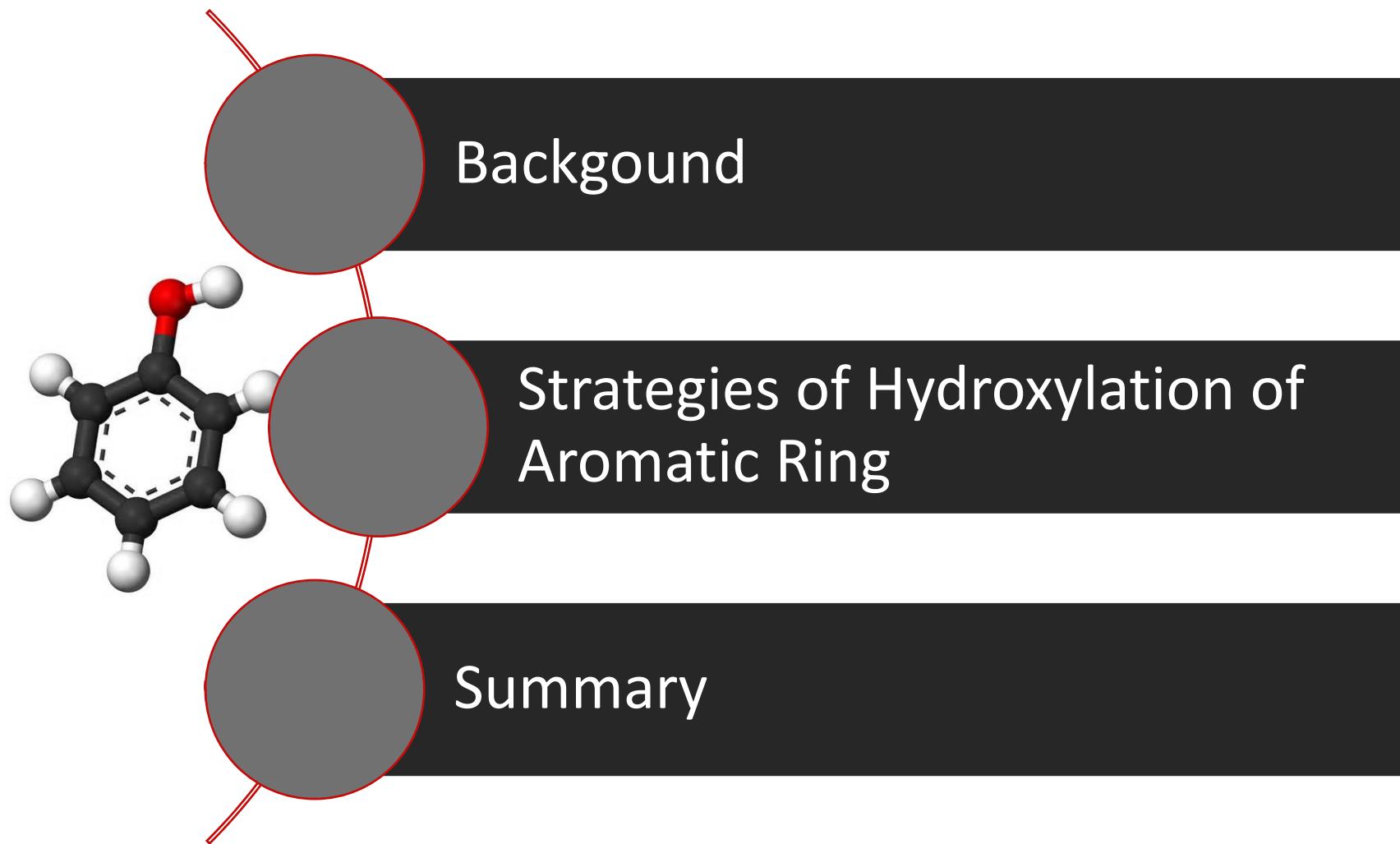


The strategies of hydroxylation of Aromatic ring and its derivatives



Rui Zhang
Hu Group, SIOC
2015-5-18

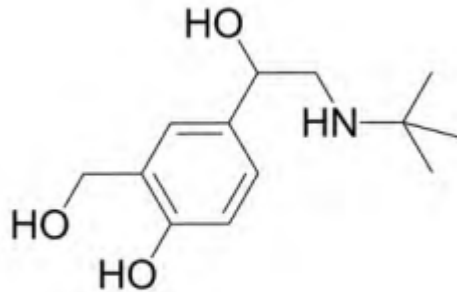


Background



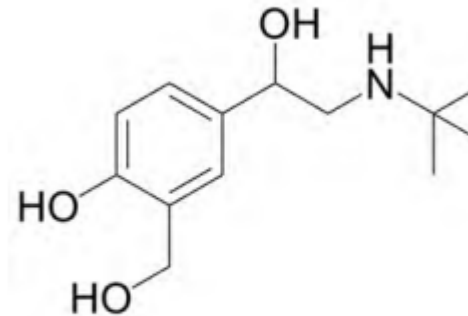
First case of aseptic operation

Ventolin HFA
(Salbutamol)



