ODLIČNI V ZNANOSTI 2013 – NARAVOSLOVJE

NASTANEK JODOVEGA(I) REAGENTA PRI OKSIDATIVNEM JODIRANJU AROMATSKIH SPOJIN Z VODIKOVIM PEROKSIDOM IN JODOM KATALIZIRANEM S KLOROVODIKOVO KISLINO

Jernej Iskra

Laboratorij za organsko in bioorgansko kemijo

Odsek za fizikalno in organsko kemijo

Institut "Jožef Stefan", Ljubljana

FKKT, 11. 12. 2014

IODO-ORGANIC COMPOUNDS

- **Starting compounds / synthetic intermediates:**
  - **Nucleophilic substitution (R – I → R – Nu)**
  - **Organometallic compounds (R – I → R – MgI → R – E)**
  - **Cross coupling reactions (R – I → R – R')**

- **Products:**
  - **Contrastors, markers (radiolabelled compounds…)**
  - **Bioactive compounds**
  - **Natural compounds**
  - **Industrial chemicals (colorants…)**

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IODO-ORGANIC COMPOUNDS

Angel‘s Bonnets (CHI_3)

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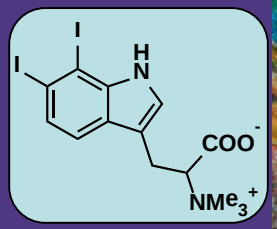
Plakortis (iodinated indols)



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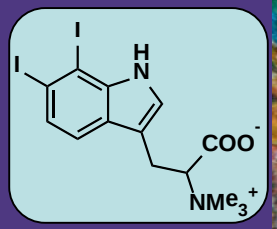
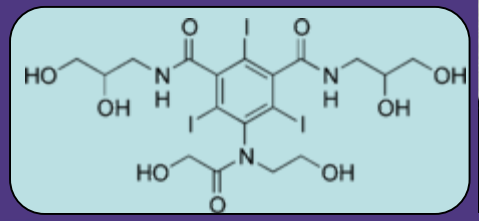
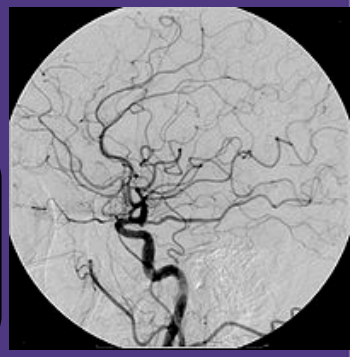


Loversol – X-ray contrastor





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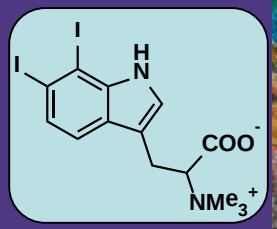
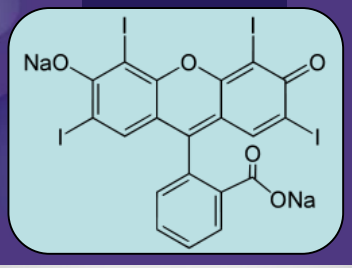


Red No. 3



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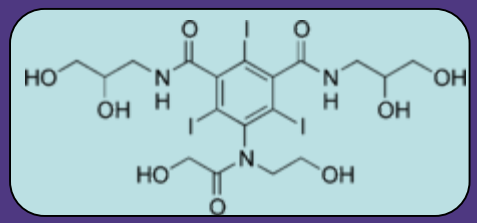

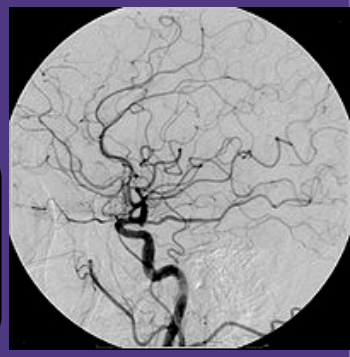

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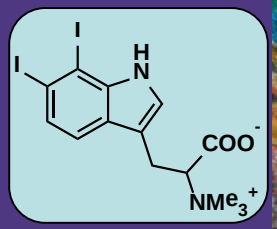
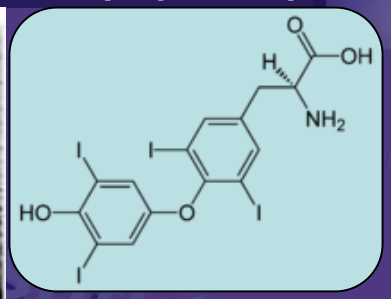


Thyroid hormone (Thyroxine)



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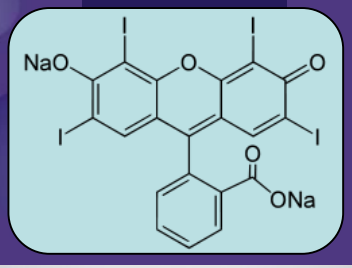

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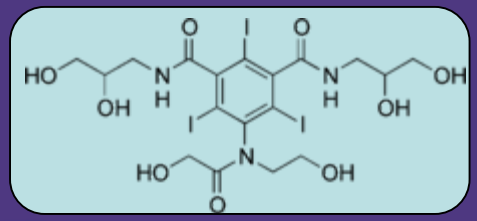

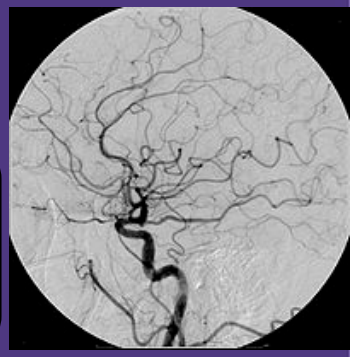

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IODINATION

Iodine (I_2):

- basic reagent for iodination of organic molecules
- weak electrophile; HI is by-product.

