)		EtOAc	12	>99%	43%

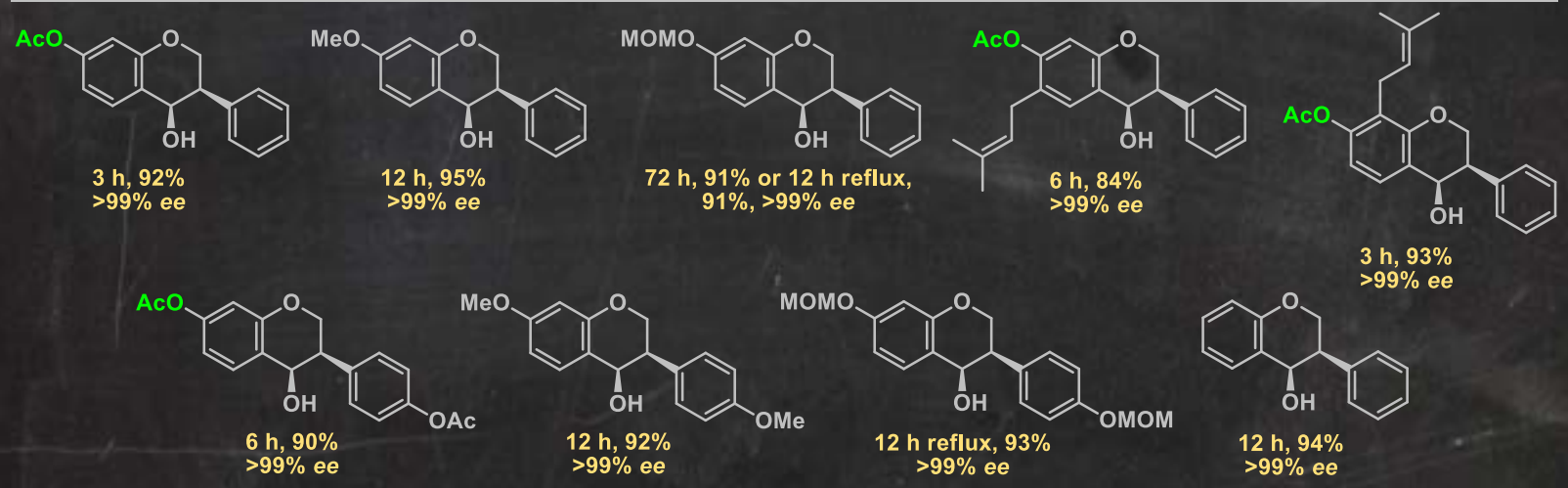
[a] Yield of isolated product. [b] Determined by HPLC on a chiral stationary phase. [c] After oxidation to give *(R)*-isoflavaone determined by optical rotation.
[d] 10 mol% catalyst(II)

2.2 *Asymmetric Transfer Hydrogenation of Isoflavanones*

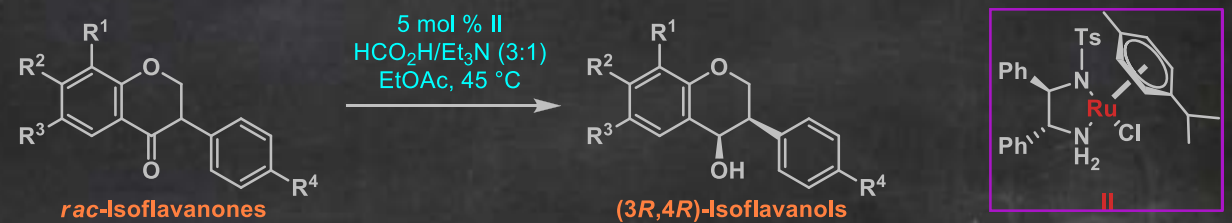


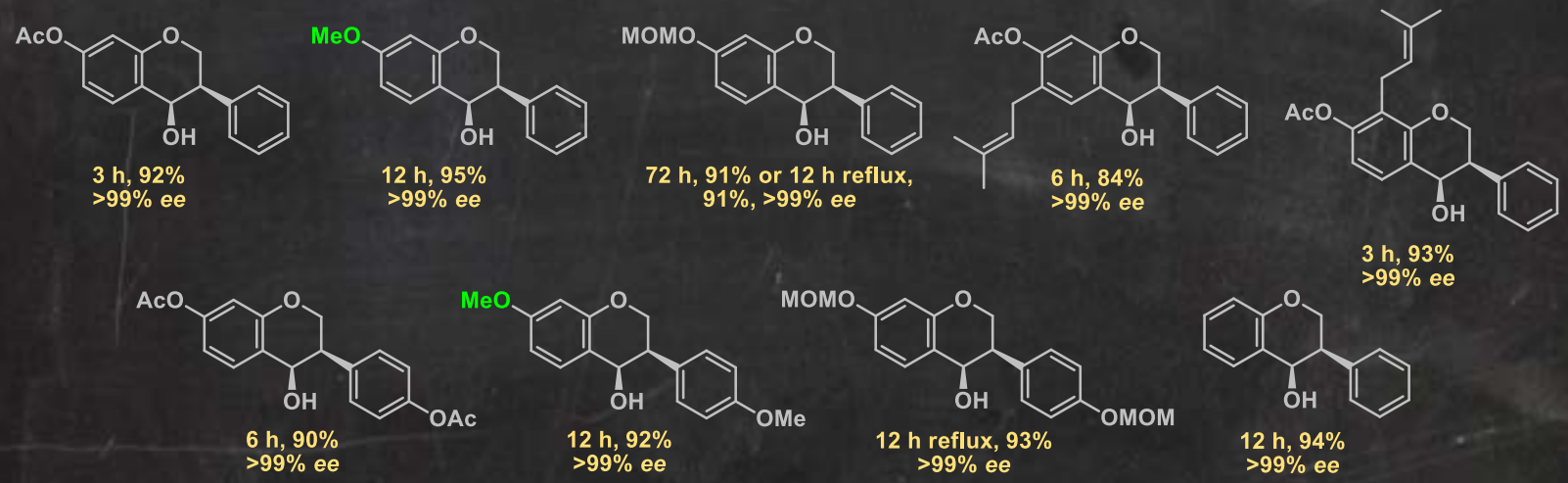
2.2 *Asymmetric Transfer Hydrogenation of Isoflavanones*



