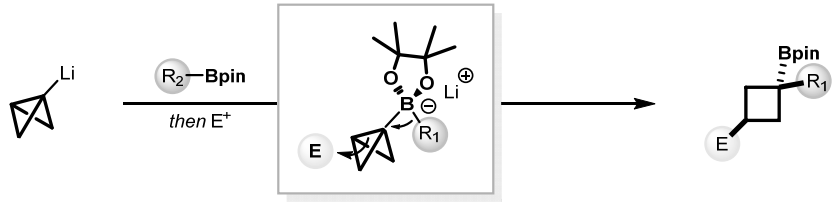
DEVELOPMENT OF BICYCLO[1.1.0]BUTYL BORONATE COMPLEXES FOR THE DIASTEREOSELECTIVE SYNTHESIS OF CYCLOBUTANES

Steven H. Bennett, Alexander Fawcett, Elliott H. Denton, Varinder K. Aggarwal*

School of Chemistry, University of Bristol, Bristol, BS8 1TS, UK

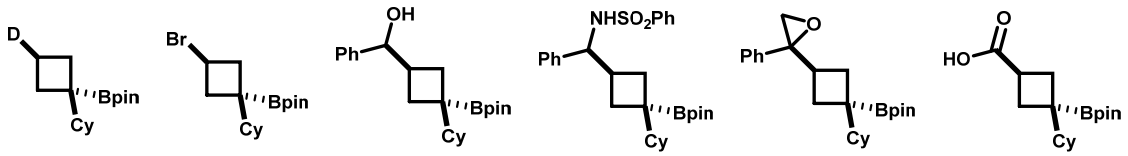
Cyclobutanes are becoming increasingly prevalent in the medicinal chemistry industry for several reasons: (i) restricted conformation, (ii) 3-dimensional exit vectors, (iii) metabolic stability and (iv) improved physicochemical properties compared with aromatic systems.[1,2] However, access to this type of scaffold is often limited by the lack of synthetic methods that permit its construction.

With respect to this, we have successfully manipulated highly strained bicyclo[1.1.0]butyl boronate complexes into engaging several electrophiles through a stereoselective 1,2-metallate rearrangement.[3] This methodology has allowed us to construct a wide-range of a diastereomerically pure borylated cyclobutanes.



• >50 cyclobutanes synthesised • wide-range of electrophiles • broad boronic ester scope • boronic ester transformations

Selected examples from this research:



D_2O
(64%, >95:5 dr)
[100% D]

DBDMH [Br^+]
(83%, >95:5 dr)

benzaldehyde
(78%, >95:5 dr)
[1.38 g]

***N*-sulfonyl imine**
(70%, 93:7 dr)

α-bromo ketone
(83%, >95:5 dr)

CO_2
(55%, >95:5 dr)

[1] Carreira, E. M.; Fessard, T. C. *Chem. Rev.* **2014**, *114*, 8257–8322.

[2] Nicolaou, K. C.; Vourloumis, D.; Totokotsopoulos, S.; Papakyriakou, A.; Karsunky, H.; Fernando, H.; Gavrilyuk, J.; Webb, D.; Stepan, A. F. *ChemMedChem* **2016**, *11*, 31–37.

[3] Fawcett, A.; Biberger, T.; Aggarwal, V. K. *Nat. Chem.* **2019**, *11*, 117–122.