

Building up Molecular Complexity via C–O cleavage: From Comprehension to Prediction

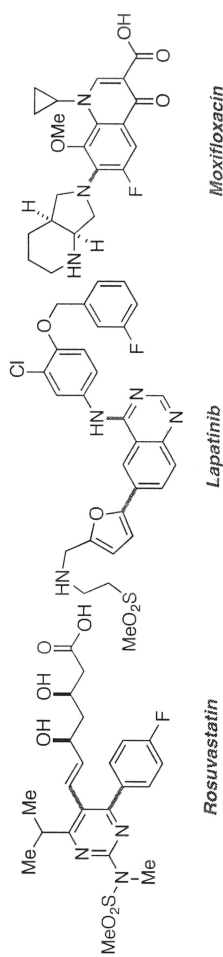
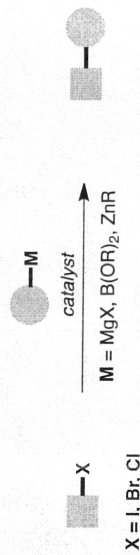
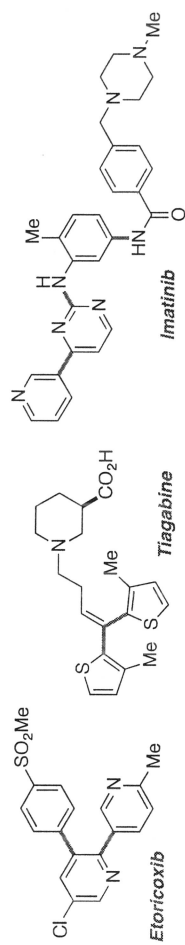
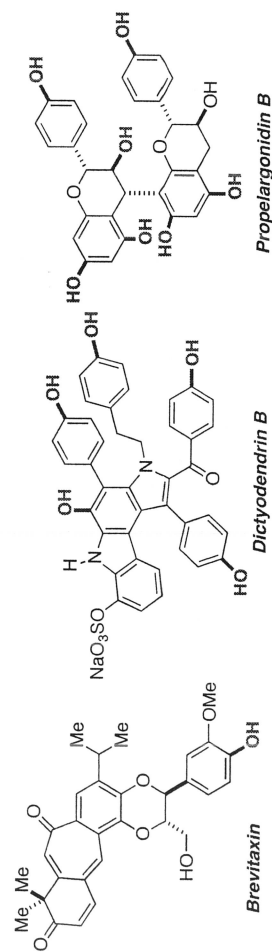
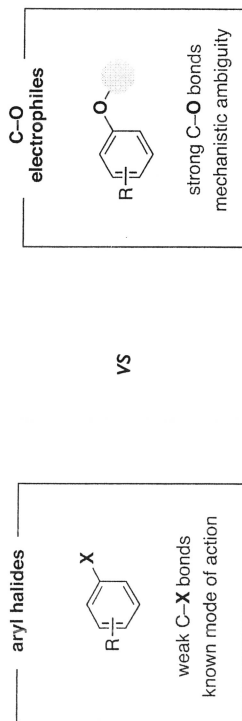


Ruben Martin

Institute of Chemical Research of Catalonia (ICIQ)

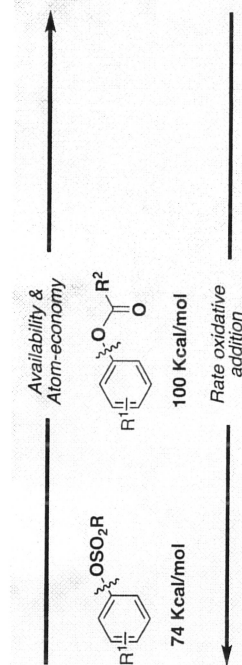
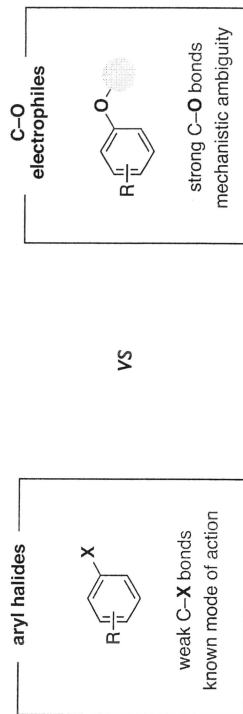
IASOC 2018, September 23, 2018

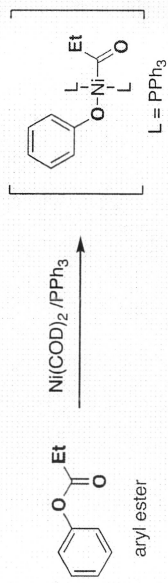
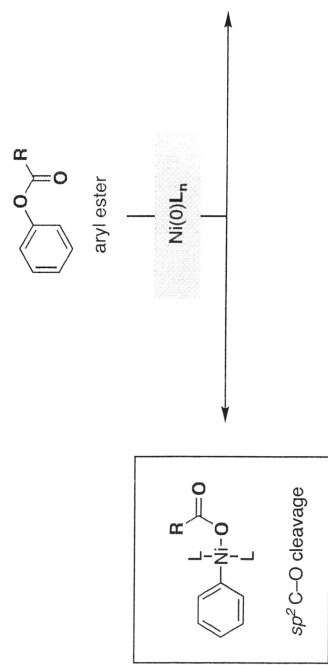
Alternatives to aryl halides in the cross-coupling arena ?



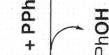
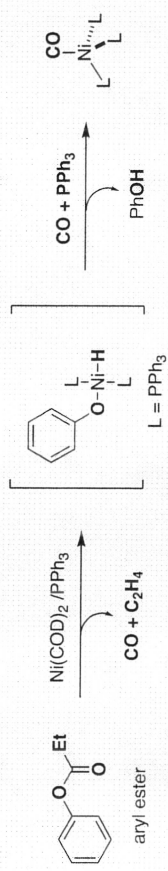
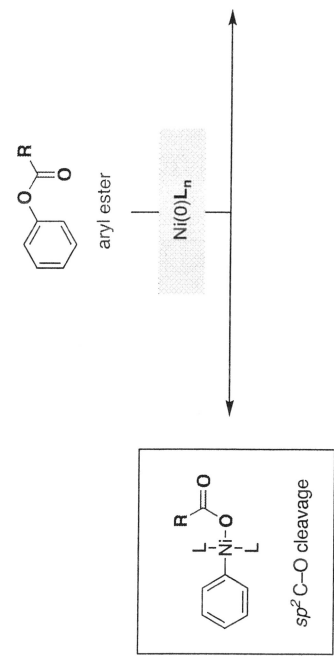
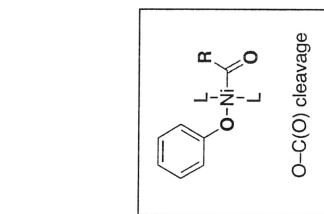
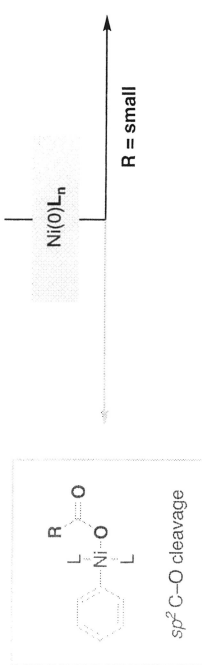
Cross-coupling reactions are primarily conducted with organic halides

Alternatives to aryl halides in the cross-coupling arena ?