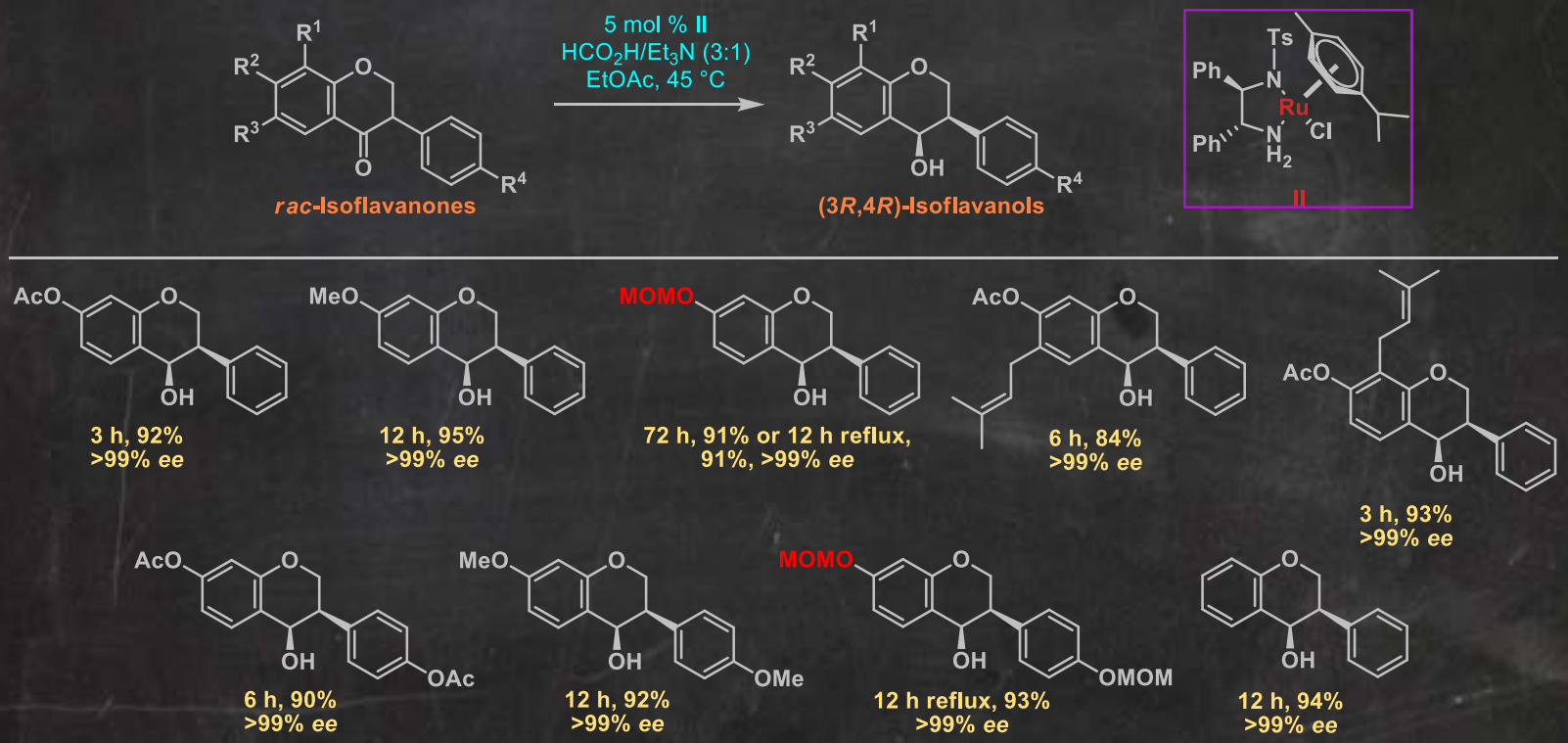


2.2 *Asymmetric Transfer Hydrogenation of Isoflavanones*

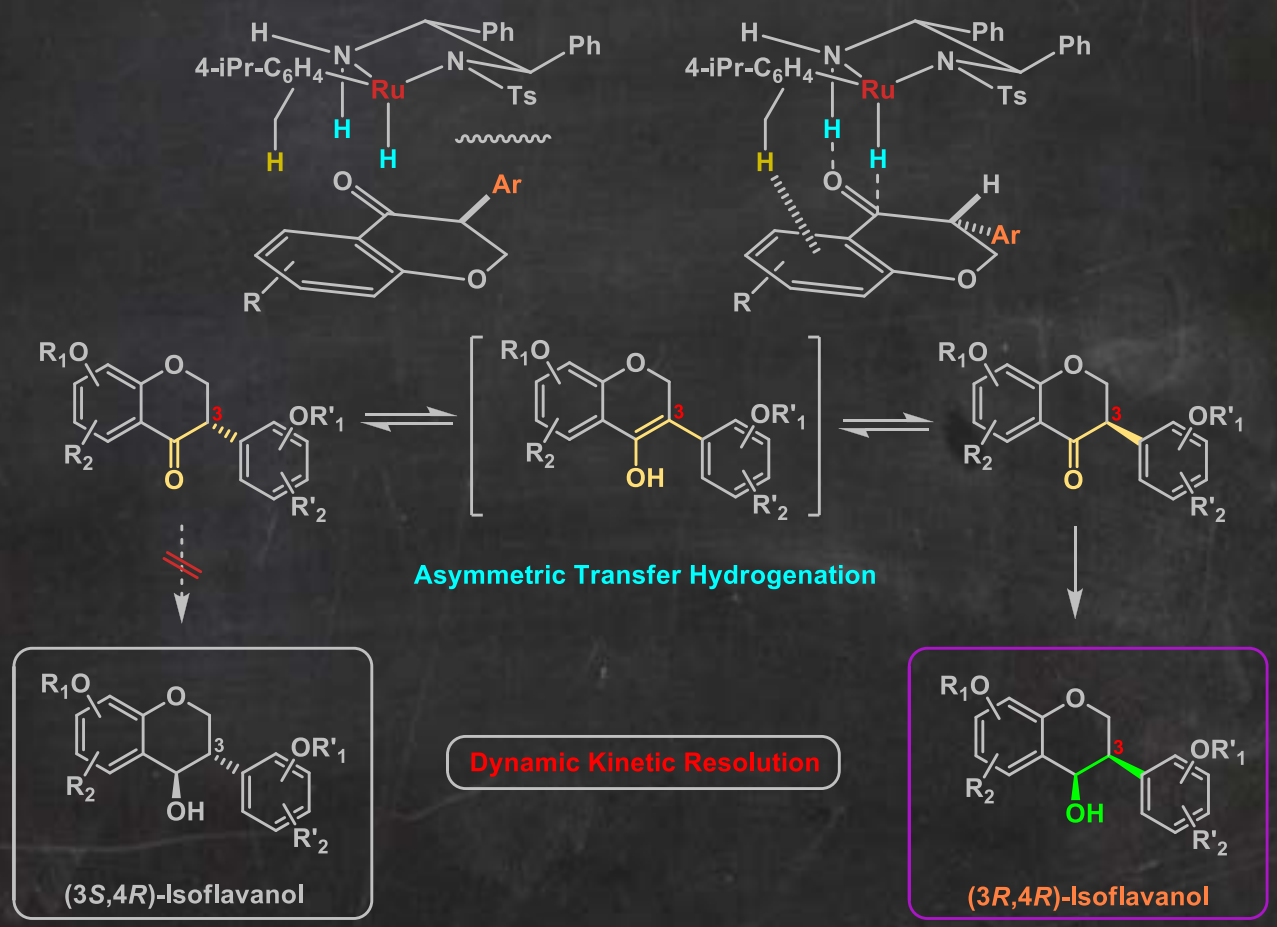




2.2 *Asymmetric Transfer Hydrogenation of Isoflavanones*

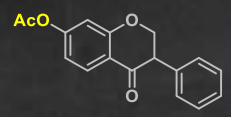
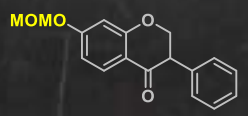
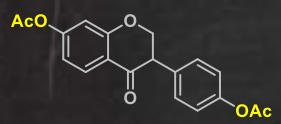
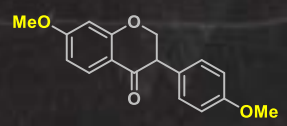


2.2 *Asymmetric Transfer Hydrogenation of Isoflavanones*



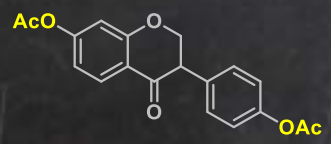
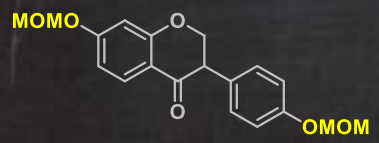
2.2 *Asymmetric Transfer Hydrogenation of Isoflavanones*

Investigation of H source:

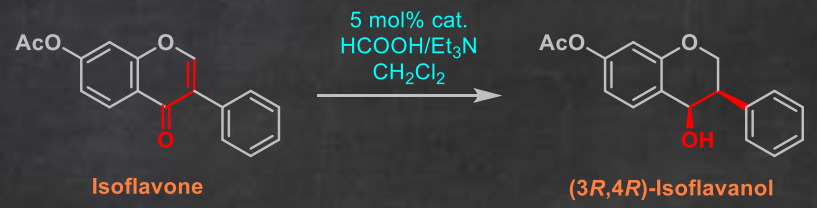
rac-Isoflavanones	Hydrogen donors	Temperature [°C]	Time [hours]	(3*R*,4*R*)-Isoflavanols	
				ee	yield
	HCO_2H/Et_3N	45	3	>99%	92%
	NH_4OOCH	45	12	>99%	88%
	HCOOH	45	24	-	-
	HCO_2H/Et_3N	reflux	12	>99%	91%
	NH_4OOCH	45	72	96%	71%
	NH_4OOCH	reflux	72	86%	90%
	HCO_2H/Et_3N	45	6	>99%	90%
	$NaOOCH/H_2O$	45	6	94%	90%
	HCOOH	45	24	-	-
	HCO_2H/Et_3N	45	12	>99%	92%
	NH_4OOCH	45	48	>99%	73%
	NH_4OOCH	45	96	91%	89%

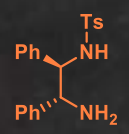
2.2 *Asymmetric Transfer Hydrogenation of Isoflavanones*

Investigation of lower load of catalyst :

rac-Isoflavanones	Mol %	T	Time [hours]	(3*R*,4*R*)-Isoflavanols	
				ee	yield
	5	45 °C	8	>99%	88%
	1		14	99%	83%
	0.5		24	96%	71%
	5	reflux	12	>99%	91%
	1		48	99%	81%
	0.5		48	98%	52%

