



Expanding the Scope of Asymmetric Redox-relay Oxidative Heck Transformations

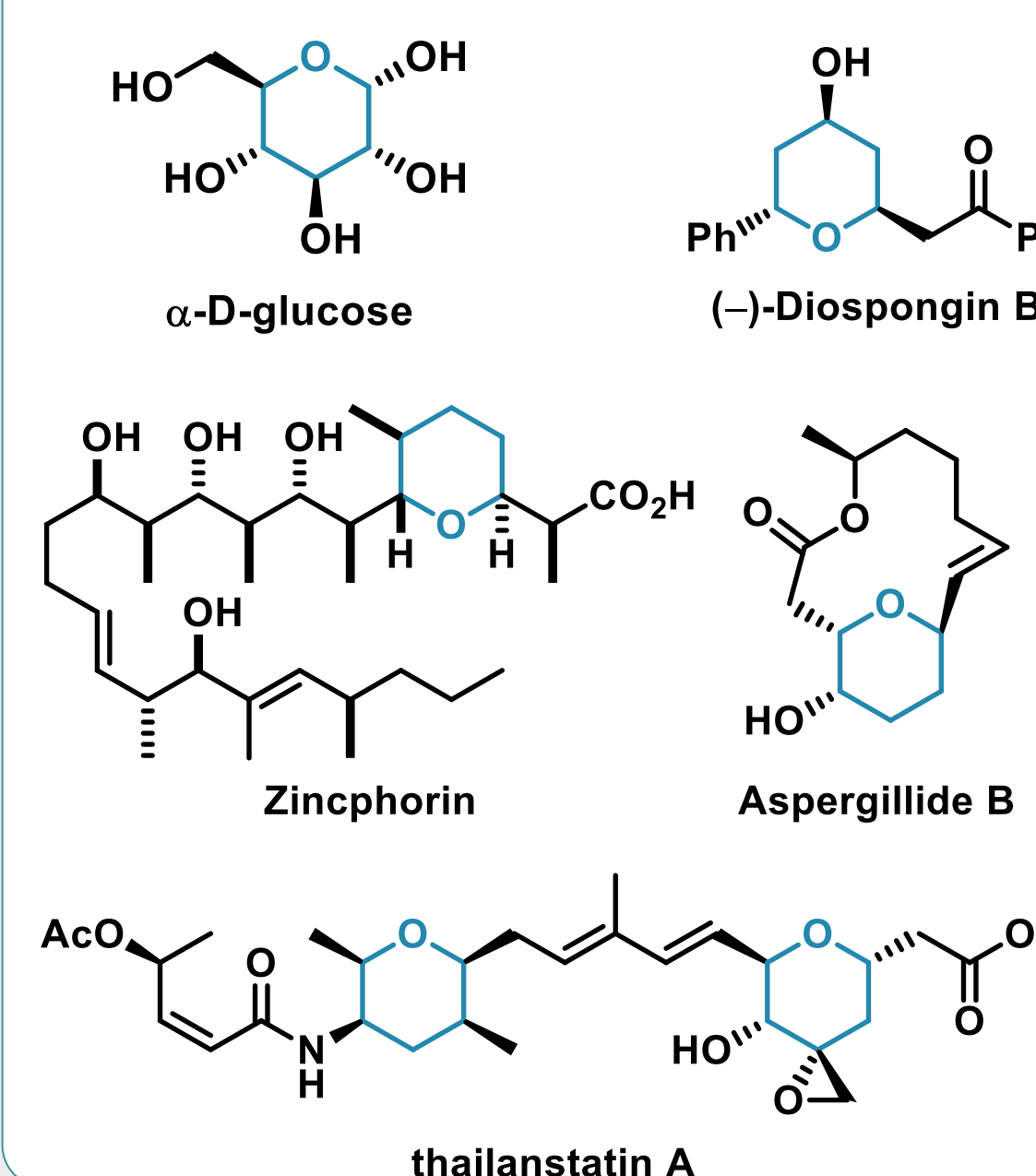
Holly Bonfield^{a,b} - holly.x.bonfield@gsk.com; David Pascoe^a; David Lindsay^b