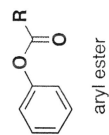
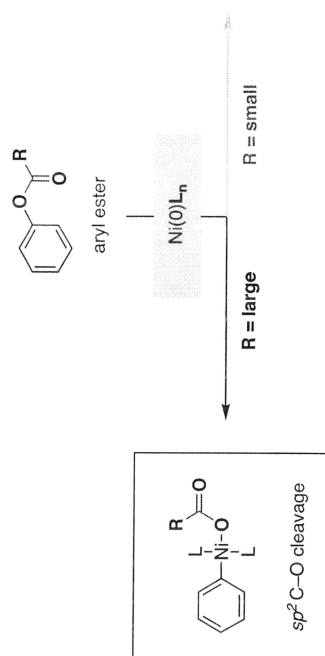




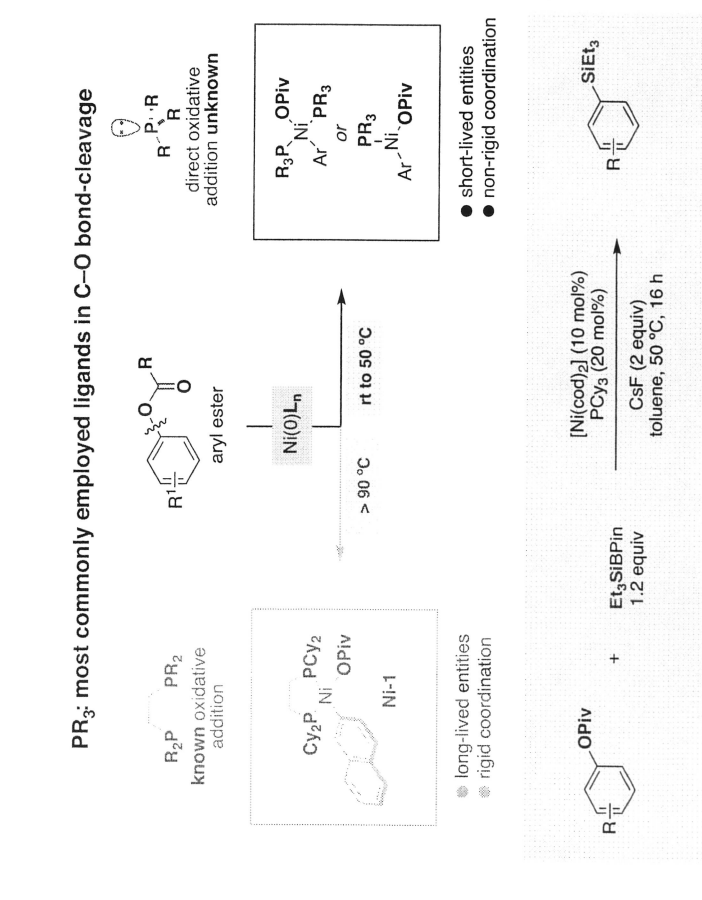
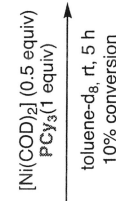
Ishizu, J.; Yamamoto, T.; Yamamoto, A. *Chem. Lett.* **1976**, 1091



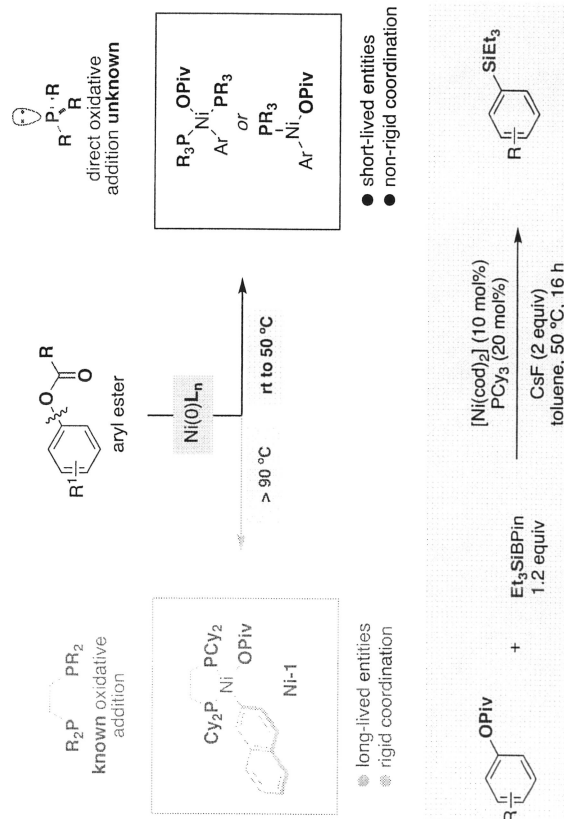
Ishizu, J.; Yamamoto, T.; Yamamoto, A. *Chem. Lett.* **1976**, 1091

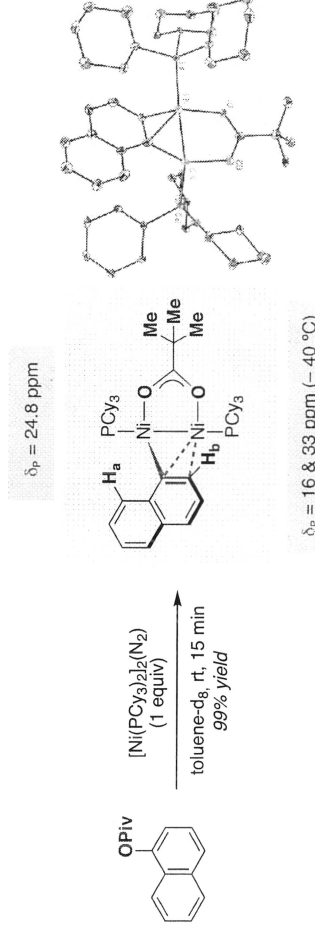
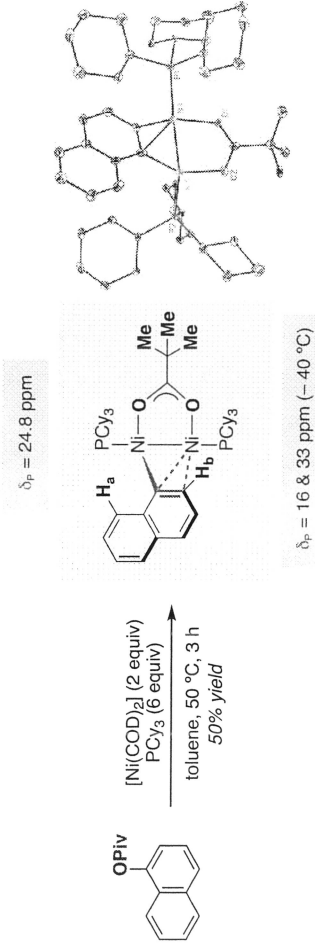
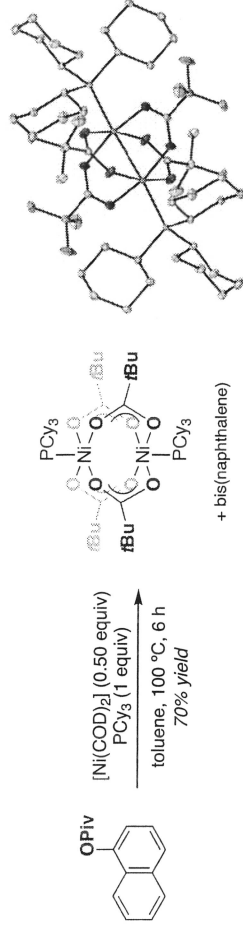
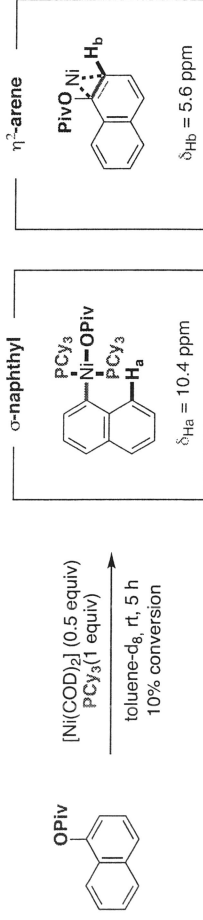


Ishizu, J.; Yamamoto, T.; Yamamoto, A. *Chem. Lett.* **1976**, 1091

Muto, K.; Yamaguchi, J.; Lei, A.; Itami, K. *J. Am. Chem. Soc.* **2013**, *135*, 16384