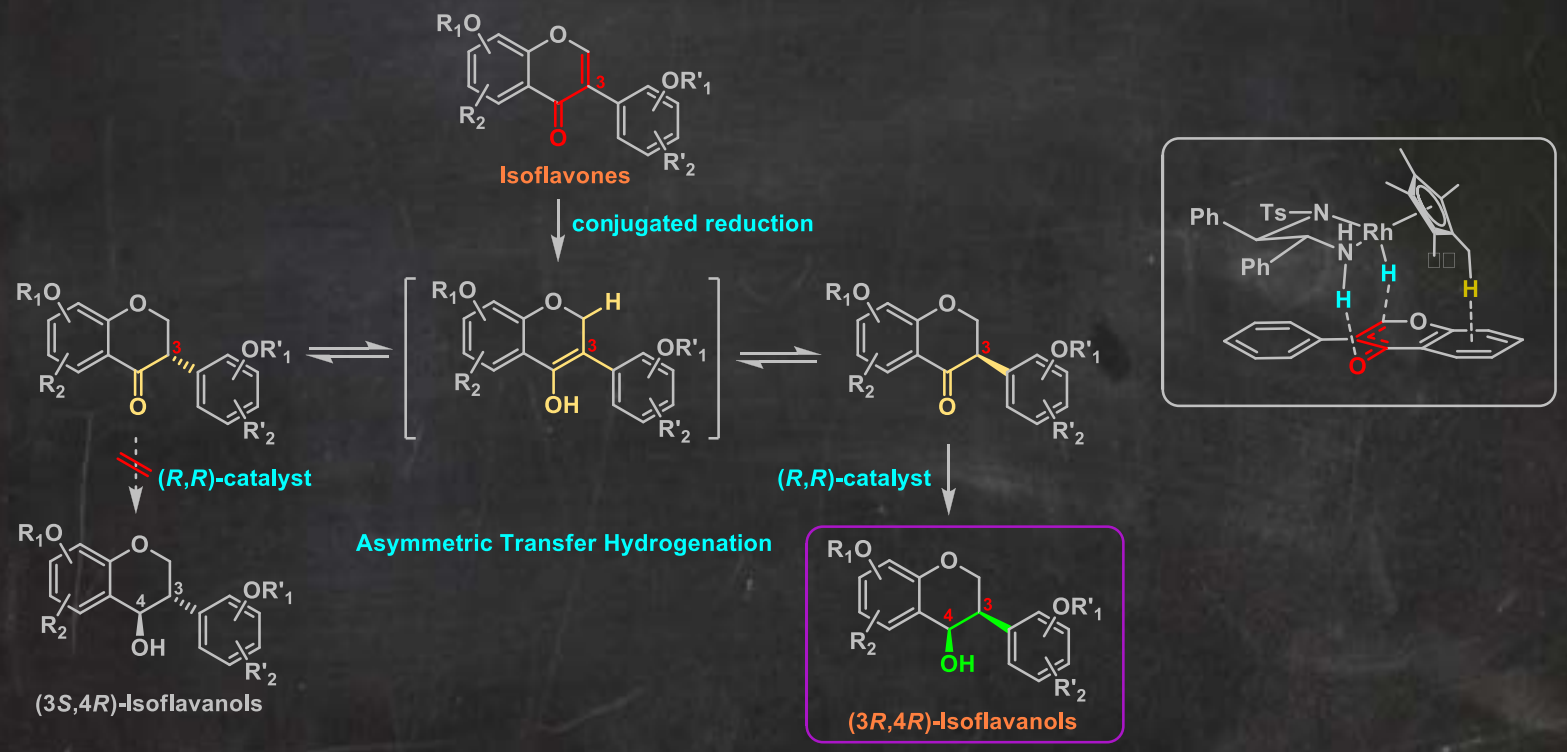
2.3 *Asymmetric Transfer Hydrogenation of Isoflavones*



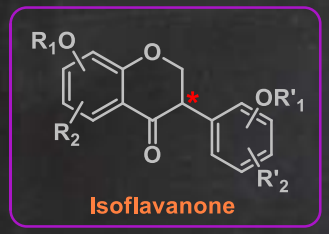
(*R*,*R*) – catalysts Ligand	Metal complex	Temperature	*ee*[b] of (3*R*,4*R*)-Isoflavanols[c]	Yield[a] of (3*R*,4*R*)-Isoflavanols[c]
 Ligand A	**Rh** complex (**I**)	0 °C	>99%	55%
	Ru complex (**II**)		>99%	5%
	Ir complex (**III**)		>99%	4%
	Rh complex (**I**)	RT	>99%	5%
	Ru complex (**II**)		>99%	10%
	Ir complex (**III**)		-	-
	Ru complex (**II**)	45 °C (EtOAc)	>99%	93%

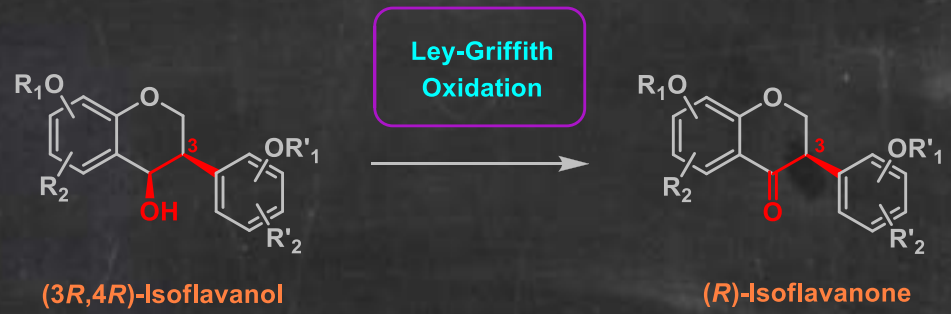
[a] Yield of isolated product. [b] Determined by HPLC on a chiral stationary phase. [c] After oxidation to give *(R)*-isoflavanone determined by optical rotation.

2.3 *Asymmetric Transfer Hydrogenation of Isoflavones*



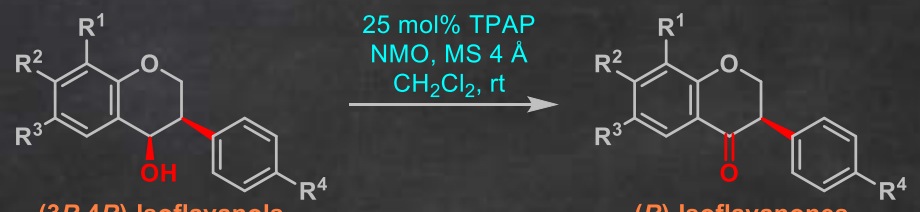
2.4 *Oxidation of Isoflavanols*





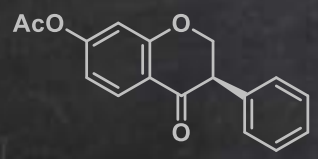
- Concentration
- Temperature
- Different Load of Catalyst