^aGlaxoSmithKline, Stevenage; ^bUniversity of Strathclyde, Glasgow

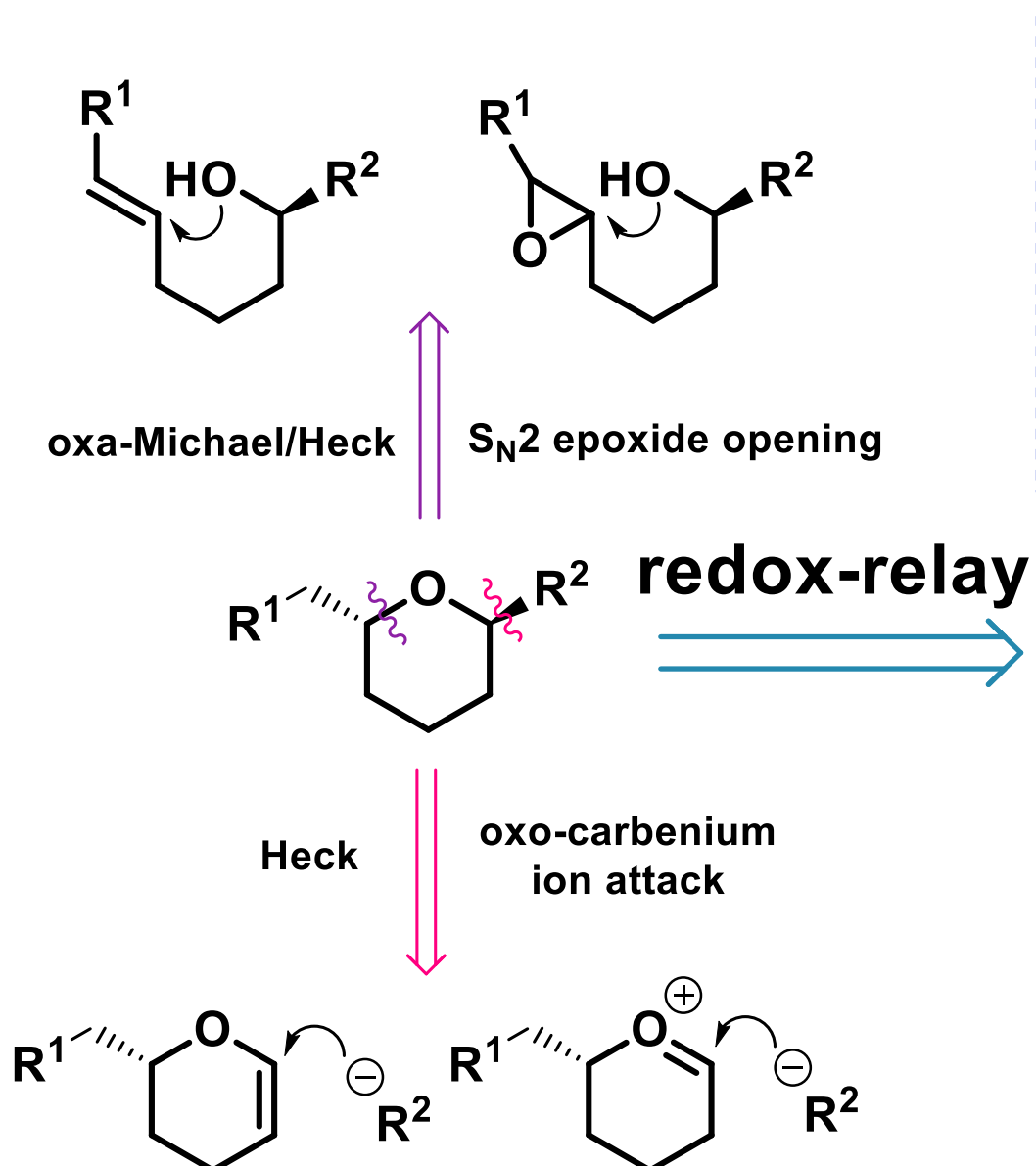


Introduction

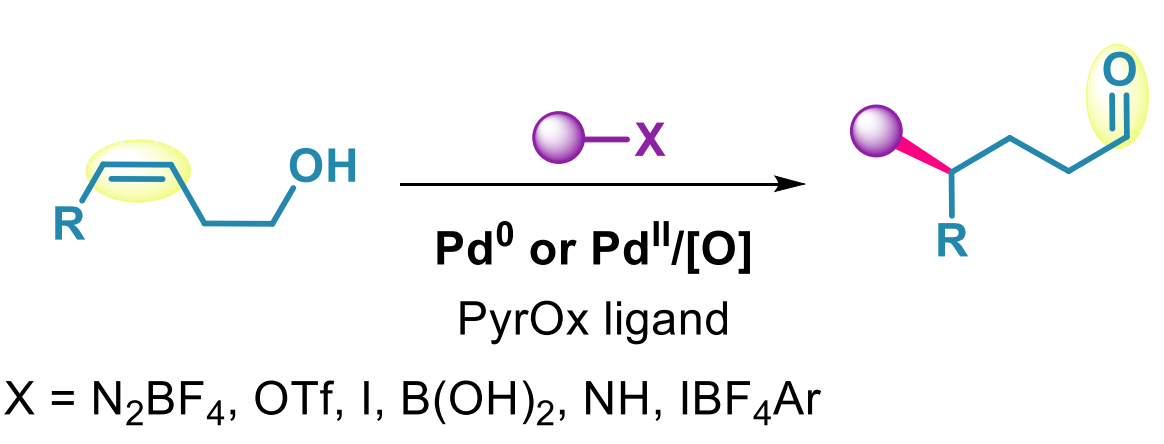
Why 2,6-trans-tetrahydropyrans?



