

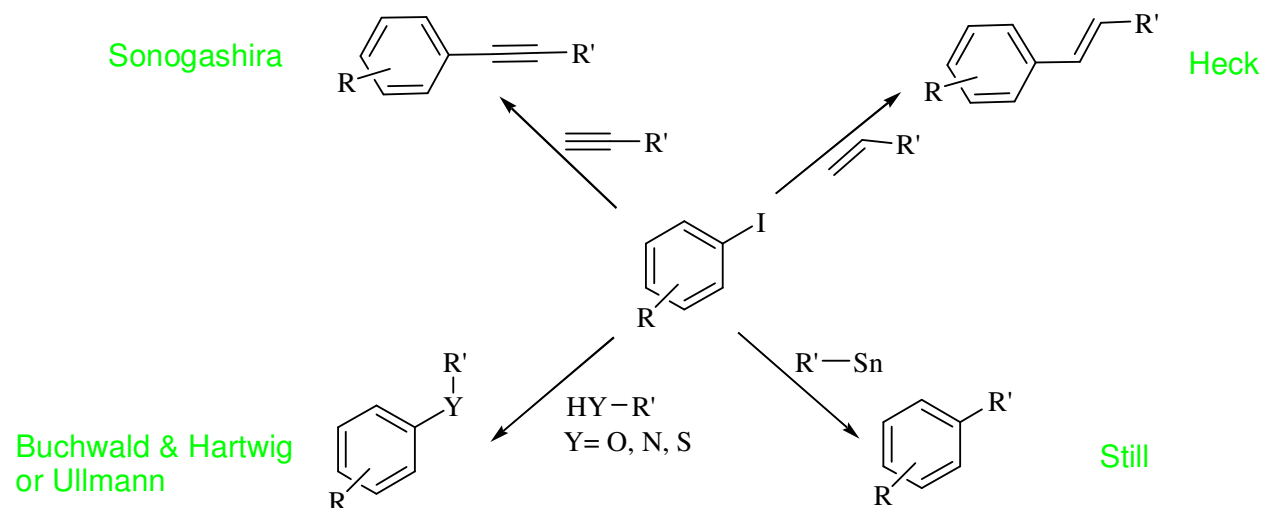
Thiourea Catalyzed Iodination of Activated Aromatic Compounds

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Giessen, 2012.06.08*

Use of organiodo compounds

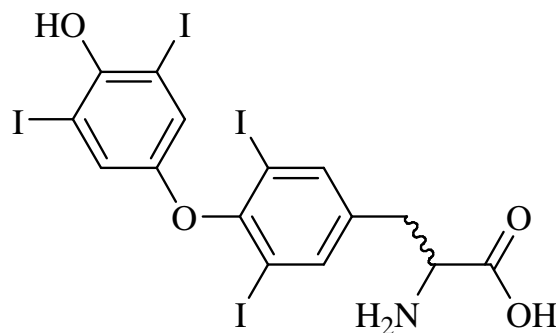
- Organiodo compounds are used as substrates in carbon–carbon, carbon–nitrogen or carbon–oxygen bond formation reactions.



(1) Diederich, F.; Stang, P. J. *Metal-Catalysed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, **1998**. (2) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, 102, 1359. (3) *Handbook of Radiopharmaceuticals: Radiochemistry and Applications*; Welch, M. J.; Redvanly, C. S., Eds.; Wiley: Chichester, **2003**.

Application of organiodo compounds

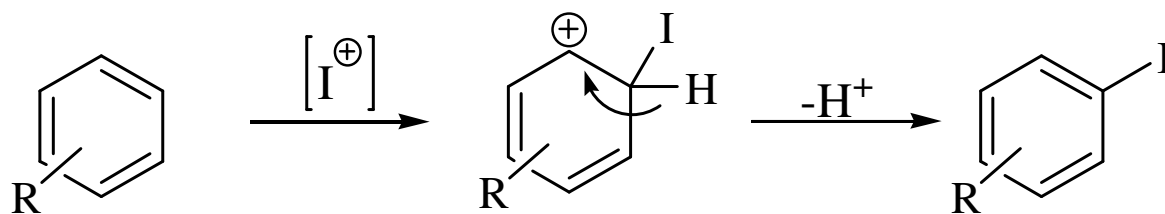
- As drugs or radioactively labelled diagnostic markers.