2.4 *Oxidation of Isoflavanols*

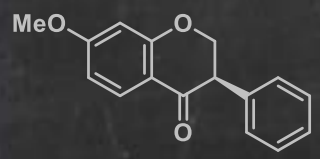


(3*R*,4*R*)-Isoflavanols

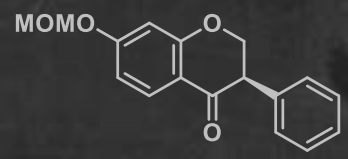
(*R*)-Isoflavanones



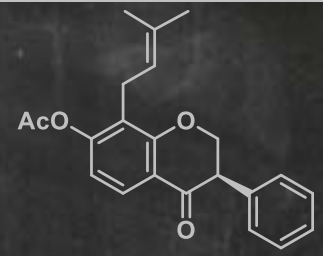
93%
>99% *ee*



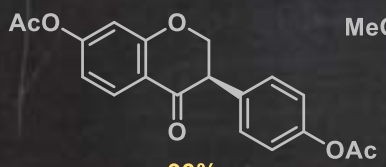
96%
96% *ee*



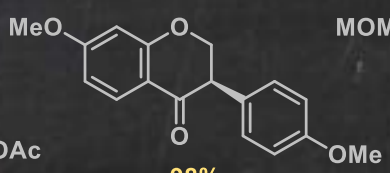
95%
>99% *ee*



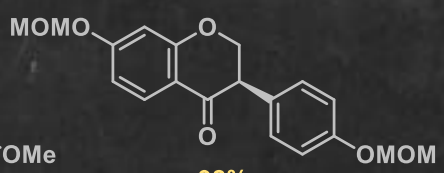
91%
96% *ee*



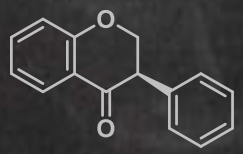
93%
97% *ee*



98%
>99% *ee*

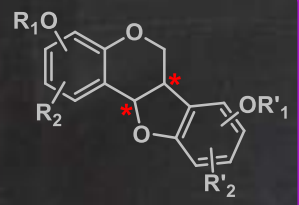


92%
96% *ee*

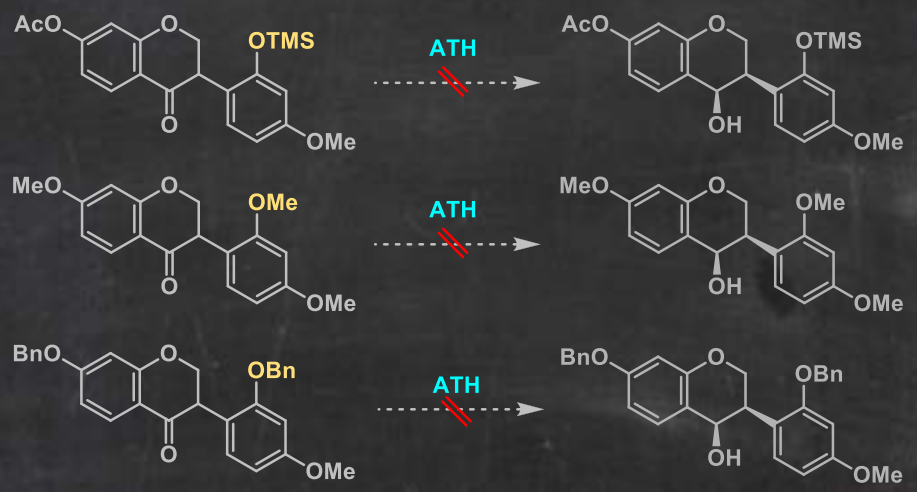


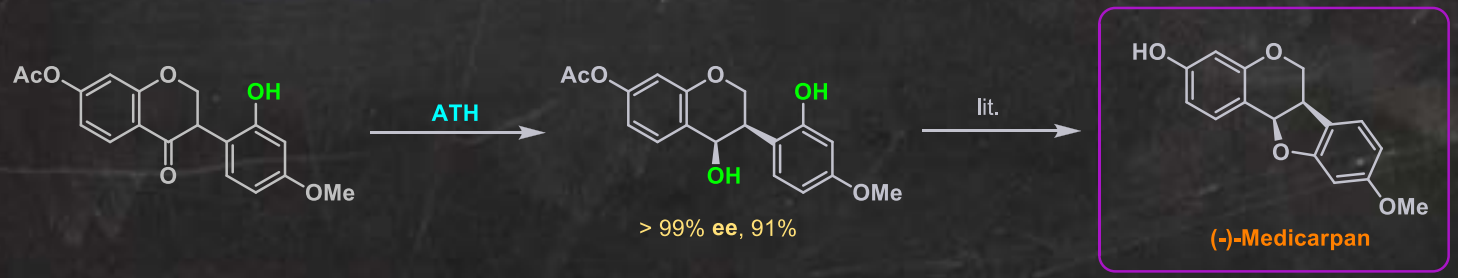
90%
97% *ee*

2.5 *Synthetic Strategy of Pteracarpans*

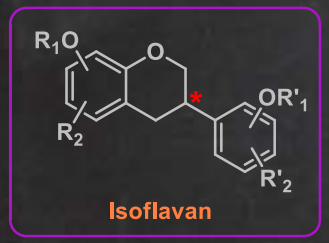


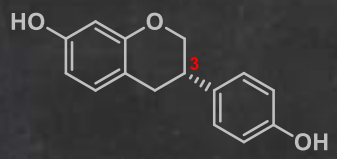
Pterocarpan



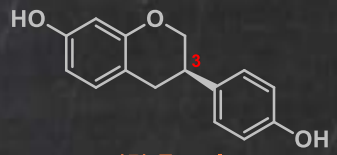


2.6 *Synthetic Application – (+)-Equol*





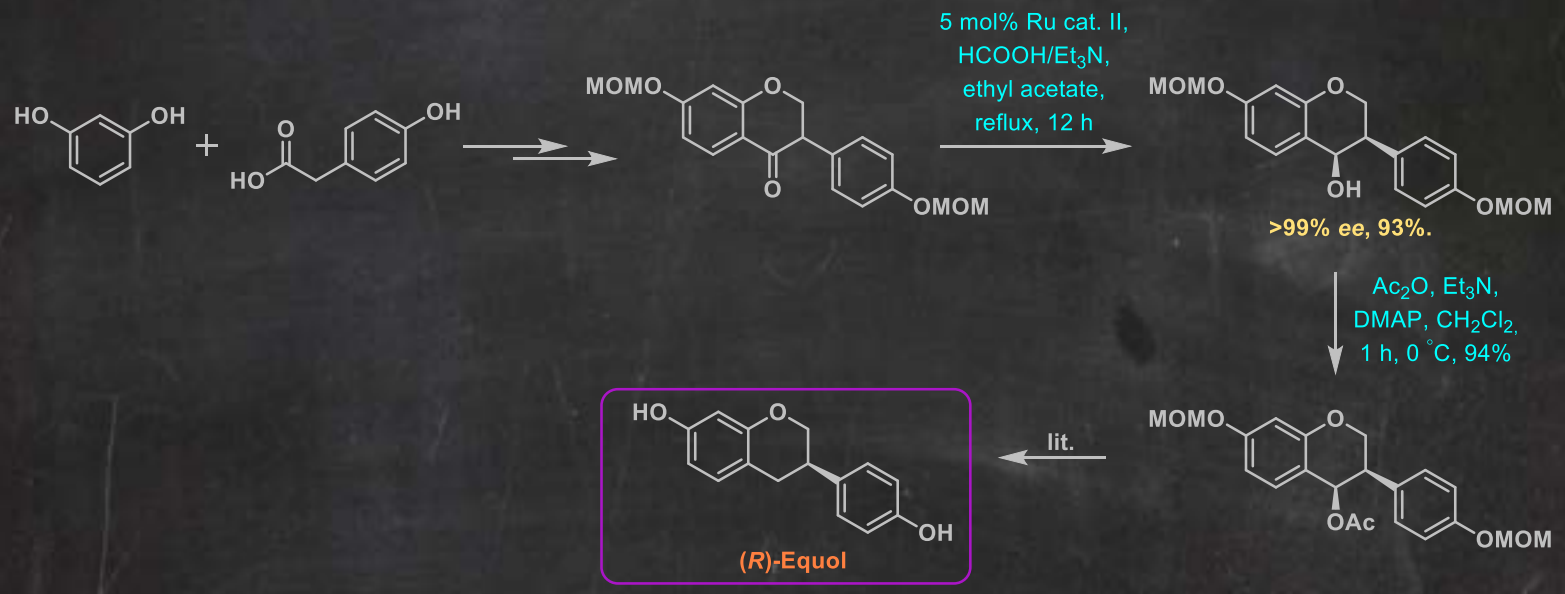
(*S*)-Equol



(*R*)-Equol

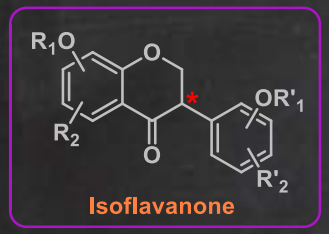
- First isolated in 1932 from equine urine and identified in 1982.
- Impressive bioactivities as strongest phytoestrogen and antioxidant.
- Both enantiomers are of interest from a clinical and pharmacological perspective and currently being developed as nuitraceutical and pharmaceutical agents.

