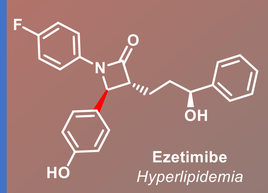
Towards Mechanistic Understanding of Palladium Speciation in Challenging Csp^2-Csp^3 Suzuki-Miyaura Cross-Couplings (SMCCs)

Stuart C. Smith, James D. Firth, Andrew Turner, Ian J. S. Fairlamb* and Peter. O'Brien*

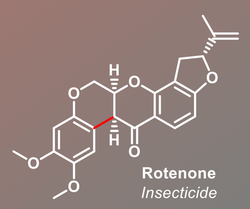
scs555@york.ac.uk, Department of Chemistry, University of York, Heslington, YO10 5DD

1. Project Motivation

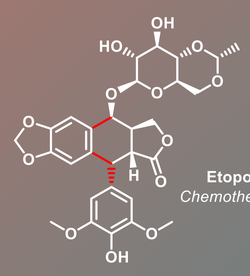
- High potential for application in pharmaceuticals/agrochemicals/fine chemical materials
- Our route allows rapid Csp^3-character increase during one-step fragment elaborations.
- Operationally simple, readily available heteroaryl bromides



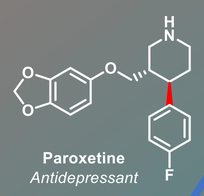
Ezetimibe
Hyperlipidemia



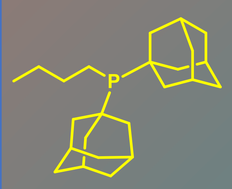
Rotenone
Insecticide



Etoposide
Chemotherapeutic



Paroxetine
Antidepressant

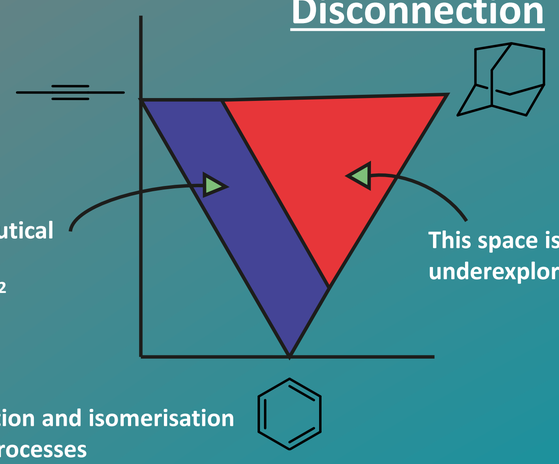


CataCXium A/$Pd(OAc)_2$

There is limited mechanistic understanding of $Pd(OAc)_2$ / $nPAd_2{}^nBu$ pre-catalytic systems used for Csp^2-Csp^3 SMCCs.

Note: CataCXium A = $PAd_2{}^nBu$

2. Stereospecific Csp^2-Csp^3 SMCCs: A Transformative Disconnection



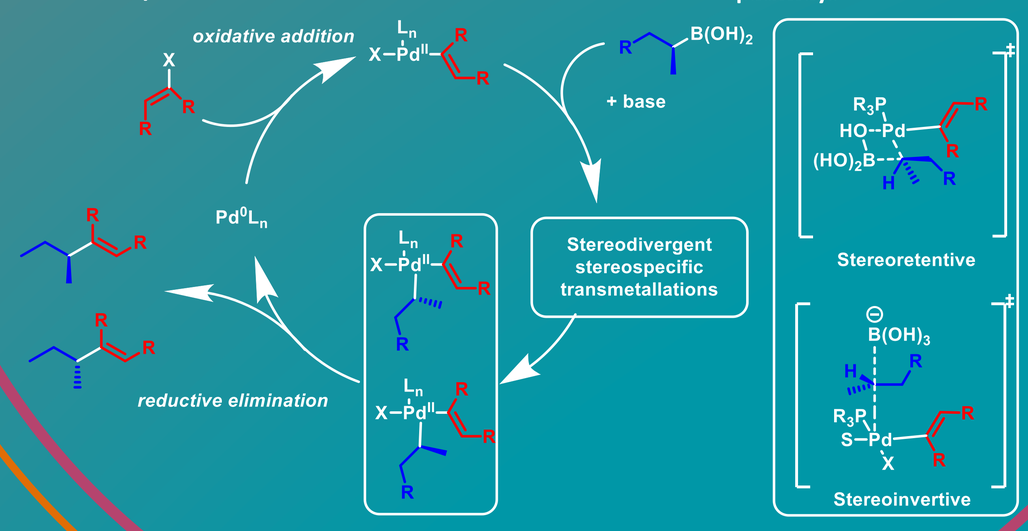
75% of pharmaceutical fragments are predominantly sp^2 character

This space is underexplored!