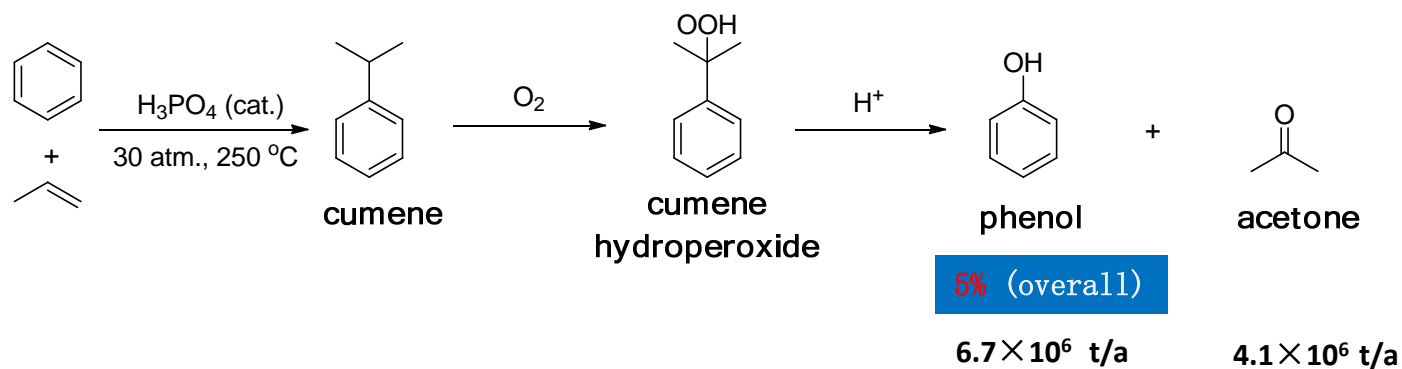
13.5 million scripts
B2-STIMULANTS

Proventil HFA
(Salbutamol)



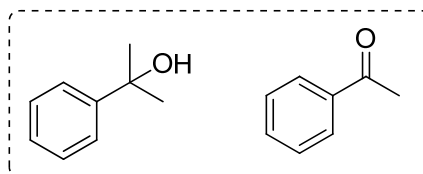
4.0 million scripts
B2-ADRENERG BRONCHODILATOR

Cumene Oxidation (Hock Process)

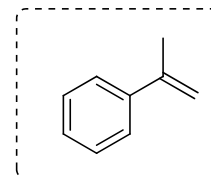


Hock, H.; Lang, S. *Ber. Dtsch. Chem. Ges.* 77, **1944**, 257

Byproducts in the process:

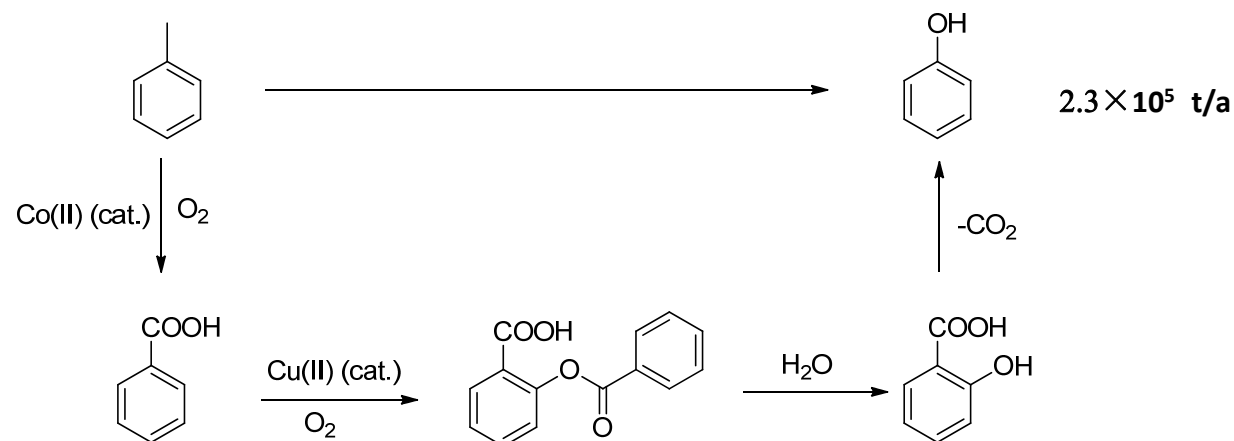


in the oxidation step



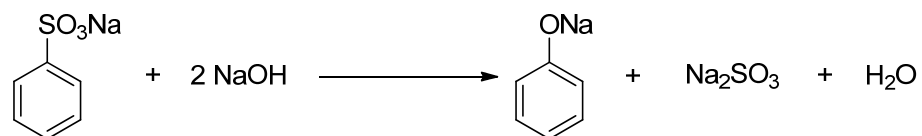
in the acid-catalyzed step

Toluene Oxidation (Dow Process)

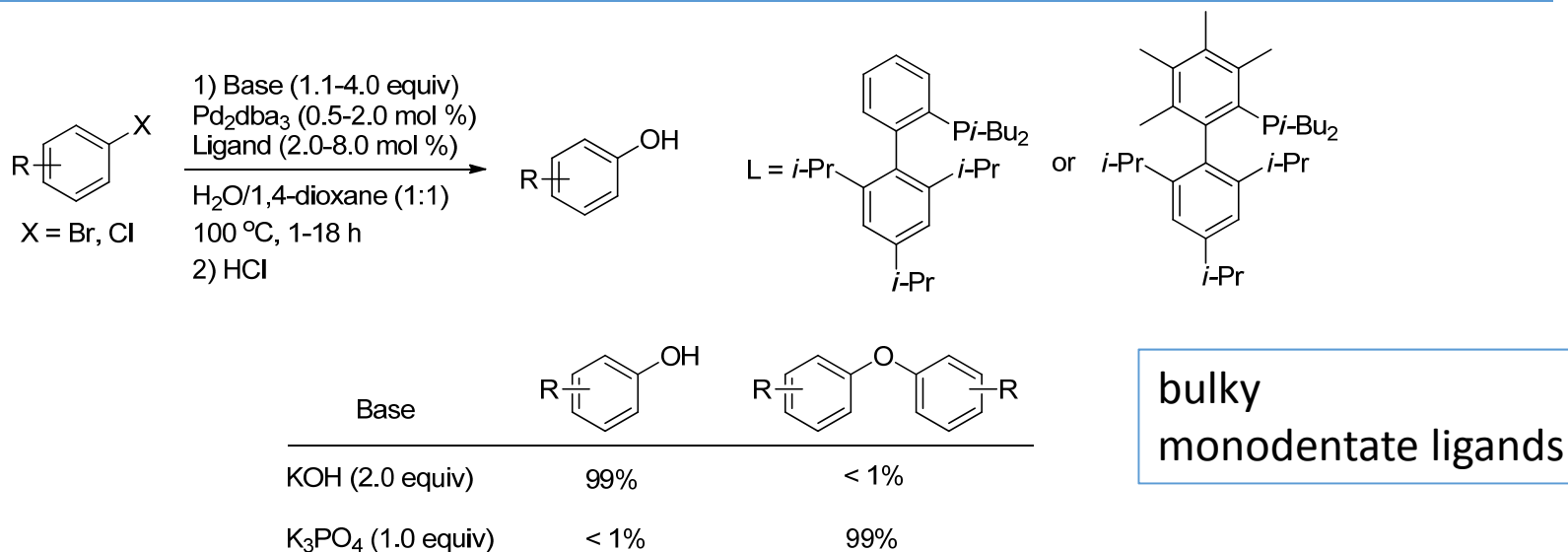


Dow Chemical Corp., US 2727326, 1995.

