

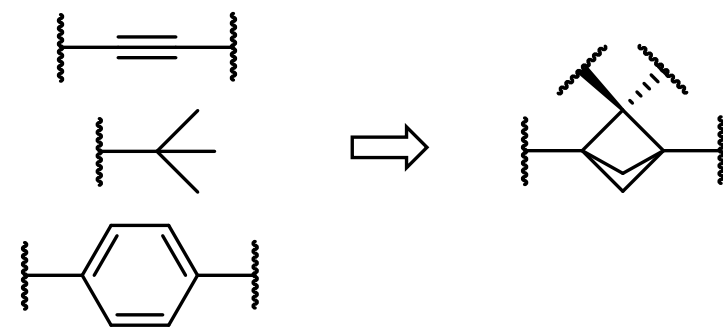
## 1 Introduction

Why bicyclo[1.1.1]pentanes (BCPs)?

Powerful bioisosteres of arenes, *tert*-butyl groups and alkynes in drug discovery and agroscience<sup>1</sup>

Frequently allow increased:

- ✓ Solubility
- ✓ Target selectivity
- ✓ Metabolic stability
- ✓ Potency



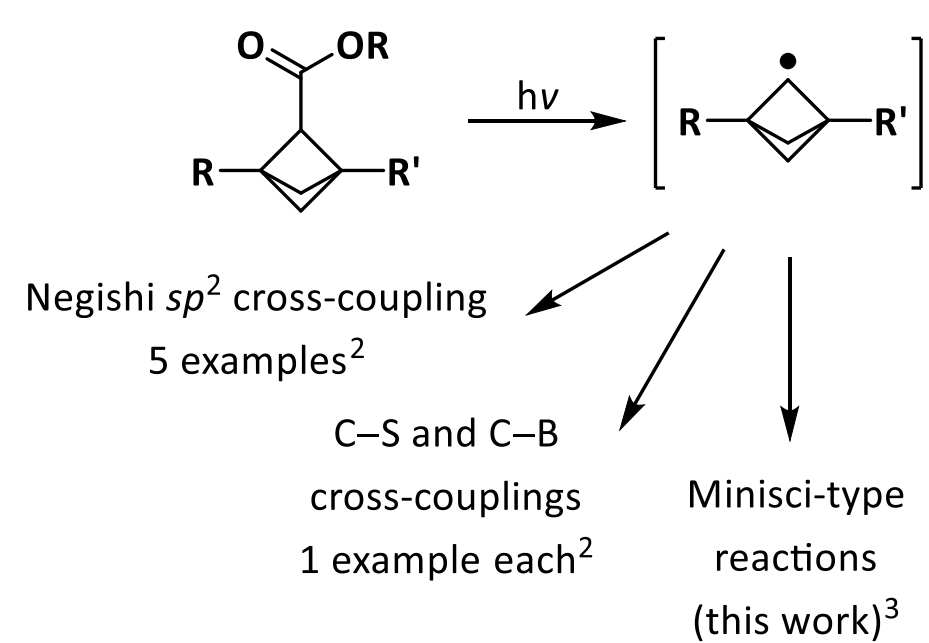
Bridge-functionalised bicyclo[1.1.1]pentanes