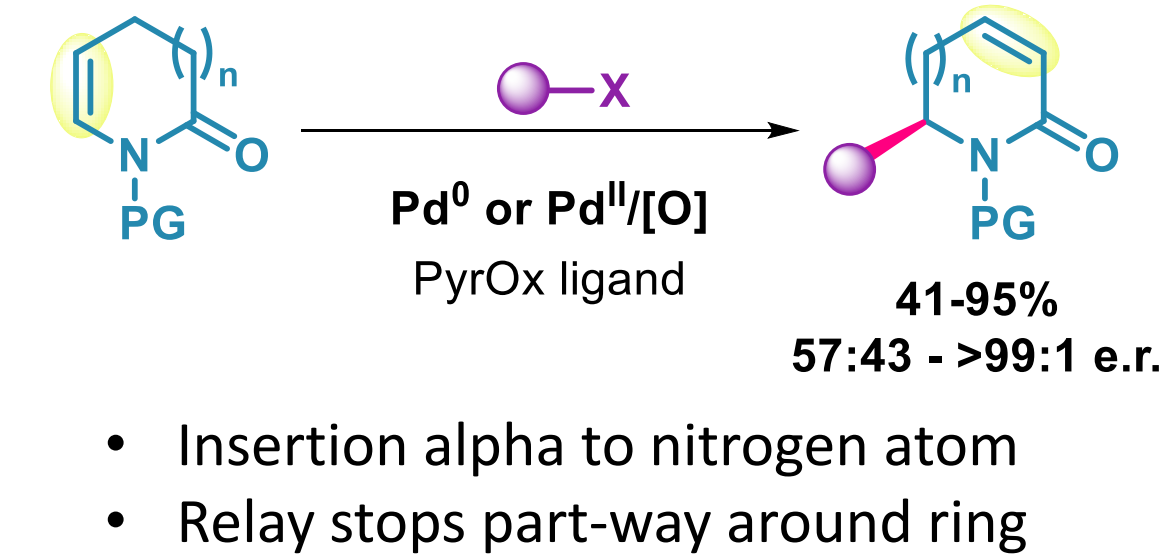
Established Synthetic Methods



Redox-relay Heck and oxidative Heck¹

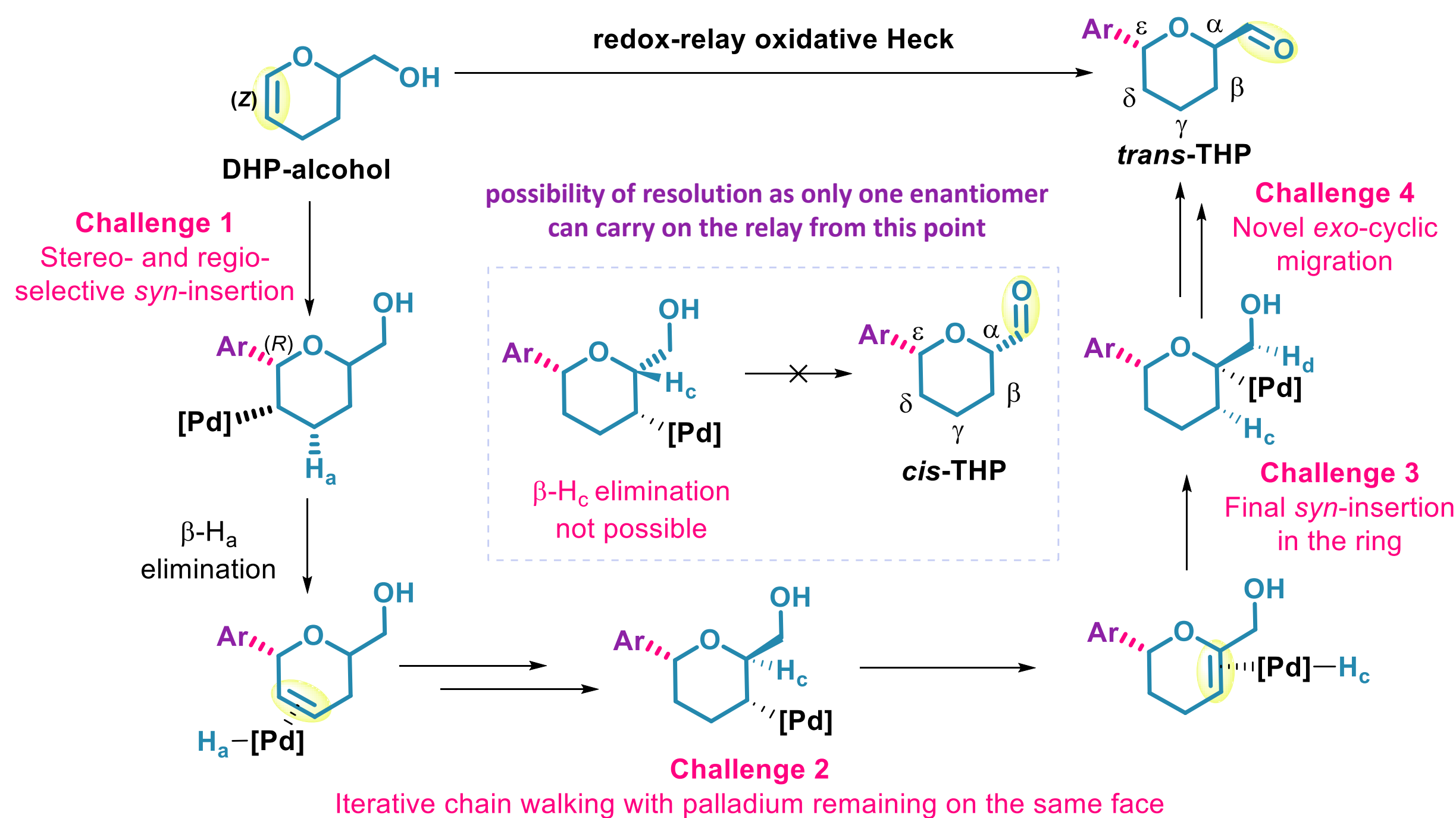


Heterocyclic redox-relay



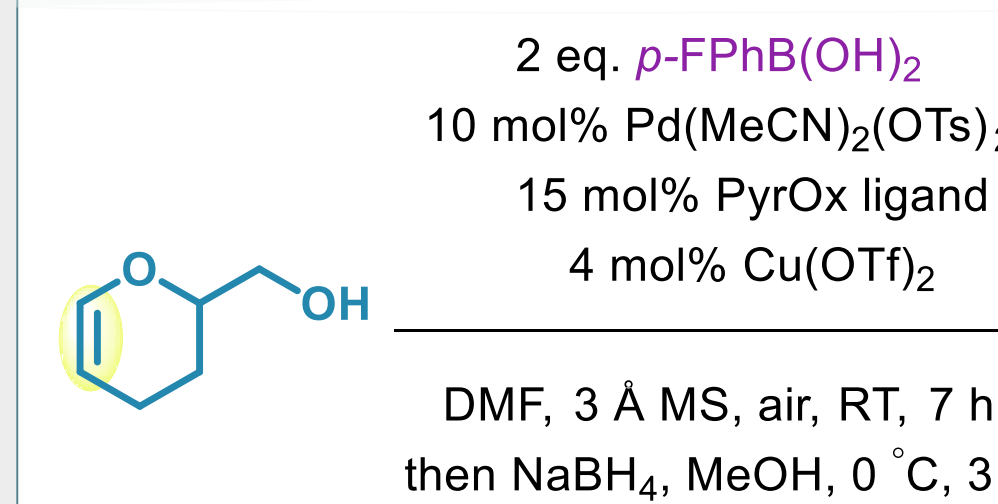