Natural organiodine compound: *thyroid hormones thyroxine (T4)*

Synthesis of iodo-substituted organic compounds

Electrophilic aromatic iodination

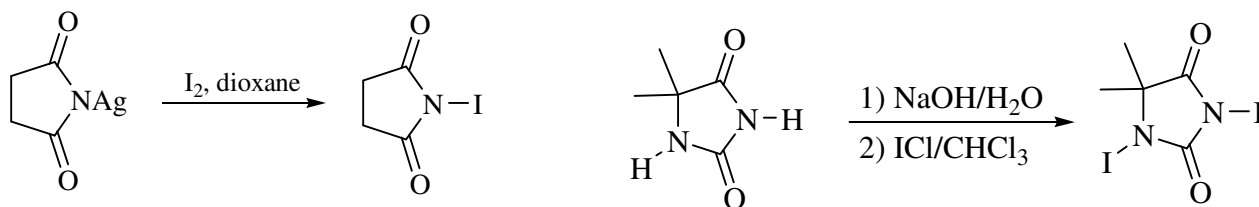


Electrophilic iodinating reagents:

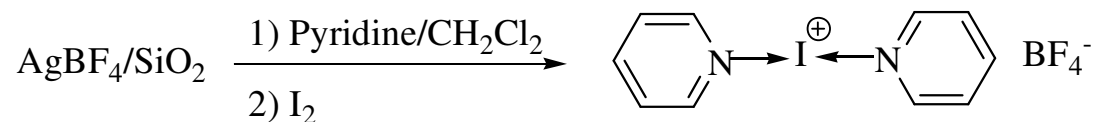
◆ Elemental iodine

Other electrophilic iodinating reagents:

◆ *N*-iodosuccinimide and other N-I compounds



◆ Bis(pyridinium)iodonium(I) tetrafluoroborate (IPy₂BF₄)



The use of elemental iodine

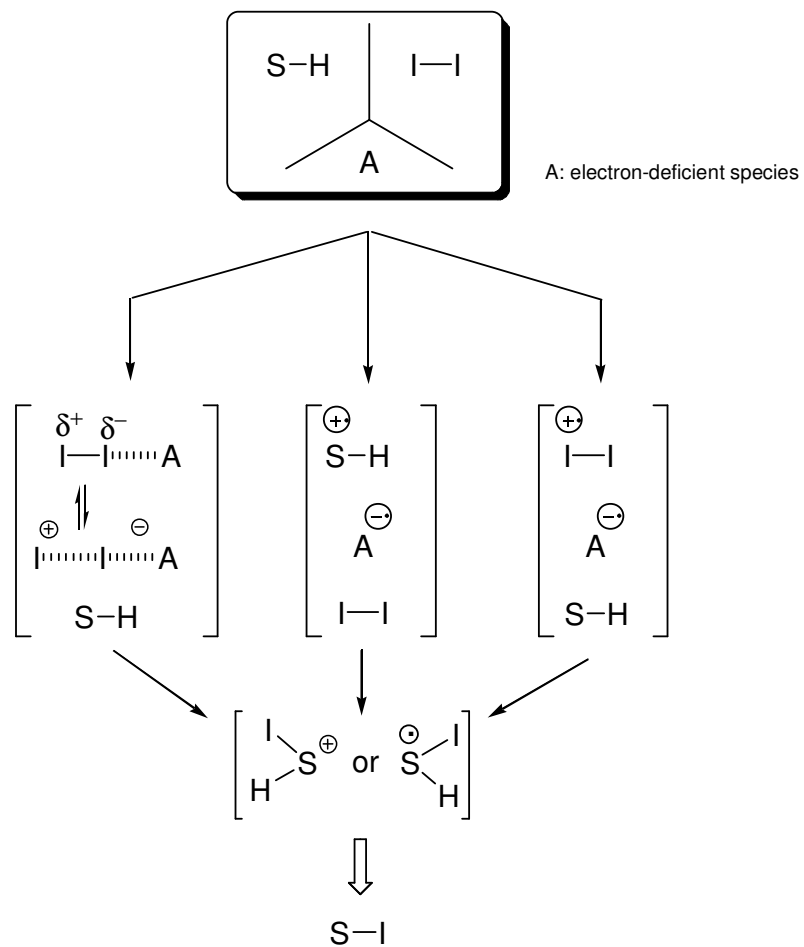
Disadvantages of using elemental iodine:

- ❑ (i) low electrophilicity of I_2 .
- ❑ (ii) release of HI during the iodination process, which ordinarily causes the rupture of carbon–iodine bond.
- ❑ (iii) low atom economy (half of the iodine atoms are lost)

Modified synthetic methodologies:

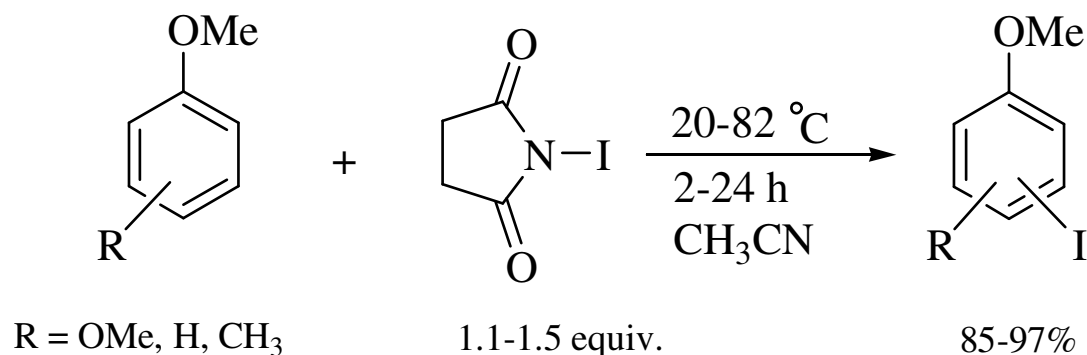
- ❑ (i) Hydrogen iodide trapping by a base, or iodide trapping by formation of insoluble metal iodides.
- ❑ (ii) Use of a Lewis or Brønsted acid which polarises the iodine molecule, thus increasing its electrophilicity.
- ❑ (iii) Oxidative activation producing iodonium species or regenerating released iodide.

Possible mechanism of iodination



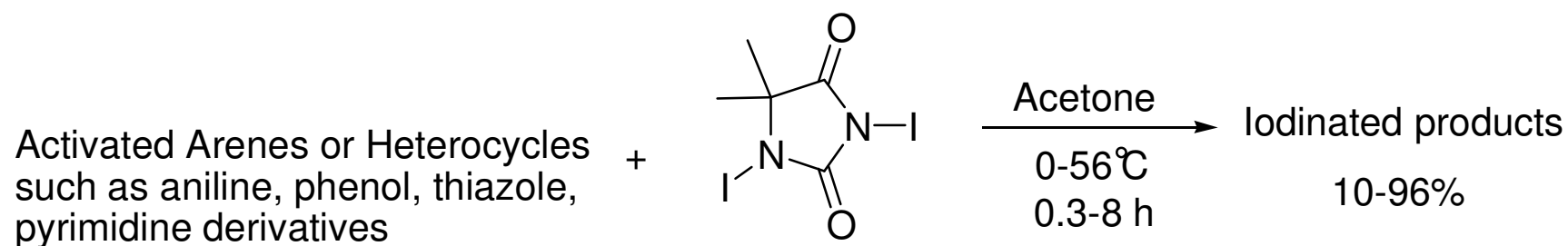
New approaches by using electrophilic iodinating reagents

Recently, *N*-iodosuccinimide (NIS) was reported to be an efficient iodinating agent either at elevated temperature or in conjunction with Lewis or Brønsted acids such as trifluoroacetic acid, triflic acid, ZrCl_4 , or $\text{BF}_3 \cdot \text{Et}_2\text{O}$ as catalysts.