Novel chemical space

Novel vectors: analogues of *ortho*-/*meta*-substituted arenes

Challenging, underexplored synthetic chemistry

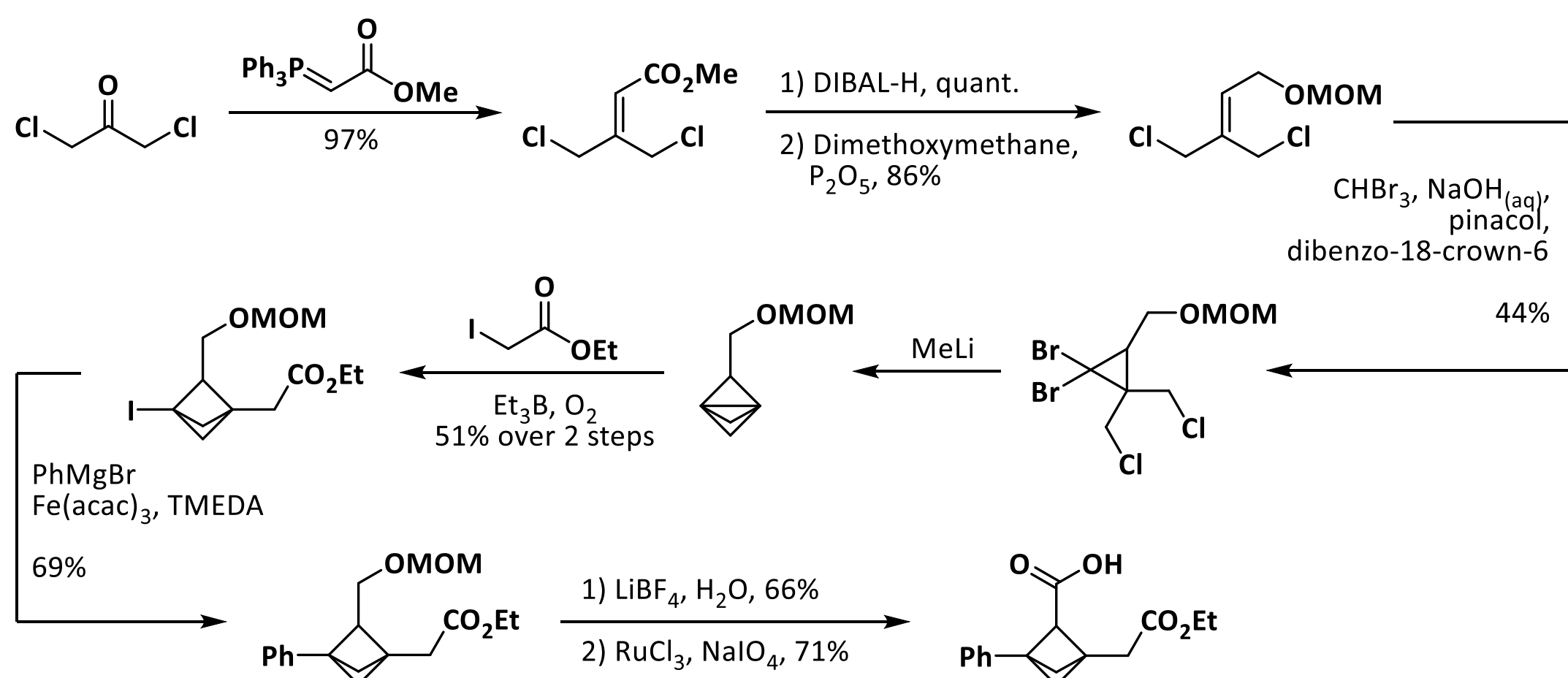
BCP bridge radicals are kinetically stable and represent an attractive divergent intermediate. Convenient access from carboxylic acids or derivatives:



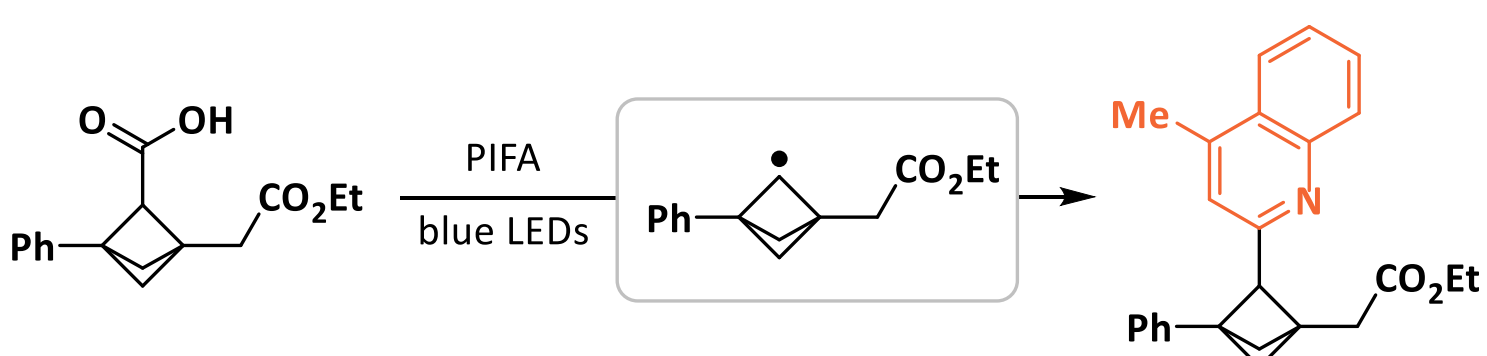
Key challenges<sup>1</sup>

1. Use of carboxylic acid as limiting reagent in decarboxylative transformations
2. Poorly defined kinetic stability and philicity of BCP radical

## 2 Synthesis of Model Substrate



## 3 Reaction Optimisation: Key Observations



Radical generation via photodecomposition of iodine(III) bis-carboxylate complex

- Exogenous photocatalyst or metal catalyst not required
- No carboxylic acid pre-activation necessary; no heterocycle prefunctionalisation necessary
- Reaction is tolerant of trace oxygen and moisture
- EtOAc and dimethyl carbonate optimal solvents
- Effective temperature control ( $T \approx 40^\circ\text{C}$ ) essential
- Reaction yield very sensitive to PIFA loading
  - Limiting factor is starting material conversion – unreacted material recoverable
  - Additive screen to increase conversion unsuccessful