- Insertion alpha to nitrogen atom
- Relay stops part-way around ring

System of study and associated challenges



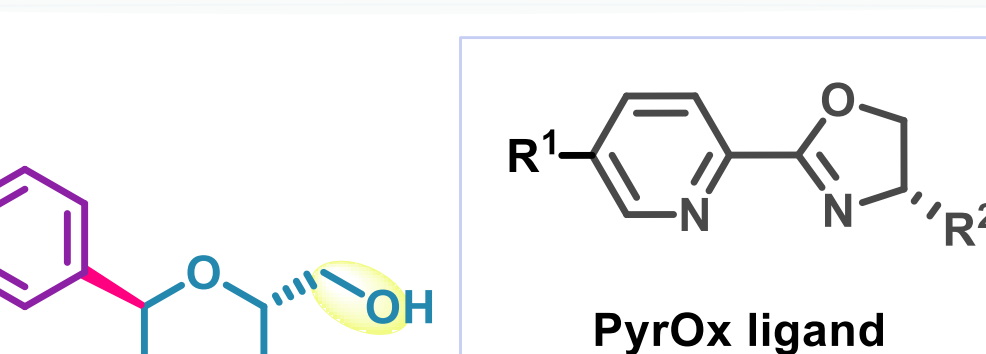
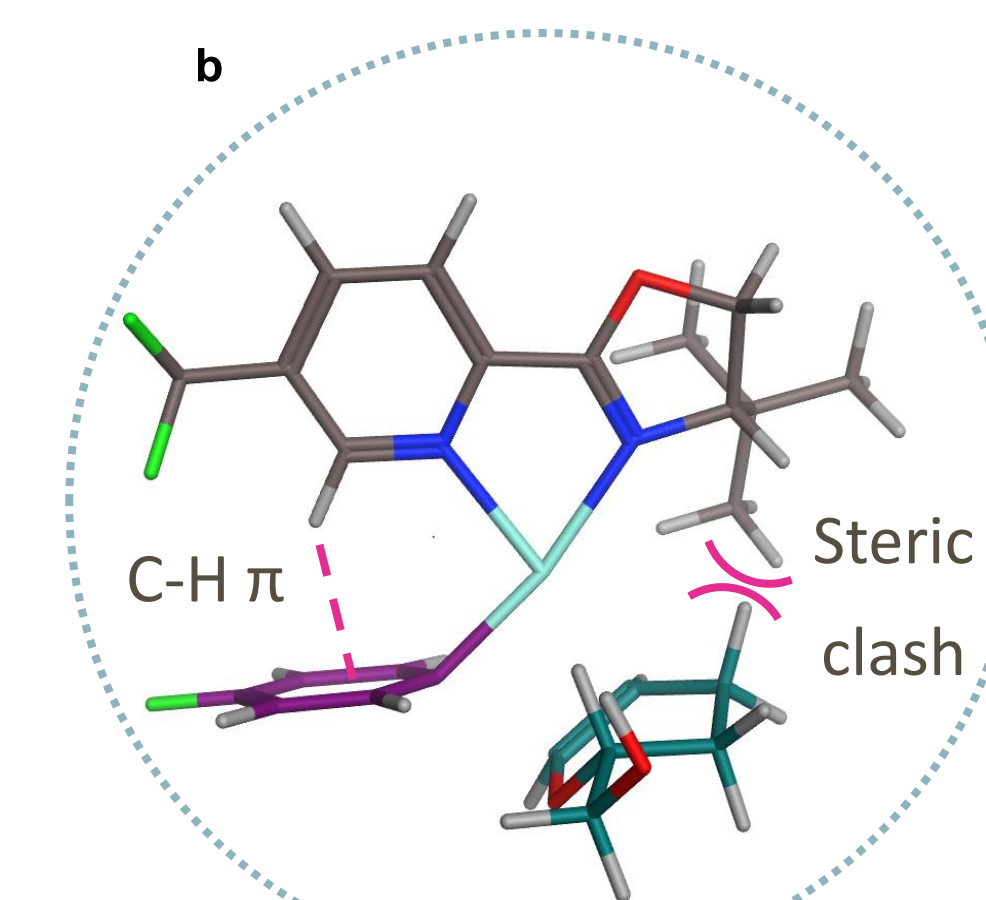
Resolution of dihydropyran