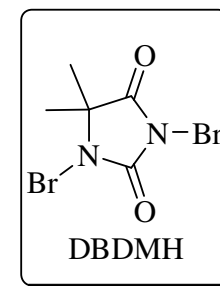
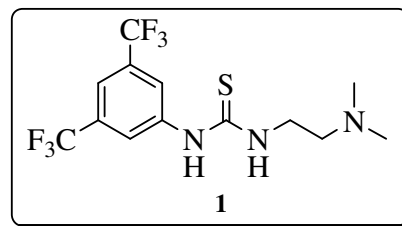
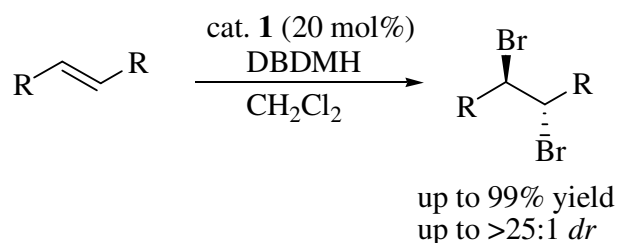
(5) Carren˜o, M. C.; Ruano, J. L. G.; Sanz, G.; Toledo, M. A.; Urbano, A. *Tetrahedron Lett.* **1996**, 37, 4081. (6) Castanet, A.-S.; Colobert, F.; Broutin, P.-E. *Tetrahedron Lett.* **2002**, 43, 5047. (7) Olah, G. A.; Wang, Q.; Sandford, G.; Surya Prakash, G. K. *J. Org. Chem.* 1993, 58, 3194. (8) Zhang, Y.; Shibatomi, K.; Yamamoto, H. *Synlett* **2005**, 18, 2837. (9) Prakash, G. K. S.; Mathew, T.; Hoole, D.; Esteves, P. M.; Wang, Q.; Rasul, G.; Olah, G. A. *J. Am. Chem. Soc.* **2004**, 126, 15770. ^

The use of 1,3-diiodo-5,5-dimethylhydantoin for iodination reaction

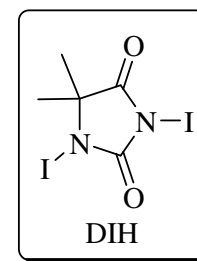
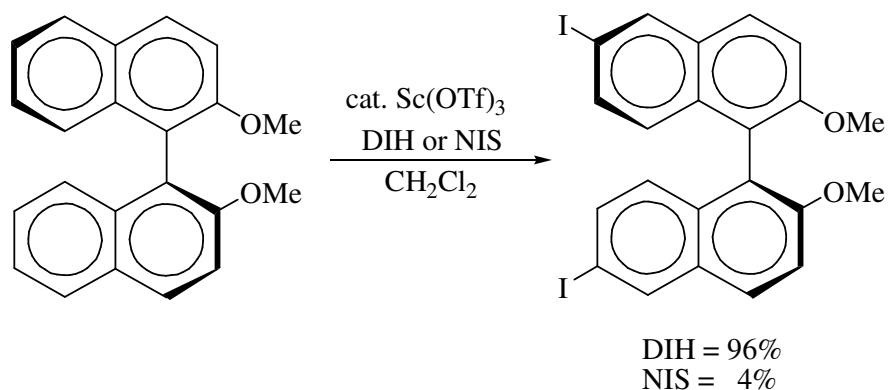


Organocatalytic bromination of alkenes

T1 also works!

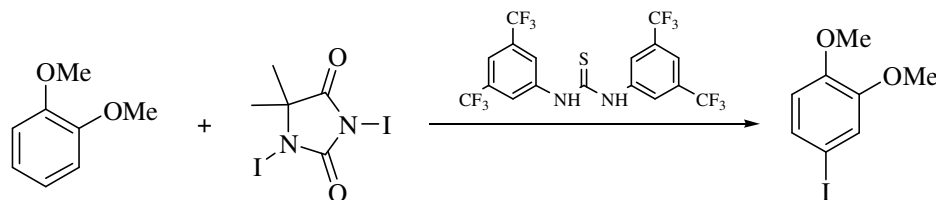


Recent application of DIH

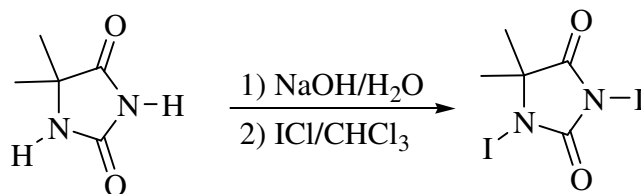


(11) Hernández-Torres, G.; Tan, B.; Barbas, C. F. *Org. Lett.*, **2012**, *14*, 1858. (12) Kamei, T.; Shibaguchi, H.; Sako, M.; Toribatake, K.; Shimada, T. *Tetrahedron Lett.* In press.