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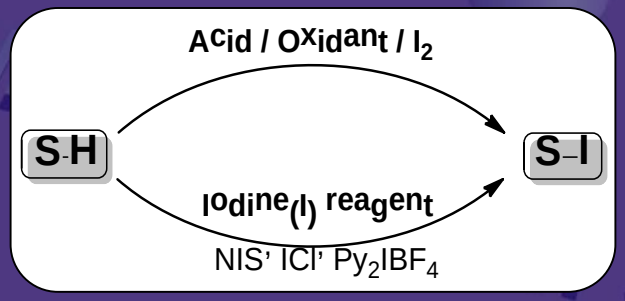
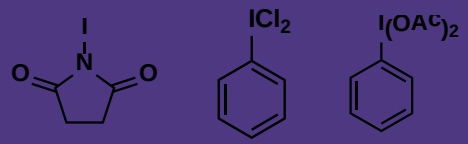
Iodination:

- **Activation of iodination:**
  - ACIDS/OXIDANTS - HNO_3/H_2SO_4, HIO_4/H_2SO_4, CF_3SO_3H, HgX_2, Ag_2SO_4, $Pb(OAc)_4$
  - IODINE(I) AND IODINE(III) COMPOUNDS – NIS, $Py_2I^{+}BF_4^{-}$, ICl, PIDA…
- **Problems:** weak atom economy, toxic waste, derivatisation, reagent residue …



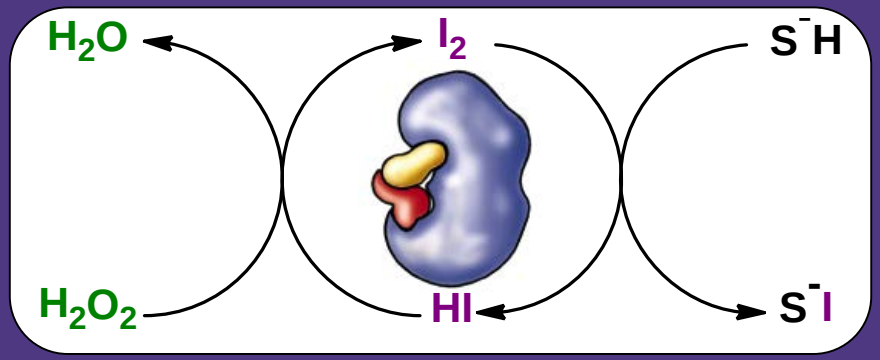
$$S^{-}H + I_2 \xrightarrow{\text{metal/acid}} S^{-}I + HI$$

$$S^{-}H + Py_2IBF_4 \longrightarrow S^{-}I + 2Py + HBF_4$$



IODINATION – GREEN CHEMISTRY

- **Enzymes *haloperoxidases*:**
  - **Nature as an inspiration for green halogenation.**
  - **Hydrogen peroxide oxidizes iodide within the enzyme‘s acidic active site into iodine.**



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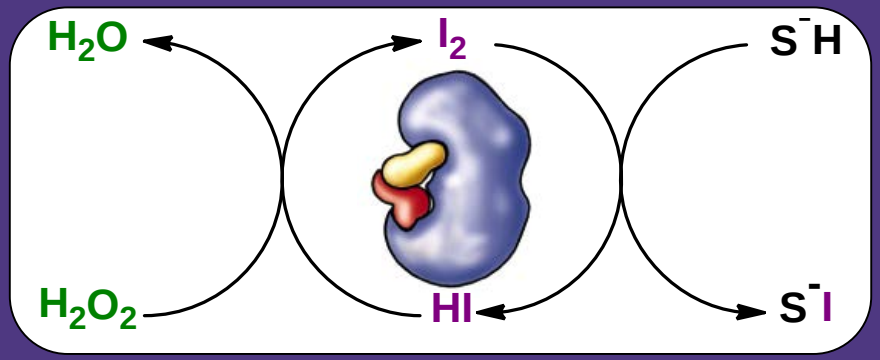

- **OXIDATIVE IODINATION:**
  - Biomimetic approach.
  - Regeneration of by-product HI into I_2 under oxidative conditions – 100% iodine atom economy.
  - Use of hydrogen peroxide for oxidation – green oxidant.

$$S^-H + I_2 \xrightarrow{\text{metal/acid}} S^-I + HI$$

$$S^-H + Py_2IBF_4 \longrightarrow S^-I + 2Py + HBF_4$$

$$S^-H + I_2 + H_2O_2 \longrightarrow S^-I + H_2O$$

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IODINATION – IODINE(I) REAGENT

❑ IODINE(I) COMPOUNDS AS REAGENTS:

- Use of iodine(I) reagents for iodination.
- Synthesis of iodine(I) compounds with green oxidant – H_2O_2.

$$I_2 \xrightarrow{H_2O_2/HA} \text{I(I) reagent} \xrightarrow{S-H} S-I$$

oxidative iodination
(100% iodine atom economy,
green oxidant – hydrogen peroxide)

iodine(I) reagent
(activation of iodination)

