

François Mazars,<sup>a</sup> Guillermo Zaragoza,<sup>b</sup> Lionel Delaude<sup>a,\*</sup>

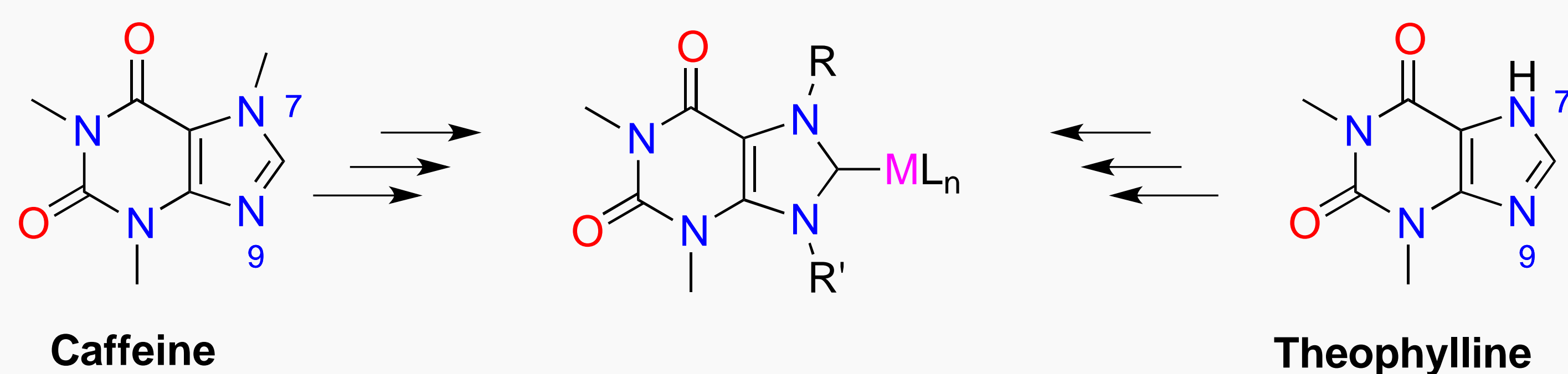
<sup>a</sup>Laboratory of Catalysis, Department of Chemistry, University of Liège, Institut de chimie organique (B6a), Allée du six Août 13, 4000 Liège, Belgium

<sup>b</sup>Unidade de Difracción de Raios X, RIAIDT, Universidade de Santiago de Compostela, Campus Vida, 15782, Santiago de Compostela, Spain

[f.mazars@uliege.be](mailto:f.mazars@uliege.be), <http://www.cata.ulg.ac.be>

### Background:

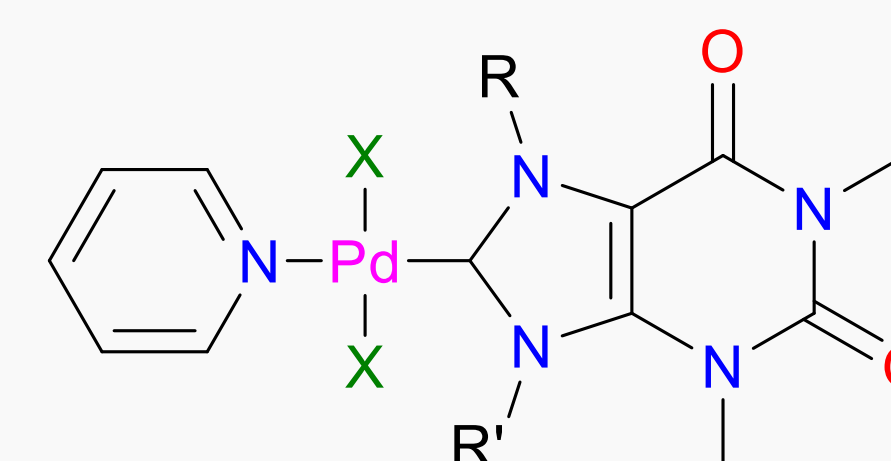
Caffeine and theophylline are two substrates of choice for generating new ligand systems, thanks to their large availability, low cost of extraction, and ability to form various types of N-heterocyclic carbenes (NHCs) [1]. Upon alkylation, their imidazole moiety may be converted into imidazolium salts, which afford imidazolylidene species upon deprotonation. Complexes bearing these xanthine-based NHCs have already found applications as catalysts and antimicrobial, anticancer, or photoluminescent agents [2].