Synthesis of 1,3-diiodo-5,5-dimethylhydantoin (DIH)



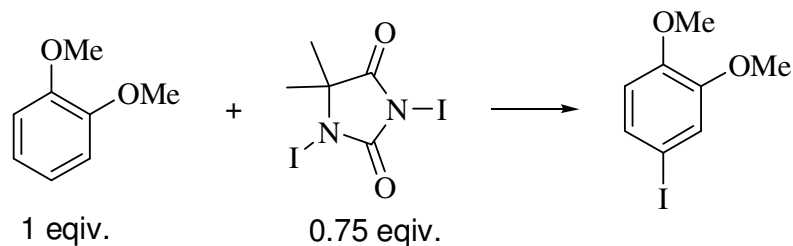
♦ Literature procedure for the synthesis of DIH



♦ The use of pure DIH

(13) Raab, c. e.; Dean, D. C.; Melillo, D. G. *J. Labelled Cpd. Radiopharm*, **2001**; 44, 815. (14) Inoue, K.; Hanamura, Y.; Miyazawa, T. U.S. Pat. Appl. Publ. 2011, US 7897785 B2.

Catalyst screening

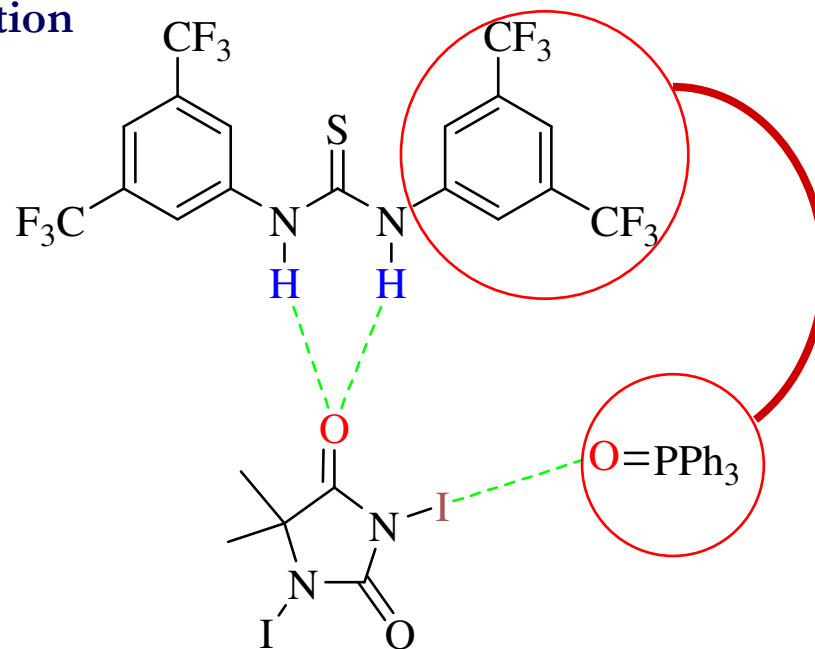


Entry	solvent	Iodinating agent	Catalyst (20%)	Co-catalyst	Time (h)	Conv. (%)
1	CH ₂ Cl ₂	DIH	-	-	72	N.R.
2	CH ₂ Cl ₂	DIH	T1	-	7	96
3	CH ₂ Cl ₂	DIH	H ₂ O (5μl)		7	30
4	CH ₂ Cl ₂	DIH	T1	H ₂ O (5μl)	6	98
5	CH ₂ Cl ₂	DIH	T1	Pyridine (20%)	24	N.R.
6	CH ₂ Cl ₂	DIH	T1	DMSO (20%)	5.5	87
7	CH ₂ Cl ₂	DIH	PPh ₃ O (20%)		24	N.R.
8	CH ₂ Cl ₂	DIH	T1	PPh ₃ O (20%)	4	95
9	CH ₂ Cl ₂	DIH	T1	Benzoic acid (20%) H ₂ O (5μl)	3	95