Sulfonation of Benzene (WURTZ and KEKULE in 1867)

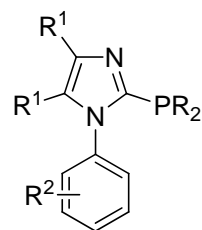


Palladium-Catalyzed Coupling of Hydroxide with Aryl Halides

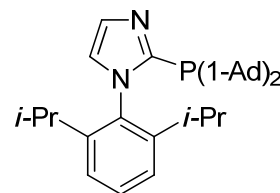


Anderson, K. W.; Ikawa, T.; Tundel, R. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 10694

Other Ligands:



Easy synthesis

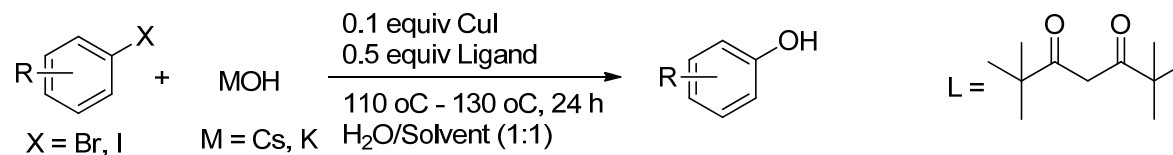


Reaction temperature: r.t.

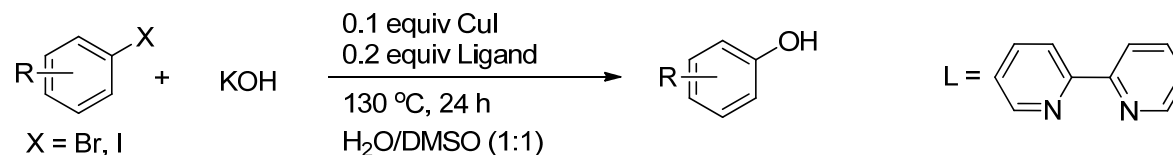
Beller, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 918

Beller, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 7595.

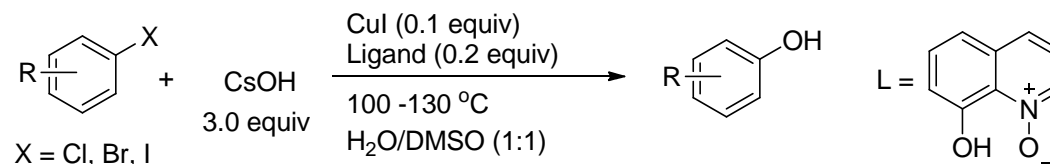
Copper-Catalyzed Coupling of Hydroxide with Aryl Halides



Tilli, A.; Xia, N.; Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 8725–8728

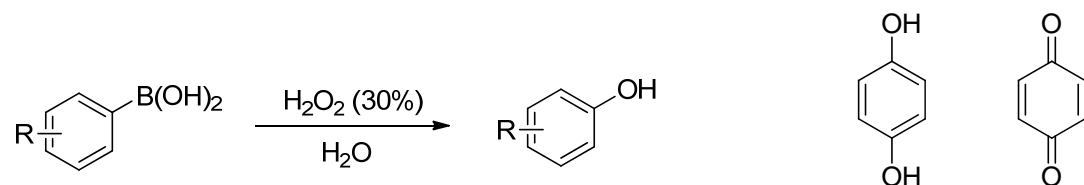


Zhao, D.; Wu, N.; Zhang, S.; Xi, P.; Su, X.; Lan, J.; You, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 8729



Yang, K.; Li, Z.; Wang, Z.; Yao, Z.; Jiang, S. *Org. Lett.* **2011**, *13*, 4340

Hydroxylation of Arylboronic Acids and Boronate Esters



Byproducts of over oxidation

Ainley, A. D.; Challenger, F. J. *Chem. Soc.* **1930**, 2171

modifications:

I₂-H₂O₂

Synlett **2012**, 23, 1079

CuSO₄-phenanthroline O₂

Org. Lett. **2010**, 12, 1964

H₂O₂-poly (N-vinylpyrrolidone)

Adv. Synth. Catal. **2009**, 351, 1567.

NH₂OH

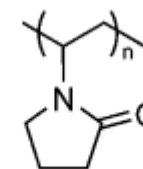
Tetrahedron Lett. **2007**, 48, 2713.