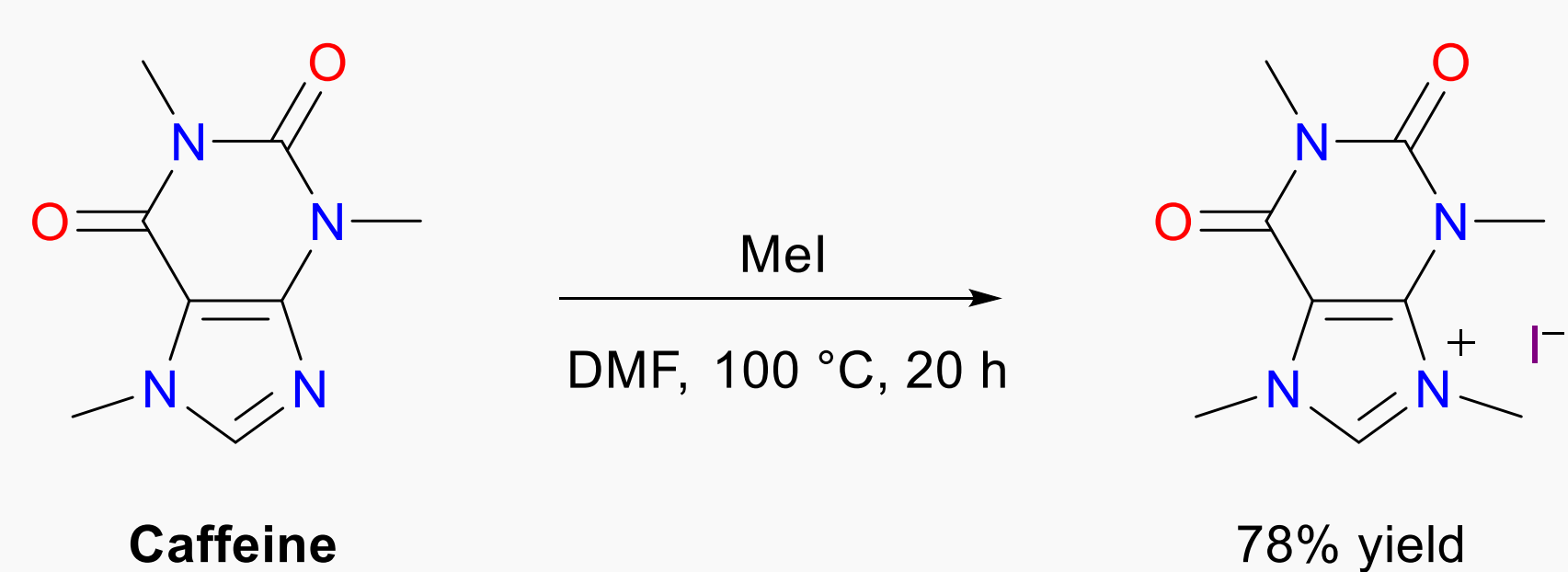
### Objectives:

In 2006, Organ *et al.* achieved a major breakthrough in palladium-catalyzed cross-coupling reactions by developing the so-called PEPPSI complexes (PEPPSI stands for Pyridine-Enhanced Precatalyst Preparation Stabilization and Initiation) [3]. They reasoned that the introduction of a labile pyridine ligand should ease the *in situ* formation of monoligated Pd(0)-NHC active species needed to trigger the catalytic cycle. As a matter of fact, Pd-PEPPSI precatalysts quickly became a commercial success due to their efficiency at promoting diverse cross-coupling reactions [4].