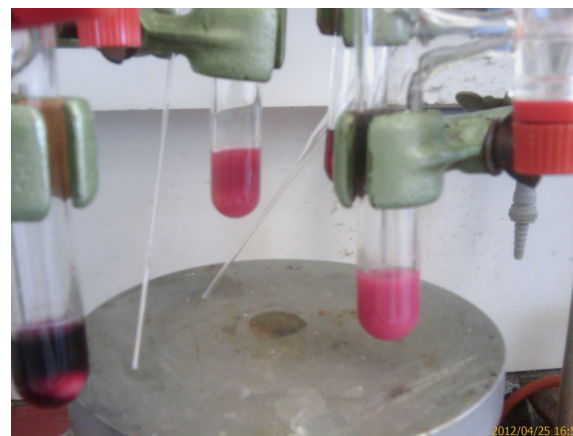
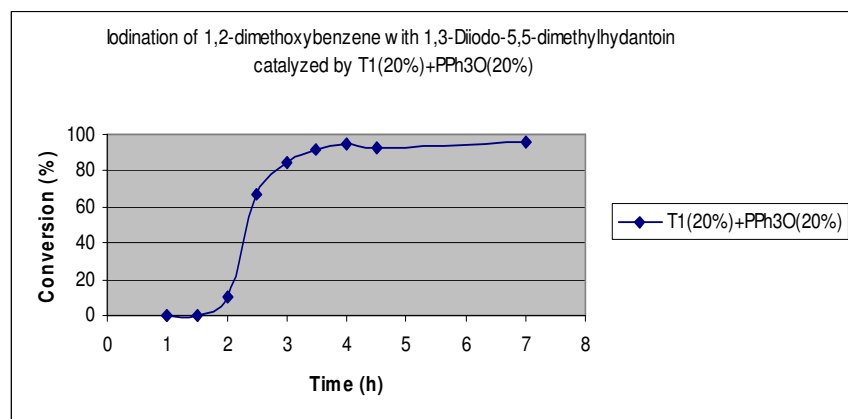
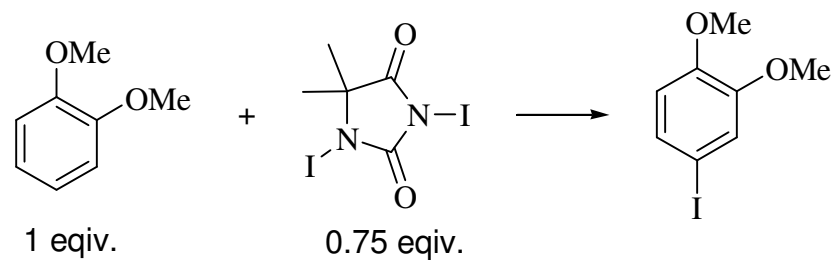
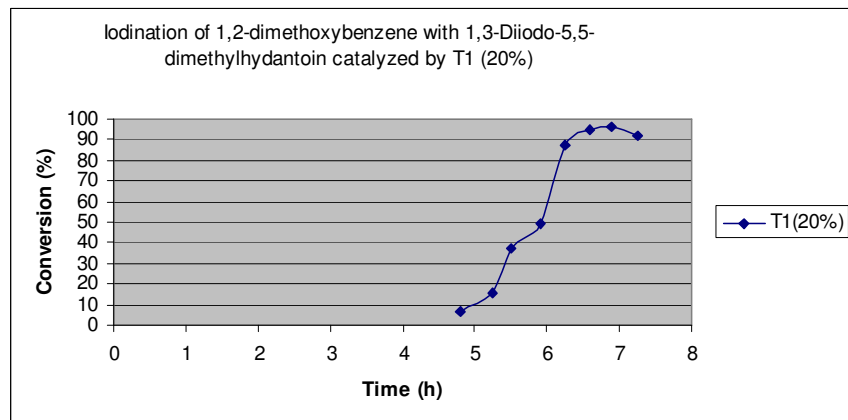
Entry	solvent	Iodinating agent	Catalyst (20%)	Co-catalyst	Time (h)	Conv. (%)
1	CH ₂ Cl ₂	NIS	T1	PPh ₃ O (20%)	18	25
1	Acetone	DIH	-	-	20	N.R.
2	Acetone	DIH	T1	PPh ₃ O (20%)	21	44*

* Iodoacetone and unknown products were also formed.