Potassium peroxymonosulfate

Tetrahedron Lett. **1995**, 36, 5117

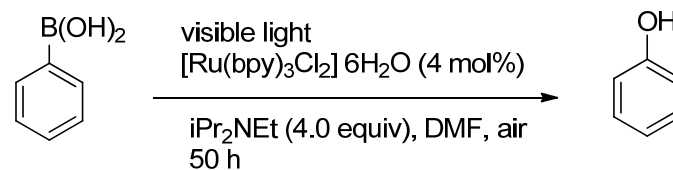
Photocatalyst/ Visible light/ air

Angew. Chem. Int. Ed. **2012**, 51, 784

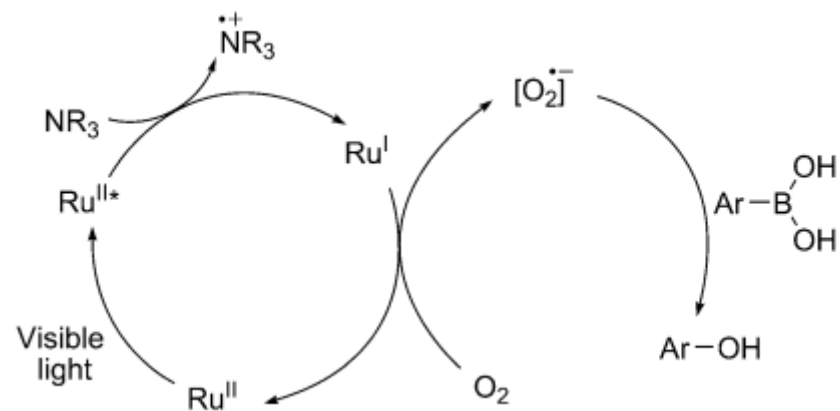


Poly(N-vinylpyrrolidone) PVD

Oxidative Hydroxylation of Arylboronic Acids with Photoredox Catalysis

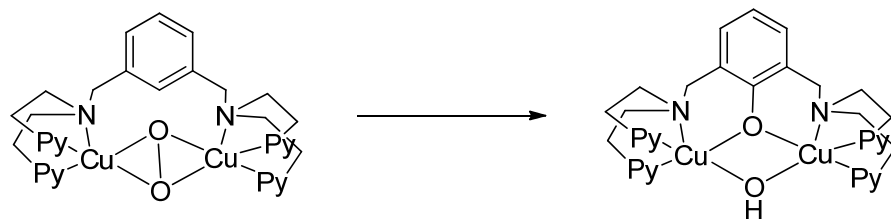


Proposed Catalytic Mechanism:

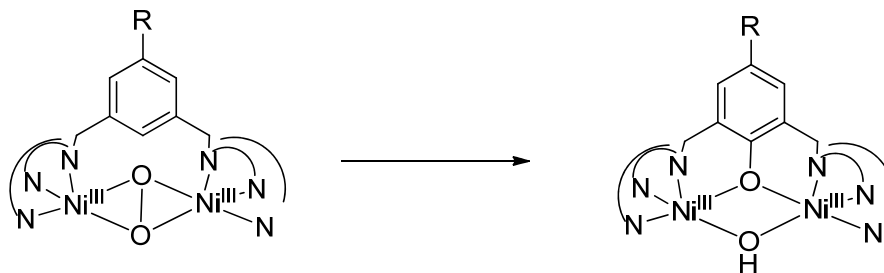


Intramolecular Hydroxylation of Aromatic Group

Transition-metal complexes of active oxygen species:

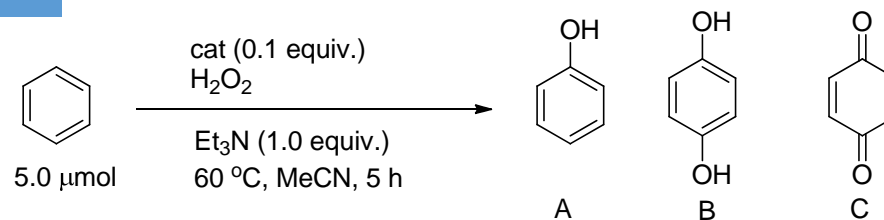


Karlin, K. D.; Nasir, M. S.; Cohen, B. I.; Cruse, R. W.; Kaderli, S.; Zuberbuehler, A. D.
J. Am. Chem. Soc. **1994**, *116*, 1324