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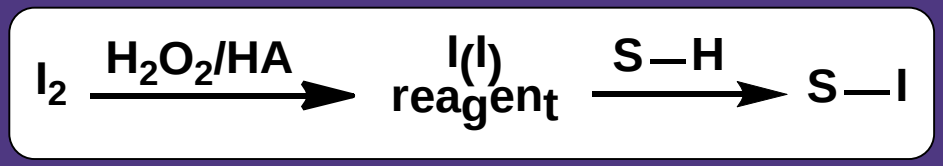

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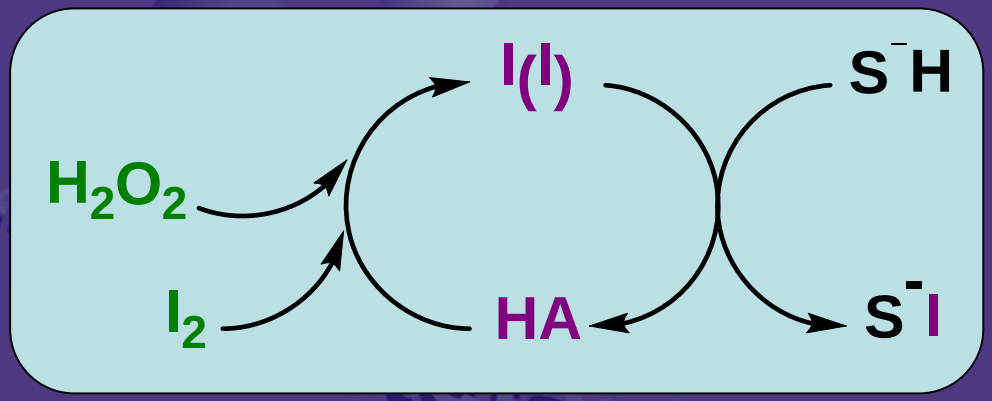
❑ CATALYTIC REACTION OF OXIDATIVE IODINATION WITH IODINE(I) REAGENTS:



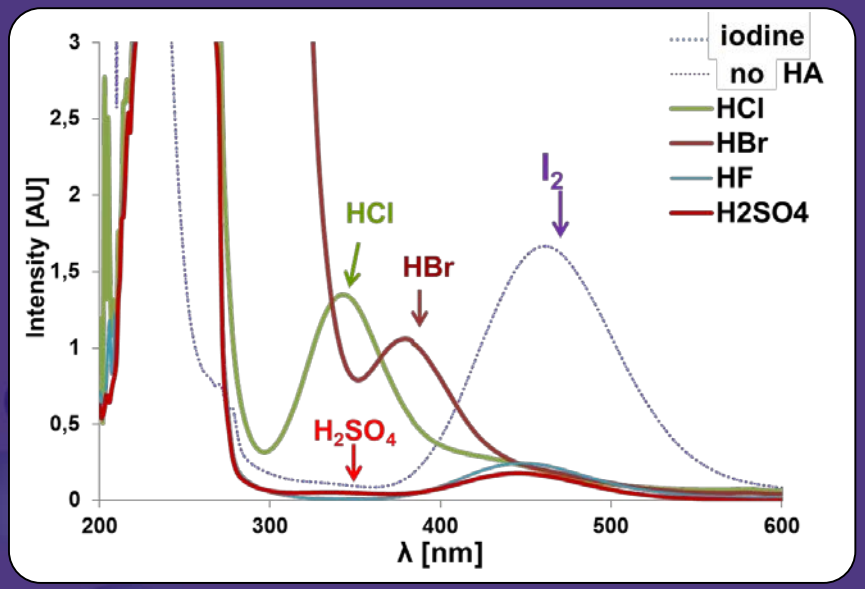
OXIDATION TO IODINE(I) REAGENT

$I_2 + H_2O_2 \xrightarrow{HA}$

- The effect of acid on oxidation of iodine with hydrogen peroxide:

$$I_2 \xrightarrow[\text{MeCN, rt, 24h}]{\text{50\% aq. } H_2O_2 \text{ / 4HA}}$$