PR₃: most commonly employed ligands in C–O bond-cleavage

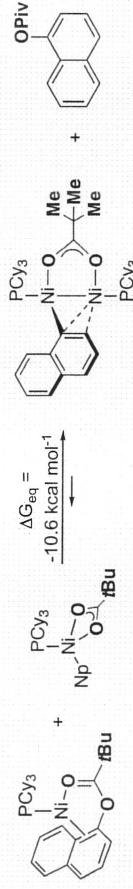




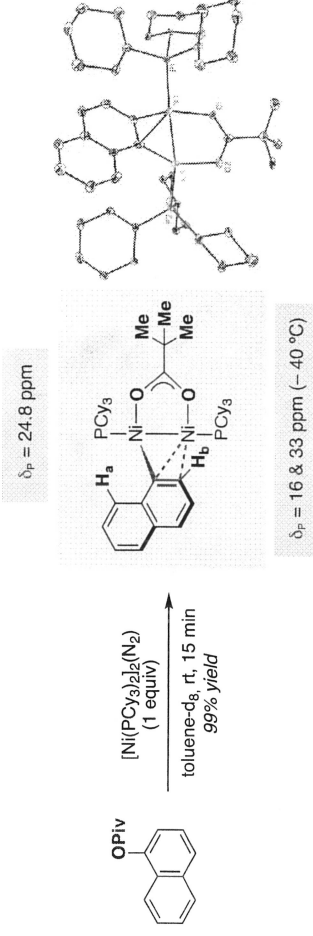
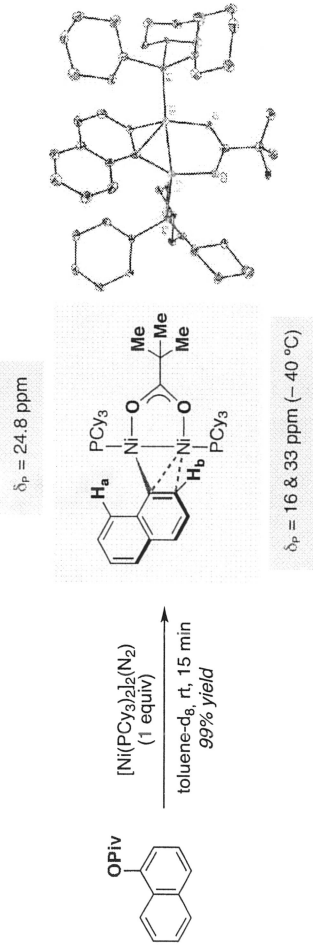
Somerville, R. J.; Hale, L. V. A.; Gómez-Bengoa, E.; Burés, J.; Martin, R. *J. Am. Chem. Soc.* **2018**, *140*, 8771

Somerville, R. J.; Hale, L. V. A.; Gómez-Bengoa, E.; Burés, J.; Martin, R. *J. Am. Chem. Soc.* **2018**, *140*, 8771

comproportionation events



For related scenarios with diphosphine ligands: Hazari, N. et al. *J. Am. Chem. Soc.* **2016**, *139*, 922

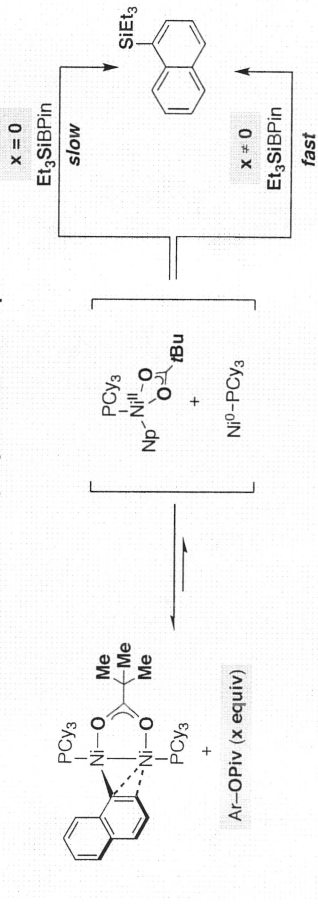


Somerville, R. J.; Hale, L. V. A.; Gómez-Bengoa, E.; Burés, J.; Martin, R. *J. Am. Chem. Soc.* **2018**, *140*, 8771

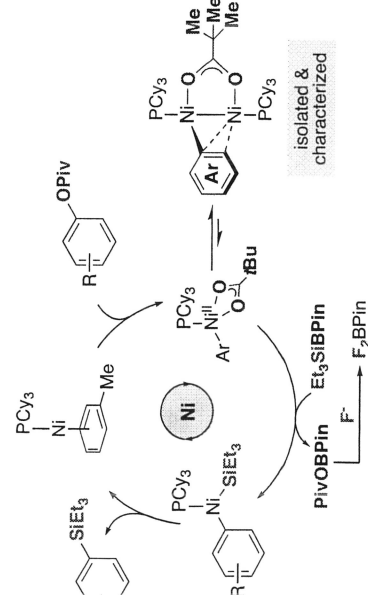
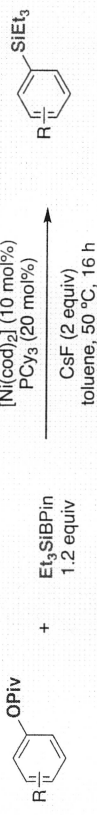
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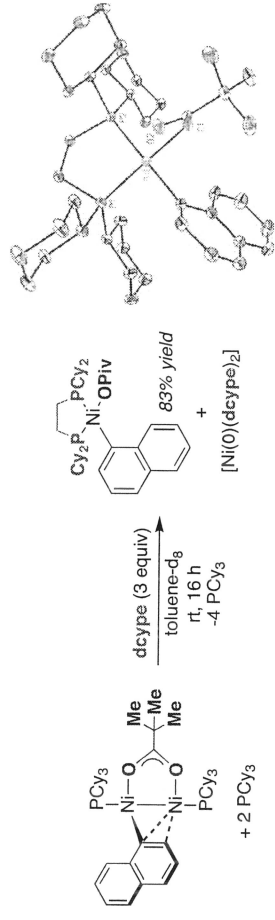
perturbation of disproportionation equilibrium



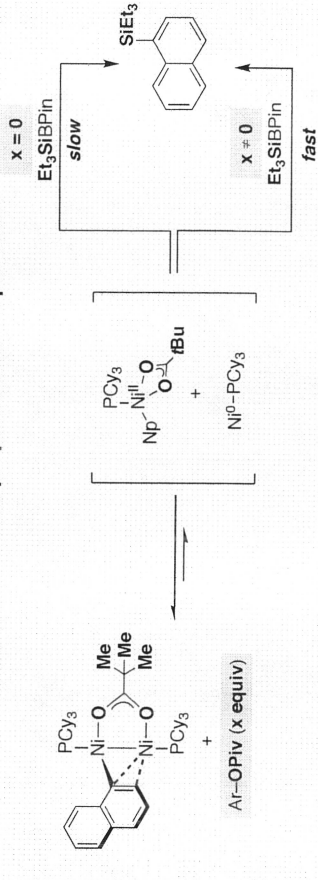
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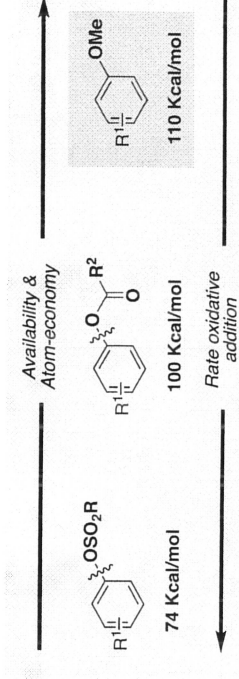
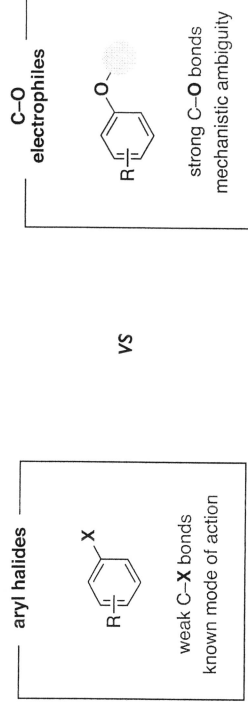


perturbation of disproportionation equilibrium



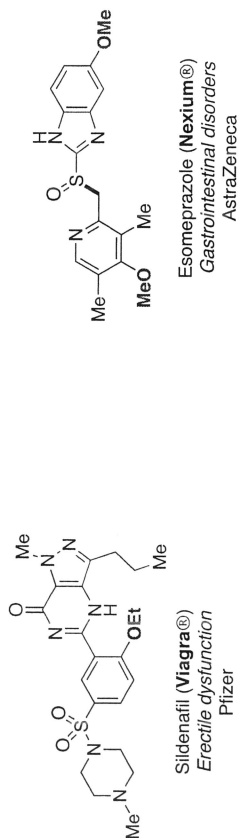
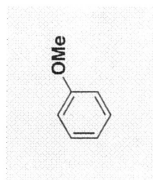
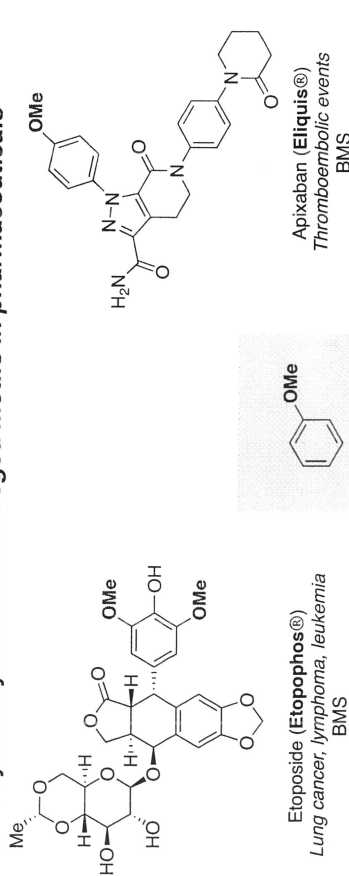
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Alternatives to aryl halides in the cross-coupling arena ?