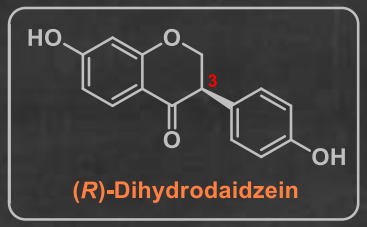
2.6 *Synthetic Application – (+)-Equol*



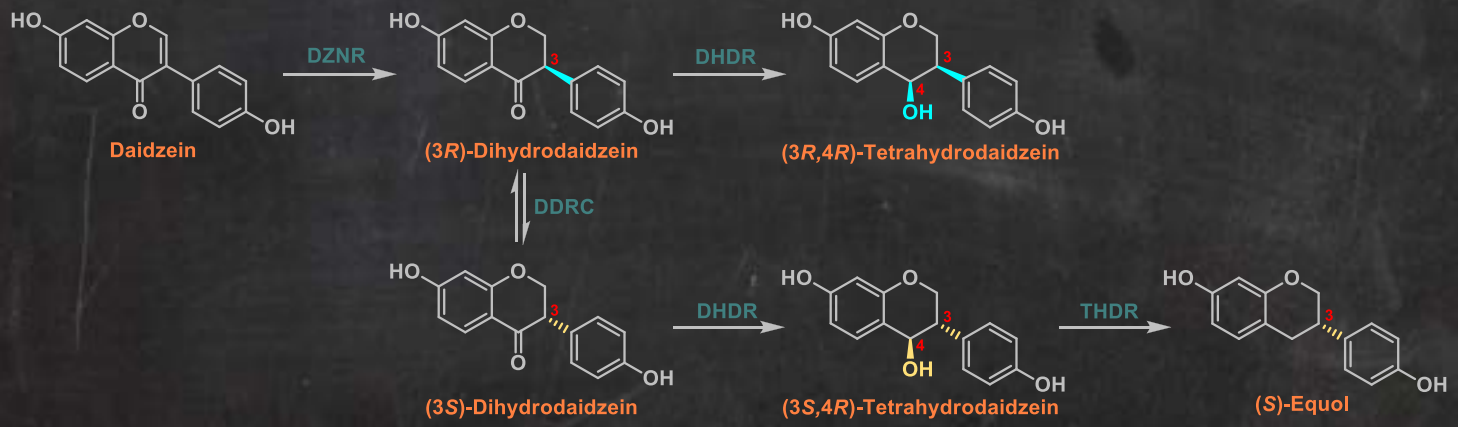
Lit.: US 2015183797A1

2.6 *Synthetic Application – (+)-Dihydrodaidzein*



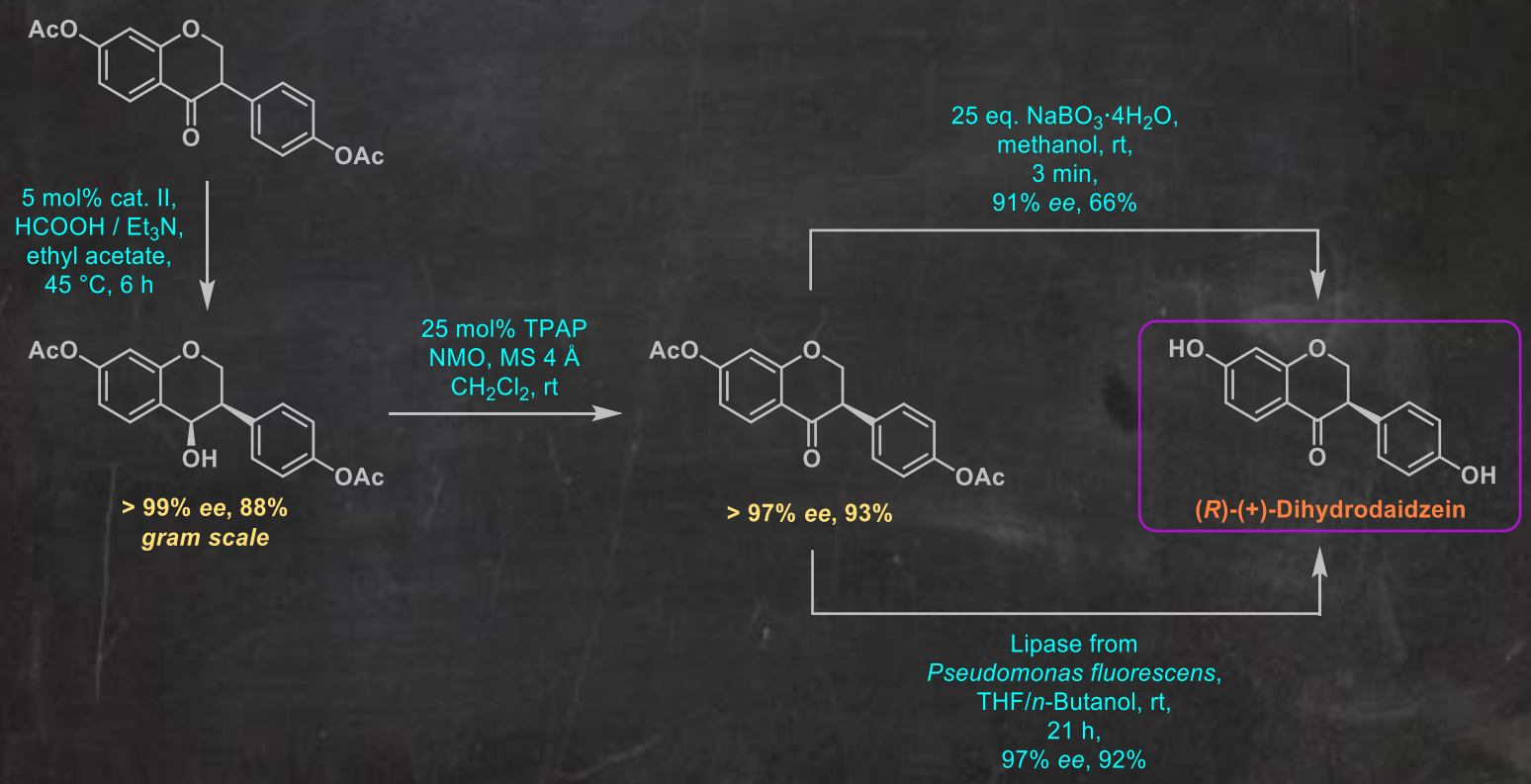


- An essential biosynthetic intermediate of isoflavonoids, the precursor of (*S*)-(-)-Equol.
- One of the most bioactive isoflavonoids as phytoestrogen and antioxidant.
- A cardioprotective agent.



Appl. Environ. Microbiol., **2016**, *82*, 1992-2002.

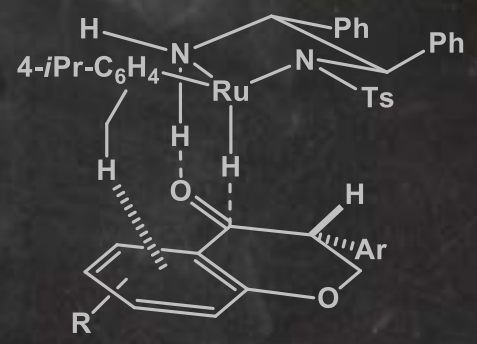
2.6 *Synthetic Application – (+)-Dihydrodaidzein*



TECHNISCHE UNIVERSITÄT DRESDEN

Enantioselective Synthesis of Isoflavonoids via Catalytic Dynamic Kinetic Resolution

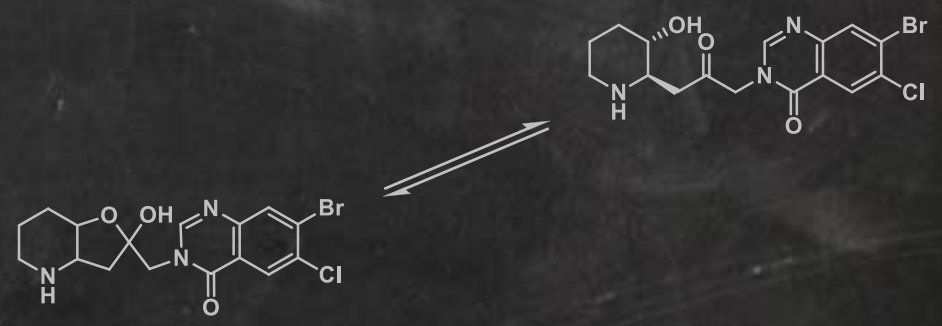
- Synthesis of *rac*-Isoflavonoid Derivatives
  - *Route* A
  - *Route* B
- Asymmetric Transfer Hydrogenation of *Isoflavanones*
- Asymmetric Transfer Hydrogenation of *Isoflavones*
- Oxidation of Isoflavanols – *Ley-Griffith* Oxidation
- Synthetic Strategy of *Pterocarpans*
- Synthetic Applications
  - (+)-*Equol*
  - (+)-*Dihydrodaidzein*



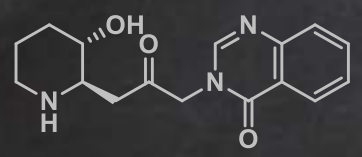
Practical Synthesis of Halofuginone Hydrobromide

-- 1. Synthesis of *rac*-Halofuginone Hydrobromide

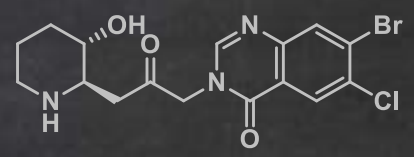
-- 2. Asymmetric Synthesis of Halofuginone Hydrobromide