Acid (HA)	pKa
H_2SO_4	-4
$HClO_4$	-8.6
p-TsOH	-2.8
HF	3.2
HBr	-9
HCl	-7
AcOH	4



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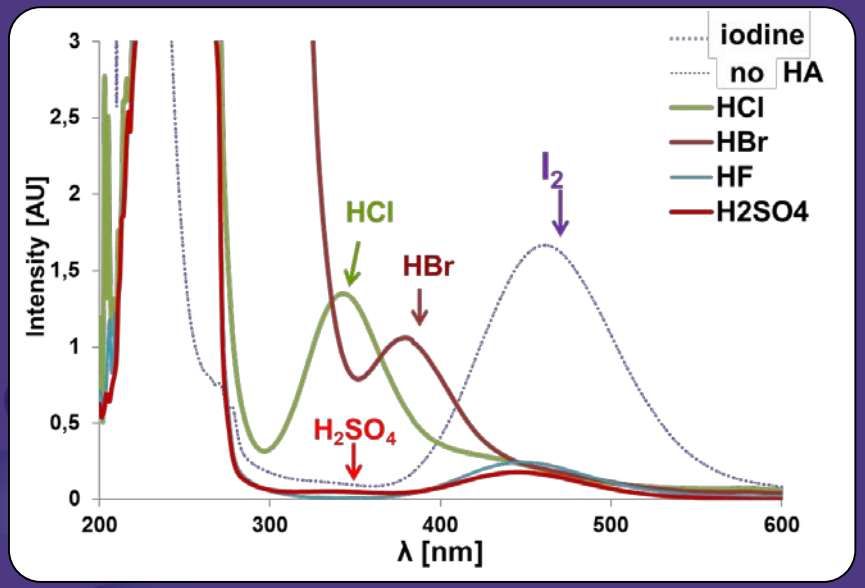
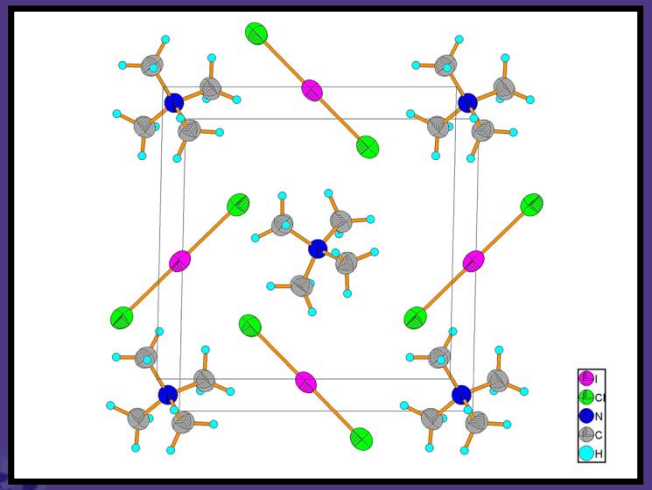


$$I_2 \xrightarrow[\text{MeCN, rt, 24h}]{H_2O_2(50\%aq) \text{ / 2HCl / 2Q}^+\text{Cl}} 2\ Q^+ICl_2^-$$

Q = Me_4N, Et_4N, $Bn(Me_3)N$, $Oct(Me_3)N$: 92-98%



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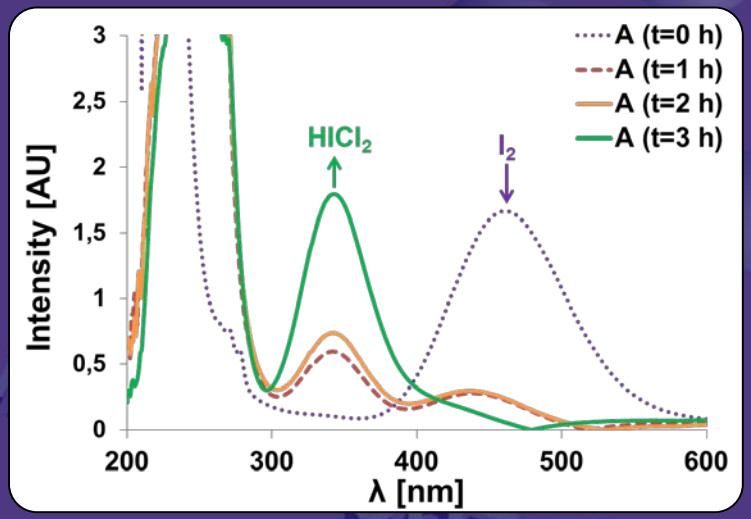
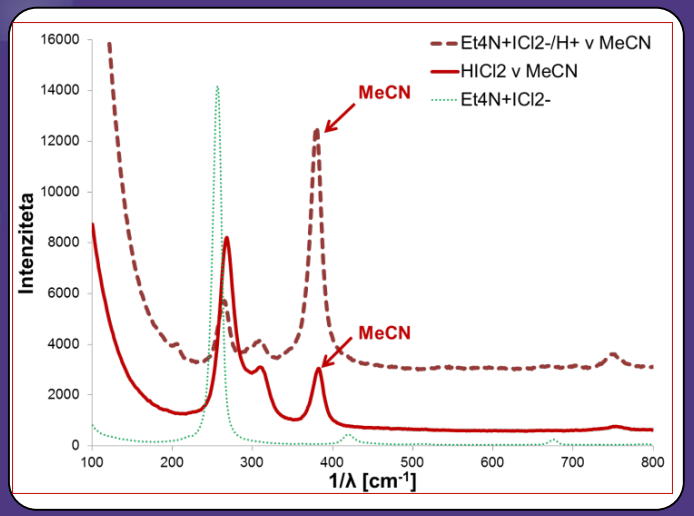
OXIDATION TO IODINE(I) REAGENT

- Dichloroiodic(I) acid (hydridodichloridoiodine):

$$0{\cdot}5\ I_2 + 0{\cdot}5\ H_2O_2 + 2\ HCl \longrightarrow HICl_2 + H_2O$$

- CH_3CN, 24 h
- CF_3CH_2OH (TFE), 1 h
- Solvent-free (SF), 3 h





Adv. Synth. Catal. 2013, *355*, 1243.