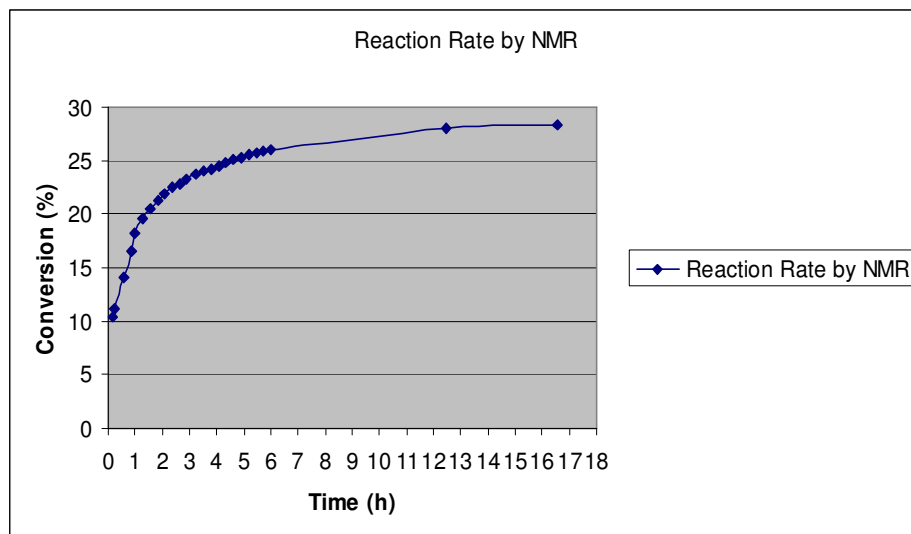
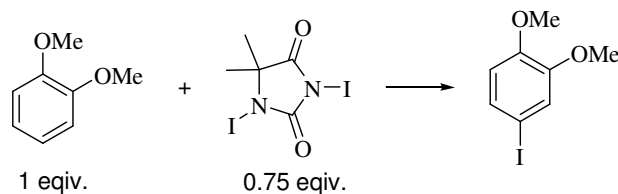
Possible mode of activation