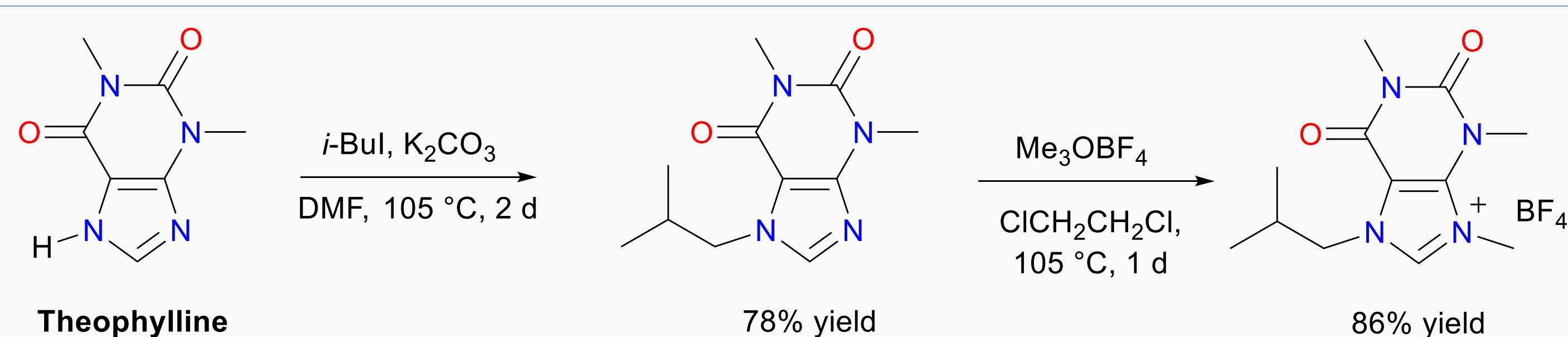
Our objectives are to extend the chemistry of Pd-PEPPSI complexes to NHC ligands derived from xanthine and to assess their catalytic activity in various cross-coupling reactions.



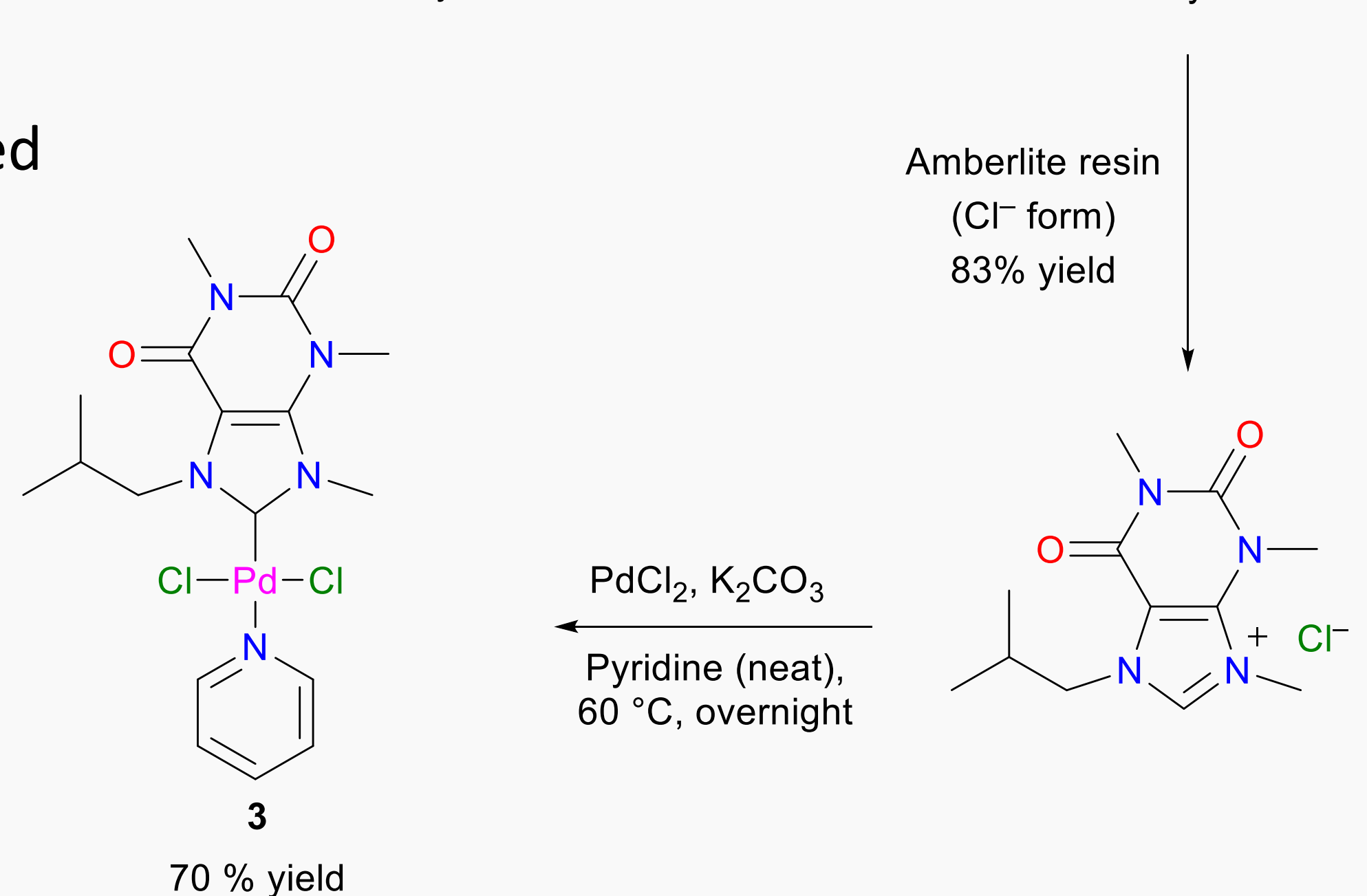
**Results:** Three new [PdX<sub>2</sub>(NHC)(py)] complexes were synthesized in high yields using simple and straightforward procedures starting from caffeine or theophylline [5].