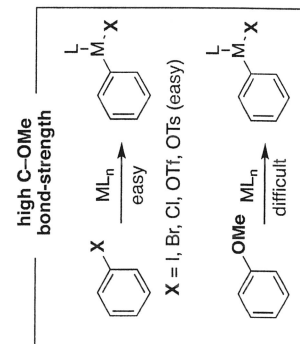
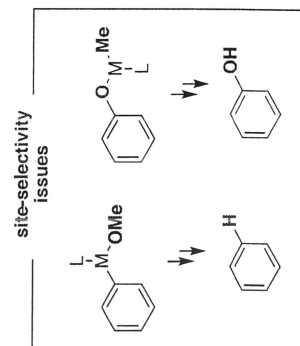
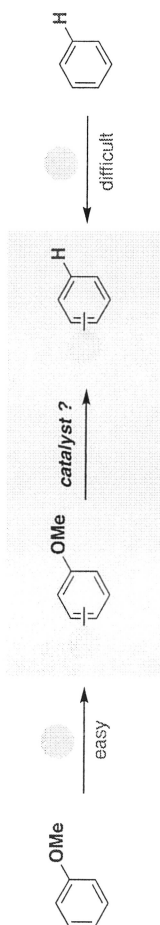


Tobisu, M.; Chatani, N. *Acc. Chem. Res.* **2015**, *48*, 1717
Cornella, J.; Zarate, C.; Martin, R. *Chem. Soc. Rev.* **2014**, *43*, 8081

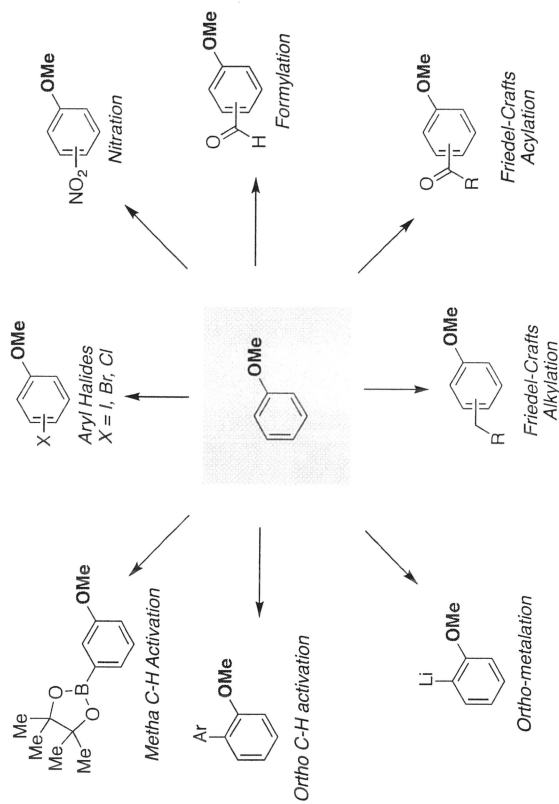
Aryl methyl ethers: Privileged motifs in pharmaceuticals



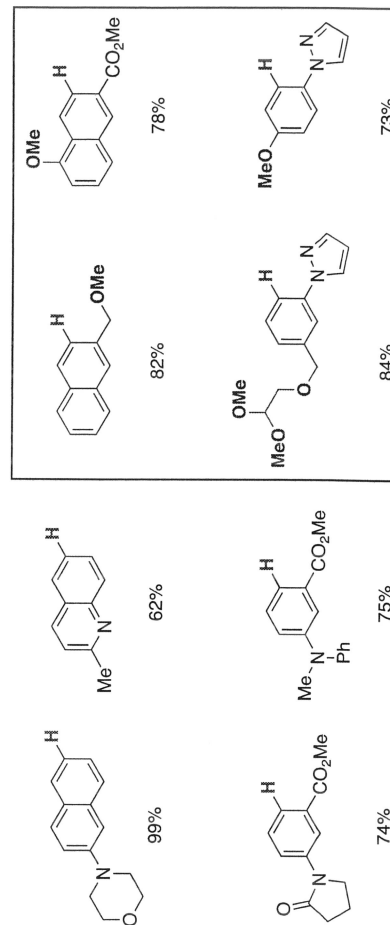
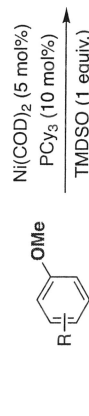
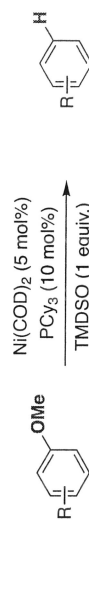
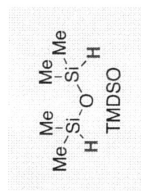
Aryl methyl ethers as temporary directing groups



Aryl methyl ethers: Useful synthons to build up molecular complexity



Mikhailid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* 2010, 110, 890.

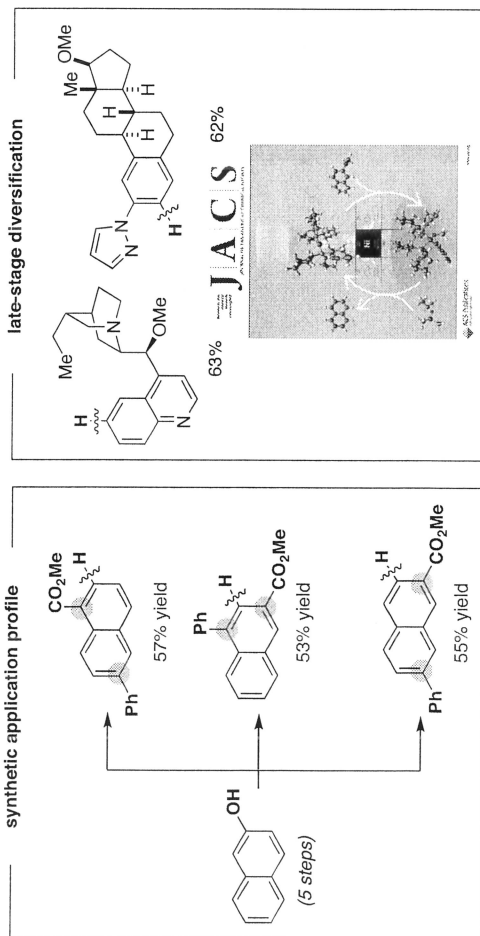


site-selectivity

Alvarez-Bercedo, P.; Martin, R. *J. Am. Chem. Soc.* 2010, 132, 17352
Cornella, J.; Zarate, C.; Martin, R. *Org. Synth.* 2014, 91, 260

Wenkert, E.; Michelotti, E. L.; Swindell, C. S. *J. Am. Chem. Soc.* 1979, 101, 2246

Aryl methyl ethers as temporary directing groups

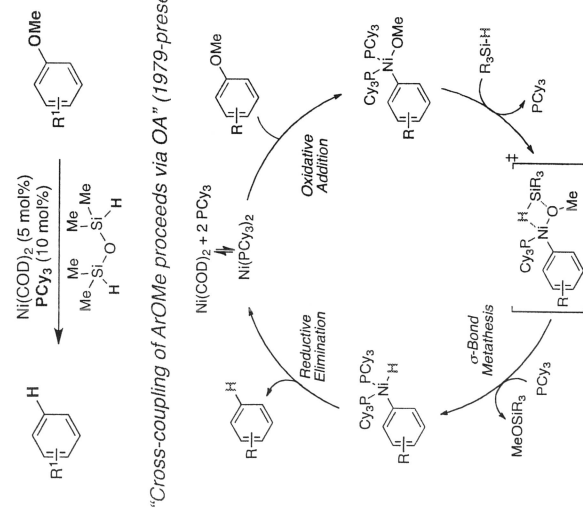


Alvarez-Bercedo, P.; Martin, R. *J. Am. Chem. Soc.* **2010**, *132*, 17352
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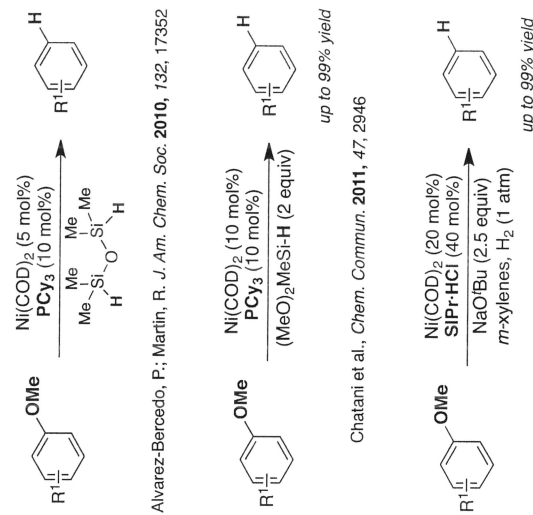
Mechanistic considerations