1. *Synthesis of rac-Halofuginone Hydrobromide*



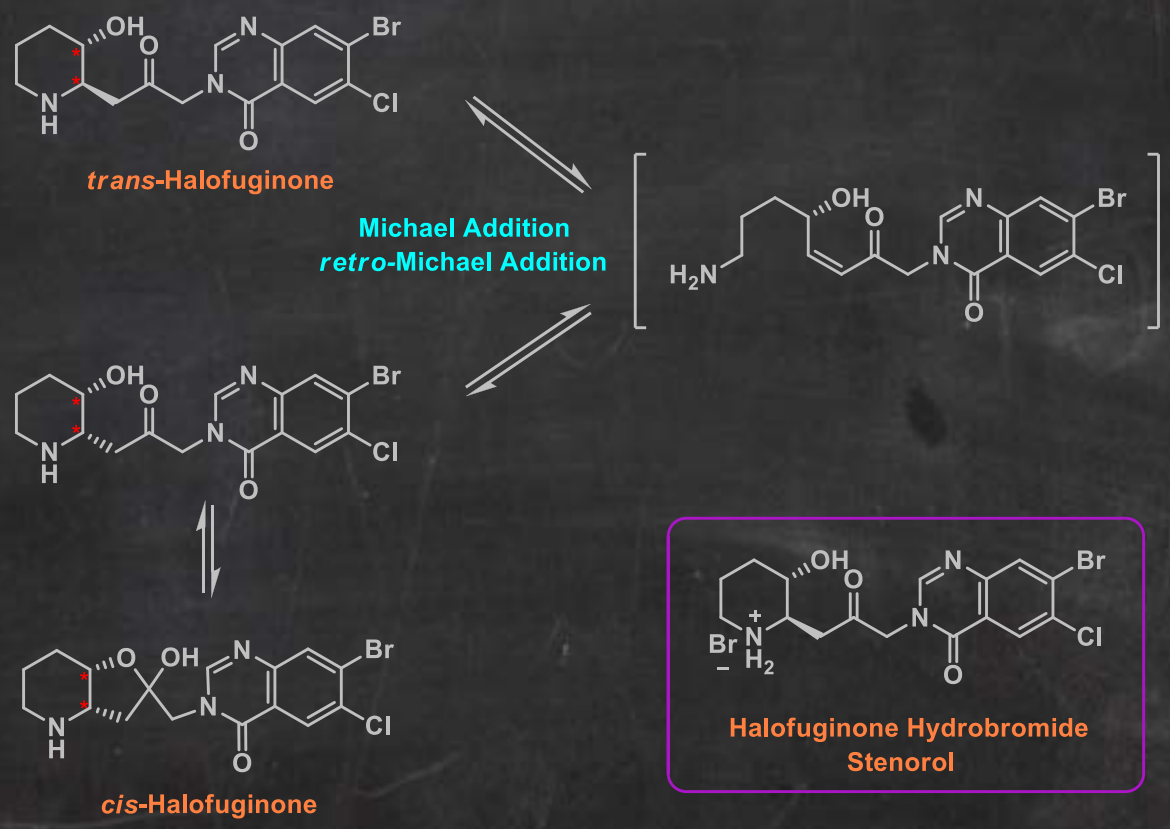
Febrifugine



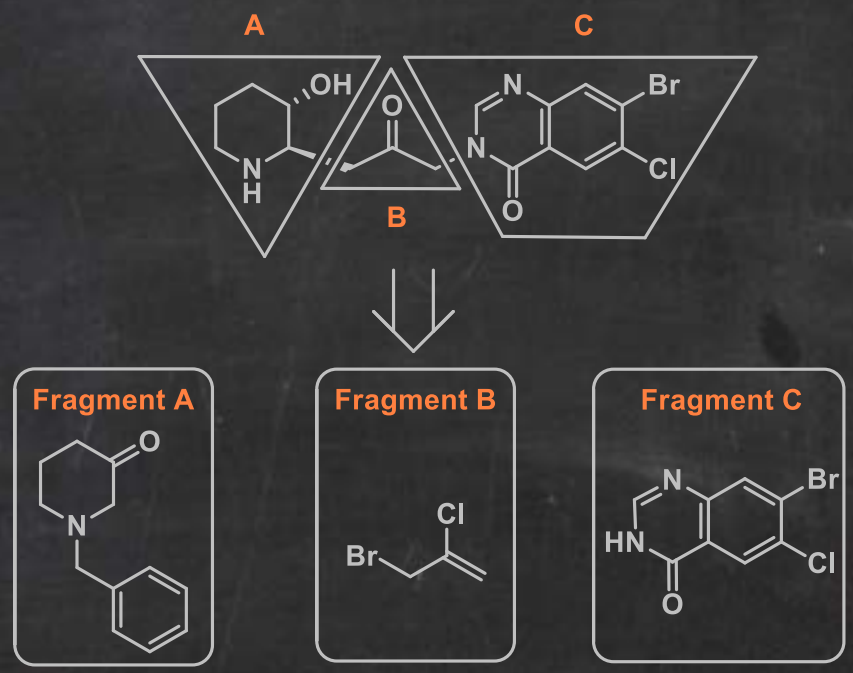
Halofuginone

- Quinazolinone alkaloid
- Traditional Chinese herb *Dichroa Febrifuga* (Chang Shan)
- High antimalarial activity
- Side effect: the gastrointestinal toxicity
- The only reversible inhibitor of collagen type I synthesis currently known
  - *Scar*
  - *Pulmonary Fibrosis*

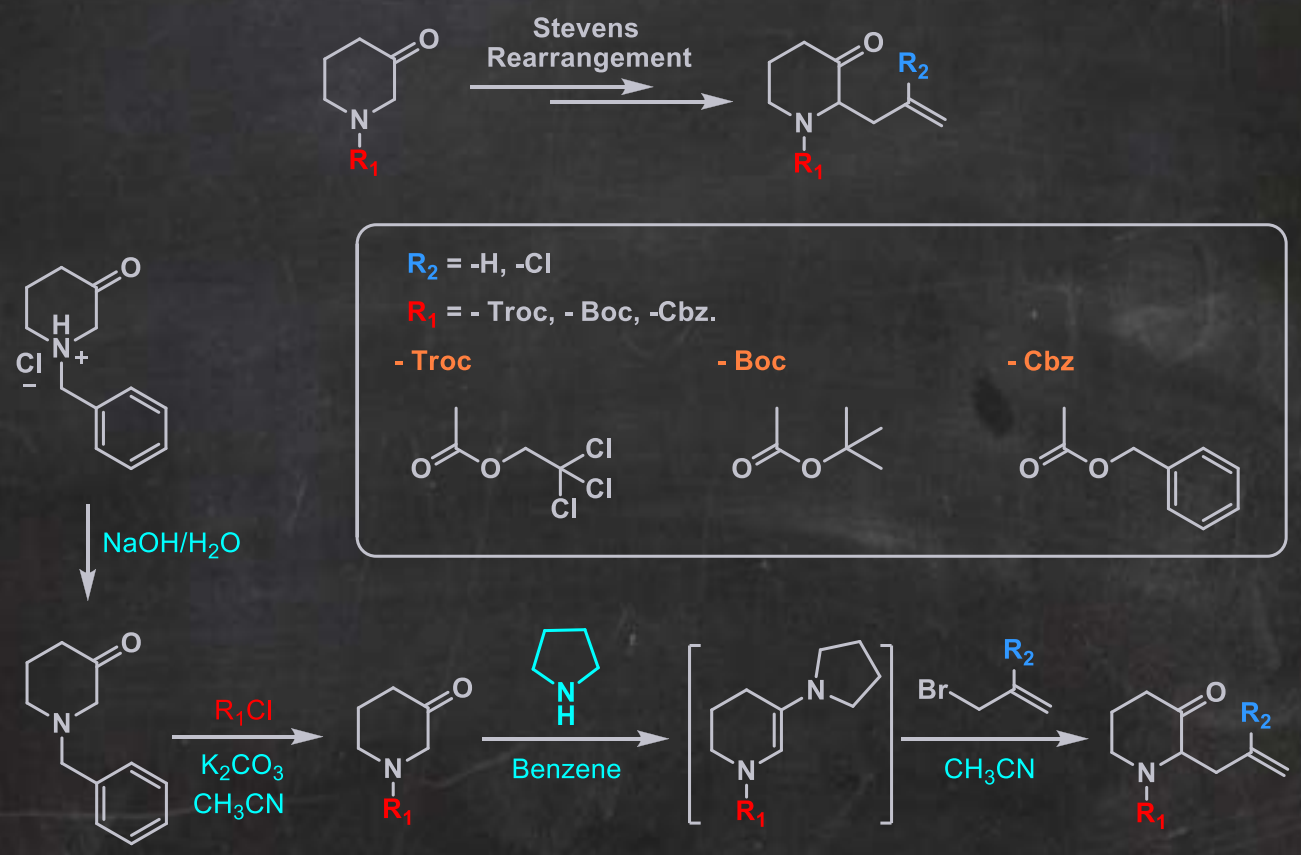
1. *Synthesis of rac-Halofuginone Hydrobromide*