Proof of Concept and Ligand Screen



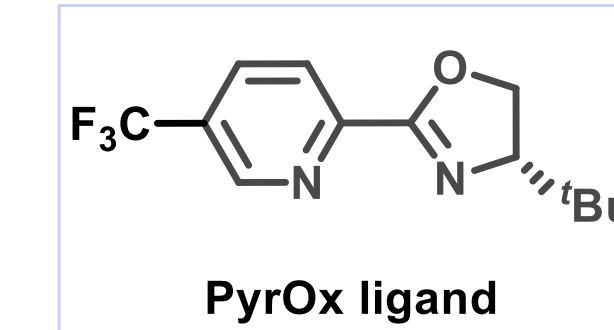
Entry	R ¹	R ²	Yield / %	a:b e.r.
1	CF ₃	^t Bu	27	94:6
2	NO ₂	^t Bu	34	93:7
3	OMe	^t Bu	5	95:5
4	CF ₃	Ph	14	69:31
5	NO ₂	Ph	44	65:35

tert-butyl group is key for high enantioselectivity achieved

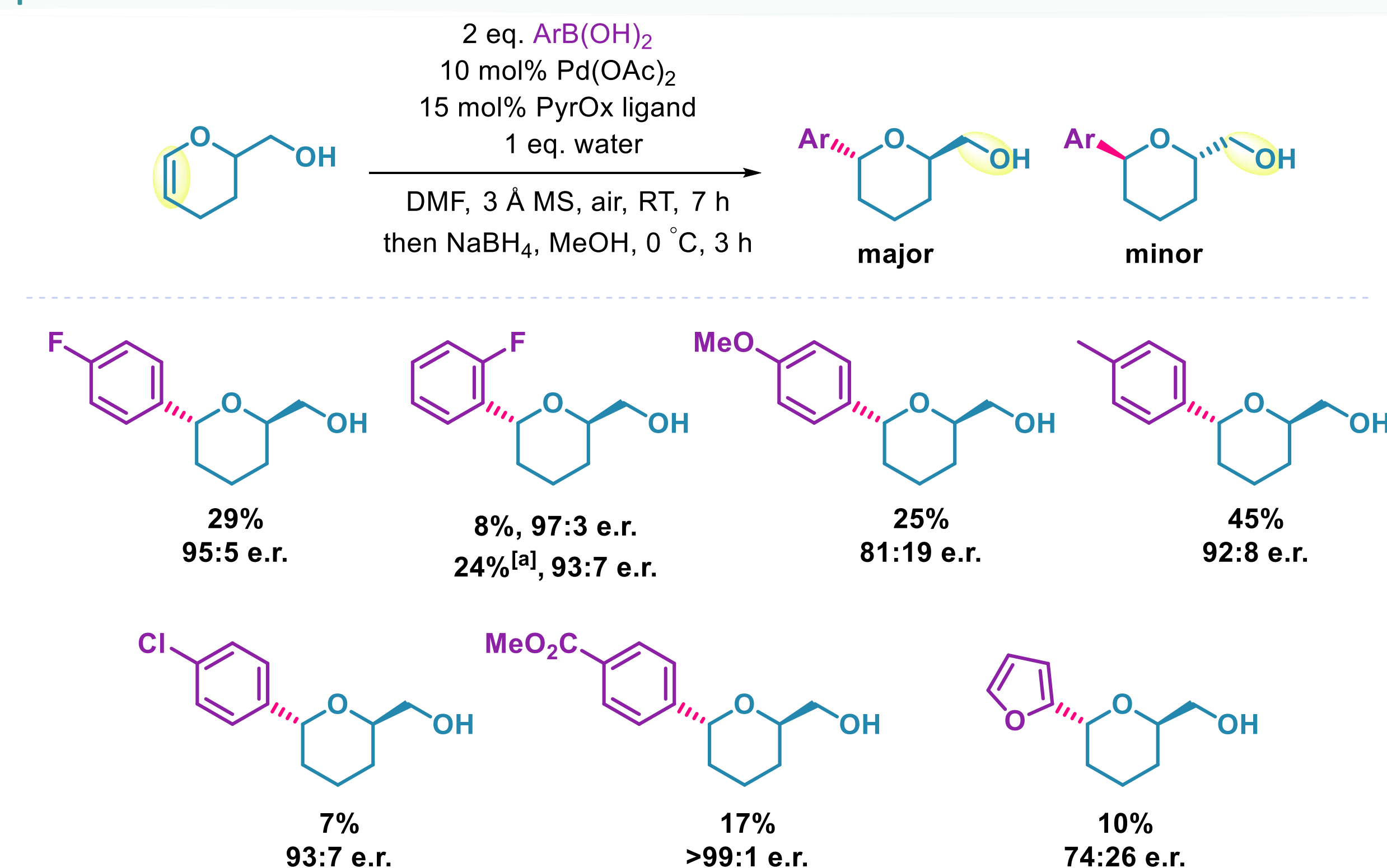


Optimisation

Entry	[Pd]	T / °C	1 eq. water	Time / h	Yield ^[a] / %	a:b e.r.
1	Pd(MeCN) ₂ (OTf) ₂	0	N	24	7	ND