Final conditions

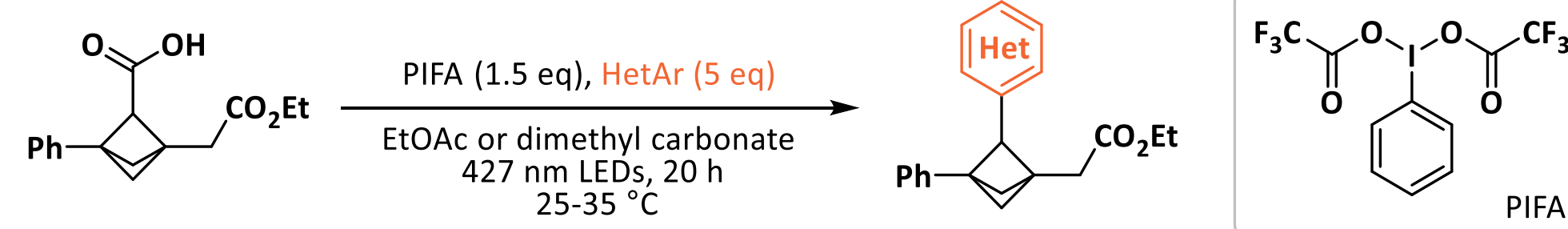
Cost economical

Step economical

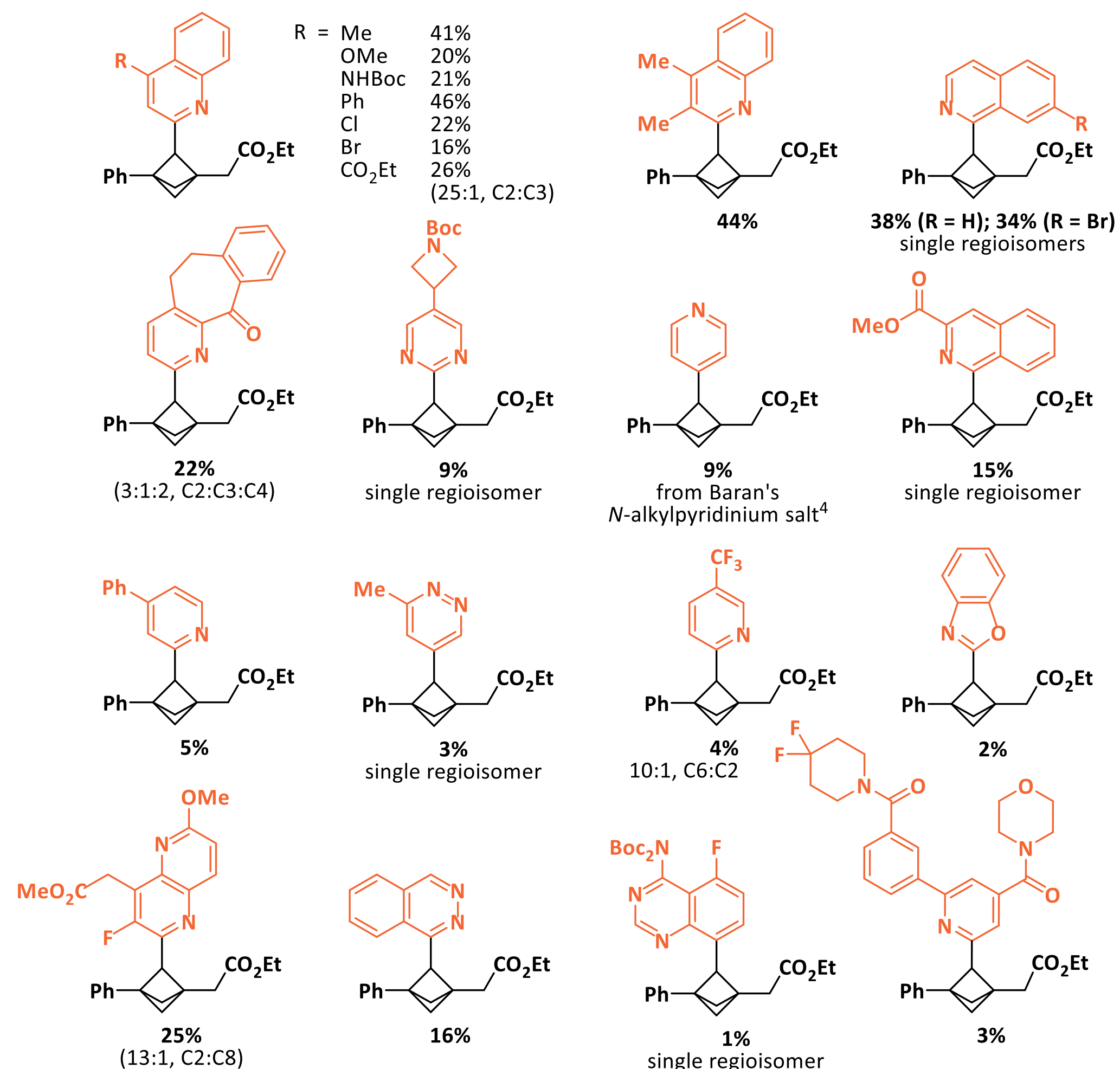
Operationally simple and suitable for parallel synthesis