"With the success of the Suzuki-Miyaura coupling reaction in generating biaryl motifs, a variant allowing routine sp^3–sp^2 couplings – ideally in an enantioselective manner – is both highly desirable and could fundamentally change the motifs being generated." [6]

❑ β-hydride elimination and isomerisation and reinsertion processes

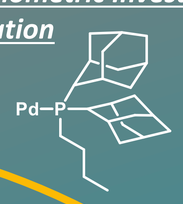
❑ Stereochemical erosion *via* mixture of retentive/invertive transmetallation pathways



❑ Slow transmetallation (sterics/electronics)

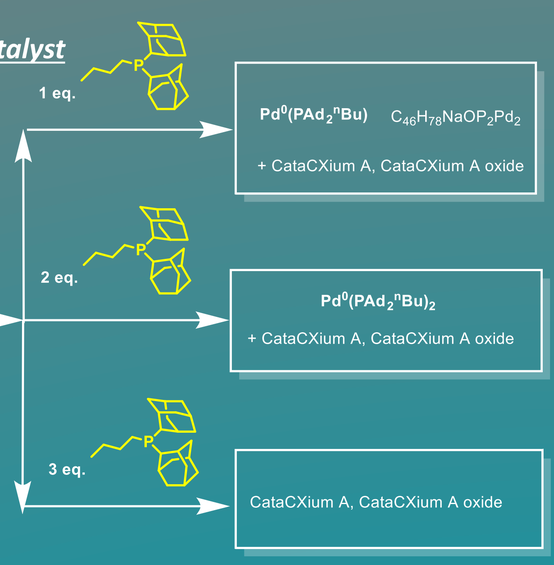
3. Mechanistic Insights

Stoichiometric Investigation of Pre-catalyst Activation

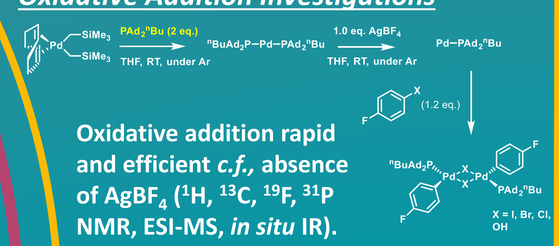


Monoligated Pd^0 appears to be major species undergoing oxidative addition

$Pd(OAc)_2$

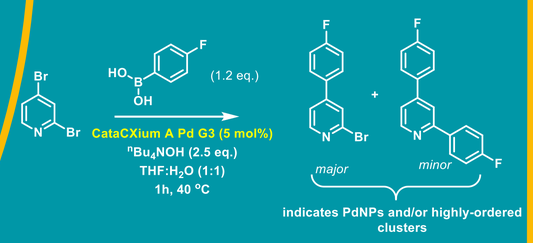


Oxidative Addition Investigations



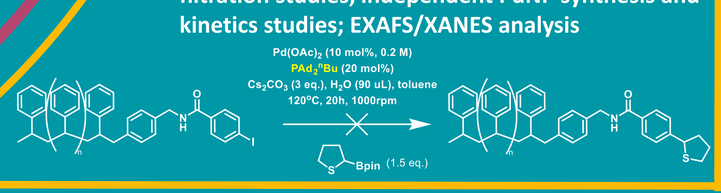
Oxidative addition rapid and efficient *c.f.*, absence of $AgBF_4$ (^1H, ^{13}C, ^{19}F, ^{31}P NMR, ESI-MS, *in situ* IR).

Are Palladium Nanoparticles Influencing an Exemplar SMCC reaction?