2	Pd(MeCN) ₂ (OTf) ₂	10	N	46	22	98:2
3	Pd(MeCN) ₂ (OTf) ₂	RT	N	7	27	94:6
4	Pd(MeCN) ₂ (OTf) ₂	RT	Y	7	36	93:7
5	Pd(OAc) ₂	RT	Y	7	46	85:15
6	Pd(OAc) ₂ No Cu(OTf) ₂	RT	Y	7	50 (29% ^[b])	95:5



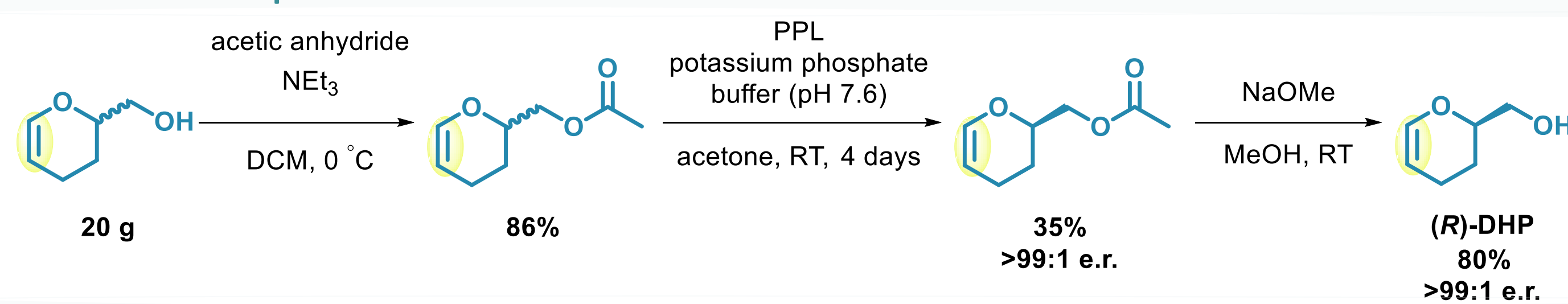
Scope



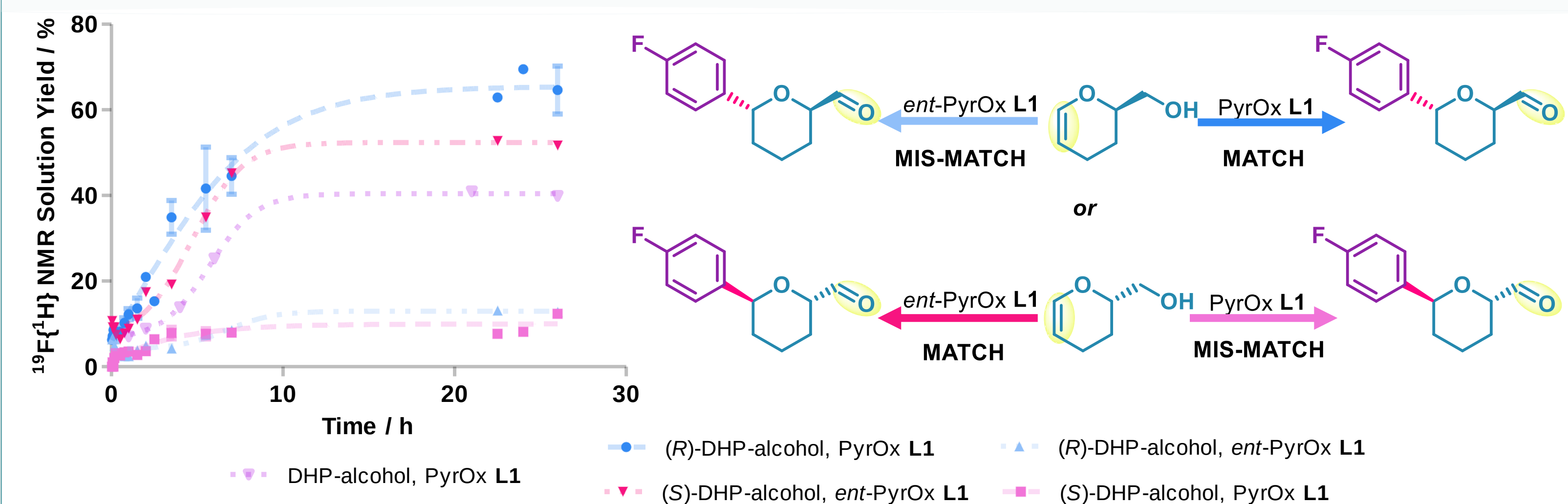
[a] conditions used: 2 eq. *p*-FPhB(OH)₂, 10 mol% Pd(MeCN)₂(OTf)₂, 15 mol% PyrOx L1, 4 mol% Cu(OTf)₂, 1 eq. water, DMF (0.1 M), 3 Å MS, air, RT, 24 h then NaBH₄, MeOH, 0 °C, 3 h.

