OFF-CYCLE CHEMISTRY OPTIMIZATION IN CATALYST DESIGN

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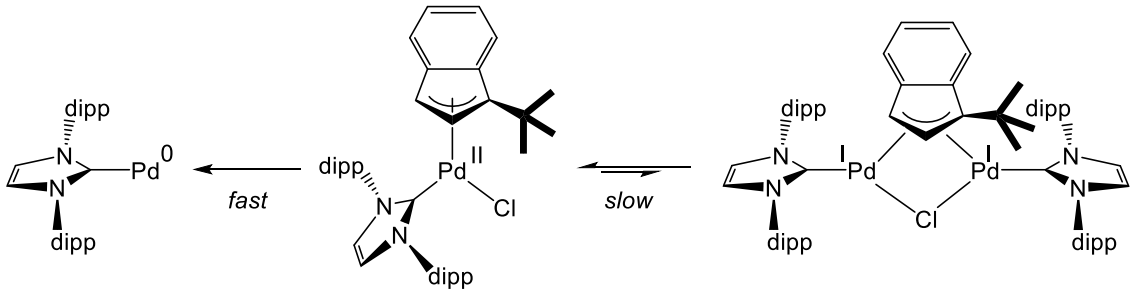
Computationally-driven catalyst design often focuses on the rate determining step (*rds*) within the catalytic cycle. However, off-cycle reactions, including the formation of the active species and catalyst degradation pathways, may also play a relevant role; *e.g.*, pre-catalyst activation being the *rds* or off-cycle species at the origin of the largest energy span. In a series of joint theoretical/experimental studies in collaboration with the group of Prof. Hazari, we explored the off-cycle chemistry of the palladium-catalyzed Suzuki-Miyaura cross couplings.[1-3] DFT calculations were used to rationalize the thermodynamic and kinetic parameters associated with the reductive activation of Pd(II) to Pd(0)[1] and the comproportionation of these two species into Pd(I)Pd(I) dimers.[2] This insight was exploited in the development of a new Suzuki-Miyaura catalytic system,[3] which promotes the activation of the pre-catalyst meanwhile mitigating the formation of less active dimer species (Figure). This catalyst, which is supported by the 1-*tert*-butyl-indenyl ligand, is one of the most active reported to date and is already commercially available. New studies currently underway focus on Ni(II)-catalyzed cross-coupling reactions, in which Ni(I) off-cycle species may also play a key role.[4]



new catalyst

1) Melvin, P.R.; Balcells, D.; Hazari, N.; Nova, A. *ACS Catal.*, **2015**, *5*, 5596.
2) (a) Hruszkewycz, D. P.; Balcells, D.; Guard, L. M.; Hazari, N.; Tilset, M. *J. Am. Chem. Soc.*, **2014**, *136*, 7300; (b) Hruszkewycz, D. P.; Guard, L. M.; Balcells, D.; Feldman, N.; Hazari, N.; Tilset, M. *Organometallics*, **2015**, *34*, 381.
3) Melvin, P. R.; Nova, A.; Balcells, D.; Dai, W.; Hazari, N.; Hruszkewycz, D.; Shah, H.; Tudge, M. *ACS Catal.*, **2015**, *5*, 3680.
4) Guard, L.M.; Beromi, M. M.; Brudvig, G. W.; Hazari, N.; Vinyard, D. J. *Angew. Chem. Int. Ed.*, **2015**, *54*, 13352.