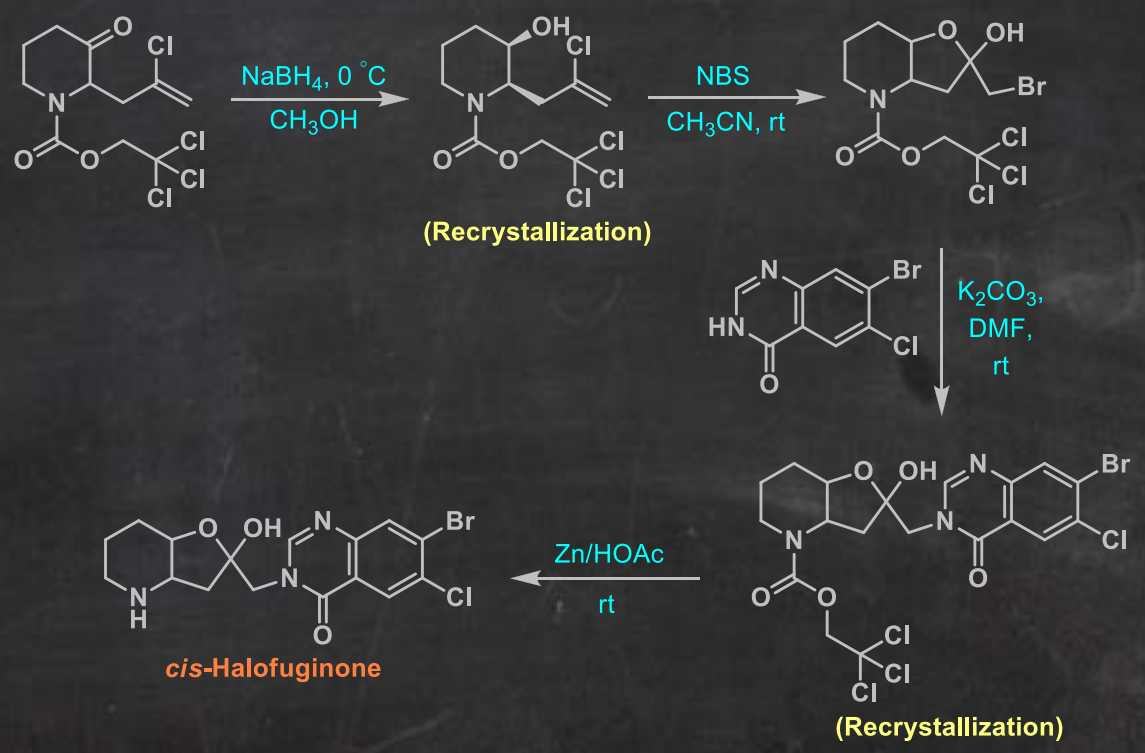
1. *Synthesis of rac-Halofuginone Hydrobromide* – Convergent Strategy



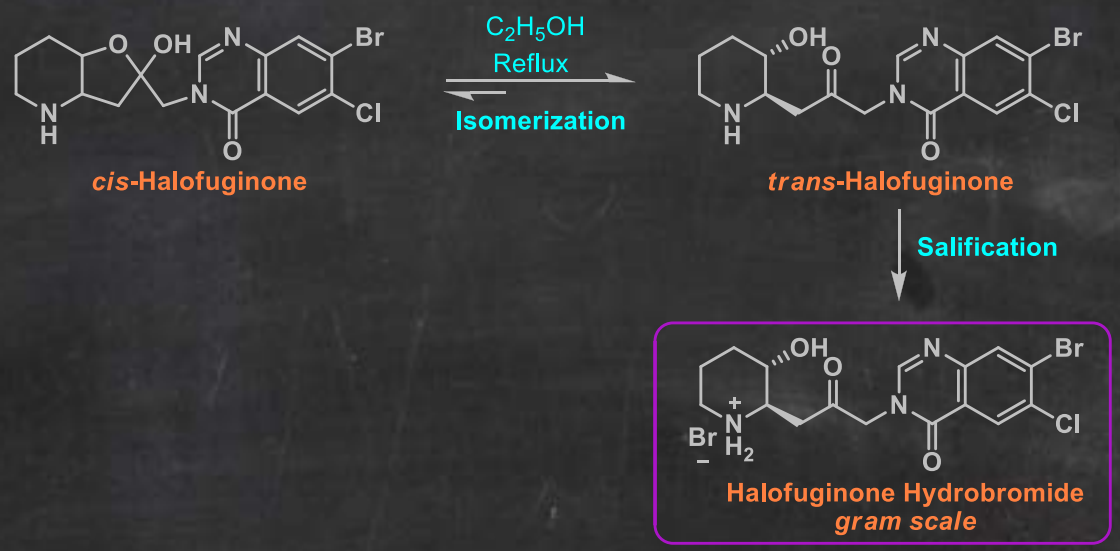
1. *Synthesis of rac-Halofuginone Hydrobromide* – Stork Enamine Alkylation



1. *Synthesis of rac-Halofuginone Hydrobromide*



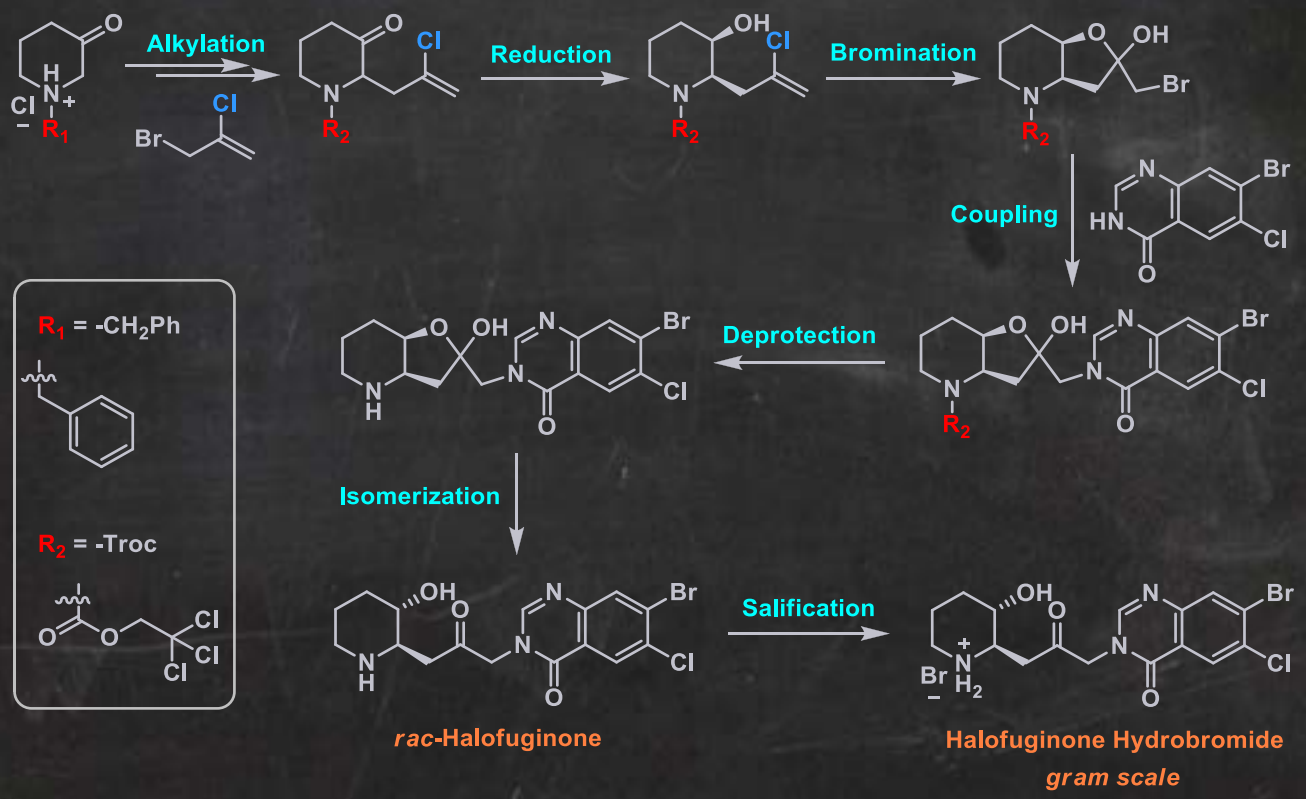
1. *Synthesis of rac-Halofuginone Hydrobromide*



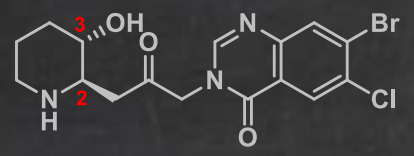
1. *Synthesis of rac-Halofuginone Hydrobromide*

- *Stork enamine alkylation to replace Stevens rearrangemnet*
- *Chromo allyl moiety*
- *Troc- protection*

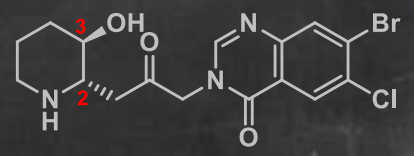
✓ *Replace all the chromatographs by crystallization and distillation*



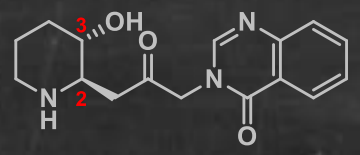
2. *Asymmetric Synthesis of Halofuginone Hydrobromide*