Iodination with $HICl_2$

$$0.5\ I_2 + 0.5\ H_2O_2 + 2\ HCl \longrightarrow HICl_2 + H_2O$$

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$$0{\cdot}5\ I_2 + 0{\cdot}5\ H_2O_2 + 2\ HCl \longrightarrow \underbrace{HICl_2 + H_2O}$$

$$\downarrow$$

$$S{-}H \xrightarrow{\text{"}HICl_2\text{"}} S{-}I + 2HCl$$

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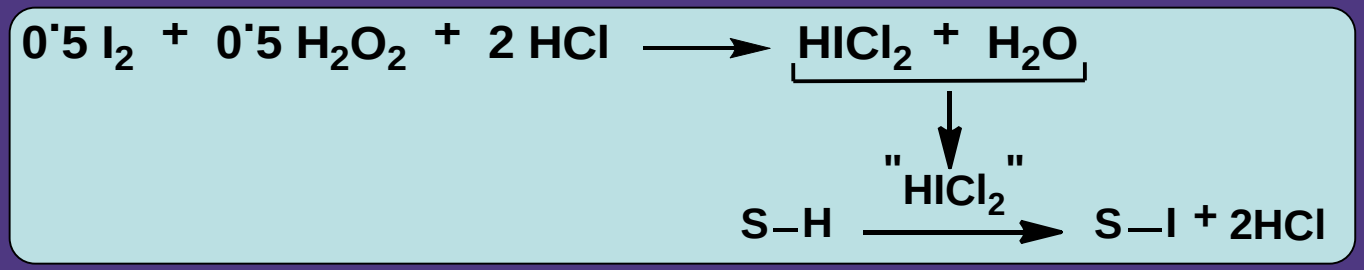

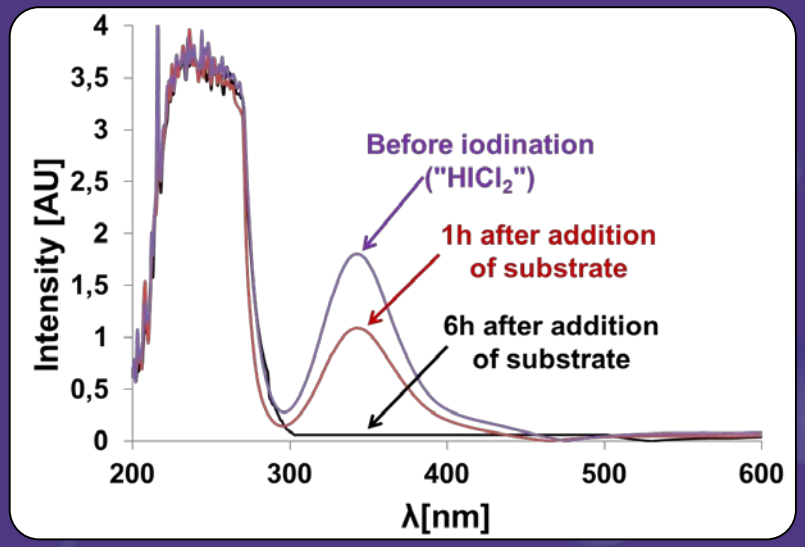

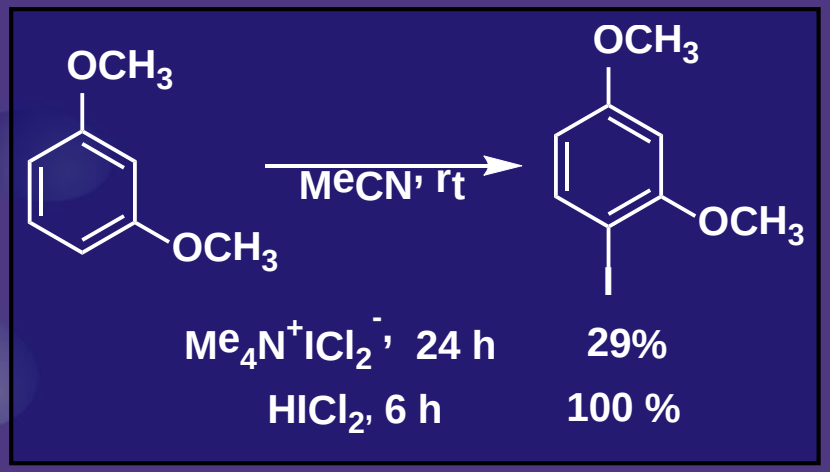

- $HICl_2$ is stronger iodinating reagent that its salt.
- No need to isolate $HICl_2$. Direct use of "$HICl_2$".
- "$HICl_2$" is stable and could be used as a stock solution.

Adv. Synth. Catal. 2013, *355*, 1243.

I(I) reagent in catalytic iodination

HCl could be a catalyst in oxidative iodination with iodine(I) reagents

$$0.5\ I_2 + 0.5\ H_2O_2 + 2\ HCl \longrightarrow HICl_2$$

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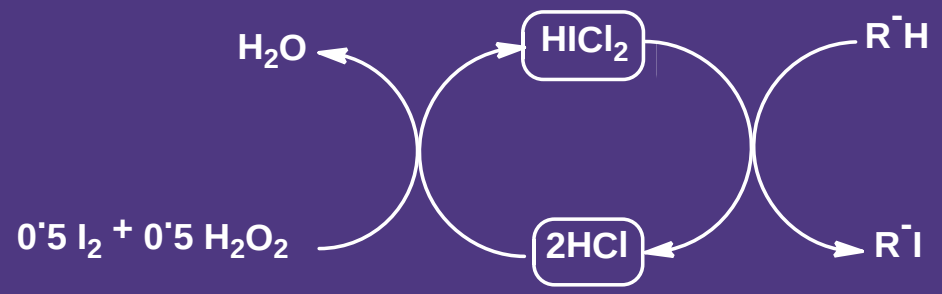