- $\text{Ni}(\text{COD})_2$ as catalyst
- PCy_3 critical for success
- Much higher reactivity for extended π -systems
- No reaction in the absence of catalyst or silane

No mechanistic studies on C-OMe bond-cleavage
 Implications in other C-O cleavage events



Alvarez-Bercedo, P.; Martin, R. *J. Am. Chem. Soc.* **2010**, *132*, 17352

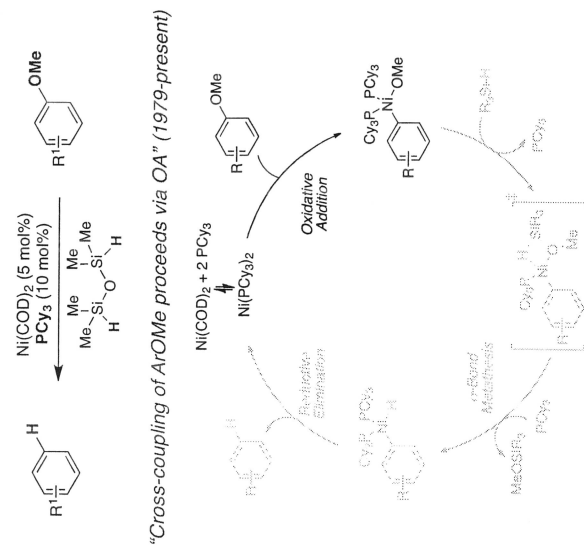


Hartwig et al., *Science* **2011**, *332*, 439

Mechanistic considerations

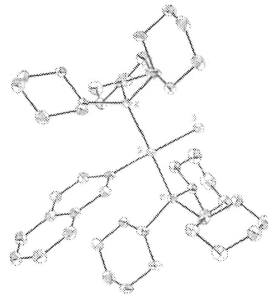
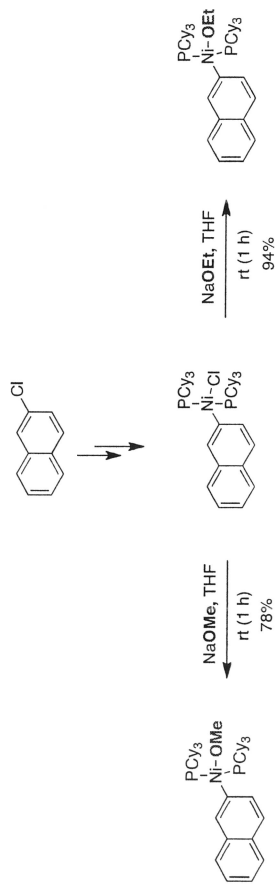
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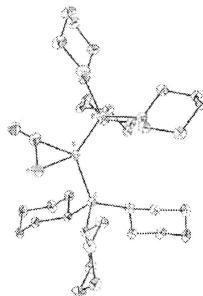
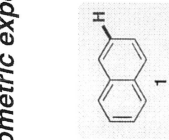
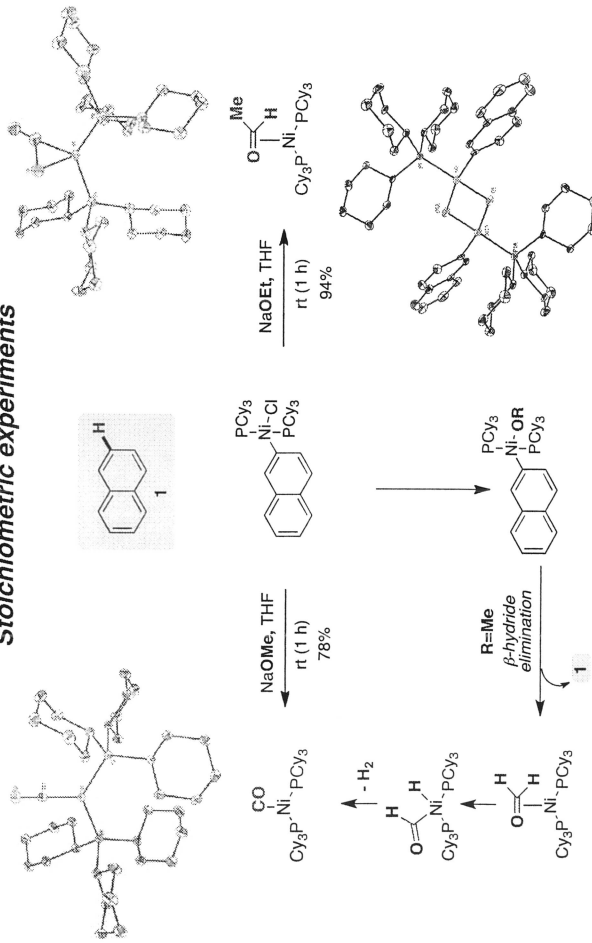
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Stoichiometric experiments



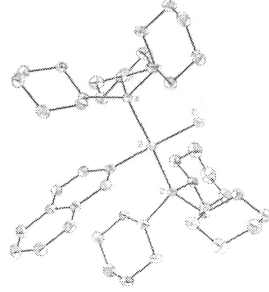
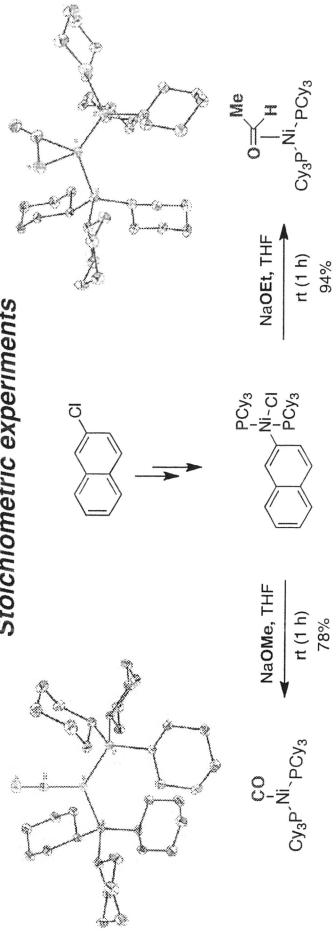
Cornellà, J.; Gómez-Bengoa, E.; Martín, R. *J. Am. Chem. Soc.* **2013**, *135*, 1997

Stoichiometric experiments



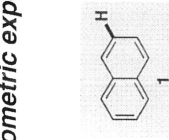
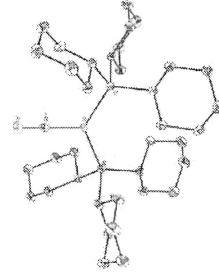
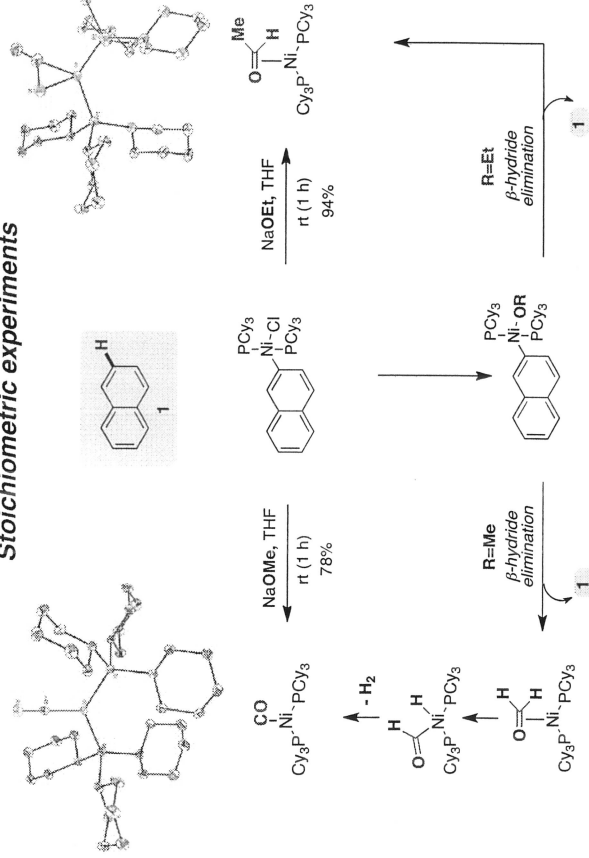
Intramolecular stoichiometric studies using pincer-type complexes: Agapie, T. *J. Am. Chem. Soc.* **2012**, *134*, 5480
 Cornellà, J.; Gómez-Bengoa, E.; Martín, R. *J. Am. Chem. Soc.* **2013**, *135*, 1997