Industry-preferred solvents

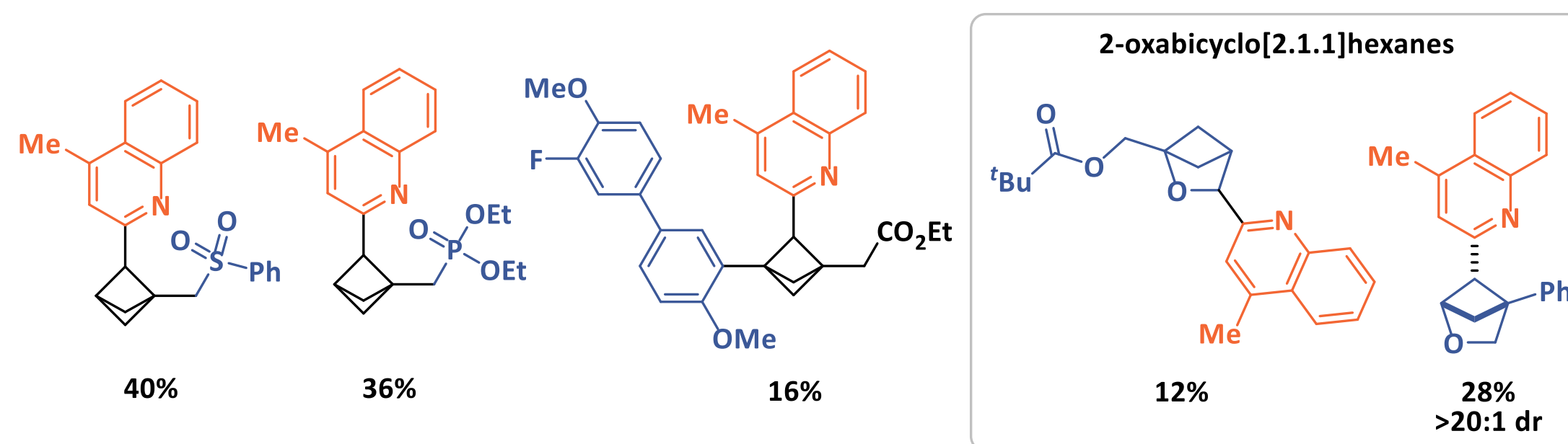
## 4 Substrate Scope



Scope of heterocycles – selected examples

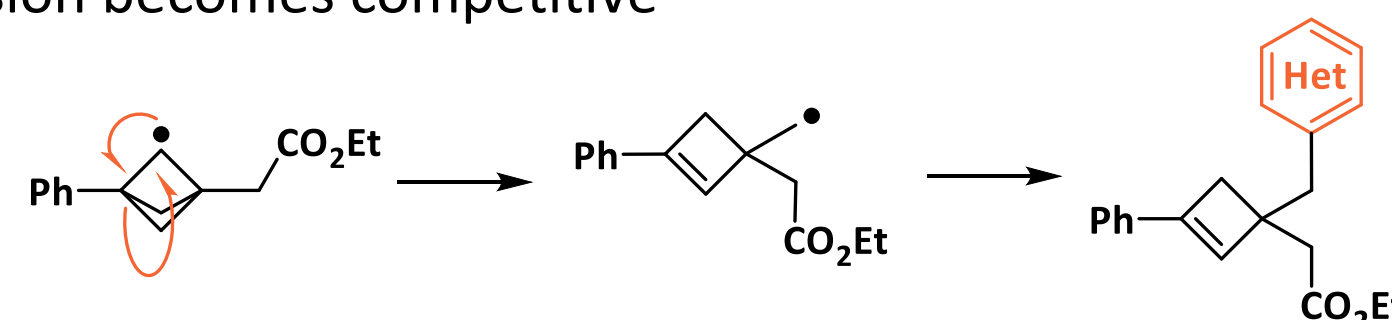


Scope of bicyclo[1.1.1]pentanes – selected examples

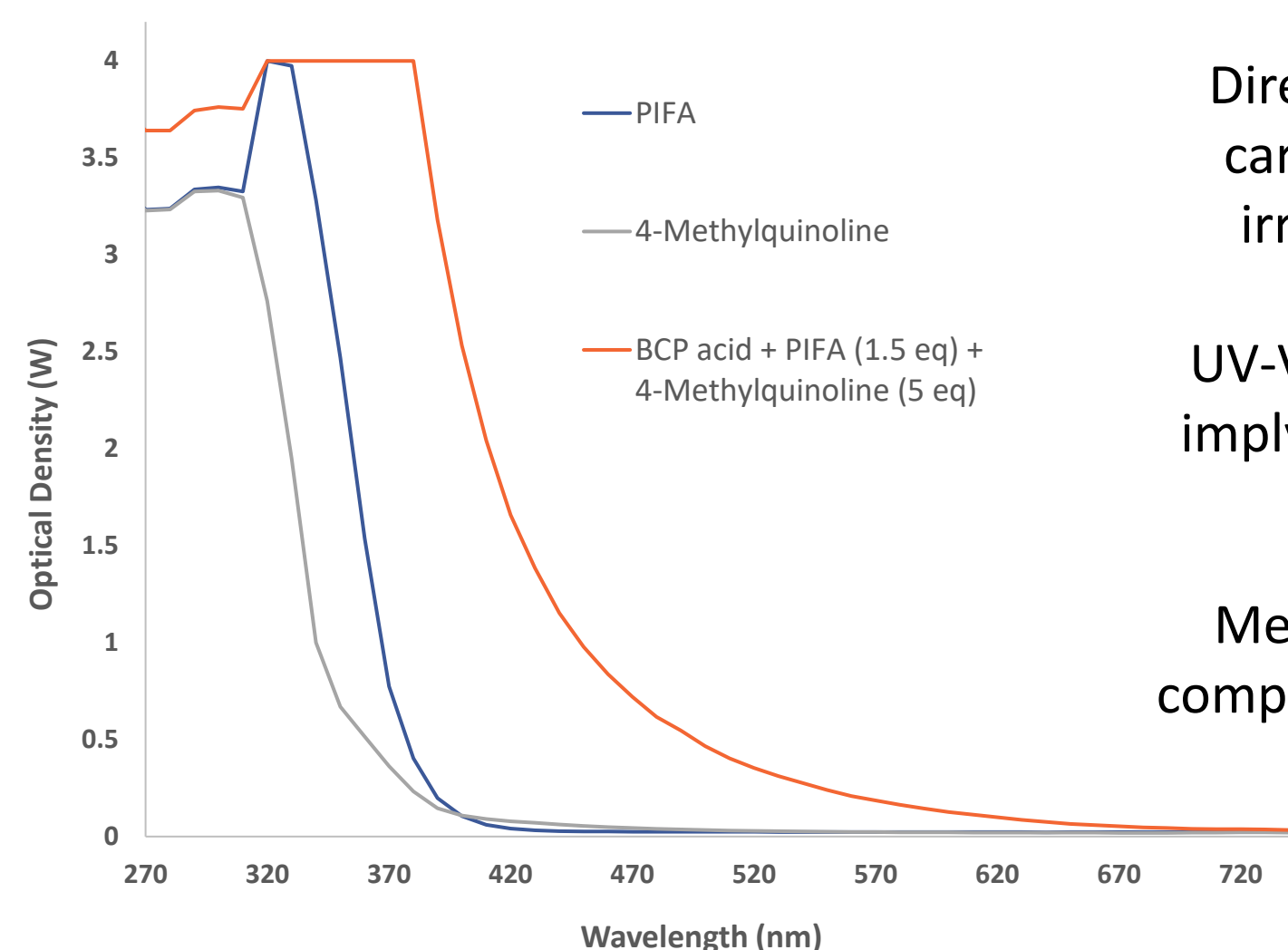


General challenges and limitations

- Nucleophilic functionality – adverse reaction with PIFA
- Heterocycle (and TFA salt) solubility
- Electron-deficient azines and high reaction temperatures – BCP radical  $\beta$ -scission becomes competitive



## 5 Mechanistic Considerations



Direct homolysis of iodine(III) carboxylates by 400-420 nm irradiation is preceded<sup>5</sup>

UV-Vis studies within this work imply unexpected **EDA complex formation**

Mechanism likely to be more complex than previously reported

### References

- (1) *Angew. Chem. Int. Ed.* **2021**, *60*, 24754-24769. (2) *Proc. Natl. Acad. Sci. USA* **2021**, *118*, e2108881118. (3) *Org. Lett.* **2023**, *25*, 2053-2057. (4) *J. Am. Chem. Soc.* **2021**, *143*, 11927-11933. (5) *Org. Lett.* **2018**, *20*, 4686-4690.

### Acknowledgements

J. A. is grateful to GSK and the EPSRC for a Studentship (Prosperity Partnership EP/S035990/1). J. A. is grateful to Society of Chemical Industry (SCI) for a Scholarship.