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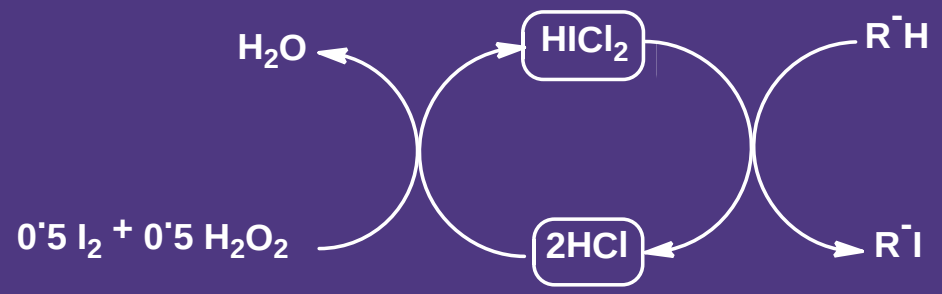
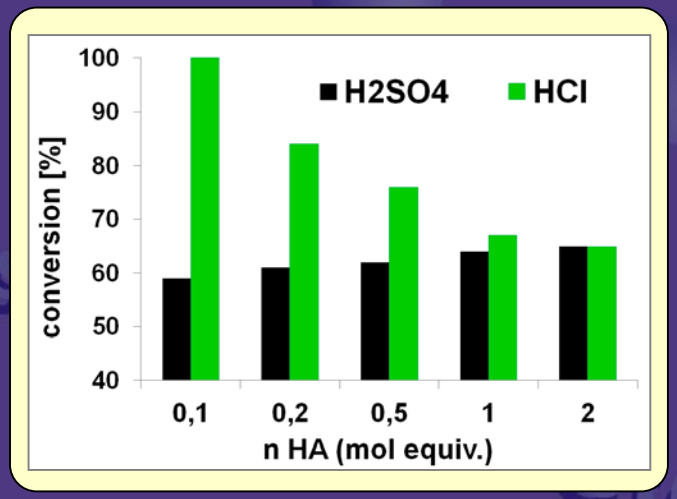


$$A^{r}\text{—}H \xrightarrow[\text{MeCN, rt, 24 h}]{0.5\ I_2\ /\ 0.5\ H_2O_2\ /\ {}^{x}HA} A^{r}\text{—}I$$



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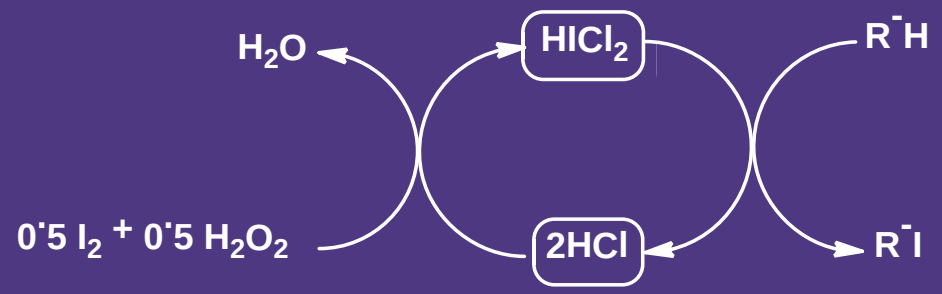
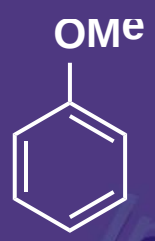
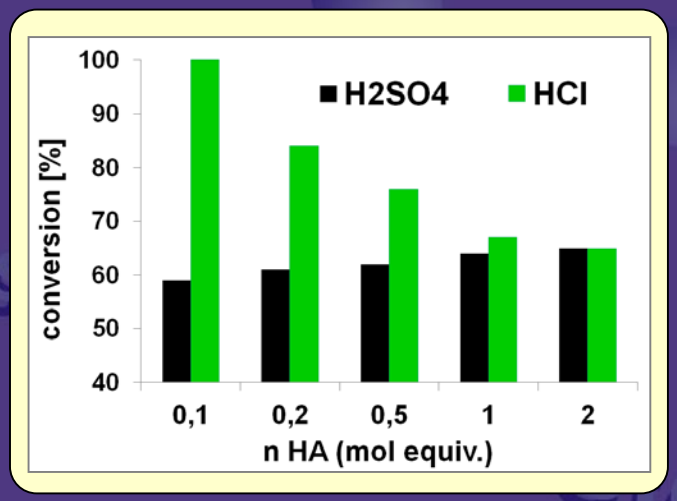
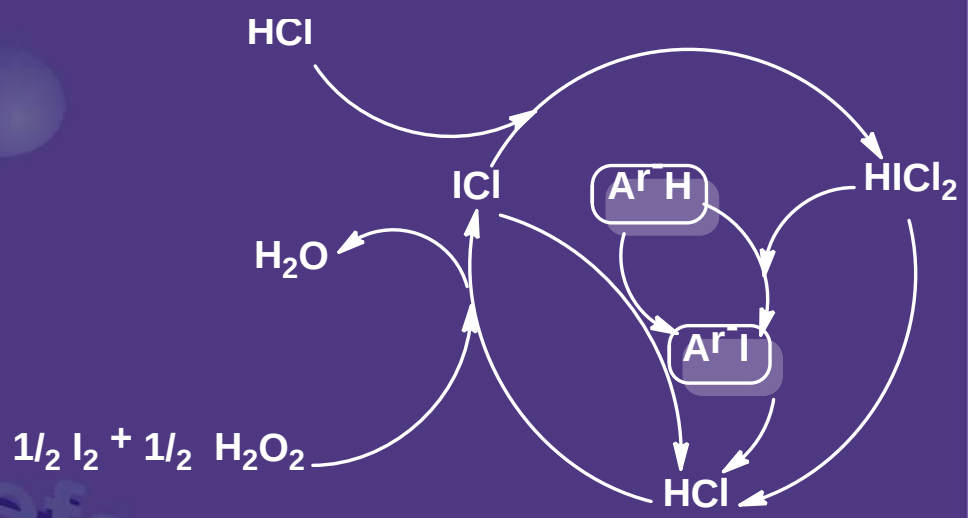