✓ Classical tests are indicating possible PdNP/cluster catalysis in this system

✓ Require further evidence (Hg-drop test, TEM, hot filtration studies, independent PdNP synthesis and kinetics studies; EXAFS/XANES analysis

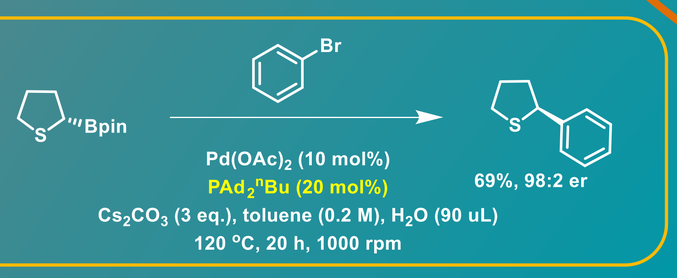


4. Csp^2-Csp^3 SMCC of α-Bpin tetrahydrothiophenes

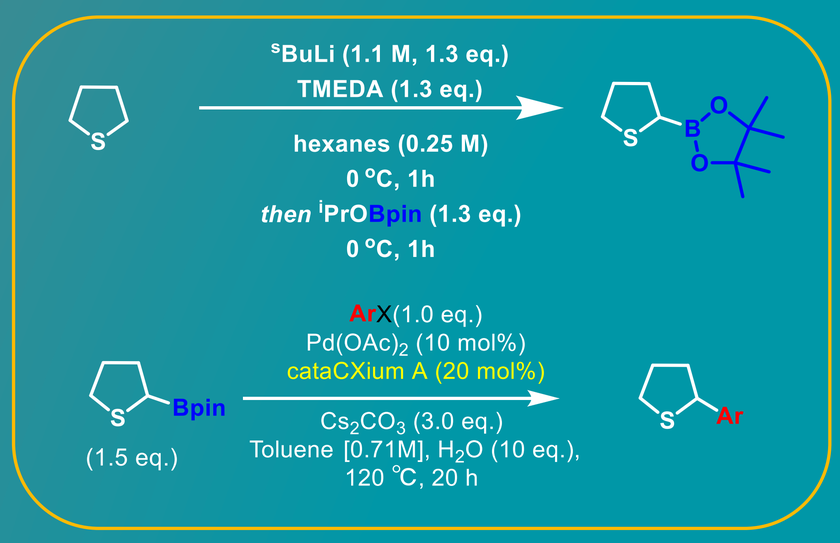
✓ Racemic scope – tolerates range of heteroaryl bromides

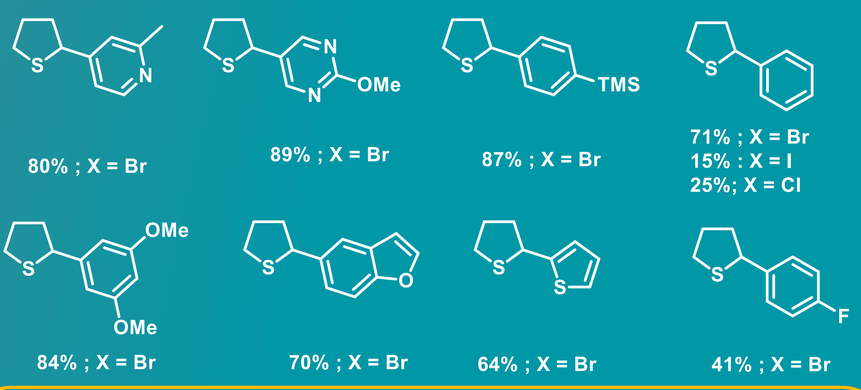
✓ Extensive optimisation activities have resulted in conditions competent to couple tetrahydrothiophenes with heteroaryl bromides

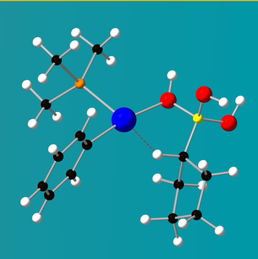
Invertive Transmetallation



α-Bpin tetrahydrothiophene preparation and SMCCs







✓ We are interrogating our model system *via* DFT

✓ Scheme shows minimised structure of $(Me_3P)Pd(Ph)(OH)$---$(OH)_2B$(cyclopentyl) Structure optimised using B3LYP/DGDZVP; implicit solvent correction (tight convergence); scrf=(cpcm, solvent=toluene), Grimme's GD3 empirical dispersion correction; superfine integration grid

5. Conclusions and Future Work

✓ Successfully developed general conditions for Csp^2-Csp^3 SMCCs of tetrahydrothiophenes with a scope of heteroaryl bromides.