Enantiopure dihydropyran

Synthesis of Enantiopure Material



Match/Mis-match Studies



Optimisation

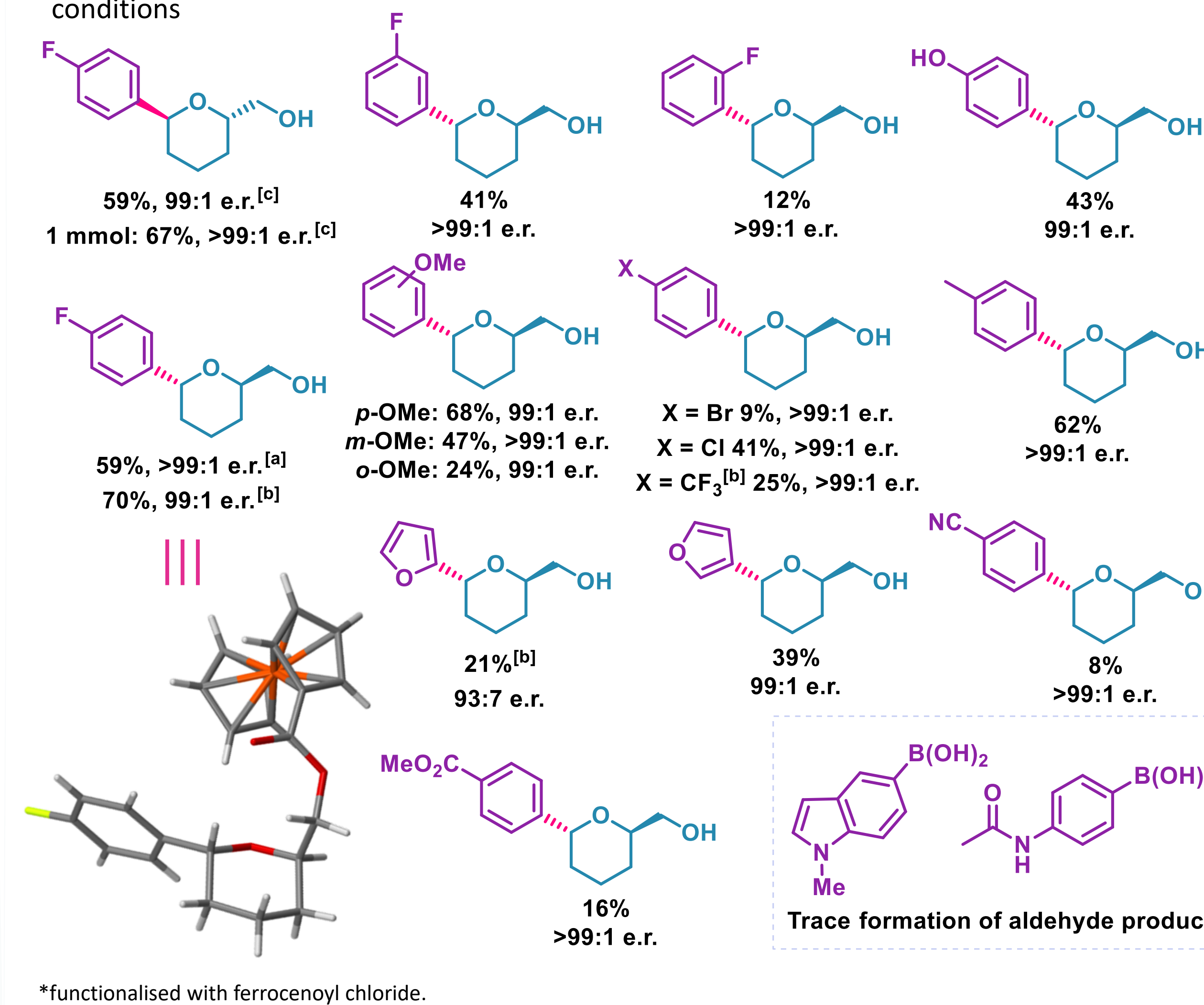
Entry	[Pd]	Pd:lig:Cu loading	1 eq. water	24 h yield ^[a] / %	e.r.
1	Pd(MeCN) ₂ (OTf) ₂	10:15:4	N	67	>99:1
2 ^[b]	Pd(MeCN) ₂ (OTf) ₂	10:15:4	Y	76	99:1
3 ^[b]	Pd(MeCN) ₂ (OTf) ₂	6:10:3	Y	80 (56% ^[c])	99:1
4	Pd(MeCN) ₂ (OTf) ₂	4:6:2	Y	77 (59% ^[c])	>99:1
5	Pd(OAc) ₂	10:15:4	Y	84 (70% ^[c])	99:1
6	Pd(OAc) ₂	6:10:3	Y	47	
7	Pd(OAc) ₂	4:6:2	Y	44	

[a] ¹⁹F(¹H) NMR solution yield; [b] Average of two runs; [c] Isolated yield

Two sets of conditions identified that delivered comparable results

Scope

- Used Entry 4 conditions by first intent
- Consistently excellent enantioselectivities achieved
- Generally higher yields are achieved with more electron-rich boronic acids
- Reduction in yields with electron-deficient boronic acids can be mitigated by employing Entry 5 conditions