$$A^{r}\text{—}H \xrightarrow[\text{MeCN, rt, 24 h}]{0.5\ I_2\ /\ 0.5\ H_2O_2\ /\ {}^{x}HA} A^{r}\text{—}I$$







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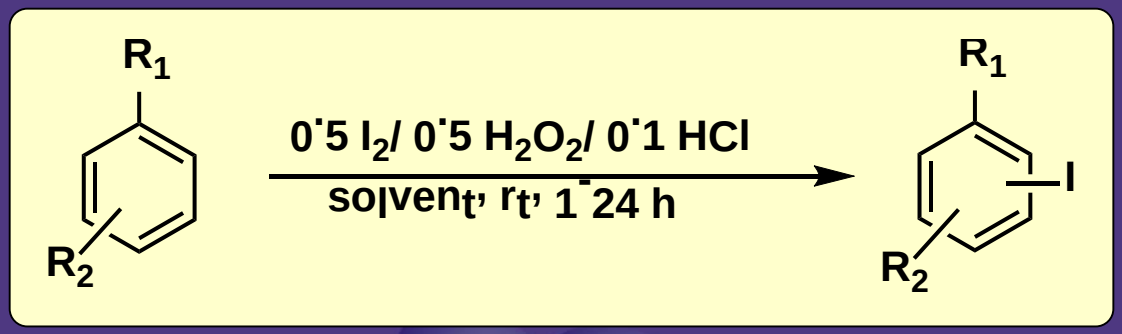
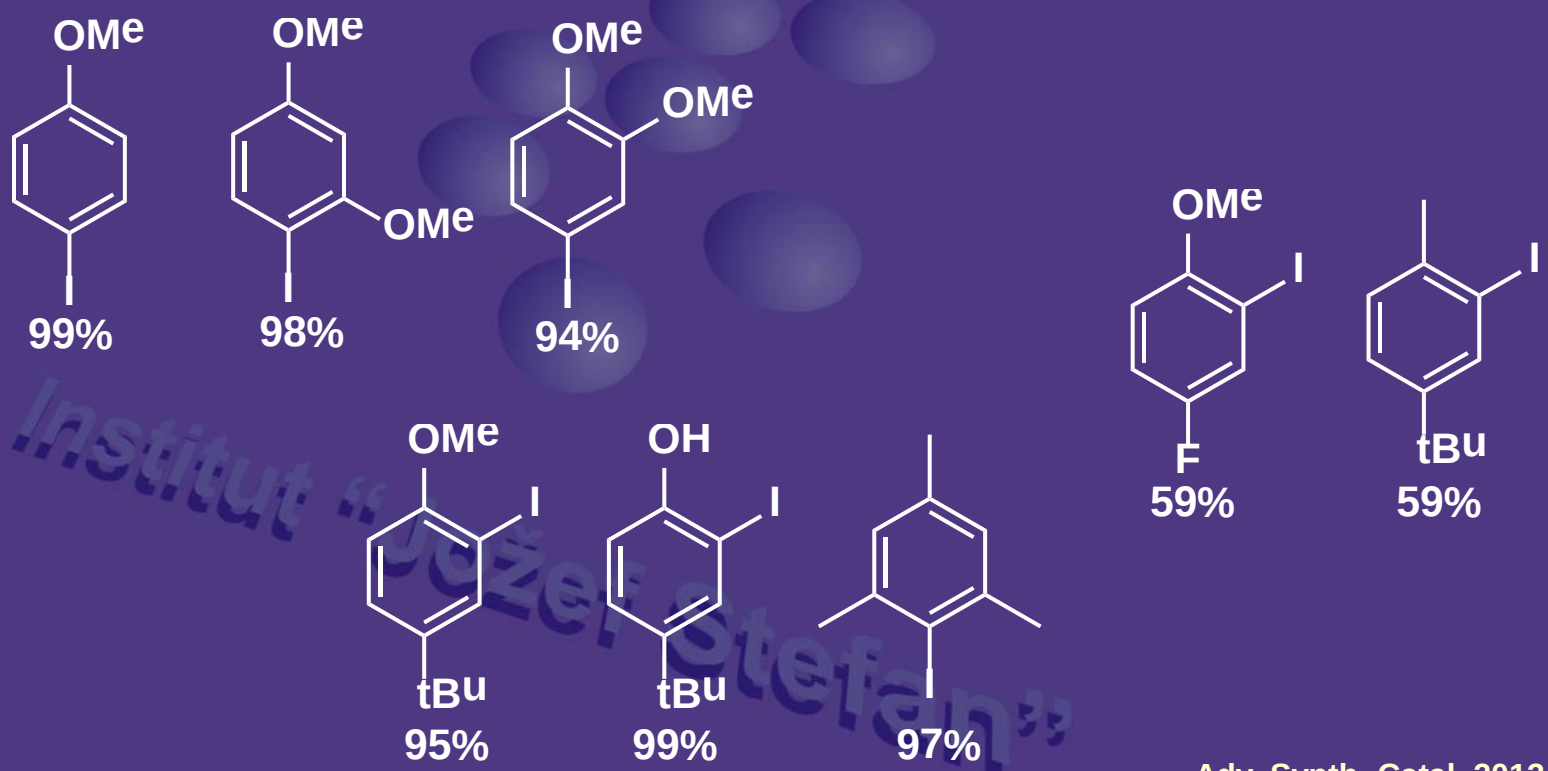
Catalytic iodination with I_2/I(I) couple