Stoichiometric experiments



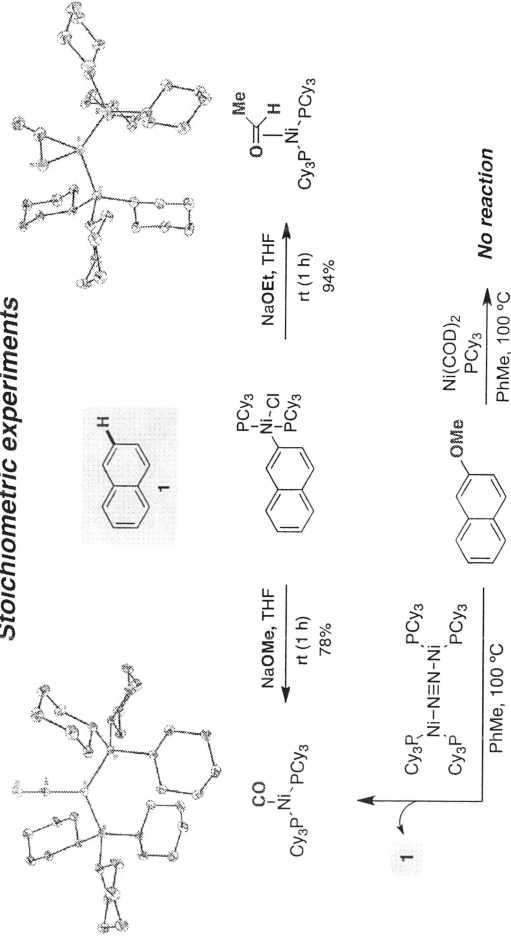
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 Cornellà, J.; Gómez-Bengoa, E.; Martín, R. *J. Am. Chem. Soc.* **2013**, *135*, 1997

Stoichiometric experiments



β -hydride elimination !!!.....in the absence of R_3SiH and COD

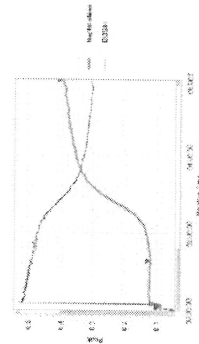
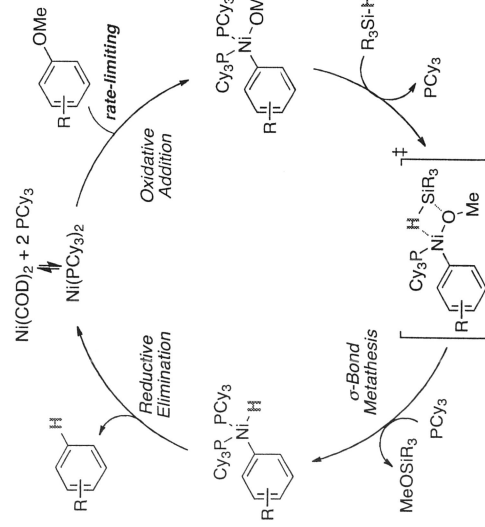
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Kinetic Experiments

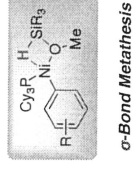
- First order in catalyst
- First order in substrate
- Et_3SiH vs. Et_3SiD $k_H/k_D = 1$

Striking Observations

- First order in silane
- Different induction period for Et_3SiH and Et_3SiD
- Consumption of Et_3SiH in the induction period



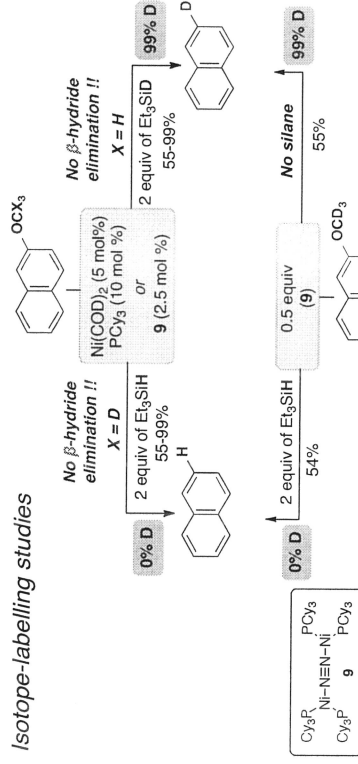
Cornellà, J.; Gómez-Bengoa, E.; Martín, R. *J. Am. Chem. Soc.* **2013**, 135, 1997



vs.

β -Hydride Elimination

Isotope-labelling studies



- With R_3SiH , no β -hydride elimination and catalytic
- With no R_3SiH , β -hydride elimination but not catalytic

Kinetic Experiments

- First order in catalyst
- First order in substrate
- Et_3SiH vs. Et_3SiD $k_H/k_D = 1$

Striking Observations

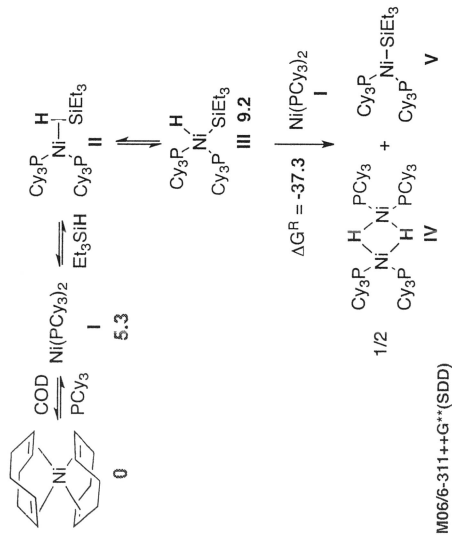
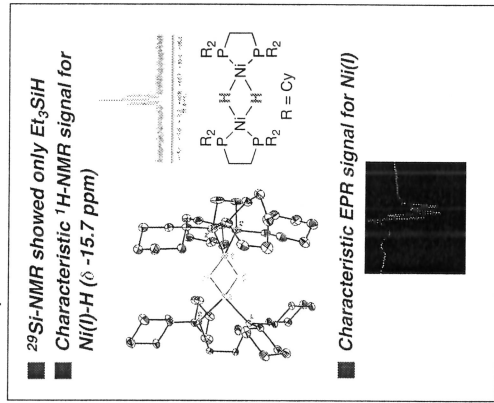
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"Classical" $\text{Ni(0)} / \text{Ni(II)}$ catalytic manifold unlikely

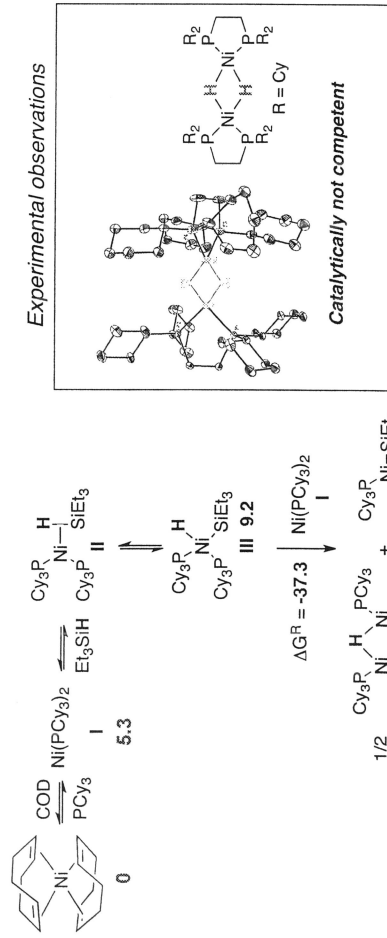
Ni(II) species ?