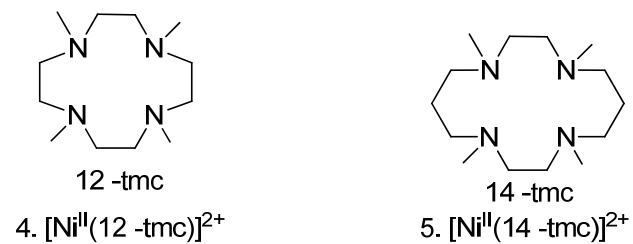
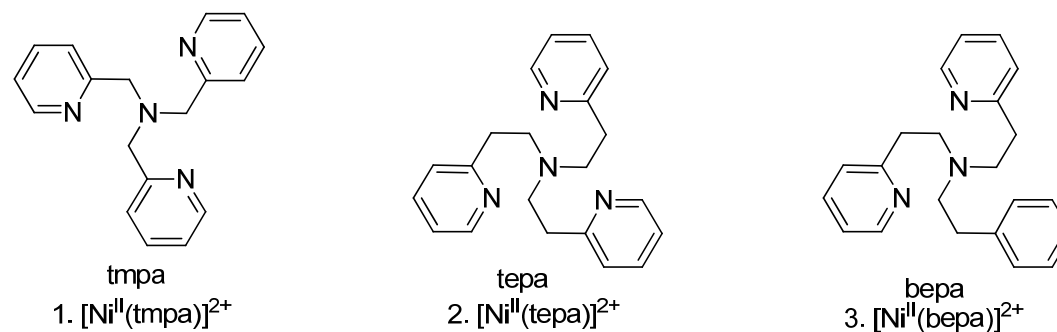
Honda, K.; Cho, J.; Matsumoto, T.; Roh, J.; Furutachi, H.; Tosha, T.; Kubo, M.; Fujinami, S.; Ogura, T.; Kitagawa, T.; Suzuki, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 3304

Active species reported:

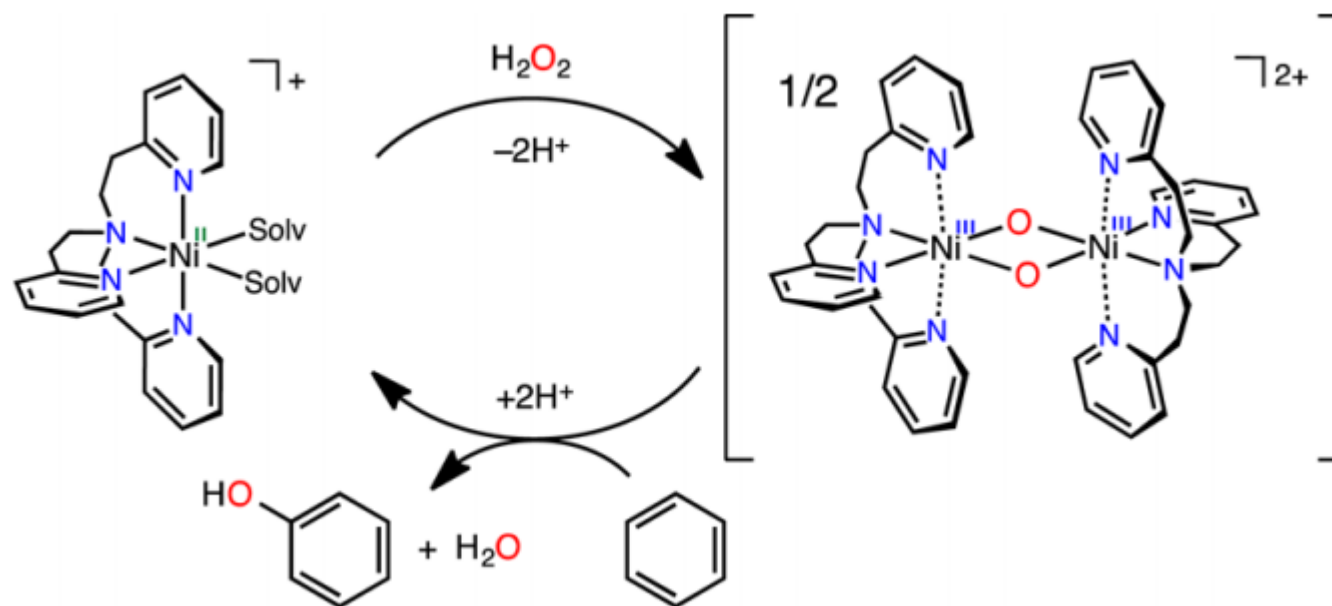


Entry	cat	conv.(%)	yield (%)	selectivity (%)
1	1	27	18	66
2	2	23	21	>99
3	3	25	2	8
4	4	7	4	-
5	5	10	5	-

$$\text{Selectivity} = A/(A+B+C)$$



Proposed Catalytic Mechanism:



Summary

- Some indirect methods of phenol synthesis have been summarized.
- The Strategies of direct benzene hydroxylation is still limited. These strategies generally go through free radical mechanism. Improve the yield and selectivity is a big challenge.

Thank you!