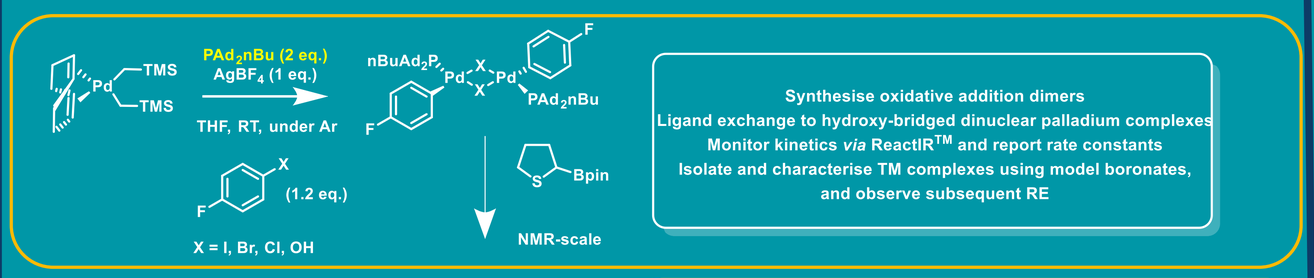
✓ We are beginning to understand more about the pre-catalyst activation and oxidative addition steps.

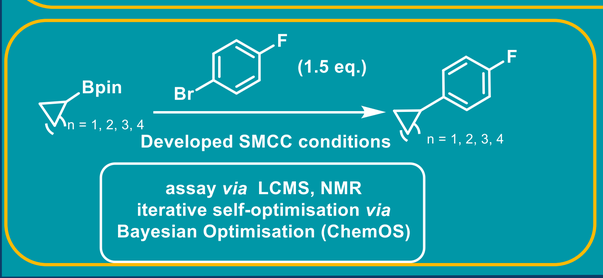
✓ Shown that there is an urgent need to elucidate the interplay between molecular and nanoparticle catalysis.

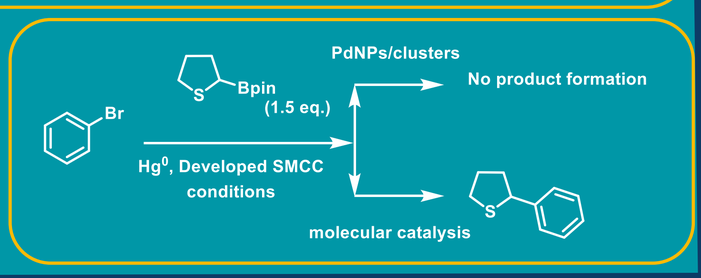
✓ Exploited this understanding to facilitate generation of Pd(0)-L species using $AgBF_4$ as a phosphine scavenger.

❑ Develop understanding of stereocontrol in transmetallation through further mechanistic studies.

❑ Further interrogate nanoparticle hypothesis.







References

(1) Reisman, S. E. et al. *Chem. Rev.* 2015, 115, 9587. (2) Rygus, J. P. G.; Crudden, C. M. *J. Am. Chem. Soc.* 2017, 139, 18124. (3) Crudden, C. M. et al. *J. Am. Chem. Soc.* 2009, 131, 5024. (4) Sigman, M. S.; Biscoe, M. R. et al. *Science* 2018, 362, 670. (5) Burke, M. D. et al. *Nat. Commun.* 2019, 10, 1263. (6) Blakemore, D. C. et al. A. *Nat. Chem.* 2018, 10, 383.

Acknowledgements

- AstraZeneca
- University of York, EPSRC and Royal Society for Industry Fellowships (IJSF & PAOB).
- Technical Analytical Services (NMR, MS, XRD) – Department of Chemistry, University of York