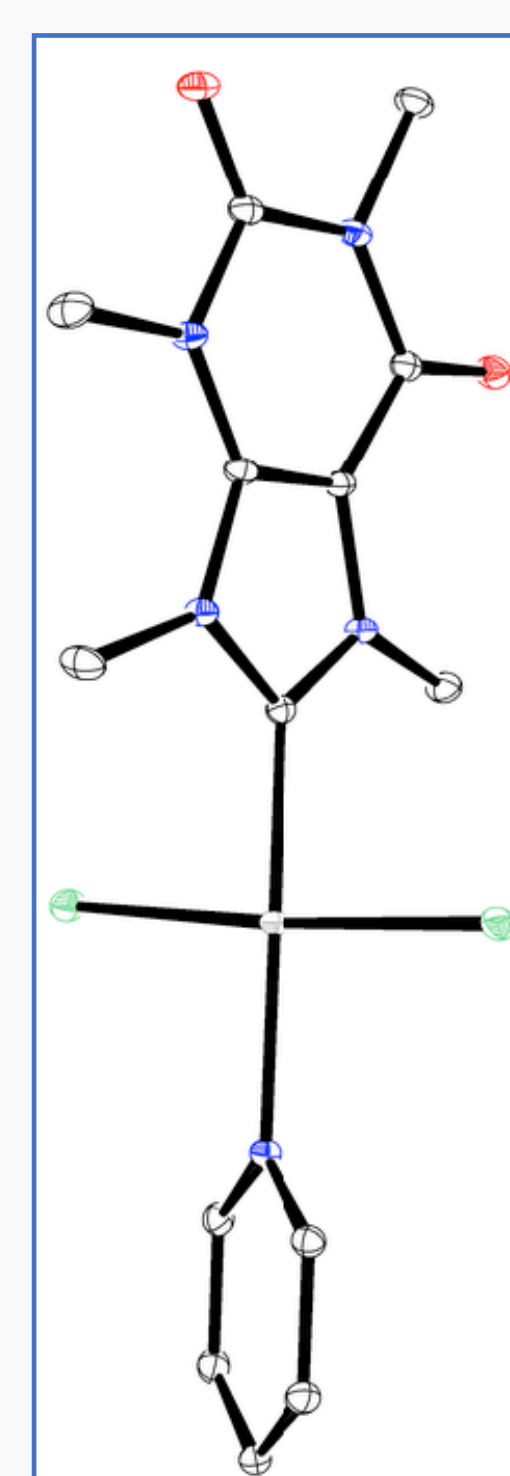
Caffeine is easily alkylated with methyl iodide.



Theophylline may be used as a starting material to introduce further alkyl substituents.



The reaction of PdCl<sub>2</sub> with an NHC-HI salt leads to halogen scrambling. We managed to selectively obtain either the diiodo or dichlorido PEPPSI complex.