The trend of reaction rate catalyzed by T1 and T1+PPh₃O

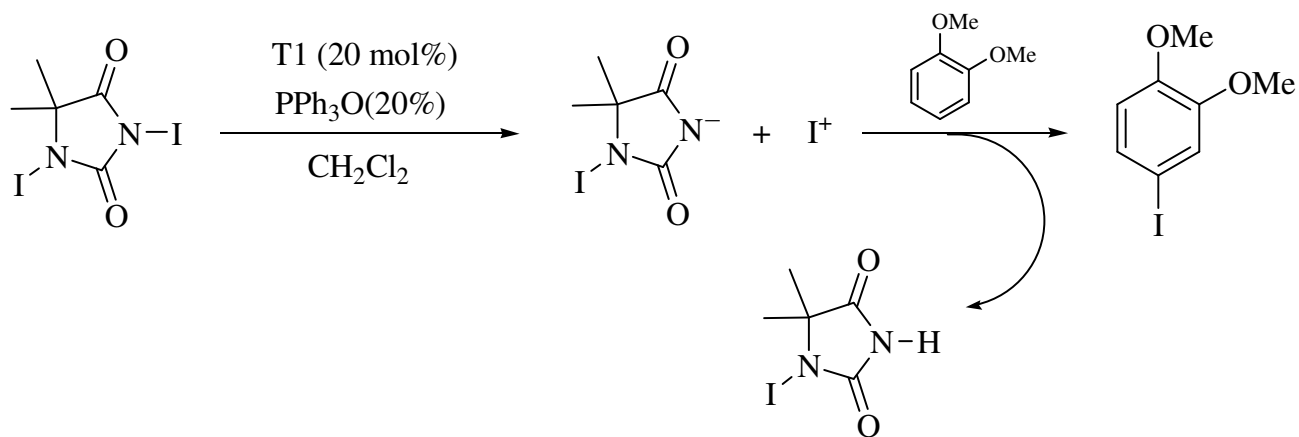


Investigating the kinetics of reaction by NMR

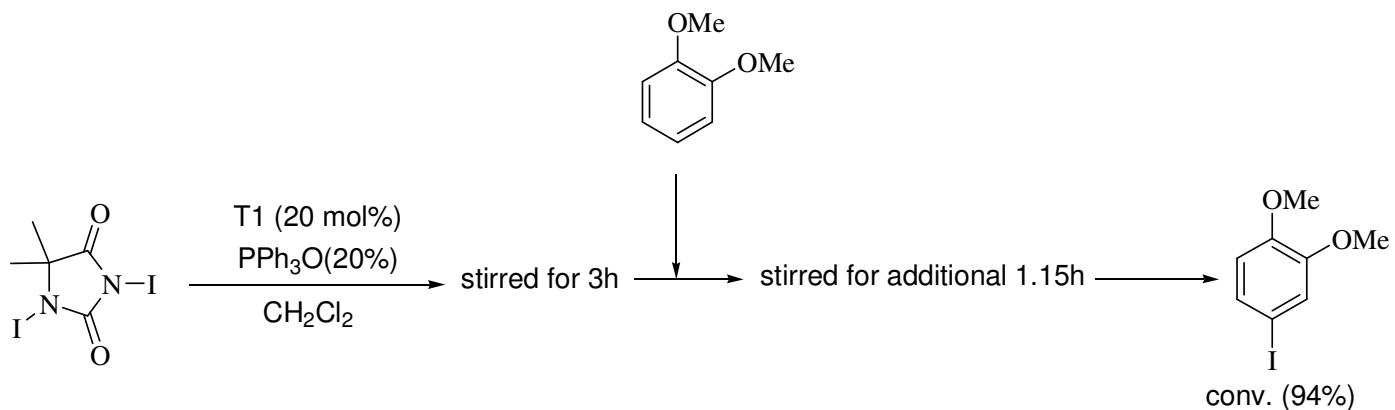


Problem: DIH has a low solubility in DCM

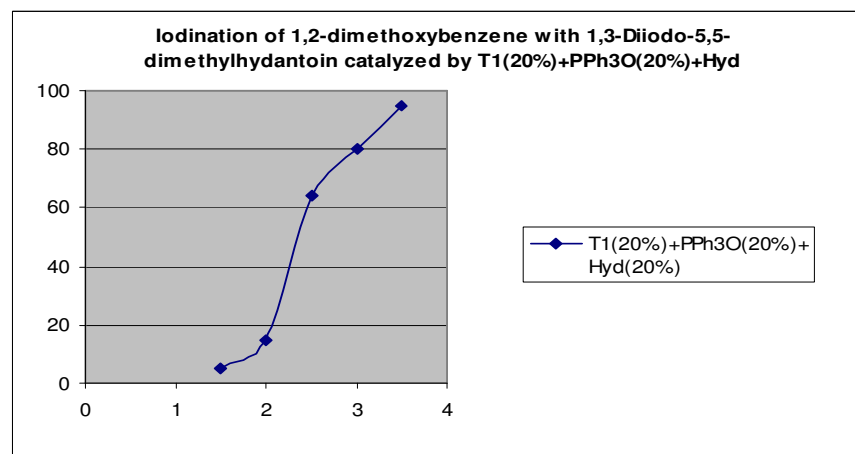
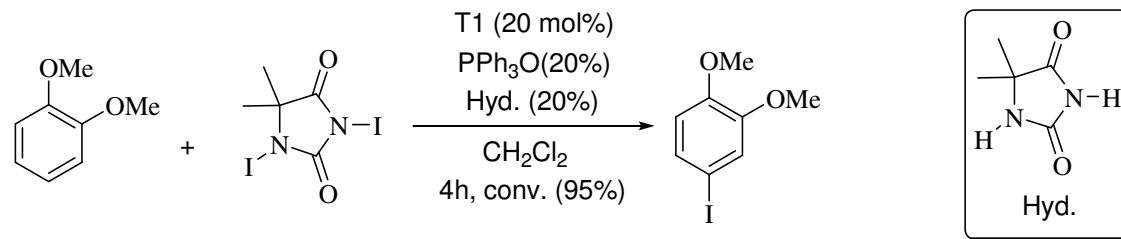
Possible explanation for the need for an initialization period



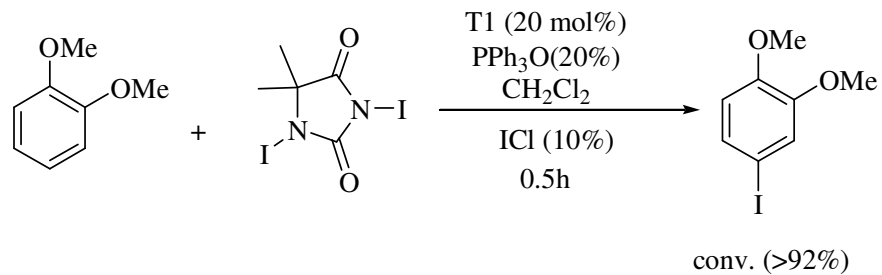
Effect of substrate



Effect of Hydantoin as co-catalyst



Effect of ICl



Future work

- ❑ Optimization of reaction conditions
- ❑ Investigate substrate limitations
- ❑ The use of alcohols as co-catalyst
- ❑ Benzoic acid and water were successful co-catalyst; what will happen if using Mandelic acid combined with T1?

Acknowledgement

- ❑ Special thanks to Professor Schreiner for his helpful discussions and the chance to work here
- ❑ I am highly thankful to Professor Ipaktchi for his support and guidance and my dear friend Gergely Jakab for his kind cooperation and dialectic discussion
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Thank you for your attention