H_2O_2-mediated oxidative iodination with iodine(I) reagents catalyzed by HCl:





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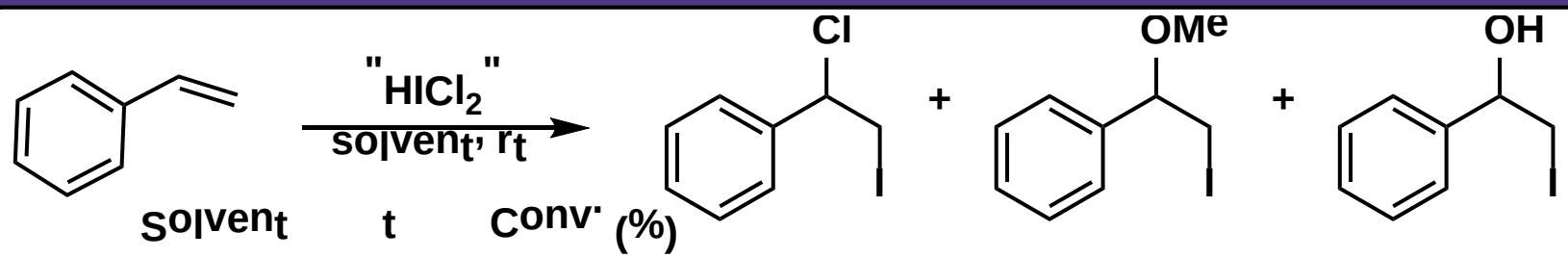
IODINATION – GREEN CHEMISTRY

- Iodination of alkenes with $HICl_2$:



Solvent	t	Conv. (%)	Cl	OMe	OH
MeCN	24 h	80	34%	/	66%
CH_2Cl_2	24 h	100	34%	/	66%
MeOH	30 min	100	50%	50%	/
TFE	<1 min	100	100%	/	/

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IODINATION – GREEN CHEMISTRY

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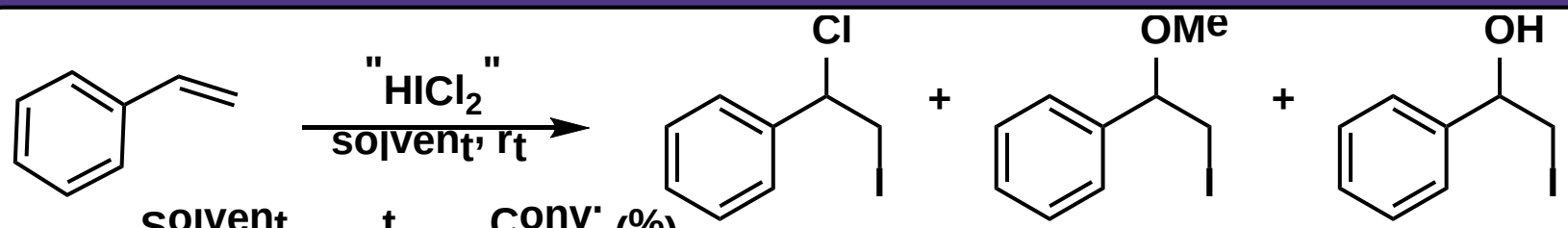

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	time [min]	Yield	Reference	Atom economy	E-factor
$I_2/HgCl_2/CH_2Cl_2$	15	99%	JCR(M), 1986, 2419.	37%	29
I_2/ $PhICl_2/CH_2Cl_2$	30	84%	SC, 2004, 34, 443.	57%	250
ICl/CCl_4	120	79%	BCSJ, 1980, 53, 1390.	100%	22
$HICl_2$/TFE	<1	98%	This work	88%	21

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CONCLUSIONS

- Combination of oxidative iodination (100% iodine atom economy) and activation of iodination with iodine(I) reagent (ICl or $HICl_2$) under catalytic conditions.
- H_2O_2 can oxidize iodine into iodine(I) compound by using HCl or HBr (solvent free, MeCN, TFE).
- $HICl_2$ is a product of oxidation of I_2 with H_2O_2/HCl and is stable, strong and efficient reagent for iodination of aromatics.
- Catalytic version of reactions is also effective with HCl as catalyst for oxidative iodination with I_2/H_2O_2 through in situ formation of $HICl_2$.

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