Cornellà, J.; Gómez-Bengoa, E.; Martín, R. *J. Am. Chem. Soc.* **2013**, 135, 1997

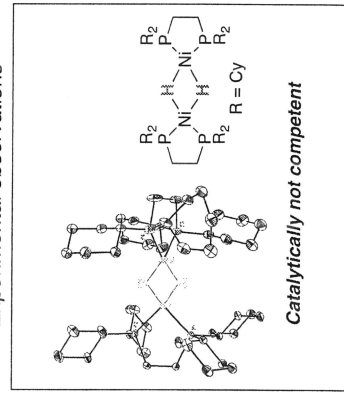
Experimental observations



Cornellà, J.; Gómez-Bengoa, E.; Martín, R. *J. Am. Chem. Soc.* **2013**, *135*, 1997

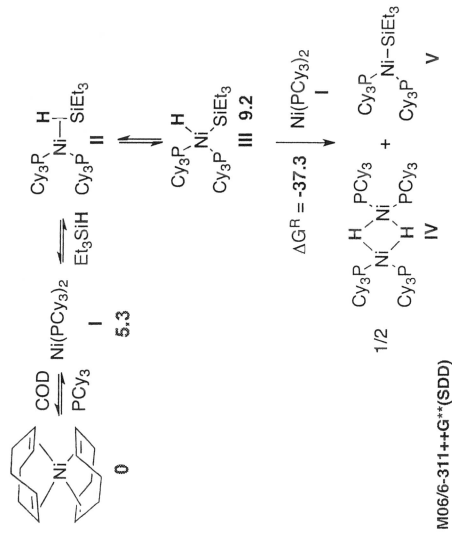


Experimental observations

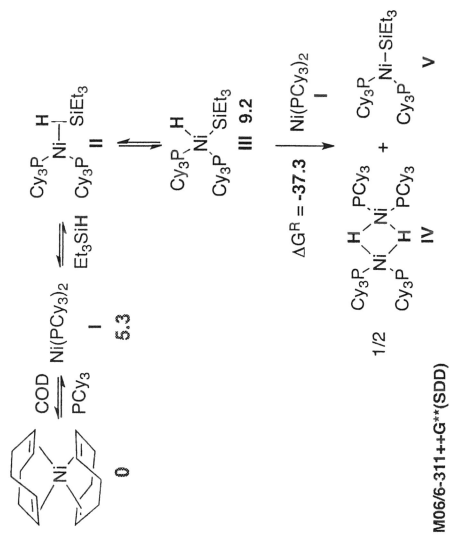


Catalytically not competent

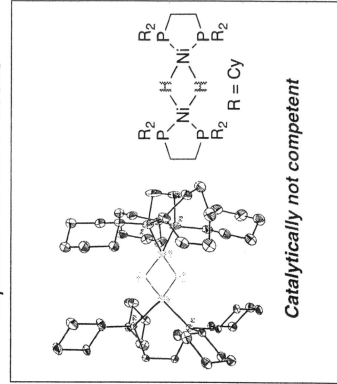
M06/6-311++G**(SDD)



Cornellà, J.; Gómez-Bengoa, E.; Martín, R. *J. Am. Chem. Soc.* **2013**, *135*, 1997



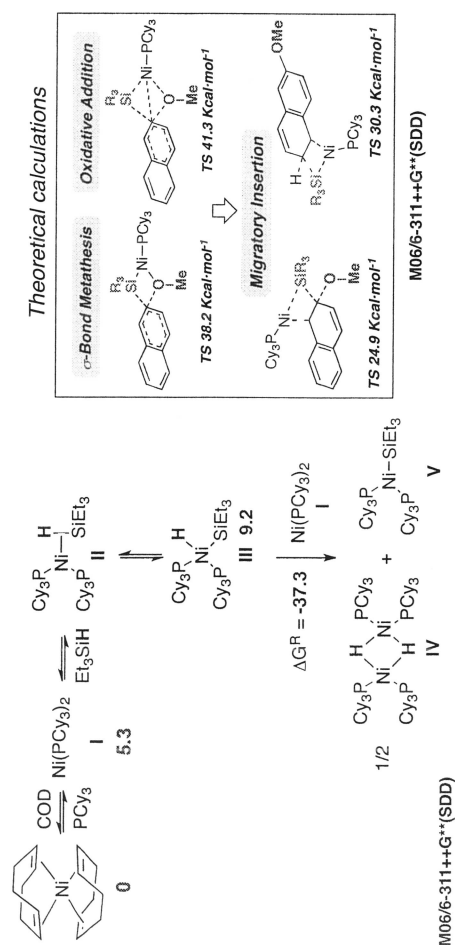
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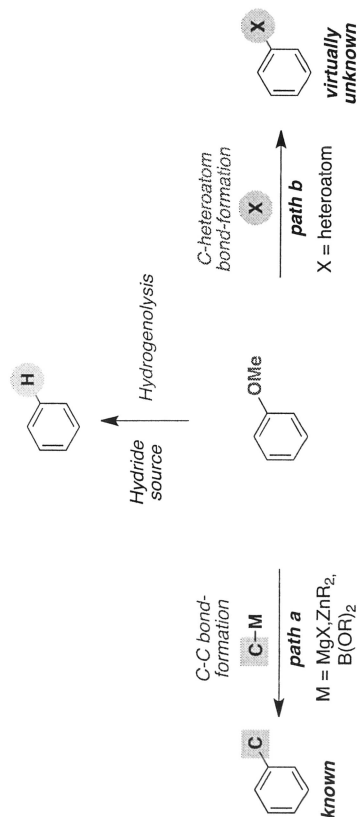
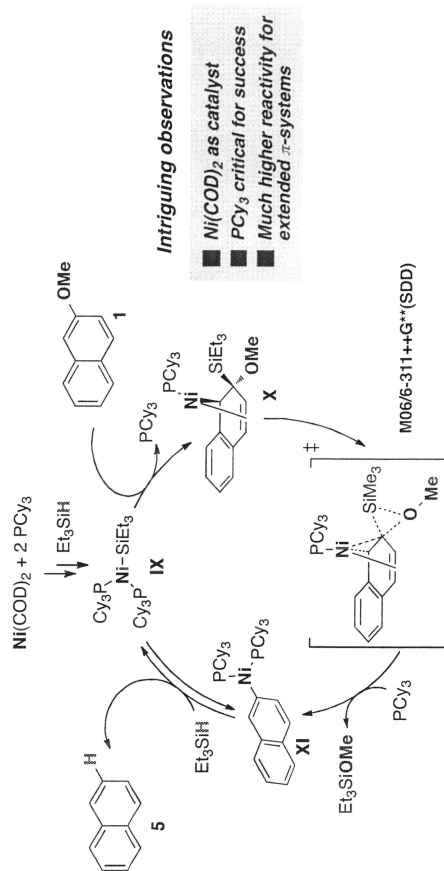
Propagating Ni(I)-SiR3 species ?

Cornellà, J.; Gómez-Bengoa, E.; Martín, R. *J. Am. Chem. Soc.* **2013**, *135*, 1997

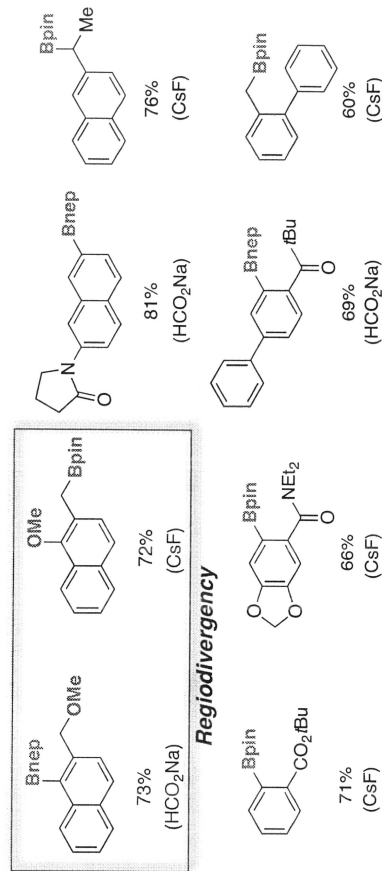
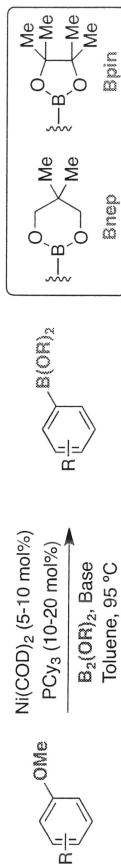
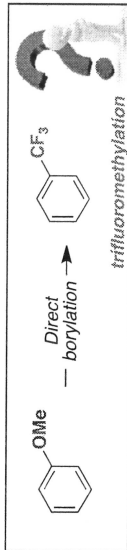
Cornellà, J.; Gómez-Bengoa, E.; Martín, R. *J. Am. Chem. Soc.* **2013**, *135*, 1997



Consistent with all the kinetic data, isotope-labelling & in situ-monitoring experiments