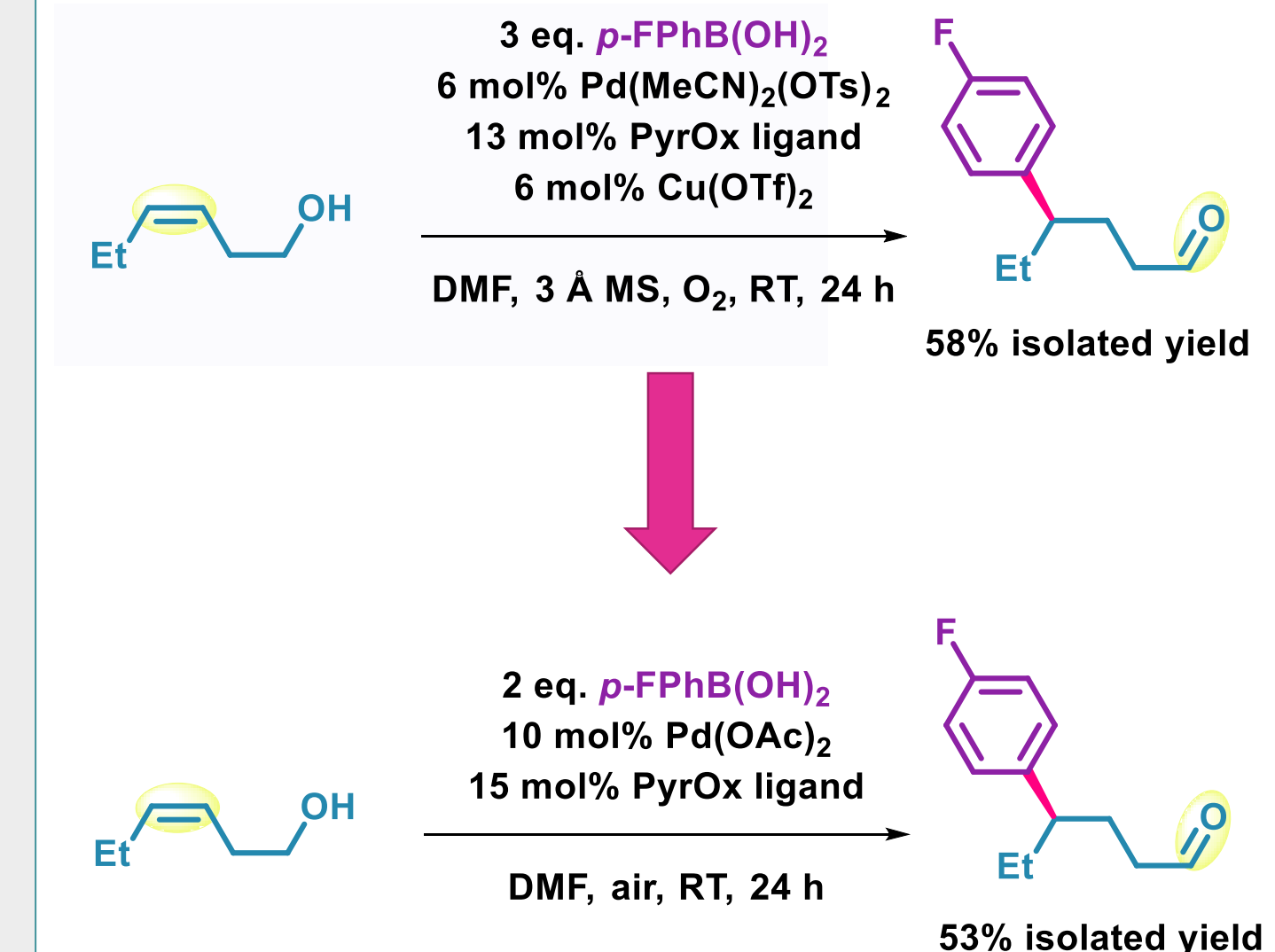
[a] Average of two runs; [b] Conditions used: Entry 5; [c] Starting from (S)-DHP-alcohol using ent-PyrOx L1.

Scalability Assessment

Aim:

To design a set of scalable redox-relay oxidative Heck conditions, which show an improved safety and sustainability profile whilst maintaining the yield and stereoselectivity

Literature substrate²:



- Reduced number of boronic acid equivalents
- Changed to a more commercially available and cheaper Pd source
- Mitigated hazardous oxygen atmosphere with air
- Removed the need for copper(II) triflate as a co-oxidant
- Removed the requirement of molecular sieves, which grind on scale

Conclusions

- A resolution of commercially available racemic dihydropyranyl starting material installs two stereocentres in a single step under mild conditions
- Further improvements in yield and enantioselectivity can be achieved using readily accessible enantiopure dihydropyranyl starting material
- Novel *exo*-cyclic migration demonstrated successfully for addition to redox-relay toolkit

Future Work

- Investigations into other systems and the formation of quaternary stereocentres are currently underway
- The scalability of redox-relay oxidative Heck reactions is also being explored further

References

- H. E. Bonfield, D. Valette, D. M. Lindsay, M. Reid *Chem Eur. J.* **2021**, *27*, 158
- T.-S. Mei, E. W. Werner, A. J. Burckle, M. S. Sigman, *J. Am. Chem. Soc.* **2013**, *135*, 6830 –6833