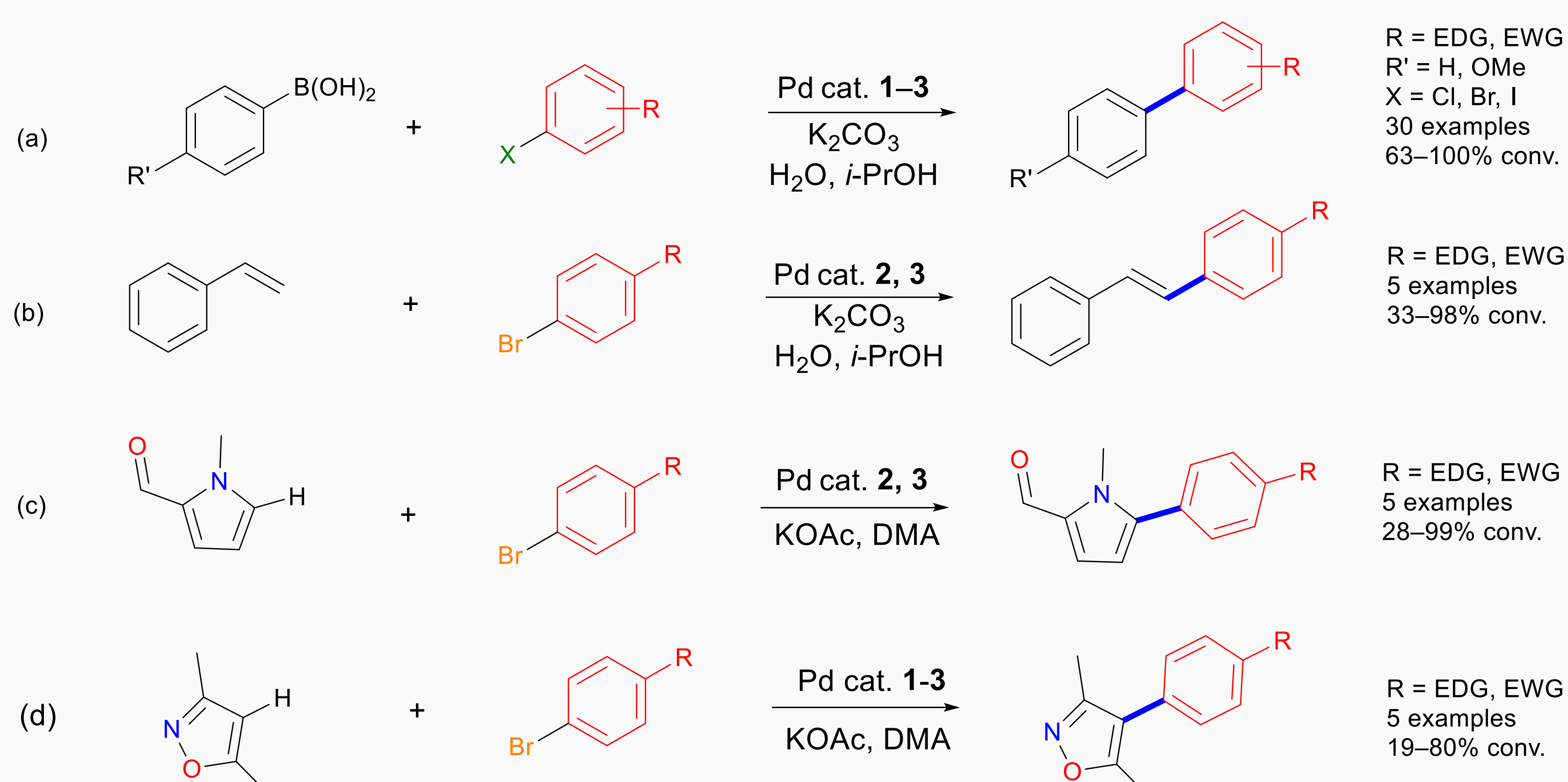
The X-ray structure of complex **2** was solved and showed the occurrence of  $\pi$ -stacking interactions between the xanthine and pyridine rings.

### Catalytic results:

A green catalytic process was devised for the Suzuki-Miyaura cross-coupling reaction (a).

A set of five representative aryl bromides with electron-withdrawing or electron-donating substituents were further selected for the Mizoroki-Heck cross-coupling reaction (b).

Two types of C-H activation reactions were also successfully catalyzed using either 1-methyl-2-pyrrole-carboxaldehyde (c) or 3,5-dimethylisoxazole (d) as substrates.



### References:

[1] Makhloufi, A.; Frank, W.; Ganter, C. *Organometallics*, **2012**, *31*, 7272–7277.

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[3] O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. G. *Chem. Eur. J* **2006**, *12*, 4743–4748.

[4] Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Angew. Chemie Int. Ed.* **2007**, *46*, 2768–2813.

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