(2*R*,3*S*)-(+)-Halofuginone

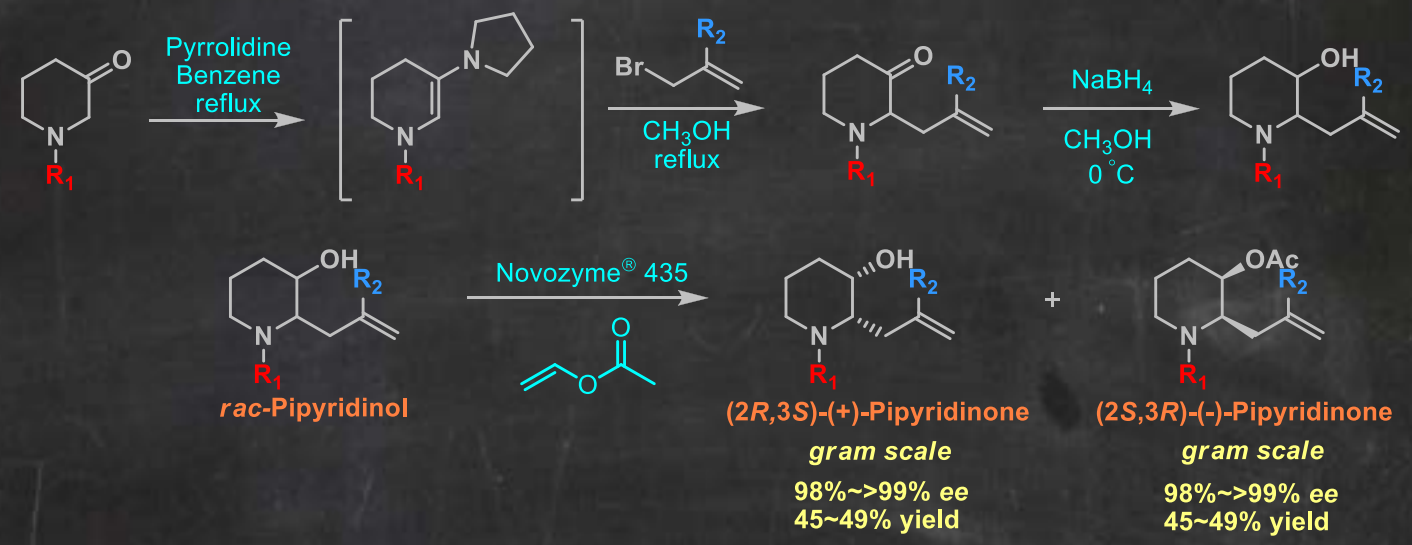


(2*S*,3*R*)-(-)-Halofuginone



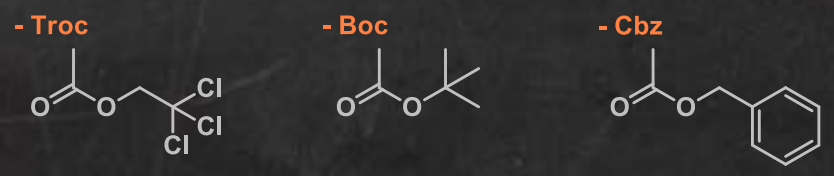
natural compound
(2*R*,3*S*)-Febrifugine

2. *Asymmetric Synthesis of Halofuginone Hydrobromide*

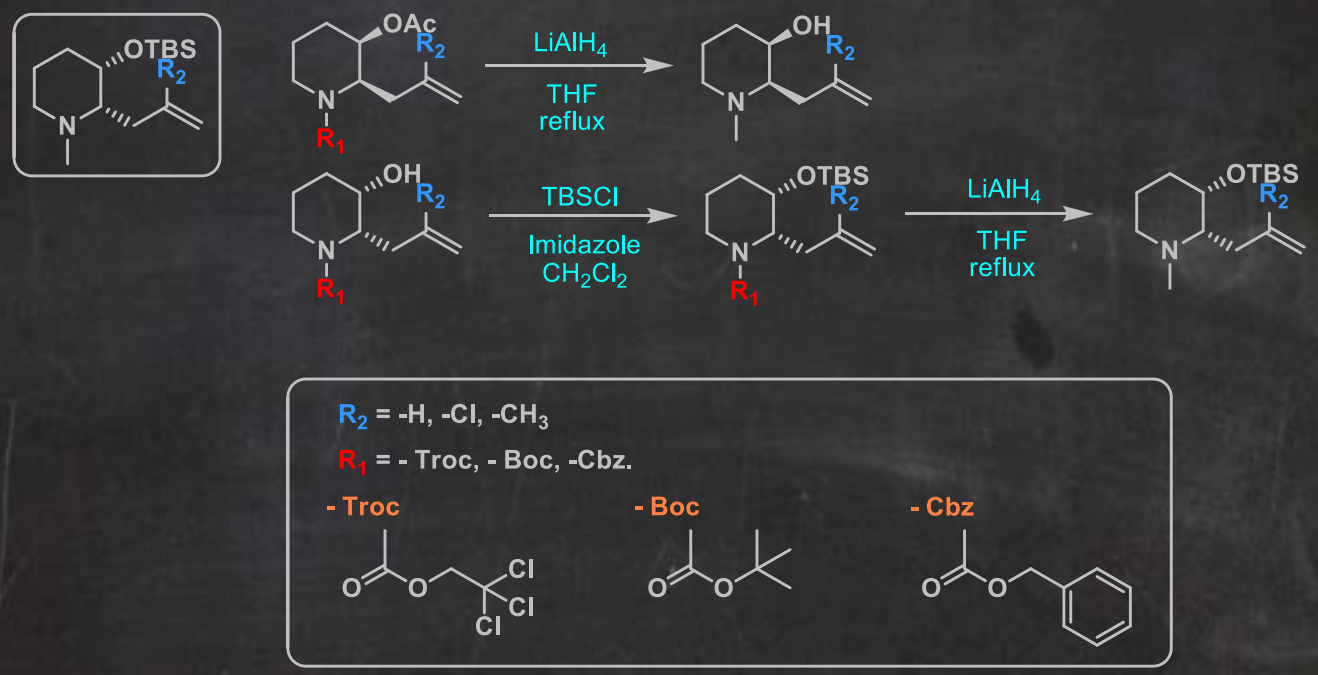


R_2 = -H, -Cl, -CH_3

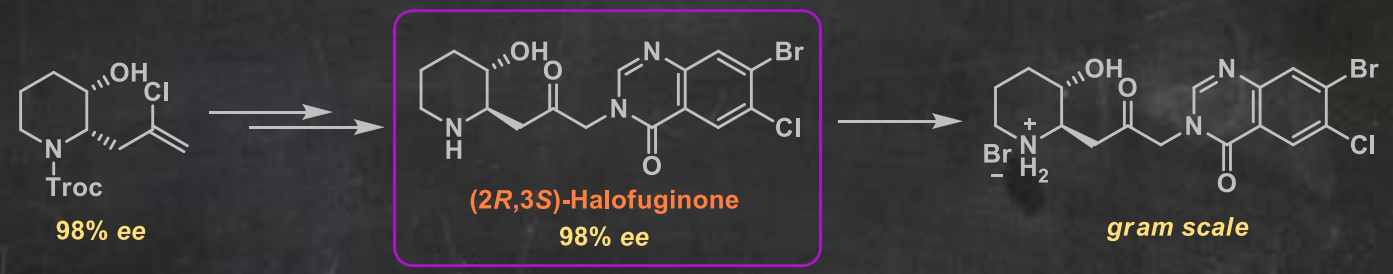
R_1 = - Troc, - Boc, -Cbz.



2. *Asymmetric Synthesis of Halofuginone Hydrobromide*

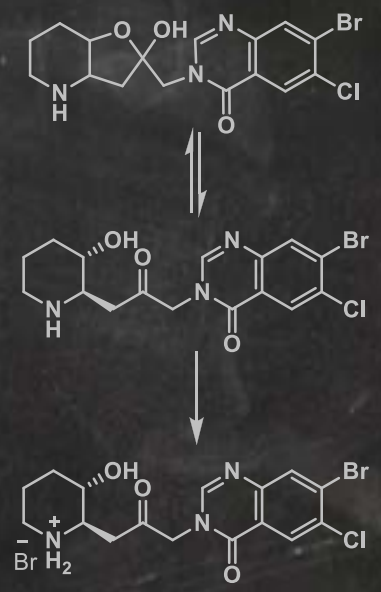


2. *Asymmetric Synthesis of Halofuginone Hydrobromide*



Practical Synthesis of Halofuginone Hydrobromide

- Synthesis of *rac*-Halofuginone Hydrobromide
  - *Stork enamine alkylation*
  - *Chromo alkylation reagent*
  - *Troc- protection*
- Asymmetric Synthesis of Halofuginone Hydrobromide
  - *Enzymetic resolution*



THANK YOU