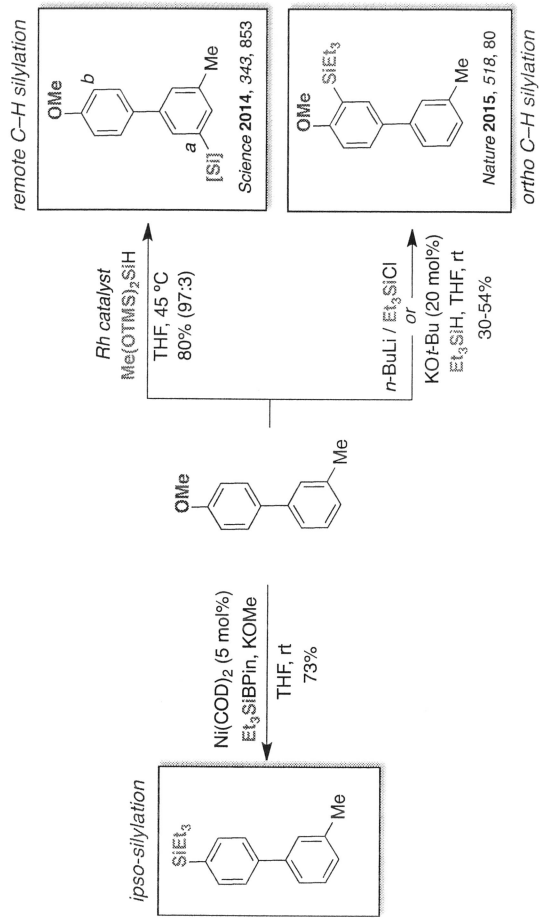


Chatani, Shi, Rueping, Percec

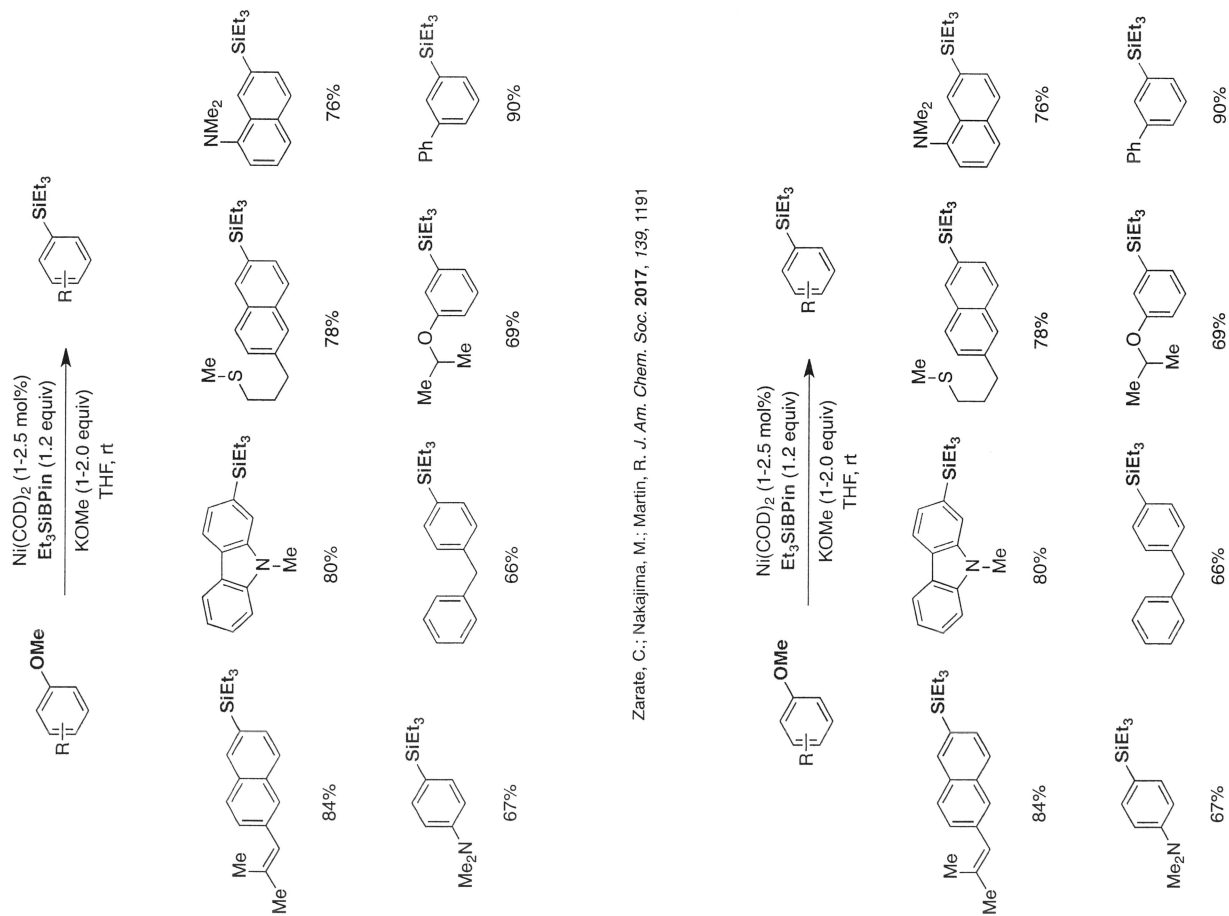


DG and high temperatures required for non- π -extended aryl ethers

Design of orthogonal silylation techniques

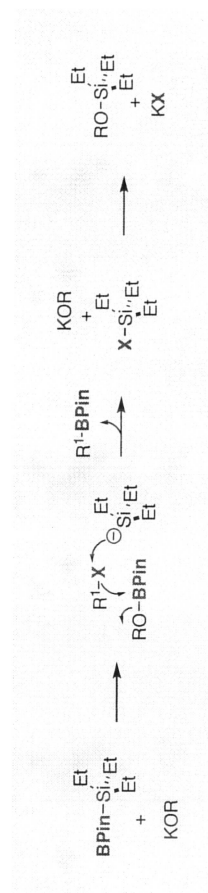
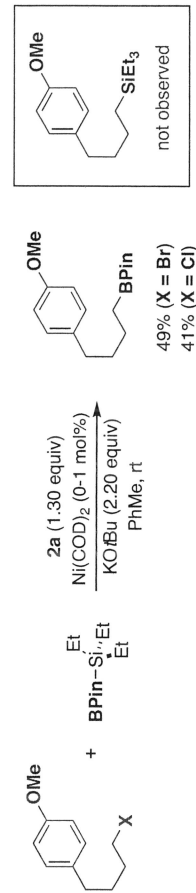


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intermediacy of silyl anionic species



Negative Hg drop test & no inhibition with silyl radical scavengers

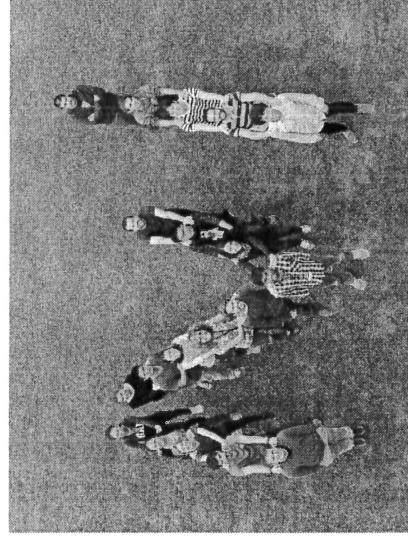
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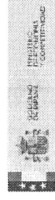
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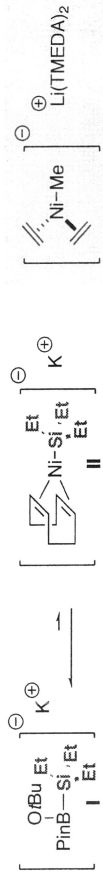
Johnson Matthey



Alexander von Humboldt
Fellowship

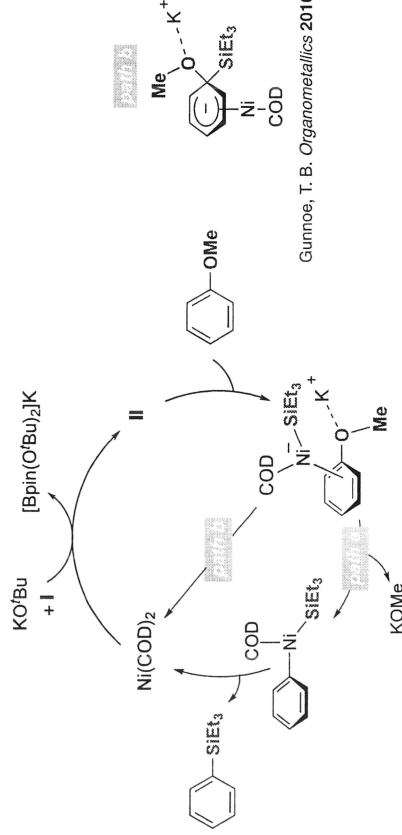


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Ni(0)-silyl ate complexes



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